~~WHAT IS CLAIMED~~CLAIMS

1. An antibody conjugate of the General Formula I, or a pharmaceutically acceptable salt thereof:

[General Formula I]

$$Ab - (X^{A})_y$$

wherein:

Ab is an anti-ROR1 antibody, or an antigen-binding fragment thereof ~~specifically binding to the extracellular domain of ROR1, the antibody comprising a heavy chain variable region and a light chain variable region~~,

the antibody or antigen-binding fragment thereof comprises:

a heavy chain variable region comprising a CDRH1 comprising the amino acid sequence of any one of SEQ ID NOs. 1-5; a CDRH2 comprising the amino acid sequence of any one of SEQ ID NOs. 6-13 and 96; and a CDRH3 comprising the amino acid sequence of any one of SEQ ID NOs. 14-21 and 97; and

a light chain variable region comprising a CDRL1 comprising the amino acid sequence of any one of SEQ ID NOs. 22-29; a CDRL2 comprising the amino acid sequence of any one of SEQ ID NOs. 30-37; and a CDRL3 comprising the amino acid sequence of any one of SEQ ID NOs. 38-42;

each X^{A} ~~is a chemical residue which independently includes~~ comprises at least one active agent and a linker;

wherein the linker covalently links Ab ~~and~~ to ~~the~~each ~~at least one~~ active agent; and

y is an integer from 1 to 20.

2. The antibody conjugate of claim 1, wherein the antibody comprises a set of CDRs: CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, in which:

(a) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 1, 6 and 14, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 22, 30 and 38, respectively;

(b) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 2, 7 and 15, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 23, 31 and 39, respectively;

(c) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 1, 8 and 16, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 24, 32 and 40, respectively;

(d) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 3, 9 and 17, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 25, 33 and 41, respectively;

(e) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 1, 10 and 18, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 26, 34 and 41, respectively;

(f) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 4, 11 and 19, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 27, 35 and 42, respectively;

(g) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs 5, 12 and 20, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs 28, 36 and 41, respectively;

(h) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 3, 13 and 21, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 29, 37 and 41, respectively;

(i) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 2, 96 and 15, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 23, 31 and 39, respectively; or

(j) CDRH1, CDRH2 and CDRH3 comprise the amino acid sequence of SEQ ID NOs. 3, 9 and 97, respectively, and CDRL1, CDRL2 and CDRL3 comprise the amino acid sequence of SEQ ID NOs. 25, 33 and 41, respectively.

3. The antibody conjugate of claim 1 or 2, wherein the antibody comprises a heavy chain variable region comprising:

the amino acid sequence of any one of SEQ ID NOs. 43-50, 98 and 99;

at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs 43-50, 98 and 99, or;
at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs 43-50, 98 and 99,
or a pharmaceutically acceptable salt or solvate thereof.

4. The antibody conjugate of any one of claims 1-3, wherein the antibody comprises a light chain variable region comprising:
the amino acid sequence of any one of SEQ ID NOs 51-58;
at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs 51-58; or
at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs 51-58,
or a pharmaceutically acceptable salt thereof.

5. The antibody conjugate of any one of claims 1-4, wherein the antibody comprises a combination of heavy chain and light chain variable regions comprising the amino acid sequence of: SEQ ID NOs. 43 and 51, respectively; SEQ ID NOs. 44 and 52, respectively; SEQ ID NOs. 45 and 53, respectively; SEQ ID NOs. 46 and 54, respectively; SEQ ID NOs. 47 and 55, respectively; SEQ ID NOs. 48 and 56, respectively; SEQ ID NOs. 49 and 57, respectively; SEQ ID NOs. 50 and 58, respectively; SEQ ID NOs. 98 and 52, respectively, or; SEQ ID NOs. 99 and 54, respectively.

6. The antibody conjugate of any one of claims 1-5, wherein the antibody comprises a combination of heavy chain and light chain variable regions comprising the amino acid sequence of: SEQ ID NOs. 59 and 67, respectively; SEQ ID NO 60 and 68, respectively; SEQ ID NO 61 and 69, respectively; SEQ ID NO 62 and 70, respectively; SEQ ID NO 63 and 71, respectively; SEQ ID NO 64 and 72, respectively; SEQ ID NO 65 and 73, respectively; or SEQ ID NO 66 and 74, respectively.

7. The antibody conjugate of claim 1 or 2, wherein the antibody is a monoclonal antibody, a domain antibody (dAb), a single chain antibody (scab), a Fab fragment, a Fab' fragment, a F(ab')2 fragment, an scFab fragment, an Fv fragment, a dsFv fragment, a single chain variable fragment (scFv), an ScFv-Fc fragment, a single domain heavy chain antibody, a single domain light chain

antibody, a variant antibody, a multimeric antibody, a minibody, a diabody, a bispecific antibody or a multispecific antibody.

8. The antibody conjugate of claim 1 or 2, wherein the antibody is a rabbit, mouse, chimeric, humanized, or fully human monoclonal antibody.

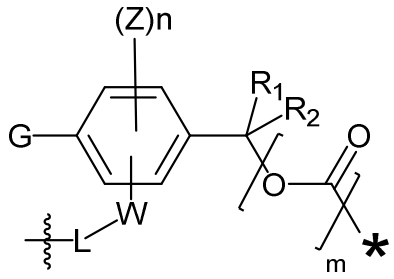
9. The antibody conjugate of any one of claims 1-8, wherein the antibody is of the IgG1, IgG2, IgG3 or IgG4 type.

~~10. The antibody conjugate of any one of claims 1-9, wherein the ROR1 is human ROR1 or mouse ROR1.~~

~~11~~10. The antibody conjugate of any one of claims 1-~~10~~9, wherein the linker between the antibody and the active agent comprises a cleavable bond ~~(e.g., a bond cleavable by an enzyme)~~.

~~12~~11. The antibody conjugate of any one of claim 1-~~11~~10, wherein ~~the antibody drug conjugate~~X^A ~~has~~ comprises a structure represented by ~~General~~ Chemical Formula IIa:

[Chemical Formula (IIa)]



or a pharmaceutically acceptable salt thereof, wherein

G is a sugar~~,~~ or a sugar acid ~~or a sugar derivative~~;

W is -C(O)-, -C(O)NR'-, -C(O)O-, SO_2NR'-, -P(O)R''NR'-, -SONR'- or $-PO_2NR'$-; wherein the C, S or P is directly bound to the phenyl ring;

each Z is independently C_1-C_8 alkyl, halogen, cyano or nitro;

n is an integer from 0 to 3; ~~and~~

m is 0 or 1;

L is absent, C_1-C_{50} alkylene or 1-50 atom heteroalkylene~~, or L contains at least one branching unit (BR) and at least one connection unit;~~;

R^1 and R^2 are independently hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl; or R_1 and R_2, combine to complete a (C_3-C_8) cycloalkyl ring;

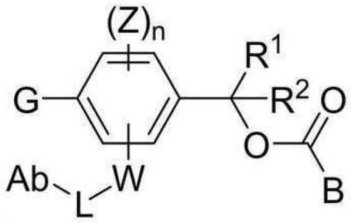
R' and R'' are each independently hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, mono-or di- C_1-C_8 alkylamino, C_3-C_{20} heteroaryl or C_6-C_{20} aryl;

* represents a connection point to the active agent; and

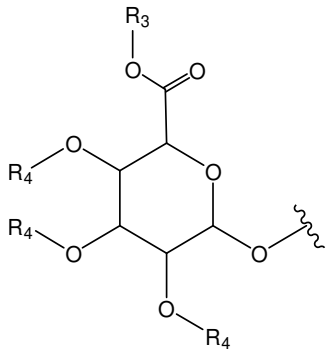
represents a connection point to the antibody.

~~13~~12. The antibody conjugate of any one of claim 1-~~12~~11, wherein the antibody drug conjugate has a structure represented by General Formula II:

[General Formula II]



or a pharmaceutically acceptable salt thereof, wherein

G is a glucuronic acid moiety or 

;

R^3 is a hydrogen or carboxyl protecting group;

each of the R4 are independently a hydrogen or hydroxyl protecting group;

B is an active agent;

R^1 and R^2 are respectively and independently hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl;

W is -C(O)-, -C(O)NR'-, -C(O)O-, SO_2NR'-, -P(O)R''NR'-, -SONR'- or $-PO_2NR'$-; wherein the C, S or P is directly bound to the phenyl ring;

R' and R'' are each independently are hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, mono-or di- C_1-C_8 alkylamino, C_3-C_{20} heteroaryl or C_6-C_{20} aryl;

each Z is independently C_1-C_8 alkyl, halogen, cyano or nitro;

n is an integer of 0 to 3; and

L comprises:

A) a C_1-C_{50} alkylene or 1-50 atom heteroalkylene satisfying at least one of the following:

(i) L includes at least one unsaturated bond;

(ii) L is substituted by a bivalent substituent where 2 atoms in L are the same as in a substituent, this completing a heteroarylene;

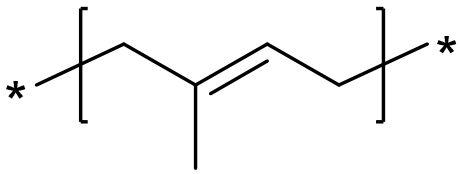
(iii) L is a 1 to 50 atom heteroalkylene;

(iv) L is substituted by at least one C_{1-20} alkyl; or

(v) L is interrupted by a heteroarylene; or

B) at least one isoprenyl derivative unit of General Formula III below which can be recognized by isoprenoid transferase :

[General Formula III]



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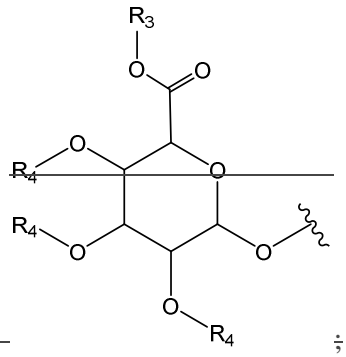
~~14. The antibody conjugate of claim 12 or 13, wherein~~

~~G is~~  ;

~~R^3 is a hydrogen or a carboxyl protecting group; and~~
~~each R^4 is, respectively and independently, a hydrogen or a hydroxyl protecting group.~~

~~15. The antibody conjugate of any one of claims 12-14, wherein R^3 is hydrogen, and each R^4 is hydrogen.~~

~~16. The antibody conjugate of any one of claims 12-15, wherein R^1 and R^2 are hydrogen.~~

~~17. The antibody conjugate of any one of claims 12-16, wherein Z is independently C_1-C_8 alkyl, halogen, cyano or nitro.~~

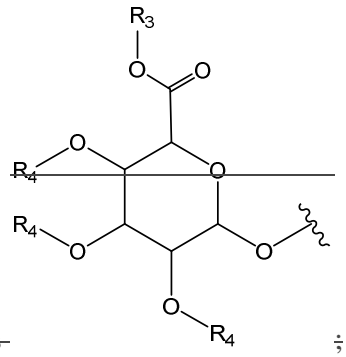
~~18. The antibody conjugate of any one of claims 12-17, wherein n is 0.~~

~~19. The antibody conjugate of any one of claims 12-18, wherein W is -C(O)-, -C(O)NR'-, -C(O)O-, SO_2NR'-, -P(O)R''NR'-, -SONR'- or -PO_2NR'-; the C, S or P is directly bound to the phenyl ring; the R' and R'' are respectively and independently compounds which are hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, mono or di-C_1-C_8 alkylamino, C_3-C_{20} heteroaryl or C_6-C_{20} aryl.~~

~~20~~13. The antibody conjugate of any one of claims ~~12~~11-~~19~~12, wherein W is -C(O)-, -C(O)NR'-, or -C(O)O-.

~~21. The antibody conjugate of any one of claims 12-20, wherein W is -C(O)NR'-; and the C(O) binds to a phenyl ring, and NR' binds to L.~~

~~22. The antibody conjugate of any one of claims 12-21, wherein~~

~~G is~~  ~~;~~

~~W is -C(O)NR'-, the C(O) is bound to the phenyl ring, NR' binds to L; and~~

~~R_3 and R_4 are hydrogen.~~

~~23. The antibody conjugate of any one of claims 12-22, wherein L is C_1-C_{50} alkylene or a 1-50 atom heteroalkylene comprising at least one of:~~

~~(i) L includes at least one unsaturated bond;~~

~~(ii) L is substituted by a bivalent substituent where 2 atoms in L are the same as in a substituent, this completing a heteroarylene;~~

~~(iii) L is a 1 to 50 atom heteroalkylene;~~

~~(iv) L is substituted by at least one C_{1-20} alkyl; or~~

~~(v) L is interrupted by a heteroarylene.~~

~~24. The antibody conjugate of any one of claims 12-23, wherein L is C_1-C_{50} alkylene or a 1-50 atom heteroalkylene comprising at least one of:~~

~~(i) an unsaturated bond;~~

~~(ii) a heteroarylene;~~

~~(iii) a 1 to 50 atom heteroalkylene; or~~

~~(iv) at least one C_{1-20} alkyl substituent.~~

~~25~~14. The antibody conjugate of any one of claims ~~12~~11-~~23~~13, wherein L ~~is a nitrogen-comprising 1-50 atom heteroalkylene, the linker includes at~~comprises at least 2 atoms of a hydrophilic amino acid and ~~; and~~ the nitrogen of W forms a peptide bond with a carbonyl of a hydrophilic amino acid.

~~26~~15. The antibody conjugate of any one of claims ~~12~~11-~~25~~14, wherein W is -C(O)NR'-~~, and the nitrogen of W is a nitrogen atom of a hydrophilic amino acid.~~.

~~27~~16. The antibody conjugate of claim ~~25~~-14 or ~~26~~15, wherein the hydrophilic amino acid ~~any one selected from a group comprising~~is selected from arginine, aspartate, asparagine, glutamate, glutamine, histidine, lysine, ornithine, proline, serine and threonine.

~~28. The antibody conjugate of any one of claims 25-27, wherein the amino acid covalently bonds an oxime of a linker to a polyethylene glycol unit of the linker.~~

~~29. The antibody conjugate of any one of claims 25-28, wherein the amino acid is selected from arginine, aspartate, asparagine, glutamate, glutamine, histidine, lysine, ornithine, proline, serine and threonine.~~

~~30. The antibody conjugate of any one of claims 25-29, wherein the hydrophilic amino acid comprises a side chain having a moiety which has electric charge in aqueous solution at a neutral pH.~~

~~31. The antibody conjugate of any one of claims 25-30, wherein the hydrophilic amino acid is aspartate or glutamate.~~

~~32. The antibody conjugate of any one of claims 25-30, wherein the hydrophilic amino acid is ornithine or lysine.~~

~~33. The antibody conjugate of any one of claims 25-30, wherein the hydrophilic amino acid is arginine.~~

~~34. The antibody conjugate of any one of claims 25-33, wherein L further comprises a peptide, and the peptide comprises at least once hydrophilic amino acid and includes a side chain having a moiety which has electric charge in aqueous solution at a neutral pH.~~

~~35. The antibody conjugate of claim 34, wherein each amino acid of the peptide is independently selected from alanine, aspartate, asparagine, glutamate, glutamine, glycine, lysine, ornithine, proline, serine and threonine.~~

~~36. The antibody conjugate of claim 34 or 35, wherein the peptide comprises at least one aspartate or glutamate.~~

~~37. The antibody conjugate of any one of claims 12-36, wherein W is -C(O)NR'-, and in that the nitrogen of W is a nitrogen atom of an N-terminal amino acid of a peptide.~~

~~38. The antibody conjugate of claim 37, wherein the peptide covalently bonds an oxime of a linker to a polyethylene glycol unit of the linker.~~

~~39. The antibody conjugate of any one of claims 34-38, wherein~~ L ~~the peptide comprises 2 to 20 amino acids.~~

~~40~~17. The antibody conjugate of any one of claims ~~12~~11-~~39~~16, wherein L is ~~covalently~~ bonded to the antibody by a thioether bond~~,~~ and the thioether bond ~~includes~~comprises a sulfur atom of ~~the~~ a cysteine of the antibody.

~~41~~18. The antibody conjugate of any one of claims ~~12~~11-~~40~~17, wherein the antibody comprises an amino acid motif which can be recognized by isoprenoid transferase at the C-terminal of the antibody~~,~~ and the thioether bond includes a sulfur atom of the cysteine of the antibody.

~~42~~19. The antibody conjugate of claim ~~41~~18, wherein the amino acid motif ~~is a~~ has a sequence of CYYX ~~sequence~~; wherein
C is cysteine;
each Y is an aliphatic amino acid; and
X is ~~any one~~ selected from glutamine, glutamate, serine, cysteine, methionine, alanine and leucin~~;~~
~~and the thioether bond includes a sulfur atom of the cysteine of the antibody.~~.

~~43~~20. The antibody conjugate of claim ~~42~~ 18 or ~~43~~19, wherein the amino acid motif has a sequence of ~~wherein the amino acid motif is a~~ CYYX ~~sequence;~~, further wherein each ~~and~~ Y is independently selected ~~any one selected~~ from alanine, isoleucine, leucine, methionine and valine.

~~44~~21. The antibody conjugate of any one of claims ~~41~~18-~~43~~20, wherein the amino acid motif ~~is a~~has a sequence of CVIM or CVLL ~~sequence~~.

