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,

the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region comprising a variable heavy chain complementarity-determining region 1 (CDRH1), a variable heavy chain complementarity-determining region 2 (CDRH2), a variable heavy chain complementarity-determining region 3 (CDRH3), a variable light chain complementarity-determining region 1 (CDRL1), a variable light chain complementarity-determining region 2 (CDRL2), and a variable light chain complementarity-determining region 3 (CDRL3); wherein,

(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;

each X^A comprises at least one active agent and a linker;

wherein the linker between Ab and the at least one active agent comprises a cleavable bond;

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

y is an integer from 1 to 20.

2. The antibody conjugate of claim 1, wherein Ab 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.

3. The antibody conjugate of claim 1 or 2, wherein Ab 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.

4. The antibody conjugate of any one of claims 1-3, wherein Ab comprises a combination of a heavy chain variable region and a light chain variable region 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.

5. The antibody conjugate of any one of claims 1-4, wherein Ab comprises a combination of a heavy chain and a light chain comprising the amino acid sequence of: SEQ ID NOs. 59 and 67, respectively; SEQ ID NOs. 60 and 68, respectively; SEQ ID NOs. 61 and 69, respectively; SEQ ID NOs. 62 and 70, respectively; SEQ ID NOs. 63 and 71, respectively; SEQ ID NOs. 64 and 72, respectively; SEQ ID NOs. 65 and 73, respectively; or SEQ ID NOs. 66 and 74, respectively.

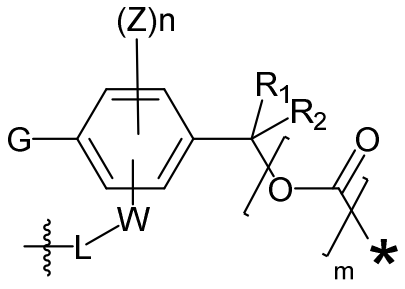
6. The antibody conjugate of any one of claims 1-4, wherein Ab is a monoclonal antibody, a domain antibody (dAb), a single chain antibody (scab), a Fab fragment, a Fab' fragment, a F(ab')2 fragment, an scFab fragment, an Fv fragment, a dsFv fragment, a single chain variable fragment (scFv), an ScFv-Fc 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.

7. The antibody conjugate of any one of claims 1-5, wherein Ab is a rabbit, mouse, chimeric, humanized, or fully human monoclonal antibody.

8. The antibody conjugate of claim 7, wherein the antibody is of the IgG1, IgG2, IgG3 or IgG4 type.

9. The antibody conjugate of any one of claims 1-8, wherein X^A comprises a structure represented by Chemical Formula IIa:

[Chemical Formula (IIa)]



or a pharmaceutically acceptable salt thereof, wherein

G is a sugar or a sugar acid;

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;

m is 0 or 1;

L is absent, C_1-C_{50} alkylene or 1-50 atom heteroalkylene;

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;

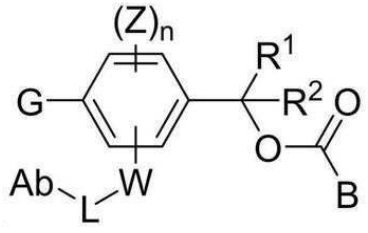
R' and R'' are each independently hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, mono-or di- C_1-C_8 alkylamino, C_3-C_{20} heteroaryl or C_6-C_{20} aryl;

* represents a connection point to the active agent; and

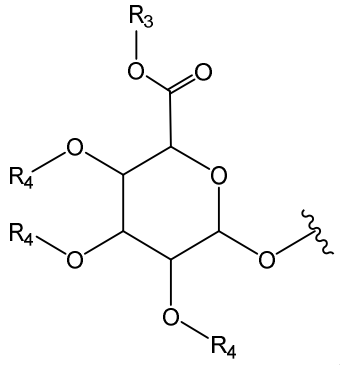
〰 represents a connection point to Ab.

10. The antibody conjugate of any one of claims 1-9, 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 R_4 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;

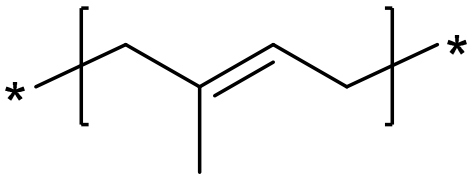
(ii) L comprises a heteroarylene;

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

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

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

[General Formula III]



11. The antibody conjugate of claim 9 or 10, wherein W is -C(O)-, -C(O)NR'-, or -C(O)O-.

12. The antibody conjugate of any one of claims 9-11, wherein W is -C(O)NR'-.

13. The antibody conjugate of any one of claims 9-12, wherein L comprises a peptide comprising at least one hydrophilic amino acid having a side chain having a moiety that bears an electric charge at a neutral pH in aqueous solution.

14. The antibody conjugate of claim 13, wherein the peptide comprises an amino acid selected from alanine, aspartate, asparagine, glutamate, glutamine, glycine, lysine, ornithine, proline, serine, and threonine.

15. The antibody conjugate of any one of claims 9-14, wherein L is bonded to Ab by a thioether bond and the thioether bond comprises a sulfur atom of a cysteine of Ab.

16. The antibody conjugate of any one of claims 9-15, wherein Ab comprises an amino acid motif which can be recognized by isoprenoid transferase at the C-terminus of Ab and the thioether bond includes a sulfur atom of the cysteine of Ab.

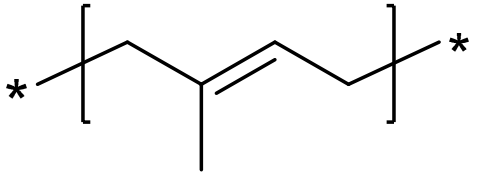
17. The antibody conjugate of claim 16, wherein the amino acid motif has a sequence of CYYX; wherein
C is cysteine;
each Y is an aliphatic amino acid; and
X is selected from glutamine, glutamate, serine, cysteine, methionine, alanine and leucin.

18. The antibody conjugate of claim 17, wherein each Y is independently selected from alanine, isoleucine, leucine, methionine and valine.

19. The antibody conjugate of any one of claims 16-18, wherein the amino acid motif has a sequence of CVIM or CVLL.

20. The antibody conjugate of any one of claims 9-19, wherein L comprises at least one isoprenyl unit represented by of General Formula III:

[General Formula III]



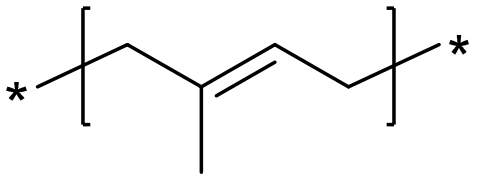
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21. The antibody conjugate of any one of claims 9-20, wherein L is a 3 to 50 atom heteroalkylene comprising an oxime and:

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.

