

DESCRIPTION

POLYPEPTIDE HAVING MMP2-INHIBITORY EFFECT

5 TECHNICAL FIELD

The present invention relates to a substituted polypeptide compound having an effect to inhibit matrix metalloprotease 2 (hereinafter, appropriately abbreviated as "MMP2").

10 BACKGROUND ART

Matrix metalloprotease is an endopeptidase having an active center of zinc, and 24 genes are known therefor. MMP degrades the extracellular matrix including collagen and gelatin, thus being involved not only in physiological response such as bone remodeling and wound healing, but also in pathological processes such as inflammation and the
15 progression of cancer (see NPTL 1).

Clinical trials for multiple MMP inhibitors have been previously carried out with focus on the anti-cancer effect by MMP inhibition, but given up because of adverse effects such as skeletal muscle pain and possible promotion of cancer metastasis that are inferred to be caused by the inhibitory effect relatively non-selective to MMP subtypes (see NPTLs
20 2 and 3).

Activation of MMP2 has been reported to play an important role in the infiltration and metastasis of cancer cells. The infiltration and metastasis of cancer cells are key factors relating to the prognosis of malignant tumor, and inhibition of MMP2 activity can serve as an effective therapeutic means in cancer control. The growth of cancer is suppressed in
25 MMP2-gene-knockout animals, and MMP2 has been reported to play an important role in the growth of cancer (see NPTL 4). Moreover, MMP2 has been reported to be associated with the progression of pathological condition in patients with various types of cancer such as breast cancer, pancreatic cancer, bladder cancer, colorectal cancer, ovarian cancer, prostate

cancer, brain tumor, gastric cancer, hepatocellular carcinoma, head and neck cancer, melanoma, uterine cancer, esophageal cancer, renal cell carcinoma, lung cancer, and glioma (see NPTLs 5 and 6). Further, MMP2 has been reported to be involved in the formation of pathological condition even in non-neoplastic diseases.

5 It has been reported that, in chronic kidney disease, MMP2 causes the epithelial-mesenchymal transition of the renal tubules by converting the structure of the tubular basement membrane, inducing tubular atrophy, fibrogenesis, and renal dysfunction (see NPTL 7). Further, increasing MMP2 concentrations in blood have been found in patients with chronic kidney disease (see NPTLs 8 and 9). Furthermore, it has been
10 reported that renal fibrosis induced by unilateral ureteral obstruction is suppressed in MMP2-gene-knockout animals (see NPTLs 10 and 11). In light of these, inhibition of MMP2 activity to regulate the progression of pathological condition of chronic kidney disease can serve as an effective therapeutic means.

 Enhanced expression of MMP2 has been found in alveolar epithelial cells,
15 fibroblasts, and macrophages in idiopathic pulmonary fibrosis, and, in particular, enhanced expression of MMP2 in alveolar lavage fluid has been found in patients with rapidly progressing idiopathic pulmonary fibrosis (see NPTLs 12 and 13). In addition, the effects of a non-selective MMP inhibitor to decrease the lung collagen contents in bleomycin-induced pulmonary fibrosis mice (see NPTL 14) and to prevent the transformation
20 of lung parenchymal fibroblasts induced by TGF β (see NPTL 15) have been reported. In light of these, inhibition of MMP2 activity to regulate the progression of pathological condition of idiopathic pulmonary fibrosis can serve as an effective therapeutic means.

 Moreover, the relationship between MMP2 and non-neoplastic diseases has been reported, the non-neoplastic diseases including multiple sclerosis, cerebral infarction,
25 arteriosclerosis, abdominal aortic aneurysm, peritoneal sclerosis, myocardial infarction, acute kidney injury, diabetic nephropathy, nephrosclerosis, glomerulonephritis, polycystic kidney disease, polycystic liver disease, alcoholic liver disease, nonalcoholic steatohepatitis, cholestatic liver injury, chronic obstructive pulmonary disease, interstitial pneumonia,

diabetic retinopathy, age-related macular degeneration, Sjogren's syndrome, meningitis, muscular dystrophy, scleroderma, inflammatory bowel disease, and tuberculosis (see NPTL 16).

In light of the matters described above, finding a means to selectively inhibit
5 MMP2 is an approach of high possibility to establish an effective therapeutic method for diseases in which MMP2 is involved.

A compound with a hydroxamic acid or carboxylic acid introduced as a zinc
chelator has been reported as a low-molecular-weight compound having MMP2-inhibitory
effect. However, no compound having selective MMP2-inhibitory effect has been known
10 (e.g., see NPTLs 17 and 18).

" β -Amyloid precursor protein (APP-IP,
Ile-Ser-Tyr-Gly-Asn-Asp-Ala-Leu-Met-Pro)", a peptide compound consisting of 10 natural
amino acids, has been reported to exhibit selective MMP2-inhibitory effect (see NPTL 19).
However, peptide compounds are in general quickly metabolized and excreted in vivo, and
15 thus it is known that even when a peptide compound is administered, the expected
pharmacological effect is not sustained.

CITATION LIST

NON PATENT LITERATURE

- 20 NPL 1: H. J. Ra and W. C. Parks Matrix Biol., 2007, 26(8), 587-596.
NPL 2: A. H. Drummond et al. Ann N Y Acad Sci., 1999, 878, 228-235.
NPL 3: A. D. Baxter et al. Bioorg Med Chem Lett., 2001, 11, 1465-1468.
NPL 4: T. Itoh et al. Cancer Res., 1998, 58, 1048-1051.
NPL 5: R. Roy et al. J Clin Oncol., 2009, 27, 5287-5297.
25 NPL 6: T. Turpeenniemi-Hujanen Biochimie., 2005, 87, 287-297.
NPL 7: S. Cheng et al. FASEB J., 2006, 20, 1898-1900.
NPL 8: K. Pawlak et al. Clin Biochem., 2011, 44, 838-843.
NPL 9: H. R. Chang et al. Clin Chim Acta., 2006, 366, 243-248.

NPL 10: X. Du et al. Lab Invest., 2012, 92, 1149-1160.

NPL 11: M. K. Tveit et al. PLoS One., 2015, 10, e0143390.

NPL 12: M. Selman et al. Am J Physiol Lung Cell Mol Physiol., 2000, 279, L562-L574.

NPL 13: M. Suga et al. Am J Respir Crit Care Med., 2000, 162, 1949-1956.

5 NPL 14: M. Corbel et al. J Pathol., 2001, 193, 538-545.

NPL 15: J. Michael et al. Am J Respir Cell Mol Biol., 2009, 41, 731-741.

NPL 16: A. Tokito et al. Int J Mol Sci., 2016, 17, E1178.

NPL 17: D. E. Levy et al. J Med Chem., 1998, 41, 199-223.

NPL 18: Y. Tamura et al. J Med Chem., 1998, 41, 640-649.

10 NPL 19: S. Higashi et al. J Biol Chem., 2003, 278, 14020-14028.

SUMMARY OF INVENTION

TECHNICAL PROBLEM

An object of the present invention is to provide a novel MMP2 inhibitor.

15

SOLUTION TO PROBLEM

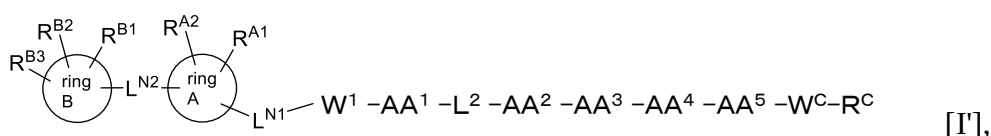
The present inventors diligently examined to achieve the object, and found that a compound represented by formula [I'] (hereinafter, occasionally referred to as compound [I']) has an effect to inhibit MMP2.

20

Hereinafter, the present invention will be described in detail.

Specifically, embodiments of the present invention are as follows.

(1) Provided as an embodiment of the present invention is a substituted polypeptide represented by formula [I']:



25

or a pharmaceutically acceptable salt thereof,

wherein

AA¹ represents:

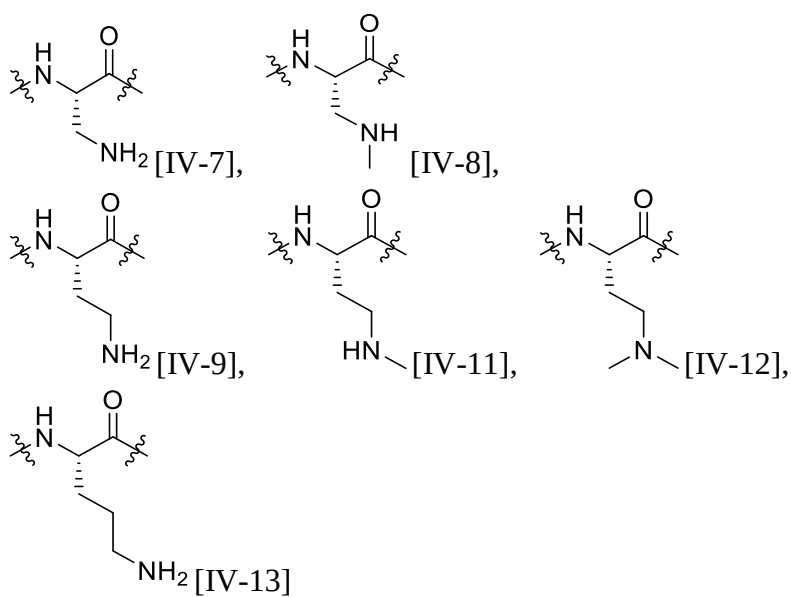
Asp,

β -Asp, β -(d)-Asp, γ -Glu, or γ -(d)-Glu;

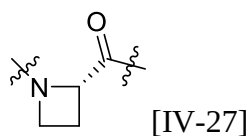
AA² represents one group selected from the group consisting of:

Ala,

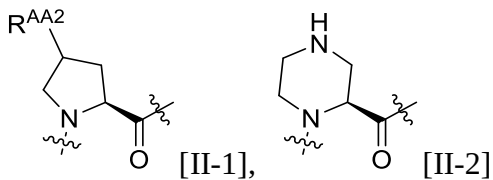
- 5 a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], [IV-12], and [IV-13]:



- 10 a group represented by formula [IV-27]:

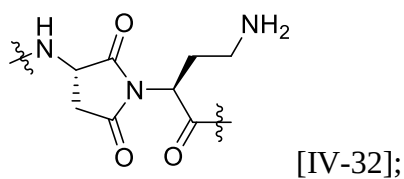


Pro, and a group represented by any of formulas [II-1] and [II-2]:



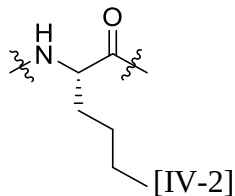
wherein R^{AA2} represents hydroxy or amino; or

- 15 AA¹ and AA² may be taken together to form a structure represented by formula [IV-32]:



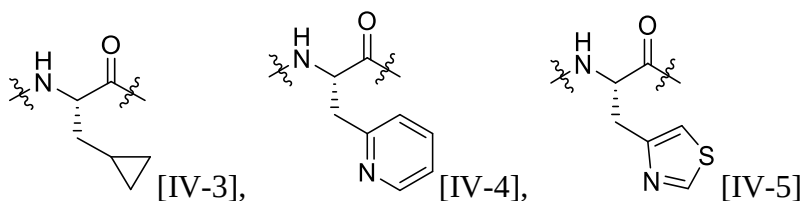
AA³ represents one group selected from the group consisting of:

Val, Leu, Ile, a group represented by formula [IV-2]:



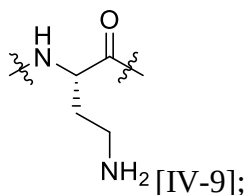
Phe, Trp,

5 Tyr, Lys, a group represented by any of formulas [IV-3], [IV-4], and [IV-5]:



and

a group represented by formula [IV-9]:



10 AA⁴ represents one group selected from the group consisting of:

a single bond,

Gly, (d)-Ala, (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile,

Pro, (d)-Pro,

(N-Me)Phe, (d)-Phe,

15 (N-Me)Tyr, (d)-Tyr,

(N-Me)Ser, (d)-Ser, homoSer, (d)-Thr,

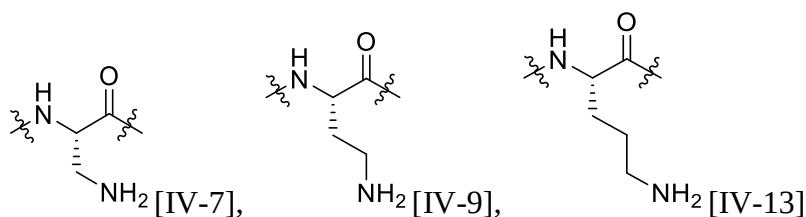
Met, (N-Me)Met,

(N-Me)Asp, Glu, (N-Me)Glu, (d)-(N-Me)Glu, homoGlu,

(N-Me)Asn,

20 (N-Me)Arg, (d)-Arg,

a group represented by any of formulas [IV-7], [IV-9], and [IV-13]:



Lys, and (N-Me)Lys,

wherein if AA⁴ represents Lys, then

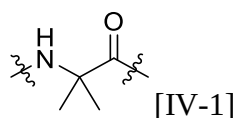
the amino in the side chain of the Lys is optionally substituted with

5 C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy;

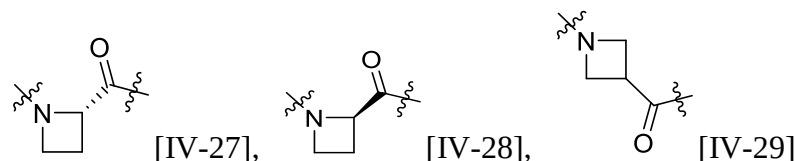
AA⁵ represents one group selected from the group consisting of:

a single bond,

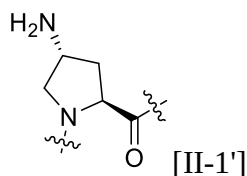
Ala, a group represented by formula [IV-1]:



10 a group represented by any of formulas [IV-27], [IV-28], and [IV-29]:



Pro, (d)-Pro, β-homoPro, homoPro, a group represented by formula [II-1']:

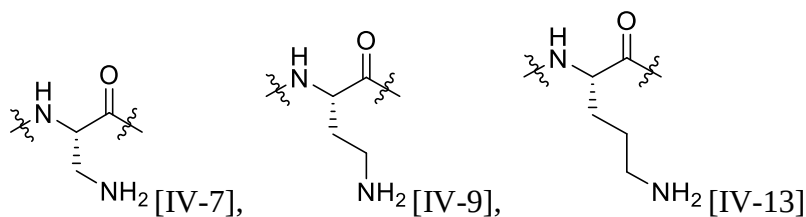


Phe, His,

15 Thr,

Arg, (d)-Arg,

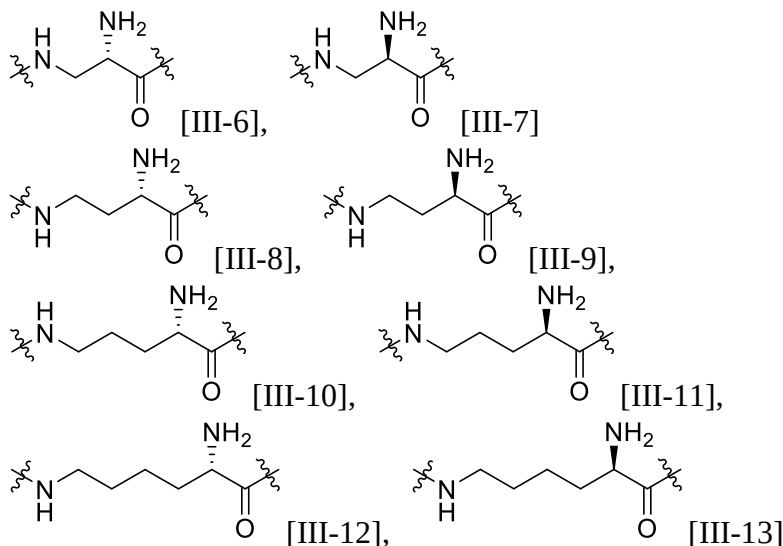
a group represented by any of formulas [IV-7], [IV-9], and [IV-13]:



Lys, (d)-Lys,

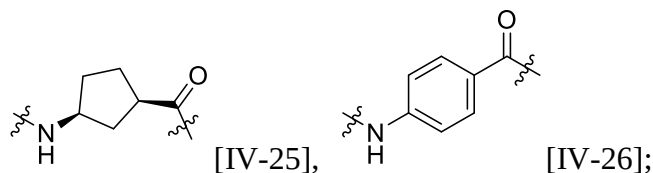
β -Ala, (N-Me)- β -Ala, GABA, Ape, Acp,

a group represented by any of formulas [III-6] to [III-13]:



and

a group represented by any of formula [IV-25] and [IV-26]:



10 W^1 represents $-L^1-$ or $-L^{1'}-L^{1''}-$; wherein

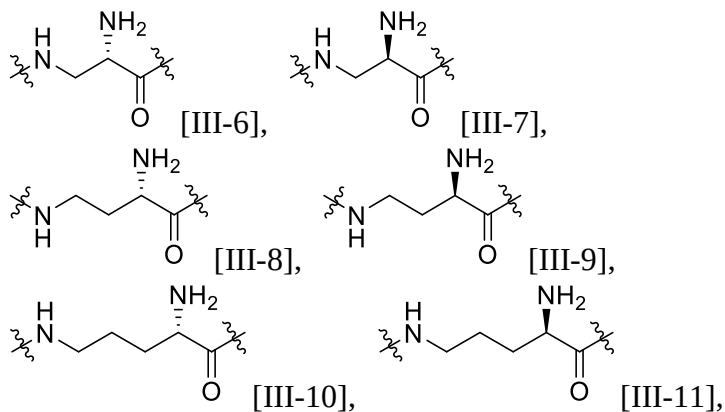
L^1 represents a single bond; and

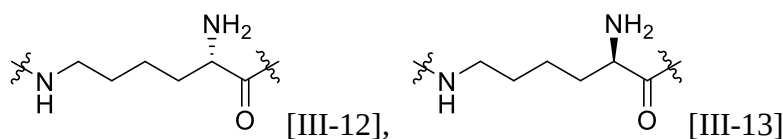
$L^{1'}$ represents one group selected from the group consisting of:

a single bond,

β -Ala, GABA, (N-Me)GABA, Ape, Acp,

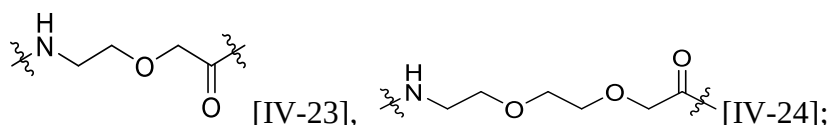
15 a group represented by any of formulas [III-6] to [III-13]





and

a group represented by any of formulas [IV-23] and [IV-24]:



5 and

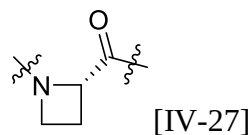
L^{1"} represents one group selected from the group consisting of:

a single bond,

Gly, (N-Me)Gly,

Ala, (N-Me)Ala, (d)-Ala, Val, (N-Me)Val, (N-Me)Leu, (N-Me)Ile,

10 a group represented by formula [IV-27]:



Pro, (d)-Pro, homoPro, Phe, (N-Me)Phe, (d)-Phe,

His, (d)-His, Trp, (N-Me)Trp, (d)-Trp,

Tyr, (N-Me)Tyr, (d)-Tyr,

15 (d)-Ser, homoSer, Thr, (N-Me)Thr, (d)-Thr,

Cys, (d)-Cys, Met, (N-Me)Met,

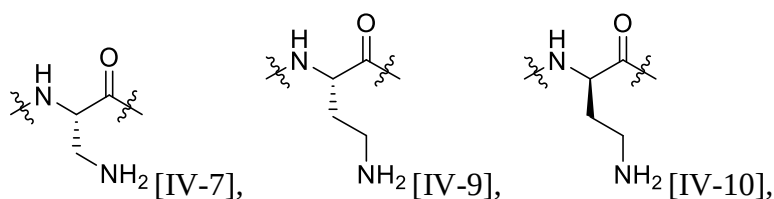
(N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu,

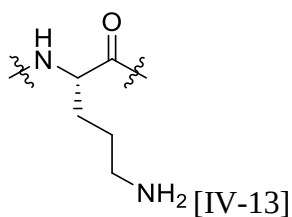
Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln,

Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit,

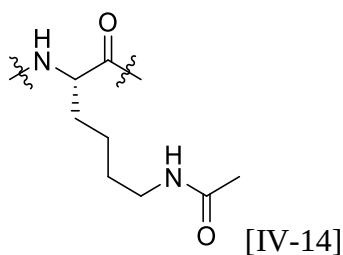
20 a group represented by any of formulas [IV-7], [IV-9], [IV-10], and

[IV-13]:





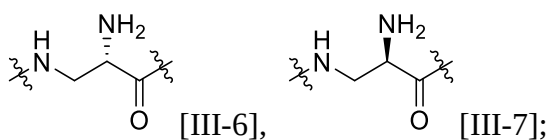
Lys, (N-Me)Lys, (d)-Lys, a group represented by formula [IV-14]:



β -Ala,

5 β -Asp, β -(d)-Asp, and

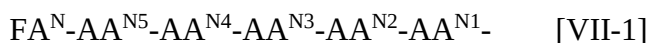
a group represented by any of formulas [III-6] and [III-7]:



wherein if $L^{1''}$ represents Lys or (d)-Lys, then

the amino in the side chain of the Lys or (d)-Lys is optionally substituted with a

10 group represented by formula [VII-1]:



wherein

FA^N represents C_{2-16} alkylcarbonyl terminally-substituted with carboxy;

AA^{N5} represents:

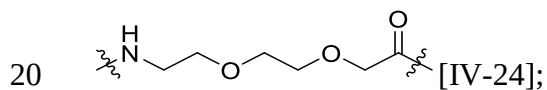
15 a single bond,

Arg, (d)-Arg,

Lys, (d)-Lys,

γ -Glu, or

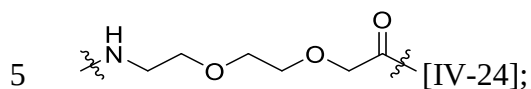
a group represented by formula [IV-24]:



AA^{N4} represents:

a single bond,
Arg, (d)-Arg,
Lys, (d)-Lys, or

a group represented by formula [IV-24]:

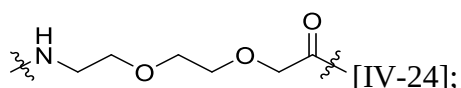


AA^{N3} represents:

a single bond,
Arg, (d)-Arg,
Lys, (d)-Lys,

10 γ -Glu, or

a group represented by formula [IV-24]:



AA^{N2} represents:

a single bond, or
(d)-Lys; and

15

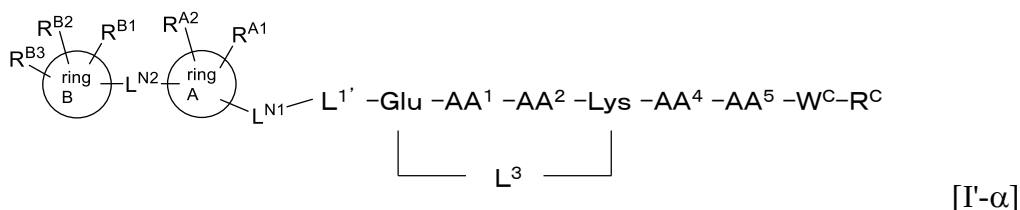
AA^{N1} represents:

a single bond, or
(d)-Lys;

wherein if L¹ⁿ represents Glu and AA³ represents Lys, then

20

the compound represented by formula [I'] may be taken together with L³ attached to each of functional groups in the side chains of the two amino acids to form a cyclic structure, as represented by formula [I'- α]:



25

wherein the L³ represents Gly, β -Ala, or GABA;

L^{N1} represents the formula -C(=O)- or the formula -S(=O)₂-;

L^{N2} represents:

a single bond,

C₁₋₃ alkanediyl,

5 C₂₋₃ alkenediyl,

ethynediyl,

the formula -O-,

the formula -C(=O)-, the formula -C(=O)-NH-, or

triazolediyl;

10 L² represents a single bond;

ring A represents an aromatic ring or a heteroaromatic ring;

R^{A1} and R^{A2} each independently represent:

a hydrogen atom,

a halogen atom,

15 C₁₋₆ alkyl, or

C₁₋₆ alkoxy;

ring B represents:

aryl or heteroaryl;

R^{B1}, R^{B2}, and R^{B3} each independently represent:

20 a hydrogen atom,

carbamoyl,

cyano,

a halogen atom,

C₁₋₆ alkyl optionally substituted with one hydroxy, halo C₁₋₆ alkyl,

25 C₁₋₆ alkoxy optionally substituted with one hydroxy, halo C₁₋₆ alkoxy,

C₁₋₆ alkylcarbonyl,

C₁₋₆ alkylcarbonylamino,

mono C₁₋₆ alkylaminocarbonyl, di C₁₋₆ alkylaminocarbonyl, wherein the alkyl in

each of the mono C₁₋₆ alkylaminocarbonyl and the di C₁₋₆ alkylaminocarbonyl is optionally substituted with one group selected from the group consisting of hydroxy, carboxy, carbamoyl, and amino,

C₁₋₆ alkylsulfonyl, or

5 aryl;

W^C is a single bond or a linker consisting of one to three amino acids, wherein the one to three amino acids forming the linker are same or different and each selected from the group consisting of:

Gly,

10 Pro,

Arg, (d)-Arg,

Lys, (d)-Lys,

β-Ala, GABA, and Ape,

wherein if Lys or (d)-Lys is included in the group represented by W^C, then

15 the amino in the side chain of the Lys or (d)-Lys is optionally substituted with:

C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy,

Lys, wherein the amino in the side chain of the Lys is optionally substituted with C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy, or

(d)-Lys, wherein the amino in the side chain of the (d)-Lys is optionally

20 substituted with C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy; and

R^C is:

the formula -OH, the formula -NH₂,

C₁₋₆ alkylamino, wherein the C₁₋₆ alkyl of the C₁₋₆ alkylamino is optionally

substituted with one group selected from the group consisting of hydroxy, amino, C₁₋₆ alkoxy,

25 and four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom, or

four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom, wherein the four- to seven-membered saturated

heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom is optionally substituted with one group selected from the group consisting of hydroxy, amino, and C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one carbamoyl; and two carbon atoms in the four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom are optionally crosslinked with C₁₋₄ alkanediyl.

(2) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to (1), wherein

W^C is:

10 a single bond,

Pro,

Arg, (d)-Arg,

Lys, (d)-Lys,

β-Ala, GABA, Ape,

15 Gly-(d)-Lys, Gly-(d)-Lys-(d)-Lys, Gly-(d)-Lys-(d)-Arg, Gly-(d)-Arg-(d)-Lys,

Lys-Lys, (d)-Lys-(d)-Lys, (d)-Lys-(d)-Lys-(d)-Lys,

Arg-Arg, (d)-Arg-(d)-Arg, (d)-Arg-(d)-Lys,

Lys-(d)-Lys-(d)-Lys, (d)-Lys-Lys-(d)-Lys, (d)-Lys-(d)-Lys-Lys,

β-Ala-(d)-Lys, β-Ala-(d)-Lys-(d)-Arg, β-Ala-(d)-Arg-(d)-Lys, or β-Ala-(d)-Arg-(d)-Arg

20 wherein if Lys is contained in the group represented by W^C,

then the amino in the side chain of the Lys is optionally substituted with:

C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy, or

(d)-Lys, wherein the amino in the side chain of the (d)-Lys is optionally substituted with C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy.

25 (3) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to (1) or (2), wherein

ring A is a benzene ring, a thiophene ring, or a pyridine ring;

R^{A1} and R^{A2} are each independently:

a hydrogen atom, or

a halogen atom;

ring B is:

phenyl, oxazolyl, thiadiazolyl, pyridyl, or benzofuranyl;

5 R^{B1} , R^{B2} , and R^{B3} are each independently:

a hydrogen atom,

carbamoyl,

cyano,

a halogen atom,

10 C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one hydroxy,

halo C_{1-6} alkyl,

C_{1-6} alkoxy, wherein the C_{1-6} alkoxy is optionally substituted with one hydroxy,

halo C_{1-6} alkoxy,

C_{1-6} alkylcarbonyl,

15 mono C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, wherein the alkyl in each of the mono C_{1-6} alkylaminocarbonyl and the di C_{1-6} alkylaminocarbonyl is optionally substituted with one group selected from the group consisting of hydroxy, carboxy, carbamoyl, and amino, or

C_{1-6} alkylsulfonyl; and

20 R^C is:

the formula -OH, the formula -NH₂,

C_{1-6} alkylamino, wherein the C_{1-6} alkyl of the C_{1-6} alkylamino is optionally

substituted with one group selected from the group consisting of hydroxy, amino, C_{1-6} alkoxy, and morpholinyl, or

25 azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl, wherein the azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl is optionally substituted with one group selected from the group consisting of hydroxy, amino, and C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one carbamoyl, wherein

two carbon atoms in the azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl are optionally crosslinked with C₁₋₄ alkanediyl.

(4) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to any of (1) to (3), wherein in the

5 substituted polypeptide represented by formula [I'],

ring A is a benzene ring;

ring B is phenyl;

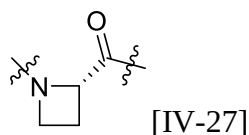
L^{1''} is one group selected from the group consisting of:

a single bond,

10 Gly, (N-Me)Gly,

Ala, (N-Me)Ala, (d)-Ala, Val, (N-Me)Val, (N-Me)Leu, (N-Me)Ile,

a group represented by formula [IV-27]:



Pro, (d)-Pro, homoPro, Phe, (N-Me)Phe, (d)-Phe,

15 His, (d)-His, Trp, (N-Me)Trp, (d)-Trp,

Tyr, (N-Me)Tyr, (d)-Tyr,

(d)-Ser, homoSer, Thr, (N-Me)Thr, (d)-Thr,

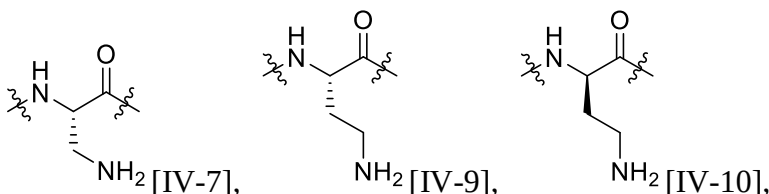
Cys, (d)-Cys, Met, (N-Me)Met,

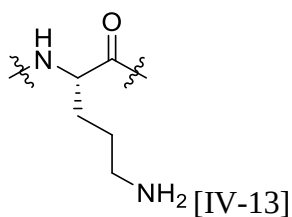
(N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu,

20 Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln,

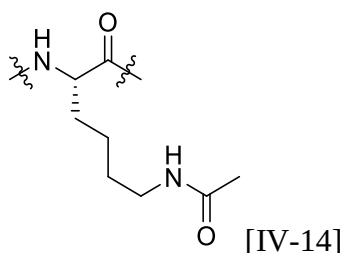
Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit,

a group represented by any of formulas [IV-7], [IV-9], [IV-10], and [IV-13]:





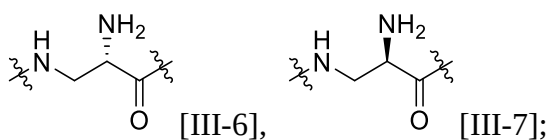
Lys, (N-Me)Lys, (d)-Lys, a group represented by formula [IV-14]:



β -Ala,

5 β -Asp, β -(d)-Asp, and

a group represented by any of formulas [III-6] and [III-7]:



and

W^C is:

10 a single bond,

Pro,

Arg, (d)-Arg,

Lys, (d)-Lys,

β -Ala, GABA, Ape,

15 Gly-(d)-Lys, Gly-(d)-Lys-(d)-Lys, Gly-(d)-Lys-(d)-Arg, Gly-(d)-Arg-(d)-Lys,

Lys-Lys, (d)-Lys-(d)-Lys, (d)-Lys-(d)-Lys-(d)-Lys,

Arg-Arg, (d)-Arg-(d)-Arg, (d)-Arg-(d)-Lys,

Lys-(d)-Lys-(d)-Lys, (d)-Lys-Lys-(d)-Lys, (d)-Lys-(d)-Lys-Lys,

β -Ala-(d)-Lys, β -Ala-(d)-Lys-(d)-Arg,

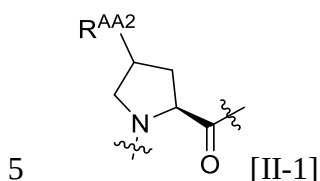
20 β -Ala-(d)-Arg-(d)-Lys, or β -Ala-(d)-Arg-(d)-Arg.

(5) Provided as another embodiment of the present invention is the substituted polypeptide or

pharmaceutically acceptable salt thereof according to any of (1) to (4), wherein in the substituted polypeptide represented by formula [I'],

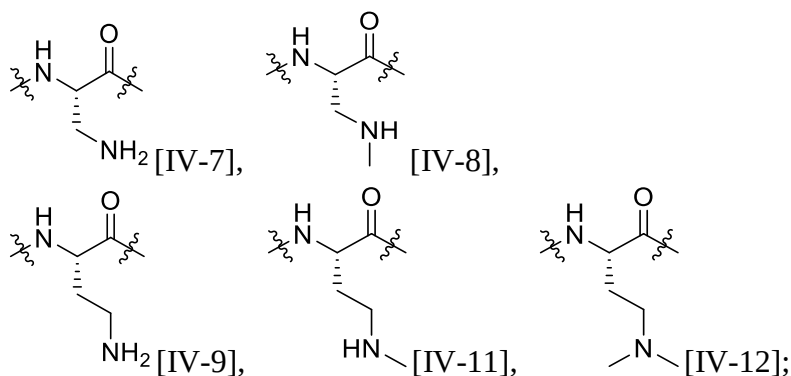
AA² is one group selected from the group consisting of:

a group represented by formula [II-1]:



and

a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], and [IV-12]:



10 wherein R^{AA2} is amino;

AA³ is Val, Leu, Ile, Phe, or Trp;

AA⁴ is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu;

AA⁵ is β-Ala, GABA, Ape, Acp, Pro, (d)-Pro, or β-homoPro;

W^C is a single bond, Arg, (d)-Arg, Lys, or (d)-Lys; and

15 R^C is the formula -OH or the formula -NH₂.

(6) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to any of (1) to (5), wherein in the substituted polypeptide represented by formula [I'],

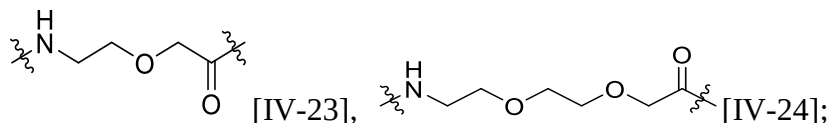
W¹ is -L^{1'}-L^{1''}-;

20 L² is a single bond;

AA¹ is Asp;

L^{1'} is one group selected from the group consisting of β-Ala, GABA, Ape, Acp, and

a group represented by any of formulas [IV-23] and [IV-24]:



$L^{1''}$ is a single bond, Asn, (d)-Ser, (d)-Thr, or Glu;

L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$;

5 L^{N2} is the formula $-O-$ or the formula $-C(=O)-NH-$;

R^{A1} and R^{A2} are each a hydrogen atom; and

R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, C_{1-6} alkoxy, or halo C_{1-6} alkoxy.

(7) Provided as another embodiment of the present invention is the substituted polypeptide or
10 pharmaceutically acceptable salt thereof according to any of (1) to (5), wherein in the substituted polypeptide represented by formula [I'],

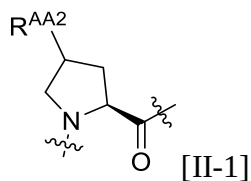
W^1 is $-L^1-$, wherein L^1 is a single bond;

L^2 is a single bond;

AA^1 is β -Asp, β -(d)-Asp, γ -Glu, or γ -(d)-Glu;

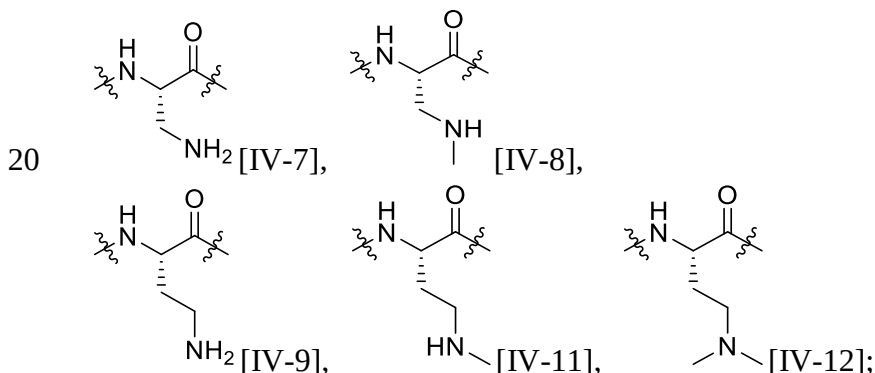
15 AA^2 is one group selected from the group consisting of:

a group represented by formula [II-1]:



and

a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], and [IV-12]:



wherein R^{AA2} is amino;

AA^3 is Val, Leu, Ile, Phe, or Trp;

AA^4 is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu;

AA^5 is β -Ala, GABA, Ape, Acp, or β -homoPro;

5 L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$;

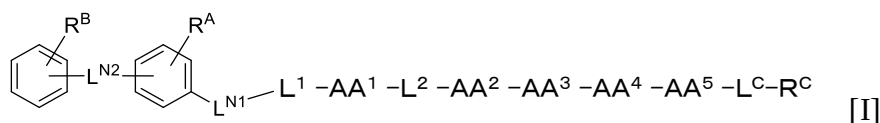
L^{N2} is a single bond, the formula $-O-$, or the formula $-C(=O)-NH-$;

R^{A1} and R^{A2} are each a hydrogen atom; and

R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom,

C_{1-6} alkoxy, or halo C_{1-6} alkoxy.

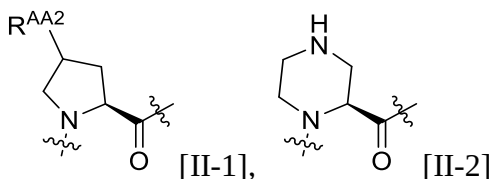
10 (8) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to any of (1) to (4), wherein the substituted polypeptide represented by formula [I'] is a substituted polypeptide represented by formula [I]:



15 wherein

AA^1 is β -Asp, γ -Glu, or γ -(d)-Glu;

AA^2 is a group represented by formula [II-1] or formula [II-2]:



wherein R^{AA2} is hydroxy or amino;

20 AA^3 is Val, Leu, Ile, Phe, or Trp;

AA^4 is a single bond, Pro, (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp, or (N-Me)Glu;

AA^5 is a single bond, Pro, (d)-Pro, β -homoPro, Arg, (d)-Arg, Lys, (d)-Lys, β -Ala, GABA, Ape, or Acp;

25 L^1 is a single bond;

L^2 is a single bond;

L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$;

L^{N2} is a single bond, C_{1-3} alkanediyl, the formula $-O-$, or the formula $-C(=O)-NH-$;

R^A is a hydrogen atom, a halogen atom, C_{1-6} alkyl, or C_{1-6} alkoxy;

5 R^B is a hydrogen atom, carbamoyl, a halogen atom, C_{1-6} alkyl, or C_{1-6} alkoxy;

L^C is a single bond, Pro, Arg, (d)-Arg, Lys, (d)-Lys, or (d)-Lys-(d)-Lys; and

R^C is the formula $-OH$ or the formula $-NH_2$.

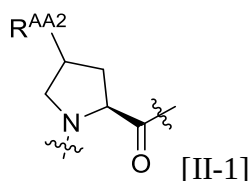
(9) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to any of (1) to (5), wherein in the

10 substituted polypeptide represented by formula [I'],

AA^1 is Asp, β -(d)-Asp, or γ -(d)-Glu;

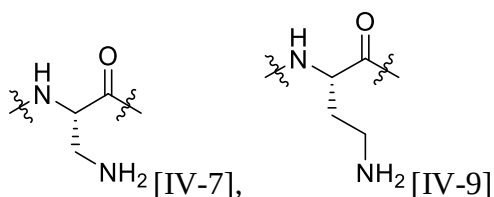
AA^2 is one group selected from the group consisting of:

a group represented by formula [II-1]:



15 and

a group represented by any of formulas [IV-7] and [IV-9]:



wherein R^{AA2} is amino;

AA^3 is Val, Leu, or Ile;

20 AA^4 is (N-Me)Ile or (N-Me)Glu;

AA^5 is Ape or β -homoPro;

W^1 is $-L^1-$ or $-L^{1'}-L^{1''}-$,

wherein

L^1 is a single bond,

$L^{1'}$ is GABA or Ape, and

$L^{1''}$ is Asn, (d)-Ser, (d)-Thr, or Glu;

L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$;

L^{N2} is the formula $-O-$ or the formula $-C(=O)-NH-$;

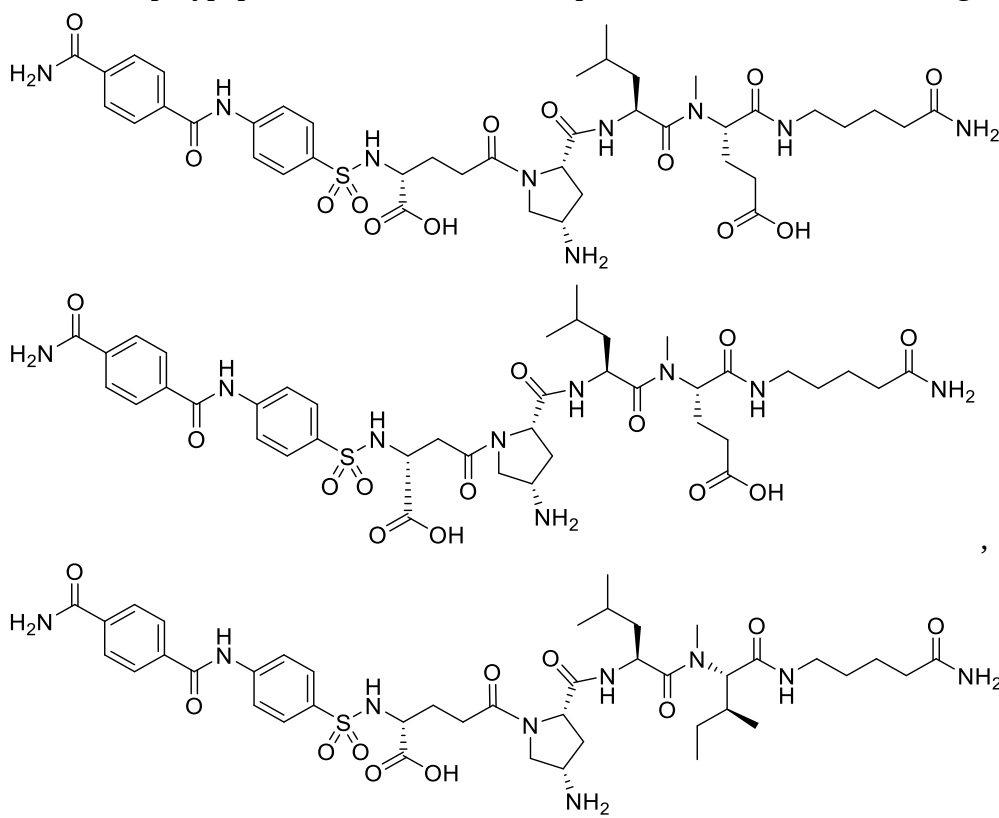
5 R^{A1} and R^{A2} are each a hydrogen atom;

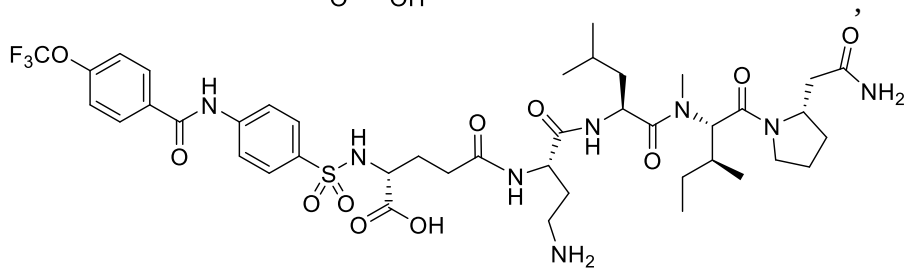
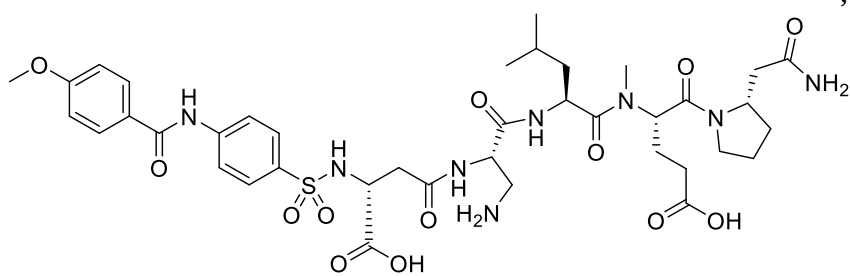
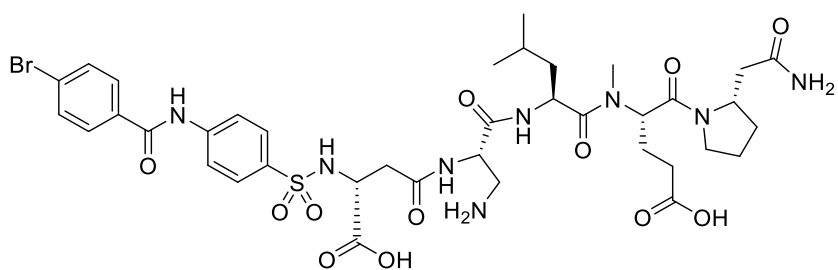
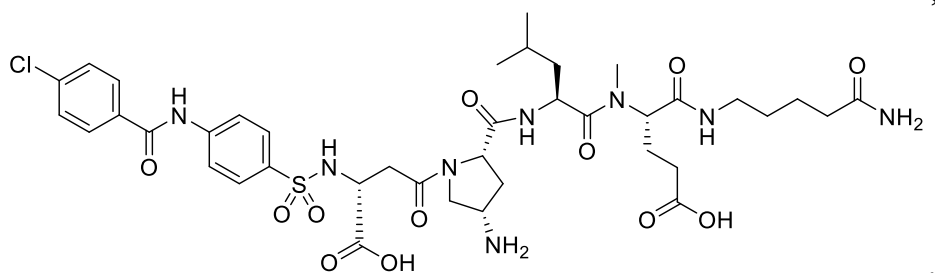
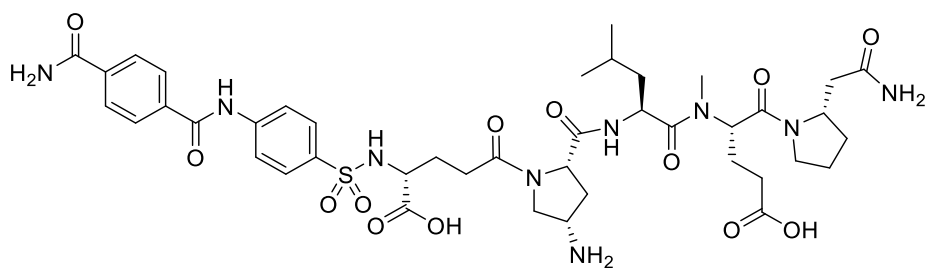
R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, C_{1-6} alkoxy, or halo C_{1-6} alkoxy;

W^C is a single bond or (d)-Lys; and

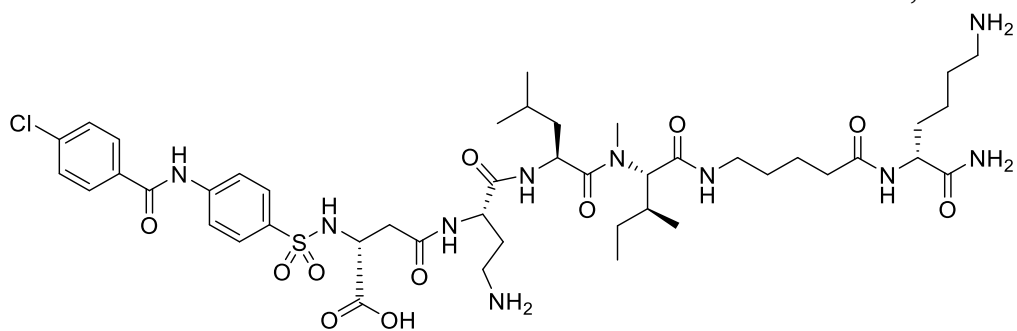
R^C is the formula $-NH_2$.

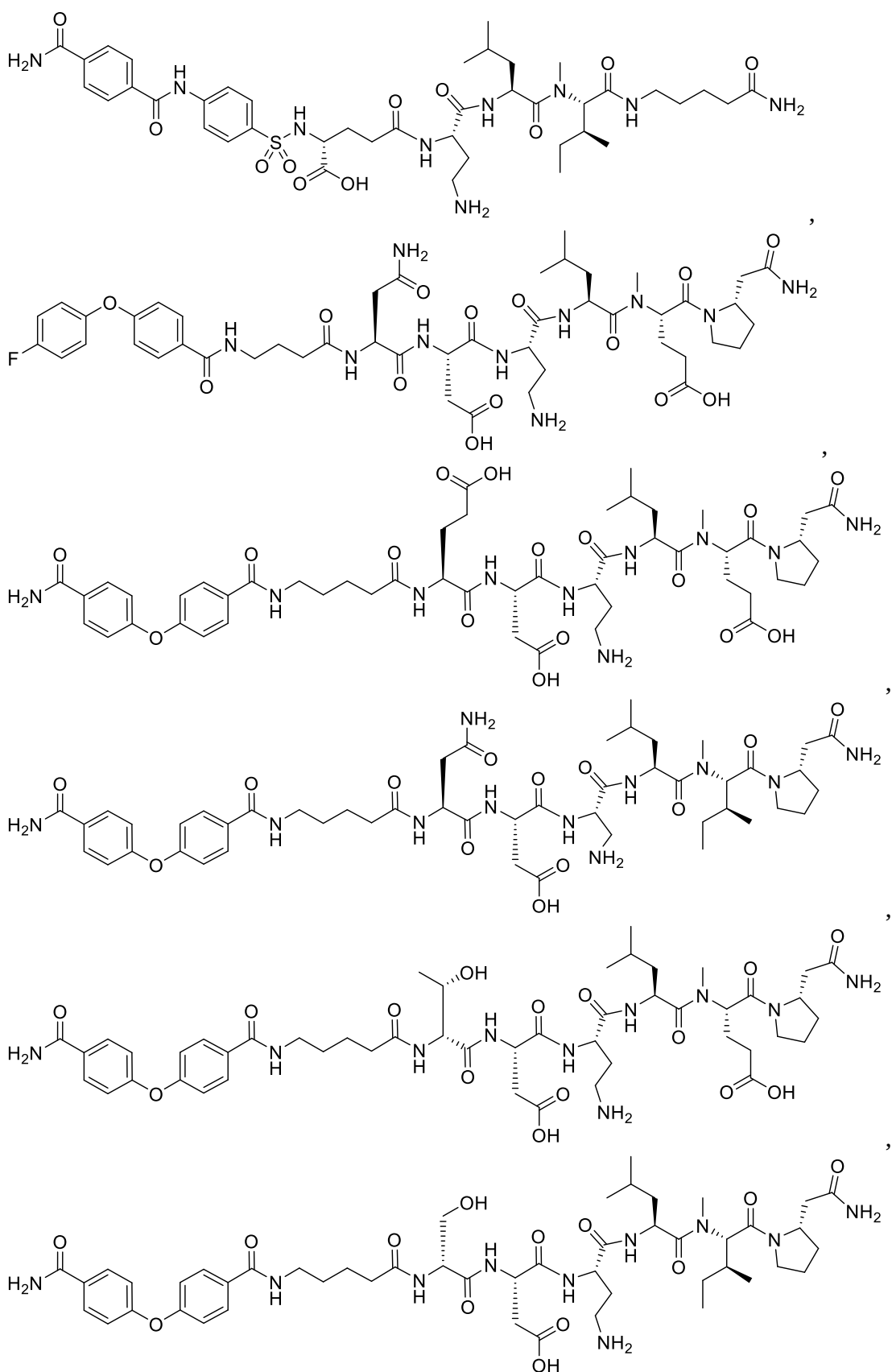
10 (10) Provided as another embodiment of the present invention is the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of (1) to (5), wherein the substituted polypeptide is selected from compounds shown in the following:





5





5

(11) Provided as another embodiment of the present invention is a pharmaceutical comprising

the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of (1) to (10) as an active ingredient.

(12) Provided as another embodiment of the present invention is an MMP2 inhibitor comprising the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of (1) to (10) as an active ingredient.

(13) Provided as another embodiment of the present invention is an agent for suppressing growth, infiltration, or metastasis of cancer cells, comprising the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of (1) to (10) as an active ingredient.

(14) Provided as another embodiment of the present invention is an agent for suppressing fibrogenesis comprising the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of (1) to (10) as an active ingredient.

(15) Provided as another embodiment of the present invention is a drug for preventing or treating cancerous disease or organ fibrosis, or a symptom associated with cancerous disease or organ fibrosis, comprising the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of (1) to (10) as an active ingredient.

ADVANTAGEOUS EFFECTS OF INVENTION

The compounds of the present invention (hereinafter, occasionally referred to as "the present inventive compounds") have an effect to inhibit MMP2. Some of the present inventive compounds have an effect to selectively inhibit MMP2.

DESCRIPTION OF EMBODIMENTS

The present invention provides a substituted polypeptide represented by formula [I], or a pharmaceutically acceptable salt thereof, having an effect to inhibit MMP2.

The compounds of the present invention will be described in more detail in the following; however, the present invention is not limited to exemplified ones.

Herein, "amino acid" is, in a broad sense, an organic compound having two

functional groups: amino and carboxy. In a narrow sense (in particular, in the field of biochemistry), "amino acid" refers to " α -amino acid" (the α -amino acid is an amino acid in which amino is bonding to the carbon atom to which carboxy is bonding (α carbon)) that serves as a constituent unit of biogenic proteins.

5 Examples of amino acids in the present specification include natural proteogenic L-amino acids; natural nonproteogenic amino acids; and nonnatural amino acids. Examples of nonnatural amino acids include the D-forms of natural proteogenic L-amino acids; chemically modified amino acids such as amino acid variants and derivatives; and chemically synthesized compounds having properties that are characteristic to amino acids and known in
10 the art.

 Herein, when "amino acid" is shown as its name without abbreviating, for example, as a three-letter code or a one-letter code, the name indicates the amino acid in the L-form, D-form, or both.

 Herein, when "amino acid" is shown as an abbreviation, for example, in a
15 three-letter code or a one-letter code, the abbreviation indicates the amino acid in the L-form. "L" or "l" is occasionally added immediately before "amino acid" to explicitly show that the amino acid is in the L-form.

 Herein, "D" or "d" added immediately before "amino acid" indicates that the amino acid is in the D-form.

20 Herein, "natural proteogenic L-amino acid" is a naturally occurring amino acid in L-form that constitutes proteins, and examples thereof include Gly, Ala, Val, Leu, Ile, Pro, Phe, His, Trp, Tyr, Ser, Thr, Met, Cys, Asp, Glu, Asn, Gln, Lys, and Arg.

 Herein, "D-form of natural proteogenic L-amino acid" refers to an enantiomer of the natural proteogenic L-amino acid. Natural proteogenic L-amino acids except glycine each
25 have at least one asymmetric carbon, thus being optically active. The structures of these amino acids are classified into L-forms and D-forms on the basis of the structures of the L-form and D-form of glyceraldehyde.

 Amino acids other than natural proteogenic L-amino acids can also have D-forms.

Herein, "natural nonproteogenic amino acid" is a naturally occurring amino acid that does not constitute proteins, and examples thereof include L-norleucine (hereinafter, also designated as Nle; hereinafter, "code following in parentheses" shows an abbreviation), β -alanine (β -Ala), and L-ornithine (Orn).

5 If a natural nonproteogenic amino acid has an asymmetric carbon, there exist an L-form and a D-form for the amino acid. There can be L-forms and D-forms also for amino acids other than natural nonproteogenic amino acids.

 Herein, "nonnatural amino acid" refers to an amino acid that does not constitute proteins and is primarily artificially produced, being an amino acid not included in the
10 above-described "natural proteogenic L-amino acid and natural nonproteogenic amino acid". Examples of nonnatural amino acids include the D-forms of natural proteogenic L-amino acids (such as D-Cys, D-Ser); α -methylamino acids (such as 2-aminoisobutyric acid (Aib)); amino acids with excessive methylene in the side chain ("homo" amino acids such as L- β -homoproline (β -Hep or β -homoPro), L-homoserine (Hes or homoSer), L-homocysteine
15 (Hec or homoCys), L-homoproline (homoPro), L-homoglutamic acid (homoGlu)); amino acids in which the side chain of an amino acid with a carboxylic acid functional group is substituted with a sulfonic acid group (such as L-cysteic acid); chemically modified amino acids such as amino acid variants and derivatives (such as hydroxyproline, L-2,3-diaminopropionic acid (Dap), L-2,4-diaminobutyric acid (Dab), N-methylglycine); and
20 chemically synthesized compounds having properties that are characteristic to amino acids and known in the art (such as 4-aminobenzoic acid).

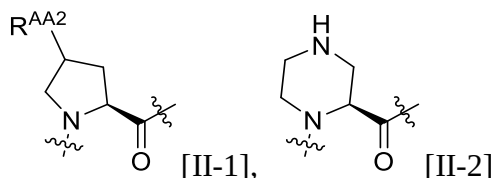
 If a nonnatural amino acid has an asymmetric carbon, there exist an L-form and a D-form for the amino acid.

 Specific examples of "nonnatural amino acid" in the present specification include
25 the followings:

- (d)-Pro, (d)-Ser, (d)-Thr, (d)-Asp, (d)-Glu, (d)-Arg, (d)-Lys
- β -homoPro
- β -Ala, GABA, Ape, Acp

- (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp, (N-Me)Glu

- a group represented by formula [II-1] or formula [II-2]:

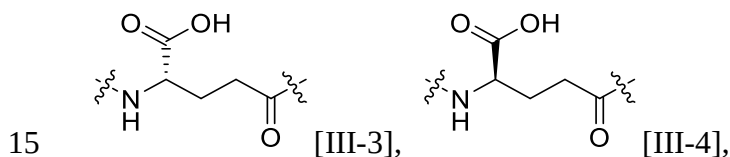
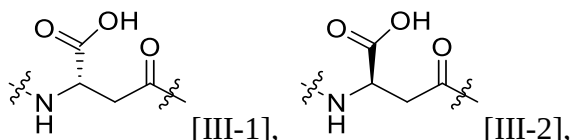


5 wherein R^{AA2} is hydroxy or amino; and

- amino acids listed later in Table 1 and Table 2

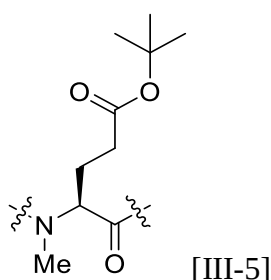
The nitrogen atom involved in peptide bonding in any amino acid in the present specification may be alkylated. In this case, the amino acid is also called "N-alkyl amino acid". Examples of the alkyl include methyl and ethyl.

10 Herein, the expression " β -Asp" means aspartic acid involved in amide bonding of the main chain via carboxy in the side chain, as illustrated in the structure represented by formula [III-1]. Likewise, the expressions " β -(d)-Asp", " γ -Glu", and " γ -(d)-Glu" mean the structures represented by formula [III-2] to formula [III-4].



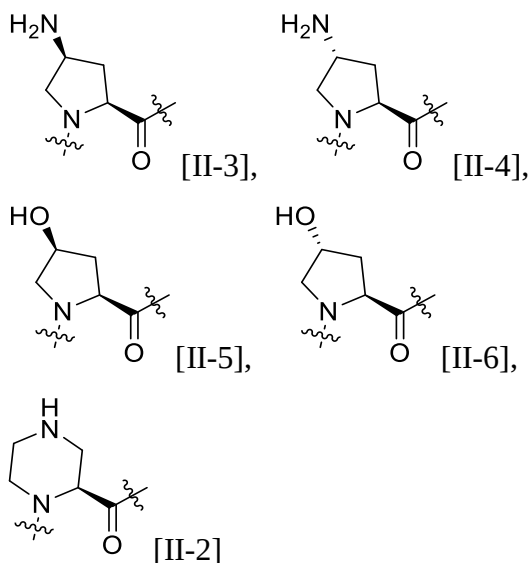
15

The expression "(N-Me)Glu(OtBu)" means the N-methyl form of the amino acid (Glu(OtBu)), as illustrated in the structure represented by formula [III-5].



The expression "(2S,4S)-(4-amino)Pro" on the structure corresponding to AA² means the structure represented by formula [II-3]. Likewise, the expressions "(2S,4R)-(4-amino)Pro", "(2S,4S)-(4-hydroxy)Pro", and "(2S,4R)-(4-hydroxy)Pro" mean the structures represented by formula [II-4] to formula [II-6]. Further, the expression

5 "(S)-piperazine" means the structure represented by formula [II-2].



Herein, "n" indicates normal, "i" indicates iso, "s" indicates secondary, "t" and "tert" each indicate tertiary, "c" indicates cyclo, "o" indicates ortho, "m" indicates meta, and "p" indicates para.

"Halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

"C₁₋₆ alkyl" refers to linear or branched alkyl having one to six carbon atoms.

15 Examples of "C₁₋₆ alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, and n-hexyl.

"Halo C₁₋₆ alkyl" refers to linear or branched alkyl having one to six carbon atoms and substituted with a halogen atom. A preferred number of halogen atoms as substituents is one to five, and a preferred halogen atom is a fluorine atom. Examples of "halo

20 C₁₋₆ alkyl" include monofluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,2,2,2-pentafluoroethyl, 2-fluoroethyl, 2-fluoro-2-methylpropyl, 2,2-difluoropropyl, 1-fluoro-2-methylpropan-2-yl,

1,1-difluoro-2-methylpropan-2-yl, 1-fluoropentyl, 1-fluorohexyl, and
2,2,2-trifluoro-1-methylethyl.

"Aryl" refers to a monocyclic aromatic hydrocarbon group or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms. Examples of "aryl" include
5 phenyl, naphthyl, and anthryl.

"Aromatic ring" refers to a monocyclic aromatic hydrocarbon group or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms. Examples of "aromatic ring" include a benzene ring, a naphthalene ring, and an anthracene ring.

Partially saturated aryl is also included in the scope of "aryl". The same is applied
10 to aromatic rings. "Partially saturated aryl" and the corresponding aromatic ring, "partially saturated aromatic ring", refer to a group wherein a monocyclic aromatic hydrocarbon group or fused polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms is partially saturated, and a ring having such a structure. Examples thereof include dihydroindenyl and a dihydroindene ring.

15 "Heteroaryl" refers to a five- to seven-membered monocyclic aromatic heterocyclic group consisting of one to six carbon atoms and one or more atoms that are same or different and selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom, or a fused polycyclic aromatic heterocyclic group composed of 9 to 14 atoms, specifically, consisting of 1 to 13 carbon atoms and one or more atoms that are same or different and
20 selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom. Examples of "heteroaryl" include imidazolyl, pyrazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isooxazolyl, oxadiazolyl, pyrrolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, benzopyrazolyl, benzotriazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, and quinoxalyl.

25 "Heteroaromatic ring" refers to a five- to seven-membered monocyclic aromatic heterocycle consisting of one to six carbon atoms and one or more atoms that are same or different and selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom, or a fused polycyclic aromatic heterocycle composed of 9 to 14 atoms,

specifically, consisting of 1 to 13 carbon atoms and one or more atoms that are same or different and selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom. Examples of "heteroaromatic ring" include an imidazole ring, a pyrazole ring, a thiophene ring, a thiazole ring, an isothiazole ring, a thiadiazole ring, an oxazole ring, an isoxazole ring, an oxadiazole ring, a pyrrole ring, a triazole ring, a tetrazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, a triazine ring, an indole ring, a benzopyrazole ring, a benzotriazole ring, a benzofuran ring, a benzothiophene ring, a quinoline ring, an isoquinoline ring, and a quinoxaline ring.

Partially saturated heteroaryl is also included in the scope of "heteroaryl". The same is applied to heteroaromatic rings. "Partially saturated heteroaryl", and the corresponding heteroaromatic ring, "partially saturated heteroaromatic ring", refer to a five- to seven-membered partially saturated monocyclic heterocyclic group consisting of one to six carbon atoms and one or more atoms that are same or different and selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom, or a partially saturated fused polycyclic heterocyclic group composed of 9 to 14 atoms, specifically, consisting of 1 to 13 carbon atoms and one or more atoms that are same or different and selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom, and a ring having such a structure. Examples thereof include oxazolidinyl, thiazolinyl, dihydropyridinyl, dihydrobenzofuranyl, chromanyl, dihydropyranopyridinyl, dihydrofuropyridinyl, tetrahydroquinolyl, dihydrobenzodioxinyl, tetrahydrotriazoloazepinyl, an oxazolidine ring, a thiazoline ring, a dihydropyridine ring, a dihydrobenzofuran ring, a chroman ring, a dihydropyranopyridine ring, a dihydrofuropyridine ring, a tetrahydroquinoline ring, a tetrahydroquinoline ring, a dihydrobenzodioxine ring, and a tetrahydrotriazoloazepine ring.

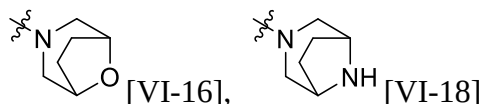
"Four- to seven-membered saturated heterocyclyl containing nitrogen atom" refers to a four- to seven-membered monocyclic saturated heterocyclic group consisting of one nitrogen atom and three to six carbon atoms, and may further contain, in addition to the nitrogen atom, one atom selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom. Examples of "four- to seven-membered saturated heterocyclyl

containing nitrogen atom" include azetidiny, pyrrolidinyl, piperidinyl, azepanyl, morpholinyl, thiomorpholinyl, and piperazinyl.

"Four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom" refers to a four- to seven-membered

5 monocyclic saturated heterocyclic group consisting of one nitrogen atom and three to six carbon atoms, and may further contain, in addition to the nitrogen atom, one atom selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom. Examples "four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom" include azetidiny, pyrrolidinyl, piperidinyl, 10 azepanyl, morpholinyl, thiomorpholinyl, and piperazinyl.

Examples of "four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom, and optionally crosslinked with C₁₋₄ alkanediyl" include 8-oxa-3-azabicyclo[3.2.1]octan-3-yl (the group represented by formula [VI-16]) and 3,8-diazabicyclo[3.2.1]octan-3-yl (the group represented by formula 15 [VI-18]):



"C₁₋₆ alkoxy" refers to linear or branched alkoxy having one to six carbon atoms.

Examples "C₁₋₆ alkoxy" include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, and n-hexyloxy.

20 "Halo C₁₋₆ alkoxy" refers to linear or branched alkoxy having one to six carbon atoms and substituted with a halogen atom. A preferred number of halogen atoms as substituents is one to five, and a preferred halogen atom is a fluorine atom. Examples of "halo C₁₋₆ alkoxy" include monofluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-fluoroethoxy, 1,1-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2-fluoroethoxy, 25 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, 1,3-difluoropropan-2-yloxy, 2-fluoro-2-methylpropoxy, 2,2-difluoropropoxy, 1-fluoro-2-methylpropan-2-yloxy, 1,1-difluoro-2-methylpropan-2-yloxy, and 4,4,4-trifluorobutoxy.

"C₁₋₆ alkylcarbonyl" refers to a group in which "C₁₋₆ alkyl" described above and carbonyl are bonding together. Examples of "C₁₋₆ alkylcarbonyl" include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, and n-hexylcarbonyl.

5 "C₁₋₆ alkylcarbonylamino" refers to a group in which "C₁₋₆ alkylcarbonyl" described above and an amino group are bonding together. Examples of "C₁₋₆ alkylcarbonylamino" include methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, n-butylcarbonylamino, isobutylcarbonylamino, sec-butylcarbonylamino, tert-butylcarbonylamino, n-pentylcarbonylamino, and
10 n-hexylcarbonylamino.

"C₁₋₆ alkylamino" refers to amino having one or two "C₁₋₆ alkyl" described above, as substituents, that are same or different. Examples of "C₁₋₆ alkylamino" include methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-pentylamino, n-hexylamino, dimethylamino, diethylamino,
15 di(n-propyl)amino, di(isopropyl)amino, ethylmethylamino, and methyl(n-propyl)amino.

"Mono C₁₋₆ alkylamino" refers to amino having one "C₁₋₆ alkyl" described above as a substituent. Examples of "mono C₁₋₆ alkylamino" include methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-pentylamino, and n-hexylamino.

20 "Di C₁₋₆ alkylamino" refers to amino having two "C₁₋₆ alkyl" described above, as substituents, that are same or different. Examples of "di C₁₋₆ alkylamino" include dimethylamino, diethylamino, di(n-propyl)amino, di(isopropyl)amino, ethylmethylamino, and methyl(n-propyl)amino.

"Mono C₁₋₆ alkylaminocarbonyl" refers to a group in which "mono C₁₋₆ alkylamino" described above and carbonyl are bonding together. Examples of "mono
25 C₁₋₆ alkylaminocarbonyl" include methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, isobutylaminocarbonyl, n-pentylaminocarbonyl, and n-hexylaminocarbonyl.

"Di C₁₋₆ alkylaminocarbonyl" refers to a group in which "di C₁₋₆ alkylamino" described above and carbonyl are bonding together. Examples of "di C₁₋₆ alkylaminocarbonyl" include dimethylaminocarbonyl, diethylaminocarbonyl, di(n-propyl)aminocarbonyl, di(isopropyl)aminocarbonyl, ethylmethylaminocarbonyl, and methyl(n-propyl)aminocarbonyl.

"C₁₋₆ alkylcarbonyl" refers to a group in which "C₁₋₆ alkyl" described above and carbonyl are bonding together. Examples of "C₁₋₆ alkylcarbonyl" include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, and n-hexylcarbonyl.

"C₂₋₁₆ alkylcarbonyl" refers to a group in which linear or branched alkyl having 2 to 16 carbon atoms and carbonyl are bonding together. Examples of "C₂₋₁₆ alkylcarbonyl" include ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-decylcarbonyl(undecanoyl), n-dodecylcarbonyl(tridecanoyl), and n-tetradecylcarbonyl(pentadecanoyl).

