[0015] Certain PNU-159682 antibody-drug conjugates have been described ("NEMORUBICIN METABOLITE AND ANALOG ANTIBODY-DRUG CONJUGATES AND METHODS", PCT/US2009/031199, filed 16 Jan 2009).

[0016] SUMMARY ~~OF THE INVENTION~~

[0017] Provided herein are~~An aspect of the present invention is to provide~~ new anthracycline derivative conjugates with carriers such as monoclonal or polyclonal antibodies reactive with a selected cell population, proteins, peptides or other carriers of synthetic origin reactive with receptor tissues.

[0018] Also provided herein~~Another aspect~~ is a process for the preparation of such conjugates as well as useful intermediates.

[0019] The conjugates of the present ~~invention~~disclosure are characterized by the formula (I)

$$[\text{Ant-L-Z-}]_m\text{-T} \qquad \text{(I)}$$

[0020] wherein

[0021] Ant is anthracycline derivative residue,

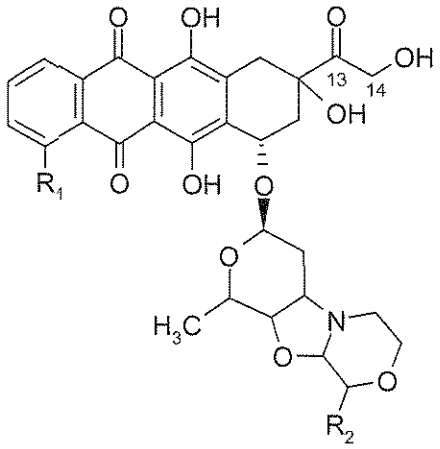
[0022] L is a linker,

[0023] Z is a spacer,

[0024] m is an integer of from 1 to 30 and

[0025] T is carrier such as a protein, peptide, monoclonal or polyclonal antibody or a chemically modified derivative thereof suitable to be attached to the [Ant-L-Z-] moiety or moieties, or a polymeric carrier;

[0026] characterized in that the anthracycline derivative residue that Ant represents can be released to give an anthracycline derivative of formula (II):



(II)

[0027] wherein R_1 is hydrogen atom, hydroxy or methoxy group and R_2 is a C_1-C_5 alkoxy group, or a pharmaceutically acceptable salt thereof.

[0028] The anthracycline derivative residue is tethered to the carrier through a linker

spacer [L-Z-], and the bond between the anthracycline derivative and the linker arm can be cleaved under physiological conditions so that to release an anthracycline derivative of formula (II) as defined above, that is the bioactive agent.

[0029] For example, conjugates wherein the bond between the anthracycline derivative and the linker is sensitive to acid conditions or to reducing conditions can release the anthracycline derivative in the conditions typically encountered within the cell, e.g., in lysosomal vesicles.

[0030] A preferred method of the present ~~invention~~disclosure is to treat specific types of cancer including but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukaemia, acute lymphocitic leukaemia, acute lymphoblastic leukaemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukaemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

[0031] Another preferred method of the present ~~invention~~disclosure is to treat specific cellular proliferation disorders such as, for example, benign prostate hyperplasia, familial adenomatosis polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis.

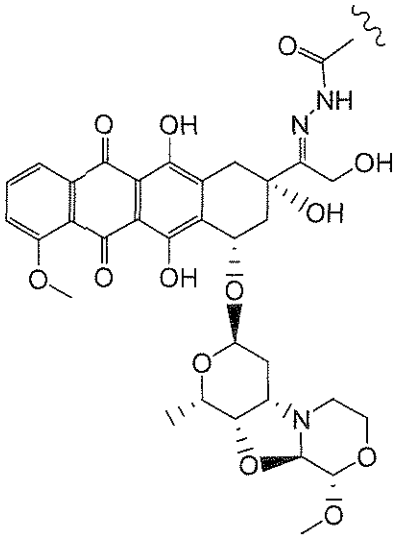
[0032] The anthracycline derivative conjugates of the formula (I) can be prepared through a process consisting of standard synthetic transformations; such process and the intermediates used in such process are also provided by the present ~~invention~~disclosure.

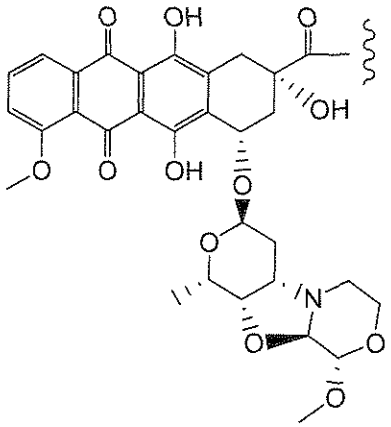
[0033] The present ~~invention~~disclosure also provides a pharmaceutical composition comprising an anthracycline derivative conjugate of the formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient or diluent.

