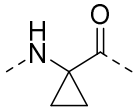
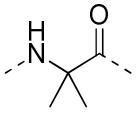
CLAIMS

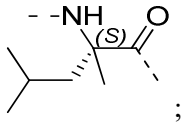
1. A polypeptide compound having a modified structure, or a pharmaceutically acceptable salt thereof, wherein a sequence of the polypeptide is as shown in Formula Z:

$X_5X_0X_6GT\ X_aTSDY\ SX_bX_1X_7X_8\ KX_9X_{10}X_{11}X_0\ X_4FX_{12}X_{13}X_{14}\ X_cX_dX_{15}GG\ PSSGA\ PPPS_0$

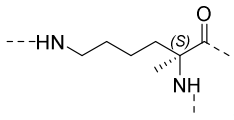
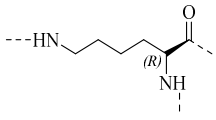
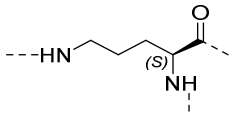
Formula Z

wherein:

X_0 is independently selected from the group consisting of , Aib, and alanine (Ala, A), with the structure of Aib being ;

X_1 is selected from the group consisting of α-methyl-substituted leucine (α-MeLeu, α-MeL), tyrosine (Tyr, Y), and Aib, with the structure of α-MeL being ;

X_4 is selected from the group consisting of α-methyl-substituted lysine (α-MeLys, α-MeK), D-lysine (d-K), L-ornithine (L-Orn), alanine (Ala, A), lysine (Lys, K), glutamic acid (Glu, E), and leucine (Leu, L);

with the structure of α-methyl-substituted lysine being , the structure of D-lysine (d-K) being , and the structure of L-ornithine (L-Orn) being ;

X_5 is selected from the group consisting of tyrosine (Tyr, Y) and histidine (His, H);

X_6 is selected from the group consisting of glutamine (Gln, Q) and histidine (His, H);

X_7 is selected from the group consisting of leucine (Leu, L) and lysine (Lys, K);

X_8 is selected from the group consisting of aspartic acid (Asp, D) and glutamic acid (Glu, E);

X_9 is selected from the group consisting of lysine (Lys, K), glutamine (Gln, Q) and glutamic acid (Glu, E);

X_{10} is selected from the group consisting of alanine (Ala, A) and tyrosine (Tyr, Y);

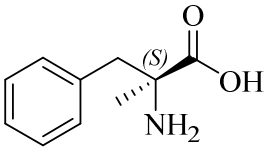
X_{11} is selected from the group consisting of lysine (Lys, K), glutamine (Gln, Q) and alanine (Ala, A);

X_{12} is selected from the group consisting of valine (Val, V) and isoleucine (Ile, I);

X_{13} is selected from the group consisting of lysine (Lys, K), glutamine (Gln, Q) and glutamic acid (Glu, E);

X_{14} is selected from the group consisting of lysine (Lys, K), tryptophan (Trp, W), tyrosine (Tyr, Y), glutamic acid (Glu, E) and phenylalanine (Phe, F);

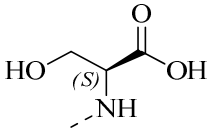
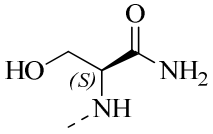
X_{15} is selected from the group consisting of lysine (Lys, K) and glutamic acid (Glu, E);

X_a is selected from the group consisting of phenylalanine (Phe, F) and α-methyl-substituted phenylalanine (α-MePhe, α-MeF), with the structure of α-methyl-substituted phenylalanine being ;

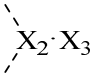
X_b is selected from the group consisting of lysine (Lys, K) and isoleucine (Ile, I);

X_c is selected from the group consisting of leucine (Leu, L) and phenylalanine (Phe, F);

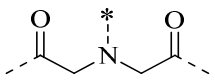
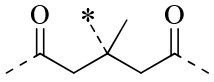
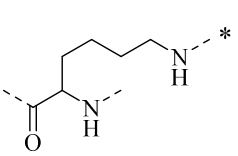
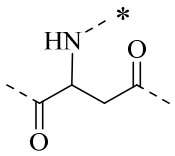
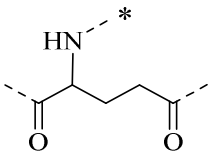
X_d is selected from the group consisting of leucine (Leu, L) and isoleucine (Ile, I);

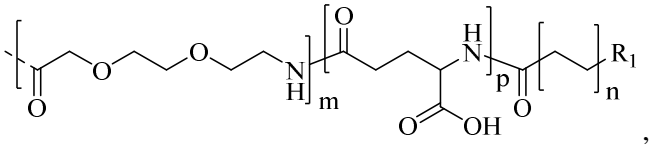
S_0 is selected from the group consisting of  and ;

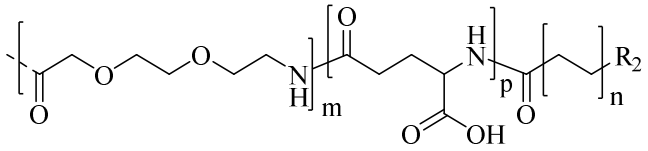
and the polypeptide compound has the following modifications:

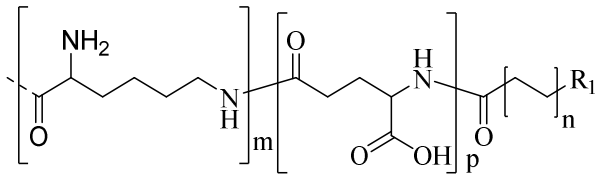
1) side chains of amino acids at positions i and i+j in the sequence are connected by a structural unit  to form a stapled body, where i is selected from the group consisting of 12, 14, 16, 17, 19, 21, 24 and 25, and j is selected from the group consisting of 2, 3, 4, 5 and 7,

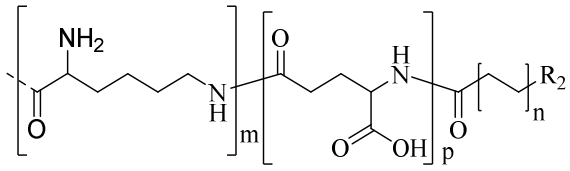
2) the stapled body is formed by the condensation connection of amino or carboxyl groups on the side chains of the two amino acids to the structural unit ;

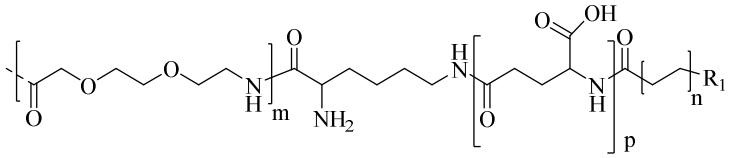
X_2 is selected from the group consisting of , , ,  and ; where, "*" indicates a position connected to X_3, and two ends are positions connected to the corresponding amino or carboxyl groups in the modified amino acids;

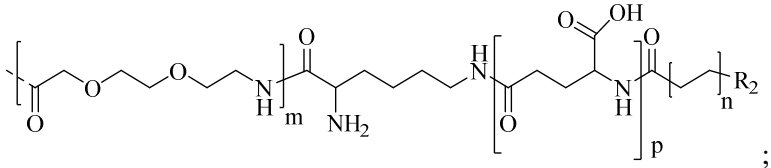
X_3 is selected from the group consisting of ,

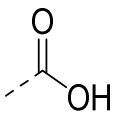
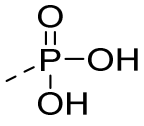

,


,


,


, and


;

R_1 and R_2 are independently selected from the group consisting of  and ;

m is independently selected from the group consisting of 1, 2 and 3; p is independently selected from the group consisting of 1 and 2; and n is independently selected from the group consisting of 8, 9 and 10.

2. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the sequence of the polypeptide is as shown in Formula Z-3:

$X_5X_0X_6$GT FTSDY SI$X_1X_7X_8$ K$X_9X_{10}X_{11}X_0$ X_4F$X_{12}X_{13}X_{14}$ LLX_{15}GG PSSGA PPPS_0

Formula Z-3

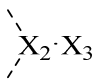
wherein:

X_1 is selected from the group consisting of α-methyl-substituted leucine (α-MeLeu, α-MeL) and tyrosine (Tyr, Y);

X_4 is selected from the group consisting of α-methyl-substituted lysine (α-MeLys, α-MeK), D-lysine (d-K), L-ornithine (L-Orn), alanine (Ala, A), lysine (Lys, K) and glutamic acid (Glu, E);

X_0, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, and S_0 are as defined in claim 1;

and the polypeptide compound has the following modifications:

1) the side chains of the amino acids at positions i and i+j in the sequence are connected by the structural unit  to form the stapled body, wherein i is selected from the group consisting of 14, 17,

19, 21, 24 and 25, and j is selected from the group consisting of 3, 4, 5 and 7,

2) the stapled body is formed by the condensation connection of the amino or carboxyl groups on the side chains of the two amino acids to the structural unit ;

X_2, X_3, R_1, R_2, m, p, and n are as defined in claim 1.

3. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the sequence of the polypeptide is as shown in Formula Z-4:

$YX_0QGT\ FTSDY\ SX_bX_1LD\ KKAQX_0\ X_4FX_{12}X_{13}X_{14}\ X_cX_dX_{15}GG\ PSSGA\ PPPS_0$

Formula Z-4

wherein:

X_1 is selected from the group consisting of α-methyl-substituted leucine (α-MeLeu, α-MeL) and tyrosine (Tyr, Y);

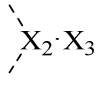
X_4 is selected from the group consisting of alanine (Ala, A) and lysine (Lys, K);

X_{13} is selected from the group consisting of lysine (Lys, K) and glutamic acid (Glu, E);

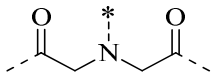
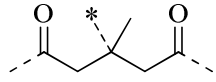
X_{14} is selected from the group consisting of lysine (Lys, K) and phenylalanine (Phe, F);

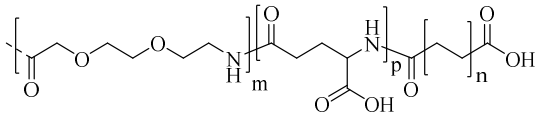
X_0, X_{12}, X_{15}, X_b, X_c, X_d, and S_0 are as defined in claim 1;

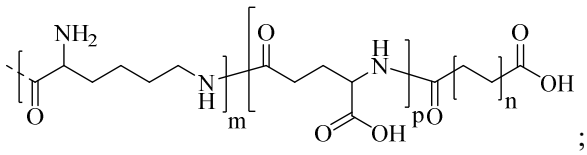
and the polypeptide compound has the following modifications:

1) the side chains of the amino acids at positions i and i+j in the sequence are connected by the structural unit  to form the stapled body, where i is selected from the group consisting of 12, 17, 21 and 25, and j is selected from the group consisting of 3, 4 and 7,

2) the stapled body is formed by the condensation connection of the amino or carboxyl groups on the side chains of the two amino acids to the structural unit ;

X_2 is selected from the group consisting of  and ; where, "*" indicates a position connected to X_3, and two ends are positions connected to the corresponding amino or carboxyl groups in the modified amino acids;

X_3 is selected from the group consisting of  and


;

m is independently selected from the group consisting of 1, 2 and 3; p is independently selected from the group consisting of 1 and 2; and n is independently selected from the group consisting of 8, 9 and 10.

4. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the sequence of the polypeptide is as shown in Formula Z-5:

$YX_0QGT\ X_aTSDY\ SIX_1KD\ KKAQX_0\ X_4FIX_{13}Y\ LLX_{15}GG\ PSSGA\ PPPS_0$

Formula Z-5

wherein:

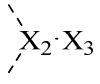
X_1 is α-methyl-substituted leucine (α-MeLeu, α-MeL);

X_4 is selected from the group consisting of alanine (Ala, A), lysine (Lys, K), glutamic acid (Glu, E) and leucine (Leu, L);

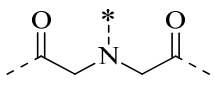
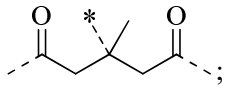
X_{13} is selected from the group consisting of glutamine (Gln, Q) and glutamic acid (Glu, E);

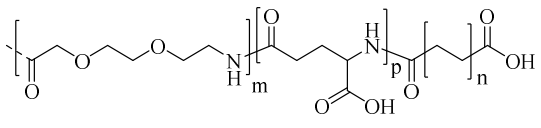
X_0, X_{15}, X_a, and S_0 are as defined in claim 1;

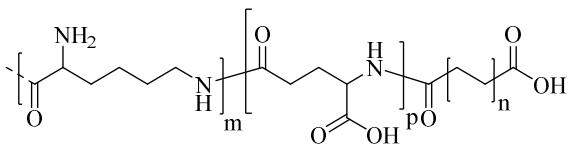
and the polypeptide compound has the following modifications:

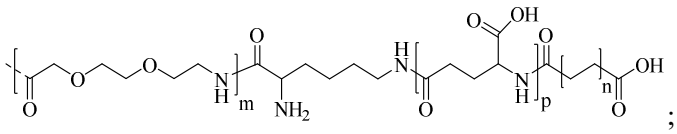
1) the side chains of the amino acids at positions i and i+j in the sequence are connected by the structural unit  to form the stapled body, where i is 14, and j is 3,

2) the stapled body is formed by the condensation connection of the amino or carboxyl groups on the side chains of the two amino acids to the structural unit ;

X_2 is selected from the group consisting of  and ; where, "*" indicates a position connected to X_3, and two ends are positions connected to the corresponding amino or carboxyl groups in the modified amino acids;

X_3 is selected from the group consisting of 


and


;

m is independently selected from the group consisting of 1, 2 and 3; p is independently selected from the group consisting of 1 and 2; and n is independently selected from the group consisting of 8, 9 and 10.

5. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein the amino acid X_0 at position 2 in the polypeptide sequence is Aib, and/or the amino acid X_0 at position 20 in the polypeptide sequence is Aib or A.

6. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein the sequence is selected from the group consisting of

YAibQGT FTSDY SI*α-MeL*LD KKAQAib KFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 1),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib AFIKW LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 2),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib AFIEK LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 3),

HAibHGT FTSDY SIYLE KKYAAib EFVKW LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 4),

HAibHGT FTSDY SIYLE KKYAAib KFVQW LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 5),

YAibQGT FTSDY SIX_1LD KKAQAib AFIQK LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 6),

YAibQGT FTSDY SIX_1LD KQAQAib AFIEK LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 7),

YAibQGT FTSDY SIX_1LD KEAQAib AFIEK LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 8),

HAibQGT FTSDY SIX_1LD KKAQAib AFIEK LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 9),

YAibQGT FTSDY SIX_1LD KKYQAib AFIEK LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 10),

YAibQGT FTSDY SIX_1LE KKAQAib AFIEK LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 11),

HAibHGT FTSDY SIYLE KKYAAib EFVQE LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 12),

YAibQGT FTSDY SIX_1LD KKAQAib AFIEE LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 13),

YAibQGT FTSDY SIX_1LD KKAQAib AFIEW LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 14),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib KFIEF LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 15),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib EFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 16),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib AFIKY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 17),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib KFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 18),

YAibQGT FTSDY SI*α-MeL*LD KKAKAib AFIKY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 19),

YAibQGT FTSDY SI*α-MeL*LD KKAQAib KFIEY LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 20),

YAibQGT FTSDY SI*α-MeL*LD KKAQA *α-MeK*FIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 21),

YAibQGT FTSDY SIα-*MeL*LD KKAQAib *d-K*FIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 22),

YAibQGT FTSDY SIα-*MeL*LD KKAQAib *L-Orn*FIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 23),

YAibQGT FTSDY SIα-*MeL*KD KKAQAib AFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 24),

YAibQGT FTSDY SIα-*MeL*LD KKAQAib KFIEF LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 25),

YAibQGT FTSDY SIα-*MeL*LD KKAQAib KFIEF LIEGG PSSGA PPPS-NH_2 (SEQ ID NO: 26),

YAibQGT FTSDY SIα-*MeL*LD KKAQAib KFVEF LIEGG PSSGA PPPS-NH_2 (SEQ ID NO: 27),

YAibQGT FTSDY SIα-*MeL*LD KKAQAib AFIEK FIKGG PSSGA PPPS-NH_2 (SEQ ID NO: 28),

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YAibQGT FTSDY SIAibLD KKAQAib KFIEF LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 30),

YAibQGT FTSDY SKα-*MeL*LD KKAQAib AFIEF LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 31),

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YAibQGT FTSDY SIα-*MeL*LD KKAQAib KFVEF LIKGG PSSGA PPPS-NH_2 (SEQ ID NO: 33),

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YAibQGT FTSDY SKα-*MeL*LD KKAQAib KFIEF LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 36),

YAibQGT FTSDY SIα-*MeL*KD KKAQAib EFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 37),

YAibQGT FTSDY SIα-*MeL*KD KKAQAib AFIEY LLKGG PSSGA PPPS-NH_2 (SEQ ID NO: 38),

YAibQGT FTSDY SIα-*MeL*KD KKAQAib AFIQY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 39),

YAibQGT FTSDY SIα-*MeL*KD KKAQAib KFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 40),

YAibQGT FTSDY SIα-*MeL*KD KKAQAib LFIEY LLEGG PSSGA PPPS-NH_2 (SEQ ID NO: 41),

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and

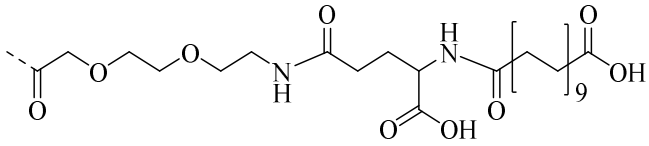
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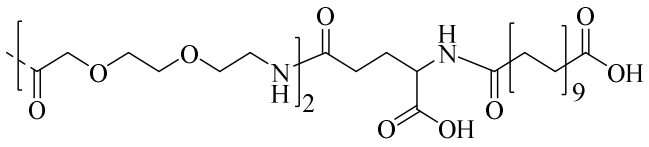
7. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 2, wherein i is 14, and j is 3; or i is 17, and j is 4; or i is 17, and j is 7; or i is 19, and j is 5; or i is 21, and j is 7; or i is 24, and j is 4; or i is 25, and j is 4.

