with toxins such as pseudomonas or diphtheria toxins, which arrest the synthesis of proteins and cells. However, the side effects include reaction of the immune system due to non-human components of the conjugates. Further, the half-life of the drug conjugates was limited due to elimination from the circulation through renal filtration, and schematic degradation, uptake by the reticuloendothelial system (RES), and accumulation in non-targeted organs and tissues.

[0006] Another approach uses passive drug carriers such as polymers, liposomes, and polymeric micelles to take advantage of the hyper-permeability of vascular endothelia of tumor tissue. Polymeric drugs and macromolecules accumulate within solid tumors due to an enhanced permeability and retention mechanism. However, barriers of using such targeted deliveries include fast clearance of foreign particles from the blood, and technological hindrances in obtaining highly standardized, pharmaceutically acceptable drug delivery systems with the necessary specificity and selectivity for binding tumor cells.

[0007] Protein conjugates, such as antibody conjugates, utilize the selective binding of a binding agent to deliver a payload to targets within tissues of subjects. The payload can be a therapeutic moiety that is capable of taking action at the target.

[0008] Several techniques for conjugating linkers and payloads to antibodies are available. Many conjugates are prepared by non-selective covalent linkage to cysteine or lysine residues in the antibody. This non-selective technique can result in a heterogeneous mixture of products with conjugations at different sites and with different numbers of conjugations per antibody. Thus, there is a need in the art for methods and techniques that provide site-selective antibody conjugation.

[0009] There is a need in the art for additional safe and effective anti-tumor targeting agents that can bind to various antigens to provide enhanced the treatment of diseases such as cancer for use in monotherapy and combination therapies. In certain embodiments, the present disclosure meets the needs and provides other advantages.

[0010] The foregoing discussion is presented solely to provide a better understanding of the nature of the problems confronting the art and should not be construed in any way as an admission as to prior art nor should the citation of any reference herein be construed as an admission that such reference constitutes “prior art” to the instant application.

SUMMARY OF THE DISCLOSURE

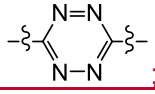
[0011] Various non-limiting ~~aspects and embodiments~~examples of the disclosure are described below.

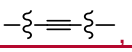
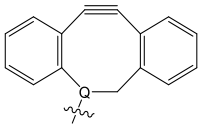
[0011a] In one aspect, there is provided a compound having a structure according to Formula (A):

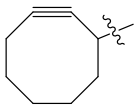
BA-(NH-L1-B-(-L2-(-M-Dxd)$_m$)$_k$)$_n$ (A), wherein:

BA is an antibody or an antigen-binding fragment thereof;

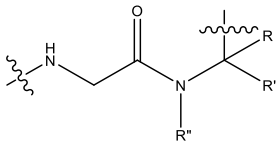
L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

B is a branching unit comprising at least one adduct of group B' and group B", wherein one of the groups B' and B" is selected from -N_3 and 

; and the other of the groups B' and B" is selected from , 

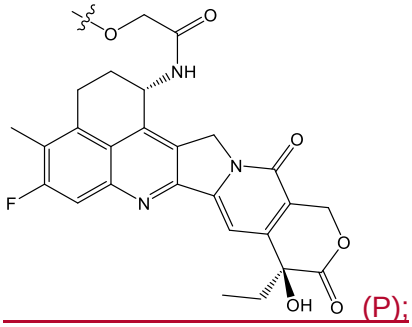
; and , where Q is C or N;

L2 is a second linker covalently attached to the branching unit B via the at least one group B";

M is absent or a moiety having the structure 

, where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):



(P);

k is an integer from 1 to 12;

m is an integer from 1 to 30, and

n is an integer from 1 to 30.

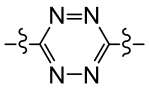
[0012] In one ~~aspect~~example, the present disclosure provides a compound having a structure according to Formula (A):

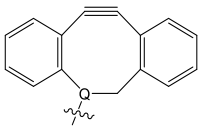
BA-(Gln-NH-L1-B-(-L2-(-M-Dxd)$_m$)$_k$)$_n$ (A), wherein:

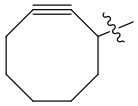
BA is an antibody or an antigen-binding fragment thereof;

Gln is a glutamine residue;

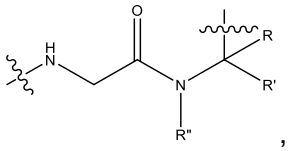
L1 is absent or a first linker;

B is a branching unit comprising at least one adduct of group B' and group B", wherein one of the groups B' and B" is selected from -N_3 and 

; and the other of the groups B' and B" is selected from , 

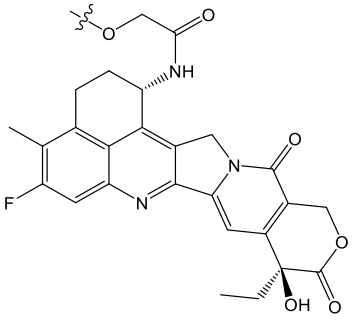
; and , where Q is C or N;

L2 is a second linker covalently attached to the branching unit B via the at least one group B";

M is absent or a moiety having the structure 

, where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):



(P);

k is an integer from 1 to 12;

m is an integer from 1 to 30, and

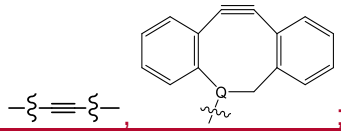
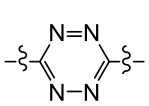
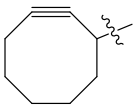
n is an integer from 1 to 30.

[0012a] In another aspect, there is provided a compound compound having a structure according to Formula (I):

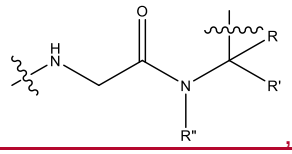
BA-(NH-L1-B-(-L2-M-Dxd)$_k$)$_n$ (I), wherein:

BA is an antibody or an antigen-binding fragment thereof;

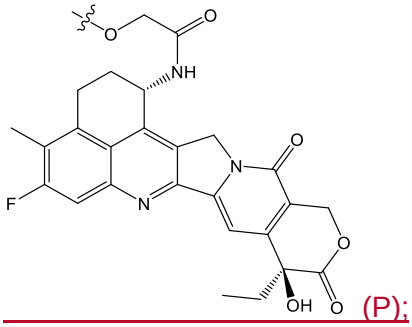
L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

B is a branching unit comprising at least one adduct of group B', where the group B' is selected from -N_3, , ; and , where Q is C or N;

L2 is a second linker covalently attached to the branching unit B via at least one group B", wherein the group B' and the group B" form the at least one adduct;

M is absent or a moiety having the structure , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):

 (P);

k is an integer from 1 to 12, and

n is an integer from 1 to 30.

[0013] In another ~~aspect~~example, the present disclosure provides a compound having a structure according to Formula (I):

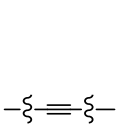
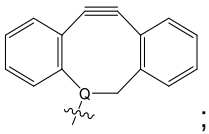
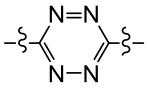
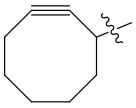
$$BA\text{-}(Gln\text{-}NH\text{-}L1\text{-}B\text{-}(\text{-}L2\text{-}M\text{-}Dxd)_k)_n \quad (I),$$

wherein:

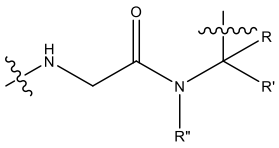
BA is an antibody or an antigen-binding fragment thereof;

Gln is a glutamine residue;

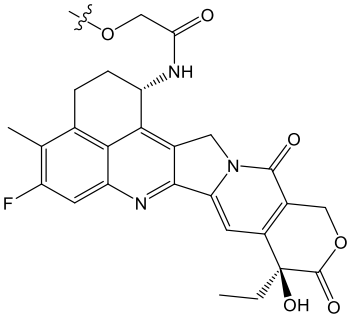
L1 is absent or a first linker;

B is a branching unit comprising at least one adduct of group B', where the group B' is selected from $-N_3$, , ; ; and , where Q is C or N;

L2 is a second linker covalently attached to the branching unit B via at least one group B", wherein the group B' and the group B" form the at least one adduct;

M is absent or a moiety having the structure , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):

 (P)

k is an integer from 1 to 12, and

n is an integer from 1 to 30.

[0014] In one ~~embodiment~~example, the BA is an antibody or an antigen-binding fragment thereof.

[0015] In one ~~embodiment~~example, the BA is an anti-HER2 antibody, an anti-HER2/HER2 bispecific antibody, an anti-STEAP2 antibody, an anti-MET antibody, an anti-MET/MET bispecific antibody, an anti-EGFRVIII antibody, an anti-MUC16 antibody, an anti-PRLR antibody, an anti-PSMA antibody, an anti-FGFR2 antibody, an anti-FOLR1 antibody, or an antigen-binding fragment thereof.

[0016] In one ~~embodiment~~example, the BA is an anti-STEAP2 antibody comprising an HCVR/LCVR amino acid sequence pair as set forth in Table 1.

[0017] In one ~~embodiment~~example, the BA is an anti-HER2/HER2 bispecific antibody. In one ~~embodiment~~example, the BA binds two separate epitopes of HER2 protein.

[0018] In one ~~embodiment~~example, the anti-HER2/HER2 bispecific antibody comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human HER2; and
wherein D2 specifically binds a second epitope of human HER2.

[0019] In one ~~embodiment~~exmaple, the D1 and D2 do not compete with one another for binding to human HER2.

[0020] In one embodiment, the BA is an anti-MET/MET bispecific antibody. In one ~~embodiment~~example, the BA binds two separate epitopes of MET protein.

[0021] In one example~~embodiment~~, the anti- MET/MET bispecific antibody comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human MET; and
wherein D2 specifically binds a second epitope of human MET.

[0022] In one example~~embodiment~~, the D1 and D2 do not compete with one another for binding to human MET.

[0023] In one example~~embodiment~~, the BA is an anti-MET/MET bispecific antibody comprising an HCVR/LCVR amino acid sequence pair as set forth in Table 3.

[0024] In one example~~embodiment~~, the BA is an anti-MET/MET bispecific antibody comprising a D1 antigen-binding domain and a D2 antigen-binding domain, wherein the D1 antigen binding domain comprises an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2012/2092, or a set of heavy and light chain CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) comprising SEQ ID NOs: 2014-2016-2018-2094-2096-2098, and wherein the D2 antigen-binding domain comprises an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2036/2092, or a set of heavy and light chain CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) comprising SEQ ID NOs: 2038-2040-2042-2094-2096-2098.

[0025] In one example~~embodiment~~, the BA is an anti-MET/MET bispecific antibody H4H14639D, which comprises a D1 derived from H4H13306P2 and a D2 derived from H4H13312P2.

[0026] In one example~~embodiment~~, the anti-STEAP2 comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs:2/10; 18/26; 34/42; 50/58; 66/58; 74/58; 82/58; 90/58; 98/58; 106/114; 122/130; 138/146; 154/162; 170/178; 186/194; 202/210; 218/226; 234/242; 250/258; 266/274; 282/290; 298/306; 314/322; 330/338; 346/354; 362/370; and 378/386.

[0027] In one example~~embodiment~~, the glutamine residue Gln is naturally present in a CH2 or CH3 domain of the BA.

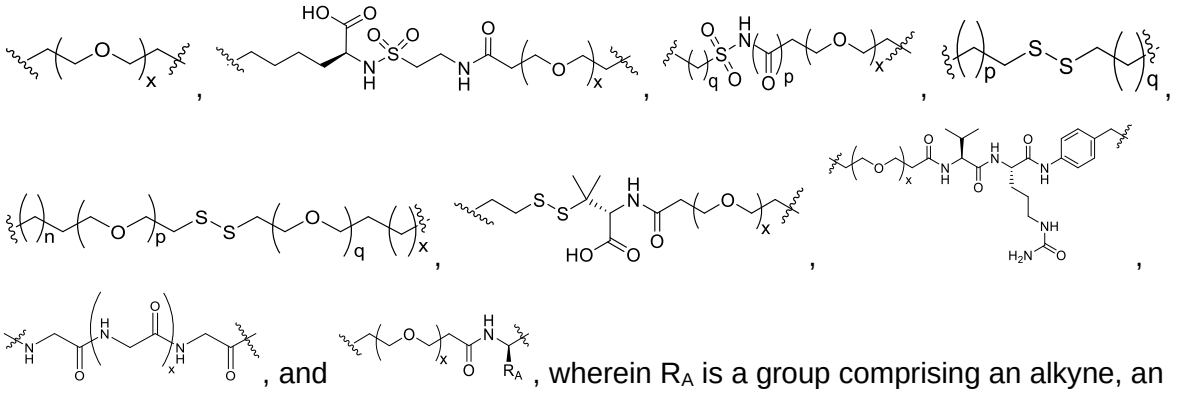
[0028] In one example~~embodiment~~, the glutamine residue Gln is introduced to the BA by modifying one or more amino acids.

[0029] In one example~~embodiment~~, the Gln is Q295 or N297Q.

[0030] In one example~~embodiment~~, the BA targets a cancer selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, lung cancer, liver cancer, or brain cancer.

[0031] In one example~~embodiment~~, L1 comprises C_{1-6} alkyl, phenyl, -NH-, -C(O)-, $-(CH_2)_u$-NH-C(O)-, $-(CH_2)_u$-C(O)-NH-, $-(CH_2-CH_2-O)_v$-, $-(CH_2)_u-(O-CH_2-CH_2)_v$-C(O)-NH-, a peptide unit comprising from 2 to 4 amino acids, or combinations thereof, each of which may be optionally substituted with one or more of -S-, $-S(O_2)$-, -C(O)-, $-C(O_2)$-; and CO_2H, wherein subscripts u and v are independently an integer from 1 to 8.

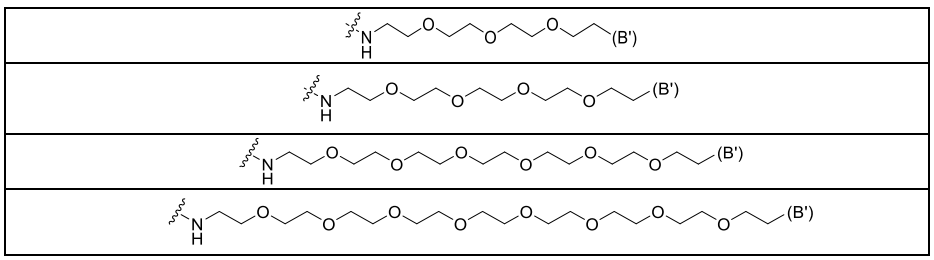
[0032] In one example~~embodiment~~, L1 is selected from the group consisting of:

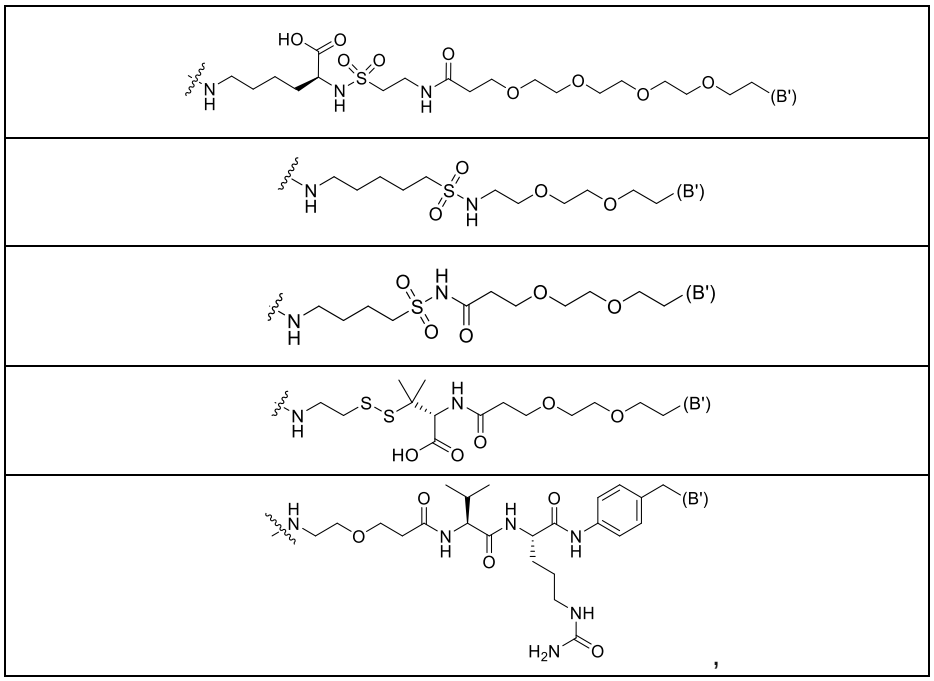


, and , wherein R_A is a group comprising an alkyne, an azide, a tetrazine, a trans-cyclooctene, a maleimide, an amine, a ketone, an aldehyde, a carboxylic acid, an ester, a thiol, a sulfonic acid, a tosylate, a halide, a silane, a cyano group, a carbohydrate group, a biotin group, a lipid residue and wherein subscripts x, n, p and q are independently an integer from 0 to 12, and combinations thereof.

[0033] In one example~~embodiment~~, B comprises one adduct of group B'.

[0034] In one example~~embodiment~~, -NH-L1-B' is selected from the group consisting of:





where the  is the amino point of attachment to the glutamine residue of the BA.

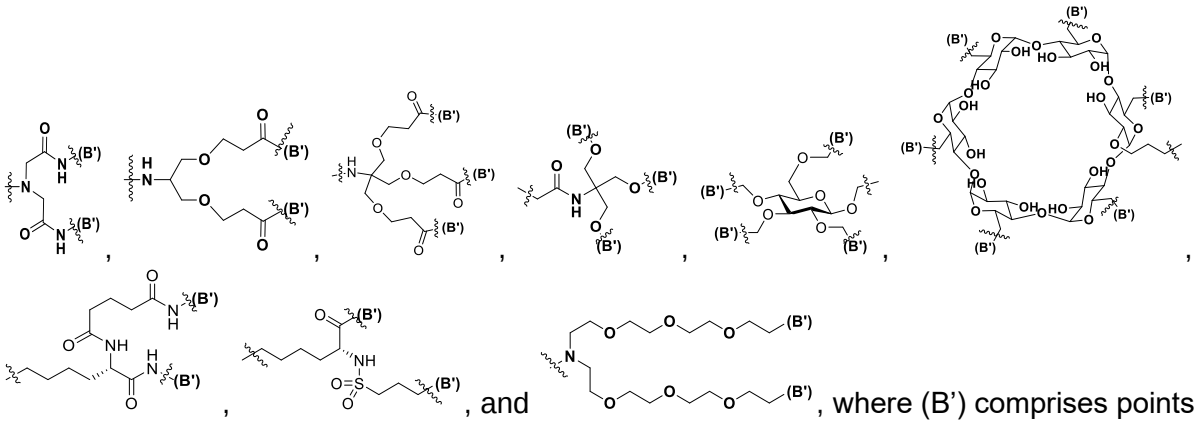
[0035] In one example~~embodiment~~, the group B' is an azide ($-N_3$), and the adduct of the group B' comprises a triazole.

[0036] In one example~~embodiment~~, B comprises two adducts of group B'.

[0037] In one example~~embodiment~~, B comprises three adducts of group B'.

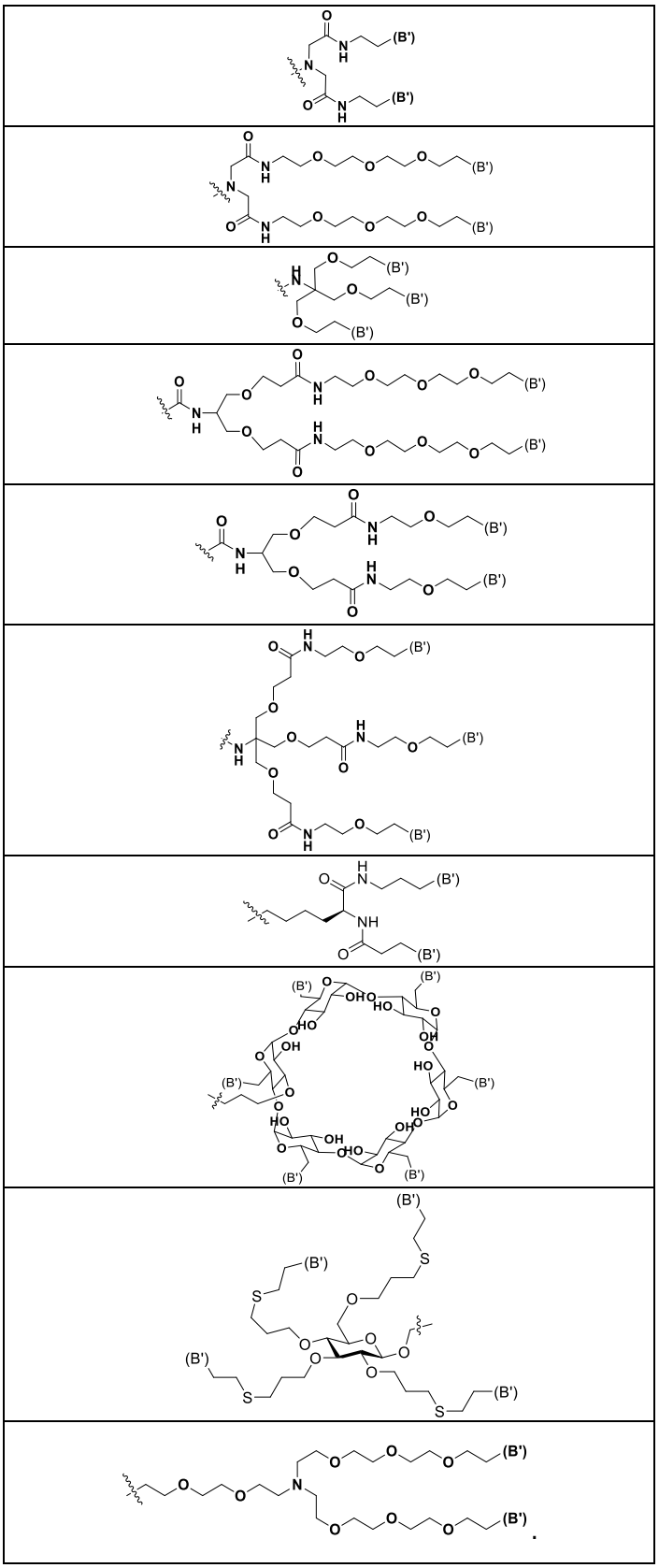
[0038] In one example~~embodiment~~, B comprises at least four adducts of group B'.

[0039] In one example~~embodiment~~, B comprises a group selected from the group consisting of:



, where (B') comprises points of attachment of the adduct of the group B'.

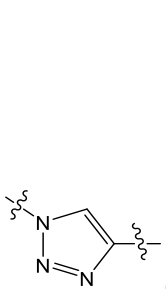
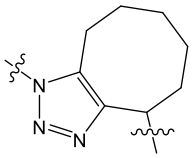
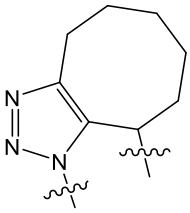
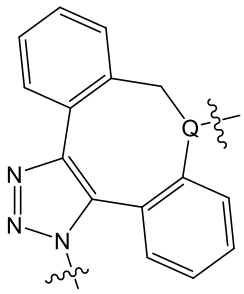
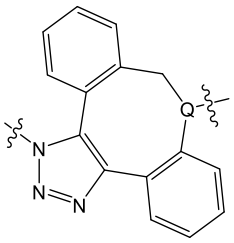
[0040] In one example~~embodiment~~, B is selected from the group consisting of:



[0041] In one example~~embodiment~~, -NH-L1-B is selected from the group consisting of:

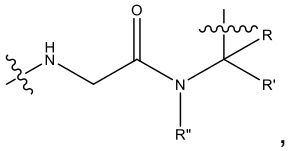
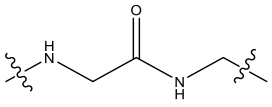
[0042] In one example~~embodiment~~, the group B' is an azide ($-N_3$), and the adduct of the group B' comprises a triazole.

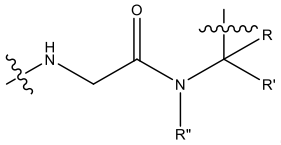
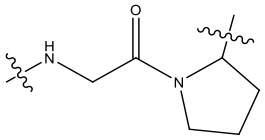
[0043] In one example~~embodiment~~, the adduct of the group B' and the group B" has a structure selected from the group consisting of:


, 
, 
, 
, and 
,

wherein Q is C or N.

[0044] In one example~~embodiment~~, M is absent.

[0045] In one example~~embodiment~~, M is , where R, R', and R" are hydrogens at each occurrence, i.e., M is .

[0046] In one example~~embodiment~~, M is , where R is hydrogen and R' and R" together form a 5-membered ring, i.e. M is .

[0047] In one example~~embodiment~~, n is 2. In one example~~embodiment~~, n is 4. In one example~~embodiment~~, n is 8. In one example~~embodiment~~, n is 12. In one example~~embodiment~~, n is 16. In one example~~embodiment~~, n is 24.

[0048] In one example~~embodiment~~, L2 has a structure according to Formula (L2):

$$B''\text{-}SP1\text{-}B2\text{-}(\text{-}SP2\text{-}AA\text{-}SP3)_p \quad (L2),$$

wherein:

B" is a group capable of covalently attaching to the group B';

SP1 is absent or a first spacer unit;

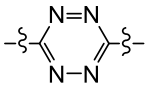
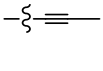
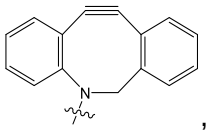
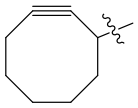
B2 is absent or a branching unit;

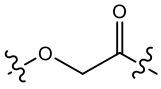
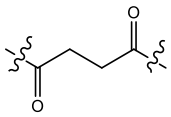
SP2 is absent or a second spacer unit;

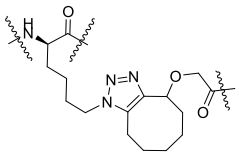
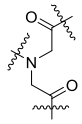
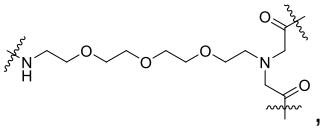
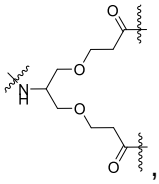
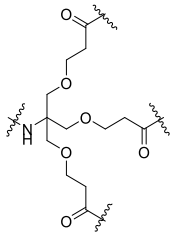
AA is absent or a peptide unit comprising from 2 to 4 amino acids;

SP3 is absent or a third spacer unit covalently attached to the Dxd, and

p is an integer from 1 to 12.

[0049] In one example~~embodiment~~, the at least one group B" is selected from the group consisting of $-N_3$, , , , , , and combinations thereof.

[0050] In one example~~embodiment~~, SP1 is absent or selected from the group consisting of  and .

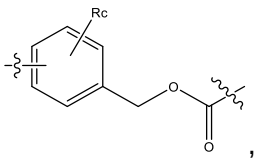
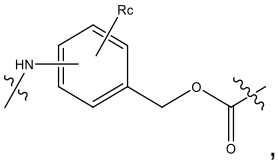
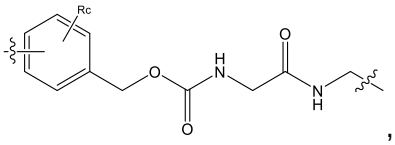
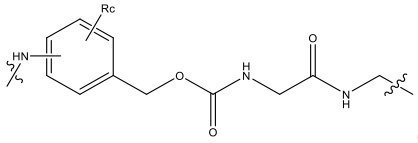
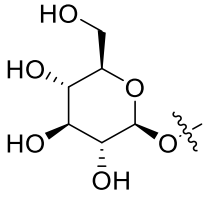
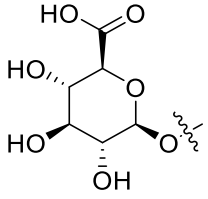
[0051] In one example~~embodiment~~, the B2 is absent or selected from the group consisting of , , , , and .

[0052] In one example~~embodiment~~, SP2 is absent or selected from the group consisting of a C_{1-6} alkyl, $-(CH_2-CH_2-O)_v-$, -NH-, -C(O)-, -NH-C(O)-, $-NH-(CH_2)_u-$, $-NH-(CH_2)_u-C(O)-$, $-NH-(CH_2-CH_2-O)_v-$, $-NH-(CH_2-CH_2-O)_v-C(O)-$, $-NH-(CH_2-CH_2-O)_v-(CH_2)_u-$, $-NH-(CH_2-CH_2-O)_v-(CH_2)_u-C(O)-$, $-(CH_2)_u-NH-C(O)-$, $-NH-(CH_2)_u-NH-C(O)-$, $-NH-(CH_2)_u-C(O)-NH-$, or combinations thereof; wherein subscripts u and v are independently an integer from 1 to 8.

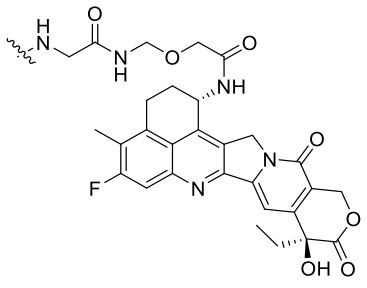
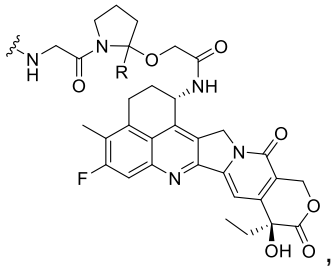
[0053] In one example~~embodiment~~, AA is a peptide unit comprising from 2 to 4 amino acids selected from glycine, valine, phenylalanine, proline, glutamic acid, lysine, phenylalanine, and citrulline, and combinations thereof.

[0054] In one example~~embodiment~~, AA is valine-citrulline, valine-alanine, or phenylalanine-lysine.

[0055] In one example~~embodiment~~, AA is selected from the group consisting of glycine-glycine-glycine (GGG), glycine-glycine-glycine-glycine (GGGG (SEQ ID NO: 2113)), glycine-glycine-phenylalanine (GGF), glycine-glycine-phenylalanine-glycine (GGFG (SEQ ID NO: 2114)), L-glutamic acid-valine-citrulline (^{L}EVC), and D-glutamic acid-valine-citrulline (^{D}EVC).

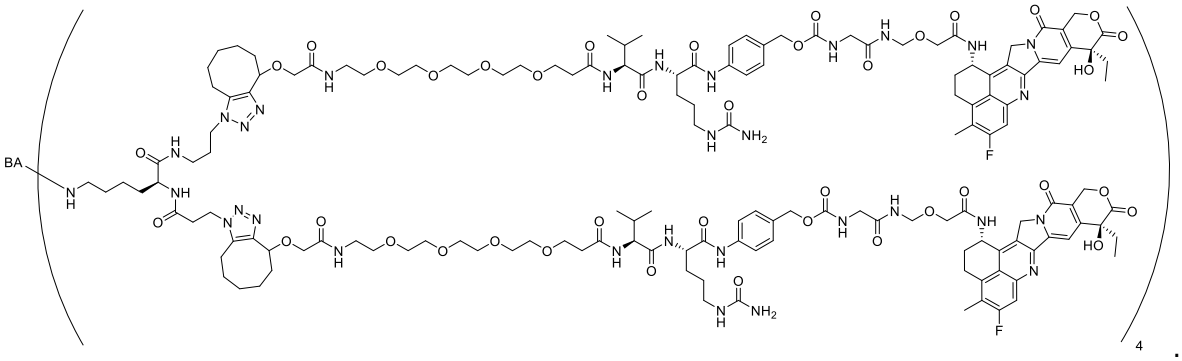
[0056] In one example~~embodiment~~, SP3 is absent or selected from the group consisting of , , , , and combinations thereof, wherein R_c is independently at each occurrence absent or a group selected from  and .

