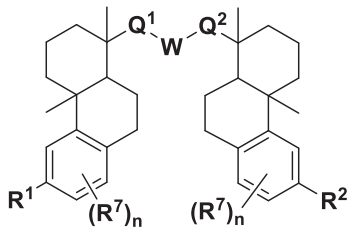
al. 2016; Meffre *et al*. 2014) Inflammation includes inflammatory bowel disease, ulcerative colitis, Crohn's disease, and arthritis. (Anderson *et al*. 2011; Huang *et al*. 2015; Cui *et al*. 2012). Macrophage LXRs are known to include anti-atherogenic activity. LXR agonists are believed to be capable of (i) inhibiting the initiation and delay the progression of atherosclerosis; (ii) mitigating atherosclerosis and stabilizing established atherosclerotic lesions; and (iii) reducing lesion macrophage content by apoptosis.

[0005] The therapeutic potential of small molecule LXR modulators is limited by, for example, undesired modulation of LXR at non-target cells and/or low bioavailability. Modulation of LXR at non-target cells can lead to undesirable side effects, and low bioavailability may manifest for myriad reasons including, without limitation, low solubility that further exacerbates poor therapeutic windows for treatment. The development of ADCs comprising LXR modulators would allow for target-specific modulation of LXR, thereby avoiding side-effects caused by off-target modulation of LXR. Furthermore, such ADCs would provide improved modulation of biological targets, improved bioavailability, and improved therapeutic window. Therefore, there is a continuing need for effective treatments of, for example, metabolic diseases using small molecule ADCs of LXR modulators.

SUMMARY

[0006] Provided herein are compounds useful, for example, for the treatment of metabolic diseases including, without limitation, dyslipidemia. Also provided herein are compounds useful, for example, for the treatment of inflammation or a neurodegenerative disease. The compounds provided herein are according to Formula I.

[0006a] In one aspect, the present disclosure relates to a compound of Formula I



(I)

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

each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently $–CH_2–$, –C(O)–, –C(H)(OH)–, $–C(OH)_2–$, $–SO_2–$, –SO–, –PO(O$\mathbf{R^{11}}$)–, –PO(N$\mathbf{R^{11}}$N$\mathbf{R^{12}}$)–, –N$\mathbf{R^{11}}$–, or –N=;

W is $–CH_2–$, –N(H)–, or –O–;

$\mathbf{R^1}$ is independently –OH, $–NH_2$, alkyl, or $–OP(O)(O\mathbf{R^6})_2$;

$\mathbf{R^2}$ is independently $–CH_2NH_2$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, or $–O–\mathbf{R^5}$;

wherein at least one of R^1 or R^2 is –OH or $–NH_2$;

$\mathbf{R^3}$ is $–N(\mathbf{R^6})_2$;

$\mathbf{R^4}$ is –**X**–**Y**–**Z**;

X is selected from the group consisting of –O– and –N(H)–;

Y is selected from the group consisting of alkylene, substituted alkylene, heteroalkylene, and substituted heteroalkylene;

Z is selected from the group consisting of –OH and $–NH_2$;

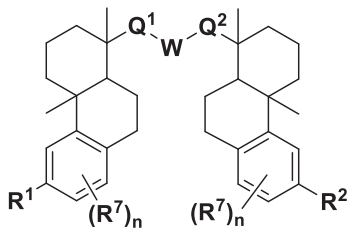
$\mathbf{R^5}$ is alkyl, heterocycloalkyl, or substituted heterocycloalkyl, wherein each heterocycloalkyl or substituted heterocycloalkyl comprises one, two, or three heteroatoms selected from nitrogen and oxygen, and includes at least one –OH and $–CH_2OH$, or at least one primary or secondary nitrogen;

each $\mathbf{R^6}$ is, independently in each instance, hydrogen, an amino acid residue, an *N*-alkyl amino acid residue, a peptide, or alkyl;

each $\mathbf{R^7}$ is independently halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, or $O\text{-}PEG_{\mathbf{n}}$, wherein each **n** is an integer from zero to three; and

each R^{11} and R^{12} are independently hydrogen, alkyl, or aryl.

[0007] In one example, provided herein are compounds according to Formula I:



(I)

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

each of Q^1 and Q^2 includes, independently, $–CH_2–$, –C(O)–, –C(H)(OH)–, $–C(OH)_2–$, $–SO_2–$, –SO–, $–PO(OR^{11})–$, $–PO(NR^{11}NR^{12})–$, $–NR^{11}–$, or –N=;

$\mathbf{R^1}$ includes –H, –OH, $–NH_2$, alkyl, or $–OP(O)(O\mathbf{R^6})_2$;

$\mathbf{R^2}$ includes –H, –OH, $–CH_2NH_2$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, or $–O–\mathbf{R^5}$, wherein $\mathbf{R^1}$ and $\mathbf{R^2}$ are not simultaneously –H;

$\mathbf{R^3}$ includes $–N(\mathbf{R^6})_2$;

$\mathbf{R^4}$ includes –**X**–**Y**–**Z**;

X includes the group consisting of –O– and –N(H)–;

Y includes the group consisting of alkylene, substituted alkylene (including, without limitation, oxo substitution (i.e., =O)), heteroalkylene, and substituted heteroalkylene (including, without limitation, oxo substitution (i.e., =O));

Z includes the group consisting of –OH and $–NH_2$;

$\mathbf{R^5}$ includes alkyl, heterocycloalkyl, or substituted heterocycloalkyl, wherein each heterocycloalkyl or substituted heterocycloalkyl includes one, two, or three heteroatoms selected from nitrogen and oxygen, and includes at least one –OH or $–CH_2OH$ substituent, or at least one primary or secondary nitrogen, for instance, O-glucose;

each $\mathbf{R^6}$ includes, independently in each instance, –H, an amino acid residue, an *N*-alkyl amino acid residue, a peptide, or alkyl; and

each $\mathbf{R^7}$ independently includes halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, and $O\text{-}PEG_n$, wherein each n is an integer from 0-3.

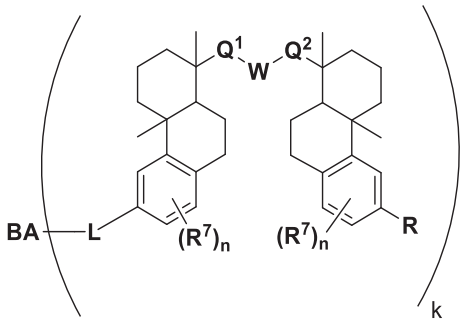
[0008a] In another aspect, the present disclosure relates to a linker-payload comprising the compound as defined herein, bonded to a linker.

[0009] In another example, set forth herein is a linker-payload having a compound according to Formula I, above.

[0009a] In another aspect, the present disclosure relates to an antibody-drug conjugate comprising the compound as defined herein or linker-payload as defined herein bonded to an antibody or an antigen binding fragment thereof.

[0010] In another example, set forth herein is an antibody-drug conjugate having a compound of Formula I or linker-payload, above, bonded to an antibody or an antigen binding fragment thereof.

[0010a] In another aspect, the present disclosure relates to a compound of Formula **A**:



(**A**)

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

L is a linker;

BA is a binding agent;

k is an integer from one to thirty;

each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently $–CH_2–$, –C(O)–, –C(H)(OH)–, or $–C(OH)_2–$;

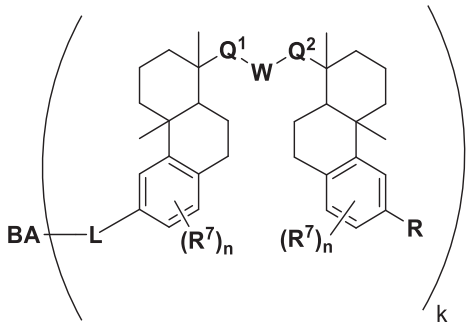
W is $–CH_2–$, –N(H)–, or –O–;

R is independently –OH, $C_{1\text{-}6}$alkyl, or $–OP(O)(O\mathbf{R^6})(OH)$;

each $\mathbf{R^6}$ is, independently in each instance, hydrogen, an amino acid residue, a peptide, or alkyl; and

each R^7 is independently halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, or $O\text{-}PEG_{\mathbf{n}}$, wherein each n is an integer from zero to three.

[0011] In another example, set forth herein are compounds according to Formula **A**:



(A)

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

L is a linker;

BA is a binding agent;

k is an integer from 1 to 30;

each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently $–CH_2–$, –C(O)–, –C(H)(OH)–, or $–C(OH)_2–$;

W is $–CH_2–$, –N(H)–, or –O–;

R is independently –H, –OH, or $–OP(O)(O\mathbf{R^6})_2$; and

each $\mathbf{R^6}$ is, independently in each instance, –H, an amino acid residue, an *N*-alkyl amino acid residue, a peptide, or alkyl; and

each $\mathbf{R^7}$ is independently halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, and $O\text{-}PEG_{\mathbf{n}}$, wherein each **n** is an integer from 0-3.

[0011a] In another aspect, the present disclosure relates to a pharmaceutical composition comprising the compound as defined herein, or the antibody-drug conjugate as defined herein, and a pharmaceutically acceptable excipient, carrier, or diluent.

[0012] In another example, set forth herein is a pharmaceutical composition, including a compound, linker-payload, or antibody-drug conjugate described herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[0013] In another example, set forth herein is a method for the treatment of dyslipidemia, a metabolic disease, inflammation, or a neurodegenerative disease in a subject including the administration to the subject of an effective treatment amount of a compound, linker-payload, or antibody-drug conjugate, or pharmaceutical composition described herein.

[0013a] In another aspect, the present disclosure relates to use of a composition comprising a compound as defined herein, or the antibody-drug conjugate as defined herein in the manufacture of a medicament for the treatment of dyslipidemia, a metabolic disease, inflammation, or a neurodegenerative disease in a subject.

[0013b] In another aspect, the present disclosure relates to use of a composition comprising a compound as defined herein, or the antibody-drug conjugate as defined herein in the manufacture of a medicament for the treatment of dyslipidemia in a subject.

[0013c] In another aspect, the present disclosure relates to use of a composition comprising a compound as defined herein, or the antibody-drug conjugate as defined herein in the manufacture of a medicament for the treatment of a metabolic disease in a subject.

[0013d] In another aspect, the present disclosure relates to use of a composition comprising a compound as defined herein, or the antibody-drug conjugate as defined herein in the manufacture of a medicament for the treatment of inflammation in a subject.

[0013e] In another aspect, the present disclosure relates to use of a composition comprising a compound as defined herein, or the antibody-drug conjugate as defined herein in the manufacture of a medicament for the treatment of a neurodegenerative disease in a subject.

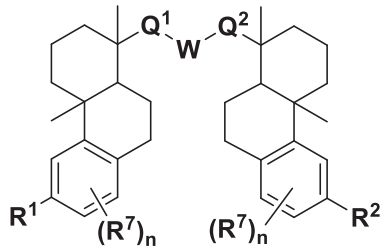
[0014] In another example, set forth herein are methods for making the compounds, linker-payloads, or antibody-drug conjugates, and compositions described herein.

BRIEF DESCRIPTIONS OF THE DRAWING

[0015] FIGS. 1, 1a-1i, 2, 3a-3e, and 4-10 show synthetic chemistry schemes for bis-octahydrophenanthrene carboxamides, cyclodextrin-based linker-payloads, and protein conjugates thereof.

WHAT IS CLAIMED IS:

1. A compound of Formula I



(I)

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

each of **Q**^{1} and **Q**^{2} is independently –CH_2–, –C(O)–, –C(H)(OH)–, –$C(OH)_2$– , –SO_2–, –SO–, –PO(O**R**^{11})–, –PO(N**R**^{11}N**R**^{12})–, –N**R**^{11}–, or –N=;

W is –CH_2–, –N(H)–, or –O–;

R^{1} is independently–OH, –NH_2, alkyl, or –OP(O)(O**R**^{6})$_2$;

R^{2} is independently –CH_2NH_2, **R**^{3}, **R**^{4}, **R**^{5}, or –O–**R**^{5};

wherein at least one of **R**^{1} or **R**^{2} is –OH or –NH_2;

R^{3} is –N(**R**^{6})$_2$;

R^{4} is –**X**–**Y**–**Z**;

X is selected from the group consisting of –O– and –N(H)–;

Y is selected from the group consisting of alkylene, substituted alkylene, heteroalkylene, and substituted heteroalkylene;

Z is selected from the group consisting of –OH and –NH_2;

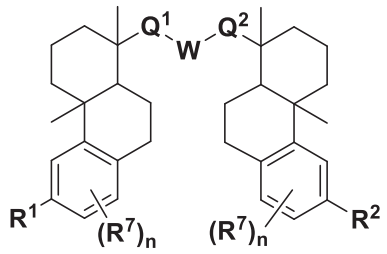
R^{5} is alkyl, heterocycloalkyl, or substituted heterocycloalkyl, wherein each heterocycloalkyl or substituted heterocycloalkyl comprises one, two, or three heteroatoms selected from nitrogen and oxygen, and includes at least one –OH and –CH_2OH, or at least one primary or secondary nitrogen;

each **R**^{6} is, independently in each instance, hydrogen, an amino acid residue, an *N*-alkyl amino acid residue, a peptide, or alkyl;

each **R**^{7} is independently halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, or O-PEG$_{\mathbf{n}}$, wherein each **n** is an integer from zero to three; and

each **R**^{11} and **R**^{12} are independently hydrogen, alkyl, or aryl.

2. The compound of claim 1, according to Formula I



(I)

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

each of **Q**^{1} and **Q**^{2} is independently –CH_2–, –C(O)–, –C(H)(OH)–, or –$C(OH)_2$–;

W is –CH_2–, –N(H)–, or –O–;

R^{1} is independently –OH, –NH_2, alkyl, or –OP(O)(O**R**^{6})$_2$;

R^{2} is independently –CH_2NH_2, **R**^{3}, **R**^{4}, **R**^{5}, or –O–**R**^{5};

R^{3} is –N(**R**^{6})$_2$;

R^{4} is –**X**–**Y**–**Z**;

X is selected from the group consisting of –O– and –N(H)–;

Y is selected from the group consisting of alkylene, substituted alkylene, heteroalkylene, and substituted heteroalkylene;

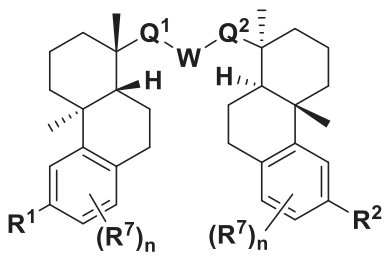
Z is selected from the group consisting of –OH and –NH_2;

R^{5} is alkyl, heterocycloalkyl, or substituted heterocycloalkyl, wherein each heterocycloalkyl or substituted heterocycloalkyl comprises one, two, or three heteroatoms selected from nitrogen and oxygen, and includes at least one –OH and –CH_2OH, or at least one primary or secondary nitrogen;

each **R**^{6} is, independently in each instance, hydrogen, an amino acid residue, an *N*-alkyl amino acid residue, a peptide, or alkyl; and

each **R**^{7} is independently halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, or O-PEG$_{\mathbf{n}}$, wherein each **n** is an integer from zero to three.

3. The compound of claim 1, according to Formula Ia



(Ia)

or a pharmaceutically acceptable salt, solvate, or stereoisomeric form thereof.

4. The compound of claim 1, wherein $\mathbf{Q^1}$ is –CH_2– and $\mathbf{Q^2}$ is –C(O)–.

5. The compound of claim 1, wherein $\mathbf{Q^1}$ is –C(H)(OH)– and $\mathbf{Q^2}$ is –C(O)–.

6. The compound of claim 1, wherein $\mathbf{Q^1}$ is –C(O)– and $\mathbf{Q^2}$ is –C(O)–.

7. The compound of claim 1, wherein $\mathbf{Q^1}$ is –C(O)– and $\mathbf{Q^2}$ is **–**CH_2–.

8. The compound of claim 1, wherein $\mathbf{Q^1}$ is –C(O)– and $\mathbf{Q^2}$ is –C(H)(OH)–.

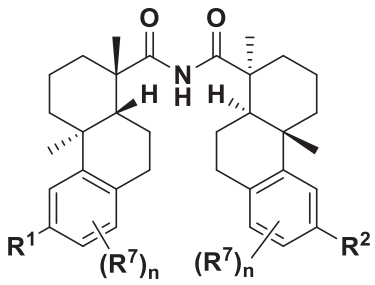
9. The compound of claim 1, wherein **W** is **–**CH_2**–**.

10. The compound of claim 1, wherein **W** is **–**O**–**.

11. The compound of claim 1, wherein **W** is **–**NH**–**.

12. The compound of claim 1, wherein $\mathbf{R^1}$ is –OH and $\mathbf{R^2}$ is $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, or –O–$\mathbf{R^5}$.

13. The compound of claim 1, according to Formula Ib



(Ib)

or a pharmaceutically acceptable salt, solvate, or stereoisomeric form thereof.

14. The compound of claim 1, wherein $\mathbf{R^1}$ is –OH.

15. The compound of claim 1, wherein $\mathbf{R^2}$ is –O–$(CH_2)_n$–**Z** and **n** is an integer from one to four.

16. The compound of claim 1, wherein $\mathbf{R^2}$ is –N(H)C(O)–$(CH_2)_n$–NH_2 and **n** is an integer from one to four.

17. The compound of claim 1, wherein $\mathbf{R^2}$ is –N(H)C(O)–(C**RR**)$_n$–NH_2 wherein each **R** is hydrogen, –OH or –CH_2OH; and **n** is an integer from one to four.

18. The compound of claim 1, wherein $\mathbf{R^2}$ is *N*-piperazinyl.

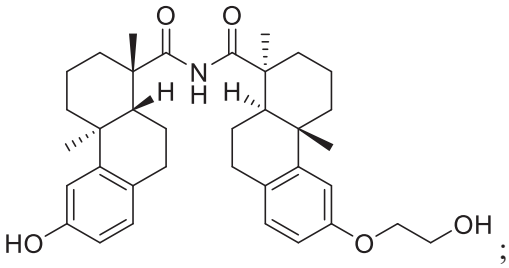
19. The compound of claim 1, wherein $\mathbf{R^2}$ is –N($\mathbf{R^6}$)$_2$.

20. The compound of claim 1, wherein $\mathbf{R^2}$ is *N*-serinyl.

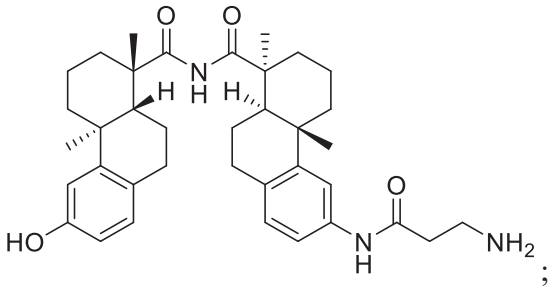
21. The compound of claim 1, wherein $\mathbf{R^2}$ is *O*-glycosyl.

22. The compound of claim 1, wherein $\mathbf{R^1}$ is –OP(O)(O$\mathbf{R^6}$)(OH) and $\mathbf{R^2}$ is –NH_2.

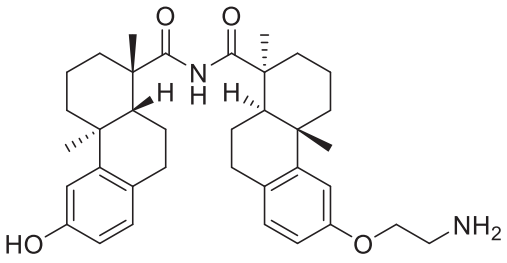
23. The compound of claim 1, selected from the group consisting of



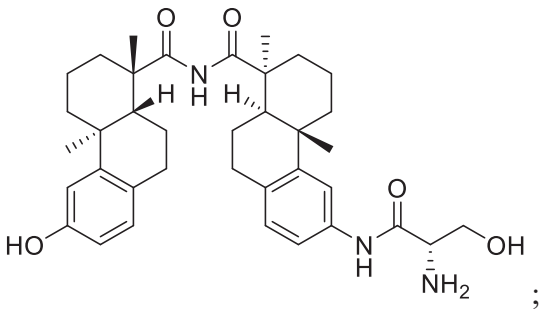
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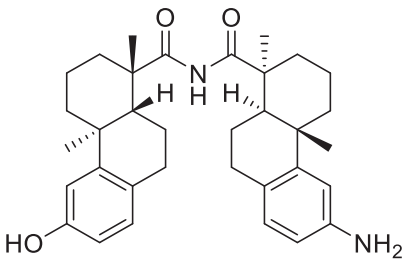
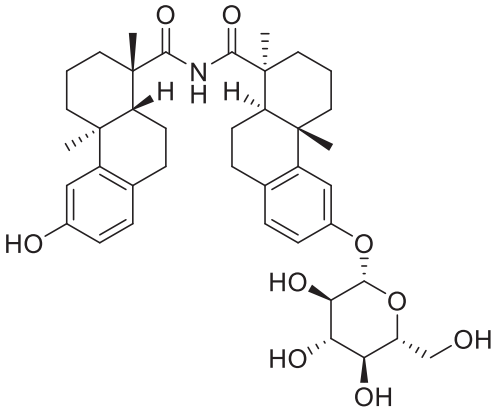
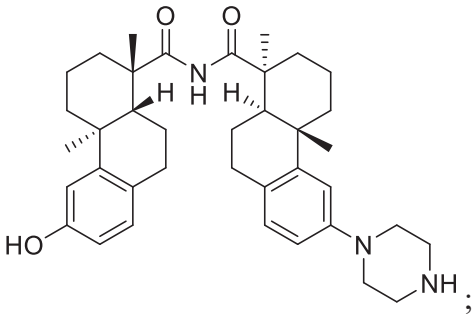
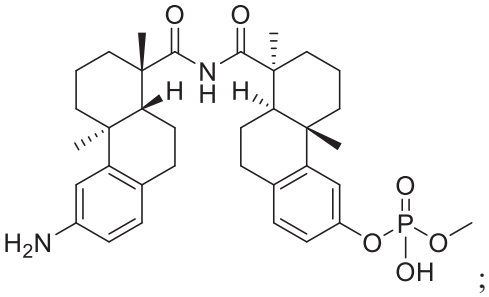
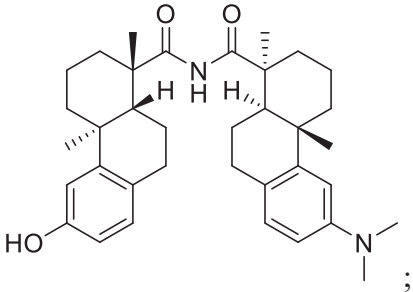
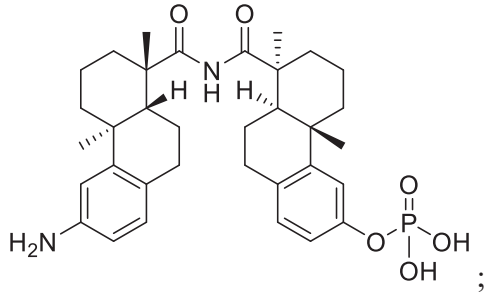
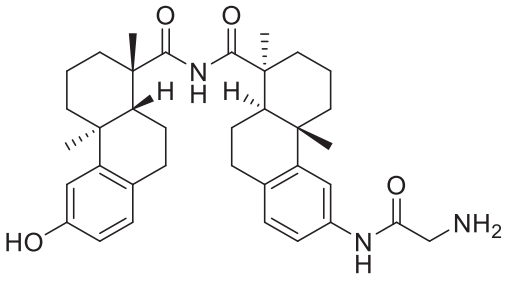
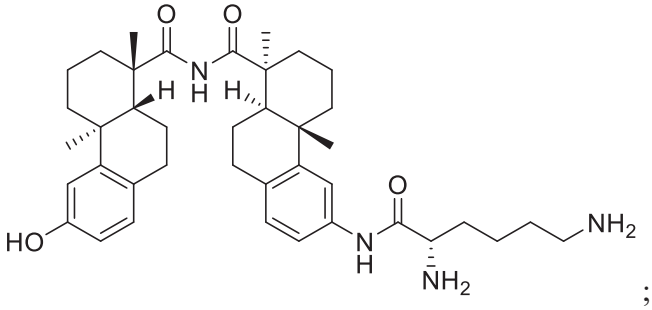
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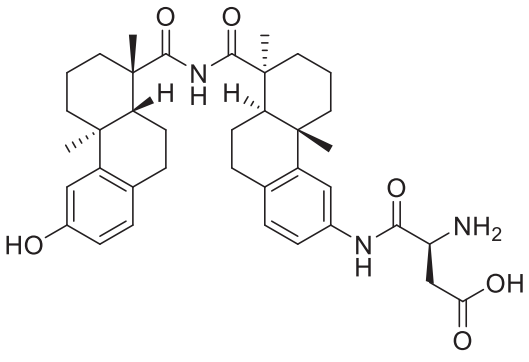
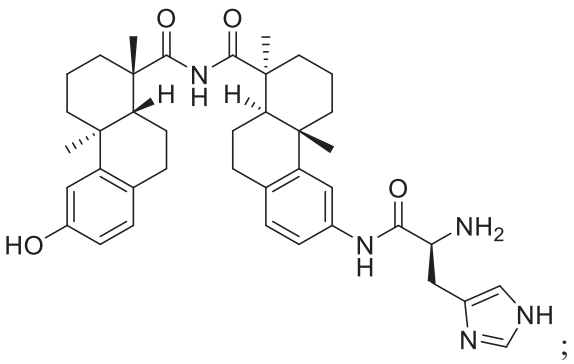
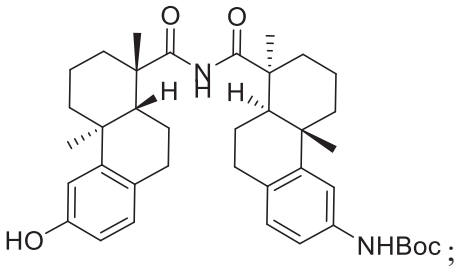
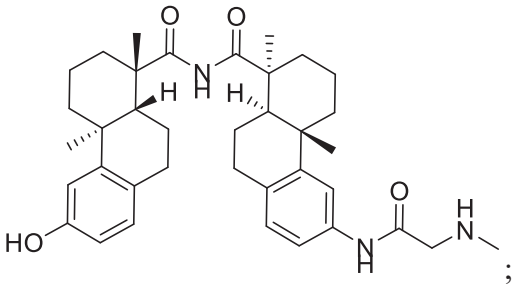
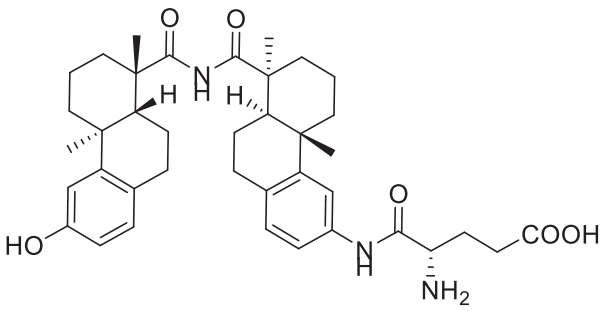
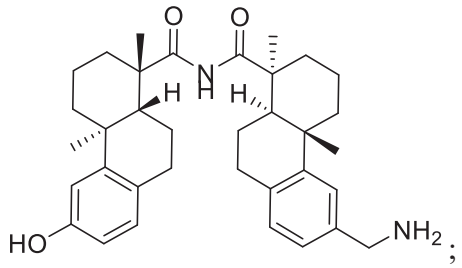
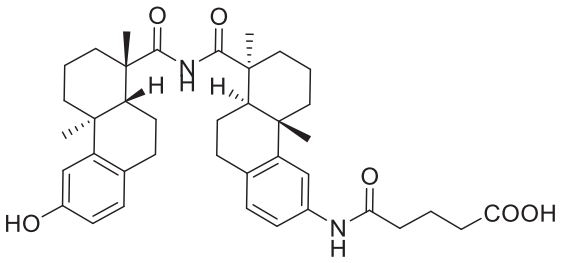
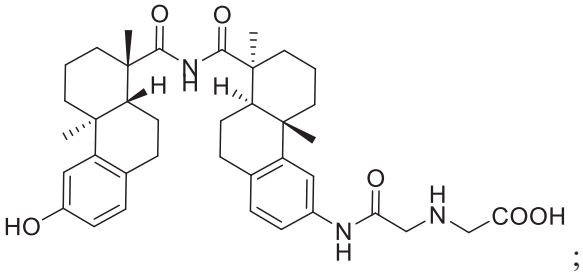
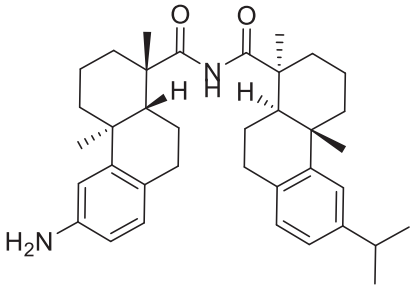


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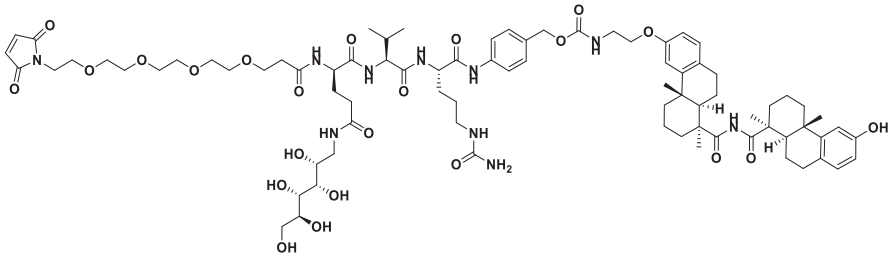

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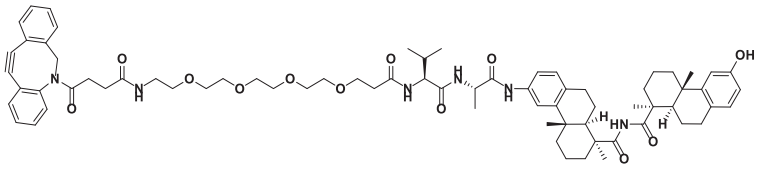

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and ; or a pharmaceutically acceptable salt, solvate, or stereoisomeric form thereof.

