HYDROPHILIC LINKERS FOR ANTIBODY DRUG CONJUGATES

[01] This PCT International application claims the benefit of priority to U.S. Provisional Application No. 62/669,034, filed on May 9, 2018; PCT International Application PCT/US17/60434 (published as WO 2018/089373), filed on November 7, 2017; and U.S. Nonprovisional Application No. 15/806,197 (published as US 2018/0155389), filed on November 7, 2017; the content of all said applications is incorporated herein by reference in its entirety for all purposes.

FIELD

[02] Provided herein are novel protein, e.g., antibody, drug conjugates comprising hydrophilic solubilizing groups and/or linkers comprising hydrophilic solubilizing groups, and methods for treating diseases, disorders, and conditions comprising administering the protein drug conjugates comprising hydrophilic solubilizing groups and/or linkers thereof.

BACKGROUND

[03] Antibody-drug conjugates (ADCs) are antibodies that are conjugated to a biologically active small molecule. ADCs deliver a potent drug selectively to target- expressing cells, leading to a potential reduction of off-target side effects and/or toxicity and improved therapeutic index. The lipophilic nature of many payloads (*i.e.*, drugs) can adversely affect the properties of the ADC to the extent that the payloads are not efficiently delivered to the target cells. Low bioavailability of lipophilic payloads can narrow therapeutic windows for ADC treatment. Furthermore, the hydropobic nature of payloads can present challenges to their conjugation to antibodies, a reaction performed in aqueous conditions. Thus there is an ongoing need for development of hydrophilic linkers for protein conjugates, e.g., ADCs, which would allow for the feasibility of conjugating lipophilc payloads, improved modulation of biological targets, improved bioavailability, and improved therapeutic window.

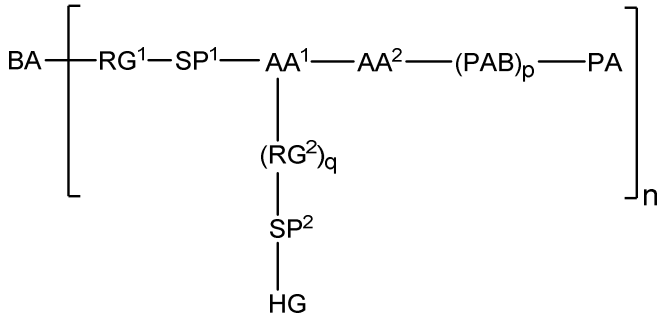
SUMMARY

[04] 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.

[05] In one example, set forth herein, is a compound or a pharmaceutically acceptable salt thereof, including: a protein binding agent linked to at least one payload moiety and linked to at least one hydrophilic 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 hydrophilic moiety.

[05a] In one aspect, set forth herein is a compound, or pharmaceutically acceptable solvate, stereoisomer, or derivative thereof, comprising a binding agent linked to at least one payload moiety and linked to at least one hydrophilic residue via a covalent linker, wherein the said covalent linker is bonded directly or indirectly to each of the binding agent, the payload moiety, and the hydrophilic residue

wherein the compound has a structure according to Formula (**IV**):



(**IV**)

wherein:

BA is a binding agent;

RG^1 and **RG^2** are reactive group residues;

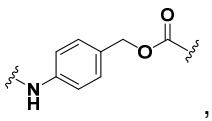
SP^1 and **SP^2** are independently, in each instance, absent, or a spacer group residue;

HG is a hydrophilic residue;

PA is a payload residue;

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

AA^2 is a dipeptide, tripeptide, or tetrapeptide residue;

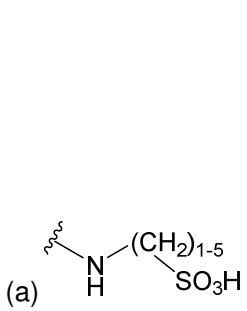
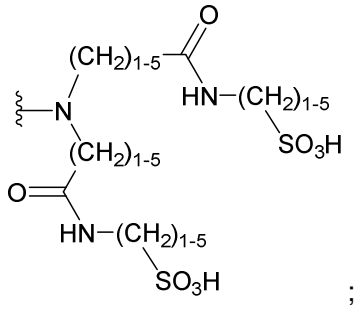
PAB is , wherein the  indicates the atom through which the **PAB** is bonded to the adjacent groups in the formula;

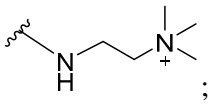
subscript **n** is an integer from 1 to 30;

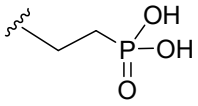
subscript **p** is 0 or 1; and

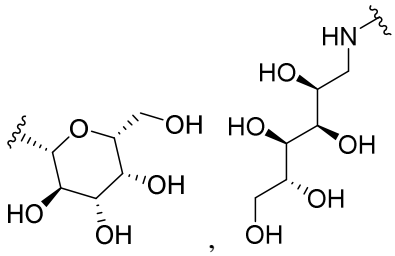
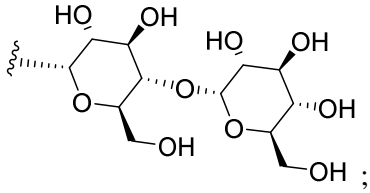
subscript **q** is 0 or 1;

wherein HG is selected from the following:

(a)  or ;

(b) ;

(c) ; or

(d) , , or ;

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

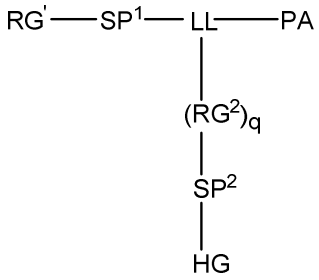
[05b] In another aspect, set forth herein, is a pharmaceutical composition comprising a compound as described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[05c] In another aspect, set forth herein, is a compound as described herein, or a composition as described herein for use in treating a disease or disorder in a patient in need thereof.

[06] 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 hydrophilic 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 hydrophilic moiety.

[06a] In another aspect, set forth herein, is a compound comprising a reactive linker bonded to at least one payload moiety and bonded to at least one hydrophilic residue via a covalent linker, wherein said covalent linker is bonded directly or indirectly to each of the reactive linker, the payload moiety, and the hydrophilic residue

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



(VII)

LL is a trivalent linker;

RG' is a reactive group;

RG^2 is a reactive group residue;

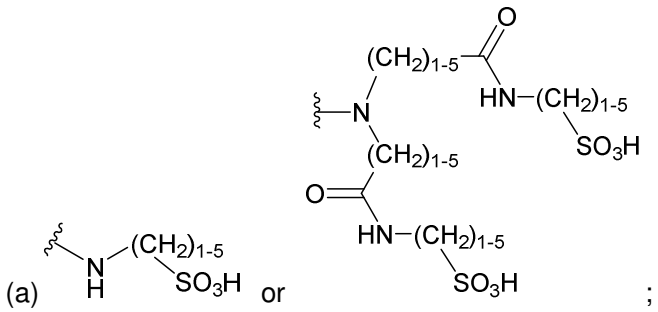
SP^1 and **SP^2** are independently, in each instance, absent, or a spacer group residue;

HG is a hydrophilic residue;

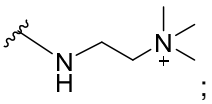
PA is a payload residue; and

subscript **q** is 0 or 1;

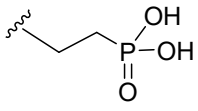
wherein **HG** is selected from the following:

(a)  or ;

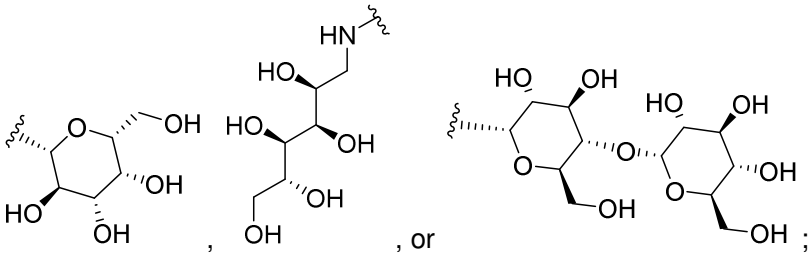
(b)

 ;

(c)

 ; or

(d)

 , , or ;

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

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

[07a] In another aspect, set forth herein is a linker-payload comprising the compound as described herein, bonded to a linker.

[07b] In another aspect, set forth herein is a linker-payload comprising the compound as described herein, bonded to an oxygen or a primary or secondary nitrogen of the payload.

[07c] In another aspect, set forth herein is an antibody-drug-conjugate comprising the compound or linker-payload as described herein bonded to an antibody, or an antigen binding fragment thereof.

[08] 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. Also provided is the use of a compound set forth herein for treating a disease, condition, or disorder set forth herein. Further provided is the use of a compound set forth herein for the manufacture of a medicament for treating a disease, condition, or disorder set forth herein. In some examples, the compound is an antibody-drug conjugate.

[08a] In another aspect, set forth herein is a compound or pharmaceutical composition as described herein for use in treating a proliferative disease, a metabolic disease, inflammation, or a neurodegenerative disease in a subject.

[08b] In another aspect, set forth herein is a compound or pharmaceutical composition as described herein for use in the treatment of a proliferative disease in a subject.

[08c] In another aspect, set forth herein is a compound or pharmaceutical composition as described herein for use in the treatment of a metabolic disease in a subject.

[08d] In another aspect, set forth herein is a compound or pharmaceutical composition as described herein for use in the treatment of inflammation in a subject.

[08e] In another aspect, set forth herein is a compound or pharmaceutical composition as described herein for use in the treatment of a neurodegenerative disease in a subject.

[08f] In another aspect, set forth herein is use of a compound or pharmaceutical composition as described herein in the manufacture of a medicament for treating a proliferative disease, a metabolic disease, inflammation, or a neurodegenerative disease in a subject.

[09] 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.

[09a] In another aspect, set forth herein is a method of preparing a compound as described herein comprising the step of contacting a binding agent with a compound as described herein, under conditions suitable for forming a bond between the binding agent and the compound.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[010] FIG. 1 shows three different types of payload compounds.

[011] FIG. 2 shows a synthetic process for preparing compounds 1a, 1c, 1e, 1f, 1i, 1j, 1k, 1m, 1q, Ib, Id, Ie-1, If-1, IIb, IIId, IIIe, and IVb.

[012] FIG. 3 shows shows a synthetic process for preparing compounds 1h, 1l, Ig, and Ih-1.

[013] FIG. 4 shows a synthetic process for preparing payloads B and C.

[014] FIG. 5 shows a synthetic process for preparing payload D.

[015] FIG. 6 shows a general synthetic procedure A for preparing intermediates 3a, 3b, 3c, and 3g.

[016] FIG. 7 shows a general synthethic procedure for preparing intermediates 3d, and 3f.

[017] FIG. 8 shows a synthethic process for preparation of intermediate 3e.

[018] FIG. 9 shows a synthethic process for preparation of intermediate 4a.

[019] FIG. 10 shows a synthetic process for preparation of intermediate 4b.

[020] FIG. 11 shows a synthetic process for preparation of intermediates 5a-g.

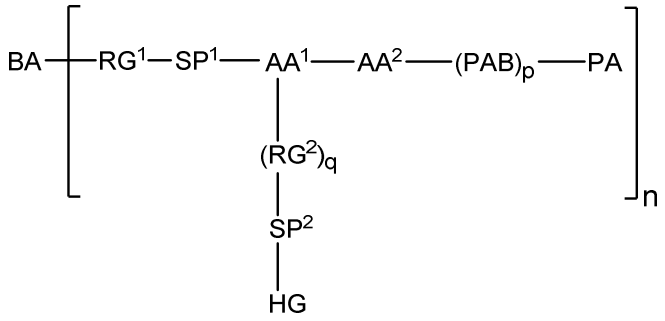
[021] FIG. 11A shows a synthetic process for preparation of intermediate 10a.

CLAIMS

What is claimed is:

1. A compound, or pharmaceutically acceptable solvate, stereoisomer, or derivative thereof, comprising a binding agent linked to at least one payload moiety and linked to at least one hydrophilic residue via a covalent linker, wherein the said covalent linker is bonded directly or indirectly to each of the binding agent, the payload moiety, and the hydrophilic residue

wherein the compound has a structure according to Formula (**IV**):



(**IV**)

wherein:

BA is a binding agent;

RG^1 and **RG^2** are reactive group residues;

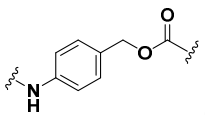
SP^1 and **SP^2** are independently, in each instance, absent, or a spacer group residue;

HG is a hydrophilic residue;

PA is a payload residue;

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

AA^2 is a dipeptide, tripeptide, or tetrapeptide residue;

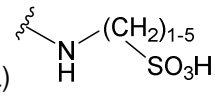
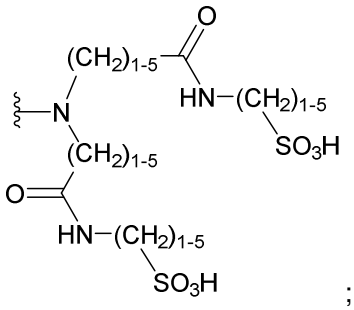
PAB is , wherein the  indicates the atom through which the **PAB** is bonded to the adjacent groups in the formula;

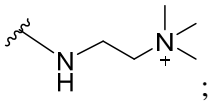
subscript **n** is an integer from 1 to 30;

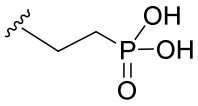
subscript **p** is 0 or 1; and

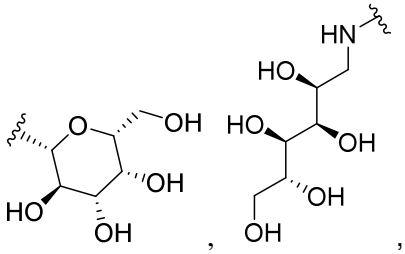
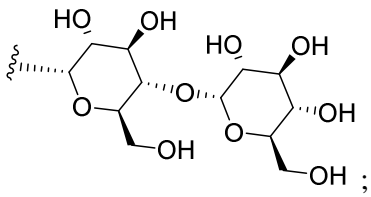
subscript **q** is 0 or 1;

wherein HG is selected from the following:

(a)  or ;

(b) ;

(c) ; or

(d) , , or ;

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

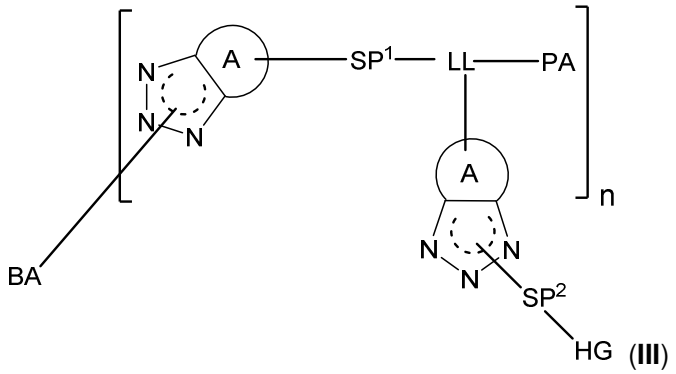
2. The compound of claim 1, wherein the hydrophilic residue comprises a terminal hydrophilic group.

3. The compound of claim 1 or claim 2, wherein the hydrophilic residue comprises a sulfonic acid group or a salt thereof.

4. The compound of claim 1 or claim 2, wherein the hydrophilic residue comprises a quarternary amine or a salt thereof, a phosphonic acid group or a salt thereof, or a sugar residue.

5. The compound of claim 1, wherein subscript **n** is 1, 2, 3 or 4.

6. The compound of claim 1, according to Formula (**III**):



(**III**)

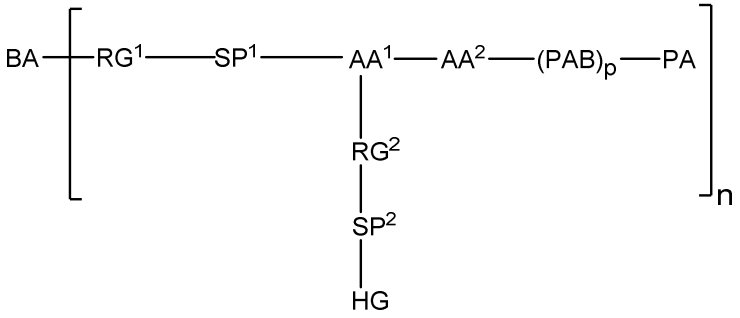
wherein

LL is –**AA**^{1}-**AA**^{2}-(**PAB**)$_{p}$-

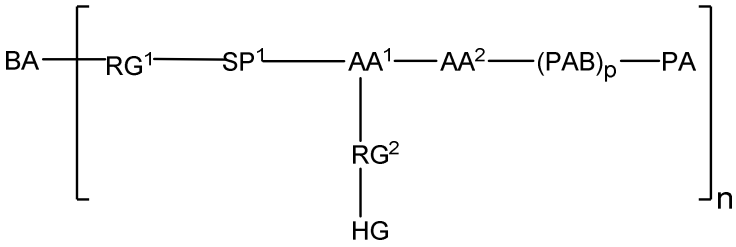
ring **A** is fused to the triazole and is selected from the group consisting of cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

wherein cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl are optionally substituted with alkyl, -OH, or -N**R**^{a}**R**^{b}, where each of **R**^{a} and **R**^{b} is alkyl or H.

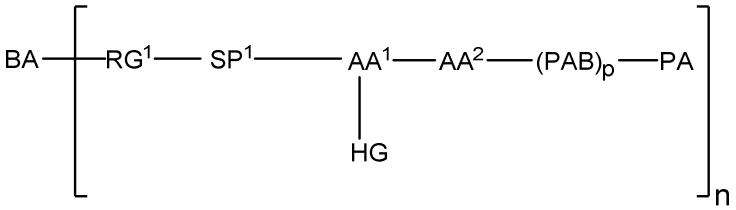
7. The compound of claim 1, according to Formula (**IVa**), Formula (**IVb**) or Formula (**IVc**):



(**IVa**),



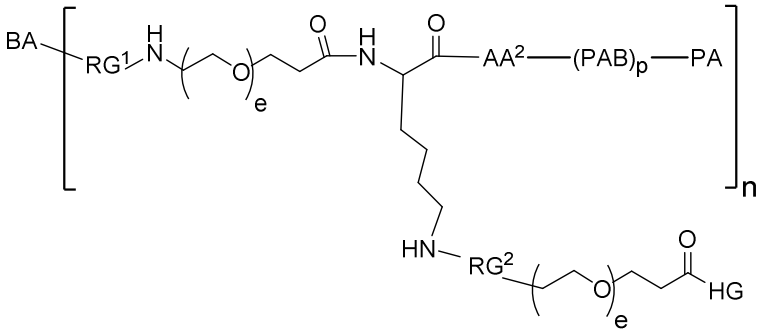
(**IVb**),



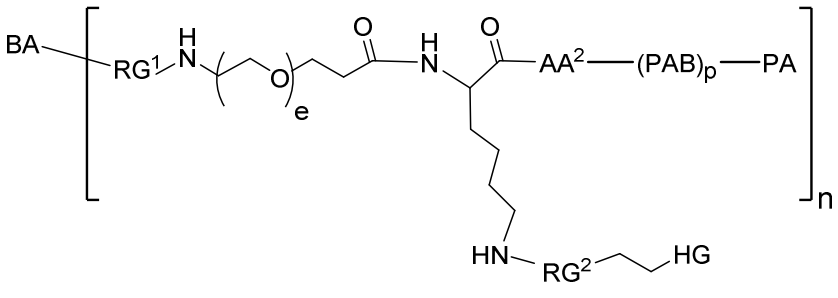
(**IVc**).

8. The compound of claim 7, wherein **AA¹** is lysine, glutamine, glutamic acid, or aspartic acid.

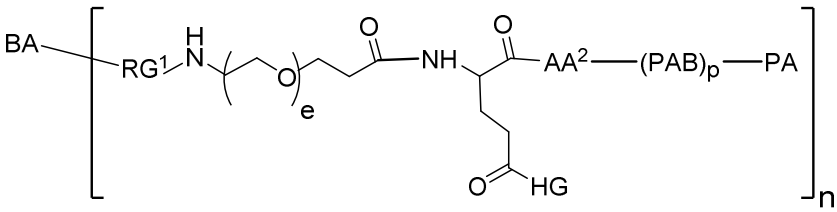
9. The compound of claim 7, according to Formula (**Va**), (**Vb**), (**Vc**) or (**Vd**) respectively:



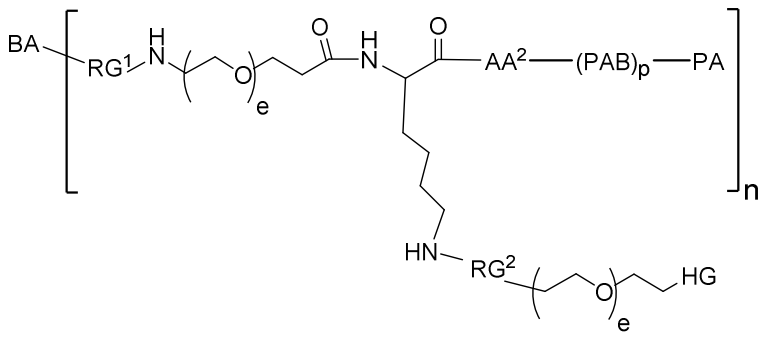
(**Va**),



(**Vb),**



(**Vc**), or



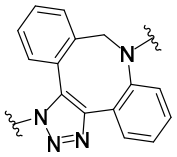
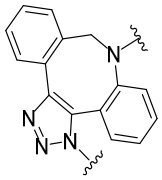
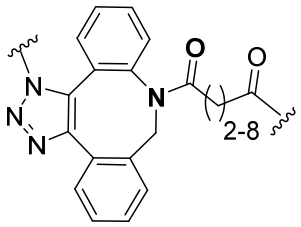
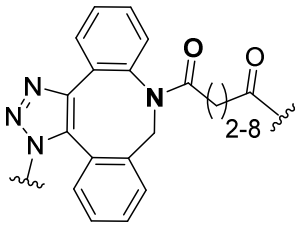
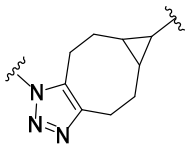
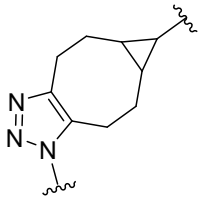
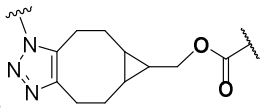
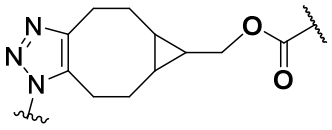
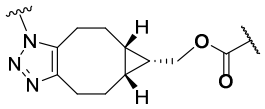
(**Vd**),

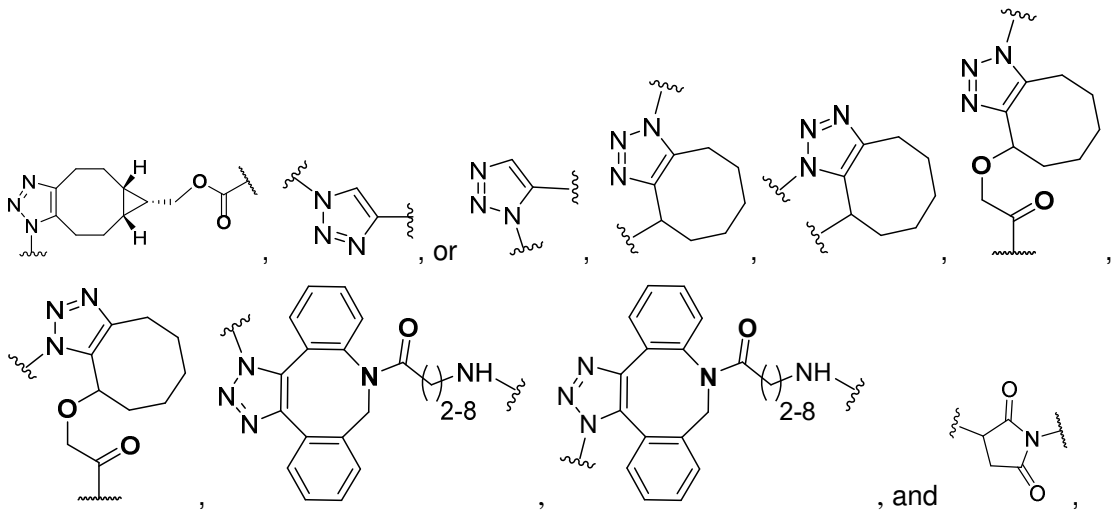
wherein:

subscript **e** is independently, in each instance, an integer from 0 to 6.

10. The compound of any one of claims 1 or 7-9, wherein **RG[1]** and **RG[2]** are independently in each instance, a click chemistry residue.

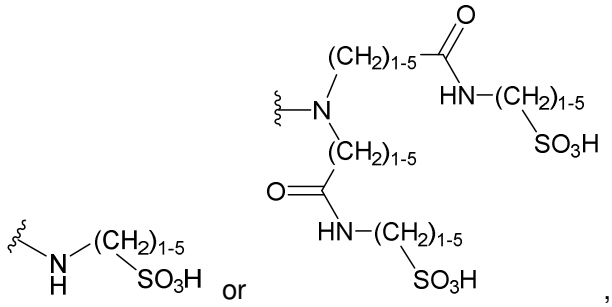
11. The compound of any one of claims 1 or 7-9, wherein **RG[1]** and **RG[2]** independently in each instance, comprise a triazaole or a fused triazole.

12. The compound of any one of claims 1 or 7-11, wherein **RG[1]** and **RG[2]** are independently, in each instance, selected from the group consisting of , , , , , , , , ,

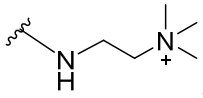


wherein the  indicates the atom through which the **RG**[1] or **RG**[2] is bonded to the adjacent groups in the formula.

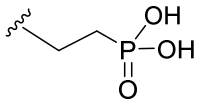
13. The compound of any one of claims 1 or 7-12, wherein **HG** is

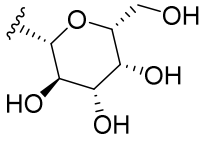
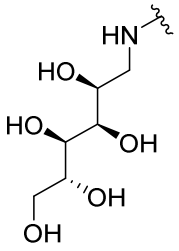
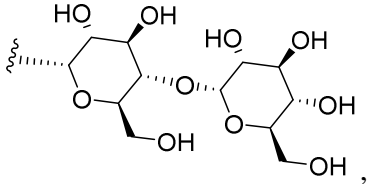


wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

14. The compound of any one of claims 1 or 7-12, wherein **HG** is ,

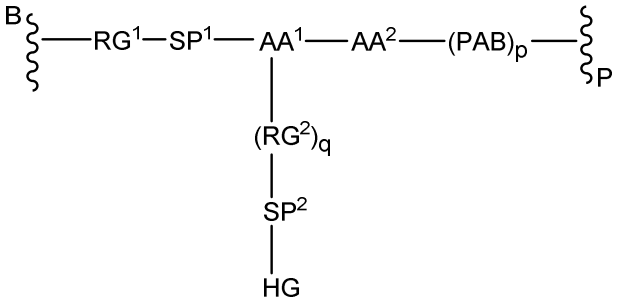
wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

15. The compound of any one of claims 1 or 7-12, wherein **HG** is  wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

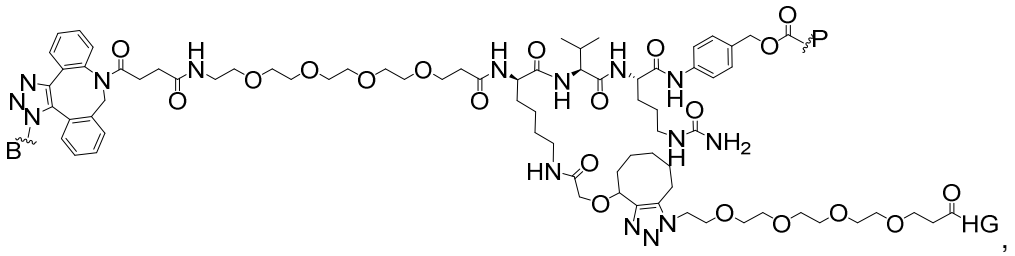
16. The compound of any one of claims 1 or 7-12, wherein **HG** is ,  , or  , wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

17. The compound of any one of claims 1 or 7-16, wherein $\mathbf{SP^1}$ and $\mathbf{SP^2}$ are independently, in each instance, absent, or selected from the group consisting of $C_{1\text{-}6}$ alkylene, -NH-, -C(O)-, $(-CH_2\text{-}CH_2\text{-}O)_e$, $-NH\text{-}CH_2\text{-}CH_2\text{-}(-O\text{-}CH_2\text{-}CH_2)_e\text{-}C(O)$-, $-C(O)\text{-}(CH_2)_u$-C(O)-, $-C(O)\text{-}NH\text{-}(CH_2)_v$-, $(glycine)_4$-serine, 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.

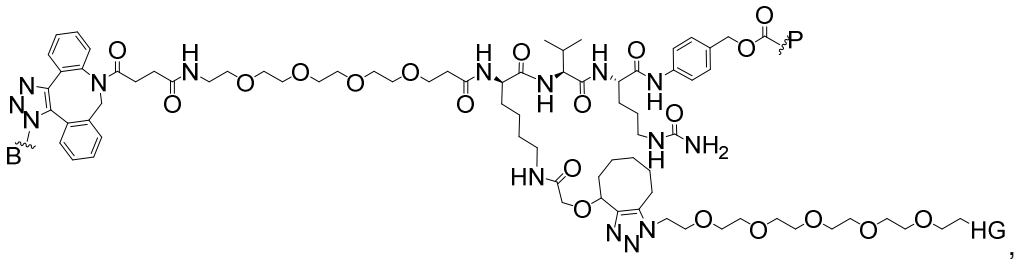
18. The compound of any one of claims 1 or 7-16, wherein



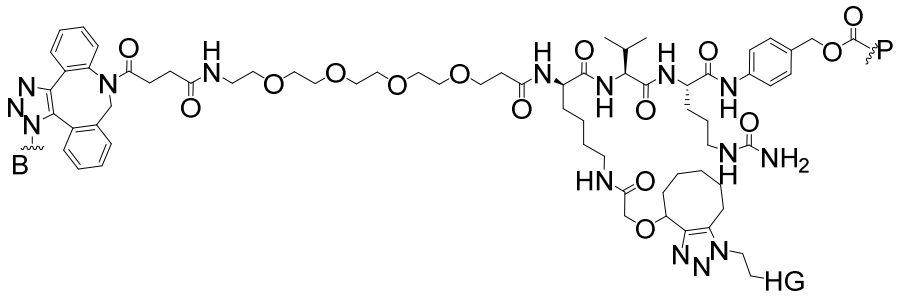
is selected from the group consisting of:



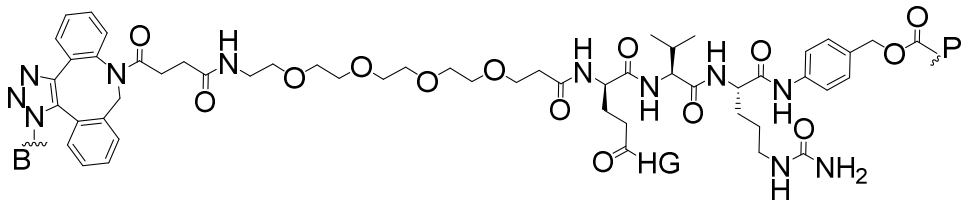
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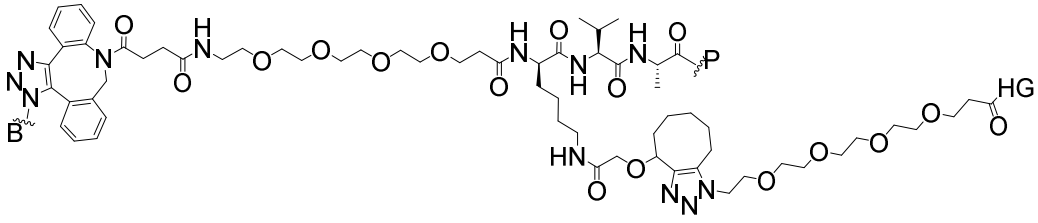
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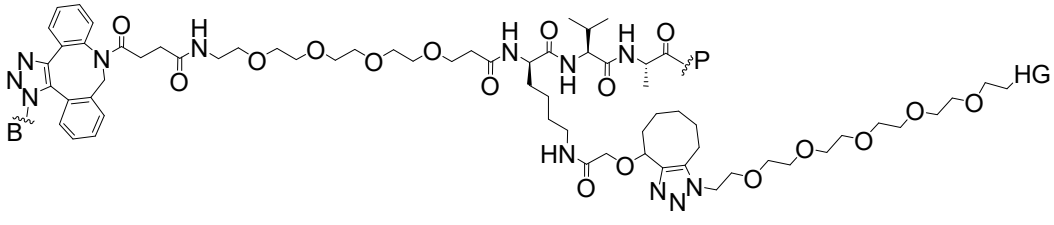
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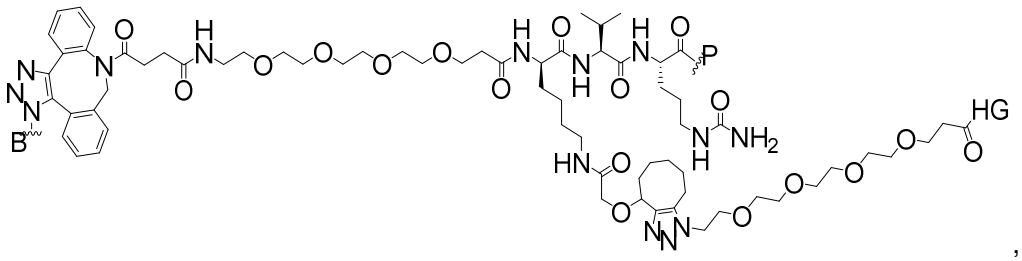
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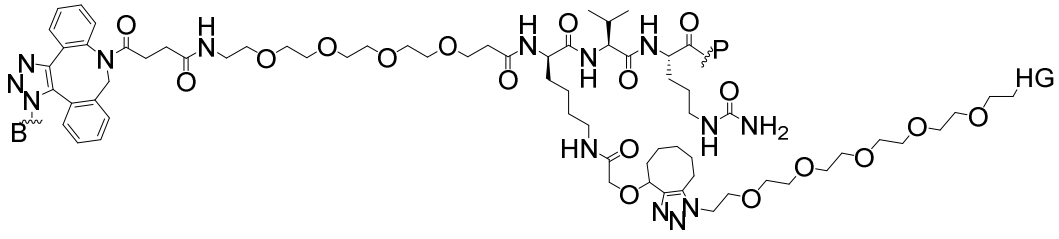
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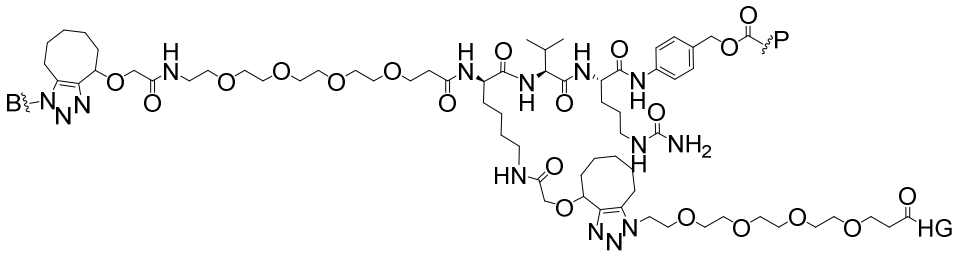
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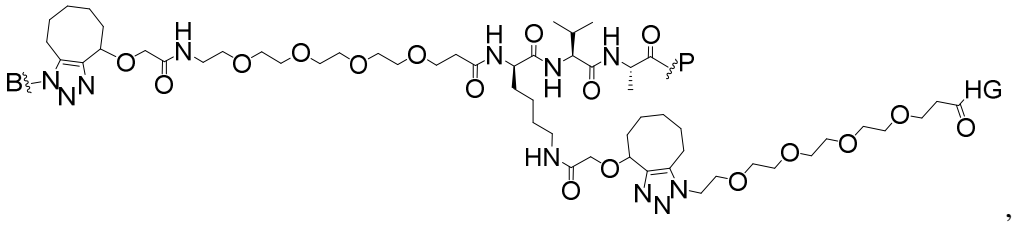
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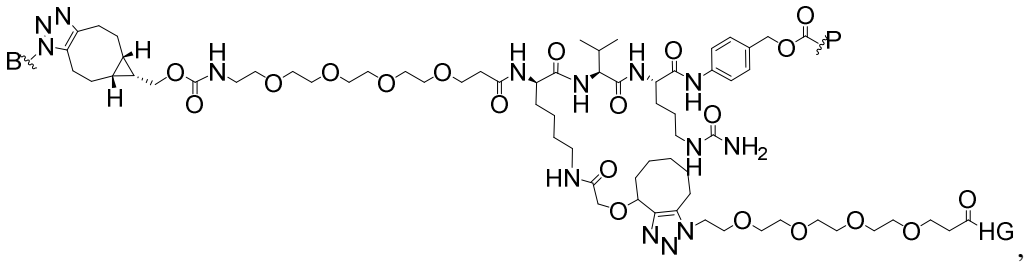
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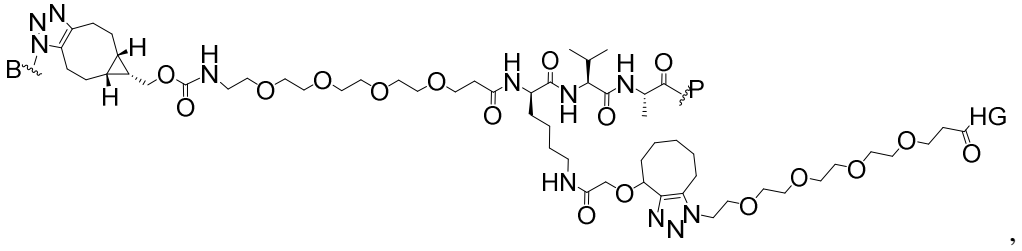
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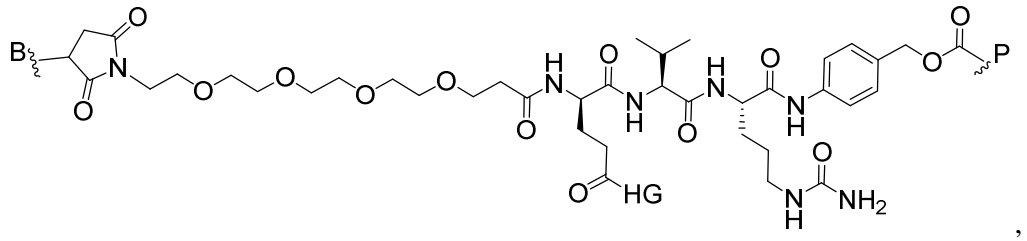
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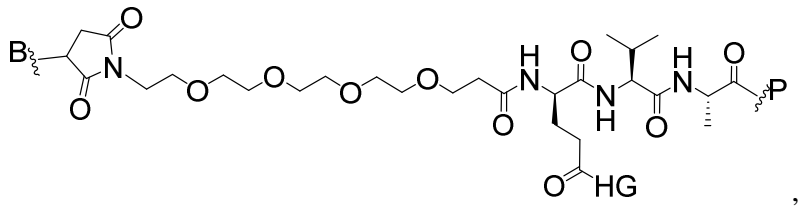


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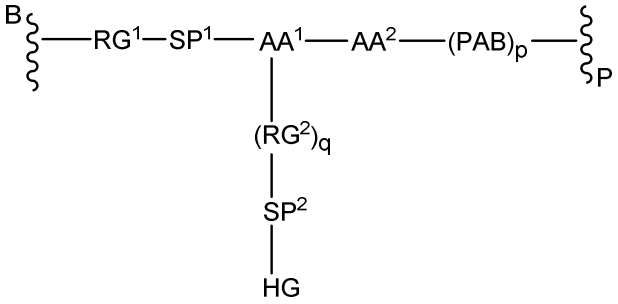
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or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

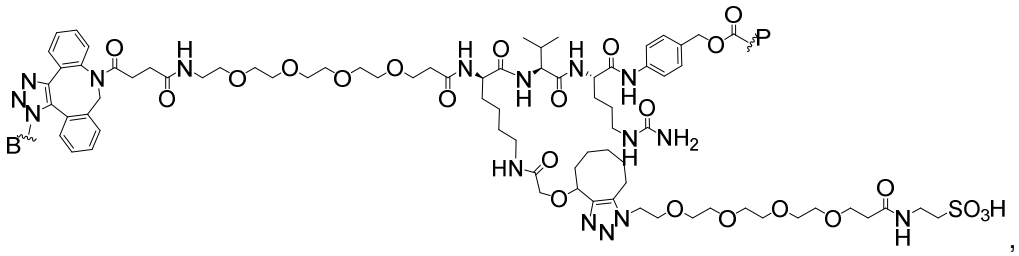
each  is a bond to the binding agent; and

each  is a bond to the payload residue.

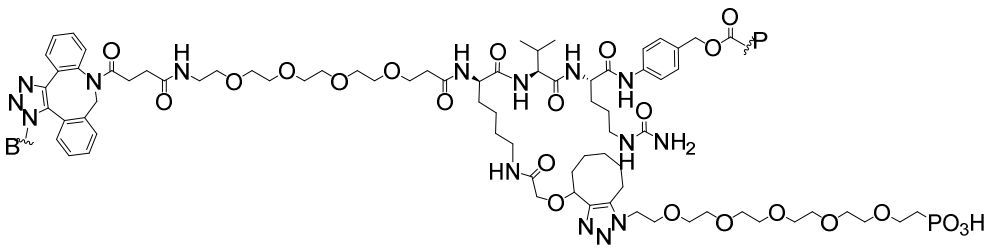
19. The compound of any one of claims 1 or 7-16, wherein

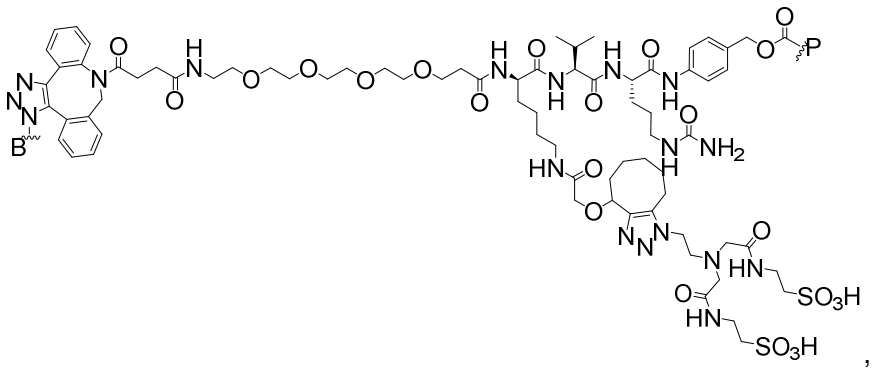


is selected from the group consisting of:

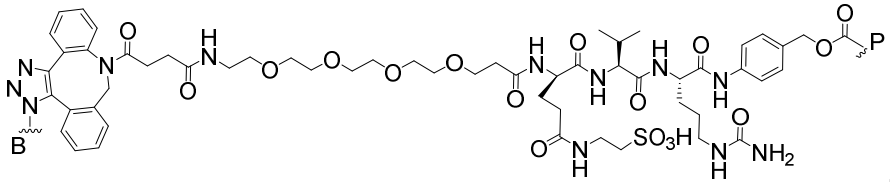


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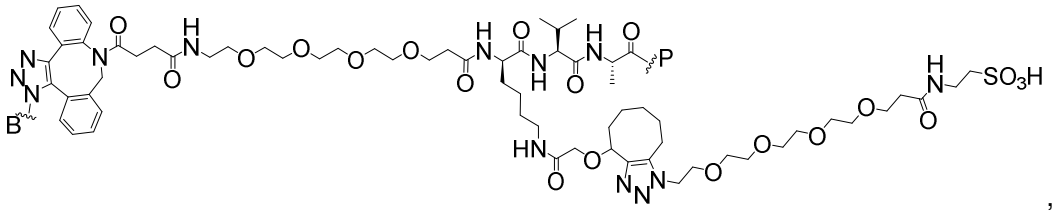




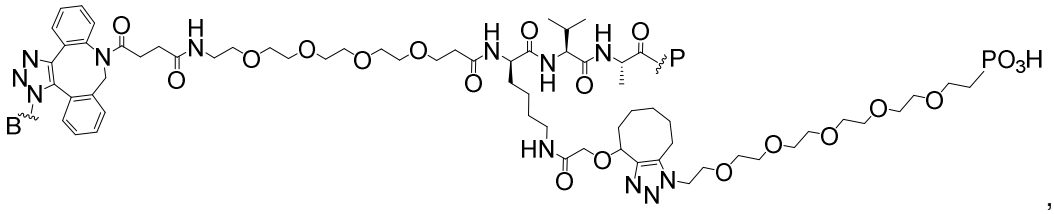
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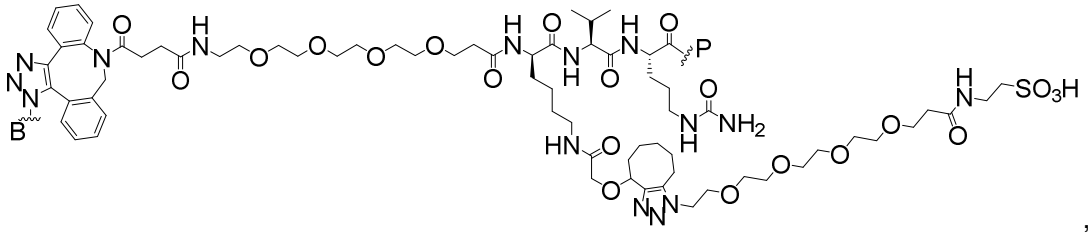
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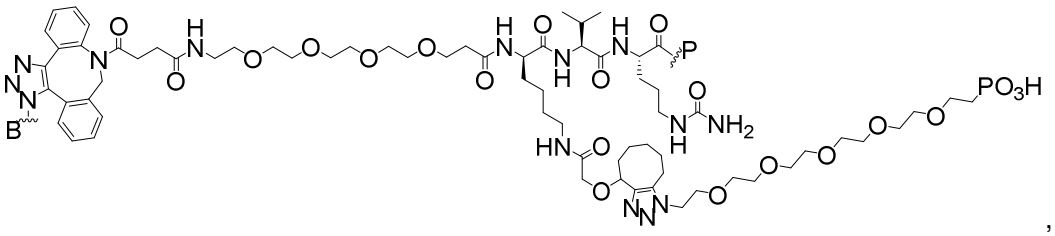
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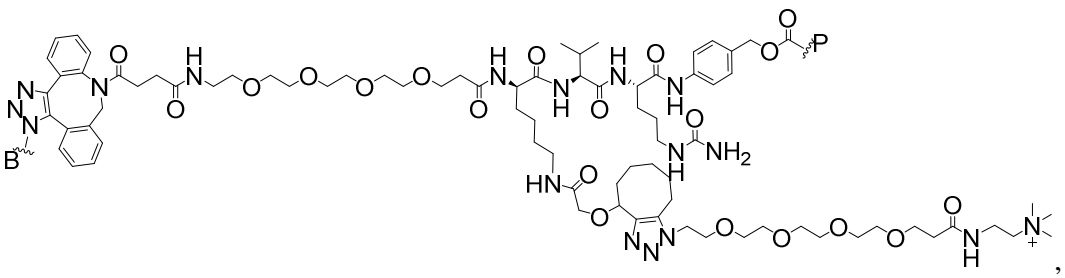
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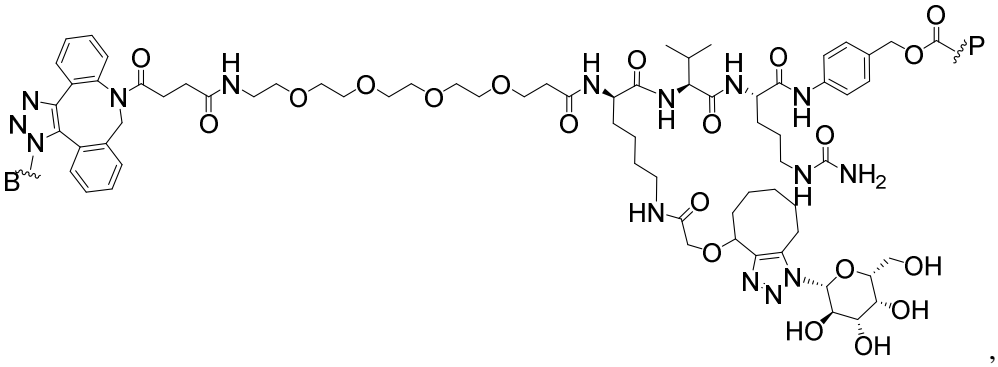
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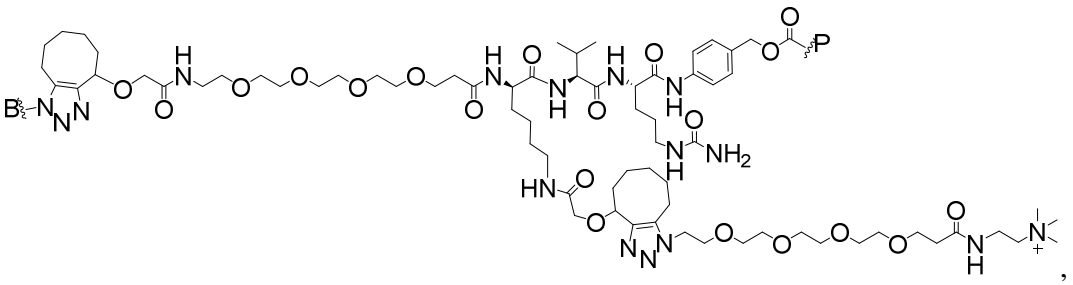
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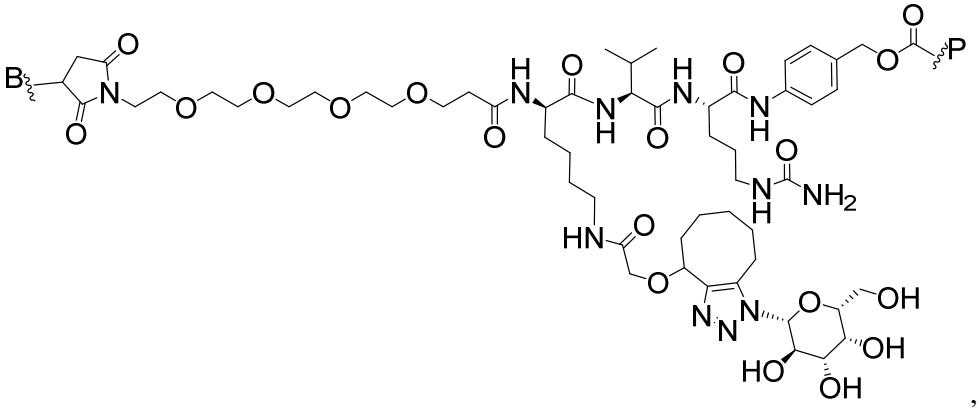
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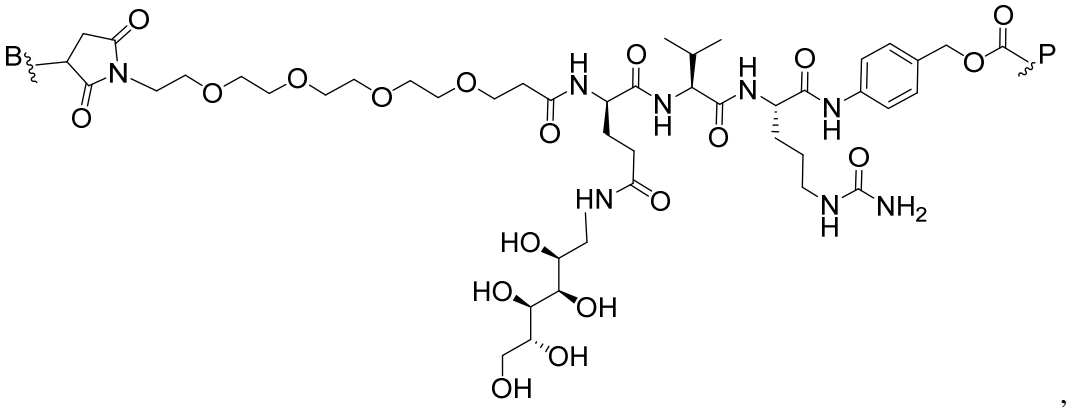
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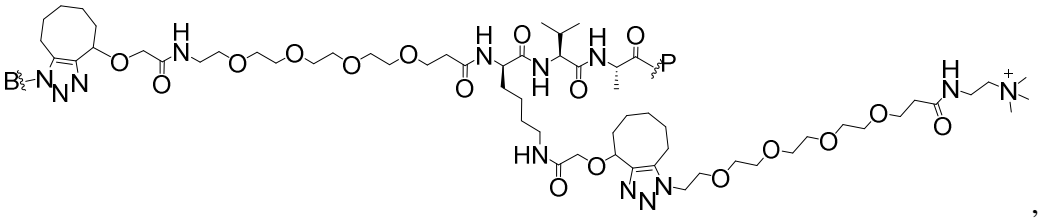
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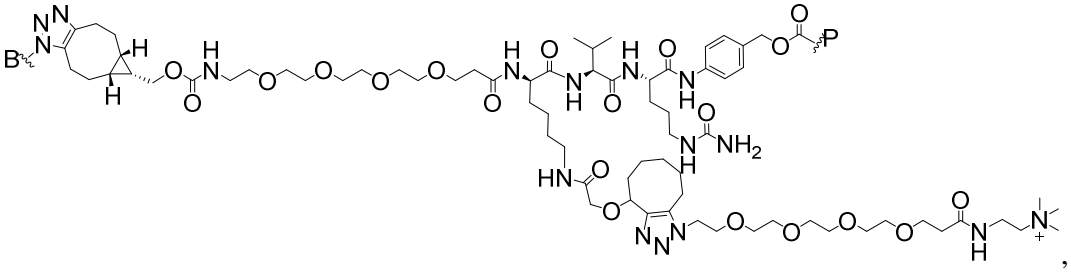
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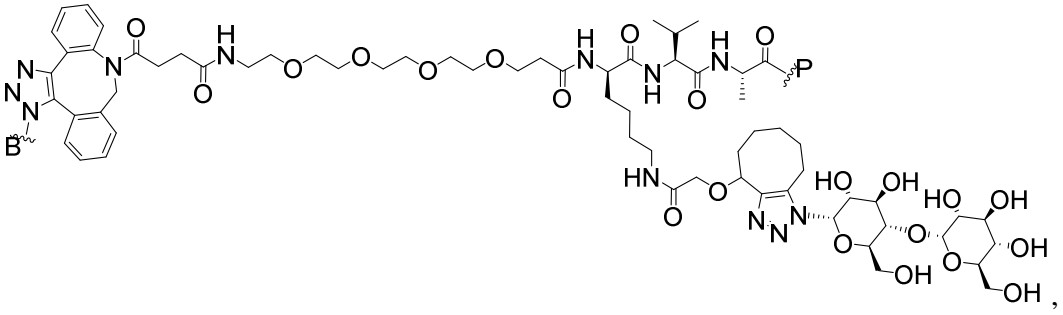


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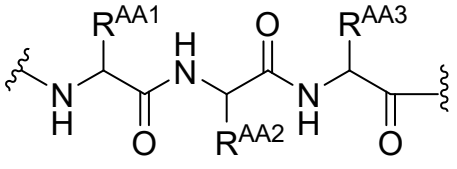
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or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

each  is a bond to the binding agent; and

each  is a bond to the payload residue.

20. The compound of claim 1, wherein **LL** is according to Formula (**LL1**):

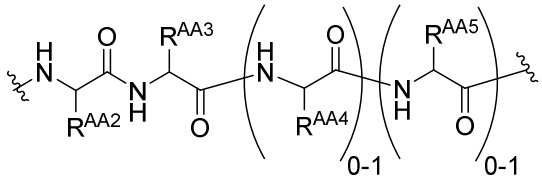


(**LL1**)

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 $\mathbf{-(RG^2)_q\text{-}SP^2\text{-}HG}$

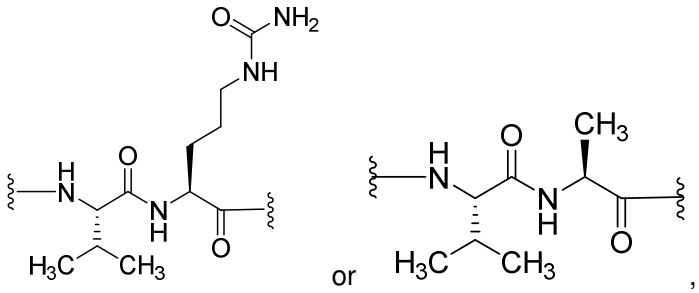
21. The compound of claim 20, wherein $\mathbf{R^{AA1}}$ is a lysine, glutamine, glutamic acid or aspartic acid side chain bonded directly or indirectly to **HG**, and $\mathbf{R^{AA2}}$ and $\mathbf{R^{AA3}}$ are either valine and alanine or valine and citrulline sidechains respectively.

22. The compound of any one of claims 1 or 7-9, wherein $\mathbf{AA^2}$ is



wherein $\mathbf{R^{AA2}}$, $\mathbf{R^{AA3}}$, $\mathbf{R^{AA4}}$, and $\mathbf{R^{AA5}}$ are each, independently, amino acid side chains, at least one of which is bonded directly or indirectly to $\mathbf{-(RG^2)_q\text{-}SP^2\text{-}HG}$, wherein the  indicates the atom through which $\mathbf{AA^2}$ is bonded to the adjacent groups in the formula.

23. The compound of any one of claims 1 or 7-9, wherein $\mathbf{AA^2}$ is



wherein the  indicates the atom through which $\mathbf{AA^2}$ is bonded to the adjacent groups in the formula.

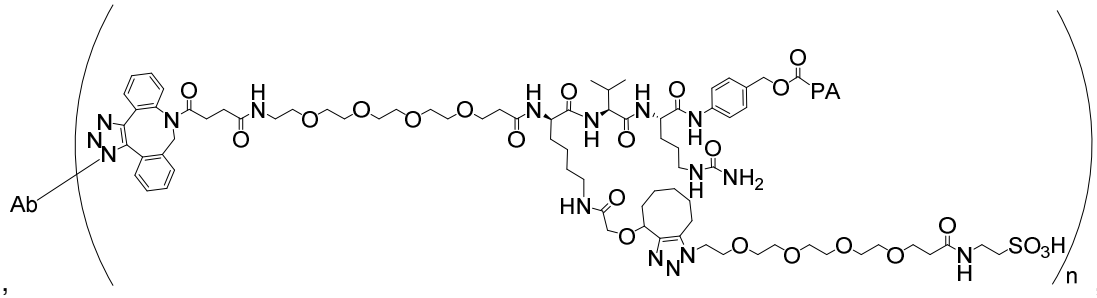
24. The compound of any one of claims 9-23, wherein subscript e is 4.

25. The compound of any one of claims 1-24, wherein the binding agent (**BA**) is an antibody or antigen-binding fragment thereof.

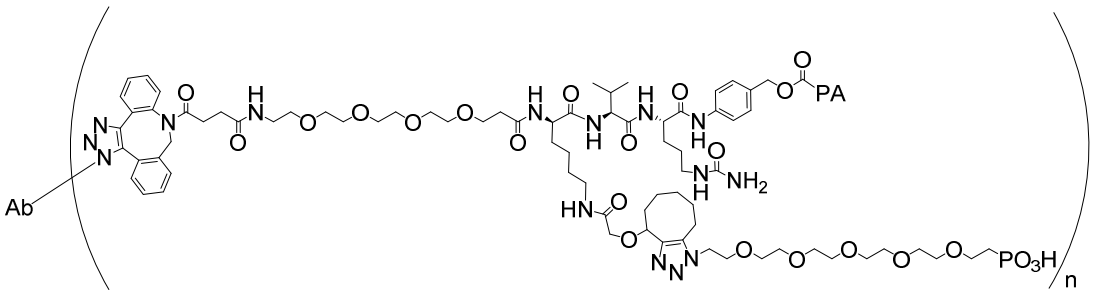
26. The compound of any one of claims 1-24, wherein the binding agent (**BA**) is an antibody, or an antigen-binding fragment thereof, selective for an antigen selected from the group consisting of AXL, BAFFR, BCMA, BCR-list components, BDCA2, BDCA4, BTLA, BTNL2, BTNL3, BTNL8, BTNL9, C10 or f54, CCR1, 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.

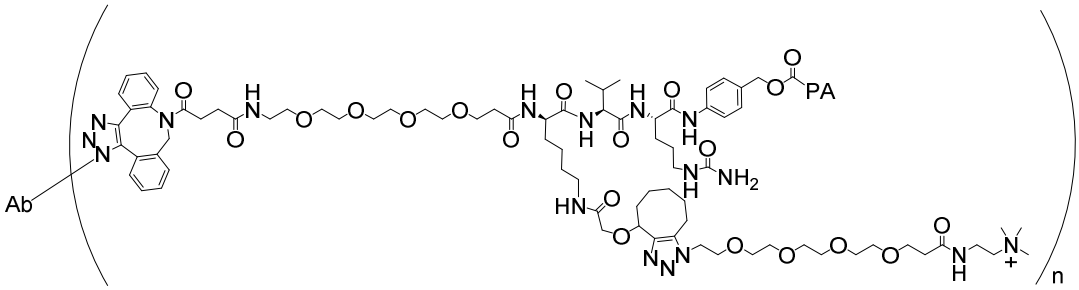
27. The compound of any one of claims 1-26, wherein **PA** is the residue of a group selected from the group consisting of a dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, a vinca alkaloid, a steroid, and a liver X receptor (LXR) modulator.

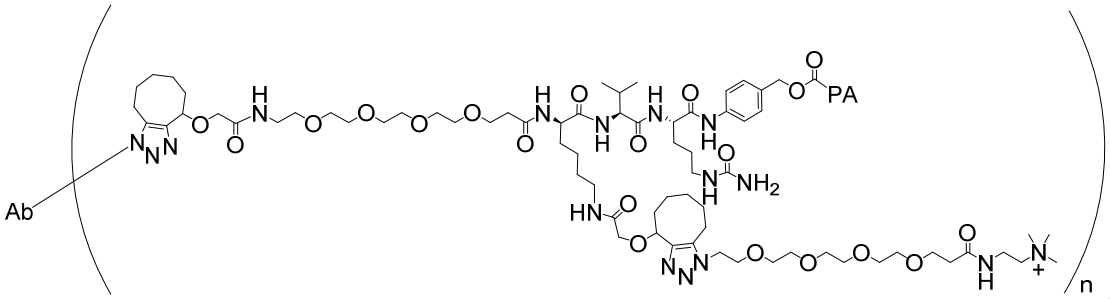
28. The compound of any one of claims 1-27, selected from the group consisting of:



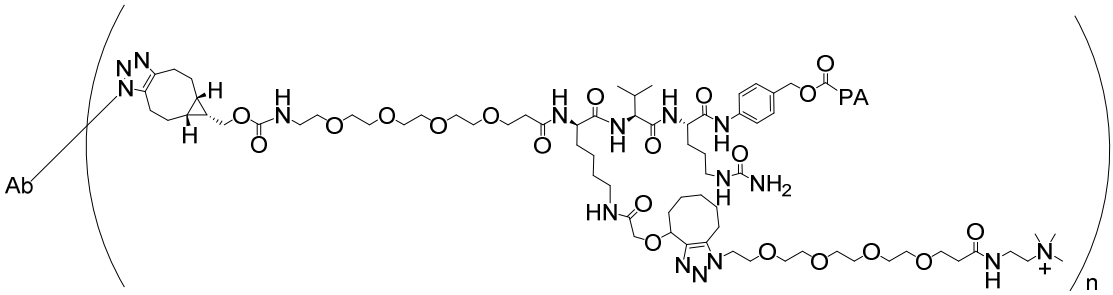
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Ab
PA
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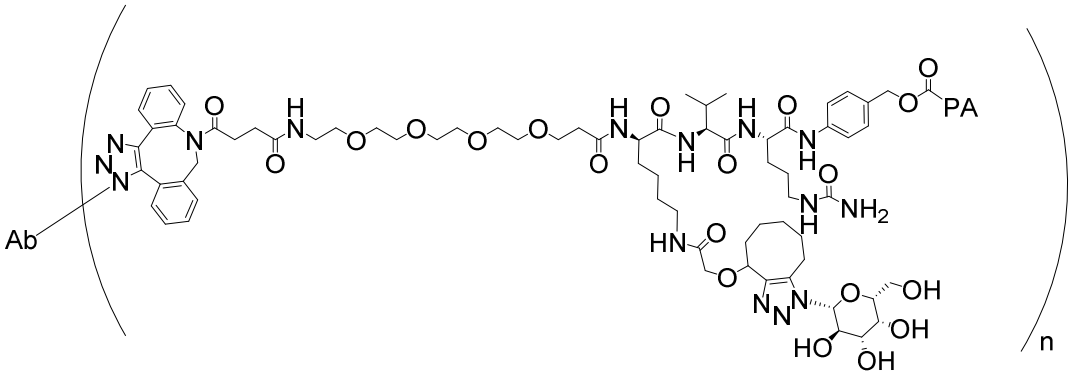

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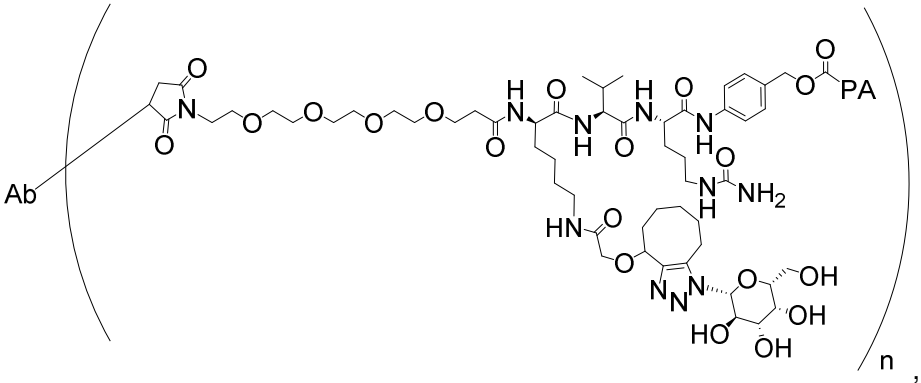
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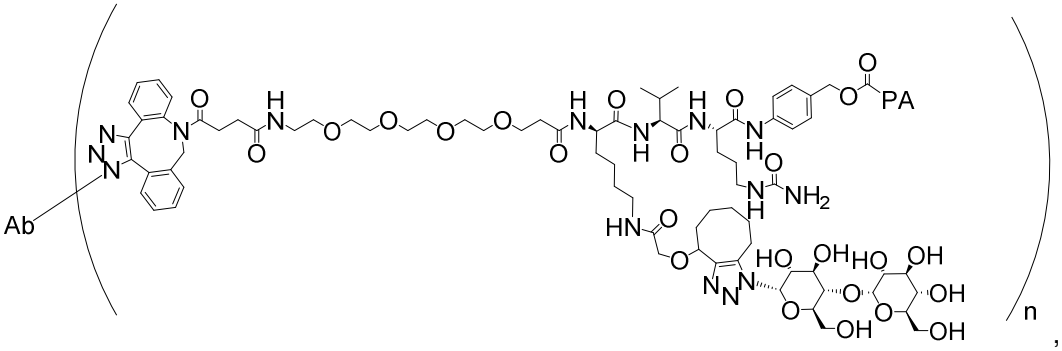
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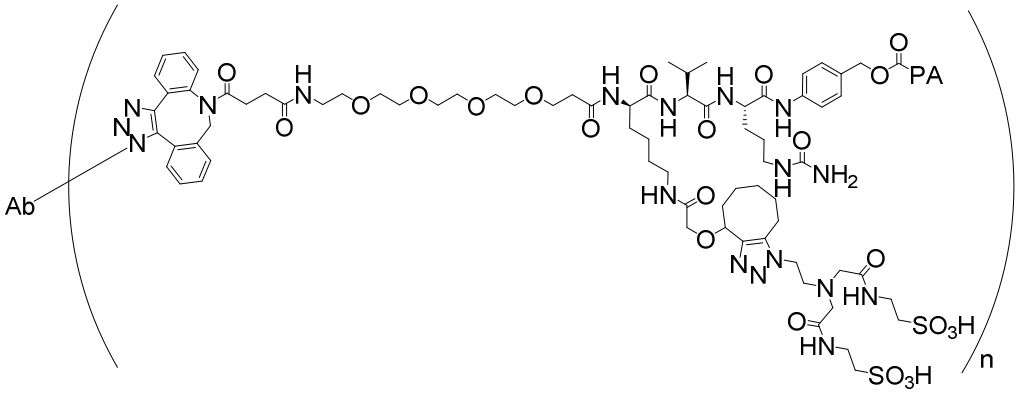
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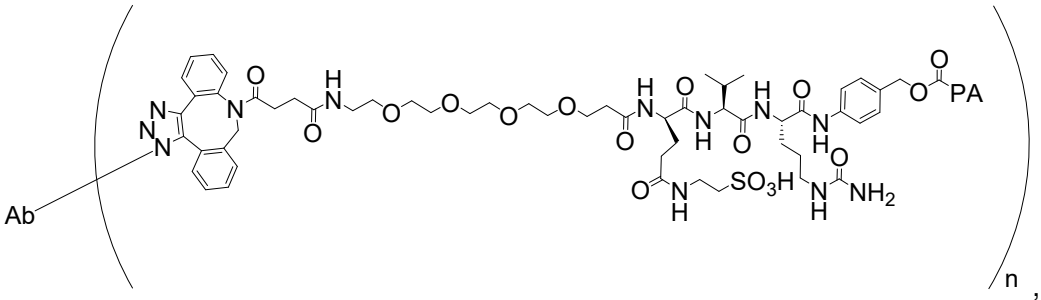
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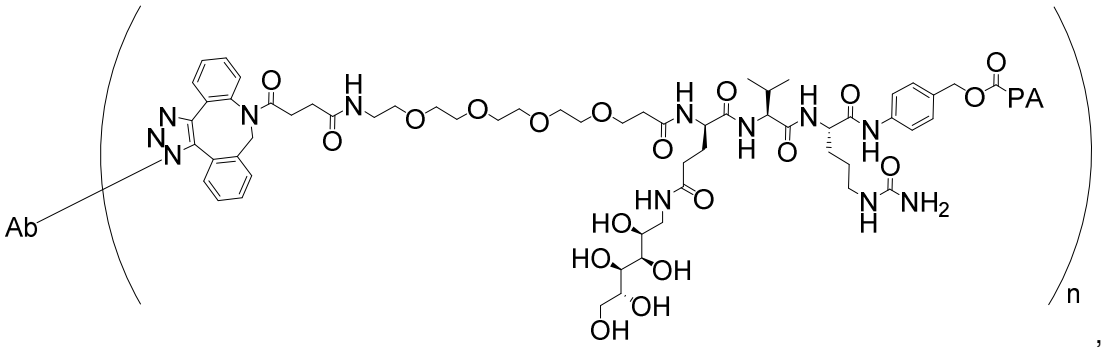
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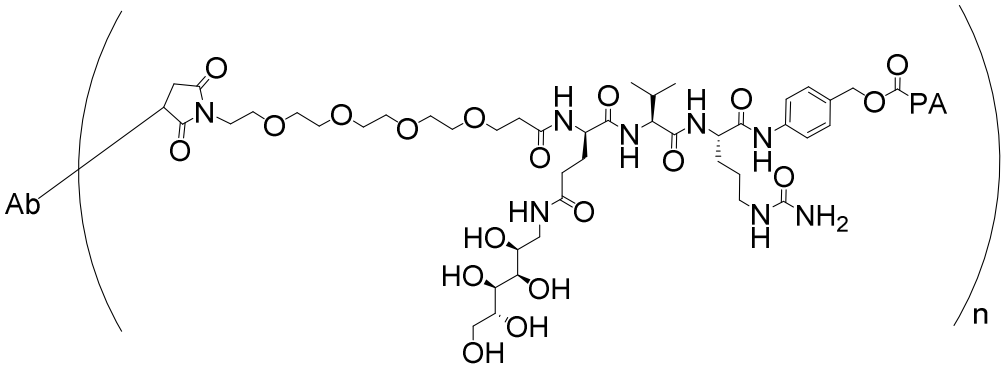
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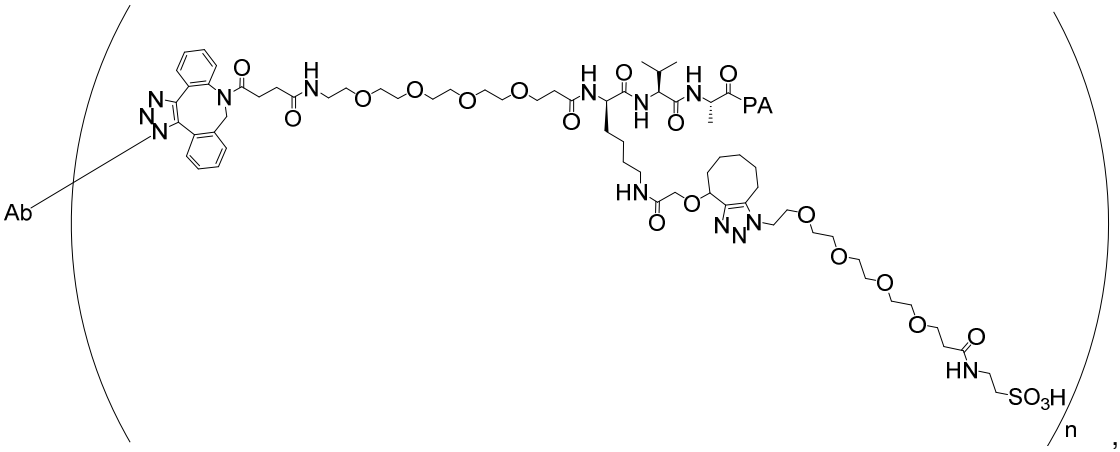
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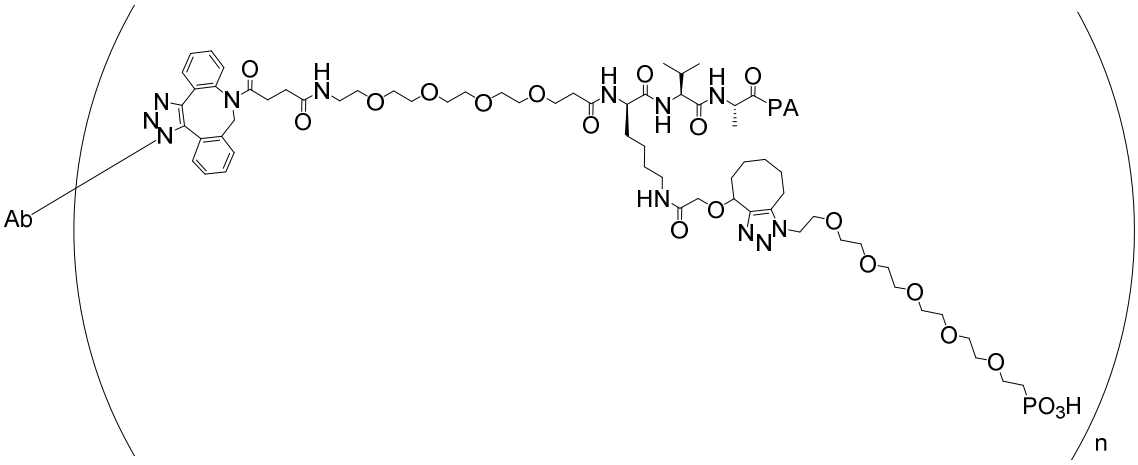
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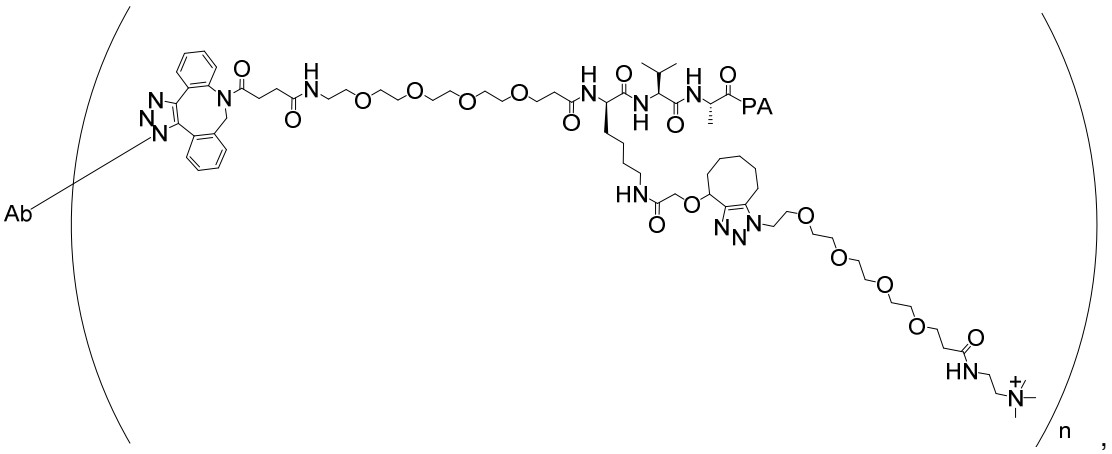
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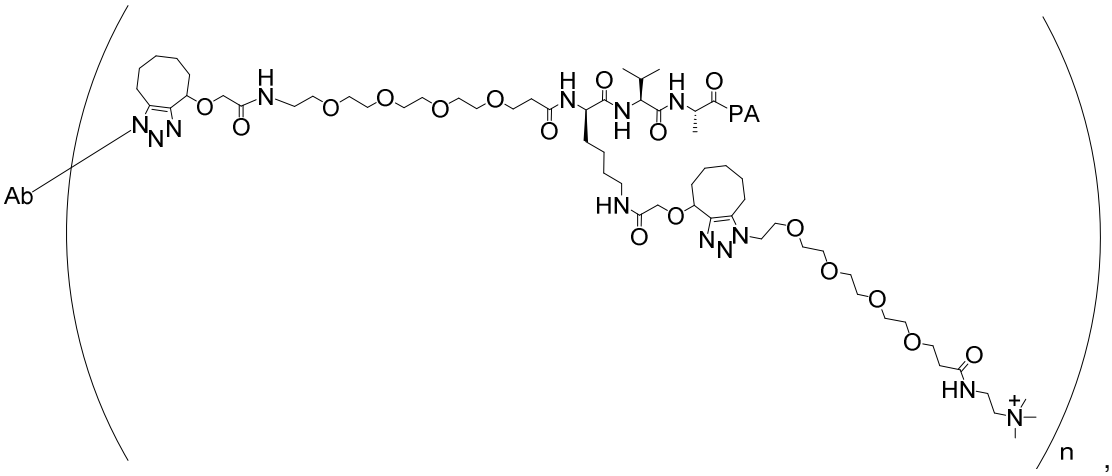
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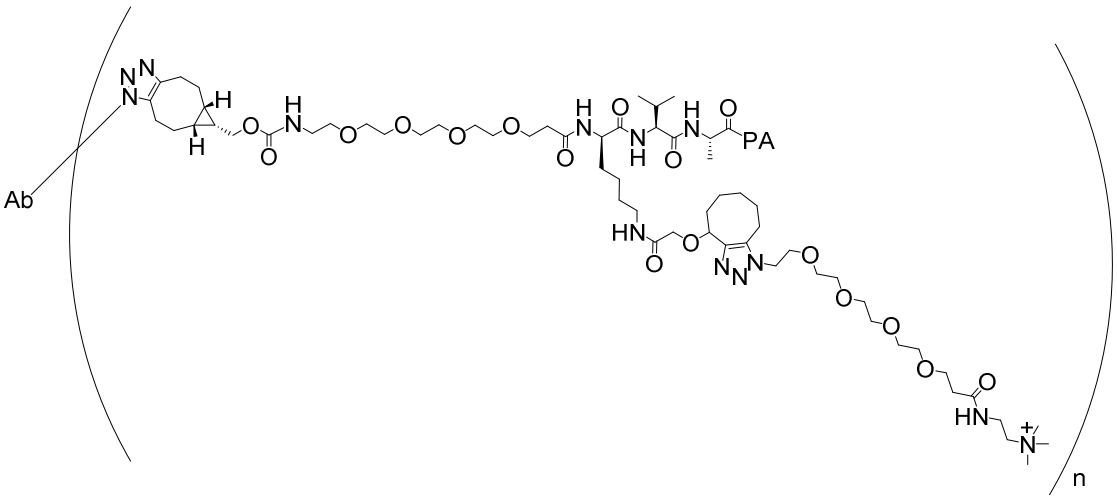
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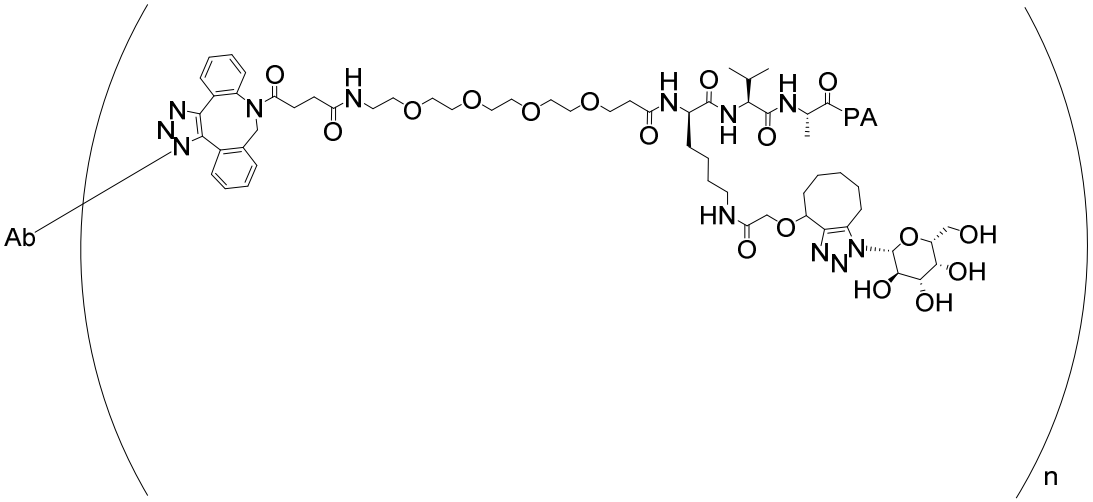
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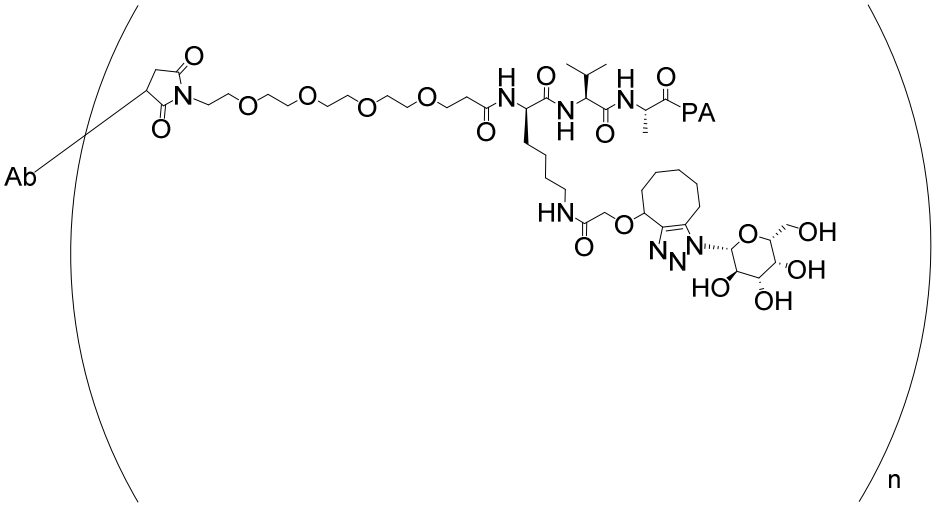

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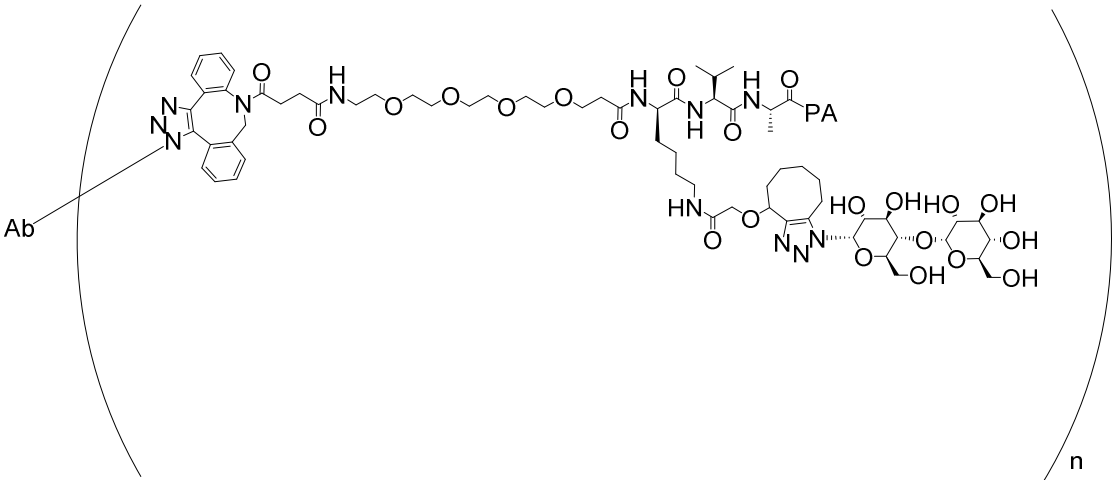

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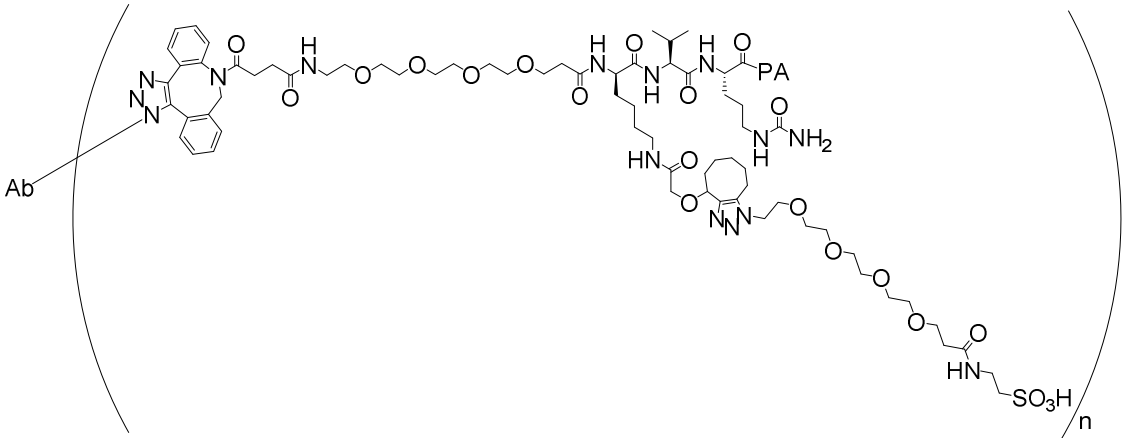
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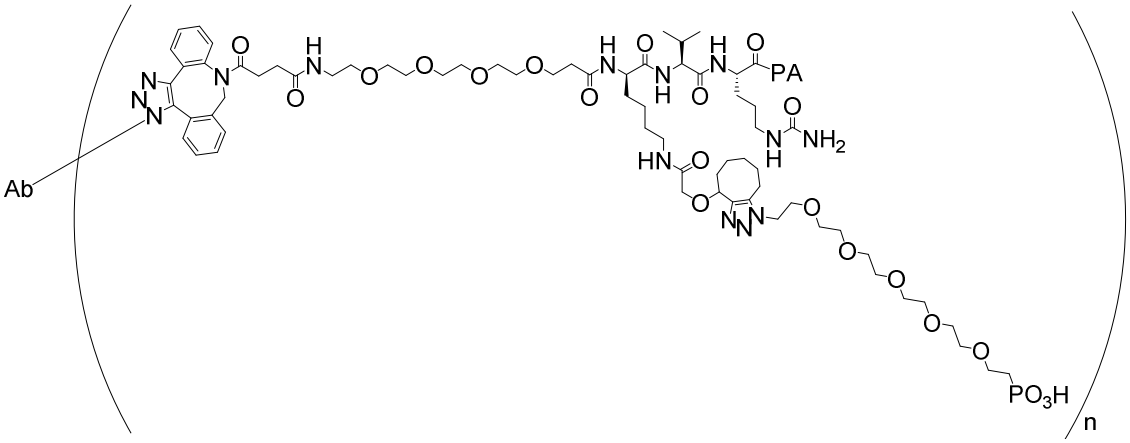

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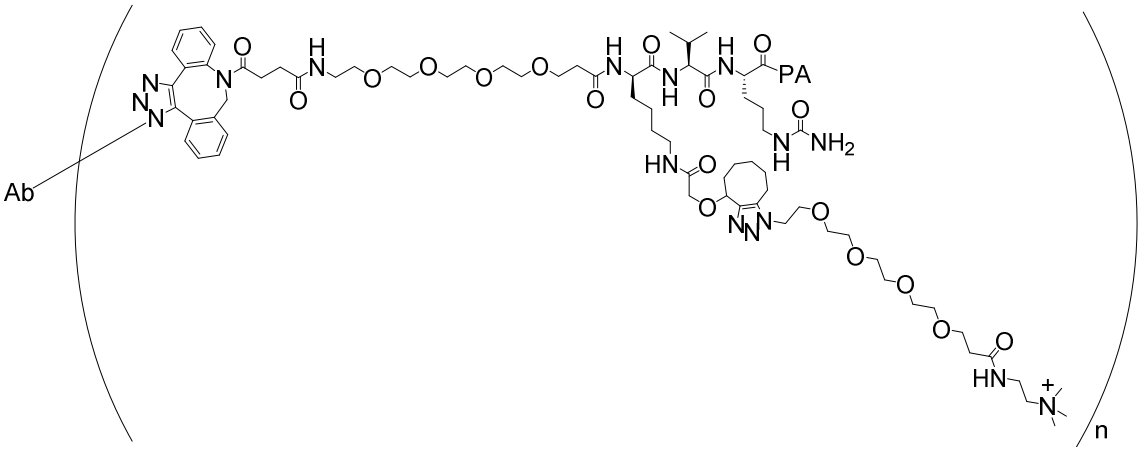
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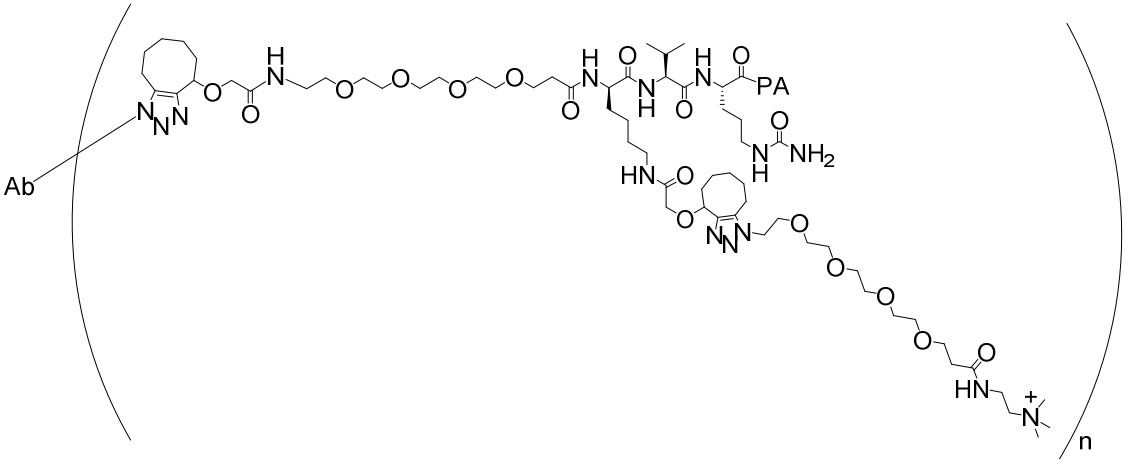

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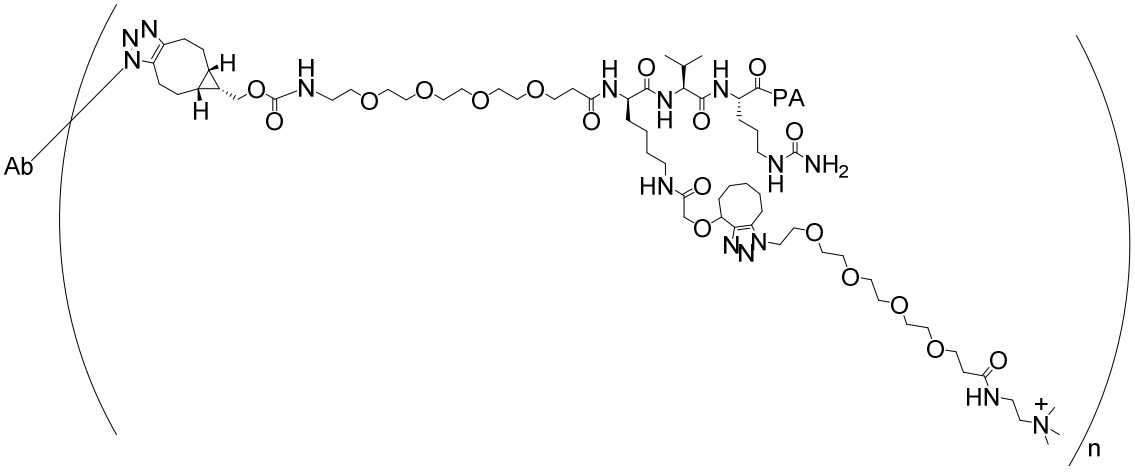

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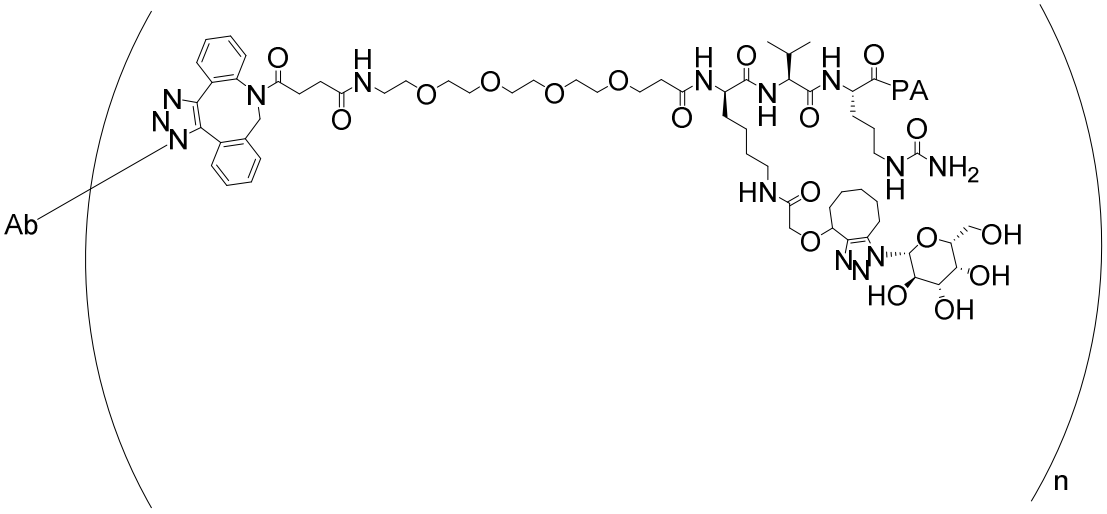
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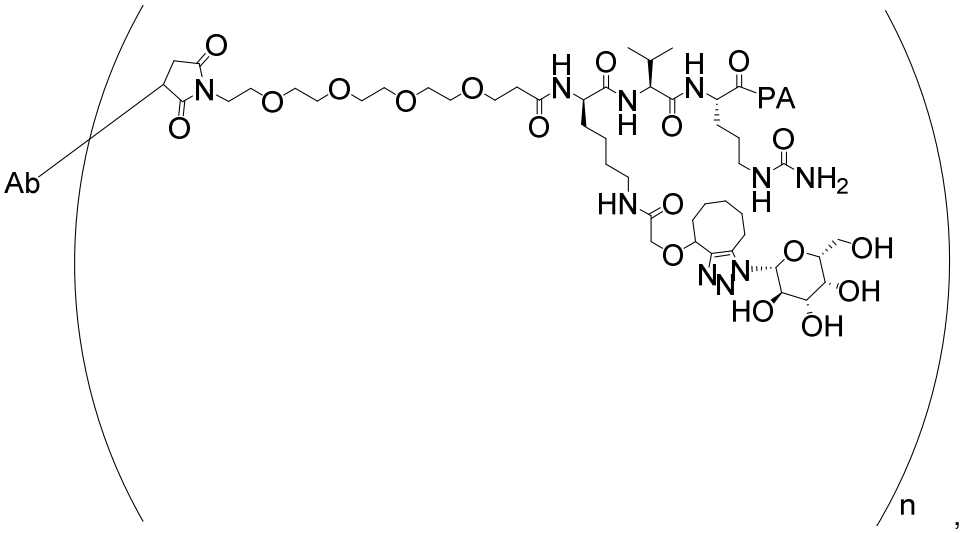
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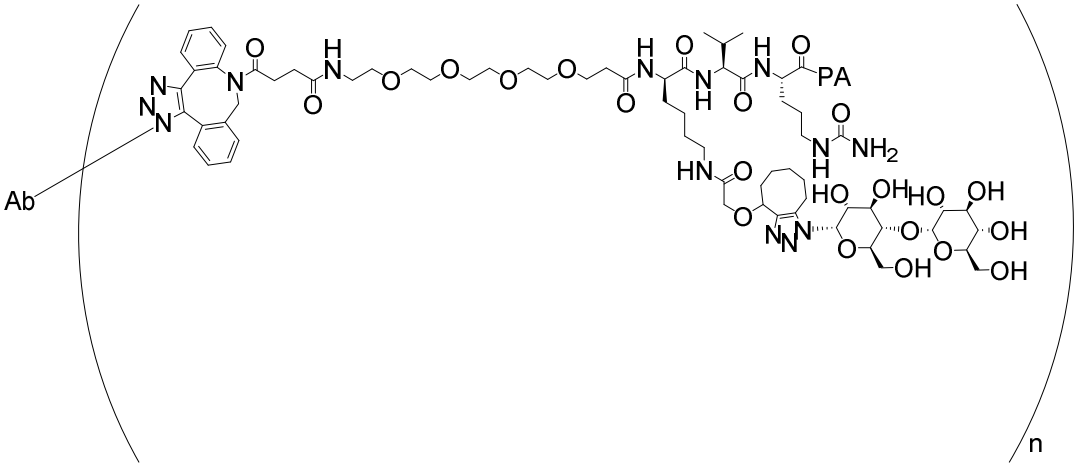
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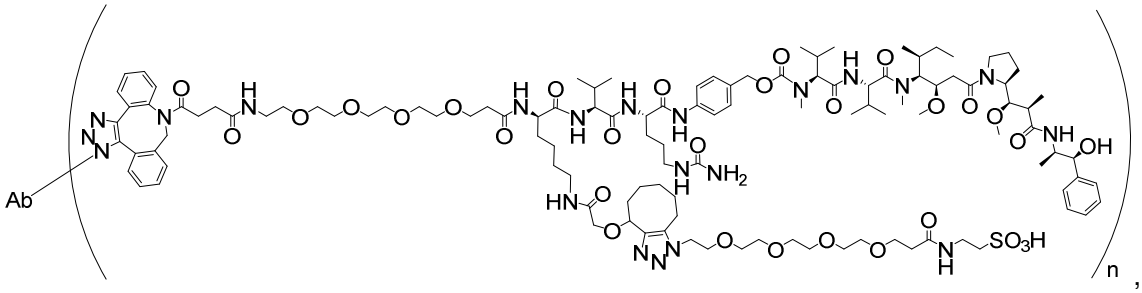
or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

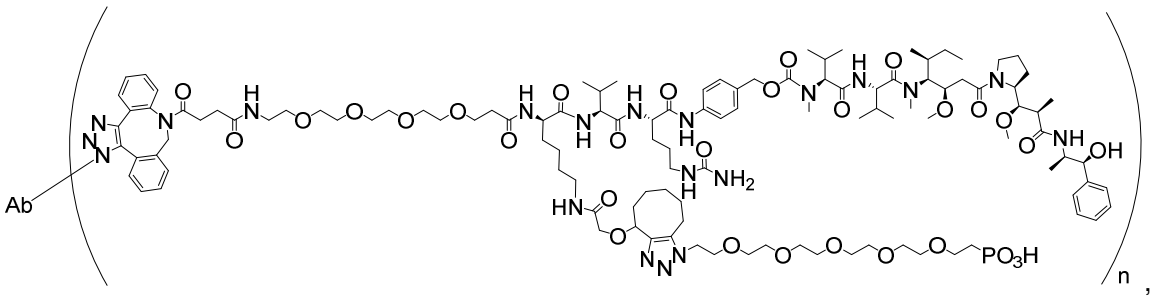
each **Ab** is an antibody, or an antigen-binding fragment thereof;

PA is a payload residue; and

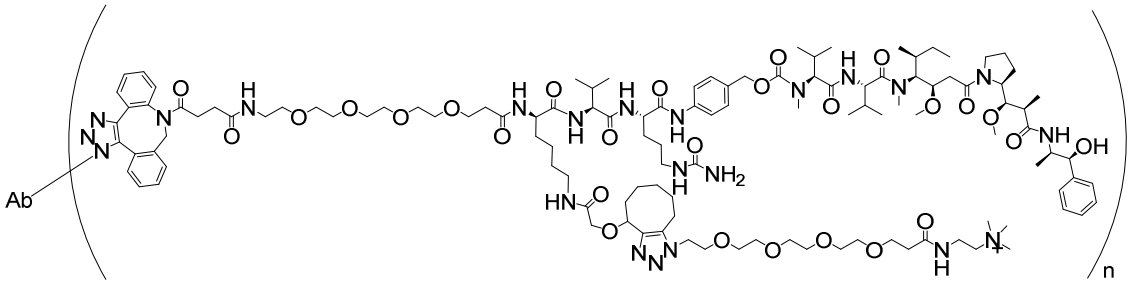
subscript **n** is an integer from 1 to 30.

