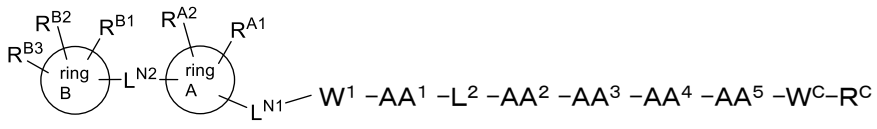
CLAIMS

1. A substituted polypeptide represented by formula [I']:



[I'],

or a pharmaceutically acceptable salt thereof,

wherein

AA^1 represents:

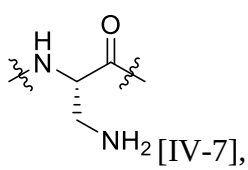
Asp,

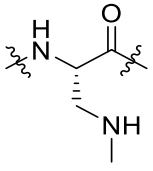
β-Asp, β-(d)-Asp, γ-Glu, or γ-(d)-Glu;

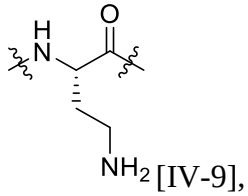
AA^2 represents one group selected from the group consisting of:

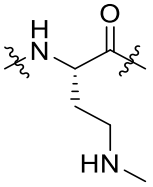
Ala,

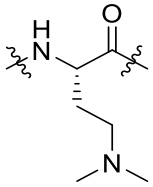
a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], [IV-12], and [IV-13]:

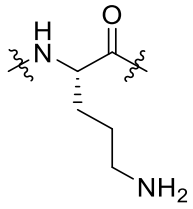

[IV-7],


[IV-8],

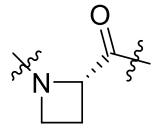

[IV-9],


[IV-11],

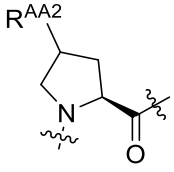
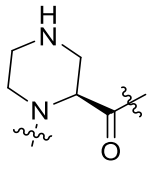

[IV-12],


[IV-13]

a group represented by formula [IV-27]:

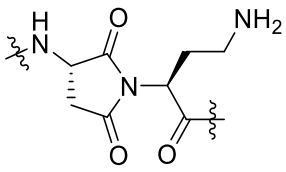

[IV-27]

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


[II-1],

[II-2]

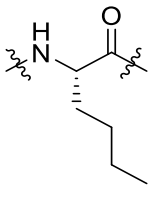
wherein R^{AA2} represents hydroxy or amino;

AA^1 and AA^2 may be taken together to form a structure represented by formula [IV-32]:


[IV-32];

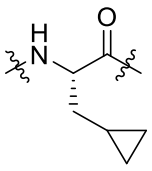
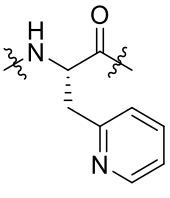
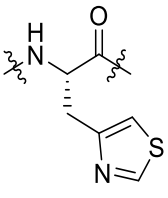
AA^3 represents one group selected from the group consisting of:

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


[IV-2]

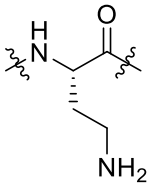
Phe, Trp,

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


[IV-3],

[IV-4],

[IV-5]

and

a group represented by formula [IV-9]:


[IV-9];

AA^4 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,

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

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

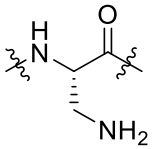
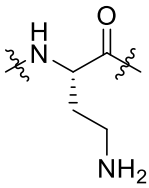
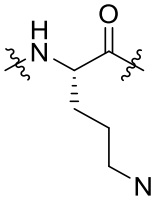
Met, (N-Me)Met,

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

(N-Me)Asn,

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

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

 [IV-7],  [IV-9],  [IV-13]

Lys, and (N-Me)Lys,

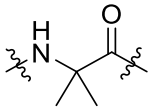
wherein if AA^4 represents Lys, then

the amino in the side chain of the Lys is optionally substituted with C_{2-16} alkylcarbonyl terminally-substituted with carboxy;