[0034] Provided herein~~An aspect of the invention~~ is an anthracycline derivative of formula (IIc)

$$Ant–L–(Z)_m–X \qquad (IIc)$$

[0035] wherein Ant is an anthracycline derivative selected from the structures:



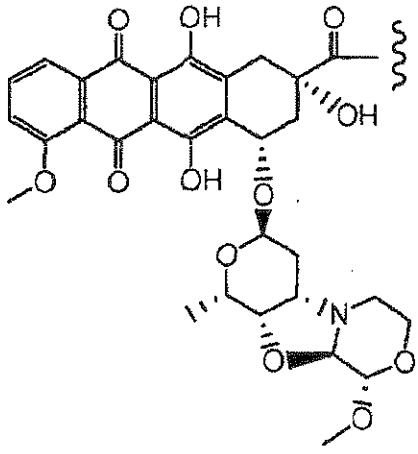


[0036] where the wavy line indicates the attachment to linker L; Z is an optional spacer; m is 0 or 1; X is a reactive functional group; and n is an integer from 1 to 6.

[0036a] In one aspect, there is provided an anthracycline derivative of Formula (IIc)

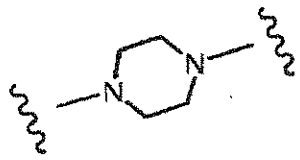
$$Ant\text{-}L\text{-}(Z)_m\text{-}X \qquad \text{(IIc)}$$

wherein Ant is selected from the structure:



where the wavy line indicates the attachment to L;

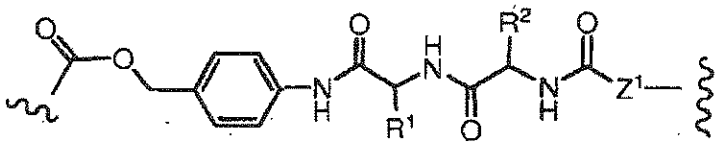
L is a linker selected from -N(R)-, $-N(R)_m(C_1\text{-}C_{12}$ alkylene)-, $-N(R)_m(C_2\text{-}C_8$ alkenylene)-, $-N(R)_m(C_2\text{-}C_8$ alkynylene)-, $-N(R)_m(CH_2CH_2O)_n$-, and the structure:

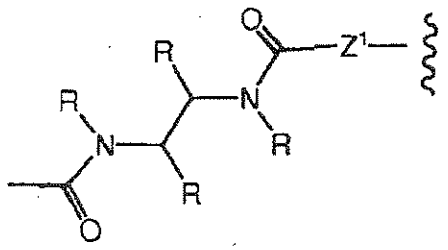


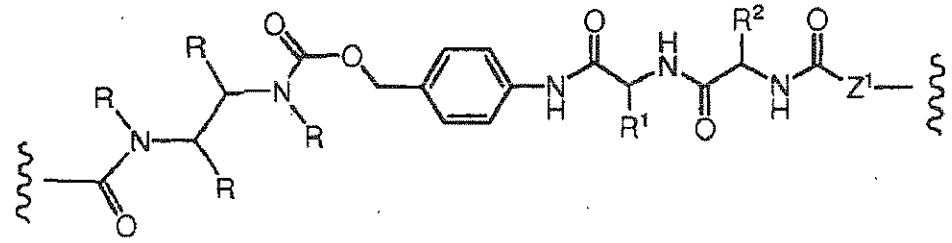
;

where the wavy lines indicate the attachments to Ant and Z; and

Z is an optional spacer selected from $-CH_2C(O)-$, $-CH_2C(O)NR(C_1-C_{12}$ alkylene$)-$, and the structures:







X is a reactive functional group selected from maleimide, thiol, amino, bromide, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;

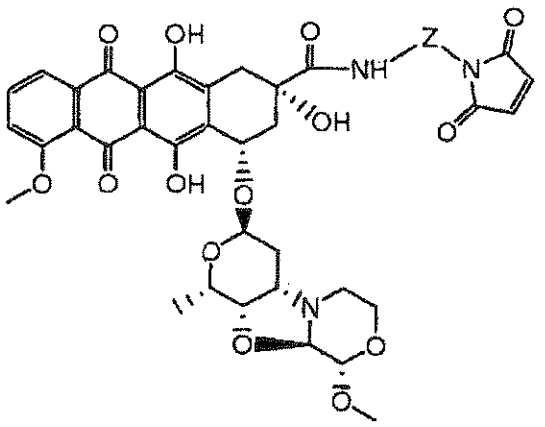
R^1 and R^2 are independently selected from an amino acid side chain;

Z^1 is selected from $-(C_1-C_{12}$ alkylene$)-$, $-(C_2-C_8$ alkenylene$)-$, $-(C_2-C_8$alkynylene$)-$, and $-(CH_2CH_2O)_n-$;

