CLAIMS

1. An antibody-drug conjugate of Formula (1):

$$Ab\text{-}(L\text{-}D)_p \qquad (1)$$

wherein Ab is an antibody or an antigen-binding fragment thereof;

L is a conjugate linker that covalently attaches Ab to D;

p is an integer from 1 to 16; and

D is a panRAS inhibitor.

2. The antibody-drug conjugate of claim 1, wherein *p* is an integer from 1 to 6 or from 2 to 4, or p is 2 or 4; or *p* is determined by liquid chromatography-mass spectrometry (LC-MS).

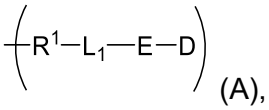
3. The antibody-drug conjugate of claim 1 or 2, wherein L comprises:

an attachment group;

at least one bridging spacer group; and

at least one cleavable group, optionally at least one cleavable group comprising a pyrophosphate group and/or a self-immolative group.

4. The antibody-drug conjugate of claim 3, wherein -(L-D) is of the formula (A):

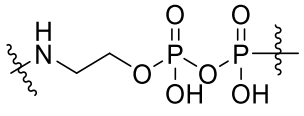

(A),

wherein:

R^1 is an attachment group;

L_1 is a bridging spacer group;

E is a cleavable group.

5. The antibody-drug conjugate of claim 3 or 4, wherein the cleavable group comprises a pyrophosphate group or the cleavable group comprises  .

6. The antibody-drug conjugate of claim 3 or 4, wherein the bridging spacer group comprises:

(i) a polyoxyethylene (PEG) group;

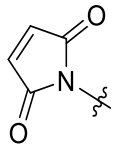
(ii) a PEG group selected from, PEG1, PEG2, PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG9, PEG10, PEG11, PEG12, PEG13, PEG14, and PEG15;

(iii) a -CO-CH_2-CH_2-PEG12- group;

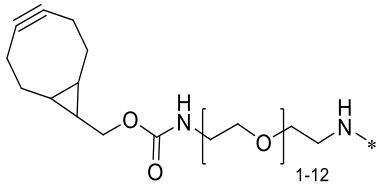
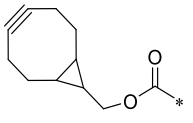
(iv) a butanoyl, pentanoyl, hexanoyl, heptanoyl, or octanoyl group; or

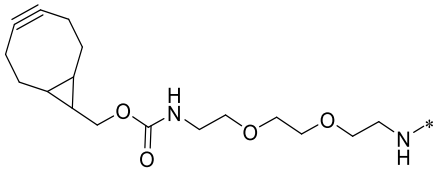
(v) a hexanoyl group.

7. The antibody-drug conjugate of claim 6, wherein (i) the attachment group is formed from at least one reactive group selected from a maleimide group, thiol group, cyclooctyne group, and an azido group; optionally wherein:

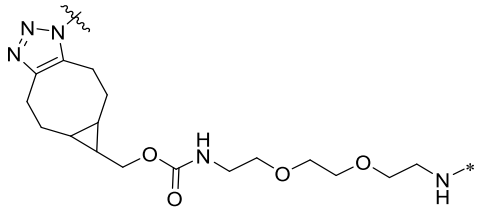
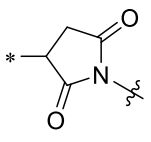
a) the maleimide group has the structure:  ;

b) the azido group has the structure: -N=N^+=N^-;

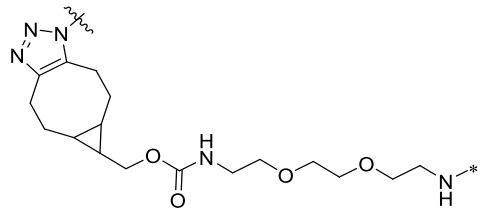
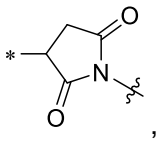
c) the cyclooctyne group has the structure:  or  , and wherein —* is a bond to the antibody or antigen-binding fragment thereof; or

d) the cyclooctyne group has the structure:  , and wherein —* is a bond to the antibody or antigen-binding fragment thereof; or

(ii) the attachment group has a formula comprising:

 or  , and wherein —* is a bond to the antibody or antigen-binding fragment thereof.

8. The antibody-drug conjugate of claim 7, wherein the antibody or antigen-binding fragment thereof is joined to the conjugate linker (L) by an attachment group selected from:

 and  ,

wherein —* is a bond to the antibody or antigen-binding fragment thereof, and wherein  is a bond to the bridging spacer group.

9. The antibody-drug conjugate of claim 8, wherein the bridging spacer group is -CH_2CH_2-O-CH_2CH_2-CO-.

10. The antibody-drug conjugate of claim 8 or 9, wherein the bridging spacer group is joined to a cleavable group; optionally the cleavable group is -pyrophosphate-CH_2-CH_2-NH_2-.

11. The antibody-drug conjugate of any one of claims 8 to 10, wherein the cleavable group is joined to the panRAS inhibitor (D).

12. The antibody-drug conjugate of any one of claims 1 to 3, wherein the conjugate linker comprises:

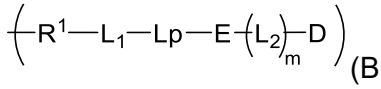
an attachment group,

at least one bridging spacer group,

a peptide group, and

at least one cleavable group.

13. The antibody-drug conjugate of claim 12, wherein -(L-D) is of the formula (B):

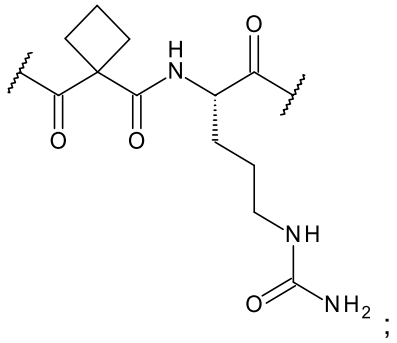
 (B),

wherein:

R^1 is an attachment group;

L_1 is a bridging spacer;

Lp is a peptide group comprising 1 to 6 amino acid residues or Lp comprises a group


;

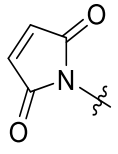
E is a cleavable group

L_2 is a bridging spacer;

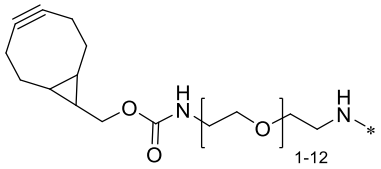
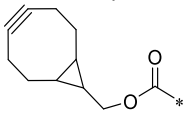
m is 0 or 1; and

D is a panRAS inhibitor.

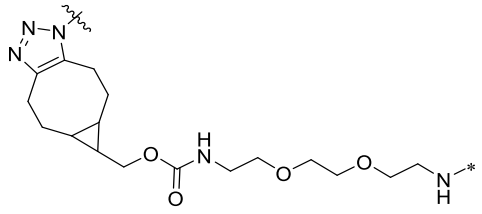
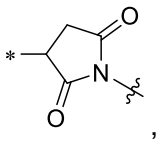
14. The antibody-drug conjugate of claim 12 or 13, wherein (i) the attachment group is formed from at least one reactive group comprising a maleimide group, thiol group, cyclooctyne group, and/or an azido group, optionally wherein:

a) the maleimide group has the structure:  ;

b) the azido group has the structure: -N=N$^+$=N$^-$;

c) the cyclooctyne group has the structure:  or  , and wherein — * is a bond to the antibody or antigen-binding fragment thereof; or

(ii) the attachment group has a formula comprising:

 or  , and

wherein —* is a bond to the antibody or antigen-binding fragment thereof.

15. The antibody-drug conjugate of any one of claims 12 to 14, wherein:

(i) at least one bridging spacer comprises a PEG group, optionally the PEG group is selected from, PEG1, PEG2, PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG9, PEG10, PEG11, PEG12, PEG13, PEG14, and PEG15; or

(ii) at least one bridging spacer is selected from *-C(O)-CH_2-CH_2-PEG1-**, *-C(O)-CH_2-PEG3-**, *-C(O)-CH_2-CH_2-PEG12**, *-NH-CH_2-CH_2-PEG1-**, a polyhydroxyalkyl group, *-C(O)-N(CH_3)-CH_2-CH_2-N(CH_3)-C(O)-**, and *-C(O)-CH_2-CH_2-PEG12-NH-C(O)CH_2-CH_2-**, wherein ** indicates the point of direct or indirect attachment of the at least one bridging spacer to the attachment group and * indicates the point of direct or indirect attachment of the at least one bridging spacer to the peptide group.

16. The antibody-drug conjugate of any one of claims 12 to 15, wherein L_1 is selected from *-C(O)-CH_2-CH_2-PEG1-**, *-C(O)-CH_2-PEG3-**, *-C(O)-CH_2-CH_2-PEG12**, *-NH-CH_2-CH_2-PEG1-**, and a polyhydroxyalkyl group, wherein ** indicates the point of direct or indirect attachment of L_1 to R^1 and * indicates the point of direct or indirect attachment of L_1 to Lp.

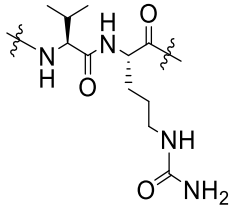
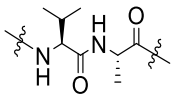
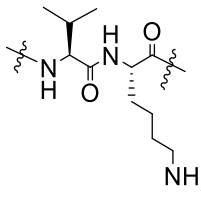
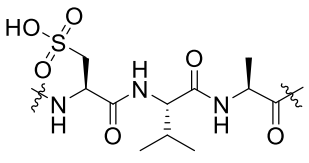
17. The antibody-drug conjugate of any one of claims 12 to 16, wherein m is 1 and L_2 is -C(O)-N(CH_3)-CH_2-CH_2-N(CH_3)-C(O)-.

18. The antibody-drug conjugate of any one of claims 12 to 17, wherein

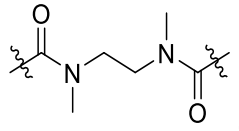
(i) the peptide group comprises 1 to 6, 1 to 4, 1 to 3 or 1 to 2 amino acid residues, optionally the amino acid residues are selected from L-glycine (Gly), L-valine (Val), L-citrulline (Cit), L-cysteic acid (sulfo-Ala), L-lysine (Lys), L-isoleucine (Ile), L-phenylalanine (Phe), L-methionine (Met), L-asparagine (Asn), L-proline (Pro), L-alanine (Ala), L-leucine (Leu), L-tryptophan (Trp), and L-tyrosine (Tyr);

(ii) the peptide group comprises Val-Cit, Val-Ala, Val-Lys, and/or sulfo-Ala-Val-Ala;

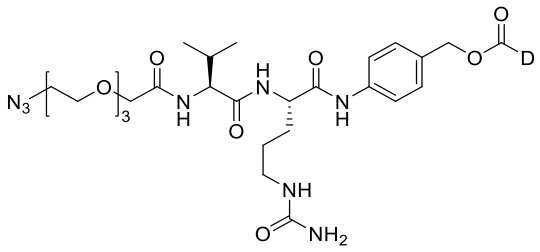
(iii) the peptide group is selected from:

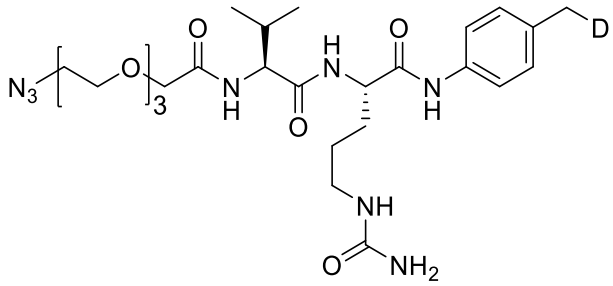
 ,  ,  , and  .

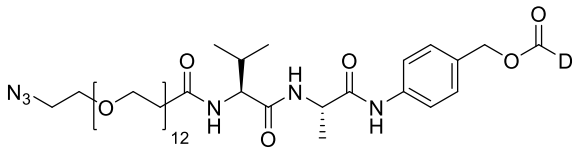
19. The antibody-drug conjugate of any one of claims 12 to 18, wherein (i) the cleavable group comprises a pyrophosphate and/or a self-immolative group; (ii) the cleavable group comprises a self-immolative group; or (iii) the cleavable group comprises a self-immolative group comprising para-aminobenzyl-carbamate, para-aminobenzyl-ammonium, para-amino-(sulfo)benzyl-ammonium, para-amino-(sulfo)benzyl-carbamate, para-amino-(alkoxy-PEG-alkyl)benzyl-carbamate, para-amino-(polyhydroxycarboxytetrahydropyranyl)alkyl-benzyl-carbamate, or para-amino-(polyhydroxycarboxytetrahydropyranyl)alkyl-benzyl-ammonium.

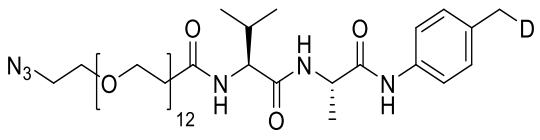
20. The antibody-drug conjugate of any one of claims 13 to 19, wherein m is 0 or 1 or m is 1 and the bridging spacer comprises  .

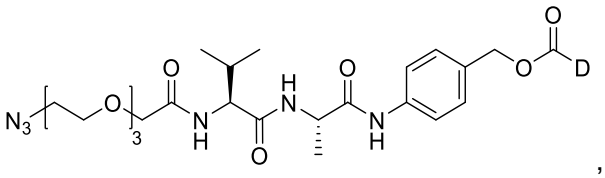
21. The antibody-drug conjugate of any one of claims 13-20, wherein -(L-D) is formed from a compound selected from:

 ,

 ,

 ,

 ,



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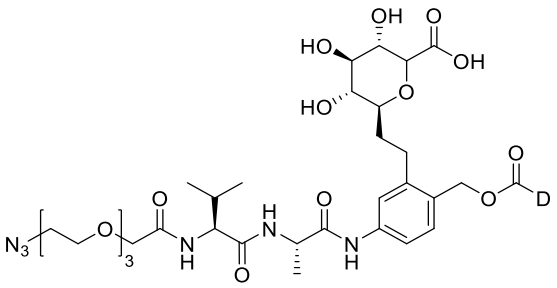

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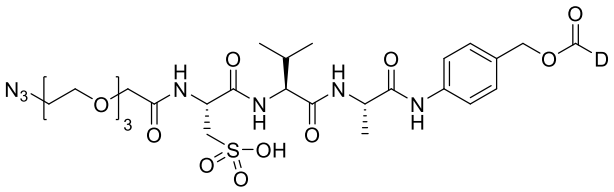

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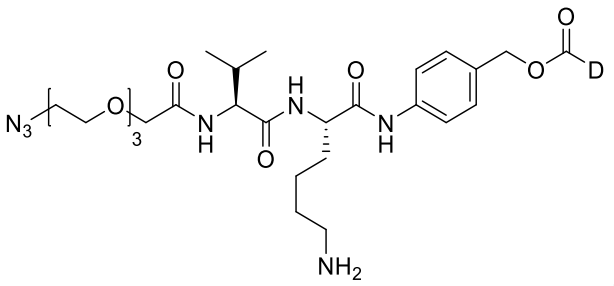

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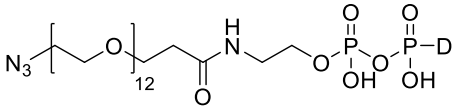

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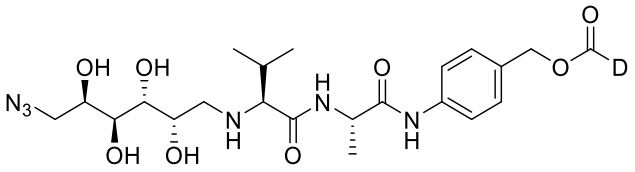

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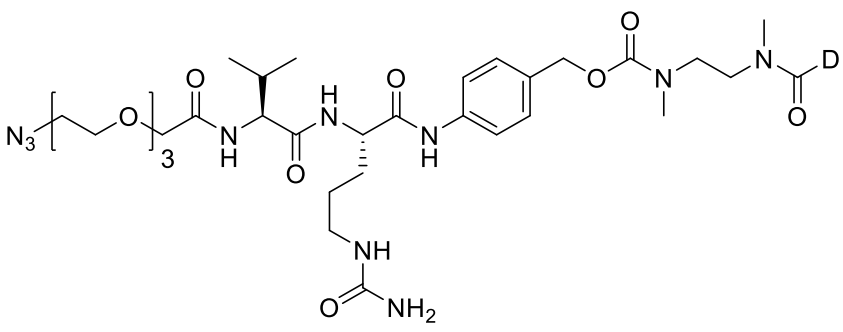

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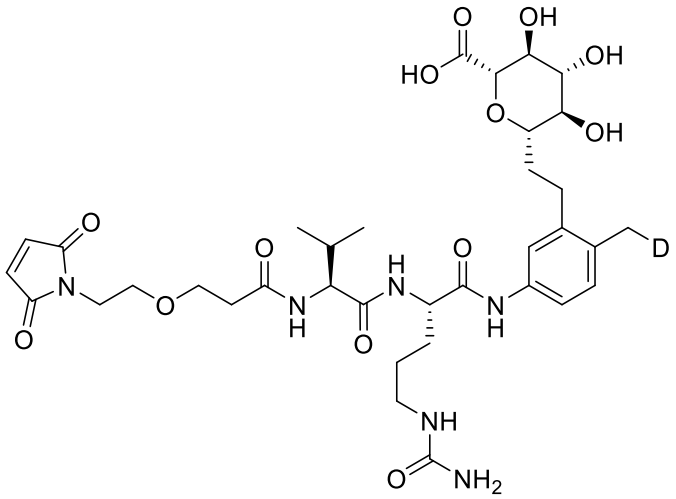
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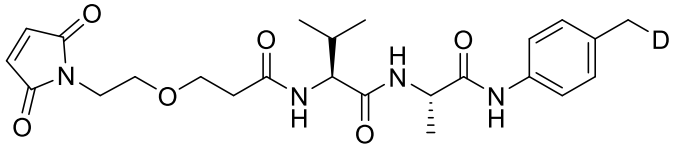
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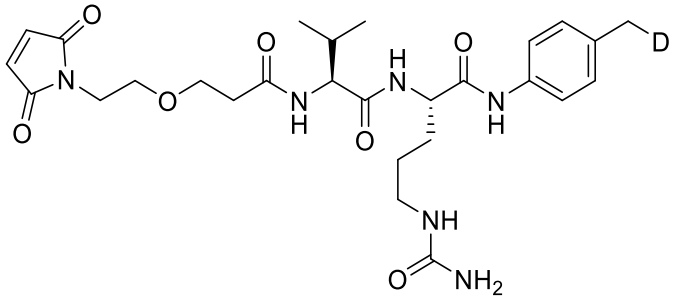
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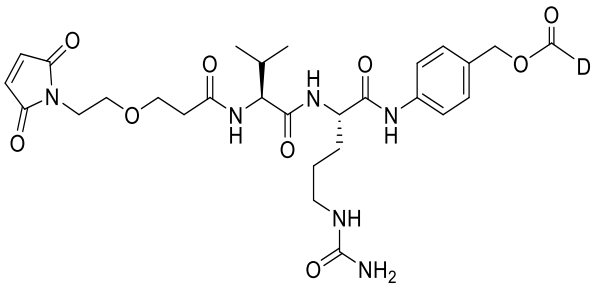
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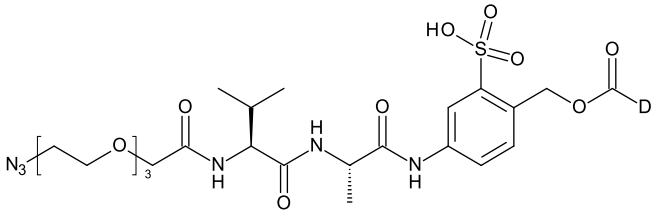
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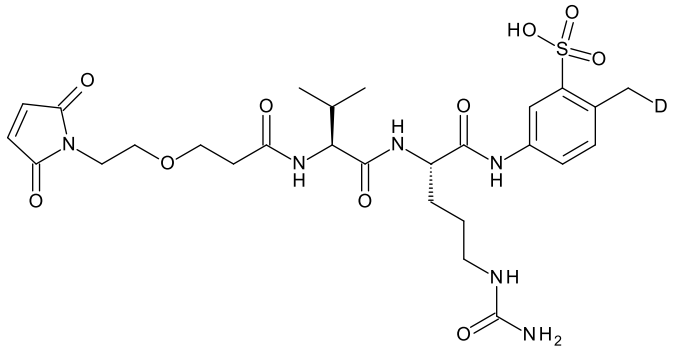

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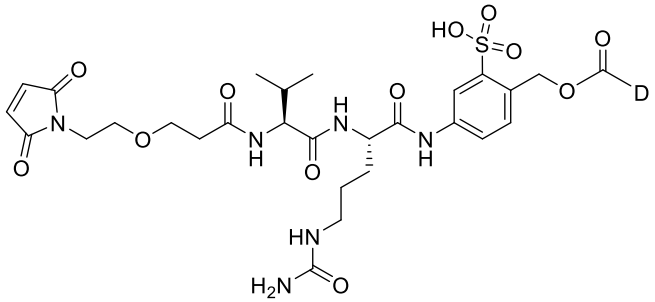