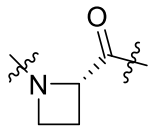
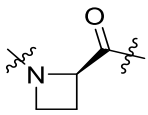
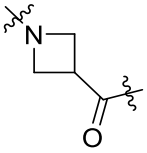
AA^5 represents one group selected from the group consisting of:

a single bond,

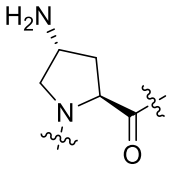
Ala, a group represented by formula [IV-1]:

 [IV-1]

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

 [IV-27],  [IV-28],  [IV-29]

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

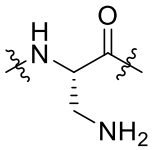
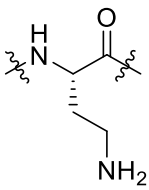
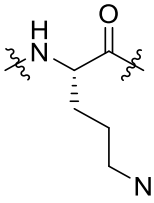
 [II-1']

Phe, His,

Thr,

Arg, (d)-Arg,

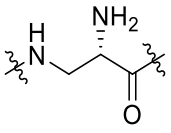
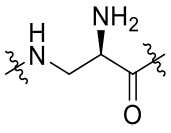
a group represented by any of formulas [IV-7], [IV-9], and [IV-13]:

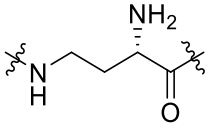
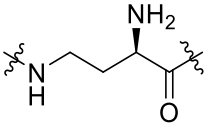
 [IV-7],  [IV-9],  [IV-13]

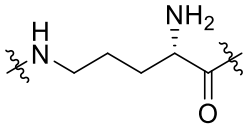
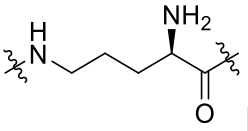
Lys, (d)-Lys,

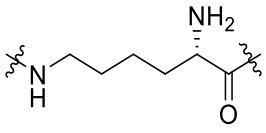
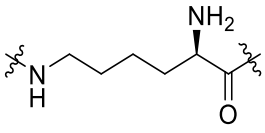
β-Ala, (N-Me)-β-Ala, GABA, Ape, Acp,

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

 [III-6],  [III-7]

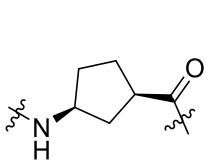
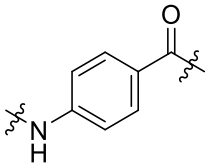
 [III-8],  [III-9],

 [III-10],  [III-11],

 [III-12],  [III-13]

and

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

 [IV-25],  [IV-26];

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

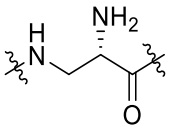
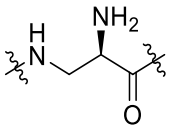
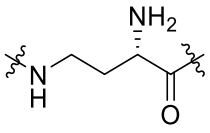
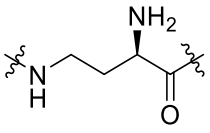
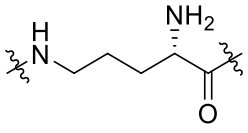
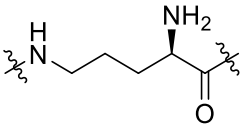
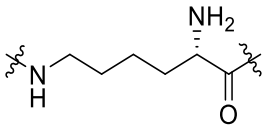
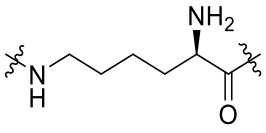
L^1 represents a single bond; and

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

a single bond,

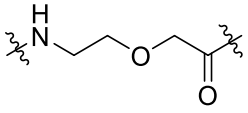
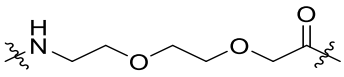
β-Ala, GABA, (N-Me)GABA, Ape, Acp,

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


[III-6],

[III-7],

[III-8],

[III-9],

[III-10],

[III-11],

[III-12],

[III-13]

and

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


[IV-23],

[IV-24];

and

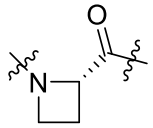
$L^{1"}$ represents one group selected from the group consisting of:

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]:


[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,

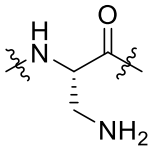
Cys, (d)-Cys, Met, (N-Me)Met,

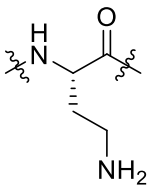
(N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu,