22. The antibody conjugate of any one of claims 9-20, wherein L comprises an oxime and at least one isoprenyl unit represented by General Formula III that covalently binds the oxime to Ab:

[General Formula III]



.

23. The antibody conjugate of any one of claims 9-22, wherein L comprises a connecting unit represented by General Formula VIII or General Formula IX:

[General Formula VIII]

$-(CH_2)_r(V(CH_2)_p)_q-$

[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.

24. The antibody conjugate of claim 23, wherein V is -O-.

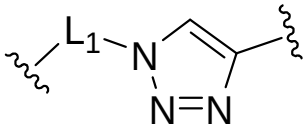
25. The antibody conjugate of claim 23 or 24, wherein X is -O-.

26. The antibody conjugate of any one of claims 23-25, wherein L comprises an oxime and the connecting unit covalently binds the oxime to the active agent.

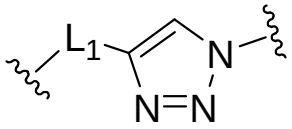
27. The antibody conjugate of any one of claims 9-26, wherein L further comprises a binding unit formed by 1,3-dipolar cycloaddition reactions, hetero-Diels-Alder reactions, nucleophilic substitution reactions, nonaldol type carbonyl reactions, additions to carbon-carbon multiple bonds, oxidation reactions or click reactions.

28. The antibody conjugate of any one of claims 9-26, wherein L comprises a binding unit represented by General Formulae IV, V, VI or VII:

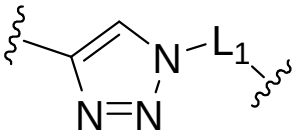
[General Formula IV]



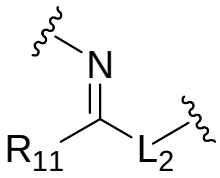
[General Formula V]



[General Formula VI]



[General Formula VII]



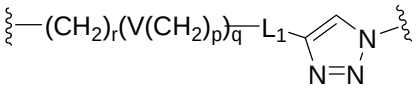
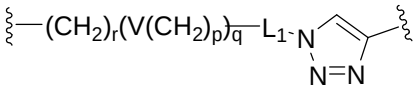
wherein

L^1 is a bond or an alkylene of C_1-C_{30};

L^2 is an alkylene having 1 to 30 carbon atoms; and

R^{11} is a hydrogen or an alkyl of C_1-C_{10}.

29. The antibody conjugate of claim 28, 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 1 to 10;

p is 0 to 10;

q is 1 to 20; and

L^1 is a bond.

30. The antibody conjugate of claim 10, wherein the isoprenoid transferase is a farnesyl protein transferase (FTase) or a geranylgeranyl transferase (GGTase).

31. The antibody conjugate of any one of claims 9-30, wherein L is a branched 1-50 atom heteroalkylene wherein each branched 1-50 atom heteroalkylene comprises:

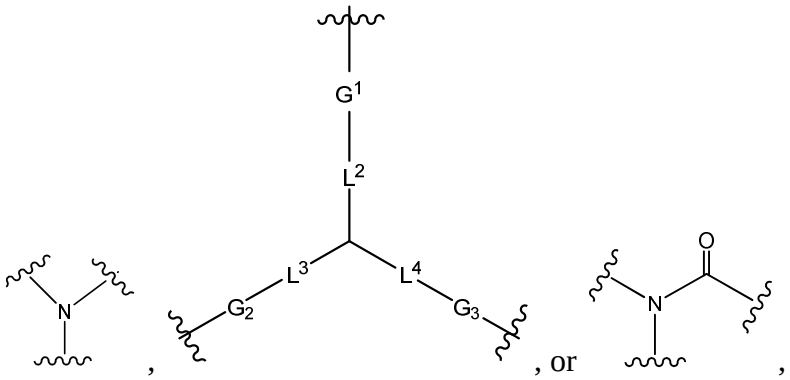
i) a branching unit (BR) covalently coupled to Ab by a primary linker (PL);

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) 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.

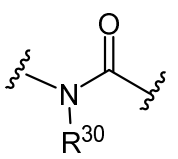
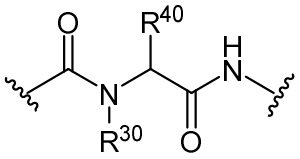
32. The antibody conjugate of claim 31, wherein the branching unit is represented by:

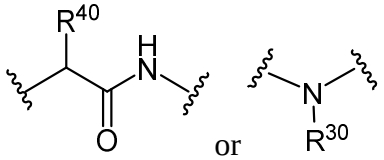


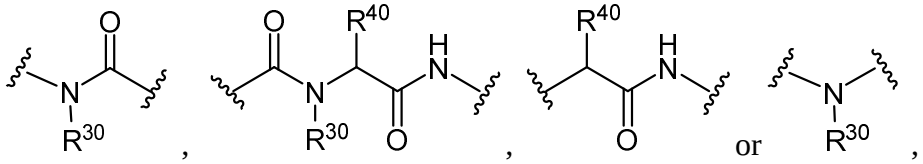
, , or ,

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,  ,  ,

 ,

 ,

or

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

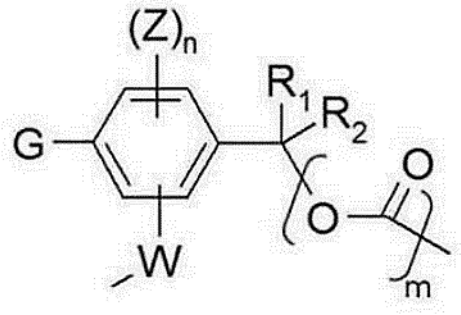
R^{40} is L^5-$COOR^{50}$, wherein L^5 is a direct bond or C_{1-10} alkylene; and