~~45. The antibody conjugate of any one of claims 41-44, wherein at least one of the 1 to 20 amino acids preceding the amino acid motif is glycine.~~

~~46. The antibody conjugate of any one of claims 41-45, wherein at least three of the 1 to 20 amino acids preceding the amino acid motif is glycine or proline.~~

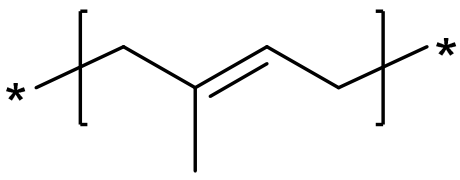
~~47. The antibody conjugate of any one of claims 41-46, wherein at least one of the 1 to 20 amino acids preceding the amino acid motif is any one selected from glycine, aspartic acid, arginine and serine.~~

~~48. The antibody conjugate of any one of claims 41-47, wherein at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids preceding the amino acid motif is (are) respectively glycine.~~

~~49. The antibody conjugate of any one of claims 41-48, wherein L further comprises the amino acid sequence GGGGGGGCVIM at the C-terminal.~~

~~50~~22. The antibody conjugate of any one of claims ~~12~~11-~~49~~21, wherein L ~~further~~ comprises at least one isoprenyl unit ~~derivative unit~~represented by of General Formula III:

[General Formula III]



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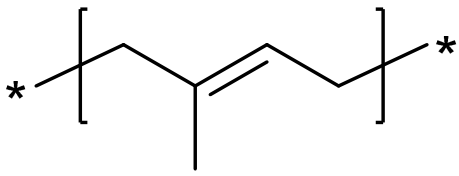
~~51~~23. The antibody conjugate of any one of claims ~~12~~11-~~50~~22, wherein L is a 3 to 50 heteroalkylene comprising an oxime and:

1) the oxygen atom of the oxime is on the side of L linked to W and the carbon atom of the oxime is on the side of L linked to Ab; or

2) the carbon atom of the oxime is on the side of L linked to W and the oxygen atom of the oxime is on the side of L linked to Ab.

~~52~~24. The antibody conjugate of any one of claims ~~12~~11-~~51~~23, wherein L ~~further~~ comprises an oxime and at least one isoprenyl unit represented by General Formula III covalently binds the oxime to Ab:

[General Formula III]



~~at least one isoprenyl unit covalently binds the oxime to Ab.~~

~~53~~25. The antibody conjugate of any one of claims ~~12~~11-~~52~~24, wherein L ~~further~~ comprises a connecting units represented by General Formula VIII or General Formula IX:

[General Formula VIII]

-(CH2)r(V(CH2)p)q-

[General Formula IX]

$-(CH_2CH_2X)_w-$

wherein

V is a single bond, -O-, -S-, $-NR^{21}-$, $-C(O)NR^{22}-$, $NR^{23}C(O)-$, $NR^{24}SO_2-$, or $-SO_2NR^{25}-$;

X is -O-, C_1-C_8 alkylene or $-NR^{21}-$;

R^{21} to R^{25} are, independently and respectively hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyl (C_6-C_{20}) aryl, or (C_1-C_6) alkyl (C_3-C_{20}) heteroaryl;

r is an integer of 0 to 10;

p is an integer of 0 to 10;
q is an integer of 1 to 20; and
w is an integer of 1 to 20.

~~54. The antibody conjugate of claim 53, wherein q is an integer of 4 to 20.~~

~~55. The antibody conjugate of claim 53 or 54, wherein q is an integer of 2 to 12.~~

~~56. The antibody conjugate of claim 53 or 54, wherein q is an integer of 6 to 20.~~

~~57. The antibody conjugate of claim any one of claims 53-55, wherein q is an integer of 2, 5 or 11.~~

~~58. The antibody conjugate of any one of claims 53-57, wherein r is an integer of 2.~~

~~59. The antibody conjugate of any one of claims 53-58, wherein p is an integer of 2.~~

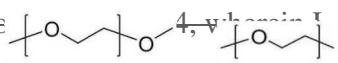
~~60~~26. The antibody conjugate of ~~any one of~~ claim~~s~~ ~~53~~25 ~~59~~, wherein V is -O-.

~~61. The antibody conjugate of claim 53, wherein :~~
~~r is an integer of 2;~~
~~p is an integer of 2;~~
~~q is an integer of 2, 5 or 11; and~~
~~V is -O- .~~

~~62~~27. The antibody conjugate of ~~any one of~~ claim~~s~~ ~~53~~25 or ~~61~~26, wherein X is -O-.

~~63. The antibody conjugate of any one of claims 63-62, wherein w is an integer of 6 to 20.~~

~~64. The antibody conjugate of any one of claims 53-63, wherein X is -O- , and w is an integer of 6 to 20.~~

~~65. The antibody conjugate of any one c~~  ~~4, v~~ ~~further comprises at least one polyethylene glycol unit represented by or .~~

~~66. The antibody conjugate of any one of claims 12-65, wherein L further comprises 1 to 12 -OCH_2CH_2- units.~~

~~67. The antibody conjugate of any one of claims 12-66, wherein L further comprises 3 to 12 -OCH_2CH_2- units.~~

~~68. The antibody conjugate of any one of claims 12-67, wherein L comprises 5 to 12 -OCH_2CH_2- units.~~

~~69. The antibody conjugate of any one of claims 12-68, wherein L comprises 6 to 12 -OCH_2CH_2- units.~~

~~70. The antibody conjugate of any one of claims 12-67, wherein L further comprises 3 -OCH_2CH_2- units.~~

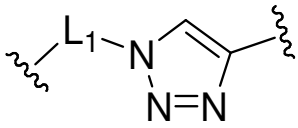
~~71~~28. The antibody conjugate of any one of claims ~~12~~11-~~68~~27, wherein L ~~further~~ comprise<u>s</u> an oxime and ~~at least one polyethylene glycol unit~~<u>the connecting unit</u> covalently ~~bonds~~ <u>binds</u> the oxime to ~~an~~ <u>the</u> active agent.

~~72~~29. The antibody conjugate of any one of claims ~~12~~11-~~71~~28, wherein L further comprises a <u>binding</u> unit formed by 1,3-dipolar cycloaddition reactions, hetero-<u>Diels-Alder</u>~~diels~~ reactions, nucleophilic substitution reactions, nonaldol type carbonyl reactions, additions to carbon-carbon multiple bonds, oxidation reactions or click reactions.

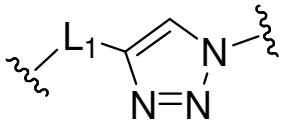
~~73. The antibody conjugate of claim 72, wherein the binding units are~~ <u>is</u> ~~formed through reaction of acetylene and azide, or through reaction of an aldehyde or ketone group with hydrazine or hydroxylamine.~~

~~74~~30. The antibody conjugate of any one of claims ~~12~~11-~~73~~29, wherein L ~~further~~ comprises a binding unit represented by General Formulae IV, V, VI or VII ~~below~~:

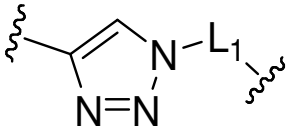
[General Formula IV]



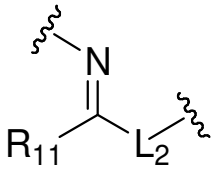
[General Formula V]



[General Formula VI]



[General Formula VII]



wherein

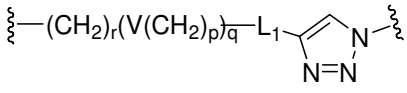
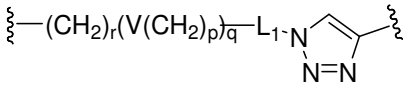
L^1 is a ~~single~~ bond or an alkylene of C_1-C_{30}; and
R^{11} is a hydrogen or an alkyl of C_1-C_{10}.

~~75. The antibody conjugate of claim 74, wherein L^+ is a single bond.~~

~~76. The antibody conjugate of claim 74, wherein L^+ is a C_{11}-alkylene.~~

~~77. The antibody conjugate of claim 74, wherein L^+ is a C_{12}-alkylene.~~

~~78~~31. The antibody conjugate of claim ~~74~~30, wherein L further comprises

 or  ; wherein

V is a single bond, -O-, -S-, -NR^{21}-, -C(O)NR^{22}-, $NR^{23}C(O)$-, $NR^{24}SO_2$-, or -SO_2NR^{25}-;

R^{21} to R^{25} are, independently and respectively hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyl C_6-C_{20} aryl, or C_1-C_6 alkyl C_3-C_{20} heteroaryl;

r is ~~an integer of~~ 1 to 10;

p is ~~an integer of~~ 0 to 10;

q is ~~an integer of~~ 1 to 20; and

L^1 is a ~~single~~ bond.

~~79. The antibody conjugate of claim 78, wherein r is an integer of 2 or 3.~~

~~80. The antibody conjugate of claim 78 or 79, wherein p is an integer of 1 or 2.~~

~~81. The antibody conjugate of any one of claims 78-80, wherein q is an integer of 1 to 6.~~

~~82. The antibody conjugate of claim 78, wherein r is an integer of 2 or 3; p is an integer of 1 or 2; and q is an integer of 1 to 6.~~

~~83~~32. The antibody conjugate of any one of claims ~~12~~11-~~83~~31, wherein the isoprenoid transferase is a farnesyl protein transferase (FTase) or a geranylgeranyl transferase (GGTase).

~~84~~33. The antibody conjugate of any one of claims ~~12~~11-~~83~~32, wherein L ~~further comprises~~is a branched 1-50 atom heteroalkylene ~~one or more branched linkers covalently coupled to Ab,~~ wherein

~~i)~~ each branched 1-50 atom heteroalkylene ~~branched linker~~ comprises:

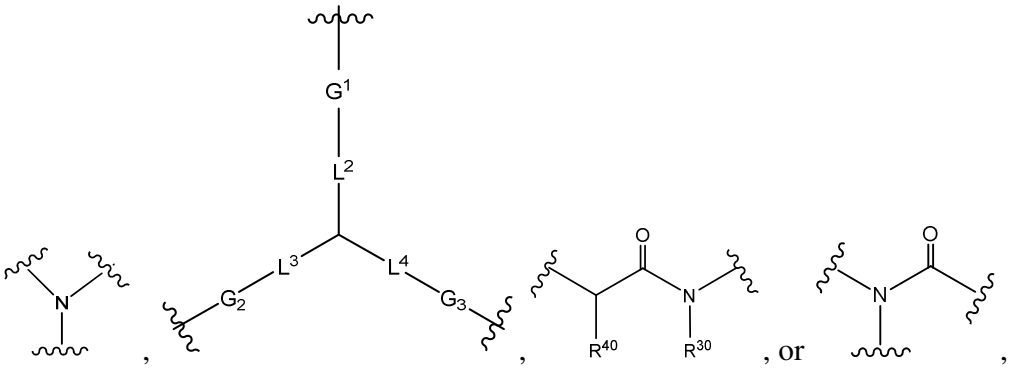
i) a branching unit (BR) covalently coupled to Ab by a primary linker (PL);

~~ii) each branched linker comprises~~ii) a first branch (B1), in which a first active agent is covalently coupled to the branching unit by a secondary linker (SL) and a cleavage group (CG); and

~~iii) each branched linker further comprises~~iii) a second branch (B2), in which either a) a second active agent is covalently coupled to the branching unit by a secondary linker (SL) and a cleavage group (CG) or b) a polyethylene glycol moiety is covalently coupled to the branching unit,

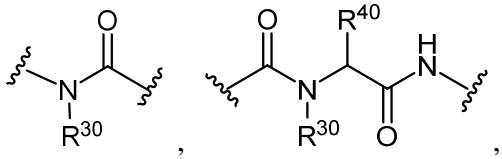
wherein each cleavage group can be hydrolyzed to release the active agent from the antibody-drug conjugate.

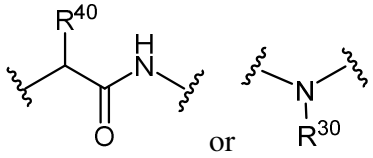
~~85~~34. The antibody conjugate of claim ~~84~~33, wherein the branching unit is represented by:

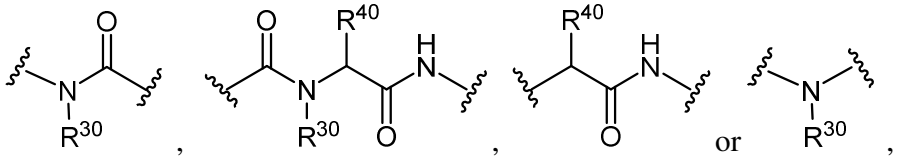


L^2, L^3 and L^4 are each independently a bond or $-C_nH_{2n}-$;

n is an integer of 1 to 30;

G^1, G^2 and G^3 are each independently, a bond, 





R^{30} is hydrogen or $C_{1\text{-}30}$ alkyl;

L^5 is a direct bond or $C_{1\text{-}10}$ alkylene; and

R^{50} is hydrogen $C_{1\text{-}30}$ alkyl.

86. The antibody conjugate of claim 84 or 85, wherein the antibody conjugate comprises at least one branched linker covalently bonded to Ab; and at least two active agents covalently linked to the branched linker.

87. The antibody conjugate of any one of claims 84-86, wherein the antibody conjugate comprises at two or more branched linker covalently bonded to Ab; and the branched linkers bind to at least two active agents.

88. The antibody conjugate of claim 86 or 87, wherein the antibody conjugate comprises 3 branched linkers.

89. The antibody conjugate of claim 86 or 87, wherein the antibody conjugate comprises 4 branched linkers.

90. The antibody conjugate of claim 86 or 87, wherein the antibody conjugate comprises 1 branched linker.

91. The antibody conjugate of claim 86 or 87, wherein the respective branched linkers each bind to two active agents.

92. The antibody conjugate of claim 86 or 87, wherein the conjugate comprises at least two different active agents.

93. The antibody conjugate of any one of claims 86-92, wherein the branched linker is bonded to at least two active agents.

94. The antibody conjugate of any one of claims 84-93, wherein the active agents are bonded to a branched linker by a cleavable bond.

95. The antibody conjugate of claim 84 or 85, wherein the active agents bind to a branching unit through a second linker; and the branching units are bonded to an anti-ROR1 antibody by a first linker.

~~96. The antibody conjugate of any one of claims 84-95, wherein the branching unit is a nitrogen atom.~~

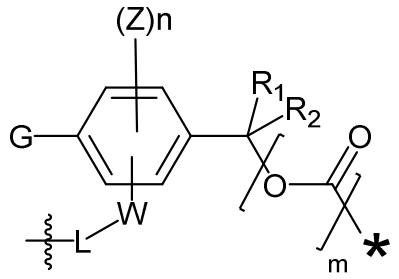
~~97. The antibody conjugate of any one of claims 84-96, wherein the branching unit is an amide, and the first linker comprises a carbonyl of the amide.~~

~~98. The antibody conjugate of any one of claims 84-96, wherein the branching unit is an amide, and the second linker comprises a carbonyl of the amide.~~

~~99~~35. The antibody conjugate of any one of claims ~~84~~33-~~98~~34, wherein the branching unit is a lysine unit.

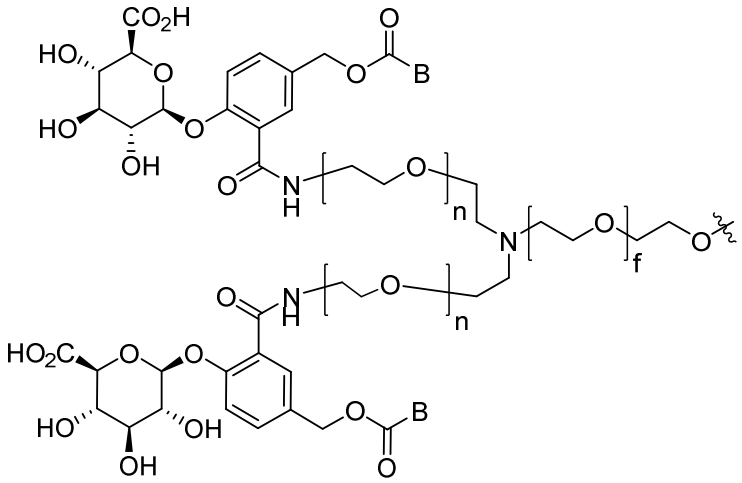
36. The antibody conjugate of any one of claims 33-35, wherein each cleavage group has a structure represented by Chemical Formula IIa:

[Chemical Formula (IIa)]



.

~~100~~37. The antibody conjugate of any one of claims ~~12~~11-~~85~~34, wherein ~~the antibody conjugate~~X^A comprises a structure represented by:



wherein

each B is an active agent~~s~~;

each n is independently ~~an integer of~~ 0 to 30; and

~~each~~ f~~n~~ is ~~independently an integer of~~ 0 to 30.

