

SPECIFICATION

[Title of the Invention]

NOVEL PEPTIDE AND PHARMACEUTICAL COMPOSITION FOR
5 TREATING AN EYE DISEASE COMPRISING THE SAME AS AN ACTIVE
PHARMACEUTICAL INGREDIENT

Technical Field

The present invention relates to novel peptides and pharmaceutical
10 compositions for treating eye diseases that comprises the same as an active
pharmaceutical ingredient.

Background Art

Dry eye syndrome or keratoconjunctivitis sicca may be defined, in a broad
15 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 dry eye syndrome is closely
related to age, the incidence thereof is increasing in younger age groups due to a
20 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 decrease in the lubrication of the eyeball. In addition, dry eye syndrome
25 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 fluorescent dye and a slit-
30 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. Since artificial tears as a representative symptom therapy merely supplement the insufficient tears; moreover, they 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.

[Disclosure of the Invention]

Problem to be Solved by the Invention

Therefore, the present inventors have endeavored to develop safe and effective therapeutic agents for treating an eye disease and, as a result, completed the present invention by way of synthesizing new 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.

Means for Solving the Problem

In order to achieve the object of the present invention, one aspect of the present invention provides a compound represented by Formula 1.

Further, another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys.

In addition, still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys.

Further, still another aspect of the present invention provides a peptide having an amino acid sequence represented by Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa.

In addition, still another aspect of the present invention provides a peptide
5 having an amino acid sequence represented by PD-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys.

Further, still another aspect of the present invention provides a peptide having any one amino acid sequence selected from the group consisting of Ala-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Ala-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala, Hyp-Gly-Gln-Glu-Gly-Leu-Gly, Hyp-Gly-Gln-Leu-Gly-Leu, _D-Hyp(2R, 4S)-Gly-_D-Gln-_D-Leu-Gly-_D-Leu, Hyp-Gly-Gln-Leu-Gly, Hyp-Gly-Gln-_D-Leu-Gly, and _D-Hyp(2R, 4S)-Gly-Gln-Leu-Gly.
10

In addition, still another aspect of the present invention provides a compound represented by Formula 8.

Further, still another aspect of the present invention provides a compound
15 represented by Formula 10.

In addition, still another aspect of the present invention provides a pharmaceutical composition for treating an eye disease, which comprises the compound or the peptide as an active pharmaceutical ingredient.

Further, still another aspect of the present invention provides a method for
20 treating an eye disease, which comprises administering the compound or the peptide to a subject.

Effects of the Invention

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

Brief Description of the Drawings

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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.

5 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 diagram confirming the purity of YDE-001 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 5 is a diagram confirming the purity of YDE-002 prepared according to an embodiment of the present invention through HPLC.

Fig. 6 is a diagram confirming the purity of YDE-003 prepared according to an embodiment of the present invention through HPLC.

Fig. 7 is a diagram confirming the purity of YDE-004 prepared according to an embodiment of the present invention through HPLC.

15 Fig. 8 is a diagram confirming the purity of YDE-005 prepared according to an embodiment of the present invention through HPLC.

Fig. 9 is a diagram confirming the purity of YDE-006 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 10 is a diagram confirming the purity of YDE-007 prepared according to an embodiment of the present invention through HPLC.

Fig. 11 is a diagram confirming the purity of YDE-008 prepared according to an embodiment of the present invention through HPLC.

Fig. 12 is a diagram confirming the purity of YDE-009 prepared according to an embodiment of the present invention through HPLC.

25 Fig. 13 is a diagram confirming the purity of YDE-010 prepared according to an embodiment of the present invention through HPLC.

Fig. 14 is a diagram confirming the purity of YDE-011 prepared according to an embodiment of the present invention through HPLC.

30 Fig. 15 is a diagram confirming the purity of YDE-012 prepared according to an embodiment of the present invention through HPLC.

Fig. 16 is a diagram confirming the purity of YDE-013 prepared according to

an embodiment of the present invention through HPLC.

Fig. 17 is a diagram confirming the purity of YDE-014 prepared according to an embodiment of the present invention through HPLC.

Fig. 18 is a diagram confirming the purity of YDE-015 prepared according to
5 an embodiment of the present invention through HPLC.

Fig. 19 is a diagram confirming the purity of YDE-016 prepared according to an embodiment of the present invention through HPLC.

Fig. 20 is a diagram confirming the purity of YDE-017 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 21 is a diagram confirming the purity of YDE-018 prepared according to an embodiment of the present invention through HPLC.

Fig. 22 is a diagram confirming the purity of YDE-019 prepared according to an embodiment of the present invention through HPLC.

Fig. 23 is a diagram confirming the purity of YDE-020 prepared according to
15 an embodiment of the present invention through HPLC.

Fig. 24 is a diagram confirming the purity of YDE-021 prepared according to an embodiment of the present invention through HPLC.

Fig. 25 is a diagram confirming the purity of YDE-022 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 26 is a diagram confirming the purity of YDE-023 prepared according to an embodiment of the present invention through HPLC.

Fig. 27 is a diagram confirming the purity of YDE-024 prepared according to an embodiment of the present invention through HPLC.

Fig. 28 is a diagram confirming the purity of YDE-025 prepared according to
25 an embodiment of the present invention through HPLC.

Fig. 29 is a diagram confirming the purity of YDE-026 prepared according to an embodiment of the present invention through HPLC.

Fig. 30 is a diagram confirming the purity of YDE-027 prepared according to an embodiment of the present invention through HPLC.

30 Fig. 31 is a diagram confirming the purity of YDE-028 prepared according to an embodiment of the present invention through HPLC.

Fig. 32 is a diagram confirming the purity of YDE-029 prepared according to an embodiment of the present invention through HPLC.

Fig. 33 is a diagram confirming the purity of YDE-030 prepared according to an embodiment of the present invention through HPLC.

5 Fig. 34 is a diagram confirming the purity of YDE-031 prepared according to an embodiment of the present invention through HPLC.

Fig. 35 is a diagram confirming the purity of YDE-032 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 36 is a diagram confirming the purity of YDE-033 prepared according to an embodiment of the present invention through HPLC.

Fig. 37 is a diagram confirming the purity of YDE-034 prepared according to an embodiment of the present invention through HPLC.

Fig. 38 is a diagram confirming the purity of YDE-035 prepared according to an embodiment of the present invention through HPLC.

15 Fig. 39 is a diagram confirming the purity of YDE-036 prepared according to an embodiment of the present invention through HPLC.

Fig. 40 is a diagram confirming the purity of YDE-037 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 41 is a diagram confirming the purity of YDE-038 prepared according to an embodiment of the present invention through HPLC.

Fig. 42 is a diagram confirming the purity of YDE-039 prepared according to an embodiment of the present invention through HPLC.

Fig. 43 is a diagram confirming the purity of YDE-040 prepared according to an embodiment of the present invention through HPLC.

25 Fig. 44 is a diagram confirming the purity of YDE-041 prepared according to an embodiment of the present invention through HPLC.

Fig. 45 is a diagram confirming the purity of YDE-042 prepared according to an embodiment of the present invention through HPLC.

30 Fig. 46 is a diagram confirming the purity of YDE-043 prepared according to an embodiment of the present invention through HPLC.

Fig. 47 is a diagram confirming the purity of YDE-044 prepared according to

an embodiment of the present invention through HPLC.

Fig. 48 is a diagram confirming the purity of YDE-045 prepared according to an embodiment of the present invention through HPLC.

Fig. 49 is a diagram confirming the purity of YDE-047 prepared according to
5 an embodiment of the present invention through HPLC.

Fig. 50 is a diagram confirming the purity of YDE-048 prepared according to an embodiment of the present invention through HPLC.

Fig. 51 is a diagram confirming the purity of YDE-049 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 52 is a diagram confirming the purity of YDE-050 prepared according to an embodiment of the present invention through HPLC.

Fig. 53 is a diagram confirming the purity of YDE-051 prepared according to an embodiment of the present invention through HPLC.

Fig. 54 is a diagram confirming the purity of YDE-052 prepared according to
15 an embodiment of the present invention through HPLC.

Fig. 55 is a diagram confirming the purity of YDE-053 prepared according to an embodiment of the present invention through HPLC.

Fig. 56 is a diagram confirming the purity of YDE-054 prepared according to an embodiment of the present invention through HPLC.

20 Fig. 57 is a diagram confirming the purity of YDE-055 prepared according to an embodiment of the present invention through HPLC.

Fig. 58 is a diagram confirming the purity of YDE-056 prepared according to an embodiment of the present invention through HPLC.

Fig. 59 is a diagram confirming the purity of YDE-057 prepared according to
25 an embodiment of the present invention through HPLC.

Fig. 60 is a diagram confirming the purity of YDE-058 prepared according to an embodiment of the present invention through HPLC.

Fig. 61 is a diagram confirming the purity of YDE-059 prepared according to an embodiment of the present invention through HPLC.

30 Fig. 62 is a diagram confirming the purity of YDE-060 prepared according to an embodiment of the present invention through HPLC.

Fig. 63 is a diagram confirming the purity of YDE-064 prepared according to an embodiment of the present invention through HPLC.

Fig. 64 is a diagram confirming the purity of YDE-066 prepared according to an embodiment of the present invention through HPLC.

5 Fig. 65 is a diagram confirming the purity of YDE-072 prepared according to an embodiment of the present invention through HPLC.

Fig. 66 is a diagram confirming the purity of YDE-073 prepared according to an embodiment of the present invention through HPLC.

10 Fig. 67 is a diagram confirming the purity of YDE-074 prepared according to an embodiment of the present invention through HPLC.

Fig. 68 is a diagram confirming the purity of YDE-075 prepared according to an embodiment of the present invention through HPLC.

Fig. 69 is a diagram confirming the molecular weight of YDE-001 prepared according to an embodiment of the present invention through Ion-Mass.

15 Fig. 70 is a diagram confirming the molecular weight of YDE-002 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 71 is a diagram confirming the molecular weight of YDE-003 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 72 is a diagram confirming the molecular weight of YDE-004 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 73 is a diagram confirming the molecular weight of YDE-005 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 74 is a diagram confirming the molecular weight of YDE-006 prepared according to an embodiment of the present invention through Ion-Mass.

25 Fig. 75 is a diagram confirming the molecular weight of YDE-007 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 76 is a diagram confirming the molecular weight of YDE-008 prepared according to an embodiment of the present invention through Ion-Mass.

30 Fig. 77 is a diagram confirming the molecular weight of YDE-009 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 78 is a diagram confirming the molecular weight of YDE-010 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 79 is a diagram confirming the molecular weight of YDE-011 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 80 is a diagram confirming the molecular weight of YDE-012 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 81 is a diagram confirming the molecular weight of YDE-013 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 82 is a diagram confirming the molecular weight of YDE-014 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 83 is a diagram confirming the molecular weight of YDE-015 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 84 is a diagram confirming the molecular weight of YDE-016 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 85 is a diagram confirming the molecular weight of YDE-017 prepared
15 according to an embodiment of the present invention through Ion-Mass.

Fig. 86 is a diagram confirming the molecular weight of YDE-018 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 87 is a diagram confirming the molecular weight of YDE-019 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 88 is a diagram confirming the molecular weight of YDE-020 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 89 is a diagram confirming the molecular weight of YDE-021 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 90 is a diagram confirming the molecular weight of YDE-022 prepared
25 according to an embodiment of the present invention through Ion-Mass.

Fig. 91 is a diagram confirming the molecular weight of YDE-023 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 92 is a diagram confirming the molecular weight of YDE-024 prepared according to an embodiment of the present invention through Ion-Mass.

30 Fig. 93 is a diagram confirming the molecular weight of YDE-025 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 94 is a diagram confirming the molecular weight of YDE-026 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 95 is a diagram confirming the molecular weight of YDE-027 prepared according to an embodiment of the present invention through Ion-Mass.

5 Fig. 96 is a diagram confirming the molecular weight of YDE-028 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 97 is a diagram confirming the molecular weight of YDE-029 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 98 is a diagram confirming the molecular weight of YDE-030 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 99 is a diagram confirming the molecular weight of YDE-031 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 100 is a diagram confirming the molecular weight of YDE-032 prepared according to an embodiment of the present invention through Ion-Mass.

15 Fig. 101 is a diagram confirming the molecular weight of YDE-033 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 102 is a diagram confirming the molecular weight of YDE-034 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 103 is a diagram confirming the molecular weight of YDE-035 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 104 is a diagram confirming the molecular weight of YDE-036 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 105 is a diagram confirming the molecular weight of YDE-037 prepared according to an embodiment of the present invention through Ion-Mass.

25 Fig. 106 is a diagram confirming the molecular weight of YDE-038 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 107 is a diagram confirming the molecular weight of YDE-039 prepared according to an embodiment of the present invention through Ion-Mass.

30 Fig. 108 is a diagram confirming the molecular weight of YDE-040 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 109 is a diagram confirming the molecular weight of YDE-041 prepared

according to an embodiment of the present invention through Ion-Mass.

Fig. 110 is a diagram confirming the molecular weight of YDE-042 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 111 is a diagram confirming the molecular weight of YDE-043 prepared
5 according to an embodiment of the present invention through Ion-Mass.

Fig. 112 is a diagram confirming the molecular weight of YDE-044 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 113 is a diagram confirming the molecular weight of YDE-045 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 114 is a diagram confirming the molecular weight of YDE-047 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 115 is a diagram confirming the molecular weight of YDE-048 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 116 is a diagram confirming the molecular weight of YDE-049 prepared
15 according to an embodiment of the present invention through Ion-Mass.

Fig. 117 is a diagram confirming the molecular weight of YDE-050 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 118 is a diagram confirming the molecular weight of YDE-051 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 119 is a diagram confirming the molecular weight of YDE-052 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 120 is a diagram confirming the molecular weight of YDE-053 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 121 is a diagram confirming the molecular weight of YDE-054 prepared
25 according to an embodiment of the present invention through Ion-Mass.

Fig. 122 is a diagram confirming the molecular weight of YDE-055 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 123 is a diagram confirming the molecular weight of YDE-056 prepared according to an embodiment of the present invention through Ion-Mass.

30 Fig. 124 is a diagram confirming the molecular weight of YDE-057 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 125 is a diagram confirming the molecular weight of YDE-058 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 126 is a diagram confirming the molecular weight of YDE-059 prepared according to an embodiment of the present invention through Ion-Mass.

5 Fig. 127 is a diagram confirming the molecular weight of YDE-060 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 128 is a diagram confirming the molecular weight of YDE-064 prepared according to an embodiment of the present invention through Ion-Mass.

10 Fig. 129 is a diagram confirming the molecular weight of YDE-066 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 130 is a diagram confirming the molecular weight of YDE-072 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 131 is a diagram confirming the molecular weight of YDE-073 prepared according to an embodiment of the present invention through Ion-Mass.

15 Fig. 132 is a diagram confirming the molecular weight of YDE-074 prepared according to an embodiment of the present invention through Ion-Mass.

Fig. 133 is a diagram confirming the molecular weight of YDE-075 prepared according to an embodiment of the present invention through Ion-Mass.

20 Fig. 134 is a photograph showing a procedure of extraorbital lacrimal gland excision.

Fig. 135 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. 136 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.

25 Fig. 137 is a photograph showing a procedure of administering an agent to the eyes of a rat model.

Fig. 138 is a photograph showing a procedure of measuring the amount of tear secretion of a rat model using cobalt chloride paper.

30 Fig. 139 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. 140 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. 141 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
5 YDE-043 using cobalt chloride paper.

Fig. 142 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. 143 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.

10 Fig. 144 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.

Fig. 145 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
15 administered with YDE-001 to YDE-028.

Fig. 146 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.

Fig. 147 is a diagram showing the permeability of a fluorescence dye to
20 confirm the recovery of corneal damage of a rat model whose eyes have been administered with YDE-029 to YDE-043.

FIG. 148 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.

FIG. 149 is a diagram showing the cell growth rate after 48 hours from the
25 treatment of hEGF on human corneal epithelial cells of plate No. 2.

FIG. 150 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. 151 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.

30 FIG. 152 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. 153 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.

FIG. 154 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.

5 FIG. 155 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.

FIG. 156 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.

10 FIG. 157 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.

FIG. 158 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. 159 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.

15 FIG. 160 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. 161 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.

20 FIG. 162 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.

FIG. 163 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. 164 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.

25 FIG. 165 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. 166 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.

30 FIG. 167 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.

FIG. 168 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. 169 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.

FIG. 170 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. 171 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. 172 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.

