CLAIMS

1. An antibody-drug conjugate having a structure of formula (I), a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, a pharmaceutically acceptable salt, a hydrate, a solvate or an isotopically labeled compound thereof:

$$A\text{-}(L\text{-}D)_m \qquad (I)$$

wherein A is a targeting ligand selected from an antibody (e.g., a monoclonal antibody) or an antigen-binding fragment, a small-molecule ligand, and a polypeptide;

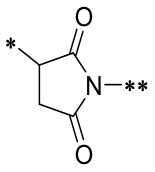
L is a linker moiety, with one end linked to the ligand A and the other end linked to a bioactive molecule D;

D is an amino-containing bioactive molecule or a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer or an isotopically labeled compound thereof, covalently linked to the linker moiety L via the amino group in its molecular structure;

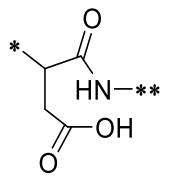
m is an integer or a decimal from 1 to 12;

the linker moiety -L- is represented by the following formula:

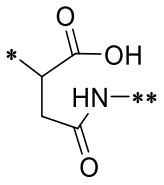
$-L_1-L_2-L_3-L_4-$,



wherein L_1 is a moiety of L linked to the ligand A; preferably, L_1 is selected from



(or a ring-opened form thereof



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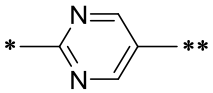

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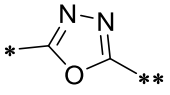


, wherein * represents linkage to a sulfhydryl group of A (e.g., a monoclonal antibody), and ** represents linkage to L_2;

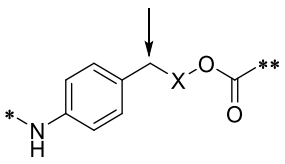
L_2 is a spacer, preferably selected from $-L_{2a}-C(O)-$, $-L_{2a}-L_{2b}-C(O)-$, $-L_{2a}-NH-C(O)-$, $-L_{2a}-C(O)-NH-$, $-L_{2a}-L_{2b}-NH-C(O)-$, $-L_{2a}-L_{2b}-C(O)-NH-$, $-L_{2a}-C(O)-NH-L_{2b}-C(O)-$, $-L_{2a}-NH-C(O)-L_{2b}-C(O)-$, $-L_{2a}-C(O)-NH-L_{2b}-C(O)-NH-$, $-L_{2a}-NH-C(O)-L_{2b}-NH-C(O)-$, $-L_{2a}-NR^1-SO_2-NH-C(O)-O-L_{2b}-C(O)-$, and $-L_{2a}-NR^1-SO_2-NH-C(O)-O-L_{2b}-NH-C(O)-$, wherein L_{2a} is selected from $-C_1-C_8$ alkylene-, $-C_1-C_8$ alkylene-C_3-C_8 cycloalkylene-, $-C_6-C_{14}$ arylene-, $-C_6-C_{14}$ arylene-C_1-C_8 alkylene-, -(5- to 6-membered heteroarylene)-, -(5- to 6-membered heteroarylene)-C_1-C_8 alkylene-, linear or branched heteroalkylene having 1-50 atoms, and (linear or branched

heteroalkylene having 1-50 atoms)-(3- to 8-membered heterocyclylene), wherein the alkylene, cycloalkylene, arylene, heteroalkylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more substituents independently selected from C_1-C_6 alkyl, heteroalkyl having 1-6 atoms, C_1-C_6 alkoxy, hydroxyl, amino, carboxyl, and C_3-C_8 cycloalkyl, the heteroalkylene, heterocyclylene, or heteroalkyl contains 1-12 heteroatoms, and the heteroatom in the heteroalkylene, heterocyclylene, heteroarylene, or heteroalkyl is selected from one or more of N, O, and S; L_{2b} is selected from -C_1-C_8 alkylene- and linear or branched heteroalkylene having 1-50 atoms, and R^1 is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, C_1-C_6 haloalkyl, heteroalkyl having 2-8 atoms, C_6-C_{14} aryl, and 5- to 6-membered heteroaryl, wherein the alkyl, heteroalkyl, aryl, and heteroaryl are each optionally substituted with one or more substituents independently selected from C_1-C_6 alkyl, heteroalkyl having 2-6 atoms, C_1-C_6 alkoxy, amino, and carboxyl, the heteroalkyl or heteroalkylene contains 1-12 heteroatoms, and the heteroatom in the heteroalkyl, heterocyclyl, heteroaryl, heteroalkylene, or heteroarylene is selected from one or more of N, O, and S;

L_3 is a polypeptide sequence, preferably selected from a peptide residue consisting of 2-8 natural or unnatural amino acids, wherein optionally, the amino acid is further substituted with one or more substituents selected from C_1-C_6 alkyl, heteroalkyl having 2-6 atoms, C_1-C_6 alkoxy, hydroxyl, amino, carboxyl, and C_3-C_8 cycloalkyl;

L_4 is a hydrophilic group-modified self-immolative fragment, and

the self-immolative fragment is selected from:



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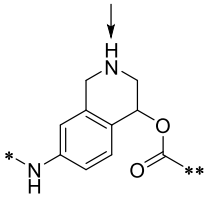

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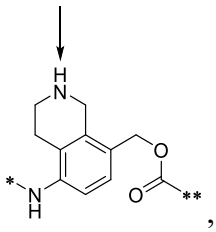
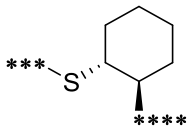
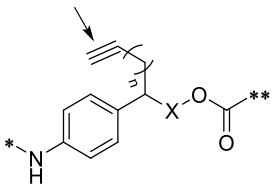
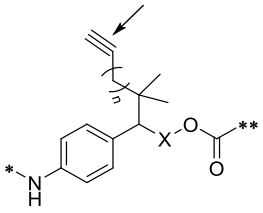
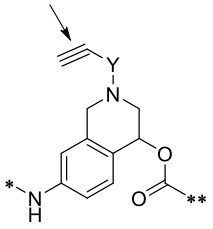
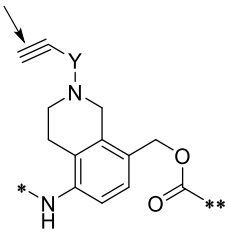


,

wherein * represents linkage to a carboxyl group of L_3 via an amide bond, ** represents linkage to the amino group of the bioactive molecule D, X is absent or


, *** represents linkage to a carbon atom, **** represents linkage to an oxygen atom, and the arrow indicates a modification site of the hydrophilic group;

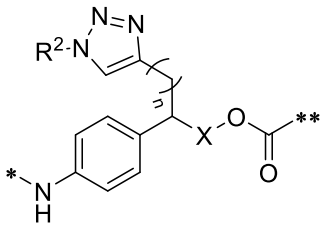
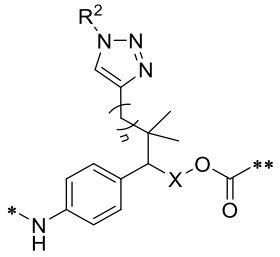
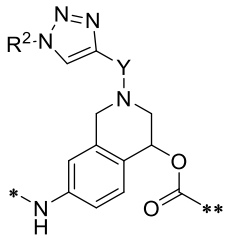
further preferably, the self-immolative fragment, prior to modification by the hydrophilic group, is selected from the following structures:

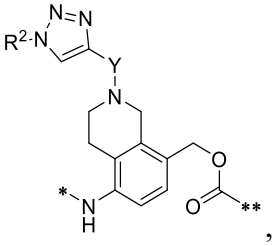
 ,  ,  , and  ,

wherein Y is C_1-C_6 alkylene or -R^3-C(O)-, wherein R^3 is C_1-C_6 alkylene or heteroalkylene containing 1-8 -OCH_2CH_2- structural units; n is an integer from 0 to 6;

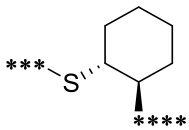
the hydrophilic group has at least one azido group and comprises a polyethylene glycol group, a poly-natural or unnatural amino acid group, a monosaccharide, an oligosaccharide, or a polysaccharide, or a combination thereof;

preferably, L_4 is selected from:

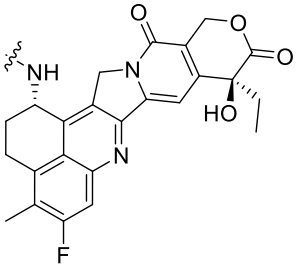
 ,  ,  , and

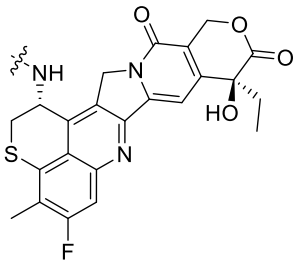
 ,

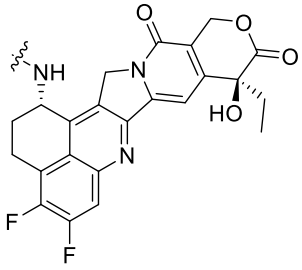
wherein * represents linkage to a carboxyl group of L_3 via an amide bond, and ** represents linkage to the amino group of the bioactive molecule D;

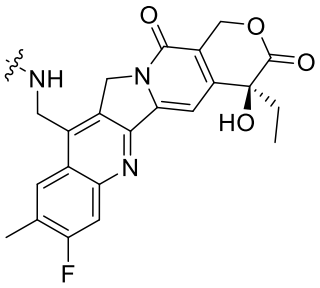
R^2 is a hydrophilic fragment, preferably selected from linear or branched heteroalkyl containing 4-50 (OCH_2CH_2) structural units, a peptide chain containing 4-50 proteinogenic amino acids (e.g., glycines) or non-proteinogenic amino acids (e.g., sarcosines), and linear or branched heteroalkyl containing a monosaccharide, an oligosaccharide, or a polysaccharide; X is absent or  ****, *** represents linkage to a carbon atom, and **** represents linkage to an oxygen atom; Y is C_1-C_6 alkylene or -R^3-C(O)-, wherein R^3 is C_1-C_6 alkylene or heteroalkylene containing 1-8 -OCH_2CH_2- structural units; n is an integer from 0 to 6;

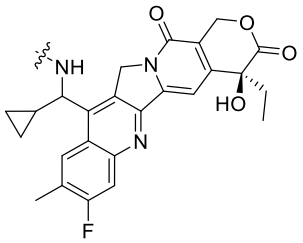
D is selected from compounds of the following formulas:

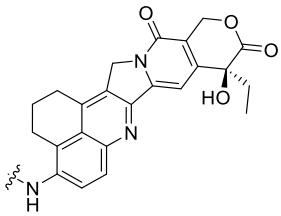


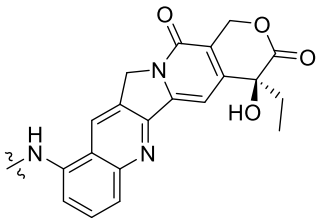


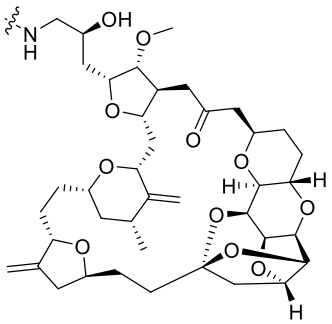


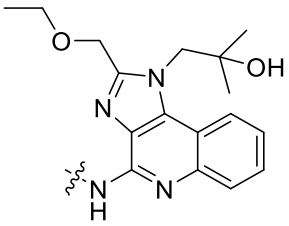


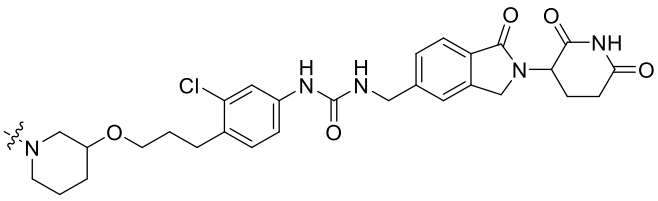


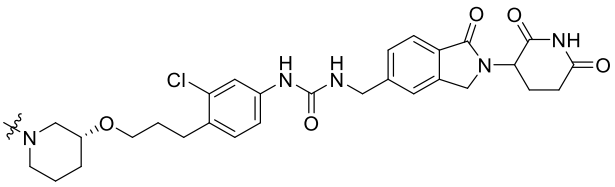


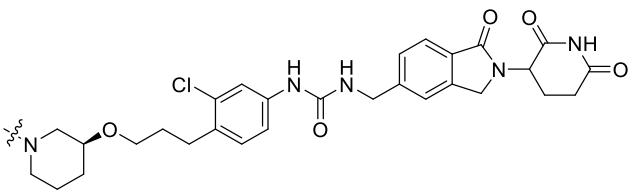


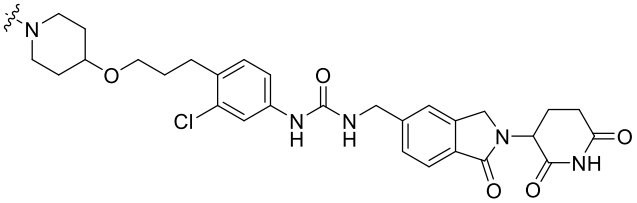












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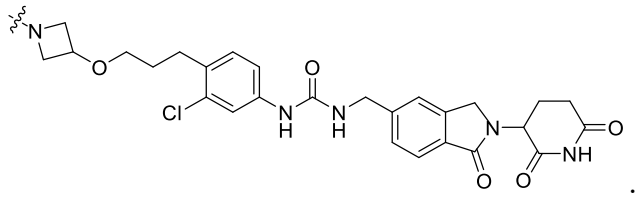
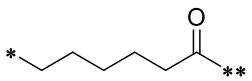
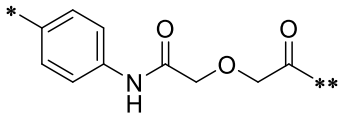
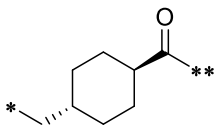
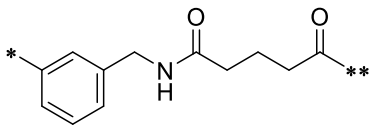
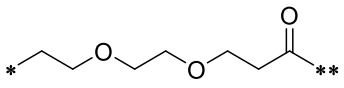
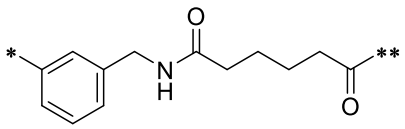
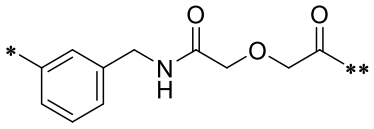
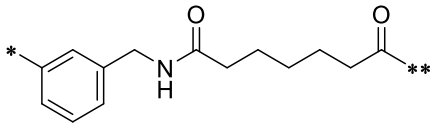
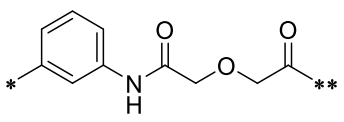
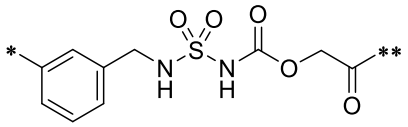
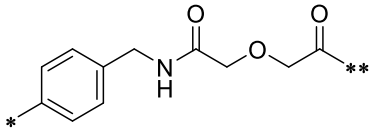
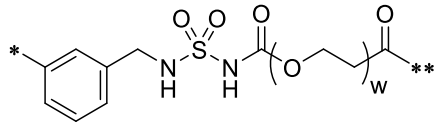


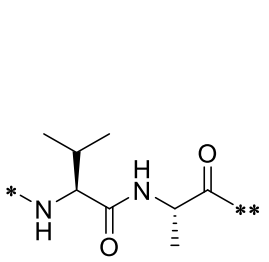
2. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to claim 1, wherein A is selected from an antibody or an antigen-binding fragment thereof targeting HER2 (ErbB2), HER3 (ErbB3), HER4 (ErbB4), EGFR, DLL3, TROP2, B7H3, c-Met, CD20, CD22, CD30, CD33, CD44, CD47, CD56, CD70, CD73, CD79b, CD105, CEA, A33, Cripto, EphA2, G250, MUC1, Lewis Y, VEGFR, VEGF, PD-1, PD-L1, MET, RET, GPNMB, Integrin, PSMA, Tenascin-C, SLC44A4, FRα, or Mesothelin; preferably A is an antibody or an antigen-binding fragment thereof targeting FRα, DLL3, B7H3, or HER2.

3. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-2, wherein L_2 is selected from the following structures:

(1) 	(7) 
(2) 	(8) 
(3) 	(9) 
(4) 	(10) 
(5) 	(11) 
(6) 	(12) 

wherein w is an integer selected from 1-12, * represents linkage to L_1, and ** represents linkage to L_3.

4. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-3, wherein L_3 is selected from the following structures: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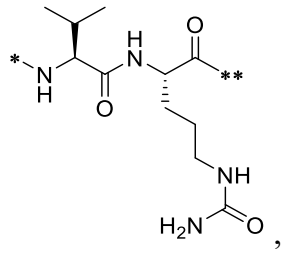
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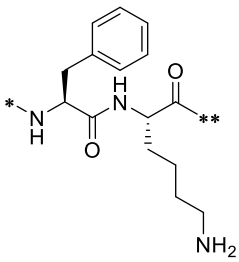
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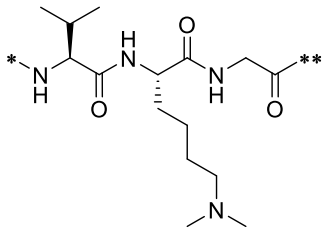
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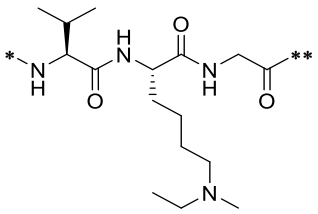
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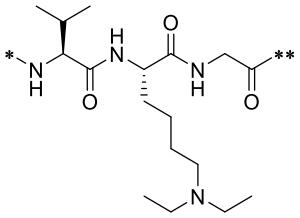
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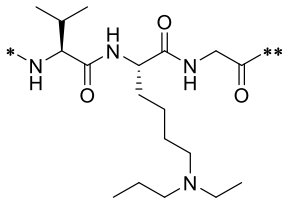
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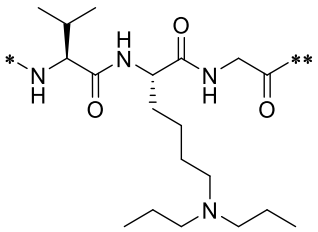
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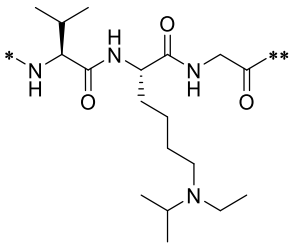
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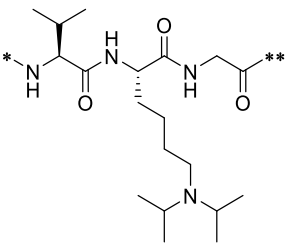
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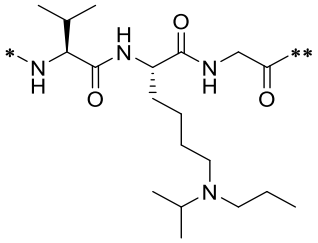
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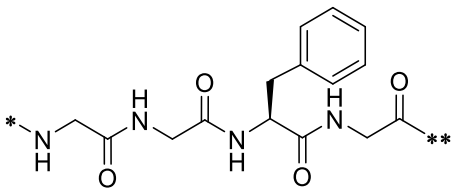
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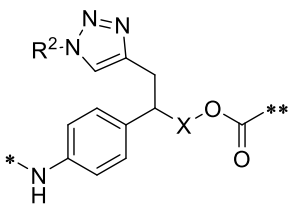
wherein * represents linkage to L_2, and ** represents linkage to L_4.

5. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-4, wherein L_4 is selected from the following structures: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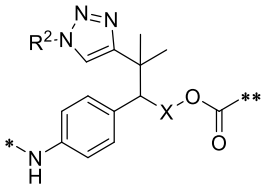
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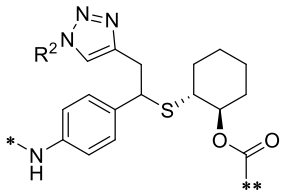
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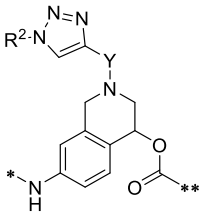
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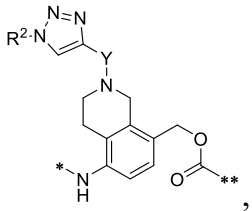
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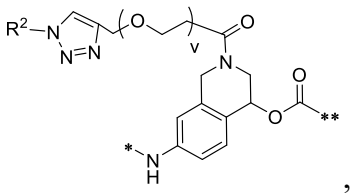
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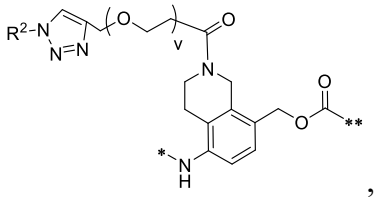
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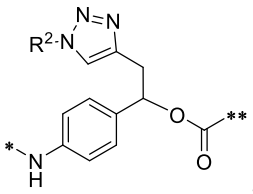
wherein v is an integer selected from 1-12, * represents linkage to a carboxyl group of L_3 via an amide bond, and ** represents linkage to the amino group of the bioactive molecule D.

6. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-5, wherein L_4 is selected from the following structures: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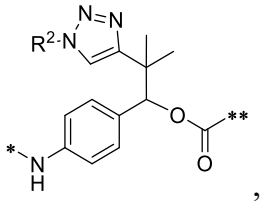
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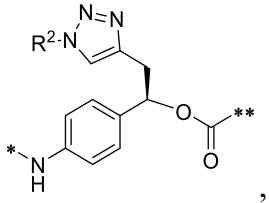
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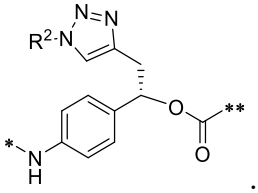
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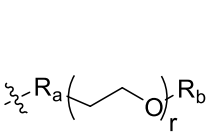
7. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-6, wherein R^2 is selected from the following structures: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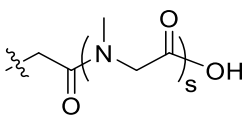
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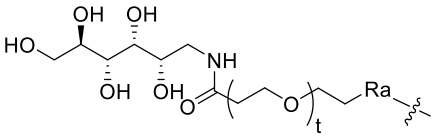
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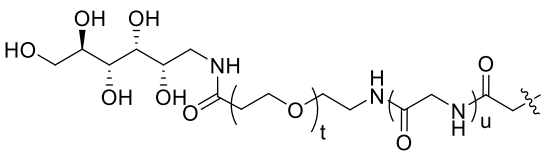
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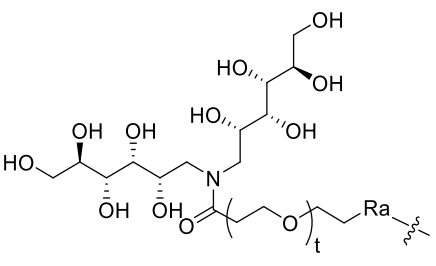
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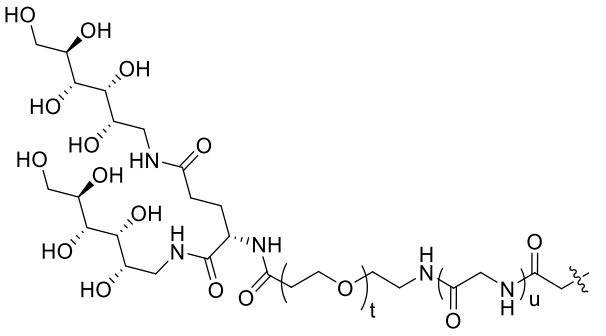
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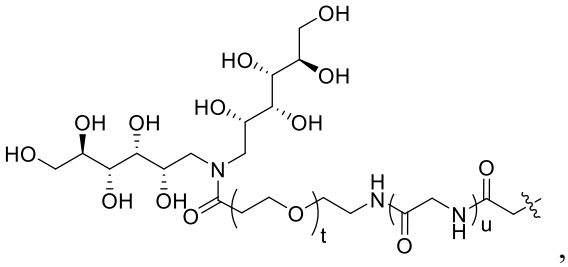
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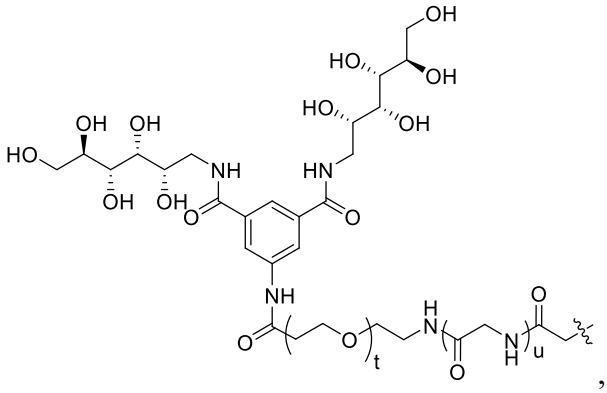
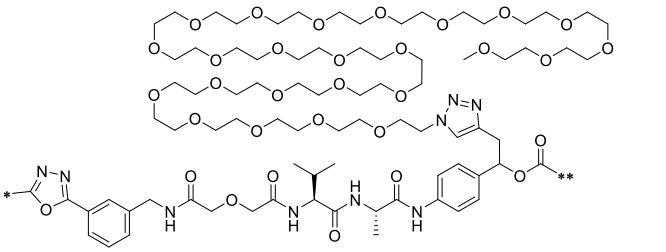
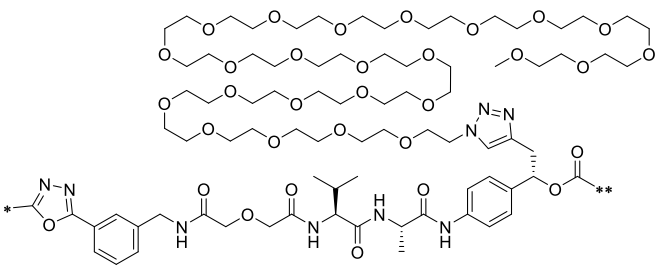
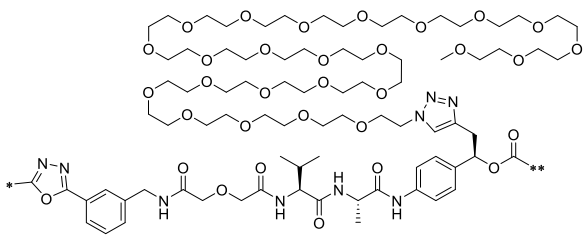

and
,

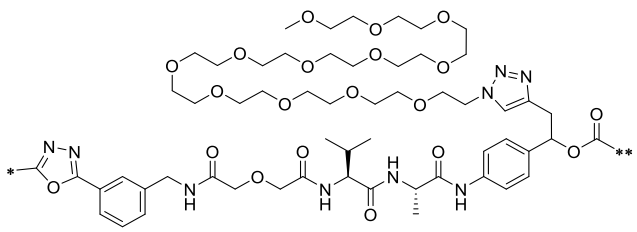
wherein r, s, t, and u are each independently an integer selected from 1-50 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50); R_a is selected from a bond and C_1-C_3 alkylene, such as methylene, ethylidene, *n*-propylidene, or isopropylidene; R_b is selected from C_1-C_3 alkyl, such as methyl, ethyl, *n*-propyl, or isopropyl.

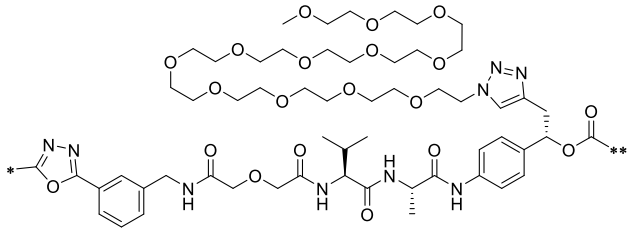
8. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-7, wherein L is selected from the following structures:

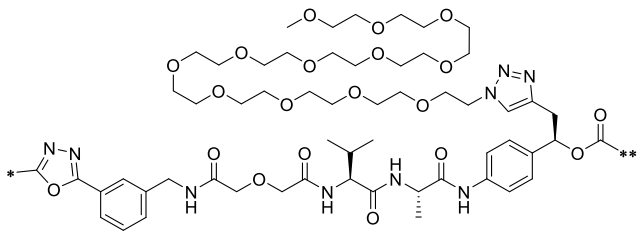


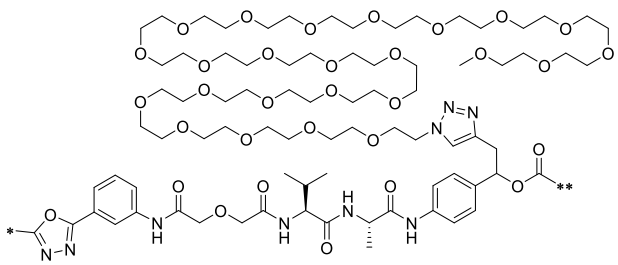












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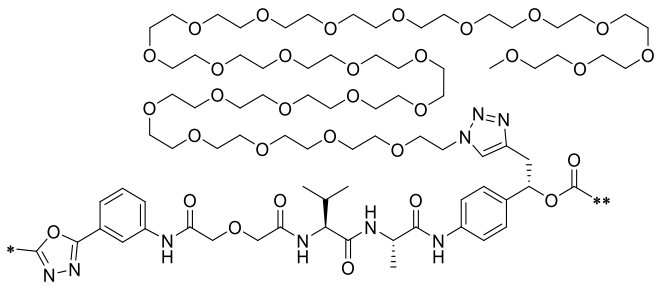

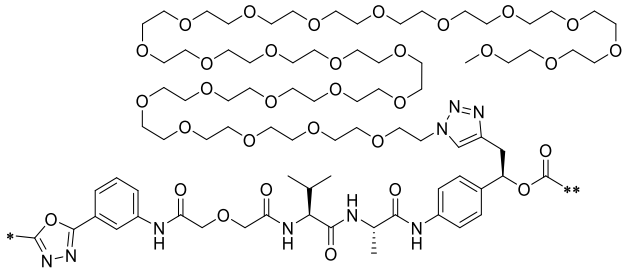

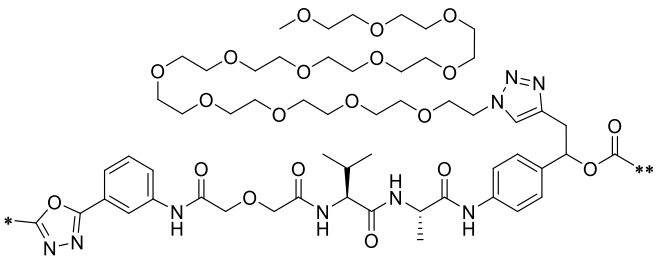

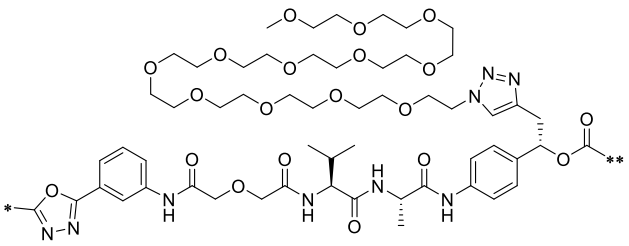

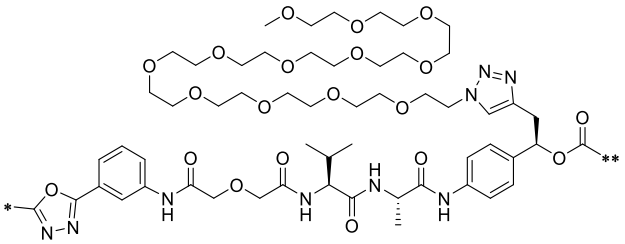

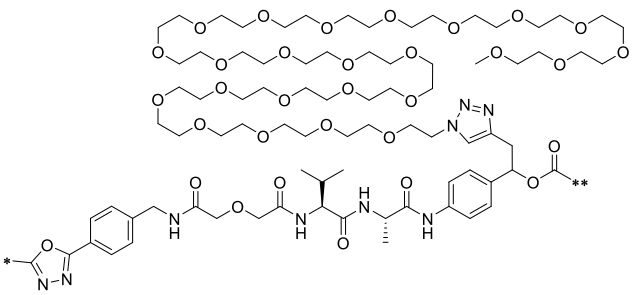

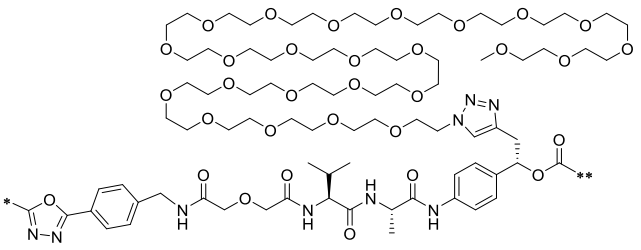

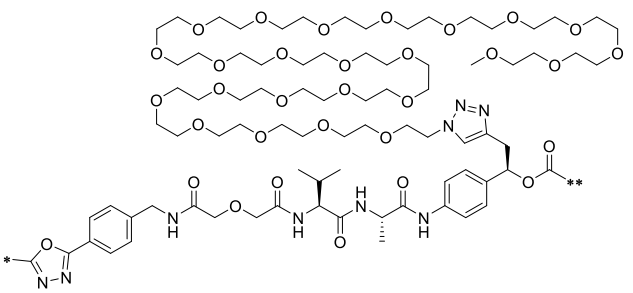

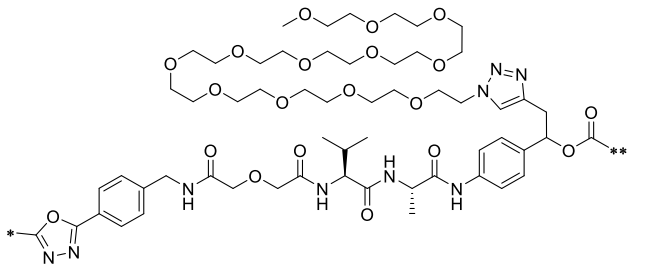

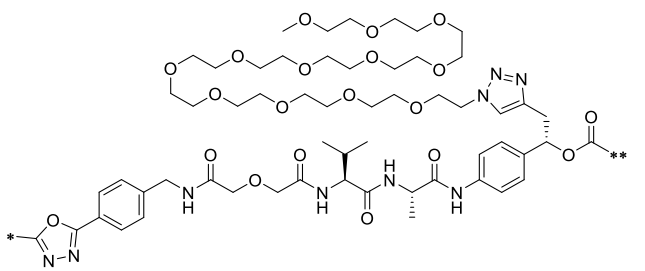

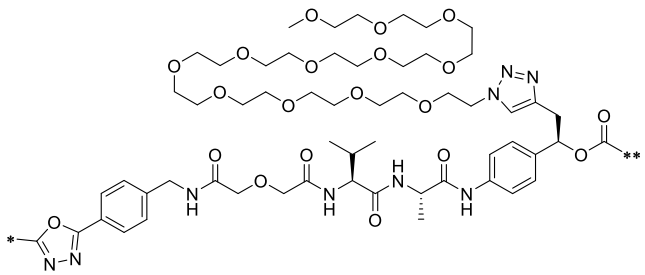

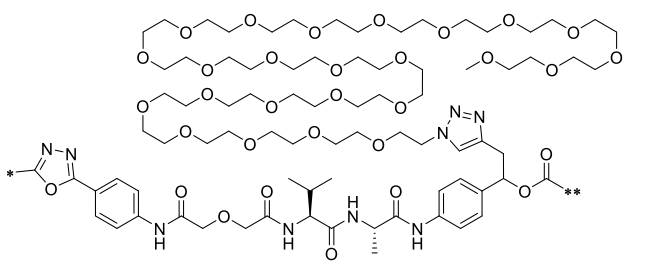

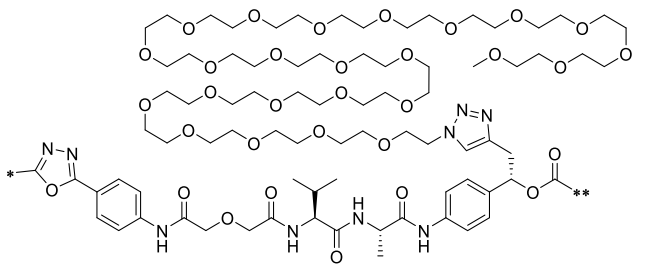

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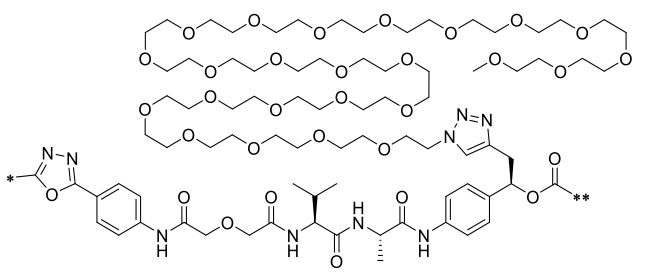

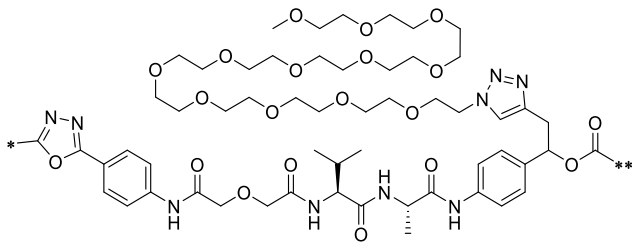

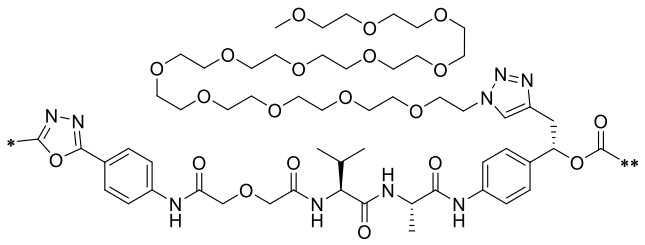

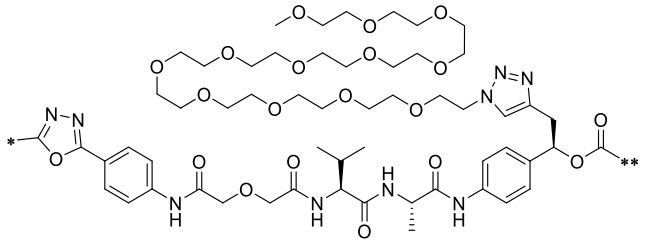

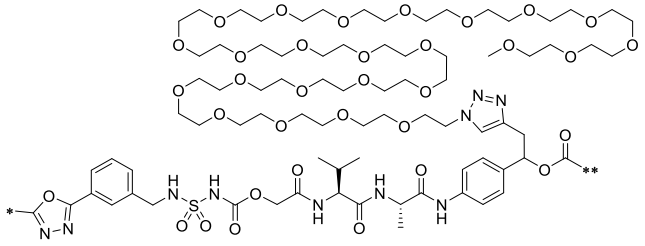

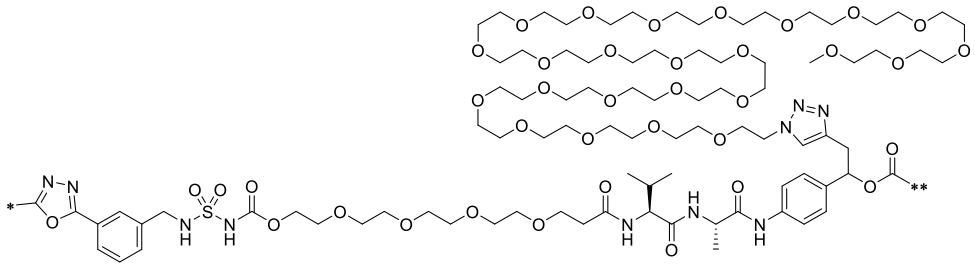

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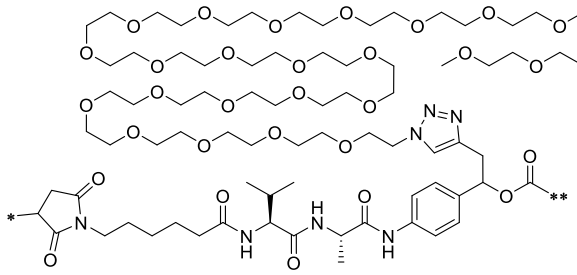