~~101. The antibody conjugate of claim 100, wherein n is an integer of 1 to 10.~~

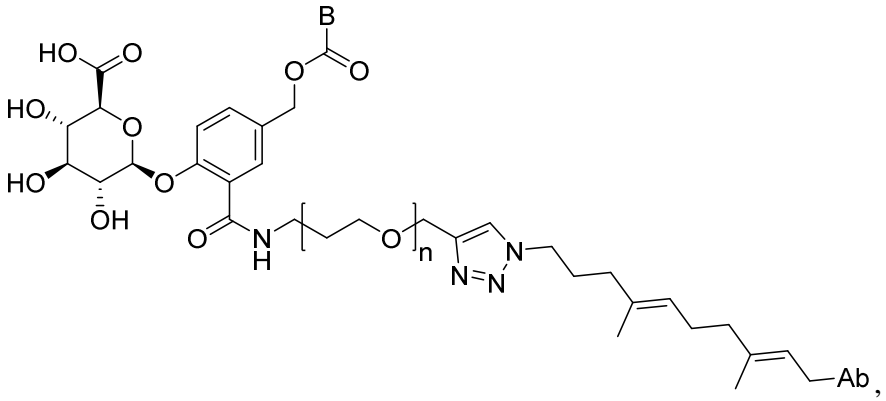
~~102. The antibody conjugate of claim 100, wherein n is an integer of 4 to 20.~~

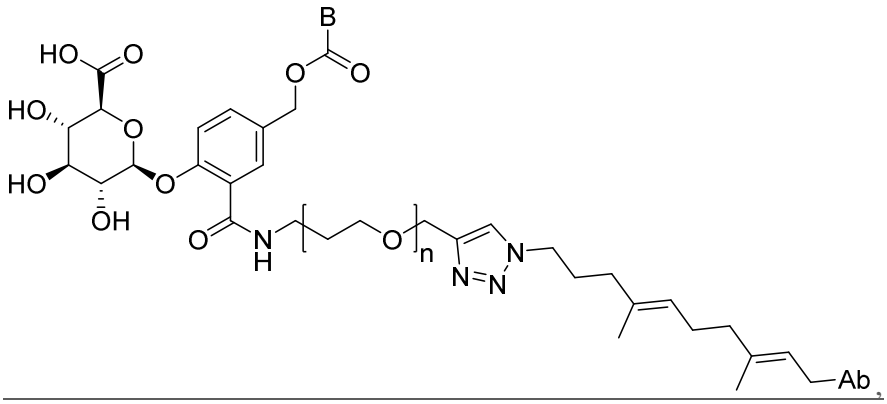
~~103. The antibody conjugate of any one of claims 100-102, wherein L comprises oxime, and at least one polyethylene glycol unit covalently binds the oxime to an active agent.~~

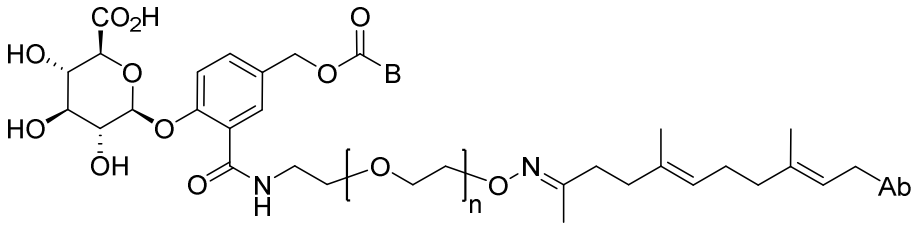
~~104. The antibody conjugate according to any one of claims 11-103, wherein the cleavable bond is cleavable within a target cell.~~

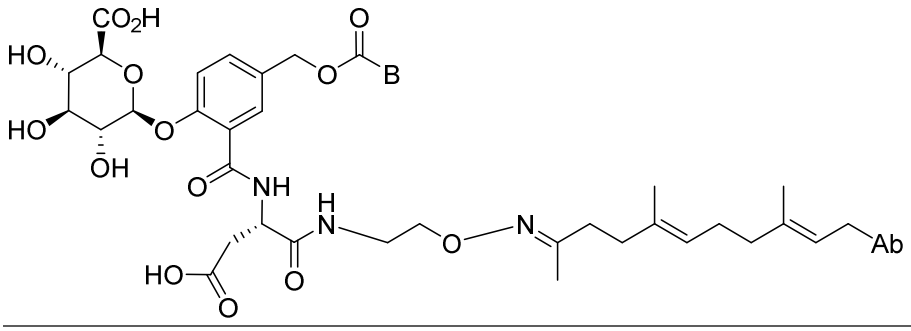
~~105. The antibody conjugate according to any one of claims 11-103, wherein the cleavable bond is cleavable by an activator (e.g., radiation, acid, base, or an enzyme).~~

~~106~~38. The antibody conjugate of any one of claims 1-10, wherein the conjugate comprises a structure represented by:~~of any one of claims 1-11, wherein the conjugate is represented by the following structure or a pharmaceutically acceptable salt thereof:~~









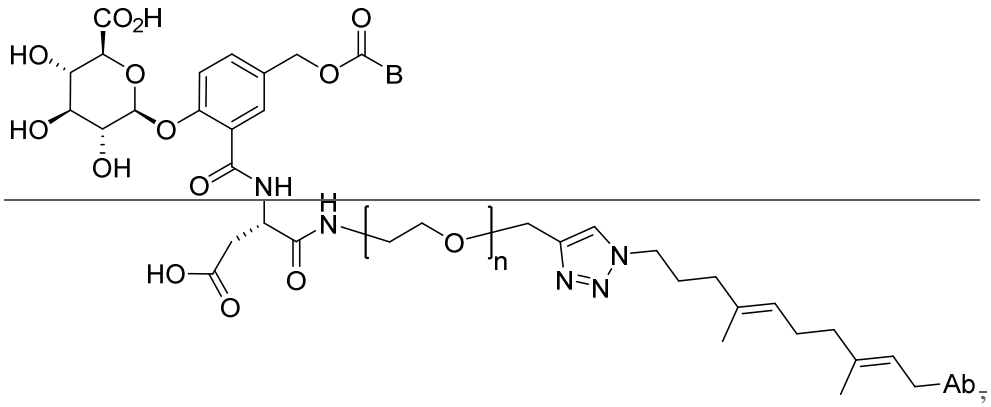
or a pharmaceutically acceptable salt thereof; and

~~wherein~~ Ab is ~~an~~ the anti-ROR1 antibody;

B is ~~an~~ the active agent; and ~~and;~~

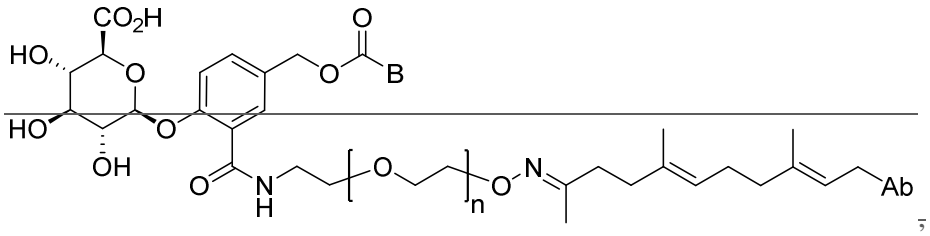
~~-~~n is ~~an integer of~~ 1 to 20.

~~107. The antibody conjugate of any one of claims 1-11, wherein the conjugate is represented by the following structure or a pharmaceutically acceptable salt thereof:~~



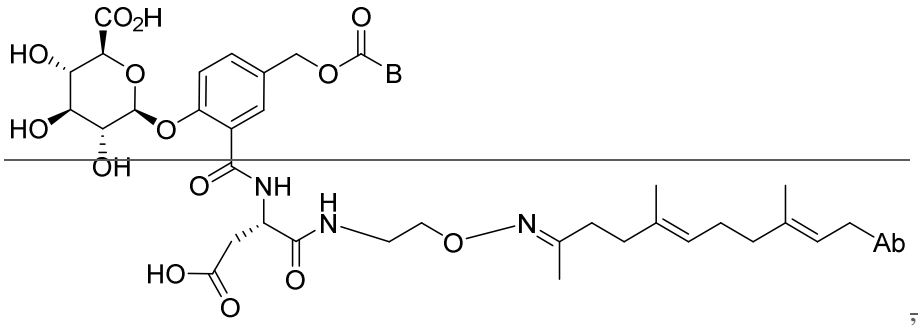
~~wherein Ab is an anti-ROR1 antibody; B is an active agent and; n is an integer of 1 to 20.~~

~~108. The antibody conjugate of any one of claims 1-11, wherein the conjugate is represented by the following structure or a pharmaceutically acceptable salt thereof:~~



~~wherein Ab is an anti-ROR1 antibody; B is an active agent and; n is an integer of 1 to 20.~~

~~109. The antibody conjugate of any one of claims 1-11, wherein the conjugate is represented by the following structure or a pharmaceutically acceptable salt thereof:~~



~~wherein Ab is an anti-ROR1 antibody; B is an active agent and; n is an integer of 1 to 20.~~

~~110~~39. The antibody conjugate of any one of claims 1-~~109~~38, wherein the active agent is a chemotherapeutic agent or a toxin.

~~111~~40. The antibody conjugate of any one of claims 1-~~110~~39, wherein the active agent is an immunoregulatory compound, anti-cancer agent, antiviral, antibacterial, antifungal, antiparasitic or a combination of these.

~~112~~41. The antibody conjugate of any one of claims 1-~~111~~40, wherein the active agent is selected from:

(a) erlotinib, bortezomib, fulvestrant, sutent, letrozole, imatinib mesylate, PTK787/ZK 222584, oxaliplatin, 5-fluorouracil, leucovorin, rapamycin, lapatinib, lonafarnib, sorafenib, gefitinib, AG1478, AG1571, thiotepa, cyclophosphamide, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, ethylenimine, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, teimethylolomelamine, bullatacin, bullataciionone, camptothecin, topotecan, bryostatin, callystatin, CC-1065, adozelesin, carzelesin, bizelesin, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, KW-2189, CB1-TM1, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotoxin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, calicheamicin gamma 1, calicheamicin omega 1, dynemicin, dynemicin A, clodronate, esperamicin, neocarzinostatin chromophore, aclacinomysins, actinomycin, antrymycin, azaserine, bleomycins, catcinomycin, carabicin, carninomycin, carzinophilin,

chromomycins, dactinomycin, daunorubicin, detorubucin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubucin, liposomal doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptomigrin, streptozocin, tudercidin, ubenimex, zinostatin, zorubicin, 5-fluororacil, denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thiguianine, ancitabine, azacytidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone, propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, folinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatrexate, defofamine, democolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, 2-ethylhydrazide, procarbazine, polysaccharide-k, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triazqiqzuone, 2,2', 2''-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, Mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside, cyclophosphamide, thiotepa, paclitaxel, albumin-engineered nanoparticle formulation of paclitaxel, docetaxel, chlorambucil, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, carboplatin, vinblastine, platinum, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, CPT-11, topoisomerase inhibitor RFS 2000, difluoromethylornithine, retinoic acid, capecitabine, or pharmaceutically acceptable salts, solvates or acids thereof;

(b) monokine, lympokine, traditional polypeptide hormone, parathyroid hormone, thyroxine, relaxin, prorelaxin, glycoprotein hormone, follicle stimulating hormone, thyroid stimulating hormone, luteinizing hormone, hepatic growth factor fibroblast growth factor, prolactin, placental lactogen, tumor necrosis factor, tumor necrosis factor-α, tumor necrosis factor-, Mullerian inhibiting substance, mouse gonadotropin associated peptide, inhibin, activin, vascular endothelial growth factor, thrombopoietin, erythropoietin, osteoinductive factor, interferon, interferon-, interferon-, interferon-, colony stimulating factor (CSF), macrophage-

CSF, granulocyte-macrophage-CSF), granulocyte-macrophage-CSF, granulocyte-CSF, interleukin (IL), IL-1, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, I L-12, tumor necrosis factor, polypeptide factor, LIF, kit ligand, or mixtures thereof;

(c) diphtheria toxin, botulinum toxin, tetanus toxin, dysentery toxin, cholera toxin, amanitin, -amatinin, pyrrolobenzodiazepine, pyrrolobenzodiazepine derivative, indolinobenzodiazepine, pyridobenzodiazepine, tetrodotoxin, brevetoxin, ciguatoxin, ricin, AM toxin, auristatin, tubulysin, geldanamycin, maytansinoid, calicheamicin, daunomycin, doxorubicin, methotrexate, vindesine, SG2285, dolastatin, dolastatin analog, auristatin, cryptophycin, camptothecin, rhizoxin, rhizoxin derivatives, CC-1065, CC-1065 analogs or derivatives, duocarmycin, enediyne antibiotic, esperamicin, epothilone, toxoid, or mixtures thereof;

(d) affinity ligand, where the affinity ligand is a substrate, inhibitor, active agent, neurotransmitter, radioactive isotope, or mixtures thereof;

(e) radioactive label, 32P, 35S, fluorescent dye, electron dense reagent, enzyme, biotin, streptavidin, dioxigenin, hapten, immunogenic protein, nucleic acid molecule with a sequence complementary to a target, or mixtures thereof;

(f) immunomodulatory compound, anti-cancer agent, anti-viral agent, anti-bacterial agent, anti-fungal agent, anti-parasitic agent, or mixtures thereof;

(g) tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone or toremifene;

(h) 4(5)-imidazole, aminoglutethimide, megestrol acetate, exemestane, letrozole or anastrozole

(i) flutamide, nilutamide, bicalutamide, leuprolide, goserelin, or troxacitabine;

(j) aromatase inhibitor;

(k) protein kinase inhibitor;

(l) lipid kinase inhibitor;

(m) antisense oligonucleotide;

(n) ribozyme;

(o) vaccine; and

(p) anti-angiogenic agent.

~~113~~42. The antibody conjugate of any one of claims 1-~~110~~39, wherein~~-~~:

Ab is an anti-ROR1 antibody;

the active agent is a pyrrolobenzodiazepine dimer;

the linker links Ab to the N10 or N'10 position of the pyrrolobenzodiazepine dimer; and

y is an integer of 1 to 20.

~~114~~43. The antibody conjugate of claim ~~113~~42, wherein:

the active agent is a pyrrolobenzodiazepine dimer;

the pyrrolobenzodiazepine dimer is substituted by X at the N10 position or by X' at the N'10 position, where X or X' links the pyrrolobenzodiazepine dimer to the linker;

X and X' are, respectively and independently, -C(O)O*, -S(O)O-*, -C(O)-*, -C(O)NR^X-*, -$S(O)_2NR^X$-*, -P(O)R'NR^X-*, -S(O)NR^X-*, or -PO_2NR^X-*;

R^X is C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-20} heteroaryl or C_{5-20} aryl;

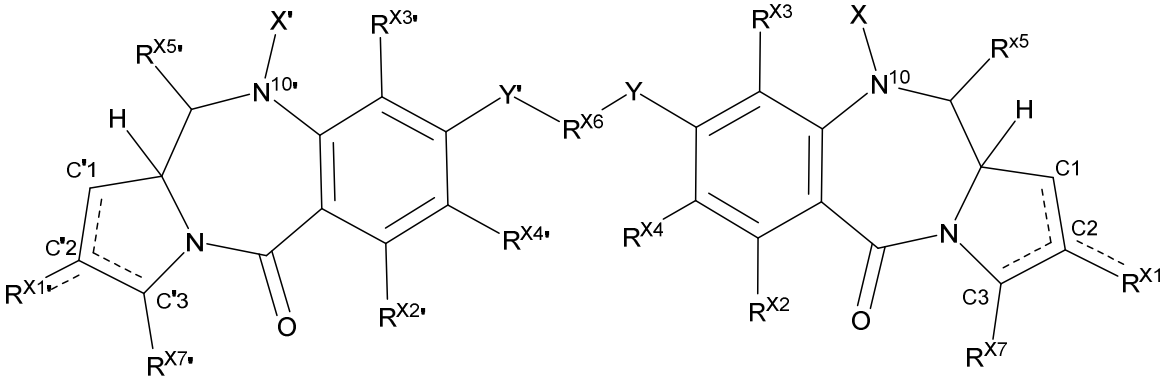
R^X' is OH, N_3, CN, SH, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{3-20} heteroaryl, C_{5-20} aryl or amino; and

* is a binding site between the pyrrolobenzodiazepine dimer and the linker.

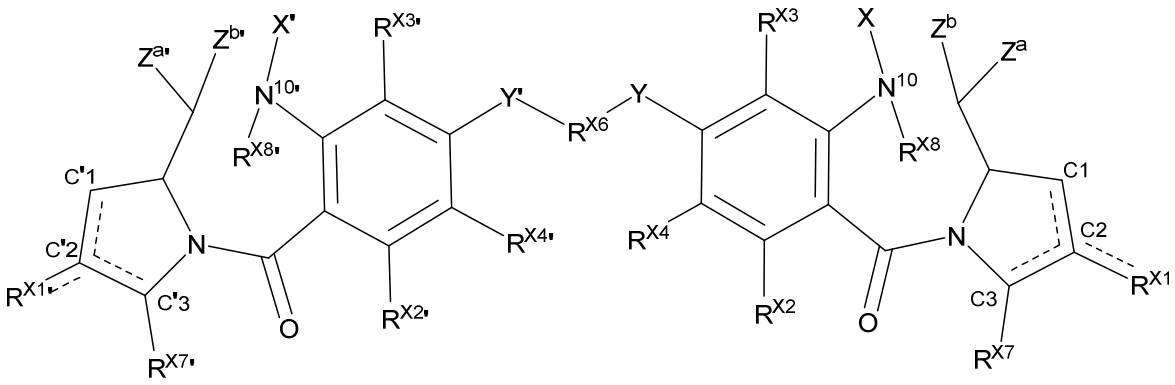
~~115. The antibody conjugate of claim 114, wherein X and X' are each independently C(O)O*, C(O) * or C(O)NR^X *.~~

~~116~~44. The antibody conjugate of claim ~~114~~ 43~~or 115~~, wherein the ~~pyrrolobenzodiazepine dimer~~active agent is represented by General Formula X or General Formula XI ~~below~~ :

[General Formula X]



[General Formula XI]



wherein:

a dotted line represents an optional double bond as permitted by valency;

R^{X1} and $R^{X1'}$ are independently selected from H, OH, =O, $=CH_2$ CN, R^m, OR^m, $=CH\text{-}R^{m'}$, $=C(R^{m'})_2$, $OSO_2\text{-}R^m$, CO_2R^m, COR^m, halo and dihalo;

$R^{m'}$ is selected from R^m, CO_2R^m, COR^m, CHO, CO_2H and halo;

Each R^m is independently selected from of $C_{1\text{-}12}$ alkyl, $C_{2\text{-}12}$ alkenyl, $C_{2\text{-}12}$ alkynyl, $C_{5\text{-}20}$ aryl, $C_{5\text{-}20}$ heteroaryl, $C_{3\text{-}6}$ cycloalkyl, 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl and 5 to 7 membered heteroaryl; or R^m is X or X`;

R^{X2}, $R^{X2'}$, R^{X3}, $R^{X3'}$, R^{X5} and $R^{X5'}$ are each independently selected from H, R^m, OH, OR^m, SH, SR^m, NH_2, NHR^m, $NR^m{}_2$, NO_2, Me_3Sn and halo;