"C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy" refers to a group in which a terminus of "C₂₋₁₆ alkyl" in "C₂₋₁₆ alkylcarbonyl" described above is substituted with carboxy. Examples of "C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy" include 11-carboxyundecanoyl, 13-carboxytridecanoyl, and 15-carboxypentadecanoyl.

"C₁₋₆ alkylsulfonyl" refers to a group in which "C₁₋₆ alkyl" described above and sulfonyl are bonding together. Examples of "C₁₋₆ alkylsulfonyl" include methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, and n-hexylsulfonyl.

"C₁₋₃ alkanediyl" refers to a divalent hydrocarbon formed by removing one hydrogen atom from alkyl having one to three carbon atoms. Examples of "C₁₋₃ alkanediyl" include methanediyl, ethane-1,1-diyl, ethane-1,2-diyl, propane-1,1-diyl, propane-1,3-diyl, and propane-2,2-diyl.

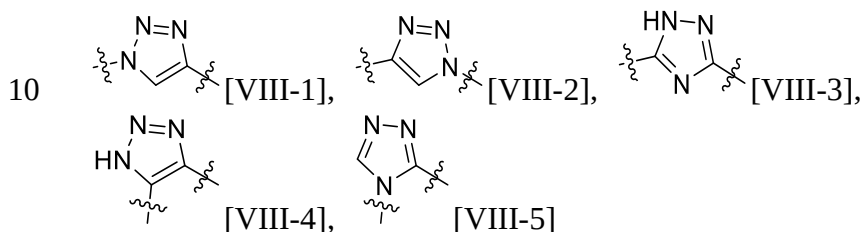
"C₁₋₄ alkanediyl" refers to a divalent hydrocarbon formed by removing one hydrogen atom from alkyl having one to four carbon atoms. Examples of "C₁₋₄ alkanediyl" include

methanediyl, ethane-1,1-diyl, ethane-1,2-diyl, propane-1,1-diyl, propane-1,3-diyl, propane-2,2-diyl, and butane-1,4-diyl.

"C₂₋₃ alkenediyl" refers to a divalent unsaturated hydrocarbon formed by removing one hydrogen atom from alkenyl having two or three carbon atoms. Examples of

- 5 "C₂₋₃ alkenediyl" include ethene-1,1-diyl, ethene-1,2-diyl, prop-1-ene-1,1-diyl, prop-2-ene-1,1-diyl, prop-1-ene-1,3-diyl, prop-2-ene-1,3-diyl, and prop-1-ene-2,2-diyl.

"Triazolediyl" refers to divalent triazole formed by removing two hydrogen atoms from a triazole ring. Examples of "triazolediyl" include structures represented by formulas [VIII-1] to [VIII-5]:



Abbreviations used herein indicate structures listed in Table 1 to Table 4.

[Table 1-1]

#	Formula number	Abbreviation	Structure
1	[III-6]	β -Dap	
2	[III-7]	β -(d)-Dap	
3	[III-8]	γ -Dab	
4	[III-9]	γ -(d)-Dab	
5	[III-10]	δ -Orn	
6	[III-11]	δ -(d)-Orn	

7	[III-12]	ϵ -Lys	
8	[III-13]	ϵ -(d)-Lys	

[Table 2-1]

#	Formula number	Abbreviation	Structure
1	[IV-1]	Aib	
2	[IV-2]	Nle	
3	[IV-3]	Ala(cPropyl)	
4	[IV-4]	Ala(2-Pyr)	
5	[IV-5]	Ala(4-Thz)	
6	[IV-6]	homoSer	
7	[IV-7]	Dap	

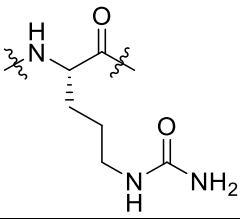
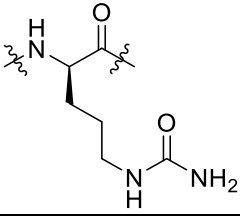
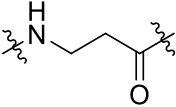
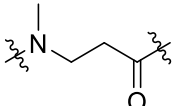
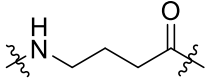
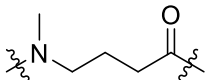
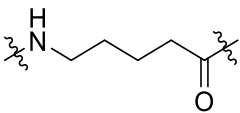
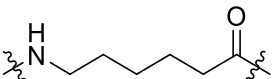
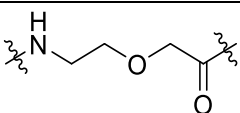
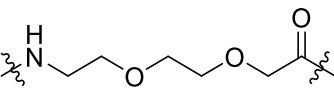
8	[IV-8]	Dap(Me)	
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[Table 2-2]

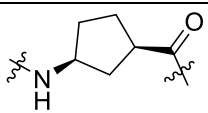
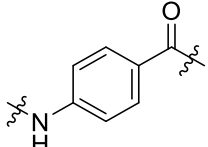
#	Formula number	Abbreviation	Structure
9	[IV-9]	Dab	
10	[IV-10]	(d)-Dab	
11	[IV-11]	Dab(Me)	
12	[IV-12]	Dab(Me) ₂	
13	[IV-13]	Orn	
14	[IV-14]	Lys(Ac)	

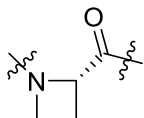
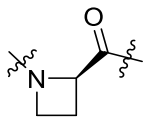
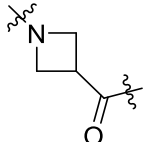
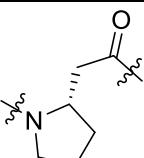
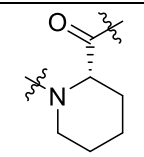
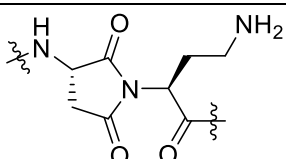
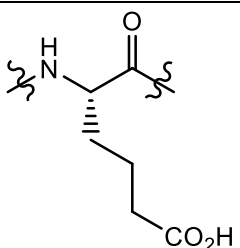
[Table 2-3]

#	Formula number	Abbreviation	Structure
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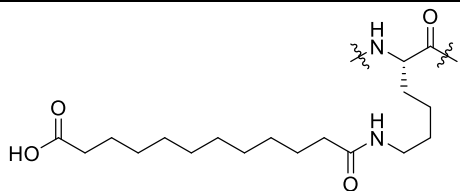
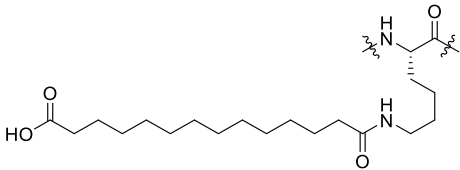
15	[IV-15]	Cit	
16	[IV-16]	(d)-Cit	
17	[IV-17]	β -Ala	
18	[IV-18]	(N-Me)- β -Ala	
19	[IV-19]	GABA	
20	[IV-20]	(N-Me)GABA	
21	[IV-21]	Ape	
22	[IV-22]	Acp	
23	[IV-23]	-NH-(CH ₂) ₂ -O-CH ₂ -CO-	
24	[IV-24]	Adox	

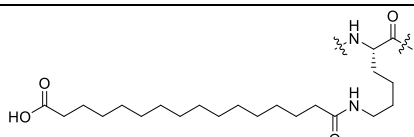
[Table 2-4]

#	Formula number	Abbreviation	Structure
25	[IV-25]	cis-NH(3)cPen	
26	[IV-26]	(4)Abz	

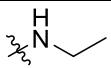
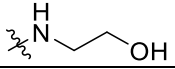
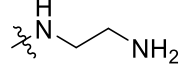
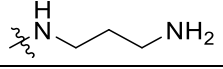
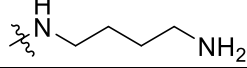
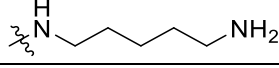
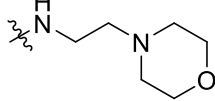
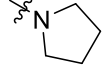
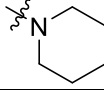
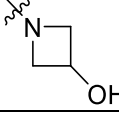
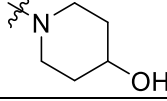
27	[IV-27]	Aze(2)	
28	[IV-28]	(d)-Aze(2)	
29	[IV-29]	Aze(3)	
30	[IV-30]	β -homoPro	
31	[IV-31]	homoPro	
32	[IV-32]	aspartimide-Dab	
33	[IV-33]	homoGlu	

[Table 3-1]

#	Formula number	Abbreviation	Structure
1	[V-1]	Lys(CO-(CH ₂) ₁₀ -CO ₂ H)	
2	[V-2]	Lys(CO-(CH ₂) ₁₂ -CO ₂ H)	

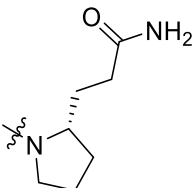
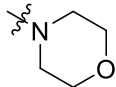
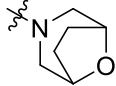
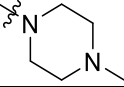
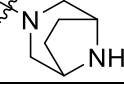
3	[V-3]	Lys(CO-(CH ₂) ₁₄ -CO ₂ H)	
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[Table 4-1]

#	Formula number	Abbreviation	Structure
1	[VI-1]	-NHMe	
2	[VI-2]	-NHEt	
3	[VI-3]	-NH-(CH ₂) ₂ -OH	
4	[VI-4]	-NH-(CH ₂) ₂ -NH ₂	
5	[VI-5]	-NH-(CH ₂) ₃ -NH ₂	
6	[VI-6]	-NH-(CH ₂) ₄ -NH ₂	
7	[VI-7]	-NH-(CH ₂) ₅ -NH ₂	
8	[VI-8]	the formula [VI-8]	
9	[VI-9]	azetidin-1-yl	
10	[VI-10]	pyrrolidin-1-yl	
11	[VI-11]	piperidin-1-yl	
12	[VI-12]	(3-OH)azetidin-1-yl	
13	[VI-13]	(4-OH)piperidin-1-yl	

[Table 4-2]

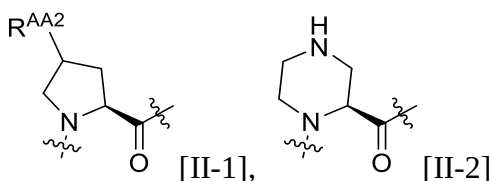
#	Formula number	Abbreviation	Structure
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14	[VI-14]	the formula [VI-14]	
15	[VI-15]	morpholin-4-yl	
16	[VI-16]	the formula [VI-16]	
17	[VI-17]	(4-Me)piperazin-1-yl	
18	[VI-18]	the formula [VI-18]	

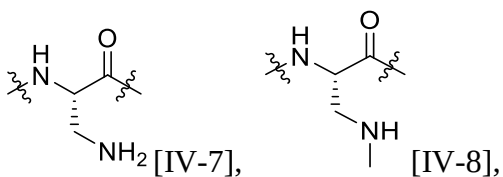
Preferable embodiments of the substituted polypeptide represented by formula [I'], or pharmaceutically acceptable salt thereof according to the present invention are as follows.

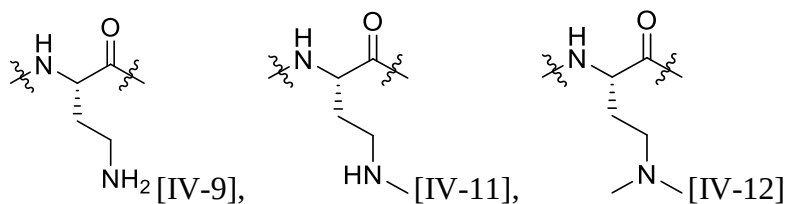
- 5 Preferable AA¹ is Asp, β-Asp, β-(d)-Asp, γ-Glu, or γ-(d)-Glu,
one more preferable AA¹ is β-Asp, γ-Glu, or γ-(d)-Glu,
wherein further preferable AA¹ is γ-(d)-Glu,
another more preferable AA¹ is β-(d)-Asp or γ-(d)-Glu,
wherein further preferable AA¹ is β-(d)-Asp, and
10 another more preferable AA¹ is Asp.

Preferable AA² is a group represented by formula [II-1] or formula [II-2]:



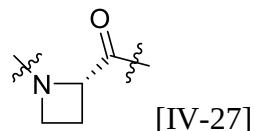
a group represented by formula [IV-7], [IV-8], [IV-9], [IV-11], or [IV-12]:





Ala,

a group represented by formula [IV-27]:

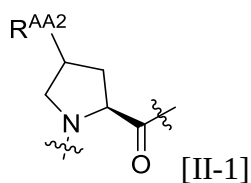


5 , or

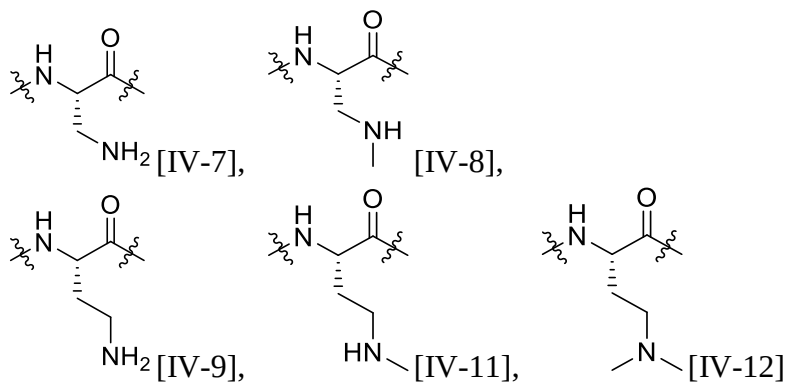
Pro,

wherein preferable $\text{R}^{\text{AA}2}$ is hydroxy or amino,

more preferable AA^2 is a group represented by formula [II-1]:



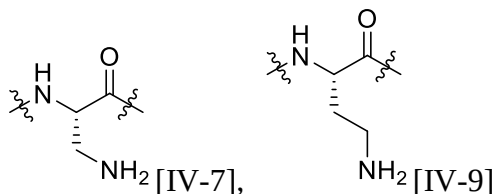
10 or a group represented by formula [IV-7], [IV-8], [IV-9], [IV-11], or [IV-12]:



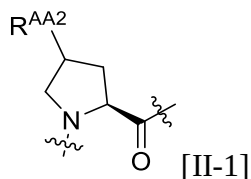
wherein preferable $\text{R}^{\text{AA}2}$ is amino,

further preferable AA^2 is

15 a group represented by formula [IV-7] or [IV-9]:



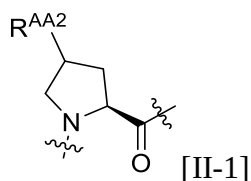
or a group represented by formula [II-1]:



wherein preferable R^{AA2} is amino,

one particularly preferable AA^2 is

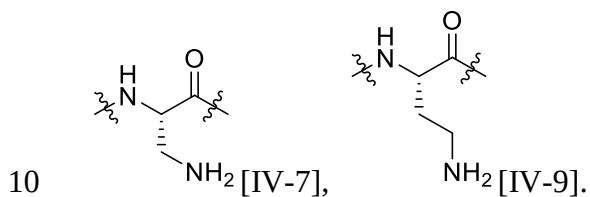
5 a group represented by formula [II-1]:



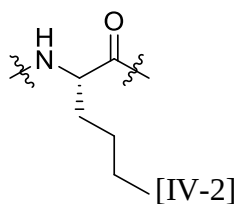
wherein preferable R^{AA2} is amino, and

another particularly preferable AA^2 is

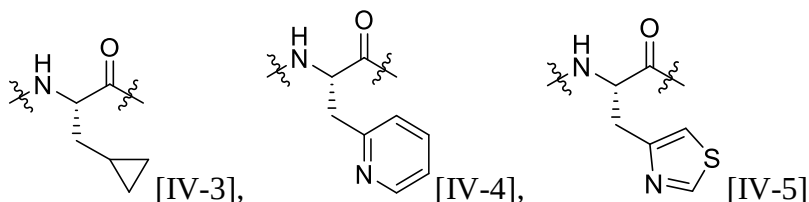
a group represented by formula [IV-7] or [IV-9]:



Preferable AA^3 is Val, Leu, Ile, a group represented by formula [IV-2]:



Phe, a group represented by formula [IV-3], [IV-4], or [IV-5]:



15 or Trp,

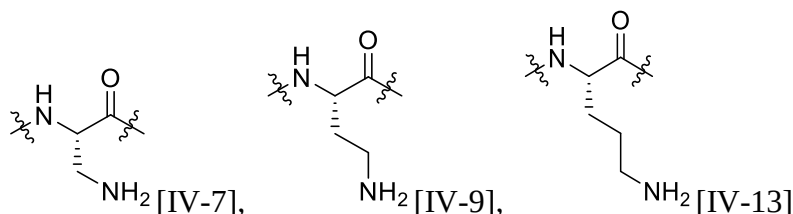
more preferable AA^3 is Val, Leu, Ile, Phe, or Trp,

further preferable AA^3 is Val, Leu, or Ile,

one particularly preferable AA³ is Val,
another particularly preferable AA³ is Leu, and
another particularly preferable AA³ is Ile.

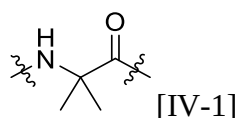
Preferable AA⁴ is a single bond, Pro, Gly, homoSer, Met, Glu, (N-Me)Ala,
5 (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Met,
(N-Me)Asp, (N-Me)Glu, (d)-Pro, (d)-Ala, (d)-Phe, (d)-Tyr, (d)-Ser, (d)-Thr, or
(d)-(N-Me)Glu,
more preferable AA⁴ is (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe,
(N-Me)Tyr, (N-Me)Ser, (N-Me)Met, (N-Me)Asp, (N-Me)Glu, (d)-Pro, (d)-Ala, (d)-Phe,
10 (d)-Tyr, (d)-Ser, (d)-Thr, or (d)-(N-Me)Glu,
one further preferable AA⁴ is (N-Me)Glu or (N-Me)Asp,
wherein particularly preferable AA⁴ is (N-Me)Glu, and
another further preferable AA⁴ is (N-Me)Ile, (N-Me)Val, or (N-Me)Leu,
wherein particularly preferable AA⁴ is (N-Me)Ile.

15 Preferable AA⁵ is β -Ala, GABA, Ape, Acp, Pro, (d)-Pro, β -homoPro, a single bond,
Arg, (d)-Arg,
a group represented by [IV-7], [IV-9], or [IV-13]:

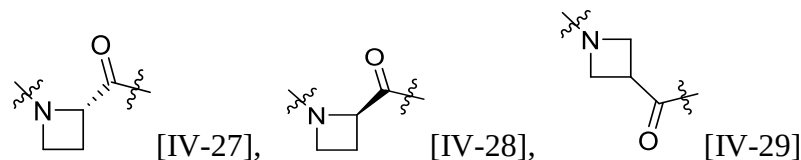


Lys, (d)-Lys,

20 Ala, a group represented by formula [IV-1]:

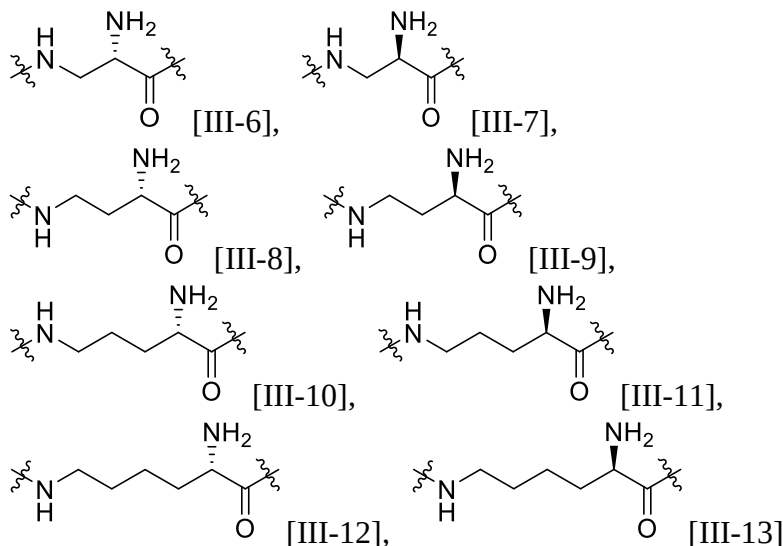


a group represented by formula [IV-27], [IV-28], or [IV-29]:



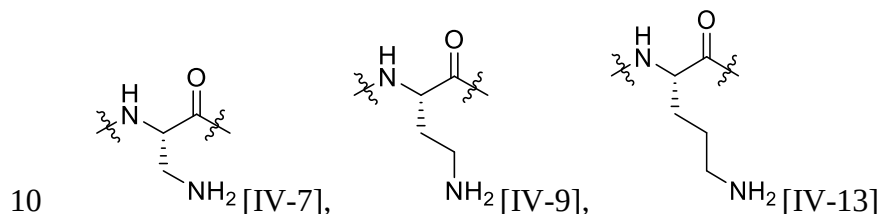
Phe, His, Thr, or

a group represented by any of formulas [III-6] to [III-13]:



more preferable AA⁵ is β-Ala, GABA, Ape, Acp, Pro, (d)-Pro, β-homoPro, a single bond, Arg, (d)-Arg,

a group represented by formula [IV-7], [IV-9], or [IV-13]:



Lys, or (d)-Lys,

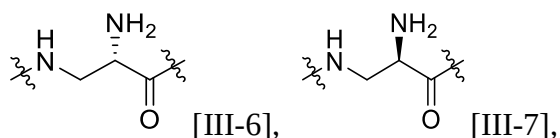
further preferable AA⁵ is β-Ala, GABA, Ape, Acp, Pro, (d)-Pro, or β-homoPro, and particularly preferable AA⁵ is β-Ala, GABA, Ape, Acp, or β-homoPro.

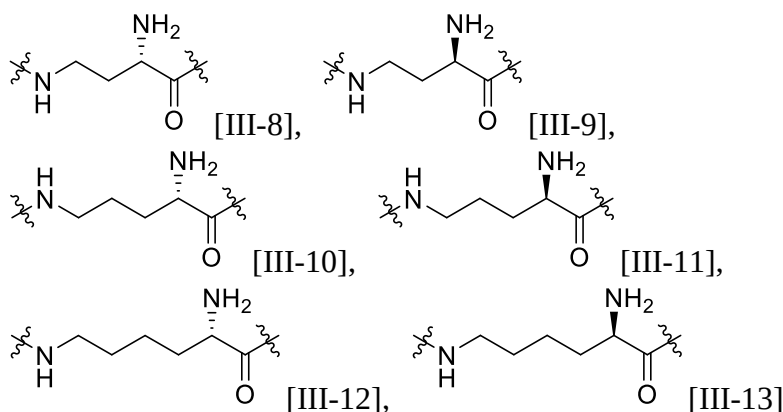
Preferable W¹ is -L¹- or -L^{1'}-L^{1''}-,

15 wherein L¹ is a single bond,

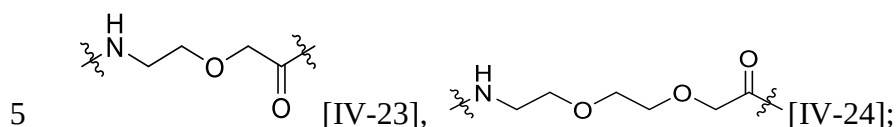
L^{1'} is selected from the group consisting of β-Ala, GABA, Ape, Acp,

a group represented by any of formulas [III-6] to [III-13]:





, and a group represented by any of formulas [IV-23] and [IV-24]:

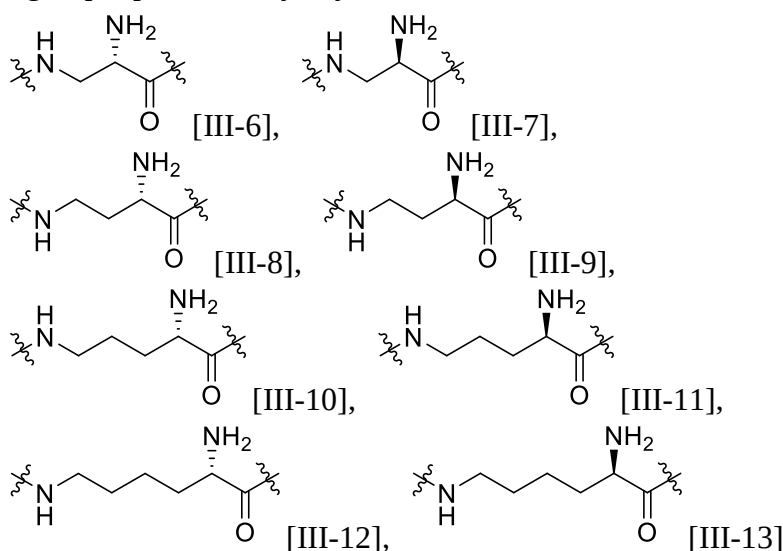


, and $L^{1''}$ is a single bond, Asn, (d)-Ser, (d)-Thr, Lys, Arg, or Glu,
one more preferable W^1 is $-L^1-$ or $-L^1-L^{1''}-$,

wherein L^1 is a single bond,

L^1 is β-Ala, GABA, Ape, Acp, or

10 a group represented by any of formulas [III-6] to [III-13]:



15 , and $L^{1''}$ is Asn, (d)-Ser, (d)-Thr, or Glu,

wherein further preferable W^1 is $-L^1-$ or $-L^1-L^{1''}-$,

wherein L^1 is a single bond,

L^1 is β-Ala, GABA, Ape, or Acp, and

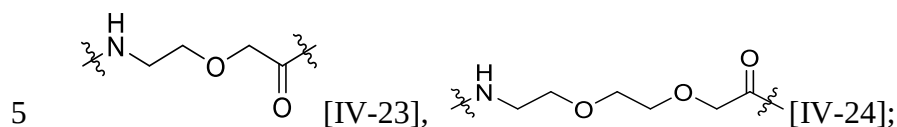
$L^{1''}$ is Asn, (d)-Ser, (d)-Thr, or Glu,

wherein particularly preferable W^1 is $-L^1-$,

wherein L^1 is a single bond, and

another more preferable W^1 is $-L^{1'}-L^{1''}-$,

wherein $L^{1'}$ is a group represented by formula [IV-23] or [IV-24]:



, and $L^{1''}$ is a single bond.

Preferable L^2 is a single bond.

Preferable L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$,

one more preferable L^{N1} is the formula $-C(=O)-$, and

10 another more preferable L^{N1} is the formula $-S(=O)_2-$.

Preferable L^{N2} is a single bond, the formula $-O-$, or the formula $-C(=O)-NH-$,

more preferable L^{N2} is the formula $-O-$ or the formula $-C(=O)-NH-$,

one further preferable L^{N2} is the formula $-O-$, and

another further preferable L^{N2} is the formula $-C(=O)-NH-$.

15 Preferable ring A is a benzene ring or a pyridine ring,

more preferable ring A is a benzene ring,

preferable R^{A1} and R^{A2} are each independently a hydrogen atom or a halogen atom, and

more preferable R^{A1} and R^{A2} are each a hydrogen atom.

Preferable ring B is phenyl or pyridyl,

20 more preferable ring B is phenyl,

preferable R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkoxy, or halo C_{1-6} alkoxy, and

more preferable R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, C_{1-6} alkoxy, or halo C_{1-6} alkoxy.

25 Preferable W^C is a single bond or a linker consisting of one to three amino acids,

wherein

the one to three amino acids forming the linker are not limited, but preferably same or

different and each selected from the group consisting of: Gly, Pro, Arg, (d)-Arg, Lys, (d)-Lys, β -Ala, GABA, and Ape, wherein

if Lys or (d)-Lys is included in the group represented by W^C ,

then the amino in the side chain of the Lys or (d)-Lys is optionally substituted with:

- 5 C_{2-16} alkylcarbonyl terminally-substituted with carboxy,
 Lys, wherein the amino in the side chain of the Lys is optionally substituted with
 C_{2-16} alkylcarbonyl terminally-substituted with carboxy, or
 (d)-Lys, wherein the amino in the side chain of the (d)-Lys is optionally substituted
 with C_{2-16} alkylcarbonyl terminally-substituted with carboxy,
- 10 more preferable W^C is a single bond, Pro, Arg, (d)-Arg, Lys, (d)-Lys, or (d)-Lys-(d)-Lys,
 further preferable W^C is a single bond, Arg, (d)-Arg, Lys, or (d)-Lys,
 one particularly preferable W^C is a single bond, and
 another particularly preferable W^C is (d)-Lys.

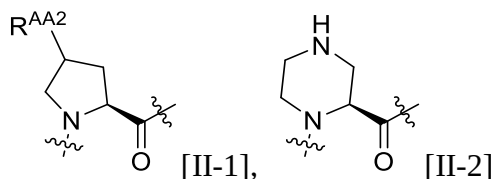
 Preferable R^C is:

- 15 the formula -OH, the formula -NH₂,
 C_{1-6} alkylamino, wherein the C_{1-6} alkyl of the C_{1-6} alkylamino is optionally
 substituted with one group selected from the group consisting of hydroxy, amino, and a four-
 to seven-membered saturated heterocyclyl containing one nitrogen atom, or
 four- to seven-membered saturated heterocyclyl containing one nitrogen atom and
20 optionally further containing one heteroatom, wherein the four- to seven-membered saturated
 heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom
 is optionally substituted with one group selected from the group consisting of hydroxy, and
 C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one carbamoyl; and two
 carbon atoms in the four- to seven-membered saturated heterocyclyl containing one nitrogen
25 atom and optionally further containing one heteroatom are optionally crosslinked with
 C_{1-4} alkanediyl,
 more preferable R^C is the formula -OH or the formula -NH₂, and
 further preferable R^C is the formula -NH₂.

Another preferable embodiment of the compounds of the present invention is a substituted polypeptide represented by formula [I'], or a pharmaceutically acceptable salt thereof, wherein

AA¹ is β-Asp, γ-Glu, or γ-(d)-Glu,

5 AA² is a group represented by formula [II-1] or formula [II-2]:



wherein R^{AA2} is hydroxy or amino,

AA³ is Val, Leu, Ile, Phe, or Trp,

AA⁴ is a single bond, Pro, (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe,

10 (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp, or (N-Me)Glu,

AA⁵ is a single bond, Pro, (d)-Pro, β-homoPro, Arg, (d)-Arg, Lys, (d)-Lys, β-Ala, GABA, Ape, or Acp,

W¹ is L¹, and L¹ is a single bond,

L² is a single bond,

15 L^{N1} is the formula -S(=O)₂-,

L^{N2} is a single bond, the formula -O-, or the formula -C(=O)-NH-,

ring A is a benzene ring,

R^{A1} and R^{A2} are each a hydrogen atom,

ring B is phenyl,

20 R^{B1}, R^{B2}, and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, or C₁₋₆ alkoxy,

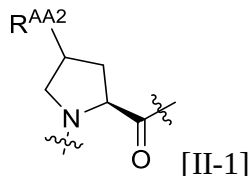
W^C is a single bond, Pro, Arg, (d)-Arg, Lys, (d)-Lys, or (d)-Lys-(d)-Lys, and

R^C is the formula -NH₂.

Another preferable embodiment of the present invention is a substituted polypeptide
 25 represented by formula [I'], or a pharmaceutically acceptable salt thereof, wherein
 AA¹ is β-Asp, γ-Glu, or γ-(d)-Glu,

wherein further preferable AA¹ is γ -(d)-Glu,

AA² is a group represented by formula [II-1]:



wherein R^{AA2} is amino,

5 AA³ is Val, Leu, or Ile,

wherein one further preferable AA³ is Val,

another further preferable AA³ is Leu, and

another further preferable AA³ is Ile,

AA⁴ is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu,

10 wherein one further preferable AA⁴ is (N-Me)Val, (N-Me)Leu, or (N-Me)Ile,

wherein particularly preferable AA⁴ is (N-Me)Ile,

another further preferable AA⁴ is (N-Me)Asp or (N-Me)Glu,

wherein particularly preferable AA⁴ is (N-Me)Glu,

AA⁵ is Pro, (d)-Pro, β -homoPro, β -Ala, GABA, Ape, or Acp,

15 wherein one further preferable AA⁵ is Pro, (d)-Pro, or β -homoPro,

wherein particularly preferable AA⁵ is β -homoPro,

another further preferable AA⁵ is β -Ala, GABA, Ape, or Acp,

wherein particularly preferable AA⁵ is β -Ala, GABA, or Ape,

W¹ is L¹,

20 L¹ is a single bond,

L² is a single bond,

L^{N1} is the formula -S(=O)₂-,

L^{N2} is a single bond, the formula -O-, or the formula -C(=O)-NH-,

wherein one further preferable L^{N1} is the formula -C(=O)-, and

25 another further preferable L^{N1} is the formula -S(=O)₂-,

ring A is a benzene ring,

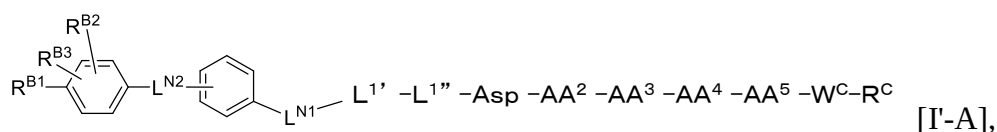
R^{A1} and R^{A2} are each a hydrogen atom,

ring B is phenyl,

R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, or C_{1-6} alkoxy,

- 5 W^C is a single bond or (d)-Lys,
wherein one further preferable W^C is a single bond, and
another further preferable W^C is (d)-Lys, and
 R^C is the formula $-NH_2$.

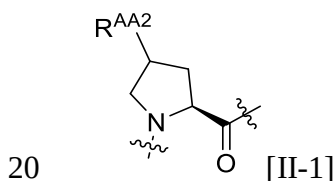
- Another preferable embodiment of the compounds of the present invention is the
10 substituted polypeptide or a pharmaceutically acceptable salt thereof, wherein
 W^1 is $-L^{1'}-L^{1''}-$,
 L^2 is a single bond, and
the polypeptide is represented by formula [I'-A]:



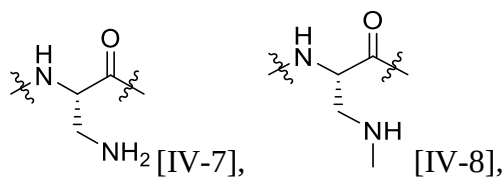
- 15 wherein preferable embodiments of AA^2 , AA^3 , AA^4 , AA^5 , $L^{1'}$, $L^{1''}$, L^{N1} , L^{N2} , R^{B1} , R^{B2} , R^{B3} , W^C , and R^C are as described above.

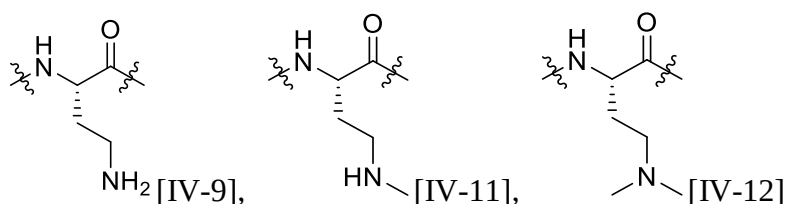
In a more preferable embodiment of the polypeptide represented by formula [I'-A] or a pharmaceutically acceptable salt thereof,

AA^2 is a group represented by formula [II-1]:



or a group represented by formula [IV-7], [IV-8], [IV-9], [IV-11], or [IV-12]:





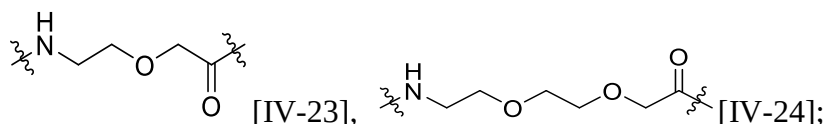
wherein $R^{\text{AA}2}$ is amino,

AA^3 is Val, Leu, Ile, Phe, or Trp,

AA^4 is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu,

5 AA^5 is β -Ala, GABA, Ape, Acp, Pro, (d)-Pro, or β -homoPro,

$L^{1'}$ is β -Ala, GABA, Ape, Acp, or a group represented by formula [IV-23] or [IV-24]:



$L^{1''}$ is a single bond, Asn, (d)-Ser, (d)-Thr, or Glu,

$L^{\text{N}1}$ is the formula $-\text{C}(=\text{O})-$ or the formula $-\text{S}(=\text{O})_2-$,

10 $L^{\text{N}2}$ is the formula $-\text{O}-$ or the formula $-\text{C}(=\text{O})-\text{NH}-$,

$R^{\text{B}1}$, $R^{\text{B}2}$, and $R^{\text{B}3}$ are each independently a hydrogen atom, carbamoyl, a halogen atom,

C_{1-6} alkoxy, or halo C_{1-6} alkoxy,

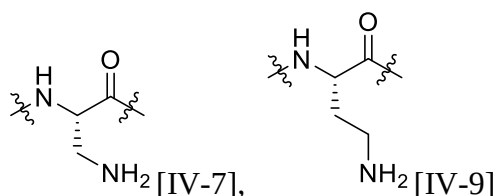
W^{C} is a single bond, Arg, (d)-Arg, Lys, or (d)-Lys, and

R^{C} is the formula $-\text{OH}$ or the formula $-\text{NH}_2$.

15 In a further preferable embodiment of the polypeptide represented by formula [I'-A]

or a pharmaceutically acceptable salt thereof,

AA^2 is a group represented by formula [IV-7] or [IV-9]:



AA^3 is Val, Leu, or Ile,

20 AA^4 is (N-Me)Ile or (N-Me)Glu,

AA^5 is β -Ala, GABA, Ape, Acp, or β -homoPro,

$L^{1'}$ is GABA or Ape,

$L^{1''}$ is Asn, Glu, (d)-Ser, or (d)-Thr,

L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$,

L^{N2} is the formula $-O-$ or the formula $-C(=O)-NH-$,

R^{B1} is carbamoyl or fluorine atom,

5 R^{B2} is a hydrogen atom,

R^{B3} is a hydrogen atom,

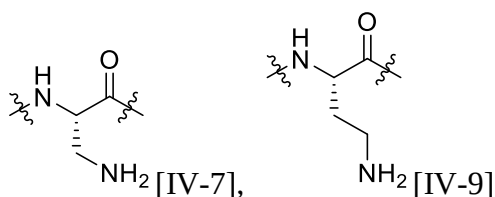
W^C is a single bond, and

R^C is the formula $-NH_2$.

One particularly preferable mode of the present embodiment is as follows.

10 In the polypeptide represented by formula [I'-A] or a pharmaceutically acceptable salt thereof,

AA^2 is a group represented by formula [IV-7] or [IV-9]:



AA^3 is Val,

15 AA^3 may be Leu,

AA^3 may be Ile,

AA^4 is (N-Me)Ile,

AA^4 may be (N-Me)Glu,

AA^5 is β -Ala, GABA, Ape, or Acp,

20 AA^5 may be β -homoPro,

$L^{1'}$ is GABA or Ape,

$L^{1''}$ is Asn, Glu, (d)-Ser, or (d)-Thr,

the combination of $L^{1'}$ and $L^{1''}$ is preferably GABA-Asn, Ape-Asn, Ape-Glu, Ape-(d)-Ser, or Ape-(d)-Thr,

25 L^{N1} is the formula $-C(=O)-$,

L^{N1} may be the formula $-S(=O)_2-$,

L^{N2} is the formula $-O-$, and L^{N2} may be the formula $-C(=O)-NH-$,

R^{B1} is carbamoyl or fluorine atom,

R^{B2} is a hydrogen atom,

5 R^{B3} is a hydrogen atom,

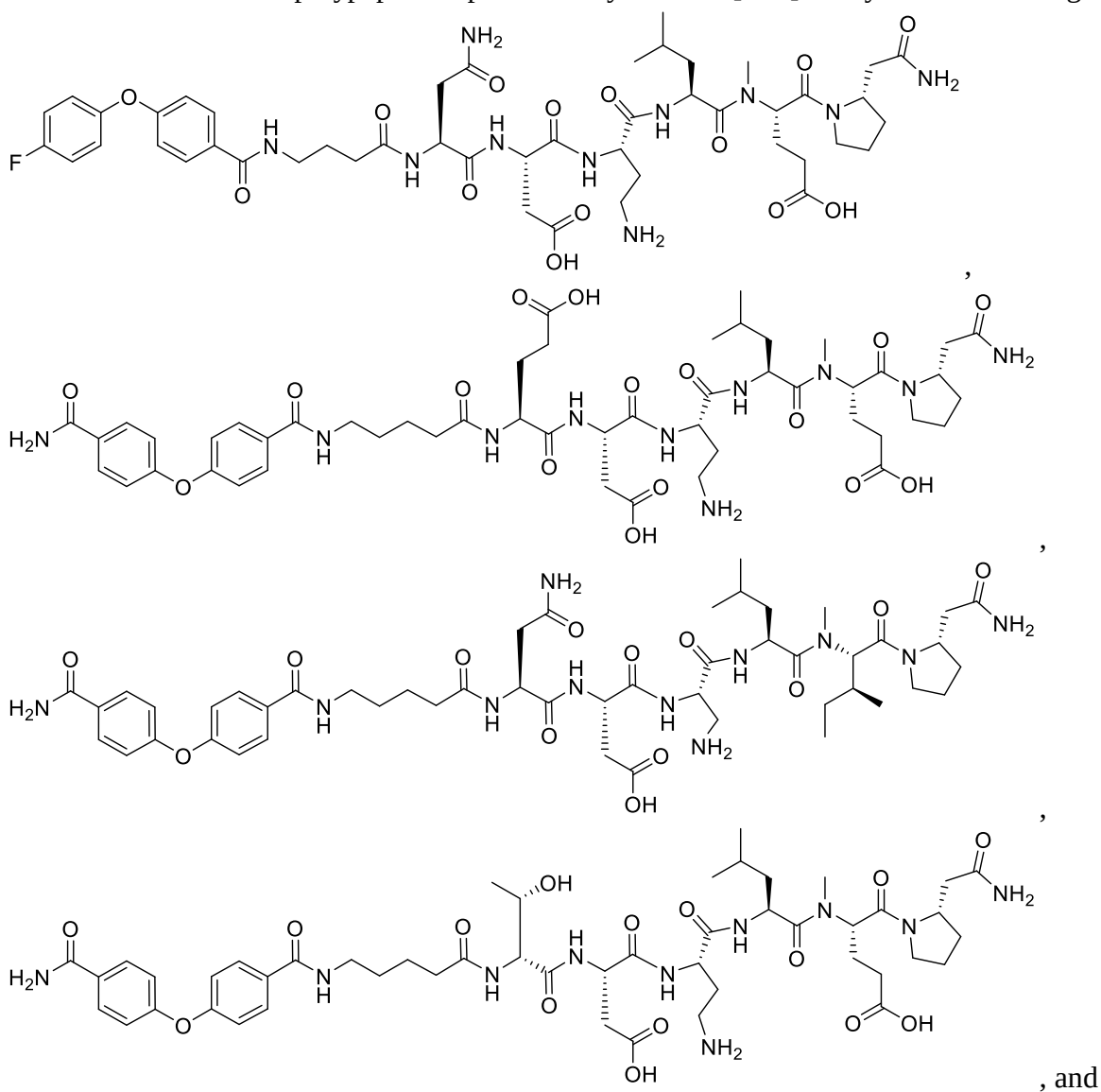
W^C is a single bond, and

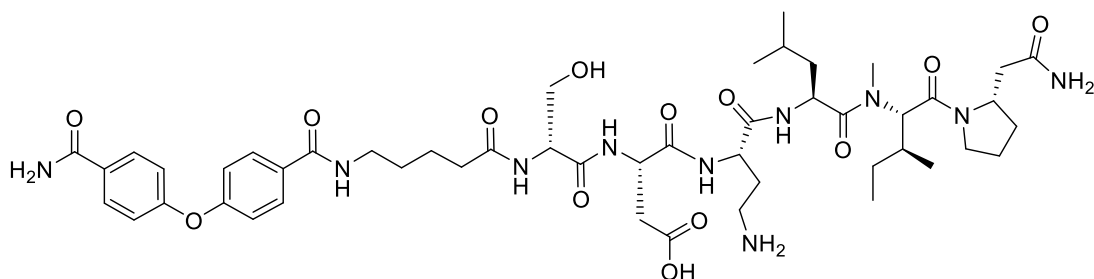
R^C is the formula $-NH_2$.

In another particularly preferable mode of the present embodiment,

the substituted polypeptide represented by formula [I'-A] is any of the followings:

10



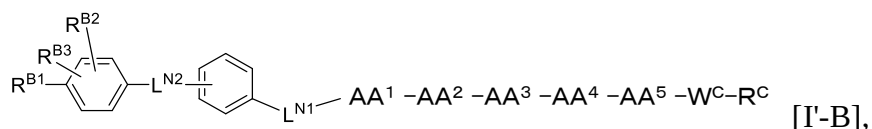


Another preferable embodiment of the compounds of the present invention is the substituted polypeptide or a pharmaceutically acceptable salt thereof,

wherein W^1 is $-L^1-$, wherein L^1 is a single bond,

5 L^2 is a single bond, and

the substituted polypeptide is represented by formula [I'-B]:

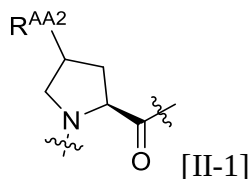


wherein preferable embodiments of AA^1 , AA^2 , AA^3 , AA^4 , AA^5 , L^{N1} , L^{N2} , R^{B1} , R^{B2} , R^{B3} , W^C , and R^C are as described above.

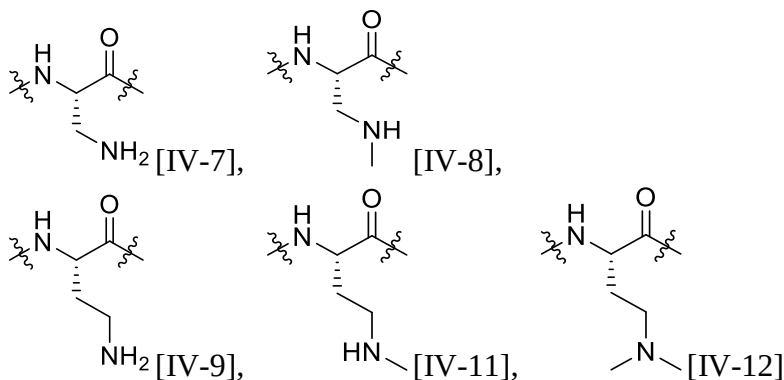
10 In a more preferable embodiment of the polypeptide represented by formula [I'-B] or a pharmaceutically acceptable salt thereof,

AA^1 is β -Asp, β -(d)-Asp, γ -Glu, or γ -(d)-Glu,

AA^2 is a group represented by formula [II-1]:



15 or a group represented by formula [IV-7], [IV-8], [IV-9], [IV-11], or [IV-12]:



wherein R^{AA2} is amino,

AA³ is Val, Leu, Ile, Phe, or Trp,

AA⁴ is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu,

AA⁵ is β -Ala, GABA, Ape, Acp, or β -homoPro,

L^{N1} is the formula -C(=O)- or the formula -S(=O)₂-,

5 L^{N2} is a single bond, the formula -O-, or the formula -C(=O)-NH-,

R^{B1}, R^{B2}, and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom,

C₁₋₆ alkoxy, or halo C₁₋₆ alkoxy,

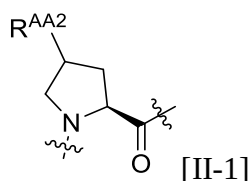
W^C is a single bond, Arg, (d)-Arg, Lys, or (d)-Lys, and

R^C is the formula -OH or the formula -NH₂.

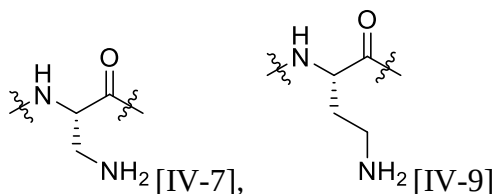
10 In a further preferable embodiment of the polypeptide represented by formula [I'-B] or a pharmaceutically acceptable salt thereof,

AA¹ is β -(d)-Asp or γ -(d)-Glu,

AA² is a group represented by formula [II-1]:



15 or a group represented by formula [IV-7] or [IV-9]:



wherein R^{AA2} is amino,

AA³ is Val, Leu, or Ile,

AA⁴ is (N-Me)Ile or (N-Me)Glu,

20 AA⁵ is β -Ala, GABA, Ape, Acp, or β -homoPro,

L^{N1} is the formula -C(=O)- or the formula -S(=O)₂-,

L^{N2} is the formula -O- or the formula -C(=O)-NH-,

R^{B1} is carbamoyl, a chlorine atom, a bromine atom, methoxy, or trifluoromethoxy,

R^{B2} is a hydrogen atom,

R^{B3} is a hydrogen atom,

W^C is a single bond or (d)-Lys, and

R^C is the formula $-NH_2$.

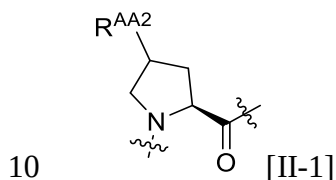
One particularly preferable mode of the present embodiment is as follows.

5 In the polypeptide represented by formula [I'-B] or a pharmaceutically acceptable salt thereof,

AA^1 is β -(d)-Asp,

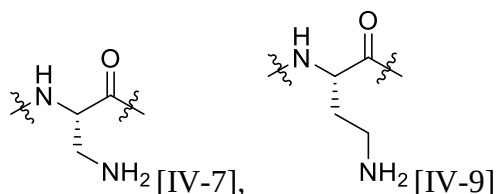
AA^1 may be γ -(d)-Glu,

AA^2 is a group represented by formula [II-1]:



wherein R^{AA2} is amino,

AA^2 may be a group represented by formula [IV-7] or [IV-9]:



AA^3 is Val,

15 AA^3 may be Leu,

AA^3 may be Ile,

AA^4 is (N-Me)Ile,

AA^4 may be (N-Me)Glu,

AA^5 is β -Ala, GABA, Ape, or Acp,

20 AA^5 may be β -homoPro,

L^{N1} is the formula $-C(=O)-$,

L^{N1} may be the formula $-S(=O)_2-$,

L^{N2} is the formula $-O-$,

L^{N2} may be the formula $-C(=O)-NH-$,

R^{B1} is carbamoyl, a chlorine atom, a bromine atom, methoxy, or trifluoromethoxy,

R^{B2} is a hydrogen atom,

R^{B3} is a hydrogen atom,

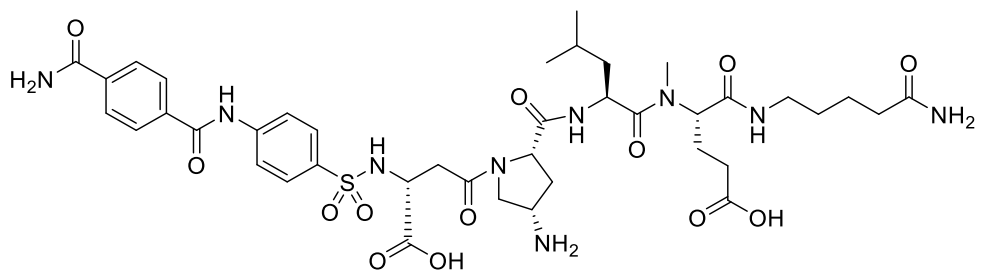
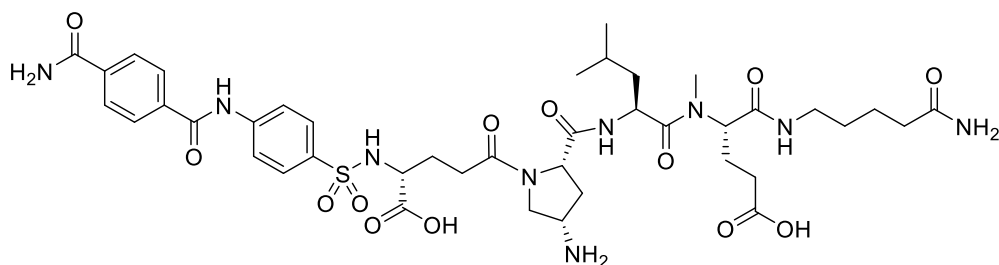
W^C is a single bond,

5 W^C may be (d)-Lys, and

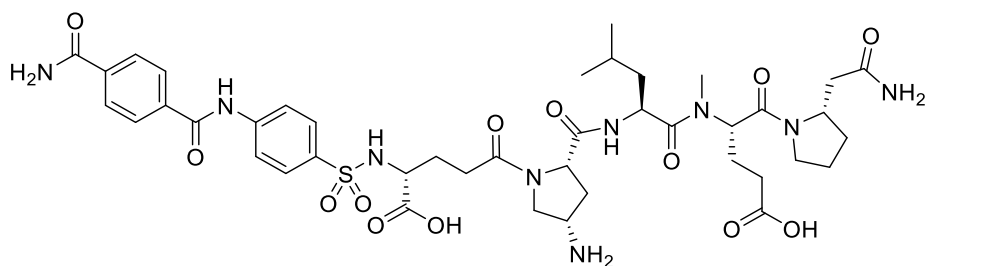
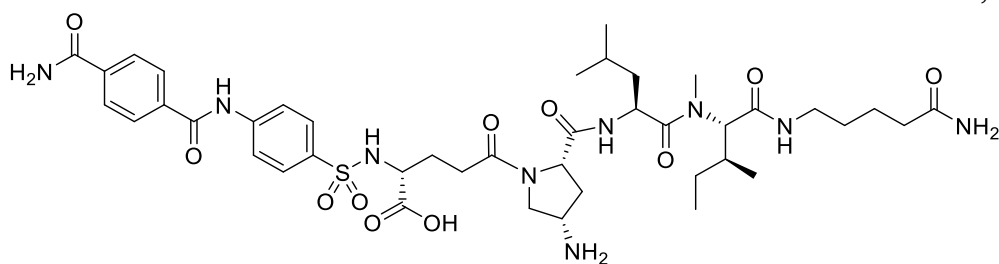
R^C is the formula $-NH_2$.

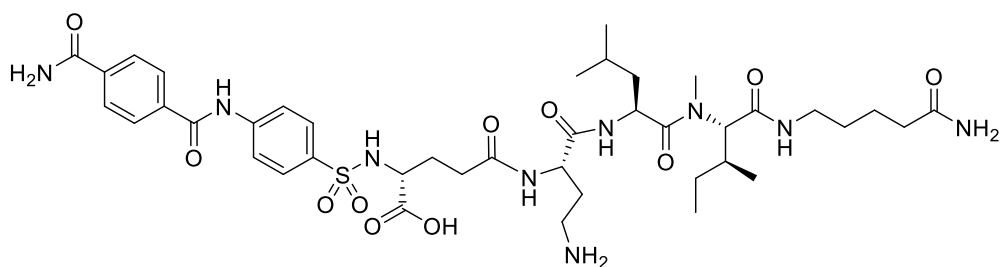
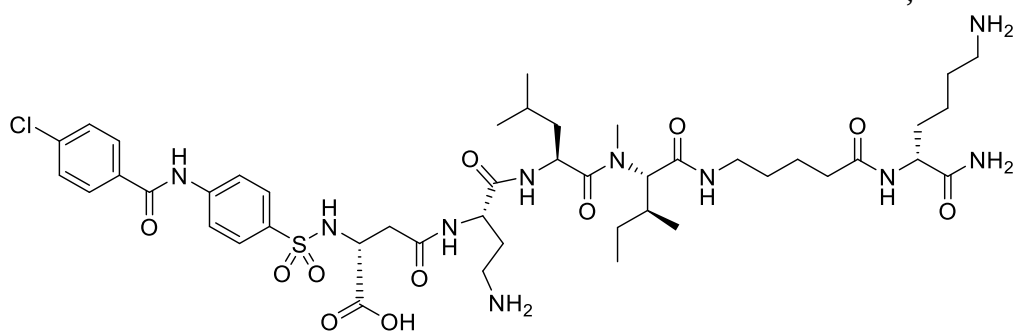
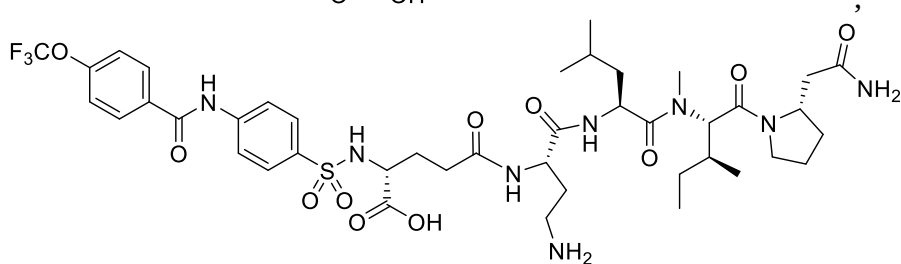
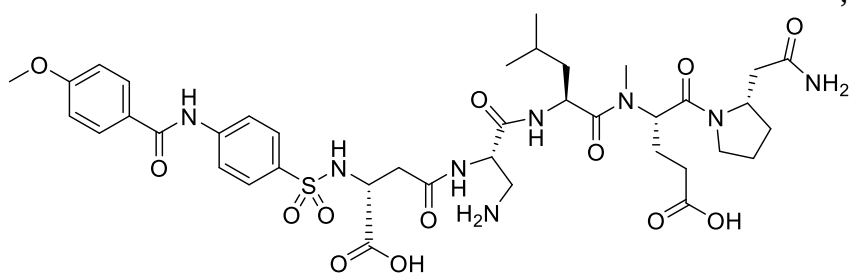
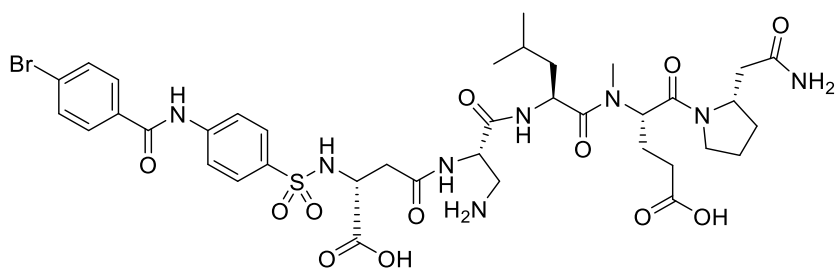
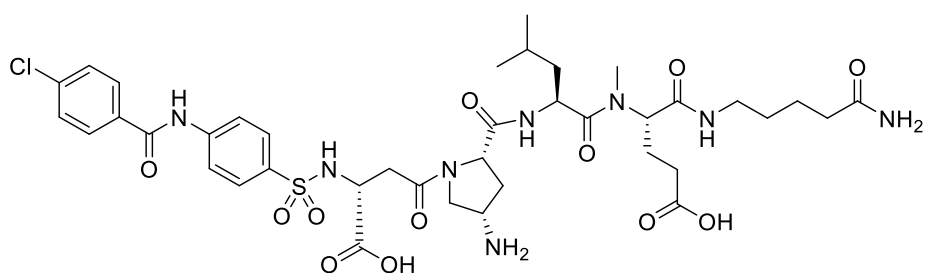
In another particularly preferable mode of the present embodiment,

the substituted polypeptide represented by formula [I'-B] is any of the followings:



10





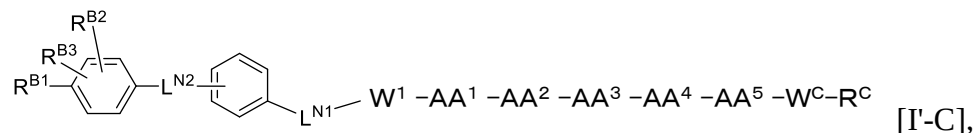
5

, and

Another preferable embodiment of the compounds of the present invention is the substituted polypeptide or a pharmaceutically acceptable salt thereof,

wherein L^2 is a single bond, and

the substituted polypeptid is represented by formula [I'-C]:



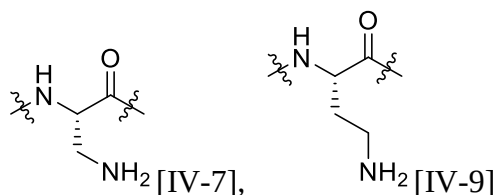
wherein

- 5 preferable embodiments of AA^1 , AA^2 , AA^3 , AA^4 , AA^5 , W^1 , L^{N1} , L^{N2} , R^{B1} , R^{B2} , R^{B3} , W^C , and R^C are as described above.

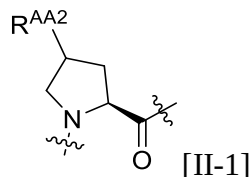
In a more preferable embodiment of the polypeptide represented by formula [I'-C] or a pharmaceutically acceptable salt thereof,

AA^1 is Asp, β -(d)-Asp, or γ -(d)-Glu,

- 10 AA^2 is a group represented by formula [IV-7] or [IV-9]:



or a group represented by formula [II-1]:



wherein R^{AA2} is amino,

- 15 AA^3 is Val, Leu, or Ile,
 AA^4 is (N-Me)Ile or (N-Me)Glu,

AA^5 is Ape or β -homoPro,

W^1 is $-L^1-$ or $-L^{1'}-L^{1''}-$,

wherein L^1 is a single bond,

- 20 $L^{1'}$ is GABA or Ape, and
 $L^{1''}$ is Asn, (d)-Ser, (d)-Thr, or Glu,
 L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$,

L^{N2} is the formula -O- or the formula -C(=O)-NH-,

R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom, C_{1-6} alkoxy, or halo C_{1-6} alkoxy,

W^C is a single bond or (d)-Lys, and

5 R^C is the formula -NH₂.

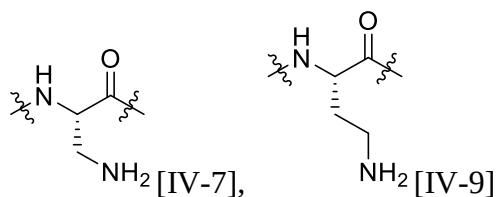
In a further preferable embodiment of the polypeptide represented by formula [I'-C] or a pharmaceutically acceptable salt thereof,

AA^1 is Asp,

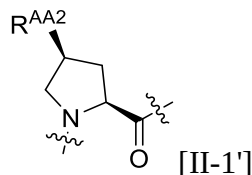
AA^1 may be β -(d)-Asp,

10 AA^1 may be γ -(d)-Glu,

AA^2 is a group represented by formula [IV-7] or [IV-9]:



AA^2 may be a group represented by formula [II-1']:



15 wherein R^{AA2} is amino,

AA^3 is Val,

AA^3 may be Leu,

AA^3 may be Ile,

AA^4 is (N-Me)Ile,

20 AA^4 may be (N-Me)Glu,

AA^5 is Ape,

AA^5 may be β -homoPro,

W^1 is -L¹- or -L^{1'}-L^{1''}-,

L^1 is a single bond,

the combination of $L^{1'}$ and $L^{1''}$ ($-L^{1'}-L^{1''}-$) is GABA-Asn, Ape-Asn, Ape-Glu, Ape-(d)-Ser, or Ape-(d)-Thr,

L^{N1} is the formula $-C(=O)-$,

L^{N1} may be the formula $-S(=O)_2-$,

5 L^{N2} is the formula $-O-$,

L^{N2} may be the formula $-C(=O)-NH-$,

R^{B1} is carbamoyl, a chlorine atom, a bromine atom, methoxy, or trifluoromethoxy,

R^{B2} is a hydrogen atom,

R^{B3} is a hydrogen atom,

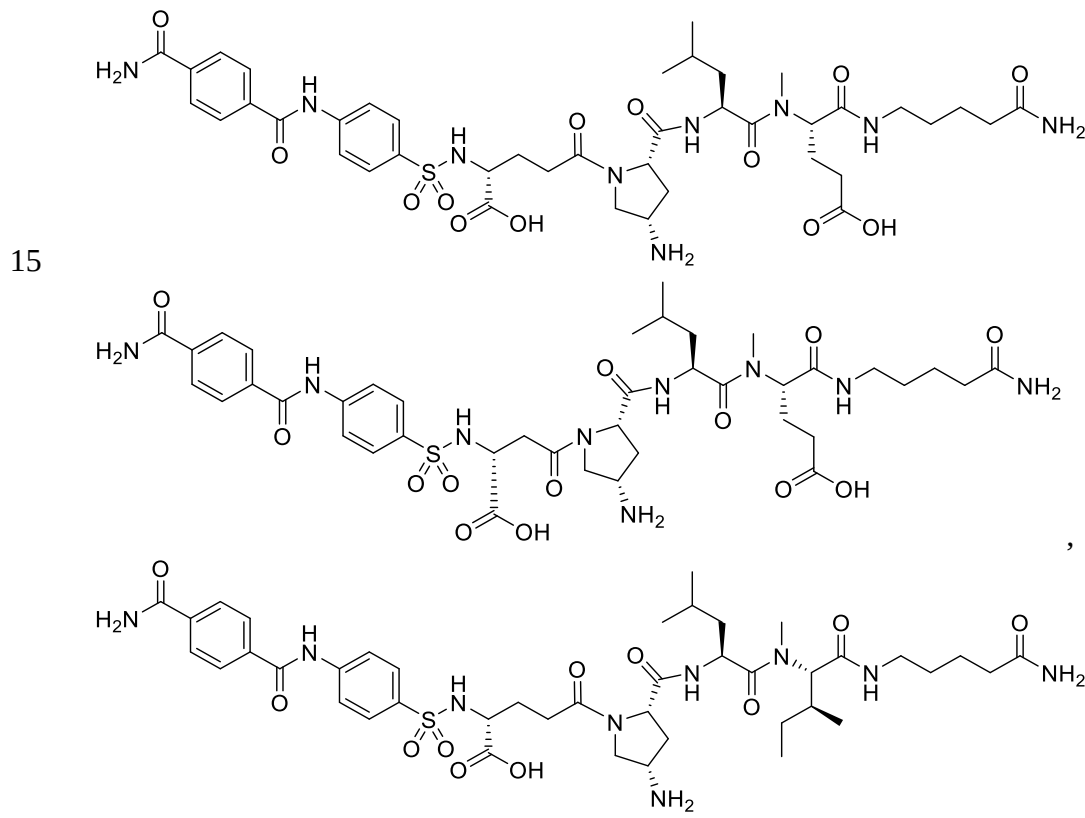
10 W^C is a single bond,

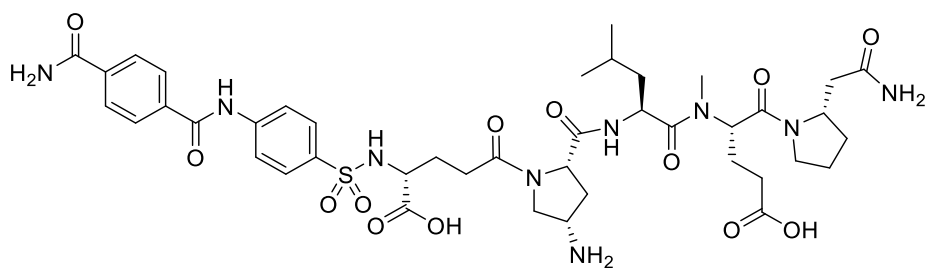
W^C may be (d)-Lys, and

R^C is the formula $-NH_2$.