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

33. The antibody conjugate of any one of claims 31-32, wherein the branching unit is a lysine unit.

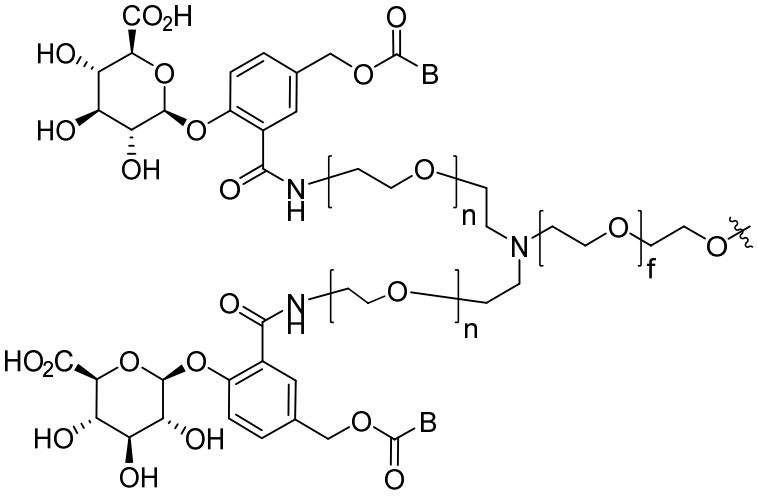
34. The antibody conjugate of any one of claims 31-35, wherein each cleavage group has a structure represented by Chemical Formula IIb:

[Chemical Formula (IIb)]



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35. The antibody conjugate of any one of claims 9-32, wherein X^A comprises a structure represented by:



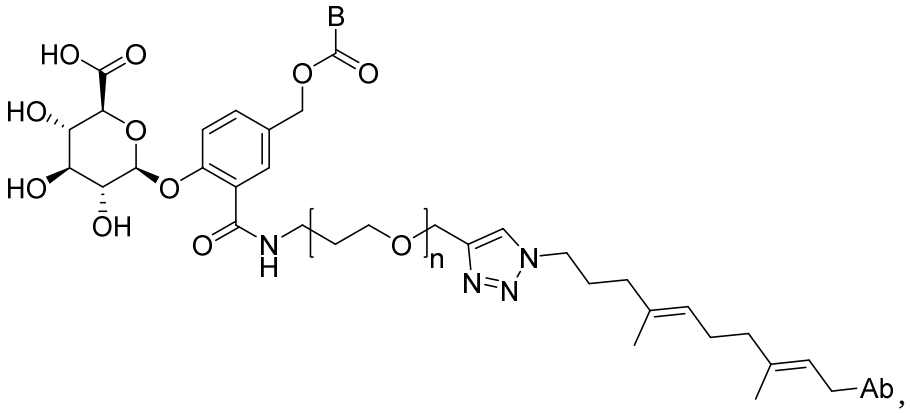
wherein

each B is an active agent;

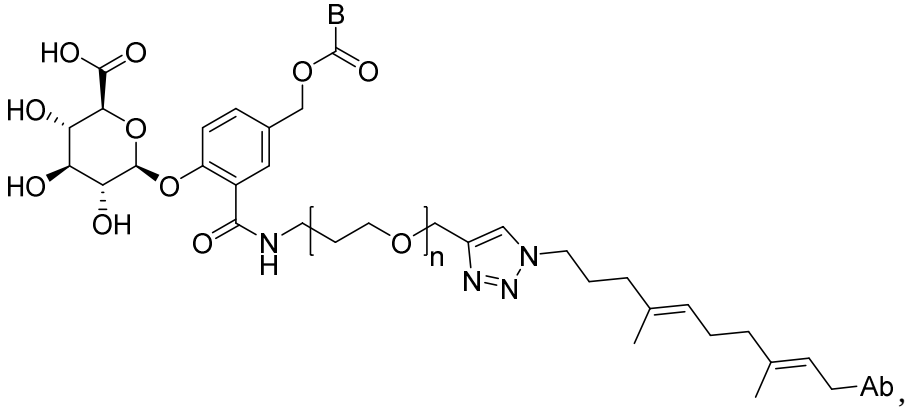
each n is independently 0 to 30; and

f is 0 to 30.

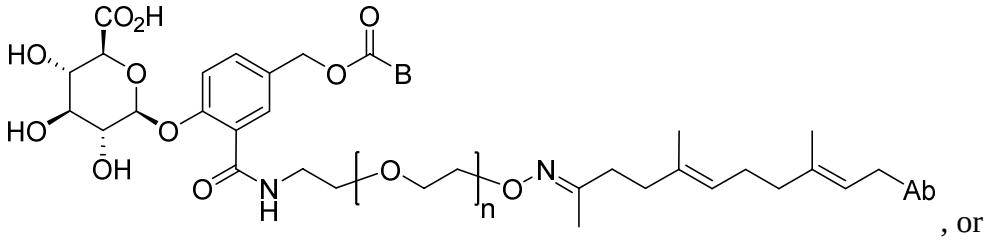
36. The antibody conjugate of any one of claims 1-8, wherein the conjugate comprises a structure represented by:



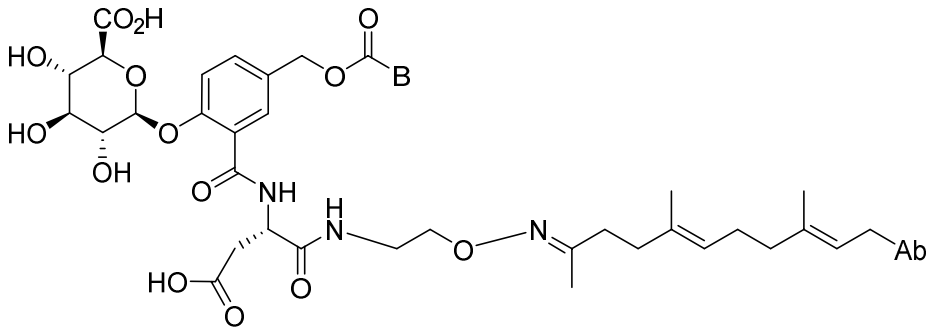
,



,



, or



or a pharmaceutically acceptable salt thereof; and

Ab is the anti-ROR1 antibody;

B is the active agent; and

n is 1 to 20.

37. The antibody conjugate of any one of claims 1-36, wherein the active agent is a chemotherapeutic agent or a toxin.

38. The antibody conjugate of any one of claims 1-37, wherein the active agent is an immunoregulatory compound, anti-cancer agent, antiviral, antibacterial, antifungal, antiparasitic or a combination of these.