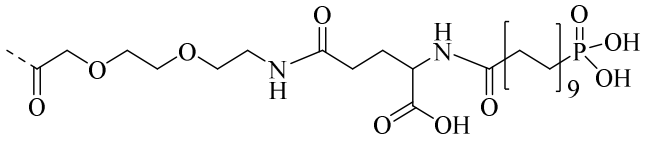
8. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 3, wherein i is 12, and j is 4; or i is 17, and j is 4; or i is 21, and j is 7; or i is 25, and j is 3.

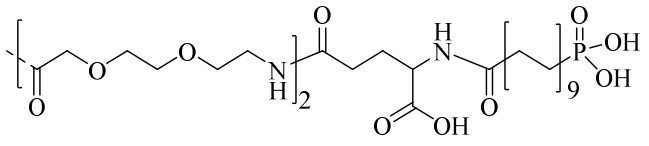
9. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein m is independently 1 or 2; and/or p is 1; and/or n is 9.

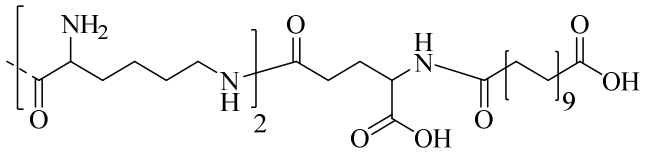
10. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein X_3 is selected from the group consisting of

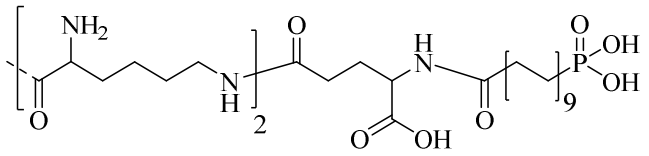

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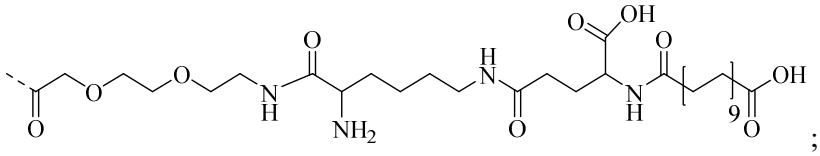

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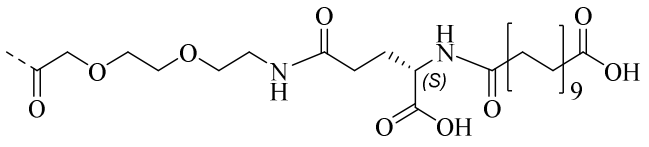

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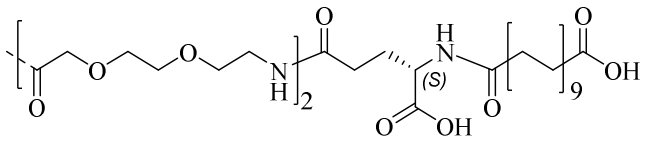

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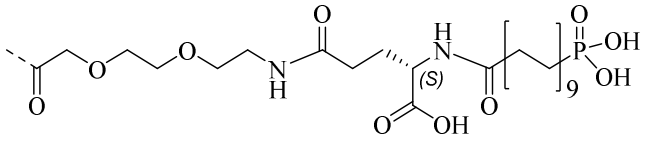

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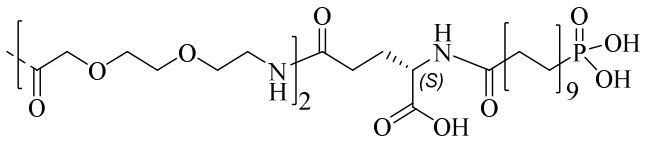

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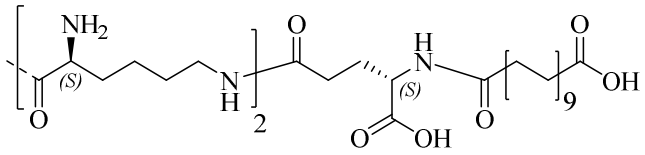
preferably, X_3 is selected from the group consisting of

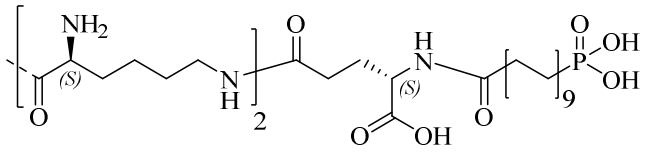

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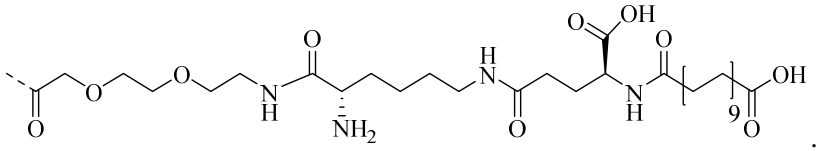

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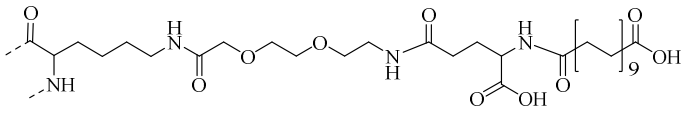

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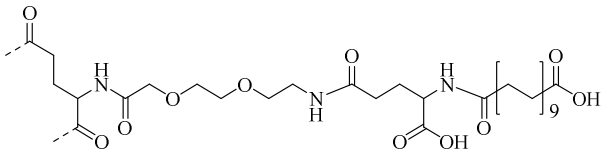

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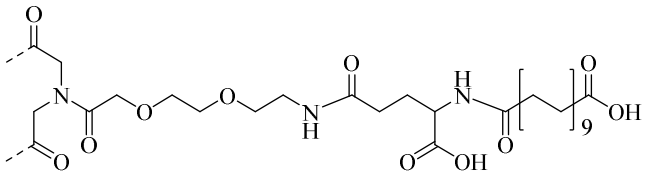

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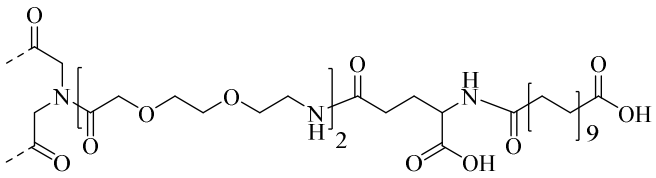

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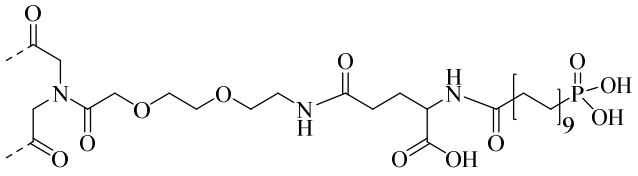
11. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein the structural unit  is selected from the group consisting of

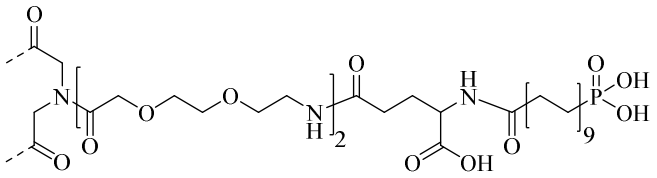

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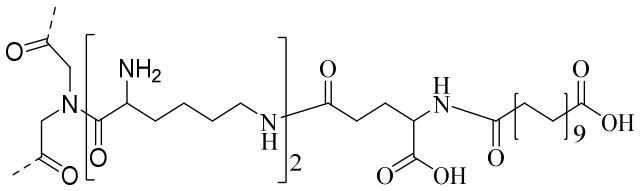

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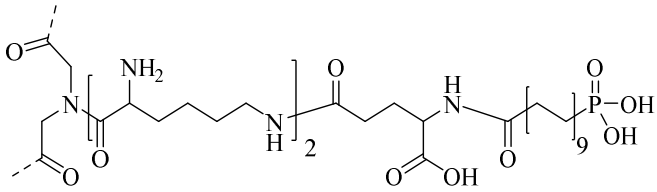

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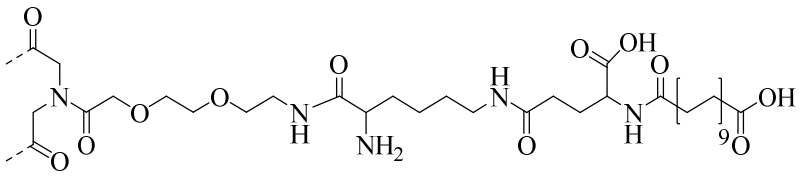

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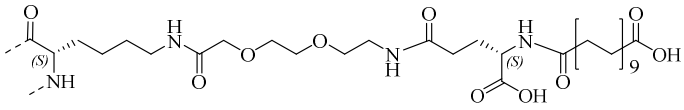

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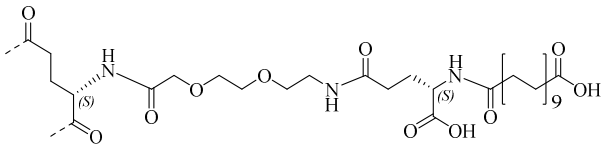

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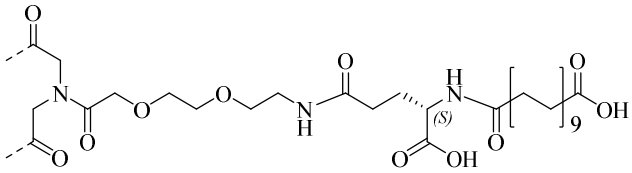

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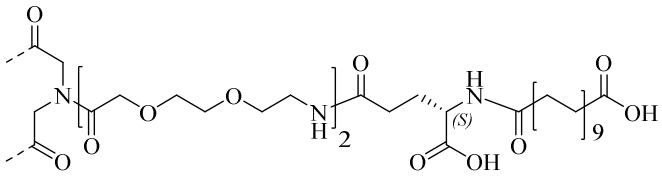

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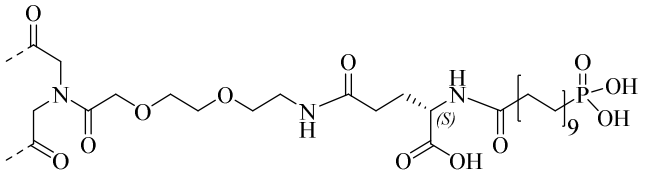
preferably, the structural unit  is selected from the group consisting of

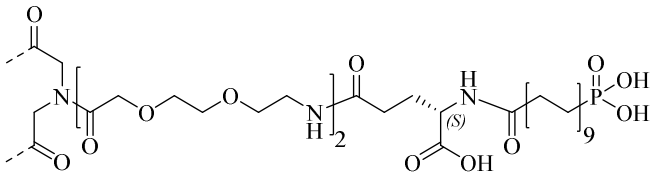

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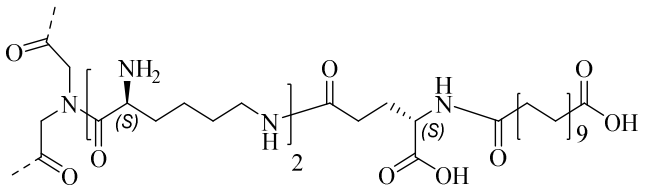

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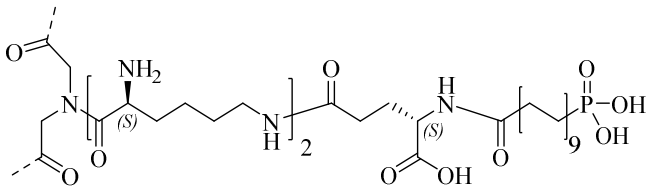

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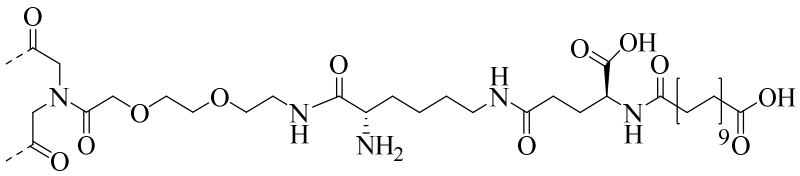

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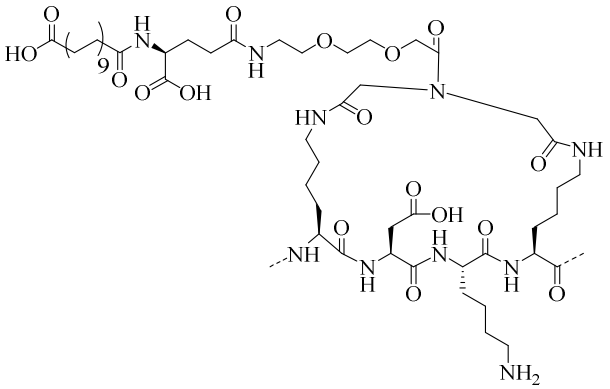

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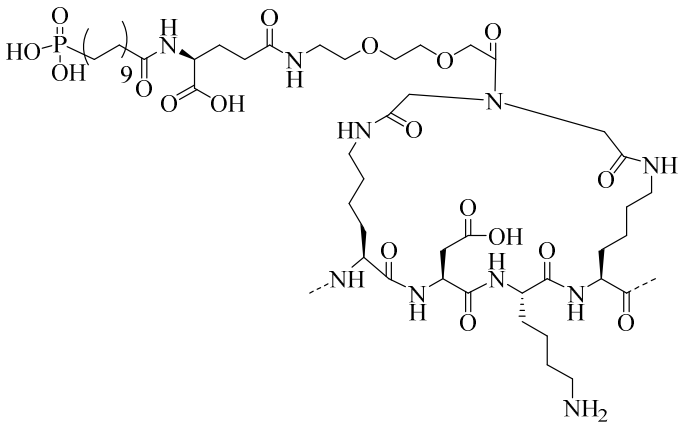

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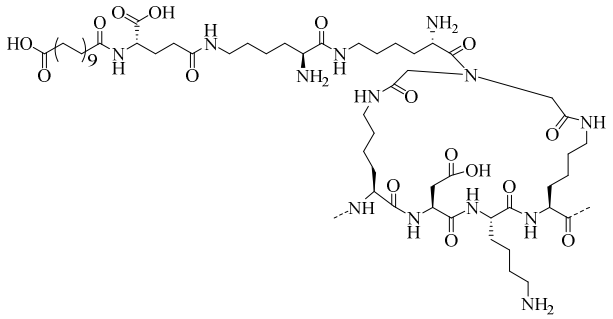

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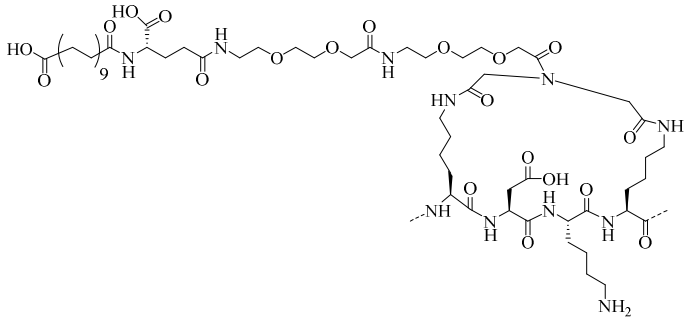
12. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 2, wherein a structure of the stapled body is selected from the group consisting of


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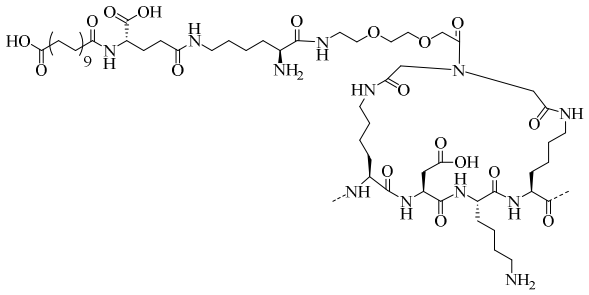

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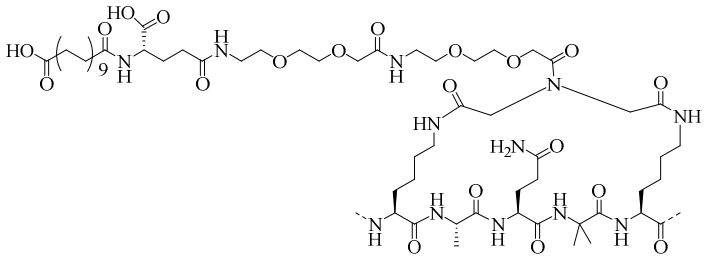
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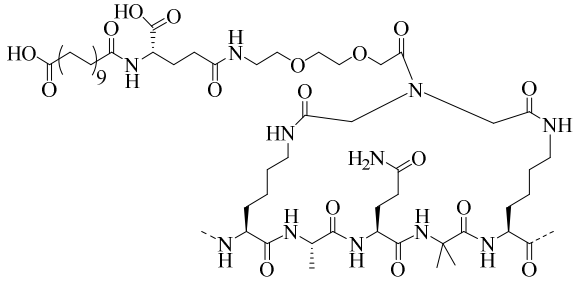
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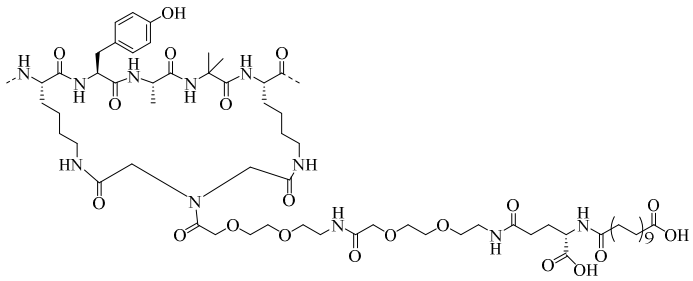
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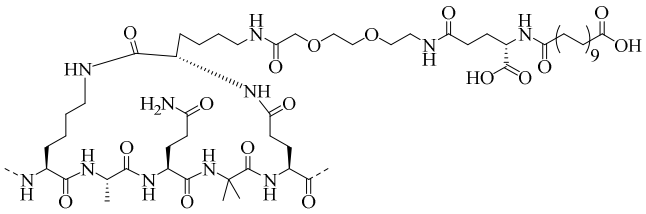
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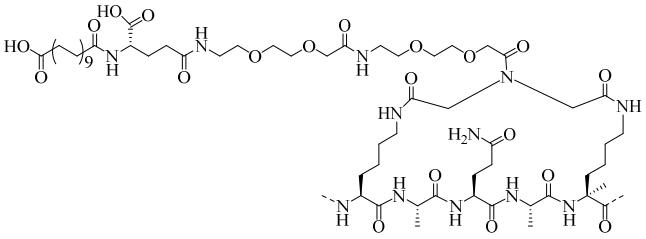