R^{X4} and $R^{X4'}$ are each independently selected from H, R^m, OH, OR^m, SH, SR^m, NH_2, NHR^m, $NR^m{}_2$, NO_2, Me_3Sn, halo, $C_{1\text{-}6}$ alkyl $C_{1\text{-}6}$ alkoxy, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{3\text{-}6}$ cycloalkyl, 3-7 membered heterocycloalkyl, $C_{5\text{-}12}$ aryl, 5 to 7 membered heteroaryl, -CN, -NCO, $-OR^n$, $-OC(O)R^n$, $-OC(O)NR^nR^{n'}$, $-OS(O)R^n$, $-OS(O)_2R^n$, $-SR^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-S(O)NR^nR^{n'}$, $-S(O)_2NR^nR^{n'}$, $-OS(O)NR^nR^{n'}$, $-OS(O)_2NR^nR^{n'}$, $-NR^nR^{n'}$, $-NR^nC(O)R^o$, $-NR^nC(O)OR^o$, $-NR^nC(O)NR^oR^{o'}$, $-NR^nS(O)R^o$, $-NR^nS(O)_2R^o$, $-NR^nS(O)NR^oR^{o'}$, $-NR^nS(O)_2NR^oR^{o'}$, $-C(O)R^n$, $-C(O)OR^n$ and $-C(O)NR^nR^{n'}$;

R^X and $R^{X'}$ are each independently selected from H, OH, N_3, CN, NO_2, SH, NH_2, ONH_2, $NHNH_2$, halo, $C_{1\text{-}8}$ alkyl, $C_{3\text{-}8}$ cycloalkyl, $C_{1\text{-}8}$ alkoxy, $C_{1\text{-}8}$ alkylthio, $C_{3\text{-}20}$ heteroaryl, $C_{5\text{-}20}$ aryl or mono- or di-$C_{1\text{-}8}$ alkylamino;

Y and Y' are each independently selected from O, S and N(H);

each R^{x6} is independently selected from $C_{3\text{-}12}$ alkylene, $C_{3\text{-}12}$ alkenylene, or $C_{3\text{-}12}$ heteroalkylene;

R^{X7} and $R^{X7'}$ are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{6-10} aryl, 5 to 7 membered heteroaryl, $-OR^r$, $-OC(O)R^r$, $-OC(O)NR^rR^{r'}$, $-OS(O)R^r$, $-OS(O)_2R^r$, $-SR^r$, $-S(O)R^r$, $-S(O)_2R^r$, $-S(O)NR^rR^{r'}$, $-S(O)_2NR^rR^{r'}$, $-OS(O)NR^rR^{r'}$, $-OS(O)_2NR^rR^{r'}$, $-NR^rR^{r'}$, $-NR^rC(O)R^s$, $-NR^rC(O)OR^s$, $-NR^rC(O)NR^sR^{s'}$, $-NR^rS(O)R^s$, $-NR^rS(O)_2R^s$, $-NR^rS(O)NR^sR^{s'}$, $-NR^rS(O)_2NR^sR^s$, $-C(O)R^r$, $-C(O)OR^s$ or $-C(O)NR^rR^{r'}$;

~~Each~~ each R^r, $R^{r'}$, R^s and $R^{s'}$ is independently selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-13} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl and 5 to 7 membered heteroaryl;

each R^{X8} and $R^{X8'}$ is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} heteroalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl, 5 to 7 membered heteroaryl, $-S(O)R^m$, $-S(O)_2R^m$, $-S(O)NR^mR^{m'}$, $-S(O)_2NR^mR^{m'}$, $-NR^mR^{m'}$, $-NR^mC(O)R^m$, $NR^mC(O)OR^n$, $-NR^mC(O)NR^nR^{n'}$, $-NR^mS(O)R^n$, $-NR^mS(O)_2R^n$, $-NR^mS(O)NR^nR^{n'}$, $-NR^mS(O)_2NR^nR^{n'}$, $-C(O)R^m$, $-C(O)OR^m$ and $-C(O)NR^mR^{m'}$;

Z^a is ~~selected from~~ OR^{X12a}, $NR^{X12a}R^{X12a}$, or SR^{X12a};

Z^b is ~~selected from~~ OR^{X13a}, $NR^{X13a}R^{X13a}$, or SR^{X13a};

$Z^{a'}$ is ~~selected from~~ OR^{X12a}, $NR^{X12a}R^{X12a}$, or SR^{X12a};

$Z^{b'}$ is ~~selected from~~ $OR^{X13a'}$, $NR^{X13a'}R^{X13a'}$, or $SR^{X13a'}$;

each R^{X12a}, $R^{X12a'}$, $R^{X13a'}$ and $R^{x13a'}$ is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3 to 7 membered heterocycloalkyl, C_{5-10} aryl, 5 to 7 membered heteroaryl,

$-C(O)R^{X15a}$, $-C(O)OR^{X15a}$ and $-C(O)NR^{X15a}R^{X15a'}$;;

each R^{X15a} and $R^{x15a'}$ is independently selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{5-20} aryl, C_{5-20} heteroaryl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl, and 5 to 7 membered heteroaryl; ~~o~~

each R^{X13a} and R^{X14a} is independently H or alkyl; or R^{X13a} and R^{X14a}, together with the atom to which it is connected, form 3-7 membered heterocyclyl, form 3-7 membered heterocycloalkyl, or form 3-7 membered heteroaryl, and the $R^{X13a'}$ and $R^{X14a'}$ arbitrarily bind to the atoms to which they are attached to form 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl, or 3-7 membered heteroaryl; and

each of R^n, $R^{n'}$, R^o, $R^{o'}$, R^p and $R^{p'}$ is independently selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-13} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl, and 5 to 7 membered heteroaryl.

~~117. The antibody conjugate of claim 116, wherein:~~

~~R^m is independently selected from of C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{5-20} aryl, C_{5-20} heteroaryl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl and 5 to 7 heteroaryl; and~~

~~R^m is substituted C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{5-20} aryl, C_{5-20} heteroaryl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl or 5 to 7 heteroaryl.~~

~~118. The antibody conjugate of claim 116 or 117, wherein:~~

~~R^{X4} and $R^{X4'}$ are independently selected from H, R^m, OH, OR^m, SH, SR^m, NH_2, NHR^m, $NR^mR^{m'}$, NO_2, Me_3SN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-12} 5 to 7 heteroaryl, CN, NCO, OR^a, $OC(O)R^a$, $OC(O)NR^aR^{a'}$, $OS(O)R^a$, $OS(O)_2R^a$, SR^a, $S(O)R^a$, $S(O)_2R^a$, $S(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $OS(O)NR^aR^{a'}$, $OS(O)_2NR^aR^{a'}$, $NR^aR^{a'}$, $NR^aC(O)R^o$, $NR^aC(O)OR^o$, $NR^aC(O)NR^oR^{o'}$, $NR^aS(O)R^o$, $NR^aS(O)_2R^o$, $NR^aS(O)NR^oR^{o'}$, $NR^aS(O)_2NR^oR^{o'}$, $C(O)R^a$, $C(O)OR^a$ and $C(O)NR^aR^{a'}$; and~~

~~R^{X4} or $R^{X4'}$ is C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-12} aryl or 5 to 7 heteroaryl, and additionally is substituted with at least one C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl, 5 to 7 heteroaryl, $-OR^p$, $-OC(O)R^p$, $-C(O)NR^pR^{p'}$, $-OS(O)R^p$, $-OS(O)_2R^p$, SR^p, $S(O)R^p$, $S(O)_2R^p$, $S(O)NR^pR^{p'}$, $S(O)_2NR^pR^{p'}$, $OS(O)NR^pR^{p'}$, $-OS(O)_2NR^pR^{p'}$, $NR^pR^{p'}$, $NR^pC(O)R^q$, $NR^pC(O)OR^q$, $NR^pC(O)NR^qR^{q'}$, $NR^pS(O)R^q$, $NR^pS(O)_2R^q$, $NR^pS(O)NR^qR^{q'}$, $NR^pS(O)_2NR^qR^{q'}$, $C(O)R^p$, $C(O)OR^p$ or $C(O)NR^pR^p$.~~

~~119. The antibody conjugate of any one of claims 116-118, wherein:~~

~~R^{X7} and $R^{X7'}$ are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{6-10} aryl, 5 to 7 heteroaryl, $-OR^f$, $-OC(O)R^f$, $-OC(O)NR^fR^{f'}$, $-OS(O)R^f$, $-OS(O)_2R^f$, $-SR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-S(O)NR^fR^{f'}$, $-S(O)_2NR^fR^{f'}$, $-OS(O)NR^fR^{f'}$, $OS(O)_2NR^fR^{f'}$, $NR^fR^{f'}$, $NR^fC(O)R^s$, $NR^fC(O)OR^s$, $NR^fC(O)NR^sR^{s'}$,~~

~~$-NR^fS(O)R^s$, $-NR^fS(O)_2R^s$, $-NR^fS(O)NR^sR^{s'}$, $-NR^fS(O)_2NR^sR^s$, $-C(O)R^f$, $-C(O)OR^s$ or~~ and ~~$-C(O)NR^fR^{f'}$;~~

~~R^{X7} and $R^{X7'}$ are C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{6-10} aryl, or 5 to 7 heteroaryl, and additionally C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{6-10} aryl, or 5 to 7 heteroaryl, $-OR^t$, $-OC(O)R^t$, $-OC(O)NR^tR^{t'}$, $-OS(O)R^t$, $-OS(O)_2R^t$, $-SR^t$, $-S(O)R^t$, $-S(O)_2R^t$, $-S(O)NR^tR^{t'}$, $-S(O)_2NR^tR^{t'}$, $-OS(O)NR^tR^{t'}$, $-OS(O)_2NR^tR^{t'}$, $-NR^tR^{t'}$, $-NR^tC(O)R^u$, $-NR^tC(O)OR^u$, $-NR^tC(O)NR^uR^{u'}$, $-NR^tS(O)R^u$, $-NR^tS(O)_2R^u$, $-NR^tS(O)NR^uR^{u'}$, $-NR^tS(O)_2NR^uR^{u'}$, $-C(O)R^t$, $-C(O)OR^t$ or $-C(O)NR^tR^{t'}$; and~~

~~R^f, $R^{f'}$, R^s, $R^{s'}$, R^t, $R^{t'}$, R^u and $R^{u'}$ are each independently selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-13} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl, and 5 to 7 heteroaryl.~~

~~120~~45. The antibody conjugate of ~~any one of~~ claim~~s~~ ~~116~~44-~~119~~, wherein R^{X1} and $R^{X1'}$ are both R^m; and R^m is C_{1-6} alkyl, C_{2-6} alkenyl, C_{5-7} aryl, or C_{3-6} heteroaryl.

~~121~~46. The antibody conjugate of any one of claims ~~116~~44-~~120~~45, wherein each of R^{X2}, $R^{X2'}$, R^{X3}, $R^{X3'}$, R^{X5} and $R^{X5'}$ are independently selected from H or OH.

~~122~~47. The antibody conjugate of any one of claims ~~116~~44-~~121~~46, wherein R^{X4} and $R^{X4'}$ are both R^m; and R^m is C_{1-6} alkoxy.

~~123. The antibody conjugate of any one of claims 116-122, wherein R^{X4} and $R^{X4'}$ are each independently selected from methoxy, ethoxy and butoxy.~~

~~124~~48. The antibody conjugate of any one of claims ~~116~~44-~~123~~47, wherein Y and Y' are each O.

~~125~~49. The antibody conjugate of any one of claims ~~116~~44-~~124~~48, wherein:

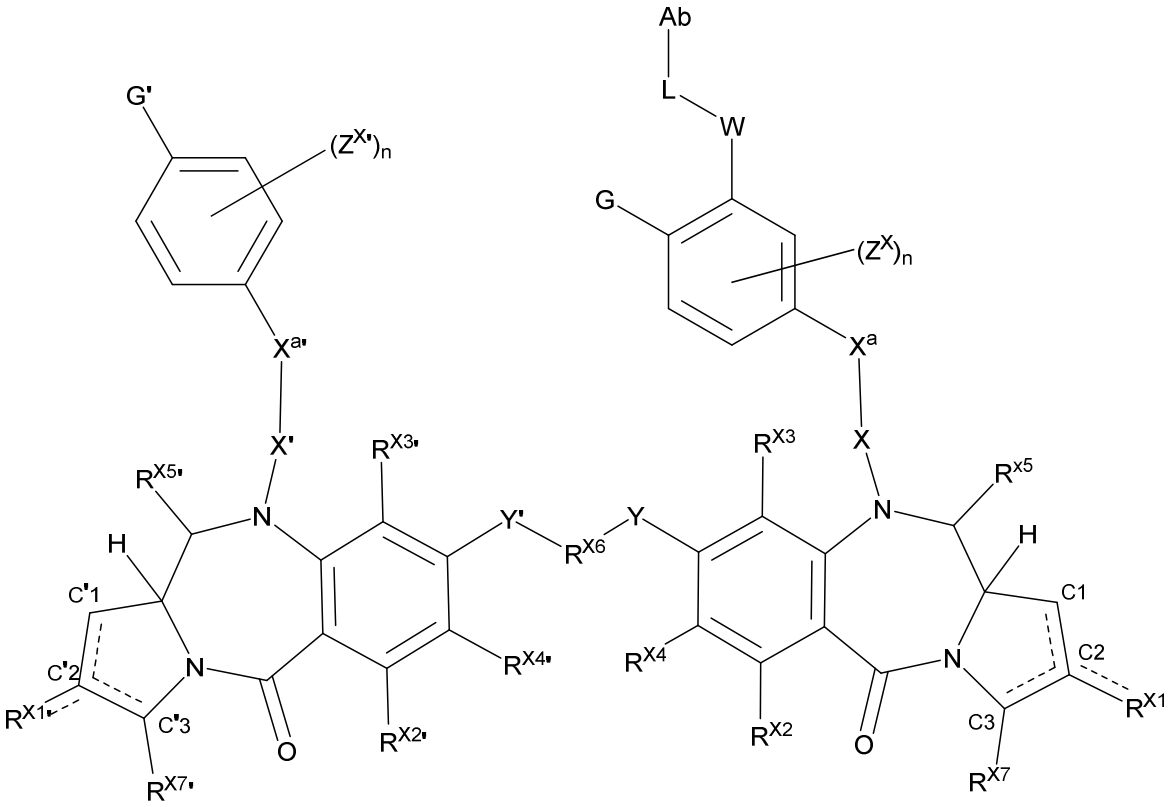
R^{x6} is C_{3-12} alkylene, C_{3-12} alkenylene or C_{3-12} heteroalkylene, where R^{x6} is substituted with $-NH_2$, $-NHR^m$, $-NHC(O)R^m$, $-NHC(O)R^m$, $-NHC(O)CH_2-[OCH_2CH_2]_n-R^{XX}$, or $-[CH_2CH_2O]^n-R^{XX}$;

R^{XX} is H, OH, N_3, CN, NO_2, SH, NH_2, ONH_2, $NHNH_2$, halo, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{3-20} heteroaryl, C_{5-20} aryl or mono- or di-C_{1-8} alkyl amino; and

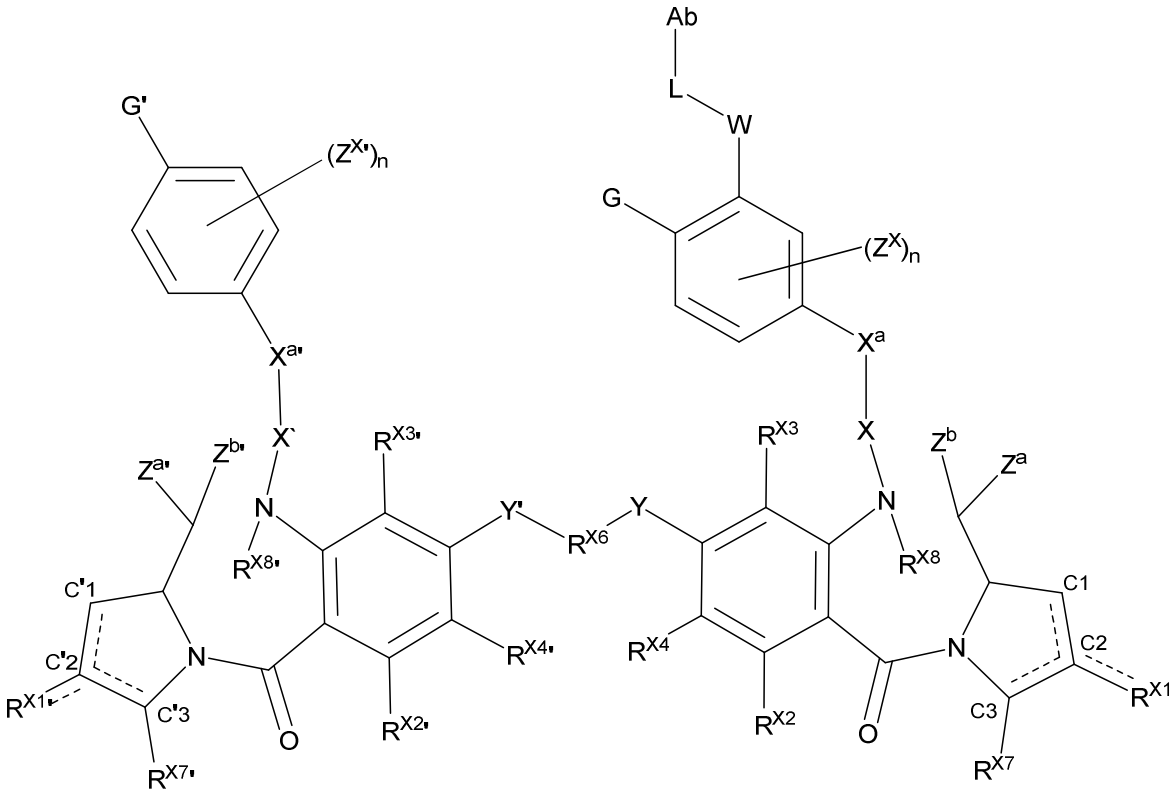
n is an integer of 1 through 6.