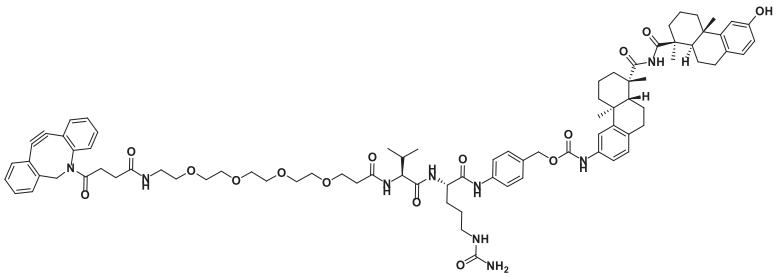
24. A linker-payload comprising the compound of claim 1, bonded to a linker.

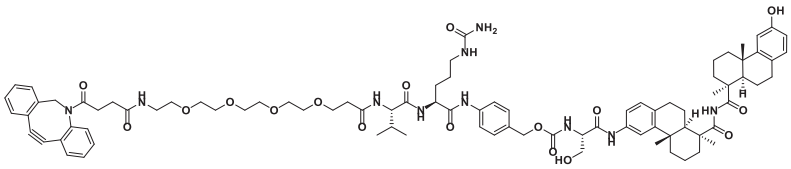
25. The linker-payload of claim 24, wherein the linker is bonded to an oxygen or a primary or secondary nitrogen of the compound of the preceding claims.

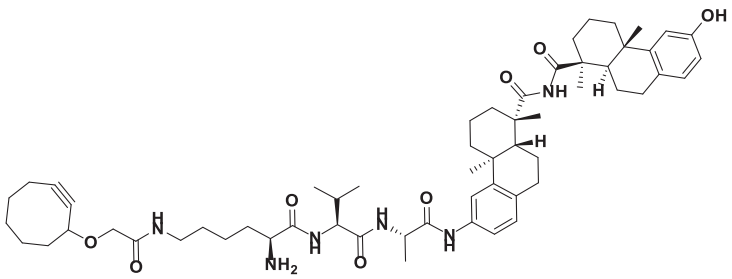
26. The linker-payload of claim 24, selected from the group consisting of

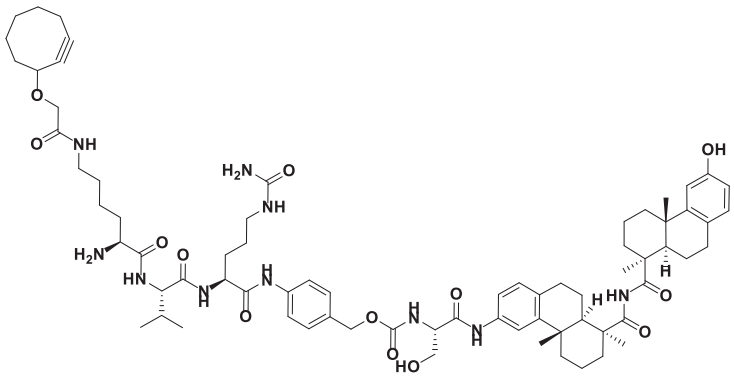

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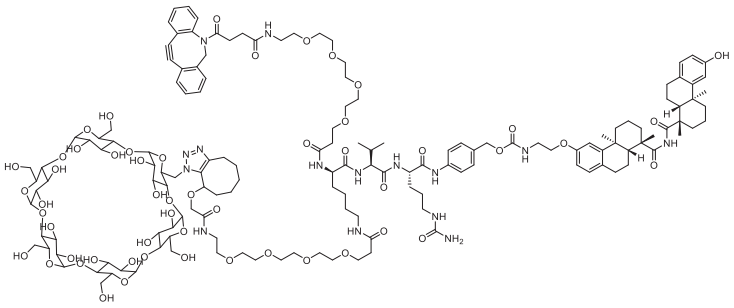

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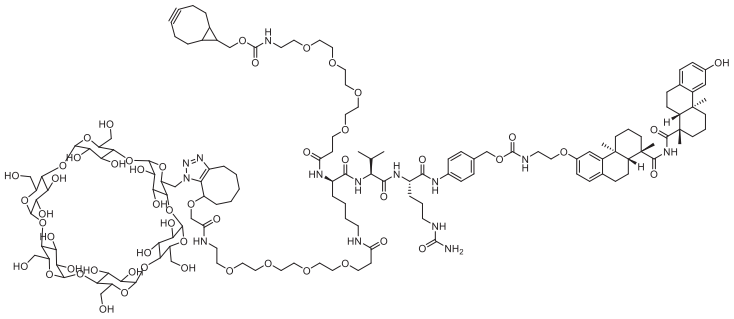

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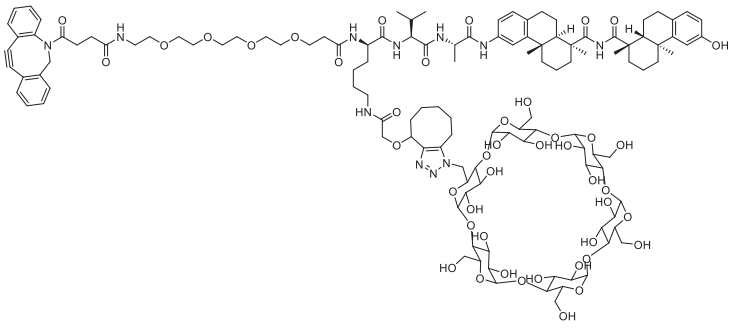
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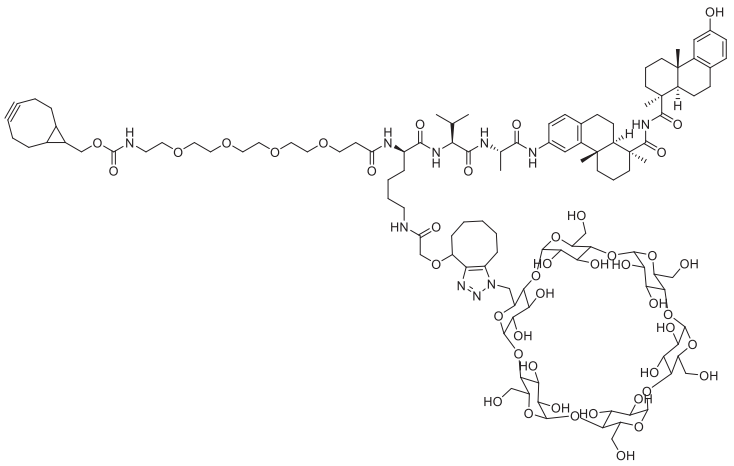
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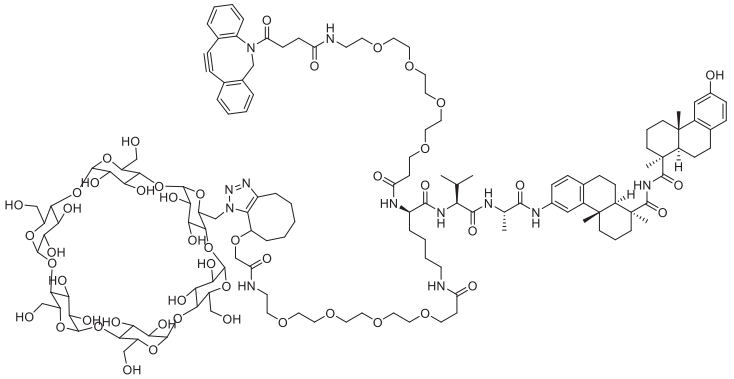
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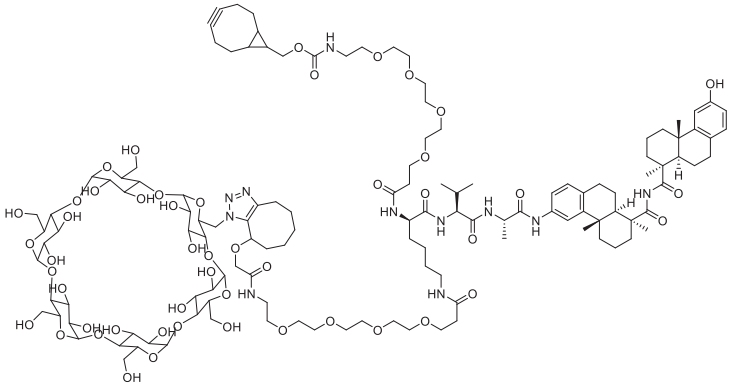
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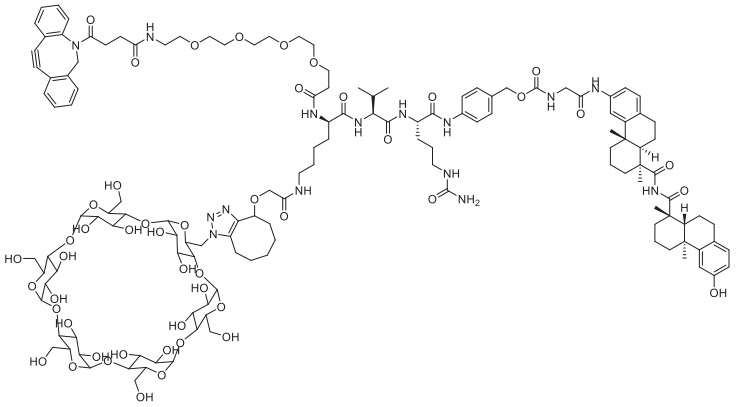
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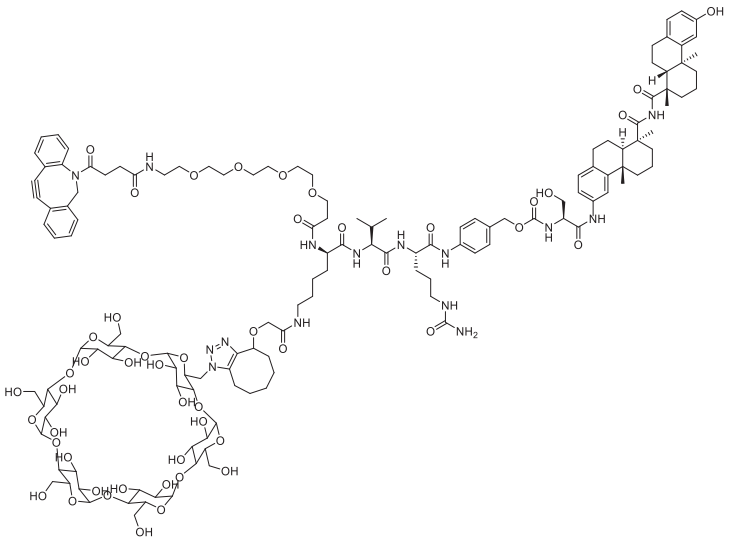
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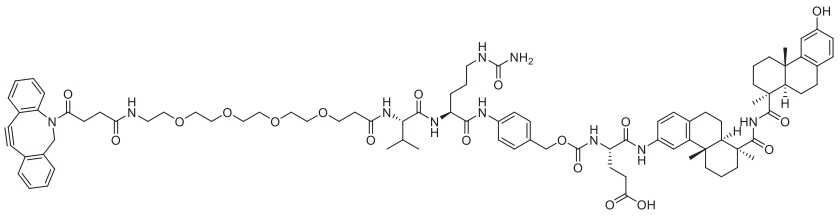
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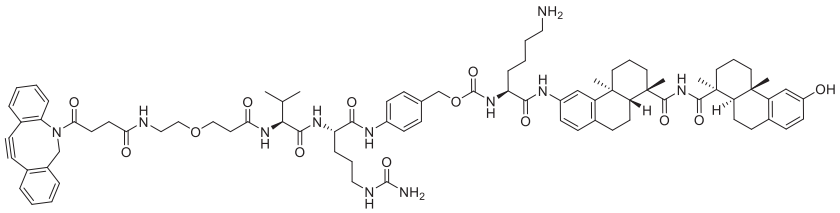
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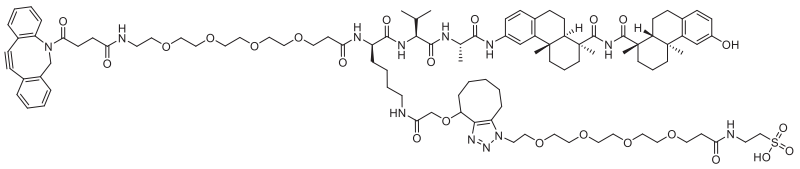
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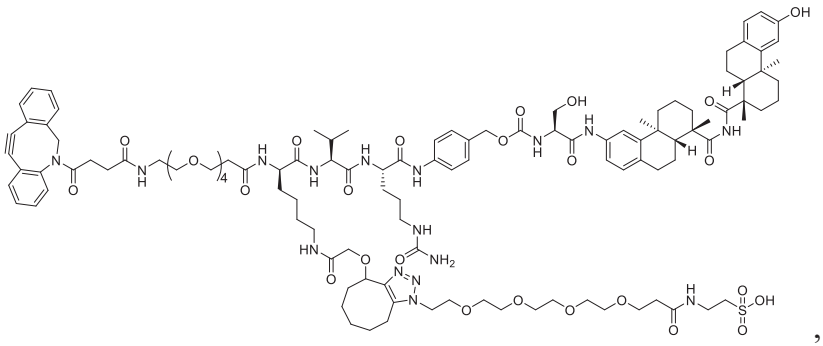
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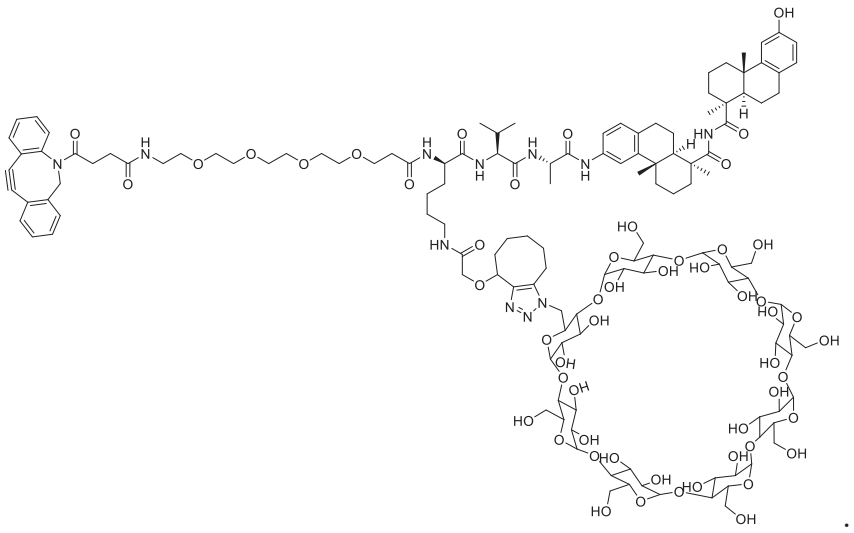
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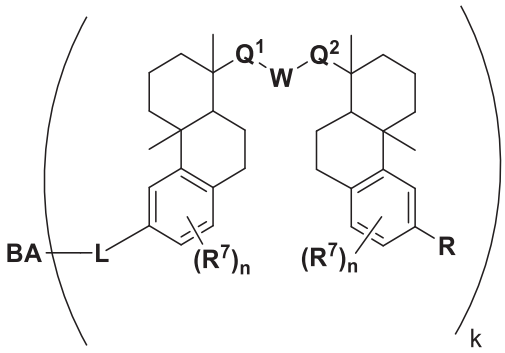


, and



27. An antibody-drug conjugate comprising the compound of any one of claims 1-23 or 47-50 or linker-payload of any one of claims 24-26 or 51-54 bonded to an antibody or an antigen binding fragment thereof.

28. A compound of Formula **A**



(**A**)

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

L is a linker;

BA is a binding agent;

k is an integer from one to thirty;

each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently $–CH_2–$, –C(O)–, –C(H)(OH)–, or $–C(OH)_2–$;

W is $–CH_2–$, –N(H)–, or –O–;

R is independently –OH, $C_{1\text{-}6}$alkyl, or $–OP(O)(O\mathbf{R^6})(OH)$;

each $\mathbf{R^6}$ is, independently in each instance, hydrogen, an amino acid residue, a peptide, or alkyl; and

each $\mathbf{R^7}$ is independently halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, –CN, O-glucose, O-amino acid residue, or O-$PEG_{\mathbf{n}}$, wherein each **n** is an integer from zero to three.

29. A pharmaceutical composition comprising the compound of any one of claims 1-23, 28, 47-50 or 55-58, or the antibody-drug conjugate of claim 27, and a pharmaceutically acceptable excipient, carrier, or diluent.

30. Use of a composition comprising a compound of any one of claims 1-23, 28, 47-50 or 55-58, or the antibody-drug conjugate of claim 27 in the manufacture of a medicament for the treatment of dyslipidemia, a metabolic disease, inflammation, or a neurodegenerative disease in a subject.

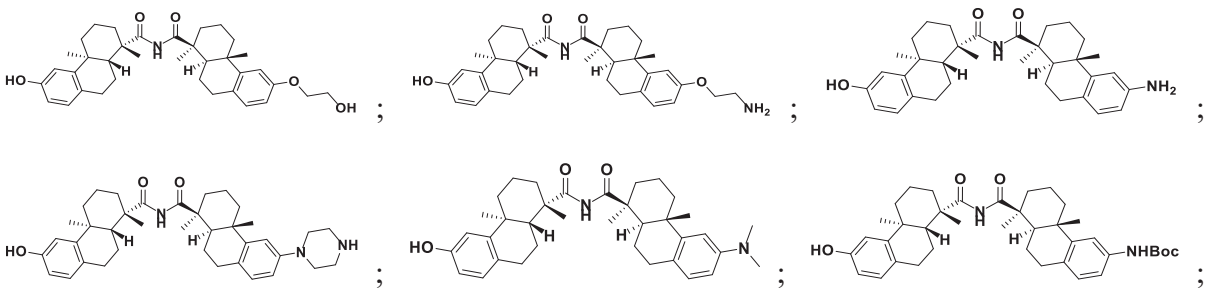
31. Use of a composition comprising a compound of any one of claims 1-23, 28, 47-50 or 55-58, or the antibody-drug conjugate of claim 27 in the manufacture of a medicament for the treatment of dyslipidemia in a subject.

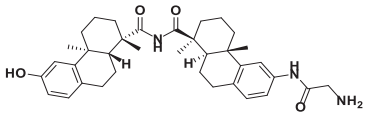
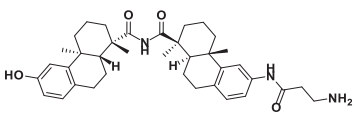
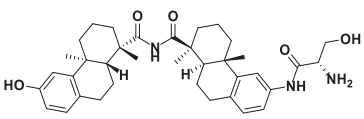
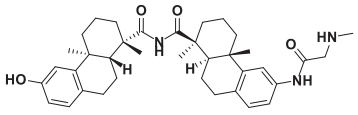
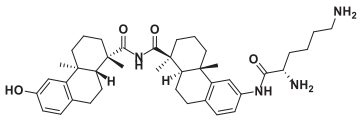
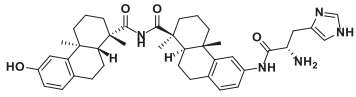
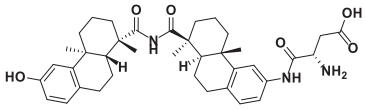
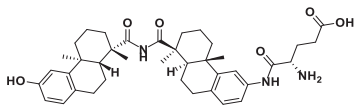
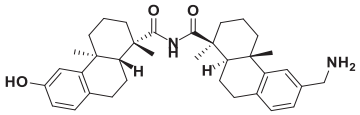
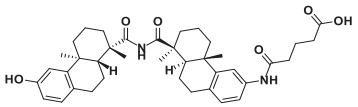
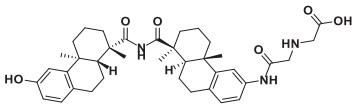
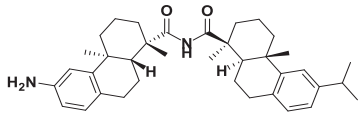
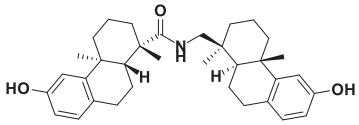
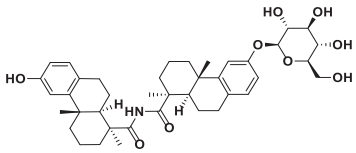
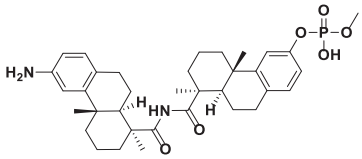
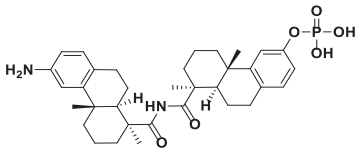
32. Use of a composition comprising a compound of any one of claims 1-23, 28, 47-50 or 55-58, or the antibody-drug conjugate of claim 27 in the manufacture of a medicament for the treatment of a metabolic disease in a subject.

33. Use of a composition comprising a compound of any one of claims 1-23, 28, 47-50 or 55-58, or the antibody-drug conjugate of claim 27 in the manufacture of a medicament for the treatment of inflammation in a subject.

34. Use of a composition comprising a compound of any one of claims 1-23, 28, 47-50 or 55-58, or the antibody-drug conjugate of claim 27 in the manufacture of a medicament for the treatment of a neurodegenerative disease in a subject.