[0057] In one example~~embodiment~~, the M-Dxd has a structure selected from the group consisting of

, and ,

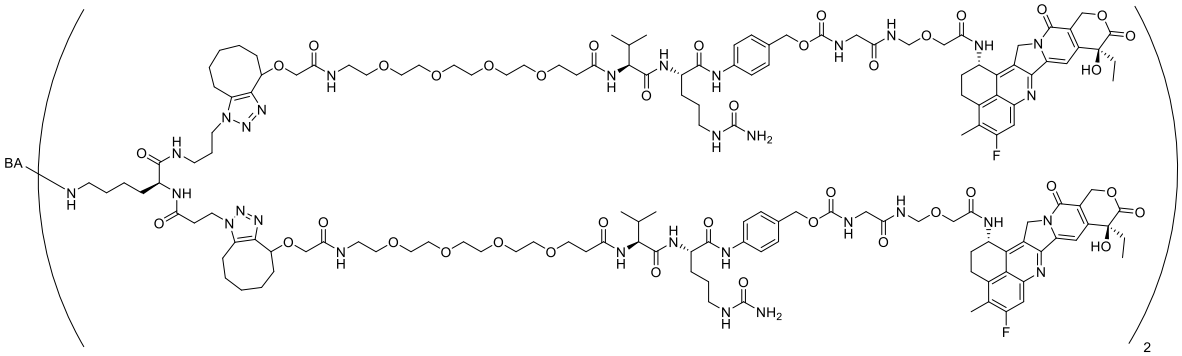
wherein R is a hydrogen or a C_1-C_4 alkyl, and where ~~~ represents the point of attachment to L2.

[0058] In one example~~embodiment~~, the compound has a structure:

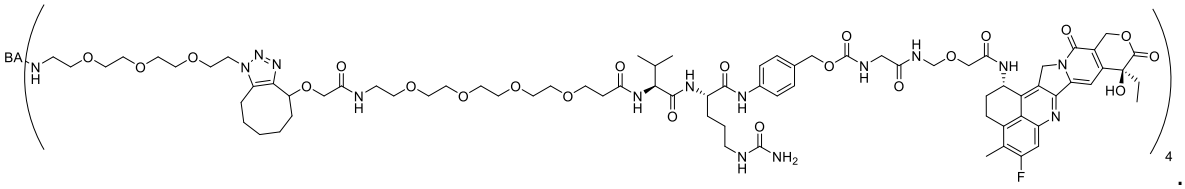


.

[0059] In one example~~embodiment~~, the compound has a structure:



[0060] In one example~~embodiment~~, the compound has a structure:



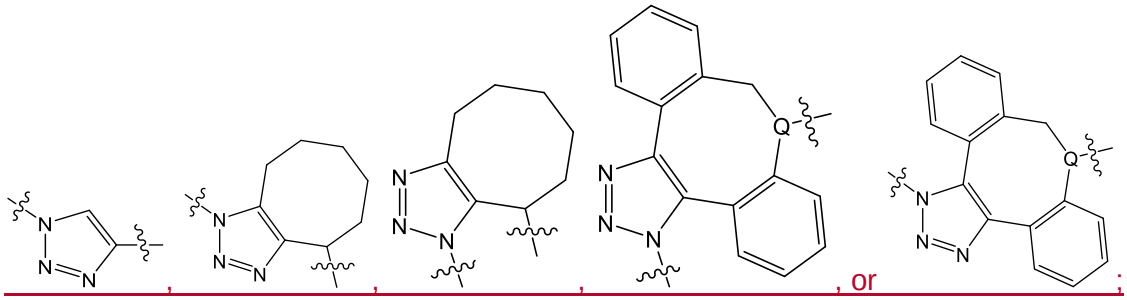
[0060a] In another aspect, there is provided a compound having a structure according to Formula (I):

$BA-(NH-L1-B-(-L2-M-Dxd)_k)_n$ (I), wherein:

BA is an antibody or an antigen-binding fragment thereof;

L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

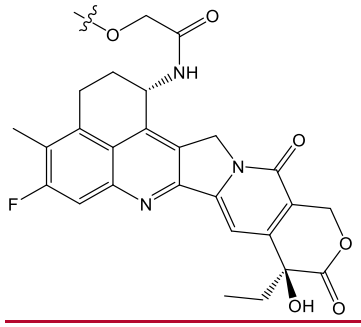
B is a branching unit comprising



, or ;

M is absent or a moiety having the structure , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):



(P);

k is an integer from 1 to 12, and

n is an integer from 1 to 30.

[0061] In another ~~aspect~~example, the present disclosure provides a compound having a structure according to Formula (I):

$$BA\text{-}(Gln\text{-}NH\text{-}L1\text{-}B\text{-}(\text{-}L2\text{-}M\text{-}Dxd)_k)_n \quad (I),$$

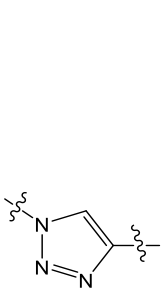
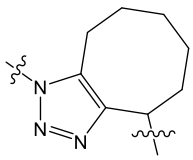
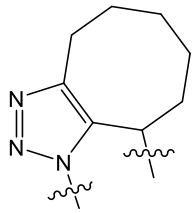
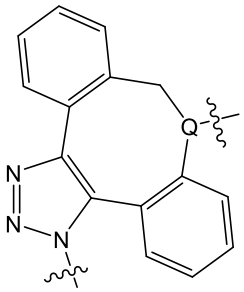
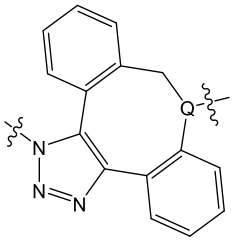
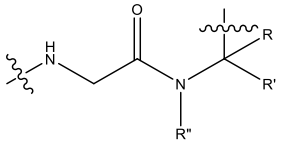
wherein:

BA is an antibody or an antigen-binding fragment thereof;

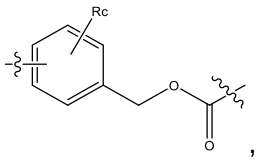
Gln is a glutamine residue;

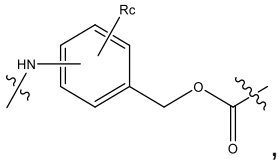
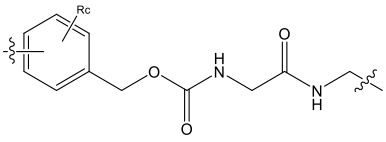
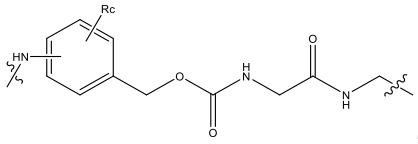
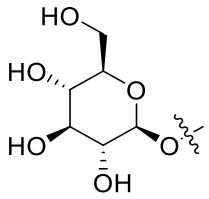
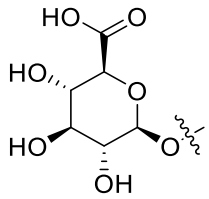
L1 is absent or a first linker;

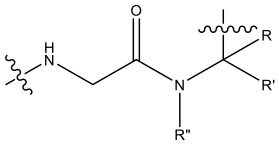
B is a branching unit comprising


, 
, 
, 
, and 
, M is absent or a moiety having the structure 
, where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

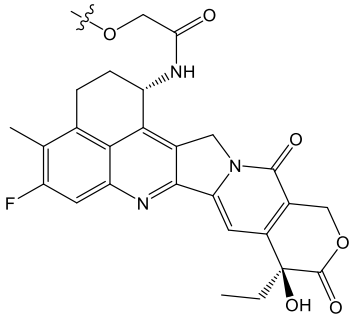
Dxd is an anti-tumor agent having a structure according to Formula (P):

SP3 is absent or a third spacer unit selected from the group consisting of, ,

, , , wherein R_c is independently at each occurrence absent or a group selected from  and ;

M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring; and

Dxd is an anti-tumor agent having a structure according to Formula (P):

 (P), and

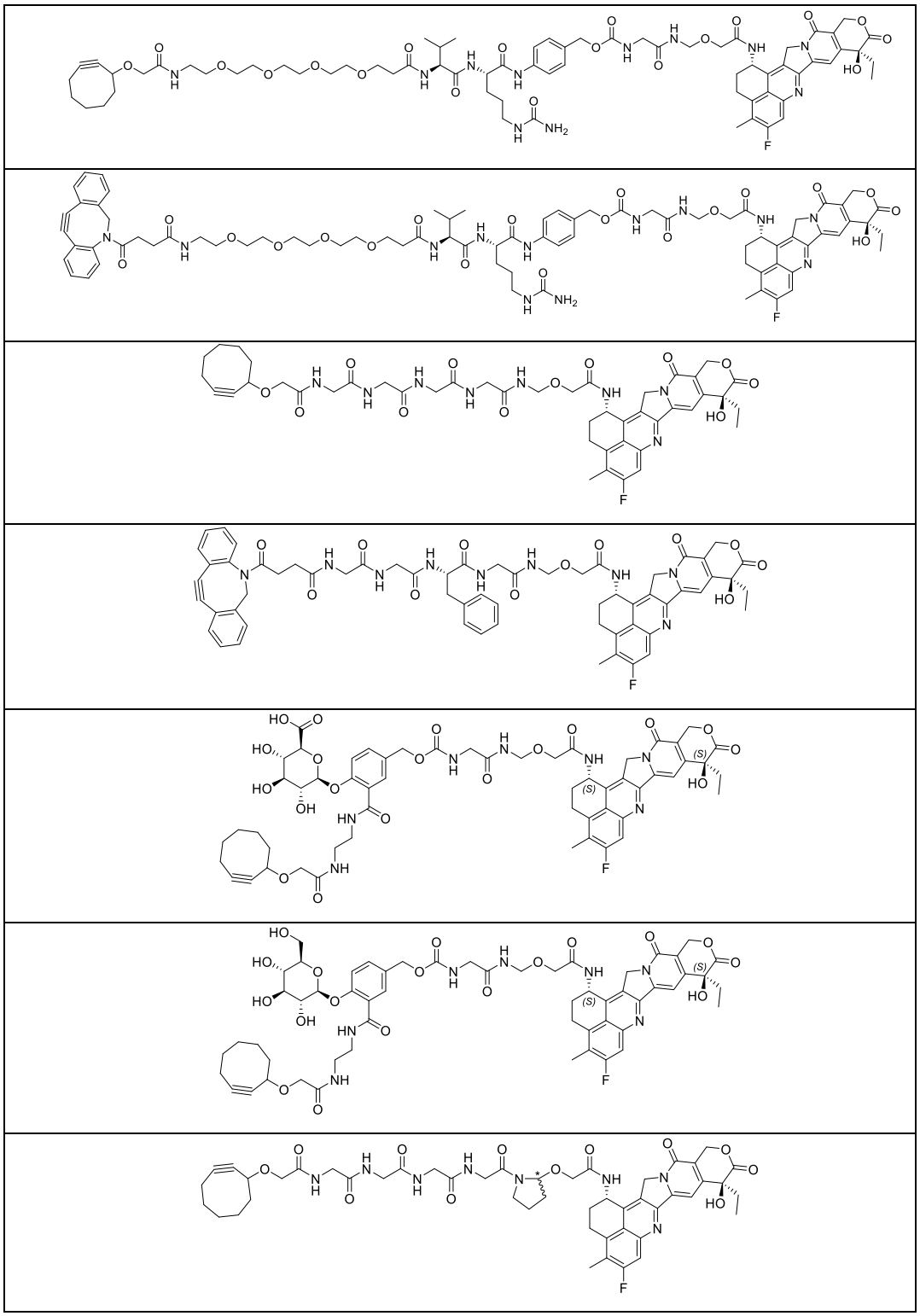
p is an integer from 1 to 12.

[0063] In one example~~embodiment~~, AA is a peptide unit comprising from 2 to 4 amino acids selected from glycine, valine, phenylalanine, proline, glutamic acid, lysine, alanine and citrulline, and combinations thereof.

[0064] In one example~~embodiment~~, AA is valine-citrulline, valine-alanine, or phenylalanine-lysine.

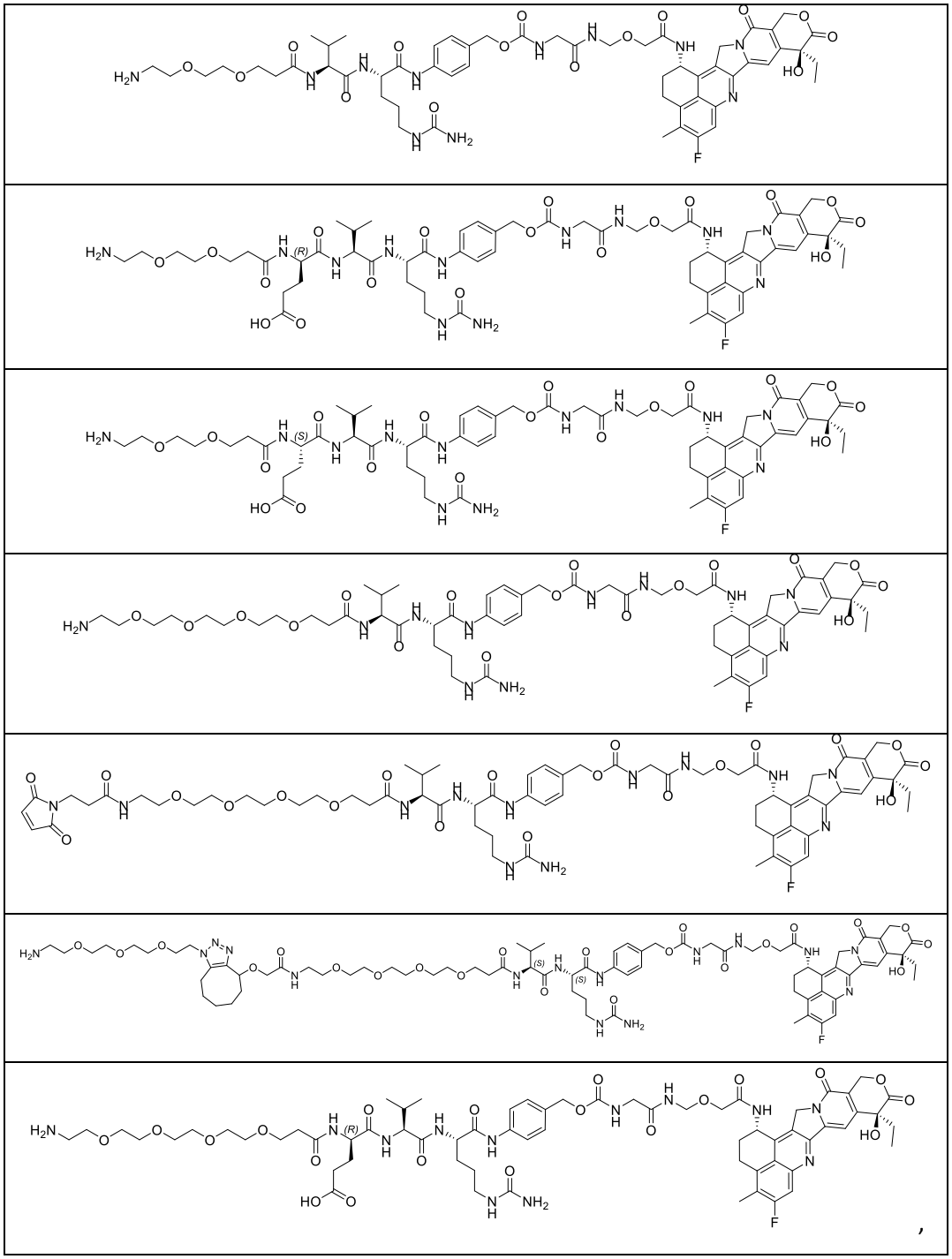
[0065] In one example~~embodiment~~, AA is selected from the group consisting of glycine-glycine-glycine (GGG), glycine-glycine-glycine-glycine (GGGG (SEQ ID NO: 2113)), glycine-glycine-phenylalanine (GGF), glycine-glycine-phenylalanine-glycine (GGFG (SEQ ID NO: 2114)) and glutamic acid-valine-citrulline (EVC).

[0066] In one example~~embodiment~~, the compound has a structure selected from the group consisting of:

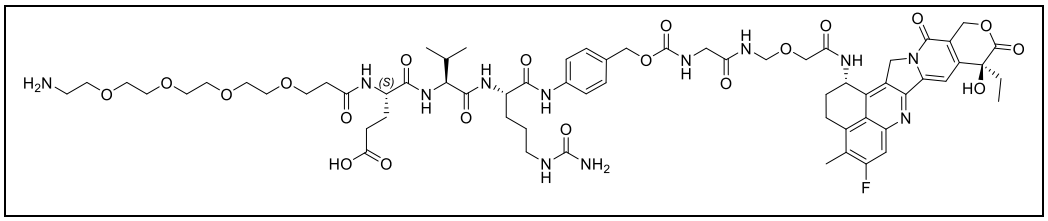


or a pharmaceutically acceptable salt thereof.

[0067] In one example~~embodiment~~, the compound has a structure selected from the group consisting of:

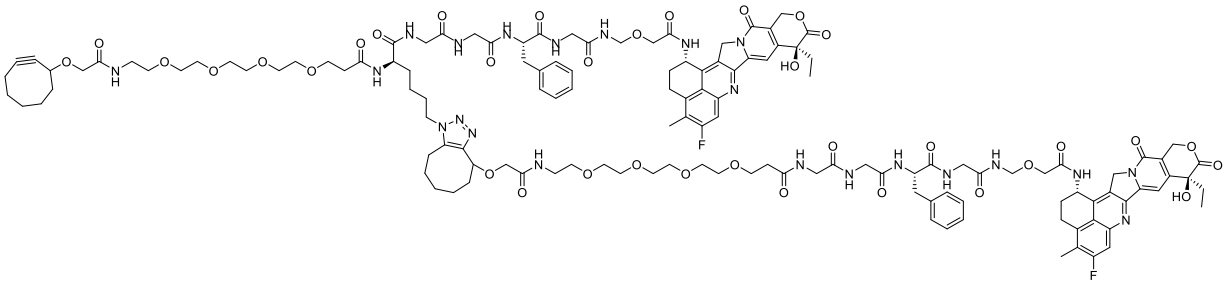


,

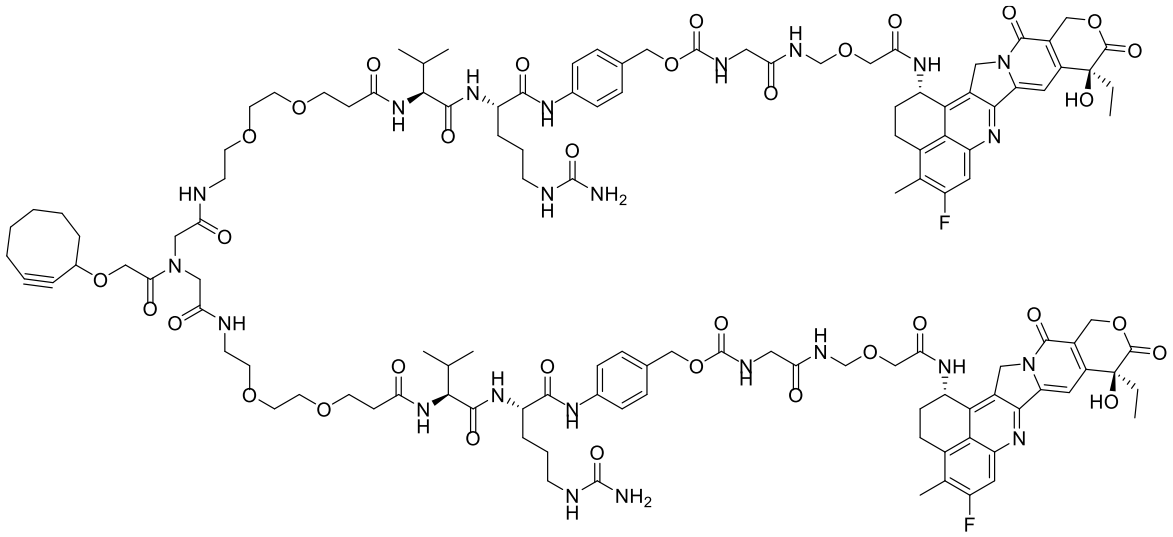


or a pharmaceutically acceptable salt thereof.

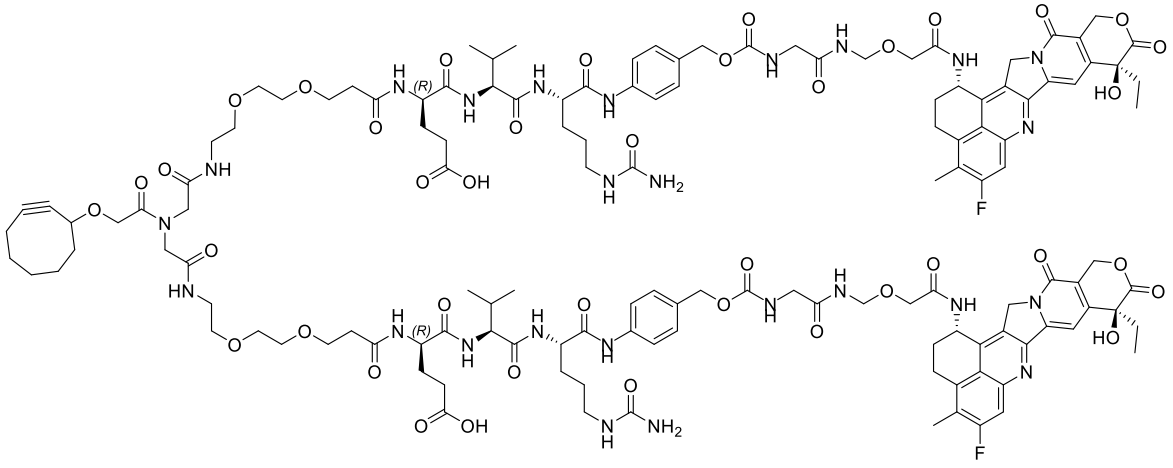
[0068] In one example~~embodiment~~, the compound has a structure according to Formula (L2-P), (L2'-P) or (L2"-P) selected from the group consisting of:



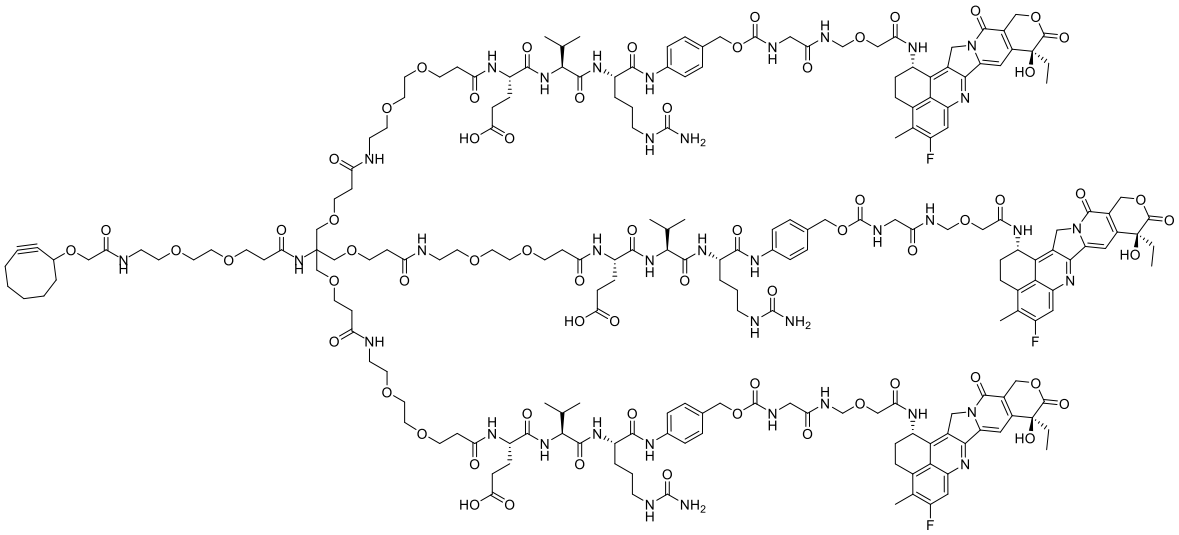
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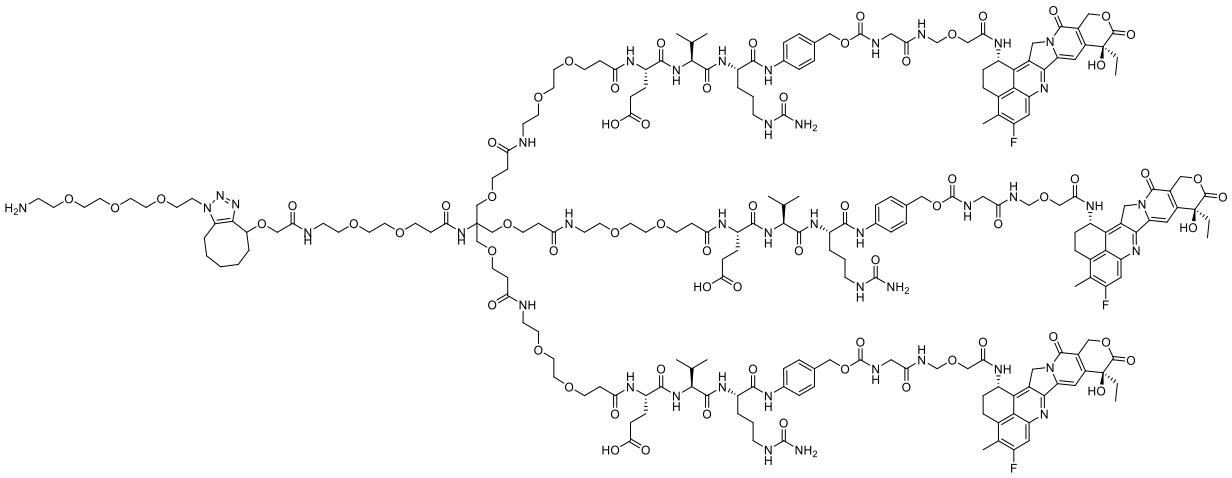
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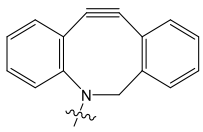
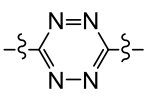
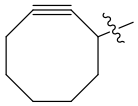
[0069] In another ~~aspect~~example, the present disclosure provides an antibody-drug conjugate according to formula (II):

$$BA\text{-}(Gln\text{-}NH\text{-}L1\text{-}B\text{-}(SP1\text{-}B2\text{-}(\text{-}SP2\text{-}AA\text{-}SP3\text{-}M\text{-}Dxd)_k)_p)_n \quad (II),$$

wherein BA is an antibody;

Gln is a glutamine residue;

L1 is absent or a first linker;

B is a branching unit comprising at least one adduct of group B' and group B", where the group B' is selected from $-N_3$, , ; ;  and at least one group B", wherein

B"-SP1-B2-(-SP2-AA-SP3-M-Dxd)p is the compound according to formula (L2-P) according to any of the preceding ~~embodiments~~examples, and wherein the compound of formula (L2-P) is

covalently attached to the antibody via the adduct of the group B' and the group B"; k is an integer from 1 to 12, p is an integer from 1 to 30, and n is an integer from 1 to 30.

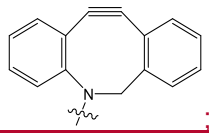
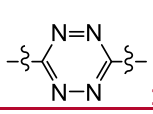
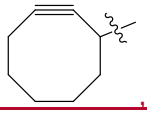
[0069a] In another aspect, there is provided an antibody-drug conjugate according to formula (II):

$$BA-(\ NH-L1-B-(SP1-B2-(-SP2-AA-SP3-M-Dxd)_k)_p)_n \quad (II),$$

wherein BA is an antibody;

L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

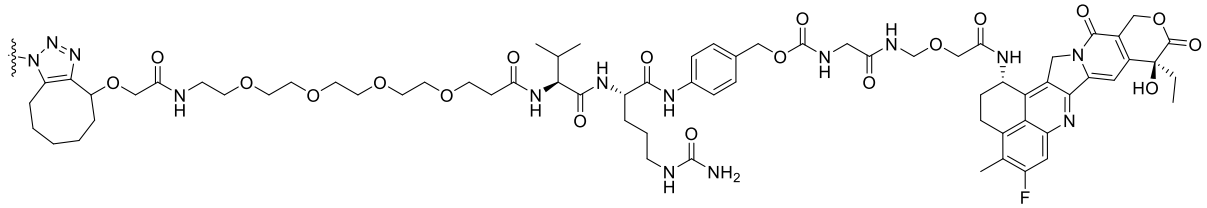
B is a branching unit comprising at least one adduct of group B' and group B", where

the group B' is selected from $-N_3$, , ; ; ,

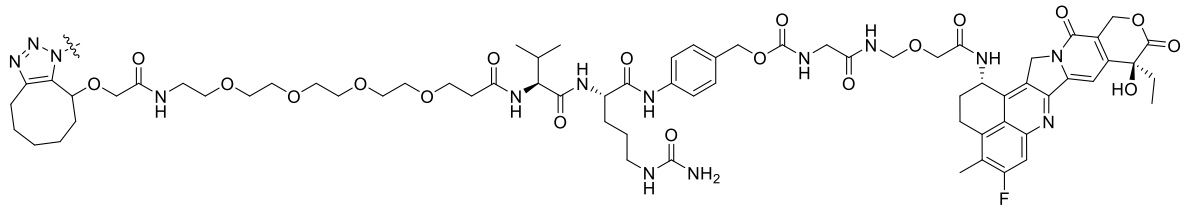
wherein

B"-SP1-B2-(-SP2-AA-SP3-M-Dxd)p is the compound according to Formula (L2-P) according to any of claims 30-34, and wherein the compound of formula (L2-P) is covalently attached to the antibody via the adduct of the group B' and the group B"; k is an integer from 1 to 12, p is an integer from 1 to 30, and n is an integer from 1 to 30.

[0070] In ~~one embodiment~~another aspect, the present disclosure provides an antibody-drug conjugate comprising an antibody and a linker-payload, wherein the linker-payload comprises the structure:



, or



,

where ~~~ represents the point of attachment to the antibody, directly or through a second linker, or a pharmaceutically acceptable salt thereof.

[0070a] In another aspect, there is provided a composition comprising a population of compounds as defined above, having a drug-antibody ratio (DAR) of about 0.5 to about 30.0.

[0071] In another exampleaspect, the present disclosure provides a composition comprising a population of compounds according to any of the preceding examplesembodiments, having a drug-antibody ratio (DAR) of about 0.5 to about 30.0.

[0072] In one exampleembodiment, the composition according to the disclosure has a DAR of about 1.0 to about 2.5. In one exampleembodiment, the composition according to the disclosure has a DAR of about 2.