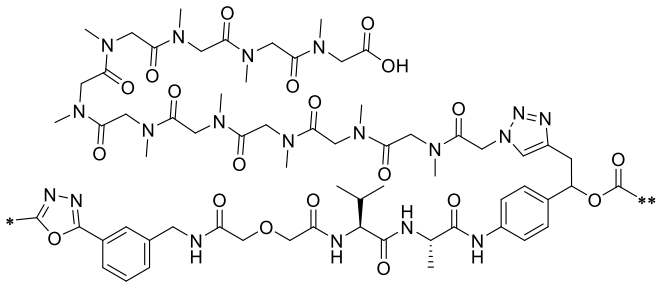

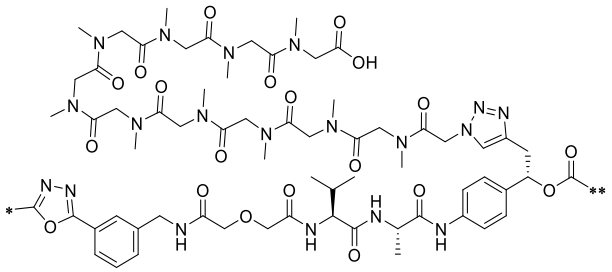

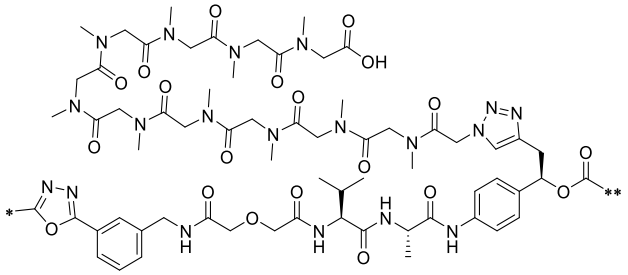

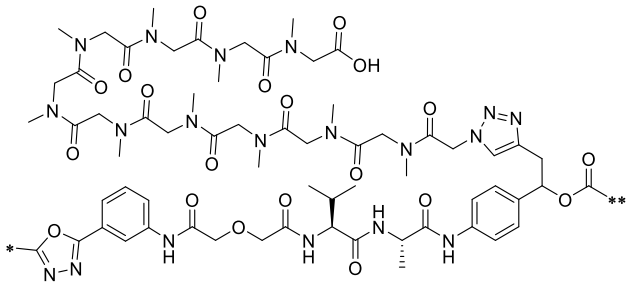

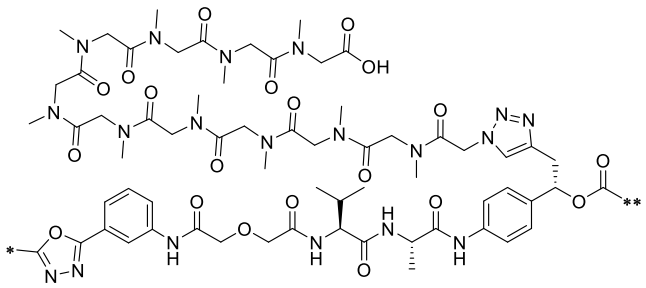

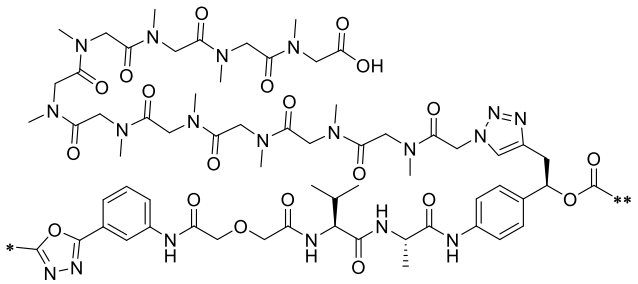

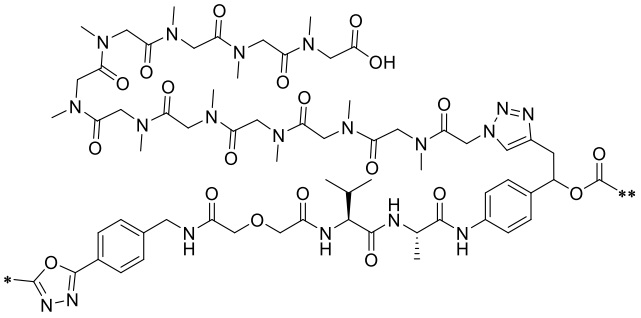

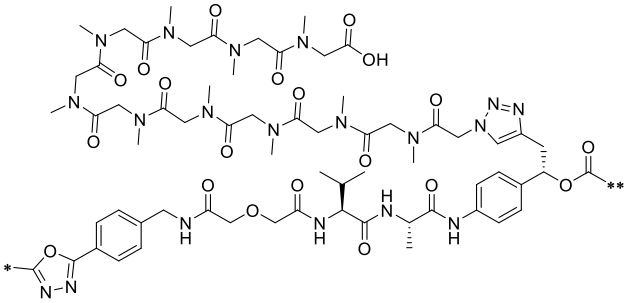

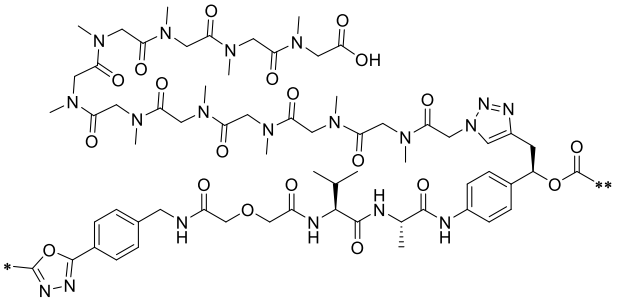

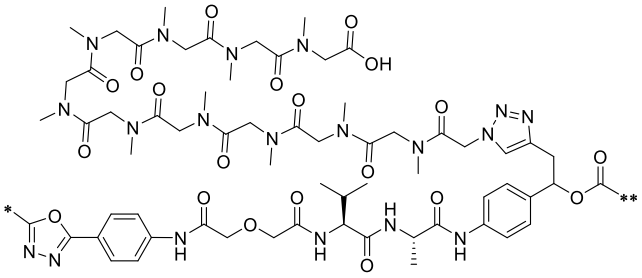

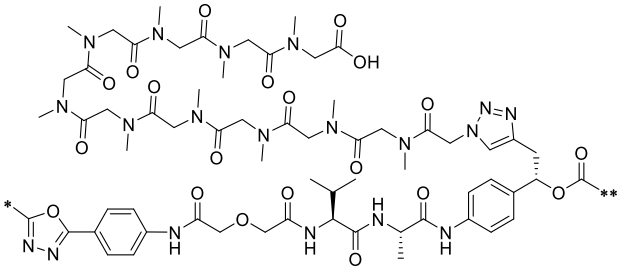

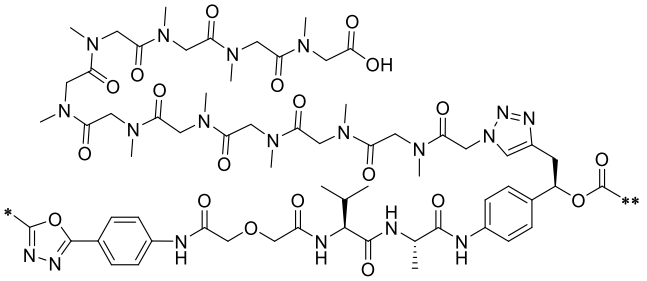

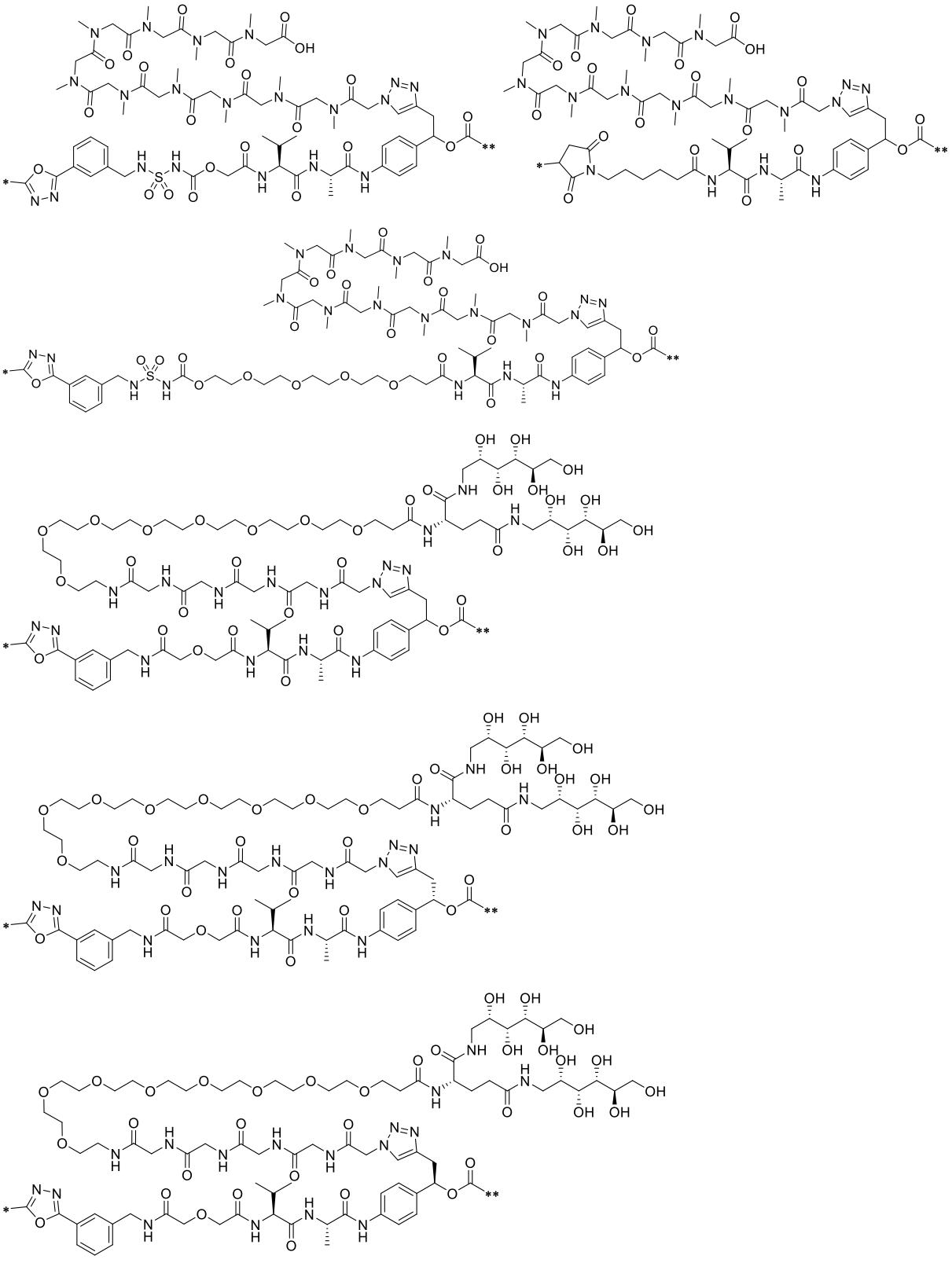

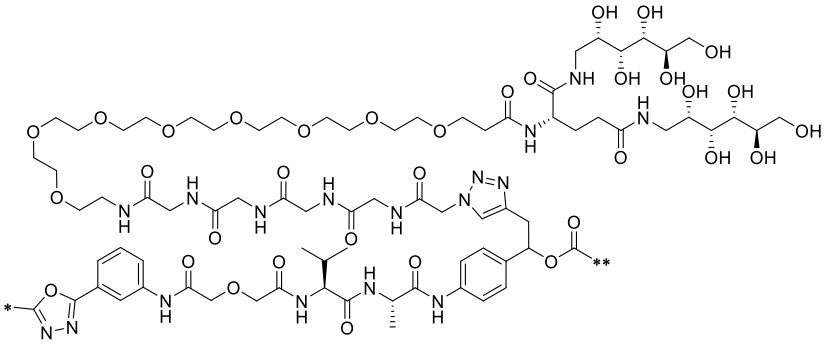

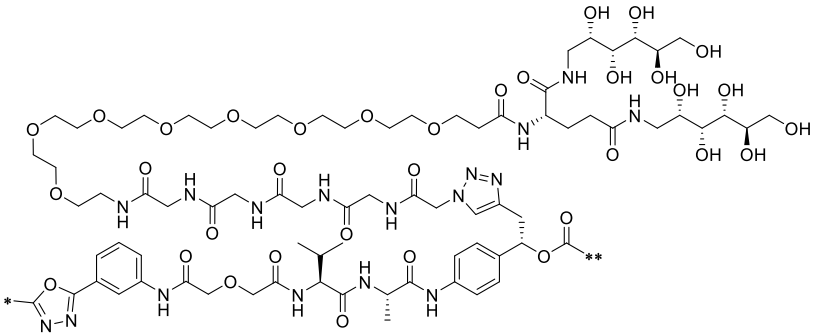

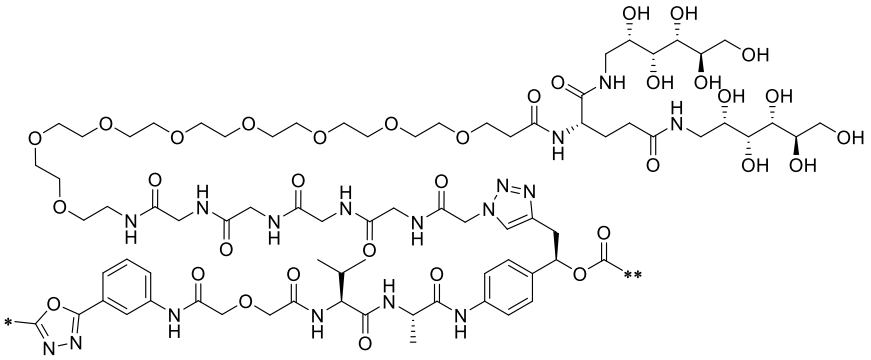

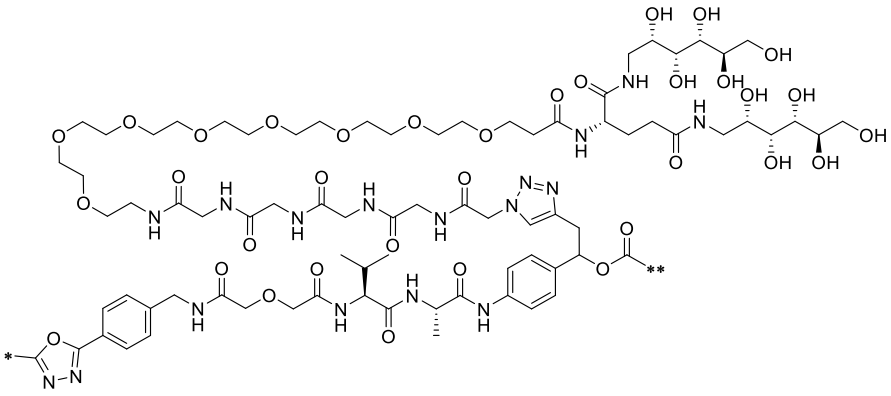

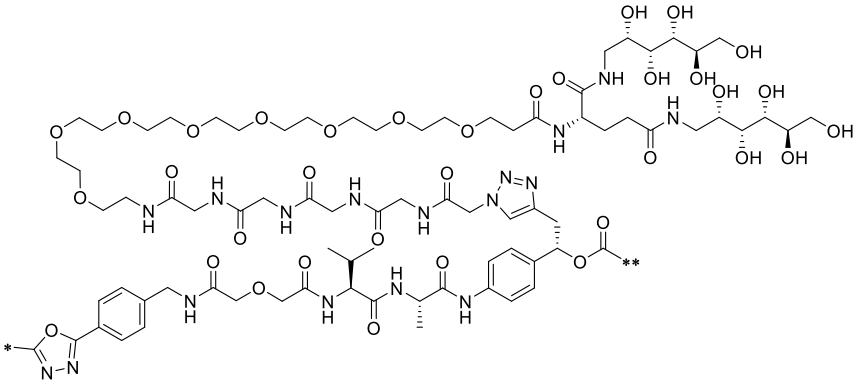

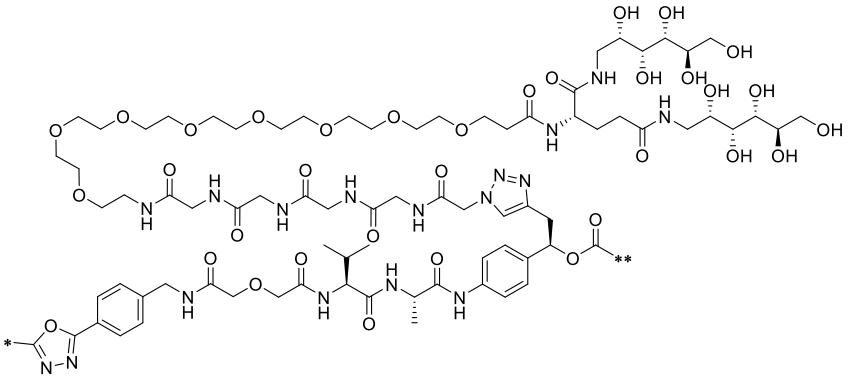

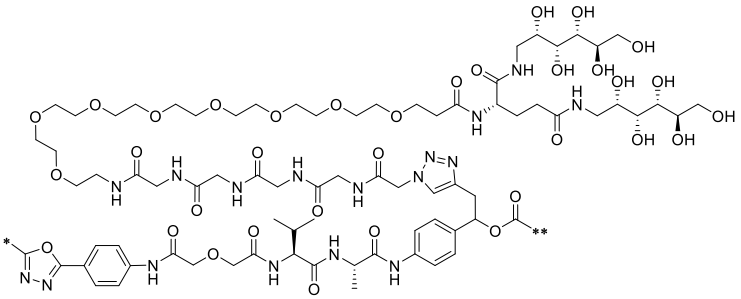

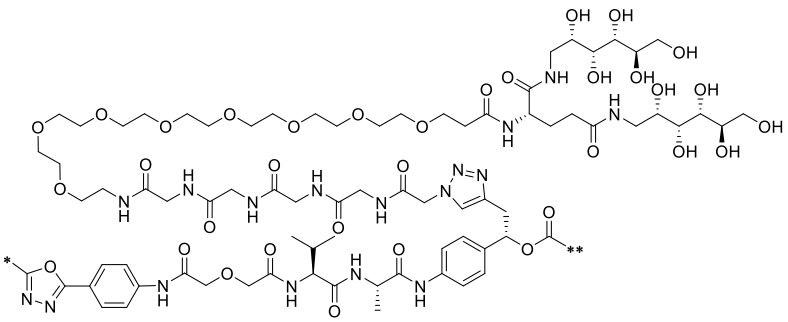

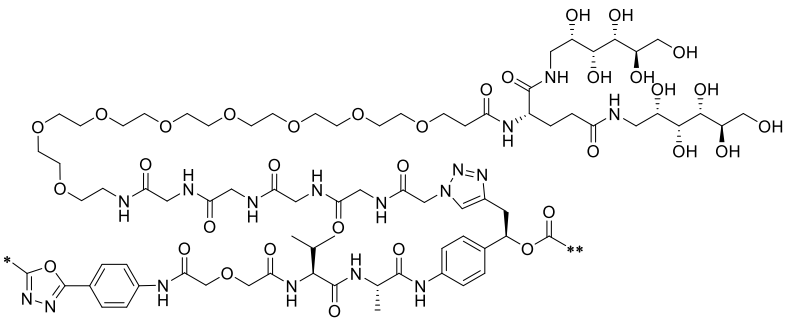