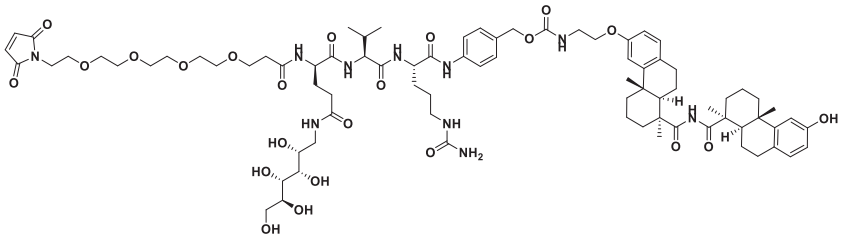
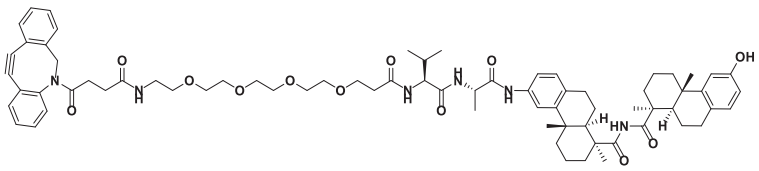
35. The compound of claim 28 comprising **BA** linked via a linker **L** to a compound selected from the group consisting of

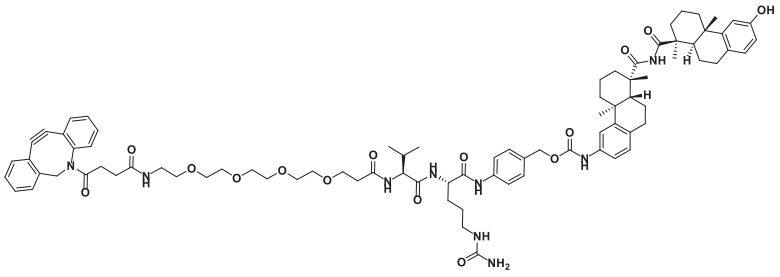



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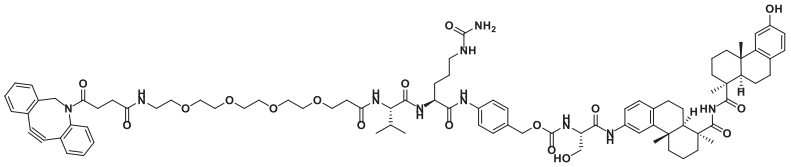
a regioisomer, stereoisomeric form, pharmaceutically acceptable salt, or solvate thereof, wherein **k** is an integer from one to four.

36. The compound of claim 28, comprising **BA** linked to a compound selected from the group consisting of

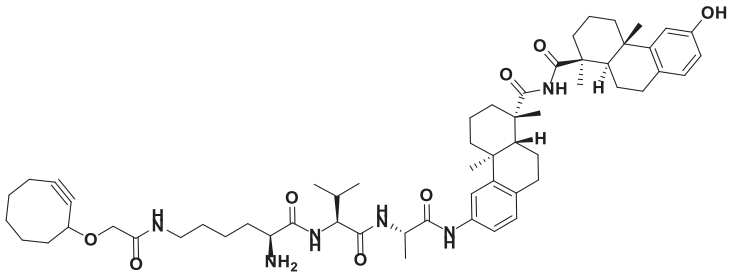

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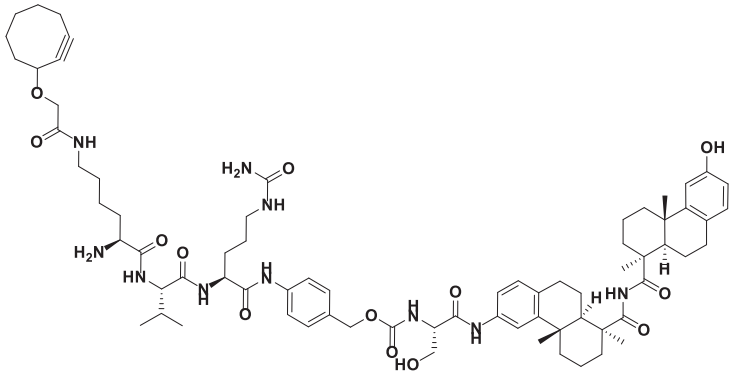
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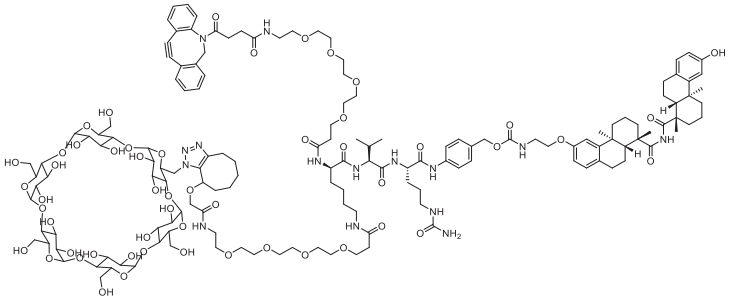
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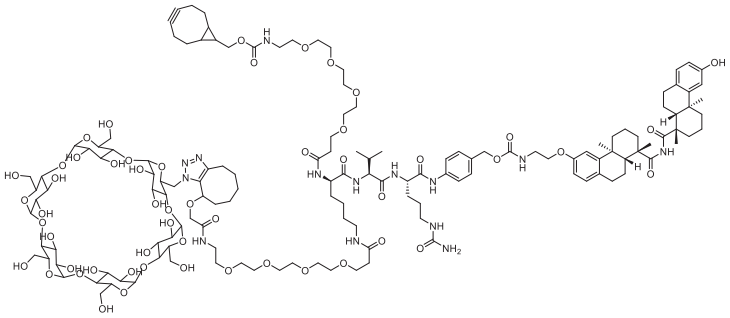
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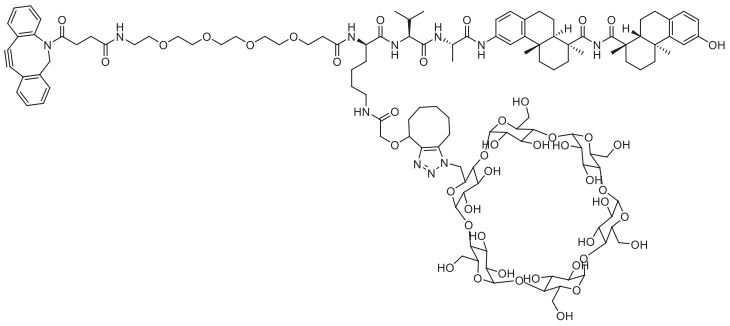
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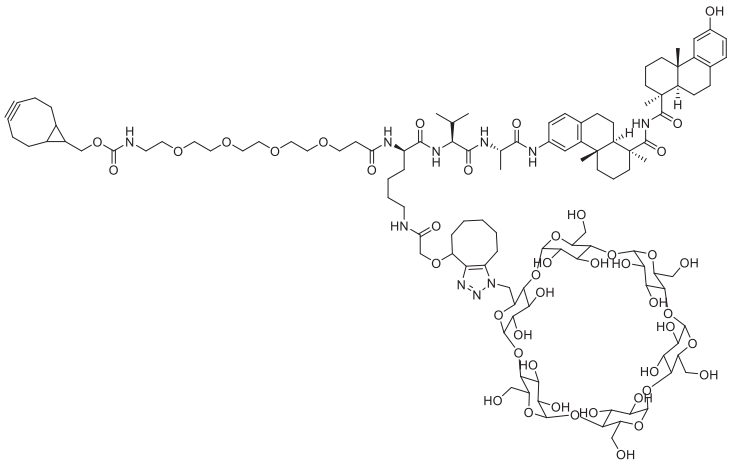
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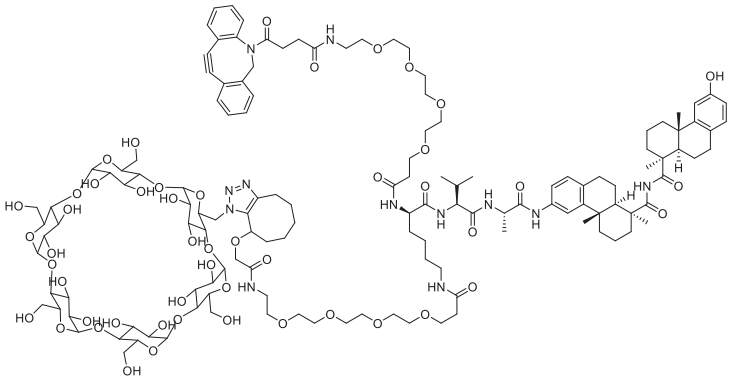
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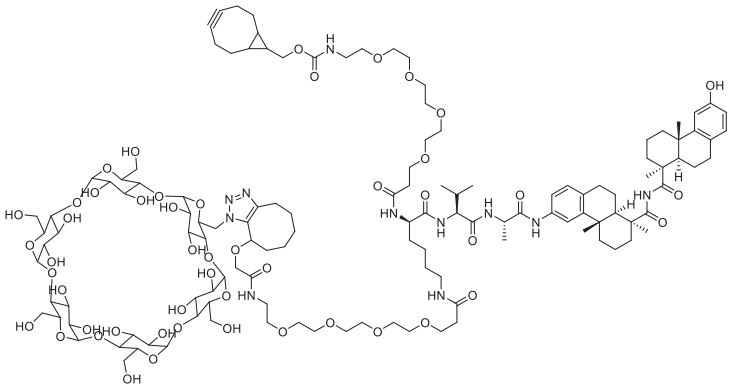
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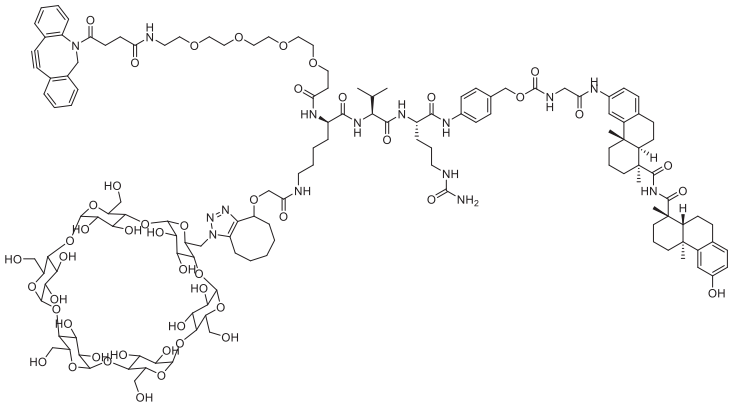
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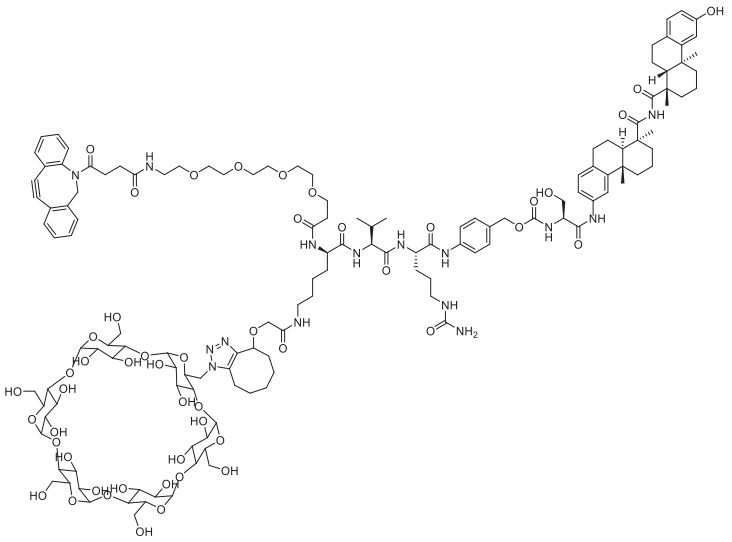
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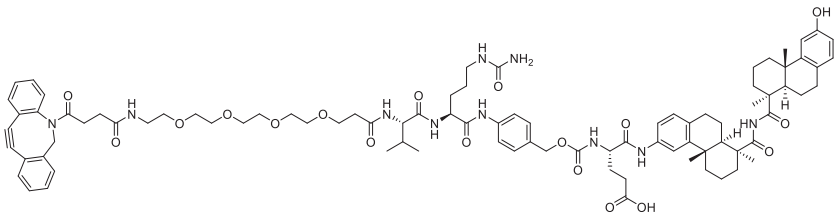
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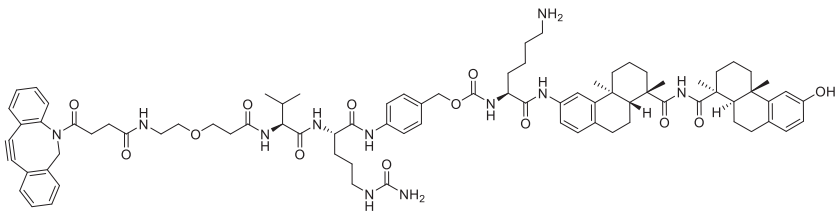
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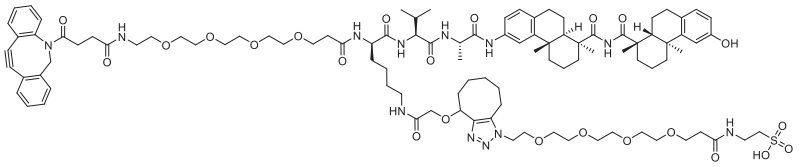
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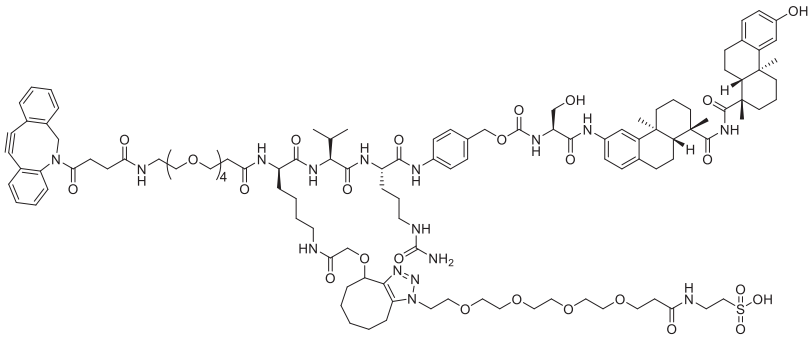
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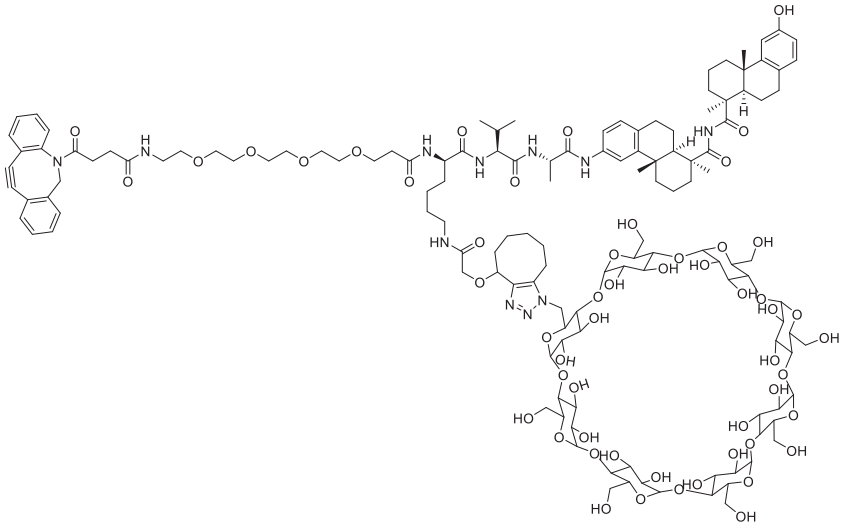
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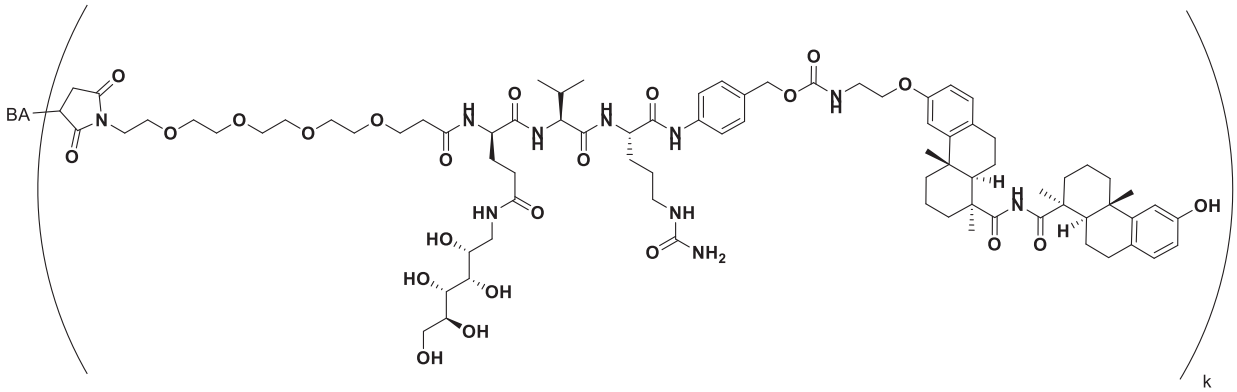
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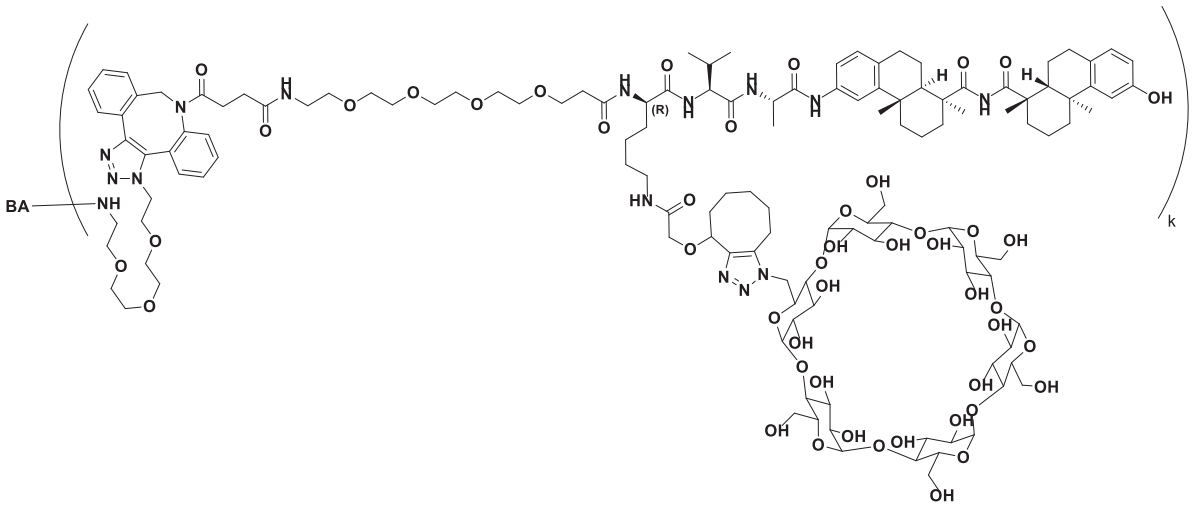
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a regioisomer, stereoisomeric form, pharmaceutically acceptable salt, or solvate thereof, wherein **k** is an integer from one to four.

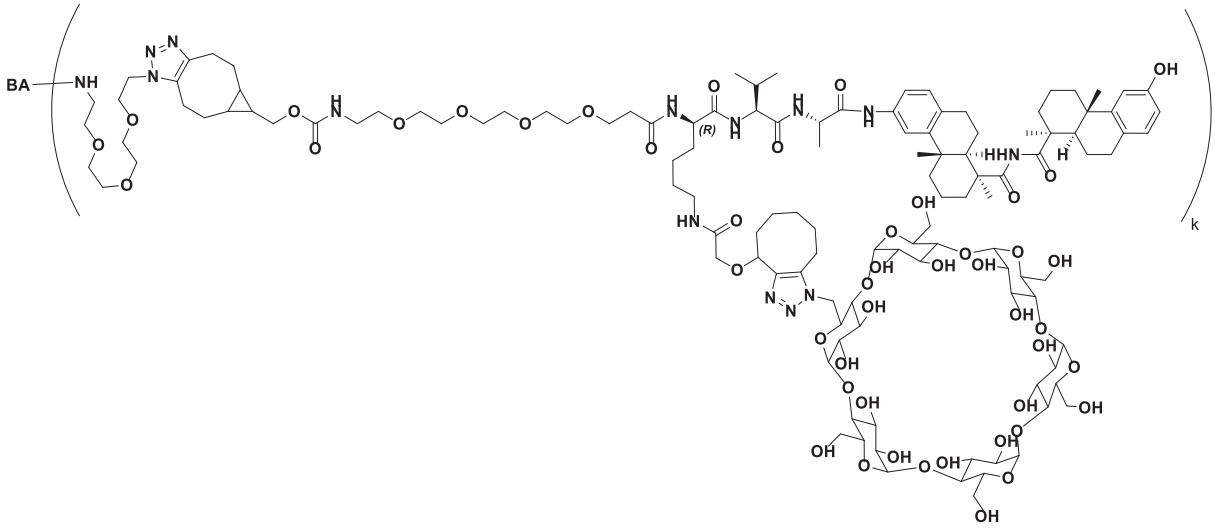
37. The compound of claim 28, selected from the group consisting of

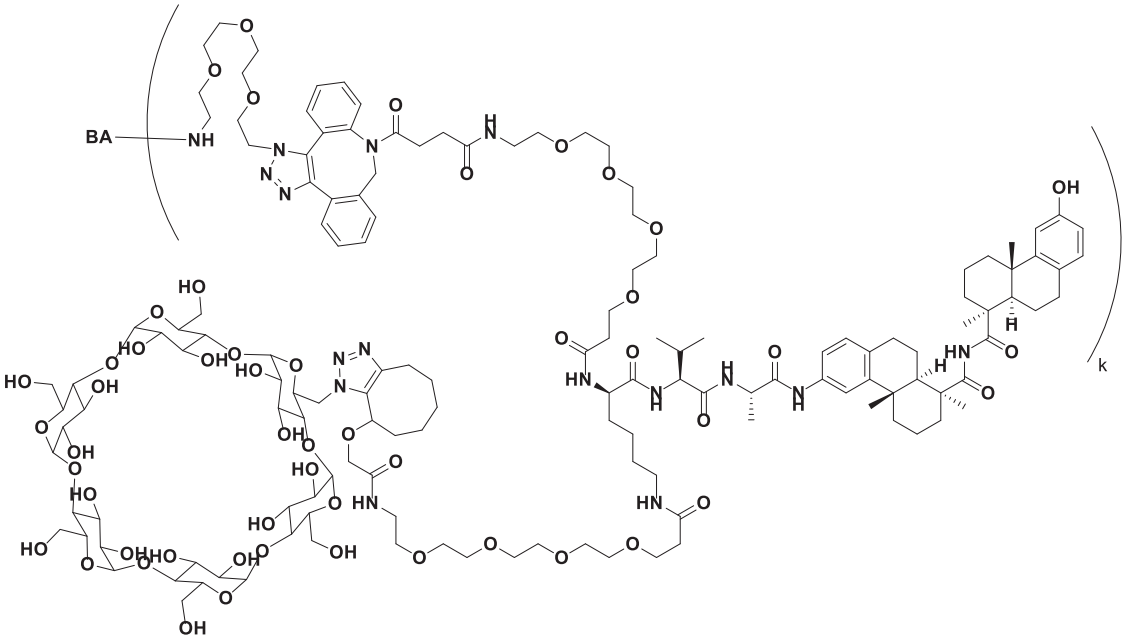


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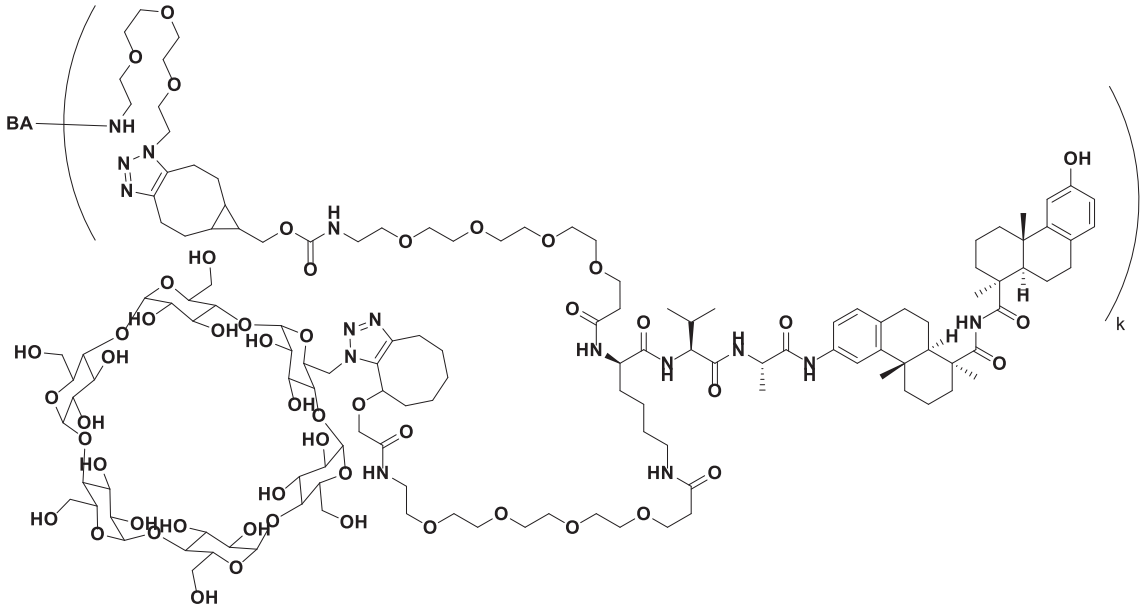


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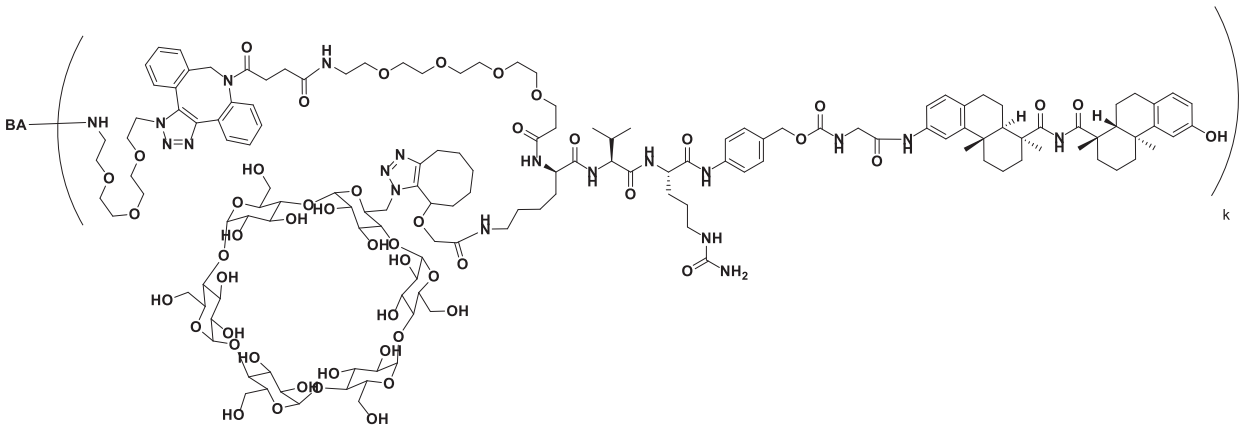