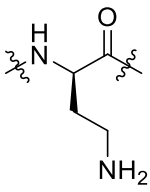
Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln,

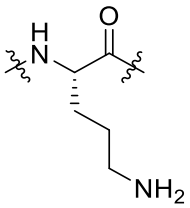
Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit,

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

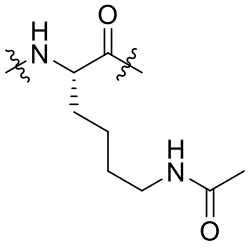
 [IV-7],

 [IV-9],

 [IV-10],

 [IV-13]

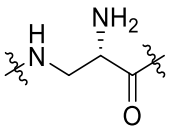
Lys, (N-Me)Lys, (d)-Lys, a group represented by formula [IV-14]:

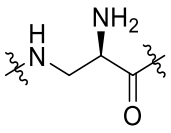
 [IV-14]

β-Ala,

β-Asp, β-(d)-Asp, and

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

 [III-6],

 [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 group represented by formula [VII-1]:

FA^{N}-AA^{N5}-AA^{N4}-AA^{N3}-AA^{N2}-AA^{N1}- [VII-1]

wherein

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

AA^{N5} represents:

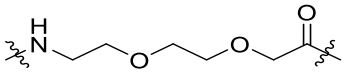
a single bond,

Arg, (d)-Arg,

Lys, (d)-Lys,

γ-Glu, or

a group represented by formula [IV-24]:

 [IV-24];

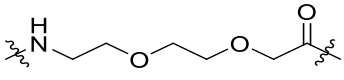
AA^{N4} represents:

a single bond,

Arg, (d)-Arg,

Lys, (d)-Lys, or

a group represented by formula [IV-24]:

 [IV-24];

AA^{N3} represents:

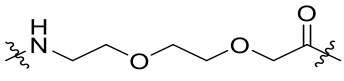
a single bond,

Arg, (d)-Arg,

Lys, (d)-Lys,

γ-Glu, or

a group represented by formula [IV-24]:

 [IV-24];

AA^{N2} represents:

a single bond, or

(d)-Lys; and

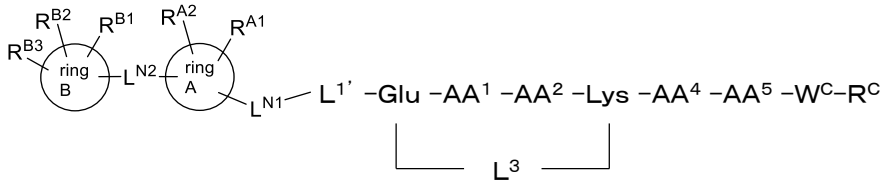
AA^{N1} represents:

a single bond, or

(d)-Lys;

wherein if $L^{1"}$ represents by Glu and AA^{3} represents Lys, then

the compound represented by formula [I'] may be taken together with L^3 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]:



[I'-α]

wherein the L^3 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,

C_{1-3} alkanediyl,

C_{2-3} alkenediyl,

ethynediyl,

the formula -O-,

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

triazolediyl;

L^2 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,

C_{1-6} alkyl, or

C_{1-6} alkoxy;

ring B represents:

aryl or heteroaryl;

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

a hydrogen atom,

carbamoyl,

cyano,

a halogen atom,

C_{1-6} alkyl optionally substituted with one hydroxy, halo C_{1-6} alkyl,

C_{1-6} alkoxy optionally substituted with one hydroxy, halo C_{1-6} alkoxy,

C_{1-6} alkylcarbonyl,

C_{1-6} alkylcarbonylamino,

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,

C_{1-6} alkylsulfonyl, or

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,

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:

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; and

R^C is:

the formula -OH, the formula -NH_2,

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 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 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 atom and optionally further containing one heteroatom are optionally crosslinked with C_{1-4} alkanediyl.