29. The compound of any one of claims 1-27, selected from the group consisting of:

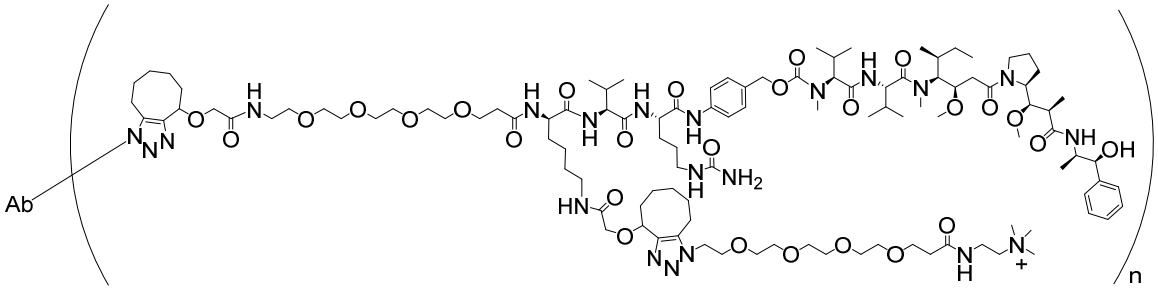




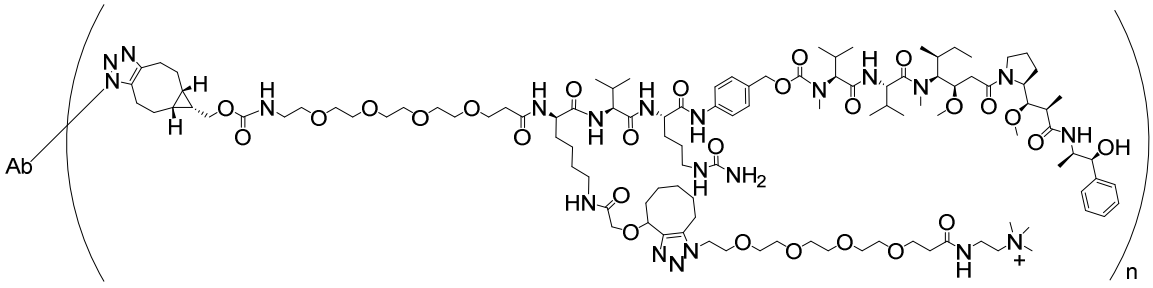
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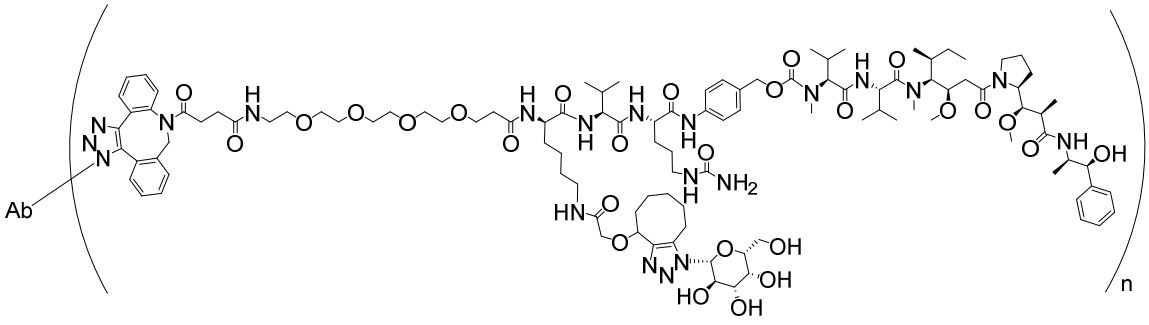
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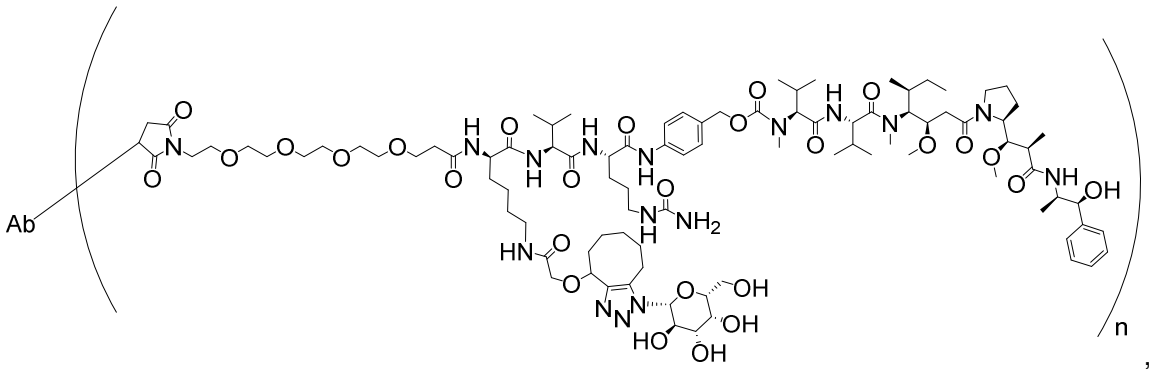
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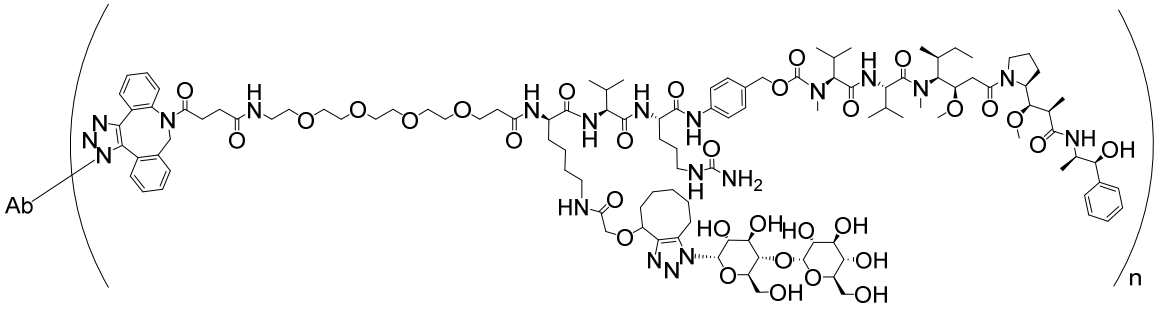
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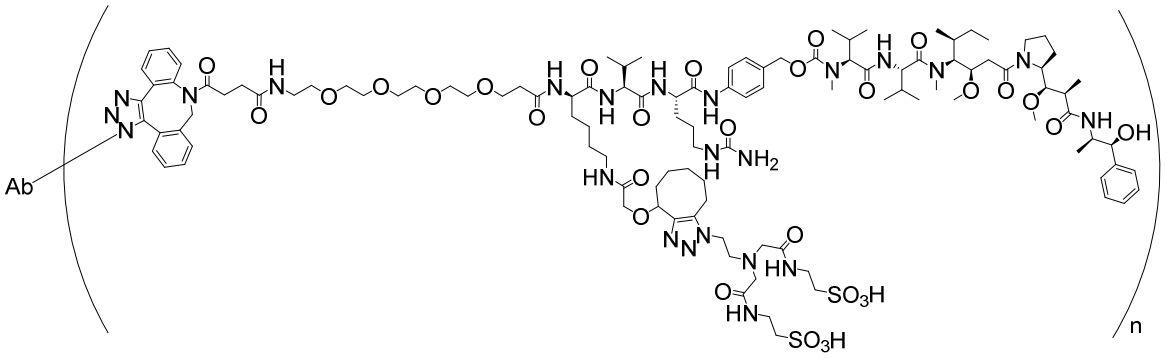
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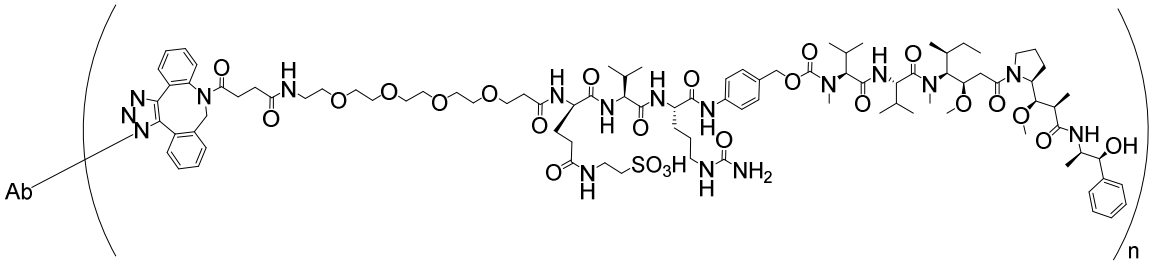
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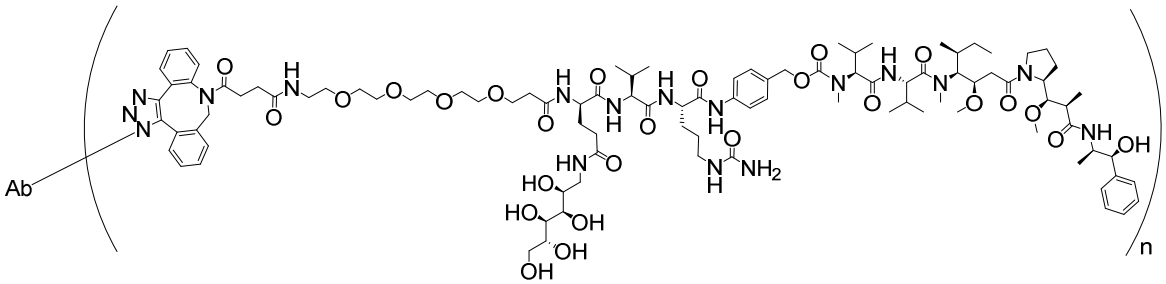
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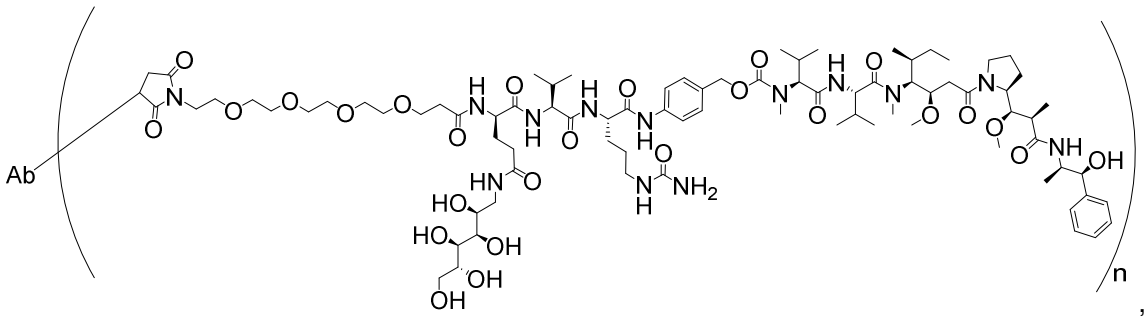
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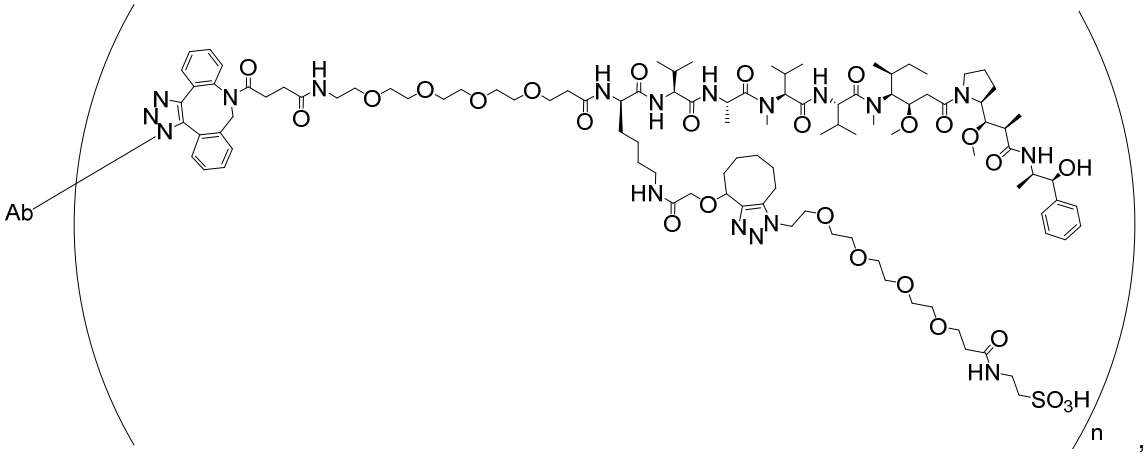
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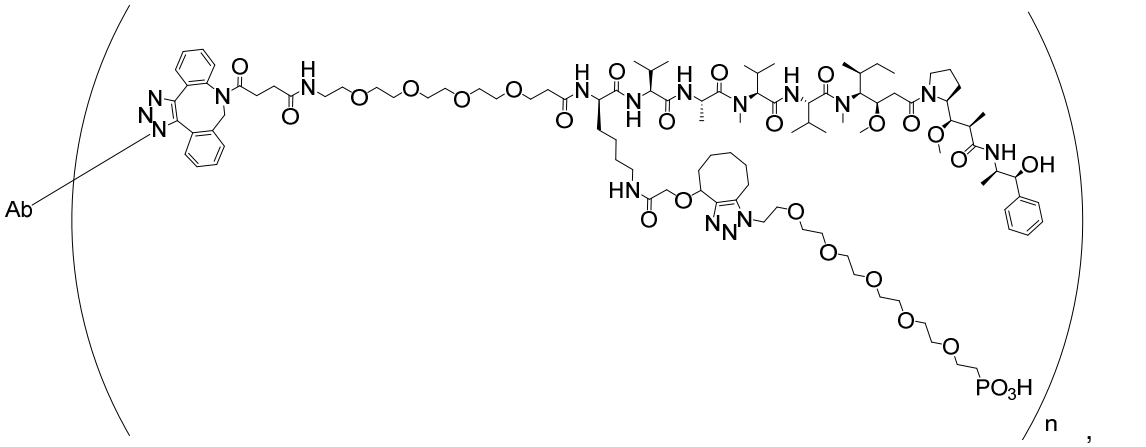
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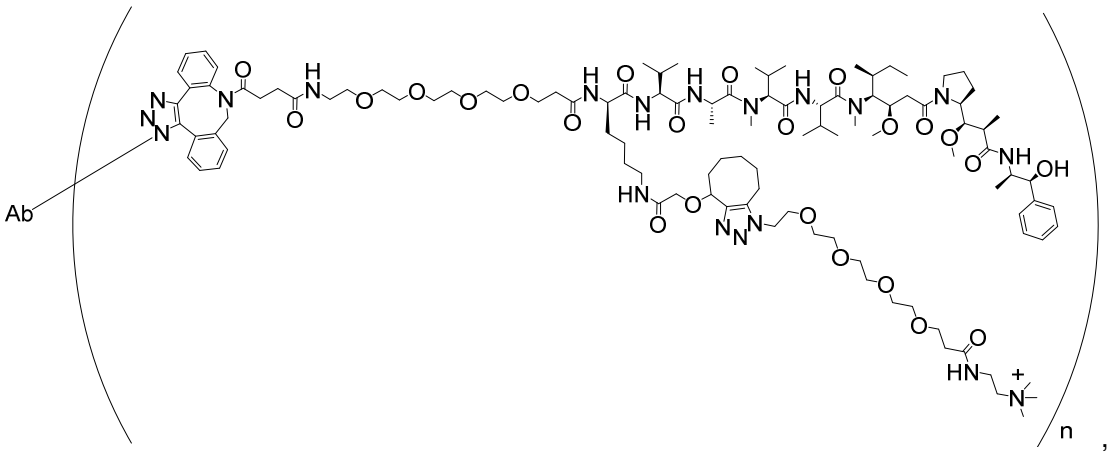
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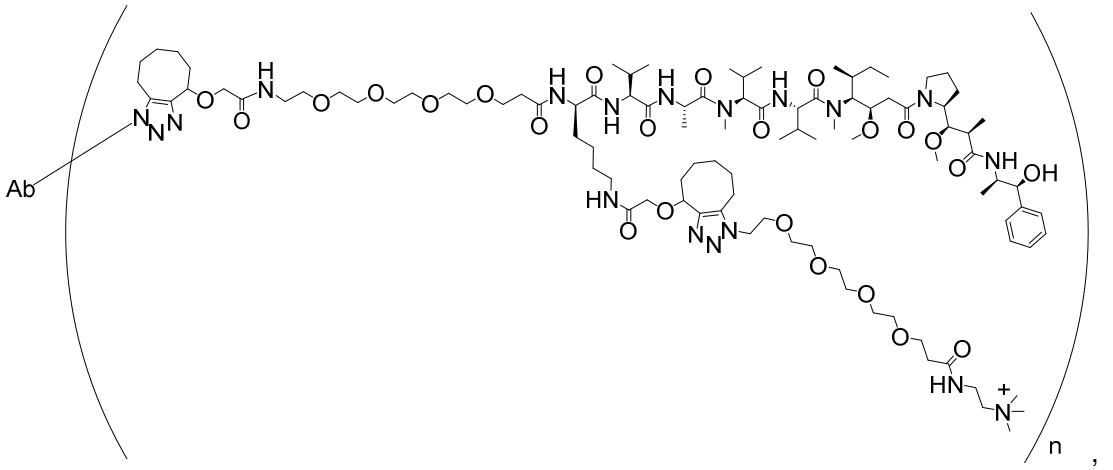


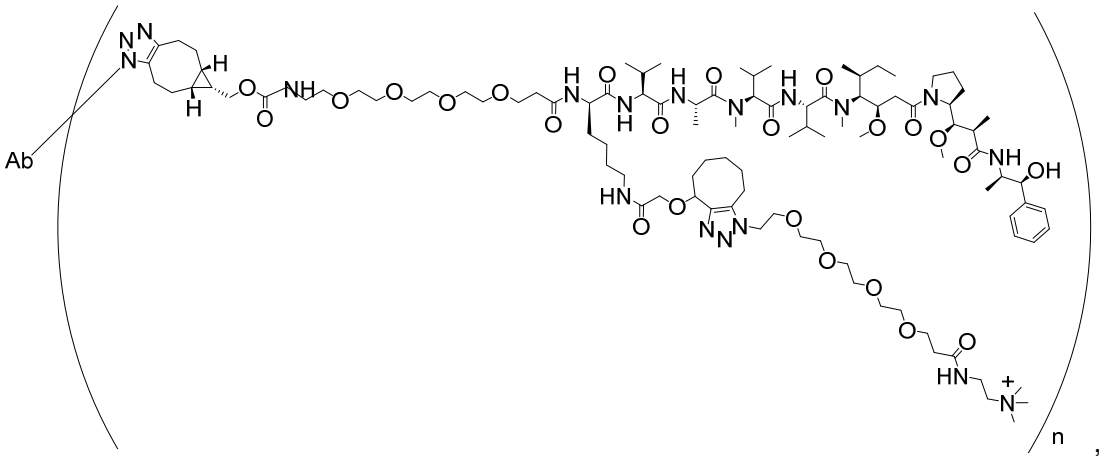
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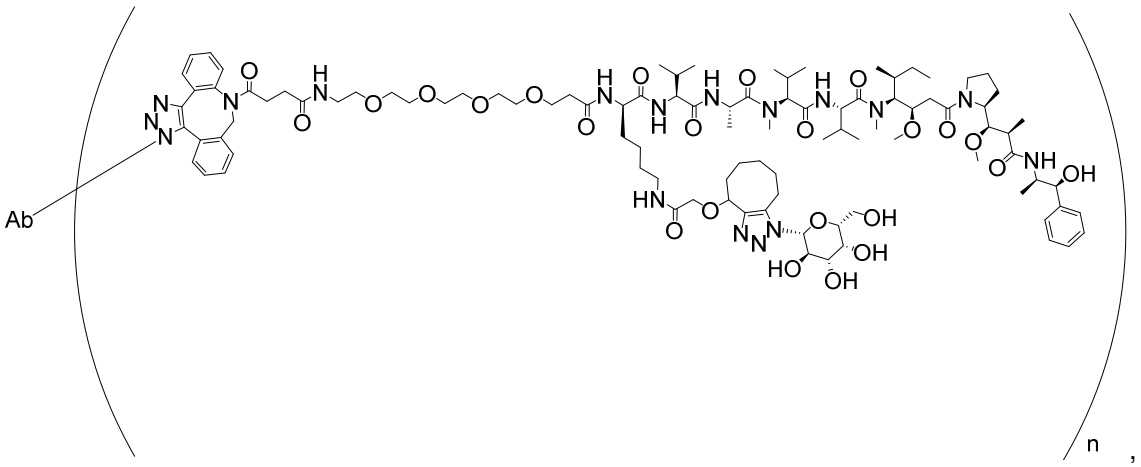


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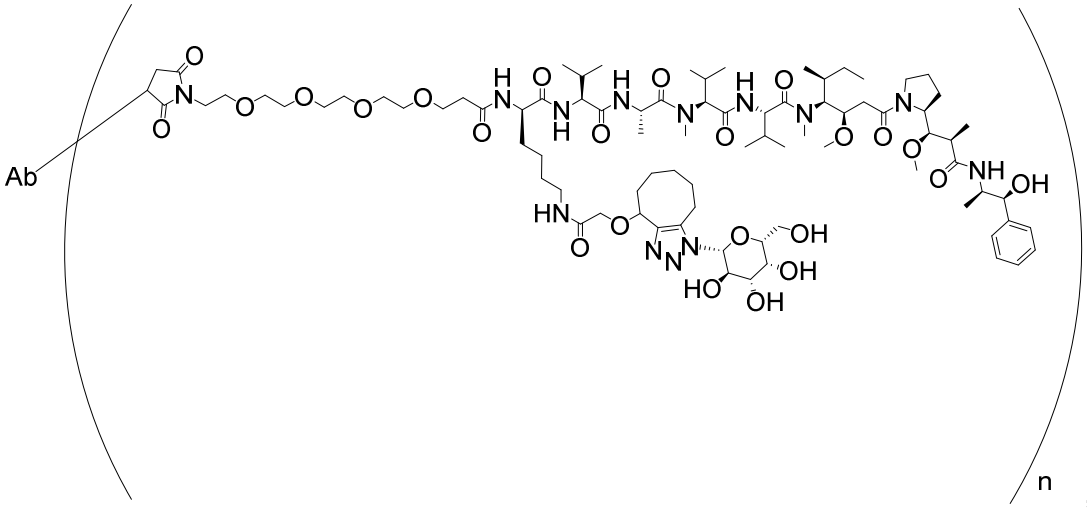




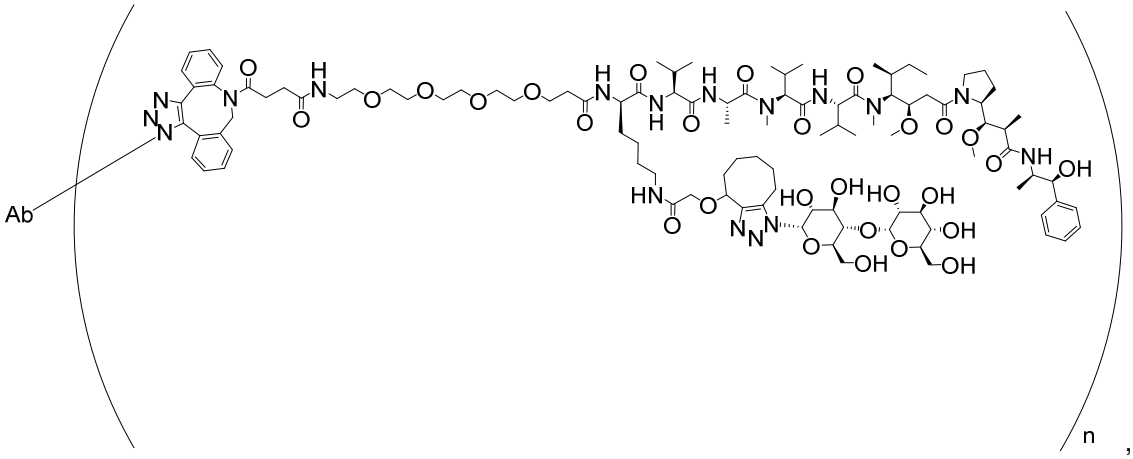



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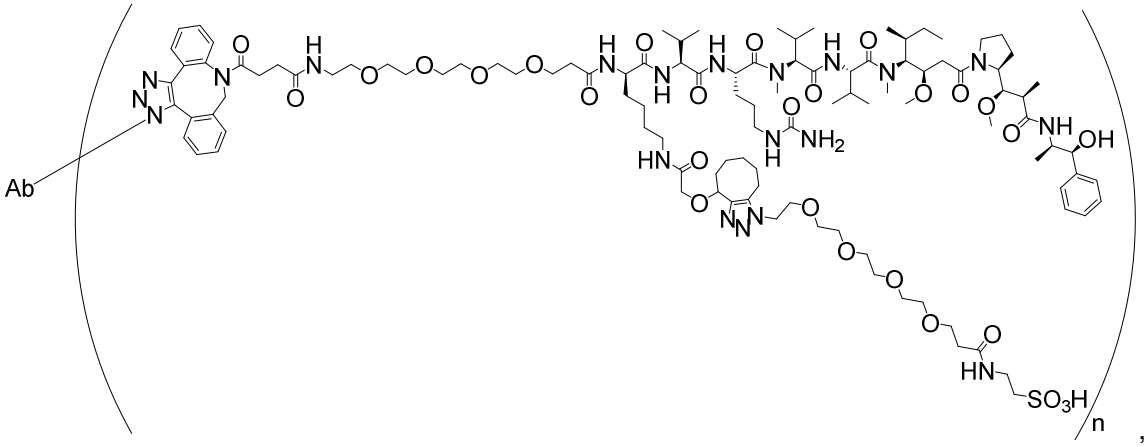
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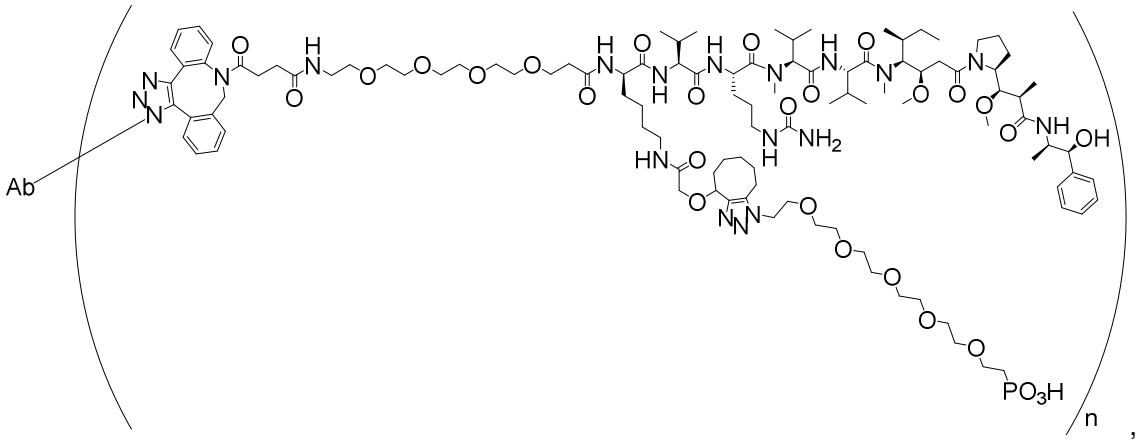
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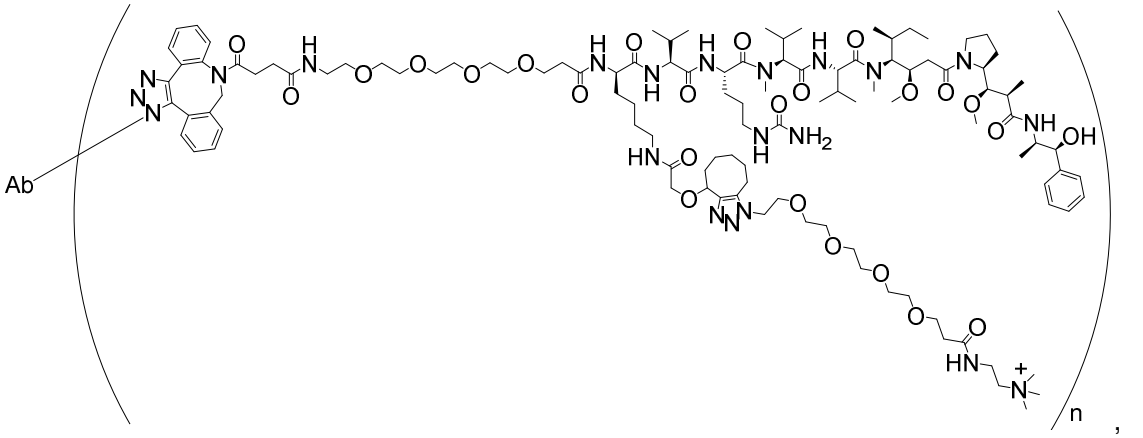
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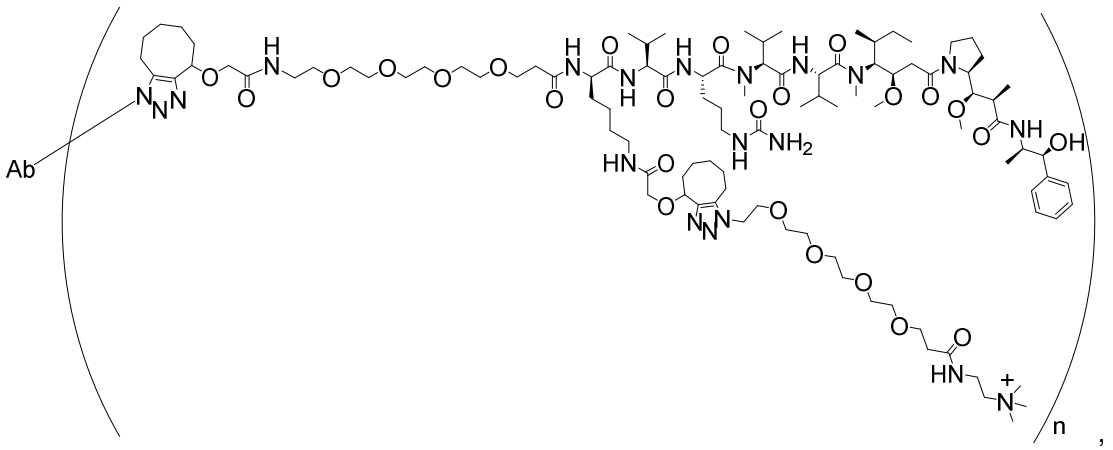
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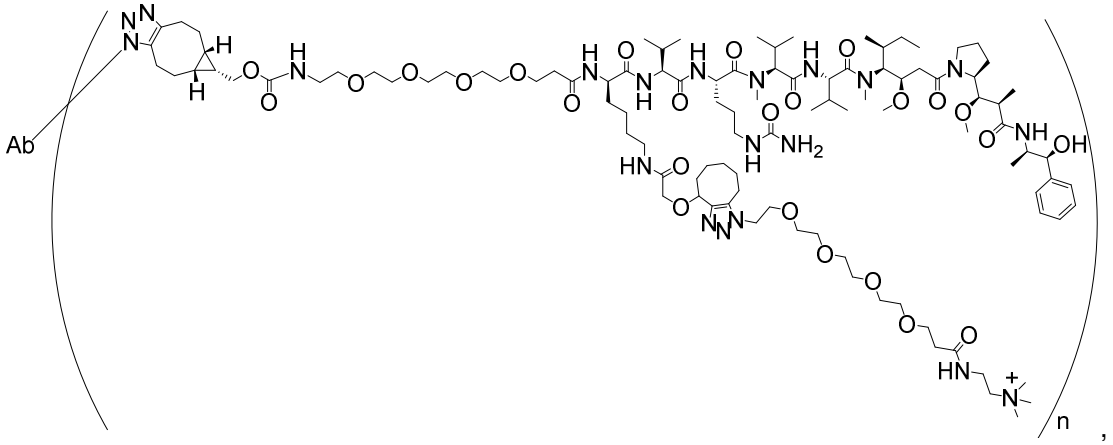
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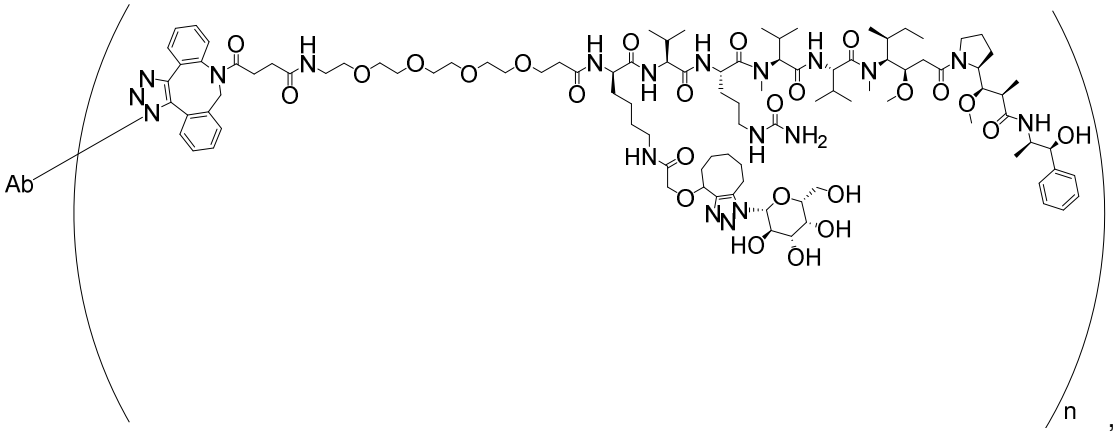
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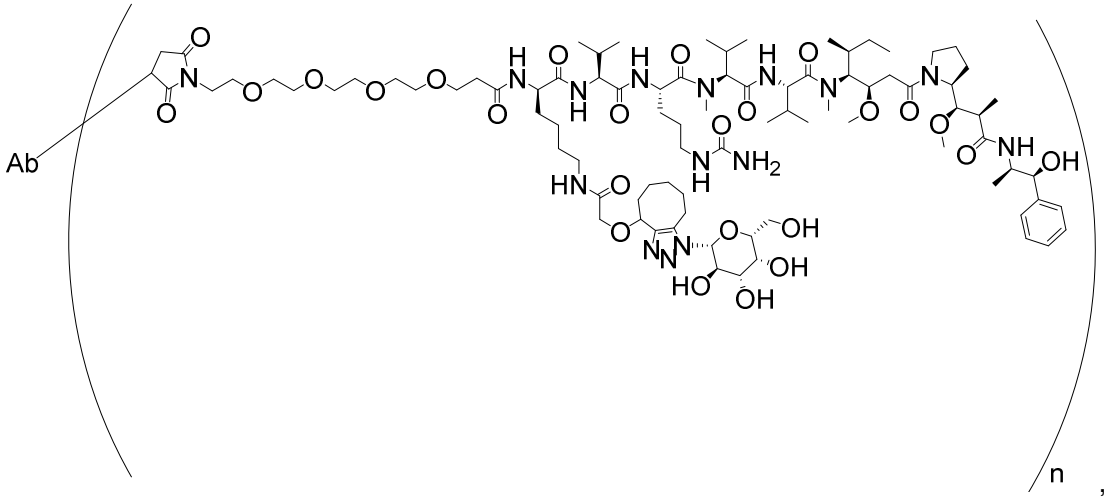
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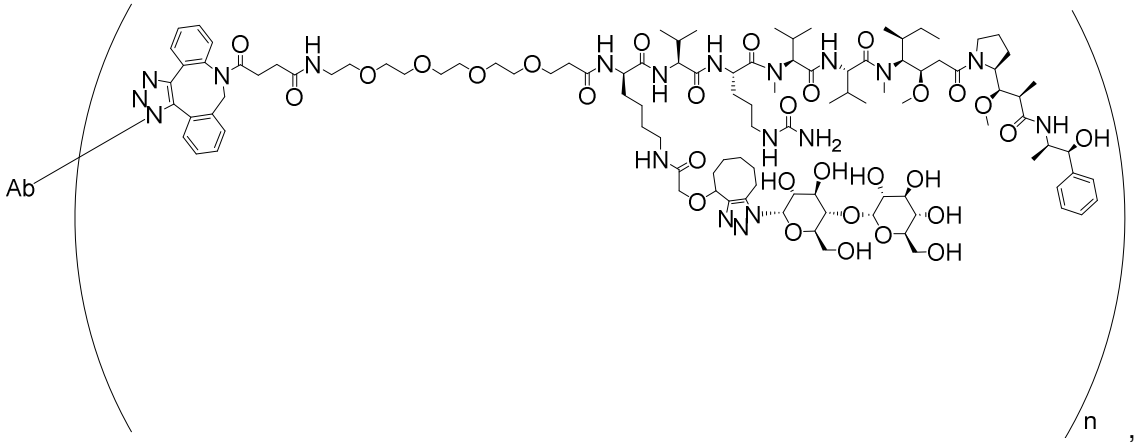
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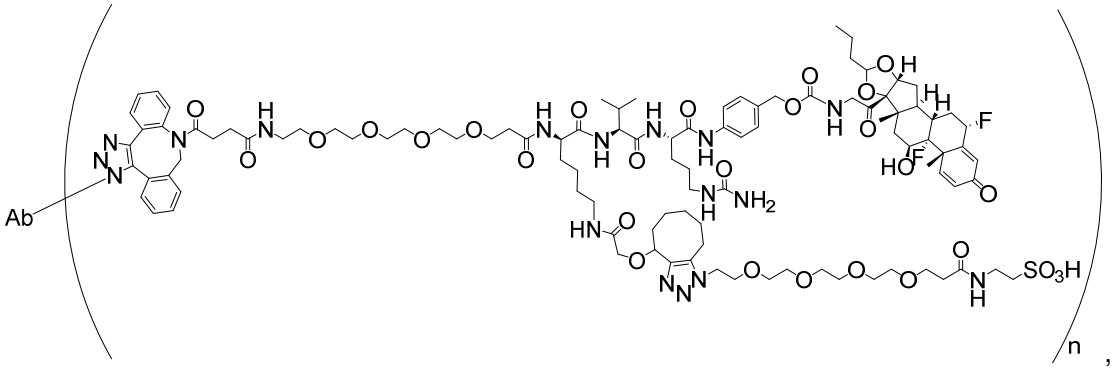
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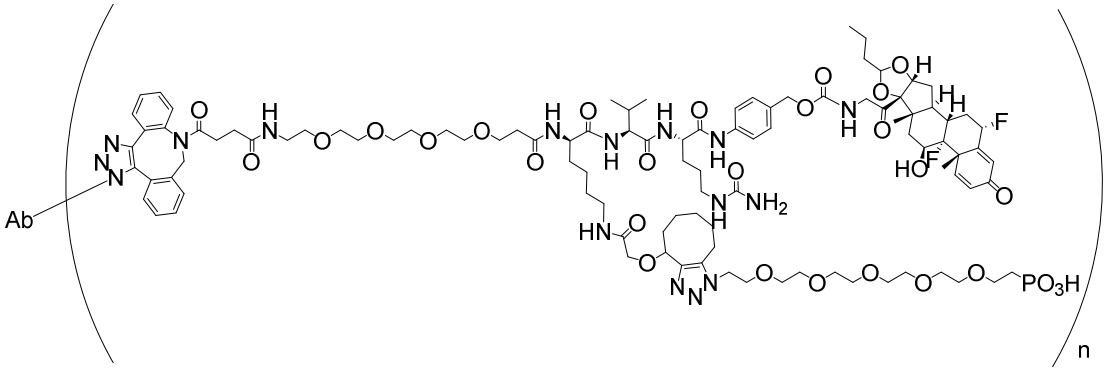
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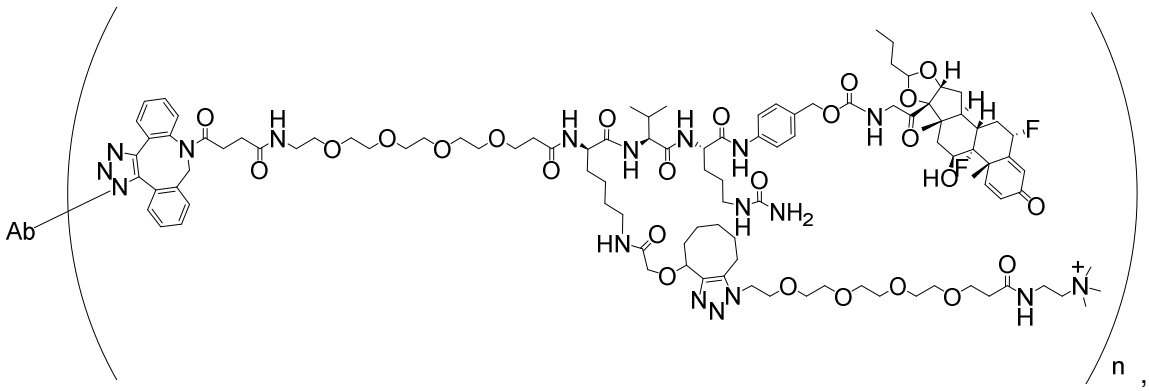
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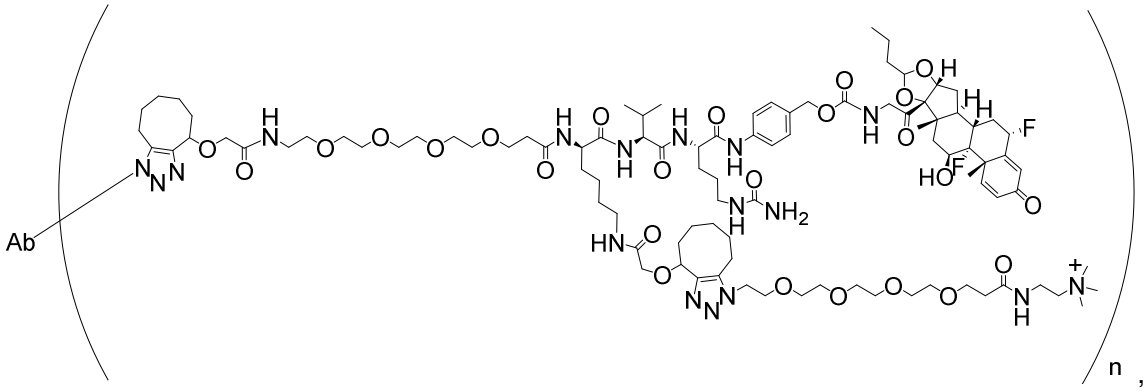

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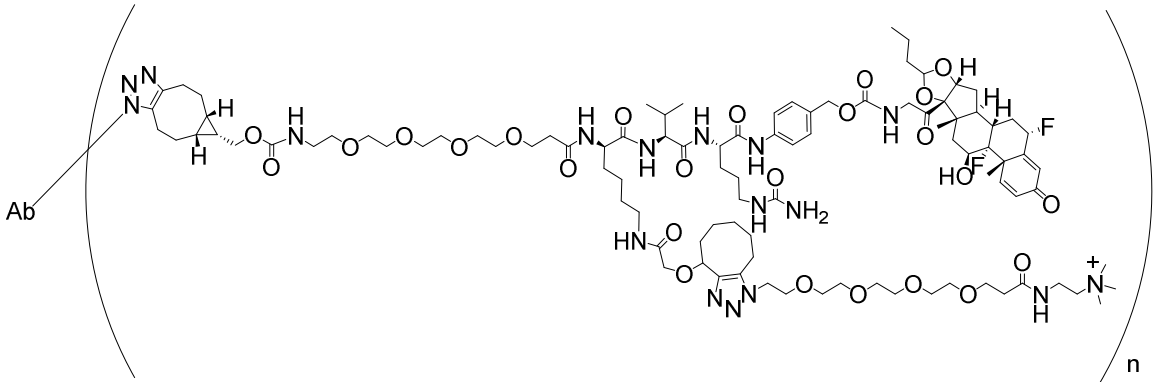
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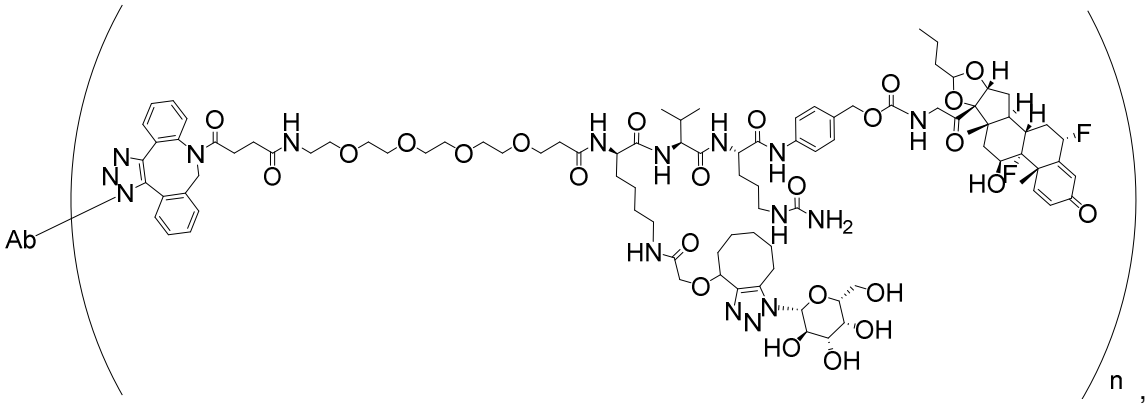
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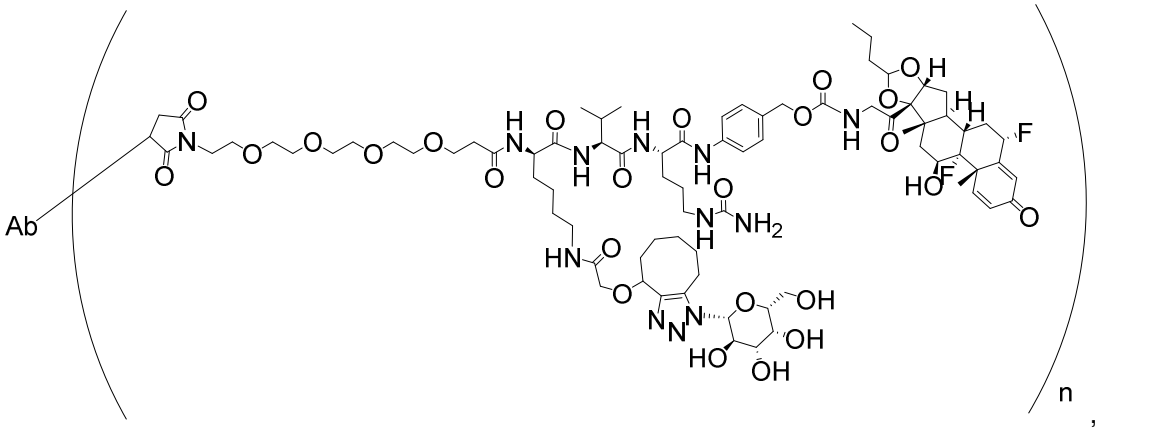




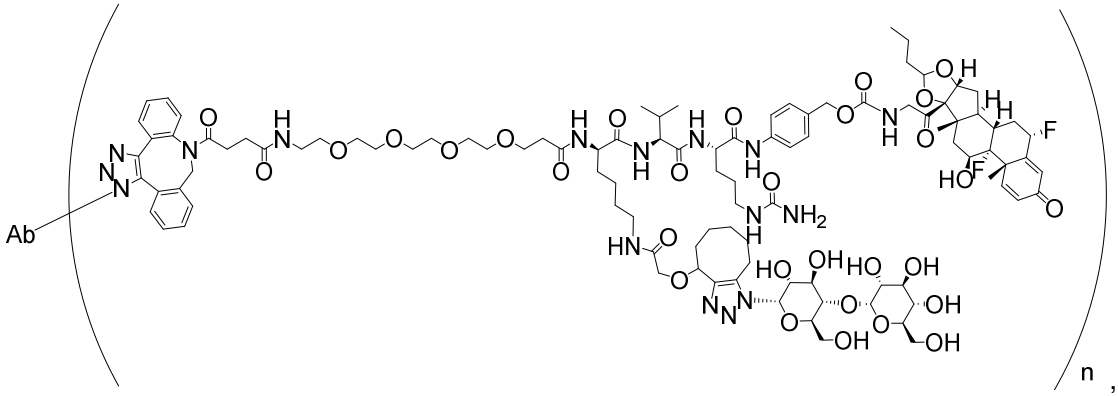


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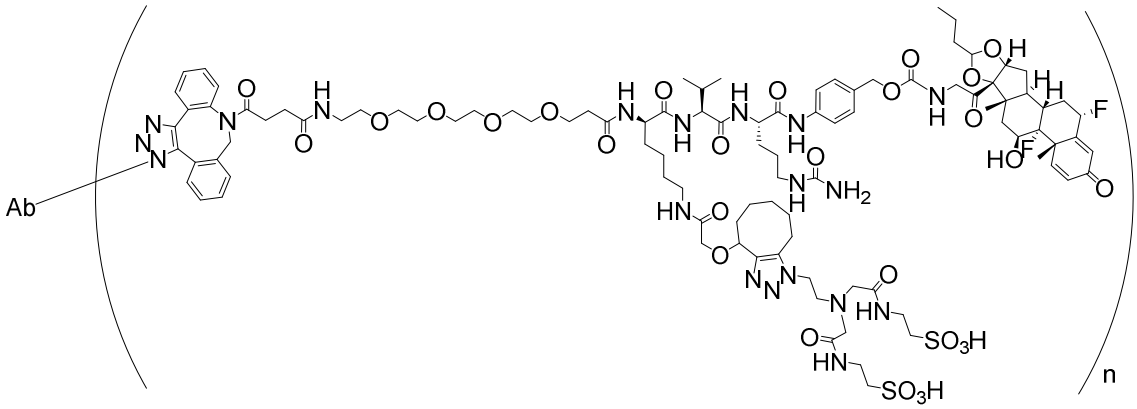



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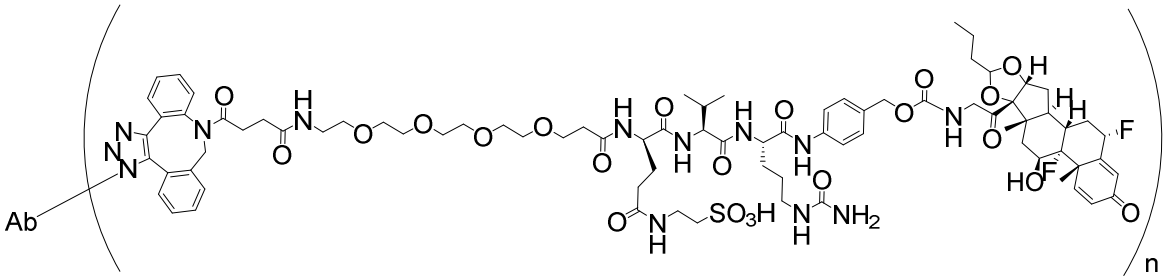
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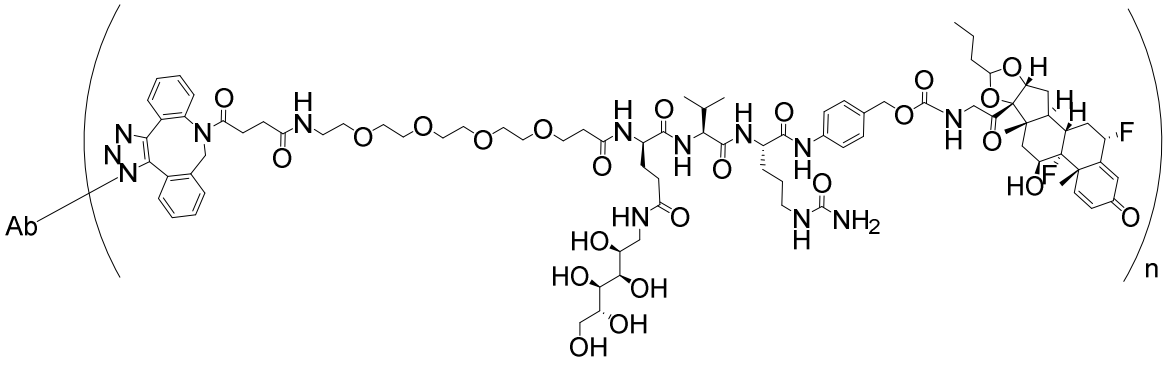
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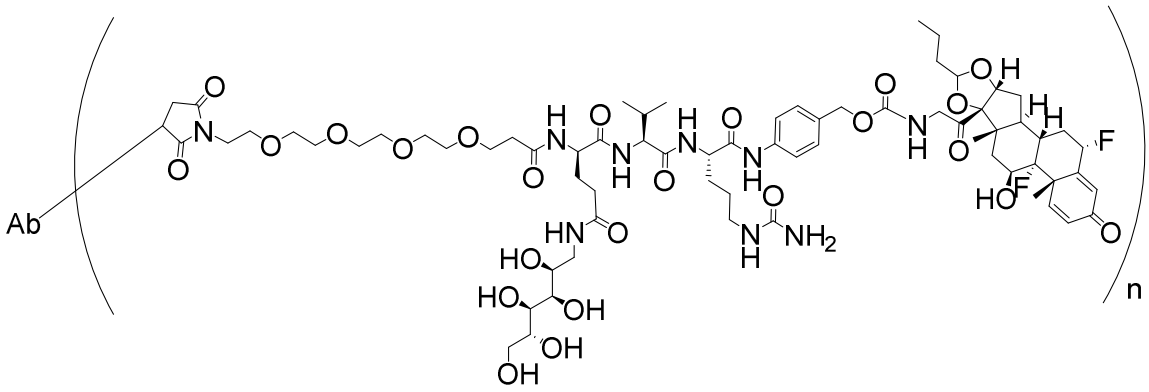
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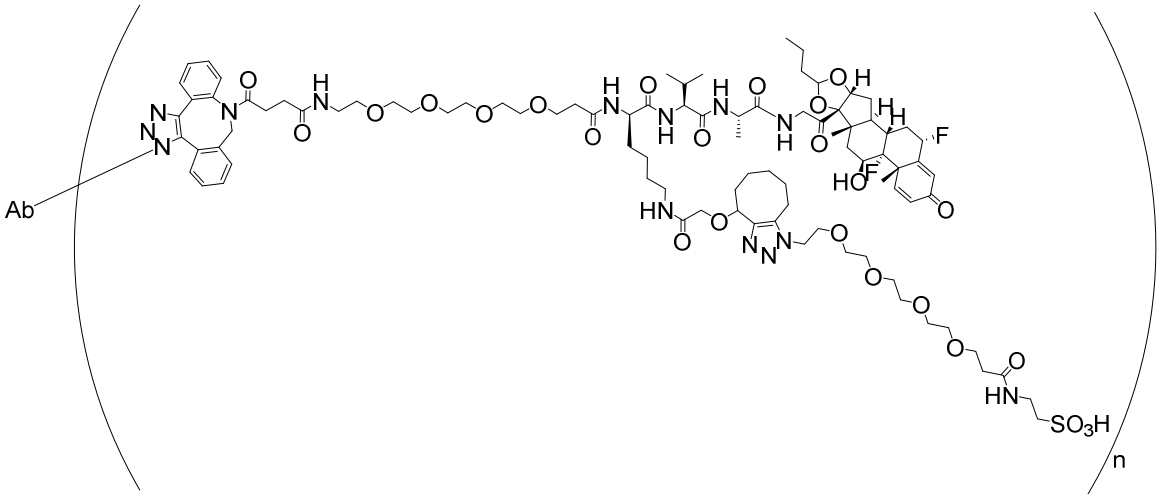
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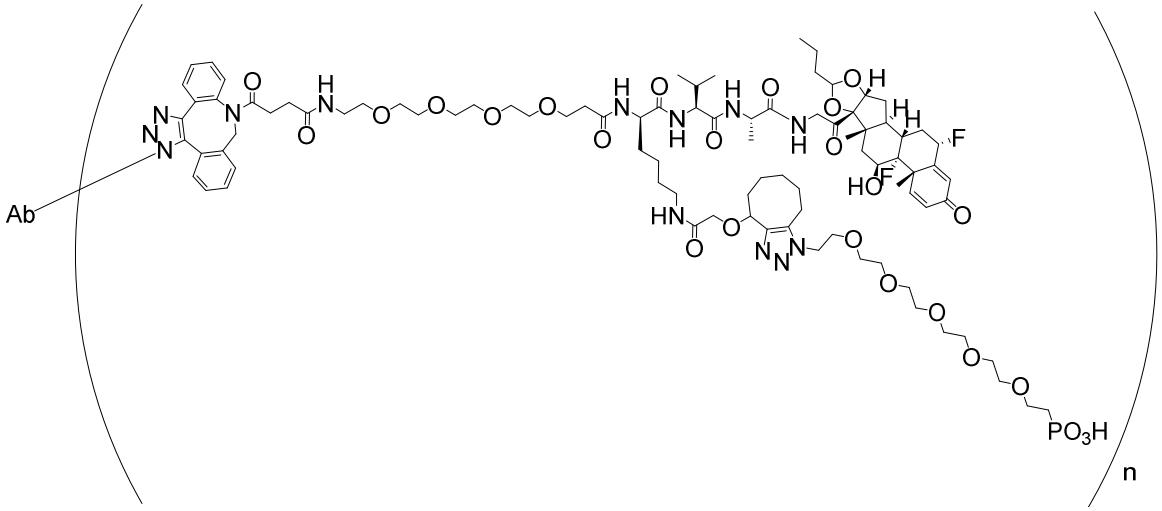
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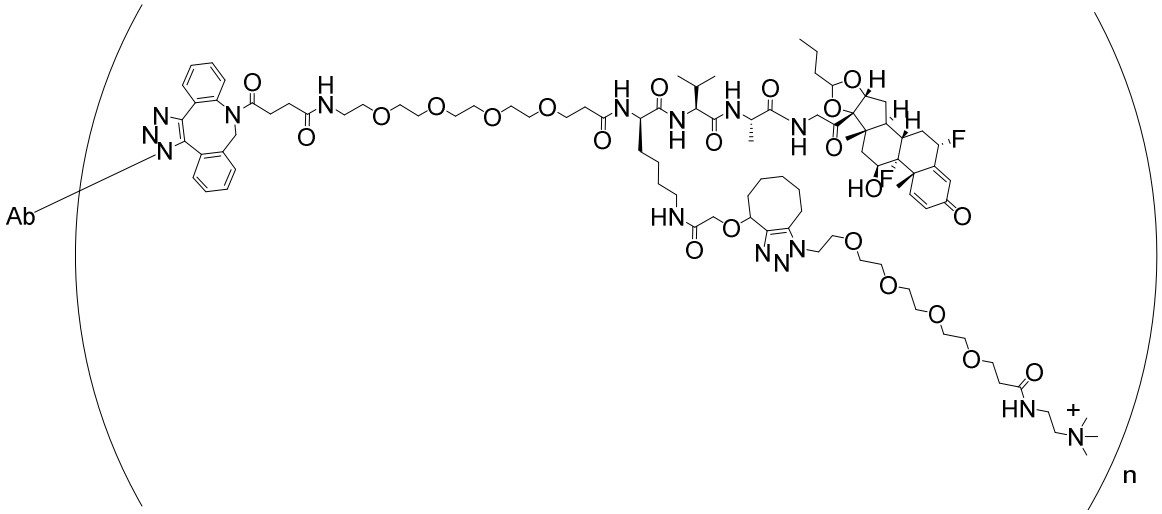
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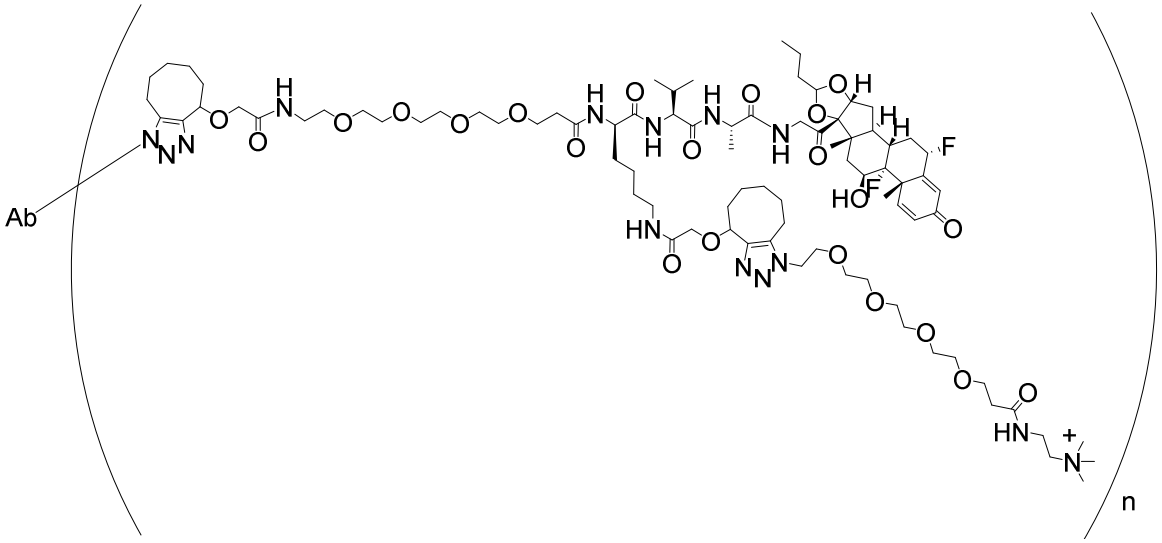
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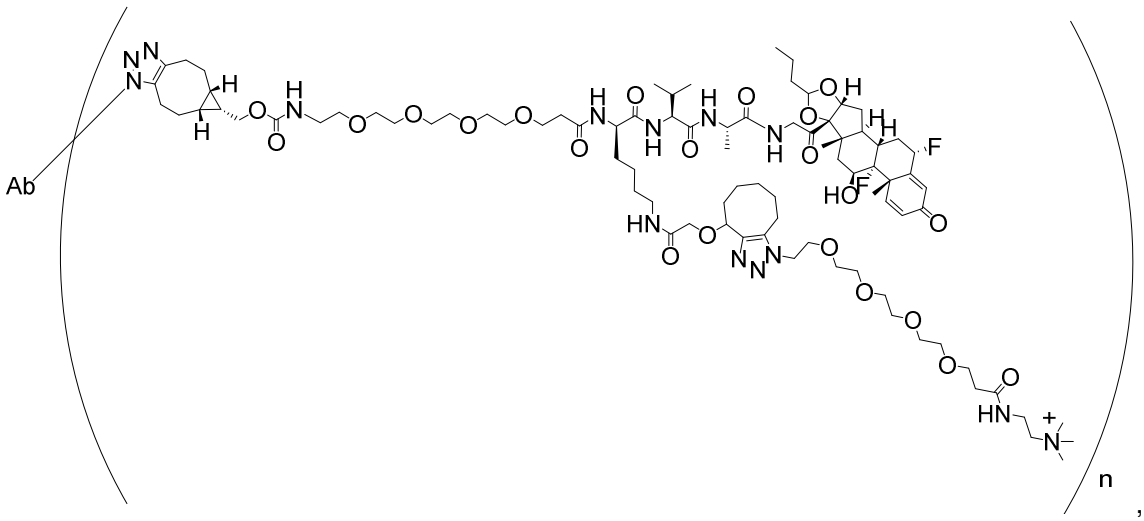
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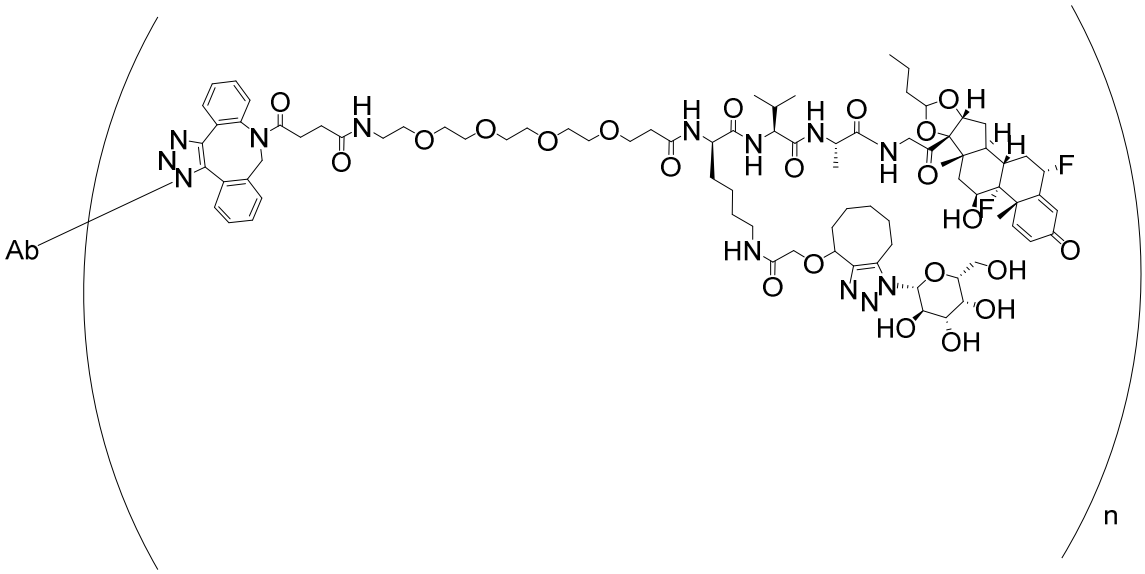
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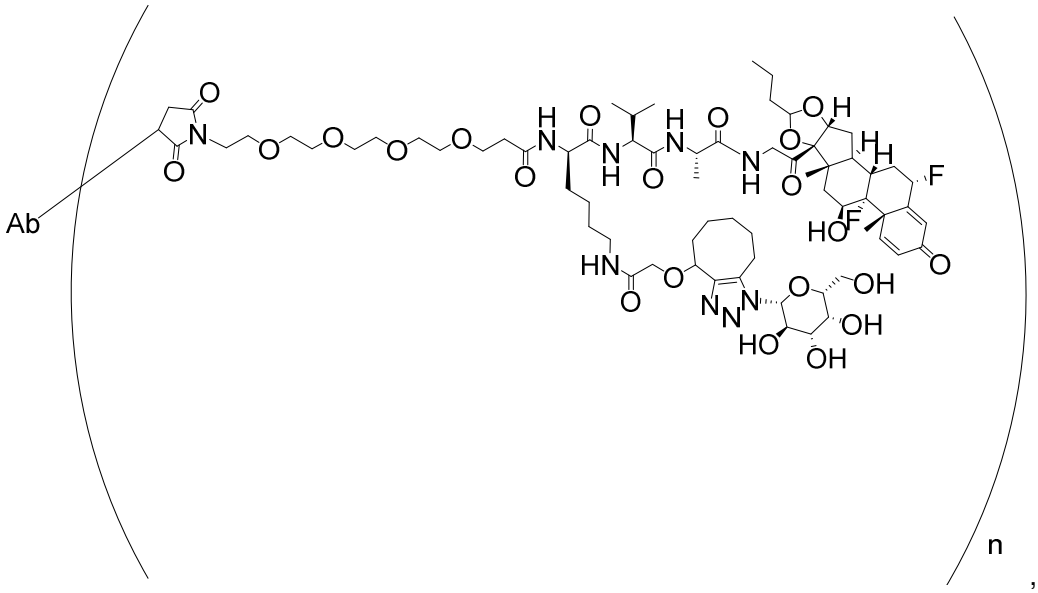
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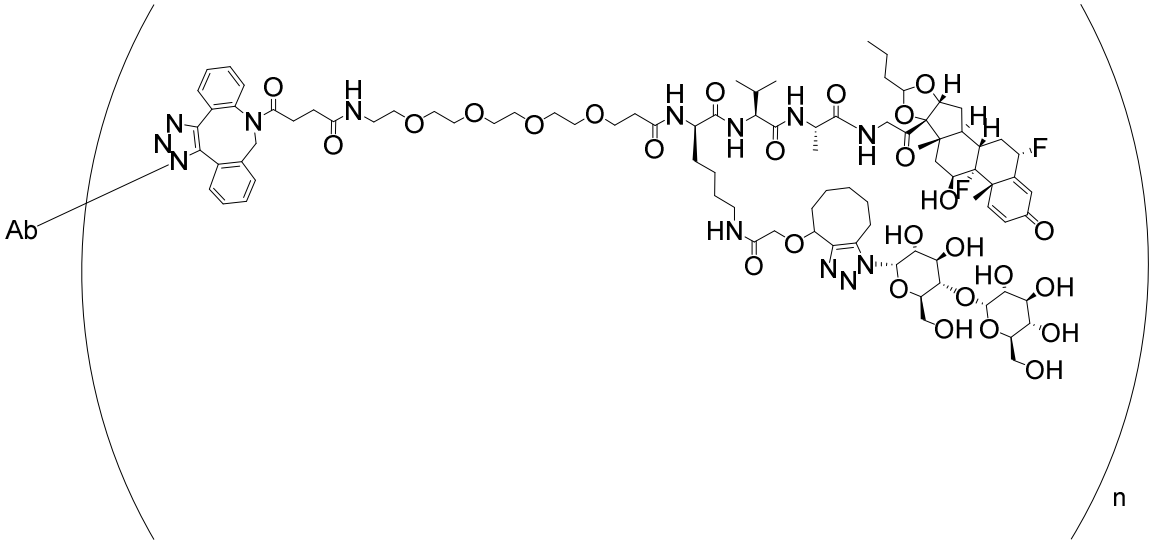
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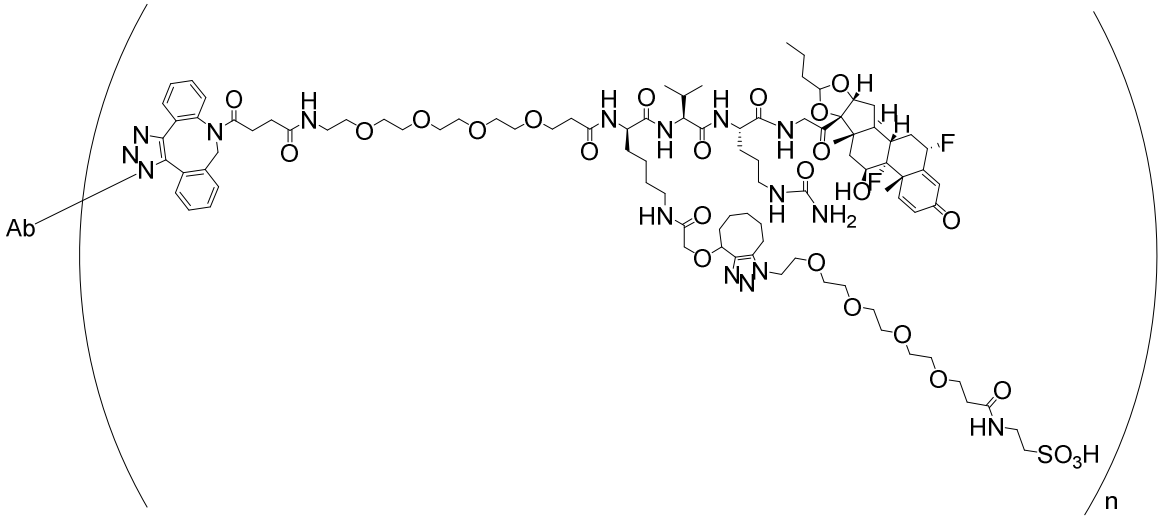
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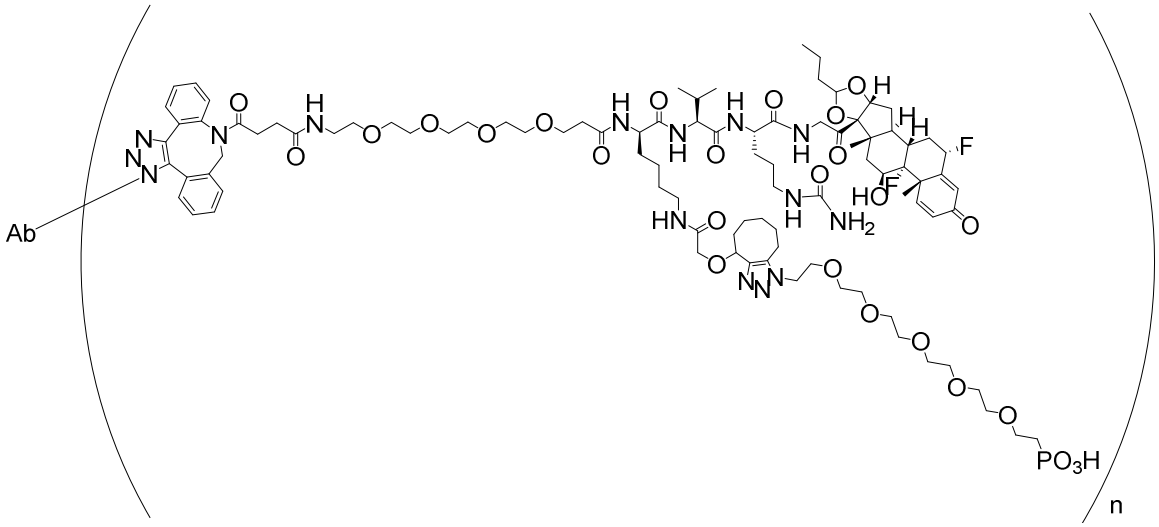
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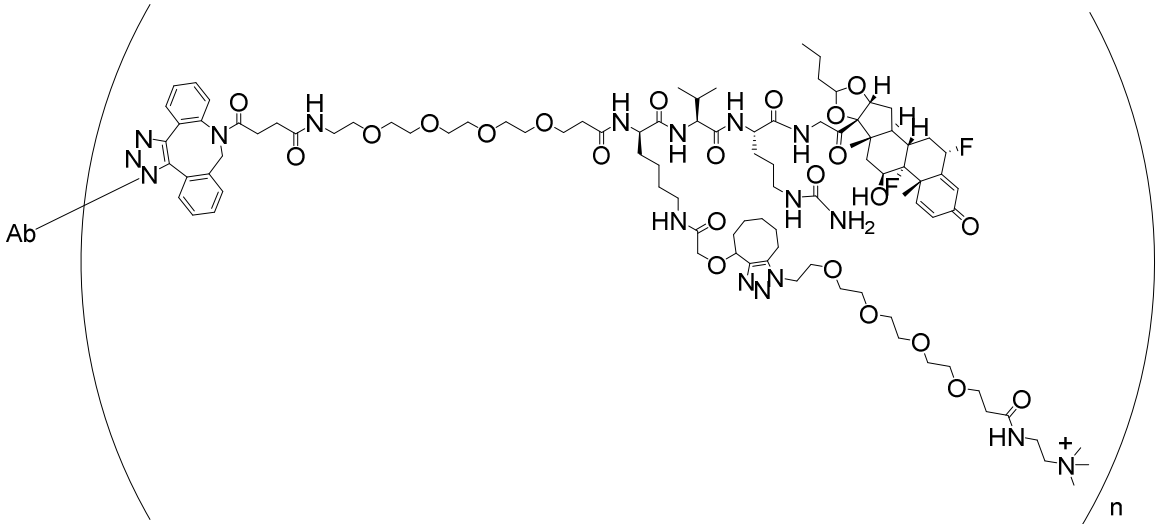
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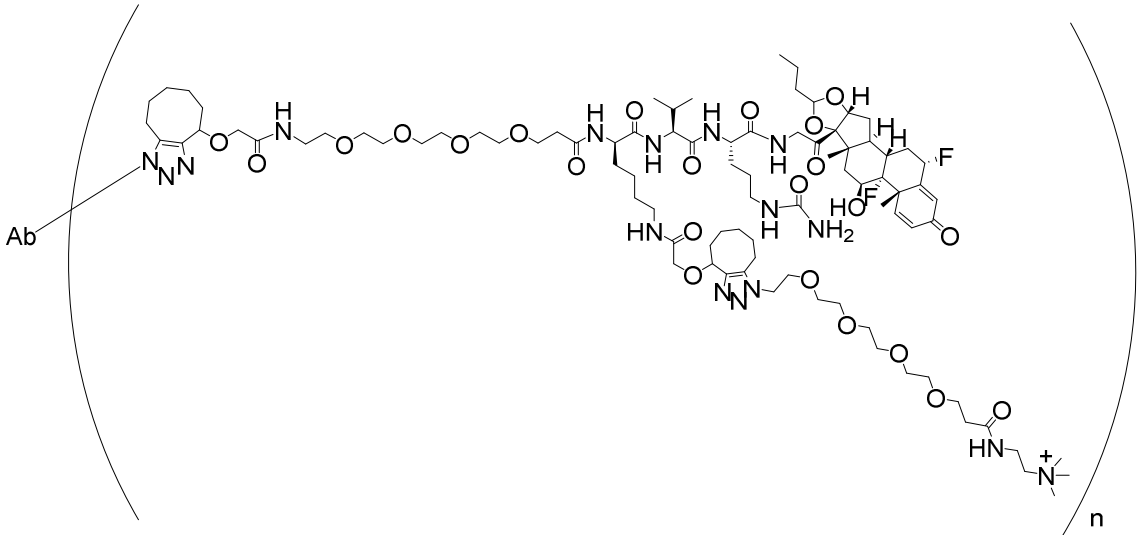
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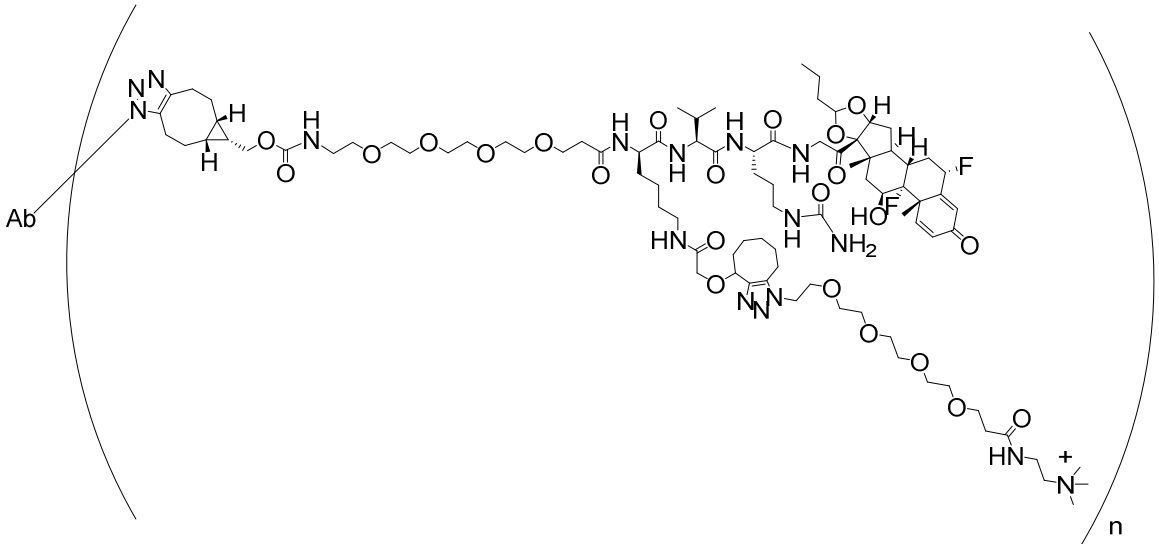
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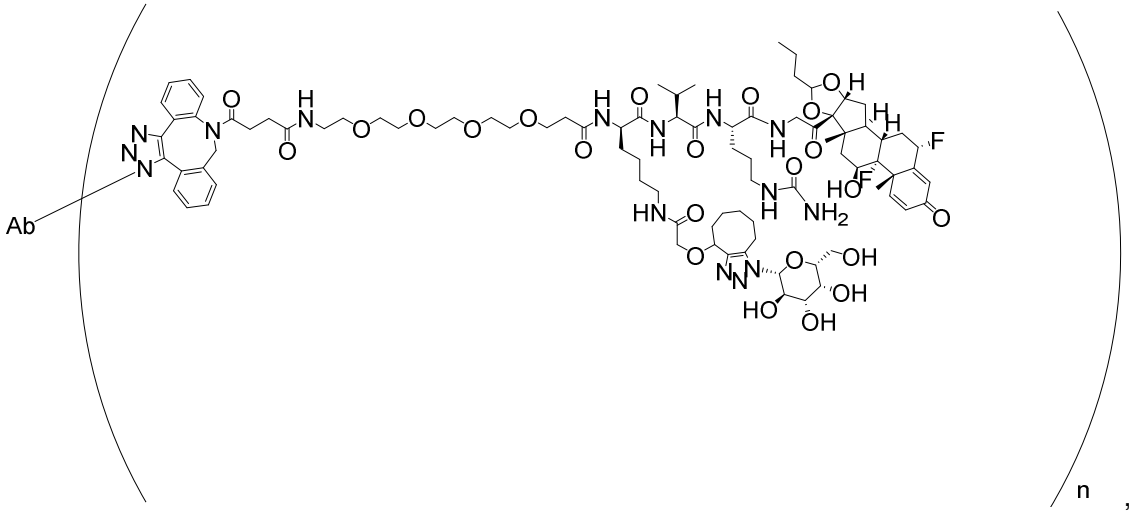
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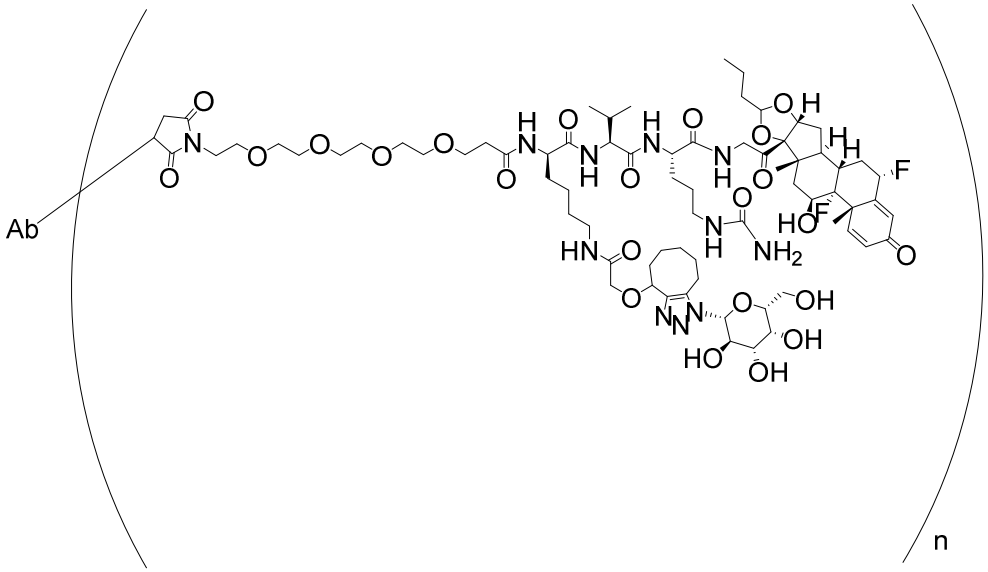
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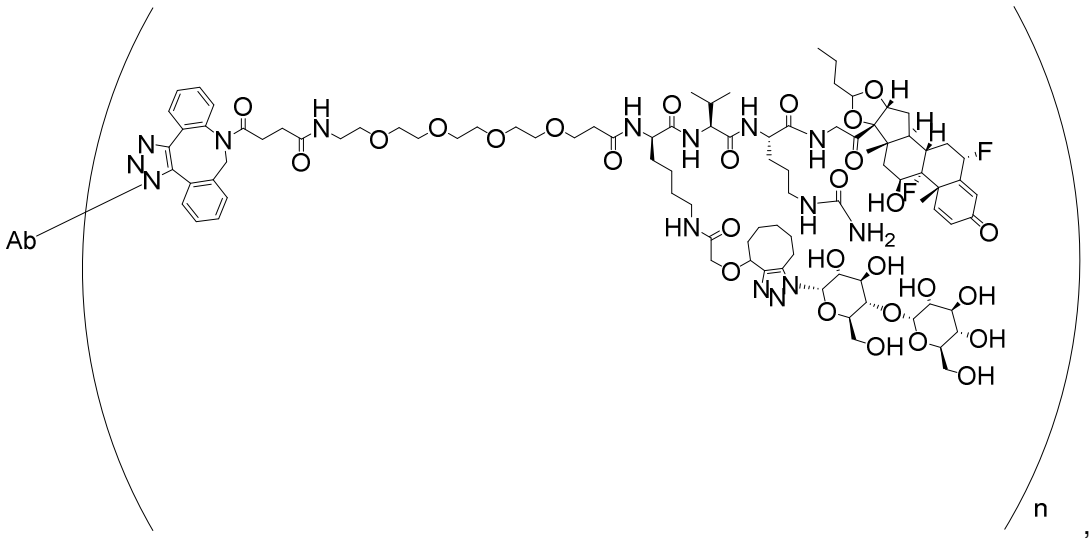
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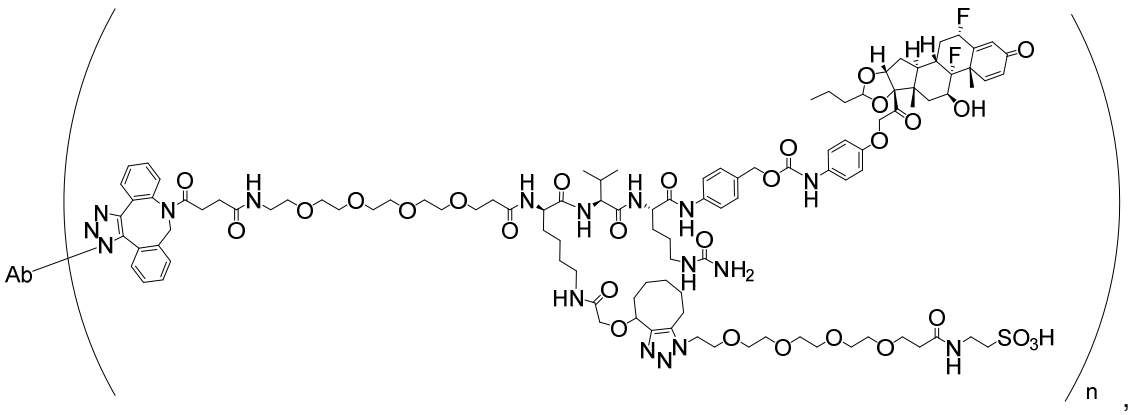
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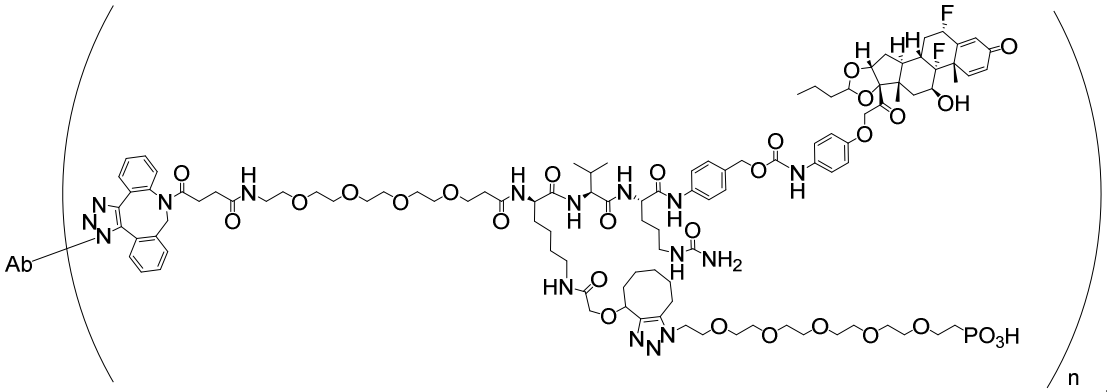


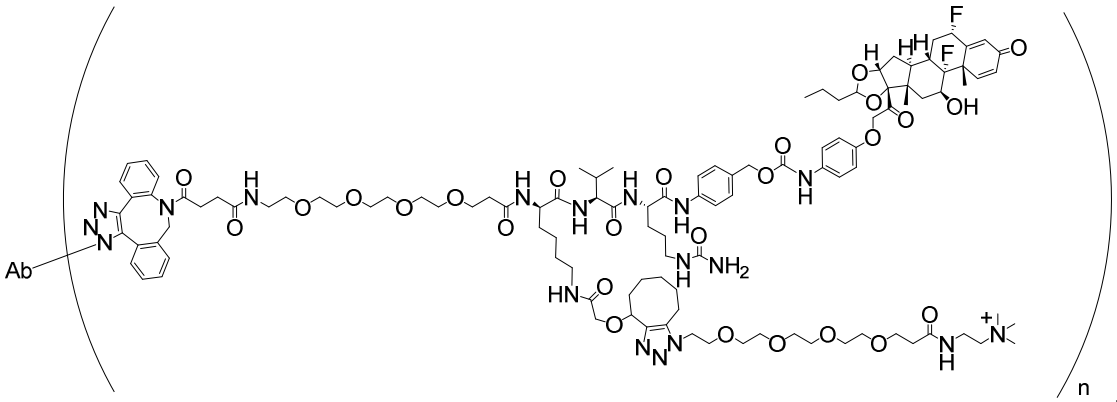
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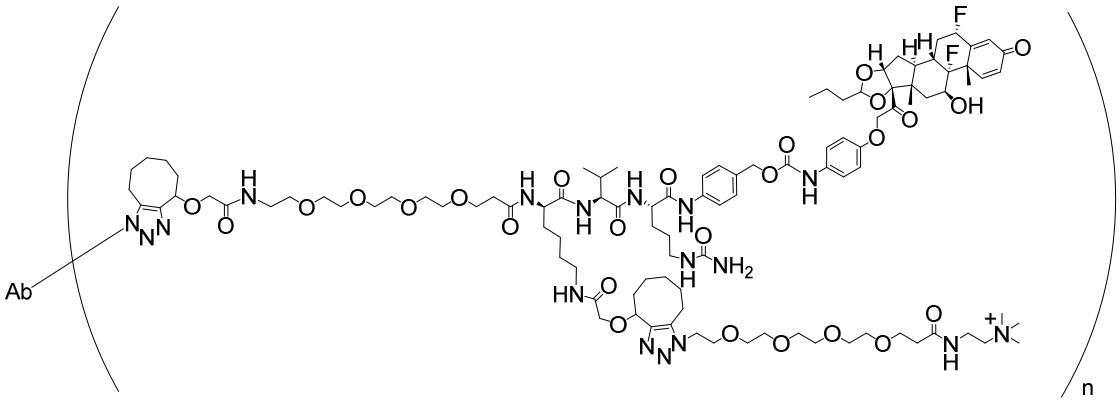


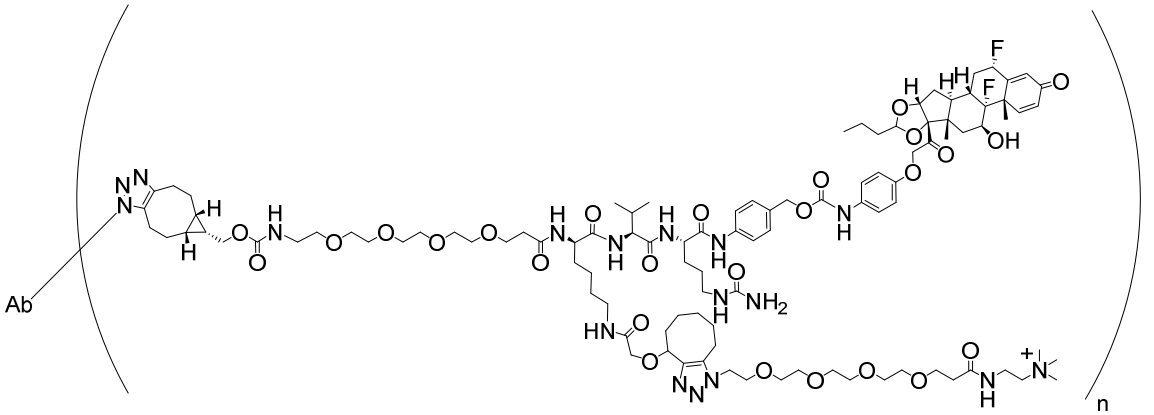
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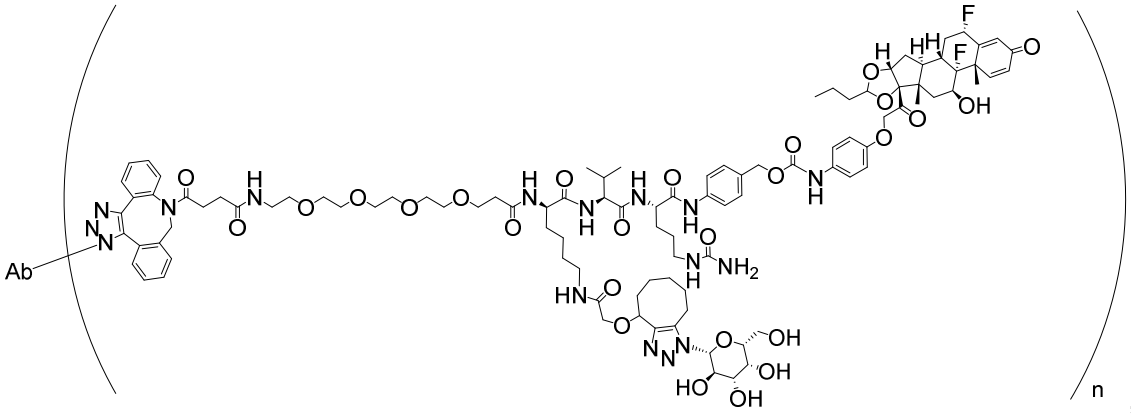

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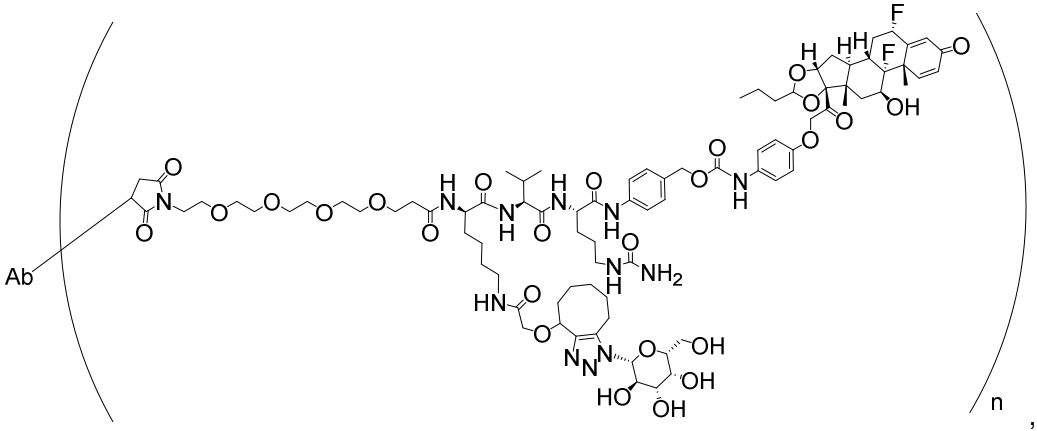