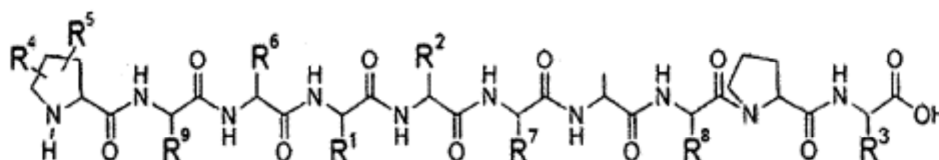
FIG. 173 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-075 on human corneal epithelial cells.

Detailed Description of the Invention

Hereinafter, the present invention will be described in detail.

An aspect of the present invention provides a compound represented by Formula 1.

[Formula 1]



In the above formula,

R¹ to R³ are each independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₁₀ alkoxy, substituted or unsubstituted C₁₋₁₀ haloalkyl, substituted or unsubstituted C₂₋₁₀ alkenyl, substituted or unsubstituted C₂₋₁₀ alkynyl, substituted or unsubstituted C₁₋₁₀ alkylene, substituted or unsubstituted C₁₋₁₀ alkenylene, substituted or unsubstituted C₁₋₁₀ alkynylene, substituted or unsubstituted C₅₋₁₂ aryl, substituted or unsubstituted C₇₋₁₂ arylalkyl, substituted or unsubstituted C₅₋₁₄ arylalkynyl, substituted or unsubstituted C₈₋₁₆ arylalkenyl, substituted or unsubstituted C₃₋₁₀ heteroalkyl, substituted or unsubstituted C₃₋₁₀ cycloalkyl, substituted or unsubstituted C₃₋₁₀ heterocycloalkyl,

or substituted or unsubstituted C₅₋₁₂ heteroaryl, the heteroalkyl, heterocycloalkyl, or heteroaryl containing at least one of N, O, and S,

the substitution refers to a substitution with one or more non-hydrogen substituents, each non-hydrogen substituent being selected from the group consisting of -X₁, -R_a, -O⁻, =O, -OR_a, -SR_a, -S⁻, -N(R_a)₂, -N⁺(R_a)₃, =NR_a, -C(X₁)₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N-OH, =N₂, -N₃, -NHC(=O)R_a, -C(=O)R_a, -C(=O)NR_aR_a, -S(=O)₂O⁻, -S(=O)₂OH, -S(=O)₂R_a, -OS(=O)₂OR_a, -S(=O)₂NR_a, -S(=O)R_a, -OP(=O)(OR_a)₂, -C(=O)R_a, alkylene-C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, alkylene-C(=O)OR_a, -C(=O)O⁻, alkylene-C(=O)O⁻, -C(=S)OR_a, -C(=O)SR_a, -C(=S)SR_a, -C(=O)NR_aR_a, alkylene-C(=O)NR_aR_a, -C(=S)NR_aR_a, and -C(-NR_a)NR_aR_a, each X₁ is independently selected from F, Cl, Br, or I, each R_a is independently selected from hydrogen, C₁₋₆ alkyl, C₅₋₁₂ aryl, C₇₋₁₂ arylalkyl, or heterocycle,

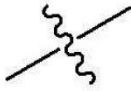
R⁴ and R⁵ are each independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, -X₂, -R_b, -O⁻, =O, -CH₂OR_b, or -OR_b, X₂ is F, Cl, Br, or I, and R_b is H, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₅₋₁₂ aryl, substituted or unsubstituted C₇₋₁₂ arylalkyl, or substituted or unsubstituted heterocycle,

R⁶ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl, the substituent being -C(=O)NH₂,

R⁷ is hydrogen or C₁₋₆ alkyl, and

R⁸ and R⁹ are each independently hydrogen or unsubstituted C₁₋₆ alkyl.

In the definition of R_b, the substitution refers to a substitution with the non-hydrogen substituent.

According to the convention used in the art,  in the formulae herein is used to denote a bond, where a moiety or a substituent is attached to the nucleus or the backbone structure.

“Alkyl” is a hydrocarbon having primary, secondary, tertiary, and/or cyclic carbon atoms. 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 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (i.e., C₁-C₁₂ 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 substituted 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), 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 cyclic carbon atoms, 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.,

C_2 - C_{20} alkenyl), 2 to 12 carbon atoms (i.e., C_2 - C_{12} alkenyl), or 2 to 6 carbon atoms (i.e., C_2 - C_6 alkenyl). Examples of a suitable alkenyl group include vinyl ($-\text{CH}=\text{CH}_2$), allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), cyclopentenyl ($-\text{C}_5\text{H}_7$), and 5-hexenyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), but it is not limited thereto.

5 “Alkynyl” is a hydrocarbon having primary, secondary, tertiary, and/or cyclic carbon atoms, and having at least two unsaturated regions, i.e., one carbon-carbon sp triple bond. For example, an alkynyl group may have 2 to 20 carbon atoms (i.e., C_2 - C_{20} alkynyl), 2 to 12 carbon atoms (i.e., C_2 - C_{12} alkynyl), or 2 to 6 carbon atoms (i.e., C_2 - C_6 alkynyl). Examples of a suitable alkenyl group include
10 acetylenic ($-\text{C}\equiv\text{CH}$) and propargyl ($-\text{CH}_2\text{C}\equiv\text{CH}$), but it is not limited thereto.

 “Alkylene” refers to a saturated hydrocarbon group that may be branched, straight, or cyclic 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
15 atoms, or 1 to 6 carbon atoms. Examples of a typical alkylene radical include methylene ($-\text{CH}_2-$), 1,1-ethylene ($-\text{CH}(\text{CH}_3)-$), 1,2-ethylene ($-\text{CH}_2\text{CH}_2-$), 1,1-propylene ($-\text{CH}(\text{CH}_2\text{CH}_3)-$), 1,2-propylene ($-\text{CH}_2\text{CH}(\text{CH}_3)-$), 1,3-propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), and 1,4-butylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), but it is not limited thereto.

 “Alkenylene” refers to an unsaturated hydrocarbon group that may be
20 branched, straight, and/or cyclic 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-ethylene ($-\text{CH}=\text{CH}-$), but it is not limited thereto.

25 “Alkynylene” refers to an unsaturated hydrocarbon group that is branched, straight, and/or cyclic 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
30 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 derived by a removal of one hydrogen atom from the six carbon atoms of a parent aromatic ring system. 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
5 from benzene (e.g., phenyl), substituted benzene, substituted or unsubstituted naphthalene, substituted or unsubstituted anthracene, substituted or unsubstituted biphenyl, 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
10 substituted by an aryl group. Examples of a typical arylalkyl group include benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethane-1-yl, naphthobenzyl, 2-naphthophenylethane-1-yl, and the like (each of which is 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
15 atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

“Arylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom although an sp^2 carbon atom is also available, is substituted with an aryl radical. The aryl moiety of the arylalkenyl may be, for example, any aryl group described
20 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.

“Cycloalkyl” refers to a saturated monocycle or polycycle that comprises
25 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 6 ring atoms, more typically 5 or 6 ring atoms. A bicyclic cycloalkyl may have 7 to 12 ring atoms arranged in a bicyclo[4,5], [5,5], [5,6], or [6,6] system or 9 to 10 ring atoms
30 arranged in a bicyclo[5,6] or [6,6] system or in a spiro-bonded ring. Non-limiting examples of a monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl,

and cyclohexyl (each of which may be substituted or unsubstituted).

“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 substituted 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.

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., substituted cycloalkyl),” means that at least one hydrogen atom of the alkyl, alkylene, aryl, arylalkyl, heterocyclyl, or carbocyclyl (e.g., cycloalkyl) is each independently substituted by a non-hydrogen substituent. Examples of the typical substituent include -X, -R, -O⁻, =O, -OR, -SR, -S⁻, -NR₂, -N⁺R₃, =NR, -C(X)₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N-OH, =N₂, -N₃, -NHC(=O)R, -C(=O)R, -C(=O)NRR, -S(=O)₂O⁻, -S(=O)₂OH, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂NR, -S(=O)R, -OP(=O)(OR)₂, -C(=O)R, alkylene-C(=O)R, -C(S)R, -C(=O)OR, alkylene-C(=O)OR, -C(=O)O⁻, alkylene-C(=O)O⁻, -C(=S)OR, -C(=O)SR, -C(=S)SR, -C(=O)NRR, alkylene-C(=O)NRR, -C(=S)NRR, and -C(-NR)NRR, wherein X is each independently halogen such as F, Cl, Br, or I, and R is independently H, alkyl, aryl, arylalkyl, or heterocycle, 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 substituted by the substituent as described herein). If the moiety of “alkyl,” “aryl,” “heterocyclyl,” or 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.

5 Those skilled in the art will recognize that the substituents and other moieties of the compound of Formula 1 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 1 having such stability is to be understood to fall within the scope of
10 the present invention.

 “Heteroalkyl” refers to an alkyl group in which at least one carbon atom is substituted 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 substituted by a heteroatom (e.g., O, N, or S), the resulting heteroalkyl group may be an alkoxy group (e.g., -OCH₃),
15 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 substituted 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
20 ether (e.g., -CH₂-S-CH₃), respectively. If the terminal carbon atom of the alkyl group is substituted 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
25 to 10 carbon atoms, or 1 to 6 carbon atoms. 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
30 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 substituted 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.

Examples of heterocycles include pyridyl, dihydropyridyl, tetrahydropyridyl(piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur-oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidinyl, pyrrolidinyl, 2-pyrrolidinyl, pyrrolinyl, tetrahydrofuranlyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocynyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranlyl, isobenzofuranlyl, chromenyl, xanthenyl, phenoxatyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phtheridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, piperazinyl, indolyl, isoindolyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolyl, isothioyl, and bis-tetrahydrofuranlyl (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 substituted by a heterocycl radical (i.e., a heterocycl-alkylene moiety). Examples of a typical heterocyclalkyl group include heterocycl- CH_2 -, 2-(heterocycl)ethan-1-yl, and the like, but it is not limited thereto. The “heterocycl” moiety thereof used herein includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocycl group described above. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocycl group may be attached to the alkyl moiety of the heterocyclalkyl through a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclalkyl group may have 2 to 20 carbon atoms. For example, the alkyl moiety of the heterocyclalkyl group may have 1 to

6 carbon atoms, and the heterocyclyl moiety thereof may have 1 to 14 carbon atoms. Examples of the heterocyclalkyl include a 5-membered heterocycle containing sulfur, oxygen, and/or nitrogen such as thiazolylmethyl, 2-thiazolylethan-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, pyrimidylmethyl, pyrazinylmethyl, and the like (each of which may be substituted or unsubstituted), but it is not limited thereto.

“Heterocyclalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom (although an sp^2 carbon atom may also be used), is substituted by a heterocycl radical (i.e., a heterocycl-alkenylene moiety). The heterocycl moiety of the heterocyclalkenyl group includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocycl group described herein. The alkenyl moiety of the heterocyclalkenyl group includes any alkenyl 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 alkenyl moiety of the heterocyclalkenyl via a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclalkenyl group may have 3 to 20 carbon atoms. For example, the alkenyl moiety of the heterocyclalkenyl group may have 2 to 6 carbon atoms, and the heterocycl moiety thereof may have 1 to 14 carbon atoms.

“Heterocyclalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom (although an sp carbon atom may also be used), is substituted by a heterocycl radical (i.e., a heterocycl-alkynylene moiety). The heterocycl moiety of the heterocyclalkynyl group includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocycl 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
 5 moiety thereof may have 1 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
 10 definition of “heterocycl” herein, inclusive of pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, furinyl, 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 “carbocycl” 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 6 ring atoms, more typically 5 or 6 ring atoms. A bicyclic carbocycle has 7 to 12 ring atoms arranged in a bicyclo[4,5], [5,5], [5,6], or [6,6]
 20 system or 9 to 10 ring atoms arranged in a bicyclo[5,6] or [6,6] system. Examples of a monocyclic or bicyclic carbocycle include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, and naphthyl (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
 30 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 substituted 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 substituted by a heteroaryl group as defined herein. Non-limiting examples of heteroarylalkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-furinyl, -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)-furinyl, -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 R comprises alkyl, aryl (which is substituted or unsubstituted), heteroaryl (which is substituted or unsubstituted), or a combination thereof. 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 1 that has one, two,

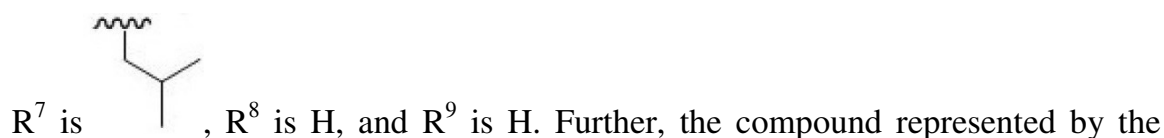
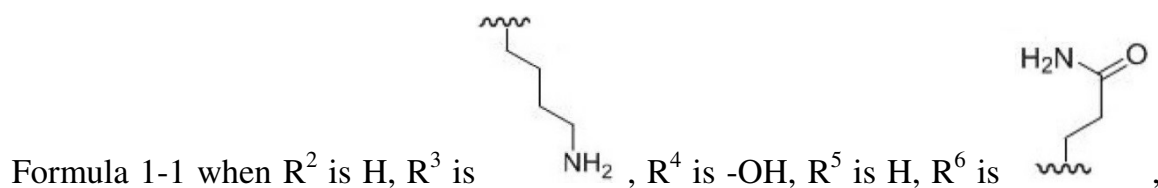
or more substituents.

The term “ester thereof” refers to any ester of a compound wherein any -COOH functional group of the molecule is substituted to a -COOR functional group or any -OH functional group of the molecule is substituted to a -C(=O)OR.

- 5 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, heterocyclylalkyl, 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.

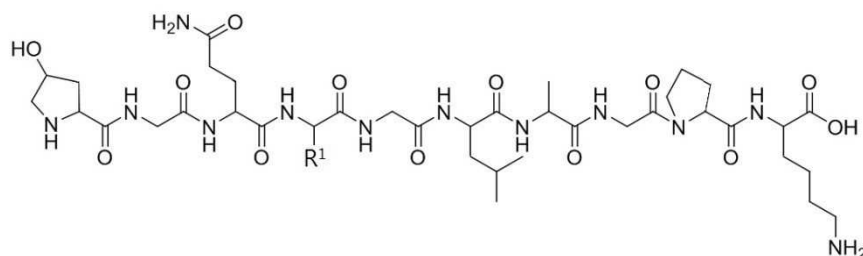
- 10 In the present invention, the compound represented by the above Formula 1 may be an optical isomer type L or D.

The compound represented by the above Formula 1 may be represented by

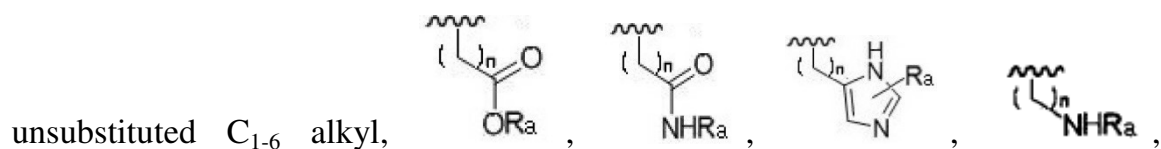


- 15 following Formula 1-1 may be an optical isomer type L or D.