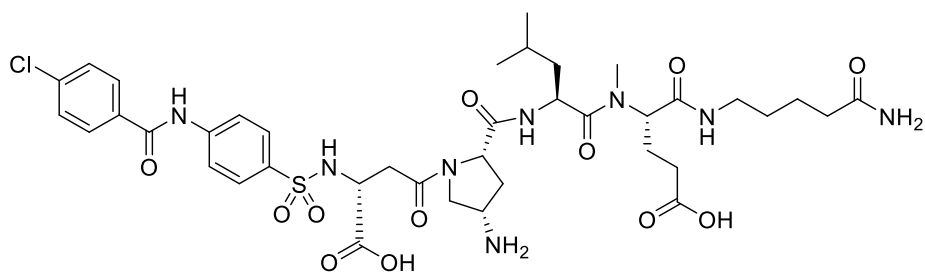
In one particularly preferable mode of the present embodiment,

the substituted polypeptide represented by formula [I'-C] is any of the followings:

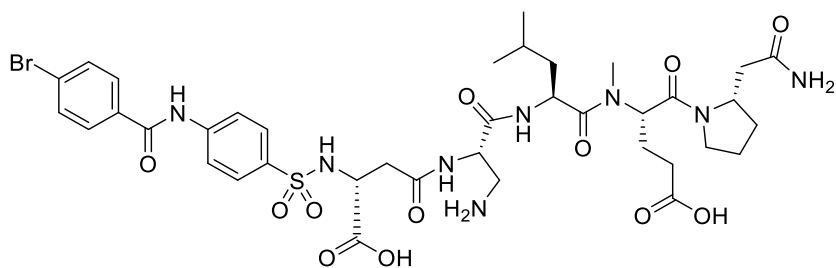




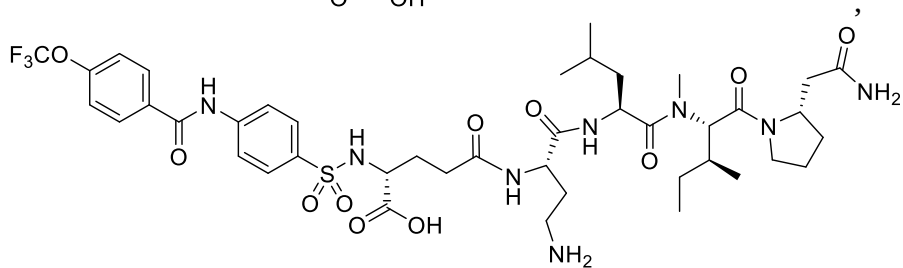
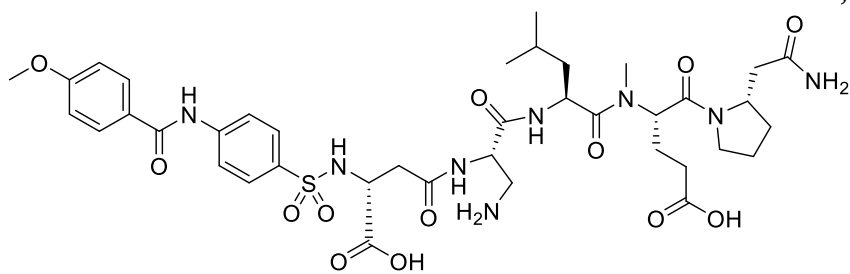
,



,

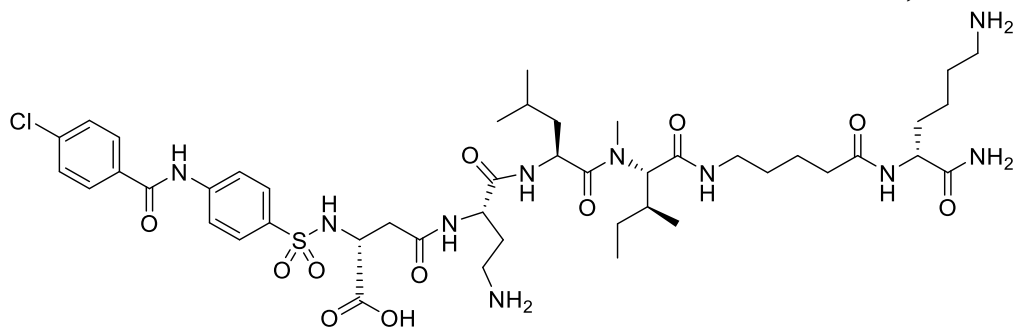


,



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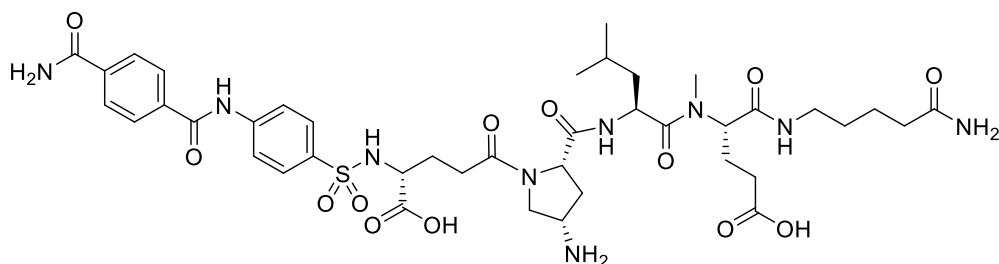
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,

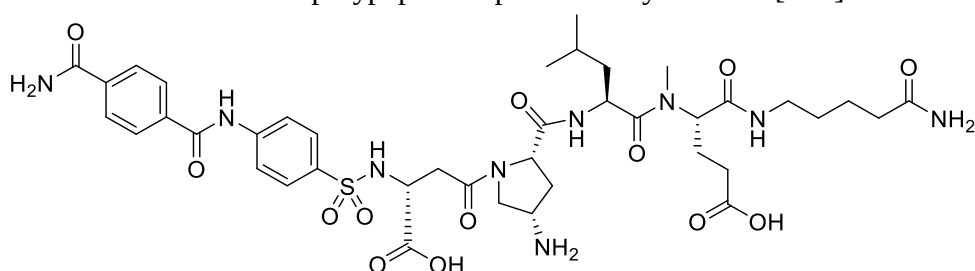
5

the substituted polypeptide represented by formula [I'-C] is the following:



In another particularly preferable mode of the present embodiment,

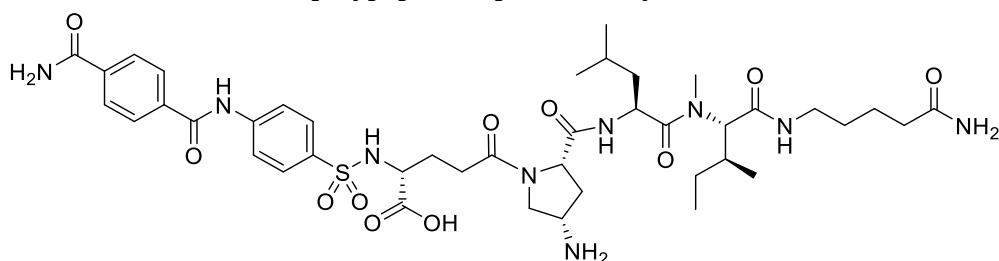
the substituted polypeptide represented by formula [I'-C] is the following:



5

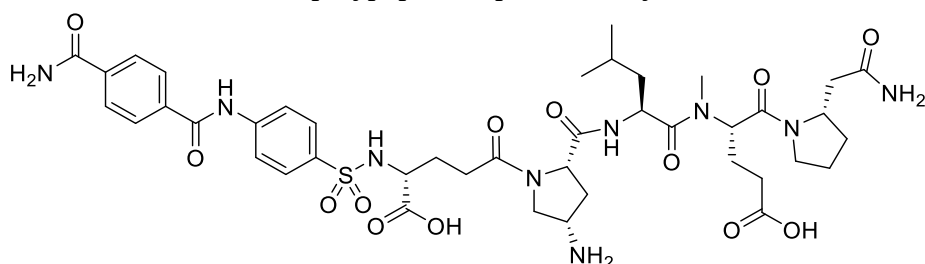
In another particularly preferable mode of the present embodiment,

the substituted polypeptide represented by formula [I'-C] is the following:



In another particularly preferable mode of the present embodiment,

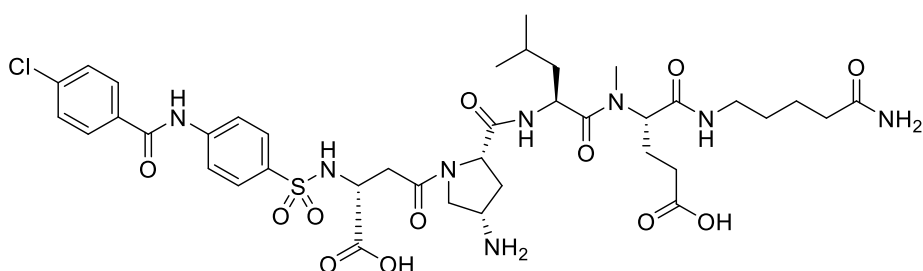
the substituted polypeptide represented by formula [I'-C] is the following:



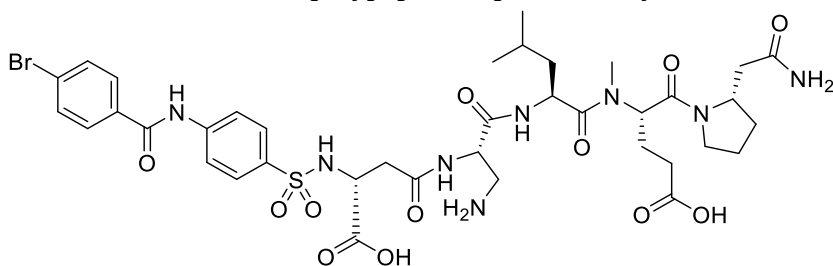
10

In another particularly preferable mode of the present embodiment,

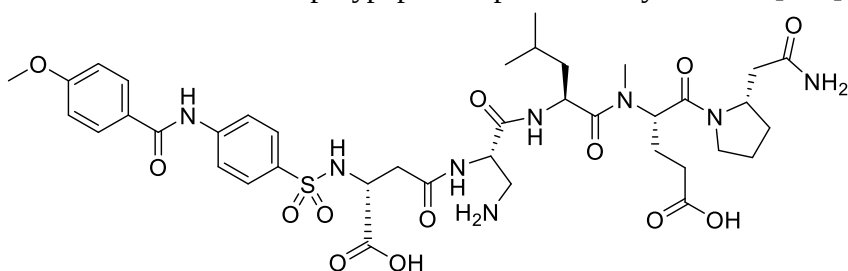
the substituted polypeptide represented by formula [I'-C] is the following:



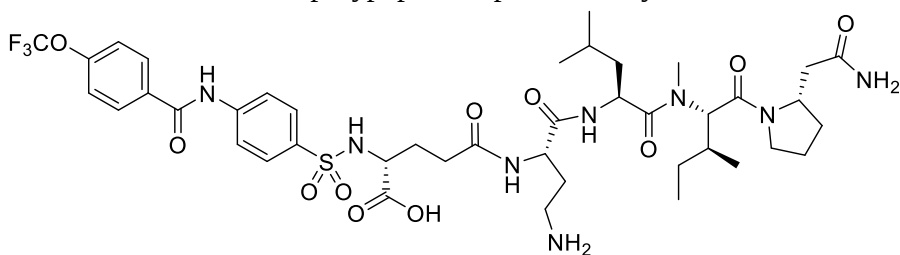
In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:



5 In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:

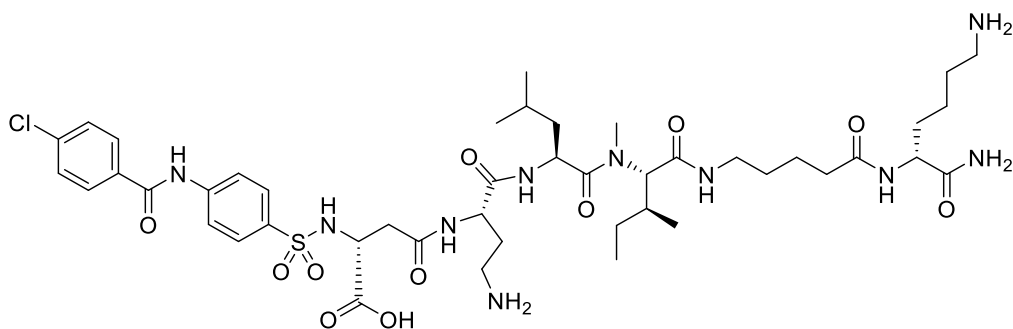


In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:

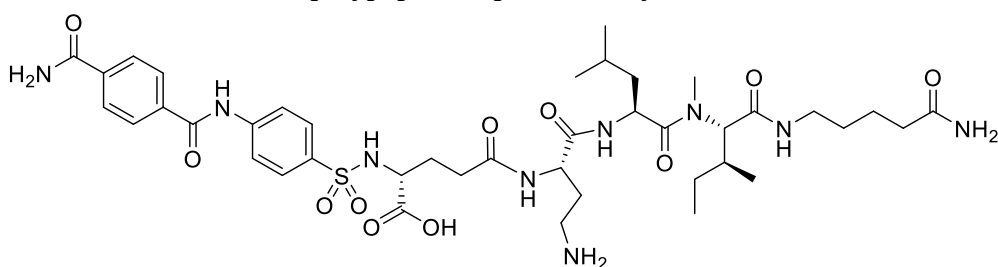


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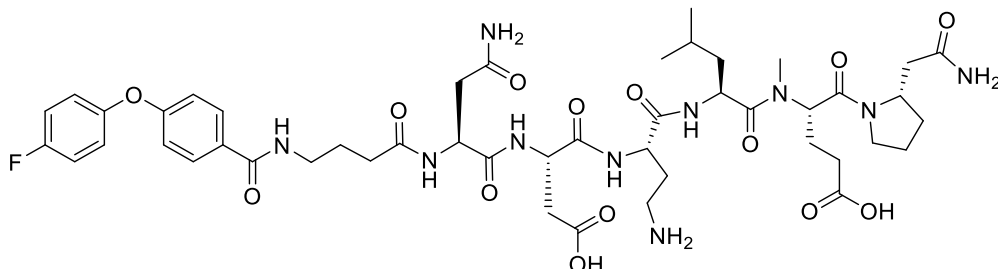
In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:



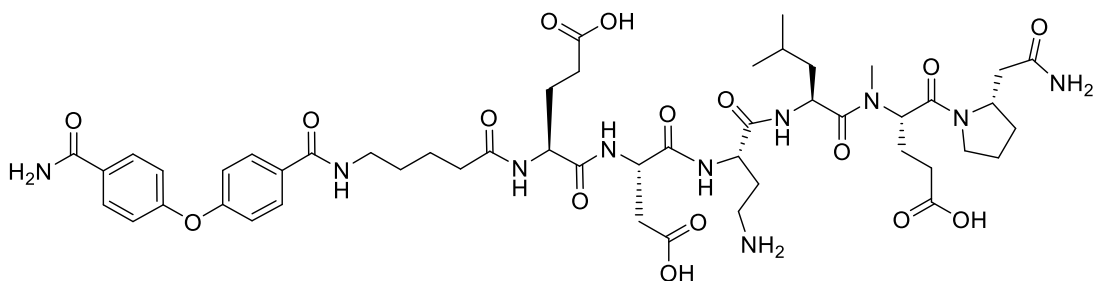
In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:



5 In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:

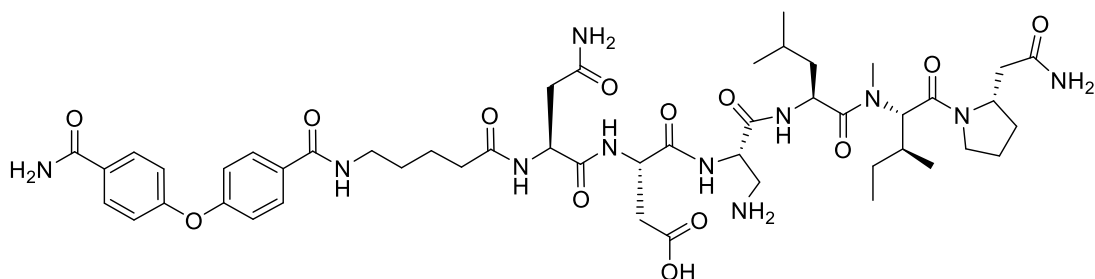


In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:

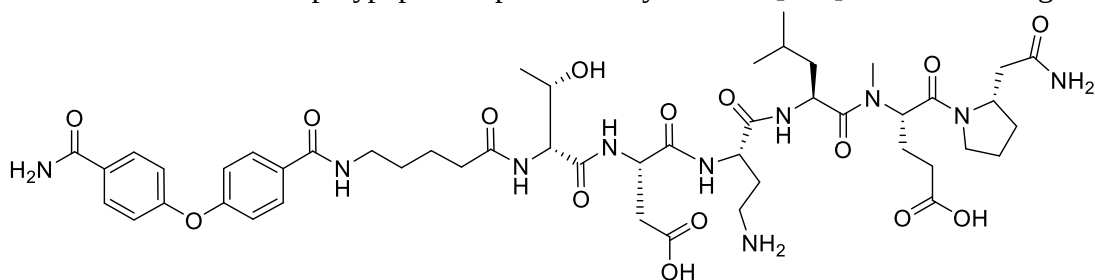


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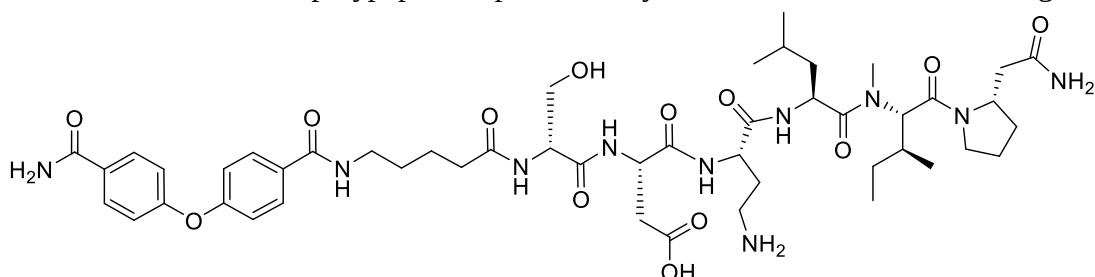
In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:



In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:



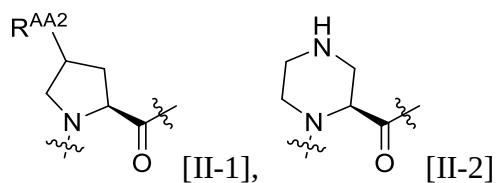
5 In another particularly preferable mode of the present embodiment,
the substituted polypeptide represented by formula [I'-C] is the following:



Another preferable embodiment of the compounds of the present invention is a
substituted polypeptide represented by formula [I], or a pharmaceutically acceptable salt
10 thereof, wherein

AA¹ is β -Asp, γ -Glu, or γ -(d)-Glu,

AA² is a group represented by formula [II-1] or formula [II-2]:



wherein R^{AA2} is hydroxy or amino,

15 AA³ is Val, Leu, Ile, Phe, or Trp,

AA⁴ is a single bond, Pro, (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp, or (N-Me)Glu,

AA⁵ is a single bond, Pro, (d)-Pro, β -homoPro, Arg, (d)-Arg, Lys, (d)-Lys, β -Ala, GABA, Ape, or Acp,

5 L¹ is a single bond,

L² is a single bond,

L^{N1} is the formula -S(=O)₂-,

L^{N2} is a single bond, the formula -O-, or the formula -C(=O)-NH-,

R^A is a hydrogen atom,

10 R^B is a hydrogen atom, carbamoyl, a halogen atom, or C₁₋₆ alkoxy,

L^C is a single bond, Pro, Arg, (d)-Arg, Lys, (d)-Lys, or (d)-Lys-(d)-Lys, and

R^C is the formula -NH₂.

The compounds of the present invention are each a compound having a basic backbone of polypeptide consisting of three to seven amino acids and further having substituted benzoyl or substituted phenylsulfonyl, and may be in the form of a pharmaceutically acceptable salt thereof.

Examples of the pharmaceutically acceptable salt include: mineral acid salts such as hydrochlorides, hydrobromides, hydroiodides, phosphates, sulfates, and nitrates; acid addition salts such as sulfonates including methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, and trifluoromethanesulfonates, and organic acid salts including oxalates, tartrates, citrates, maleates, succinates, acetates, trifluoroacetates, benzoates, mandelates, ascorbates, lactates, gluconates, and malates; amino acid salts such as glycines, lysinates, arginates, ornithinates, glutamates, and aspartates; inorganic salts such as lithium salts, sodium salts, potassium salts, calcium salts, and magnesium salts; and salts with organic base such as ammonium salts, triethylamine salts, diisopropylamine salts, and cyclohexylamine salts. Salts include hydrate salts.

Each of the compounds of the present invention may have an asymmetric center, and in this case various optical isomers exist therefor. Thus, each of the compounds of the

present invention may exist as an individual optically active substance in any of the (R)-form and the (S)-form, or as a racemate or an (RS) mixture. For a compound having two or more asymmetric centers, diastereomers due to the optical isomerism of them further exist. The scope of the compounds of the present invention also includes mixtures containing all the forms at any ratio. For example, diastereomers can be separated with a method well known to those skilled in the art such as a fractional crystallization method, and optically active substances can be obtained with a technique of organic chemistry well known to those skilled in the art for that purpose. In addition, geometric isomers such as a cis form and a trans form may exist for each of the compounds of the present invention. Moreover, the compounds of the present invention each exhibit tautomerism, and there exist various tautomers therefor. The scope of the compounds of the present invention also includes those isomers and mixtures containing them at any ratio.

Further, if any of the compounds of the present invention or a salt thereof forms a hydrate or solvate, the hydrate or solvate is also included in the scope of the compounds of the present invention or a salt thereof.

"Matrix metalloprotease 2 (MMP2)" is one of endopeptidases having an active center of zinc.

As described above, MMP2 degrades the extracellular matrix including collagen and gelatin, and hence is involved in cell infiltration and migration, metastasis, and so on, thus being involved in pathological condition of cancerous disease, organ fibrosis, and so on.

Therefore, cancerous disease and organ fibrosis, and symptoms relating to cancerous disease and organ fibrosis can be prevented or treated by inhibiting MMP2.

The compounds of the present invention have an effect to inhibit MMP2. Accordingly, the compounds of the present invention can be used as an MMP2 inhibitor, or an active ingredient of a drug for preventing or treating cancerous disease and organ fibrosis.

In addition, the compounds of the present invention can be used as an active ingredient of a drug for preventing or treating symptoms relating to cancerous disease and organ fibrosis.

Examples of "cancerous disease" include breast cancer, pancreatic cancer, bladder cancer, colorectal cancer, ovarian cancer, prostate cancer, brain tumor, gastric cancer, hepatocellular carcinoma, head and neck cancer, melanoma, uterine cancer, esophageal cancer, renal cell carcinoma, lung cancer, and glioma. Examples of "symptoms relating to cancerous disease" include pain associated with neoplastic cell multiplication or tumor growth, loss of body weight, and paraneoplastic syndrome.

Examples of "organ fibrosis" include chronic kidney disease, interstitial pneumonia, and idiopathic pulmonary fibrosis. Examples of "symptoms relating to organ fibrosis" include proteinuria, kidney dysfunction, and so on in chronic kidney disease, and exertional dyspnea, dry cough, and so on in interstitial pneumonia and idiopathic pulmonary fibrosis.

Evaluation of the effect of any of the compounds of the present invention to inhibit MMP2 can be carried out with a known procedure such as a method described later in Test Examples in the present specification.

For the pharmaceutical according to the present invention, a compound having an effect to inhibit MMP2, being any of the compounds of the present invention contained in the pharmaceutical, or a pharmaceutically acceptable salt thereof may be administered singly, or together with a pharmaceutically acceptable additive.

A common excipient or diluent, and, as necessary, a binder, a disintegrant, a lubricating agent, a coating agent, a sugar-coating agent, a pH adjuster, and a solubilizer or aqueous or nonaqueous solvent which is commonly used can be used as the additive. Specific examples of the additives may include water, lactose, dextrose, fructose, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, starch, cornstarch, gum, gelatin, arginate, calcium silicate, calcium phosphate, cellulose, water syrup, methylcellulose, polyvinylpyrrolidone, alkyl para-hydroxybenzoate, talc, stearic acid, magnesium stearate, agar, pectin, gum arabic, glycerin, sesame oil, olive oil, soybean oil cocoa butter, ethylene glycol, low-viscosity hydroxypropylcellulose (HPC-L), microcrystalline cellulose, carboxymethylcellulose (CMC), carboxymethylcellulose sodium (CMC-Na), and other common additives.

The pharmaceutical according to the present invention may be in any form of solid compositions, liquid compositions, and other compositions, and an optimum form is selected according to necessity.

5 The pharmaceutical according to the present invention can be prepared, for example, as a tablet, a pill, a capsule, a granule, a powdered agent, a powder, a solution, an emulsion, a suspension, or an injection through a common formulation technique with addition of the aforementioned additive to any of the compounds of the present invention.

10 The pharmaceutical according to the present invention can be formulated by forming a clathrate compound with any of the compounds of the present invention and α -, β -, or γ -cyclodextrin or methylated cyclodextrin.

With respect to compounds that can be used in combination with any of the compounds of the present invention, the pharmaceutical according to the present invention can be prepared as a single formulation (combination drug) or two or more formulations (concomitant drugs) obtained by separately formulating.

15 If those compounds are separately formulated into two or more formulations, the individual formulations can be administered simultaneously, or separately at specific time intervals. In the latter case, any formulation may be first administered. The two or more formulations may be administered in different numbers of doses per day. The two or more formulations may be administered through different routes.

20 If those compounds are separately formulated into two or more formulations, they may be administered simultaneously, or separately at very short intervals, and it is preferable to instruct to use them in combination by means of a document such as an accompanying document or sales brochure of a commercially available pharmaceutical.

25 It is also preferable to separately formulate those active ingredients into the form of a kit consisting of two formulations.

The form of administration when any of the compounds of the present invention is used as an MMP2 inhibitor or the like is not limited, and any of the compounds of the present invention can be directly administered orally or parenterally. Alternatively, an agent

containing any of the compounds of the present invention as an active ingredient may be orally or parenterally administered.

Also in the case that any of the compounds of the present invention is used as an agent for preventing or treating cancerous disease and organ fibrosis, and symptoms relating to cancerous disease and organ fibrosis, any of the compounds of the present invention can be directly administered orally or parenterally. Alternatively, an agent containing any of the compounds of the present invention as an active ingredient may be orally or parenterally administered.

In the parenteral administration, it is preferable to perform intravenous administration, subcutaneous administration, or transdermal administration.

Examples of the dosage form for parenteral administration include an injection, an infusion drip, an implant drug, a transdermal drug, a transmucosal drug, and a patch, and the dosage form may be a microsphere formulation.

The dose of any of the compounds of the present invention differs among subjects, routes of administration, target diseases, symptoms, and so on, and it is typically desirable in oral administration or parenteral administration to an adult patient to administer a single dose of 0.1 mg to 1000 mg, preferably of 1 mg to 200 mg, once to three times per day, or once every 2 to 3 days.

Production Examples for formulations of the compounds of the present invention will be shown in the following.

Production Example 1

A granule containing the following components is produced.

Components: compound represented by general formula [I], lactose, and cornstarch, HPC-L.

The compound represented by general formula [I] and lactose are sieved. Cornstarch is sieved. These are mixed by using a mixer. HPC-L aqueous solution is added to the mixed powder, and the resultant is kneaded, granulated (extrusion granulation),

and then dried. The resulting dry granule is sieved through a vibrating screen to obtain a granule.

Production Example 2

5 A powder for encapsulation containing the following components is produced.

Components: compound represented by general formula [I'], lactose, and cornstarch, magnesium stearate.

The compound represented by general formula [I'] and lactose are sieved.

Cornstarch is sieved. These together with magnesium stearate are mixed by using a mixer
10 to obtain a powder. The powder obtained can be encapsulated.

Production Example 3

A granule for encapsulation containing the following components is produced.

Components: compound represented by general formula [I'], lactose, and cornstarch,
15 HPC-L.

The compound represented by general formula [I'] and lactose are sieved.

Cornstarch is sieved. These are mixed by using a mixer. HPC-L aqueous solution is added to the mixed powder, and the resultant is kneaded, granulated, and then dried. The resulting dry granule is sieved through a vibrating screen to regulate the particle size, and a
20 granule is obtained. The granule obtained can be encapsulated.

Production Example 4

Tablets containing the following components are produced.

Components: compound represented by general formula [I'], lactose,
25 microcrystalline cellulose, magnesium stearate, and CMC-Na.

The compound represented by general formula [I'], lactose, microcrystalline cellulose, and CMC-Na are sieved, and mixed together. Magnesium stearate is added to the mixed powder to obtain a mixed powder for formulation. This mixed powder is subjected

to direct compression to obtain tablets.

Production Example 5

An injection containing the following compositions is produced.

- 5 Components: compound represented by general formula [I'], purified egg yolk lecithin, oleic acid, purified soybean oil, glycerin, and water for injection.

The compound represented by general formula [I'], purified egg yolk lecithin, and oleic acid are added to purified soybean oil to dissolve therein; water for injection, mixed with glycerin, is then added; and the resultant is emulsified by using an emulsifying machine.

- 10 Thereto, water for injection is added, and the resultant is aliquoted into ampules, which are sealed and sterilized to form an injection.

- Production methods for compound [I'] according to the present invention will be described in detail in the following, but the production is not limited to the exemplified production methods. Solvent to be used for the production may be any solvent that does not
15 inhibit individual reactions, and is not limited by the following description.

In the production of compound [I'], the order of steps in the production can be appropriately changed.

In the production, each raw material compound may be used as a salt thereof, and examples of such salts include "pharmaceutically acceptable salt" presented above.

- 20 Compound [I'] can be produced through solid-phase synthesis, liquid-phase synthesis, or a combination of them. Production examples with solid-phase synthesis will be shown in the following production methods.

Compound [I'] can be produced through methods shown in any of Schemes 1 to 9 or any combination of them.

- 25 The side chain of each amino acid to form the polypeptide moiety of compound [I'] may have a functional group, and the functional group may be protected with a protecting group. Examples of the protecting group include tBu for carboxy, Trt for carbamoyl, tBu for hydroxy, tBu for phenolic hydroxy, tBu for thiol (sulfanyl), Boc for amino, Trt for

imidazolyl, Boc for indolyl, and Pbf for guanidino. These protecting groups can be each subjected to deprotection by treating with an acid.

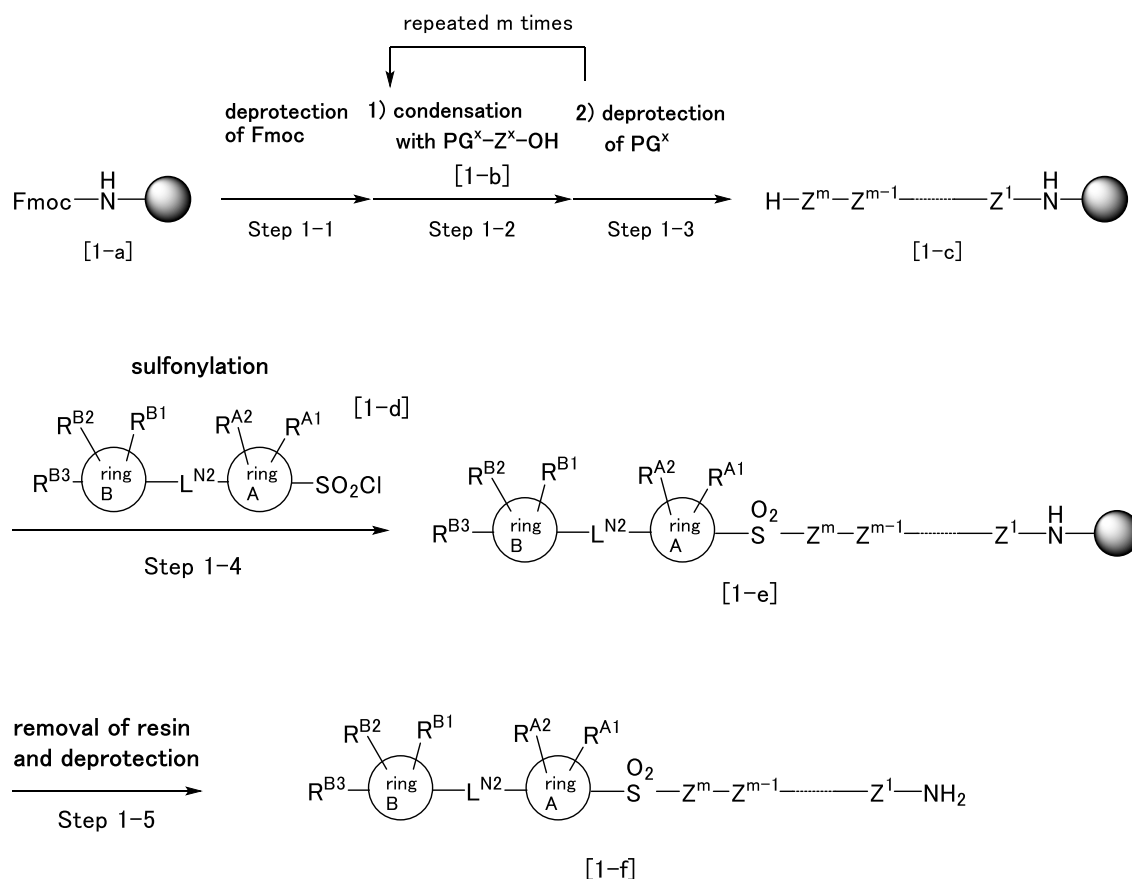
Each of the amino acids can be used for the production even if the functional group in the side chain is not protected.

5

Method A: a method for producing compound [1-f], a compound in which the amino of the N-terminal amino acid of the polypeptide moiety is sulfonylated and the carboxy of the C-terminal amino acid is amidated (-CONH₂)

Compound [1-f] can be produced, for example, through solid-phase synthesis the summary of which is described in the following (Scheme 1).

Scheme 1



wherein

15 R^{A1}, R^{A2}, R^{B1}, R^{B2}, R^{B3}, L^{N2}, ring A, and ring B have the same definitions as those described

above,

H-Z^x-OH represents an amino acid,

x represents an integer of 1 to m,

m represents an integer of 2 to 15,

- 5 wherein Z^x corresponds to AA^x, L², W¹, or W^c in the compound represented by formula [I'], and may represent a single bond, and

PG^x represents a liposoluble protecting group protecting the amino of the amino acid (H-Z^x-OH).

(1) [Step 1-1]

- 10 A resin having amino protected with Fmoc (compound [1-a]) is subjected to deFmoc by using a base.

(2) [Step 1-2]

- The resin obtained in (1) is reacted with an amino acid whose amino has been protected with a liposoluble protecting group (PG^x) (compound [1-b]) for amidation reaction
15 between the free amino in the resin and the carboxy in compound [1-b].

(3) [Step 1-3]

The liposoluble protecting group of the amino of the N-terminal amino acid of the polypeptide moiety in the compound obtained in (2) is subjected to deprotection.

(4)

- 20 By repeating steps (2) and (3) twice or more times, compound [1-c] can be produced in which the carboxy of the C-terminal amino acid of the polypeptide moiety is bonding to the resin and the amino of the N-terminal amino acid is free.

(5) [Step 1-4]

- Compound [1-e] can be produced by reacting compound [1-c] obtained in (4) with
25 compound [1-d] to sulfonylate the free amino in compound [1-c].

(6) [Step 1-5]

Compound [1-f], one of the present inventive compounds, can be produced by using an acid on compound [1-e] obtained in (5) to cleave the bond to the resin. Examples of the

acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be simultaneously deprotected.

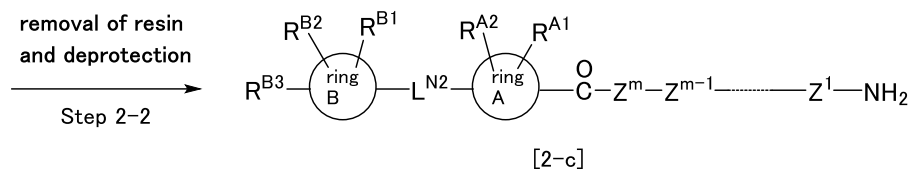
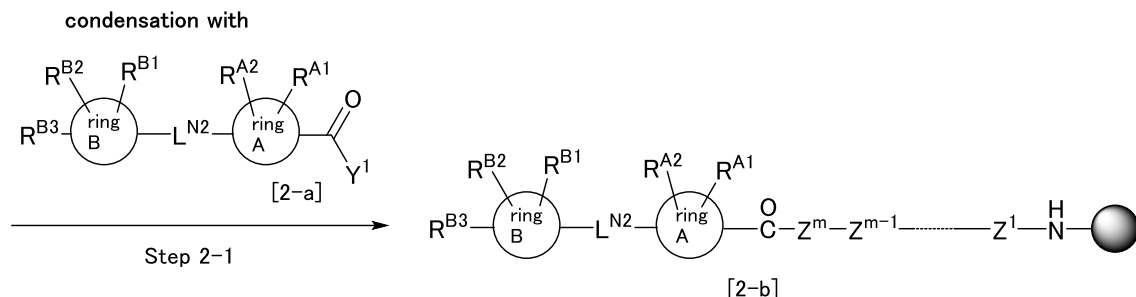
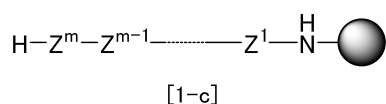
5 Compound [1-f] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

 In the method described in Scheme 1, resin [1-a], compound [1-b], and compound [1-d] to be used as raw material compounds can be obtained by producing with a method
10 known per se, or purchasing commercially available products of them.

Method B: a method for producing compound [2-c], a compound in which the amino of the N-terminal amino acid of the polypeptide moiety is acylated and the carboxy of the C-terminal amino acid is amidated (-CONH₂)

15 Compound [2-c] can be produced, for example, through solid-phase synthesis the summary of which is described in the following (Scheme 2) with use of compound [1-c] as a starting material.

Scheme 2



wherein

$\text{R}^{\text{A}1}$, $\text{R}^{\text{A}2}$, $\text{R}^{\text{B}1}$, $\text{R}^{\text{B}2}$, $\text{R}^{\text{B}3}$, $\text{L}^{\text{N}2}$, ring A, ring B, $\text{H}-\text{Z}^x-\text{OH}$, x , m , and Z^x have the same definitions as those described above, and

5 Y^1 represents hydroxy or a chlorine atom.

(1) [Step 2-1]

Compound [2-b] can be produced by allowing compound [2-a] to act on compound [1-c] for amidation reaction.

(2) [Step 2-2]

10 Compound [2-c], one of the present inventive compounds, can be produced by using an acid on compound [2-b] obtained in (1) to cleave the bond to the resin. Examples of the acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be
15 simultaneously deprotected.

Compound [2-c] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

In the method described in Scheme 2, compound [2-a] to be used as a raw material compound can be obtained by producing with a method known per se, or purchasing a commercially available product of it. Compound [1-c] can be produced with the method described in Scheme 1.

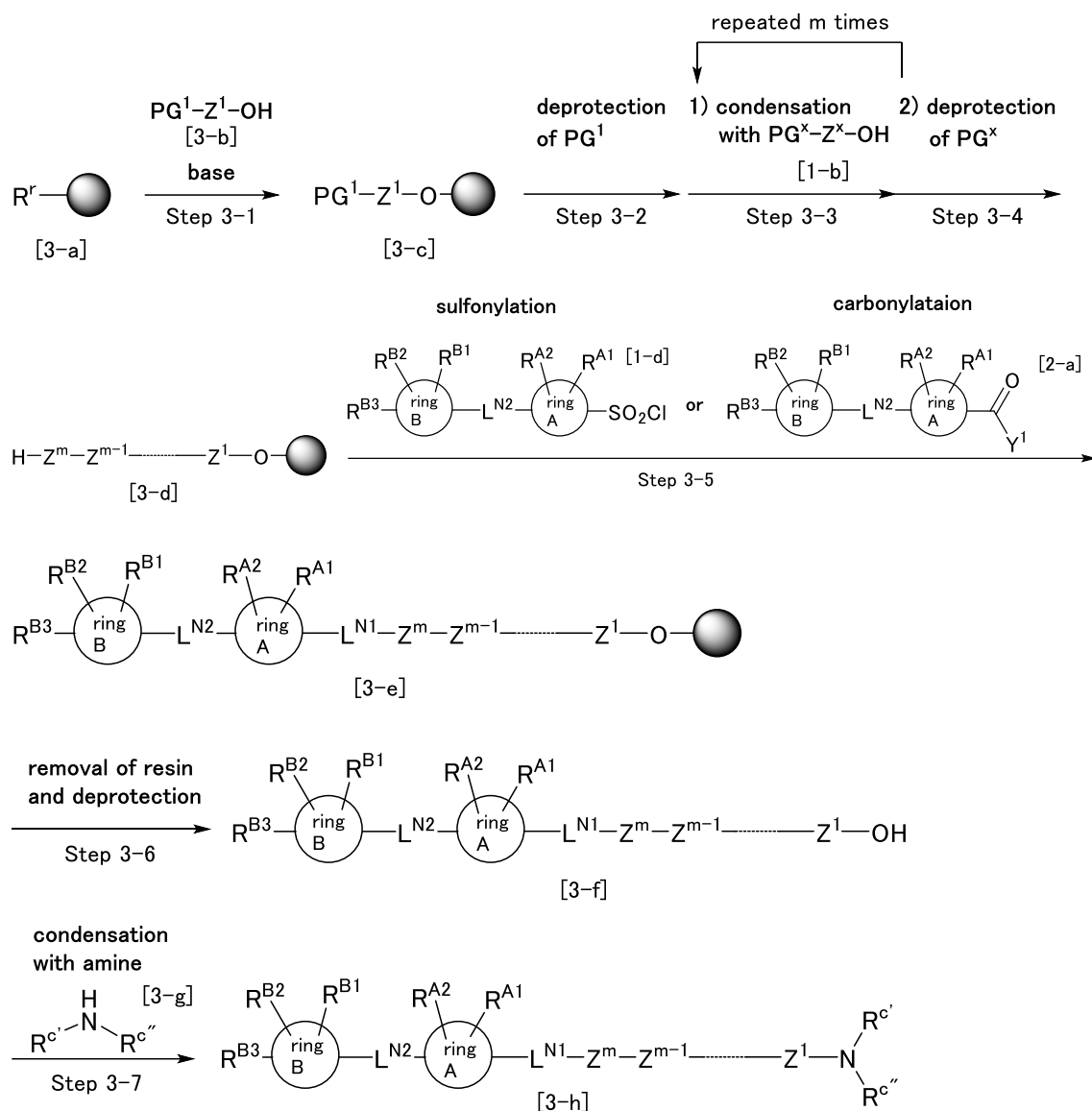
5

Method C-1: a method for producing compound [3-h], a compound in which the amino of the N-terminal amino acid of the polypeptide moiety is sulfonylated or acylated and the carboxy of the C-terminal amino acid is secondary- or tertiary-amidated

10 Compound [3-h] can be produced, for example, through solid-phase synthesis the summary of which is described in the following (Scheme 3).

Examples of the resin (resin [3-a]) applicable in the present production method may include chlorotriethyl chloride resin and Wang resin.

Scheme 3



wherein

R^{A1} , R^{A2} , R^{B1} , R^{B2} , R^{B3} , L^{N1} , L^{N2} , ring A, ring B, $\text{H-Z}^x\text{-OH}$, x , m , Z^x , PG^x , and Y^1 have the same definitions as those described above,

5 R^r represents hydroxy or a chlorine atom,

$\text{R}^{\text{c}'}$ and $\text{R}^{\text{c}''}$ are same or different and each represent a hydrogen atom or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one group selected from the group consisting of hydroxy, amino, and C_{1-6} alkoxy,

$\text{R}^{\text{c}'}$ and $\text{R}^{\text{c}''}$ may be taken together with the neighboring nitrogen atom to form a four- to

10 seven-membered saturated heterocycle containing a nitrogen atom, wherein

the four- to seven-membered saturated heterocycle containing a nitrogen atom, formed by R^{c'} and R^{c''} taken together with the neighboring nitrogen atom, is optionally substituted with one group selected from the group consisting of hydroxy, amino, C₁₋₆ alkyl, and C₁₋₆ alkoxy, and

5 two carbon atoms in the four- to seven-membered saturated heterocycle containing a nitrogen atom, formed by R^{c'} and R^{c''} taken together with the neighboring nitrogen atom, are optionally crosslinked with C₁₋₄ alkanediyl.

(1) [Step 3-1]

Compound [3-c] can be produced by reacting the resin (compound [3-a]) with an
10 amino acid whose amino has been protected with a liposoluble protecting group (PG¹) (compound [3-b]).

(2) [Step 3-2]

The liposoluble protecting group (PG¹) in compound [3-c] obtained in (1) is subjected to deprotection.

15 (3) [Step 3-3]

The compound obtained in (2) is reacted with an amino acid whose amino has been protected with a liposoluble protecting group (PG^x) (compound [1-b]) for amidation reaction between the free amino in the compound obtained in (1) and the carboxy in compound [1-b].

(4) [Step 3-4]

20 The liposoluble protecting group of the amino of the N-terminal amino acid of the polypeptide moiety in the compound obtained in (3) is subjected to deprotection.

(5)

By repeating steps (3) and (4) twice or more times, compound [3-d] can be produced in which the carboxy of the C-terminal amino acid of the polypeptide moiety is bonding to
25 the resin and the amino of the N-terminal amino acid is free.

(6) [Step 3-5]

Compound [3-e] can be produced by reacting compound [3-d] obtained in (5) with compound [1-d] or compound [2-a] to sulfonylate or acylate the free amino in compound

[3-d].

(7) [Step 3-6]

Compound [3-f], in which the carboxy of the C-terminal amino acid of the polypeptide moiety is free, can be produced by using an acid on compound [3-e] obtained in
5 (6) to cleave the bond to the resin. Examples of the acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be simultaneously deprotected.

10 (8) [Step 3-7]

Compound [3-h], one of the present inventive compounds, can be produced by allowing compound [3-g] to act on compound [3-f] obtained in (7) for amidation reaction.

Compound [3-h] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced
15 pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

In the method described in Scheme 3, compound [3-a], compound [3-b], compound [1-b], compound [1-d], compound [2-a], and [3-g] to be used as raw material compounds can be obtained by producing with a method known per se, or purchasing commercially available products of them.

20

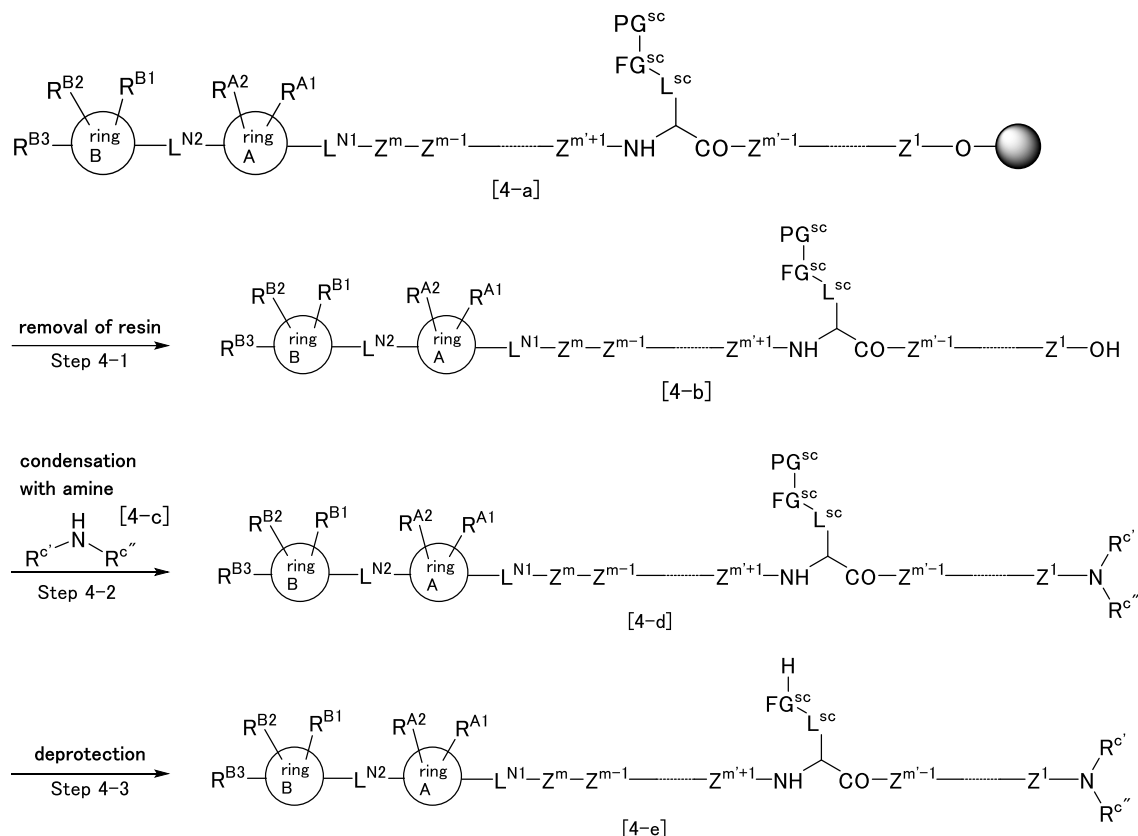
Method C-2: a method for producing compound [4-e], a compound in which the amino of the N-terminal amino acid of the polypeptide moiety is sulfonylated or acylated and the carboxy of the C-terminal amino acid is secondary- or tertiary-amidated

Alternatively, compound [4-e] can be produced, for example, through solid-phase
25 synthesis the summary of which is described in the following (Scheme 4).

In Scheme 4, a method for producing a compound wherein a functional group is present in the side chain of the m'th amino acid counted from the C-terminal amino acid of the polypeptide moiety in compound [4-e] is presented as an example.

Examples of the resin applicable in the present production method may include, as in Scheme 3, chlorotriyl chloride resin and Wang resin.

Scheme 4



5 wherein

R^{A1} , R^{A2} , R^{B1} , R^{B2} , R^{B3} , L^{N1} , L^{N2} , ring A, ring B, $H-Z^x-OH$, x , m , Z^x , $R^{c'}$, and $R^{c''}$ have the same definitions as those described above,

m' represents an integer of 1 to 15, provided that the relationship " $m' \leq m$ " is satisfied,

L^{sc} represents C_{1-4} alkanediyl,

10 FG^{sc} represents the aforementioned functional group present in the side chain of the m' th amino acid counted from the C-terminal amino acid of the polypeptide moiety,

wherein examples of the functional group may include the formula $-O-$ (the formula $-OH$), the formula $-S-$ (the formula $-SH$), the formula $-NH-$ (the formula $-NH_2$), the formula

$-C(=O)O-$ (the formula $-C(=O)OH$), the formula $-C(=O)NH-$ (the formula $-C(=O)NH_2$), and

15 the formula $-NHC(=NH)NH-$ ($-NHC(=NH)NH_2$), and

PG^{sc} represents a protecting group for the functional group,

wherein examples of the functional group may include, as described above, tBu, Trt, Boc, and Pbf.

(1) [Step 4-1]

Compound [4-b], in which the carboxy of the C-terminal amino acid of the polypeptide moiety is free, can be produced by using an acid on compound [4-a] to cleave the bond to the resin.

At that time, the deprotection for the protecting group (PG^{sc}) present in the side chain of the m'th amino acid counted from the C-terminal amino acid can be prevented by using a weak acid as the acid. Examples of the weak acid may include HFIP, acetic acid, and diluted TFA.

(2) [Step 4-2]

Compound [4-d] can be produced by allowing compound "4-c" to act on compound [4-b] obtained in (1) for amidation reaction between the free carboxy in compound [4-b] and the amino in compound [4-c].

(3) [Step 4-3]

Compound [4-e], one of the present inventive compounds, can be produced by using an acid for deprotection for the aforementioned protecting group (PG^{sc}) present in the side chain of the m'th amino acid counted from the C-terminal amino acid. Examples of the acid applicable in the present step may include TFA.

Compound [4-e] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

In the method described in Scheme 4, compound [4-c] to be used as a raw material compound can be obtained by producing with a method known per se, or purchasing a commercially available product of it. Compound [4-a] can be produced with the method described in Scheme 3.

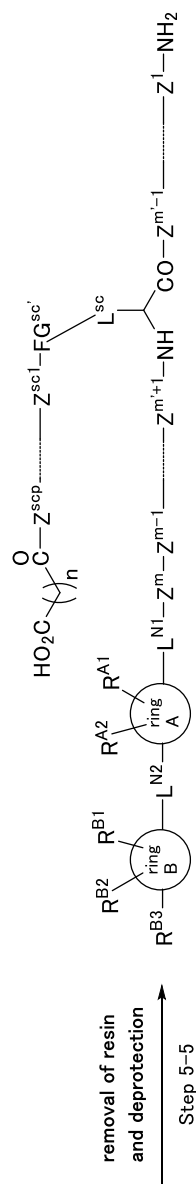
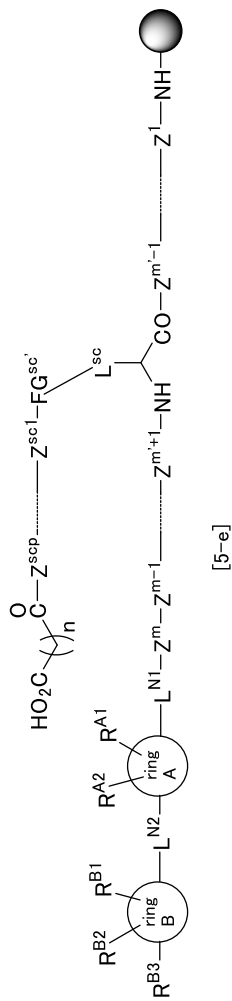
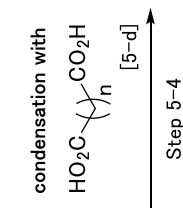
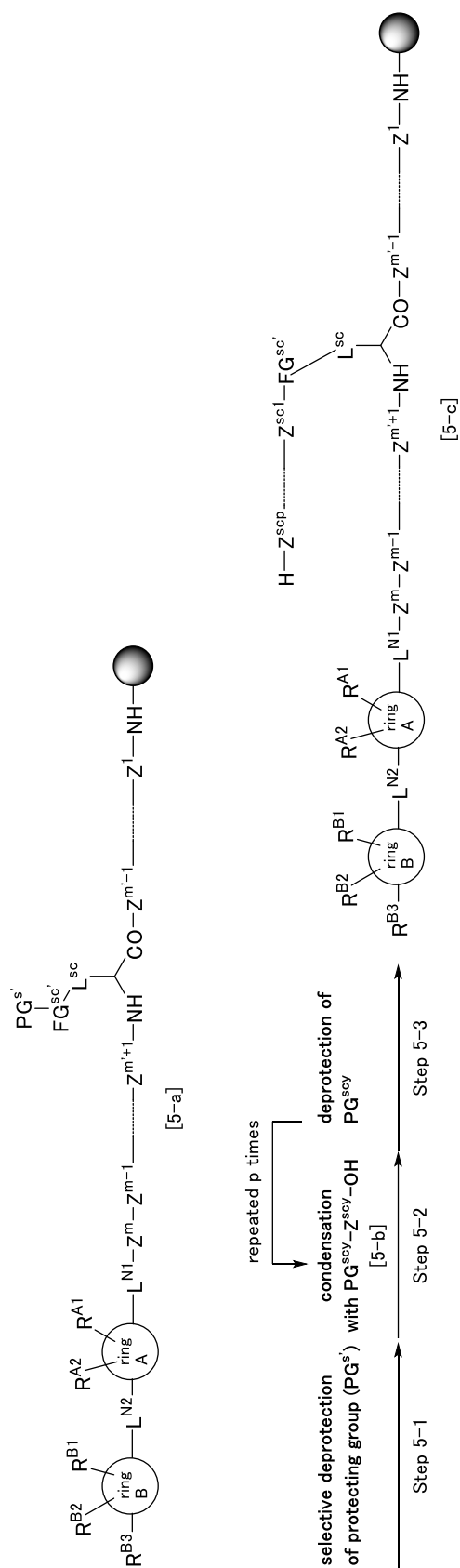
Method D: a method for producing compound [5-f], in which a functional group is present in

the side chain of an amino acid forming the polypeptide moiety, the functional group is substituted with a polypeptide linker and the amino of the N-terminal amino acid of the polypeptide linker is substituted with "C₁₋₂₀ alkylcarbonyl substituted with carboxy"

Compound [5-f] can be produced through solid-phase synthesis the summary of
5 which is described in the following (Scheme 5).

Here, the polypeptide linker consists of one to five amino acids.

In Scheme 5, a method for producing a compound wherein a functional group is present in the side chain of the m'th amino acid counted from the C-terminal amino acid of the polypeptide moiety in compound [5-f], the functional group is substituted with a
10 polypeptide linker, and the amino of the N-terminal amino acid of the polypeptide linker is substituted with "C₁₋₂₀ alkylcarbonyl substituted with carboxy" is presented as an example.
Scheme 5



wherein

R^{A1} , R^{A2} , R^{B1} , R^{B2} , R^{B3} , L^{N1} , L^{N2} , ring A, ring B, $H-Z^x-OH$, x , m , m' , Z^x , and L^{sc} have the same definitions as those described above,

$PG^{s'}$ represents a protecting group for the aforementioned functional group ($FG^{sc'}$) present in

5 the side chain of an amino acid, wherein examples of the protecting group include Dde, ivDde, Alloc, and Mtt for amino,

$H-Z^{sc\ y}-OH$ represents an amino acid forming the polypeptide linker attached to the functional group ($FG^{sc'}$),

y represents an integer of 1 to p ,

10 p represents an integer of 0 to 5,

$PG^{sc\ y}$ represents a liposoluble protecting group protecting the amino of the amino acid ($H-Z^{sc\ y}-OH$),

$FG^{sc'}$ represents a functional group present in the side chain of an amino acid; examples of the functional group may include the formula $-NH-$ (the formula $-NH_2$) and the formula $-COO-$ (the formula $-COOH$); Scheme 5 shows the case that $FG^{sc'}$ is the formula $-NH-$ (the formula $-NH_2$), and

15

n represents an integer of 1 to 20.

(1) [Step 5-1]

The protecting group ($PG^{s'}$) for the functional group present in the side chain of the

20 m' th amino acid counted from the C-terminal amino acid of the polypeptide moiety in compound [5-a] is subjected to selective deprotection.

(2) [Step 5-2]

The compound obtained in (1) is reacted with an amino acid whose amino has been protected with a liposoluble protecting group ($PG^{sc\ y}$) (compound [5-b]) for amidation

25 reaction between the free functional group ($FG^{sc'}$) in the compound obtained in (1) and the carboxy in compound [5-b].

(3) [Step 5-3]

The liposoluble protecting group ($PG^{sc\ y}$) is subjected to deprotection.

(4)

By repeating steps (2) and (3) once or more times, compound [5-c], in which the carboxy of the C-terminal amino acid of the polypeptide moiety is bonding to the resin, the functional group present in the side chain of the m'th amino acid counted from the C-terminal amino acid is substituted with a polypeptide linker, and the amino of the N-terminal amino acid of the polypeptide linker is free, can be produced.

(5) [Step 5-4]

Compound [5-e] can be produced by reacting compound [5-c] obtained in (4) with compound [5-d], which is an alkanedicarboxylic acid, for amidation reaction of the free amino in compound [5-c] with one carboxy in compound [5-d].

(6) [Step 5-5]

Compound [5-f], one of the present inventive compounds, can be produced by using an acid on compound [5-e] obtained in (5) to cleave the bond to the resin. Examples of the acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be simultaneously deprotected.

Compound [5-f] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

In the method described in Scheme 5, compound [5-b] and compound [5-d] to be used as raw material compounds can be obtained by producing with a method known per se, or purchasing commercially available products of them. Compound [5-a] can be produced with the method described in Scheme 1 or Scheme 2, or a method similar to any of these.

Method E: a method for producing compound [6-c], in which a functional group is present in the side chain of each of two amino acids among the amino acids forming the polypeptide moiety, and the functional groups are substituted with the same polypeptide linker ($-Z^{sc1}-Z^{sc}$

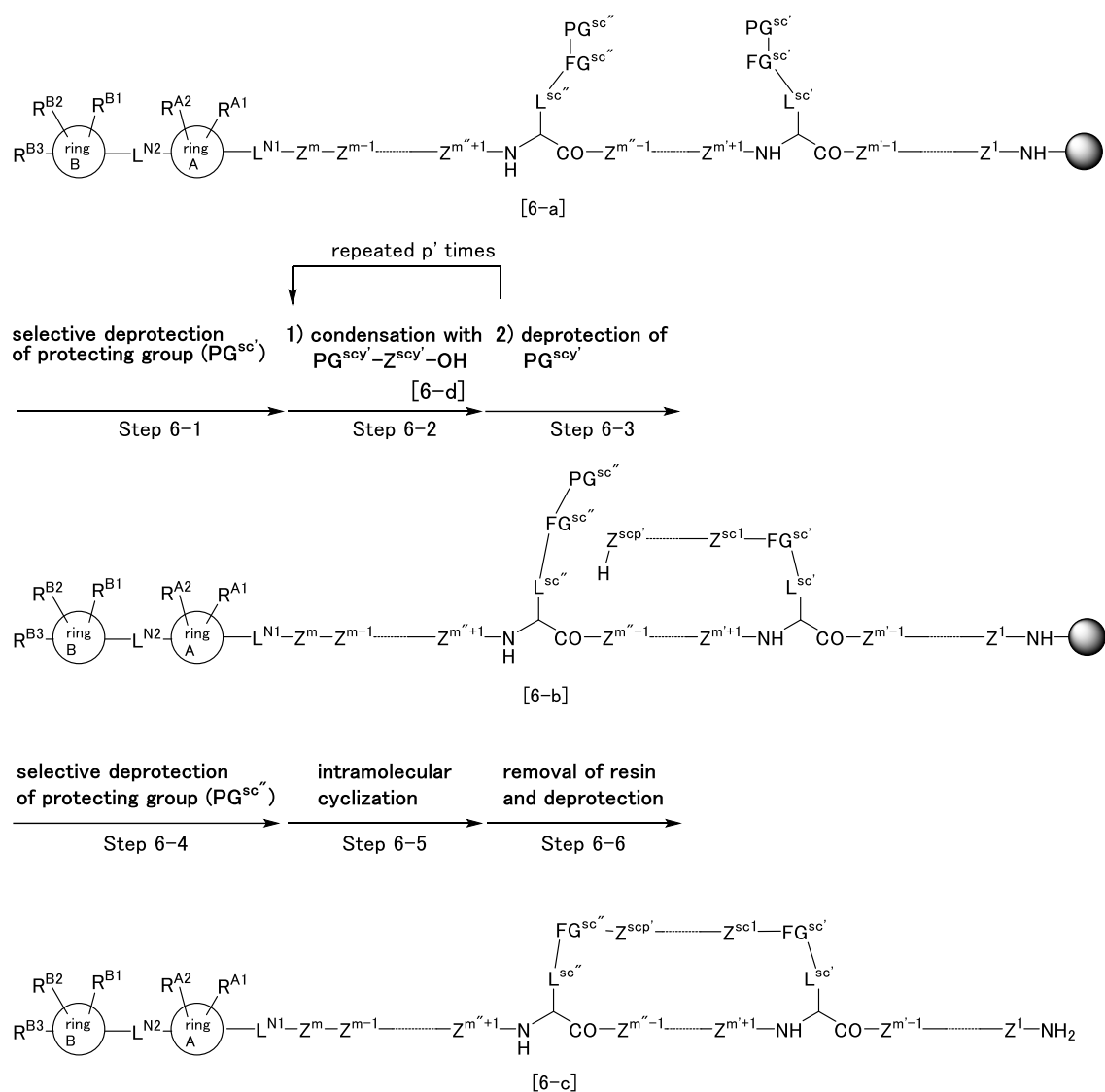
²...-Z^{sc y'}-) to form a ring

Compound [6-c] can be produced, for example, through solid-phase synthesis the summary of which is described in the following (Scheme 6).

Here, the polypeptide linker consists of one to four amino acids.

- 5 In Scheme 6, a method for producing a compound wherein a functional group is present in the side chain of each of the m'th and m''th amino acids counted from the C-terminal amino acid of the polypeptide moiety, and the functional groups are substituted with the same polypeptide linker to form a ring is presented as an example.

Scheme 6



wherein

R^{A1} , R^{A2} , R^{B1} , R^{B2} , R^{B3} , L^{N1} , L^{N2} , ring A, ring B, $H-Z^x-OH$, x , m , m' , Z^x , and L^{sc} have the same definitions as those described above,

m'' represents an integer of 2 to 15, provided that the relationship " $m' < m'' \leq m$ " is satisfied, the polypeptide linker ($-Z^{sc1}-Z^{sc2}-\dots-Z^{scy'}-$) in compound [6-c] corresponds to L^3 in the

5 compound represented by formula [I'], wherein L^3 represents Gly, β -Ala, or GABA,

y' represents an integer of 1 to p' ,

p' represents an integer of 1 to 4,

$L^{sc'}$ and $L^{sc''}$ each represent C_{1-4} alkanediyl,

$FG^{sc'}$ and $FG^{sc''}$ each represent a functional group present in the side chain of an amino acid,

10 wherein the functional group represents the formula -O- (the formula -OH), the formula -S- (the formula -SH), the formula -NH- (the formula -NH₂), the formula -C(=O)O- (the formula -C(=O)OH), or the formula -C(=O)NH- (the formula -C(=O)NH₂), and

$PG^{sc'}$ and $PG^{sc''}$ each represent a protecting group for a functional group present in the side chain of an amino acid, wherein the functional group is, for example, Dde, ivDde, Alloc, or

15 allyl.

(1) [Step 6-1]

The protecting group ($PG^{sc'}$) for the functional group present in the side chain of the m' th amino acid counted from the C-terminal amino acid of the polypeptide moiety in compound [6-a] is subjected to selective deprotection.

20 (2) [Step 6-2]

The compound obtained in (1) is reacted with an amino acid whose amino has been protected with a liposoluble protecting group ($PG^{scy'}$) (compound [6-d]) for amidation reaction between the free functional group ($FG^{sc'}$) in the compound obtained in (1) and the carboxy in compound [6-d], the amino of which has been protected with the liposoluble protecting group.

25

(3) [Step 6-3]

The liposoluble protecting group is subjected to deprotection.

(4)

By repeating steps (2) and (3) once or more times, compound [6-b], in which the functional group present in the side chain of the m'th amino acid counted from the C-terminal amino acid of the polypeptide moiety is substituted with a polypeptide linker, the amino of the N-terminal amino acid of the polypeptide linker is free, and the functional group (FG^{sc}) present in the side chain of the m'th amino acid counted from the C-terminal amino acid is protected with a protecting group (PG^{sc}), can be produced.

(5) [Step 6-4]

The protecting group (PG^{sc}) present in the side chain of the m'th amino acid counted from the C-terminal amino acid of the polypeptide moiety in compound [6-b] is subjected to selective deprotection.

(6) [Step 6-5]

"Free functional group (FG^{sc})" and "free amino in Z^{scp}" in the compound obtained in (5) are reacted for intramolecular cyclization reaction.

(7) [Step 6-6]

Compound [6-c], one of the present inventive compounds, can be produced by using an acid on the compound obtained in (6) to cleave the bond to the resin. Examples of the acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be simultaneously deprotected.

Compound [6-c] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

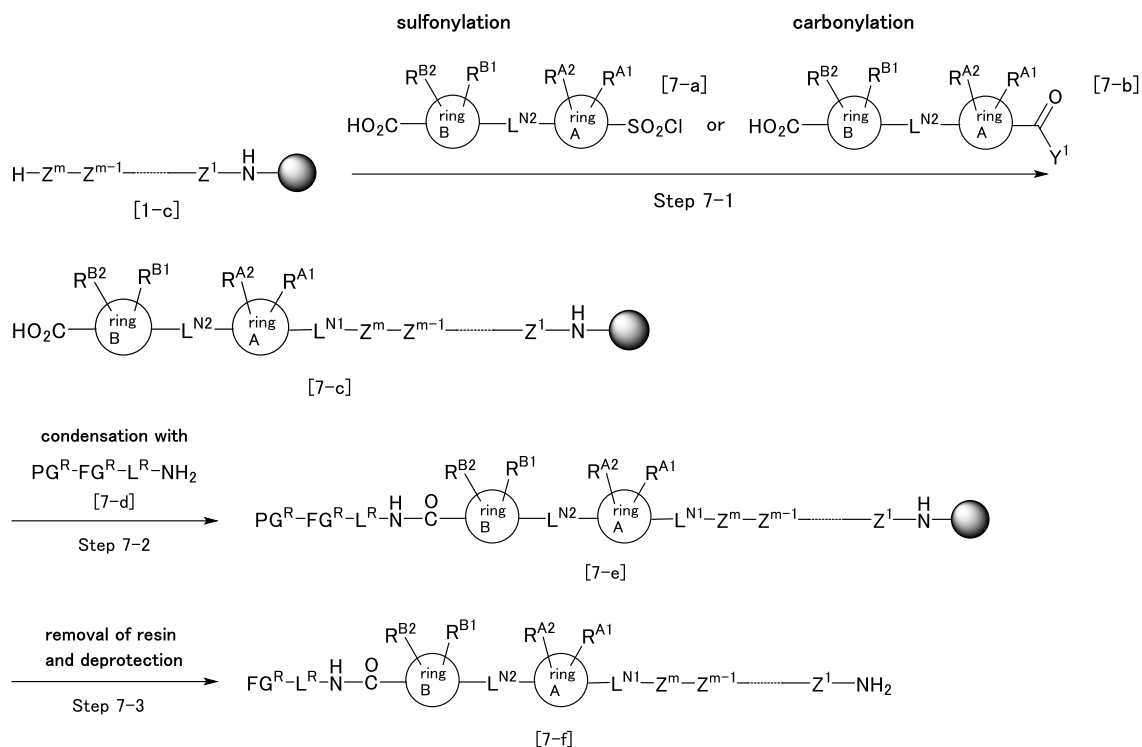
In the method described in Scheme 6, compound [6-d] to be used as a raw material compound can be obtained by producing with a method known per se, or purchasing a commercially available product of it. Compound [6-a] can be produced with the method described in Scheme 1 or Scheme 2, or a method similar to any of these.

Method F: a method for producing compound [7-f], which has a substituent,

"alkylaminocarbonyl substituted with functional group", on ring B

Compound [7-f] can be produced, for example, through solid-phase synthesis the summary of which is described in the following (Scheme 7).

5 Scheme 7



wherein

$R^{A1}, R^{A2}, R^{B1}, R^{B2}, L^{N1}, L^{N2}$, ring A, ring B, $H-Z^x-OH$, x, m, Z^x , and Y^1 have the same definitions as those described above,

10 L^R represents C_{1-4} alkanediyl,

FG^R represents a functional group attached to "alkyl (L^R)" of "alkylaminocarbonyl ($L^R-NHC(=O)-$)", a substituent present on ring B, and examples thereof may include the formula -O- (the formula -OH), the formula -S- (the formula -SH), the formula -NH- (the formula -NH₂), the formula -C(=O)O- (the formula -C(=O)OH), and the formula -C(=O)NH- (the formula -C(=O)NH₂),

15 PG^R represents a protecting group for the functional group (FG^R), wherein examples of the protecting group include tBu for carboxy, Trt for carbamoyl, tBu for hydroxy, tBu for thiol

(sulfanyl), and Boc for amino, and these protecting groups can be each deprotected by treating with an acid.

(1) [Step 7-1]

Compound [7-c], which has carboxy on ring B, can be produced by reacting
5 compound [1-c] with compound [7-a] or compound [7-b] to sulfonylate or acylate the free amino of the N-terminal amino acid of the polypeptide moiety in compound [1-c].

(2) [Step 7-2]

Compound [7-e] can be produced by reacting compound [7-c] with compound [7-d]
10 for amidation reaction between the carboxy in compound [7-c] and the amino in compound [7-d].

(3) [Step 7-3]

Compound [7-f], one of the present inventive compounds, can be produced by using an acid on compound [7-e] obtained in (2) to cleave the bond to the resin and simultaneously deprotect the protecting group (PG^R) of the functional group of "alkylaminocarbonyl
15 substituted with functional group (FG^R)" present on ring B. Examples of the acid applicable in the present step may include TFA. At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be simultaneously deprotected.