[0073] In one exampleembodiment, the composition according to the disclosure has a DAR of about 3.0 to about 4.5. In one exampleembodiment, the composition according to the disclosure has a DAR of about 4.

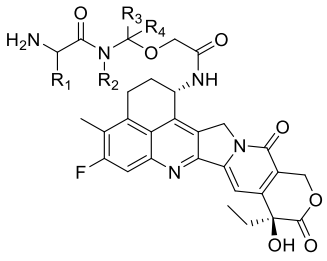
[0074] In one exampleembodiment, the composition according to the disclosure has a DAR of about 6.5 to about 8.5. In one exampleembodiment, the composition according to the disclosure has a DAR of about 8.

[0075] In one exampleembodiment, the composition according to the disclosure has a DAR of about 10 to about 14. In one exampleembodiment, the composition according to the disclosure has a DAR of about 12.

[0076] In one exampleembodiment, the composition according to the disclosure has a DAR of about 14 to about 18. In one exampleembodiment, the composition according to the disclosure has a DAR of about 16.

[0077] In one exampleembodiment, the composition according to the disclosure has a DAR of about 22 to about 24.5. In one exampleembodiment, the composition according to the disclosure has a DAR of about 24.

[0078] In another exampleaspect, the present disclosure provides a compound having a structure according to Formula (P-I):

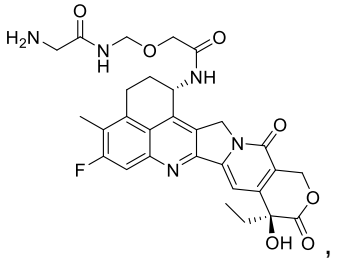


(P-I),

wherein R_1, R_2, R_3, and R_4 are independently a hydrogen or a C_1-C_4 alkyl, or wherein R_2 and R_3 form a 5-membered or a 6-membered ring,

or a pharmaceutically acceptable salt thereof.

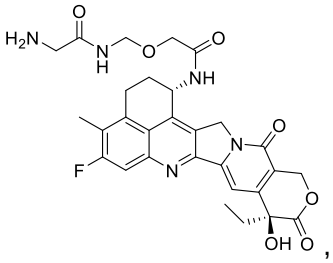
[0079] In one exampleembodiment, the compound is



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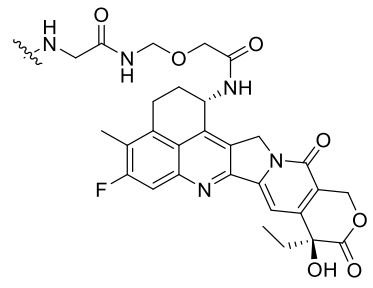
or a pharmaceutically acceptable salt thereof.

[0080] An antibody-drug conjugate comprising an antibody, a linker, and a payload, wherein the payload is

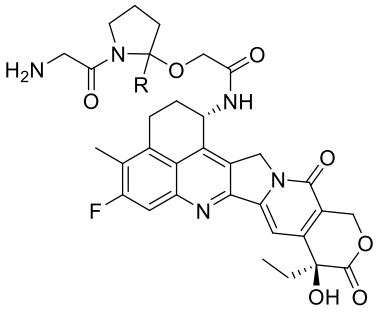


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or a pharmaceutically acceptable salt thereof.

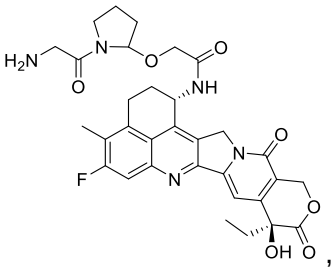
[0081] An antibody-drug conjugate comprising an antibody, a linker, and a payload, wherein the payload is , or a pharmaceutically acceptable salt thereof, where ~~~ represents the point of attachment to the linker.

[0082] In one example~~embodiment~~, the compound has a structure according to Formula (P2):

 (P2),

wherein R is a hydrogen or a C_1-C_4 alkyl, or a pharmaceutically acceptable salt thereof.

[0083] In one example~~embodiment~~, the compound is

, or a pharmaceutically acceptable salt thereof.

[0084] In one ~~aspect~~example, the present ~~invention~~ disclosure provides a pharmaceutical composition comprising the compound according to any of the preceding examples~~embodiments~~, and a diluent, a carrier, and/or an excipient.

[0084a] In another aspect, there is provided a use of the compound, or the composition as described above, in the manufacture of a medicament for the treatment of a condition in a subject in need thereof, comprising the compound or composition to be administered to the subject.

[0085] In one example~~aspect~~, the present ~~invention~~ disclosure provides a method of treating a condition in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound according to any of the preceding examples~~embodiments~~, or the composition of any one of the preceding examples~~embodiments~~.

[0086] In one example~~embodiment~~, the condition is cancer.

[0087] In one exampleembodiment, the cancer is selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, lung cancer, liver cancer, or brain cancer.

[0088] In one exampleembodiment, the condition is HER2+ breast cancer.

[0089] In one another aspect, the present invention disclosure provides a method of selectively delivering a compound into a cell, wherein the compound is according to any one of the preceding examplesembodiments.

[0090] In one another aspect, the present invention disclosure provides a method of selectively targeting an antigen on a surface of a cell with a compound, wherein the compound is according to any one of the preceding examplesembodiments.

[0090a] In another aspect, there is provided a compound or a composition as described above for use in therapy.

[0091] In one exampleembodiment, the cell is a mammalian cell.

[0092] In one exampleembodiment, the cell is a human cell.

[0093] In one exampleembodiment, the cell is a cancer cell.

[0094] In one exampleembodiment, the cancer cell is selected from the group consisting of a breast cancer cell, an ovarian cancer cell, a prostate cancer cell, a lung cancer cell, a liver cancer cell, or a brain cancer cell.

[0095] In one aspectexample, the present disclosure provides a method of producing a compound having a structure according to Formula (A):

$$BA\text{-}(Gln\text{-}NH\text{-}L1\text{-}B\text{-}(\text{-}L2\text{-}(\text{-}M\text{-}Dxd)_m)_k)_n \quad (A),$$

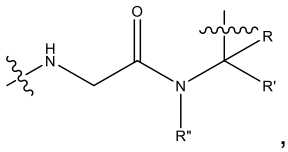
wherein BA is an antibody or an antigen-binding fragment thereof;

Gln is a glutamine residue;

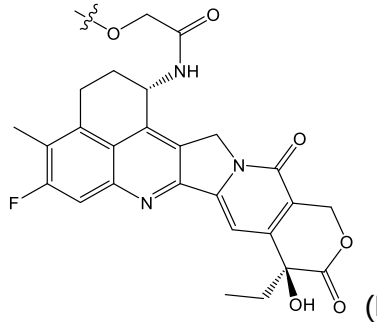
L1 is a first linker;

B is a branching unit comprising at least one adduct of a group B' and a group B";

L2 is a second linker covalently attached to the branching unit B via at least one group B";

M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent comprising a structure according to Formula (P):

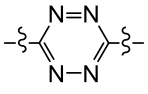
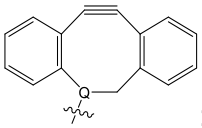
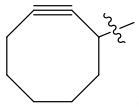

(P),

k and m are independently an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with a compound L1-B, wherein the branching unit B comprises the at least one group B',

b) contacting the product of step a) with k or more equivalents of a compound L2-(-M-Dxd)$_m$, wherein the linker L2 comprises at least one group B",

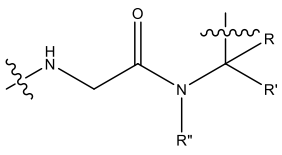
wherein one of the groups B' and B" is selected from -N_3 and  ; and the other of the groups B' and B" is selected from ,  ; and  , where Q is C or N; and

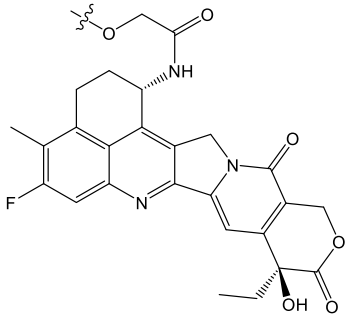
c) isolating the produced compound of Formula (I).

[0096] In one example~~aspect~~, the present disclosure provides a method of producing a compound having a structure according to Formula (A):

BA-(Gln-NH-L1-B-(-L2-(-M-Dxd)$_m$)$_k$)$_n$ (A),

wherein BA is an antibody or an antigen-binding fragment thereof; Gln is a glutamine residue; L1 is a first linker as described above; B is a branching unit comprising at least one adduct of a group B' and a group B" as described above; L2 is a second linker as described above covalently attached to the branching unit B via at least one group B" as described above; M is absent or

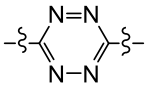
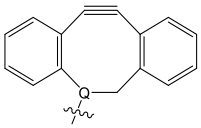
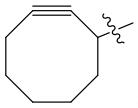
 , where R, R', and R" are as described above; Dxd is an anti-tumor agent comprising a structure according to Formula (P):



(P), k and m are independently an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting a compound L1-B, wherein the branching unit B comprises the at least one group B', with k or more equivalents of a compound L2-(-M-Dxd)$_m$, wherein the linker L2 comprises at least one group B" capable of covalently binding with the group B',

wherein one of the groups B' and B" is selected from -N_3 and ; and the other of the groups B' and B" is selected from , ; and , where Q is C or N;

thereby producting L1-B-(-L2-(-M-Dxd)$_m$)$_k$;

b) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with the L1-B-(-L2-(-M-Dxd)$_m$)$_k$ product of step a), and

c) isolating the produced compound of Formula (I).

[0097] In one example~~aspect~~, the present disclosure provides a method of producing a compound having a structure according to Formula (I):

BA-(Gln-NH-L1-B-(-L2-M-Dxd)$_k$)$_n$

(I),

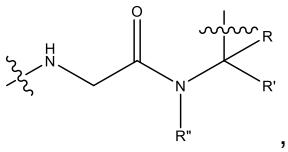
wherein BA is an antibody or an antigen-binding fragment thereof;

Gln is a glutamine residue;

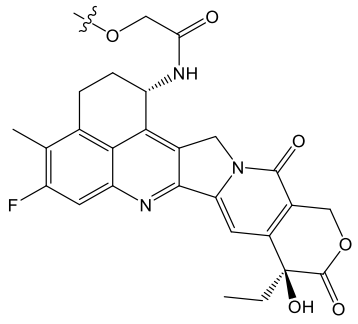
L1 is a first linker;

B is a branching unit comprising at least one adduct of a group B' and a group B";

L2 is a second linker covalently attached to the branching unit B via at least one group B";

M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent comprising a structure according to Formula (P):

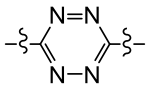
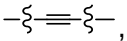
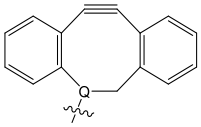
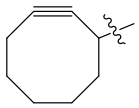
 (P),

k is an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with a compound L1-B, wherein the branching unit B comprises the at least one group B',

b) contacting the product of step a) with k or more equivalents of a compound L2-M-Dxd, wherein the linker L2 comprises the at least one group B" capable of covalently attaching to the group B',

wherein one of the groups B' and B" is selected from -N_3 and ; and the other of the groups B' and B" is selected from , ; and , where Q is C or N; and

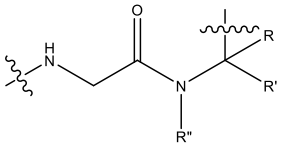
c) isolating the produced compound of Formula (I).

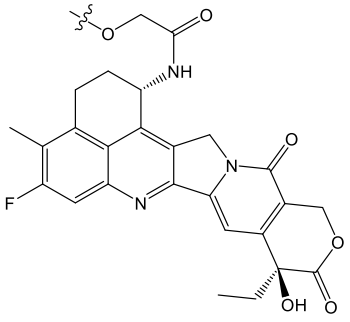
[0098] In one example~~aspect~~, the present disclosure provides a method of producing a compound having a structure according to Formula (I):

$$BA\text{-}(Gln\text{-}NH\text{-}L1\text{-}B\text{-}(\text{-}L2\text{-}M\text{-}Dxd)_k)_n \quad (I),$$

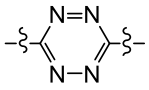
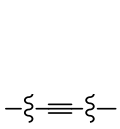
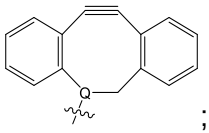
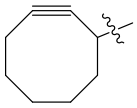
wherein BA is an antibody or an antigen-binding fragment thereof; Gln is a glutamine residue; L1 is a first linker as described above; B is a branching unit comprising at least one adduct of a group B' and a group B" as described above; L2 is a second linker as described above

covalently attached to the branching unit B via at least one group B" as described above; M is

absent or , where R, R', and R" are as described above; Dxd is an anti-tumor agent comprising a structure according to Formula (P):

 (P), k is an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting a compound L1-B, wherein the branching unit B comprises the at least one group B' with k or more equivalents of a compound L2-M-Dxd, wherein the linker L2 comprises at least one group B", thereby producting L1-B-(-L2-M-Dxd)$_k$, wherein one of the groups B' and B" is selected from -N_3 and  ; and the other of the groups B' and B" is selected from ,  ; and , where Q is C or N;

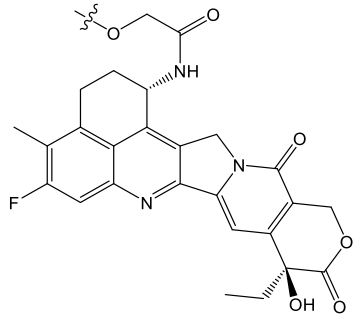
b) contacting, in the presence of a transglutaminase, the binding agent BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with the L1-B-(-L2-M-Dxd)$_k$ product of step a), and

c) isolating the produced compound of Formula (I).

[0099] In one example~~aspect~~, the present disclosure provides a method of producing a compound having a structure according to Formula (III):

BA-(Gln-NH-L2'-P))$_n$ (III),

wherein BA is an antibody or an antigen-binding fragment thereof; Gln is a glutamine residue; L2'-P is H_2N-SP1-B2-(-SP2-AA-SP3-M-Dxd)p as described above, and n is an integer from 1 to 30;


(P),

p is an integer from 1 to 30;

wherein the method comprises the steps of:

b) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with the L2'-P, and

c) isolating the produced compound of Formula (III).

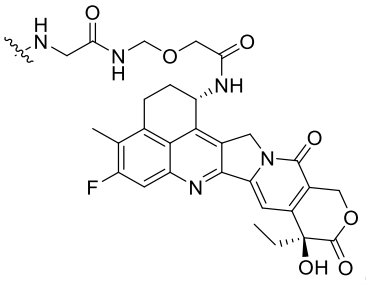
[0100] In one example~~embodiment~~, the glutamine residue Gln is naturally present in a CH2 or CH3 domain of the BA.

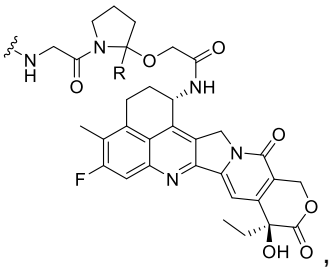
[0101] In one example~~embodiment~~, wherein the glutamine residue Gln is introduced to the BA by modifying one or more amino acids.

[0102] In one example~~embodiment~~, wherein the Gln is Q295 or N297Q.

[0103] In one example~~embodiment~~, wherein the transglutaminase is microbial transglutaminase (MTG).

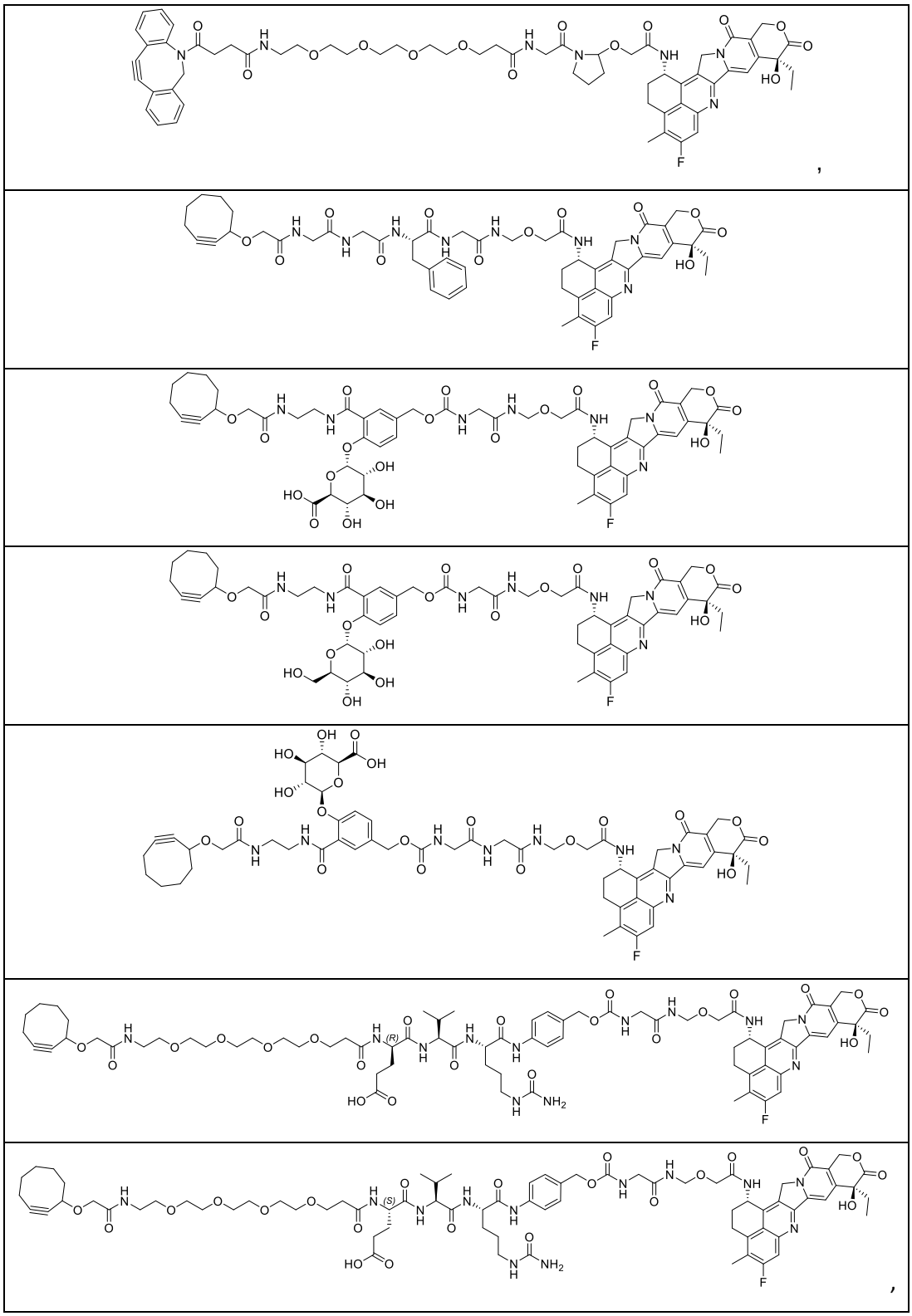
[0104] In one example~~embodiment~~, M is absent, or the M-Dxd has a structure selected from the group consisting of


, and


,

wherein R is a hydrogen or a C_1-C_4 alkyl, and where ~~~ represents the point of attachment to L2.

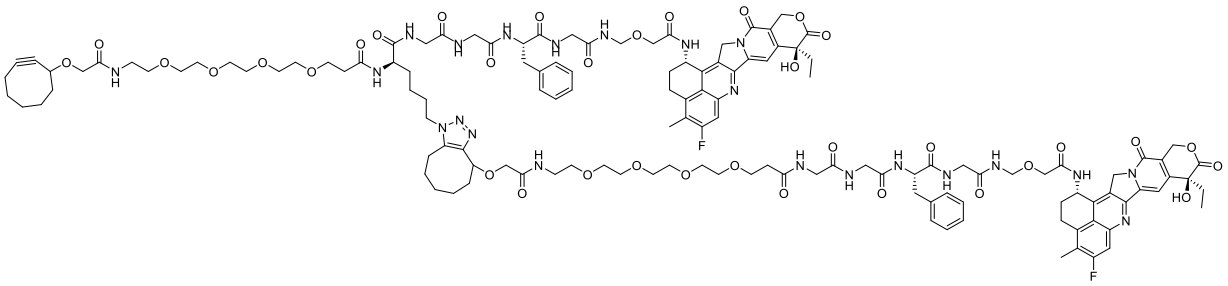
[0105] In one example~~embodiment~~, the compound L2-Dxd has a structure selected from the group consisting of:



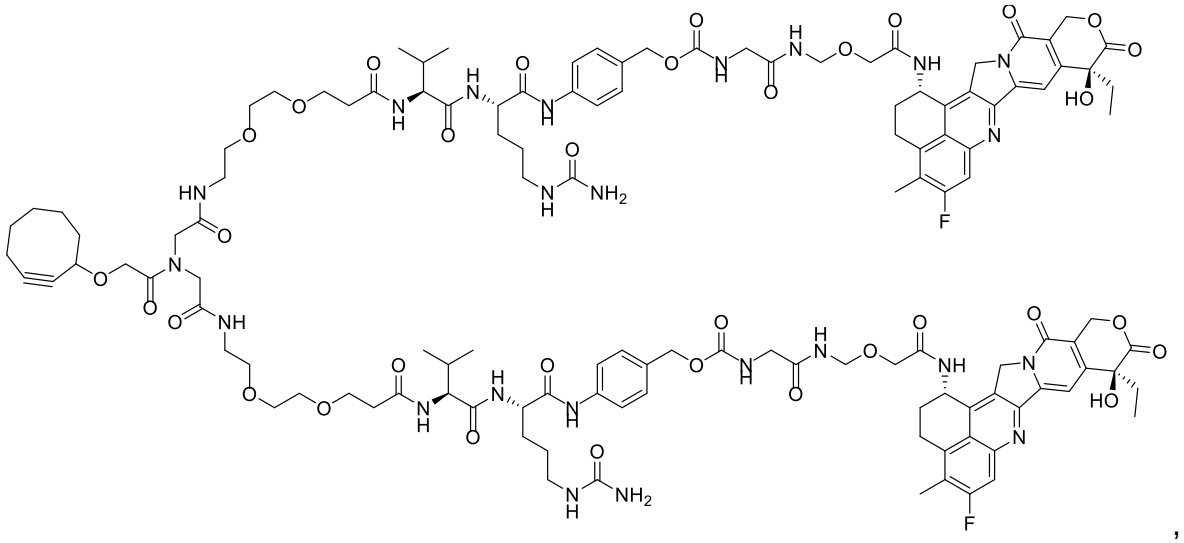
or a pharmaceutically acceptable salt thereof.

[0106] In one example~~embodiment~~, the compound L2-Dxd has a structure selected from the group consisting of:

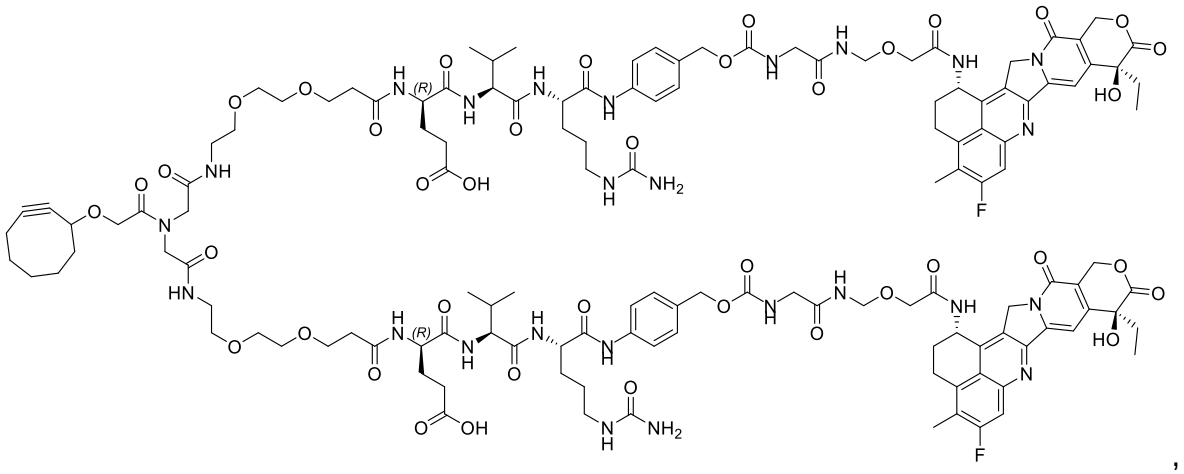
[0107] In one example~~embodiment~~, the compound L2-Dxd has a structure selected from the group consisting of:



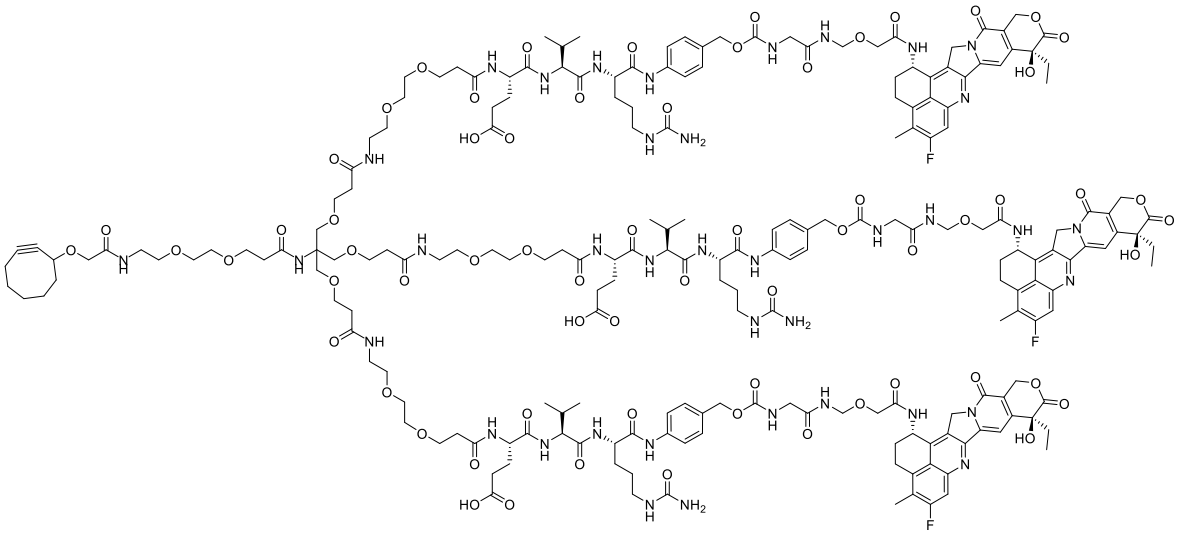
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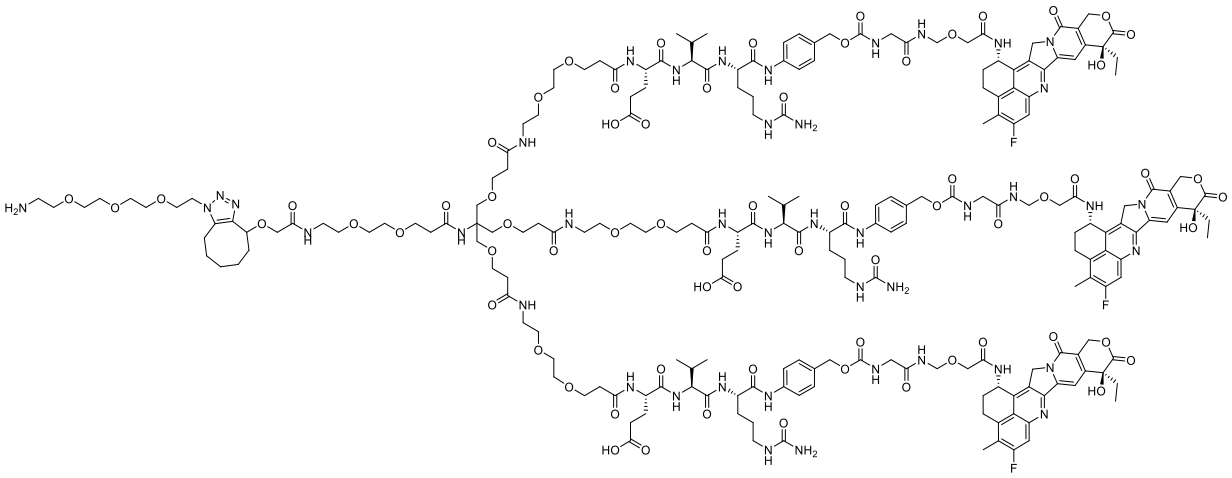
,



,



, and



.

[0108] These and other examples~~aspects~~ of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the disclosure, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0109] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0110] **Figure 1** is a schematic demonstrating two-step site-specific generation of Dxd-ADCs according to an embodiment of the disclosure. The first step is conjugation of one or more first linkers (**L1-B'**) with a glutamine residue on an antibody via a transglutaminase (e.g., MTG)-mediated conjugation reaction. The second step is conjugation of antibody-L1-B to one or more Linker 2-Payloads (**L2P**).

WHAT IS CLAIMED IS:

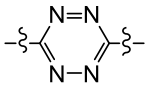
1. A compound having a structure according to Formula (A):

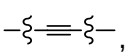
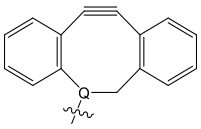
BA-(~~Gln~~-NH-L1-B-(-L2-(-M-Dxd)$_m$)$_k$)$_n$ (A), wherein:

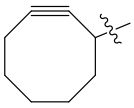
BA is an antibody or an antigen-binding fragment thereof;

~~Gln is a glutamine residue;~~

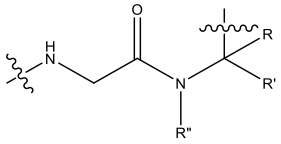
L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

B is a branching unit comprising at least one adduct of group B' and group B", wherein one of the groups B' and B" is selected from -N_3 and 

; and the other of the groups B' and B" is selected from , 

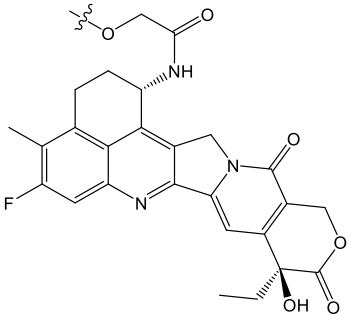
; and , where Q is C or N;

L2 is a second linker covalently attached to the branching unit B via the at least one group B";

M is absent or a moiety having the structure 

, where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):



(P);

k is an integer from 1 to 12;

m is an integer from 1 to 30, and

n is an integer from 1 to 30.