~~126~~50. The antibody conjugate of any one of claims 1-~~125~~49, X^A comprises a structure represented by ~~wherein the active agent has a structure represented by~~ General Formula XII or General Formula XIII:~~;~~

[General Formula XII]



[General Formula XIII]



wWherein

a dotted line represents an optional double bond as permitted by valency;

R^{X1} and $R^{X1'}$ are independently selected from H, OH, =O, $=CH_2$ CN, R^m, OR^m, $=CH\text{-}R^{m'}$, $=C(R^{m'})_2$, $OSO_2\text{-}R^m$, CO_2R^m, COR^m, halo and dihalo;

$R^{m'}$ is selected from R^m, CO_2R^m, COR^m, CHO, CO_2H and halo;

Each R^m is independently selected from of $C_{1\text{-}12}$ alkyl, $C_{2\text{-}12}$ alkenyl, $C_{2\text{-}12}$ alkynyl, $C_{5\text{-}20}$ aryl, $C_{5\text{-}20}$ heteroaryl, $C_{3\text{-}6}$ cycloalkyl, 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl and 5 to 7 membered heteroaryl; or R^m is X or X`;

R^{X2}, $R^{X2'}$, R^{X3}, $R^{X3'}$, R^{X5} and $R^{X5'}$ are each independently selected from H, R^m, OH, OR^m, SH, SR^m, NH_2, NHR^m, $NR^m{}_2$, NO_2, Me_3Sn and halo;

R^{X4} and $R^{X4'}$ are each independently selected from H, R^m, OH, OR^m, SH, SR^m, NH_2, NHR^m, $NR^m{}_2$, NO_2, Me_3Sn, halo, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{3\text{-}6}$ cycloalkyl, 3-7 membered heterocycloalkyl, $C_{5\text{-}12}$ aryl, 5 to 7 membered heteroaryl, -CN, -NCO, $-OR^n$, $-OC(O)R^n$, $-OC(O)NR^nR^{n'}$, $-OS(O)R^n$, $-OS(O)_2R^n$, $-SR^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-S(O)NR^nR^{n'}$, $-S(O)_2NR^nR^{n'}$, $-OS(O)NR^nR^{n'}$, $-OS(O)_2NR^nR^{n'}$, $-NR^nR^{n'}$, $-NR^nC(O)R^o$, $-NR^nC(O)OR^o$, -

$NR^nC(O)NR^oR^{o'}$, $-NR^nS(O)R^o$, $-NR^nS(O)_2R^o$, $-NR^nS(O)NR^oR^{o'}$, $-NR^nS(O)_2NR^oR^{o'}$, $-C(O)R^n$, $-C(O)OR^n$ and $-C(O)NR^nR^{n'}$;

R^X and $R^{X'}$ are each independently selected from H, OH, N_3, CN, NO_2, SH, NH_2, ONH_2, $NHNH_2$, halo, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{3-20} heteroaryl, C_{5-20} aryl or mono- or di-C_{1-8} alkylamino;

Y and Y' are each independently selected from O, S and N(H);

each R^{x6} is independently selected from C_{3-12} alkylene, C_{3-12} alkenylene, or C_{3-12} heteroalkylene;

R^{X7} and $R^{X7'}$ are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-7 membered heterocycloalkyl, C_{6-10} aryl, 5 to 7 membered heteroaryl, $-OR^r$, $-OC(O)R^r$, $-OC(O)NR^rR^{r'}$, $-OS(O)R^r$, $-OS(O)_2R^r$, $-SR^r$, $-S(O)R^r$, $-S(O)_2R^r$, $-S(O)NR^rR^{r'}$, $-S(O)_2NR^rR^{r'}$, $-OS(O)NR^rR^{r'}$, $-OS(O)_2NR^rR^{r'}$, $-NR^rR^{r'}$, $-NR^rC(O)R^s$, $-NR^rC(O)OR^s$, $-NR^rC(O)NR^sR^{s'}$, $-NR^rS(O)R^s$, $-NR^rS(O)_2R^s$, $-NR^rS(O)NR^sR^{s'}$, $-NR^rS(O)_2NR^sR^s$, $-C(O)R^r$, $-C(O)OR^s$ or $-C(O)NR^rR^{r'}$;

each R^r, $R^{r'}$, R^s and $R^{s'}$ is independently selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-13} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl and 5 to 7 membered heteroaryl;

each R^{X8} and $R^{X8'}$ is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} heteroalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl, 5 to 7 membered heteroaryl, $-S(O)R^m$, $-S(O)_2R^m$, $-S(O)NR^mR^{m'}$, $-S(O)_2NR^mR^{m'}$, $-NR^mR^{m'}$, $-NR^mC(O)R^m$, $NR^mC(O)OR^n$, $-NR^mC(O)NR^nR^{n'}$, $-NR^mS(O)R^n$, $-NR^mS(O)_2R^n$, $-NR^mS(O)NR^nR^{n'}$, $-NR^mS(O)_2NR^nR^{n'}$, $-C(O)R^m$, $-C(O)OR^m$ and $-C(O)NR^mR^{m'}$;

Z^a is OR^{X12a}, $NR^{X12a}R^{X12a}$, or SR^{X12a};

Z^b is OR^{X13a}, $NR^{X13a}R^{X13a}$, or SR^{X13a};

$Z^{a'}$ is OR^{X12a}, $NR^{X12a}R^{X12a}$, or SR^{X12a};

$Z^{b'}$ is $OR^{X13a'}$, $NR^{X13a'}R^{X13a'}$, or $SR^{X13a'}$;

each R^{X12a}, $R^{X12a'}$, $R^{X13a'}$ and $R^{x13a'}$ is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3 to 7 membered heterocycloalkyl, C_{5-10} aryl, 5 to 7 membered heteroaryl,
$-C(O)R^{X15a}$, $-C(O)OR^{X15a}$ and $-C(O)NR^{X15a}R^{X15a'}$;

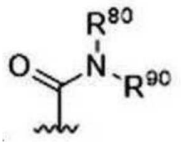
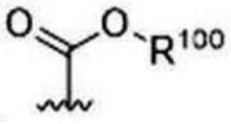
each R^{X15a} and $R^{x15a'}$ is independently selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{5-20} aryl, C_{5-20} heteroaryl, C_{3-6} cycloalkyl, 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl, and 5 to 7 membered heteroaryl;

each R^{X13a} and R^{X14a} is independently H or alkyl; or R^{X13a} and R^{X14a}, together with the atom to which it is connected, form 3-7 membered heterocyclyl, form 3-7 membered heterocycloalkyl, or form 3-7 membered heteroaryl, and the $R^{X13a'}$ and $R^{X14a'}$ arbitrarily bind to the atoms to which they are attached to form 3-7 membered heterocyclyl, 3-7 membered heterocycloalkyl, or 3-7 membered heteroaryl; and

each of R^n, $R^{n'}$, R^o, $R^{o'}$, R^p and $R^{p'}$ is independently selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-13} cycloalkyl, 3-7 membered heterocycloalkyl, C_{5-10} aryl, and 5 to 7 membered heteroaryl;

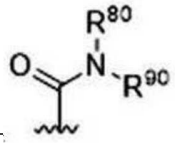
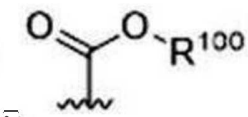
X^a and $X^{a'}$ are each independently a bond or C_{1-6} alkylene;

$Z^{X'}$ and Z^X are each independently selected from hydrogen, C_{1-8} alkyl, halogen, cyano, nitro,


,  and $-(CH_2)_m-OCH_3$;

each R^{80}, R^{90} and R^{100} is independently selected from hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl and C_{1-6} alkoxy; and

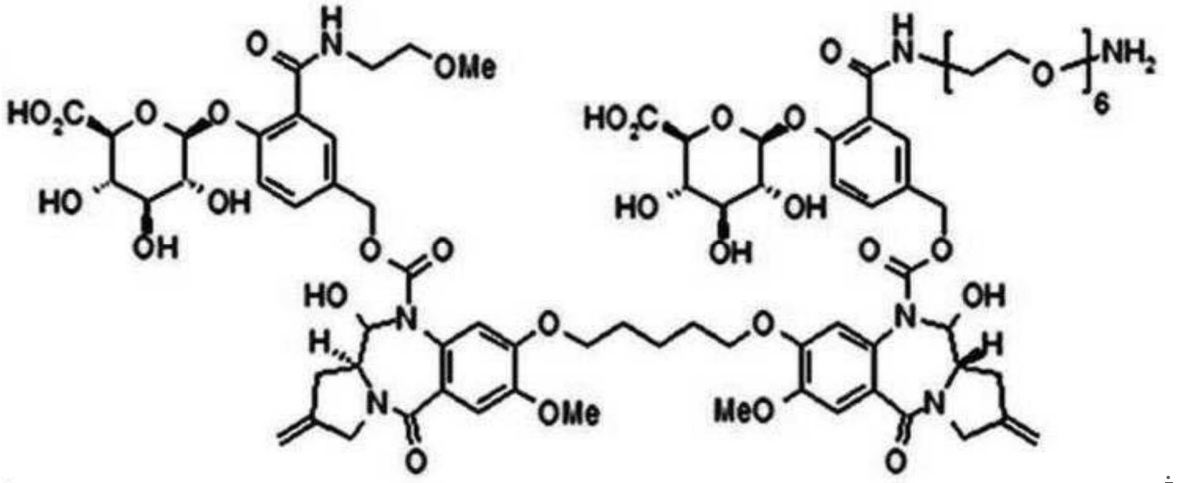
m is an integer of 0 to 12.

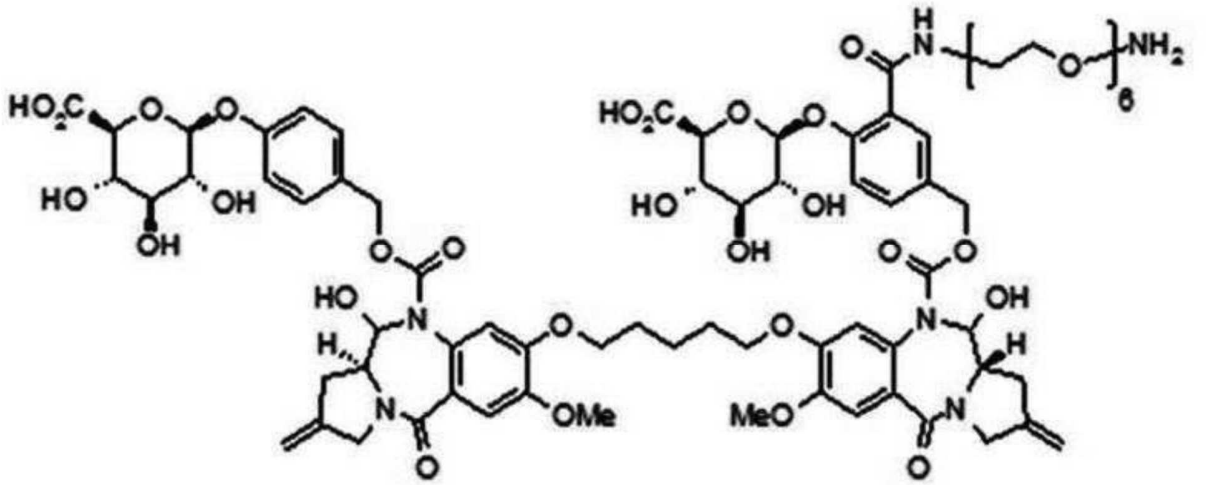
~~127. The antibody conjugate of any one of claims 116-126, wherein the $Z^{X'}$ and Z^X are each independently selected from hydrogen,~~ 
~~,~~  ~~and $-(CH_2)_m-OCH_3$;~~

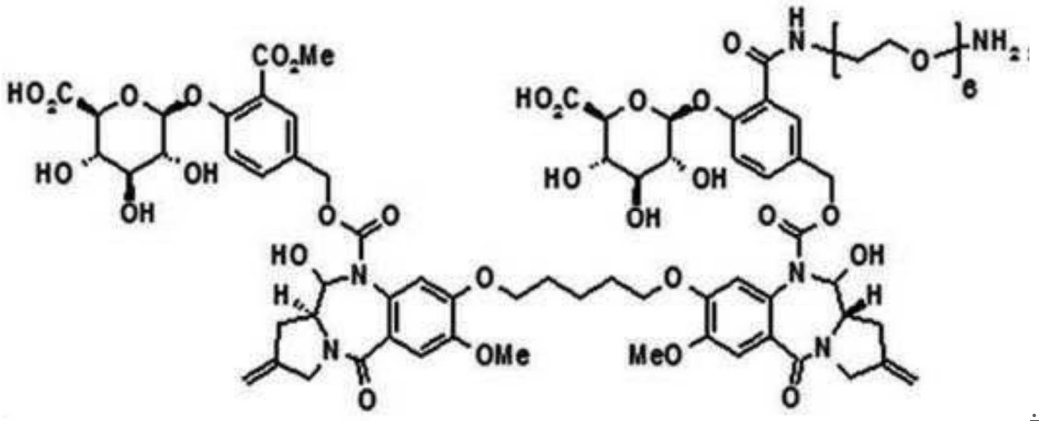
~~R^{80}, R^{90} and R^{100} are each independently selected from hydrogen, C_{1-3} alkyl and C_{1-3} alkoxy; and~~

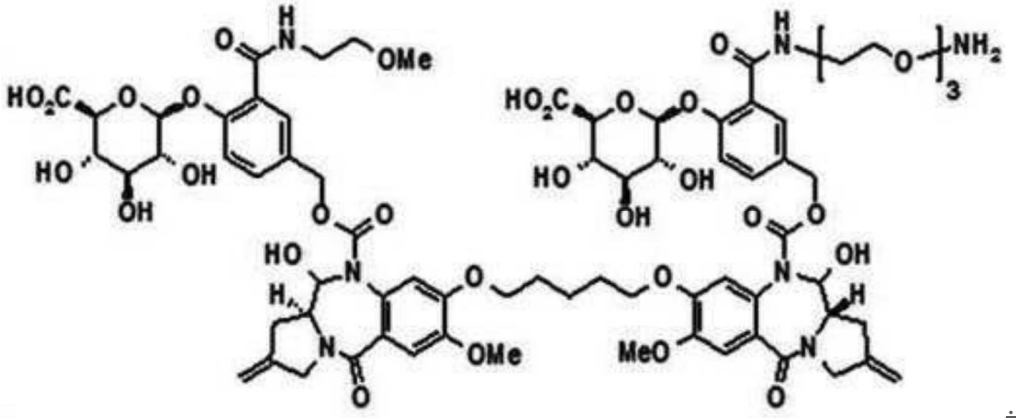
~~m is an integer of 1 to 6.~~

~~128. The antibody conjugate of any one of claims 1-127, wherein the active agent is selected from~~









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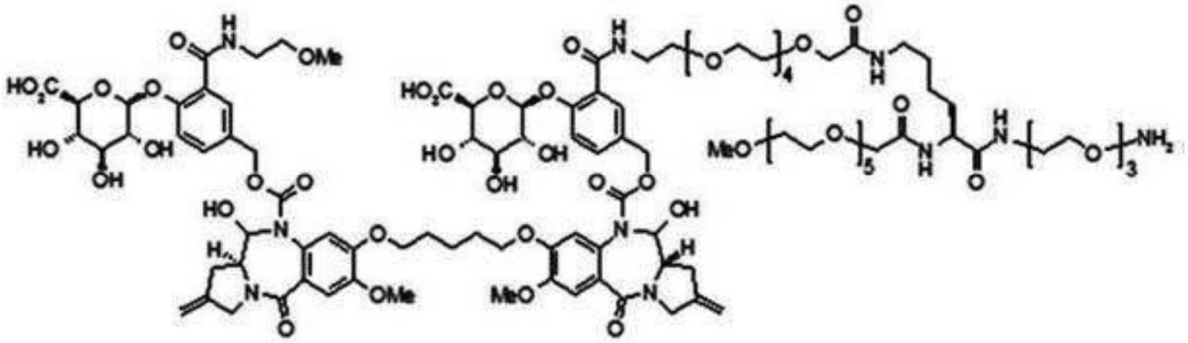

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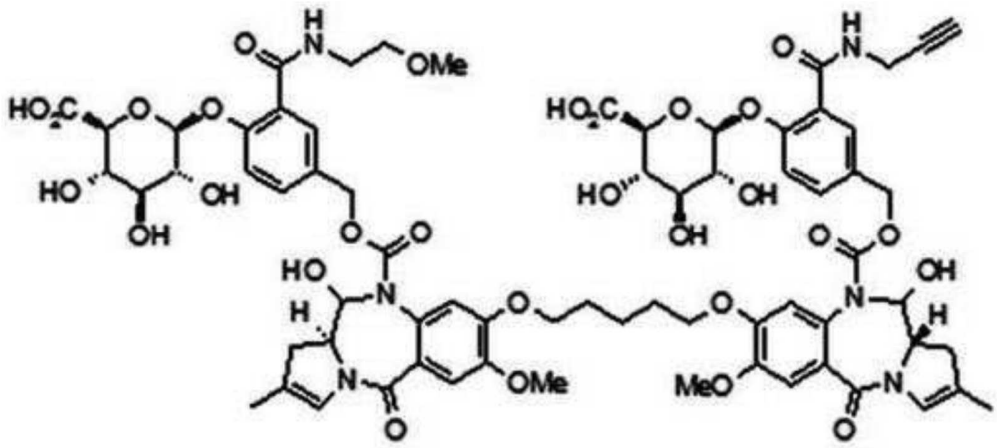