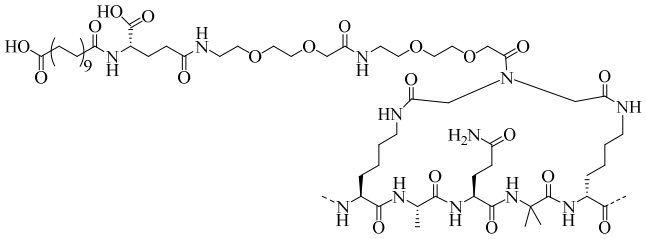
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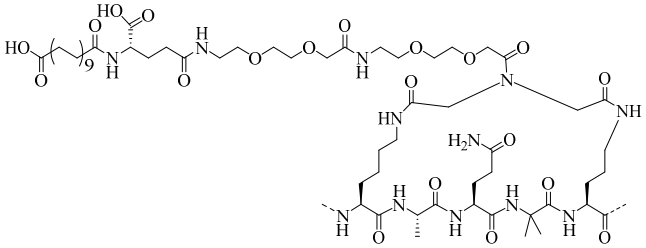


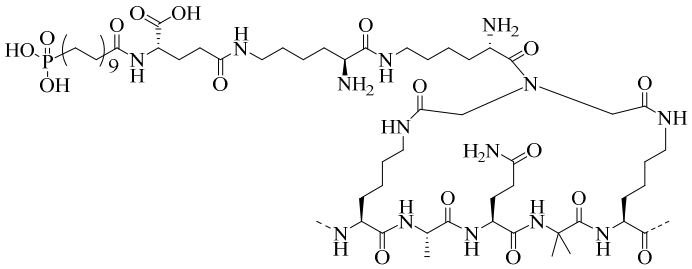
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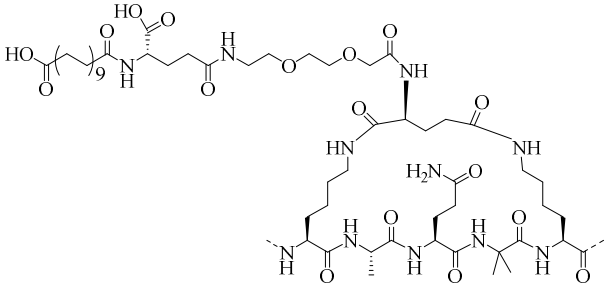

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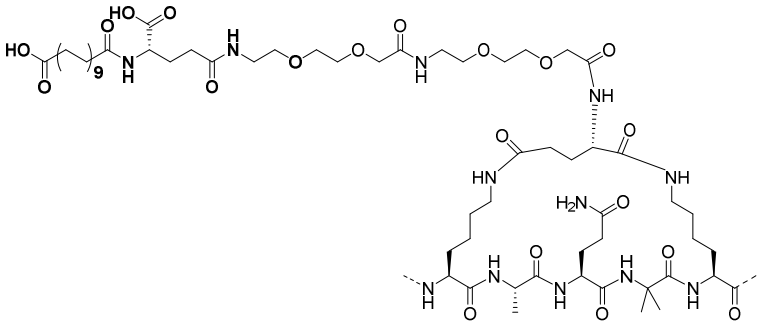

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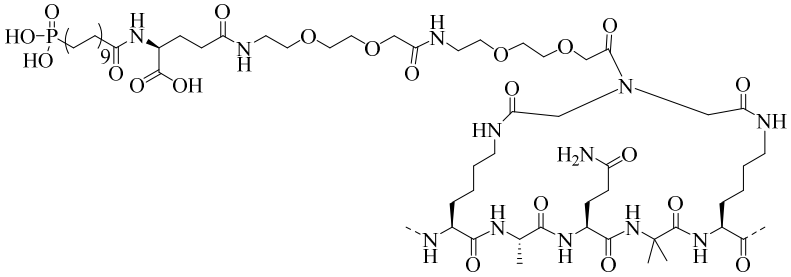

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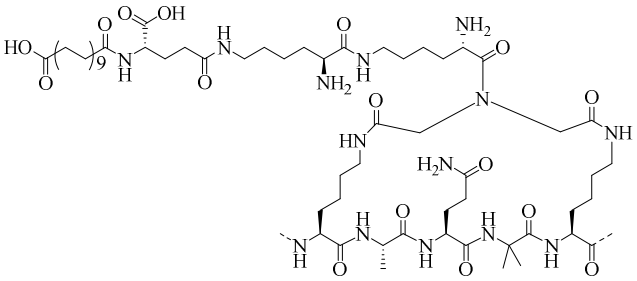

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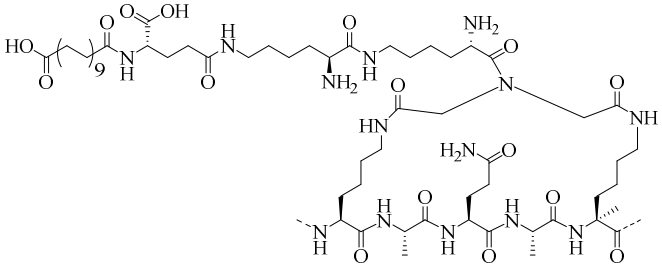

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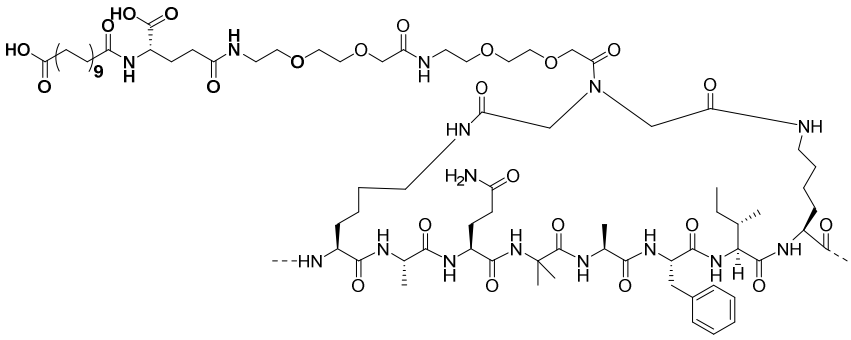

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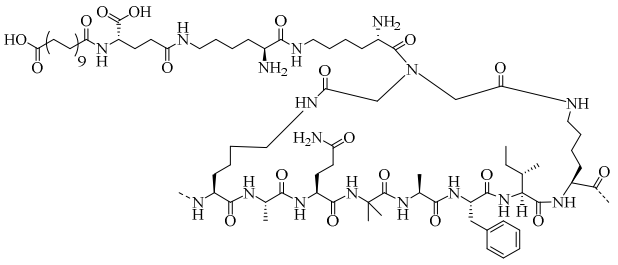

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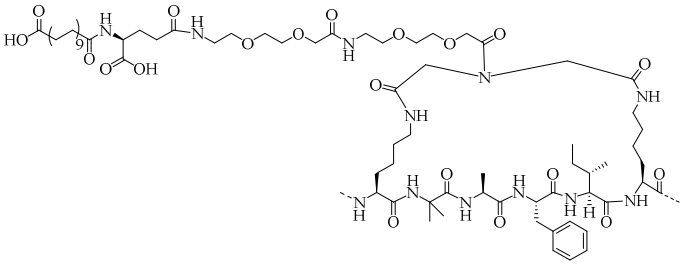

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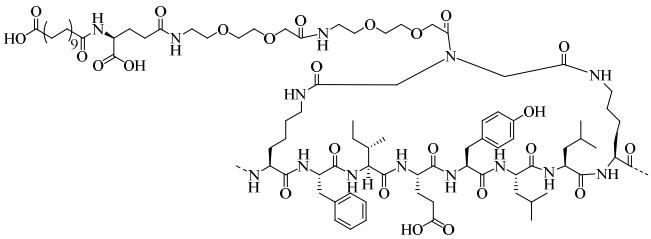

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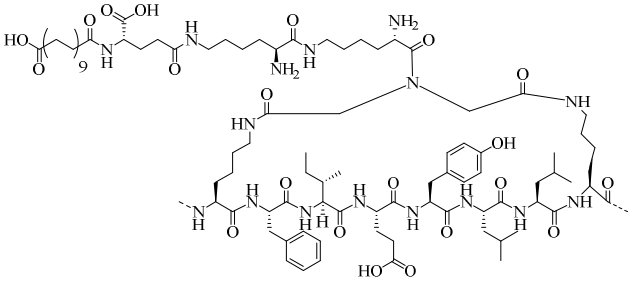

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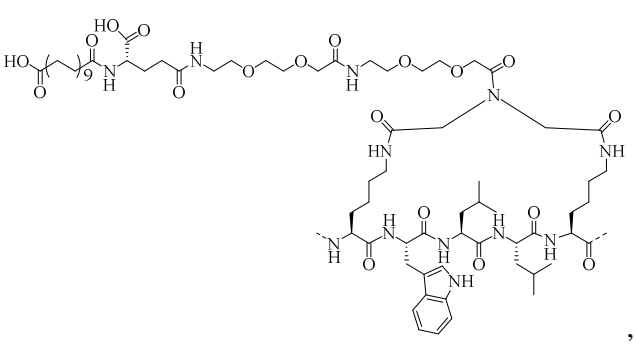
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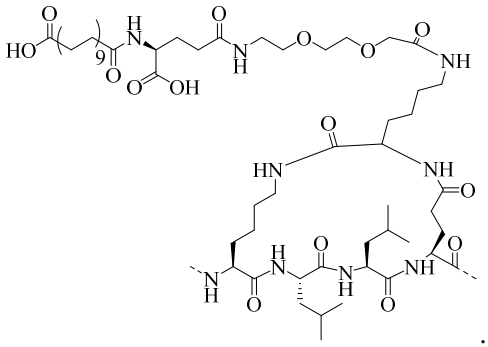
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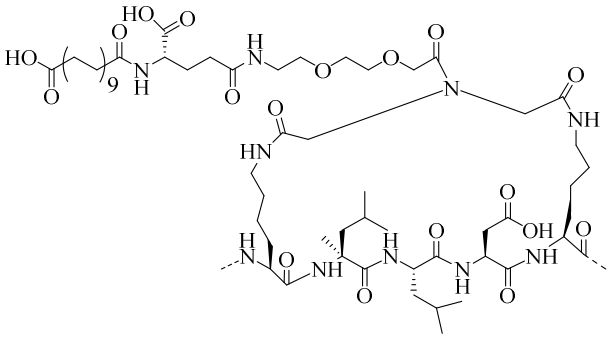


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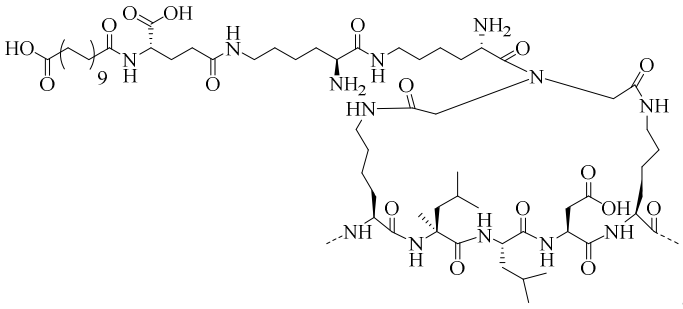


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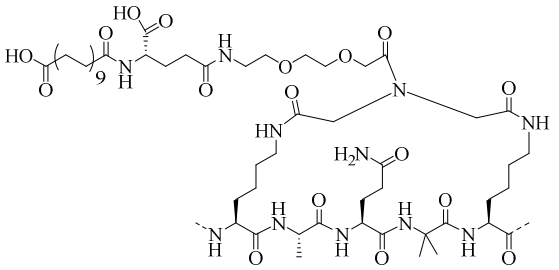
13. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 3, wherein a structure of the stapled body is selected from the group consisting of



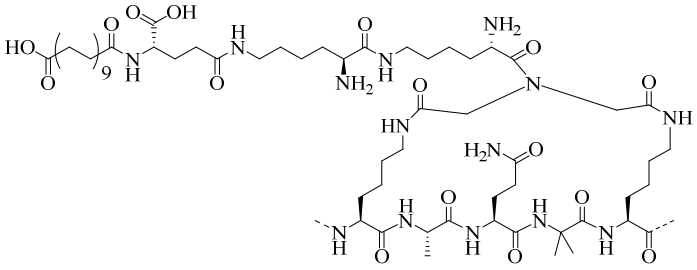
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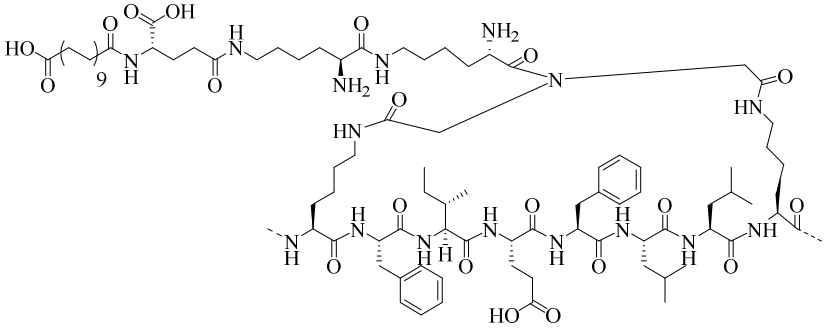
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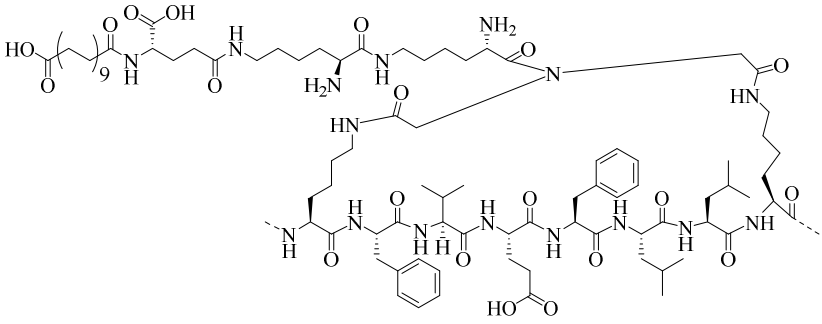
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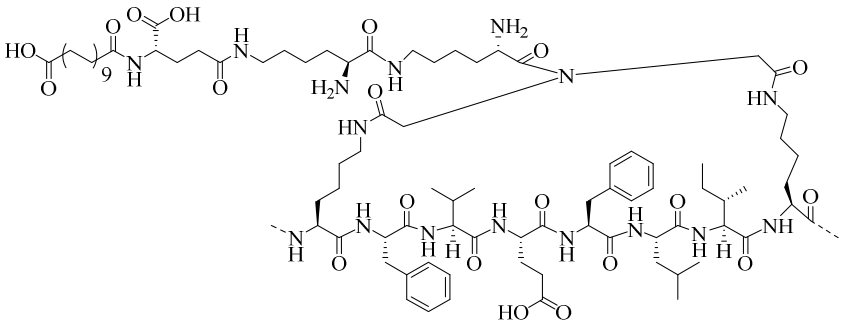
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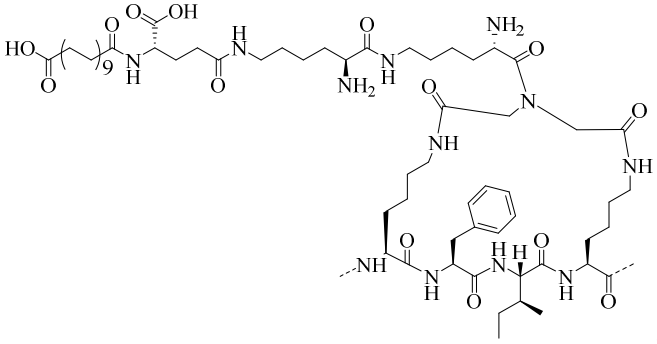
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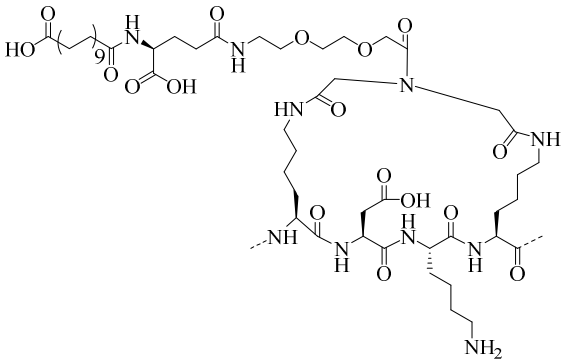


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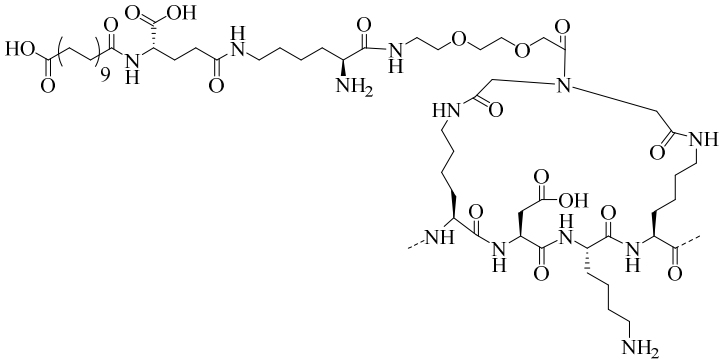