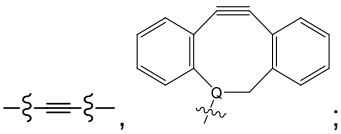
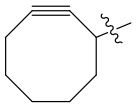
2. A compound having a structure according to Formula (I):

BA-(~~Gln~~-NH-L1-B-(-L2-M-Dxd)$_k$)$_n$ (I), wherein:

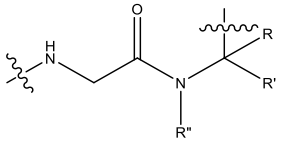
BA is an antibody or an antigen-binding fragment thereof;

~~Gln is a glutamine residue;~~

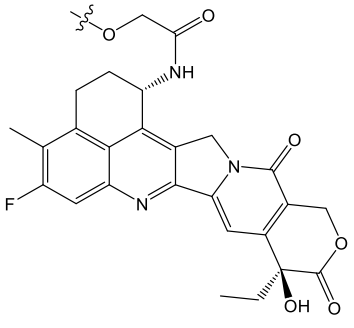
L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

B is a branching unit comprising at least one adduct of group B', where the group B' is selected from -N_3, ; and , where Q is C or N;

L2 is a second linker covalently attached to the branching unit B via at least one group B", wherein the group B' and the group B" form the at least one adduct;

M is absent or a moiety having the structure , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):

 (P);

k is an integer from 1 to 12, and

n is an integer from 1 to 30.

~~3. The compound of claims 1 or 2, wherein the BA is an antibody or an antigen-binding fragment thereof.~~

~~4.~~3. The compound of claim 1 or claim 2~~any of claims 1-3~~, wherein the BA is an anti-HER2 antibody, an anti-STEAP2 antibody, an anti-MET antibody, an anti-EGFRVIII antibody, an anti-MUC16 antibody, an anti-PRLR antibody, an anti-PSMA antibody, an anti-FGFR2 antibody, an anti-FOLR1 antibody, an anti-HER2/HER2 bispecific antibody, an anti-MET/MET bispecific antibody, or an antigen-binding fragment thereof.

5. The compound of any of claims 1-3, wherein the BA is an anti-HER2/HER2 bispecific antibody.

6. The compound of claim 5, wherein the anti-HER2/HER2 bispecific antibody comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human HER2; and

wherein D2 specifically binds a second epitope of human HER2.

7. The compound of claim 6, wherein D1 and D2 do not compete with one another for binding to human HER2.

8. The compound of any of claims 1-4, wherein the BA is an anti-STEAP2 antibody comprising an HCVR/LCVR amino acid sequence pair as set forth in Table 1.

9. The compound of claim 7, wherein the anti-STEAP2 comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs:2/10; 18/26; 34/42; 50/58; 66/58; 74/58; 82/58; 90/58; 98/58; 106/114; 122/130; 138/146; 154/162; 170/178; 186/194; 202/210; 218/226; 234/242; 250/258; 266/274; 282/290; 298/306; 314/322; 330/338; 346/354; 362/370; and 378/386.

10. The compound of any of claims 1-4, wherein the BA is an anti-MET/MET bispecific antibody.

11. The compound of claim 10, wherein the anti- MET/MET bispecific antibody comprises:

a first antigen-binding domain (D1); and

a second antigen-binding domain (D2);

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET.

12. The compound of claim 11, wherein D1 and D2 do not compete with one another for binding to human MET.

~~13. The compound of any of claims 1-4 and 10-12, wherein the BA is an anti-MET/MET bispecific antibody comprising an HCVR/LCVR amino acid sequence pair as set forth in Table 3.~~

~~14. The compound of any of claims 1-4 and 10-13, wherein the BA is an anti-MET/MET bispecific antibody comprising a D1 antigen-binding domain and a D2 antigen-binding domain, wherein the D1 antigen binding domain comprises an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2012/2092, or a set of heavy and light chain CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) comprising SEQ ID NOs: 2014-2016-2018-2094-2096-2098, and wherein the D2 antigen-binding domain comprises an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2036/2092, or a set of heavy and light chain CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) comprising SEQ ID NOs: 2038-2040-2042-2094-2096-2098.~~

~~15. The compound of any of claims 1-4 and 10-13, wherein the BA is an anti-MET/MET bispecific antibody H4H14639D, which comprises a D1 derived from H4H13306P2 and a D2 derived from H4H13312P2.~~

~~16.~~4. The compound of any of claims 1-~~9~~3, wherein the glutamine residue ~~Gln~~ is naturally present in a CH2 or CH3 domain of the BA, or wherein the glutamine residue is introduced to the BA by modifying one or more amino acids.

~~17. The compound of any of claims 1-9, wherein the glutamine residue Gln is introduced to the BA by modifying one or more amino acids.~~

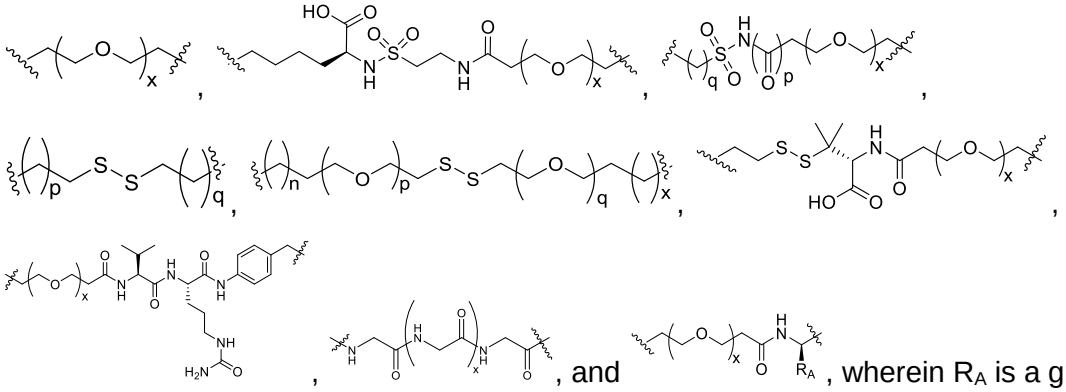
~~18.~~5. The compound of claim any of claims 1-~~9~~3, wherein the ~~Gln~~ glutamine residue is Q295 or N297Q.

~~19.~~6. The compound of any of claims 1-~~18~~5, wherein the BA targets a cancer selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, lung cancer, liver cancer, or brain cancer.

~~20.~~7. The compound of any of claims 1-~~19~~6, wherein L1 comprises C_{1-6} alkyl, phenyl, -NH-, -C(O)-, $-(CH_2)_u$-NH-C(O)-, $-(CH_2)_u$-C(O)-NH-, $-(CH_2-CH_2-O)_v$-, $-(CH_2)_u-(O-CH_2-CH_2)_v$-

C(O)-NH-, a peptide unit comprising from 2 to 4 amino acids, or combinations thereof, each of which may be optionally substituted with one or more of -S-, -S(O_2)-, -C(O)-, -C(O_2)-; and CO_2H, wherein subscripts u and v are independently an integer from 1 to 8.

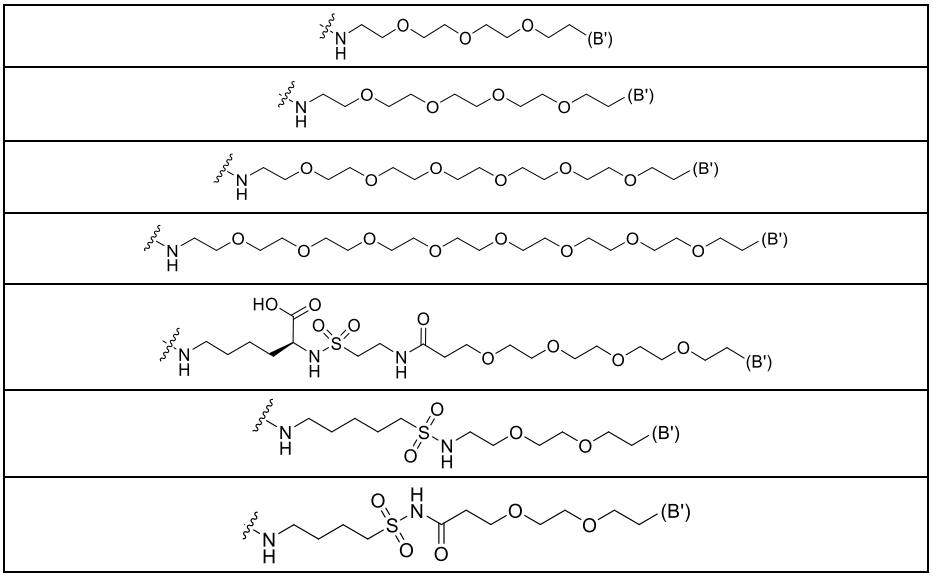
~~21.~~8. The compound of claim 1, wherein L1 is selected from the group consisting of:

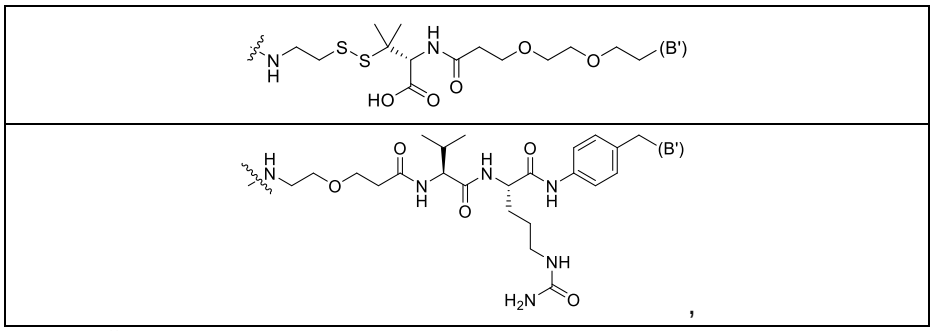


, and , wherein R_A is a group comprising an alkyne, an azide, a tetrazine, a trans-cyclooctene, a maleimide, an amine, a ketone, an aldehyde, a carboxylic acid, an ester, a thiol, a sulfonic acid, a tosylate, a halide, a silane, a cyano group, a carbohydrate group, a biotin group, a lipid residue and wherein subscripts x, n, p and q are independently an integer from 0 to 12, and combinations thereof.

~~22.~~9. The compound of any of claims 1-~~21~~8, wherein B comprises one adduct of group B'.

~~23.~~10. The compound of claim ~~22~~9, wherein -NH-L1-B' is selected from the group consisting of:





where the  is the amino point of attachment to the glutamine residue of the BA.

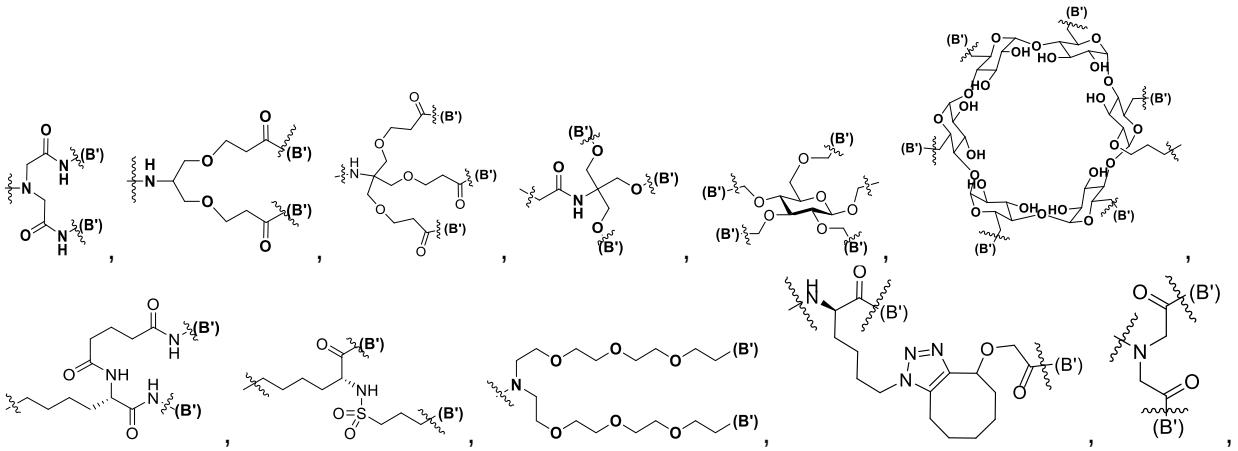
~~24. The compound of claim 23, wherein the group B' is an azide (-N_3), and the adduct of the group B' comprises a triazole.~~

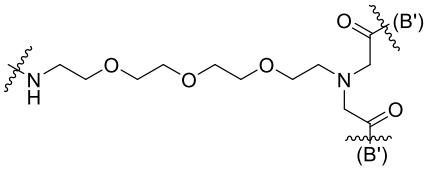
~~25.~~11. The compound of any of claims 1-~~21~~8, wherein B comprises two adducts of group B', or wherein B comprises three adducts of group B', or wherein B comprises at least four adducts of group B'.

~~26. The compound of any of claims 1-21, wherein B comprises three adducts of group B'.~~

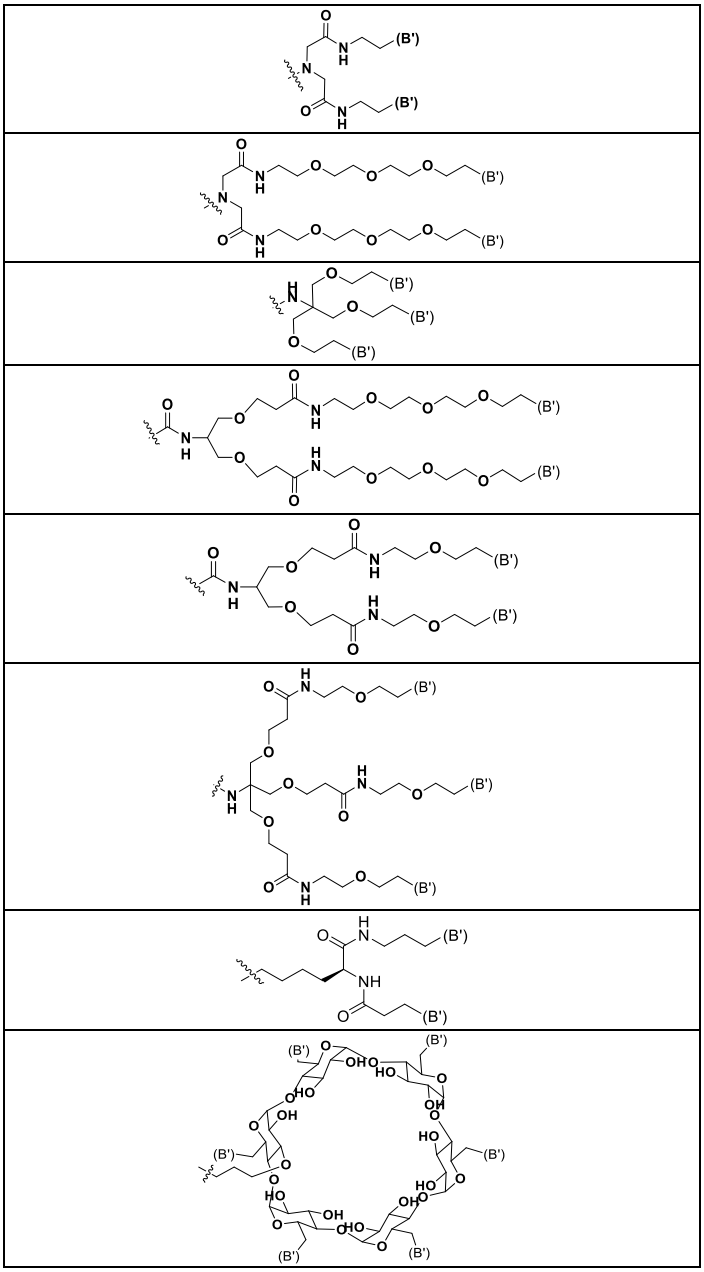
~~27. The compound of any of claims 1-21, wherein B comprises at least four adducts of group B'.~~

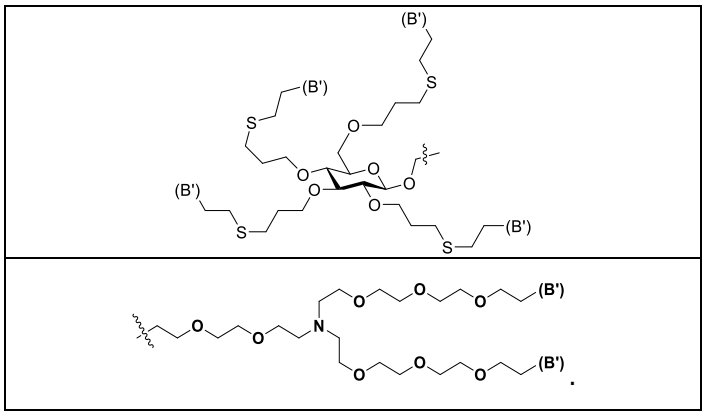
~~28.~~12. The compound of any of claims 1-~~21~~8, wherein B comprises a group selected from the group consisting of:



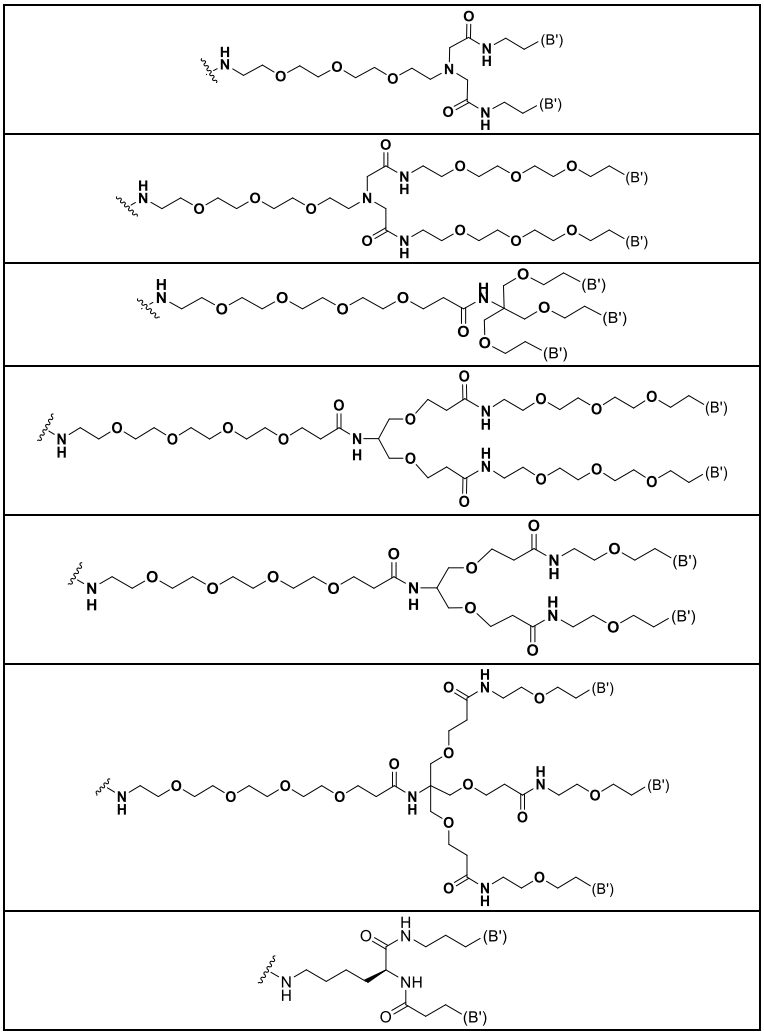
and  , where (B’) comprises points of attachment of the adduct of the group B’ and the group B”.

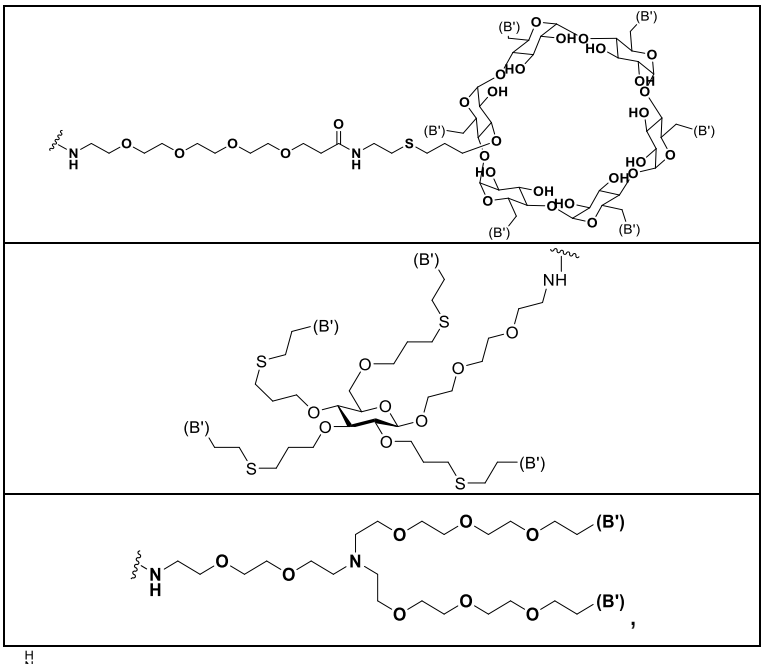
~~29.~~13. The compound of claim ~~28~~12, wherein B is selected from the group consisting of:





~~30.~~14. The compound of claim 1, wherein -NH-L1-B is selected from the group consisting of:

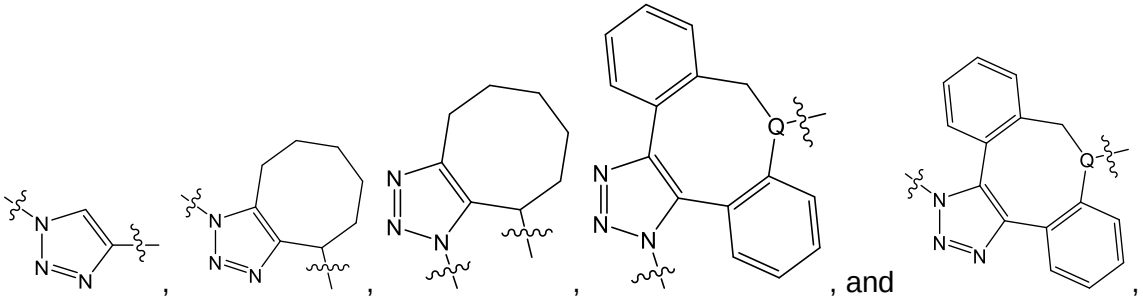




where the  is the amino point of attachment to the glutamine residue of the BA.

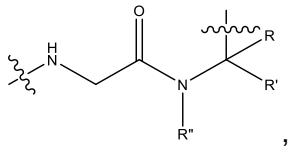
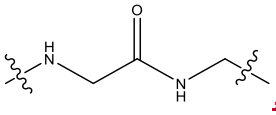
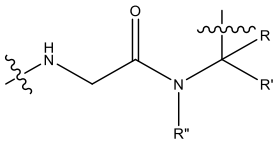
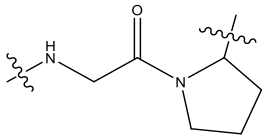
~~31.~~15. The compound of claim ~~30~~10 or claim 14, wherein the group B' is an azide ($-N_3$), and the adduct of the group B' and the group B" comprises a triazole.

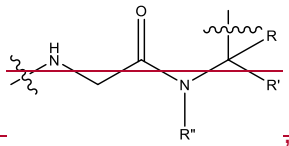
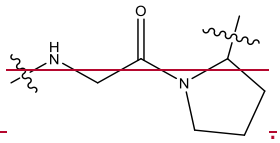
~~32.~~16. The compound of any of claims 1-~~31~~15, wherein the adduct of the group B' and the group B" has a structure selected from the group consisting of:



wherein Q is C or N.

~~33.~~17. The compound of any of claims 1-~~32~~16, wherein M is absent.

~~34.~~18. The compound of any of claims 1-~~32~~16, wherein M is , where R, R', and R" are hydrogens at each occurrence, i.e. M is , or wherein M is , where R is hydrogen and R' and R" together form a 5-membered ring, i.e. M is .

~~35. The compound of any of claims 1-32, wherein M is~~  ~~, where R is hydrogen and R' and R" together form a 5-membered ring, i.e. M is~~  ~~.~~

~~36.~~19. The compound of any of claims 1-~~35~~18, wherein n is 2, or n is 4, or n is 8, or n is 12, or n is 16, or n is 24.

~~37. The compound of any of claims 1-35, wherein n is 4.~~

~~38. The compound of any of claims 1-35, wherein n is 8.~~

~~39. The compound of any of claims 1-35, wherein n is 12.~~

~~40. The compound of any of claims 1-35, wherein n is 16.~~

~~41. The compound of any of claims 1-35, wherein n is 24.~~

~~42.~~20. The compound of any of claims 1-~~41~~19, wherein L2 has a structure according to Formula (L2):

$$B''\text{-}SP1\text{-}B2\text{-}(\text{-}SP2\text{-}AA\text{-}SP3)_p \quad (L2),$$

wherein:

B" is a group capable of covalently attaching to the group B';

SP1 is absent or a first spacer unit;

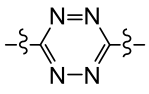
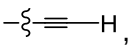
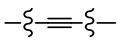
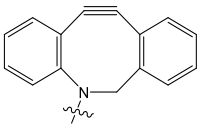
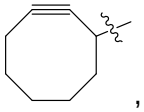
B2 is absent or a branching unit;

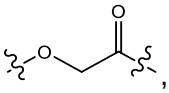
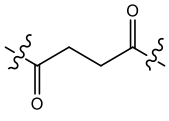
SP2 is absent or a second spacer unit;

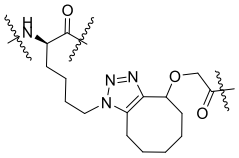
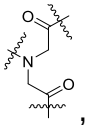
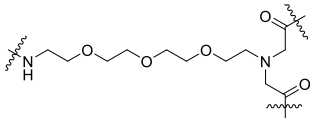
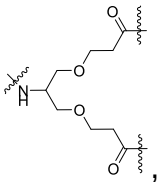
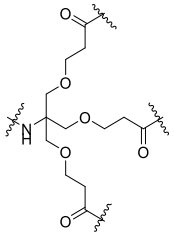
AA is absent or a peptide unit comprising from 2 to 4 amino acids;

SP3 is absent or a third spacer unit covalently attached to the Dxd, and

p is an integer from 1 to 12.

~~43.~~21. The compound of claim ~~42~~20, wherein the at least one group B" is selected from the group consisting of $-N_3$, , , , , , and combinations thereof.

~~44.~~22. The compound of any of claims ~~42~~ 20 or ~~43~~21, wherein SP1 is absent or selected from the group consisting of , , $C_{1\text{-}6}$ alkyl, $-(CH_2\text{-}CH_2\text{-}O)_v$-, -NH-, -C(O)-, -NH-C(O)-, -NH-$(CH_2)_u$-, -NH-$(CH_2)_u$-C(O)-, -NH-$(CH_2\text{-}CH_2\text{-}O)_v$-, -NH-$(CH_2\text{-}CH_2\text{-}O)_v$-C(O)-, -NH-$(CH_2\text{-}CH_2\text{-}O)_v$-$(CH_2)_u$-, -NH-$(CH_2\text{-}CH_2\text{-}O)_v$-$(CH_2)_u$-C(O)-, -$(CH_2)_u$-NH-C(O)-, -NH-$(CH_2)_u$-NH-C(O)-, -NH-$(CH_2)_u$-C(O)-NH-, or combinations thereof; wherein subscripts u and v are independently an integer from 1 to 8.

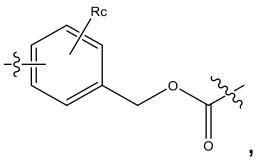
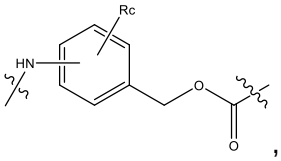
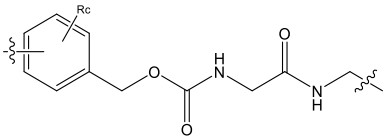
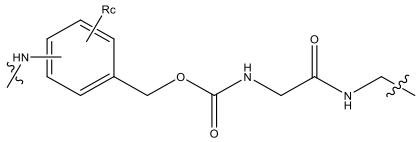
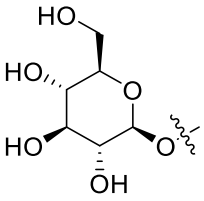
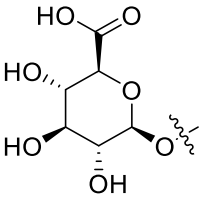
45.23. The compound of any of claims 4220-4422, wherein B2 is absent or selected from the group consisting of , , , , and .

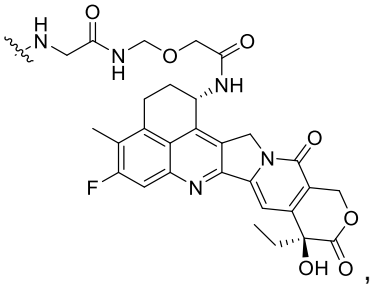
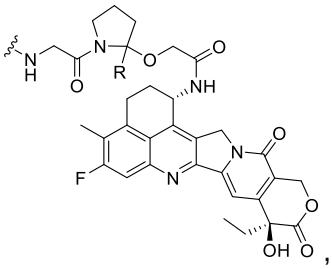
46.24. The compound of any of claims 4220-4422, wherein SP2 is absent or selected from the group consisting of a C_{1-6} alkyl, -$(CH_2$-CH_2-$O)_v$-, -NH-, -C(O)-, -NH-C(O)-, -NH-$(CH_2)_u$-, -NH-$(CH_2)_u$-C(O)-, -NH-$(CH_2$-CH_2-$O)_v$-, -NH-$(CH_2$-CH_2-$O)_v$-C(O)-, -NH-$(CH_2$-CH_2-$O)_v$-$(CH_2)_u$-, -NH-$(CH_2$-CH_2-$O)_v$-$(CH_2)_u$-C(O)-, -$(CH_2)_u$-NH-C(O)-, -NH-$(CH_2)_u$-NH-C(O)-, -NH-$(CH_2)_u$-C(O)-NH-, or combinations thereof; wherein subscripts u and v are independently an integer from 1 to 8.

47.25. The compound of any of claims 4220-4523, wherein AA is a peptide unit comprising from 2 to 4 amino acids selected from glycine, valine, phenylalanine, proline, glutamic acid, lysine, phenylalanine, and citrulline, and combinations thereof.

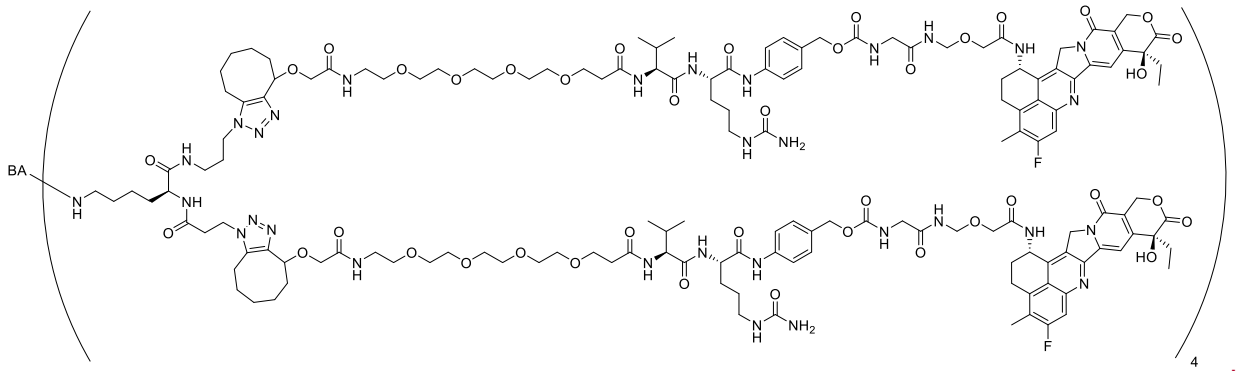
48.26. The compound of claim 4725, wherein AA is selected from the group consisting of valine-citrulline, valine-alanine, or phenylalanine-lysine, glycine-glycine-glycine (GGG), glycine-glycine-glycine-glycine (GGGG (SEQ ID NO: 2113)), glycine-glycine-phenylalanine (GGF), glycine-glycine-phenylalanine-glycine (GGFG (SEQ ID NO: 2114)), L-glutamic acid-valine-citrulline (^{L}EVC), and D-glutamic acid-valine-citrulline (^{D}EVC).