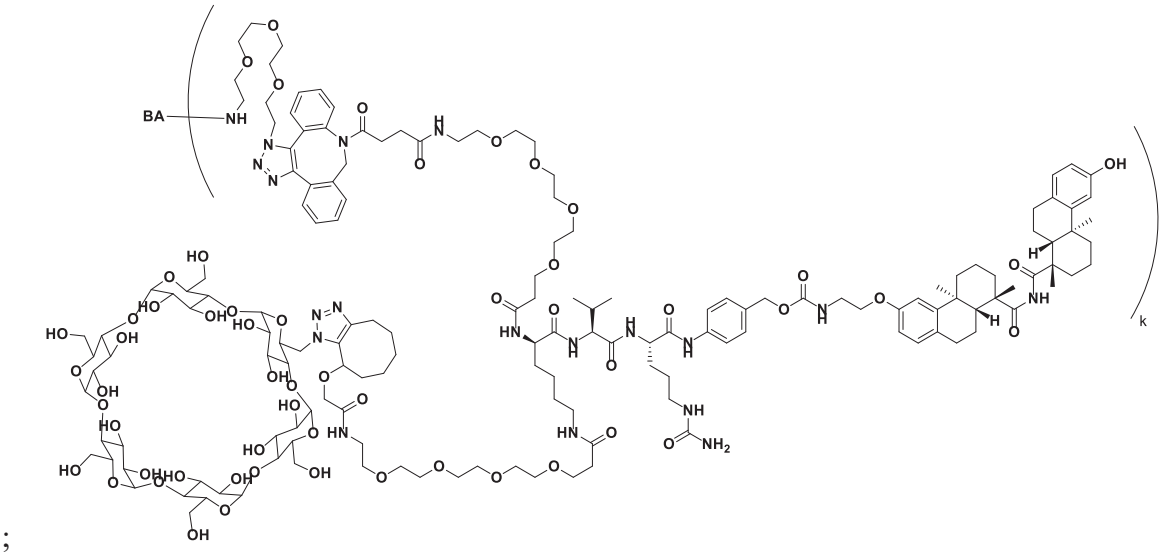


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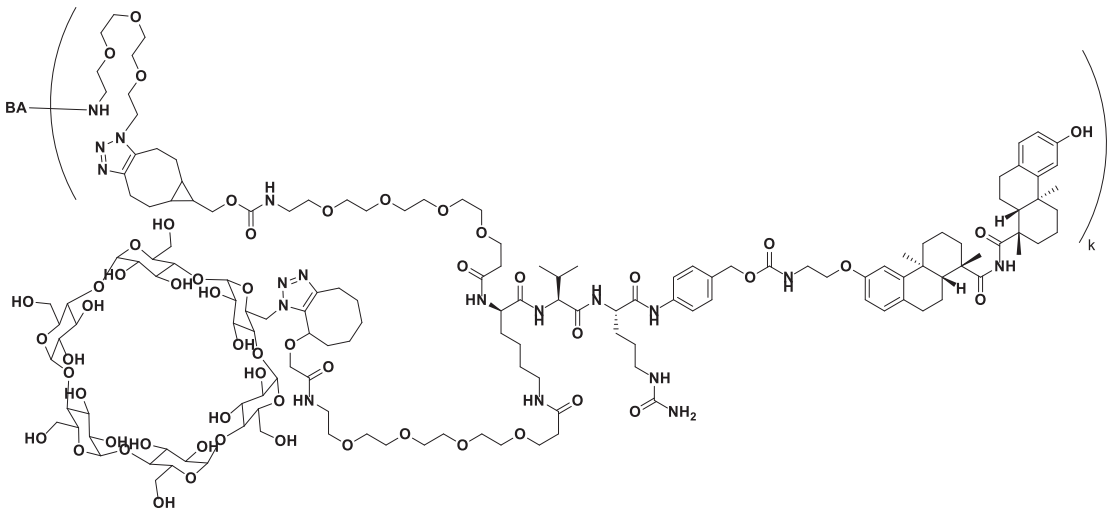
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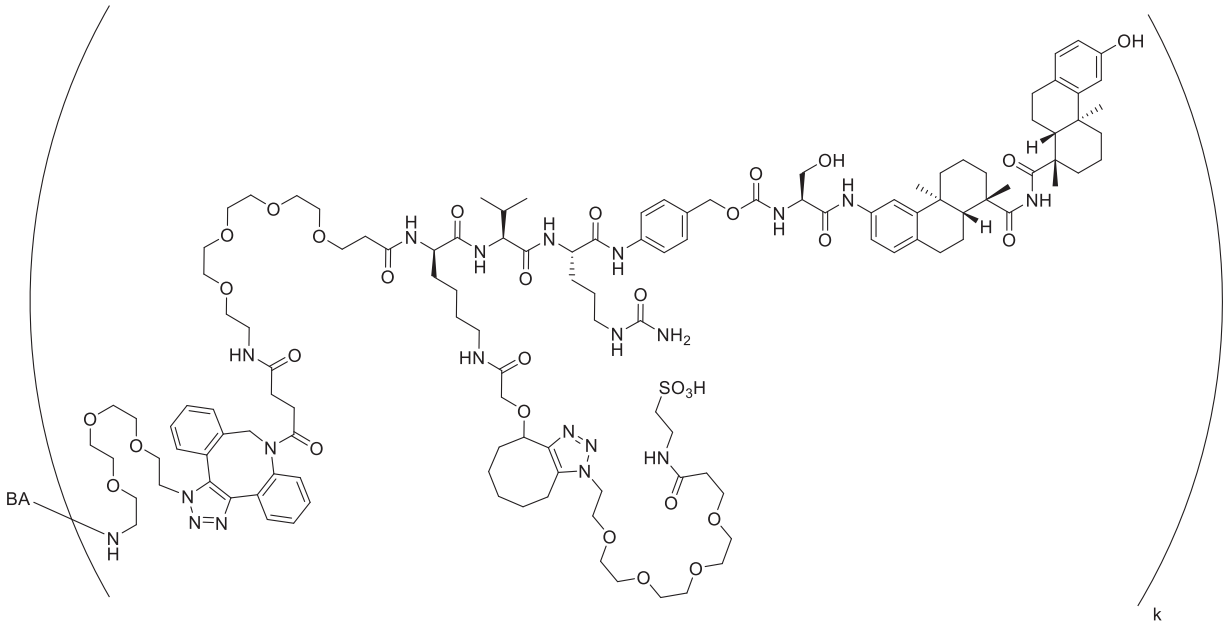


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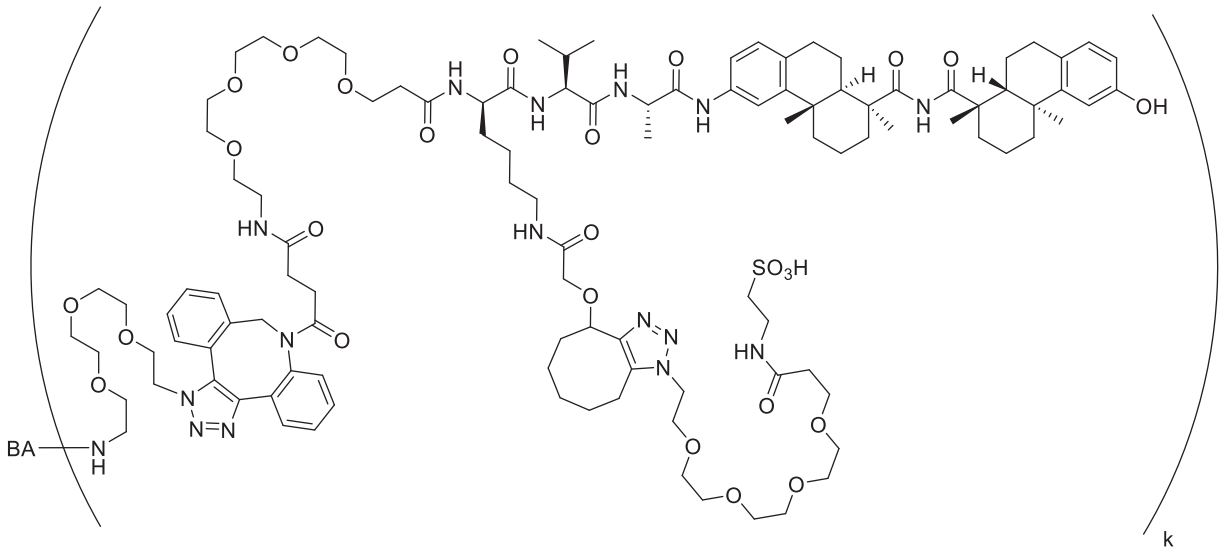
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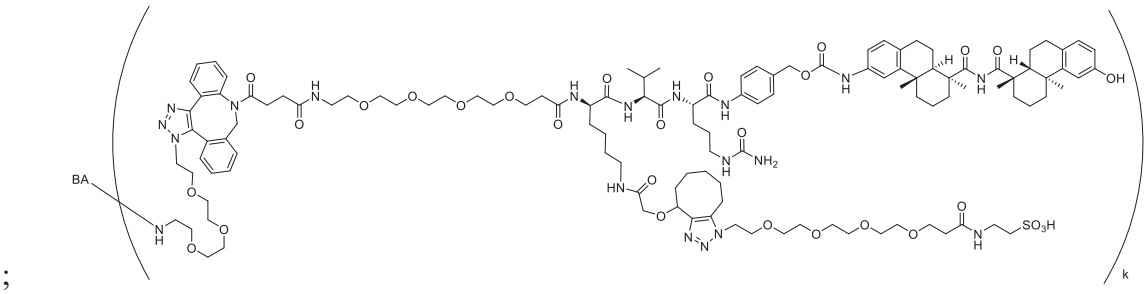


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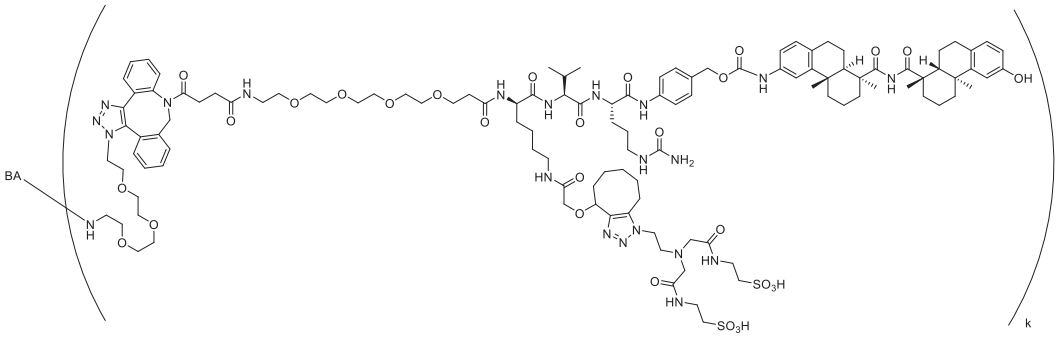


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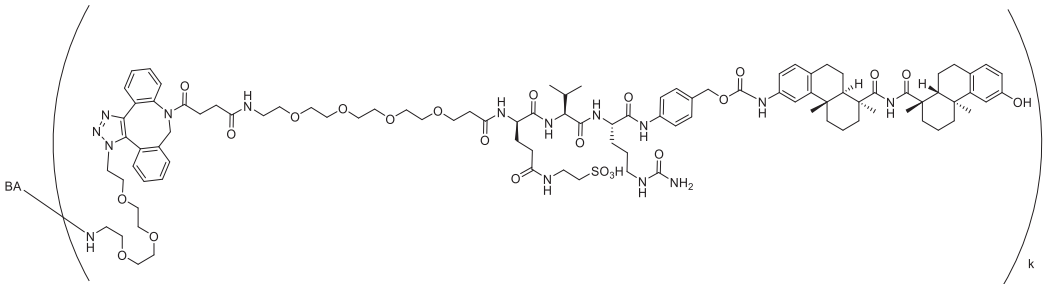



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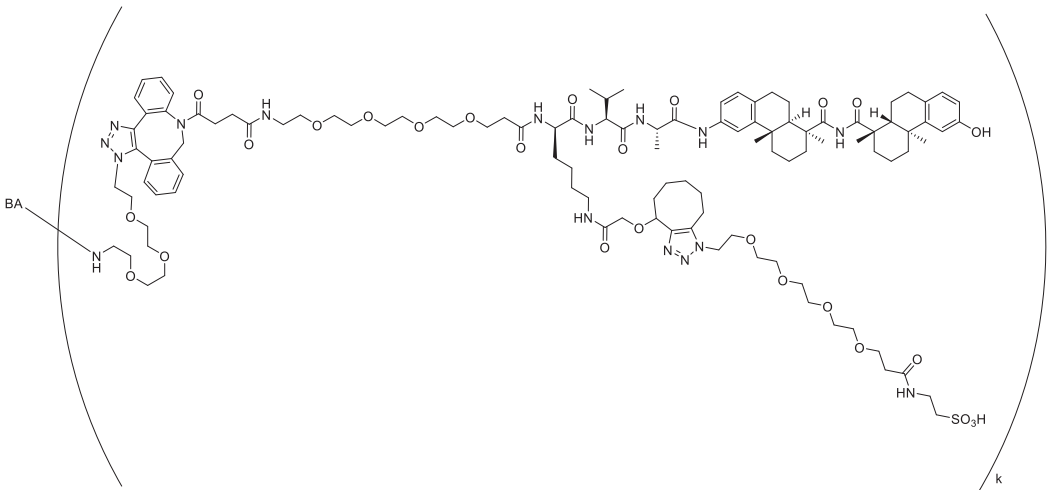
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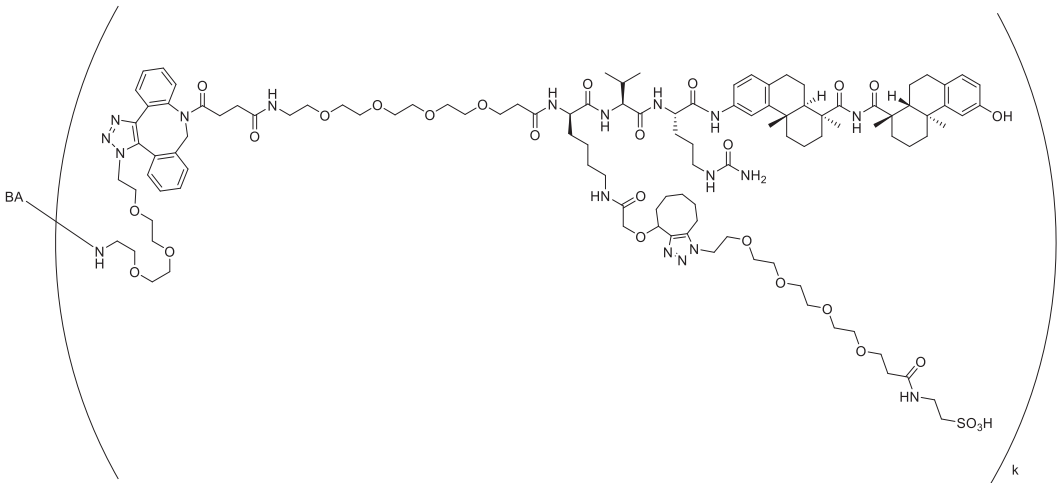
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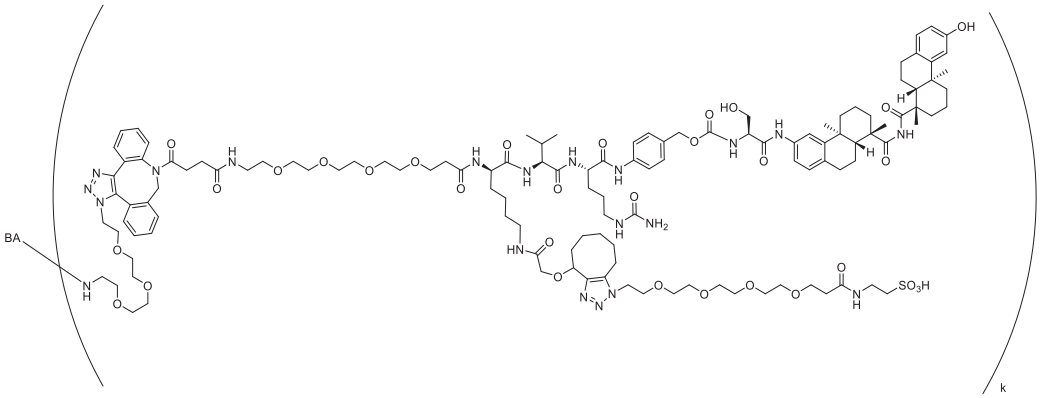
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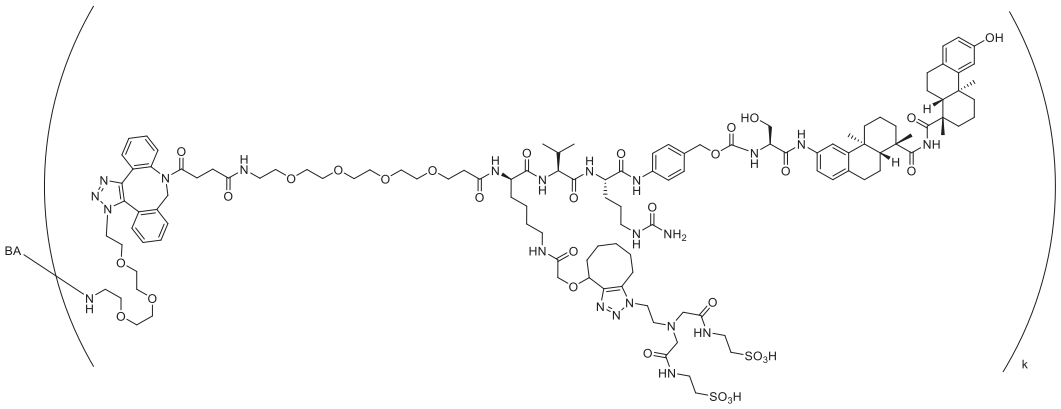
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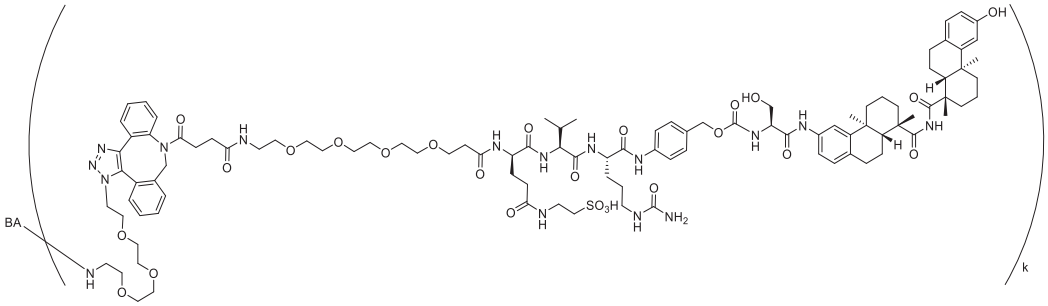
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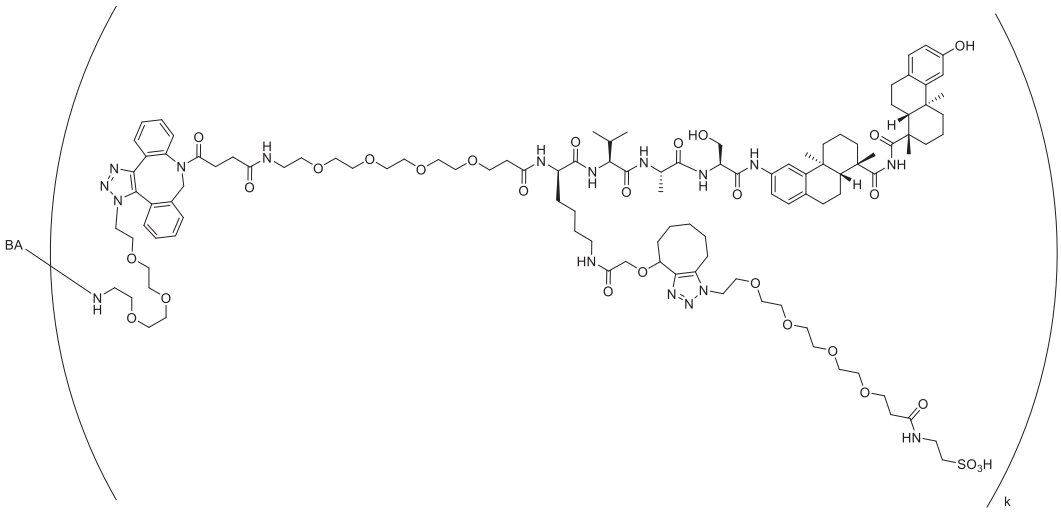
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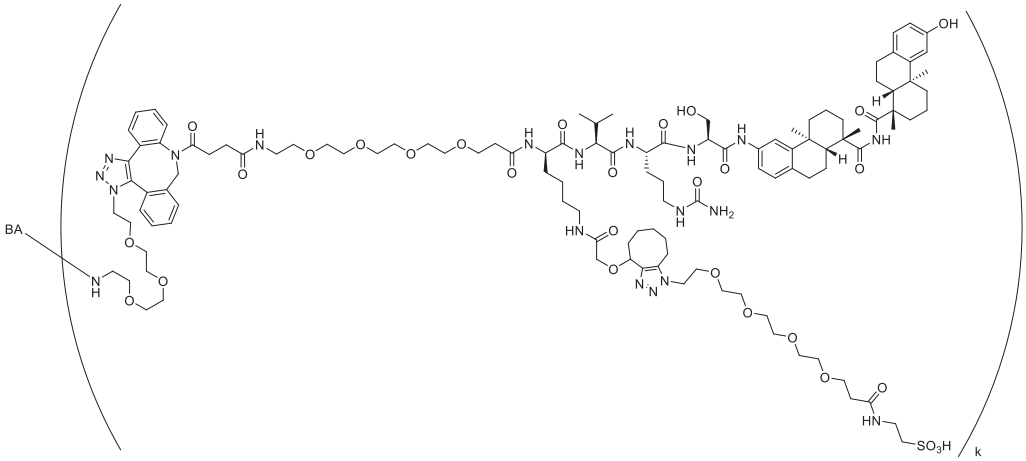
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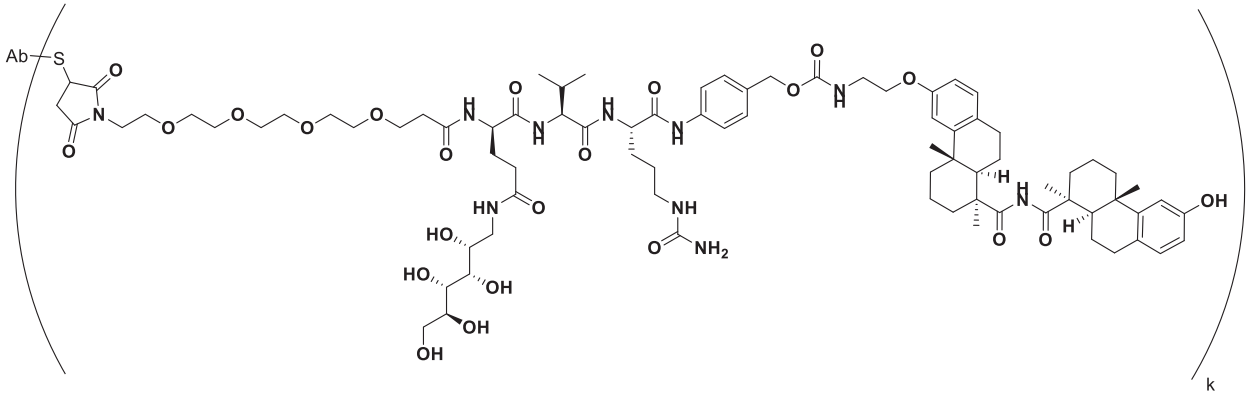
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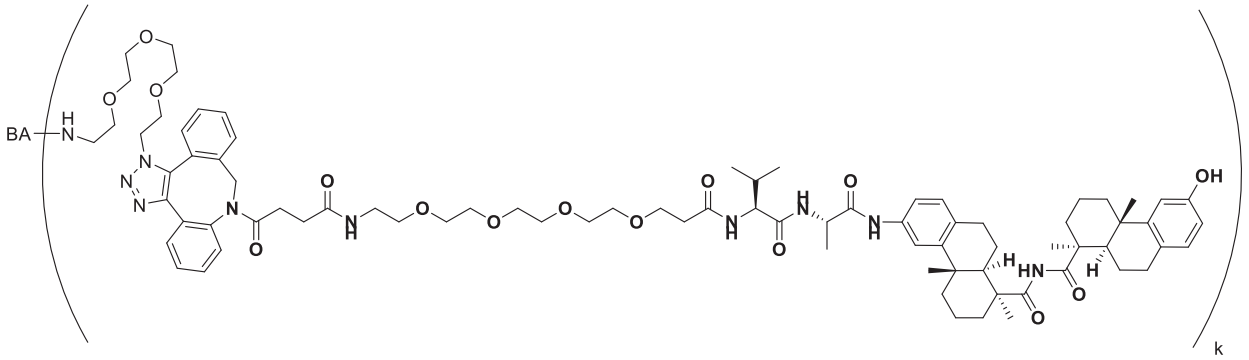
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a regioisomer, stereoisomeric form, pharmaceutically acceptable salt, or solvate thereof, wherein **k** is an integer from one to four.