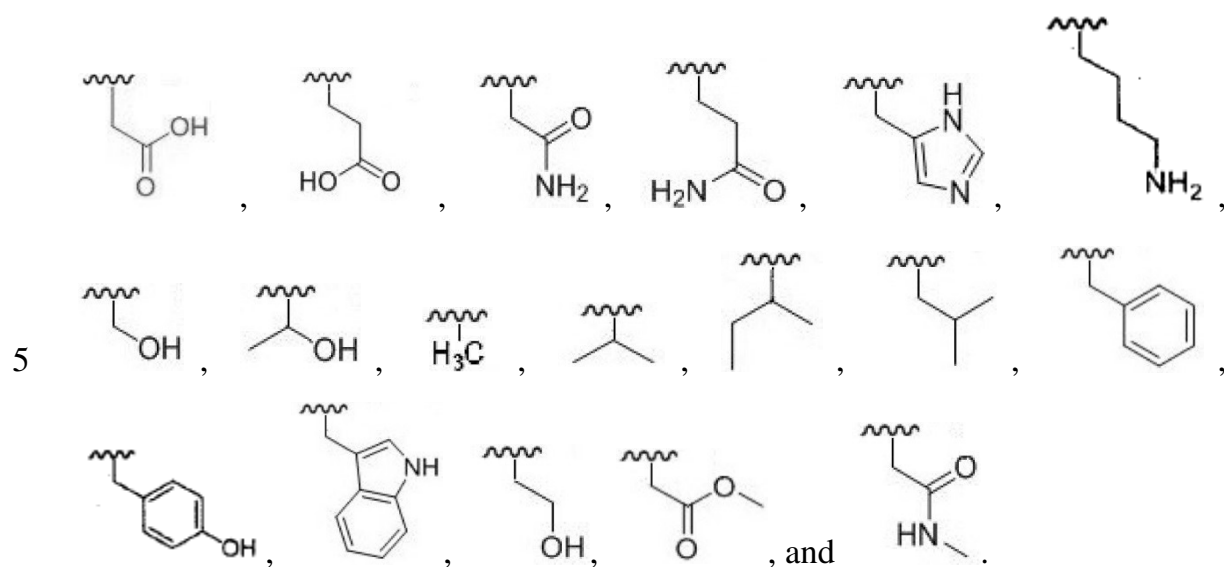
[Formula 1-1]



R^1 may be one selected from the group consisting of substituted or

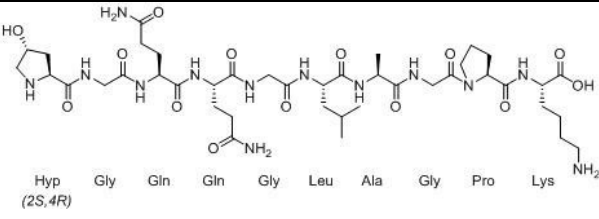
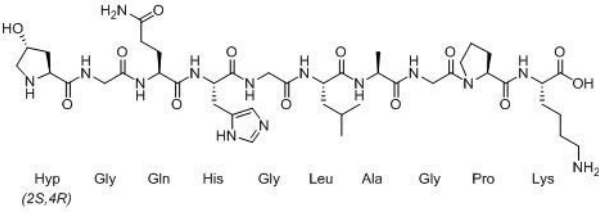
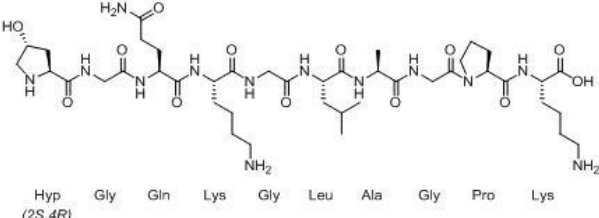
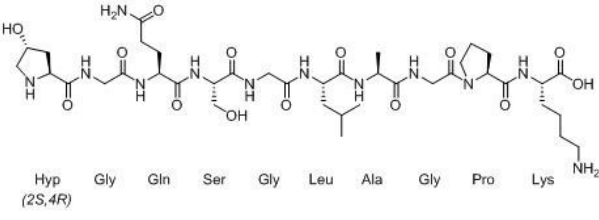
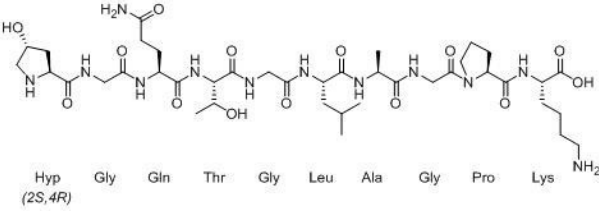
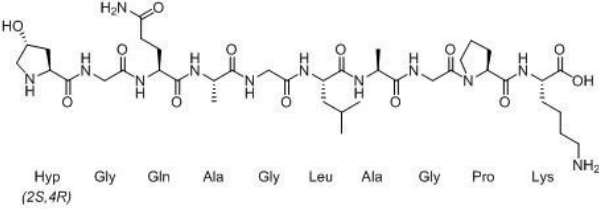
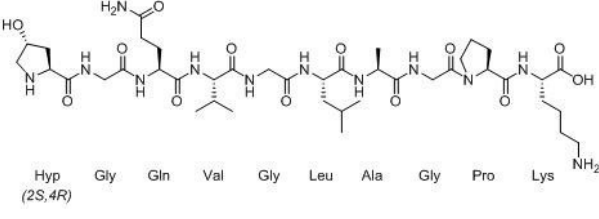


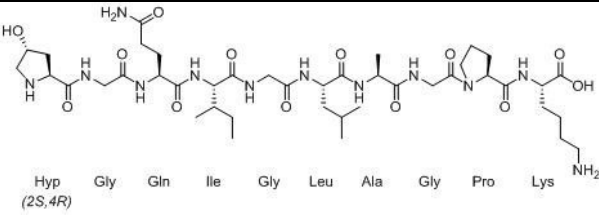
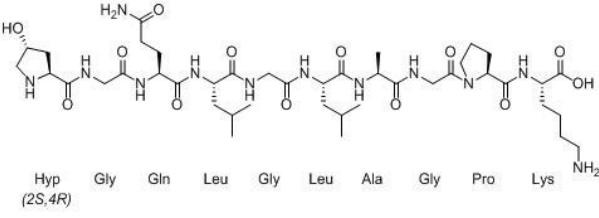
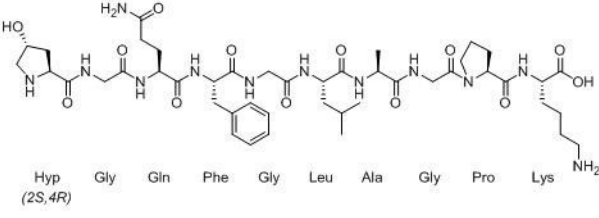
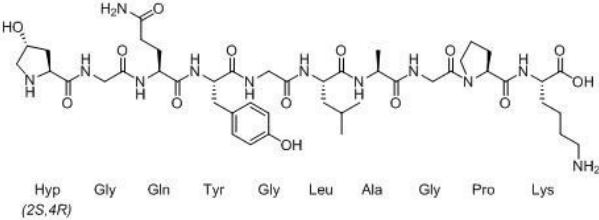
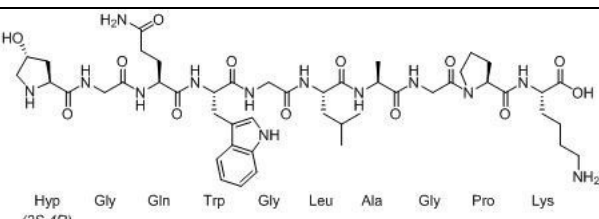
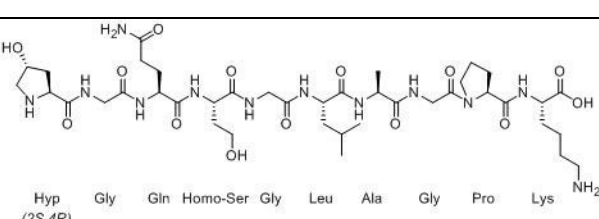
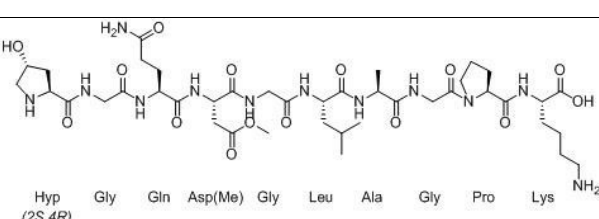
Specifically, R^1 may be one selected from the group consisting of

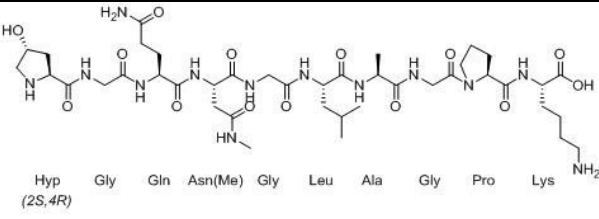
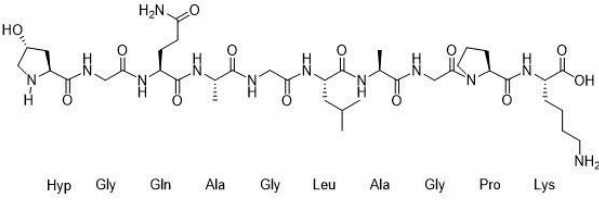
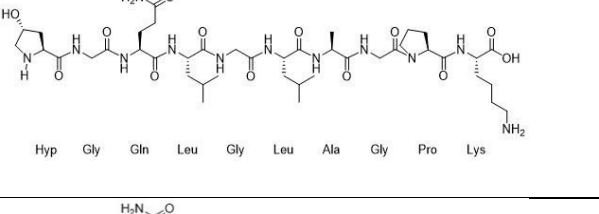
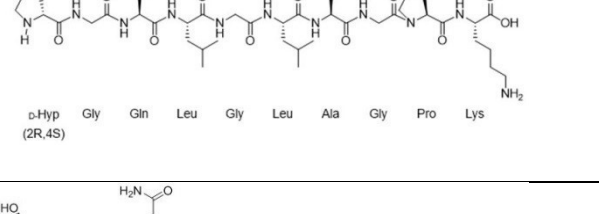
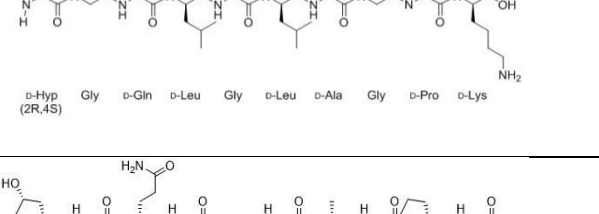
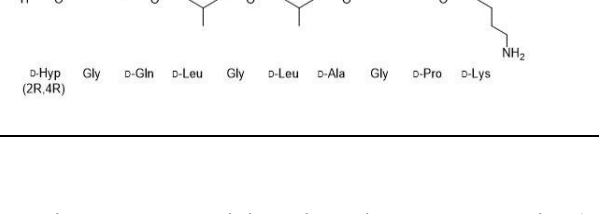


[Table 1]

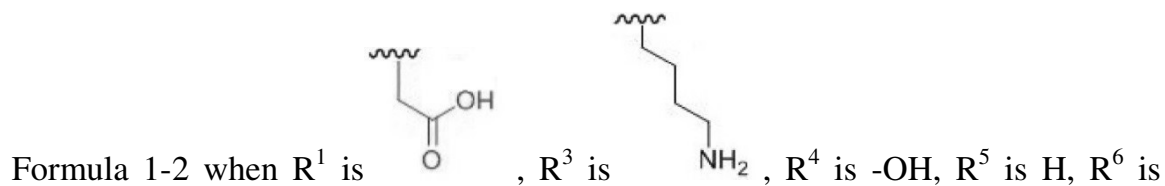
YDE-001	Hyp (2S,4R) Gly Gln Glu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 1
YDE-002	Hyp (2S,4R) Gly Gln Asn Gly Leu Ala Gly Pro Lys	SEQ ID NO: 2

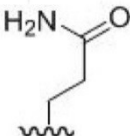
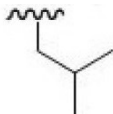
YDE-003	 Hyp (2S,4R) Gly Gln Gln Gly Leu Ala Gly Pro Lys	SEQ ID NO: 3
YDE-004	 Hyp (2S,4R) Gly Gln His Gly Leu Ala Gly Pro Lys	SEQ ID NO: 4
YDE-005	 Hyp (2S,4R) Gly Gln Lys Gly Leu Ala Gly Pro Lys	SEQ ID NO: 5
YDE-006	 Hyp (2S,4R) Gly Gln Ser Gly Leu Ala Gly Pro Lys	SEQ ID NO: 6
YDE-007	 Hyp (2S,4R) Gly Gln Thr Gly Leu Ala Gly Pro Lys	SEQ ID NO: 7
YDE-008	 Hyp (2S,4R) Gly Gln Ala Gly Leu Ala Gly Pro Lys	SEQ ID NO: 8
YDE-009	 Hyp (2S,4R) Gly Gln Val Gly Leu Ala Gly Pro Lys	SEQ ID NO: 9

YDE-010	 Hyp (2S,4R) Gly Gln Ile Gly Leu Ala Gly Pro Lys	SEQ ID NO: 10
YDE-011	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 11
YDE-012	 Hyp (2S,4R) Gly Gln Phe Gly Leu Ala Gly Pro Lys	SEQ ID NO: 12
YDE-013	 Hyp (2S,4R) Gly Gln Tyr Gly Leu Ala Gly Pro Lys	SEQ ID NO: 13
YDE-014	 Hyp (2S,4R) Gly Gln Trp Gly Leu Ala Gly Pro Lys	SEQ ID NO: 14
YDE-026	 Hyp (2S,4R) Gly Gln Homo-Ser Gly Leu Ala Gly Pro Lys	SEQ ID NO: 15
YDE-027	 Hyp (2S,4R) Gly Gln Asp(Me) Gly Leu Ala Gly Pro Lys	SEQ ID NO: 16

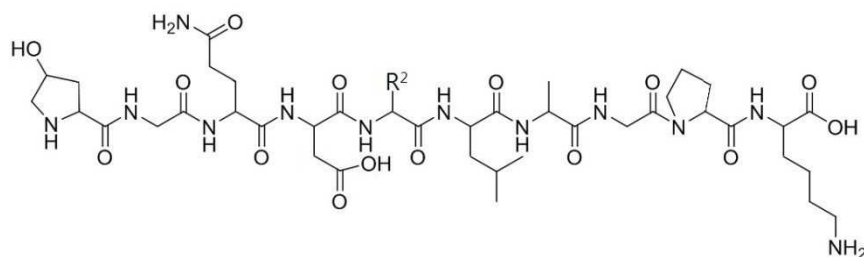
YDE-028	 Hyp (2S,4R) Gly Gln Asn(Me) Gly Leu Ala Gly Pro Lys	SEQ ID NO: 17
YDE-050	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys	SEQ ID NO: 8
YDE-053	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 11
YDE-057	 D-Hyp (2R,4S) Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 18
YDE-058	 D-Hyp (2R,4S) Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys	SEQ ID NO: 19
YDE-060	 D-Hyp (2R,4R) Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys	SEQ ID NO: 20

The compound represented by the above Formula 1 may be represented by

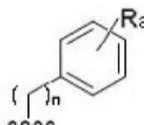
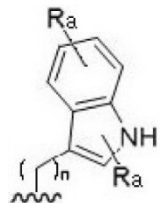
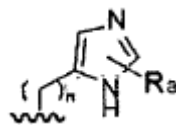



, R^7 is 
, R^8 is H, and R^9 is H. Further, the compound represented by the following Formula 1-2 may be an optical isomer type L or D.