~~49. The compound of claim 47, wherein AA is selected from the group consisting of glycine-glycine-glycine (GGG), glycine-glycine-glycine-glycine (GGGG (SEQ ID NO: 2113)), glycine-glycine-phenylalanine (GGF), glycine-glycine-phenylalanine-glycine (GGFG (SEQ ID NO: 2114)), L-glutamic acid-valine-citrulline (^{L}EVC), and D-glutamic acid-valine-citrulline (^{D}EVC).~~

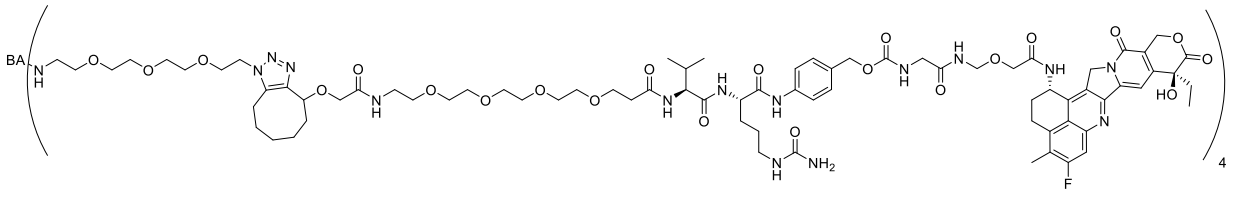
~~50.~~27. The compound of any of claims ~~42~~20-~~49~~26, wherein SP3 is absent or selected from the group consisting of , , , , and combinations thereof, wherein R_c is independently at each occurrence absent or a group selected from  and .

~~51.~~28. The compound of any of claims 1-~~50~~27, wherein the M-Dxd has a structure selected from the group consisting of , and , wherein R is a hydrogen or a C_1-C_4 alkyl, and where ~~~ represents the point of attachment to L2 or L2'.

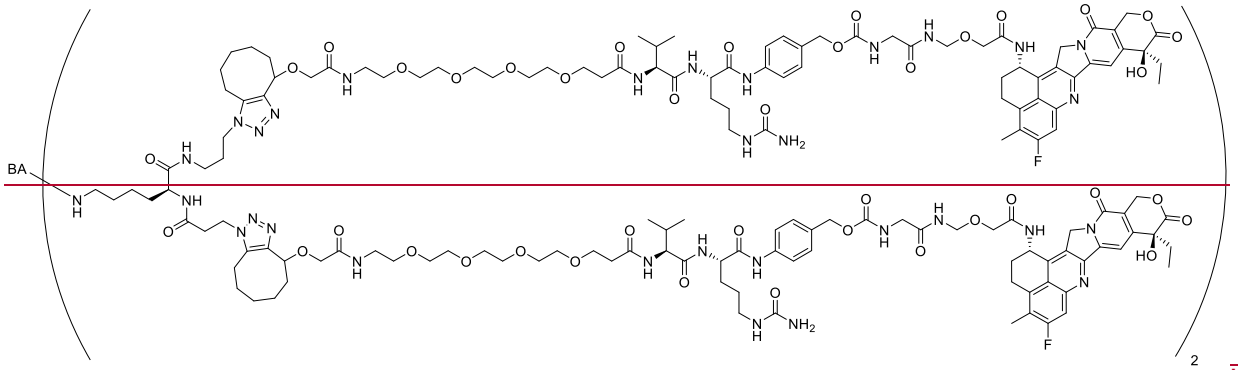
~~52.~~29. The compound of claim 1 or 2 having a structure:



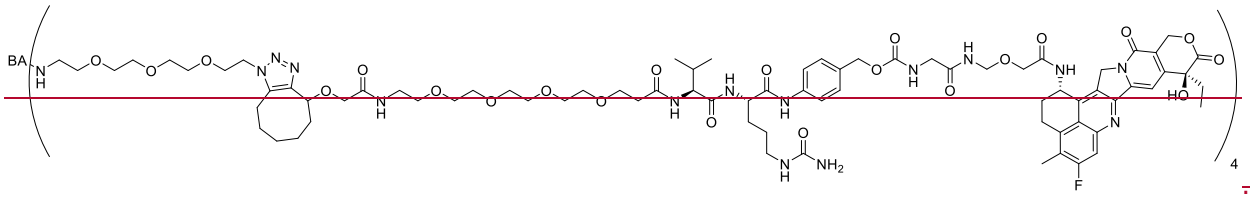
or



~~53. The compound of claim 1 or 2 having a structure:~~



~~54. The compound of claim 1 or 2 having a structure:~~



~~55.~~30. A compound having a structure according to Formula (I):

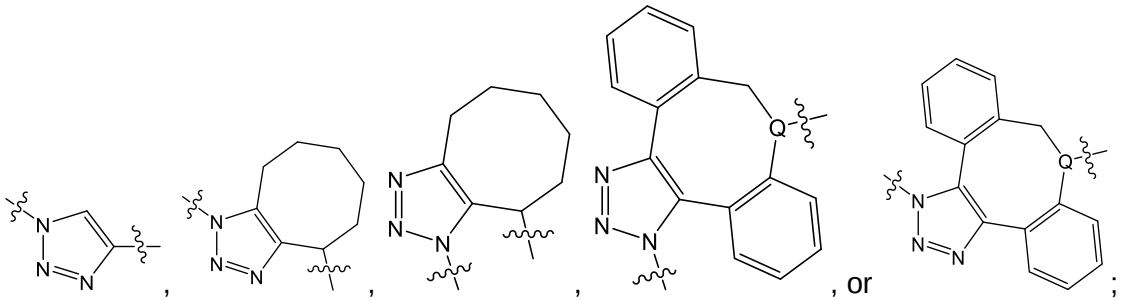
BA-(~~ Gln-~~NH-L1-B-(-L2-M-Dxd)$_k$)$_n$ (I), wherein:

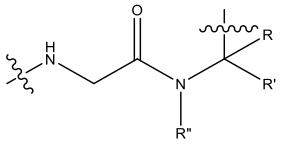
BA is an antibody or an antigen-binding fragment thereof;

~~Gln is a glutamine residue;~~

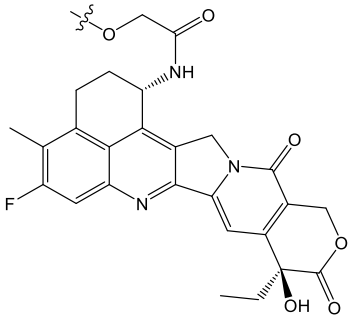
L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

B is a branching unit comprising


, or ;

M is absent or a moiety having the structure  , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent having a structure according to Formula (P):


(P);

k is an integer from 1 to 12, and

n is an integer from 1 to 30.

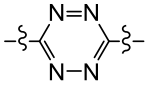
~~56.~~31. A compound according to Formula (L2-P), (L2'-P), or (L2"-P):

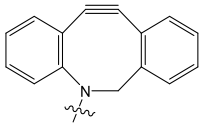
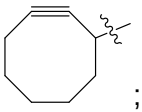
B”-SP1-B2-(-SP2-AA-SP3-M-Dxd)p (L2-P),

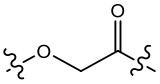
H_2N-SP1-B2-(-SP2-AA-SP3-M-Dxd)$_p$ (L2’-P),

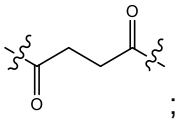
maleimide-N-SP1-B2-(-SP2-AA-SP3-M-Dxd)$_p$ (L2”-P),

wherein:

B” is selected from the group consisting of -N_3, , , ,

 and ;

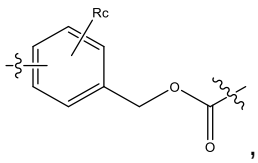
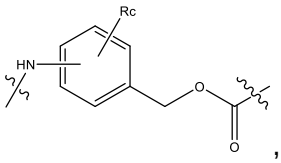
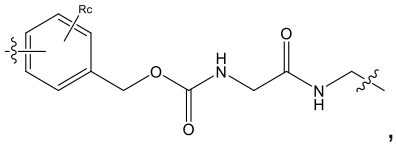
SP1 is absent or a first spacer unit selected from the group consisting of 

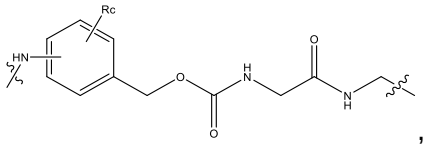
and ;

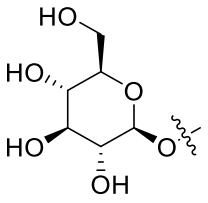
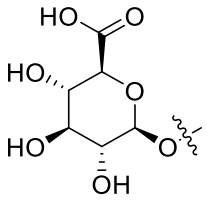
SP2 is absent or a second spacer unit selected from the group consisting of a C_{1-6} alkyl, -(CH_2-CH_2-O)$_v$-, -NH-, -C(O)-, -NH-C(O)-, -NH-(CH_2)$_u$-, -NH-(CH_2)$_u$-C(O)-, -NH-(CH_2-CH_2-O)$_v$-, -NH-(CH_2-CH_2-O)$_v$-C(O)-, -NH-(CH_2-CH_2-O)$_v$-(CH_2)$_u$-, -NH-(CH_2-CH_2-O)$_v$-(CH_2)$_u$-C(O)-, -(CH_2)$_u$-NH-C(O)-, -NH-(CH_2)$_u$-NH-C(O)-, -NH-(CH_2)$_u$-C(O)-NH-, or combinations thereof; wherein subscripts u and v are independently an integer from 1 to 8;

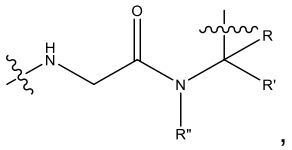
AA is absent or a peptide unit comprising from 2 to 4 amino acids;

SP3 is absent or a third spacer unit selected from the group consisting of,

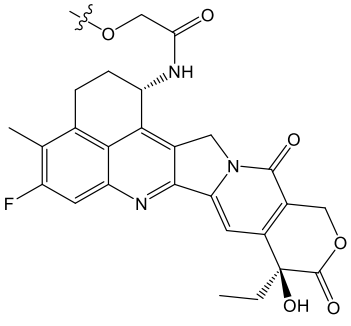
, , ,

, wherein R_c is independently at each occurrence absent

or a group selected from  and ;

M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring; and

Dxd is an anti-tumor agent having a structure according to Formula (P):

 (P), and

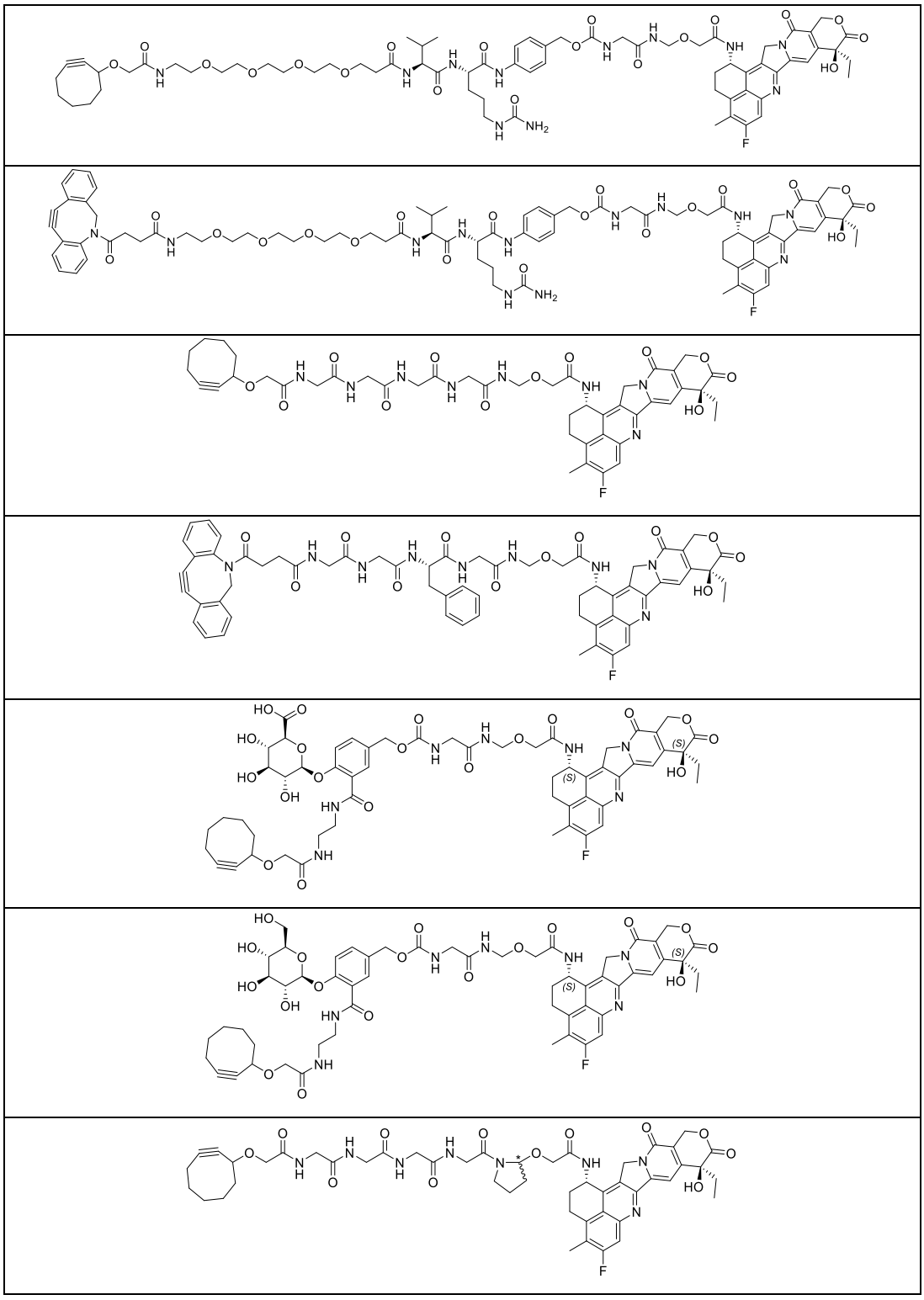
p is an integer from 1 to 12.

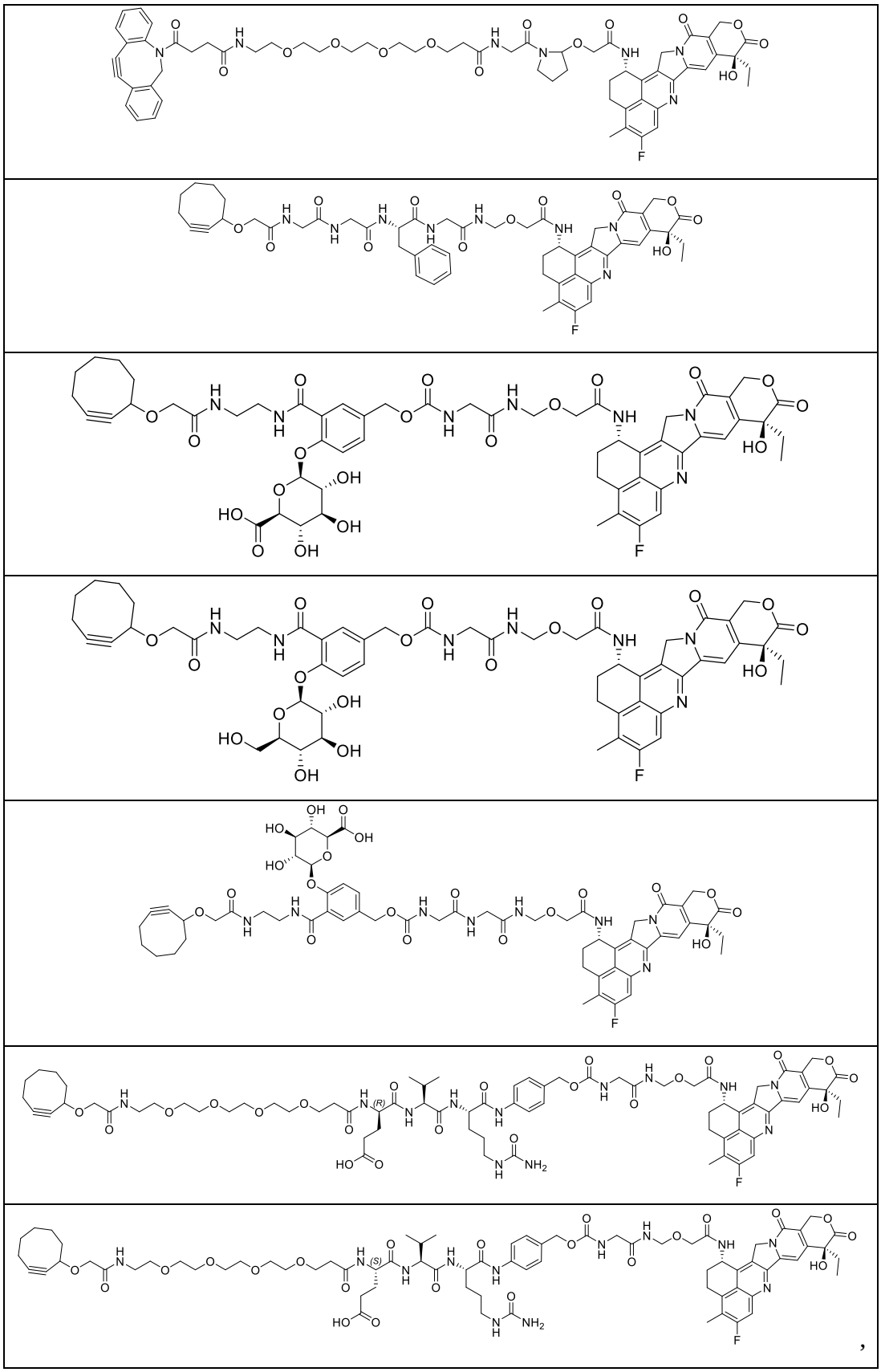
~~57.~~32. The compound of claim ~~56~~31, wherein AA is a peptide unit comprising from 2 to 4 amino acids selected from glycine, valine, phenylalanine, proline, glutamic acid, lysine, alanine and citrulline, and combinations thereof.

~~58.~~33. The compound of claim ~~57~~32, wherein AA is selected from the group consisting of valine-citrulline, valine-alanine, ~~or~~ phenylalanine-lysine, glycine-glycine-glycine (GGG), glycine-glycine-glycine-glycine (GGGG (SEQ ID NO: 2113)), glycine-glycine-phenylalanine (GGF),glycine-glycine-phenylalanine-glycine (GGFG (SEQ ID NO: 2114)) and glutamic acid-valine-citrulline (EVC).

~~59. The compound of claim 57, wherein AA is selected from the group consisting of glycine-glycine-glycine (GGG), glycine-glycine-glycine-glycine (GGGG (SEQ ID NO: 2113)), glycine-glycine-phenylalanine (GGF),glycine-glycine-phenylalanine-glycine (GGFG (SEQ ID NO: 2114)) and glutamic acid-valine-citrulline (EVC).~~

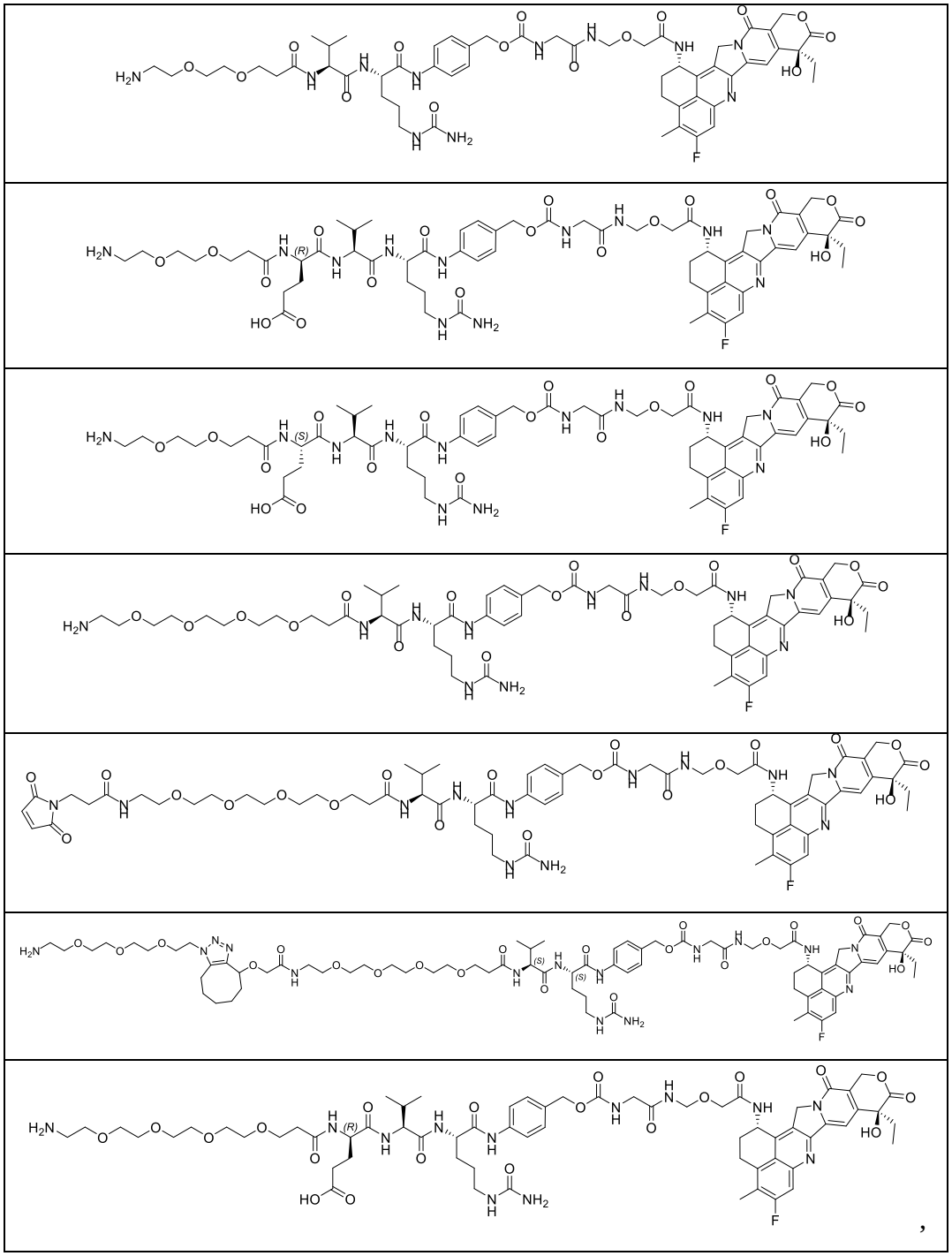
~~60.~~34. The compound of claim ~~56~~31, wherein the compound has a structure according to Formula (L2-P) selected from the group consisting of:

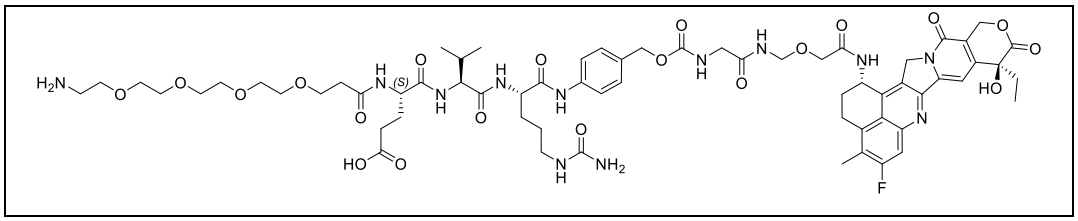




or a pharmaceutically acceptable salt thereof.

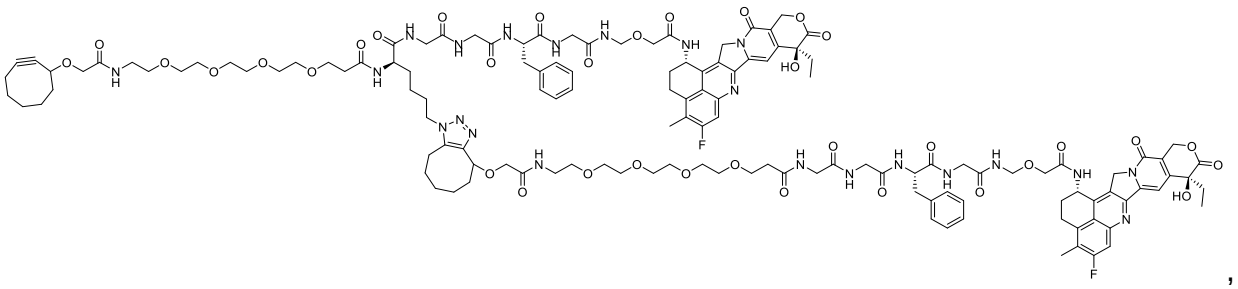
~~61.~~35. The compound of claim ~~56~~31, wherein the compound has a structure according to Formula (L2'-P) or (L2''-P) selected from the group consisting of:



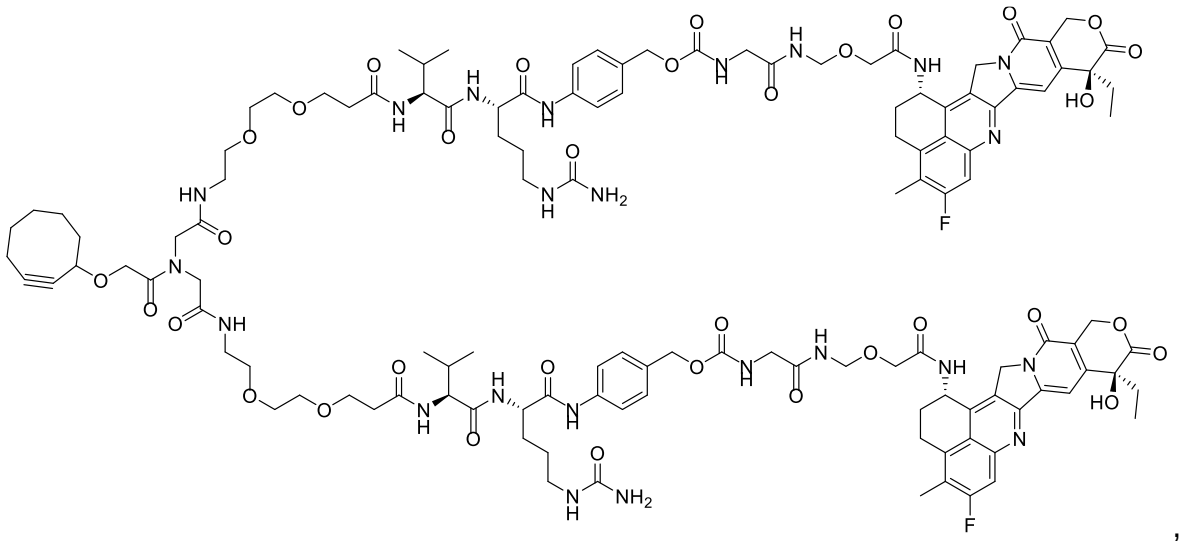


or a pharmaceutically acceptable salt thereof.