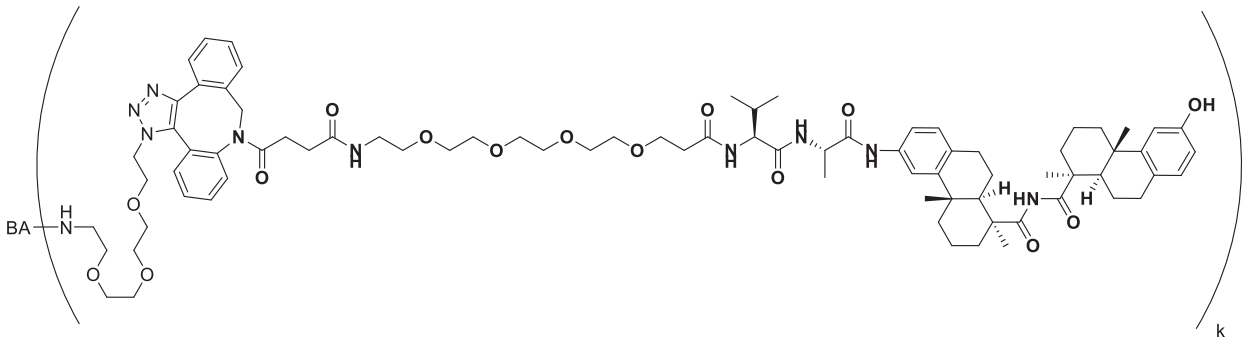
38. The compound of claim 28, selected from the group consisting of



