[0007] Accordingly, there is a need in the art for GLP1R agonists with longer duration and better safety. In certain embodiments, the present disclosure meets the needs and provides other advantages.

[0008] The foregoing discussion is presented solely to provide a better understanding of the nature of the problems confronting the art and should not be construed in any way as an admission as to prior art nor should the citation of any reference herein be construed as an admission that such reference constitutes “prior art” to the instant application.

SUMMARY OF THE DISCLOSURE

[0009] Various non-limiting examples of the disclosure are described below.

[00010] In one aspect, there is provided a compound having a structure of Formula (A):

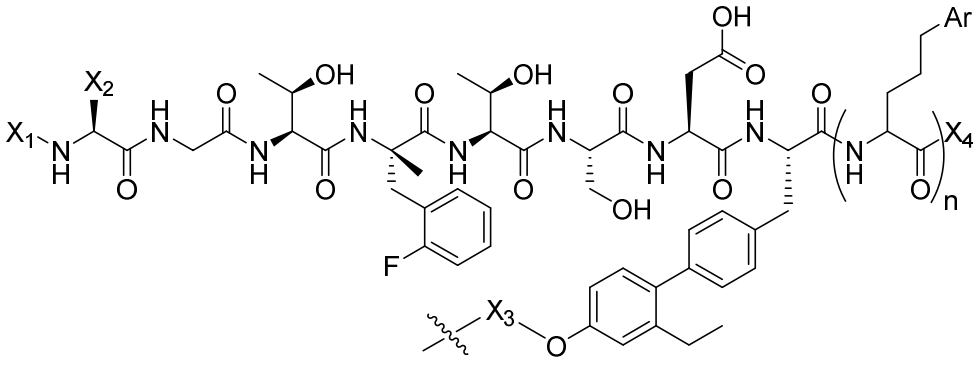
$$BA\text{-}(L\text{-}P)_m \quad (A),$$

wherein:

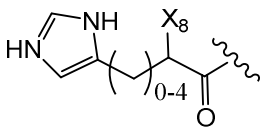
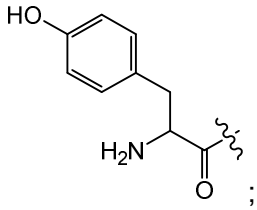
BA is an antibody or an antigen-binding fragment thereof;

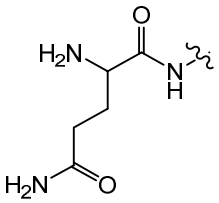
L is a non-cleavable linker;

P is a payload having the structure selected from the group consisting of:



(P-IA),

X_7 is selected from H, , and ;

X_8 is selected from H, -OH, $-NH_2$, and ,

or a pharmaceutically acceptable salt thereof.

[00012] In some examples of the compound described herein, BA is a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof. In some examples, the GLP1R-targeting antibody is a GLP1R agonist antibody. In some examples, the GLP1R-targeting antibody is 5A10, 9A10, AB9433-I, h38C2, PA5-111834, NLS1205, MAB2814, EPR21819, or glutazumab.

[00013] In some examples, the linker L is attached to one or both heavy chains of the BA. In some examples, the linker L is attached to one or both heavy chain variable domains of the BA. In some examples, the linker L is attached to one or both light chains of the BA. In some examples, the linker L is attached to one or both light chain variable domains of the BA.

[00014] In some examples, the linker L is attached to BA via a glutamine residue. In some examples, the glutamine residue is introduced to the N-terminus of one or both heavy chains of the BA. In some examples, the glutamine residue is introduced to the N-terminus of one or both light chains of the BA. In some examples, the glutamine residue is naturally present in a CH2 or CH3 domain of the BA. In some examples, the glutamine residue is introduced to the BA by modifying one or more amino acids. In some examples, the glutamine residue is Q295 or N297Q.

[00015] In some examples, the linker L is attached to BA via a lysine residue.

[00016] In some examples, the antibody or antigen-binding fragment thereof is aglycosylated. In some examples, the antibody or antigen-binding fragment thereof is deglycosylated. In some examples, the antigen-binding fragment is an Fab fragment.

[00017] In one example, m is 1. In one example, m is an integer from 2 to 4. In one example, m is 2.

[00018] In some examples, more than one L-P is attached to the BA. In some examples, two L-Ps are attached to the BA.

[00019] In some examples, the linker L has the structure of formula (L'):

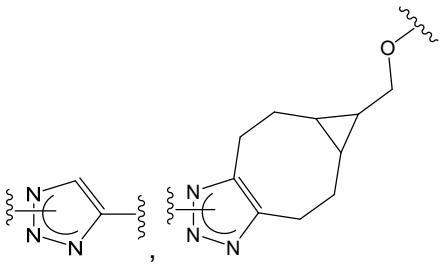
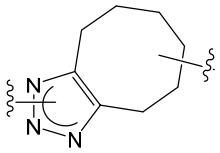
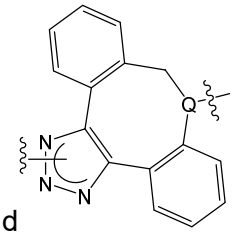
-La-Y-Lp- (L'),

wherein La is a first linker covalently attached to the BA;

Y is a group comprising a triazole, and

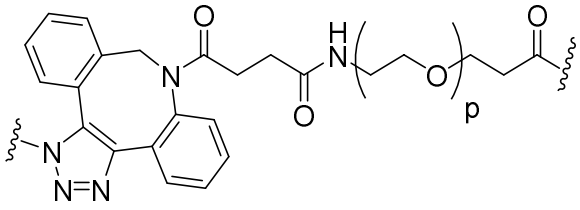
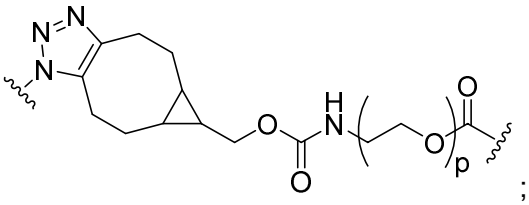
Lp is absent or a second linker covalently attached to the P, wherein when Lp is absent, Y is also absent.

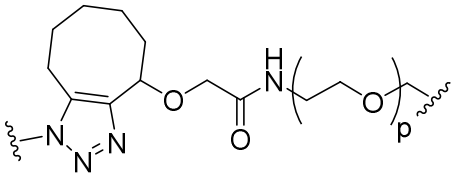
[00020] In some examples, Y has a structure selected from the group consisting of:


,
, 
, and 
, wherein Q is C or N.

[00021] In some examples, Lp comprises a polyethylene glycol (PEG) segment having 1 to 36 $-CH_2CH_2O-$ (EG) units. In some examples, the PEG segment comprises between 2 and 30 EG units. In some examples, the PEG segment comprises between 4 and 24 EG units. In some examples, the PEG segment comprises 4 EG units, or 8 EG units, or 12 EG units, or 24 EG units. In some examples, the PEG segment comprises 4 EG units. In some examples, the PEG segment comprises 8 EG units.

[00022] In some examples, Y-Lp has a structure selected from the group consisting of:


; 
;

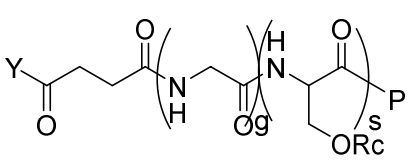
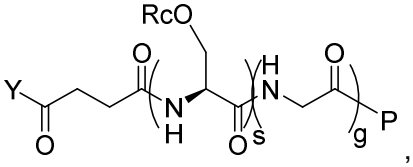

, or a triazole regioisomer thereof,

wherein p is an integer from 1 to 36.

[00023] In some examples, the Lp comprises one or more amino acids selected from glycine, serine, glutamic acid, alanine, valine, and proline and combinations thereof. In some examples, the Lp comprises 1 to 10 glycines. In some examples, the Lp comprises 1 to 6 serines. In some examples, the Lp comprises 1 to 10 glycines and 1 to 6 serines. In some examples, the Lp comprises 4 glycines and 1 serine. In some examples, the Lp is selected from the group consisting of Gly-Gly-Gly-Gly-Ser (G_4S) (SEQ ID NO: 1), Ser-Gly-Gly-Gly-Gly (SG_4) (SEQ ID NO: 2), and Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (G_4S-G_4S) (SEQ ID NO: 3).

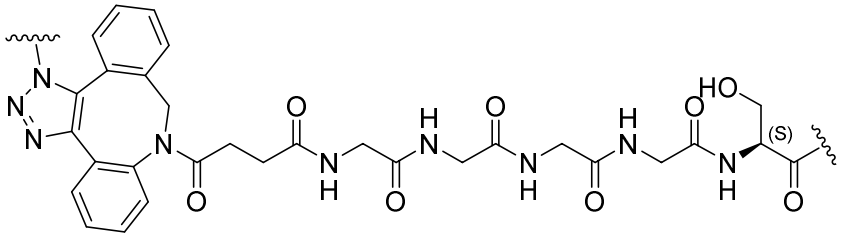
[00024] In some examples, the Lp comprises a combination of a PEG segment having 1 to 36 EG units and one or more amino acids selected from glycine, serine, glutamic acid, alanine, valine, and proline and combinations thereof. In some examples, the serine residue comprises a carbohydrate group. In some examples, the serine residue comprises a glucose group.

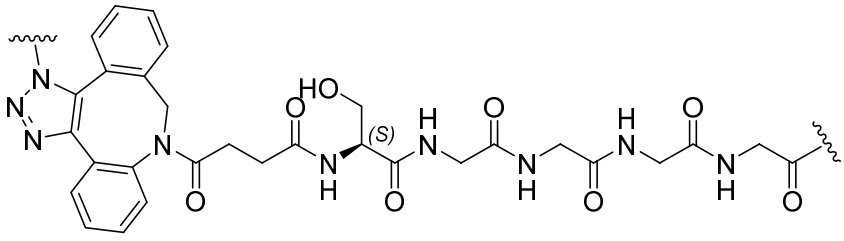
[00025] In some examples, Lp has a structure selected from the group consisting of:

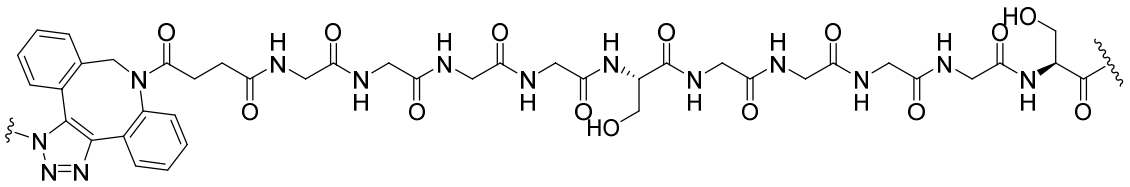

and

,

wherein Y is the group comprising a triazole and P is the payload, and wherein Rc is selected from H and glucose, g is an integer from 1 to 10 and s is an integer from 0 to 4.

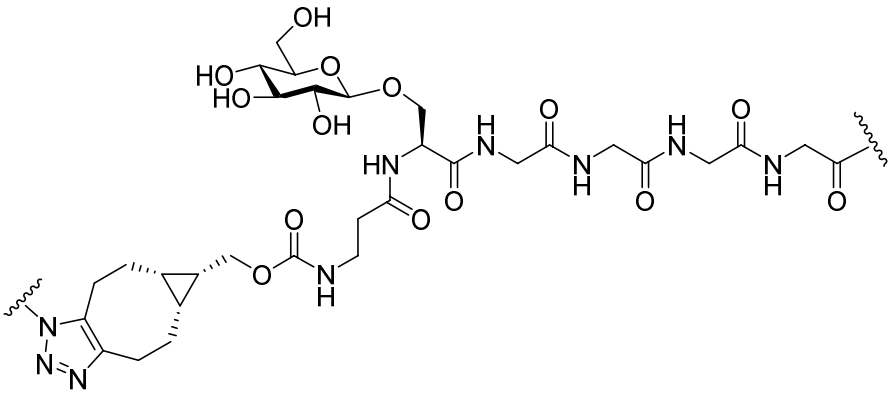
[00026] In some examples, Y-Lp has a structure selected from the group consisting of:


;

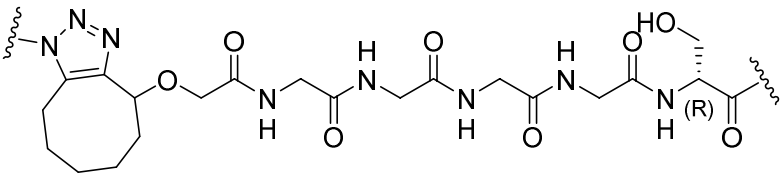

;



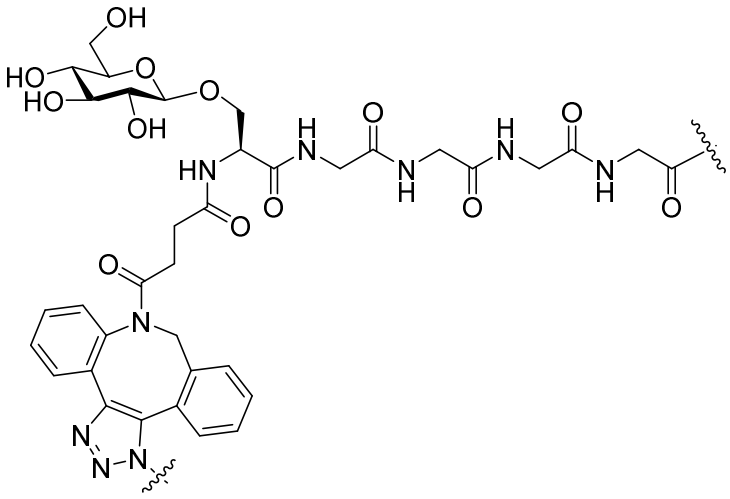
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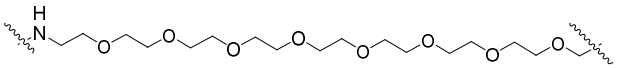


; and

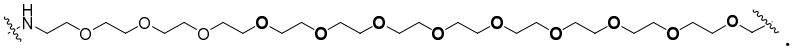


, or a triazole regioisomer thereof.

[00027] In some examples, La comprises a polyethylene glycol (PEG) segment having 1 to 36 -CH_2CH_2O- (EG) units. In some examples, the PEG segment comprises 4 EG units, or 8 EG units, or 12 EG units, or 24 EG units. In some examples, the PEG segment comprises 8 EG units. In some examples, La has a structure selected from the group consisting of



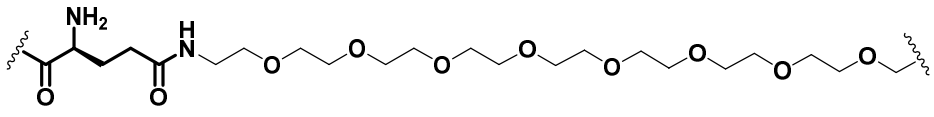
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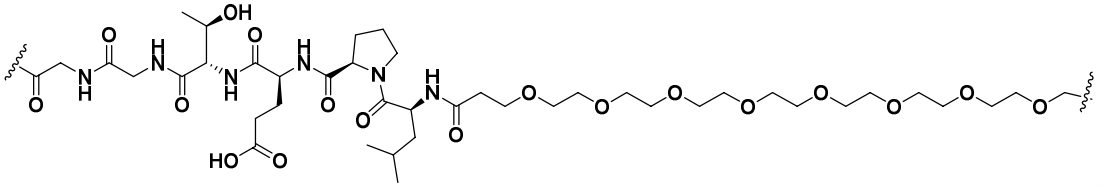
.

[00028] In some examples, La comprises one or more amino acids selected from glycine, threonine, serine, glutamine, glutamic acid, alanine, valine, leucine, and proline and combinations thereof. In some examples, La comprises 1 to 10 glycines and 1 to 6 serines. In some examples, La comprises 4 glycines and 1 serine. In some examples, La is selected from the group consisting of Gly-Gly-Gly-Gly-Ser (G_4S), Ser-Gly-Gly-Gly-Gly (SG_4), Gly-Gly-Ser-Gly-Gly-Ser-Gly-Gly (G_2S-G_2S-G_2), and Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly (G_4S-G_4).

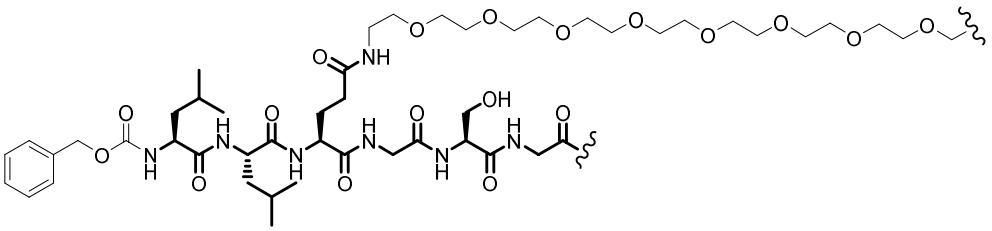
[00029] In some examples, La comprises a combination of a PEG segment having 1 to 36 EG units and one or more amino acids selected from glycine, threonine, serine, glutamine, glutamic acid, alanine, valine, leucine, and proline and combinations thereof. In some examples, La is selected from the group consisting of:



,

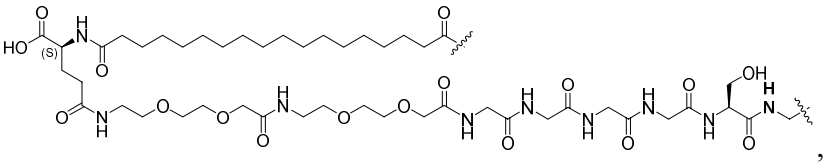


, and

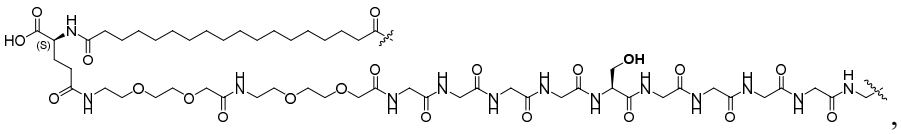


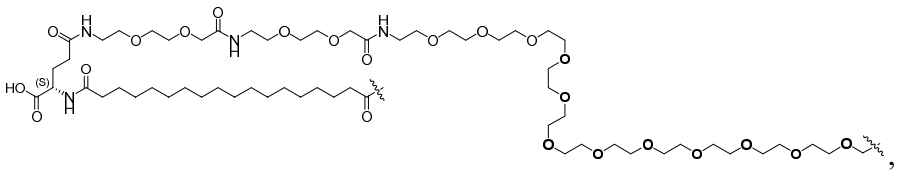
.

[00030] In some examples, La comprises a $–(CH_2)_{2-24}$- chain. In some examples, In some examples, La comprises a combination of a $–(CH_2)_{2-24}$- chain, a PEG segment having 1 to 36 EG units and one or more amino acids selected from glycine, threonine, serine, glutamine, glutamic acid, alanine, valine, leucine, and proline and combinations thereof. La is selected from the group consisting of:

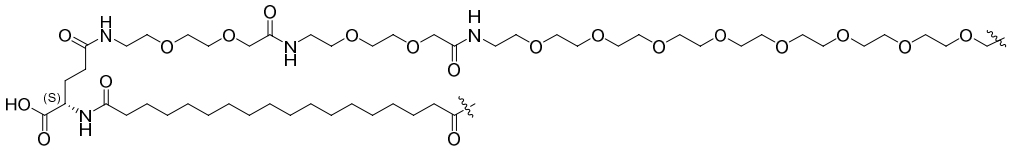


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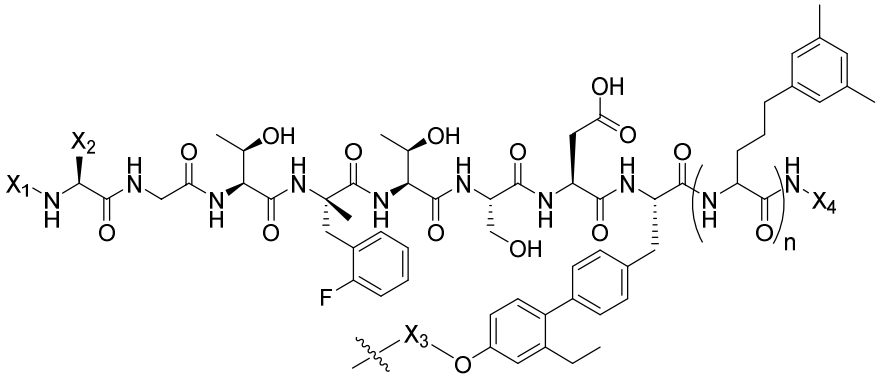


, and .

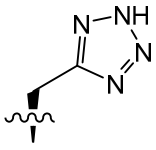


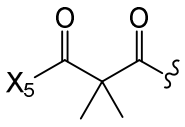
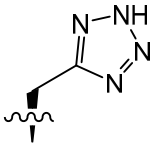
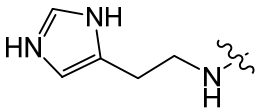
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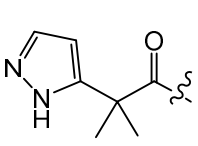
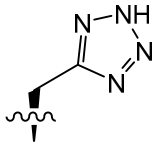
[00031] In various examples of the compound described herein, P has the structure

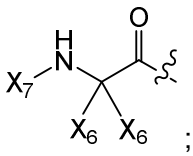
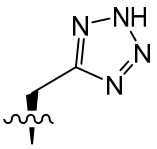


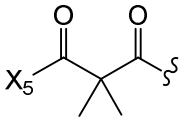
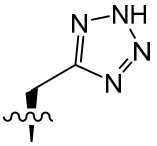
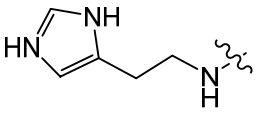
(P-I).

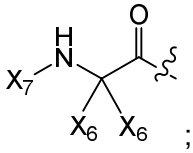
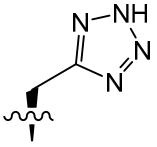
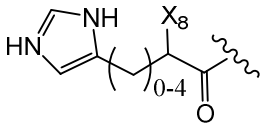
[00032] In some examples, X_1 is H; X_2 is  ; X_3 is selected from $–(CH_2)_{2\text{-}6}–NH–$ and $–(CH_2)_{2\text{-}6}–Tr–$, where Tr is a triazole moiety; n is 1, and X_4 is H.

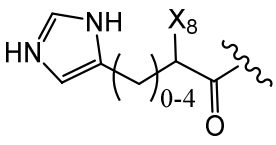
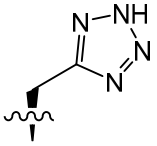
[00033] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H, and X_5 is selected from -OH, $-NH_2$, -NH-OH, and  .

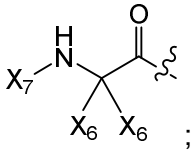
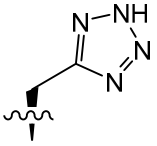
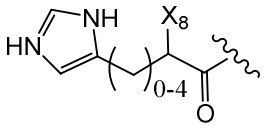
[00034] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1, and X_4 is H.

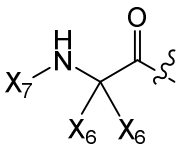
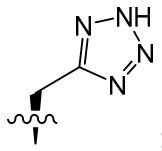
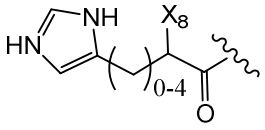
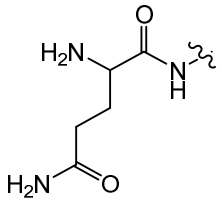
[00035] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H; X_6 is independently at each occurrence selected from H and $-CH_2OH$, and X_7 is H.

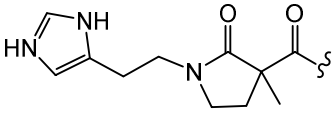
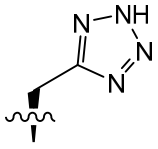
[00036] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–Tr–$, where Tr is a triazole moiety; n is 1; X_4 is H, and X_5 is  .

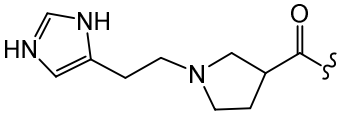
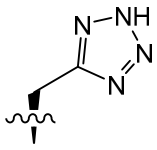
[00037] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H; X_6 is independently at each occurrence selected from H and $-CH_3$; X_7 is  , and X_8 is $-NH_2$.

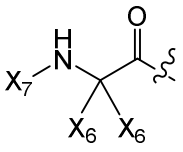
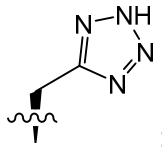
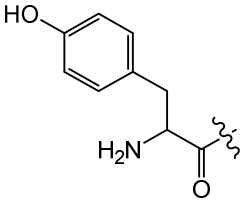
[00038] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H, and X_8 is H.

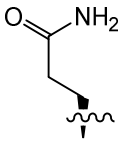
[00039] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H; X_6 is H at each occurrence; X_7 is  , and X_8 is H.

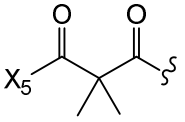
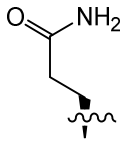
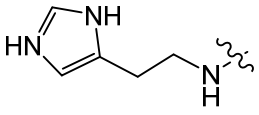
[00040] In some examples, X_1 is ; X_2 is ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H; X_6 is independently at each occurrence selected from H and $-CH_3$; X_7 is , and X_8 is .

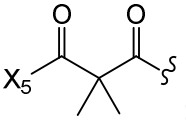
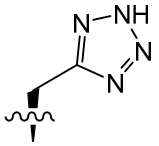
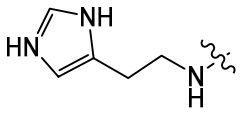
[00041] In some examples, X_1 is ; X_2 is ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1, and X_4 is H.

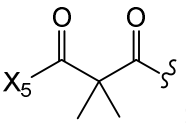
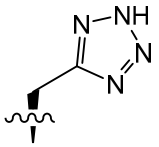
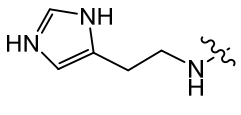
[00042] In some examples, X_1 is ; X_2 is ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1, and X_4 is H.

[00043] In some examples, X_1 is ; X_2 is ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1; X_4 is H; X_6 is independently at each occurrence selected from H and $-CH_3$, and X_7 is .

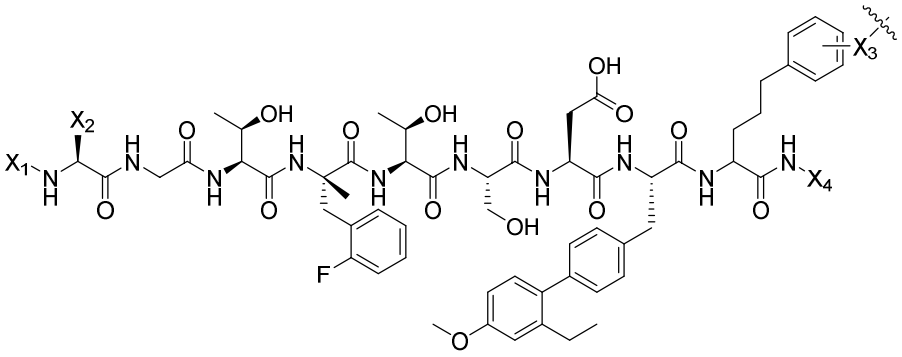
[00044] In some examples, X_1 is H; X_2 is ; X_3 is $–(CH_2)_{2\text{-}6}–NH–$; n is 1, and X_4 is H.

[00045] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2-6}–NH–$; n is 1; X_4 is H, and X_5 is  .

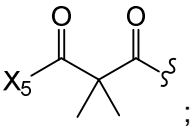
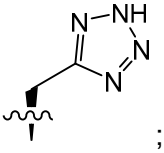
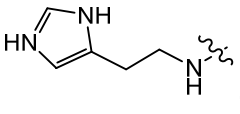
[00046] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2-6}–NH–$; n is 0; X_4 is phenyl, and X_5 is  .

[00047] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2-6}–NH–$; n is 1; X_4 is phenyl, and X_5 is  .