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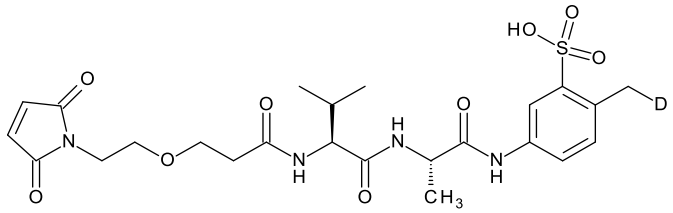

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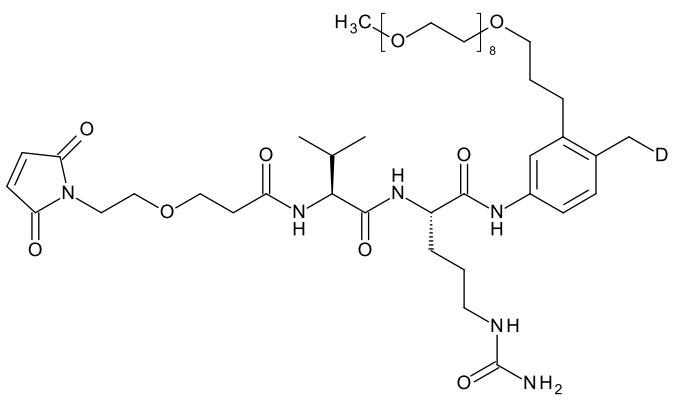

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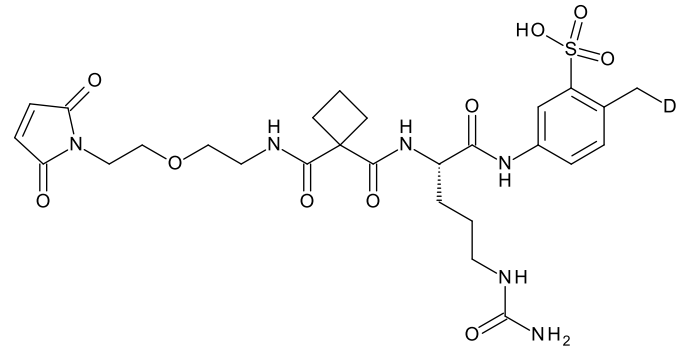

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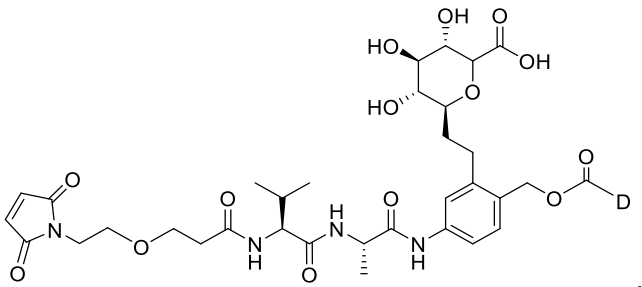

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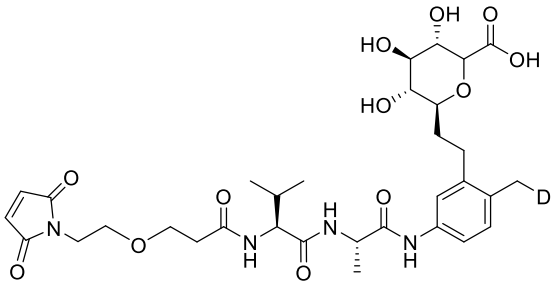

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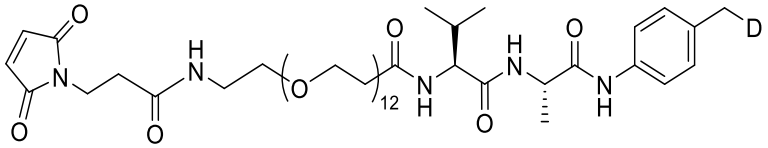

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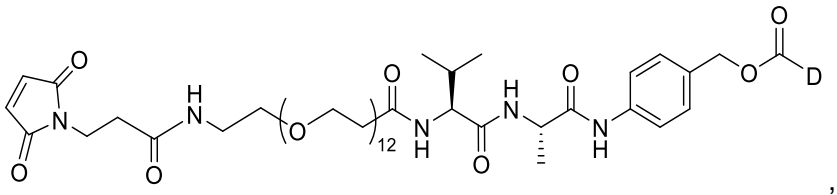

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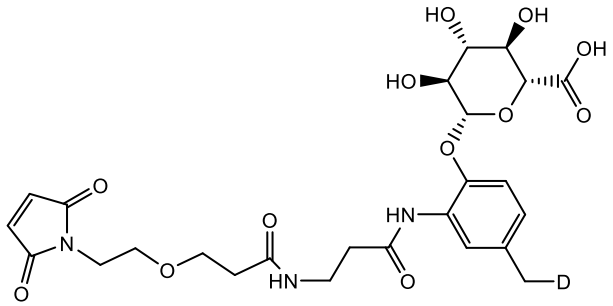

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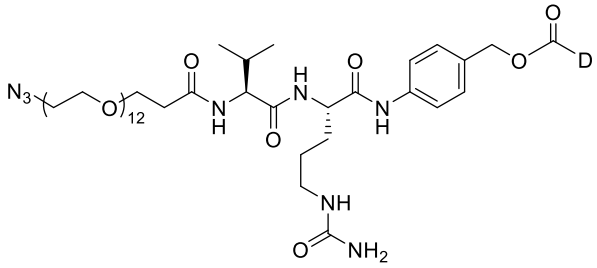

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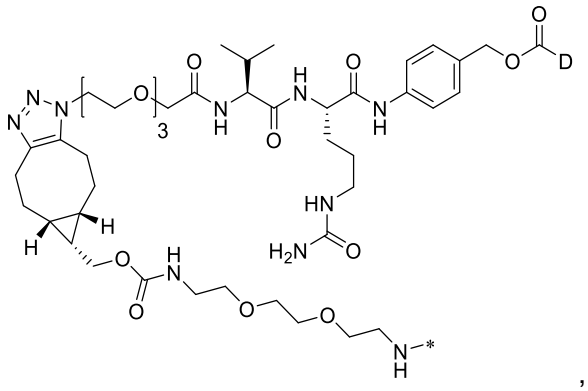
22. The antibody-drug conjugate of any one of claims 13-21, wherein -(L-D) comprises a formula selected from:



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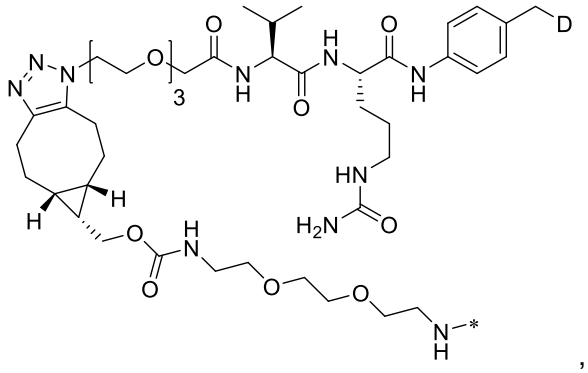

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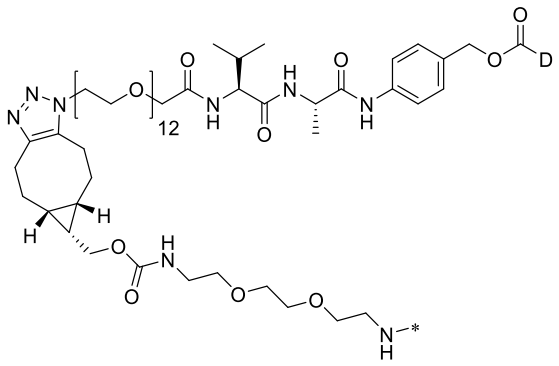

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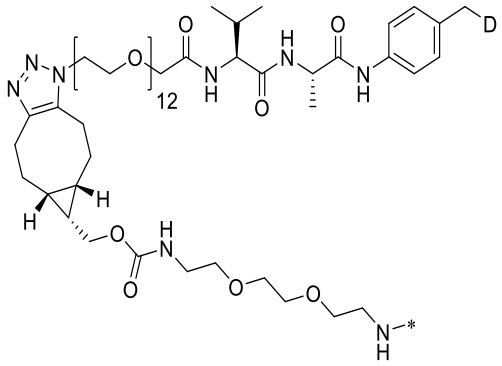

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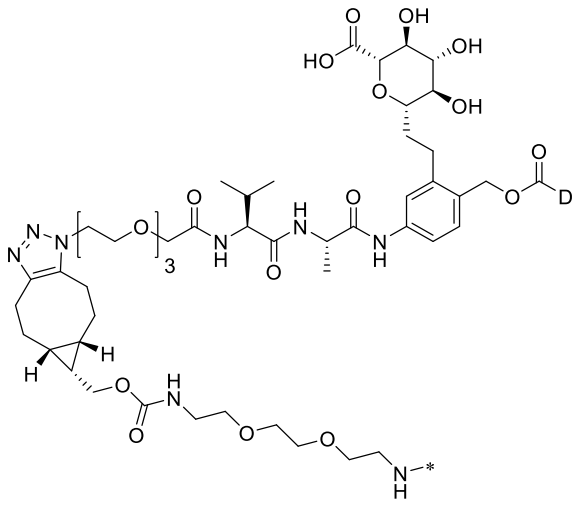

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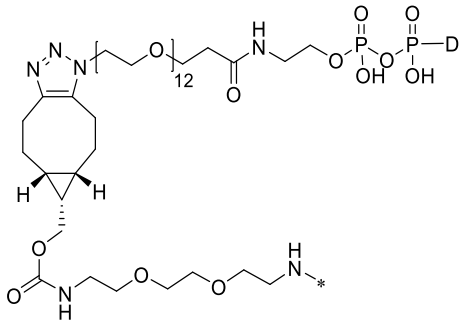

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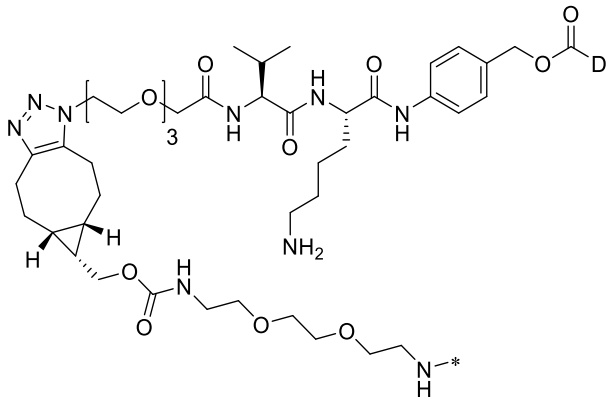

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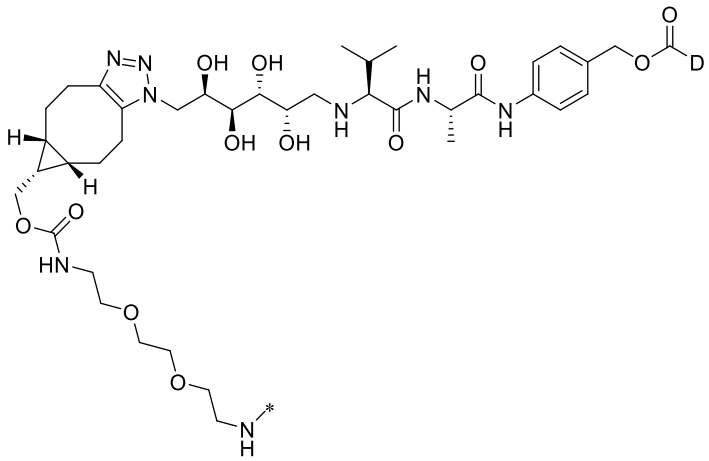

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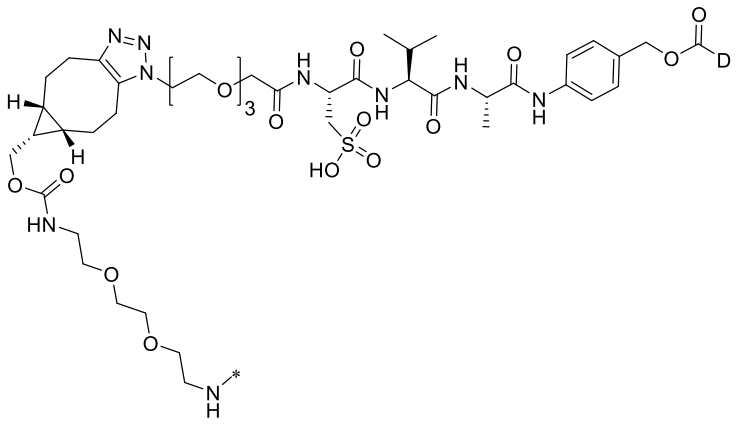

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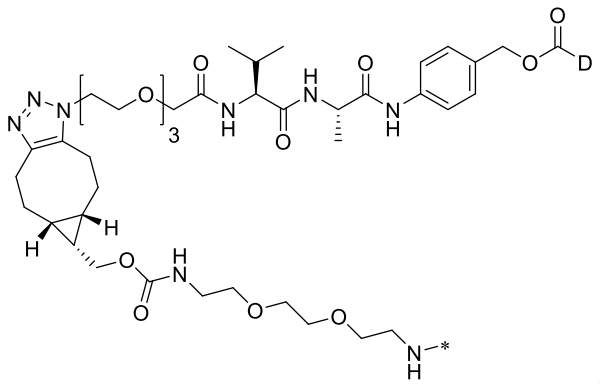

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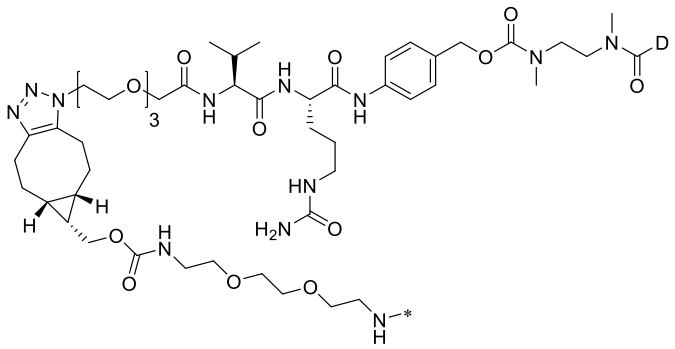

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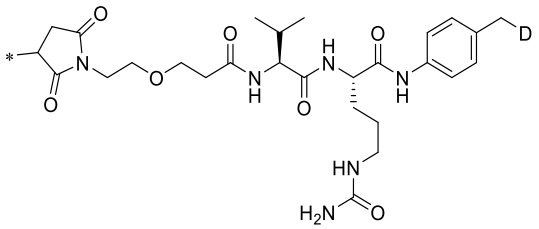

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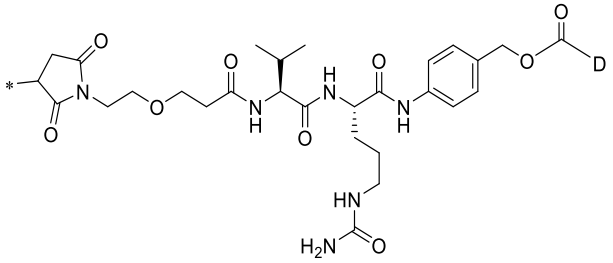

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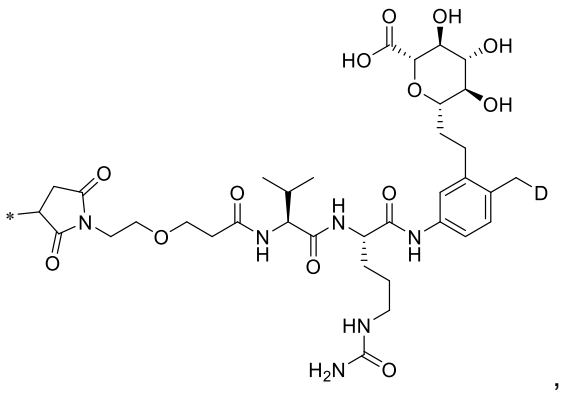

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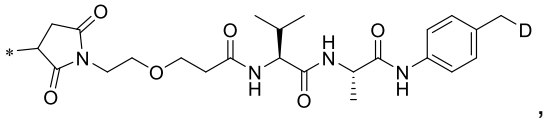

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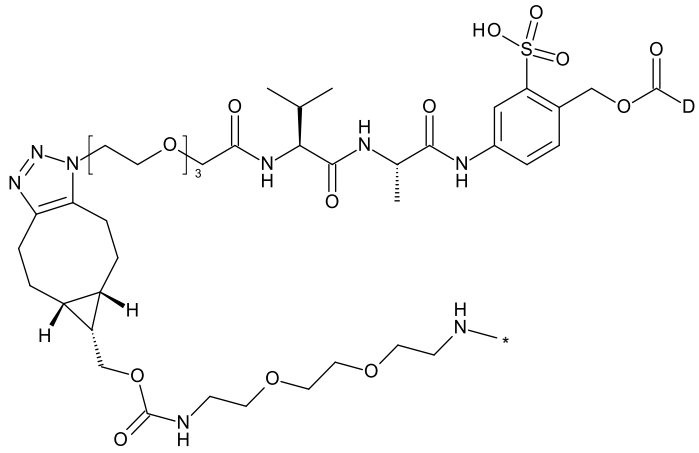

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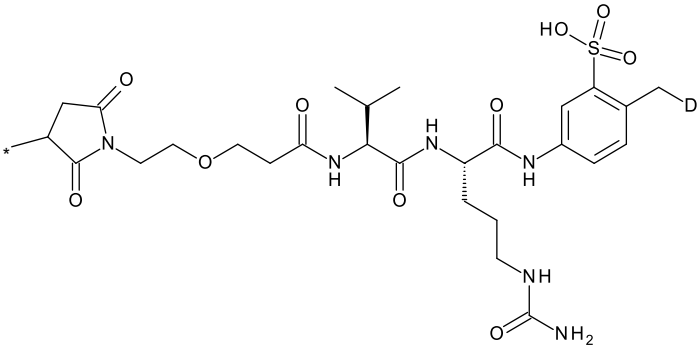

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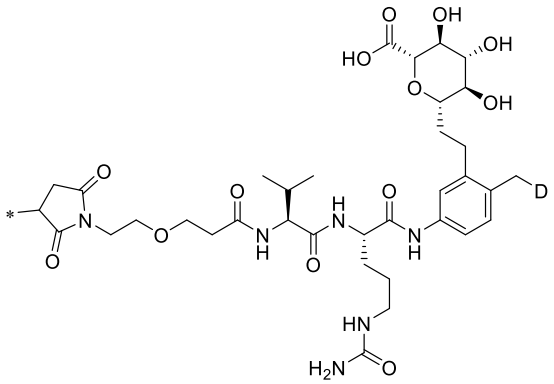

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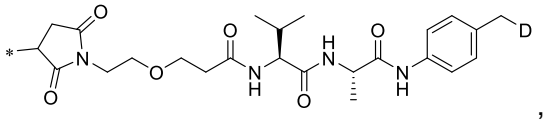

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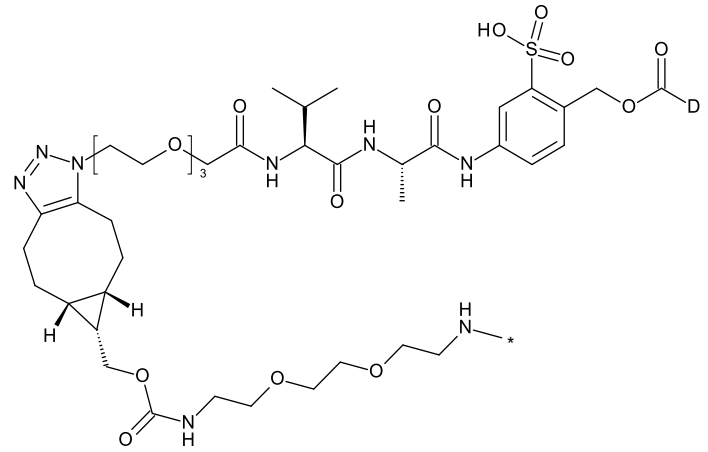

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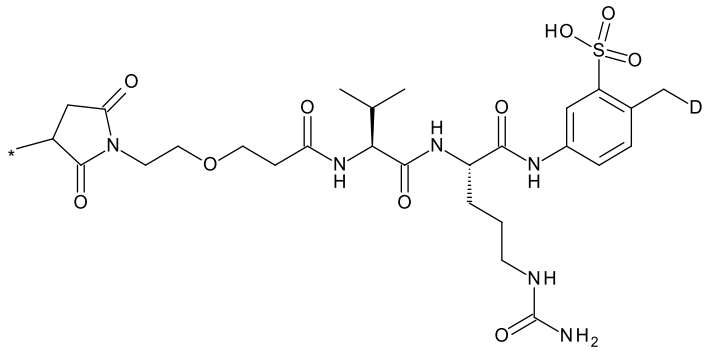

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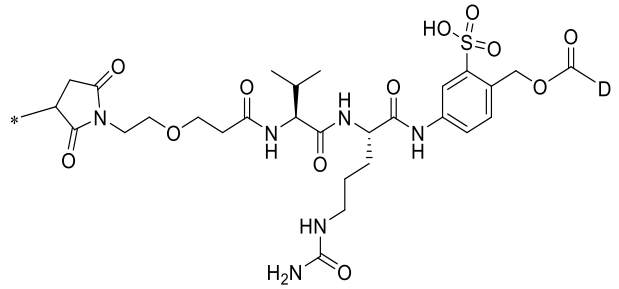