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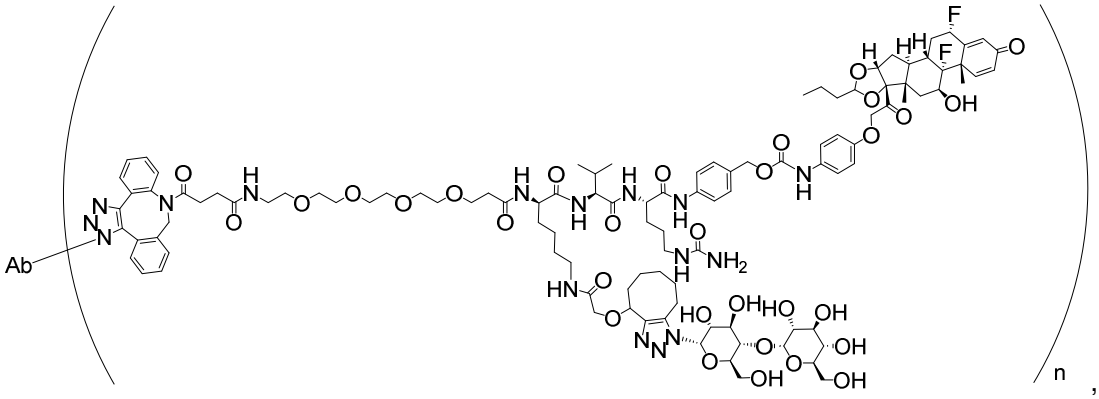
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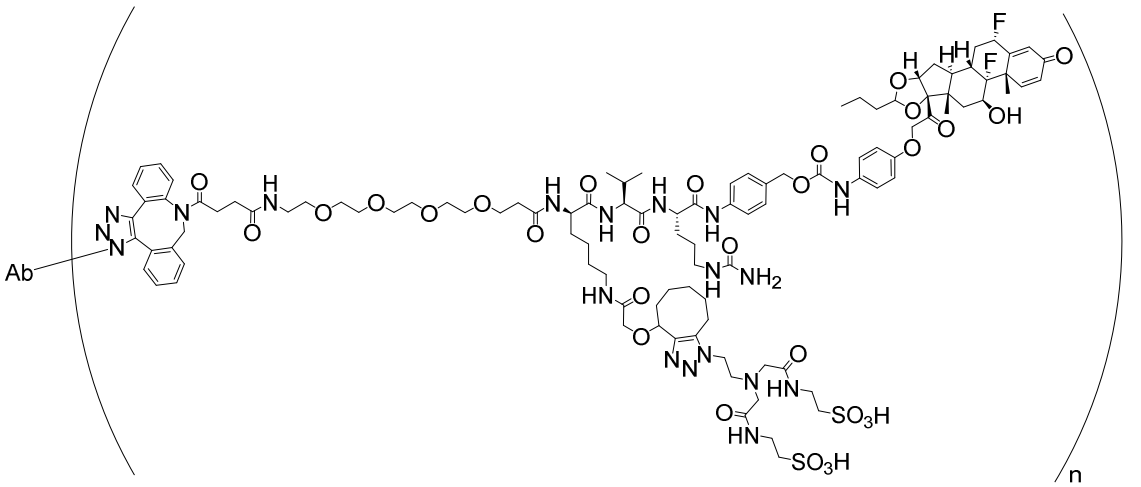
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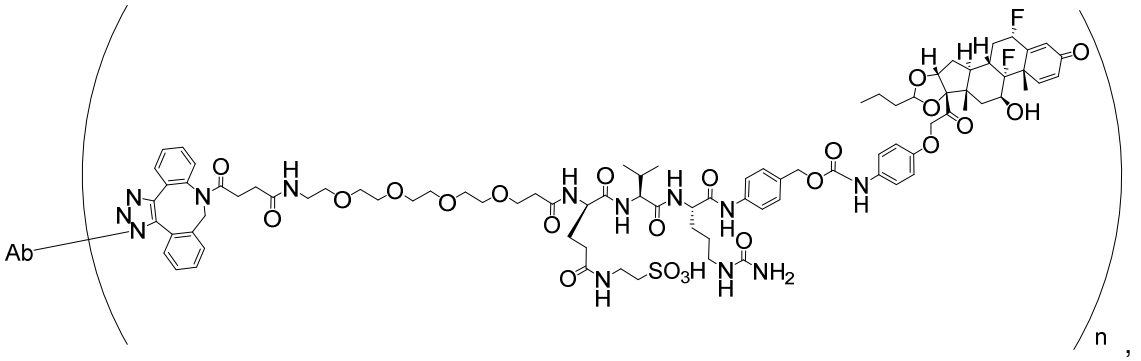
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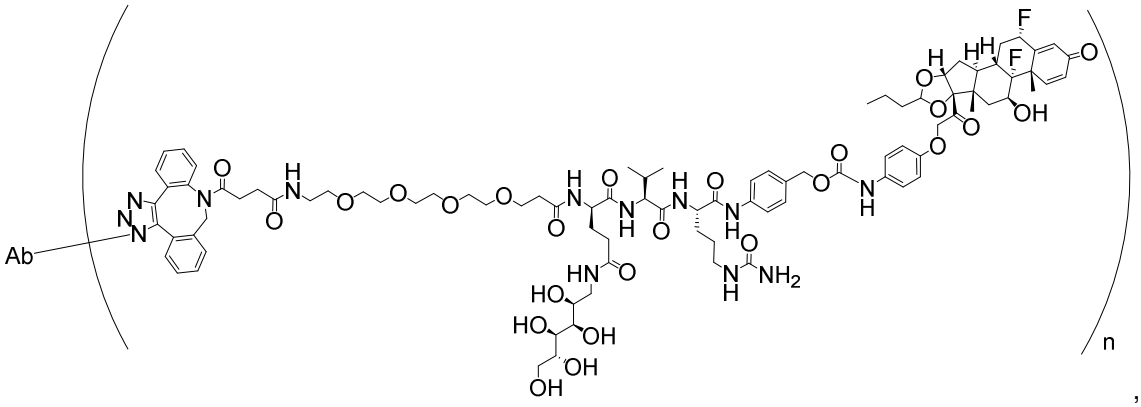
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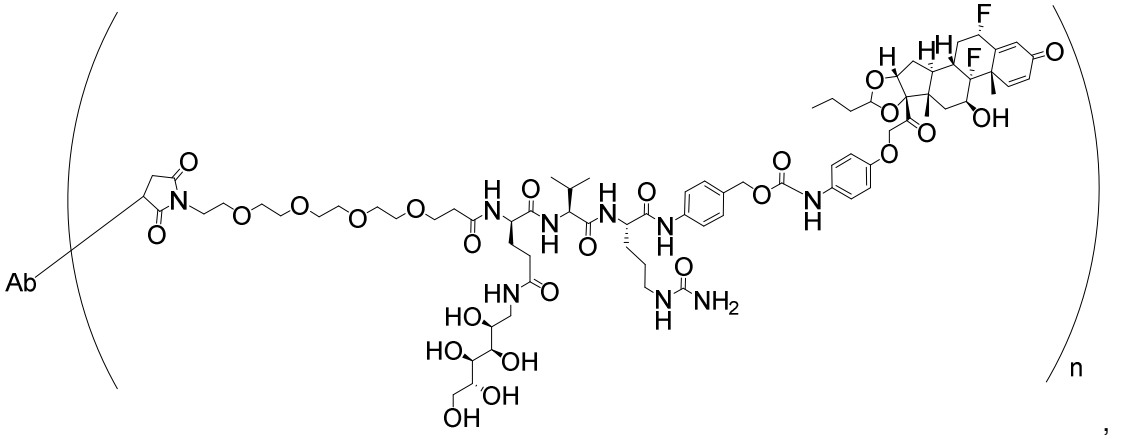
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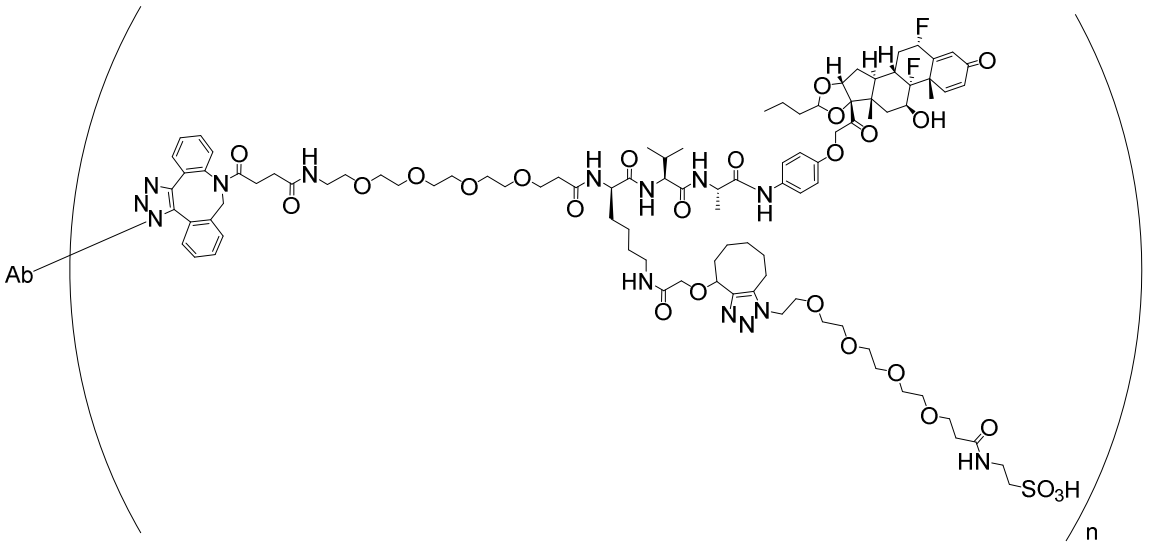
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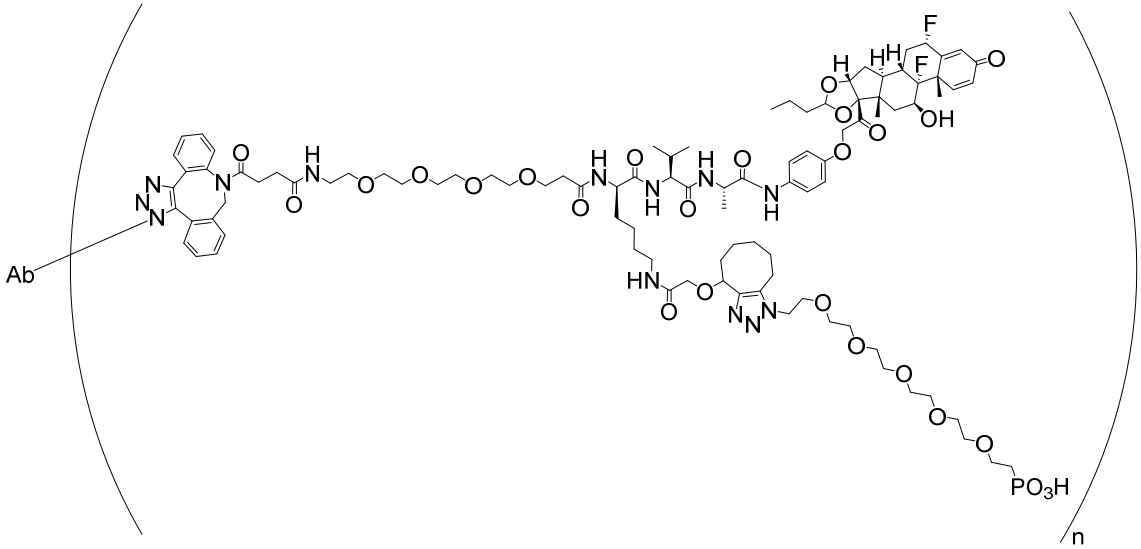
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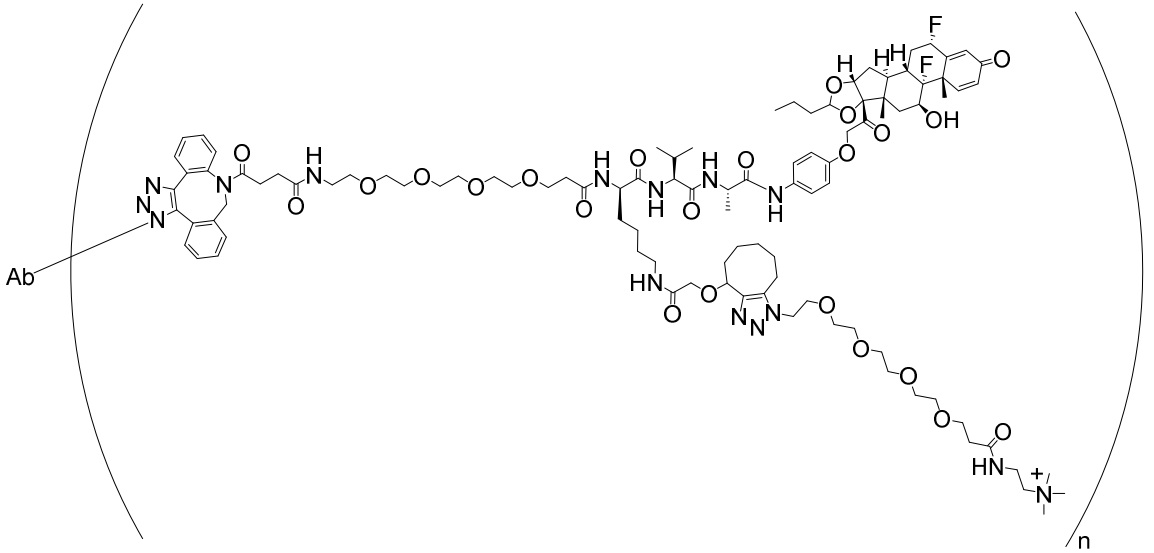
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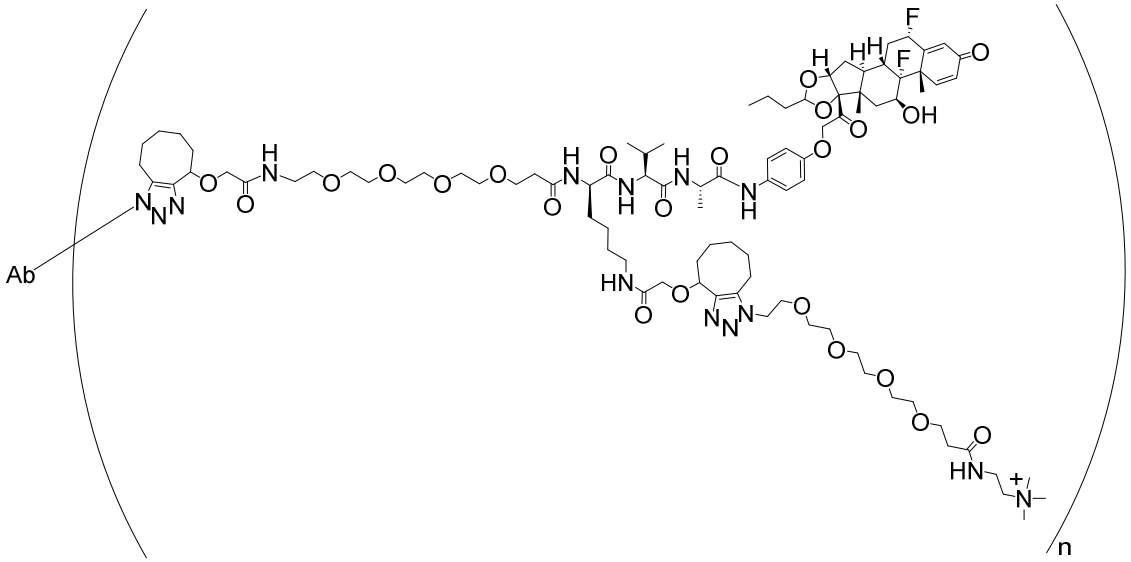
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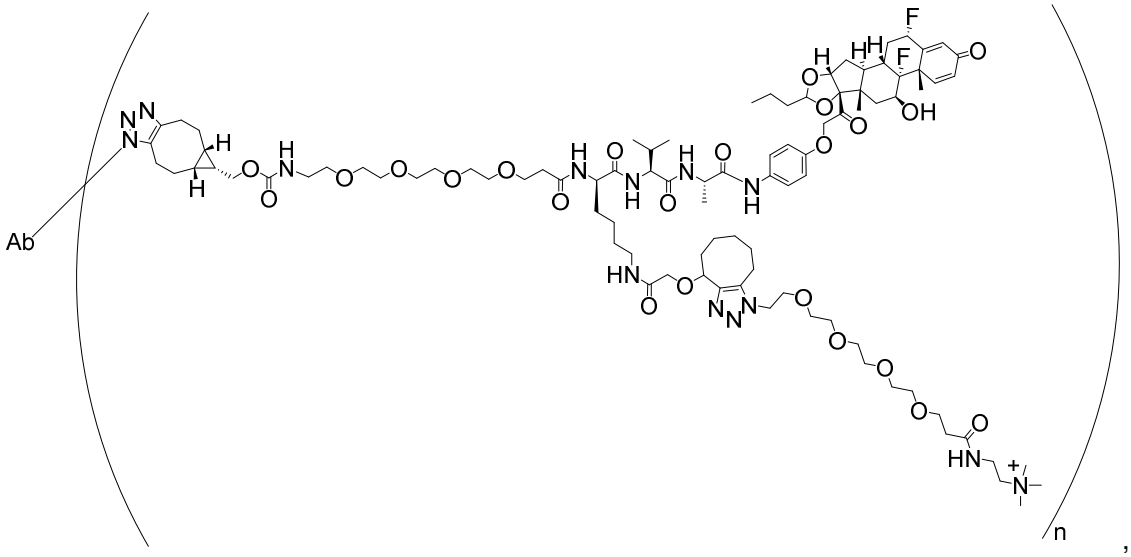

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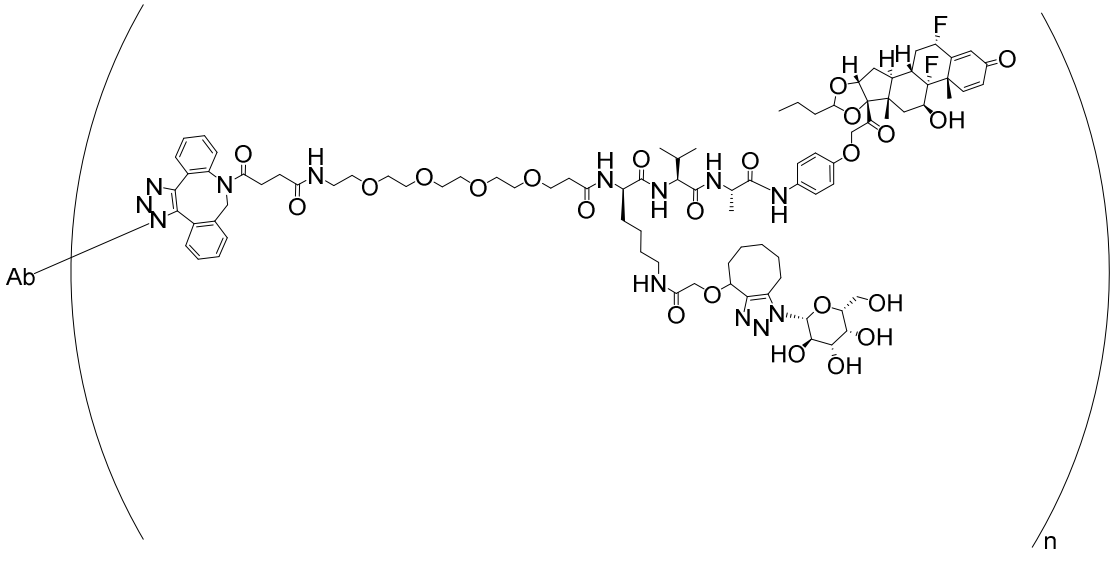

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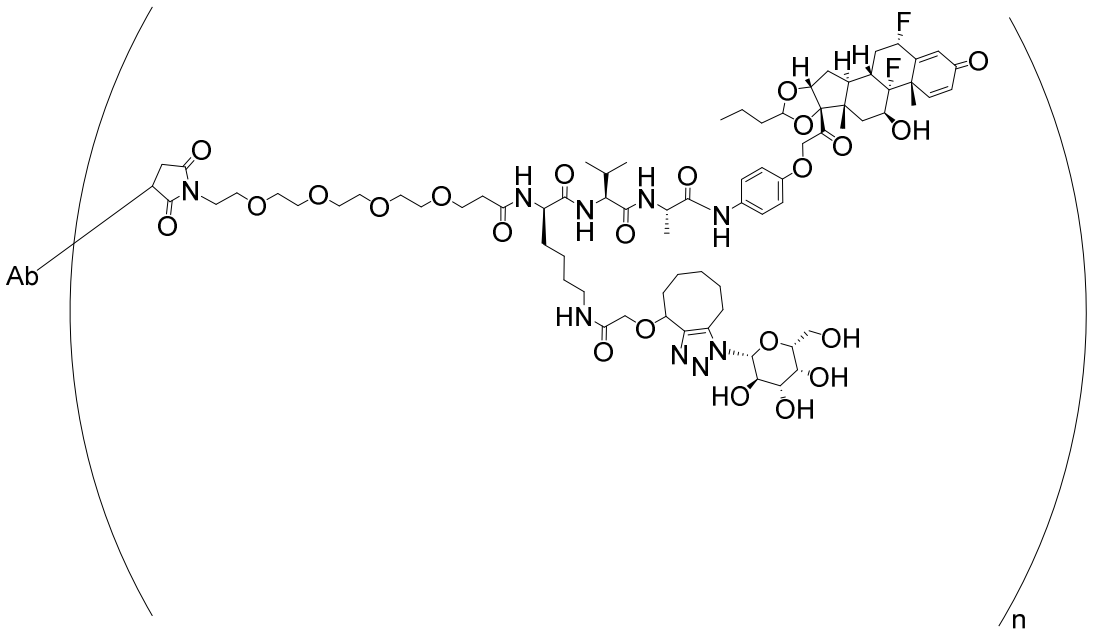




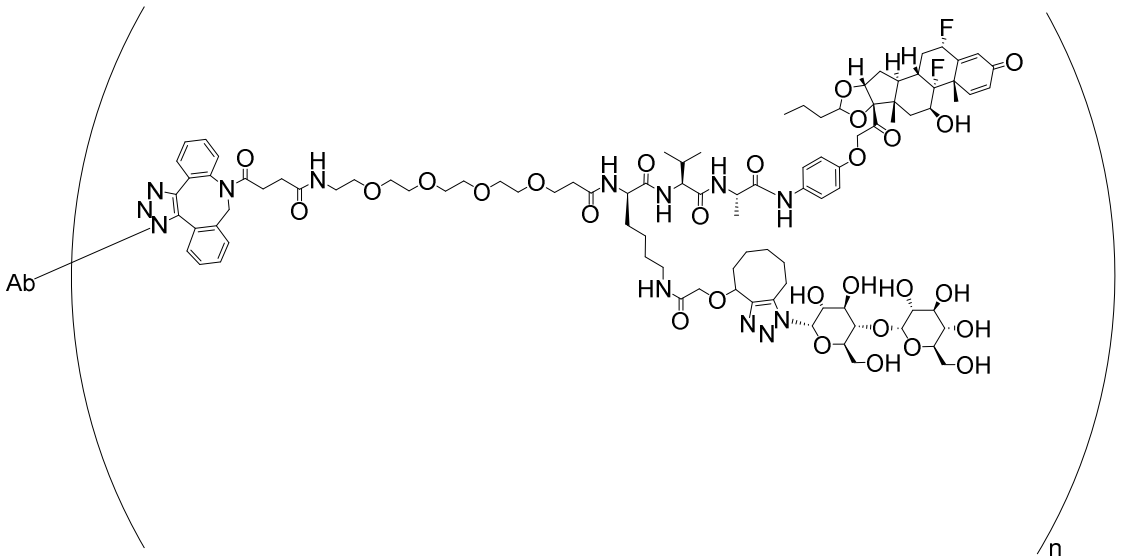
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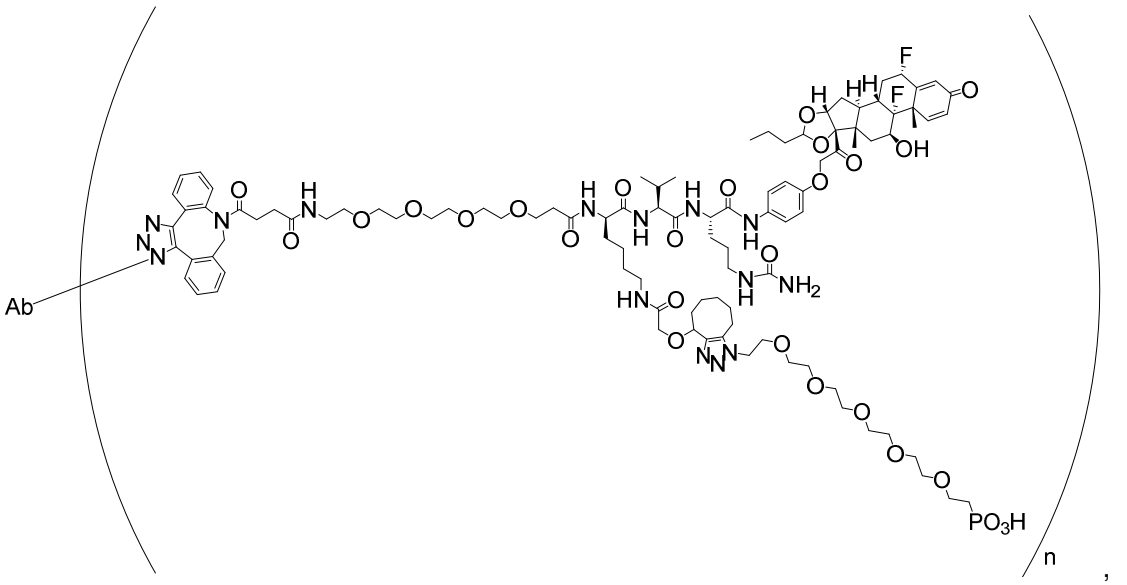
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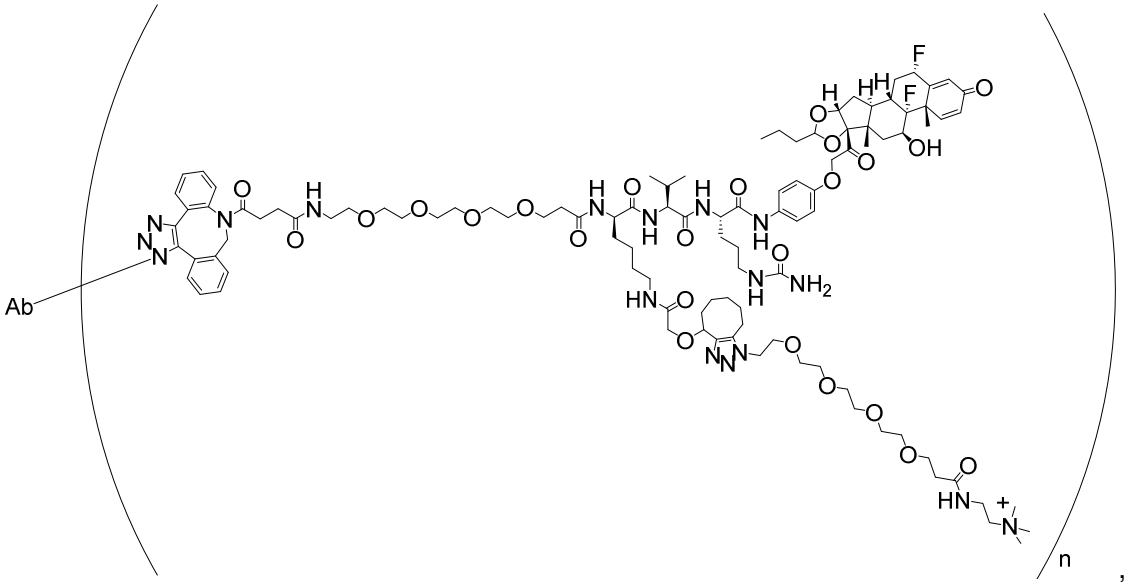
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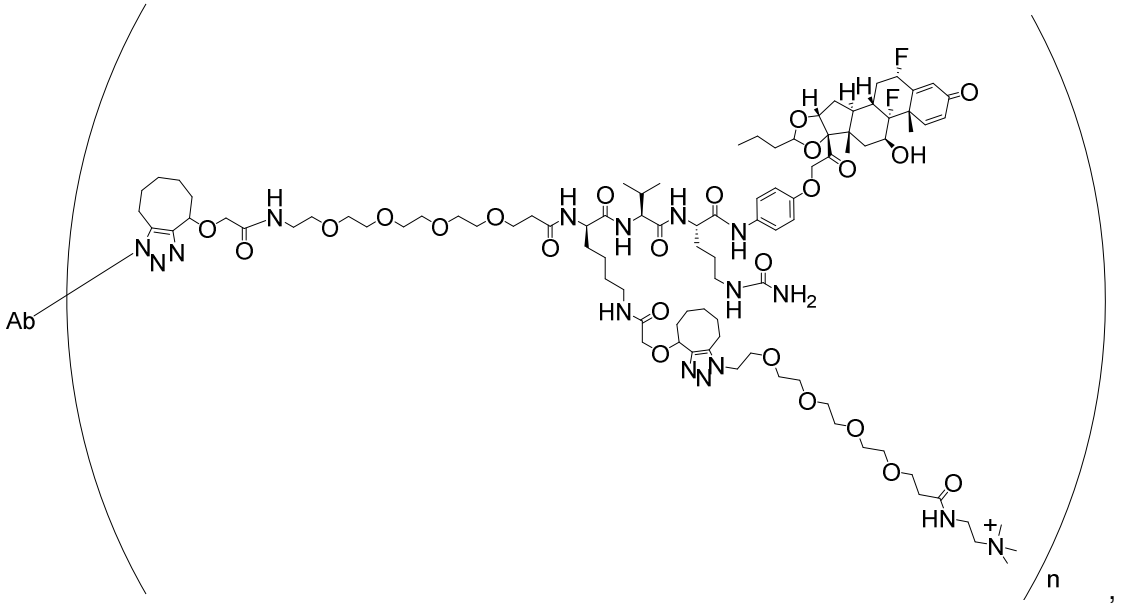
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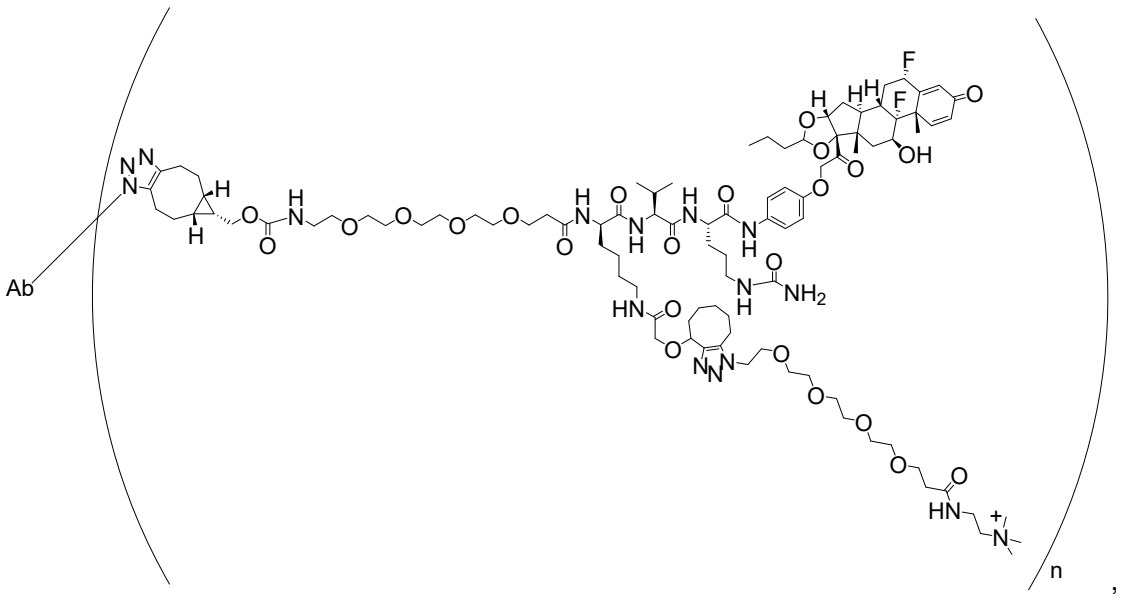
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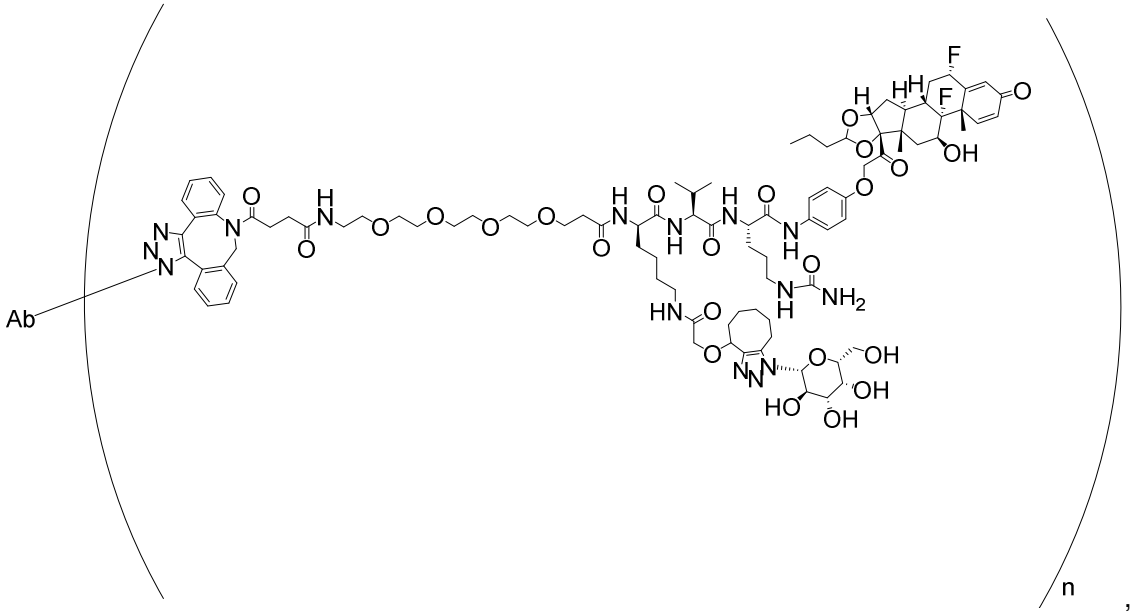
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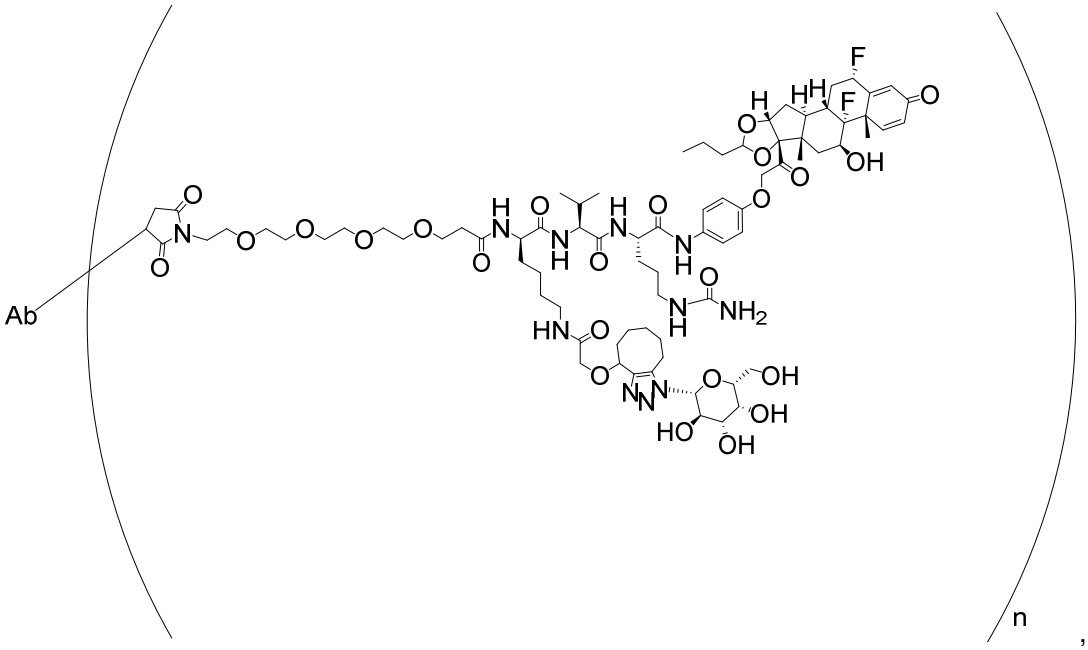
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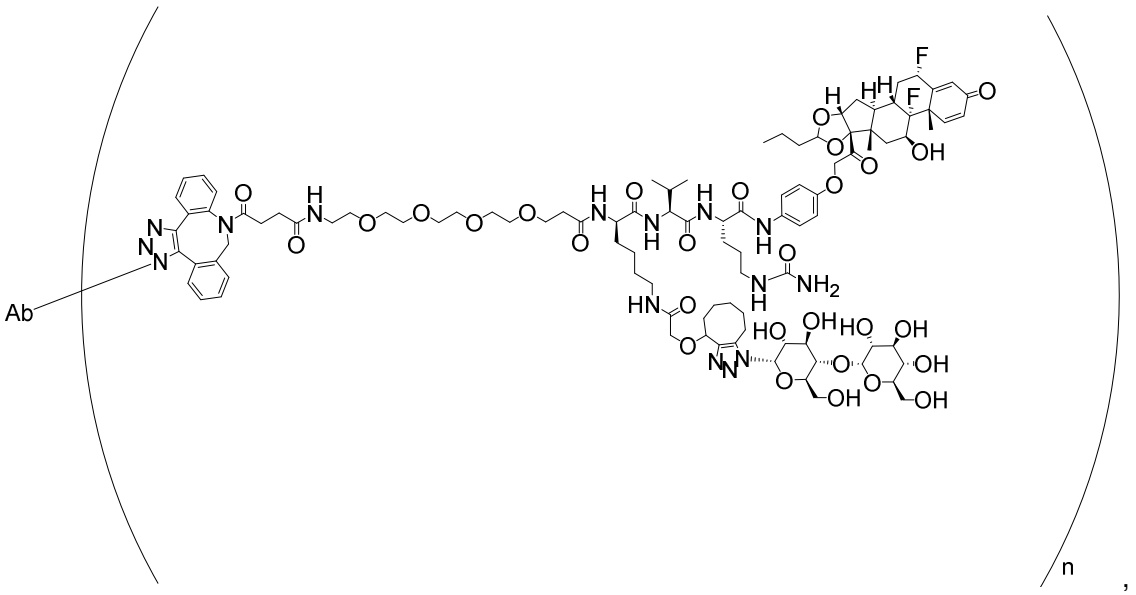
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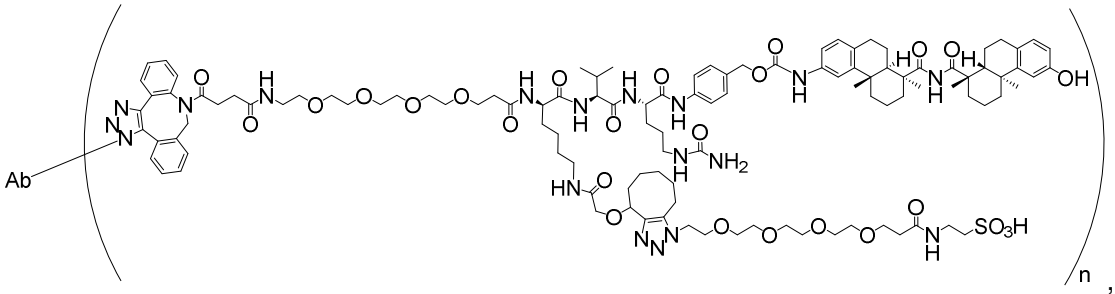
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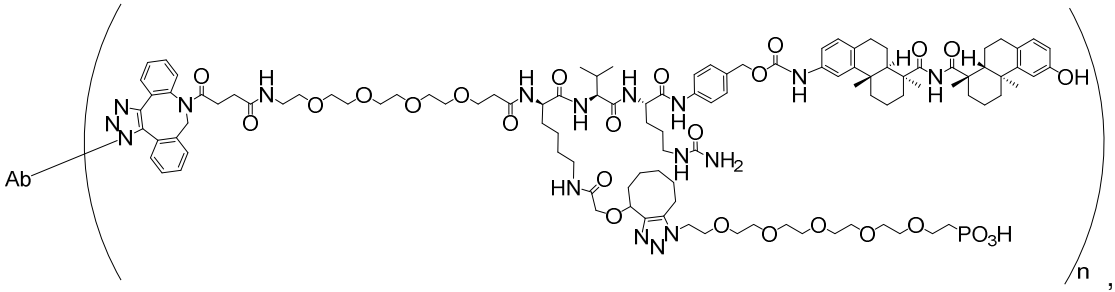
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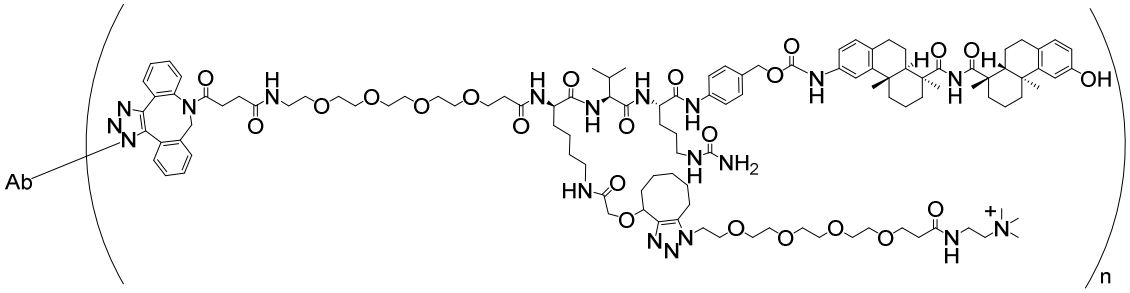
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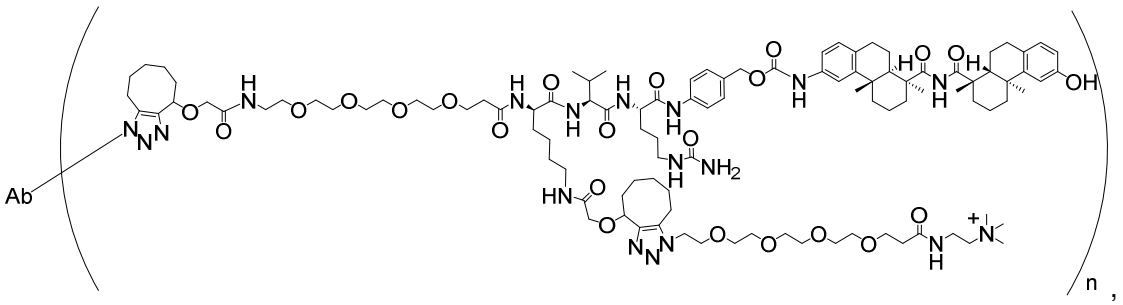
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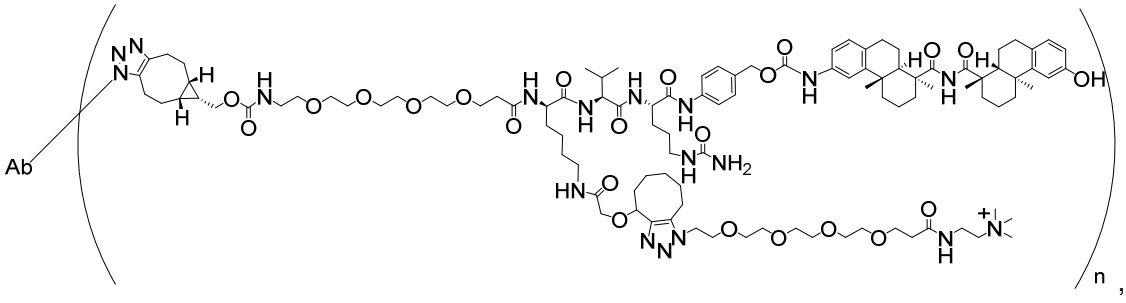

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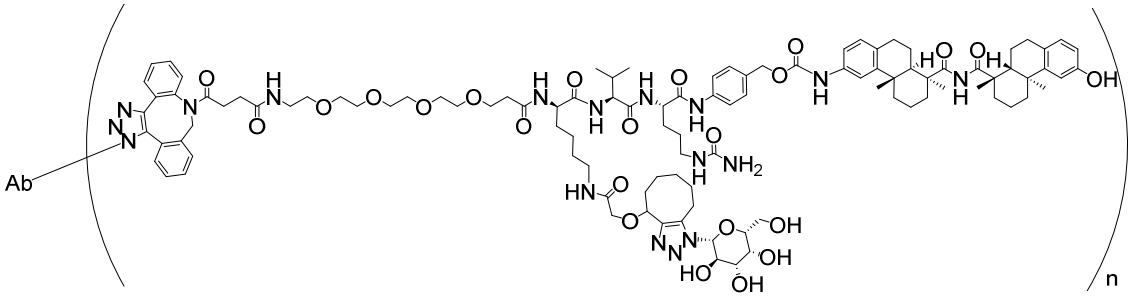
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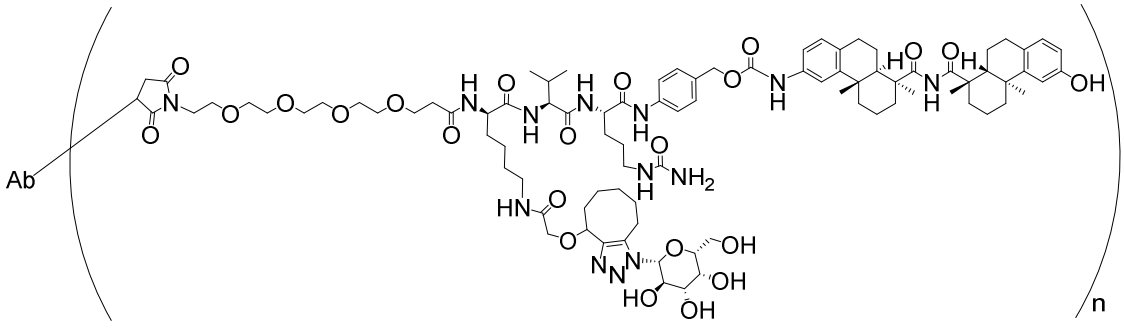

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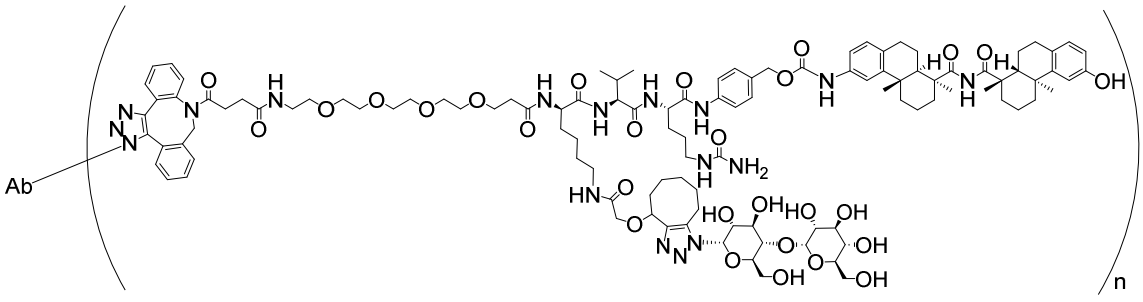
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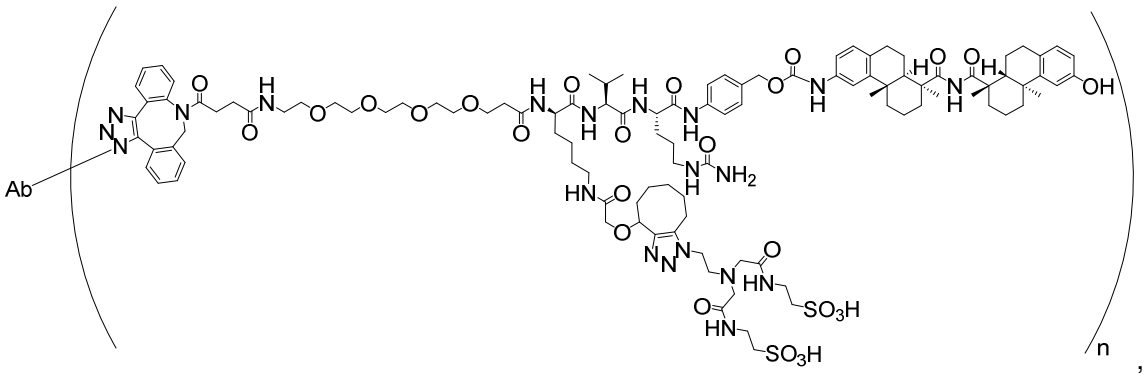




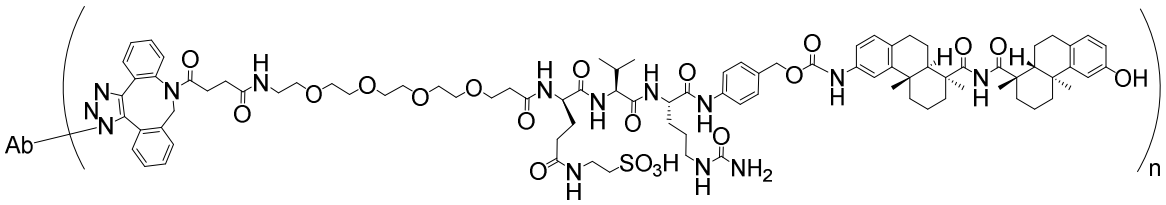




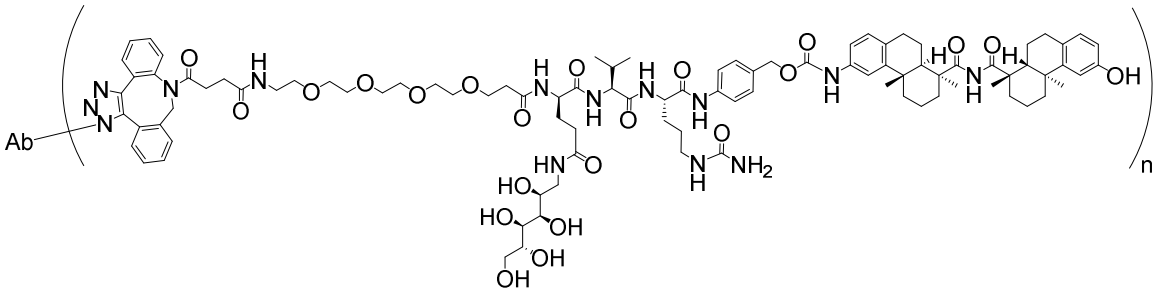



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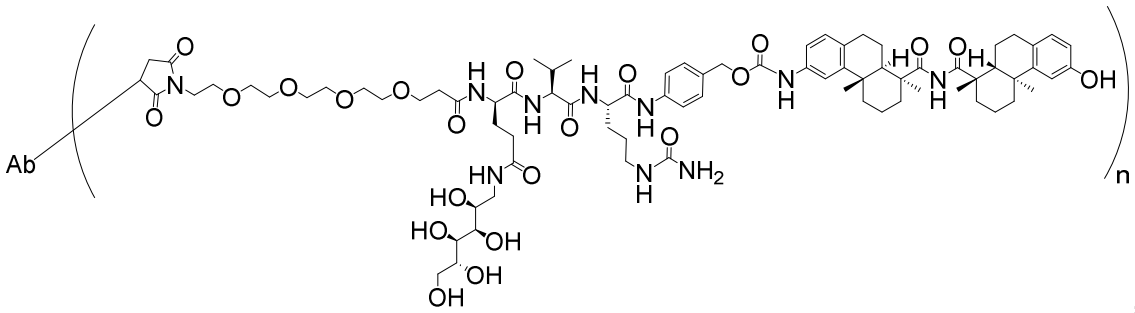
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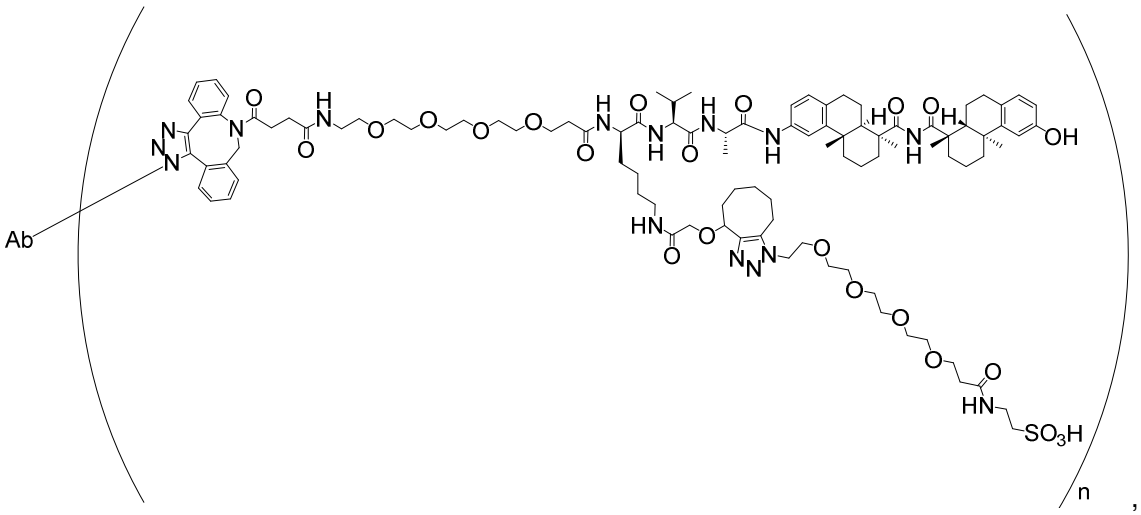
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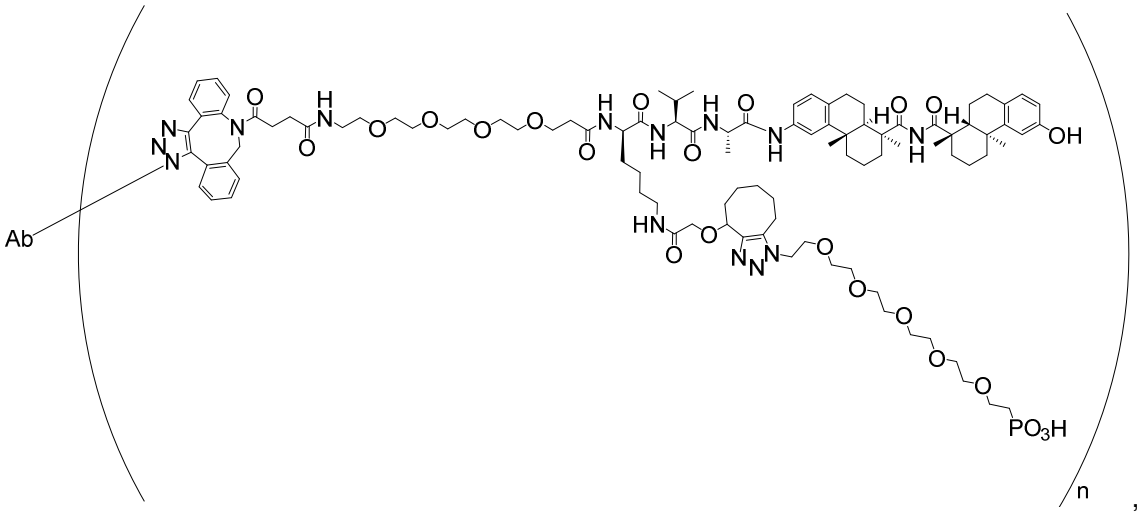
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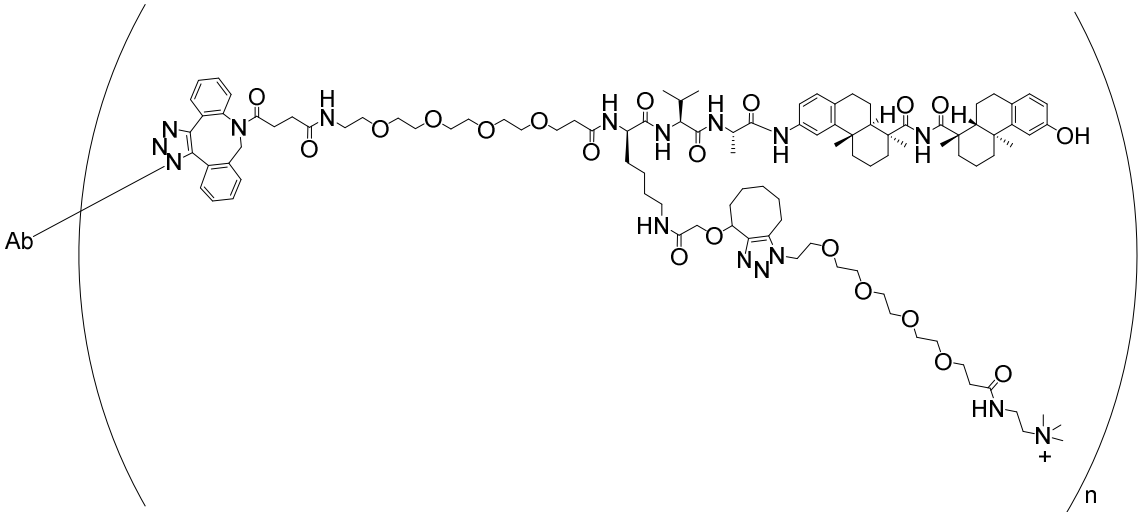
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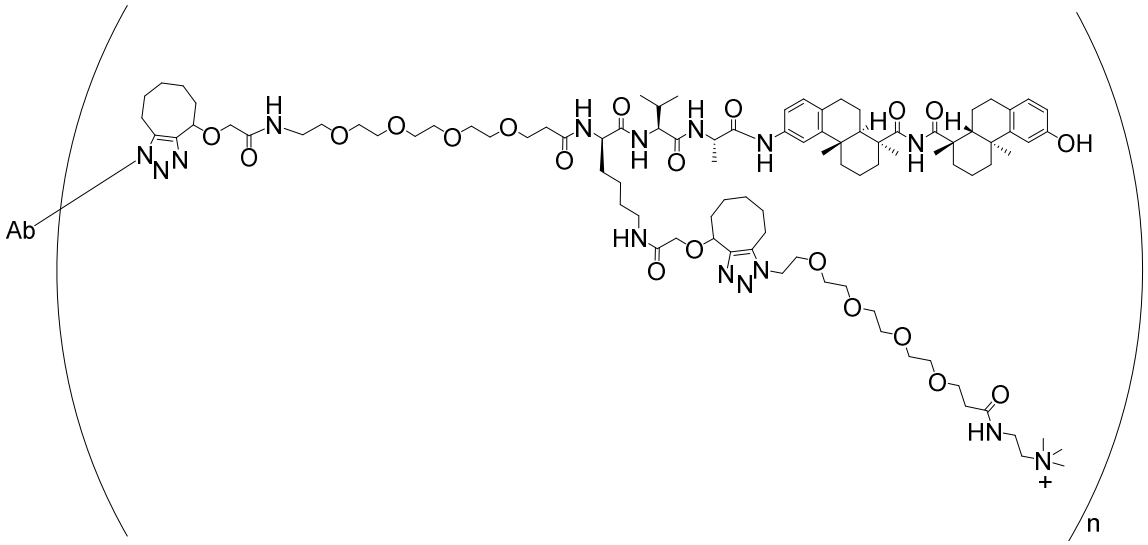
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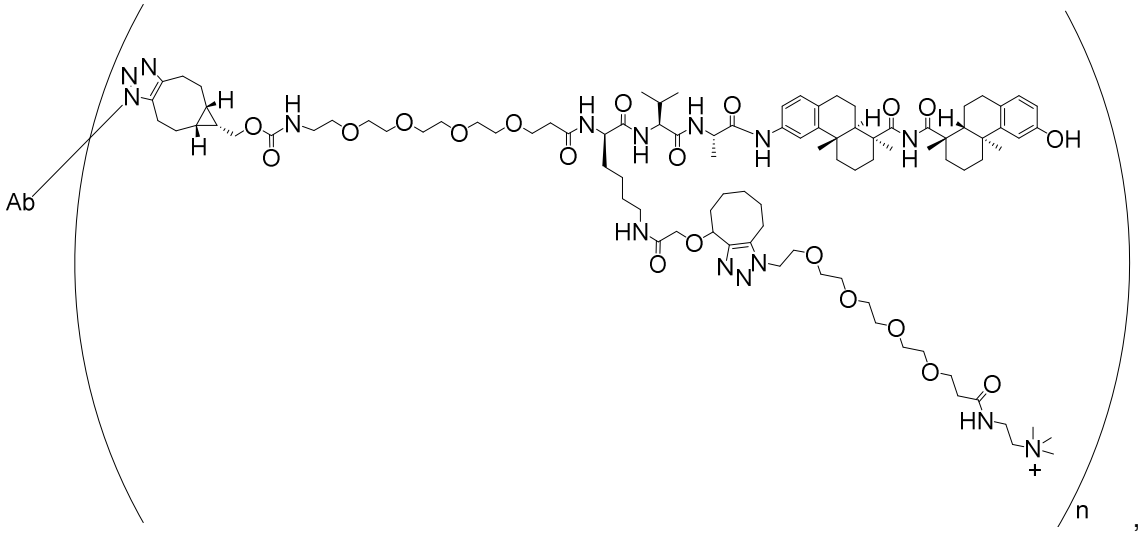
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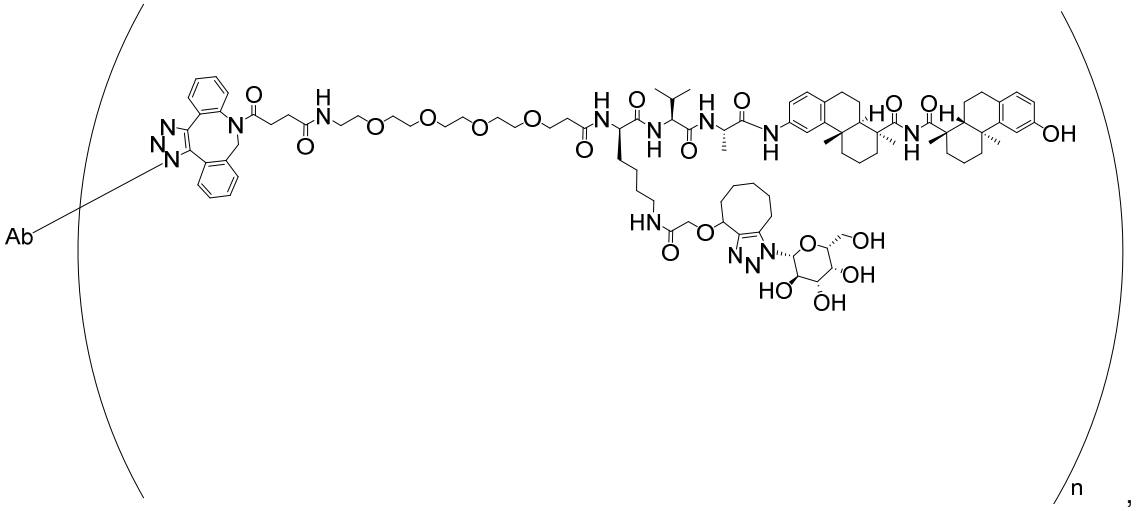
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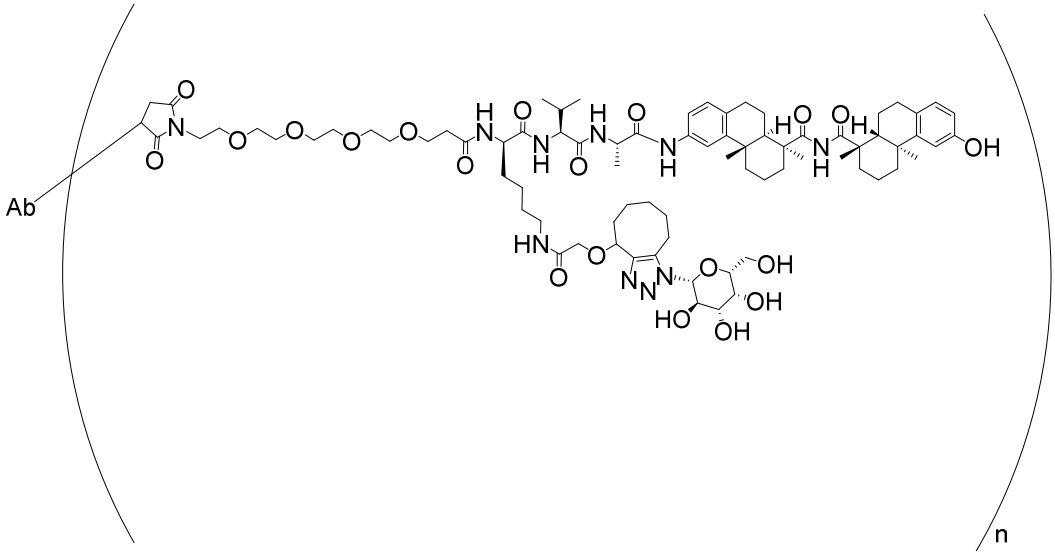
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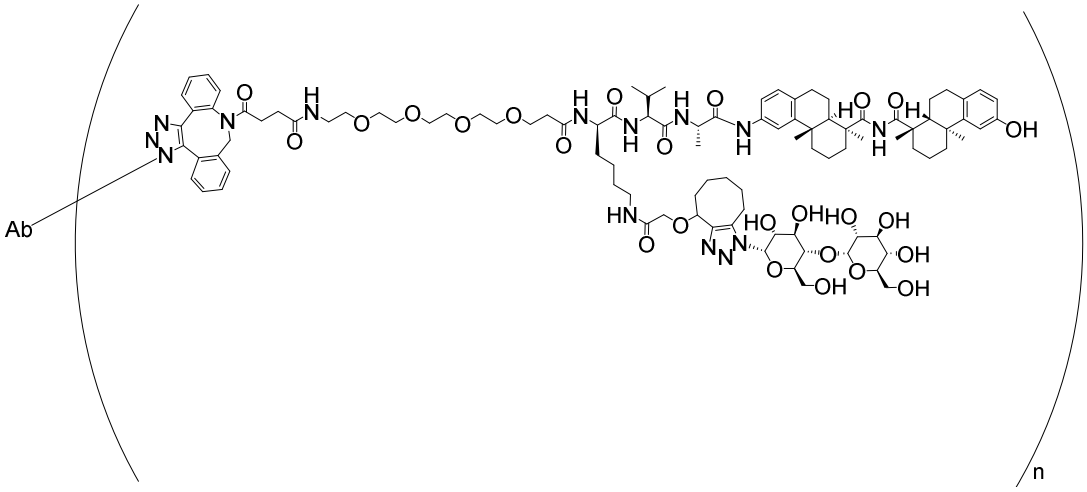
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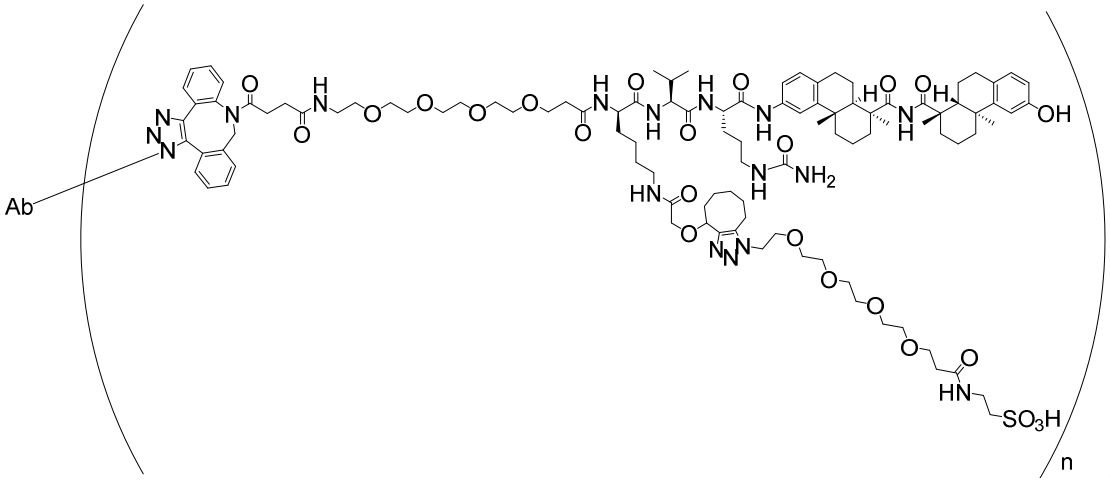
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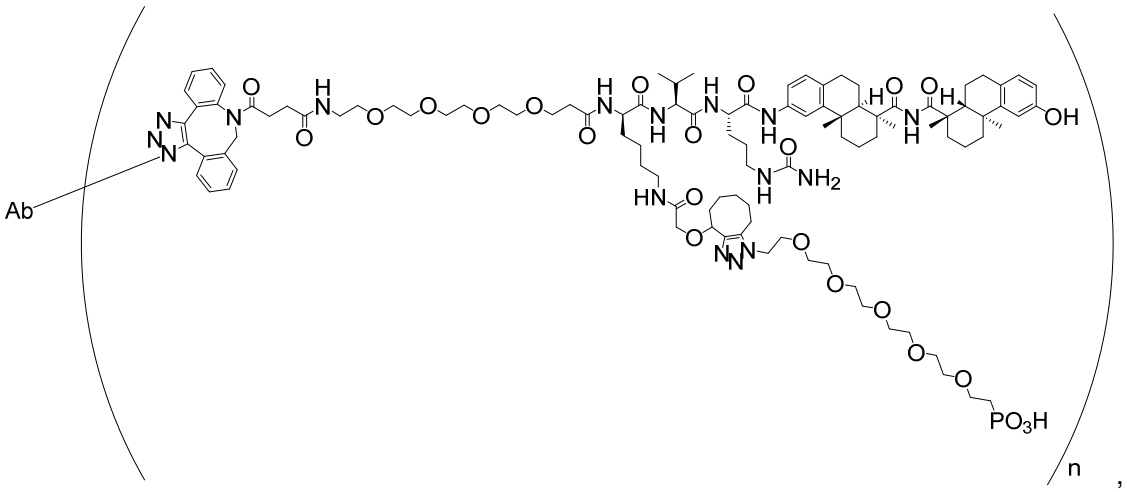
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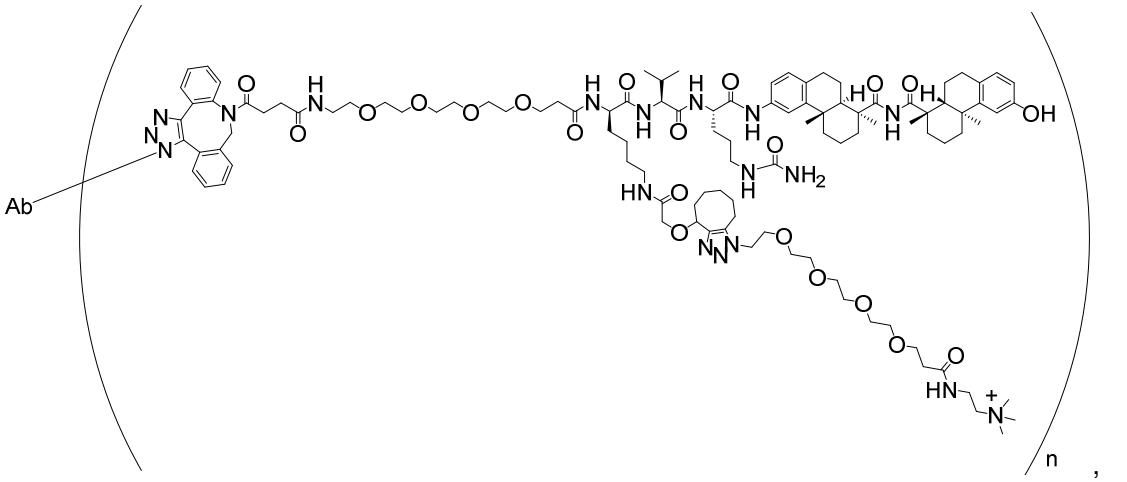

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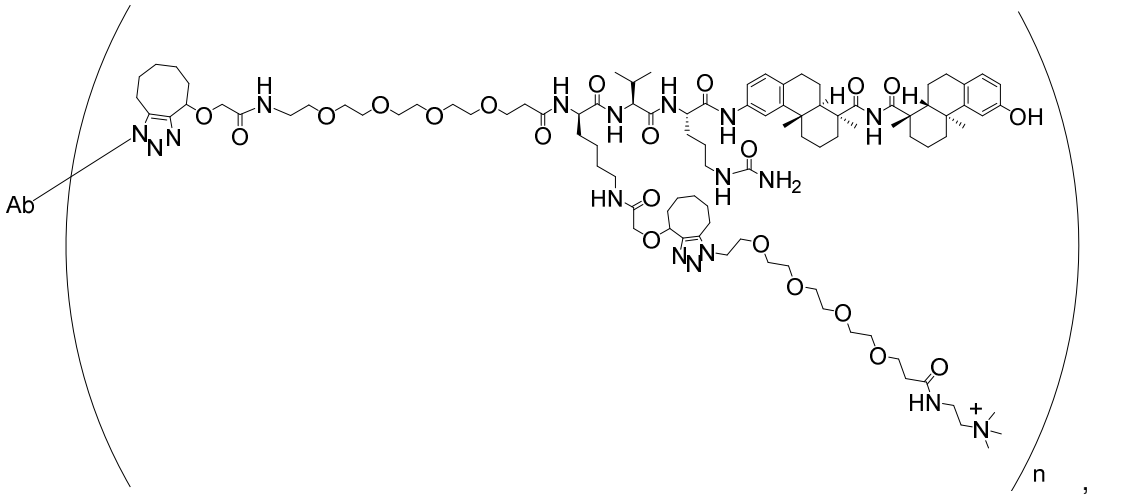
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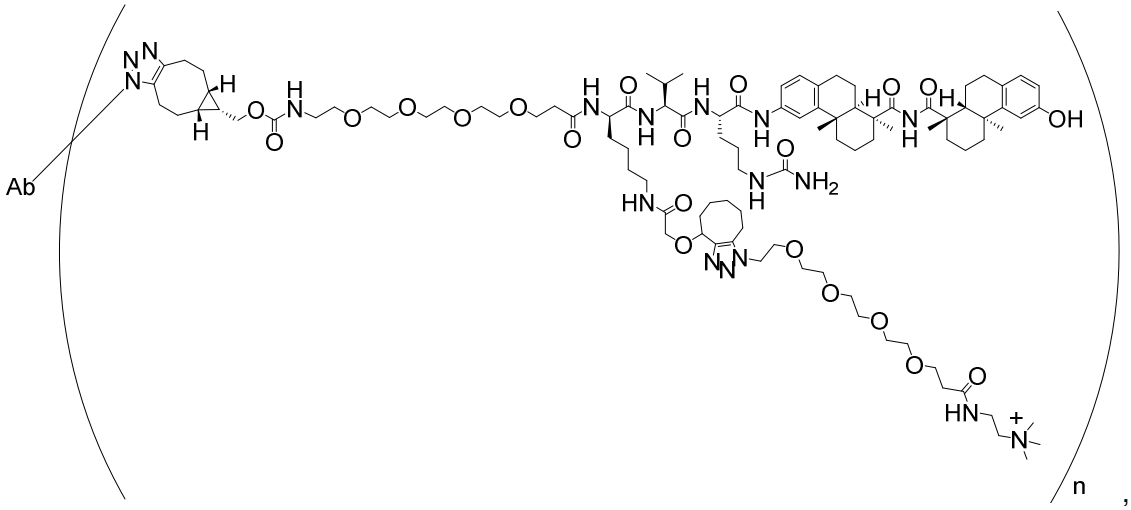

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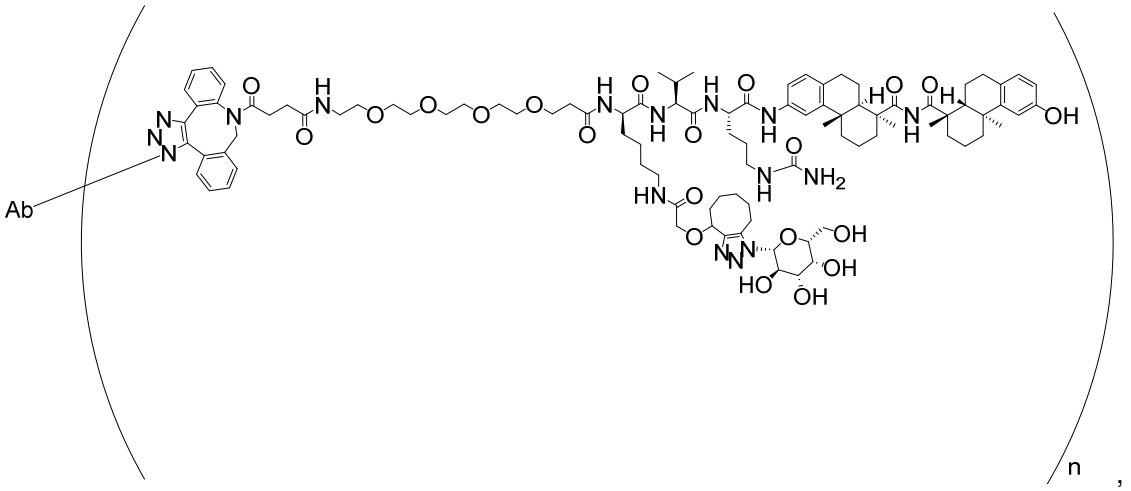
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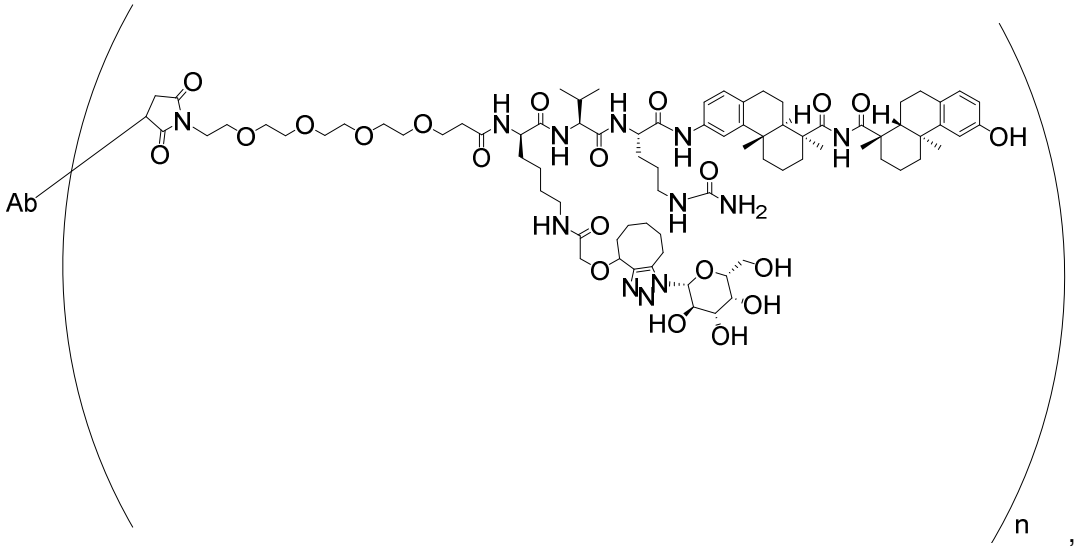


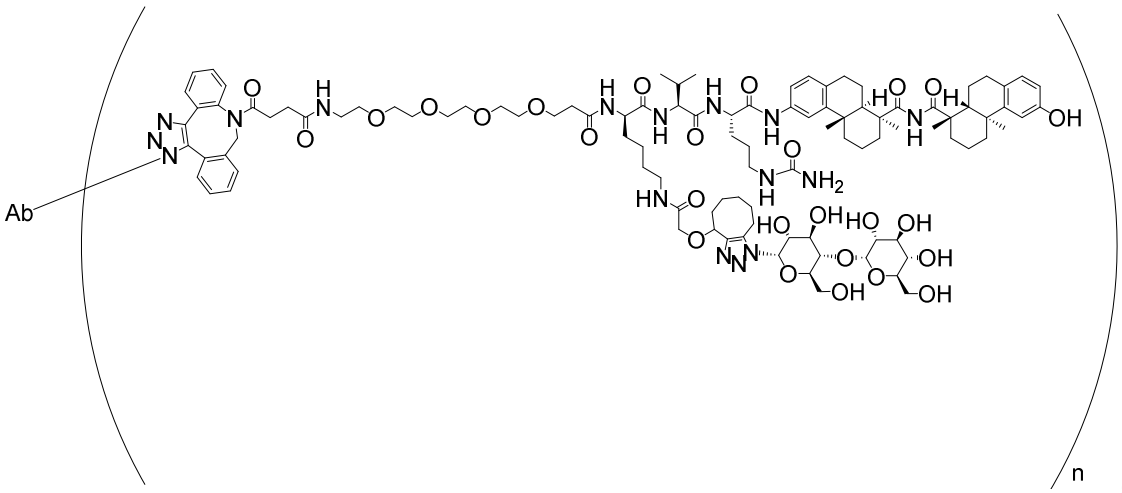




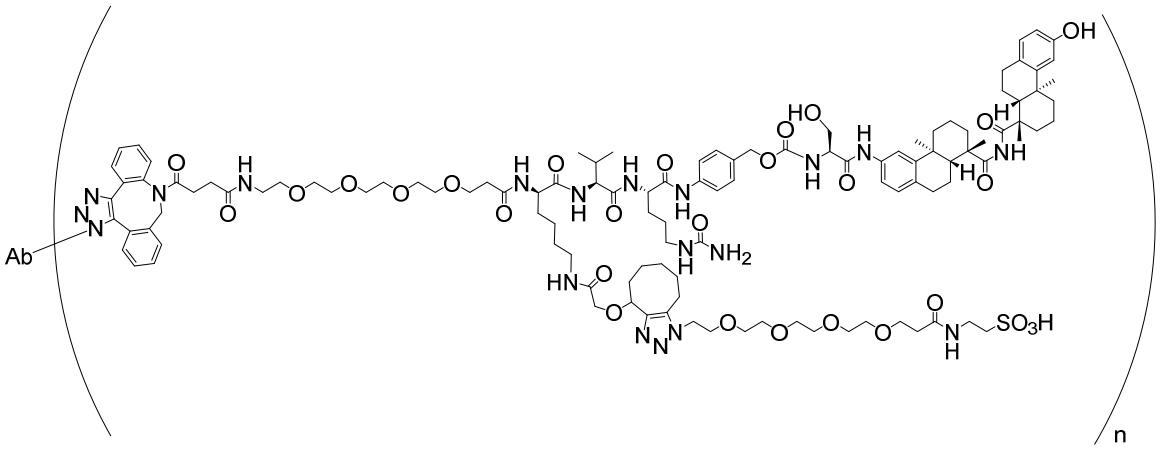




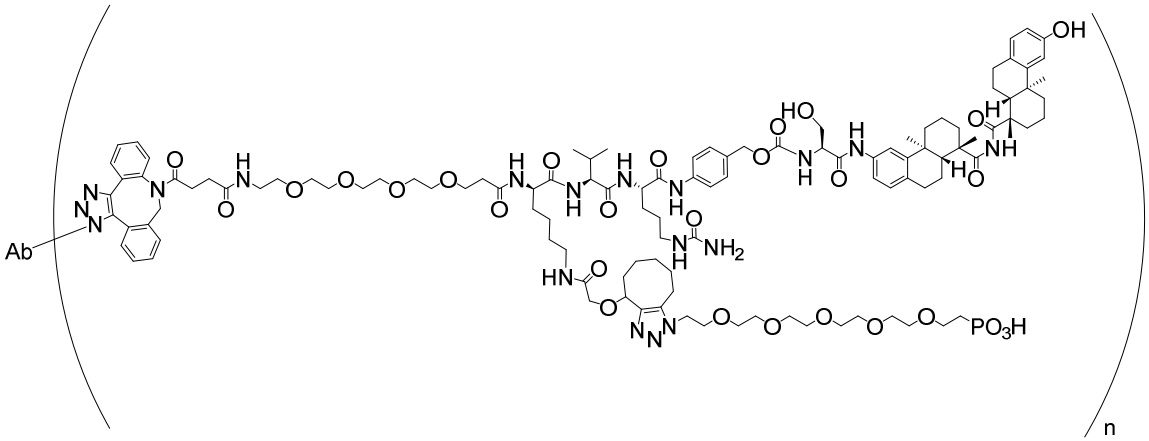



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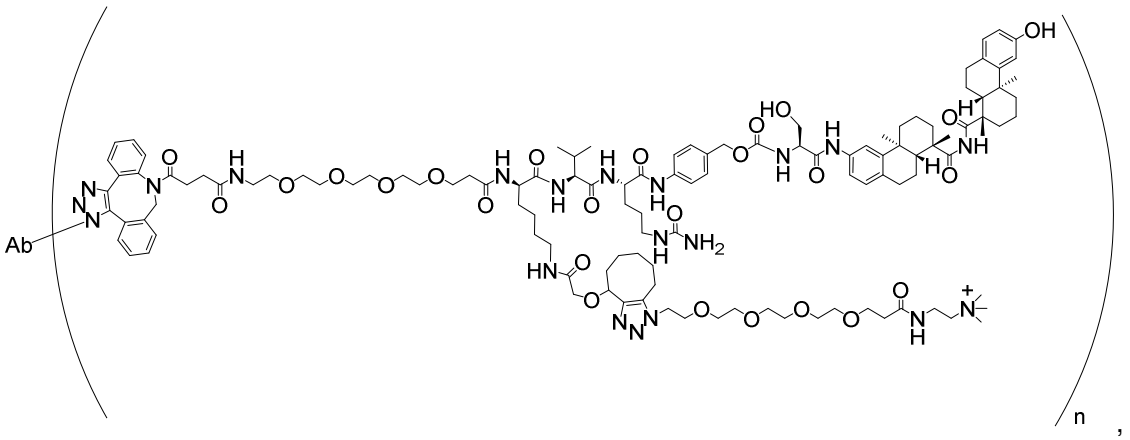
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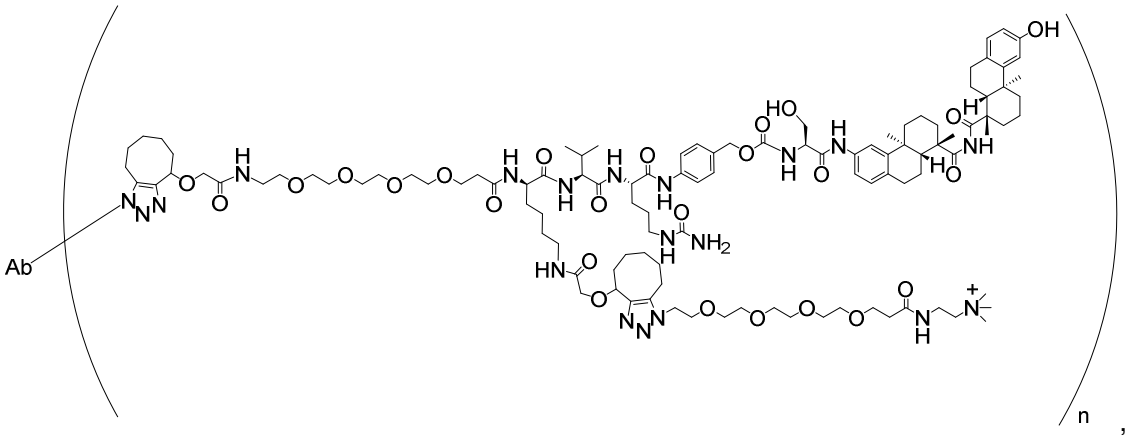

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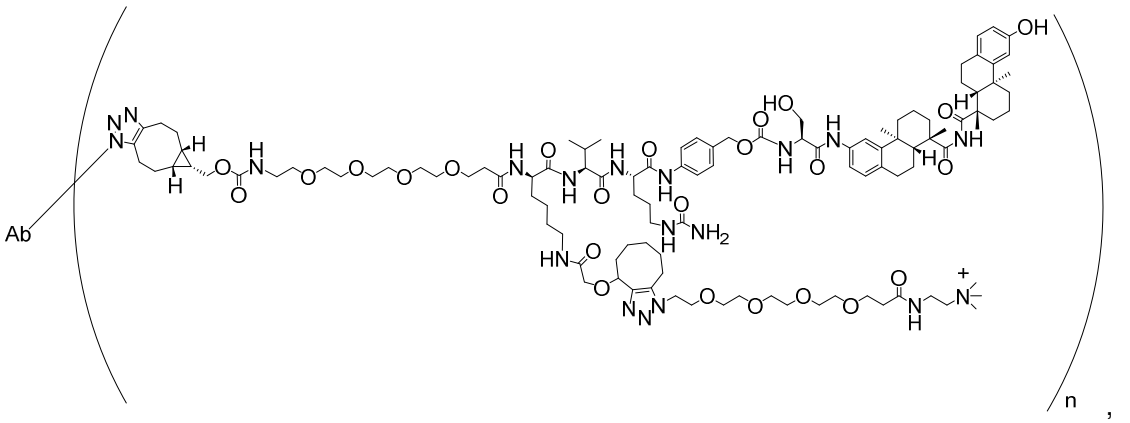
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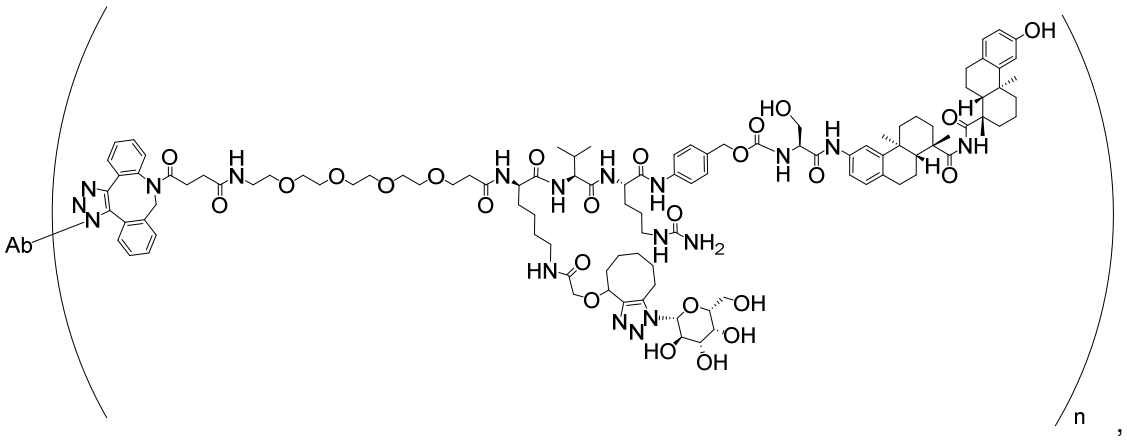

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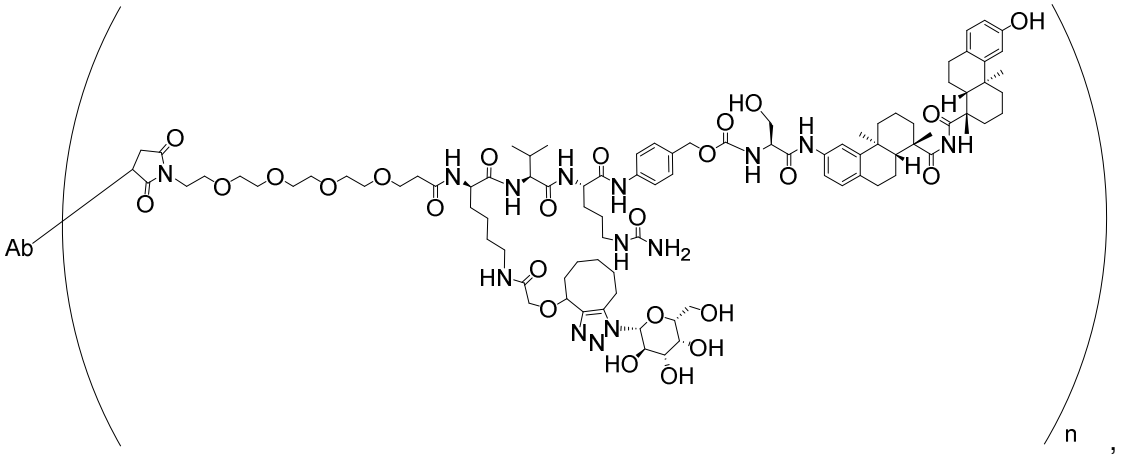




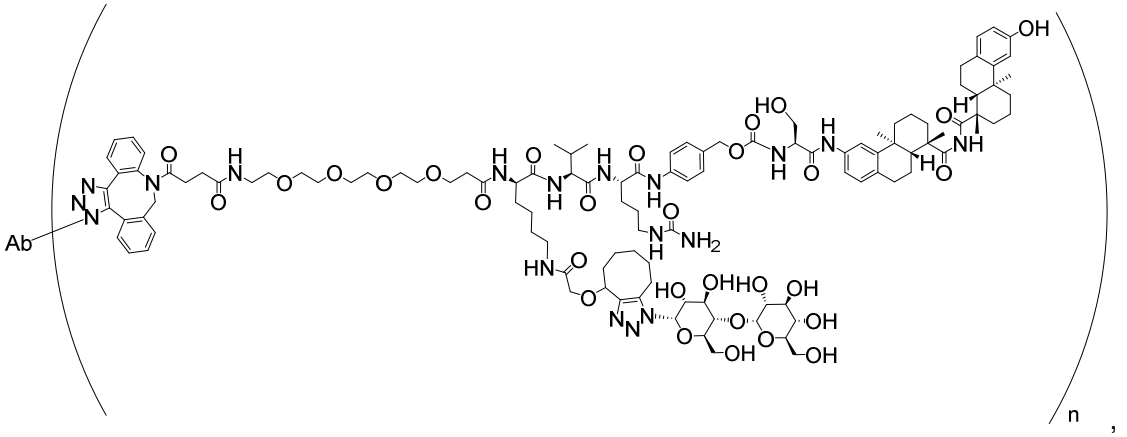



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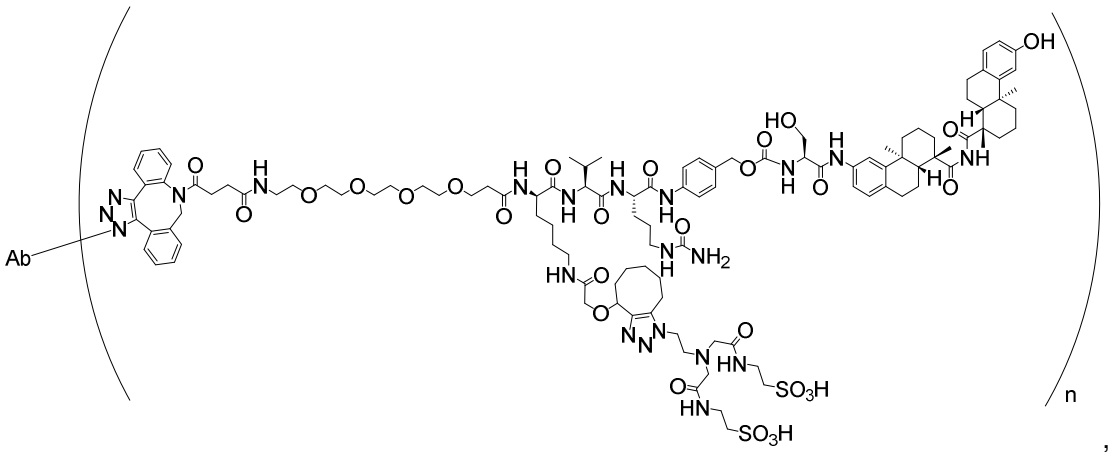
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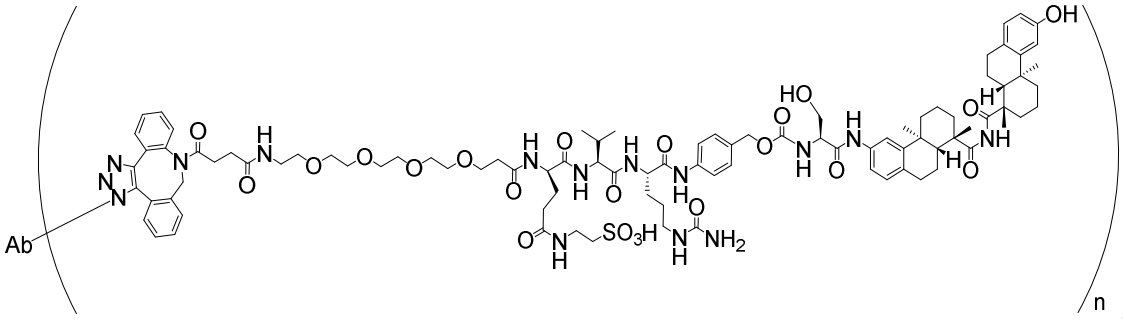
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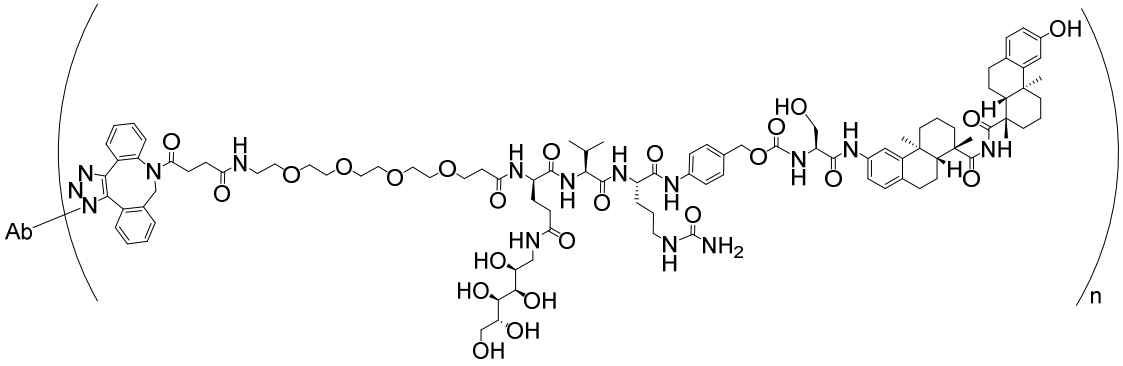
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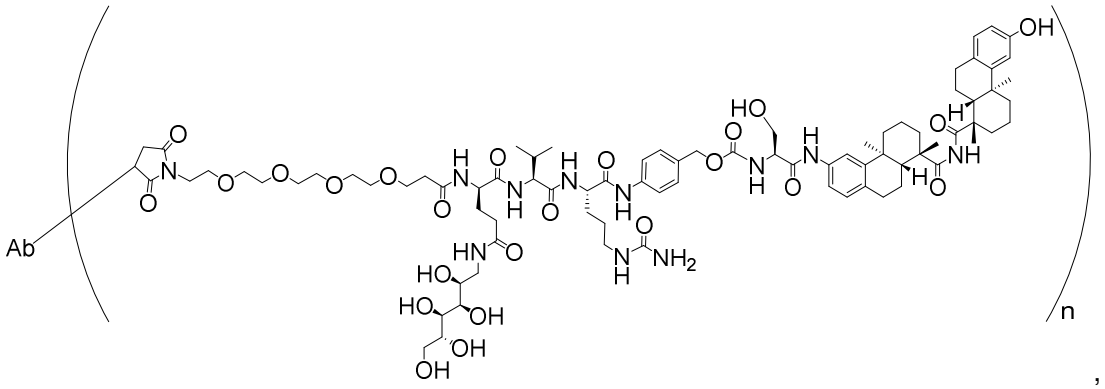
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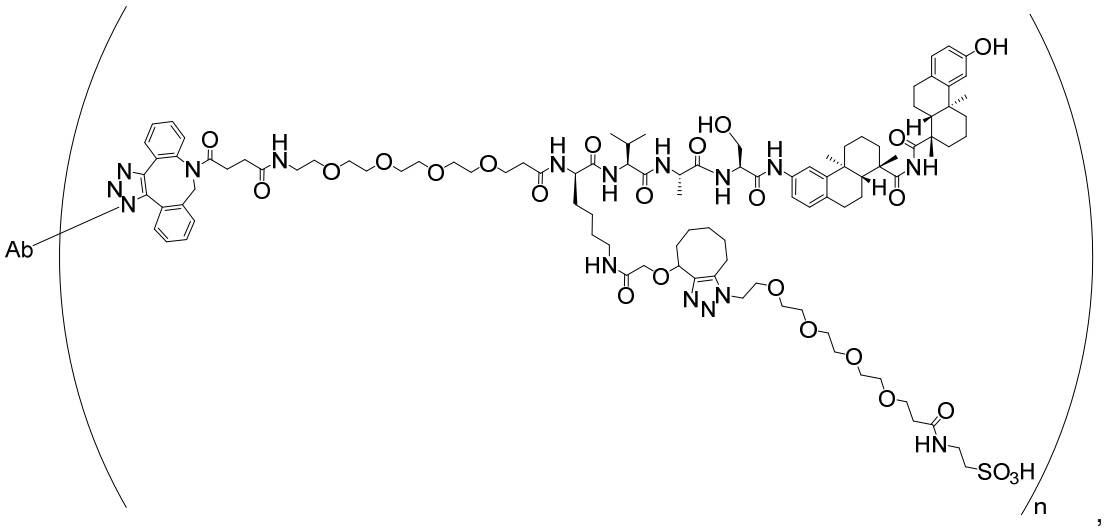
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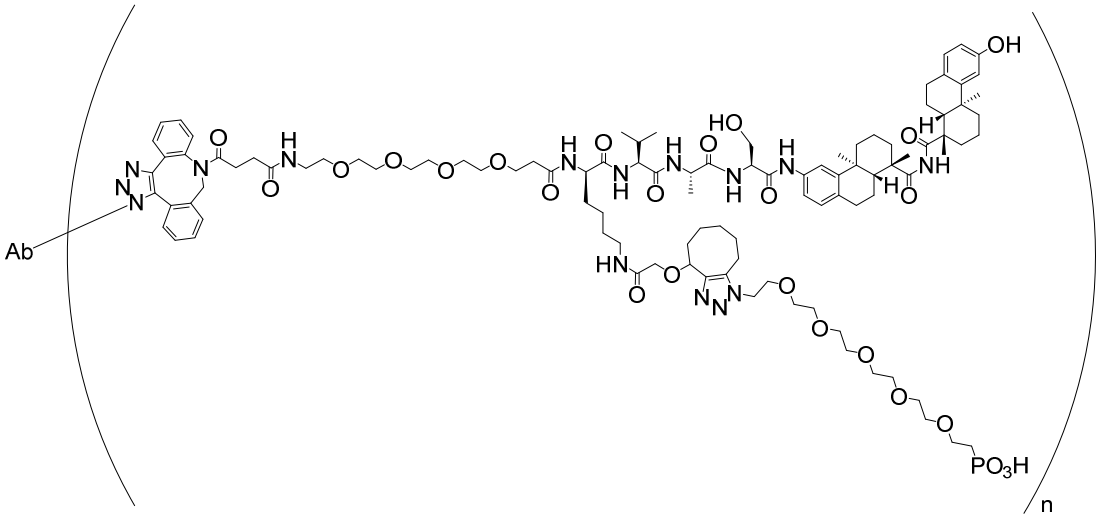