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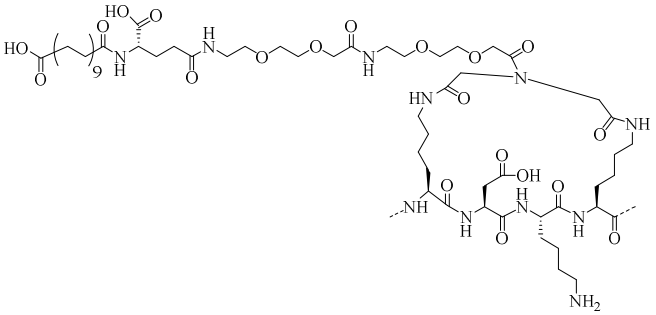
14. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 4, wherein a structure of the stapled body is selected from the group consisting of



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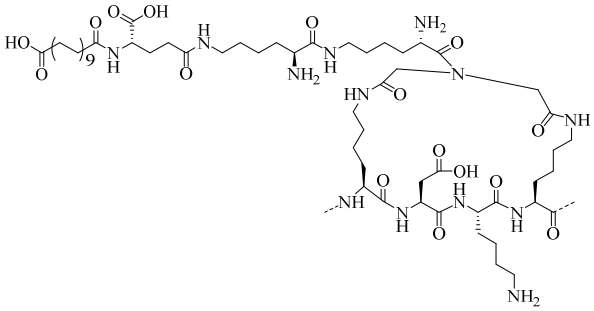


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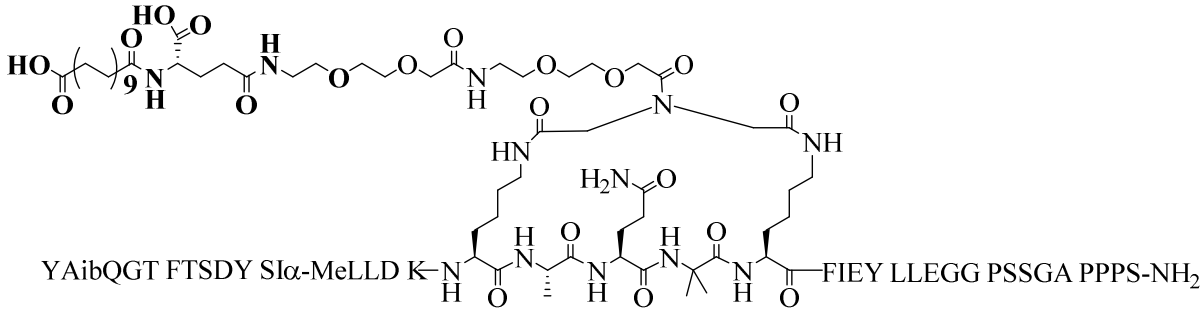
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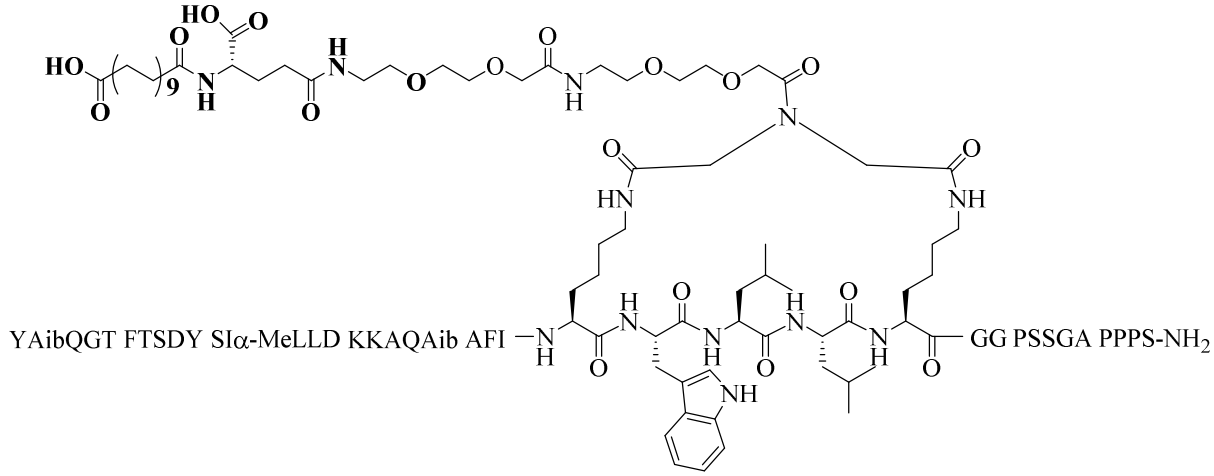


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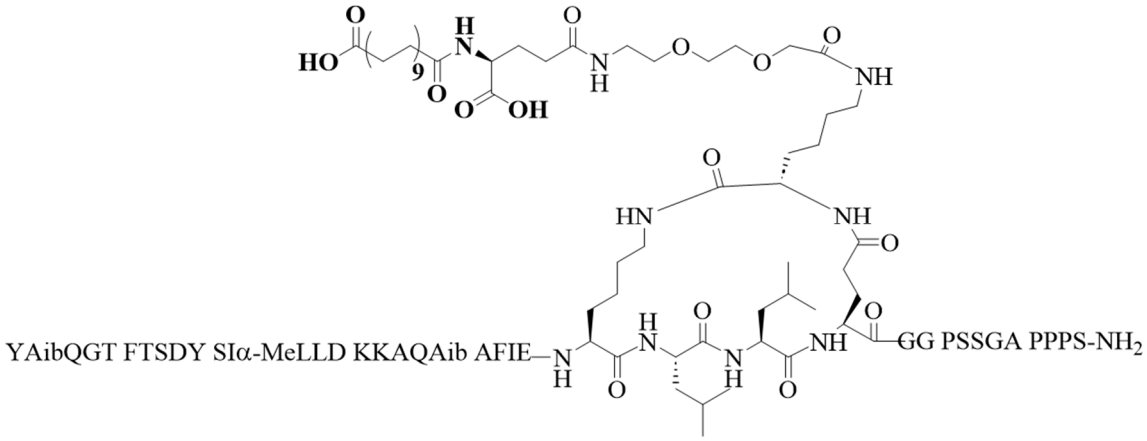
15. A polypeptide compound of a formula selected from the group consisting of