2. The substituted polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein

W^C is:

a single bond,

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,

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 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:

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:

a hydrogen atom,

carbamoyl,

cyano,

a halogen atom,

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,

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

R^C is:

the formula -OH, the formula -NH_2,

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,

azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl, wherein the azetidinyl, 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 azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl are optionally crosslinked with C_{1-4} 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;

ring B is phenyl;

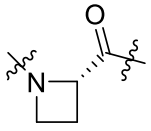
$L^{1"}$ is one group selected from the group consisting of:

a single bond,

Gly, (N-Me)Gly,

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

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,

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

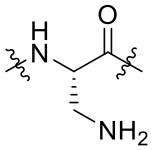
Cys, (d)-Cys, Met, (N-Me)Met,

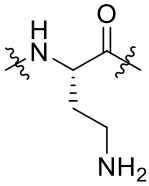
(N-Me)Asp, Glu, (N-Me)Glu, (d)-Glu,

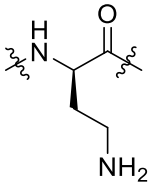
Asn, (N-Me)Asn, (d)-Asn, Gln, (N-Me)Gln, (d)-Gln,

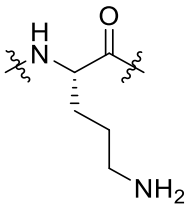
Arg, (N-Me)Arg, (d)-Arg, Cit, (d)-Cit,

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

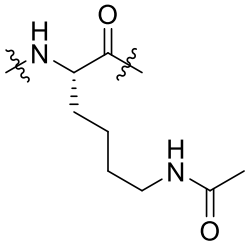
 [IV-7],

 [IV-9],

 [IV-10],

 [IV-13]

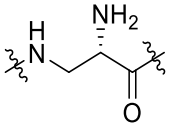
Lys, (N-Me)Lys, (d)-Lys, a group represented by formula [IV-14]:

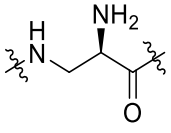
 [IV-14]

β-Ala,

β-Asp, β-(d)-Asp, and

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

 [III-6],

 [III-7]; and

W^C is:

a single bond,

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,

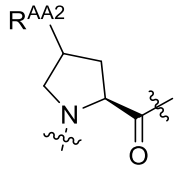
Lys-(d)-Lys-(d)-Lys, (d)-Lys-Lys-(d)-Lys, (d)-Lys-(d)-Lys-Lys,

β-Ala-(d)-Lys, β-Ala-(d)-Lys-(d)-Arg,

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

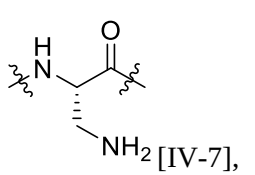
5. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein in the substituted polypeptide represented by formula [I'], AA^2 is one group selected from the group consisting of:

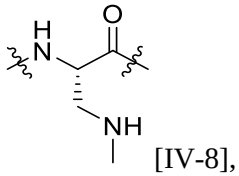
a group represented by formula [II-1]:

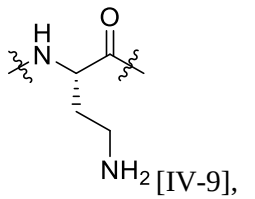

[II-1]

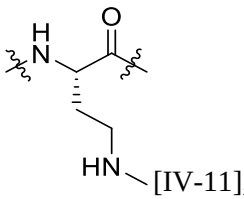
and

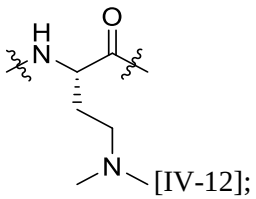
a group represented by any of formulas [IV-7], [IV-8], [IV-9], [IV-11], and [IV-12]:


[IV-7],


[IV-8],


[IV-9],


[IV-11],


[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, Pro, (d)-Pro, or β-homoPro;

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

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

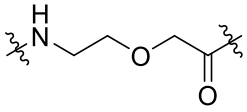
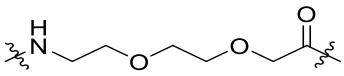
6. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein in the substituted polypeptide represented by formula [I'],

W^1 is $-L^{1'}-L^{1''}-$;

L^2 is a single bond;

AA^1 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]:

 [IV-23],  [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-;

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. 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'],

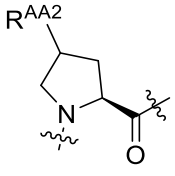
W^1 is $-L^1-$, wherein L^1 is a single bond;

L^2 is a single bond;

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

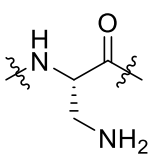
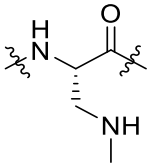
AA^2 is one group selected from the group consisting of:

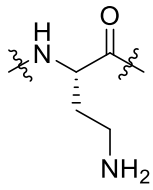
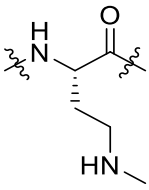
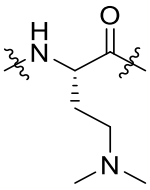
a group represented by formula [II-1]:

 [II-1]

and

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

 [IV-7],  [IV-8],

 [IV-9],  [IV-11],  [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;

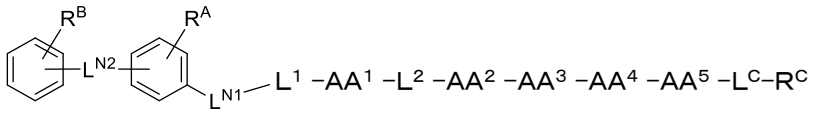
L^{N1} is the formula -C(=O)- or the formula $-S(=O)_2-$;

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.

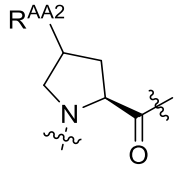
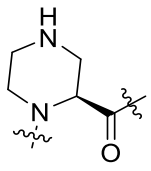
8. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein the substituted polypeptide represented by formula [I'] is a substituted polypeptide represented by formula [I]:

 [I]

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]:

 [II-1],  [II-2]

wherein R^{AA2} is hydroxy or amino;

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;

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;

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

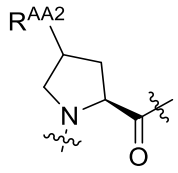
R^C is the formula -OH or the formula $-NH_2$.

9. 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'],

AA^1 is Asp, β-(d)-Asp, or γ-(d)-Glu;

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

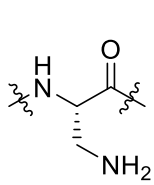
a group represented by formula [II-1]:



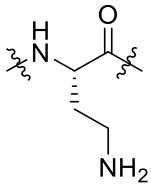
[II-1]

and

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



[IV-7],



[IV-9]

wherein R^{AA2} is amino;

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,

$L^{1'}$ 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-;

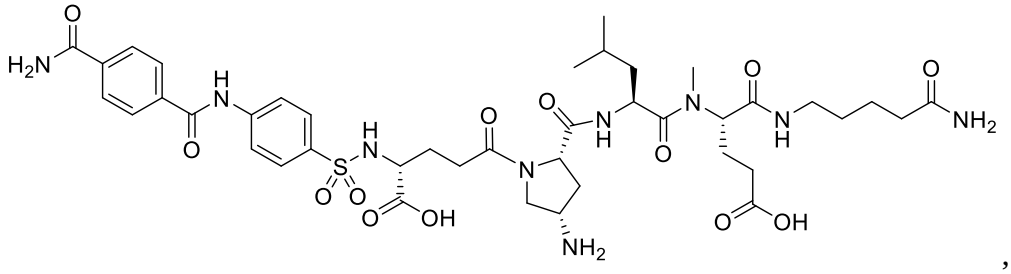
R^{A1} and R^{A2} are each a hydrogen atom;

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;

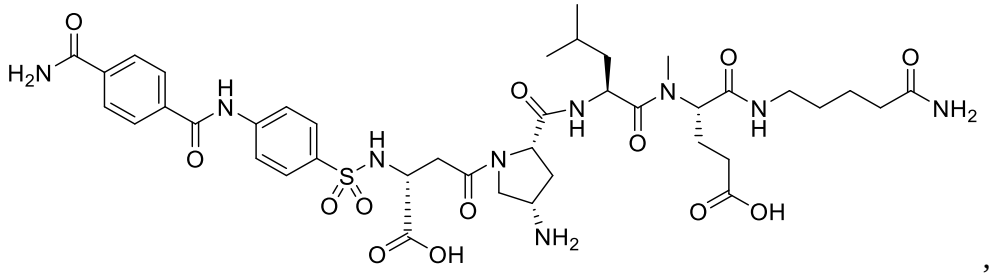
W^C is a single bond or (d)-Lys; and

R^C is the formula -NH_2.