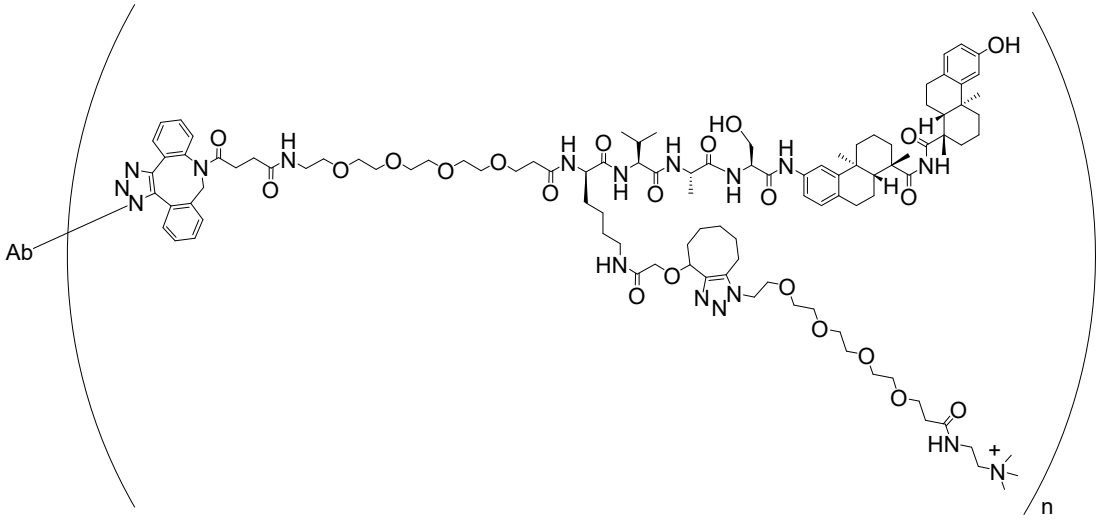
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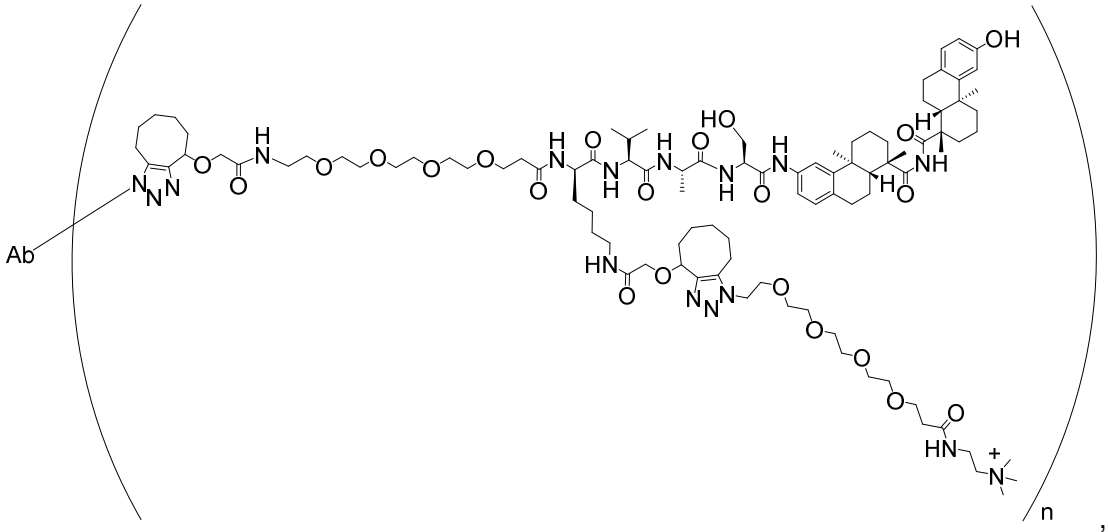


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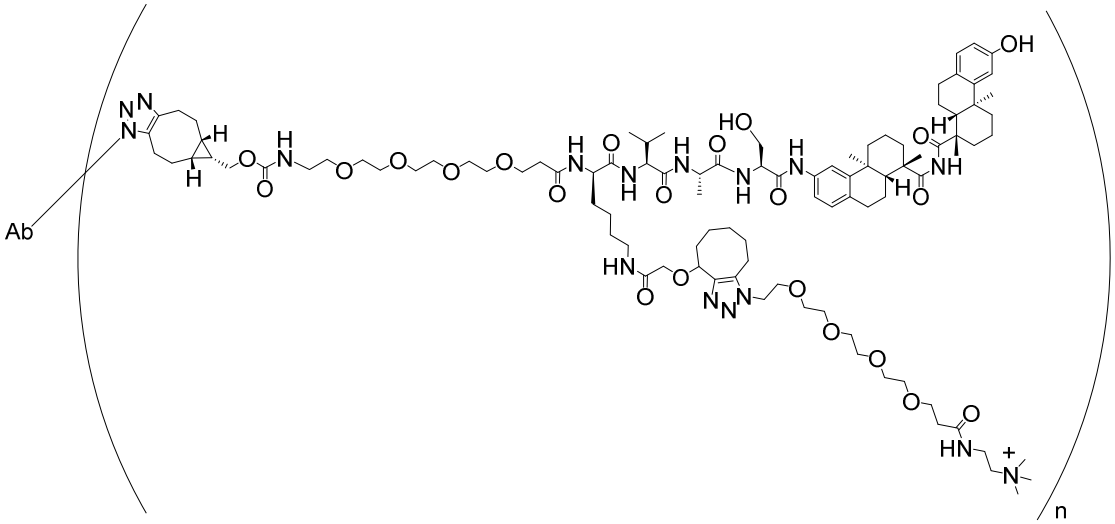

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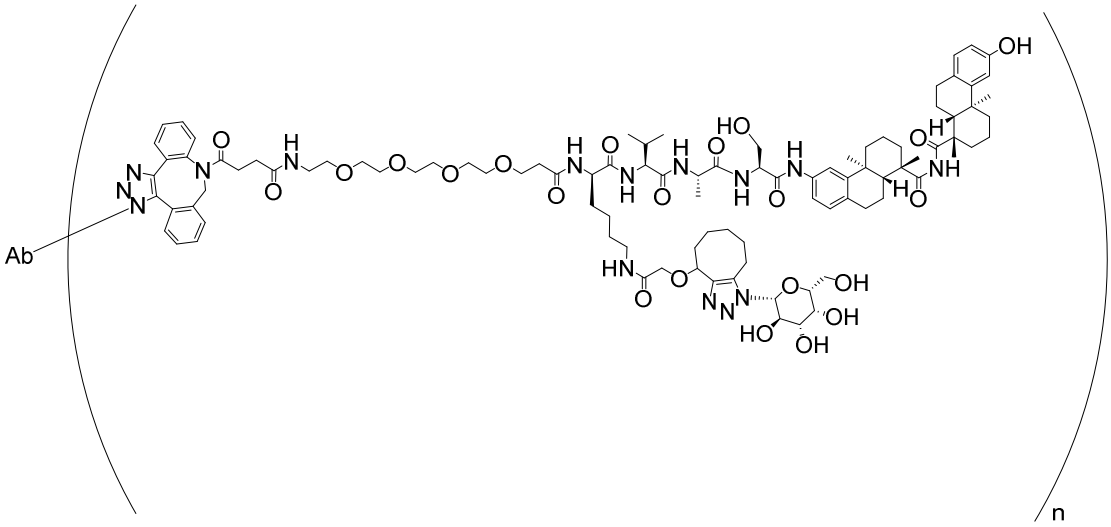

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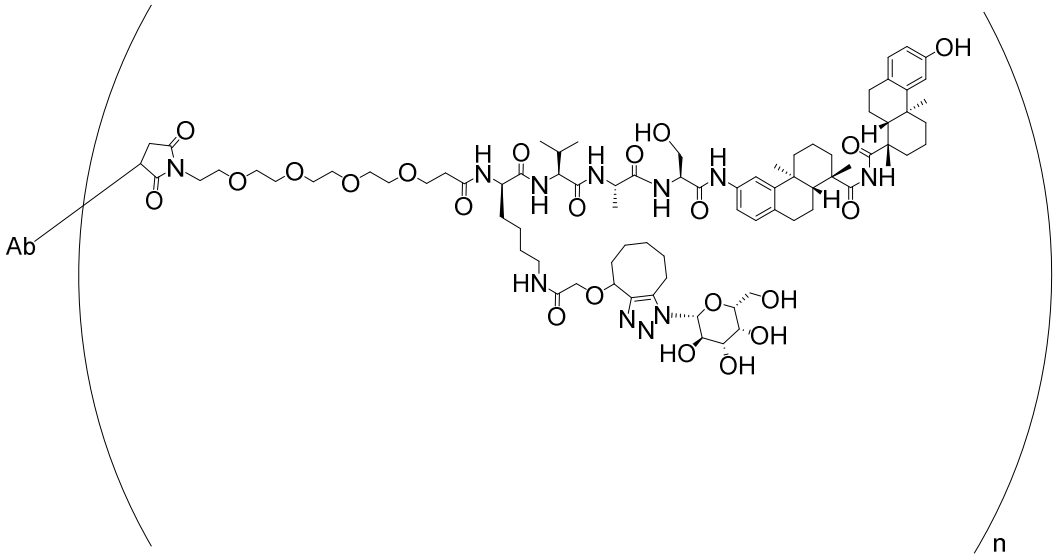
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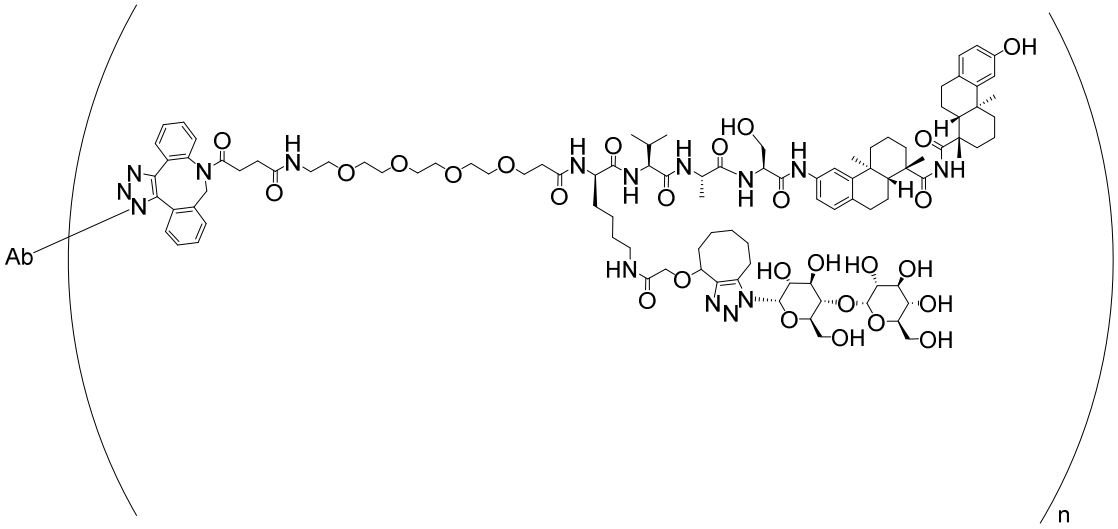
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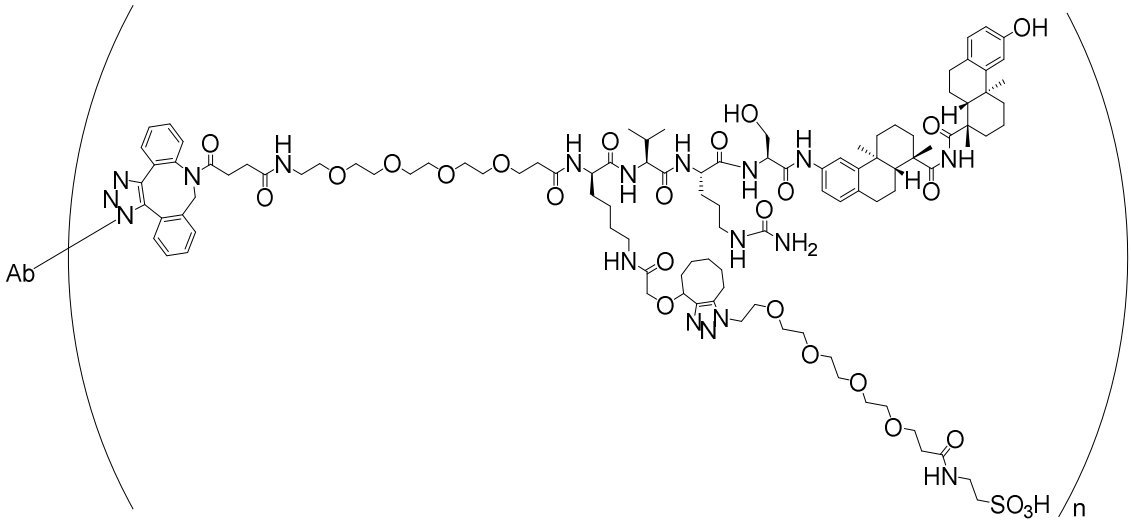
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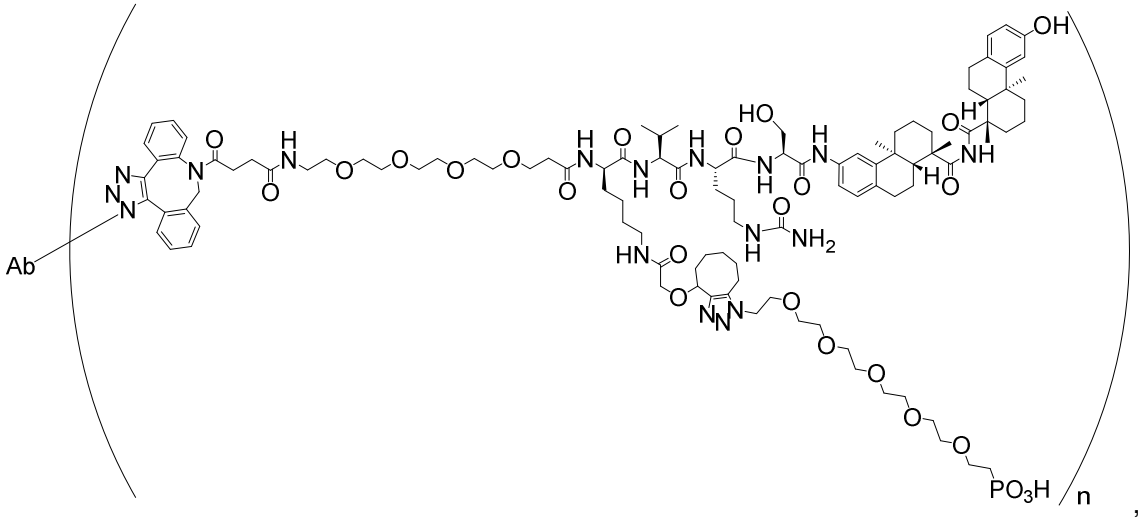
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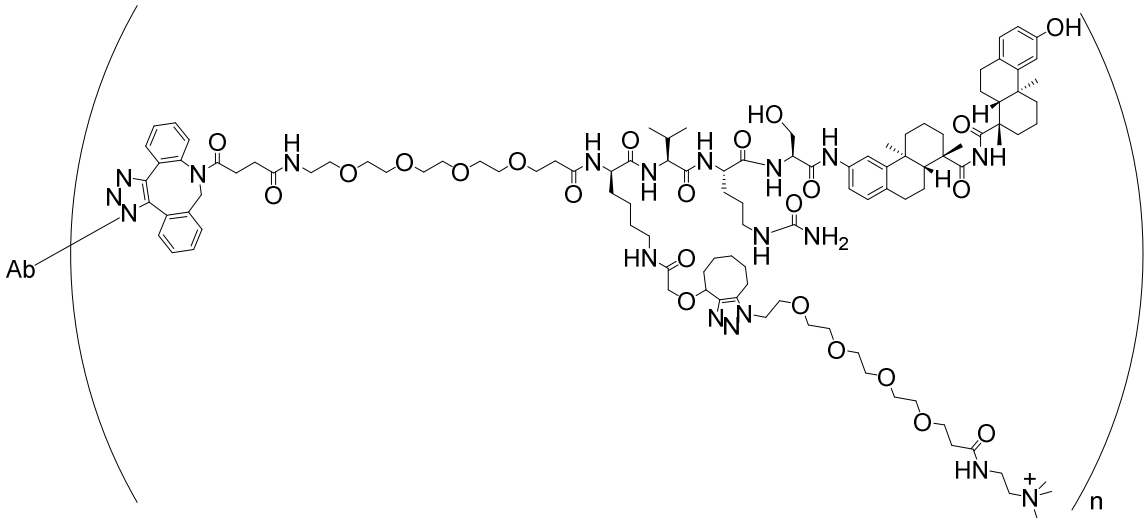
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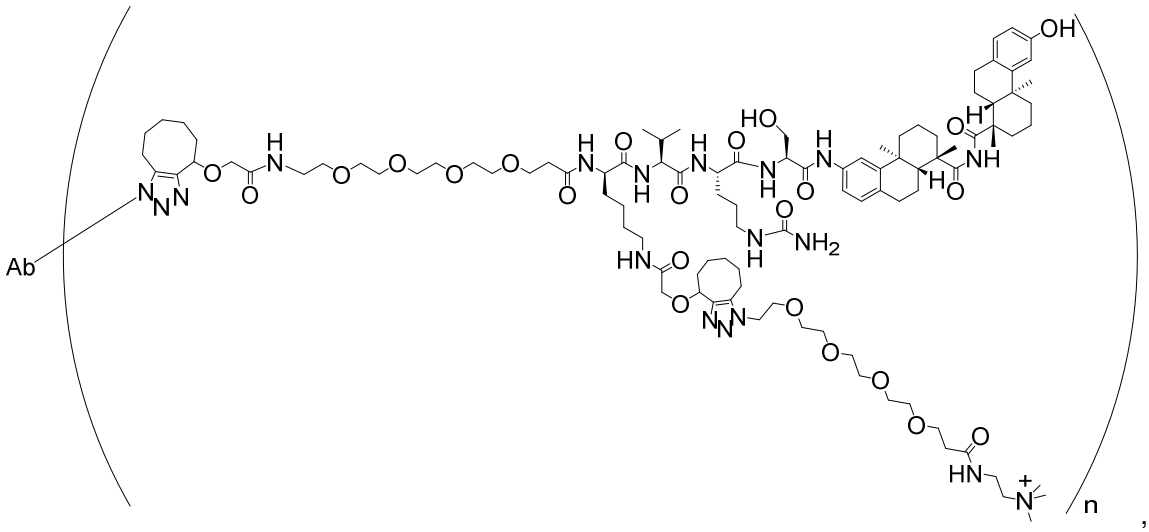
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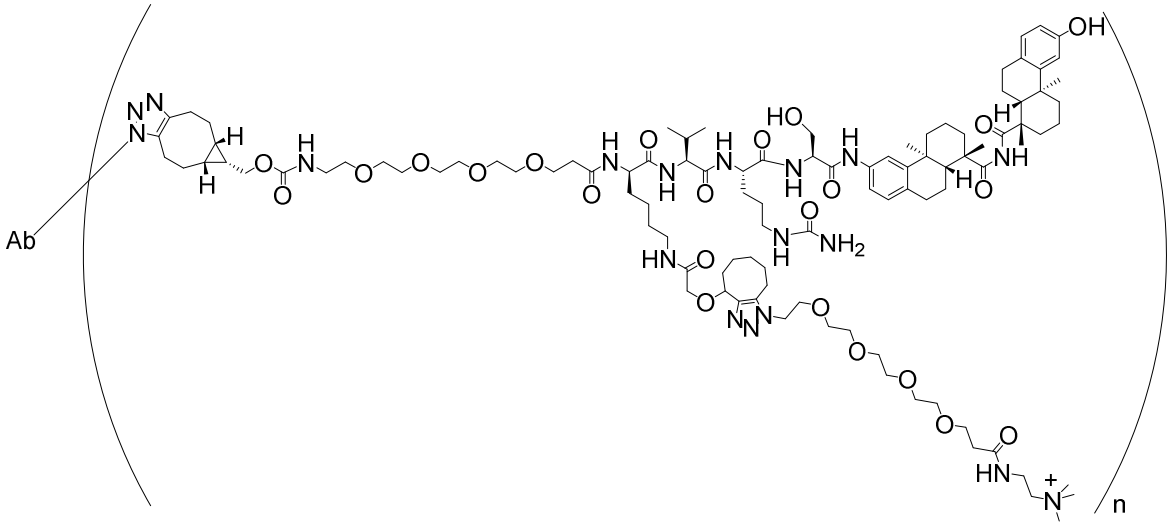
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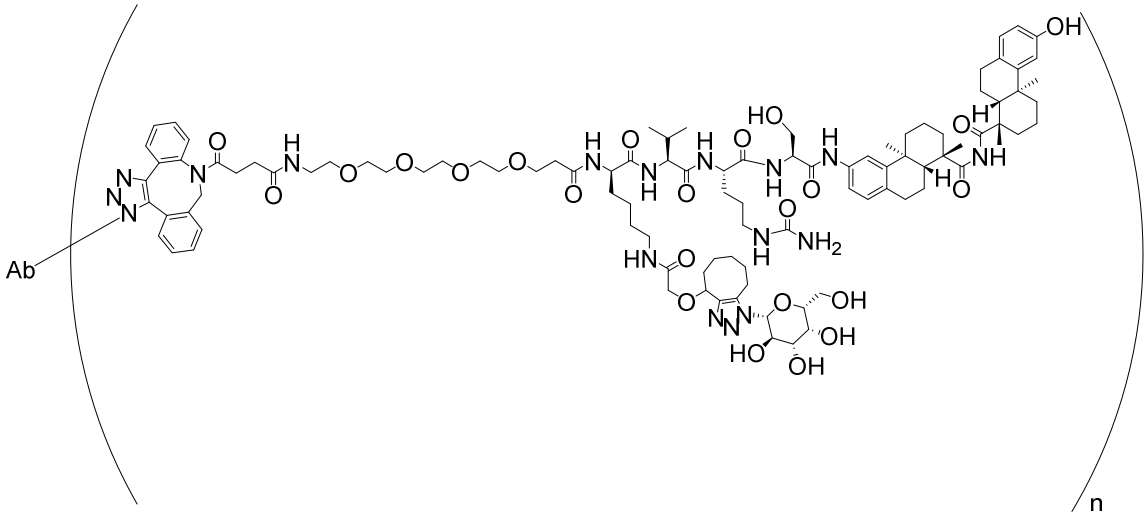
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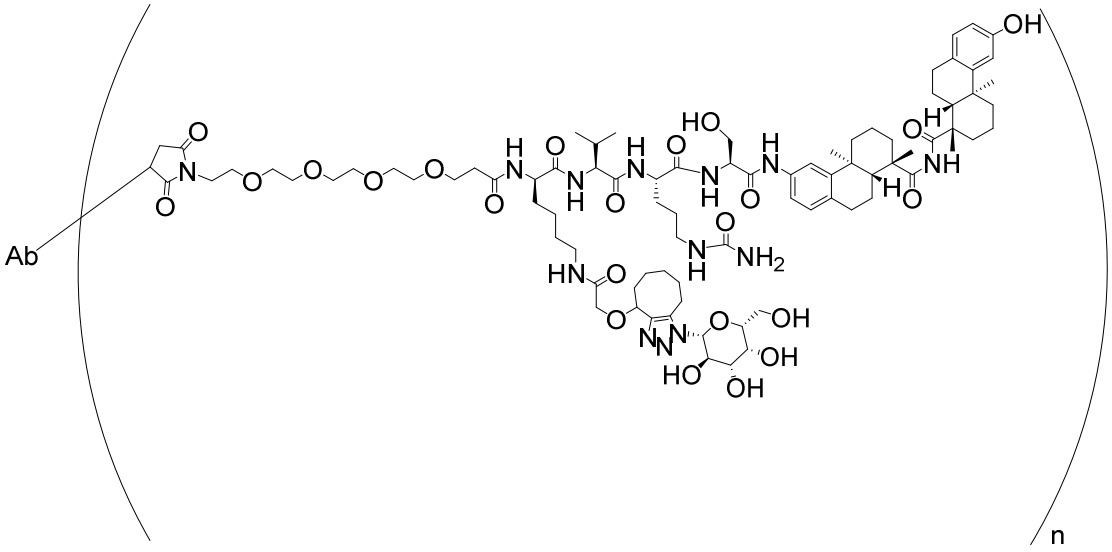
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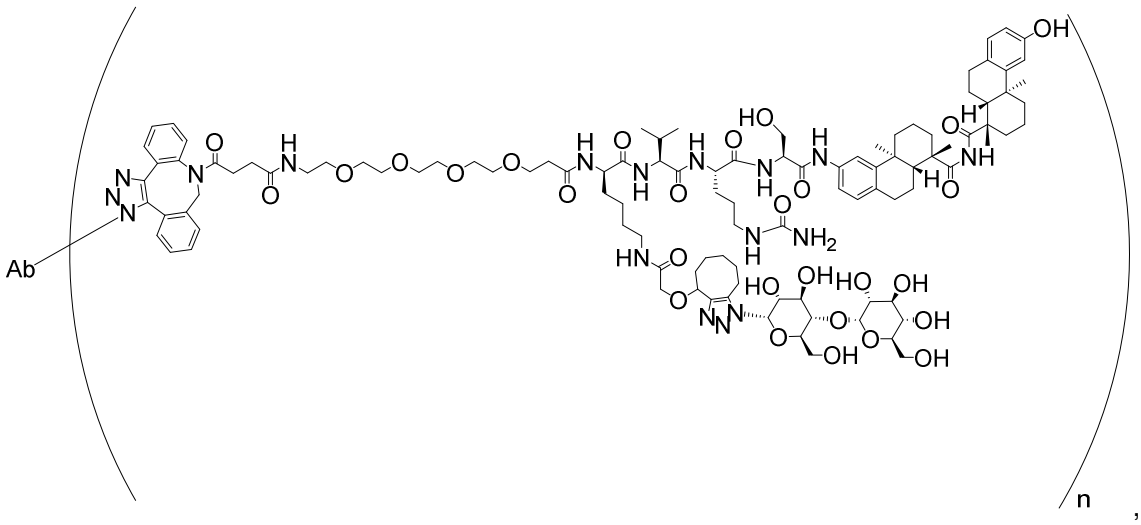


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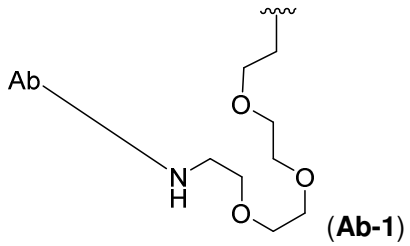
and



or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

each **Ab** is an antibody, or an antigen-binding fragment thereof; and
subscript **n** is an integer from 1 to 30.

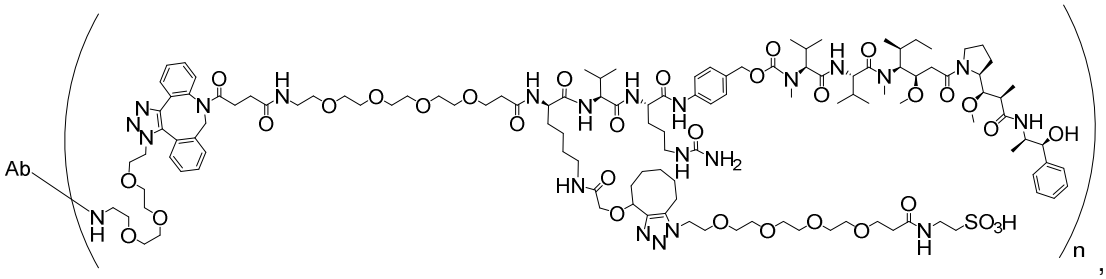
30. The compound of any one of claims 1-29, wherein **BA** is a modified antibody of formula (**Ab-1**)

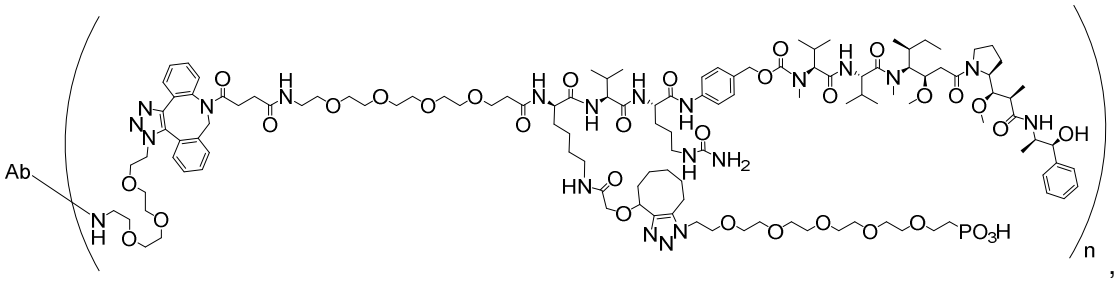


(**Ab-1**)

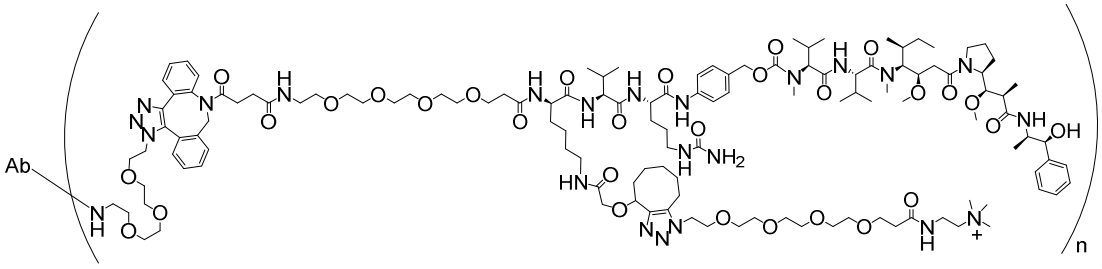
wherein the  indicates the atom through which **Ab-1** is bonded to the adjacent groups in the formula.

31. The compound of any one of claims 1-29, selected from the group consisting of:

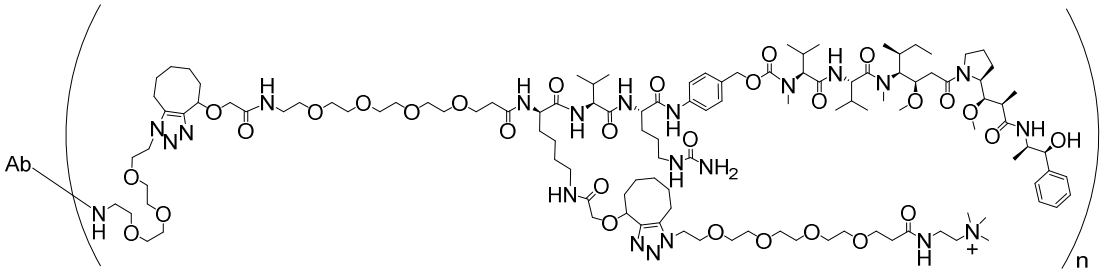



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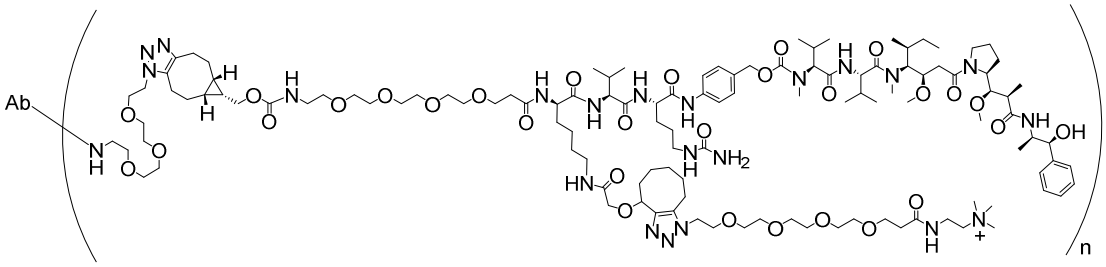
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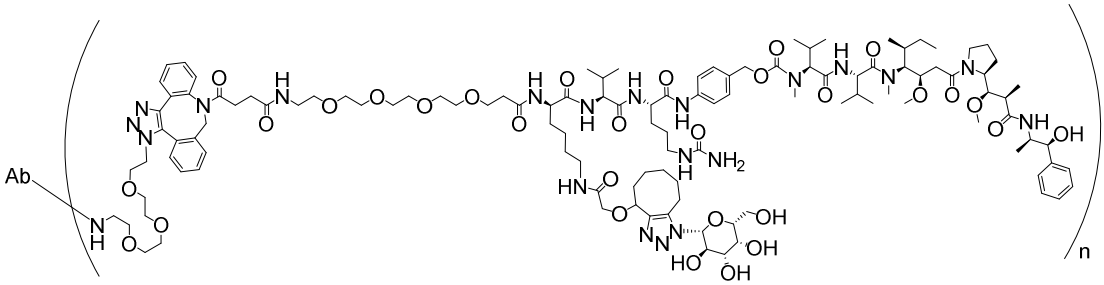
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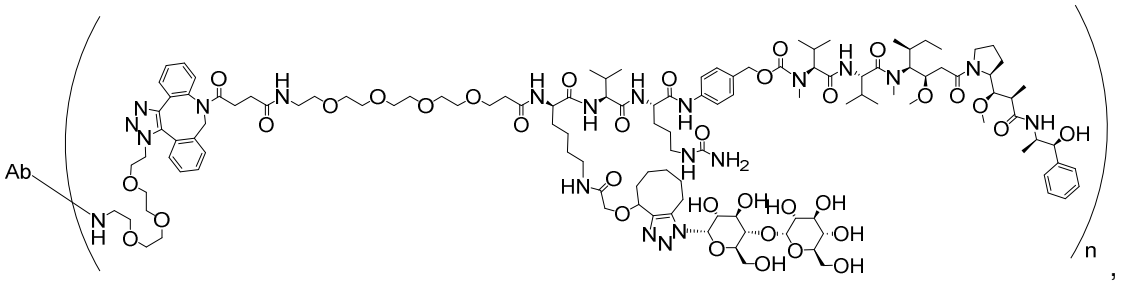
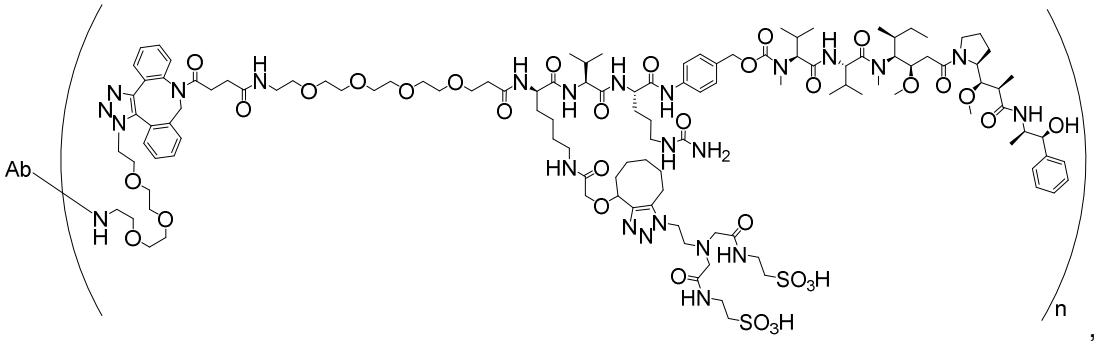
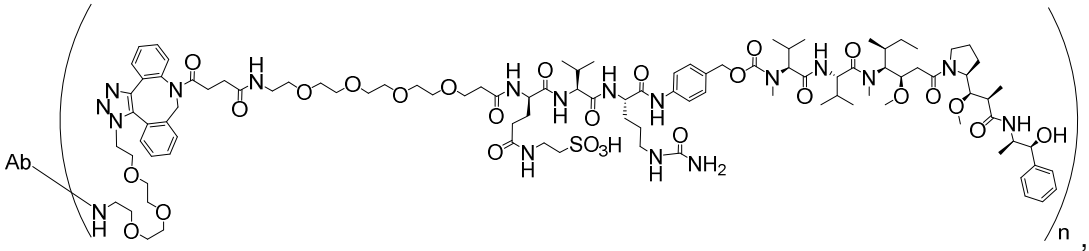
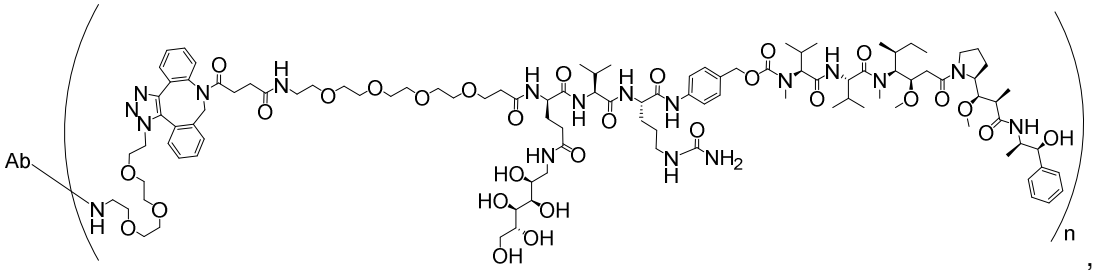
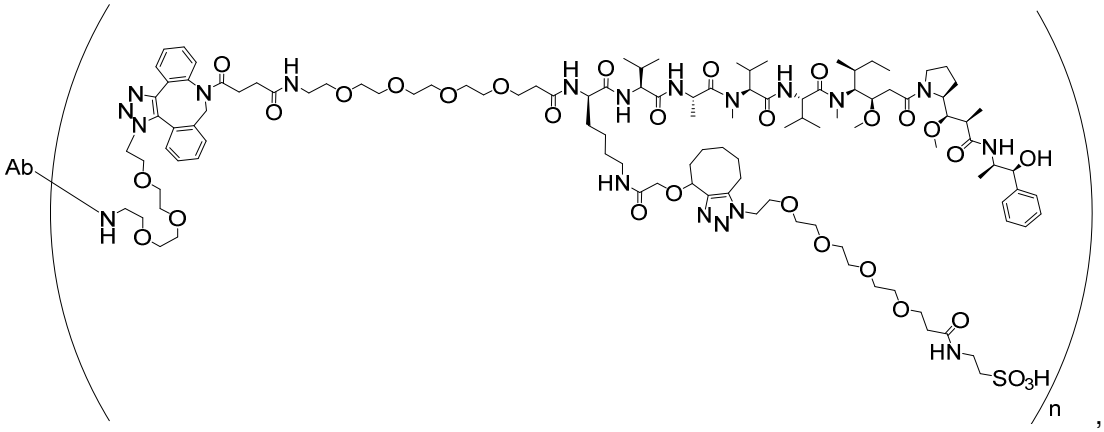
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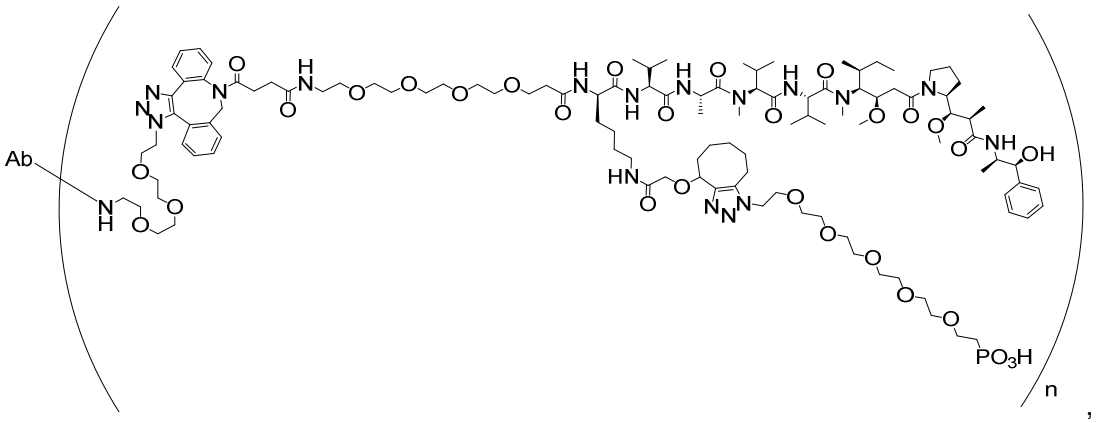

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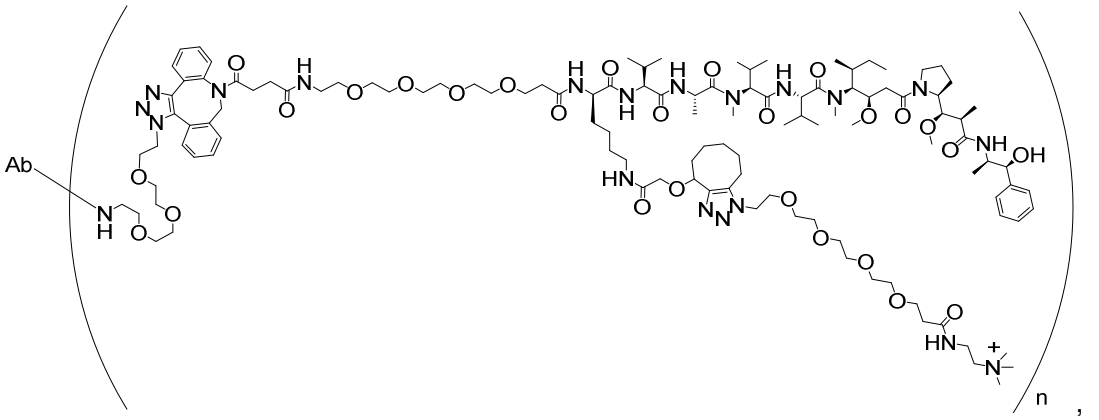

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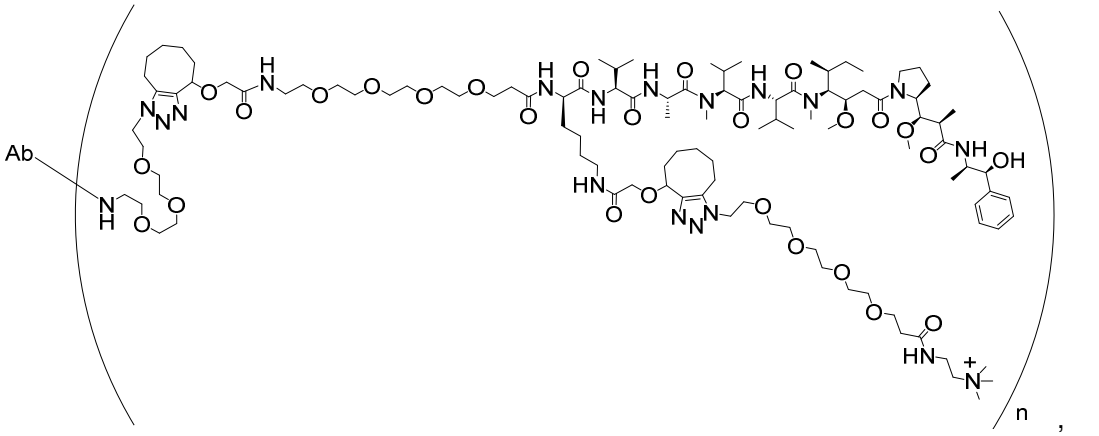

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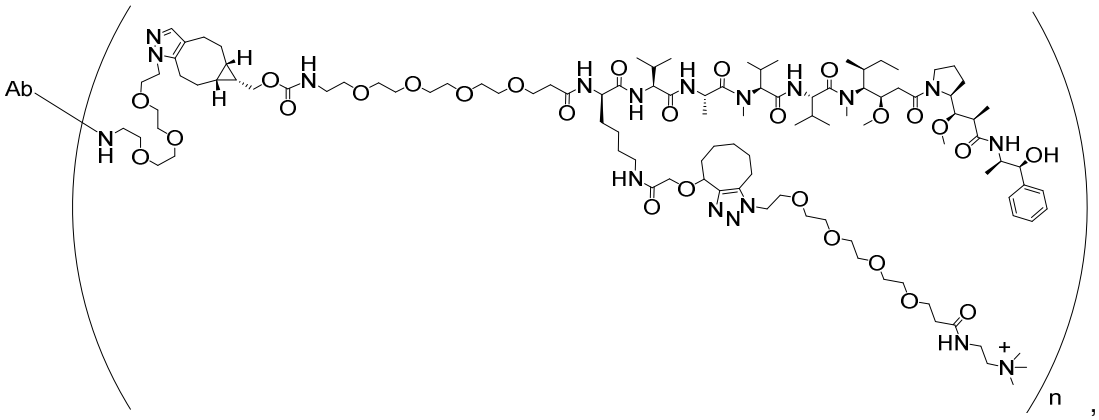
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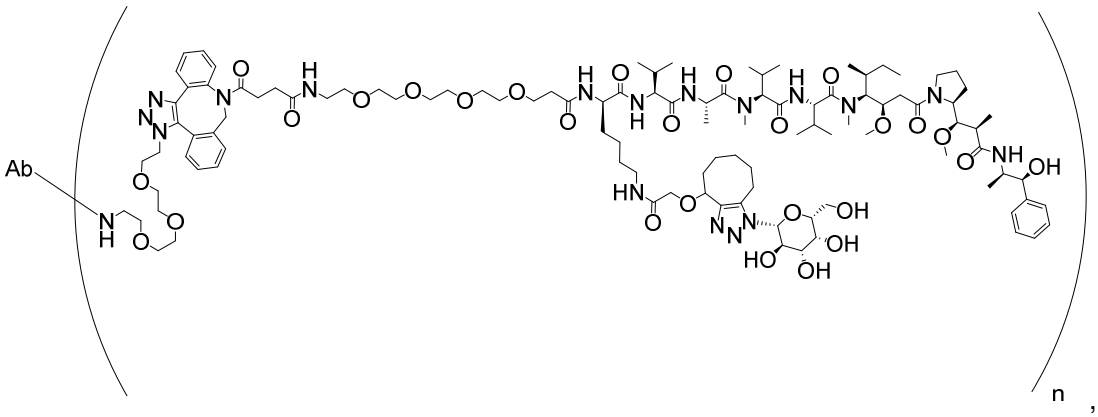
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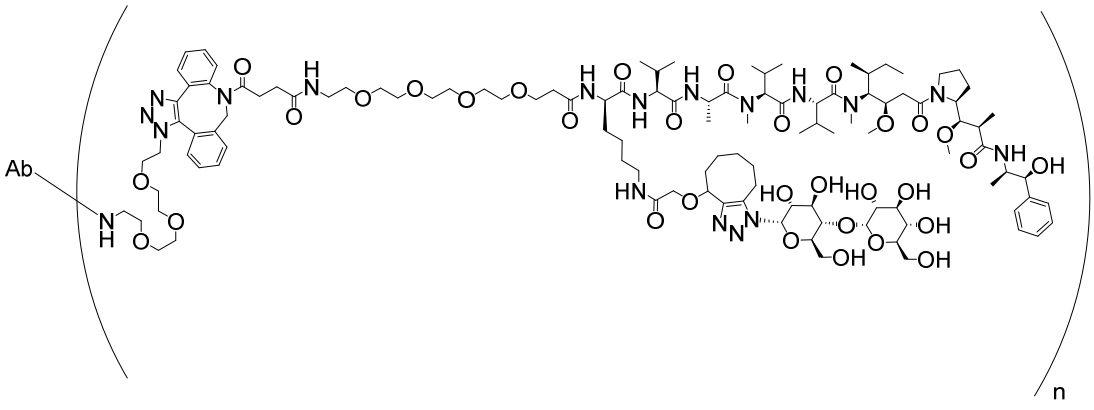
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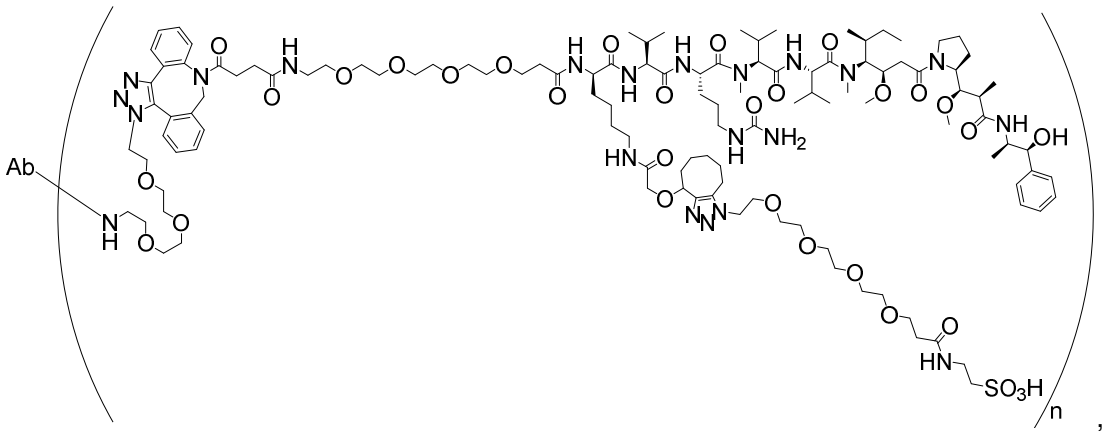
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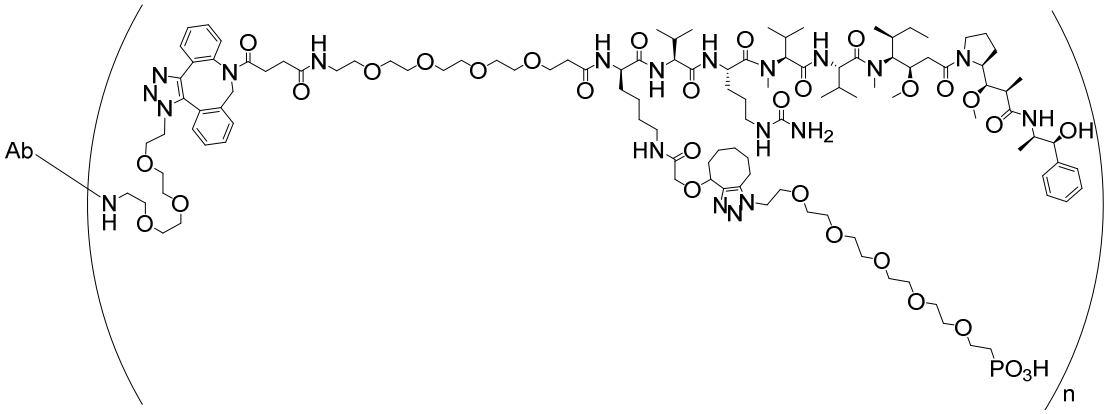
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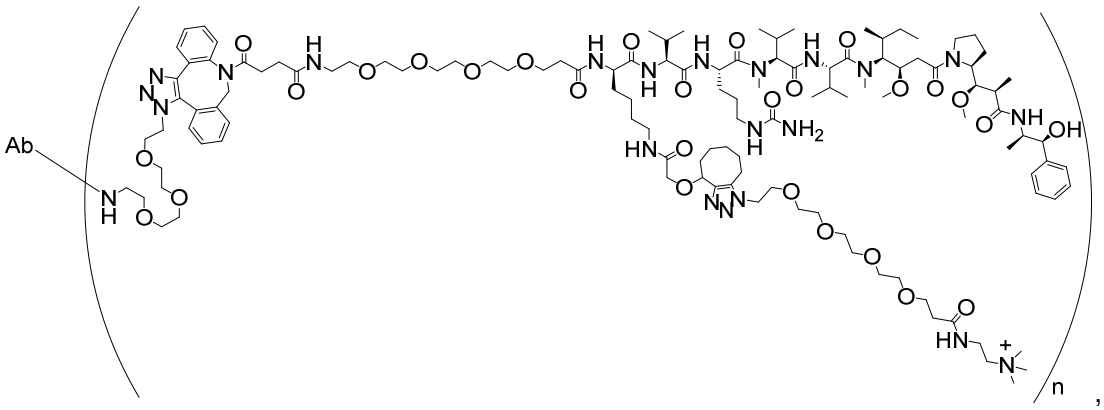
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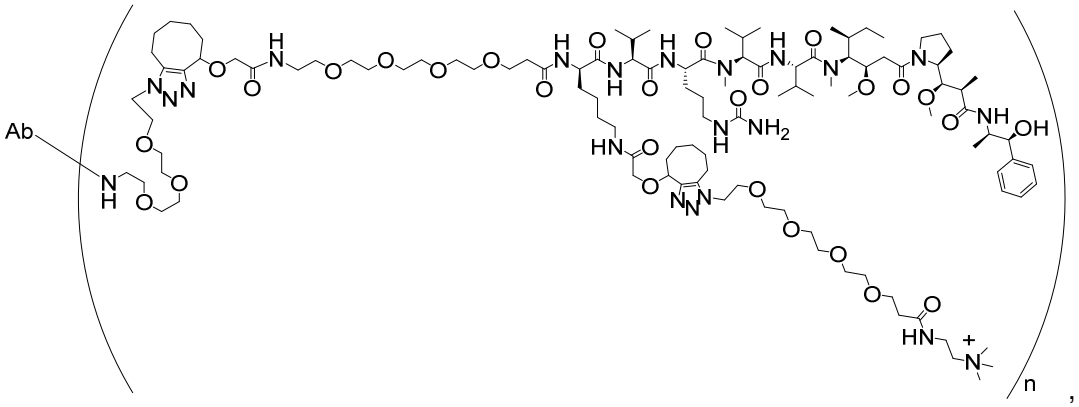

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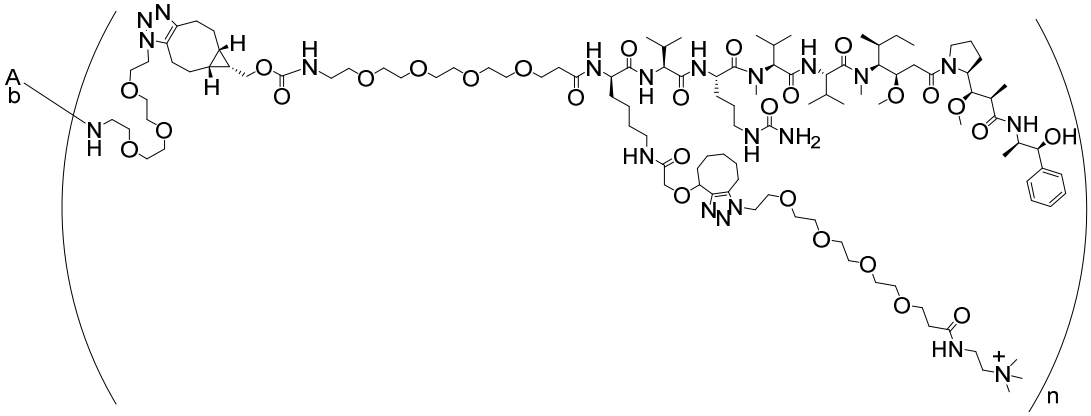
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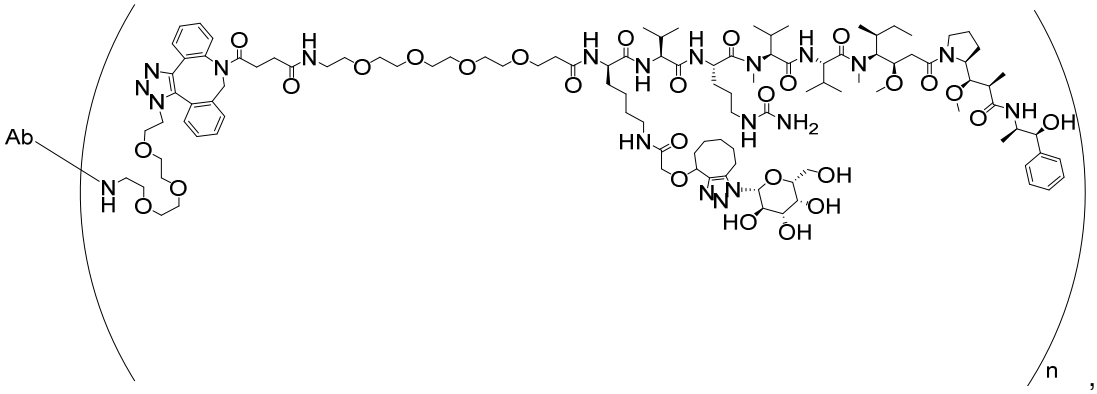

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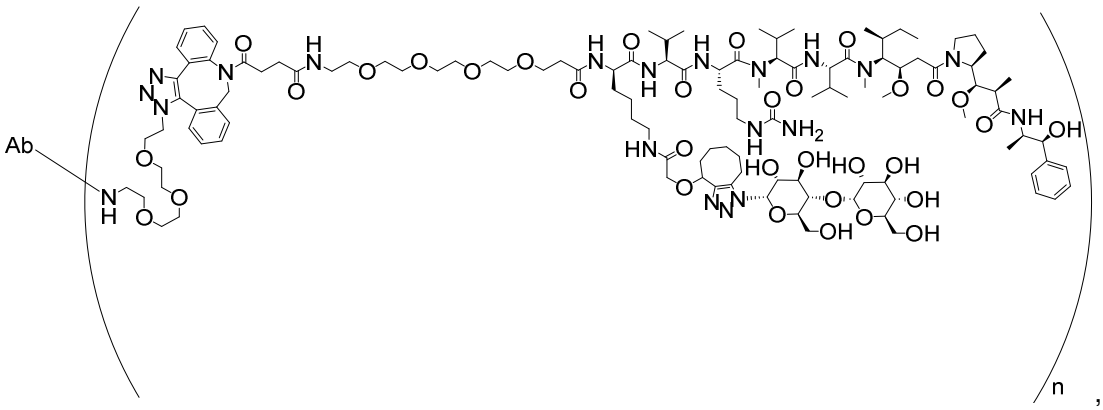
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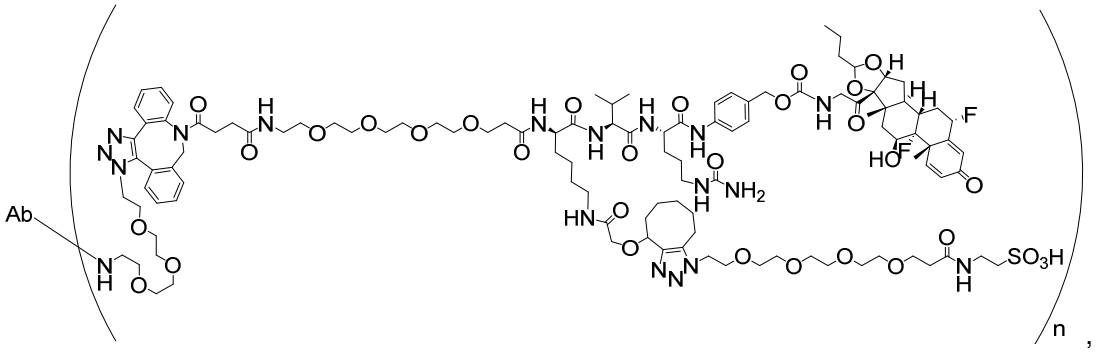




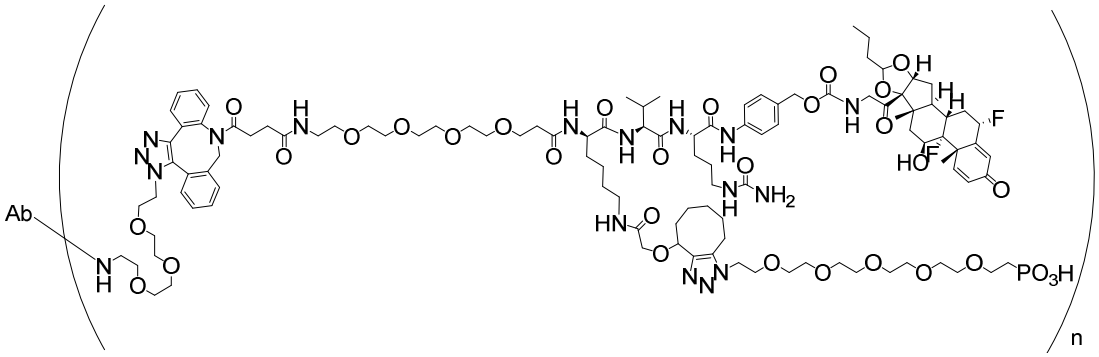



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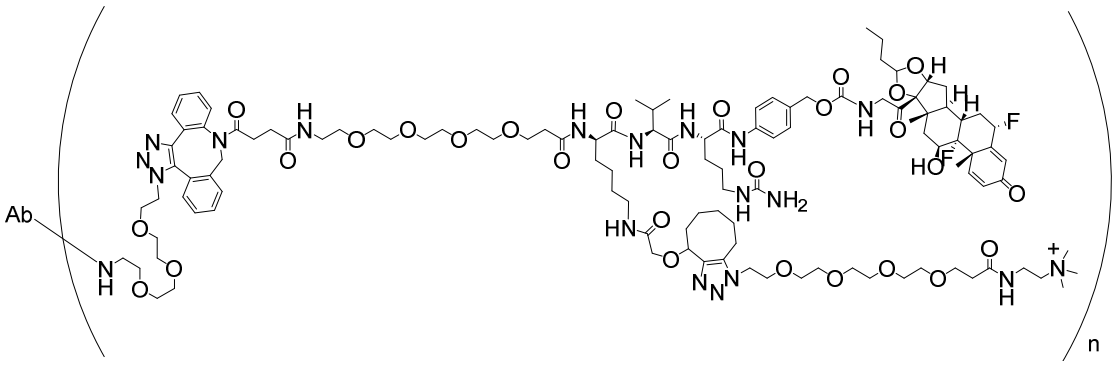
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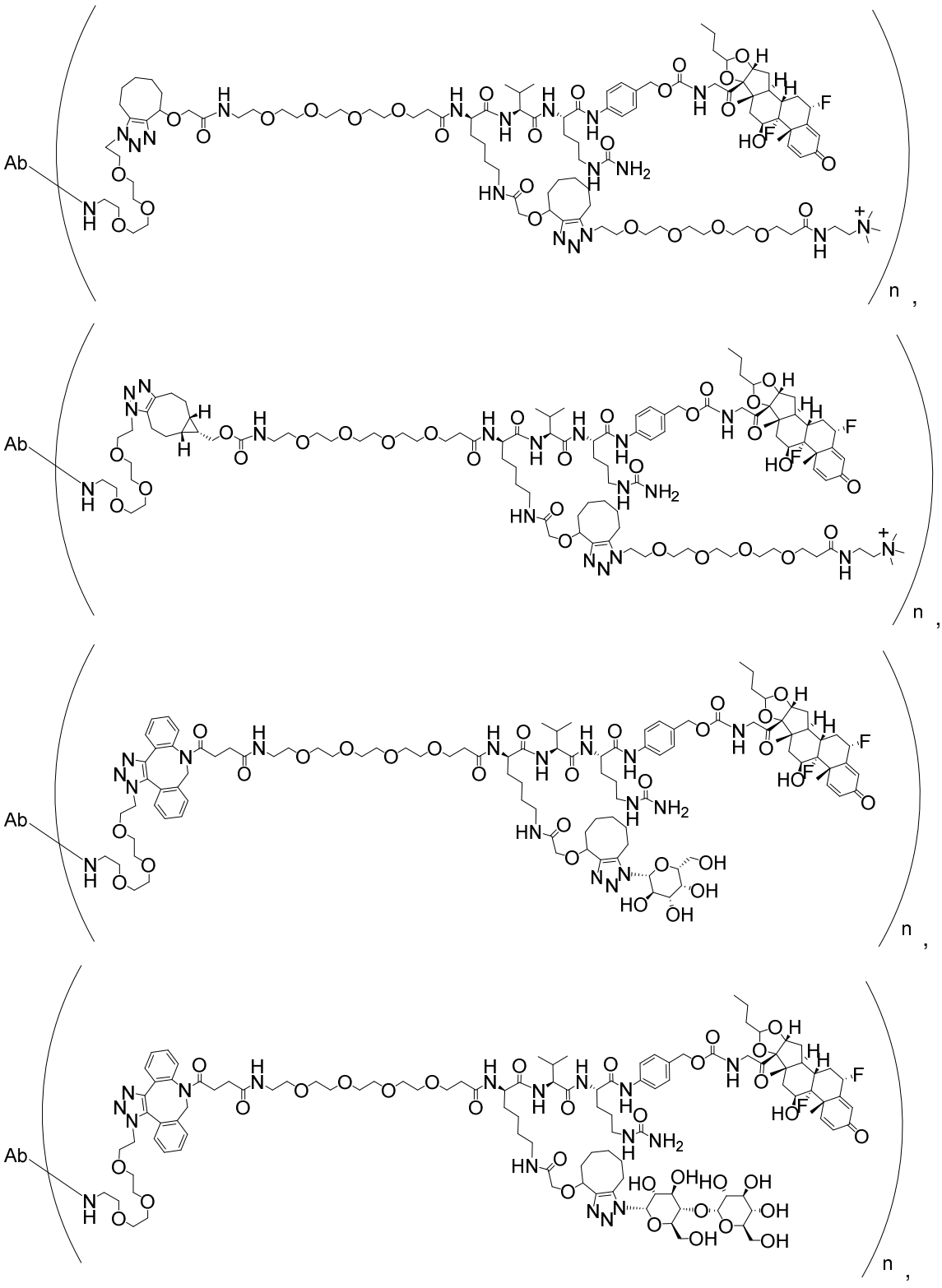
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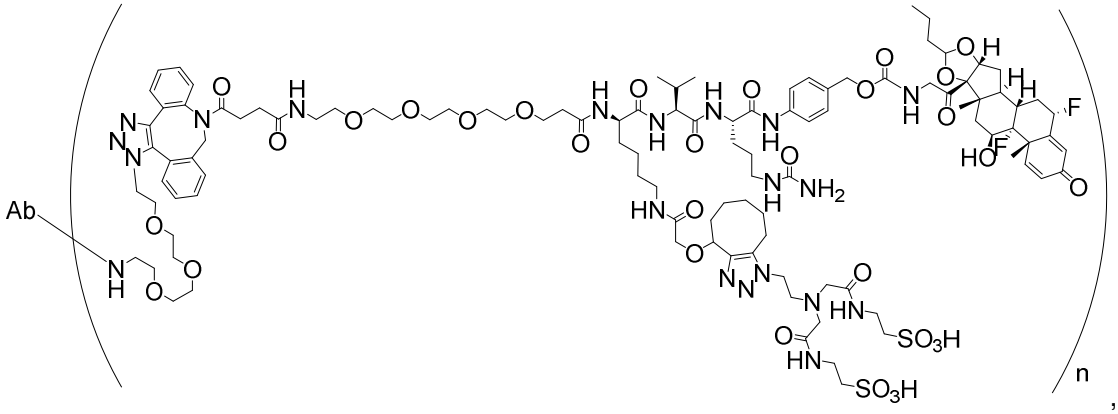

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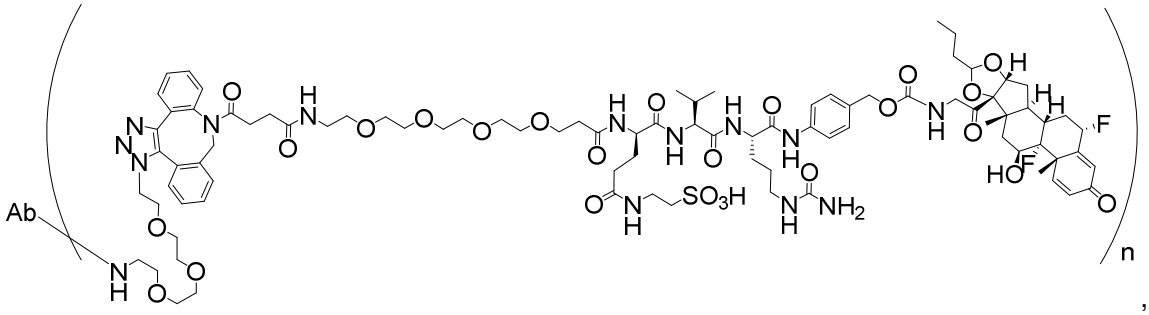

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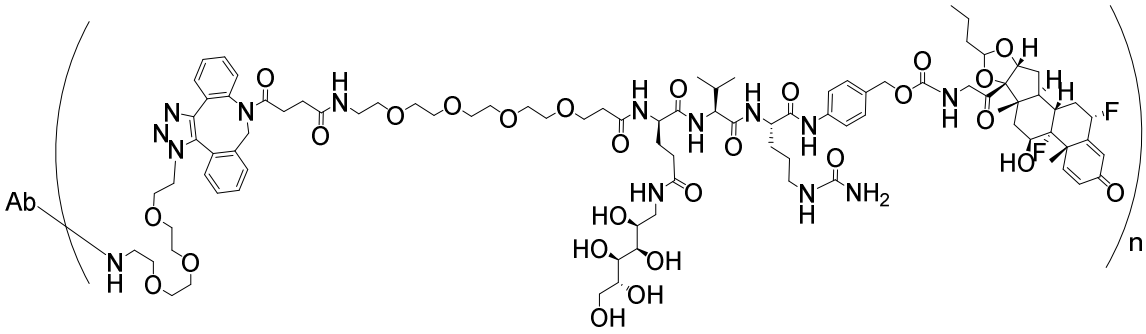



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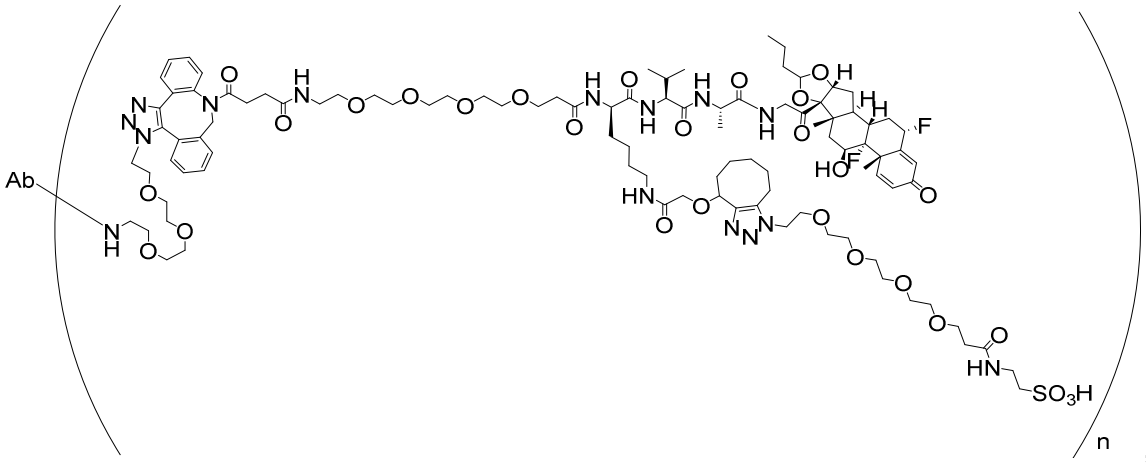
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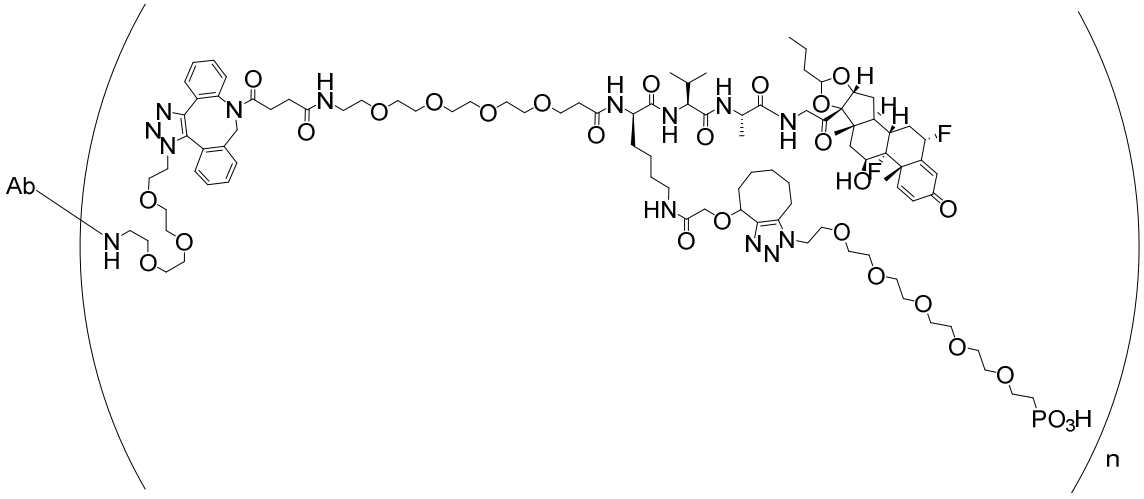
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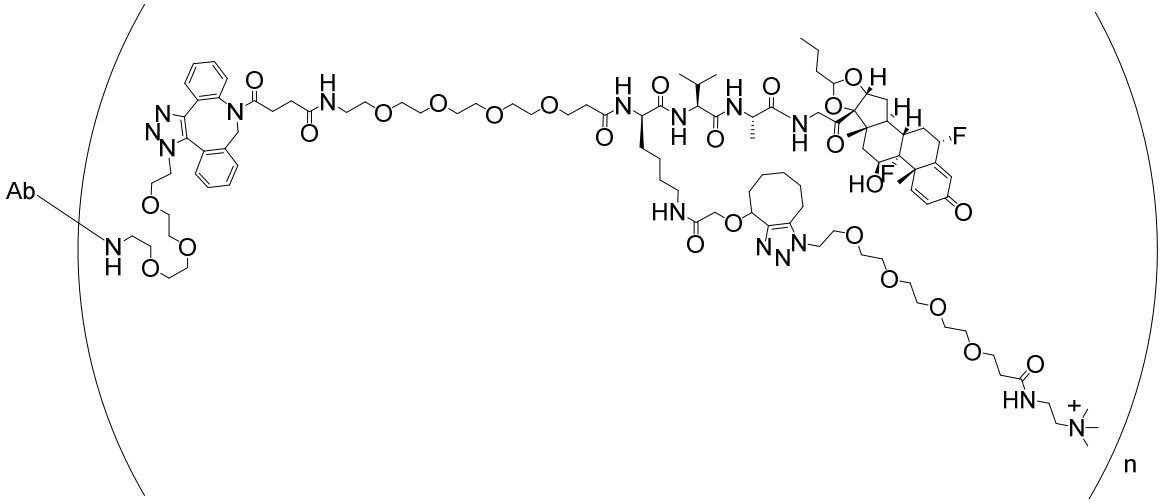
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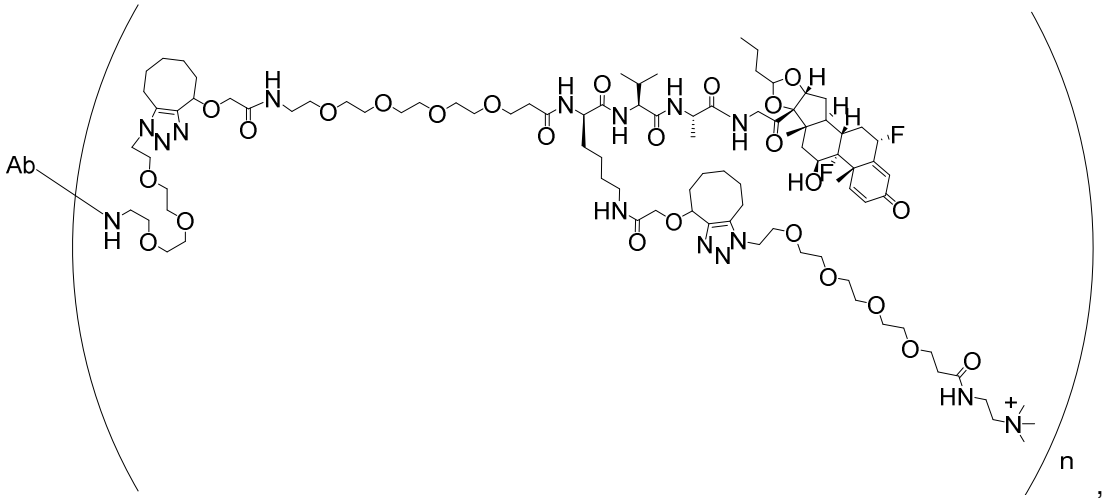
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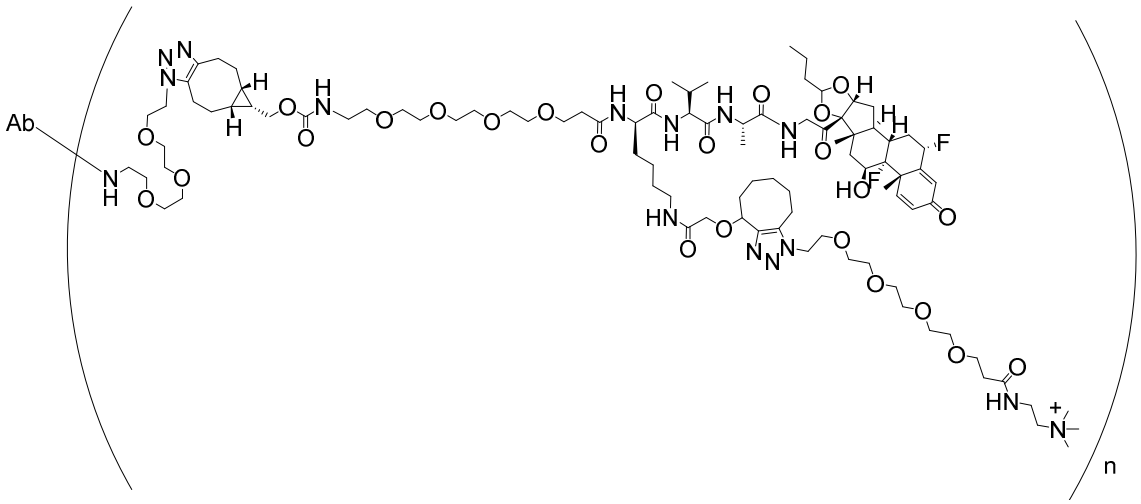
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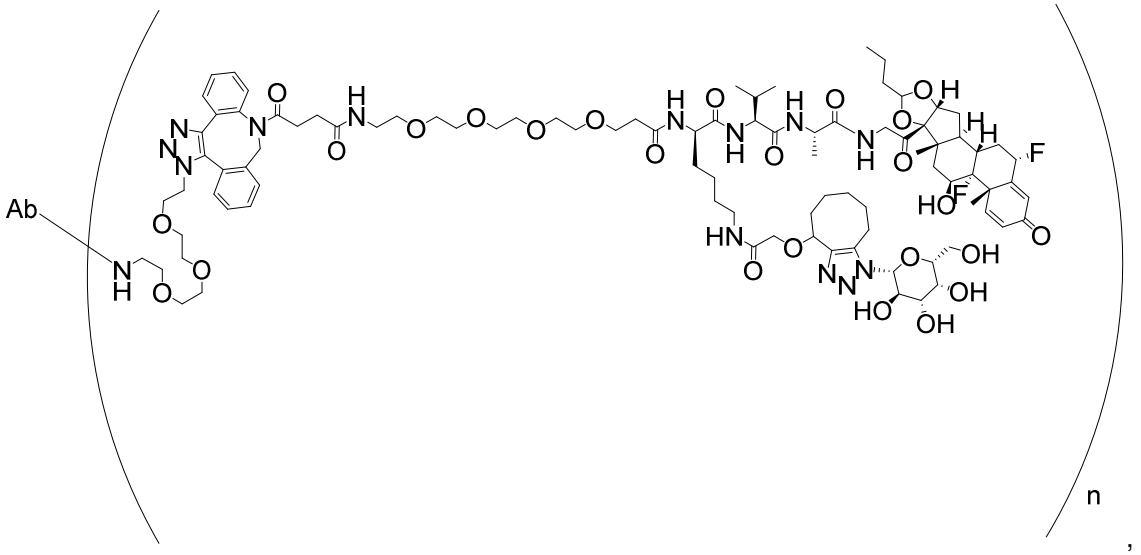
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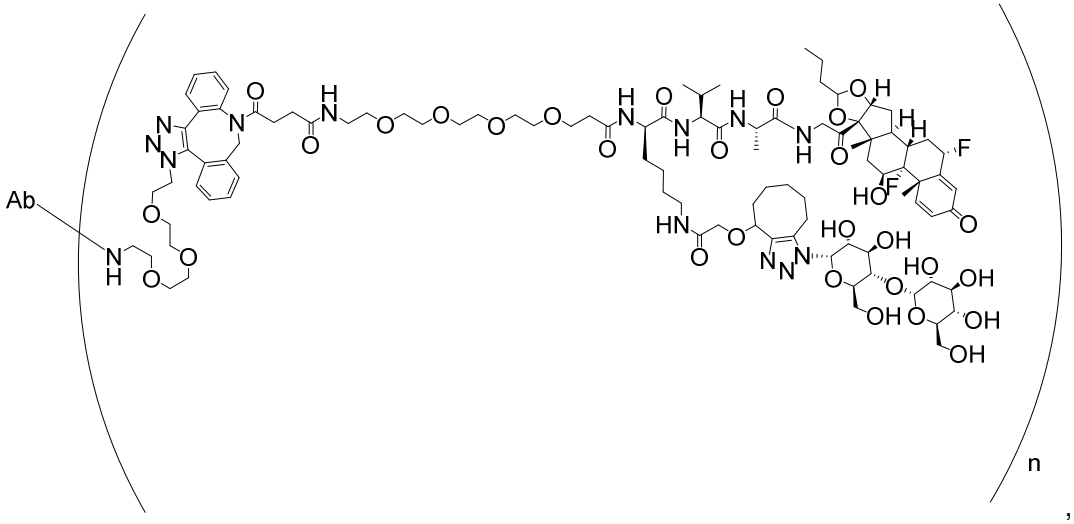
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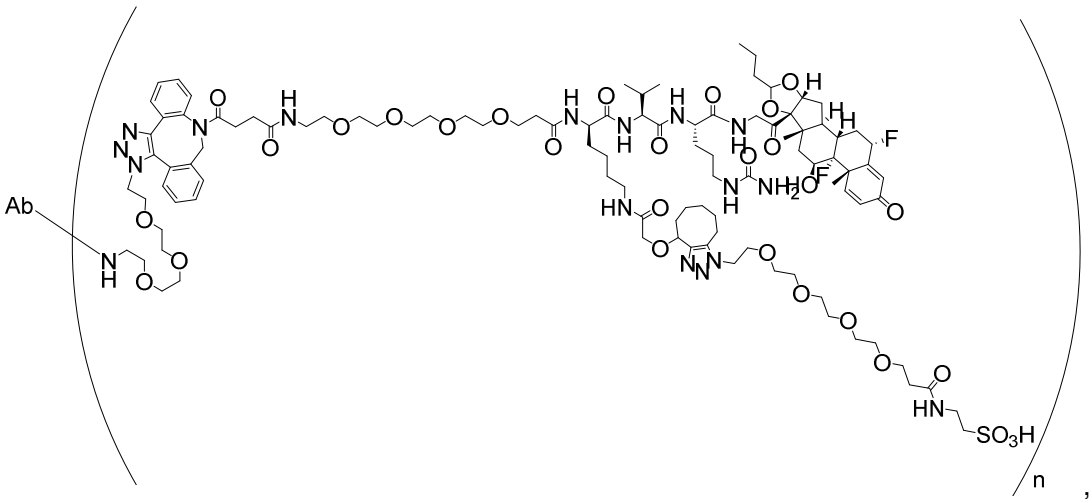
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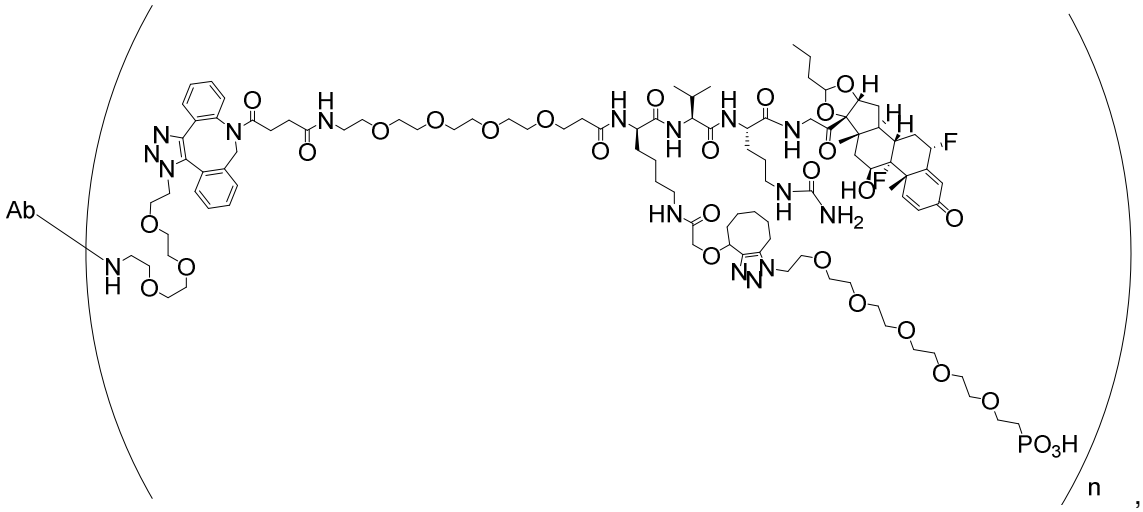


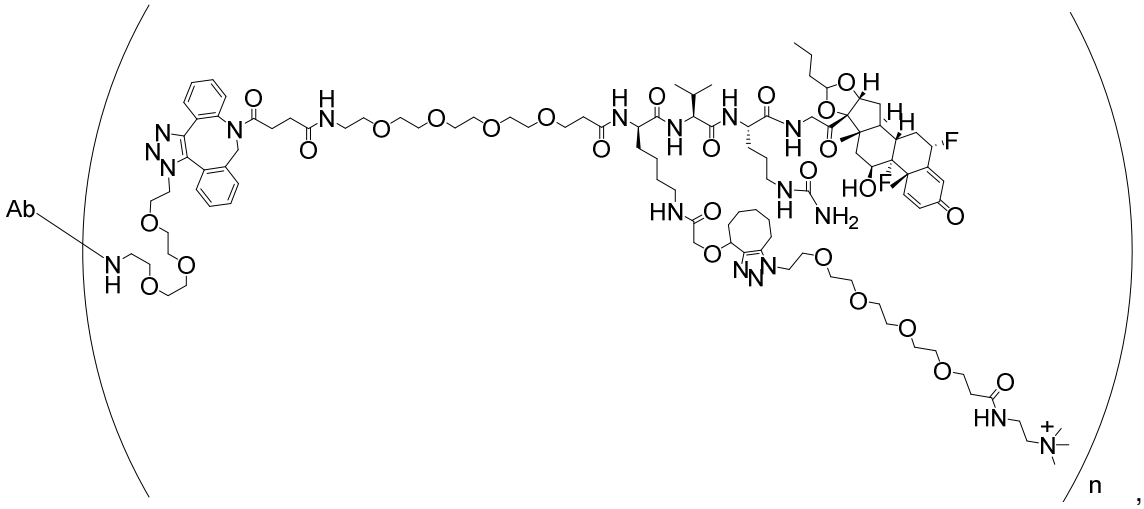
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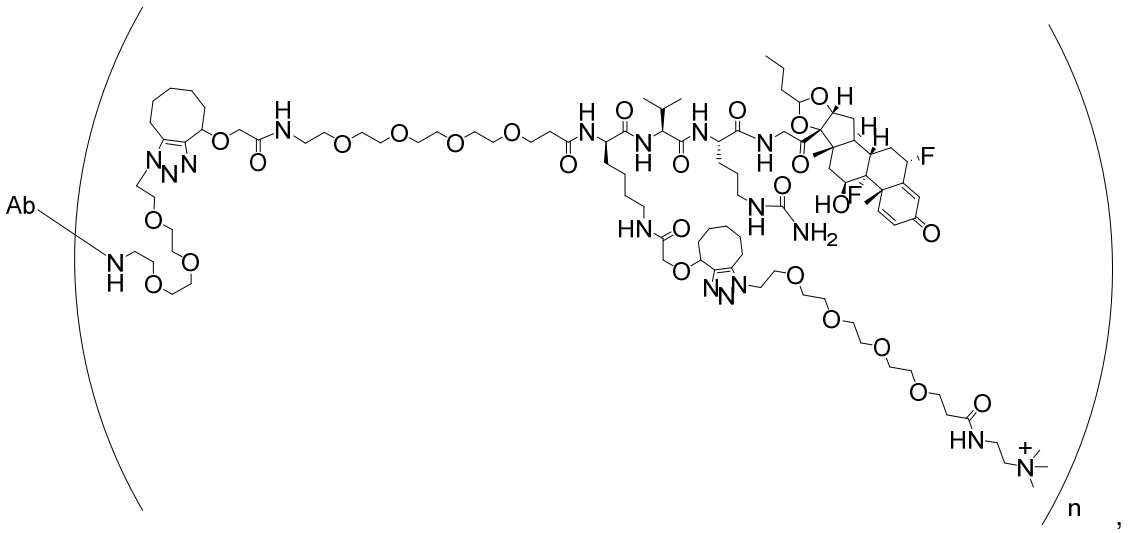


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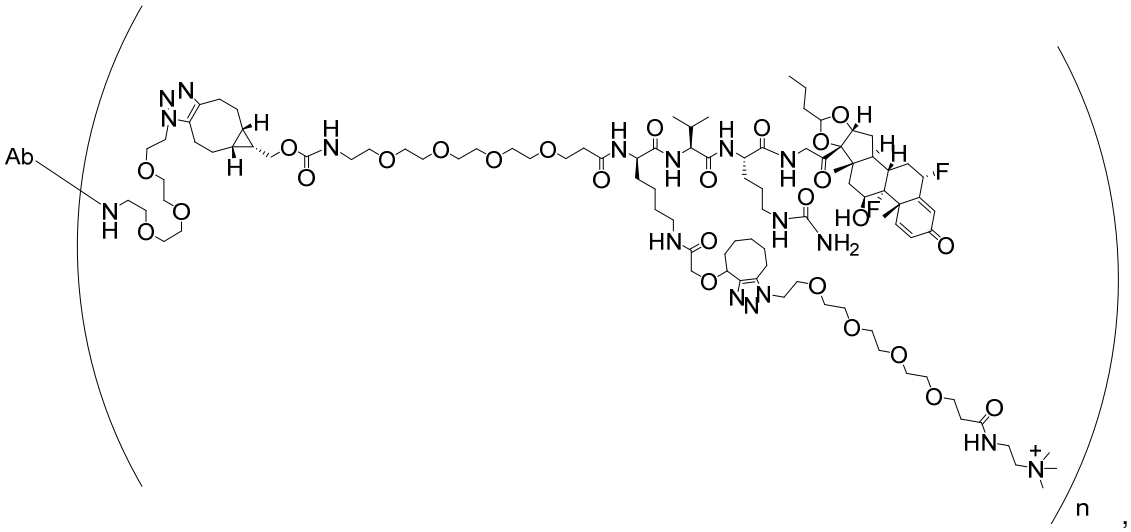