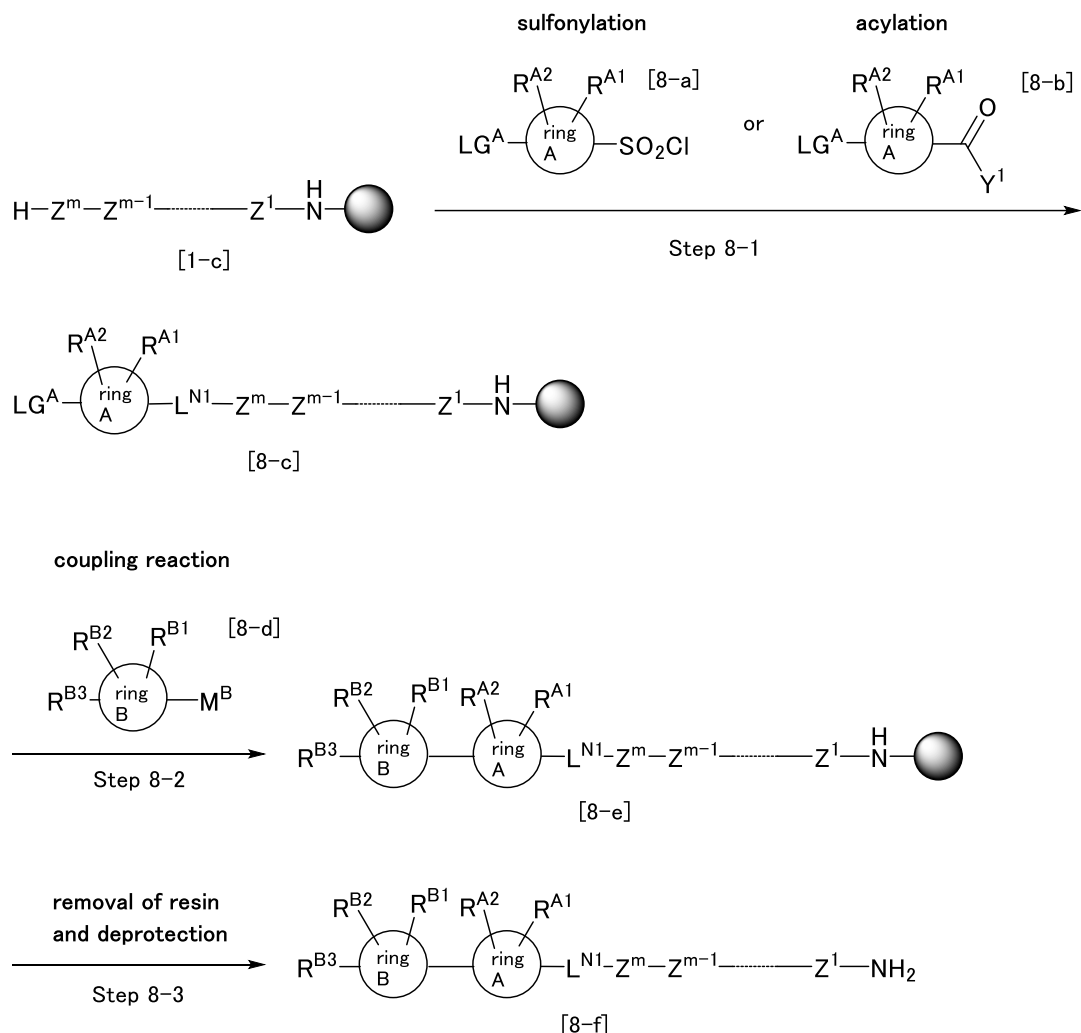
Compound [7-f] obtained in the described manner can be isolate/purified by a
20 known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

In the method described in Scheme 7, compound [7-a], compound [7-b], and compound [7-d] to be used as raw material compounds can be obtained by producing with a method known per se, or purchasing commercially available products of them. Compound
25 [1-c] can be produced with the method described in Scheme 1, or a method similar to it.

Method G: a method for producing compound [8-f], in which ring A is directly substituted with ring B

Compound [8-f] can be produced, for example, through solid-phase synthesis the summary of which is described in the following (Scheme 8).

Scheme 8



5 wherein

$\text{R}^{\text{A}1}$, $\text{R}^{\text{A}2}$, $\text{R}^{\text{B}1}$, $\text{R}^{\text{B}2}$, $\text{R}^{\text{B}3}$, $\text{L}^{\text{N}1}$, ring A, ring B, $\text{H-Z}^{\text{x}}\text{---OH}$, x, m, Z^{x} , and Y^1 have the same definitions as those described above,

LG^{A} represents a leaving group, wherein examples of the leaving group may include a chlorine atom, a bromine atom, an iodine atom, and halo C_{1-6} alkylsulfonyloxy, and

10 M^{B} represents boronic acid, boronic acid ester, alkyltin, alkylsilane, or alkoxy silane.

(1) [Step 8-1]

Compound [8-c] can be produced by reacting compound [1-c] with compound [8-a]

or compound [8-b] to sulfonylate or acylate the free amino of the N-terminal amino acid of the polypeptide moiety in compound [1-c].

(2) [Step 8-2]

Compound [8-e], in which ring A is directly substituted with ring B, can be produced by subjecting compound [8-c] to coupling reaction with compound [8-d] in the presence of a metal catalyst and a base. Examples of the metal catalyst may include tetrakis(triphenylphosphine)palladium, palladium acetate, and tris(dibenzylideneacetone)dipalladium. Examples of the base may include metal carbonates such as cesium carbonate, potassium carbonate, and sodium carbonate, and potassium phosphate, cesium fluoride, potassium fluoride, and tetrabutylammonium fluoride.

(3) [Step 8-3]

Compound [8-f], one of the present inventive compounds, can be produced by using an acid on compound [8-e] obtained in (2) to cleave the bond to the resin. Examples of the acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be simultaneously deprotected.

Compound [8-f] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

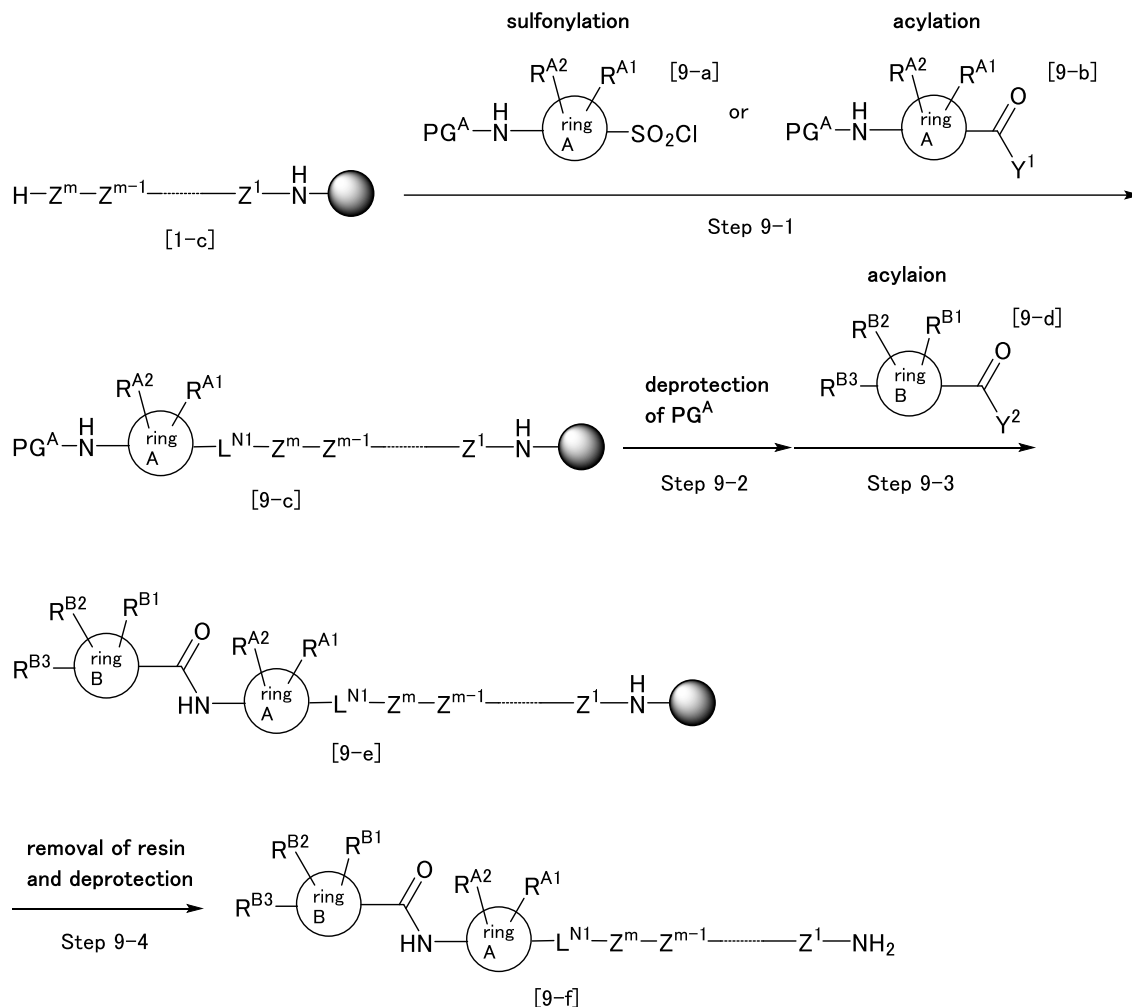
In the method described in Scheme 8, compound [8-a], compound [8-b], and compound [8-d] to be used as raw material compounds can be obtained by producing with a method known per se, or purchasing commercially available products of them. Compound [1-c] can be produced with the method described in Scheme 1, or a method similar to it.

Method H: a method for producing compound [9-f], which has the substituent "arylcarbonylamino (the formula ring B-C(=O)NH-)" on ring A

Compound [9-f] can be produced, for example, through solid-phase synthesis the

summary of which is described in the following (Scheme 9).

Scheme 9



5 wherein

$\text{R}^{\text{A}1}$, $\text{R}^{\text{A}2}$, $\text{R}^{\text{B}1}$, $\text{R}^{\text{B}2}$, $\text{R}^{\text{B}3}$, $\text{L}^{\text{N}1}$, ring A, ring B, $\text{H}-\text{Z}^x-\text{OH}$, x , m , Z^x , and Y^1 have the same definitions as those described above,

Y^2 represents hydroxy or a chlorine atom, and

PG^A represents a liposoluble protecting group protecting amino present on ring A,

10 wherein examples of the liposoluble protecting group may include Fmoc.

(1) [Step 9-1]

As in step 8-1 of Scheme 8, compound [9-c] can be produced by reacting compound [1-c] with compound [9-a] or compound [9-b] to sulfonylate or acylate the free amino of the

N-terminal amino acid of the polypeptide moiety in compound [1-c].

(2) [Step 9-2]

The liposoluble protecting group (PG^A) in compound [9-c] obtained in (1) is subjected to deprotection.

5 (3) [Step 9-3]

Compound [9-e] can be produced by reacting the compound obtained in (2) with compound [9-d] for amidation (acylation) reaction between the free amino in the compound obtained in (2) and the carboxy in compound [9-d].

(4) [Step 9-4]

10 Compound [9-f], one of the present inventive compounds, can be produced by using an acid on compound [9-e] obtained in (3) to cleave the bond to the resin. Examples of the acid applicable in the present step may include TFA.

At that time, if a protected functional group is present in the side chain of an amino acid forming the polypeptide moiety, the protecting group of the functional group can be
15 simultaneously deprotected.

Compound [9-f] obtained in the described manner can be isolate/purified by a known separation/purification means such as concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, and chromatography.

In the method described in Scheme 9, compound [9-a], compound [9-b], and
20 compound [9-d] to be used as raw material compounds can be obtained by producing with a method known per se, or purchasing commercially available products of them. Compound [1-c] can be produced with the method described in Scheme 1, or a method similar to it.

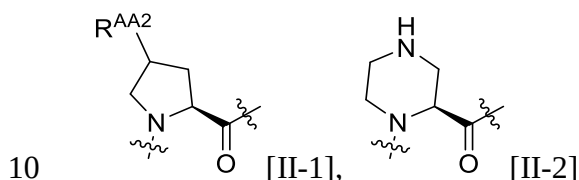
All kinds of amino acids can be used for the amino acids in the methods shown in Schemes 1 to 9 for producing compound [I'] according to the present invention, and examples
25 of the amino acids include natural proteogenic L-amino acids: Gly, Ala, Val, Leu, Ile, Pro, Phe, His, Trp, Tyr, Ser, Thr, Met, Cys, Asp, Glu, Asn, Gln, Lys, and Arg.

In addition, nonnatural amino acids including natural nonproteogenic amino acids and the D-forms of the natural proteogenic L-amino acids described above may be used in

the present production methods.

Here, examples of nonnatural amino acids applicable in the present production methods include the following:

- (d)-Pro, (d)-Ser, (d)-Thr, (d)-Asp, (d)-Glu, (d)-Arg, (d)-Lys
- 5 - β -homoPro
- β -Ala, GABA, Ape, Acp
- (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp, (N-Me)Glu
- a group represented by formula [II-1] or formula [II-2]:



wherein R^{AA2} is hydroxy or amino; and

- the amino acids listed in Table 1 and Table 2

Examples of liposoluble protecting groups may include carbonate protecting groups, amide protecting groups, and alkyl protecting groups such as 9-fluorenylmethoxycarbonyl (Fmoc), tert-butyloxycarbonyl (Boc), benzyl (Bn), allyl (Allyl), allyloxycarbonyl (Alloc), and acetyl (Ac). Introduction of a liposoluble protecting group to an amino acid, for example, introduction of Fmoc, can be achieved by adding 9-fluorenylmethyl-N-succinidyl carbonate and sodium hydrogen carbonate for reaction. It is recommended to perform the reaction at 0 to 50°C, preferably at room temperature, for about 1 to 5 hours.

Commercially available amino acids protected with a liposoluble protecting group may be used. Examples thereof may include Fmoc-Ser-OH, Fmoc-Asn-OH, Fmoc-Val-OH, Fmoc-Leu-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Tyr-OH, Fmoc-Gly-OH, Fmoc-Lys-OH, Fmoc-Arg-OH, Fmoc-His-OH, Fmoc-Asp-OH, Fmoc-Glu-OH, Fmoc-Gln-OH, Fmoc-Thr-OH, Fmoc-Cys-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Trp-OH, and Fmoc-Pro-OH.

Examples of amino acids protected with a liposoluble protecting group and having a

protecting group introduced into the side chain may include Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Cys(tBu)-OH, Fmoc-Glu(OtBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-His(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Trp(Boc)-OH, and Fmoc-Tyr(tBu)-OH.

5 The resin may be any resin commonly used for solid-phase synthesis, and, for example, 2-chlorotrityl chloride resin, which is functionalized with a chlorine atom, Wang resin, HMPA-PEGA resin, and Amino-PEGA resin, which is functionalized with amino, are applicable.

10 Solid-phase synthesis using resin for amide synthesis is recommended as a method for obtaining an amide formed at the C terminus of peptide. For example, Rink-Amide-AM resin, SAL-PEG resin, SAL-MBHA resin, or Rink-Amide-PEGA resin can be used. An amide formed at the C terminus of peptide can be obtained by cleaving off peptide from the resin.

15 To bond an amino acid whose amino has been protected with a liposoluble protecting group to resin, for example, in the case that resin having hydroxy or resin functionalized with a chlorine atom is used, the bonding can be achieved by allowing the carboxy of the amino acid to form an ester bond to the resin.

 In the case that resin functionalized with amino is used, the bonding can be achieved by allowing the carboxy of the amino acid to form an amide bond to the resin.

20 In the case that 2-chlorotrityl chloride resin is used, esterification can be performed by using a base such as diisopropylethylamine (DIPEA), triethylamine, pyridine, and 2,4,6-collidine.

 In the case that resin having hydroxy is used, a known dehydrating/condensing agent such as 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4,-triazole (MSNT), dicyclohexylcarbodiimide (DCC), and diisopropylcarbodiimide (DIC) can be used as an esterification catalyst.
25 Regarding the usage ratio between an amino acid and a dehydrating/condensing agent, the amount of the latter is typically 1 to 10 equivalents, and preferably 2 to 5 equivalents per equivalent of the former.

For example, it is preferable to perform esterification reaction in such a manner that a resin is put in a solid-phase column, this resin is washed with a solvent, and a solution of an amino acid is then added thereto. Examples of the washing solvent may include chloroform, dimethylformamide (DMF), 2-propanol, and dichloromethane. Examples of the solvent to
5 dissolve an amino acid therein include chloroform, dimethyl sulfoxide (DMSO), DMF, and dichloromethane. It is recommended to perform esterification reaction at 0 to 50°C, preferably at room temperature, for about 10 minutes to 30 hours, preferably for about 15 minutes to 24 hours.

At that time, it is also preferable to acetylate unreacted hydroxy on the solid phase
10 by using acetic anhydride or the like for capping.

Elimination of a liposoluble protecting group can be performed, for example, by treating with a base. Examples of the base may include piperidine and morpholine. At that time, it is preferable that the elimination be performed in the presence of a solvent. Examples of the solvent may include DMF, DMSO, and methanol.

15 It is preferable to perform amidation reaction between the liberated amino and the carboxy of any amino acid whose amino has been protected with a liposoluble protecting group in the presence of an activator and a solvent.

Examples of the activator may include dicyclohexylcarbodiimide (DCC),
1-ethyl-3-(dimethylaminopropyl)carbodiimide-hydrochloride (WSC/HCl),
20 diphenylphosphorylazide (DPPA), carbonyldiimidazole (CDI), diethylcyanophosphonate (DEPC), benzotriazol-1-yloxy-trispyrrolidinophosphonium (DIPCI),
benzotriazol-1-yloxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP),
1-hydroxybenzotriazole (HOBt), hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP), 1-hydroxy-7-azabenzotriazole (HOAt), hydroxyphthalimide (HOPht),
25 pentafluorophenol (Pfp-OH), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU),
1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium 3-oxide hexafluorophosphate (HCTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate (HATU), O-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 3,4-dihydro-3-hydrodi-4-oxa-1,2,3-benzotriazine (Dhbt), N-[1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino (morpholino)]uronium hexafluorophosphate (COMU), and ethyl cyano(hydroxyimino)acetate (Oxyma).

5 It is preferable to set the amount of usage of the activator to 1 to 20 equivalents, preferably to 1 to 10 equivalents, more preferably to 1 to 5 equivalents, with respect to any amino acid whose amino has been protected with a protecting group having liposolubility.

 Examples of the solvent may include DMF, DMSO, and dichloromethane. It is recommended to perform the reaction at 0 to 50°C, preferably at room temperature, for about
10 10 minutes to 30 hours, preferably for about 15 minutes to 2 hours.

 Cleaving-off of a peptide chain from resin can be performed through treatment with an acid. Examples of the acid may include trifluoroacetic acid (TFA) and hydrogen fluoride (HF). It is recommended to perform the reaction for separation from resin at 0 to 50°C, preferably at room temperature, for about 10 minutes to 10 hours, preferably for about
15 30 minutes to 4 hours.

 The present invention is described in more detail with reference to Examples, Reference Examples, and Test Examples below; however, these do not limit the present invention, and any modification may be made without departing from the scope of the present invention.

20 Abbreviations in the present specification are shown in the following.

APCI: atmospheric pressure chemical ionization

Arg (Pbf): N^ω-2,2,4,6,7-pentamethyldihydrobenzofuransulfonylarginine

Bu: butyl

BuOH: butanol

25 Dde: 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-ethyl

DMSO-d₆: hexadeutrated dimethyl sulfoxide

ELSD: evaporative light scattering detector

ESI: electrospray ionization

HPLC: high-performance liquid chromatography

ivDde: 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl

LCMS: liquid chromatography/mass spectrometry

NMP: 1-methyl-2-pyrrolidone

5 Trt: trityl

UV: ultraviolet ray

Herein, "room temperature" refers to 20 to 30°C, unless otherwise specified.

"Under ice-cooling" refers to 0 to 5°C, unless otherwise specified.

Herein, Biotage (registered trademark) SNAP Ultra manufactured by Biotage AB or

10 REVELERIS (registered trademark) Silica 40 µm manufactured by BUCHI Labortechnik AG was used for "silica gel cartridge" in purification with column chromatography.

In purification with reversed-phase column chromatography (hereinafter, occasionally referred to as preparative LCMS), an appropriate condition was selected from two conditions shown in the following, and purification was performed.

15 Separation apparatus: used was Agilent 1260 Infinity and Agilent 6130 (ionization method: Electron Spray Ionization: ESI), or Agilent 385-ELSD when an ELSD detector was involved, each apparatus being from Agilent Technologies

Solvent: solution A; water with 0.1% formic acid, solution B; acetonitrile with 0.1% formic acid

20 Flow rate: 50 mL/min

One of the following columns was used.

Waters XBridge Prep C18, 5 µm, 30 × 50 mm

Waters XSelect CSH C18, 5 µm, 30 × 50 mm

(Separation condition A)

25 0.0-0.5 min (solution A/solution B = 90/10)

0.5-7.5 min (solution A/solution B = 90/10 to 20/80)

7.5-7.95 min (solution A/solution B = 20/80)

7.95-8.0 min (solution A/solution B = 20/80 to 5/95)

8.0-9.0 min (solution A/solution B = 5/95)

(Separation condition B)

0.0-0.5 min (solution A/solution B = 95/5)

0.5-7.5 min (solution A/solution B = 95/5 to 50/50)

5 7.5-7.95 min (solution A/solution B = 50/50)

7.95-8.0 min (solution A/solution B = 50/50 to 5/95)

8.0-9.0 min (solution A/solution B = 5/95)

Instrumental data shown herein were determined with the following instruments.

Microwave reactor: Initiator (Biotage AB)

10 NMR spectra: [1H-NMR] 600 MHz: JNM-ECA600 (JEOL Ltd.), 400 MHz: AVANCE III HD 400 (Bruker)

Mass spectra of high-performance liquid chromatography (LCMS) and retention time (RT) in the present specification were determined under conditions shown in the following.

15 Measurement apparatus: LCMS-2010EV, Shimadzu Corporation

Column: Shimadzu XR-ODS, 2.2 μ m, 2.0 $\times$ 30 mm

Ionization method: ESI/APCI dual source

Solvent: solution A; water with 0.1% formic acid, solution B; acetonitrile with 0.1% formic acid

20 Flow rate: 0.6 mL/min, detection method: UV 210 nm, 254 nm

(Analysis condition A)

0.0-1.0 min (solution A/solution B = 90/10 to 60/40)

1.0-2.0 min (solution A/solution B = 60/40 to 1/99)

2.0-2.6 min (solution A/solution B = 1/99)

25 (Analysis condition B)

0.0-0.5 min (solution A/solution B = 90/10)

0.5-1.5 min (solution A/solution B = 90/10 to 70/30)

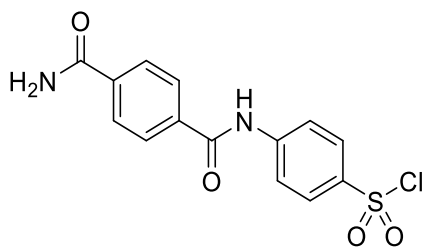
1.5-2.5 min (solution A/solution B = 70/30 to 1/99)

2.5-5.0 min (solution A/solution B = 1/99)

Compound names in Production Examples, Reference Examples, and Examples were given in accordance with "ACD/Name 2019.1.2 (ACD Labs 2019.1.2, Advanced Chemistry Development Inc.)".

5

Reference Example 1 4-(4-Carbamoylbenzamide)benzenesulfonyl chloride



To a solution of 4-carbamoylbenzoic acid (150 g) in DMF (180 mL), WSC monohydrochloride (209 g), HOBt monohydrate (167 g), and DIPEA (380 mL) were added.

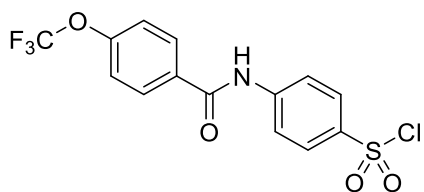
10 After stirring at room temperature for 5 minutes, aniline (99 mL) was added, and the resultant was stirred at room temperature for 72 hours. Water was added to the reaction solution, and a solid precipitated was collected through filtration to afford N-phenylterephthalamide (147 g) as a yellow amorphous.

15 To N-phenylterephthalamide obtained, chlorosulfonic acid (407 mL) was added, and the resultant was stirred at 60°C for 1 hour with heating. The reaction mixture was ice-cooled, and then added to iced water. A solid precipitated was collected through filtration, washed with water, and then dried to afford the title compound (198 g) as a light-yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.54 (bs, 1 H), 7.62 (d, J=8.2 Hz, 2 H), 7.79 (d, J=8.2 Hz, 2 H), 7.96-8.09 (m, 4 H), 8.14 (bs, 1 H), 10.46 (s, 1 H)

20

Reference Example 2 4-(4-(Trifluoromethoxy)benzamide)benzenesulfonyl chloride

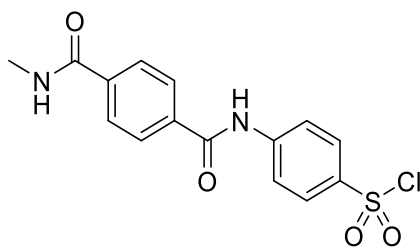


With the same procedure as in Reference Example 1, the title compound was obtained as a yellow solid from the corresponding raw material.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.52 (d, $J=8.3$ Hz, 2 H), 7.58 (d, $J=8.3$ Hz, 2 H), 7.72 (d, $J=8.3$ Hz, 2 H), 8.08 (d, $J=8.3$ Hz, 2 H), 10.42 (s, 1 H)

5

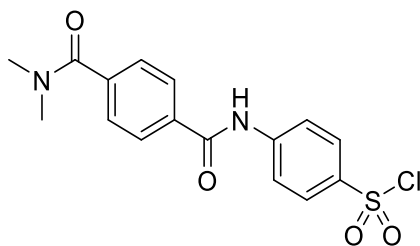
Reference Example 3 4-(4-(Methylcarbamoyl)benzamide)benzenesulfonyl chloride



With the same procedure as in Reference Example 1, the title compound was obtained as a gray solid from the corresponding raw material.

10 ^1H NMR (600 MHz, DMSO- d_6) δ ppm 2.81 (d, $J=4.1$ Hz, 3 H), 7.57-7.61 (m, 2 H), 7.72-7.78 (m, 2 H), 7.96 (d, $J=8.7$ Hz, 2 H), 8.03 (d, $J=8.7$ Hz, 2 H), 8.62 (q, $J=4.1$, 1 H), 10.42 (s, 1 H)

Reference Example 4 4-(4-(Dimethylcarbamoyl)benzamide)benzenesulfonyl chloride



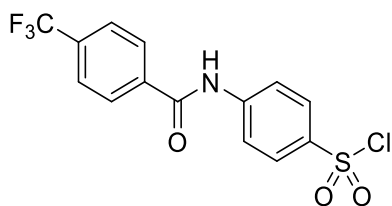
15

With the same procedure as in Reference Example 1, the title compound was obtained as a brown solid from the corresponding raw material.

^1H NMR (600 MHz, DMSO- d_6) δ ppm 2.91 (s, 3 H), 3.01 (s, 3 H), 7.54 (d, $J=8.3$ Hz, 2 H), 7.58 (d, $J=8.3$ Hz, 2 H), 7.74 (d, $J=8.3$ Hz, 2 H), 8.01 (d, $J=8.3$ Hz, 2 H), 10.41 (s, 1 H)

20

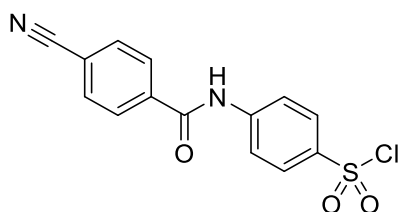
Reference Example 5 4-(4-(Trifluoromethyl)benzamide)benzenesulfonyl chloride



With the same procedure as in Reference Example 1, the title compound was obtained as a white solid from the corresponding raw material.

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.81 (d, J=8.2 Hz, 2 H), 7.93 (d, J=8.1 Hz, 2 H), 8.01 (d, J=8.2 Hz, 2 H), 8.08 (d, J=8.1 Hz, 3 H)

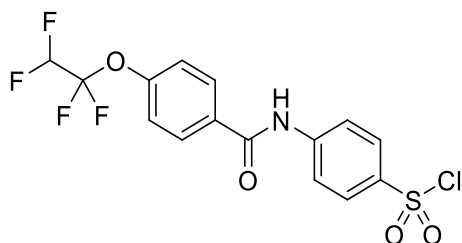
Reference Example 6 4-(4-Cyanobenzamido)benzenesulfonyl chloride



With the same procedure as in Reference Example 1, the title compound was obtained as a light brown solid from the corresponding raw material.

¹H NMR (600 MHz, DMSO-d₆) δ ppm 7.58 (d, J=8.3 Hz, 2 H), 7.74 (d, J=8.3 Hz, 2 H), 7.99 (d, J=8.3 Hz, 2 H), 8.01 (d, J=8.3 Hz, 2 H), 10.42 (s, 1 H)

Reference Example 7 4-(4-(1,1,2,2-Tetrafluoroethoxy)benzamido)benzenesulfonyl chloride

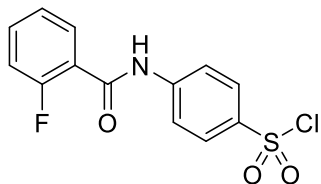


With the same procedure as in Reference Example 1, the title compound was obtained as a yellow solid from the corresponding raw material.

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 5.95 (tt, J=53.2 Hz, 2.8 Hz, 1 H), 7.37 (d, J=8.6 Hz, 2 H), 7.92 (d, J=7.2 Hz, 2 H), 7.94 (d, J=7.2 Hz, 2 H), 8.05 (d, J=8.6 Hz, 2 H),

8.12 (s, 1 H)

Reference Example 8 4-(2-Fluorobenzamide)benzenesulfonyl chloride

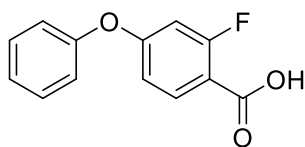


5 With the same procedure as in Reference Example 1, the title compound was obtained as a white solid from the corresponding raw material.

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.20-7.27 (m, 1 H), 7.37 (dd, J=7.6 Hz, 7.6 Hz, 1 H), 7.56-7.63 (m, 1 H), 7.95 (d, J=9.1 Hz, 2 H), 8.06 (d, J=9.1 Hz, 2 H), 8.20 (td, J=8.0 Hz, 1.8 Hz, 1 H), 8.75 (d, J=16.9 Hz, 1 H)

10

Reference Example 9 2-Fluoro-4-phenoxybenzoic acid

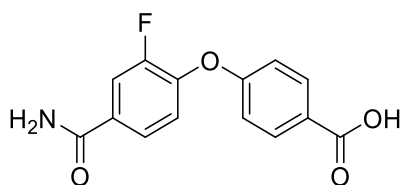


To a solution of 2,4-difluorobenzaldehyde (250 mg) and phenol (199 mg) in DMF (10 mL), potassium carbonate (535 mg) was added, and the resultant was stirred at 120°C for 15 4 hours with heating. After allowing to cool to room temperature, the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to afford 2-fluoro-4-phenoxybenzaldehyde.

In tetrahydrofuran (5 mL) and water (5 mL), 2-fluoro-4-phenoxybenzaldehyde 20 obtained was dissolved, to which sodium dihydrogen phosphate (844 mg), 2-methyl-2-butene (1.49 mL), and sodium chlorite (636 mg) were added, and the resultant was stirred at room temperature for 3 hours. Chloroform was added to the reaction solution, which was washed with water. The organic layer was allowed to pass through a Phase separator, and concentrated under reduced pressure to afford the title compound (182 mg) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 6.75-6.92 (m, 2 H), 7.17 (d, $J=7.5$ Hz, 2 H), 7.24-7.33 (m, 1 H), 7.43-7.55 (m, 2 H), 7.83-7.97 (m, 1 H), 13.0 (br s, 1 H)

Reference Example 10 4-(4-Carbamoyl-2-fluorophenoxy)benzoic acid

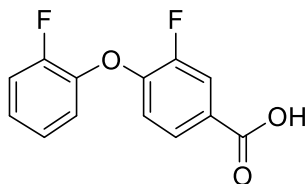


With the same procedure as in Reference Example 9, the title compound was obtained as a white solid from the corresponding raw material.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.12 (d, $J=8.4$ Hz, 1 H), 7.19 (d, $J=8.4$ Hz, 2 H), 7.40 (t, $J=8.3$ Hz, 1 H), 7.53 (br s, 1 H), 7.82 (t, $J=8.3$ Hz, 1 H), 7.90-8.00 (m, 2 H), 8.07 (br s, 1 H), 9.95 (s, 1 H)

10

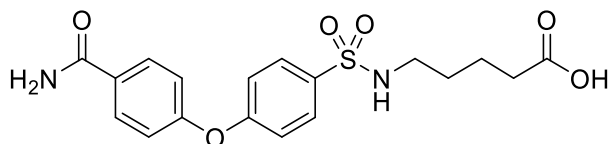
Reference Example 11 3-Fluoro-4-(2-fluorophenoxy)benzoic acid



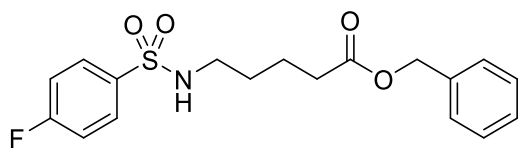
With the same procedure as in Reference Example 9, the title compound was obtained as a white solid from the corresponding raw material.

^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 6.89 (t, $J=8.1$ Hz, 1 H), 7.10-7.25 (m, 4H), 7.80 (d, $J=8.4$ Hz, 1 H), 7.89 (d, $J=11.3$ Hz, 1 H)

Reference Example 12 5-((4-(4-Carbamoylphenoxy)phenyl)sulfonamide)pentanoic acid



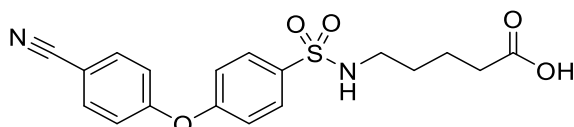
(1)



To a solution of benzyl 5-aminopentanoate-tosilate (1.48 g) in chloroform (20 mL), triethylamine (2.3 mL) and 4-fluorobenzenesulfonyl chloride (800 mg) were added under ice-cooling, and the resultant was stirred under ice-cooling for 1 hour. After the completion of the reaction, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture, and extraction was performed with chloroform. The organic layer was allowed to pass through a Phase separator, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel cartridge, hexane:ethyl acetate = 80:20 to 50:50) to afford benzyl 5-((4-fluorophenyl)sulfonamide)pentanoate (1.24 g) as a colorless oily substance.

^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 1.46-1.56 (m, 2 H), 1.58-1.68 (m, 2 H), 2.33 (t, $J=7.0$ Hz, 2 H), 2.96 (q, $J=6.5$ Hz, 2 H), 4.40-4.47 (m, 1 H), 5.09 (s, 2 H), 7.18 (t, $J=8.2$ Hz, 2 H), 7.31-7.39 (m, 5 H), 7.86 (dd, $J=7.6$ Hz, 5.3 Hz, 2 H)

(2)



To a solution of benzyl 5-((4-fluorophenyl)sulfonamide)pentanoate (500 mg) obtained in (1) in DMF (13 mL), 4-hydroxybenzonitrile (179 mg) and potassium carbonate (567 mg) were added, and the resultant was stirred under microwave irradiation at 180°C for 1 hour. After the reaction solution was allowed to cool, ethyl acetate and water were added to the reaction mixture for liquid separation. After the aqueous layer was washed with ethyl acetate, the pH was adjusted to 1 with 1 M hydrochloric acid aqueous solution, and extraction was performed with ethyl acetate/toluene mixed solvent. The organic layer was washed with water, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to afford 5-((4-(4-cyanophenoxy)phenyl)sulfonamide)pentanoic acid (285 mg) as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.32-1.49 (m, 4 H), 2.10-2.17 (m, 2 H), 2.69-2.78 (m, 2 H), 7.23-7.31 (m, 2 H), 7.43 (t, J=8.7 Hz, 2 H), 7.59-7.66 (m, 1 H), 7.81-7.87 (m, 3 H), 7.91 (d, J=8.3 Hz, 1 H)

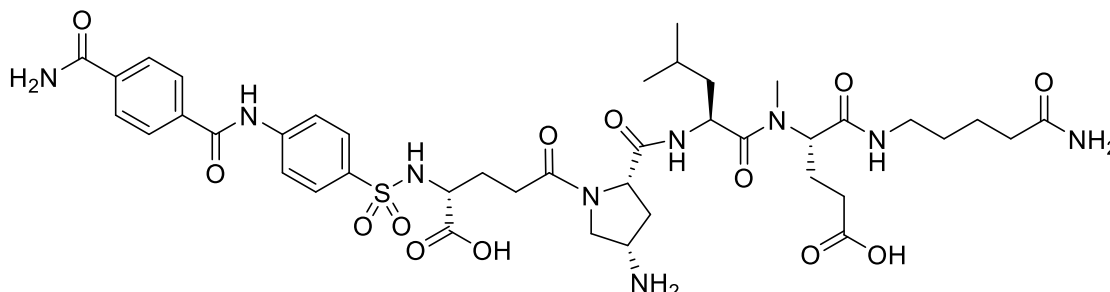
(3)

5 To a solution of 5-((4-(4-cyanophenoxy)phenyl)sulfonamide)pentanoic acid (100 mg) obtained in (2) in DMSO (2 mL), potassium carbonate (81 mg) and 30% hydrogen peroxide solution (0.15 mL) were added, and the resultant was stirred at room temperature for 2 hours. After the completion of the reaction, sodium thiosulfate aqueous solution and 1 M hydrochloric acid aqueous solution were added, and extraction was performed with ethyl
10 acetate. The organic layer was washed with water, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to afford the title compound (89 mg) as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.32-1.50 (m, 4 H), 2.10-2.18 (m, 2 H), 2.69-2.78 (m, 2 H), 7.16 (d, J= 8.2 Hz, 1 H), 7.19 (d, J= 8.6 Hz, 1 H), 7.34 (br s, 1 H), 7.43 (t, J= 8.6 Hz, 2 H), 7.52-7.58 (m, 1 H), 7.59-7.66 (m, 1 H), 7.86- 7.79 (m 3 H), 7.96 (d, J=7.7 Hz, 1 H),
15 12.0 (br s, 1 H)

Example 1 Synthesis of compound of compound No. 1:

(N-[4-(4-carbamoylbenzamido)benzene-1-sulfonyl]-D-γ-glutamyl-(4S)-4-amino-L-prolyl-L-I
20 eucyl-N-(5-amino-5-oxopentyl)-N²-methyl-L-α-glutamine)



(1)

Fmoc-Rink Amide AM resin (0.10 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.6 mL) for 3 minutes, and then treated with DMF solution

of piperidine (concentration: 20%, 1.6 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc-Ape-OH (0.40 mmol) in DMF (0.8 mL), a solution of COMU (0.40 mmol) and Oxyma (0.40 mmol) in DMF (0.8 mL), and a solution of DIPEA (0.80 mmol) in NMP (0.4 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce an Ape residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(N-Me)Glu(OtBu)-OH, Fmoc-Leu-OH, Fmoc-(2S,4S)-(4-NHBoc)Pro-OH, and Fmoc-(d)-Glu-OtBu were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by piperidine/DMF treatment in the above manner, and H- γ -(d)-Glu(OtBu)-(2S,4S)-(4-NHBoc)Pro-Leu-(N-Me)Glu(OtBu)-Ape-Rink Amide AM resin was synthesized.

(2)

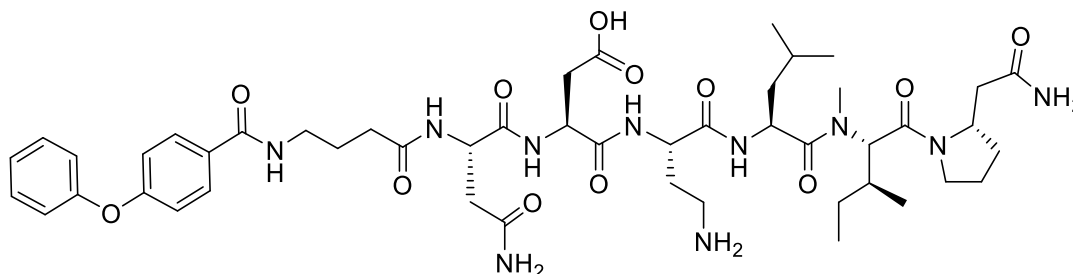
To the resin obtained in (1), a solution of 4-(4-carbamoylbenzamide)benzenesulfonyl chloride (0.30 mmol) obtained in Reference Example 1 and DIPEA (0.60 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 1 hour. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times) and chloroform (3 mL $\times$ three times).

(3)

To the resin obtained in (2), TFA:water:triisopropylsilane (92.5:2.5:5, 4 mL) was added, the mixture was shaken at room temperature for 1.5 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition B). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (46 mg) as a white powder.

Example 2 Synthesis of compound of compound No. 106:

(*N*²-[4-(4-phenoxybenzamido)butanoyl]-L-asparaginy]-*N*-[(2*S*)-4-amino-1-({(2*S*)-1-[(2*S*,3*S*)-1-[(2*S*)-2-(2-amino-2-oxoethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}(methyl)amino]-4-methyl-1-oxopentan-2-yl}amino)-1-oxobutan-2-yl]-L- α -asparagine)



5 (1)

Fmoc-NH-SAL-PEG resin (0.12 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.9 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.9 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc- β -homoPro-OH (0.48 mmol) in DMF (1.0 mL), a solution of COMU (0.48 mmol) and Oxyma (0.48 mmol) in DMF (1.0 mL), and a solution of DIPEA (0.96 mmol) in NMP (0.48 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a β -homoPro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(*N*-Me)Ile-OH, Fmoc-Leu-OH, Fmoc-Dab(Boc)-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-GABA-OH, and 4-phenoxybenzoic acid were sequentially condensed, and Ph-O-Ph-CO-GABA-Asn(Trt)-Asp(OtBu)-Dab(Boc)-Leu-(*N*-Me)Ile- β -homoPro-NH-SAL-PEG resin was synthesized. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times) and chloroform (3 mL $\times$ three times).

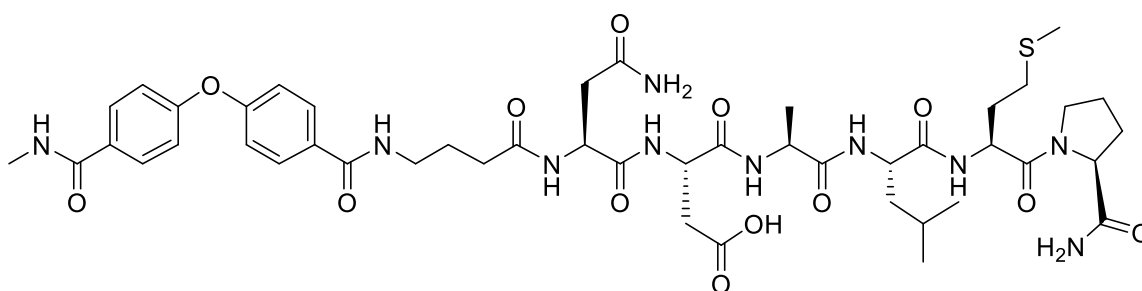
(2)

20 To the resin obtained in (1), TFA:water:triisopropylsilane:dithiothreitol (90:2.5:5:2.5, 4 mL) was added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The

crude product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (14 mg) as a white powder.

5 Example 3 Synthesis of compound of compound No. 177:

(*N*²-(4-{4-[4-(methylcarbamoyl)phenoxy]benzamido}butanoyl)-L-asparaginy-L- α -aspartyl-L-alanyl-L-leucyl-L-methionyl-L-prolinamide)



10 (1)

Fmoc-NH-SAL-PEG resin (0.10 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.6 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.6 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc-Pro-OH (0.40 mmol) in DMF (0.8 mL), a solution of COMU (0.40 mmol) and Oxyma (0.40 mmol) in DMF (0.8 mL), and a solution of DIPEA (0.80 mmol) in NMP (0.4 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a Pro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-Met-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Asn(Trt)-OH, and Fmoc-GABA-OH were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by piperidine/DMF treatment in the above manner, and H-GABA-Asn(Trt)-Asp(OtBu)-Ala-Leu-Met-Pro-NH-SAL-PEG resin was synthesized.

(2)

To the resin obtained in (1), a solution of 4,4'-oxybisbenzoic acid (0.75 mmol),

HATU (0.15 mmol), and DIPEA (2.0 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 2 hours. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times).

(3)

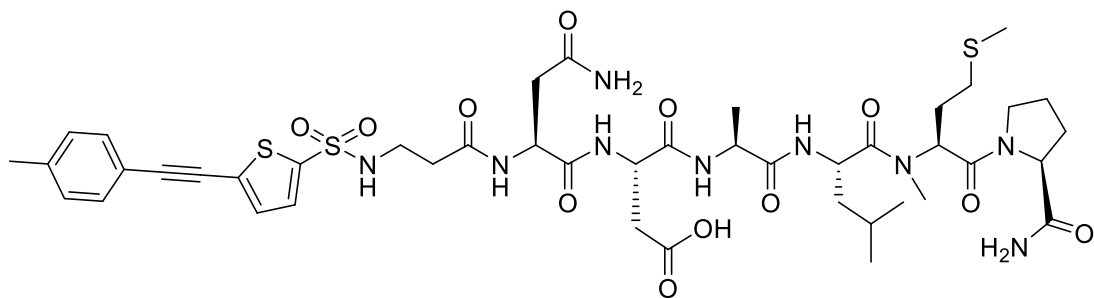
5 To the resin obtained in (2), a solution of HATU (0.30 mmol), DIPEA (0.60 mmol), and methanol solution of methylamine (concentration: 9.8 mol/L, 0.30 mmol) in DMF (3 mL) was added, and the mixture was stirred at room temperature for 4 hours. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times) and chloroform (3 mL $\times$ three times).

10 (4)

To the resin obtained in (3), TFA:water:triisopropylsilane:dithiothreitol (90:2.5:5:2.5, 4 mL) was added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (30 mg) as a white powder.

20 Example 4 Synthesis of compound of compound No. 587:

(*N*-{5-[(4-methylphenyl)ethynyl]thiophene-2-sulfonyl}- β -alanyl-L-asparaginyl-L- α -aspartyl-L-alanyl-L-leucyl-*N*-methyl-L-methionyl-L-prolinamide)



(1)

Fmoc-NH-SAL-PEG resin (0.10 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.6 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.6 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc-Pro-OH (0.40 mmol) in DMF (0.8 mL) solution, a solution of COMU (0.40 mmol) and Oxyma (0.40 mmol) in DMF (0.8 mL), and a solution of DIPEA (0.80 mmol) in NMP (0.4 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a Pro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(N-Me)Met-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Asn(Trt)-OH, and Fmoc- β -Ala-OH were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by piperidine/DMF treatment in the above manner, and H- β -Ala-Asn(Trt)-Asp(OtBu)-Ala-Leu-(N-Me)Met-Pro-NH-SAL-PEG resin was synthesized.

(2)

To the resin obtained in (1), a solution of 5-bromothiophene-2-sulfonyl chloride (0.20 mmol) and DIPEA (0.40 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 2 hours. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times) and chloroform (3 mL $\times$ three times).

(3)

To the resin obtained in (2), TFA:water:triisopropylsilane:dithiothreitol (90:2.5:5:2.5, 4 mL) was added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition B). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford

5-Br-thiophene-2-SO₂- β -Ala-Asn-Asp-Ala-Leu-(N-Me)Met-Pro-NH₂ (27 mg) as a white

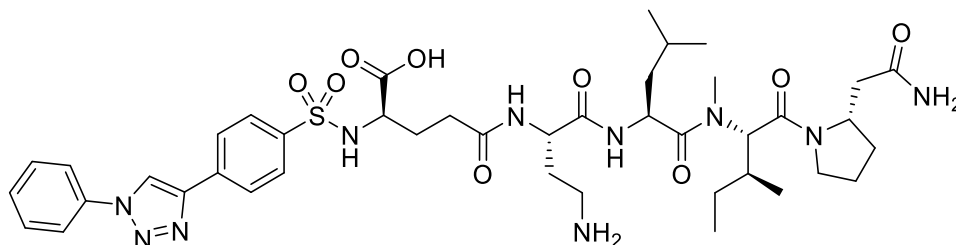
powder.

(4)

The compound obtained in (3) was dissolved in DMF (0.5 mL), 4-ethynyltoluene (0.30 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.01 mmol), triethylamine (0.18 mmol), and copper iodide (0.01 mmol) were added thereto, and the mixture was stirred under nitrogen atmosphere at 50°C for 5 hours with heating. After allowing to cool to room temperature, the reaction solution was diluted with DMSO, filtered, and purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (4 mg) as a white powder.

Example 5 Synthesis of compound of compound No. 608:

(*N*-[(2*S*)-4-amino-1-({(2*S*)-1-[(2*S*,3*S*)-1-[(2*S*)-2-(2-amino-2-oxoethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}(methyl)amino)-4-methyl-1-oxopentan-2-yl}amino)-1-oxobutan-2-yl]-*N*²-[4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)benzene-1-sulfonyl]-*D*-glutamine)



(1)

Fmoc-Rink Amide AM resin (0.10 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.6 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.6 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc-β-homoPro-OH (0.40 mmol) in DMF (0.8 mL), a solution of COMU (0.40 mmol) and Oxyma (0.40 mmol) in DMF (0.8 mL), and a solution of DIPEA (0.80 mmol) in NMP (0.4 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a β-homoPro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(*N*-Me)Ile-OH, Fmoc-Leu-OH,

Fmoc-Dab(Boc)-OH, and Fmoc-(d)-Glu-OtBu were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by piperidine/DMF treatment in the above manner, and H- γ -(d)-Glu(OtBu)-Dab(Boc)-Leu-(N-Me)Ile- β -homoPro-Rink Amide AM resin was synthesized.

(2)

To the resin obtained in (1), a solution of 4-bromobenzenesulfonyl chloride (0.30 mmol) and DIPEA (0.60 mmol) in DMF (2 mL) was added, and the mixture was shaken at room temperature for 2 hours. After the completion of the reaction, the resulting resin was washed with DMF (2 mL $\times$ three times).

(3)

To the resin obtained in (2), a solution of trimethylsilylacetylene (0.30 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.03 mmol), and copper iodide (0.03 mmol) in DMF (2 mL) was added, and the mixture was stirred under microwave irradiation at 80°C for 30 minutes with heating. After the completion of the reaction, the resulting resin was washed with DMF (2 mL $\times$ three times) and chloroform (2 mL $\times$ three times).

To the resin obtained, tetrahydrofuran solution of tetrabutylammonium fluoride (concentration: 0.33 mol/L, 0.50 mmol) was added, and the mixture was shaken at room temperature for 1 hour. After the completion of the reaction, the resulting resin was washed with DMF (2 mL $\times$ three times) and chloroform (2 mL $\times$ three times).

(4)

To the resin obtained in (3), a solution of azidobenzene (0.20 mmol), copper(II) sulfate pentahydrate (0.40 mmol), and ascorbic acid (0.40 mmol) in water (2 mL) and tBuOH (1 mL) was added, and the mixture was stirred under microwave irradiation at 60°C for 1 hour with heating. After the completion of the reaction, the resulting resin was washed with DMF (2 mL $\times$ three times) and chloroform (2 mL $\times$ three times).

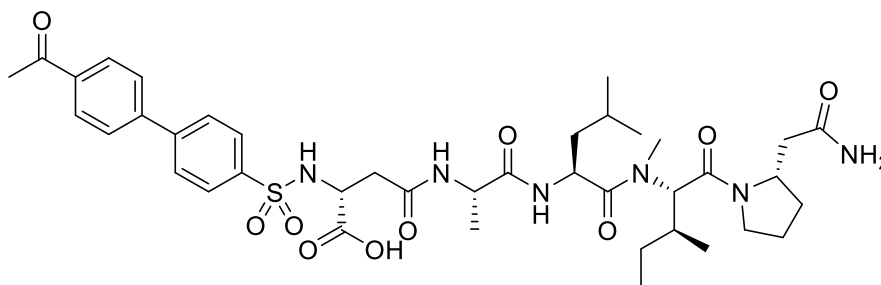
(5)

To the resin obtained in (4), TFA:water:triisopropylsilane (92.5:2.5:5, 4 mL) was

added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude
5 product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (12 mg) as a white powder.

Example 6 Synthesis of compound of compound No. 634:

- 10 (*N*²-(4'-acetyl[1,1'-biphenyl]-4-sulfonyl)-*N*-[(2*S*)-1-({(2*S*)-1-[{(2*S*,3*S*)-1-[(2*S*)-2-(2-amino-2-oxoethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}(methyl)amino]-4-methyl-1-oxopentan-2-yl}amino)-1-oxopropan-2-yl]-*D*-asparagine)



(1)

- 15 Fmoc-NH-SAL-PEG resin (0.10 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.6 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.6 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc-β-homoPro-OH (0.40 mmol) in DMF (0.8 mL), a solution of COMU (0.40 mmol) and Oxyma (0.40 mmol) in DMF (0.8 mL), and a solution of DIPEA
20 (0.80 mmol) in NMP (0.4 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a β-homoPro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(*N*-Me)Ile-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, and Fmoc-(*d*)-Asp-OtBu were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by

piperidine/DMF treatment in the above manner, and

H- β -(d)-Asp(OtBu)-Ala-Leu-(N-Me)Ile- β -homoPro-NH-SAL-PEG resin was synthesized.

(2)

To the resin obtained in (1), a solution of 4-iodobenzenesulfonyl chloride

5 (0.30 mmol) and DIPEA (0.60 mmol) in DMF (2 mL) was added, and the mixture was shaken at room temperature for 2 hours. After the completion of the reaction, the resulting resin was washed with DMF (2 mL $\times$ three times) and chloroform (2 mL $\times$ three times).

(3)

To the resin obtained in (2), a solution of 4-acetylphenylboronic acid (0.40 mmol),

10 tetrakis(triphenylphosphine)palladium(0) (0.03 mmol), and potassium phosphate (0.50 mmol) in 1,4-dioxane (1.5 mL) and water (1.5 mL) was added, and the mixture was stirred under microwave irradiation at 100°C for 30 minutes with heating. After the completion of the reaction, the resulting resin was washed with DMF (2 mL $\times$ three times) and chloroform (2 mL $\times$ three times).

15 (4)

To the resin obtained in (3), TFA:water:triisopropylsilane (92.5:2.5:5, 4 mL) was

added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by

20 decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (8 mg) as a white powder.

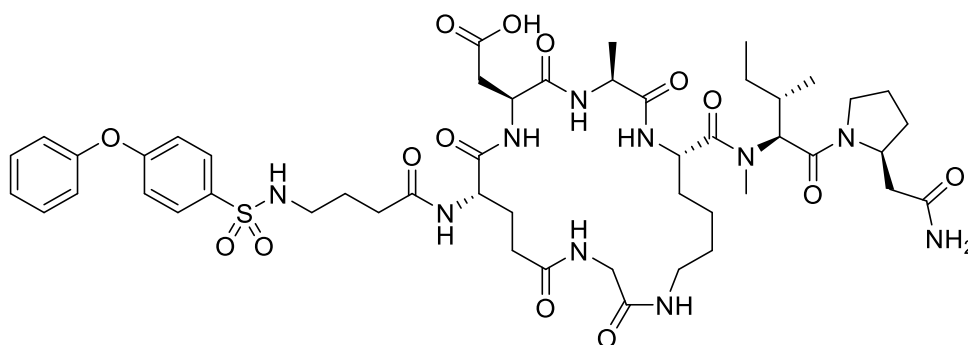
25 Example 7 Synthesis of compound of compound No. 692:

(N-[(2S)-3-amino-1-({(2S)-1-[(2S,3S)-1-[(2S)-2-(2-amino-2-oxoethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}(methyl)amino)-4-methyl-1-oxopentan-2-yl}amino)-1-oxopropan-2-yl]-N²-[4-(4-methoxybenzamido)benzene-1-sulfonyl]-D-asparagine)

To the resin obtained in (2), a solution of 4-methoxybenzoyl chloride (0.30 mmol)

To the resin obtained in (3), TFA:water:triisopropylsilane:dithiothreitol (90:2.5:5:2.5, 4 mL) was added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (12 mg) as a white powder.

[(2S,5S,8S,20S)-8-[[{(2S,3S)-1-[(2S)-2-(2-amino-2-oxoethyl)pyrrolidin-1-yl]-3-methyl-1-oxo
pentan-2-yl](methyl)carbamoyl]-5-methyl-3,6,14,17,21-pentaoxo-20-{4-[(4-phenoxybenzene
-1-sulfonyl)amino]butanamido}-1,4,7,13,16-pentaazacyclohenicosan-2-yl]acetic acid)



Fmoc-NH-SAL-PEG resin (0.12 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.9 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.9 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc- β -homoPro-OH (0.48 mmol) in DMF (1.0 mL), a solution

of COMU (0.48 mmol) and Oxyma (0.48 mmol) in DMF (1.0 mL), and a solution of DIPEA (0.96 mmol) in NMP (0.48 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a β -homoPro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(N-Me)Ile-OH,

5 Fmoc-Lys(Dde)-OH, Fmoc-Ala-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Glu(OAllyl)-OH, and Fmoc-GABA-OH were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by piperidine/DMF treatment in the above manner,
and H-GABA-Glu(OAllyl)-Asp(OtBu)-Ala-Lys(Dde)-(N-Me)Ile- β -homoPro-SAL-PEG resin
10 was synthesized.

(2)

To the resin obtained in (1), a solution of 4-phenoxybenzenesulfonyl chloride (0.36 mmol) and DIPEA (0.72 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 1.5 hours. After the completion of the reaction, the
15 resulting resin was washed with DMF (3 mL $\times$ three times).

(3)

To the resin obtained in (2), DMF solution of hydrazine monohydrate (concentration: 5%, 3 mL) and allyl alcohol (3.1 mmol) were added, and the mixture was shaken at room temperature for 30 minutes to deprotect the Dde of the Lys side chain.
20 Subsequently, a solution of Fmoc-Gly-OH (0.48 mmol), COMU (0.48 mmol), Oxyma (0.48 mmol), and DIPEA (0.96 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 30 minutes to introduce a Gly residue. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times) and chloroform (3 mL $\times$ three times).

25 (4)

To the resin obtained in (3), a solution of tetrakis(triphenylphosphine)palladium(0) (0.12 mmol) and phenylsilane (0.60 mmol) in chloroform (4 mL) was added, and the mixture was shaken at room temperature for 1.5 hours to deprotect the Allyl of the Glu side chain.

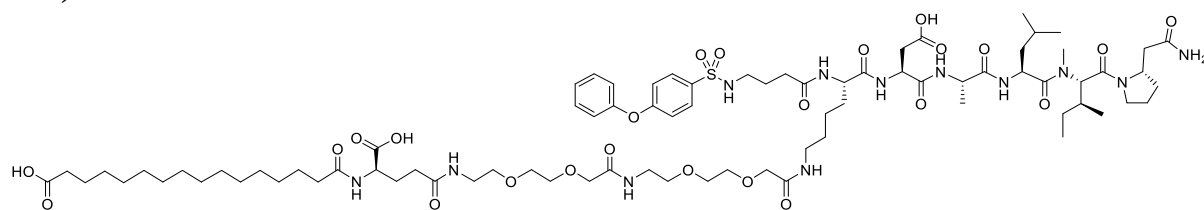
Subsequently, DMF solution of piperidine (concentration: 20%, 3 mL) was added, and the mixture was shaken at room temperature for 30 minutes to deprotect the Fmoc. After the completion of the reaction, the resulting residue was washed with DMF (3 mL $\times$ five times).
(5)

To the resin obtained in (4), a solution of PyBOP (0.36 mmol) and DIPEA (0.12 mmol) in DMF (4 mL) was added, and the mixture was shaken at room temperature for 2 hours. After the completion of the reaction, the resulting residue was washed with DMF (3 mL $\times$ three times) and chloroform (3 mL $\times$ three times).
(6)

To the resin obtained in (5), TFA:water:triisopropylsilane:dithiothreitol (90:2.5:5:2.5, 4 mL) was added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (10 mg) as a white powder.

Example 9 Synthesis of compound of compound No. 903:

((2*S*,5*S*,32*R*)-2-{[(2*S*)-1-({(2*S*)-1-[(2*S*,3*S*)-1-[(2*S*)-2-(2-amino-2-oxoethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}(methyl)amino]-4-methyl-1-oxopentan-2-yl}amino)-1-oxopropan-2-yl]carbamoyl}-4,11,20,29,34-pentaoxo-5-{4-[(4-phenoxybenzene-1-sulfonyl)amino]butanamido}-13,16,22,25-tetraoxa-3,10,19,28,33-pentaazaocstatetracontane-1,32,48-tricarboxylic acid)



(1)

Fmoc-Rink Amide AM resin (0.12 mmol) was treated with DMF solution of piperidine (concentration: 40%, 1.9 mL) for 3 minutes, and then treated with DMF solution of piperidine (concentration: 20%, 1.9 mL) for 12 minutes to deprotect the Fmoc on the resin. Subsequently, a solution of Fmoc- β -homoPro-OH (0.48 mmol) in DMF (1.0 mL), a solution of COMU (0.48 mmol) and Oxyma (0.48 mmol) in DMF (1.0 mL), and a solution of DIPEA (0.96 mmol) in NMP (0.48 mL) were added, and the mixture was shaken at room temperature for 40 minutes to introduce a β -homoPro residue. In the same manner, deprotection for Fmoc and condensation were repeated: specifically, Fmoc-(N-Me)Ile-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Lys(Dde)-OH, and Fmoc-GABA-OH were sequentially condensed, wherein deprotection was performed for the N-terminal Fmoc formed in the resin after each condensation by piperidine/DMF treatment in the above manner, and H-GABA-Lys(Dde)-Asp(OtBu)-Ala-Leu-(N-Me)Ile- β -homoPro-Rink Amide AM resin was synthesized.

(2)

To the resin obtained in (1), a solution of 4-phenoxybenzenesulfonyl chloride (0.36 mmol) and DIPEA (0.72 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 2 hours. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ three times).

(3)

To the resin obtained in (2), DMF solution of hydrazine monohydrate (concentration: 5%, 3 mL) was added, and the mixture was shaken at room temperature for 30 minutes. This operation was repeated four times to deprotect the Dde of the Lys side chain. For the resulting resin, condensation and deFmoc were repeatedly performed: specifically, Fmoc-Adox-OH, Fmoc-Adox-OH, and Fmoc-Glu-OtBu were sequentially condensed to extend the Lys side chain with a peptide. Deprotection was performed for the N-terminal Fmoc of the Lys side chain by piperidine/DMF treatment.

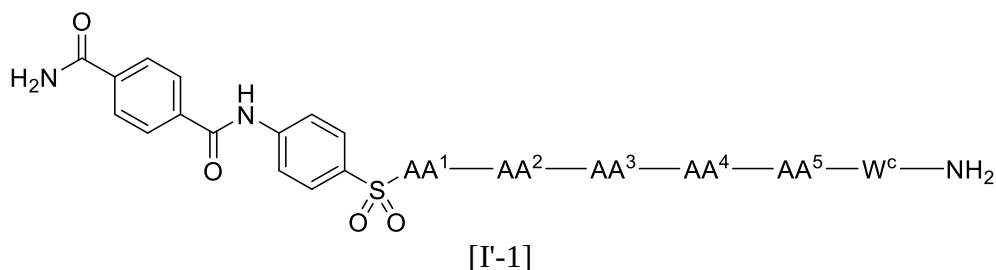
(4)

To the resin obtained in (3), a solution of hexadecanedioic acid (0.96 mmol), COMU (0.18 mmol), Oxyma (0.18 mmol), and DIPEA (0.96 mmol) in DMF (3 mL) was added, and the mixture was shaken at room temperature for 1 hour. After the completion of the reaction, the resulting resin was washed with DMF (3 mL $\times$ four times) and chloroform (3 mL $\times$ three times).

(5)

To the resin obtained in (4), TFA:water:triisopropylsilane:dithiothreitol (90:2.5:5:2.5, 4 mL) was added, the mixture was shaken at room temperature for 2 hours, and the resin was removed through filtration. An operation in which cooled diethyl ether was added to the filtrate, a resulting white powder was precipitated by centrifugation, and diethyl ether was removed by decantation was repeated three times to afford a crude product of peptide. The crude product obtained was purified by preparative LCMS (separation condition A). The eluate was fractionated using test tubes, and eluted fractions containing the target product were collected and lyophilized to afford the title compound (29 mg) as a white powder.

The structures of compounds represented by formula [I'-1], which were synthesized in Example 1 or with the same method as in Example 1, are shown in the following table.

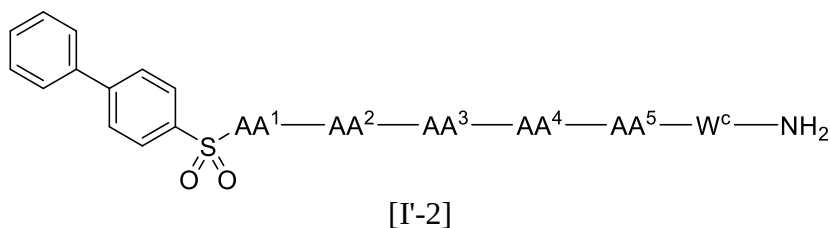


[Table 5]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
1	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond
2	β -Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond
3	β -(d)-Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond
4	γ -Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond
5	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Val	(N-Me)Glu	Ape	single bond
6	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Ile	(N-Me)Glu	Ape	single bond
7	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Phe	(N-Me)Glu	Ape	single bond
8	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Trp	(N-Me)Glu	Ape	single bond
9	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	Ape	single bond
10	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Val	Ape	single bond
11	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Leu	Ape	single bond
12	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Leu	Ape	single bond
13	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Phe	Ape	single bond
14	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Tyr	Ape	single bond
15	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ser	Ape	single bond
16	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	Pro	Ape	single bond
17	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Asp	β -homoPro	single bond
18	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Asp	Pro	single bond
19	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Asp	(d)-Pro	single bond
20	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	β -homoPro	single bond
21	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Pro	single bond
22	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	β -Ala	single bond
23	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	GABA	single bond
24	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Acp	single bond
25	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	(d)-Pro	single bond

26	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Lys	single bond
27	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	(d)-Lys	single bond
28	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Arg	single bond
29	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	(d)-Arg	single bond
30	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	single bond	single bond
31	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	single bond	single bond	single bond
32	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	Pro
33	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	Lys
34	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	(d)-Lys
35	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	Arg
36	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	(d)-Arg
37	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	(d)-Lys-(d)-Lys
38	β -(d)-Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	β -homoPro	single bond
39	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	β -homoPro	single bond

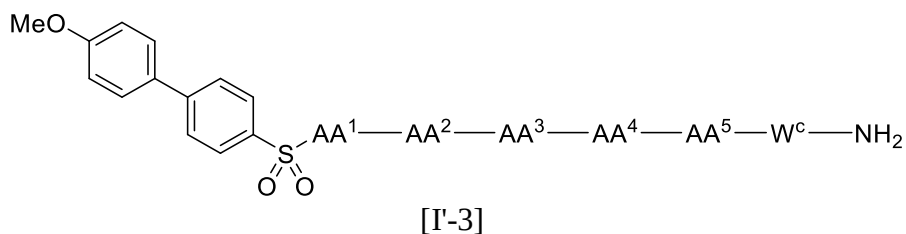
The structure of a compound represented by formula [I'-2], which was synthesized with the same method as in Example 1, is shown in the following table.



[Table 6]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
40	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond

The structure of a compound represented by formula [I'-3], which was synthesized with the same method as in Example 1, is shown in the following table.



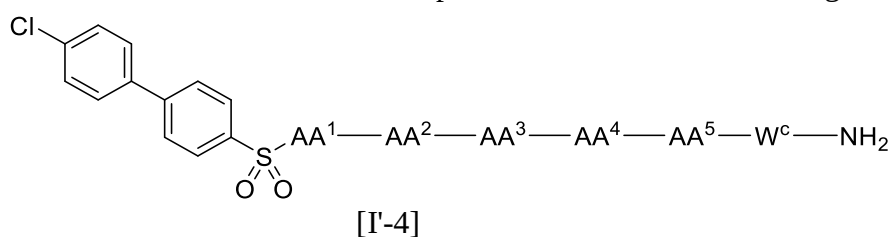
5

[Table 7]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
41	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond

The structure of a compound represented by formula [I'-4], which was synthesized with the same method as in Example 1, is shown in the following table.

10

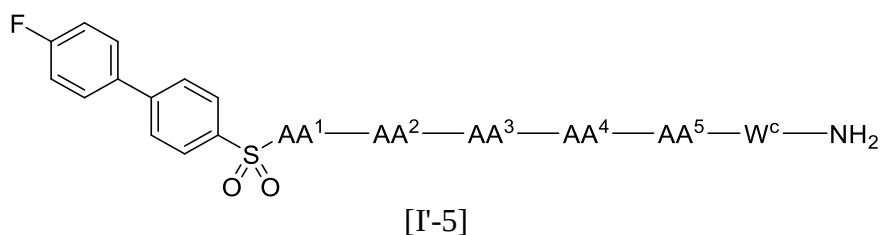


[Table 8]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
42	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond

15

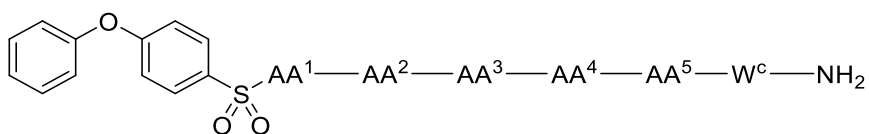
The structure of a compound represented by formula [I'-5], which was synthesized with the same method as in Example 1, is shown in the following table.



[Table 9]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
43	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond

The structure of a compound represented by formula [I'-6], which was synthesized with the same method as in Example 1, is shown in the following table.

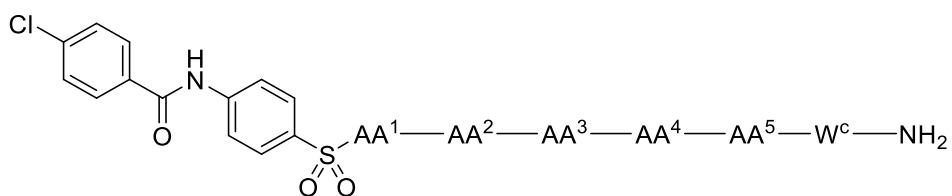


[I'-6]

[Table 10]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
44	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond

The structures of compounds represented by formula [I'-7], which were synthesized with the same method as in Example 1, are shown in the following table.



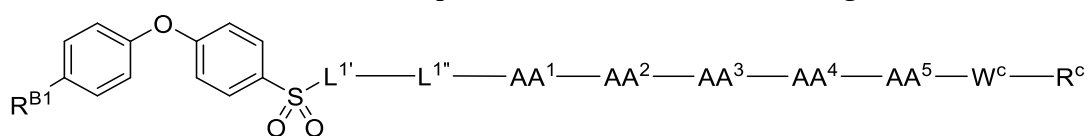
[I'-7]

[Table 11]

Compound No.	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c
45	β -(d)-Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	Ape	single bond
46	β -(d)-Asp	(S)-piperazine	Leu	(N-Me)Ile	Ape	single bond
47	β -(d)-Asp	(2S, 4R)-(4-amino)Pro	Leu	(N-Me)Ile	Ape	single bond
48	β -(d)-Asp	(2S, 4S)-(4-hydroxy)Pro	Leu	(N-Me)Ile	β -homoPro	single bond
49	β -(d)-Asp	(2S, 4R)-(4-hydroxy)Pro	Leu	(N-Me)Ile	Ape	single bond
50	β -(d)-Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	β -homoPro	single bond
51	β -(d)-Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	β -homoPro	single bond
52	β -(d)-Asp	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond
53	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond
54	γ -Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	β -homoPro	single bond
55	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Ile	β -homoPro	single bond

The structures of compounds represented by formula [I'-8], which were synthesized

5 with the same method as in Example 1, are shown in the following table.