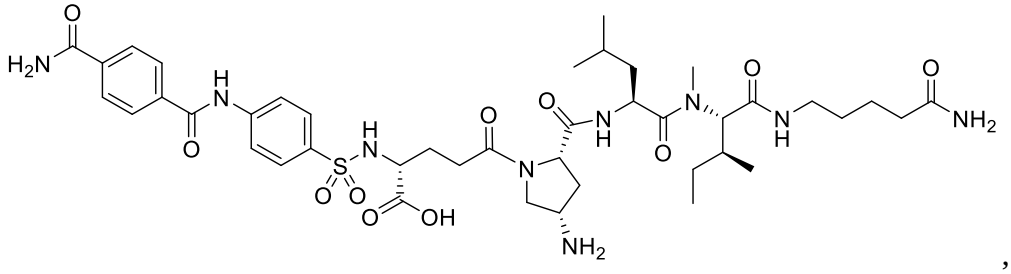
10. The substituted polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein the substituted polypeptide is selected from compounds shown in the following:



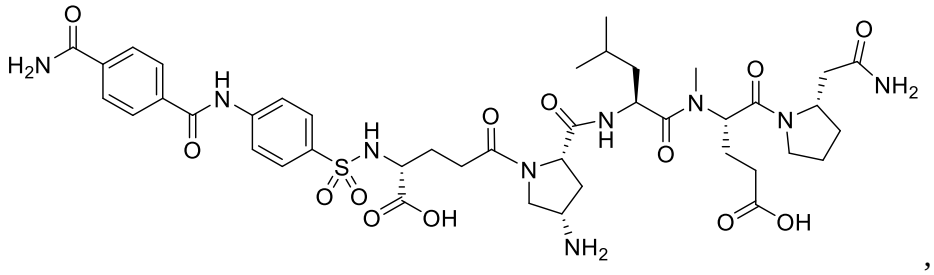
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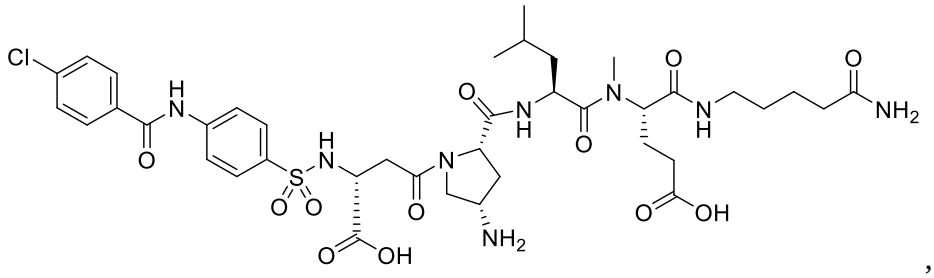
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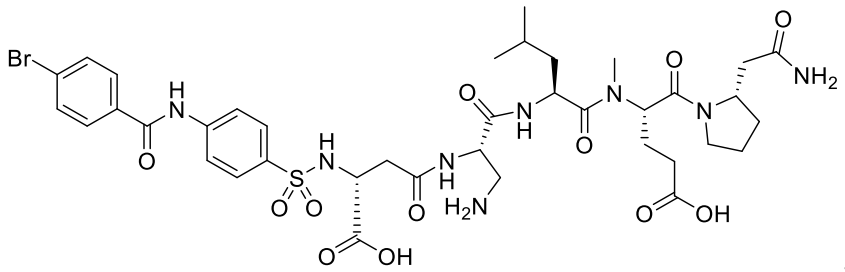