[00048] In various examples of the compound described herein, P has the structure

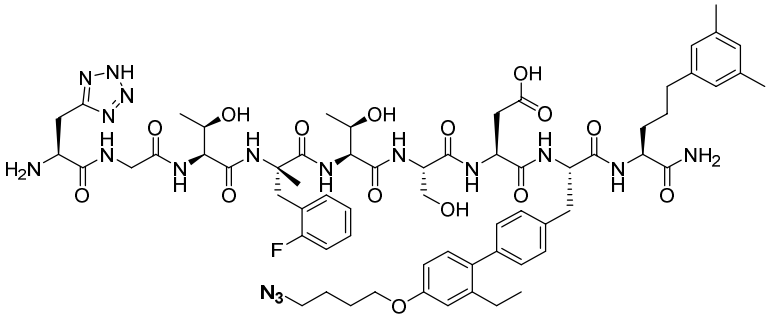


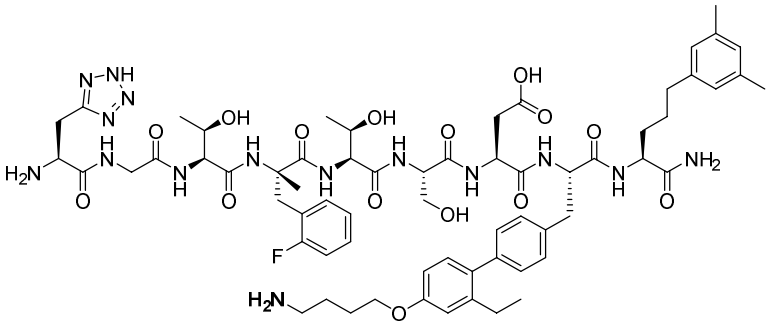
(P-II).

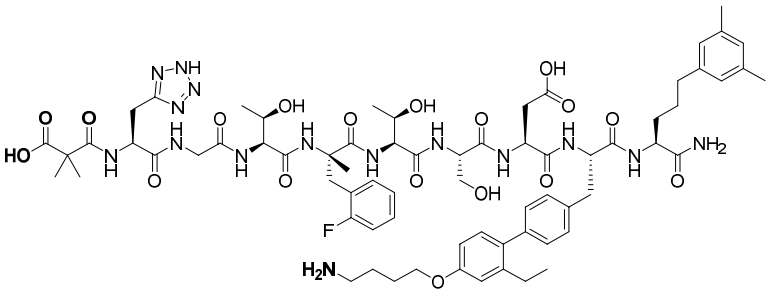
[00049] In some examples, X_1 is  ; X_2 is  ; X_3 is $–(CH_2)_{2-6}–NH–$;X_4 is H, and X_5 is  .

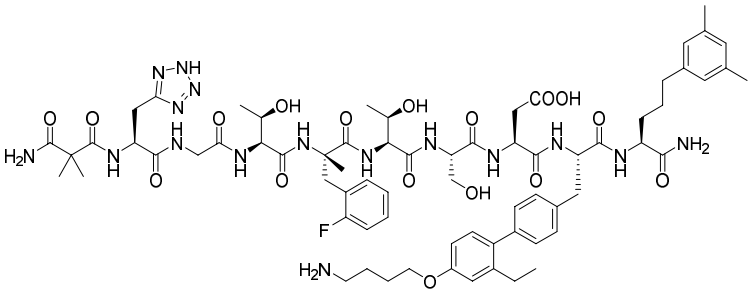
[00050] In various examples of the compound described herein, P has the structure selected from the group consisting of:

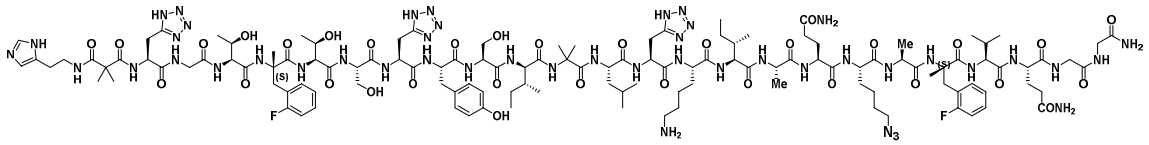
Structure


;


;


;


;



[00051] In various examples of the compound described herein, the compound has a half life of longer than 7 days in plasma.

[00052] In various examples of the compound described herein, the compound does not bind to G protein-coupled receptors (GPCRs) other than GLP1R.

[00053] In another aspect, provided herein is a pharmaceutical composition comprising the compound of any of the examples described herein.

[00054] In another aspect, provided herein is a pharmaceutical dosage form comprising the compound of any of the examples described herein.

[00055] In another aspect, provided herein is a method of selectively targeting GLP1R on a surface of a cell with the compound of any of the examples described herein. In some examples, the cell is a mammalian cell. In some examples, the cell is a human cell. In some examples, the cell is a pancreatic cell, a brain cell, a heart cell, a vascular tissue cell, a kidney cell, an adipose tissue cell, a liver cell, or a muscle cell.

[00056] In another example, provided herein is a method of enhancing GLP1R activity in an individual in need thereof comprising administering to the individual an effective amount of the compound of any of the examples described herein, the composition described herein, or the dosage form described herein.

[00056a] In another aspect, provided herein is a use of the compound described herein, in the manufacture of a medicament for enhancing GLP1R activity.

[00057] In another example, provided herein is a method of lowering blood glucose levels in an individual in need thereof comprising administering to the individual an effective amount of the compound of any of the examples described herein, the composition described herein, or the dosage form described herein.

[00057a] In another aspect, provided herein is a use of the compound described herein, in the manufacture of a medicament for lowering blood glucose levels.

[00058] In another example, provided herein is a method of lowering body weight in an individual in need thereof comprising administering to the individual an effective amount of the

compound of any of the examples described herein, the composition described herein, or the dosage form described herein.

[00058a] In another aspect, provided herein is a use of the compound described herein, in the manufacture of a medicament for lowering body weight.

[00059] In another example, provided herein is a method of treating a GLP1R-associated condition in an individual in need thereof comprising administering to the individual an effective amount of the compound of any of the examples described herein, the composition described herein, or the dosage form described herein. In some examples, the GLP1R-associated

condition is type II diabetes, obesity, liver disease, coronary artery disease, or kidney disease. In some examples, the GLP1R-associated condition is type II diabetes and/or obesity. In some examples,

[00059a] In another aspect, provided herein is a use of the compound described herein, in the manufacture of a medicament for treating a GLP1R-associated condition.

[00059b] In another aspect, provided herein is a compound described herein for use in therapy.

[00060] In various examples of any of the method described herein, the compound, the composition, or the dosage form of the present disclosure is administered subcutaneously, intravenously, intradermally, intraperitoneally, or intramuscularly. In another aspect, provided herein is a method of producing the compound described herein having a structure of Formula (A):

$$BA\text{-}(L\text{-}P)_m \quad (A),$$

the method comprising the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least m glutamine residues Gln with at least m equivalents of compound L-P, and

b) isolating the produced compound of Formula (A).

[00061] In another example, provided herein is a method of producing the compound described herein having a structure of Formula (I):

$$BA\text{-}L\text{-}P \quad (I),$$

the method comprising the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln with a compound L-P, and

b) isolating the produced compound of Formula (I).

[00062] In another example, provided herein is a method of producing the compound of claim 1 having a structure of Formula (A):

$$BA\text{-}(L\text{-}P)_m \quad (A),$$

wherein the linker L has has the structure of formula (L'):

$$\text{-La-Y-Lp-} \quad (L'),$$

wherein La is a first linker covalently attached to the BA;
Y is a group comprising a triazole, and
Lp is a second linker covalently attached to the P,
the method comprising the steps of:
a) contacting, in the presence of a transglutaminase, the BA comprising at least m glutamine residues Gln with the first linker La comprising an azide or an alkyne moiety;

b) contacting the product of step a) with at least m equivalents of compound Lp-P, wherein the second linker Lp comprises an azide or an alkyne moiety, wherein La and Lp are capable of reacting to produce a triazole, and

c) isolating the produced compound of Formula (A).

[00063] In another example, provided herein is a method of producing the compound described herein having a structure of Formula (I):

BA-L-P (I),

wherein the linker L has has the structure of formula (L'):

-La-Y-Lp- (L'),

wherein La is a first linker covalently attached to the BA;

Y is a group comprising a triazole, and

Lp is a second linker covalently attached to the P,

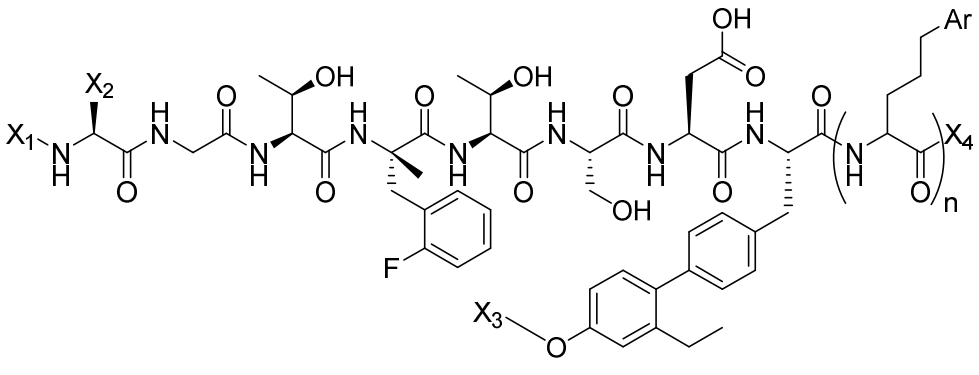
the method comprising the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln with the first linker La comprising an azide or an alkyne moiety;

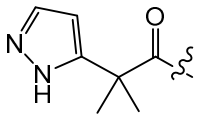
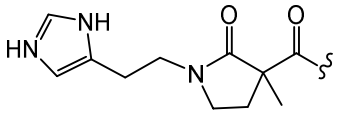
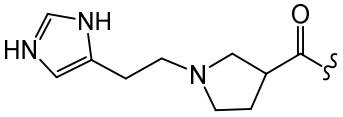
b) contacting the product of step a) with a compound Lp-P, wherein the second linker Lp comprises an azide or an alkyne moiety, wherein La and Lp are capable of reacting to produce a triazole, and

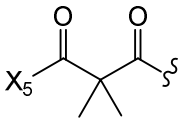
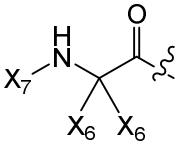
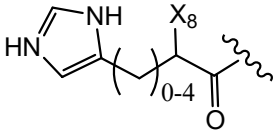
c) isolating the produced compound of Formula (I).

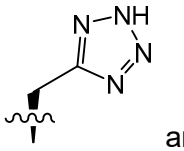
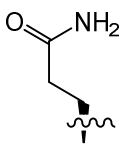
[00064] In another aspect, provided herein is a compound having a structure selected from the group consisting of Formula (P-IB), Formula (P-IIB), and Formula (P-IIIB):



(P-IB),

X_1 is selected from H;  ;  ;  ;

 ;  ; and  ;

X_2 is selected from  and  ;

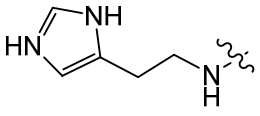
X_3 is selected from $–(CH_2)_{2\text{-}6}–NH_2$, $–(CH_2)_{2\text{-}6}–N_3$, and $-CH_3$, with the proviso that when X_3 is $-CH_3$, n is 1 and Ra in at least one occurrence is selected from $–(CH_2)_{2\text{-}6}–NH_2$ and $–(CH_2)_{2\text{-}6}–N_3$;

n is 0 or 1;

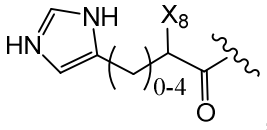
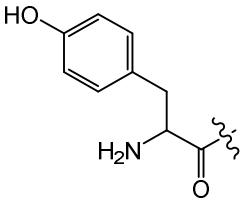
m is an integer from 0 to 3;

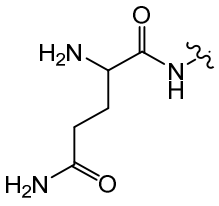
Ra is independently at each occurrence selected from $-CH_3$, $–(CH_2)_{2\text{-}6}–NH_2$, and $–(CH_2)_{2\text{-}6}–N_3$;

X_4 is selected from H and phenyl;

X_5 is selected from -OH, $-NH_2$, -NH-OH, and  ;

X_6 is independently at each occurrence selected from H, -OH, $-CH_3$, and $-CH_2OH$;

X_7 is selected from H,  , and  ;

X_8 is selected from H, -OH, $-NH_2$, and  ,

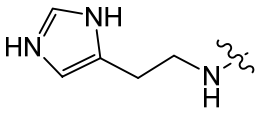
and pharmaceutically acceptable salts thereof.

[00066] In some example, P has the structure selected from the group consisting of:

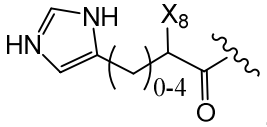
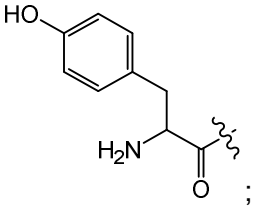
Structure

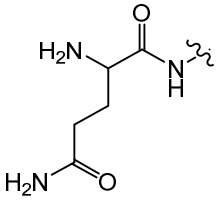
Ra is independently at each occurrence selected from H, -CH_3, –$(CH_2)_{2-6}$–NH_2, and –$(CH_2)_{2-6}$–N_3;

X_4 is selected from H and phenyl;

X_5 is selected from -OH, -NH_2, -NH-OH, and ;

X_6 is independently at each occurrence selected from H, -OH, -CH_3, and -CH_2OH;

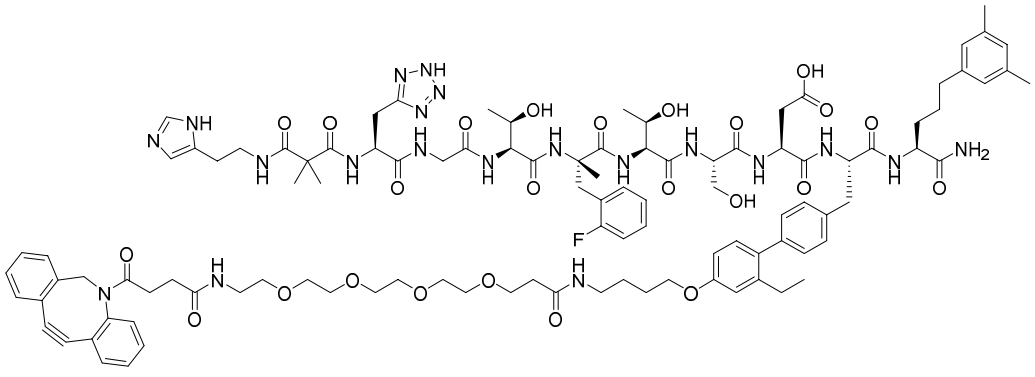
X_7 is selected from H, , and ;

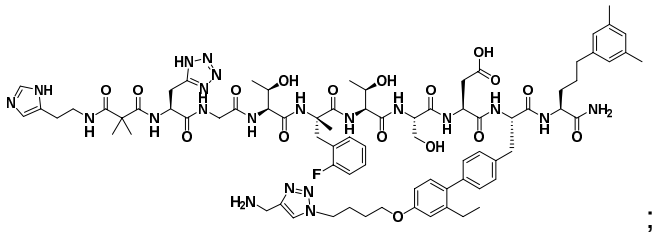
X_8 is selected from H, -OH, -NH_2, and ,

and pharmaceutically acceptable salts thereof.

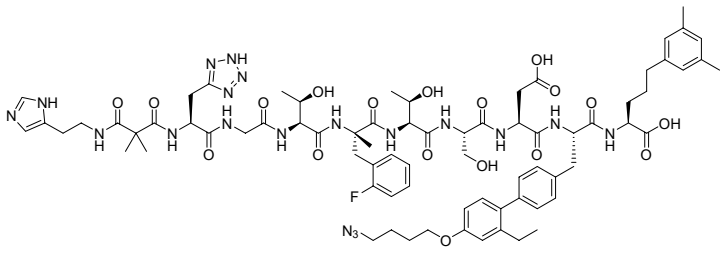
[00069] In some examples, The compound described above has a structure selected from the group consisting of:

Structure

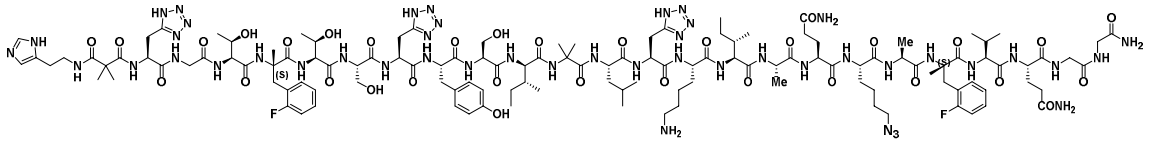
;



;



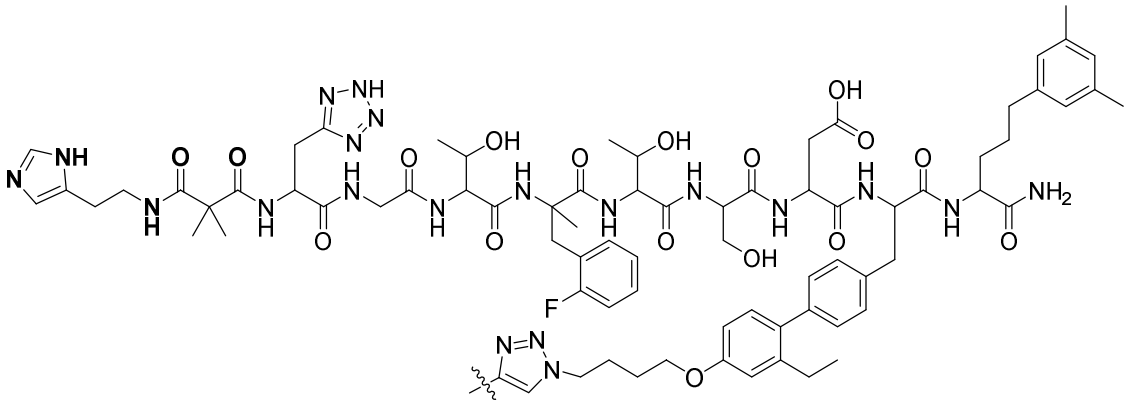
, and



,

or a pharmaceutically acceptable salt thereof.

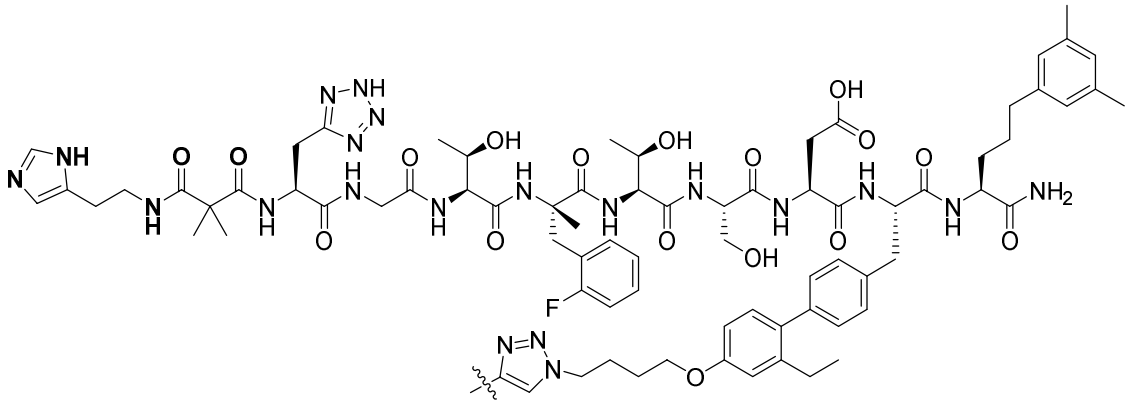
[00071] In yet another aspect, provided herein is an antibody-drug conjugate comprising a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof and a payload having the structure:



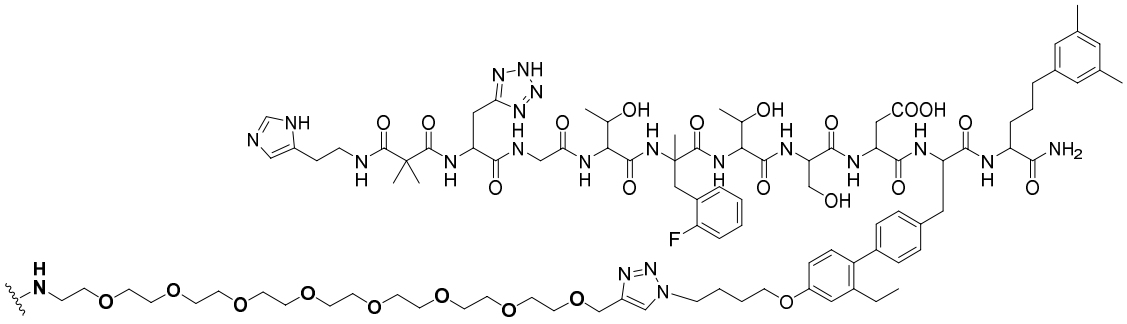
,

wherein  is the point of attachment of the payload to the antibody or the antigen-binding fragment thereof directly or through a linker.

[00072] In one example, the payload has the structure:

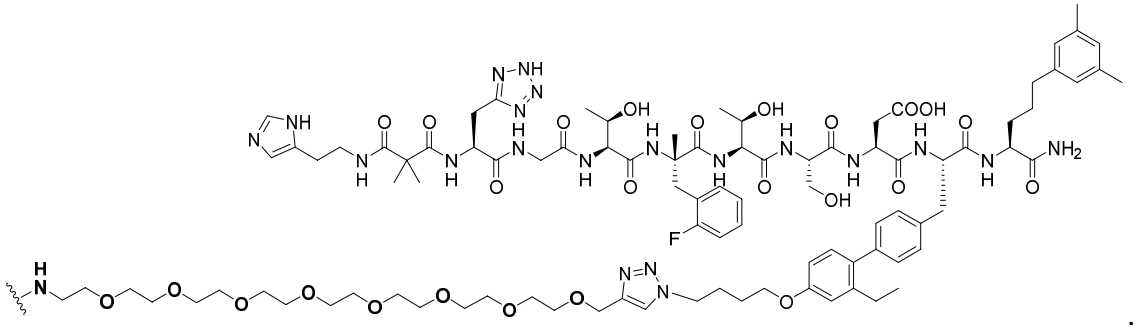


[00073] In yet another aspect, provided herein is an antibody-drug conjugate comprising a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof and a linker-payload having the structure:



wherein —§– is the point of attachment of the linker-payload to the antibody or the antigen-binding fragment thereof.

[00074] In one example, the linker-payload has the structure:



[00075] These and other examples of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the disclosure, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

WHAT IS CLAIMED IS:

1. A compound having a structure of Formula (A):

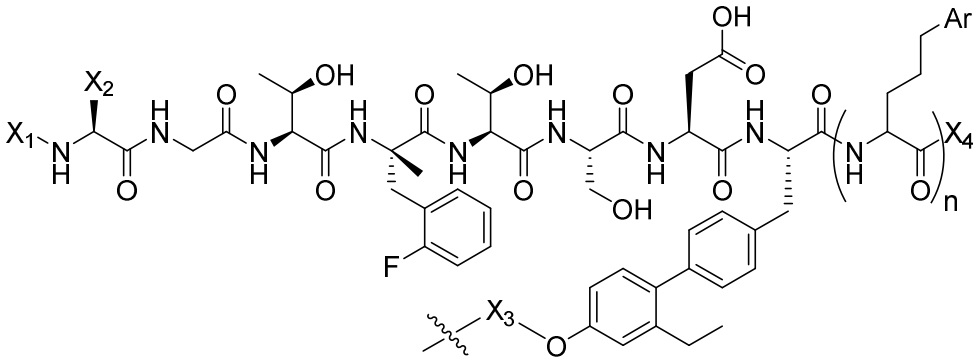
$$BA\text{-}(L\text{-}P)_m \quad (A),$$

wherein:

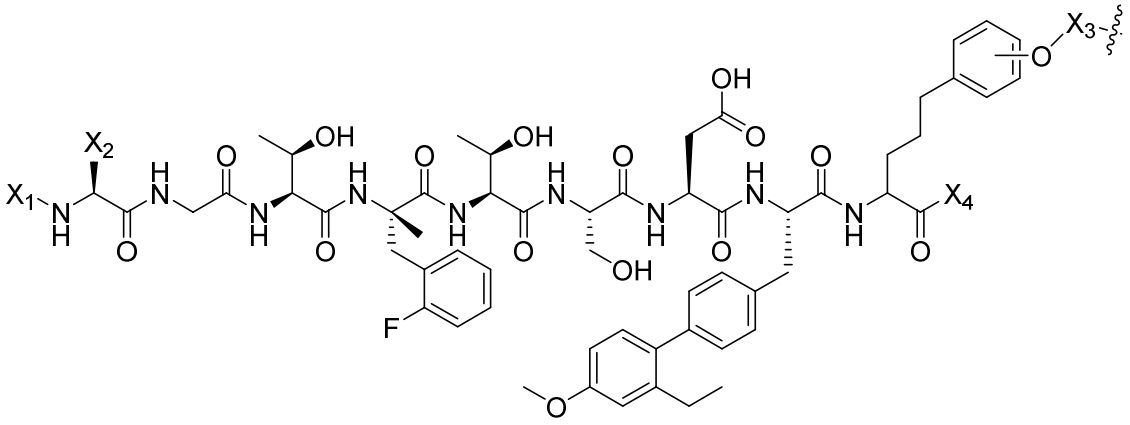
BA is an antibody or an antigen-binding fragment thereof;

L is a non-cleavable linker;

P is a payload having the structure selected from the group consisting of:

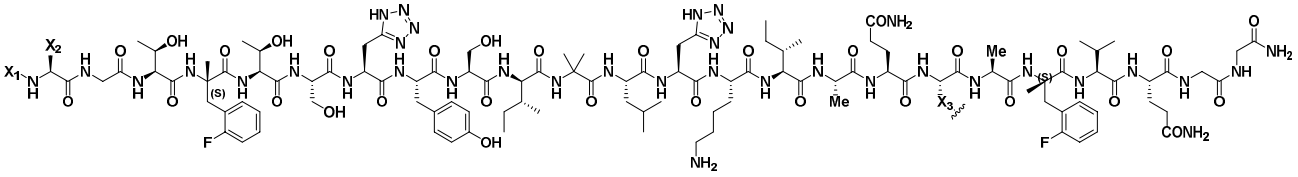


(P-IA),



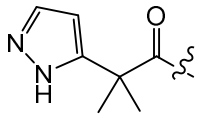
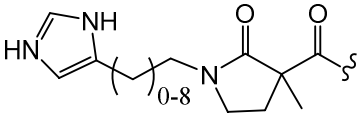
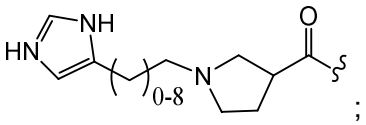
(P-IIA),

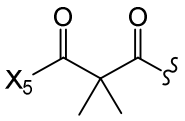
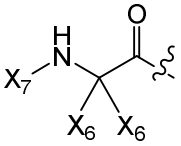
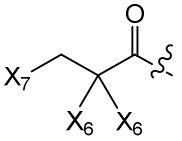
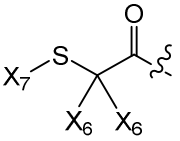
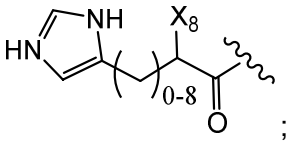
and

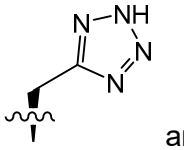
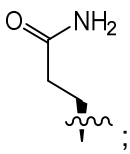


(P-IIIA),

wherein  is the point of attachment of the payload to L;

X_1 is selected from H;  ;  ;  ;

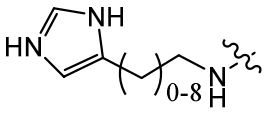
 ;  ;  ;  , and  ;

X_2 is selected from  and  ;

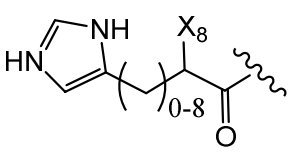
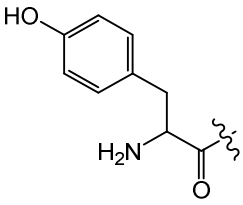
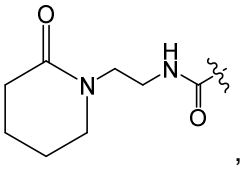
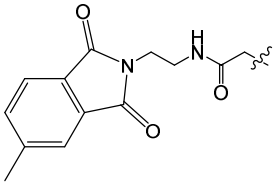
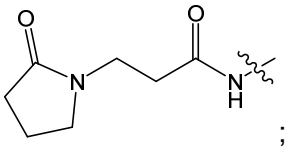
X_3 is selected from a bond, $–(CH_2)_{2\text{-}6}–NH–$, $–(CH_2)_{2\text{-}6}–Tr–$, and $–(CH_2)_{2\text{-}6}–Tr–(CH_2)_{1\text{-}6}–NH$, where Tr is a triazole moiety;

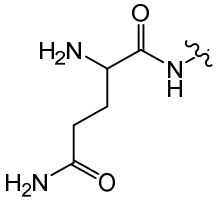
n is 0 or 1;

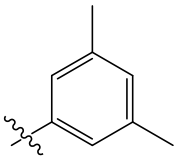
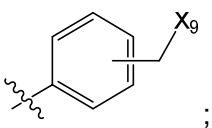
X_4 is selected from $-NH_2$, -OH and -N(H)(phenyl);

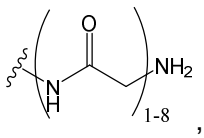
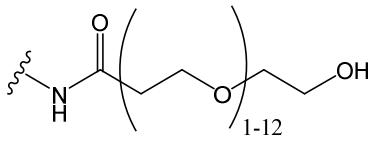
X_5 is selected from -OH, $-NH_2$, -NH-OH, and  ;

X_6 is independently at each occurrence selected from H, -OH, $-CH_3$, and $-CH_2OH$;

X_7 is selected from H,  ,  ,  ,  ,  ;

X_8 is selected from H, -OH, $-NH_2$, and  ;

Ar is selected from  and  ;

X_9 is selected from -NH_2,  , and  , and

m is an integer from 1 to 4

or a pharmaceutically acceptable salt thereof.