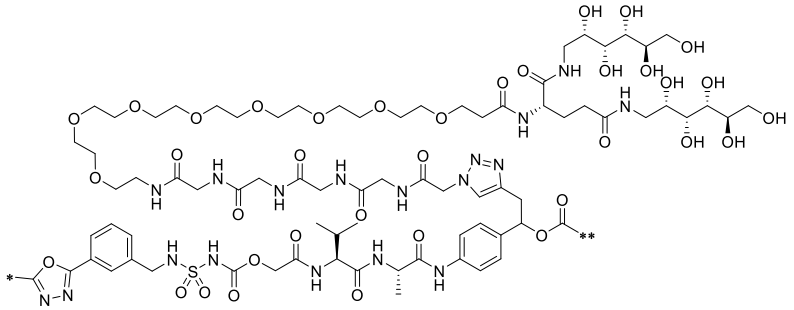

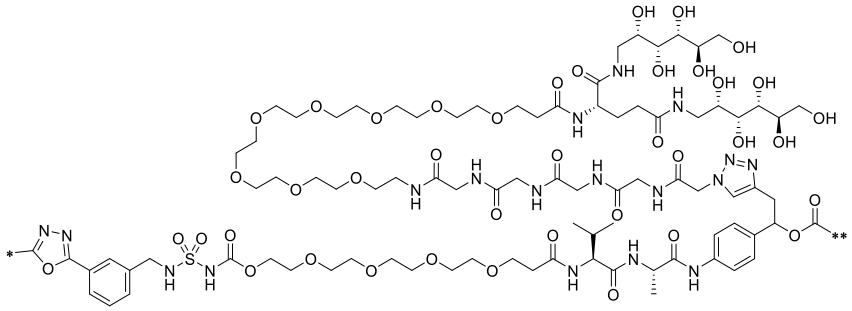

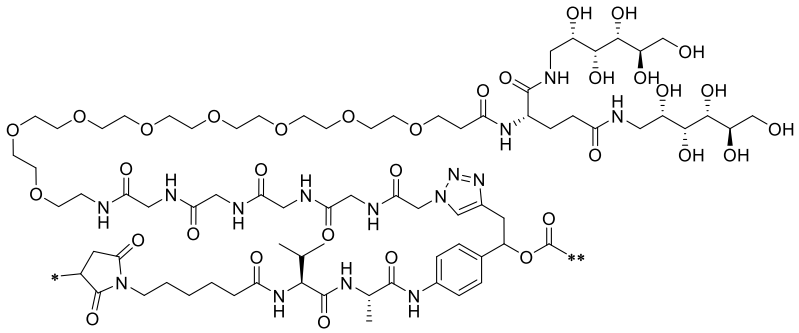

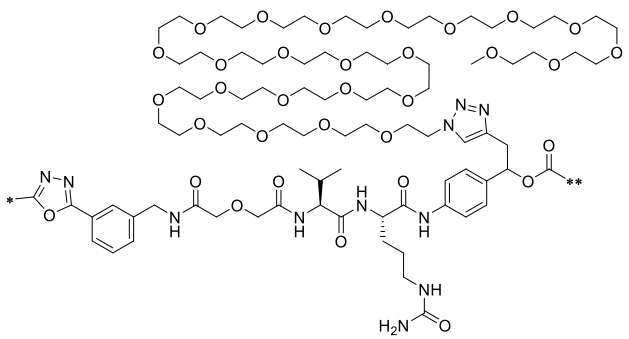

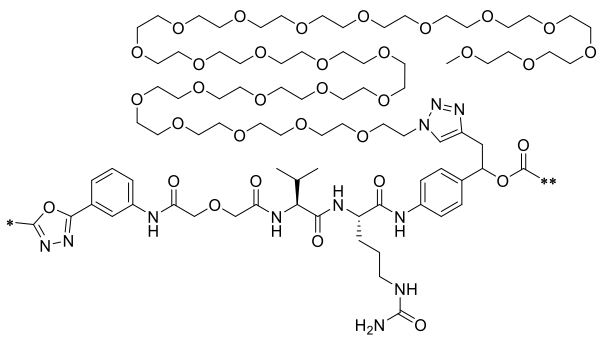

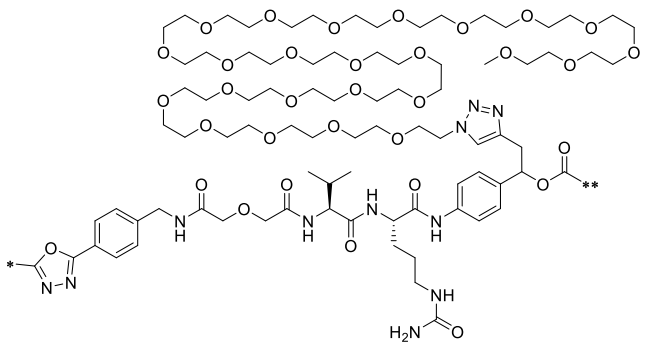

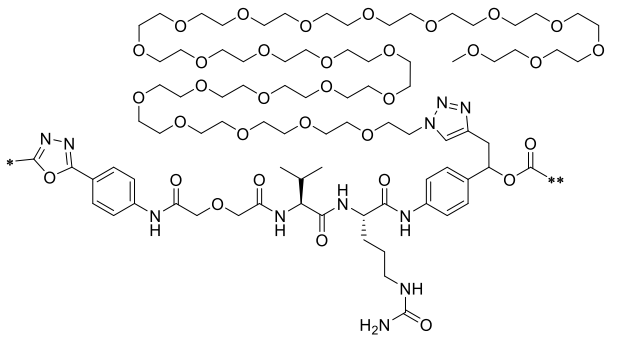

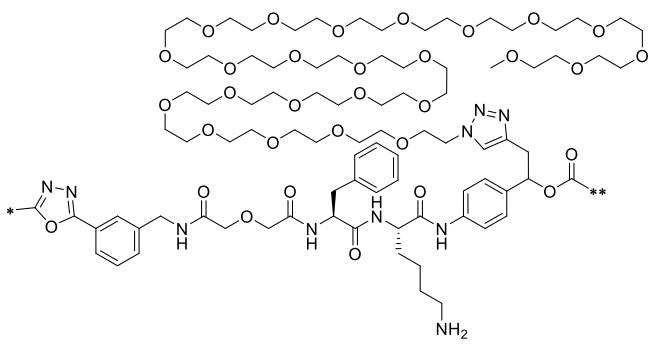

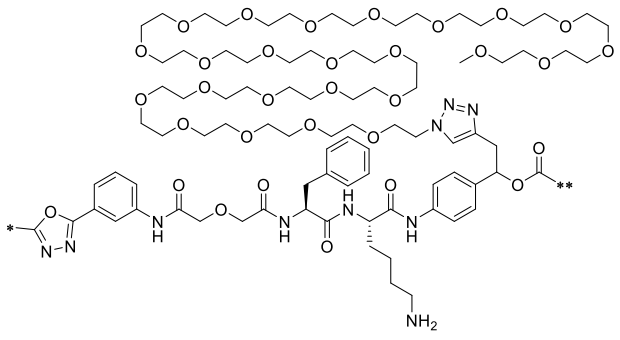

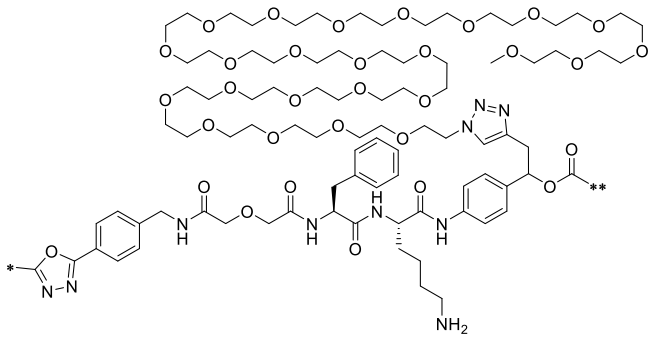

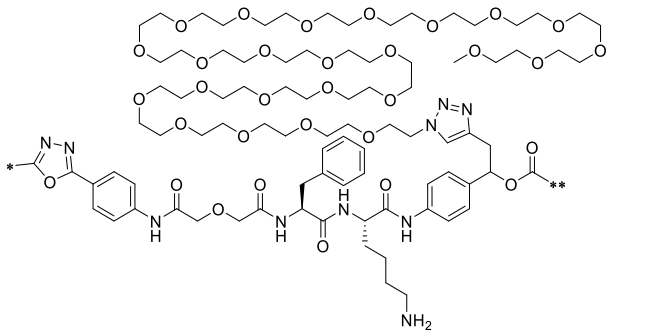

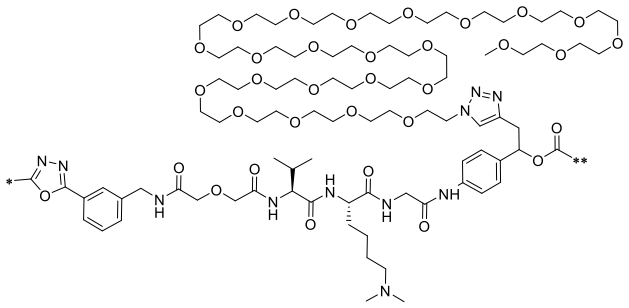

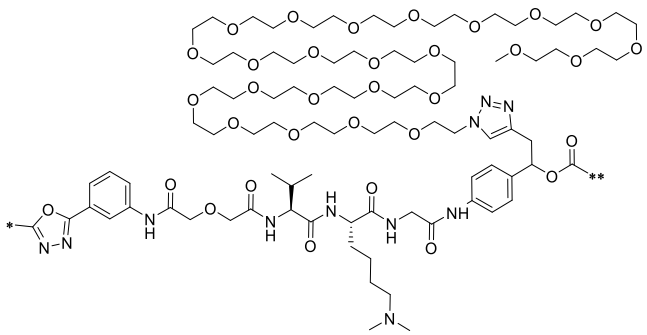

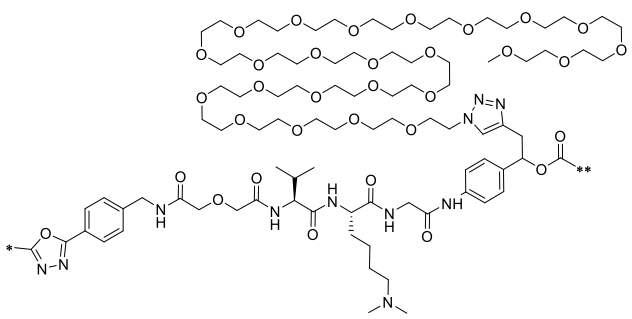

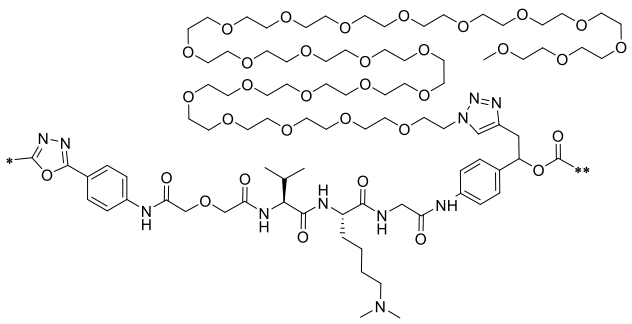

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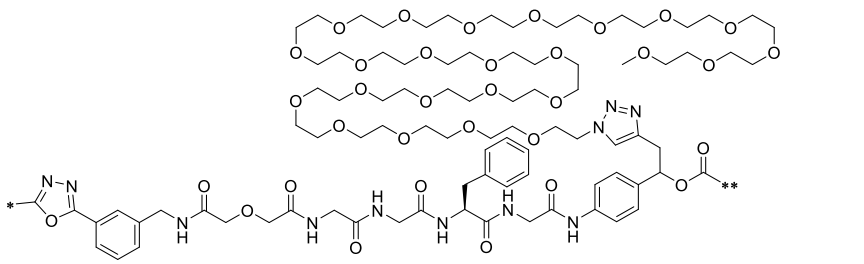
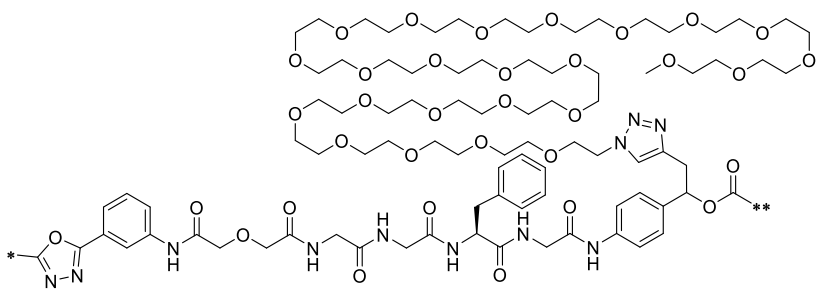
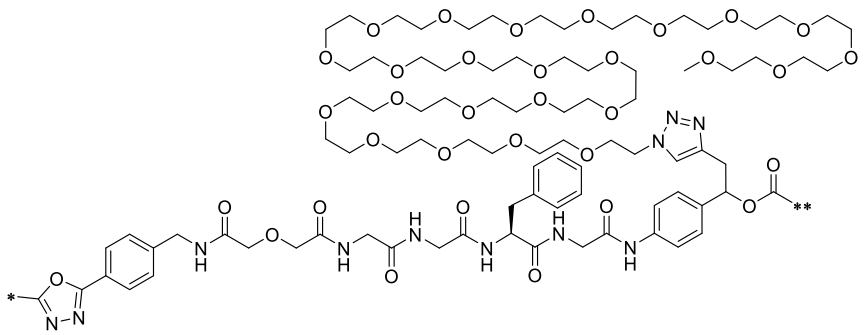
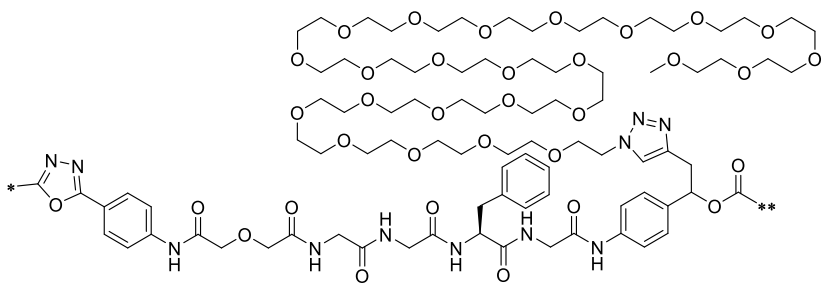
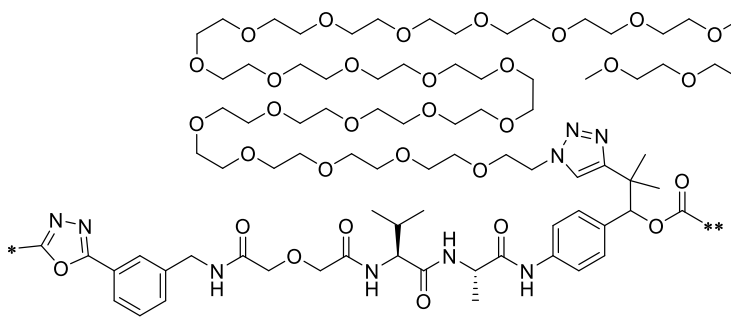
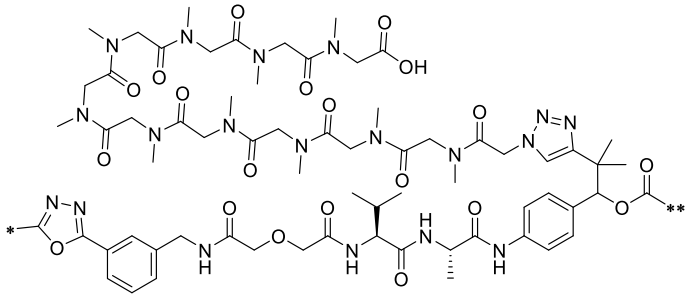