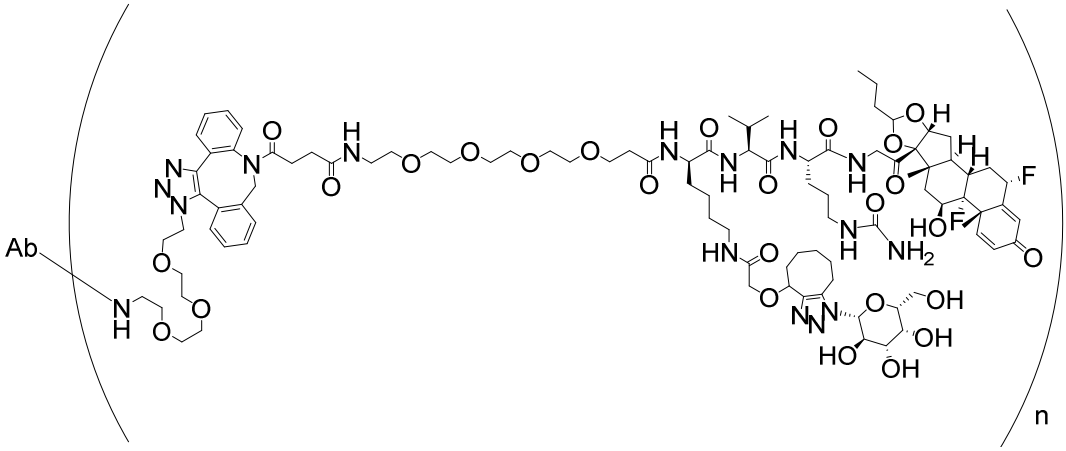



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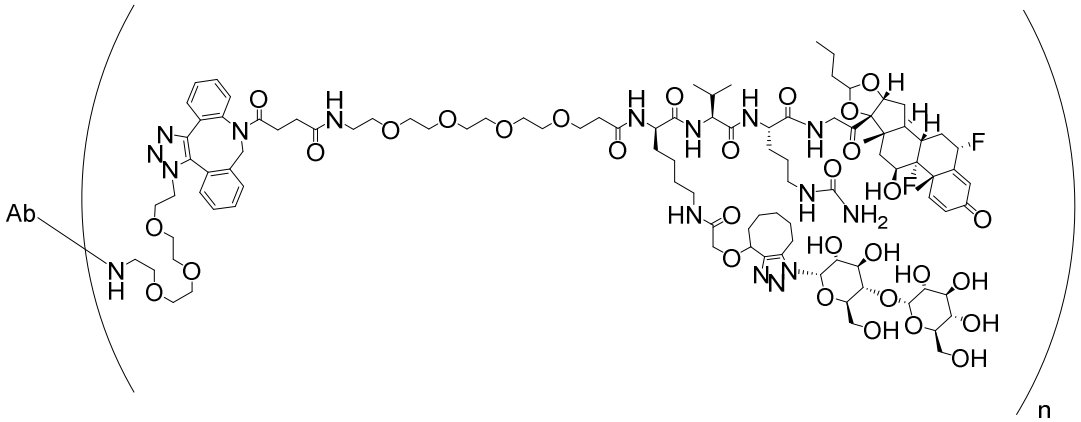
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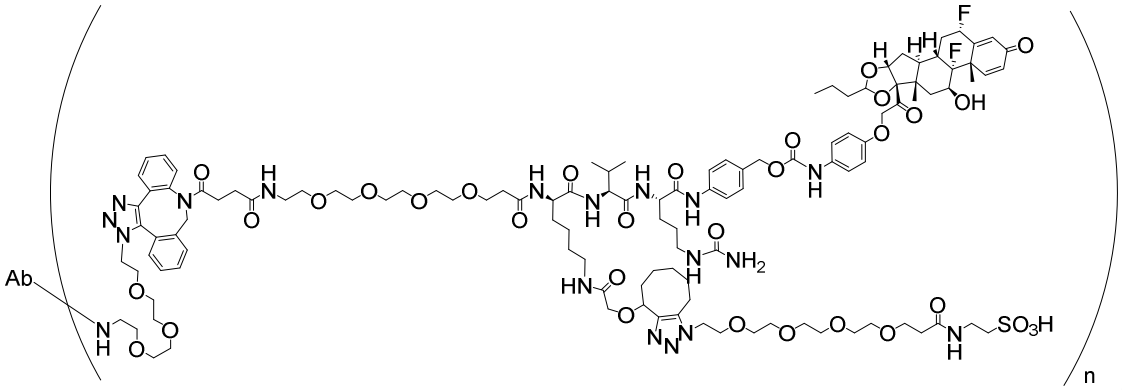
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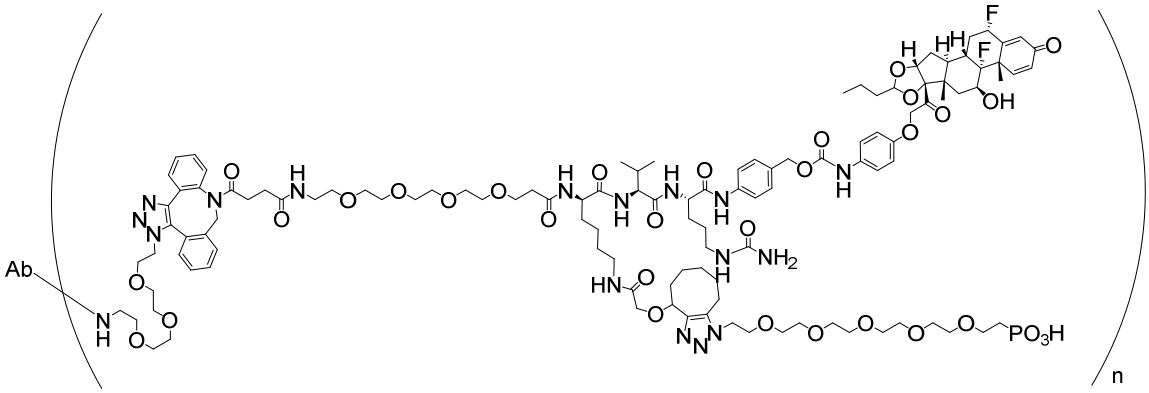
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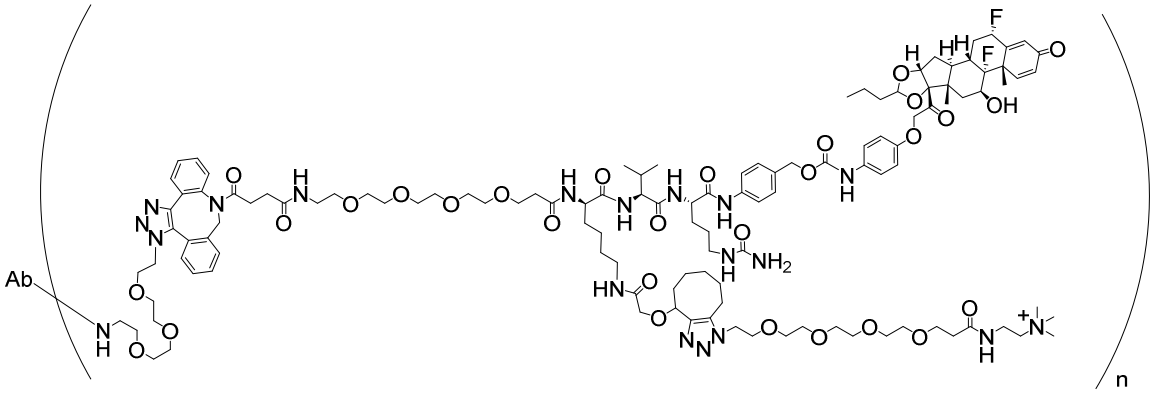
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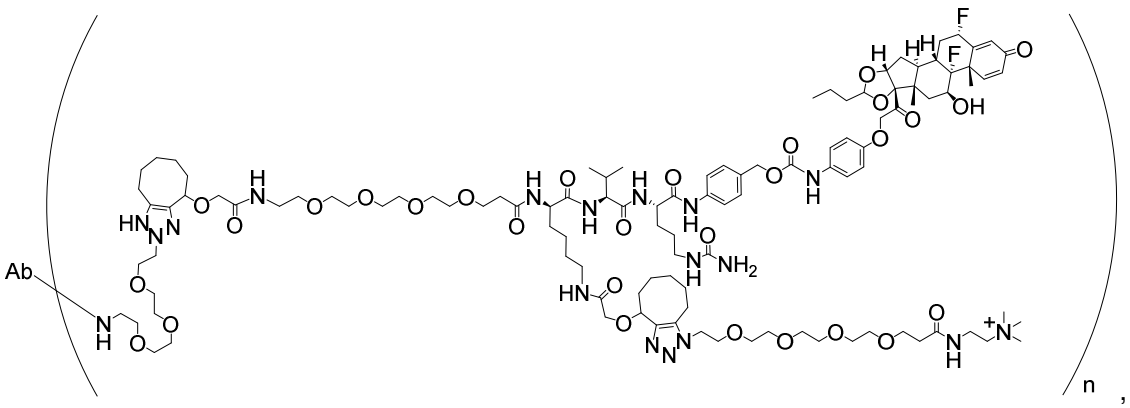
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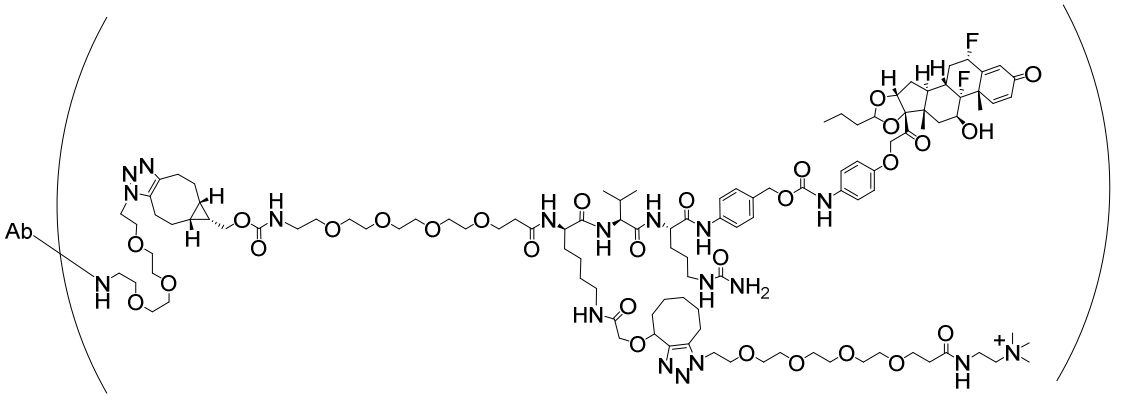
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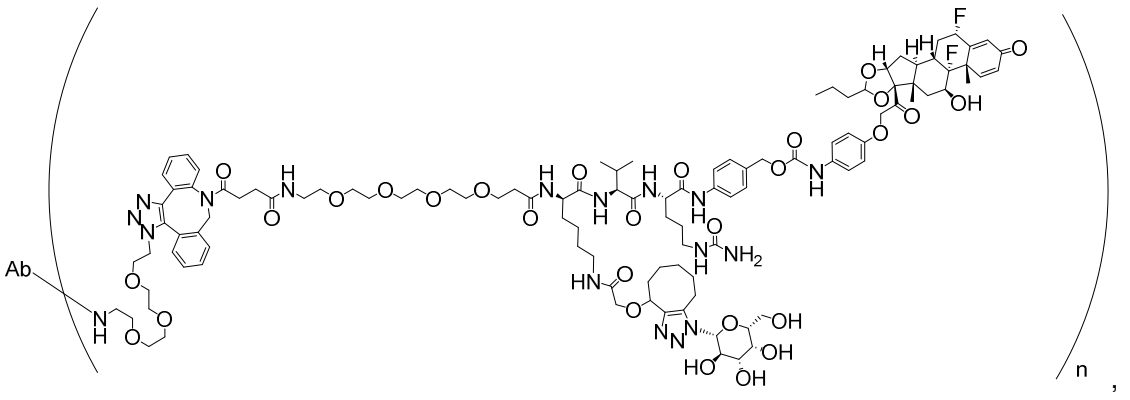
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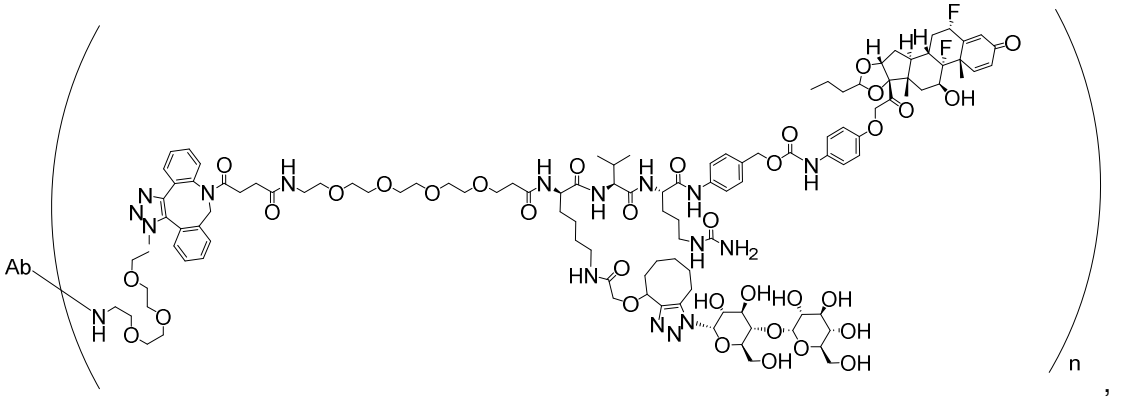
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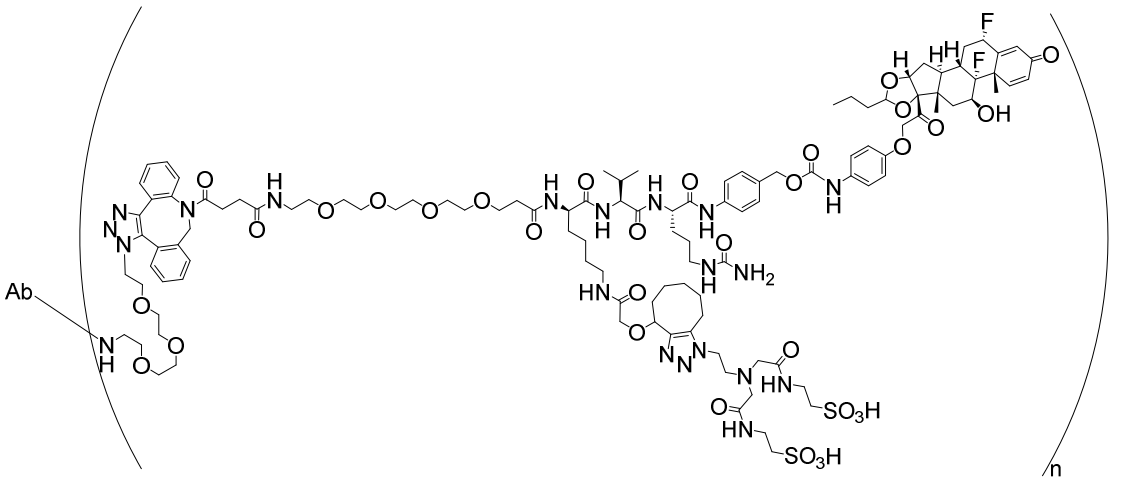
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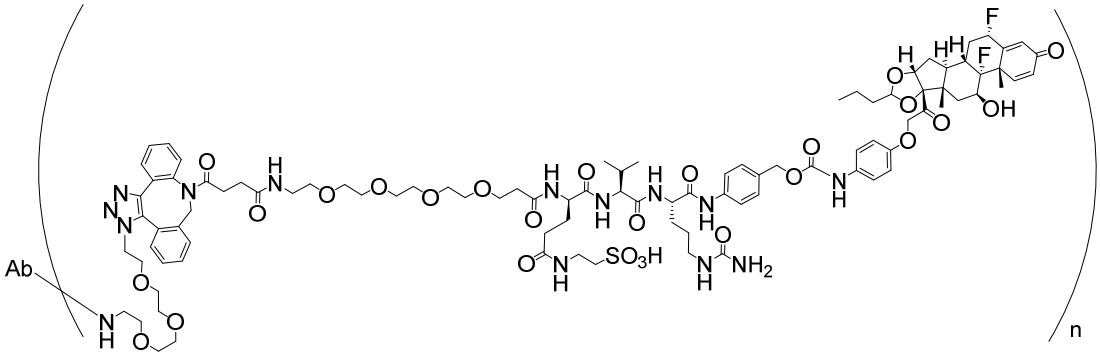
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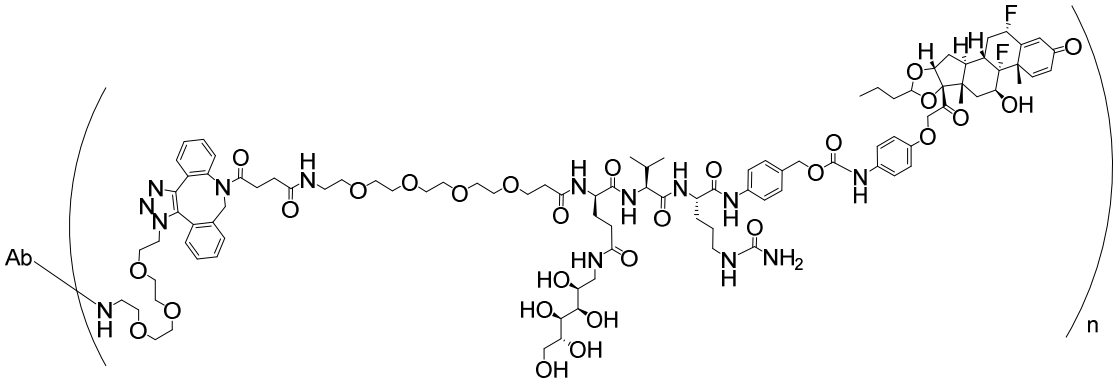
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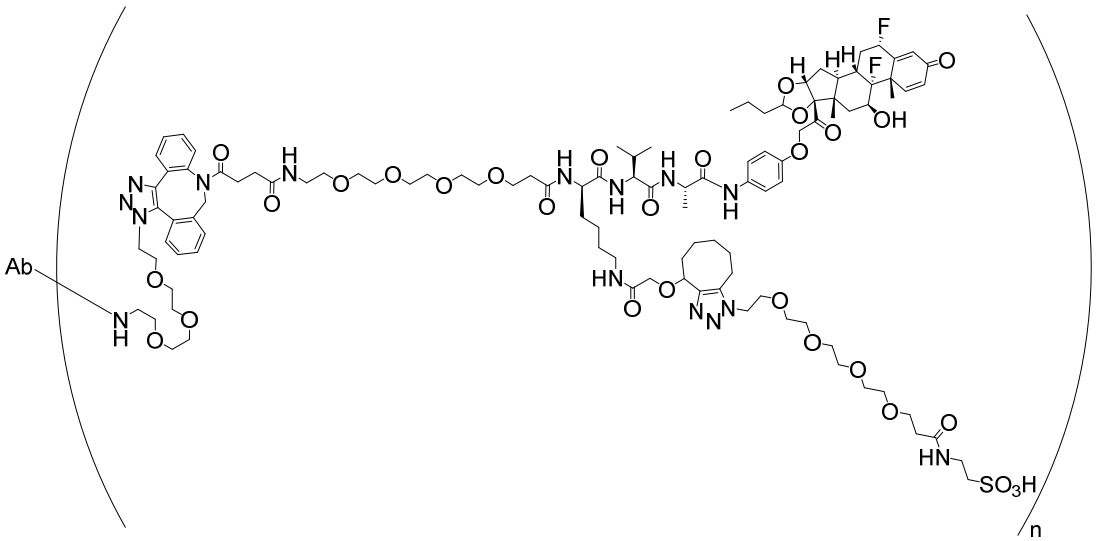
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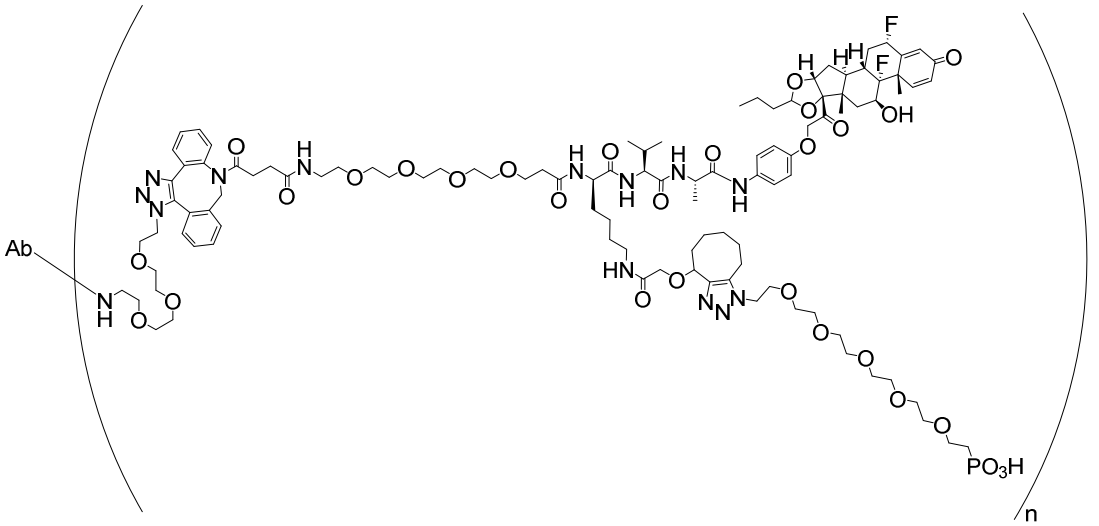
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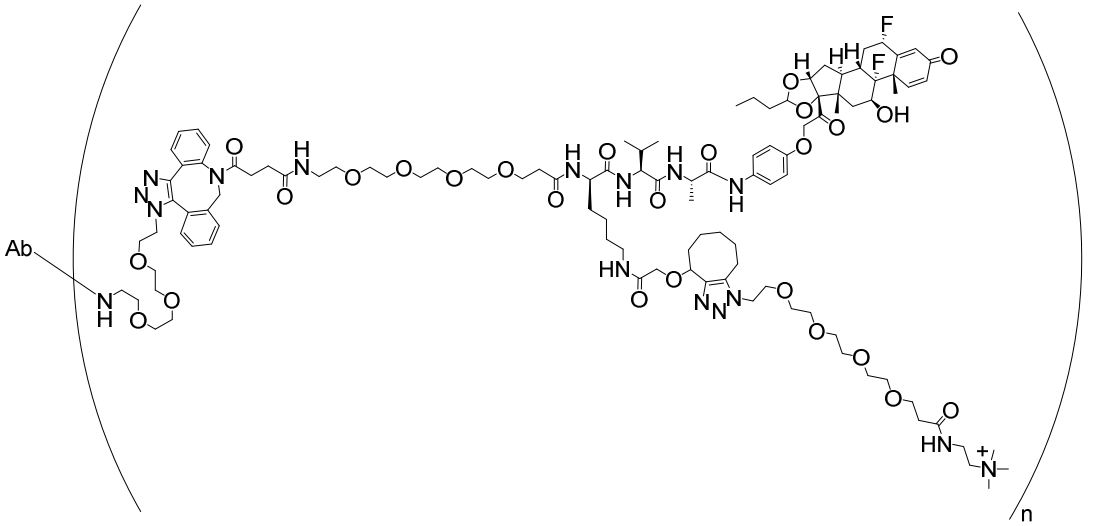
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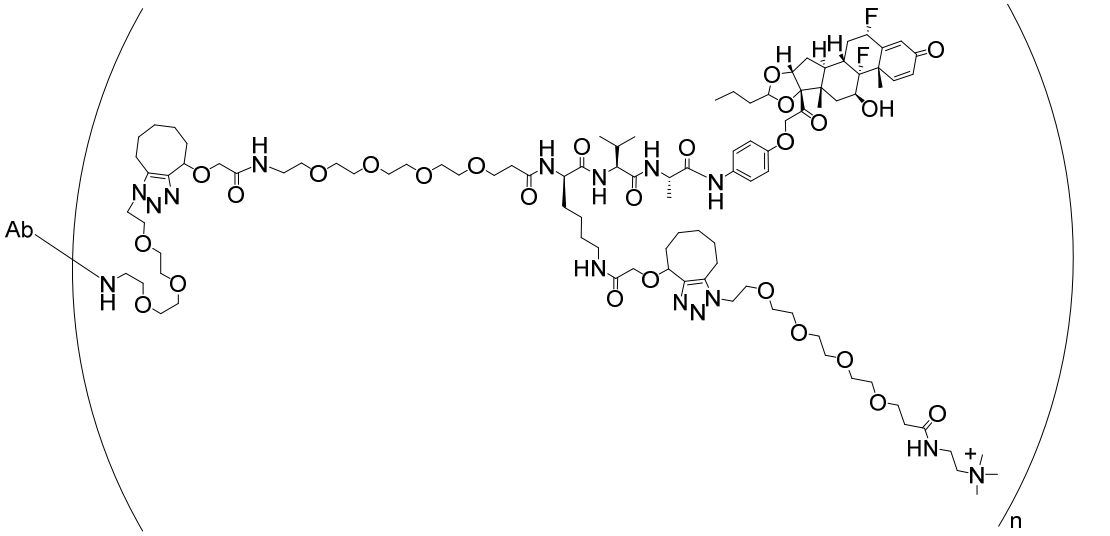
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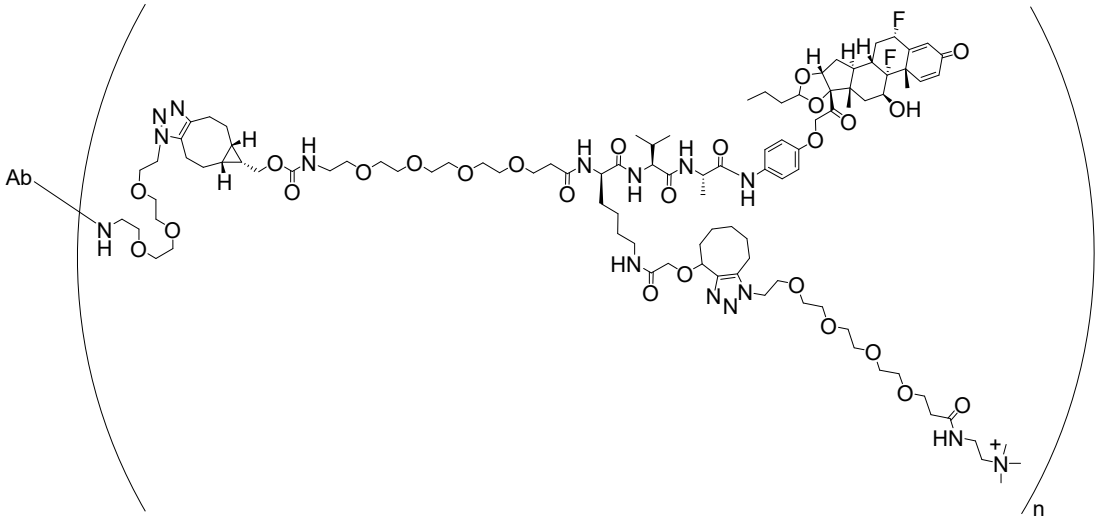

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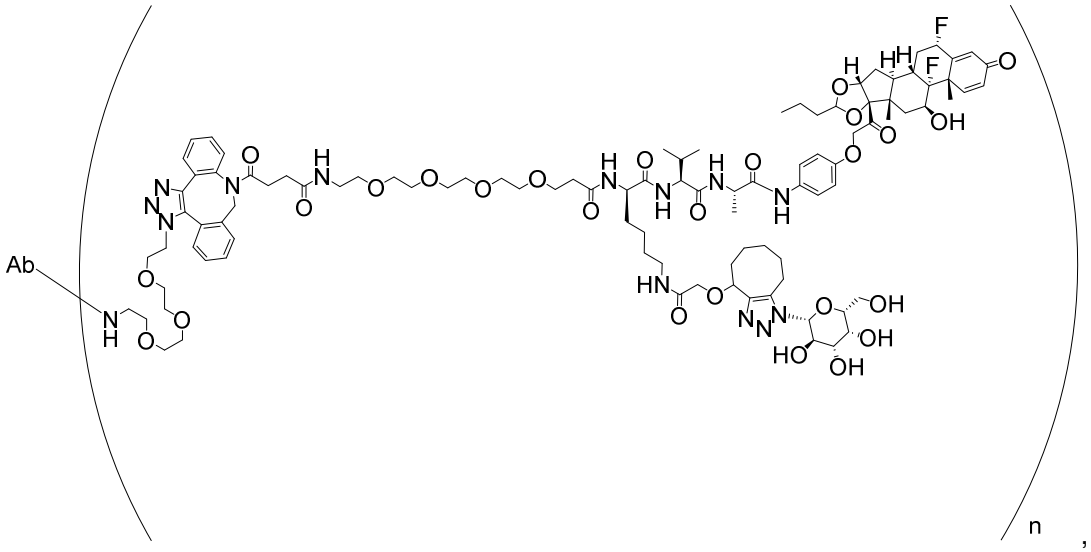

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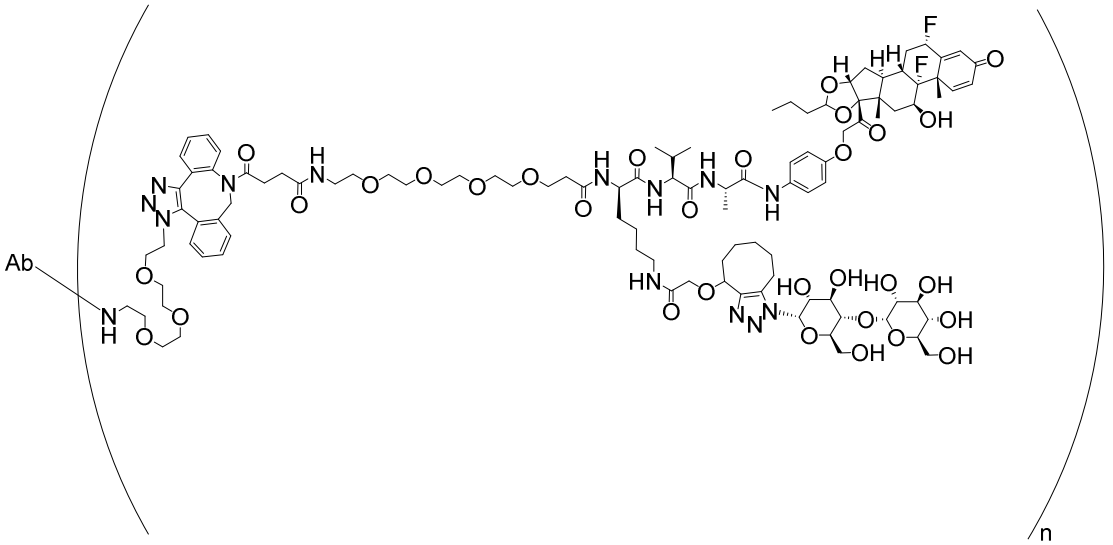




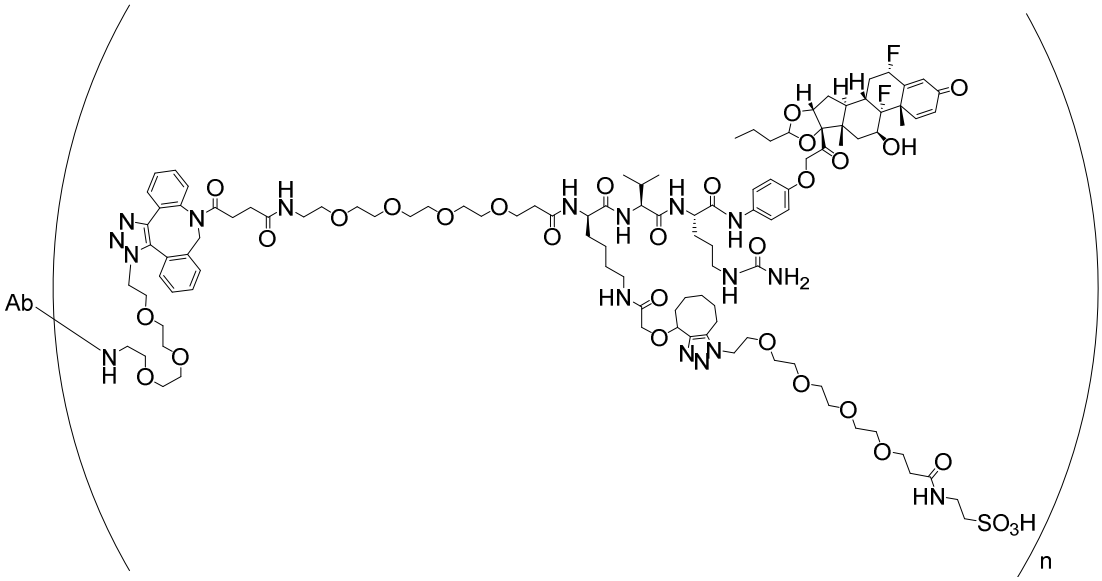
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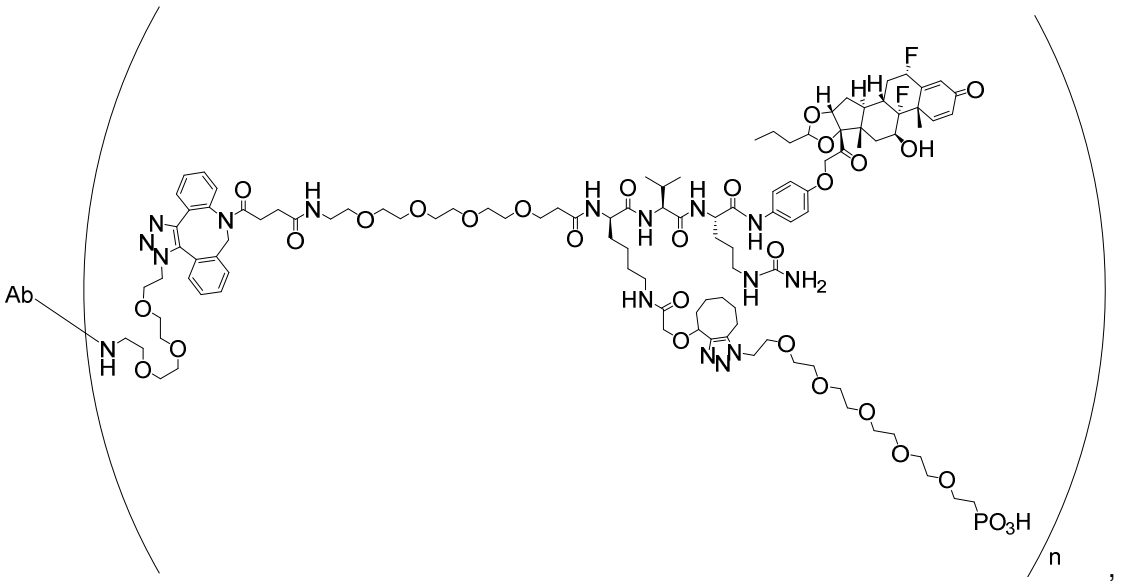
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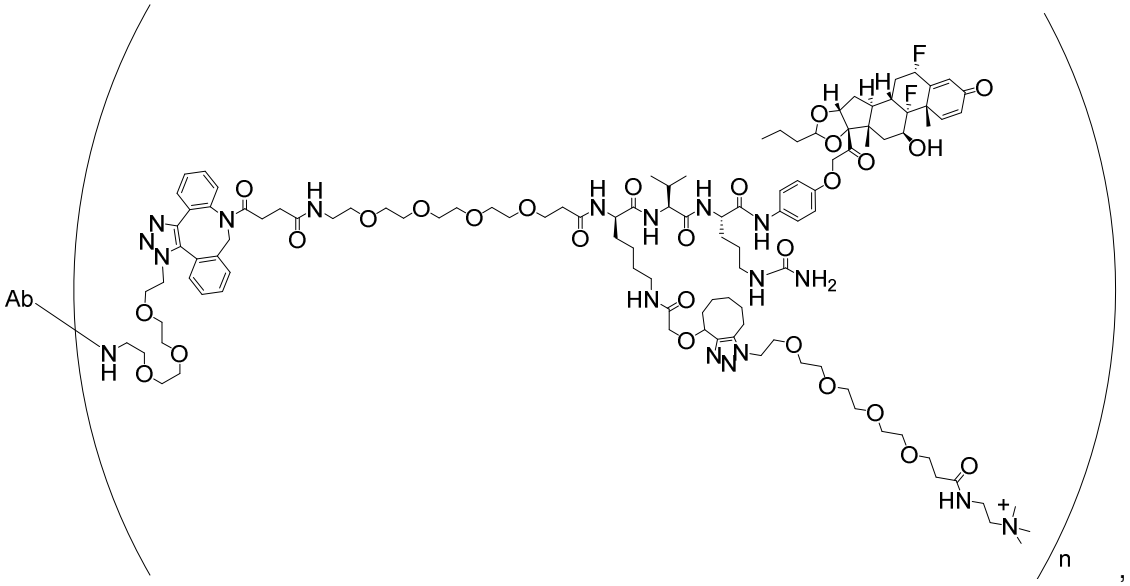
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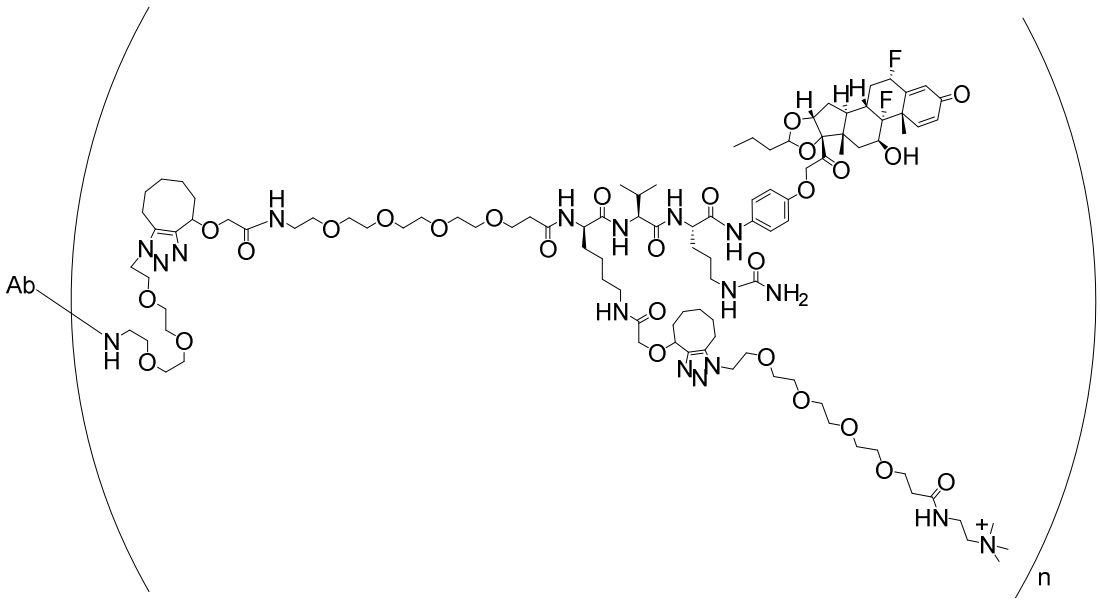
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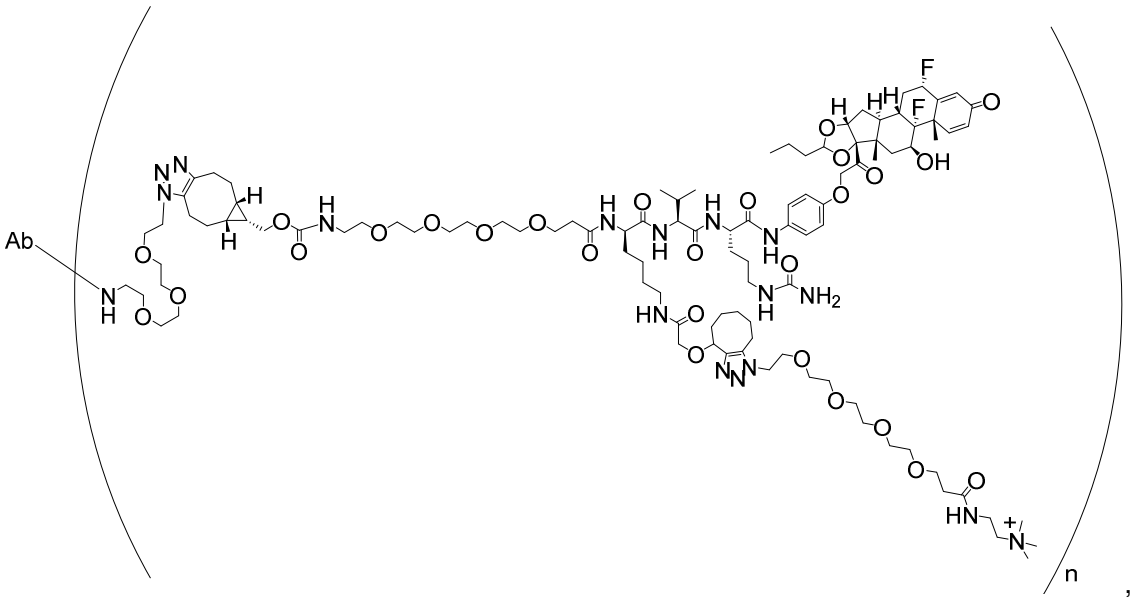
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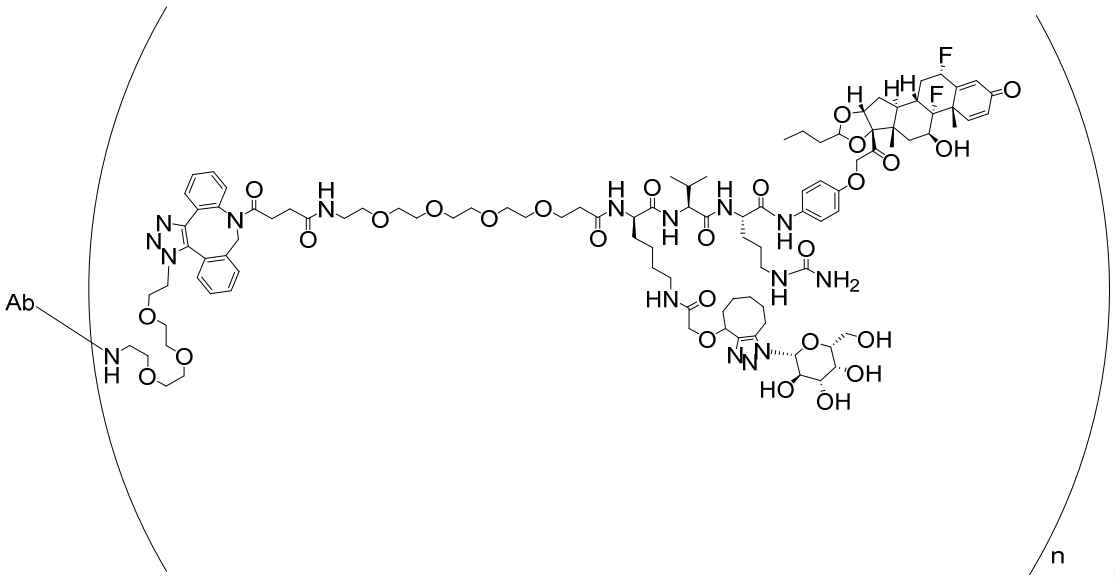
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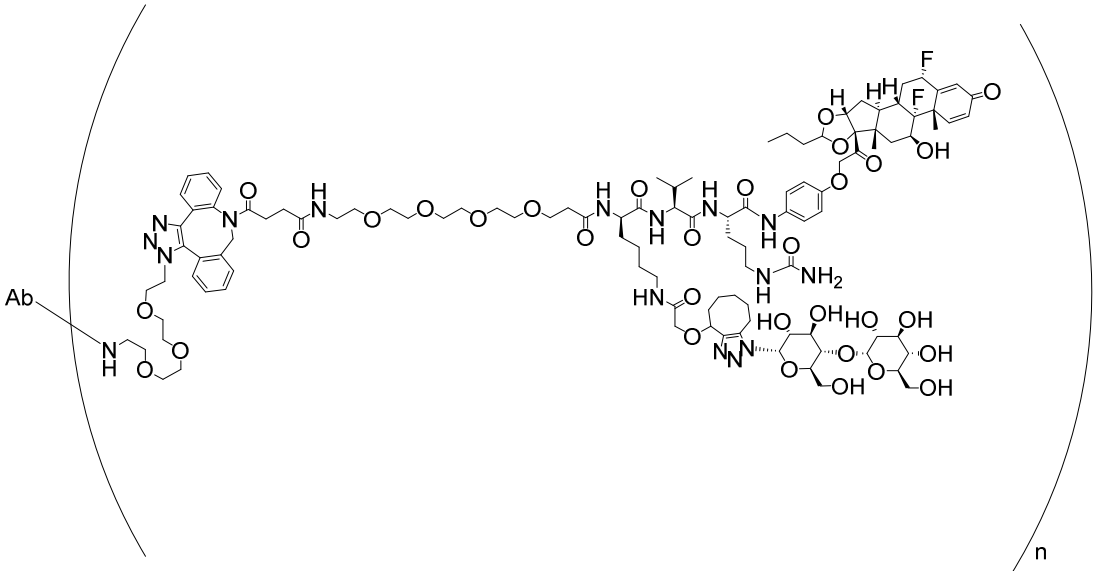
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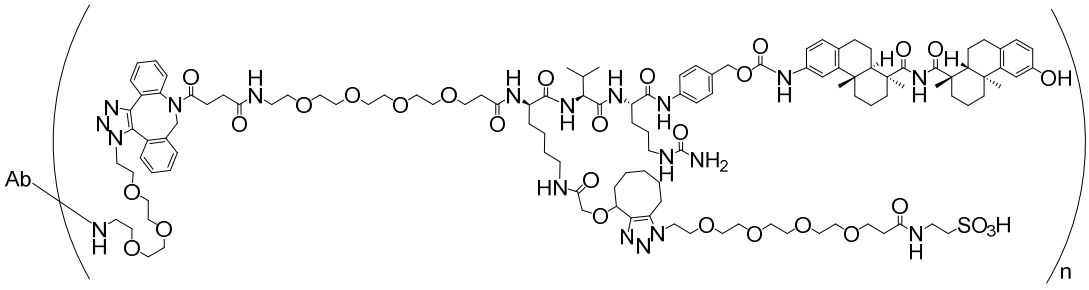
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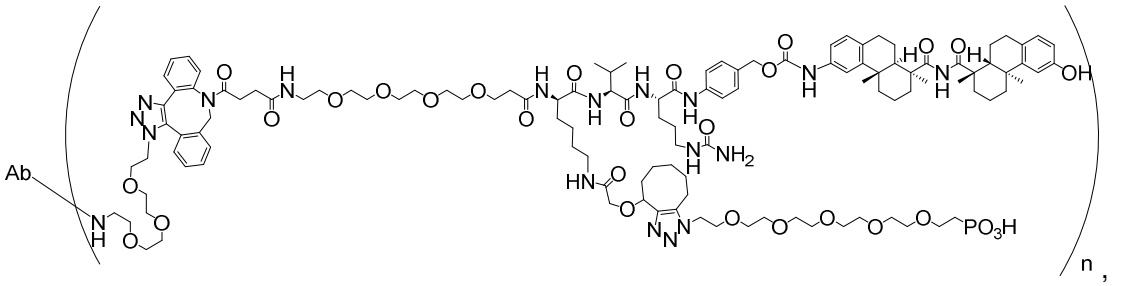
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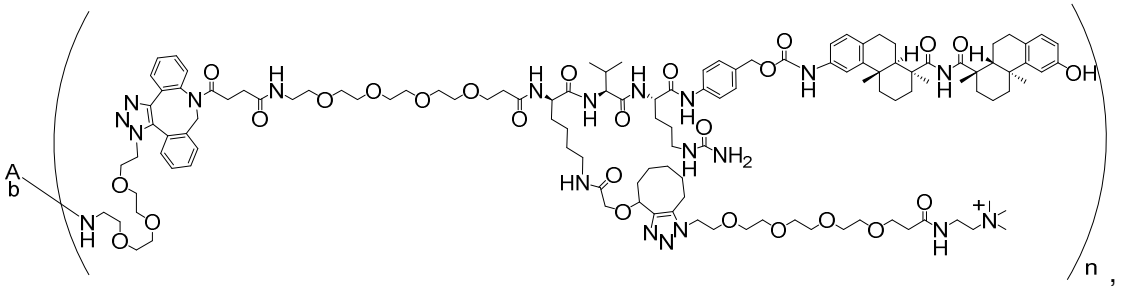

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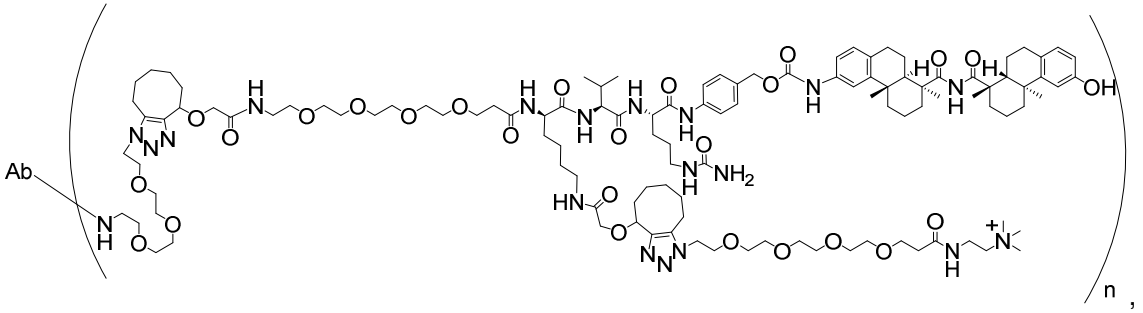
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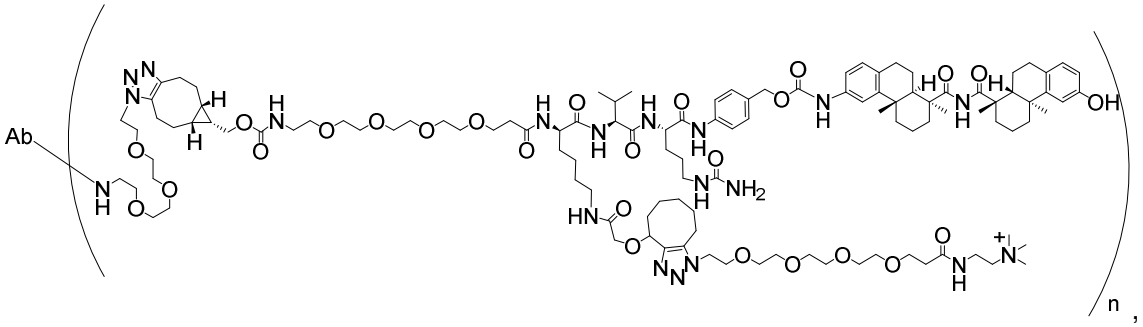

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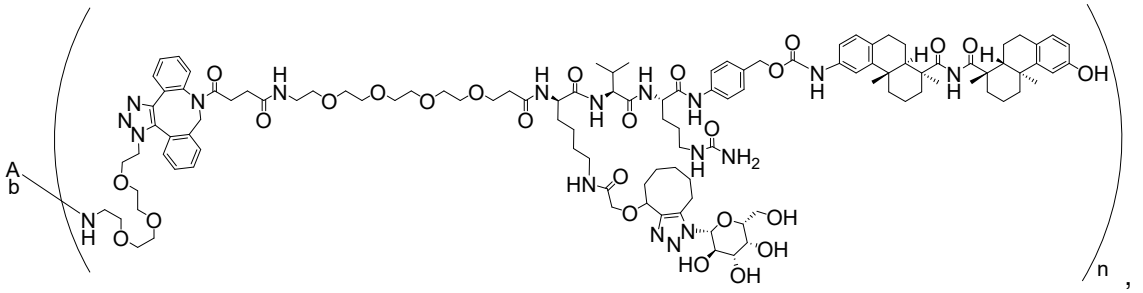
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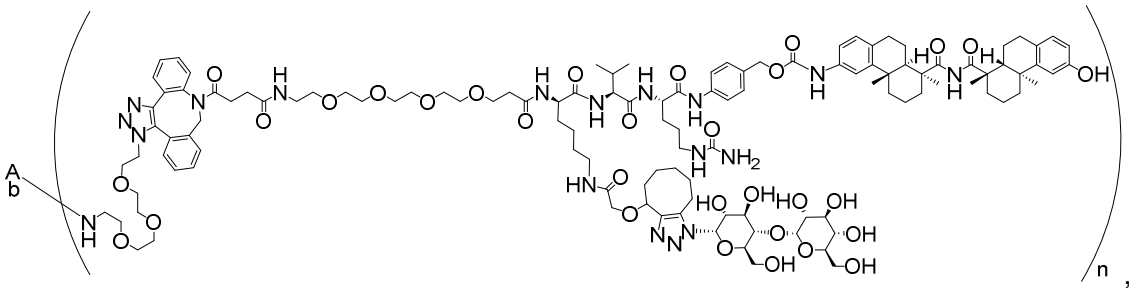
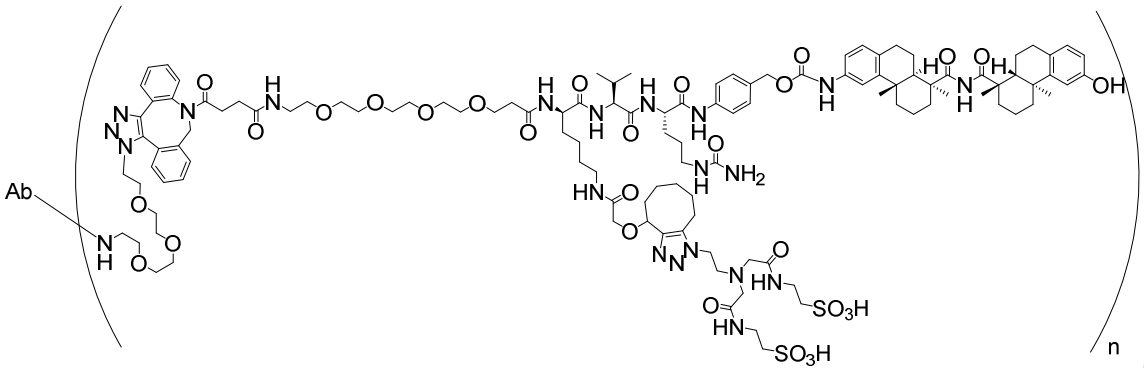
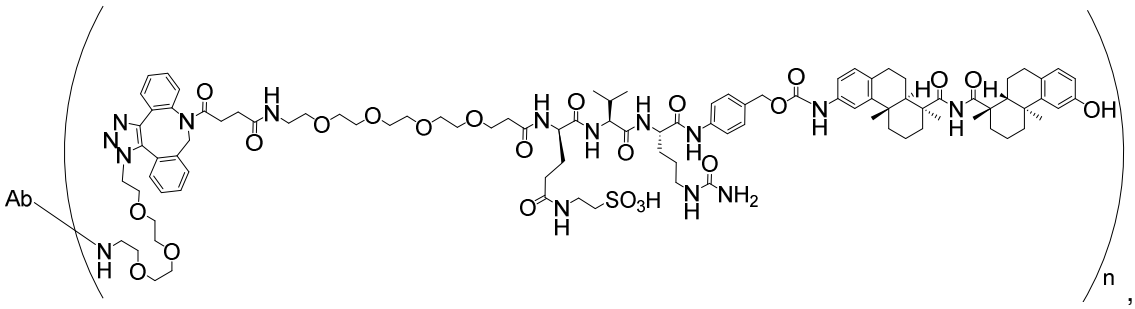
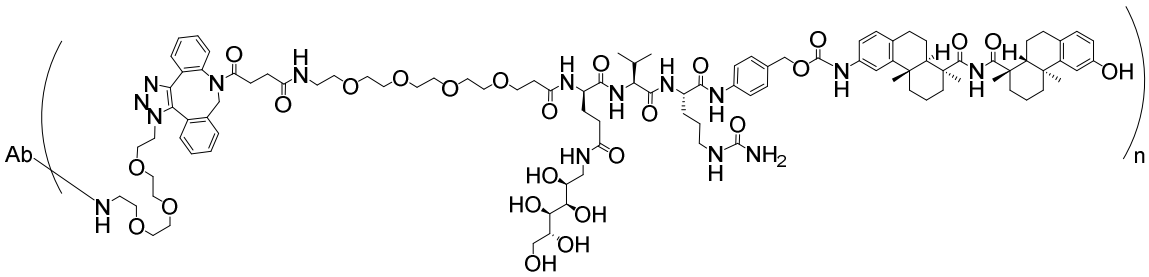


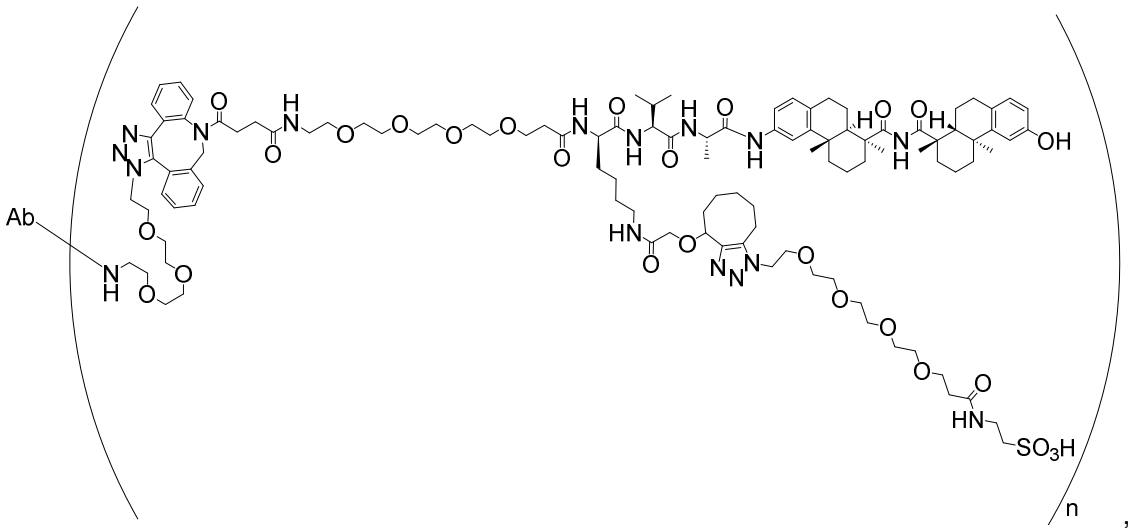




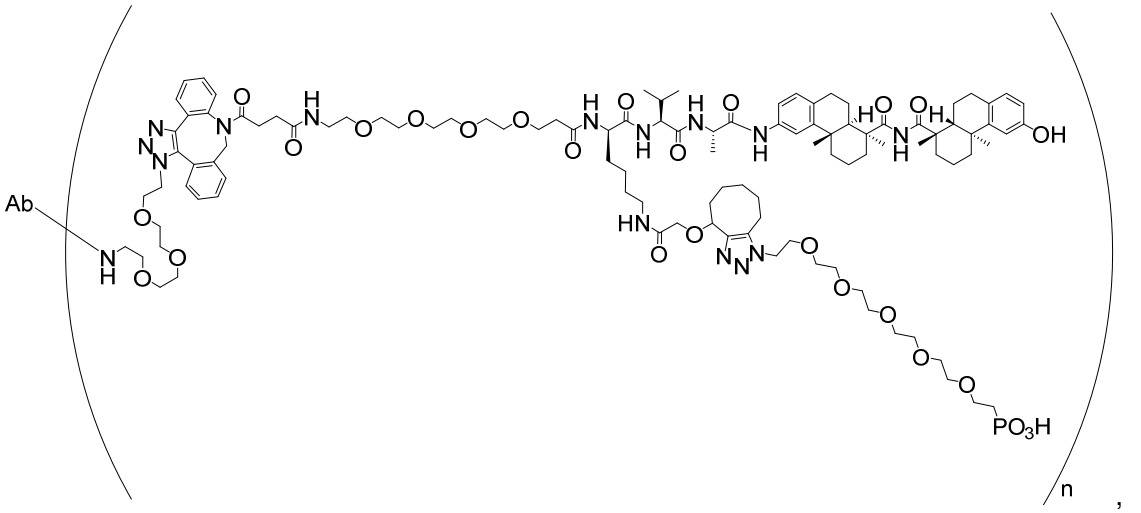




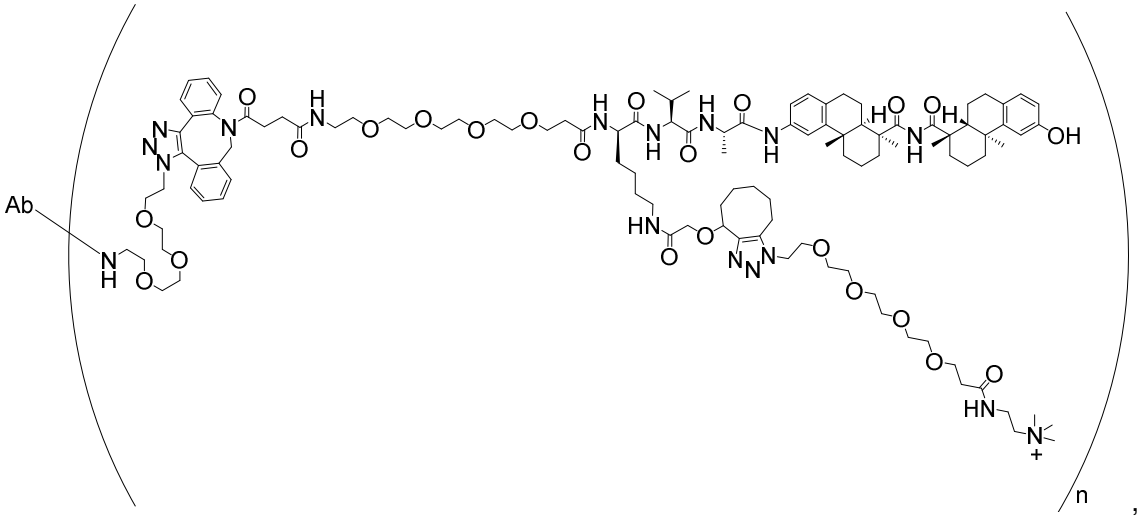

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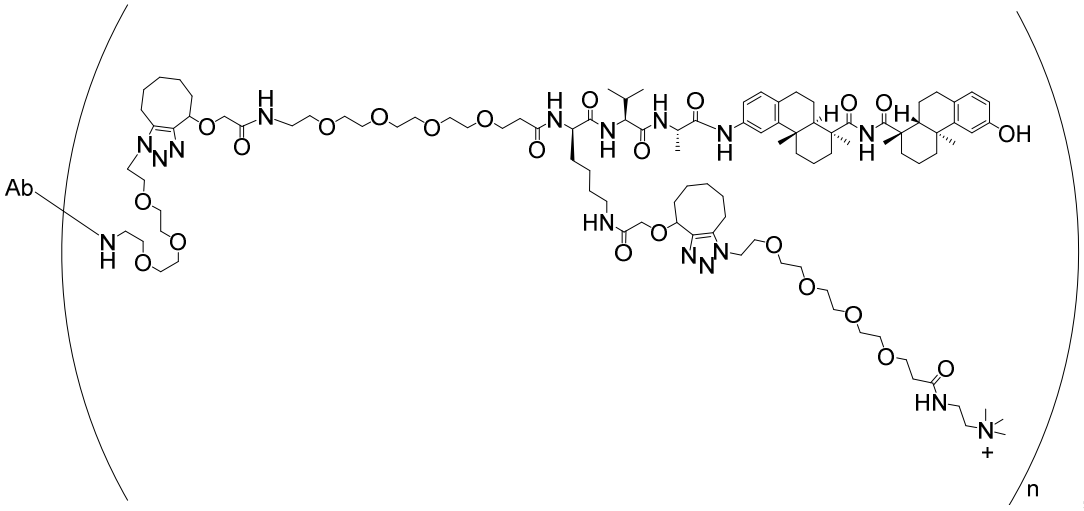
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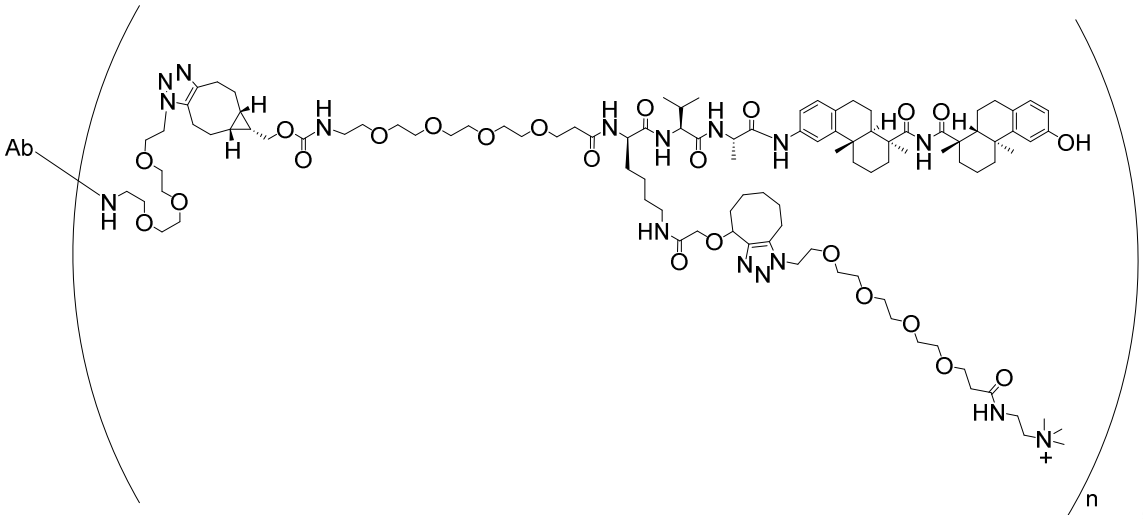
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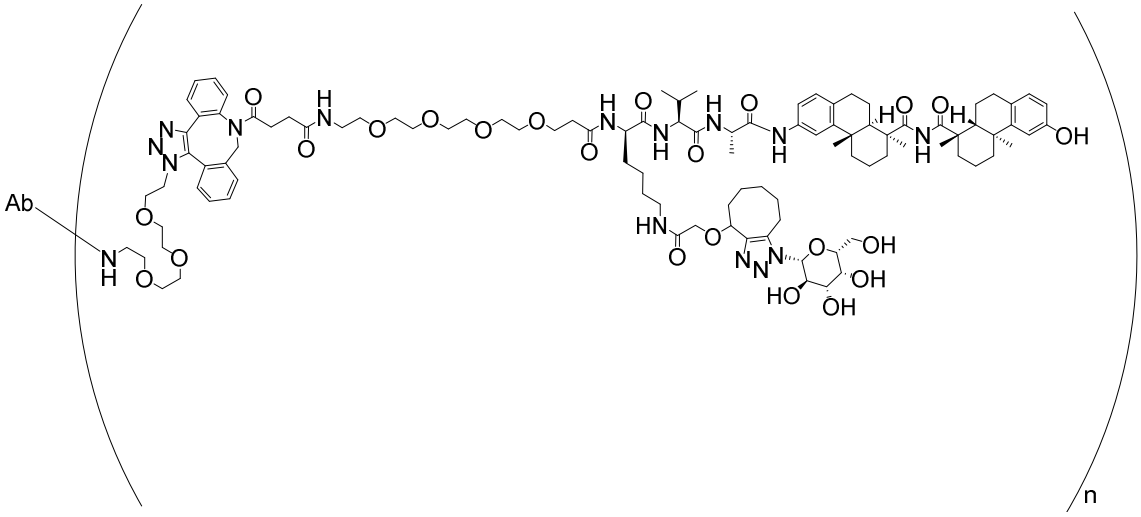
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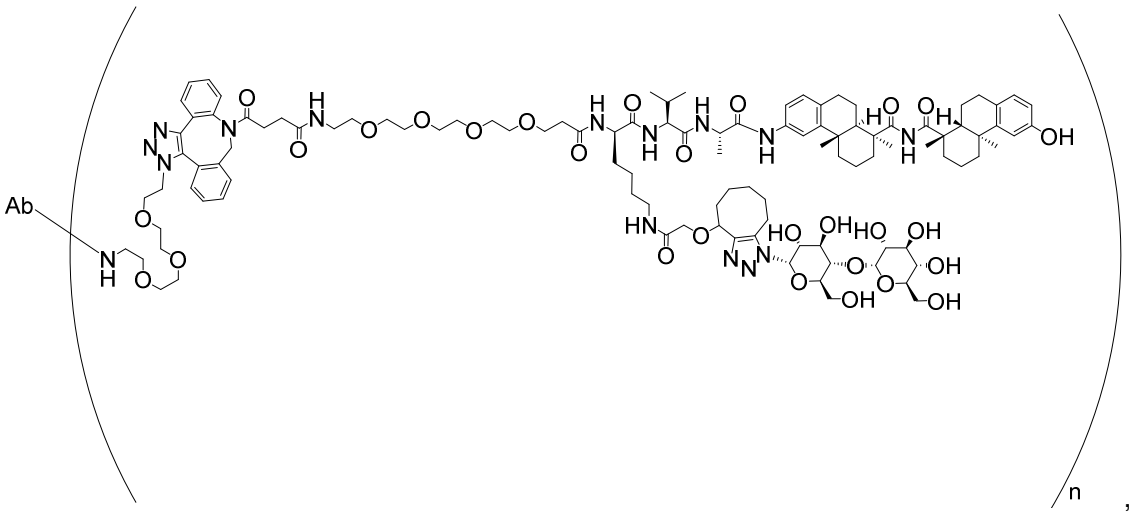
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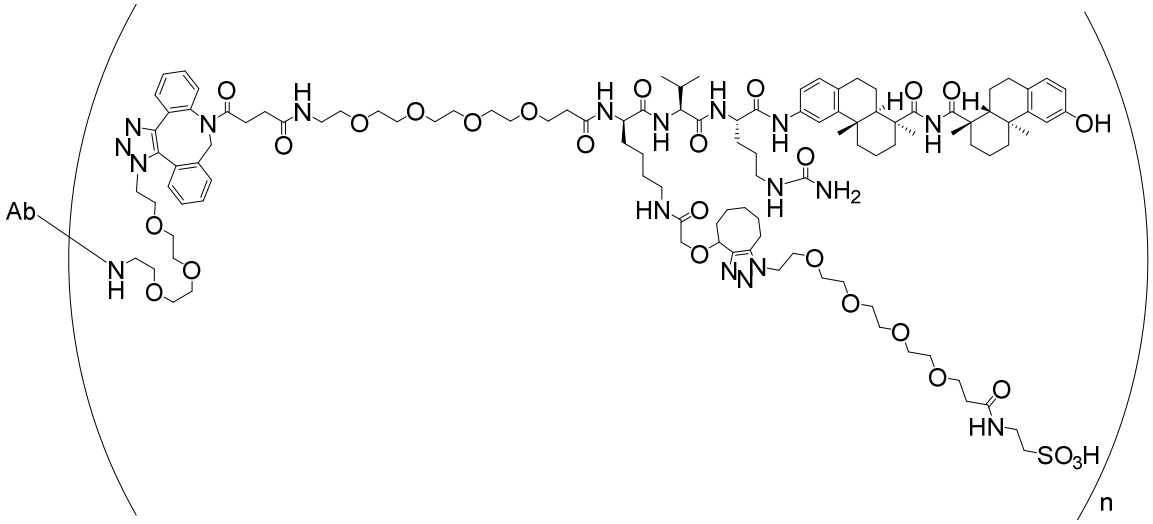
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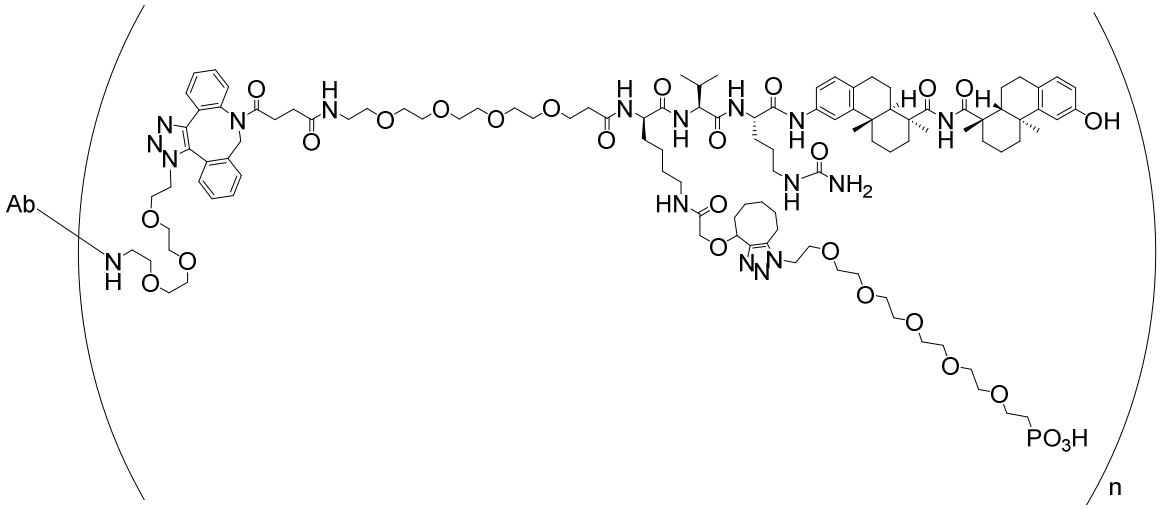
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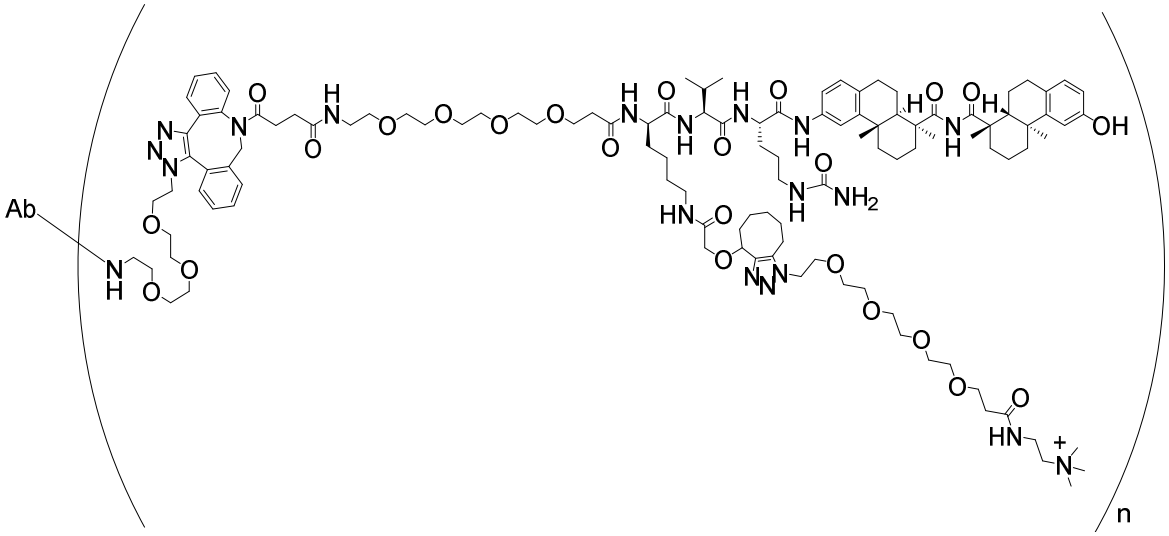
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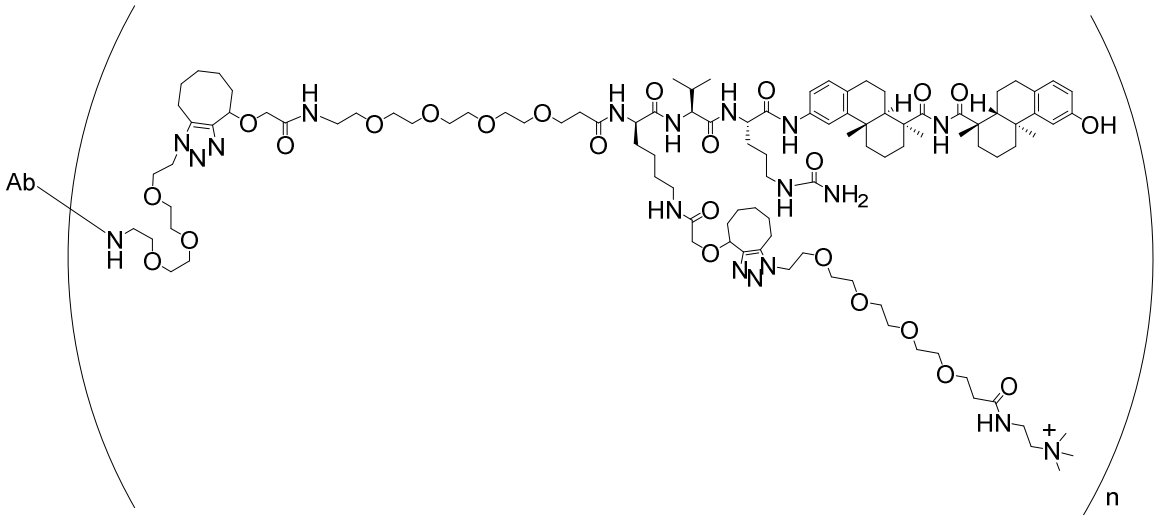
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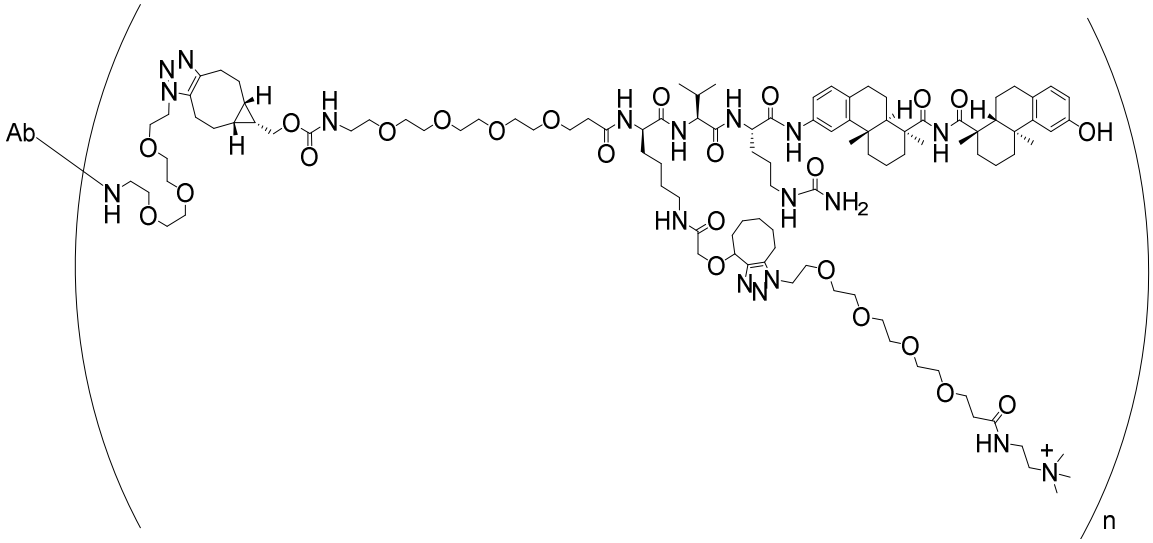
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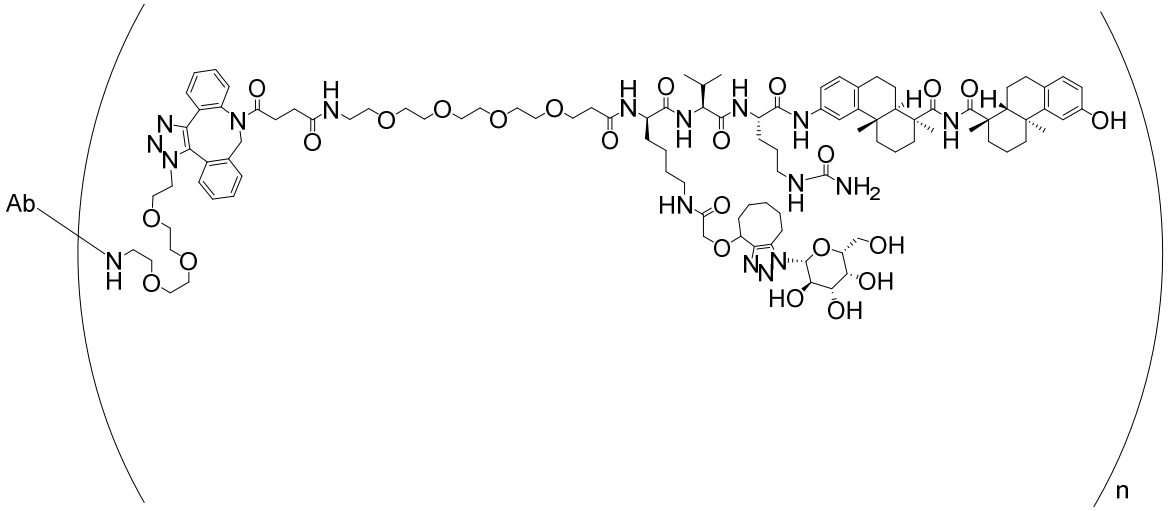
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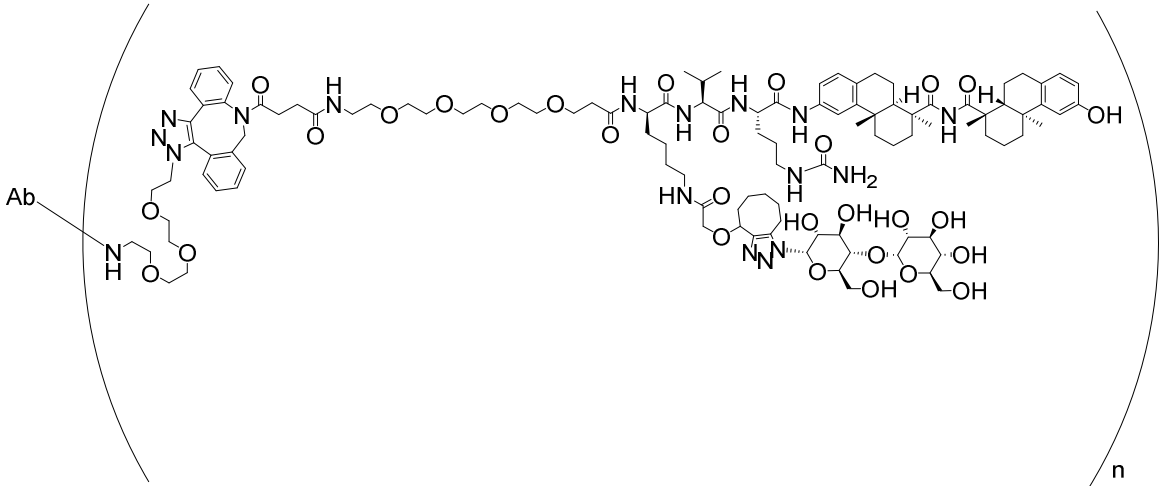
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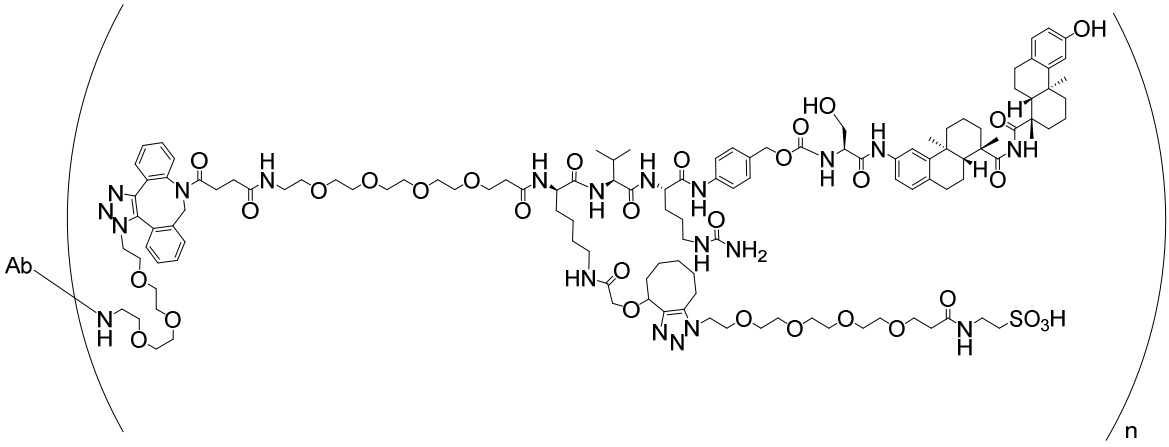
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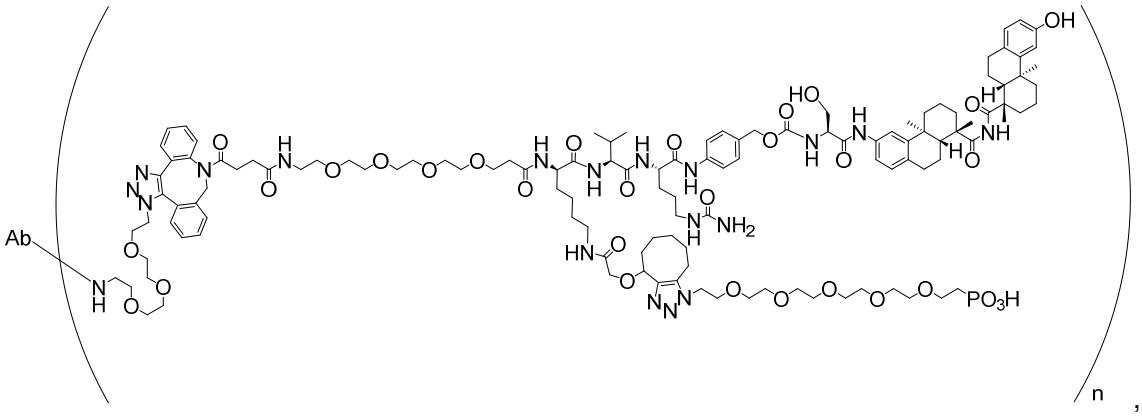
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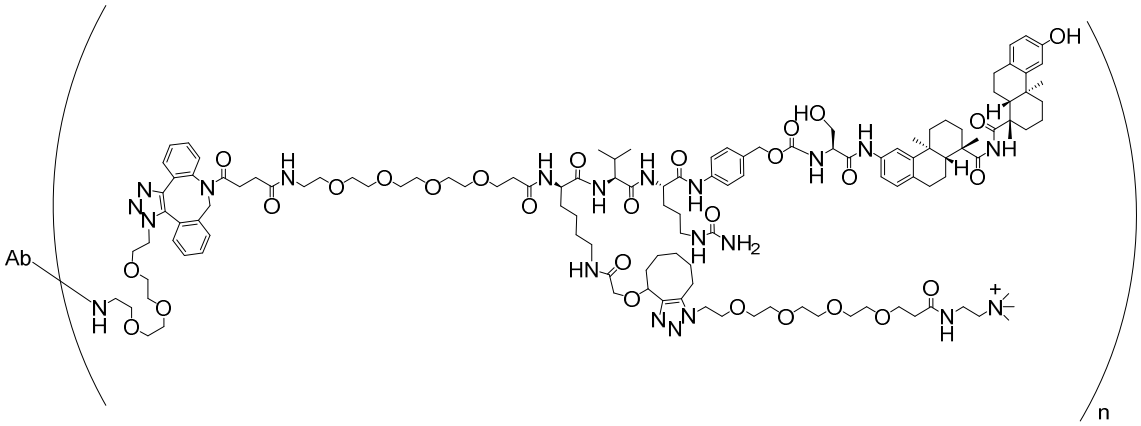
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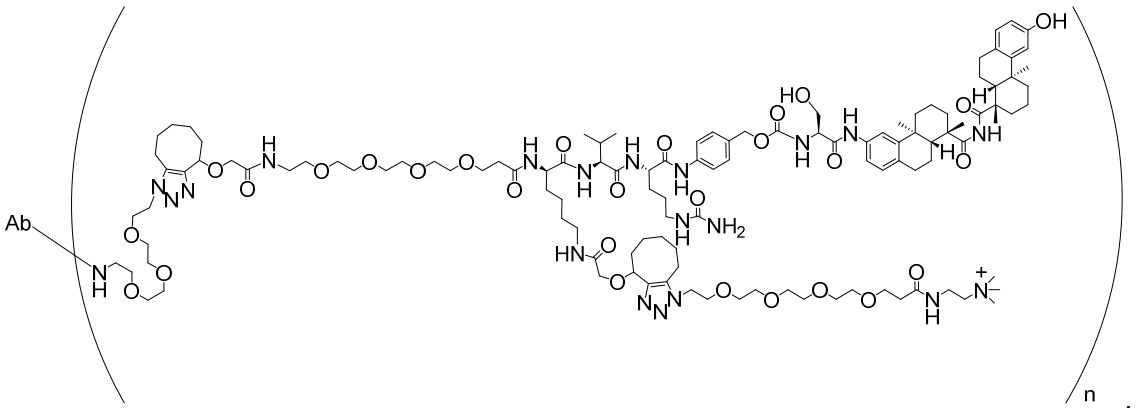
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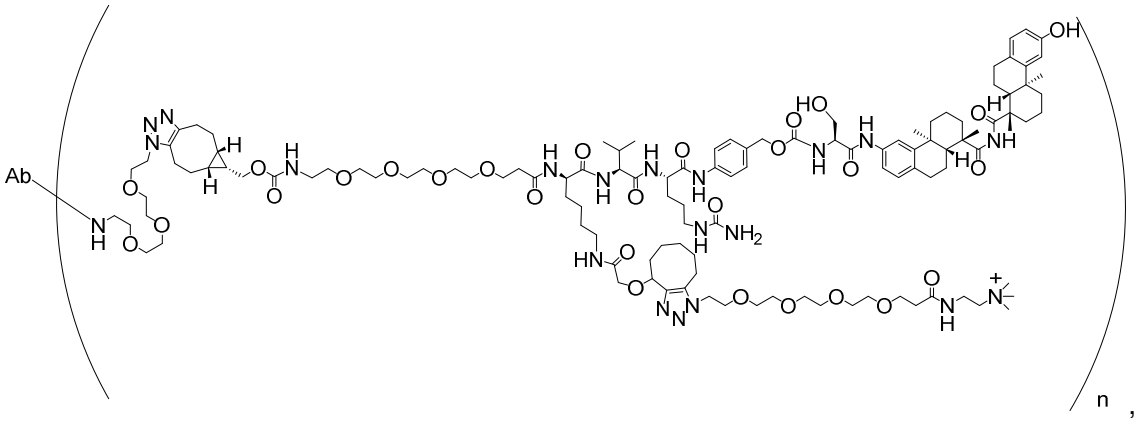
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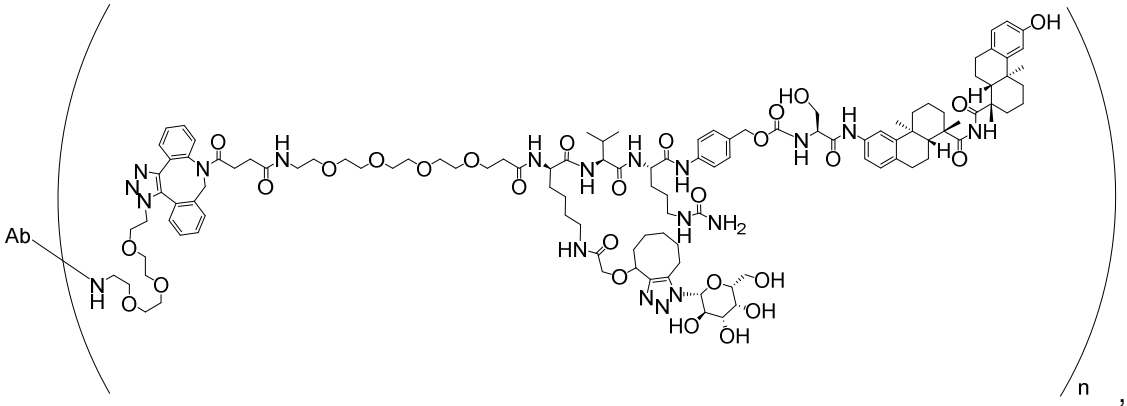
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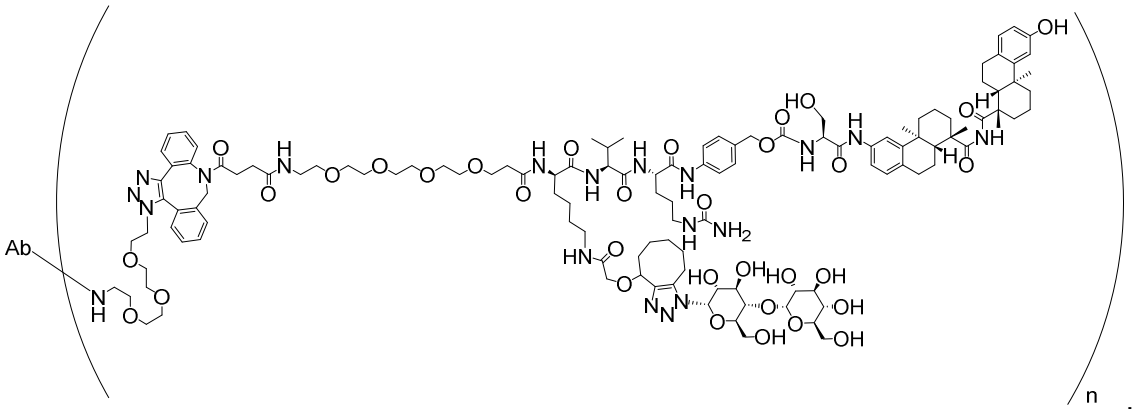
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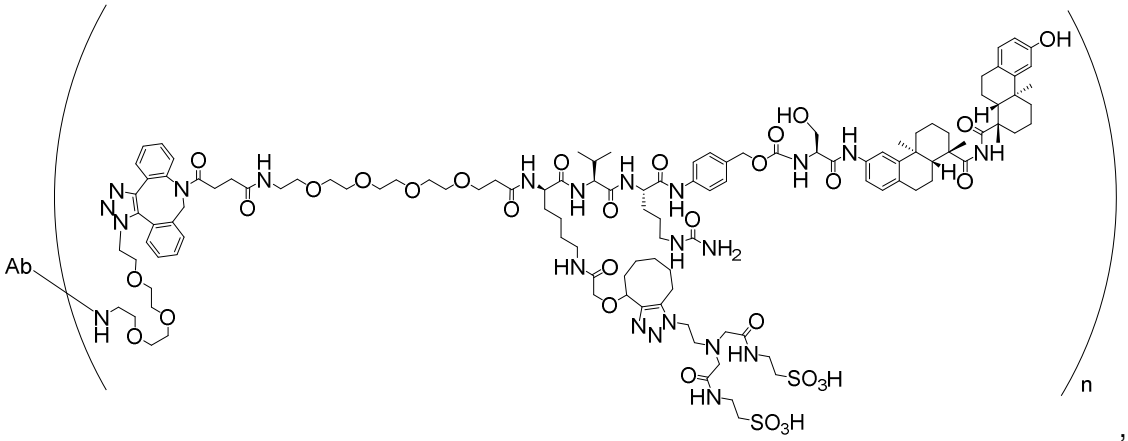
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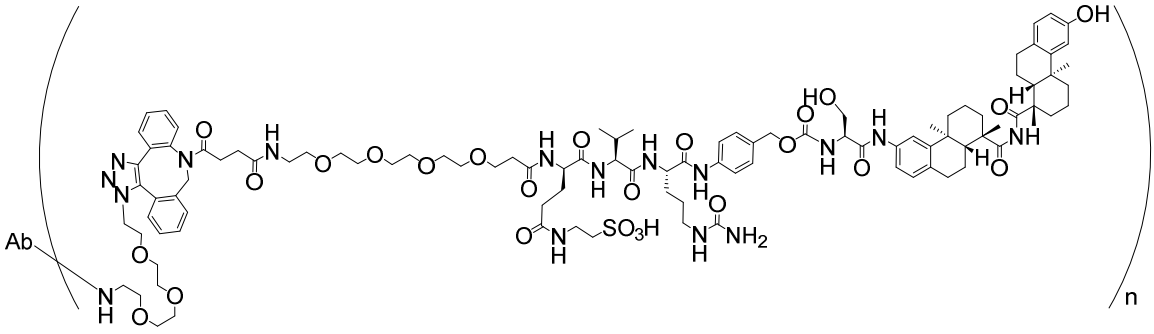
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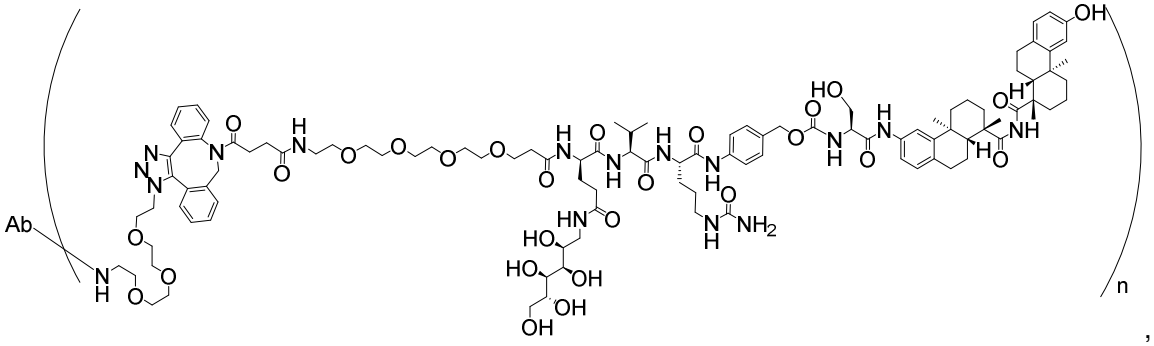
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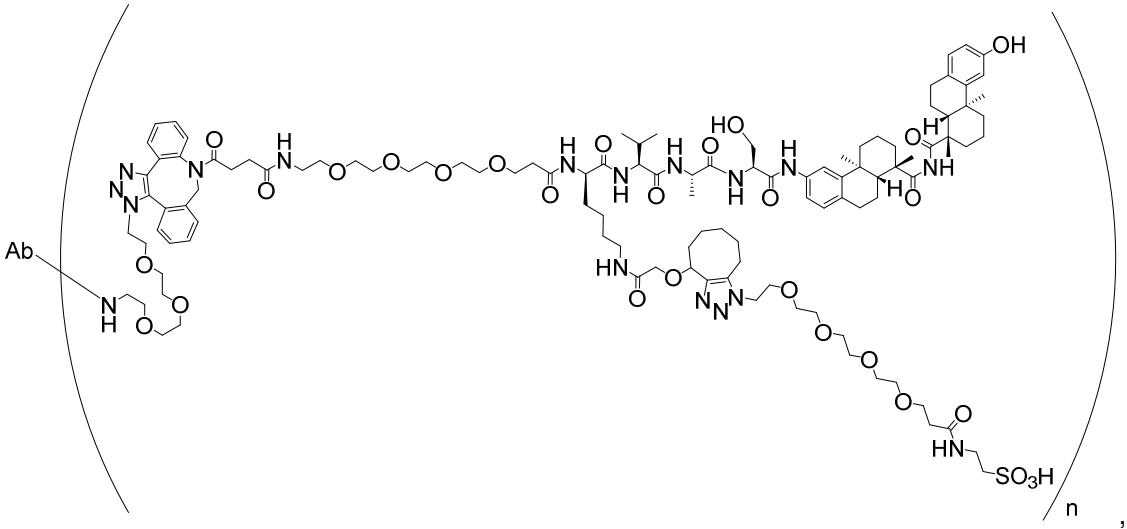
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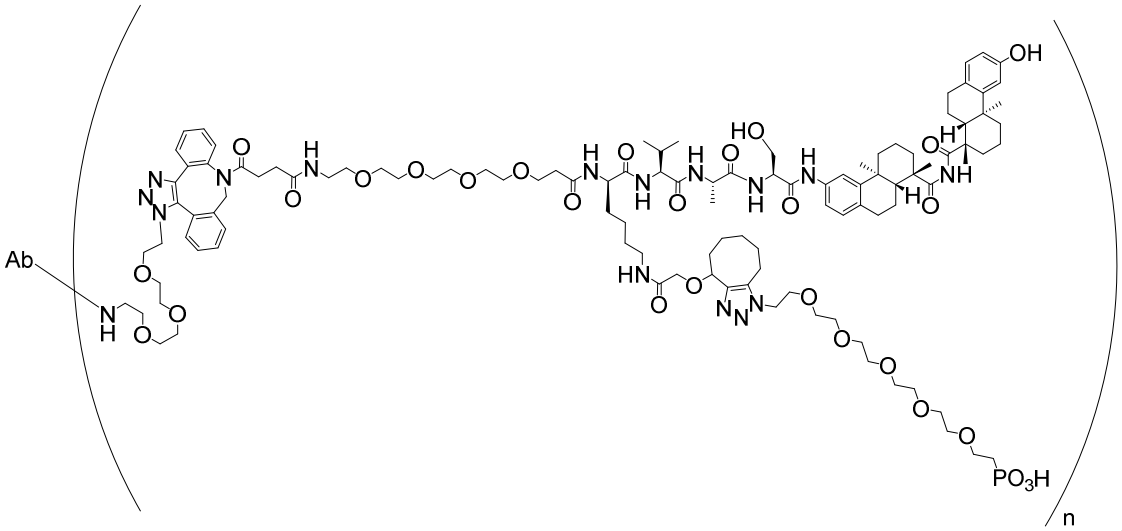
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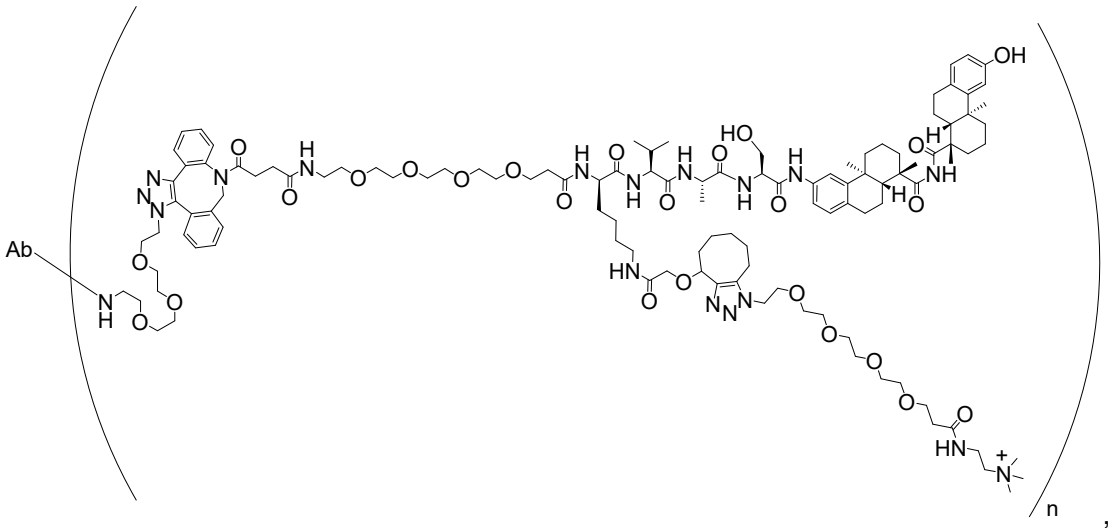
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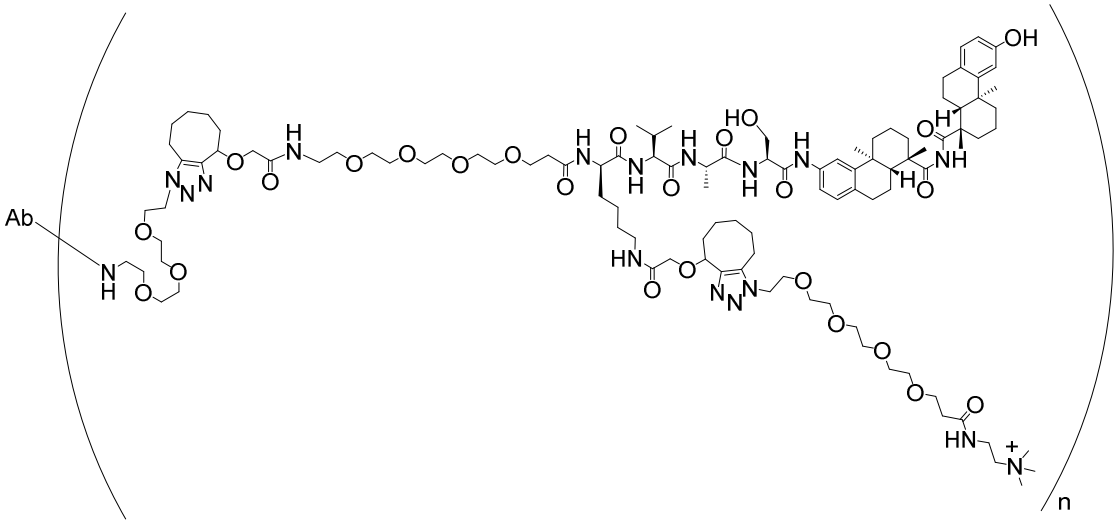
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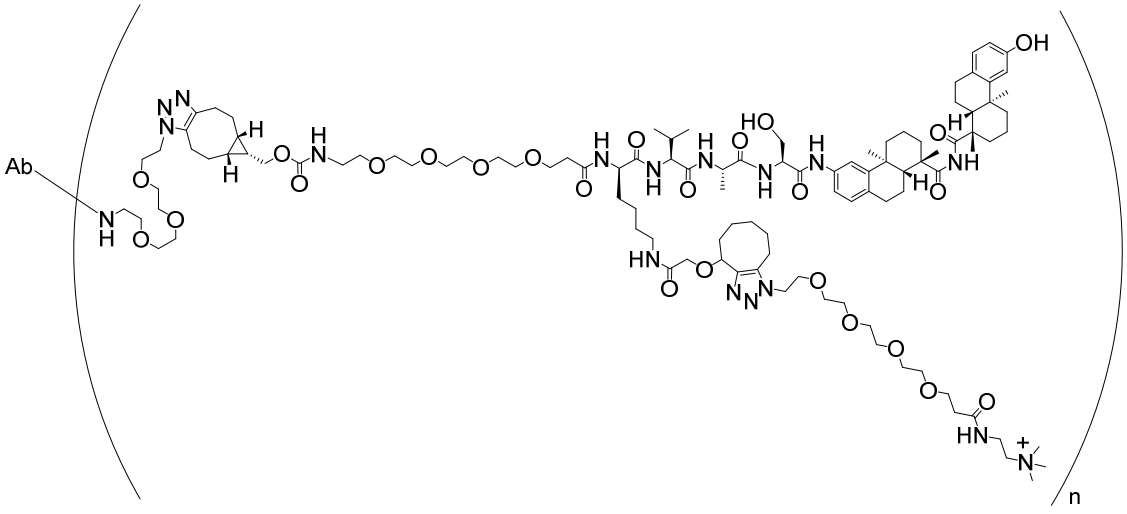
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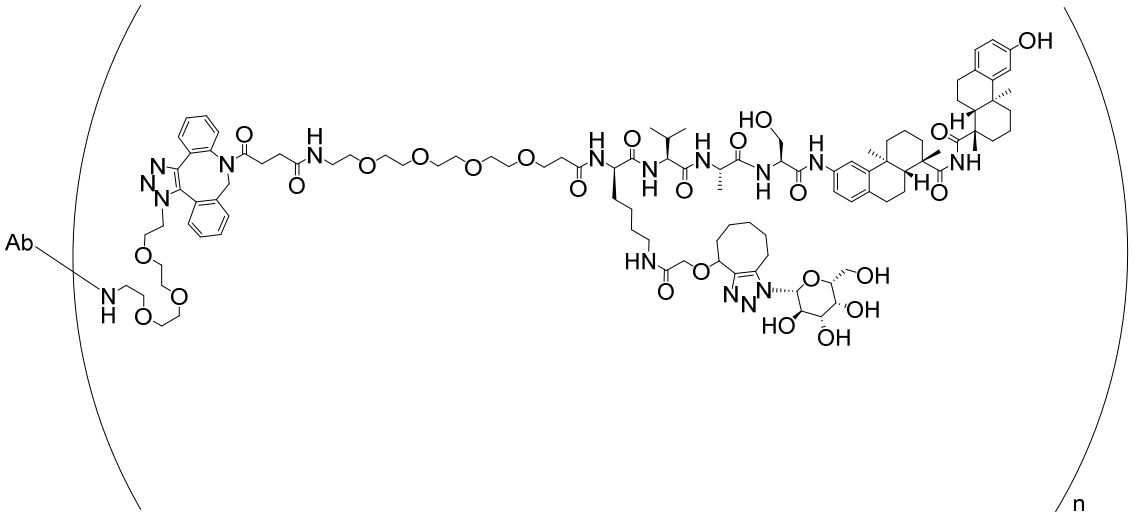
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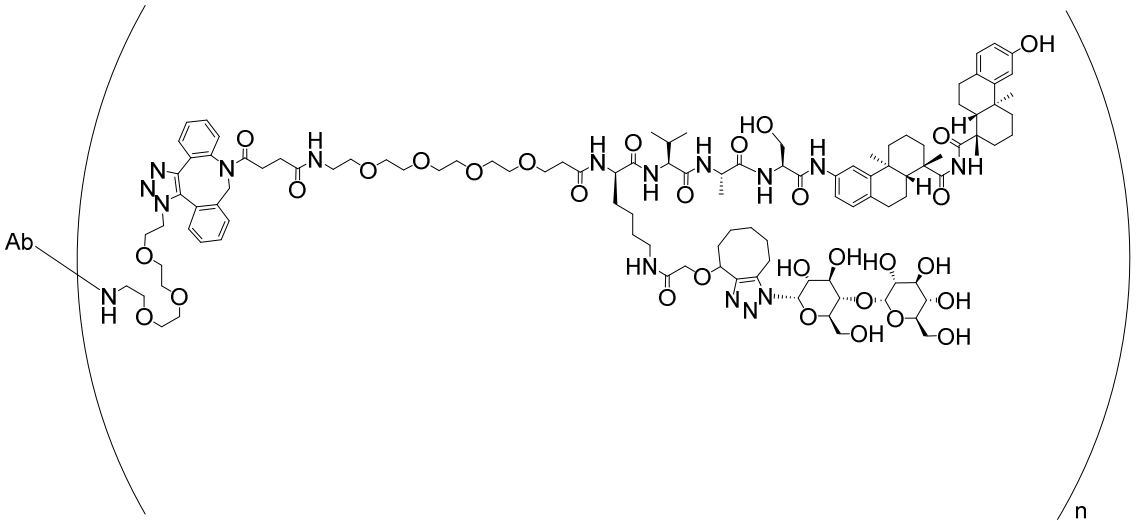
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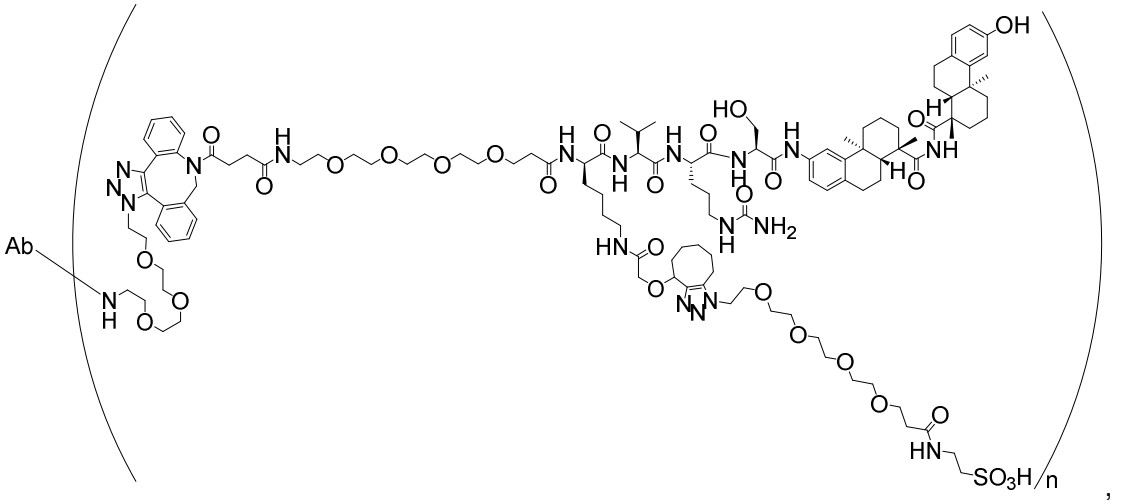
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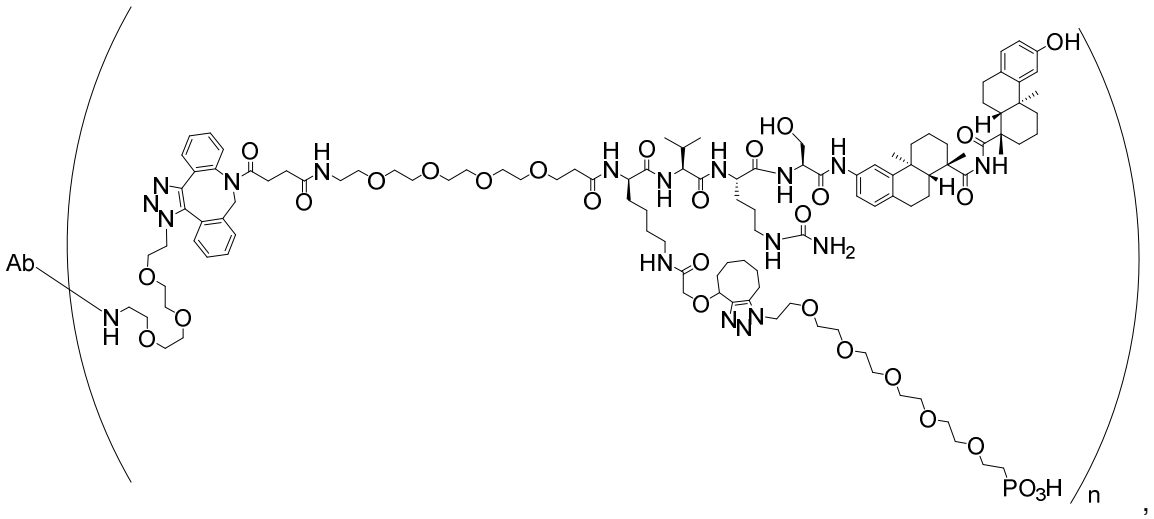
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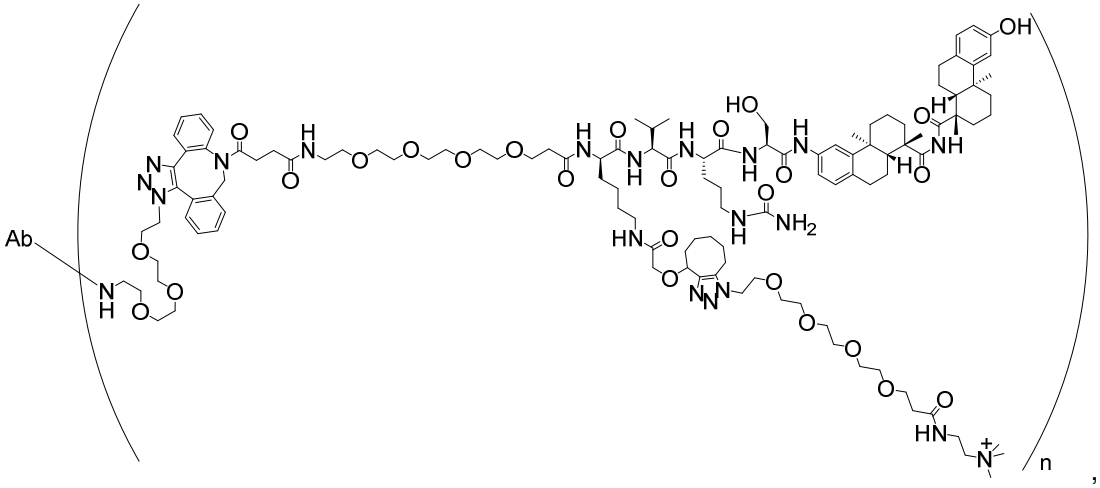
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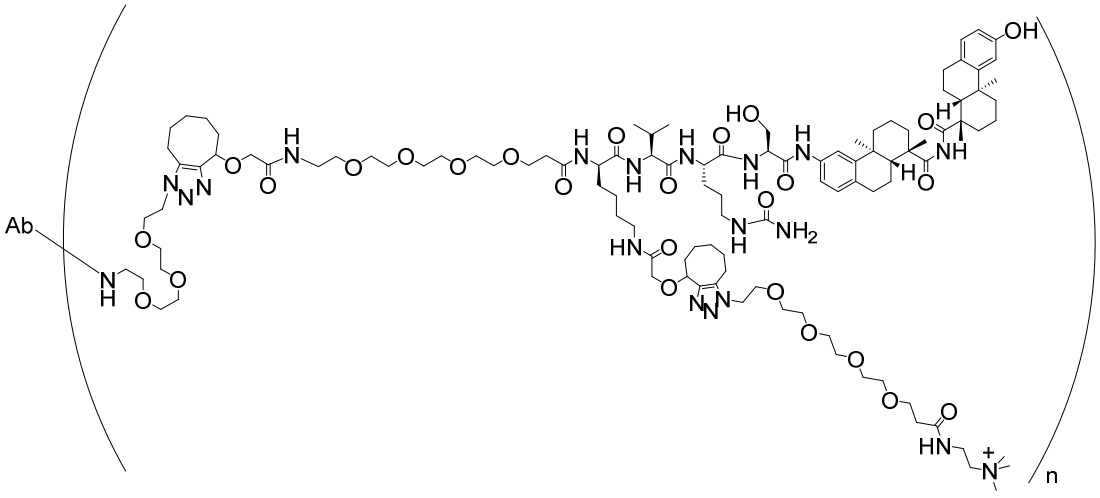
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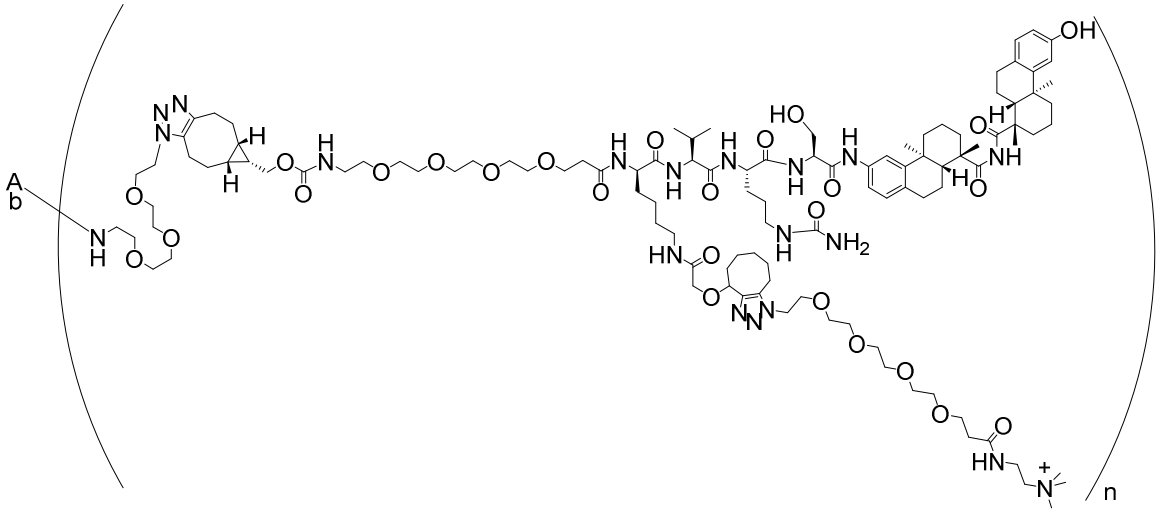
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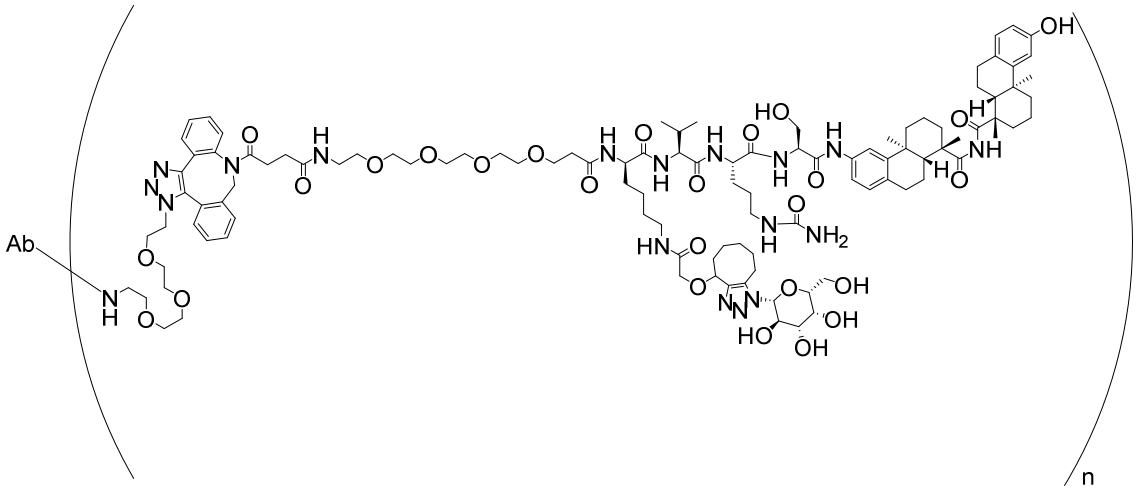
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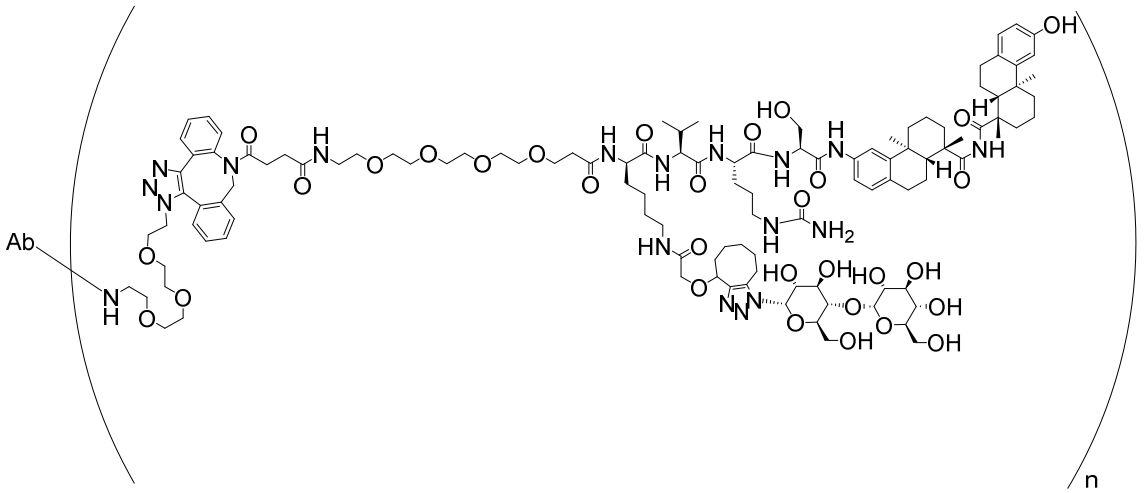
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or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