39. The antibody conjugate of any one of claims 1-37, wherein the active agent is selected from:

(a) erlotinib, bortezomib, fulvestrant, sunitinib, 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, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, topotecan, bryostatin, callystatin, adozelesin, carzelesin, bizelesin, cryptophycin 1, cryptophycin 8, 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, anthramycin, azaserine, bleomycins, catcinomycin, carabicin, carninomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, 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, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, 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, democolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansine, ansamitocins, mitoguazone, mitoxantrone, mopidanmol, pentostatin, phenamet, pirarubicin, losoxantrone, 2-ethylhydrazide, procarbazine, polysaccharide-k, razoxane, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2', 2''-trichlorotriethylamine, T-2 toxin, verracurin A, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, arabinoside, paclitaxel, albumin-engineered nanoparticle formulation of paclitaxel, docetaxel, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, carboplatin, vinblastine, platinum, etoposide, vincristine, vinorelbine, novantrone, teniposide, daunomycin, aminopterin, ibandronate, CPT-11, topoisomerase inhibitor RFS 2000, difluoromethylornithine, retinoic acid, capecitabine, or pharmaceutically acceptable salts, solvates or acids thereof;

(b) monokine, lymphokine, 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-β, Mullerian inhibiting substance, mouse gonadotropin associated peptide,

inhibin, activin, vascular endothelial growth factor, thrombopoietin, erythropoietin, osteoinductive factor, interferon, interferon-α, interferon-β, interferon- γ, colony stimulating factor (CSF), macrophage-CSF, granulocyte-macrophage-CSF, granulocyte-CSF, interleukin (IL), IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, polypeptide factor, LIF, kit ligand, or mixtures thereof;

(c) diphtheria toxin, botulinum toxin, tetanus toxin, dysentery toxin, cholera toxin, amanitin, α-amatinin, pyrrolobenzodiazepine, pyrrolobenzodiazepine derivative, indolinobenzodiazepine, pyridobenzodiazepine, tetrodotoxin, brevetoxin, ciguatoxin, ricin, AM toxin, auristatin, tubulysin, geldanamycin, maytansinoid, SG2285, dolastatin, dolastatin analog, cryptophycin, rhizoxin, rhizoxin derivatives, CC-1065, CC-1065 analogs or derivatives, enediyne antibiotic, 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, digoxigenin, 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, LY117018, onapristone or toremifene;

(h) 4(5)-imidazole, 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.

40. The antibody conjugate of any one of claims 1-37, wherein:

the active agent is a pyrrolobenzodiazepine dimer;

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

41. The antibody conjugate of claim 40, wherein:

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^X'NR^X-*, -S(O)NR^X-*, or -PO_2NR^X-*;

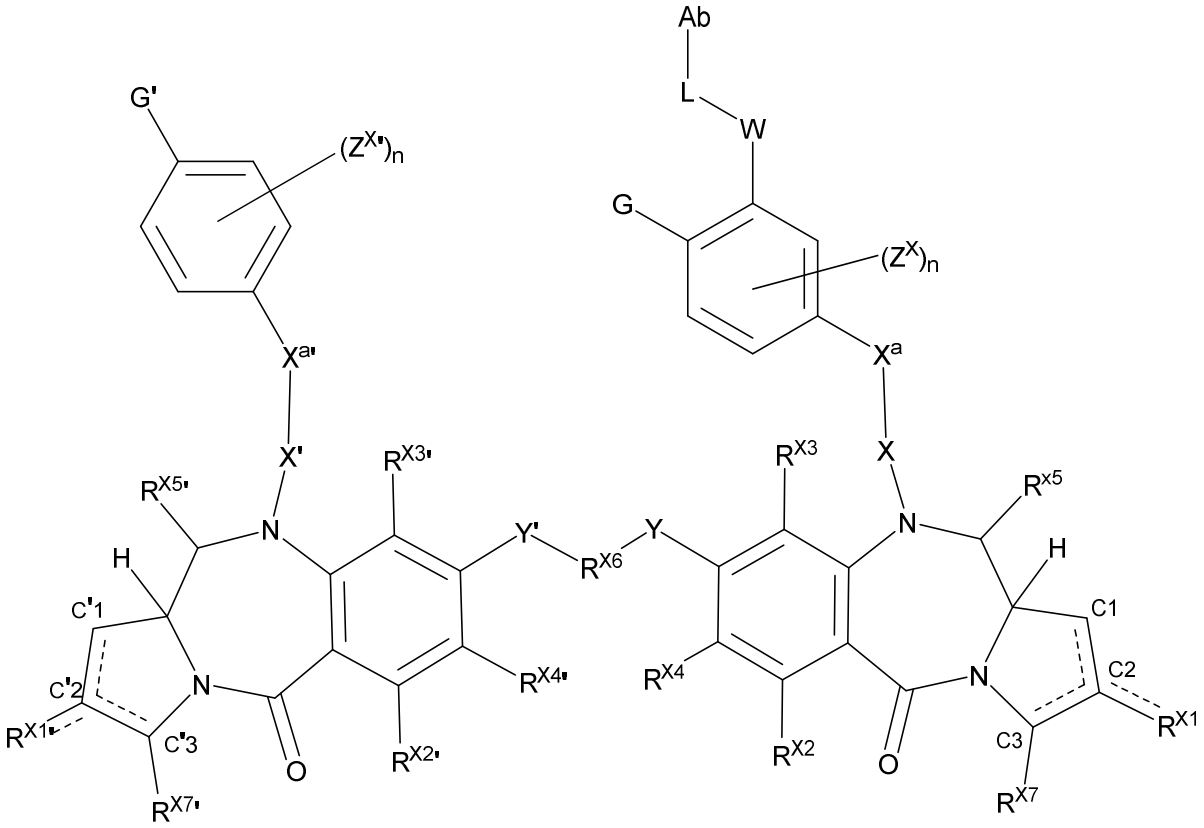
R^X is C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-20} heteroaryl or C_{5-20} aryl;