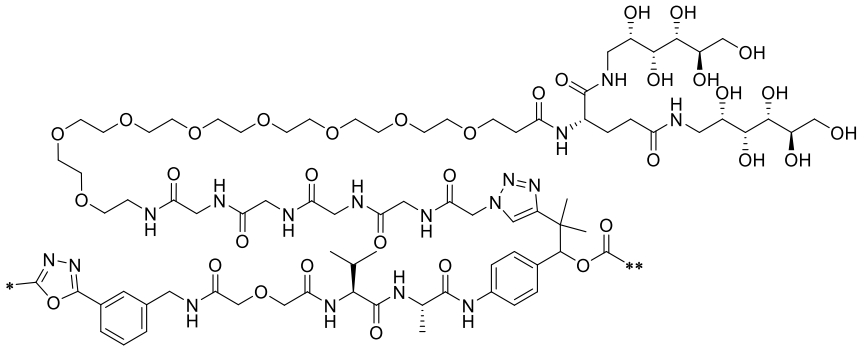


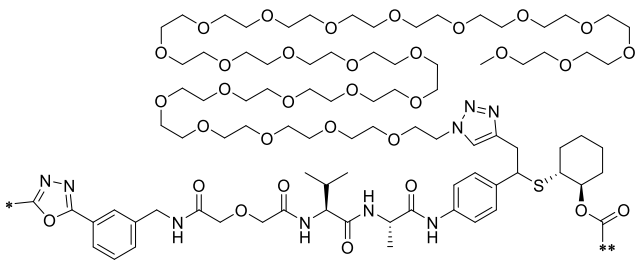


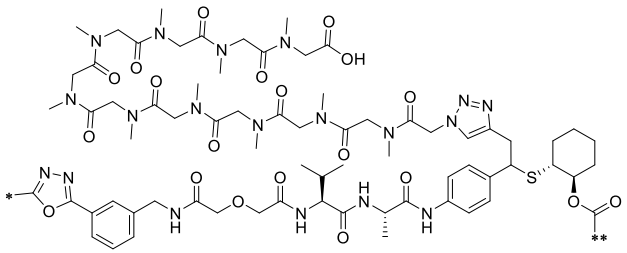


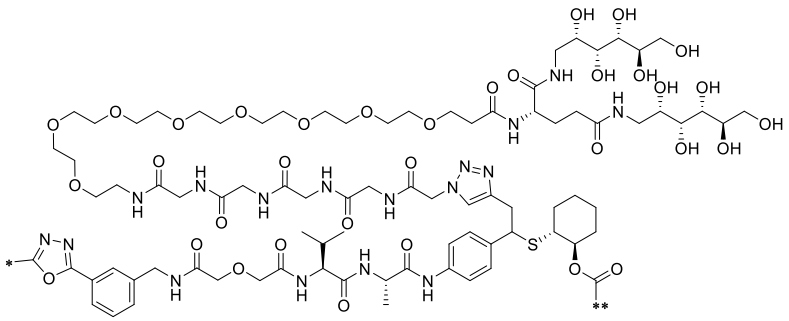


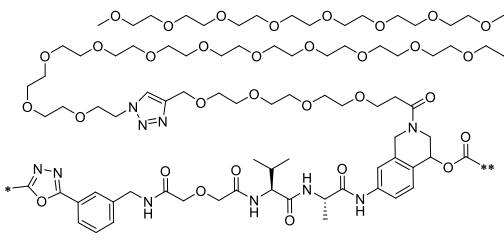


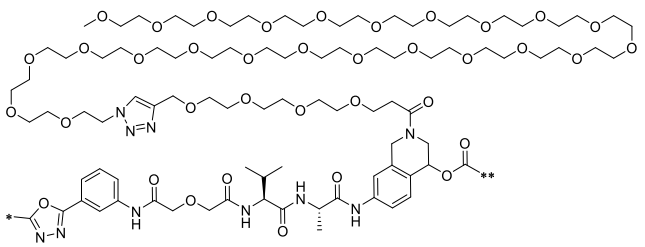


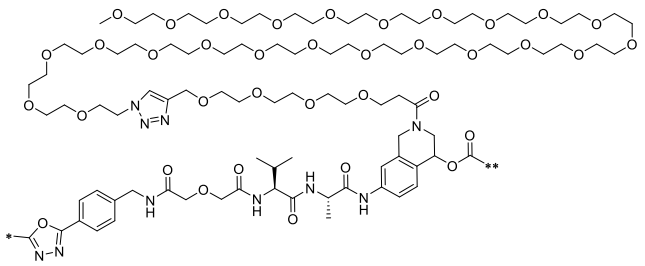


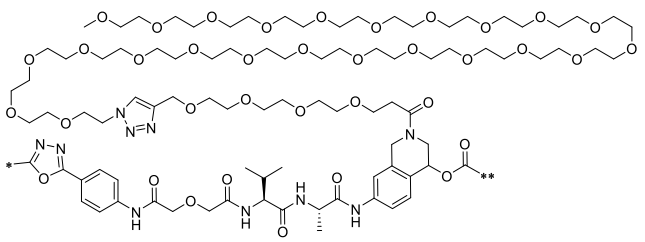


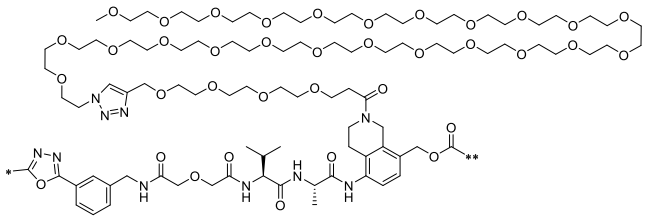


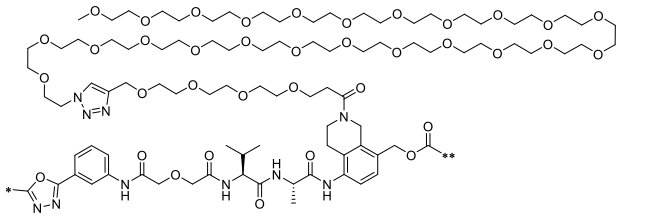


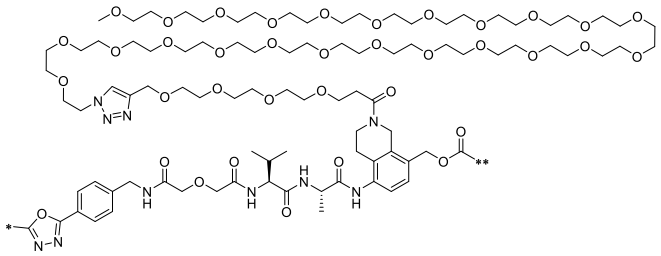


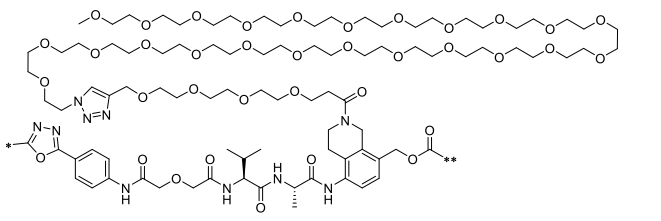


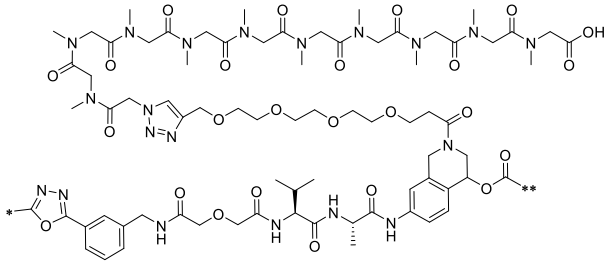


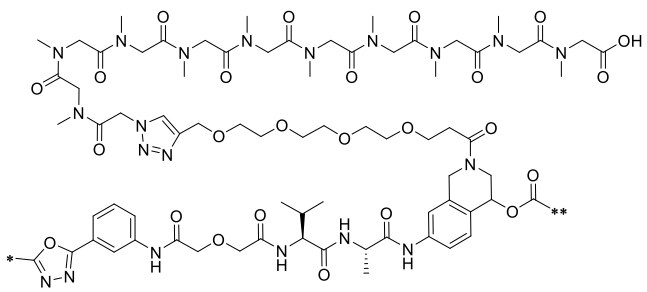


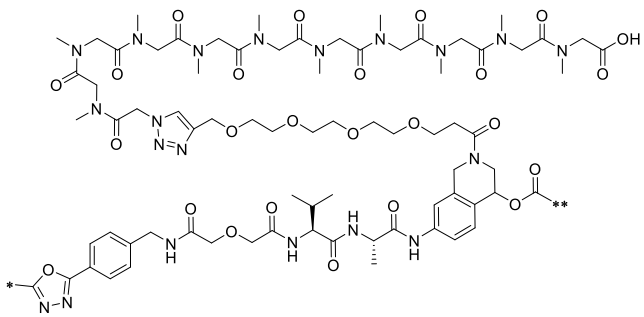


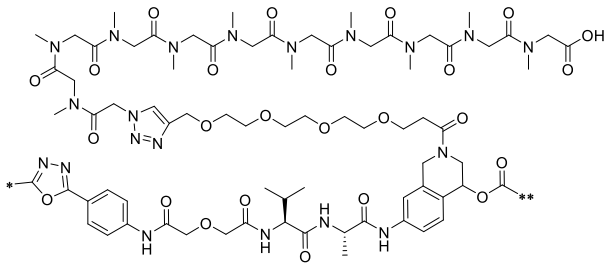


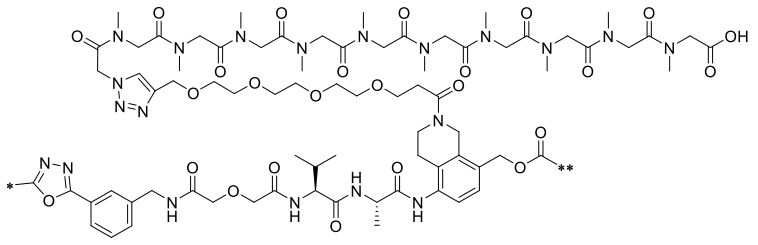


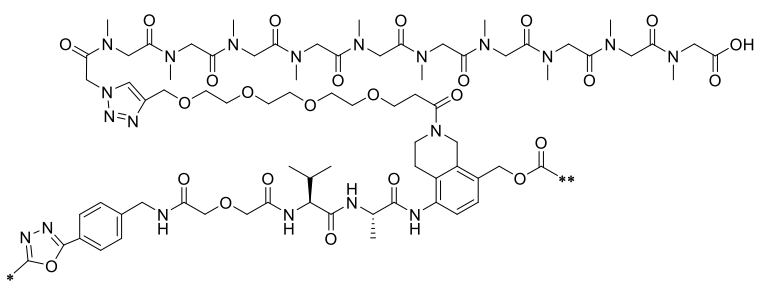


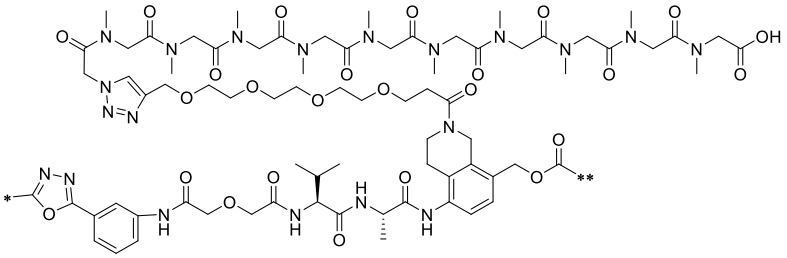


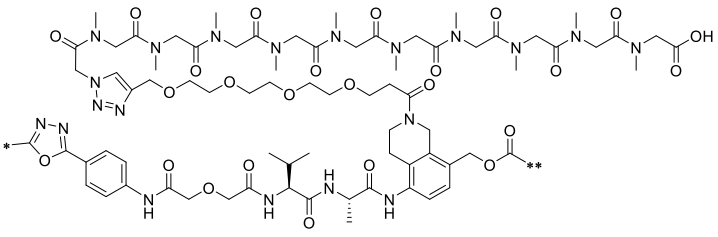


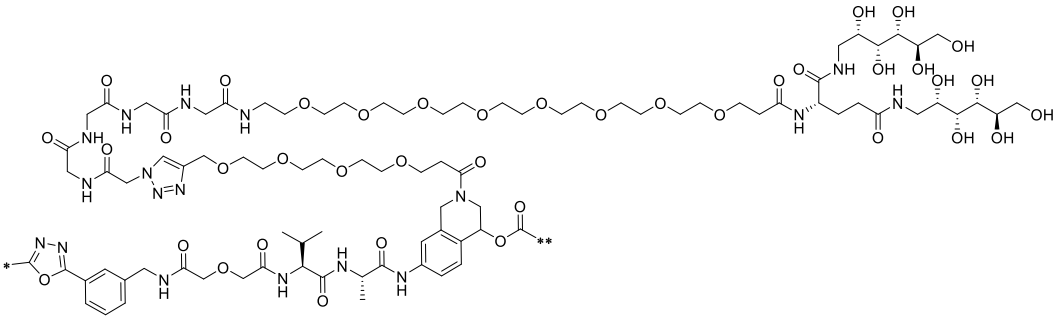


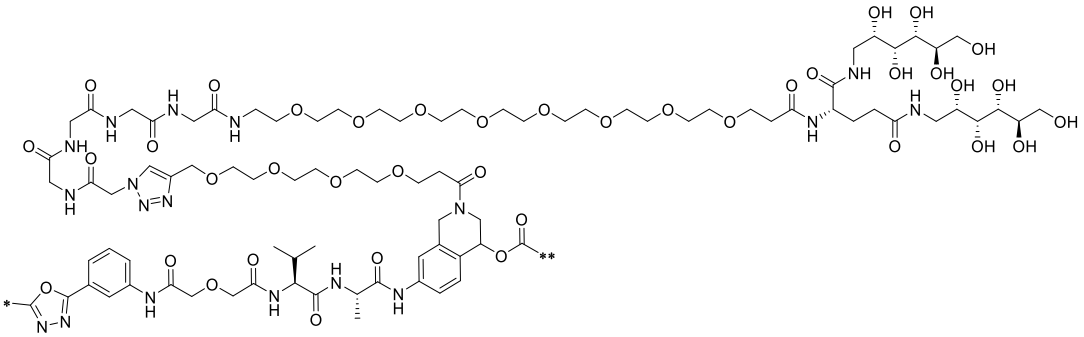


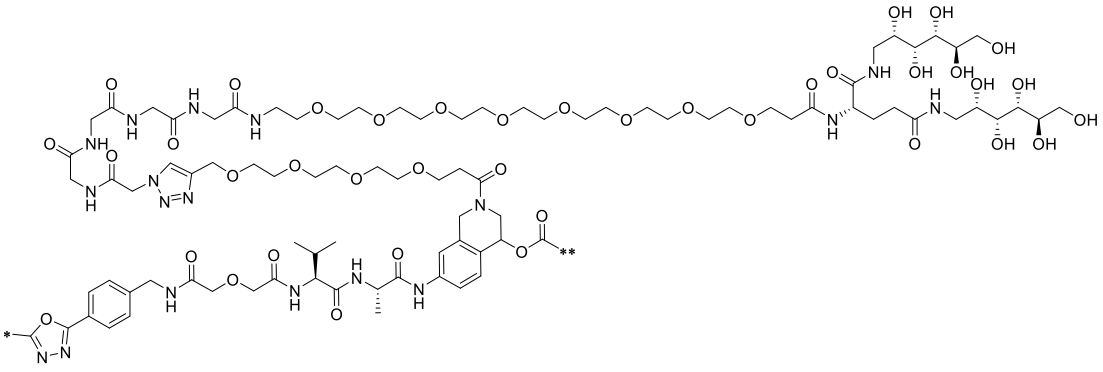


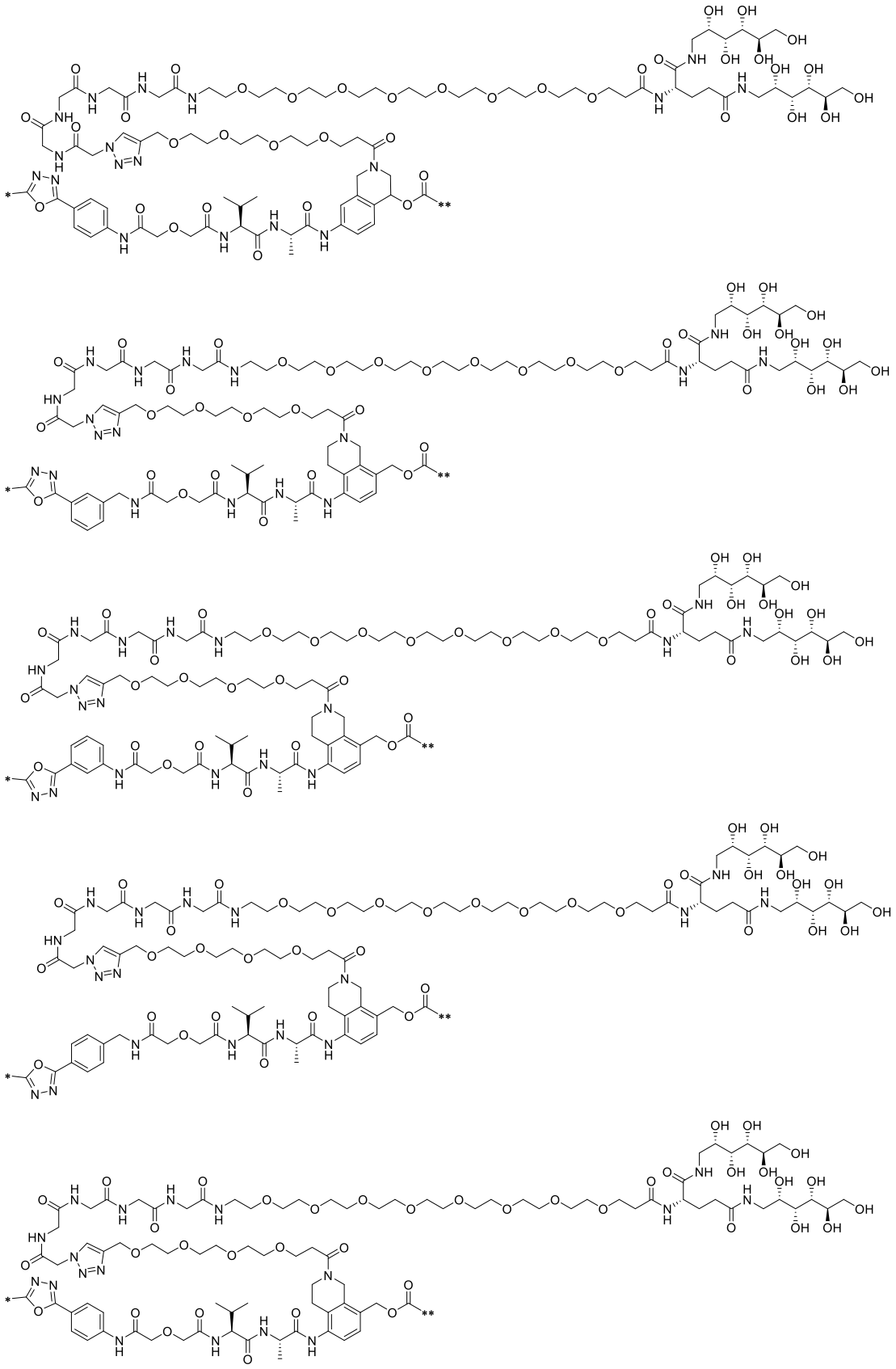












wherein * represents linkage to a sulfhydryl group of the antibody A, and ** represents linkage to the amino group of the bioactive molecule D.

9. The antibody-drug conjugate having the structure of formula (I), and the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-8, wherein

A is an antibody or an antigen-binding fragment thereof targeting FRα, wherein the antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the heavy chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the heavy chain complementarity determining region 1 (HCDR1) is set forth in SEQ ID NO: 22, the amino acid sequence of the heavy chain complementarity determining region 2 (HCDR2) is set forth in SEQ ID NO: 23, and the amino acid sequence of the heavy chain complementarity determining region 3 (HCDR3) is set forth in SEQ ID NO: 24; the light chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the light chain complementarity determining region 1 (LCDR1) is set forth in SEQ ID NO: 25, the amino acid sequence of the light chain complementarity determining region 2 (LCDR2) is set forth in SEQ ID NO: 26, and the amino acid sequence of the light chain complementarity determining region 3 (LCDR3) is set forth in SEQ ID NO: 27, wherein the CDRs are determined according to the Kabat numbering scheme; or

A is an antibody or an antigen-binding fragment thereof targeting DLL3, wherein the antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the heavy chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the heavy chain complementarity determining region 1 (HCDR1) is set forth in SEQ ID NO: 12, the amino acid sequence of the heavy chain complementarity determining region 2 (HCDR2) is set forth in SEQ ID NO: 13, and the amino acid sequence of the heavy chain complementarity determining region 3 (HCDR3) is set forth in SEQ ID NO: 14; the light chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the light chain complementarity determining region 1 (LCDR1) is set forth in SEQ ID NO: 15, the amino acid sequence of the light chain complementarity determining region 2 (LCDR2) is set forth in SEQ ID NO: 16, and the amino acid sequence of the light chain complementarity determining region 3 (LCDR3) is set forth in SEQ ID NO: 17, wherein the CDRs are determined according to the Kabat numbering scheme; or

A is an antibody or an antigen-binding fragment thereof targeting B7H3, wherein the antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the heavy chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the heavy chain complementarity determining region 1 (HCDR1) is set forth

in SEQ ID NO: 1, the amino acid sequence of the heavy chain complementarity determining region 2 (HCDR2) is set forth in SEQ ID NO: 2, and the amino acid sequence of the heavy chain complementarity determining region 3 (HCDR3) is set forth in SEQ ID NO: 3; the light chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the light chain complementarity determining region 1 (LCDR1) is set forth in SEQ ID NO: 4, the amino acid sequence of the light chain complementarity determining region 2 (LCDR2) is set forth in SEQ ID NO: 5, and the amino acid sequence of the light chain complementarity determining region 3 (LCDR3) is set forth in SEQ ID NO: 6, wherein the CDRs are determined according to the Kabat numbering scheme; or

A is an antibody or an antigen-binding fragment thereof targeting HER2, wherein the antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the heavy chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the heavy chain complementarity determining region 1 (HCDR1) is set forth in SEQ ID NO: 37, the amino acid sequence of the heavy chain complementarity determining region 2 (HCDR2) is set forth in SEQ ID NO: 38, and the amino acid sequence of the heavy chain complementarity determining region 3 (HCDR3) is set forth in SEQ ID NO: 39; the light chain comprises 3 complementarity determining regions (CDRs), wherein the amino acid sequence of the light chain complementarity determining region 1 (LCDR1) is set forth in SEQ ID NO: 40, the amino acid sequence of the light chain complementarity determining region 2 (LCDR2) is set forth in SEQ ID NO: 41, and the amino acid sequence of the light chain complementarity determining region 3 (LCDR3) is set forth in SEQ ID NO: 42, wherein the CDRs are determined according to the Kabat numbering scheme;

or

A is an antibody or an antigen-binding fragment thereof targeting FRα, wherein the anti-FRα antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the sequence of a variable region of the heavy chain (HV) is set forth in SEQ ID NO: 28, and the sequence of a variable region of the light chain (LV) is set forth in SEQ ID NO: 29;

or

A is an antibody or an antigen-binding fragment thereof targeting DLL3, wherein the anti-DLL3 antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the sequence of a variable region of the heavy chain (HV) is set forth in SEQ ID NO: 18, and the sequence of a variable region of the light chain (LV) is set forth in SEQ ID NO: 19;

or

A is an antibody or an antigen-binding fragment thereof targeting B7H3, wherein the anti-B7H3

antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the sequence of a variable region of the heavy chain (HV) is set forth in SEQ ID NO: 7, and the sequence of a variable region of the light chain (LV) is set forth in SEQ ID NO: 8; or

A is an antibody or an antigen-binding fragment thereof targeting HER2, wherein the anti-HER2 antibody or the antigen-binding fragment thereof comprises a heavy chain and/or a light chain, wherein the sequence of a variable region of the heavy chain (HV) is set forth in SEQ ID NO: 35, and the sequence of a variable region of the light chain (LV) is set forth in SEQ ID NO: 36

; or

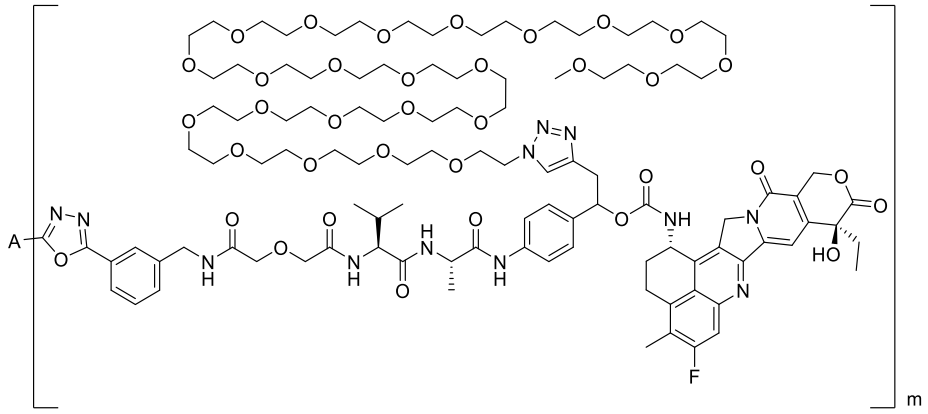
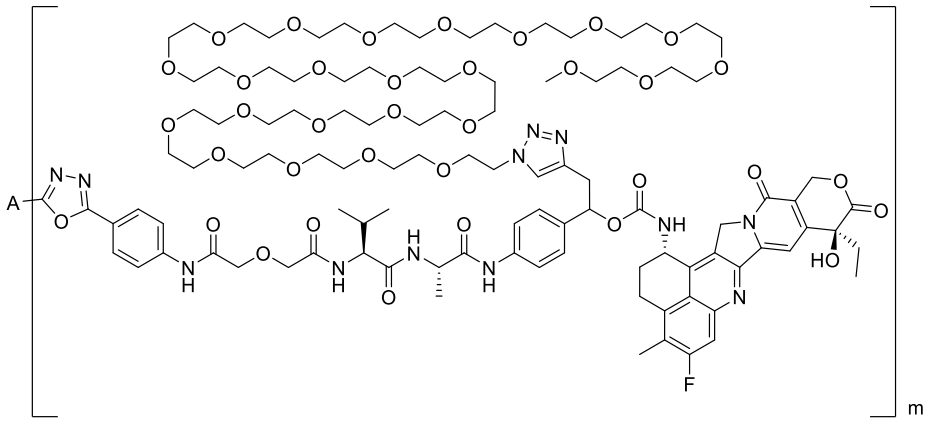
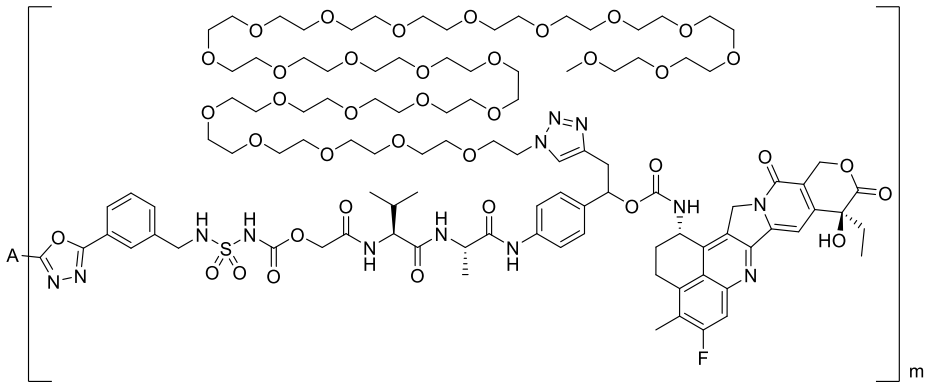
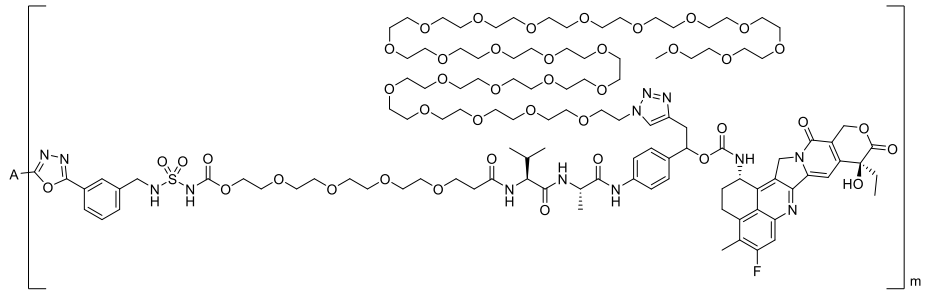
A is an antibody or an antigen-binding fragment thereof targeting FRα, wherein the anti-FRα antibody comprises a heavy chain and/or a light chain, wherein the amino acid sequence of the heavy chain is set forth in SEQ ID NO: 30 or SEQ ID NO: 32, and the amino acid sequence of the light chain is set forth in SEQ ID NO: 31; or

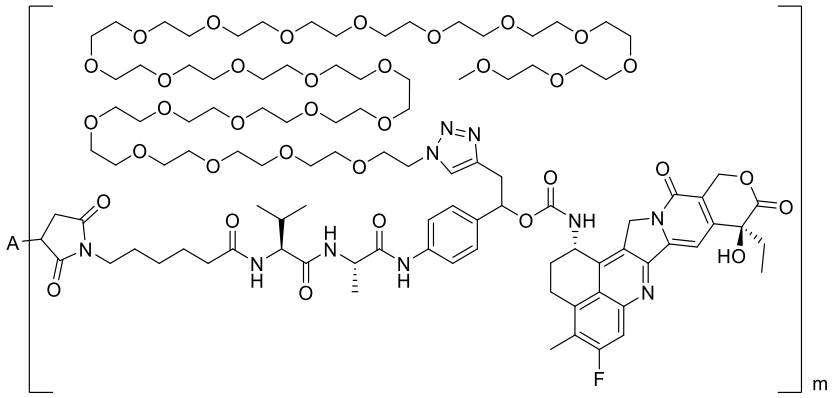
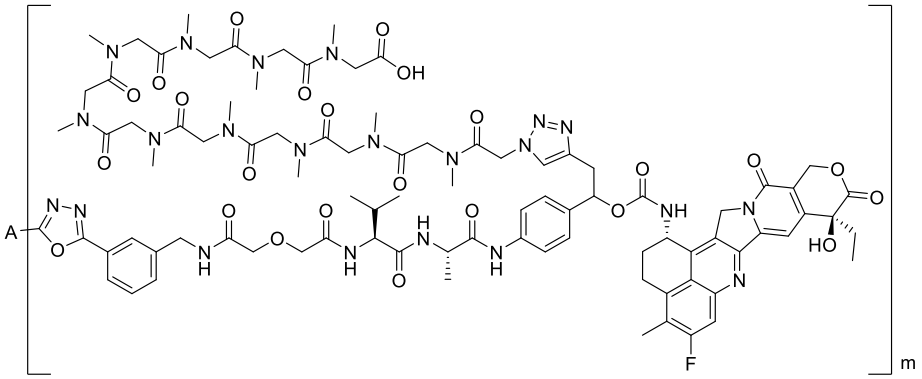
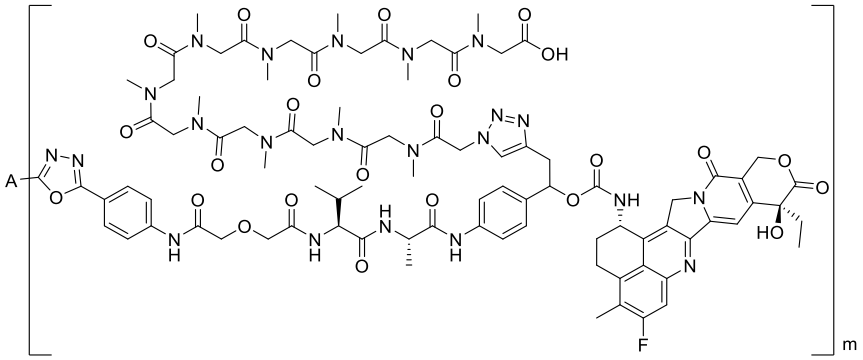
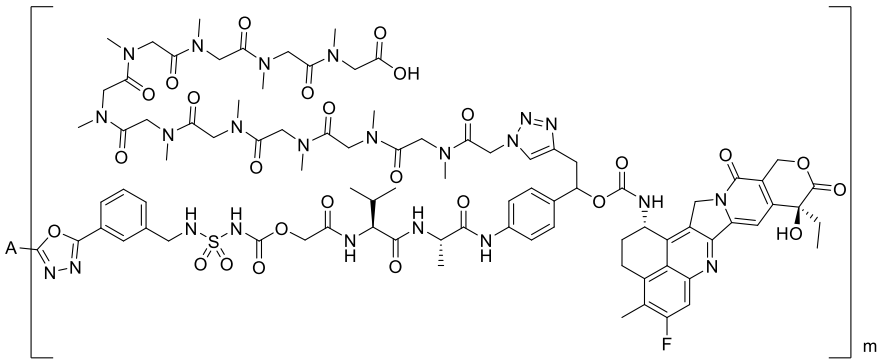
A is an antibody or an antigen-binding fragment thereof targeting DLL3, wherein the anti-DLL3 antibody comprises a heavy chain and/or a light chain, wherein the amino acid sequence of the heavy chain is set forth in SEQ ID NO: 20, and the amino acid sequence of the light chain is set forth in SEQ ID NO: 21; or