[Formula 1-2]

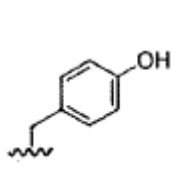
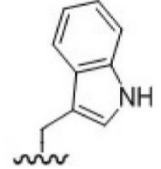
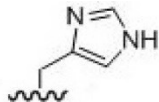
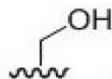
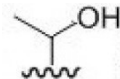


5 In addition, R^2 may be one selected from the group consisting of hydrogen,

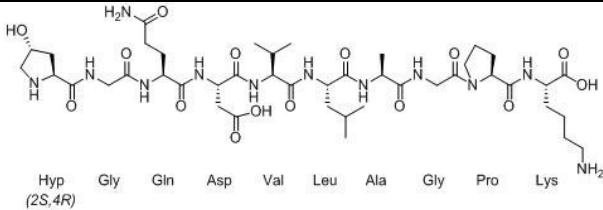
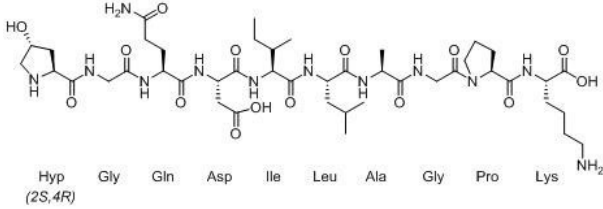
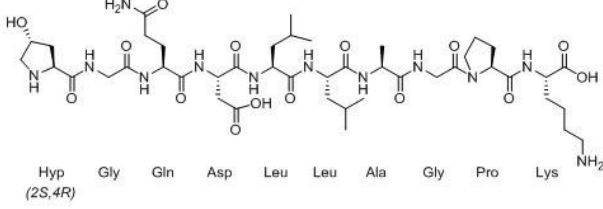
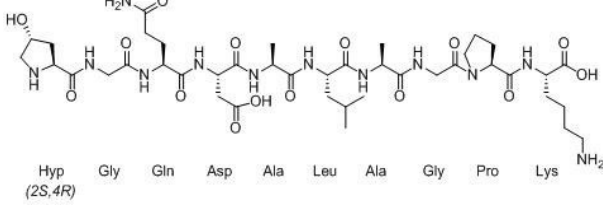
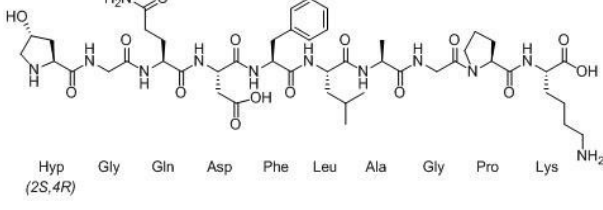
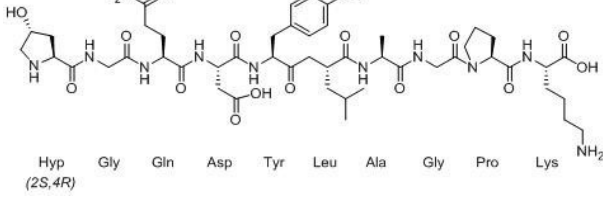
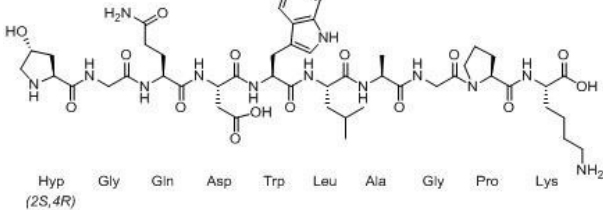
substituted or unsubstituted C_{1-6} alkyl, , , ,

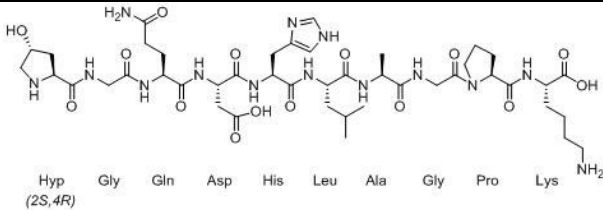
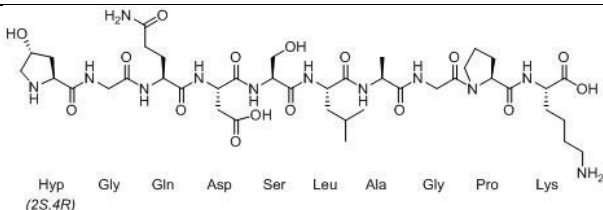
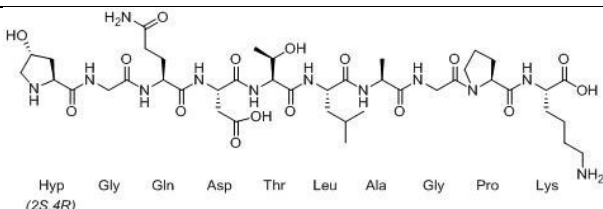
and . Here, n may be an integer of 1 to 10, but it is not limited thereto. R_a may be hydrogen or C_{1-6} alkyl.

Specifically, R^2 may be one selected from the group consisting of ,

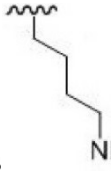
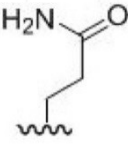
10 , , , , , , , , , and . More specifically, the compound may be a compound described in Table 2 below.

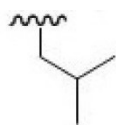
[Table 2]

YDE-015	 Hyp (2S,4R) Gly Gln Asp Val Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 21
YDE-016	 Hyp (2S,4R) Gly Gln Asp Ile Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 22
YDE-017	 Hyp (2S,4R) Gly Gln Asp Leu Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 23
YDE-018	 Hyp (2S,4R) Gly Gln Asp Ala Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 24
YDE-019	 Hyp (2S,4R) Gly Gln Asp Phe Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 25
YDE-020	 Hyp (2S,4R) Gly Gln Asp Tyr Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 26
YDE-021	 Hyp (2S,4R) Gly Gln Asp Trp Leu Ala Gly Pro Lys NH₂	SEQ ID NO: 27

YDE-022	 Hyp (2S,4R) Gly Gln Asp His Leu Ala Gly Pro Lys	SEQ ID NO: 28
YDE-023	 Hyp (2S,4R) Gly Gln Asp Ser Leu Ala Gly Pro Lys	SEQ ID NO: 29
YDE-024	 Hyp (2S,4R) Gly Gln Asp Thr Leu Ala Gly Pro Lys	SEQ ID NO: 30

The compound represented by the above Formula 1 may be represented by

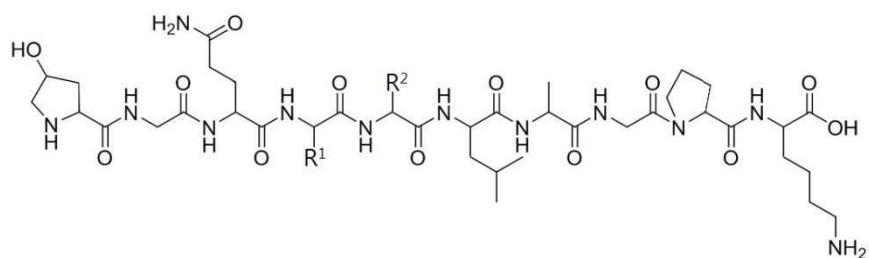
Formula 1-3 when R^3 is , R^4 is -OH, R^5 is H, R^6 is , R^7 is



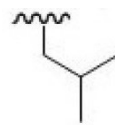
, R^8 is H, and R^9 is H. Further, the compound represented by the

5 following Formula 1-3 may be an optical isomer type L or D.

[Formula 1-3]



R^1 may be C_{1-6} alkyl. Specifically, R^1 may be



R^2 may be C_{1-6} alkyl. Specifically, R^2 may be



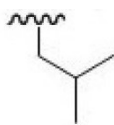
More specifically, the compound may be a compound described in Table 3 below.

5 [Table 3]

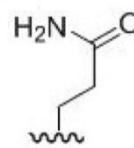
YDE-051	Hyp Gly Gln Leu Ala Leu Ala Gly Pro Lys	SEQ ID NO: 32
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The compound represented by the above Formula 1 may be represented by

Formula 1-4 when R^1 is

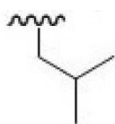


, R^2 is H, R^4 is -OH, R^5 is H, R^6 is



, R^7

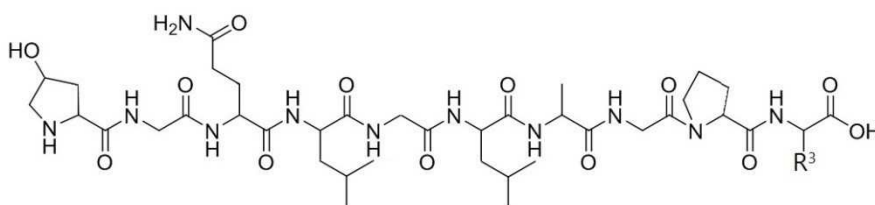
is



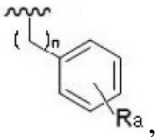
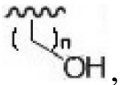
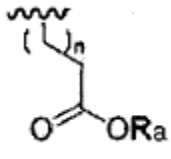
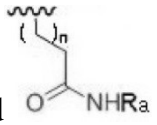
, R^8 is H, and R^9 is H. Further, the compound represented by the

10 following Formula 1-4 may be an optical isomer type L or D.

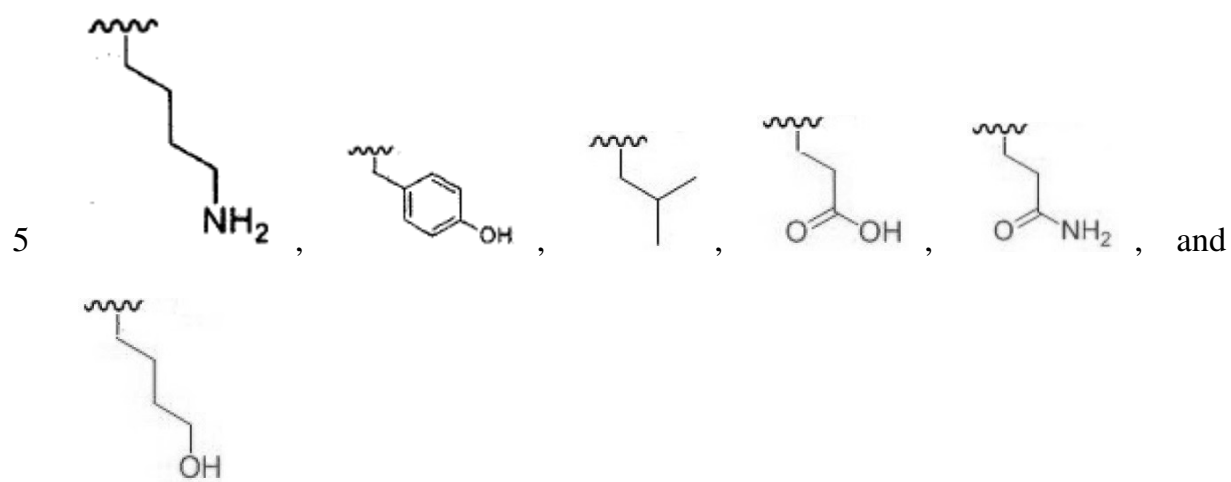
[Formula 1-4]



R^3 may be one selected from the group consisting of substituted or

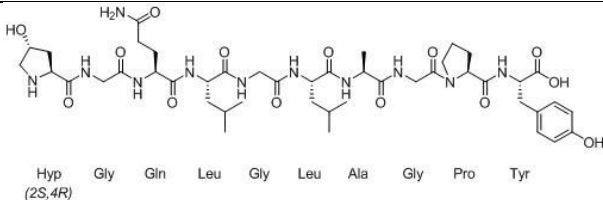
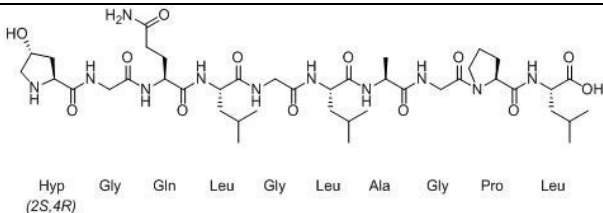
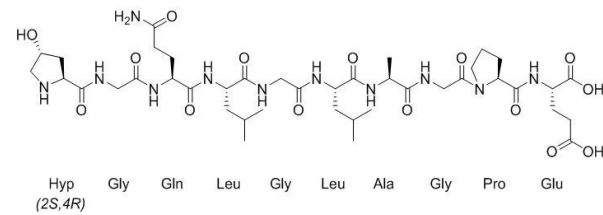
unsubstituted C₁₋₆ alkyl, , , , and . Here, n may be an integer of 1 to 10, but it is not limited thereto. R_a may be hydrogen or C₁₋₆ alkyl.

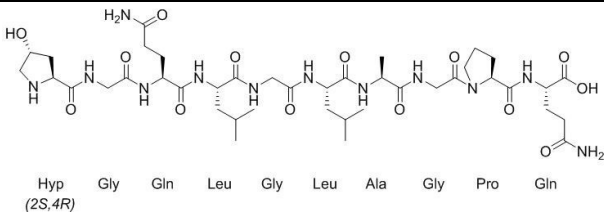
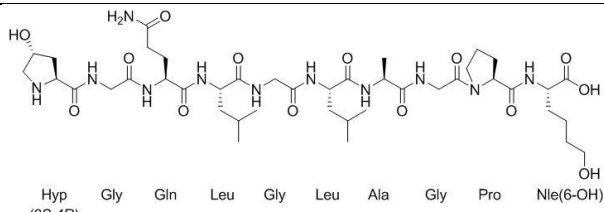
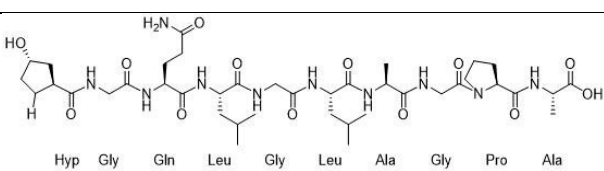
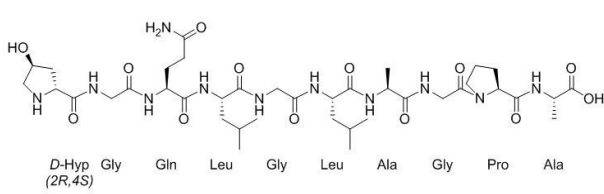
Specifically, R³ may be one selected from the group consisting of,



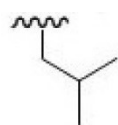
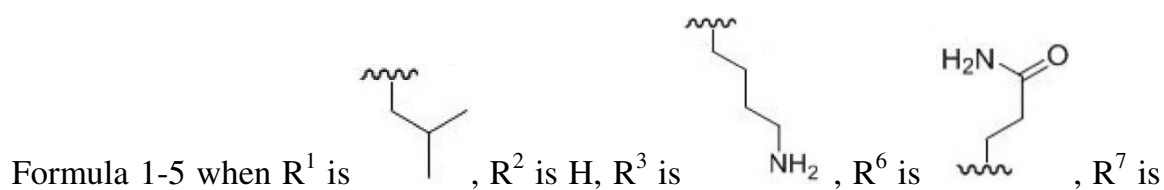
More specifically, the compound may be a compound described in Table 4 below.

[Table 4]

YDE-029	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Tyr	SEQ ID NO: 33
YDE-030	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Leu	SEQ ID NO: 34
YDE-031	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Glu	SEQ ID NO: 35

YDE-032	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Gln	SEQ ID NO: 36
YDE-033	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro Nle(6-OH)	SEQ ID NO: 37
YDE-056	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala	SEQ ID NO: 38
YDE-073	 D-Hyp (2R,4S) Gly Gln Leu Gly Leu Ala Gly Pro Ala	SEQ ID NO: 39

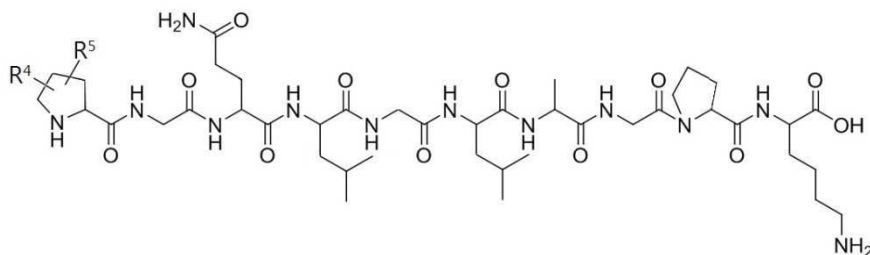
The compound represented by the above Formula 1 may be represented by



, R⁸ is H, and R⁹ is H. Further, the compound represented by the

5 following Formula 1-5 may be an optical isomer type L or D.