each **Ab** is an antibody, or an antigen-binding fragment thereof; and

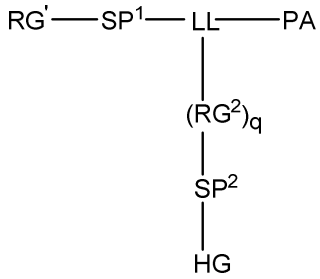
subscript **n** is an integer from 1 to 30.

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

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

34. A compound comprising a reactive linker bonded to at least one payload moiety and bonded to at least one hydrophilic residue via a covalent linker, wherein said covalent linker is bonded directly or indirectly to each of the reactive linker, the payload moiety, and the hydrophilic residue

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



(VII)

LL is a trivalent linker;

RG' is a reactive group;

RG^2 is a reactive group residue;

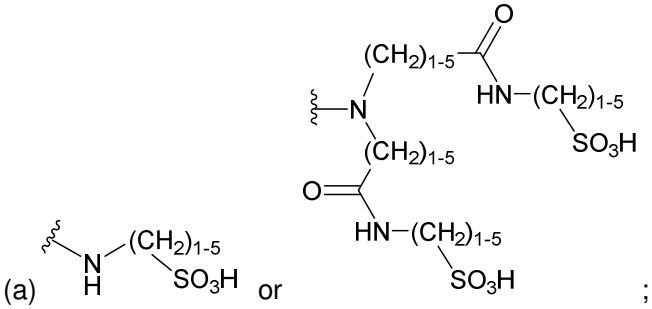
SP^1 and **SP^2** are independently, in each instance, absent, or a spacer group residue;

HG is a hydrophilic residue;

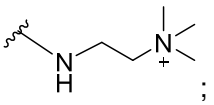
PA is a payload residue; and

subscript **q** is 0 or 1;

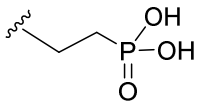
wherein **HG** is selected from the following:

(a)  or ;

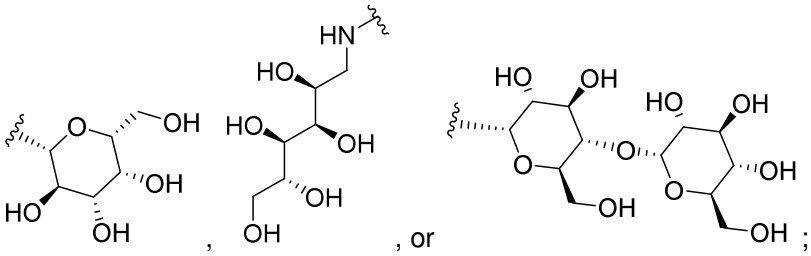
(b)

 ;

(c)

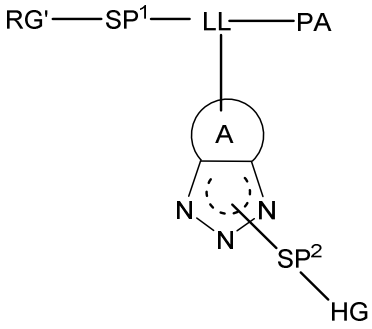
 ; or

(d)

 ;

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

35. The compound of claim 34, according to Formula (**VIII**):



(**VIII**)

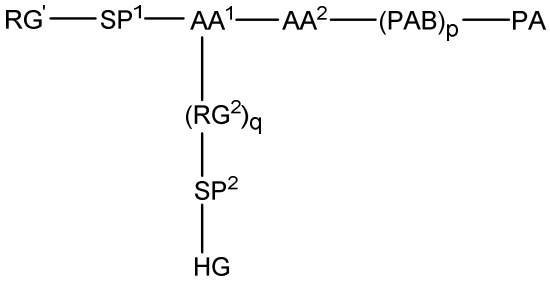
wherein

LL is –**AA**^{1}-**AA**^{2}-(**PAB**)$_{p}$,

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 -N**R**^{a}**R**^{b}, where each of **R**^{a} and **R**^{b} is alkyl or -H.

36. The compound of claim 34, according to Formula (**IX**):

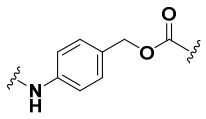


(**IX**)

wherein:

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

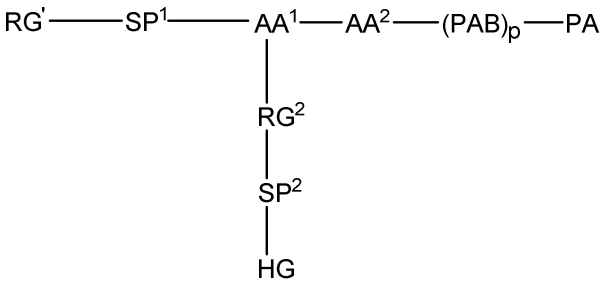
AA^{2} is a dipeptide, tripeptide or tetrapeptide residue; and

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

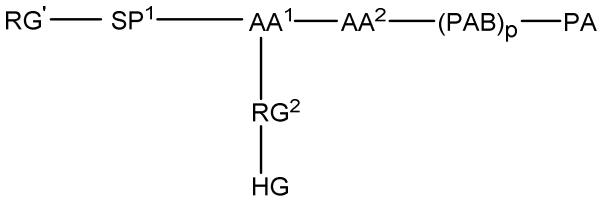
subscript **p** is 0 or 1; and

subscript **q** is 0 or 1.

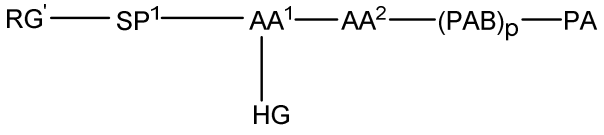
37. The compound of claim 36, according to Formula (**IXa**), Formula (**IXb**) or Formula (**IXc**):



(**IXa**),



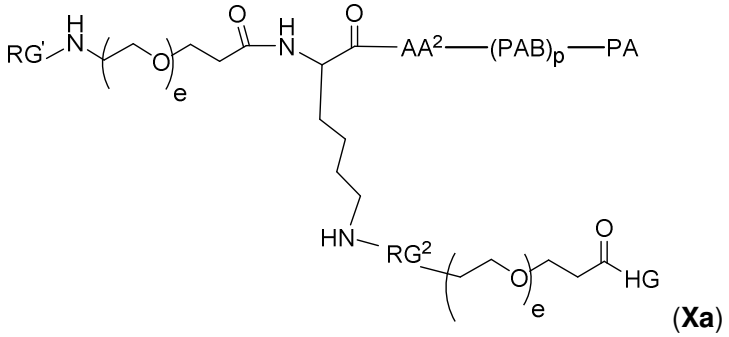
(**IXb**),



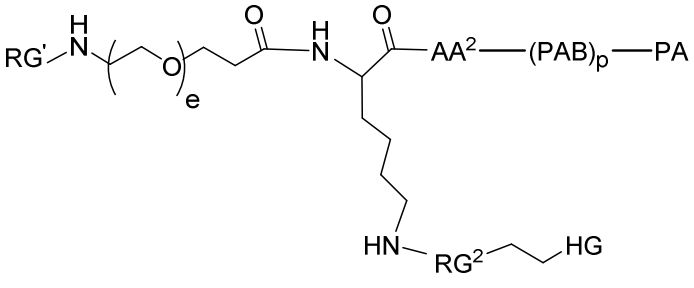
(**IXc**).

38. The compound according to claim 37, wherein **AA**^{1} is lysine, glutamine, glutamic acid, or aspartic acid.

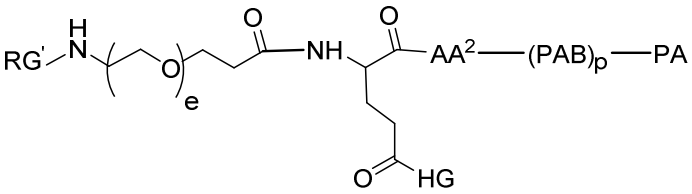
39. The compound of claim 37, according to Formula (**Xa**), (**Xb**), (**Xc**), or (**Xd**):



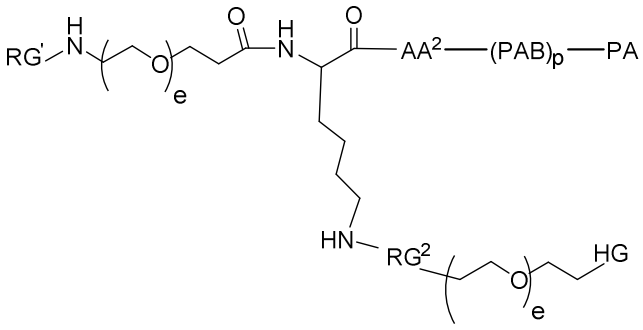
(**Xa**)



(**Xb)**



(**Xc**), or

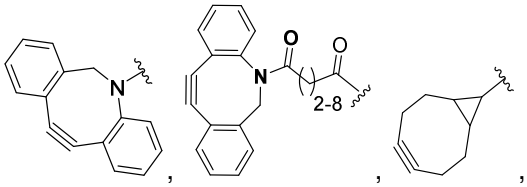


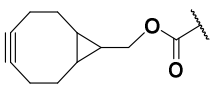
(**Xd**),

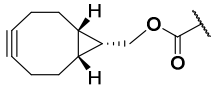
wherein:

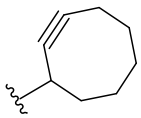
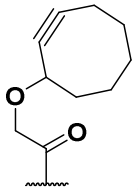
subscript **e** is independently, in each instance, an integer from 0 to 6.

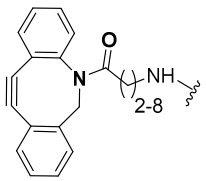
40. The compound of any one of claims 35-39, wherein **RG′** is, independently in each instance, a click chemistry residue.

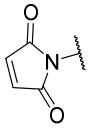
41. The compound of any one of claims 35-39, wherein **RG′** is, independently in each instance, selected from the group consisting of 

, 

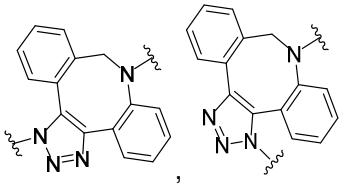
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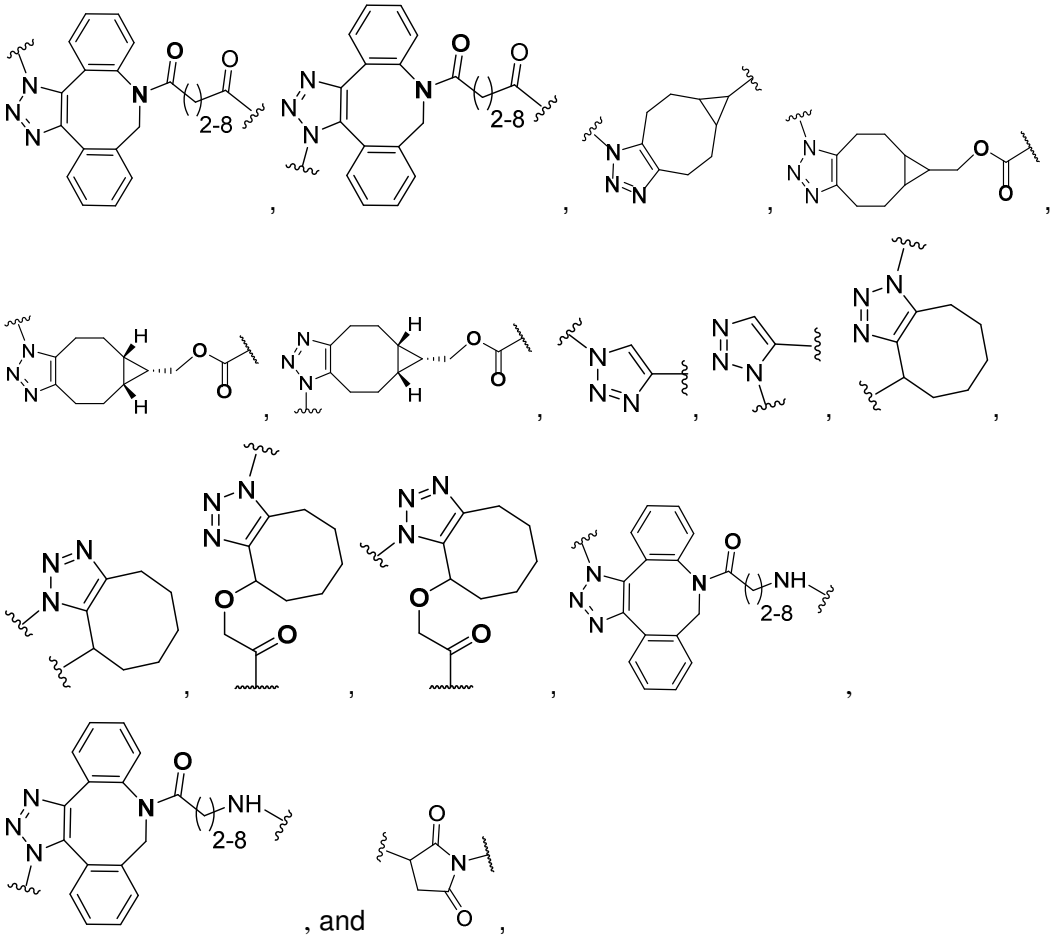
, 

and 

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

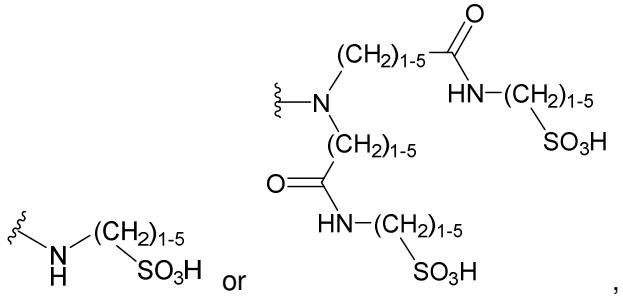
42. The compound of any one of claims 35-41, wherein **RG²** is independently, in each instance, selected from the group consisting of 

,



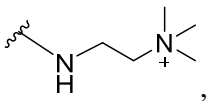
wherein the indicates the atom through which the **RG²** is bonded to the adjacent groups in the formula.

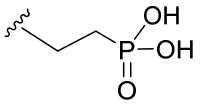
43. The compound of any one of claims 35-42, wherein **HG** is

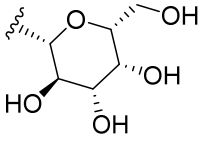
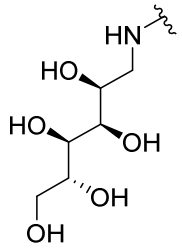
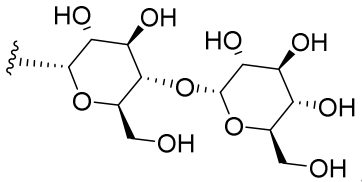


wherein

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

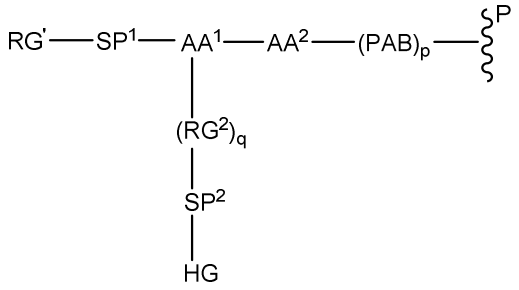
44. The compound of any one of claims 35-42, wherein **HG** is , wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

45. The compound of any one of claims 35-42, wherein **HG** is  wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

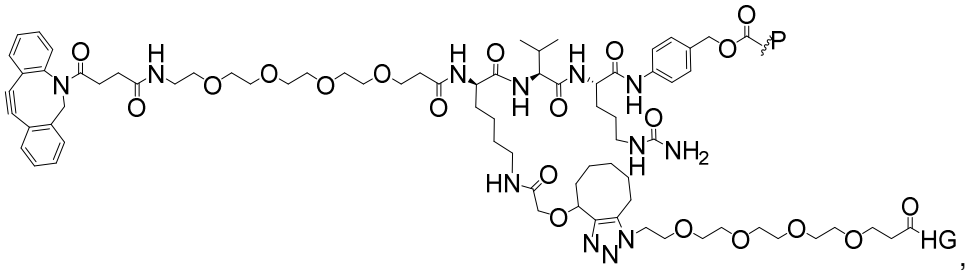
46. The compound of any one of claims 35-42, wherein **HG** is ,  , or  , wherein the  indicates the atom through which the **HG** is bonded to the adjacent groups in the formula.

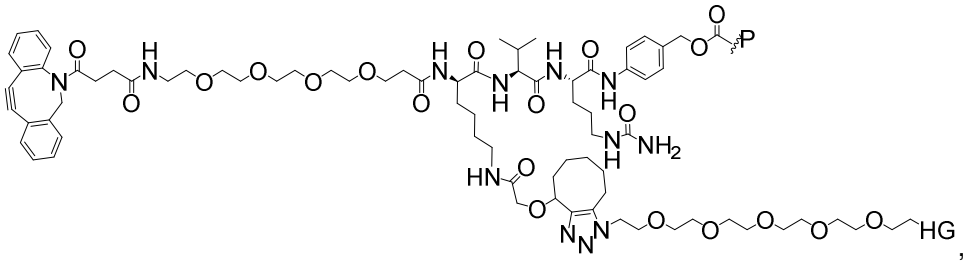
47. The compound of any one of claims 35-46, wherein **SP[1]** and **SP[2]** are independently, in each instance, absent, or selected from the group consisting of $C_{1\text{-}6}$ alkylene, -NH-, -C(O)-, $(\text{-}CH_2\text{-}CH_2\text{-}O)_e$, -NH-$CH_2$-$CH_2$-$(\text{-}O\text{-}CH_2\text{-}CH_2)_e$-C(O)-, -C(O)-$(CH_2)_u$-C(O)-, -C(O)-NH-$(CH_2)_v$-, $(\text{glycine})_4$-serine, 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.

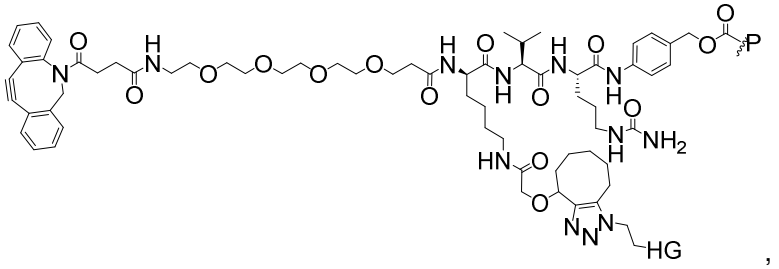
48. The compound of any one of claims 35-47, wherein

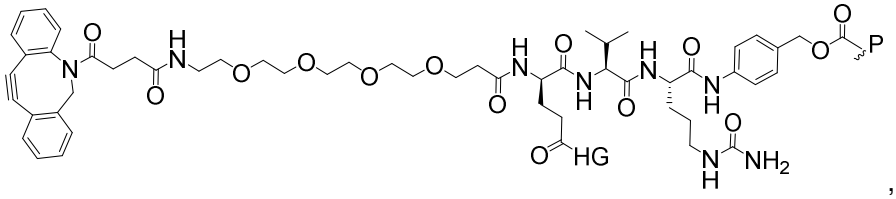


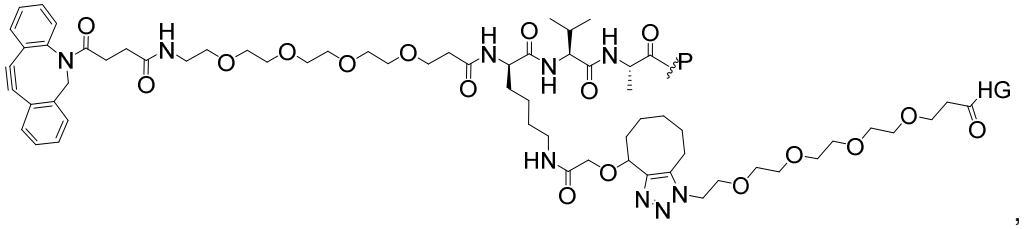
is selected from the group consisting of:

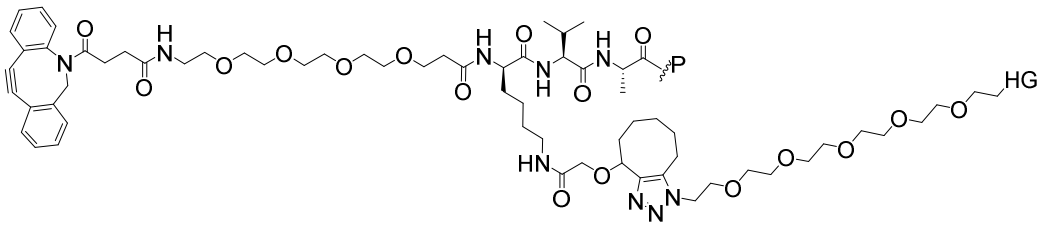

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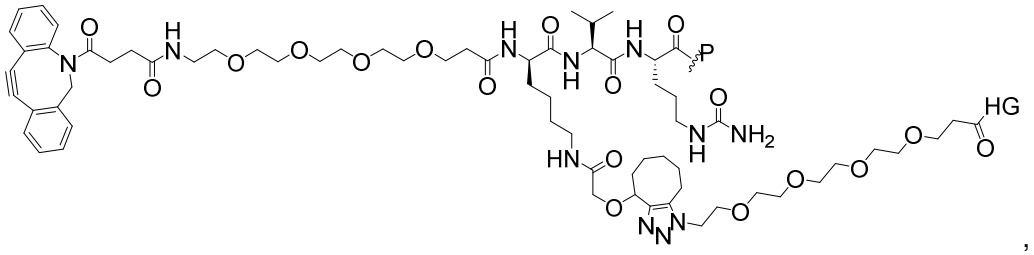

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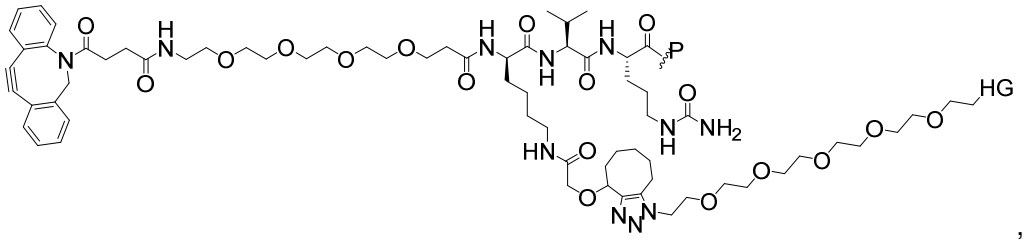

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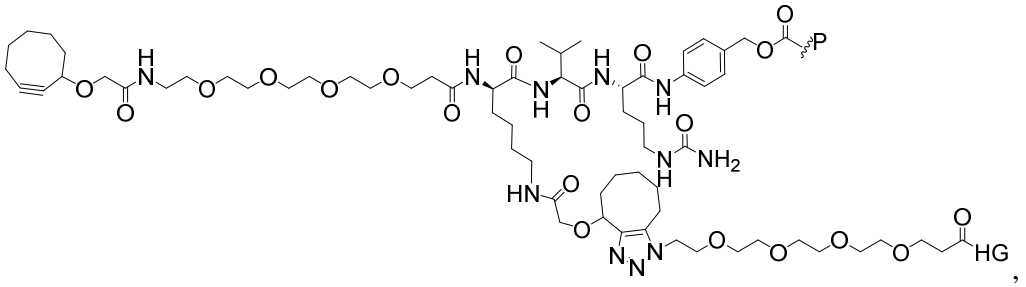
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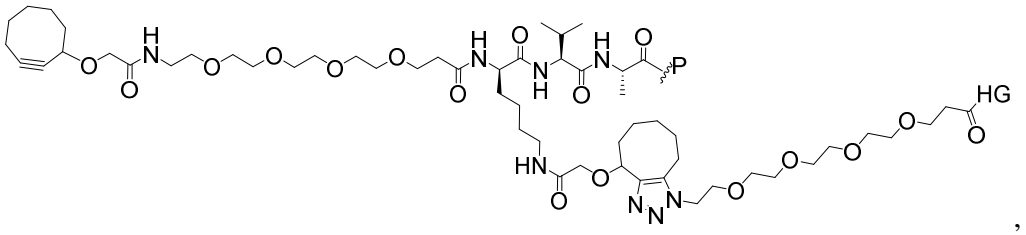
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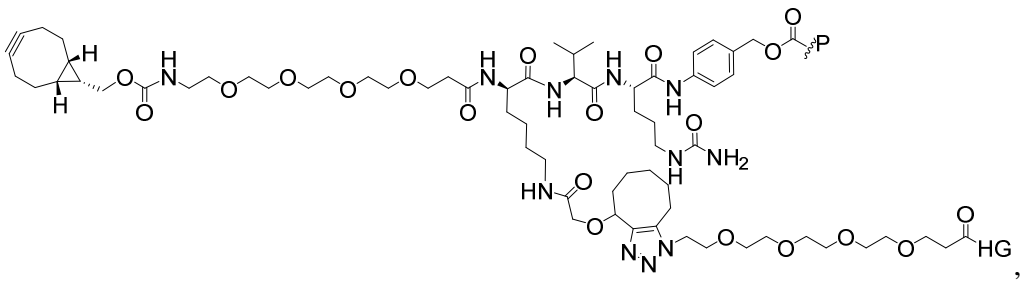
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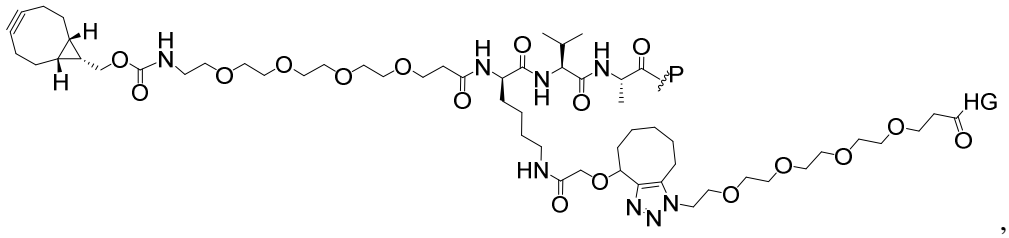
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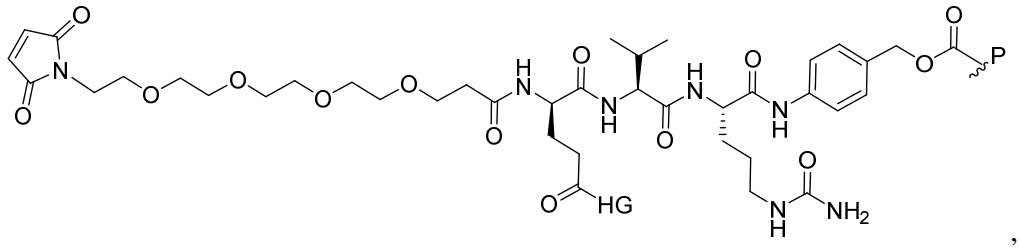
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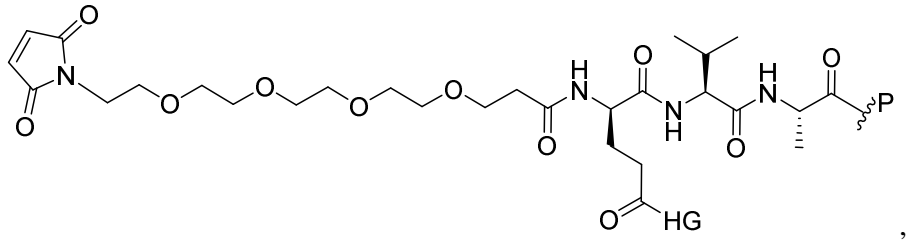


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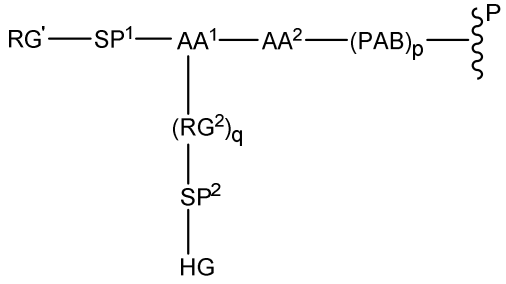


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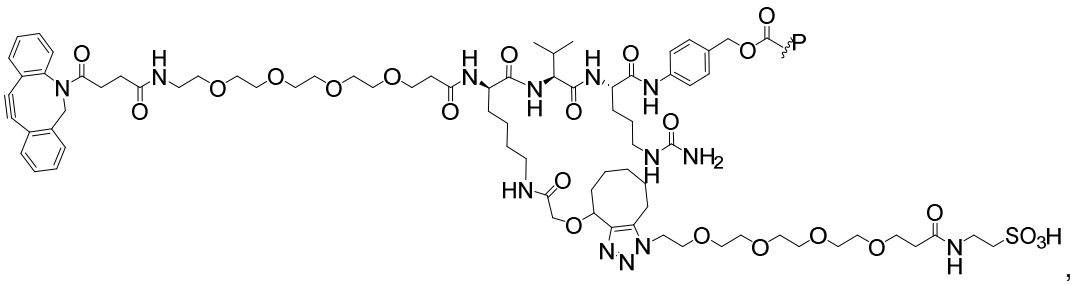
or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

each  is a bond to the payload residue.

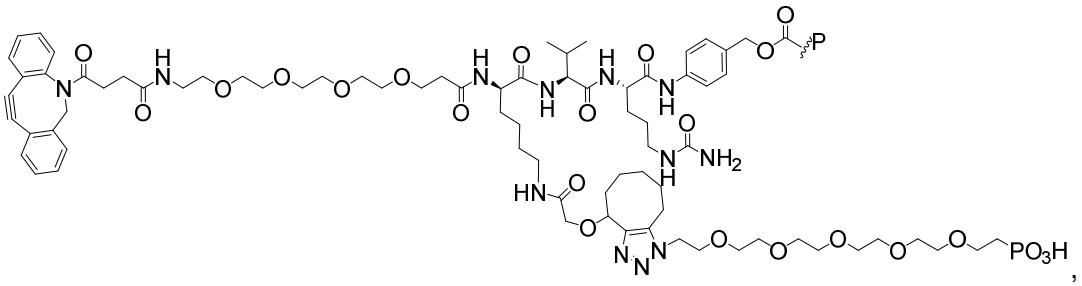
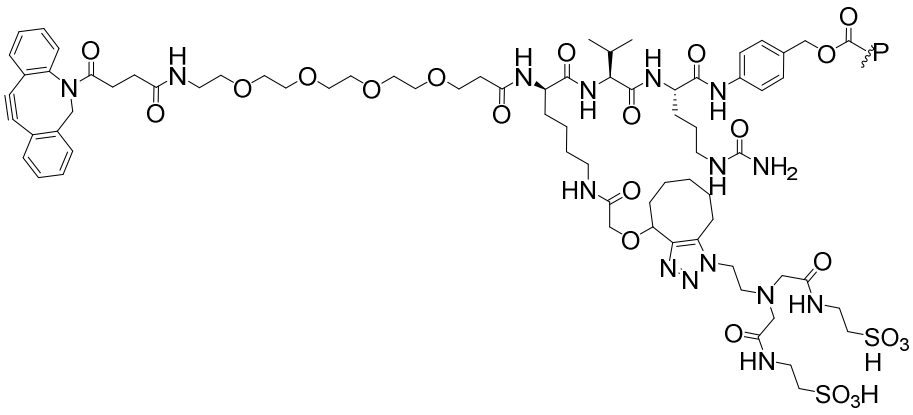
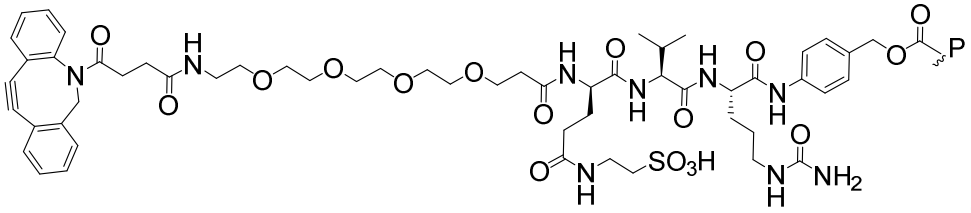
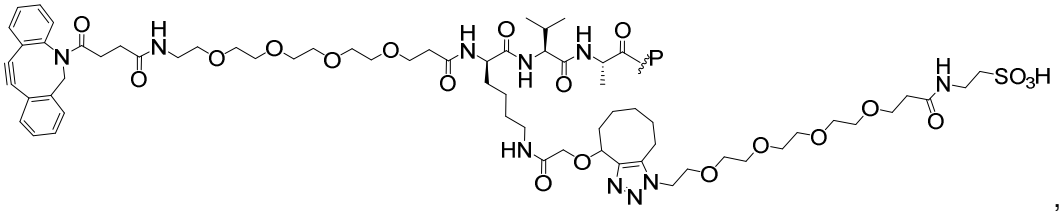
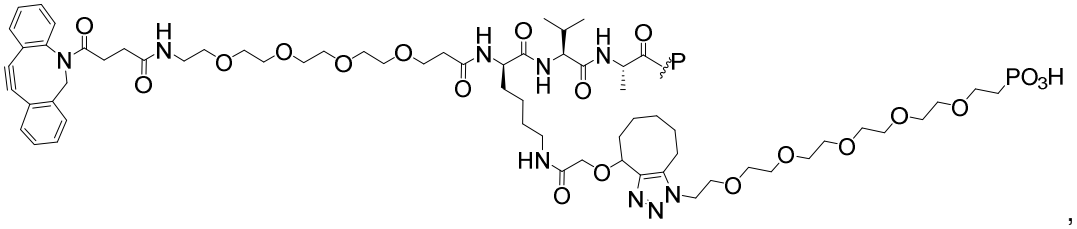
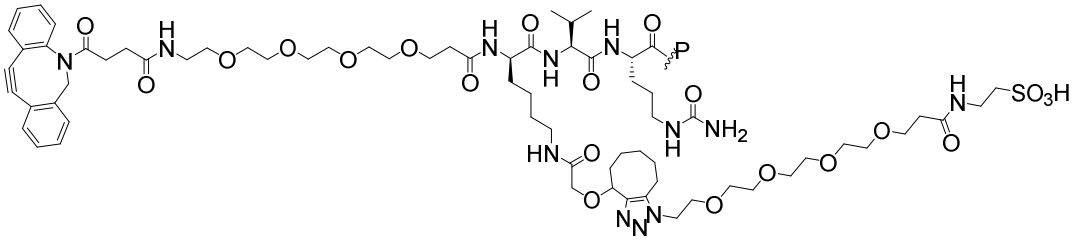
49. The compound of any one of claims 35-47, wherein

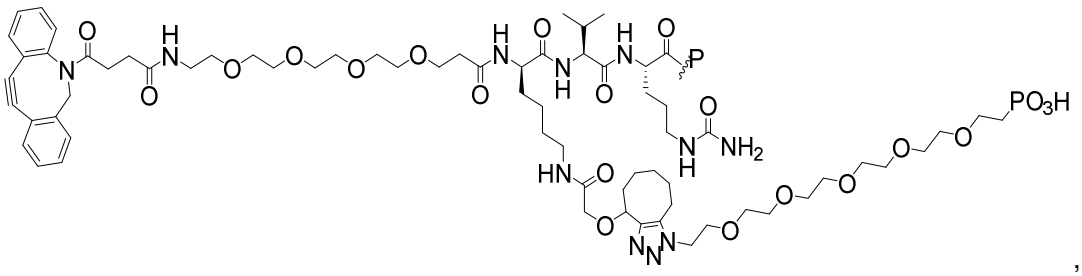


is selected from the group consisting of:

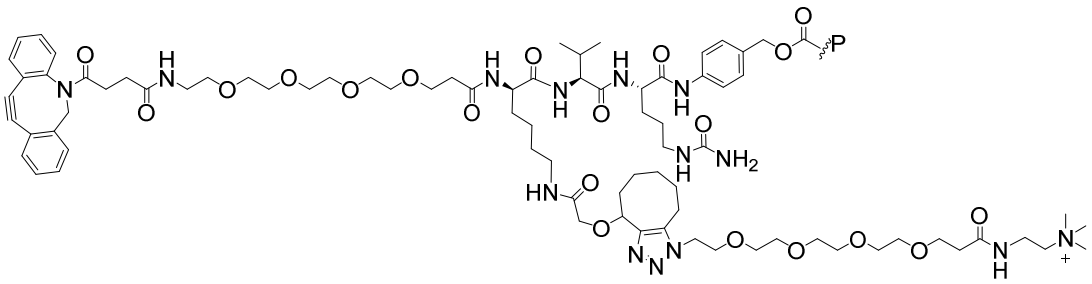


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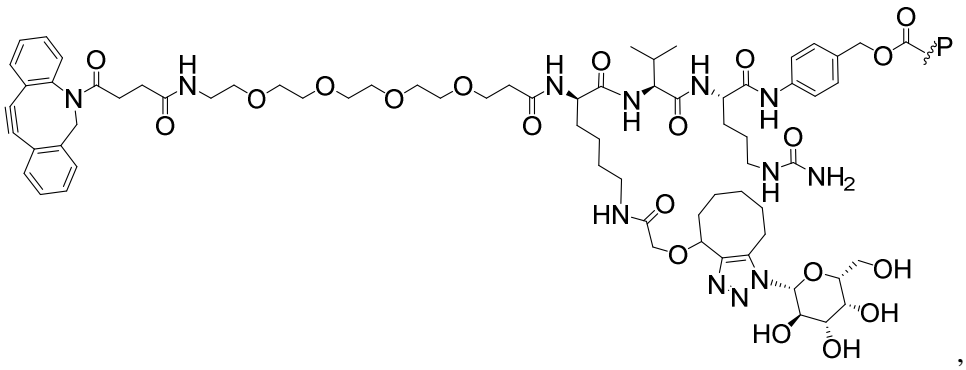

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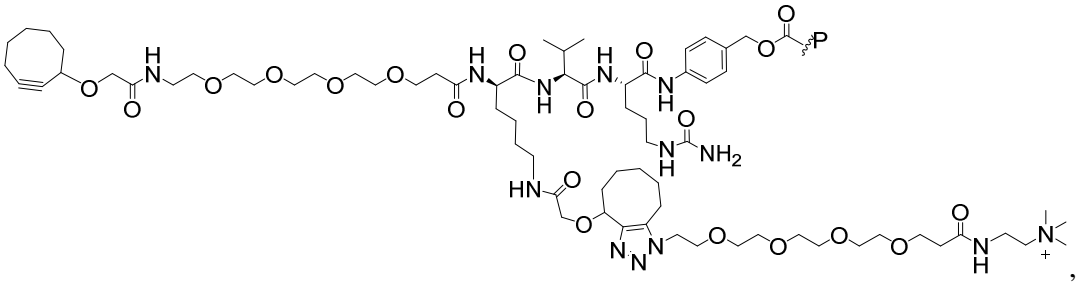
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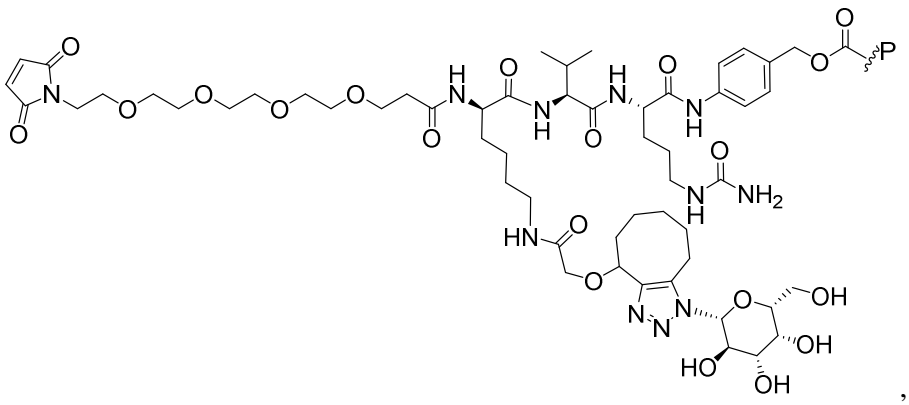
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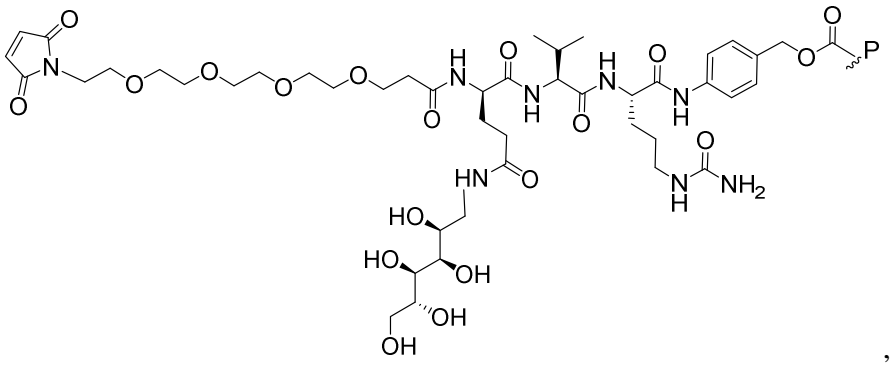
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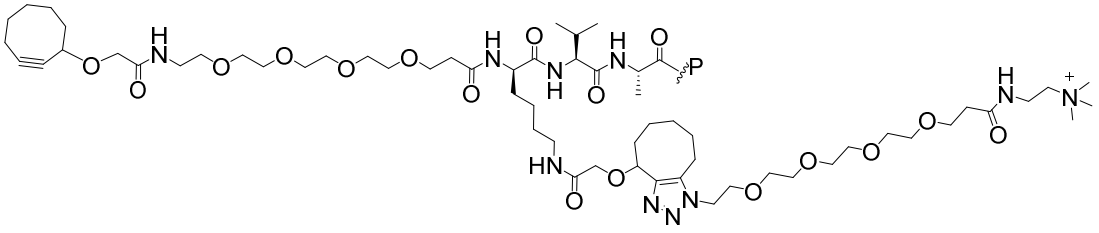
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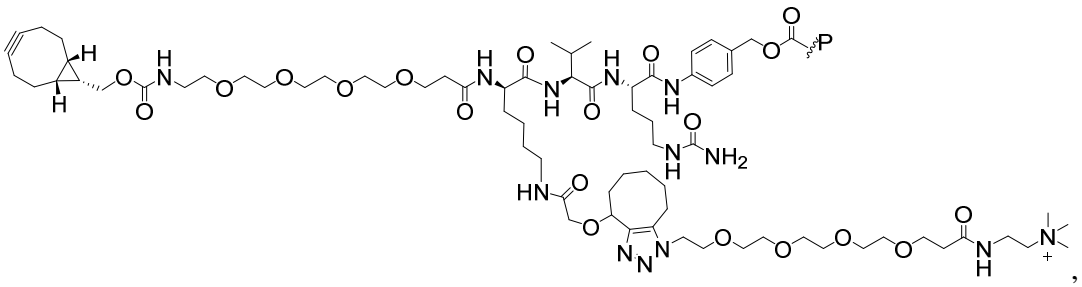
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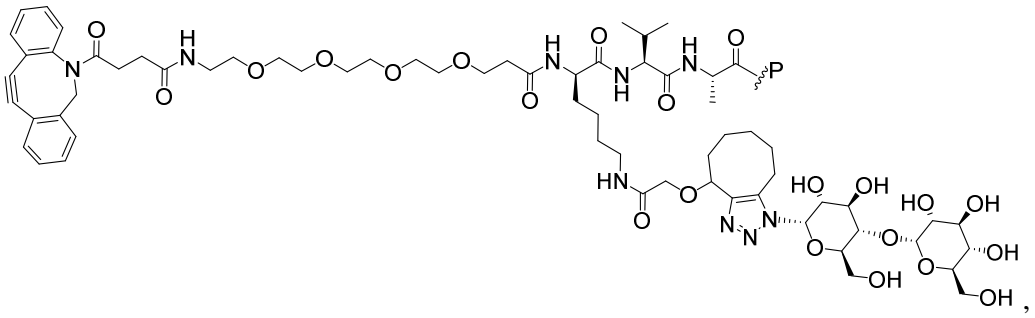


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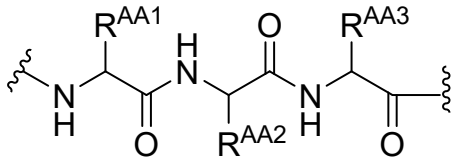
and



or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein

each  is a bond to the payload residue.

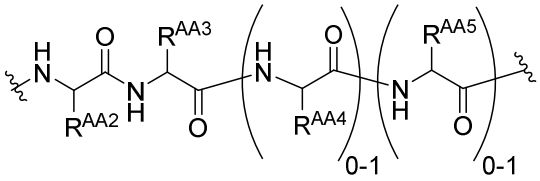
50. The compound of claim 34, wherein **LL** is according to Formula (**LL1**):

 (**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 $\mathbf{-(RG^2)_q\text{-}SP^2\text{-}HG}$

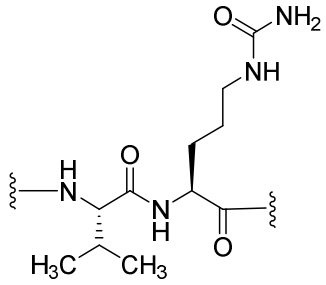
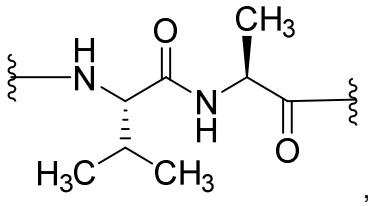
51. The compound of claim 50, wherein $\mathbf{R^{AA1}}$ is a lysine, glutamine, glutamic acid or aspartic acid side chain bonded directly or indirectly to **HG**, and $\mathbf{R^{AA2}}$ and $\mathbf{R^{AA3}}$ are either valine and alanine or valine and citrulline sidechains respectively.

52. The compound of any one of claims 36-49, wherein $\mathbf{AA^2}$ is



wherein $\mathbf{R^{AA2}}$, $\mathbf{R^{AA3}}$, $\mathbf{R^{AA4}}$, and $\mathbf{R^{AA5}}$ are each, independently, amino acid side chains, at least one of which is bonded directly or indirectly to $\mathbf{-(RG^2)_q\text{-}SP^2\text{-}HG}$, wherein the  indicates the atom through which $\mathbf{AA^2}$ is bonded to the adjacent groups in the formula.

53. The compound of any one of claims 36-49, wherein $\mathbf{AA^2}$ is

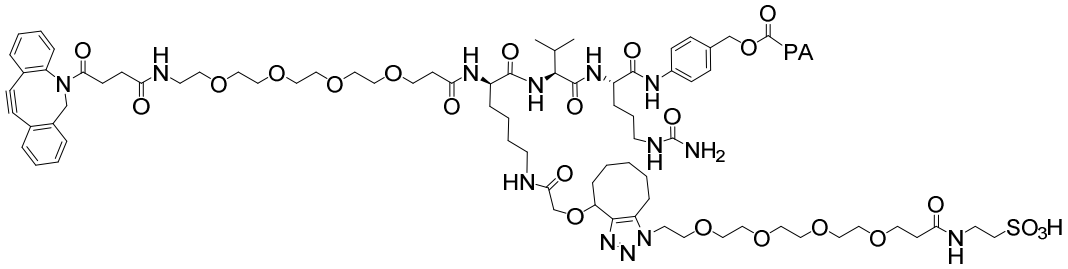
or ,

wherein the  indicates the atom through which **AA²** is bonded to the adjacent groups in the formula.

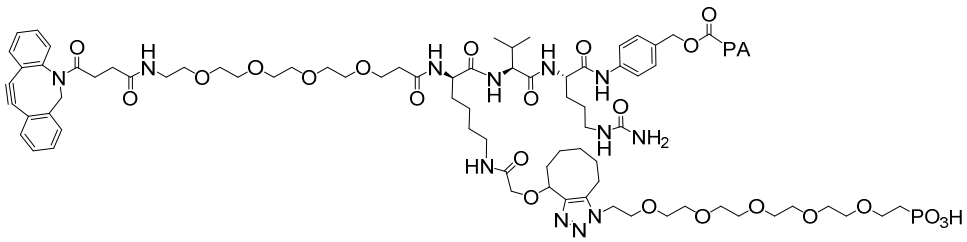
54. The compound of any one of claims 36-47, wherein subscript **e** is 4.

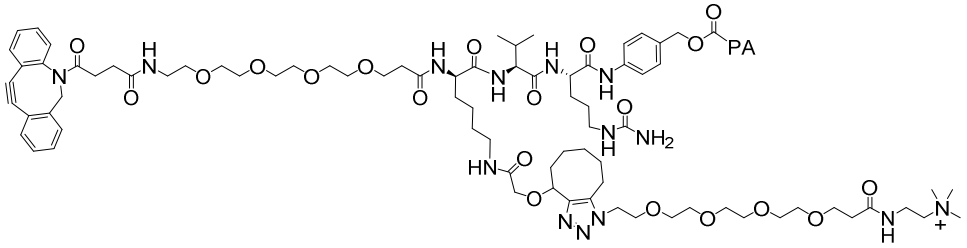
55. The compound of any one of claims 34-54, wherein **PA** is the residue of a group selected from the group consisting of a dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, a vinca alkaloid, a steroid, and a liver X receptor (LXR) modulator.

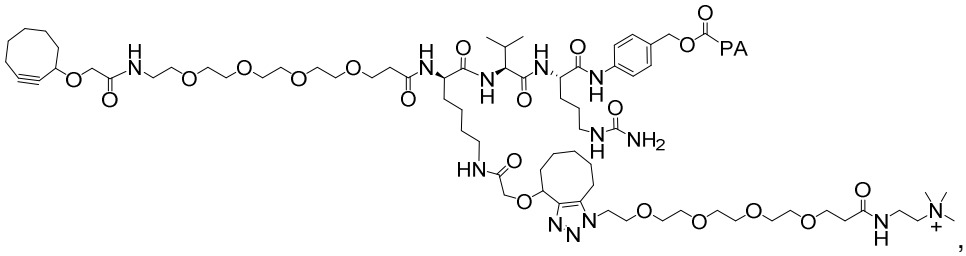
56. The compound of any one of claims 34-55, selected from the group consisting of:



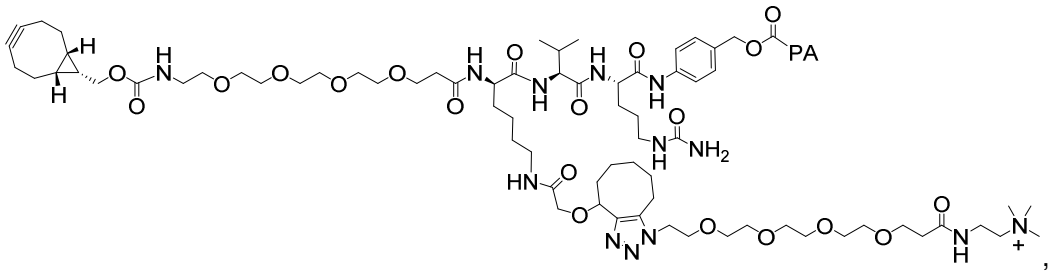
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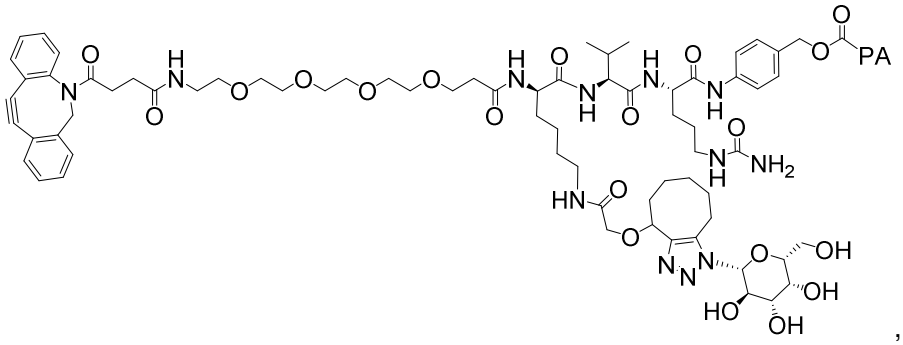




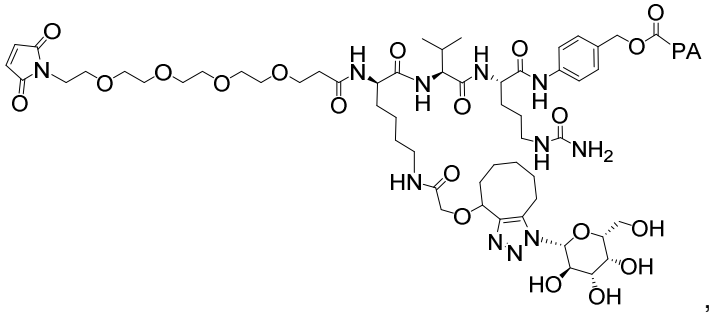
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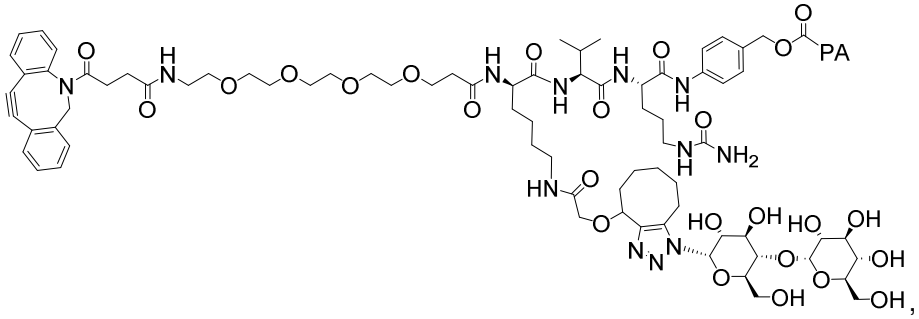
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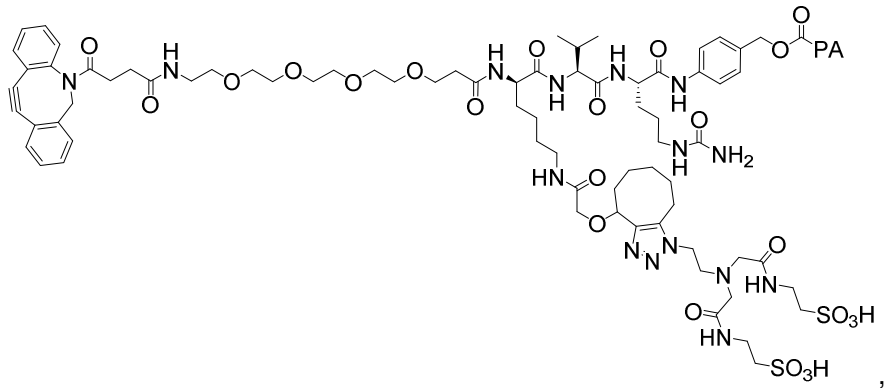
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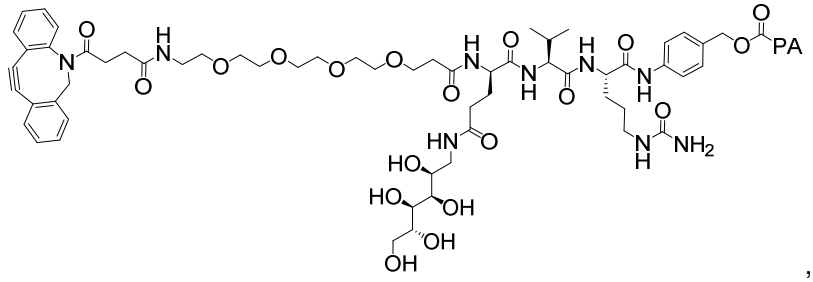


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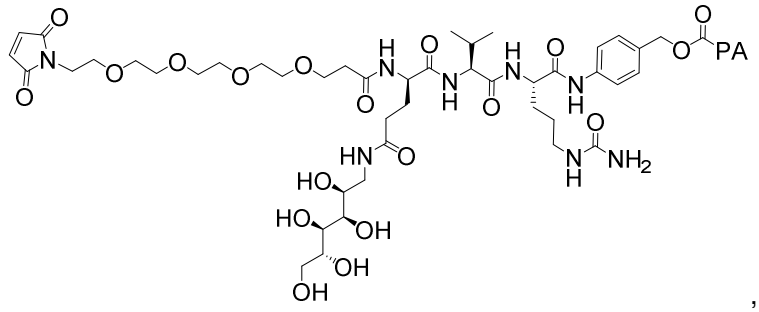


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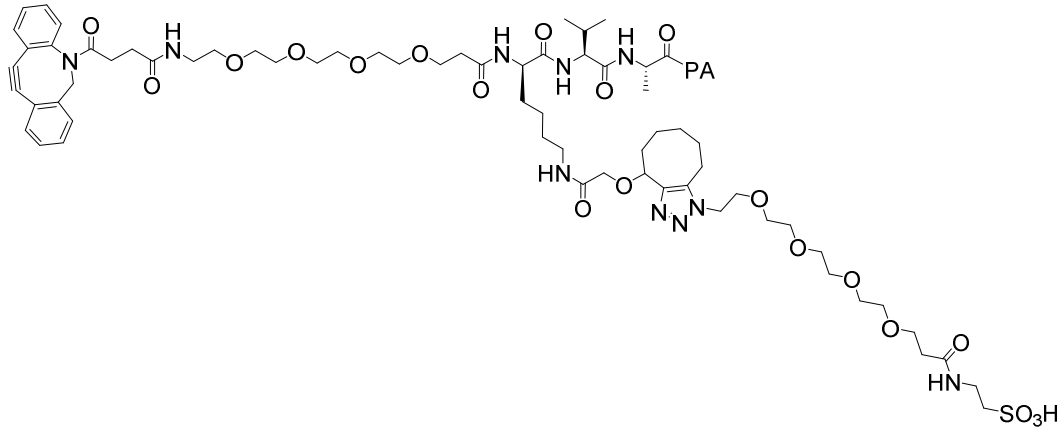
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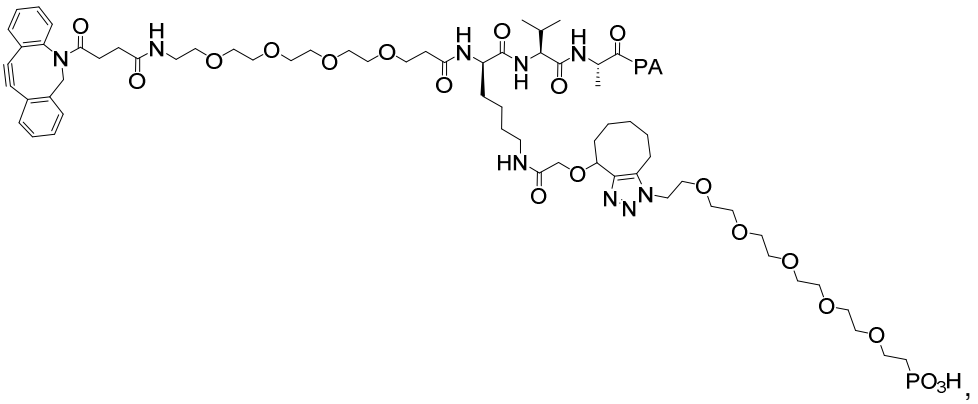
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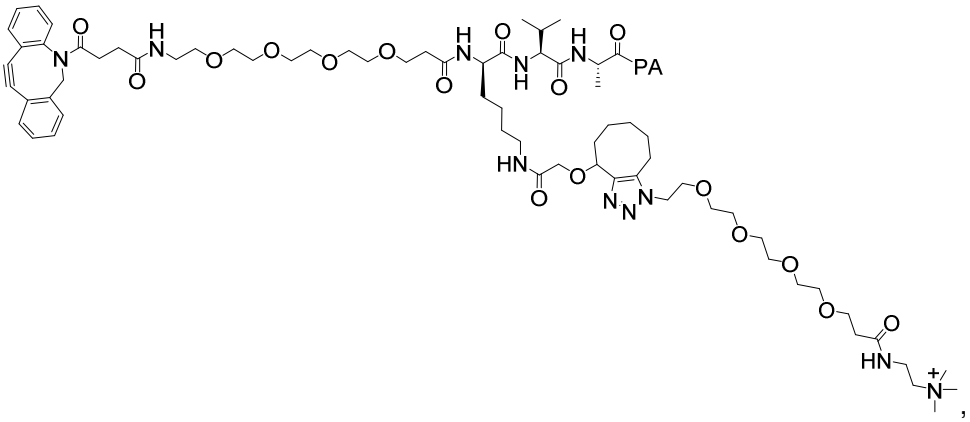


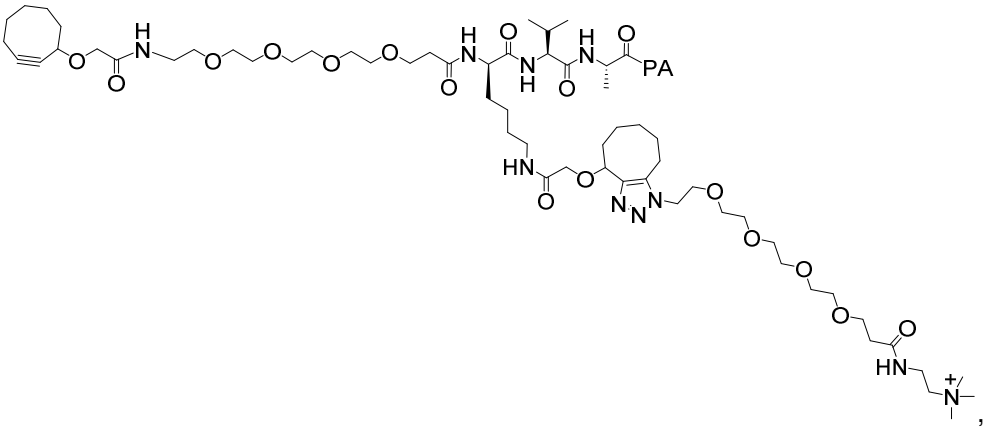
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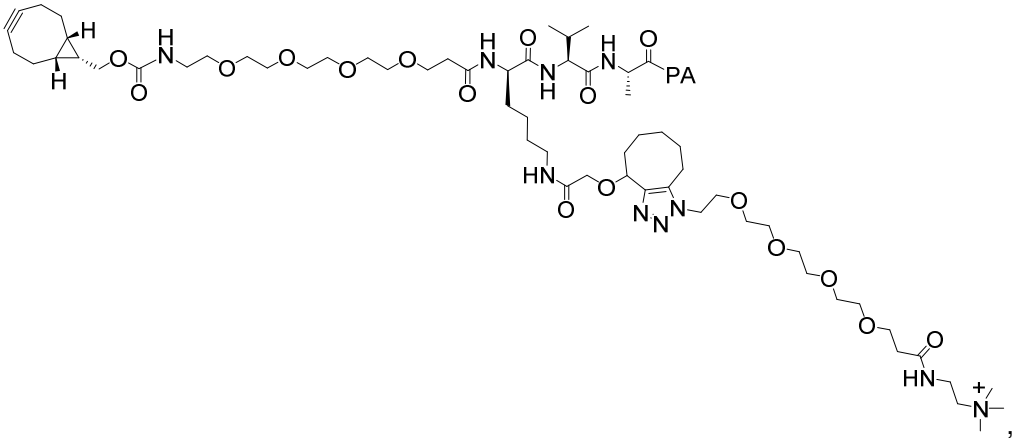


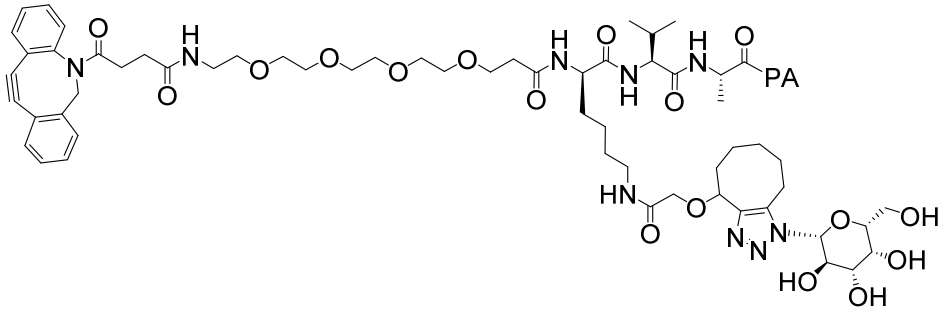
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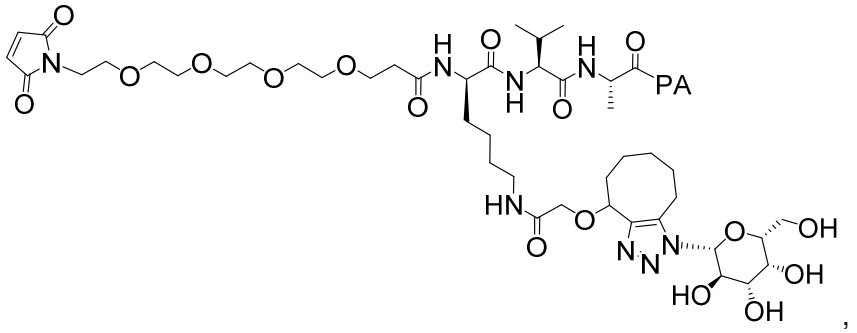

PA
PO3H


PA

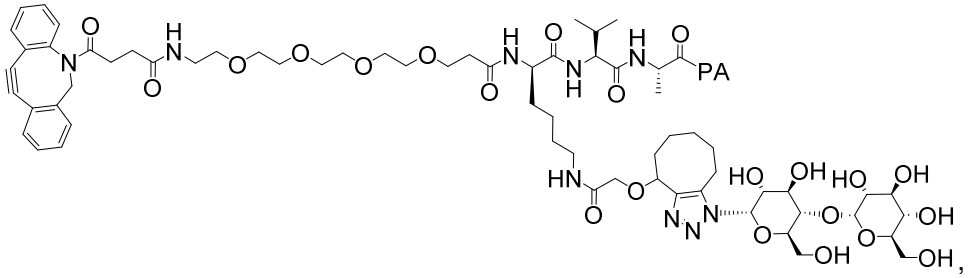

PA


PA

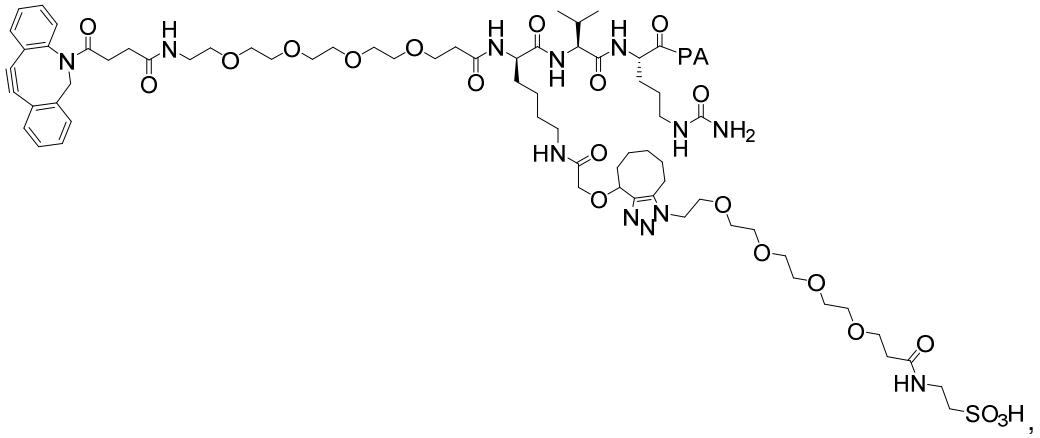




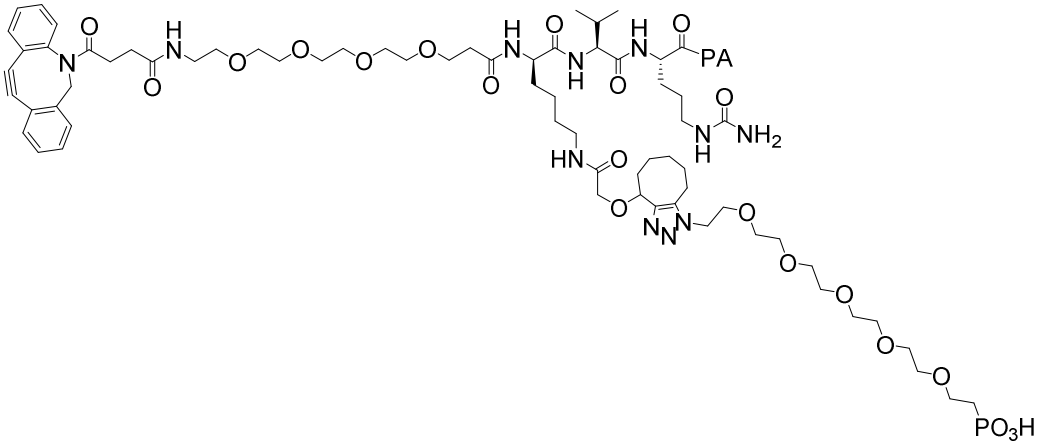
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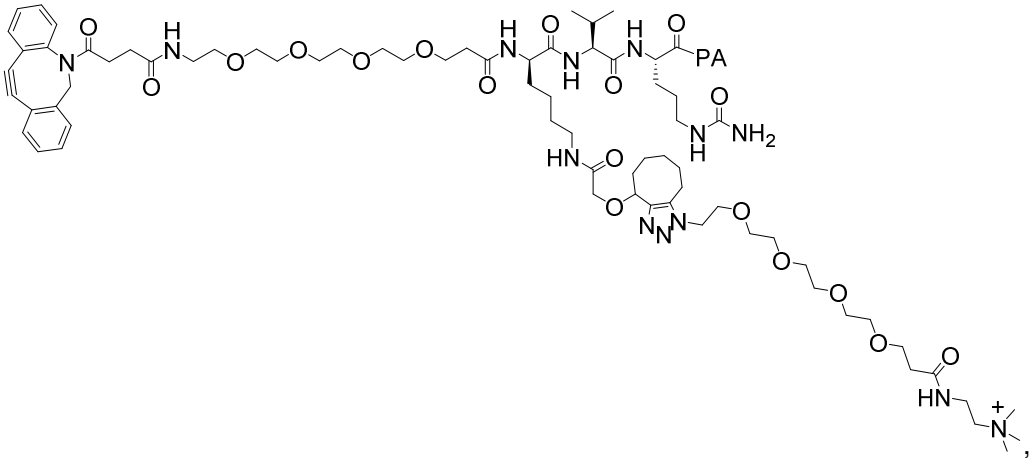


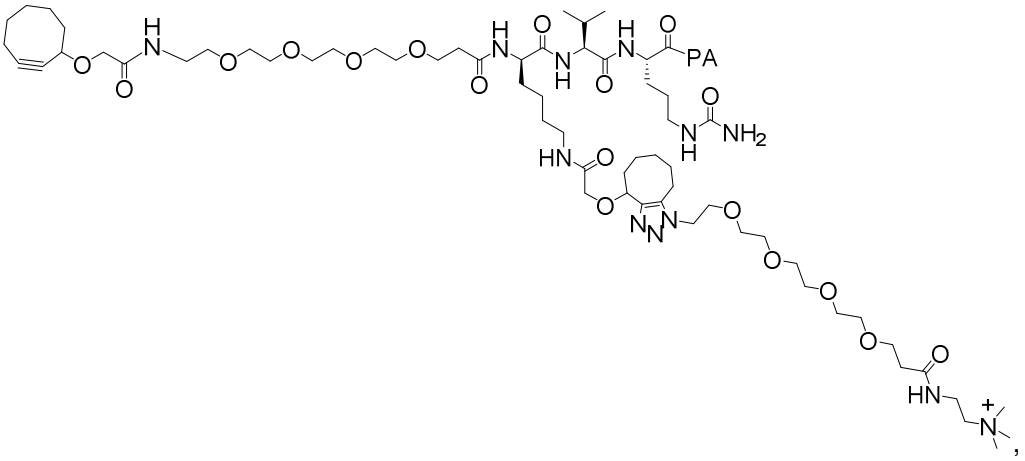
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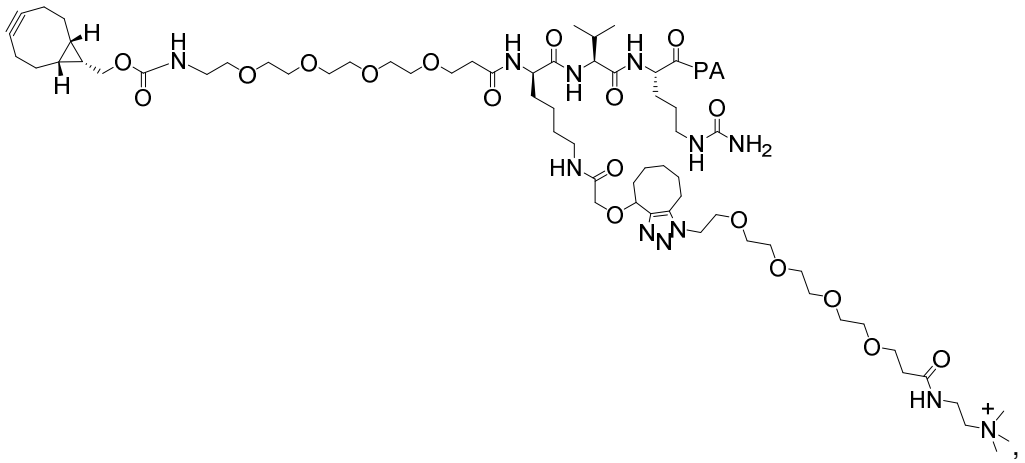


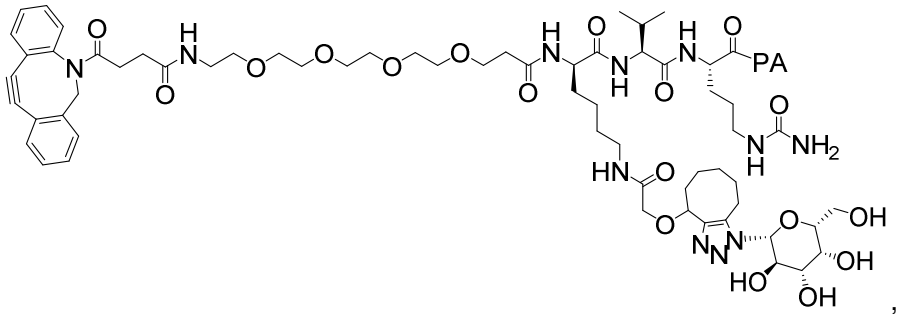
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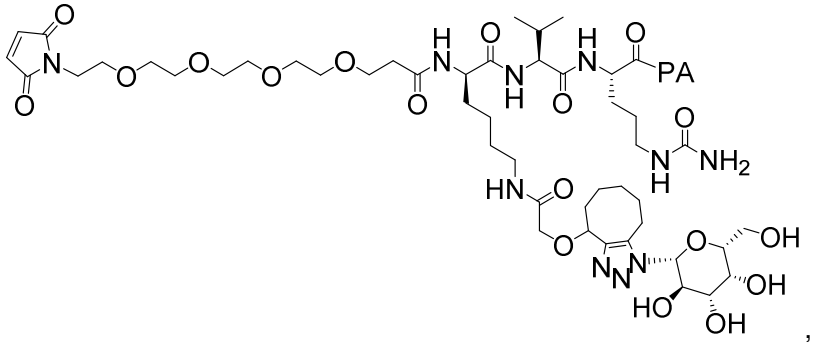




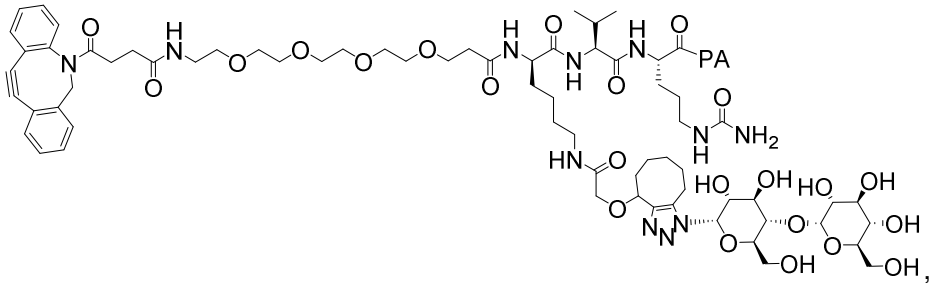






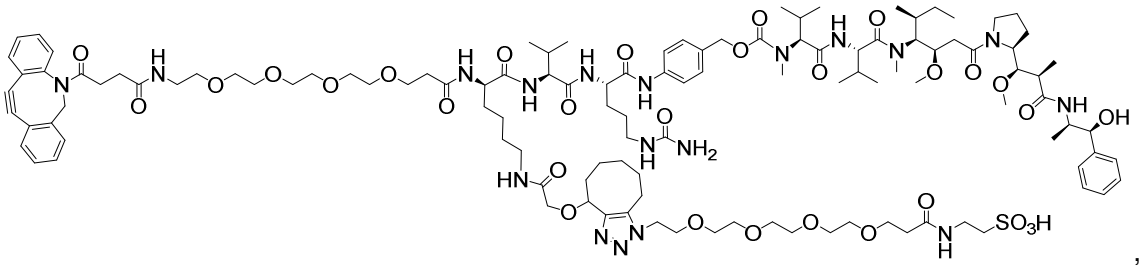


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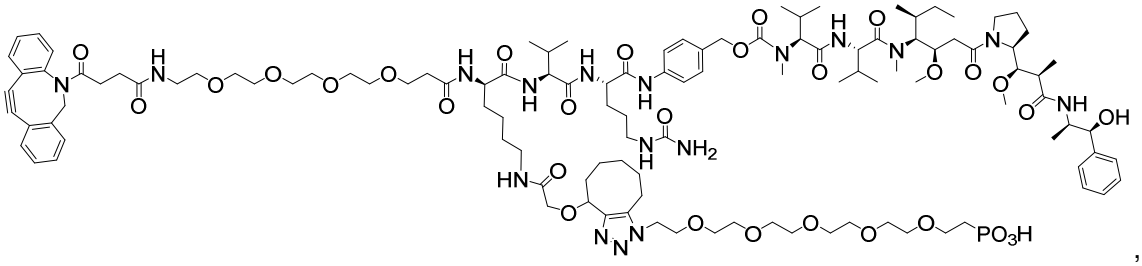


or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof, wherein **PA** is a payload residue.