2. A compound having a structure of Formula (I):

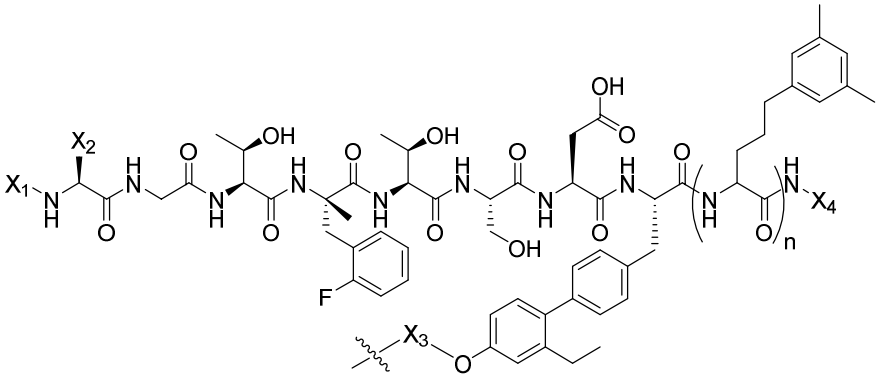
BA-L-P (I),

wherein:

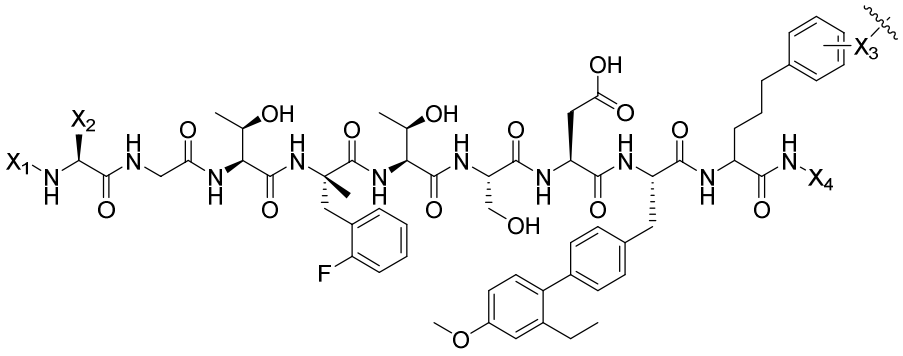
BA is an antibody or an antigen-binding fragment thereof;

L is a non-cleavable linker;

P is a payload having the structure selected from the group consisting of:

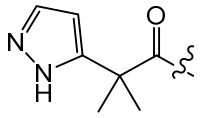
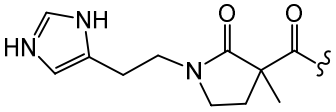
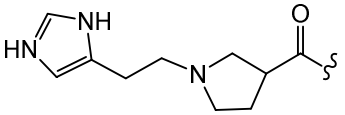


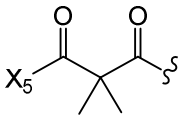
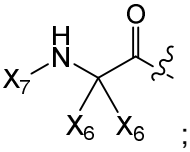
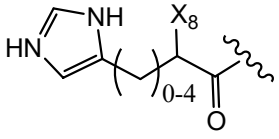
(P-I) and

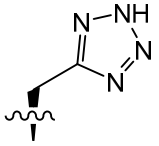
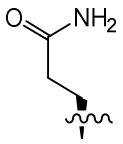


(P-II),

wherein  is the point of attachment of the payload to L;

X_1 is selected from H;  ;  ;  ;

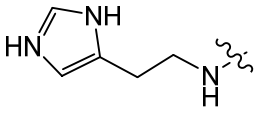
 ;  ; and  ;

X_2 is selected from  and  ;

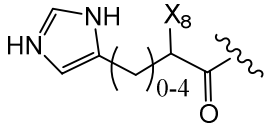
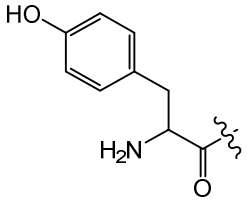
X_3 is selected from $–(CH_2)_{2\text{-}6}–NH–$ and $–(CH_2)_{2\text{-}6}–Tr–$, where Tr is a triazole moiety;

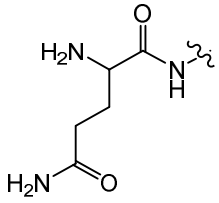
n is 0 or 1;

X_4 is selected from H and phenyl;

X_5 is selected from -OH, $-NH_2$, -NH-OH, and  ;

X_6 is independently at each occurrence selected from H, -OH, $-CH_3$, and $-CH_2OH$;

X_7 is selected from H,  , and  ;

X_8 is selected from H, -OH, $-NH_2$, and  ,

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein BA is a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof.

4. The compound of claim 3, wherein the GLP1R-targeting antibody is a GLP1R agonist antibody selected from the group consisting of 5A10, 9A10, AB9433-I, h38C2, PA5-111834, NLS1205, MAB2814, EPR21819, or glutazumab.

5. The compound of claim 1, wherein the linker L is attached to one or both heavy chains of the BA or to one or both light chains of the BA.

6. The compound of claim 5, wherein the linker L is attached to one or both heavy chain variable domains of the BA or to one or both light chain variable domains of the BA.

7. The compound of claim 1, wherein the linker L is attached to BA via a glutamine residue or a lysine residue.

8. The compoud of claim 1, wherein m is 1 or 2.

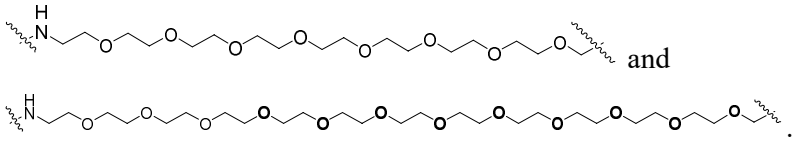
9. The compound of claim 1, wherein the linker L has the structure of formula (L'):

-La-Y-Lp- (L'),

wherein La is a first linker covalently attached to the BA;
Y is a group comprising a triazole, and
Lp is absent or a second linker covalently attached to the P, wherein when Lp is absent, Y is also absent.

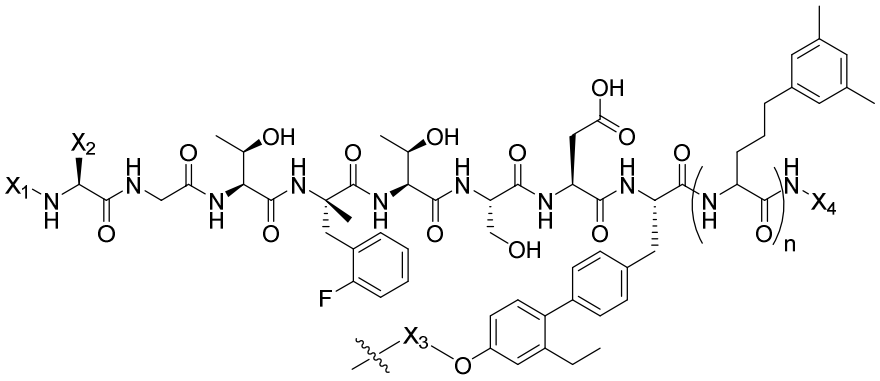
10. The compound of claim 9, wherein Y-Lp is absent.

11. The compound of claim 9, wherein La has a structure selected from the group consisting of:

 and

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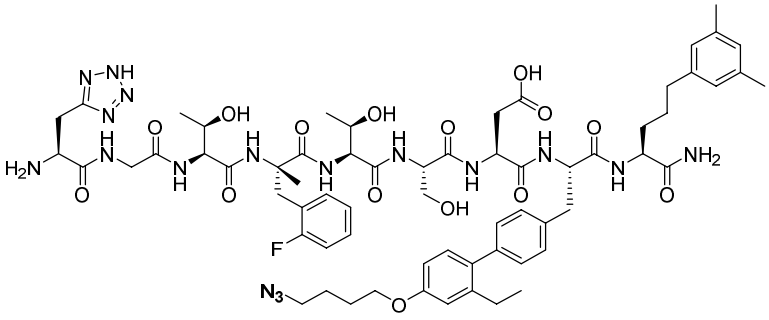
12. The compound of claim 1, wherein P has the structure



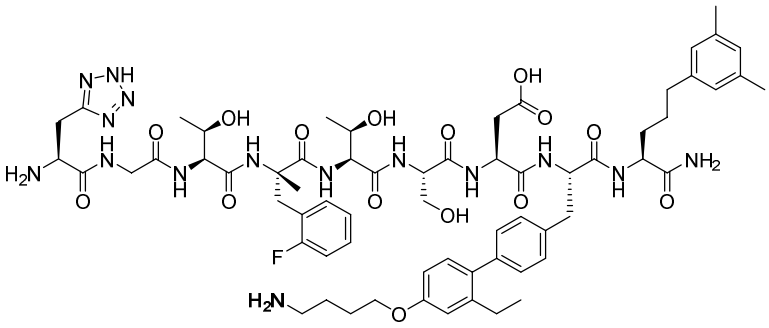
(P-I).

13. The compound of claim 1, wherein P has the structure selected from the group consisting of:

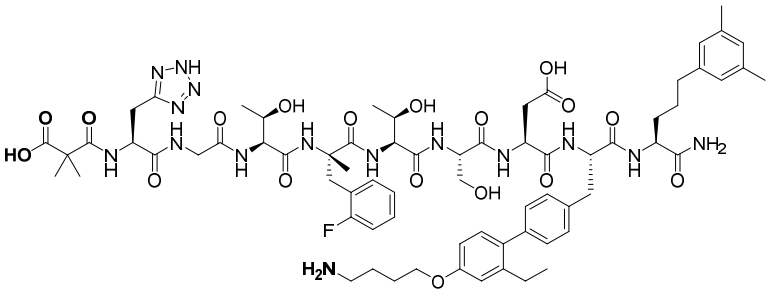
Structure



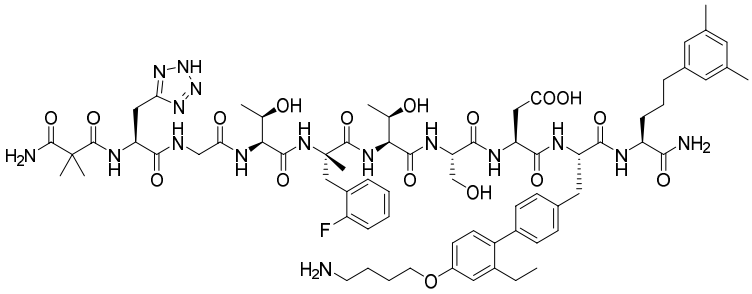
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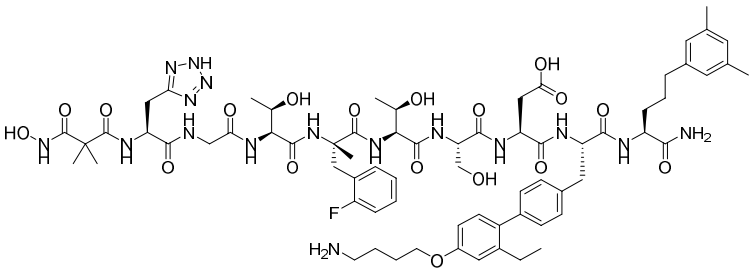


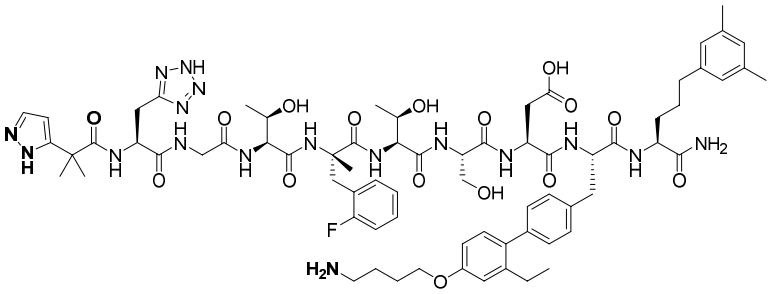
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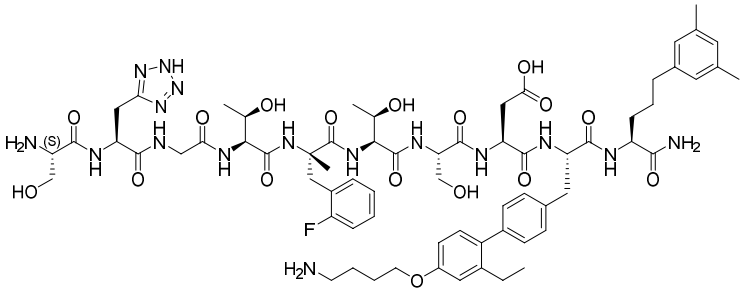


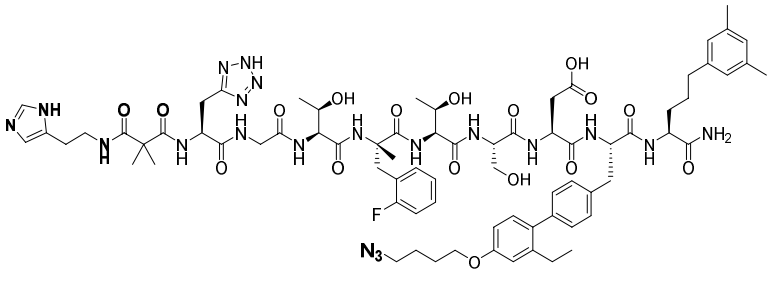
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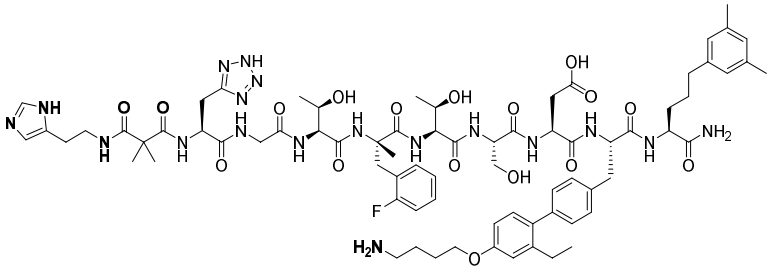

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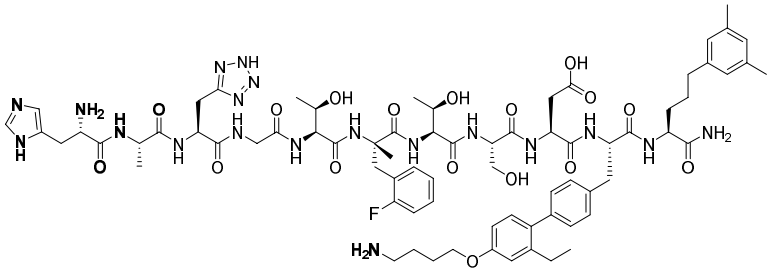

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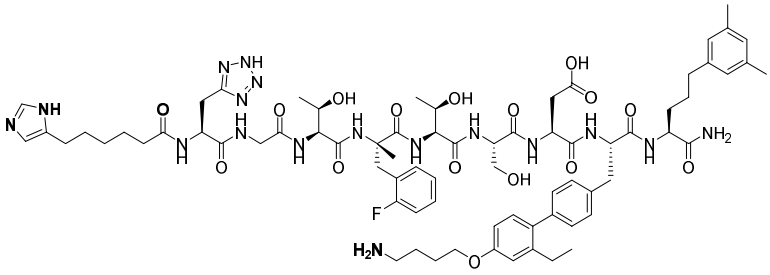

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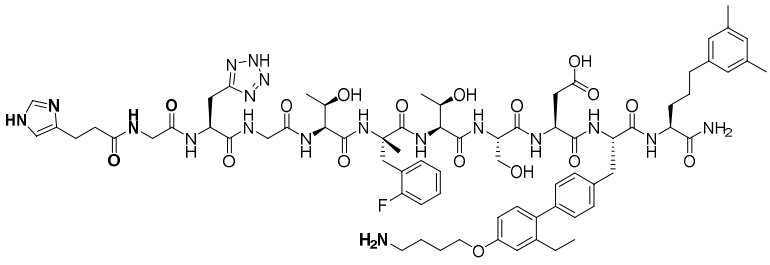

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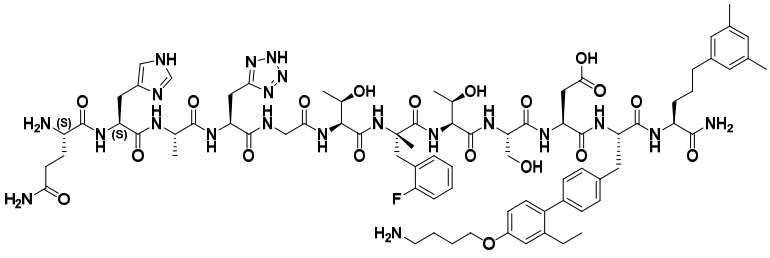

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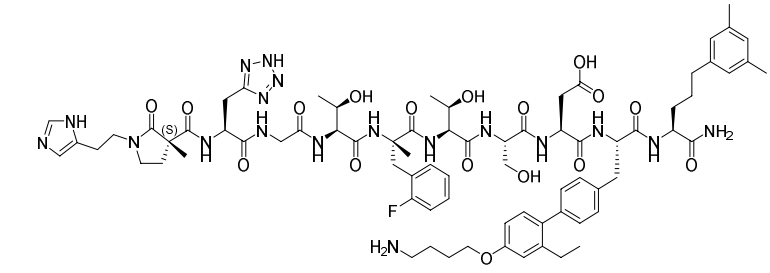

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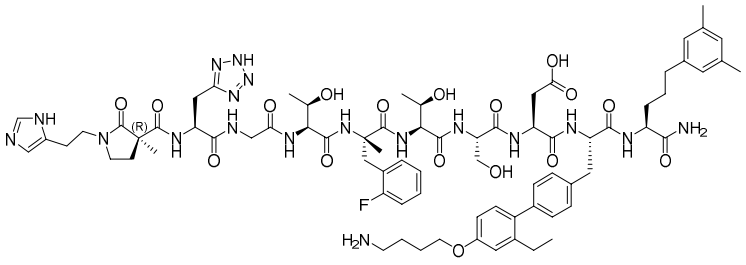
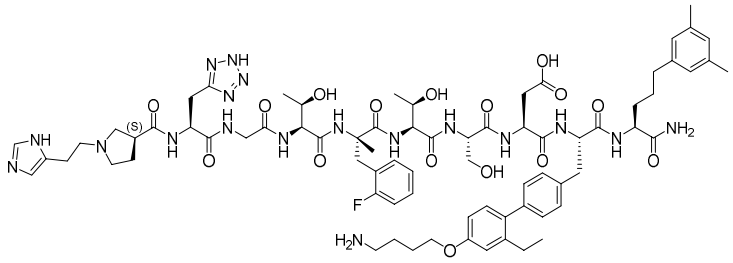
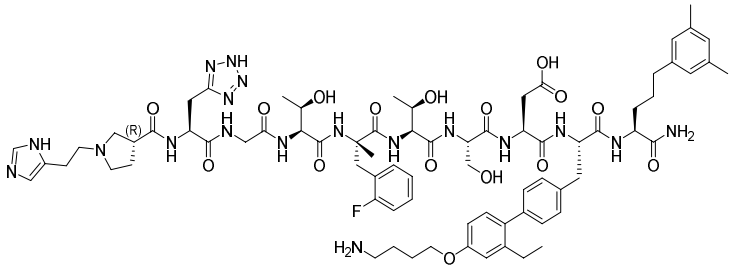
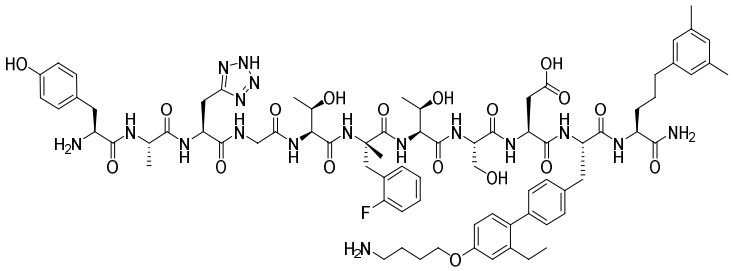
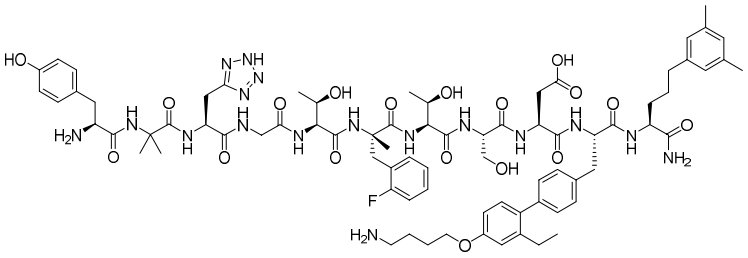
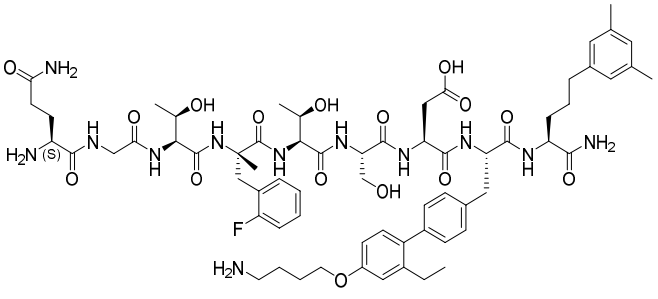

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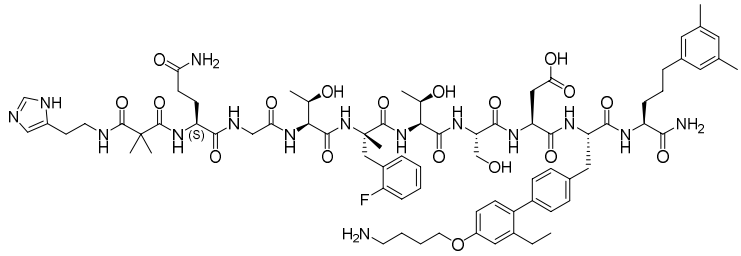
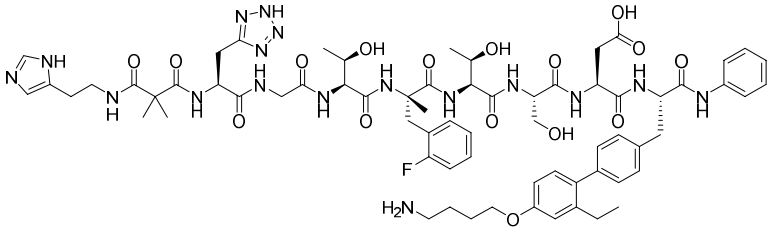
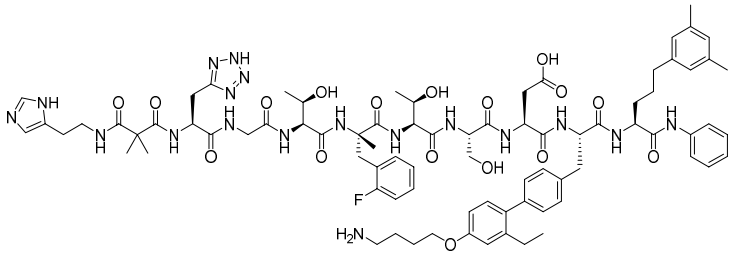
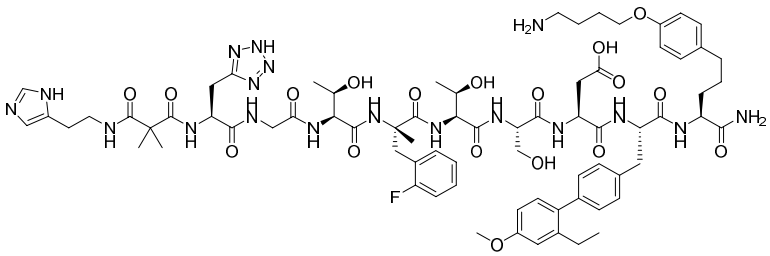
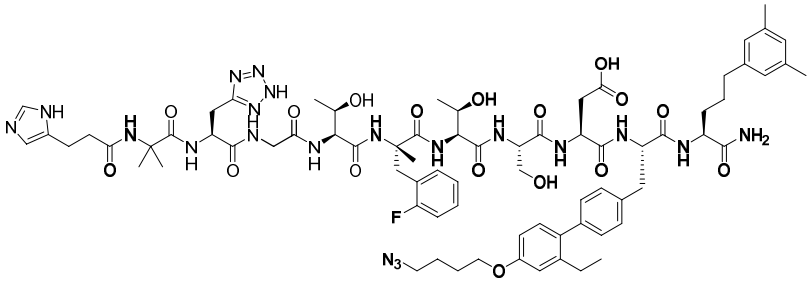
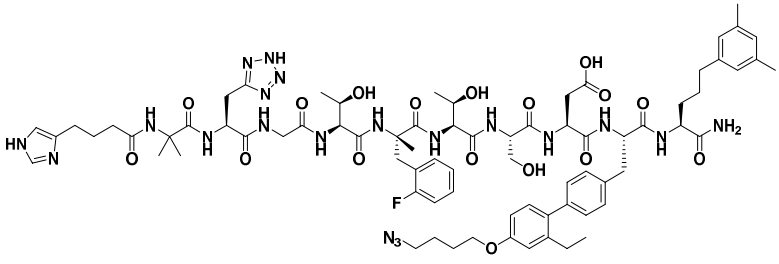