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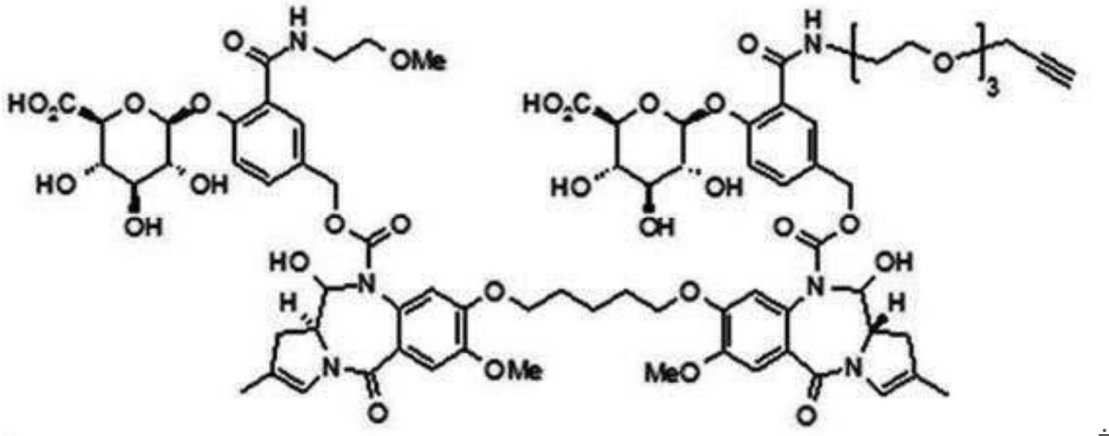

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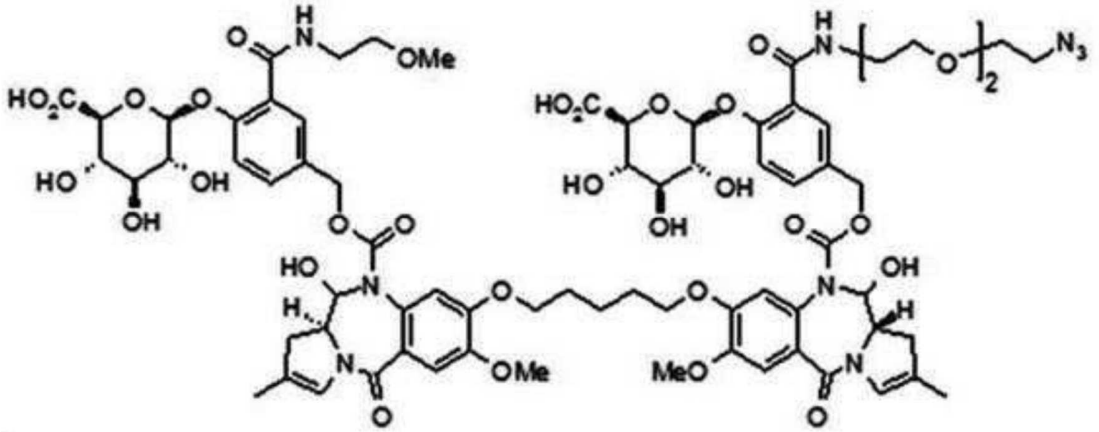

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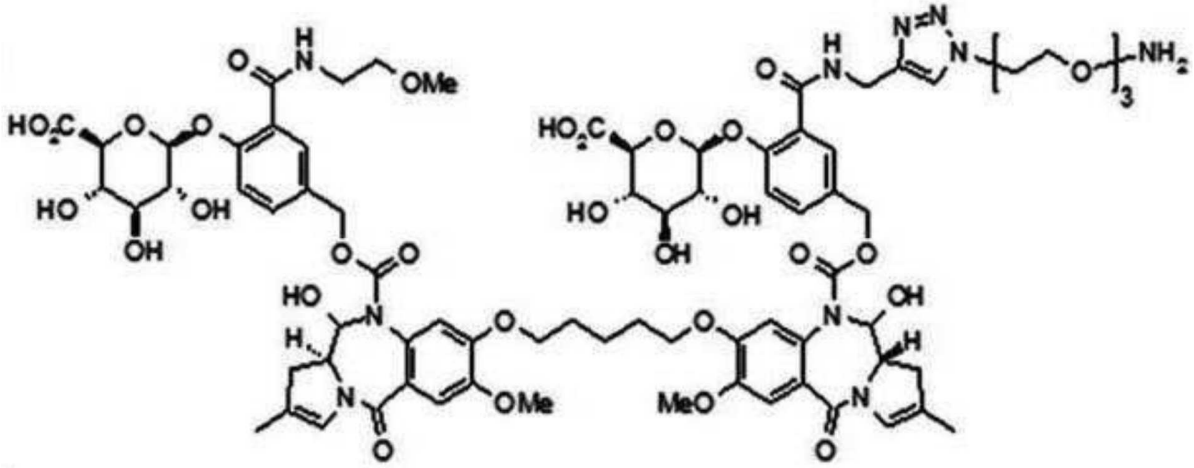

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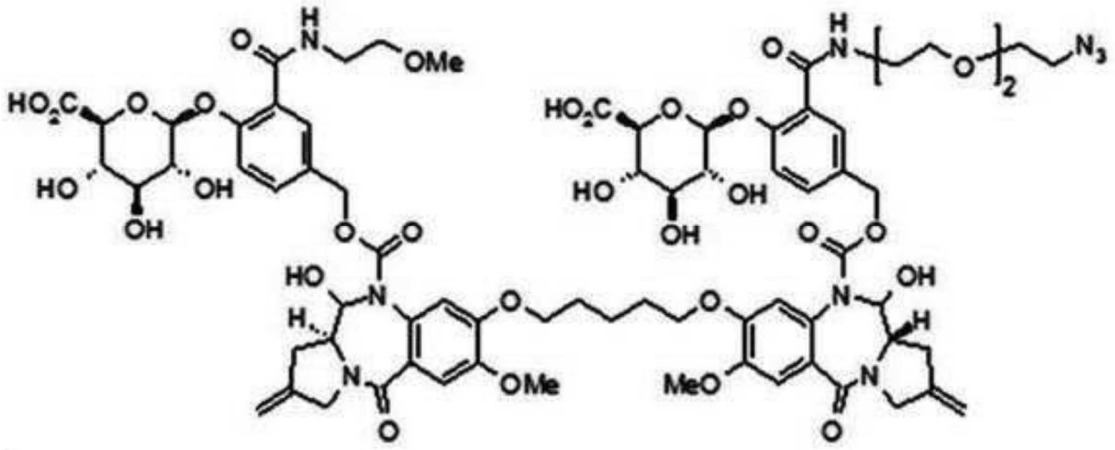

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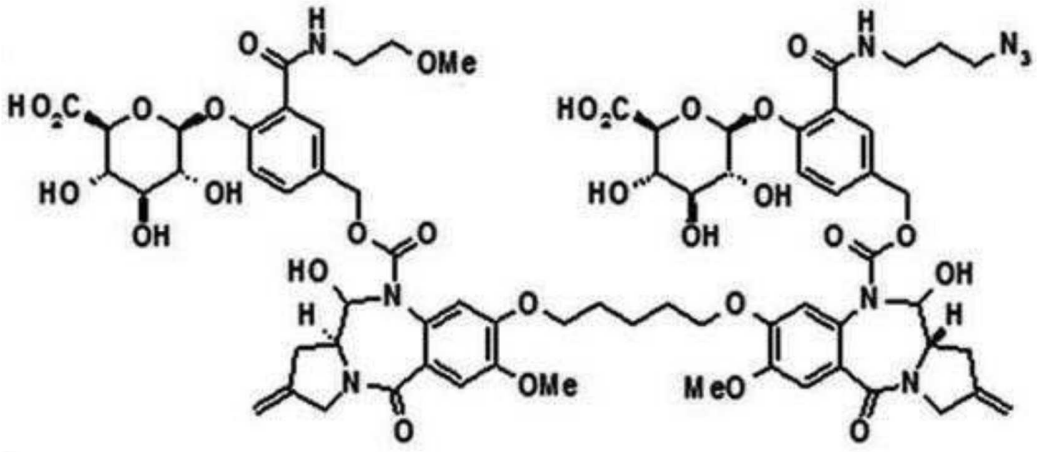

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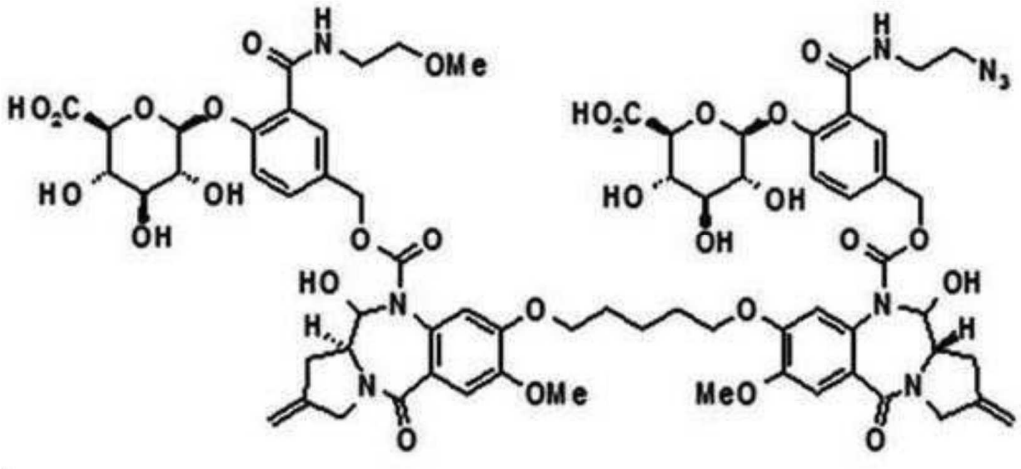

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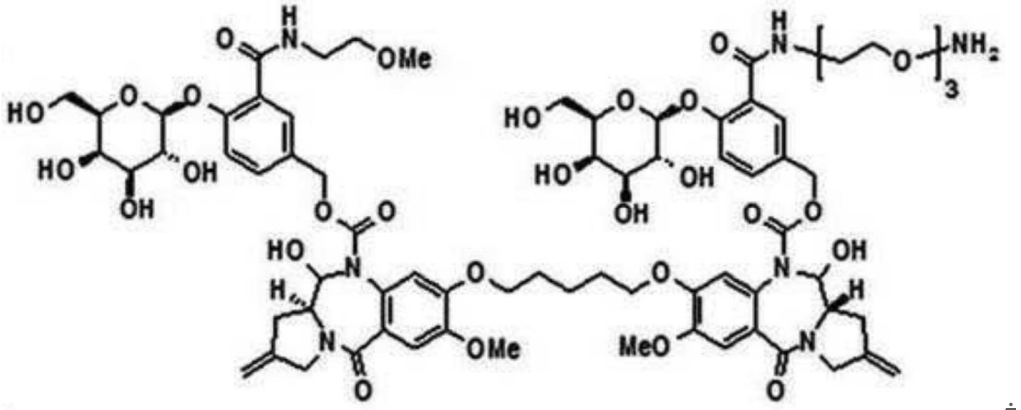

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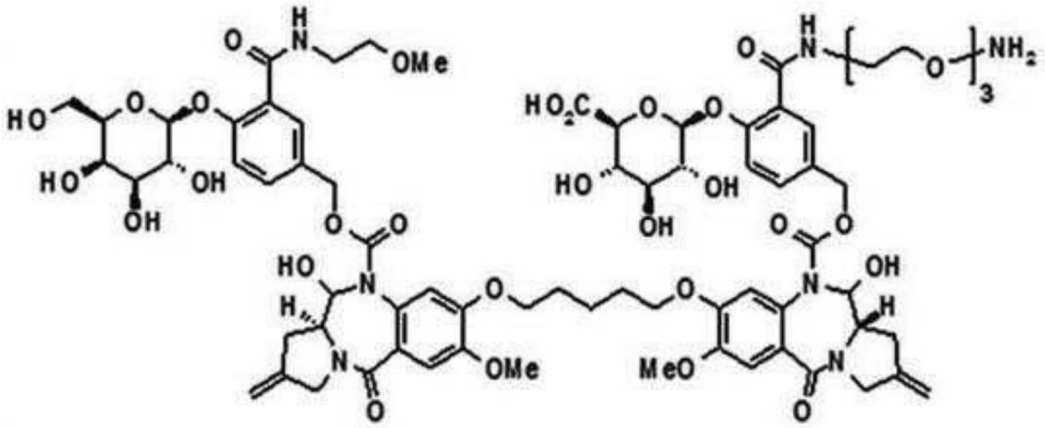

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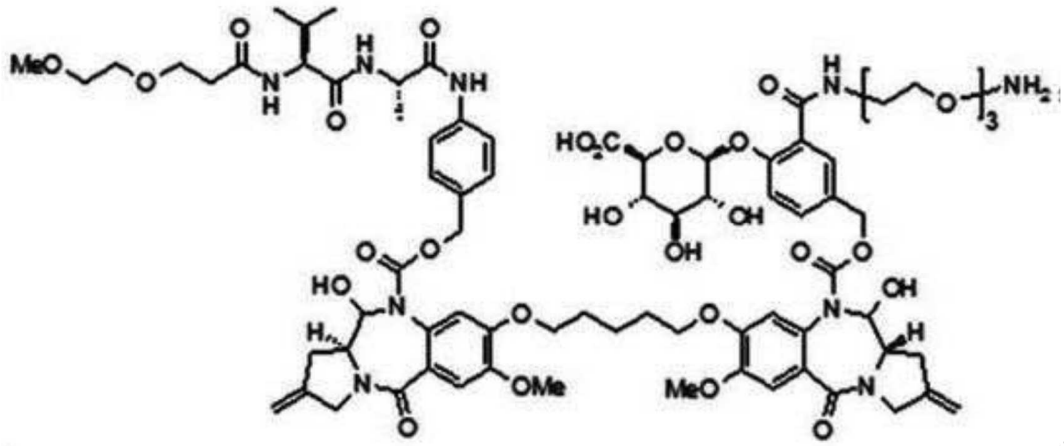

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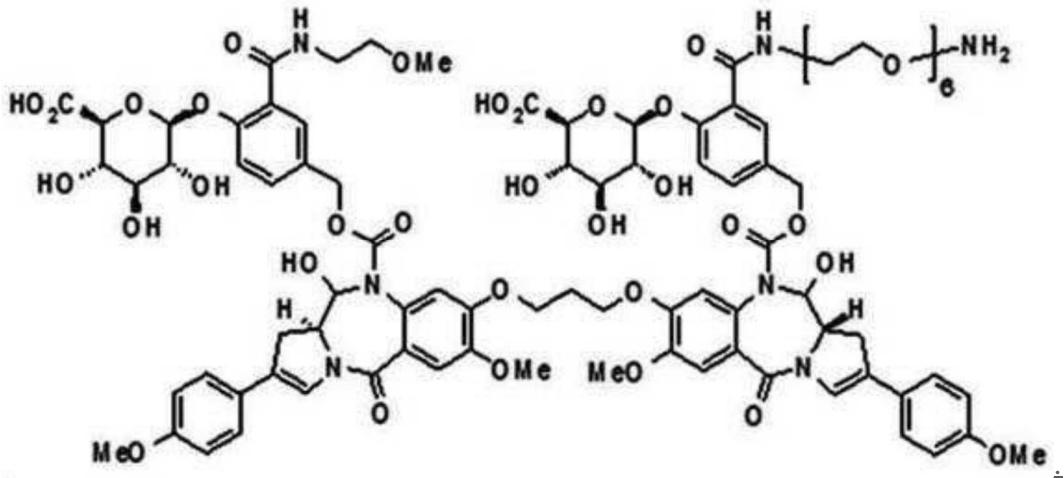

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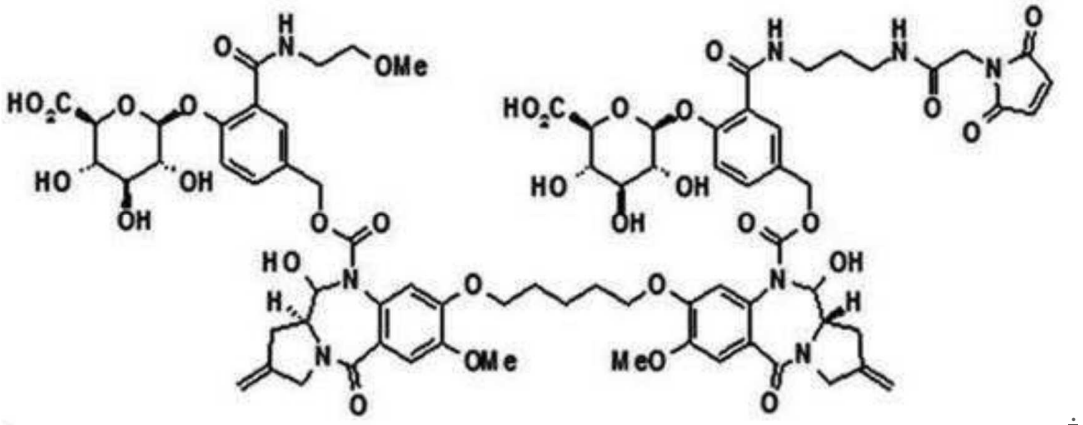

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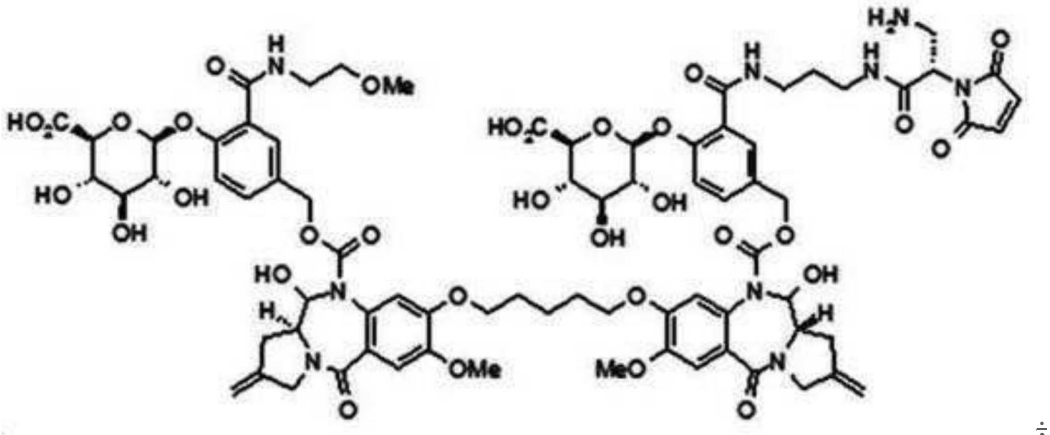