[Formula 1-5]



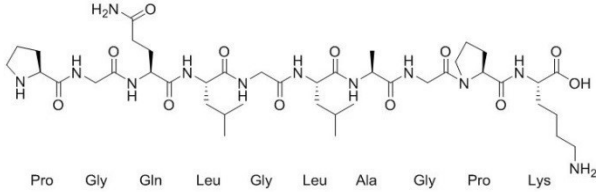
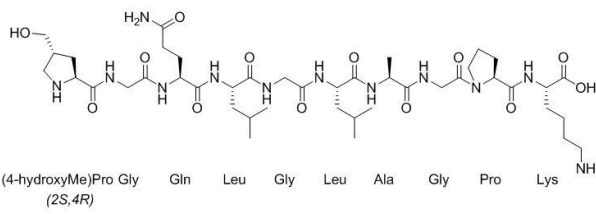
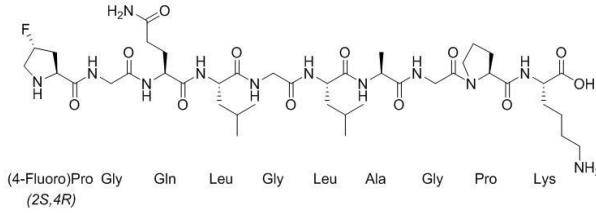
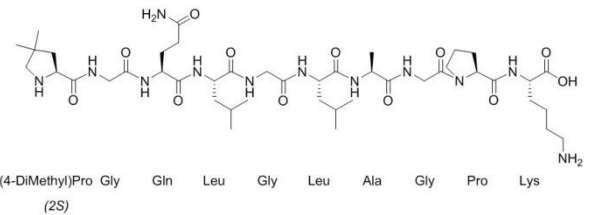
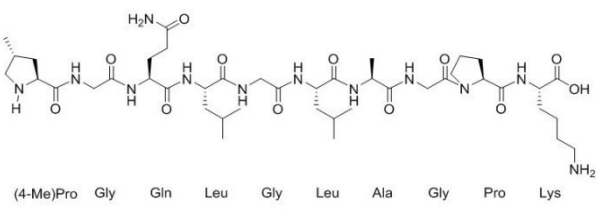
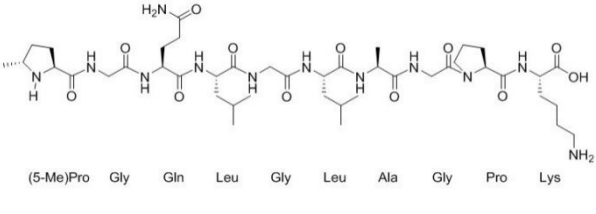
R^4 and R^5 may be each independently one selected from the group consisting of substituted or unsubstituted C_{1-6} alkyl, $-OR_b$, $=O$, $-CH_2OR_b$, and $-X_2$. Here, X_2 may be independently halogen such as F, Cl, Br, or I. R_b may be hydrogen or C_{1-6} alkyl.

Specifically, R^4 may be one selected from the group consisting of H, $-OH$, $=O$, $-CH_2OR_b$, and F; in such event, R^5 may be H. Further, R^4 may be CH_3 ; in such event, R^5 may be CH_3 .

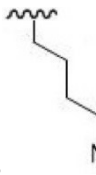
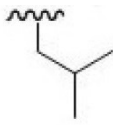
More specifically, the compound may be a compound described in Table 5 below.

[Table 5]

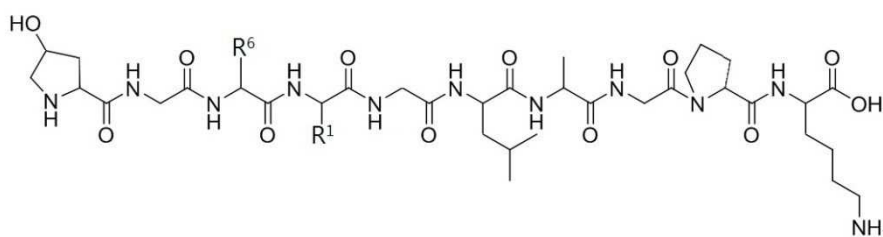
YDE-034	Hyp (2S,4S) Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 63
YDE-035	(4-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 40
YDE-036	(5-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 41

YDE-037	 Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 42
YDE-038	 (4-hydroxyMe)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 43
YDE-039	 (4-Fluoro)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 44
YDE-040	 (4-Dimethyl)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (2<i>S</i>)	SEQ ID NO: 45
YDE-044	 (4-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 46
YDE-045	 (5-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 47

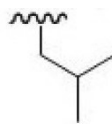
The compound represented by the above Formula 1 may be represented by

Formula 1-6 when R² is H, R³ is , R⁴ is -OH, R⁵ is H, R⁷ is , R⁸ is H, and R⁹ is H. Further, the compound represented by the following Formula 1-6 may be an optical isomer type L or D.

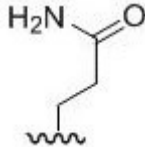
[Formula 1-6]



5

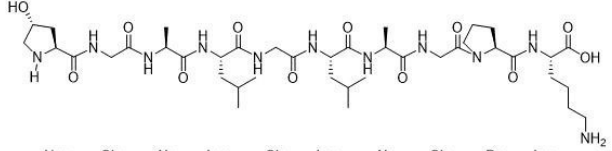
R¹ may be C₁₋₆ alkyl. Specifically, R¹ may be .

R⁶ may be substituted or unsubstituted C₁₋₆ alkyl, wherein the substituent

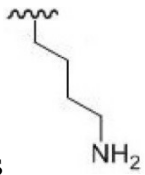
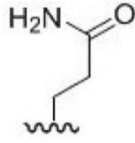
may be -C(=O)NH₂. Specifically, R⁶ may be  or .

More specifically, the compound may be a compound described in Table 6
10 below.

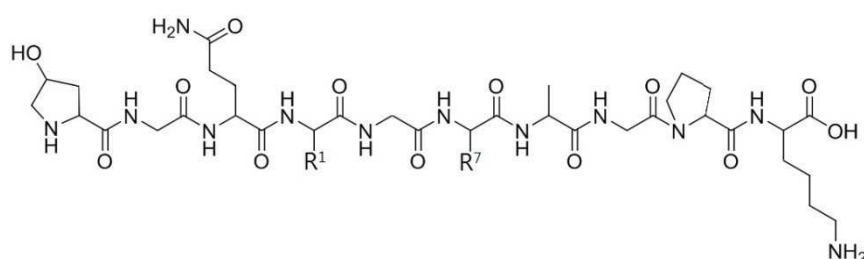
[Table 6]

YDE-049	 Hyp Gly Ala Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 48
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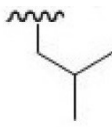
The compound represented by the above Formula 1 may be represented by

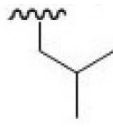
Formula 1-7 when R^2 is H, R^3 is , R^4 is -OH, R^5 is H, R^6 is , R^8 is H, and R^9 is H. Further, the compound represented by the following Formula 1-7 may be an optical isomer type L or D.

[Formula 1-7]



5

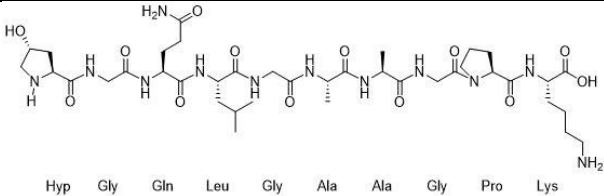
R^1 may be C_{1-6} alkyl. Specifically, R^1 may be .

R^7 may be unsubstituted C_{1-6} alkyl. Specifically, R^7 may be  or

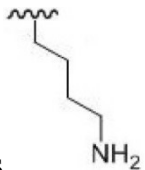
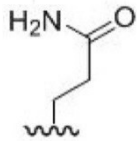


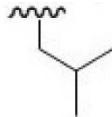
More specifically, the compound may be a compound described in Table 7 below.

[Table 7]

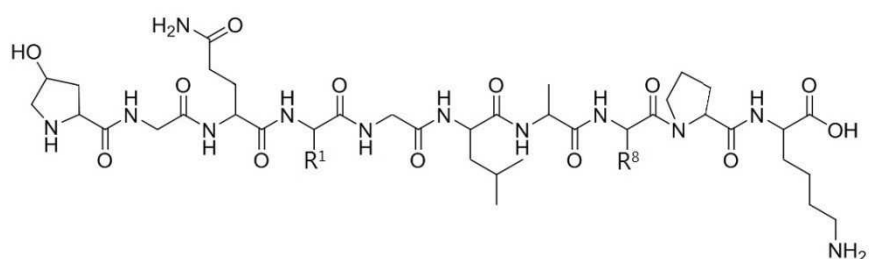
YDE-052	 Hyp Gly Gln Leu Gly Ala Ala Gly Pro Lys	SEQ ID NO: 49
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The compound represented by the above Formula 1 may be represented by

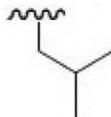
Formula 1-8 when R^2 is H, R^3 is , R^4 is -OH, R^5 is H, R^6 is ,

R^7 is , and R^9 is H. Further, the compound represented by the following Formula 1-8 may be an optical isomer type L or D.

[Formula 1-8]



5

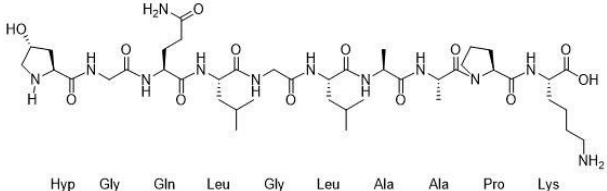
R^1 may be C_{1-6} alkyl. Specifically, R^1 may be .

R^8 may be hydrogen or C_{1-6} alkyl. Specifically, R^8 may be  or .

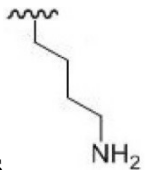
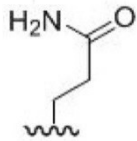
More specifically, the compound may be a compound described in Table 8 below.

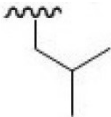
10

[Table 8]

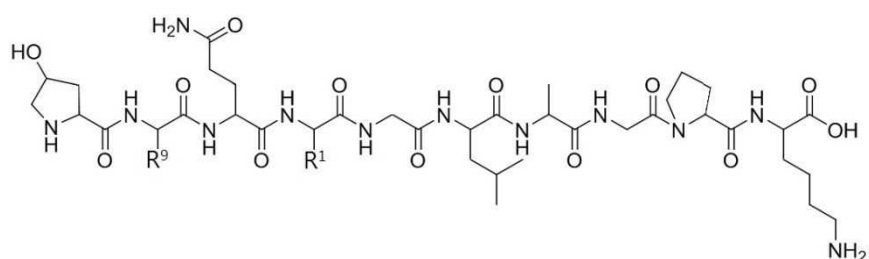
YDE-054	 Hyp Gly Gln Leu Gly Leu Ala Ala Pro Lys	SEQ ID NO: 50
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The compound represented by the above Formula 1 may be represented by

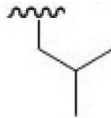
Formula 1-9 when R² is H, R³ is , R⁴ is -OH, R⁵ is H, R⁶ is ,

R⁷ is , and R⁸ is H. Further, the compound represented by the following Formula 1-9 may be an optical isomer type L or D.

[Formula 1-9]



5

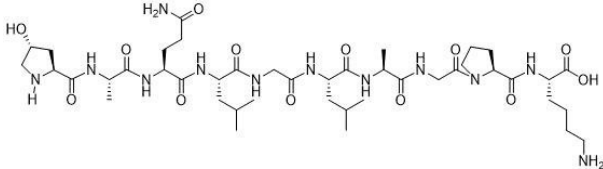
R¹ may be C₁₋₆ alkyl. Specifically, R¹ may be .

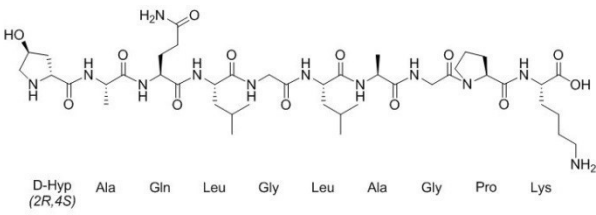
R⁹ may be hydrogen or C₁₋₆ alkyl. Specifically, R⁹ may be  or .

More specifically, the compound may be a compound described in Table 9 below.

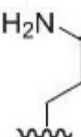
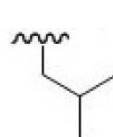
10

[Table 9]

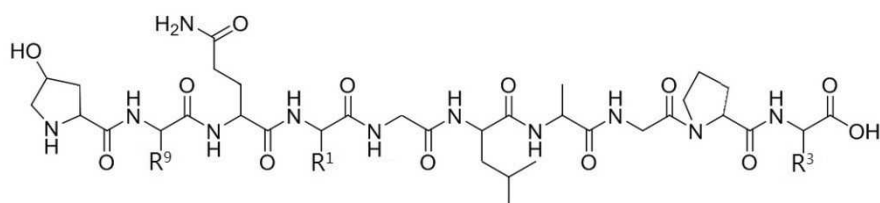
YDE-048	 Hyp Ala Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 51
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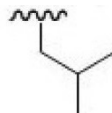
YDE-072	 D-Hyp (2R,4S) Ala Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 53
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The compound represented by the above Formula 1 may be represented by

Formula 1-10 when R^2 is H, R^4 is -OH, R^5 is H, R^6 is , R^7 is , and R^8 is H. Further, the compound represented by the following Formula 1-10
5 may be an optical isomer type L or D.

[Formula 1-10]



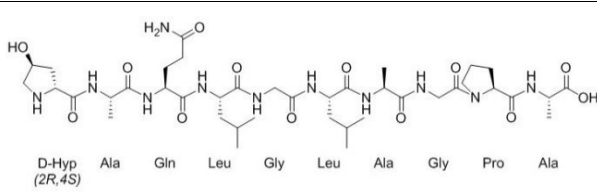
R^1 may be C_{1-6} alkyl. Specifically, R^1 may be .

In such event, R^3 may be C_{1-6} alkyl. Specifically, R^3 may be .

10 In such event, R^9 may be C_{1-6} alkyl. Specifically, R^9 may be .

More specifically, the compound may be a compound described in Table 10 below.

[Table 10]

YDE-074	 D-Hyp (2R,4S) Ala Gln Leu Gly Leu Ala Gly Pro Ala	SEQ ID NO: 52
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The compounds represented by the above Formulae 1-1 to 1-10 may be any one selected from the group consisting of HyP-Gly-Gln-Glu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Gln-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-His-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Lys-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Thr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ala-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Val-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ile-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Phe-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Tyr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Trp-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser(Homo)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp(Me)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn(Me)-Gly-Leu-Ala-Gly-Pro-Lys, $_D$ -HyP(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, $_D$ -Hyp(2R,4S)-Gly- $_D$ -Gln- $_D$ -Leu-Gly- $_D$ -Leu- $_D$ -Ala-Gly- $_D$ -Pro- $_D$ -Lys, $_D$ -Hyp(2R, 4R)-Gly- $_D$ -Gln- $_D$ -Leu-Gly- $_D$ -Leu- $_D$ -Ala-Gly- $_D$ -Pro- $_D$ -Lys, HyP-Gly-Gln-Asp-Val-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ile-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Leu-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ala-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Phe-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Tyr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Trp-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-His-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ser-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Thr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Ala-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Tyr, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Leu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Glu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Gln, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Nle(6-OH), HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala, $_D$ -HyP(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala, Hyp(2S, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-hydroxyMe)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Fluoro)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-

Pro-Lys, (4-Dimethyl)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys,

Hyp-Gly-Ala-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Ala-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Ala-Pro-Lys, Hyp-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, D -Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys and D -Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala.

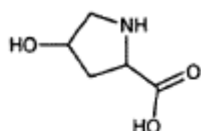
Another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys. Here, Xaa may be one selected from the group consisting of Glu, Asn, Gln, His, Lys, Ser, Thr, Ala, Val, Ile, Leu, Phe, Tyr, Trp, homo-Ser, Asp(Me), and Asn(Me).

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 represented by the following Formula 2.

[Formula 2]

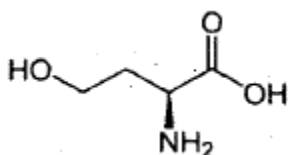


HyP may include all isomers. In addition, HyP may be an isomer represented by the stereochemistry of “2S,4R” unless otherwise specified.

The term “2S,4R” is represented by R and S that indicate a stereochemical configuration of a chiral molecule. A typical chiral molecule has a chiral center
 5 such as an asymmetric carbon atom. Since the chiral center has four different substituent groups (or substitution atoms), their priority is determined by a predetermined procedure. Once the order of the four substituents is determined by (1), (2), (3), and (4), the lowest order substituent (4) is placed farthest away from the eye direction, and the remaining substituents are arranged from the higher
 10 order to the lower order. R (or rectus in Latin, right) indicate the arrangement in which the sequence of (1) to (2) to (3) turns right. S (or sinister, left) indicates the arrangement in which this sequence turns left.

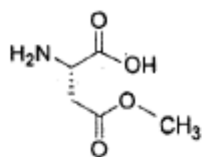
The term “homo-Ser” used in the present invention is called homoserine and refers to an α -amino acid having a hydroxyl group in the side chain. Homo-Ser is
 15 not an amino acid that constitutes a protein and is an intermediate present in the biosynthesis of threonine and methionine in microorganisms and plants. Homo-Ser may have the following Formula 3.

[Formula 3]



20 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 (CH₃). Asp(Me) may have the following Formula 4.

[Formula 4]

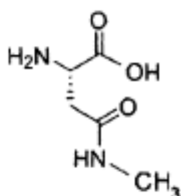


25

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 have the following Formula 5.