[I'-8]

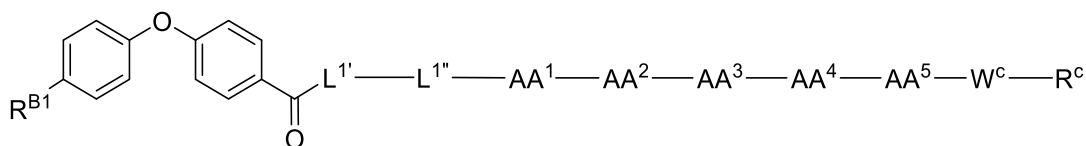
[Table 12]

Compound No.	R ^{Bi}	L ^{1'}	L ^{1*}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
56	H	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂
57	H	GABA	Asn	Asp	Ala	Leu	(N-Me) Val	Pro	single bond	NH ₂
58	H	GABA	Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
59	H	GABA	Asn	Asp	Ala	Leu	(N-Me) Val	β - homo Pro	single bond	NH ₂
60	H	(N-Me) GABA	Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
61	H	GABA	Asn	Asp	Dap	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
62	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
63	H	GABA	Asn	Asp	Orn	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
64	H	GABA	Asn	Asp	Ala	Leu	Glu	β - homo Pro	single bond	NH ₂

65	H	GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
66	H	GABA	Asn	Asp	Ala	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
67	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
68	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
69	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
70	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
71	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
72	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
73	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
74	H	GABA	Asn	Asp	Ala	Dab	(N-Me) Ile	β - homo Pro	single bond	NH ₂
75	H	GABA	Asn	Asp	Ala	Leu	homoGlu	β - homo Pro	single bond	NH ₂
76	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	OH
77	F	Ape	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
78	F	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
79	F	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
80	H ₂ NCO	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
81	H ₂ NCO	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
82	H ₂ NCO	Ape	(d)- Ser	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
83	H ₂ NCO	Ape	homo Ser	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂

84	H	Ape	(d)-Thr	Asp	Dab	Leu	(N-Me)Glu	β -homo Pro	single bond	NH ₂
85	H	Ape	(d)-Thr	Asp	Dab	Leu	(N-Me)Ile	β -homo Pro	single bond	NH ₂
86	F	Ape	(d)-Thr	Asp	Dab	Leu	(N-Me)Glu	β -homo Pro	single bond	NH ₂
87	F	Ape	(d)-Thr	Asp	Dab	Leu	(N-Me)Ile	β -homo Pro	single bond	NH ₂
88	F	Ape	Arg	Asp	Dab	Leu	(N-Me)Glu	β -homo Pro	single bond	NH ₂
89	F	Ape	Arg	Asp	Dab	Leu	(N-Me)Ile	β -homo Pro	single bond	NH ₂
90	F	Ape	Gln	Asp	Dab	Leu	(N-Me)Ile	β -homo Pro	(d)-Lys	NH ₂
91	F	Ape	Gln	Asp	Dab	Leu	(N-Me)Ile	β -homo Pro	(d)-Arg	NH ₂

The structures of compounds represented by formula [I'-9], which were synthesized in Example 2 or with the same method as in Example 2, are shown in the following table.



[I'-9]

[Table 13]

Compound No.	R ^{B1}	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
92	H	GABA	(N-Me)Ala	Asp	Ala	Leu	(N-Me)Ile	Pro	single bond	NH ₂
93	F	GABA	(N-Me)Ala	Asp	Ala	Leu	(N-Me)Ile	Pro	single bond	NH ₂
94	H	GABA	(N-Me)Asn	Asp	Ala	Leu	(N-Me)Ile	Pro	single bond	NH ₂

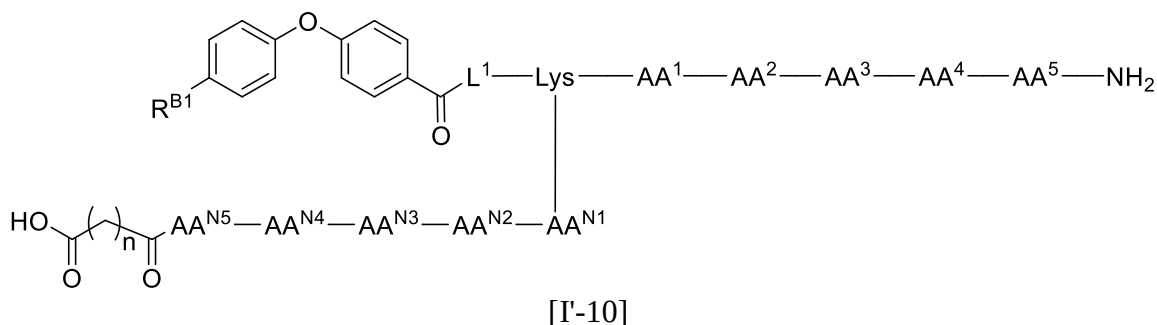
95	F	GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
96	H	GABA	(N-Me) Ala	Asp	Ala	Leu	(N-Me) Ile	Aib	single bond	NH ₂
97	F	GABA	(N-Me) Ala	Asp	Ala	Leu	(N-Me) Ile	Aib	single bond	NH ₂
98	H	GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Aib	single bond	NH ₂
99	F	GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Aib	single bond	NH ₂
100	H	(N-Me) GABA	(N-Me) Ala	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
101	F	(N-Me) GABA	(N-Me) Ala	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
102	Me	(N-Me) GABA	(N-Me) Ala	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
103	H	(N-Me) GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
104	F	(N-Me) GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
105	Me	(N-Me) GABA	(N-Me) Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
106	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
107	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
108	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
109	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
110	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
111	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
112	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
113	H	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
114	H	GABA	(d) - Asn	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
115	H	GABA	(N-Me) Gly	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
116	H	GABA	Aze (2)	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
117	H	GABA	Pro	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂

118	H	GABA	homo Pro	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
119	H	GABA	(N-Me) Val	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
120	H	GABA	(N-Me) Leu	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
121	H	GABA	(N-Me) Ile	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
122	H	GABA	(N-Me) Met	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
123	H	GABA	(d)- Lys	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
124	H	GABA	(N-Me) Phe	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
125	H	GABA	(N-Me) Asp	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
126	H	GABA	(N-Me) Glu	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
127	H	GABA	(N-Me) Lys	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
128	H	GABA	Gln	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
129	H	GABA	(N-Me) Tyr	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
130	H	GABA	(N-Me) Trp	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
131	H	GABA	(N-Me) Thr	Asp	Ala	Leu	(N-Me) Ile	Pro	single bond	NH ₂
132	H	GABA	Aze (2)	Asp	Dap	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
133	H	GABA	Aze (2)	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
134	H	GABA	(N-Me) Met	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
135	H	GABA	(N-Me) Val	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
136	H	GABA	(N-Me) Leu	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
137	F	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
138	F	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
139	F	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Asp	β - homo Pro	single bond	NH ₂
140	F	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂

141	F	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Asp	Pro	single bond	NH ₂
142	F	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
143	H	GABA	Val	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
144	H	GABA	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
145	H	GABA	Orn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
146	H	GABA	Val	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
147	H	GABA	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
148	H	GABA	Orn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
149	F	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
150	F	GABA	Val	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
151	F	GABA	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
152	F	GABA	Orn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
153	F	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
154	H	GABA	(N-Me) Asn	Asp	Dap (M e)	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
155	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
156	H	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂

The structures of compounds represented by formula [I'-10], which were synthesized

with the same method as in Example 9, are shown in the following table.

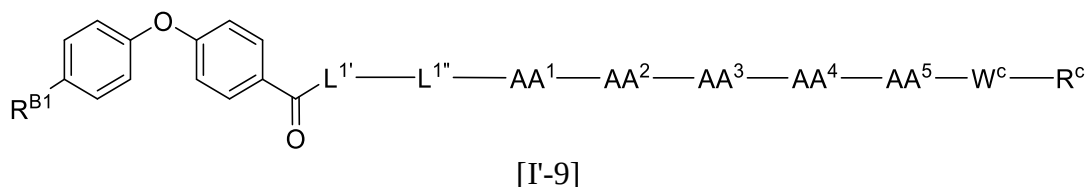


[Table 14]

Compound No.	R ^{B1}	L ¹	AA ^{N5}	AA ^{N4}	AA ^{N3}	AA ^{N2}	AA ^{N1}	n	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵
157	H ₂ NC O	GAB A	γ - Glu	Ado x	Ado x	single bond	single bond	12	Asp	Dab	Leu	(N- Me) Glu	β - hom oPr o
158	H ₂ NC O	GAB A	γ - Glu	Ado x	Ado x	single bond	single bond	14	Asp	Dab	Leu	(N- Me) Glu	β - hom oPr o
159	H ₂ NC O	GAB A	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	12	Asp	Dab	Leu	(N- Me) Glu	β - hom oPr o
160	H ₂ NC O	GAB A	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me) Glu	β - hom oPr o

5

The structures of compounds represented by formula [I'-9], which were synthesized in Example 2 or with the same method as in Example 2, are shown in the following table.

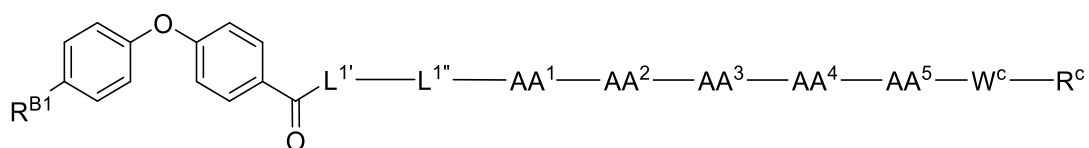


[Table 15]

10

Compound No.	R ^{B1}	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
161	F	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
162	F	GABA	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
163	F	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
164	F	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
165	F	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
166	H	Adox	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
167	H	Adox	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
168	MeSO ₂	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
169	MeSO ₂	Ape	(d) - Ser	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
170	F	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
171	F	Ape	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
172	F	Ape	(d) - Ser	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
173	H	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
174	H	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
175	F	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d) - Lys	NH ₂
176	F	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d) - Arg	NH ₂

The structures of compounds represented by formula [I'-9], which were synthesized in Example 3 or with the same method as in Example 3, are shown in the following table.



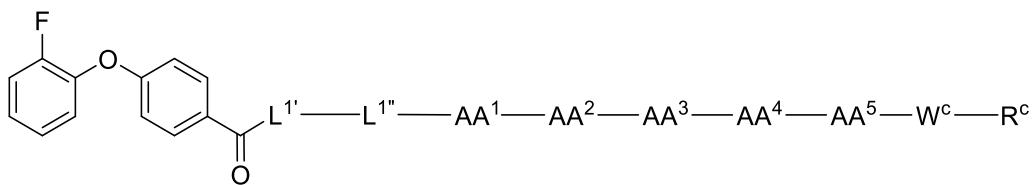
[I'-9]

[Table 16]

Compound No.	R ^{B1}	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
177	MeHNC O	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂
178	HO ₂ C- H ₂ CHN CO	Ape	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂
179	H ₂ N-(CH ₂) ₂ - NHCO	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
180	H ₂ N-(CH ₂) ₃ - NHCO	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
181	H ₂ N-(CH ₂) ₄ - NHCO	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
182	HO-(C H ₂) ₃ -N HCO	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
183	HO ₂ C- (CH ₂) ₂ - NHCO	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
184	MeNH O	Ape	Lys	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
185	MeNH O	Ape	Lys	Asp	Dab	Leu	(N-Me) Ile	β-homo Pro	single bond	NH ₂
186	MeNH O	Acp	Lys	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
187	MeNH O	Acp	Lys	Asp	Dab	Leu	(N-Me) Ile	β-homo Pro	single bond	NH ₂
188	MeNH O	Ape	Arg	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
189	MeNH O	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	β-homo Pro	single bond	NH ₂
190	MeNH O	Acp	Arg	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
191	MeNH O	Acp	Arg	Asp	Dab	Leu	(N-Me) Ile	β-homo Pro	single bond	NH ₂
192	EtNH O	Ape	Lys	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂
193	EtNH O	Ape	Lys	Asp	Dab	Leu	(N-Me) Ile	β-homo Pro	single bond	NH ₂
194	EtNH O	Acp	Lys	Asp	Dab	Leu	(N-Me) Glu	β-homo Pro	single bond	NH ₂

195	EtNHC O	Acp	Lys	Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
196	EtNHC O	Ape	Arg	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
197	EtNHC O	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
198	EtNHC O	Acp	Arg	Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
199	H ₂ NCO -(CH ₂) ₄ -NH CO	Ape	Glu	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
200	HO ₂ C- (CH ₂) ₄ - NHCO	Ape	Glu	Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
201	H ₂ NCO -(CH ₂) ₄ -NH CO	Ape	Glu	Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂

The structure of a compound represented by formula [I'-11], which was synthesized with the same method as in Example 2, is shown in the following table.

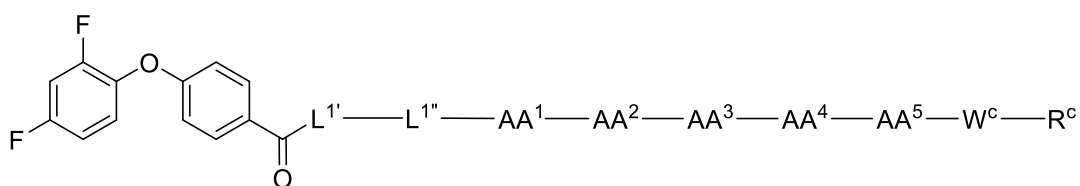


[I'-11]

[Table 17]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
202	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

The structures of compounds represented by formula [I'-12], which were synthesized with the same method as in Example 2, are shown in the following table.



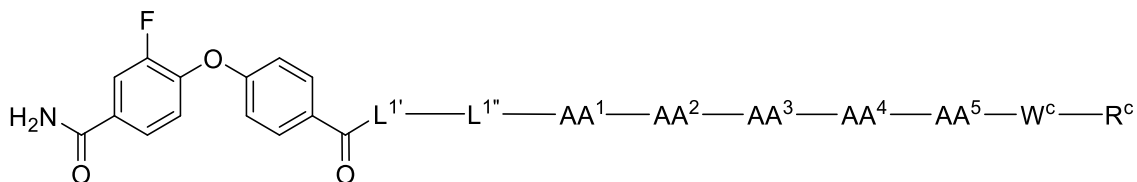
[I'-12]

[Table 18]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
203	Acp	Asn	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
204	Acp	Gln	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
205	Acp	Ala	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂

5

The structures of compounds represented by formula [I'-13], which were synthesized with the same method as in Example 2, are shown in the following table.



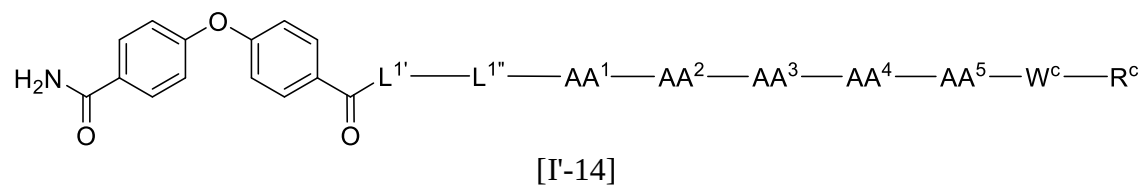
[I'-13]

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[Table 19]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
206	Acp	Asn	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
207	Acp	Gln	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
208	Acp	Ala	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
209	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂

The structures of compounds represented by formula [I'-14], which were synthesized with the same method as in Example 2, are shown in the following table.



5 [Table 20]

Compound No.	L ^{1*}	L ^{2*}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
210	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
211	GABA	Val	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
212	GABA	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
213	GABA	Orn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
214	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
215	GABA	Val	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
216	GABA	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
217	GABA	Orn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
218	GABA	(N-Me) Asn	Asp	Dap(Me)	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
219	GABA	(N-Me) Asn	Asp	Dap(Me)	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
220	GABA	(N-Me) Asn	Asp	Dab(Me)	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
221	β -Ala	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
222	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
223	Ape	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
224	β -Ala	Asn	Asp	Dap	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
225	GABA	Asn	Asp	Dap	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
226	Ape	Asn	Asp	Dap	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
227	GABA	Glu	Asp	Dap	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
228	Ape	Glu	Asp	Dap	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
229	β -Ala	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
230	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
231	β -Ala	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
232	Ape	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂

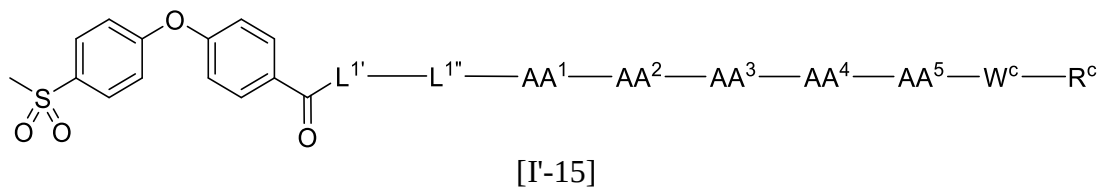
233	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
234	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
235	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
236	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	OH
237	GABA	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
238	GABA	(d) - Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
239	GABA	(d) - Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	OH
240	GABA	Asn	Asp	Dab	Leu	(N-Me) Asp	β - homoPro	single bond	OH
241	GABA	Asn	Asp	Dab	Leu	(N-Me) Asn	β - homoPro	single bond	OH
242	GABA	(d) - Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
243	GABA	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
244	GABA	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
245	ϵ -Lys	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
246	ϵ -Lys	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
247	ϵ - (d) - Lys	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
248	GABA	Asn	Asp	Dab(Me)) ₂	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
249	GABA	Gln	Asp	Dab(Me)) ₂	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
250	GABA	(d) - Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
251	GABA	(d) - Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
252	GABA	Asn	Asp	Dab	Leu	(N-Me) Asp	β - homoPro	single bond	NH ₂
253	GABA	(d) - Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
254	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NHEt
255	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	pipe ridi n-1- yl
256	Acp	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂

257	Acp	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
258	Acp	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
259	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
260	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	OH
261	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	OH
262	Adox	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
263	Adox	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
264	Adox	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
265	Adox	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
266	Adox	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
267	Adox	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
268	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NHMe
269	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	azet idin -1- yl
270	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	pyrr olid in- 1-yl
271	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	(4- OH)p iper idin -1- yl
272	Ape	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH- (CH ₂) ₂ - OH
273	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	azet idin -1- yl
274	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	(3- OH)a zeti din- 1-yl

275	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	pyrr olid in- 1-yl
276	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	(4- OH)p iper idin -1- yl
277	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH- (CH ₂) ₂ - OH
278	Ape	Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
279	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
280	GABA	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
281	Ape	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
282	Ape	(N-Me) Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
283	Ape	(d)- Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
284	Ape	(d)- Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
285	Ape	(d)- Ser	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
286	Ape	(d)- Ala	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
287	Ape	Phe	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
288	Ape	(d)- Phe	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
289	Ape	Tyr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
290	Ape	(d)- Tyr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
291	γ -Dab	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
292	δ - (d)- Orn	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
293	GABA	β -Dap	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
294	GABA	β - (d)- Dap	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂

295	GABA	β -Ala	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
296	Ape	Dab	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
297	Ape	Dap	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
298	Ape	(d)- Dab	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
299	γ - (d)- Dab	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
300	GABA	Aze(2)	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
301	GABA	Aze(2)	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
302	Ape	Aze(2)	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
303	Ape	Aze(2)	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
304	GABA	(N-Me) Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
305	GABA	(N-Me) Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
306	β -Dap	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
307	β - (d)- Dap	Asn	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
308	Ape	(N-Me) Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
309	GABA	(N-Me) Ile	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
310	GABA	(N-Me) Lys	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
311	GABA	(N-Me) Lys	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
312	Ape	(N-Me))Lys	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
313	Ape	(N-Me) Lys	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
314	-NH- (CH ₂) ₂ -O- CH ₂ - CO-	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
315	-NH- (CH ₂) ₂ -O- CH ₂ - CO-	(d)- Ser	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂

The structures of compounds represented by formula [I'-15], which were synthesized with the same method as in Example 2, are shown in the following table.

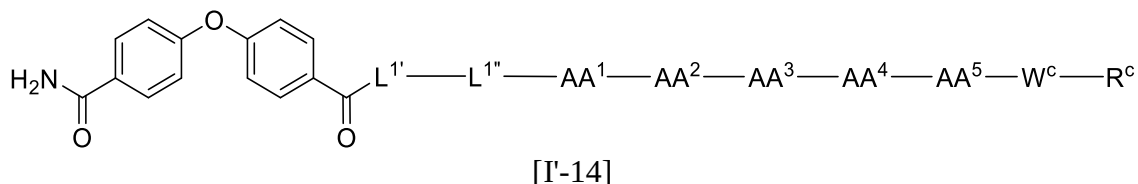


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[Table 21]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
316	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
317	Ape	(d) - Ser	Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂

10 The structures of compounds represented by formula [I'-14], which were synthesized with the same method as in Example 2, are shown in the following table.



[Table 22]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
318	Ape	(N-Me) Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
319	Ape	Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
320	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
321	Ape	(d) - Pro	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂

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322	Ape	Trp	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
323	Ape	(N-Me) Leu	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
324	Ape	(N-Me) Leu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
325	Ape	(N-Me) Met	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
326	Ape	(N-Me) Met	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
327	Ape	(d) - Trp	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
328	Ape	His	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
329	Ape	(d) - His	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
330	Ape	Cys	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
331	Ape	(d) - Cys	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
332	Ape	Arg	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
333	Ape	(d) - Arg	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
334	Ape	(d) - Glu	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
335	-NH- (CH ₂) ₂ -O- CH ₂ - CO-	(d) - Ser	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
336	Ape	Lys (Ac)	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
337	Ape	Lys (Ac)	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
338	Ape	Cit	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
339	Ape	(d) - Cit	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
340	Ape	Cit	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
341	Ape	(d) - Cit	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
342	Ape	β -Asp	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
343	Ape	β - (d) - Asp	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
344	Ape	Lys	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂

345	Ape	Met	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
346	Ape	Met	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
347	Ape	(d) - Ser	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
348	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
349	Adox	単結合	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
350	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d) - Lys- (d) - Lys- (d) - Lys	NH ₂
351	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d) - Lys- (d) - Lys- (d) - Lys	NH ₂
352	GABA	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
353	GABA	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
354	Acp	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
355	Acp	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
356	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
357	Ape	(N-Me) Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
358	Ape	(N-Me) Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
359	Ape	Asn	Asp	Dab	Phe	(N-Me) Ile	β - homoPro	single bond	NH ₂
360	Ape	Asn	Asp	Dab	Phe	(N-Me) Glu	β - homoPro	single bond	NH ₂
361	δ -Orn	(d) - Ser	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
362	δ -Orn	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
363	δ -Orn	Lys	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
364	δ -Orn	(d) - Ser	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
365	δ -Orn	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂

366	δ -Orn	Lys	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
367	Ape	(N-Me) Arg	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
368	Ape	(N-Me) Arg	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
369	Ape	(d)- Lys	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	single bond	NH ₂
370	Ape	(d)- Lys	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
371	Ape	Lys	Asp	Dab	Leu	Dap	β - homoPro	single bond	NH ₂
372	Ape	Lys	Asp	Dab	Leu	Dab	β - homoPro	single bond	NH ₂
373	Ape	Lys	Asp	Dab	Leu	Orn	β - homoPro	single bond	NH ₂
374	Ape	Lys	Asp	Dab	Leu	(N-Me) Arg	β - homoPro	single bond	NH ₂
375	Ape	Arg	Asp	Dab	Leu	Dap	β - homoPro	single bond	NH ₂
376	Ape	Arg	Asp	Dab	Leu	Dab	β - homoPro	single bond	NH ₂
377	Ape	Lys	Asp	Dab	Leu	Orn	β - homoPro	single bond	NH ₂
378	Ape	Arg	Asp	Dab	Leu	(N-Me) Lys	β - homoPro	single bond	NH ₂
379	Ape	Gln	Asp	Dap	Leu	(N-Me) Ile	single bond	single bond	NH ₂
380	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	single bond	single bond	NH ₂
381	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	single bond	single bond	NH ₂
382	Ape	Gln	Asp	Dab	Leu	単結合	single bond	single bond	NH ₂
383	Ape	Gln	aspart imide	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
384	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d)- Lys	NH ₂
385	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d)- Lys	NH ₂
386	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d)- Arg	NH ₂
387	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d)- Arg	NH ₂
388	Ape	Arg	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d)- Lys	NH ₂
389	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d)- Lys	NH ₂
390	Ape	Arg	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d)- Arg	NH ₂

391	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d) - Arg	NH ₂
392	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
393	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
394	Ape	Glu	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
395	Ape	Glu	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
396	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
397	Ape	Arg	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
398	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
399	Ape	(d) - Thr	Asp	Dab	Leu	(N-Me) Glu	Pro	single bond	NH ₂
400	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	(d) - Arg	NH ₂
401	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	(d) - Arg	NH ₂
402	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	(d) - Lys	NH ₂
403	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	(d) - Lys	NH ₂
404	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	Lys	NH ₂
405	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	Lys	NH ₂
406	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	Arg	NH ₂
407	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	Arg	NH ₂
408	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Arg	single bond	NH ₂
409	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Arg	single bond	NH ₂
410	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Lys	single bond	NH ₂
411	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Lys	single bond	NH ₂
412	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β -Ala	single bond	NH ₂
413	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β -Ala	single bond	NH ₂
414	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	single bond	NH ₂
415	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	single bond	NH ₂

416	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Ape	single bond	NH ₂
417	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	His	single bond	NH ₂
418	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	(d)-Arg	single bond	NH ₂
419	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	(d)-Arg	single bond	NH ₂
420	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	(d)-Lys	single bond	NH ₂
421	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	(d)-Lys	single bond	NH ₂
422	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Dap	single bond	NH ₂
423	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Dab	single bond	NH ₂
424	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Orn	single bond	NH ₂
425	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Orn	single bond	NH ₂
426	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	homoPro	single bond	NH ₂
427	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
428	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	(2S, 4R) -(4- amino)P ro	single bond	NH ₂
429	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	Arg- Arg	NH ₂
430	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	Arg- Arg	NH ₂
431	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	Arg- Arg	NH ₂
432	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	Arg- Arg	NH ₂
433	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d)- Arg- (d)- Arg	NH ₂
434	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d)- Arg- (d)- Arg	NH ₂
435	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	(d)- Arg- (d)- Arg	NH ₂

436	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	(d)- Arg- (d)- Arg	NH ₂
437	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β -Dap	single bond	NH ₂
438	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β -(d)- Dap	single bond	NH ₂
439	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	γ -Dab	single bond	NH ₂
440	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	Lys- Lys	NH ₂
441	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	Lys- Lys	NH ₂
442	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	Lys- Lys	NH ₂
443	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	Lys- Lys	NH ₂
444	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	β - homoPro	(d)- Lys- (d)- Lys	NH ₂
445	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	(d)- Lys- (d)- Lys	NH ₂
446	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	Pro	(d)- Lys- (d)- Lys	NH ₂
447	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Pro	(d)- Lys- (d)- Lys	NH ₂
448	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β -(d)- Dap	single bond	NH ₂
449	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	δ -Orn	single bond	NH ₂
450	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	δ -(d)- Orn	single bond	NH ₂
451	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
452	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
453	Ape	Gln	β -Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
454	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Aze(2)	single bond	NH ₂

455	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	(d)- Aze(2)	single bond	NH ₂
456	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	(N-Me)- β-Ala	single bond	NH ₂
457	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	Arg	NH ₂
458	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	(d)- Arg	NH ₂
459	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	Lys	NH ₂
460	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	(d)- Lys	NH ₂
461	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	Arg- Arg	NH ₂
462	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	(d)- Arg- (d)- Arg	NH ₂
463	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	GABA	(d)- Lys- (d)- Lys	NH ₂
464	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	Arg	NH ₂
465	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	(d)- Arg	NH ₂
466	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	Lys	NH ₂
467	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	(d)- Lys	NH ₂
468	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	Arg- Arg	NH ₂
469	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	(d)- Arg- (d)- Arg	NH ₂
470	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	Lys- Lys	NH ₂
471	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	GABA	(d)- Lys- (d)- Lys	NH ₂
472	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	Arg	NH ₂
473	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	(d)- Arg	NH ₂
474	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	Lys	NH ₂

475	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	(d)- Lys	NH ₂
476	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	Arg- Arg	NH ₂
477	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	(d)- Arg- (d)- Arg	NH ₂
478	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	Lys- Lys	NH ₂
479	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	(d)- Lys- (d)- Lys	NH ₂
480	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Acp	single bond	NH ₂
481	Ape	Gln	Asp	Dab	Ile	(N-Me) Glu	Ape	single bond	NH ₂
482	Ape	Gln	Asp	Dab	Ile	(N-Me) Ile	Ape	single bond	NH ₂
483	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	Arg	NH ₂
484	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	Lys	NH ₂
485	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	Ape	single bond	NH ₂
486	Ape	Gln	Asp	Dab	Leu	(N-Me) Leu	Ape	single bond	NH ₂
487	Ape	Gln	Asp	Dab	Ile	(N-Me) Ile	Ape	(d)- Lys	NH ₂
488	Ape	Gln	Asp	Dab	Ile	(N-Me) Ile	Ape	(d)- Arg	NH ₂
489	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	Ape	(d)- Arg	NH ₂
490	Ape	Gln	Asp	Dab	Leu	(N-Me) Leu	Ape	(d)- Lys	NH ₂
491	Ape	Gln	Asp	Dab	Leu	(N-Me) Leu	Ape	(d)- Arg	NH ₂
492	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	single bond	single bond	NH- (CH ₂) ₂ -NH ₂
493	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH- (CH ₂) ₂ -NH ₂
494	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	single bond	single bond	NH- (CH ₂) ₄ -NH ₂

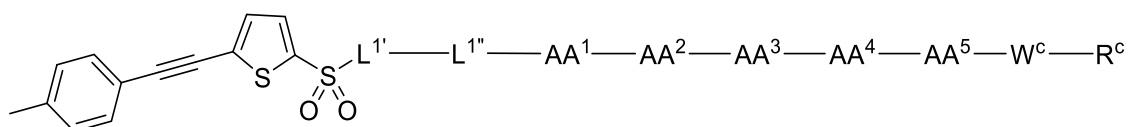
495	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	single bond	single bond	NH- (CH ₂) ₅ -NH ₂
496	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
497	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
498	δ -Orn	Ala	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
499	δ -Orn	Ala	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
500	δ -Orn	Lys(Ac)	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
501	δ -Orn	Lys(Ac)	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
502	δ -Orn	Dap	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
503	δ -Orn	Dab	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
504	δ -Orn	Gly	Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
505	δ -Orn	Gly	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
506	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	β - homoPro	single bond	NH ₂
507	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	Ape	single bond	NH ₂
508	Ape	(d)- Thr	Asp	Dab	Leu	(N-Me) Val	Pro	single bond	NH ₂
509	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	β - homoPro	(d)- Arg	NH ₂
510	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	β - homoPro	(d)- Lys	NH ₂
511	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	β -Ala	single bond	NH ₂
512	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	GABA	single bond	NH ₂
513	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	ε - (d)- Lys	single bond	NH ₂
514	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	Ape	(d)- Arg	NH ₂
515	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	Ape	(d)- Lys	NH ₂
516	δ -Orn	Dap	Asp	Dab	Leu	(N-Me) Val	β - homoPro	single bond	NH ₂
517	δ -Orn	Dap	Asp	Dab	Leu	(N-Me) Val	Ape	single bond	NH ₂
518	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	ε - (d)- Lys	(d)- Arg	NH ₂

519	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	(d)- Lys	NH ₂
520	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	γ -Dab	β -Ala	NH ₂
521	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	γ -Dab	GABA	NH ₂
522	ϵ -(d)- Lys	single bond	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
523	ϵ -Lys	single bond	Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
524	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	ϵ -(d)- Lys	single bond	NH ₂
525	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	ϵ -Lys	single bond	NH ₂
526	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
527	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
528	δ -Orn	Arg	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
529	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	β -Dap	single bond	NH ₂
530	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	β -(d)- Dap	single bond	NH ₂
531	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	γ -Dab	single bond	NH ₂
532	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	γ -(d)- Dab	single bond	NH ₂
533	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	δ -(d)- Orn	single bond	NH ₂
534	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	ϵ -Lys	single bond	NH ₂
535	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	β -Dap	single bond	NH ₂
536	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	β -(d)- Dap	single bond	NH ₂
537	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	γ -Dab	single bond	NH ₂
538	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	δ -Orn	single bond	NH ₂
539	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	δ -(d)- Orn	single bond	NH ₂
540	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	γ -Dab	β -Ala	NH ₂
541	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	γ -Dab	GABA	NH ₂
542	Ape	Gln	Asp	Dab	Leu	(N-Me) Val	δ -Orn	single bond	NH ₂

543	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
544	Ape	Arg	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
545	Ape	Arg	Asp	Dab	Leu	(N-Me) Val	ϵ -Lys	single bond	NH ₂
546	Ape	Arg	Asp	Dab	Leu	(N-Me) Val	ϵ -(d)- Lys	single bond	NH ₂
547	Ape	(d)- Thr	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
548	Ape	(d)- Thr	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
549	Ape	(d)- Thr	Asp	Dab	Leu	(N-Me) Val	ϵ -Lys	single bond	NH ₂
550	Ape	(d)- Thr	Asp	Dab	Leu	(N-Me) Val	ϵ -(d)- Lys	single bond	NH ₂
551	δ -Orn	Arg	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
552	δ -Orn	Arg	Asp	Dab	Leu	(N-Me) Val	ϵ -Lys	single bond	NH ₂
553	δ -Orn	Arg	Asp	Dab	Leu	(N-Me) Val	ϵ -(d)- Lys	single bond	NH ₂
554	δ -Orn	(d)- Thr	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
555	δ -Orn	(d)- Thr	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
556	δ -Orn	(d)- Thr	Asp	Dab	Leu	(N-Me) Val	ϵ -Lys	single bond	NH ₂
557	δ -Orn	(d)- Thr	Asp	Dab	Leu	(N-Me) Val	ϵ -(d)- Lys	single bond	NH ₂
558	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	β -Dap	β -Ala	NH ₂
559	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	β -Dap	β -Ala	NH ₂
560	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Val	β -Dap	β -Ala	NH ₂
561	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	β -Dap	single bond	NH ₂
562	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	β -(d)- Dap	single bond	NH ₂
563	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	γ -Dab	single bond	NH ₂
564	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	γ -(d)- Dab	single bond	NH ₂
565	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	δ -Orn	single bond	NH ₂
566	δ -Orn	Gln	Asp	Dab	Leu	(N-Me) Ile	δ -(d)- Orn	single bond	NH ₂

567	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
568	Ape	Asn	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
569	Ape	Gln	Asp	Dap	Leu	(N-Me) Ile	ϵ -Lys	single bond	NH ₂
570	Ape	Gln	Asp	Dap	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	NH ₂
571	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	ϵ -Lys	single bond	NH ₂
572	Ape	Gln	Asp	Dab	Leu	(N-Me) Glu	ϵ -(d)- Lys	single bond	NH ₂
573	Ape	Gln	Asp	Dab	Leu	(N-Me) Ala	ϵ -Lys	single bond	NH ₂
574	Ape	Gln	Asp	Dab	Leu	(N-Me) Ala	ϵ -(d)- Lys	single bond	NH ₂
575	Ape	Gln	Asp	Dab	Leu	(N-Me) Leu	ϵ -Lys	single bond	NH ₂
576	Ape	Gln	Asp	Dab	Leu	(N-Me) Leu	ϵ -(d)- Lys	single bond	NH ₂
577	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	ϵ -(d)- Lys	single bond	OH
578	Ape	Gln	Asp	Dab	Leu	(N-Me) Ile	Aze(2)	single bond	OH
579	Ape	Gln	Asp	Aze (2)	Leu	(N-Me) Ile	ϵ β - homoPro	single bond	NH ₂
580	Ape	Lys	Asp	Aze (2)	Leu	(N-Me) Ile	Ape	single bond	NH ₂
581	Ape	Lys	Asp	Aze (2)	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
582	Ape	Arg	Asp	Aze (2)	Leu	(N-Me) Ile	Ape	single bond	NH ₂
583	Ape	Arg	Asp	Aze (2)	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
584	Ape	(d)- Ser	Asp	Aze (2)	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
585	Ape	(d)- Thr	Asp	Aze (2)	Leu	(N-Me) Ile	Ape	single bond	NH ₂
586	Ape	(d)- Thr	Asp	Aze (2)	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂

The structures of compounds represented by formula [I-16], which were synthesized in Example 4 or with the same method as in Example 4, are shown in the following table.



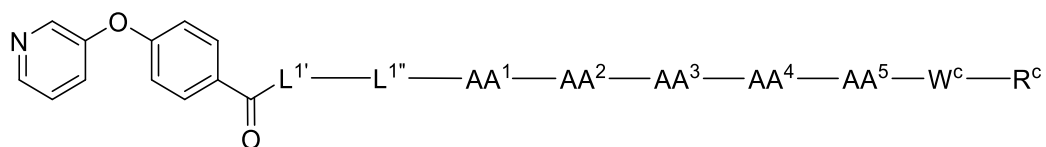
[I'-16]

[Table 23]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
587	β -Ala	Asn	Asp	Ala	Leu	(N-Me) Met	Pro	single bond	NH ₂
588	GABA	Asn	Asp	Ala	Leu	(N-Me) Met	Pro	single bond	NH ₂
589	β -Ala	Asn	Asp	Ala	Leu	(N-Me) Val	Pro	single bond	NH ₂

5

The structure of a compound represented by formula [I'-17], which was synthesized with the same method as in Example 2, is shown in the following table.



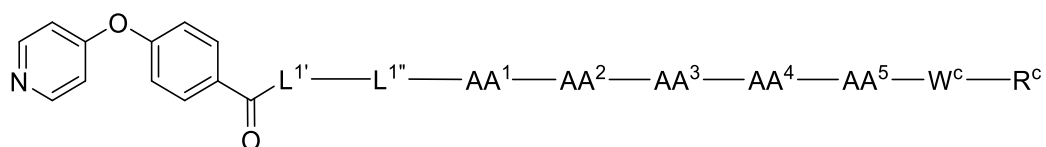
[I'-17]

10

[Table 24]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
590	Ape	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

The structure of a compound represented by formula [I'-18], which was synthesized with the same method as in Example 2, is shown in the following table.

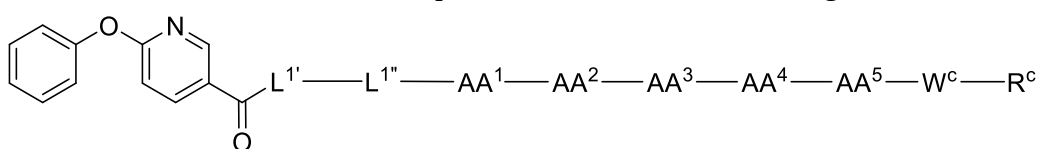


[I'-18]

[Table 25]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
591	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

The structure of a compound represented by formula [I'-19], which was synthesized with the same method as in Example 2, is shown in the following table.

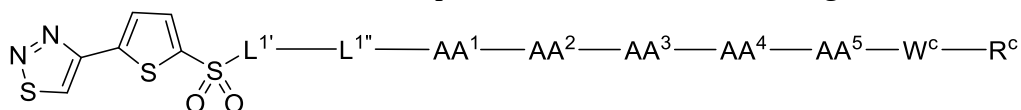


[I'-19]

[Table 26]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
592	Ape	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

10 The structure of a compound represented by formula [I'-20], which was synthesized with the same method as in Example 1, is shown in the following table.

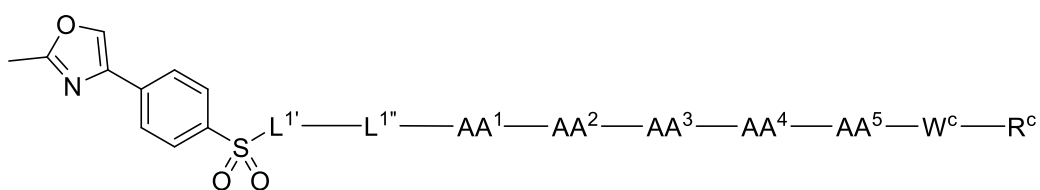


[I'-20]

[Table 27]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
593	single bond	single bond	β-(d) -Asp	Ala	Leu	(N-Me) Glu	β-hom oPro	single bond	NH ₂

The structures of compounds represented by formula [I'-21], which were synthesized with the same method as in Example 1, are shown in the following table.



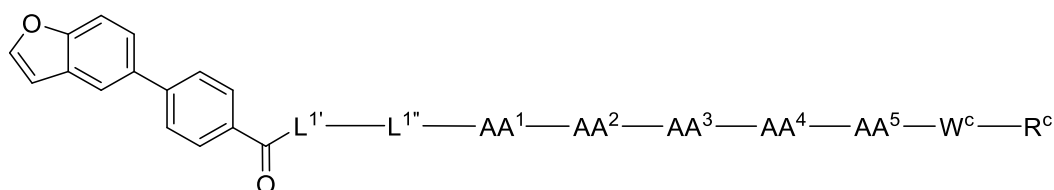
[I'-21]

[Table 28]

Compound No.	L'1'	L'1''	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
594	single bond	single bond	β -(d)-Asp	Ala	Leu	(N-Me) Ile	β -hom oPro	single bond	NH ₂
595	single bond	single bond	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me) Glu	Ape	single bond	NH ₂

5

The structure of a compound represented by formula [I'-22], which was synthesized with the same method as in Example 2, is shown in the following table.



[I'-22]

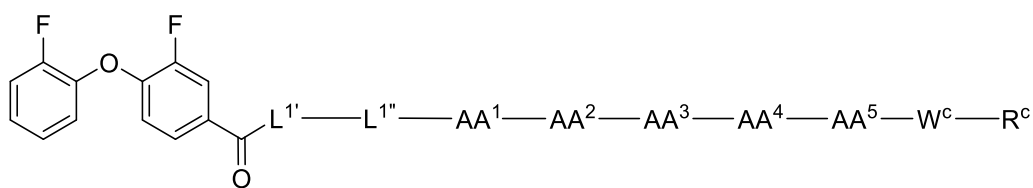
10

[Table 29]

Compound No.	L'1'	L'1''	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
596	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂

15

The structure of a compound represented by formula [I'-23], was synthesized with the same method as in Example 2, is shown in the following table.

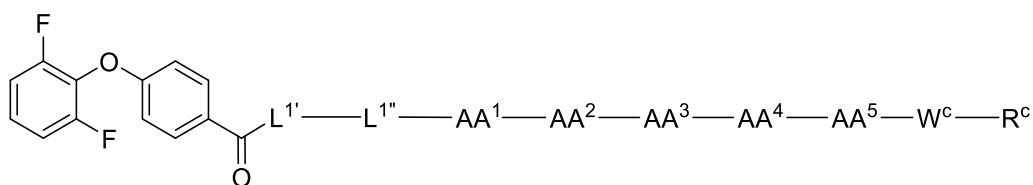


[I'-23]

[Table 30]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
597	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

The structure of a compound represented by formula [I'-24], which was synthesized with the same method as in Example 2, is shown in the following table.

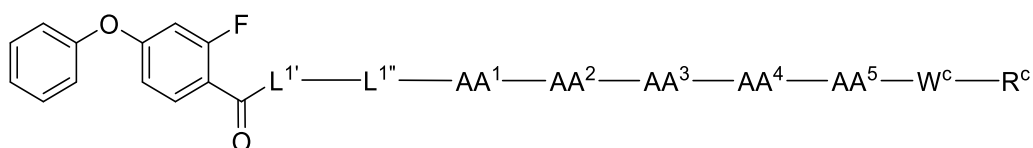


[I'-24]

[Table 31]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
598	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

The structure of a compound represented by formula [I'-25], which was synthesized with the same method as in Example 2, is shown in the following table.

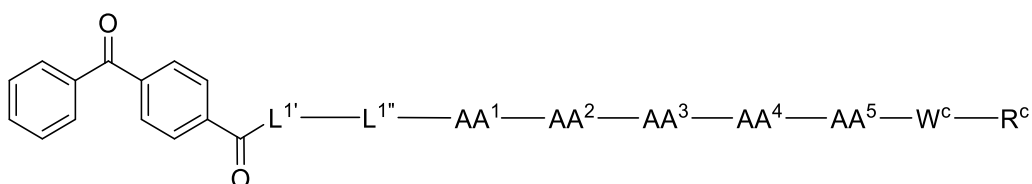


[I'-25]

[Table 32]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
599	GABA	Asn	Asp	Ala	Leu	Met	Pro	single bond	NH ₂

The structures of compounds represented by formula [I'-26], which were synthesized with the same method as in Example 2, are shown in the following table.

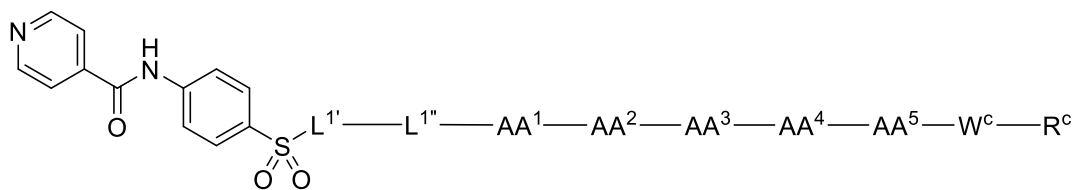


[I'-26]

[Table 33]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
600	GABA	Asn	Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
601	GABA	Asn	Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂

The structures of compounds represented by formula [I'-27], which were synthesized with the same method as in Example 1, each are shown in the following table.

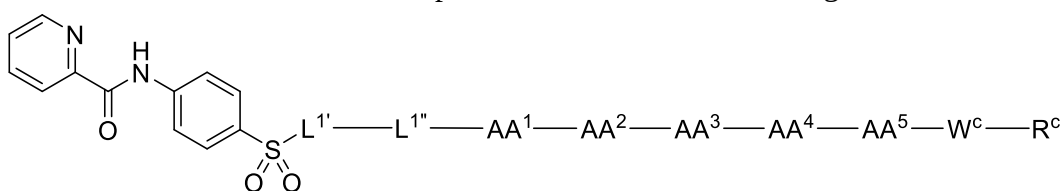


[I'-27]

[Table 34]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
602	single bond	single bond	β -(d)-Asp	Dap	Leu	(N-Me)Glu	β -homoPro	single bond	NH ₂
603	single bond	single bond	β -(d)-Asp	Dab	Leu	(N-Me)Glu	β -homoPro	single bond	NH ₂
604	single bond	single bond	β -(d)-Asp	Dap	Leu	(N-Me)Ile	β -homoPro	single bond	NH ₂
605	single bond	single bond	β -(d)-Asp	Dab	Leu	(N-Me)Ile	β -homoPro	single bond	NH ₂

The structure of a compound represented by formula [I'-28], which was synthesized with the same method as in Example 1, is shown in the following table.

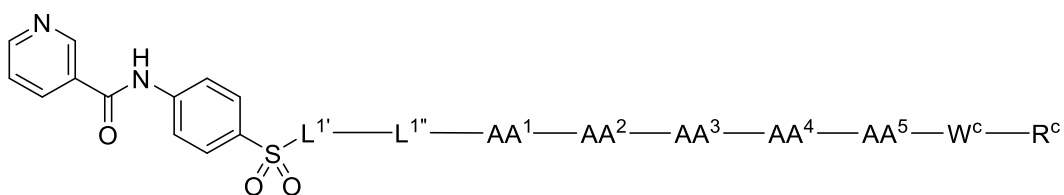


[I'-28]

[Table 35]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
606	single bond	single bond	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond	OH

The structure of a compound represented by formula [I'-29], which was synthesized with the same method as in Example 1, is shown in the following table.

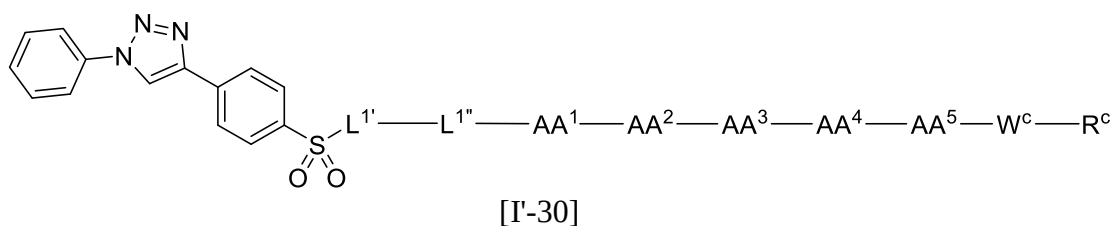


[I'-29]

[Table 36]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
607	single bond	single bond	γ -(d)-Glu	(2S, 4S)-(4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond	OH

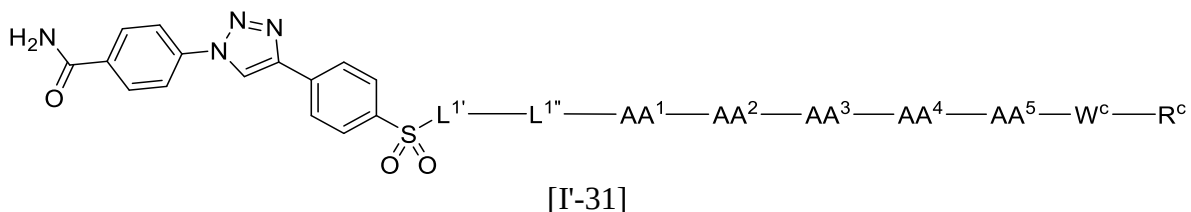
The structure of a compound represented by formula [I'-30], which was synthesized with the same method as in Example 5, is shown in the following table.



[Table 37]

Compound No.	L ¹	L ²	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
608	single bond	single bond	γ -(d)-Glu	Dab	Leu	(N-Me)Ile	β -homo Pro	single bond	NH ₂

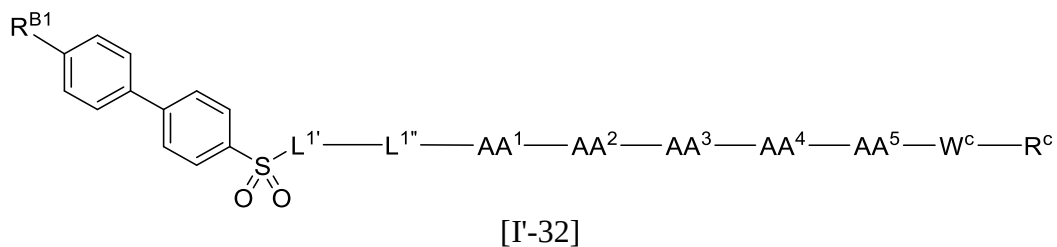
The structure of a compound represented by formula [I'-31], which was synthesized with the same method as in Example 5, is shown in the following table.



[Table 38]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
609	single bond	single bond	γ -(d)-Glu	Dab	Leu	(N-Me)Glu	Ape	single bond	NH ₂

The structures of compounds represented by formula [I'-32], which were synthesized with the same method as in Example 1, are shown in the following table.



5

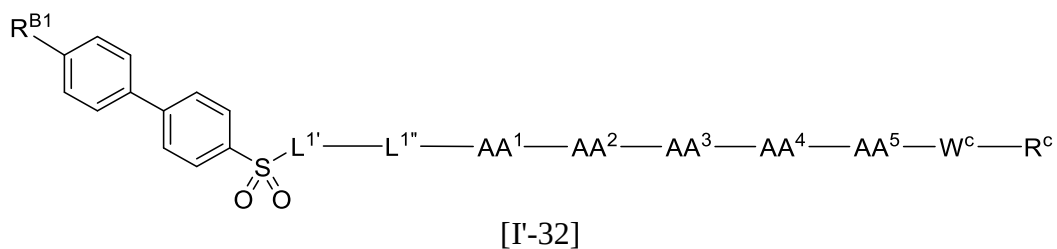
[Table 39]

Compound No.	R ^{B1}	L ^{1'}	L ^{1*}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
610	MeO	single bond	single bond	β - (d) - Asp	Ala	Ala (2 -Pyr)	Met	Pro	single bond	NH ₂
611	MeO	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
612	MeO	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
613	MeO	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
614	MeO	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
615	F ₃ CO	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
616	F ₃ CO	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
617	EtO	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
618	EtO	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
619	EtO	single bond	single bond	β - (d) - Asp	Orn	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
620	H	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂

621	H	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
622	MeO	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
623	MeO	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
624	F	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
625	F	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
626	Cl	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
627	Cl	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
628	Ac	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
629	Ac	single bond	single bond	β - (d) - Asp	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂

630	MeO	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	β - homo Pro	single bond	NH ₂
631	MeO	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Ile	β - homo Pro	single bond	NH ₂
632	MeO	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	Ape	single bond	NH ₂
633	MeO	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4-amino)Pro	Leu	(N-Me) Glu	single bond	single bond	NH ₂

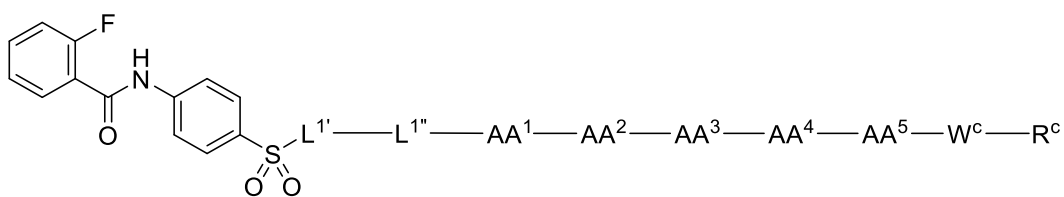
The structures of compounds represented by formula [I'-32], which were synthesized in Example 6 or with the same method as in Example 6, are shown in the following table.



[Table 40]

Compound No.	R ^{B1}	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
634	Ac	single bond	single bond	β - (d) - Asp	Ala	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
635	H ₂ NCO	single bond	single bond	β - (d) - Asp	Ala	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
636	MeCONH	single bond	single bond	β - (d) - Asp	Ala	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
637	HO-CH ₂	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
638	HO-(CH ₂) ₂ -O	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
639	HO-CH ₂	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
640	HO-(CH ₂) ₂ -O	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
641	HO-CH ₂	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
642	HO-CH ₂	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂

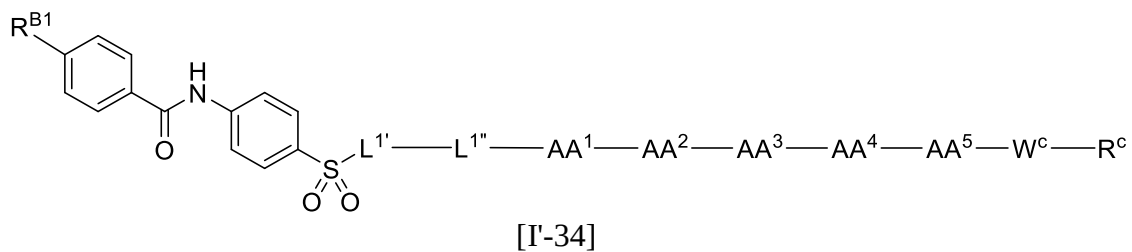
The structure of a compound represented by formula [I'-33], which was synthesized with the same method as in Example 1, is shown in the following table.



[Table 41]

Compound No.	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
643	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	Ape	single bond	OH

The structures of compounds represented by formula [I'-34], which were synthesized with the same method as in Example 1, are shown in the following table.



5 [Table 42]

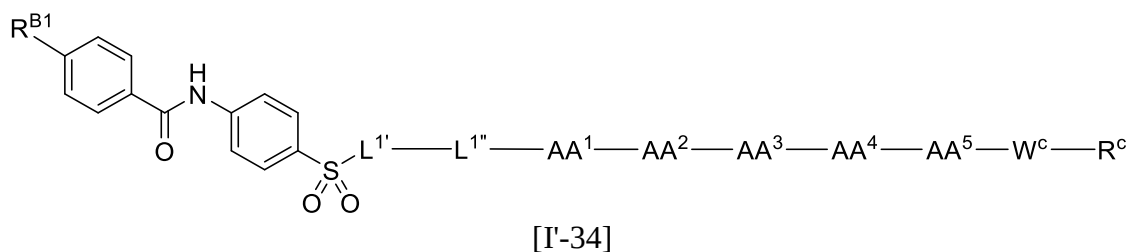
Compound No.	R ^{B1}	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
644	H	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
645	H	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
646	H	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
647	H	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
648	H	single bond	single bond	β - Asp	Dap	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
649	H	single bond	single bond	γ - Glu	Dap	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
650	H	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
651	H	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
652	H	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
653	H	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
654	F	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
655	F	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
656	F	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂
657	F	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	β - homoPro	single bond	NH ₂
658	Me	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Glu	β - homoPro	single bond	NH ₂

659	Me	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
660	Me	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
661	Me	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
662	CF ₃	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
663	CF ₃	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
664	CF ₃	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
665	CF ₃	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
666	Br	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
667	Br	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
668	CN	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
669	CN	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homoP ro	single bond	NH ₂
670	H	Ape	Glu	Asp	Dab	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
671	Br	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
672	CN	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
673	Br	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂
674	MeNHC O	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homoP ro	single bond	NH ₂

675	Me ₂ NC O	single bond	single bond	β - (d) - Asp	Dap	Leu	(N- Me) Ile	β - homoP ro	single bond	NH ₂
676	MeNHC O	single bond	single bond	β - (d) - Asp	Dab	Leu	(N- Me) Ile	β - homoP ro	single bond	NH ₂
677	Me ₂ NC O	single bond	single bond	β - (d) - Asp	Dab	Leu	(N- Me) Ile	β - homoP ro	single bond	NH ₂
678	MeNHC O	single bond	single bond	β - (d) - Asp	Dap	Leu	(N- Me) Glu	β - homoP ro	single bond	NH ₂
679	Me ₂ NC O	single bond	single bond	β - (d) - Asp	Dap	Leu	(N- Me) Glu	β - homoP ro	single bond	NH ₂
680	MeNHC O	single bond	single bond	β - (d) - Asp	Dab	Leu	(N- Me) Glu	β - homoP ro	single bond	NH ₂
681	Me ₂ NC O	single bond	single bond	β - (d) - Asp	Dab	Leu	(N- Me) Glu	β - homoP ro	single bond	NH ₂
682	F	single bond	single bond	γ - Glu	(2S, 4 S) - (4- amino)Pro	Leu	(N- Me) Ile	Ape	single bond	NH ₂
683	F	single bond	single bond	γ - Glu	(2S, 4 S) - (4- amino)Pro	Leu	(N- Me) Val	Ape	single bond	NH ₂
684	H	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4- amino)Pro	Leu	(N- Me) Glu	Ape	single bond	OH
685	F	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4- amino)Pro	Leu	(N- Me) Glu	Ape	single bond	OH
686	Me	single bond	single bond	γ - (d) - Glu	(2S, 4 S) - (4- amino)Pro	Leu	(N- Me) Glu	Ape	single bond	OH

687	F ₂ CO	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond	OH
688	F ₂ C	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond	OH
689	F ₂ HC-CF ₂	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond	OH
690	CN	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino)Pro	Leu	(N-Me)Glu	Ape	single bond	OH

The structures of compounds represented by formula [I'-34], which were synthesized in Example 7 or with the same method as in Example 7, are shown in the following table.

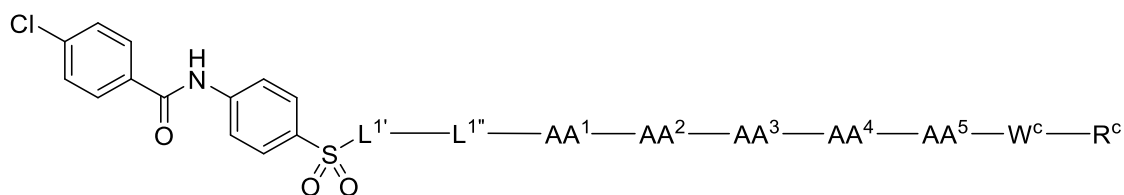


[Table 43]

Compound No.	R ^{B1}	L ^{1'}	L ^{1''}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
691	MeO	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
692	MeO	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
693	MeO	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
694	MeO	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
695	MeO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
696	n-PrO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
697	MeO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
698	EtO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
699	i-PrO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
700	c-PrO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
701	F ₃ CO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β -homo Pro	single bond	NH ₂
702	EtO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
703	c-PrO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂
704	F ₃ CO	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Glu	β -homo Pro	single bond	NH ₂

The structures of compounds represented by formula [I'-35], which were synthesized

5 with the same method as in Example 1, are shown in the following table.



[Table 44]

Compound No.	L ¹	L ^{1'}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
705	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	β - homoPr o	single bond	NH ₂
706	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	β - homoPr o	single bond	NH ₂
707	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	β - homoPr o	single bond	NH ₂
708	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homoPr o	single bond	NH ₂
709	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Glu	single bond	single bond	NH ₂
710	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me) Ile	single bond	single bond	NH ₂
711	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	single bond	single bond	NH ₂
712	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	single bond	single bond	NH ₂
713	single bond	single bond	β - (d) - Asp	Ala	Leu	(N-Me) Glu	single bond	single bond	NH ₂
714	single bond	single bond	β - (d) - Asp	Ala	Leu	(N-Me) Glu	β - homoPr o	single bond	NH ₂
715	single bond	single bond	β - (d) - Asp	Ala	Leu	(N-Me) Ile	β - homoPr o	single bond	NH ₂
716	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me) Glu	β - homoPr o	single bond	NH ₂
717	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me) Ile	β - homoPr o	single bond	NH ₂
718	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - homoPr o	single bond	NH ₂
719	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Glu	β - homoPr o	single bond	NH ₂

720	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me) Ile	β - homoPr o	(d) - Lys	NH ₂
721	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me) Ile	β - homoPr o	(d) - Arg	NH ₂
722	single bond	single bond	γ - (d) - Glu	Dap	Leu	(N-Me) Ile	β - homoPr o	single bond	NH - (CH ₂) ₂ - NH ₂
723	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - homoPr o	(d) - Lys	NH ₂
724	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - homoPr o	(d) - Arg	NH ₂
725	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - homoPr o	single bond	NH - (CH ₂) ₂ - NH ₂
726	single bond	single bond	γ - (d) - Glu	Dab	Nle	(N-Me) Ile	β - homoPr o	single bond	NH ₂
727	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ala	single bond	NH ₂
728	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Thr	single bond	NH ₂
729	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Phe	single bond	NH ₂
730	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Lys	single bond	NH ₂
731	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - Ala	single bond	NH ₂
732	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	GABA	single bond	NH ₂
733	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
734	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Acp	single bond	NH ₂
735	single bond	single bond	γ - (d) - Glu	Dab	Leu	Lys (CO - (CH ₂) ₁₀ - CO ₂ H)	β - homoPr o	single bond	NH ₂

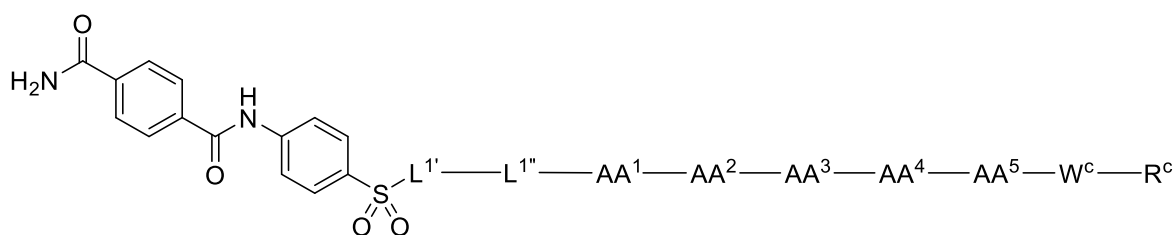
736	single bond	single bond	γ - (d) - Glu	Dab	Leu	Lys (CO - (CH ₂) ₁₂ - CO ₂ H)	β - homoPr o	single bond	NH ₂
737	single bond	single bond	γ - (d) - Glu	Dab	Leu	Lys (CO - (CH ₂) ₁₄ - CO ₂ H)	β - homoPr o	single bond	NH ₂
738	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - Dap	single bond	NH ₂
739	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - (d) - Dap	single bond	NH ₂
740	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	γ - Dab	single bond	NH ₂
741	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	γ - (d) - Dab	single bond	NH ₂
742	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	δ - Orn	single bond	NH ₂
743	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	ϵ - Lys	single bond	NH ₂
744	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	ϵ - (d) - Lys	single bond	NH ₂
745	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Glu	ϵ - Lys	single bond	NH ₂
746	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	single bond	single bond	NH - (CH ₂) ₄ - NH ₂
747	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - Ala	single bond	NH - (CH ₂) ₂ - NH ₂
748	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - Ala	single bond	NH - (CH ₂) ₃ - NH ₂
749	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - Ala	single bond	NH - (CH ₂) ₄ - NH ₂
750	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	β - Ala	single bond	NH - (CH ₂) ₅ - NH ₂

751	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	GABA	single bond	NH- (CH ₂) ₂ -NH ₂
752	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	GABA	single bond	NH- (CH ₂) ₃ -NH ₂
753	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	GABA	single bond	NH- (CH ₂) ₄ -NH ₂
754	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	GABA	single bond	NH- (CH ₂) ₅ -NH ₂
755	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	NH- (CH ₂) ₂ -NH ₂
756	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	NH- (CH ₂) ₃ -NH ₂
757	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	NH- (CH ₂) ₄ -NH ₂
758	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	NH- (CH ₂) ₅ -NH ₂
759	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	(4) Abz	single bond	NH ₂
760	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	(4-Me) pip erazin -1-yl
761	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	morpho lin-4-yl
762	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	[VI-8]
763	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	[VI-16]
764	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	[VI-18]
765	single bond	single bond	γ - (d) - Glu	Dab	Leu	homoSe r	Ape	single bond	NH ₂

766	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Lys	NH ₂
767	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Arg	NH ₂
768	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Arg (d) - Lys	NH ₂
769	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Arg (d) - Arg	NH ₂
770	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Lys (d) - Arg	NH ₂
771	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Lys (d) - Lys	NH ₂
772	single bond	single bond	β - (d) - Asp	(S) - piperazine	Leu	(N-Me) Ile	Ape	(d) - Lys	NH ₂
773	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	Ape	(d) - Arg (d) - Lys	NH ₂
774	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	Ape	(d) - Arg (d) - Arg	NH ₂
775	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	Ape	(d) - Lys (d) - Arg	NH ₂
776	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	Ape	(d) - Lys (d) - Lys	NH ₂
777	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	γ - (d) - Dab	single bond	NH ₂
778	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	δ - Orn	single bond	NH ₂
779	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	δ - (d) - Orn	single bond	NH ₂
780	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	ϵ - Lys	single bond	NH ₂
781	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	ϵ - (d) - Lys	single bond	NH ₂

782	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Val	Ape	(d) - Lys	NH ₂
783	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Leu	Ape	(d) - Lys	NH ₂
784	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Glu	Ape	(d) - Lys	NH ₂
785	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	(d) - Lys	OH
786	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	Pro	single bond	NH ₂
787	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	GABA	single bond	NH ₂
788	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	Acp	single bond	NH ₂
789	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Asp	β - homoPro	single bond	NH ₂
790	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Asp	Pro	single bond	NH ₂
791	single bond	single bond	γ - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Ile	Ape	single bond	NH ₂

The structures of compounds represented by formula [I'-36], which were synthesized with the same method as in Example 1, are shown in the following table.