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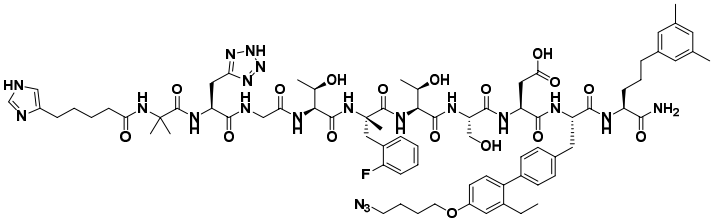
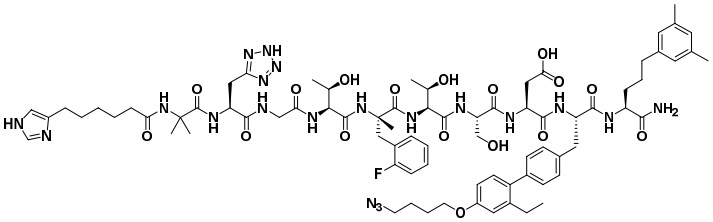
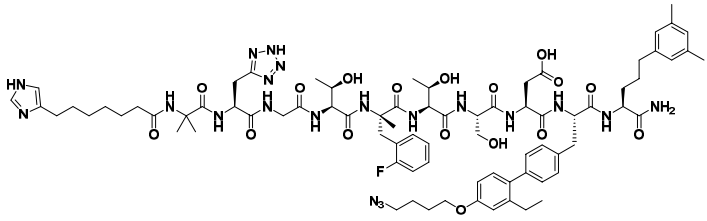
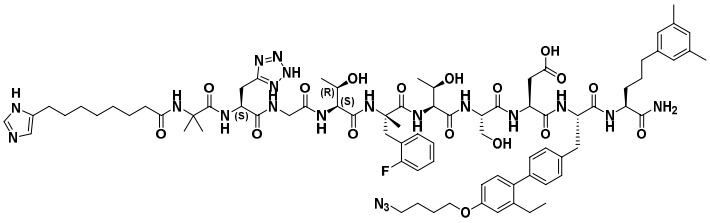
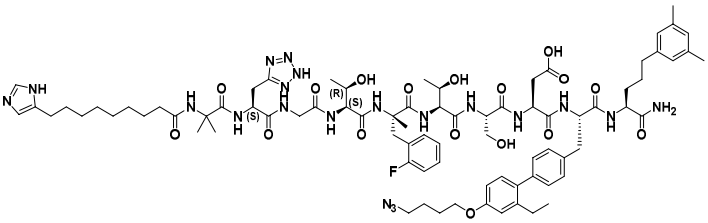
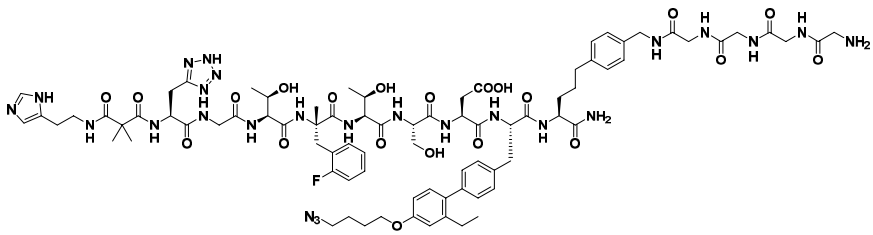
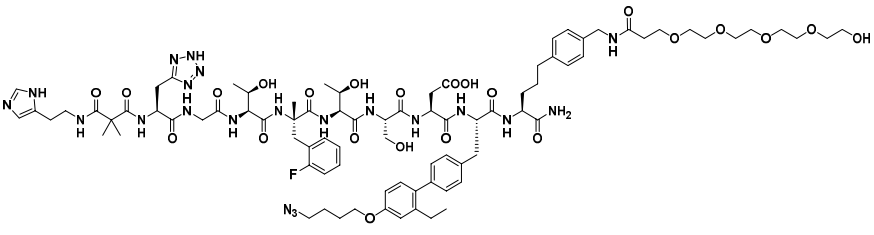

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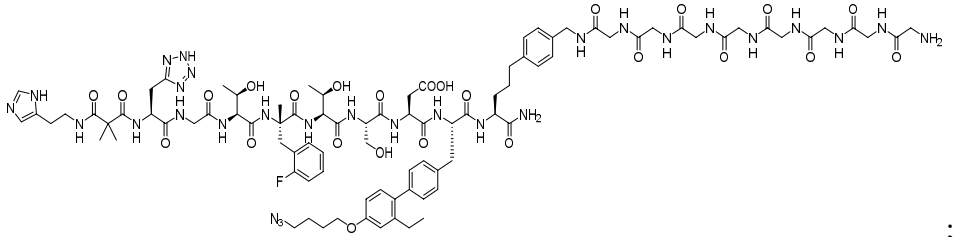
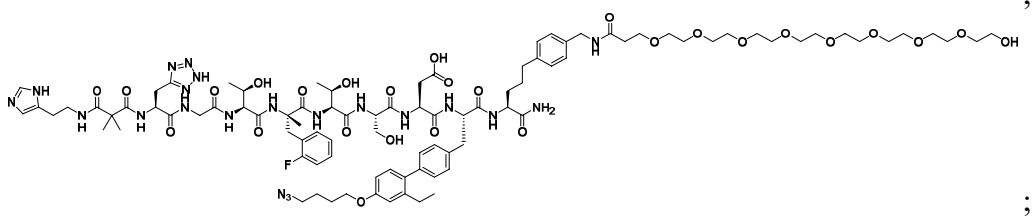
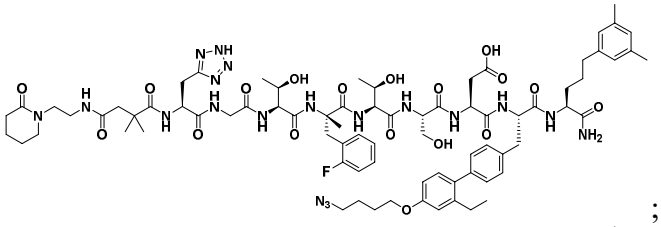
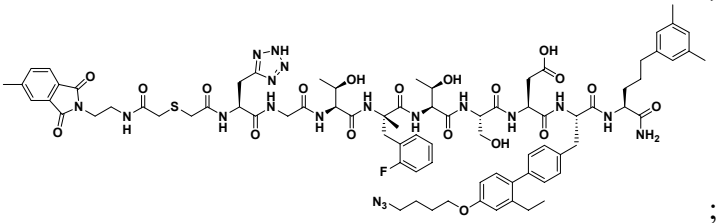
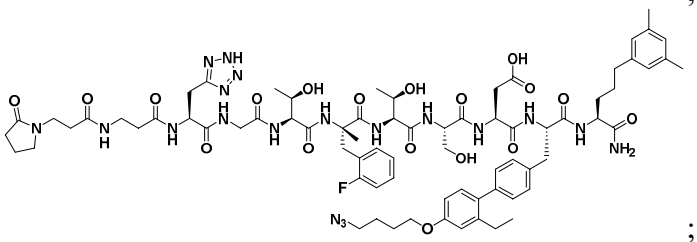
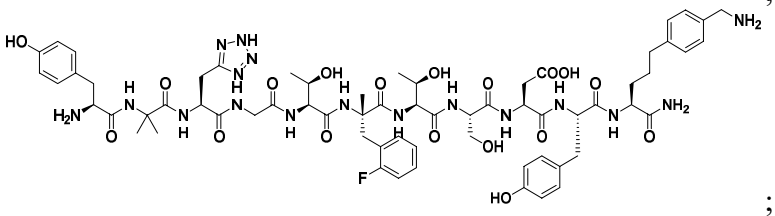
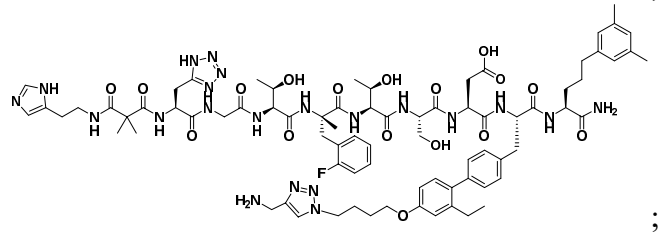

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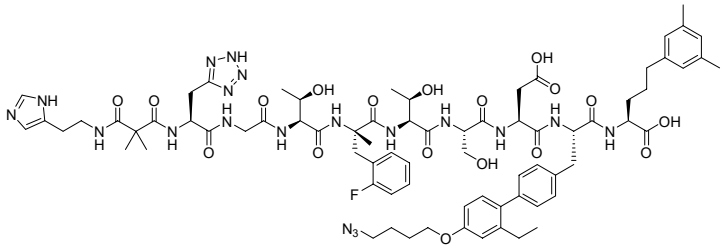

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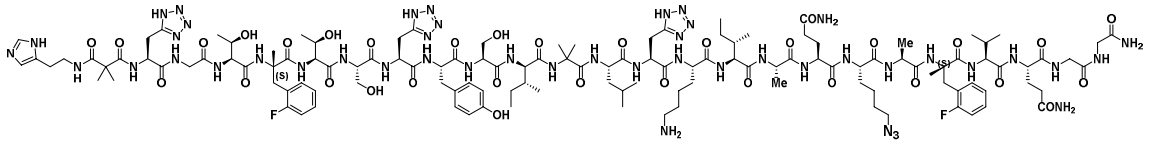

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14. The compound of claim 1, wherein the compound has a half life of longer than 7 days in plasma.

15. The compound of claim 1, wherein the compound does not bind to G protein-coupled receptors (GPCRs) other than GLP1R.

16. A pharmaceutical composition comprising the compound of claim 1.

17. A pharmaceutical dosage form comprising the compound of claim 1.

18. A method of selectively targeting GLP1R on a surface of a cell with the compound of claim 1.

19. Use of the compound of claim 1, in the manufacture of a medicament for enhancing GLP1R activity.

20. Use of the compound of claim 1, in the manufacture of a medicament for lowering blood glucose levels.

21. Use of the compound of claim 1, in the manufacture of a medicament for lowering body weight.

22. Use of the compound of claim 1, in the manufacture of a medicament for treating a GLP1R-associated condition.

23. A compound of claim 1 for use in therapy.

24. A method of producing the compound of claim 1 having a structure of Formula (A):

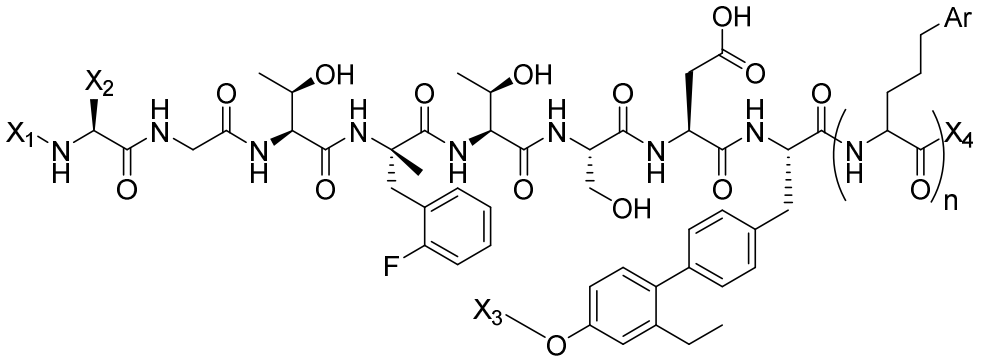
$$BA\text{-}(L\text{-}P)_m \quad (A),$$

the method comprising the steps of:

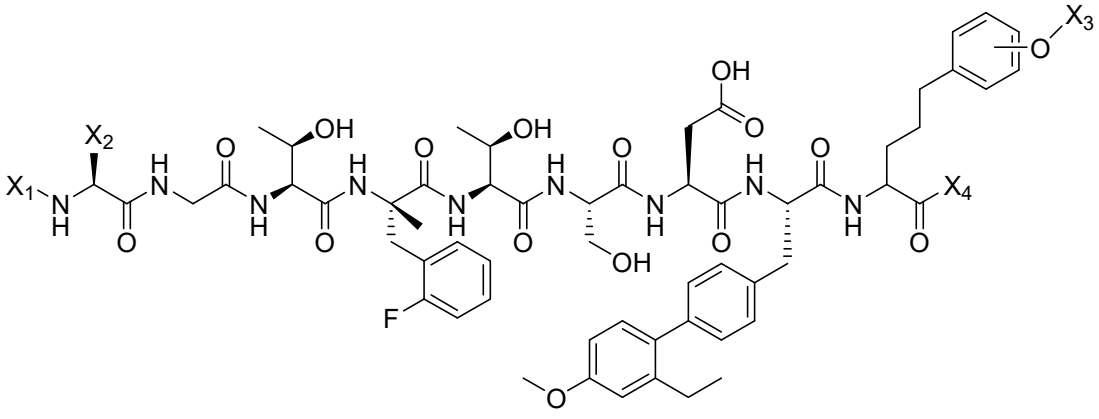
a) contacting, in the presence of a transglutaminase, the BA comprising at least m glutamine residues Gln with at least m equivalents of compound L-P, and

b) isolating the produced compound of Formula (A).

25. A compound having a structure selected from the group consisting of Formula (P-IB), Formula (P-IIB), and Formula (P-IIIB):

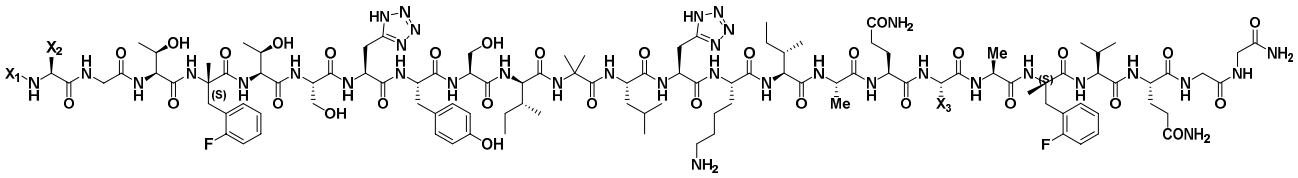


(P-IB),

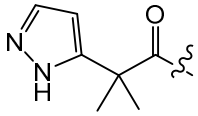
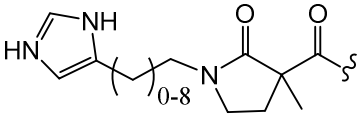
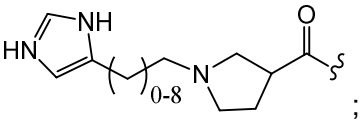


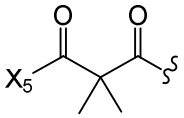
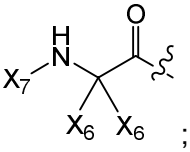
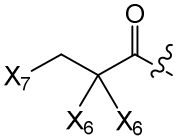
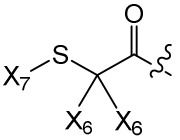
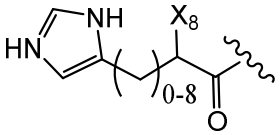
(P-IIB),

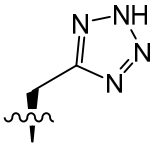
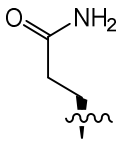
and



(P-IIIB), wherein:

X_1 is selected from H;  ;  ;  ;

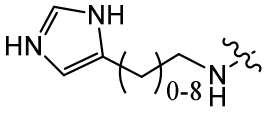
 ;  ;  ;  , and  ;

X_2 is selected from  and  ;

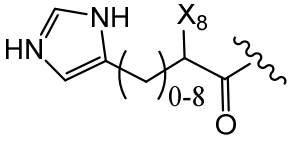
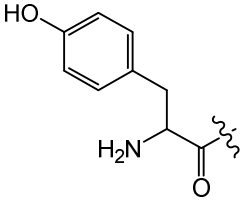
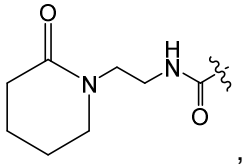
X_3 is selected from $-CH_3$, $–(CH_2)_{2-6}–NH_2$, $–(CH_2)_{2-6}–N_3$, and $–(CH_2)_{2-6}–Tr–(CH_2)_{1-6}–NH_2$, where Tr is a triazole moiety;

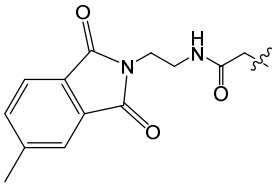
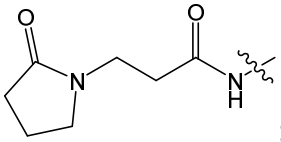
n is 0 or 1;

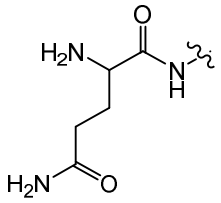
X_4 is selected from $-NH_2$, -OH and -N(H)(phenyl);

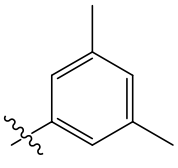
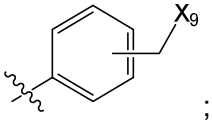
X_5 is selected from -OH, $-NH_2$, -NH-OH, and  ;

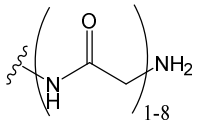
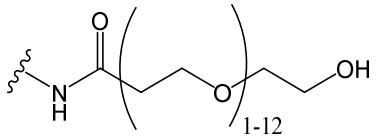
X_6 is independently at each occurrence selected from H, -OH, $-CH_3$, and $-CH_2OH$;

X_7 is selected from H,  ,  ,  ,

 ,  ;

X_8 is selected from H, -OH, $-NH_2$, and  ;

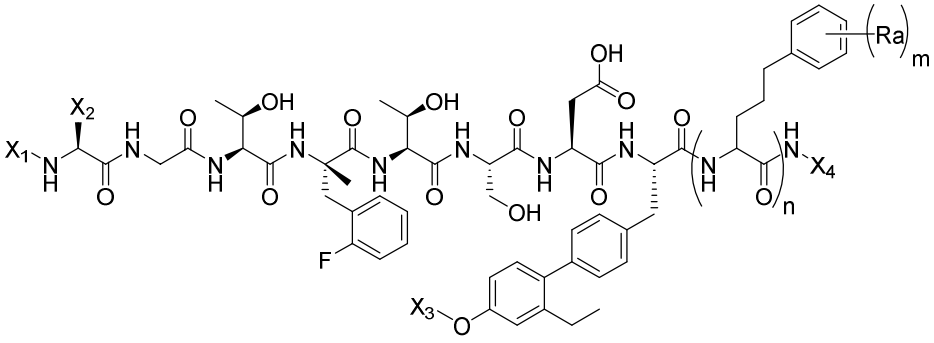
Ar is selected from  and  ;

X_9 is selected from $-NH_2$,  , and  , and

m is an integer from 1 to 4

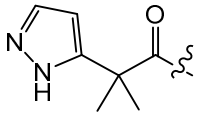
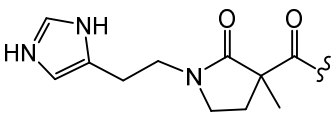
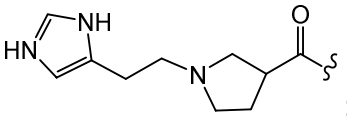
or a pharmaceutically acceptable salt thereof.

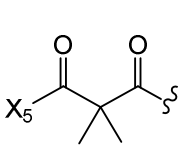
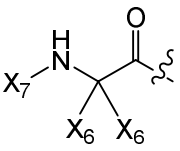
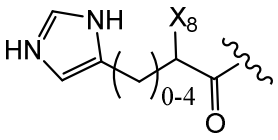
26. A compound having a structure of Formula (II):

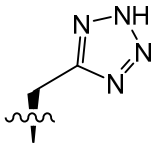
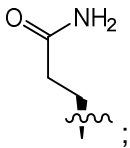


(II),

wherein:

X_1 is selected from H;  ;  ;  ;

 ;  ; and  ;

X_2 is selected from  and ;

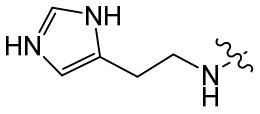
X_3 is selected from $–(CH_2)_{2-6}–NH_2$, $–(CH_2)_{2-6}–N_3$, and $-CH_3$, with the proviso that when X_3 is $-CH_3$, n is 1 and Ra in at least one occurrence is selected from $–(CH_2)_{2-6}–NH_2$ and $–(CH_2)_{2-6}–N_3$;

n is 0 or 1;

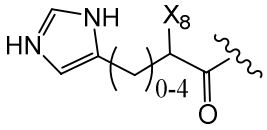
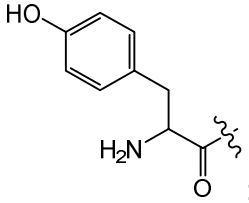
m is an integer from 0 to 3;

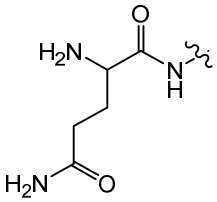
Ra is independently at each occurrence selected from $-CH_3$, $–(CH_2)_{2-6}–NH_2$, and $–(CH_2)_{2-6}–N_3$;

X_4 is selected from H and phenyl;

X_5 is selected from -OH, $-NH_2$, -NH-OH, and ;

X_6 is independently at each occurrence selected from H, -OH, $-CH_3$, and $-CH_2OH$;

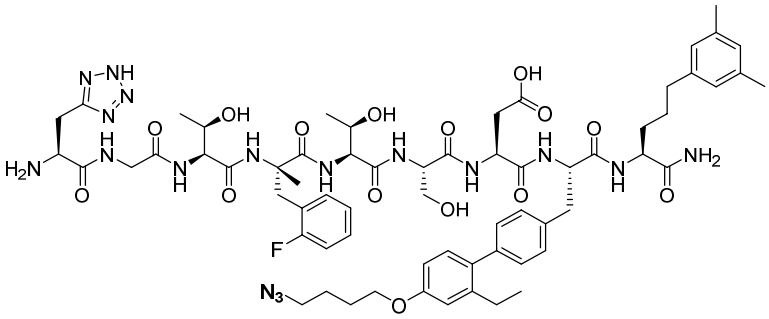
X_7 is selected from H, , and ;

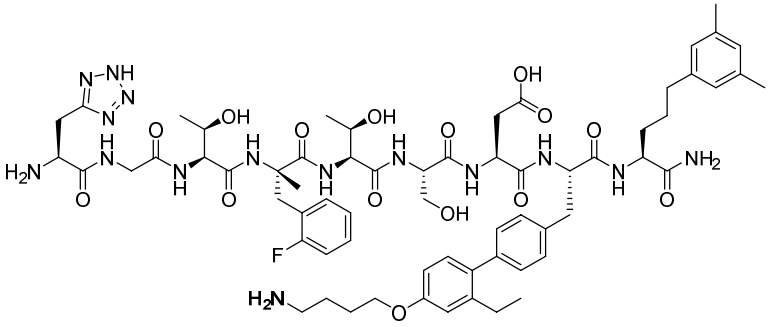
X_8 is selected from H, -OH, $-NH_2$, and ,

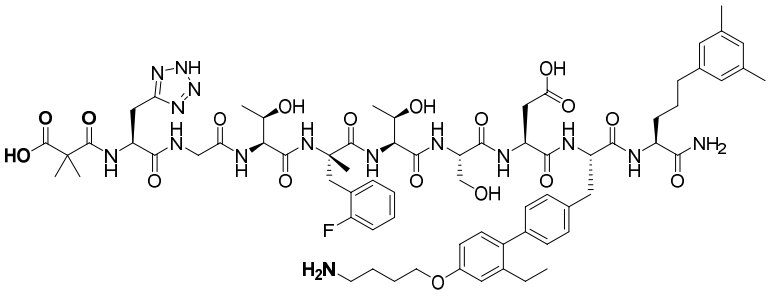
and pharmaceutically acceptable salts thereof.

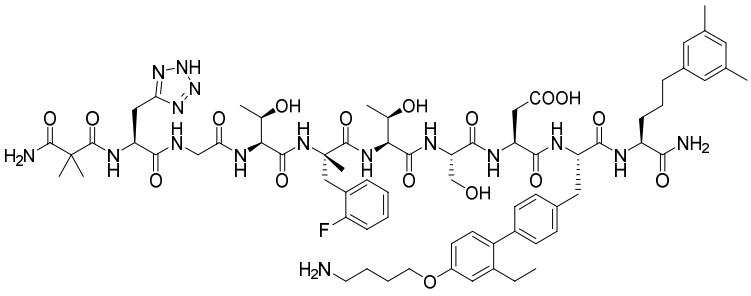
27. The compound of claim 25, wherein P has the structure selected from the group consisting of:

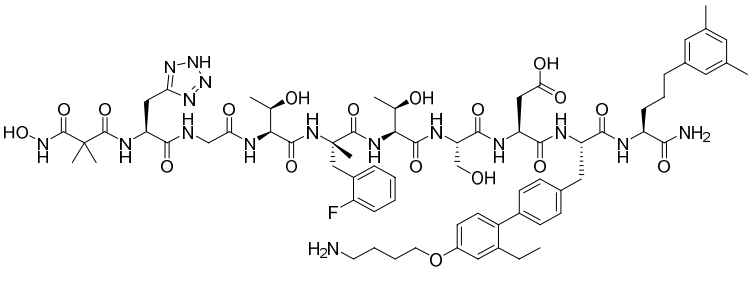
Structure

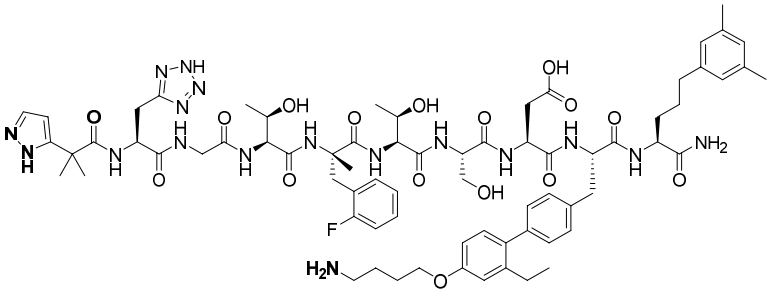

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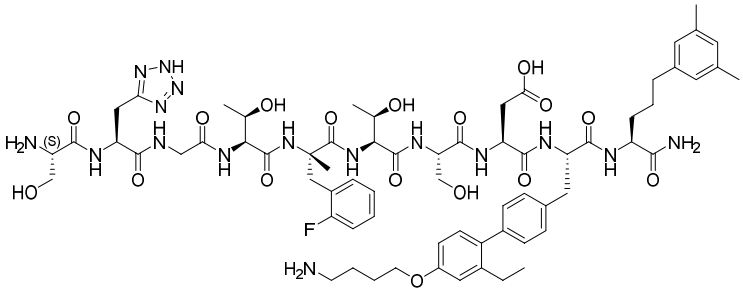

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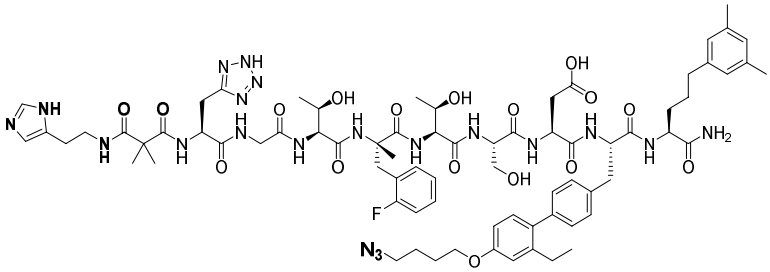

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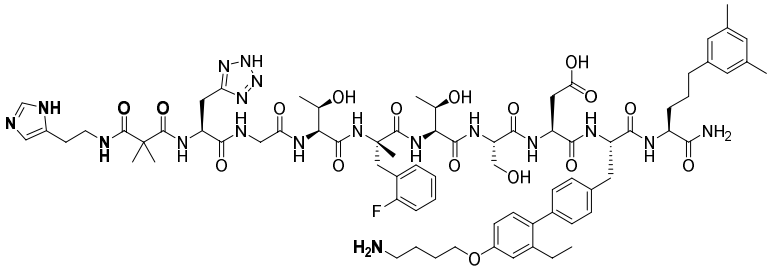

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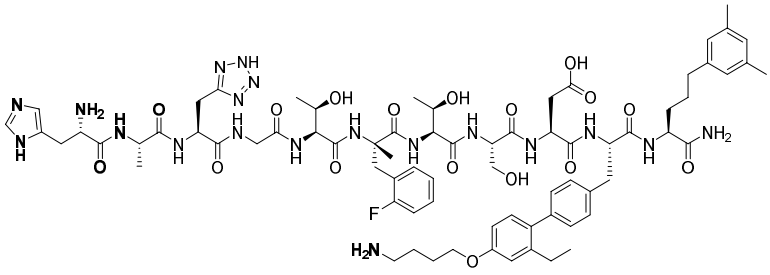