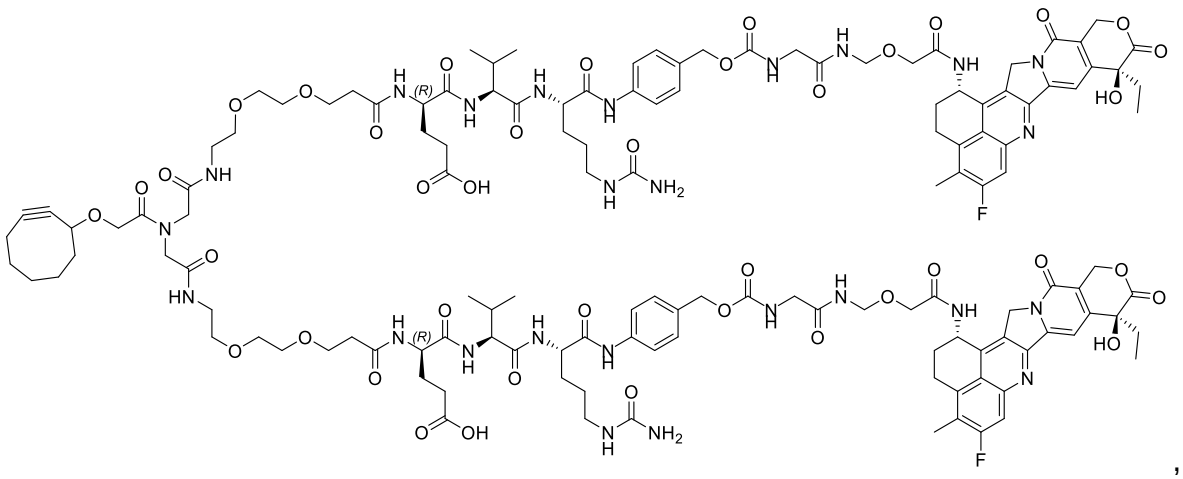
~~62.~~36. The compound of any of claims ~~56~~31, wherein the compound has a structure according to Formula (L2-P), (L2'-P) or (L2"-P) selected from the group consisting of:



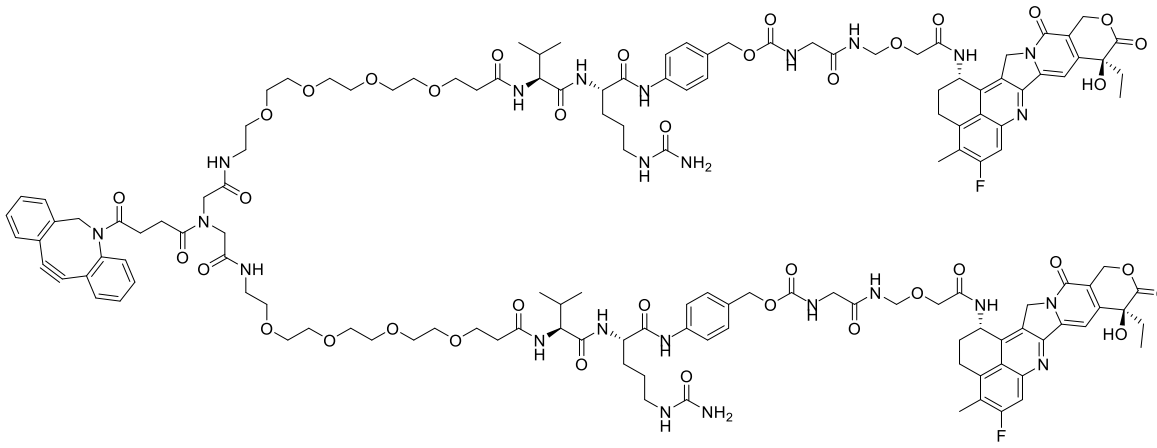
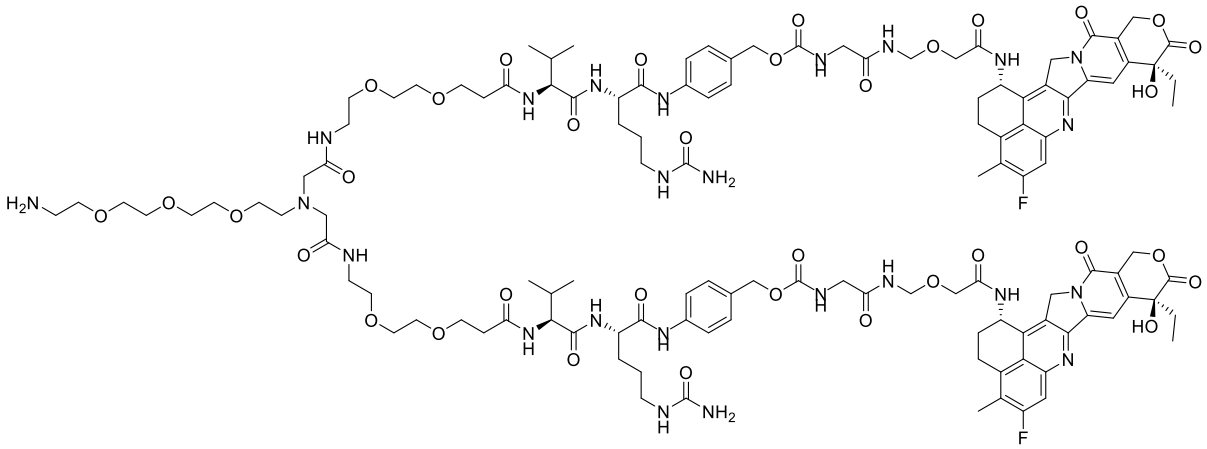
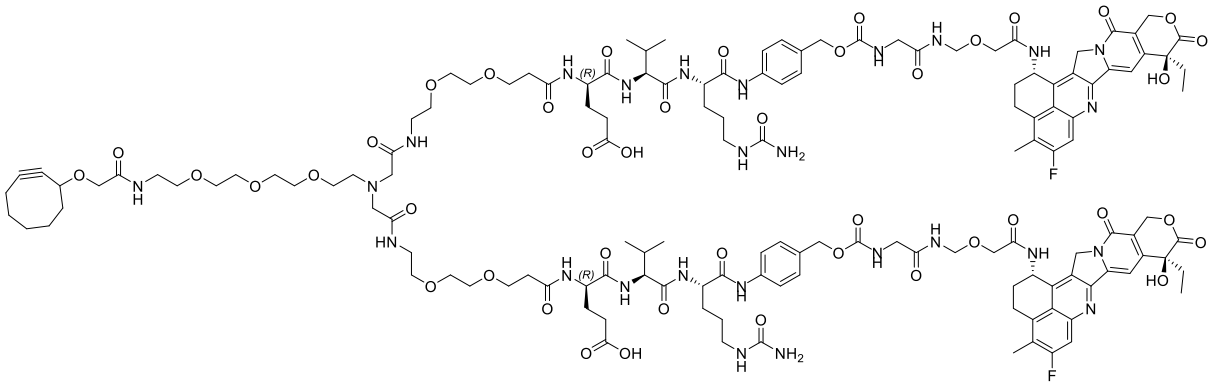
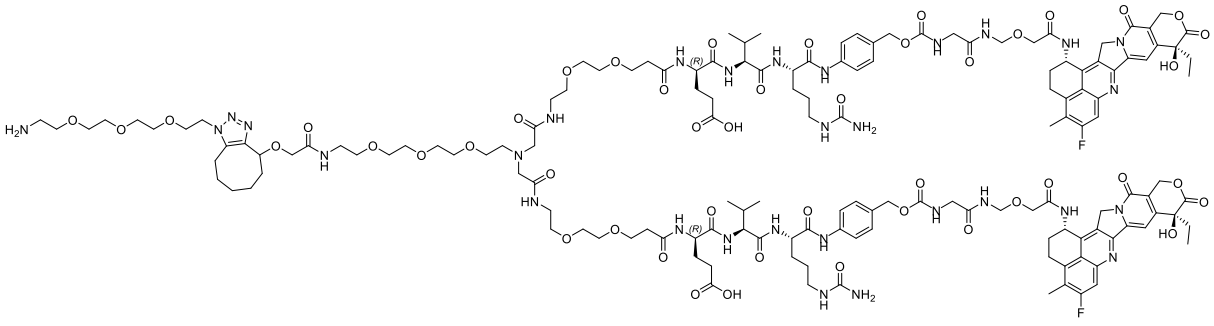
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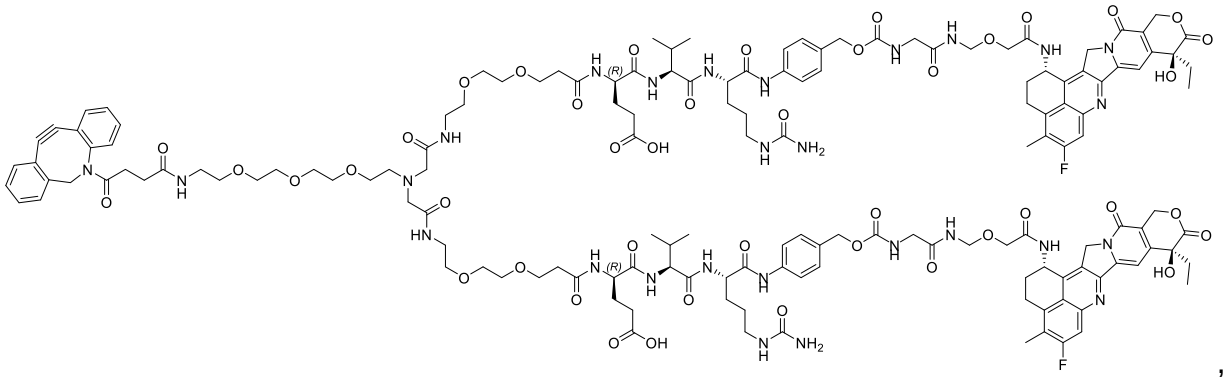
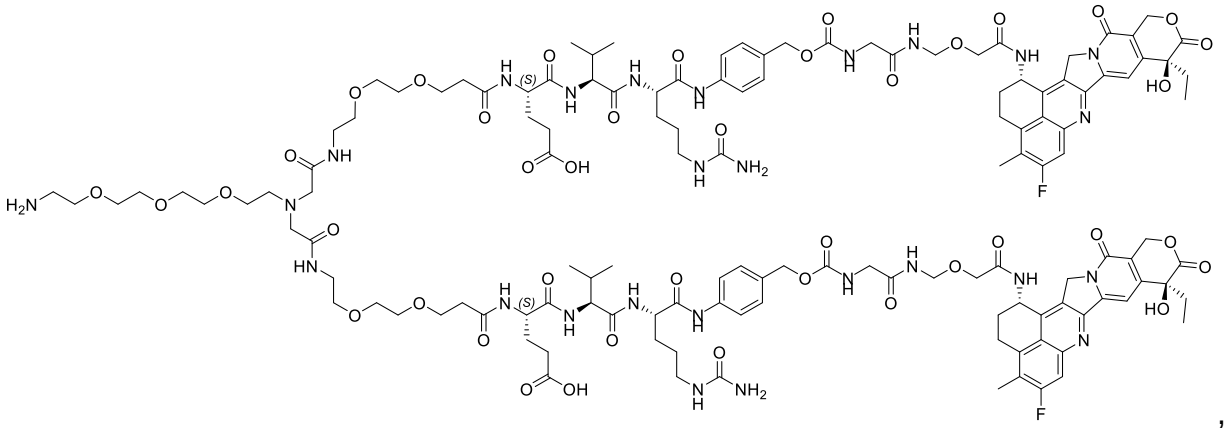
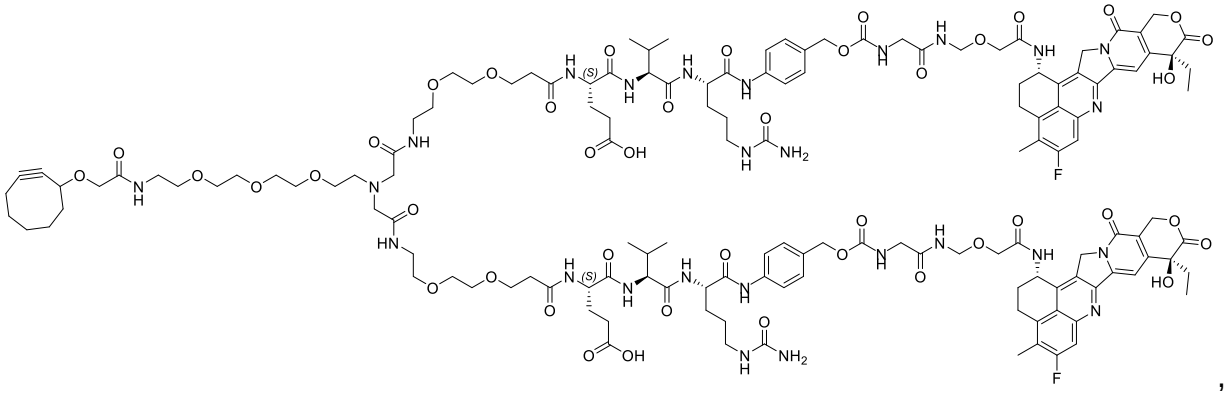
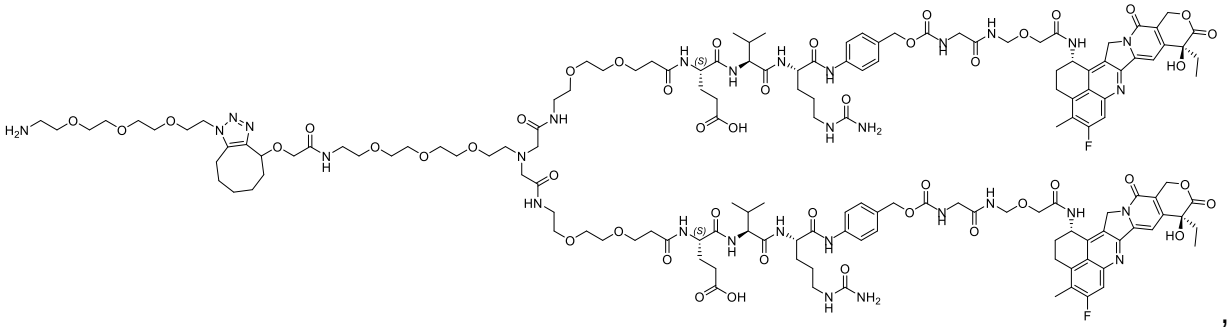


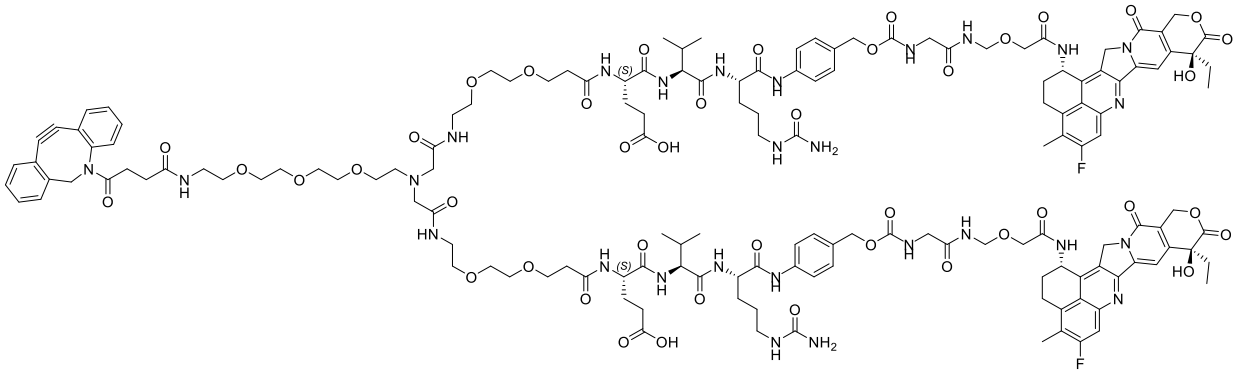
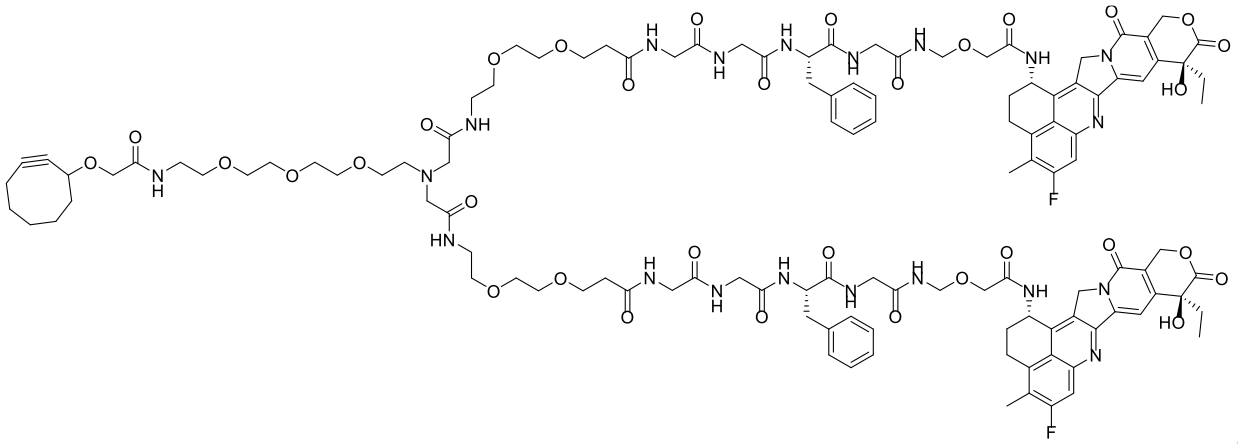
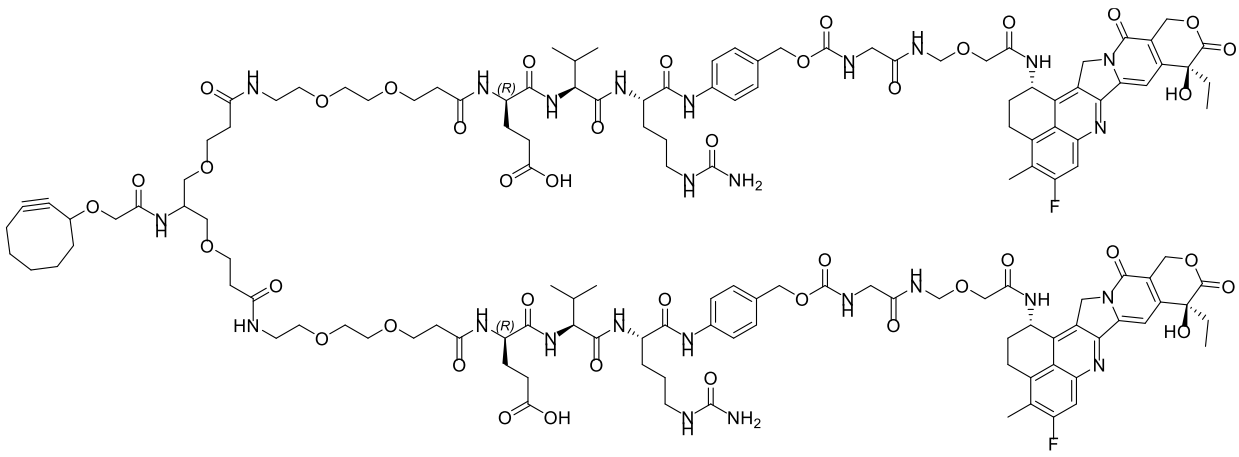
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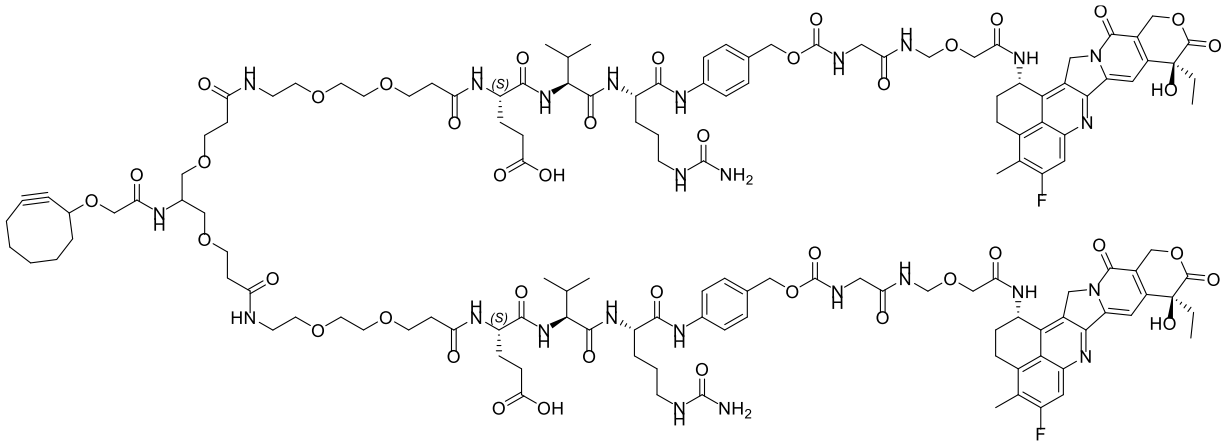


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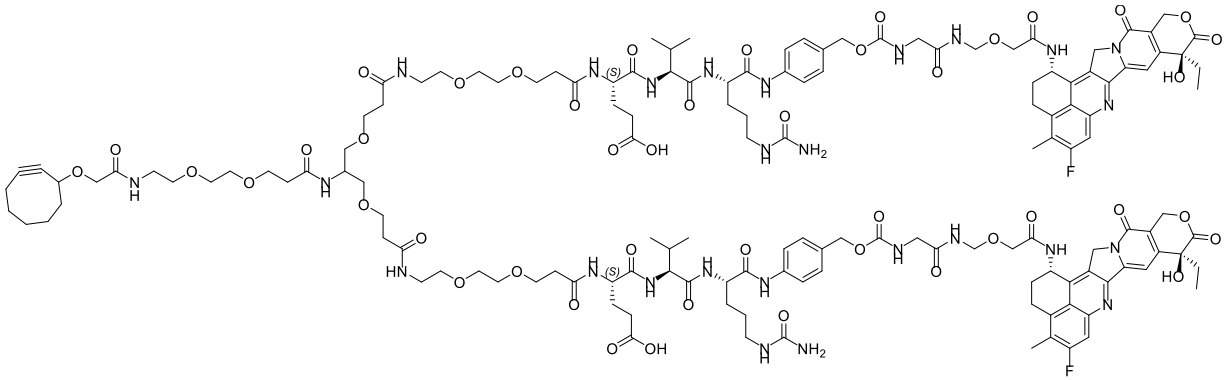

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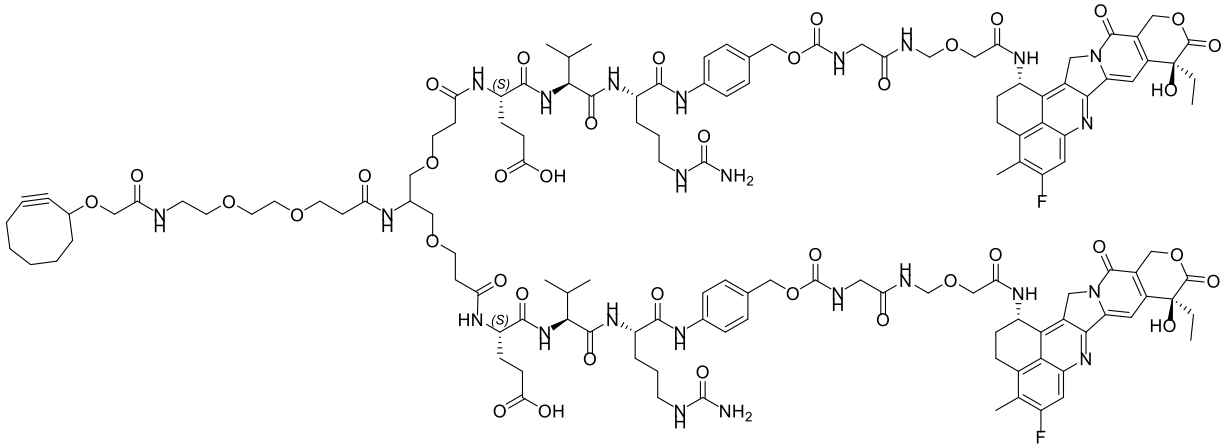

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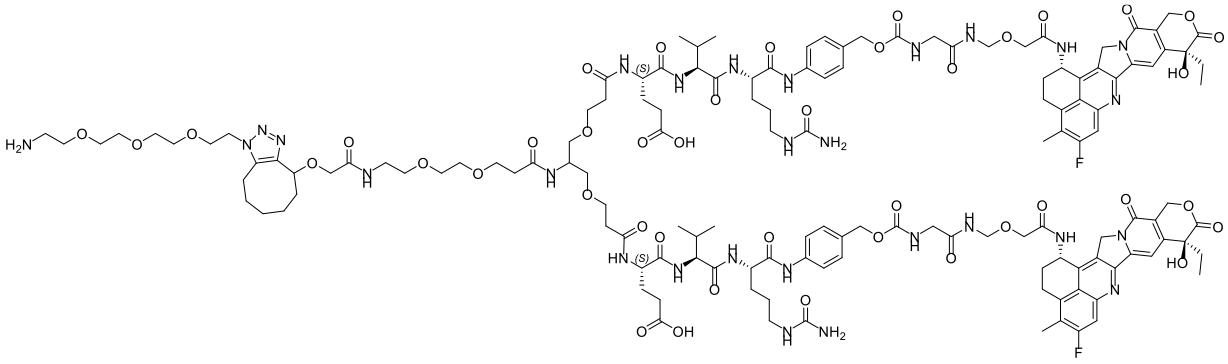
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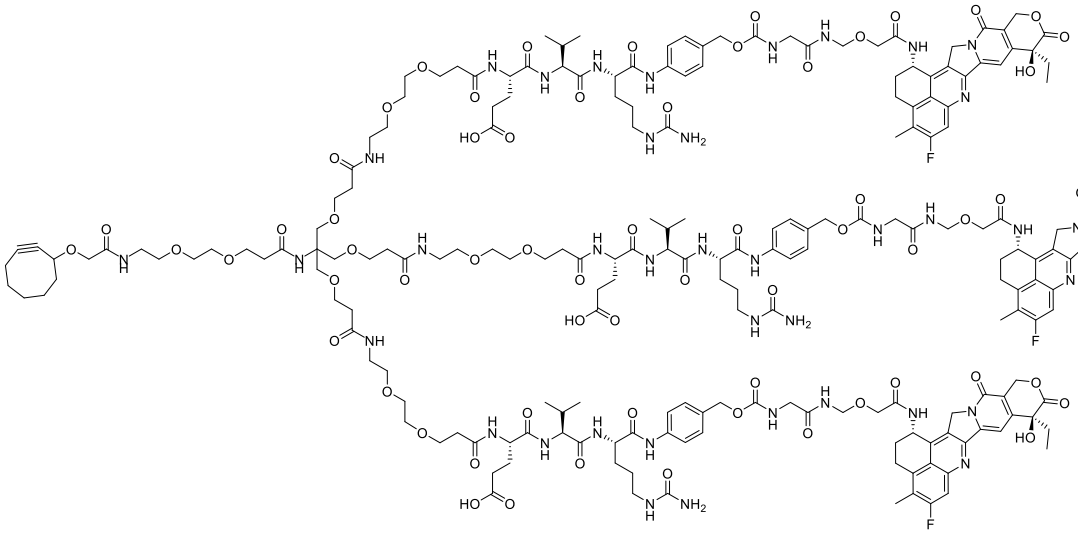
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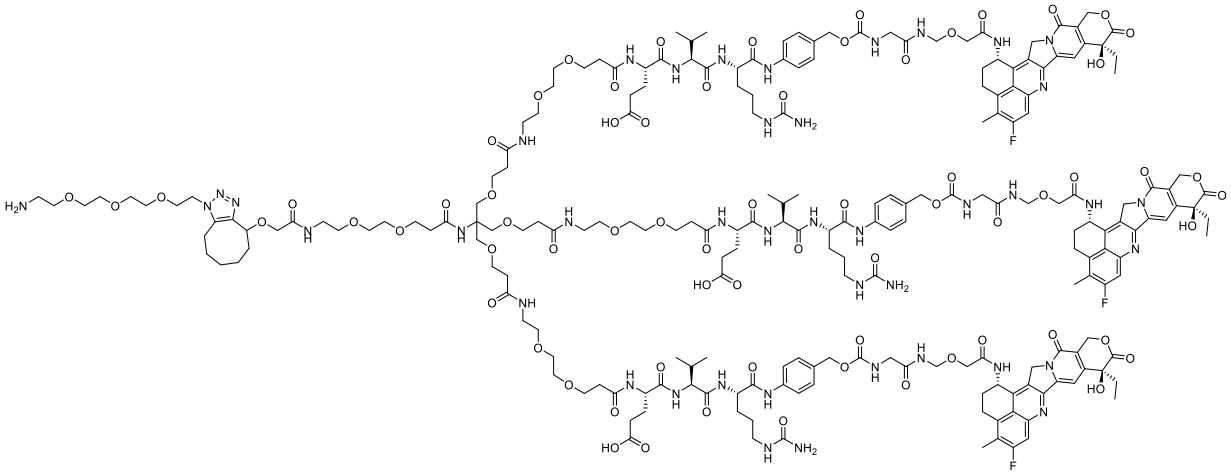
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~~63.~~37. An antibody-drug conjugate according to formula (II):

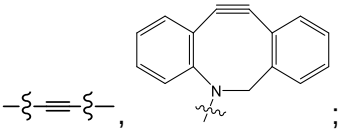
BA-(~~Gln-~~NH-L1-B-(SP1-B2-(-SP2-AA-SP3-M-Dxd)$_k$)$_p$)$_n$ (II),

wherein BA is an antibody;

~~Gln is a glutamine residue;~~

L1 is absent or a first linker linked to said BA through side chain of a glutamine residue;

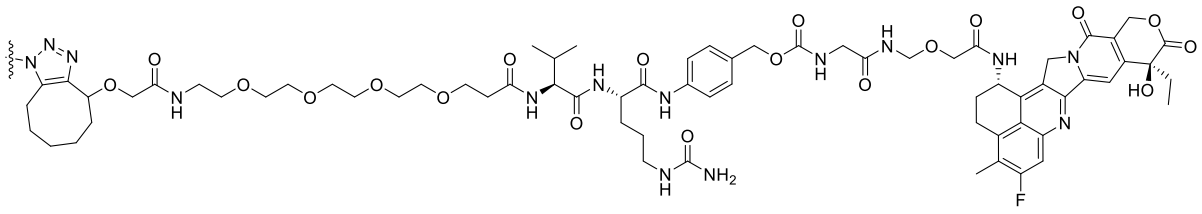
B is a branching unit comprising at least one adduct of group B' and group B", where

the group B' is selected from -N_3, , wherein

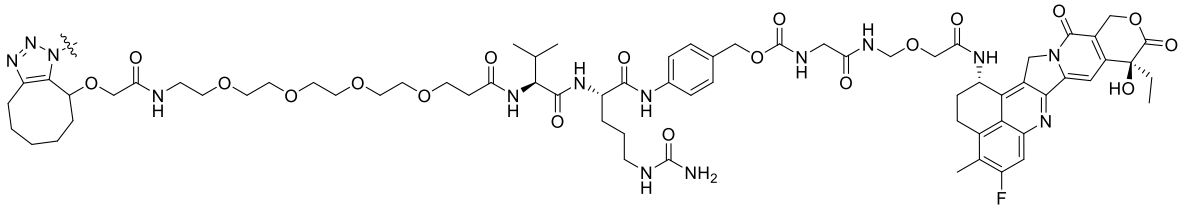
B"-SP1-B2-(-SP2-AA-SP3-M-Dxd)p is the compound according to Formula (L2-P) according to any of claims ~~55~~30-~~60~~34, and wherein the compound of formula (L2-P) is

covalently attached to the antibody via the adduct of the group B' and the group B"; k is an integer from 1 to 12, p is an integer from 1 to 30, and n is an integer from 1 to 30.

~~64.~~38. An antibody-drug conjugate comprising an antibody and a linker-payload, wherein the linker-payload comprises the structure:



, or



,

where ~~~~ represents the point of attachment to the antibody, directly or through a second linker, or a pharmaceutically acceptable salt thereof.

~~65.~~39. A composition comprising a population of compounds according to any one of claims 1-~~61~~35, having a drug-antibody ratio (DAR) of about 0.5 to about 30.0.

~~66.~~40. The composition of claim ~~64~~ 38 having a DAR of about 1.0 to about 2.5, or a DAR of about 3.0 to about 4.5, or a DAR of about 6.5 to about 8.5, or a DAR of about 10 to about 14, or a DAR of about 14 to about 18, or a DAR of about 22 to about 24.5.

~~67.~~41. The composition of claim ~~66~~ 40 having a DAR of about 2, or about 4, or about 8, or about 12, or about 16, or about 24.

~~68. The composition of claim 64 having a DAR of about 3.0 to about 4.5.~~

~~69. The composition of claim 68 having a DAR of about 4.~~

~~70. The composition of claim 64 having a DAR of about 6.5 to about 8.5.~~

~~71. The composition of claim 70 having a DAR of about 8.~~

~~72. The composition of claim 64 having a DAR of about 10 to about 14.~~

~~73. The composition of claim 72 having a DAR of about 12.~~

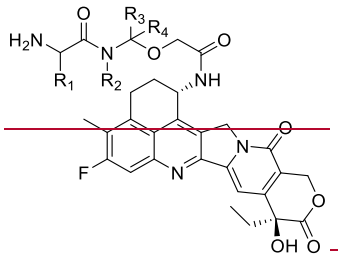
~~74. The composition of claim 64 having a DAR of about 14 to about 18.~~

~~75. The composition of claim 74 having a DAR of about 16.~~

~~76. The composition of claim 64 having a DAR of about 22 to about 24.5.~~

~~77. The composition of claim 76 having a DAR of about 24.~~

~~78. A compound having a structure according to Formula (P-I):~~

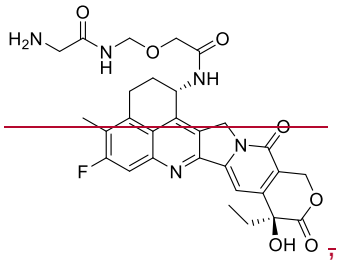


(P-I),

wherein R_1, R_2,R_3, and R_4 are independently a hydrogen or a C_1-C_4 alkyl, or wherein R_2 and R_3 form a 5-membered or a 6-membered ring,

or a pharmaceutically acceptable salt thereof.