[Formula 5]

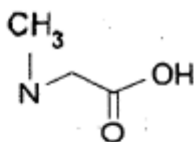


5

In addition, still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys. Here, Xaa may be one selected from the group consisting of Val, Ile, Leu, Ala, Phe, Tyr, Trp, Ser, Thr, and (N-Me)Gly.

10 The term “(N-Me)Gly” 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 2-position of glycine is substituted by a methyl group (CH_3). (N-Me)Gly may have the following Formula 6.

[Formula 6]

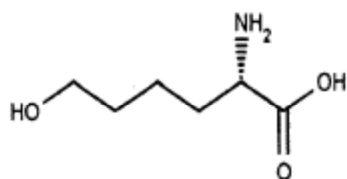


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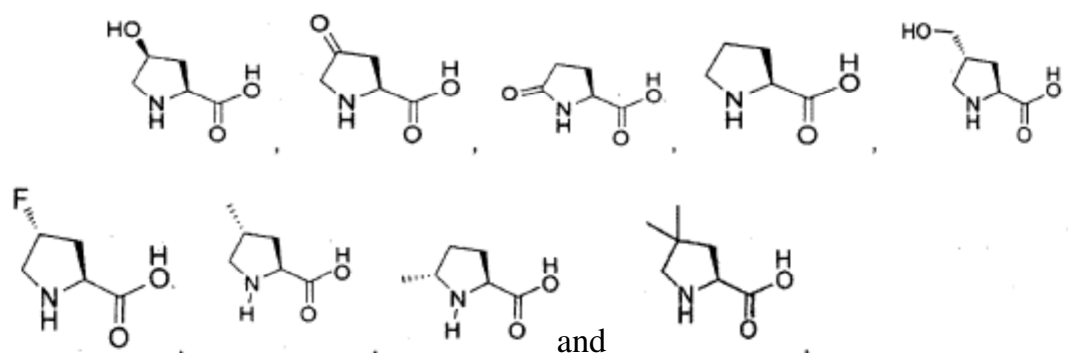
Still another aspect of the present invention provides a peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa. Here, Xaa may be one selected from the group consisting of Tyr, Leu, Glu, Gln, Ala, and Nle(6-OH).

20 The term “Nle(6-OH)” used in the present invention refers to an amino acid in which a hydroxyl group ($-\text{OH}$) is bonded to the carbon atom at the 6-position of norleucine. Nle(6-OH) has a structure of $\text{C}_5\text{H}_{11}\text{NO}_3$ and may be represented by the following Formula 7.

[Formula 7]



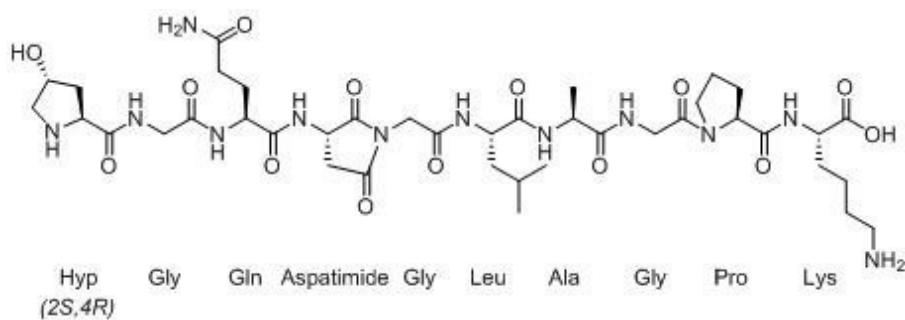
Still another aspect of the present invention provides a peptide having an amino acid sequence represented by PD-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys. Here, PD may be any one selected from the group consisting of the following
5 formulae.



Still another aspect of the present invention provides a peptide having any
10 one amino acid sequence selected from the group consisting of Ala-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys (SEQ ID NO: 54), Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Ala-Lys (SEQ ID NO: 55), HyP-Gly-Gln-Leu-Gly-Leu-Ala (SEQ ID NO: 56), HyP-Gly-Gln-Glu-Gly-Leu-Gly (SEQ ID NO: 57), HyP-Gly-Gln-Leu-Gly-Leu (SEQ ID NO: 58), _D-HyP(2R, 4S)-Gly-_D-Gln-_D-Leu-Gly-_D-Leu (SEQ ID NO: 59),
15 HyP-Gly-Gln-Leu-Gly (SEQ ID NO: 60), HyP-Gly-Gln-_D-Leu-Gly (SEQ ID NO: 61), and _D-HyP(2R, 4S)-Gly-Gln-Leu-Gly (SEQ ID NO: 62).

Still another aspect of the present invention provides a compound represented by Formula 8.

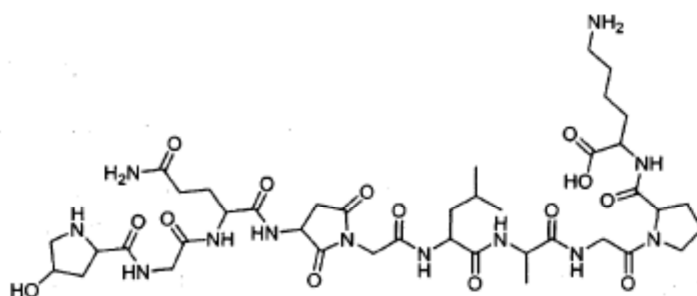
20 [Formula 8]



The compound represented by the above Formula 8 indicates a compound in which Asp is modified to Aspartimide by a dehydration condensation reaction of the hydroxyl group (-OH) bonded to the carbon atom at the 4-position of Asp in the amino acid sequence represented by HyP-Gly-Gln-Asp-Gly-Leu-Ala-Gly-Pro-Lys with the Asp-Gly peptide bond.

The modified compound may be a compound represented by the following Formula 9.

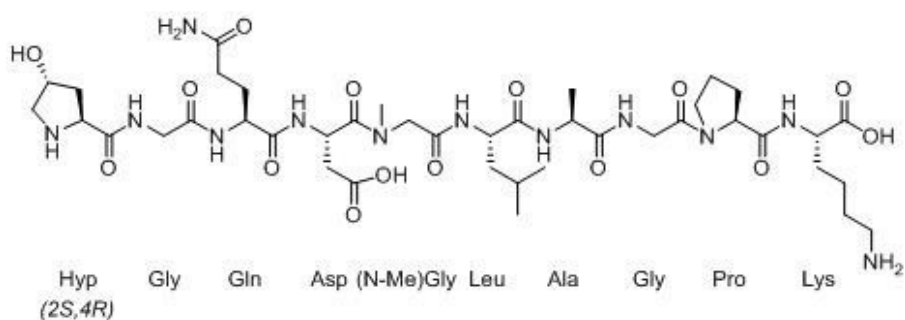
[Formula 9]



10

Still another aspect of the present invention provides a compound represented by Formula 10.

[Formula 10]



15

The compound represented by Formula 10 may be a compound represented

by the amino acid sequence of SEQ ID NO: 31.

Further, the present invention provides a pharmaceutical composition for treating an eye disease, which comprises the compound or the peptide as an active pharmaceutical ingredient.

5 Specifically, the eye disease may be one selected from the group consisting of 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
10 retinopathy, epidemic keratoconjunctivitis, atopic keratitis, superior 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
15 histoplasmosis, central retinal vein occlusion, Sjogren syndrome and Stevens-Johnson syndrome. Preferably, the eye disease may be one selected from the group consisting of retinopathy, keratitis, macular degeneration, dry eye syndrome and keratoconjunctival epithelium disorder.

The keratoconjunctival epithelium disorder may be due to post-operative
20 surgery, drug, trauma or contact lens wear.

Specifically, the composition for treating an eye disease, which comprises the compound or the peptide 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,
25 a slip agent, a flavor, an antioxidant, a buffer, a bacteriostat, a diluent, a dispersant, a surfactant, and a 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.

Still another aspect of the present invention provides a method for treating an
30 eye disease, which comprises administering the compound or the peptide to a subject.

The dose of the compound or the peptide may be adjusted depending on such various factors as the kind of the disease, the severity 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, 5 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 compound or the peptide contained in the pharmaceutical composition may be 0.0001 $\mu\text{g/day}$ to 100 $\mu\text{g/day}$. In such event, the administration may be carried out once a day, or divided 10 into several doses. Specifically, the concentration of the compound or the peptide contained in the pharmaceutical composition may be 1000 μM to 0.001 μM . Also, the concentration of the compound or the peptide 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 compound or the peptide 15 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 20 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. In particular, it may 25 preferably be applied to the eye for use as an eye drop.

Still another aspect of the present invention provides the use of the compound or the peptides for the treatment of an eye disease.

Still another aspect of the present invention provides the use of the 30 compound or the peptides for the preparation of a pharmaceutical composition for treating an eye disease.

Hereinafter, the present invention is explained in more detail by the following working examples. However, the following working examples are intended to further illustrate the present invention. The scope of the present invention is not limited thereby.

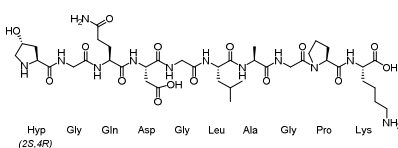
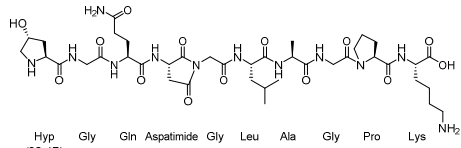
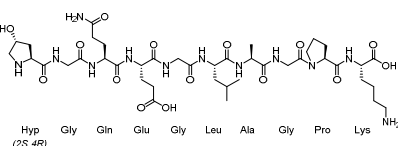
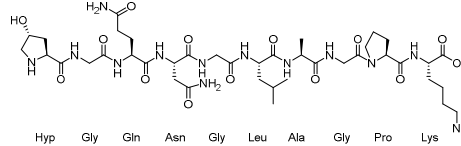
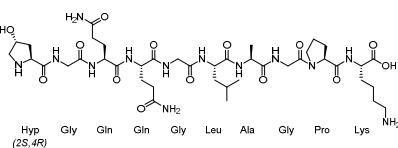
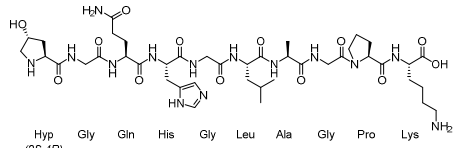
5

Working Example 1: Preparation of YDE derivatives

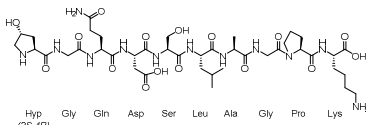
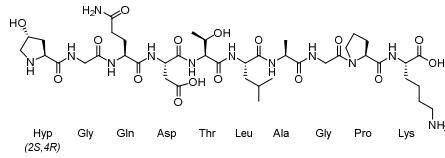
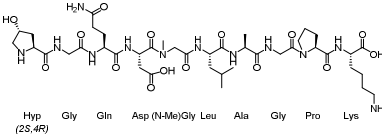
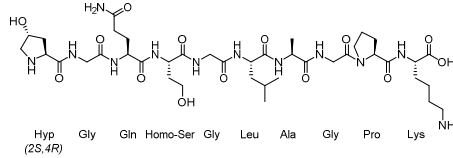
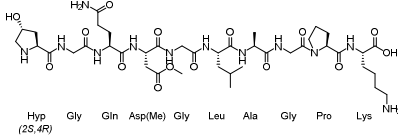
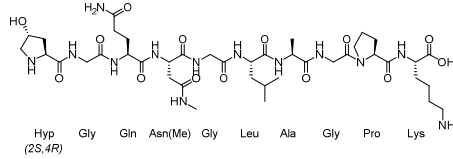
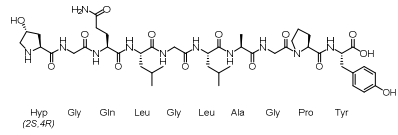
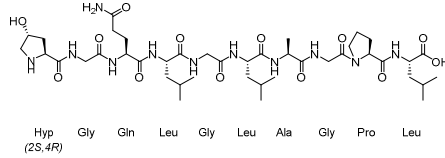
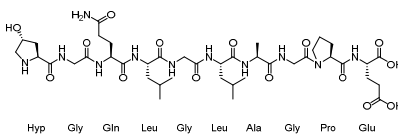
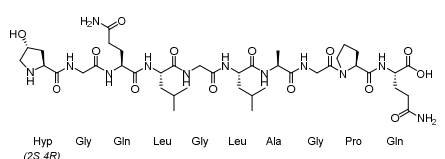
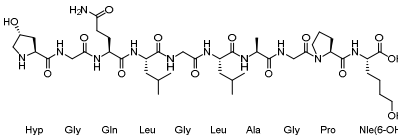
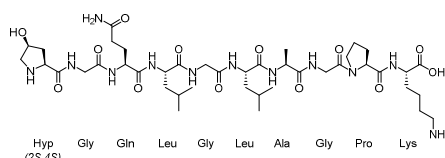
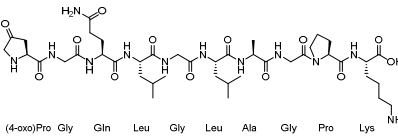
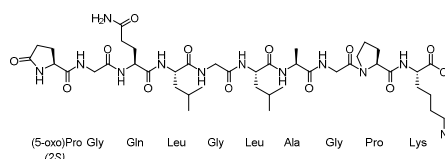
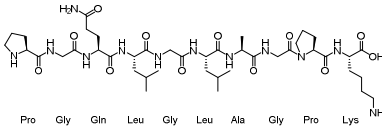
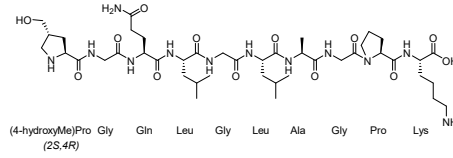
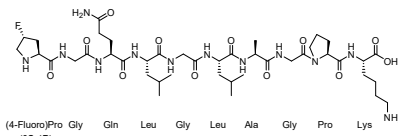
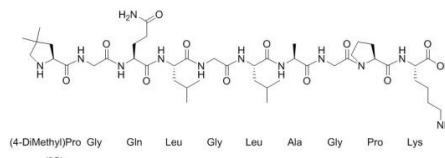
A protein analysis of the extracellular matrix derived from animal chondrocytes was performed in Baek's group of Center of Biomedical Mass Spectrometry (Diatech Korea Co., Ltd., Seoul, Korea). Proline-GQDGLAGPK (P-GQDGLAGPK), which is a part of the amino acid sequence of the collagen type II $\alpha 1$ protein, was obtained through the above protein analysis. YDE-001 to YDE-075 peptides were synthesized by ANYGEN (Gwangju, Korea) by substituting a part of the above peptide (Fig. 1 and Table 11).