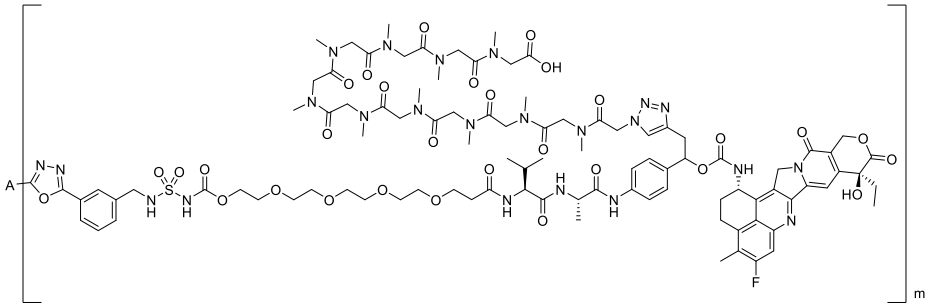
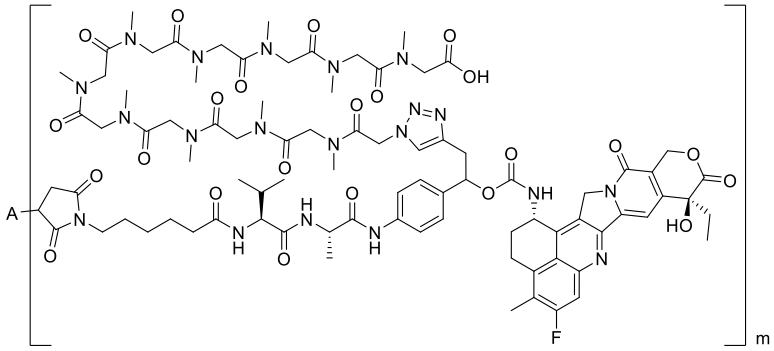
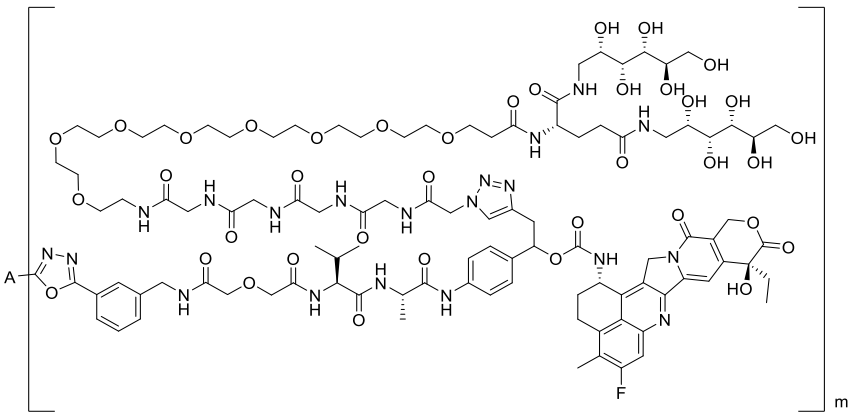
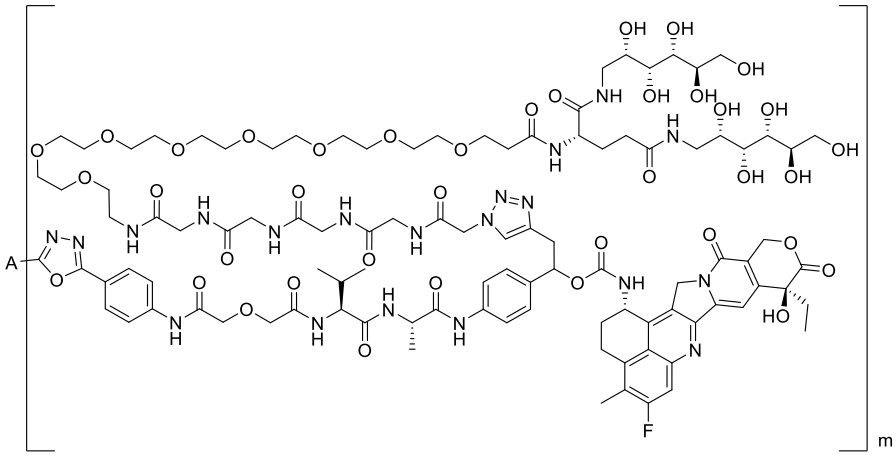
A is an antibody or an antigen-binding fragment thereof targeting B7H3, wherein the anti-B7H3 antibody comprises a heavy chain and/or a light chain, wherein the amino acid sequence of the heavy chain is set forth in SEQ ID NO: 9 or SEQ ID NO: 10, and the amino acid sequence of the light chain is set forth in SEQ ID NO: 11; or

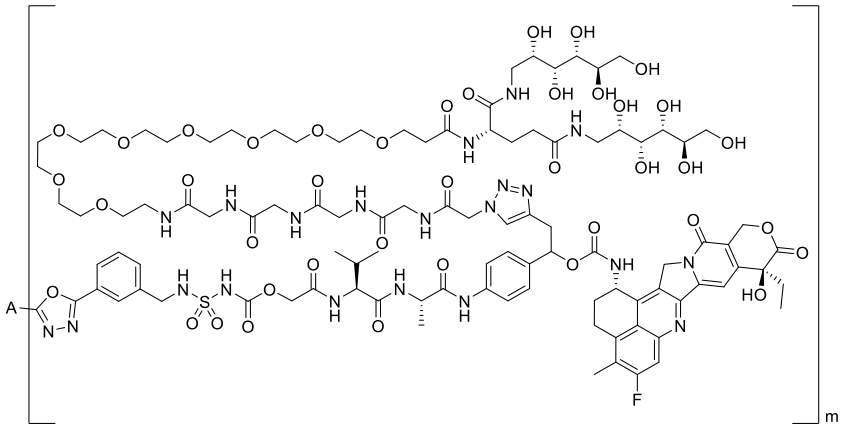
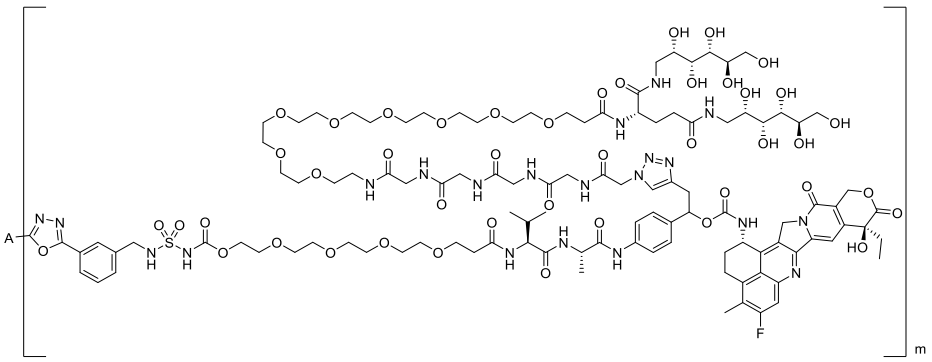
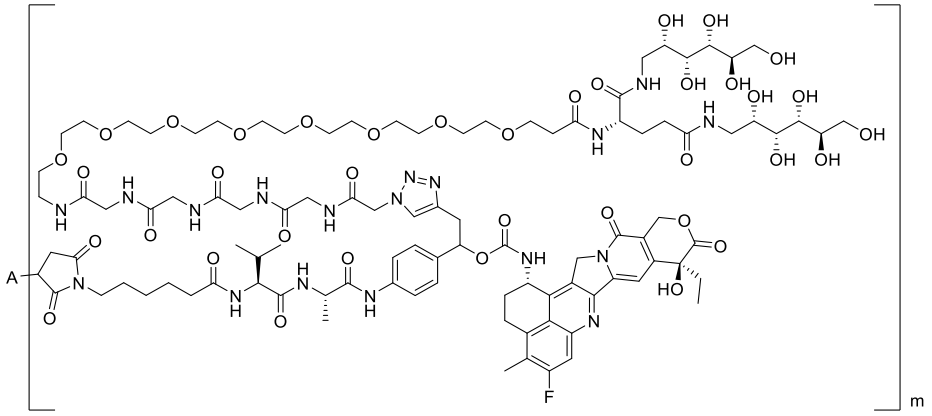
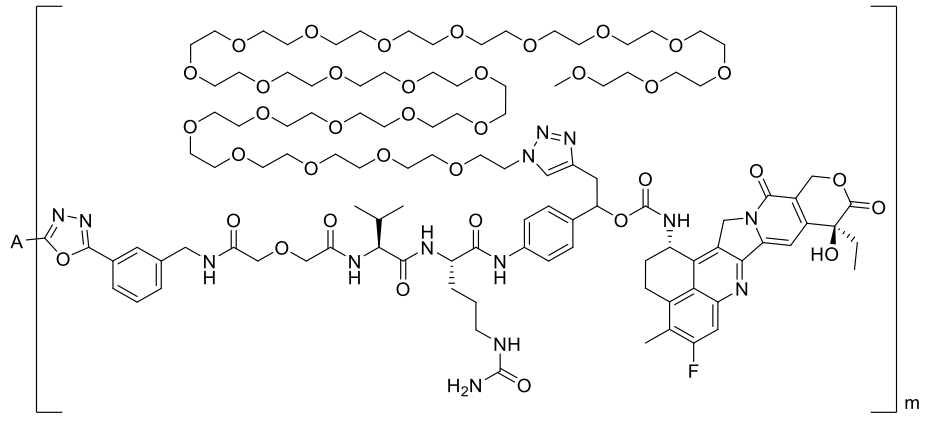
A is an antibody or an antigen-binding fragment thereof targeting HER2, wherein the anti-HER2 antibody comprises a heavy chain and/or a light chain, wherein the amino acid sequence of the heavy chain is set forth in SEQ ID NO: 33, and the amino acid sequence of the light chain is set forth in SEQ ID NO: 34.

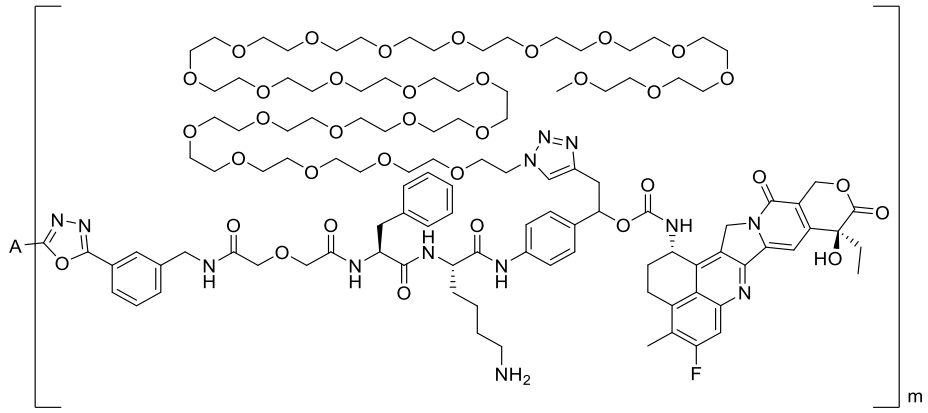
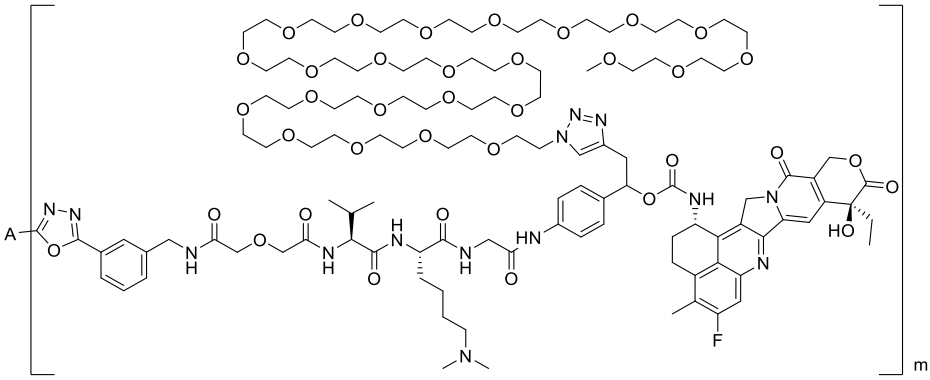
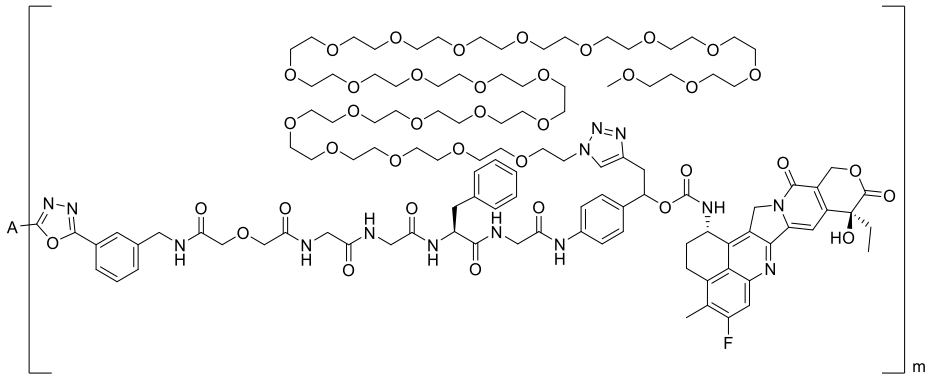
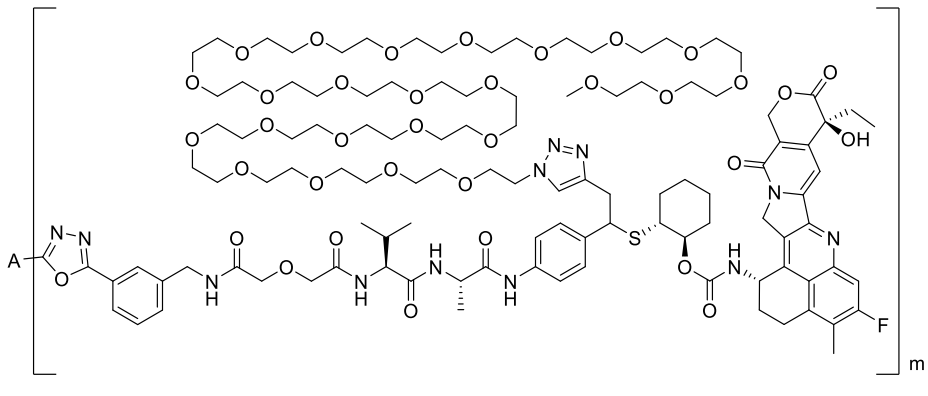
10. The antibody-drug conjugate having the structure of formula (I), the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-9, selected from the following structures:

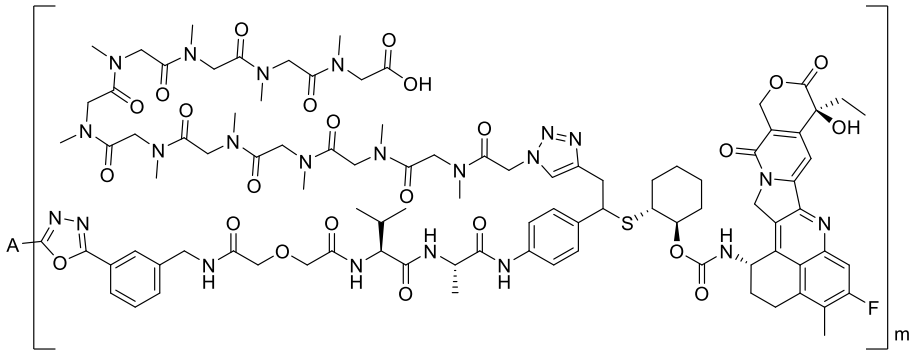
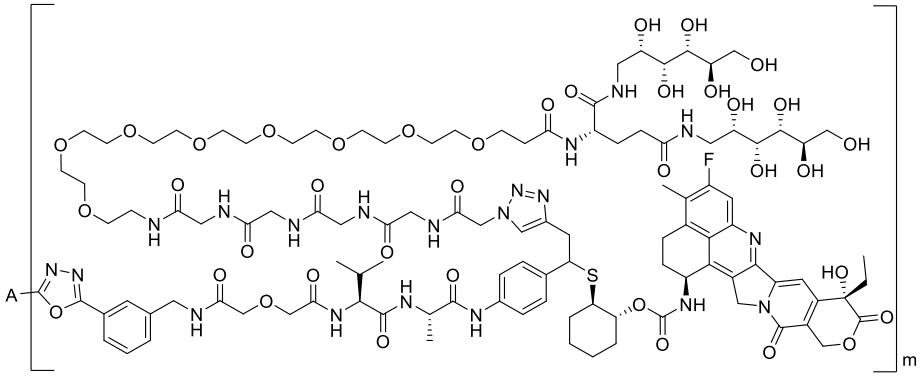
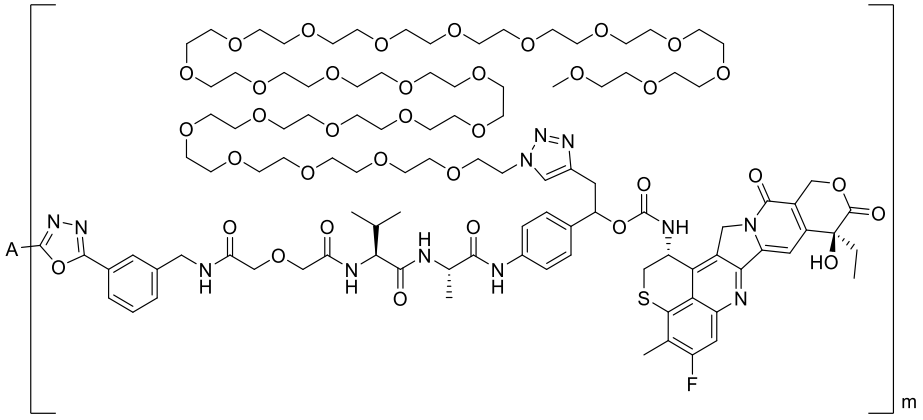
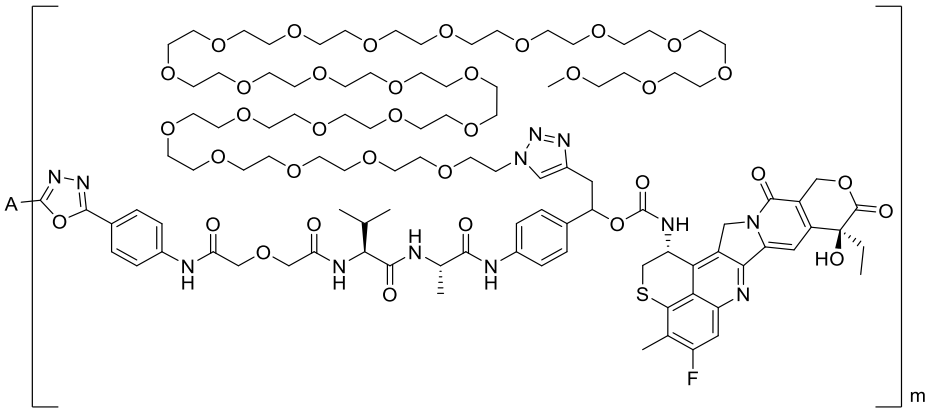
No.	Structure
ADC1	
ADC2	
ADC3	
ADC4	

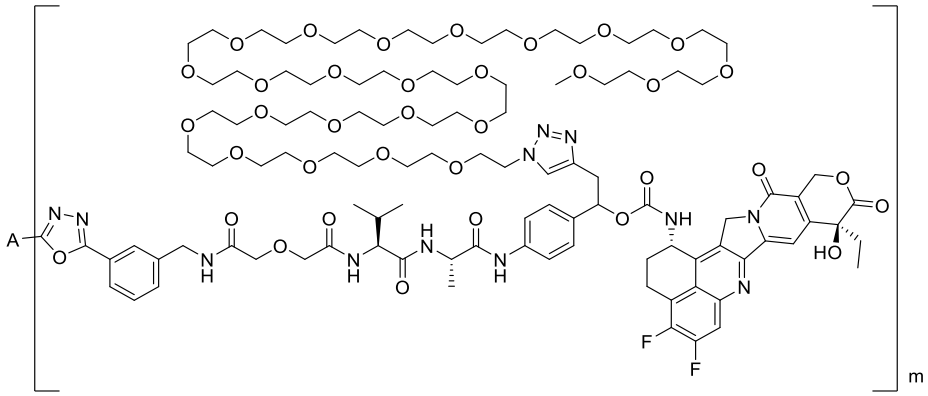
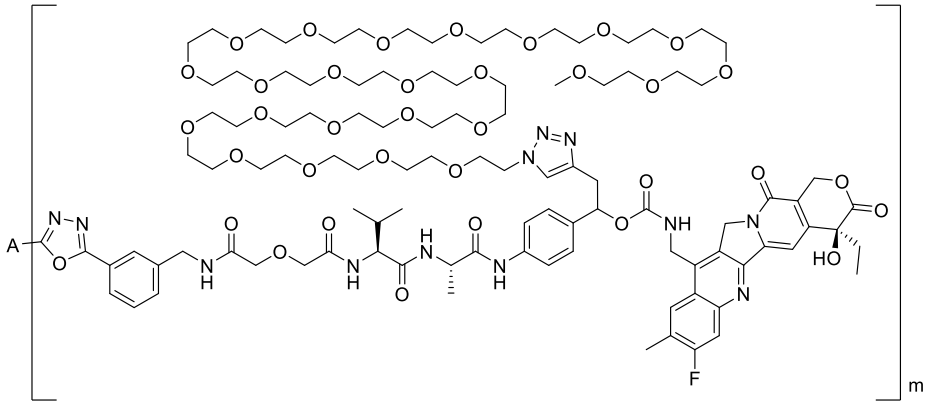
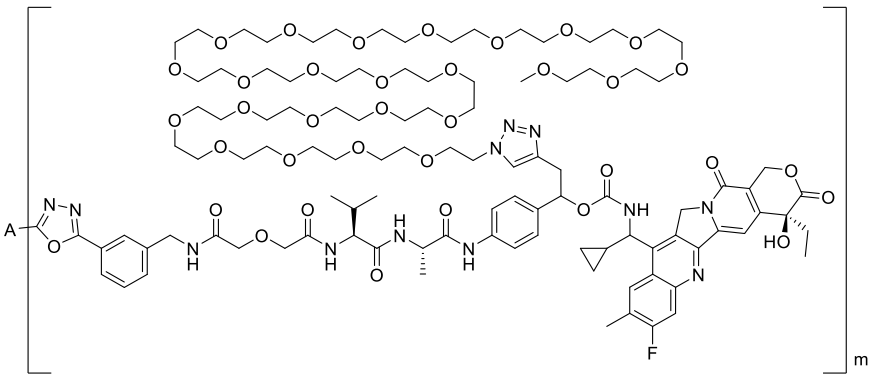
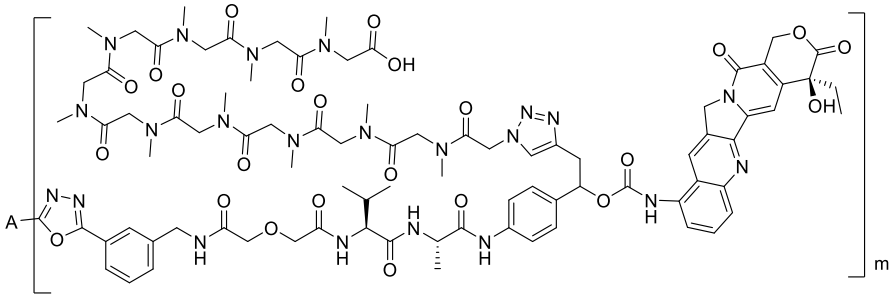
ADC5	
ADC6	
ADC7	
ADC8	