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

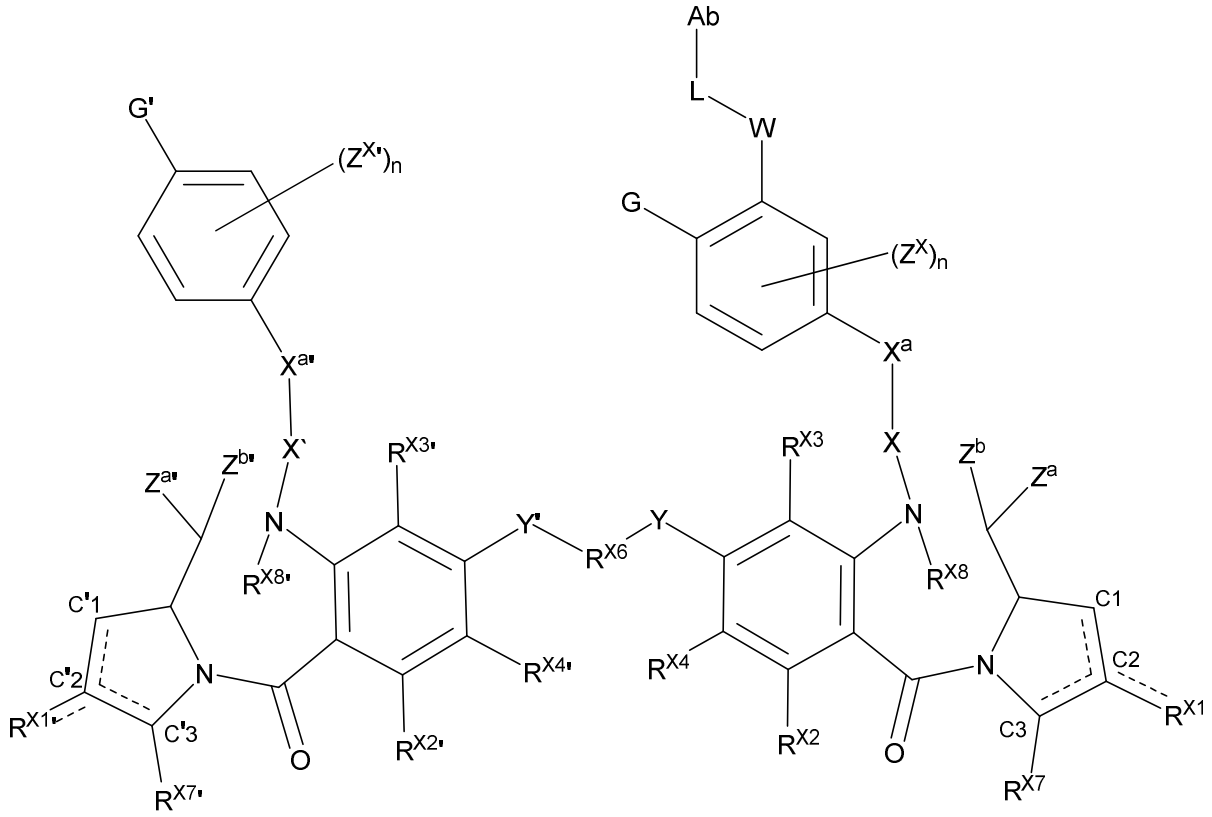
* is a binding site between the pyrrolobenzodiazepine dimer and the linker.

42. The antibody conjugate of claim 9 or 10, comprising a structure represented by General Formula XII or General Formula XIII:

[General Formula XII]



[General Formula XIII]



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- to 7-membered heterocyclyl, 3- to 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- to 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, and C_{1-8} alkyl;

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

X and X' are each independently selected from $-C(O)O-$, $-S(O)O-$, $-C(O)-$, $-C(O)NR^X-$, $-S(O)_2NR^X-$, $-P(O)R^{X'}NR^X-$, $-S(O)NR^X-$, and $-PO_2NR^X-$;

each R^{x6} is independently selected from C_{3-12} alkylene, C_{3-12} alkenylene, and 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- to 7- membered heterocycloalkyl, C_{6-10} aryl, 5- to 7- membered heteroaryl, $-OR^r$, $-OC(O)R^r$, $-OC(O)NR^rR^{r'}$, $-OS(O)R^r$, $-OS(O)_2R^r$, $-SR^r$, $-S(O)R^r$, $-S(O)_2R^r$, $-S(O)NR^rR^{r'}$, $-S(O)_2NR^rR^{r'}$, $-OS(O)NR^rR^{r'}$, $-OS(O)_2NR^rR^{r'}$, $-NR^rR^{r'}$, $-NR^rC(O)R^s$, $-NR^rC(O)OR^s$, $-NR^rC(O)NR^sR^{s'}$, $-NR^rS(O)R^s$, $-NR^rS(O)_2R^s$, $-NR^rS(O)NR^sR^{s'}$, $-NR^rS(O)_2NR^sR^s$, $-C(O)R^r$, $-C(O)OR^s$ and $-C(O)NR^rR^{r'}$;

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- to 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- to 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- to 7- membered heterocyclyl, 3- to 7- membered heterocycloalkyl, and 5- to 7- membered heteroaryl;

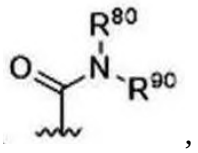
R^{X12a} and R^{X13a} optionally join the atoms to which they are attached to form a 3- to 7-membered heterocyclyl, 3- to 7-membered heterocycloalkyl, or 3- to 7-membered heteroaryl, and

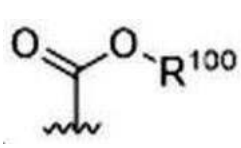
$R^{X12a'}$ and $R^{X13a'}$ optionally join the atoms to which they are attached to form a 3- to 7-membered heterocyclyl, 3- to 7-membered heterocycloalkyl, or 3- to 7-membered heteroaryl; and

each of R^{n}, $R^{n'}$, R^{o}, $R^{o'}$, is independently selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-13} cycloalkyl, 3- to 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 $-(CH_2)_m-OCH_3$;

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

R^{100} is selected from H, C_{1-8} alkyl, C_{2-6} alkenyl, and C_{1-6} alkoxy; and

m is an integer of 1 to 12.

43. The antibody conjugate of claim 42, wherein R^{X1} and $R^{X1'}$ are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} heteroaryl, or C_{5-7} aryl.

44. The antibody conjugate of claim 42 or 43, wherein each of R^{X2}, $R^{X2'}$, R^{X3}, $R^{X3'}$, R^{X5} and $R^{X5'}$ are independently selected from H or OH.

45. The antibody conjugate of any one of claims 42-44, wherein R^{X4} and $R^{X4'}$ are both C_{1-6} alkoxy.

46. The antibody conjugate of any one of claims 42-45, wherein Y and Y' are each O.

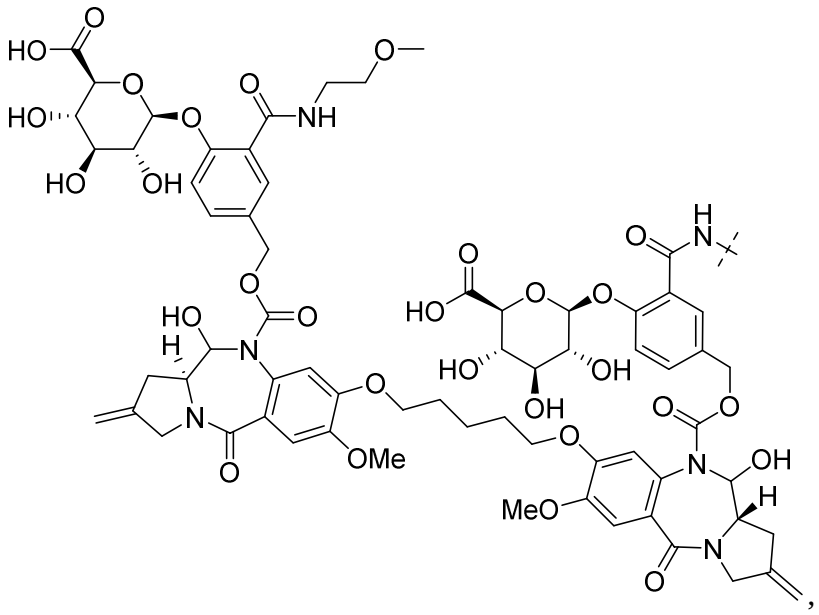
47. The antibody conjugate of any one of claims 42-46, wherein:

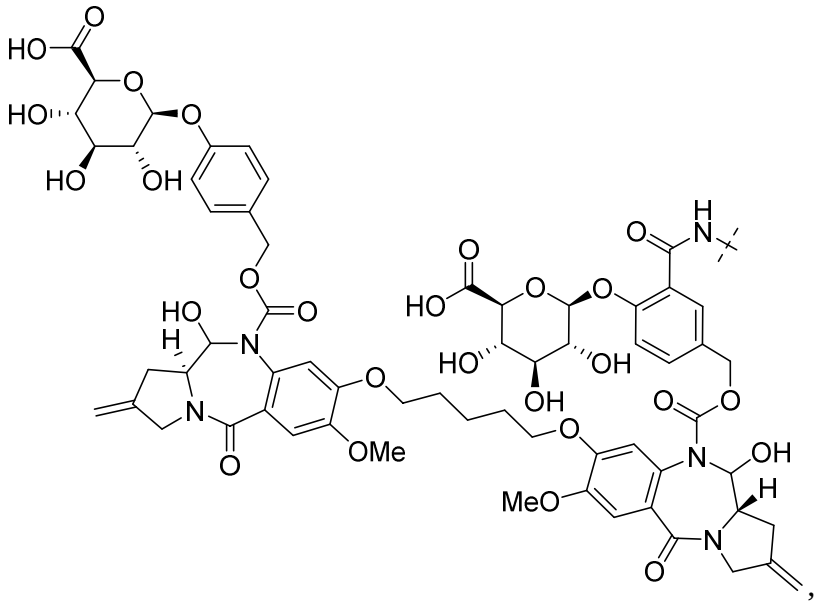
R^{x6} is C_{3-12} alkylene, C_{3-12} alkenylene or C_{3-12} heteroalkylene, where R^{x6} is substituted with $-NH_2$, $-NHR^m$, $-NHC(O)R^m$, $-NHC(O)R^m$, $-NHC(O)CH_2-[OCH_2CH_2]_n-R^{XX}$, or $-[CH_2CH_2O]^n-R^{XX}$;

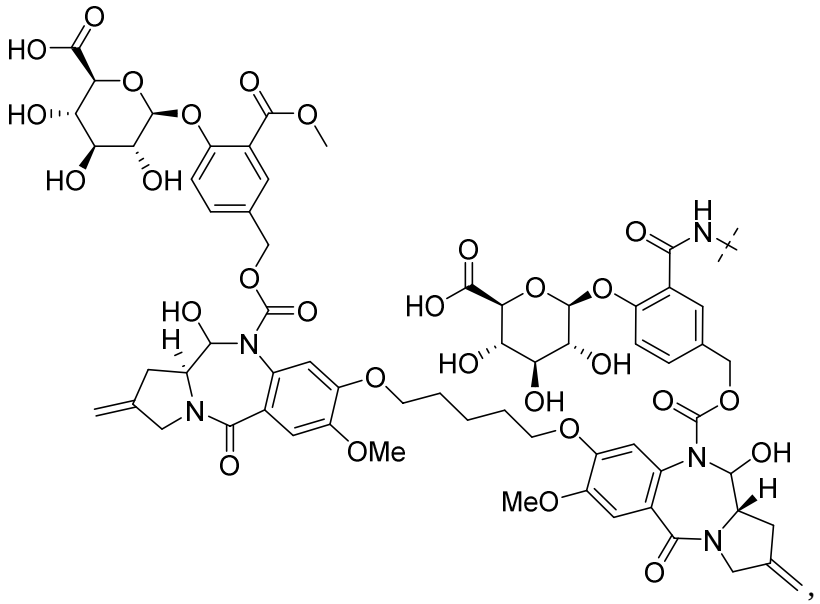
R^{XX} is H, OH, N_3, CN, NO_2, SH, NH_2, ONH_2, $NHNH_2$, halo, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{3-20} heteroaryl, C_{5-20} aryl or mono- or di-C_{1-8} alkyl amino; and

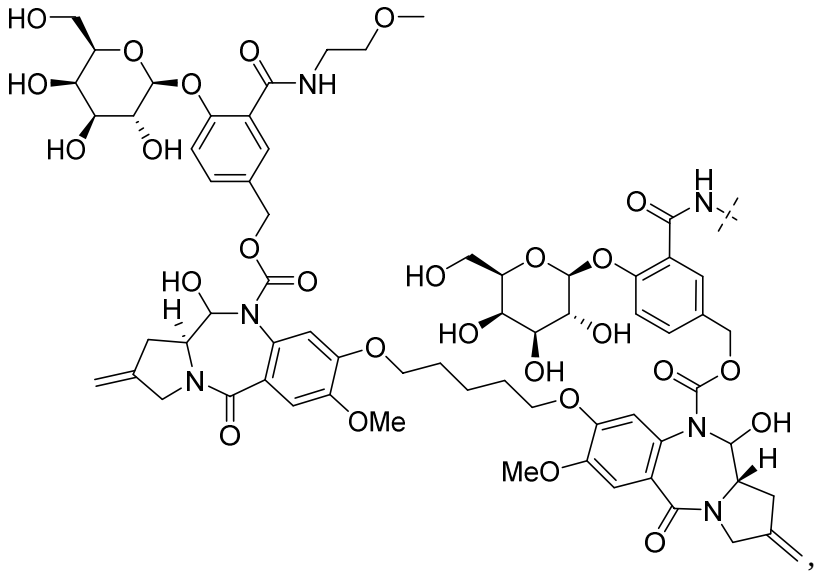
n is an integer of 1 through 6.