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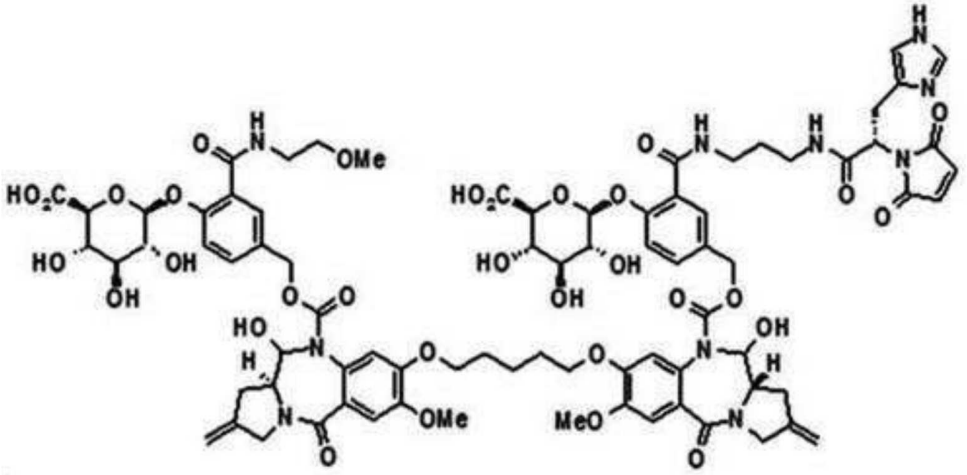

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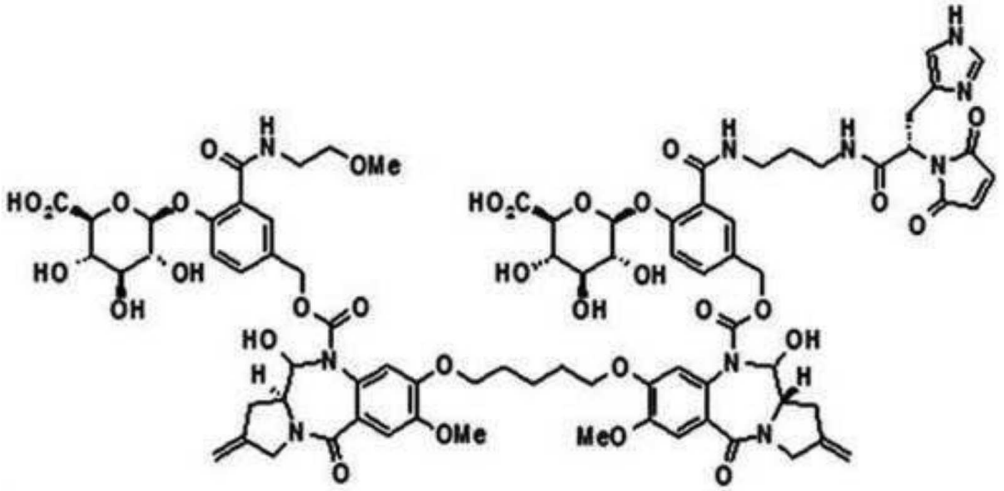

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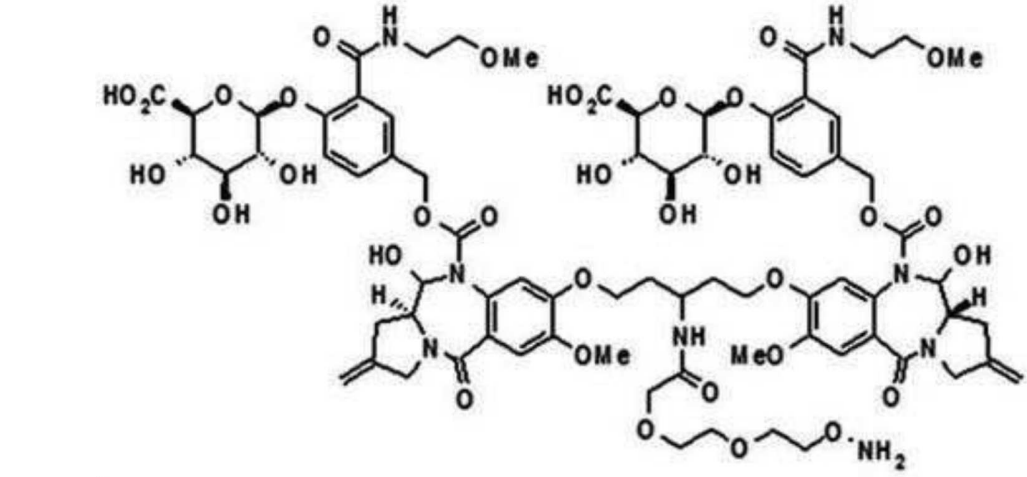

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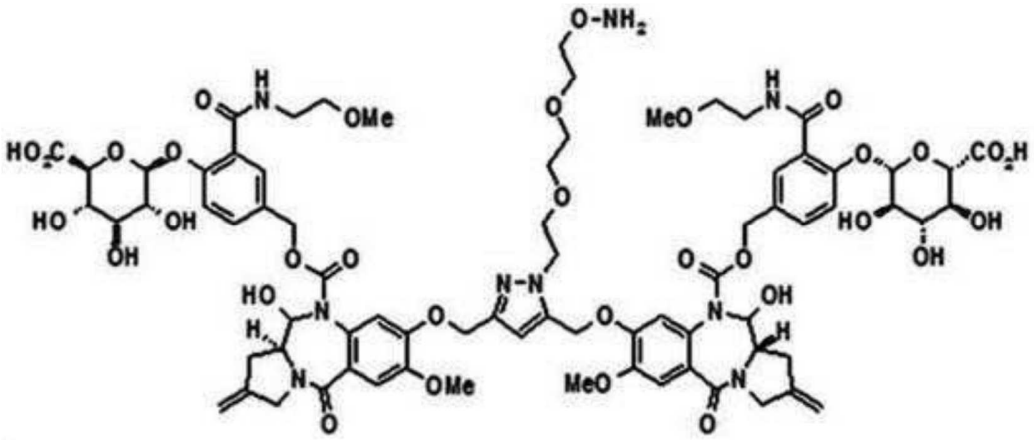

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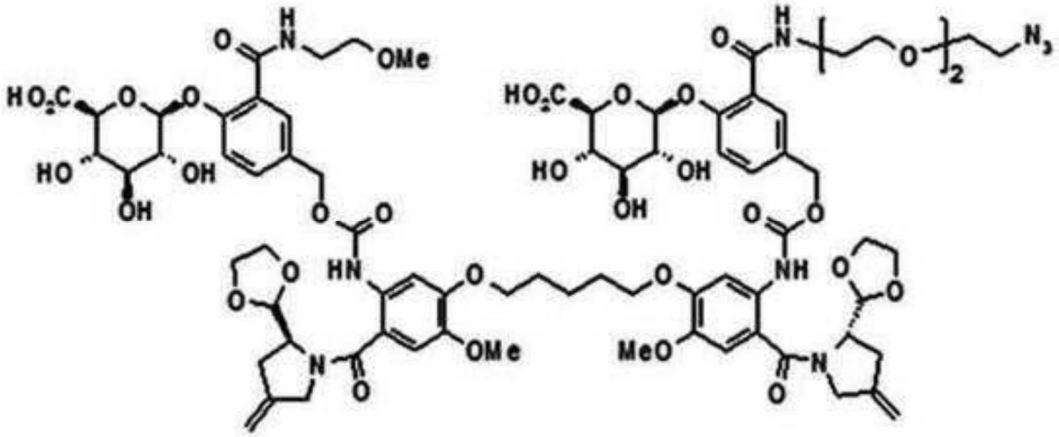

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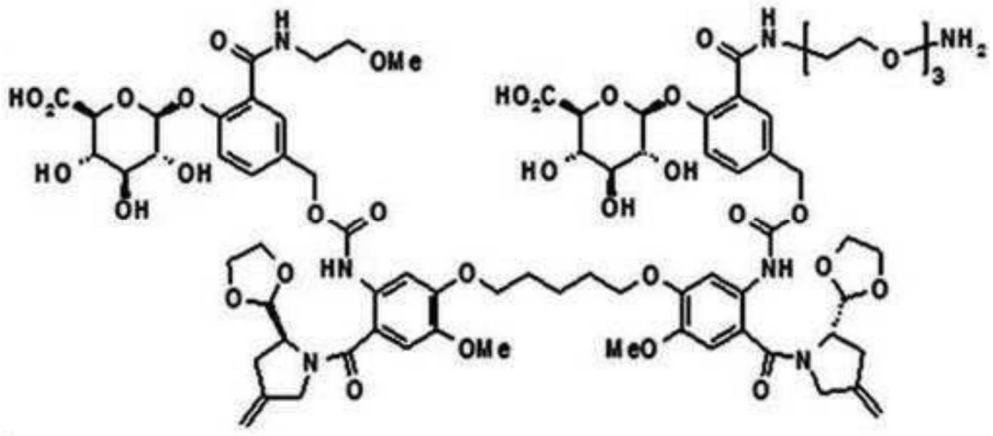

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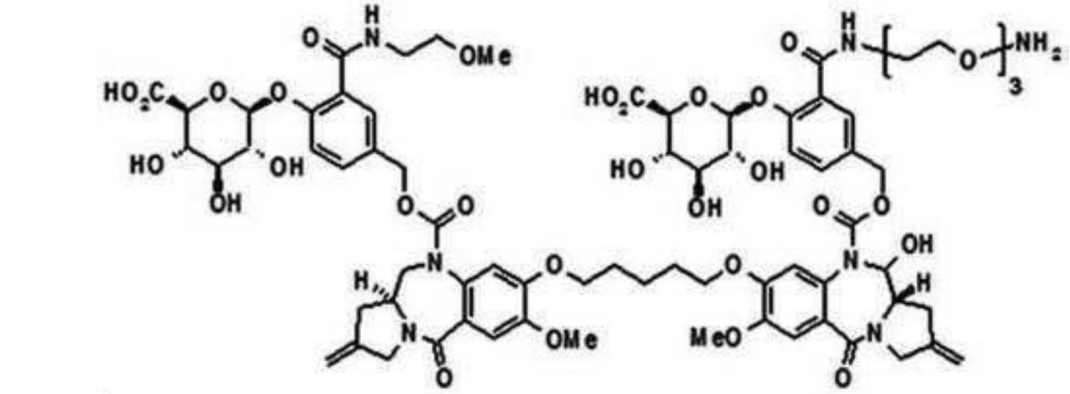

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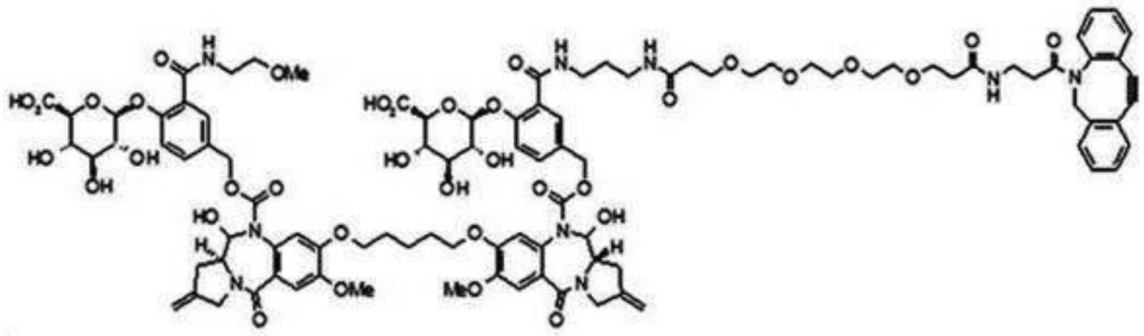
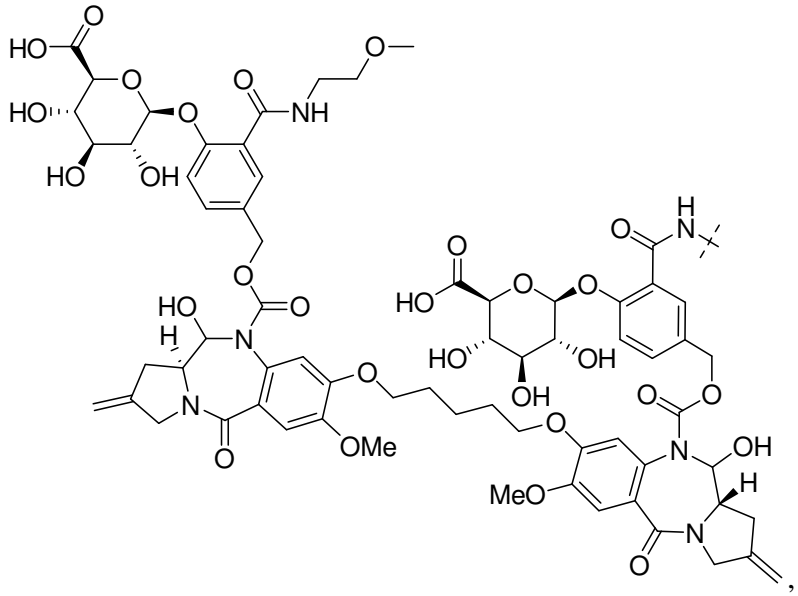
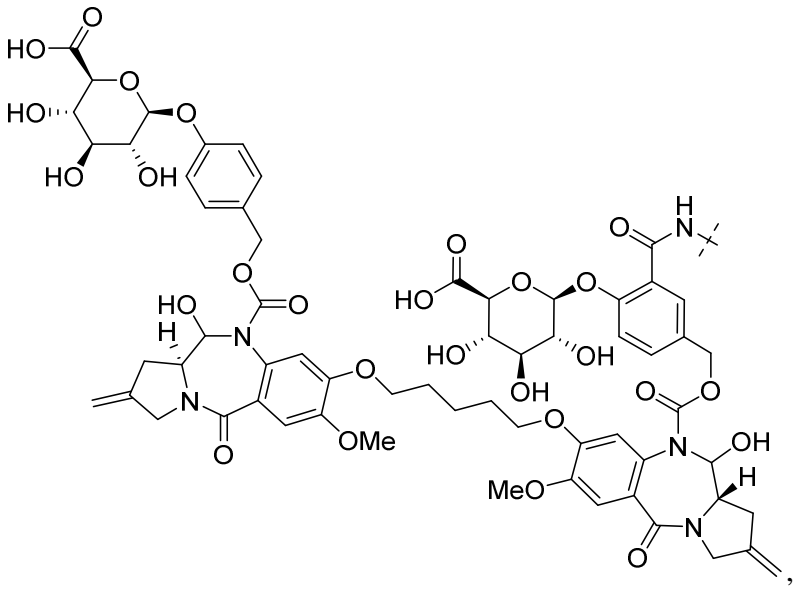


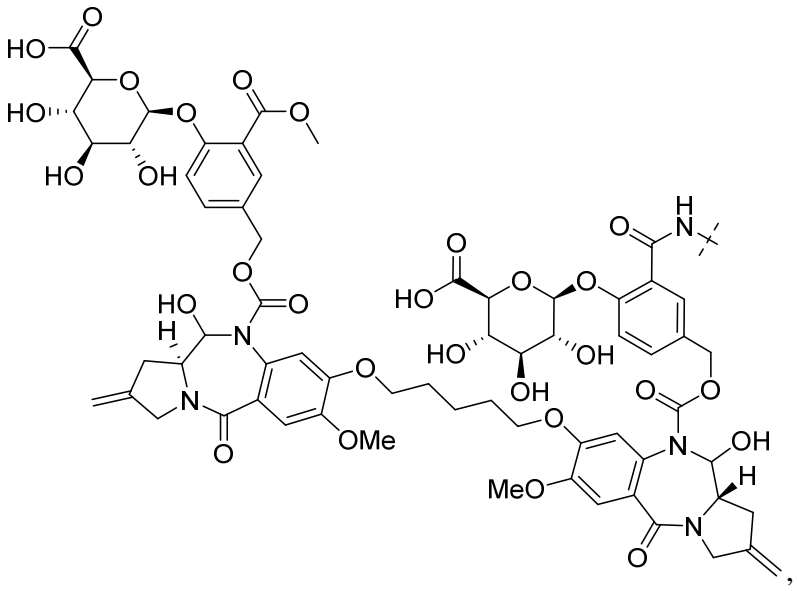
~~; or a~~

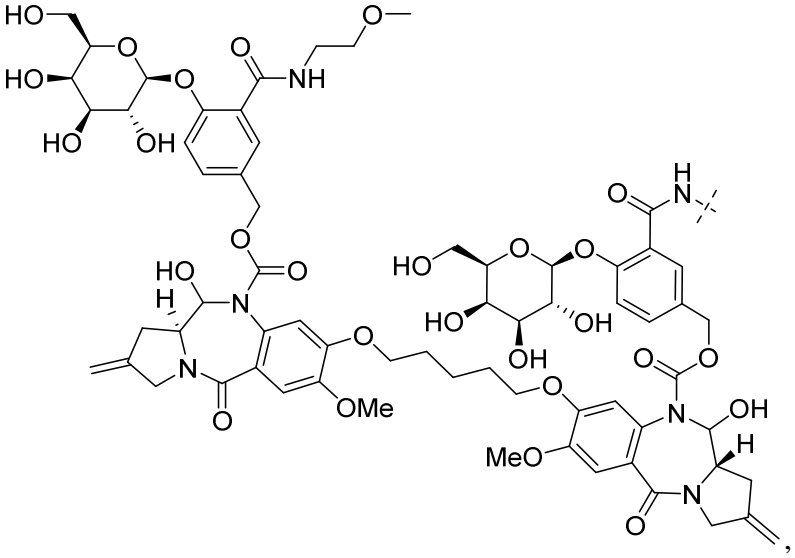
~~pharmaceutically acceptable salt thereof.~~