79. The compound of claim 64, wherein the compound is

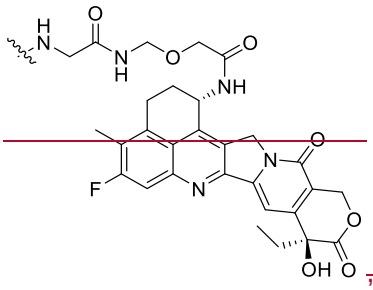


,

or a pharmaceutically acceptable salt thereof.

80. An antibody-drug conjugate comprising an antibody, a linker, and a payload, wherein the payload is the compound of claim 79.

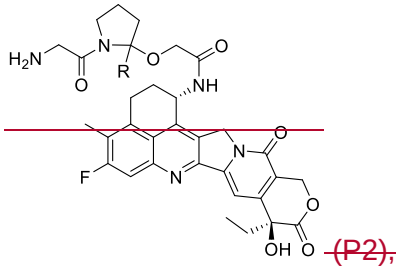
81. An antibody-drug conjugate comprising an antibody, a linker, and a payload, wherein the payload is



, or a pharmaceutically acceptable salt thereof,

where ~~~ represents the point of attachment to the linker.

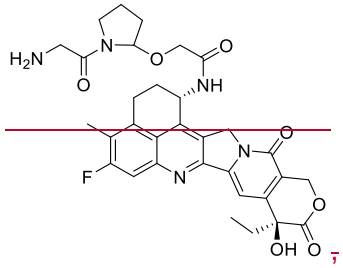
82. A compound having a structure according to Formula (P2):



(P2),

wherein R is a hydrogen or a C_1-C_4 alkyl, or a pharmaceutically acceptable salt thereof.

83. The compound of claim 80, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

84. A pharmaceutical composition comprising the compound according to any one of claims 78-83, and a diluent, a carrier, and/or an excipient.

85.42. A method of treating a condition in a subject in need thereof comprising administering to the subject a therapeutically effective amountUse of the compound according to any one of claims 1-61 or 78-8335, or the composition of any one of claims 6438-71 41or 84, in the manufacture of a medicament for the treatment of a condition in a subject in need thereof.

86.43. The method use of the compound or composition of claim 8542, wherein the condition is cancer.

87.44. The method use of the compound or composition of claim 8643, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, lung cancer, liver cancer, or brain cancer.

88. The method of claims 86 or 87, wherein the condition is HER2+ breast cancer.

89.45. A method of selectively delivering a compound into a cell, wherein the compound is according to any one of claims 781-8335.

90.46. A method of selectively targeting an antigen on a surface of a cell with a compound, wherein the compound is according to any one of claims 781-8335.

47. A compound according to claims 1-35 or a composition of any one of claims 38-41 for use in therapy

91. The method of claims 89 or 90, wherein the cell is a mammalian cell.

92. The method of any of claims 89-91, wherein the cell is a human cell.

93. The method of any one of claims 89-92, wherein the cell is a cancer cell.

94. The method of claim 93, wherein the cancer cell is selected from the group consisting of a breast cancer cell, an ovarian cancer cell, a prostate cancer cell, a lung cancer cell, a liver cancer cell, or a brain cancer cell.

95. A method of producing a compound having a structure according to Formula (A):

$$BA\text{-}(Gln\text{-}NH\text{-}L1\text{-}B\text{-}(\text{-}L2\text{-}(\text{-}M\text{-}Dxd)_m)_k)_n \quad (A),$$

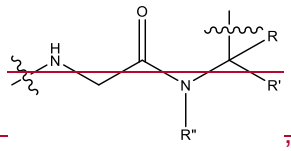
wherein BA is an antibody or an antigen-binding fragment thereof;

Gln is a glutamine residue;

L1 is a first linker;

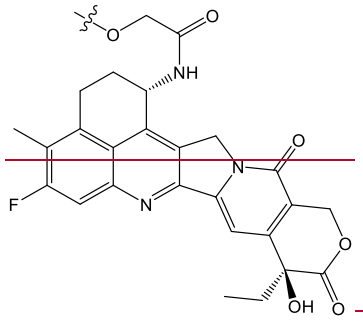
B is a branching unit comprising at least one adduct of a group B' and a group B";

L2 is a second linker covalently attached to the branching unit B via at least one group B";



M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent comprising a structure according to Formula (P):



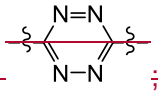
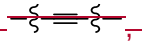
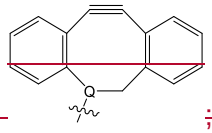
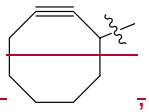
(P),

k and m are independently an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with a compound L1-B, wherein the branching unit B comprises the at least one group B',

b) contacting the product of step a) with k or more equivalents of a compound L2-(-M-Dxd)$_m$, wherein the linker L2 comprises at least one group B",

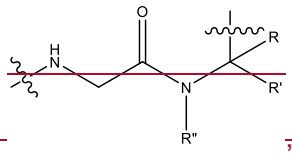
wherein one of the groups B' and B" is selected from -N_3 and  ; and the other of the groups B' and B" is selected from ,  ; and  , where Q is C or N; and

c) isolating the produced compound of Formula (I).

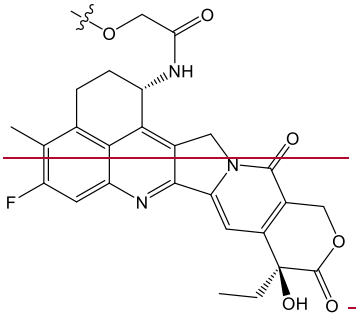
96. A method of producing a compound having a structure according to Formula (A):

BA-(Gln-NH-L1-B-(-L2-(-M-Dxd)$_m$)$_k$)$_n$ (A),

wherein BA is an antibody or an antigen-binding fragment thereof; Gln is a glutamine residue; L1 is a first linker as described above; B is a branching unit comprising at least one adduct of a group B' and a group B" as described above; L2 is a second linker as described above covalently attached to the branching unit B via at least one group B" as described above; M is



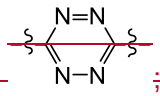
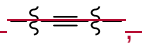
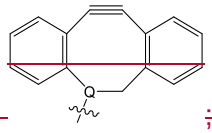
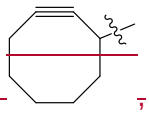
absent or , where R, R', and R" are as described above; Dxd is an anti-tumor agent comprising a structure according to Formula (P):



(P), k and m are independently an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting a compound L1-B, wherein the branching unit B comprises the at least one group B', with k or more equivalents of a compound L2-(-M-Dxd)$_m$, wherein the linker L2 comprises at least one group B" capable of covalently binding with the group B',

wherein one of the groups B' and B" is selected from -N_3 and  ; and the other of the groups B' and B" is selected from ,  ; and  , where Q is C or N;

thereby producting L1-B-(-L2-(-M-Dxd)$_m$)$_k$;

b) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with the L1-B-(-L2-(-M-Dxd)$_m$)$_k$ product of step a), and

c) isolating the produced compound of Formula (I).

97. A method of producing a compound having a structure according to Formula (I):

BA-(Gln-NH-L1-B-(-L2-M-Dxd)$_k$)$_n$

(I),

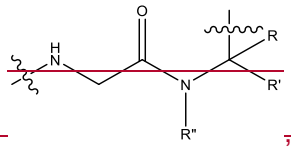
wherein BA is an antibody or an antigen-binding fragment thereof;

Gln is a glutamine residue;

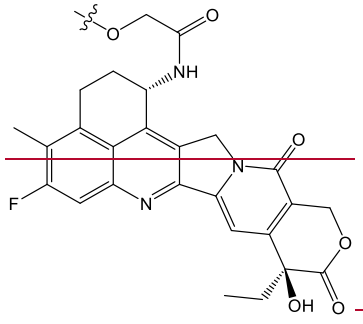
L1 is a first linker;

B is a branching unit comprising at least one adduct of a group B' and a group B";

L2 is a second linker covalently attached to the branching unit B via at least one group B";

M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring;

Dxd is an anti-tumor agent comprising a structure according to Formula (P):



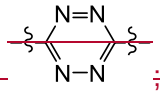
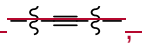
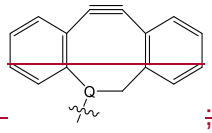
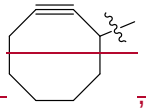
(P),

k is an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with a compound L1-B, wherein the branching unit B comprises the at least one group B',

b) contacting the product of step a) with k or more equivalents of a compound L2-M-Dxd, wherein the linker L2 comprises the at least one group B" capable of covalently attaching to the group B',

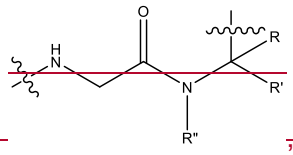
wherein one of the groups B' and B" is selected from $-N_3$ and ; and the other of the groups B' and B" is selected from , ; and , where Q is C or N; and

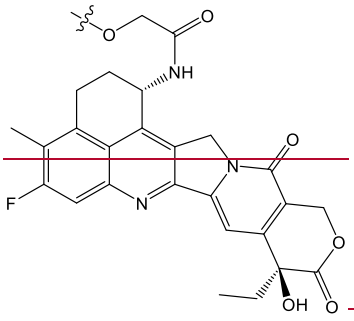
c) isolating the produced compound of Formula (I).

98. A method of producing a compound having a structure according to Formula (I):

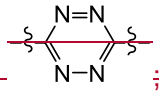
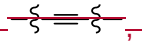
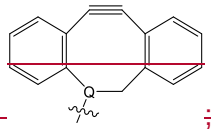
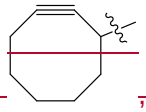
$$BA-(Gln-NH-L1-B-(-L2-M-Dxd)_k)_n \quad (I),$$

wherein BA is an antibody or an antigen-binding fragment thereof; Gln is a glutamine residue; L1 is a first linker as described above; B is a branching unit comprising at least one adduct of a group B' and a group B" as described above; L2 is a second linker as described above

covalently attached to the branching unit B via at least one group B" as described above; M is absent or  , where R, R', and R" are as described above; Dxd is an anti-tumor agent comprising a structure according to Formula (P):

 (P), k is an integer from 1 to 12, and n is an integer from 1 to 30, wherein:

the method comprises the steps of:

a) contacting a compound L1-B, wherein the branching unit B comprises the at least one group B' with k or more equivalents of a compound L2-M-Dxd, wherein the linker L2 comprises at least one group B", thereby producting L1-B-(-L2-M-Dxd)$_k$, wherein one of the groups B' and B" is selected from -N_3 and  ; and the other of the groups B' and B" is selected from  ,  ; and  , where Q is C or N;

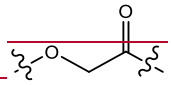
b) contacting, in the presence of a transglutaminase, the binding agent BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with the L1-B-(-L2-M-Dxd)$_k$ product of step a), and

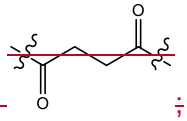
c) isolating the produced compound of Formula (I).

99. A method of producing a compound having a structure according to Formula (III):

BA-(Gln-NH-L2'-P))$_n$ (III),

wherein BA is an antibody or an antigen-binding fragment thereof; Gln is a glutamine residue; L2'-P is H_2N-SP1-B2-(-SP2-AA-SP3-M-Dxd)p as described above, and n is an integer from 1 to 30;

SP1 is absent or a first spacer unit selected from the group consisting of 



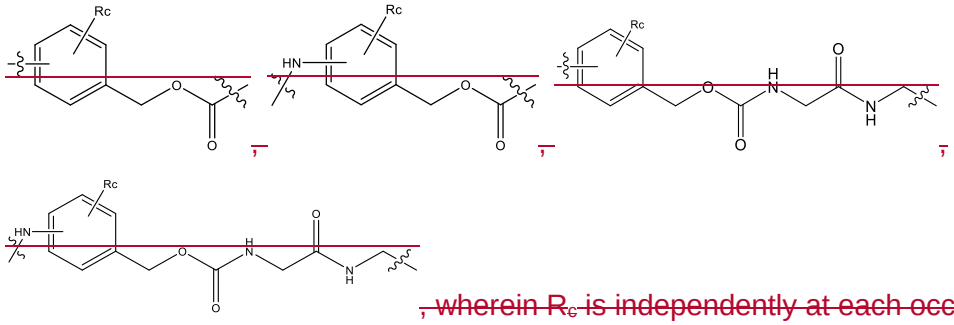
and ;

B2 is absent or a branching unit;

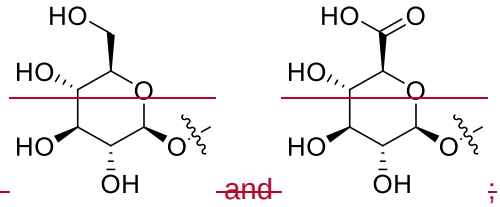
SP2 is absent or a second spacer unit selected from the group consisting of a C_{1-6} alkyl, $-(CH_2-CH_2-O)_v-$, $-NH-$, $-C(O)-$, $-NH-C(O)-$, $-NH-(CH_2)_u-$, $-NH-(CH_2)_u-C(O)-$, $-NH-(CH_2-CH_2-O)_v-$, $-NH-(CH_2-CH_2-O)_v-C(O)-$, $-NH-(CH_2-CH_2-O)_v-(CH_2)_u-$, $-NH-(CH_2-CH_2-O)_v-(CH_2)_u-C(O)-$, $-(CH_2)_u-NH-C(O)-$, $-NH-(CH_2)_u-NH-C(O)-$, $-NH-(CH_2)_u-C(O)-NH-$, or combinations thereof; wherein subscripts u and v are independently an integer from 1 to 8;

AA is absent or a peptide unit comprising from 2 to 4 amino acids;

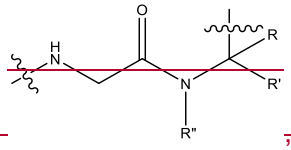
SP3 is absent or a third spacer unit selected from the group consisting of,



, wherein R_c is independently at each occurrence absent

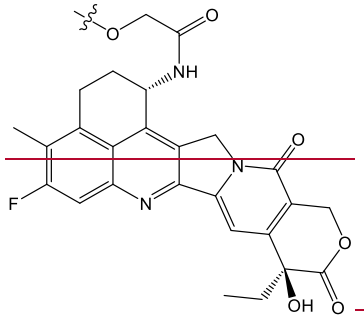


or a group selected from and ;



M is absent or , where R, R', and R" are independently at each occurrence hydrogen or a C_1-C_4 alkyl, or wherein R' and R" together form a 5-membered or a 6-membered ring; and

Dxd is an anti-tumor agent having a structure according to Formula (P):



(P),

p is an integer from 1 to 30;

wherein the method comprises the steps of:

b) contacting, in the presence of a transglutaminase, the BA comprising at least one glutamine residue Gln (BA-Gln-NH_2) with the L2'-P, and

c) isolating the produced compound of Formula (III).

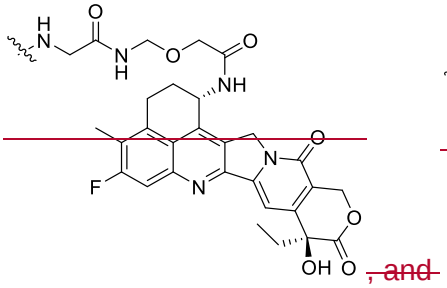
100. The method of any one of claims 95-98, wherein the glutamine residue Gln is naturally present in a CH2 or CH3 domain of the BA.

101. The method of any one of claims 95-98, wherein the glutamine residue Gln is introduced to the BA by modifying one or more amino acids.

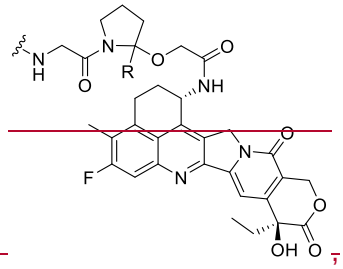
102. The method of any one of claims 95-98, wherein the Gln is Q295 or N297Q.

103. The method of any one of claims 95-98, wherein the transglutaminase is microbial transglutaminase (MTG).

104. The method of any of claims 95-103, wherein M is absent, or wherein the M-Dxd has a structure selected from the group consisting of



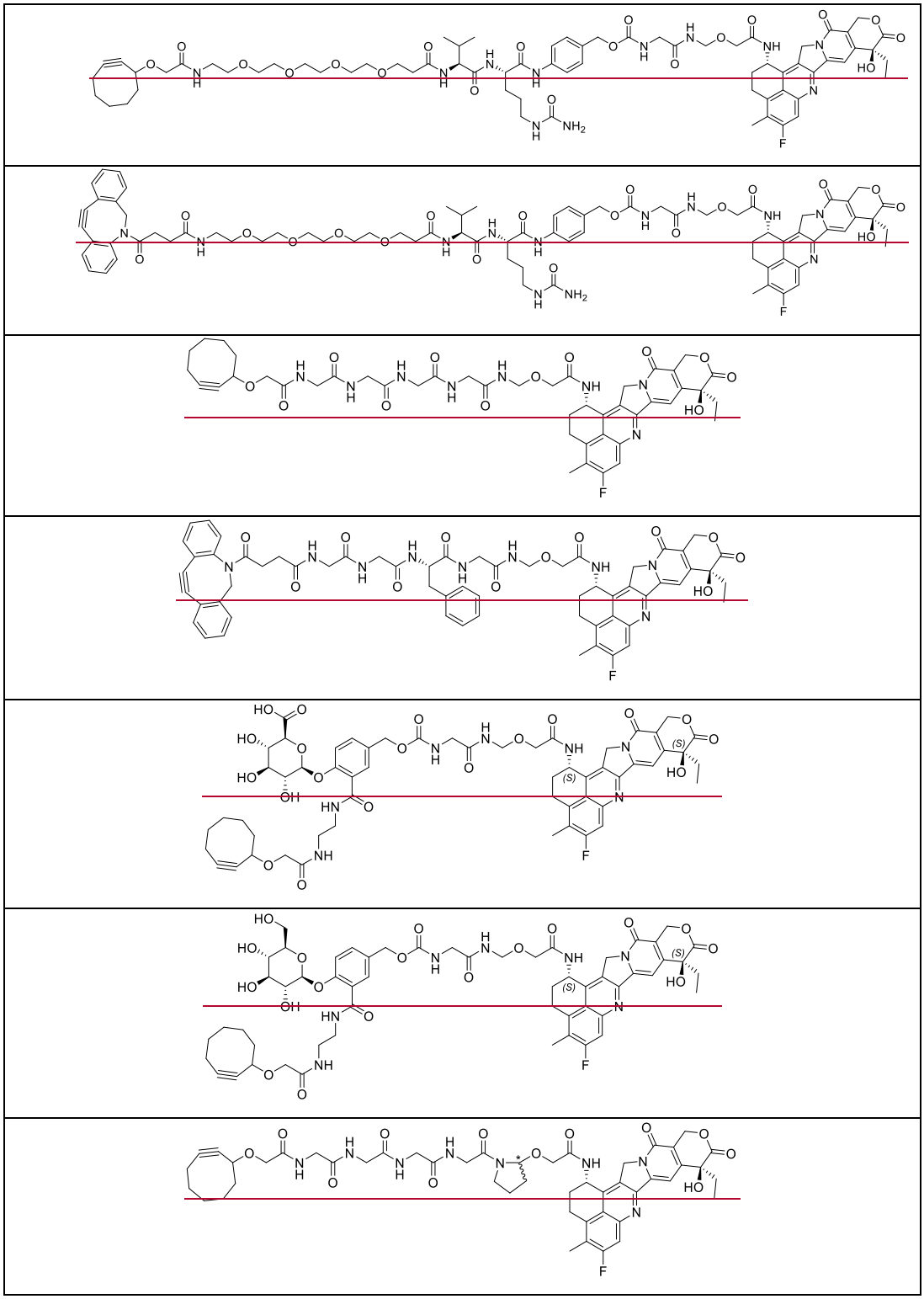
, and

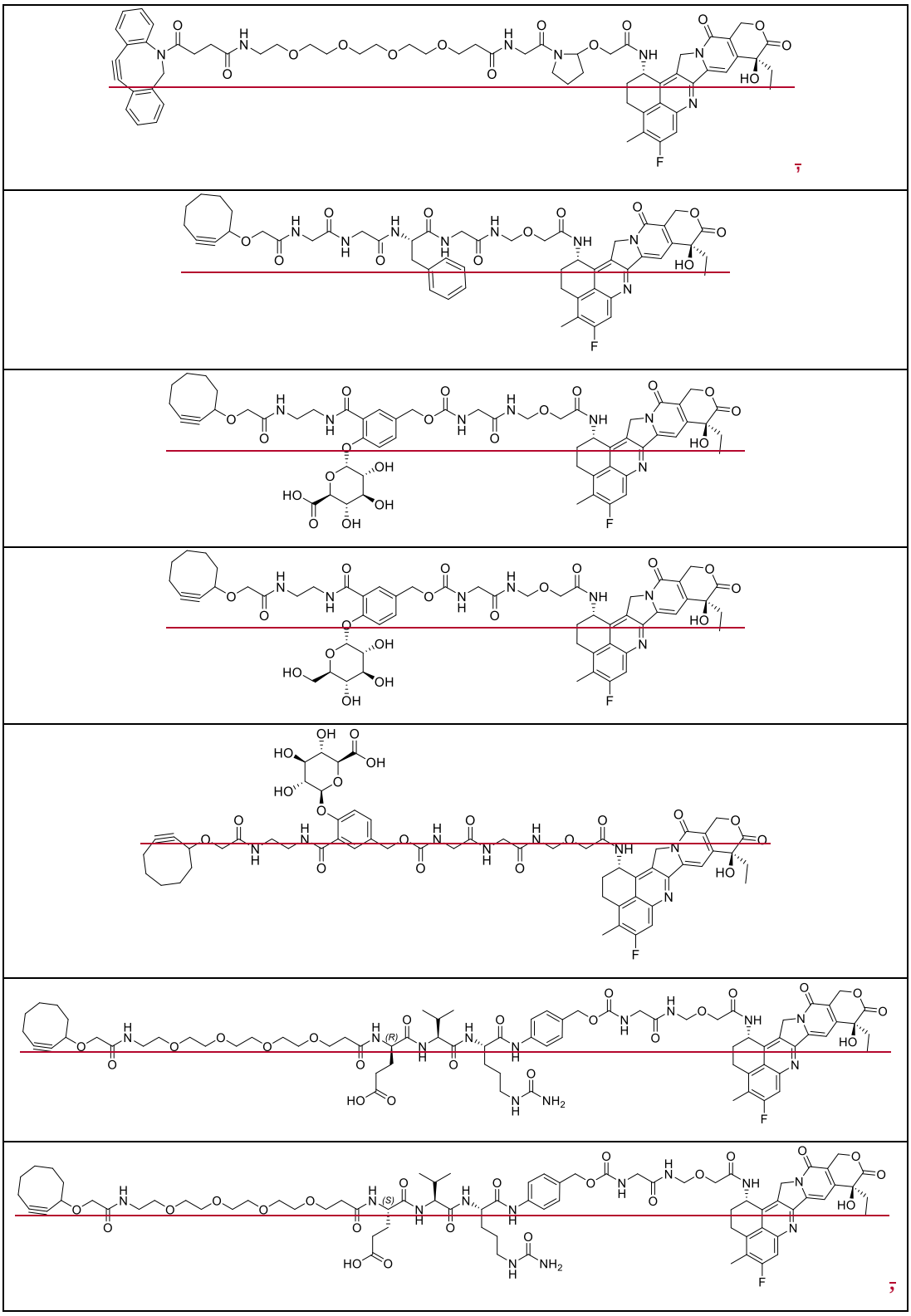


,

wherein R is a hydrogen or a C_1-C_4 alkyl, and where ~~~ represents the point of attachment to L2.

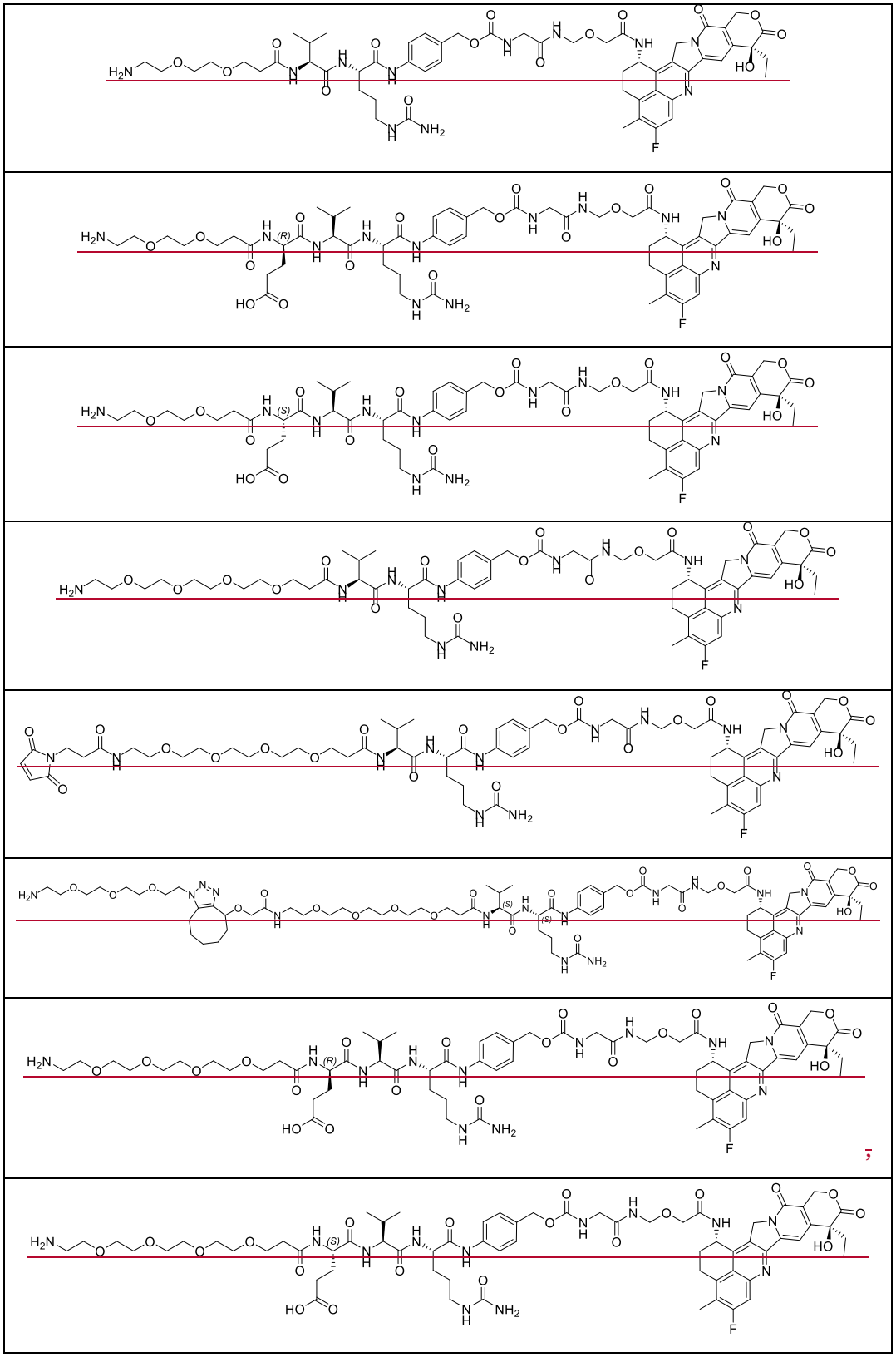
105. The method of any of claims 95-104, wherein the compound L2-Dxd has a structure selected from the group consisting of:





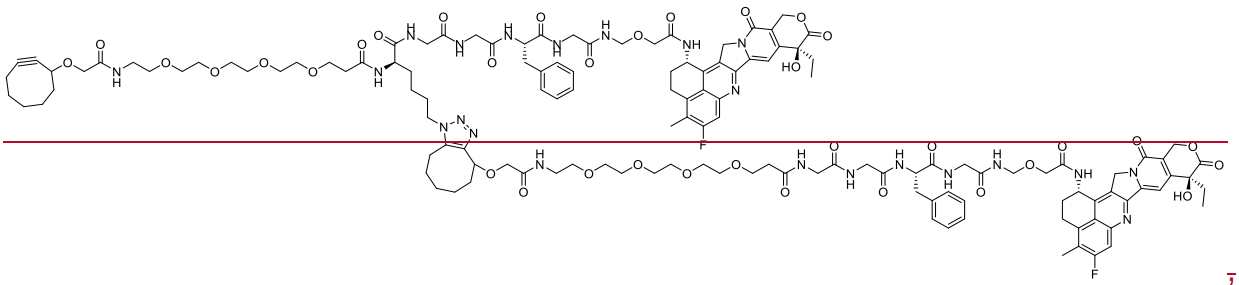
~~or a pharmaceutically acceptable salt thereof.~~

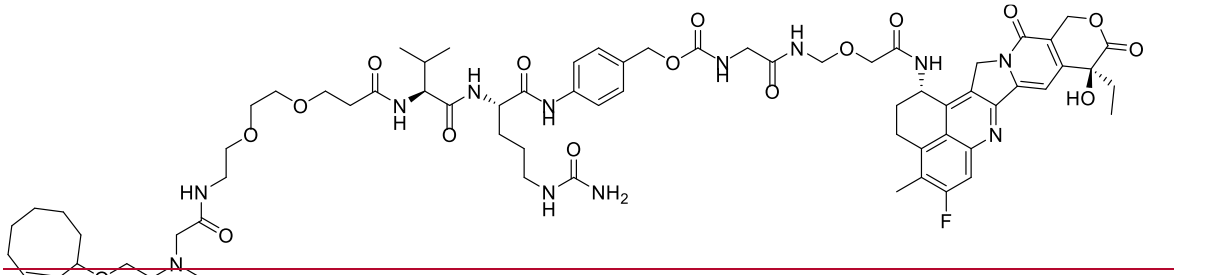
106. The method of any of claims 95-104, wherein the compound L2-Dxd has a structure selected from the group consisting of:

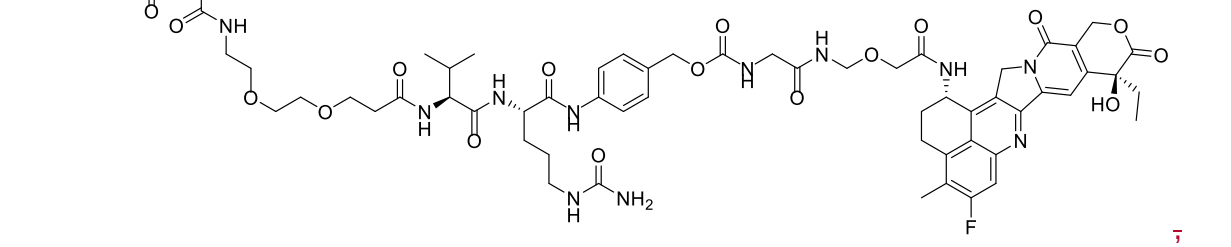


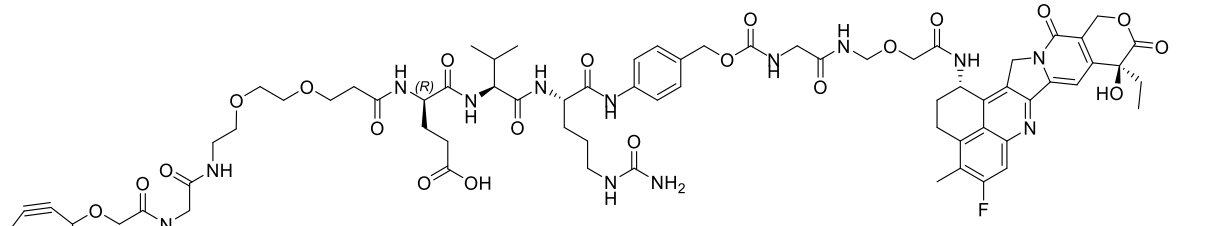
~~or a pharmaceutically acceptable salt thereof.~~