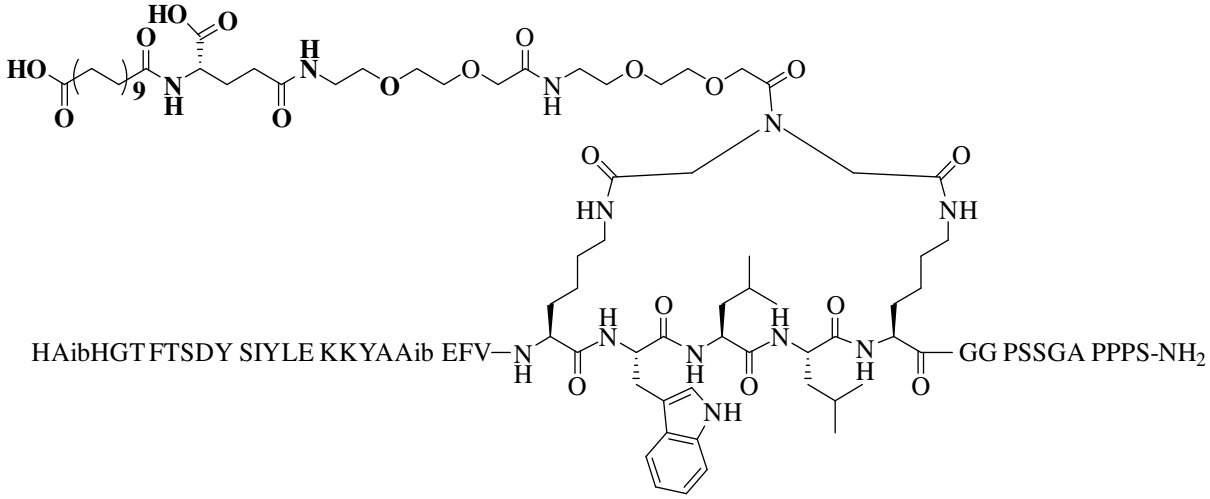
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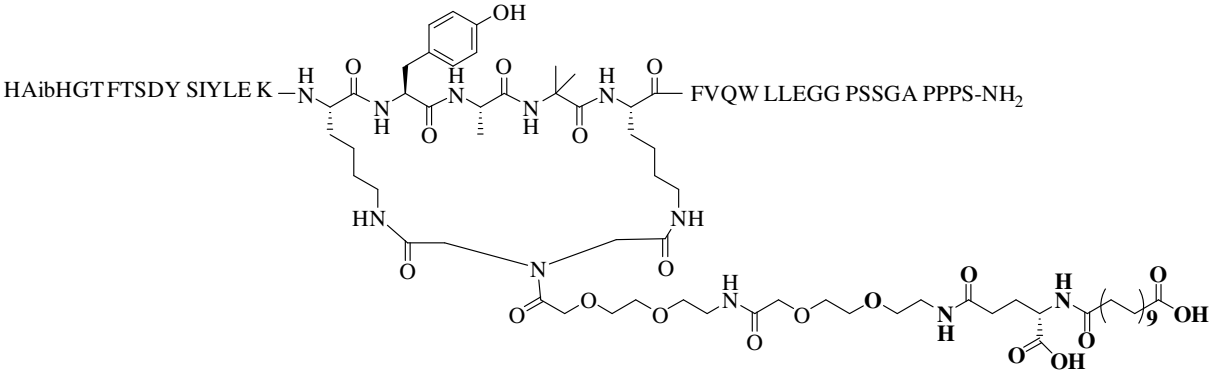
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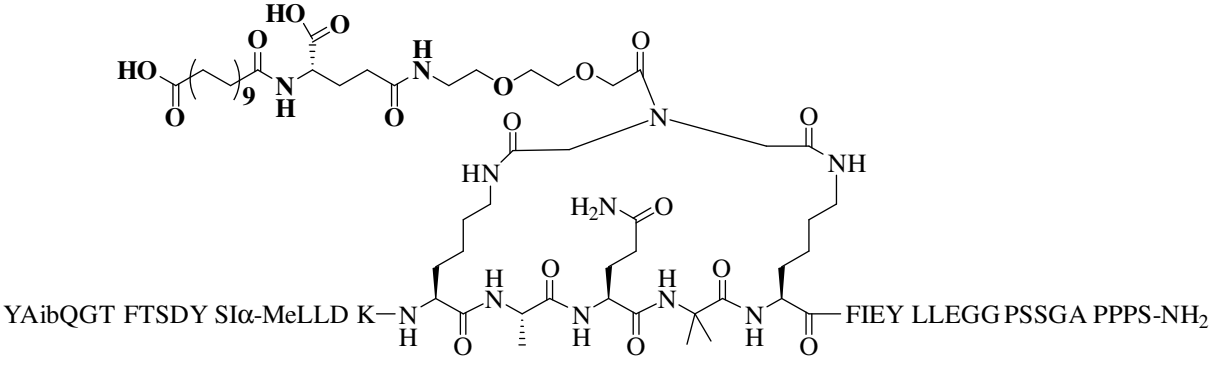
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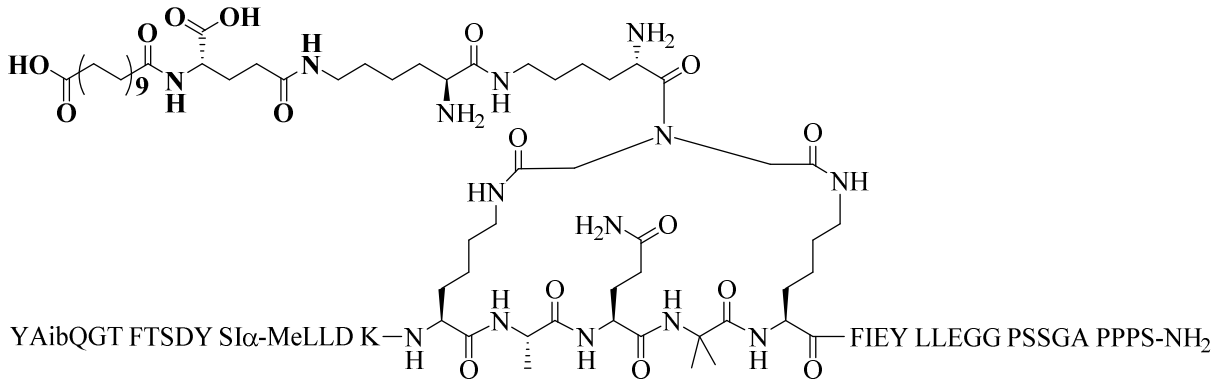
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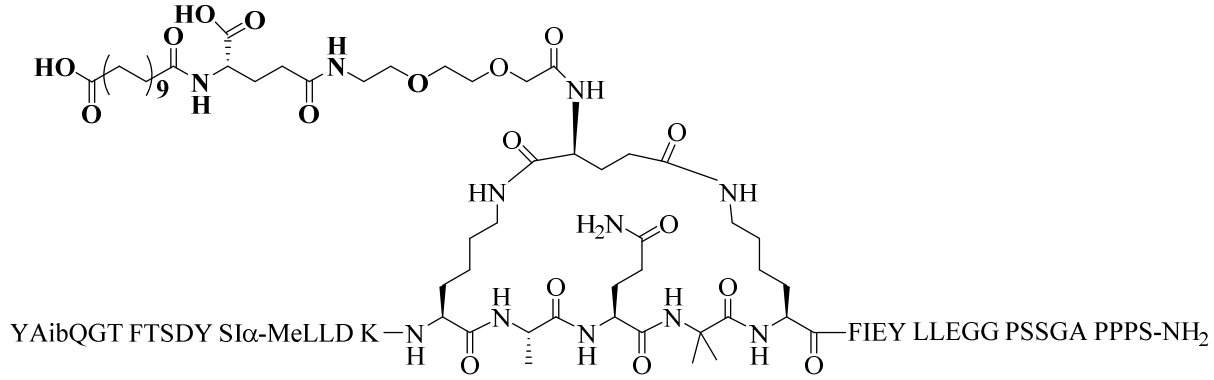
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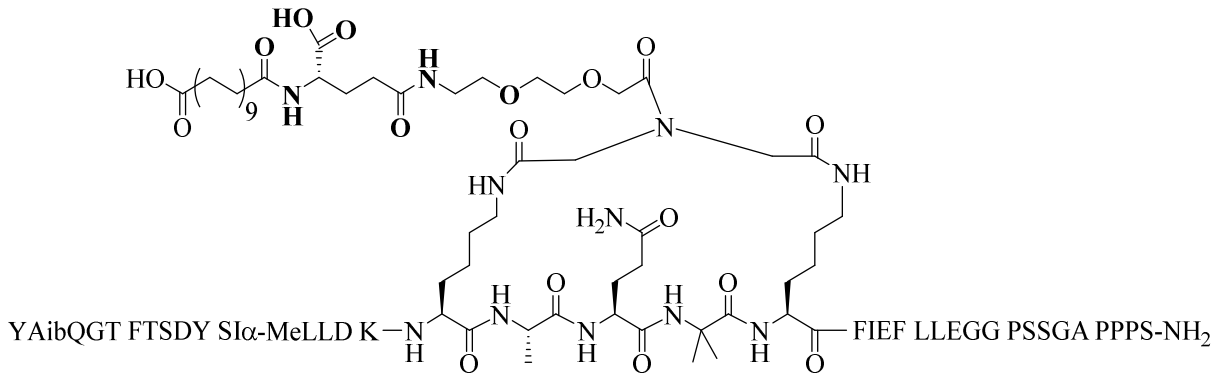
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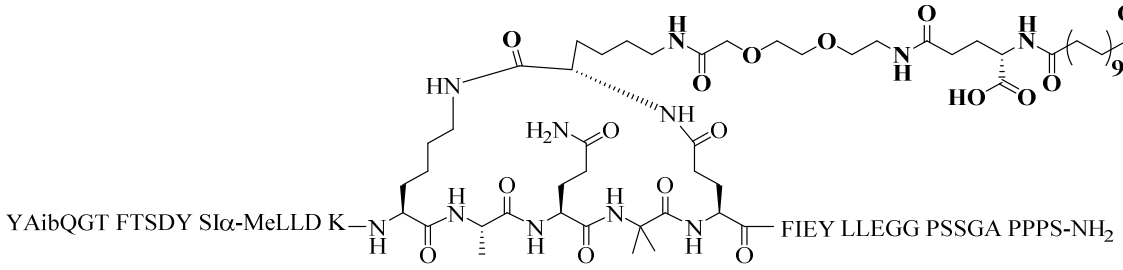
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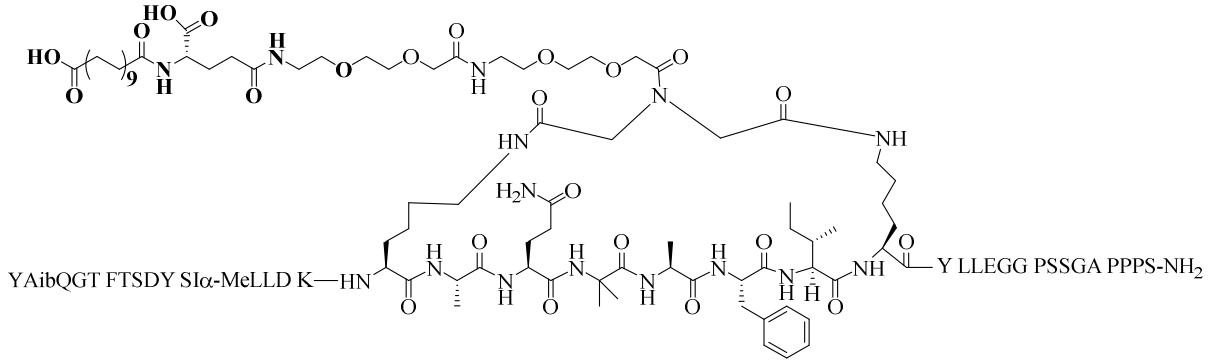
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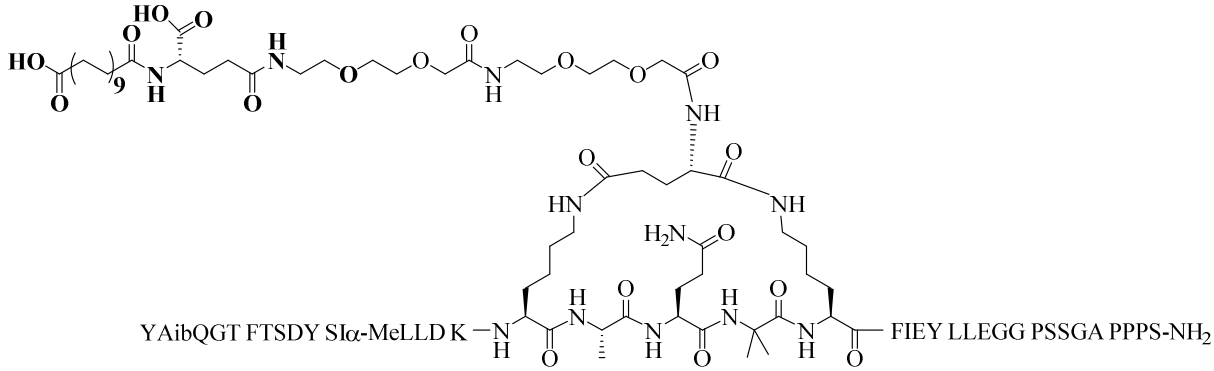
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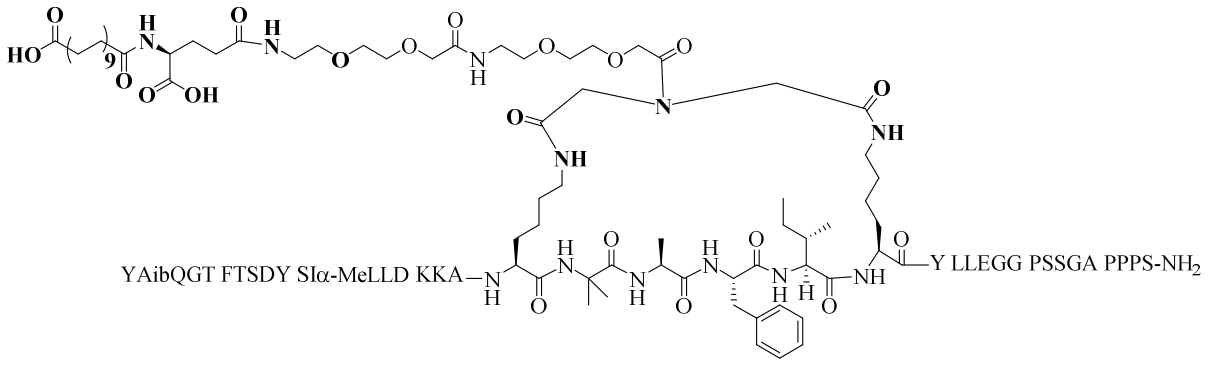
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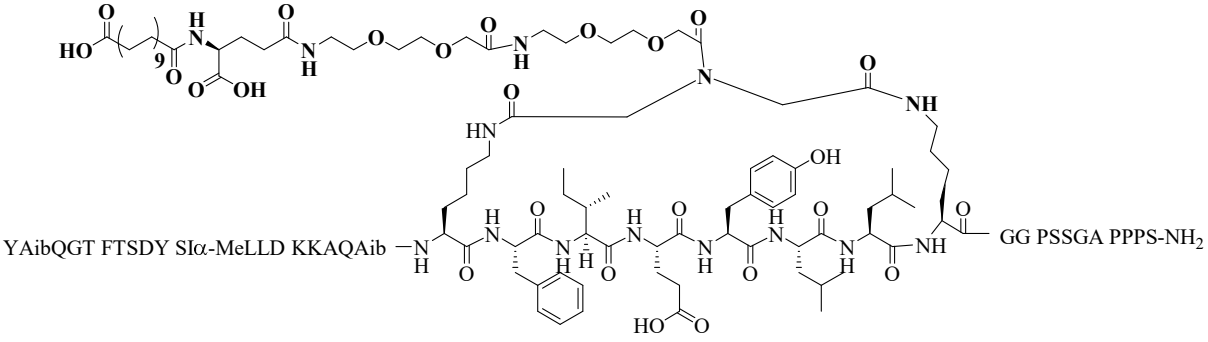
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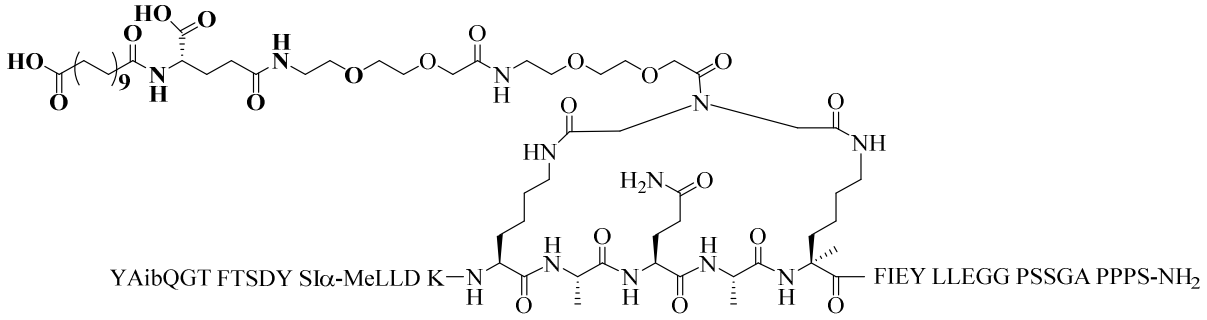
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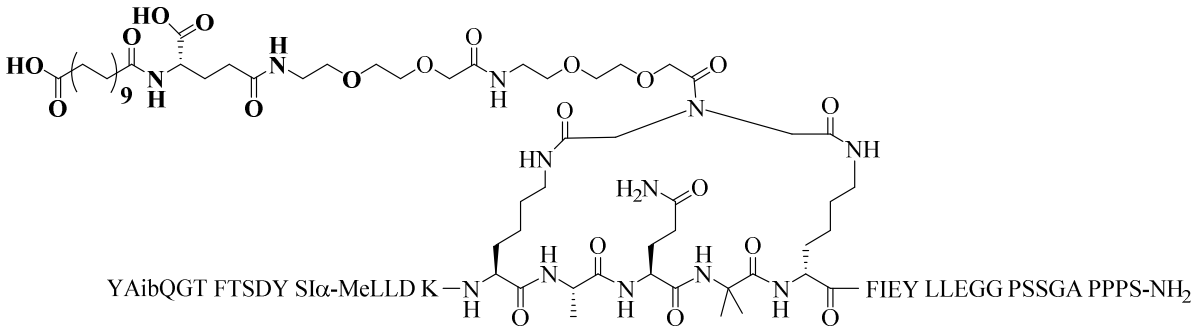