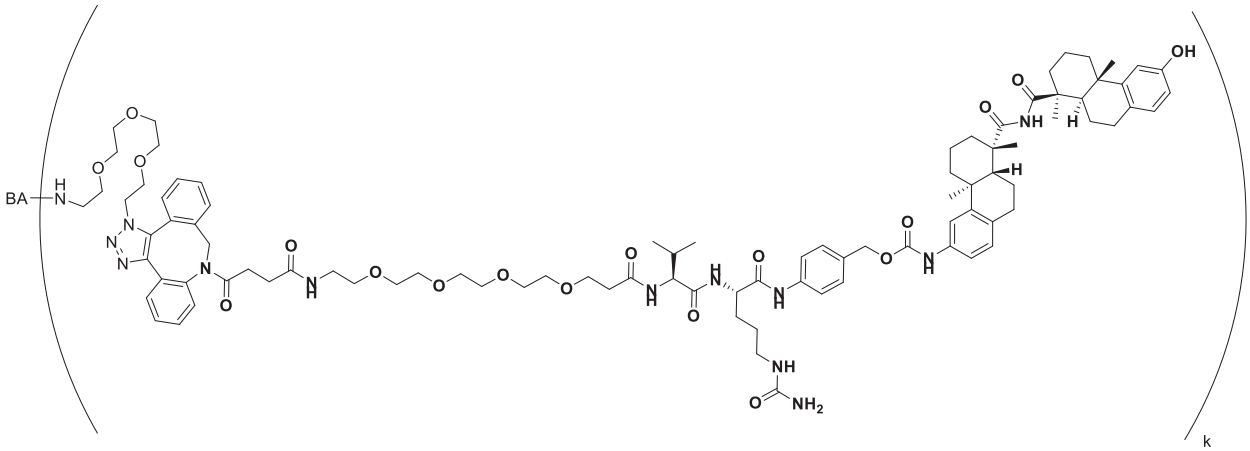
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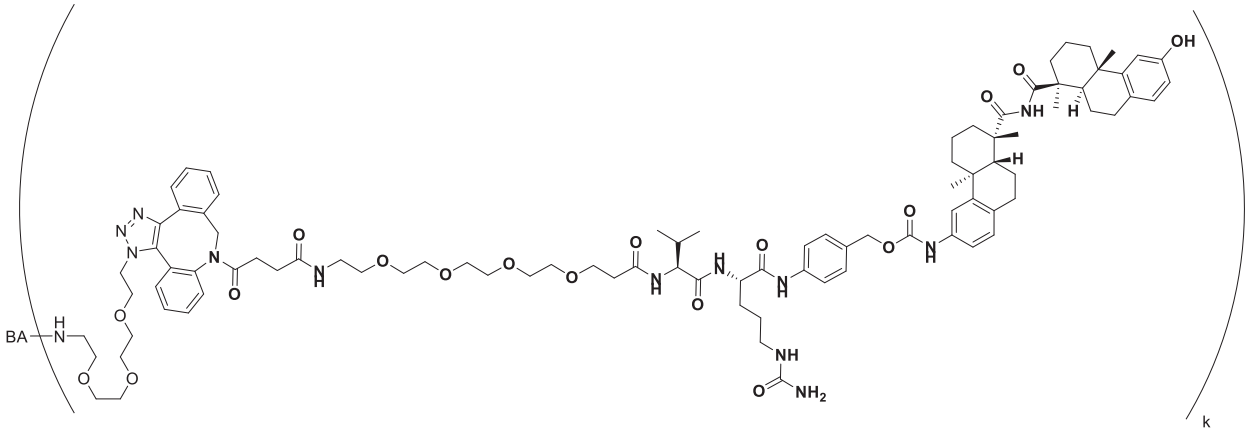
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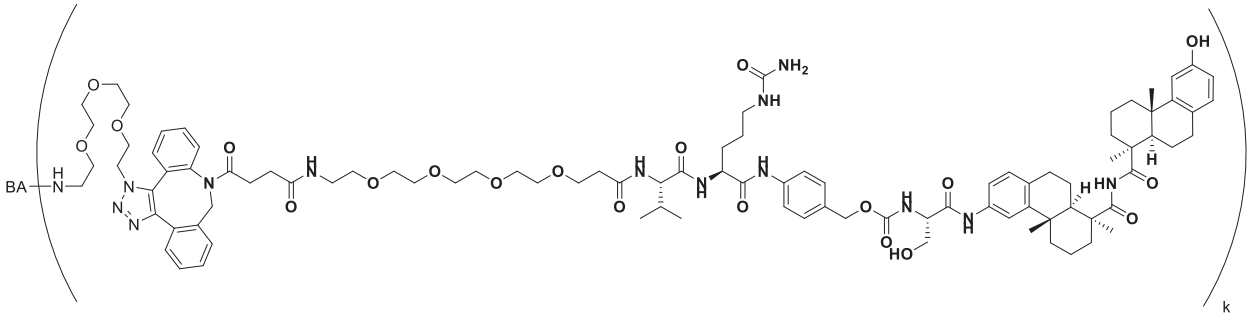
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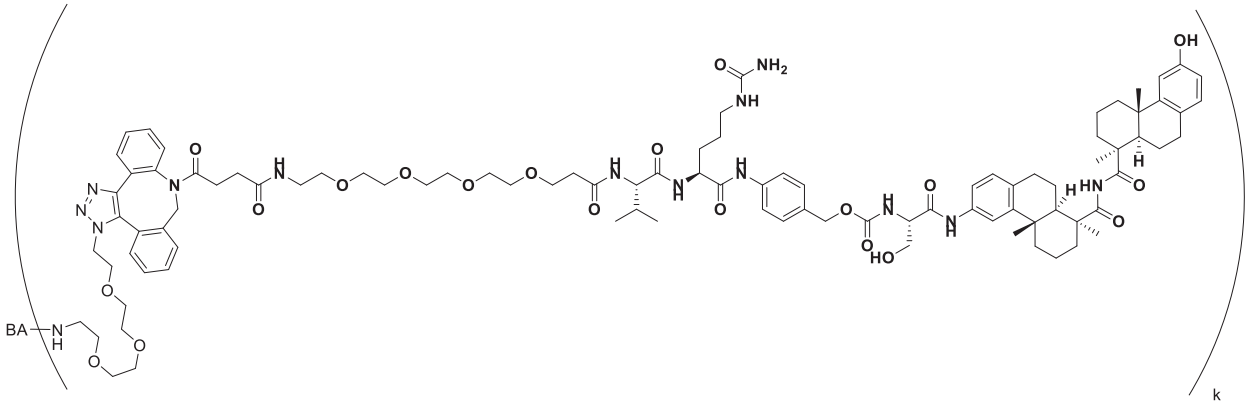
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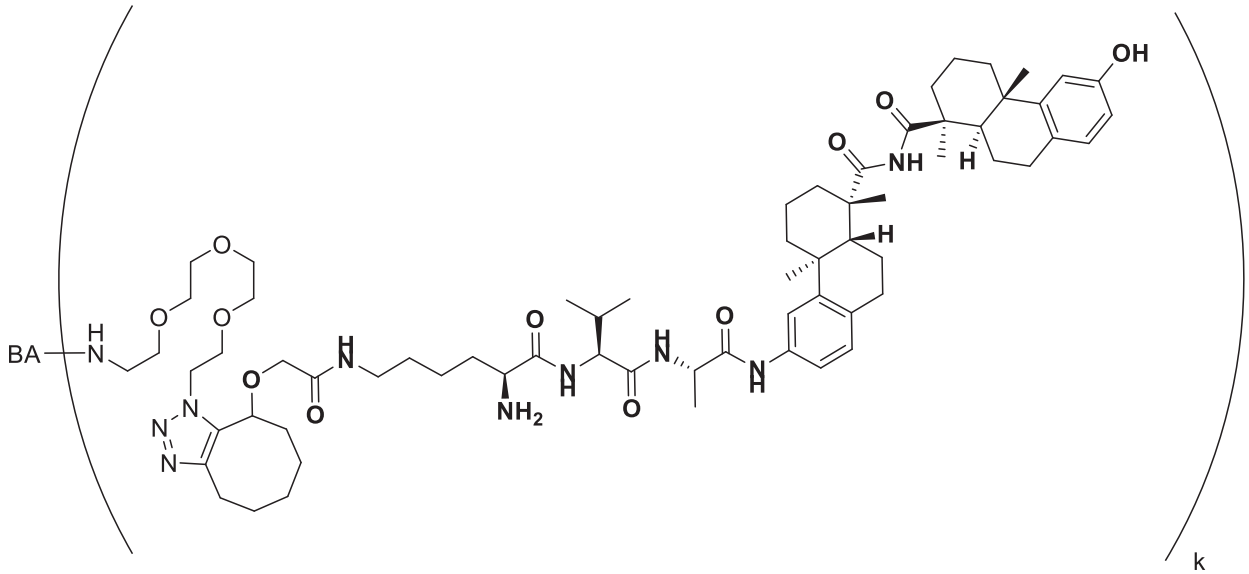
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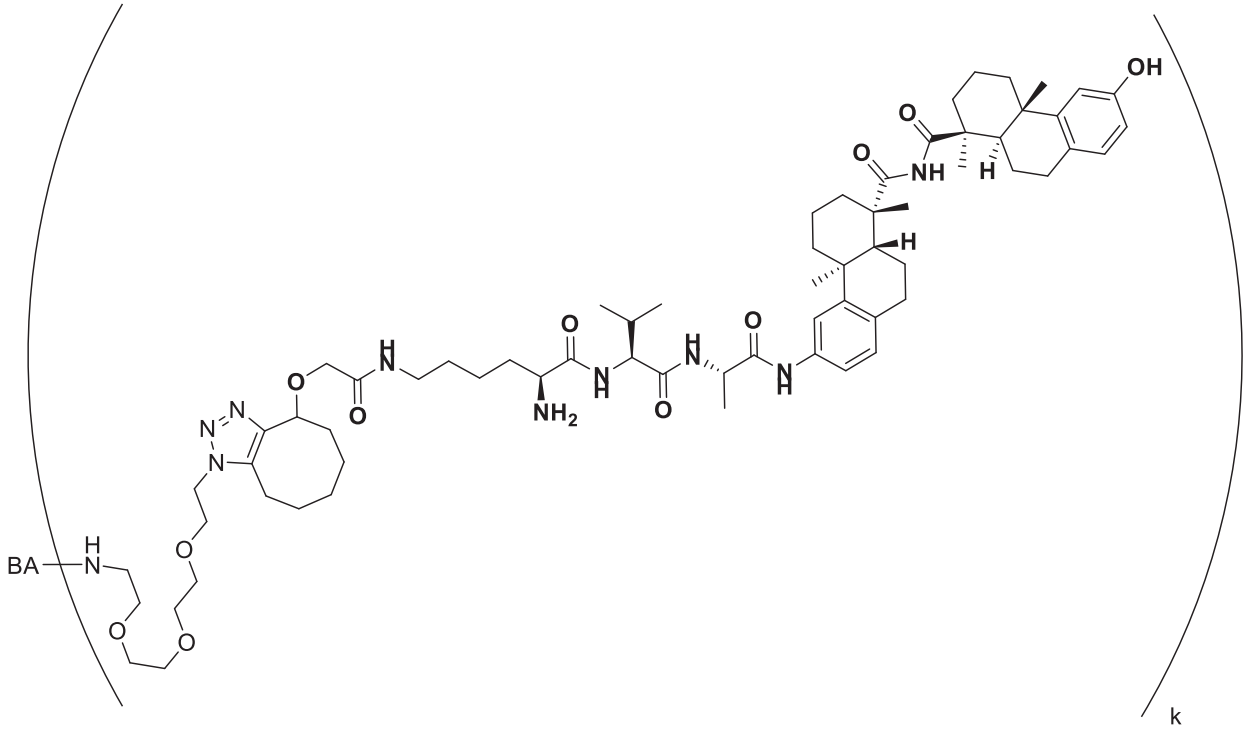
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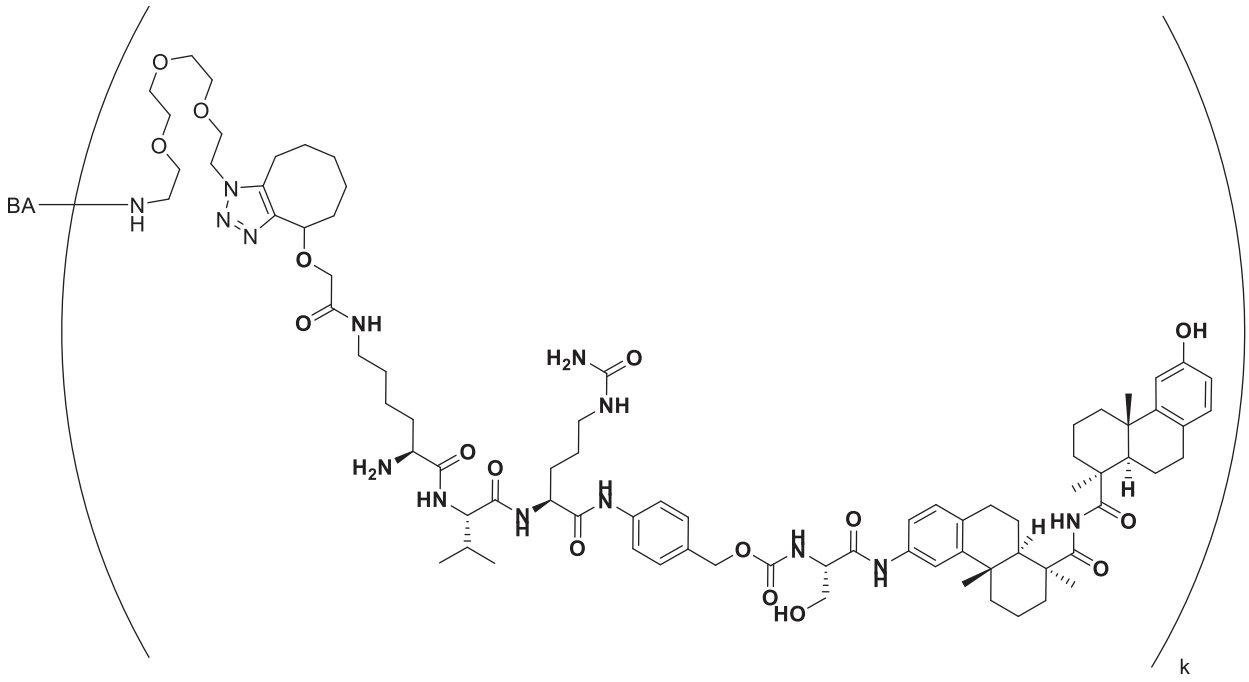
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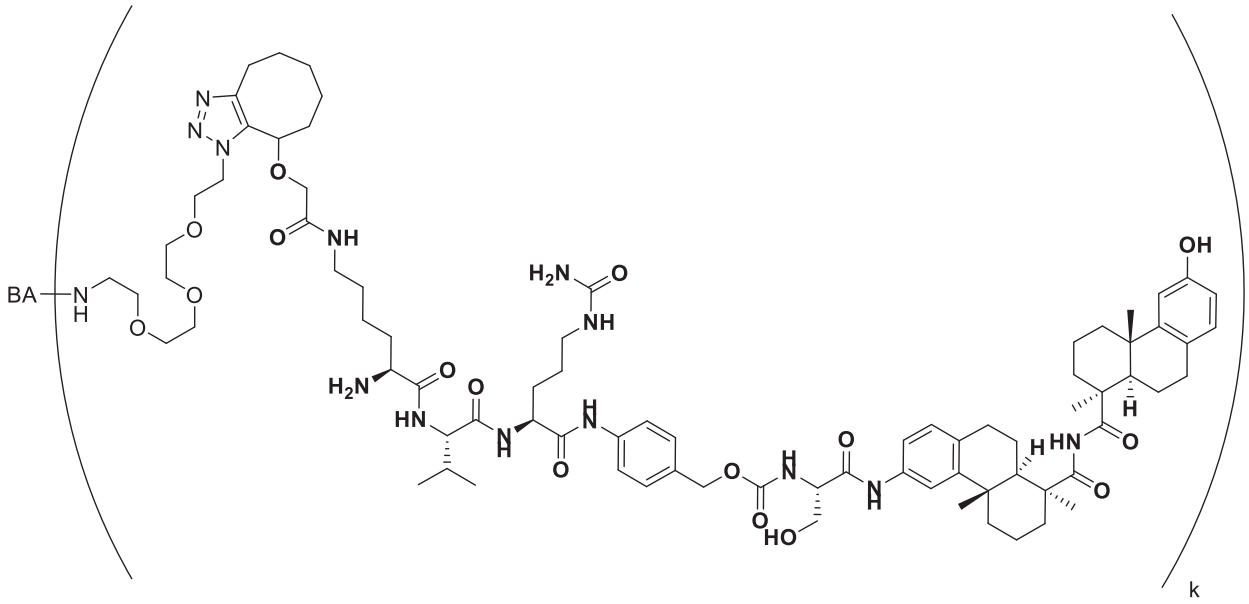
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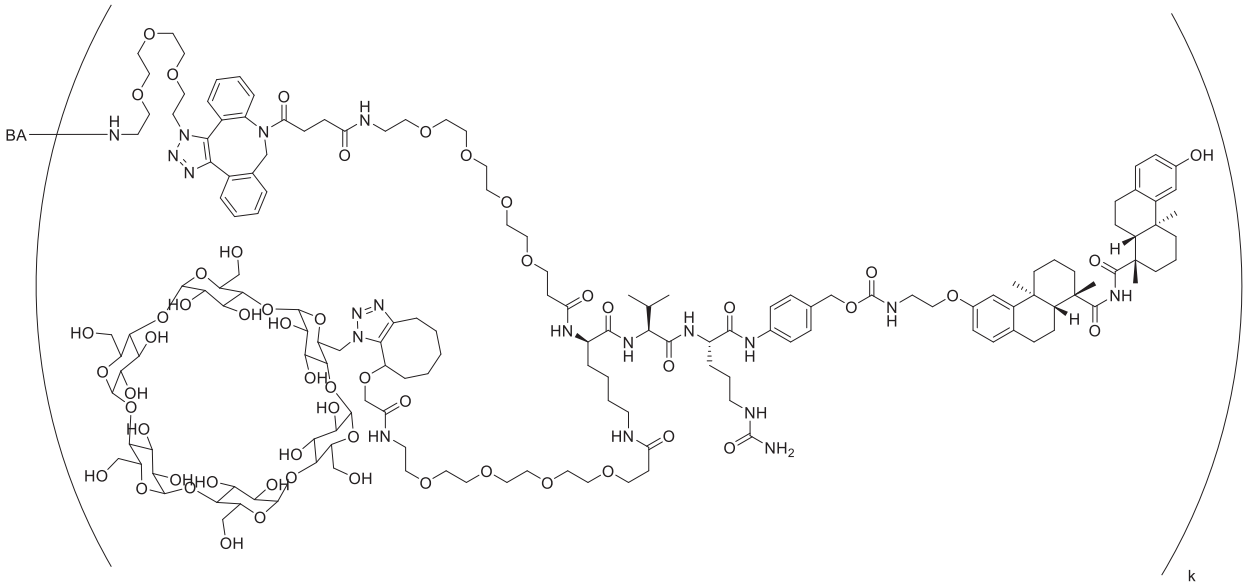
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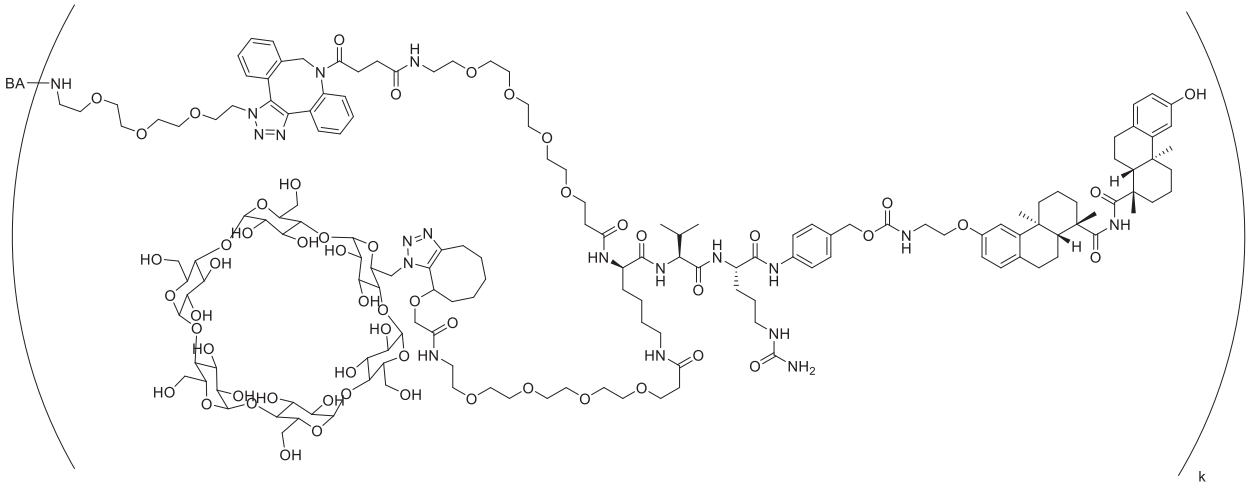
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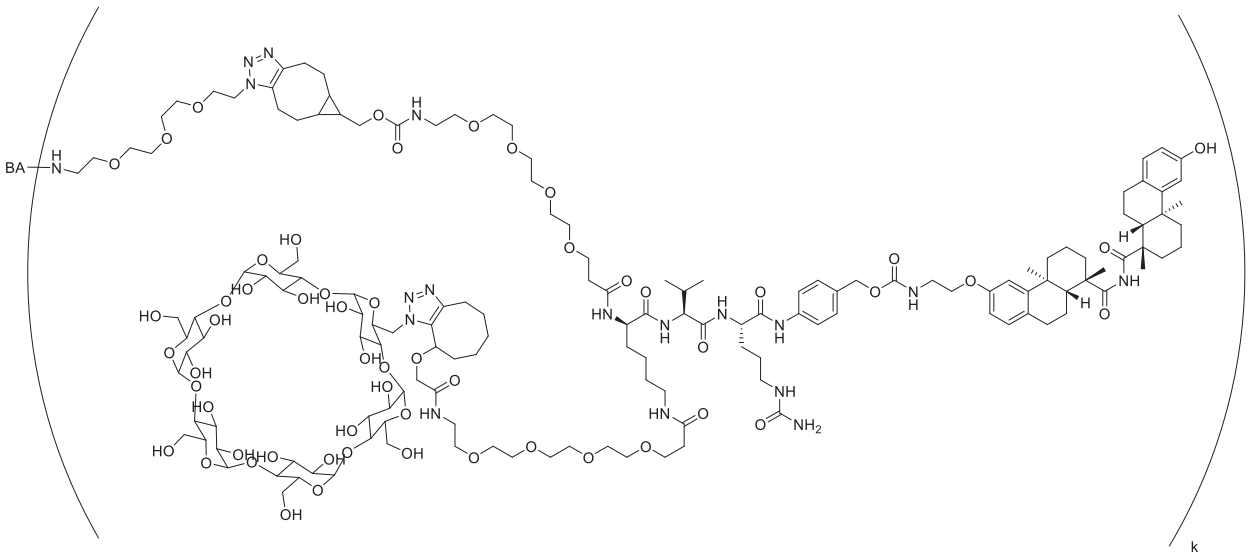
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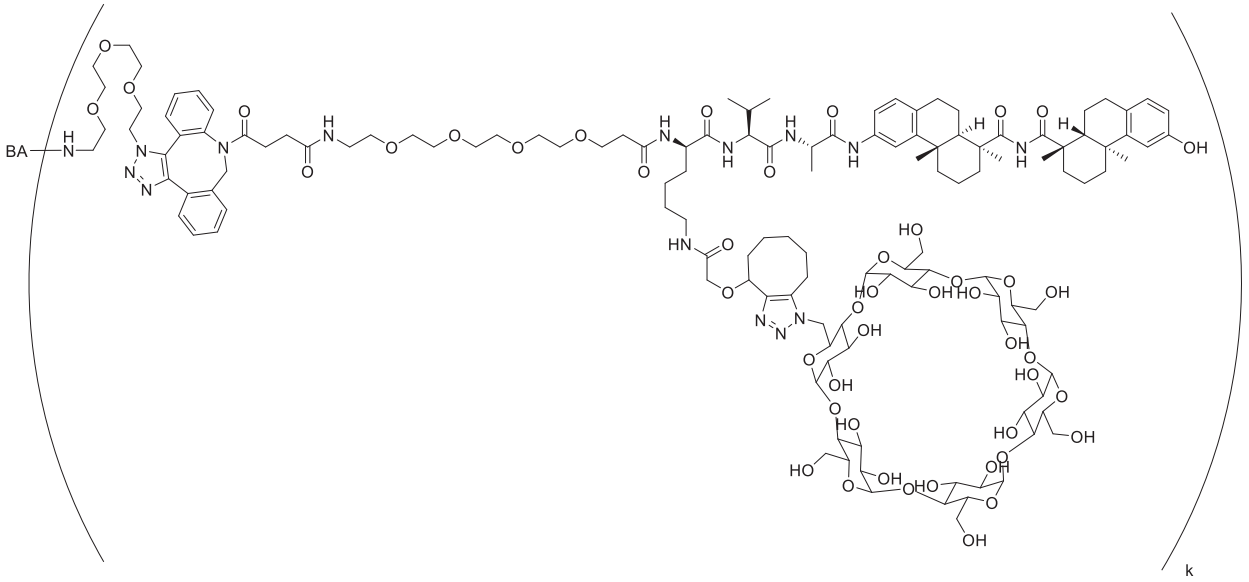
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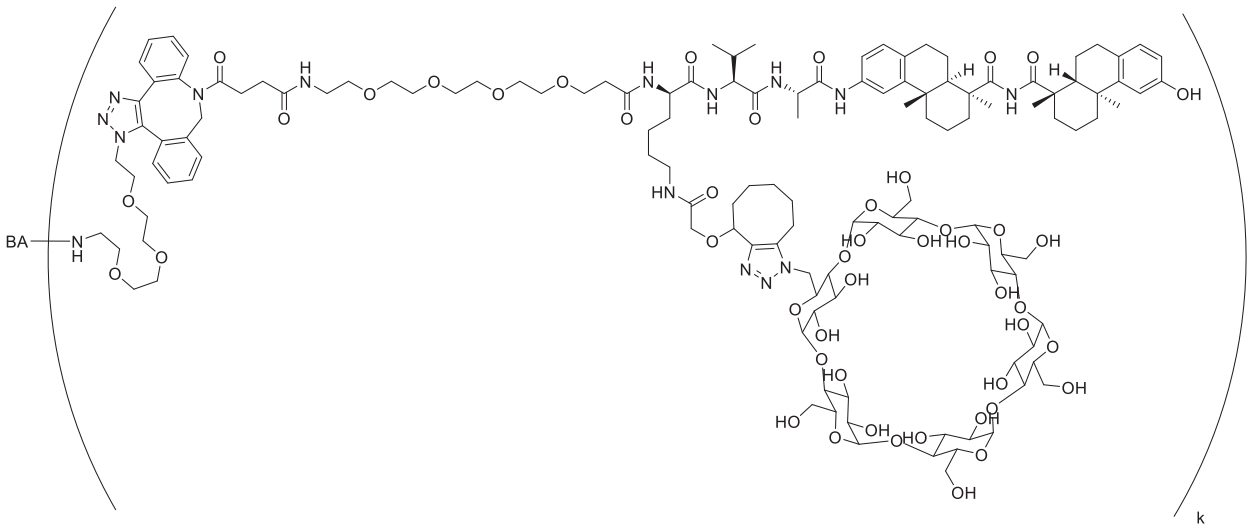
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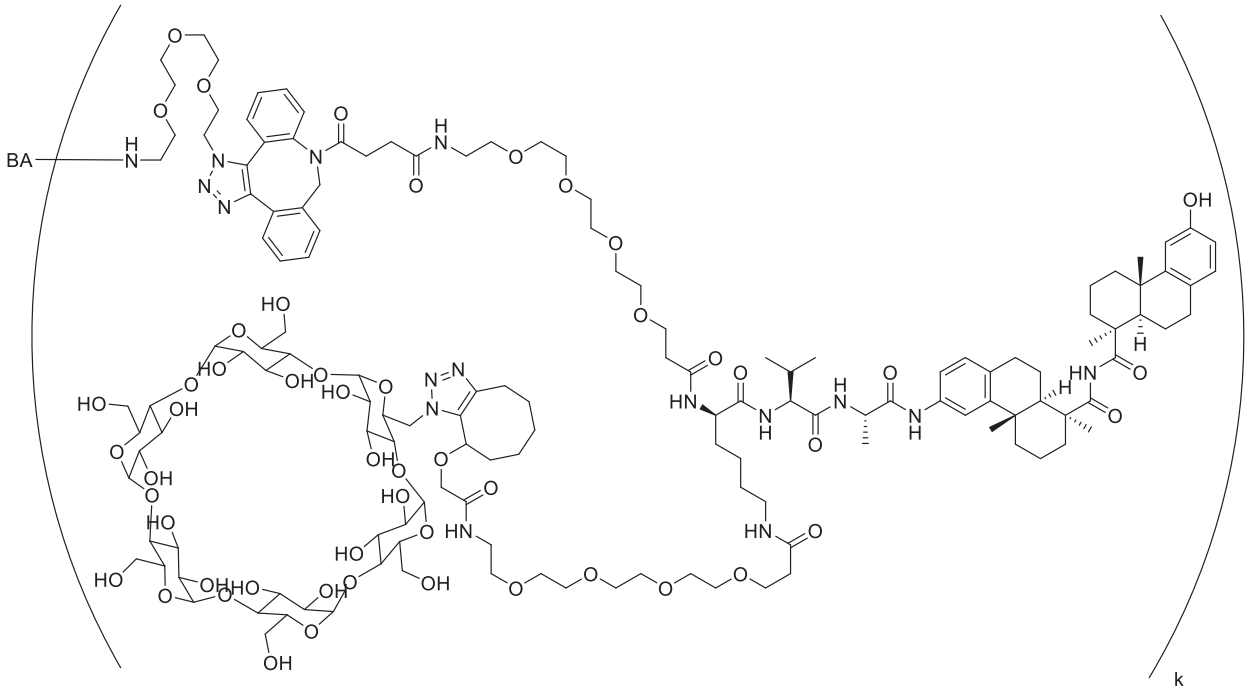
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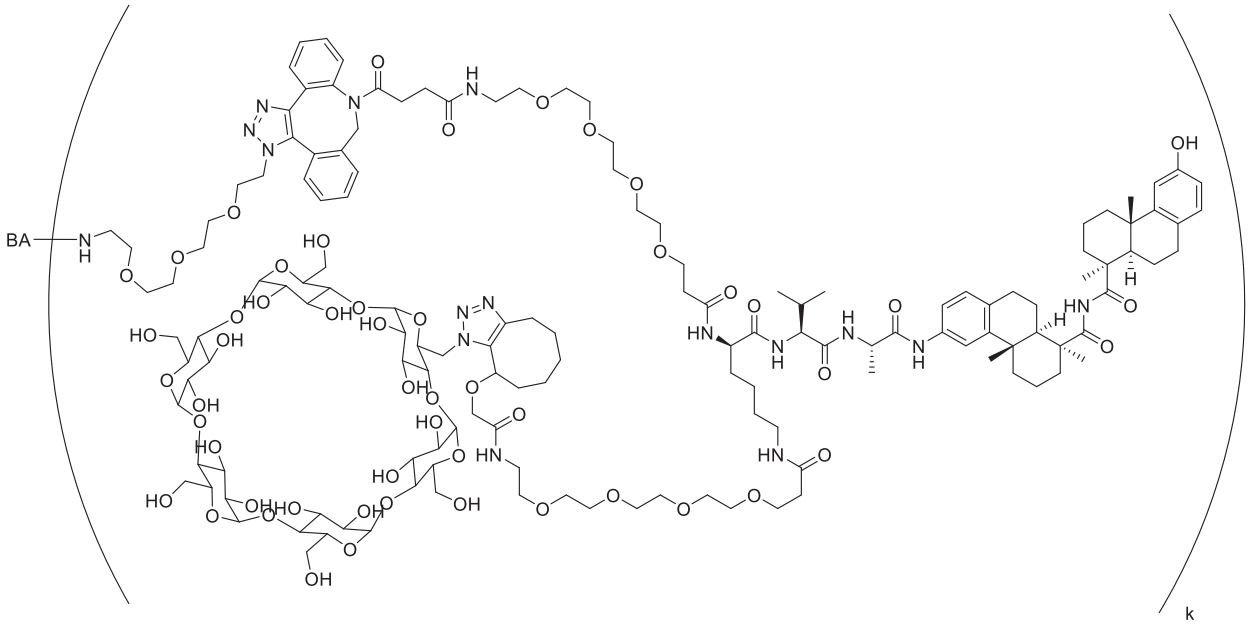
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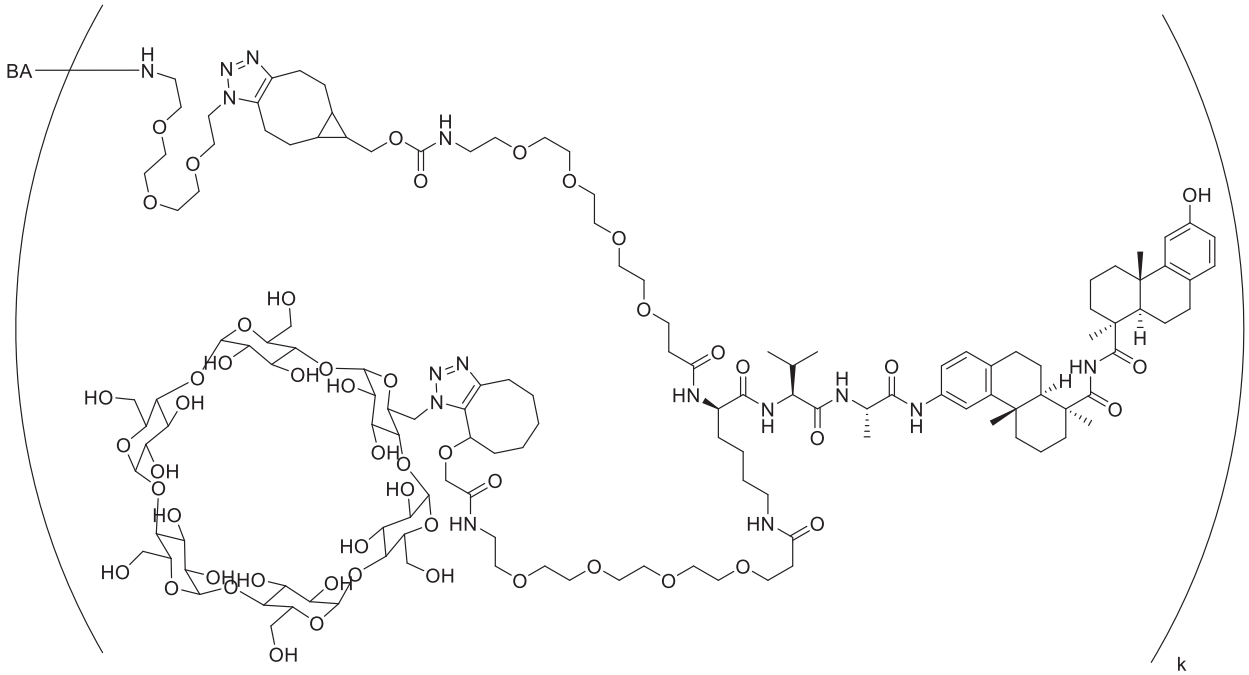
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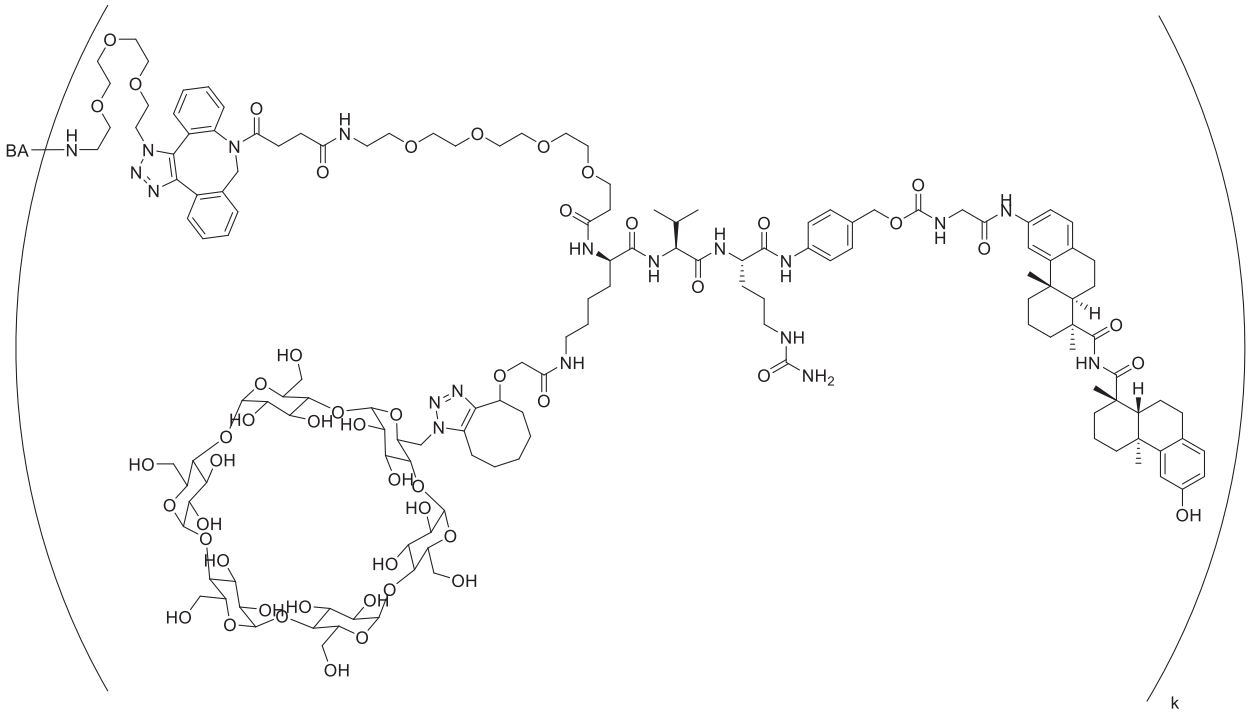
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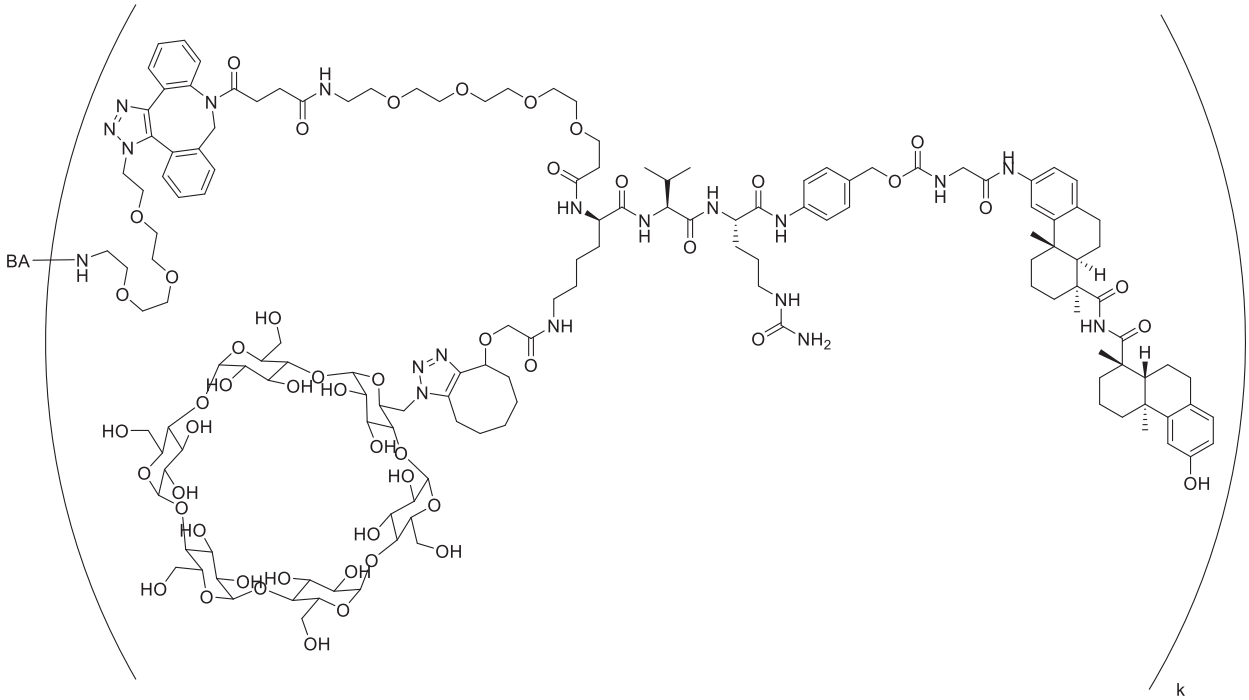
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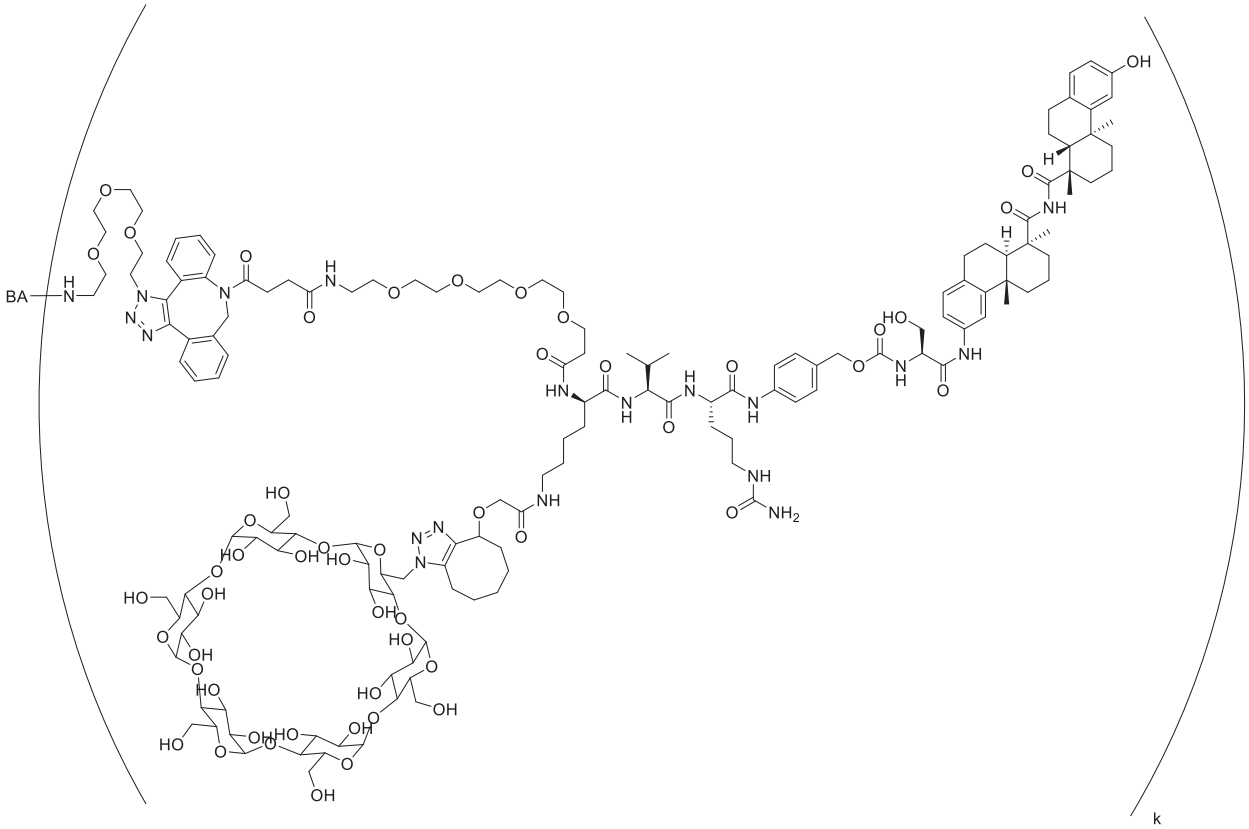
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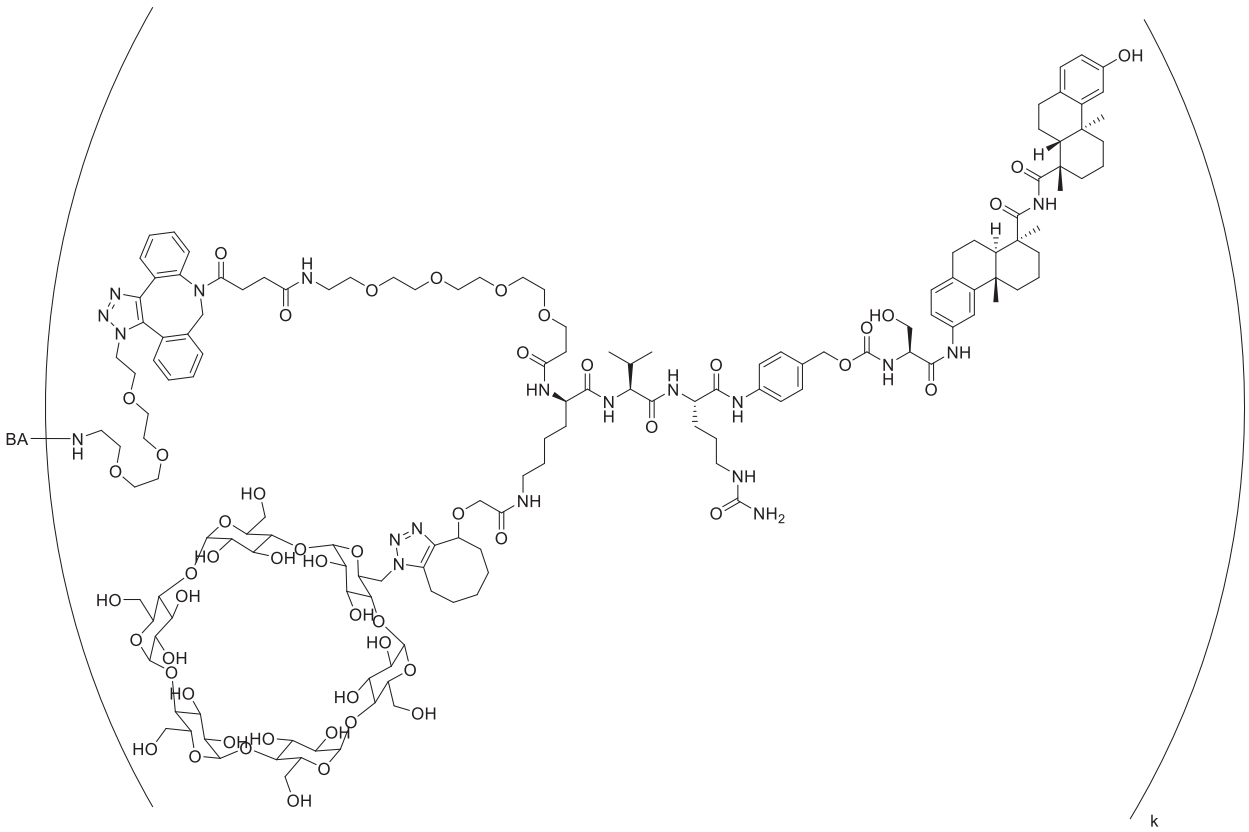
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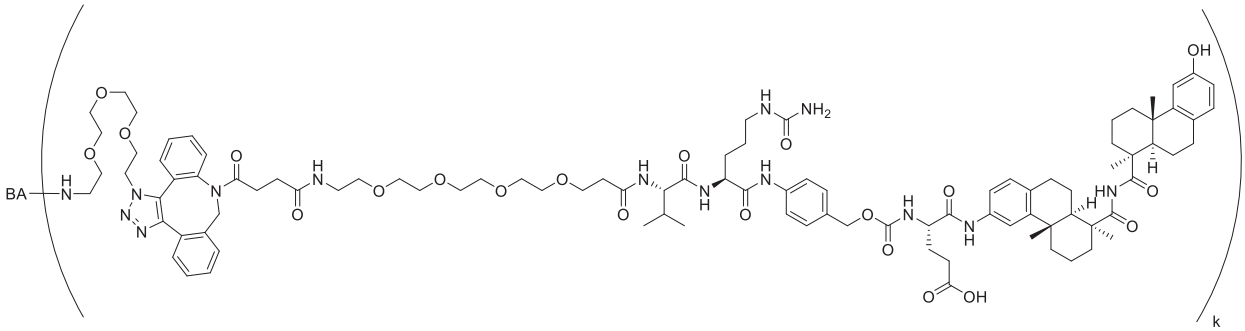
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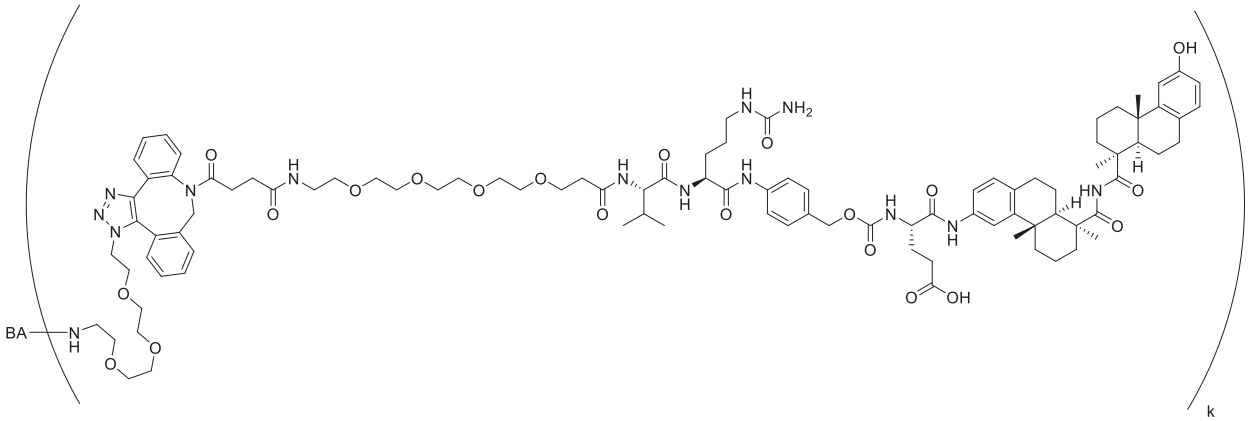
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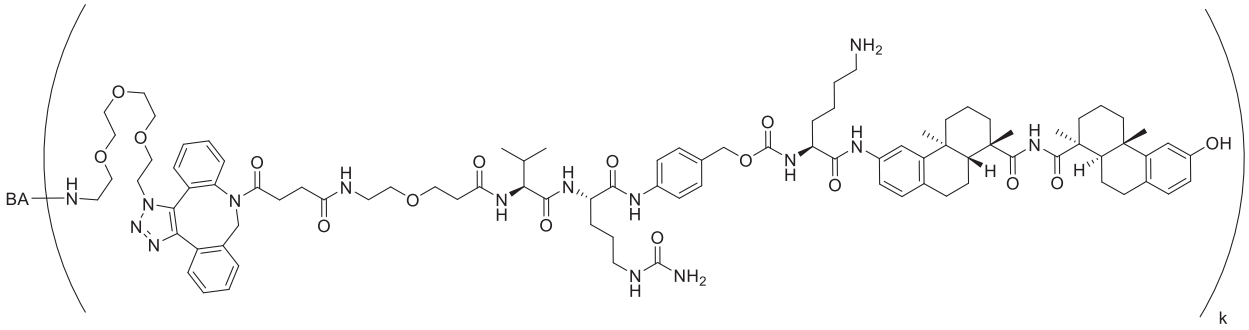
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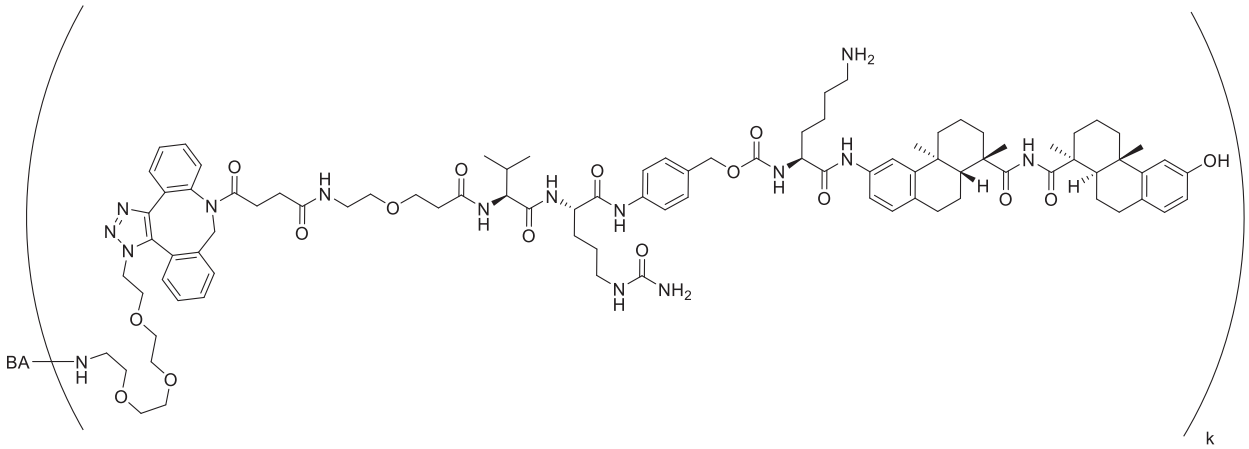
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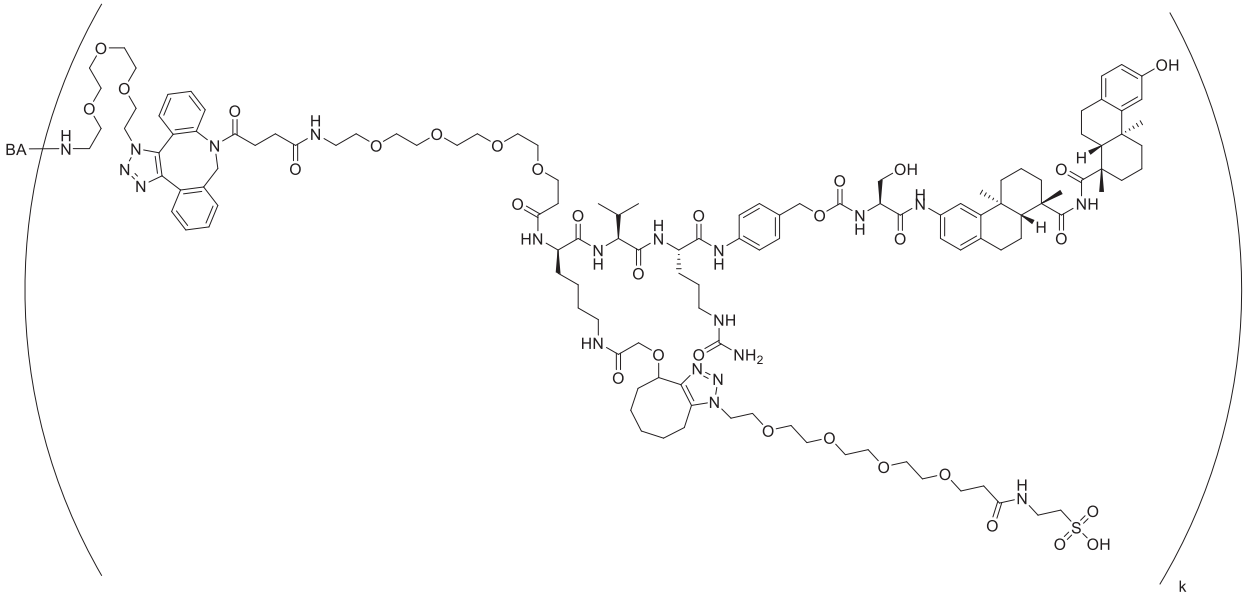
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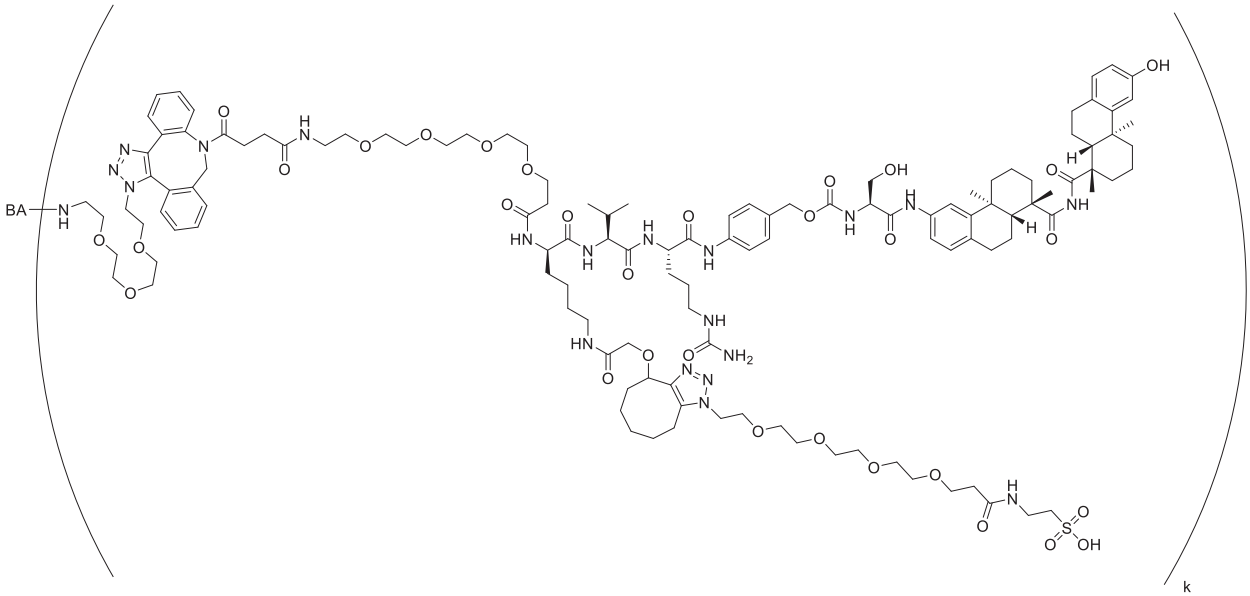
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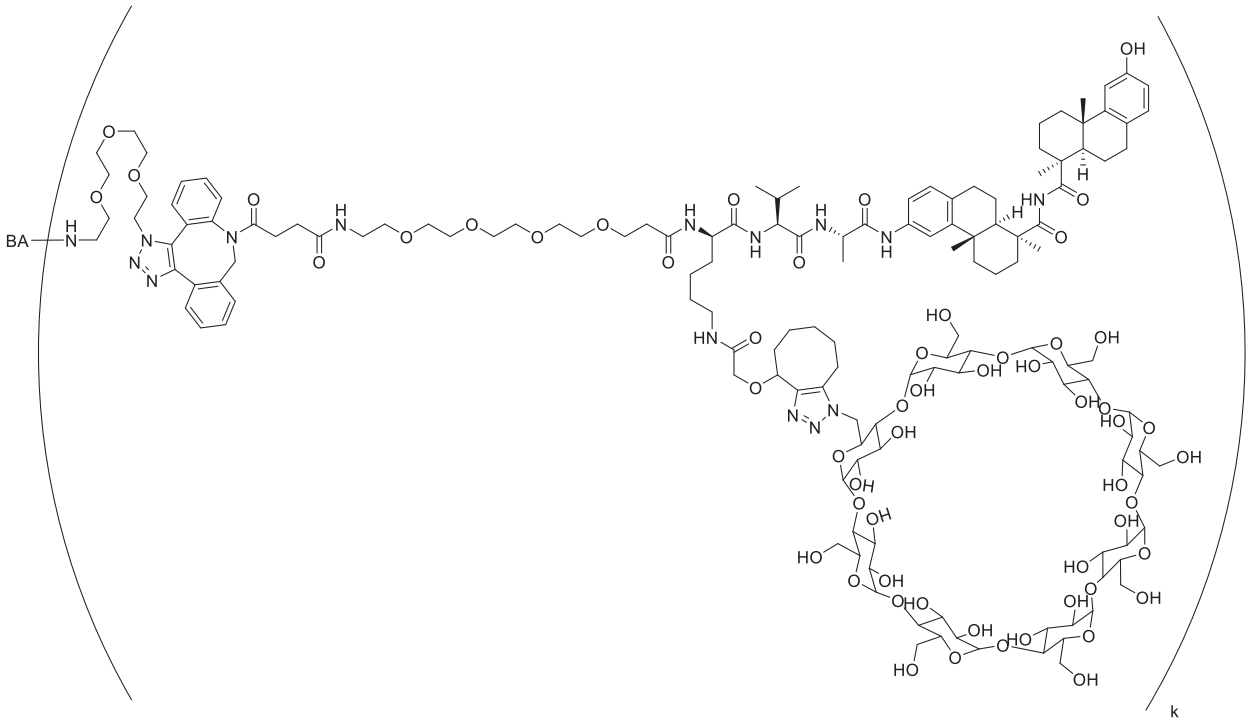
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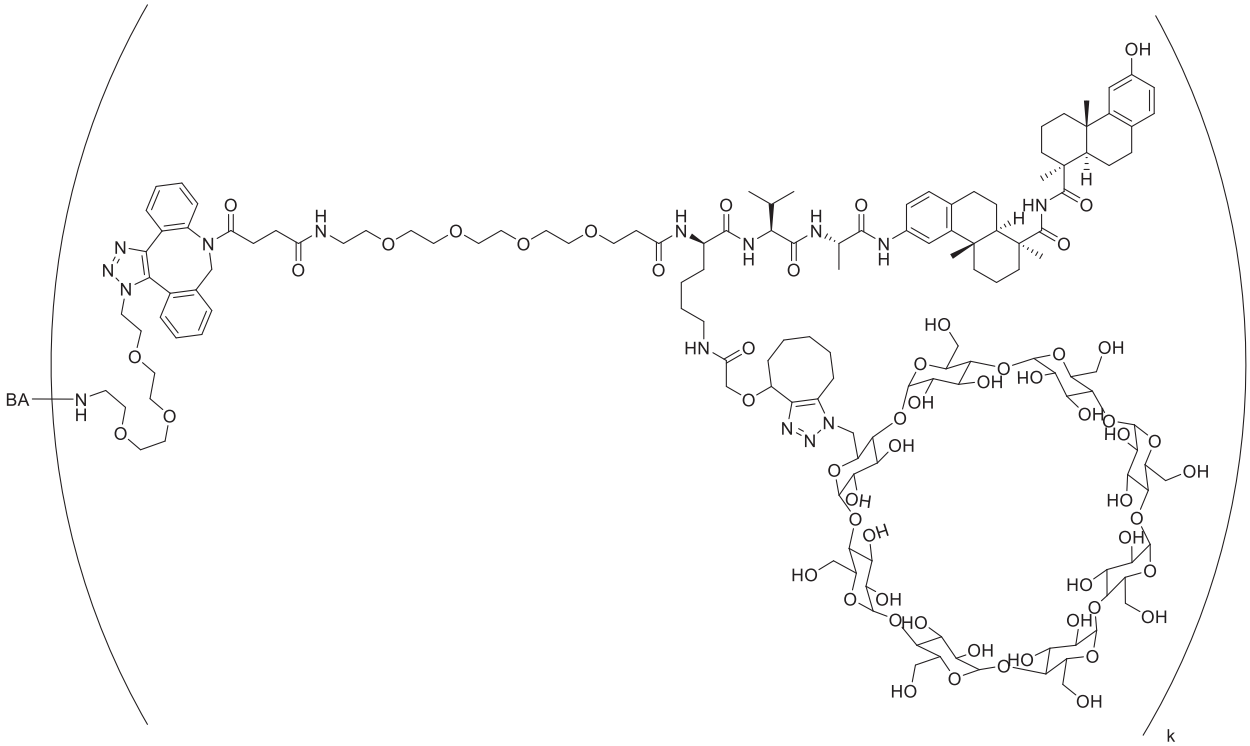
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or a regioisomer, stereoisomeric form, pharmaceutically acceptable salt, or solvate thereof, wherein **k** is an integer from one to four.