[I'-36]

[Table 45]

Compound No.	L ^{1*}	L ^{1*}	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	W ^c	R ^c
792	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Glu	β - homoPr o	single bond	NH ₂
793	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Glu	β - homoPr o	single bond	NH ₂
794	single bond	single bond	β - (d) - Asp	Dap	Leu	(N-Me)Ile	β - homoPr o	single bond	NH ₂
795	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	β - homoPr o	single bond	NH ₂
796	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Ile	Ape	single bond	NH ₂
797	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Ile	Acp	single bond	NH ₂
798	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Glu	Ape	single bond	NH ₂
799	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Glu	Acp	single bond	NH ₂
800	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me)Glu	γ -Dab	single bond	NH ₂
801	single bond	single bond	γ - (d) - Glu	Dab	Ala(cP rotyl)	(N-Me)Ile	Ape	single bond	NH ₂
802	single bond	single bond	γ - (d) - Glu	Dab	Ala(4- Thz)	(N-Me)Ile	Ape	single bond	NH ₂
803	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	Ape	(d) - Lys	NH ₂
804	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	Ape	(d) - Arg	NH ₂
805	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	Ape	(d) - Arg- (d) - Lys	NH ₂
806	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me)Ile	Ape	(d) - Arg(d) -Arg	NH ₂

807	single bond	single bond	β - (d) - Asp	Dab	Leu	(N- Me) Ile	Ape	(d) - Lys(d) -Lys	NH ₂
808	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	Ape	(d) - Arg	NH ₂
809	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	Ape	(d) - Arg(d) -Lys	NH ₂
810	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	Ape	(d) - Lys(d) -Arg	NH ₂
811	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	Ape	(d) - Lys(d) -Lys	NH ₂
812	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	Ape	(d) - Lys	NH ₂
813	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	Ape	(d) - Arg(d) -Arg	NH ₂
814	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	β - (d) - Dap	single bond	NH ₂
815	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	δ -Orn	single bond	NH ₂
816	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	δ - (d) - Orn	single bond	NH ₂
817	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	ϵ -Lys	single bond	NH ₂
818	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	ϵ - (d) - Lys	single bond	NH ₂
819	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	β - homoPr o	single bond	NH ₂
820	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	β - homoPr o	(d) - Lys	NH ₂
821	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	β - homoPr o	(d) - Arg	NH ₂
822	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N- Me) Ile	β - homoPr o	(d) - Arg(d) -Lys	NH ₂

823	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	β - homoPr o	(d) - Arg (d) -Arg	NH ₂
824	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	β - homoPr o	(d) - Lys (d) -Arg	NH ₂
825	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	β - homoPr o	(d) - Lys (d) -Lys	NH ₂
826	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Val	Ape	single bond	NH ₂
827	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Val	β - homoPr o	single bond	NH ₂
828	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	Gly - (d) - Lys	NH ₂
829	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	Gly - (d) - Arg	NH ₂
830	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	Gly - (d) - Arg - (d) - Arg	NH ₂
831	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	Gly - (d) - Lys (d) -Arg	NH ₂
832	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	β - Ala - (d) - Lys	NH ₂
833	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	β - Ala - (d) - Arg - (d) - Lys	NH ₂
834	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N - Me) Ile	Ape	β - Ala - (d) - Arg - (d) - Arg	NH ₂

835	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	β - Ala - (d) - Lys - (d) - Arg	NH ₂
836	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	Gly - (d) - Arg - (d) - Lys	NH ₂
837	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	Gly - (d) - Lys - (d) - Lys	NH ₂
838	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
839	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Pro	single bond	NH ₂
840	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - Ala	single bond	NH ₂
841	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	GABA	single bond	NH ₂
842	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
843	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	Acp	single bond	NH ₂
844	single bond	single bond	β - (d) - Asp	Dab	Leu	(N-Me) Ile	β - Dap	single bond	NH ₂
845	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Aze (2)	single bond	NH ₂
846	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	(d) - Aze (2)	single bond	NH ₂
847	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Aze (3)	single bond	NH ₂
848	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	cis-NH (3)c Pen	single bond	NH ₂

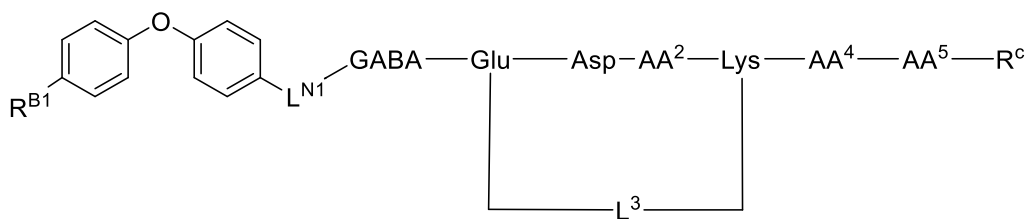
849	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	cis-NH(3)c Pen	single bond	NH ₂
850	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	single bond	single bond	[VI-14]
851	single bond	single bond	β - (d) - Asp	(S) - piperazine	Leu	(N-Me) Ile	Ape	single bond	NH ₂
852	single bond	single bond	γ - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	NH ₂
853	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Leu	Ape	single bond	NH ₂
854	single bond	single bond	γ - (d) - Glu	Dab	Leu	(N-Me) Ile	Ape	single bond	OH
855	single bond	single bond	γ - (d) - Glu	(S) - piperazine	Leu	(N-Me) Ile	Ape	single bond	NH ₂
856	single bond	single bond	β - (d) - Asp	(S) - piperazine	Leu	(N-Me) Ile	β - homoPro	single bond	NH ₂
857	single bond	single bond	γ - (d) - Glu	Pro	Leu	(N-Me) Glu	Ape	single bond	NH ₂
858	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	Ape	single bond	OH
859	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	single bond	single bond	OH
860	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	single bond	Ape	single bond	NH ₂
861	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	single bond	β - Ala	single bond	NH ₂
862	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	single bond	GABA	single bond	NH ₂

863	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	single bond	Acp	single bond	NH ₂
864	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	single bond	(d) - Lys	single bond	NH ₂
865	single bond	single bond	β - (d) - Asp	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Glu	single bond	single bond	NH ₂
866	single bond	single bond	γ -Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Glu	single bond	single bond	NH ₂
867	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Ile	(N-Me)Glu	single bond	single bond	NH ₂
868	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Ser	single bond	single bond	NH ₂
869	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Tyr	single bond	single bond	NH ₂
870	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Phe	single bond	single bond	NH ₂
871	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Ala	single bond	single bond	NH ₂
872	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Ile	single bond	single bond	NH ₂
873	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Val	single bond	single bond	NH ₂
874	single bond	single bond	γ - (d) - Glu	(2S, 4S))-(4-amino) Pro	Leu	(N-Me)Leu	single bond	single bond	NH ₂

875	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Asp	single bond	single bond	NH ₂
876	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Lys	single bond	single bond	NH ₂
877	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	Gly	single bond	single bond	NH ₂
878	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Arg	single bond	single bond	NH ₂
879	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Pro	single bond	single bond	NH ₂
880	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Ser	single bond	single bond	NH ₂
881	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Tyr	single bond	single bond	NH ₂
882	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Phe	single bond	single bond	NH ₂
883	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Ala	single bond	single bond	NH ₂
884	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - Thr	single bond	single bond	NH ₂
885	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Arg	single bond	single bond	NH ₂
886	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Val	(N-Me) Glu	single bond	single bond	NH ₂

887	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Tyr	(N-Me) Glu	single bond	single bond	NH ₂
888	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(d) - (N-Me) Glu	Ape	single bond	NH ₂
889	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	Glu	Ape	single bond	NH ₂
890	single bond	single bond	γ - (d) - Glu	(2S, 4S) - (4-amino) Pro	Leu	(N-Me) Glu	Ape	Ape	NH ₂

The structures of compounds represented by formula [I'-37], which were synthesized in Example 8 or with the same method as in Example 8, are shown in the following table.

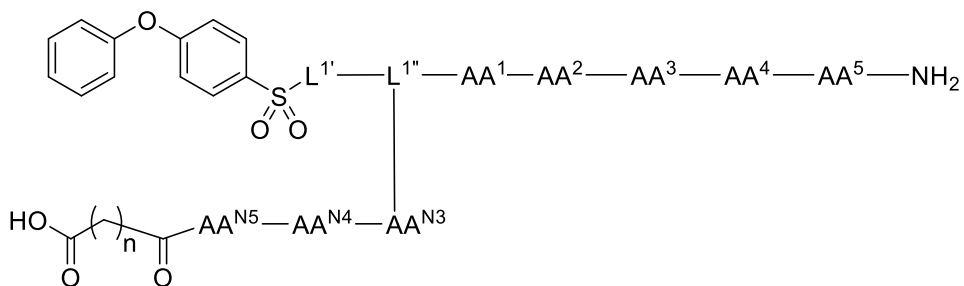


[I'-37]

[Table 46]

Compound No.	R ^{B1}	L ^{N1}	AA ²	L ³	AA ⁴	AA ⁵	R ^c
891	H	SO ₂	Ala	Gly	(N-Me) Ile	β - homoPro	OH
892	H	SO ₂	Ala	Gly	(N-Me) Ile	β - homoPro	NH ₂
893	H	SO ₂	Ala	GABA	(N-Me) Ile	β - homoPro	NH ₂
894	H	SO ₂	Dab	β -Ala	(N-Me) Ile	β - homoPro	NH ₂
895	H	SO ₂	Dab	β -Ala	(N-Me) Asp	β - homoPro	NH ₂
896	H	SO ₂	Dab	β -Ala	(N-Me) Ile	single bond	NH ₂
897	F	CO	Ala	β -Ala	(N-Me) Ile	β - homoPro	NH ₂
898	F	CO	Dab	β -Ala	(N-Me) Ile	β - homoPro	NH ₂
899	F	CO	Dab	β -Ala	(N-Me) Asp	β - homoPro	NH ₂

The structures of compounds represented by formula [I'-38], which were synthesized in Example 9 or with the same method as in Example 9, are shown in the following table.

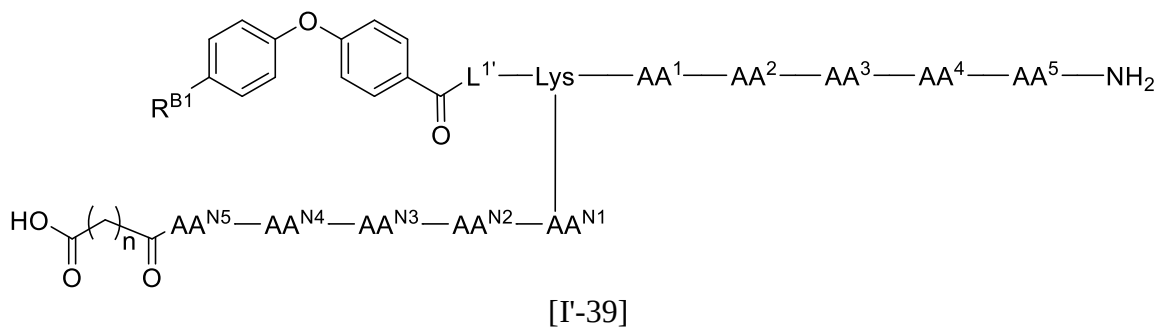


[I'-38]

[Table 47]

Compound No.	L ^{1'}	L ^{1'}	AA ^{N5}	AA ^{N4}	AA ^{N3}	n	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵
900	GABA	Lys	γ - Glu	Adox	Adox	4	Asp	Ala	Leu	(N-Me) Ile	β - homoPro
901	GABA	Lys	γ - Glu	Adox	Adox	6	Asp	Ala	Leu	(N-Me) Ile	β - homoPro
902	GABA	Lys	Lys	Lys	Lys	8	Asp	Ala	Leu	(N-Me) Ile	β - homoPro
903	GABA	Lys	γ - Glu	Adox	Adox	14	Asp	Ala	Leu	(N-Me) Ile	β - homoPro
904	GABA	Lys	γ - Glu	Adox	Adox	16	Asp	Ala	Leu	(N-Me) Ile	β - homoPro
905	GABA	Lys	Lys	Lys	Lys	14	Asp	Ala	Leu	(N-Me) Ile	β - homoPro
906	GABA	Lys	γ - Glu	Adox	Adox	14	Asp	Dab	Leu	(N-Me) Glu	β - homoPro
907	GABA	Lys	Lys	Lys	Lys	14	Asp	Dab	Leu	(N-Me) Glu	β - homoPro
908	GABA	Lys	(d) - Lys	(d) - Lys	(d) - Lys	14	Asp	Dab	Leu	(N-Me) Ile	β - homoPro
909	GABA	Lys	(d) - Lys	(d) - Lys	(d) - Lys	14	Asp	Dab	Leu	(N-Me) Glu	β - homoPro
910	GABA	(d) - Lys	γ - Glu	Adox	Adox	14	Asp	Dab	Leu	(N-Me) Glu	β - homoPro
911	GABA	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	14	Asp	Dab	Leu	(N-Me) Glu	β - homoPro

5 The structures of compounds represented by formula [I'-39], which were synthesized with the same method as in Example 9, are shown in the following table.



[Table 48]

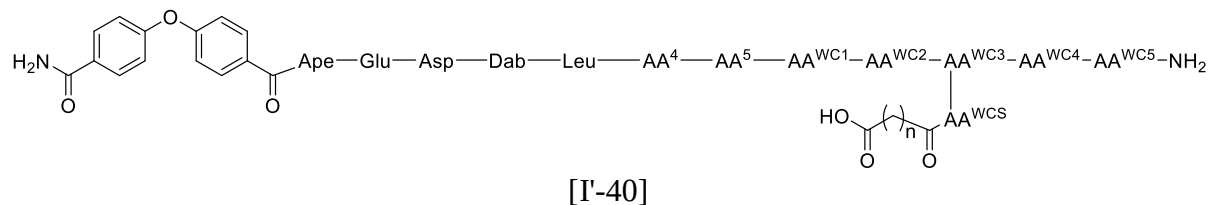
Compound No.	R ^{B1}	L ^{1'}	AA ^{N5}	AA ^{N4}	AA ^{N3}	AA ^{N2}	AA ^{N1}	n	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵
912	F	GAB A	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me) I le	β - hom oPr o
913	F	GAB A	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me) A sp	β - hom oPr o
914	H ₂ NC O	GAB A	γ - Glu	Ado x	Ado x	single bond	single bond	14	Asp	Dab	Leu	(N- Me) I le	β - hom oPr o
915	H ₂ NC O	GAB A	γ - Glu	Ado x	Ado x	single bond	single bond	14	Asp	Dab	Leu	(N- Me) A sp	β - hom oPr o
916	H ₂ NC O	GAB A	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me) I le	β - hom oPr o
917	H ₂ NC O	GAB A	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me) A sp	β - hom oPr o
918	H ₂ NC O	Ape	γ - Glu	Ado x	Ado x	single bond	single bond	14	Asp	Dab	Leu	(N- Me) G lu	β - hom oPr o
919	H ₂ NC O	Ape	γ - Glu	Ado x	Ado x	single bond	single bond	14	Asp	Dab	Leu	(N- Me) I le	β - hom oPr o

920	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
921	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	14	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
922	H ₂ NC O	Ape	γ - Glu	Ado x	Ado x	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
923	H ₂ NC O	Ape	γ - Glu	Ado x	Ado x	single bond	single bond	12	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
924	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
925	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	12	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
926	H ₂ NC O	Ape	(d) - Lys	single bond	single bond	single bond	single bond	14	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
927	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	single bond	single bond	single bond	14	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
928	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	single bond	14	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
929	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	14	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
930	H ₂ NC O	Ape	(d) - Lys	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
931	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o

932	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
933	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	(d) - Lys	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
934	H ₂ NC O	Ape	Lys	Lys	Lys	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
935	H ₂ NC O	Ape	Arg	Arg	Arg	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
936	H ₂ NC O	Ape	(d) - Arg	(d) - Arg	(d) - Arg	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
937	H ₂ NC O	Ape	Ado x	Ado x	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
938	H ₂ NC O	Ape	Ado x	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
939	H ₂ NC O	Ape	γ - Glu	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
940	H ₂ NC O	Ape	Ado x	Ado x	γ - Glu	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
941	H ₂ NC O	Ape	single bond	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
942	H ₂ NC O	Ape	(d) - Lys	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
943	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o

944	H ₂ NC O	Ape	(d) - Lys	single bond	single bond	single bond	single bond	14	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
945	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	single bond	single bond	single bond	14	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
946	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	10	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
947	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	10	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
948	H ₂ NC O	Ape	(d) - Arg	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
949	H ₂ NC O	Ape	(d) - Arg	(d) - Arg	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
950	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	12	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
951	H ₂ NC O	Ape	single bond	single bond	single bond	single bond	single bond	12	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
952	H ₂ NC O	Ape	single bond	single bond	single bond	single bond	single bond	14	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
953	H ₂ NC O	Ape	single bond	single bond	single bond	single bond	single bond	14	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o
954	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	16	Asp	Dab	Leu	(N- Me)G lu	β - hom oPr o
955	H ₂ NC O	Ape	(d) - Lys	(d) - Lys	(d) - Lys	single bond	single bond	16	Asp	Dab	Leu	(N- Me)I le	β - hom oPr o

The structures of compounds represented by formula [I'-40], which were synthesized with the same method as in Example 9, are shown in the following table:



5

wherein

the structure represented by formula [VII-2]:



corresponds to W^C , which is "linker consisting of one to three amino acids" in the compound

10 represented by formula [I'],

wherein

AA^{WC1} , AA^{WC2} , AA^{WC4} , and AA^{WC5} are same or different and each selected from the group consisting of a single bond and (d)-Lys,

AA^{WC3} is Lys or (d)-Lys, and

15 AA^{WCS} is a single bond or (d)-Lys.

[Table 49]

Compound No.	AA ⁴	AA ⁵	AA ^{FC1}	AA ^{FC2}	AA ^{FC3}	AA ^{FC4}	AA ^{FC5}	AA ^{FC6}	n
956	(N-Me) Ile	β - homoPro	(d) - Lys	(d) - Lys	Lys	single bond	single bond	single bond	12
957	(N-Me) Ile	β - homoPro	(d) - Lys	(d) - Lys	Lys	single bond	single bond	single bond	14
958	(N-Me) Glu	β - homoPro	(d) - Lys	(d) - Lys	Lys	single bond	single bond	single bond	14
959	(N-Me) Ile	β - homoPro	(d) - Lys	single bond	Lys	(d) - Lys	single bond	single bond	12
960	(N-Me) Ile	β - homoPro	(d) - Lys	single bond	Lys	(d) - Lys	single bond	single bond	14
961	(N-Me) Glu	β - homoPro	(d) - Lys	single bond	Lys	(d) - Lys	single bond	single bond	12
962	(N-Me) Glu	β - homoPro	(d) - Lys	single bond	Lys	(d) - Lys	single bond	single bond	14
963	(N-Me) Ile	β - homoPro	single bond	single bond	Lys	(d) - Lys	(d) - Lys	single bond	12
964	(N-Me) Ile	β - homoPro	single bond	single bond	Lys	(d) - Lys	(d) - Lys	single bond	14
965	(N-Me) Glu	β - homoPro	single bond	single bond	Lys	(d) - Lys	(d) - Lys	single bond	12
966	(N-Me) Glu	β - homoPro	single bond	single bond	Lys	(d) - Lys	(d) - Lys	single bond	14
967	(N-Me) Ile	β - homoPro	single bond	single bond	Lys	single bond	single bond	single bond	12
968	(N-Me) Ile	β - homoPro	single bond	single bond	Lys	single bond	single bond	single bond	14
969	(N-Me) Ile	β - homoPro	single bond	single bond	(d) - Lys	single bond	single bond	single bond	12
970	(N-Me) Ile	β - homoPro	single bond	single bond	(d) - Lys	single bond	single bond	single bond	14
971	(N-Me) Ile	β - homoPro	single bond	single bond	Lys	single bond	single bond	(d) - Lys	12
972	(N-Me) Ile	β - homoPro	single bond	single bond	Lys	single bond	single bond	(d) - Lys	14

Mass spectra of high-performance liquid chromatography (LCMS), retention time (RT), and analysis conditions for the present inventive compounds are shown in the following table.

[Table 50]

Compound No.	LCMS analysis			
	MS (found)	MS (calc.)	Retention time RT (min)	Analysis condition
1	916.7 [M+H] ⁺	916.4 [M+H] ⁺	0.97	A
2	902.5 [M+H] ⁺	902.4 [M+H] ⁺	0.98	A
3	902.5 [M+H] ⁺	902.4 [M+H] ⁺	0.99	A
4	916.4 [M+H] ⁺	916.4 [M+H] ⁺	0.94	A
5	902.4 [M+H] ⁺	902.4 [M+H] ⁺	0.81	A
6	916.4 [M+H] ⁺	916.4 [M+H] ⁺	0.90	A
7	950.4 [M+H] ⁺	950.4 [M+H] ⁺	0.99	A
8	989.4 [M+H] ⁺	989.4 [M+H] ⁺	1.01	A
9	900.6 [M+H] ⁺	900.4 [M+H] ⁺	1.08	A
10	886.4 [M+H] ⁺	886.4 [M+H] ⁺	1.02	A
11	900.5 [M+H] ⁺	900.4 [M+H] ⁺	1.10	A
12	858.4 [M+H] ⁺	858.4 [M+H] ⁺	0.98	A
13	934.4 [M+H] ⁺	934.4 [M+H] ⁺	1.20	A
14	950.5 [M+H] ⁺	950.4 [M+H] ⁺	1.02	A
15	874.4 [M+H] ⁺	874.4 [M+H] ⁺	0.88	A
16	870.4 [M+H] ⁺	870.4 [M+H] ⁺	0.96	A
17	914.5 [M+H] ⁺	914.4 [M+H] ⁺	0.99	A
18	900.4 [M+H] ⁺	900.3 [M+H] ⁺	0.95	A
19	900.3 [M+H] ⁺	900.3 [M+H] ⁺	0.92	A
20	928.6 [M+H] ⁺	928.4 [M+H] ⁺	1.01	A
21	914.4 [M+H] ⁺	914.4 [M+H] ⁺	0.94	A
22	888.3 [M+H] ⁺	888.3 [M+H] ⁺	0.87	A
23	902.4 [M+H] ⁺	902.4 [M+H] ⁺	0.89	A
24	930.4 [M+H] ⁺	930.4 [M+H] ⁺	0.99	A
25	914.4 [M+H] ⁺	914.4 [M+H] ⁺	0.91	A
26	945.5 [M+H] ⁺	945.4 [M+H] ⁺	0.69	A
27	945.4 [M+H] ⁺	945.4 [M+H] ⁺	0.69	A
28	973.4 [M+H] ⁺	973.4 [M+H] ⁺	0.70	A
29	973.4 [M+H] ⁺	973.4 [M+H] ⁺	0.71	A
30	817.3 [M+H] ⁺	817.3 [M+H] ⁺	0.89	A
31	674.1 [M+H] ⁺	674.3 [M+H] ⁺	0.85	A
32	1013.5 [M+H] ⁺	1013.4 [M+H] ⁺	1.00	A
33	1042.7 [M-H] ⁻	1042.5 [M-H] ⁻	0.74	A
34	1042.6 [M-H] ⁻	1042.5 [M-H] ⁻	0.74	A
35	1070.7 [M-H] ⁻	1070.5 [M-H] ⁻	0.75	A
36	1070.5 [M-H] ⁻	1070.5 [M-H] ⁻	0.76	A
37	587.0 [M+2H] ²⁺	586.8 [M+2H] ²⁺	0.64	A
38	898.7 [M+H] ⁺	898.4 [M+H] ⁺	1.07	A
39	912.6 [M+H] ⁺	912.4 [M+H] ⁺	1.06	A
40	830.3 [M+H] ⁺	830.4 [M+H] ⁺	1.28	A
41	860.4 [M+H] ⁺	860.4 [M+H] ⁺	1.27	A
42	864.4 [M+H] ⁺	864.3 [M+H] ⁺	1.38	A
43	848.4 [M+H] ⁺	848.4 [M+H] ⁺	1.30	A
44	846.4 [M+H] ⁺	846.4 [M+H] ⁺	1.28	A
45	877.5 [M+H] ⁺	877.4 [M+H] ⁺	1.46	A
46	877.5 [M+H] ⁺	877.4 [M+H] ⁺	1.47	A

47	875.5 [M-H] ⁻	875.4 [M-H] ⁻	1.48	A
48	888.5 [M-H] ⁻	888.3 [M-H] ⁻	1.74	A
49	876.5 [M-H] ⁻	876.3 [M-H] ⁻	1.71	A
50	905.6 [M+H] ⁺	905.3 [M+H] ⁺	1.36	A
51	889.5 [M+H] ⁺	889.4 [M+H] ⁺	1.44	A
52	893.5 [M+H] ⁺	893.3 [M+H] ⁺	1.32	A
53	907.5 [M+H] ⁺	907.3 [M+H] ⁺	1.29	A
54	903.6 [M+H] ⁺	903.4 [M+H] ⁺	1.40	A
55	903.6 [M+H] ⁺	903.4 [M+H] ⁺	1.40	A
56	976.4 [M+H] ⁺	976.4 [M+H] ⁺	1.66	A
57	956.6 [M-H] ⁻	956.4 [M-H] ⁻	1.63	A
58	970.7 [M-H] ⁻	970.4 [M-H] ⁻	1.65	A
59	970.6 [M-H] ⁻	970.4 [M-H] ⁻	1.64	A
60	985.0 [M-H] ⁻	984.5 [M-H] ⁻	1.72	A
61	1001.6 [M+H] ⁺	1001.5 [M+H] ⁺	1.37	A
62	1015.6 [M+H] ⁺	1015.5 [M+H] ⁺	1.35	A
63	1029.6 [M+H] ⁺	1029.5 [M+H] ⁺	1.35	A
64	988.6 [M+H] ⁺	988.4 [M+H] ⁺	1.59	A
65	984.6 [M-H] ⁻	984.5 [M-H] ⁻	1.66	A
66	1000.6 [M-H] ⁻	1000.4 [M-H] ⁻	1.58	A
67	1001.6 [M+H] ⁺	1001.5 [M+H] ⁺	1.33	A
68	1031.6 [M+H] ⁺	1031.4 [M+H] ⁺	1.29	A
69	1017.5 [M+H] ⁺	1017.4 [M+H] ⁺	1.29	A
70	1027.7 [M-H] ⁻	1027.5 [M-H] ⁻	1.40	A
71	1015.6 [M+H] ⁺	1015.5 [M+H] ⁺	1.37	A
72	1045.6 [M+H] ⁺	1045.5 [M+H] ⁺	1.31	A
73	1031.5 [M+H] ⁺	1031.4 [M+H] ⁺	1.30	A
74	973.6 [M+H] ⁺	973.4 [M+H] ⁺	1.31	A
75	1002.6 [M+H] ⁺	1002.4 [M+H] ⁺	1.60	A
76	1032.7 [M+H] ⁺	1032.4 [M+H] ⁺	1.35	A
77	1078.7 [M+H] ⁺	1078.4 [M+H] ⁺	1.39	A
78	1047.7 [M+H] ⁺	1047.5 [M+H] ⁺	1.44	A
79	1063.6 [M+H] ⁺	1063.4 [M+H] ⁺	1.37	A
80	1088.8 [M+H] ⁺	1088.5 [M+H] ⁺	1.06	A
81	1102.7 [M+H] ⁺	1102.5 [M+H] ⁺	1.06	A
82	1025.6 [M+H] ⁺	1025.5 [M+H] ⁺	1.03	A
83	1037.7 [M-H] ⁻	1037.5 [M-H] ⁻	1.02	A
84	1032.8 [M+H] ⁺	1032.5 [M+H] ⁺	1.37	A
85	1016.7 [M+H] ⁺	1016.5 [M+H] ⁺	1.45	A
86	1050.7 [M+H] ⁺	1050.5 [M+H] ⁺	1.42	A
87	1034.7 [M+H] ⁺	1034.5 [M+H] ⁺	1.48	A
88	1103.8 [M-H] ⁻	1103.5 [M-H] ⁻	1.20	A
89	1089.8 [M+H] ⁺	1089.5 [M+H] ⁺	1.25	A
90	1188.1 [M-H] ⁻	1187.6 [M-H] ⁻	1.16	A
91	1216.0 [M-H] ⁻	1215.6 [M-H] ⁻	1.19	A
92	905.7 [M-H] ⁻	905.5 [M-H] ⁻	1.72	A
93	923.6 [M-H] ⁻	923.5 [M-H] ⁻	1.73	A
94	948.7 [M-H] ⁻	948.5 [M-H] ⁻	1.62	A
95	966.6 [M-H] ⁻	966.5 [M-H] ⁻	1.65	A
96	893.7 [M-H] ⁻	893.5 [M-H] ⁻	1.80	A
97	911.7 [M-H] ⁻	911.5 [M-H] ⁻	1.82	A

98	938.7 [M+H] ⁺	938.5 [M+H] ⁺	1.71	A
99	956.7 [M+H] ⁺	956.5 [M+H] ⁺	1.74	A
100	919.7 [M-H] ⁻	919.5 [M-H] ⁻	1.73	A
101	937.7 [M-H] ⁻	937.5 [M-H] ⁻	1.75	A
102	933.7 [M-H] ⁻	933.5 [M-H] ⁻	1.81	A
103	962.6 [M-H] ⁻	962.5 [M-H] ⁻	1.63	A
104	980.7 [M-H] ⁻	980.5 [M-H] ⁻	1.66	A
105	976.7 [M-H] ⁻	976.5 [M-H] ⁻	1.71	A
106	979.7 [M+H] ⁺	979.5 [M+H] ⁺	1.33	A
107	965.7 [M+H] ⁺	965.5 [M+H] ⁺	1.28	A
108	995.6 [M+H] ⁺	995.5 [M+H] ⁺	1.25	A
109	981.6 [M+H] ⁺	981.5 [M+H] ⁺	1.23	A
110	993.7 [M+H] ⁺	993.5 [M+H] ⁺	1.34	A
111	979.6 [M+H] ⁺	979.5 [M+H] ⁺	1.31	A
112	1009.6 [M+H] ⁺	1009.5 [M+H] ⁺	1.26	A
113	995.6 [M+H] ⁺	995.5 [M+H] ⁺	1.25	A
114	934.7 [M-H] ⁻	934.5 [M-H] ⁻	1.60	A
115	891.6 [M-H] ⁻	891.5 [M-H] ⁻	1.66	A
116	903.6 [M-H] ⁻	903.5 [M-H] ⁻	1.68	A
117	917.6 [M-H] ⁻	917.5 [M-H] ⁻	1.74	A
118	931.7 [M-H] ⁻	931.5 [M-H] ⁻	1.76	A
119	933.7 [M-H] ⁻	933.5 [M-H] ⁻	1.80	A
120	947.7 [M-H] ⁻	947.5 [M-H] ⁻	1.85	A
121	947.7 [M-H] ⁻	947.5 [M-H] ⁻	1.85	A
122	965.6 [M-H] ⁻	965.5 [M-H] ⁻	1.79	A
123	948.7 [M-H] ⁻	948.5 [M-H] ⁻	1.33	A
124	981.7 [M-H] ⁻	981.5 [M-H] ⁻	1.87	A
125	949.6 [M-H] ⁻	949.5 [M-H] ⁻	1.65	A
126	963.7 [M-H] ⁻	963.5 [M-H] ⁻	1.67	A
127	962.6 [M-H] ⁻	962.5 [M-H] ⁻	1.35	A
128	948.7 [M-H] ⁻	948.5 [M-H] ⁻	1.60	A
129	997.7 [M-H] ⁻	997.5 [M-H] ⁻	1.74	A
130	1020.6 [M-H] ⁻	1020.5 [M-H] ⁻	1.85	A
131	935.7 [M-H] ⁻	935.5 [M-H] ⁻	1.41	A
132	932.8 [M-H] ⁻	932.5 [M-H] ⁻	1.40	A
133	946.7 [M-H] ⁻	946.5 [M-H] ⁻	1.39	A
134	996.6 [M+H] ⁺	996.5 [M+H] ⁺	1.50	A
135	962.7 [M-H] ⁻	962.5 [M-H] ⁻	1.49	A
136	978.7 [M+H] ⁺	978.6 [M+H] ⁺	1.54	A
137	997.7 [M+H] ⁺	997.5 [M+H] ⁺	1.32	A
138	1011.8 [M+H] ⁺	1011.5 [M+H] ⁺	1.35	A
139	1013.6 [M+H] ⁺	1013.5 [M+H] ⁺	1.29	A
140	1027.7 [M+H] ⁺	1027.5 [M+H] ⁺	1.28	A
141	999.6 [M+H] ⁺	999.5 [M+H] ⁺	1.28	A
142	1013.6 [M+H] ⁺	1013.5 [M+H] ⁺	1.28	A
143	980.8 [M+H] ⁺	980.5 [M+H] ⁺	1.38	A
144	1010.7 [M+H] ⁺	1010.5 [M+H] ⁺	1.27	A
145	995.7 [M+H] ⁺	995.5 [M+H] ⁺	1.07	A
146	964.7 [M+H] ⁺	964.5 [M+H] ⁺	1.46	A
147	994.7 [M+H] ⁺	994.5 [M+H] ⁺	1.34	A
148	977.9 [M-H] ⁻	977.6 [M-H] ⁻	1.10	A

149	1013.7 [M+H] ⁺	1013.5 [M+H] ⁺	1.26	A
150	998.7 [M+H] ⁺	998.5 [M+H] ⁺	1.42	A
151	1028.6 [M+H] ⁺	1028.5 [M+H] ⁺	1.30	A
152	1013.6 [M+H] ⁺	1013.5 [M+H] ⁺	1.09	A
153	997.7 [M+H] ⁺	997.5 [M+H] ⁺	1.35	A
154	993.7 [M+H] ⁺	993.5 [M+H] ⁺	1.37	A
155	996.7 [M+H] ⁺	996.5 [M+H] ⁺	1.30	A
156	980.7 [M+H] ⁺	980.5 [M+H] ⁺	1.39	A
157	854.4 [M-2H] ²⁻	854.5 [M-2H] ²⁻	1.44	A
158	870.7 [M+2H] ²⁺	870.5 [M+2H] ²⁺	1.56	A
159	1675.3 [M-H] ⁻	1675.0 [M-H] ⁻	1.01	A
160	853.4 [M+2H] ²⁺	853.0 [M+2H] ²⁺	1.10	A
161	1012.6 [M-H] ⁻	1012.5 [M-H] ⁻	1.36	A
162	1025.7 [M-H] ⁻	1025.5 [M-H] ⁻	1.28	A
163	1026.0 [M-H] ⁻	1025.5 [M-H] ⁻	1.31	A
164	1041.8 [M+H] ⁺	1041.5 [M+H] ⁺	1.28	A
165	1025.8 [M+H] ⁺	1025.5 [M+H] ⁺	1.35	A
166	1039.7 [M+H] ⁺	1039.5 [M+H] ⁺	1.33	A
167	1055.7 [M+H] ⁺	1055.5 [M+H] ⁺	1.25	A
168	1087.7 [M+H] ⁺	1087.5 [M+H] ⁺	1.10	A
169	1060.6 [M+H] ⁺	1060.5 [M+H] ⁺	1.10	A
170	1059.6 [M-H] ⁻	1059.5 [M-H] ⁻	1.94	B
171	1062.6 [M+H] ⁺	1062.5 [M+H] ⁺	1.98	B
172	1020.6 [M+H] ⁺	1020.5 [M+H] ⁺	1.97	B
173	996.8 [M+H] ⁺	996.5 [M+H] ⁺	1.30	A
174	980.8 [M+H] ⁺	980.5 [M+H] ⁺	1.38	A
175	1152.0 [M-H] ⁻	1151.6 [M-H] ⁻	1.11	A
176	1180.0 [M-H] ⁻	1179.6 [M-H] ⁻	1.14	A
177	995.7 [M-H] ⁻	995.4 [M-H] ⁻	1.30	A
178	1055.4 [M+H] ⁺	1055.4 [M+H] ⁺	1.29	A
179	548.7 [M+2H] ²⁺	548.3 [M+2H] ²⁺	0.82	A
180	555.7 [M+2H] ²⁺	555.3 [M+2H] ²⁺	0.84	A
181	1121.8 [M-H] ⁻	1121.6 [M-H] ⁻	0.86	A
182	1110.7 [M+H] ⁺	1110.5 [M+H] ⁺	1.03	A
183	1124.7 [M+H] ⁺	1124.5 [M+H] ⁺	1.04	A
184	1079.0 [M-H] ⁻	1078.6 [M-H] ⁻	0.91	A
185	1063.4 [M-H] ⁻	1062.6 [M-H] ⁻	1.00	A
186	1093.0 [M-H] ⁻	1092.6 [M-H] ⁻	0.97	A
187	1077.0 [M-H] ⁻	1076.6 [M-H] ⁻	1.01	A
188	1106.9 [M-H] ⁻	1106.6 [M-H] ⁻	0.94	A
189	1090.9 [M-H] ⁻	1090.6 [M-H] ⁻	1.00	A
190	1121.1 [M-H] ⁻	1120.6 [M-H] ⁻	0.97	A
191	1105.0 [M-H] ⁻	1104.6 [M-H] ⁻	1.02	A
192	1093.1 [M-H] ⁻	1092.6 [M-H] ⁻	0.99	A
193	1077.0 [M-H] ⁻	1076.6 [M-H] ⁻	1.03	A
194	1106.9 [M-H] ⁻	1106.6 [M-H] ⁻	1.01	A
195	1091.0 [M-H] ⁻	1090.6 [M-H] ⁻	1.05	A
196	1121.0 [M-H] ⁻	1120.6 [M-H] ⁻	1.00	A
197	1105.0 [M-H] ⁻	1104.6 [M-H] ⁻	1.04	A
198	1118.9 [M-H] ⁻	1118.6 [M-H] ⁻	1.06	A
199	1164.8 [M-H] ⁻	1164.6 [M-H] ⁻	1.05	A

200	1151.7 [M+H] ⁺	1151.6 [M+H] ⁺	1.17	A
201	1150.7 [M+H] ⁺	1150.6 [M+H] ⁺	1.12	A
202	958.5 [M+H] ⁺	958.4 [M+H] ⁺	1.62	A
203	1059.7 [M+H] ⁺	1059.5 [M+H] ⁺	1.36	A
204	1073.7 [M+H] ⁺	1073.5 [M+H] ⁺	1.34	A
205	1016.7 [M+H] ⁺	1016.5 [M+H] ⁺	1.40	A
206	1084.7 [M+H] ⁺	1084.5 [M+H] ⁺	1.07	A
207	1098.7 [M+H] ⁺	1098.5 [M+H] ⁺	1.07	A
208	1041.7 [M+H] ⁺	1041.5 [M+H] ⁺	1.12	A
209	1070.6 [M+H] ⁺	1070.5 [M+H] ⁺	1.04	A
210	1038.7 [M+H] ⁺	1038.5 [M+H] ⁺	1.49	B
211	1023.7 [M+H] ⁺	1023.5 [M+H] ⁺	1.62	B
212	1053.7 [M+H] ⁺	1053.5 [M+H] ⁺	1.52	B
213	1038.7 [M+H] ⁺	1038.5 [M+H] ⁺	1.33	B
214	1022.7 [M+H] ⁺	1022.5 [M+H] ⁺	1.57	B
215	1007.7 [M+H] ⁺	1007.6 [M+H] ⁺	1.70	B
216	1037.6 [M+H] ⁺	1037.5 [M+H] ⁺	1.59	B
217	1020.6 [M-H] ⁻	1020.6 [M-H] ⁻	1.44	B
218	1036.7 [M+H] ⁺	1036.5 [M+H] ⁺	1.08	A
219	1052.7 [M+H] ⁺	1052.5 [M+H] ⁺	1.03	A
220	1066.6 [M+H] ⁺	1066.5 [M+H] ⁺	1.03	A
221	1024.7 [M+H] ⁺	1024.5 [M+H] ⁺	0.98	A
222	1052.7 [M+H] ⁺	1052.5 [M+H] ⁺	1.02	A
223	1067.7 [M+H] ⁺	1067.5 [M+H] ⁺	1.04	A
224	1010.6 [M+H] ⁺	1010.5 [M+H] ⁺	1.00	A
225	1024.5 [M+H] ⁺	1024.5 [M+H] ⁺	1.01	A
226	1038.6 [M+H] ⁺	1038.5 [M+H] ⁺	1.03	A
227	1039.6 [M+H] ⁺	1039.5 [M+H] ⁺	1.03	A
228	1053.6 [M+H] ⁺	1053.5 [M+H] ⁺	1.04	A
229	1008.7 [M+H] ⁺	1008.5 [M+H] ⁺	1.05	A
230	1036.7 [M+H] ⁺	1036.5 [M+H] ⁺	1.09	A
231	1023.7 [M+H] ⁺	1023.5 [M+H] ⁺	1.07	A
232	1051.7 [M+H] ⁺	1051.5 [M+H] ⁺	1.10	A
233	1066.6 [M+H] ⁺	1066.5 [M+H] ⁺	1.02	A
234	1050.6 [M+H] ⁺	1050.6 [M+H] ⁺	1.07	A
235	1039.7 [M+H] ⁺	1039.5 [M+H] ⁺	1.04	A
236	1023.7 [M+H] ⁺	1023.5 [M+H] ⁺	1.12	A
237	1053.7 [M+H] ⁺	1053.5 [M+H] ⁺	1.04	A
238	1039.7 [M+H] ⁺	1039.5 [M+H] ⁺	1.04	A
239	1023.7 [M+H] ⁺	1023.5 [M+H] ⁺	1.11	A
240	1025.6 [M+H] ⁺	1025.5 [M+H] ⁺	1.04	A
241	1024.6 [M+H] ⁺	1024.5 [M+H] ⁺	1.02	A
242	1053.6 [M+H] ⁺	1053.5 [M+H] ⁺	1.04	A
243	1052.6 [M+H] ⁺	1052.5 [M+H] ⁺	1.00	A
244	1036.7 [M-H] ⁺	1036.5 [M-H] ⁺	1.05	A
245	1065.8 [M+H] ⁺	1065.6 [M+H] ⁺	0.95	A
246	1079.8 [M+H] ⁺	1079.6 [M+H] ⁺	0.95	A
247	533.6 [M+2H] ²⁺	533.3 [M+2H] ²⁺	0.90	A
248	1050.7 [M+H] ⁺	1050.6 [M+H] ⁺	1.06	A
249	1064.7 [M+H] ⁺	1064.6 [M+H] ⁺	1.07	A
250	1038.7 [M+H] ⁺	1038.5 [M+H] ⁺	0.99	A

251	1022.7 [M+H] ⁺	1022.5 [M+H] ⁺	1.05	A
252	1024.7 [M+H] ⁺	1024.5 [M+H] ⁺	1.00	A
253	1052.6 [M+H] ⁺	1052.5 [M+H] ⁺	1.00	A
254	1064.8 [M+H] ⁺	1064.6 [M+H] ⁺	1.16	A
255	1104.8 [M+H] ⁺	1104.6 [M+H] ⁺	1.31	A
256	1066.7 [M+H] ⁺	1066.5 [M+H] ⁺	1.04	A
257	1080.7 [M+H] ⁺	1080.5 [M+H] ⁺	1.04	A
258	1081.7 [M+H] ⁺	1081.5 [M+H] ⁺	1.07	A
259	1053.6 [M+H] ⁺	1053.5 [M+H] ⁺	1.07	A
260	1067.7 [M+H] ⁺	1067.5 [M+H] ⁺	1.06	A
261	1051.6 [M+H] ⁺	1051.5 [M+H] ⁺	1.13	A
262	1082.7 [M+H] ⁺	1082.5 [M+H] ⁺	1.09	A
263	1098.6 [M+H] ⁺	1098.5 [M+H] ⁺	1.03	A
264	1097.7 [M+H] ⁺	1097.5 [M+H] ⁺	1.11	A
265	1113.6 [M+H] ⁺	1113.5 [M+H] ⁺	1.05	A
266	1096.6 [M+H] ⁺	1096.6 [M+H] ⁺	1.07	A
267	1112.7 [M+H] ⁺	1112.5 [M+H] ⁺	1.03	A
268	1066.7 [M+H] ⁺	1066.5 [M+H] ⁺	1.03	A
269	1092.7 [M+H] ⁺	1092.5 [M+H] ⁺	1.06	A
270	1106.7 [M+H] ⁺	1106.6 [M+H] ⁺	1.11	A
271	1136.7 [M+H] ⁺	1136.6 [M+H] ⁺	1.03	A
272	1096.6 [M+H] ⁺	1096.5 [M+H] ⁺	1.01	A
273	1076.7 [M+H] ⁺	1076.6 [M+H] ⁺	1.16	A
274	1092.6 [M+H] ⁺	1092.6 [M+H] ⁺	1.07	A
275	1090.7 [M+H] ⁺	1090.6 [M+H] ⁺	1.22	A
276	1120.7 [M+H] ⁺	1120.6 [M+H] ⁺	1.10	A
277	1080.6 [M+H] ⁺	1080.6 [M+H] ⁺	1.07	A
278	1103.7 [M+H] ⁺	1103.5 [M+H] ⁺	1.09	A
279	1036.8 [M+H] ⁺	1036.5 [M+H] ⁺	1.06	A
280	1052.7 [M+H] ⁺	1052.5 [M+H] ⁺	1.02	A
281	1050.7 [M+H] ⁺	1050.6 [M+H] ⁺	1.08	A
282	1066.7 [M+H] ⁺	1066.5 [M+H] ⁺	1.03	A
283	1036.8 [M+H] ⁺	1036.5 [M+H] ⁺	1.06	A
284	1052.6 [M+H] ⁺	1052.5 [M+H] ⁺	1.00	A
285	1025.7 [M+H] ⁺	1025.5 [M+H] ⁺	1.02	A
286	1007.7 [M-H] ⁻	1007.5 [M-H] ⁻	1.04	A
287	1085.7 [M+H] ⁺	1085.5 [M+H] ⁺	1.22	A
288	1085.7 [M+H] ⁺	1085.5 [M+H] ⁺	1.21	A
289	1101.7 [M+H] ⁺	1101.5 [M+H] ⁺	1.11	A
290	1101.5 [M+H] ⁺	1101.5 [M+H] ⁺	1.11	A
291	527.6 [M+2H] ²⁺	527.3 [M+2H] ²⁺	0.83	A
292	534.5 [M+2H] ²⁺	534.3 [M+2H] ²⁺	0.80	A
293	505.9 [M+2H] ²⁺	505.8 [M+2H] ²⁺	0.86	A
294	506.0 [M+2H] ²⁺	505.8 [M+2H] ²⁺	0.86	A
295	993.5 [M-H] ⁻	993.5 [M-H] ⁻	1.03	A
296	520.0 [M+2H] ²⁺	519.8 [M+2H] ²⁺	0.85	A
297	513.1 [M+2H] ²⁺	512.8 [M+2H] ²⁺	0.87	A
298	1036.8 [M-H] ⁻	1036.5 [M-H] ⁻	0.86	A
299	1051.8 [M-H] ⁻	1051.5 [M-H] ⁻	0.76	A
300	991.7 [M+H] ⁺	991.5 [M+H] ⁺	1.11	A
301	1007.6 [M+H] ⁺	1007.5 [M+H] ⁺	1.04	A

302	1005.6 [M+H] ⁺	1005.5 [M+H] ⁺	1.12	A
303	1021.6 [M+H] ⁺	1021.5 [M+H] ⁺	1.06	A
304	1051.7 [M+H] ⁺	1051.5 [M+H] ⁺	1.11	A
305	534.5 [M+2H] ²⁺	534.2 [M+2H] ²⁺	1.05	A
306	1037.7 [M-H] ⁻	1037.5 [M-H] ⁻	0.78	A
307	1037.7 [M-H] ⁻	1037.5 [M-H] ⁻	0.75	A
308	1081.8 [M+H] ⁺	1081.5 [M+H] ⁺	1.07	A
309	1035.8 [M+H] ⁺	1035.6 [M+H] ⁺	1.31	A
310	1048.9 [M-H] ⁻	1048.6 [M-H] ⁻	0.98	A
311	1066.8 [M+H] ⁺	1066.6 [M+H] ⁺	0.88	A
312	1062.8 [M-H] ⁻	1062.6 [M-H] ⁻	1.00	A
313	1078.9 [M-H] ⁻	1078.6 [M-H] ⁻	0.91	A
314	1038.7 [M+H] ⁺	1038.5 [M+H] ⁺	1.06	A
315	1011.7 [M+H] ⁺	1011.5 [M+H] ⁺	1.07	A
316	1071.7 [M+H] ⁺	1071.5 [M+H] ⁺	1.18	A
317	1044.7 [M+H] ⁺	1044.5 [M+H] ⁺	1.18	A
318	1065.7 [M+H] ⁺	1065.6 [M+H] ⁺	1.11	A
319	1039.8 [M+H] ⁺	1039.5 [M+H] ⁺	1.04	A
320	1039.7 [M+H] ⁺	1039.5 [M+H] ⁺	1.03	A
321	1035.7 [M+H] ⁺	1035.5 [M+H] ⁺	1.09	A
322	1124.7 [M+H] ⁺	1124.5 [M+H] ⁺	1.22	A
323	1049.8 [M+H] ⁺	1049.6 [M+H] ⁺	1.32	A
324	1064.8 [M+H] ⁺	1065.6 [M+H] ⁺	1.24	A
325	1067.8 [M+H] ⁺	1067.6 [M+H] ⁺	1.26	A
326	1082.7 [M+H] ⁺	1083.5 [M+H] ⁺	1.17	A
327	1124.7 [M+H] ⁺	1124.5 [M+H] ⁺	1.21	A
328	538.6 [M+2H] ²⁺	538.3 [M+2H] ²⁺	0.85	A
329	1073.8 [M-H] ⁻	1073.5 [M-H] ⁻	0.85	A
330	1041.7 [M+H] ⁺	1041.5 [M+H] ⁺	1.08	A
331	1041.7 [M+H] ⁺	1041.5 [M+H] ⁺	1.07	A
332	1092.7 [M-H] ⁻	1092.6 [M-H] ⁻	0.86	A
333	1092.9 [M-H] ⁻	1092.6 [M-H] ⁻	0.86	A
334	534.6 [M+2H] ²⁺	534.3 [M+2H] ²⁺	1.03	A
335	1027.7 [M+H] ⁺	1027.5 [M+H] ⁺	1.00	A
336	1092.8 [M+H] ⁺	1092.6 [M+H] ⁺	1.09	A
337	1108.7 [M+H] ⁺	1108.6 [M+H] ⁺	1.05	A
338	1079.8 [M+H] ⁺	1079.6 [M+H] ⁺	1.06	A
339	1079.8 [M+H] ⁺	1079.6 [M+H] ⁺	1.05	A
340	1095.7 [M+H] ⁺	1095.5 [M+H] ⁺	1.01	A
341	1095.7 [M+H] ⁺	1095.5 [M+H] ⁺	1.01	A
342	1053.7 [M+H] ⁺	1053.5 [M+H] ⁺	1.04	A
343	1053.6 [M+H] ⁺	1053.5 [M+H] ⁺	1.04	A
344	1048.9 [M-H] ⁻	1048.6 [M-H] ⁻	0.92	A
345	1053.7 [M+H] ⁺	1053.5 [M+H] ⁺	1.20	A
346	1069.7 [M+H] ⁺	1069.5 [M+H] ⁺	1.14	A
347	1009.8 [M+H] ⁺	1009.5 [M+H] ⁺	1.06	A
348	1023.8 [M+H] ⁺	1023.5 [M+H] ⁺	1.08	A
349	984.6 [M+H] ⁺	984.5 [M+H] ⁺	1.04	A
350	1422.4 [M-H] ⁻	1421.8 [M-H] ⁻	0.60	A
351	470.1 [M+3H] ³⁺	469.9 [M+3H] ³⁺	0.67	A
352	1025.7 [M+H] ⁺	1025.5 [M+H] ⁺	1.02	A

353	1009.7 [M+H] ⁺	1009.5 [M+H] ⁺	1.07	A
354	1053.7 [M+H] ⁺	1053.5 [M+H] ⁺	1.06	A
355	1037.7 [M+H] ⁺	1037.6 [M+H] ⁺	1.13	A
356	1076.8 [M-H] ⁻	1076.6 [M-H] ⁻	0.99	A
357	1064.7 [M+H] ⁺	1064.6 [M+H] ⁺	1.09	A
358	1080.7 [M+H] ⁺	1080.5 [M+H] ⁺	1.04	A
359	1070.6 [M+H] ⁺	1070.5 [M+H] ⁺	1.07	A
360	1086.6 [M+H] ⁺	1086.5 [M+H] ⁺	1.04	A
361	1038.9 [M-H] ⁻	1038.5 [M-H] ⁻	0.80	A
362	1052.7 [M-H] ⁻	1052.5 [M-H] ⁻	0.83	A
363	1079.8 [M-H] ⁻	1079.6 [M-H] ⁻	0.71	A
364	513.1 [M+2H] ²⁺	512.8 [M+2H] ²⁺	0.91	A
365	520.1 [M+2H] ²⁺	519.8 [M+2H] ²⁺	0.98	A
366	1064.0 [M-H] ⁻	1063.6 [M-H] ⁻	0.78	A
367	1107.0 [M-H] ⁻	1106.6 [M-H] ⁻	0.94	A
368	1091.1 [M-H] ⁻	1090.6 [M-H] ⁻	1.00	A
369	1064.9 [M-H] ⁻	1064.5 [M-H] ⁻	0.86	A
370	1049.1 [M-H] ⁻	1048.6 [M-H] ⁻	0.99	A
371	1009.9 [M+H] ⁺	1009.5 [M+H] ⁺	0.66	A
372	1021.8 [M-H] ⁻	1021.5 [M-H] ⁻	0.66	A
373	1035.9 [M-H] ⁻	1035.6 [M-H] ⁻	0.62	A
374	1092.0 [M-H] ⁻	1091.6 [M-H] ⁻	0.73	A
375	1035.9 [M-H] ⁻	1035.5 [M-H] ⁻	0.68	A
376	1049.9 [M-H] ⁻	1049.6 [M-H] ⁻	0.68	A
377	1065.8 [M+H] ⁺	1065.6 [M+H] ⁺	0.67	A
378	1093.8 [M+H] ⁺	1093.6 [M+H] ⁺	0.73	A
379	925.5 [M+H] ⁺	925.5 [M+H] ⁺	1.13	A
380	955.5 [M+H] ⁺	955.5 [M+H] ⁺	1.00	A
381	939.6 [M+H] ⁺	939.5 [M+H] ⁺	1.13	A
382	812.5 [M+H] ⁺	812.4 [M+H] ⁺	0.97	A
383	1032.7 [M+H] ⁺	1032.6 [M+H] ⁺	1.09	A
384	1192.9 [M-H] ⁻	1192.6 [M-H] ⁻	0.86	A
385	1176.9 [M-H] ⁻	1176.6 [M-H] ⁻	0.89	A
386	1221.0 [M-H] ⁻	1220.6 [M-H] ⁻	0.85	A
387	1204.9 [M-H] ⁻	1204.6 [M-H] ⁻	0.93	A
388	1220.9 [M-H] ⁻	1220.6 [M-H] ⁻	0.72	A
389	1205.0 [M-H] ⁻	1204.7 [M-H] ⁻	0.80	A
390	1249.0 [M-H] ⁻	1248.6 [M-H] ⁻	0.74	A
391	1232.9 [M-H] ⁻	1232.7 [M-H] ⁻	0.81	A
392	1036.7 [M+H] ⁺	1036.5 [M+H] ⁺	1.05	A
393	1052.7 [M+H] ⁺	1052.5 [M+H] ⁺	1.01	A
394	1037.7 [M+H] ⁺	1037.5 [M+H] ⁺	1.07	A
395	1053.6 [M+H] ⁺	1053.5 [M+H] ⁺	1.04	A
396	1062.9 [M-H] ⁻	1062.6 [M-H] ⁻	0.93	A
397	1078.9 [M-H] ⁻	1078.5 [M-H] ⁻	0.85	A
398	1009.7 [M+H] ⁺	1009.5 [M+H] ⁺	1.06	A
399	1025.7 [M+H] ⁺	1025.5 [M+H] ⁺	1.02	A
400	1206.8 [M-H] ⁻	1206.6 [M-H] ⁻	0.83	A
401	1191.0 [M-H] ⁻	1190.6 [M-H] ⁻	0.90	A
402	1178.9 [M-H] ⁻	1178.6 [M-H] ⁻	0.82	A
403	1163.0 [M-H] ⁻	1162.6 [M-H] ⁻	0.86	A

404	1179.0 [M-H] ⁻	1178.6 [M-H] ⁻	0.83	A
405	1163.1 [M-H] ⁻	1162.6 [M-H] ⁻	0.86	A
406	1206.9 [M-H] ⁻	1206.6 [M-H] ⁻	0.84	A
407	1191.0 [M-H] ⁻	1190.6 [M-H] ⁻	0.88	A
408	1110.0 [M-H] ⁻	1109.5 [M-H] ⁻	0.79	A
409	1093.9 [M-H] ⁻	1093.6 [M-H] ⁻	0.99	A
410	1081.9 [M-H] ⁻	1081.5 [M-H] ⁻	0.78	A
411	1065.7 [M-H] ⁻	1065.6 [M-H] ⁻	0.98	A
412	1026.7 [M+H] ⁺	1026.5 [M+H] ⁺	0.97	A
413	1010.7 [M+H] ⁺	1010.5 [M+H] ⁺	1.09	A
414	1040.7 [M+H] ⁺	1040.5 [M+H] ⁺	0.99	A
415	1024.8 [M+H] ⁺	1024.5 [M+H] ⁺	1.10	A
416	1054.7 [M+H] ⁺	1054.5 [M+H] ⁺	1.01	A
417	1092.7 [M+H] ⁺	1092.5 [M+H] ⁺	0.81	A
418	1093.9 [M-H] ⁻	1093.6 [M-H] ⁻	0.97	A
419	1109.9 [M-H] ⁻	1109.5 [M-H] ⁻	0.81	A
420	1065.8 [M-H] ⁻	1065.6 [M-H] ⁻	0.95	A
421	1081.8 [M-H] ⁻	1081.5 [M-H] ⁻	0.78	A
422	1039.8 [M-H] ⁻	1039.5 [M-H] ⁻	0.79	A
423	1053.7 [M-H] ⁻	1053.5 [M-H] ⁻	0.78	A
424	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.97	A
425	1067.8 [M-H] ⁻	1067.5 [M-H] ⁻	0.77	A
426	1066.7 [M+H] ⁺	1066.5 [M+H] ⁺	1.07	A
427	1038.8 [M+H] ⁺	1038.6 [M+H] ⁺	1.11	A
428	1049.8 [M-H] ⁻	1049.5 [M-H] ⁻	0.85	A
429	1377.2 [M-H] ⁻	1376.7 [M-H] ⁻	0.75	A
430	1361.0 [M-H] ⁻	1360.7 [M-H] ⁻	0.80	A
431	680.9 [M-2H] ²⁻	680.8 [M-2H] ²⁻	0.72	A
432	1347.1 [M-H] ⁻	1346.7 [M-H] ⁻	0.75	A
433	1376.8 [M-H] ⁻	1376.7 [M-H] ⁻	0.74	A
434	1361.2 [M-H] ⁻	1360.7 [M-H] ⁻	0.80	A
435	1363.0 [M-H] ⁻	1362.7 [M-H] ⁻	0.73	A
436	1347.1 [M-H] ⁻	1346.7 [M-H] ⁻	0.77	A
437	1025.8 [M+H] ⁺	1025.5 [M+H] ⁺	0.96	A
438	1023.8 [M-H] ⁻	1023.5 [M-H] ⁻	0.96	A
439	1038.1 [M-H] ⁻	1037.5 [M-H] ⁻	0.95	A
440	1321.1 [M-H] ⁻	1320.7 [M-H] ⁻	0.72	A
441	1305.1 [M-H] ⁻	1304.7 [M-H] ⁻	0.76	A
442	1307.1 [M-H] ⁻	1306.7 [M-H] ⁻	0.71	A
443	1291.1 [M-H] ⁻	1290.7 [M-H] ⁻	0.73	A
444	1321.1 [M-H] ⁻	1320.7 [M-H] ⁻	0.70	A
445	1305.1 [M-H] ⁻	1304.7 [M-H] ⁻	0.75	A
446	1307.0 [M-H] ⁻	1306.7 [M-H] ⁻	0.70	A
447	1291.2 [M-H] ⁻	1290.7 [M-H] ⁻	0.73	A
448	1037.9 [M-H] ⁻	1037.5 [M-H] ⁻	0.97	A
449	1053.8 [M+H] ⁺	1053.6 [M+H] ⁺	0.97	A
450	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.98	A
451	1065.8 [M-H] ⁻	1065.6 [M-H] ⁻	0.99	A
452	1065.9 [M-H] ⁻	1065.6 [M-H] ⁻	0.97	A
453	1050.8 [M+H] ⁺	1050.6 [M+H] ⁺	1.08	A
454	1020.8 [M-H] ⁻	1020.5 [M-H] ⁻	1.04	A

455	1020.9 [M-H] ⁻	1020.5 [M-H] ⁻	1.08	A
456	1022.9 [M-H] ⁻	1022.5 [M-H] ⁻	1.05	A
457	1179.0 [M-H] ⁻	1178.6 [M-H] ⁻	1.00	A
458	1179.0 [M-H] ⁻	1178.6 [M-H] ⁻	0.98	A
459	1150.9 [M-H] ⁻	1150.6 [M-H] ⁻	0.98	A
460	1151.0 [M-H] ⁻	1150.6 [M-H] ⁻	0.98	A
461	1335.1 [M-H] ⁻	1334.7 [M-H] ⁻	0.85	A
462	669.1 [M+2H] ²⁺	668.9 [M+2H] ²⁺	0.86	A
463	1279.3 [M-H] ⁻	1278.7 [M-H] ⁻	0.82	A
464	1194.9 [M-H] ⁻	1194.6 [M-H] ⁻	0.82	A
465	1195.0 [M-H] ⁻	1194.6 [M-H] ⁻	0.83	A
466	1167.1 [M-H] ⁻	1166.6 [M-H] ⁻	0.80	A
467	1166.9 [M-H] ⁻	1166.6 [M-H] ⁻	0.79	A
468	1351.2 [M-H] ⁻	1350.7 [M-H] ⁻	0.71	A
469	1351.1 [M-H] ⁻	1350.7 [M-H] ⁻	0.70	A
470	1295.1 [M-H] ⁻	1294.7 [M-H] ⁻	0.69	A
471	1295.0 [M-H] ⁻	1294.7 [M-H] ⁻	0.68	A
472	1193.0 [M-H] ⁻	1192.7 [M-H] ⁻	0.99	A
473	1193.0 [M-H] ⁻	1192.7 [M-H] ⁻	0.99	A
474	1165.1 [M-H] ⁻	1164.6 [M-H] ⁻	0.99	A
475	1165.0 [M-H] ⁻	1164.6 [M-H] ⁻	0.99	A
476	1349.2 [M-H] ⁻	1348.8 [M-H] ⁻	0.87	A
477	1349.5 [M-H] ⁻	1348.8 [M-H] ⁻	0.86	A
478	1293.1 [M-H] ⁻	1292.7 [M-H] ⁻	0.84	A
479	648.0 [M+2H] ²⁺	647.9 [M+2H] ²⁺	0.83	A
480	1052.9 [M+H] ⁺	1052.6 [M+H] ⁺	1.13	A
481	1052.9 [M-H] ⁻	1052.5 [M-H] ⁻	1.01	A
482	1037.0 [M-H] ⁻	1036.6 [M-H] ⁻	1.07	A
483	1205.2 [M-H] ⁻	1204.7 [M-H] ⁻	0.94	A
484	1177.2 [M-H] ⁻	1176.6 [M-H] ⁻	0.91	A
485	1022.9 [M-H] ⁻	1022.5 [M-H] ⁻	1.08	A
486	1037.0 [M-H] ⁻	1036.6 [M-H] ⁻	1.15	A
487	1164.9 [M-H] ⁻	1164.7 [M-H] ⁻	0.91	A
488	1193.0 [M-H] ⁻	1192.7 [M-H] ⁻	0.96	A
489	1178.9 [M-H] ⁻	1178.6 [M-H] ⁻	0.97	A
490	1165.1 [M-H] ⁻	1164.6 [M-H] ⁻	1.01	A
491	1193.1 [M-H] ⁻	1192.7 [M-H] ⁻	1.01	A
492	980.9 [M-H] ⁻	980.5 [M-H] ⁻	1.00	A
493	1080.1 [M-H] ⁻	1079.6 [M-H] ⁻	0.99	A
494	1008.9 [M-H] ⁻	1008.6 [M-H] ⁻	0.98	A
495	1023.0 [M-H] ⁻	1022.6 [M-H] ⁻	0.99	A
496	1063.9 [M-H] ⁻	1063.6 [M-H] ⁻	0.92	A
497	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.98	A
498	1006.9 [M-H] ⁻	1006.5 [M-H] ⁻	0.94	A
499	994.8 [M-H] ⁻	994.5 [M-H] ⁻	0.99	A
500	1105.7 [M-H] ⁻	1105.6 [M-H] ⁻	0.96	A
501	1093.8 [M-H] ⁻	1093.6 [M-H] ⁻	1.00	A
502	1021.9 [M-H] ⁻	1021.6 [M-H] ⁻	0.77	A
503	1009.9 [M-H] ⁻	1009.6 [M-H] ⁻	0.81	A
504	992.9 [M-H] ⁻	992.5 [M-H] ⁻	0.91	A
505	980.8 [M-H] ⁻	980.5 [M-H] ⁻	0.98	A

506	1050.0 [M-H] ⁻	1049.5 [M-H] ⁻	0.86	A
507	1037.9 [M-H] ⁻	1037.5 [M-H] ⁻	0.87	A
508	993.9 [M-H] ⁻	994.5 [M-H] ⁻	1.04	A
509	1191.0 [M-H] ⁻	1190.6 [M-H] ⁻	0.88	A
510	1163.0 [M-H] ⁻	1162.6 [M-H] ⁻	0.87	A
511	994.8 [M-H] ⁻	994.5 [M-H] ⁻	1.04	A
512	1008.8 [M-H] ⁻	1008.5 [M-H] ⁻	1.05	A
513	1052.0 [M-H] ⁻	1051.6 [M-H] ⁻	0.92	A
514	1179.0 [M-H] ⁻	1178.6 [M-H] ⁻	0.94	A
515	1150.9 [M-H] ⁻	1150.6 [M-H] ⁻	0.92	A
516	1007.7 [M-H] ⁻	1007.5 [M-H] ⁻	0.76	A
517	995.7 [M-H] ⁻	995.5 [M-H] ⁻	0.77	A
518	1221.9 [M-H] ⁻	1221.7 [M-H] ⁻	0.84	A
519	1193.9 [M-H] ⁻	1193.7 [M-H] ⁻	0.83	A
520	1109.0 [M-H] ⁻	1108.6 [M-H] ⁻	0.93	A
521	1123.0 [M-H] ⁻	1122.6 [M-H] ⁻	0.93	A
522	937.8 [M-H] ⁻	937.5 [M-H] ⁻	1.00	A
523	937.8 [M-H] ⁻	937.5 [M-H] ⁻	1.01	A
524	1067.1 [M-H] ⁻	1066.6 [M-H] ⁻	0.72	A
525	1067.0 [M-H] ⁻	1066.6 [M-H] ⁻	0.72	A
526	1080.8 [M-H] ⁻	1080.6 [M-H] ⁻	0.77	A
527	1080.5 [M-H] ⁻	1080.6 [M-H] ⁻	0.77	A
528	1108.9 [M-H] ⁻	1108.6 [M-H] ⁻	0.68	A
529	1009.9 [M-H] ⁻	1009.5 [M-H] ⁻	0.88	A
530	1009.9 [M-H] ⁻	1009.5 [M-H] ⁻	0.89	A
531	1023.8 [M-H] ⁻	1023.5 [M-H] ⁻	0.88	A
532	1023.9 [M-H] ⁻	1023.5 [M-H] ⁻	0.88	A
533	1037.9 [M-H] ⁻	1037.5 [M-H] ⁻	0.89	A
534	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.89	A
535	514.3 [M+2H] ²⁺	513.8 [M+2H] ²⁺	0.73	A
536	514.2 [M+2H] ²⁺	513.8 [M+2H] ²⁺	0.69	A
537	521.2 [M+2H] ²⁺	520.8 [M+2H] ²⁺	0.69	A
538	1053.0 [M-H] ⁻	1052.6 [M-H] ⁻	0.72	A
539	1052.9 [M-H] ⁻	1052.6 [M-H] ⁻	0.70	A
540	1095.0 [M-H] ⁻	1094.6 [M-H] ⁻	0.88	A
541	1108.9 [M-H] ⁻	1108.6 [M-H] ⁻	0.88	A
542	1038.0 [M-H] ⁻	1037.5 [M-H] ⁻	0.87	A
543	1094.0 [M-H] ⁻	1093.6 [M-H] ⁻	0.82	A
544	1094.0 [M-H] ⁻	1093.6 [M-H] ⁻	0.82	A
545	1080.0 [M-H] ⁻	1079.6 [M-H] ⁻	0.76	A
546	1079.8 [M-H] ⁻	1079.6 [M-H] ⁻	0.78	A
547	1038.8 [M-H] ⁻	1038.6 [M-H] ⁻	0.99	A
548	1038.9 [M-H] ⁻	1038.6 [M-H] ⁻	1.00	A
549	1024.9 [M-H] ⁻	1024.6 [M-H] ⁻	0.93	A
550	1024.9 [M-H] ⁻	1024.6 [M-H] ⁻	0.98	A
551	1109.0 [M-H] ⁻	1108.6 [M-H] ⁻	0.71	A
552	1095.0 [M-H] ⁻	1094.6 [M-H] ⁻	0.64	A
553	1095.0 [M-H] ⁻	1094.6 [M-H] ⁻	0.66	A
554	1053.7 [M-H] ⁻	1053.6 [M-H] ⁻	0.80	A
555	1053.8 [M-H] ⁻	1053.6 [M-H] ⁻	0.80	A
556	1039.8 [M-H] ⁻	1039.6 [M-H] ⁻	0.74	A

557	1039.8 [M-H] ⁻	1039.6 [M-H] ⁻	0.74	A
558	1094.9 [M-H] ⁻	1094.6 [M-H] ⁻	0.99	A
559	1109.9 [M-H] ⁻	1109.6 [M-H] ⁻	0.78	A
560	1095.8 [M-H] ⁻	1095.6 [M-H] ⁻	0.72	A
561	1039.0 [M-H] ⁻	1038.5 [M-H] ⁻	0.77	A
562	1038.8 [M-H] ⁻	1038.5 [M-H] ⁻	0.76	A
563	1053.0 [M-H] ⁻	1052.6 [M-H] ⁻	0.76	A
564	1052.9 [M-H] ⁻	1052.6 [M-H] ⁻	0.75	A
565	1066.9 [M-H] ⁻	1066.6 [M-H] ⁻	0.75	A
566	1067.0 [M-H] ⁻	1066.6 [M-H] ⁻	0.75	A
567	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.99	A
568	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.99	A
569	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.99	A
570	1051.9 [M-H] ⁻	1051.6 [M-H] ⁻	0.99	A
571	1081.9 [M-H] ⁻	1081.5 [M-H] ⁻	0.82	A
572	1081.9 [M-H] ⁻	1081.5 [M-H] ⁻	0.80	A
573	1023.9 [M-H] ⁻	1023.5 [M-H] ⁻	0.82	A
574	1023.9 [M-H] ⁻	1023.5 [M-H] ⁻	0.82	A
575	1065.9 [M-H] ⁻	1065.6 [M-H] ⁻	1.02	A
576	1065.8 [M-H] ⁻	1065.6 [M-H] ⁻	0.99	A
577	1066.9 [M-H] ⁻	1066.6 [M-H] ⁻	1.05	A
578	1021.8 [M-H] ⁻	1021.5 [M-H] ⁻	1.10	A
579	1031.9 [M-H] ⁻	1031.5 [M-H] ⁻	1.30	A
580	1019.8 [M-H] ⁻	1019.6 [M-H] ⁻	1.14	A
581	1031.8 [M-H] ⁻	1031.6 [M-H] ⁻	1.12	A
582	1047.8 [M-H] ⁻	1047.6 [M-H] ⁻	1.17	A
583	1059.8 [M-H] ⁻	1059.6 [M-H] ⁻	1.14	A
584	990.8 [M-H] ⁻	990.5 [M-H] ⁻	1.32	A
585	992.7 [M-H] ⁻	992.5 [M-H] ⁻	1.38	A
586	1004.7 [M-H] ⁻	1004.5 [M-H] ⁻	1.35	A
587	1002.7 [M-H] ⁻	1002.4 [M-H] ⁻	1.81	A
588	1016.7 [M-H] ⁻	1016.4 [M-H] ⁻	1.83	A
589	970.7 [M-H] ⁻	970.4 [M-H] ⁻	1.79	A
590	939.5 [M-H] ⁻	939.4 [M-H] ⁻	1.08	A
591	941.6 [M+H] ⁺	941.4 [M+H] ⁺	0.89	A
592	939.4 [M-H] ⁻	939.4 [M-H] ⁻	1.49	A
593	801.3 [M+H] ⁺	801.2 [M+H] ⁺	1.89	B
594	774.5 [M-H] ⁻	774.4 [M-H] ⁻	1.53	A
595	835.3 [M+H] ⁺	835.4 [M+H] ⁺	1.04	A
596	989.6 [M+H] ⁺	989.5 [M+H] ⁺	1.34	A
597	974.5 [M-H] ⁻	974.4 [M-H] ⁻	1.65	A
598	974.5 [M-H] ⁻	974.4 [M-H] ⁻	1.63	A
599	958.6 [M+H] ⁺	958.4 [M+H] ⁺	1.64	A
600	991.7 [M+H] ⁺	991.5 [M+H] ⁺	1.22	A
601	1007.7 [M+H] ⁺	1007.5 [M+H] ⁺	1.15	A
602	844.6 [M-H] ⁻	844.3 [M-H] ⁻	0.98	A
603	858.5 [M-H] ⁻	858.4 [M-H] ⁻	0.97	A
604	828.4 [M-H] ⁻	828.4 [M-H] ⁻	1.06	A
605	842.5 [M-H] ⁻	842.5 [M-H] ⁻	1.04	A
606	872.7 [M-H] ⁻	872.4 [M-H] ⁻	1.07	A
607	872.5 [M-H] ⁻	872.4 [M-H] ⁻	0.87	A