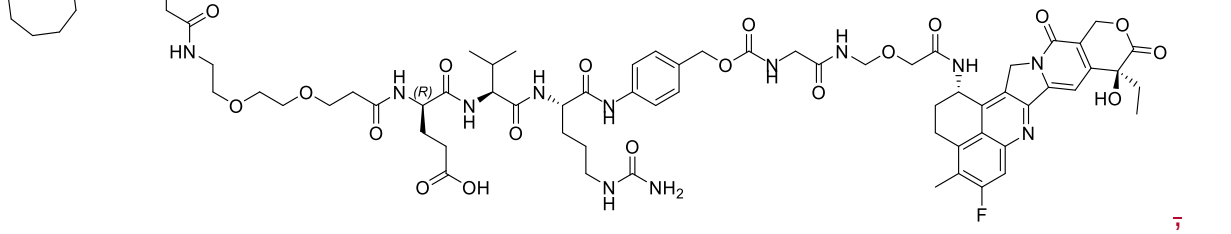
~~107. The method of any of claims 95-104, wherein the compound L2-Dxd has a structure selected from the group consisting of:~~

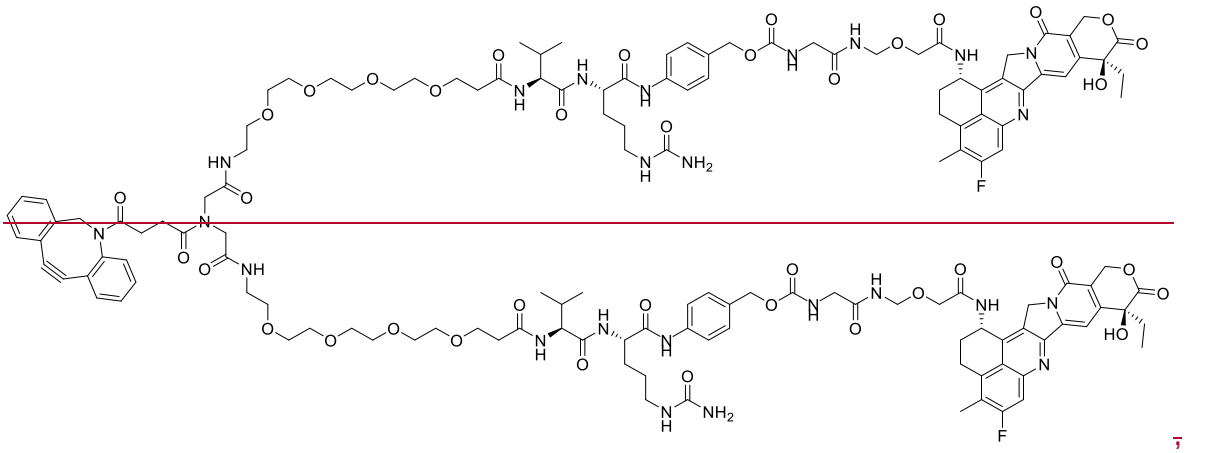


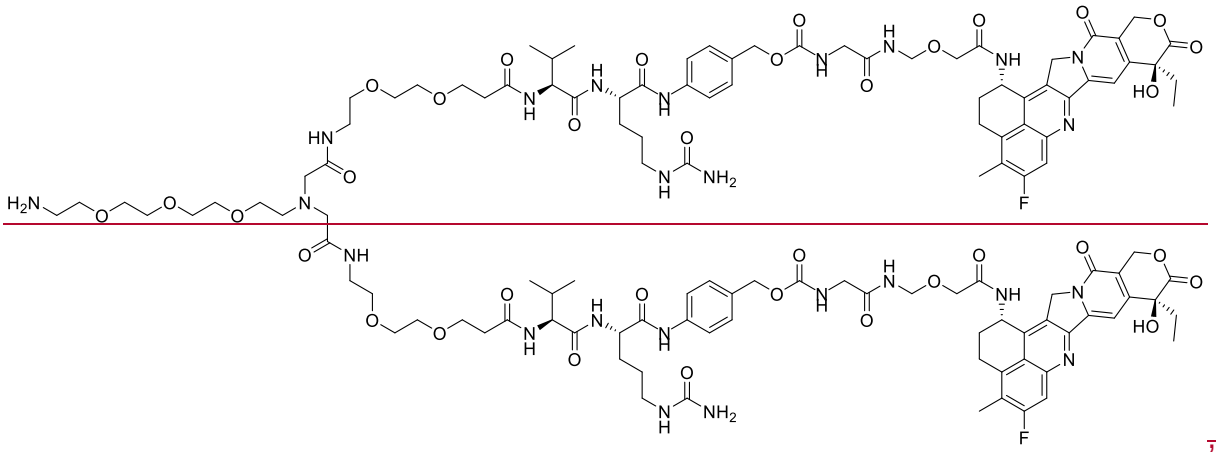


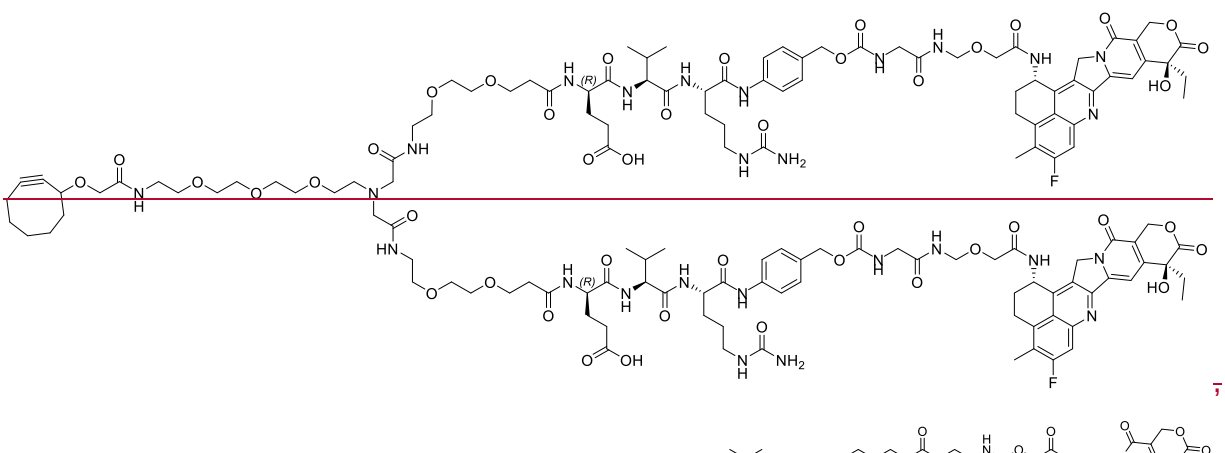


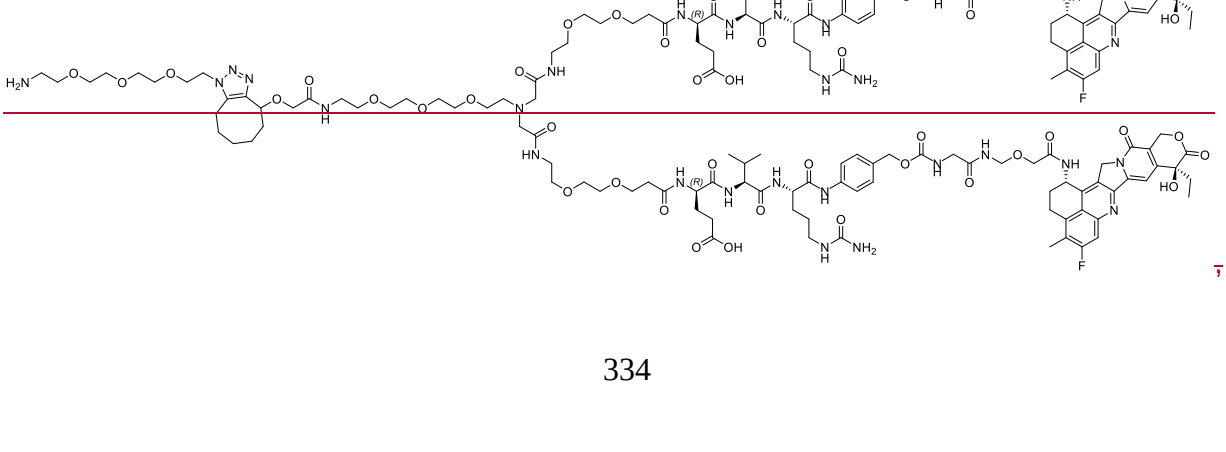


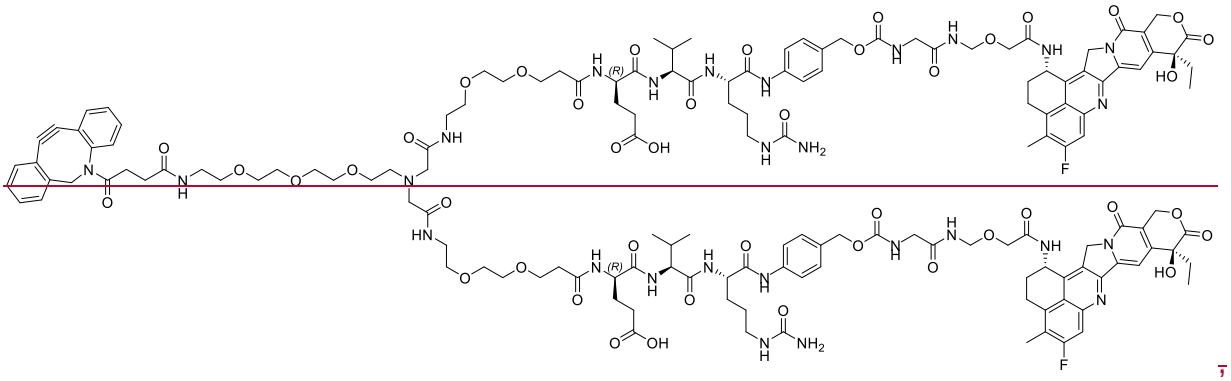


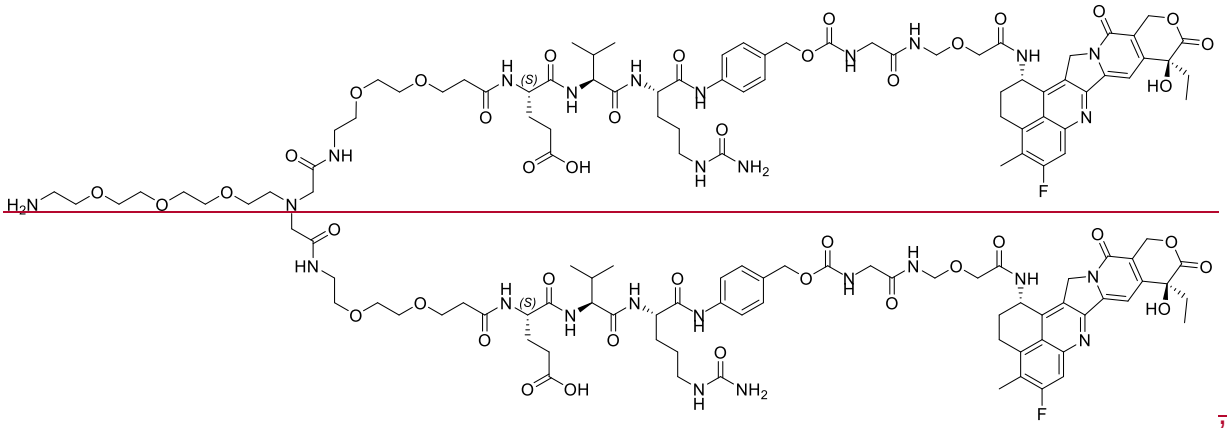


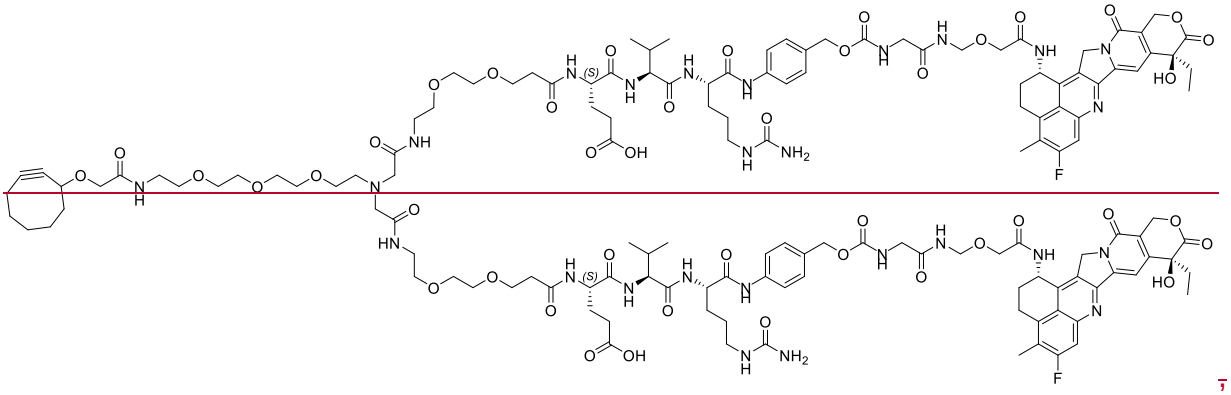


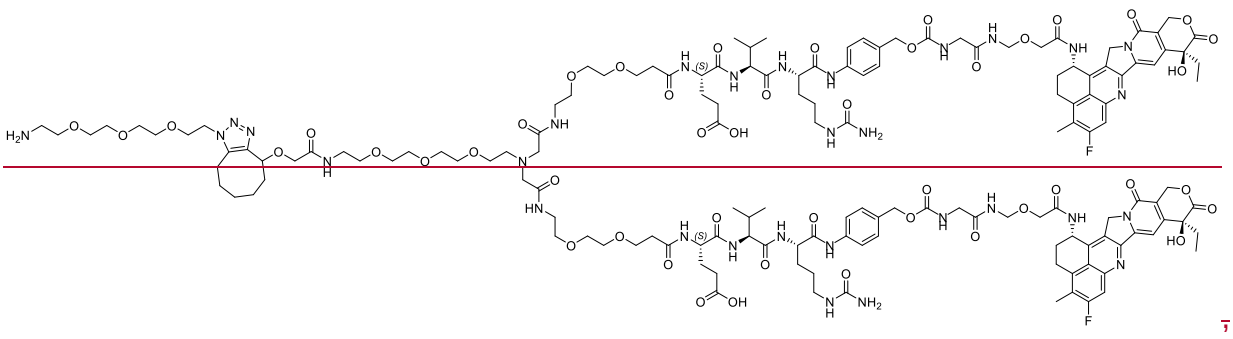


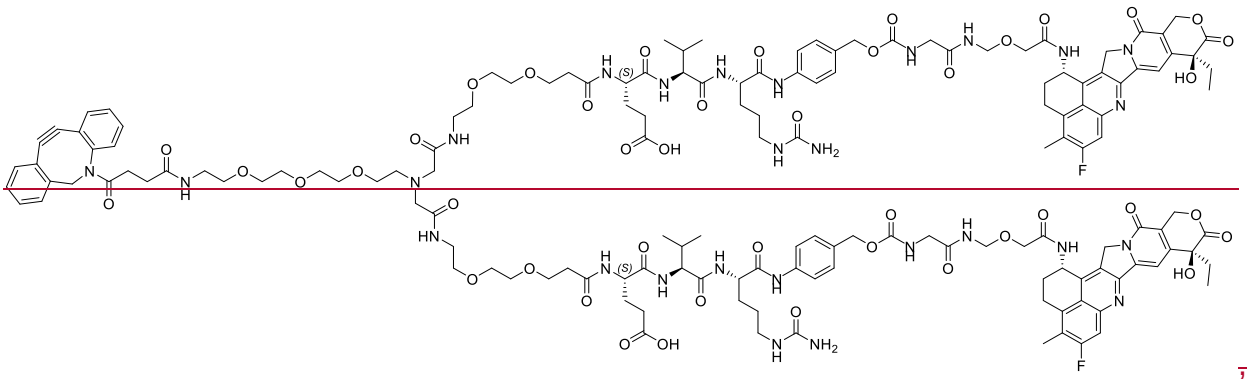


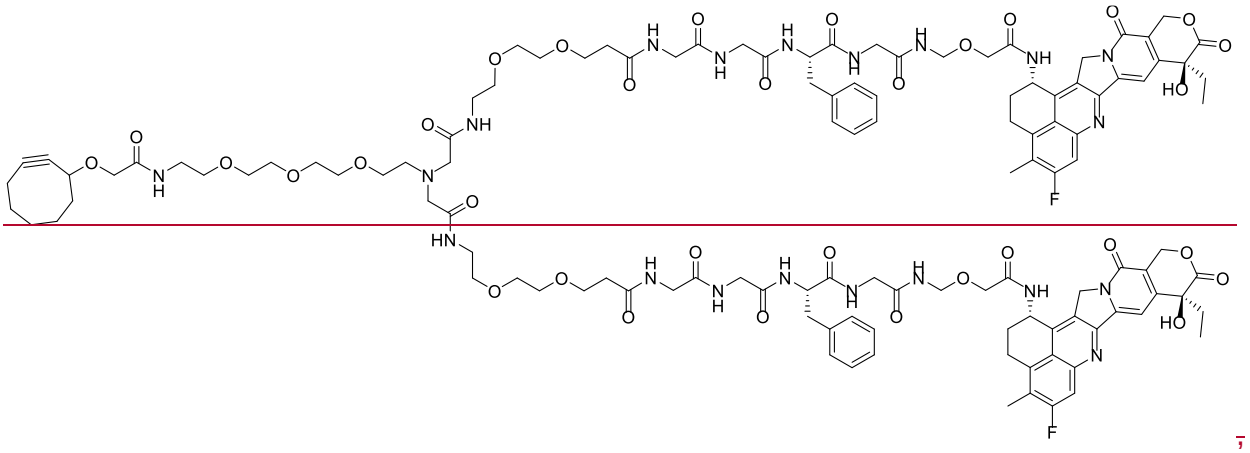


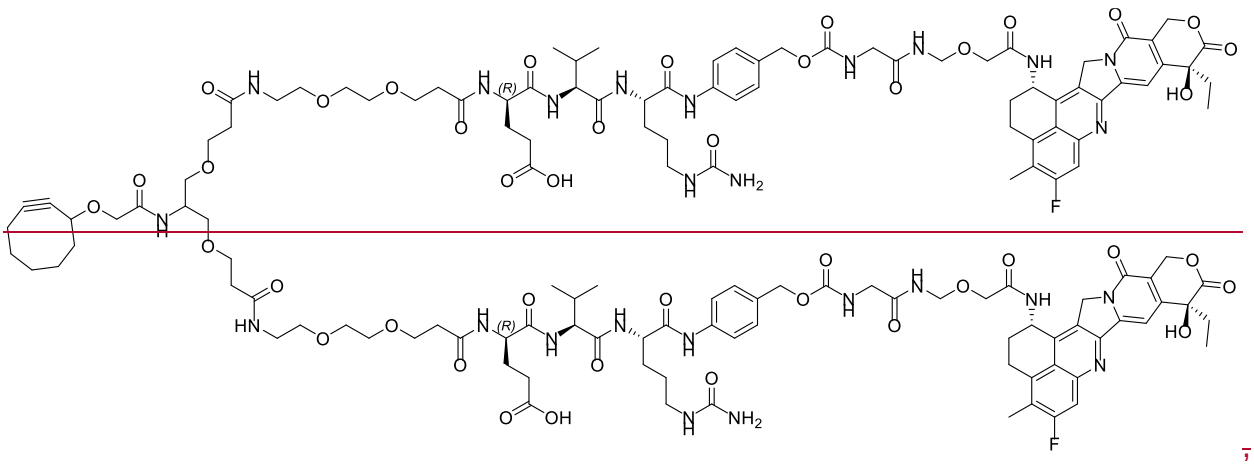


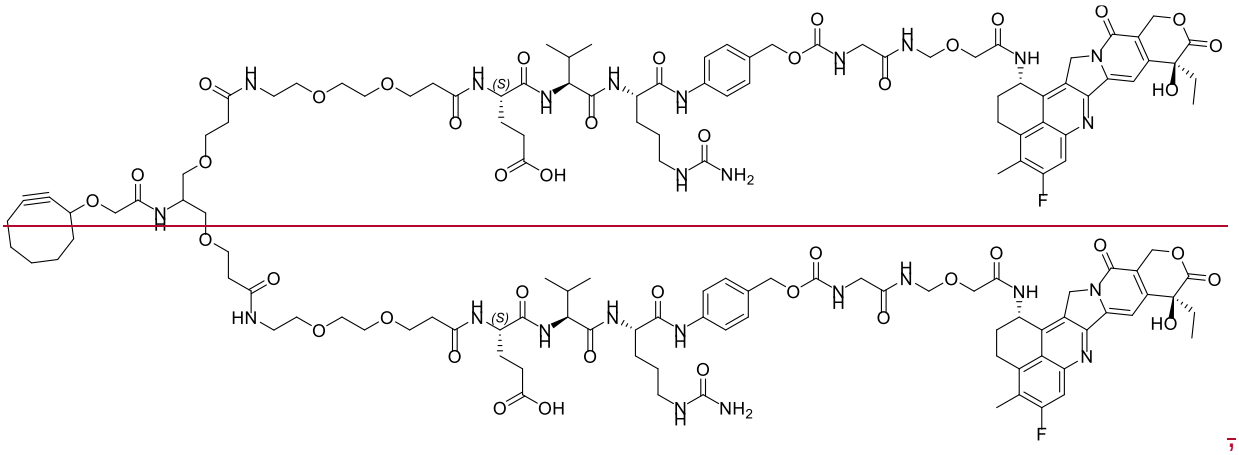


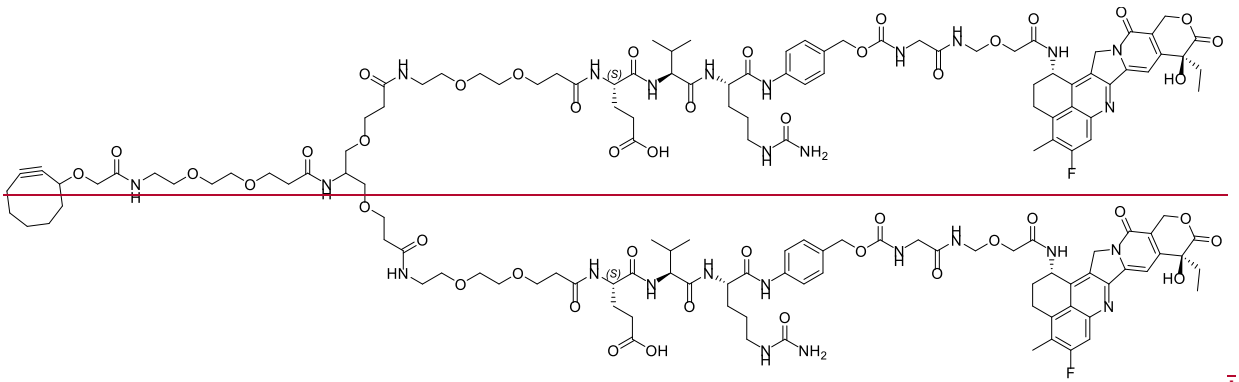


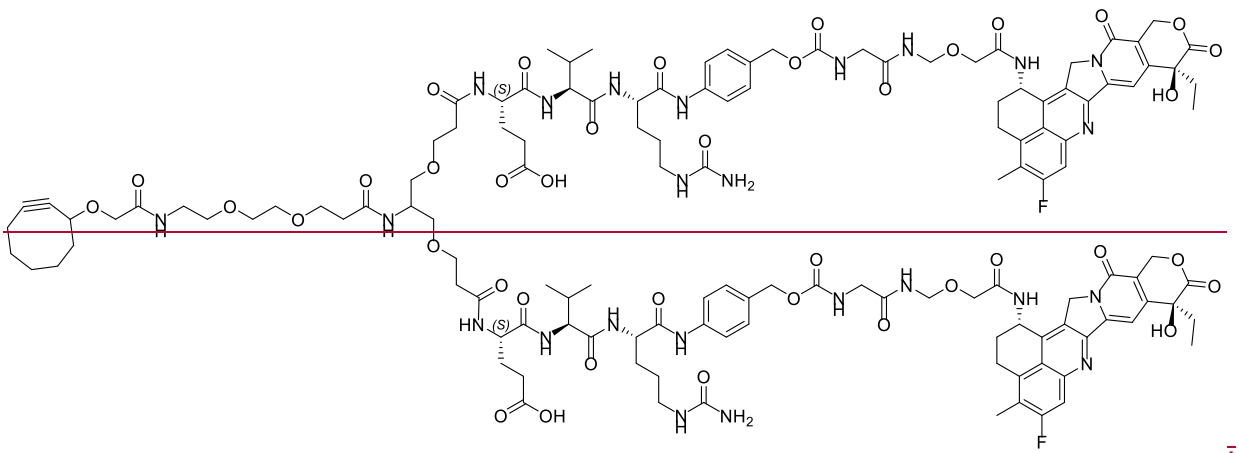


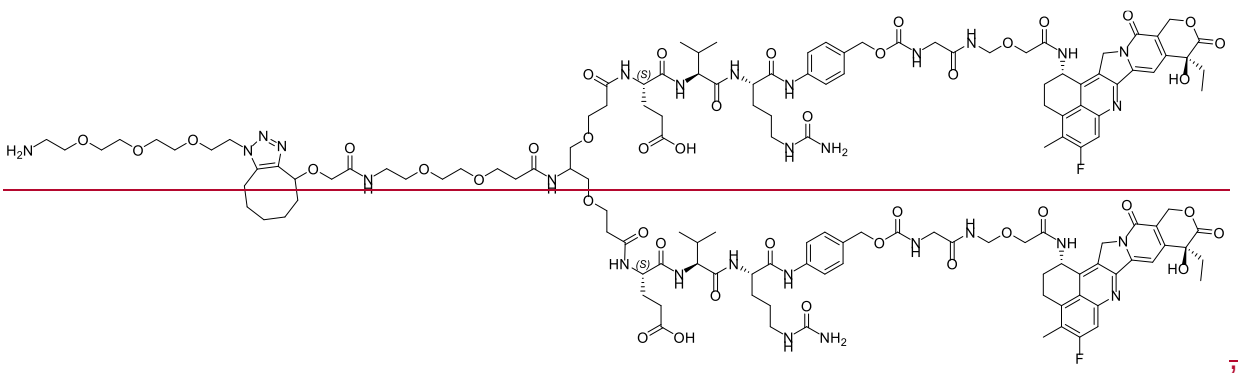


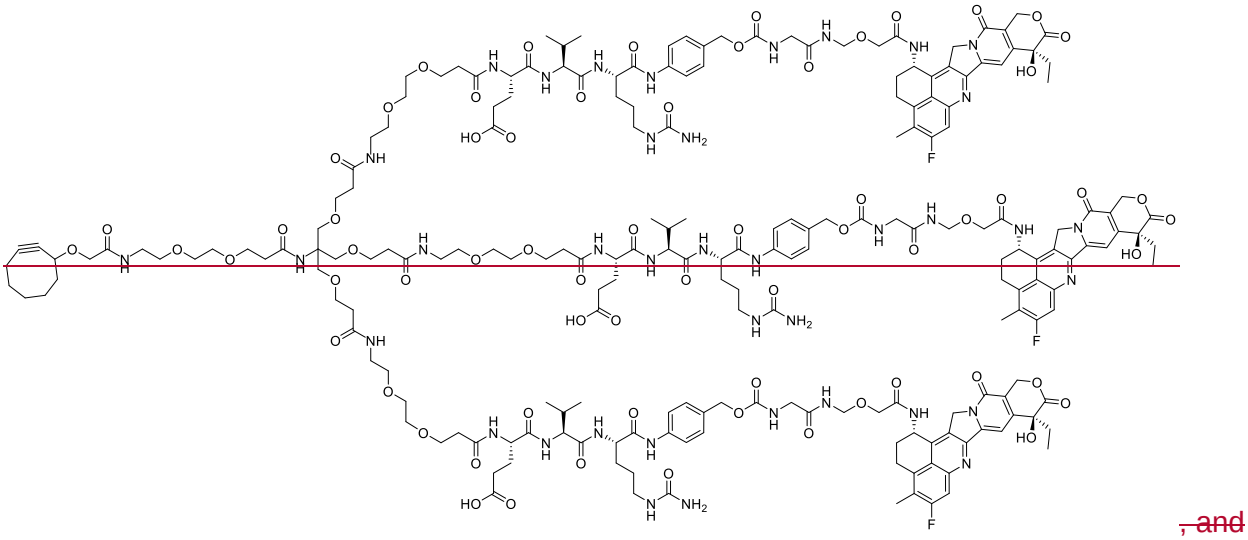




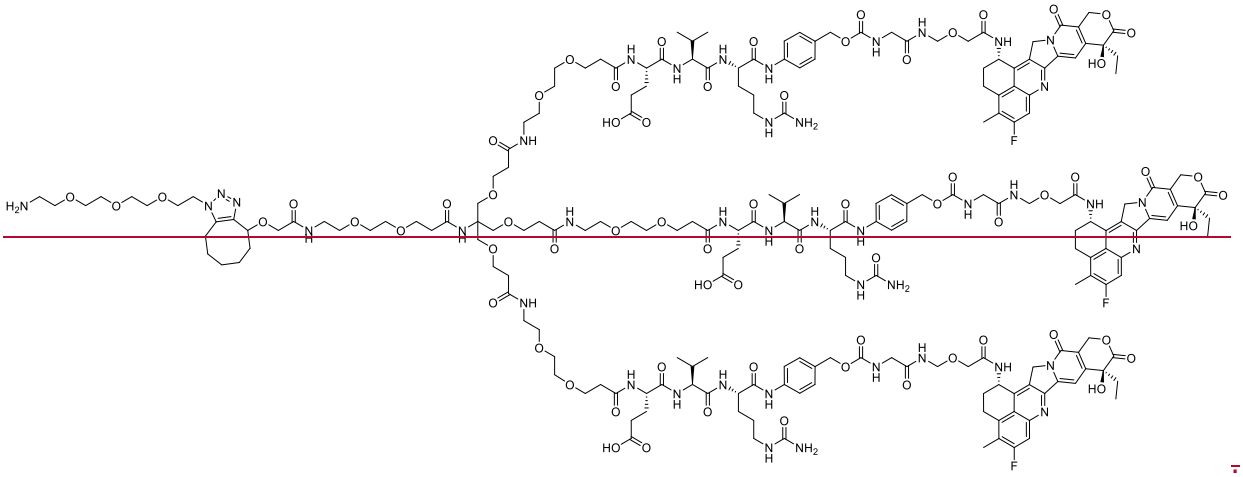








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