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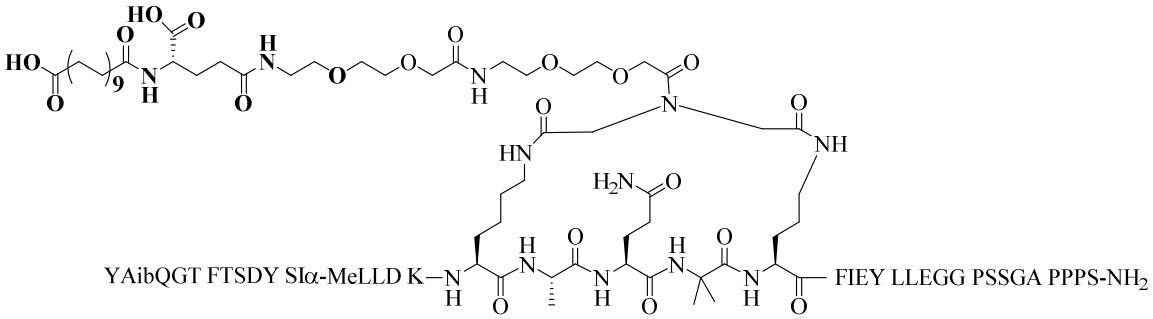
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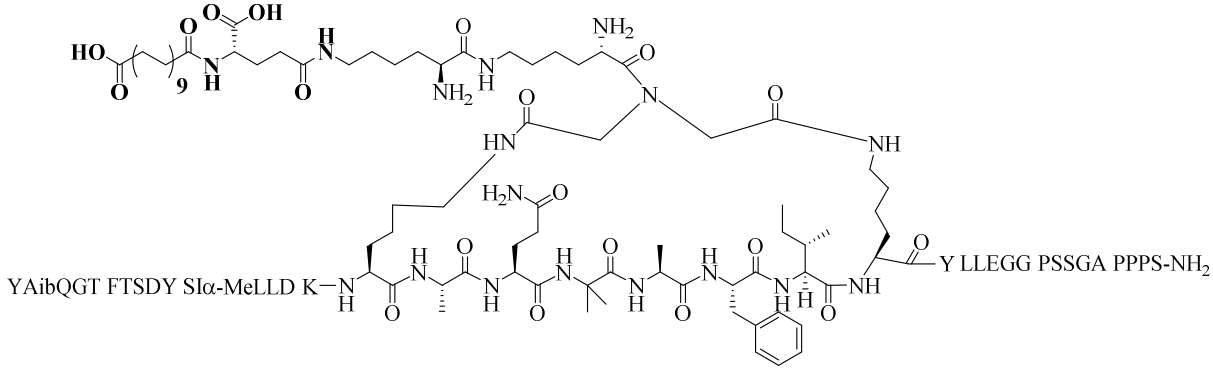
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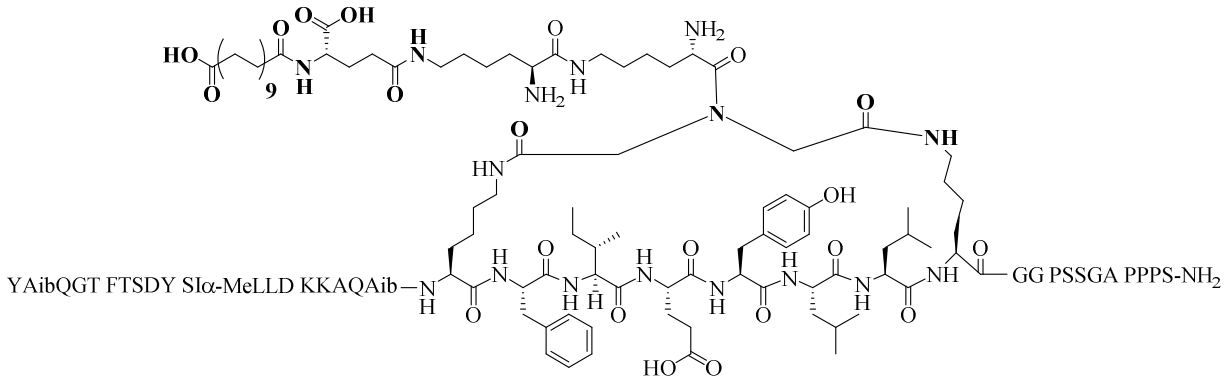
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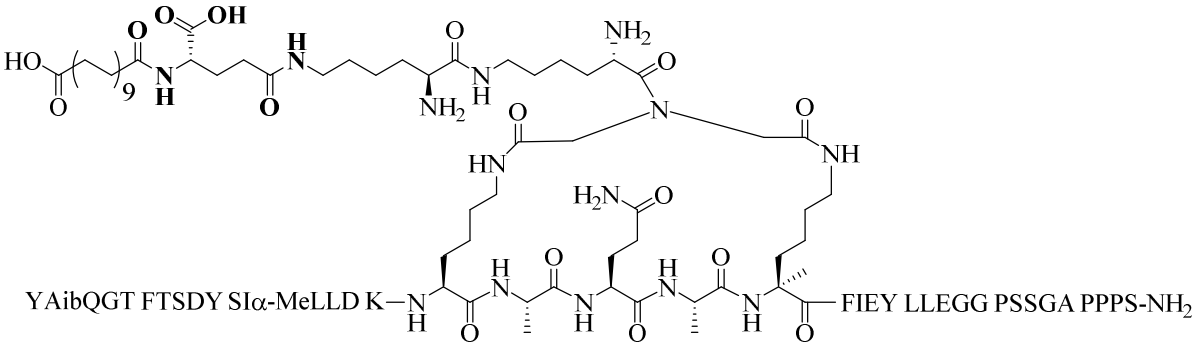
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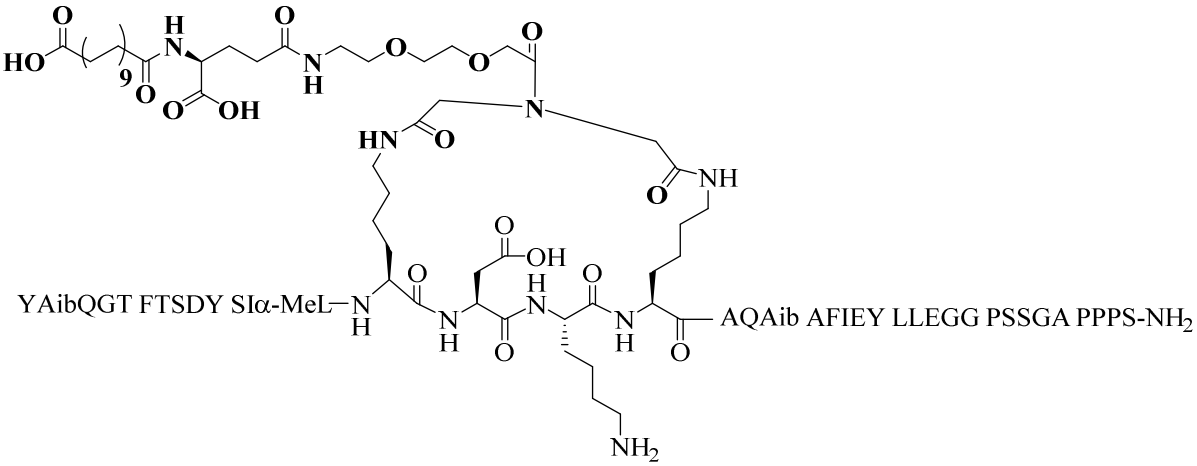
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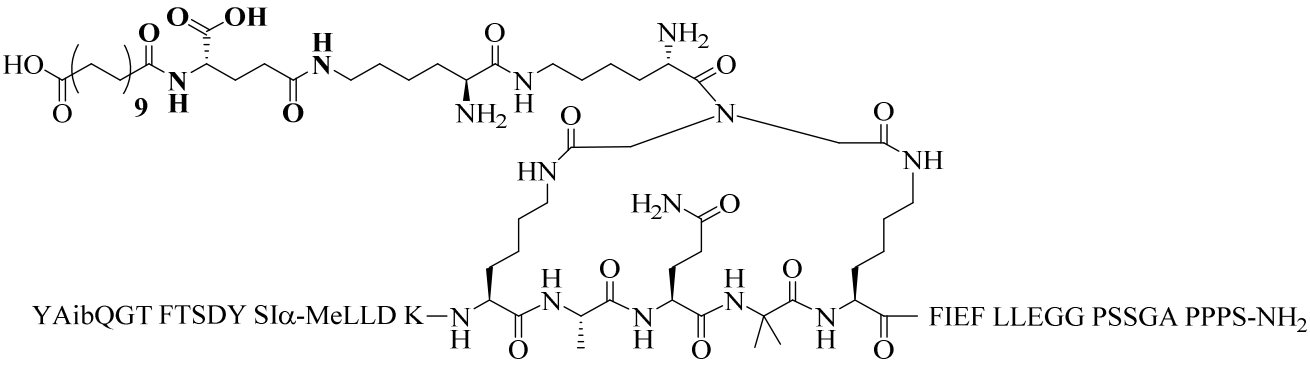
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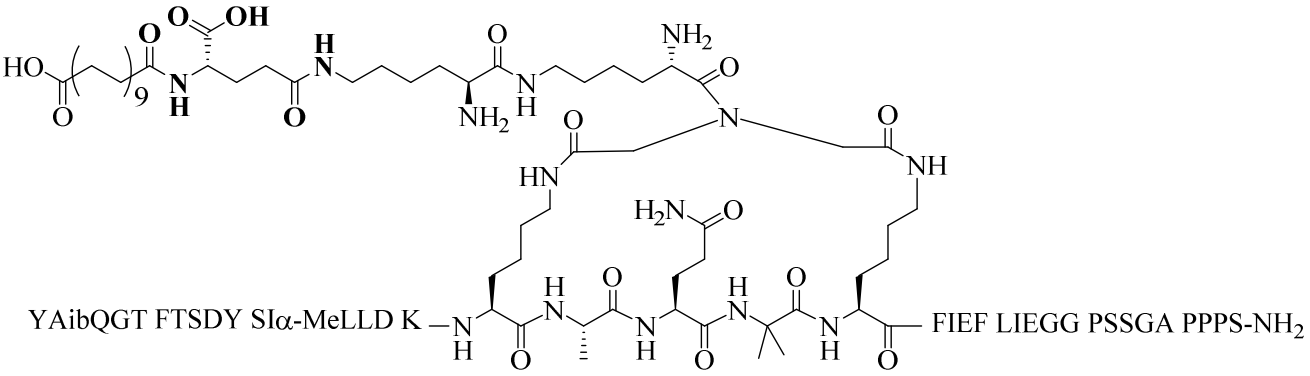
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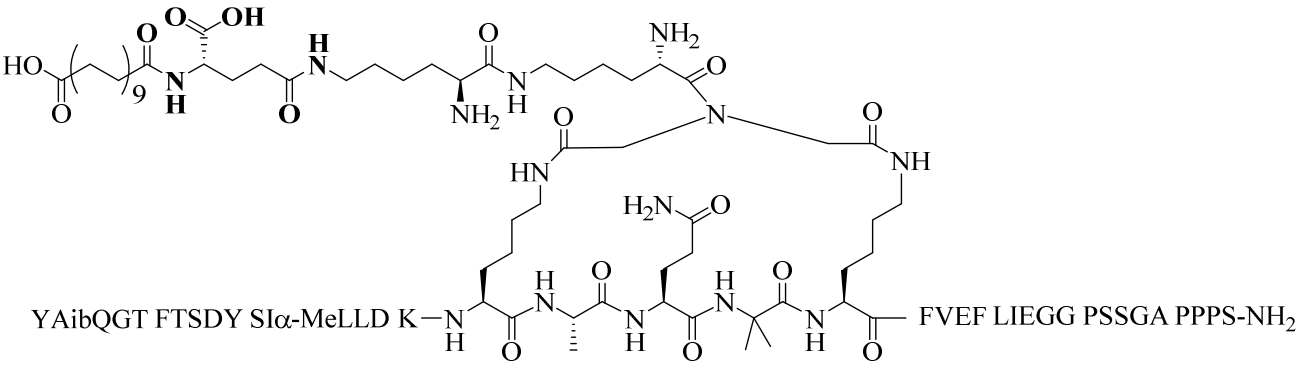
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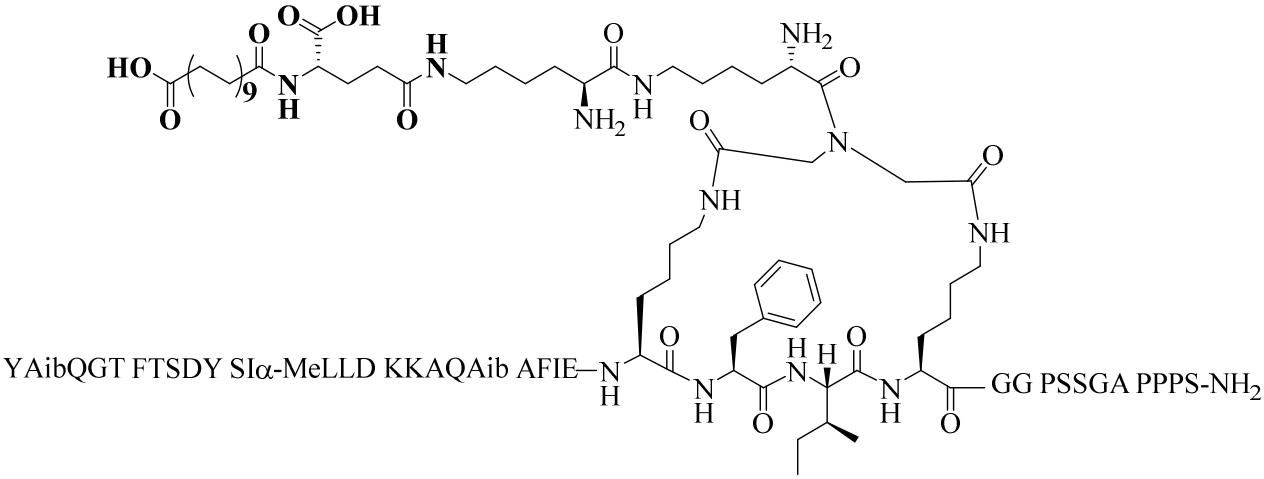
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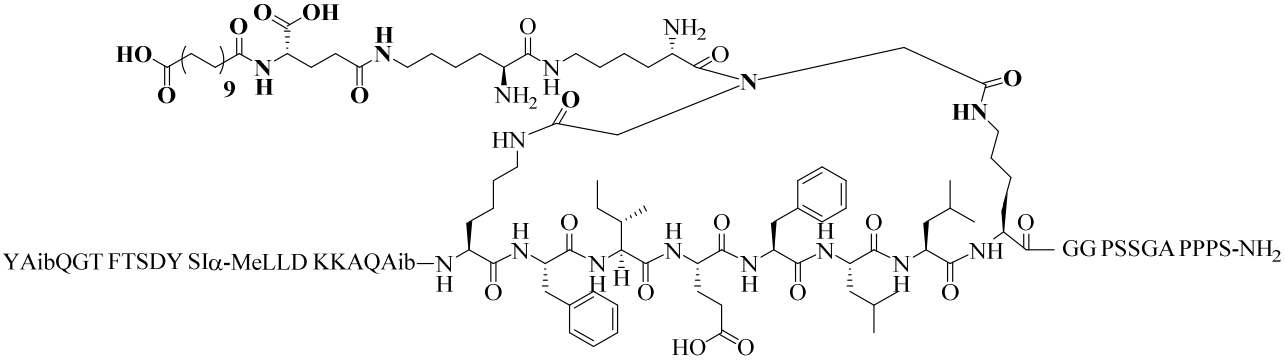
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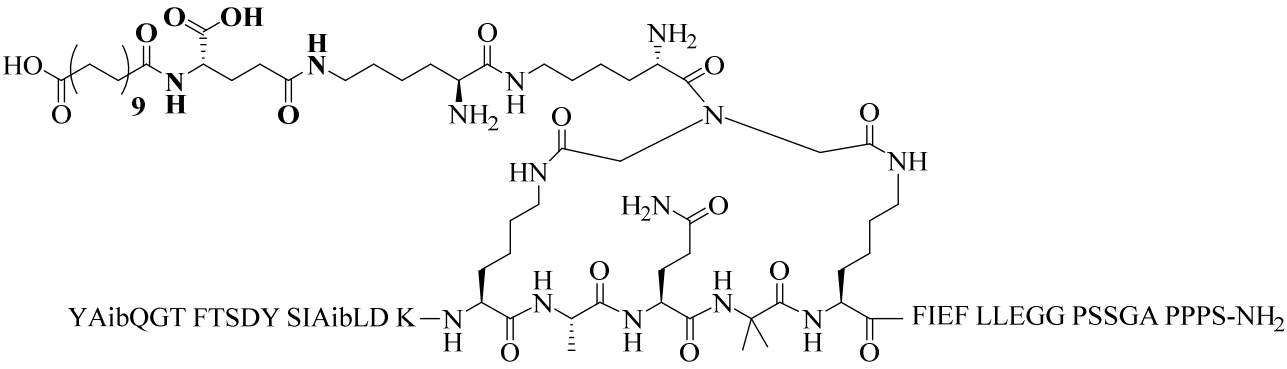
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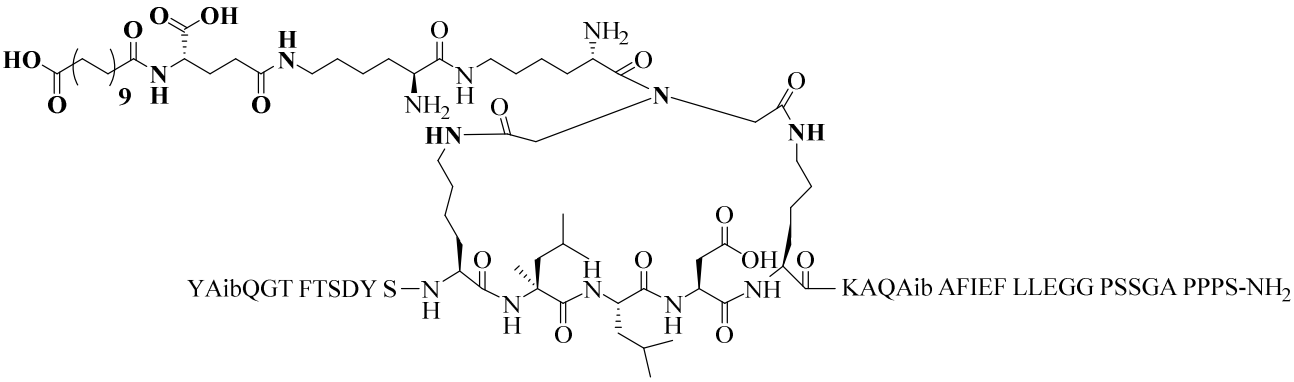