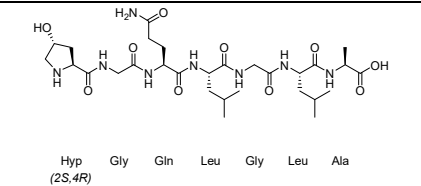
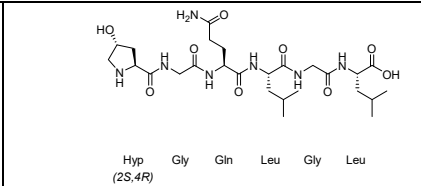
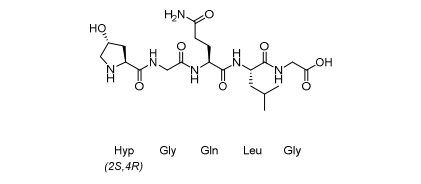
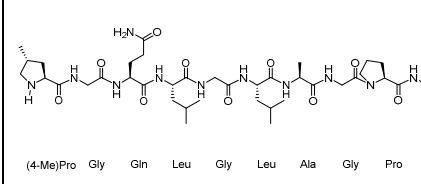
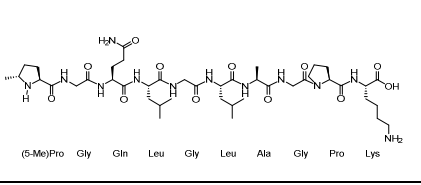
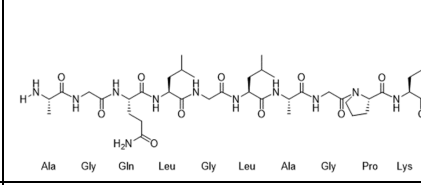
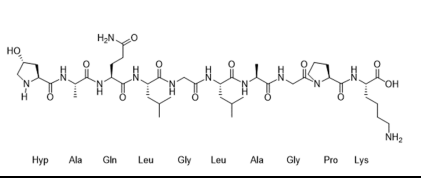
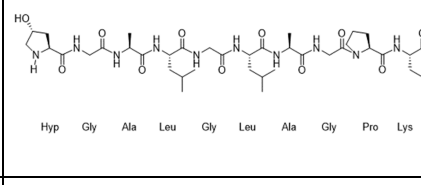
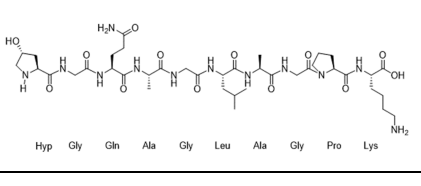
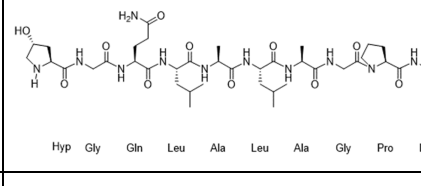
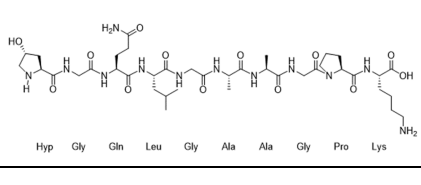
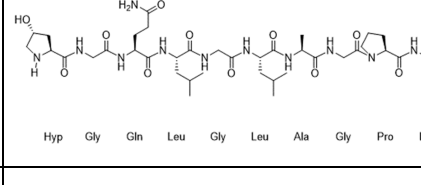
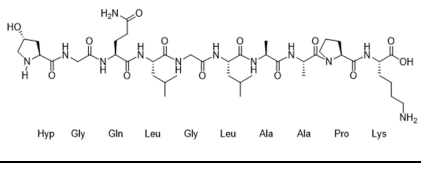
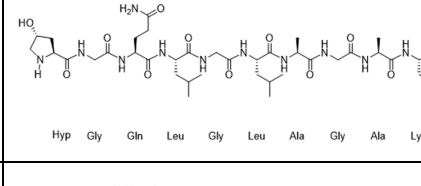
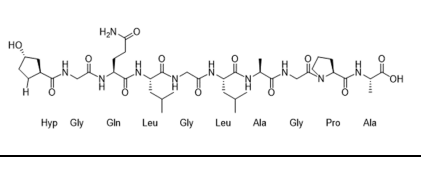
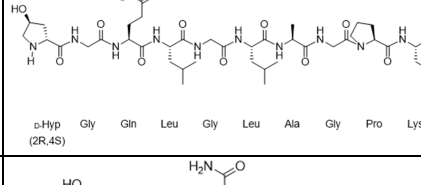
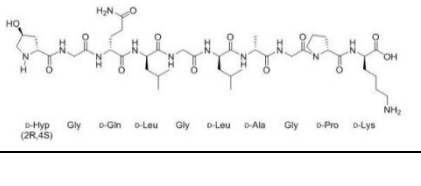
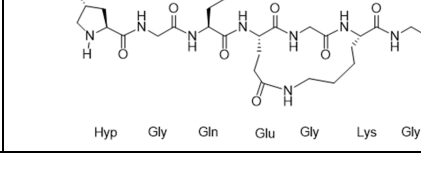
The process for synthesizing the YDE-001 to YDE-075 peptides and the purification procedure thereof conducted by ANYGEN were depicted in Figs. 2 and 3.

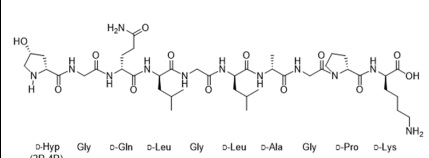
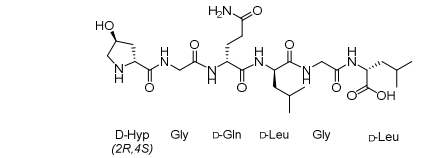
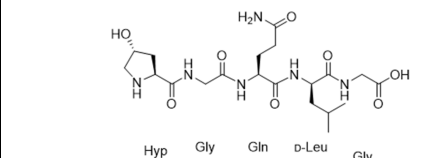
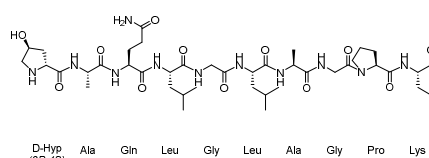
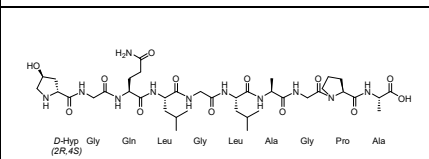
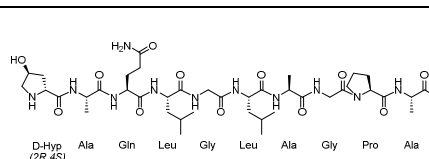
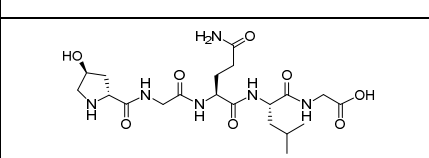
[Table 11]

No.	Structure of compound	No.	Structure of compound
YY-101		YY-102	
YDE-001		YDE-002	
YDE-003		YDE-004	

YDE -005	 Hyp Gly Gln Lys Gly Leu Ala Gly Pro Lys	YDE -006	 Hyp Gly Gln Ser Gly Leu Ala Gly Pro Lys
YDE -007	 Hyp Gly Gln Thr Gly Leu Ala Gly Pro Lys	YDE -008	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys
YDE -009	 Hyp Gly Gln Val Gly Leu Ala Gly Pro Lys	YDE -010	 Hyp Gly Gln Ile Gly Leu Ala Gly Pro Lys
YDE -011	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys	YDE -012	 Hyp Gly Gln Phe Gly Leu Ala Gly Pro Lys
YDE -013	 Hyp Gly Gln Tyr Gly Leu Ala Gly Pro Lys	YDE -014	 Hyp Gly Gln Trp Gly Leu Ala Gly Pro Lys
YDE -015	 Hyp Gly Gln Asp Val Leu Ala Gly Pro Lys	YDE -016	 Hyp Gly Gln Asp Ile Leu Ala Gly Pro Lys
YDE -017	 Hyp Gly Gln Asp Leu Leu Ala Gly Pro Lys	YDE -018	 Hyp Gly Gln Asp Ala Leu Ala Gly Pro Lys
YDE -019	 Hyp Gly Gln Asp Phe Leu Ala Gly Pro Lys	YDE -020	 Hyp Gly Gln Asp Tyr Leu Ala Gly Pro Lys
YDE -021	 Hyp Gly Gln Asp Trp Leu Ala Gly Pro Lys	YDE -022	 Hyp Gly Gln Asp His Leu Ala Gly Pro Lys

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	 Hyp Gly Gln Leu Gly Leu Ala (2S,4R)	YDE -042	 Hyp Gly Gln Leu Gly Leu (2S,4R)
YDE -043	 Hyp Gly Gln Leu Gly (2S,4R)	YDE -044	 (4-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -045	 (5-Me)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	YDE -047	 Ala Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -048	 Hyp Ala Gln Leu Gly Leu Ala Gly Pro Lys	YDE -049	 Hyp Gly Ala Leu Gly Leu Ala Gly Pro Lys
YDE -050	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys	YDE -051	 Hyp Gly Gln Leu Ala Leu Ala Gly Pro Lys
YDE -052	 Hyp Gly Gln Leu Gly Ala Ala Gly Pro Lys	YDE -053	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys
YDE -054	 Hyp Gly Gln Leu Gly Leu Ala Ala Pro Lys	YDE -055	 Hyp Gly Gln Leu Gly Leu Ala Gly Ala Lys
YDE -056	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala	YDE -057	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys (2R,4S)
YDE -058	 D-Hyp Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys (2R,4S)	YDE -059	 Hyp Gly Gln Glu Gly Lys Gly

YDE -060	 D-Hyp (2R,4R) Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys	YDE -064	 D-Hyp (2R,4S) Gly D-Gln D-Leu Gly D-Leu
YDE -066	 Hyp Gly Gln D-Leu Gly	YDE -072	 D-Hyp (2R,4S) Ala Gln Leu Gly Leu Ala Gly Pro Lys
YDE -073	 D-Hyp (2R,4S) Gly Gln Leu Gly Leu Ala Gly Pro Ala	YDE -074	 D-Hyp (2R,4S) Ala Gln Leu Gly Leu Ala Gly Pro Ala
YDE -075	 D-Hyp (2R,4S) Gly Gln Leu Gly		

Experimental Example 1: Analysis of YDE derivatives

The YDE derivatives prepared in Working Example 1 were analyzed by HPLC. As a result, it was confirmed that the purities of synthesized 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, and YDE-075 were 99.7%, 99.7%, 99.7%, 99.7%, 99.5%, 98.9%, 98.0%, 98.8%, 98.1%, 99.0%, 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%, and 96.3%, respectively (Figs. 4 to 68).

In addition, the YDE derivatives prepared in Working Example 1 were analyzed by Ion-Mass. As a result, it was confirmed that the molecular weights of synthesized 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, and YDE-075 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, and 486.4, respectively (Figs. 69 to 133).

20

Experimental Example 2: Evaluation of the eye protection effect on dry eye syndrome by the YDE derivatives

Experimental Example 2.1: 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 Working 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 rats were 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

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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 following the ELGE operation, confirmation was performed 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. 134).

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. 135).

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 caused to fast for 18 hours before the ELGE operation and final sacrifice except for feeding water.

The 32 groups were summarized in Table 12.

[Table 12]

Group classification	32 groups in total; 8 rats per group
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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 Working 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. 136).

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 prior approval of the Animal Experimental Ethics Committee of Daegu Haany University (Approval No. DHU2017-050, June 08, 2017). All test animals were caused to fast for 18 hours before the ELGE operation and final sacrifice except for feeding water.

The 20 groups were summarized in Table 13.

[Table 13]

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)

Experimental Example 2.2: 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 μ l/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 μ l/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 μ l/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 μ l/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. 137).

Test Example 2.3: Confirmation of the changes in the amount of tear secretion by the YDE 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).

The cobalt chloride paper was placed in the lateral canthus of a rat for 60 seconds to absorb tears (Fig. 139). 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. 138).

Fig. 139 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, 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 increased as compared with the ELGE control group, except for the groups treated with a 0.3% 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 0.3% 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 amounts of tear secretion are shown in Fig. 140 and Table 14.

[Table 14]

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. 141 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 increased as compared with the ELGE control group, except for the groups treated with a 0.3% 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 increased by more than 20% in the groups treated with a 0.3% solution of YDE-040, YDE-043, and YDE-042 in order as compared with the DS reference group.

The specific amounts of tear secretion are shown in Fig. 142 and Table 15.

[Table 15]

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

Experimental Example 2.4: 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. 142). 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; Takaci Seiko Co., Nakano, Japan) (Fig. 143).

- 5 Fig. 144 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 0.3% 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 0.3% 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 0.3% 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. 145 and Table 16.

[Table 16]

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. 146).

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 0.3% 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 0.3% 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 0.3% 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. 147 and

Table 17.

[Table 17]

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

5 Experimental Example 3: 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 18.

[Table 18]

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

Test Example 4: 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.

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 μ l of the diluted YDE derivative was added to a 96-well microplate (Greiner Bio-One, 651201) containing 380 μ l of the Corneal Epithelial Cell Basal Medium such that the concentration of DMSO was diluted to 5%.

After 24 hours, 20 μ l 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. 148 to 155).

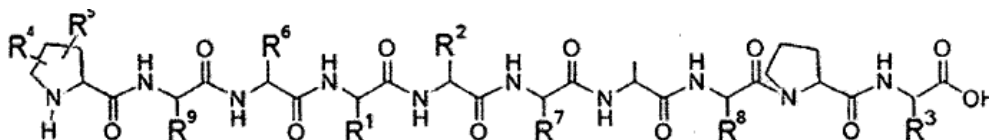
The cultured cells were treated with the CellTiter-Glo luminescent reagent (Promega, G7573) according to the manufacturer's instructions and reacted for 30 minutes at room temperature. Thereafter, the fluorescent signal (or luminescence signal) was checked using an Envision 2014 Multi-label plate reader. 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 μ M 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. 156 to 173).

WHAT IS CLAIMED IS:

1. A compound represented by Formula 1:

[Formula 1]



wherein R^1 to R^3 are each independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-10} alkoxy, substituted or unsubstituted C_{1-10} haloalkyl, substituted or unsubstituted C_{2-10} alkenyl, substituted or unsubstituted C_{2-10} alkynyl, substituted or unsubstituted C_{1-10} alkylene, substituted or unsubstituted C_{1-10} alkenylene, substituted or unsubstituted C_{1-10} alkynylene, substituted or unsubstituted C_{5-12} aryl, substituted or unsubstituted C_{7-12} arylalkyl, substituted or unsubstituted C_{5-14} arylalkynyl, substituted or unsubstituted C_{8-16} arylalkenyl, substituted or unsubstituted C_{3-10} heteroalkyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{3-10} heterocycloalkyl, or substituted or unsubstituted C_{5-12} heteroaryl, the heteroalkyl, heterocycloalkyl, or heteroaryl containing at least one of N, O, and S,

the substitution refers to a substitution with a non-hydrogen substituent, the non-hydrogen substituent may be at least one selected from the group consisting of $-X_1$, $-R_a$, $-O^-$, $=O$, $-OR_a$, $-SR_a$, $-S^-$, $-N(R_a)_2$, $-N^+(R_a)_3$, $=NR_a$, $-C(X_1)_3$, $-CN$, $-OCN$, $-SCN$, $-N=C=O$, $-NCS$, $-NO$, $-NO_2$, $=N-OH$, $=N_2$, $-N_3$, $-NHC(=O)R_a$, $-C(=O)R_a$, $-C(=O)NR_aR_a$, $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R_a$, $-OS(=O)_2OR_a$, $-S(=O)_2NR_a$, $-S(=O)R_a$, $-OP(=O)(OR_a)_2$, $-C(=O)R_a$, alkylene- $C(=O)R_a$, $-C(=S)R_a$, $-C(=O)OR_a$, alkylene- $C(=O)OR_a$, $-C(=O)O^-$, alkylene- $C(=O)O^-$, $-C(=S)OR_a$, $-C(=O)SR_a$, $-C(=S)SR_a$, $-C(=O)NR_aR_a$, alkylene- $C(=O)NR_aR_a$, $-C(=S)NR_aR_a$, and $-C(-NR_a)NR_aR_a$, X_1 is F, Cl, Br, or I, R_a is hydrogen, C_{1-6} alkyl, C_{5-12} aryl, C_{7-12} arylalkyl, or heterocycle,

R^4 and R^5 are each independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, $-X_2$, $-R_b$, $-O^-$, $=O$, $-CH_2OR_b$, or $-OR_b$, X_2 is F, Cl, Br, or I, R_b is H,

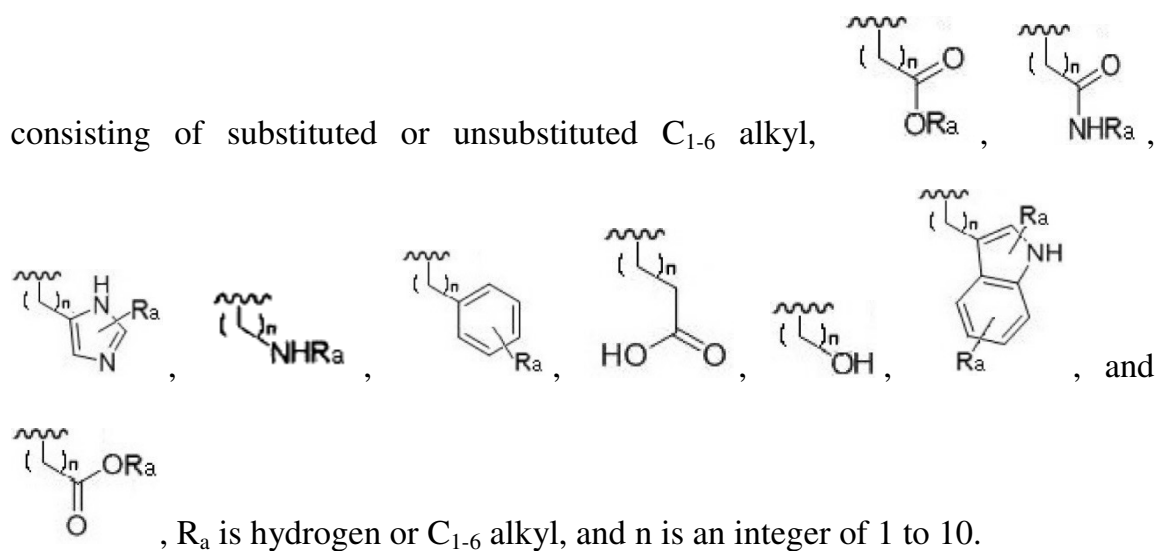
substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₅₋₁₂ aryl, substituted or unsubstituted C₇₋₁₂ arylalkyl, or substituted or unsubstituted heterocycle,