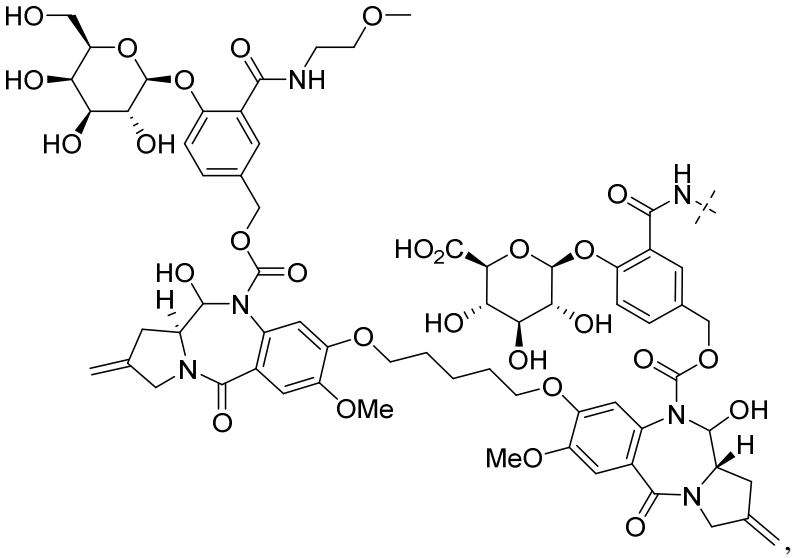
~~129~~51. The antibody conjugate of any one of claims 1-~~127~~50, wherein X^A comprises a structure represented by~~the active agent is selected from~~:

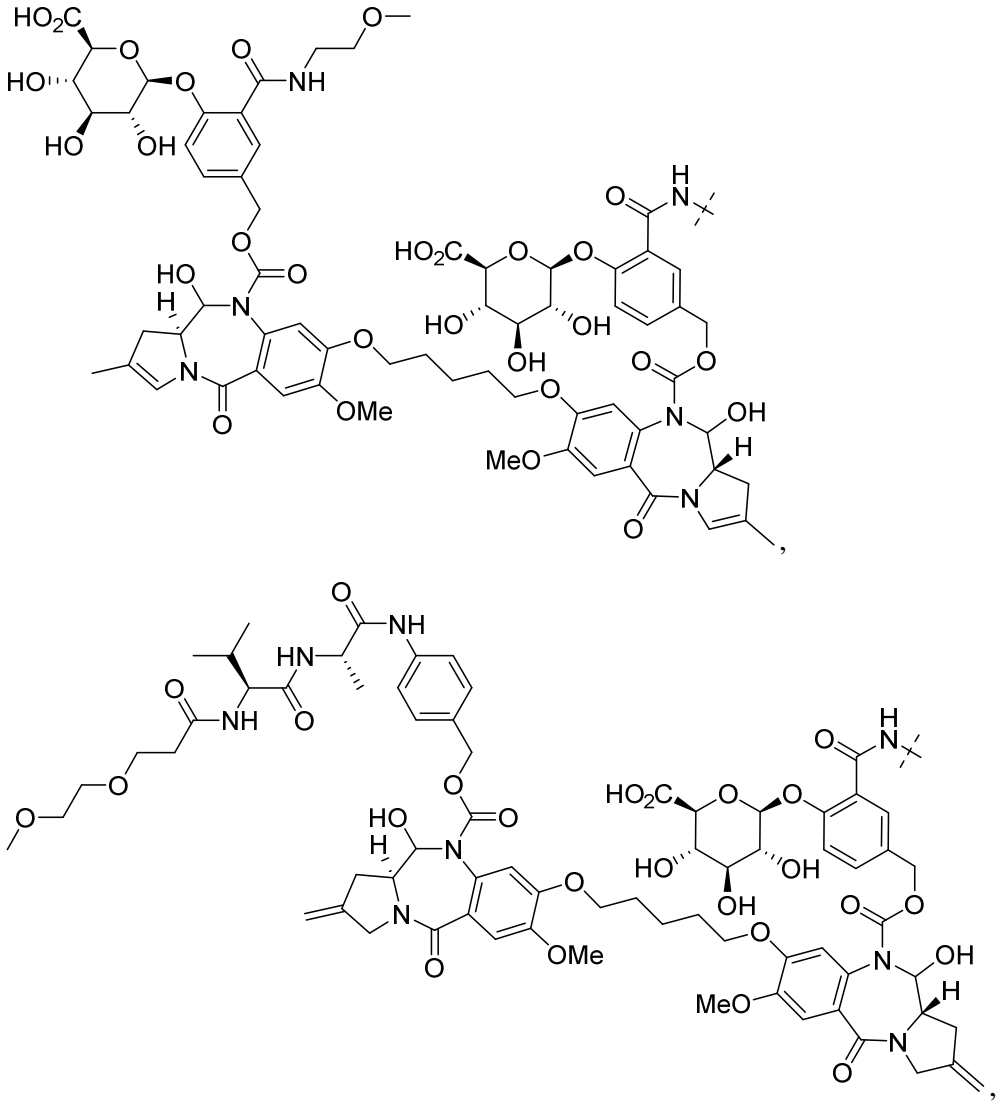


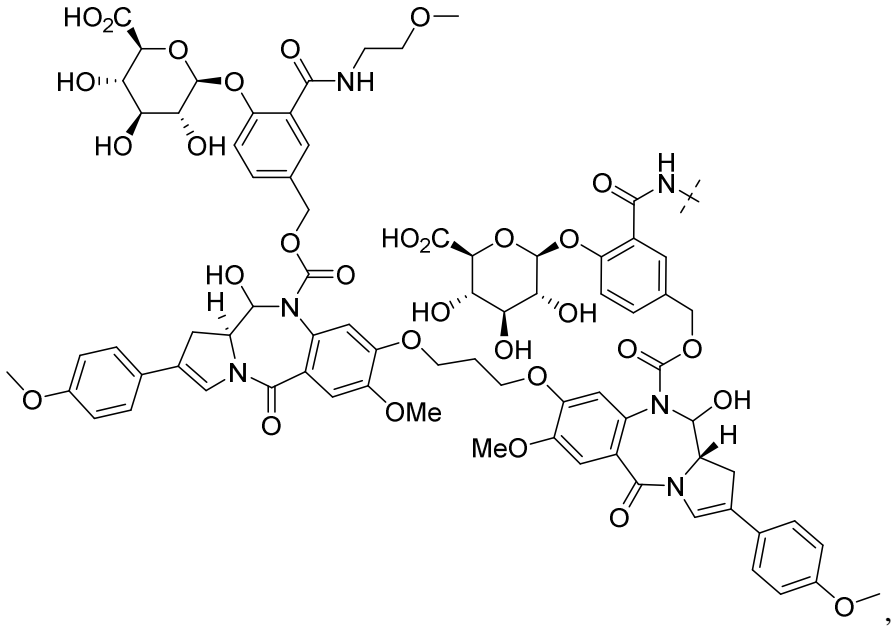












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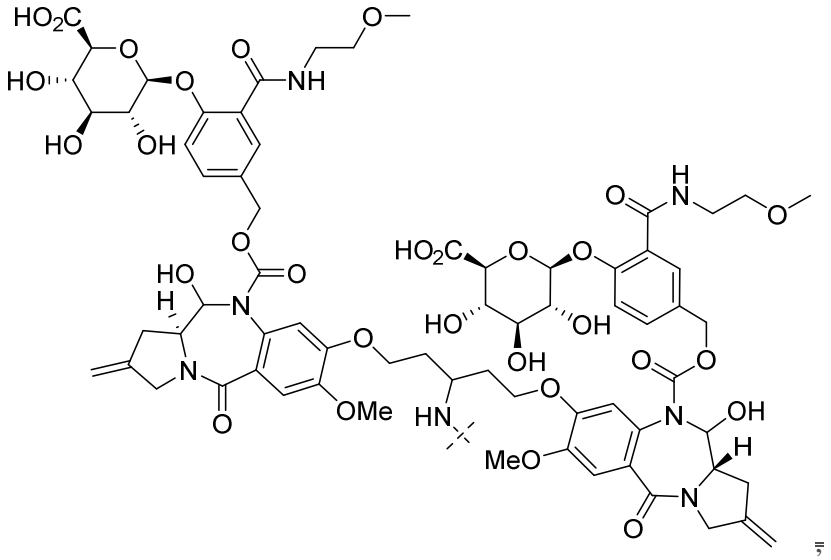

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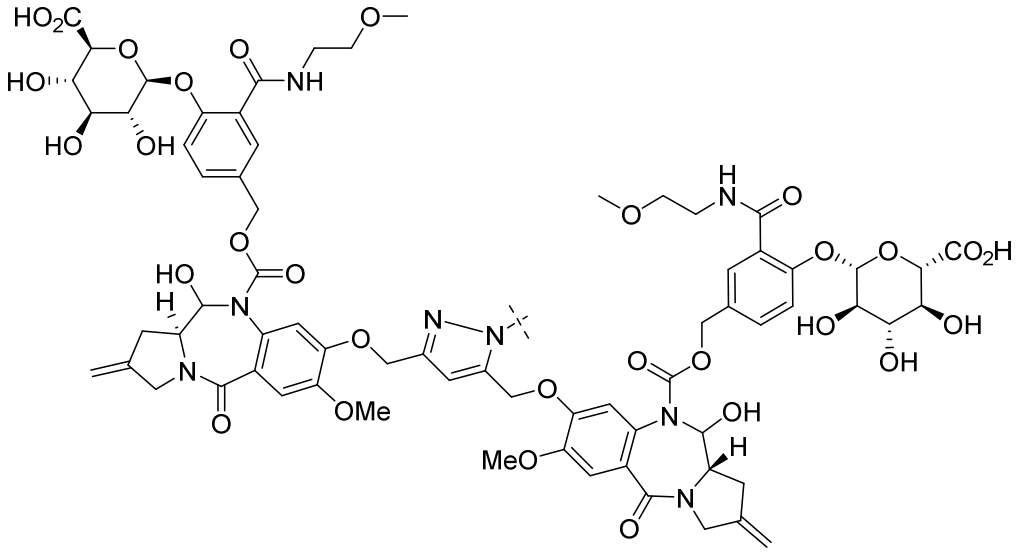

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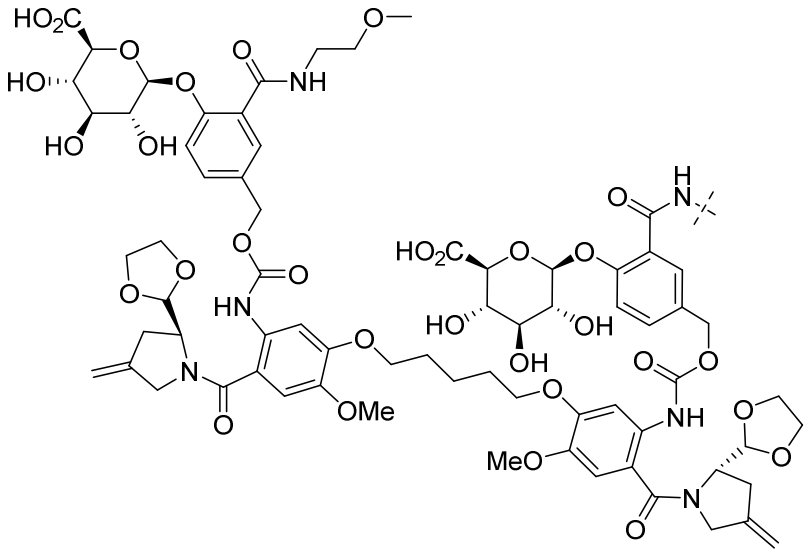
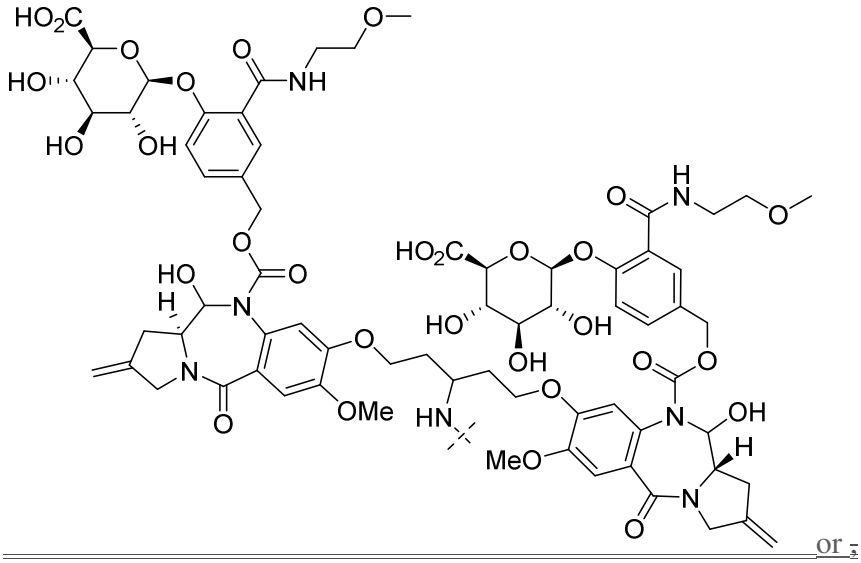


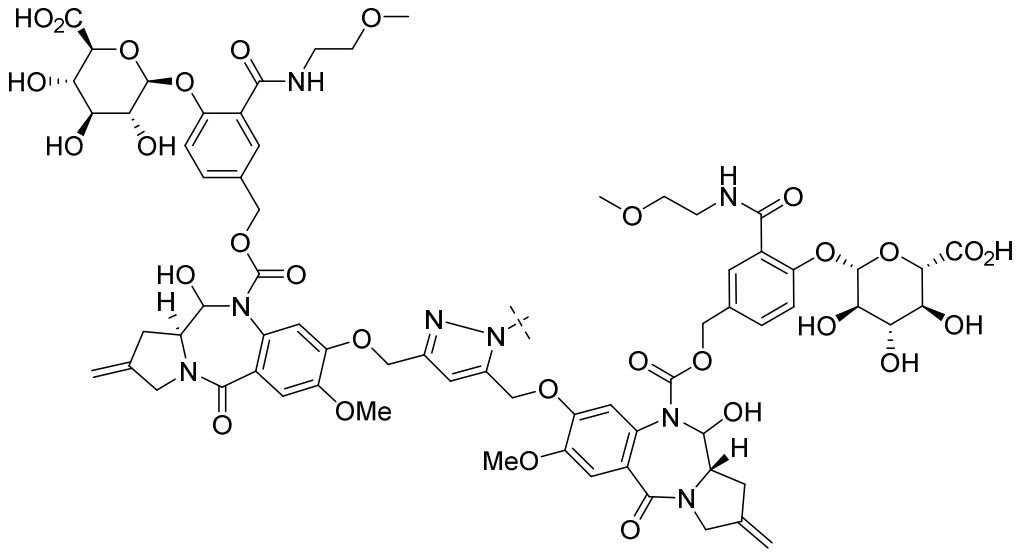
; or a pharmaceutically acceptable salt thereof; and

the bond overlaid with a dashed line represents a connection point to L.

52. The antibody conjugate of any one of claims 1-33, wherein the active agent is:



or ;



; or a pharmaceutically acceptable salt thereof.

~~130~~53. A pharmaceutical composition comprising an antibody drug conjugate of any one of claims 1-~~129~~ 52 and a pharmaceutically acceptable excipient.

~~131. A pharmaceutical composition for prevention, amelioration or treatment of illness associated with over-expression of ROR1, the composition comprising the antibody conjugate of any one of claims 1-129 or a pharmaceutically acceptable salt or solvate thereof.~~

~~132. The pharmaceutical composition according to claim 131, wherein the pharmaceutical composition further comprises a pharmaceutically efficacious amount of a chemotherapeutic agent.~~

~~133. The pharmaceutical composition according to claim 131 or 132, wherein the illness associated with over-expression of ROR1 is cancer.~~

~~134. The pharmaceutical composition of any one of claims 131-133, wherein the cancer is selected from chronic lymphocytic leukemia (CLL), B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer and adrenal cancer.~~

~~135. A method of treating a disease or disorder associated with the over-expression of ROR1 in a subject, comprising administering an antibody drug conjugate of any one of claims 1-129 or a pharmaceutically acceptable salt thereof to the subject.~~

~~136. The method of claim 135, wherein the disease or disorder associated with the over-expression of ROR1 is cancer.~~

~~137. The method of claim 136, wherein the cancer is selected from chronic lymphocytic leukemia (CLL), B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer and adrenal cancer.~~

~~138~~54. ~~A~~ Use of an antibody drug conjugate selected from any one of claims 1-52 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for~~method of~~ treating cancer ~~in a subject, comprising administering an antibody drug conjugate of any one of claims 1-129 or a pharmaceutically acceptable salt thereof to the subject~~.

~~139~~55. The ~~method~~ use of claim ~~138~~54, wherein the cancer is selected from chronic lymphocytic leukemia (CLL), B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer and adrenal cancer.

56. An antibody drug conjugate selected from any one of claims 1-52 or a pharmaceutically acceptable salt thereof for use in therapy.