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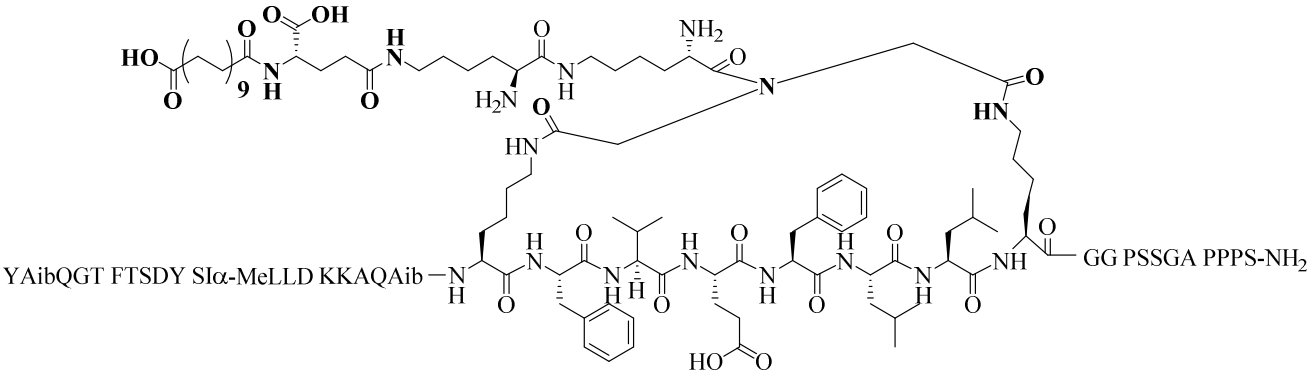
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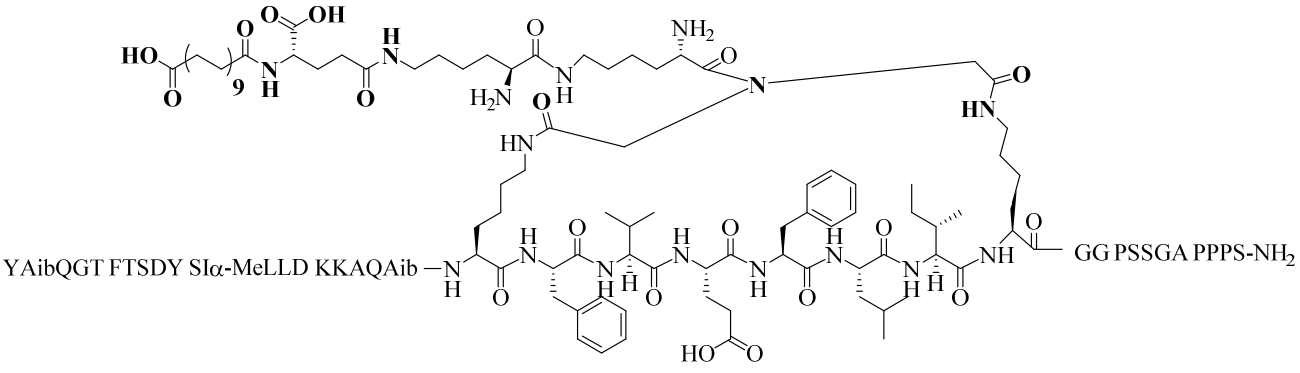
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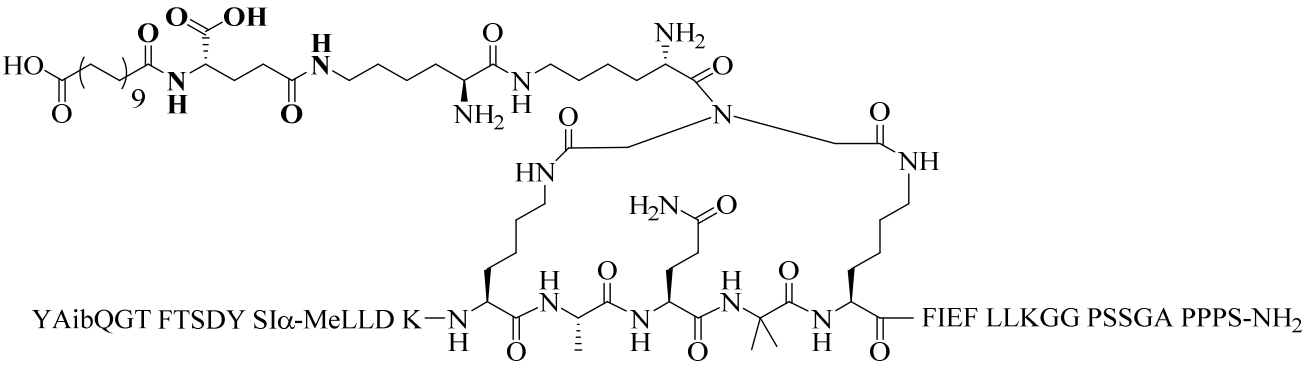
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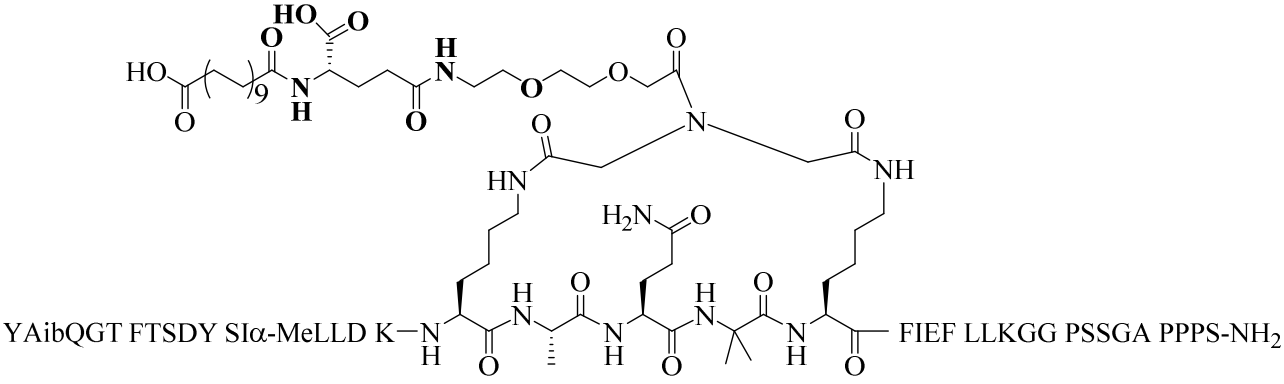
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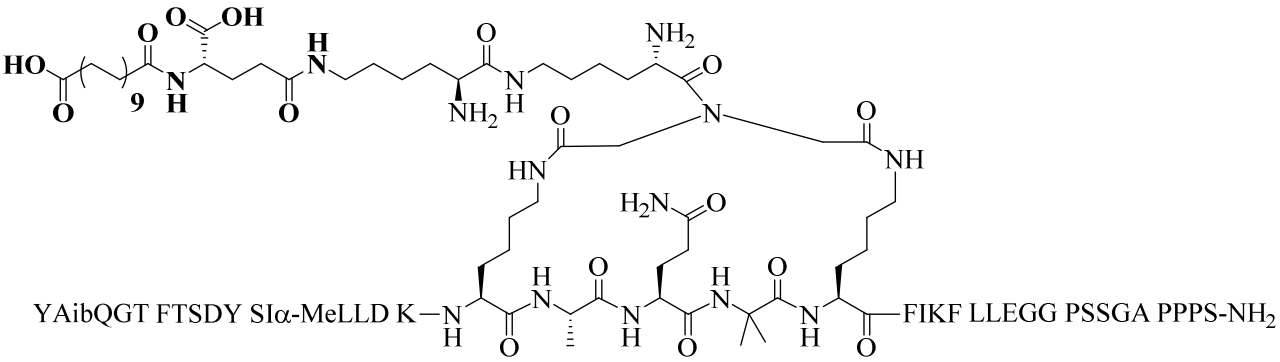
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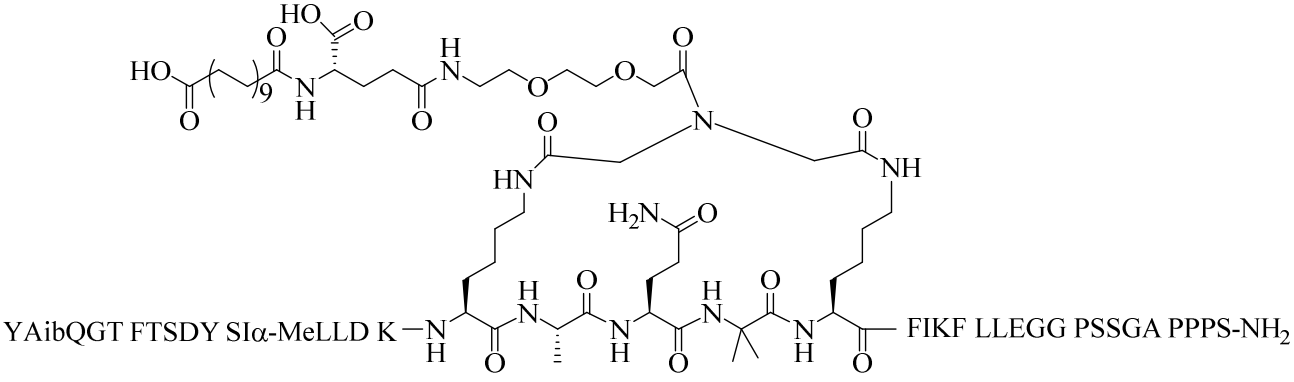
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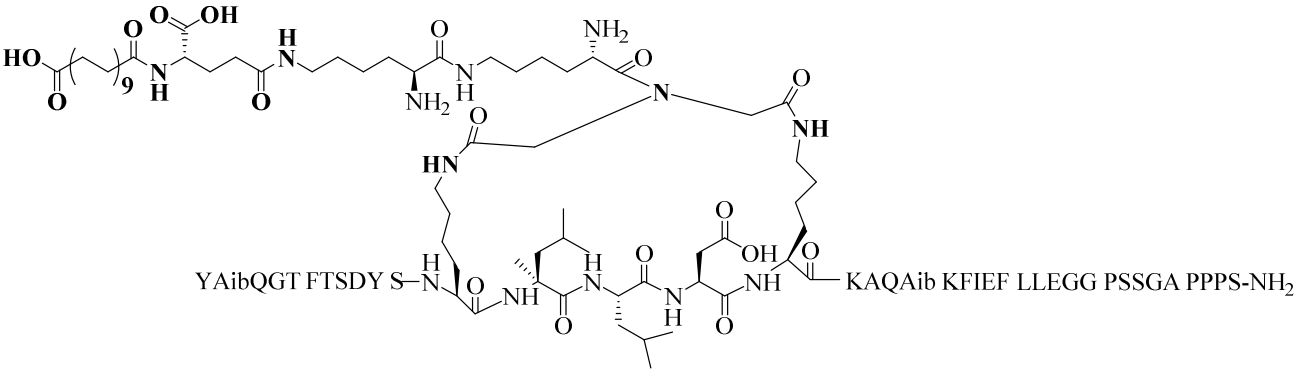
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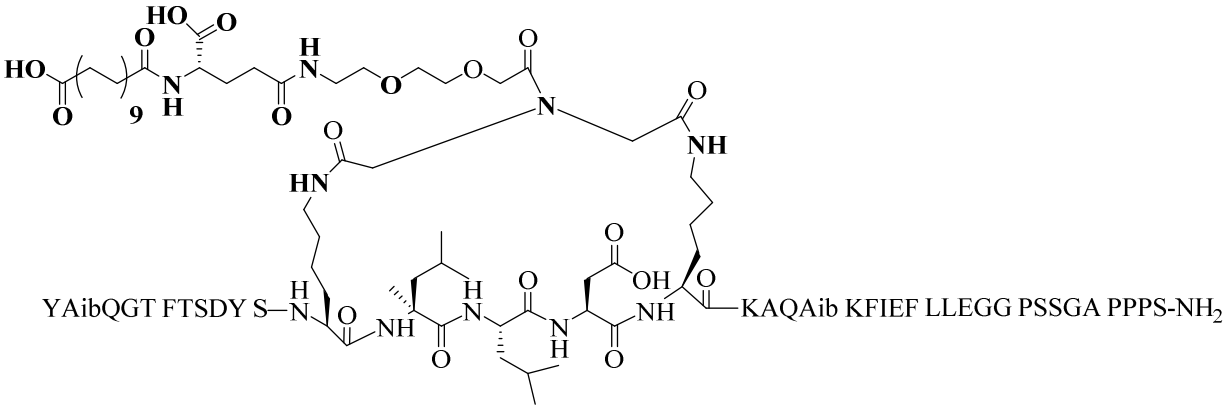
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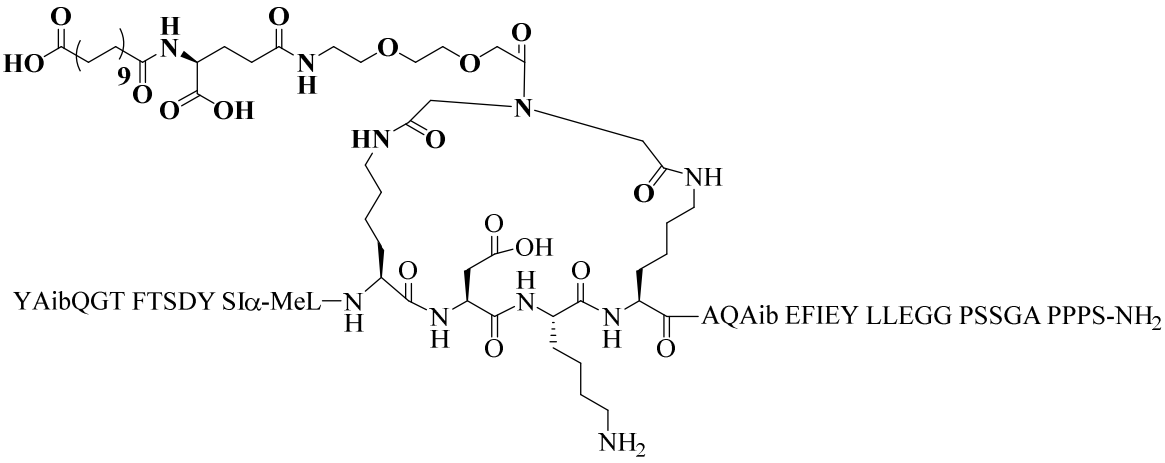
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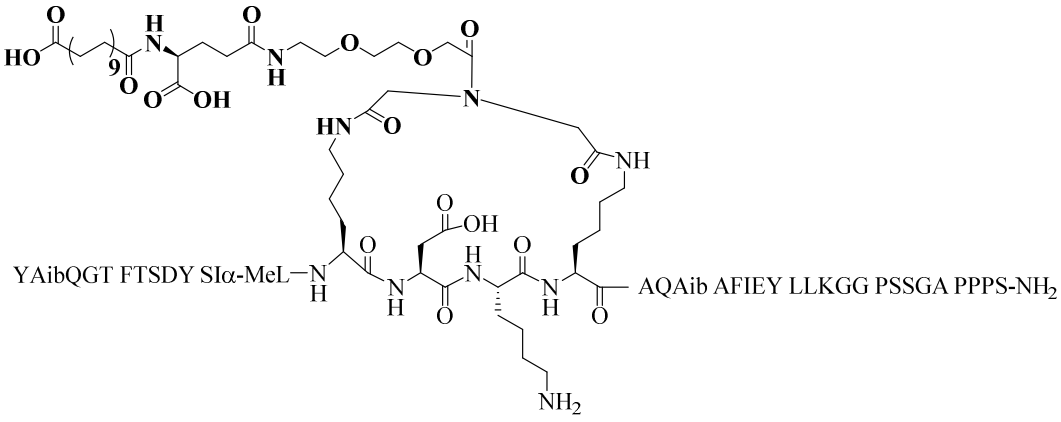
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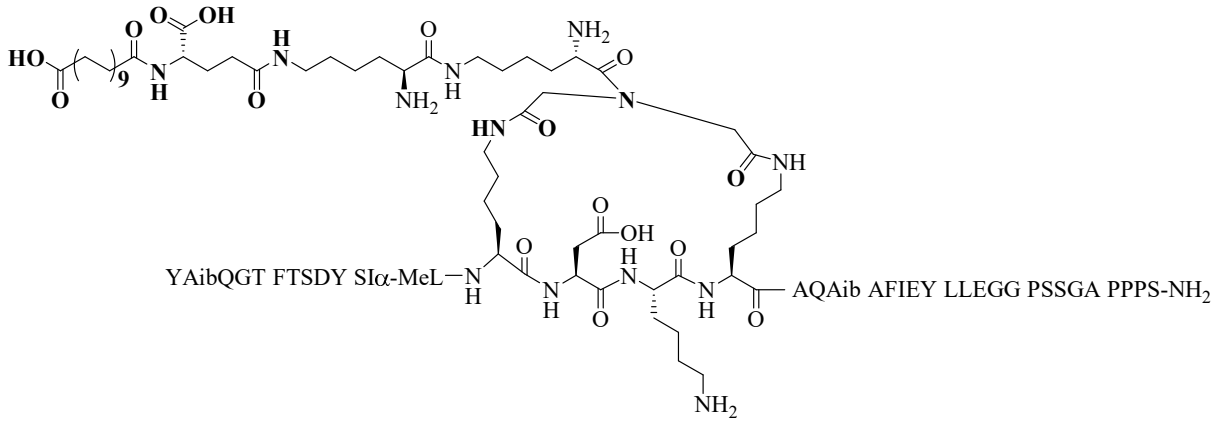
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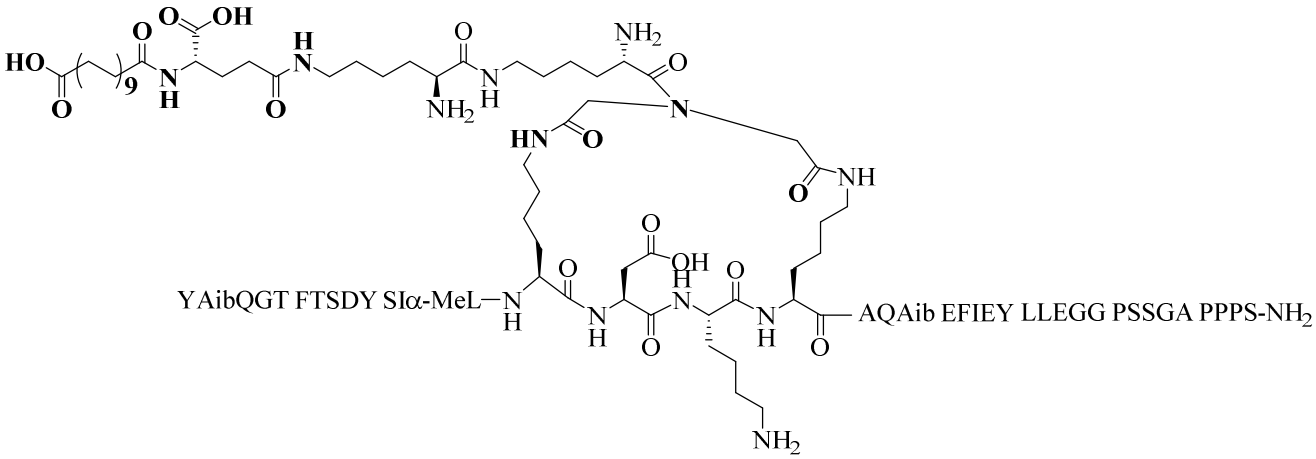
Compound 37,