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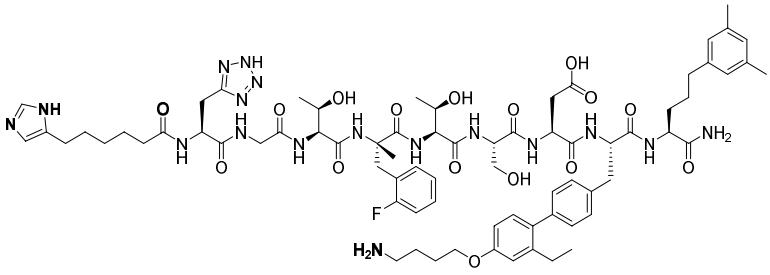

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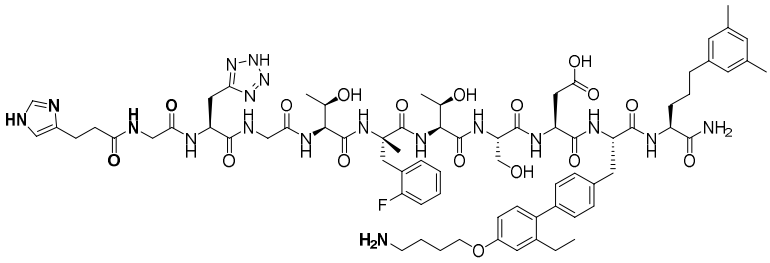

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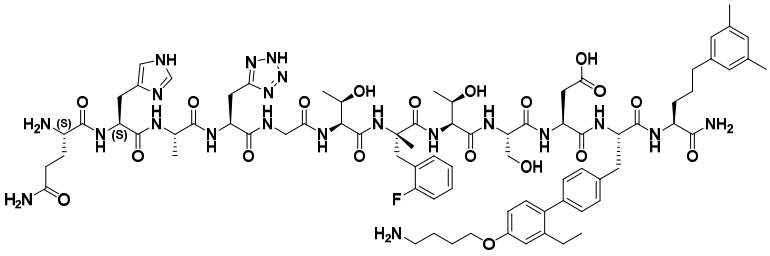

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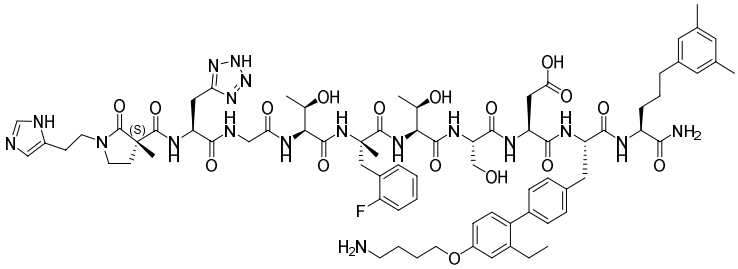

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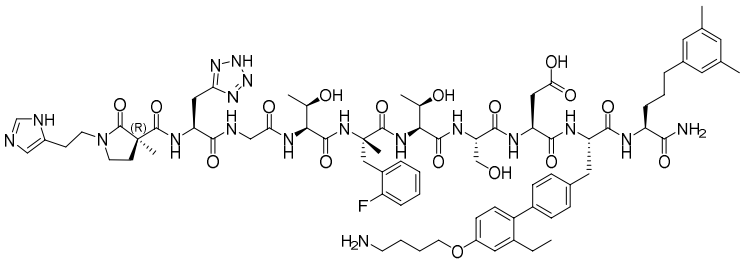

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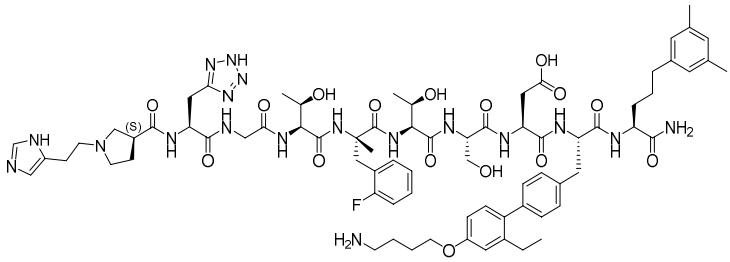

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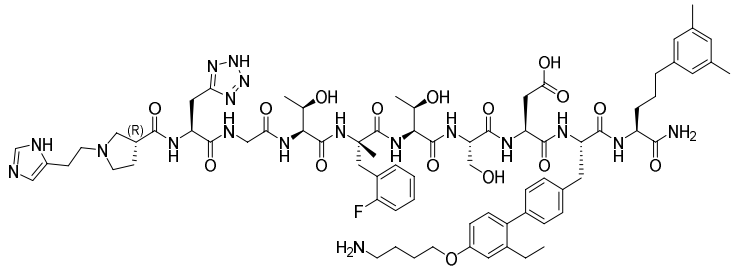
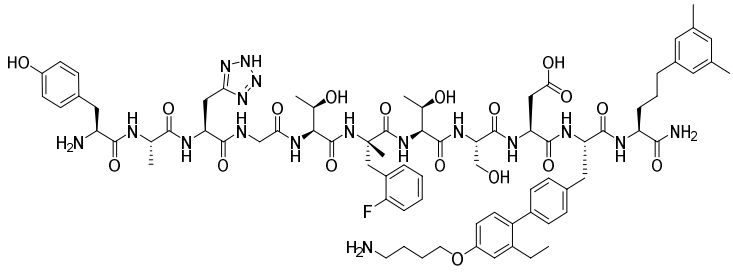
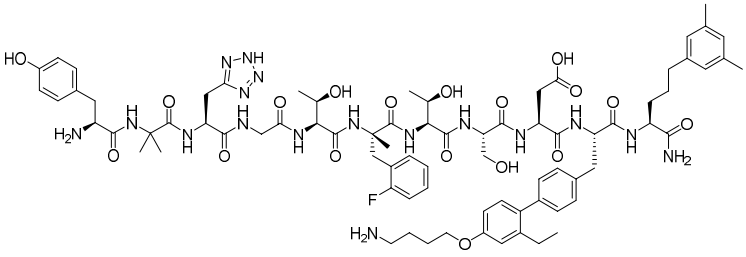
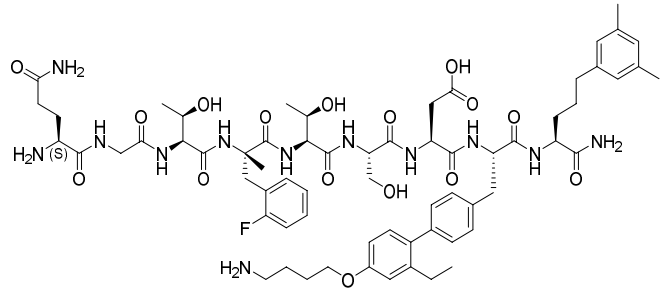
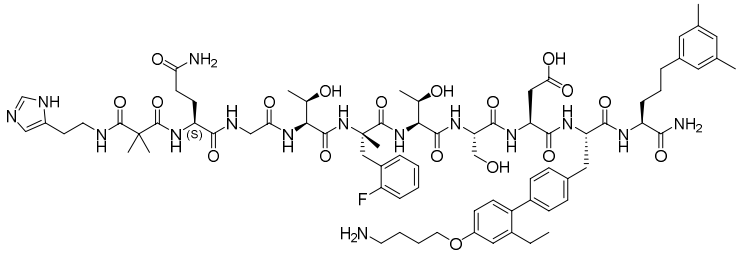
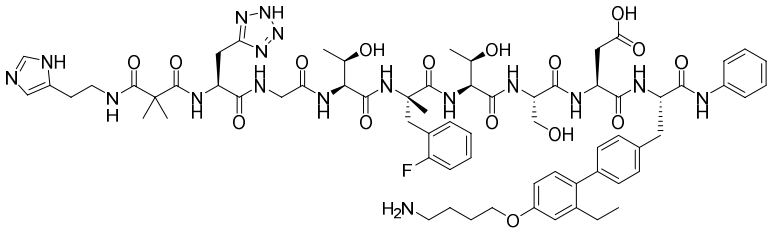

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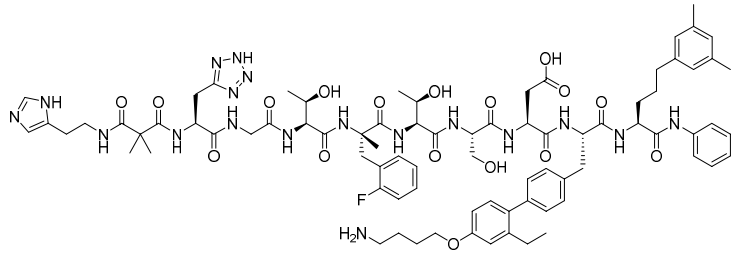
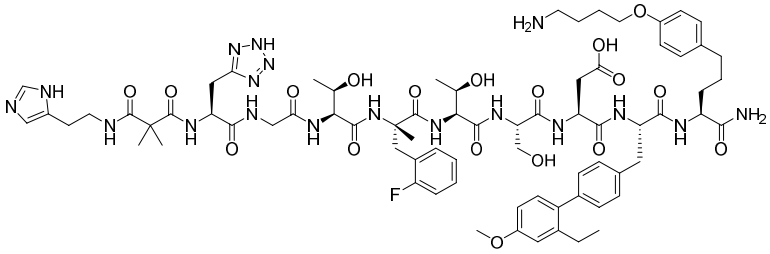
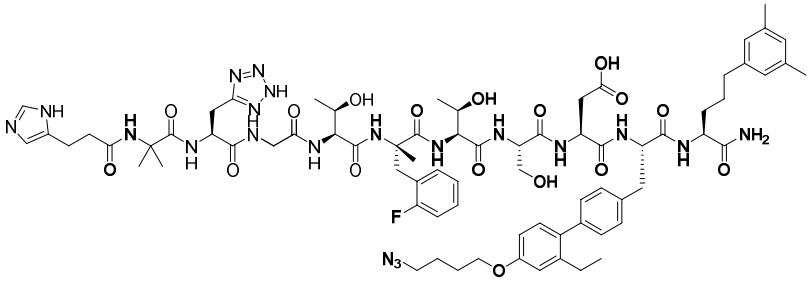
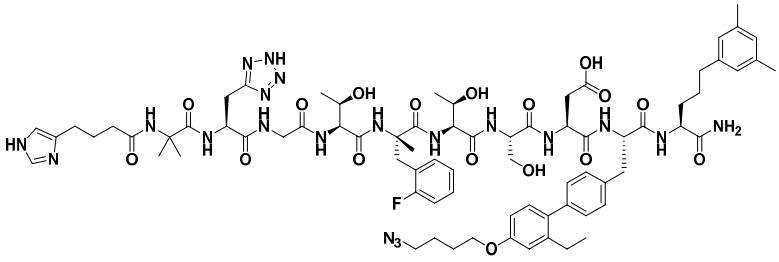
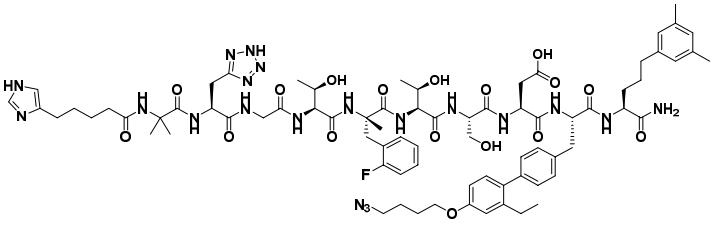
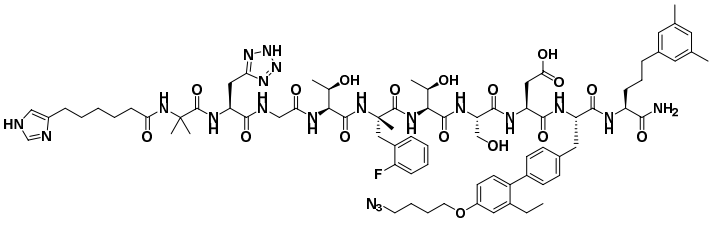

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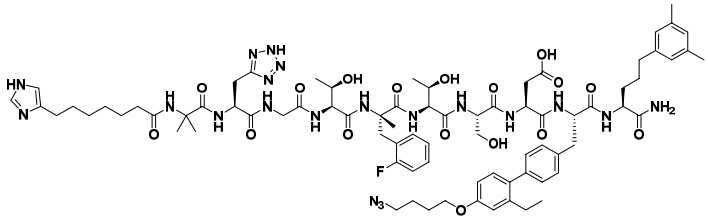
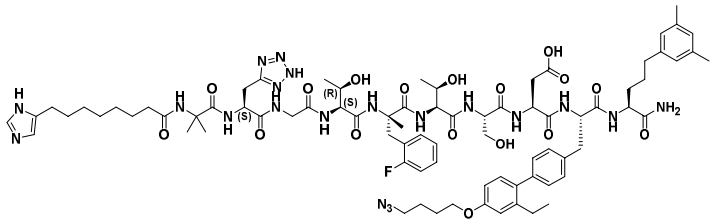
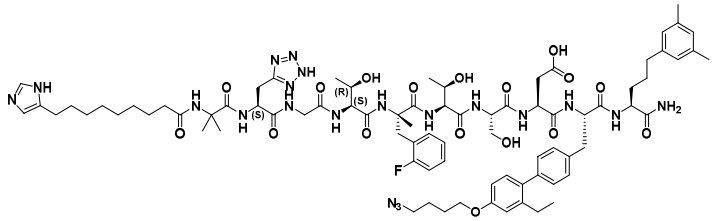
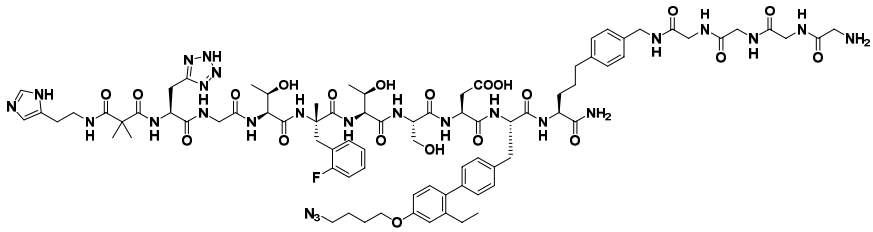
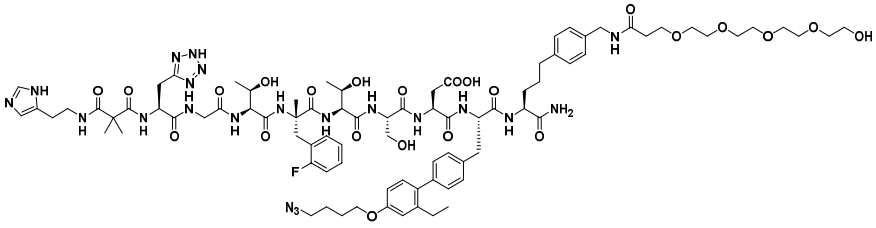
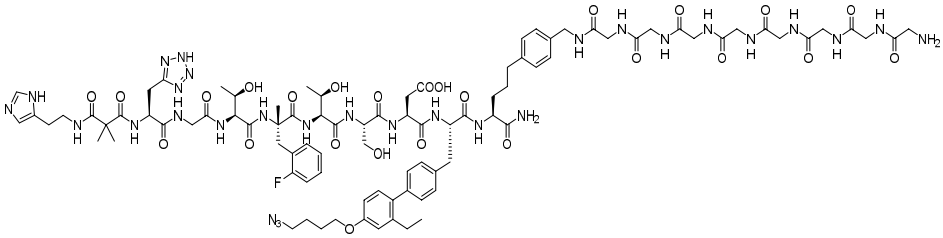
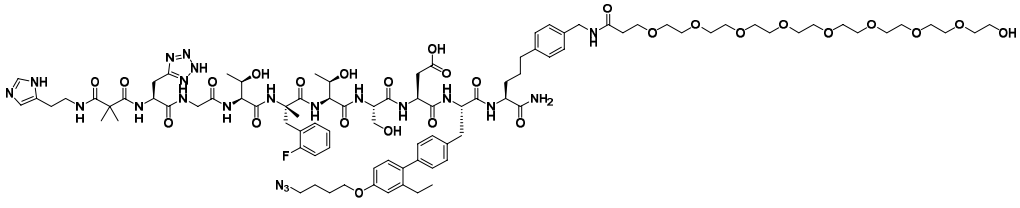

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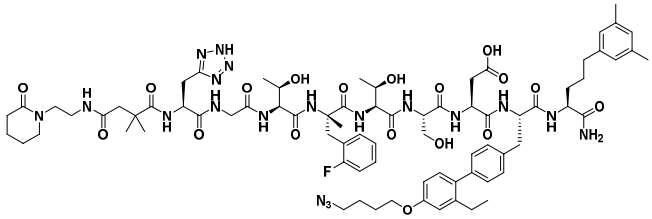
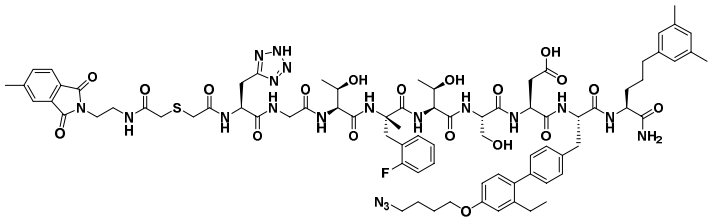
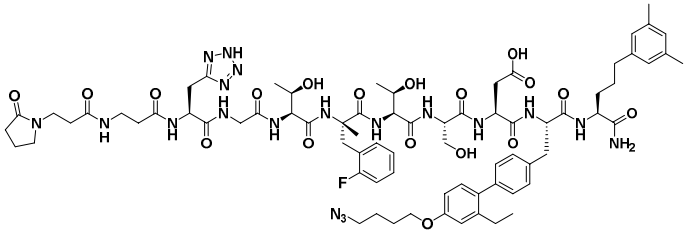
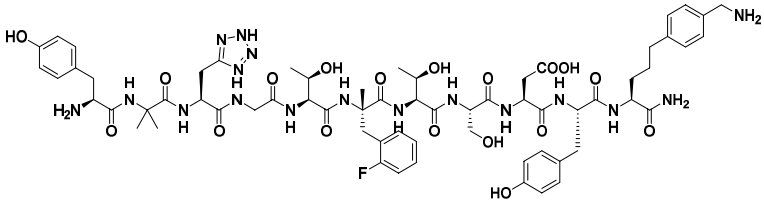
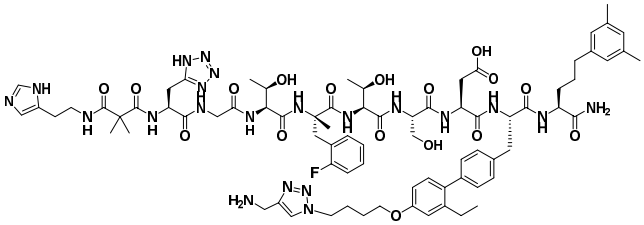
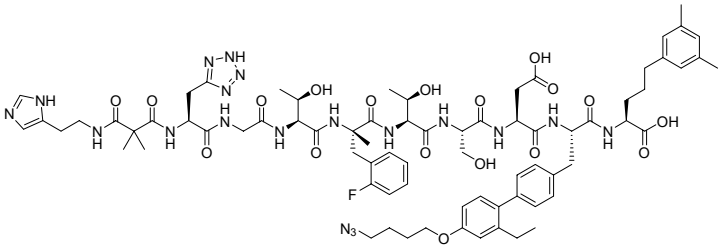
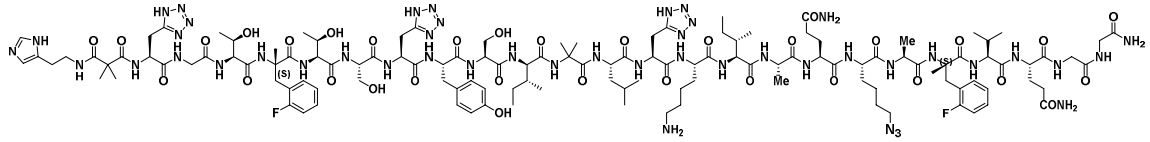

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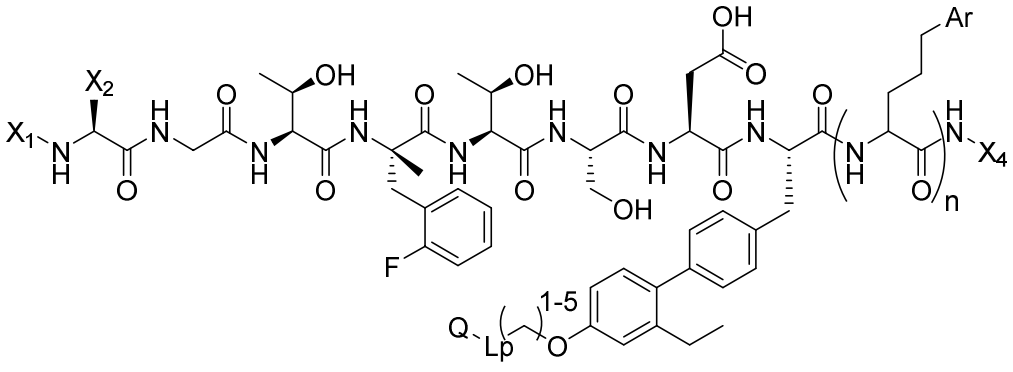

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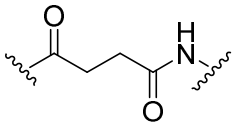

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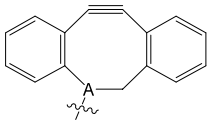
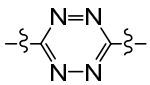
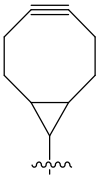
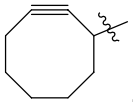
28. A compound having a structure of Formula (C):

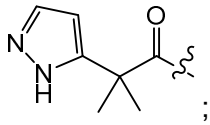
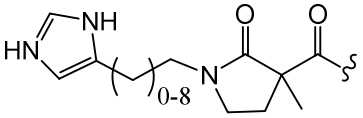
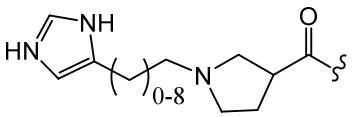


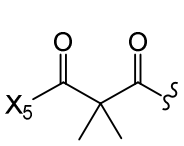
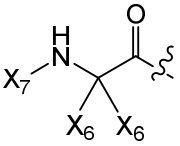
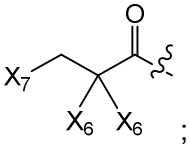
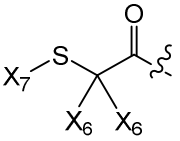
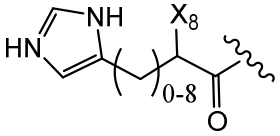
(C),

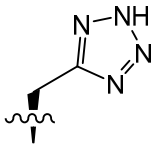
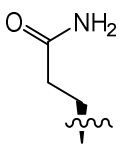
wherein:

L_p is absent or a linker comprising one or more of  ; a carbamate group; a cyclodextrin; a polyethylene glycol (PEG) segment having 1 to 36 -CH_2CH_2O- (EG) units; a –$(CH_2)_{2-24}$- chain; a triazole; one or more amino acids selected from glycine, serine, glutamic acid, alanine, valine, and proline, and combinations thereof;

Q is a moiety selected from -NH_2, -N_3, ,  ;  ;  ; and , where A is C or N;

X_1 is selected from H;  ;  ;  ;

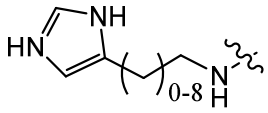
 ;  ;  ;  , and  ;

X_2 is selected from  and  ;

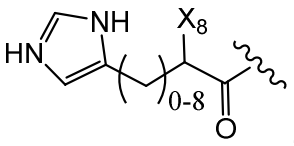
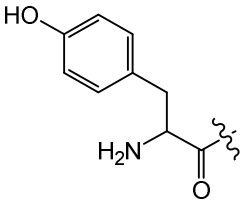
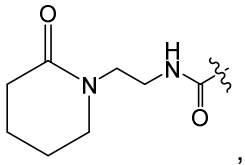
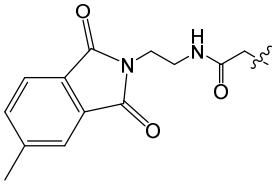
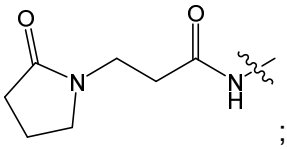
X_3 is selected from -CH_3, –$(CH_2)_{2-6}$–NH_2, –$(CH_2)_{2-6}$–N_3, and –$(CH_2)_{2-6}$–Tr–($CH_2)_{1-6}$–NH_2, where Tr is a triazole moiety;

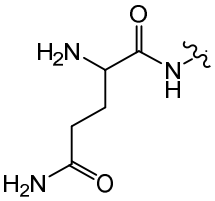
n is 0 or 1;

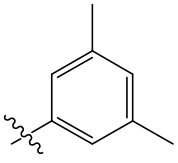
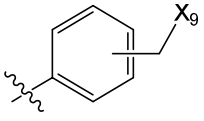
X_4 is selected from $-NH_2$, -OH and -N(H)(phenyl);

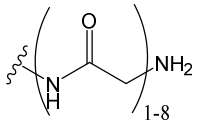
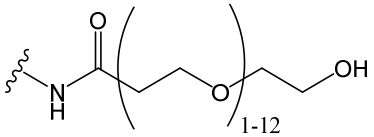
X_5 is selected from -OH, $-NH_2$, -NH-OH, and ;

X_6 is independently at each occurrence selected from H, -OH, $-CH_3$, and $-CH_2OH$;

X_7 is selected from H, , , , , ;

X_8 is selected from H, -OH, $-NH_2$, and ;

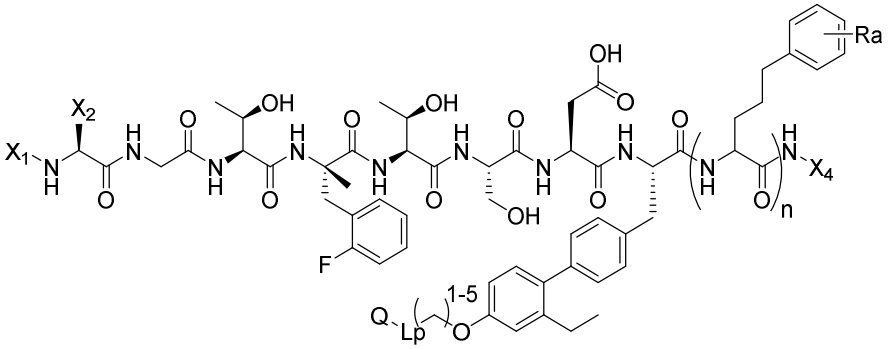
Ar is selected from  and ;

X_9 is selected from $-NH_2$, , and , and

m is an integer from 1 to 4

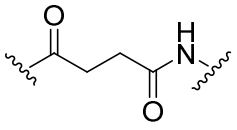
or a pharmaceutically acceptable salt thereof.