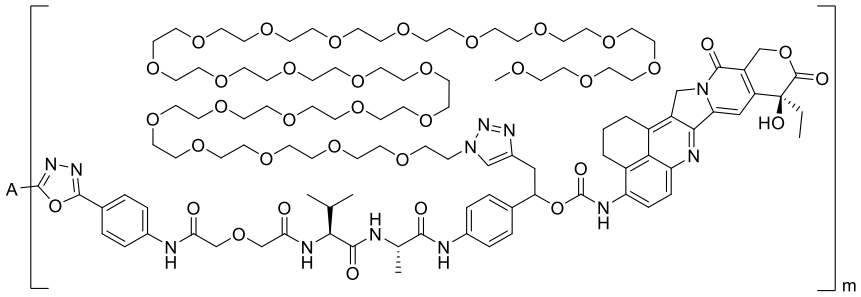
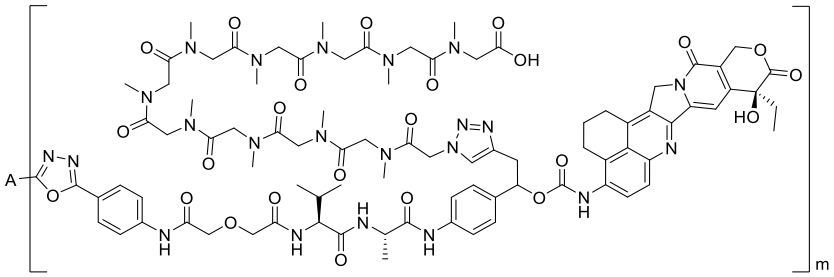
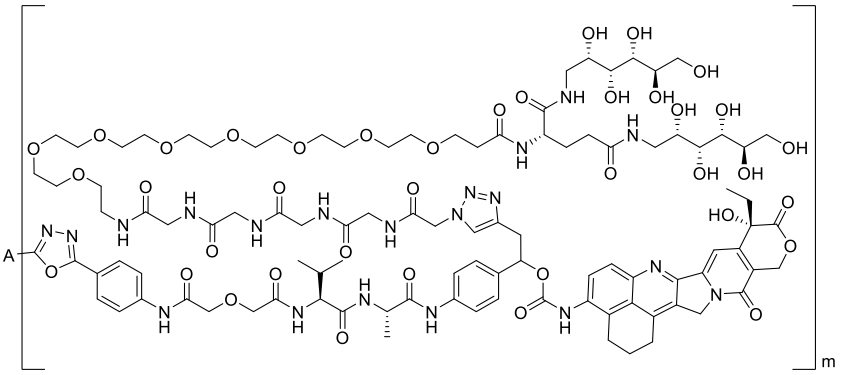
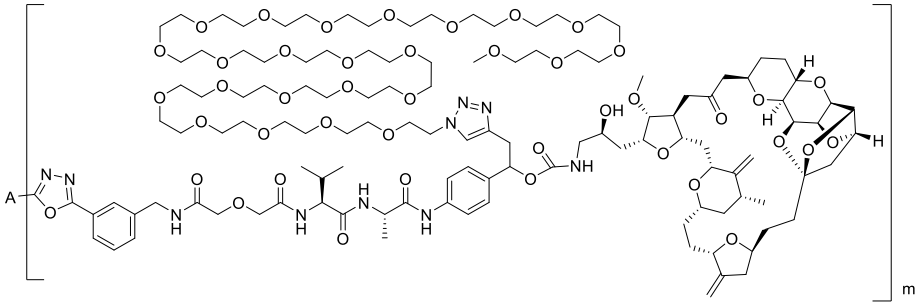
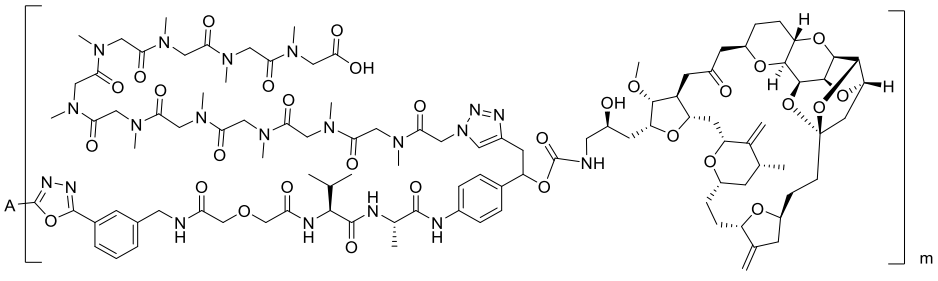
ADC9	
ADC10	
ADC11	
ADC12	

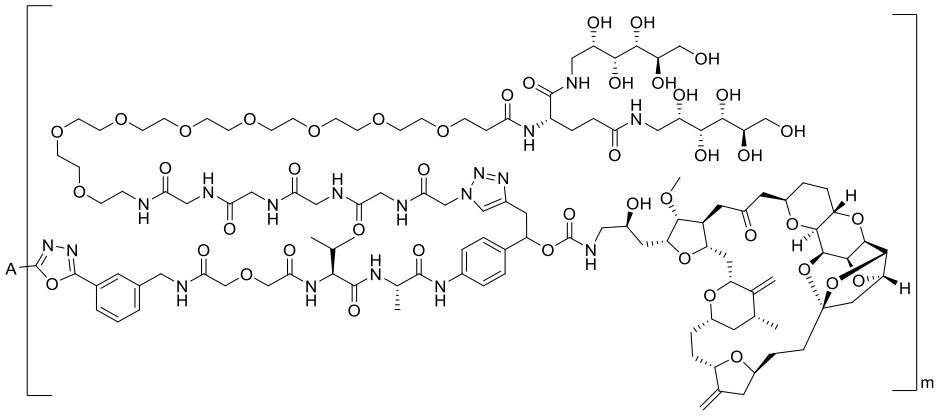
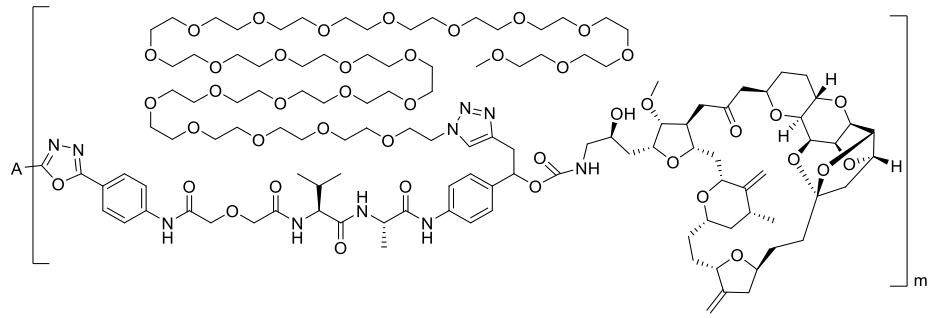
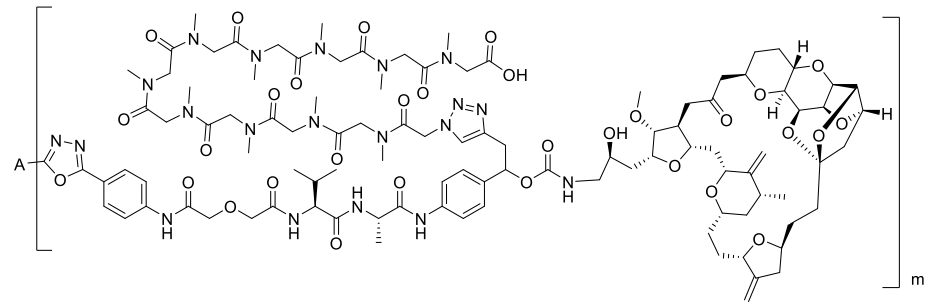
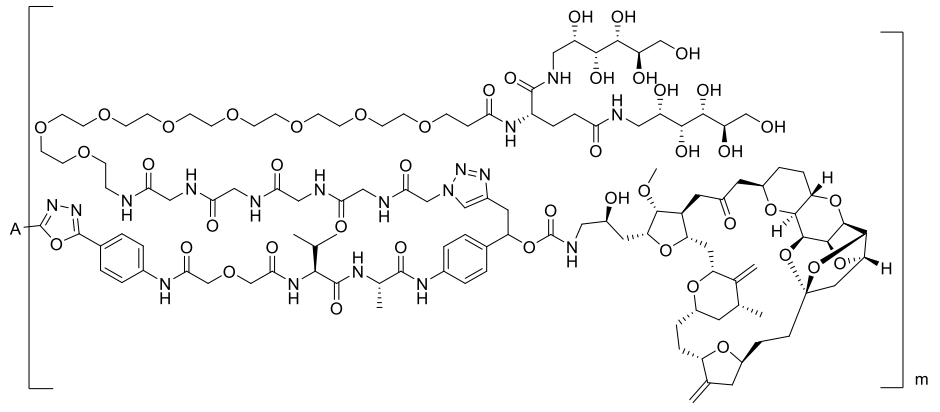
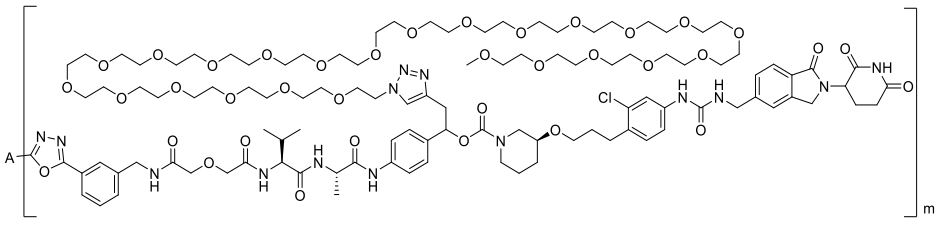
ADC13	
ADC14	
ADC15	
ADC16	

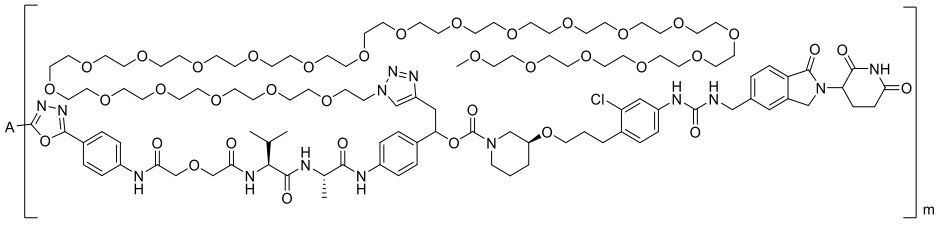
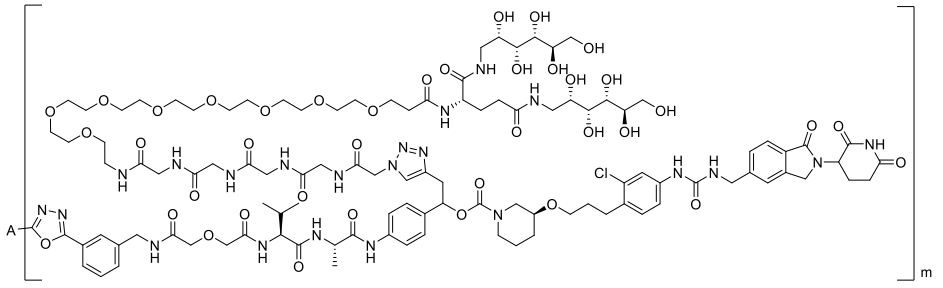
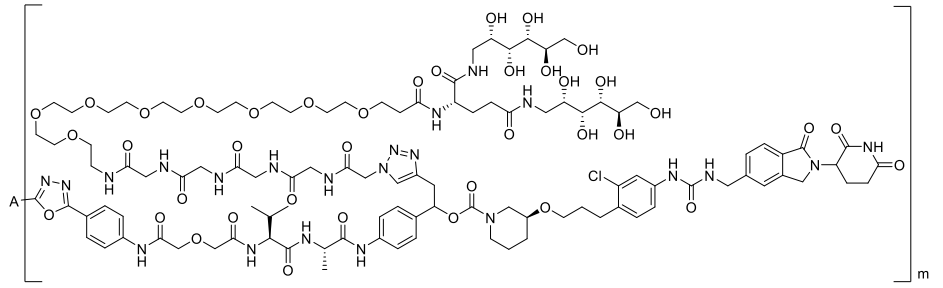
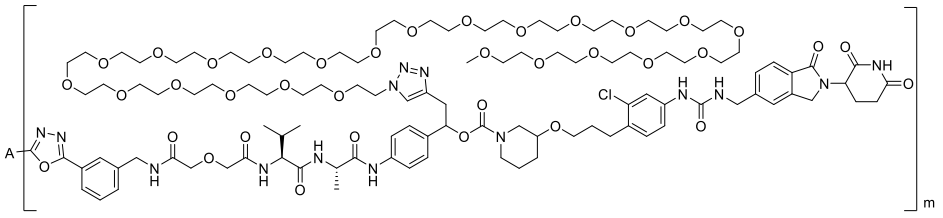
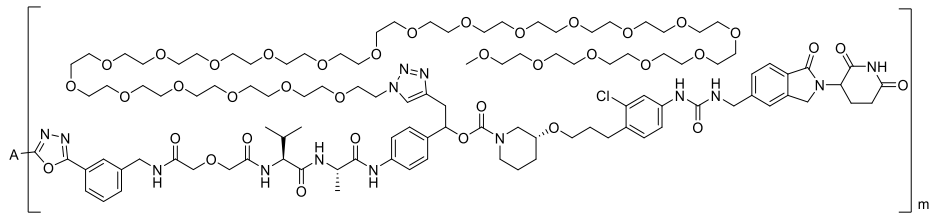
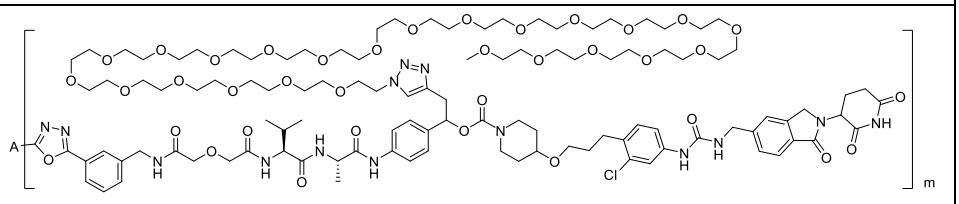
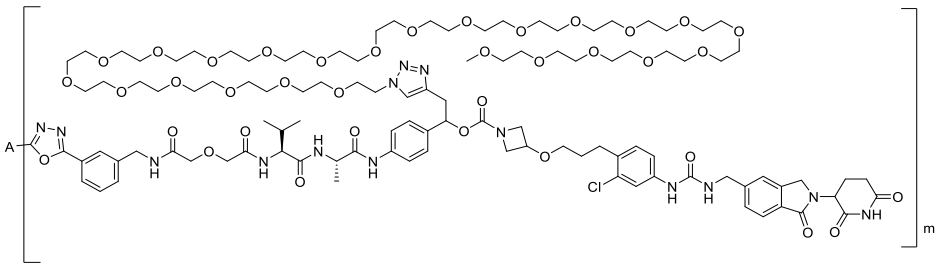
ADC17	
ADC18	
ADC19	
ADC20	

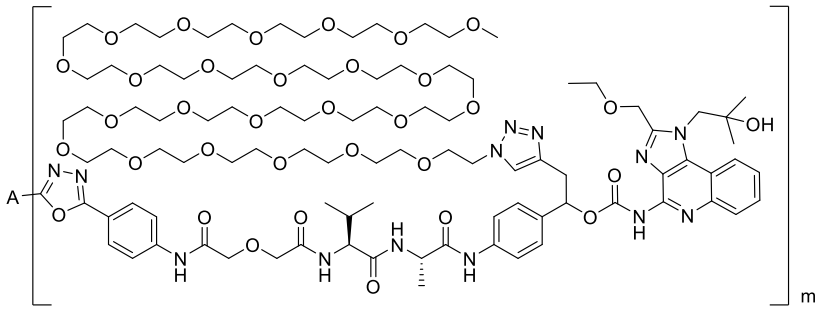
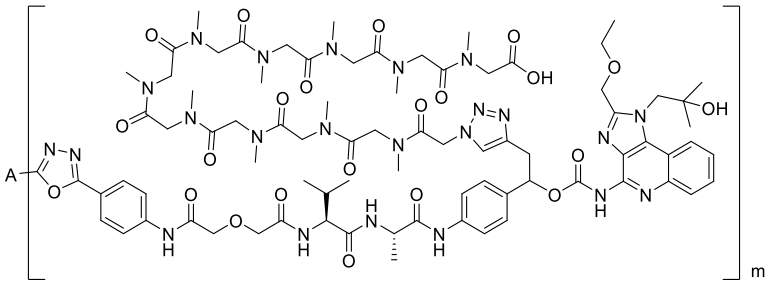
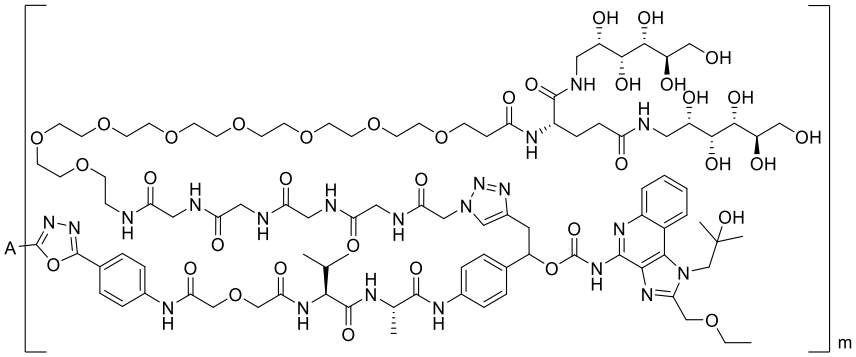
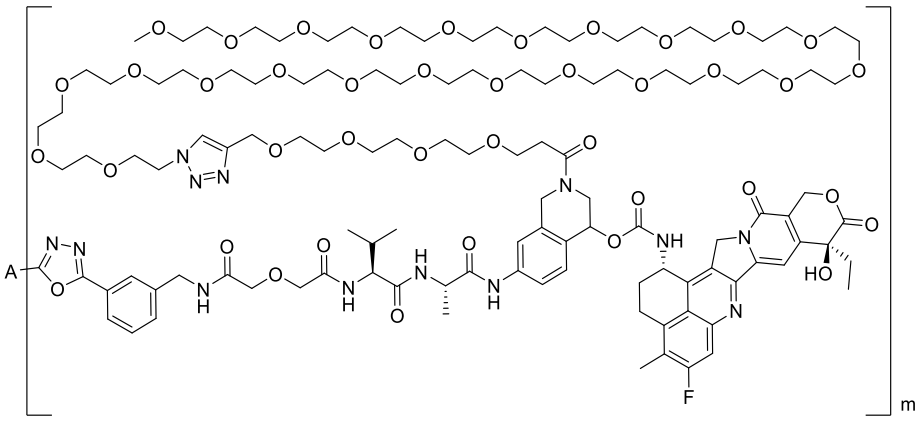
ADC21	
ADC22	
ADC23	
ADC24	