608	881.6 [M+H] ⁺	881.4 [M+H] ⁺	1.38	A
609	928.6 [M+H] ⁺	928.4 [M+H] ⁺	1.07	A
610	826.4 [M+H] ⁺	826.3 [M+H] ⁺	1.39	A
611	830.8 [M-H] ⁻	830.3 [M-H] ⁻	1.37	A
612	846.5 [M+H] ⁺	846.4 [M+H] ⁺	1.34	A
613	816.5 [M+H] ⁺	816.4 [M+H] ⁺	1.45	A
614	830.5 [M+H] ⁺	830.4 [M+H] ⁺	1.42	A
615	870.4 [M+H] ⁺	870.4 [M+H] ⁺	1.63	A
616	884.4 [M+H] ⁺	884.4 [M+H] ⁺	1.61	A
617	846.4 [M+H] ⁺	846.4 [M+H] ⁺	1.48	A
618	860.4 [M+H] ⁺	860.4 [M+H] ⁺	1.45	A
619	858.5 [M+H] ⁺	858.4 [M+H] ⁺	1.51	A
620	826.5 [M-H] ⁻	826.4 [M-H] ⁻	1.35	A
621	810.5 [M-H] ⁻	810.4 [M-H] ⁻	1.44	A
622	856.5 [M-H] ⁻	856.4 [M-H] ⁻	1.36	A
623	840.6 [M-H] ⁻	840.4 [M-H] ⁻	1.43	A
624	844.5 [M-H] ⁻	844.3 [M-H] ⁻	1.40	A
625	828.5 [M-H] ⁻	828.4 [M-H] ⁻	1.47	A
626	860.5 [M-H] ⁻	860.3 [M-H] ⁻	1.49	A
627	844.6 [M-H] ⁻	844.3 [M-H] ⁻	1.55	A
628	868.6 [M-H] ⁻	868.4 [M-H] ⁻	1.28	A
629	852.6 [M-H] ⁻	852.4 [M-H] ⁻	1.36	A
630	870.5 [M-H] ⁻	870.4 [M-H] ⁻	1.33	A
631	854.6 [M-H] ⁻	854.4 [M-H] ⁻	1.40	A
632	858.5 [M-H] ⁻	858.4 [M-H] ⁻	1.29	A
633	759.3 [M-H] ⁻	759.3 [M-H] ⁻	1.28	A
634	811.6 [M-H] ⁻	811.4 [M-H] ⁻	1.67	A
635	812.6 [M-H] ⁻	812.4 [M-H] ⁻	1.38	A
636	826.5 [M-H] ⁻	826.4 [M-H] ⁻	1.50	A
637	832.6 [M+H] ⁺	832.3 [M+H] ⁺	1.14	A
638	862.5 [M+H] ⁺	862.4 [M+H] ⁺	1.16	A
639	846.6 [M+H] ⁺	846.4 [M+H] ⁺	1.12	A
640	876.6 [M+H] ⁺	876.4 [M+H] ⁺	1.15	A
641	816.5 [M+H] ⁺	816.4 [M+H] ⁺	1.22	A
642	830.5 [M+H] ⁺	830.4 [M+H] ⁺	1.20	A
643	889.6 [M-H] ⁻	889.4 [M-H] ⁻	1.10	A
644	845.5 [M+H] ⁺	845.3 [M+H] ⁺	1.22	A
645	827.6 [M-H] ⁻	827.4 [M-H] ⁻	1.32	A
646	859.5 [M+H] ⁺	859.4 [M+H] ⁺	1.21	A
647	843.5 [M+H] ⁺	843.4 [M+H] ⁺	1.29	A
648	845.5 [M+H] ⁺	845.3 [M+H] ⁺	1.71	B
649	843.5 [M+H] ⁺	843.4 [M+H] ⁺	1.79	B
650	859.5 [M+H] ⁺	859.4 [M+H] ⁺	1.70	B
651	843.5 [M+H] ⁺	843.4 [M+H] ⁺	1.80	B
652	873.6 [M+H] ⁺	873.4 [M+H] ⁺	1.71	B
653	857.6 [M+H] ⁺	857.4 [M+H] ⁺	1.79	B
654	863.5 [M+H] ⁺	863.3 [M+H] ⁺	1.27	A
655	847.6 [M+H] ⁺	847.4 [M+H] ⁺	1.35	A
656	877.6 [M+H] ⁺	877.3 [M+H] ⁺	1.25	A
657	861.6 [M+H] ⁺	861.4 [M+H] ⁺	1.33	A
658	859.5 [M+H] ⁺	859.4 [M+H] ⁺	1.32	A

659	843.6 [M+H] ⁺	843.4 [M+H] ⁺	1.44	A
660	873.6 [M+H] ⁺	873.4 [M+H] ⁺	1.30	A
661	857.6 [M+H] ⁺	857.4 [M+H] ⁺	1.39	A
662	913.5 [M+H] ⁺	913.3 [M+H] ⁺	1.48	A
663	897.5 [M+H] ⁺	897.4 [M+H] ⁺	1.54	A
664	927.6 [M+H] ⁺	927.3 [M+H] ⁺	1.45	A
665	911.6 [M+H] ⁺	911.4 [M+H] ⁺	1.51	A
666	921.5 [M-H] ⁻	921.4 [M-H] ⁻	1.42	A
667	937.3 [M+H] ⁺	937.3 [M+H] ⁺	1.36	A
668	870.5 [M+H] ⁺	870.3 [M+H] ⁺	1.23	A
669	884.6 [M+H] ⁺	884.4 [M+H] ⁺	1.21	A
670	1071.7 [M+H] ⁺	1071.5 [M+H] ⁺	1.28	A
671	907.3 [M+H] ⁺	907.3 [M+H] ⁺	1.48	A
672	852.5 [M-H] ⁻	852.4 [M-H] ⁻	1.32	A
673	921.3 [M+H] ⁺	921.3 [M+H] ⁺	1.44	A
674	886.5 [M+H] ⁺	886.4 [M+H] ⁺	1.13	A
675	900.6 [M+H] ⁺	900.4 [M+H] ⁺	1.18	A
676	900.6 [M+H] ⁺	900.4 [M+H] ⁺	1.12	A
677	912.6 [M-H] ⁻	912.4 [M-H] ⁻	1.17	A
678	902.5 [M+H] ⁺	902.4 [M+H] ⁺	1.06	A
679	916.5 [M+H] ⁺	916.4 [M+H] ⁺	1.11	A
680	914.6 [M-H] ⁻	914.4 [M-H] ⁻	1.05	A
681	930.5 [M+H] ⁺	930.4 [M+H] ⁺	1.10	A
682	848.4 [M+H] ⁺	848.4 [M+H] ⁺	1.44	A
683	834.4 [M+H] ⁺	834.4 [M+H] ⁺	1.39	A
684	871.6 [M-H] ⁻	871.4 [M-H] ⁻	1.10	A
685	889.6 [M-H] ⁻	889.4 [M-H] ⁻	1.15	A
686	885.6 [M-H] ⁻	885.4 [M-H] ⁻	1.19	A
687	955.6 [M-H] ⁻	955.4 [M-H] ⁻	1.36	A
688	939.7 [M-H] ⁻	939.4 [M-H] ⁻	1.34	A
689	987.6 [M-H] ⁻	987.4 [M-H] ⁻	1.38	A
690	898.4 [M+H] ⁺	898.4 [M+H] ⁺	1.10	A
691	875.4 [M+H] ⁺	875.4 [M+H] ⁺	1.26	A
692	859.5 [M+H] ⁺	859.4 [M+H] ⁺	1.35	A
693	889.4 [M+H] ⁺	889.4 [M+H] ⁺	1.24	A
694	873.4 [M+H] ⁺	873.4 [M+H] ⁺	1.33	A
695	887.6 [M+H] ⁺	887.4 [M+H] ⁺	1.31	A
696	915.6 [M+H] ⁺	915.5 [M+H] ⁺	1.51	A
697	903.5 [M+H] ⁺	903.4 [M+H] ⁺	1.23	A
698	901.6 [M+H] ⁺	901.4 [M+H] ⁺	1.37	A
699	915.6 [M+H] ⁺	915.5 [M+H] ⁺	1.46	A
700	913.6 [M+H] ⁺	913.4 [M+H] ⁺	1.43	A
701	941.5 [M+H] ⁺	941.4 [M+H] ⁺	1.51	A
702	917.6 [M+H] ⁺	917.4 [M+H] ⁺	1.31	A
703	929.6 [M+H] ⁺	929.4 [M+H] ⁺	1.36	A
704	957.5 [M+H] ⁺	957.4 [M+H] ⁺	1.45	A
705	879.5 [M+H] ⁺	879.3 [M+H] ⁺	1.39	A
706	863.5 [M+H] ⁺	863.3 [M+H] ⁺	1.47	A
707	893.5 [M+H] ⁺	893.3 [M+H] ⁺	1.37	A
708	877.5 [M+H] ⁺	877.4 [M+H] ⁺	1.45	A
709	768.4 [M+H] ⁺	768.2 [M+H] ⁺	1.37	A

710	752.4 [M+H] ⁺	752.3 [M+H] ⁺	1.53	A
711	782.4 [M+H] ⁺	782.3 [M+H] ⁺	1.35	A
712	766.4 [M+H] ⁺	766.3 [M+H] ⁺	1.52	A
713	751.2 [M-H] ⁻	751.2 [M-H] ⁻	1.64	A
714	864.5 [M+H] ⁺	864.3 [M+H] ⁺	1.65	A
715	846.3 [M-H] ⁻	846.3 [M-H] ⁻	1.75	A
716	893.5 [M+H] ⁺	893.3 [M+H] ⁺	1.34	A
717	877.5 [M+H] ⁺	877.4 [M+H] ⁺	1.43	A
718	891.5 [M+H] ⁺	891.4 [M+H] ⁺	1.43	A
719	907.5 [M+H] ⁺	907.3 [M+H] ⁺	1.34	A
720	1003.8 [M-H] ⁻	1003.5 [M-H] ⁻	1.15	A
721	1031.7 [M-H] ⁻	1031.5 [M-H] ⁻	1.17	A
722	918.7 [M-H] ⁻	918.4 [M-H] ⁻	1.16	A
723	1017.8 [M-H] ⁻	1017.5 [M-H] ⁻	1.15	A
724	1045.8 [M-H] ⁻	1045.5 [M-H] ⁻	1.17	A
725	932.7 [M-H] ⁻	932.4 [M-H] ⁻	1.15	A
726	891.6 [M+H] ⁺	891.4 [M+H] ⁺	1.40	A
727	851.5 [M+H] ⁺	851.3 [M+H] ⁺	1.46	A
728	881.5 [M+H] ⁺	881.4 [M+H] ⁺	1.47	A
729	927.5 [M+H] ⁺	927.4 [M+H] ⁺	1.58	A
730	906.6 [M-H] ⁻	906.4 [M-H] ⁻	1.21	A
731	851.5 [M+H] ⁺	851.3 [M+H] ⁺	1.45	A
732	865.5 [M+H] ⁺	865.4 [M+H] ⁺	1.47	A
733	879.5 [M+H] ⁺	879.4 [M+H] ⁺	1.47	A
734	893.6 [M+H] ⁺	893.4 [M+H] ⁺	1.48	A
735	1104.7 [M+H] ⁺	1104.5 [M+H] ⁺	1.61	A
736	1132.8 [M+H] ⁺	1132.5 [M+H] ⁺	1.68	A
737	1159.0 [M-H] ⁻	1158.6 [M-H] ⁻	1.77	A
738	864.5 [M-H] ⁻	864.4 [M-H] ⁻	1.27	A
739	864.5 [M-H] ⁻	864.4 [M-H] ⁻	1.23	A
740	878.7 [M-H] ⁻	878.4 [M-H] ⁻	1.22	A
741	878.6 [M-H] ⁻	878.4 [M-H] ⁻	1.21	A
742	892.6 [M-H] ⁻	892.4 [M-H] ⁻	1.20	A
743	906.6 [M-H] ⁻	906.4 [M-H] ⁻	1.20	A
744	906.6 [M-H] ⁻	906.4 [M-H] ⁻	1.18	A
745	922.6 [M-H] ⁻	922.4 [M-H] ⁻	1.10	A
746	849.6 [M-H] ⁻	849.4 [M-H] ⁻	1.23	A
747	892.6 [M-H] ⁻	892.4 [M-H] ⁻	1.20	A
748	906.6 [M-H] ⁻	906.4 [M-H] ⁻	1.22	A
749	920.7 [M-H] ⁻	920.4 [M-H] ⁻	1.20	A
750	934.9 [M-H] ⁻	934.4 [M-H] ⁻	1.23	A
751	906.6 [M-H] ⁻	906.4 [M-H] ⁻	1.22	A
752	920.6 [M-H] ⁻	920.4 [M-H] ⁻	1.22	A
753	934.7 [M-H] ⁻	934.4 [M-H] ⁻	1.22	A
754	948.6 [M-H] ⁻	948.4 [M-H] ⁻	1.24	A
755	920.6 [M-H] ⁻	920.4 [M-H] ⁻	1.21	A
756	934.7 [M-H] ⁻	934.4 [M-H] ⁻	1.23	A
757	948.7 [M-H] ⁻	948.6 [M-H] ⁻	1.23	A
758	962.7 [M-H] ⁻	962.7 [M-H] ⁻	1.24	A
759	899.6 [M+H] ⁺	899.4 [M+H] ⁺	1.55	A
760	960.7 [M-H] ⁻	960.6 [M-H] ⁻	1.22	A

761	949.5 [M+H] ⁺	949.4 [M+H] ⁺	1.53	A
762	990.8 [M-H] ⁻	990.5 [M-H] ⁻	1.23	A
763	975.6 [M+H] ⁺	975.4 [M+H] ⁺	1.54	A
764	972.7 [M-H] ⁻	972.6 [M-H] ⁻	1.23	A
765	853.5 [M+H] ⁺	853.3 [M+H] ⁺	1.26	A
766	991.7 [M-H] ⁻	991.8 [M-H] ⁻	1.22	A
767	1019.8 [M-H] ⁻	1019.6 [M-H] ⁻	1.23	A
768	1147.9 [M-H] ⁻	1147.9 [M-H] ⁻	1.09	A
769	1175.9 [M-H] ⁻	1175.7 [M-H] ⁻	1.11	A
770	1147.9 [M-H] ⁻	1147.9 [M-H] ⁻	1.08	A
771	1119.7 [M-H] ⁻	1119.7 [M-H] ⁻	1.09	A
772	1003.7 [M-H] ⁻	1003.5 [M-H] ⁻	1.22	A
773	1164.0 [M-H] ⁻	1163.7 [M-H] ⁻	1.00	A
774	595.5 [M-2H] ²⁻	595.3 [M-2H] ²⁻	1.01	A
775	1163.9 [M-H] ⁻	1163.7 [M-H] ⁻	1.00	A
776	1136.0 [M-H] ⁻	1135.6 [M-H] ⁻	0.98	A
777	864.5 [M-H] ⁻	864.6 [M-H] ⁻	1.25	A
778	878.5 [M-H] ⁻	878.6 [M-H] ⁻	1.23	A
779	878.5 [M-H] ⁻	878.6 [M-H] ⁻	1.23	A
780	892.7 [M-H] ⁻	892.5 [M-H] ⁻	1.23	A
781	892.5 [M-H] ⁻	892.5 [M-H] ⁻	1.23	A
782	977.8 [M-H] ⁻	977.4 [M-H] ⁻	1.19	A
783	991.8 [M-H] ⁻	991.4 [M-H] ⁻	1.27	A
784	1007.8 [M-H] ⁻	1007.4 [M-H] ⁻	1.11	A
785	992.8 [M-H] ⁻	992.4 [M-H] ⁻	1.28	A
786	905.5 [M+H] ⁺	905.3 [M+H] ⁺	1.30	A
787	893.5 [M+H] ⁺	893.3 [M+H] ⁺	1.26	A
788	921.5 [M+H] ⁺	921.4 [M+H] ⁺	1.32	A
789	905.5 [M+H] ⁺	905.3 [M+H] ⁺	1.31	A
790	891.4 [M+H] ⁺	891.3 [M+H] ⁺	1.31	A
791	864.4 [M+H] ⁺	864.4 [M+H] ⁺	1.51	A
792	888.6 [M+H] ⁺	888.5 [M+H] ⁺	1.03	A
793	902.6 [M+H] ⁺	902.4 [M+H] ⁺	1.02	A
794	870.5 [M-H] ⁻	870.6 [M-H] ⁻	1.10	A
795	886.5 [M+H] ⁺	886.6 [M+H] ⁺	1.08	A
796	888.6 [M+H] ⁺	888.4 [M+H] ⁺	1.13	A
797	902.7 [M+H] ⁺	902.7 [M+H] ⁺	1.15	A
798	904.6 [M+H] ⁺	904.7 [M+H] ⁺	1.00	A
799	918.6 [M+H] ⁺	918.5 [M+H] ⁺	1.02	A
800	903.7 [M-H] ⁻	903.5 [M-H] ⁻	0.77	A
801	884.6 [M-H] ⁻	884.6 [M-H] ⁻	1.05	A
802	927.5 [M-H] ⁻	927.5 [M-H] ⁻	1.02	A
803	1000.8 [M-H] ⁻	1000.5 [M-H] ⁻	1.00	A
804	1028.7 [M-H] ⁻	1028.8 [M-H] ⁻	1.00	A
805	1156.9 [M-H] ⁻	1156.8 [M-H] ⁻	0.89	A
806	1184.9 [M-H] ⁻	1184.6 [M-H] ⁻	0.91	A
807	1129.0 [M-H] ⁻	1128.7 [M-H] ⁻	0.87	A
808	1043.0 [M-H] ⁻	1042.5 [M-H] ⁻	1.00	A
809	1171.0 [M-H] ⁻	1170.7 [M-H] ⁻	0.85	A
810	1171.0 [M-H] ⁻	1170.7 [M-H] ⁻	0.84	A
811	1142.8 [M-H] ⁻	1142.6 [M-H] ⁻	0.83	A

812	1014.8 [M-H] ⁻	1014.7 [M-H] ⁻	0.99	A
813	1199.0 [M-H] ⁻	1198.6 [M-H] ⁻	0.86	A
814	873.5 [M-H] ⁻	873.4 [M-H] ⁻	1.01	A
815	901.6 [M-H] ⁻	901.4 [M-H] ⁻	1.00	A
816	901.7 [M-H] ⁻	901.4 [M-H] ⁻	0.99	A
817	915.8 [M-H] ⁻	915.7 [M-H] ⁻	0.99	A
818	915.6 [M-H] ⁻	915.7 [M-H] ⁻	0.99	A
819	900.6 [M+H] ⁺	900.4 [M+H] ⁺	1.08	A
820	1026.8 [M-H] ⁻	1026.7 [M-H] ⁻	0.90	A
821	1054.7 [M-H] ⁻	1054.5 [M-H] ⁻	0.92	A
822	1183.0 [M-H] ⁻	1182.7 [M-H] ⁻	0.75	A
823	1211.0 [M-H] ⁻	1210.6 [M-H] ⁻	0.76	A
824	1183.1 [M-H] ⁻	1182.7 [M-H] ⁻	0.75	A
825	1155.0 [M-H] ⁻	1154.6 [M-H] ⁻	0.73	A
826	874.6 [M+H] ⁺	874.6 [M+H] ⁺	1.07	A
827	886.6 [M+H] ⁺	886.6 [M+H] ⁺	1.04	A
828	1072.0 [M-H] ⁻	1071.8 [M-H] ⁻	0.99	A
829	1099.9 [M-H] ⁻	1099.5 [M-H] ⁻	1.00	A
830	1256.0 [M-H] ⁻	1255.6 [M-H] ⁻	0.86	A
831	1228.1 [M-H] ⁻	1227.6 [M-H] ⁻	0.82	A
832	1085.8 [M-H] ⁻	1085.6 [M-H] ⁻	0.99	A
833	1242.1 [M-H] ⁻	1241.7 [M-H] ⁻	0.83	A
834	1270.1 [M-H] ⁻	1269.8 [M-H] ⁻	0.85	A
835	1242.1 [M-H] ⁻	1241.7 [M-H] ⁻	0.83	A
836	1228.0 [M-H] ⁻	1227.9 [M-H] ⁻	0.86	A
837	1199.8 [M-H] ⁻	1199.6 [M-H] ⁻	0.85	A
838	884.5 [M-H] ⁻	884.6 [M-H] ⁻	1.09	A
839	872.5 [M+H] ⁺	872.6 [M+H] ⁺	1.06	A
840	844.5 [M-H] ⁻	844.5 [M-H] ⁻	1.13	A
841	858.5 [M-H] ⁻	858.6 [M-H] ⁻	1.13	A
842	872.8 [M-H] ⁻	872.6 [M-H] ⁻	1.14	A
843	886.7 [M-H] ⁻	886.4 [M-H] ⁻	1.16	A
844	859.6 [M-H] ⁻	859.6 [M-H] ⁻	1.00	A
845	870.5 [M-H] ⁻	870.6 [M-H] ⁻	1.06	A
846	872.5 [M+H] ⁺	872.6 [M+H] ⁺	1.09	A
847	872.5 [M+H] ⁺	872.6 [M+H] ⁺	1.06	A
848	900.5 [M+H] ⁺	900.4 [M+H] ⁺	1.17	A
849	900.6 [M+H] ⁺	900.4 [M+H] ⁺	1.20	A
850	914.6 [M+H] ⁺	914.7 [M+H] ⁺	1.10	A
851	886.5 [M+H] ⁺	886.4 [M+H] ⁺	1.12	A
852	886.7 [M-H] ⁻	886.4 [M-H] ⁻	1.11	A
853	886.7 [M-H] ⁻	886.4 [M-H] ⁻	1.13	A
854	887.7 [M-H] ⁻	887.4 [M-H] ⁻	1.18	A
855	891.6 [M+H] ⁺	891.4 [M+H] ⁺	1.45	A
856	887.6 [M-H] ⁻	887.4 [M-H] ⁻	1.44	A
857	901.4 [M+H] ⁺	901.4 [M+H] ⁺	1.24	A
858	915.5 [M-H] ⁻	915.4 [M-H] ⁻	1.02	A
859	816.3 [M-H] ⁻	816.3 [M-H] ⁻	0.96	A
860	771.3 [M-H] ⁻	771.3 [M-H] ⁻	0.90	A
861	743.2 [M-H] ⁻	743.3 [M-H] ⁻	0.82	A
862	757.2 [M-H] ⁻	757.3 [M-H] ⁻	0.86	A

863	785.4 [M-H] ⁻	785.3 [M-H] ⁻	0.94	A
864	800.4 [M-H] ⁻	800.3 [M-H] ⁻	0.64	A
865	803.3 [M+H] ⁺	803.3 [M+H] ⁺	0.93	A
866	817.4 [M+H] ⁺	817.3 [M+H] ⁺	0.91	A
867	817.4 [M+H] ⁺	817.3 [M+H] ⁺	0.86	A
868	775.3 [M+H] ⁺	775.3 [M+H] ⁺	0.84	A
869	851.4 [M+H] ⁺	851.3 [M+H] ⁺	1.01	A
870	835.3 [M+H] ⁺	835.3 [M+H] ⁺	1.22	A
871	759.3 [M+H] ⁺	759.3 [M+H] ⁺	0.96	A
872	799.4 [M-H] ⁻	799.4 [M-H] ⁻	1.08	A
873	787.4 [M+H] ⁺	787.3 [M+H] ⁺	1.03	A
874	801.4 [M+H] ⁺	801.4 [M+H] ⁺	1.12	A
875	803.3 [M+H] ⁺	803.3 [M+H] ⁺	0.89	A
876	816.4 [M+H] ⁺	816.4 [M+H] ⁺	0.68	A
877	729.3 [M-H] ⁻	729.3 [M-H] ⁻	0.85	A
878	828.3 [M-H] ⁻	828.3 [M-H] ⁻	0.64	A
879	769.5 [M-H] ⁻	769.3 [M-H] ⁻	1.01	A
880	759.5 [M-H] ⁻	759.3 [M-H] ⁻	0.81	A
881	835.3 [M-H] ⁻	835.3 [M-H] ⁻	1.00	A
882	819.3 [M-H] ⁻	819.3 [M-H] ⁻	1.20	A
883	743.3 [M-H] ⁻	743.3 [M-H] ⁻	0.94	A
884	773.3 [M-H] ⁻	773.3 [M-H] ⁻	0.89	A
885	844.4 [M+H] ⁺	844.4 [M+H] ⁺	0.72	A
886	803.3 [M+H] ⁺	803.3 [M+H] ⁺	0.78	A
887	867.4 [M+H] ⁺	867.3 [M+H] ⁺	0.77	A
888	914.7 [M-H] ⁻	914.4 [M-H] ⁻	0.92	A
889	900.6 [M-H] ⁻	900.4 [M-H] ⁻	0.83	A
890	1015.5 [M+H] ⁺	1015.4 [M+H] ⁺	0.96	A
891	1054.7 [M-H] ⁻	1054.5 [M-H] ⁻	1.67	A
892	1053.7 [M-H] ⁻	1053.5 [M-H] ⁻	1.62	A
893	1105.8 [M+Na] ⁺	1105.5 [M+Na] ⁺	1.60	A
894	1098.6 [M+H] ⁺	1098.5 [M+H] ⁺	1.26	A
895	1100.6 [M+H] ⁺	1100.5 [M+H] ⁺	1.19	A
896	987.6 [M+H] ⁺	987.5 [M+H] ⁺	1.29	A
897	1073.6 [M+Na] ⁺	1073.5 [M+Na] ⁺	1.59	A
898	1080.8 [M+H] ⁺	1080.5 [M+H] ⁺	1.23	A
899	1082.7 [M+H] ⁺	1082.5 [M+H] ⁺	1.17	A
900	1546.2 [M-H] ⁻	1545.8 [M-H] ⁻	1.64	A
901	1598.2 [M+Na] ⁺	1597.8 [M+Na] ⁺	1.67	A
902	785.1 [M+2H] ²⁺	785.0 [M+2H] ²⁺	1.17	A
903	1686.5 [M-H] ⁻	1685.9 [M-H] ⁻	1.95	A
904	1714.3 [M-H] ⁻	1713.9 [M-H] ⁻	2.06	A
905	1651.7 [M-H] ⁻	1651.0 [M-H] ⁻	1.40	A
906	1733.4 [M+H] ⁺	1732.9 [M+H] ⁺	1.67	A
907	1696.5 [M-H] ⁻	1696.0 [M-H] ⁻	1.21	A
908	841.6 [M+2H] ²⁺	841.5 [M+2H] ²⁺	1.25	A
909	1696.4 [M-H] ⁻	1696.0 [M-H] ⁻	1.22	A
910	1733.2 [M+H] ⁺	1732.9 [M+H] ⁺	1.67	A
911	1695.9 [M-H] ⁻	1696.0 [M-H] ⁻	1.23	A
912	1662.8 [M-H] ⁻	1662.1 [M-H] ⁻	1.23	A
913	1664.4 [M-H] ⁻	1664.0 [M-H] ⁻	1.20	A

914	1724.6 [M+H] ⁺	1724.0 [M+H] ⁺	2.05	B
915	1726.5 [M+H] ⁺	1725.9 [M+H] ⁺	1.54	A
916	1687.6 [M-H] ⁻	1687.1 [M-H] ⁻	1.10	A
917	1689.6 [M-H] ⁻	1689.0 [M-H] ⁻	1.06	A
918	1754.5 [M+H] ⁺	1753.9 [M+H] ⁺	2.05	B
919	1736.6 [M-H] ⁻	1736.0 [M-H] ⁻	2.07	B
920	1717.6 [M-H] ⁻	1717.0 [M-H] ⁻	1.60	B
921	1701.2 [M-H] ⁻	1701.1 [M-H] ⁻	1.63	B
922	1723.9 [M-H] ⁻	1723.9 [M-H] ⁻	1.95	B
923	1710.6 [M+H] ⁺	1710.0 [M+H] ⁺	1.97	B
924	1689.5 [M-H] ⁻	1689.0 [M-H] ⁻	1.53	B
925	1673.0 [M-H] ⁻	1673.0 [M-H] ⁻	1.57	B
926	1445.0 [M-H] ⁻	1444.9 [M-H] ⁻	1.94	B
927	1573.7 [M-H] ⁻	1573.0 [M-H] ⁻	1.77	B
928	1829.7 [M-H] ⁻	1829.2 [M-H] ⁻	1.56	B
929	1957.9 [M-H] ⁻	1957.3 [M-H] ⁻	1.52	B
930	1433.4 [M-H] ⁻	1432.8 [M-H] ⁻	1.77	B
931	1561.4 [M-H] ⁻	1560.9 [M-H] ⁻	1.63	B
932	1817.3 [M-H] ⁻	1817.1 [M-H] ⁻	1.49	B
933	1945.8 [M-H] ⁻	1945.2 [M-H] ⁻	1.39	B
934	1689.7 [M-H] ⁻	1689.0 [M-H] ⁻	1.52	B
935	1773.7 [M-H] ⁻	1773.0 [M-H] ⁻	1.55	B
936	886.3 [M-2H] ²⁻	886.0 [M-2H] ²⁻	1.60	B
937	1597.3 [M+H] ⁺	1596.9 [M+H] ⁺	1.97	B
938	1452.3 [M+H] ⁺	1451.8 [M+H] ⁺	1.98	B
939	1434.3 [M-H] ⁻	1433.8 [M-H] ⁻	1.97	B
940	1726.5 [M+H] ⁺	1725.9 [M+H] ⁺	1.98	B
941	1307.0 [M+H] ⁺	1306.7 [M+H] ⁺	2.01	B
942	1417.5 [M-H] ⁻	1416.9 [M-H] ⁻	1.32	A
943	1545.6 [M-H] ⁻	1545.0 [M-H] ⁻	1.16	A
944	1461.0 [M-H] ⁻	1460.9 [M-H] ⁻	1.39	A
945	1589.7 [M-H] ⁻	1588.9 [M-H] ⁻	1.21	A
946	1661.6 [M-H] ⁻	1661.0 [M-H] ⁻	0.97	A
947	1645.8 [M-H] ⁻	1645.0 [M-H] ⁻	1.00	A
948	1461.3 [M-H] ⁻	1460.8 [M-H] ⁻	1.29	A
949	1617.2 [M-H] ⁻	1616.9 [M-H] ⁻	1.14	A
950	1675.4 [M-H] ⁻	1675.0 [M-H] ⁻	1.03	A
951	1291.0 [M+H] ⁺	1290.8 [M+H] ⁺	1.55	A
952	1335.1 [M+H] ⁺	1334.8 [M+H] ⁺	1.61	A
953	1319.1 [M+H] ⁺	1318.8 [M+H] ⁺	1.64	A
954	1745.5 [M-H] ⁻	1745.1 [M-H] ⁻	1.20	A
955	1729.8 [M-H] ⁻	1729.1 [M-H] ⁻	1.23	A
956	839.2 [M+2H] ²⁺	838.5 [M+2H] ²⁺	1.18	A
957	1702.8 [M-H] ⁻	1702.0 [M-H] ⁻	1.30	A
958	1718.3 [M-H] ⁻	1718.0 [M-H] ⁻	1.26	A
959	1674.3 [M-H] ⁻	1674.0 [M-H] ⁻	1.16	A
960	1702.4 [M-H] ⁻	1702.0 [M-H] ⁻	1.25	A
961	1690.2 [M-H] ⁻	1690.0 [M-H] ⁻	1.15	A
962	1719.3 [M-H] ⁻	1719.0 [M-H] ⁻	1.28	A
963	1675.2 [M-H] ⁻	1675.0 [M-H] ⁻	1.21	A
964	1703.4 [M-H] ⁻	1703.0 [M-H] ⁻	1.34	A

965	1691.1 [M-H] ⁻	1691.0 [M-H] ⁻	1.20	A
966	1719.4 [M-H] ⁻	1719.0 [M-H] ⁻	1.32	A
967	1418.0 [M-H] ⁻	1417.8 [M-H] ⁻	1.54	A
968	1448.0 [M+H] ⁺	1447.8 [M+H] ⁺	1.63	A
969	1420.0 [M+H] ⁺	1419.8 [M+H] ⁺	1.53	A
970	1446.1 [M-H] ⁻	1445.8 [M-H] ⁻	1.63	A
971	1546.3 [M-H] ⁻	1545.9 [M-H] ⁻	1.30	A
972	1573.9 [M-H] ⁻	1573.9 [M-H] ⁻	1.41	A

The inhibitory effects of the present inventive compounds on MMP2 were determined with the method described in Test Examples 1-1 and 1-2 shown below.

5 Test Example 1-1: Evaluation Test for Inhibitory Effects of Compounds of Present Invention on Human MMP2 (Method 1)

The human-MMP2-inhibitory effects of the compounds were determined through enzyme assay using MOCac-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂,
10 0.05% Brij L23], 100 μg/mL human recombinant MMP2 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate were mixed together, and reacted at 37°C for 60 minutes. The human MMP2 activated through the reaction was poured into a 96-well microplate to reach a final concentration of 0.7 or 7 ng/mL. Further, the compounds of the present invention, which had been diluted to different concentrations, were added, and left to stand at
15 room temperature for 15 minutes. Then, MOCac-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ was added to reach a final concentration of 5 or 16 μmol/L, and enzymatic reaction was initiated. After reacting at room temperature for 2 hours, fluorescence intensity (Ex 320 nm/Em 400 nm) was measured by using a microplate reader. Enzyme inhibition rates (%) were calculated with the
20 measured fluorescence values in accordance with the following formula, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds were calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

Test Example 1-2: Evaluation Test for Inhibitory Effects of Compounds of Present Invention
on Human MMP2 (Method 2)

The human-MMP2-inhibitory effects of the compounds were determined through enzyme assay using MOCac-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 12.5 µg/mL human recombinant MMP2 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate were mixed together, and reacted at 37°C for 60 minutes. The human MMP2 activated through the reaction was poured into a 384-well microplate to reach a final concentration of 7 or 2.8 ng/mL. Further, the compounds of the present invention, which had been diluted to different concentrations, were added, and left to stand at room temperature for 10 minutes. Then,

MOCac-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ was added to reach a final concentration of 16 or 5 µmol/L, and enzymatic reaction was initiated. After reacting at room temperature for 1 to 2 hours, fluorescence intensity (Ex 320 nm/Em 405 nm) was measured by using a microplate reader. Enzyme inhibition rates (%) were calculated with the measured fluorescence values in accordance with the following formula, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds were calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

The results on the inhibitory effects of the present inventive compounds on human MMP2 enzyme activity are shown in the following tables.

[Table 51-1]

Compound	Human MMP2,	Test	Compound	Human MMP2,	Test
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No.	IC ₅₀ (nmol/L)	Example No.	No.	IC ₅₀ (nmol/L)	Example No.
1	0.22	1-1	29	0.140	1-2
2	2.04	1-2	30	0.107	1-2
3	0.25	1-1	31	0.199	1-2
4	0.128	1-2	32	0.0996	1-2
5	0.608	1-2	33	0.144	1-2
6	0.198	1-2	34	0.130	1-2
7	0.898	1-2	35	0.147	1-2
8	3.15	1-2	36	0.152	1-2
9	0.29	1-1	37	0.178	1-2
10	0.107	1-2	38	0.27	1-1
11	0.109	1-2	39	0.27	1-1
12	0.109	1-2	40	0.451	1-2
13	0.0784	1-2	41	0.0719	1-2
14	0.0897	1-2	42	0.113	1-2
15	0.108	1-2	43	0.594	1-2
16	0.119	1-2	44	4.75	1-2
17	0.199	1-2	45	0.32	1-1
18	0.135	1-2	46	0.31	1-1
19	0.148	1-2	47	4.1	1-1
20	0.20	1-1	48	0.0740	1-2
21	0.101	1-2	49	0.113	1-2
22	0.109	1-2	50	0.089	1-1
23	0.0923	1-2	51	0.21	1-1
24	0.105	1-2	52	0.12	1-1
25	0.178	1-2	53	0.0702	1-2
26	0.151	1-2	54	0.095	1-1
27	0.152	1-2	55	0.13	1-1
28	0.136	1-2			

[Table 51-2]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
56	0.083	1-1	86	0.40	1-1
57	0.078	1-1	87	0.84	1-1
58	0.097	1-1	88	0.97	1-1
59	0.046	1-1	89	0.58	1-1
60	0.97	1-1	90	1.4	1-1
61	0.13	1-1	91	1.5	1-1
62	0.090	1-1	92	0.31	1-1
63	0.61	1-1	93	0.34	1-1
64	0.060	1-1	94	0.088	1-1
65	0.083	1-1	95	0.13	1-1
66	0.047	1-1	96	0.74	1-1
67	0.11	1-1	97	0.84	1-1

68	0.068	1-1	98	0.27	1-1
69	0.19	1-1	99	0.33	1-1
70	0.34	1-1	100	1.2	1-1
71	0.89	1-1	101	1.2	1-1
72	0.52	1-1	102	0.55	1-1
73	1.9	1-1	103	0.67	1-1
74	8.1	1-1	104	0.51	1-1
75	0.097	1-1	105	0.30	1-1
76	0.055	1-1	106	0.16	1-1
77	0.25	1-1	107	0.32	1-1
78	0.037	1-1	108	0.19	1-1
79	0.091	1-1	109	0.70	1-1
80	0.22	1-1	110	0.37	1-1
81	0.48	1-1	111	0.96	1-1
82	0.83	1-1	112	0.55	1-1
83	0.37	1-1	113	2.2	1-1
84	0.17	1-1	114	0.072	1-1
85	0.49	1-1	115	0.42	1-1

[Table 51-3]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
116	0.055	1-1	146	1.7	1-1
117	0.55	1-1	147	0.14	1-1
118	0.40	1-1	148	0.48	1-1
119	0.17	1-1	149	0.11	1-1
120	0.21	1-1	150	3.3	1-1
121	0.19	1-1	151	0.33	1-1
122	0.16	1-1	152	0.85	1-1
123	1.11	1-1	153	0.066	1-1
124	0.31	1-1	154	0.44	1-1
125	0.47	1-1	155	0.19	1-1
126	0.29	1-1	156	0.088	1-1
127	0.24	1-1	157	1.24	1-1
128	0.15	1-1	158	1.38	1-1
129	0.46	1-1	159	0.37	1-1
130	0.36	1-1	160	0.68	1-1
131	0.36	1-1	161	0.33	1-1
132	0.43	1-1	162	0.60	1-1
133	0.88	1-1	163	0.12	1-1
134	2.0	1-1	164	0.37	1-1
135	9.3	1-1	165	0.23	1-1
136	4.7	1-1	166	0.39	1-1
137	0.60	1-1	167	0.58	1-1
138	0.26	1-1	168	1.2	1-1
139	1.1	1-1	169	2.5	1-1

140	0.43	1-1	170	0.072	1-1
141	1.0	1-1	171	0.068	1-1
142	2.1	1-1	172	0.13	1-1
143	2.6	1-1	173	0.19	1-1
144	0.26	1-1	174	0.55	1-1
145	0.72	1-1	175	2.0	1-1

[Table 51-4]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
176	1.9	1-1	206	0.101	1-1
177	0.21	1-1	207	0.49	1-1
178	3.6	1-1	208	0.61	1-1
179	3.5	1-1	209	0.094	1-1
180	2.6	1-1	210	0.17	1-1
181	3.1	1-1	211	2.9	1-1
182	0.49	1-1	212	0.62	1-1
183	7.0	1-1	213	1.9	1-1
184	0.61	1-1	214	0.096	1-1
185	1.0	1-1	215	2.6	1-1
186	2.0	1-1	216	0.21	1-1
187	2.8	1-1	217	0.72	1-1
188	0.81	1-1	218	0.32	1-1
189	0.86	1-1	219	0.47	1-1
190	1.8	1-1	220	0.12	1-1
191	2.7	1-1	221	0.53	1-1
192	1.9	1-1	222	0.051	1-1
193	1.7	1-1	223	0.20	1-1
194	3.7	1-1	224	1.1	1-1
195	2.7	1-1	225	0.33	1-1
196	1.7	1-1	226	0.12	1-1
197	2.6	1-1	227	0.49	1-1
198	5.1	1-1	228	0.19	1-1
199	1.4	1-1	229	0.39	1-1
200	7.4	1-1	230	0.103	1-1
201	1.4	1-1	231	1.1	1-1
202	0.097	1-1	232	0.18	1-1
203	0.13	1-1	233	0.17	1-1
204	0.42	1-1	234	0.14	1-1
205	0.80	1-1	235	0.22	1-1

[Table 51-5]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
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236	0.10	1-1	266	1.5	1-1
237	0.53	1-1	267	1.6	1-1
238	0.11	1-1	268	0.16	1-1
239	0.108	1-1	269	0.15	1-1
240	0.44	1-1	270	0.12	1-1
241	0.32	1-1	271	0.084	1-1
242	6.3	1-1	272	0.13	1-1
243	0.33	1-1	273	0.071	1-1
244	0.27	1-1	274	0.12	1-1
245	0.16	1-1	275	0.096	1-1
246	0.64	1-1	276	0.103	1-1
247	1.9	1-1	277	0.12	1-1
248	6.0	1-1	278	0.71	1-1
249	8.9	1-1	279	0.084	1-1
250	0.093	1-1	280	0.15	1-1
251	0.18	1-1	281	0.047	1-1
252	0.31	1-1	282	0.059	1-1
253	3.5	1-1	283	0.046	1-1
254	0.18	1-1	284	0.064	1-1
255	0.072	1-1	285	0.091	1-1
256	0.13	1-1	286	1.15	1-1
257	0.68	1-1	287	0.35	1-1
258	0.94	1-1	288	1.9	1-1
259	0.083	1-1	289	0.29	1-1
260	0.15	1-1	290	1.3	1-1
261	0.13	1-1	291	0.11	1-1
262	0.14	1-1	292	0.14	1-1
263	0.17	1-1	293	2.8	1-1
264	0.97	1-1	294	2.1	1-1
265	2.0	1-1	295	2.8	1-1

[Table 51-6]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
296	0.96	1-1	326	1.9	1-1
297	0.35	1-1	327	0.92	1-1
298	3.4	1-1	328	0.43	1-1
299	0.62	1-1	329	2.5	1-1
300	0.86	1-1	330	0.22	1-1
301	2.0	1-1	331	0.22	1-1
302	0.29	1-1	332	0.14	1-1
303	0.21	1-1	333	0.84	1-1
304	1.05	1-1	334	0.63	1-1
305	1.9	1-1	335	0.56	1-1
306	2.2	1-1	336	0.13	1-1
307	3.7	1-1	337	0.17	1-1

308	0.48	1-1	338	0.13	1-1
309	1.4	1-1	339	0.62	1-1
310	3.2	1-1	340	0.16	1-1
311	4.5	1-1	341	0.77	1-1
312	0.29	1-1	342	3.9	1-1
313	0.57	1-1	343	7.0	1-1
314	0.11	1-1	344	0.13	1-1
315	0.54	1-1	345	0.10	1-1
316	1.06	1-1	346	0.11	1-1
317	2.3	1-1	347	0.059	1-1
318	0.15	1-1	348	0.083	1-1
319	0.75	1-1	349	1.4	1-1
320	0.061	1-1	350	0.21	1-1
321	5.8	1-1	351	0.34	1-1
322	0.27	1-1	352	0.26	1-1
323	0.17	1-1	353	0.28	1-1
324	7.8	1-1	354	0.076	1-1
325	0.17	1-1	355	0.12	1-1

[Table 51-7]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
356	0.19	1-1	386	0.12	1-1
357	0.10	1-1	387	0.12	1-1
358	0.14	1-1	388	0.20	1-1
359	5.1	1-1	389	0.39	1-1
360	2.5	1-1	390	0.36	1-1
361	0.20	1-1	391	0.37	1-1
362	0.27	1-1	392	0.15	1-1
363	0.24	1-1	393	0.28	1-1
364	0.25	1-1	394	0.17	1-1
365	0.49	1-1	395	0.48	1-1
366	0.33	1-1	396	0.40	1-1
367	0.17	1-1	397	0.61	1-1
368	0.28	1-1	398	0.12	1-1
369	0.76	1-1	399	0.13	1-1
370	1.2	1-1	400	0.43	1-1
371	2.1	1-1	401	0.43	1-1
372	6.5	1-1	402	0.31	1-1
373	4.7	1-1	403	0.20	1-1
374	1.9	1-1	404	0.42	1-1
375	2.4	1-1	405	0.15	1-1
376	3.4	1-1	406	0.45	1-1
377	2.8	1-1	407	0.15	1-1
378	2.6	1-1	408	2.0	1-1
379	0.20	1-1	409	1.8	1-1

380	0.75	1-1	410	1.1	1-1
381	0.23	1-1	411	0.59	1-1
382	5.3	1-1	412	0.30	1-1
383	6.3	1-1	413	0.13	1-1
384	0.13	1-1	414	0.27	1-1
385	0.17	1-1	415	0.082	1-1

[Table 51-8]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
416	0.29	1-1	446	0.46	1-1
417	1.5	1-1	447	0.50	1-1
418	2.1	1-1	448	0.19	1-1
419	1.8	1-1	449	0.17	1-1
420	1.5	1-1	450	0.24	1-1
421	2.6	1-1	451	0.16	1-1
422	1.8	1-1	452	0.14	1-1
423	1.9	1-1	453	30	1-1
424	0.44	1-1	454	0.19	1-1
425	0.62	1-1	455	0.46	1-1
426	0.27	1-1	456	0.61	1-1
427	0.073	1-1	457	0.24	1-1
428	1.0	1-1	458	0.27	1-1
429	0.15	1-1	459	0.25	1-1
430	0.071	1-1	460	0.29	1-1
431	0.69	1-1	461	0.29	1-1
432	0.38	1-1	462	0.33	1-1
433	0.19	1-1	463	0.76	1-1
434	0.23	1-1	464	0.79	1-1
435	0.45	1-1	465	0.82	1-1
436	0.30	1-1	466	1.1	1-1
437	0.21	1-1	467	0.85	1-1
438	0.26	1-1	468	0.52	1-1
439	0.16	1-1	469	0.85	1-1
440	0.28	1-1	470	0.81	1-1
441	0.29	1-1	471	1.6	1-1
442	0.67	1-1	472	0.21	1-1
443	0.32	1-1	473	0.18	1-1
444	0.17	1-1	474	0.30	1-1
445	0.24	1-1	475	0.19	1-1

[Table 51-9]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
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476	0.20	1-1	506	0.15	1-1
477	0.46	1-1	507	0.16	1-1
478	0.53	1-1	508	0.30	1-1
479	0.66	1-1	509	0.28	1-1
480	0.45	1-1	510	0.40	1-1
481	2.4	1-1	511	0.20	1-1
482	0.90	1-1	512	0.15	1-1
483	0.22	1-1	513	0.18	1-1
484	0.26	1-1	514	0.22	1-1
485	0.096	1-1	515	0.29	1-1
486	0.39	1-1	516	1.3	1-1
487	1.4	1-1	517	1.3	1-1
488	1.8	1-1	518	1.4	1-1
489	0.27	1-1	519	1.6	1-1
490	0.86	1-1	520	0.32	1-1
491	0.81	1-1	521	0.41	1-1
492	0.68	1-1	522	3.1	1-1
493	0.55	1-1	523	1.9	1-1
494	0.37	1-1	524	0.12	1-1
495	0.44	1-1	525	0.15	1-1
496	0.23	1-1	526	0.21	1-1
497	0.24	1-1	527	0.32	1-1
498	0.32	1-1	528	0.23	1-1
499	0.31	1-1	529	0.49	1-1
500	0.25	1-1	530	0.42	1-1
501	0.32	1-1	531	0.35	1-1
502	0.30	1-1	532	0.31	1-1
503	0.45	1-1	533	0.34	1-1
504	0.34	1-1	534	0.29	1-1
505	0.38	1-1	535	0.31	1-1

[Table 51-10]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
536	0.35	1-1	566	0.59	1-1
537	0.28	1-1	567	0.54	1-1
538	0.22	1-1	568	0.92	1-1
539	0.23	1-1	569	0.93	1-1
540	0.29	1-1	570	1.0	1-1
541	0.35	1-1	571	1.7	1-1
542	0.45	1-1	572	1.8	1-1
543	1.3	1-1	573	4.3	1-1
544	1.3	1-1	574	4.8	1-1
545	1.0	1-1	575	2.0	1-1
546	0.98	1-1	576	2.8	1-1
547	0.59	1-1	577	0.34	1-1

548	0.67	1-1	578	0.36	1-1
549	0.52	1-1	579	0.249	1-2
550	0.52	1-1	580	0.436	1-2
551	0.92	1-1	581	0.412	1-2
552	0.62	1-1	582	0.254	1-2
553	1.1	1-1	583	0.217	1-2
554	0.89	1-1	584	1.82	1-2
555	0.87	1-1	585	1.20	1-2
556	0.55	1-1	586	1.03	1-2
557	0.44	1-1	587	0.19	1-1
558	0.66	1-1	588	0.12	1-1
559	0.42	1-1	589	0.12	1-1
560	0.42	1-1	590	3.2	1-1
561	0.74	1-1	591	0.98	1-1
562	0.58	1-1	592	0.38	1-1
563	0.49	1-1	593	2.6	1-1
564	0.44	1-1	594	1.8	1-1
565	0.42	1-1	595	3.83	1-2

[Table 51-11]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
596	1.3	1-1	626	0.18	1-1
597	0.27	1-1	627	<0.05	1-2
598	4.1	1-1	628	0.0914	1-2
599	0.39	1-1	629	0.0655	1-2
600	0.98	1-1	630	0.11	1-1
601	1.03	1-1	631	<0.05	1-2
602	0.59	1-1	632	0.0682	1-2
603	1.6	1-1	633	0.135	1-2
604	0.94	1-1	634	0.13	1-1
605	0.80	1-1	635	0.83	1-1
606	0.355	1-2	636	0.94	1-1
607	2.68	1-2	637	0.48	1-1
608	0.34	1-1	638	0.14	1-1
609	0.24	1-1	639	1.0	1-1
610	0.70	1-1	640	0.38	1-1
611	0.15	1-1	641	0.57	1-1
612	0.31	1-1	642	1.6	1-1
613	0.12	1-1	643	0.320	1-2
614	0.35	1-1	644	0.26	1-1
615	0.18	1-1	645	0.41	1-1
616	0.36	1-1	646	0.29	1-1
617	0.087	1-1	647	0.35	1-1
618	0.17	1-1	648	5.9	1-1
619	0.30	1-1	649	0.70	1-1

620	0.132	1-2	650	1.6	1-1
621	0.0867	1-2	651	2.0	1-1
622	<0.05	1-2	652	1.1	1-1
623	<0.05	1-2	653	0.74	1-1
624	0.159	1-2	654	0.21	1-1
625	0.103	1-2	655	0.27	1-1

[Table 51-12]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
656	0.72	1-1	686	0.0488	1-2
657	0.56	1-1	687	0.0577	1-2
658	0.055	1-1	688	0.0513	1-2
659	0.065	1-1	689	0.0319	1-2
660	0.12	1-1	690	0.0974	1-2
661	0.11	1-1	691	0.065	1-1
662	0.093	1-1	692	0.068	1-1
663	0.13	1-1	693	0.079	1-1
664	0.19	1-1	694	0.094	1-1
665	0.17	1-1	695	0.53	1-1
666	0.035	1-1	696	0.22	1-1
667	0.079	1-1	697	0.28	1-1
668	0.25	1-1	698	0.31	1-1
669	0.37	1-1	699	0.27	1-1
670	5.3	1-1	700	0.41	1-1
671	0.069	1-1	701	0.27	1-1
672	0.23	1-1	702	0.25	1-1
673	0.061	1-1	703	0.33	1-1
674	0.22	1-1	704	0.42	1-1
675	3.7	1-1	705	0.066	1-1
676	0.49	1-1	706	0.080	1-1
677	6.3	1-1	707	0.14	1-1
678	0.20	1-1	708	0.16	1-1
679	1.5	1-1	709	0.41	1-1
680	0.33	1-1	710	0.29	1-1
681	4.1	1-1	711	1.0	1-1
682	1.68	1-2	712	0.27	1-1
683	1.86	1-2	713	0.11	1-1
684	0.126	1-2	714	0.065	1-1
685	0.134	1-2	715	0.069	1-1

[Table 51-13]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
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716	0.48	1-1	746	1.0	1-1
717	0.80	1-1	747	0.88	1-1
718	0.43	1-1	748	0.96	1-1
719	0.55	1-1	749	1.1	1-1
720	0.72	1-1	750	0.78	1-1
721	0.43	1-1	751	1.4	1-1
722	0.66	1-1	752	1.6	1-1
723	0.41	1-1	753	1.7	1-1
724	0.45	1-1	754	2.3	1-1
725	0.51	1-1	755	1.9	1-1
726	2.4	1-1	756	1.3	1-1
727	0.39	1-1	757	1.4	1-1
728	1.9	1-1	758	0.86	1-1
729	1.4	1-1	759	2.1	1-1
730	2.9	1-1	760	1.4	1-1
731	0.20	1-1	761	1.5	1-1
732	0.16	1-1	762	1.1	1-1
733	0.11	1-1	763	0.78	1-1
734	0.10	1-1	764	1.7	1-1
735	0.65	1-1	765	1.7	1-1
736	1.2	1-1	766	0.27	1-1
737	4.5	1-1	767	0.29	1-1
738	1.2	1-1	768	0.35	1-1
739	1.0	1-1	769	0.34	1-1
740	1.4	1-1	770	0.31	1-1
741	0.61	1-1	771	0.44	1-1
742	0.57	1-1	772	0.81	1-1
743	0.78	1-1	773	5.4	1-1
744	1.0	1-1	774	5.1	1-1
745	1.7	1-1	775	4.4	1-1

[Table 51-14]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
776	5.2	1-1	806	0.28	1-1
777	1.0	1-1	807	1.0	1-1
778	1.1	1-1	808	0.55	1-1
779	1.3	1-1	809	1.9	1-1
780	0.97	1-1	810	0.99	1-1
781	1.8	1-1	811	0.82	1-1
782	0.41	1-1	812	1.3	1-1
783	2.1	1-1	813	1.6	1-1
784	2.1	1-1	814	1.5	1-1
785	0.51	1-1	815	0.98	1-1
786	0.0830	1-2	816	1.3	1-1
787	0.0670	1-2	817	0.93	1-1

788	0.0645	1-2	818	1.1	1-1
789	0.0553	1-2	819	0.42	1-1
790	0.0605	1-2	820	0.70	1-1
791	0.584	1-2	821	1.2	1-1
792	0.11	1-1	822	1.1	1-1
793	0.23	1-1	823	0.95	1-1
794	0.15	1-1	824	1.0	1-1
795	0.19	1-1	825	1.1	1-1
796	0.22	1-1	826	0.32	1-1
797	0.30	1-1	827	0.58	1-1
798	0.59	1-1	828	1.4	1-1
799	0.72	1-1	829	1.5	1-1
800	1.6	1-1	830	1.7	1-1
801	1.3	1-1	831	1.1	1-1
802	1.4	1-1	832	1.1	1-1
803	0.46	1-1	833	1.4	1-1
804	0.32	1-1	834	1.2	1-1
805	0.46	1-1	835	1.2	1-1

[Table 51-15]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
836	1.2	1-1	866	0.137	1-2
837	1.0	1-1	867	0.213	1-2
838	0.61	1-1	868	0.143	1-2
839	0.62	1-1	869	0.106	1-2
840	0.80	1-1	870	0.124	1-2
841	0.74	1-1	871	0.140	1-2
842	0.82	1-1	872	0.123	1-2
843	1.1	1-1	873	0.135	1-2
844	1.4	1-1	874	0.133	1-2
845	1.3	1-1	875	0.191	1-2
846	2.3	1-1	876	0.158	1-2
847	2.1	1-1	877	0.136	1-2
848	1.1	1-1	878	0.124	1-2
849	1.3	1-1	879	0.133	1-2
850	0.92	1-1	880	0.146	1-2
851	0.66	1-1	881	0.106	1-2
852	0.64	1-1	882	0.0996	1-2
853	0.57	1-1	883	0.143	1-2
854	0.89	1-1	884	0.153	1-2
855	0.67	1-1	885	0.128	1-2
856	0.19	1-1	886	1.09	1-2
857	0.307	1-2	887	1.34	1-2
858	0.17	1-1	888	0.153	1-2
859	0.25	1-1	889	0.170	1-2

860	0.108	1-2	890	0.158	1-2
861	0.124	1-2	891	1.6	1-1
862	0.114	1-2	892	1.7	1-1
863	0.118	1-2	893	1.15	1-1
864	0.107	1-2	894	1.1	1-1
865	0.150	1-2	895	1.3	1-1

[Table 51-16]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
896	1.2	1-1	926	0.090	1-1
897	0.87	1-1	927	0.090	1-1
898	6.4	1-1	928	0.081	1-1
899	4.2	1-1	929	0.12	1-1
900	0.055	1-1	930	0.074	1-1
901	0.054	1-1	931	0.081	1-1
902	0.049	1-1	932	0.077	1-1
903	0.127	1-1	933	0.084	1-1
904	0.20	1-1	934	0.086	1-1
905	0.092	1-1	935	0.079	1-1
906	0.19	1-1	936	0.11	1-1
907	0.080	1-1	937	0.13	1-1
908	0.049	1-1	938	0.21	1-1
909	0.13	1-1	939	0.20	1-1
910	2.5	1-1	940	0.26	1-1
911	3.1	1-1	941	0.22	1-1
912	0.111	1-1	942	0.080	1-1
913	0.38	1-1	943	0.081	1-1
914	0.23	1-1	944	0.15	1-1
915	1.19	1-1	945	0.11	1-1
916	0.19	1-1	946	0.093	1-1
917	0.61	1-1	947	0.082	1-1
918	0.31	1-1	948	0.12	1-1
919	0.18	1-1	949	0.12	1-1
920	0.18	1-1	950	0.19	1-1
921	0.085	1-1	951	0.088	1-1
922	0.27	1-1	952	0.29	1-1
923	0.13	1-1	953	0.21	1-1
924	0.096	1-1	954	0.11	1-1
925	0.16	1-1	955	0.17	1-1

[Table 51-17]

Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.	Compound No.	Human MMP2, IC ₅₀ (nmol/L)	Test Example No.
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956	0.18	1-1	965	0.50	1-1
957	0.12	1-1	966	0.37	1-1
958	0.35	1-1	967	0.18	1-1
959	0.23	1-1	968	0.23	1-1
960	0.28	1-1	969	0.14	1-1
961	0.28	1-1	970	0.25	1-1
962	0.38	1-1	971	0.16	1-1
963	0.26	1-1	972	0.36	1-1
964	0.27	1-1			

The inhibitory effects of the present inventive compounds on different types of MMP can be determined with the methods described in Test Examples 2 to 9.

5 Test Example 2: Evaluation Test for Inhibitory Effects of Compounds of Present Invention on Human MMP1

The human-MMP1-inhibitory effects of the compounds are determined through enzyme assay using MOCAC-Lys-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 50 μg/mL human recombinant MMP1 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate are mixed together, and reacted at 37°C for 120 minutes. The human MMP1 activated through the reaction is poured into a 96-well microplate to reach a final concentration of 8 ng/mL. Further, the compounds of the present invention, which have been diluted to different concentrations, are added, and left to stand at room temperature for 15 minutes. Then, MOCAC-Lys-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ is added to reach a final concentration of 11 μmol/L, and enzymatic reaction is initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) is determined by using a microplate reader. Enzyme inhibition rates (%) are calculated with the measured fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds are calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

Test Example 3: Evaluation Test for Inhibitory Effects of Compounds of Present Invention
on Human MMP3

The human-MMP3-inhibitory effects of the compounds are determined through enzyme assay using MOCAC-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 3 μg/mL human recombinant MMP3 enzyme and 5 μg/mL Chymotrypsin are mixed together. After reacting at 37°C for 30 minutes, PMSF is added to reach 2 mmol/L, thereby terminating the reaction. The human MMP3 activated through the reaction is poured into a 96-well microplate to reach a final concentration of 52 ng/mL. Further, the compounds of the present invention, which have been diluted to different concentrations, are added, and left to stand at room temperature for 15 minutes. Then, MOCAC-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂ is added to reach a final concentration of 26 μmol/L, and enzymatic reaction is initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) is determined by using a microplate reader. Enzyme inhibition rates (%) are calculated with the measured fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds are calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

Test Example 4: Evaluation Test for Inhibitory Effects of Compounds of Present Invention
on Human MMP7

The human-MMP7-inhibitory effects of the compounds are determined through

enzyme assay using MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 50 µg/mL human recombinant MMP7 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate are mixed together, and reacted at 37°C for 60 minutes.

- 5 The human MMP7 activated through the reaction is poured into a 96-well microplate to reach a final concentration of 18 ng/mL. Further, the compounds of the present invention, which have been diluted to different concentrations, are added, and left to stand at room temperature for 15 minutes. Then, MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ is added to reach a final concentration of 22 µmol/L, and enzymatic reaction is initiated. After reacting
- 10 at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) is determined by using a microplate reader. Enzyme inhibition rates (%) are calculated with the measured fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds are calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

- 15 A: Fluorescence value with addition of compound
B: Fluorescence value without addition of compound and enzyme
C: Fluorescence value without addition of compound

Test Example 5: Evaluation Test for Inhibitory Effects of Compounds of Present Invention

20 on Human MMP8

- The human-MMP8-inhibitory effects of the compounds are determined through enzyme assay using MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 100 µg/mL human recombinant MMP8 enzyme and 1 mmol/L
- 25 4-Aminophenylmercuric acetate are mixed together, and reacted at 37°C for 60 minutes. The human MMP8 activated through the reaction is poured into a 96-well microplate to reach a final concentration of 149 ng/mL. Further, the compounds of the present invention, which have been diluted to different concentrations, are added, and left to stand at room temperature

for 15 minutes. Then, MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ is added to reach a final concentration of 25 µmol/L, and enzymatic reaction is initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) is determined by using a microplate reader. Enzyme inhibition rates (%) are calculated with the measured
5 fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds are calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

10 C: Fluorescence value without addition of compound

Test Example 6: Evaluation Test for Inhibitory Effects of Compounds of Present Invention on Human MMP9

The human-MMP9-inhibitory effects of the compounds are determined through
15 enzyme assay using MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 50 µg/mL human recombinant MMP9 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate are mixed together, and reacted at 37°C for 24 hours. The human MMP9 activated through the reaction is poured into a 96-well microplate to reach a
20 final concentration of 58 ng/mL. Further, the compounds of the present invention, which have been diluted to different concentrations, are added, and left to stand at room temperature for 15 minutes. Then, MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ is added to reach a final concentration of 3 µmol/L, and enzymatic reaction is initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) is determined
25 by using a microplate reader. Enzyme inhibition rates (%) are calculated with the measured fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds are calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

5 Test Example 7: Evaluation Test for Inhibitory Effects of Compounds of Present Invention on Human MMP12

The human-MMP12-inhibitory effects of the compounds were determined through enzyme assay using MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂,
10 0.05% Brij L23], 50 µg/mL human recombinant MMP12 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate were mixed together, and reacted at 37°C for 4 or 24 hours. The human MMP12 activated through the reaction was poured into a 96-well microplate to reach a final concentration of 17 or 5.2 ng/mL. Further, the compounds of the present invention, which had been diluted to different concentrations, were added, and left to stand at
15 room temperature for 15 minutes. Then, MOCAc-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ was added to reach a final concentration of 5 or 14 µmol/L, and enzymatic reaction was initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) was determined by using a microplate reader. Enzyme inhibition rates (%) were calculated with the
20 measured fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds were calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

25 C: Fluorescence value without addition of compound

The results on the inhibitory effects of the present inventive compounds on human MMP12 enzyme activity are shown in the following table.

[Table 52]

Compound No.	Human MMP12, IC ₅₀ (nmol/L)
1	253
3	502
9	160
20	254
52	190
149	4478
223	1367
230	1270
320	1897
347	2769
666	80
691	101
701	169
766	756
796	411

Test Example 8: Evaluation Test for Inhibitory Effects of Compounds of Present Invention on Human MMP13

5 The human-MMP13-inhibitory effects of the compounds were determined through enzyme assay using MOCAC-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate. In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.05% Brij L23], 50 μg/mL human recombinant MMP13 enzyme and 1 mmol/L 4-Aminophenylmercuric acetate were mixed together, and reacted at 37°C for 2 hours. The

10 human MMP13 activated through the reaction was poured into a 96-well microplate to reach a final concentration of 5 ng/mL. Further, the compounds of the present invention, which had been diluted to different concentrations, were added, and left to stand at room temperature for 15 minutes. Then,

15 MOCAC-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ was added to reach a final concentration of 6 μmol/L, and enzymatic reaction was initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) was determined by using a microplate reader. Enzyme inhibition rates (%) were calculated with the measured

fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds were calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

5 B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

The results on the inhibitory effects of the present inventive compounds on human MMP13 enzyme activity are shown in the following table.

[Table 53]

Compound No.	Human MMP13, IC ₅₀ (nmol/L)
1	240
3	732
9	250
20	224
52	679
149	1293
223	174
230	114
320	94
347	162
666	81
691	142
701	116
766	699
796	685

10

Test Example 9: Evaluation Test for Inhibitory Effects of Compounds of Present Invention on Human MMP14

The human-MMP14-inhibitory effects of the compounds are determined through enzyme assay using MOCAc-Lys-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ as a substrate.

15 In a reaction solution [50 mmol/L Tris-HCl (pH 7.5), 200 mmol/L NaCl, 5 mmol/L CaCl₂, 20 μmol/L ZnSO₄, 0.05% Brij L23], 100 μg/mL human recombinant MMP14 enzyme and 5 μg/mL trypsin are mixed together. After reacting at room temperature for 25 minutes, a

trypsin inhibitor is added to reach 25 µg/mL, thereby terminating the reaction. The human MMP14 activated through the reaction is poured into a 96-well microplate to reach a final concentration of 6 ng/mL. Further, the compounds of the present invention, which have been diluted to different concentrations, are added, and left to stand at room temperature for 15 minutes. Then, MOCAC-Lys-Pro-Leu-Gly-Leu-A2pr(Dnp)-Ala-Arg-NH₂ is added to reach a final concentration of 5 µmol/L, and enzymatic reaction is initiated. After reacting at room temperature for 1 hour, fluorescence intensity (Ex 320 nm/Em 400 nm) is determined by using a microplate reader. Enzyme inhibition rates (%) are calculated with the measured fluorescence values in accordance with the following formulation, and the 50% inhibitory concentrations (IC₅₀ values) of the inventive compounds are calculated.

$$\text{Enzyme inhibition rate (\%)} = [1 - (A - B) / (C - B)] * 100$$

A: Fluorescence value with addition of compound

B: Fluorescence value without addition of compound and enzyme

C: Fluorescence value without addition of compound

INDUSTRIAL APPLICABILITY

The compounds of the present invention have a superior effect to inhibit MMP2, and the present invention can provide a pharmaceutical product effective for preventing or treating cancerous disease and organ fibrosis, and symptoms relating to cancerous disease and organ fibrosis, and is expected to reduce burdens on patients, thereby contributing to the development of the pharmaceutical industry.

SEQUENCE LISTING

<110> TAISHO PHARMACEUTICAL CO., LTD.