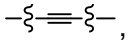
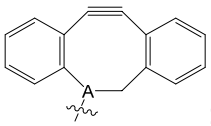
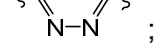
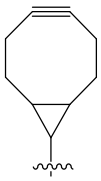
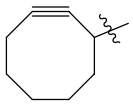
29. A compound having a structure of Formula (III):

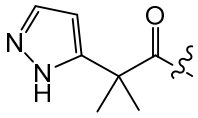
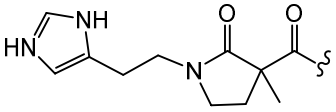
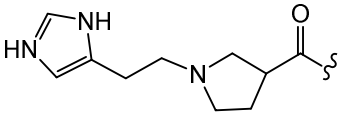


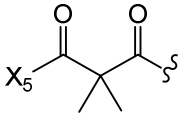
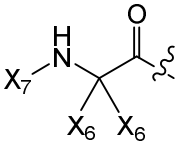
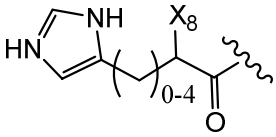
(III),

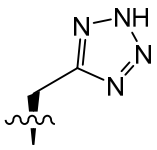
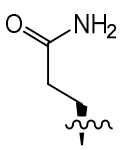
wherein:

L_p is absent or a linker comprising one or more of  ; a carbamate group; a cyclodextrin; a polyethylene glycol (PEG) segment having 1 to 36 -CH_2CH_2O- (EG) units; one or more amino acids selected from glycine, serine, glutamic acid, alanine, valine, and proline, and combinations thereof;

Q is a moiety selected from -N_3, , ; ; ; and , where A is C or N;

X_1 is selected from H; ; ; ;

; ; and ;

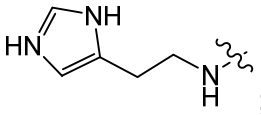
X_2 is selected from  and ;

X_3 is selected from –$(CH_2)_{2-6}$–NH_2, –$(CH_2)_{2-6}$–N_3, and -CH_3, with the proviso that when X_3 is -CH_3, n is 1 and Ra in at least one occurrence is selected from –$(CH_2)_{2-6}$–NH_2 and –$(CH_2)_{2-6}$–N_3;

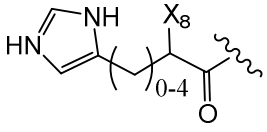
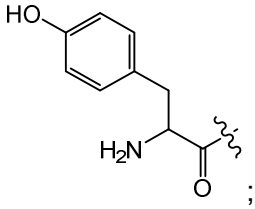
n is 0 or 1;

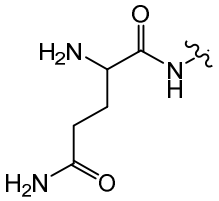
Ra is independently at each occurrence selected from H, -CH_3, –$(CH_2)_{2-6}$–NH_2, and –$(CH_2)_{2-6}$–N_3;

X_4 is selected from H and phenyl;

X_5 is selected from -OH, -NH_2, -NH-OH, and ;

X_6 is independently at each occurrence selected from H, -OH, -CH_3, and -CH_2OH;

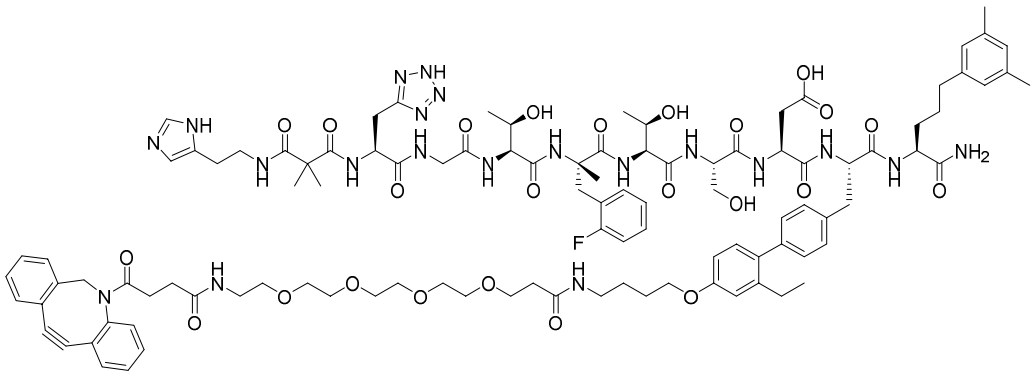
X_7 is selected from H, , and ;

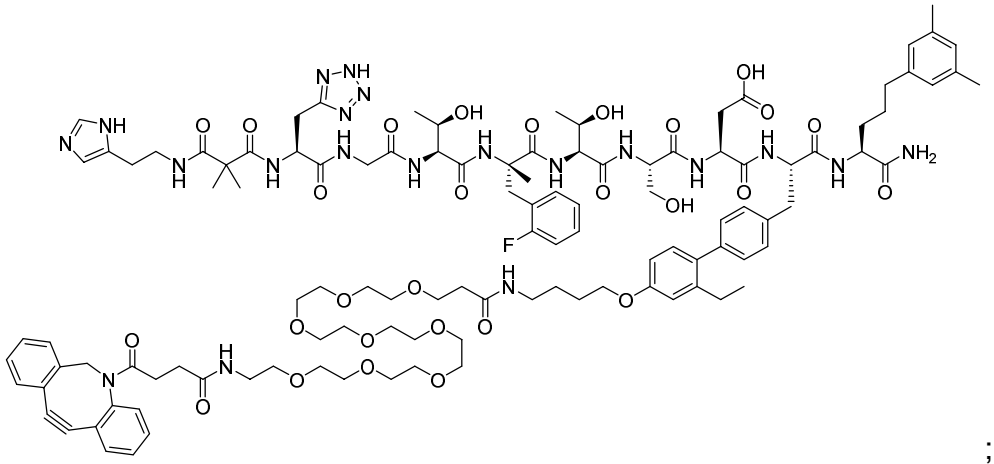
X_8 is selected from H, -OH, -NH_2, and ,

and pharmaceutically acceptable salts thereof.

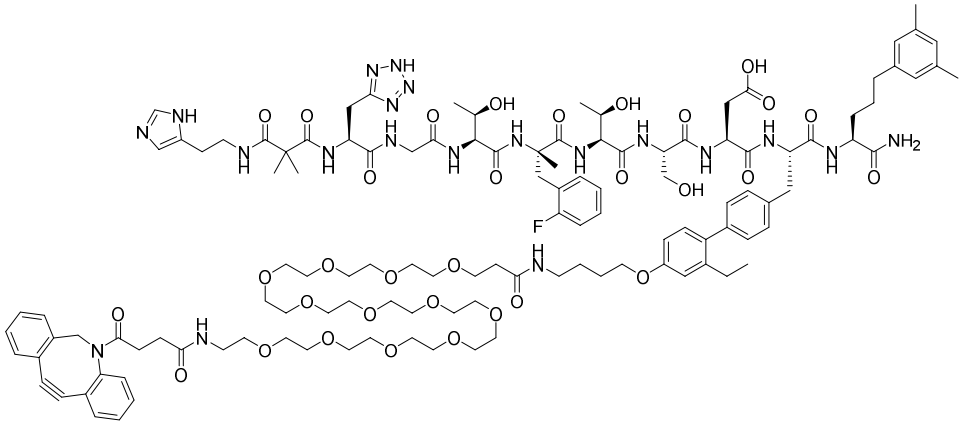
30. The compound of claim 29 having the structure selected from the group consisting of:

Structure

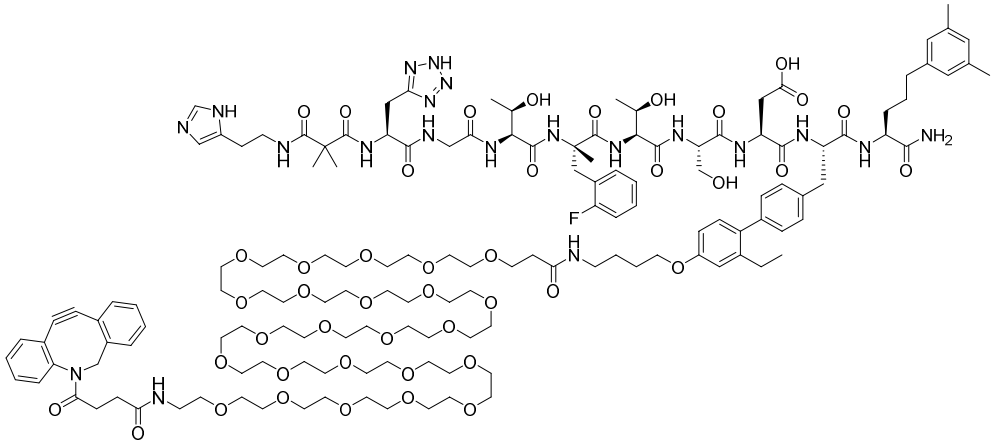
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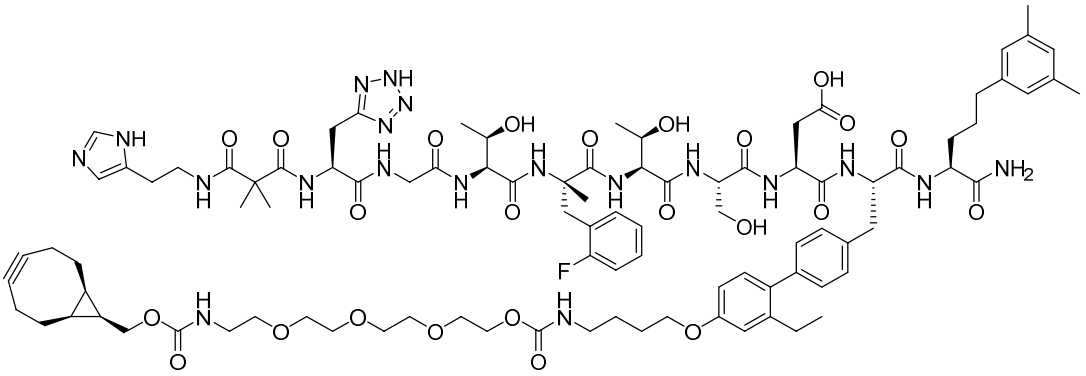
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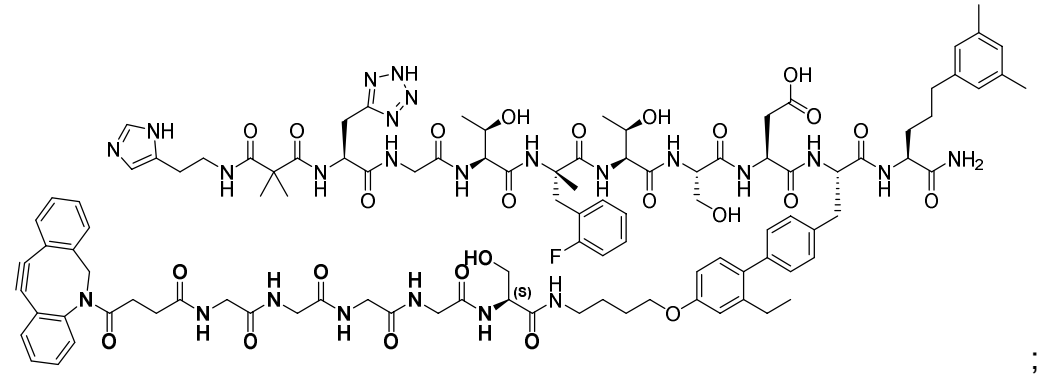
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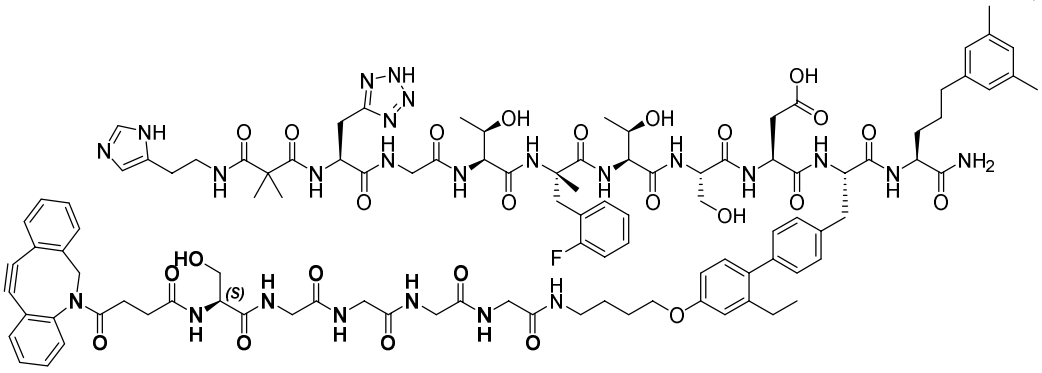
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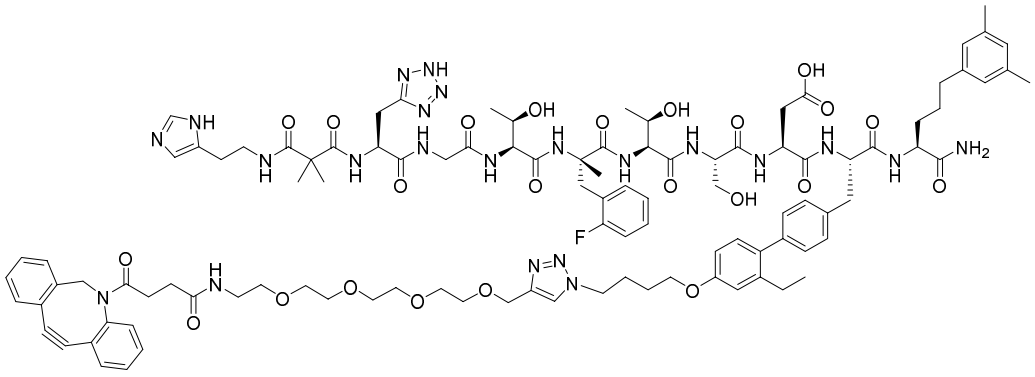
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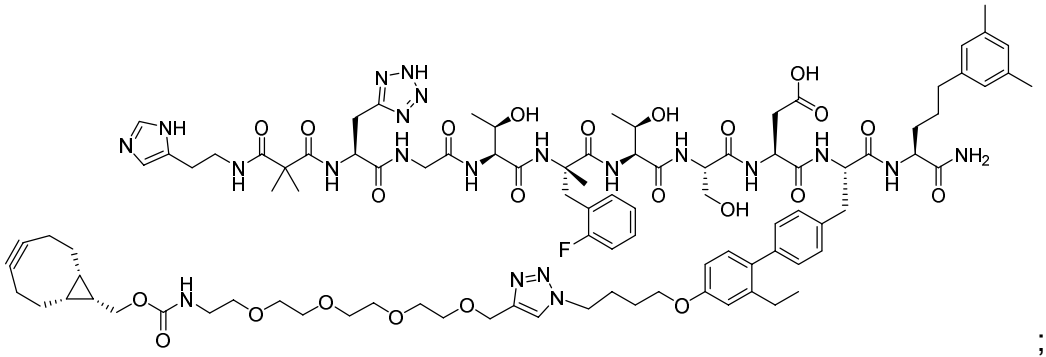
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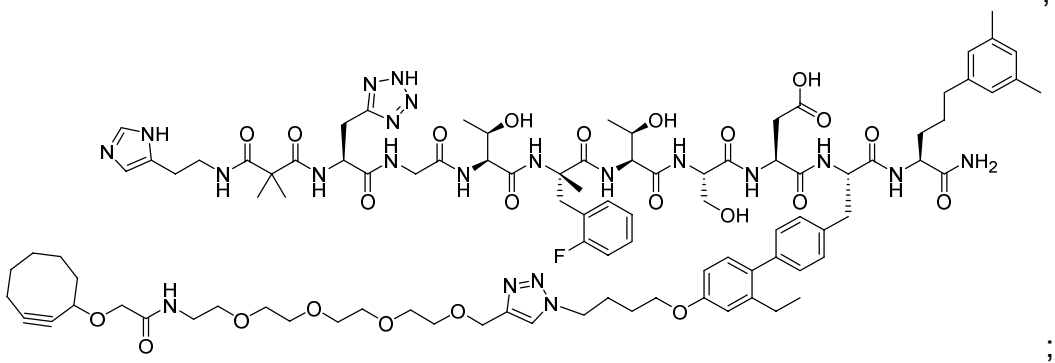
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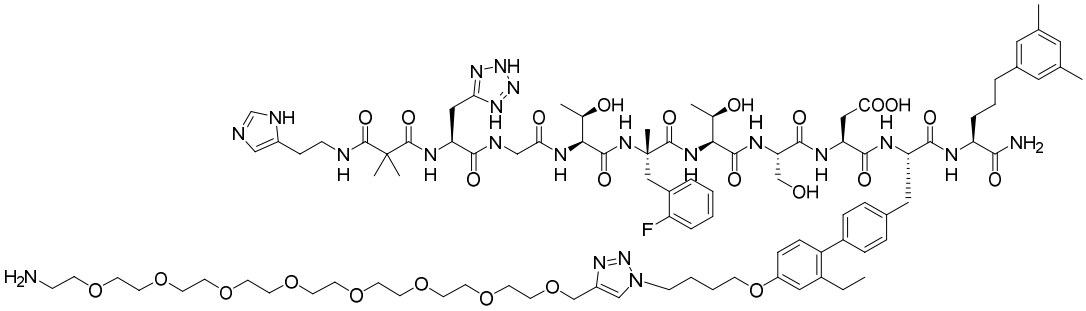
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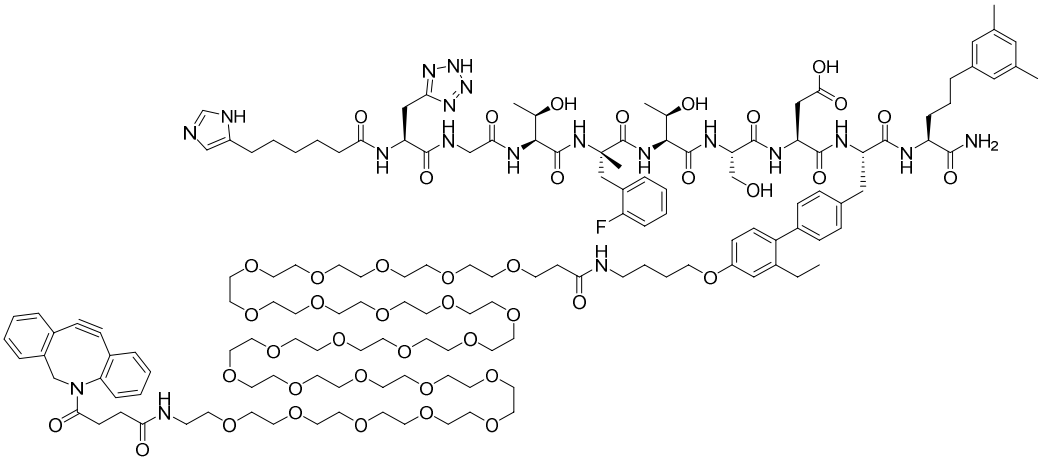
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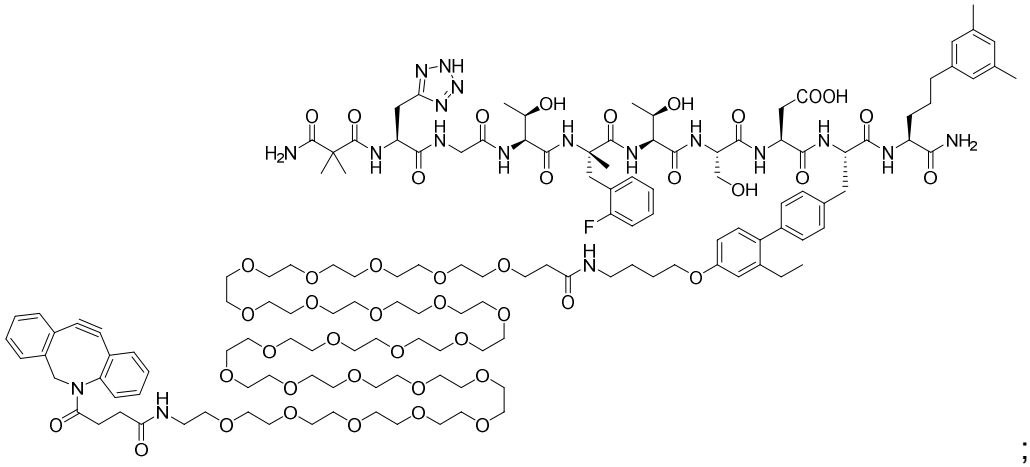
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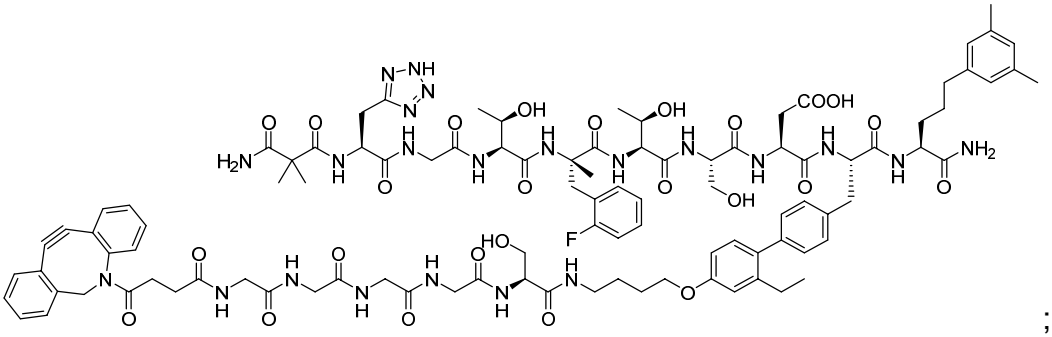
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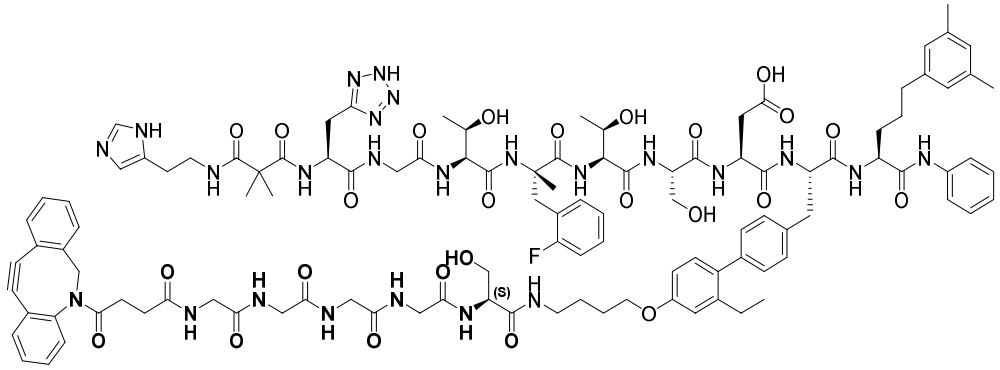
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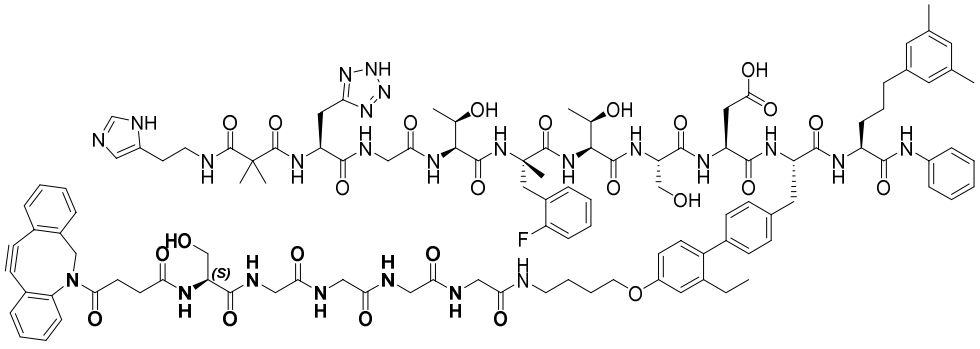
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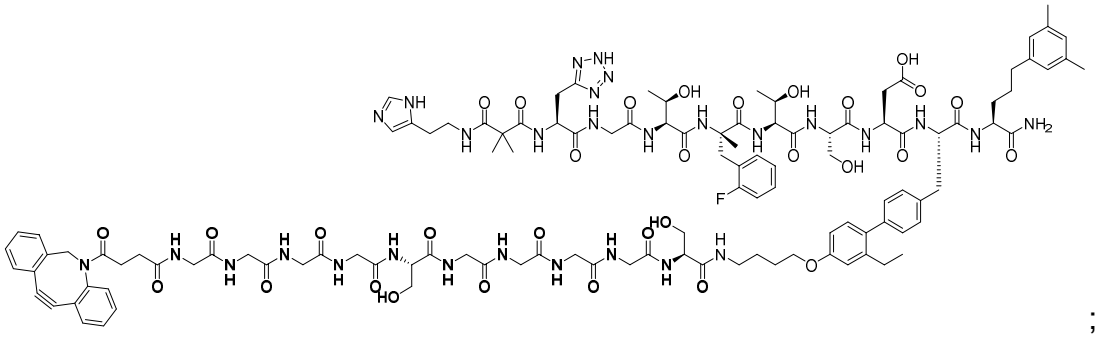
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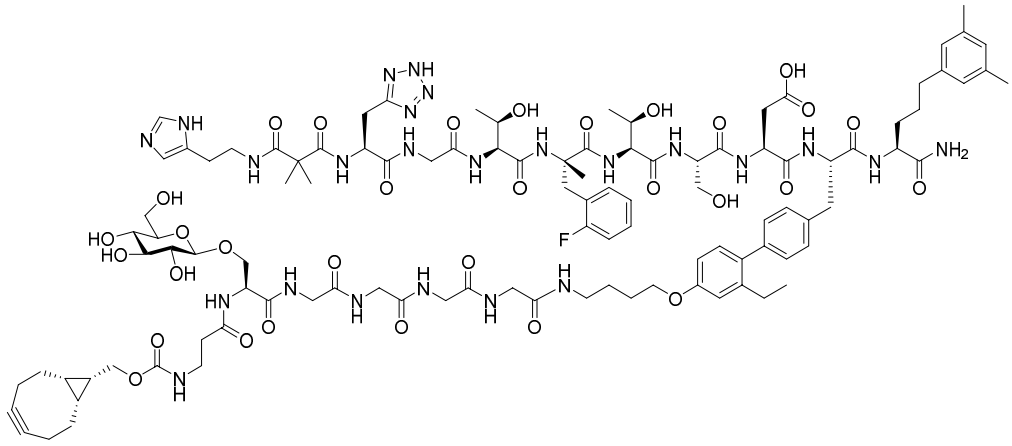
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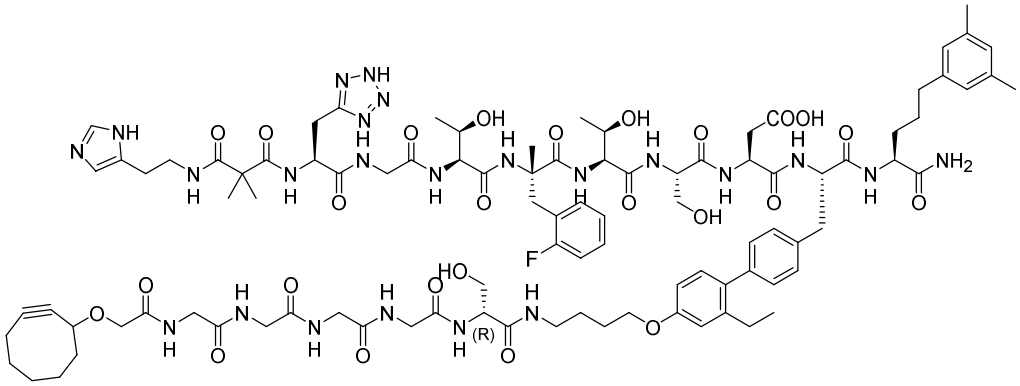
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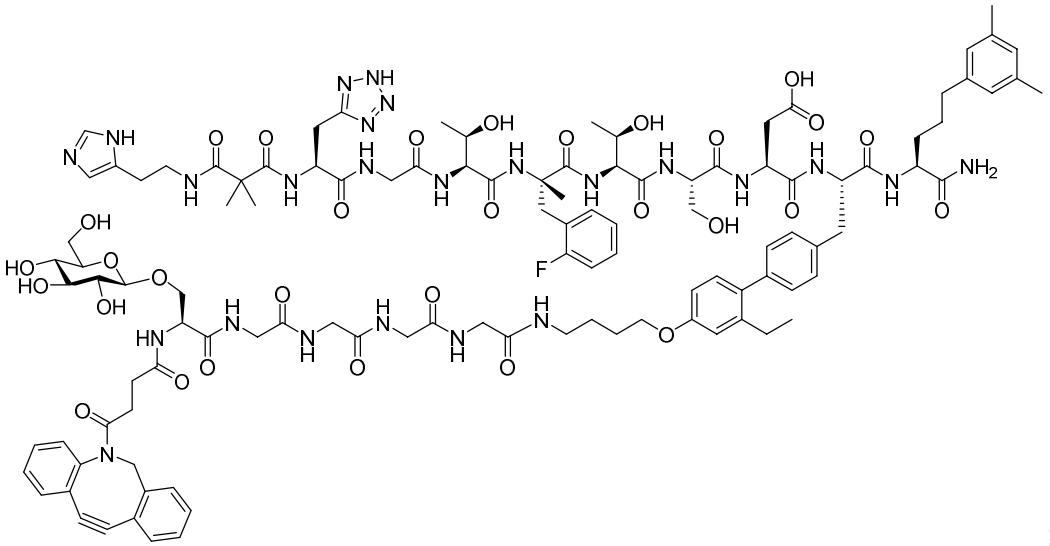
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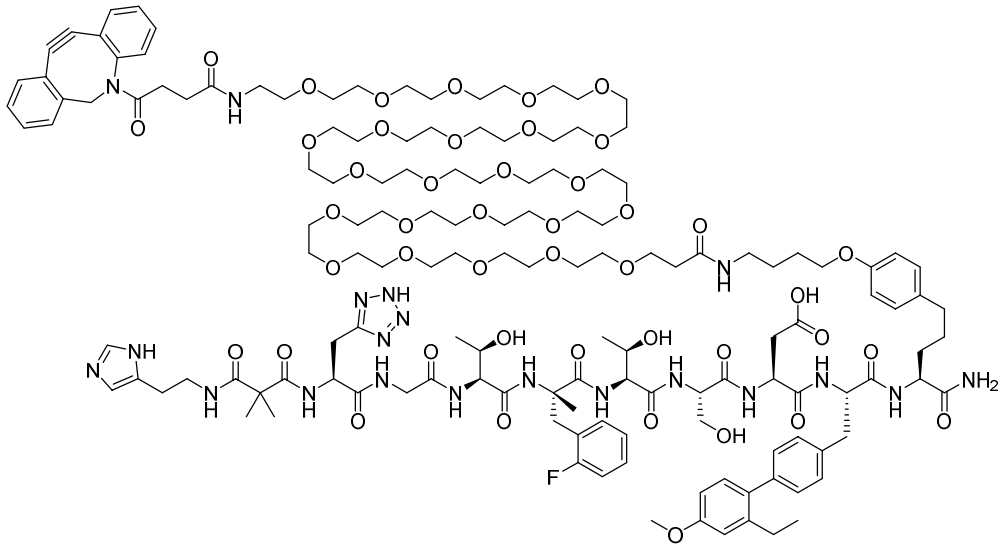
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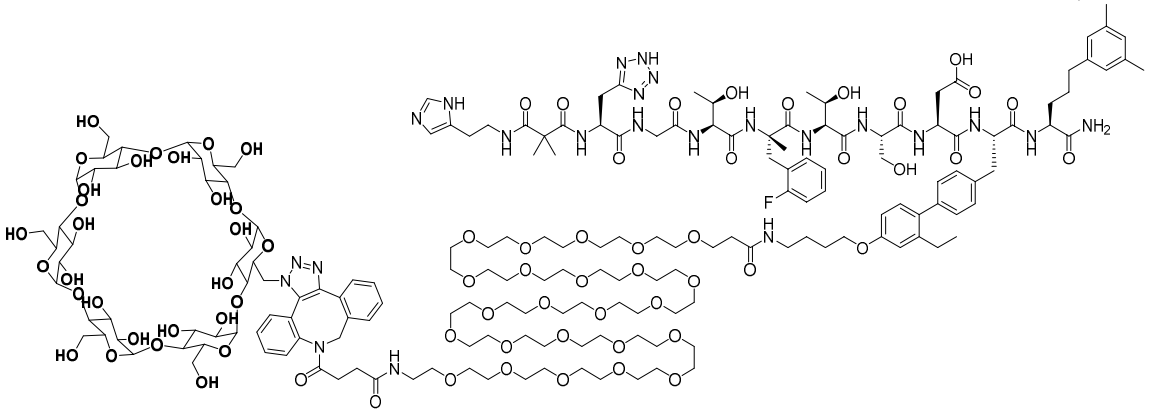
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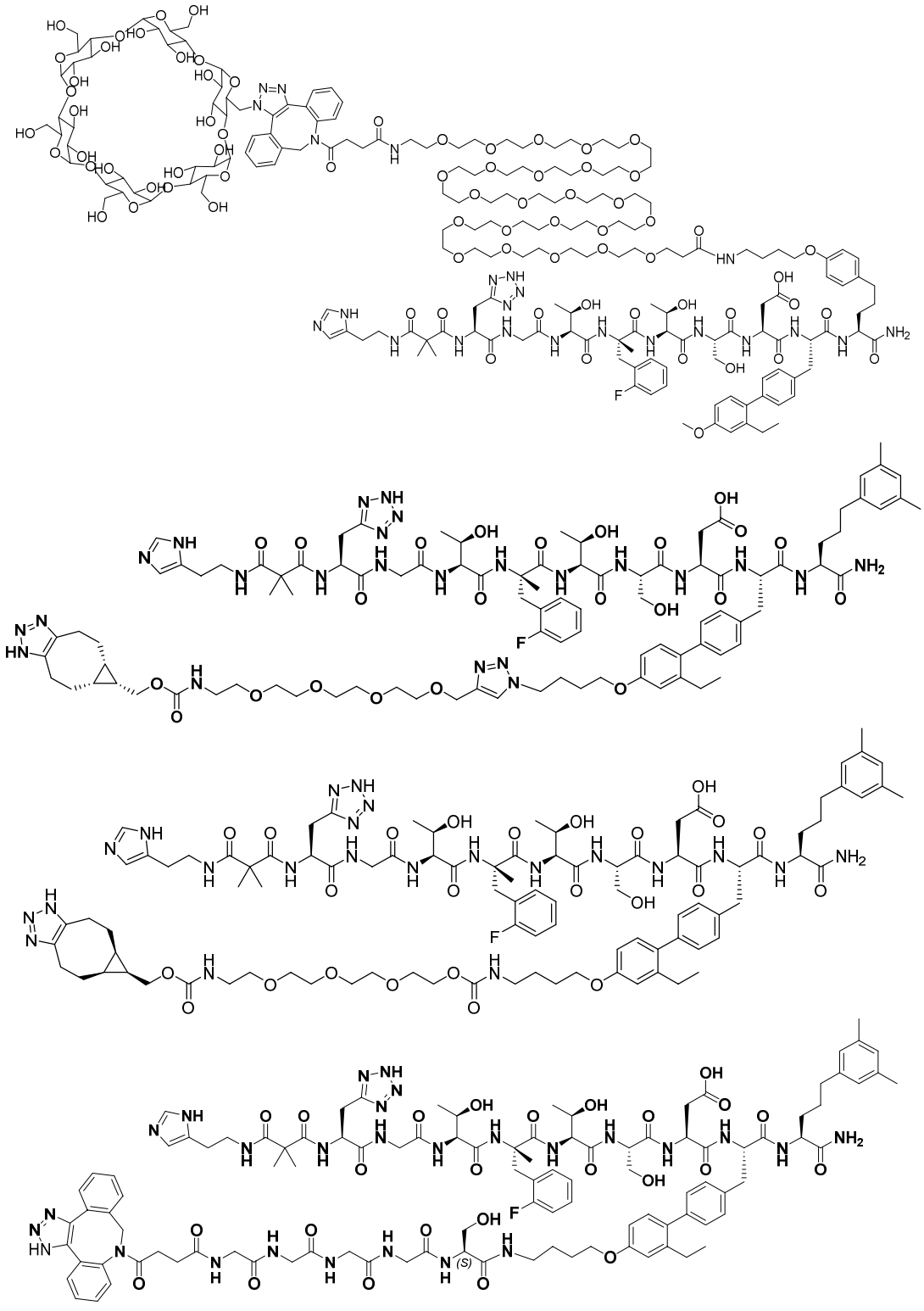
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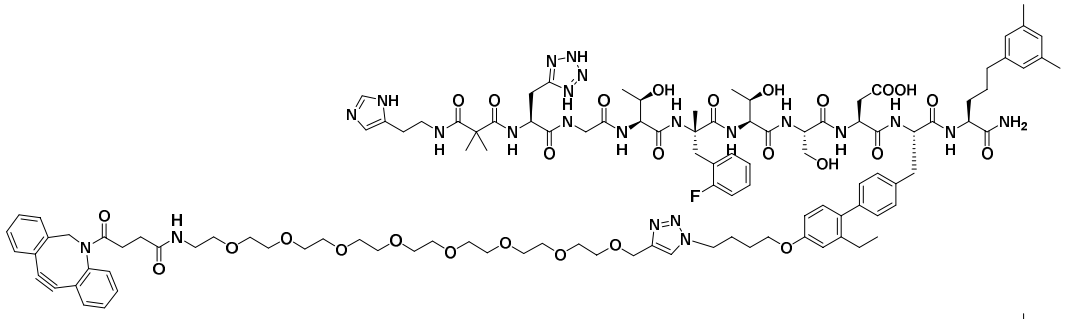