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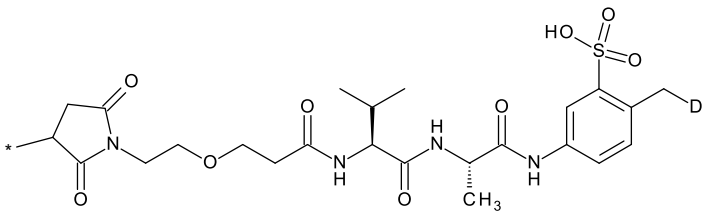

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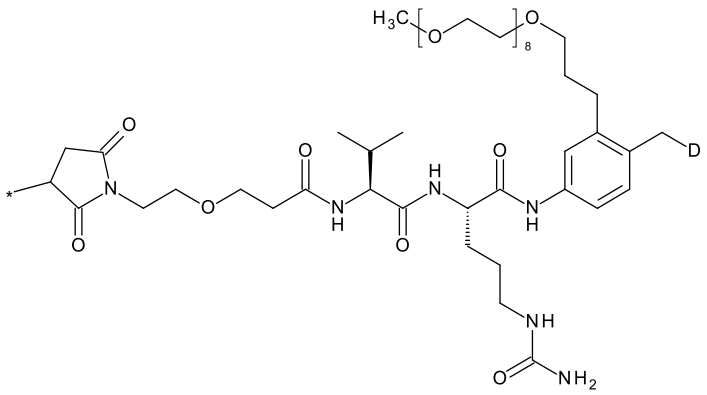

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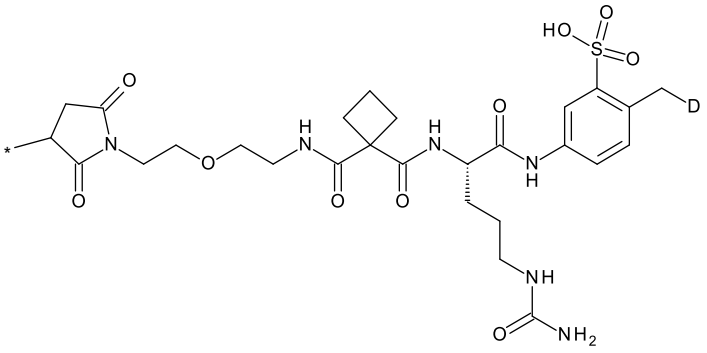

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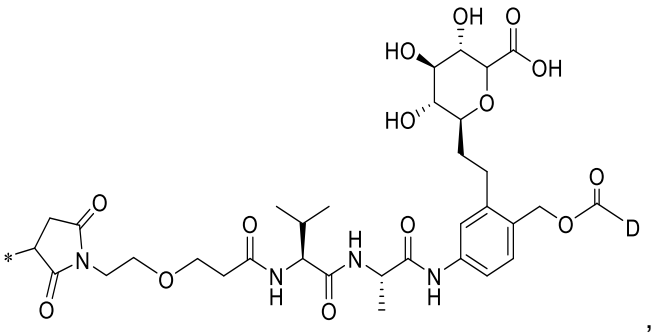

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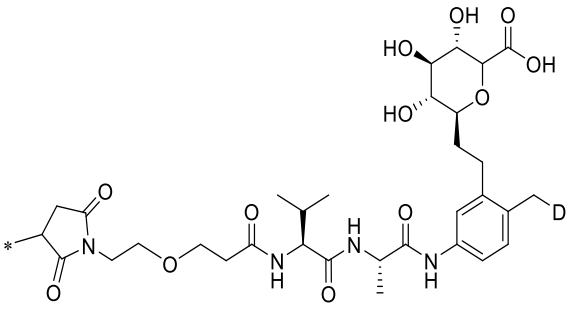

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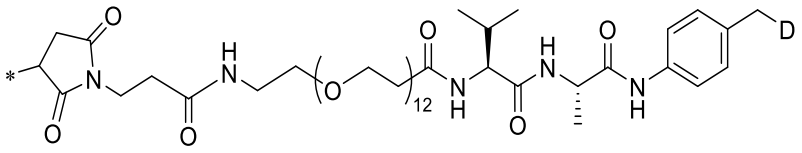

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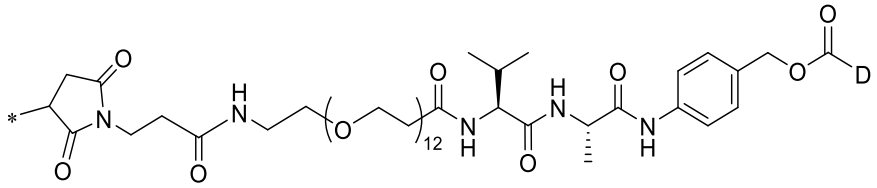

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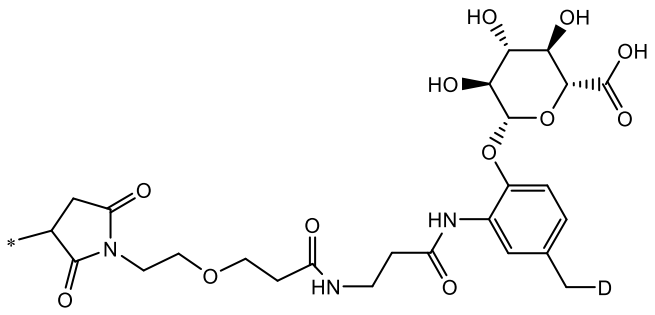

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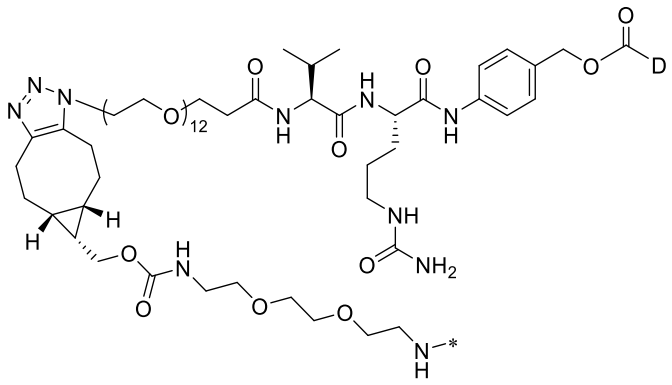
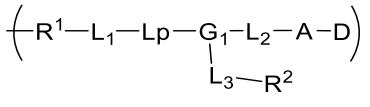


,

and

wherein $^{—*}$ is a bond to the antibody or antigen-binding fragment thereof.

23. The antibody-drug conjugate of claim 1 or 2, wherein -(L-D) is of the formula (C):



(C),

wherein:

R^1 is an attachment group;

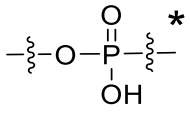
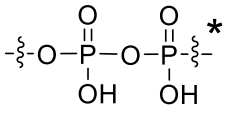
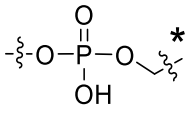
L_1 is a bridging spacer;

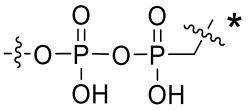
L_p is a peptide group comprising 1 to 6 amino acids;

D is a panRAS inhibitor;

G_1-L_2-A is a self-immolative spacer;

L_2 is a bond, a methylene, a neopentylene or a C_2-C_3 alkenylene;

A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

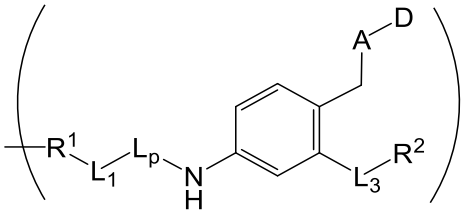
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D;

L_3 is a spacer moiety; and

R^2 is a hydrophilic moiety.

24. The antibody-drug conjugate of claim 23, or pharmaceutically acceptable salt thereof, wherein -(L-D) is of Formula (D):

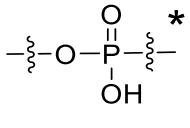
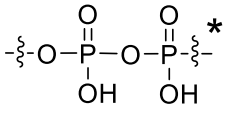
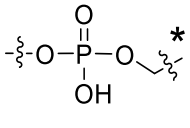
 (D)

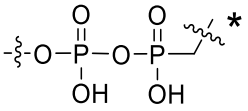
wherein:

R^1 is an attachment group;

L_1 is a bridging spacer;

Lp is a peptide group comprising 1 to 6 amino acids;

A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

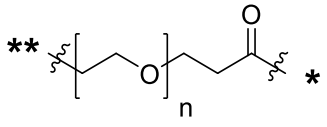
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D;

L_3 is a spacer moiety; and

R^2 is a hydrophilic moiety.

25. The antibody-drug conjugate of claim 23 or 24, wherein:

(1) L_1 comprises: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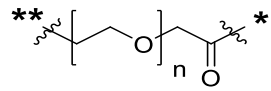
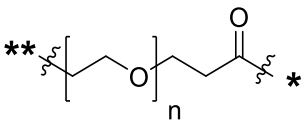
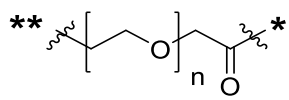
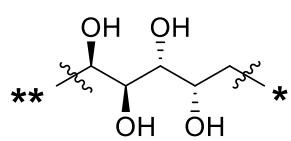

, or

*-CH(OH)CH(OH)CH(OH)CH(OH)-**,

wherein each n is an integer from 1 to 12, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(2) L_1 is  , and n is an integer from 1 to 12 or n is 1 or n is 12, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(3) L_1 is  , and n is an integer from 1 to 12, wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(4) L_1 comprises  , wherein the * of L_1 indicates the point of direct or indirect attachment to Lp, and the ** of L_1 indicates the point of direct or indirect attachment to R^1;

(5) L_1 is a bridging spacer comprising:

*-C(=O)$(CH_2)_m$O$(CH_2)_m$-**; *-C(=O)$((CH_2)_m$O$)_t(CH_2)_n$-**; *-C(=O)$(CH_2)_m$-**;
*-C(=O)NH$((CH_2)_m$O$)_t(CH_2)_n$-**;
*-C(=O)O$(CH_2)_m$SSC$(R^3)_2(CH_2)_m$C(=O)N$R^3(CH_2)_m$NR^3C(=O)$(CH_2)_m$-**;
*-C(=O)O$(CH_2)_m$C(=O)NH$(CH_2)_m$-**; *-C(=O)$(CH_2)_m$NH$(CH_2)_m$-**;
*-C(=O)$(CH_2)_m$NH$(CH_2)_n$C(=O)-**; *-C(=O)$(CH_2)_m X_1(CH_2)_m$-**;
*-C(=O)$((CH_2)_m$O$)_t(CH_2)_n X_1(CH_2)_n$-**; *-C(=O)$(CH_2)_m$NHC(=O)$(CH_2)_n$-**;

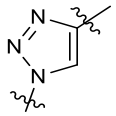
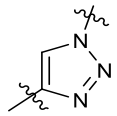
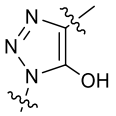
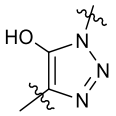
*-C(=O)((CH$_2$)$_m$O)$_t$(CH$_2$)$_n$NHC(=O)(CH$_2$)$_n$-**;

*-C(=O)(CH$_2$)$_m$NHC(=O)(CH$_2$)$_n$X$_1$(CH$_2$)$_n$-**;

*-C(=O)((CH$_2$)$_m$O)$_t$(CH$_2$)$_n$NHC(=O)(CH$_2$)$_n$X$_1$(CH$_2$)$_n$-**;

*-C(=O)((CH$_2$)$_m$O)$_t$(CH$_2$)$_n$C(=O)NH(CH$_2$)$_m$-**; *-C(=O)(CH$_2$)$_m$C(R^3)$_2$-** or

*-C(=O)(CH$_2$)$_m$C(=O)NH(CH$_2$)$_m$-**, wherein the * of L$_1$ indicates the point of direct or indirect attachment to Lp, and the ** of L$_1$ indicates the point of direct or indirect attachment to R^1;

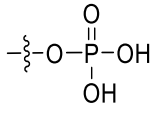
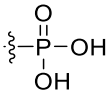
X$_1$ is  ,  ,  or  ; and

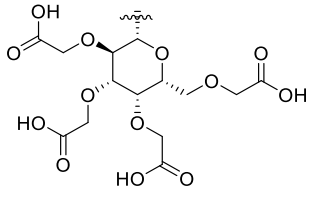
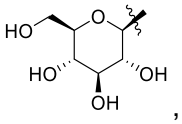
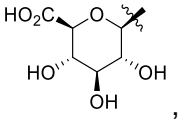
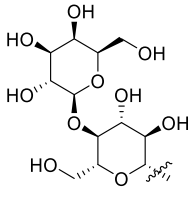
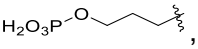
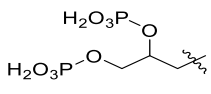
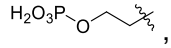
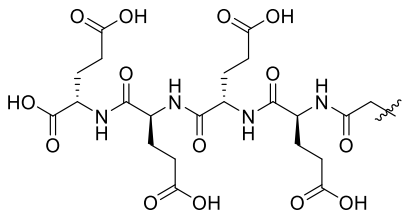
each m is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

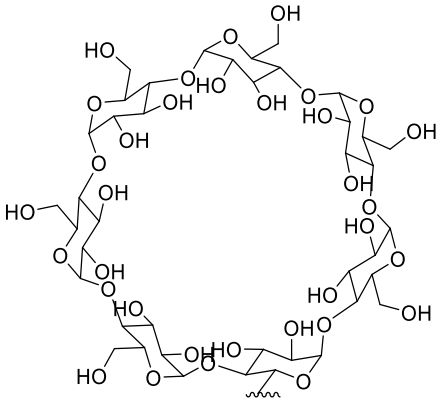
each n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

each t is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30;

and each R^3 is independently selected from H and C$_1$-C$_6$alkyl.

26. The antibody-drug conjugate of any one of claims 23 to 25, wherein R^2 is a hydrophilic moiety comprising polyethylene glycol, polyalkylene glycol, a polyol, a polysarcosine, a sugar, an oligosaccharide, a polypeptide, C$_2$-C$_6$ alkyl substituted with 1 to 3  or  , or C$_2$-C$_6$alkyl substituted with 1 to 2 substituents independently selected from -OC(=O)NHS(O)$_2$NHCH$_2$CH$_2$OCH$_3$, -NHC(=O)C$_{1-4}$alkylene-P(O)(OCH$_2$CH$_3$)$_2$ and -COOH groups.

27. The antibody-drug conjugate of any one of claims 23 to 26, wherein R^2 is  ,  ,  ,  ,  ,  ,  ,  ,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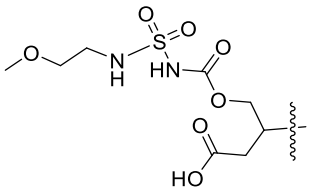
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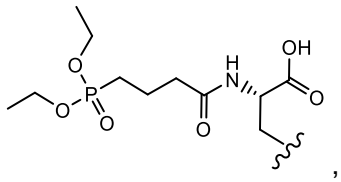
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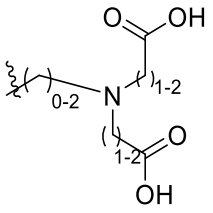
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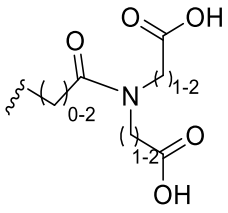
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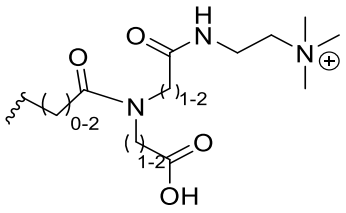
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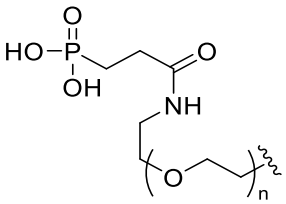
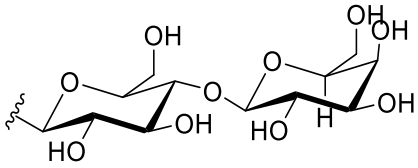

,
wherein n is an integer between 1 and 6,

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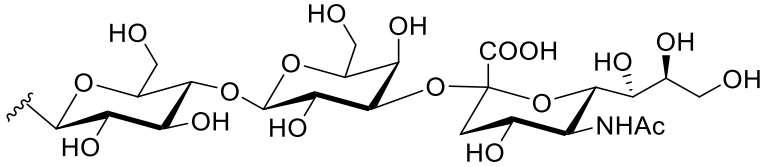
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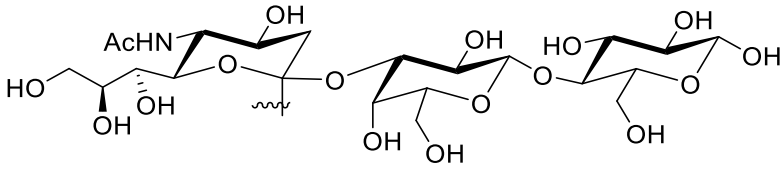
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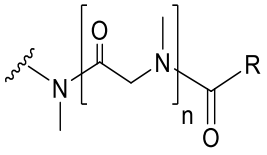
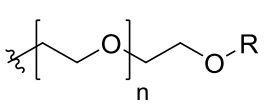
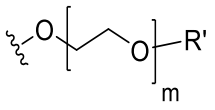
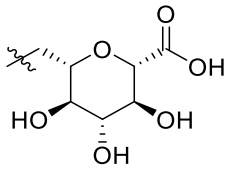
28. The antibody-drug conjugate of claim 23 or 24, wherein the hydrophilic moiety comprises:

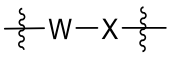
(i) a polysarcosine with the following moiety:


, wherein n is an integer between 3 and 25; and R is H, $–CH_3$ or -$CH_2CH_2C(=O)OH$; or

(ii) a polyethylene glycol of formula:  or  ,wherein R is H, -CH_3, $CH_2CH_2NHC(=O)OR_a$, -$CH_2CH_2NHC(=O)R_a$, or -$CH_2CH_2C(=O)OR_a$, R' is OH, -OCH_3, -$CH_2CH_2NHC(=O)OR_a$, -$CH_2CH_2NHC(=O)R_a$, or -$OCH_2CH_2C(=O)OR_a$, in which R_a is H or C_{1-4} alkyl optionally substituted with either OH or C_{1-4} alkoxyl, and each of m and n is independently an integer between 2 and 25.

29. The antibody-drug conjugate of any one of claims 23 to 27, wherein the hydrophilic moiety comprises  .

30. The antibody-drug conjugate of any one of claims 23 to 29, wherein:

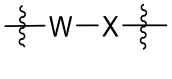
(i) L_3 is a spacer moiety having the structure  ,

wherein:

W is -CH_2-, -CH_2O-, -$CH_2N(R^b)C(=O)O$-, -$NHC(=O)C(R^b)_2NHC(=O)O$-, -$NHC(=O)C(R^b)_2NH$-, -$NHC(=O)C(R^b)_2NHC(=O)$-, -$CH_2N(X\text{-}R^2)C(=O)O$-, -$C(=O)N(X\text{-}R^2)$-, -$CH_2N(X\text{-}R^2)C(=O)$-, -$C(=O)NR^b$-, -C(=O)NH-, -$CH_2N\ R^b\ C(=O)$-, -$CH_2NR^b\ C(=O)NH$-, -$CH_2NR^bC(=O)NR^b$-, -NHC(=O)-, -NHC(=O)O-, -NHC(=O)NH-, -OC(=O)NH-, -$S(O)_2NH$-, -$NHS(O)_2$-, -C(=O)-, -C(=O)O- or -NH-, wherein each R^b is independently selected from H, C_1-C_6alkyl, and C_3-C_8 cycloalkyl; and

X is a bond, triazolyl, or -CH_2-triazolyl-,

wherein X is connected to R^2; or

(ii) L_3 is a spacer moiety having the structure  ,

wherein:

W is -CH_2-, -CH_2O-, -$CH_2N(R^b)C(=O)O$-, -$NHC(=O)C(R^b)_2NHC(=O)O$-, -$NHC(=O)C(R^b)_2NH$-, -$NHC(=O)C(R^b)_2NHC(=O)$-, -$CH_2N(X\text{-}R^2)C(=O)O$-, -$C(=O)N(X\text{-}R^2)$-, -$CH_2N(X\text{-}R^2)C(=O)$-, -$C(=O)NR^b$-, -C(=O)NH-, -$CH_2NR^bC(=O)$-, -$CH_2NR^bC(=O)NH$-, -$CH_2NR^bC(=O)NR^b$-, -NHC(=O)-, -NHC(=O)O-, -NHC(=O)NH-, -OC(=O)NH-,

-$S(O)_2NH$-, -$NHS(O)_2$-, -C(=O)-, -C(=O)O- or -NH-, wherein each R^b is independently selected from H, C_1-C_6alkyl, and C_3-C_8 cycloalkyl; and

X is -CH_2-triazolyl-C_{1-4} alkylene-$OC(O)NHS(O)_2NH$-, -C_{4-6} cycloalkylene-$OC(O)NHS(O)_2NH$-, -$(CH_2CH_2O)_n$-$C(O)NHS(O)_2NH$-, -$(CH_2CH_2O)_n$-$C(O)NHS(O)_2NH$-$(CH_2CH_2O)_n$-, -CH_2-triazolyl-C_{1-4} alkylene-$OC(O)NHS(O)_2NH$-$(CH_2CH_2O)_n$-, -C_{4-6}cycloalkylene-$OC(O)NHS(O)_2NH$-$(CH_2CH_2O)_n$-,wherein each n independently is 1, 2, or 3,

wherein X is connected to R^2.

31. The antibody-drug conjugate of any one of claims 3 to 30, wherein the attachment group is formed by a reaction comprising at least one reactive group.

32. The antibody-drug conjugate of any one of claims 3 to 31, wherein the attachment group is formed by reacting:

a first reactive group that is attached to the conjugate linker, and

a second reactive group that is attached to the antibody or antigen-binding fragment thereof or is an amino acid residue of the antibody or antigen-binding fragment thereof, wherein optionally,

(i) at least one of the reactive groups comprises:

a thiol,

a maleimide,

a haloacetamide,

an azide,

an alkyne,

a cyclcooctene,

a triaryl phosphine,

an oxanobornadiene,

a cyclooctyne,

a diaryl tetrazine,

a monoaryl tetrazine,

a norbornene,

an aldehyde,

a hydroxylamine,

a hydrazine,

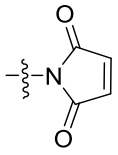
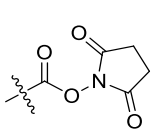
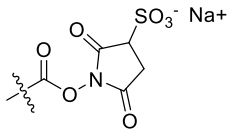
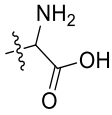
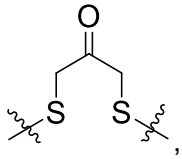
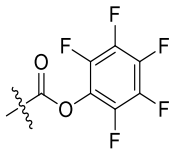
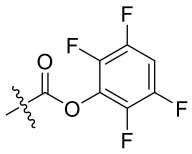
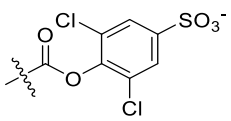
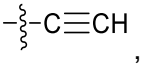
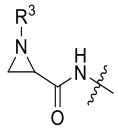
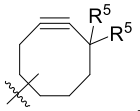
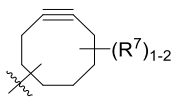
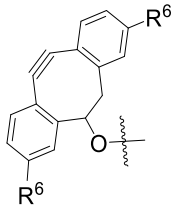
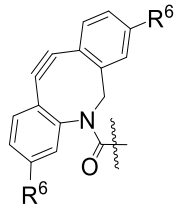
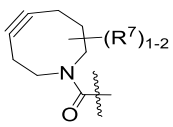
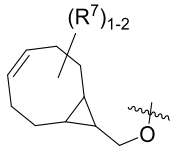
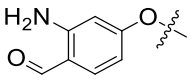
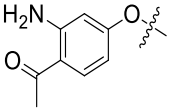
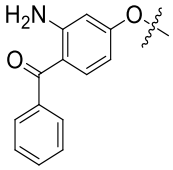
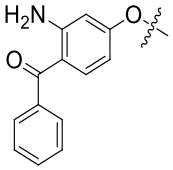
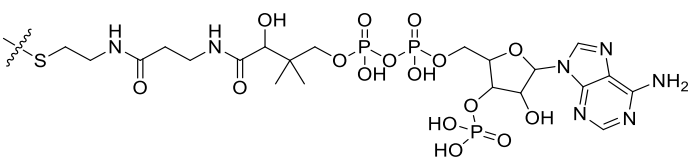
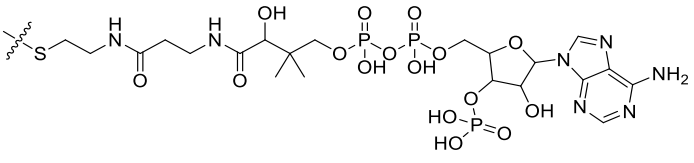
NH_2-NH-C(=O)-,

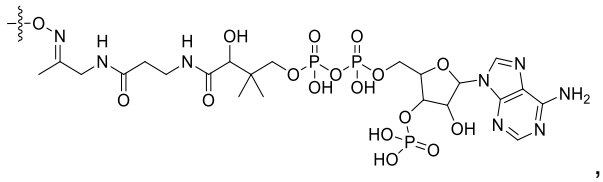
a ketone,

a vinyl sulfone,

an aziridine,

an amino acid residue,

 , -ONH_2, -NH_2,  ,  ,  ,  ,  ,  ,  , -N_3,  , -SH, -SR^3, -SSR^4, -$S(=O)_2(CH=CH_2)$, -$(CH_2)_2S(=O)_2(CH=CH_2)$, -$NHS(=O)_2(CH=CH_2)$, -$NHC(=O)CH_2Br$, -$NHC(=O)CH_2I$,  , -$C(O)NHNH_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .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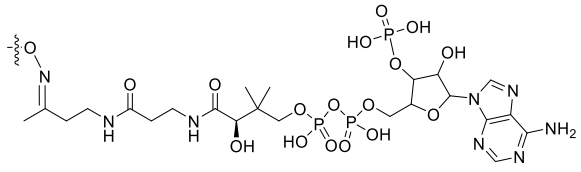
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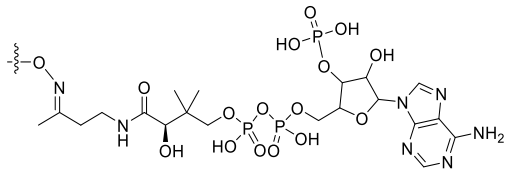
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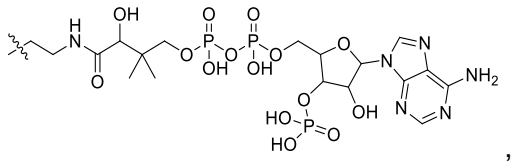
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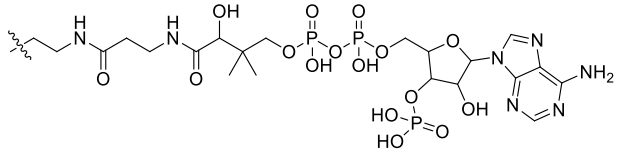
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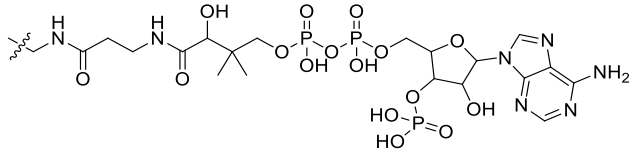

;

wherein:

each R^3 is independently selected from H and C_1-C_6alkyl;

each R^4 is 2-pyridyl or 4-pyridyl;

each R^5 is independently selected from H, C_1-C_6alkyl, F, Cl, and –OH;

each R^6 is independently selected from H, C_1-C_6alkyl, F, Cl, -NH_2, -OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -CN, -NO_2 and –OH;

each R^7 is independently selected from H, C_{1-6}alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4}alkoxy substituted with –C(=O)OH and C_{1-4}alkyl substituted with –C(=O)OH; and/or

(ii) the first reactive group and second reactive group comprise:

a thiol and a maleimide,

a thiol and a haloacetamide,

a thiol and a vinyl sulfone,

a thiol and an aziridine,

an azide and an alkyne,

an azide and a cyclooctyne,

an azide and a cyclooctene,

an azide and a triaryl phosphine,

an azide and an oxanobornadiene,

a diaryl tetrazine and a cyclooctene,

a monoaryl tetrazine and a nonbornene,

an aldehyde and a hydroxylamine,

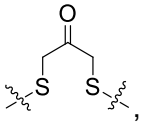
an aldehyde and a hydrazine,

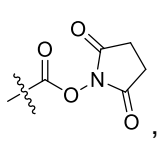
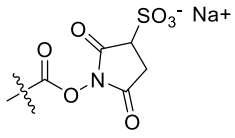
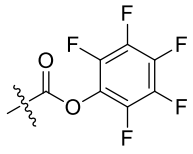
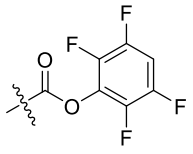
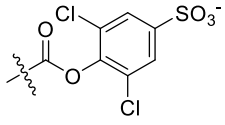
an aldehyde and NH_2-NH-C(=O)-,

a ketone and a hydroxylamine,

a ketone and a hydrazine,

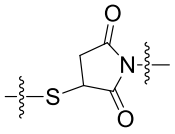
a ketone and NH_2-NH-C(=O)-,

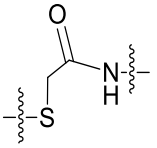
a hydroxylamine and  ,

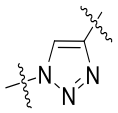
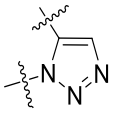
an amine and  ,  ,  ,  , or  , or

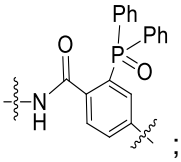
a CoA or CoA analogue and a serine residue.

33. The antibody-drug conjugate any one of claims 3 to 32, where the attachment group comprises a group selected from:

 ;

 ;

 or  ;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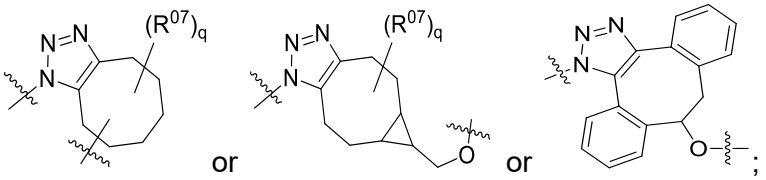
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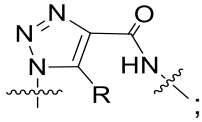
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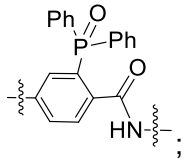
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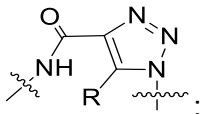
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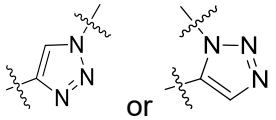
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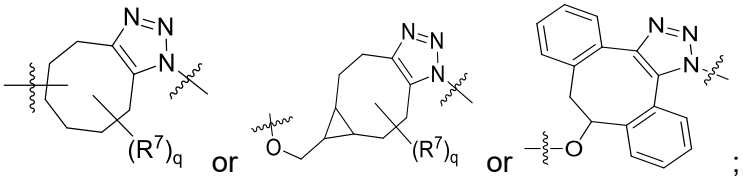
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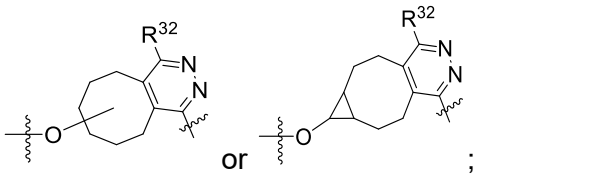
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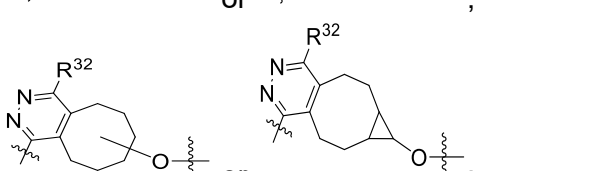
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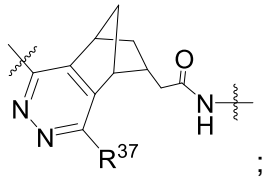
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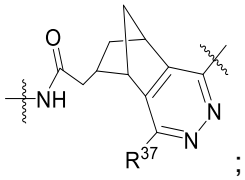
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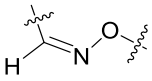
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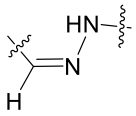
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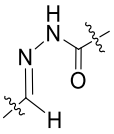
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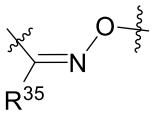
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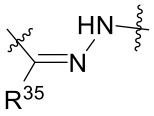
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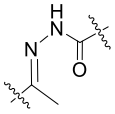
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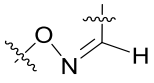
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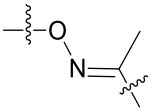
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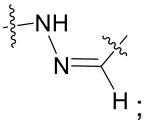
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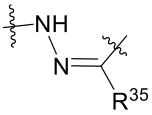
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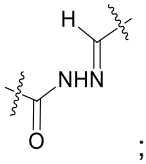
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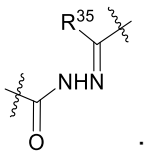
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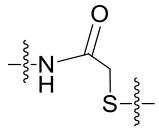
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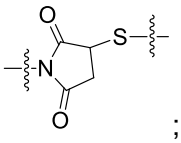
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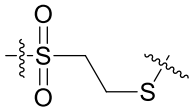
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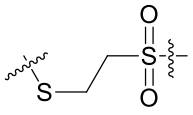
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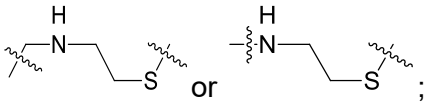
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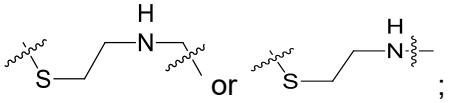
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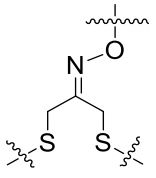
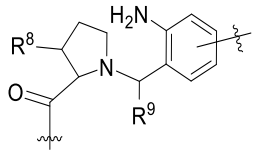

;

amide;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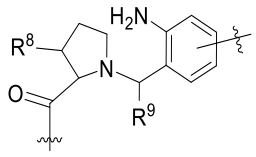
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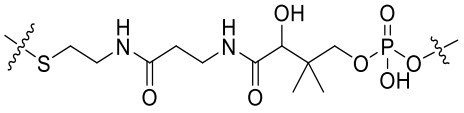
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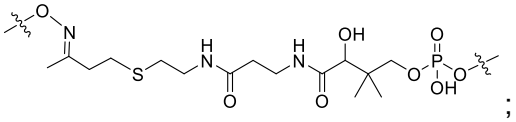
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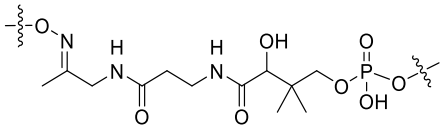
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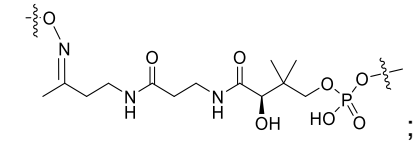
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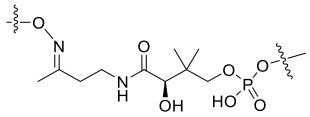
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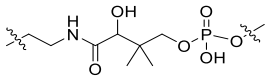
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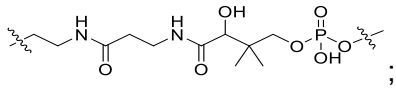
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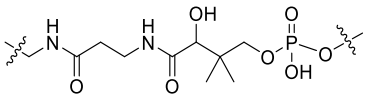

; and

disulfide,

wherein:

R^{32} is H, C_{1-4} alkyl, phenyl, pyrimidine or pyridine;

R^{35} is H, C_{1-6} alkyl, phenyl or C_{1-4} alkyl substituted with 1 to 3 –OH groups;

each R^7 is independently selected from H, C_{1-6} alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4} alkoxy substituted with –C(=O)OH and C_{1-4} alkyl substituted with –C(=O)OH;

R^{37} is independently selected from H, phenyl and pyridine;

q is 0, 1, 2 or 3;

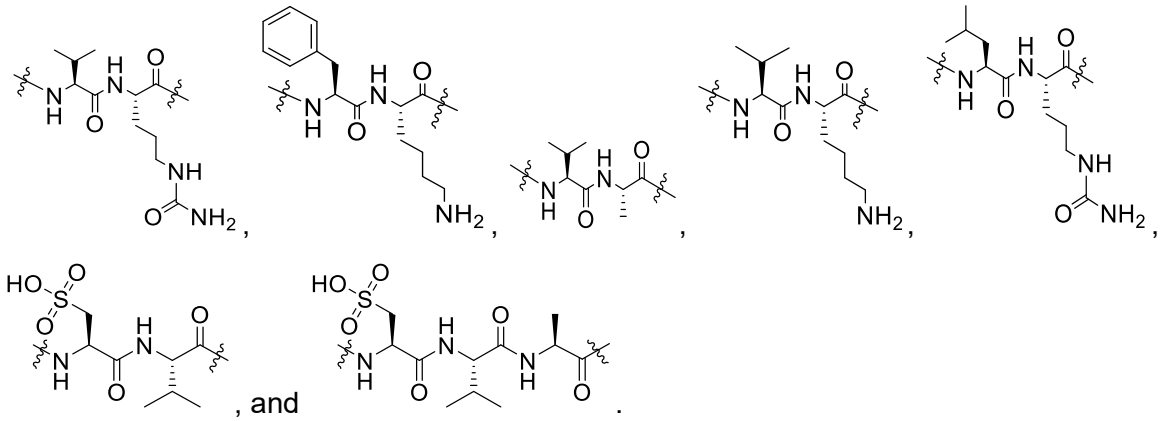
R^8 is H or methyl; and

R^9 is H, $-CH_3$ or phenyl.

34. The antibody-drug conjugate any one of claims 23 to 33, wherein the peptide group comprises 1 to 4 or 1 to 3 or 1 or 2 amino acid residues, optionally the amino acid residues are selected from L-glycine (Gly), L-valine (Val), L-citrulline (Cit), L-cysteic acid (sulfo-Ala), L-lysine (Lys), L-isoleucine (Ile), L-phenylalanine (Phe), L-methionine (Met), L-asparagine (Asn), L-proline (Pro), L-alanine (Ala), L-leucine (Leu), L-tryptophan (Trp), and L-tyrosine (Tyr).

35. The antibody-drug conjugate any one of claims 23 to 33, wherein the peptide group comprises Val-Cit, Phe-Lys, Val-Ala, Val-Lys, Leu-Cit, sulfo-Ala-Val, and/or sulfo-Ala-Val-Ala.

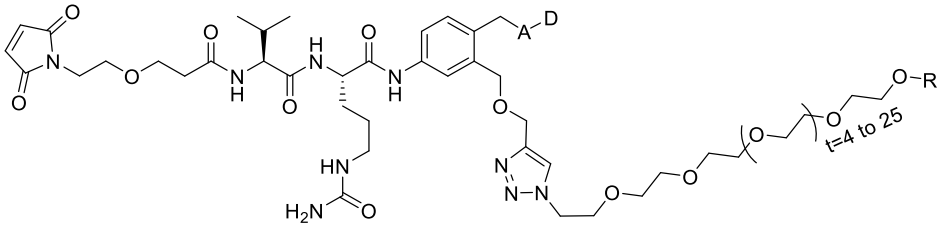
36. The antibody-drug conjugate any one of claims 23 to 35, wherein Lp is selected from:



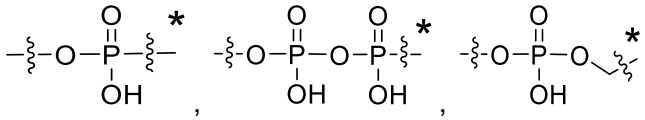
, and .

37. The antibody-drug conjugate of any one of claims 23 to 36, wherein:

-(L-D) comprises or is formed from a compound of formula:

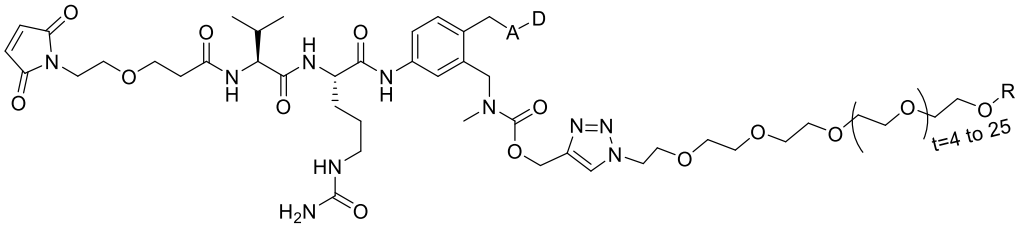
(1)  , wherein:

R is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

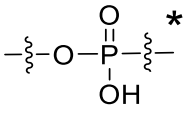
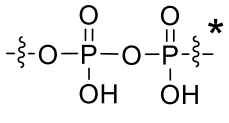
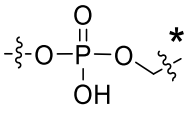
A is a bond, -OC(=O)-*,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

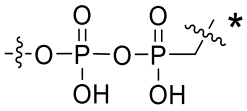
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(2)  , wherein:

R is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

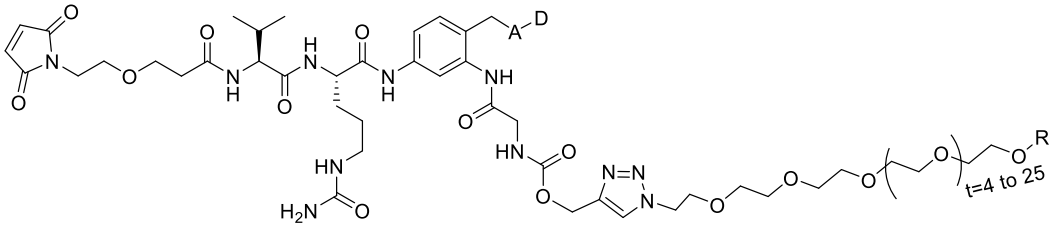
A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

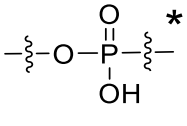
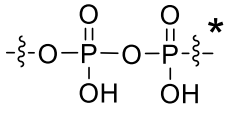
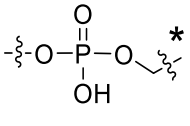
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

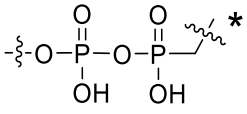
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(3)  , wherein:

R is H, -CH_3 or -CH_2CH_2C(=O)OH;

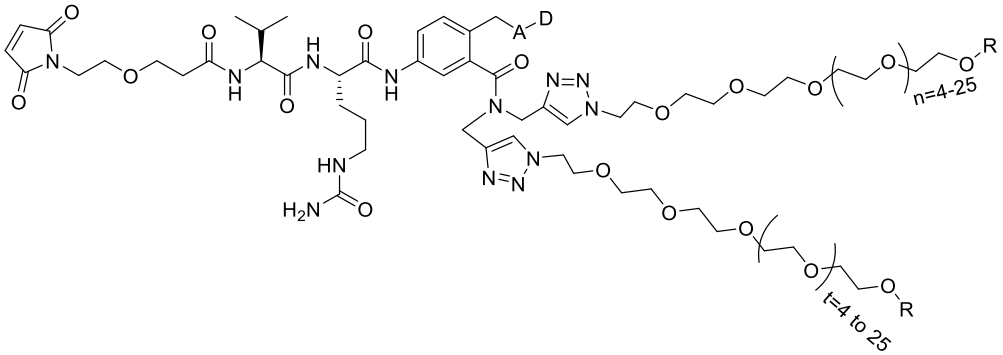
A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

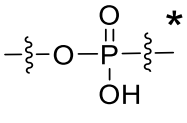
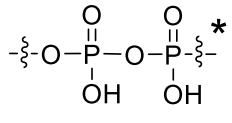
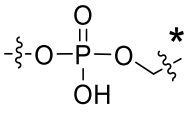
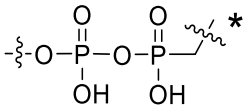
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

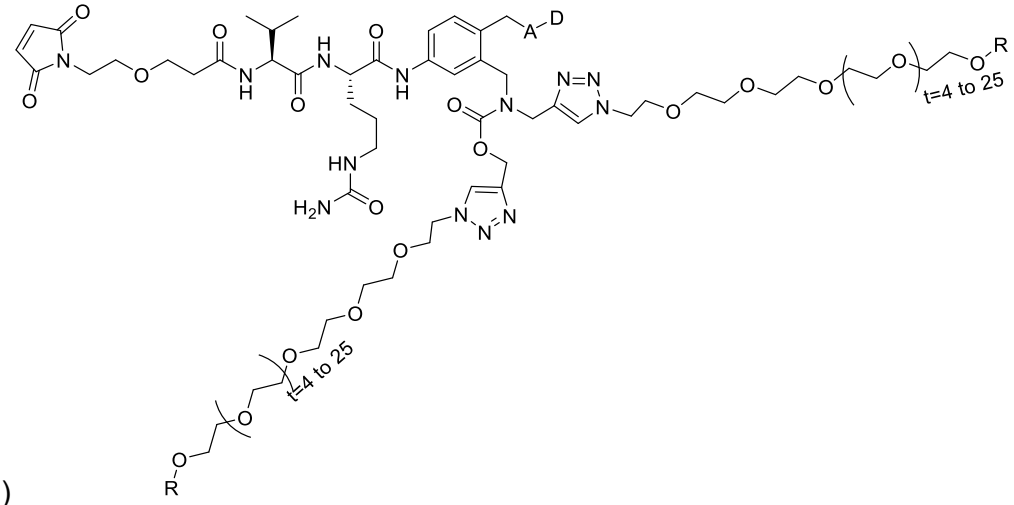
(4)  , wherein:

each R is independently selected from H, -CH_3, and -CH_2CH_2C(=O)OH;

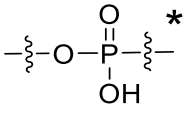
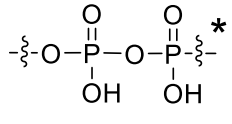
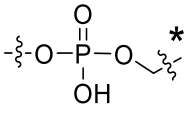
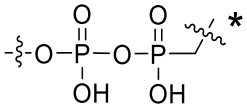
A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

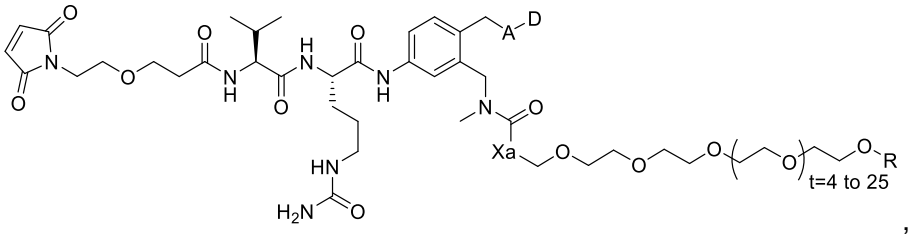
(5)  , wherein:

each R is independently selected from H, -CH_3, and -CH_2CH_2C(=O)OH;

A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

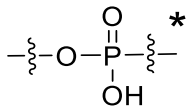
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

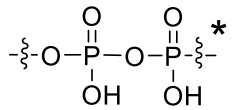
D is a panRAS inhibitor;

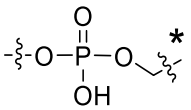
(6) 

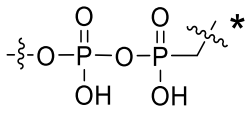
, wherein:

Xa is –CH_2-, -OCH_2-, -$NHCH_2$- or –$NRCH_2$- and each R independently is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*, 

, 

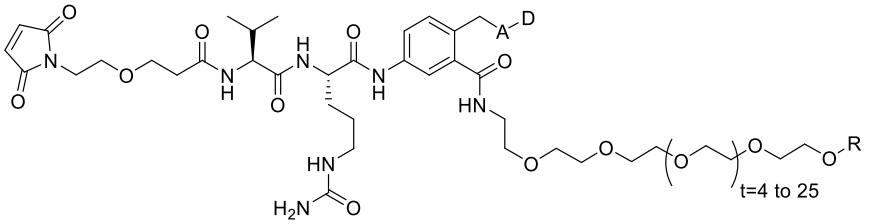
, 

, 

, -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

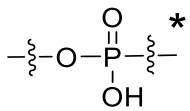
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

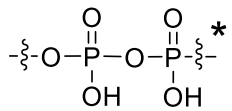
D is a panRAS inhibitor;

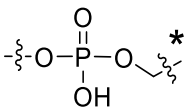
(7) 

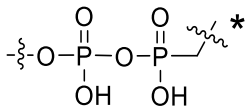
, wherein:

R is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*, 

, 

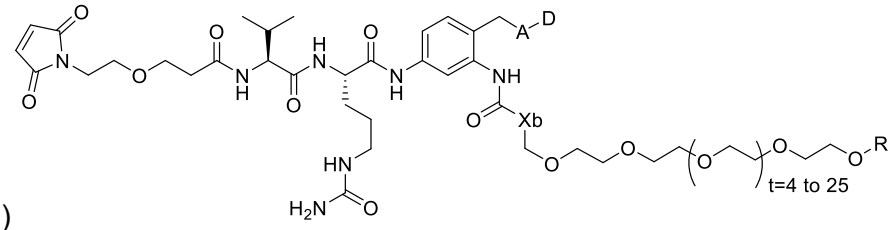
, 

, 

, -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

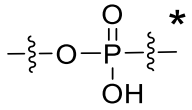
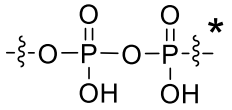
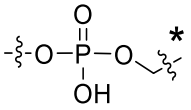
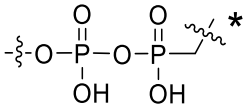
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(8) 

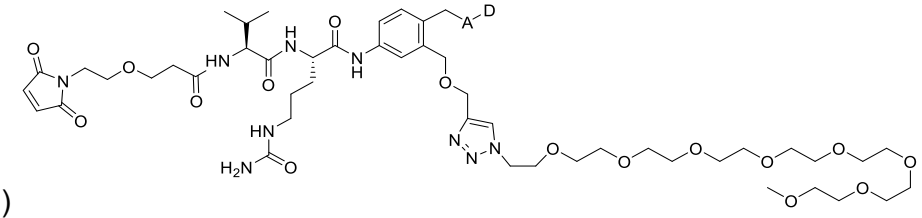
, wherein:

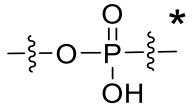
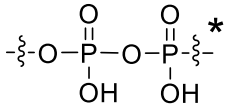
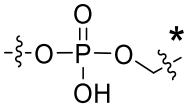
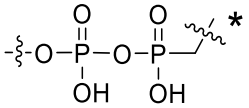
Xb is -CH_2-, -OCH_2-, -$NHCH_2$- or –$NRCH_2$- and each R independently is H, -CH_3 or -$CH_2CH_2C(=O)OH$;

A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

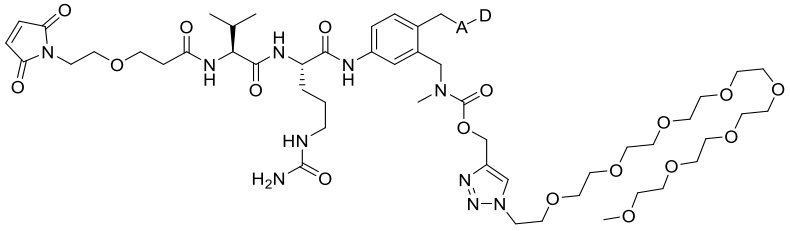
D is a panRAS inhibitor;

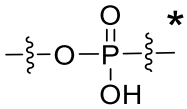
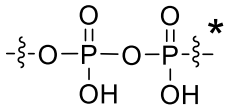
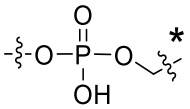
(9) 
, wherein:

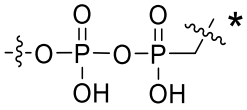
A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(10)  , wherein:

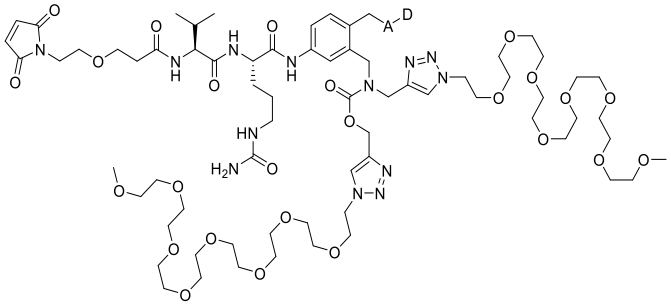
A is a bond, -OC(=O)-*,  ,  ,  ,

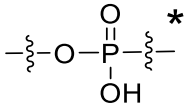
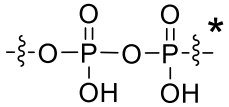
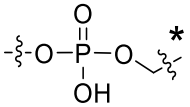
 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

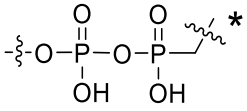
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(11)  , wherein:

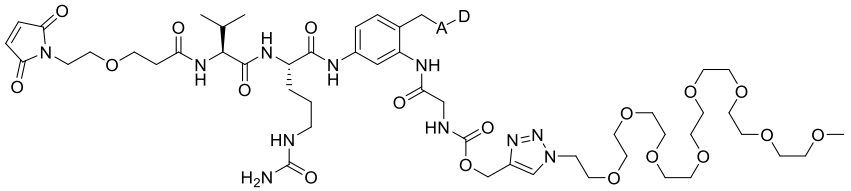
A is a bond, -OC(=O)-*,  ,  ,  ,

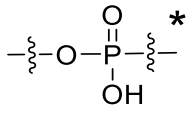
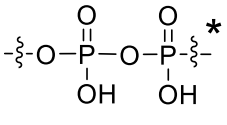
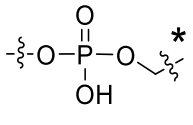
 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

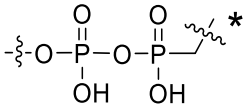
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(12)  , wherein:

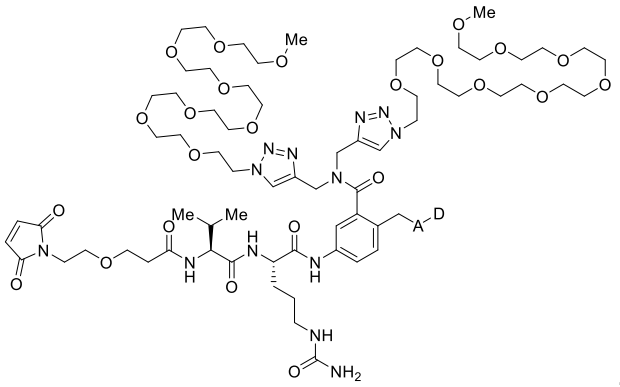
A is a bond, -OC(=O)-*,  ,  ,  ,

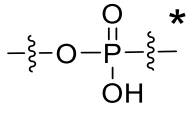
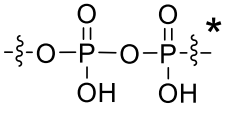
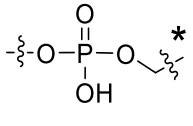
 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

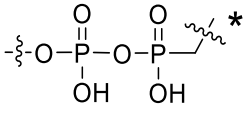
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor;

(13)  , wherein:

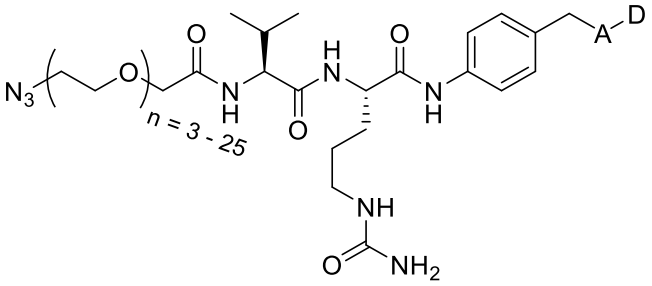
A is a bond, -OC(=O)-*,  ,  ,  ,

 , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

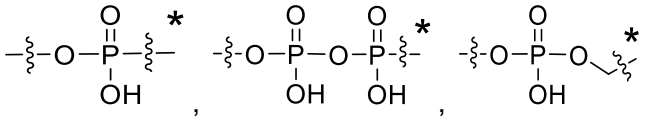
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

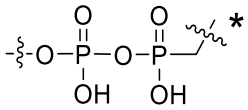
D is a panRAS inhibitor;



(14) , wherein:



A is a bond, -OC(=O)-*, , , ,

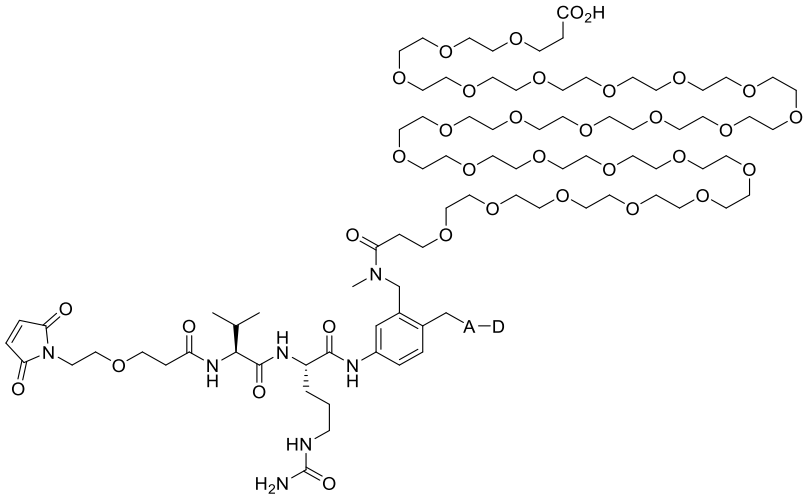


, -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

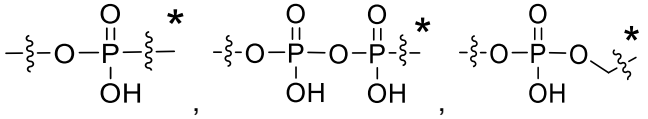
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

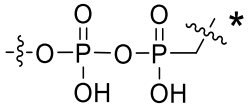
D is a panRAS inhibitor;



(15) , wherein:



A is a bond, -OC(=O)-*, , , ,

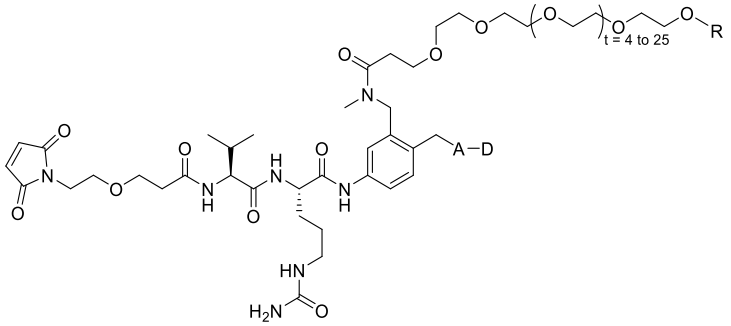


, -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or

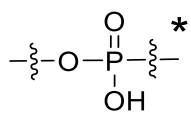
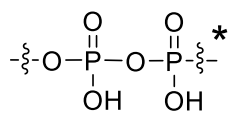
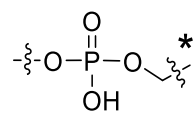
-OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

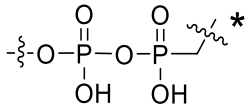
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor; or

(16)  , wherein:

each R independently is H, $-CH_3$ or $-CH_2CH_2C(=O)OH$;

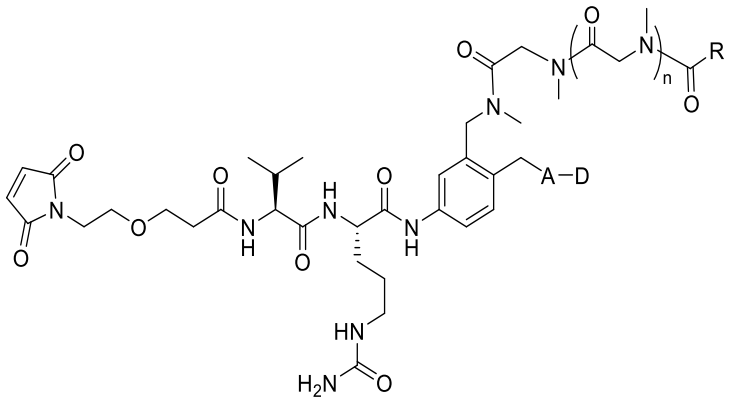
A is a bond, -OC(=O)-*,  ,  ,  ,

 , $-OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)$-* or

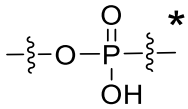
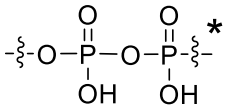
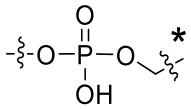
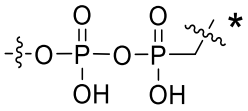
$-OC(=O)N(CH_3)C(R^a)_2C(R^a)_2N(CH_3)C(=O)$-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor, or

(17)  ,wherein:

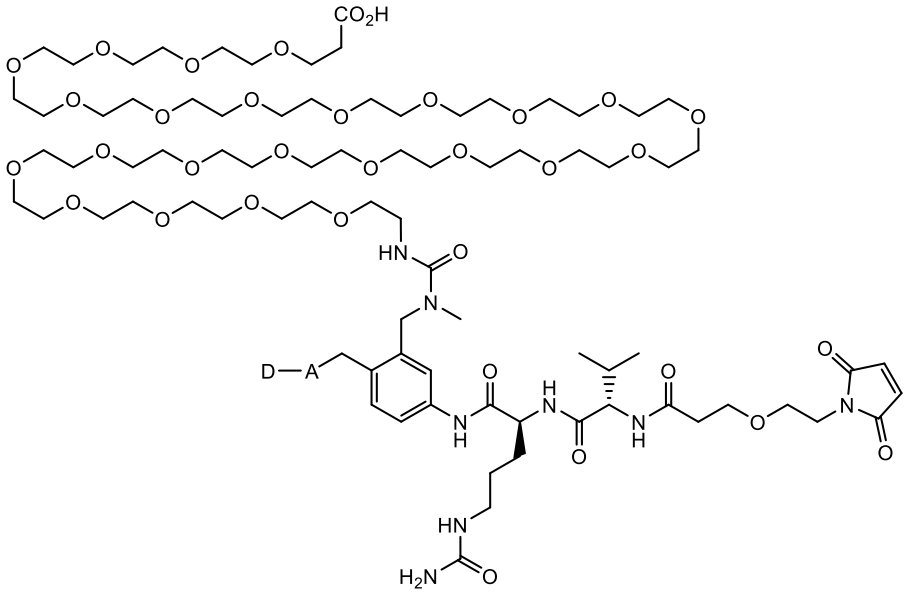
each R independently is H, $-CH_3$ or $-CH_2CH_2C(=O)OH$;

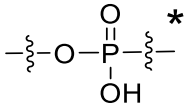
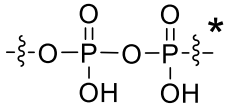
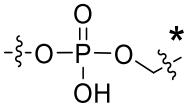
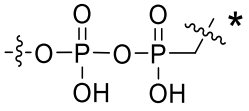
A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D;

n is an integer between 2 and 24; and

D is a PanRAS inhibitor, or

(18)  , wherein:

A is a bond, -OC(=O)-*,  ,  ,  ,  , -OC(=O)N(CH_3)CH_2CH_2N(CH_3)C(=O)-* or -OC(=O)N(CH_3)C(R^a)$_2$C(R^a)$_2$N(CH_3)C(=O)-*,

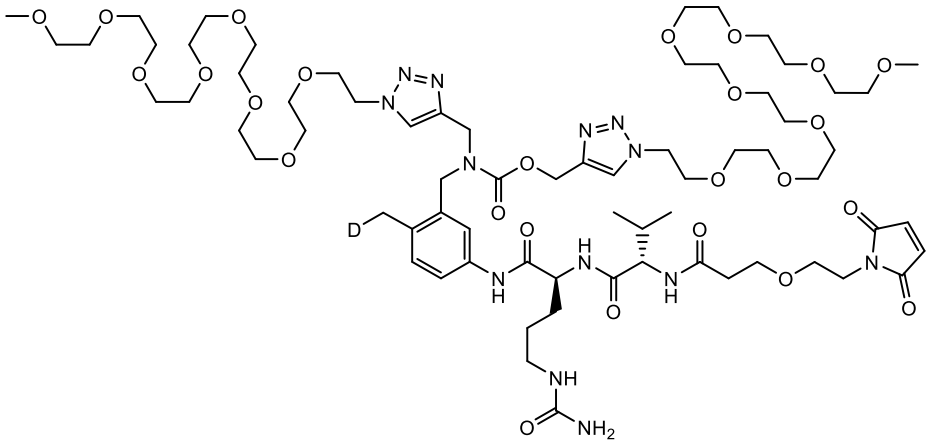
wherein each R^a is independently selected from H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl and the * of A indicates the point of attachment to D; and

D is a panRAS inhibitor.

38. The antibody-drug conjugate of any one of claims 23 to 37, wherein A is a bond and/or R is $–CH_3$ or $–CH_2CH_2COOH$.

39. The antibody-drug conjugate of any one of claims 23 to 37, wherein A is -OC(=O)-* and/or R is $–CH_3$ or $–CH_2CH_2COOH$.

40. The antibody-drug conjugate of any one of claims 23-39, wherein –(L-D) is formed from a compound selected from:



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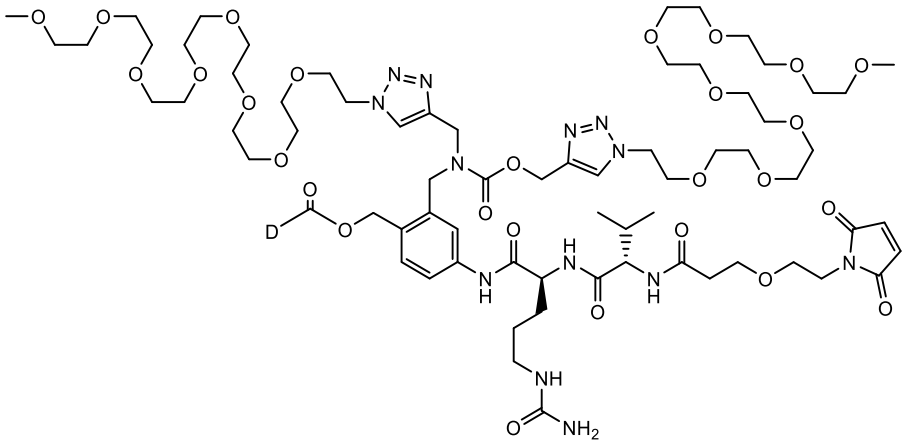

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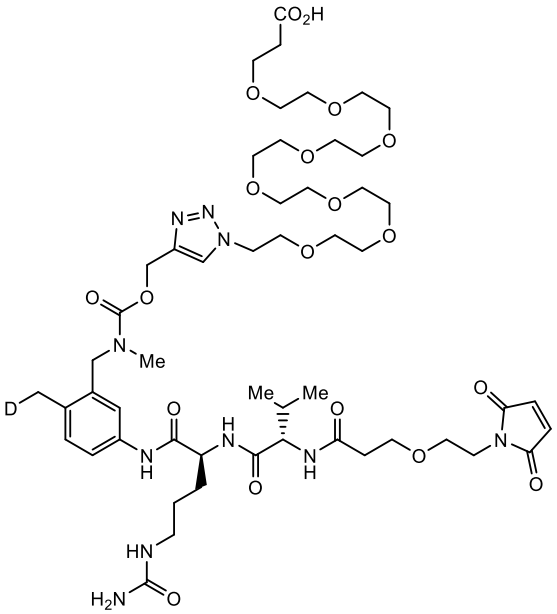

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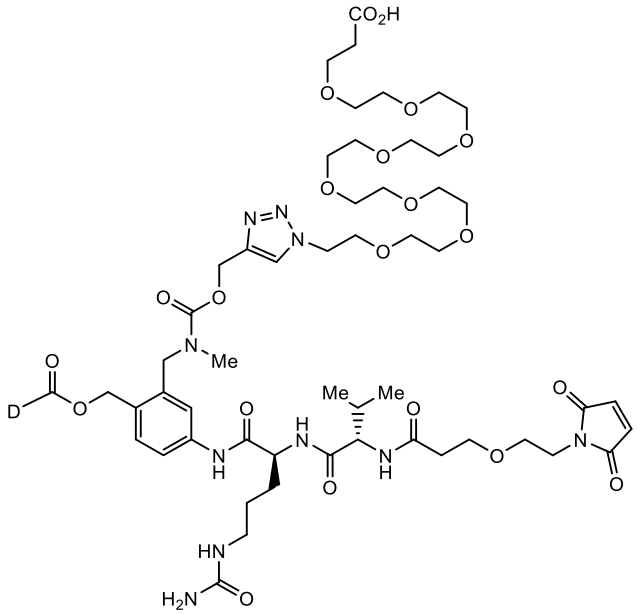

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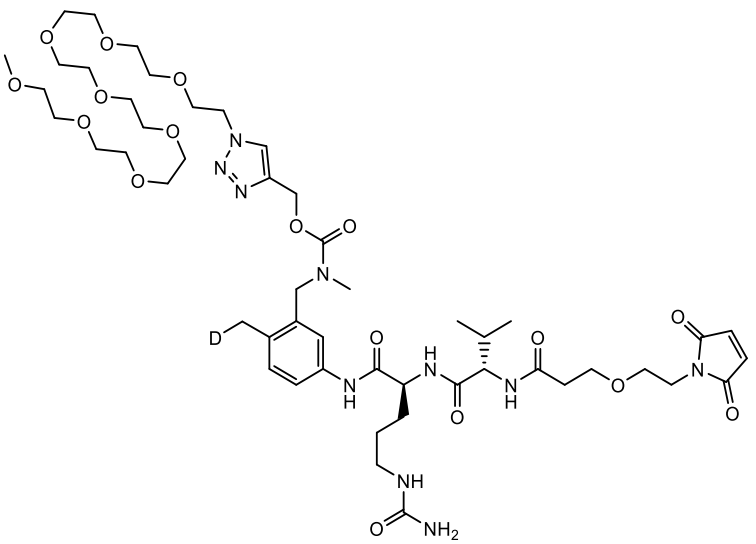

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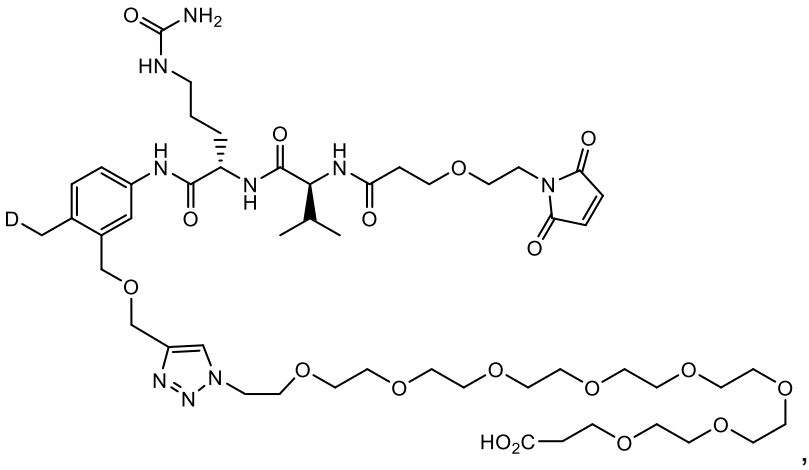

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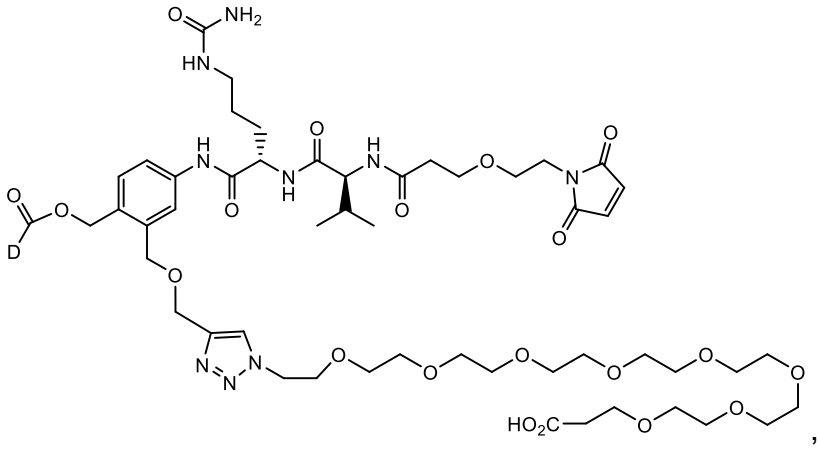

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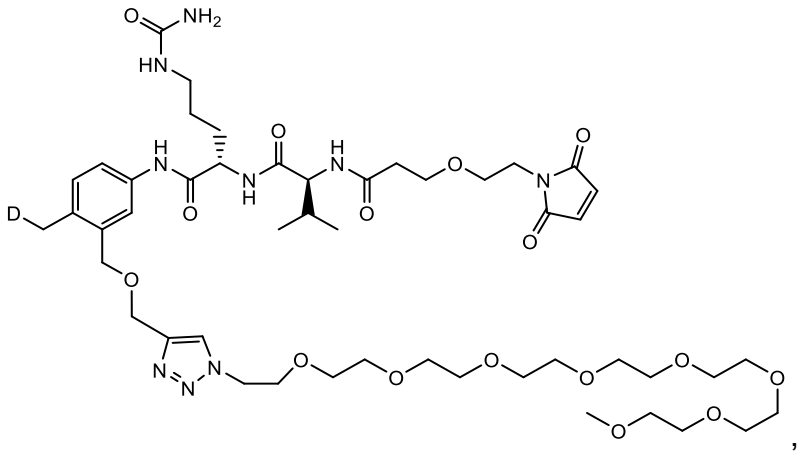

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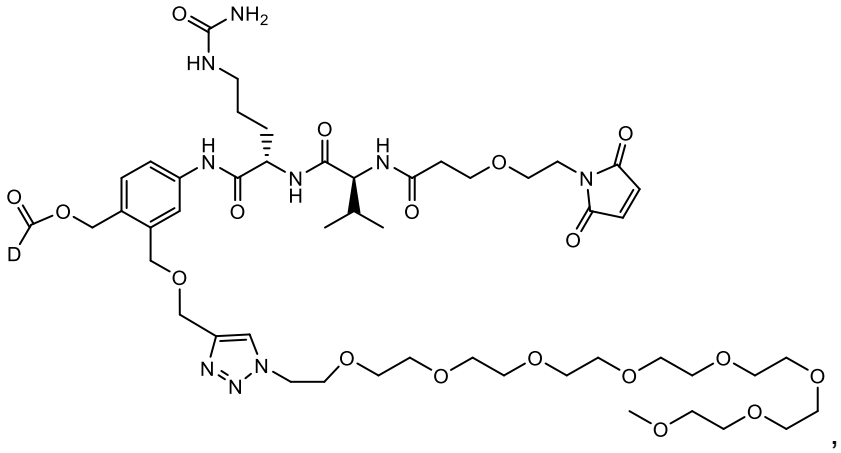

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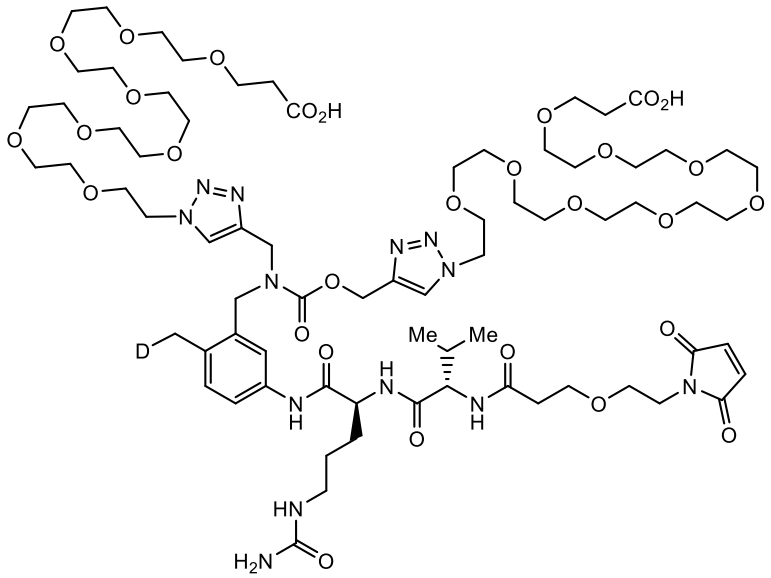

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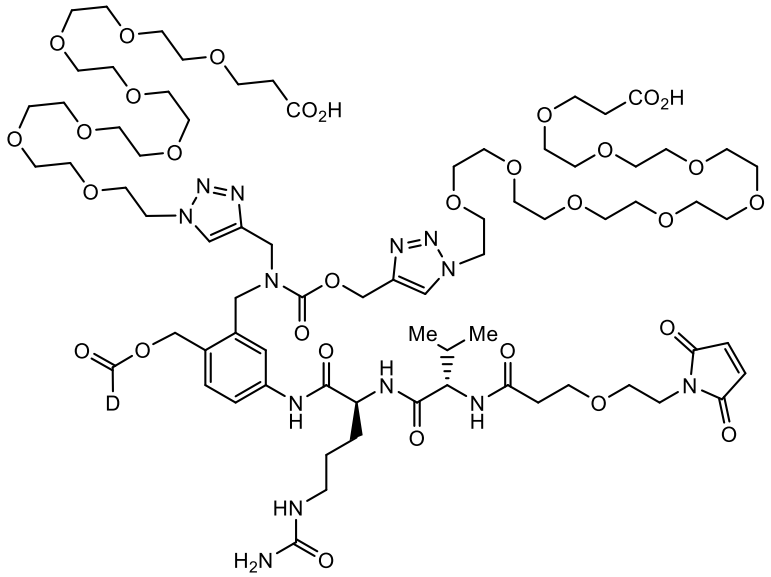

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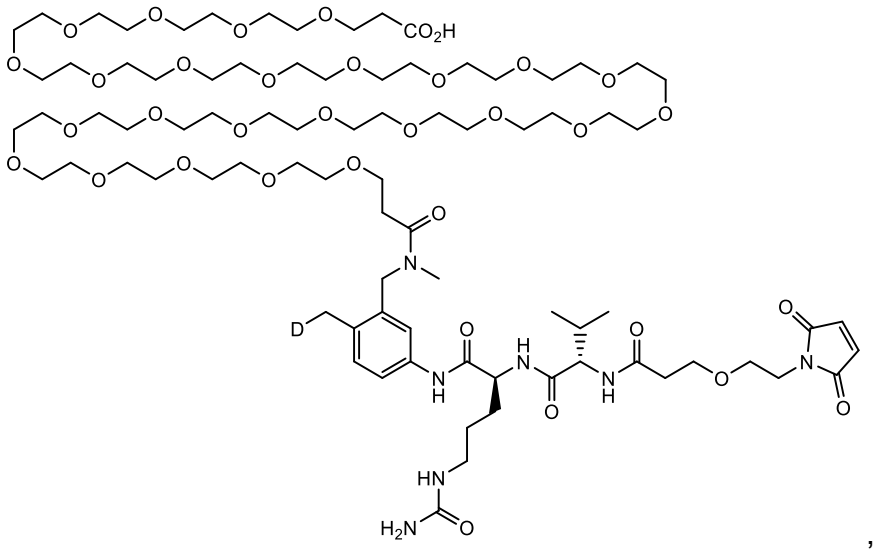

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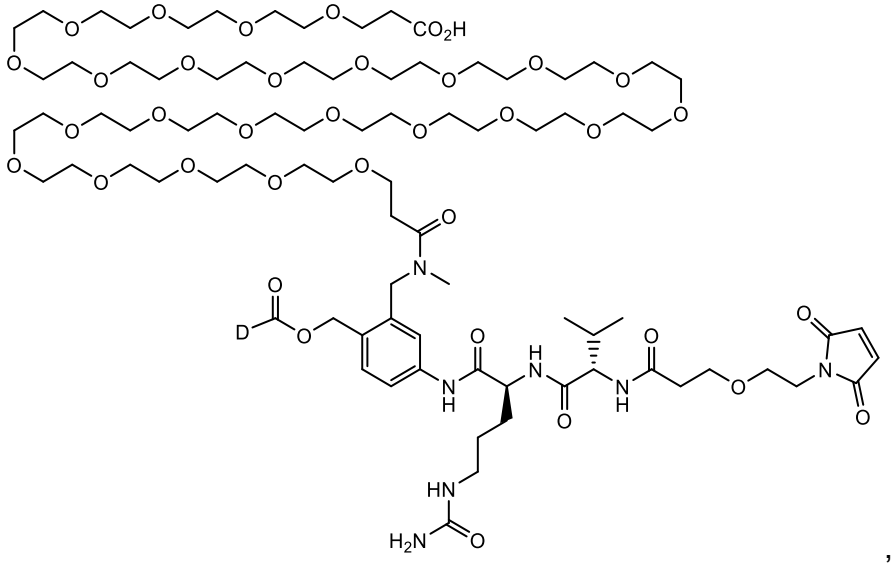

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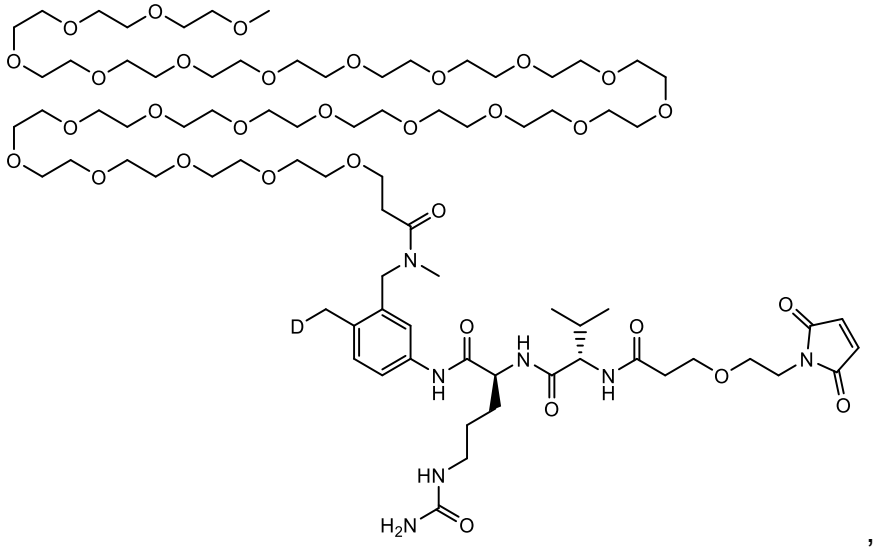

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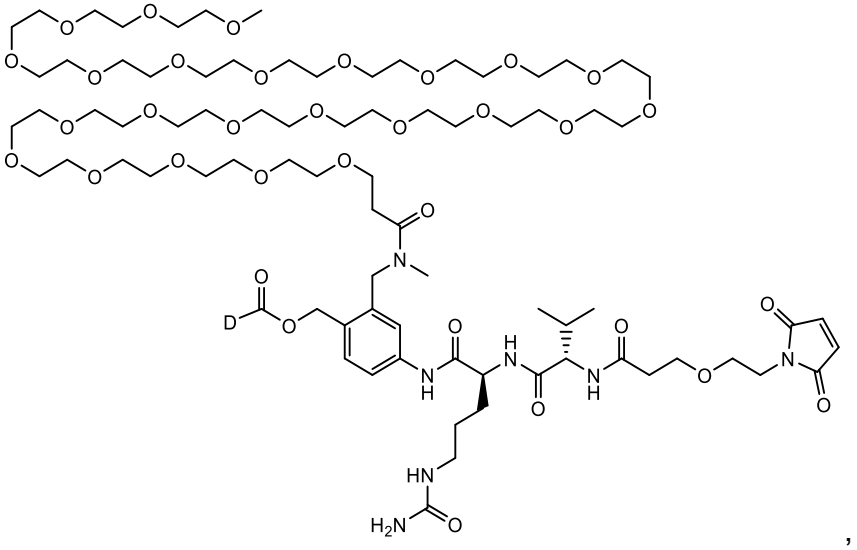

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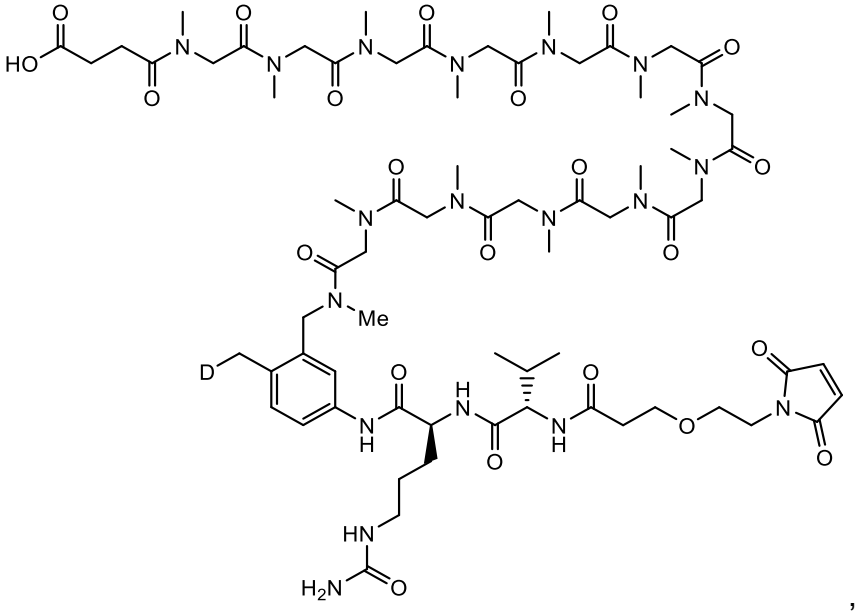

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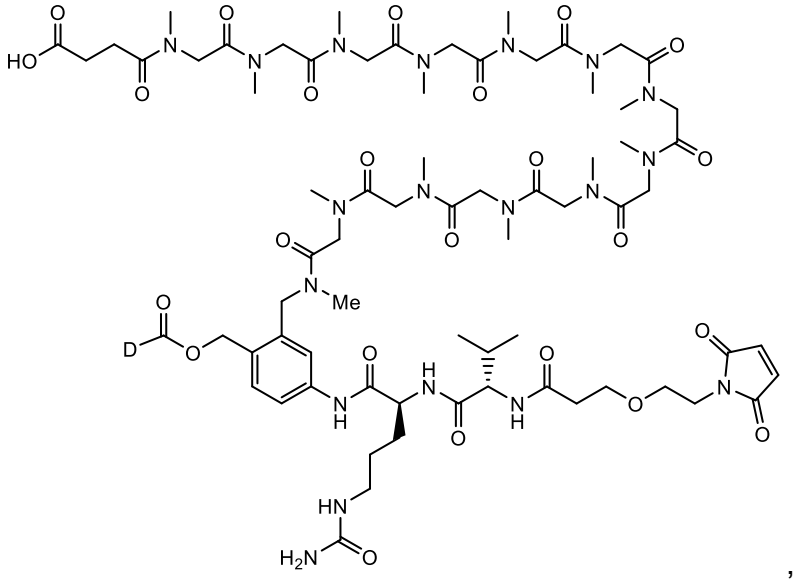

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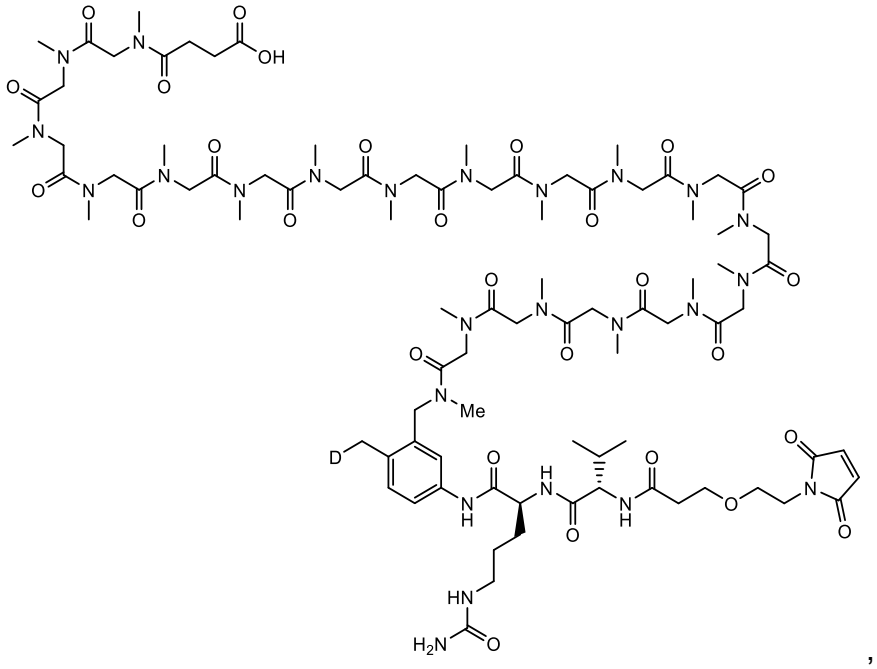

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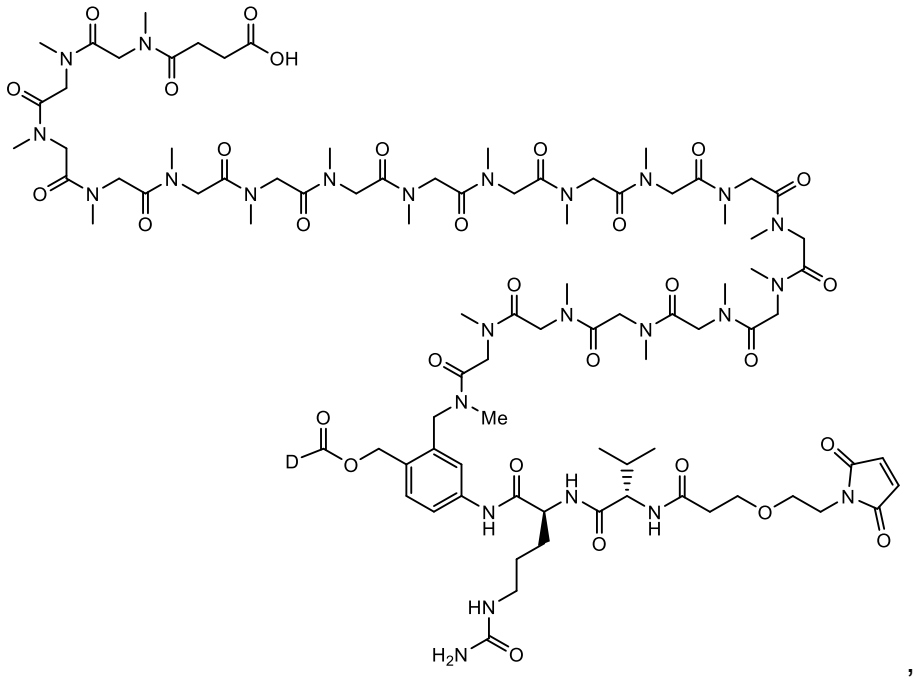

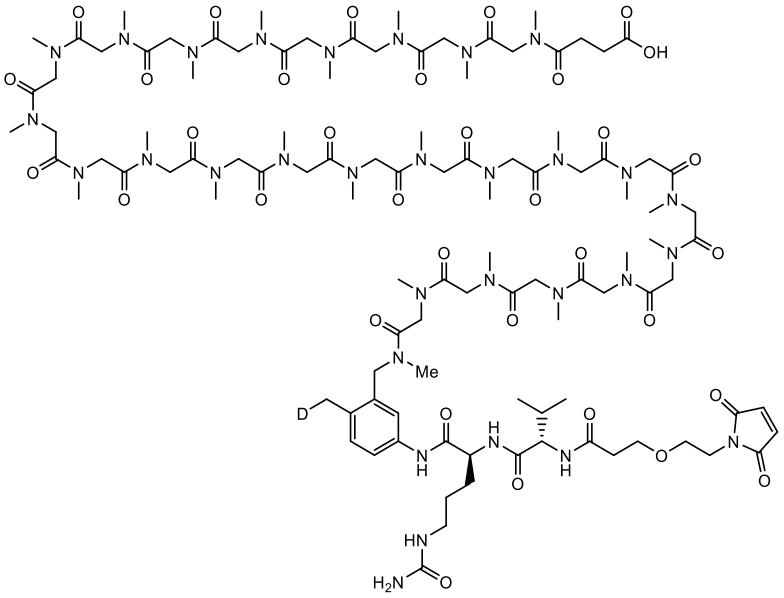

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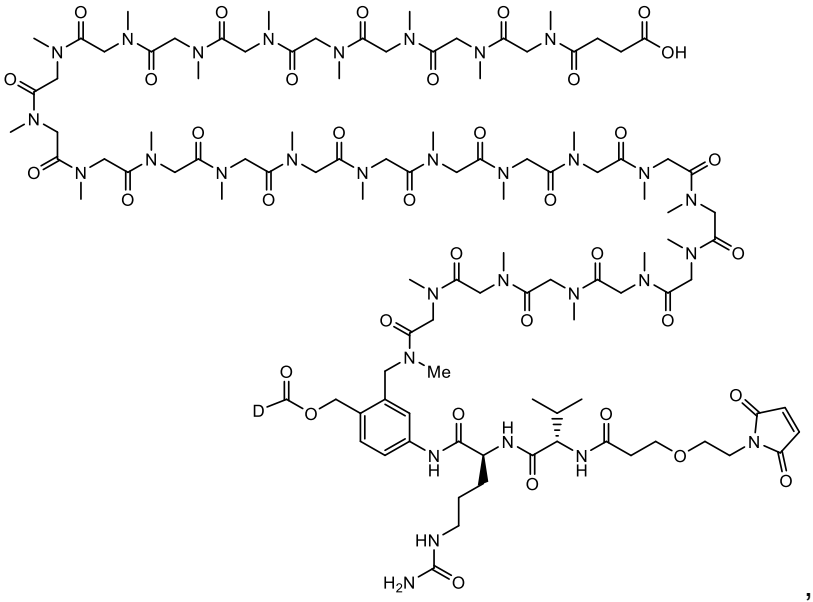

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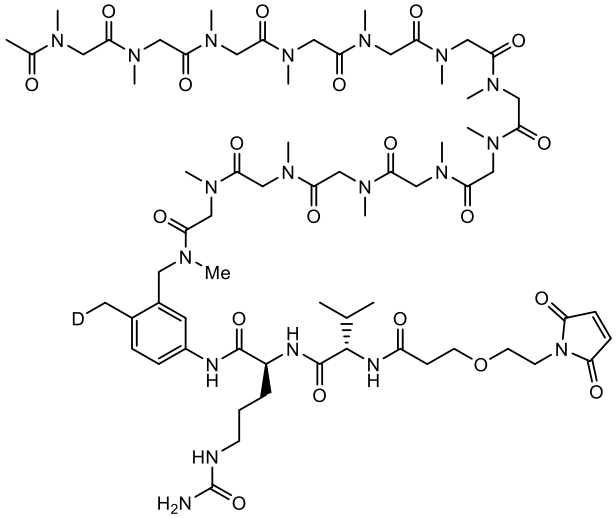

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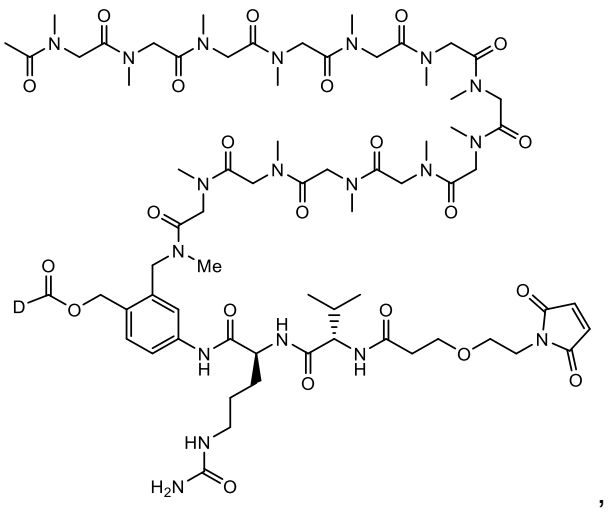

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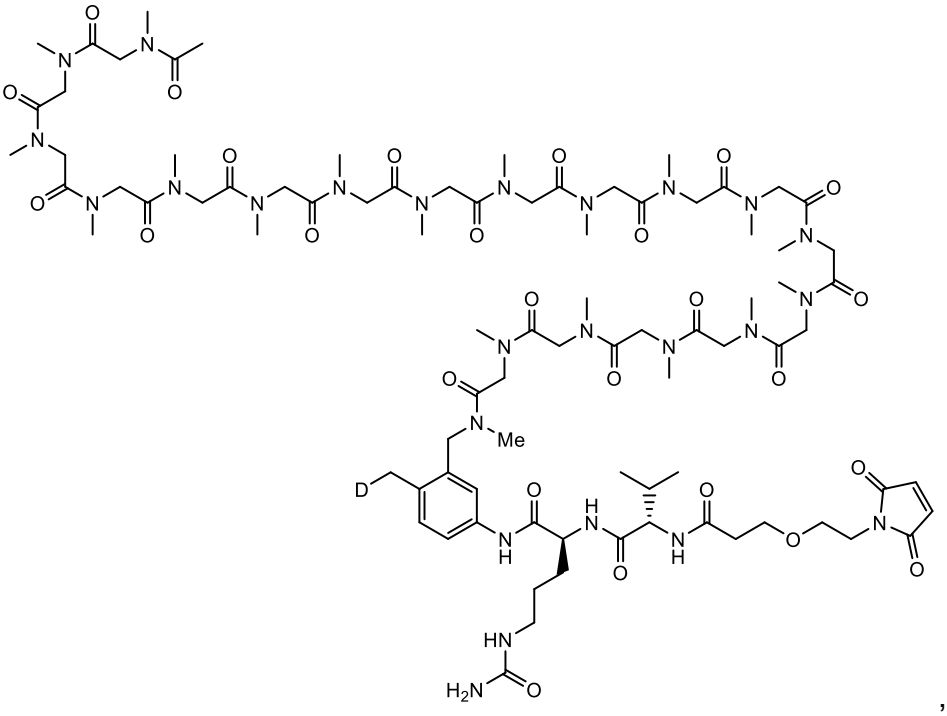

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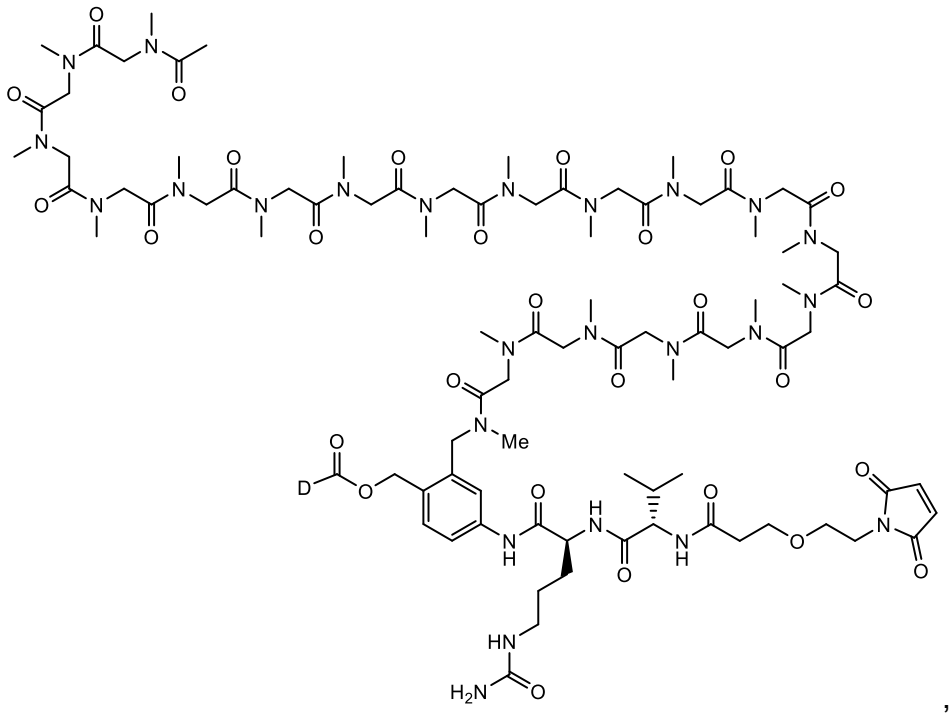

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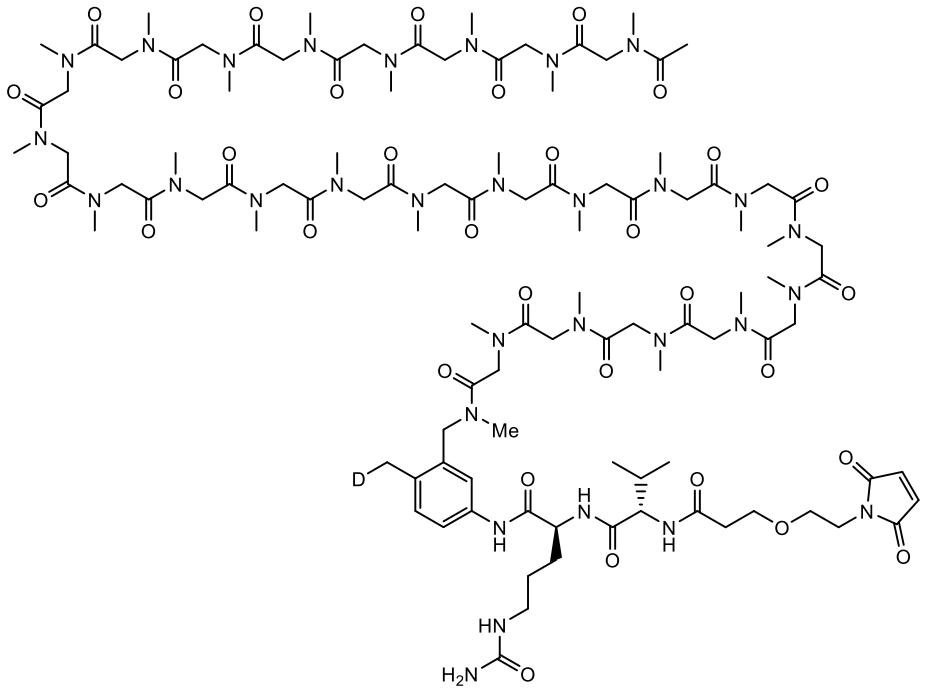

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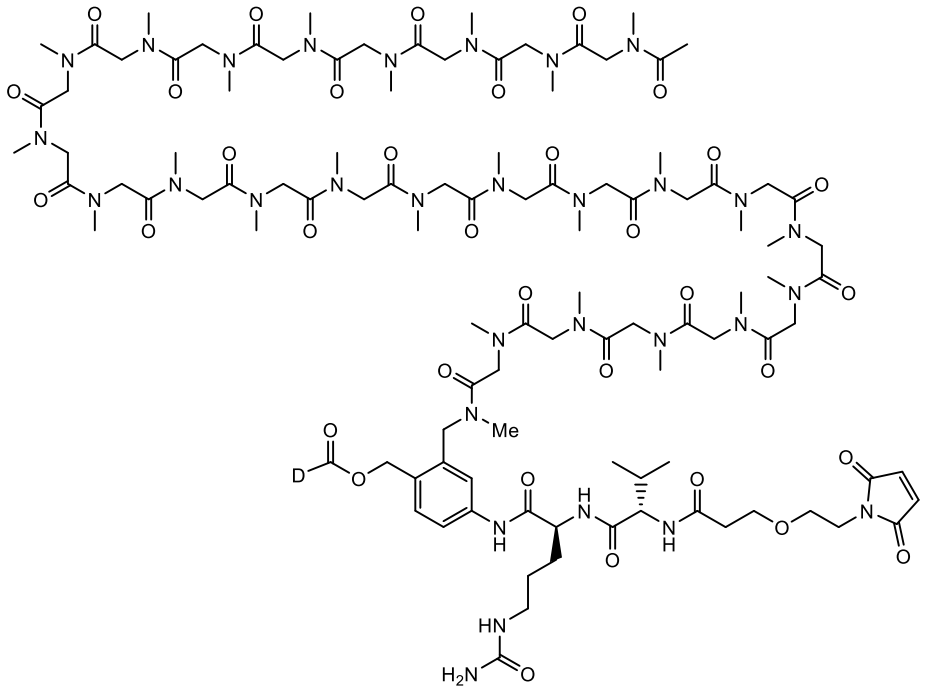

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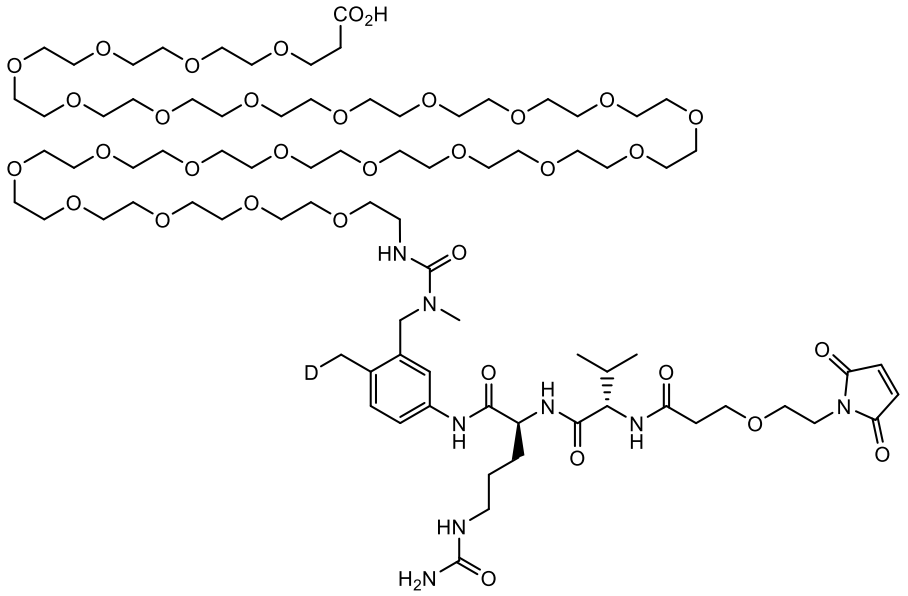

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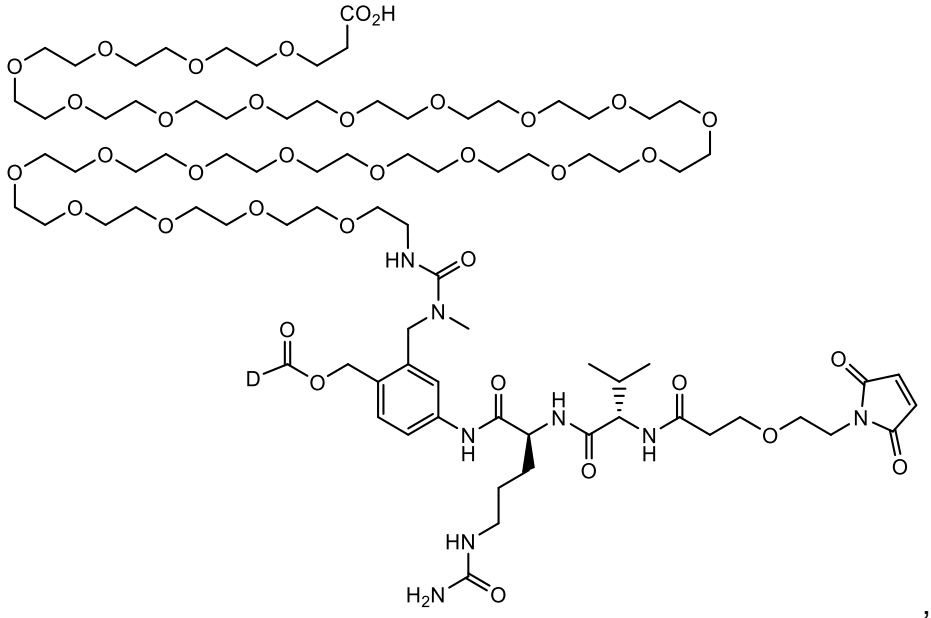

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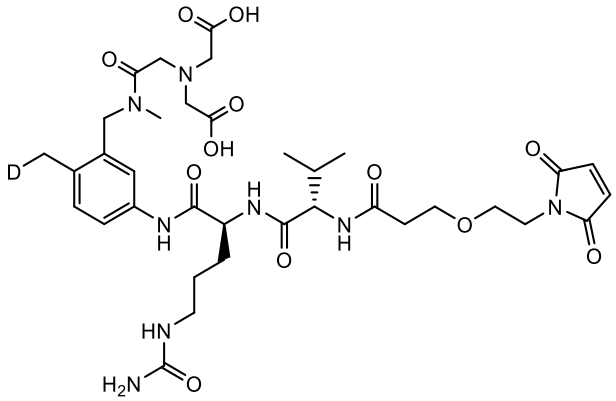

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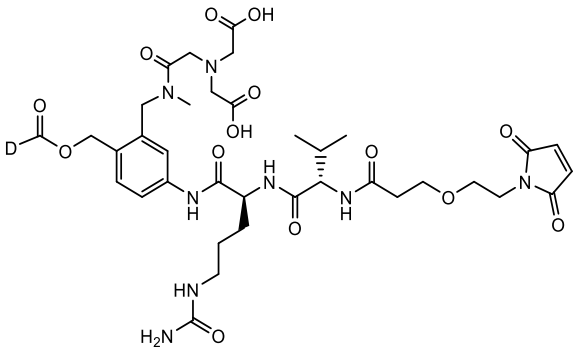

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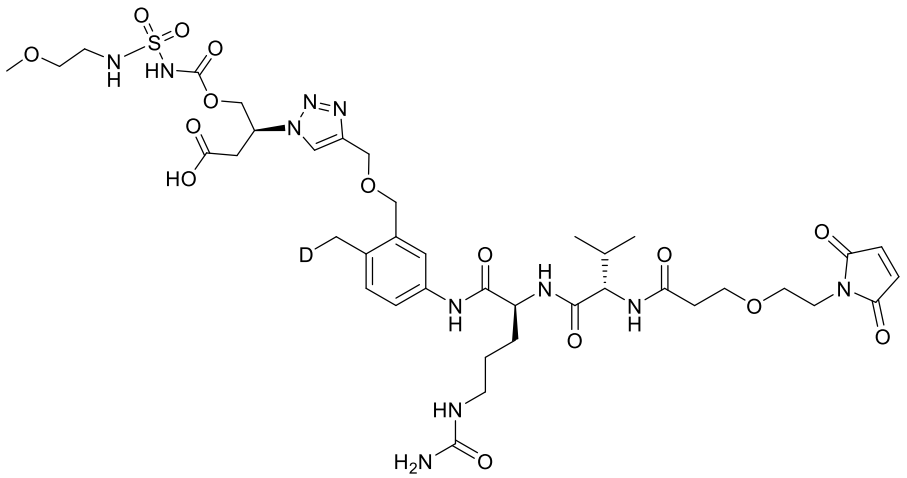

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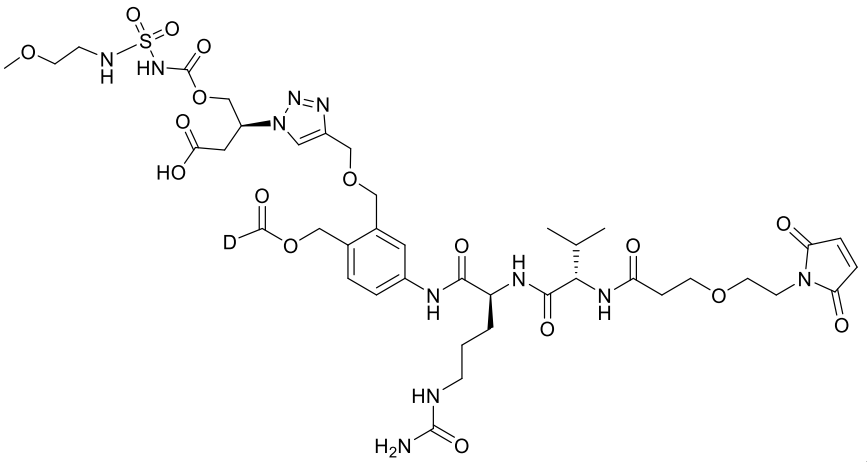

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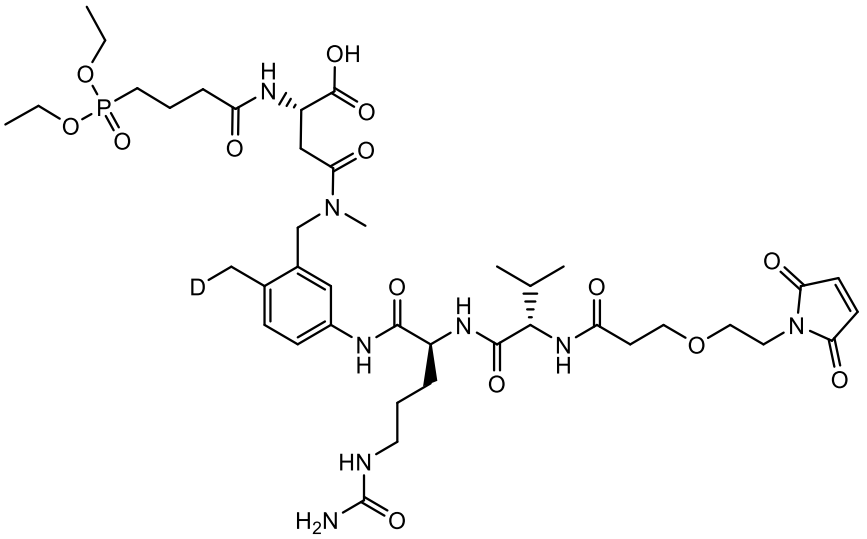

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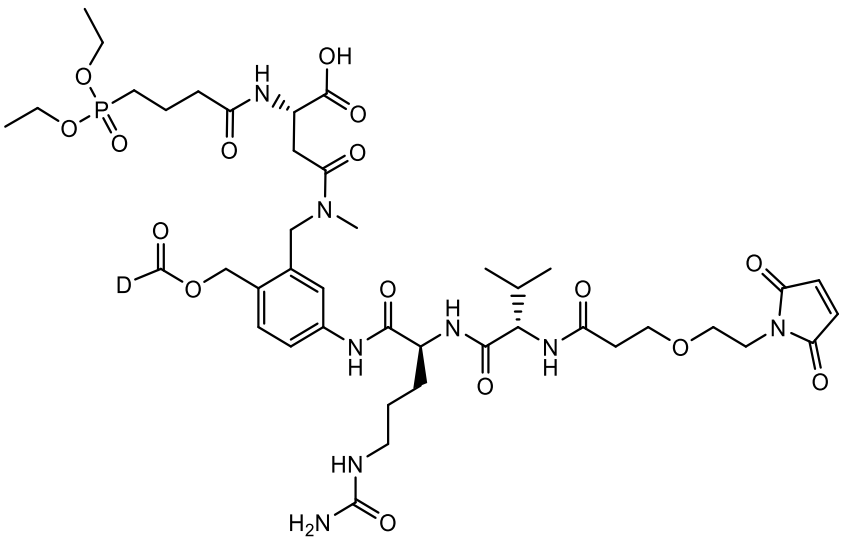

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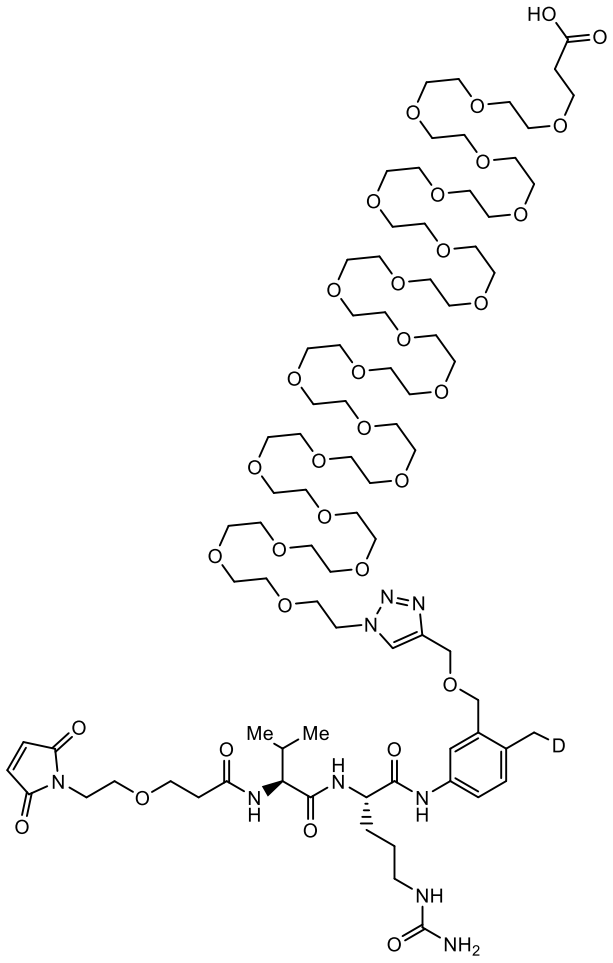

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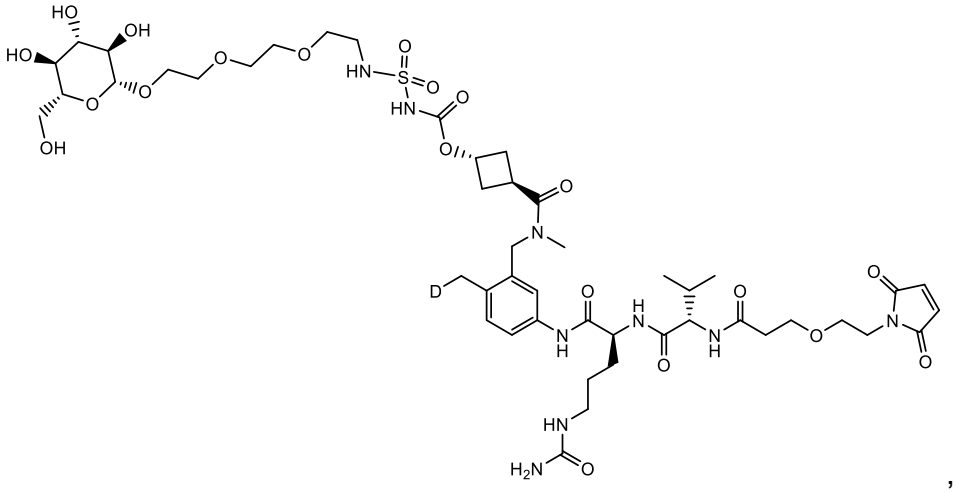

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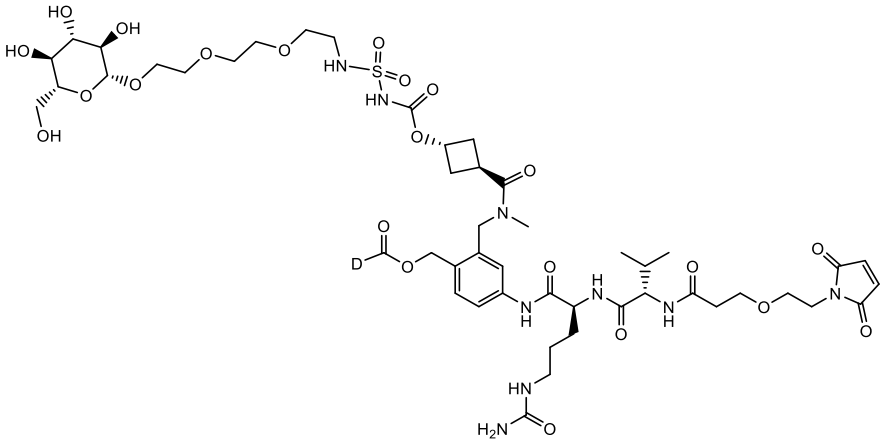

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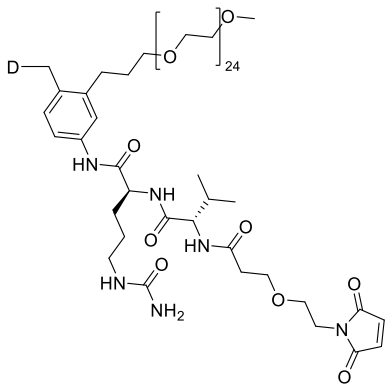

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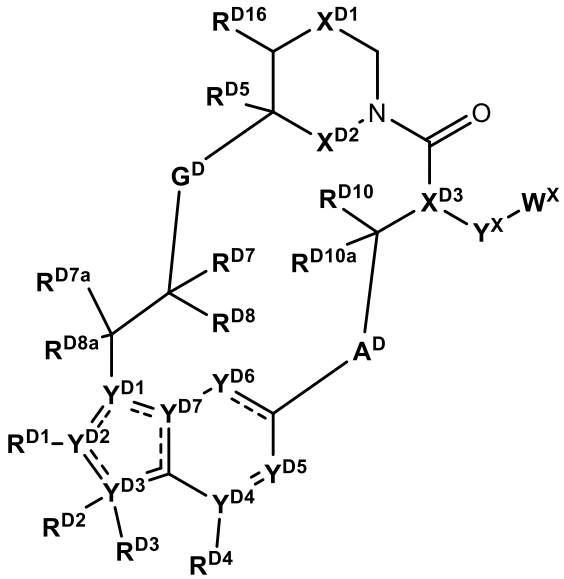
41. The antibody-drug conjugate of any one of claims 1 to 40, wherein D comprises a compound of Formula (Ia):



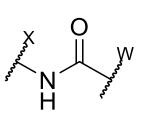
(Ia), or

a pharmaceutically acceptable salt thereof, wherein:

the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A^D is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -C(R^{D10a})(R^{D10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

Y^X is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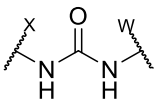
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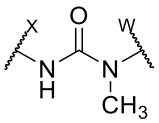
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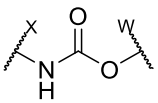
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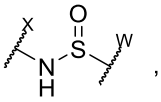
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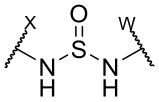
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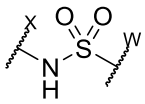
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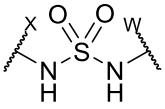
; wherein

indicates the point that connects with X^{D3}; and

indicates the point that connects with W^X; or

Y^X is -N(R^{D11})-CO-B^D-L^D-;

B^D is -CH(R^{D9})- or >C=C$R^{D9}R^{D9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{D11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

L^D is absent or a linker;

G^D is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-CH(R^{D6})- where -CH(R^{D6})- is bound to -C($R^{D7}R^{D8}$)-, -C(O)NH-CH(R^{D6})- where -CH(R^{D6})- is bound to -C($R^{D7}R^{D8}$)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

W^X is hydrogen, cyano, optionally substituted C_1-C_3 heteroalkyl, optionally substituted amino, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 3 to 8-membered heteroaryl;

X^{D1} is optionally substituted C_1-C_2 alkylene, NR^D, O, or $S(O)_{nD}$;

X^{D2} is O or NH;

X^{D3} is N or CH;

nD is 0, 1, or 2;

R^D is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, $C(O)R^{D'}$, $C(O)OR^{D'}$, $C(O)N(R^{D'})_2$, $S(O)R^{D'}$,

$S(O)_2R^{D'}$, or $S(O)_2N(R^{D'})_2$; each $R^{D'}$ is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^{D1} is C, CH, or N;

Y^{D2}, Y^{D3}, Y^{D4}, and Y^{D7} are, independently, C or N;

Y^{D5} is CH, CH_2, or N;

Y^{D6} is C(O), CH, CH_2, or N;

R^{D1} is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^{D1} and R^{D2} combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^{D2} is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^{D3} is absent or R^{D2} and R^{D3} combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^{D4} is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^{D5} is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^{D6} is hydrogen or methyl;

R^{D7} is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^{D6} and R^{D7} combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{D8} is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^{D7} and R^{D8} combine with the carbon atom to which they are attached to form $C=CR^{D7'}R^{D8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-

membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{D7a} and R^{D8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{D7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl;

$R^{D8'}$ is hydrogen, halogen, hydroxyl, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{D7'}$ and $R^{D8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{D9} is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{D9} and L^D combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{D9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{D10} is hydrogen, halo, hydroxyl, C_1-C_3 alkoxyl, or C_1-C_3 alkyl;

R^{D10a} is hydrogen or halogen;

R^{D11} is hydrogen or C_1-C_3 alkyl; and

R^{D16} is hydrogen or C_1-C_3 alkyl.

42. The antibody-drug conjugate any one of claims 1 to 41, wherein D comprises a group represented by a formula selected from those in Table A2.

43. The antibody-drug conjugate of any one of claims 1 to 41, wherein the antibody or antigen-binding fragment thereof binds to a target antigen on a cancer cell.

44. A composition comprising multiple copies of the antibody-drug conjugate of any one of claims 1 to 43, wherein the average *p* of the antibody-drug conjugates in the composition is from about 2 to about 16, e.g., about 2 to about 8, e.g., about 2 to about 4.

45. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 1 to 43 or the composition of claim 44, and a pharmaceutically acceptable carrier.

46. The antibody-drug conjugate of any one of claims 1 to 43, the composition of claim 44, or the pharmaceutical composition of claim 45 for use in the treatment of cancer.

47. The antibody-drug conjugate of any one of claims 1 to 43, the composition of claim 44, or the pharmaceutical composition of claim 45 for use in reducing or inhibiting tumor growth.

48. Use of the antibody-drug conjugate of any one of claims 1 to 43, the composition of claim 44, or the pharmaceutical composition of claim 45, for manufacture of a medicament for treating a subject having or suspected of having a cancer.

49. Use of the antibody-drug conjugate of any one of claims 1 to 43, the composition of claim 44, or the pharmaceutical composition of claim 45, for manufacture of a medicament for reducing or inhibiting the growth of a tumor in a subject.

50. Use of the antibody-drug conjugate of any one of claims 1 to 43, the composition of claim 44, or the pharmaceutical composition of claim 45, for manufacture of a medicament for reducing or inhibiting a hematological cancer in a subject.

51. Use of the antibody-drug conjugate of any one of claims 1 to 43, the composition of claim 44, or the pharmaceutical composition of claim 45, for manufacture of a medicament for reducing or slowing the expansion of a cancer cell population in a subject.