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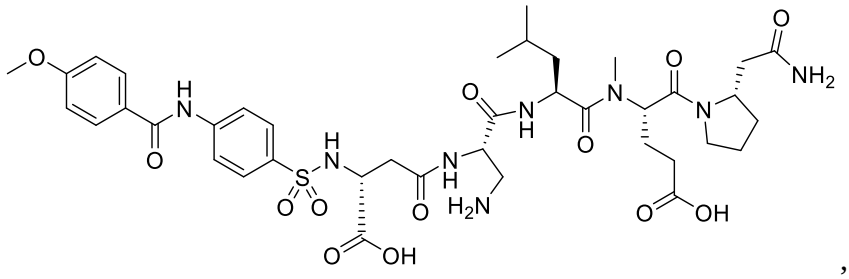
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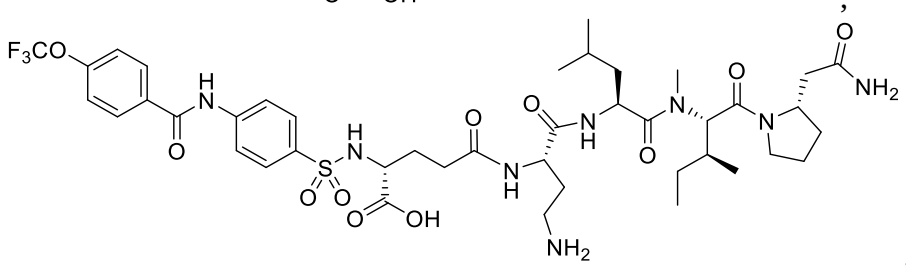
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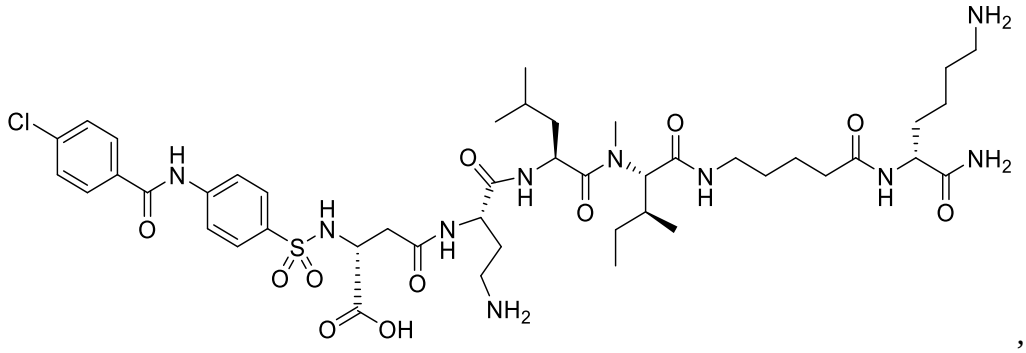
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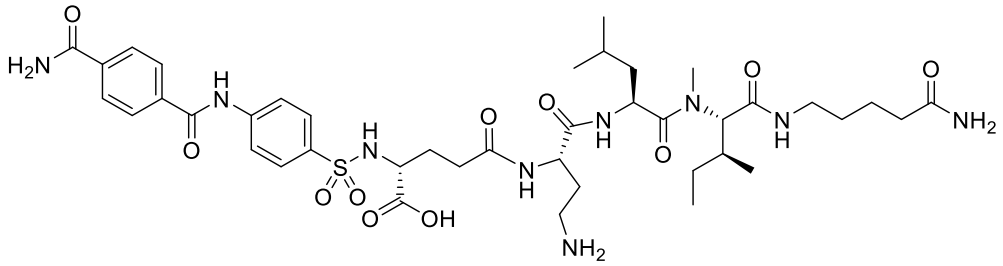
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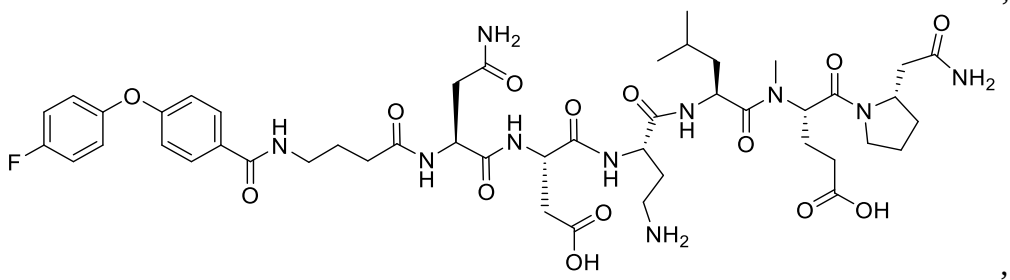