39. The compound of any one of claims 35-38, wherein **k** is two.

40. The compound of any one of claims 35-38, wherein **k** is four.

41. The compound of any one of claims 35-38, wherein **BA** is an antibody having binding specificity for an antigen selected from the group consisting of class A-J scavenger receptors.

42. The compound of any of claims 35-38, wherein **BA** is an antibody having binding specificity for an antigen selected from the group consisting of MSR1, MARCO, SRCL, SCARA5, COLEC12, CD36, LIMPII, SRBI, SRBII, CD68, LAMP, LOX-1, Dectin-1, SREC-I, SREC-II, MEGF, CXCL16, Fasciclin, FEEL-1, FEEL-2, CD163, RAGE, C-type lectin superfamily members, DEC205, CD206, Dectin-2, Mincle, DC-SIGN, DNGR-1, VSIG4, CSF1R, ASGPR, and APLP-2.

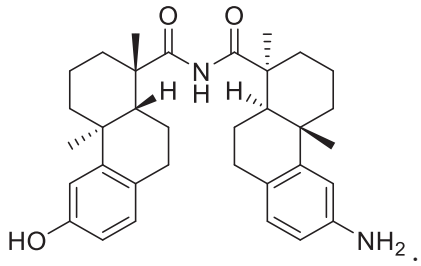
43. The compound of any of claims 35-38, wherein **BA** is an antibody having binding specificity for Her2 or PRLR.

44. The compound of any of claims 35-38, wherein **BA** is an antibody having binding specificity for MSR1.

45. The compound of any of claims 35-38, wherein **BA** is an antibody linked through one or more N295 residues.

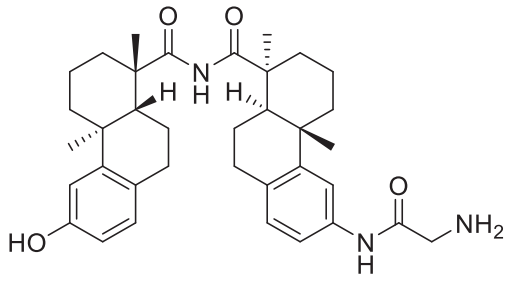
46. The compound of any of claims 35-38, wherein **BA** is an antibody linked through one or more N295 and N297Q residues.

47. The compound of claim 1, having the structure



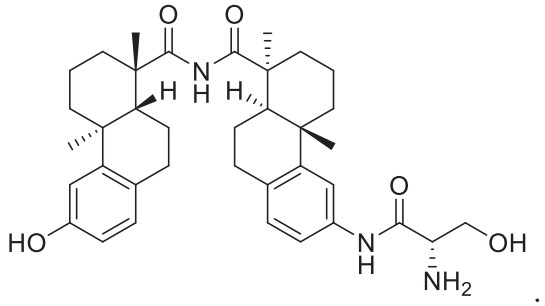
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48. The compound of claim 1, having the structure



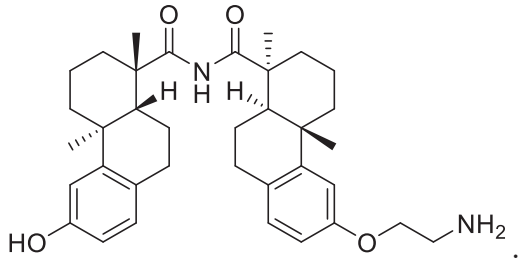
.

49. The compound of claim 1, having the structure



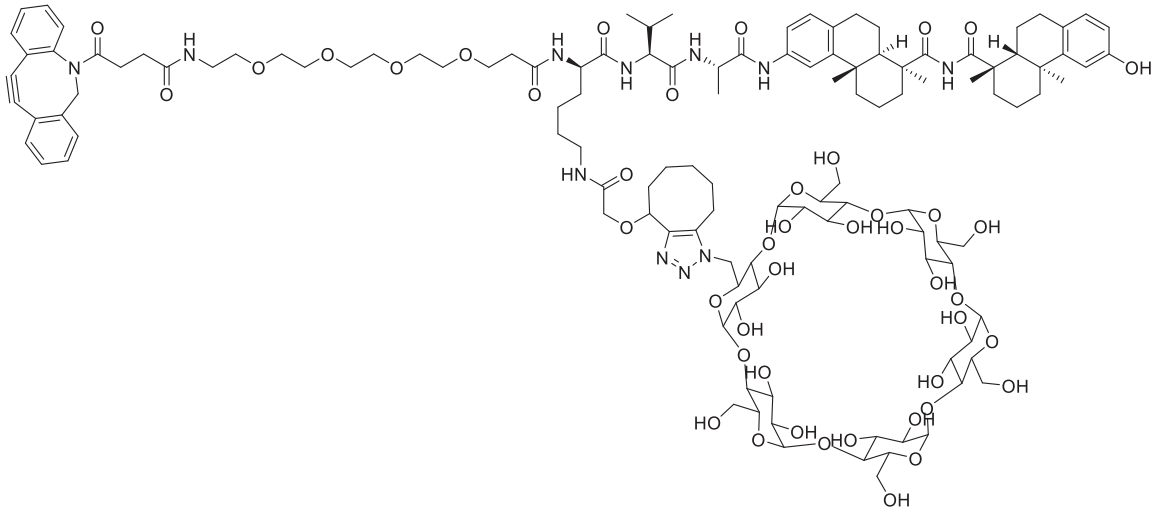
.

50. The compound of claim 1, having the structure

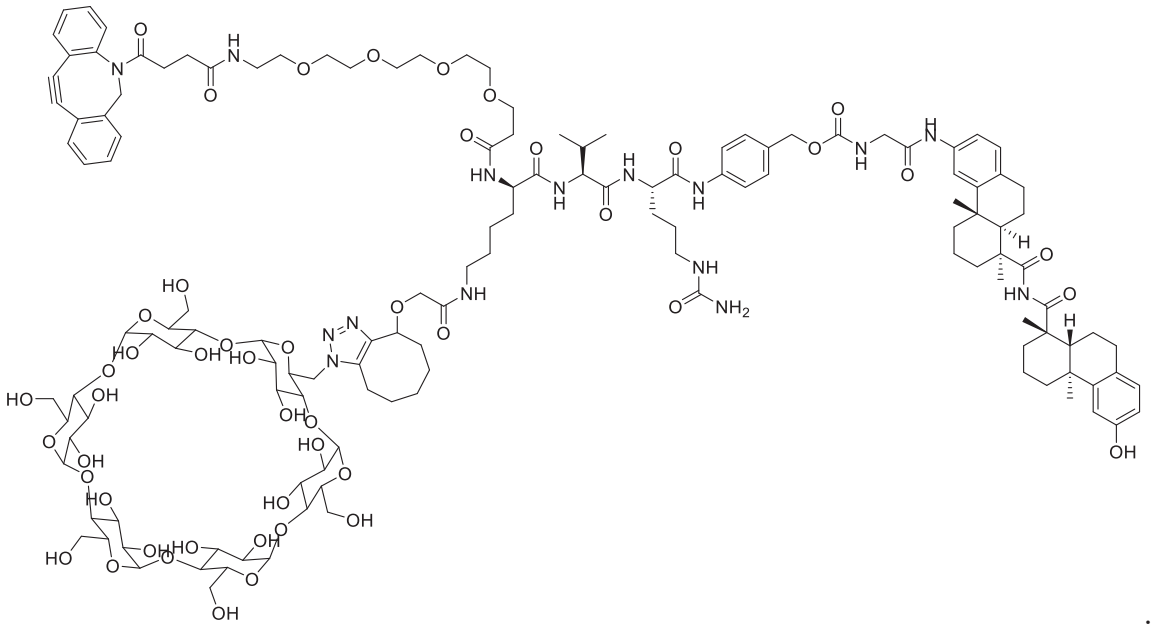


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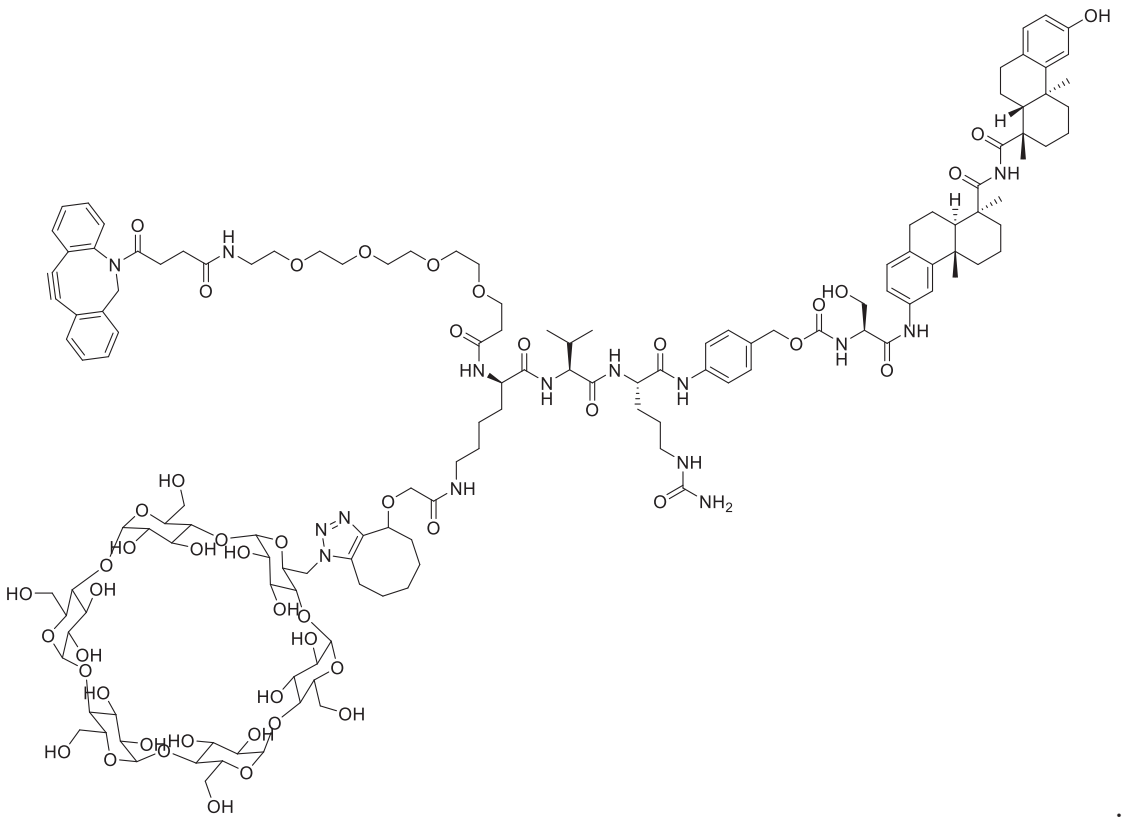
51. The linker-payload of claim 24, having the structure



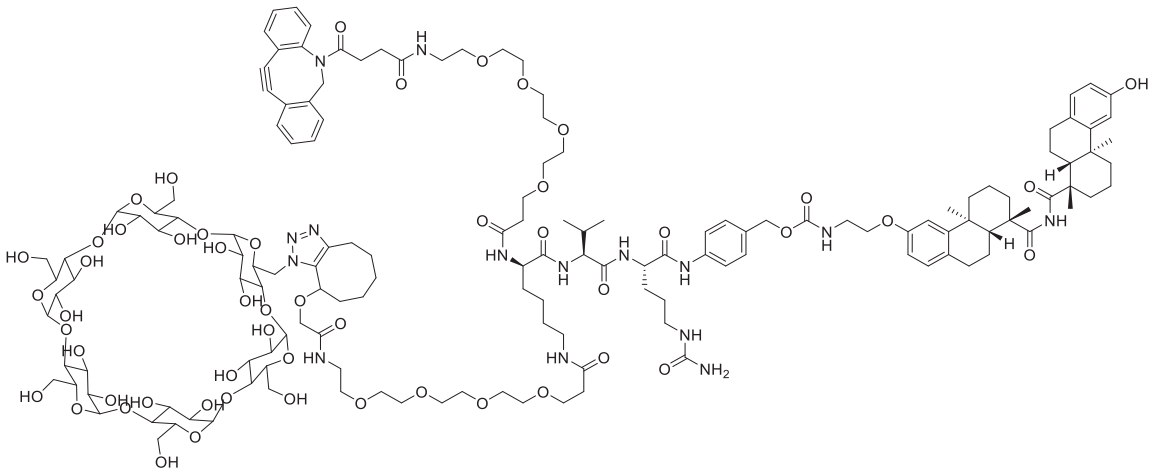
52. The linker-payload of claim 24, having the structure