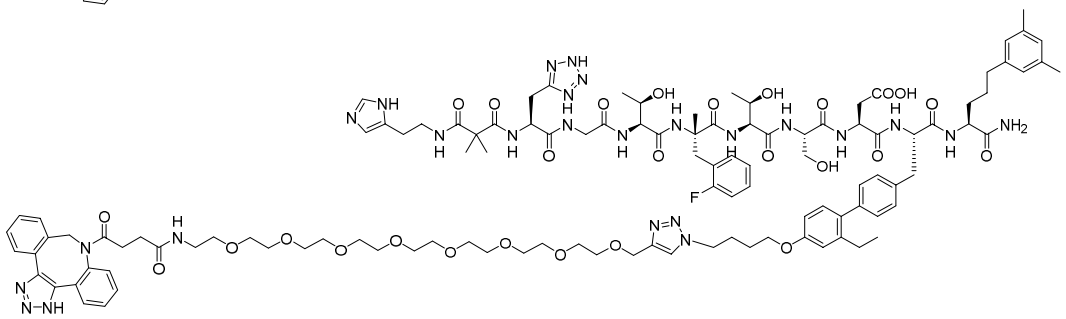
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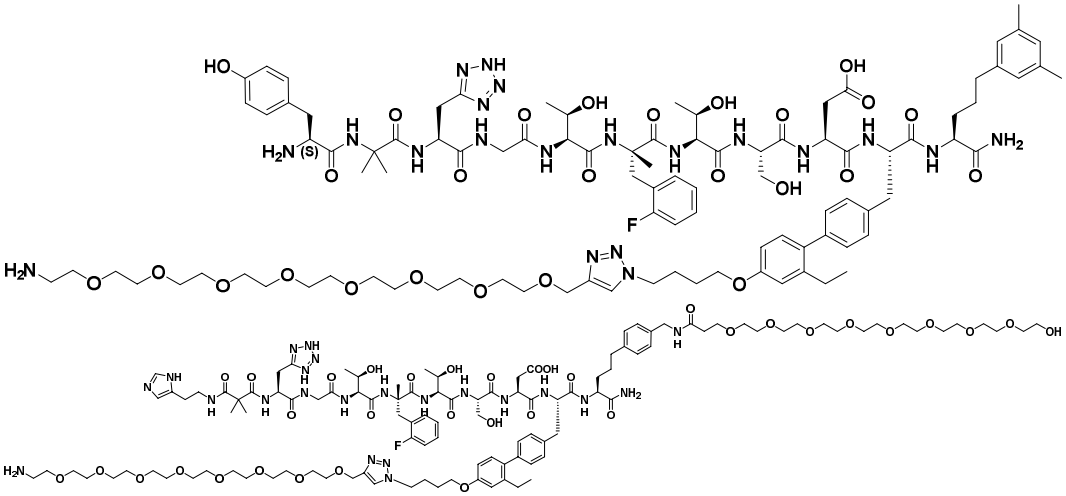


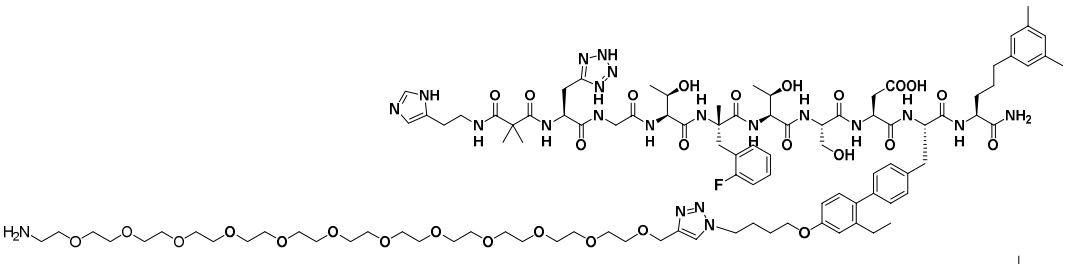
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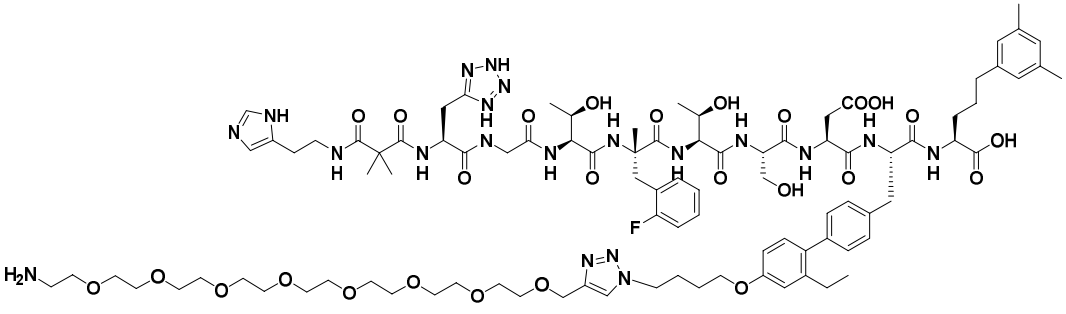


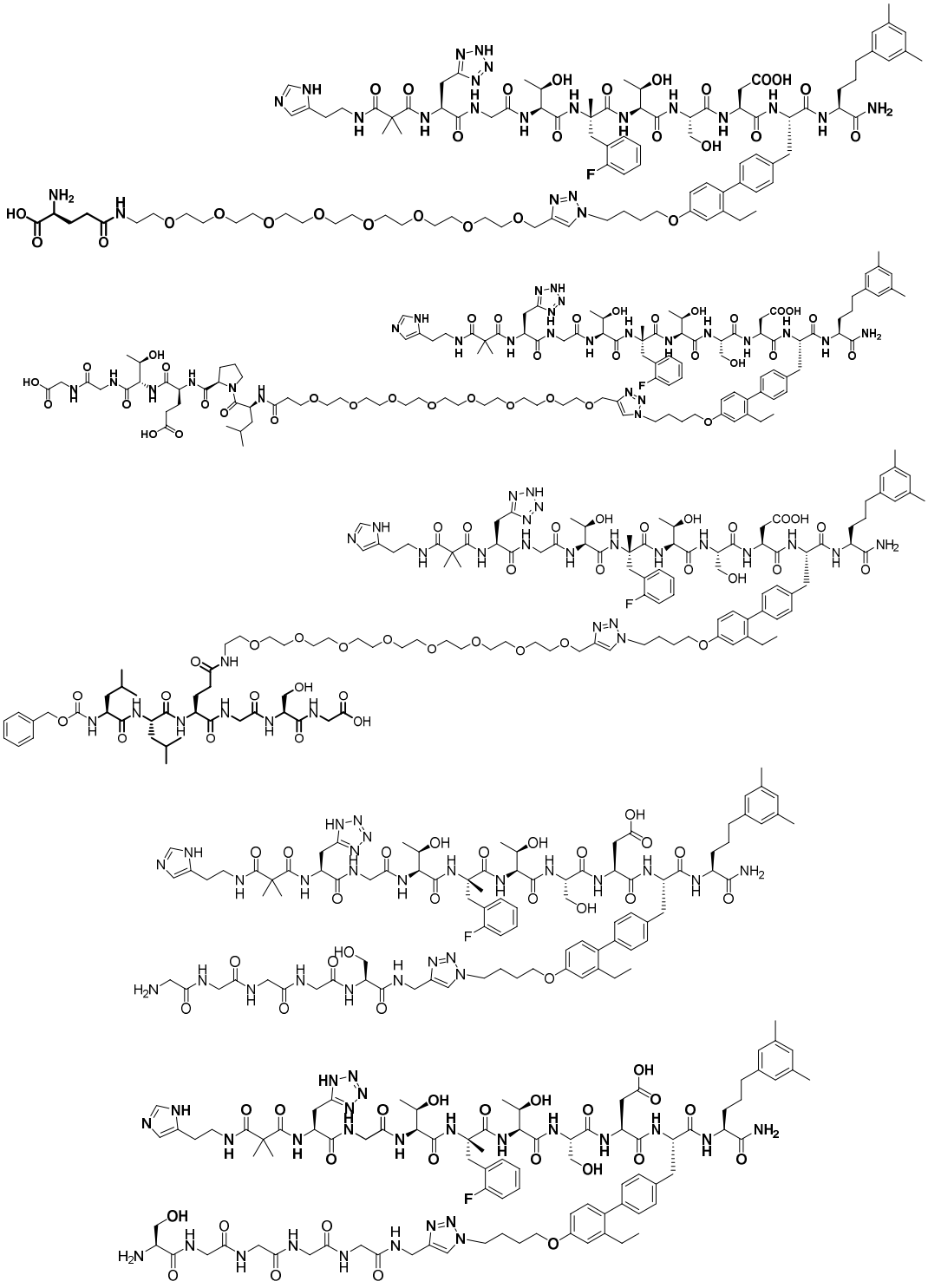


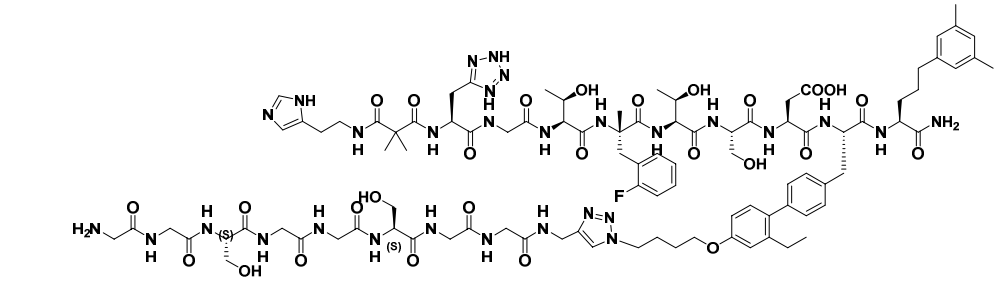


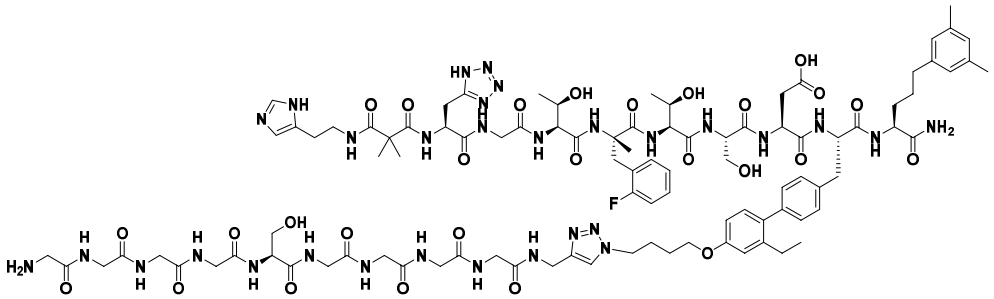


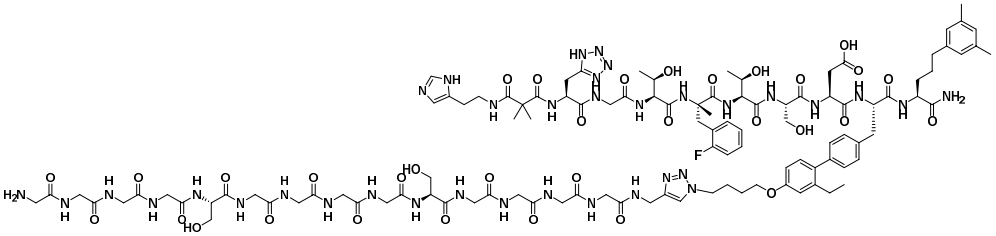


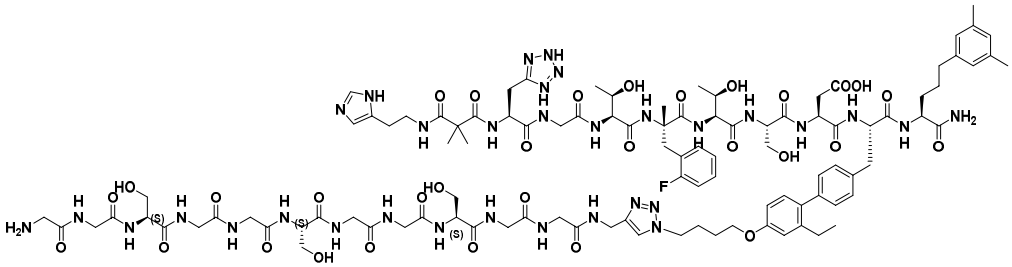


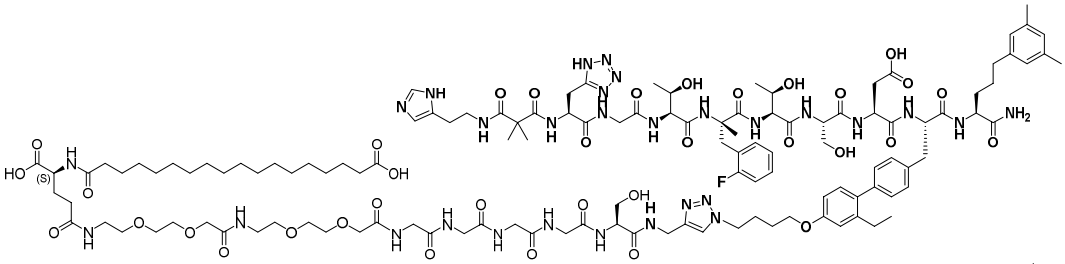


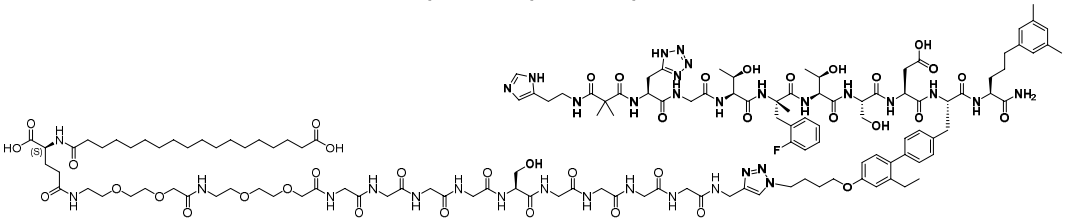


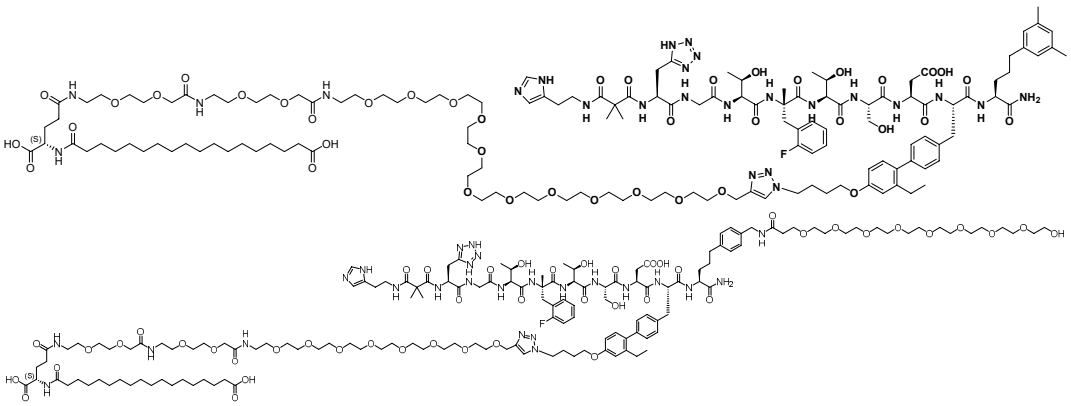








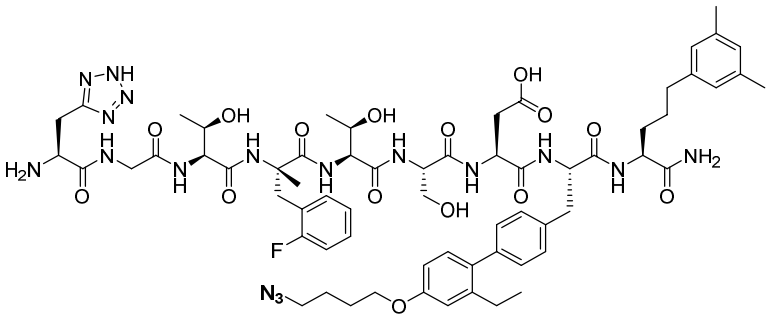




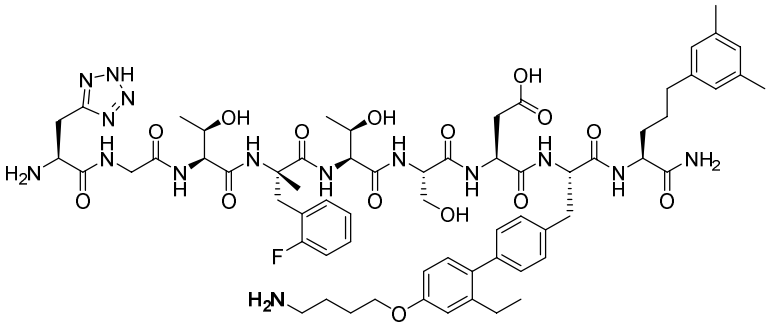
or a pharmaceutically acceptable salt thereof.