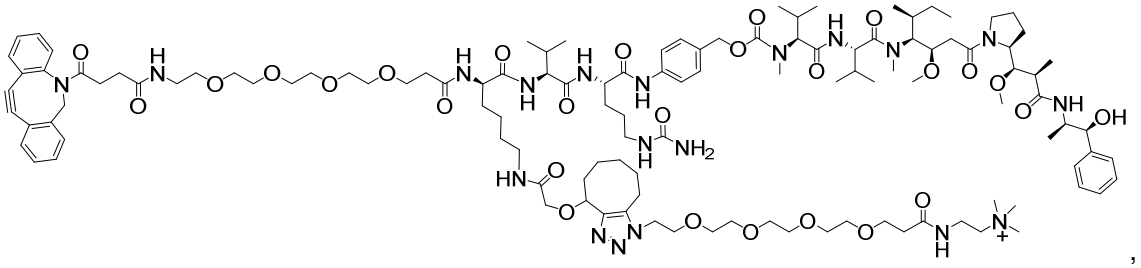
57. The compound of any one of claims 34-55, selected from the group consisting of:



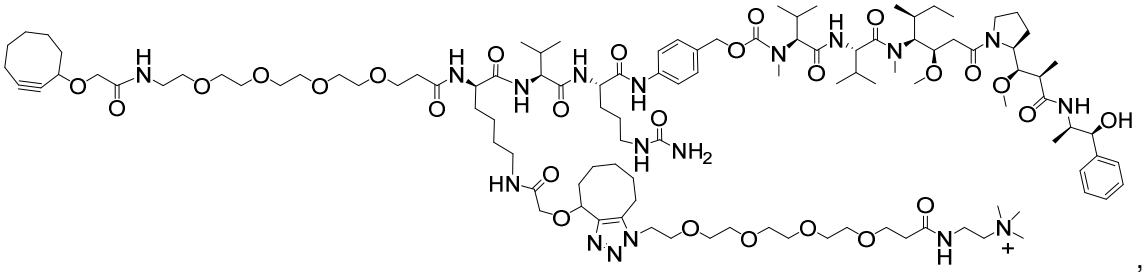
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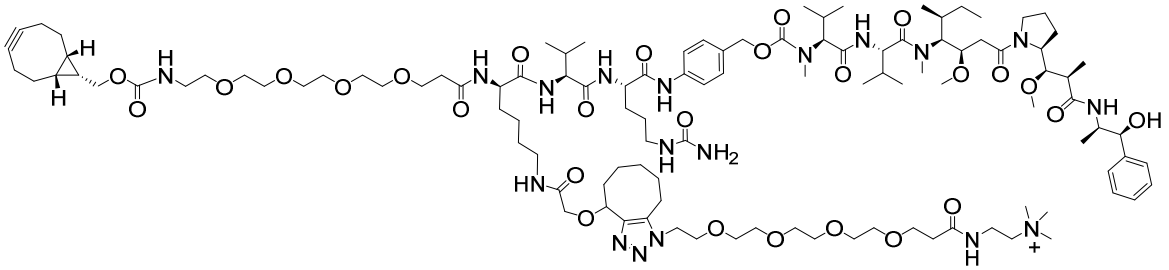
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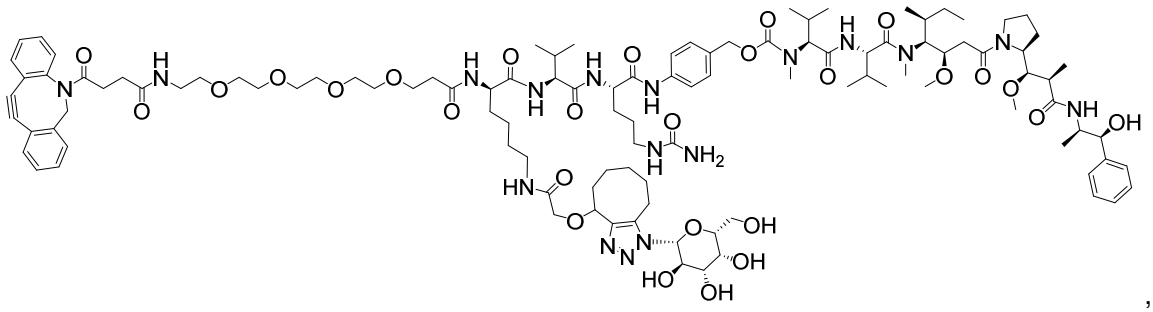
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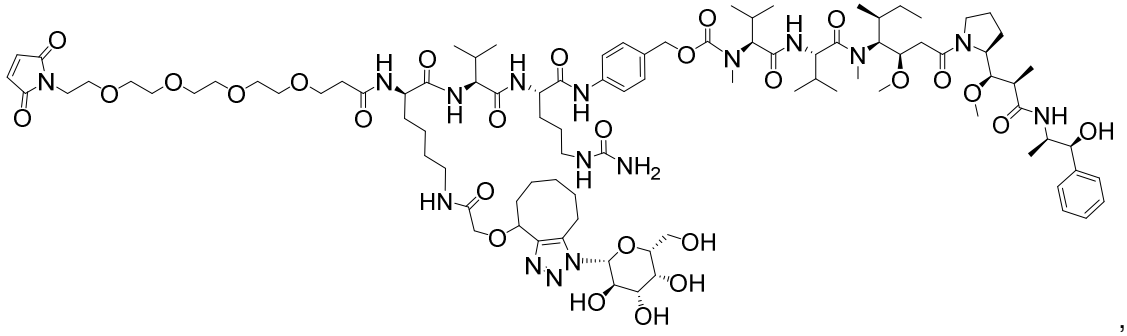
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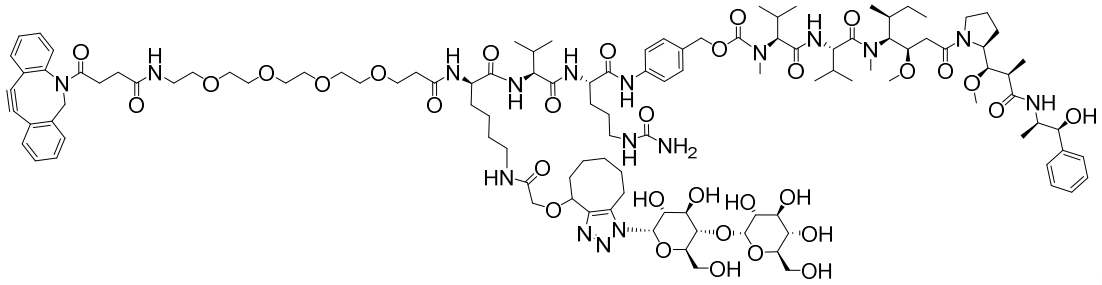
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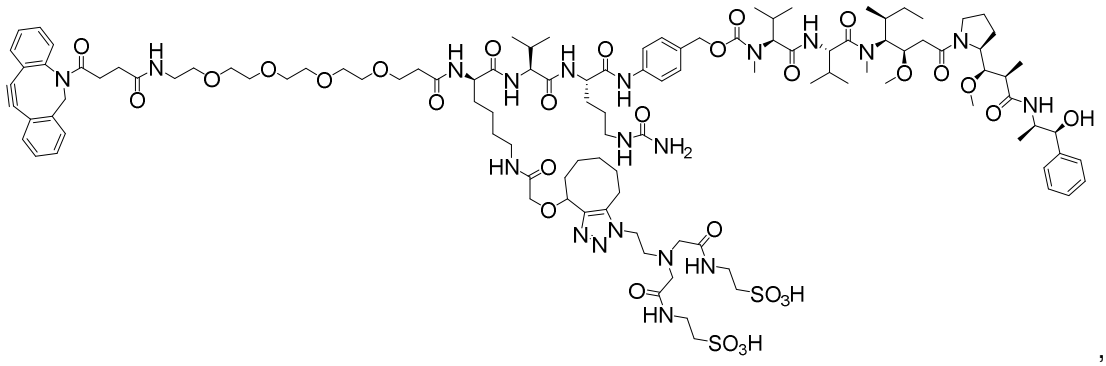
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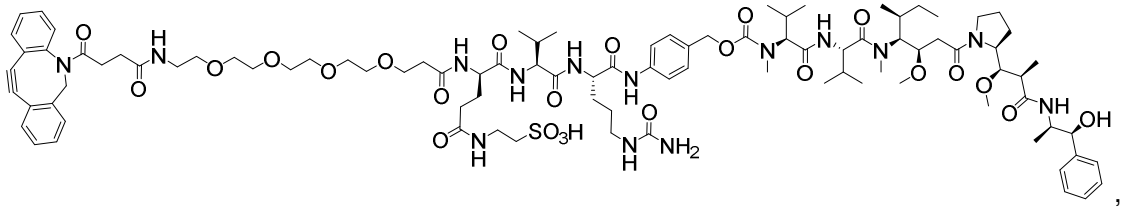
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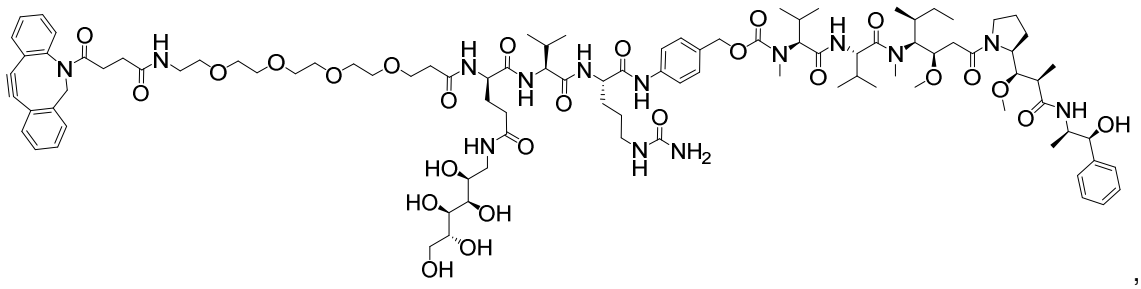
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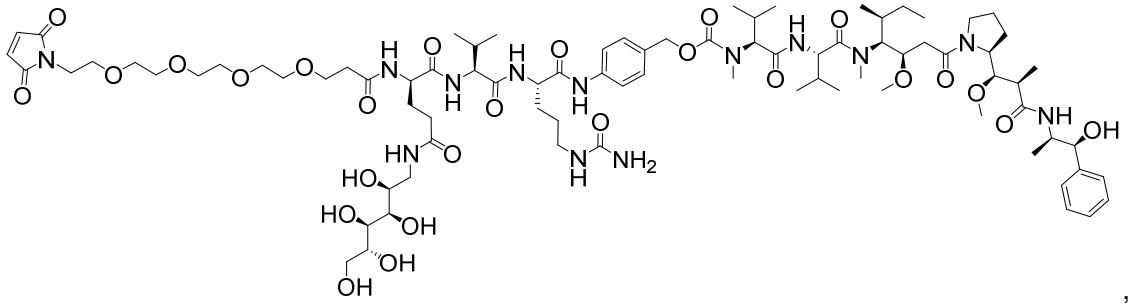
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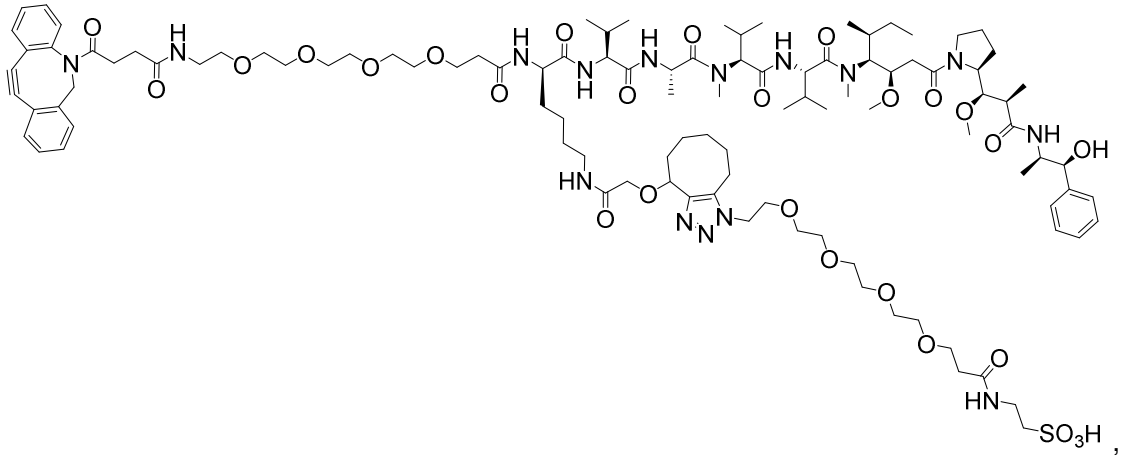
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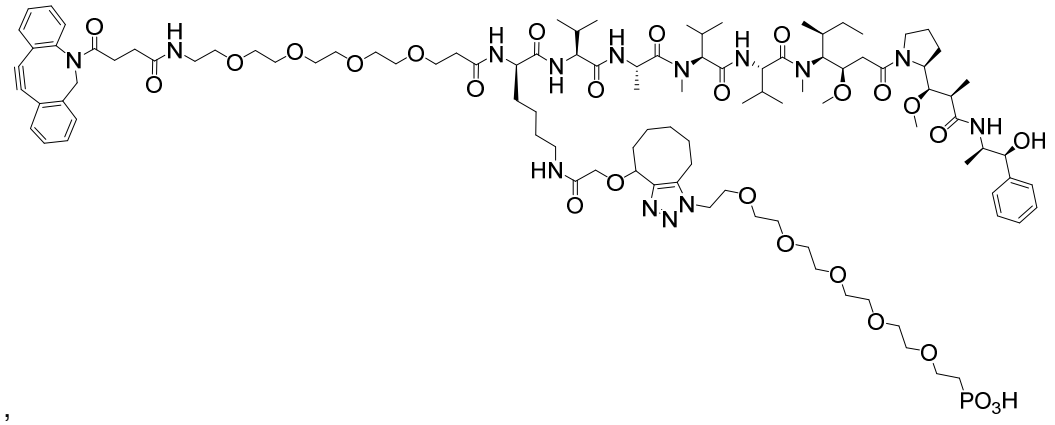
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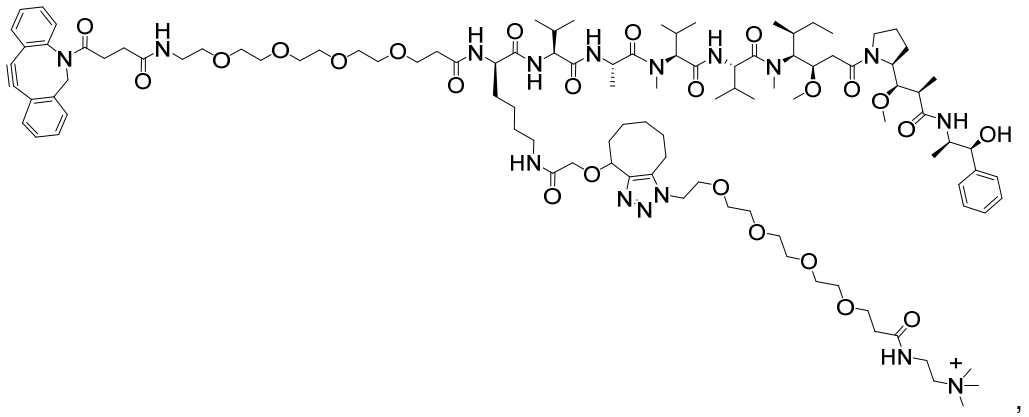
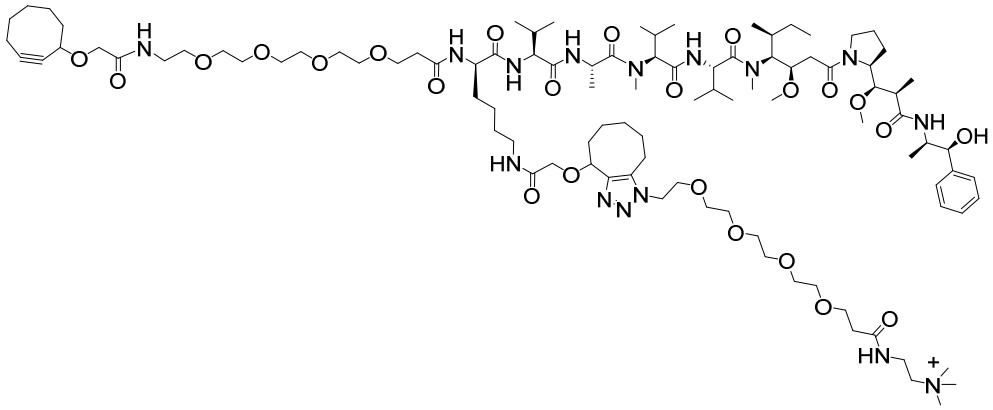
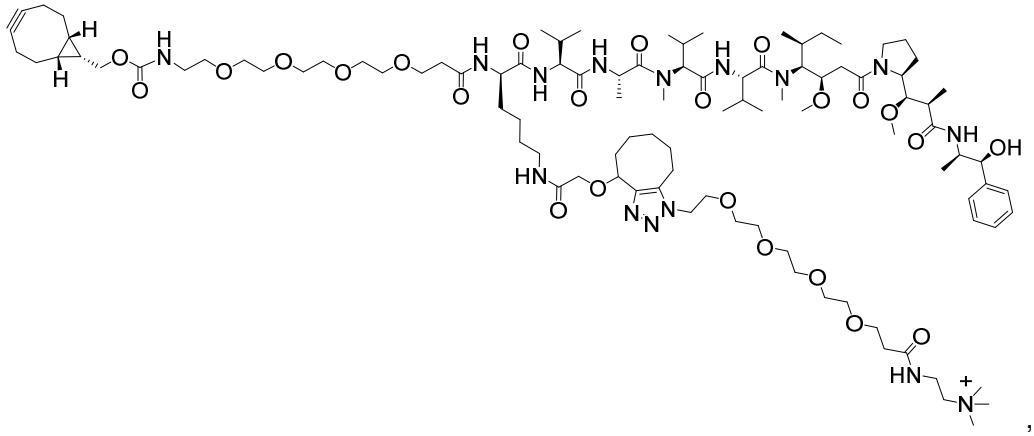
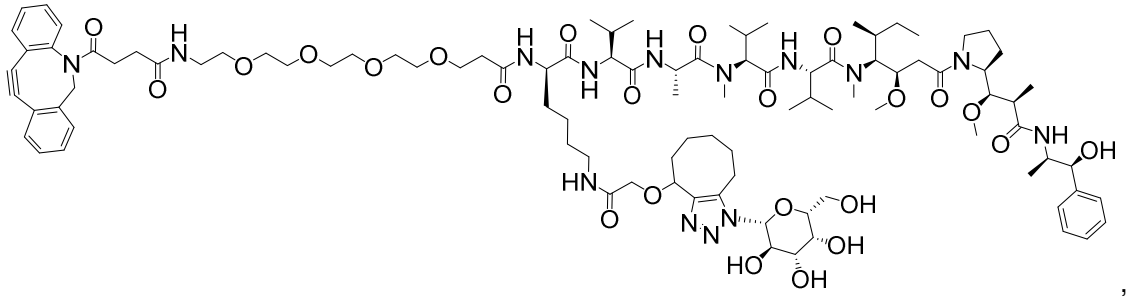
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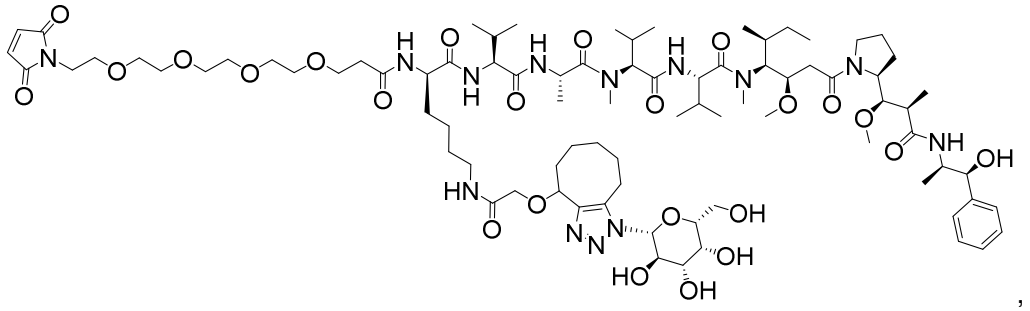
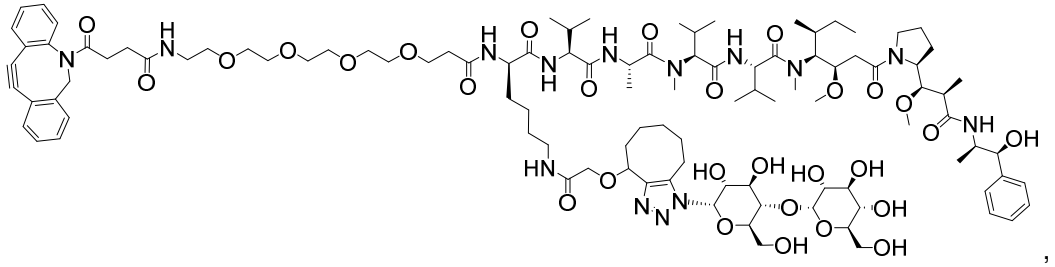
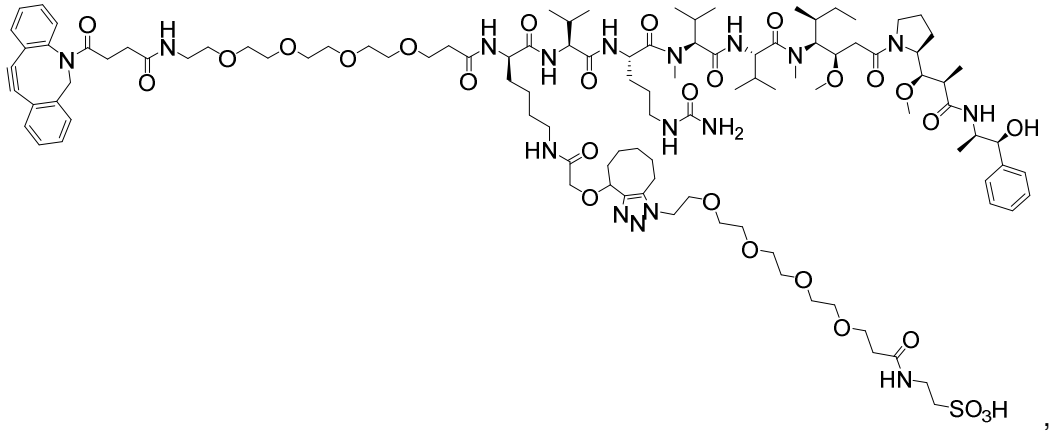
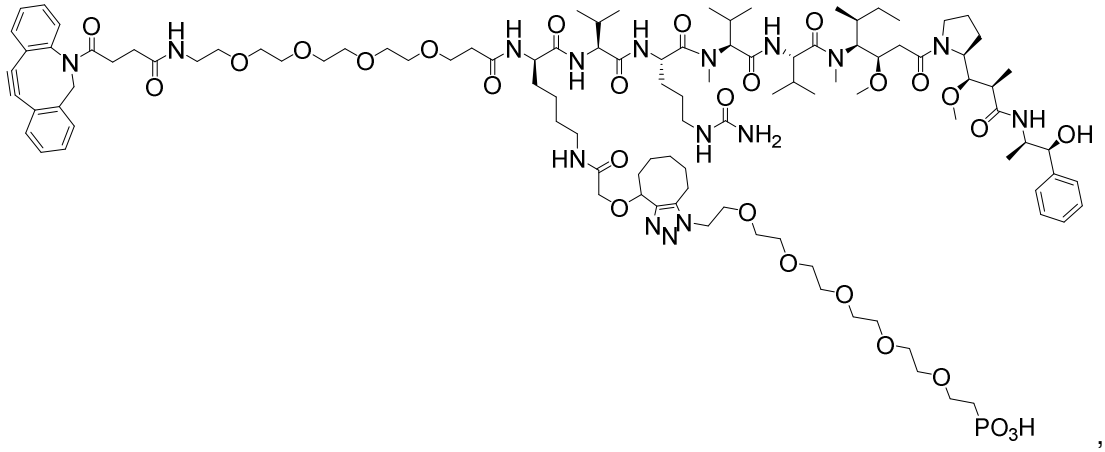


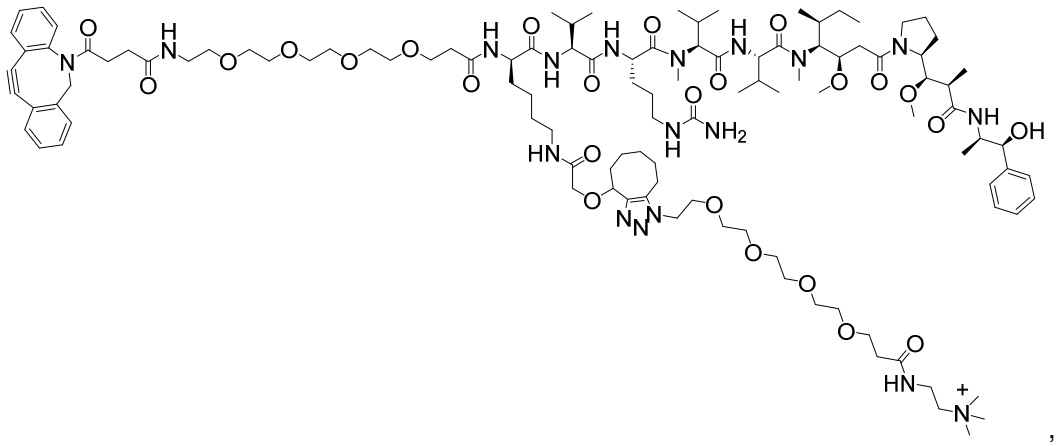
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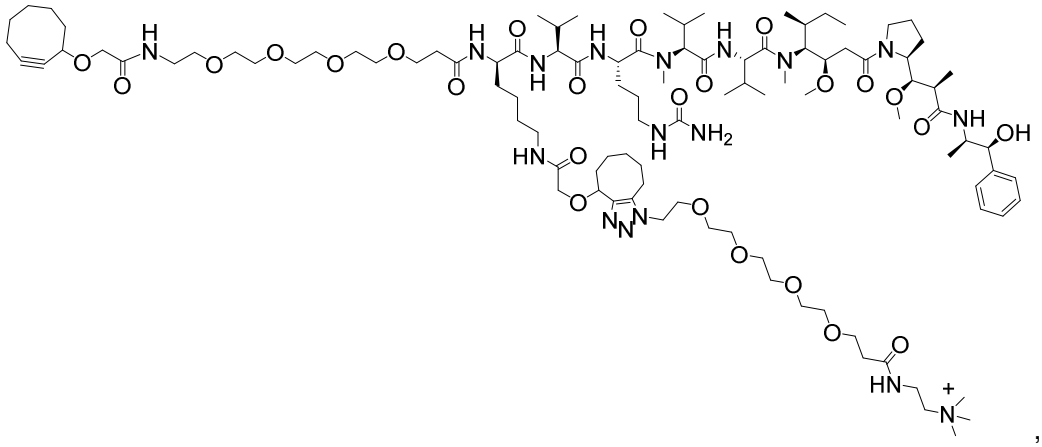
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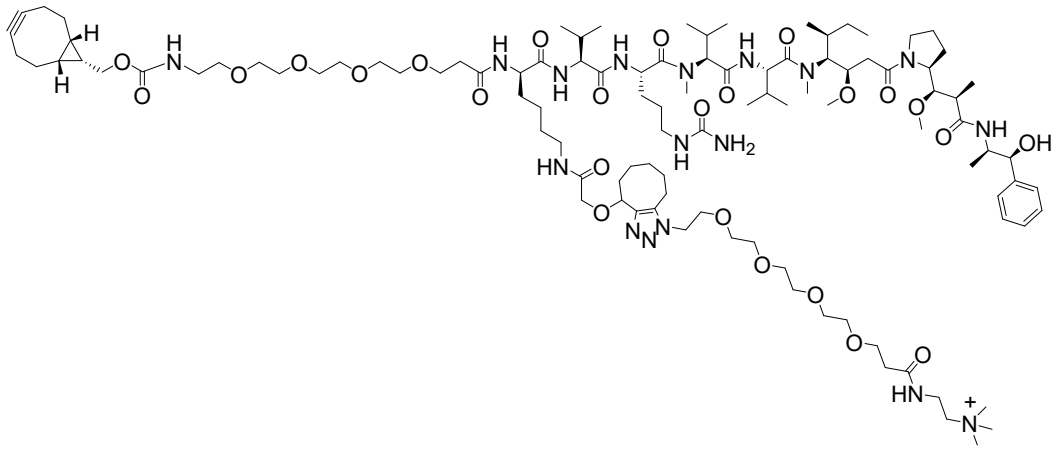

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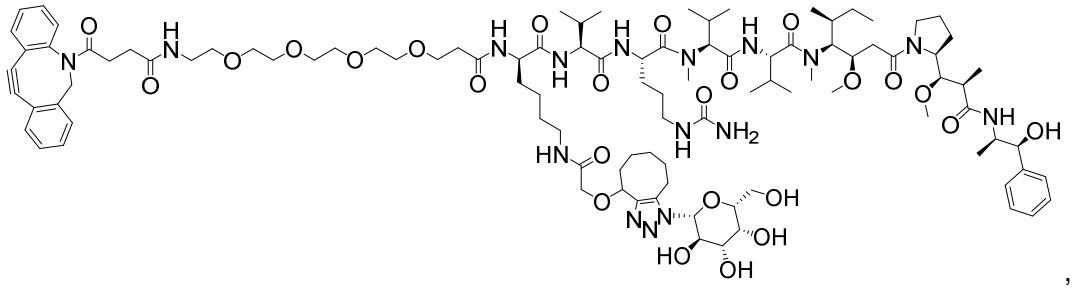
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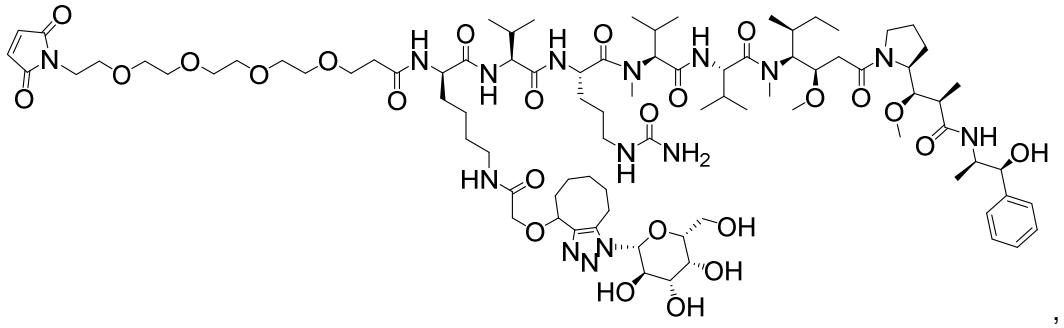
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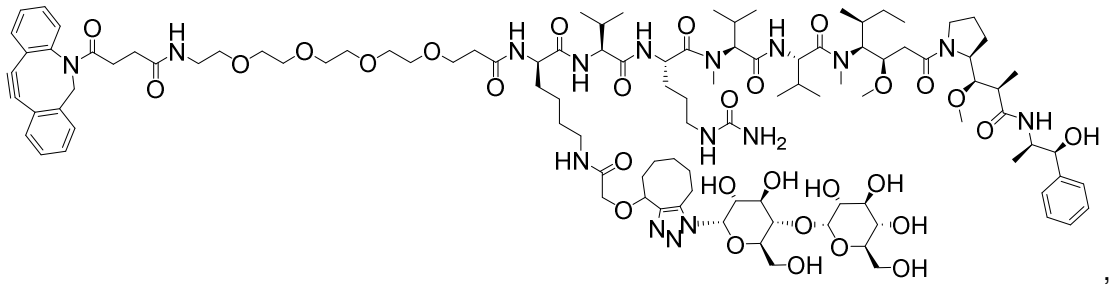
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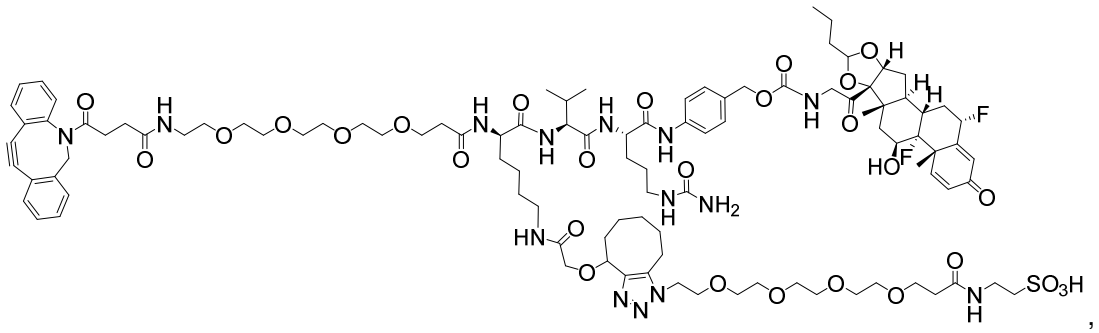
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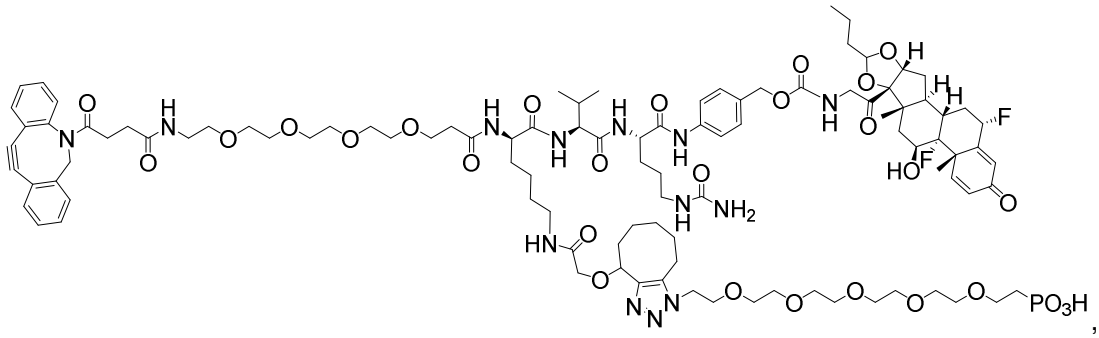
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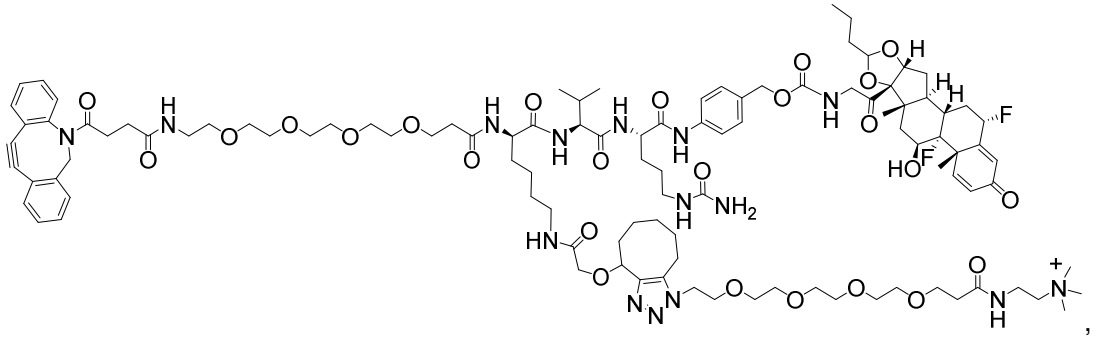
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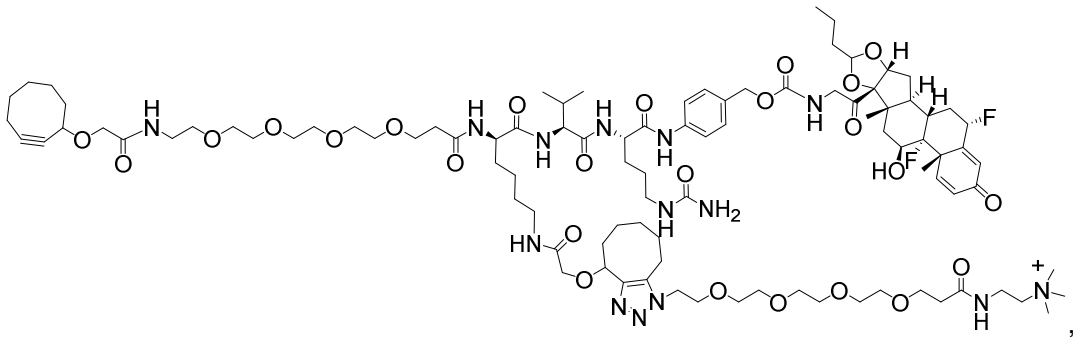
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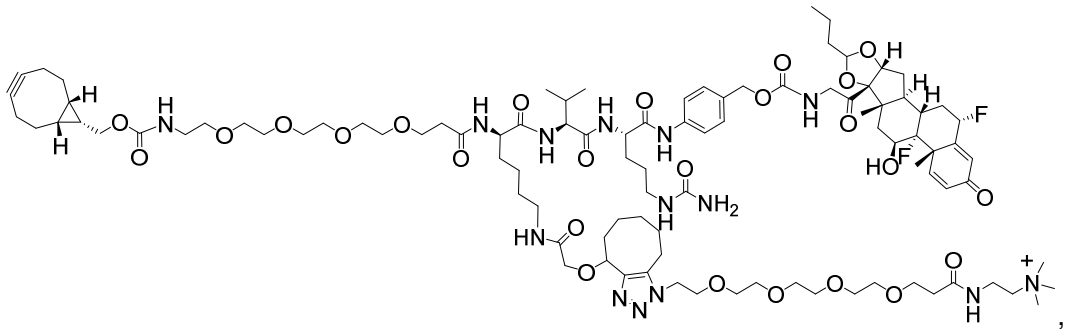
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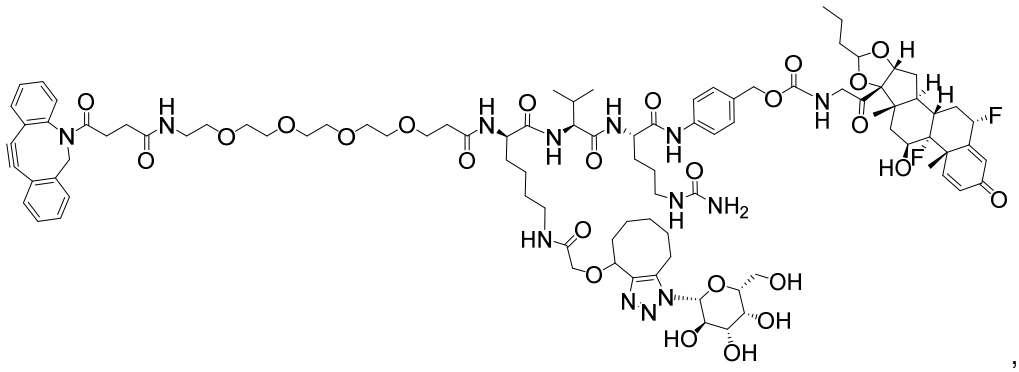
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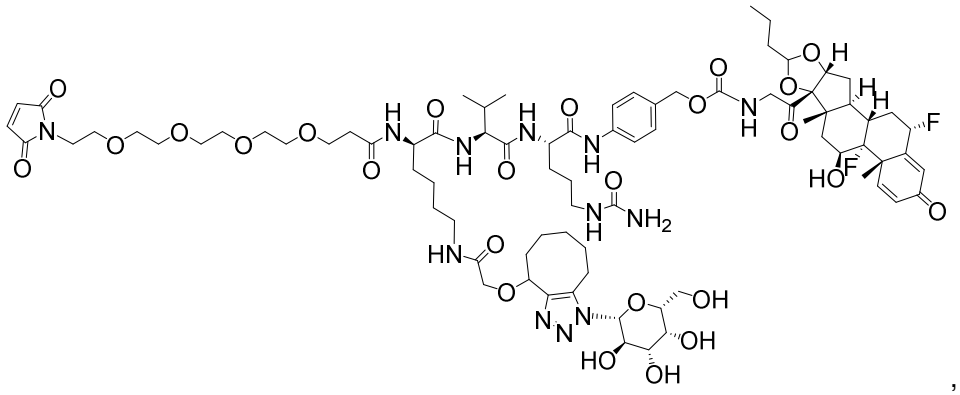
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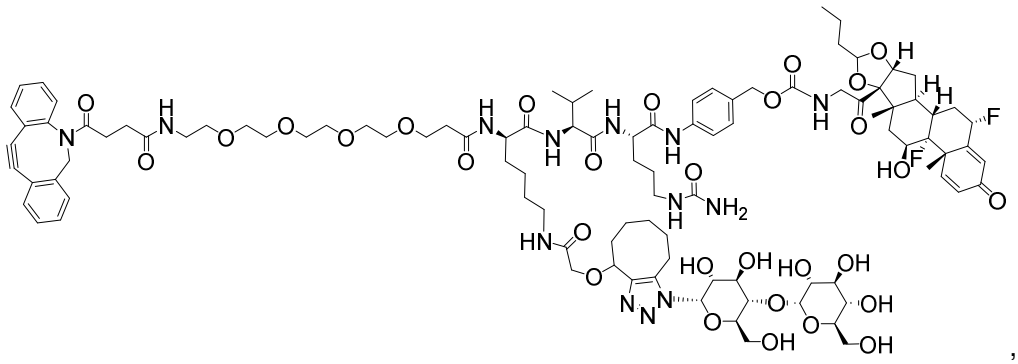
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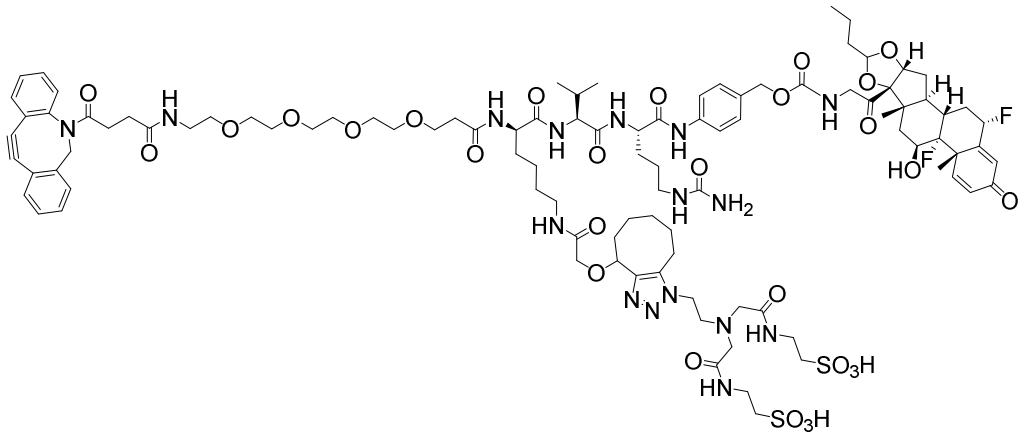
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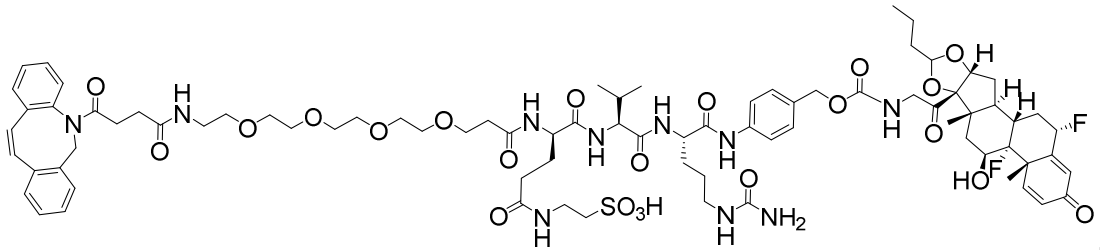
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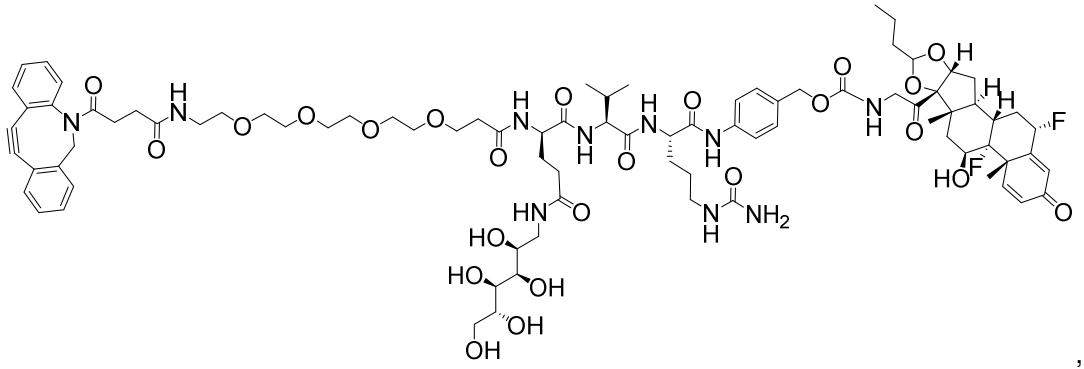
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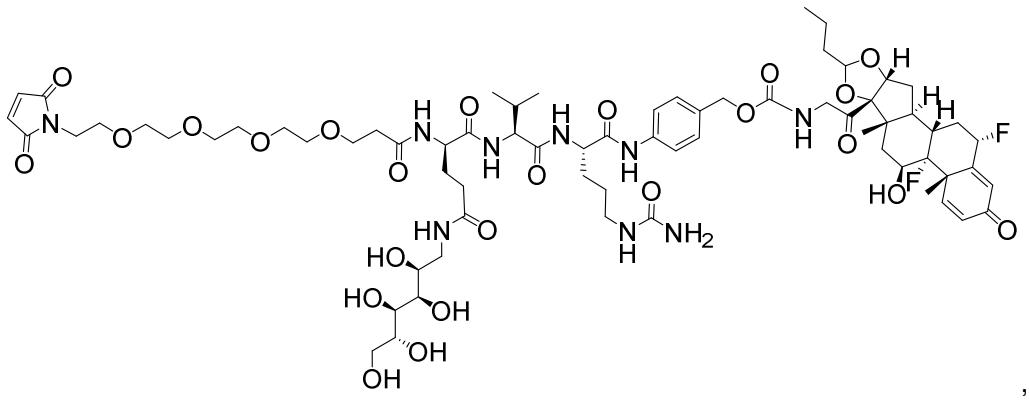
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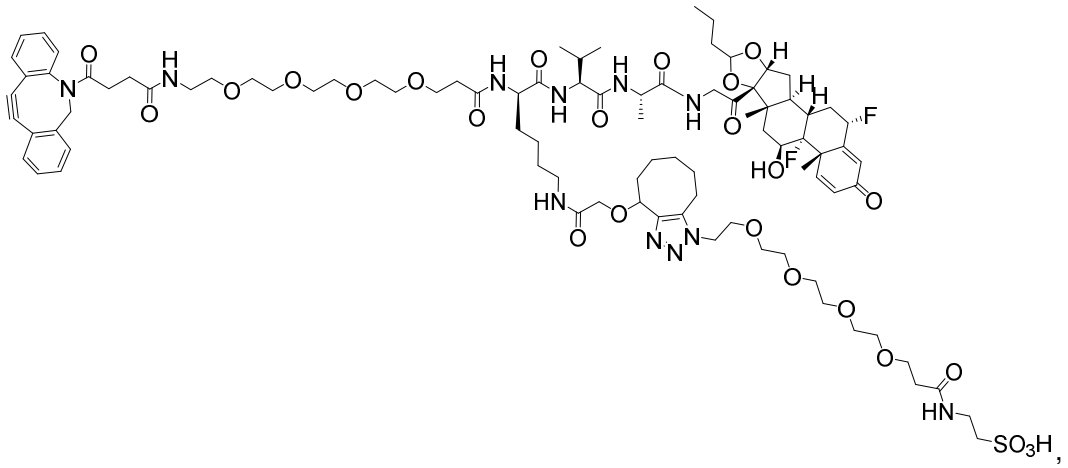
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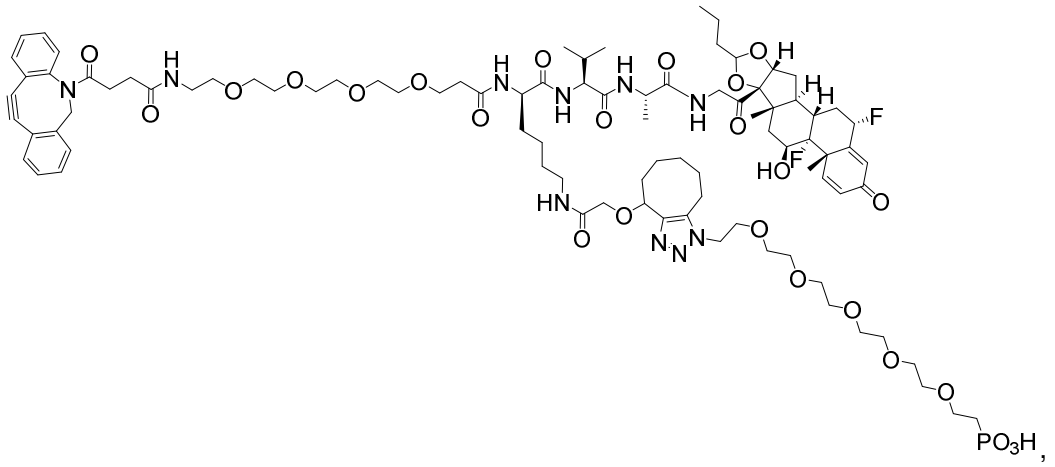
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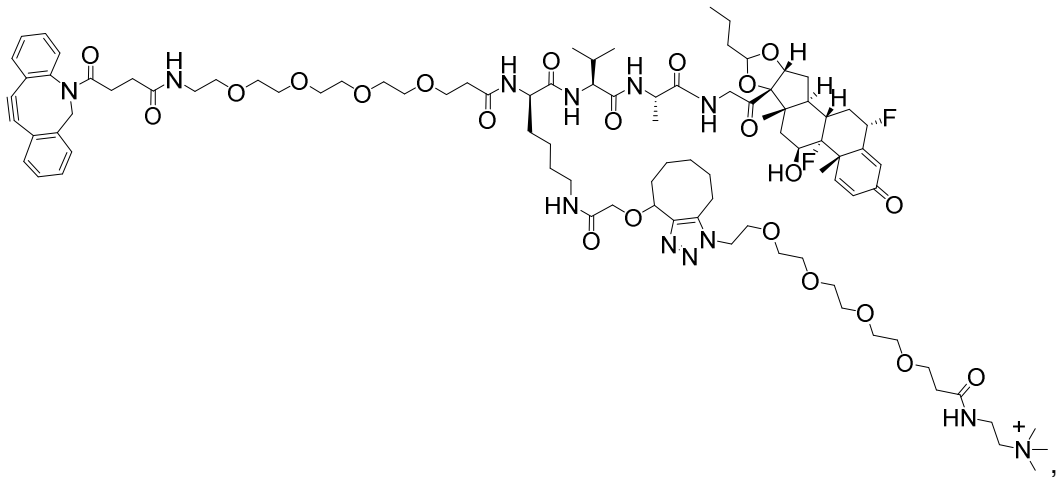
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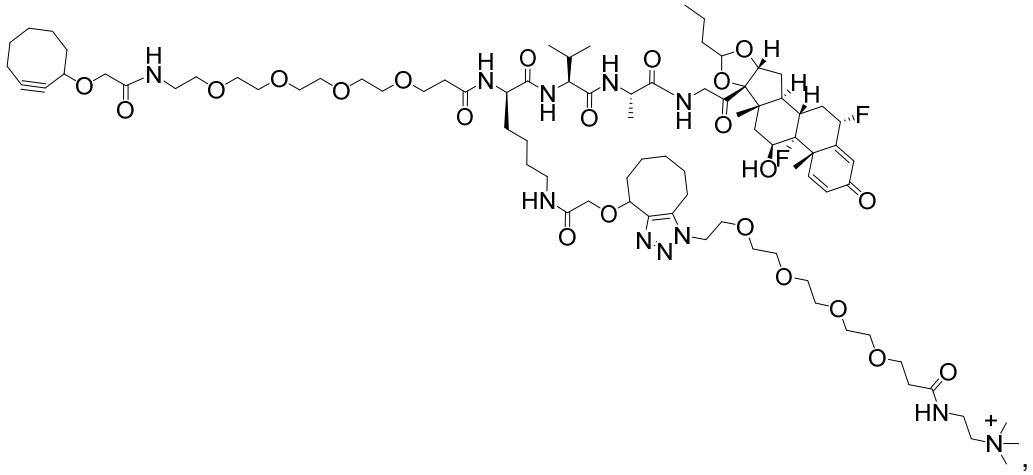


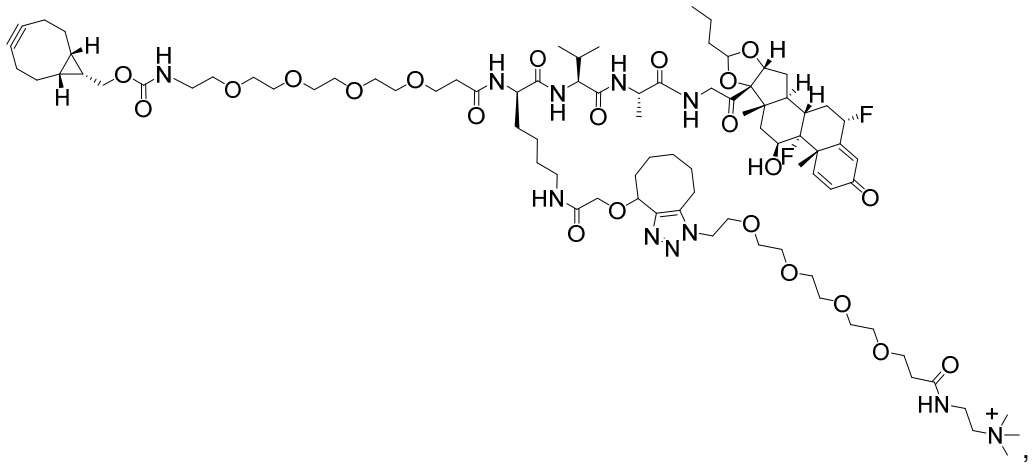
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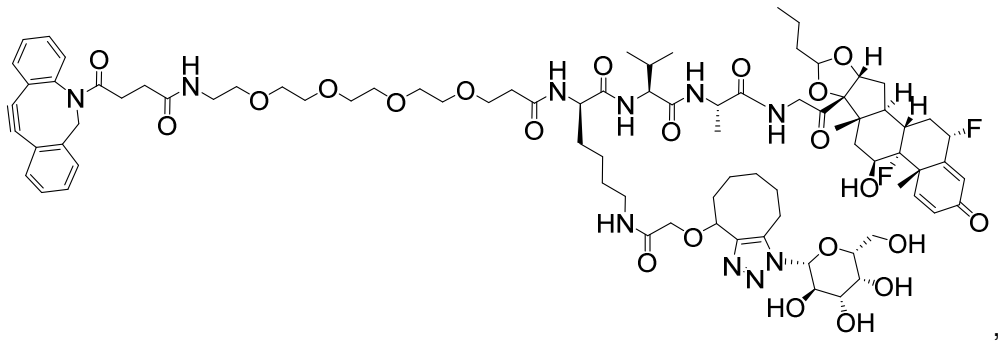


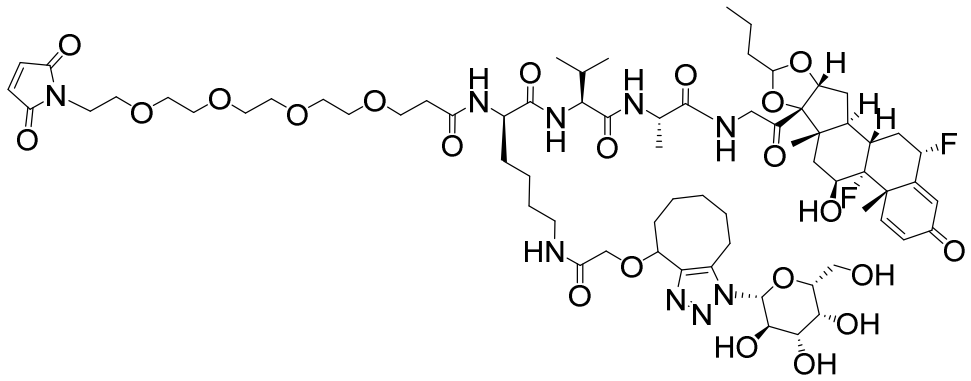
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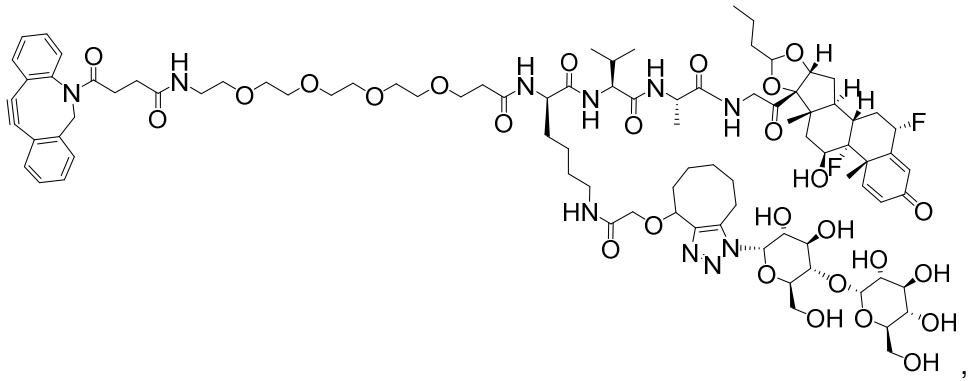


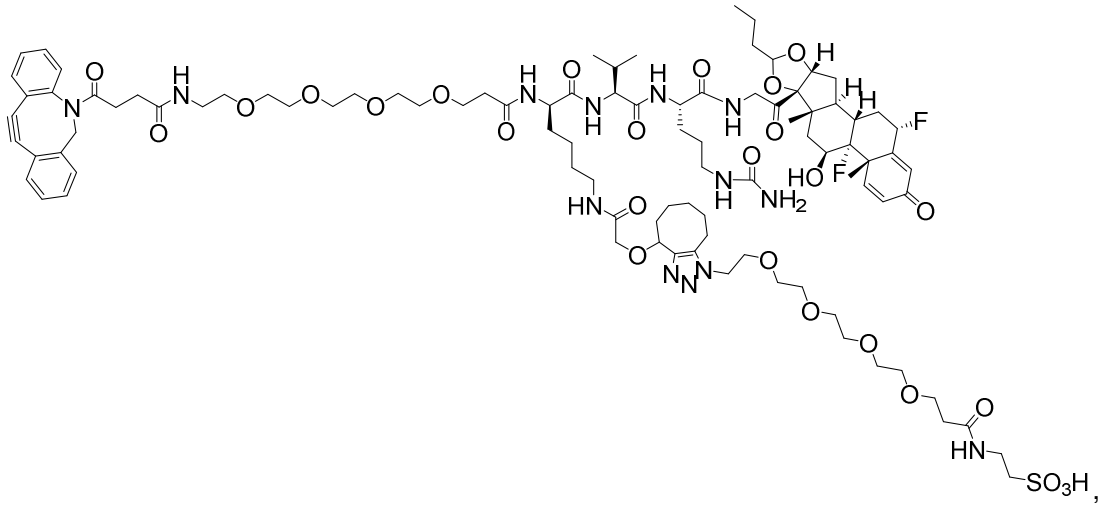


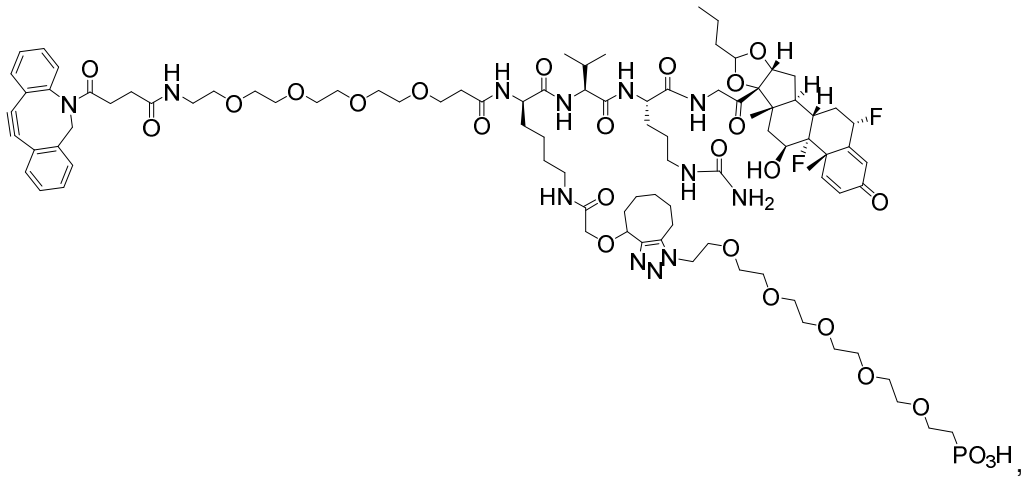


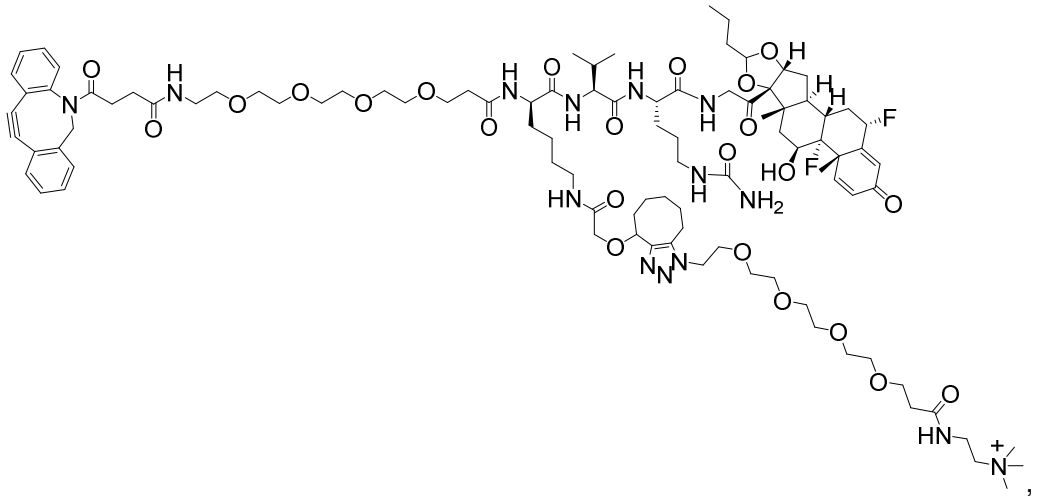

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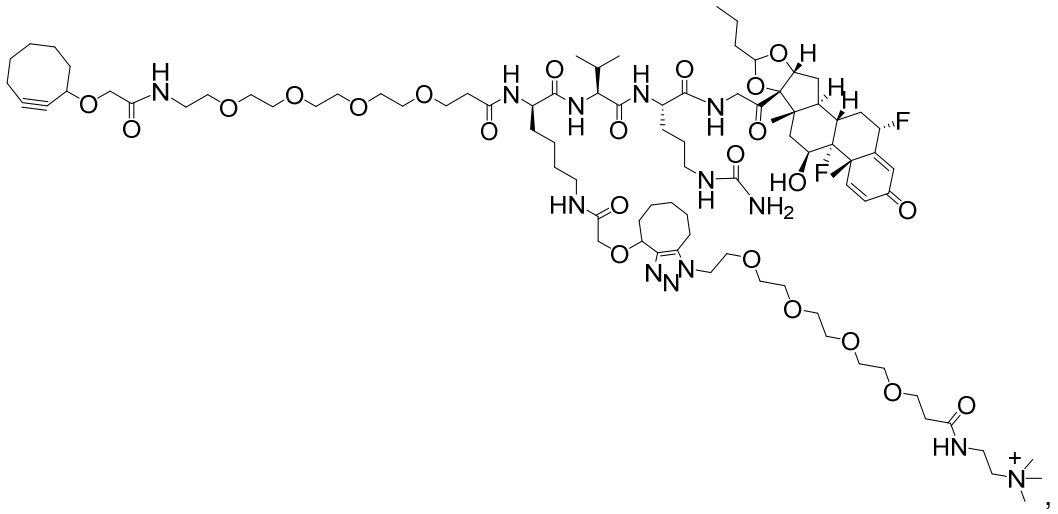

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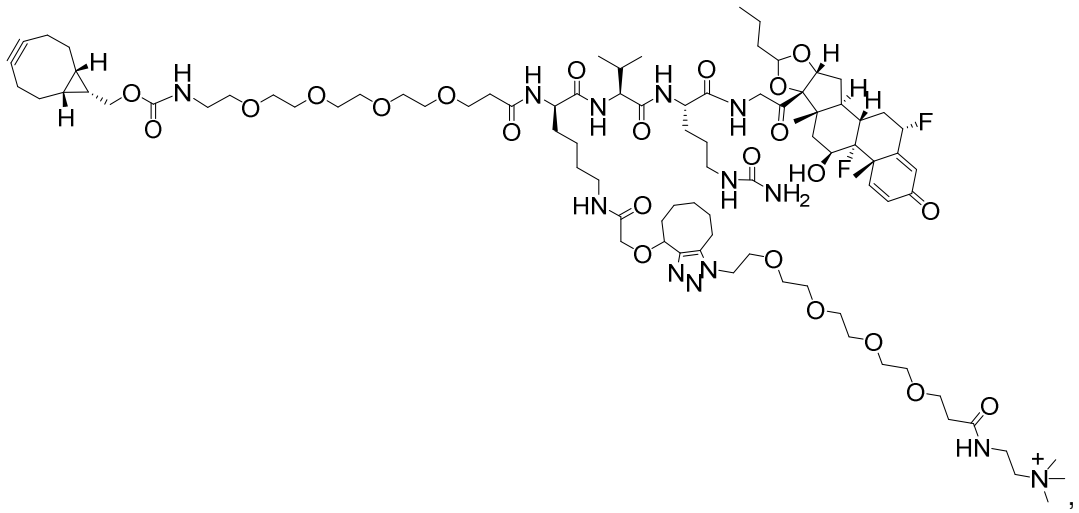

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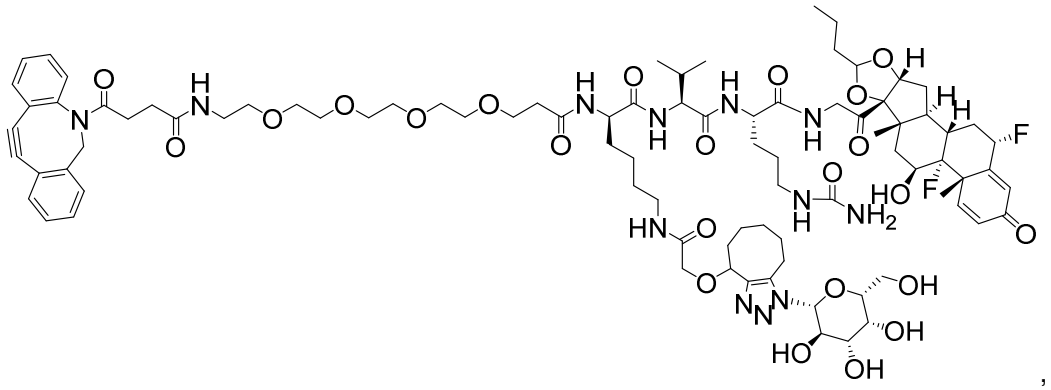




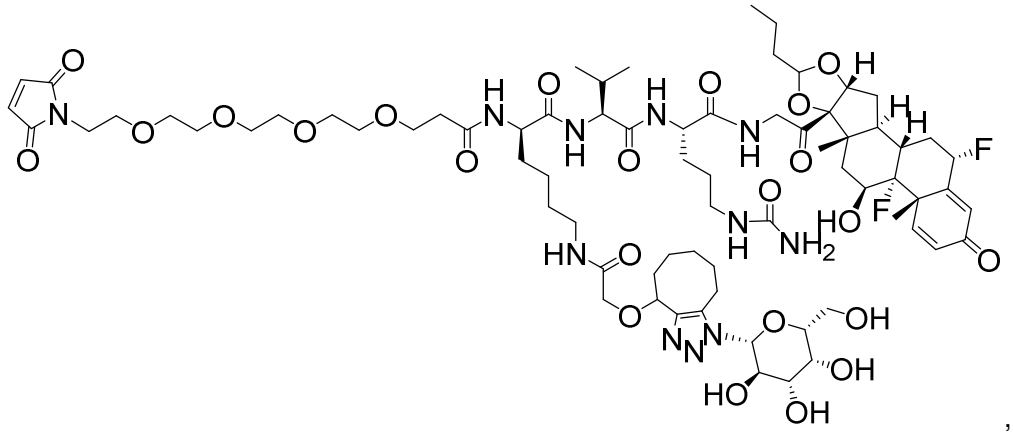




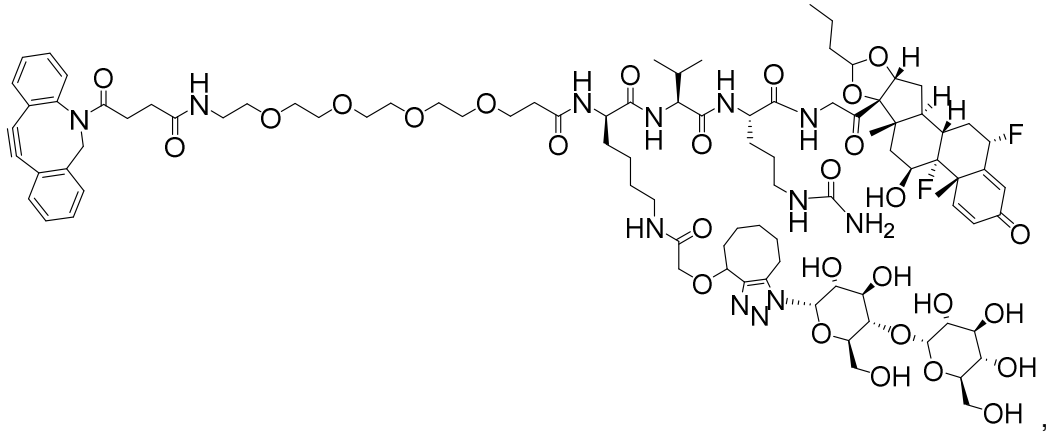
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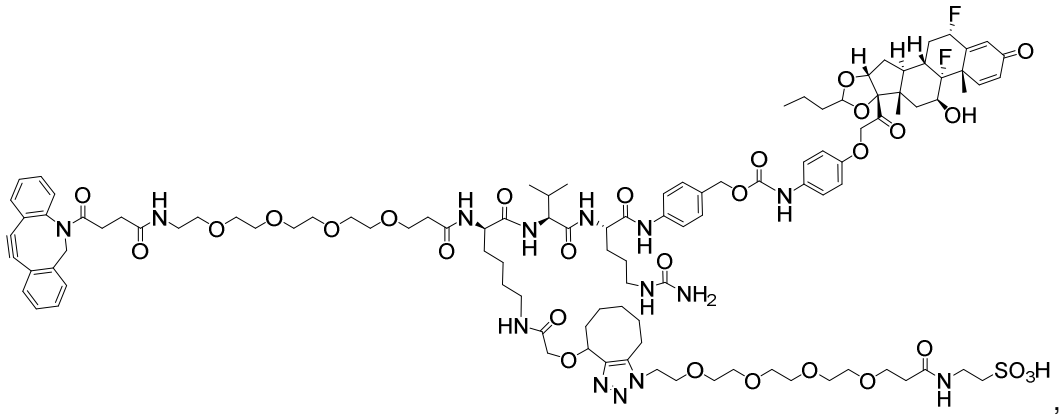
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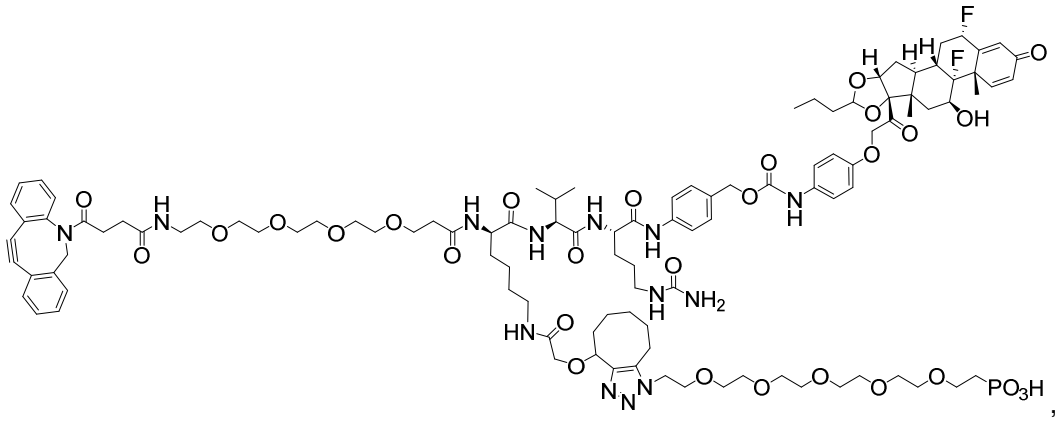
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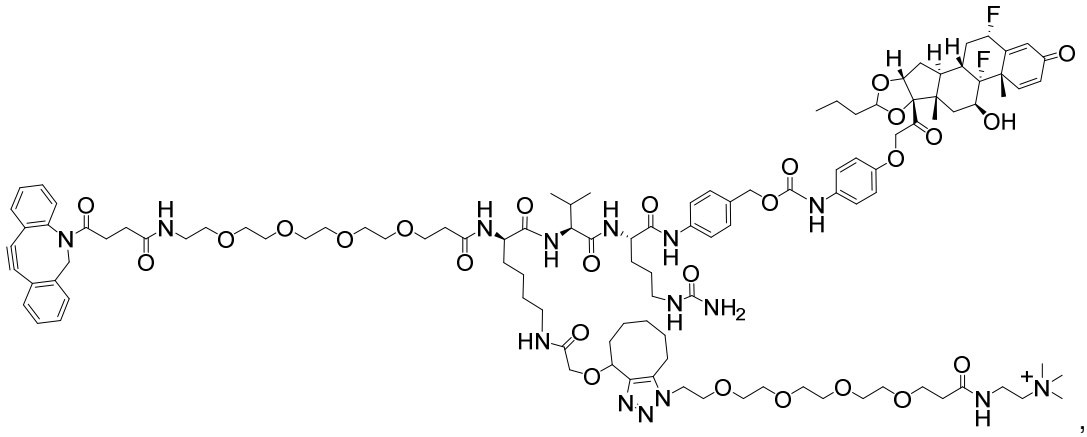
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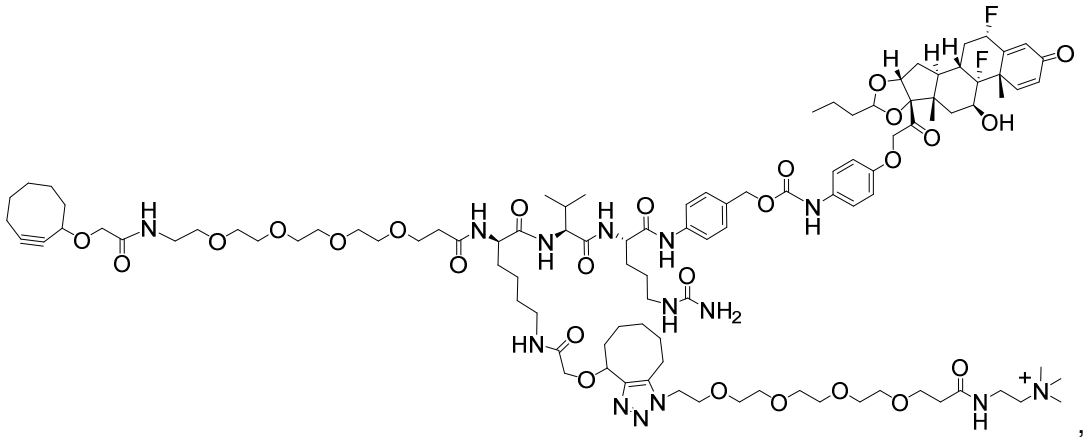
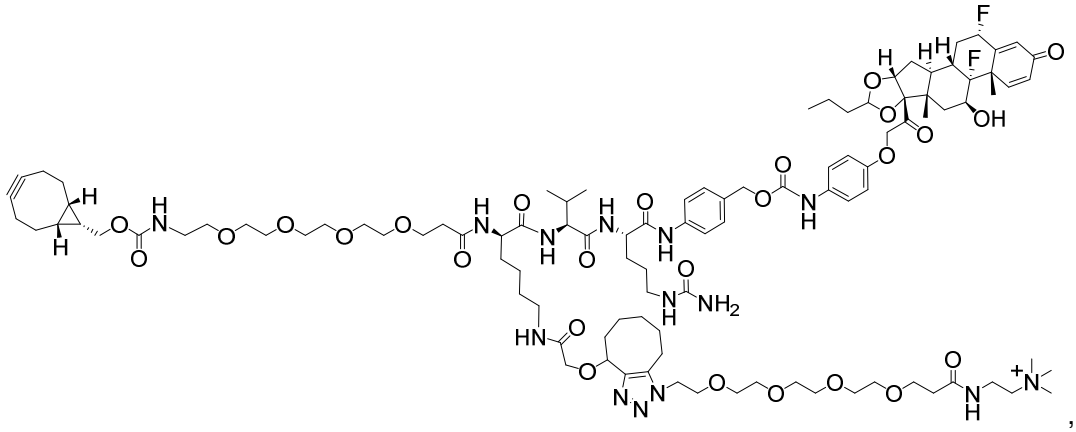
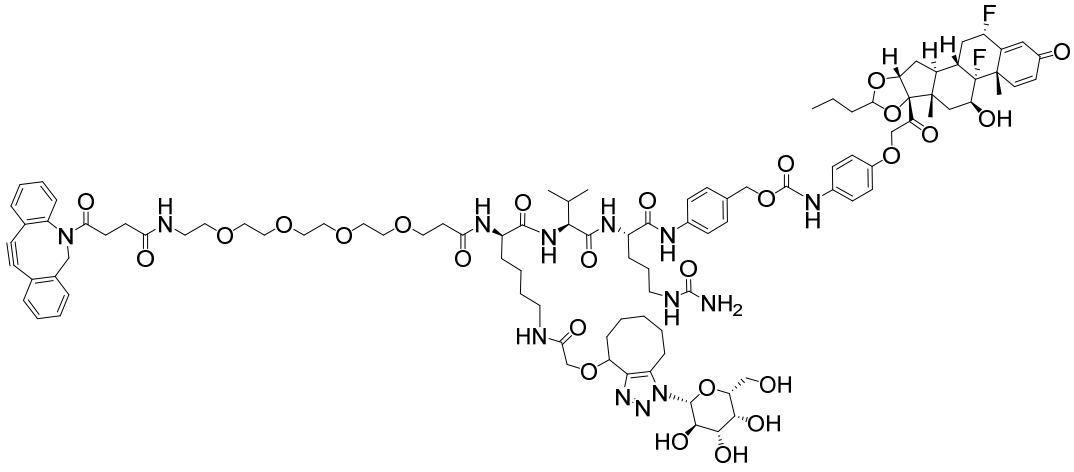
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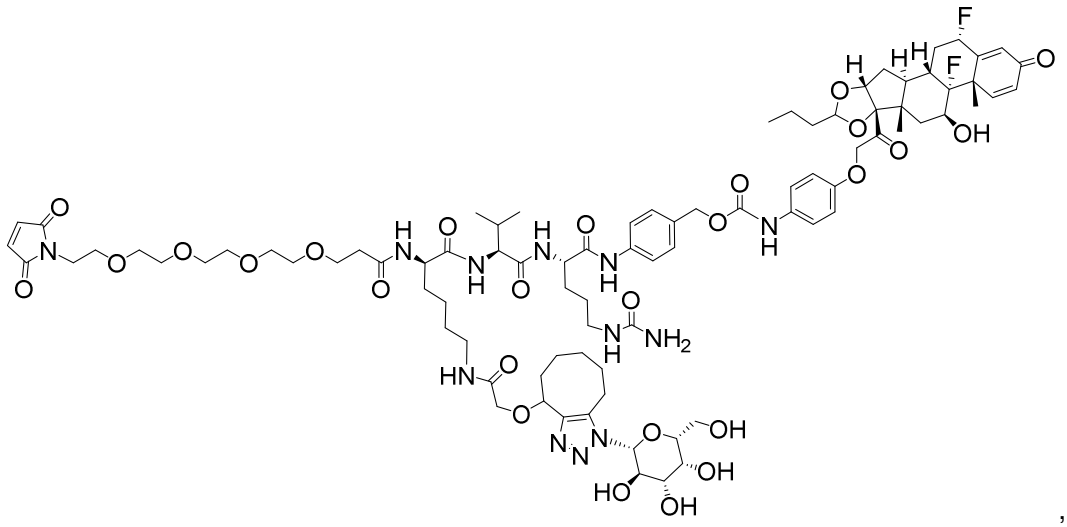


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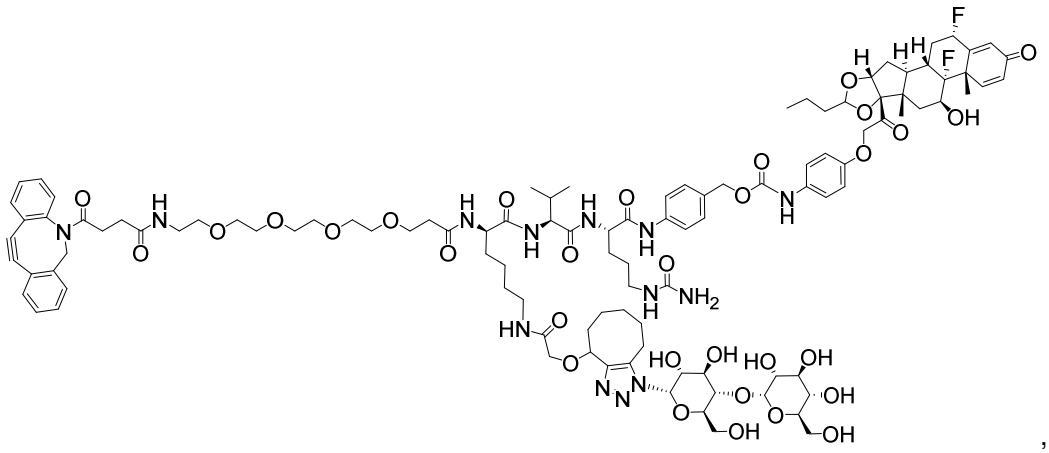


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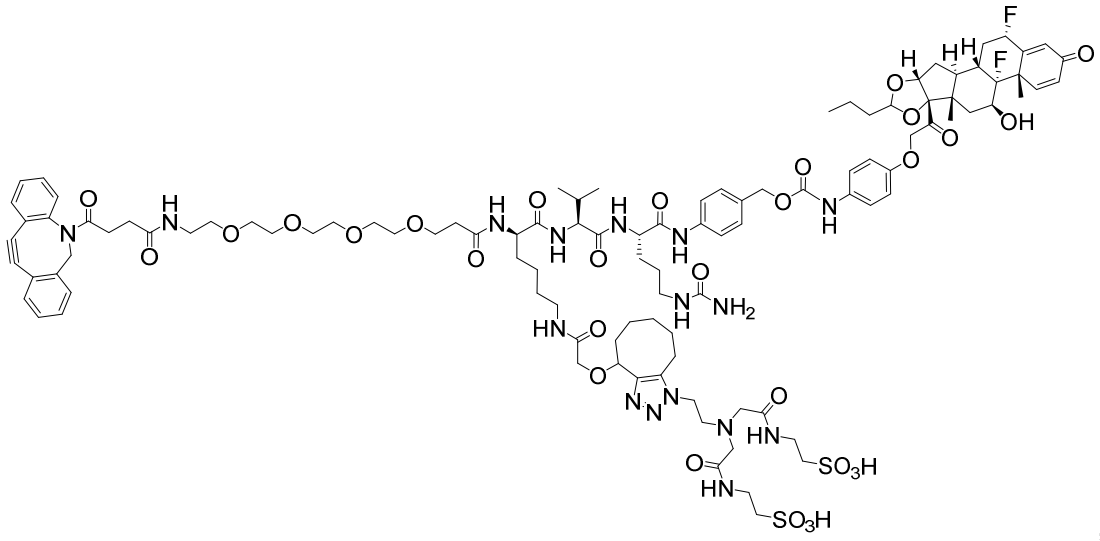

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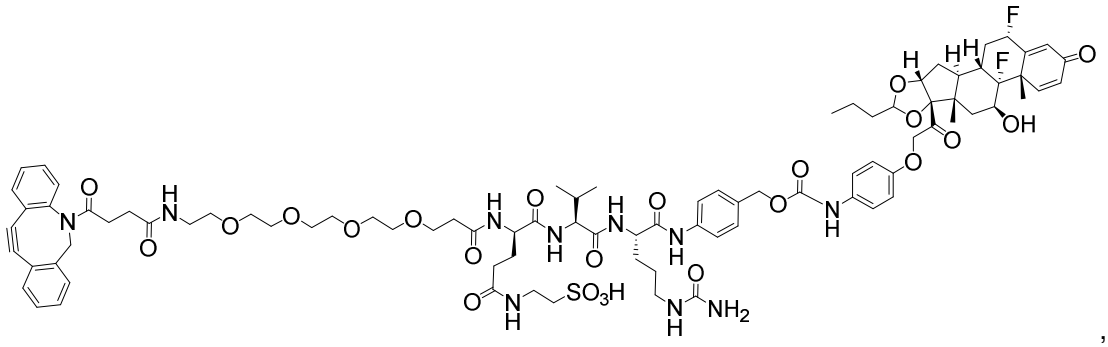
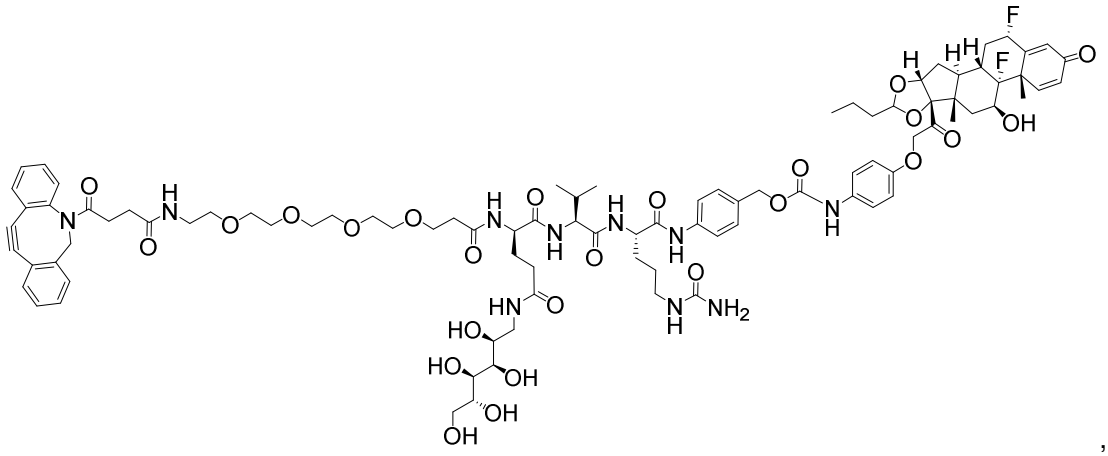
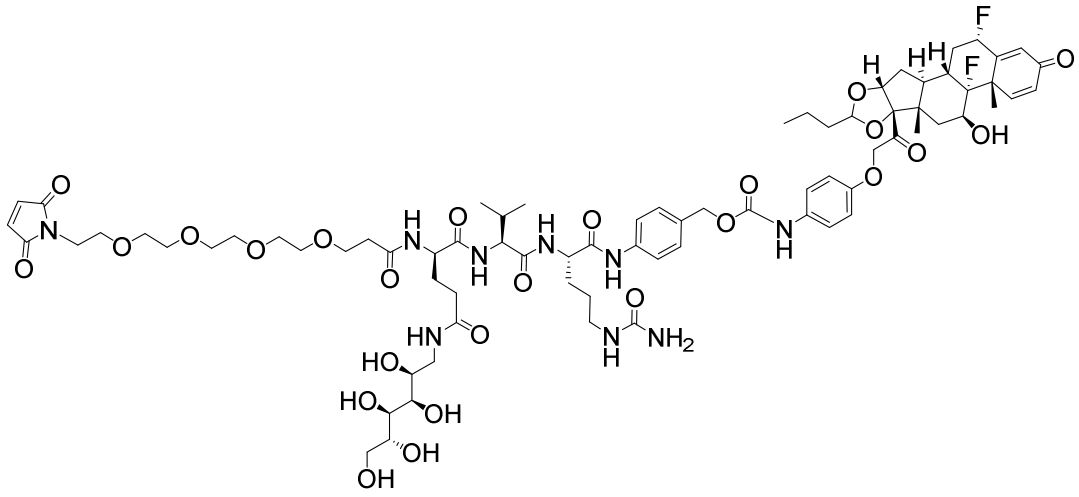
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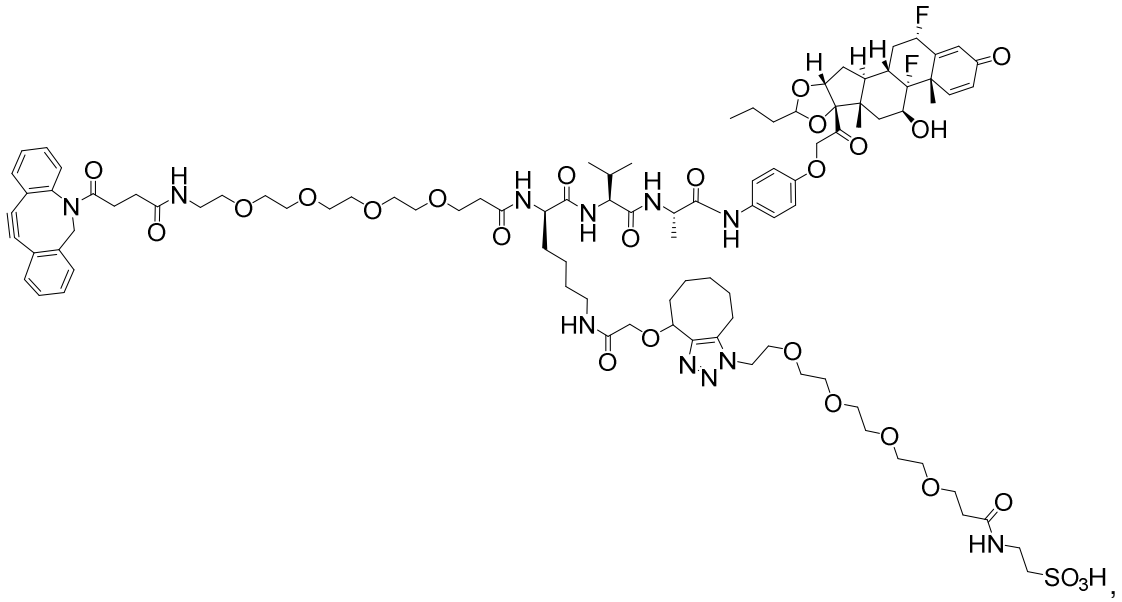


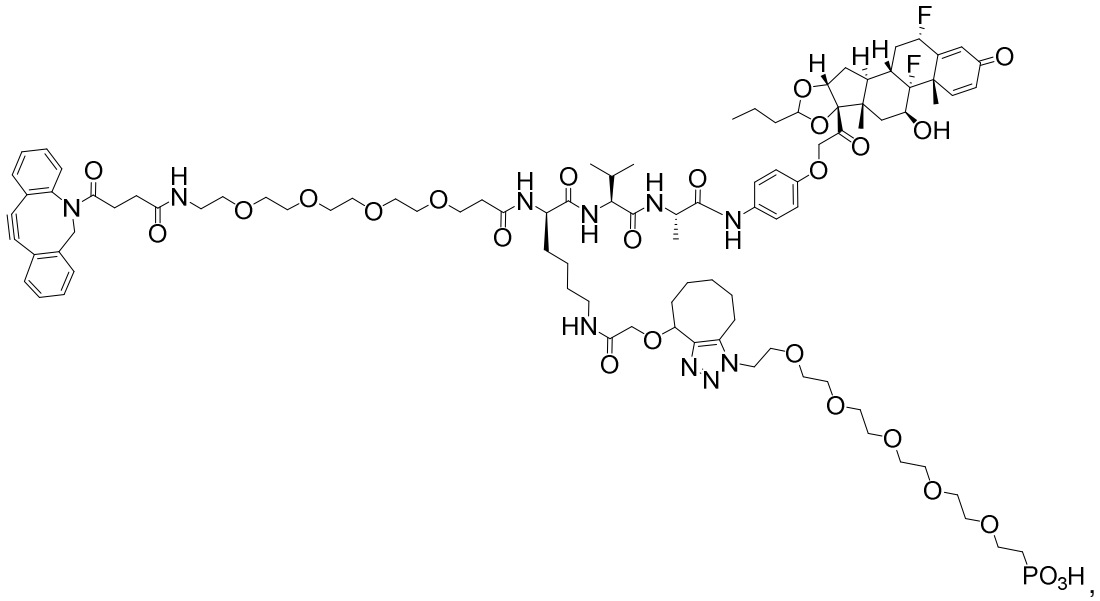
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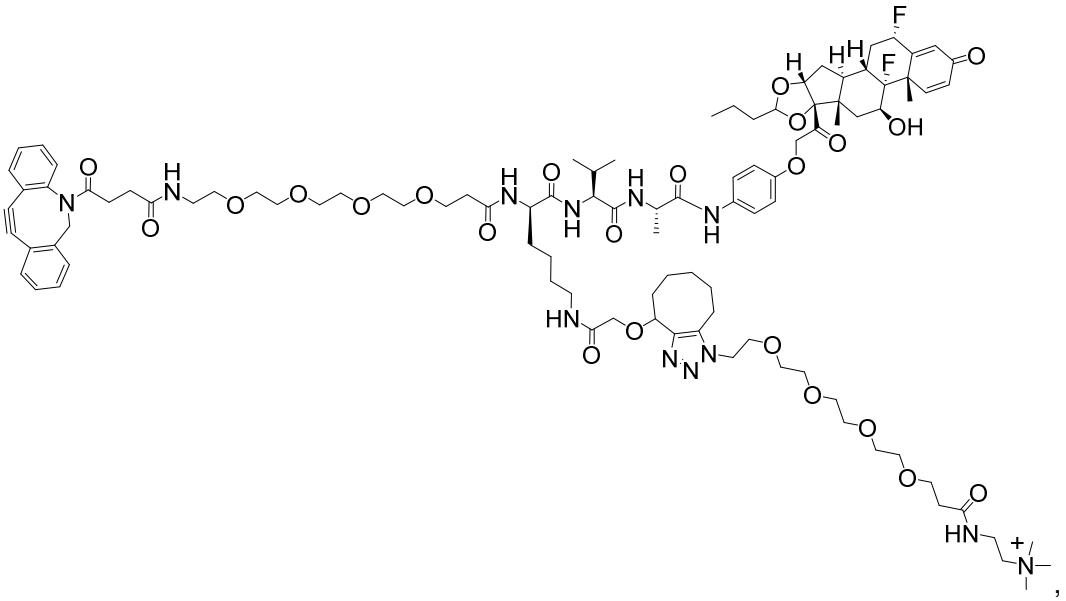


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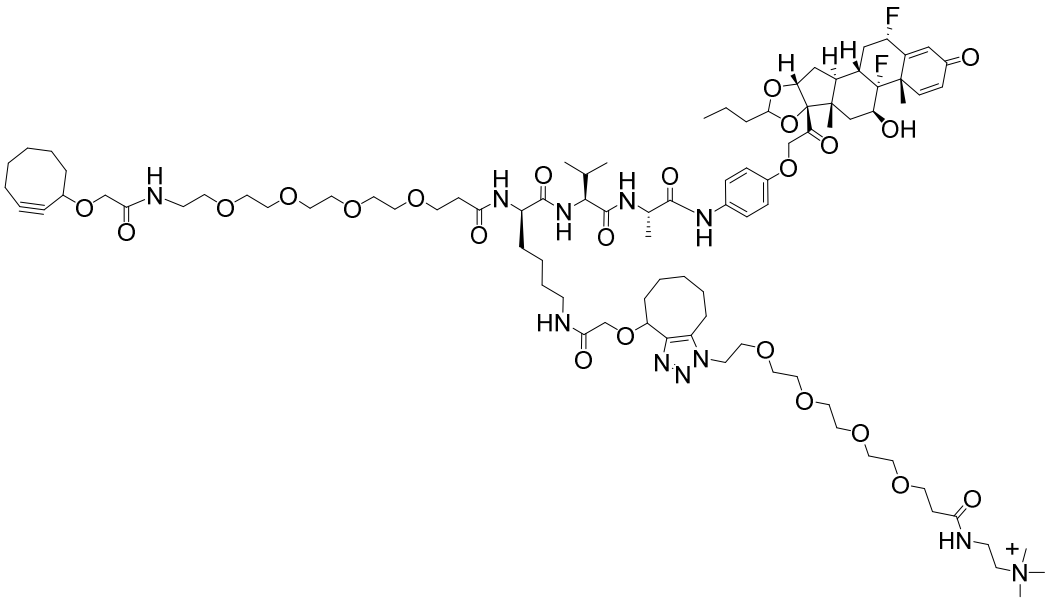

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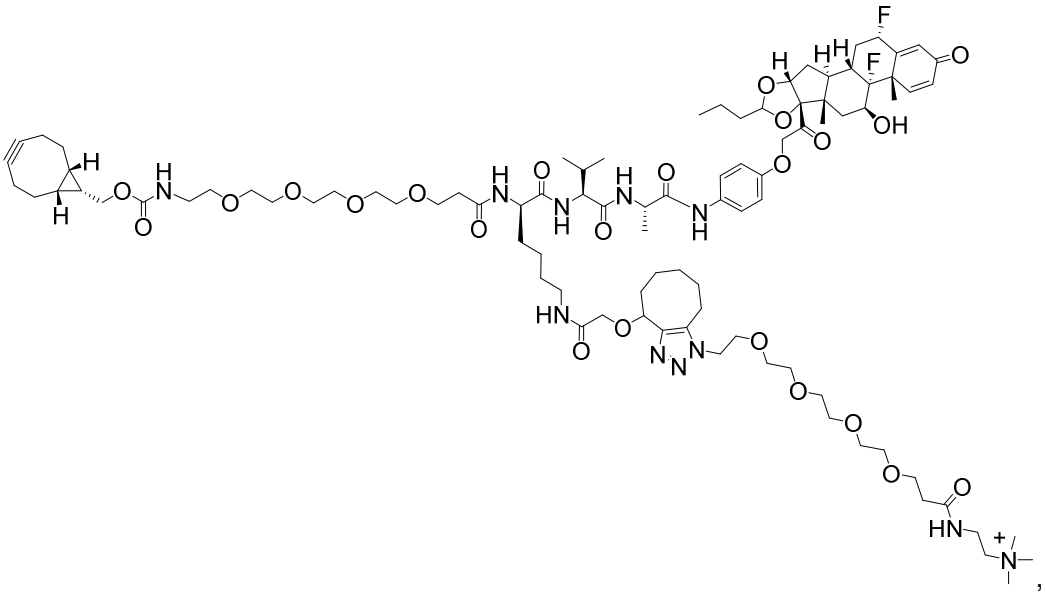
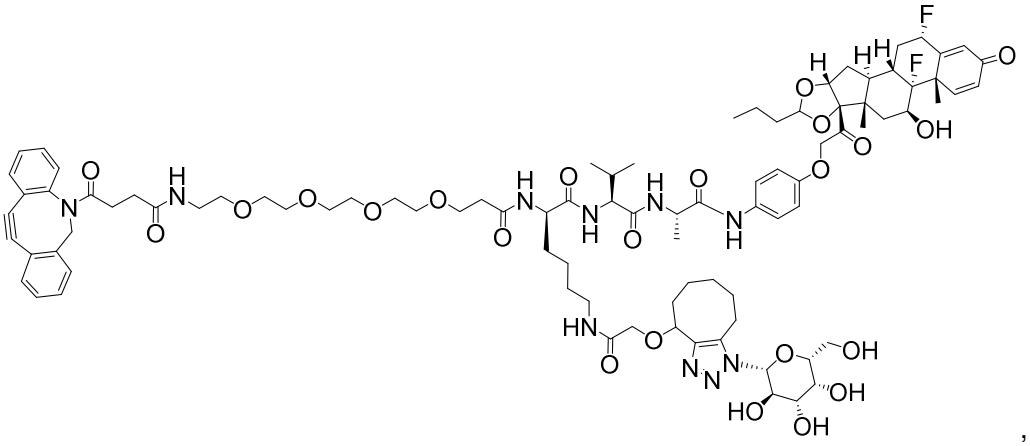
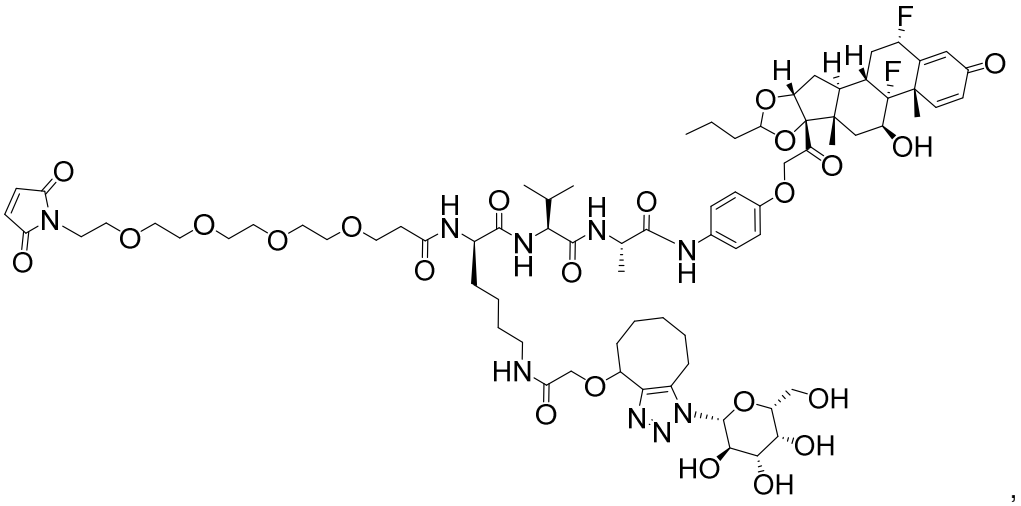


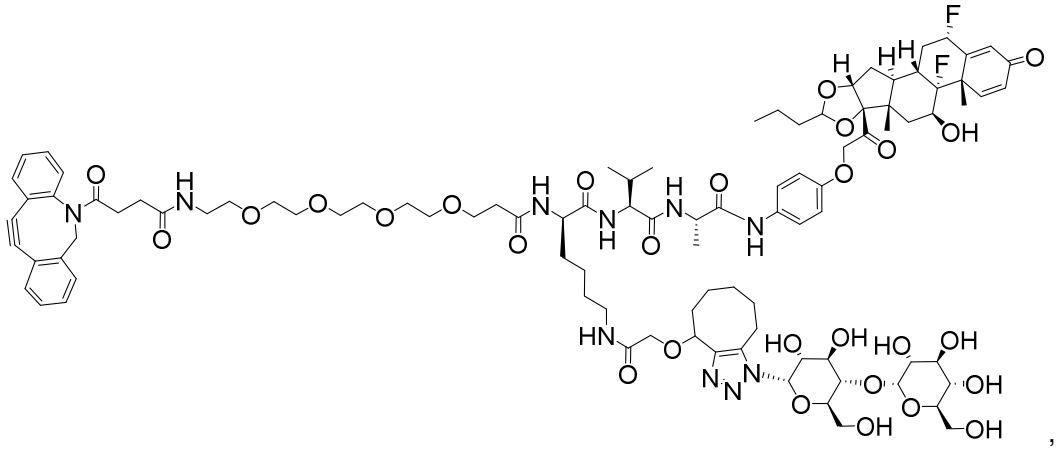




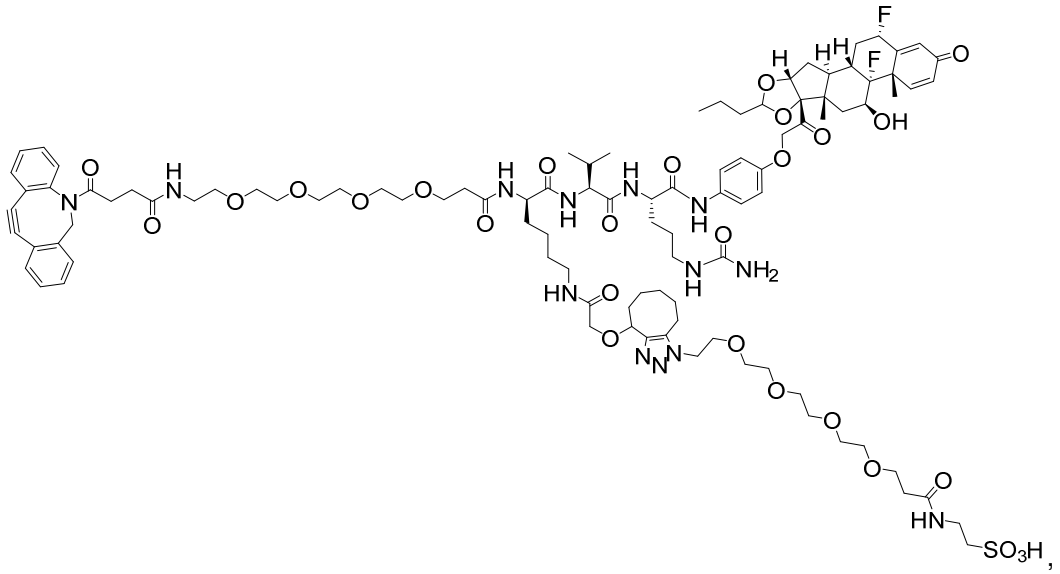
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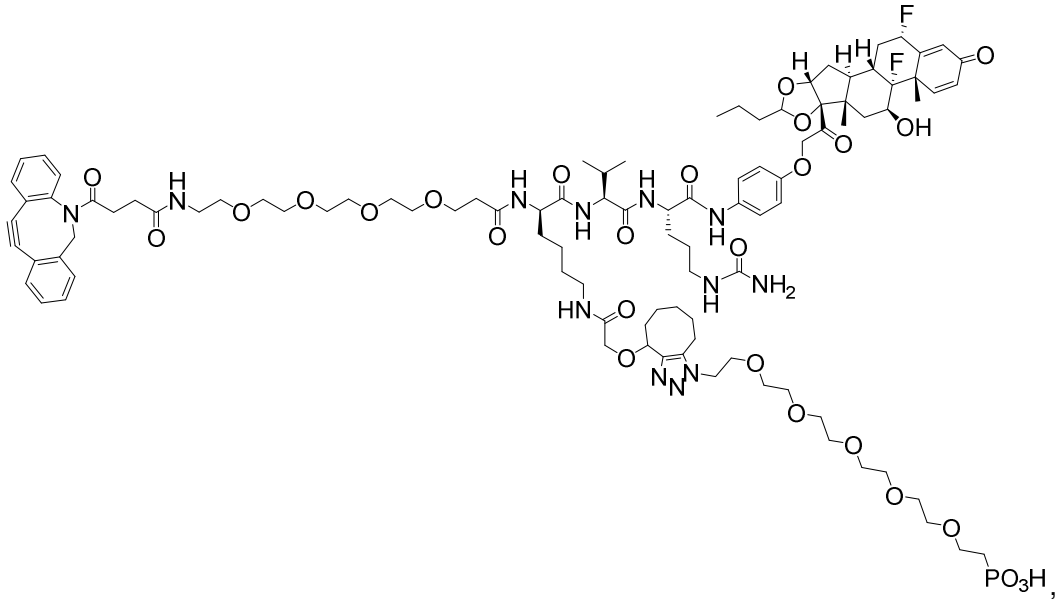