<120> POLYPEPTIDE HAVING MMP2-INHIBITORY EFFECT

<130> FA0061-20155

<150> JP 2019-203338

<151> 2019-11-08

<160> 47

<170> PatentIn version 3.5

<210> 1

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<223> peptide chain of [I'-1]: Compound No. 1-39

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<222> (1)..(1)

<223> gamma-(d)-Glu, beta-Asp, beta-(d)-Asp, or gamma-Glu

<220>

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<222> (2)..(2)

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<221> MISC_FEATURE

<222> (3)..(3)

<223> Leu, Val, Ile, Phe or Trp

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> (N-Me)Glu, (N-Me)Ile, (N-Me)Val, (N-Me)Leu, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, Pro, (N-Me)Asp or single bond

<220>

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<222> (5)..(5)

<223> Ape, beta-homoPro, Pro, (d)-Pro, beta-Ala, GABA, Acp, Lys,

(d)-Lys, Arg, (d)-Arg or single bond

<220>

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<222> (6)..(6)

<223> single bond, Pro, Lys, (d)-Lys, Arg, (d)-Arg (d)-Lys-(d)-Lys

<400> 1

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1 5

<210> 2

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<213> Artificial Sequence

<220>

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<222> (1)..(1)

<223> gamma-(d)-Glu

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> (2S,4S)-(4-amino)Pro

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> (N-Me)Glu

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Ape

<220>

<221> MISC_FEATURE

<222> (6)..(6)
<223> single bond

<400> 2

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1 5

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<220>
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<220>
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<223> gamma-(d)-Glu

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<221> MISC_FEATURE
<222> (2)..(2)
<223> (2S,4S)-(4-amino)Pro

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> (N-Me)Glu

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Ape

<220>
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<222> (6)..(6)
<223> single bond

<400> 3

Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 4
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<220>
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<223> gamma-(d)-Glu

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<222> (2)..(2)
<223> (2S,4S)-(4-amino)Pro

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<223> Leu

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<223> Ape

<220>
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<222> (6)..(6)
<223> single bond

<400> 4

Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 5
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<220>
<223> peptide chain of [I'-5]: Compound No. 43

<220>
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<222> (1)..(1)
<223> gamma-(d)-Glu

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> (2S,4S)-(4-amino)Pro

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<222> (3)..(3)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> (N-Me)Glu

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Ape

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> single bond

<400> 5

Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 6
<211> 6
<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-6]: Compound No. 44

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<223> gamma-(d)-Glu

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> (2S,4S)-(4-amino)Pro

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> (N-Me)Glu

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Ape

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> single bond

<400> 6

Xaa Xaa Xaa Xaa Xaa Xaa

1

5

<210> 7

<211> 6

<212> PRT

<213> Artificial Sequence

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<223> peptide chain of [I'-7]: Compound No. 45-55

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<223> beta-(d)-Asp, gamma-(d)-Glu or gamma-Glu

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<222> (2)..(2)
<223> (2S,4S)-(4-amino)Pro, (S)-piperazine, (2S,4R)-(4-amino)Pro,
(2S,4S)-(4-hydroxy)Pro or (2S,4R)-(4-hydroxy)Pro

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Leu

<220>
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<222> (4)..(4)
<223> (N-Me)Ile or (N-Me)Glu

<220>
<221> MISC_FEATURE
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<223> Ape or beta-homoPro

<220>
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<400> 7

Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 8
<211> 9
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<223> peptide chain of [I'-8]: Compound No. 56-91

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<222> (1)..(1)
<223> GABA, (N-Me)GABA or Ape

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<223> Asn, (N-Me)Asn, Glu, Gln, (d)-Ser, homoSer, (d)-Thr or Arg

<220>
<221> MISC_FEATURE
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<223> Leu or Dab

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<223> Met, (N-Me)Val, (N-Me)Ile, Glu, (N-Me)Glu or homoGlu

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<222> (7)..(7)
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<220>
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<400> 8

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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 <223> (N-Me)Ala, (N-Me)Asn, Asn, (d)-Asn, (N-Me)Gly, Aze(2), Pro, homoPro, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Met, (d)-Lys, (N-Me)Phe, (N-Me)Asp, (N-Me)Glu, (N-Me)Lys, Gln, (N-Me)Tyr, (N-Me)Trp, (N-Me)Thr, Val, Glu or Orn

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 <221> MISC_FEATURE
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 <223> Leu

<220>
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<220>

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<222> (8)..(8)
<223> single bond

<220>
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<223> -NH2

<400> 9

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1 5

<210> 10
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<223> gamma-Glu or (d)-Lys

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<223> beta-homoPro

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> 11
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<400> 11

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1 5

<210> 12
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<212> PRT
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 <223> Asp

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 <222> (4)..(4)
 <223> Ala or Dab

<220>
 <221> MISC_FEATURE
 <222> (5)..(5)
 <223> Leu

<220>
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<223> -NH2

<400> 12

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1

5

<210> 13

<211> 9

<212> PRT

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<220>

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<221> MISC_FEATURE

<222> (1)..(1)

<223> GABA

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 14
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<223> single bond

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<223> -NH2

<400> 14

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1 5

<210> 15
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<222> (7)..(7)
<223> beta-homoPro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 16
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-14]: Compound No. 210-315

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> GABA, beta-Ala, Ape, epsilon-Lys, epsilon-(d)-Lys, Acp, Adox,
gamma-Dab, delta-(d)-Orn, gamma-(d)-Dab, beta-Dap, beta-(d)-Dap
or -NH-(CH₂)₂-O-CH₂-CO-

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Asn, Val, Glu, Orn, (N-Me)Asn, Gln, (d)-Asn, (d)-Gln, (d)-Ser,
(d)-Ala, Phe, (d)-Phe, Tyr, (d)-Tyr, beta-Dap, beta-(d)-Dap,
beta-Ala, Dab, Dap, (d)-Dab, Aze(2), (N-Me)Glu, (N-Me)Ile or
(N-Me)Lys

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Dab, Dap, Dap(Me), Dab(Me) or Dab(Me)₂

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Glu, (N-Me)Ile, (N-Me)Asp or (N-Me)Asn

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE

<222> (9)..(9)
<223> NH₂, OH, NH₂Et, piperidin-1-yl, NHMe, azetidin-1-yl,
pyrrolidin-1-yl, (4-OH)piperidin-1-yl, NH-(CH₂)₂-OH or
(3-OH)azetidin-1-yl

<400> 16

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 17
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-15]: Compound No. 316-317

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Ape

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Asn or (d)-Ser

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Dab

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Ile

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 17

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 18
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-14]: Compound No. 318-586

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Ape, -NH-(CH2)2-O-CH2-CO-, Adox, GABA, Acp, delta-Orn,
epsilon-(d)-Lys or epsilon-Lys

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> (N-Me)Glu, Thr, (d)-Thr, (d)-Pro, Trp, (N-Me)Leu, (N-Me)Met,
(d)-Trp, His, (d)-His, Cys, (d)-Cys, Arg, (d)-Arg, (d)-Glu,
(d)-Ser, Lys(Ac), Cit, (d)-Cit, beta-Asp, beta-(d)-Asp, Lys, Met,
single bond, (N-Me)Gln, Asn, (N-Me)Arg, (d)-Lys, Gln, Glu, Ala,

<220>
<221> MISC_FEATURE
<222> (2)..(2)

<223> Dap, Dab or Gly

 <220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> Asp, aspartimide or beta-Asp

 <220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> Dab, Dap or Aze(2)

 <220>
 <221> MISC_FEATURE
 <222> (5)..(5)
 <223> Leu, Phe or Ile

 <220>
 <221> MISC_FEATURE
 <222> (6)..(6)
 <223> (N-Me)Ile, (N-Me)Glu, Dap, Dab, Orn, (N-Me)Arg, (N-Me)Lys, single bond, (N-Me)Val, (N-Me)Ala or (N-Me)Leu

 <220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> beta-homoPro, single bond, Pro, Arg, Lys, beta-Ala, GABA, Ape, His, (d)-Arg, (d)-Lys, Dap, Dab, Orn, homoPro, (2S,4R)-(4-amino)Pro, beta-Dap, beta-(d)-Dap, gamma-Dab, delta-Orn, delta-(d)-Orn, epsilon-Lys, epsilon-(d)-Lys, Aze(2),

 <220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> (d)-Aze(2), (N-Me)beta-Ala, Acp or gamma-(d)-Dab

 <220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> single bond, (d)-Lys-(d)-Lys-(d)-Lys, (d)-Lys, (d)-Arg, Lys, Arg, Arg-Arg, (d)-Arg-(d)-Arg, Lys-Lys, (d)-Lys-(d)-Lys, beta-Ala or GABA

 <220>
 <221> MISC_FEATURE
 <222> (9)..(9)
 <223> -NH₂, -OH, -NH-(CH₂)₂-NH₂, -NH-(CH₂)₄-NH₂ or -NH-(CH₂)₅-NH₂

<400> 18

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 19

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-16]: Compound No. 587-589

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> beta-Ala or GABA

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> Asn

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Asp

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Ala

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> (N-Me)Met or (N-Me)Val

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> Pro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 19

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 20
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-17]: Compound No. 590

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Ape

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Asn

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> Met

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> Pro

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> -NH2

<400> 20

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1

5

<210> 21

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-18]: Compound No. 591

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> GABA

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> Asn

<220>

<221> MISC_FEATURE

<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Met

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Pro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 21

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 22
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-19]: Compound No. 592

<220>

<221> MISC_FEATURE
<222> (1)..(1)
<223> Ape

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Asn

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Met

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Pro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 22

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 23
 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> peptide chain of [I'-20]: Compound No. 593

 <220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> single bond

 <220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> single bond

 <220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> beta-(d)-Asp

 <220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> Ala

 <220>
 <221> MISC_FEATURE
 <222> (5)..(5)
 <223> Leu

 <220>
 <221> MISC_FEATURE
 <222> (6)..(6)
 <223> (N-Me)Glu

 <220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> beta-homoPro

 <220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 23

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 24
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-21]: Compound No. 594-595

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> beta-(d)-Asp or gamma-(d)-Glu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala or (2S,4S)-(4-amino)Pro

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)

<223> (N-Me)Ile or (N-Me)Glu

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> beta-homoPro or Ape

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> -NH2

<400> 24

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1 5

<210> 25

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-22]: Compound No. 596

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> GABA

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> Asn

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Asp

<220>

<221> MISC_FEATURE

<222> (4)..(4)
<223> Dab

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Ile

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Pro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 25

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 26
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-23]: Compound No. 597

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> GABA

<220>

<221> MISC_FEATURE
<222> (2)..(2)
<223> Asn

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Met

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Pro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 26

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 27
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-24]: Compound No. 598

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> GABA

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Asn

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Met

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Pro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 27

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 28

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-25]: Compound No. 599

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> GABA

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> Asn

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Asp

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Ala

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> Met

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> Pro

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> -NH2

<400> 28

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1 5

<210> 29

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-26]: Compound No. 600-601

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> GABA

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> Asn

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Asp

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Dab

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> (N-Me)Ile or (N-Me)Glu

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> beta-homoPro

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> -NH2

<400> 29

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1

5

<210> 30

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-27]: Compound No. 602-605

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> single bond

<220>

<221> MISC_FEATURE
<222> (3)..(3)
<223> beta-(d)-Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Dap or Dab

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Glu or (N-Me)Ile

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 31
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-28]: Compound No. 606

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> gamma-(d)-Glu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> (2S,4S)-(4-amino)Pro

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Glu

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Ape

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -OH

<400> 31

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 32
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> peptide chain of [I'-29]: Compound No. 607

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> single bond

<220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> single bond

<220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> gamma-(d)-Glu

<220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> (2S,4S)-(4-amino)Pro

<220>
 <221> MISC_FEATURE
 <222> (5)..(5)
 <223> Leu

<220>
 <221> MISC_FEATURE
 <222> (6)..(6)
 <223> (N-Me)Glu

<220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> Ape

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> -OH

<400> 32

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1 5

<210> 33

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-30]: Compound No. 608

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> gamma-(d)-Glu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Dab

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (6)..(6)
<223> (N-Me)Ile

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 33

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 34
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-31]: Compound No. 609

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> gamma-(d)-Glu

<220>

<221> MISC_FEATURE
<222> (4)..(4)
<223> Dab

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Glu

<220>
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<222> (7)..(7)
<223> Ape

<220>
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<222> (8)..(8)
<223> single bond

<220>
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<222> (9)..(9)
<223> -NH2

<400> 34

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 35
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-32]: Compound No. 610-633

<220>
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<222> (1)..(1)
<223> single bond

<220>
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 <222> (2)..(2)
 <223> single bond

 <220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> beta-(d)-Asp or gamma-(d)-Glu

 <220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> Ala, Dap, Dab, Orn or (2S,4S)-(4-amino)Pro

 <220>
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 <222> (5)..(5)
 <223> Ala(2-Pyr) or Leu

 <220>
 <221> MISC_FEATURE
 <222> (6)..(6)
 <223> Met, (N-Me)Ile or (N-Me)Glu

 <220>
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 <222> (7)..(7)
 <223> Pro, beta-homoPro, Ape or single bond

 <220>
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 <222> (8)..(8)
 <223> single bond

 <220>
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 <222> (9)..(9)
 <223> -NH2

 <400> 35

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5

<210> 36
 <211> 9
 <212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-32]: Compound No. 634-642

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> beta-(d)-Asp

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Ala, Dap or Dab

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> (N-Me)Glu or (N-Me)Ile

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> beta-homoPro

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> -NH2

<400> 36

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 37

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-33]: Compound No. 643

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<221> MISC_FEATURE

<222> (1)..(1)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> gamma-(d)-Glu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> (2S,4S)-(4-amino)Pro

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu

<220>

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<222> (6)..(6)

<223> (N-Me)Glu

<220>

<221> MISC_FEATURE

<222> (7)..(7)
<223> Ape

<220>
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<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -OH

<400> 37

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 38
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-34]: Compound No. 644-690

<220>
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<222> (1)..(1)
<223> single bond or Ape

<220>
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<222> (2)..(2)
<223> single bond or Glu

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> beta-(d)-Asp, beta-Asp, gamma-Glu, gamma-(d)-Glu or Asp

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Dap, Dab or (2S,4S)-(4-amino)Pro

<220>

<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Glu, (N-Me)Ile or (N-Me)Val

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro or Ape

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2 or -OH

<400> 38

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 39
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-34]: Compound No. 691-704

<220>
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<222> (1)..(1)
<223> single bond

<220>
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<222> (2)..(2)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> beta-(d)-Asp or gamma-(d)-Glu

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Dap or Dab

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Glu or (N-Me)Ile

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> -NH2

<400> 39

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 40
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-35]: Compound No. 705-791

<220>
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 <222> (1)..(1)
 <223> single bond

<220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> single bond

<220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> beta-(d)-Asp, gamma-(d)-Glu, or gamma-Glu

<220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> Dap, Dab, Ala, (S)-piperazine, or (2S,4S)-(4-amino)Pro

<220>
 <221> MISC_FEATURE
 <222> (5)..(5)
 <223> Leu or Nle

<220>
 <221> MISC_FEATURE
 <222> (6)..(6)
 <223> (N-Me)Glu, (N-Me)Ile, Lys(CO-(CH₂)₁₀-CO₂H), Lys(CO-(CH₂)₁₂-CO₂H),
 Lys(CO-(CH₂)₁₄-CO₂H), homoSer, (N-Me)Val, (N-Me)Leu, or (N-Me)Asp

<220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> beta-homoPro, single bond, Ala, Thr, Phe, Lys, beta-Ala, GABA,
 Ape, Acp, beta-Dap, beta-(d)-Dap, gamma-Dab, gamma-(d)-Dab,
 delta-Orn, epsilon-Lys, epsilon-(d)-Lys, (4)Abz, Pro, or
 delta-(d)-Orn

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> single bond, (d)-Lys, (d)-Arg, (d)-Arg-(d)-Lys, (d)-Arg-(d)-Arg,
 (d)-Lys-(d)-Arg or (d)-Lys-(d)-Lys

<220>
 <221> MISC_FEATURE
 <222> (9)..(9)

<223> NH₂, NH-(CH₂)₂-NH₂, NH-(CH₂)₃-NH₂, NH-(CH₂)₄-NH₂, NH-(CH₂)₅-NH₂,
(4-Me)piperazin-1-yl, morpholin-4-yl, [VI-8], [VI-16], [VI-18] or
OH

<400> 40

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 41

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-36]: Compound No. 792-890

<220>

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<222> (1)..(1)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> single bond

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> beta-(d)-Asp, gamma-(d)-Glu or gamma-Glu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Dap, Dab, (S)-piperazine, Pro or (2S,4S)-(4-amino)Pro

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Leu, Ala(cPropyl), Ala(4-Thz), Ile, Val or Tyr

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> (N-Me)Glu, (N-Me)Ile, (N-Me)Val, (N-Me)Leu, single bond,
(N-Me)Ser, (N-Me)Tyr, (N-Me)Phe, (N-Me)Ala, (N-Me)Asp, (N-Me)Lys,

Gly, (d)-Arg, (d)-Pro, (d)-Ser, (d)-Tyr, (d)-Phe, (d)-Ala,
(d)-Thr, (N-Me)Arg, (d)-(N-Me)Glu or Glu

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> beta-homoPro, Ape, Acp, gamma-Dab, beta-(d)-Dap, delta-Orn,
delta-(d)-Orn, epsilon-Lys, epsilon-(d)-Lys, Pro, beta-Ala, GABA,
beta-Dap, Aze(2), (d)-Aze(2), Aze(3), cis-NH(3)cPen, single bond
or (d)-Lys

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> single bond, (d)-Lys, (d)-Arg, (d)-Arg-(d)-Lys, (d)-Arg-(d)-Arg,
(d)-Lys-(d)-Lys, (d)-Lys-(d)-Arg, Gly-(d)-Lys, Gly-(d)-Arg,
Gly-(d)-Arg-(d)-Arg, Gly-(d)-Lys-(d)-Arg, beta-Ala-(d)-Lys,
beta-Ala-(d)-Arg-(d)-Lys, beta-Ala-(d)-Arg-(d)-Arg,

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> beta-Ala-(d)-Lys-(d)-Arg, Gly-(d)-Arg-(d)-Lys,
Gly-(d)-Lys-(d)-Lys or Ape

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> NH₂, [VI-14] or OH

<400> 41

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1

5

<210> 42

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I'-37]: Compound No. 891-899

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> GABA

<220>
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<222> (2)..(2)
<223> crosslinked to Lys at position No. 5 through Gly, GABA or
beta-Ala

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Ala or Dab

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> (N-Me)Ile or (N-Me)Asp

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro or single bond

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> -OH or -NH2

<400> 42

Xaa Glu Asp Xaa Lys Xaa Xaa Xaa
1 5

<210> 43
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-38]: Compound No. 900-911

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<222> (1)..(1)
<223> gamma-Glu, Lys or (d)-Lys

<220>
<221> MISC_FEATURE

<222> (2)..(2)
<223> Adox, Lys or (d)-Lys

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Adox, Lys or (d)-Lys

<220>
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<222> (4)..(4)
<223> Lys or (d)-Lys

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<221> MOD_RES
<222> (4)..(4)
<223> GABA

<220>
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<222> (5)..(5)
<223> Asp

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Ala or Dab

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> (N-Me)Ile or (N-Me)Glu

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> beta-homoPro

<400> 43

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 44
 <211> 11
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> peptide chain of [I'-39]: Compound No. 912-955

 <220>
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 <222> (1)..(1)
 <223> (d)-Lys, gamma-Glu, Lys, Arg, (d)-Arg, Adox or single bond

 <220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> (d)-Lys, Adox, single bond, Lys, Arg or (d)-Arg

 <220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> (d)-Lys, Adox, single bond, Lys, Arg, (d)-Arg or gamma-Glu

 <220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> Single bond or (d)-Lys

 <220>
 <221> MISC_FEATURE
 <222> (5)..(5)
 <223> Single bond or (d)-Lys

 <220>
 <221> MOD_RES
 <222> (6)..(6)
 <223> GABA or Ape

 <220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> Asp

 <220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> Dab

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Leu

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> (N-Me)Ile, (N-Me)Asp or (N-Me)Glu

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> beta-homoPro

<400> 44

Xaa Xaa Xaa Xaa Xaa Lys Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 45
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'-40]: Compound No. 956-972

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<222> (1)..(1)
<223> Ape

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<222> (4)..(4)
<223> Dab

<220>
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<222> (6)..(6)
<223> (N-Me)Ile or (N-Me)Glu

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> beta-homoPro

<220>
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<222> (8)..(8)
<223> (d)-Lys or single bond

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> (d)-Lys or single bond

<220>
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<222> (10)..(10)
<223> Lys or (d)-Lys

<220>
<221> MOD_RES
<222> (10)..(10)
<223> (d)-Lys or single bond

<220>
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<222> (11)..(11)
<223> (d)-Lys or single bond

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> (d)-Lys or single bond

<400> 45

Xaa Glu Asp Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 46
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide chain of [I'] recited in claim 1

<220>
<221> MISC_FEATURE
<222> (1)..(1)

<223> L(N1):-C(=O)- or -S(=O)2-

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> W(1):L1 or L1'-L1''; L1 is single bond, and L1' is Single bond, beta-Ala, GABA, (N-Me)GABA, Ape, Acp, [III-6], [III-7], [III-8], [III-9], [III-10], [III-11], [III-12], [III-13], [IV-23] or [IV-24]

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> W(1):L1 or L1'-L1''; L1'' is single bond, Gly, (N-Me)Gly, Ala, (N-Me)Ala, (d)-Ala, Val, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, [IV-27], Pro, (d)-Pro, homoPro, Phe, (N-Me)Phe, (d)-Phe, His, (d)-His, Trp, (N-Me)Trp, (d)-Trp, Tyr, (N-Me)Tyr, (d)-Tyr,

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> W(1):L1 or L1'-L1''; L1'' is Thr, (N-Me)Thr, (d)-Thr, Cys, (d)-Cys, Met, (N-Me)Met, (N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu, Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln, Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit, [IV-7], [IV-9], [IV-10], [IV-13], Lys,

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> W(1):L1 or L1'-L1''; L1'' is (N-Me)Lys, (d)-Lys, [IV-14], beta-Ala, beta-Asp, beta-(d)-Asp, [III-6], [III-7], (d)-Ser, or homoSer

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> AA1: Asp, beta-Asp, beta-(d)-Asp, gamma-Glu or gamma-(d)-Glu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> L2: single bond

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> AA2: Ala, [IV-7], [IV-8], [IV-9], [IV-11], [IV-12], [IV-13], [IV-27], Pro, [II-1] or [II-2]

<220>
 <221> MISC_FEATURE
 <222> (6)..(6)
 <223> AA3: Val, Leu, Ile, [IV-2], Phe, Trp, Tyr, Lys, [IV-3], [IV-4],
 [IV-5] or [IV-9]

<220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> AA4: Single bond, Gly, (d)-Ala, (N-Me)Ala, (N-Me)Val, (N-Me)Leu,
 (N-Me)Ile, Pro, (d)-Pro, (N-Me)Phe, (d)-Phe, (N-Me)Tyr, (d)-Tyr,
 (N-Me)Ser, (d)-Ser, homoSer, (d)-Thr, Met, (N-Me)Met, (N-Me)Asp,
 Glu, (N-Me)Glu, (d)-(N-Me)Glu, homoGlu, (N-Me)Asn,

<220>
 <221> MISC_FEATURE
 <222> (7)..(7)
 <223> AA4: ... (N-Me)Arg, (d)-Arg, [IV-7], [IV-9], [IV-13], Lys or
 (N-Me)Lys

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> AA5: Single bond, Ala, [IV-1], [IV-27], [IV-28], [IV-29], Pro,
 (d)-Pro, beta-homoPro, homoPro, [II-1'], Phe, His, Thr, Arg,
 (d)-Arg, [IV-7], [IV-9], [IV-13], Lys, (d)-Lys, beta-Ala,
 (N-Me)-beta-Ala, GABA, Ape, Acp, [III-6], [III-7], [III-8],

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> AA5: ...[III-9], [III-10], [III-11], [III-12], [III-13], [IV-25]
 or[IV-26]

<220>
 <221> MISC_FEATURE
 <222> (9)..(9)
 <223> Wc: single bond or linker consisting of 1 to 3 amino acids,
 wherein the 1 to 3 amino acids can be the same or different,
 and are selected from the group consisting of Gly, Pro,
 Arg, (d) -Arg, Lys, (d) -Lys, beta-Ala, GABA, and Ape

<220>
 <221> MISC_FEATURE
 <222> (10)..(10)
 <223> Rc: -OH, -NH₂, C1-6 alkylamino, or a 4-7 membered saturated
 heterocyclyl containing one nitrogen and optionally one
 heteroatom.

<400> 46

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 47

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> peptide chain of [I] recited in claim 8

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> L(N1):-C(=O)- or -S(=O)2-

<220>

<221> MISC_FEATURE

<222> (2)..(2)

<223> L1: single bond

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> AA1: beta-Asp, gamma-Glu or gamma-(d)-Glu

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> L2: single bond

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> AA2: [II-1] or [II-2]

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> AA3: Val, Leu, Ile, Phe or Trp

<220>

<221> MISC_FEATURE

<222> (7)..(7)

<223> AA4: Single bond, Pro, (N-Me)Ala, (N-Me)Val, (N-Me)Leu,
(N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp or
(N-Me)Glu

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> AA5: Single bond, Pro, (d)-Pro, beta-homoPro, Arg, (d)-Arg, Lys,
(d)-Lys, beta-Ala, GABA, Ape or Acp

<220>

<221> MISC_FEATURE

<222> (9)..(9)

<223> Lc: single bond, Pro, Arg, (d) -Arg, Lys, (d) -Lys or (d)
-Lys-(d) -Lys

<220>

<221> MISC_FEATURE

<222> (10)..(10)

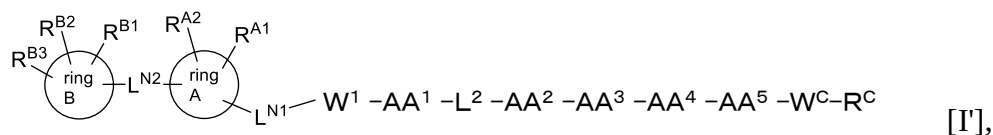
<223> Rc: -OH or -NH2

<400> 47

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

CLAIMS

1. A substituted polypeptide represented by formula [I]:



- 5 or a pharmaceutically acceptable salt thereof,

wherein

AA¹ represents:

Asp,

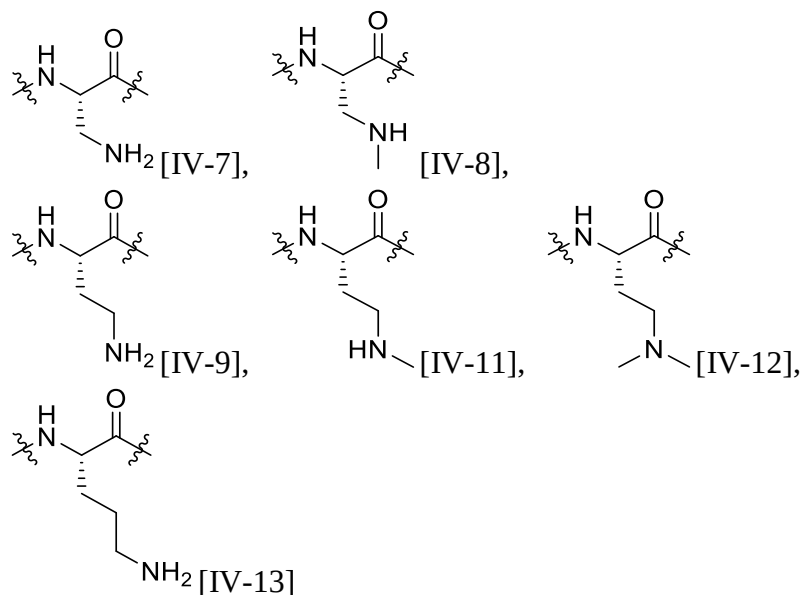
β-Asp, β-(d)-Asp, γ-Glu, or γ-(d)-Glu;

- 10 AA² represents one group selected from the group consisting of:

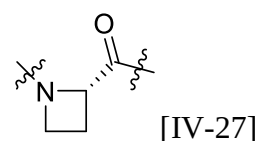
Ala,

a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], [IV-12], and

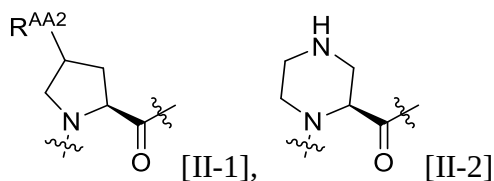
[IV-13]:



a group represented by formula [IV-27]:

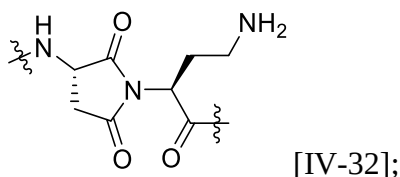


Pro, and a group represented by any of formulas [II-1] and [II-2]:



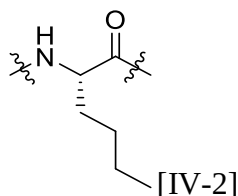
wherein R^{AA2} represents hydroxy or amino;

AA^1 and AA^2 may be taken together to form a structure represented by formula [IV-32]:



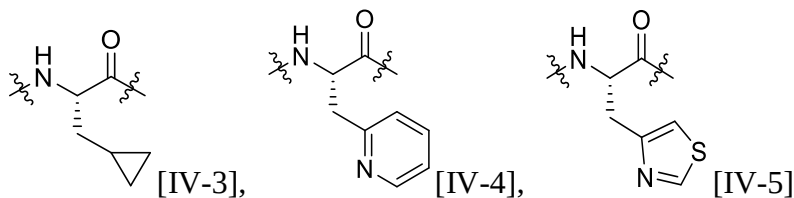
5 AA^3 represents one group selected from the group consisting of:

Val, Leu, Ile, a group represented by formula [IV-2]:



Phe, Trp,

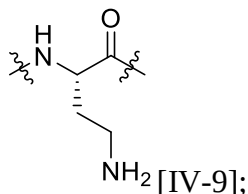
Tyr, Lys, a group represented by any of formulas [IV-3], [IV-4], and [IV-5]:



10

and

a group represented by formula [IV-9]:



AA^4 represents one group selected from the group consisting of:

15

a single bond,

Gly, (d)-Ala, (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile,

Pro, (d)-Pro,

(N-Me)Phe, (d)-Phe,

(N-Me)Tyr, (d)-Tyr,

(N-Me)Ser, (d)-Ser, homoSer, (d)-Thr,

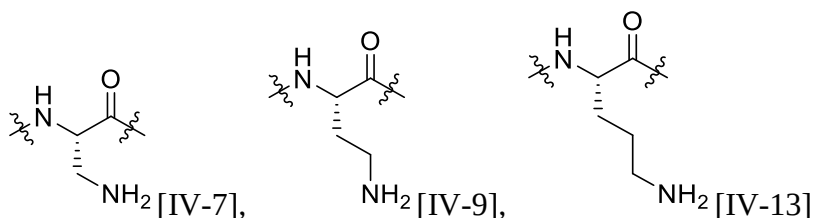
Met, (N-Me)Met,

5 (N-Me)Asp, Glu, (N-Me)Glu, (d)-(N-Me)Glu, homoGlu,

(N-Me)Asn,

(N-Me)Arg, (d)-Arg,

a group represented by any of formulas [IV-7], [IV-9], and [IV-13]:



10 Lys, and (N-Me)Lys,

wherein if AA⁴ represents Lys, then

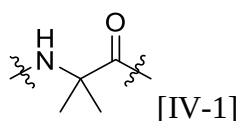
the amino in the side chain of the Lys is optionally substituted with

C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy;

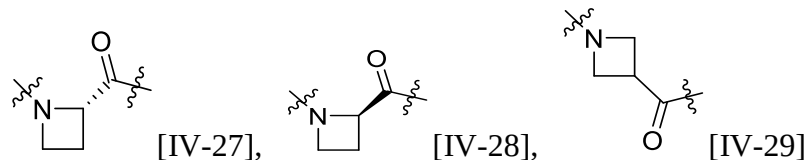
AA⁵ represents one group selected from the group consisting of:

15 a single bond,

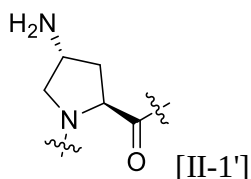
Ala, a group represented by formula [IV-1]:



a group represented by any of formulas [IV-27], [IV-28], and [IV-29]:



20 Pro, (d)-Pro, β-homoPro, homoPro, a group represented by formula [II-1']:

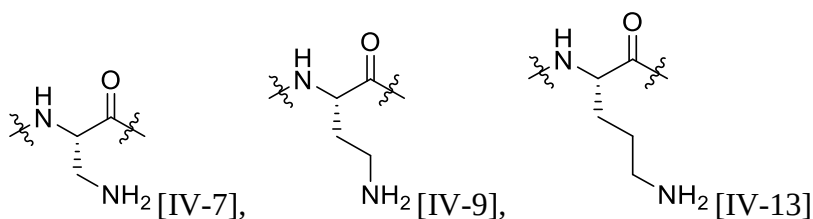


Phe, His,

Thr,

Arg, (d)-Arg,

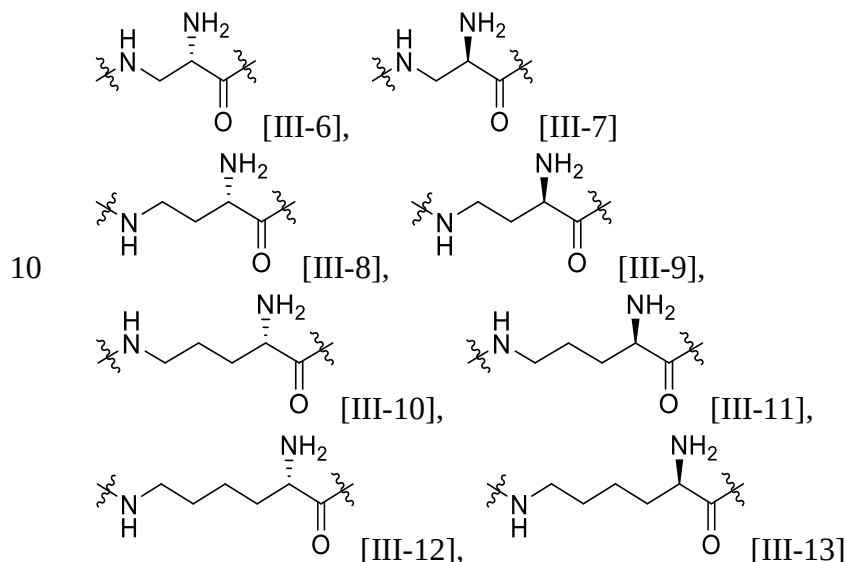
a group represented by any of formulas [IV-7], [IV-9], and [IV-13]:



Lys, (d)-Lys,

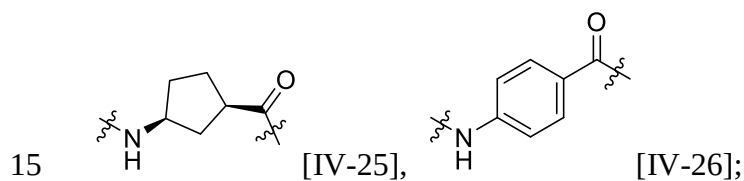
β -Ala, (N-Me)- β -Ala, GABA, Ape, Acp,

a group represented by any of formulas [III-6] to [III-13]:



and

a group represented by any of formula [IV-25] and [IV-26]:



W^1 represents $-L^1-$ or $-L^1-L^{1'}-$; wherein

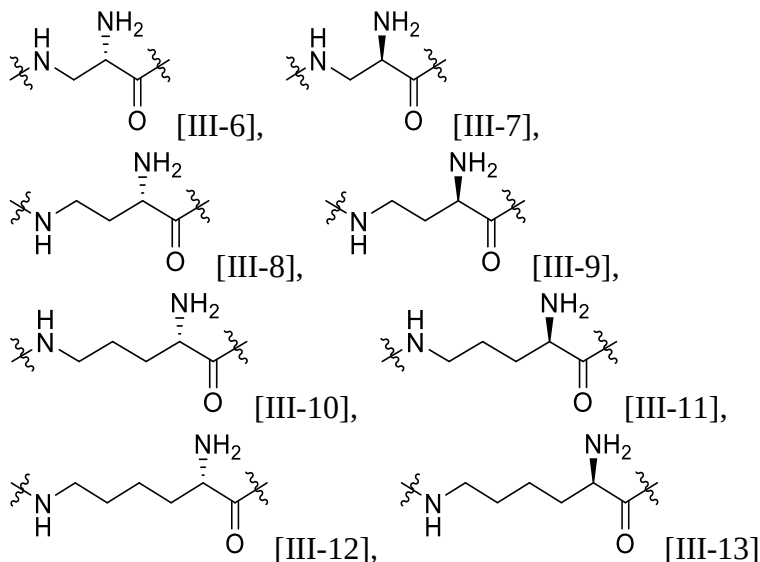
L^1 represents a single bond; and

$L^{1'}$ represents one group selected from the group consisting of:

a single bond,

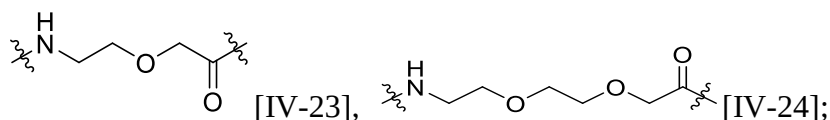
β -Ala, GABA, (N-Me)GABA, Ape, Acp,

a group represented by any of formulas [III-6] to [III-13]



and

a group represented by any of formulas [IV-23] and [IV-24]:



and

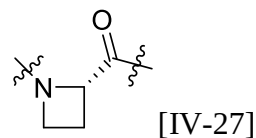
L^{1''} represents one group selected from the group consisting of:

a single bond,

Gly, (N-Me)Gly,

Ala, (N-Me)Ala, (d)-Ala, Val, (N-Me)Val, (N-Me)Leu, (N-Me)Ile,

a group represented by formula [IV-27]:



Pro, (d)-Pro, homoPro, Phe, (N-Me)Phe, (d)-Phe,

His, (d)-His, Trp, (N-Me)Trp, (d)-Trp,

Tyr, (N-Me)Tyr, (d)-Tyr,

(d)-Ser, homoSer, Thr, (N-Me)Thr, (d)-Thr,

Cys, (d)-Cys, Met, (N-Me)Met,

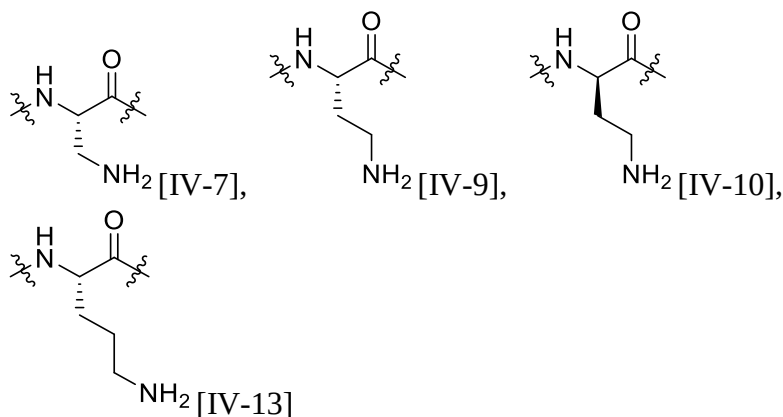
(N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu,

Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln,

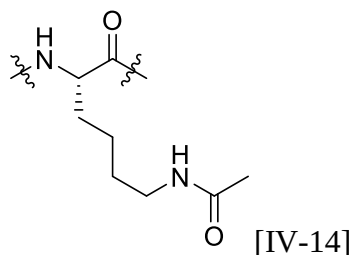
Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit,

a group represented by any of formulas [IV-7], [IV-9], [IV-10], and

5 [IV-13]:



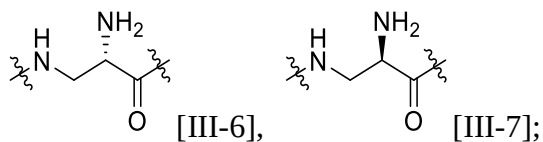
Lys, (N-Me)Lys, (d)-Lys, a group represented by formula [IV-14]:



10 β -Ala,

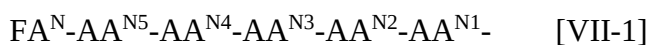
β -Asp, β -(d)-Asp, and

a group represented by any of formulas [III-6] and [III-7]:



wherein if L^{1"} represents Lys or (d)-Lys, then

15 the amino in the side chain of the Lys or (d)-Lys is optionally substituted with a group represented by formula [VII-1]:



wherein

FA^N represents C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy;

AA^{N5} represents:

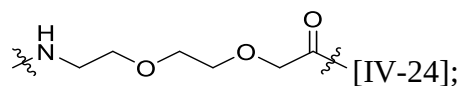
a single bond,

Arg, (d)-Arg,

Lys, (d)-Lys,

5 γ -Glu, or

a group represented by formula [IV-24]:



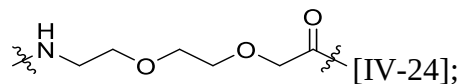
AA^{N4} represents:

a single bond,

10 Arg, (d)-Arg,

Lys, (d)-Lys, or

a group represented by formula [IV-24]:



AA^{N3} represents:

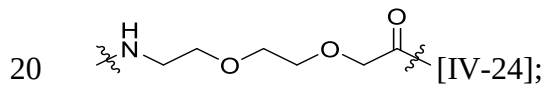
15 a single bond,

Arg, (d)-Arg,

Lys, (d)-Lys,

γ -Glu, or

a group represented by formula [IV-24]:



AA^{N2} represents:

a single bond, or

(d)-Lys; and

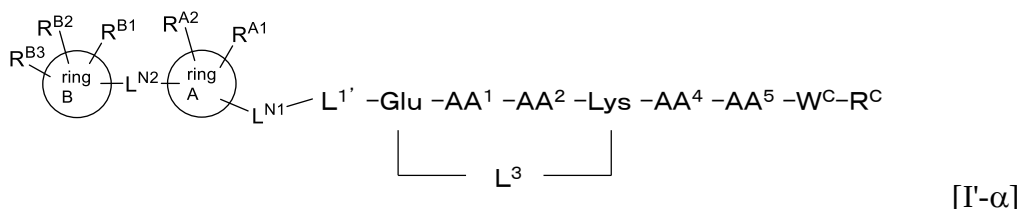
AA^{N1} represents:

25 a single bond, or

(d)-Lys;

wherein if L^{1''} represents by Glu and AA³ represents Lys, then

the compound represented by formula [I'] may be taken together with L³ attached to each of functional groups in the side chains of the two amino acids to form a cyclic structure, as represented by formula [I'-α]:



- 5 wherein the L³ represents Gly, β-Ala, or GABA;
 L^{N1} represents the formula -C(=O)- or the formula -S(=O)₂-;
 L^{N2} represents:

a single bond,
 C₁₋₃ alkanediyl,
 10 C₂₋₃ alkenediyl,
 ethynediyl,
 the formula -O-,
 the formula -C(=O)-, the formula -C(=O)-NH-, or
 triazolediyl;

- 15 L² represents a single bond;
 ring A represents an aromatic ring or a heteroaromatic ring;
 R^{A1} and R^{A2} each independently represent:

a hydrogen atom,
 a halogen atom,
 20 C₁₋₆ alkyl, or
 C₁₋₆ alkoxy;

ring B represents:

aryl or heteroaryl;

R^{B1}, R^{B2}, and R^{B3} each independently represent:

- 25 a hydrogen atom,

carbamoyl,

cyano,

a halogen atom,

C₁₋₆ alkyl optionally substituted with one hydroxy, halo C₁₋₆ alkyl,

5 C₁₋₆ alkoxy optionally substituted with one hydroxy, halo C₁₋₆ alkoxy,

C₁₋₆ alkylcarbonyl,

C₁₋₆ alkylcarbonylamino,

mono C₁₋₆ alkylaminocarbonyl, di C₁₋₆ alkylaminocarbonyl, wherein the alkyl in

each of the mono C₁₋₆ alkylaminocarbonyl and the di C₁₋₆ alkylaminocarbonyl is optionally

10 substituted with one group selected from the group consisting of hydroxy, carboxy,

carbamoyl, and amino,

C₁₋₆ alkylsulfonyl, or

aryl;

W^C is a single bond or a linker consisting of one to three amino acids, wherein the one to

15 three amino acids forming the linker are same or different and each selected from the group

consisting of:

Gly,

Pro,

Arg, (d)-Arg,

20 Lys, (d)-Lys,

β-Ala, GABA, and Ape,

wherein if Lys or (d)-Lys is included in the group represented by W^C, then

the amino in the side chain of the Lys or (d)-Lys is optionally substituted with:

C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy,

25 Lys, wherein the amino in the side chain of the Lys is optionally substituted

with C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy, or

(d)-Lys, wherein the amino in the side chain of the (d)-Lys is optionally

substituted with C₂₋₁₆ alkylcarbonyl terminally-substituted with carboxy; and

R^C is:

the formula -OH, the formula -NH₂,

C₁₋₆ alkylamino, wherein the C₁₋₆ alkyl of the C₁₋₆ alkylamino is optionally

substituted with one group selected from the group consisting of hydroxy, amino, C₁₋₆ alkoxy,

5 and four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom, or

four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom; wherein the four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom

10 is optionally substituted with one group selected from the group consisting of hydroxy, amino, and C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one carbamoyl; and two carbon atoms in the four- to seven-membered saturated heterocyclyl containing one nitrogen atom and optionally further containing one heteroatom are optionally crosslinked with C₁₋₄ alkanediyl.

15 2. The substituted polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein

W^C is:

a single bond,

Pro,

20 Arg, (d)-Arg,

Lys, (d)-Lys,

β-Ala, GABA, Ape,

Gly-(d)-Lys, Gly-(d)-Lys-(d)-Lys, Gly-(d)-Lys-(d)-Arg, Gly-(d)-Arg-(d)-Lys,

Lys-Lys, (d)-Lys-(d)-Lys, (d)-Lys-(d)-Lys-(d)-Lys,

25 Arg-Arg, (d)-Arg-(d)-Arg, (d)-Arg-(d)-Lys,

Lys-(d)-Lys-(d)-Lys, (d)-Lys-Lys-(d)-Lys, (d)-Lys-(d)-Lys-Lys,

β-Ala-(d)-Lys, β-Ala-(d)-Lys-(d)-Arg,

β-Ala-(d)-Arg-(d)-Lys, or β-Ala-(d)-Arg-(d)-Arg,

wherein if Lys is contained in the group represented by W^C , then
the amino in the side chain of the Lys is optionally substituted with:

C_{2-16} alkylcarbonyl terminally-substituted with carboxy, or

(d)-Lys, wherein the amino in the side chain of the (d)-Lys is optionally substituted

5 with C_{2-16} alkylcarbonyl terminally-substituted with carboxy.

3. The substituted polypeptide or pharmaceutically acceptable salt thereof according to
claim 1 or 2, wherein

ring A is a benzene ring, a thiophene ring, or a pyridine ring;

R^{A1} and R^{A2} are each independently:

10 a hydrogen atom, or

a halogen atom;

ring B is:

phenyl, oxazolyl, thiadiazolyl, pyridyl, or benzofuranyl;

R^{B1} , R^{B2} , and R^{B3} are each independently:

15 a hydrogen atom,

carbamoyl,

cyano,

a halogen atom,

C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one hydroxy,

20 halo C_{1-6} alkyl,

C_{1-6} alkoxy, wherein the C_{1-6} alkoxy is optionally substituted with one hydroxy,

halo C_{1-6} alkoxy,

C_{1-6} alkylcarbonyl,

mono C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, wherein the alkyl in

25 each of the mono C_{1-6} alkylaminocarbonyl and the di C_{1-6} alkylaminocarbonyl is optionally
substituted with one group selected from the group consisting of hydroxy, carboxy,
carbamoyl, and amino, or

C_{1-6} alkylsulfonyl; and

R^C is:

the formula -OH, the formula -NH₂,

C₁₋₆ alkylamino, wherein the C₁₋₆ alkyl of the C₁₋₆ alkylamino is optionally

substituted with one group selected from the group consisting of hydroxy, amino, C₁₋₆ alkoxy,

5 and morpholinyl,

azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl, wherein the

azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl is optionally substituted with

one group selected from the group consisting of hydroxy, amino, and C₁₋₆ alkyl, wherein the

C₁₋₆ alkyl is optionally substituted with one carbamoyl, wherein

10 two carbon atoms in the azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or

piperazinyl are optionally crosslinked with C₁₋₄ alkanediyl.

4. The substituted polypeptide or pharmaceutically acceptable salt thereof according to

any one of claims 1 to 3, wherein in the substituted polypeptide represented by formula [I'],

ring A is a benzene ring;

15 ring B is phenyl;

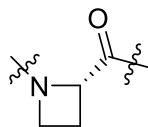
L^{1''} is one group selected from the group consisting of:

a single bond,

Gly, (N-Me)Gly,

Ala, (N-Me)Ala, (d)-Ala, Val, (N-Me)Val, (N-Me)Leu, (N-Me)Ile,

20 a group represented by formula [IV-27]:



[IV-27]

Pro, (d)-Pro, homoPro, Phe, (N-Me)Phe, (d)-Phe,

His, (d)-His, Trp, (N-Me)Trp, (d)-Trp,

Tyr, (N-Me)Tyr, (d)-Tyr,

25 (d)-Ser, homoSer, Thr, (N-Me)Thr, (d)-Thr,

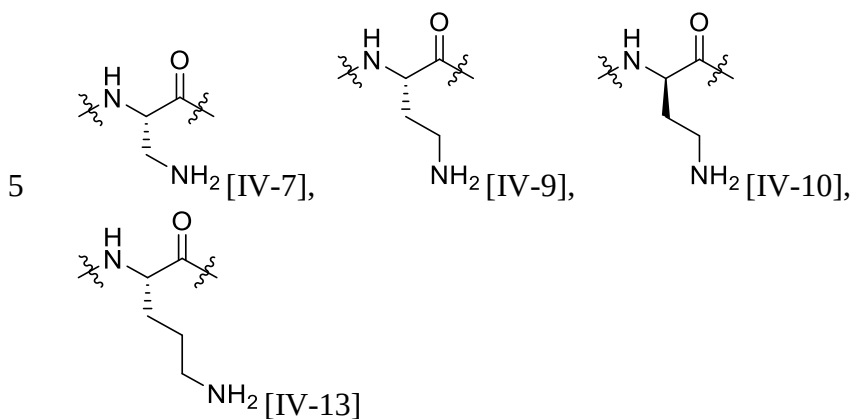
Cys, (d)-Cys, Met, (N-Me)Met,

(N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu,

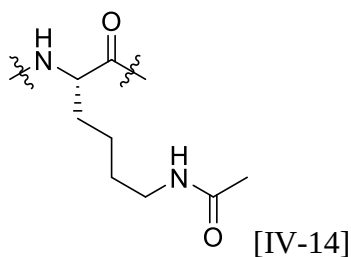
Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln,

Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit,

a group represented by any of formulas [IV-7], [IV-9], [IV-10], and [IV-13]:



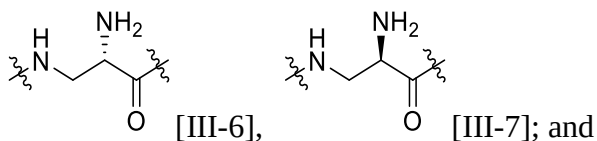
Lys, (N-Me)Lys, (d)-Lys, a group represented by formula [IV-14]:



β -Ala,

10 β -Asp, β -(d)-Asp, and

a group represented by any of formulas [III-6] and [III-7]:



W^C is:

a single bond,

15 Pro,

Arg, (d)-Arg,

Lys, (d)-Lys,

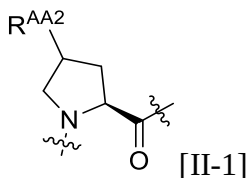
β -Ala, GABA, Ape,

Gly-(d)-Lys, Gly-(d)-Lys-(d)-Lys, Gly-(d)-Lys-(d)-Arg, Gly-(d)-Arg-(d)-Lys,

Lys-Lys, (d)-Lys-(d)-Lys, (d)-Lys-(d)-Lys-(d)-Lys,
 Arg-Arg, (d)-Arg-(d)-Arg, (d)-Arg-(d)-Lys,
 Lys-(d)-Lys-(d)-Lys, (d)-Lys-Lys-(d)-Lys, (d)-Lys-(d)-Lys-Lys,
 β -Ala-(d)-Lys, β -Ala-(d)-Lys-(d)-Arg,
 β -Ala-(d)-Arg-(d)-Lys, or β -Ala-(d)-Arg-(d)-Arg.

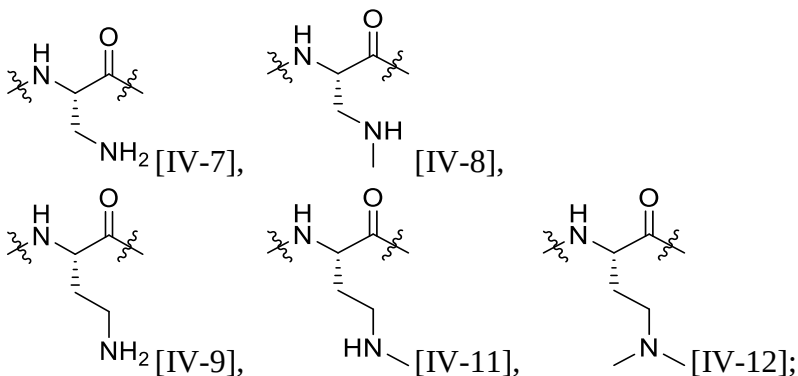
5. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein in the substituted polypeptide represented by formula [I'], AA^2 is one group selected from the group consisting of:

a group represented by formula [II-1]:



and

a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], and [IV-12]:



15 wherein R^{AA2} is amino;

AA^3 is Val, Leu, Ile, Phe, or Trp;

AA^4 is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu;

AA^5 is β -Ala, GABA, Ape, Acp, Pro, (d)-Pro, or β -homoPro;

W^C is a single bond, Arg, (d)-Arg, Lys, or (d)-Lys; and

20 R^C is the formula -OH or the formula -NH₂.

6. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein in the substituted polypeptide represented by formula [I'],

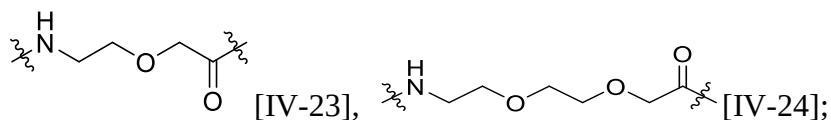
W¹ is -L^{1'}-L^{1''}-;

L² is a single bond;

AA¹ is Asp;

L^{1'} is one group selected from the group consisting of β-Ala, GABA, Ape, Acp, and

5 a group represented by any of formulas [IV-23] and [IV-24]:



L^{1''} is a single bond, Asn, (d)-Ser, (d)-Thr, or Glu;

L^{N1} is the formula -C(=O)- or the formula -S(=O)₂-;

L^{N2} is the formula -O- or the formula -C(=O)-NH-;

10 R^{A1} and R^{A2} are each a hydrogen atom; and

R^{B1}, R^{B2}, and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom,

C₁₋₆ alkoxy, or halo C₁₋₆ alkoxy.

7. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein in the substituted polypeptide represented by formula [I'],

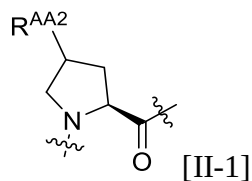
15 W¹ is -L¹-, wherein L¹ is a single bond;

L² is a single bond;

AA¹ is β-Asp, β-(d)-Asp, γ-Glu, or γ-(d)-Glu;

AA² is one group selected from the group consisting of:

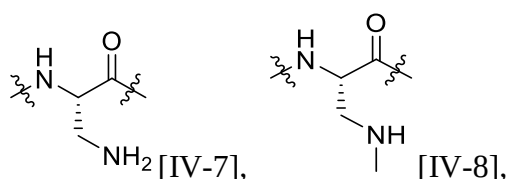
a group represented by formula [II-1]:

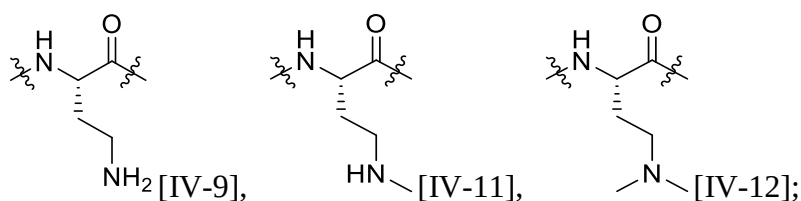


20

and

a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], and [IV-12]:





wherein R^{AA2} is amino;

AA^3 is Val, Leu, Ile, Phe, or Trp;

AA^4 is (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Asp, or (N-Me)Glu;

5 AA^5 is β -Ala, GABA, Ape, Acp, or β -homoPro;

L^{N1} is the formula $-\text{C}(=\text{O})-$ or the formula $-\text{S}(=\text{O})_2-$;

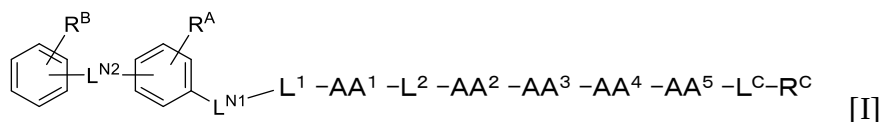
L^{N2} is a single bond, the formula $-\text{O}-$, or the formula $-\text{C}(=\text{O})-\text{NH}-$;

R^{A1} and R^{A2} are each a hydrogen atom; and

R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom,

10 C_{1-6} alkoxy, or halo C_{1-6} alkoxy.

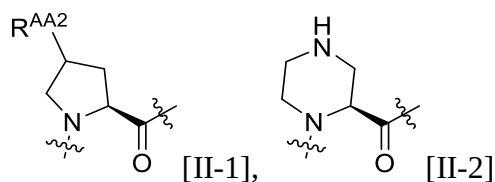
8. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein the substituted polypeptide represented by formula [I'] is a substituted polypeptide represented by formula [I]:



15 wherein

AA^1 is β -Asp, γ -Glu, or γ -(d)-Glu;

AA^2 is a group represented by formula [II-1] or formula [II-2]:



wherein R^{AA2} is hydroxy or amino;

20 AA^3 is Val, Leu, Ile, Phe, or Trp;

AA^4 is a single bond, Pro, (N-Me)Ala, (N-Me)Val, (N-Me)Leu, (N-Me)Ile, (N-Me)Phe, (N-Me)Tyr, (N-Me)Ser, (N-Me)Asp, or (N-Me)Glu;

AA⁵ is a single bond, Pro, (d)-Pro, β-homoPro, Arg, (d)-Arg, Lys, (d)-Lys, β-Ala, GABA, Ape, or Acp;

L¹ is a single bond;

L² is a single bond;

5 L^{N1} is the formula -C(=O)- or the formula -S(=O)₂-;

L^{N2} is a single bond, C₁₋₃ alkanediyl, the formula -O-, or the formula -C(=O)-NH-;

R^A is a hydrogen atom, a halogen atom, C₁₋₆ alkyl, or C₁₋₆ alkoxy;

R^B is a hydrogen atom, carbamoyl, a halogen atom, C₁₋₆ alkyl, or C₁₋₆ alkoxy;

L^C is a single bond, Pro, Arg, (d)-Arg, Lys, (d)-Lys, or (d)-Lys-(d)-Lys; and

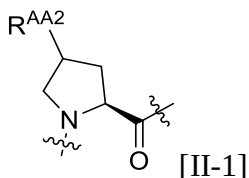
10 R^C is the formula -OH or the formula -NH₂.

9. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein in the substituted polypeptide represented by formula [I],

AA¹ is Asp, β-(d)-Asp, or γ-(d)-Glu;

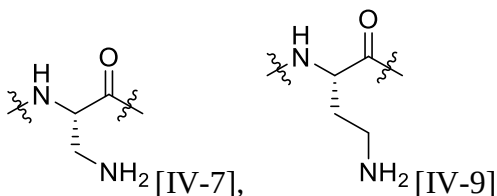
AA² is one group selected from the group consisting of:

15 a group represented by formula [II-1]:



and

a group represented by any of formulas [IV-7] and [IV-9]:



20 wherein R^{AA2} is amino;

AA³ is Val, Leu, or Ile;

AA⁴ is (N-Me)Ile or (N-Me)Glu;

AA⁵ is Ape or β-homoPro;

W¹ is -L¹- or -L^{1'}-L^{1''}-,

wherein

L^1 is a single bond,

$L^{1'}$ is GABA or Ape, and

$L^{1''}$ is Asn, (d)-Ser, (d)-Thr, or Glu;

5 L^{N1} is the formula $-C(=O)-$ or the formula $-S(=O)_2-$;

L^{N2} is the formula $-O-$ or the formula $-C(=O)-NH-$;

R^{A1} and R^{A2} are each a hydrogen atom;

R^{B1} , R^{B2} , and R^{B3} are each independently a hydrogen atom, carbamoyl, a halogen atom,

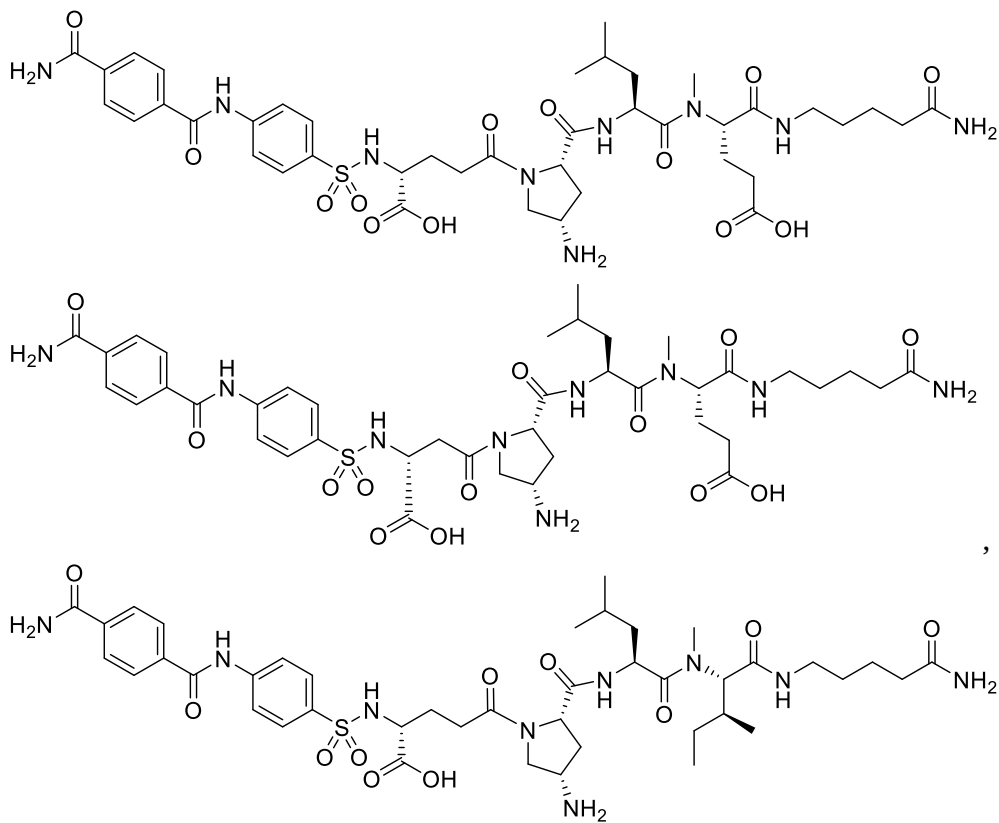
C_{1-6} alkoxy, or halo C_{1-6} alkoxy;

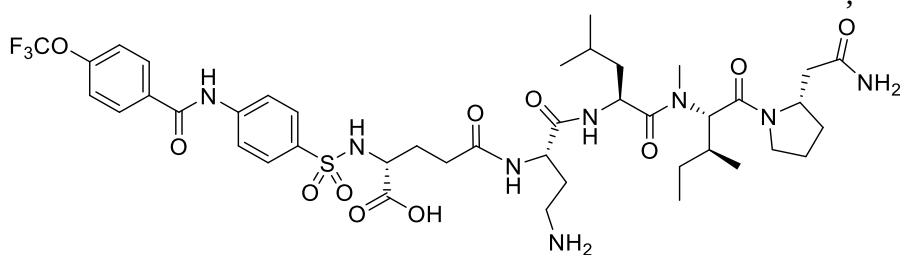
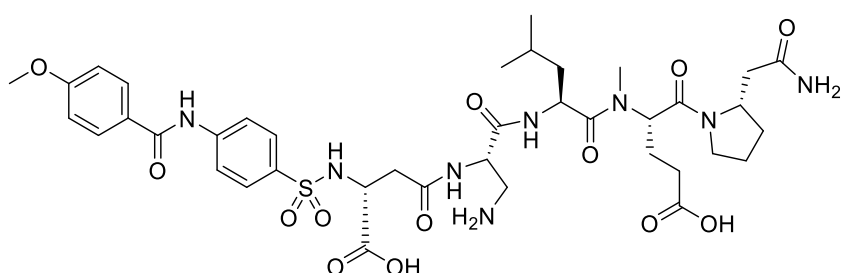
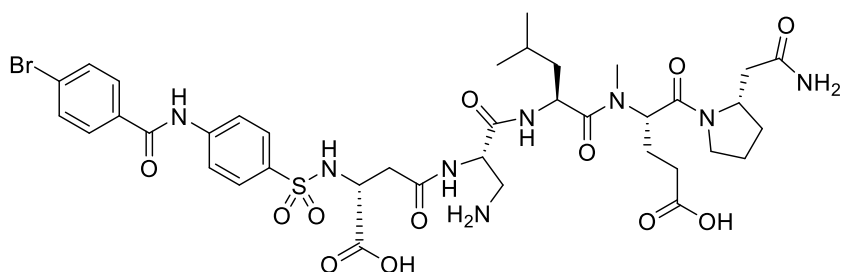
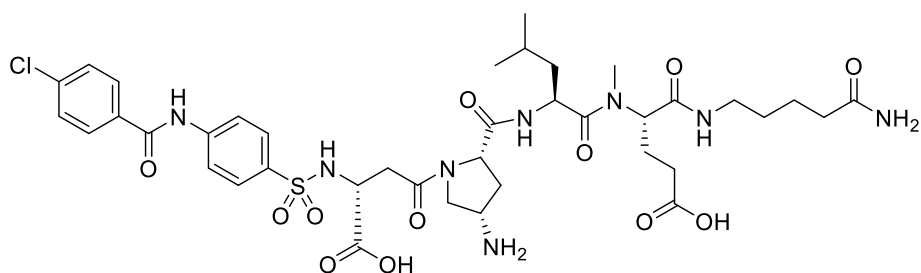
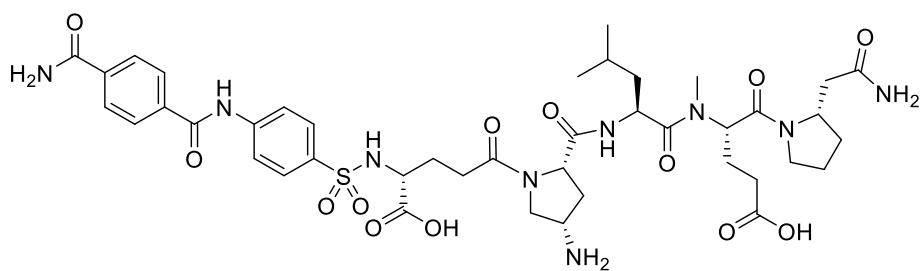
10 W^C is a single bond or (d)-Lys; and

R^C is the formula $-NH_2$.

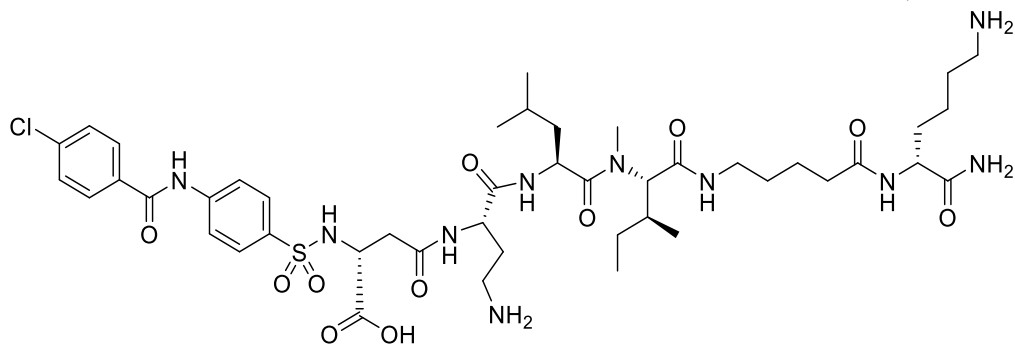
10. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein the substituted polypeptide is selected from compounds shown in the following:

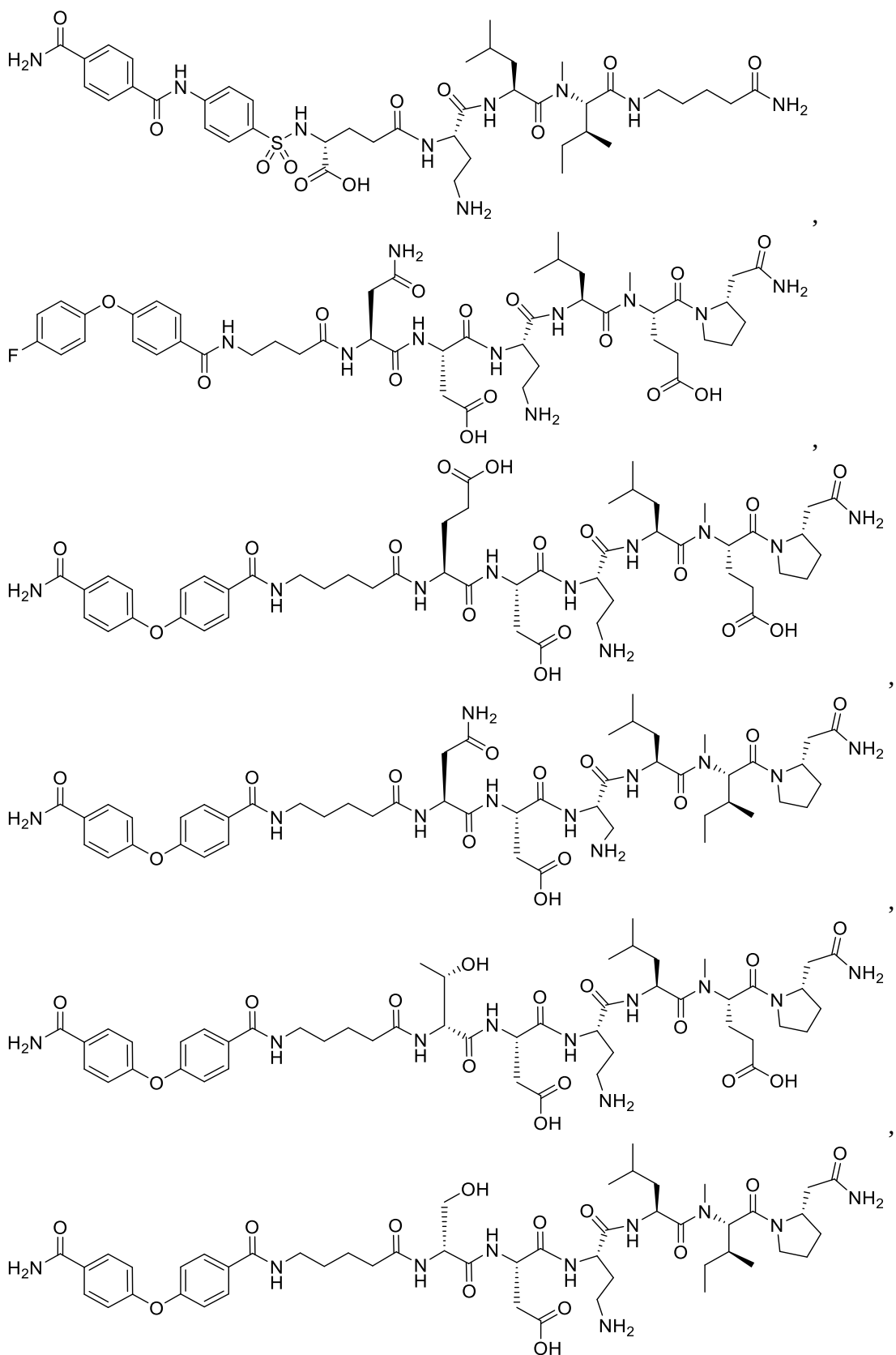
15





5





11. A pharmaceutical comprising the substituted polypeptide or pharmaceutically

acceptable salt thereof according to any one of claims 1 to 10 as an active ingredient.

12. An MMP2 inhibitor comprising the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 as an active ingredient.

13. A drug for preventing or treating cancerous disease or organ fibrosis, or a symptom
5 associated with cancerous disease or organ fibrosis, comprising the substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 as an active ingredient.