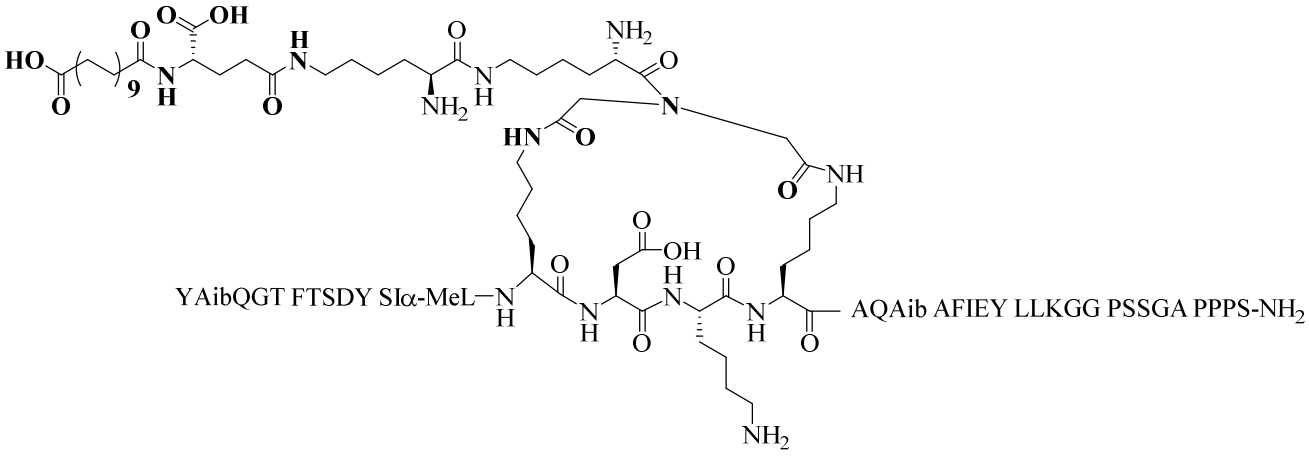
Compound 38,



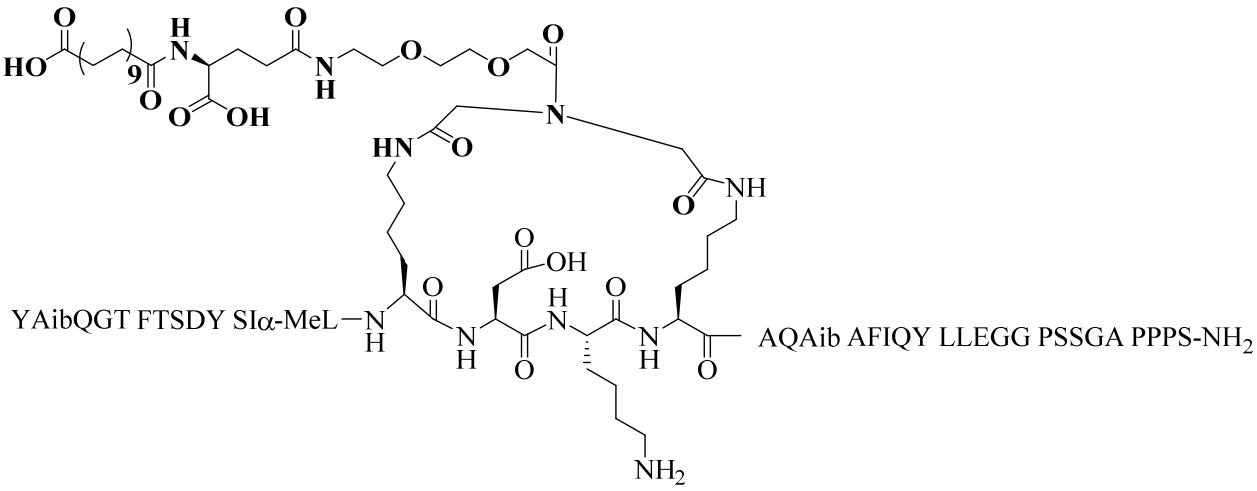
Compound 39,



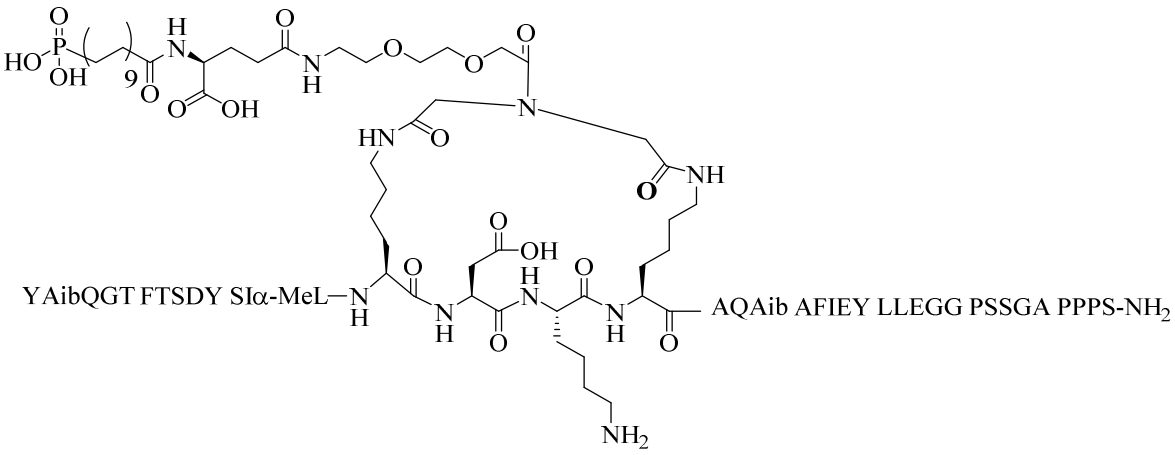
Compound 40,



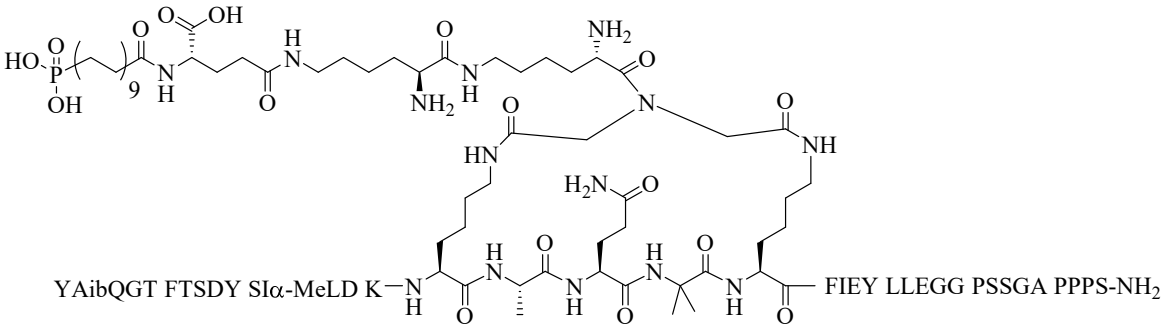
Compound 41,



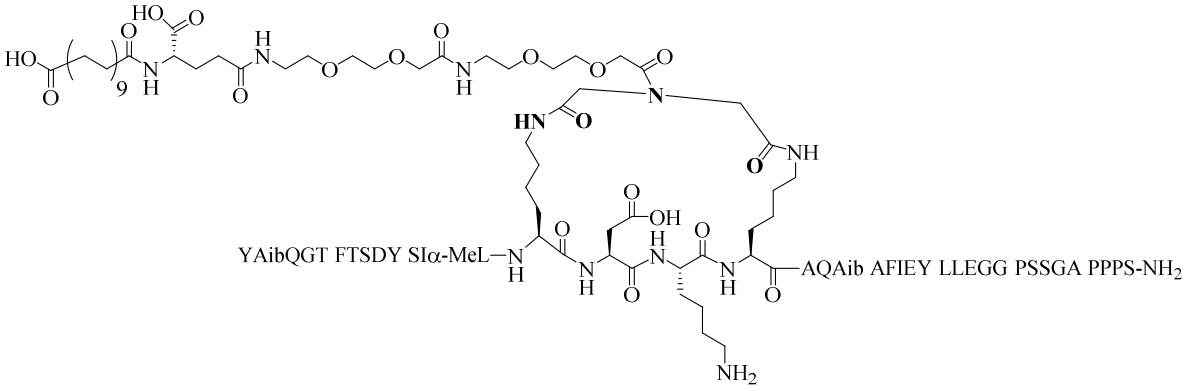
Compound 42,



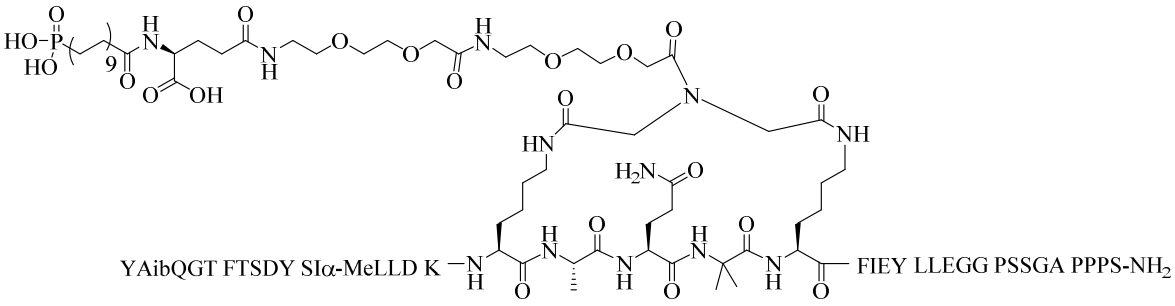
Compound 43,



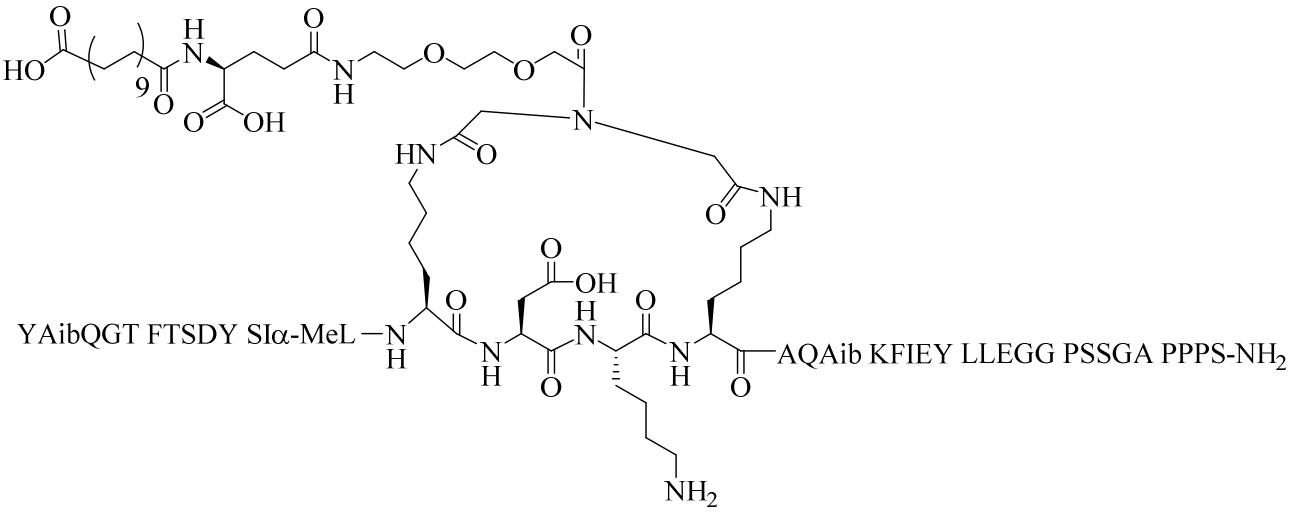
Compound 44,



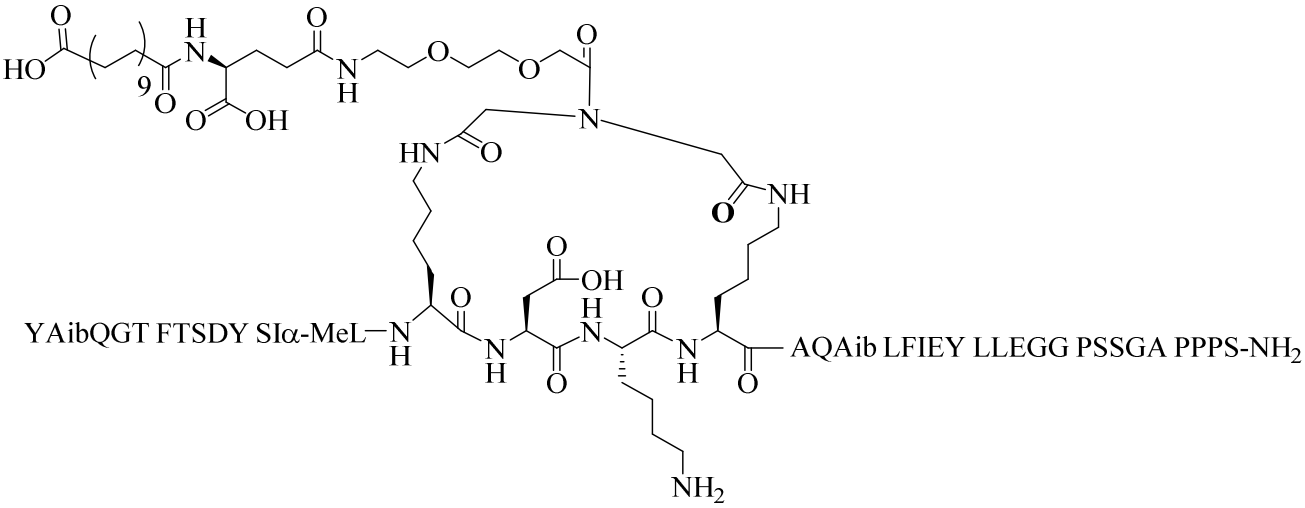
Compound 45,



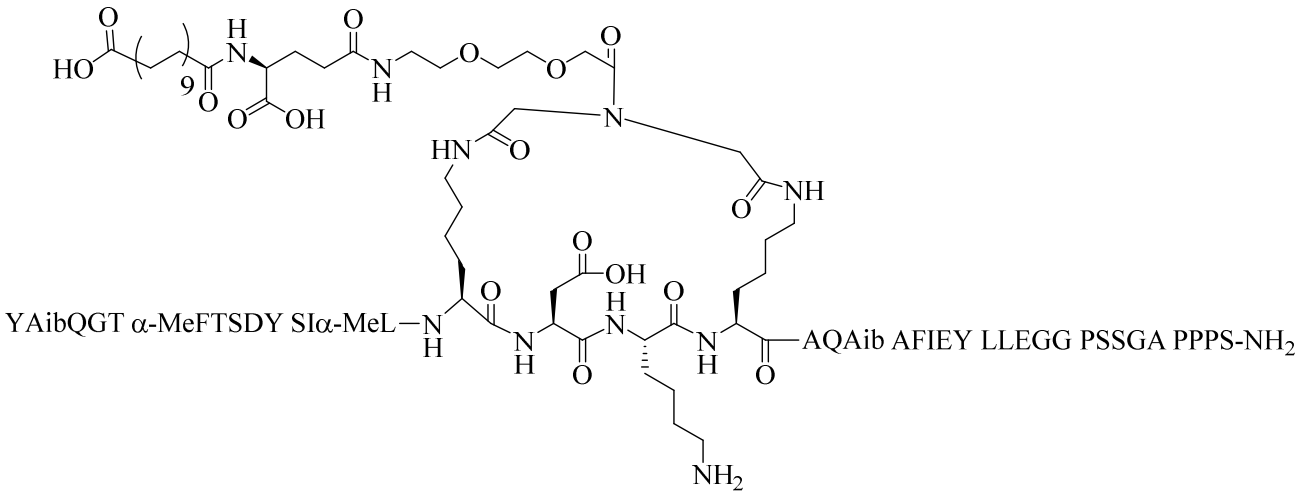
Compound 46,



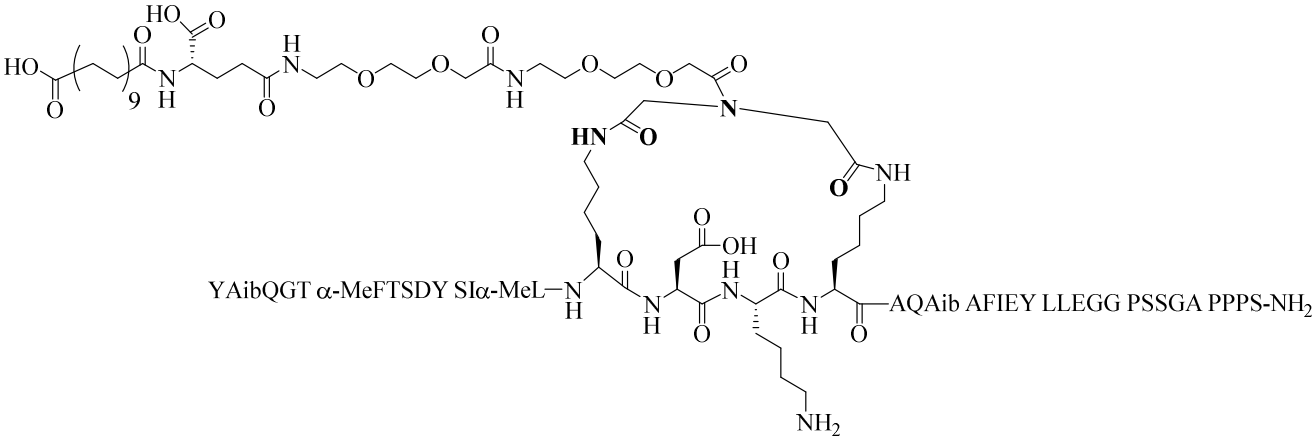
Compound 47,



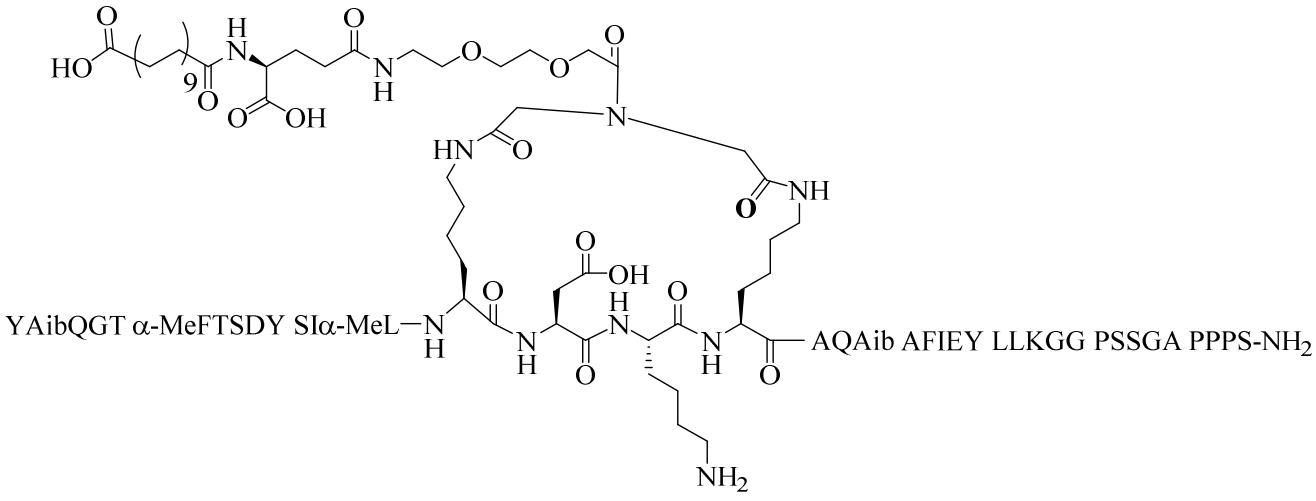
Compound 48,



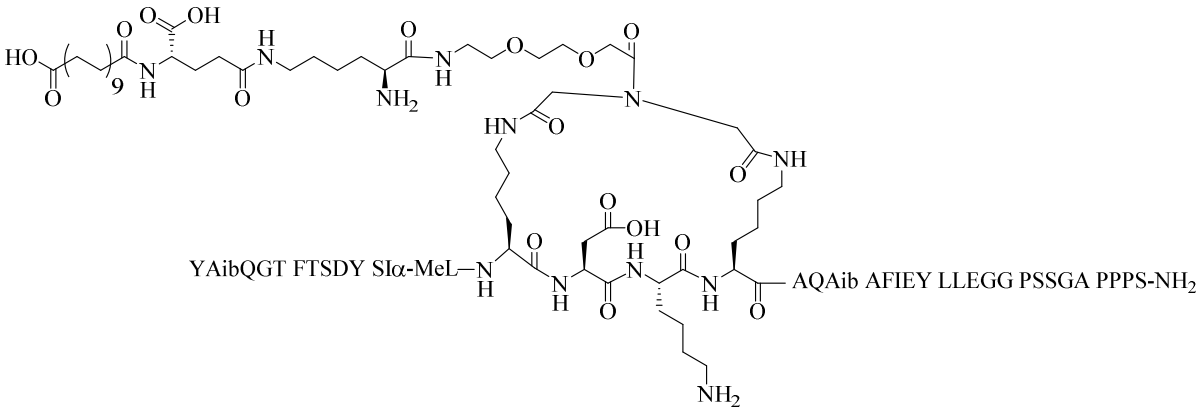
Compound 49,



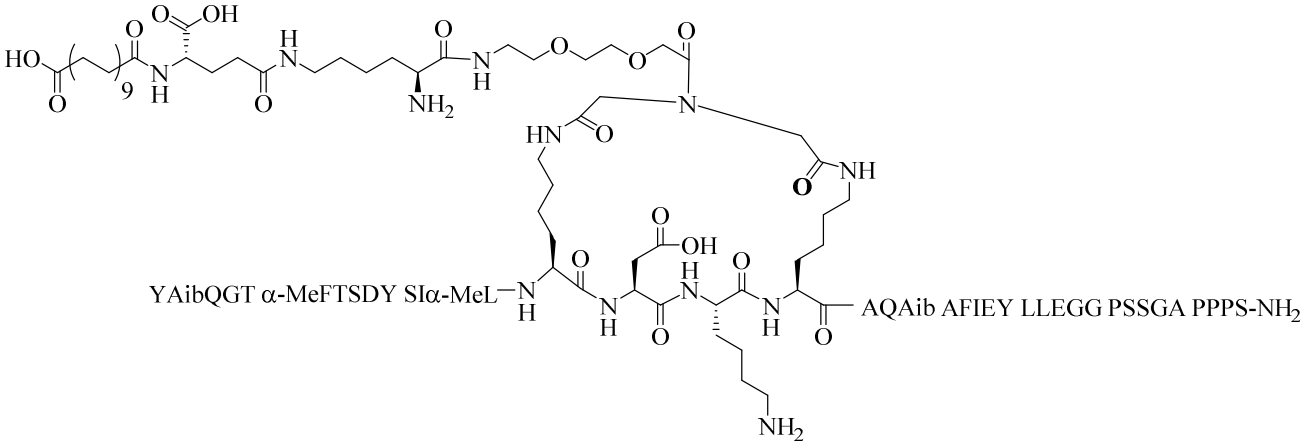
Compound 50,



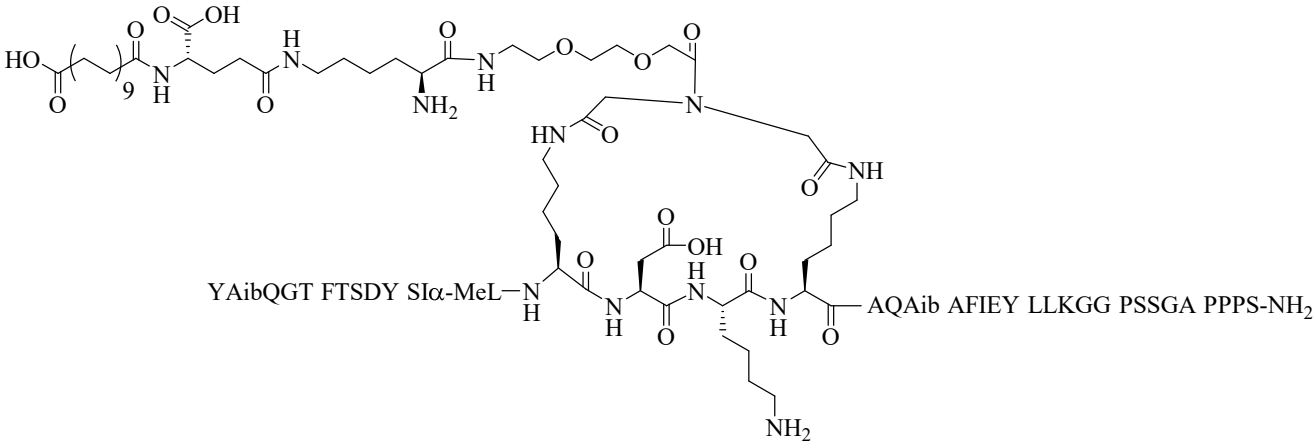
Compound 51,



Compound 52,



Compound 53, and



Compound 54;

or a pharmaceutically acceptable salt thereof.

16. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-15, wherein the salt is an acid addition salt or a base addition salt.

17. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to claim 16, wherein the acid addition salt is a salt formed by the polypeptide compound with any one of: inorganic acids, comprising hydrochloric acid, hydrobromic acid, nitric acid, carbonic acid, bicarbonate, phosphoric

acid, monohydrogen phosphate, dihydrogen phosphate, sulfuric acid, hydrosulfate, hydroiodic acid, and phosphorous acid; and organic acids, comprising acetic acid, trifluoroacetic acid, propionic acid, isobutyric acid, maleic acid, malonic acid, benzoic acid, succinic acid, octanedioic acid, fumaric acid, lactic acid, mandelic acid, phthalic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, tartaric acid, methanesulfonic acid, pamoic acid, arginine, and glucuronic acid; and/or

the base addition salt comprises sodium, potassium, calcium, ammonium, organic amine or magnesium salt.

18. A pharmaceutical composition, wherein the pharmaceutical composition comprises the polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-17.

19. The polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-17, or the pharmaceutical composition according to claim 18 for use in treating metabolic diseases and related diseases thereof.

20. The polypeptide compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition for use according to claim 19, wherein the metabolic diseases comprise diabetes, obesity and non-alcoholic steatohepatitis and related diseases thereof.

21. Use of the polypeptide compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-17, or the pharmaceutical composition according to claim 18 in the preparation of a drug for treating metabolic diseases and related diseases thereof.

22. The use according to claim 21, wherein the metabolic diseases comprise diabetes, obesity and non-alcoholic steatohepatitis and related diseases thereof.