R⁶ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl, the substituent being -C(=O)NH₂,

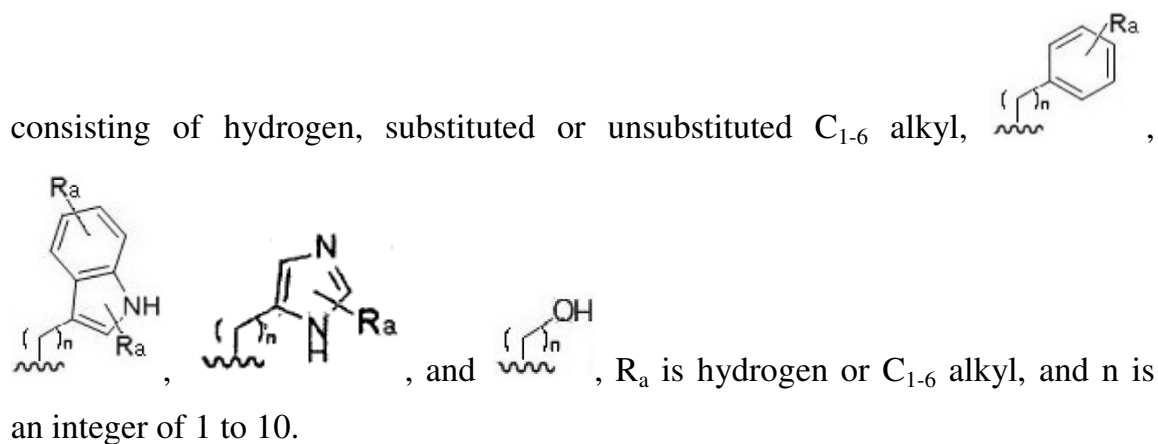
R⁷ is hydrogen or C₁₋₆ alkyl, and

R⁸ and R⁹ are hydrogen or unsubstituted C₁₋₆ alkyl.

2. The compound of claim 1, wherein R¹ is selected from the group

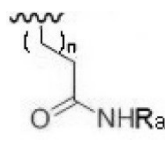
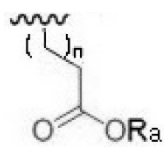
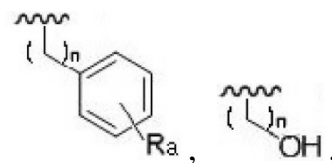


3. The compound of claim 1, wherein R² is selected from the group



4. The compound of claim 1, wherein R^3 is selected from the group

consisting of substituted or unsubstituted C₁₋₆ alkyl,



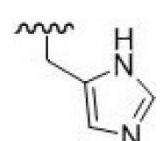
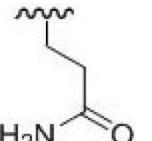
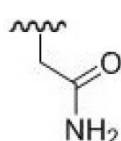
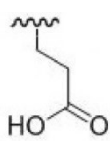
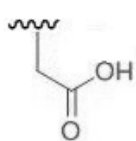
$\text{O}-\text{OR}_a$, and $\text{O}=\text{NHR}_a$, R_a is hydrogen or C_{1-6} alkyl, and n is an integer of 1 to 10.

5. The compound of claim 1, wherein R⁴ and R⁵ are each independently selected from the group consisting of substituted or unsubstituted C₁₋₆ alkyl, -OR_b, =O, -CH₂OR_b, and -X₂, and R_b is hydrogen or C₁₋₆ alkyl.

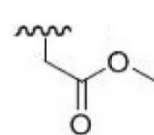
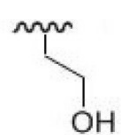
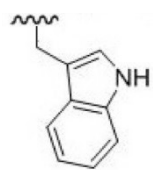
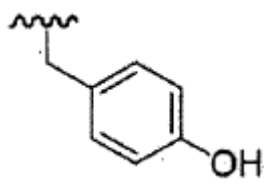
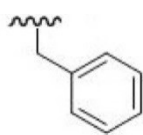
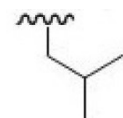
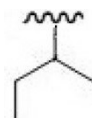
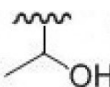
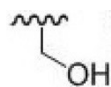
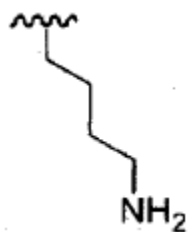
6. The compound of claim 5, wherein X₂ is F, Cl, Br, or I.

7. The compound of claim 1, wherein R⁶ to R⁹ are each independently hydrogen or substituted or unsubstituted C₁₋₆ alkyl, and the substituent is -C(=O)NH₂,

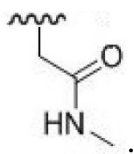
8. The compound of claim 2, wherein R¹ is selected from the group



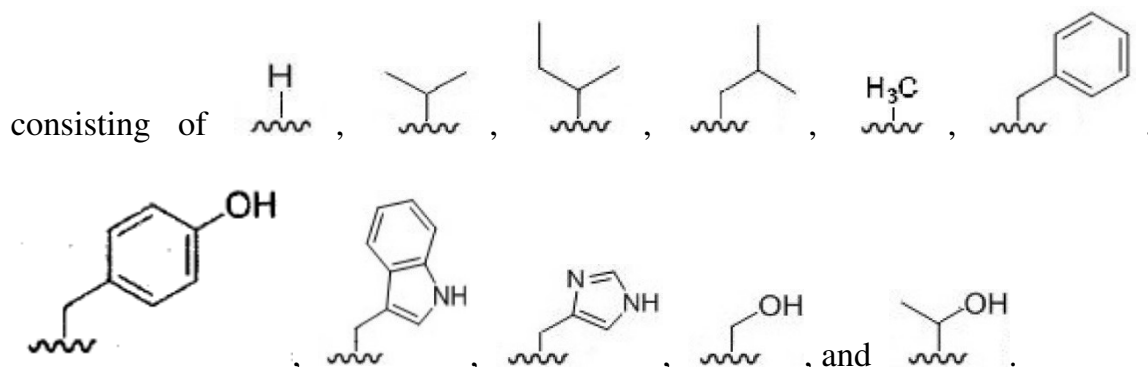
consisting of



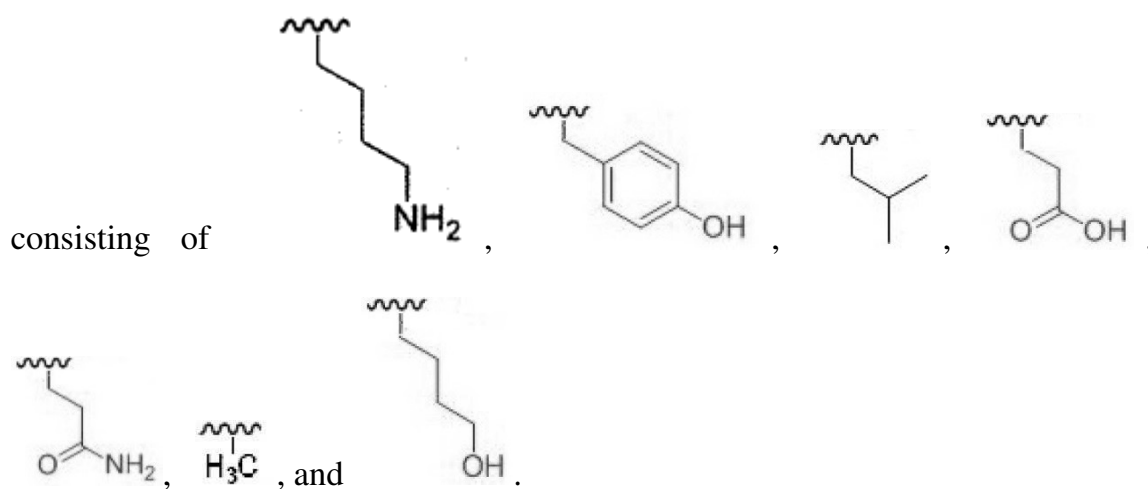
, and



9. The compound of claim 3, wherein R^2 is selected from the group



10. The compound of claim 4, wherein R^3 is one selected from the group



11. The compound of claim 6, wherein R^4 is selected from the group consisting of H, -OH, =O, and -CH₃.

12. The compound of claim 1, which is any one selected from the group consisting of HyP-Gly-Gln-Glu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Gln-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-His-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Lys-Gly-Leu-Ala-Gly-

Pro-Lys, HyP-Gly-Gln-Ser-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Thr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ala-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Val-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ile-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Phe-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Tyr-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Trp-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Ser(Homo)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp(Me)-Gly-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asn(Me)-Gly-Leu-Ala-Gly-Pro-Lys, $_D$ -Hyp(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, $_D$ -Hyp(2R,4S)-Gly- $_D$ -Gln- $_D$ -Leu-Gly- $_D$ -Leu- $_D$ -Ala-Gly- $_D$ -Pro- $_D$ -Lys, $_D$ -Hyp(2R, 4R)-Gly- $_D$ -Gln- $_D$ -Leu-Gly- $_D$ -Leu- $_D$ -Ala-Gly- $_D$ -Pro- $_D$ -Lys,

HyP-Gly-Gln-Asp-Val-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ile-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Leu-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ala-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Phe-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Tyr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Trp-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-His-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Ser-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Asp-Thr-Leu-Ala-Gly-Pro-Lys, HyP-Gly-Gln-Leu-Ala-Leu-Ala-Gly-Pro-Lys,

HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Tyr, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Leu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Glu, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Gln, HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Nle(6-OH), HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala, $_D$ -Hyp(2R, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala,

Hyp(2S, 4S)-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-oxo)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-hydroxyMe)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Fluoro)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Dimethyl)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (4-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, (5-Me)Pro-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys,

Hyp-Gly-Ala-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Ala-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Ala-Pro-Lys, Hyp-Ala-Gln-

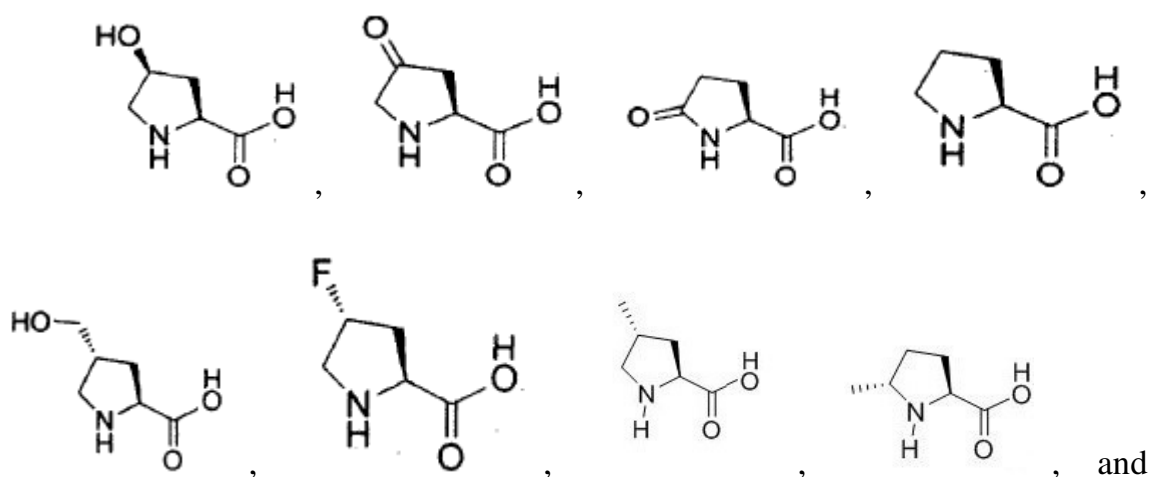
Leu-Gly-Leu-Ala-Gly-Pro-Lys, D -Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, and D -Hyp(2R, 4S)-Ala-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Ala.

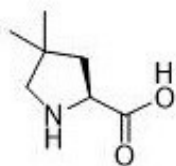
13. A peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys, wherein Xaa is selected from the group consisting of Glu, Asn, Gln, His, Lys, Ser, Thr, Ala, Val, Ile, Leu, Phe, Tyr, Trp, homo-Ser, Asp(Me), and Asn(Me).

14. A peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys, wherein Xaa is selected from the group consisting of Val, Ile, Leu, Ala, Phe, Tyr, Trp, Ser, Thr, and (N-Me)Gly.

15. A peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa, wherein Xaa is selected from the group consisting of Tyr, Leu, Glu, Gln, Ala, and Nle(6-OH).

16. A peptide having an amino acid sequence represented by PD-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, wherein PD is any one selected from the group consisting of the following formulae:

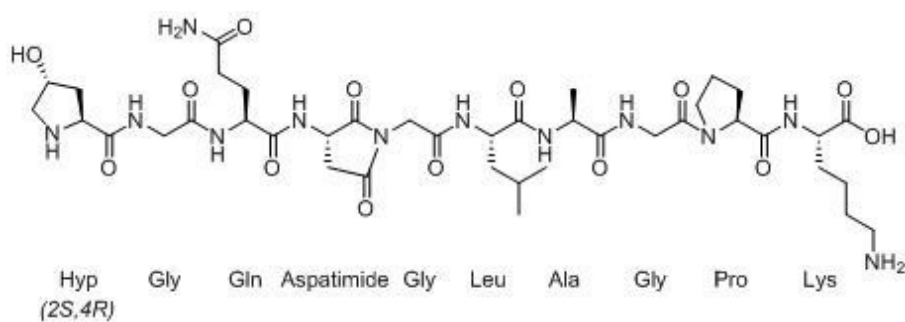




17. A peptide having any one amino acid sequence selected from the group consisting of Ala-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys, Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Ala-Lys, HyP-Gly-Gln-Leu-Gly-Leu-Ala, HyP-Gly-Gln-Glu-Gly-Leu-Gly, HyP-Gly-Gln-Leu-Gly-Leu, D -HyP(2R, 4S)-Gly- D -Gln- D -Leu-Gly- D -Leu, HyP-Gly-Gln-Leu-Gly, HyP-Gly-Gln- D -Leu-Gly, and D -HyP(2R, 4S)-Gly-Gln-Leu-Gly.

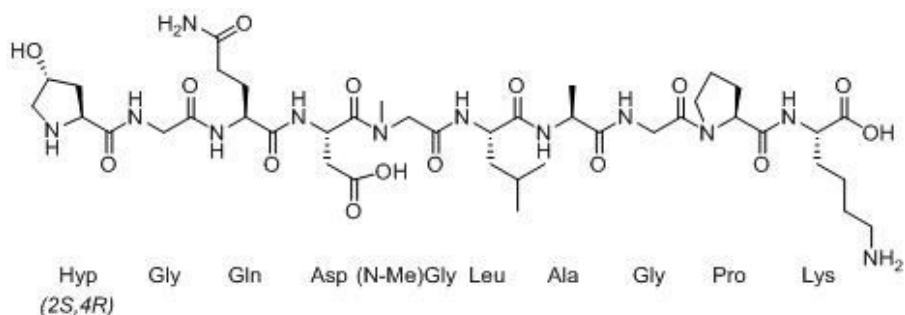
18. A compound represented by Formula 8:

[Formula 8]



19. A compound represented by Formula 10:

[Formula 10]



20. A pharmaceutical composition for treating an eye disease, which

comprises the compound according to any one of claims 1 to 12, 18, and 19, or the peptide according to any one of claims 13 to 17, as an active pharmaceutical ingredient.

21. The pharmaceutical composition of claim 20, wherein eye disease is one selected from the group consisting of retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, heratoconjunctivitis sicca and keratoconjunctival epithelium disorder.

22. A method for treating an eye disease, which comprises administering the compound according to any one of claims 1 to 12, 18, and 19, or the peptide according to any one of claims 13 to 17, to a subject.