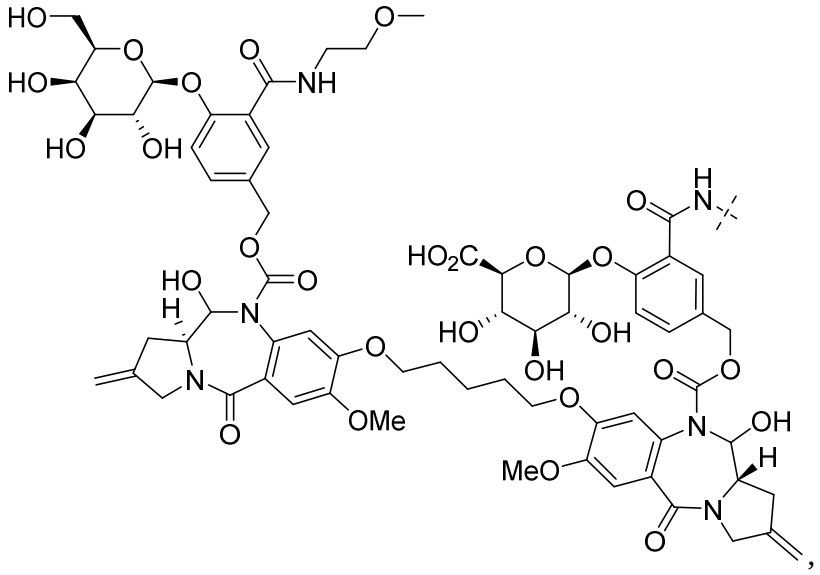
48. The antibody conjugate of any one of claims 1-47, wherein X^A comprises a structure represented by:

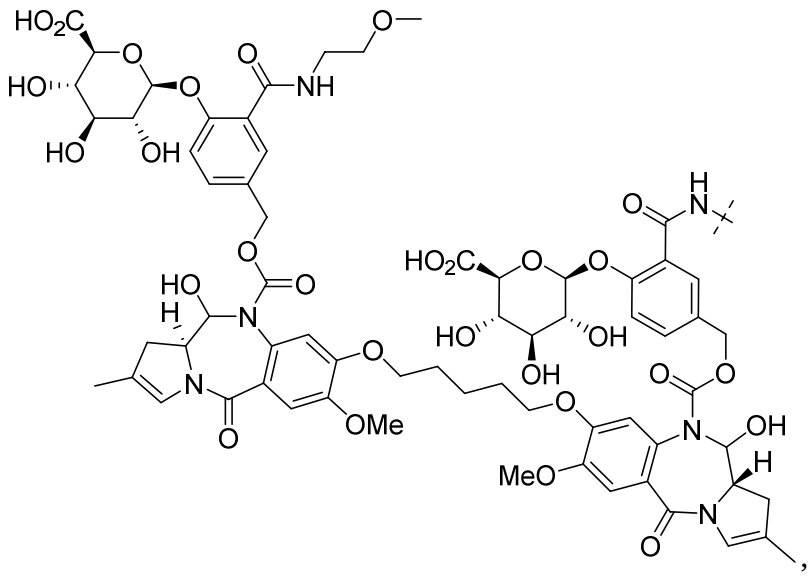


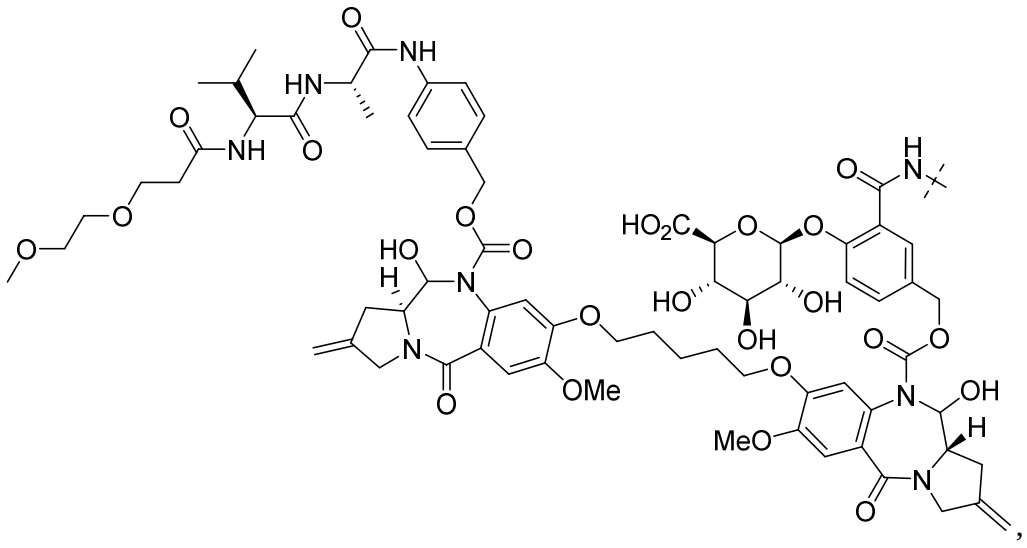


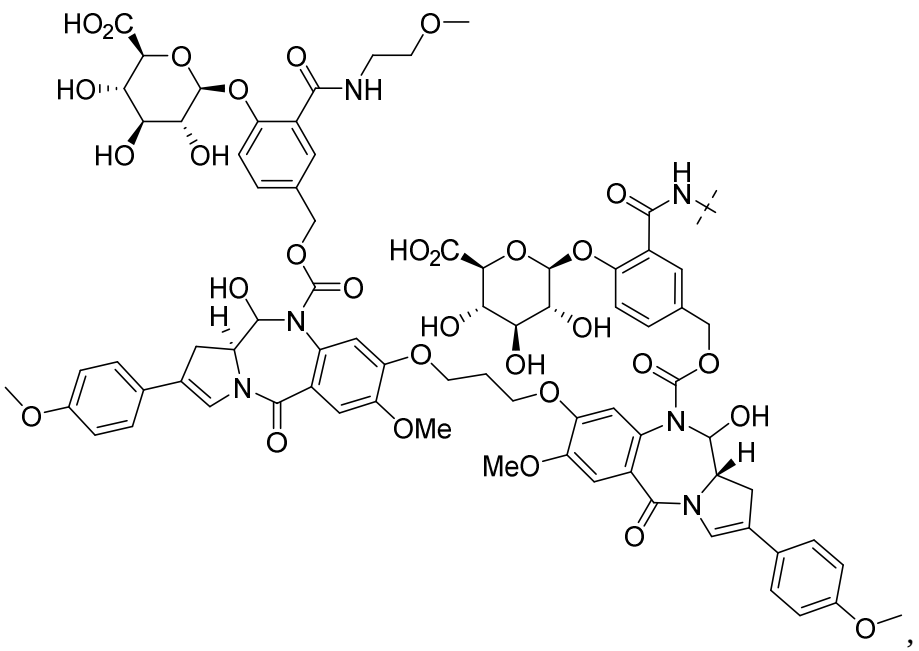


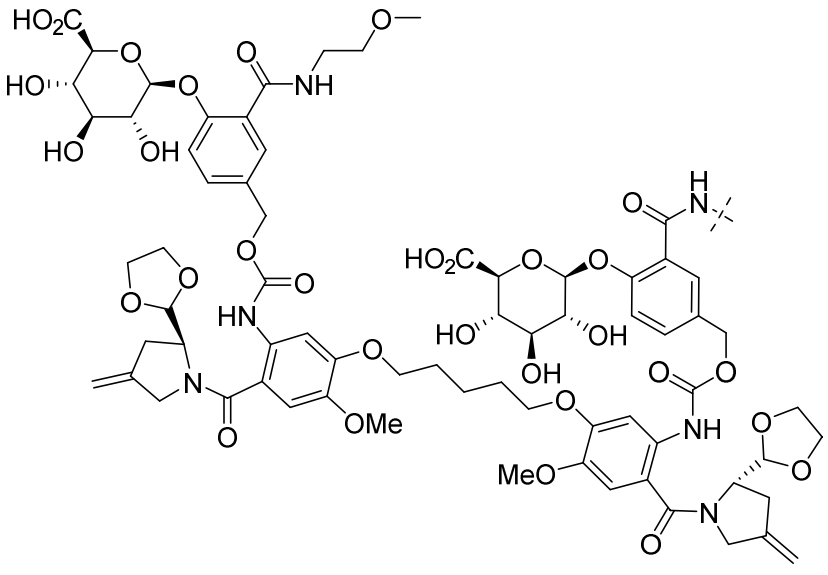




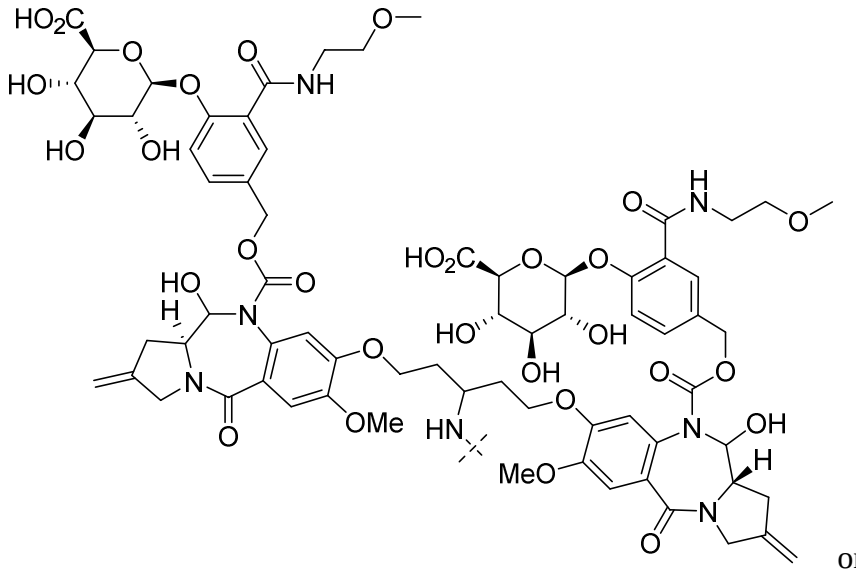




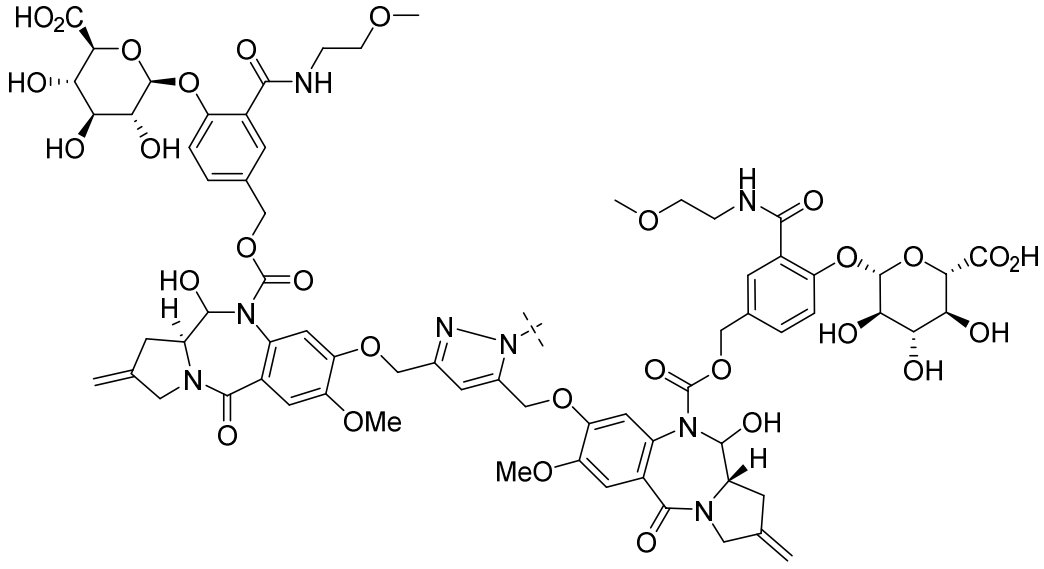

,


; or a pharmaceutically acceptable salt thereof.

49. The antibody conjugate of any one of claims 1-8, wherein X^A comprises a structure represented by:



or



; or a pharmaceutically acceptable salt thereof.

50. A pharmaceutical composition comprising an antibody conjugate of any one of claims 1-49 and a pharmaceutically acceptable excipient.

51. Use of an antibody conjugate selected from any one of claims 1-49 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer.

52. The use of claim 51, wherein the cancer is selected from chronic lymphocytic leukemia (CLL), B-cell leukemia, lymphoma, acute myeloid leukemia (AML), acute lymphoblastic

leukemia (ALL), 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, neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

53. The use of claim 52, wherein the lung cancer is non-small cell lung cancer (NSCLC).

54. The use of claim 52, wherein the lymphoma is Burkitt lymphoma, mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), or follicular lymphoma (FL) and marginal zone lymphoma (MZL).

55. An antibody conjugate selected from any one of claims 1-49 or a pharmaceutically acceptable salt thereof for use in therapy.