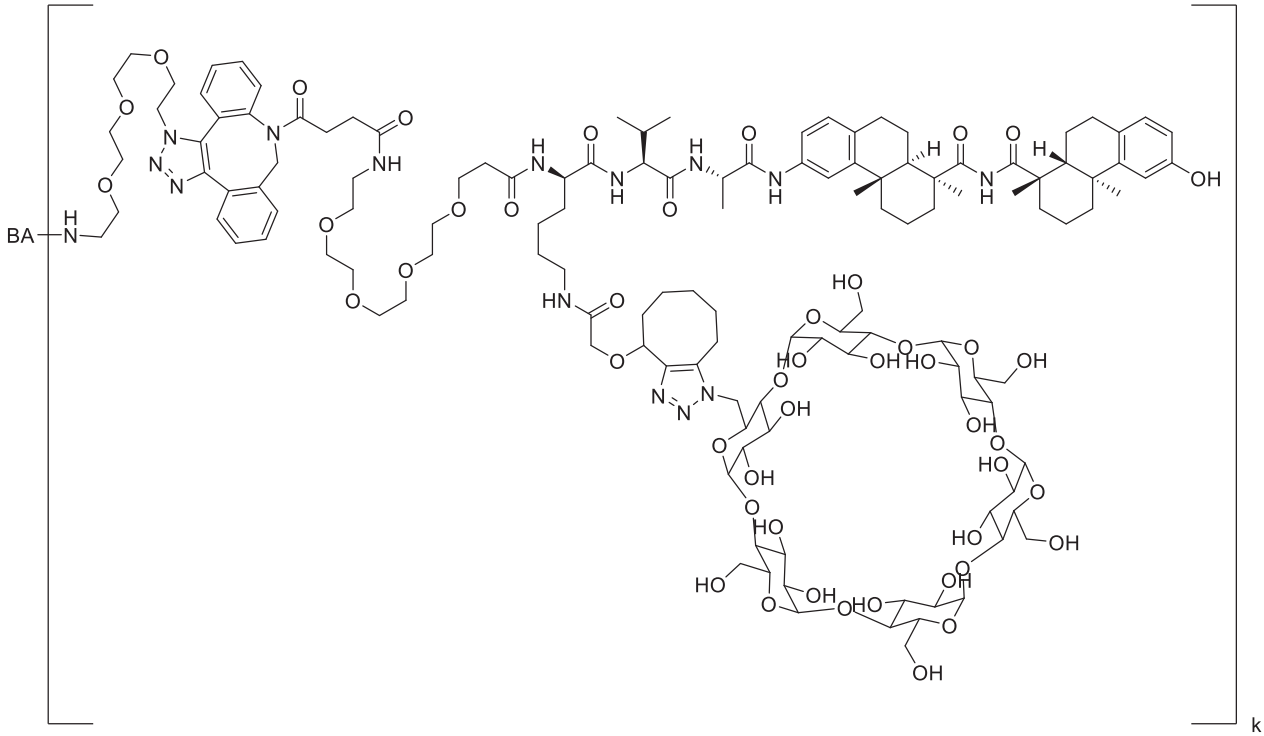
53. The linker-payload of claim 24, having the structure



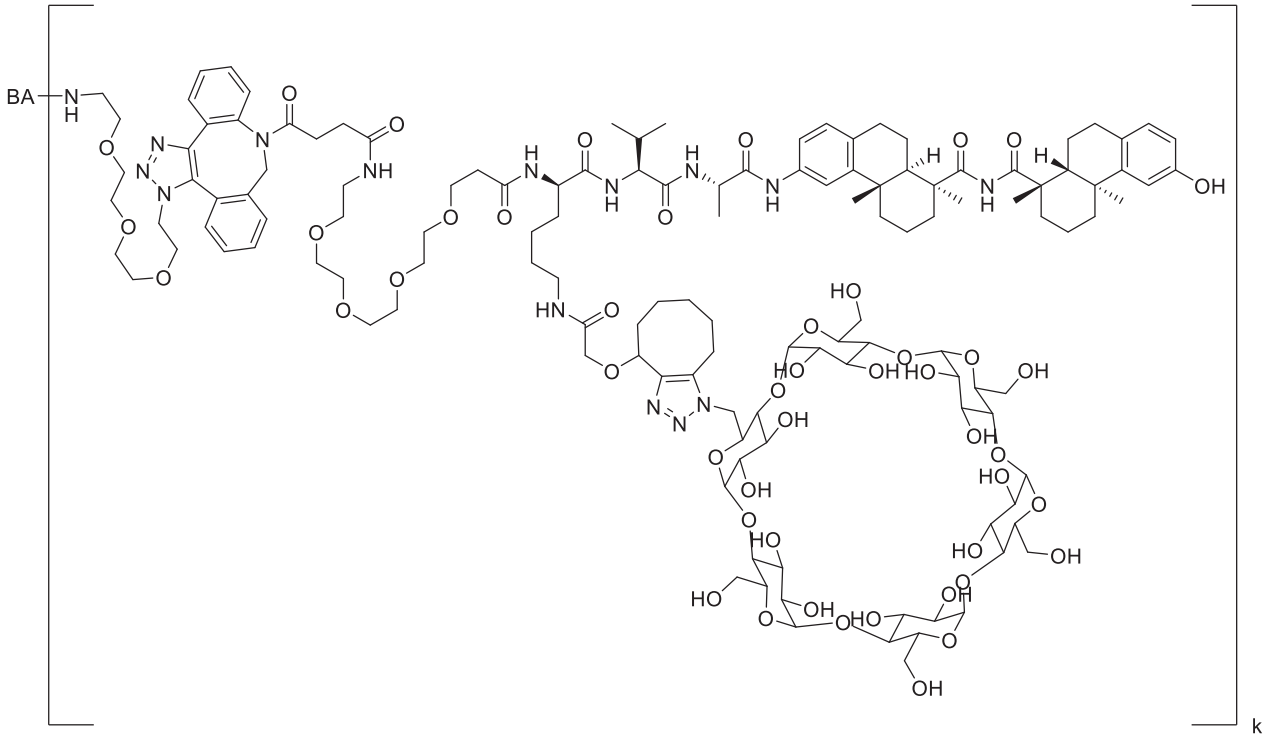
54. The linker-payload of claim 24, having the structure



55. The compound of claim 28, having the structure

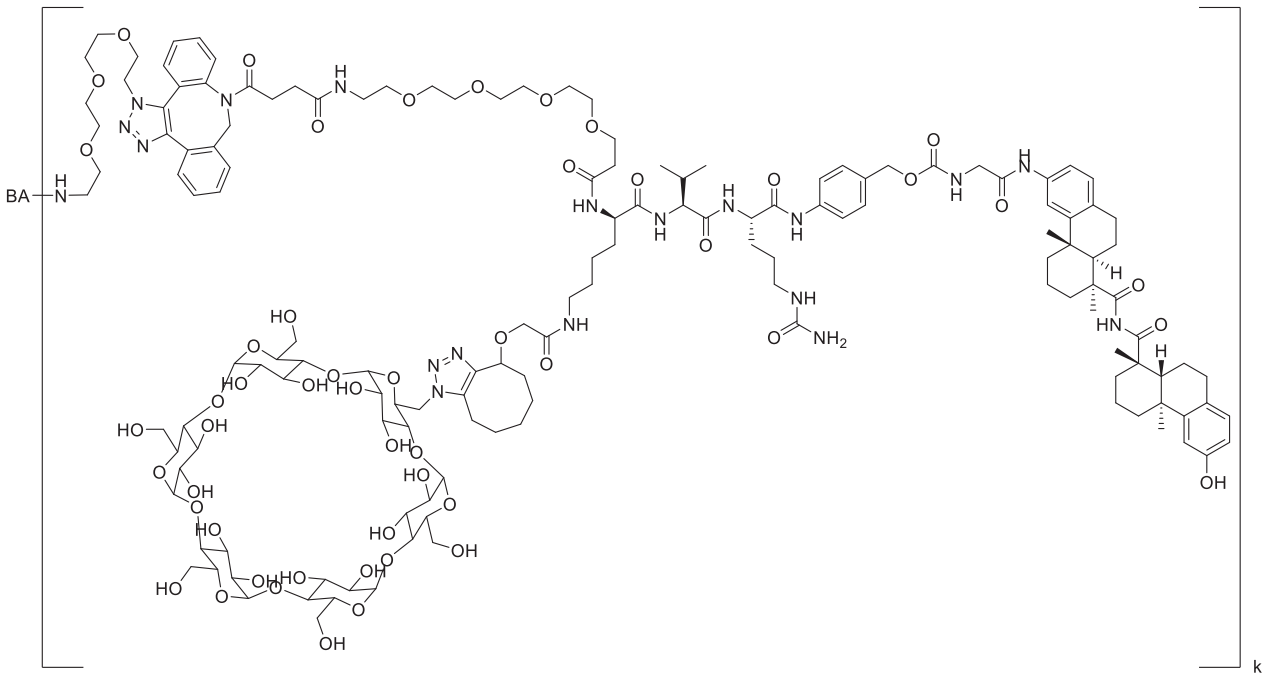


or

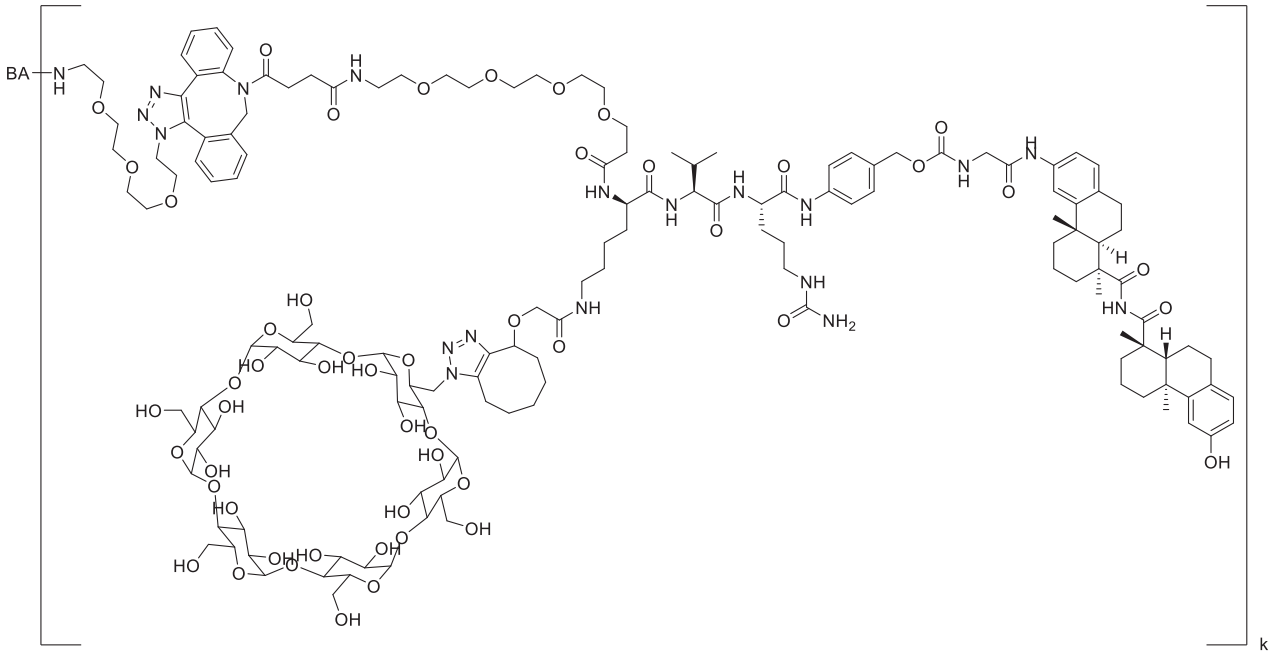


wherein **BA** is a binding agent; and **k** is an integer from one to thirty.

56. The compound of claim 28, having the structure

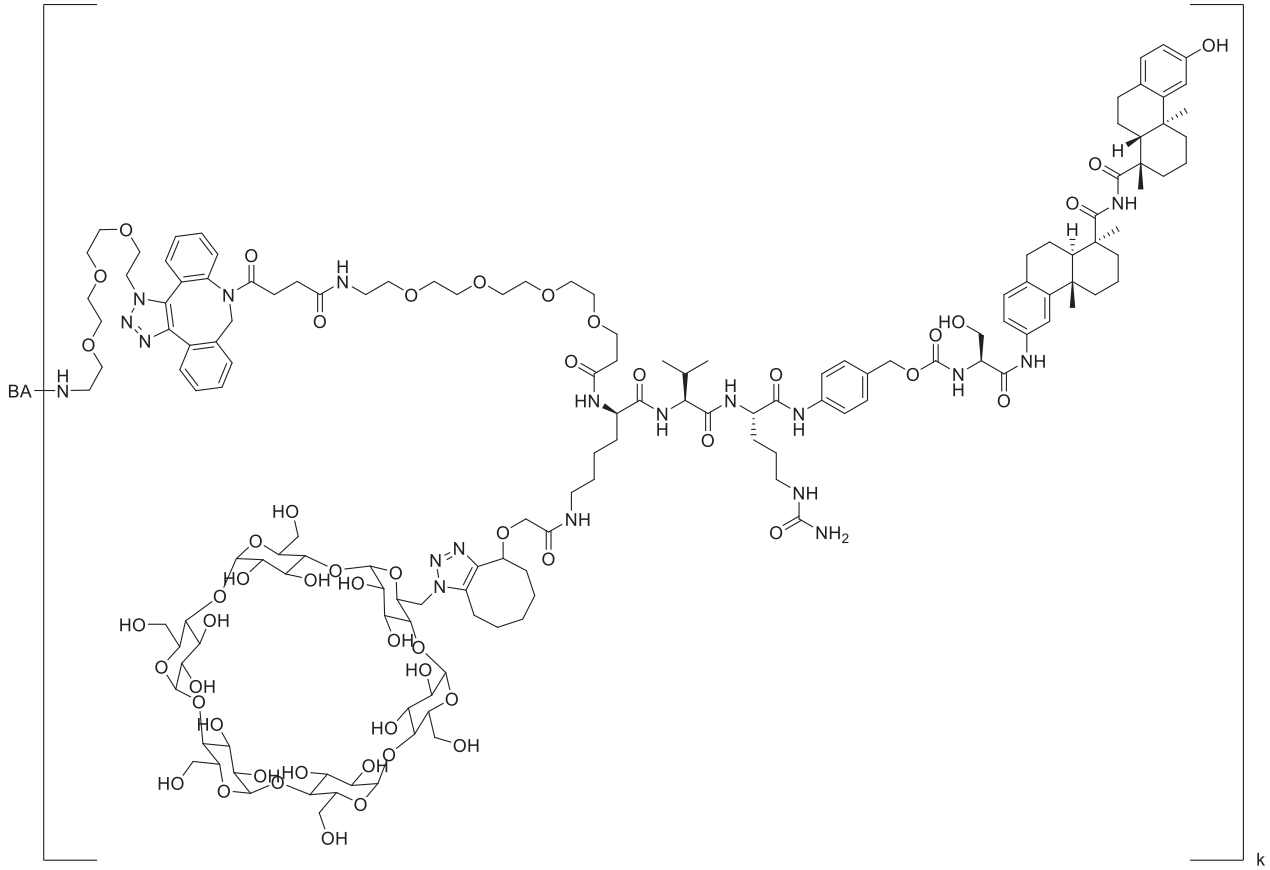


or

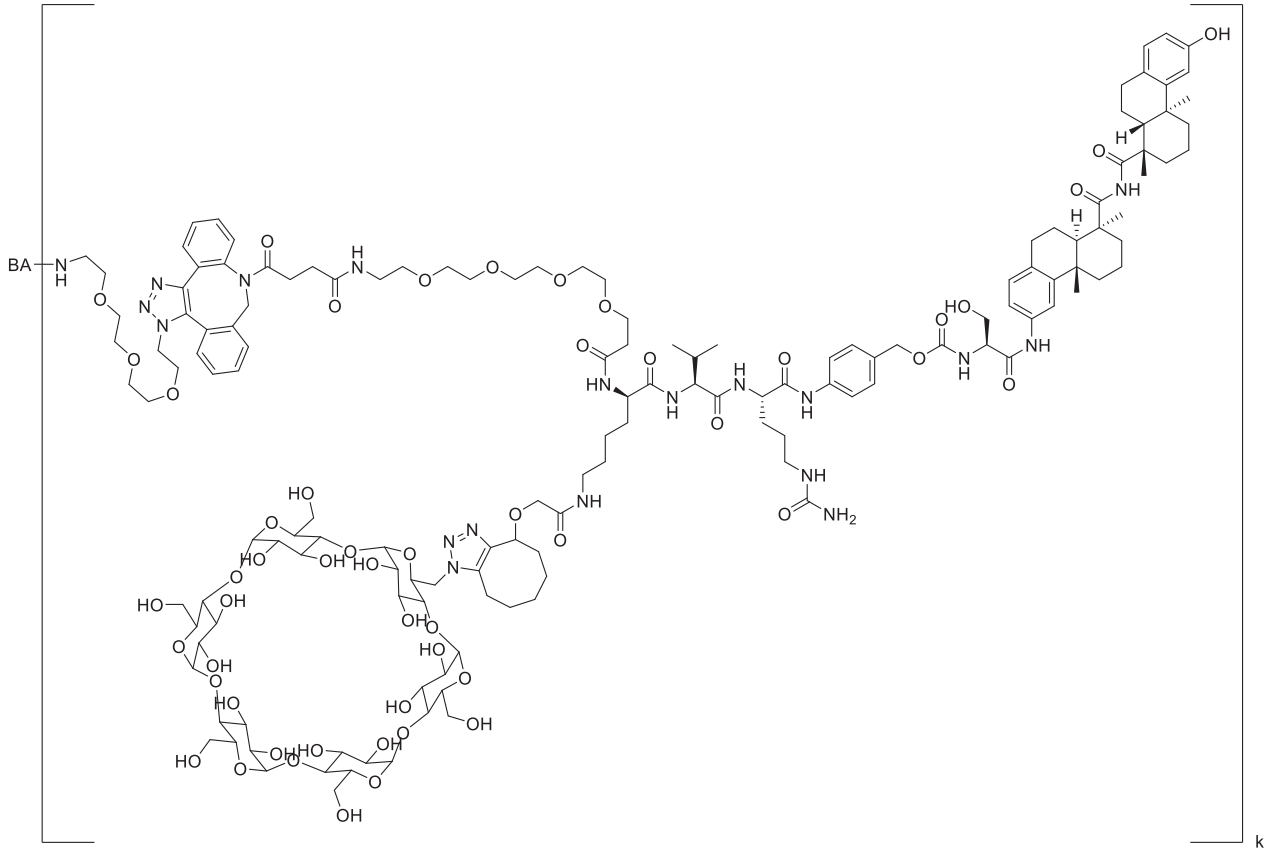


wherein **BA** is a binding agent; and **k** is an integer from one to thirty.

57. The compound of claim 28, having the structure

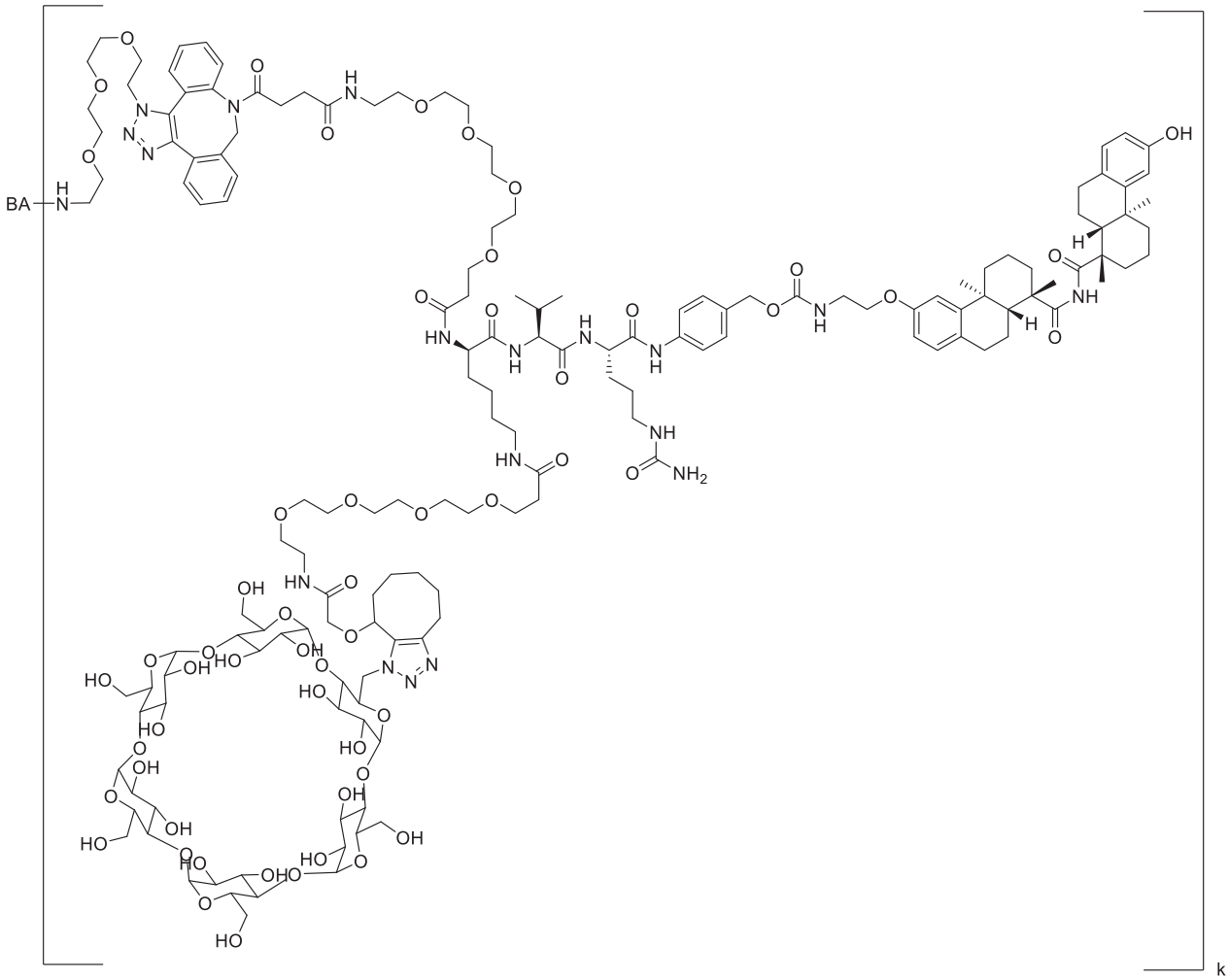


or

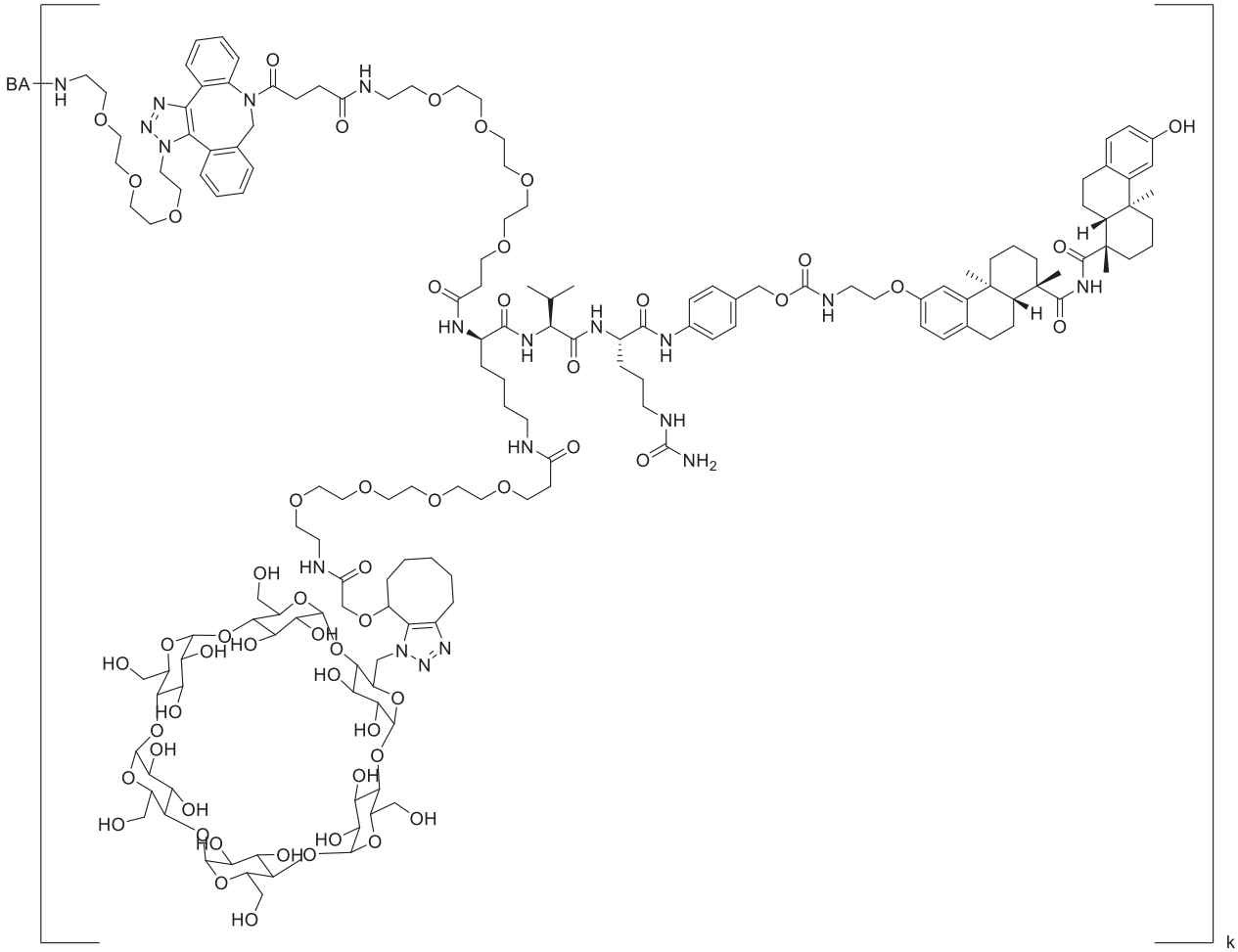


wherein **BA** is a binding agent; and **k** is an integer from one to thirty.

58. The compound of claim 28, having the structure

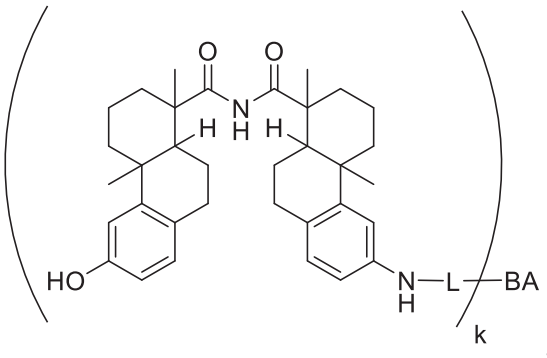


or



wherein **BA** is a binding agent; and **k** is an integer from one to thirty.

59. The compound of claim 28, having the following formula



.

60. The compound of any one of claims 28-46 or 55-59, wherein **BA** or **Ab** is a transglutaminase-modified antibody or antigen binding fragment thereof.