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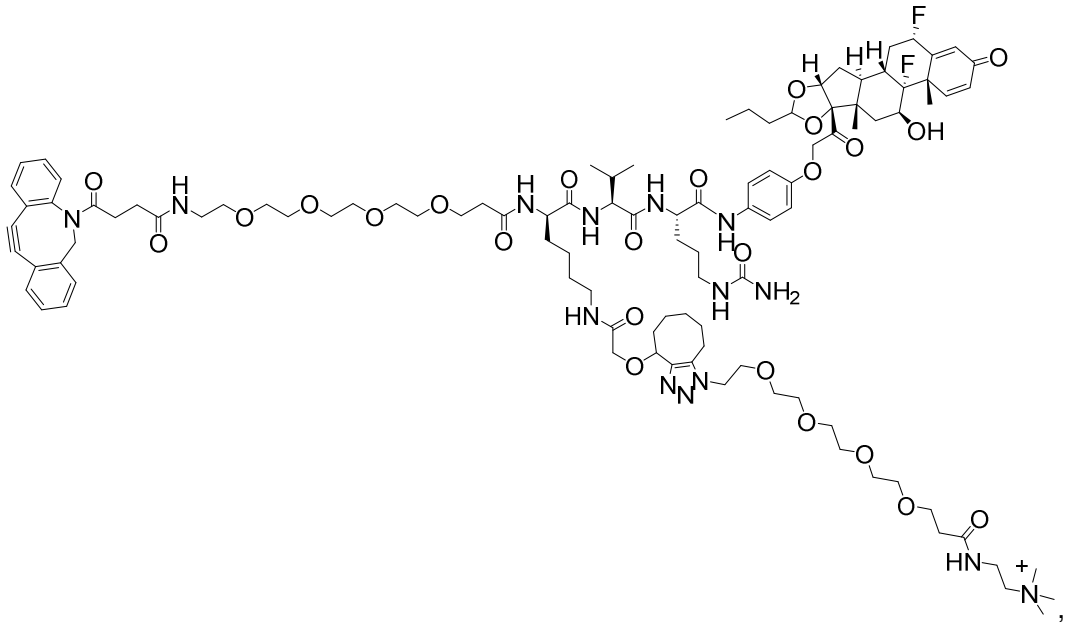
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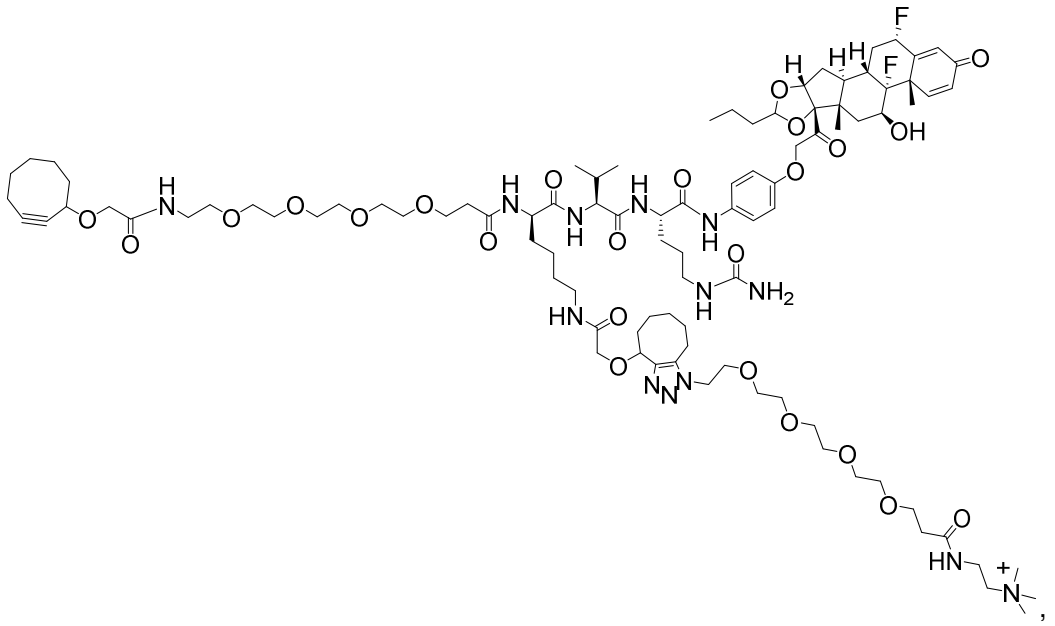


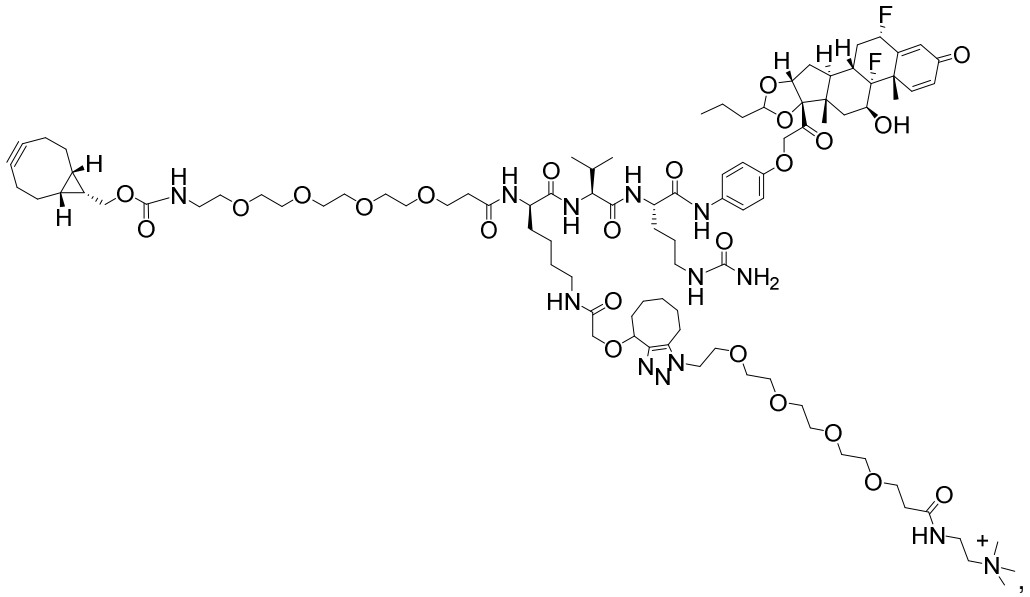
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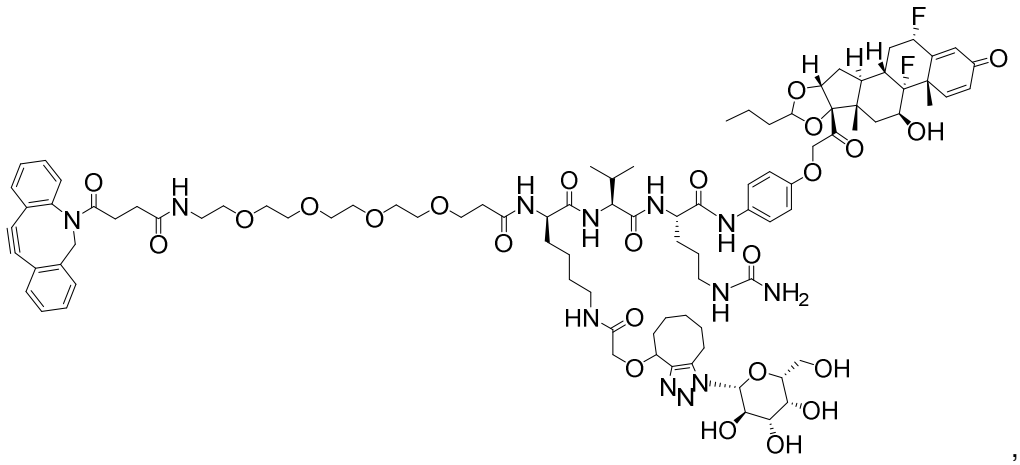
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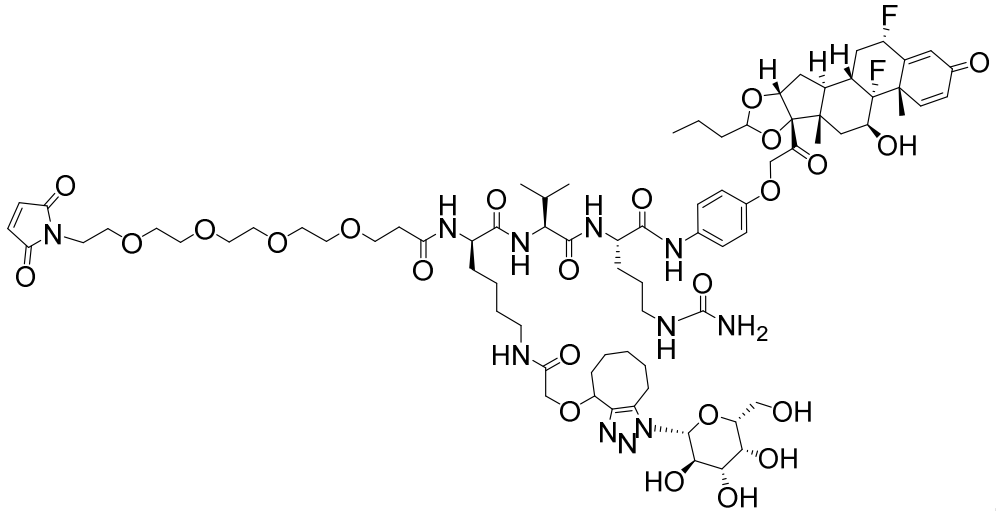




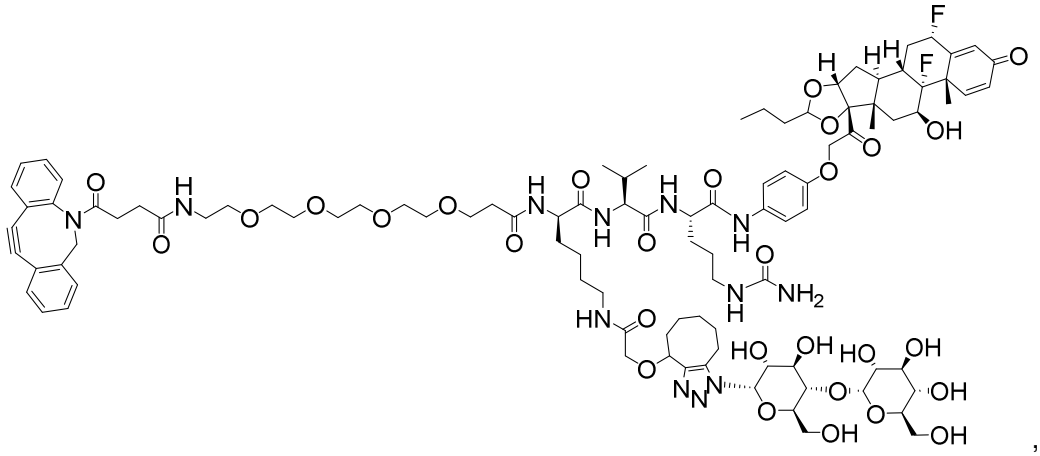
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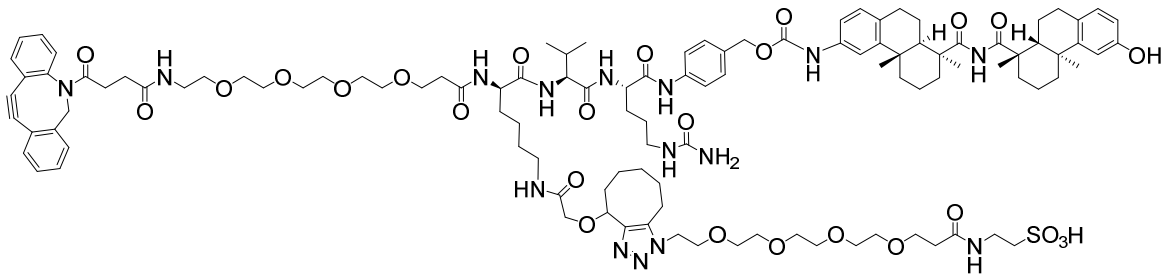
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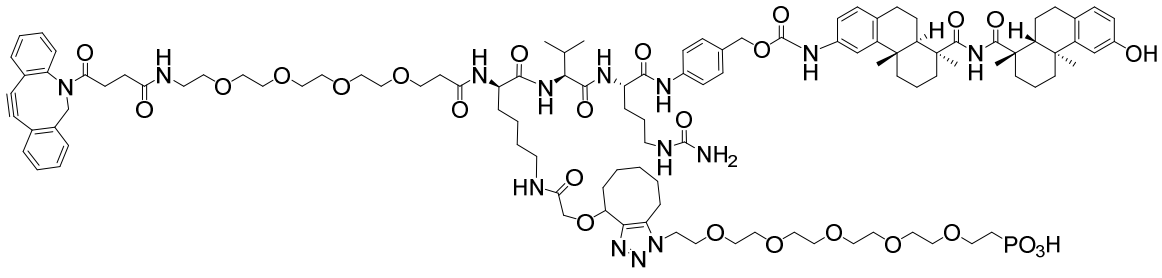
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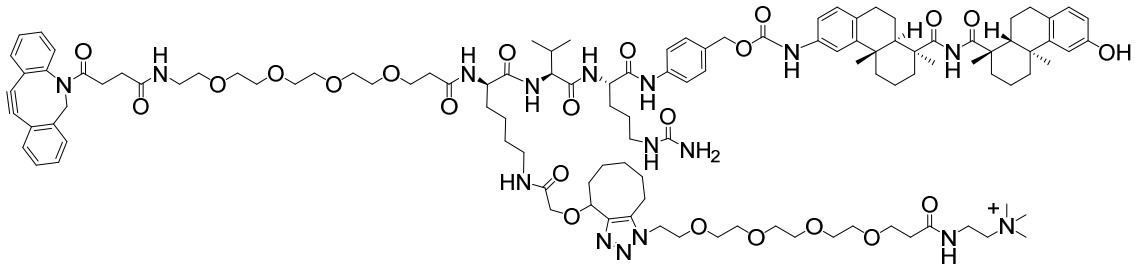
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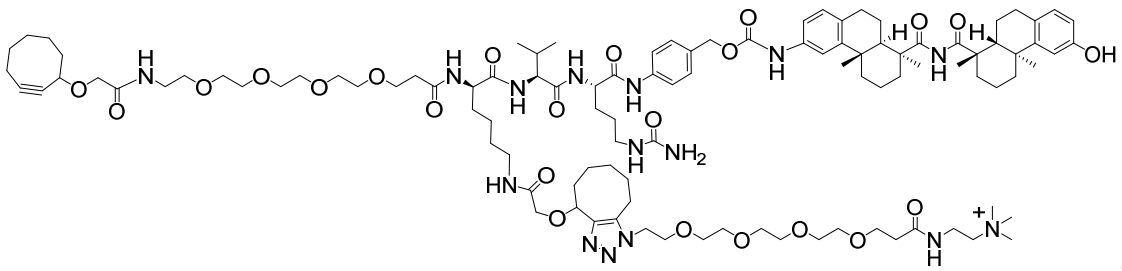
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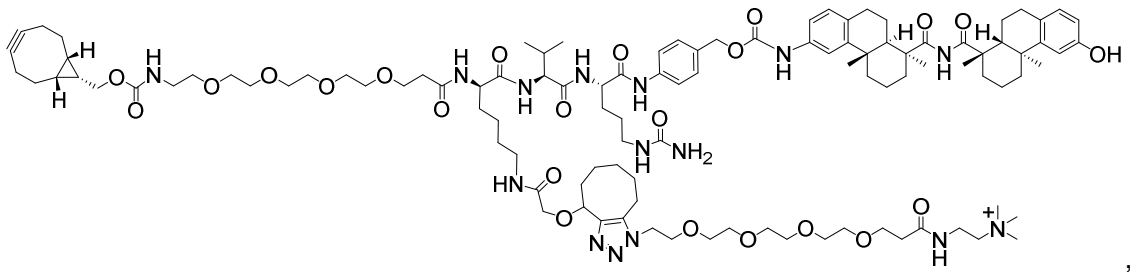
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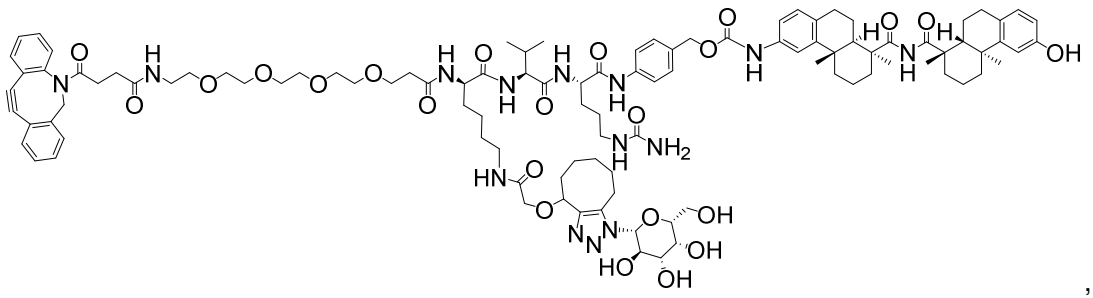
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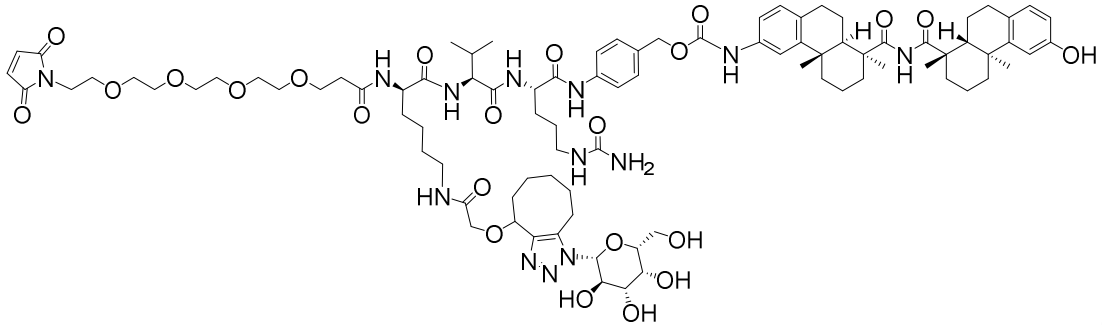
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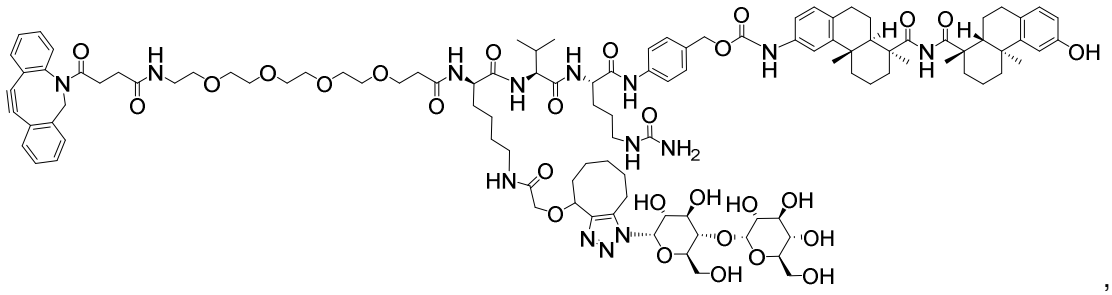
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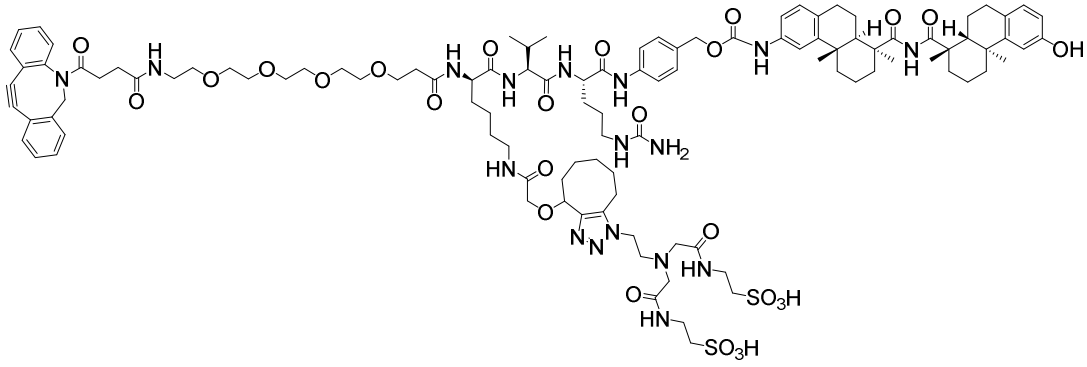
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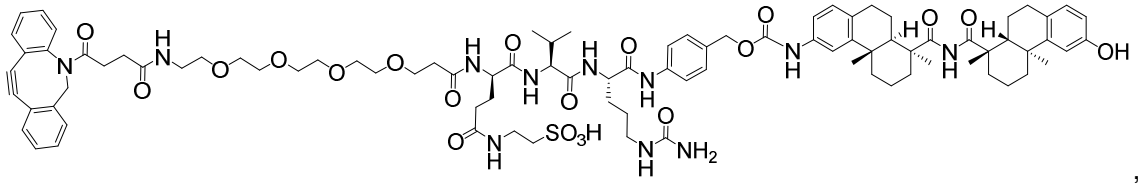
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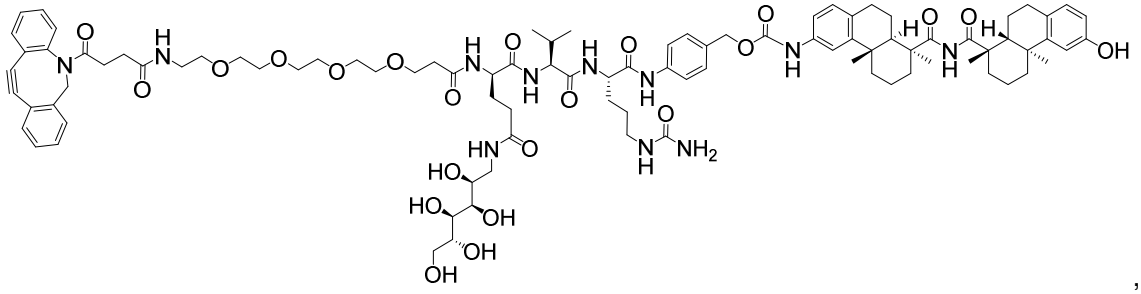
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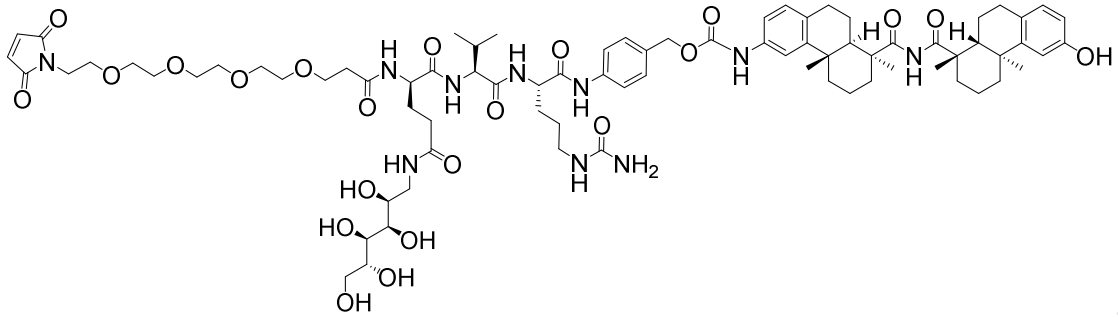
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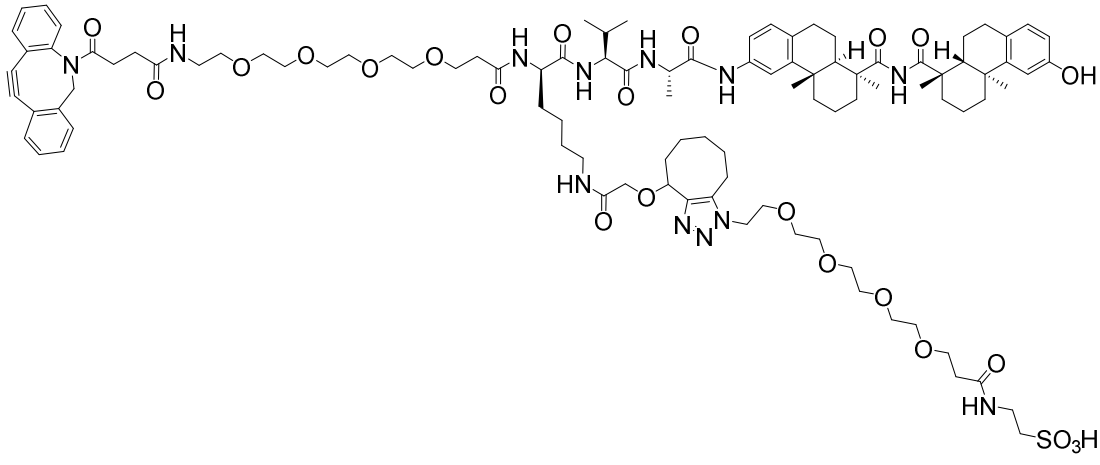
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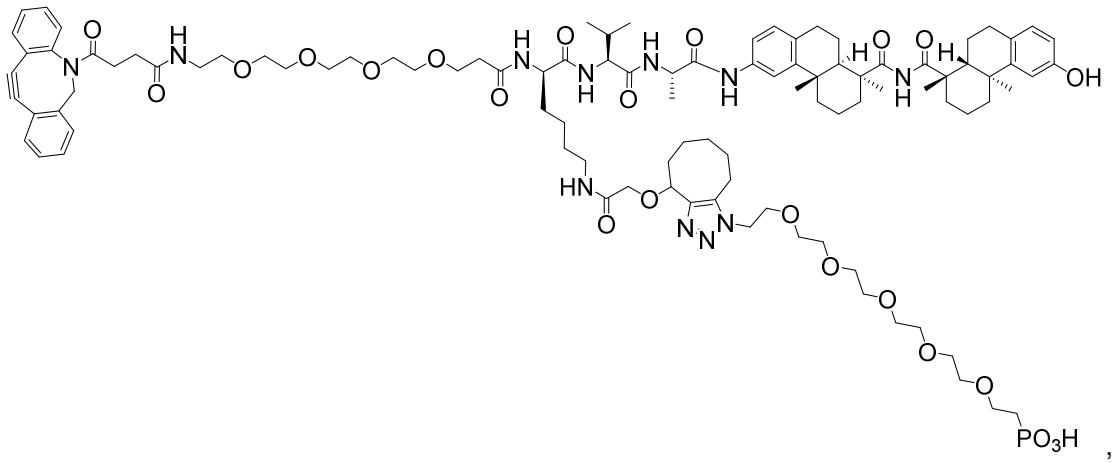
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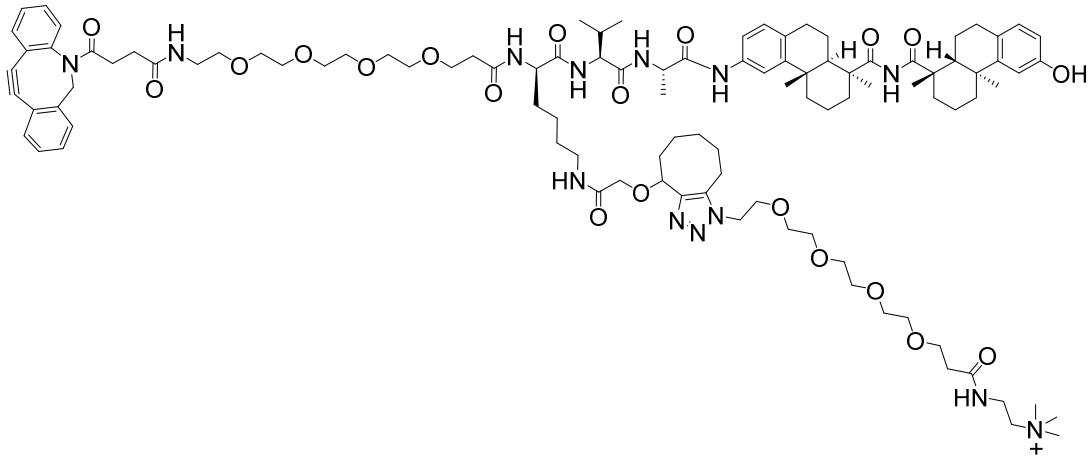


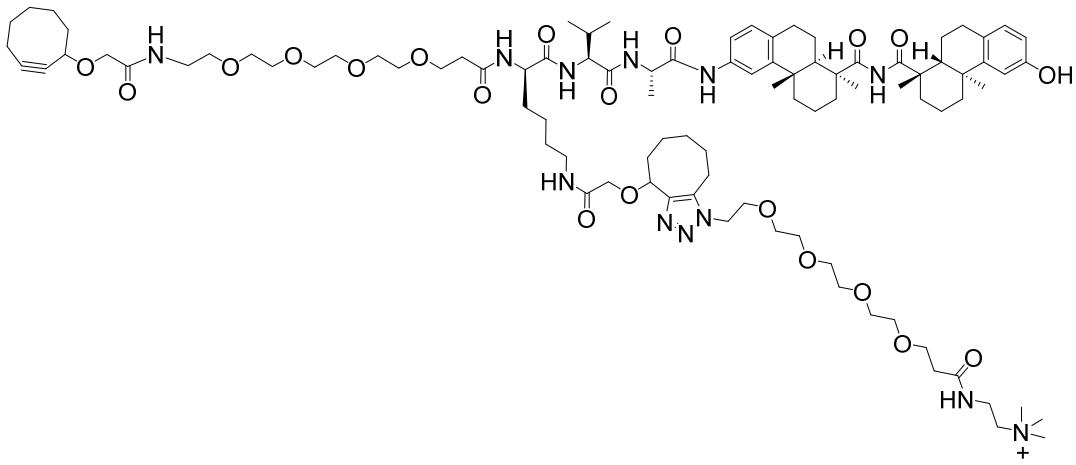
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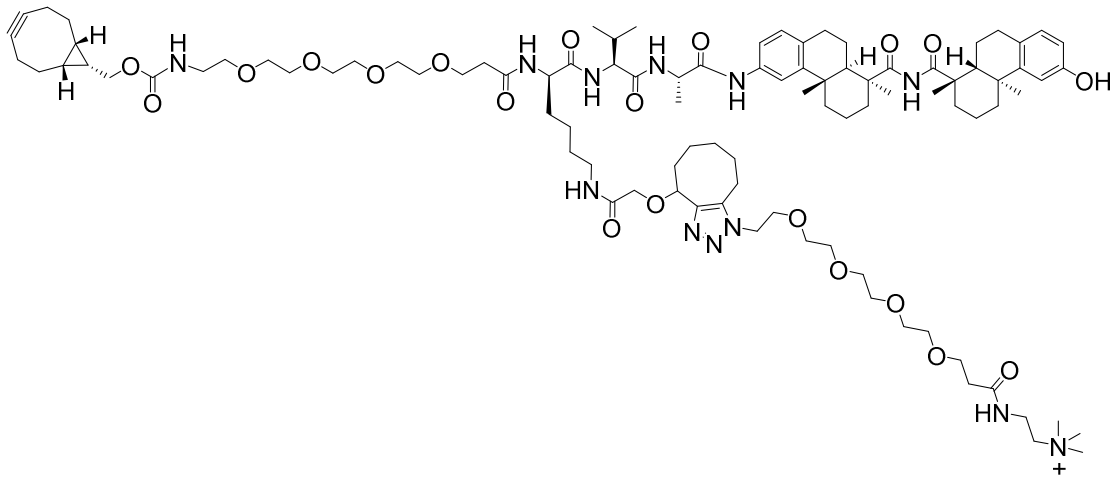
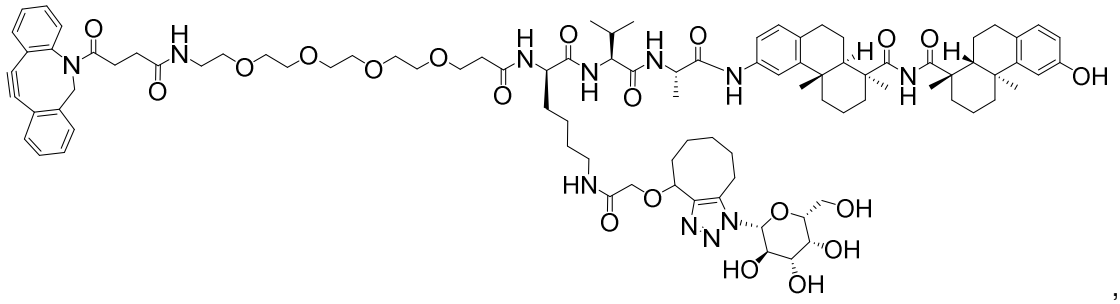
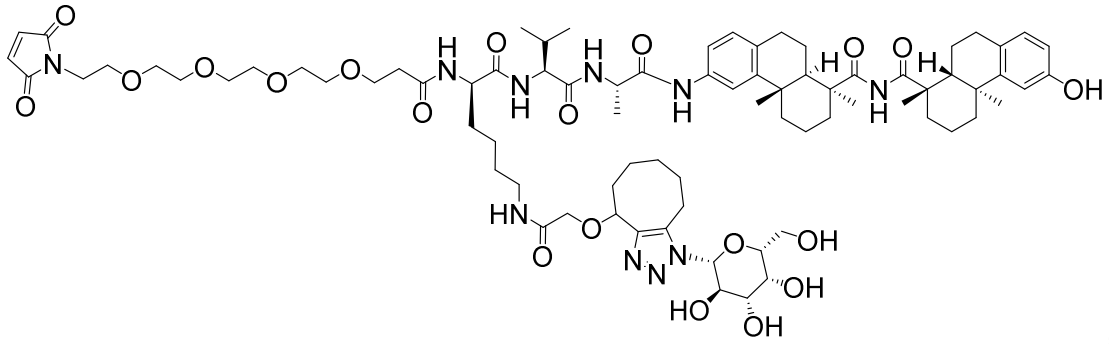
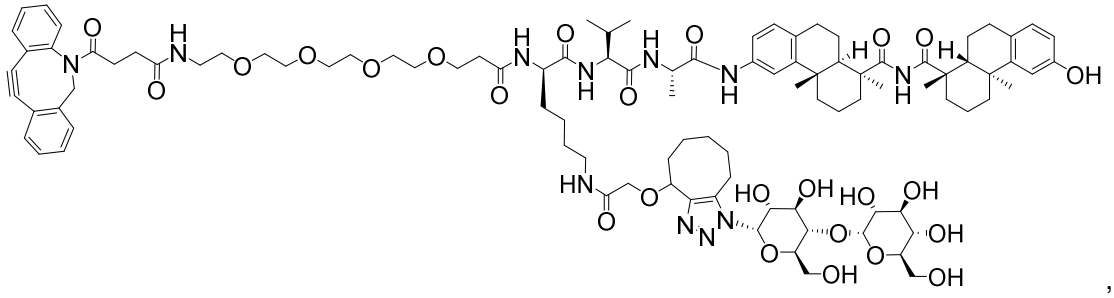


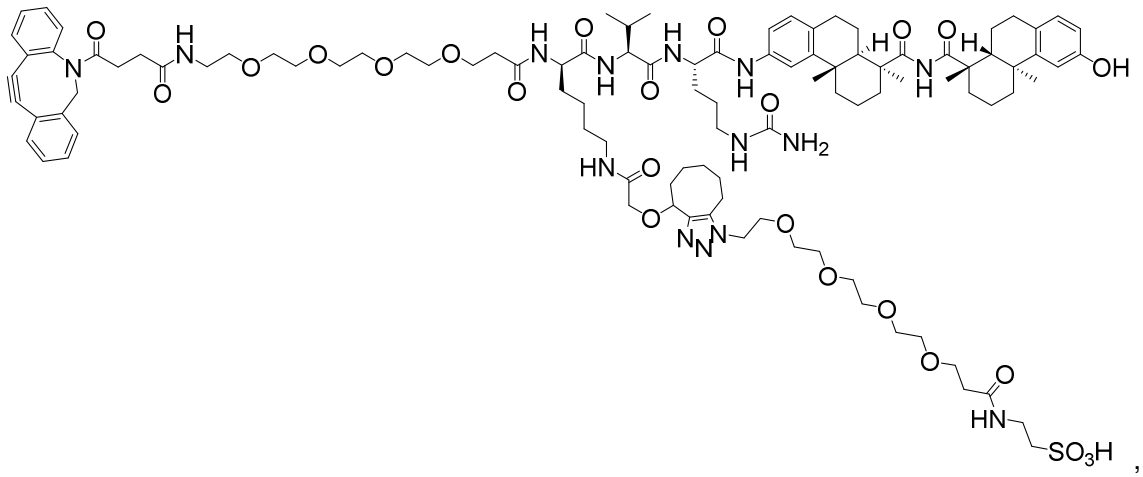
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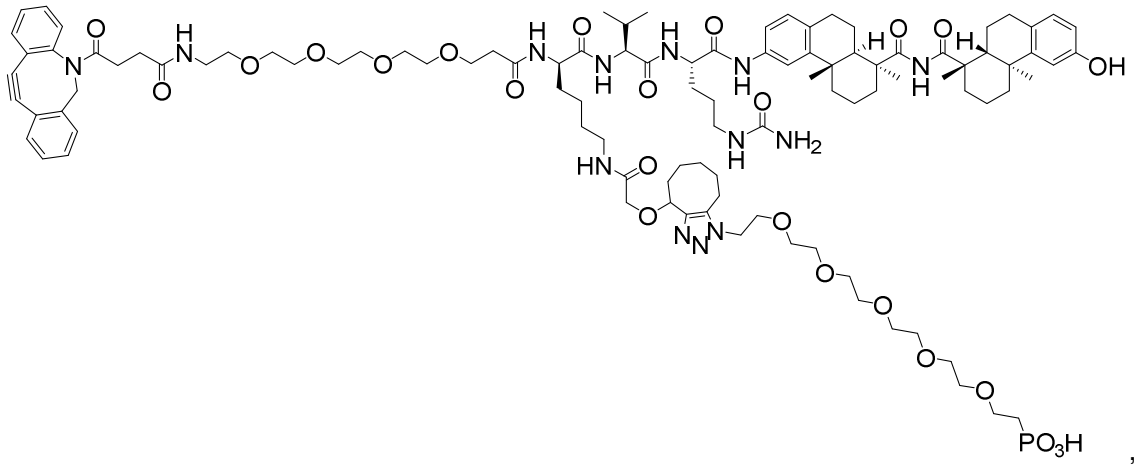

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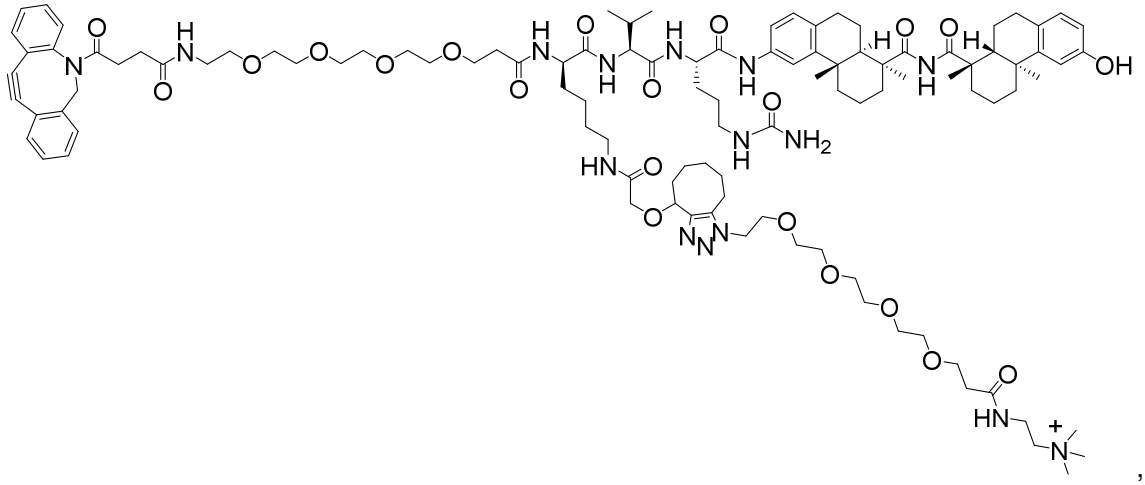

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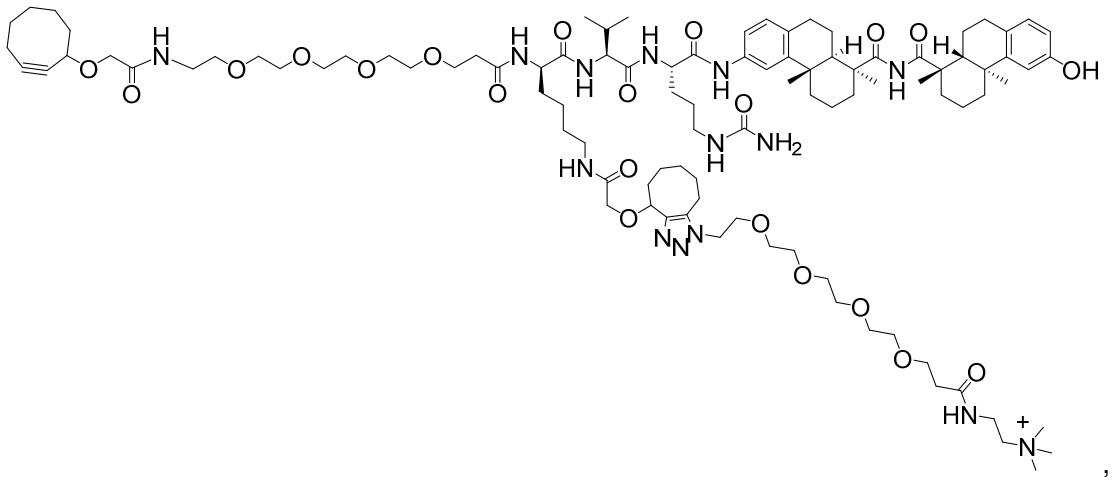
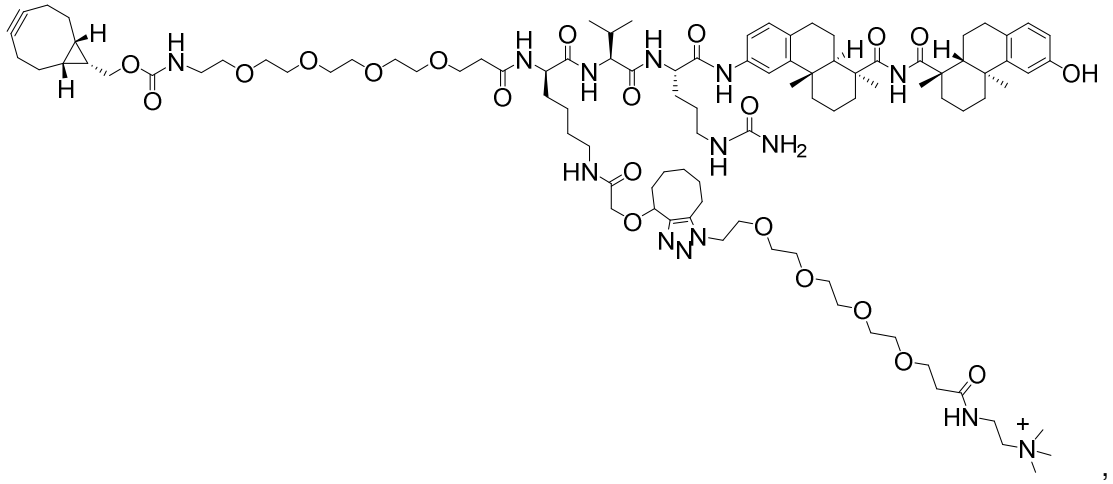
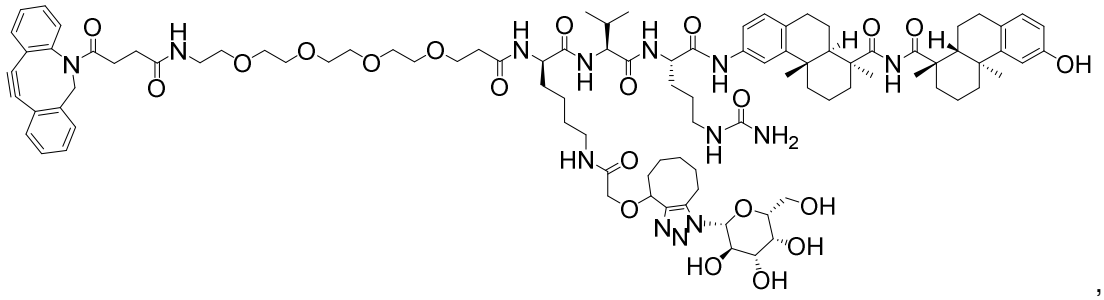
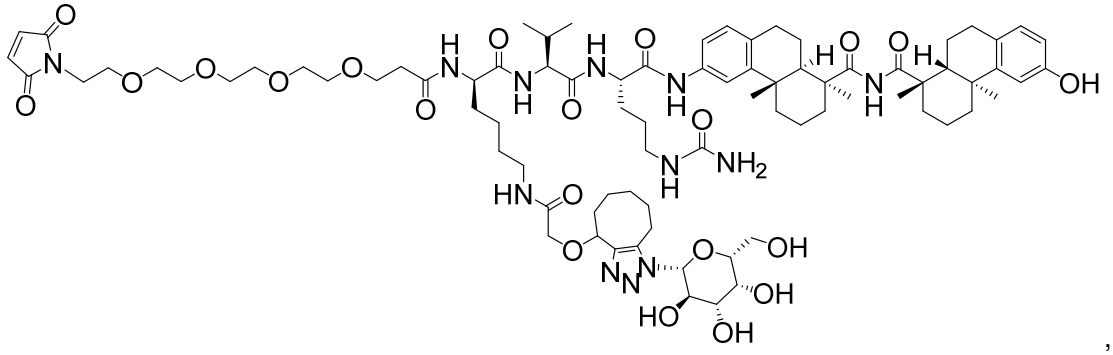
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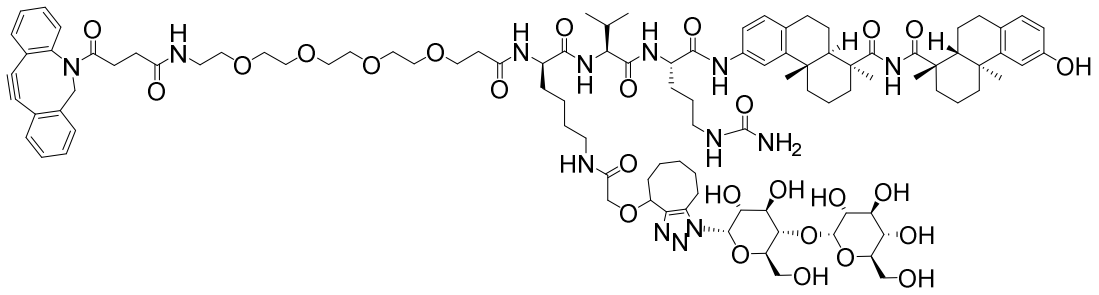


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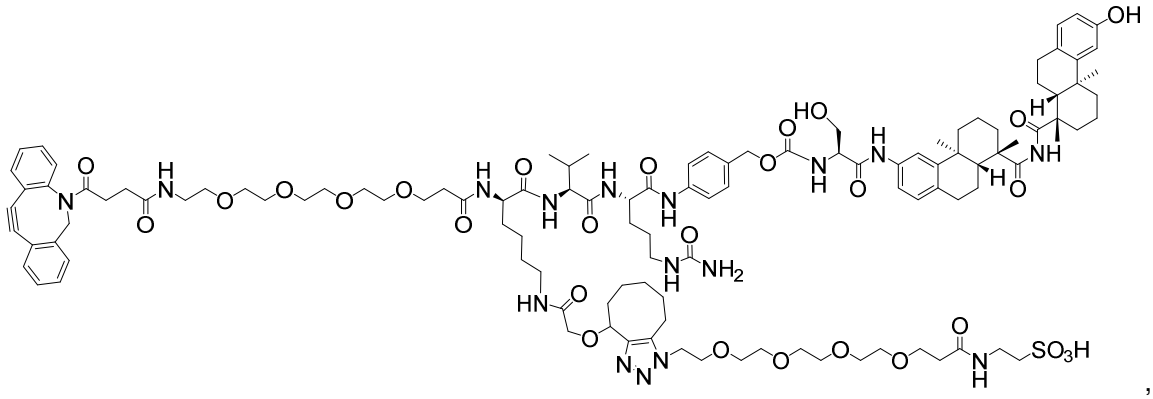


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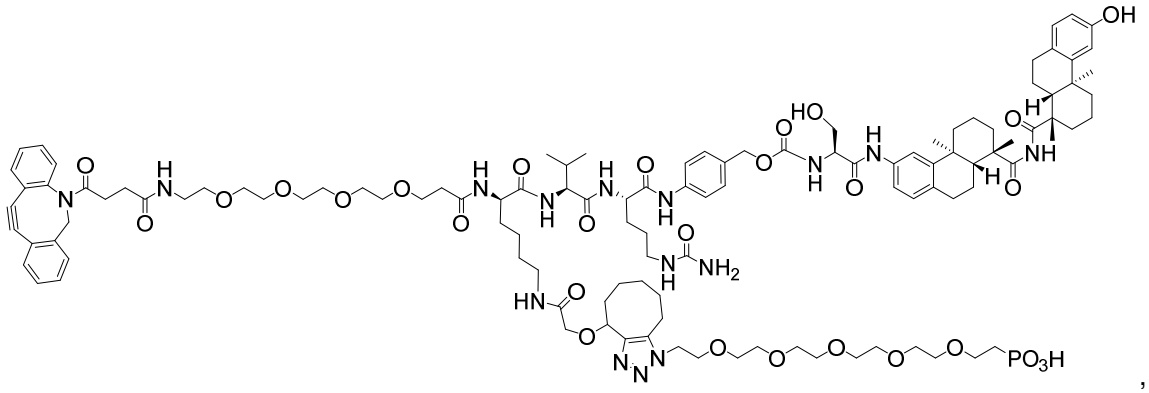

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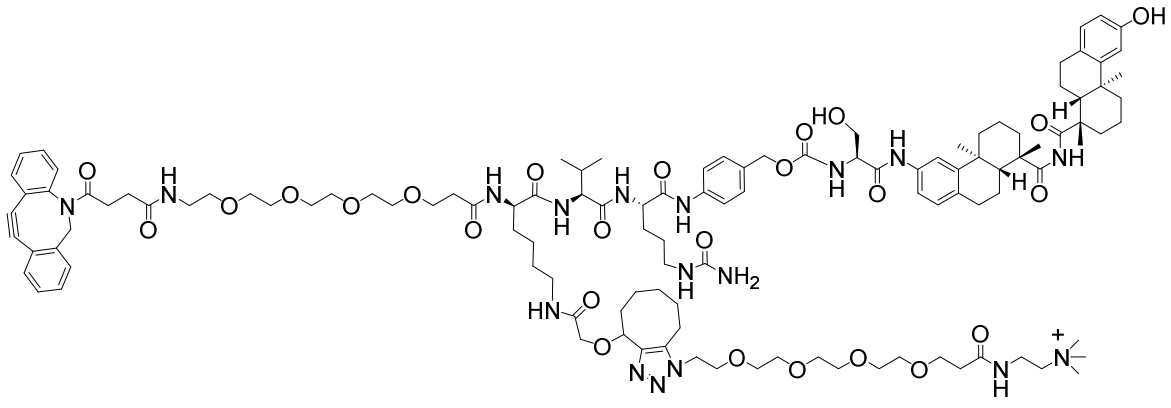
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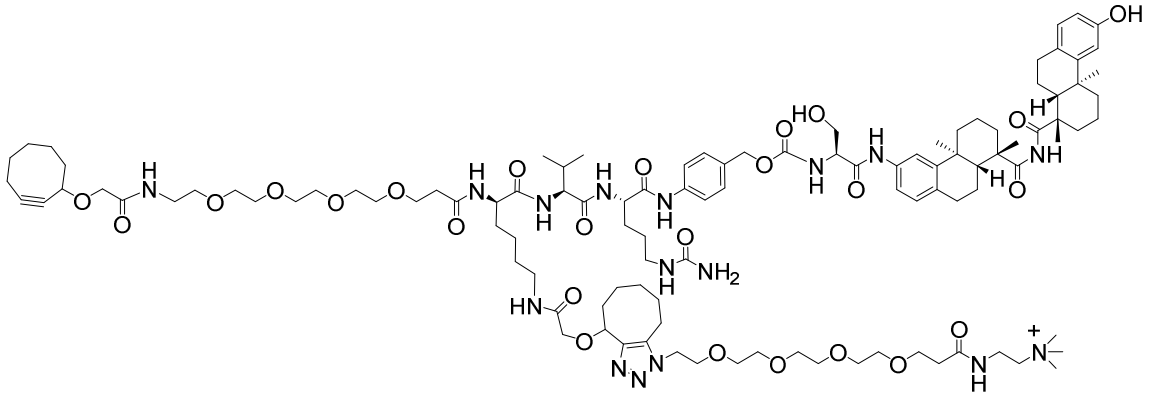
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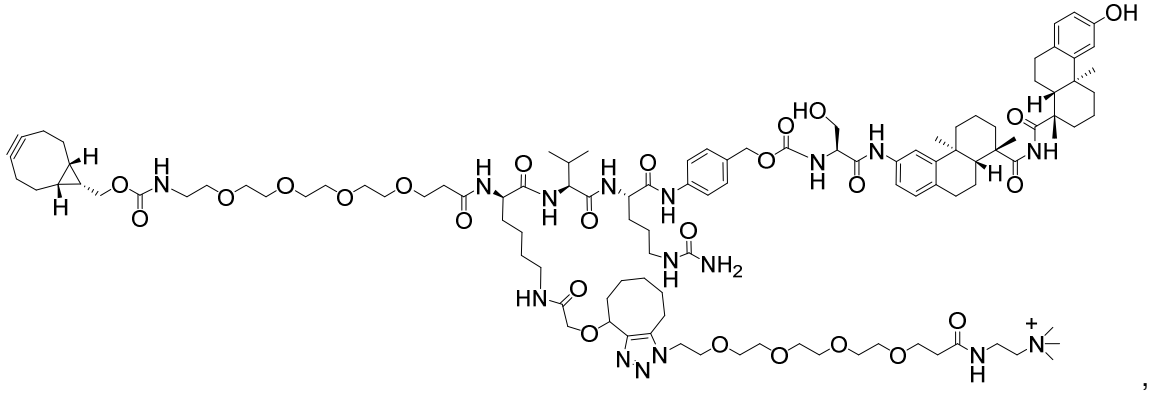
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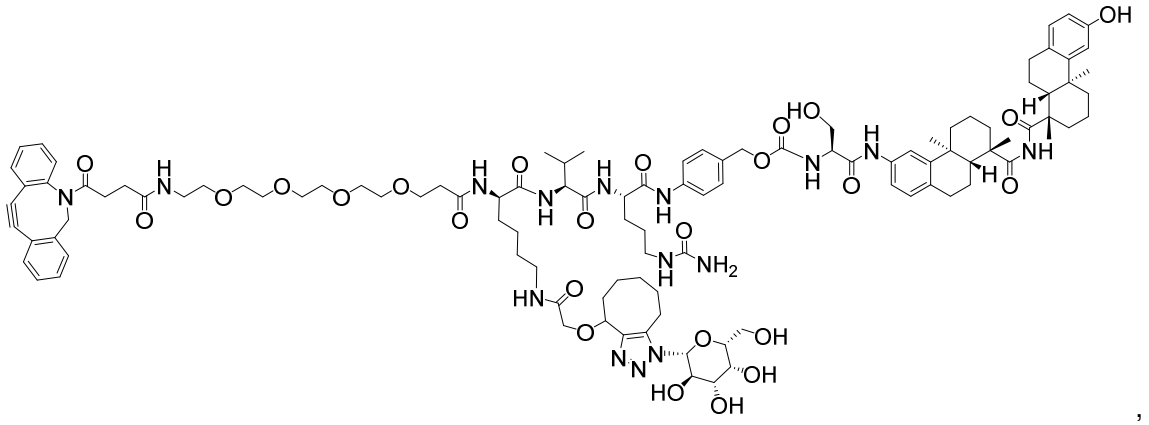
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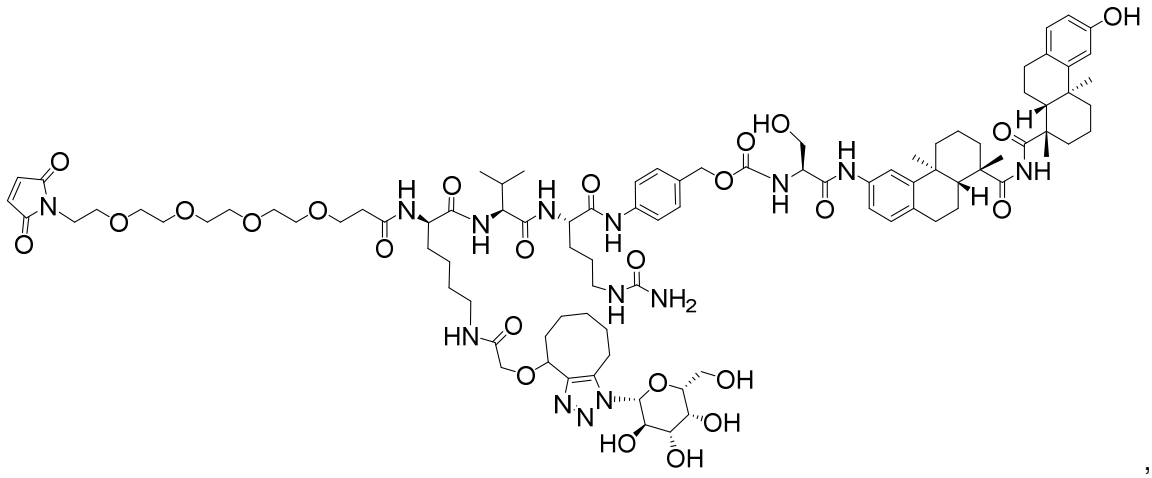
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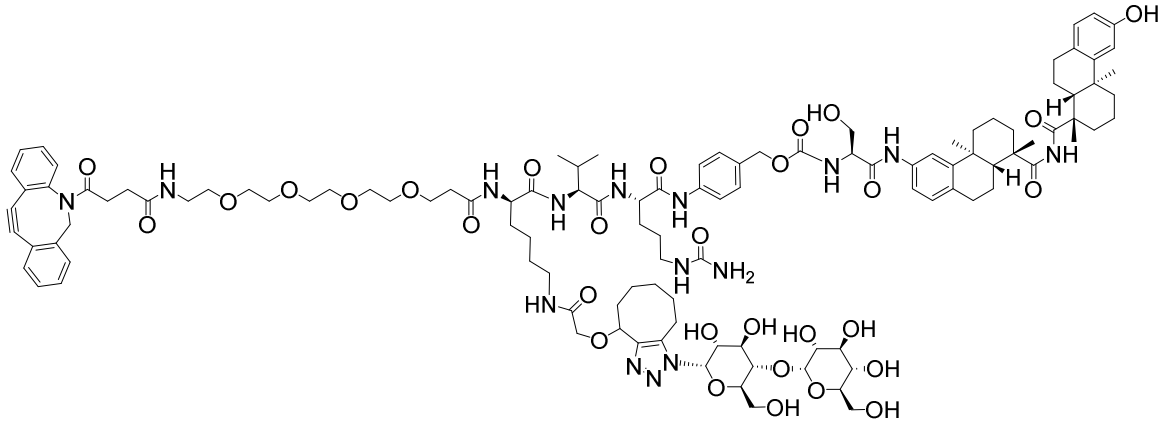
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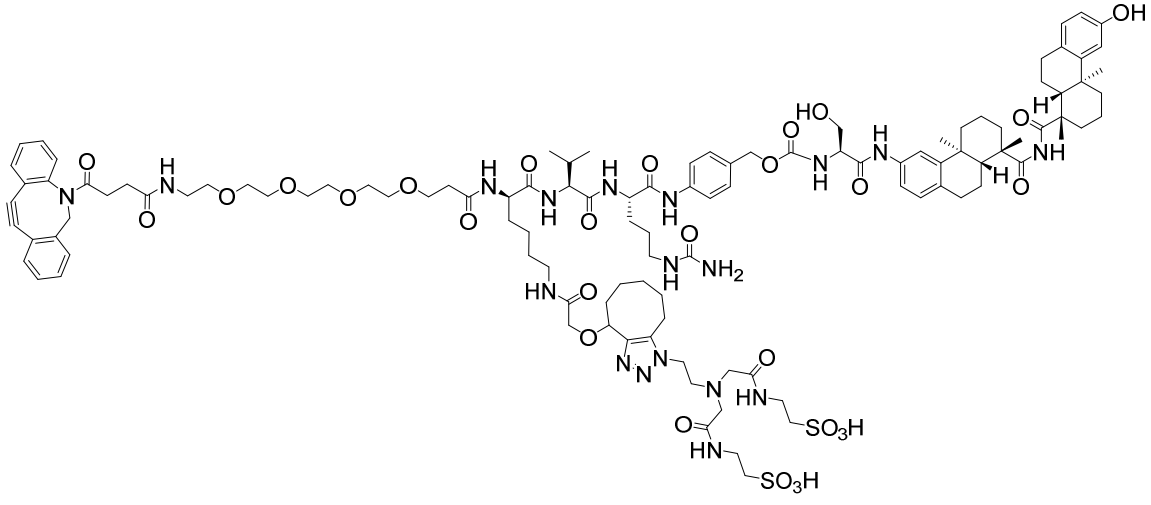
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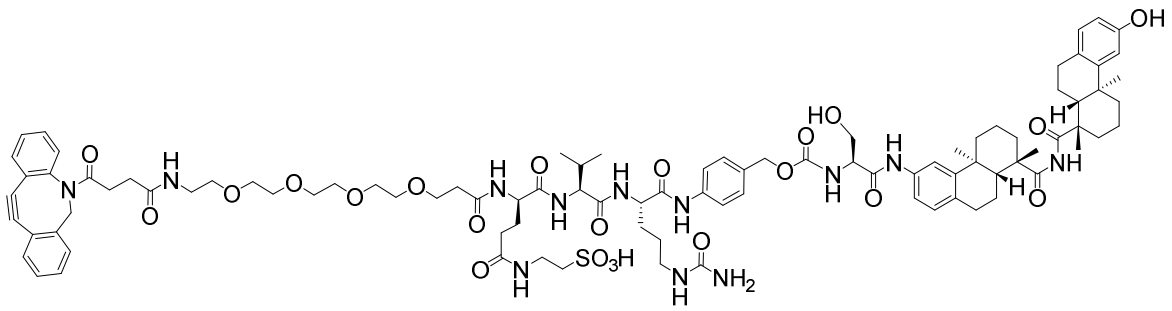
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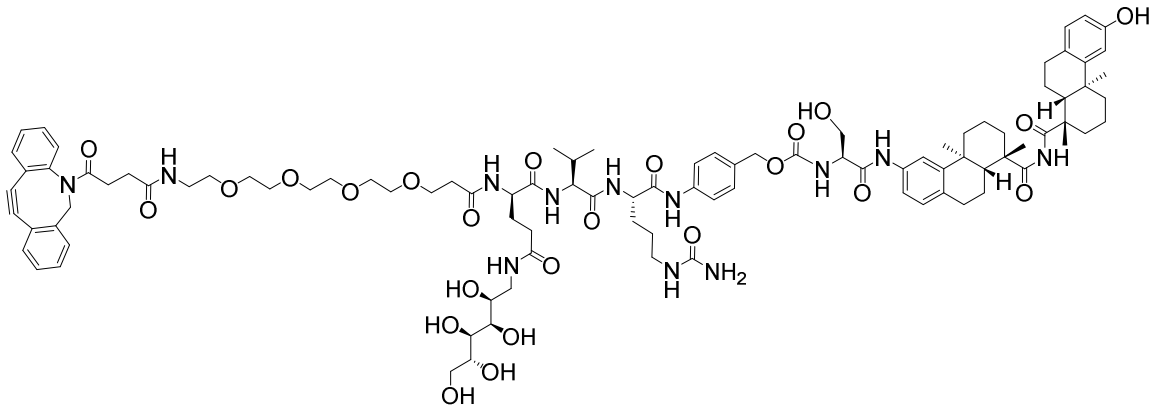
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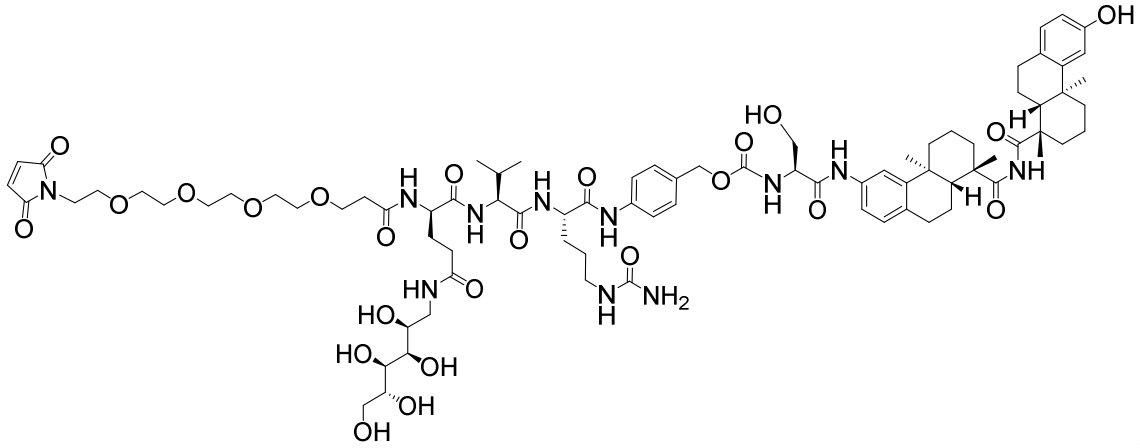
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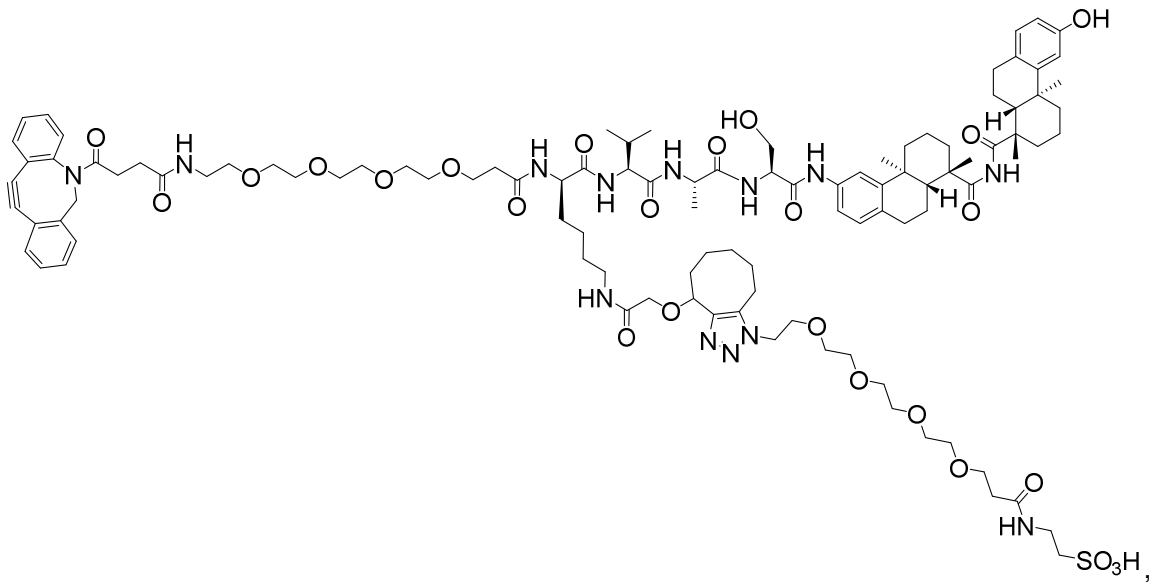
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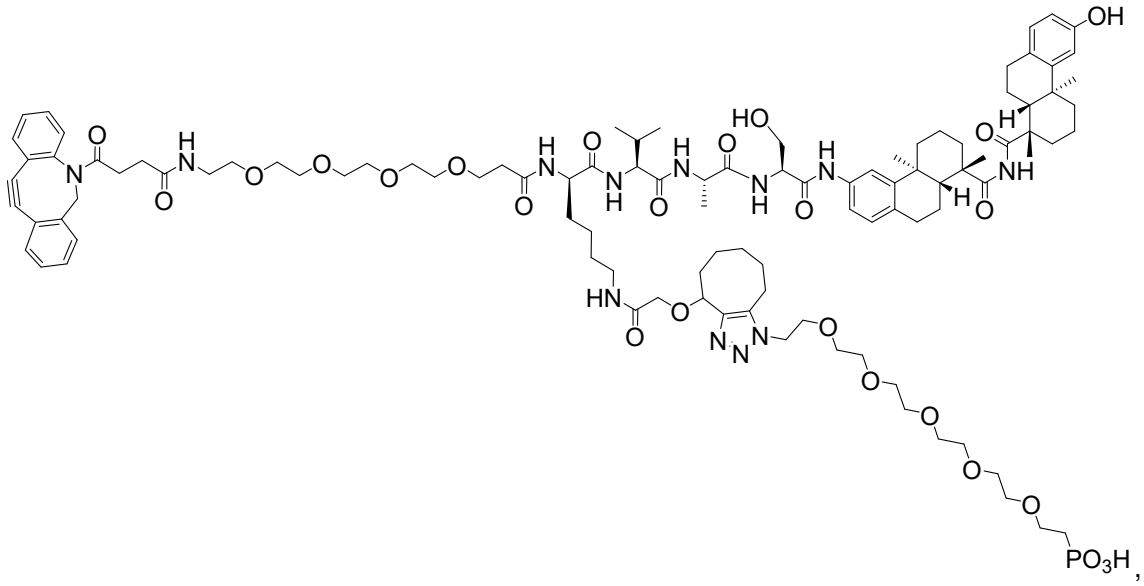


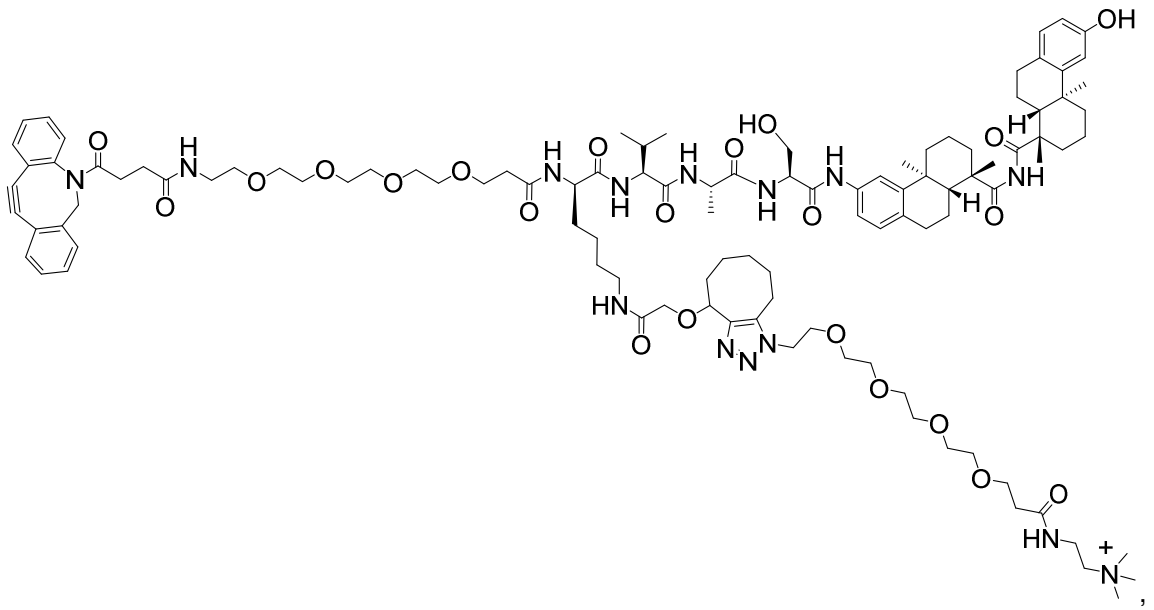
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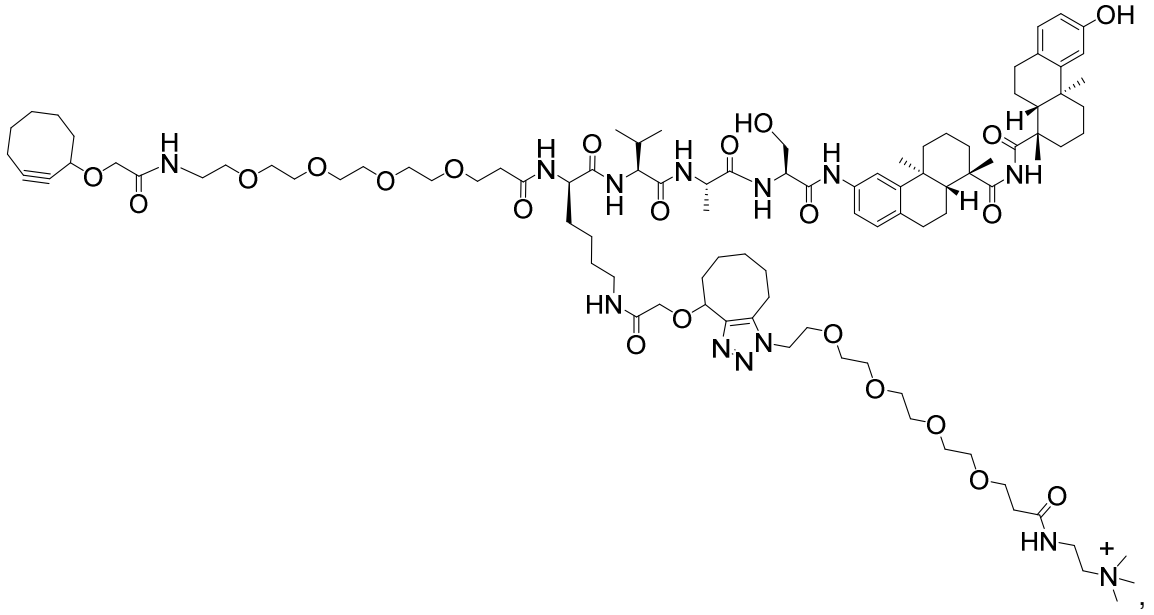


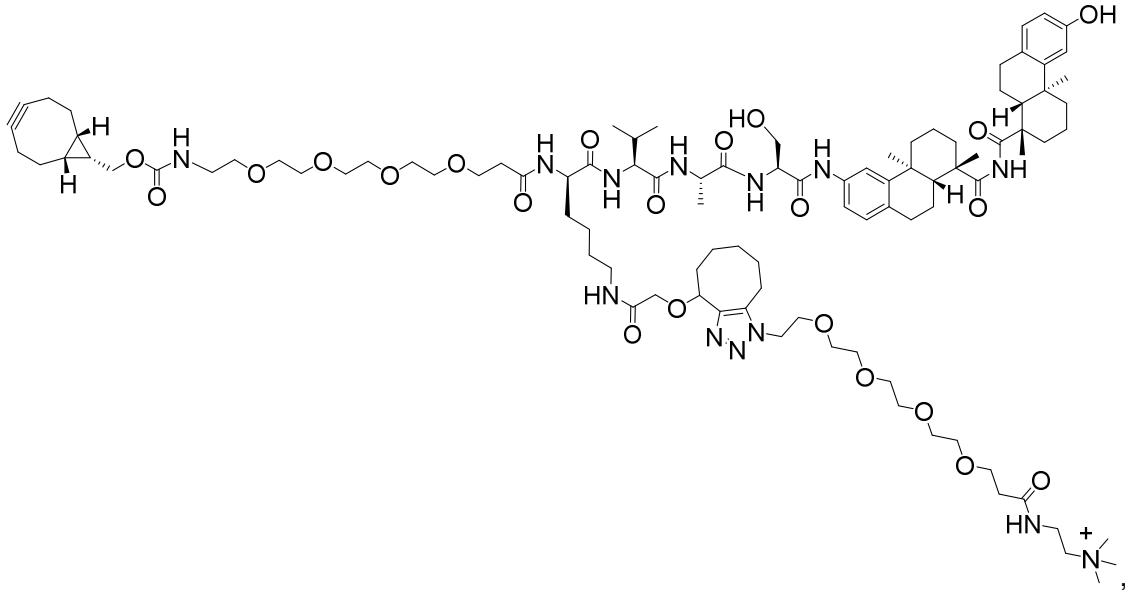
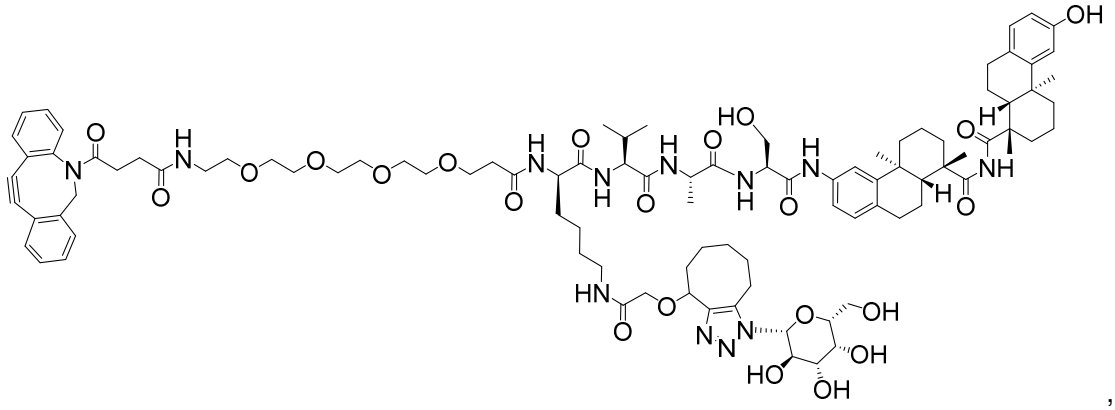
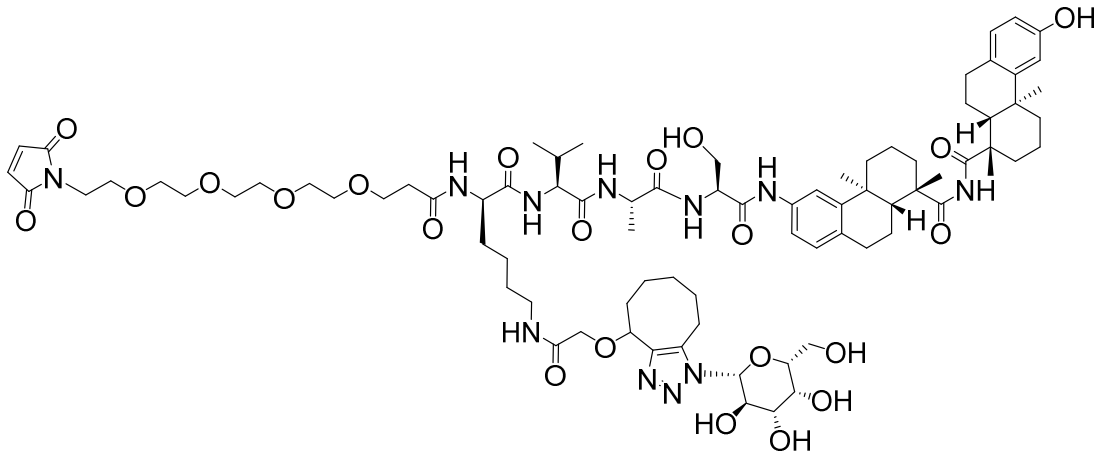
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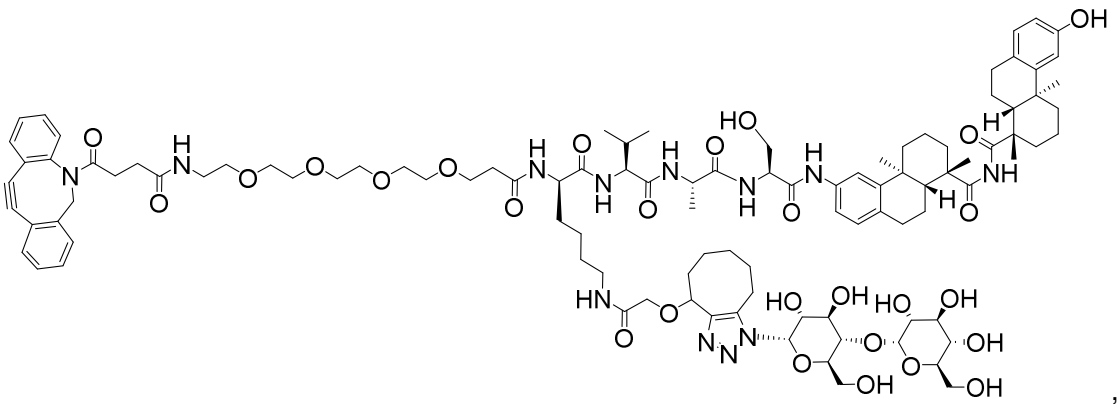


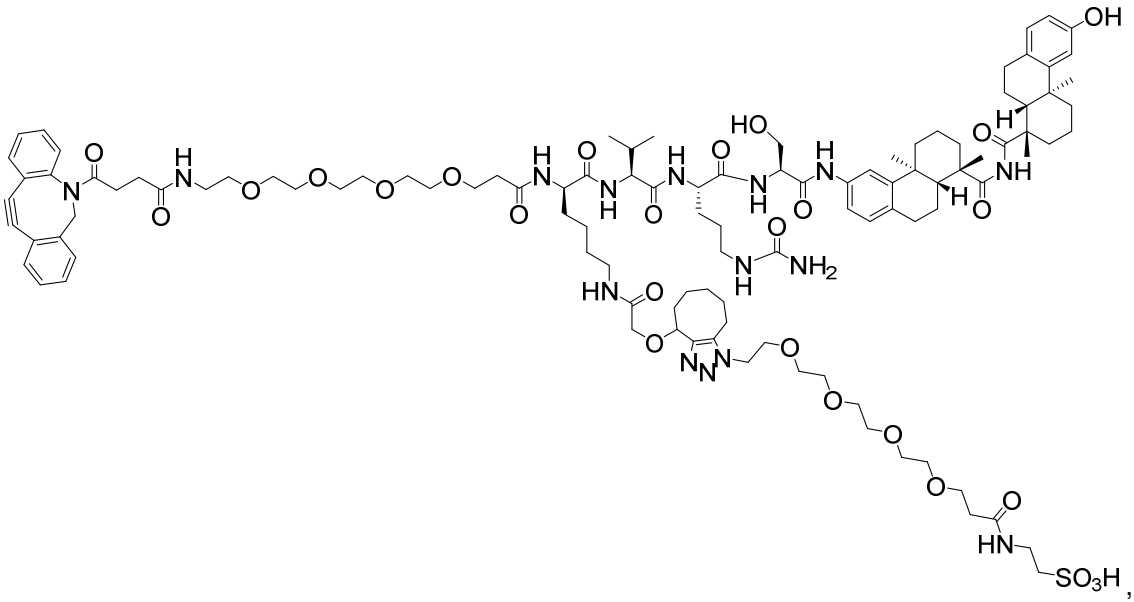


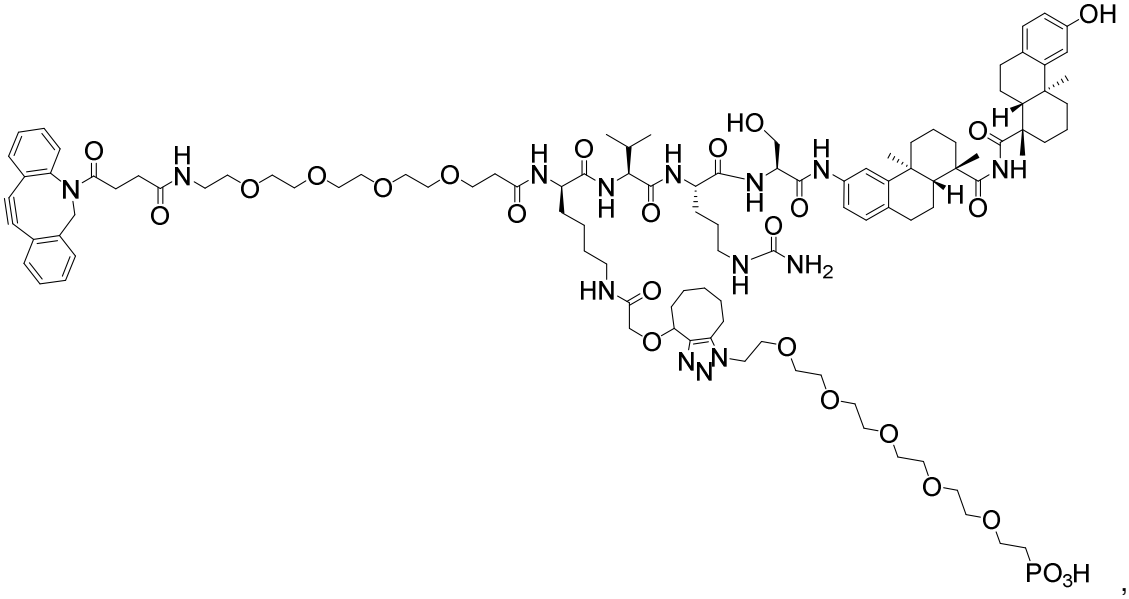


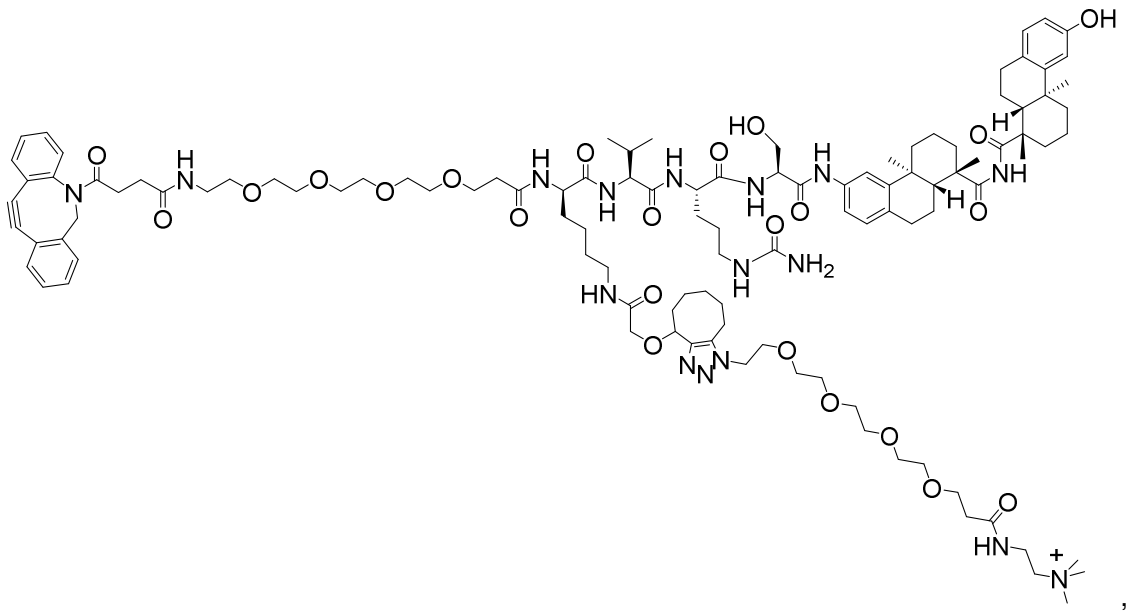



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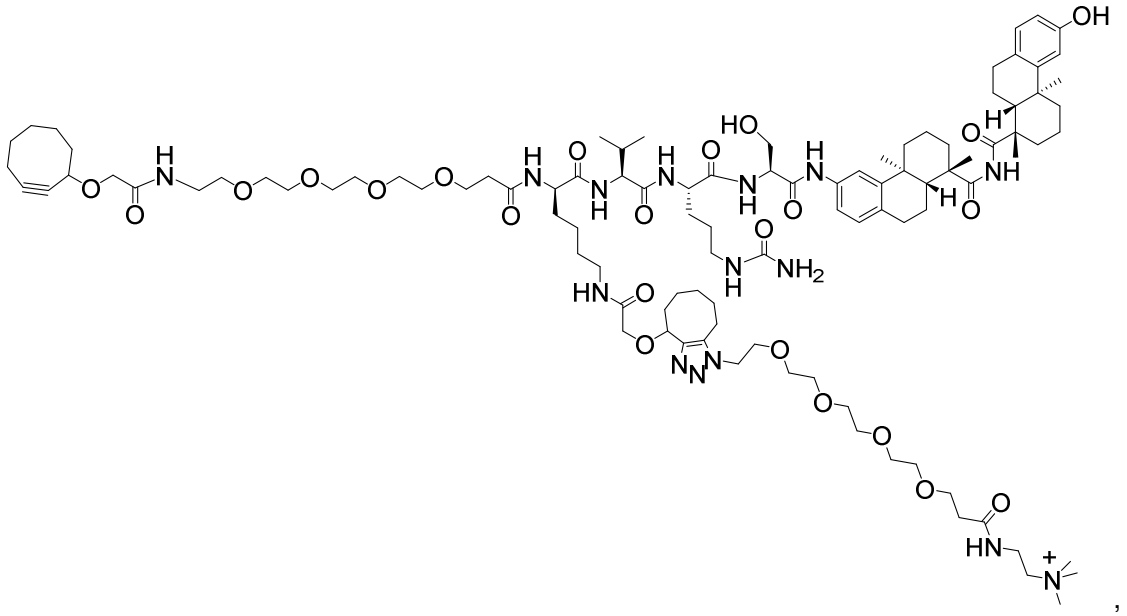

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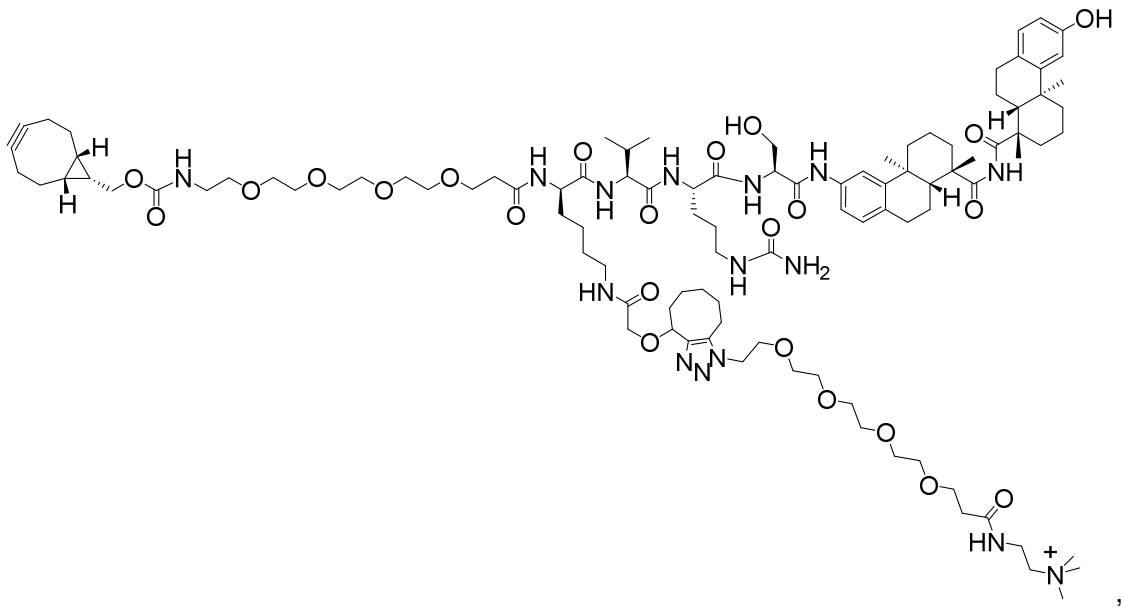
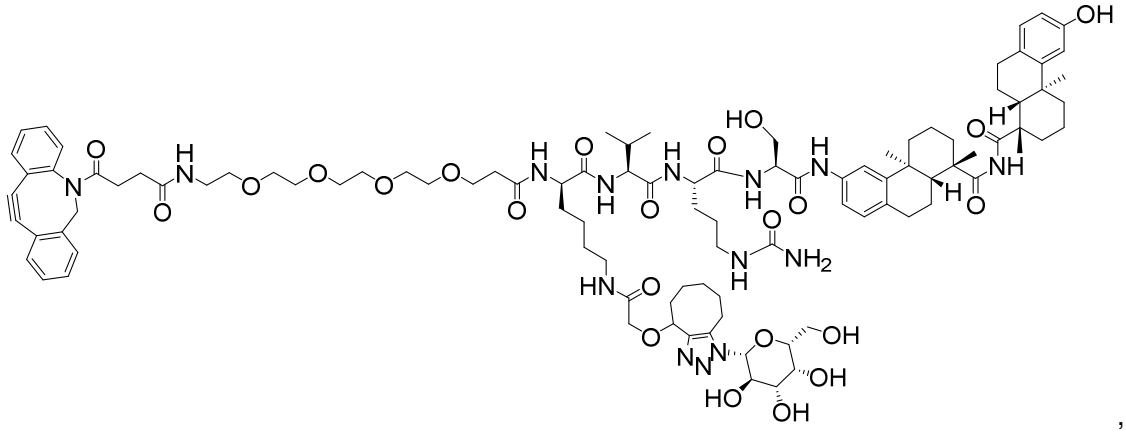
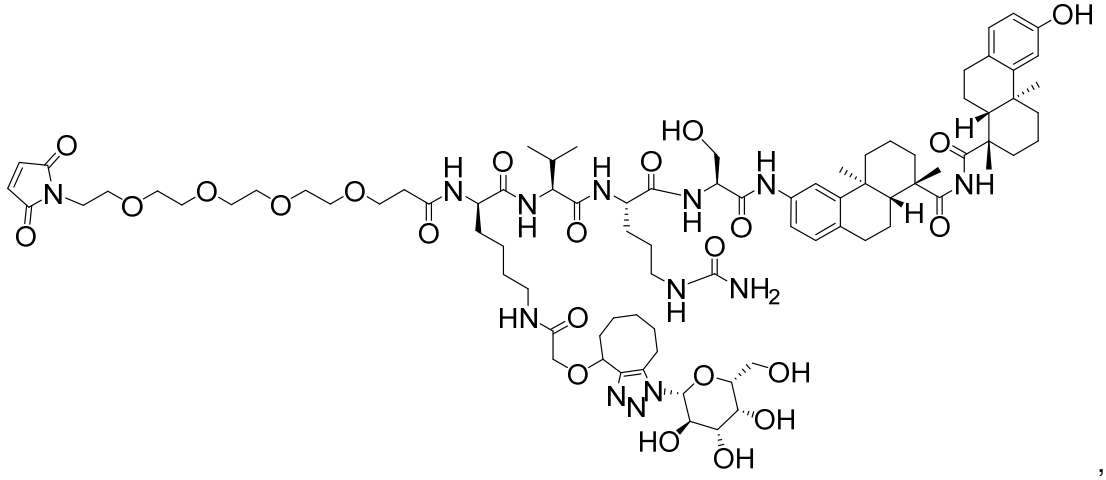

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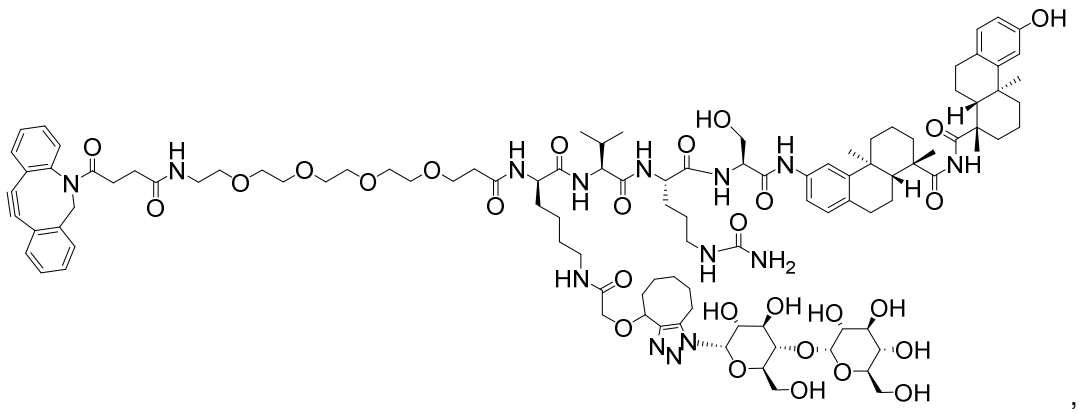


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or a stereoisomeric form thereof, or a regioisomer thereof, or a mixture of regioisomers thereof.

58. A method of preparing a compound of claim 1 comprising the step of contacting a binding agent with a compound according to any of claim 34-57, under conditions suitable for forming a bond between the binding agent and the compound.

59. The method of claim 58, wherein the binding agent is a modified binding agent comprising an azido group ($\sim N_3$) wherein the $\sim$ indicates the atom through which the azido group is bonded to the adjacent groups in the formula.

60. A linker-payload comprising the compound of any of claims 34-57, bonded to a linker.

61. A linker-payload comprising the compound of any of claims 34-57, bonded to an oxygen or a primary or secondary nitrogen of the payload.

62. An antibody-drug-conjugate comprising the compound or linker-payload of any of the preceding claims bonded to an antibody, or an antigen binding fragment thereof.

63. A compound of any one of claims 1-31 or a pharmaceutical composition of claim 32 for use in treating a proliferative disease, a metabolic disease, inflammation, or a neurodegenerative disease in a subject.

64. A compound of any one of claims 1-31 or a pharmaceutical composition of claim 32 for use in the treatment of a proliferative disease in a subject.

65. A compound of any one of claims 1-31 or a pharmaceutical composition of claim 32 for use in the treatment of a metabolic disease in a subject.

66. A compound of any one of claims 1-31 or a pharmaceutical composition of claim 32 for use in the treatment of inflammation in a subject.

67. A compound of any one of claims 1-31 or a pharmaceutical composition of claim 32 for use in the treatment of a neurodegenerative disease in a subject.

68. Use of a compound of any one of claims 1-31 or a pharmaceutical composition of claim 32 in the manufacture of a medicament for treating a proliferative disease, a metabolic disease, inflammation, or a neurodegenerative disease in a subject.