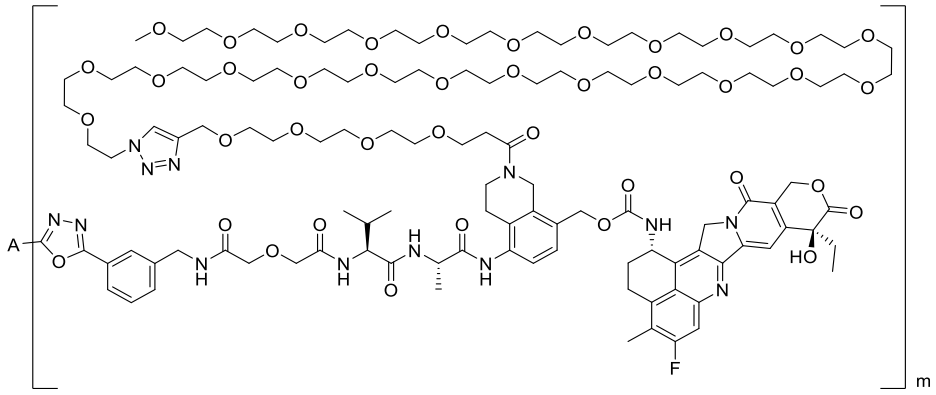
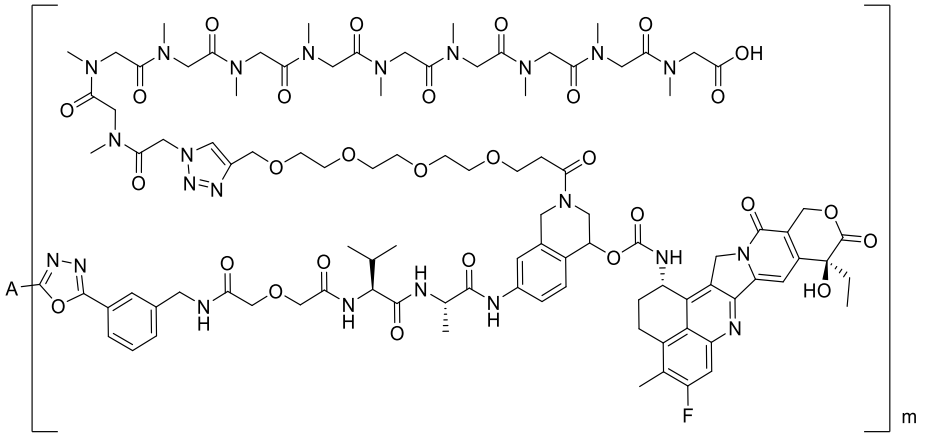
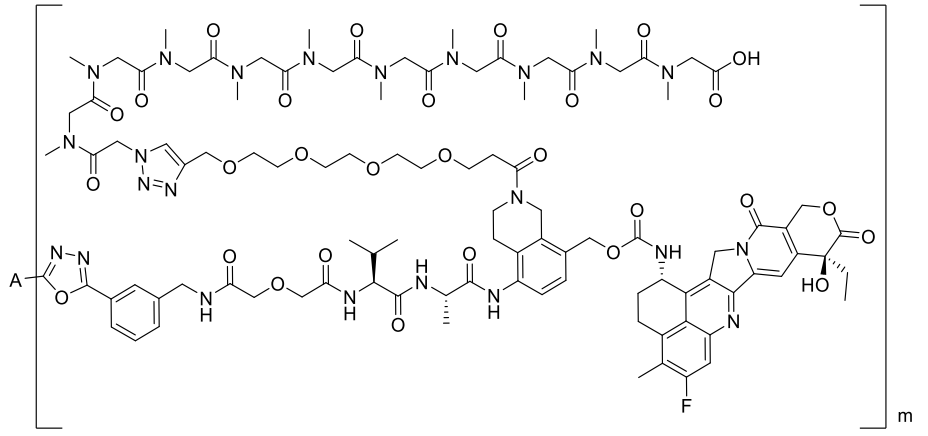
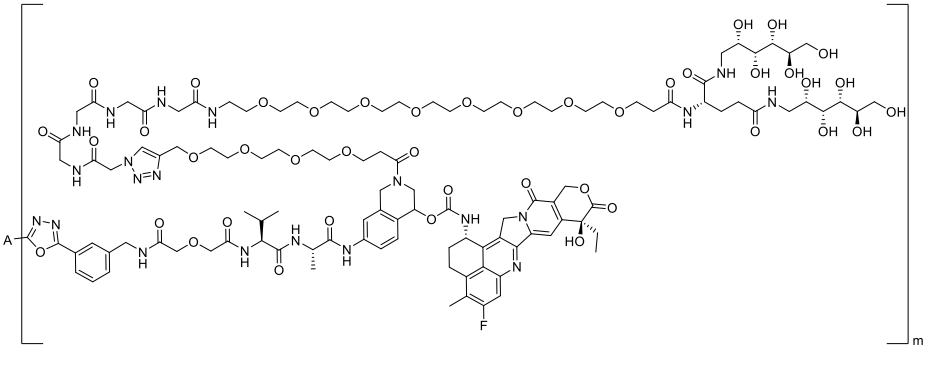
ADC25	
ADC26	
ADC27	
ADC28	

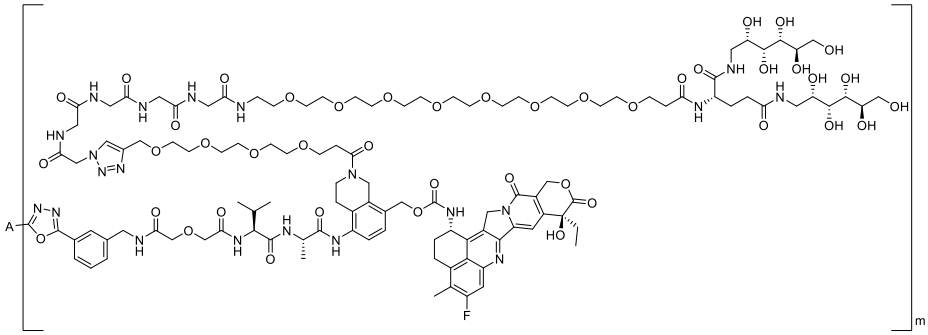
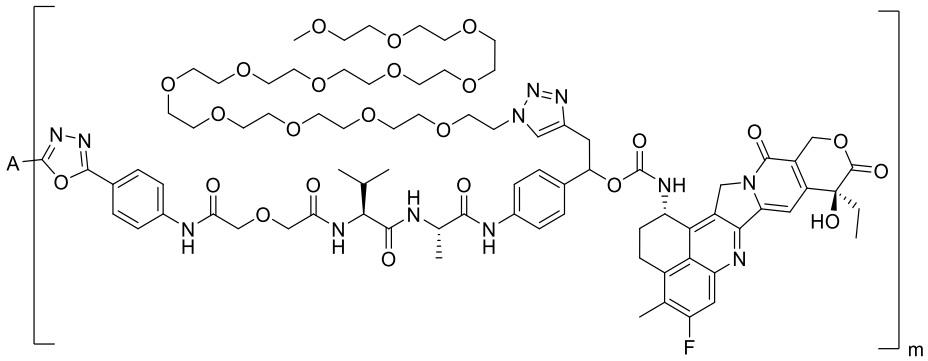
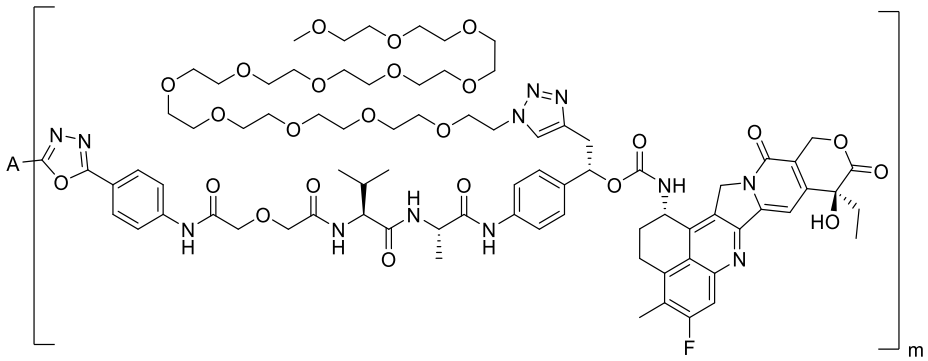
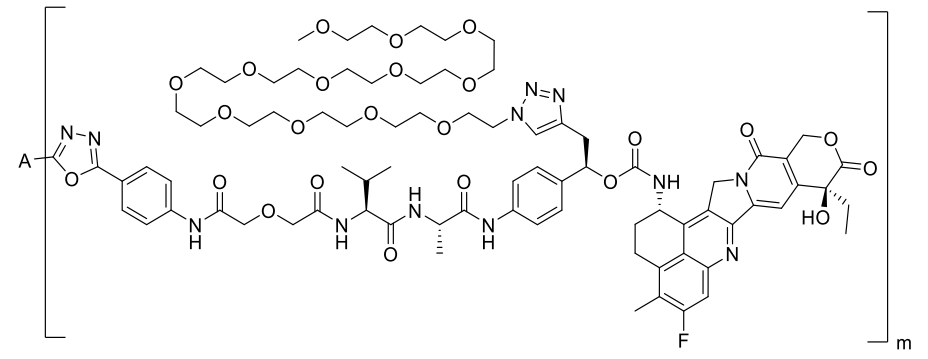
ADC29	
ADC30	
ADC31	
ADC32	
ADC33	

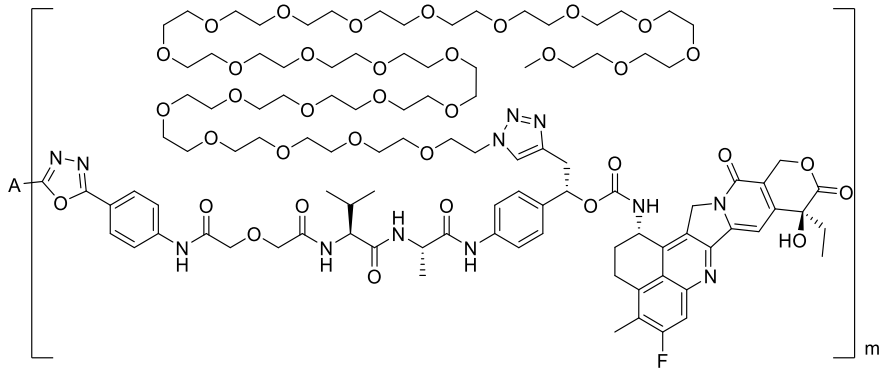
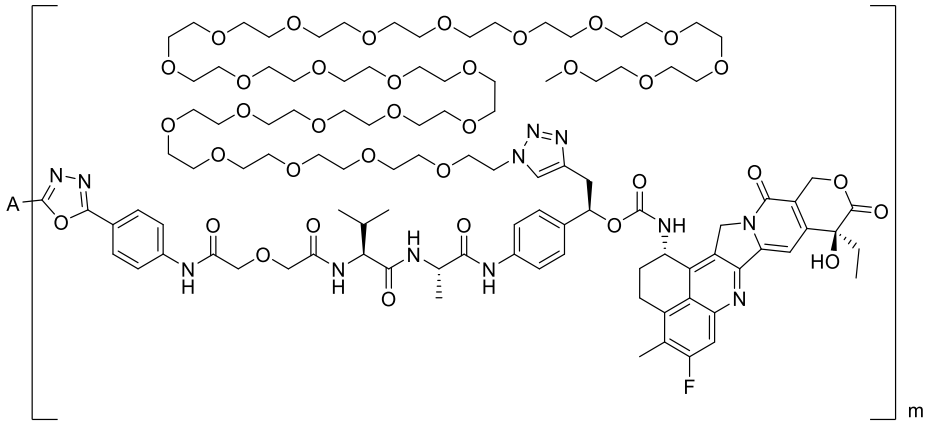
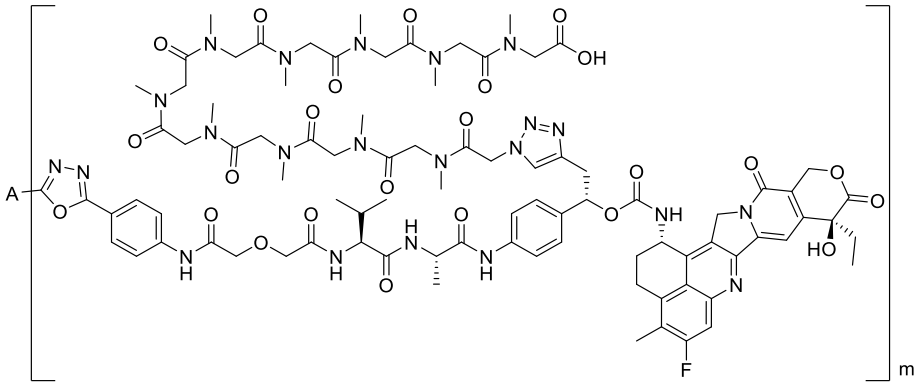
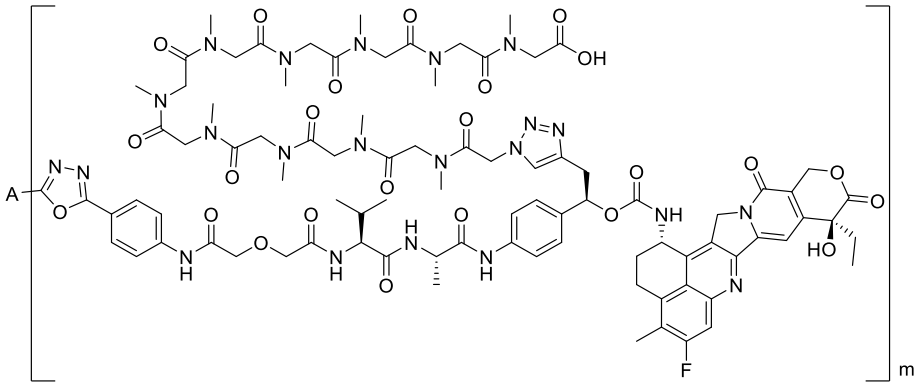
ADC34	
ADC35	
ADC36	
ADC37	
ADC38	

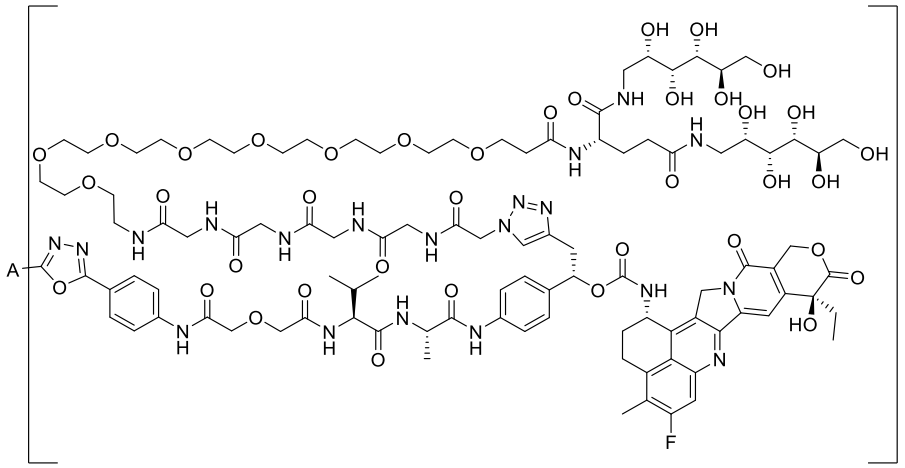
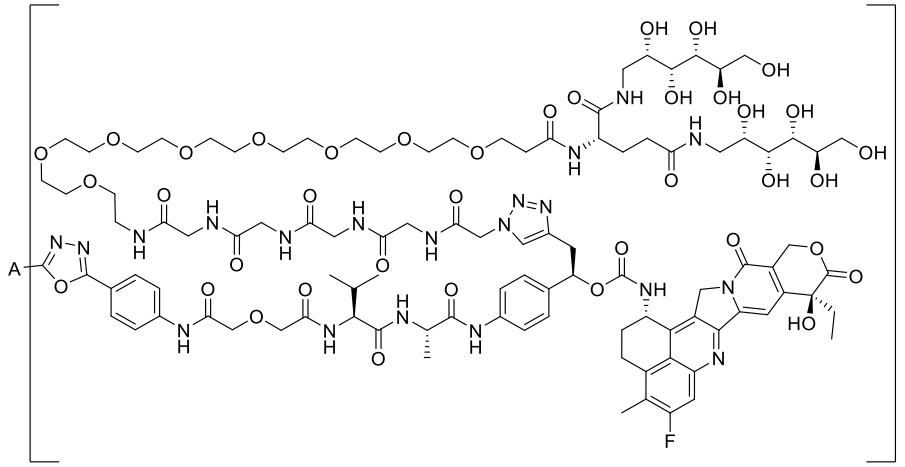
ADC39	
ADC40	
ADC41	
ADC42	
ADC43	
ADC44	
ADC45	

ADC46	
ADC47	
ADC48	
ADC49	

ADC50	
ADC51	
ADC52	
ADC53	

ADC54	
ADC55	
ADC55-1	
ADC55-2	

ADC2-1	
ADC2-2	
ADC7-1	
ADC7-2	

ADC12-1	
ADC12-2	

wherein m is an integer or a decimal from 1 to 12, preferably an integer or a decimal from 2 to 8, and further preferably 2, 4, 6, or 8.

11. A pharmaceutical composition, comprising the antibody-drug conjugate having the structure of formula (I), the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-10, and one or more pharmaceutically acceptable auxiliary materials.

12. Use of the antibody-drug conjugate having the structure of formula (I), the tautomer, the mesomer, the racemate, the enantiomer, the diastereoisomer, the pharmaceutically acceptable salt, the hydrate, the solvate or the isotopically labeled compound thereof according to any one of claims 1-10, or the pharmaceutical composition according to claim 11 for the manufacturing of a medicament for the treatment of a cancer

; preferably, the cancer comprises liver cancer, kidney cancer, lung cancer (e.g., small cell lung cancer and non-small cell lung cancer), gastric cancer, esophageal cancer, oral cancer, urethral

cancer, bladder cancer, colon cancer, rectal cancer, prostate cancer, breast cancer, ovarian cancer, pancreatic cancer, melanoma, hematological tumors or glioblastoma multiforme, lymphoma (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or recurrent anaplastic large cell lymphoma), cervical cancer, uterine cancer, endometrial cancer, salivary gland cancer, glioma, neuroblastoma, sarcoma, colorectal cancer, leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, acute promyelocytic leukemia, chronic myeloid leukemia, or chronic lymphocytic leukemia), bone cancer, skin cancer, thyroid cancer, etc.

13. A linker-drug compound represented by formula (II), or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof, a pharmaceutically acceptable salt, a hydrate, a solvate or an isotopically labeled compound thereof:

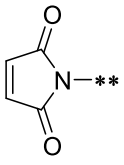
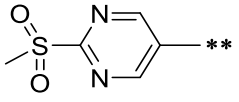
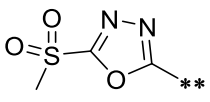
L'-D (II)

wherein L' is a linker moiety;

D is an amino-containing bioactive molecule or a pharmaceutically acceptable salt thereof, covalently linked to the linker moiety L' via an amine group in its molecular structure;

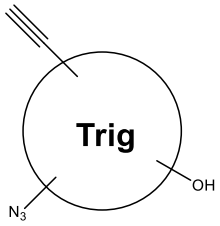
L' is represented by the following formula:

L_1'-L_2-L_3-L_4-,

wherein L_1' is selected from  ,  , and  , wherein ** represents linkage to L_2;

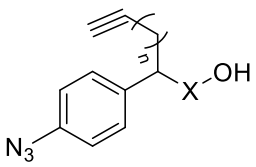
L_2, L_3, L_4, and D are as defined in claims 1-8.

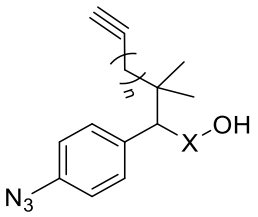
14. A compound of formula (III), or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof, a pharmaceutically acceptable salt, a hydrate, a solvate or an isotopically labeled compound thereof:

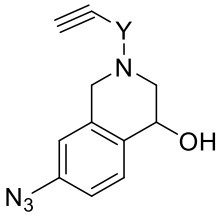


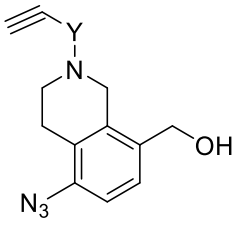
((III),

wherein formula (III) has the following structure:

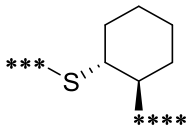


(III-1),


(III-2),


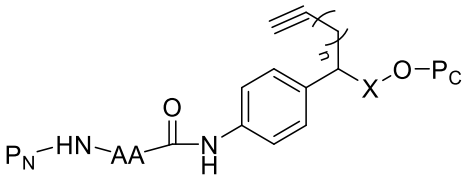
(III-3), or


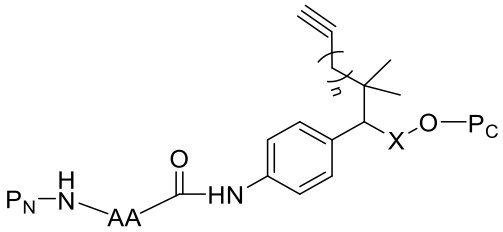
(III-4),

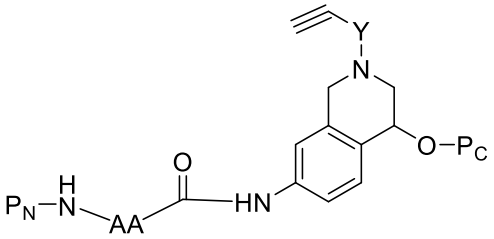
wherein X is absent or 

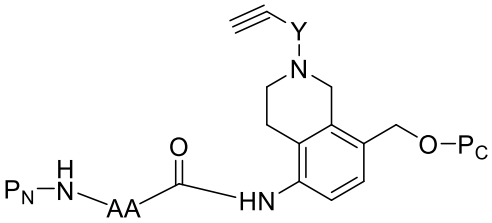
, *** represents linkage to a carbon atom, and **** represents linkage to an oxygen atom; Y is C_1-C_6 alkylene or -R^3-C(O)-, wherein R^3 is C_1-C_6 alkylene or heteroalkylene containing 1-8 -OCH_2CH_2- structural units; n is an integer from 0 to 6.

15. A compound of formula (IV), or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof, a pharmaceutically acceptable salt, a hydrate, a solvate or an isotopically labeled compound thereof:

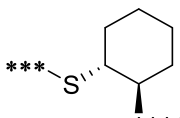


(IV-1),


(IV-2),


(IV-3), or


(IV-4),

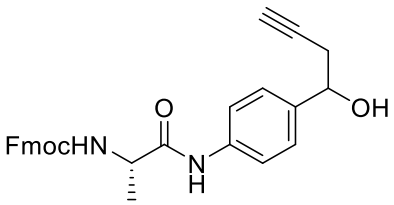
wherein X is absent or 

, *** represents linkage to a carbon atom, and **** represents linkage to an oxygen atom; Y is C_1-C_6 alkylene or -R^3-C(O)-, wherein R^3 is C_1-C_6

alkylene or heteroalkylene containing 1-8 -OCH_2CH_2- structural units; n is an integer from 0 to 6;

wherein AA is L_3 or a sub-fragment consisting of the first 1, 2, or more amino acids from the C-terminus of L_3, P_N is H or an amino protecting group such as Boc or Fmoc, and P_C is H, a hydroxyl protecting group, or a carbonate active ester group such as *p*-nitrophenyl carbonate;

the compound of formula (IV) is preferably:



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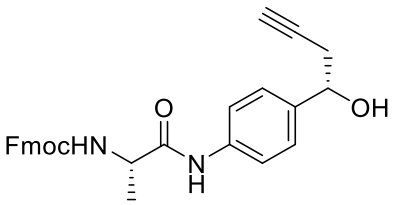
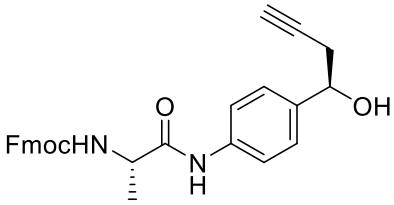


, or



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