31. An antibody-drug conjugate comprising a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof conjugated, optionally through a linker, to a payload having the structure selected from the group consisting of:

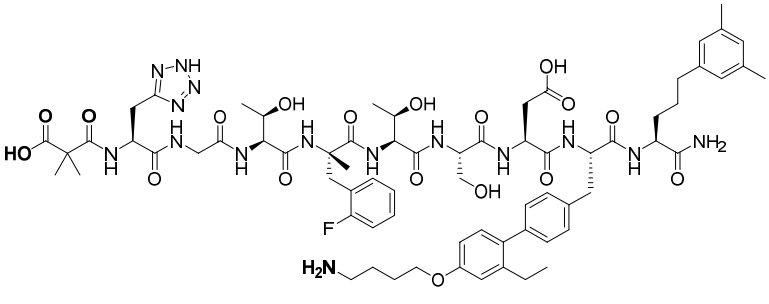
Structure



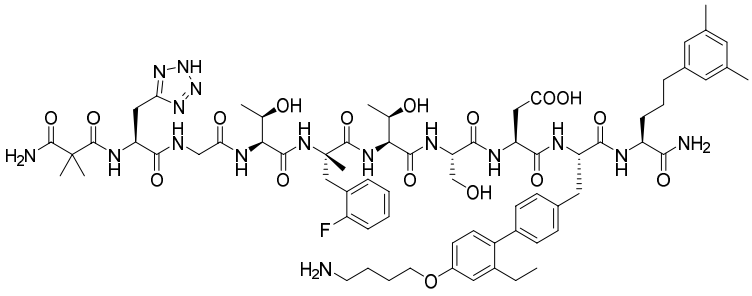
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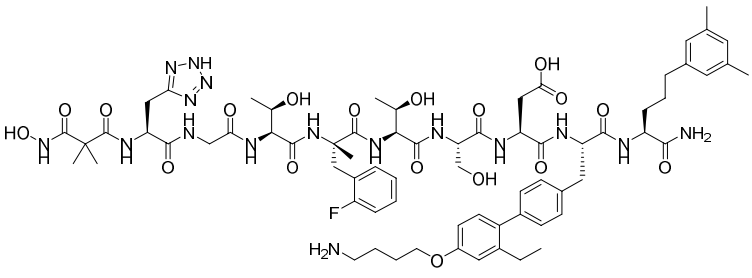


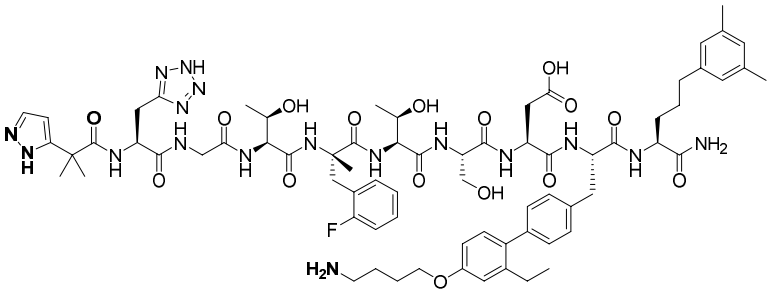
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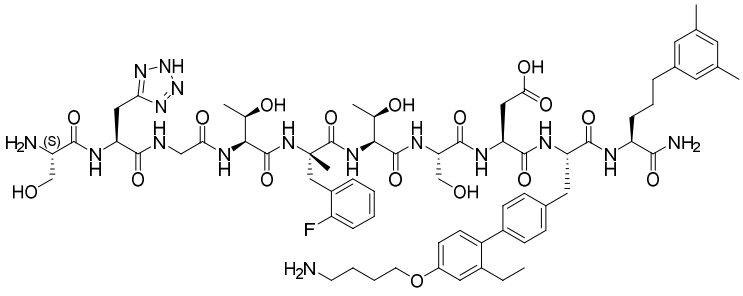


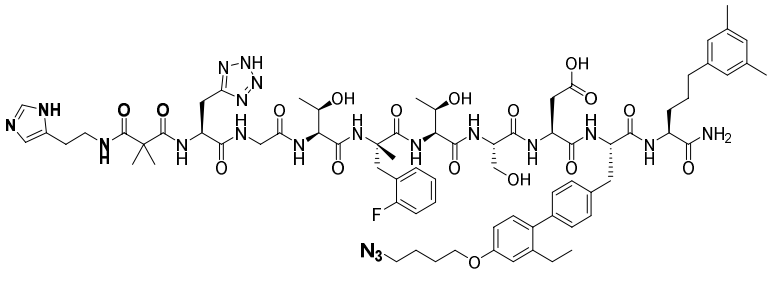
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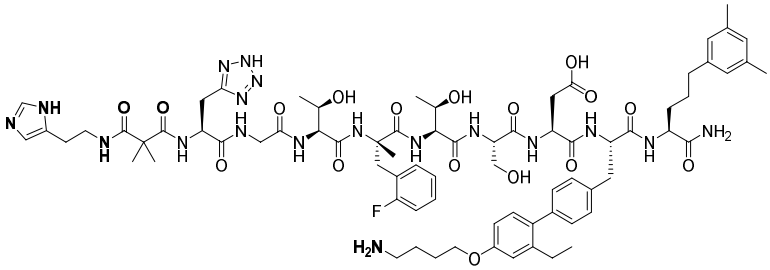
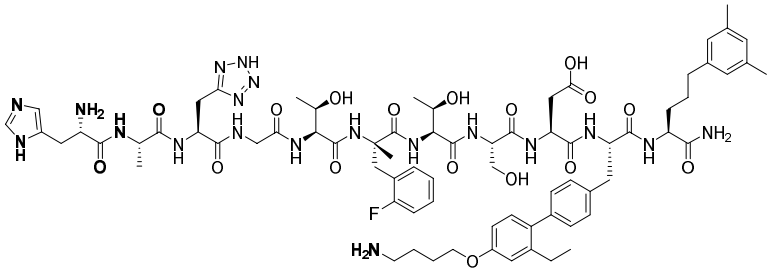
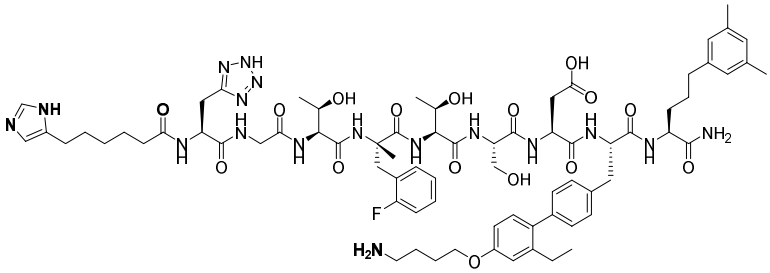
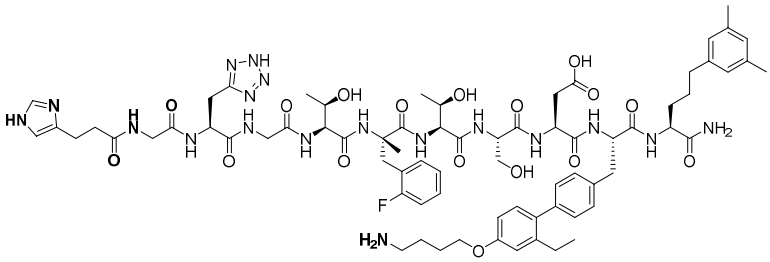
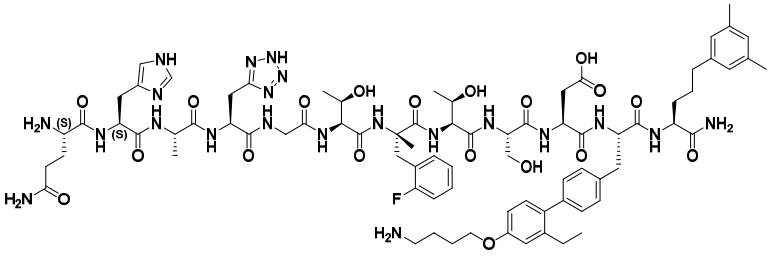
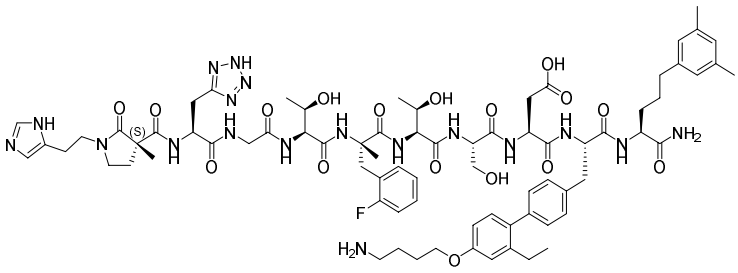

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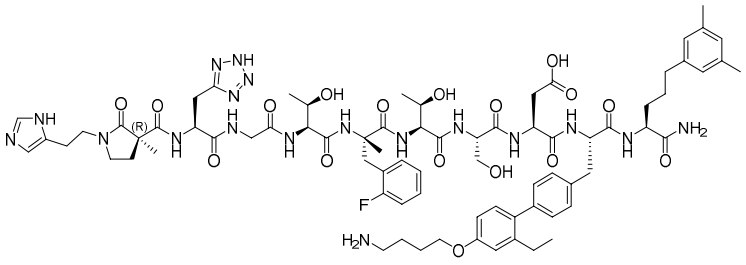
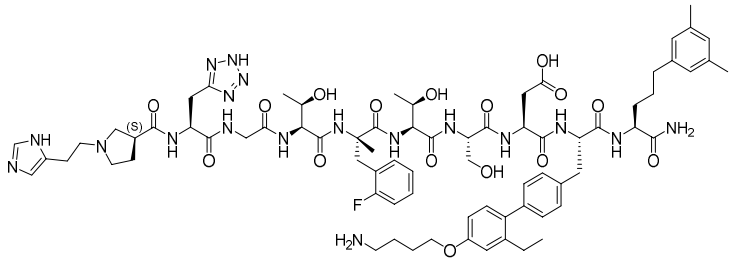
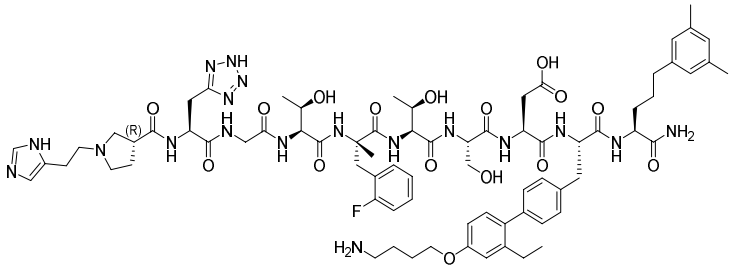
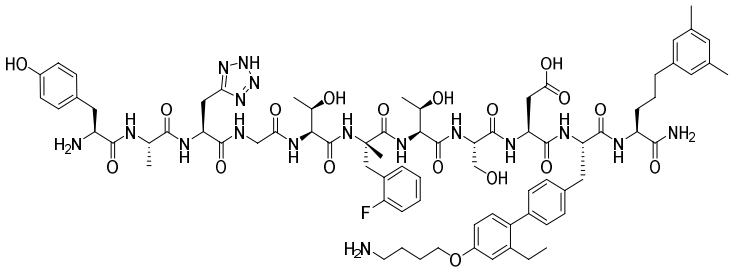
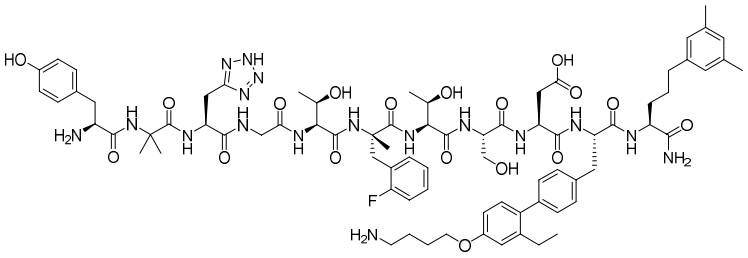
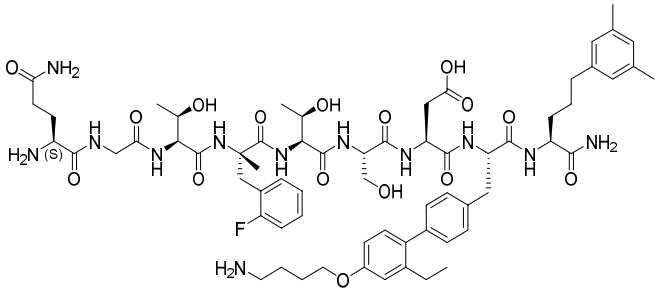

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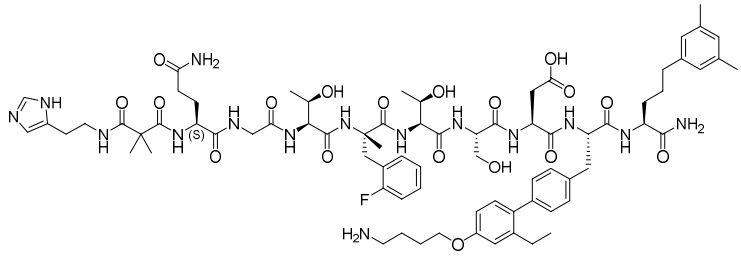
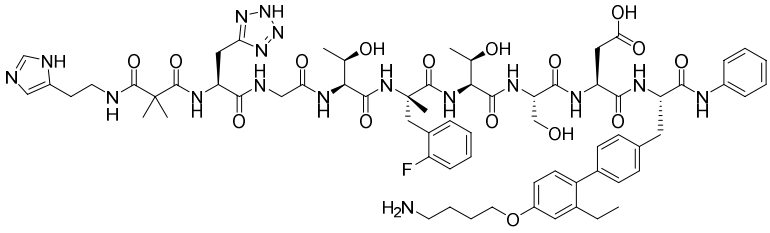
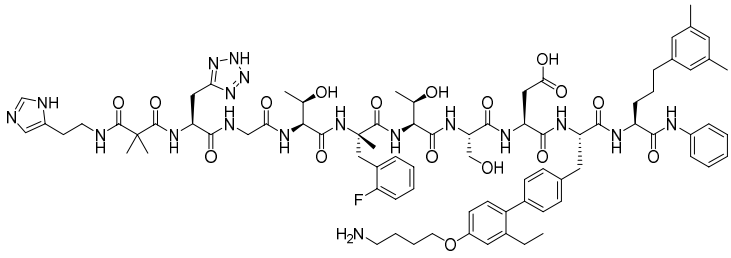
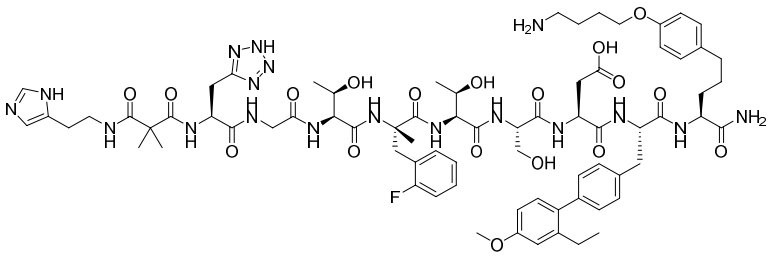
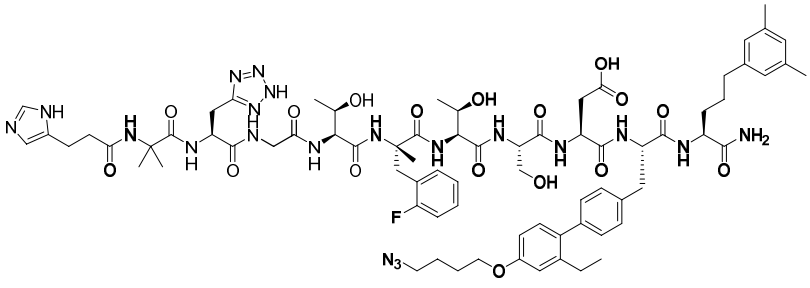
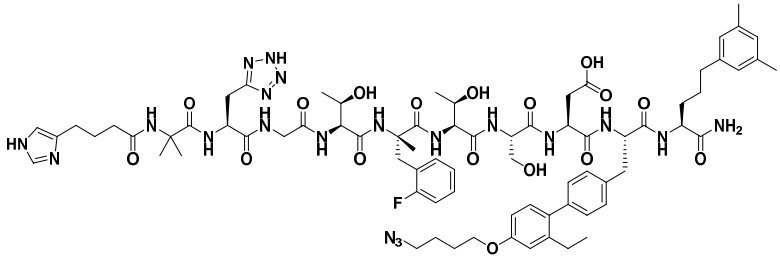

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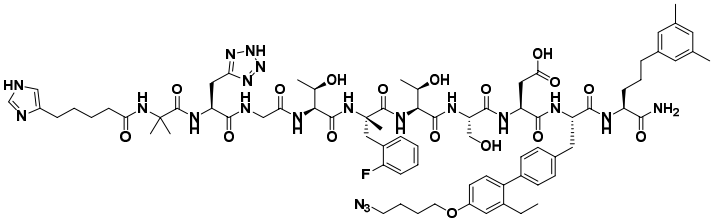
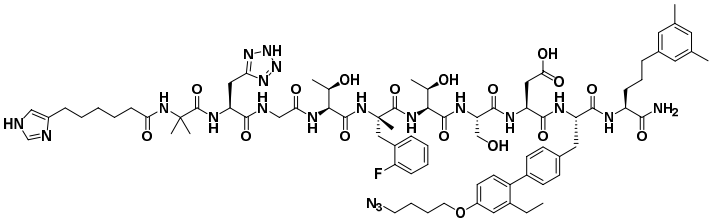
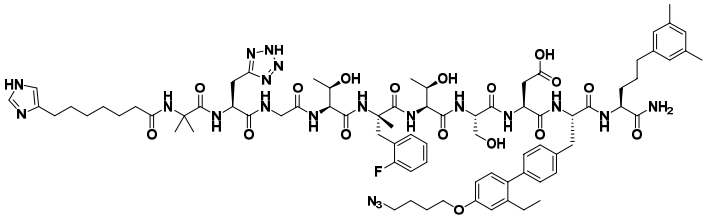
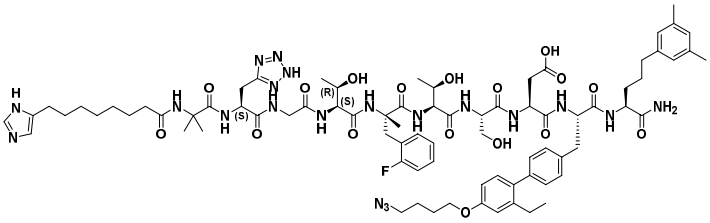
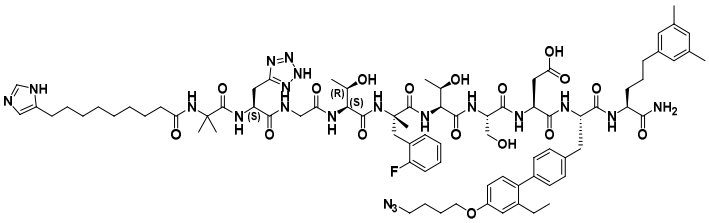
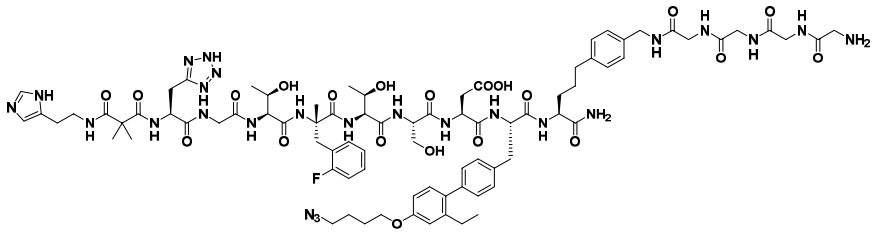
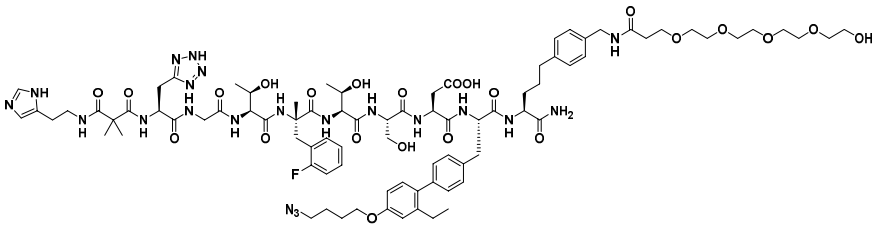

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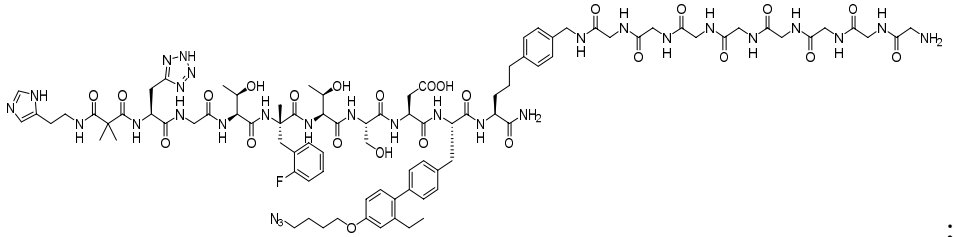
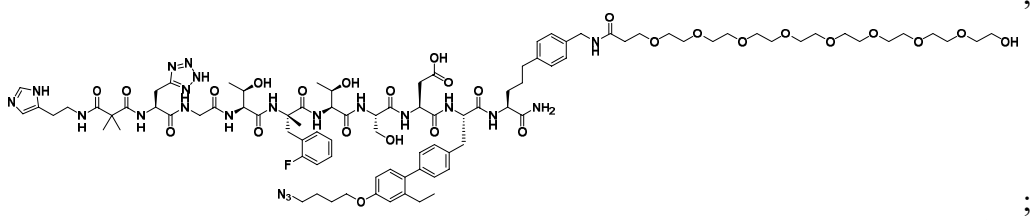
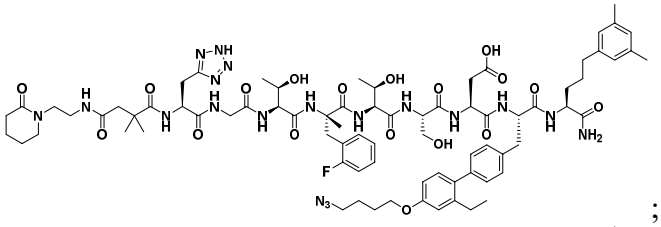
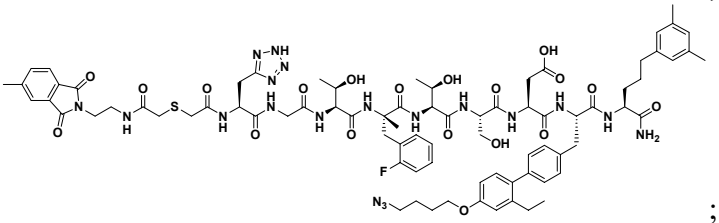
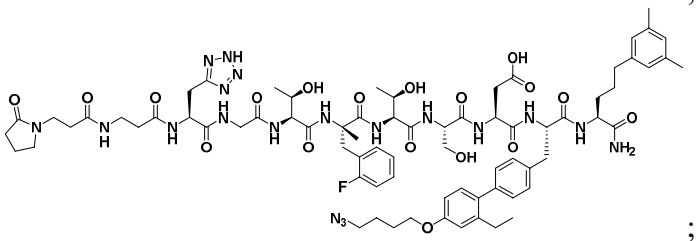
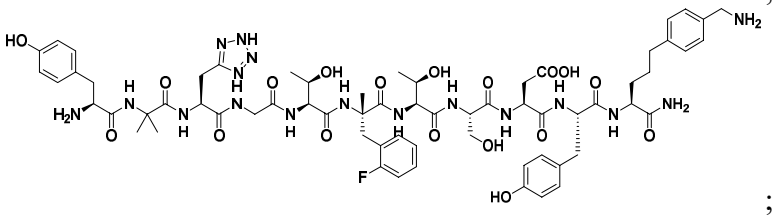
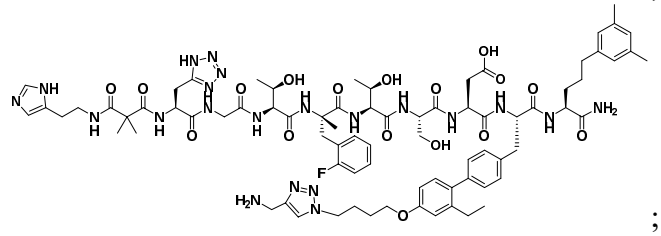

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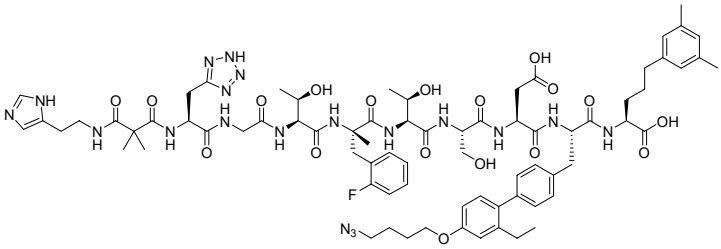

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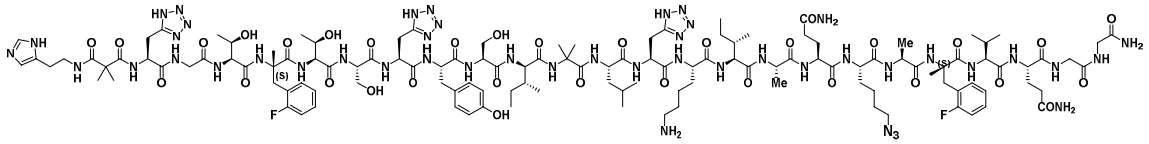

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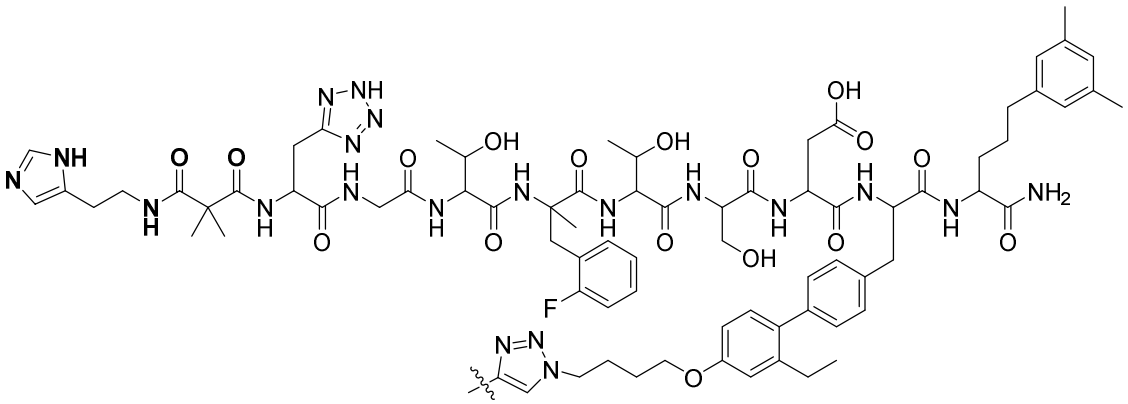
, and



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or a pharmaceutically acceptable salt thereof.

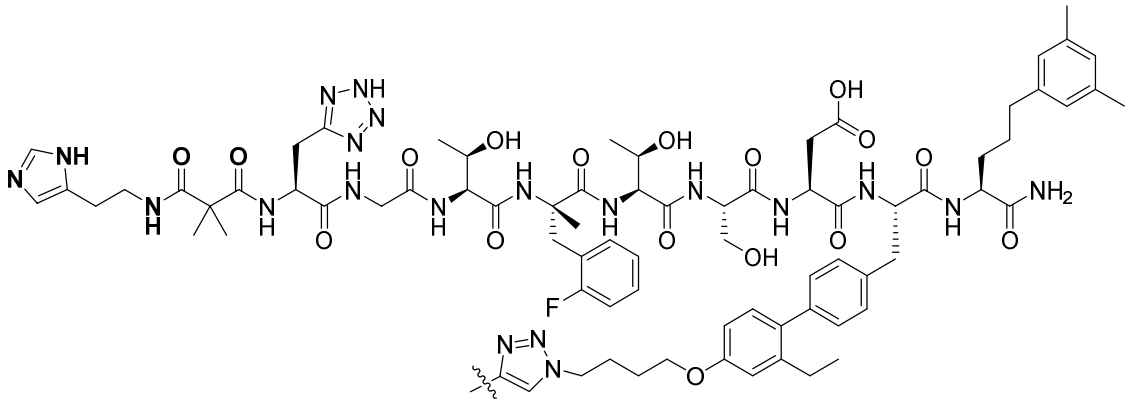
32. An antibody-drug conjugate comprising a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof and a payload having the structure:



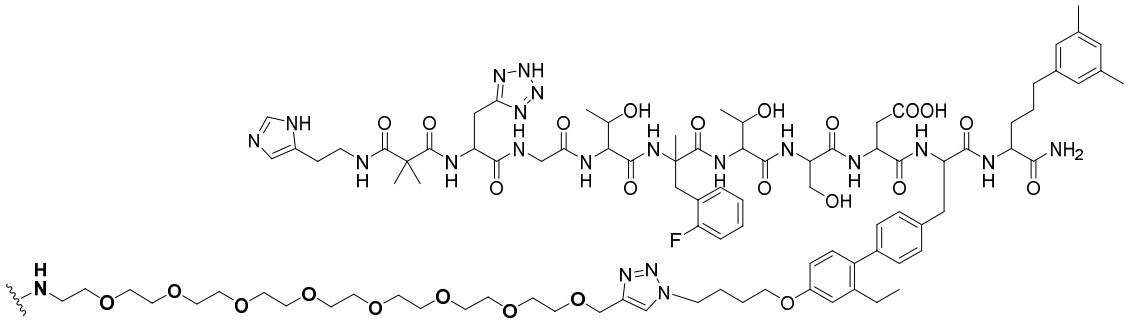
,

wherein  is the point of attachment of the payload to the antibody or the antigen-binding fragment thereof directly or through a linker.

33. The antibody-drug conjugate of claim 32,wherein the payload has the structure:



34. An antibody-drug conjugate comprising a Glucagon-like peptide-1 receptor (GLP1R)-targeting antibody or an antigen-binding fragment thereof and a linker-payload having the structure:



wherein —§– is the point of attachment of the linker-payload to the antibody or the antigen-binding fragment thereof.

35. The antibody-drug conjugate of claim 34, wherein the linker-payload has the structure:

