improved therapeutic windows, particularly when lipophilic payloads are included in the ADC. Therefore, there is a continuing need for effective treatments of, for example, diseases using agents in cyclodextrin protein drug conjugates.

SUMMARY

[0007] Provided herein are compounds useful, for example, for the treatment of diseases, conditions, and disorders including, without limitation, metabolic diseases, proliferative diseases, and other diseases and conditions.

[0007a] In one aspect, the present disclosure relates to a compound, or a pharmaceutically acceptable salt thereof, comprising: a binding agent linked to at least one payload moiety;

wherein the binding agent (**BA**) is an antibody or an antigen-binding fragment thereof;

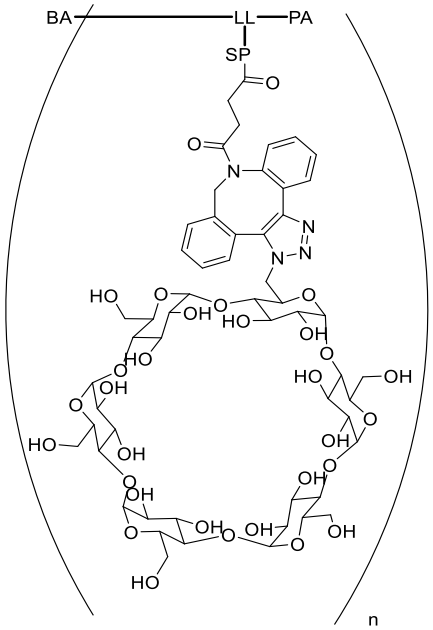
wherein each linker payload moiety comprises at least one cyclodextrin moiety (**CD**), a payload moiety (**PA**), and a covalent linker, wherein said covalent linker is bonded to each of said binding agent, said payload moiety, and said cyclodextrin moiety; and

wherein the compound comprises at least one feature that is selected from the group consisting of:

(i) each linker payload is conjugated to a single residue of the binding agent, wherein said single residue is a glutamine, lysine, or cysteine residue;

(ii) the linker payload is conjugated to a primary amine compound, wherein the primary amine compound is conjugated to one or more glutamine residues of the binding agent;

(iii) the compound is according to formula (**Ib1**) or (**Ib2**):



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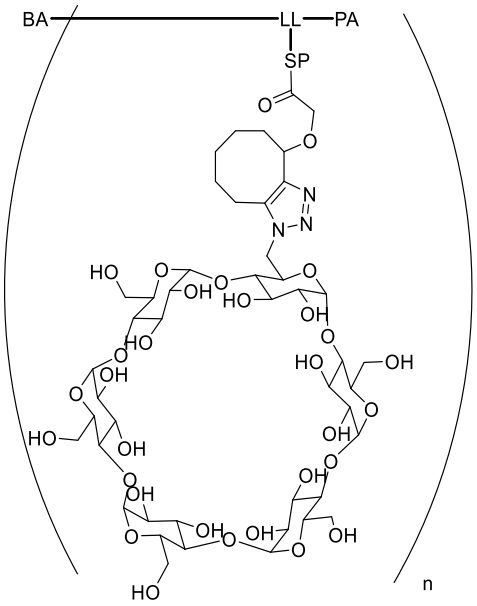


,

(Ib1) **(Ib2)**

or a triazole linkage regioisomer thereof;

wherein **BA** is the binding agent;

LL is a trivalent linker;

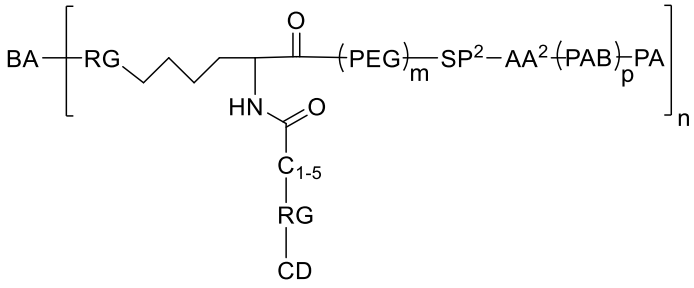
SP is, independently in each instance, absent or is a spacer group;

n is an integer from 1 to 30; and

PA is the payload moiety;

and

(iv) the compound is according to Formula (**Ie**):



(Ie)

wherein:

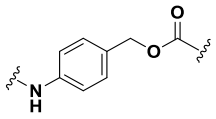
BA is the binding agent;

RG is, independently in each instance, a reactive group residue;

SP² is, independently in each instance, absent or a spacer group residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the **PAB** is bonded to the adjacent groups in the formula;

$\mathbf{C_{1\text{-}5}}$ is a spacer group of 1 to 5 carbons;

CD is the cyclodextrin moiety,

subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

[0008] In one example, set forth herein, is a compound or a pharmaceutically acceptable salt thereof, including: a protein linked to at least one payload moiety and linked to at least one cyclodextrin moiety via a covalent linker, wherein said covalent linker is bonded directly or indirectly to each of the binding agent, the payload moiety, and the cyclodextrin moiety.

[0009] In one example, set forth herein, is a compound or a pharmaceutically acceptable salt thereof, including: a binding agent linked to at least one payload moiety and linked to at least one cyclodextrin moiety via a covalent linker, wherein said covalent linker is bonded directly or indirectly to each of the binding agent, the payload moiety, and the cyclodextrin moiety.

[0010] In another example, set forth herein, is a compound, including: a reactive group linked to at least one payload moiety and linked to at least one cyclodextrin moiety via a covalent linker, wherein said covalent linker is bonded directly or indirectly to each of the reactive group, the payload moiety, and the cyclodextrin moiety.

[0010a] In anothor aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

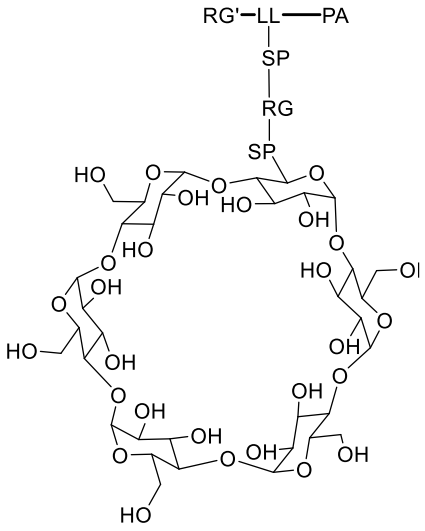
[**0010b**] In anothor aspect, the present disclosure relates to a compound as defined herein or composition as defined herein for use in the treatment of a disease or disorder in a patient in need thereof.

[**0010c**] In anothor aspect, the present disclosure relates to a compound comprising a reactive linker, at least one payload moiety, at least one cyclodextrin moiety, and a covalent linker, wherein said covalent linker is bonded to each of the reactive linker, the payload moiety, and the cyclodextrin moiety;

wherein the at least one payload moiety is a residue of an auristatin or a residue of a maytansinoid;

wherein the compound comprises at least one feature that is selected from the group consisting of:

(i) the compound is according to Formula (**IIa**):



(**IIa**)

wherein:

L is composed of LL, SP, and RG;

RG' is a reactive group;

RG is a reactive linker residue;

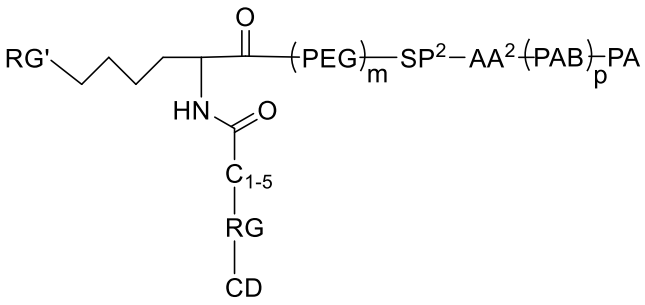
LL is a trivalent linker;

SP is, independently in each instance, absent or a spacer group; and

PA is the payload moiety;

and

(ii) the compound is according to Formula (**IIe**):



(IIe)

wherein:

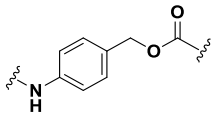
RG' is a reactive group;

SP^2 is, independently in each instance, absent or a spacer group residue;

AA^1 is a trivalent linker comprising an amino acid residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

C$_{1-5}$ is an alkyl spacer group of 1 to 5 carbons;

CD is, independently in each instance, absent or a cyclodextrin moiety, wherein at least one CD is present;

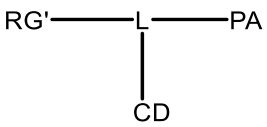
subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

[0010e] In another aspect the present disclosure relates to a compound comprising a reactive linker, at least one payload moiety (PA), at least one cyclodextrin moiety (CD), and a covalent linker; wherein said covalent linker is bonded to each of said reactive linker, said payload moiety, and said cyclodextrin moiety;

wherein the compound is according to Formula (**II**):



(**II**)

wherein:

RG' is a reactive group;

L is a trivalent linker;

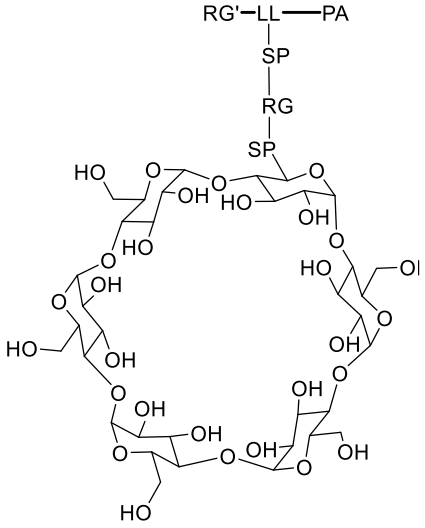
CD is a cyclodextrin moiety; and

PA is a payload residue**;**

PA is the payload moiety;

wherein the compound comprises at least one feature that is selected from the group consisting of:

(i) the compound is according to Formula (**IIa**):

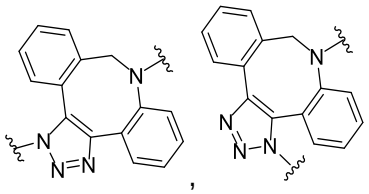
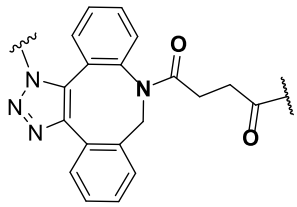
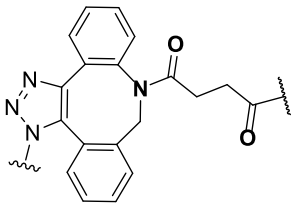
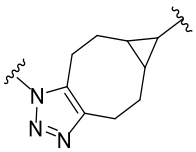
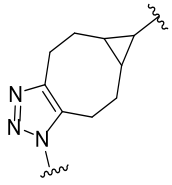
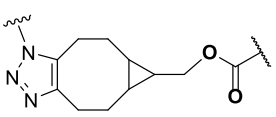
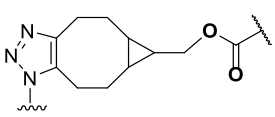
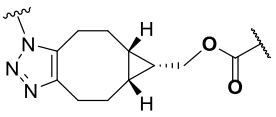


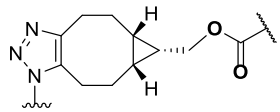
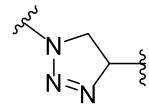
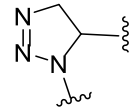
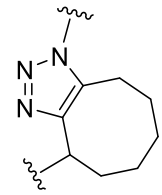
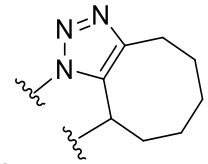
(IIa)

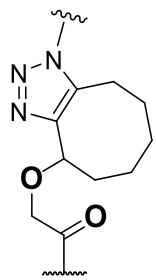
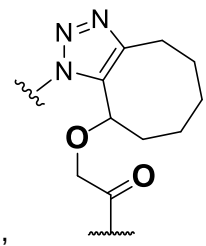
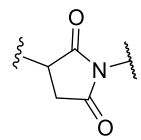
wherein:

L is composed of LL, SP, and RG;

RG' is the reactive group;

RG is a reactive linker residue; wherein RG is selected from the group consisting of  , ,  ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  , and  , wherein the  indicates the atom through which the **RG** is bonded to the adjacent groups in the formula;

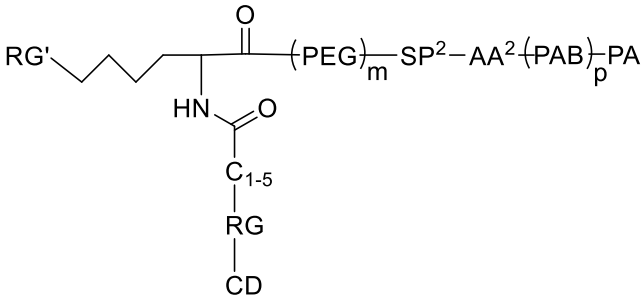
LL is a trivalent linker;

SP is, independently in each instance, absent or a spacer group; and

PA is the payload moiety;

and

(ii) the compound is according to Formula (**IIe**):



(IIe)

wherein:

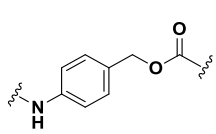
RG' is the reactive group;

SP^2 is, independently in each instance, absent or a spacer group residue;

AA^1 is a trivalent linker comprising an amino acid residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

C$_{1-5}$ is an alkyl spacer group of 1 to 5 carbons;

CD is, independently in each instance, absent or a cyclodextrin moiety, wherein at least one CD is present;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

[**0010e**] In anothor aspect, the present disclosure relates to a linker-payload compound comprising the compound as defined herein bonded to a linker.

[**0010f**] In anothor aspect, the present disclosure relates to a linker-payload compound comprising the compound as defined herein wherein the payload moiety is bonded to an oxygen or a primary or secondary nitrogen of the covalent linker.

[**0010g**] In anothor aspect, the present disclosure relates to an antibody-drug-conjugate comprising the compound or linker-payload compound as defined herein bonded to an antibody, or an antigen binding fragment thereof.

[0011] In another example, set forth herein is an antibody-drug conjugate having a compound, above, bonded to an antibody or an antigen binding fragment thereof.

[0012] In another example, set forth herein is a method of treating a disease, condition, or disorder in a patient in need thereof including administering to the patient a compound set forth herein.

[**0012a**] In anothor aspect, the present disclosure relates to use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for treating a proliferative disease, a metabolic disease, inflammation, or a neurodegenerative disease in a subject; wherein the payload moiety is a therapeutic agent for treating a proliferative disease.

[**0012b**] In anothor aspect, the present disclosure relates to use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a disease, disorder, or condition in a subject, where the disease, disorder, or condition is a proliferative disease or inflammation; and wherein the payload moiety is a therapeutic agent for treating a proliferative disease or a therapeutic agent for treating inflammation.

[**0012c**] In anothor aspect, the present disclosure relates to use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a proliferative disease in a subject; wherein the payload moiety is a therapeutic agent for treating a proliferative disease.

[**0012d**] In anothor aspect, the present disclosure relates to use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a metabolic disease in a subject; wherein the payload moiety is a therapeutic agent for treating a metabolic disease.

[**0012e**] In anothor aspect, the present disclosure relates to use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of inflammation in a subject; wherein the payload moiety is a therapeutic agent for treating inflammation.

[**0012f**] In anothor aspect, the present disclosure relates to use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a neurodegenerative disease in a subject; wherein the payload moiety is a therapeutic agent for treating a neurodegenerative disease.

[**0012g**] In anothor aspect, the present disclosure relates to a method of preparing the compound as defined herein comprising the step of contacting the binding agent with the compound as defined herein under conditions suitable for forming a bond between the binding agent and the compound.

[0013] In another example, set forth herein is a method of preparing an antibody-drug conjugate including the step of contacting a binding agent with a linker-payload compound set forth herein under conditions suitable for forming a bond between the binding agent and the linker-payload compound.

[0013a] In another aspect, the present disclosure relates to a process for preparing an antibody-drug-conjugate comprising reacting the linker-payload compound as defined herein with an antibody, or an antigen binding fragment thereof.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0014] **Figure 1A** shows three different types of payload compounds.

[0015] **Figure 1B** shows a synthetic process for preparing payload compound **1h** or **1i**.

[0016] **Figure 1C** shows a synthetic process for preparing payload compound **1d**.

WHAT IS CLAIMED IS:

1. A compound, or a pharmaceutically acceptable salt thereof, comprising: a binding agent linked to at least one linker payload moiety;

wherein the binding agent (**BA**) is an antibody or an antigen-binding fragment thereof;

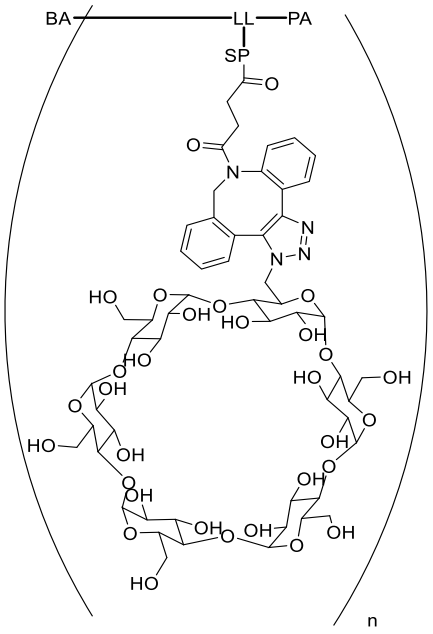
wherein each linker payload moiety comprises at least one cyclodextrin moiety (**CD**), a payload moiety (**PA**), and a covalent linker, wherein said covalent linker is bonded to each of said binding agent, said payload moiety, and said cyclodextrin moiety; and

wherein the compound comprises at least one feature that is selected from the group consisting of:

(i) each linker payload is conjugated to a single residue of the binding agent, wherein said single residue is a glutamine, lysine, or cysteine residue;

(ii) the linker payload is conjugated to a primary amine compound, wherein the primary amine compound is conjugated to one or more glutamine residues of the binding agent;

(iii) the compound is according to formula (**Ib1**) or (**Ib2**):



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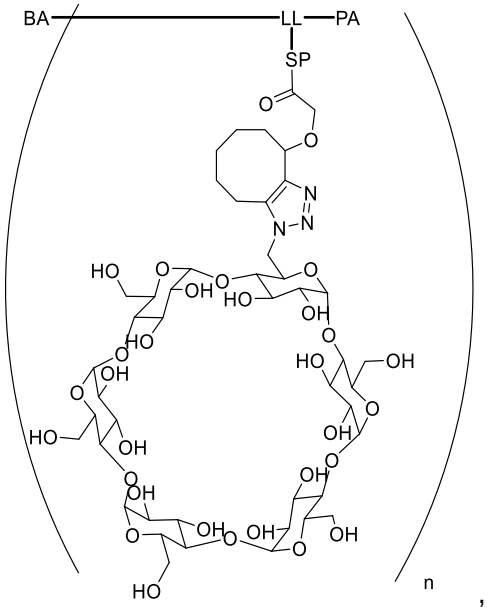


,

(Ib1) **(Ib2)**

or a triazole linkage regioisomer thereof;

wherein **BA** is the binding agent;

LL is a trivalent linker;

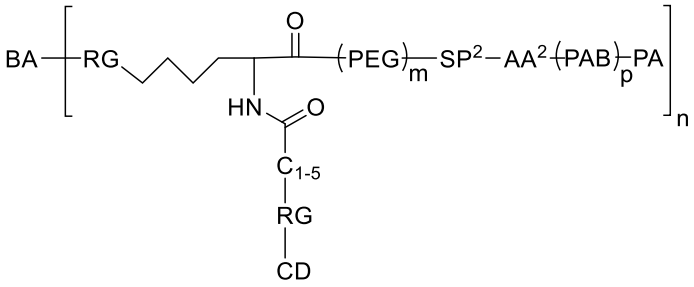
SP is, independently in each instance, absent or is a spacer group;

n is an integer from 1 to 30; and

PA is the payload moiety;

and

(iv) the compound is according to Formula (**Ie**):



(Ie)

wherein:

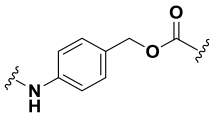
BA is the binding agent;

RG is, independently in each instance, a reactive group residue;

SP² is, independently in each instance, absent or a spacer group residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the **PAB** is bonded to the adjacent groups in the formula;

C_{1-5} is a spacer group of 1 to 5 carbons;

CD is the cyclodextrin moiety,

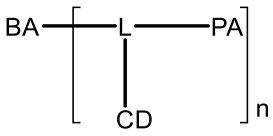
subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

2. The compound of claim 1, according to Formula (**I**):



(**I**)

wherein:

BA is the binding agent;

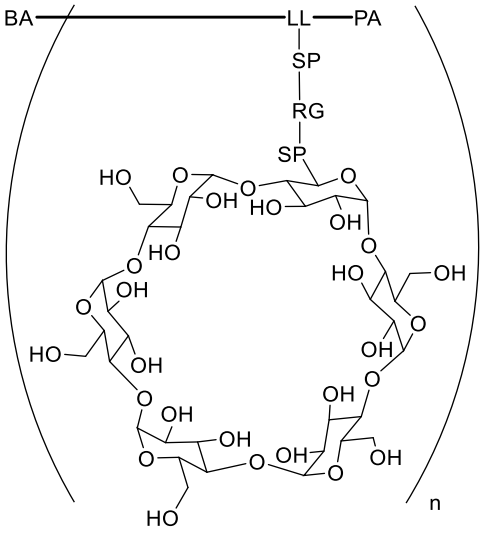
L is a trivalent linker;

CD is the cyclodextrin moiety;

subscript **n** is an integer from 1 to 30; and

PA is the payload moiety.

3. The compound of any one of claims 1 or 2, according to Formula (**Ia**):



(**Ia**)

wherein:

BA is the binding agent;

L comprises LL, each SP, and RG;

LL is a trivalent linker;

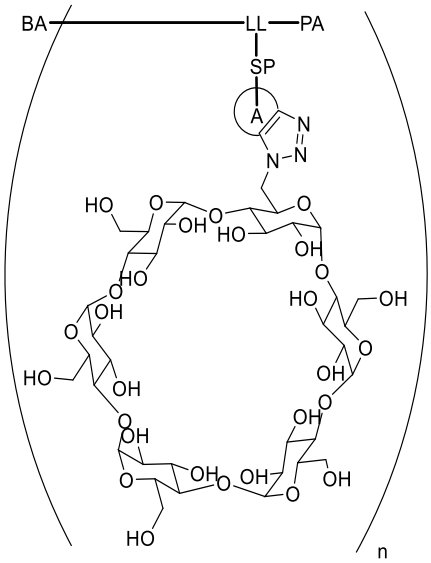
RG is a reactive linker residue;

SP is, independently in each instance, absent or a spacer group;

subscript **n** is an integer from 1 to 30, for instance from 1 to 4; and

PA is the payload moiety.

4. The compound of any one of claims 1-3, according to formula (**Ib**) or (**Ic**):



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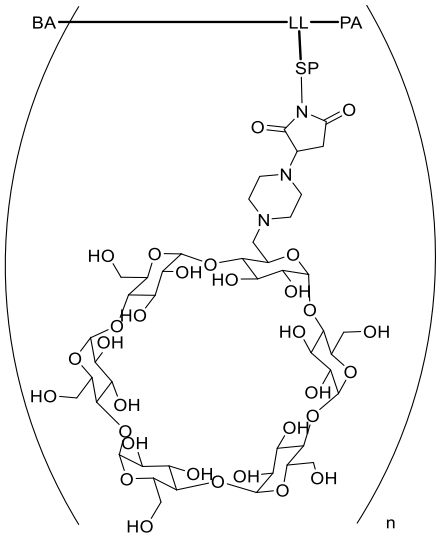


,

(**Ib**) (**Ic**)

wherein

BA is the binding agent;

LL is a trivalent linker;

SP is, independently in each instance, absent or is a spacer group;

ring **A** is fused to the triazole and is selected from the group consisting of cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

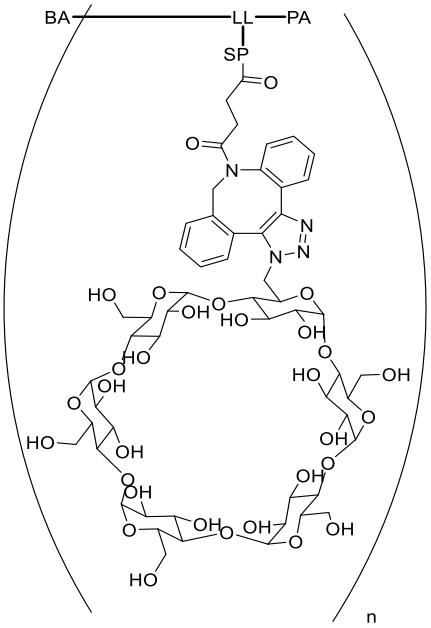
wherein cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl, are optionally substituted with alkyl, OH, or NR^aR^b, where each of R^a and R^b is alkyl or H;

n is an integer from 1 to 30;

PA is the payload moiety; and

stereoisomers thereof.

5. The compound of any one of claims 1-4, according to formula (**Ib1**) or (**Ib2**):



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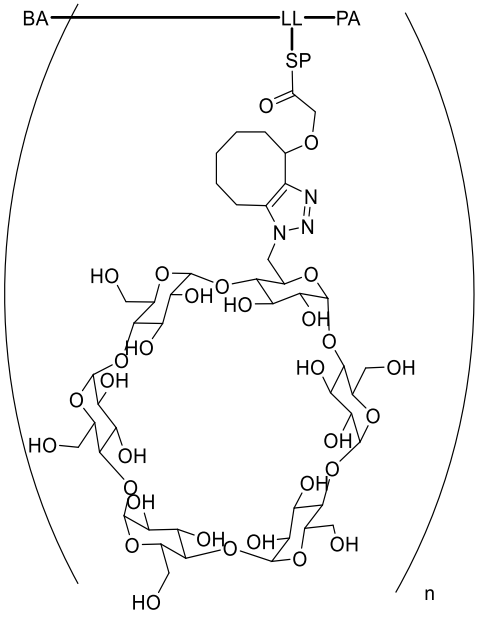


,

(**Ib1**) (**Ib2**)

wherein **BA** is the binding agent;

LL is a trivalent linker;

SP is, independently in each instance, absent or is a spacer group;

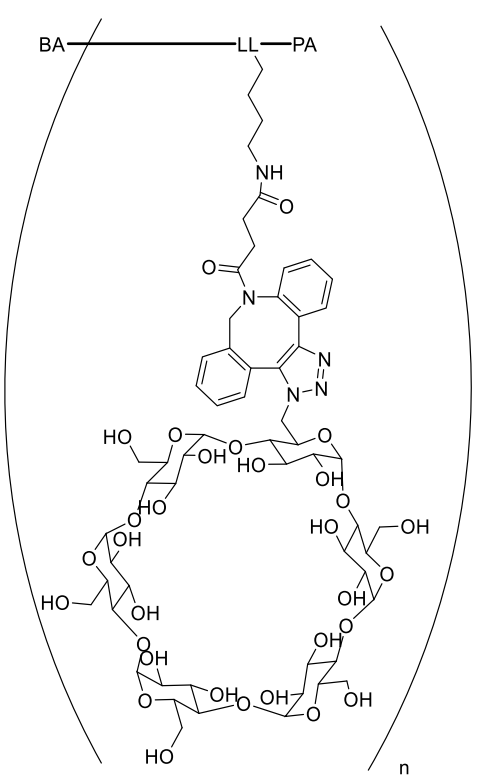
n is an integer from 1 to 30;

PA is the payload moiety;

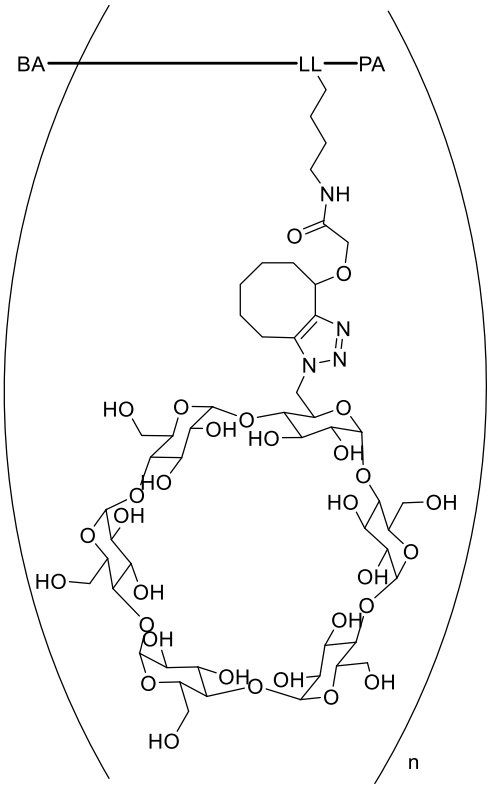
triazole linkage regioisomers;

and stereoisomers thereof.

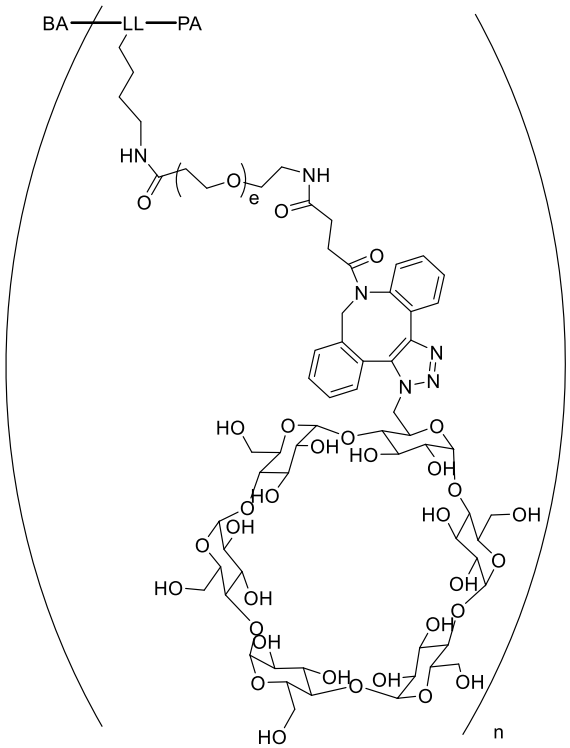
6. The compound of claim 1 according to formula (**Ib3**), (**Ib4**), (**Ib5**), or (**Ib6**):

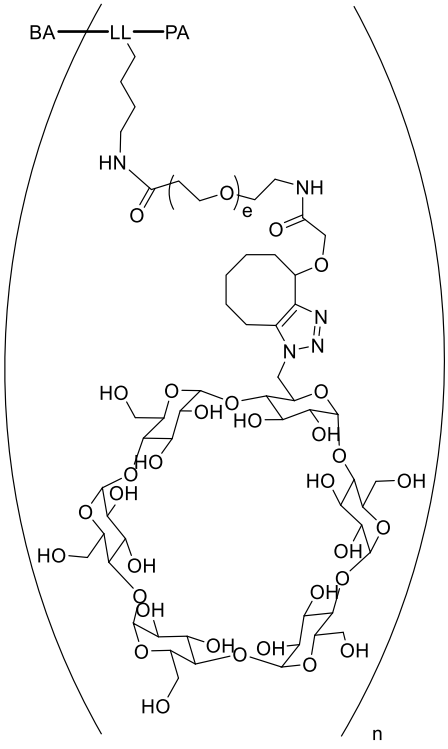


(**Ib3**)



(**Ib4**)



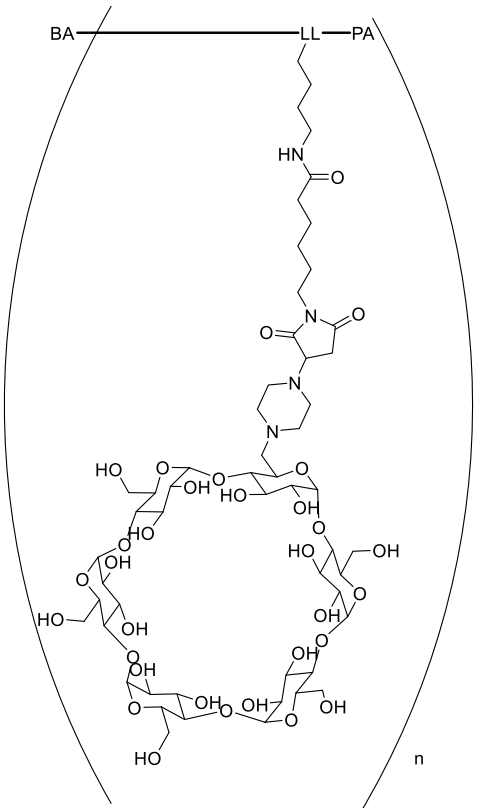


(**Ib5**) (**Ib6**)

wherein e is an integer from 0 to 4; and

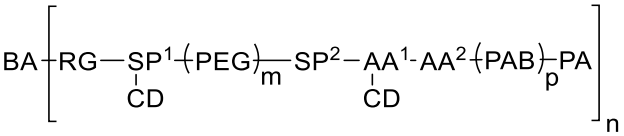
triazole linkage regioisomers thereof.

7. The compound of claim 1 according to formula (**Ic1**):



(**Ic1**).

8. The compound of claim 1 or 2 according to Formula (**Id**):



(**Id**)

wherein:

BA is the binding agent;

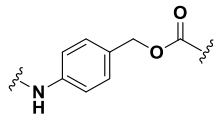
RG is a reactive group residue;

SP^1 and **SP^2** are each, independently in each instance, absent or a spacer group residue, and wherein **SP^1** comprises a trivalent linker;

AA^1 is a trivalent linker comprising an amino acid residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

CD is, independently in each instance, absent or a cyclodextrin-moiety, wherein at least one of **CD** is present;

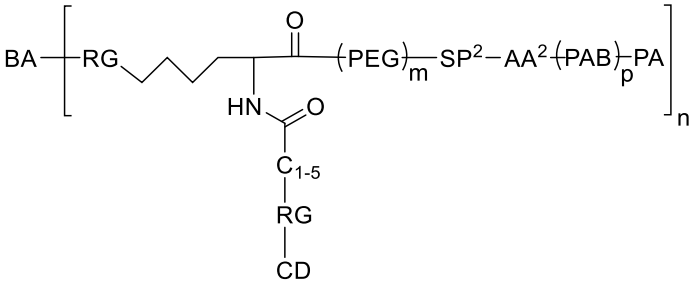
subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is a payload moiety.

9. The compound of any one of claims 1-3, according to Formula (**Ie**):



(**Ie**)

wherein:

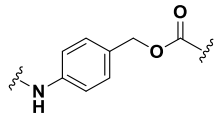
BA is the binding agent;

RG is, independently in each instance, a reactive group residue;

SP^2 is, independently in each instance, absent or a spacer group residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

C_{1-5} is a spacer group of 1 to 5 carbons;

CD is the cyclodextrin moiety,

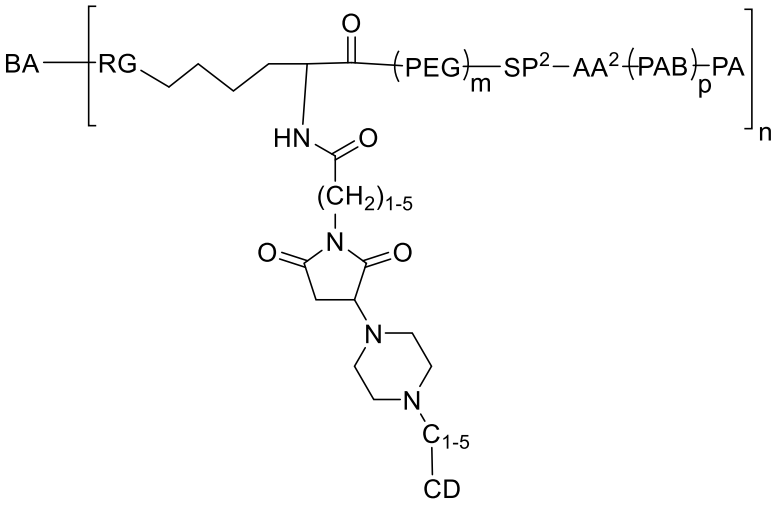
subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

10. The compound of any one of claims 1-3, according to Formula (**Ie1**):



(**Ie1**)

wherein:

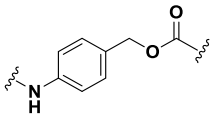
BA is the binding agent;

RG is a reactive group residue;

SP² is, independently in each instance, absent or a spacer group residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

CD is the cyclodextrin moiety;

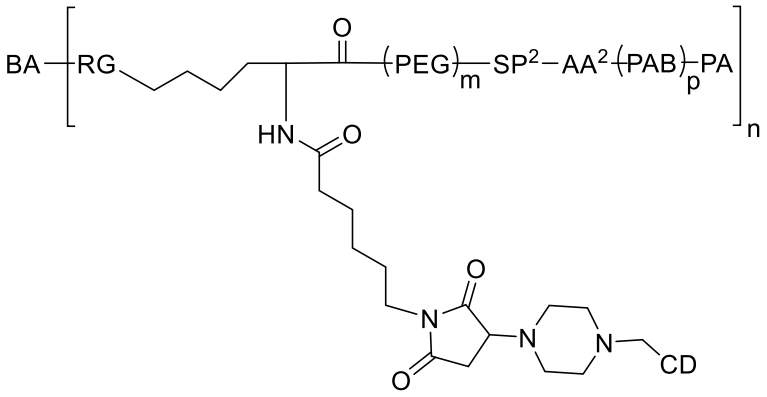
subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

11. The compound of any one of claims 1-3, according to Formula (**Ie2**):



(**Ie2**)

wherein:

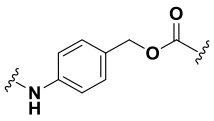
BA is the binding agent;

RG is a reactive group residue;

SP² is, independently in each instance, absent or a spacer group residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

CD is the cyclodextrin moiety;

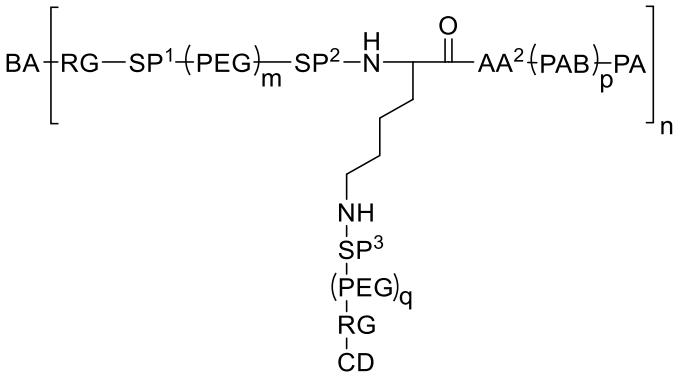
subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

12. The compound of any one of claims 1-8, according to Formula (**If**):



(**If**)

wherein:

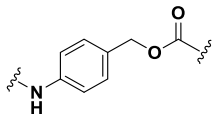
BA is a binding agent;

RG is, independently in each instance, a reactive linker residue;

SP^1, **SP^2**, and **SP^3** are each, independently in each instance, absent or a spacer group residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

CD is the cyclodextrin moiety;

subscript **n** is an integer from 1 to 30;

subscript **m** is an integer from 0 to 5;

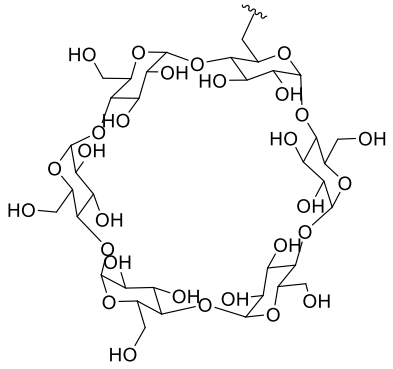
subscript **q** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

13. The compound of any one of claims 1-12, wherein **CD** is, independently in each instance, selected from the group consisting of α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin.

14. The compound of any one of claims 1-4 and 7-12, wherein **CD** is, independently in each instance, selected from the group consisting of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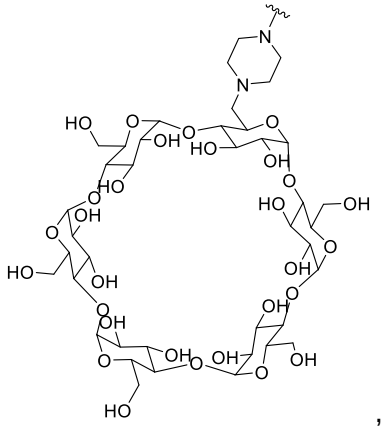
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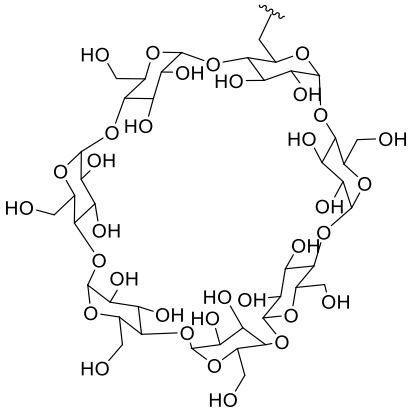
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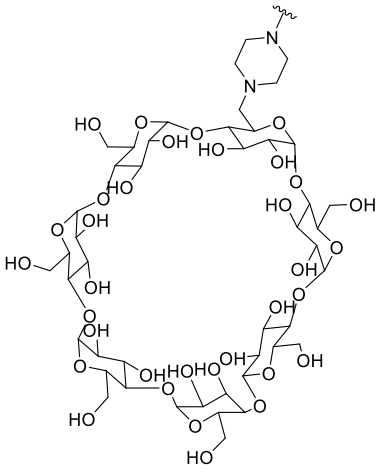
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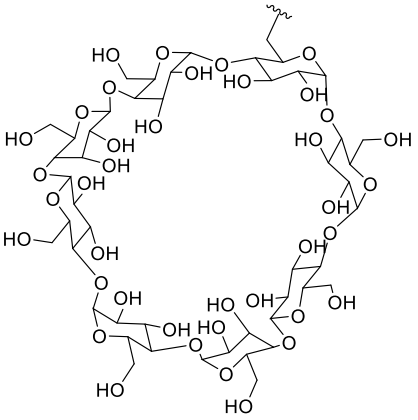
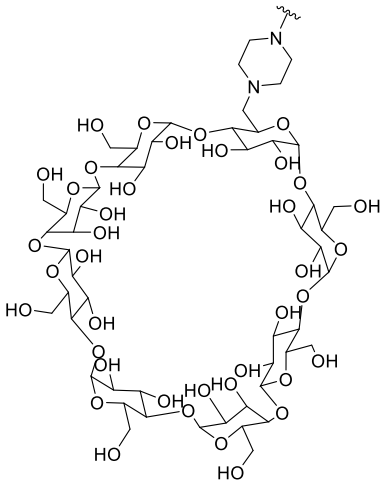
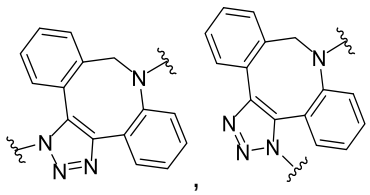
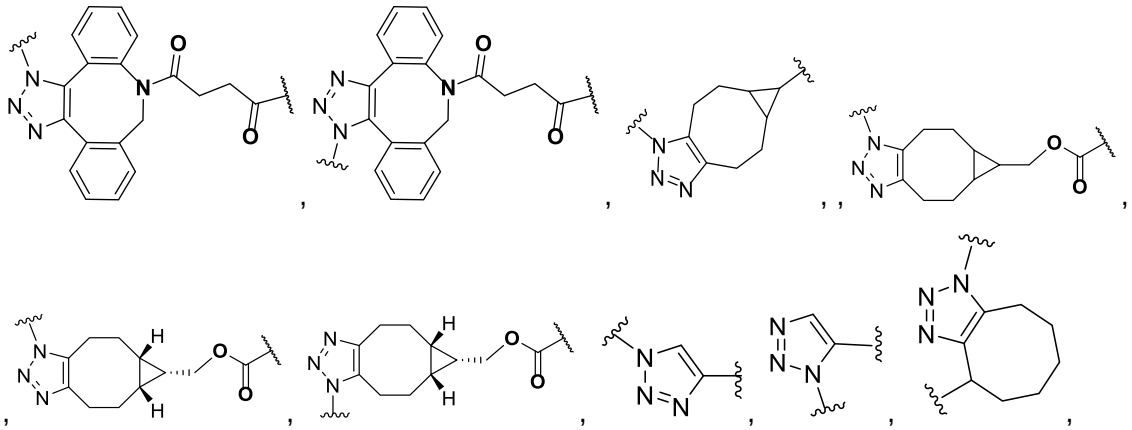

, and  ,

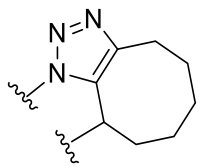
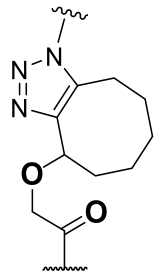
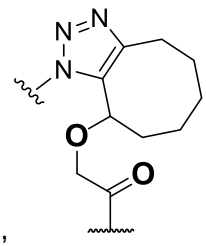
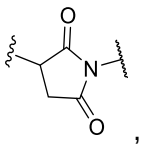
wherein the  indicates the atom through which the **CD** is bonded to the adjacent groups in the formula.

15. The compound of any one of claims 1-12, wherein RG comprises a triazole or fused triazole.

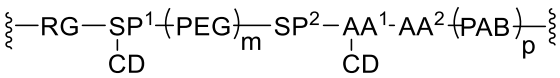
16. The compound of any one of claims 1-12, wherein **RG**, independently in each instance, comprises a triazole or a fused triazole.

17. The compound of any one of claims 1-12, wherein **RG** is, independently in each instance, selected from the group consisting of  ,

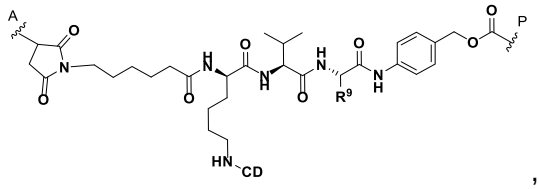


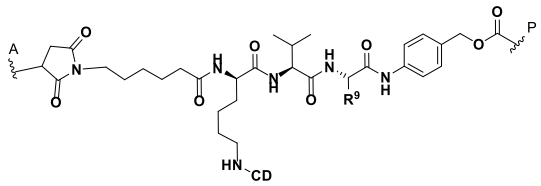
 ,  ,  , and  , wherein the  indicates the atom through which the **RG** is bonded to the adjacent groups in the formula.

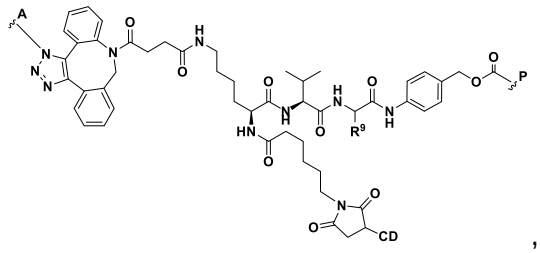
18. The compound of any one of claims 8-17, wherein

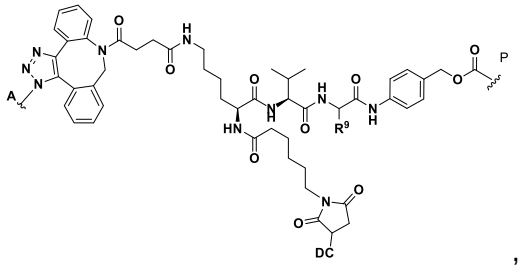


is selected from the group consisting of

 ,

 ,

 ,



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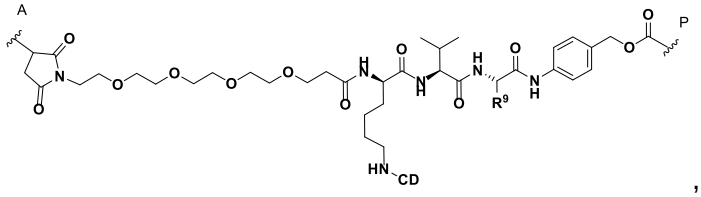

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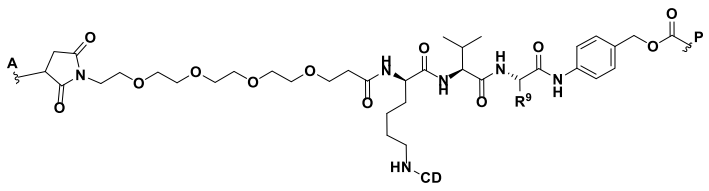

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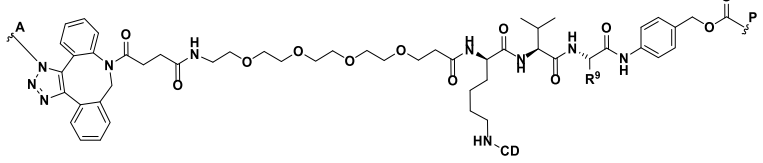

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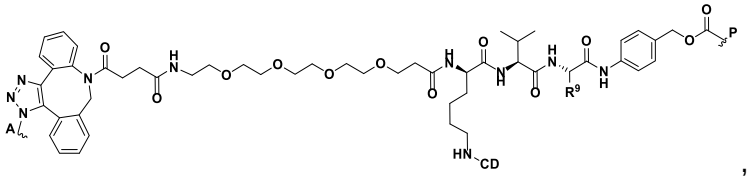

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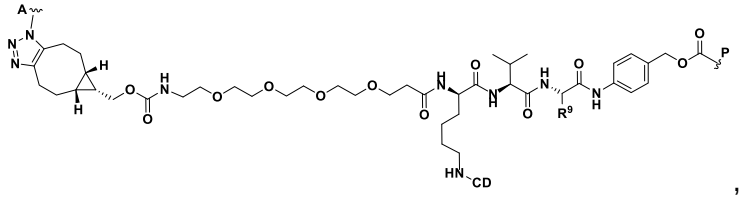

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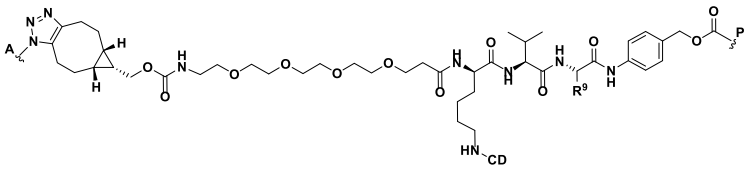

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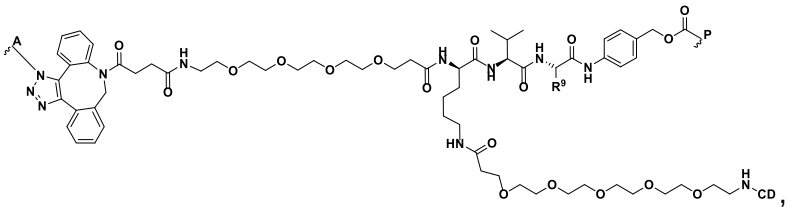

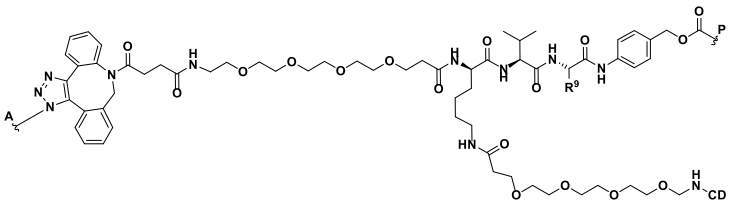

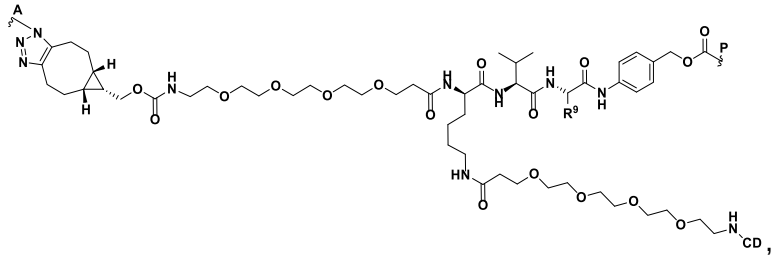

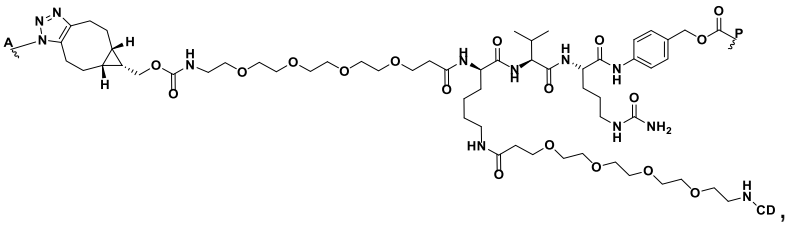

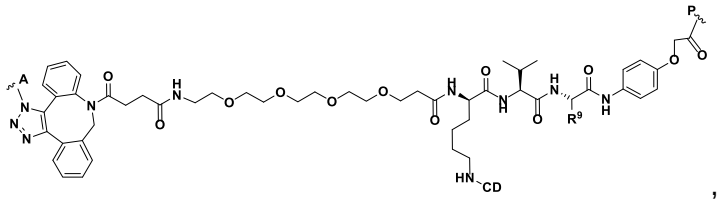

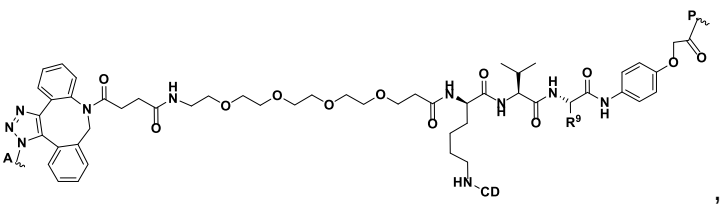

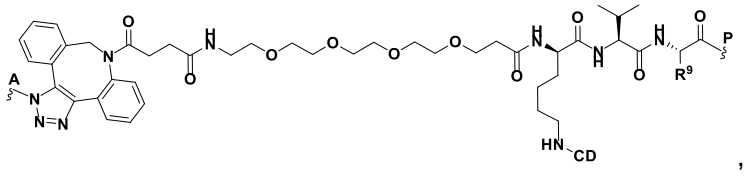

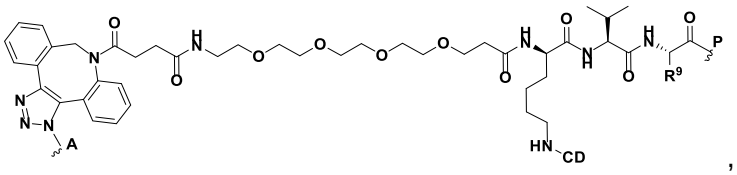

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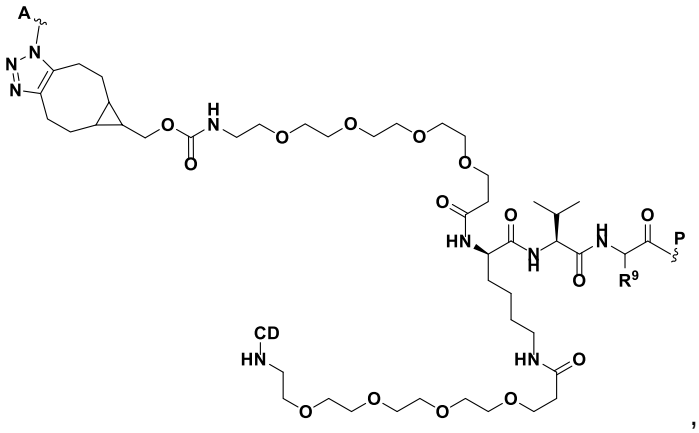

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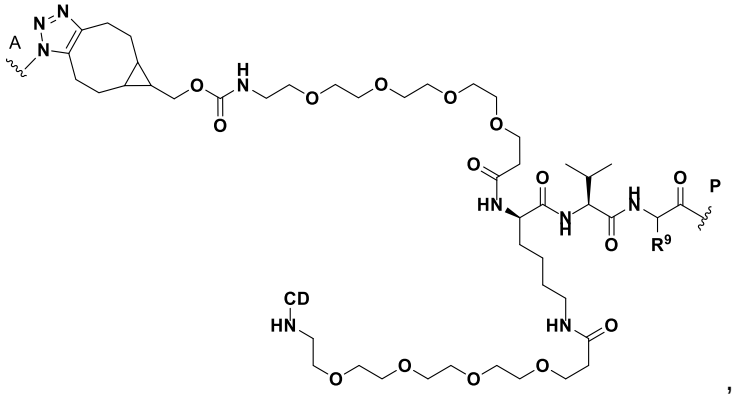

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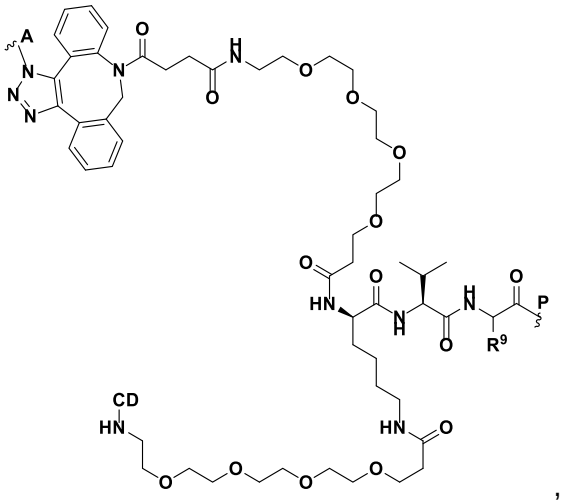

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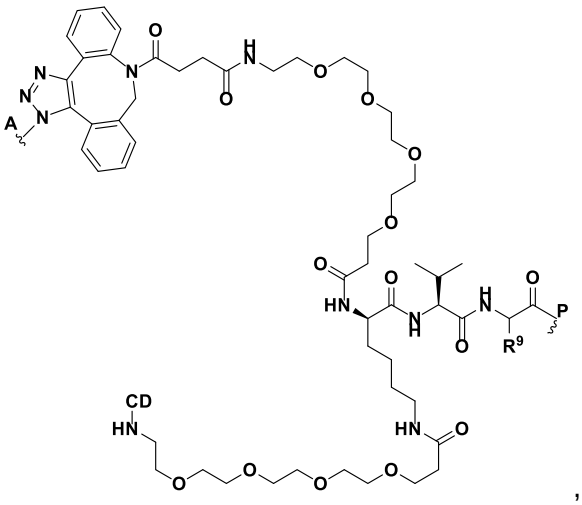

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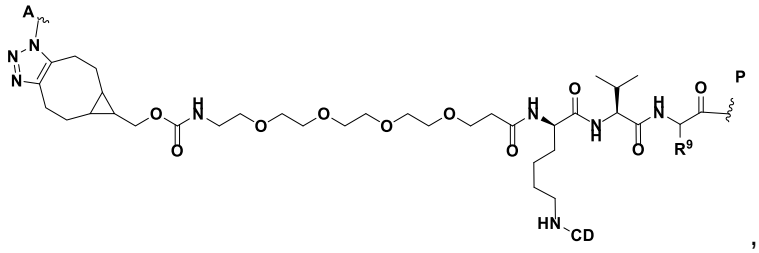

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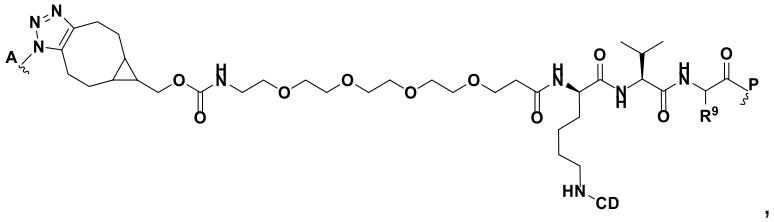

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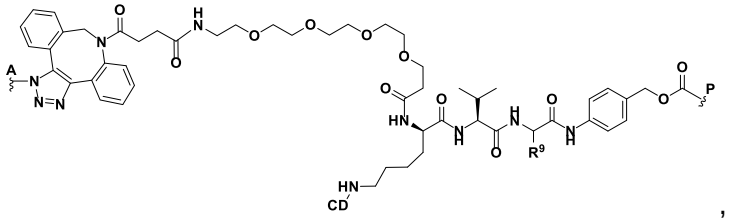

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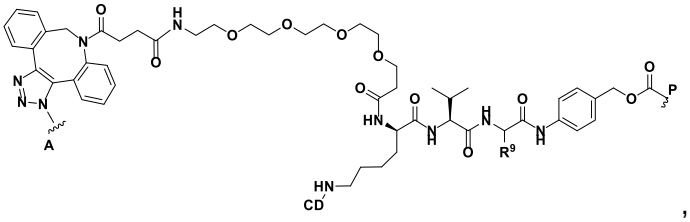

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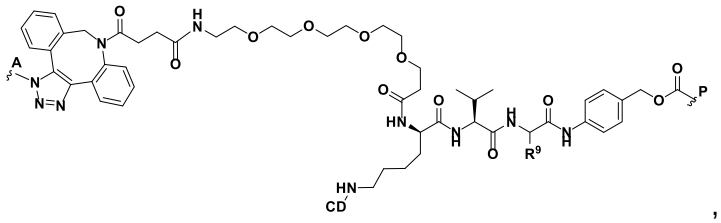

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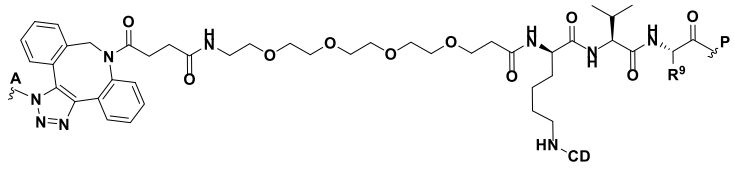

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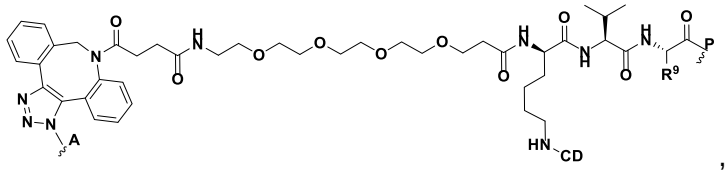

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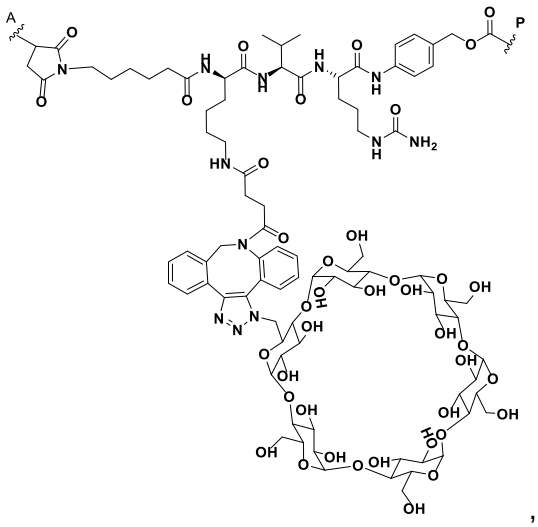
or a pharmaceutically acceptable salt, or stereoisomeric form thereof, or a triazole linkage regioisomer thereof, or mixture of triazole linkage regioisomers thereof, wherein:

each  is a bond to the binding agent;

each  is a bond to the payload moiety; and

R^9 is $–CH_3$ or $–(CH_2)_3N(H)C(O)NH_2$.

19. The compound of any one of claims 8-17, comprising a group selected from the group consisting of



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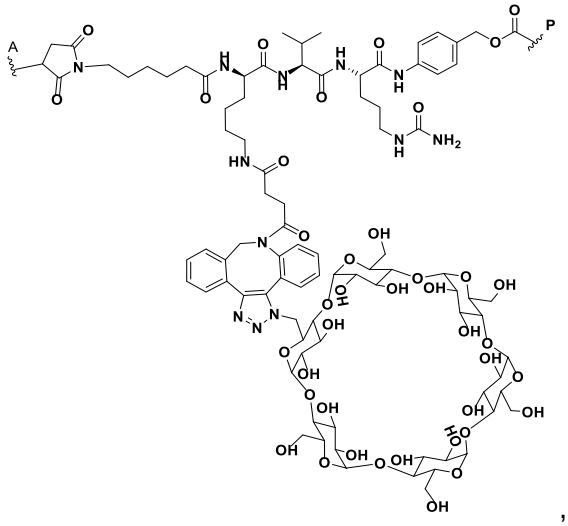

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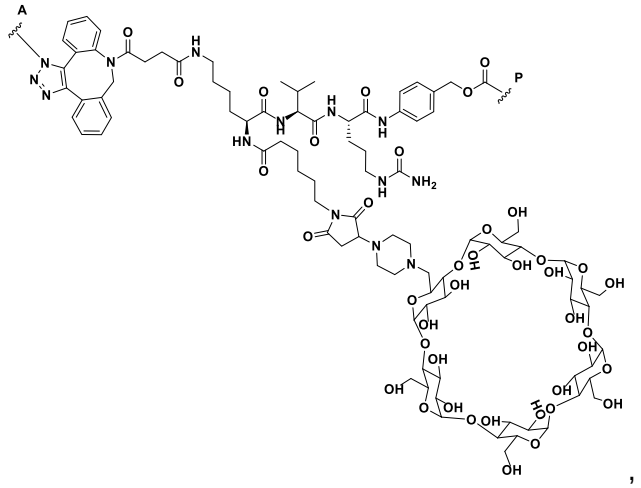

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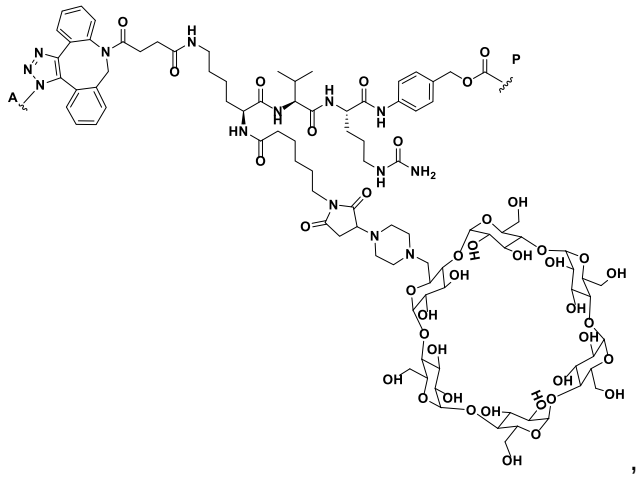

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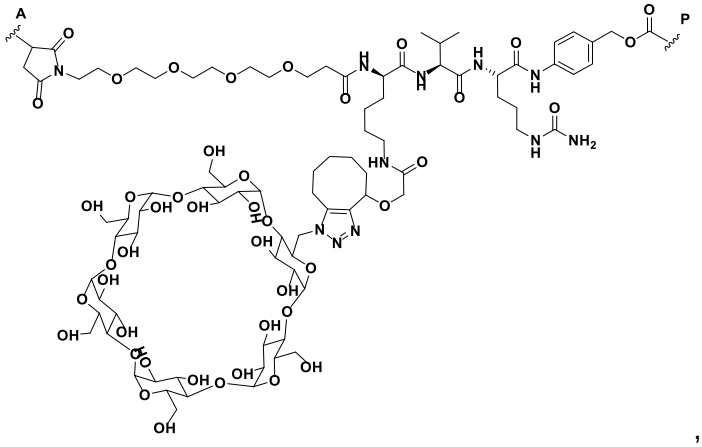

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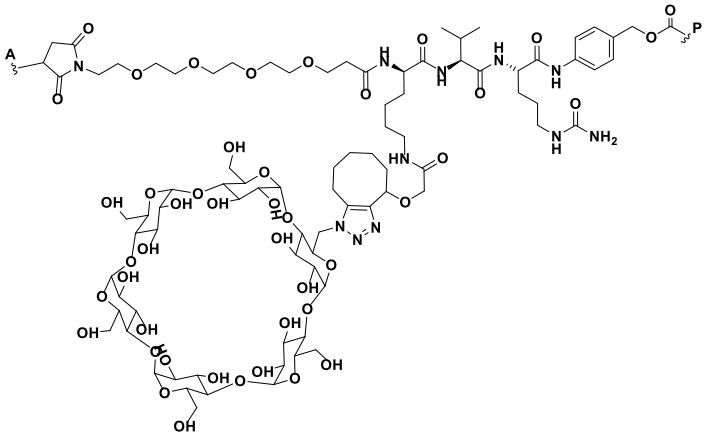

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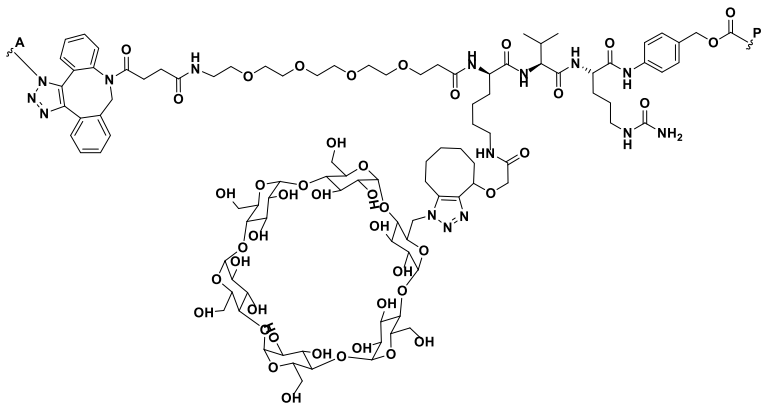

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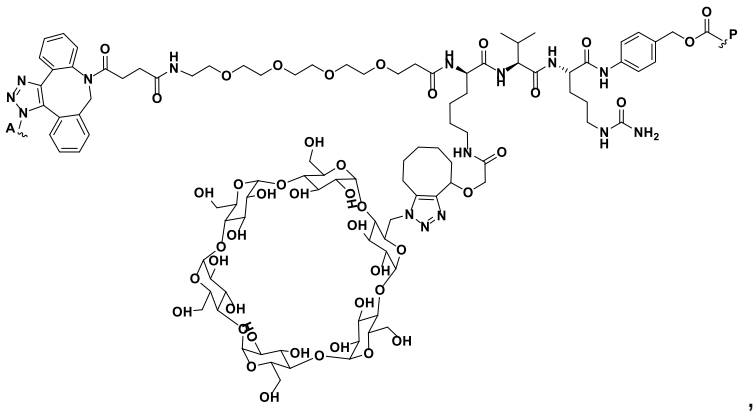

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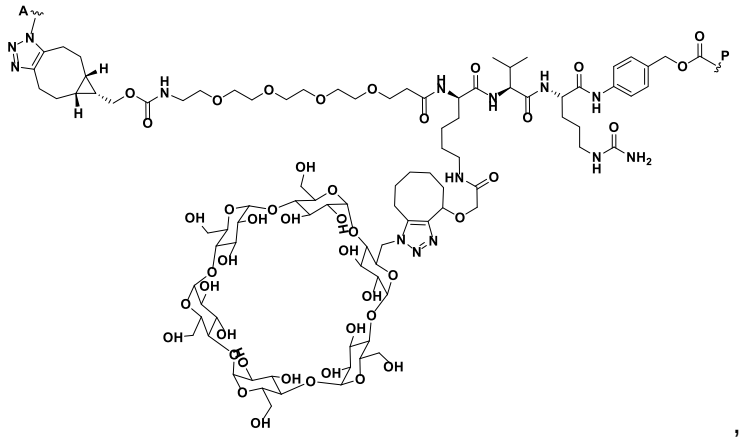

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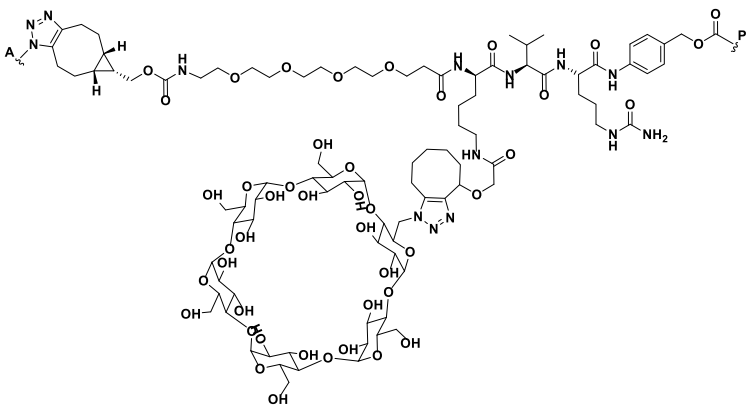

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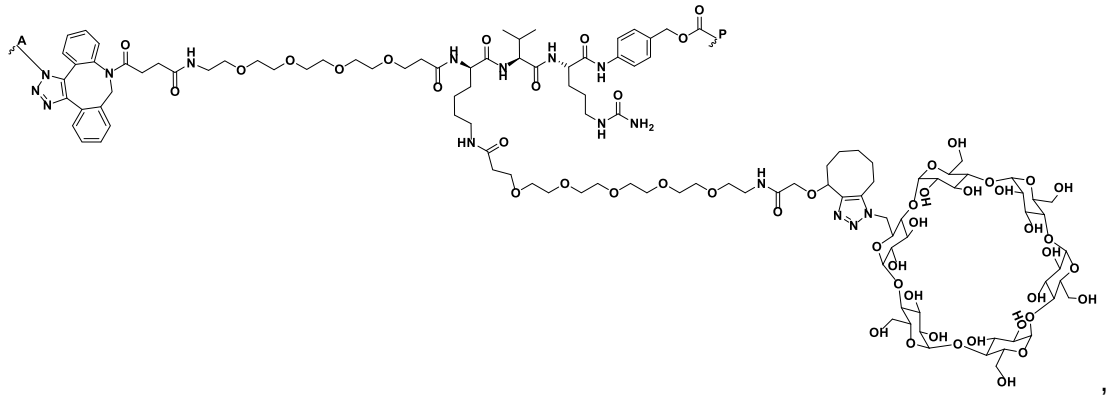

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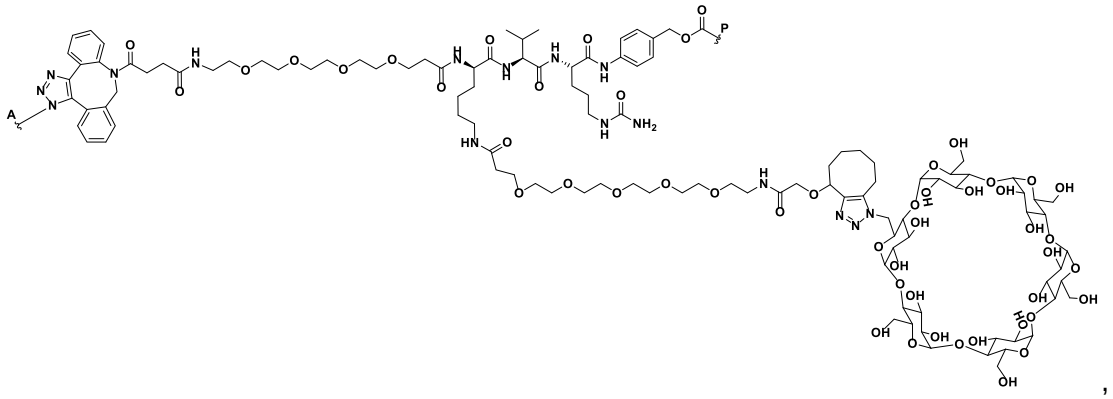

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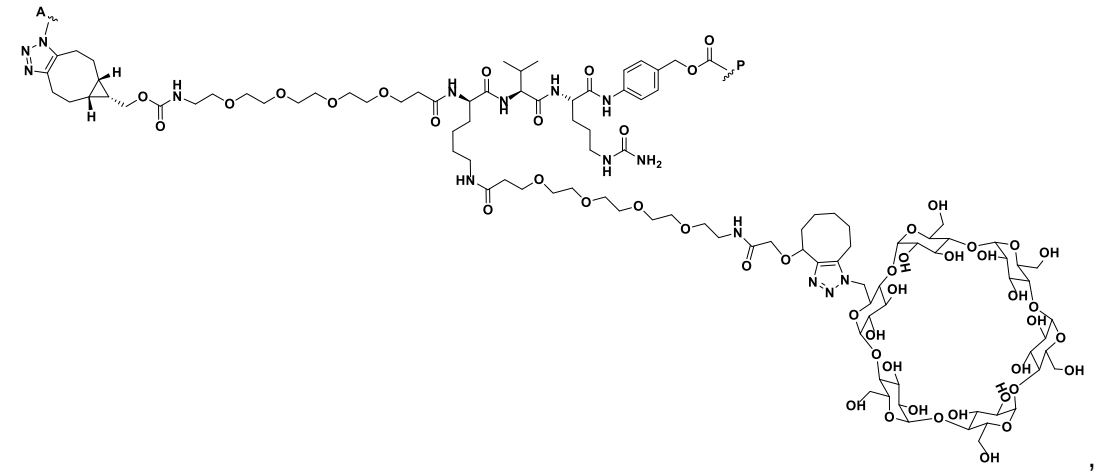

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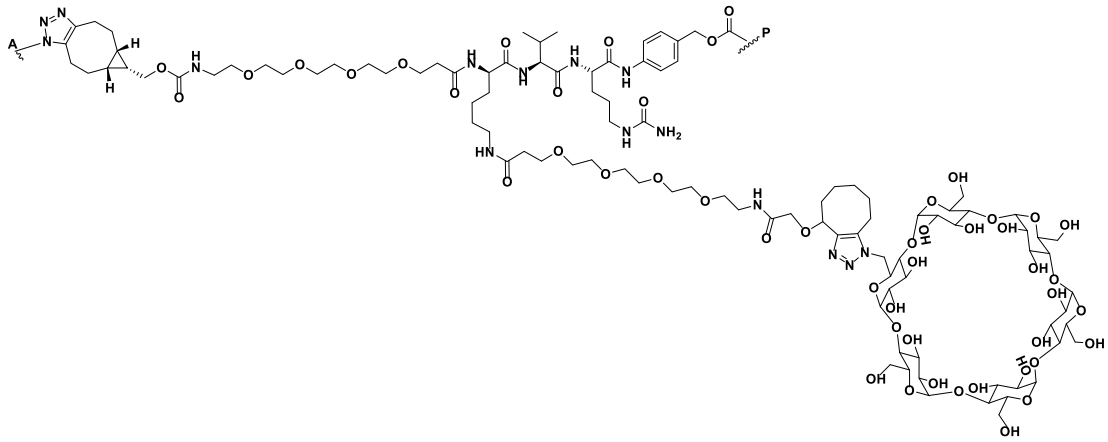

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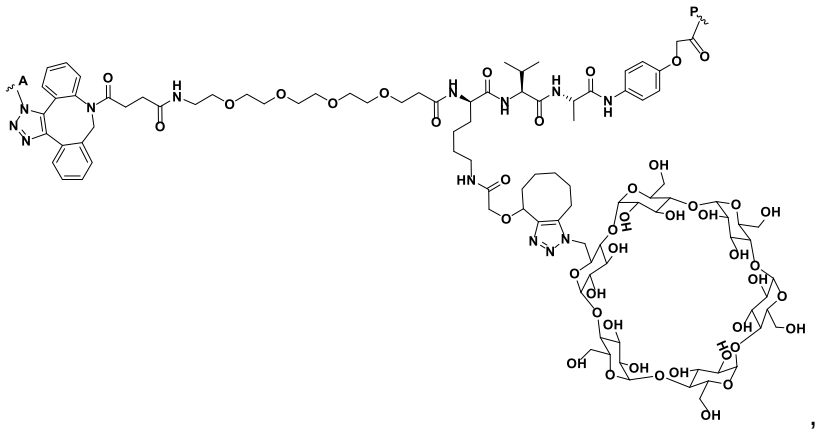

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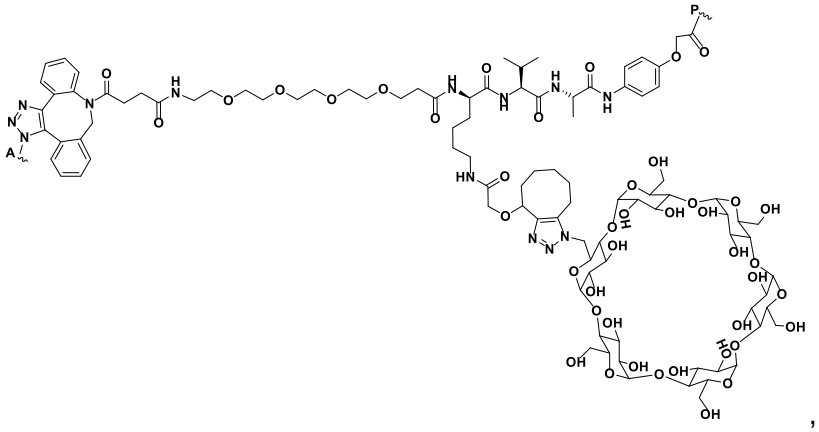

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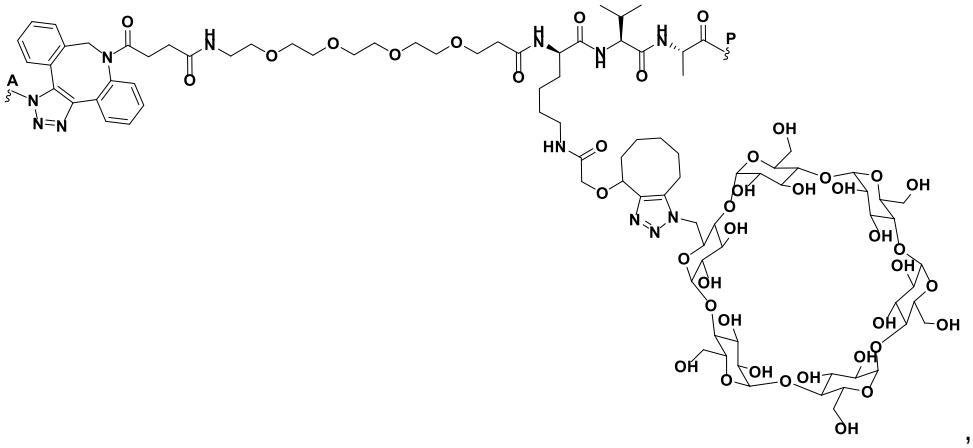

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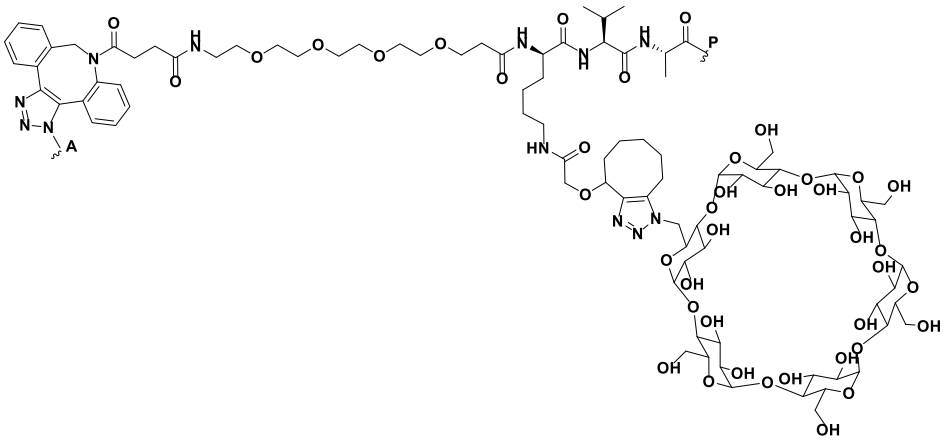

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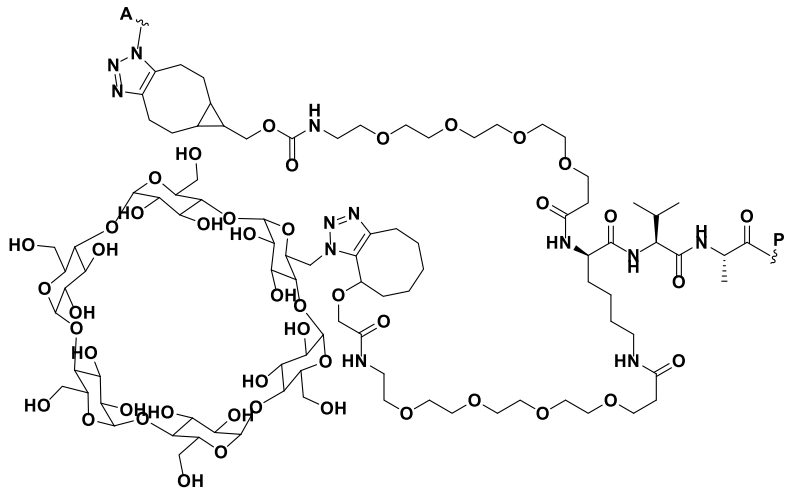

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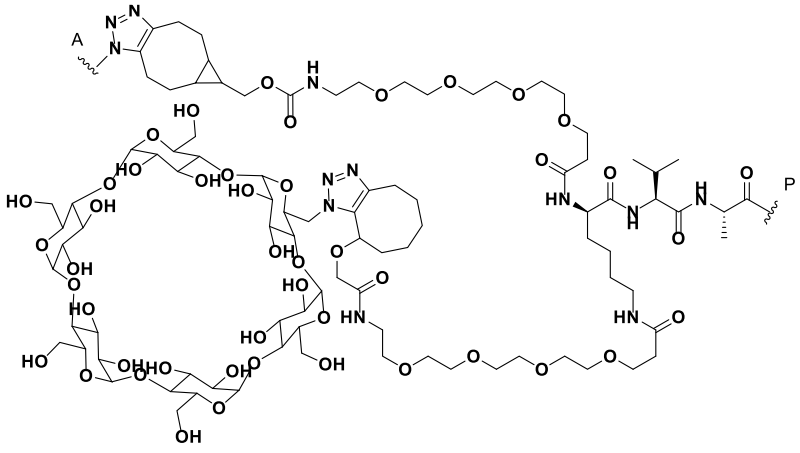

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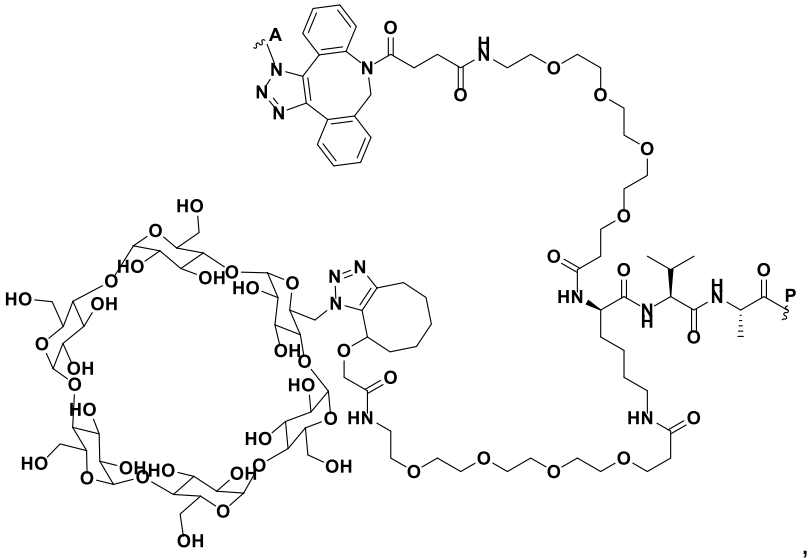

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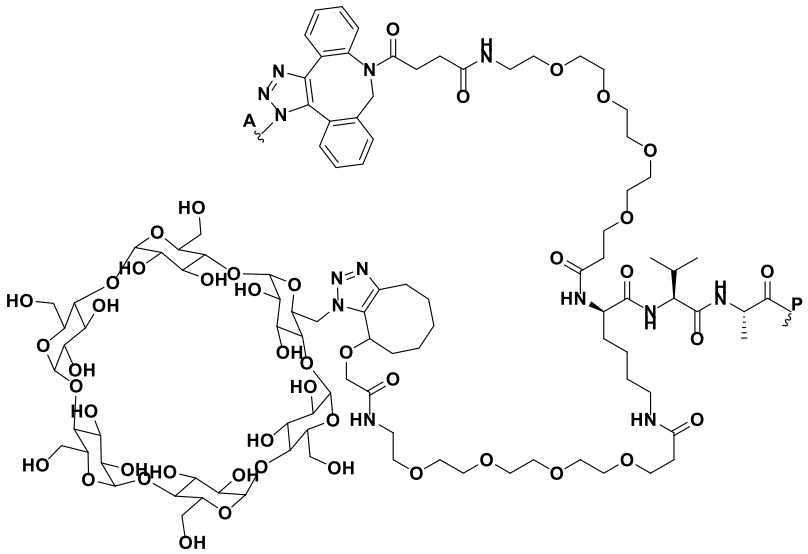

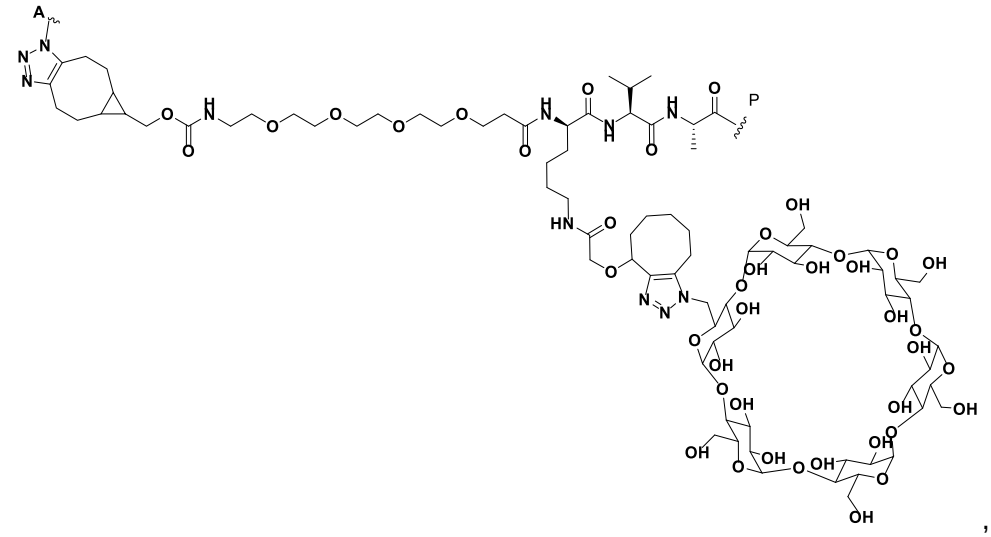

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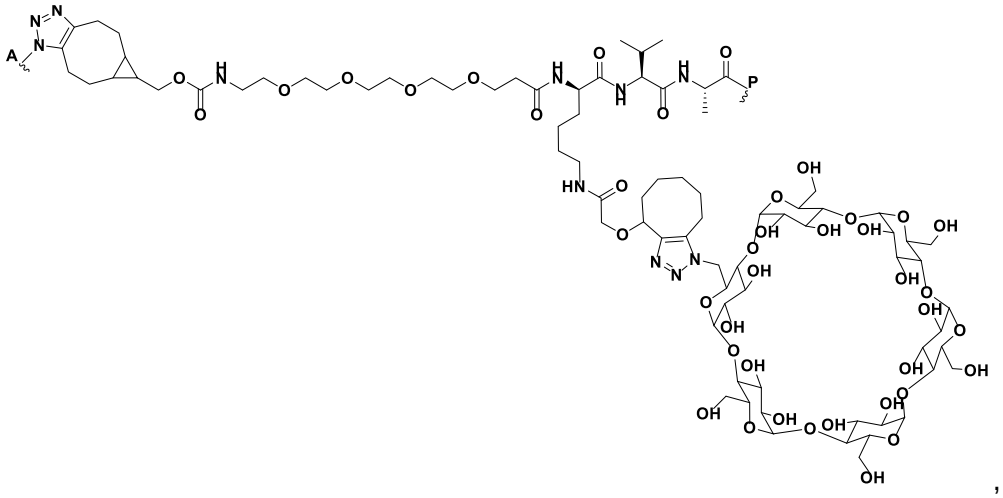

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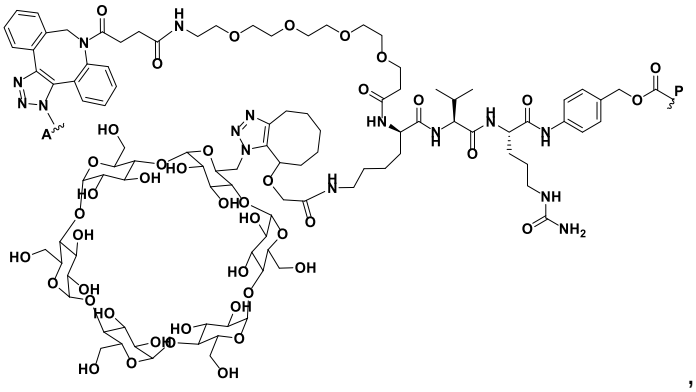

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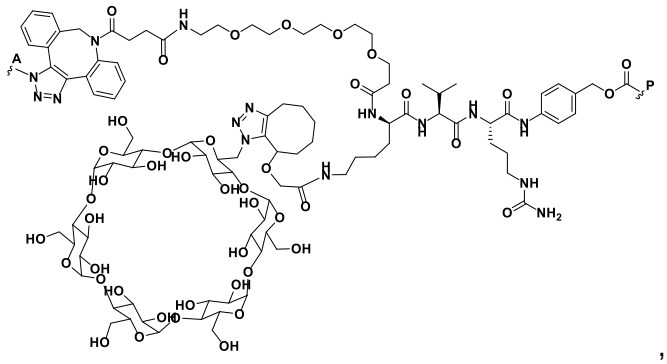

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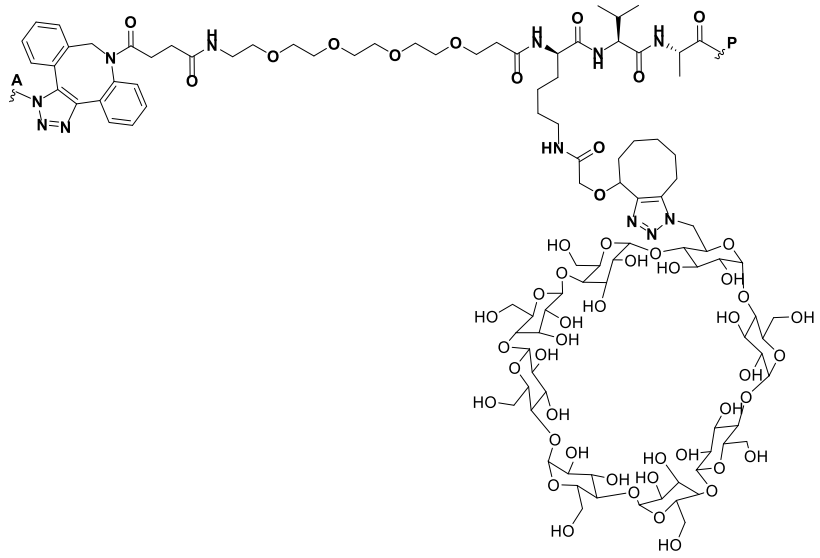

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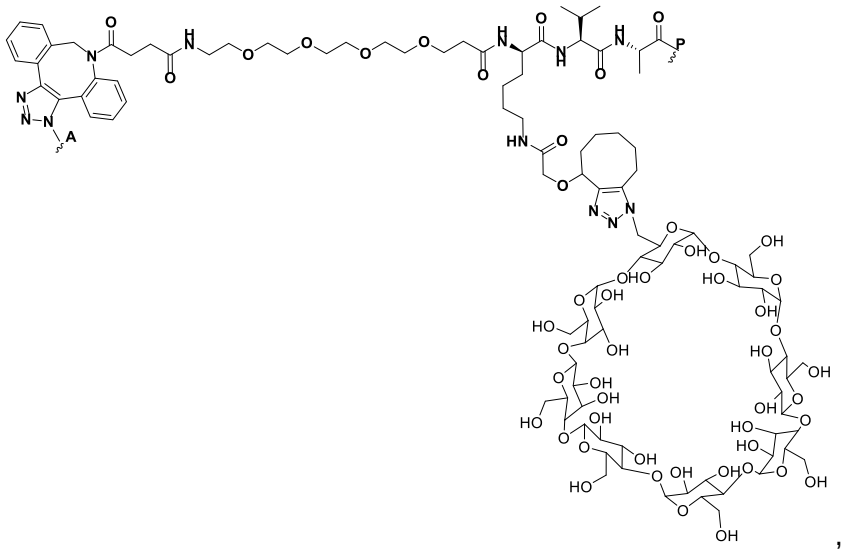


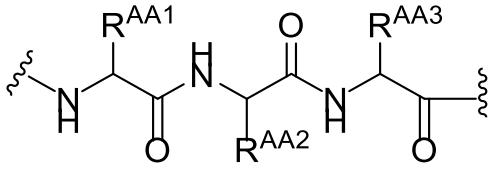
or a pharmaceutically acceptable salt, or stereoisomeric form thereof, or a triazole linkage regioisomer thereof, or mixture of triazole linkage regioisomers thereof, wherein:

each  is a bond to the binding agent; and

each  is a bond to the payload moiety.

20. The compound of claim 3, wherein

-**LL**- is according to the Formula (**LL1**):



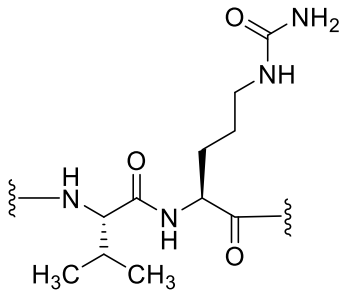
(**LL1**)

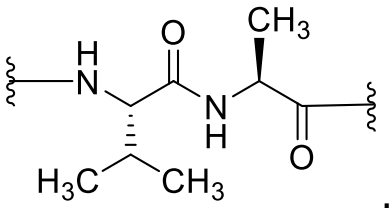
wherein $\mathbf{R^{AA1}}$, $\mathbf{R^{AA2}}$, and $\mathbf{R^{AA3}}$ are each, independently, amino acid side chains, at least one of which is bonded directly or indirectly to **-SP-RG-SP-CD**, wherein one or both SP may be absent.

21. The compound of claim 20, wherein $\mathbf{R^{AA1}}$ is a lysine side chain bonded directly or indirectly to **CD** and $\mathbf{R^{AA2}}$ and $\mathbf{R^{AA3}}$ are either valine and citrulline or valine and alanine side chains, respectively.

22. The compound of any one of claims 8-12, wherein

LL1 comprises



or


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23. The compound of any one of claims 1-12, wherein the spacer group is, independently in each instance, selected from the group consisting of C_{1-6} alkylene, -NH-, -C(O)-, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, and combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8.

24. The compound of any one of claims 8-12 or 23, wherein any one of subscript **m**, **q**, or **e** is 4.

25. The compound of any one of claims 8-12, wherein subscript **p** is 1.

26. The compound of any one of claims 1-12, wherein subscript **n** is 2-4.

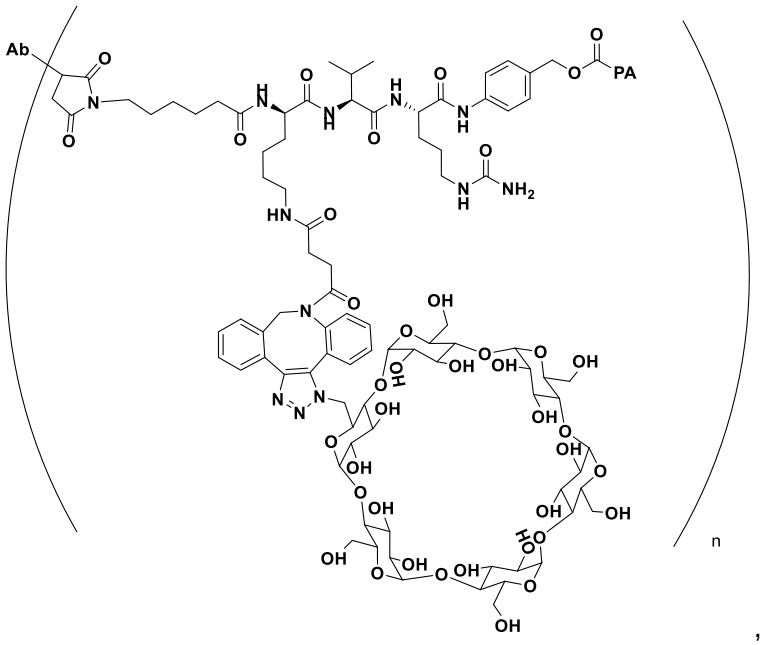
27. The compound of any one of claims 1-26, wherein the binding agent (**BA**) is an antibody.

28. The compound of any one of claims 1-26, wherein the wherein the binding agent is an antibody, or an antigen-binding fragment thereof, selective for an antigen selected from the group consisting of AXL, BAFFR, BCMA, BCR-list components, BDCA2, BDCA4, BTLA, BTNL2, BTNL3, BTNL8, BTNL9, C10 or f54, CCR1, CCR3, CCR4, CCR5, CCR6, CCR7, CCR9, CCR10, CD11c, CD137, CD138, CD14, CD168, CD177, CD19, CD20, CD209, CD209L, CD22, CD226, CD248, CD25, CD27, CD274, CD276, CD28, CD30, CD300A, CD33, CD37, CD38, CD4, CD40, CD44, CD45, CD46, CD48, CD5, CD52, CD55, CD56, CD59, CD62E, CD68, CD69, CD70, CD74, CD79a, CD79b, CD8, CD80, CD86, CD90.2, CD96, CLEC12A, CLEC12B, CLEC7A, CLEC9A, CR1, CR3, CRTAM, CSF1R, CTLA4, CXCR1/2, CXCR4, CXCR5, DDR1, DDR2, DEC-205, DLL4, DR6, FAP, FCamR, FCMR, FcR's, Fire, GITR, HHLA2, HLA class II, HVEM, ICOSLG, IFNLR1, IL10R1, IL10R2, IL12R, IL13RA1, IL13RA2, IL15R, IL17RA, IL17RB, IL17RC, IL17RE,

IL20R1, IL20R2, IL21R, IL22R1, IL22RA, IL23R, IL27R, IL29R, IL2Rg, IL31R, IL36R, IL3RA, IL4R, IL6R, IL5R, IL7R, IL9R, Integrins, LAG3, LIFR, MAG/Siglec-4, MMR, MSR1, NCR3LG1, NKG2D, NKp30, NKp46, PDCD1, PROKR1, PVR, PVRIG, PVRL2, PVRL3, RELT, SIGIRR, Siglec-1, Siglec-10, Siglec-5, Siglec-6, Siglec-7, Siglec-8, Siglec-9, SIRPA, SLAMF7, TACI, TCR-list components/assoc, PTCRA, TCRb, CD3z, CD3, TEK, TGFBR1, TGFBR2, TGFBR3, TIGIT, TLR2, TLR4, TROY, TSLPR, TYRO, VLDLR, VSIG4, and VTCN1.

29. The compound of claim 1, wherein **PA** is the residue of a group selected from the group consisting of a dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, a vinca alkaloid, a steroid, an LXR modulator, and combinations thereof.

30. The compound of claim 1, wherein the compound is selected from:



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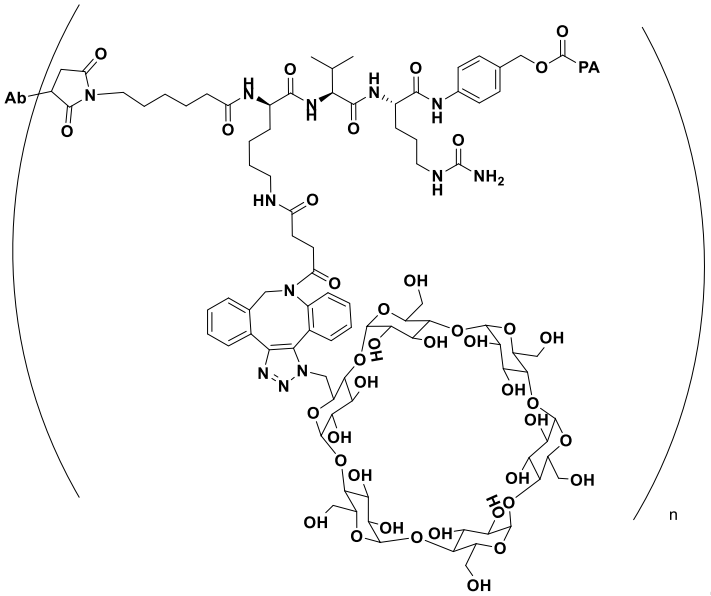
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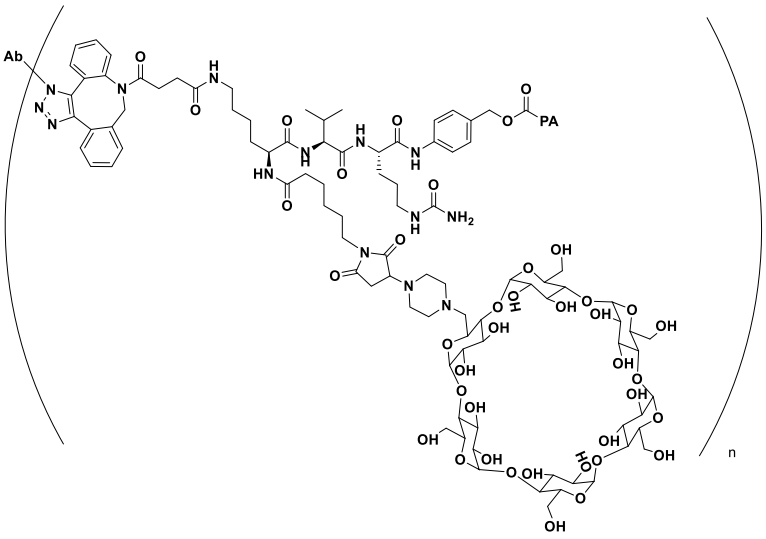
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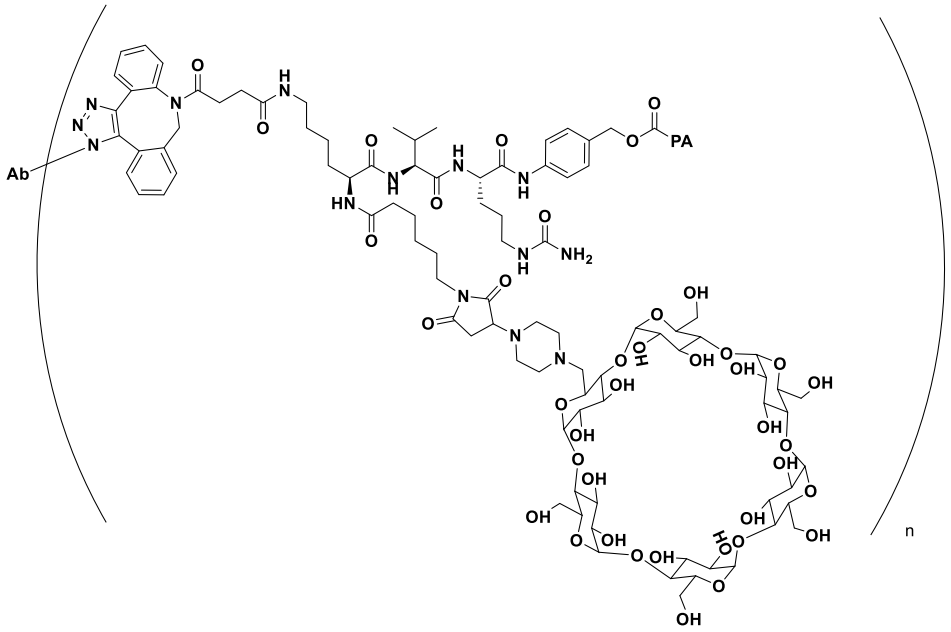
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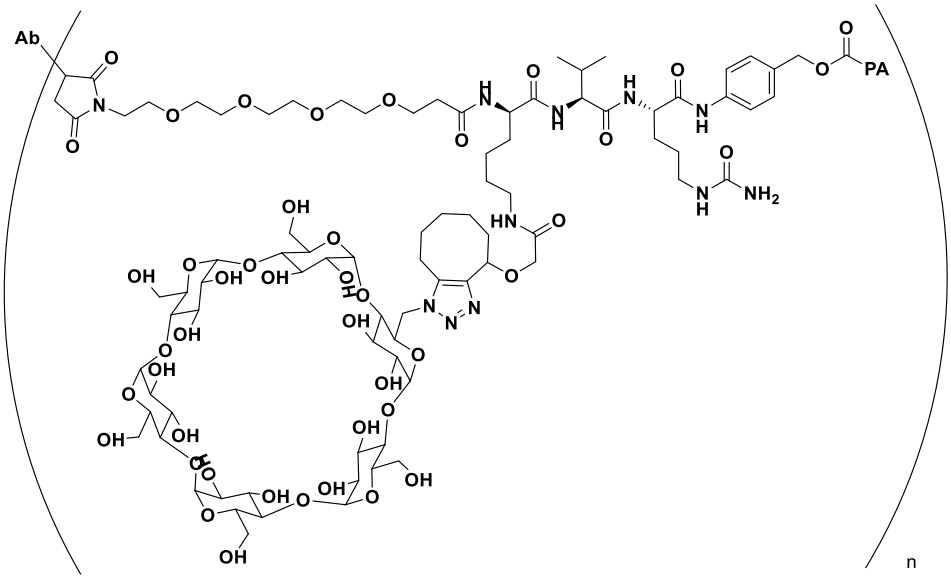
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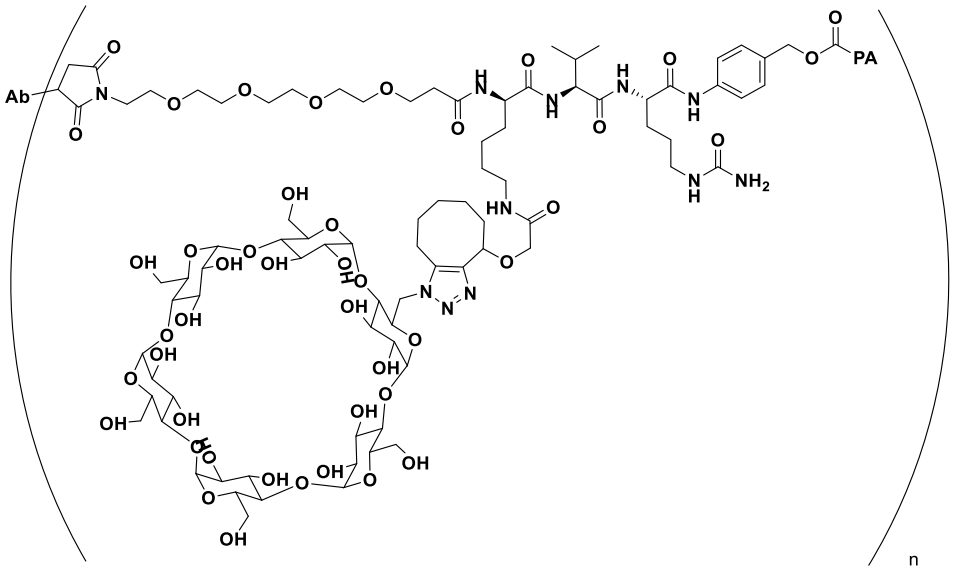

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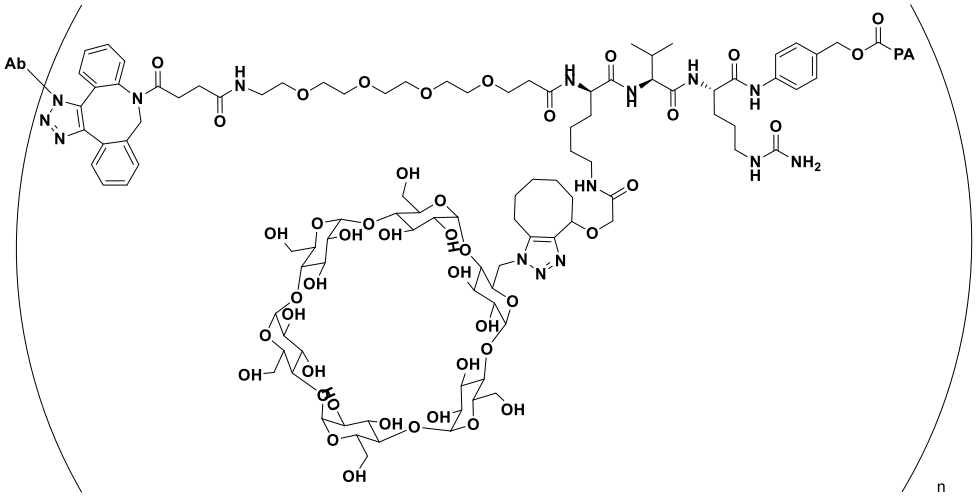

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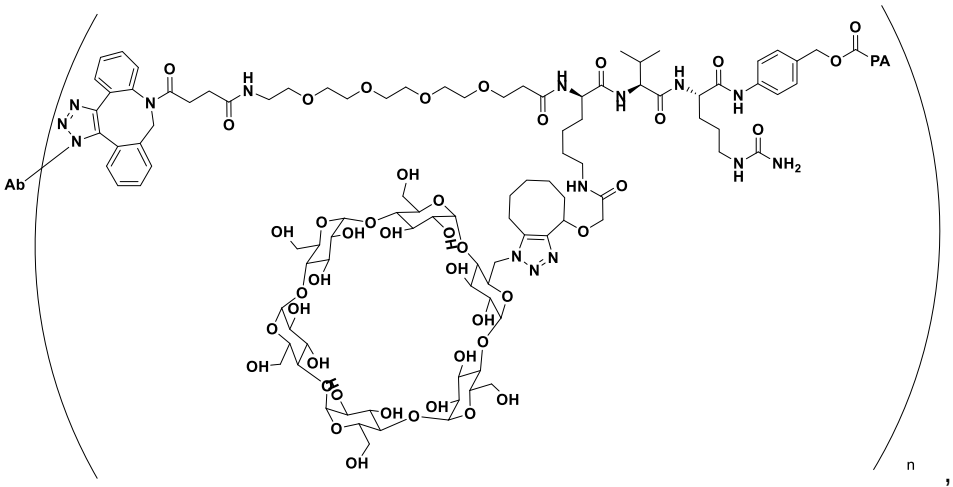

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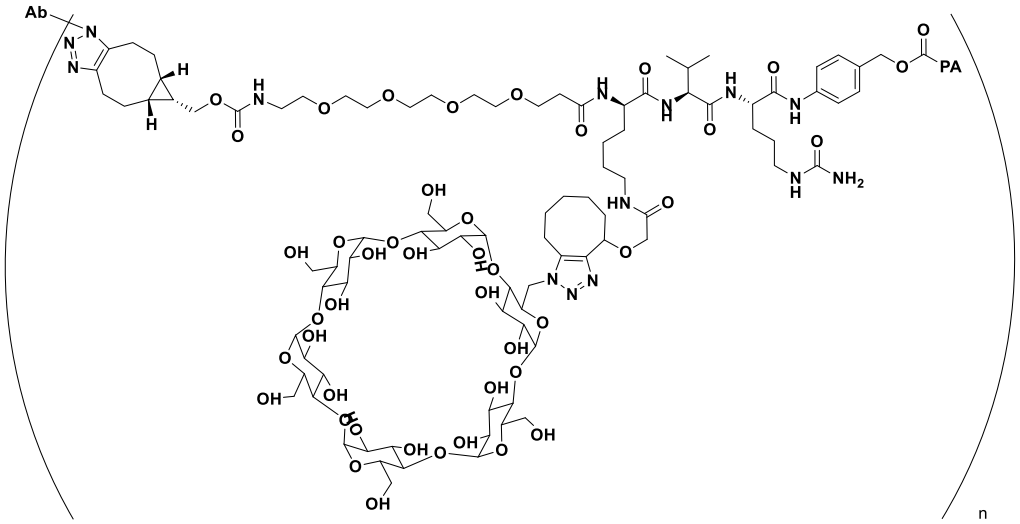

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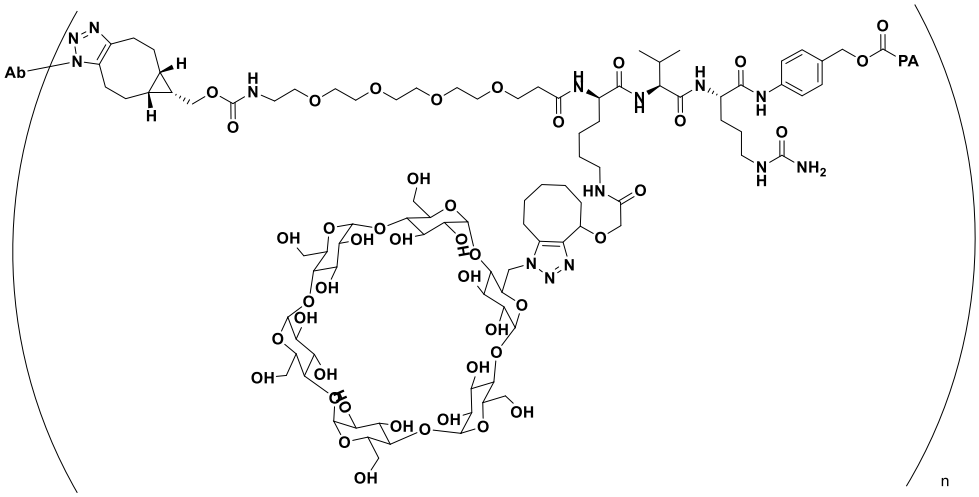

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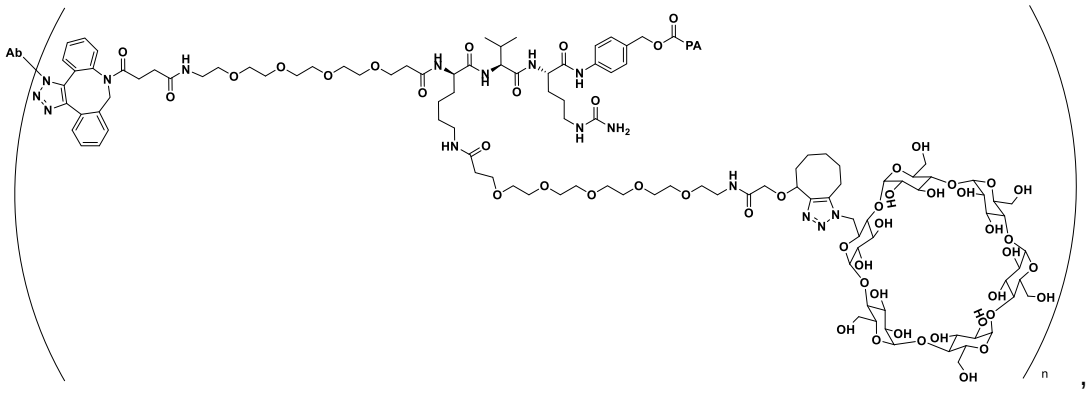

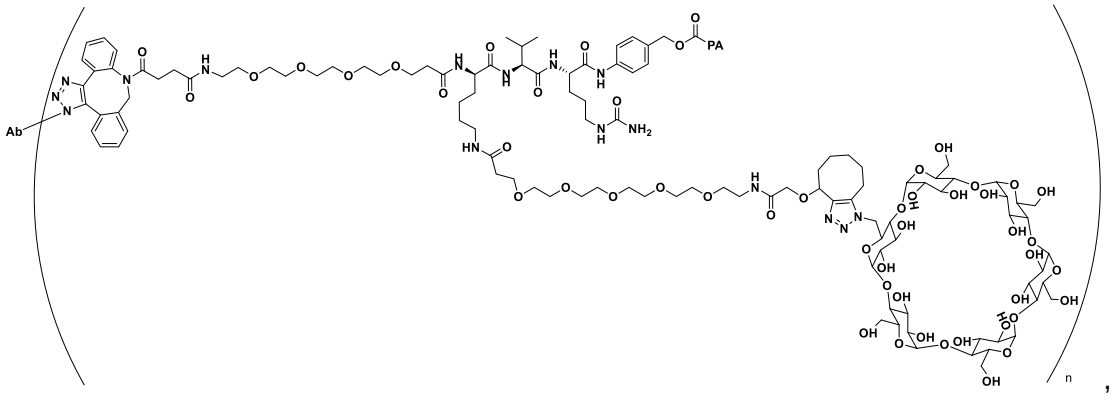

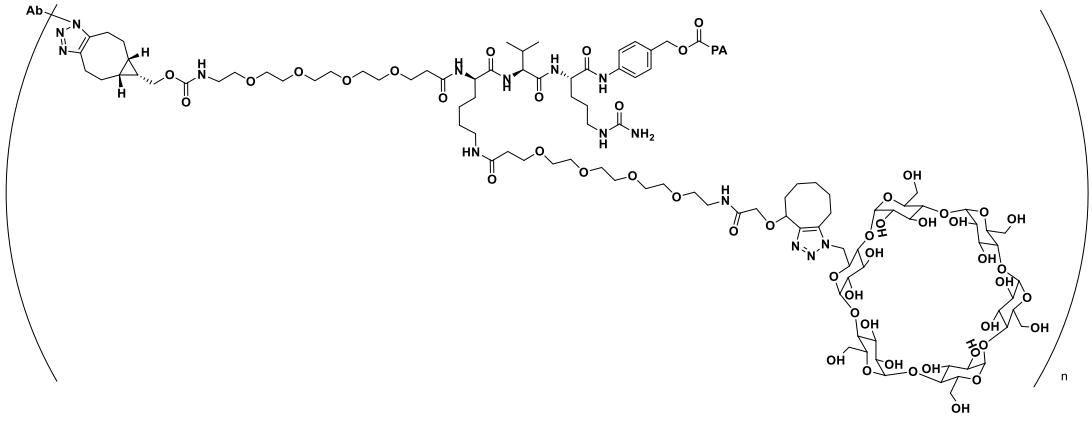

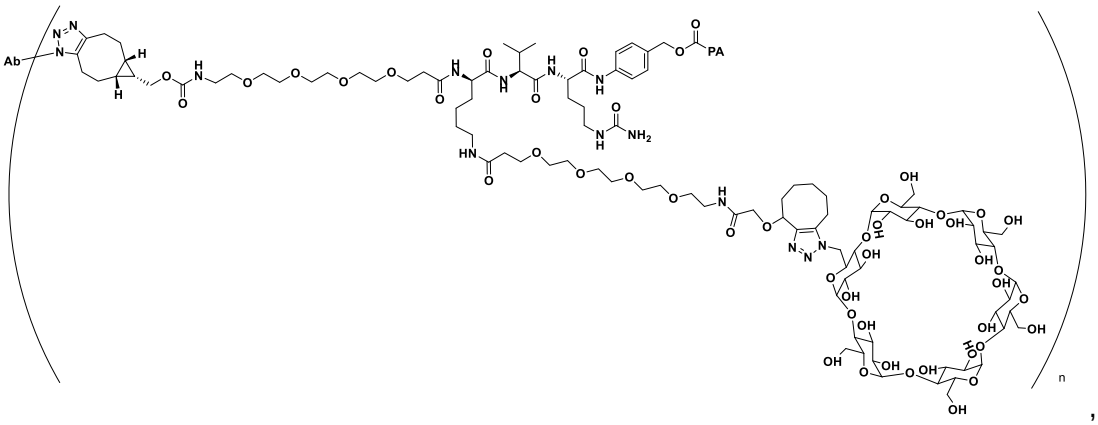

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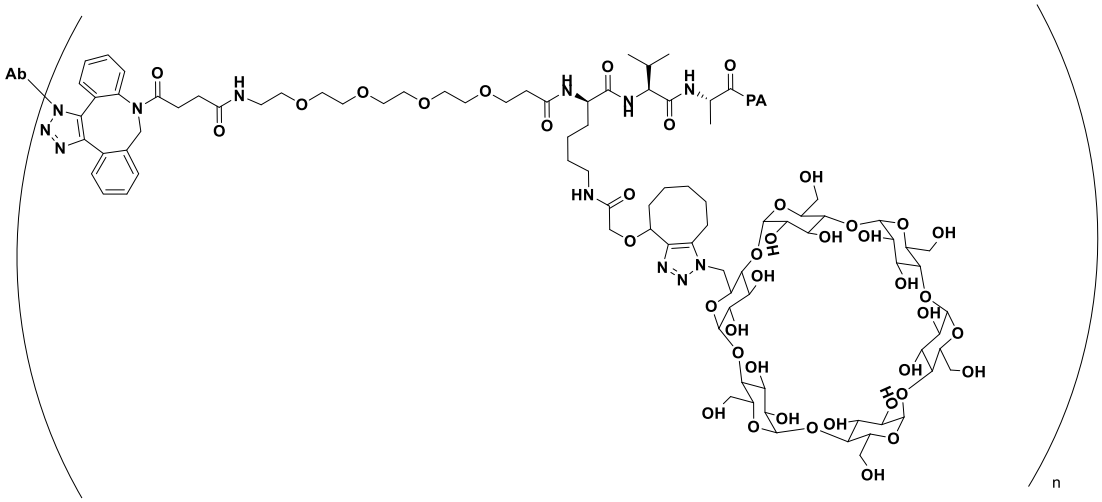

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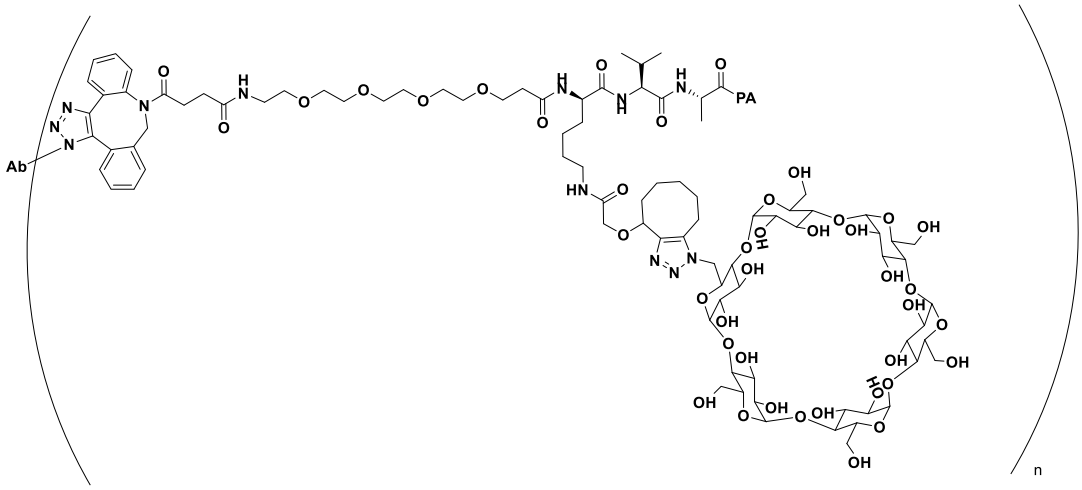

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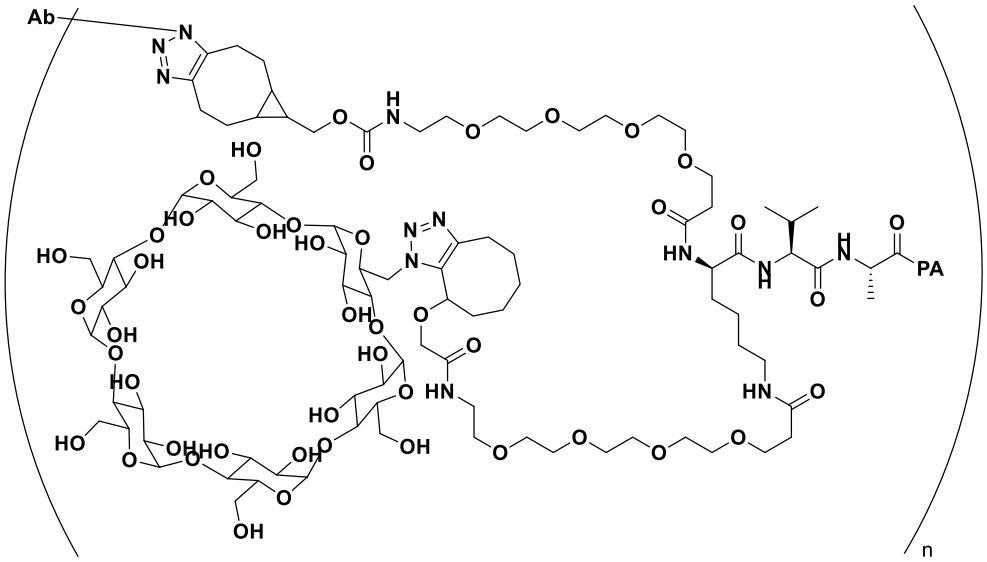
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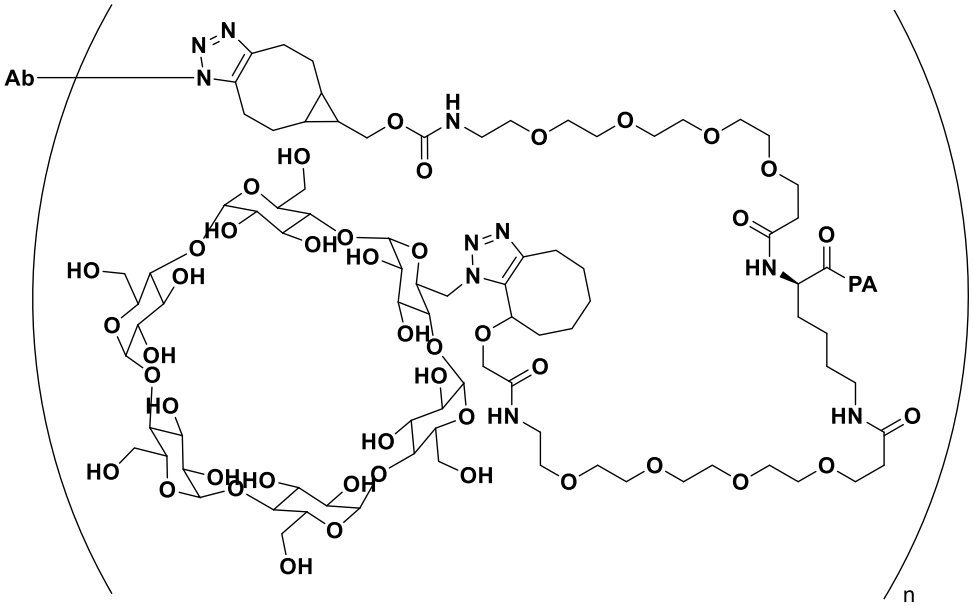
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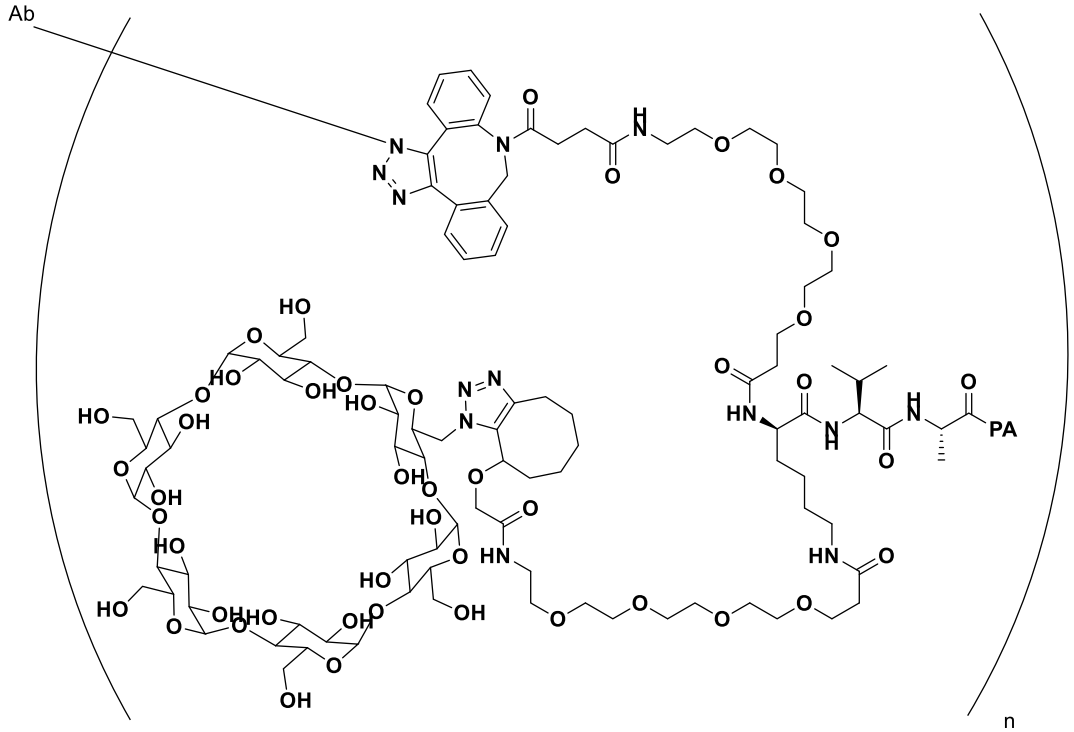
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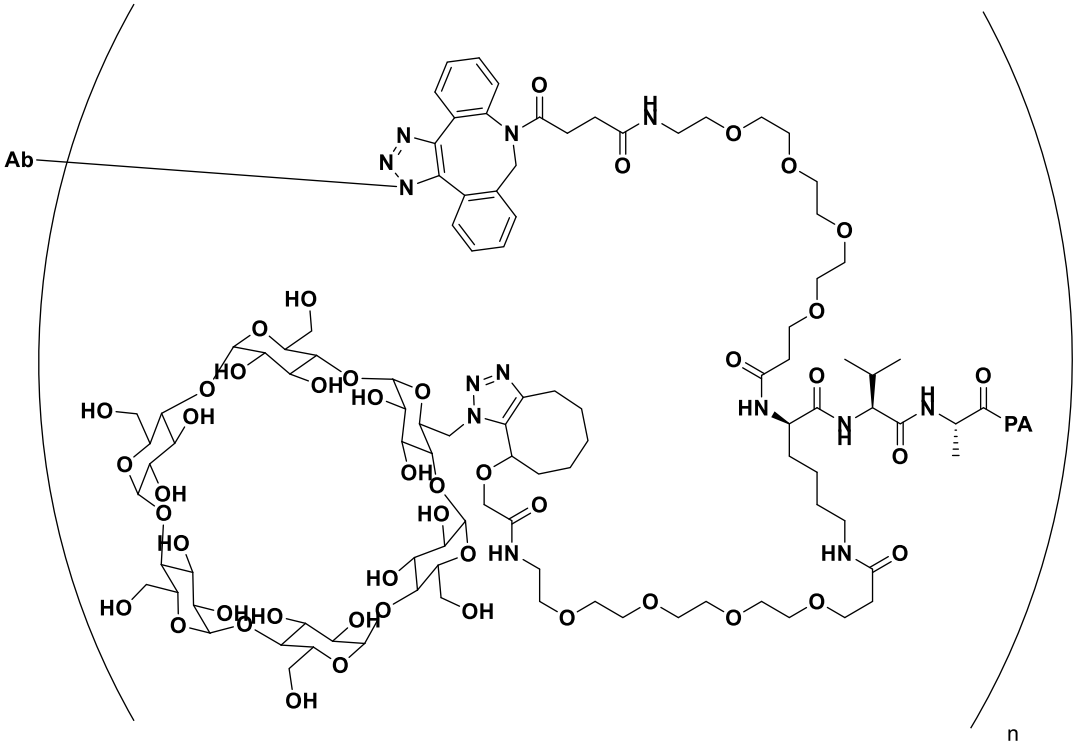
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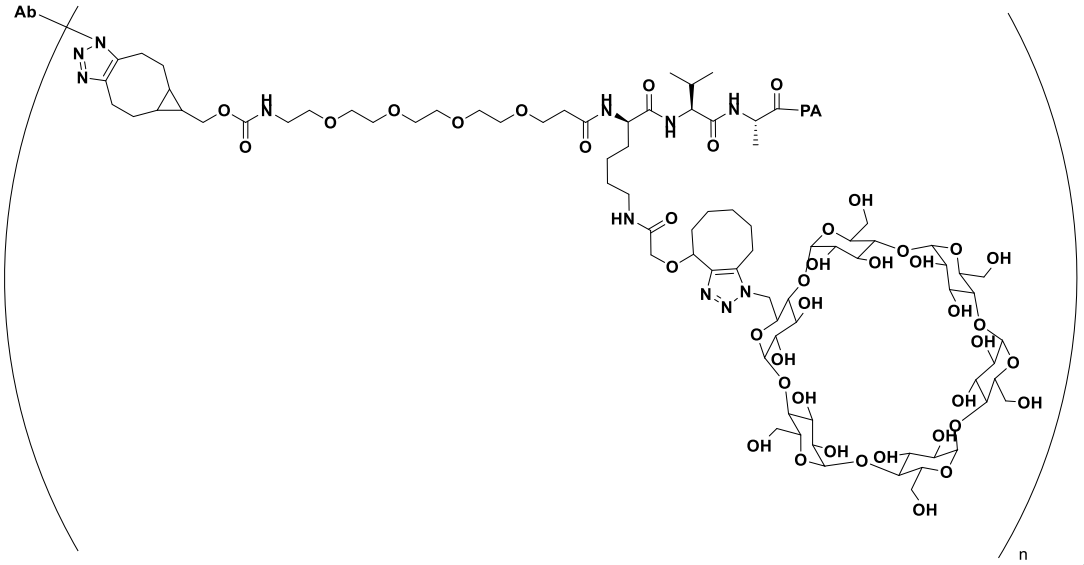

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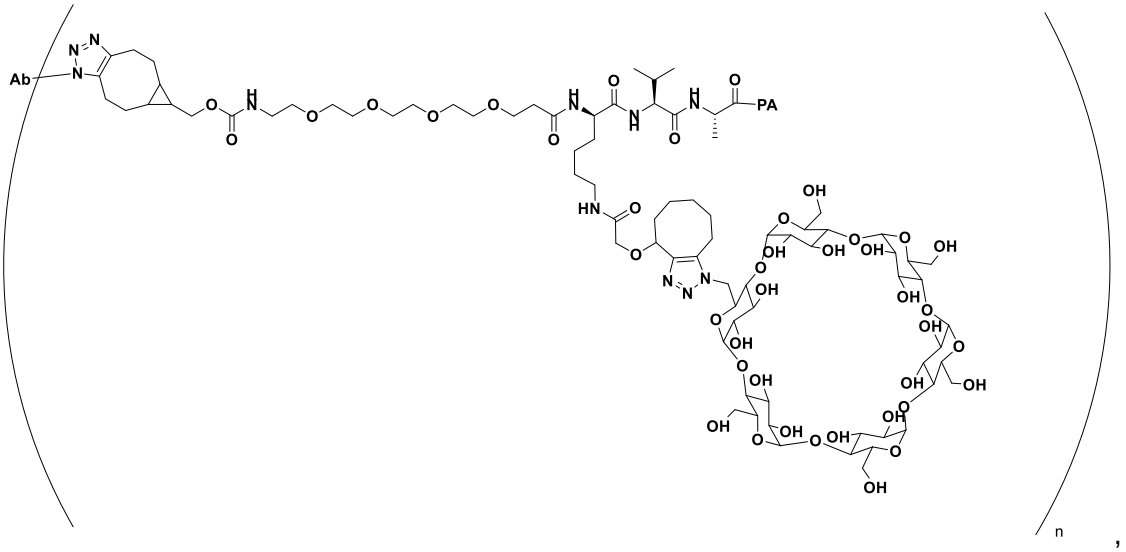

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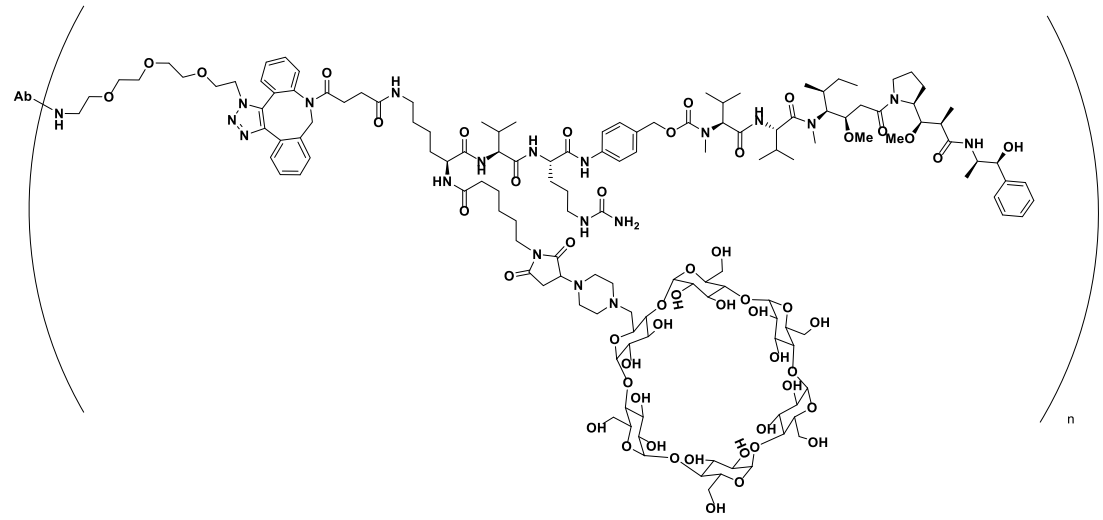
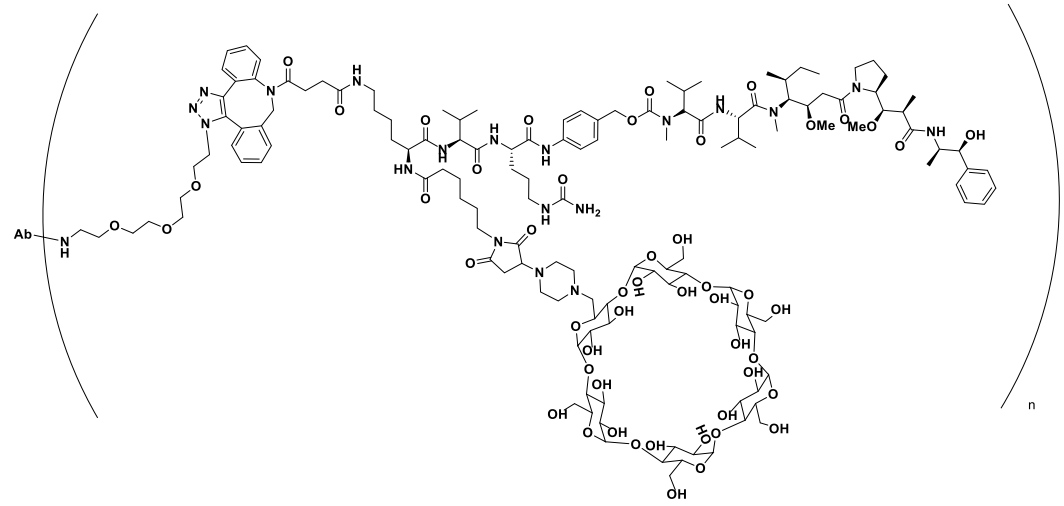
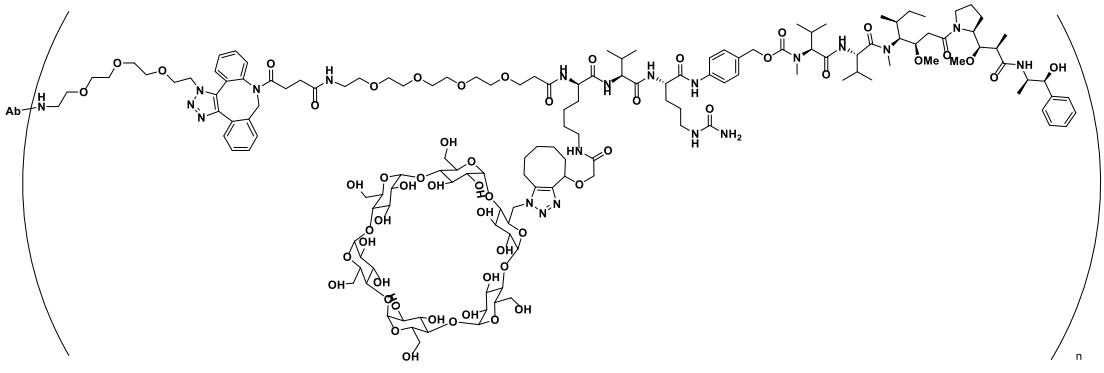
or stereoisomeric form, triazole linkage regioisomer thereof, mixture of triazole linkage regioisomers thereof, or pharmaceutically acceptable salt thereof,

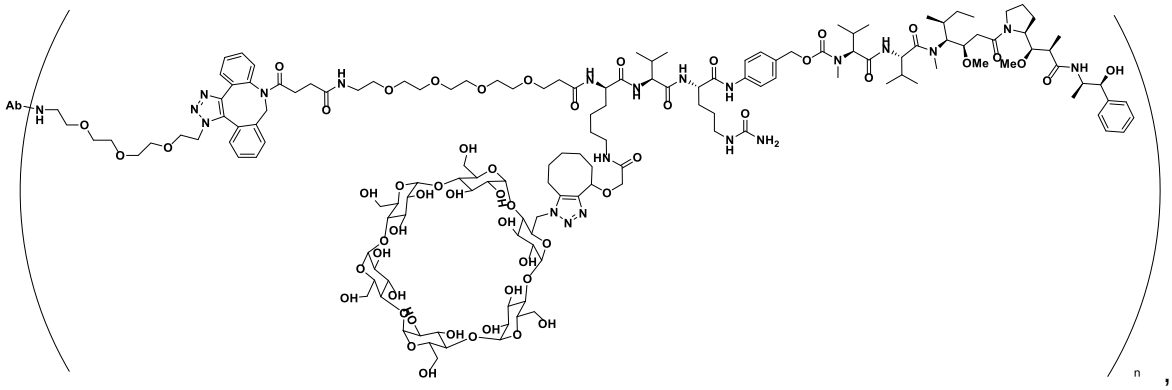
wherein Ab is the antibody or antigen-binding fragment thereof;
PA is the payload moiety; and
n is an integer from 1 to 30.

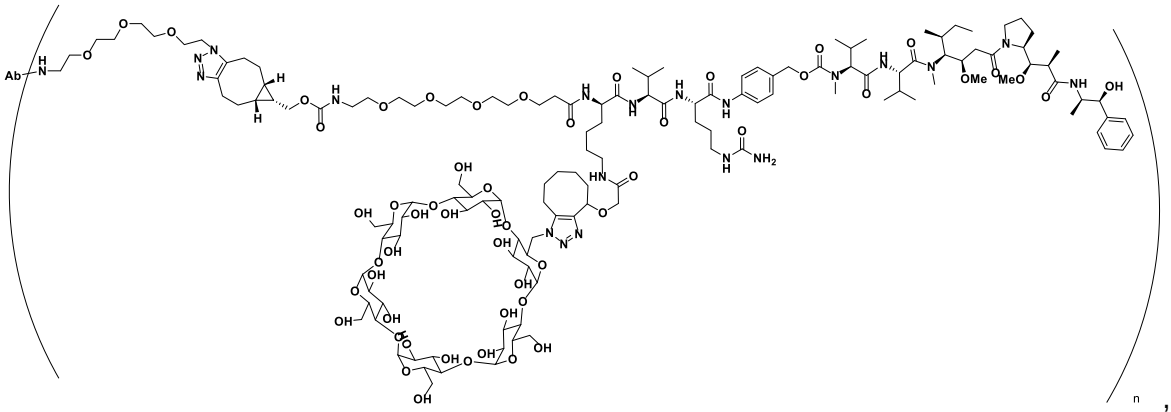
31. The compound of claim 1, wherein the compound is selected from:

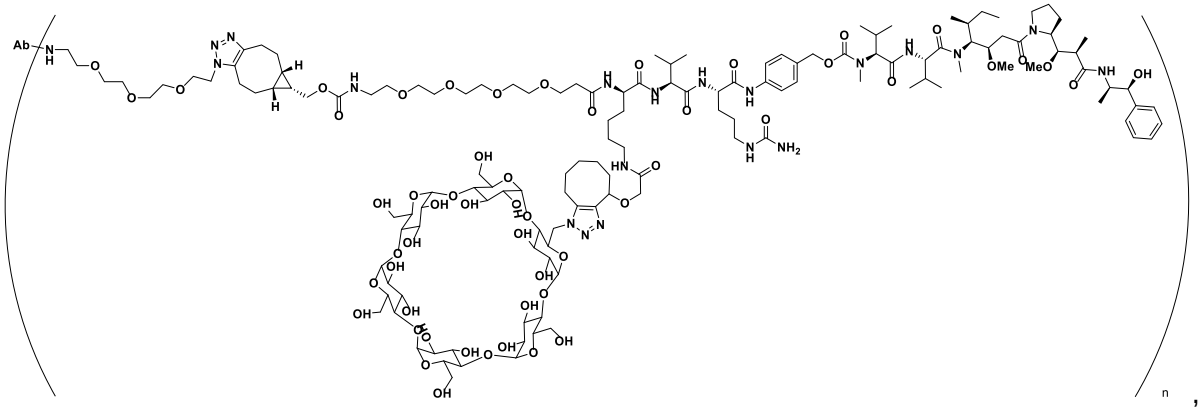


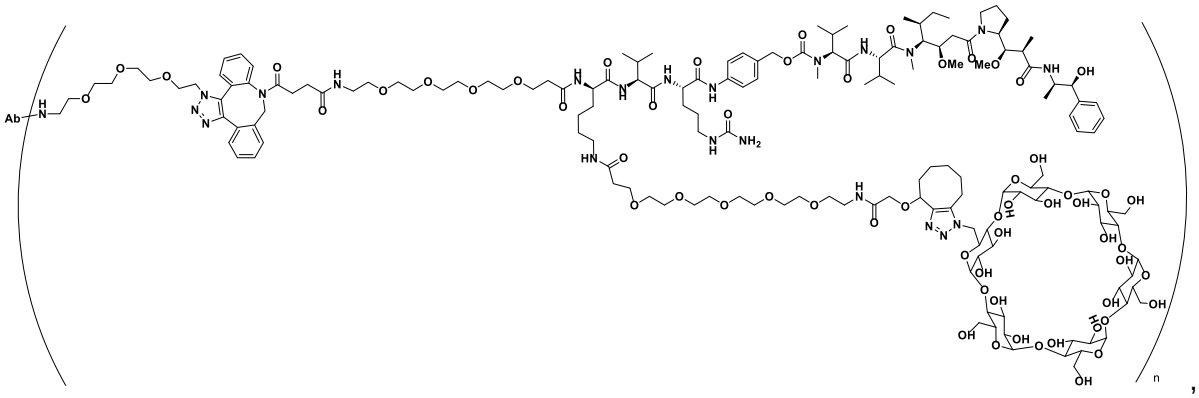












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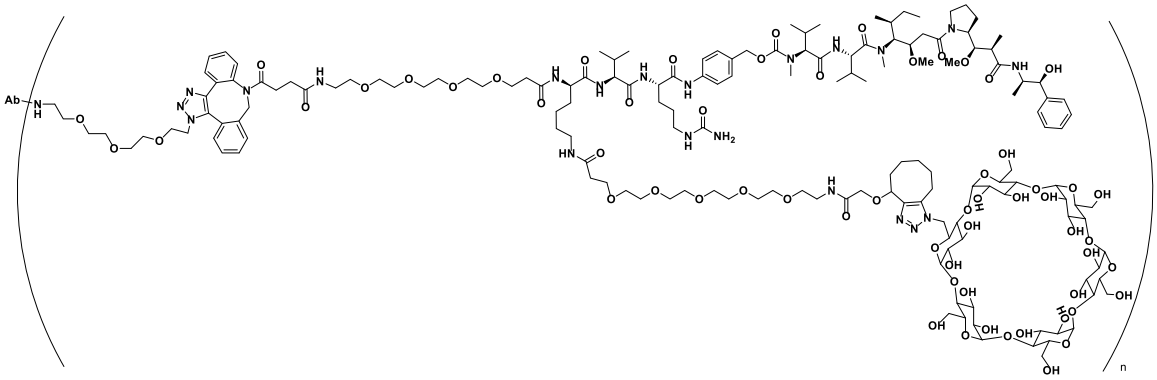

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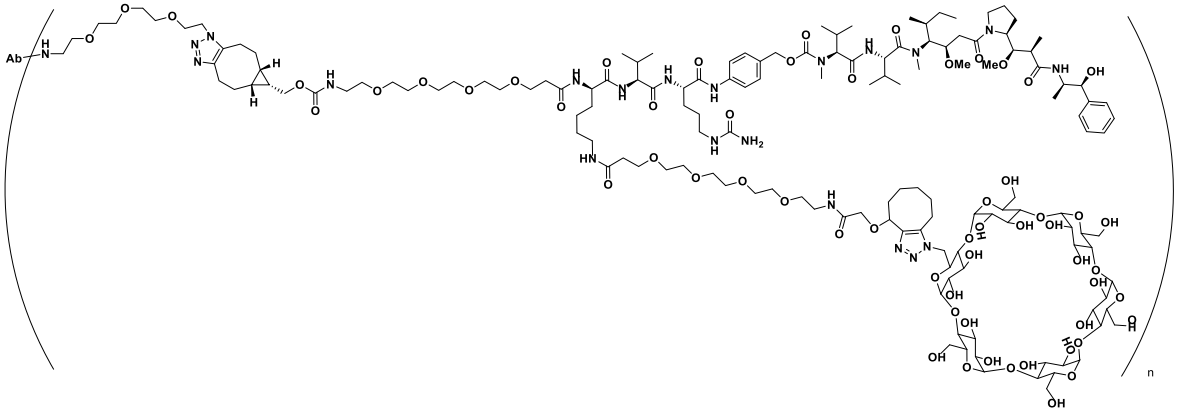

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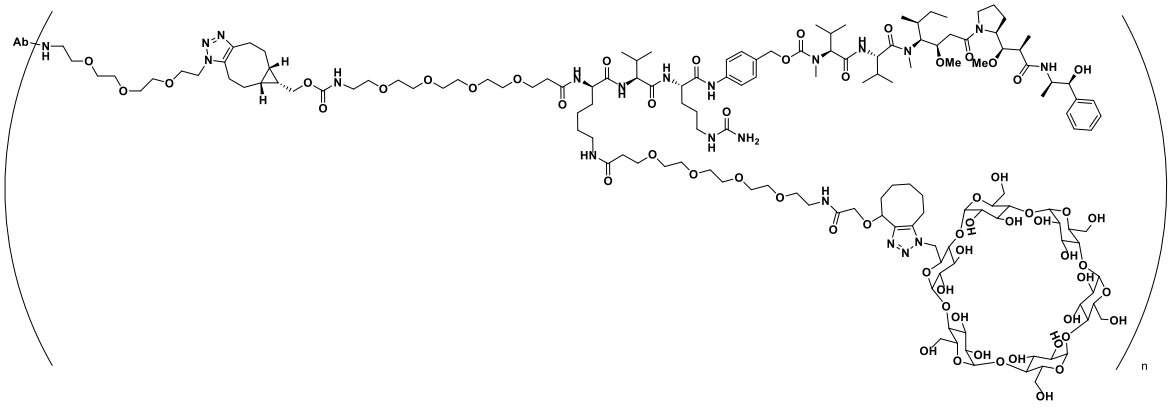

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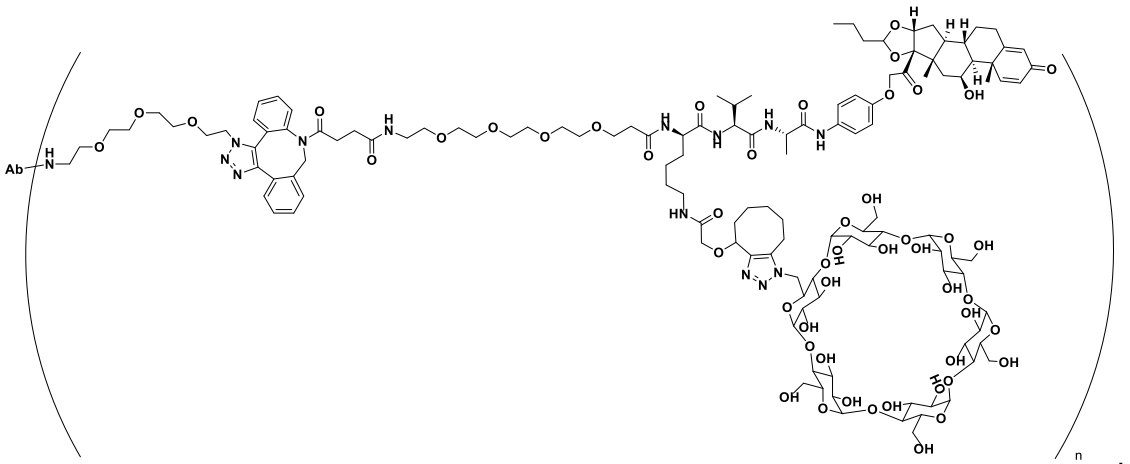

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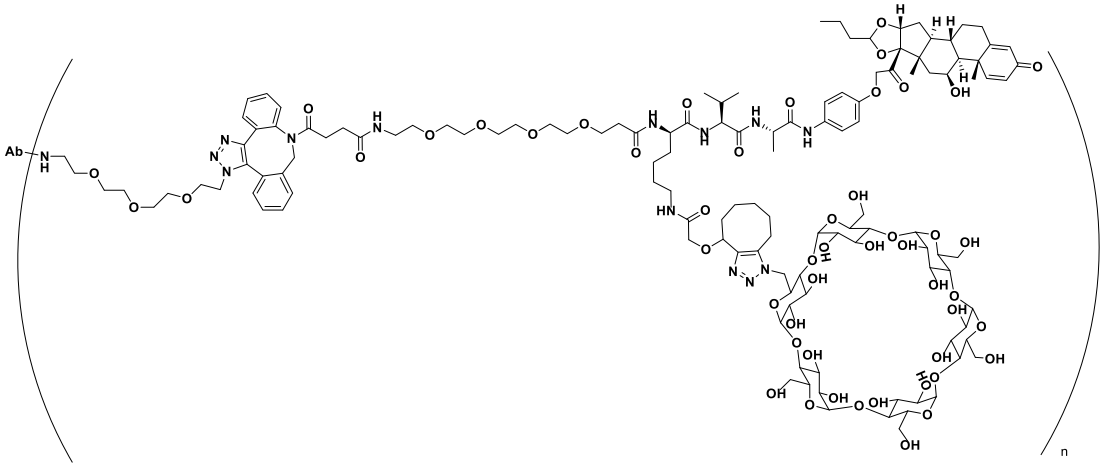

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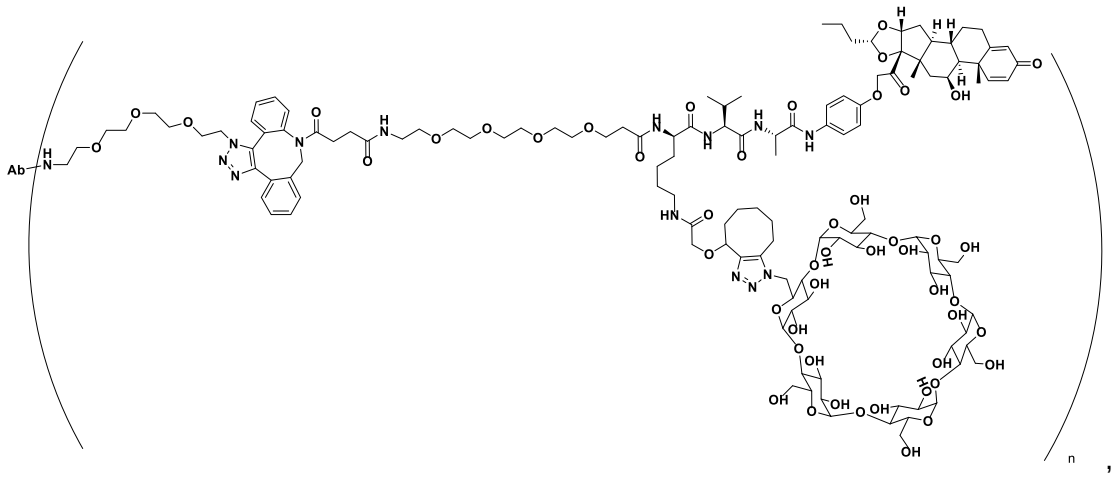

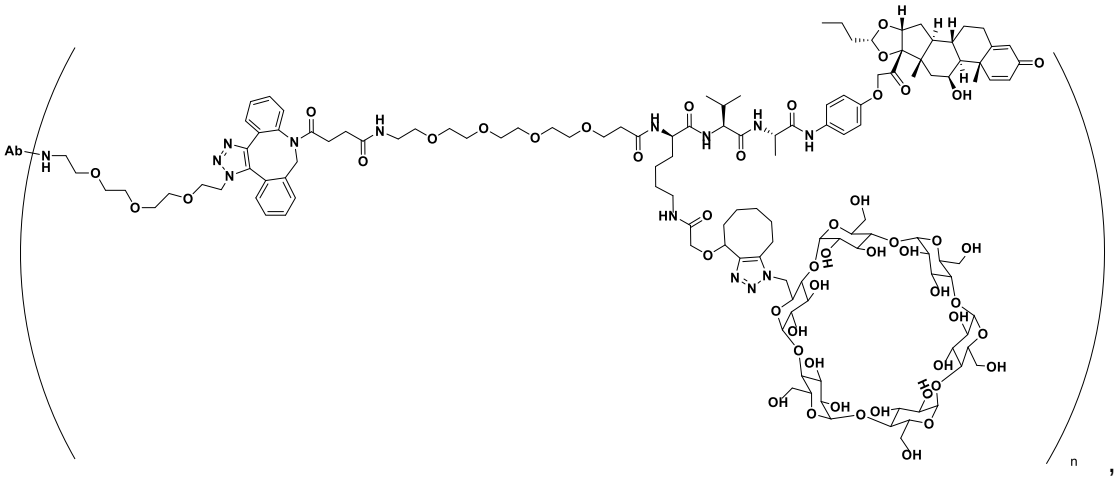

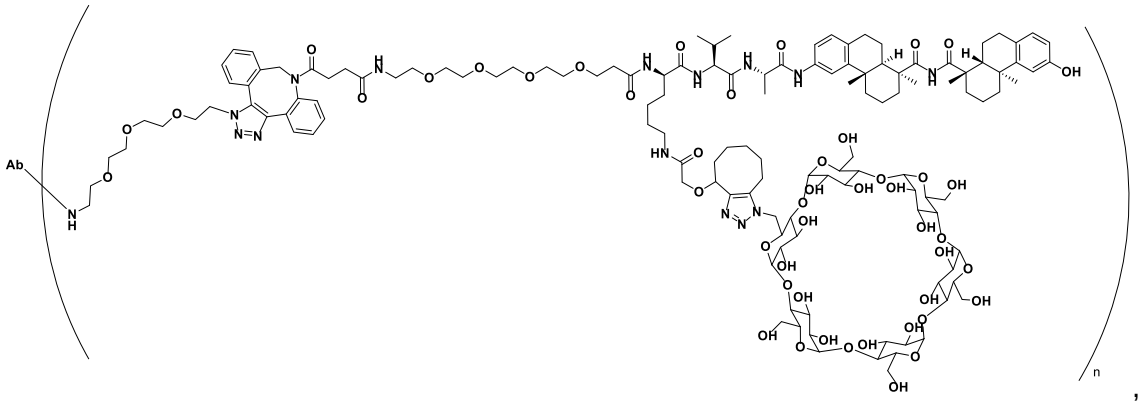

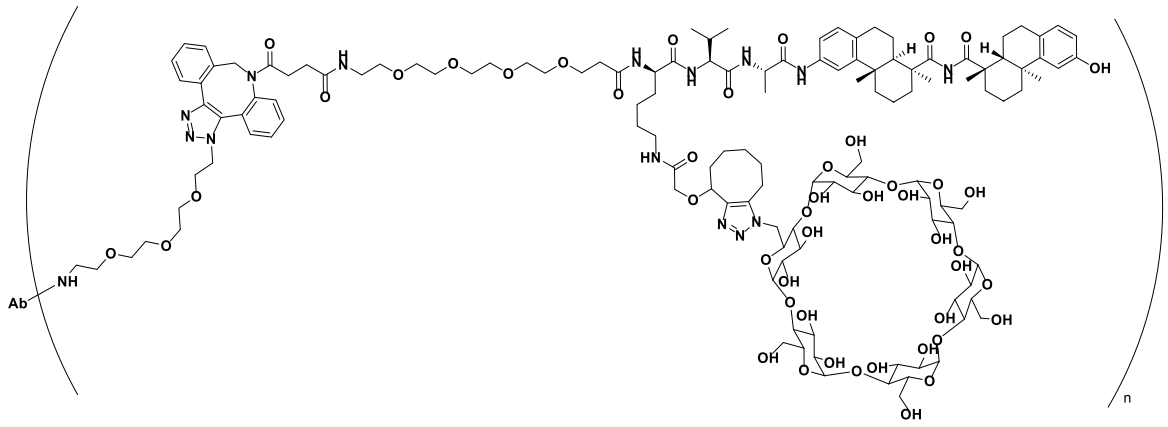

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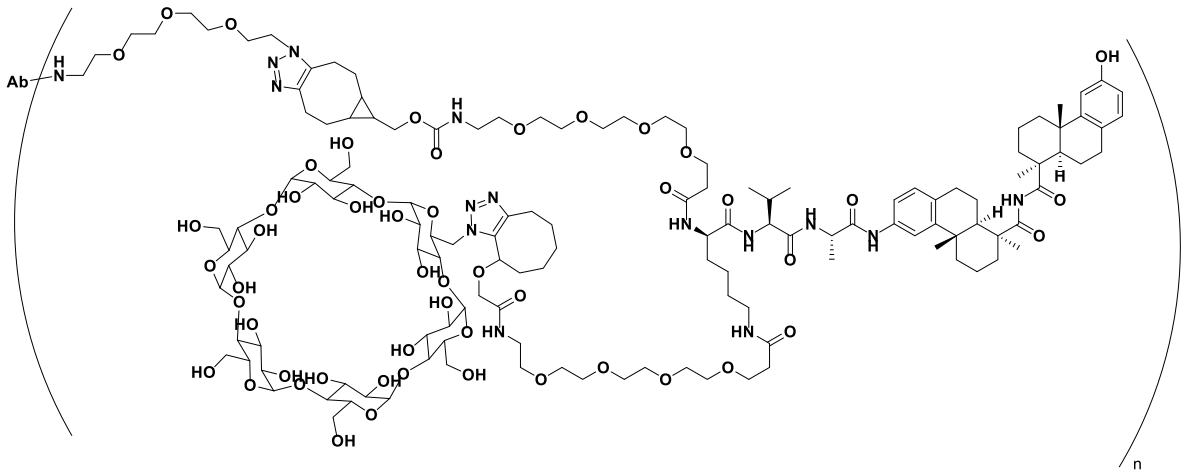

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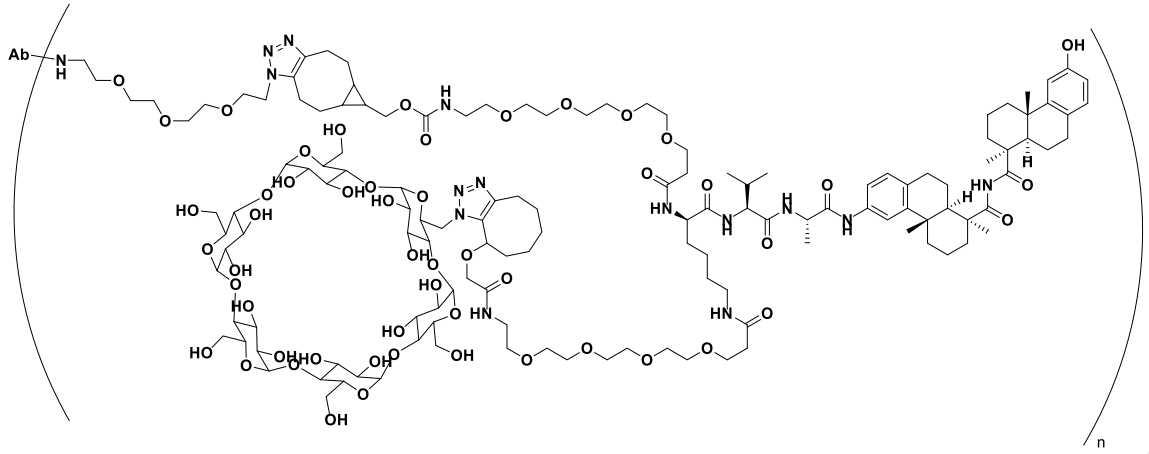

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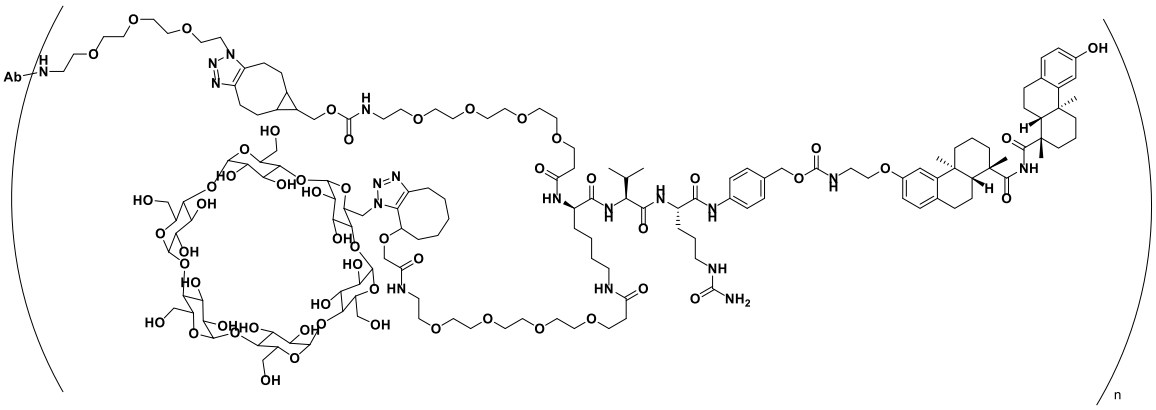

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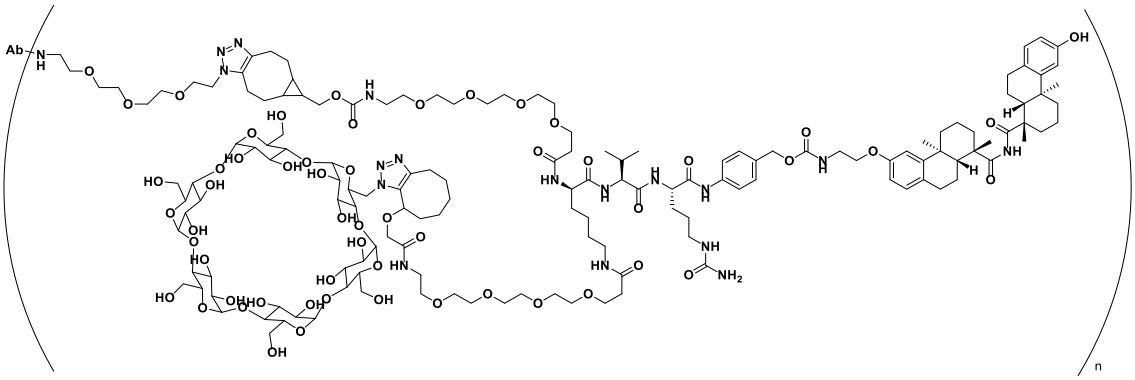

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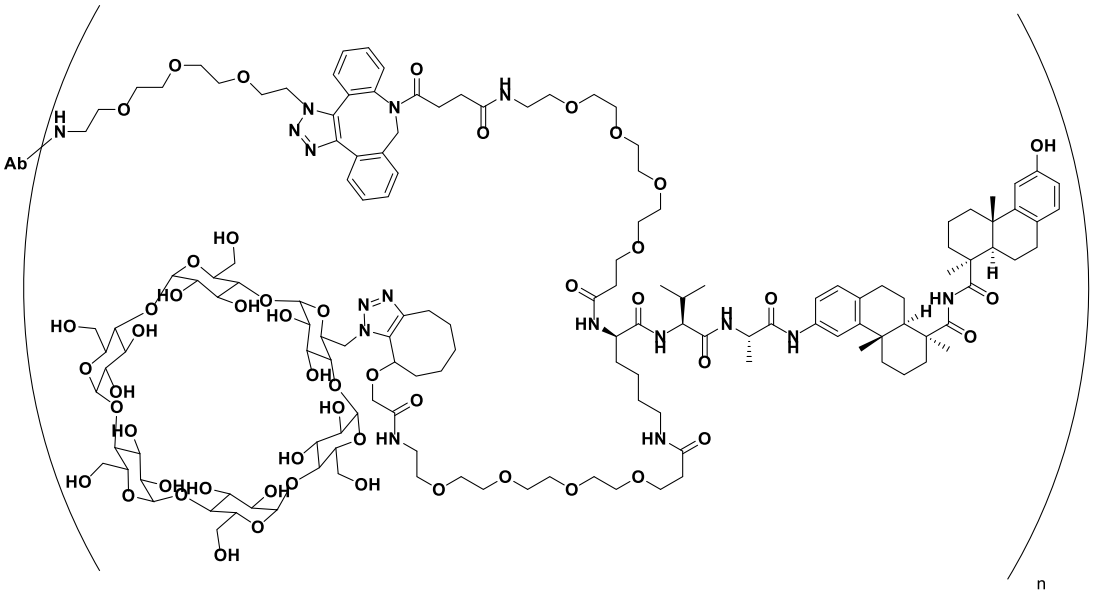

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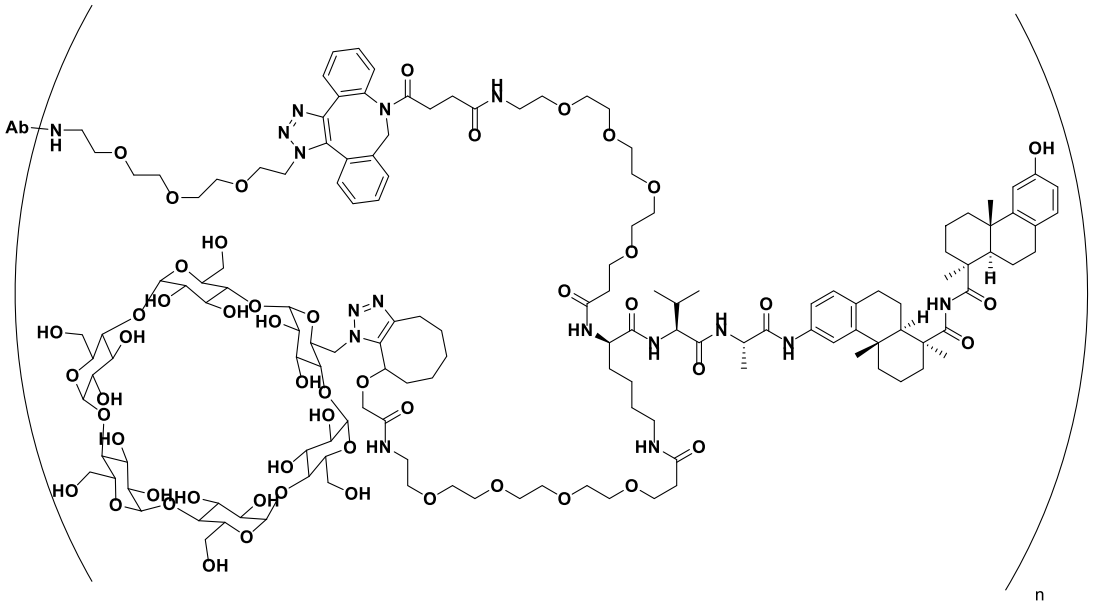

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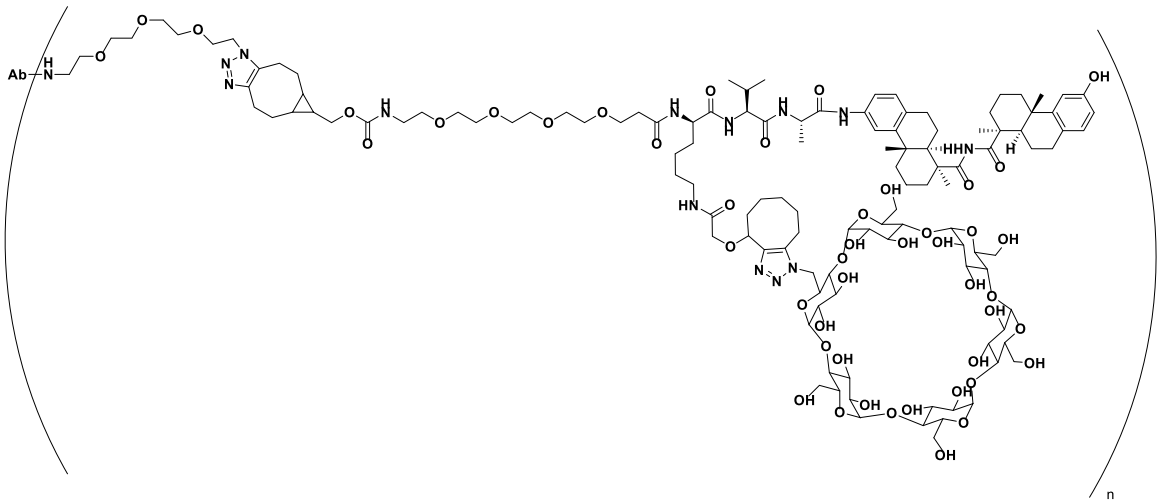

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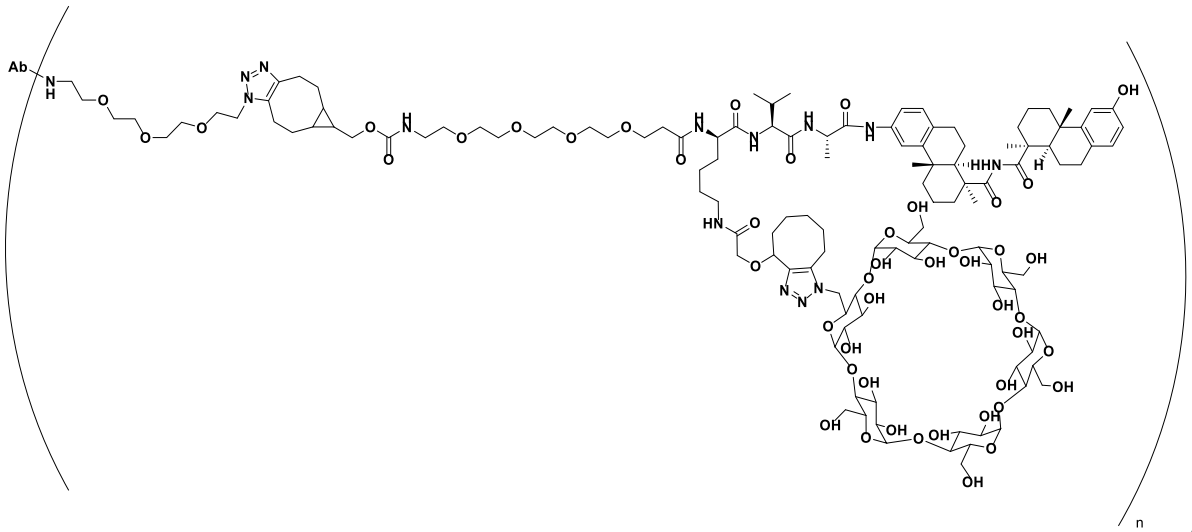

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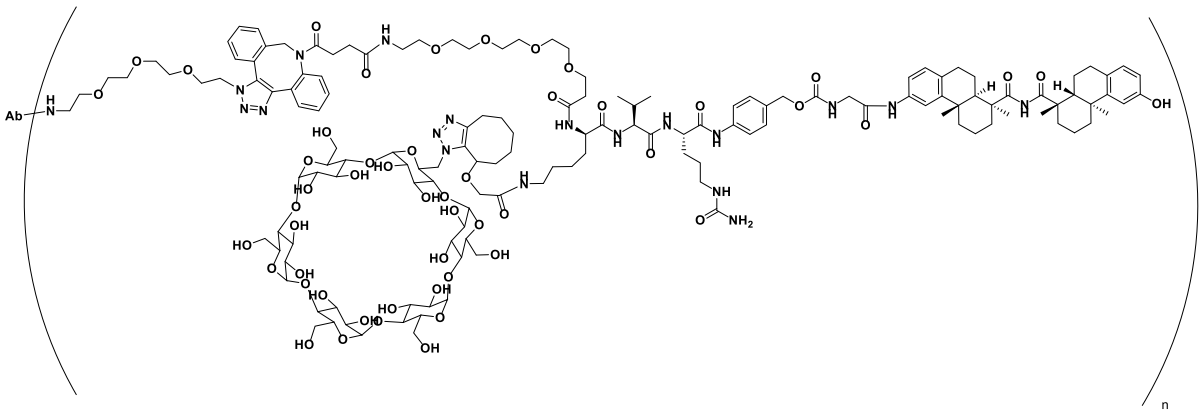

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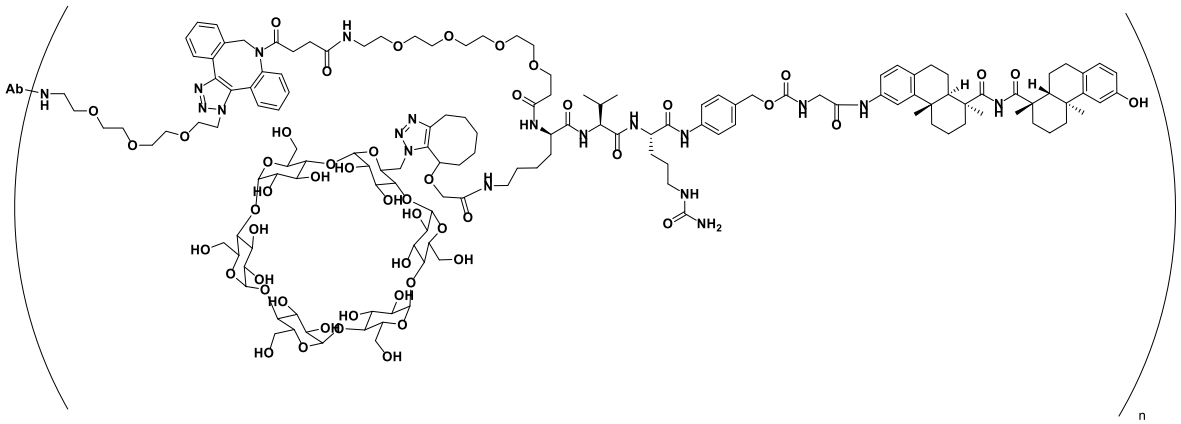

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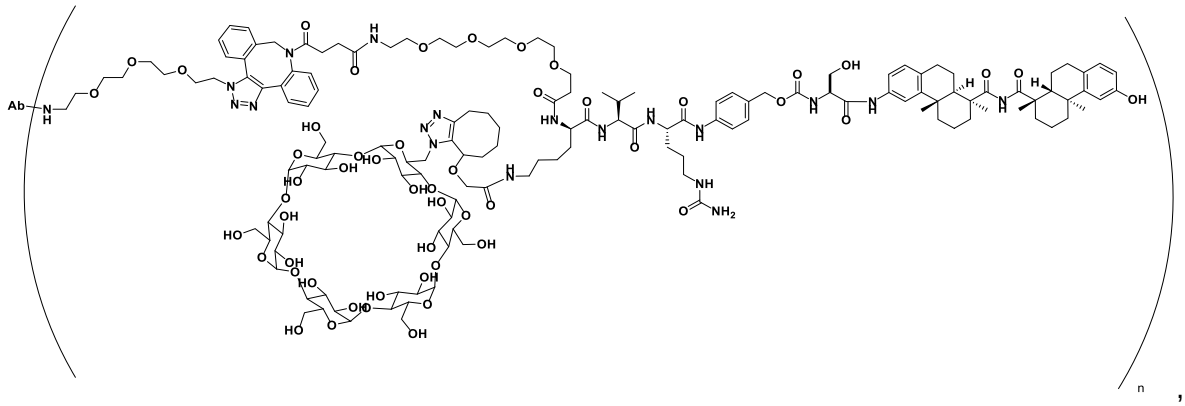

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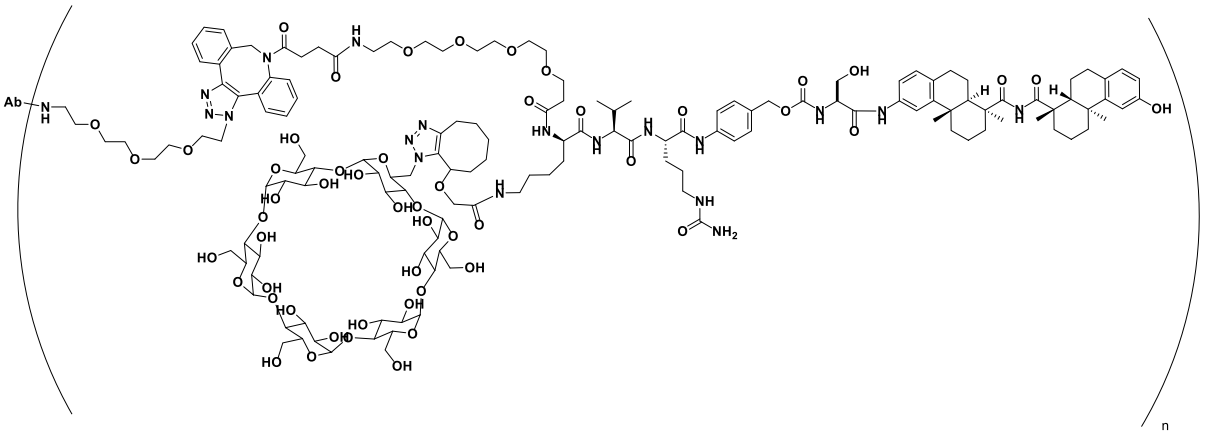

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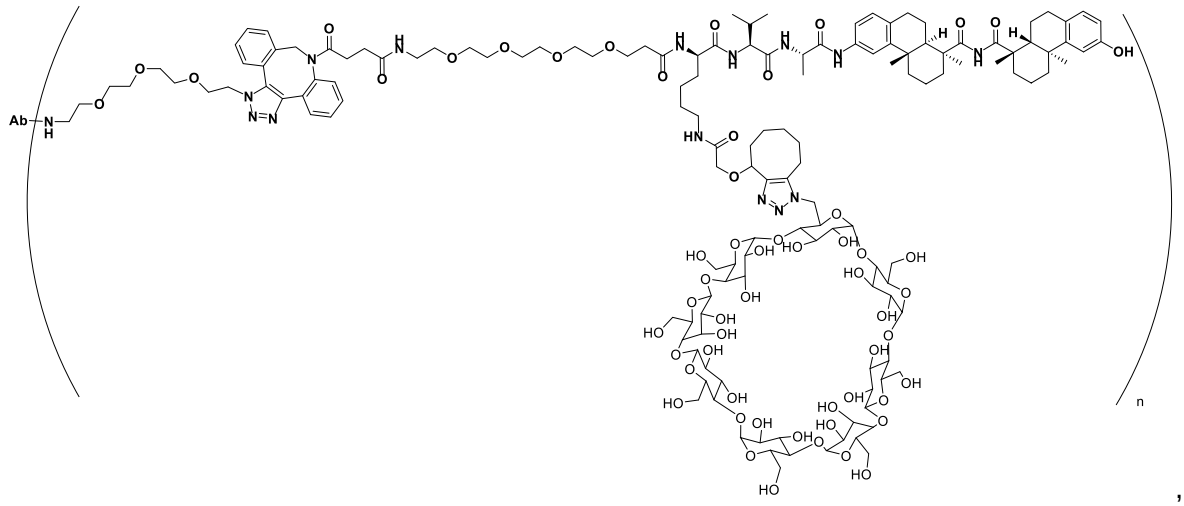

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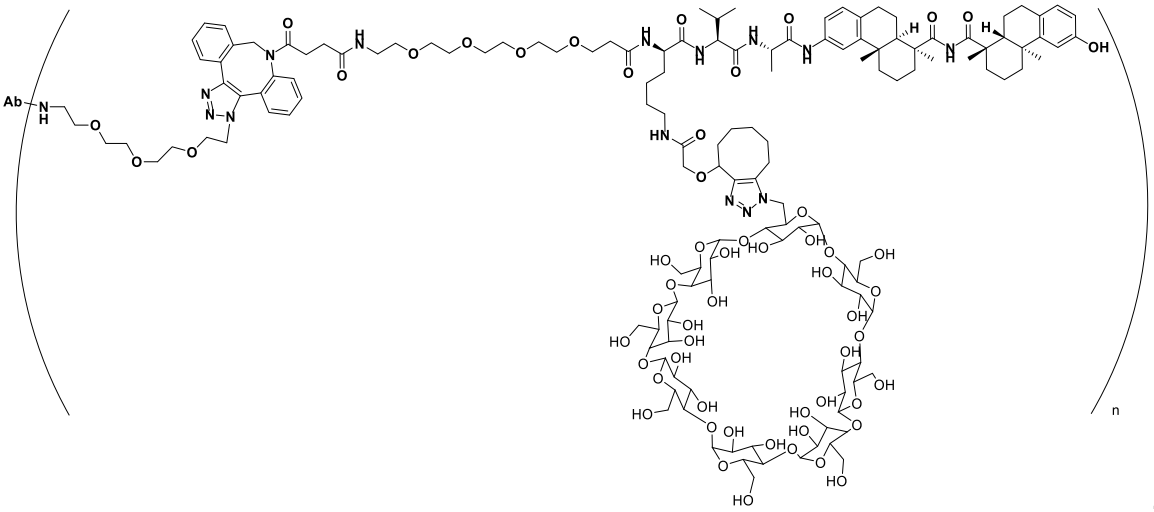

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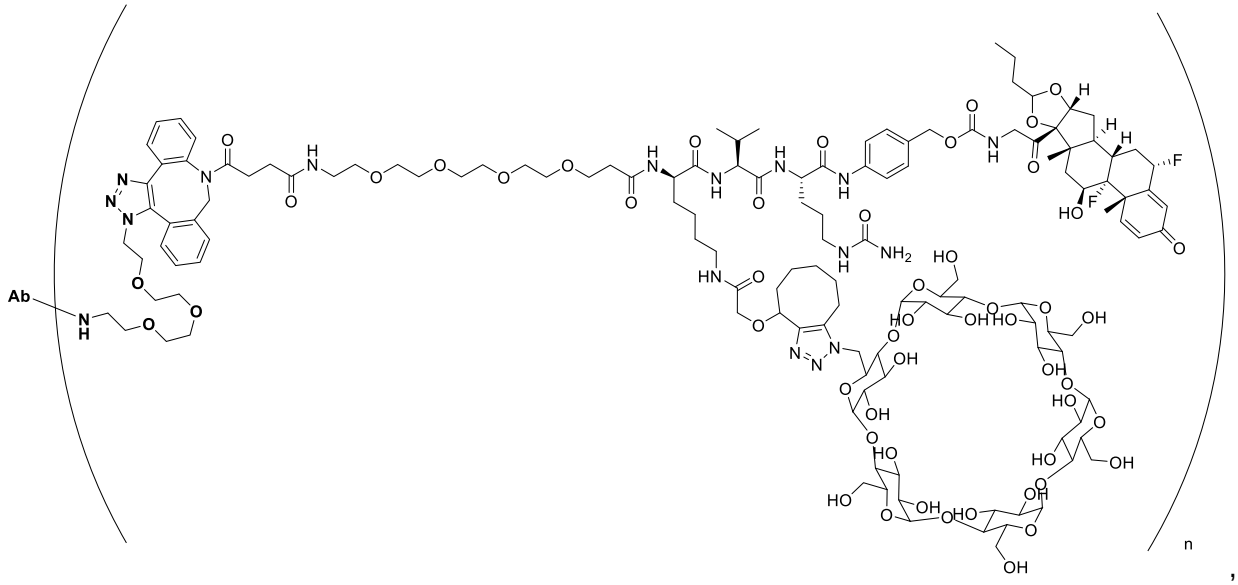

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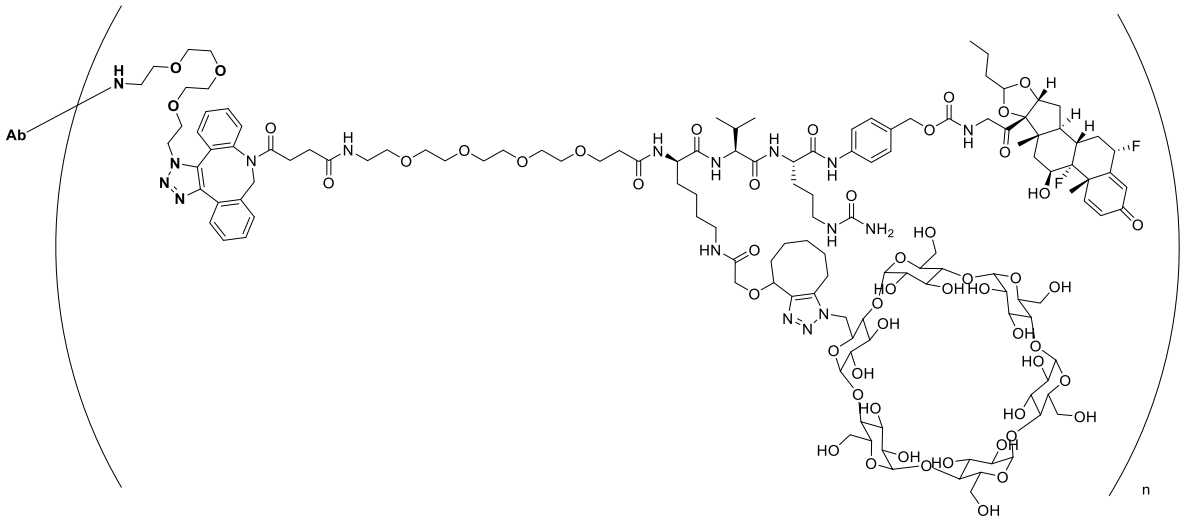

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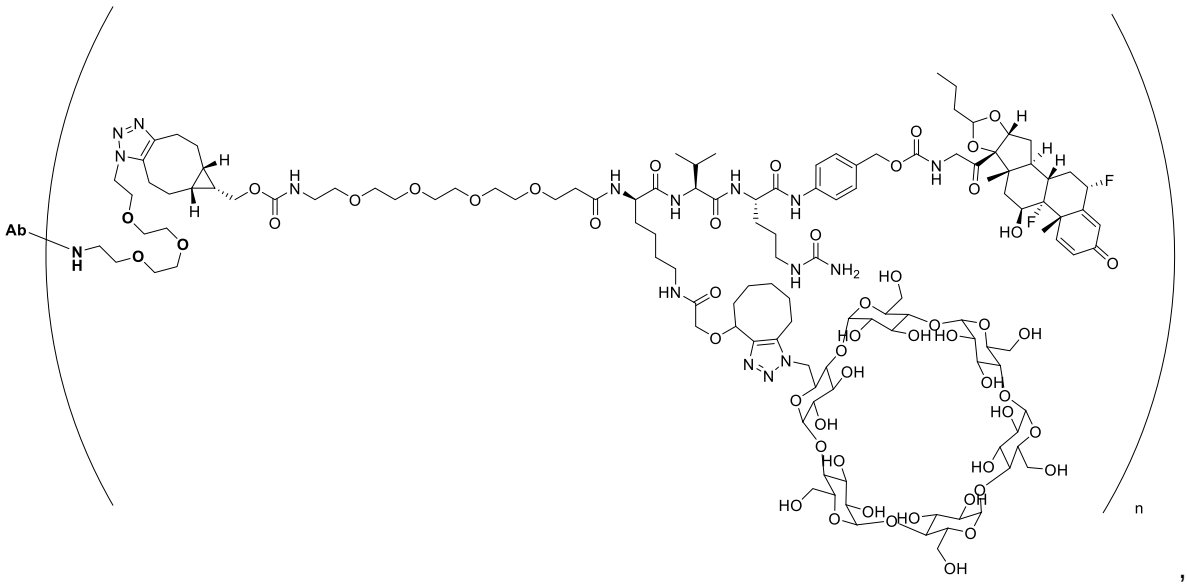

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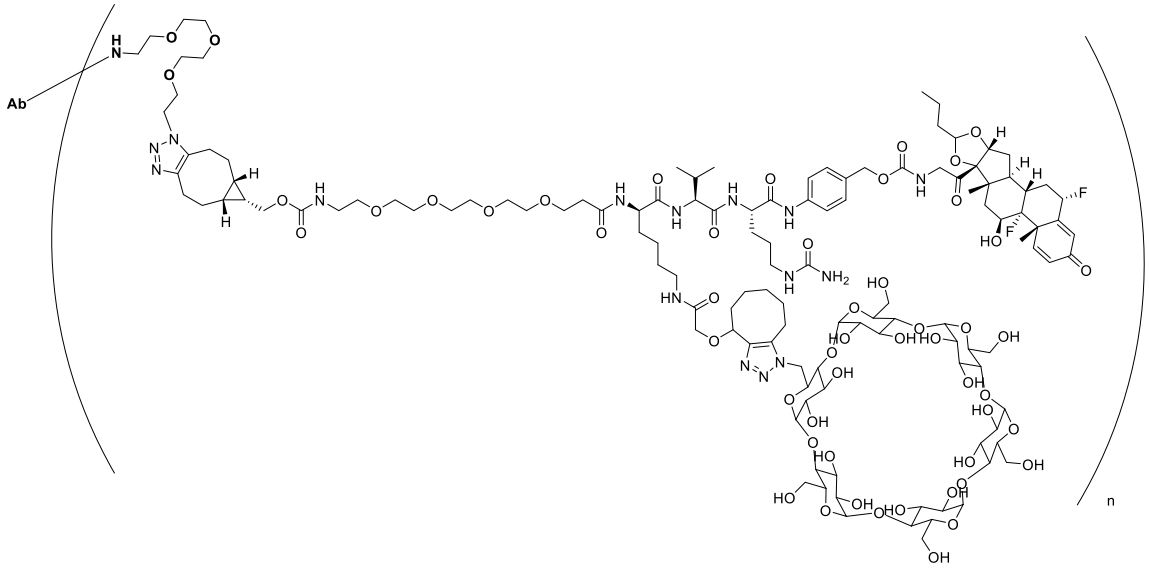

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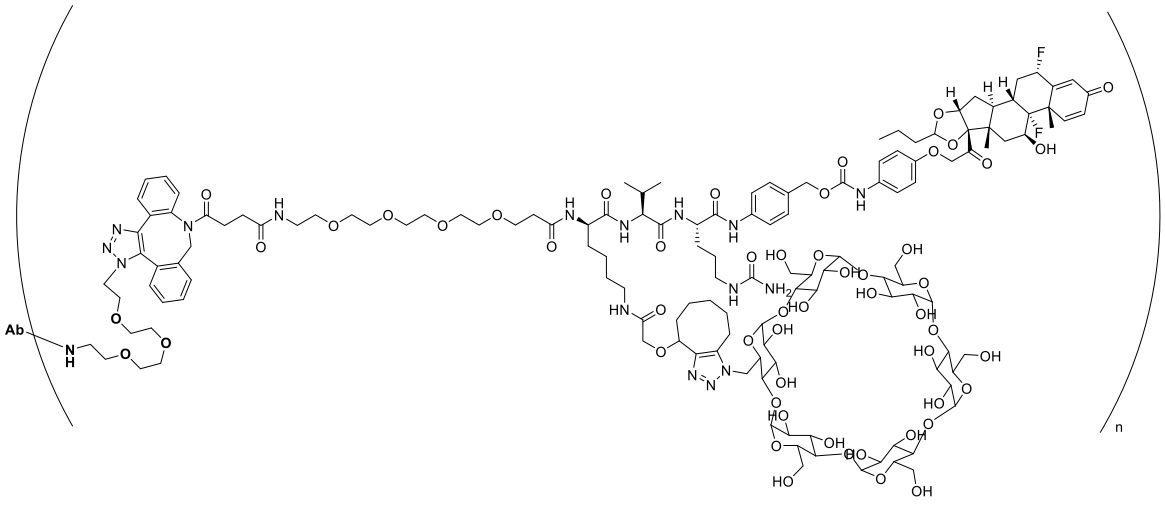

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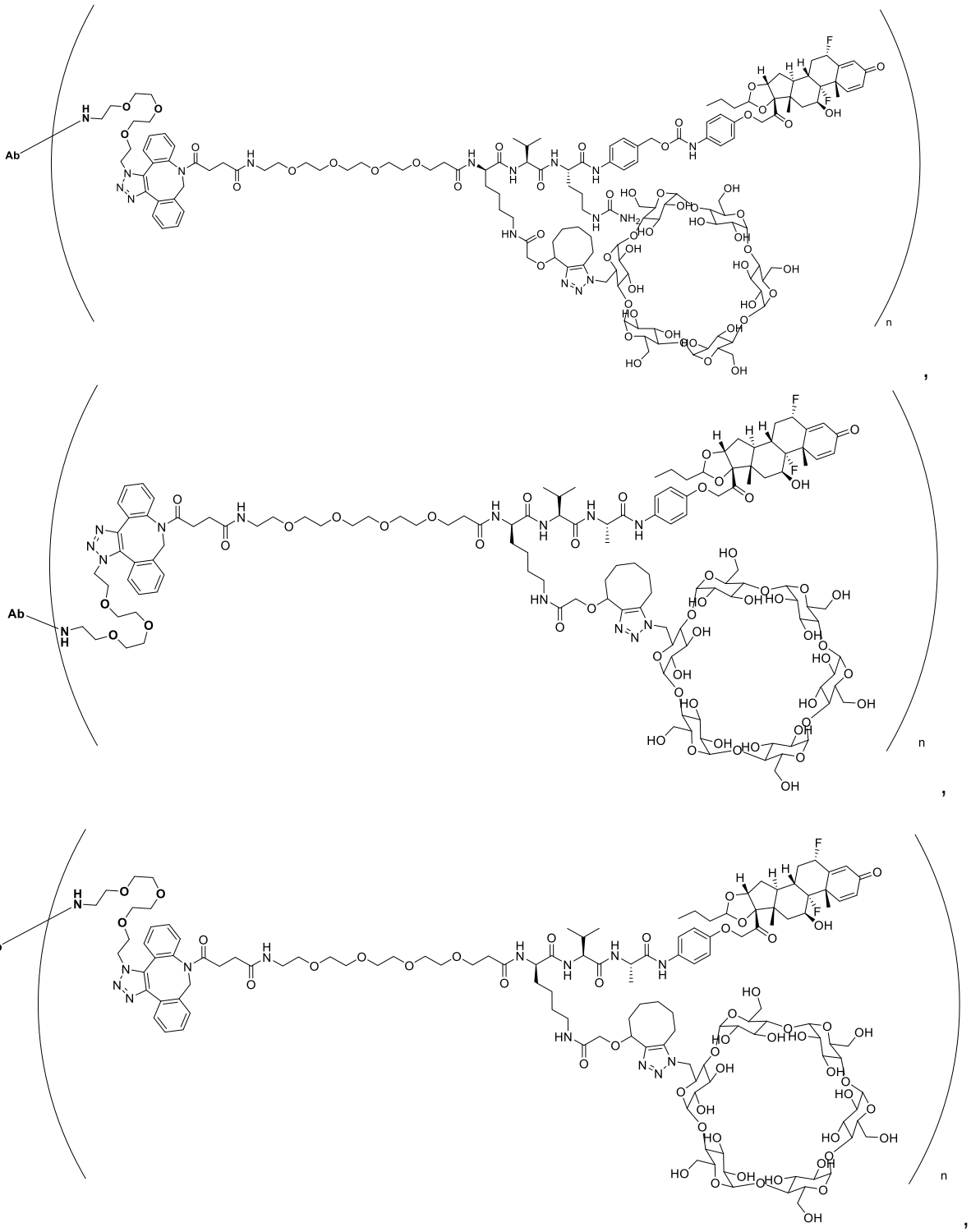


or stereoisomeric form, triazole linkage regioisomer thereof, mixture of triazole linkage regioisomers thereof, or pharmaceutically acceptable salt thereof,

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

32. A pharmaceutical composition comprising the compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

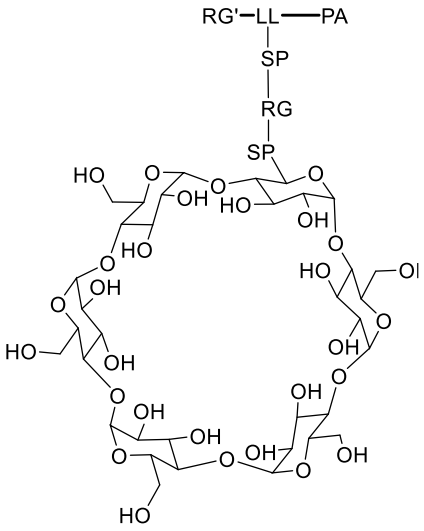
33. A compound of any one of claims 1-31 or the composition of claim 32 for use in the treatment of a disease or disorder in a patient in need thereof.

34. A compound comprising a reactive linker, at least one payload moiety (PA), at least one cyclodextrin moiety (CD), and a covalent linker, wherein said covalent linker is bonded to each of said reactive linker, said payload moiety, and said cyclodextrin moiety;

wherein the at least one payload moiety is a residue of an auristatin or a residue of a maytansinoid;

wherein the compound comprises at least one feature that is selected from the group consisting of:

(i) the compound is according to Formula (**IIa**):



(**IIa**)

wherein:

L is composed of LL, SP, and RG;

RG' is a reactive group;

RG is a reactive linker residue;

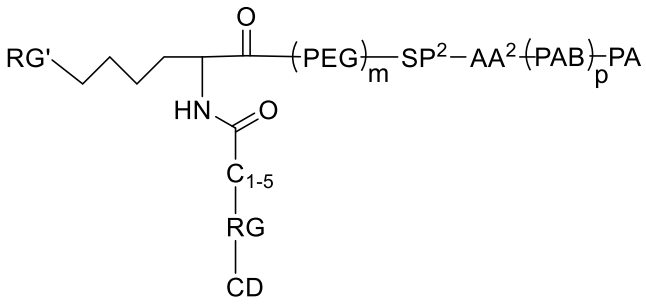
LL is a trivalent linker;

SP is, independently in each instance, absent or a spacer group; and

PA is the payload moiety;

and

(ii) the compound is according to Formula (**IIe**):



(IIe)

wherein:

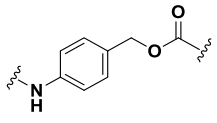
RG' is a reactive group;

SP^2 is, independently in each instance, absent or a spacer group residue;

AA^1 is a trivalent linker comprising an amino acid residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

C$_{1-5}$ is an alkyl spacer group of 1 to 5 carbons;

CD is, independently in each instance, absent or a cyclodextrin moiety, wherein at least one CD is present;

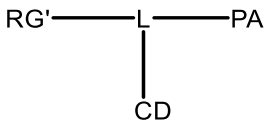
subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

35. A compound comprising a reactive linker, at least one payload moiety (PA), at least one cyclodextrin moiety (CD), and a covalent linker; wherein said covalent linker is bonded to each of said reactive linker, said payload moiety, and said cyclodextrin moiety;

wherein the compound is according to Formula (**II**):



(**II**)

wherein:

RG' is a reactive group;

L is a trivalent linker;

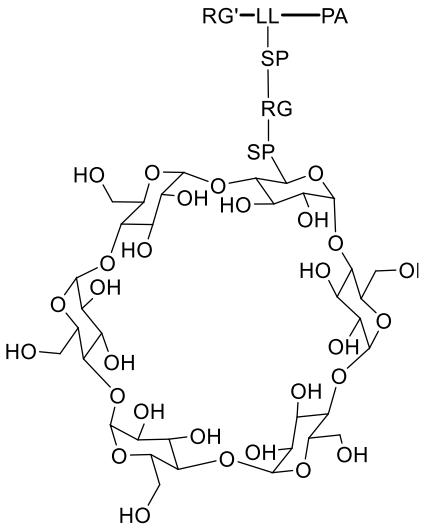
CD is a cyclodextrin moiety; and

PA is a payload residue**;**

PA is the payload moiety;

wherein the compound comprises at least one feature that is selected from the group consisting of:

(i) the compound is according to Formula (**IIa**):

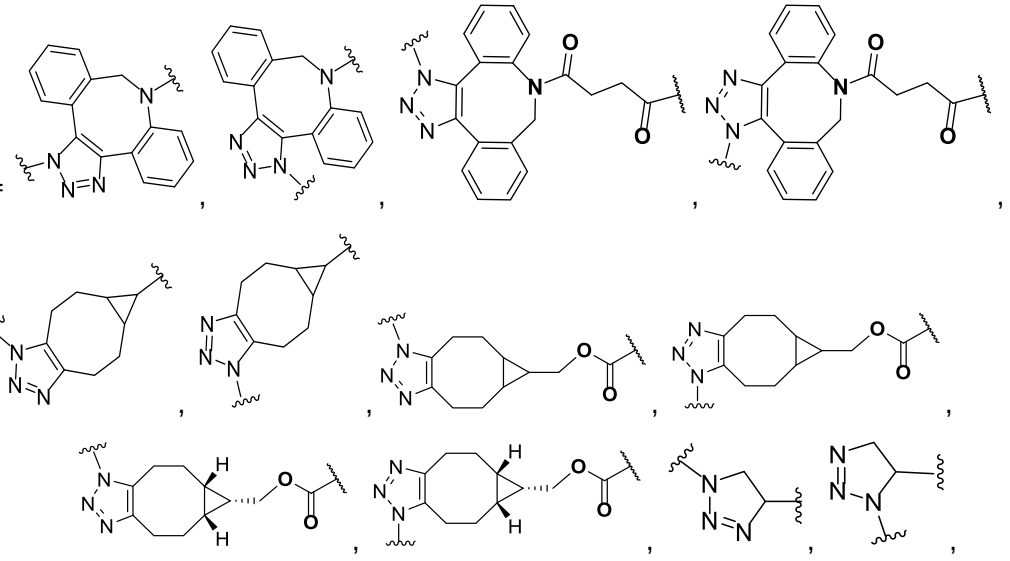


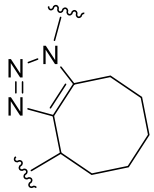
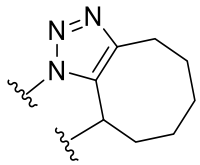
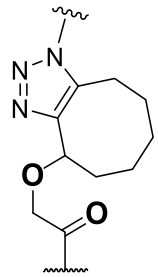
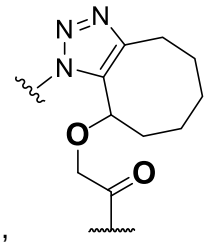
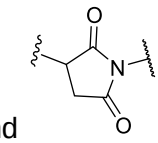
(IIa)

wherein:

L is composed of LL, SP, and RG;

RG' is the reactive group;

RG is a reactive linker residue; wherein RG is selected from the group consisting of  .

 ,  ,  ,  , and  , wherein the  indicates the atom through which the **RG** is bonded to the adjacent groups in the formula;

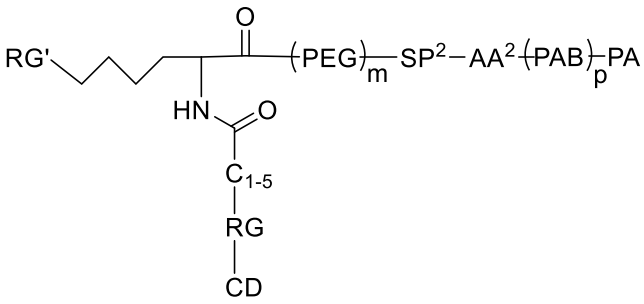
LL is a trivalent linker;

SP is, independently in each instance, absent or a spacer group; and

PA is the payload moiety;

and

(ii) the compound is according to Formula (**IIe**):



(IIe)

wherein:

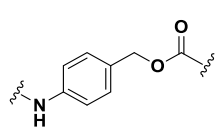
RG' is the reactive group;

SP² is, independently in each instance, absent or a spacer group residue;

AA¹ is a trivalent linker comprising an amino acid residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

C_{1-5} is an alkyl spacer group of 1 to 5 carbons;

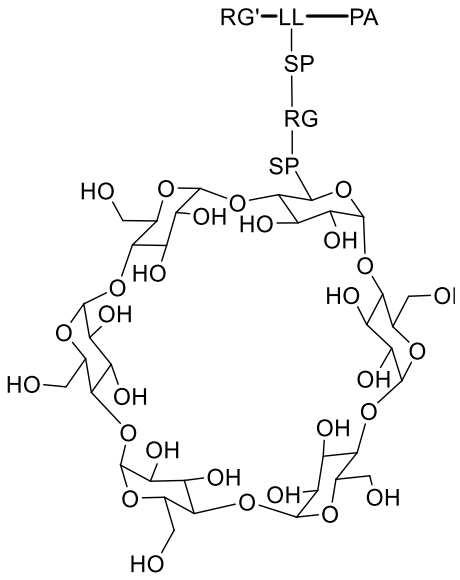
CD is, independently in each instance, absent or a cyclodextrin moiety, wherein at least one CD is present;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

36. The compound of any one of claims 34 or 35, according to Formula (**IIa**):



(**IIa**)

wherein:

L comprises LL, SP, and RG;

RG' is the reactive group;

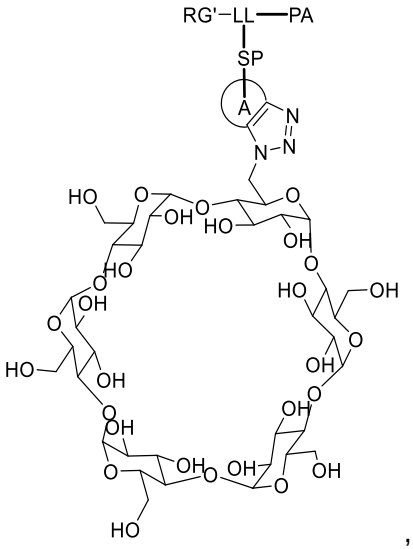
RG is a reactive linker residue;

LL is a trivalent linker;

SP is, independently in each instance, absent or a spacer group; and

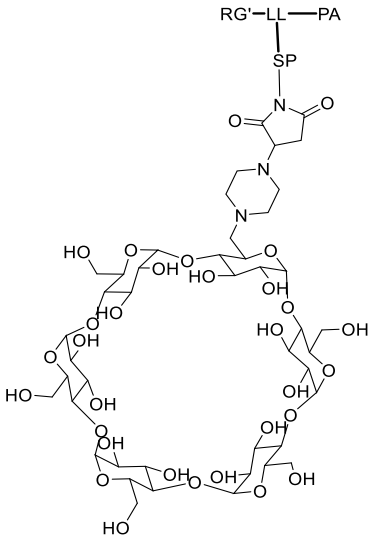
PA is the payload moiety.

37. The compound of any one of claims 34-36, according to formula (**IIb**) or (**IIc**):



(**IIb**)

,



(**IIc**)

wherein:

RG' is the reactive group;

LL is a trivalent linker;

SP is, independently in each instance, absent or is a spacer;

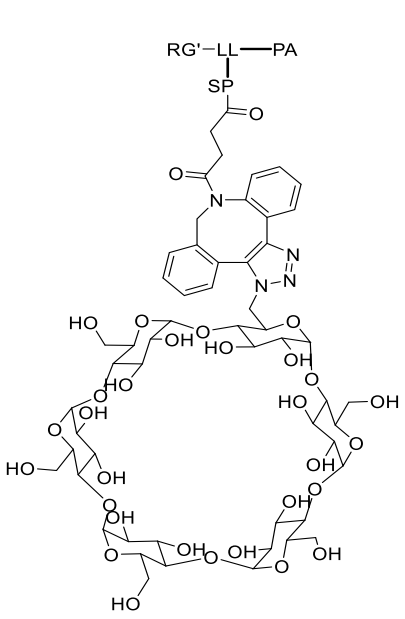
ring **A** is fused to the triazole and is selected from the group consisting of cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl;

wherein cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl are optionally substituted with alkyl, OH, or NR^aR^b, where each of R^a and R^b is alkyl or H;

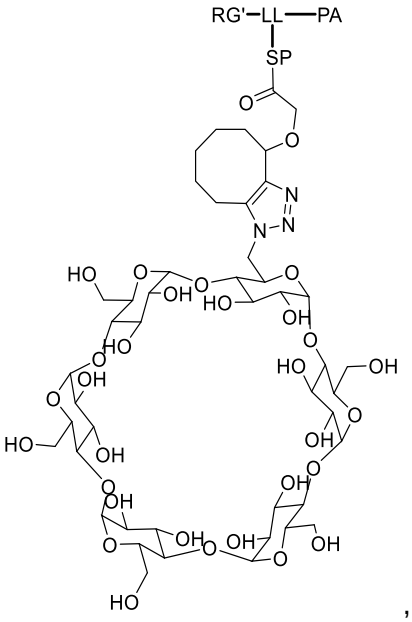
PA is the payload moiety; and

stereoisomers, and mixtures thereof.

38. The compound of any one of claims 34-36, according to formula (**IIb1**) or (**IIb2**):



(**IIb1**)



(**IIb2**)

wherein **RG'** is the reactive group;

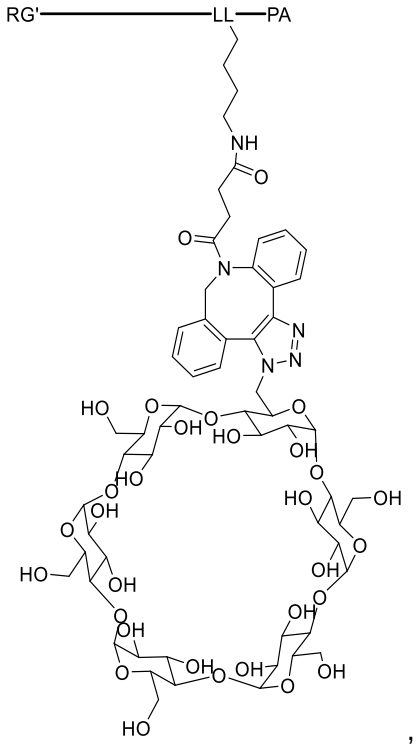
LL is a trivalent linker;

SP is, independently in each instance, absent or is a spacer;

PA is the payload moiety; and

triazole linkage regioisomers, stereoisomers, and mixtures thereof.

39. The compound of claim 36, according to formula (**IIb3**), (**IIb4**), (**IIb5**), or (**IIb6**):



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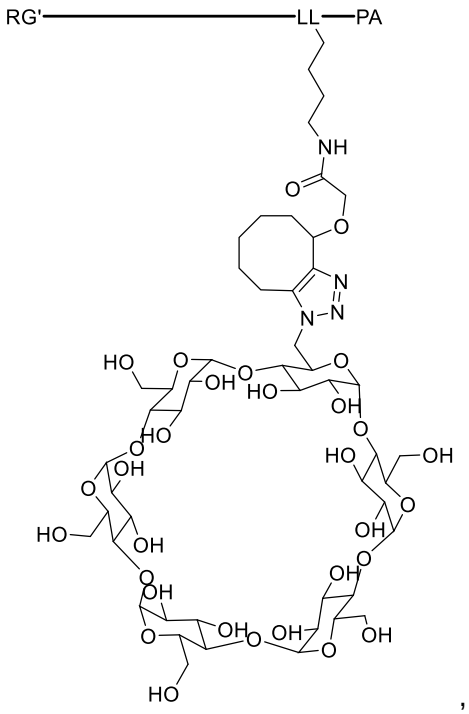
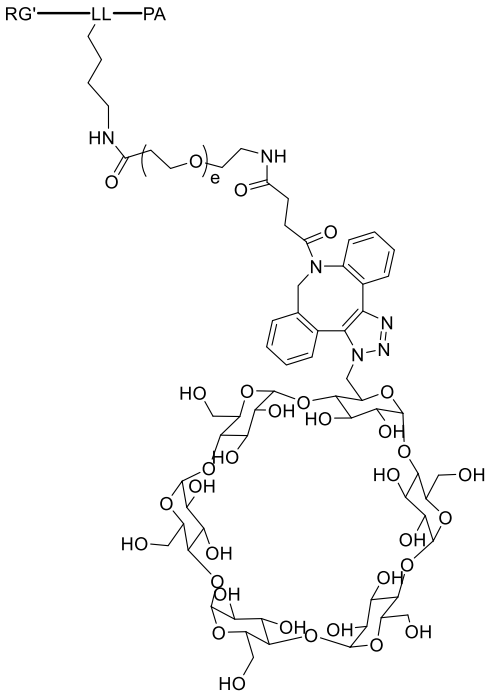


,

(**IIb3**) (**IIb4**)



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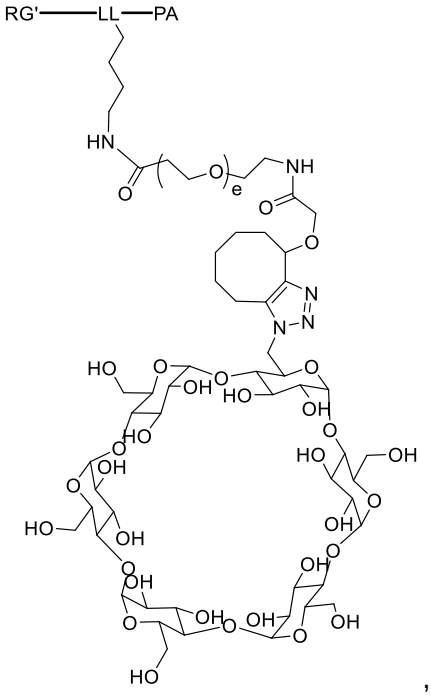


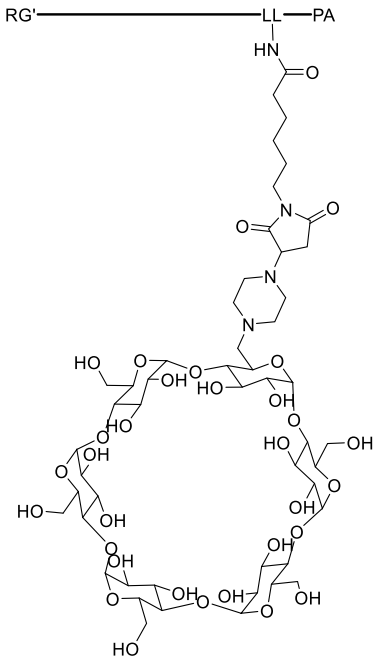
,

(**IIb5**) (**IIb6**)

wherein subscript **e** is an integer from 0 to 4**;**

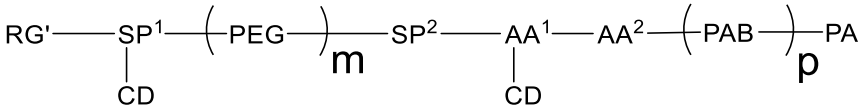
a triazole linkage regioisomer thereof, or a mixture of triazole linkage regioisomers thereof.

40. The compound of claim 36, according to formula (**IIc1**):



(**IIc1**).

41. The compound of claim 34 or 35 according to Formula (**IId**):



(**IId**)

wherein:

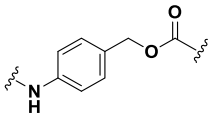
RG' is a reactive group residue;

SP^1 and **SP^2** are each, independently in each instance, absent or a spacer group residue;

AA^1 is a trivalent linker comprising an amino acid residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the **PAB** is bonded to the adjacent groups in the formula;

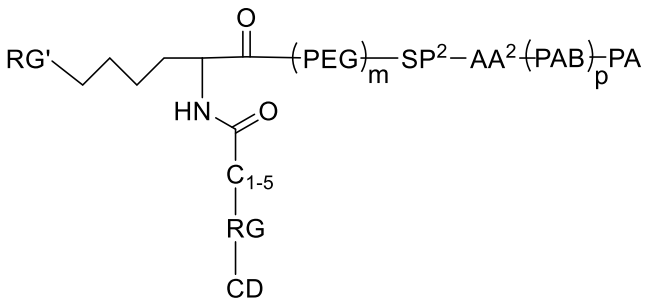
CD is, independently in each instance, absent or a cyclodextrin residue, wherein at least one **CD** is present;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

42. The compound of any one of claims 34-37, according to Formula (**IIe**):



(**IIe**)

wherein:

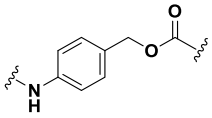
RG' is the reactive group;

RG is, independently in each instance, a reactive group residue;

SP² is, independently in each instance, absent or a spacer group residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

C_{1-5} is an alkyl spacer group of 1 to 5 carbons;

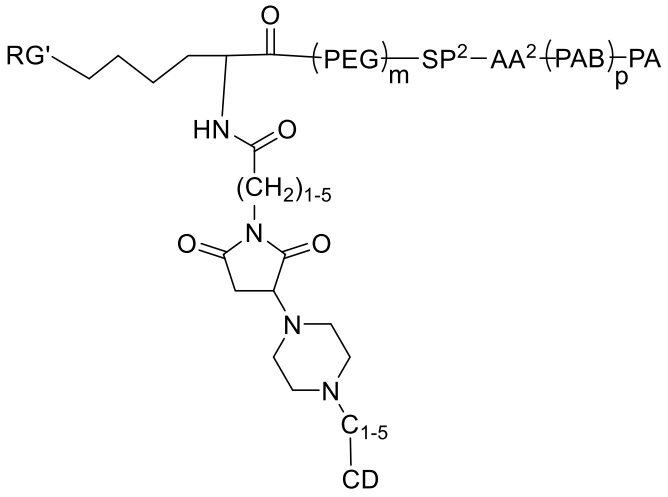
CD is the cyclodextrin residue,

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is a payload moiety.

43. The compound of any one of claims 34-37, according to Formula (**IIe1**):



(**IIe1**)

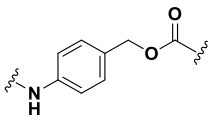
wherein:

RG' is the reactive group;

SP² is, independently in each instance, absent or a spacer group residue;

AA² is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

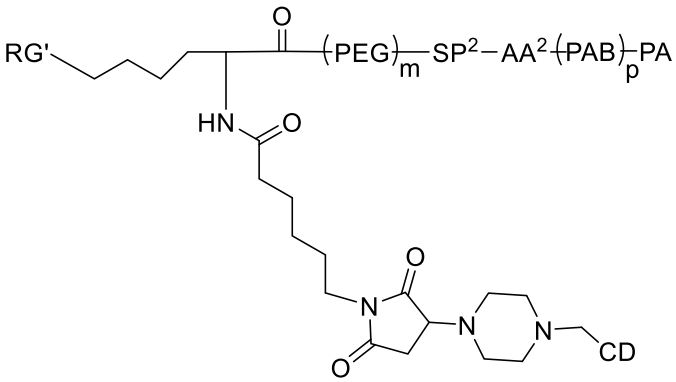
CD is the cyclodextrin residue;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

44. The compound of any one of claims 34-37, according to Formula (**IIe2**):



(**IIe2**)

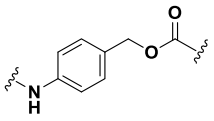
wherein:

RG' is the reactive group;

SP^2 is, independently in each instance, absent or a spacer group residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

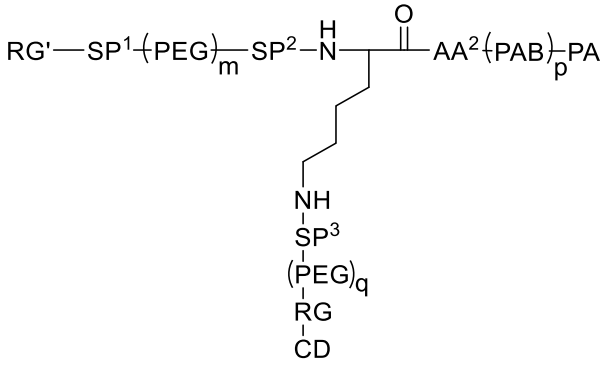
CD is the cyclodextrin residue;

subscript **m** is an integer from 0 to 5;

subscript **p** is 0 or 1; and

PA is the payload moiety.

45. The compound of any one of claims 34-42, according to Formula (**IIf**):



(**IIf**)

wherein:

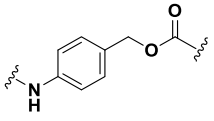
RG' is a reactive group;

RG is a reactive group residue;

SP^1, **SP^2**, and **SP^3** are each, independently in each instance, absent or a spacer group residue;

AA^2 is a di-peptide residue;

PEG is a polyethylene glycol residue;

PAB is  , wherein the  indicates the atom through which the PAB is bonded to the adjacent groups in the formula;

CD is a cyclodextrin residue;

subscript **m** is an integer from 0 to 5;

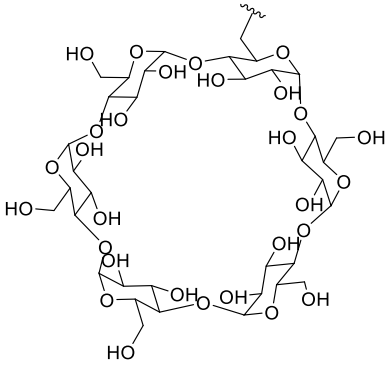
subscript **p** is 0 or 1;

subscript **q** is an integer from 0 to 5; and

PA the payload moiety.

46. The compound of any one of claims 34-45, wherein **CD** is, independently in each instance, selected from the group consisting α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin.

47. The compound of any one of claims 34-45, wherein **CD** is, independently in each instance, selected from the group consisting of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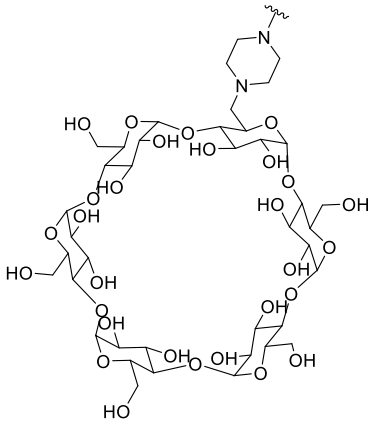
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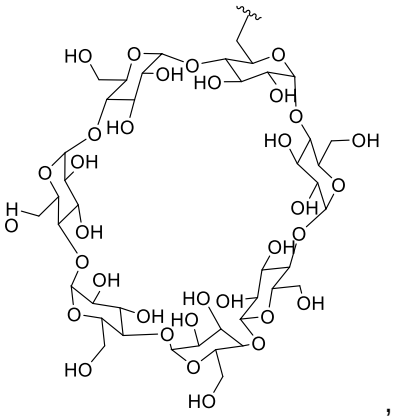
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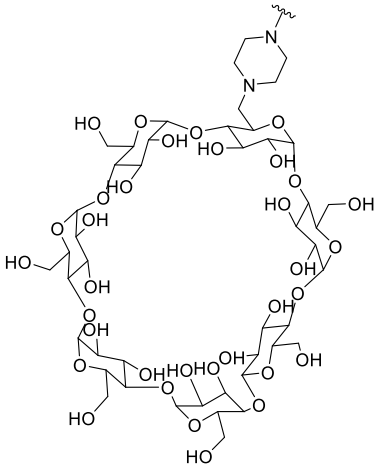
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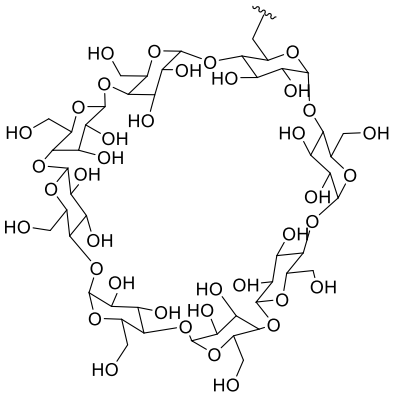
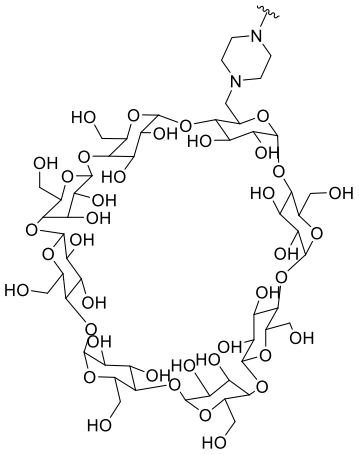
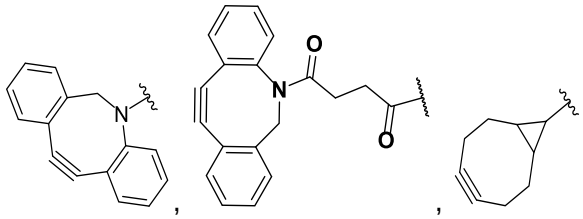
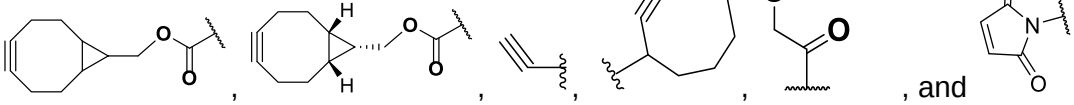
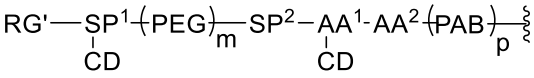

, and 
,

wherein the  indicates the atom through which the **CD** is bonded to the adjacent groups in the formula.

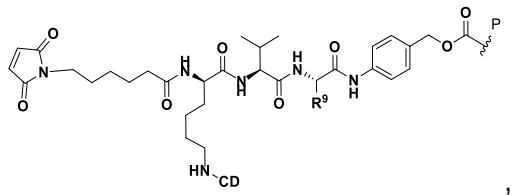
48. The compound of any one of claims 34-45, wherein RG' comprises a triazole or fused triazole.

49. The compound of any one of claims 34-45, wherein **RG'** is, independently in each instance, selected from the group consisting of 
, 
, and
, wherein the  indicates the atom through which the **RG'** is bonded to the adjacent groups in the formula.

50. The compound any one of claims 41-49, wherein



is selected from the group consisting of



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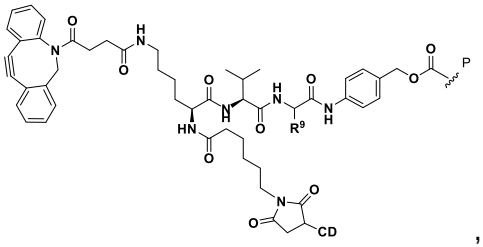

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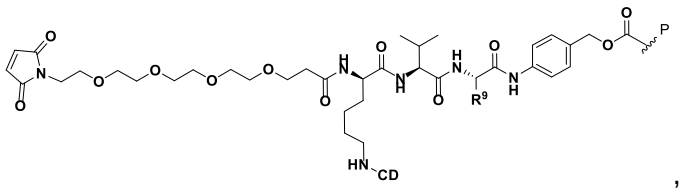

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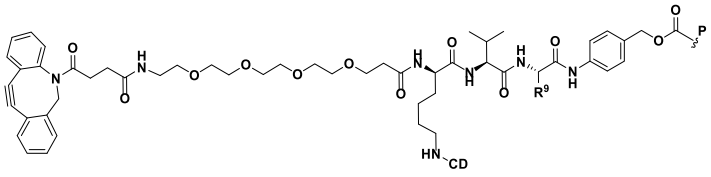

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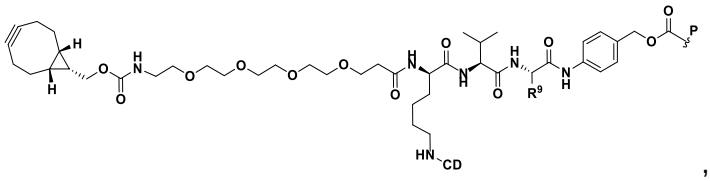

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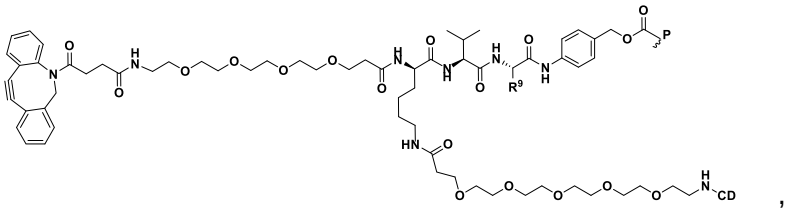

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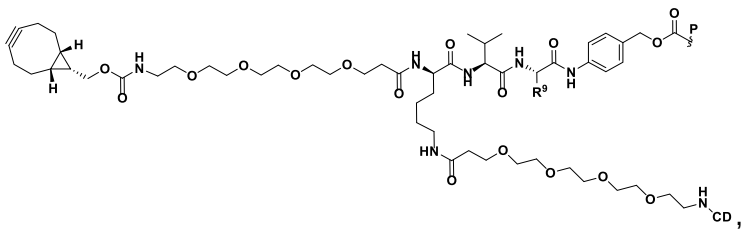

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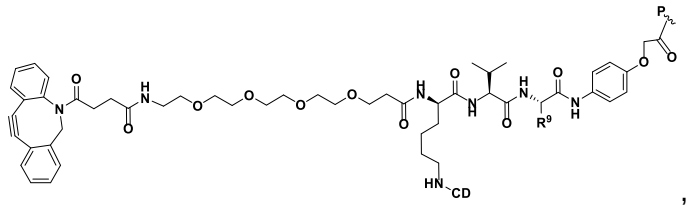

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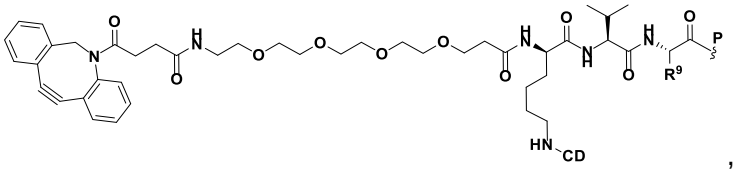

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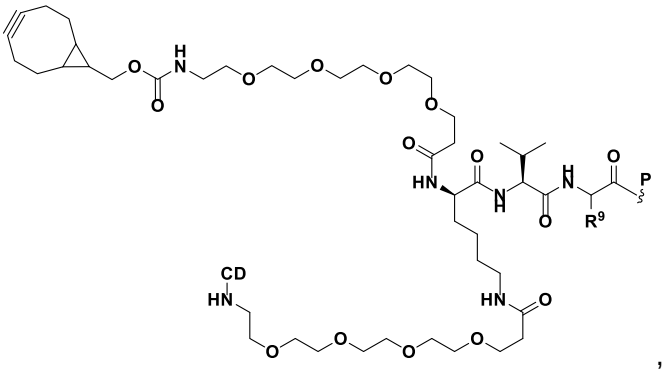

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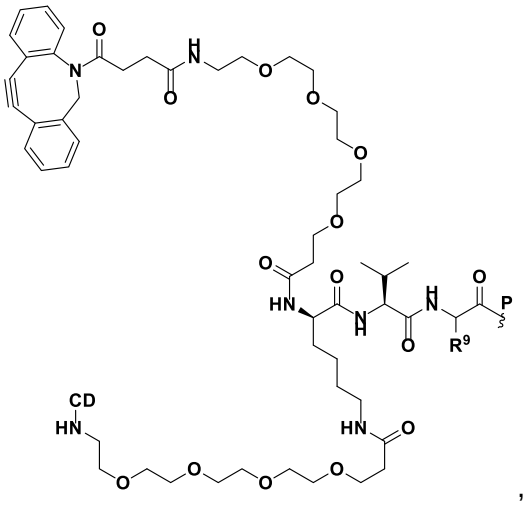

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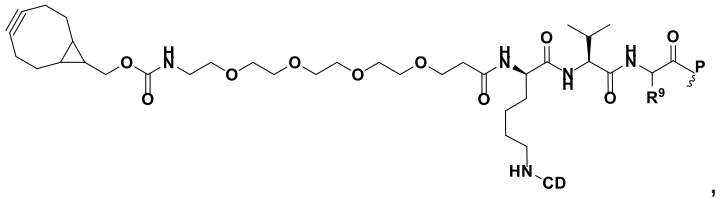
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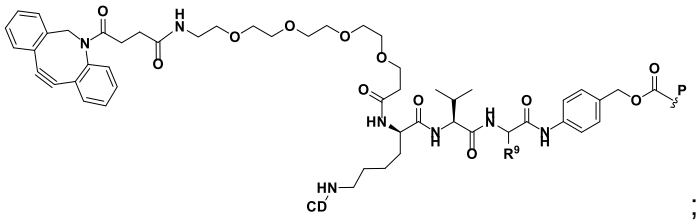

; and

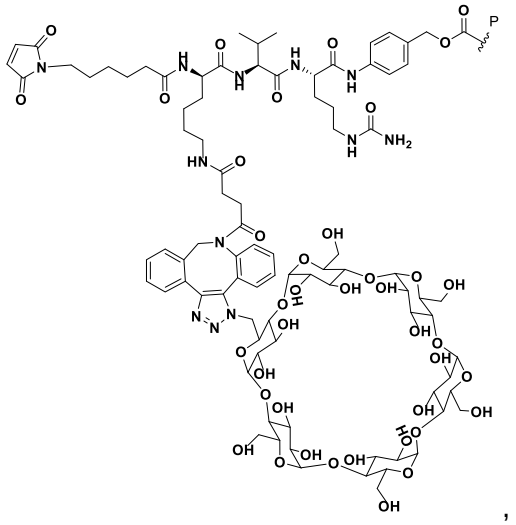
or a pharmaceutically acceptable salt, or stereoisomeric form thereof, wherein:

each  is a bond to the binding agent;

each  is a bond to the payload moiety; and

R^9 is $–CH_3$ or $–(CH_2)_3N(H)C(O)NH_2$.

51. The compound of any one of claims 41-50, comprising a group selected from the group consisting of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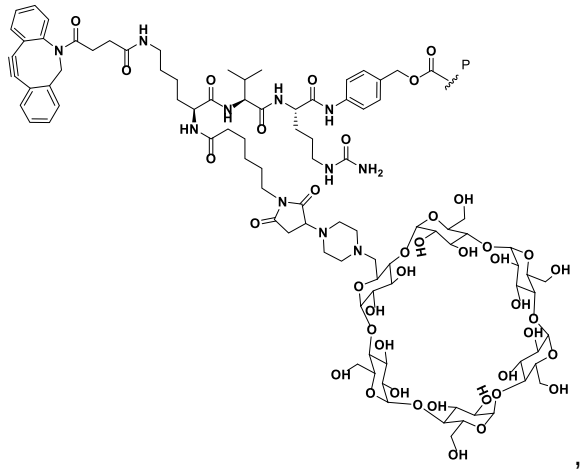

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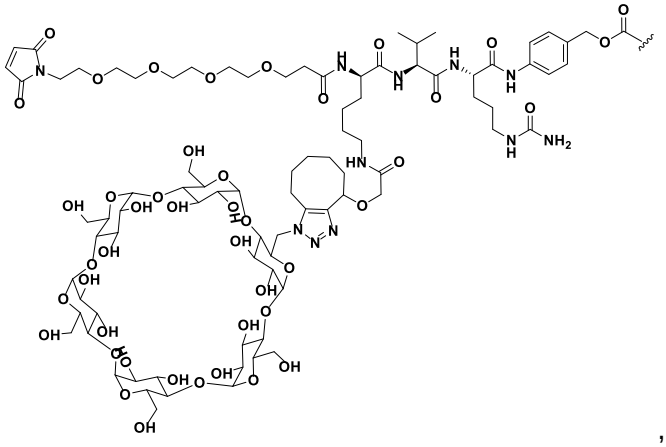

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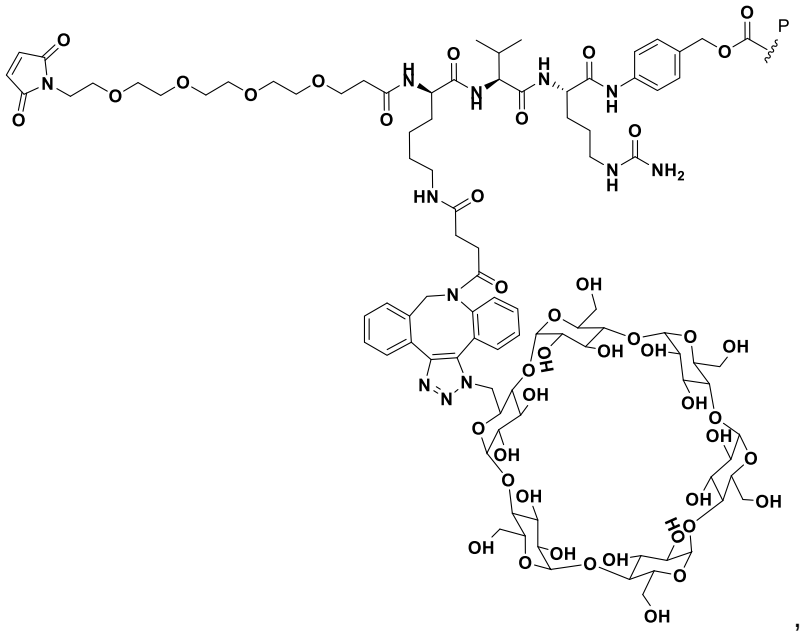

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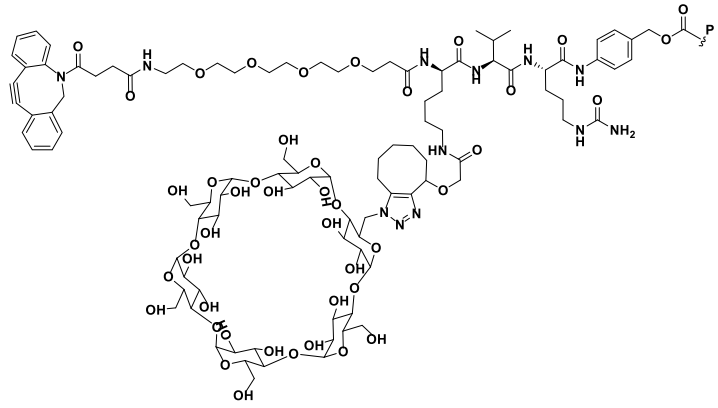

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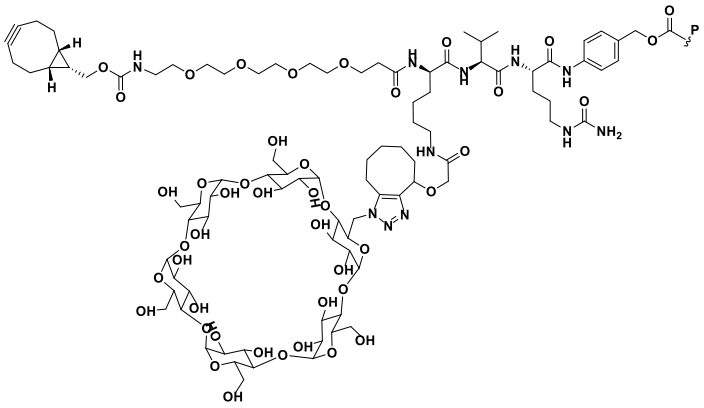

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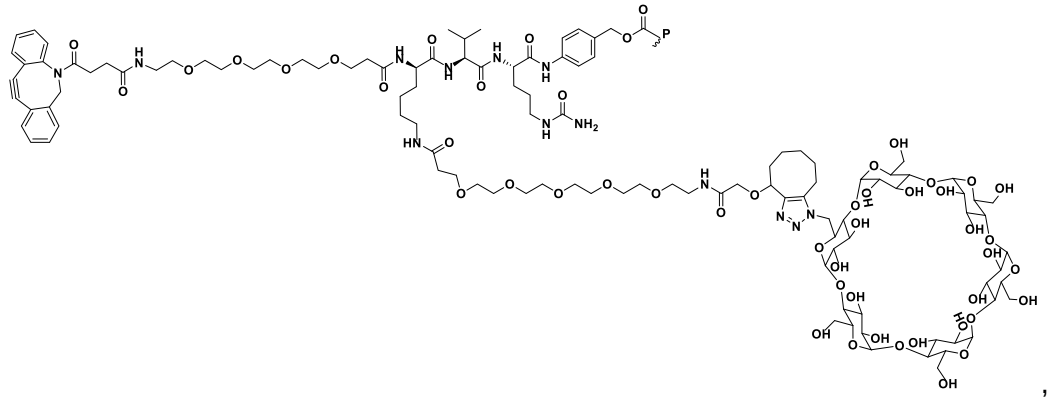

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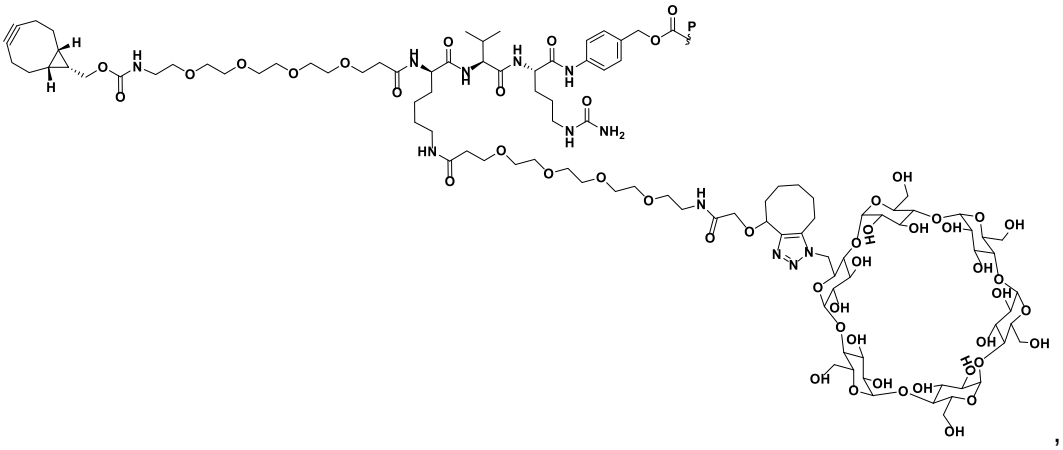

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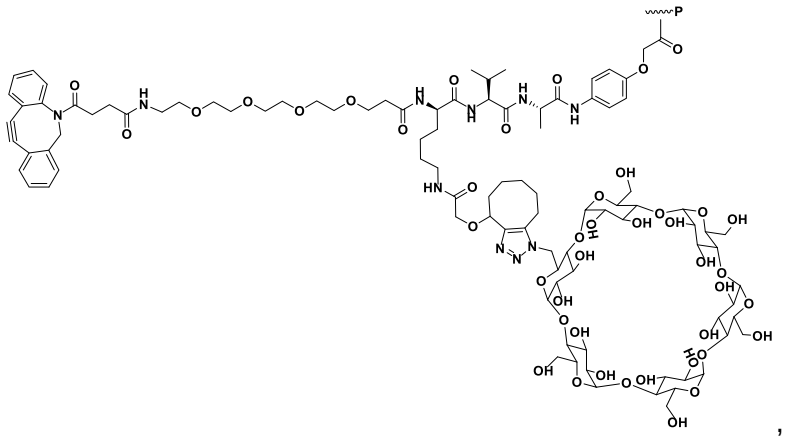

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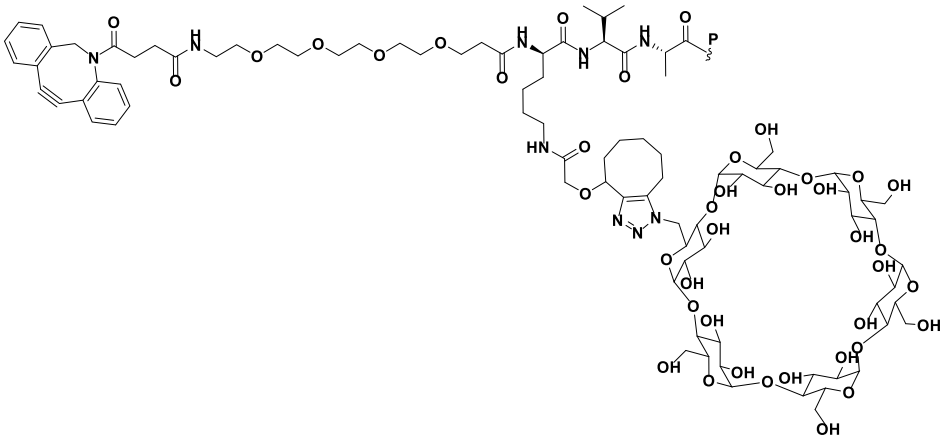

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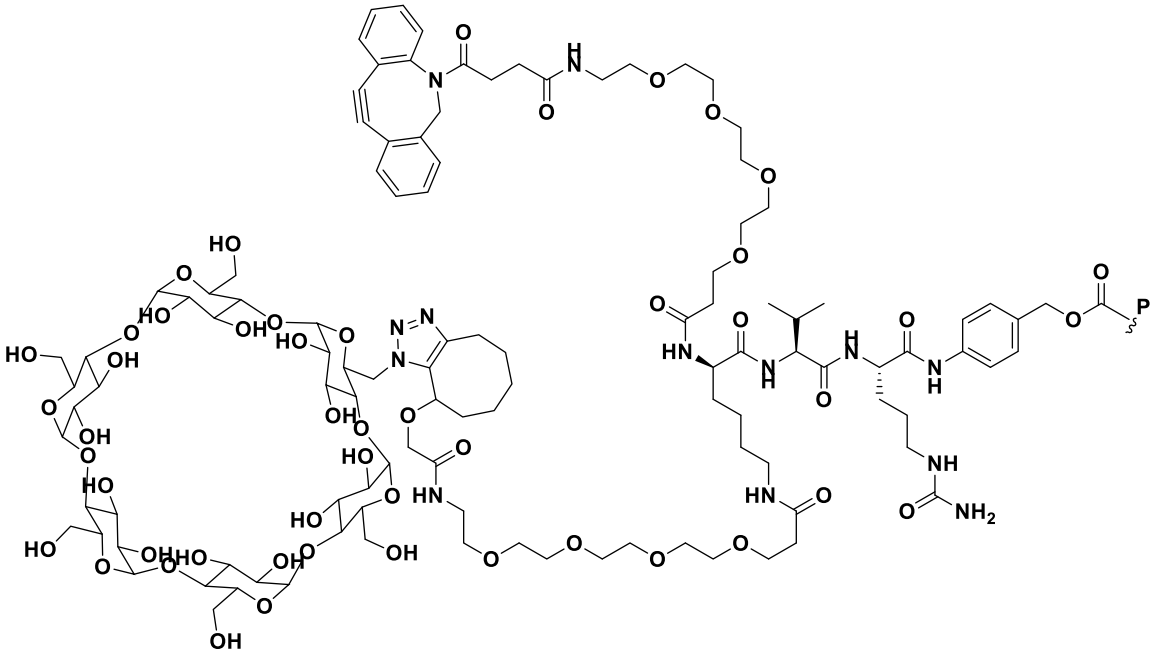

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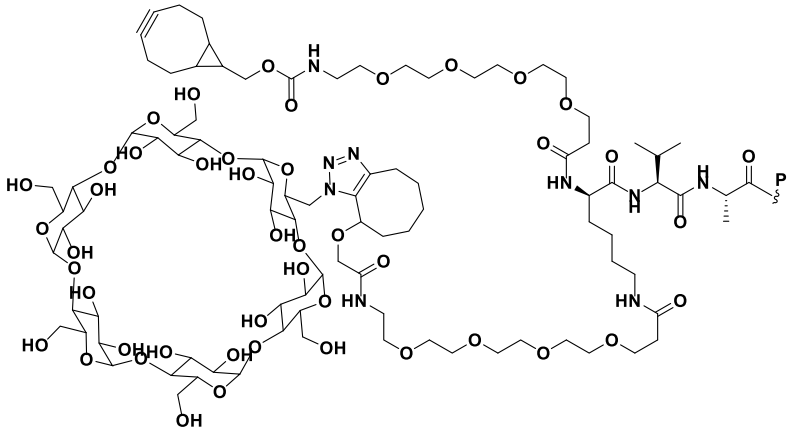

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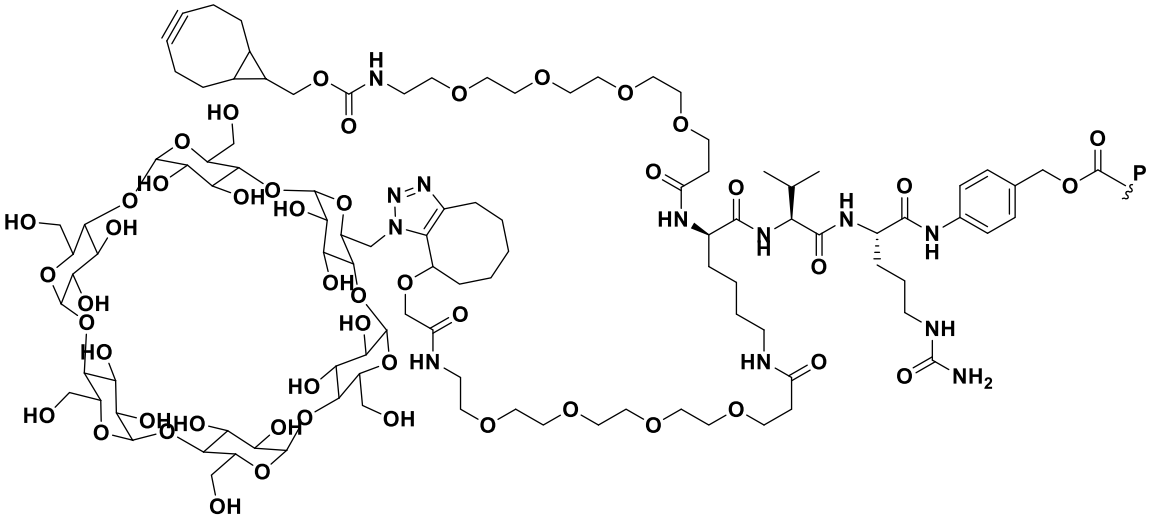

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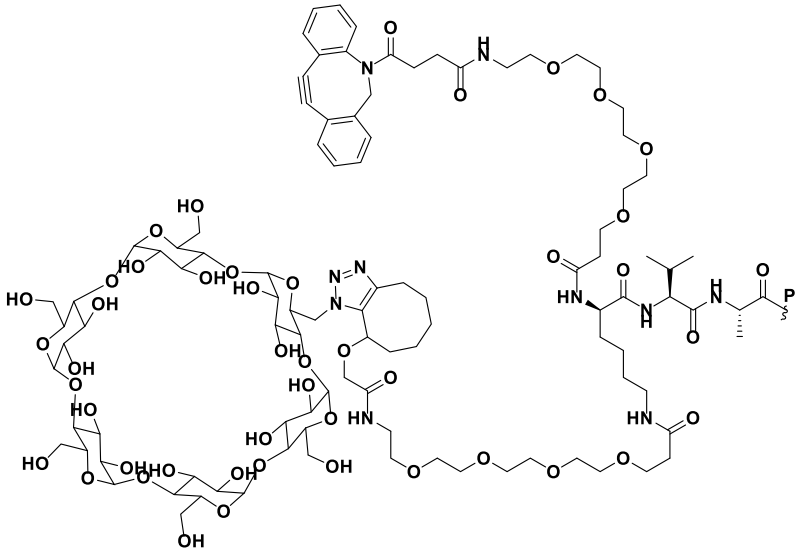

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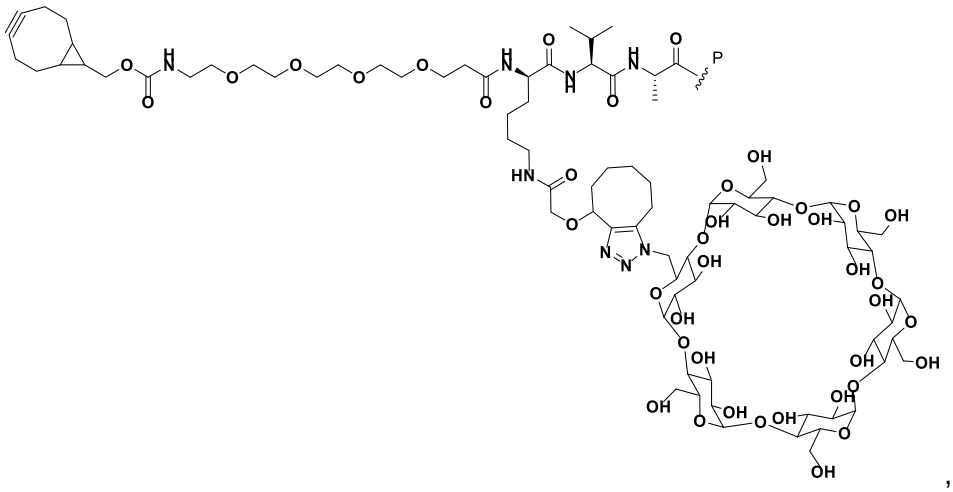

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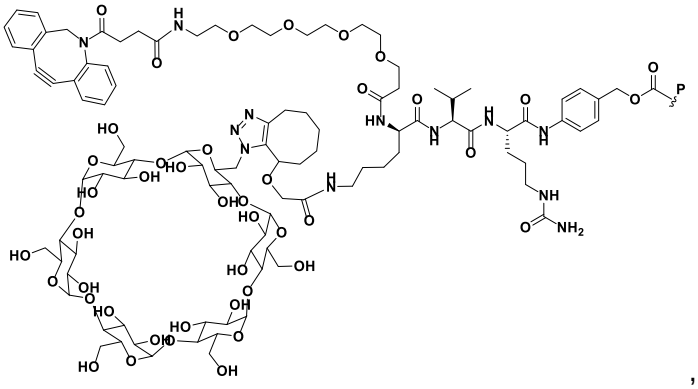

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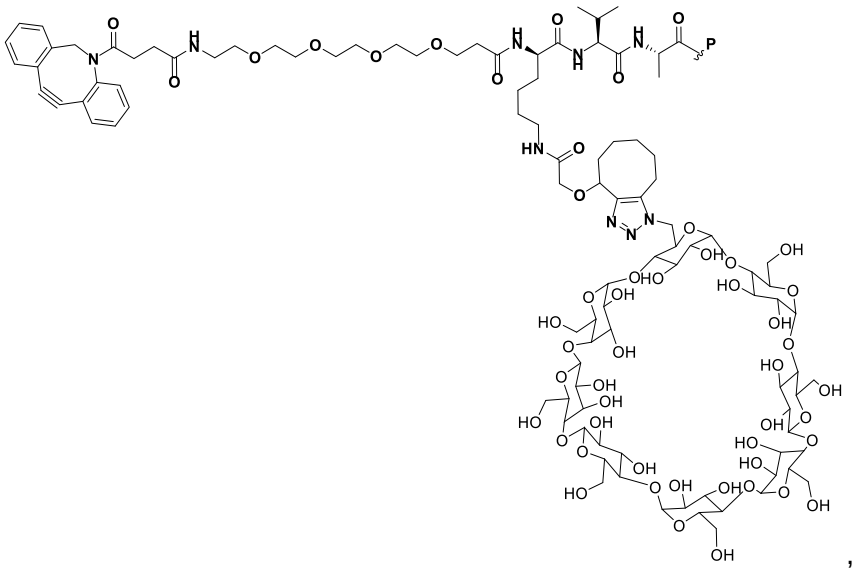

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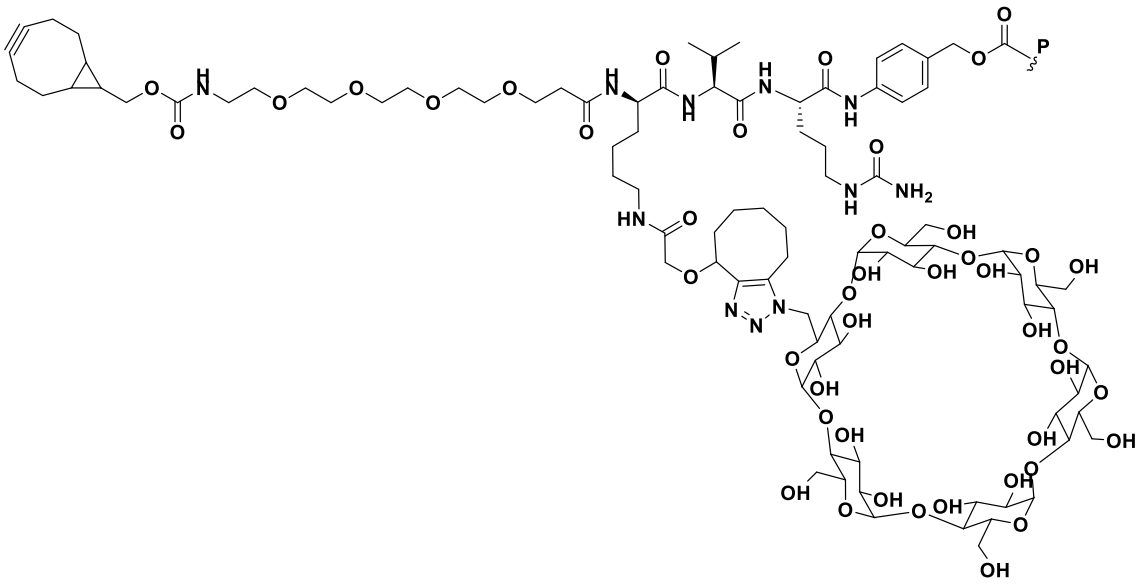

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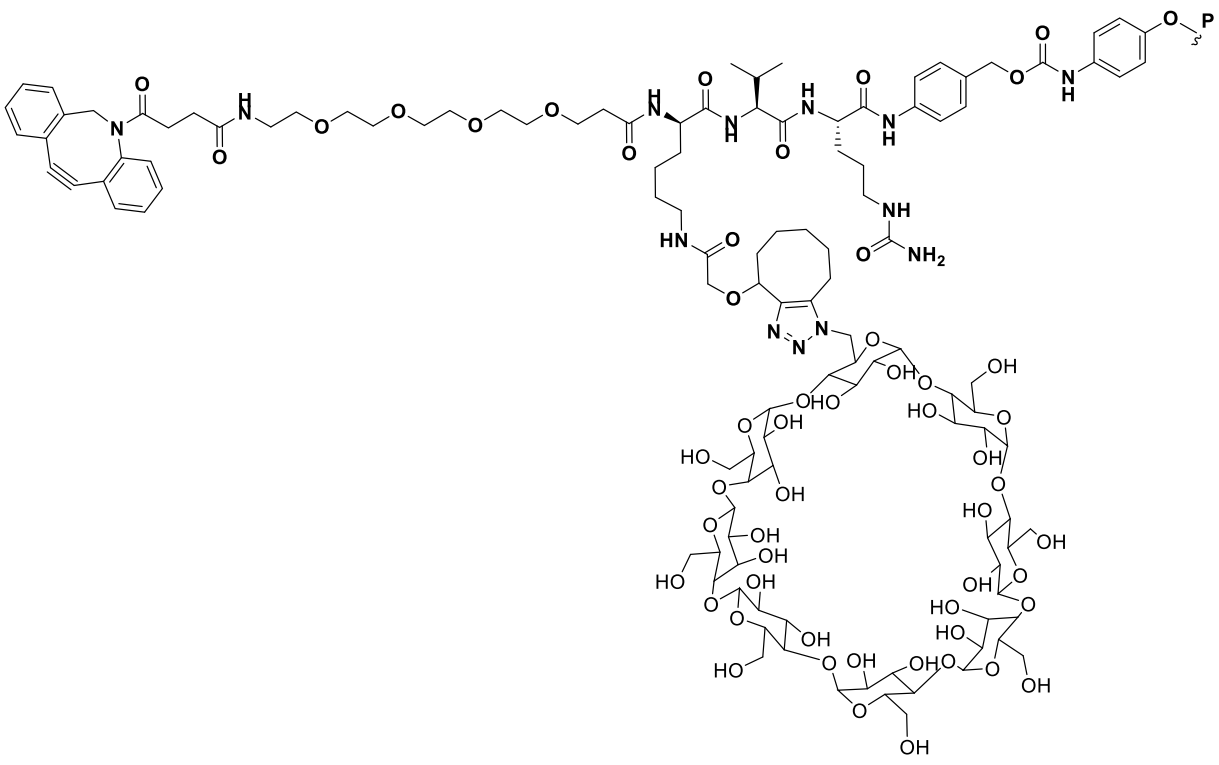

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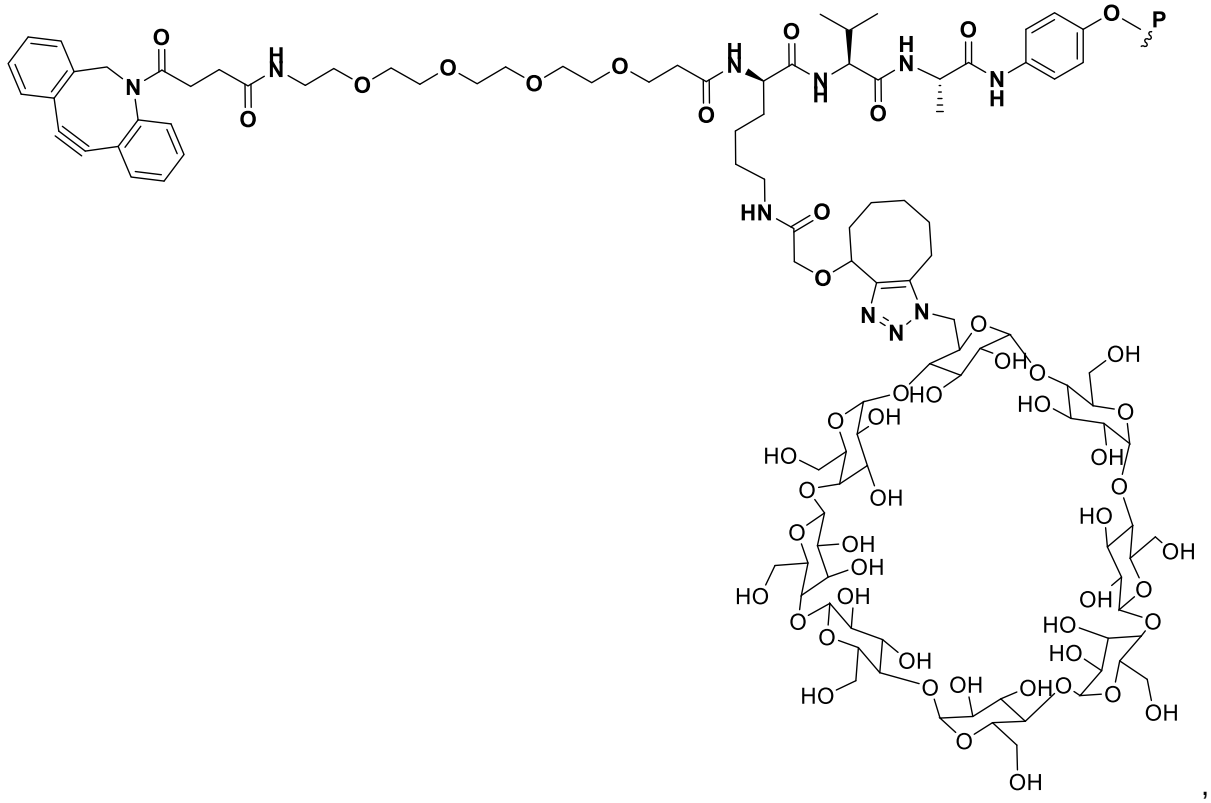
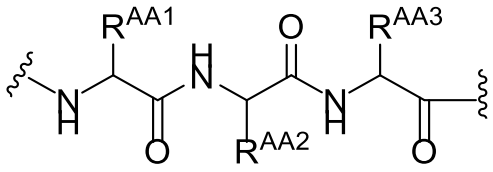


or a pharmaceutically acceptable salt, stereoisomeric form thereof, a triazole linkage regioisomer thereof, or a mixture of triazole linkage regioisomers thereof;
wherein:

each  is a bond to the payload moiety.

52. The compound of any one of claims 36-40, wherein

-**LL**- is according to the formula:

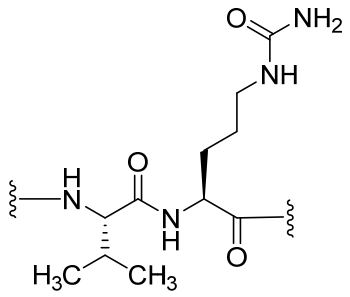
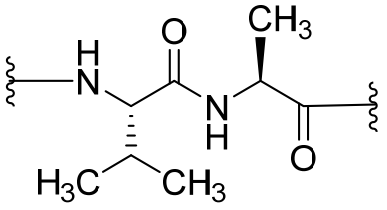


(**BL**^{A1})

wherein $\mathbf{R}^{\mathbf{AA1}}$, $\mathbf{R}^{\mathbf{AA2}}$, and $\mathbf{R}^{\mathbf{AA3}}$ are each, independently, amino acid side chains, at least one of which is bonded directly or indirectly to **-SP-RG-SP-CD**.

53. The compound of claim 52, wherein $\mathbf{R^{AA1}}$ is a lysine side chain bonded directly or indirectly to **CD** and $\mathbf{R^{AA2}}$ and $\mathbf{R^{AA3}}$ are either valine and cirulline or valine and alanine side chains, respectively.

54. The compound of any one of claims 41-45, wherein

-AA^2- is  or 

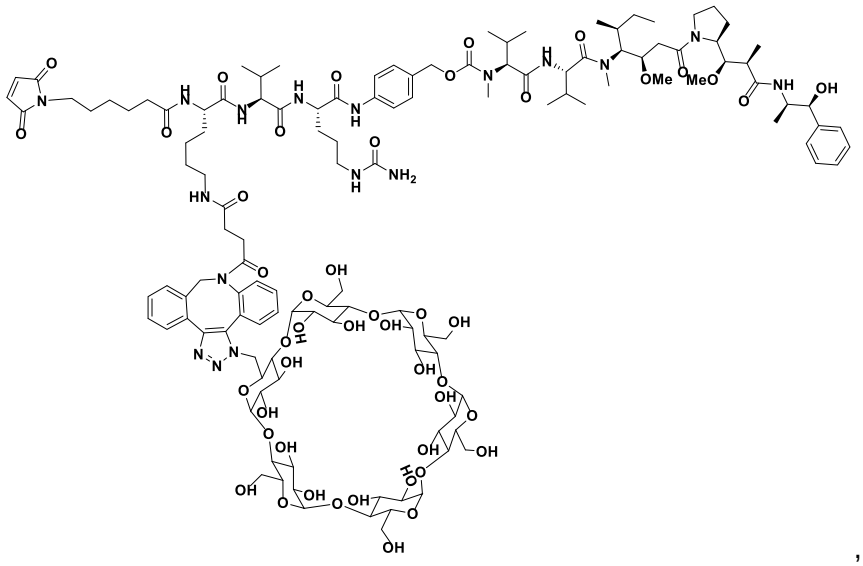
55. The compound of any one of claims 36-45, wherein the spacer group is, independently in each instance, selected from the group consisting of C_{1-6} alkylene, -NH-, -C(O)-, $(-CH_2-CH_2-O)_e$, -NH-CH_2-CH_2-$(-O-CH_2-CH_2)_e$-C(O)-, -C(O)-$(CH_2)_u$-C(O)-, -C(O)-NH-$(CH_2)_v$-, and combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8.

56. The compound of any one of claims 41-45, wherein any one of subscript **m** or **q** is 4.

57. The compound of any one of claims 41-45, wherein subscript **p** is 1.

58. The compound of any one of claims 34-52**,** wherein **PA** is the residue of a group selected from the group consisting of a dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, and a vinca alkaloid.

59. The compound of claim 34, wherein the compound is:



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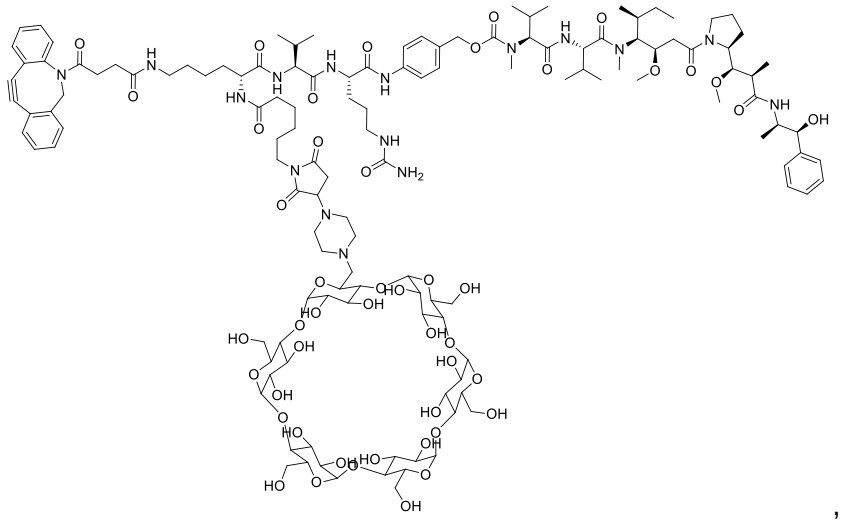

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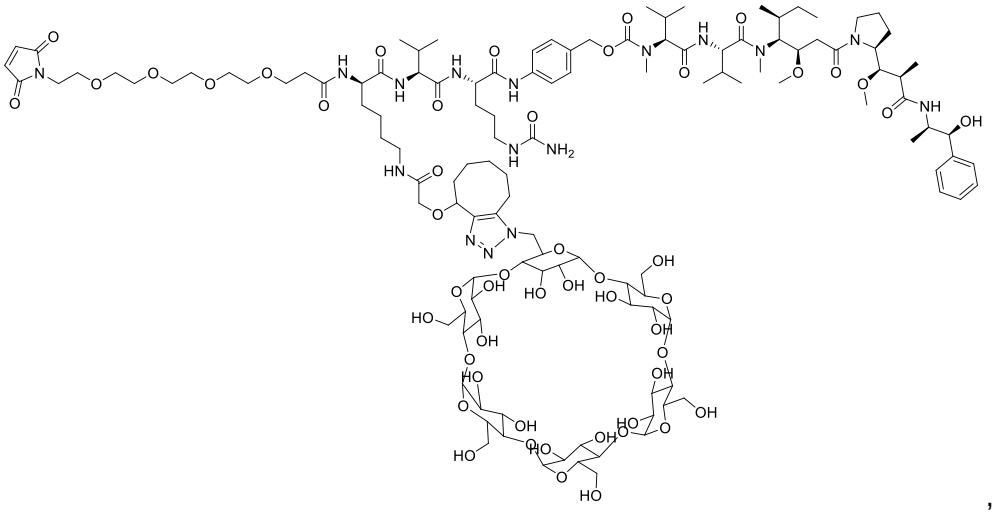

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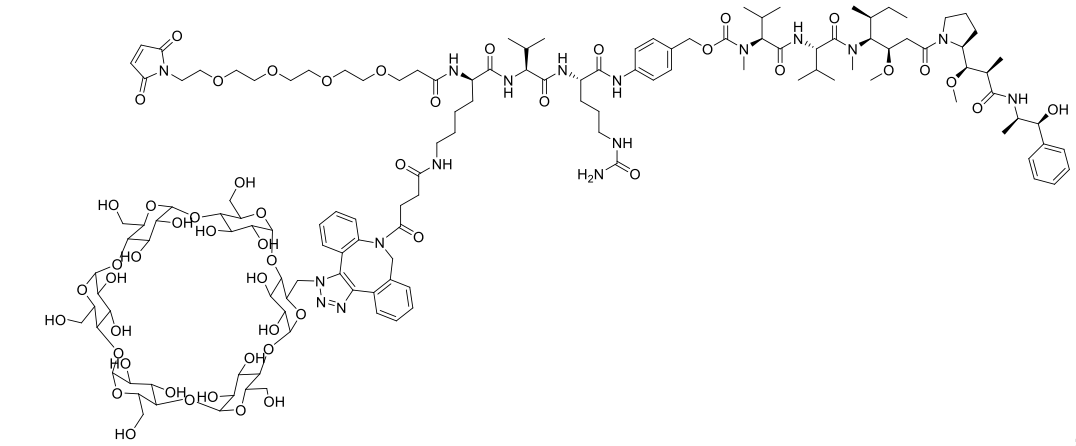

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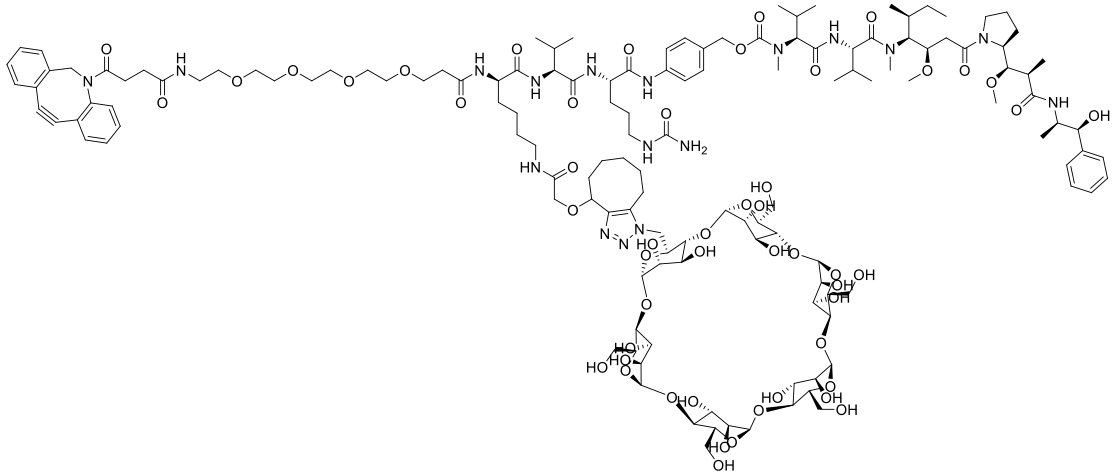

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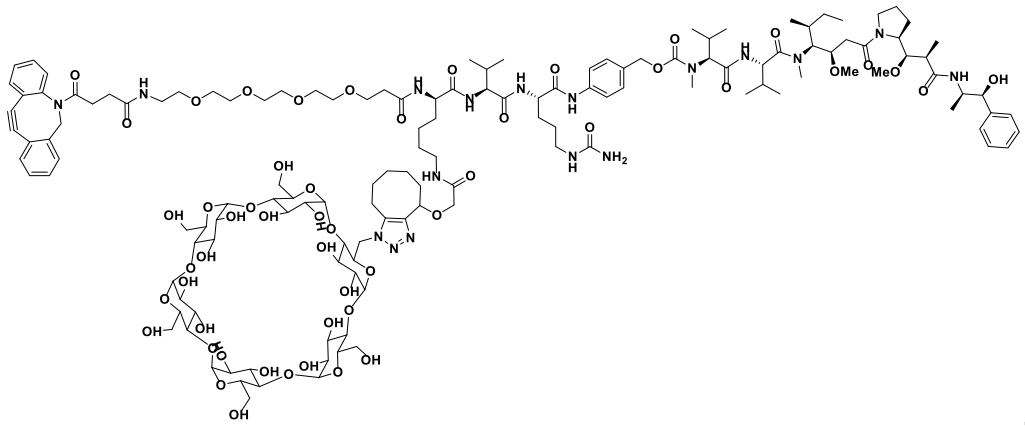

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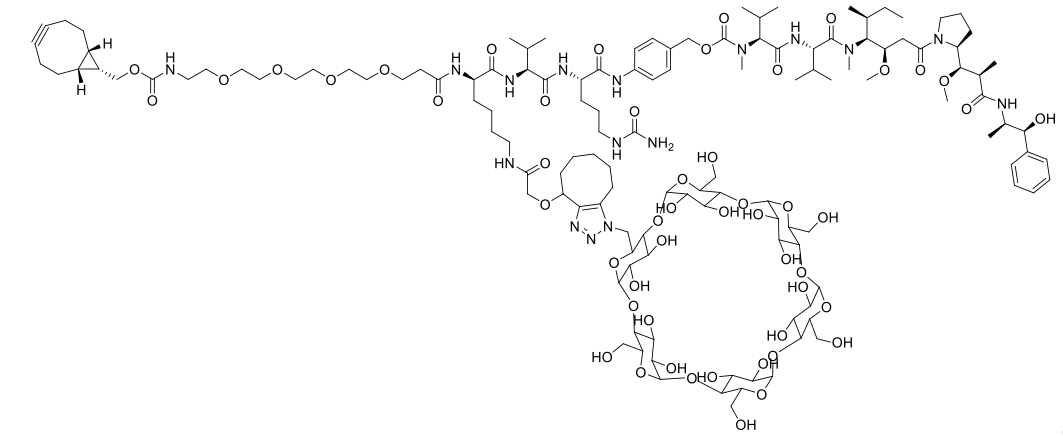

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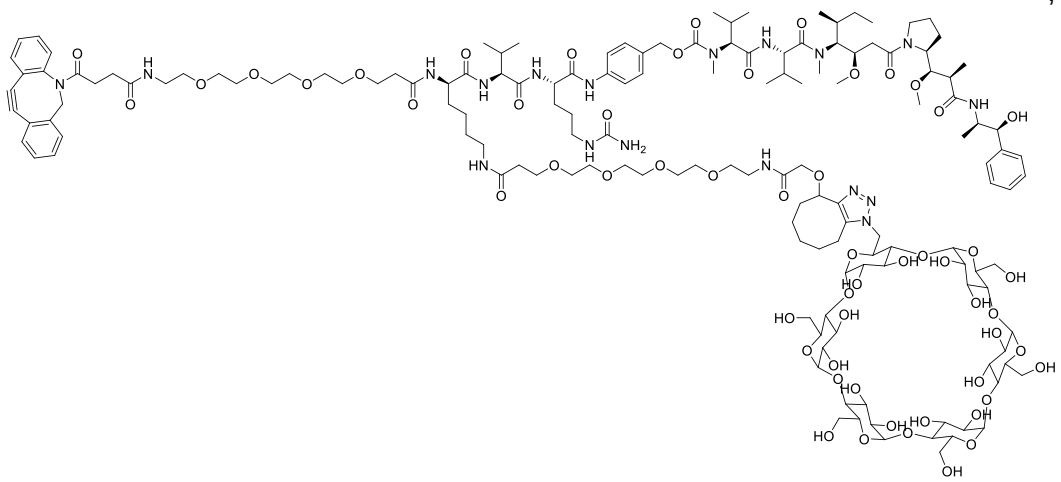

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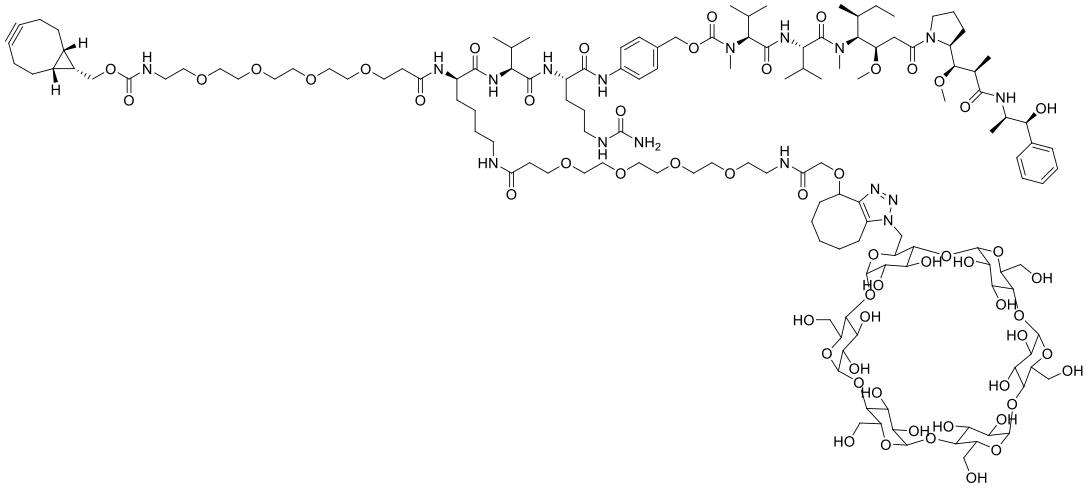

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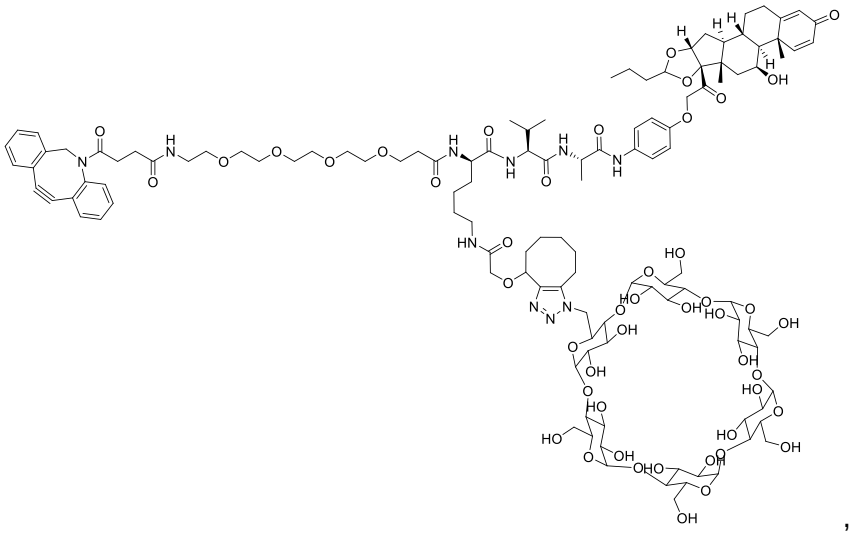

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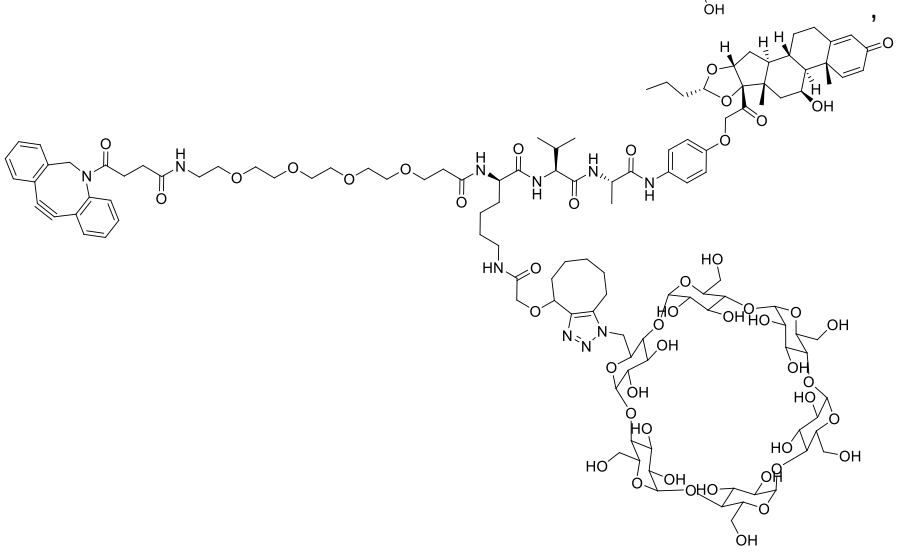

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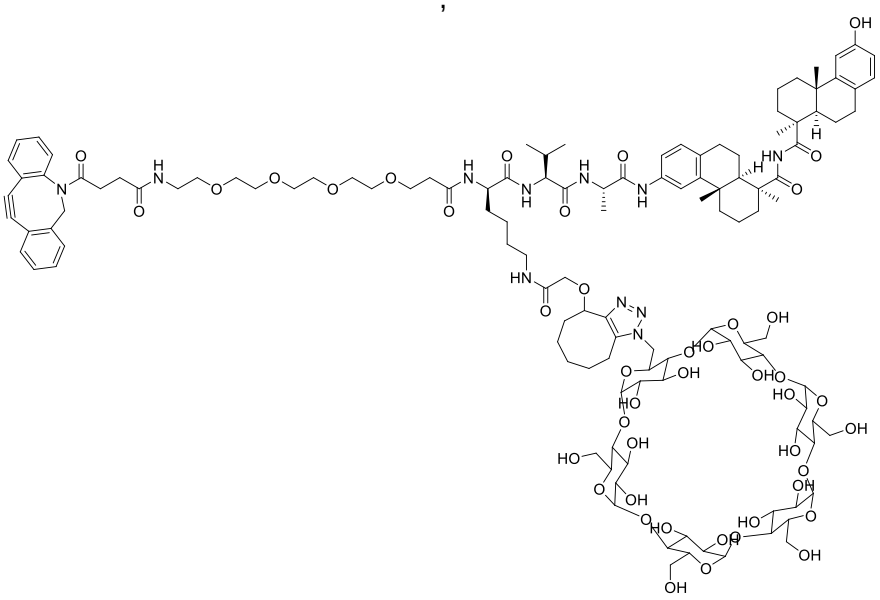

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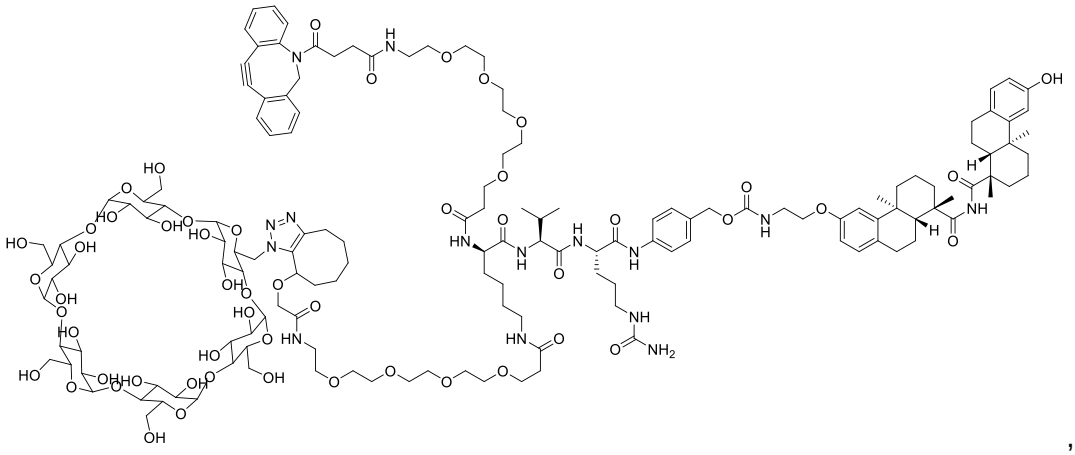

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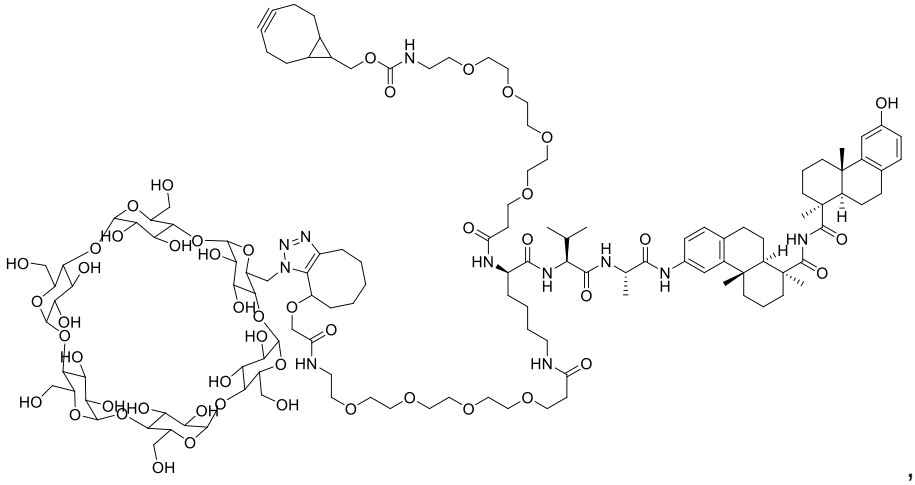

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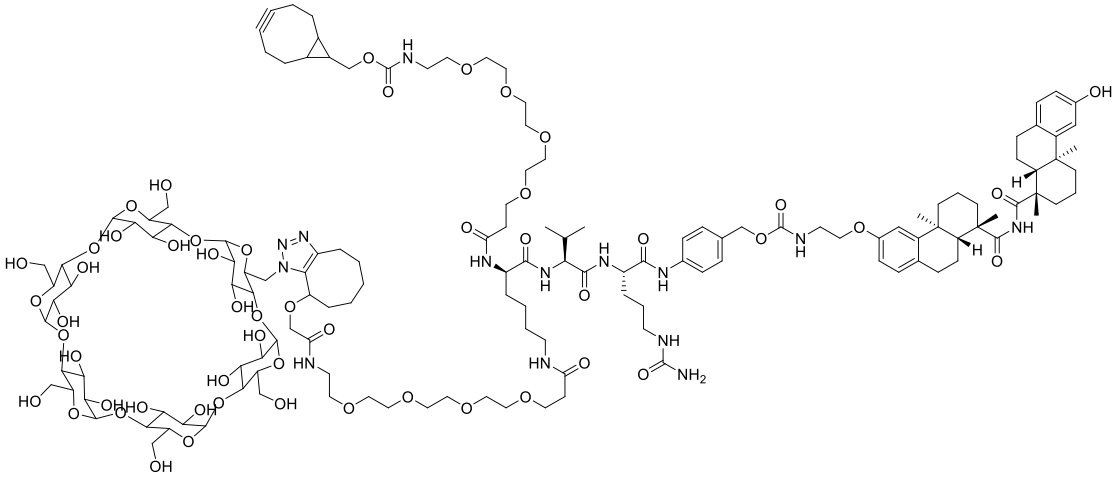

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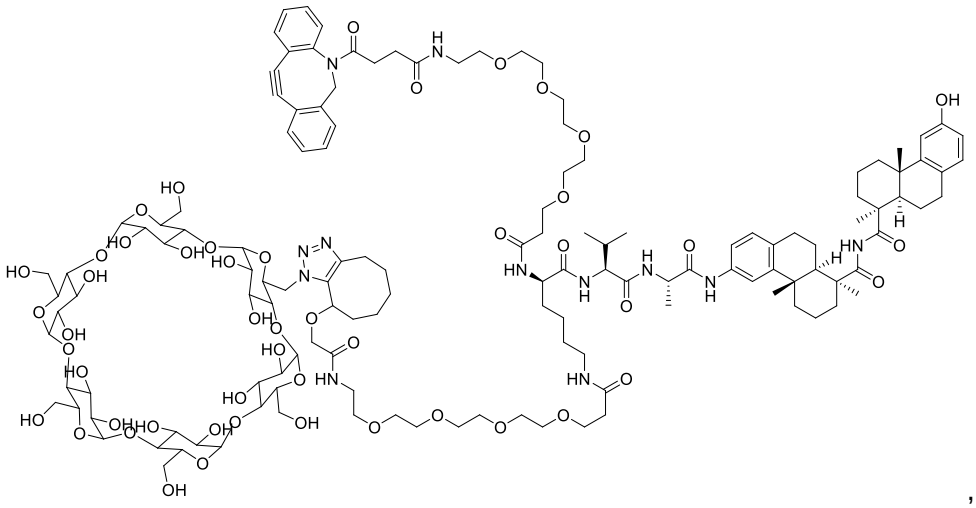

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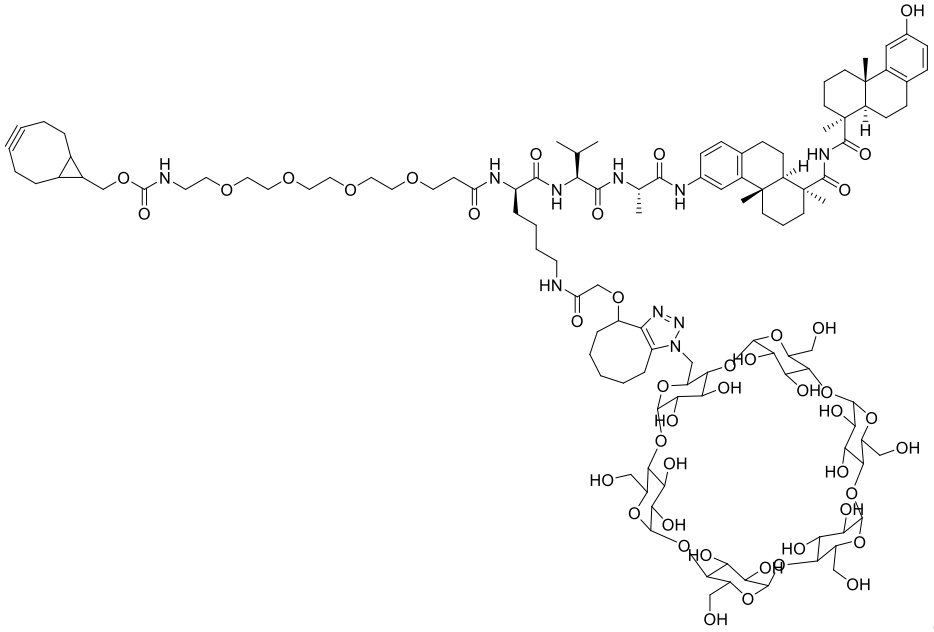

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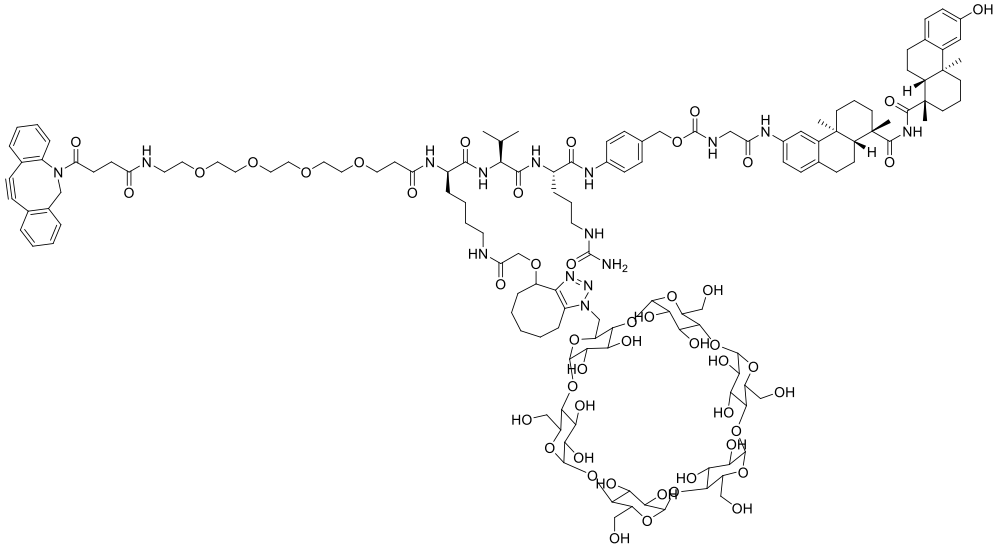

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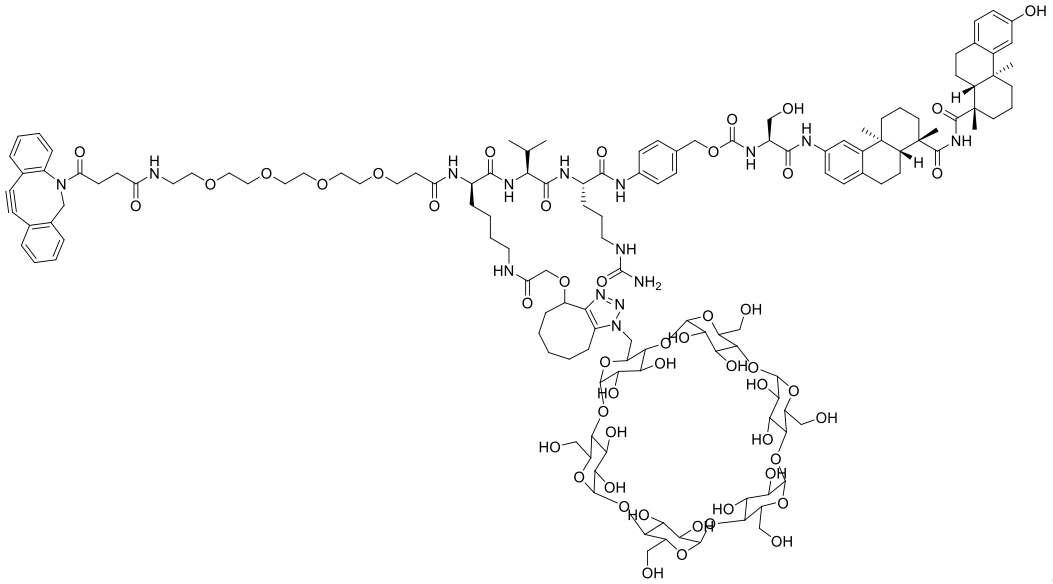

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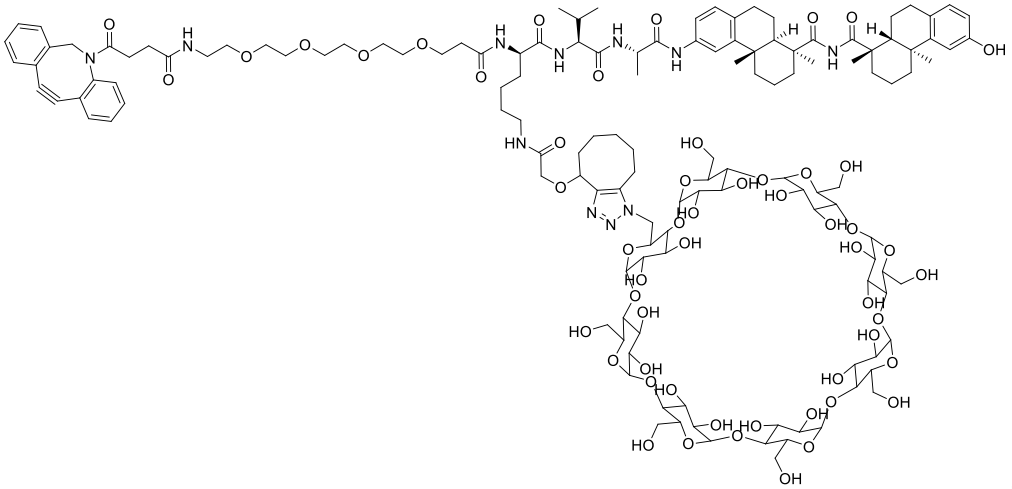

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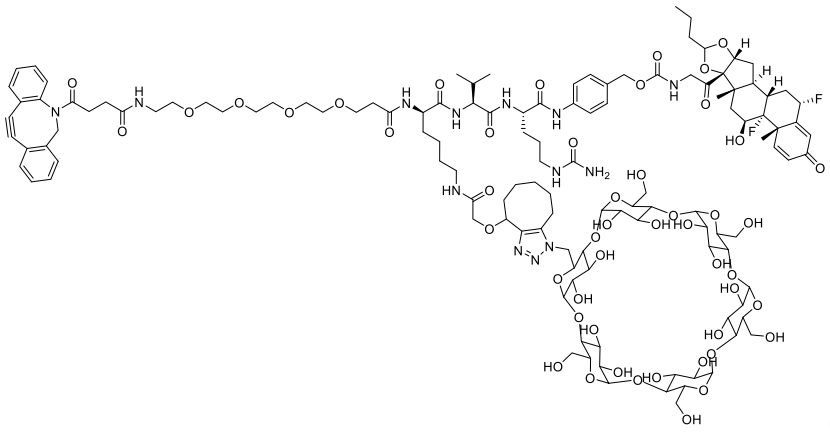

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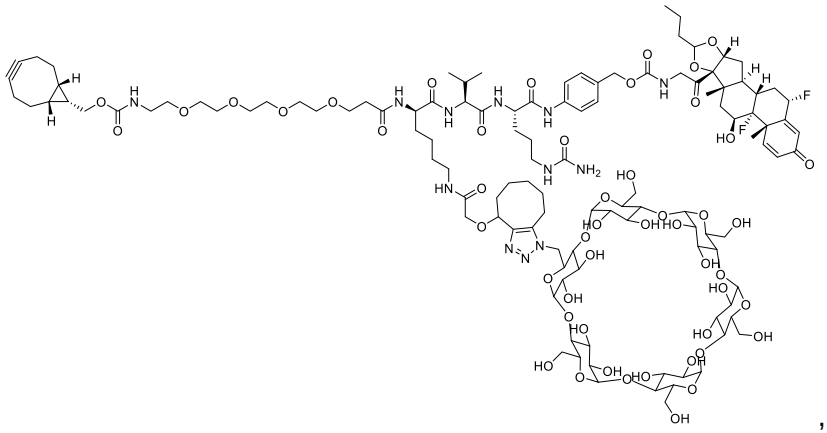

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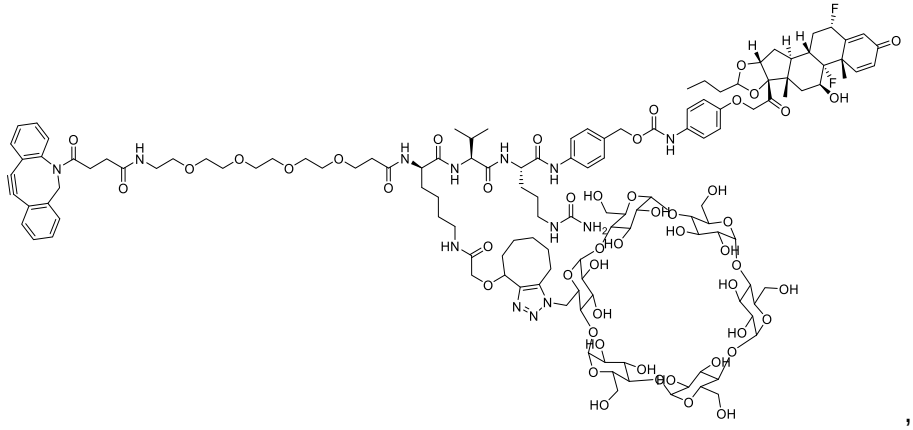

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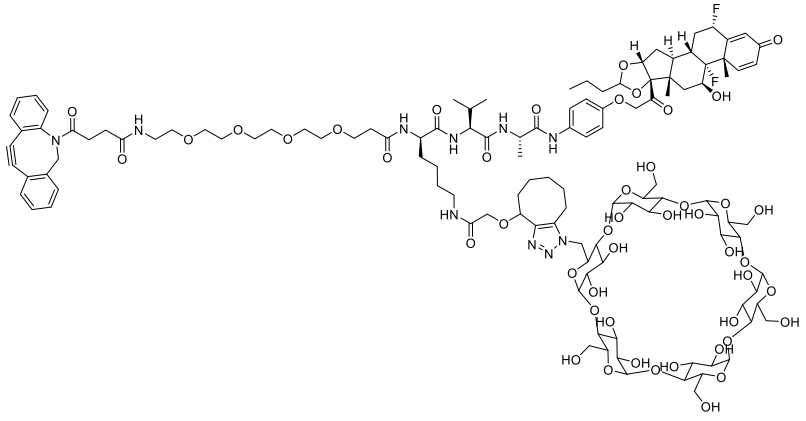


or stereoisomeric form thereof, a triazole linkage regioisomer thereof, or a mixture of triazole linkage regioisomers thereof.

60. A method of preparing the compound of claim 1 comprising the step of contacting the binding agent with the compound according to any one of claims 34-59 under conditions suitable for forming a bond between the binding agent and the compound.

61. A linker-payload compound comprising the compound of any one of claims 34-59 bonded to another linker.

62. A linker-payload compound comprising the compound of any one of claims 34-59, wherein the payload moiety is bonded to an oxygen or a primary or secondary nitrogen of the covalent linker.

63. An antibody-drug-conjugate comprising the compound or linker-payload compound of any one of claims 34-59 bonded to an antibody, or an antigen binding fragment thereof.

64. Use of a compound or pharmaceutical composition of any of claims 1-32 in the manufacture of a medicament for treating a proliferative disease, a metabolic disease, inflammation, or a neurodegenerative disease in a subject; wherein the payload moiety is a therapeutic agent for treating a proliferative disease.

65. Use of a compound or pharmaceutical composition of any of claims 1-32 in the manufacture of a medicament for the treatment of a disease, disorder, or condition in a subject, where the disease, disorder, or condition is a proliferative disease or inflammation; and wherein the payload moiety is a therapeutic agent for treating a proliferative disease or a therapeutic agent for treating inflammation.

66. Use of a compound or pharmaceutical composition of any of claims 1-32 in the manufacture of a medicament for the treatment of a proliferative disease in a subject; wherein the payload moiety is a therapeutic agent for treating a proliferative disease.

67. Use of a compound or pharmaceutical composition of any of claims 1-32 in the manufacture of a medicament for the treatment of a metabolic disease in a subject; wherein the payload moiety is a therapeutic agent for treating a metabolic disease.

68. Use of a compound or pharmaceutical composition of any of claims 1-32 in the manufacture of a medicament for the treatment of inflammation in a subject; wherein the payload moiety is a therapeutic agent for treating inflammation.

69. Use of a compound or pharmaceutical composition of any of claims 1-32 in the manufacture of a medicament for the treatment of a neurodegenerative disease in a subject; wherein the payload moiety is a therapeutic agent for treating a neurodegenerative disease.

70. The compound of claim 8, wherein subscript **m** is 4.

71. The compound of claim 9, wherein subscript **m** is 4.

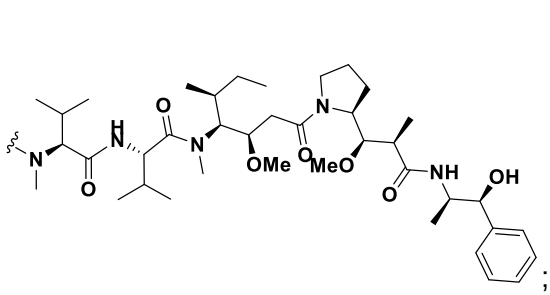
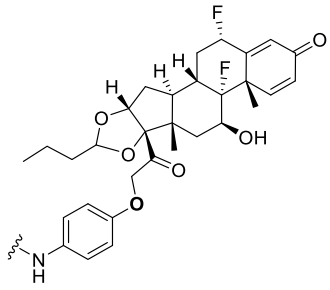
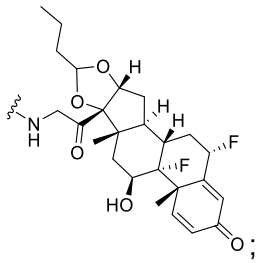
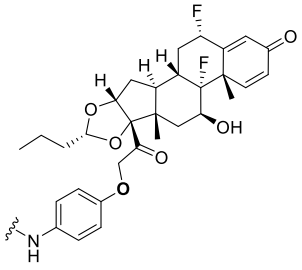
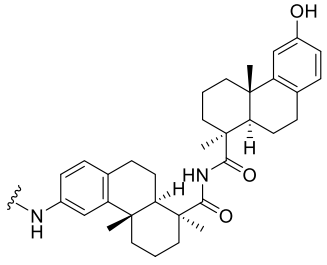
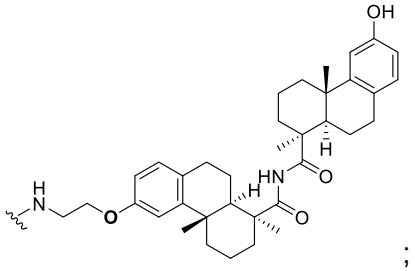
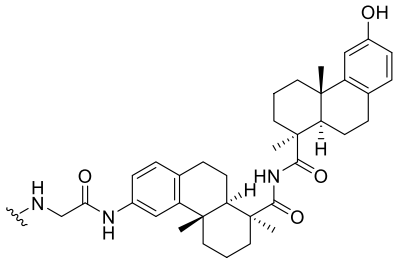
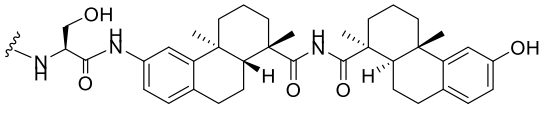
72. The compound of claim 10, wherein subscript **m** is 4.

73. The compound of claim 11, wherein subscript **m** is 4.

74. The compound of claim 12, wherein any one of subscript **m** and **q** is 4.

75. A process for preparing an antibody-drug-conjugate comprising reacting the linker-payload compound of claim 34 with an antibody, or an antigen binding fragment thereof.

76. The compound of claim 29, wherein **PA** is selected from the group consisting of


; 
; 
; 
; 
; 
; 
; and 
;

wherein the  indicates the atom through which the **PA** is bonded to the adjacent groups in the formula.

77. The compound of claim 1, wherein the payload moiety is a drug moiety.

78. The compound of claim 1, wherein the payload moiety is a biologically active molecule.

79. The compound of claim 1, wherein the payload moiety is the residue of a group selected from the group consisting of dolastatins, auristatins, maytansinoids, plant alkaloids, taxanes, vinca alkaloids, steroids, LXR modulators, pyrrolobenzodiazepines, tubulysins, and camptothecins.

80. The compound of claim 1, wherein the payload moiety is the residue of a maytansinoid, steroid, LXR modulator, pyrrolobenzodiezepine, tubulysin, or camptothecin.

81. The compound of claim 1 wherein the payload moiety is a residue of an auristatin.

82. The compound of claim 1 wherein the payload moiety is a residue of a maytansinoid.

83. The compound of claim 1 wherein the payload moiety is a residue of a glucocorticoid.

84. The compound of claim 1 wherein the payload moiety is a residue of a liver X receptor modulator.

85. The compound of claim 35 wherein the payload moiety is a drug moiety.

86. The compound of claim 35 wherein the payload moiety is a biologically active molecule.

87. The compound of claim 35 wherein the payload moiety is the residue of ~~a~~ dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, a vinca alkaloid, a steroid, an LXR modulator, a pyrrolobenzodiazepine, and SN-38.

88. The compound of claim 35 wherein the payload moiety is the residue of a maytansinoid, a steroid, an LXR modulator, a pyrrolobenzodiezepine, or camptothecin.

89. The compound of claim 34 wherein the payload moiety is a residue of an auristatin.

90. The compound of claim 34 wherein the payload moiety is a residue of a maytansinoid.

91. The compound of claim 35 wherein the payload moiety is a residue of a glucocorticoid.

92. The compound of claim 35 wherein the payload moiety is a residue of a liver X receptor modulator.

93. The compound of any one of claims 1-31, wherein the binding agent is a glutaminyl-modified antibody.

94. The compound of claim 93, wherein the glutaminyl-modified antibody is an antibody modified with an azido-polyethylene glycol-primary amine compound.

95. The compound of claim 1, wherein the binding agent is an antibody conjugated to a primary amine compound at a glutamine residue, and L is bonded to BA through said primary amine compound.

96. The compound of claim 95, wherein the primary amine compound comprises a divalent PEG group.