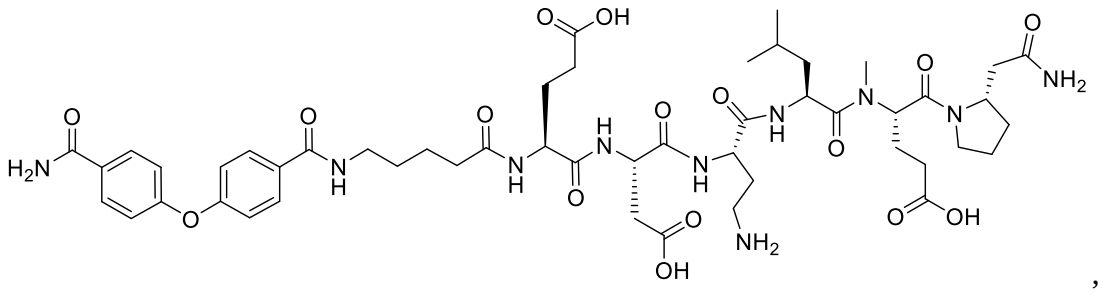
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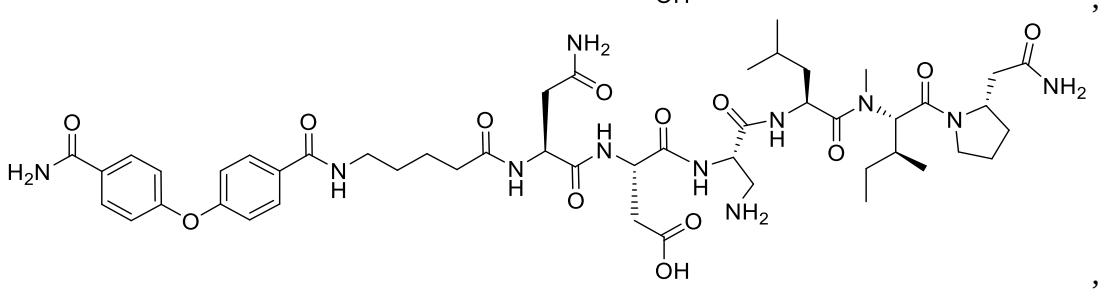


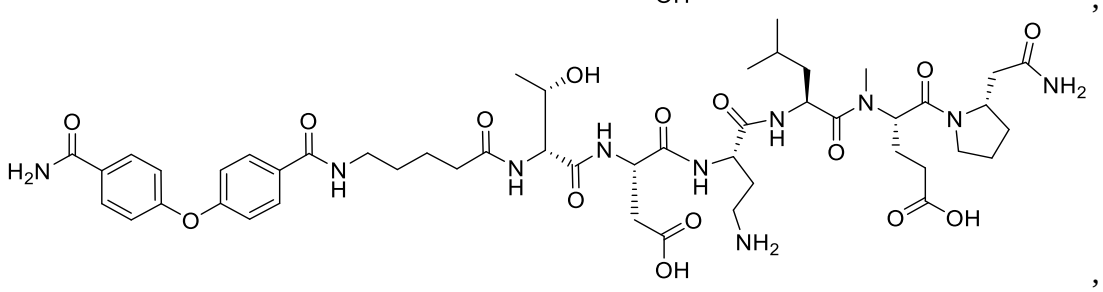
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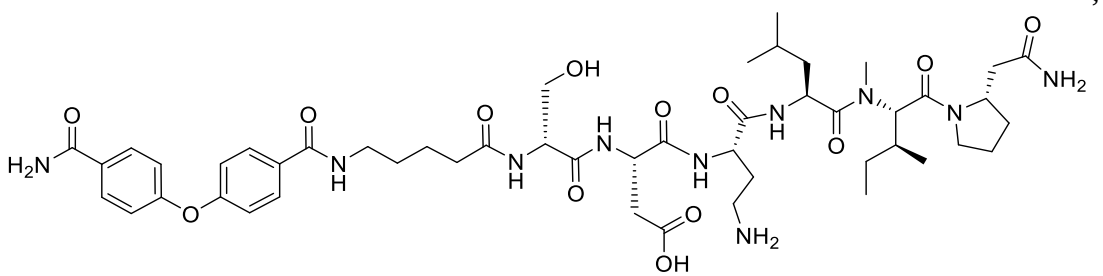

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11. A pharmaceutical comprising the substituted polypeptide or pharmaceutically

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 use in 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 claims 1 to 10 as an active ingredient.

14. Use of substituted polypeptide or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10 as an active ingredient, in the manufacture of a medicament for preventing or treating cancerous disease or organ fibrosis, or a symptom associated with cancerous disease or organ fibrosis.