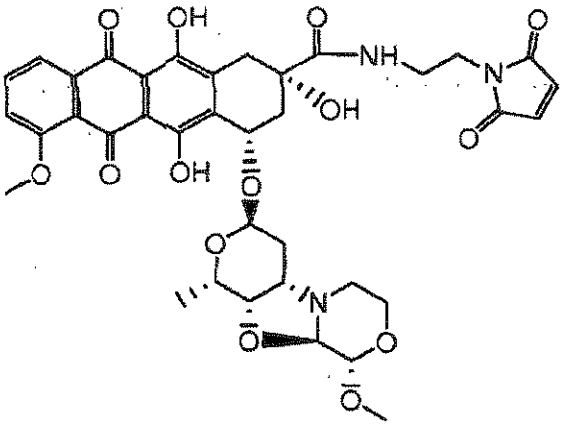
m is 0 or 1; and

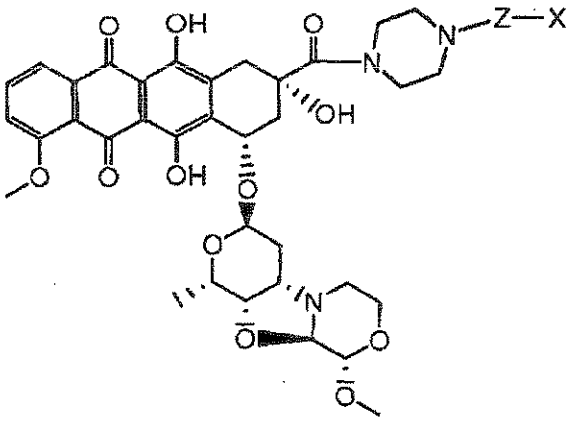
n is 1 to 6;

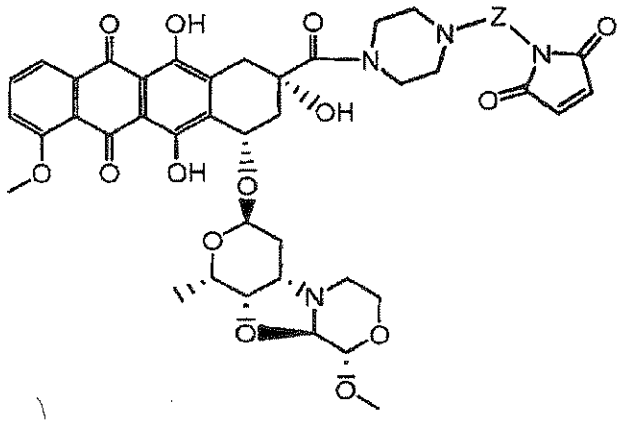
or wherein the anthracycline derivative is selected from the structures:

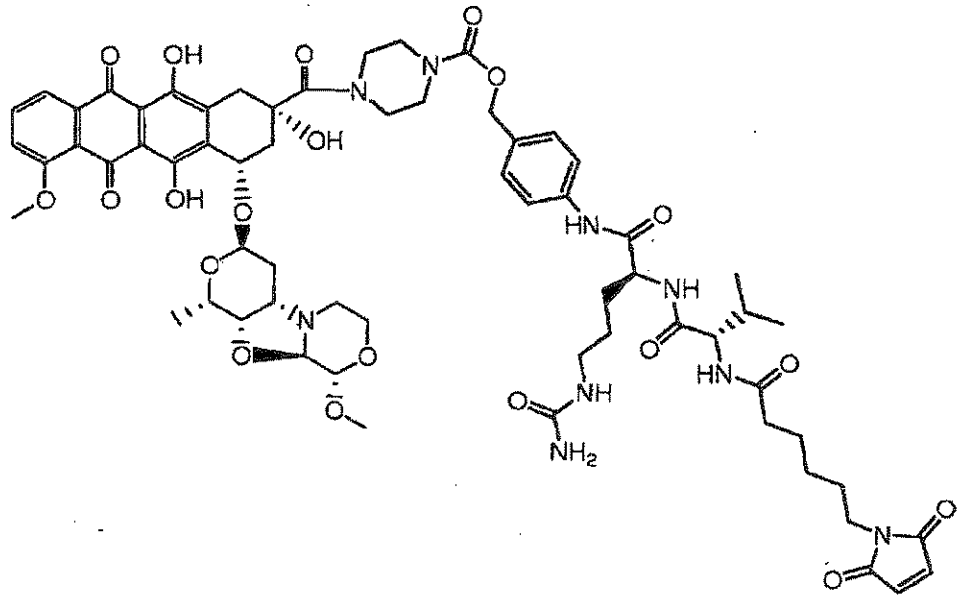


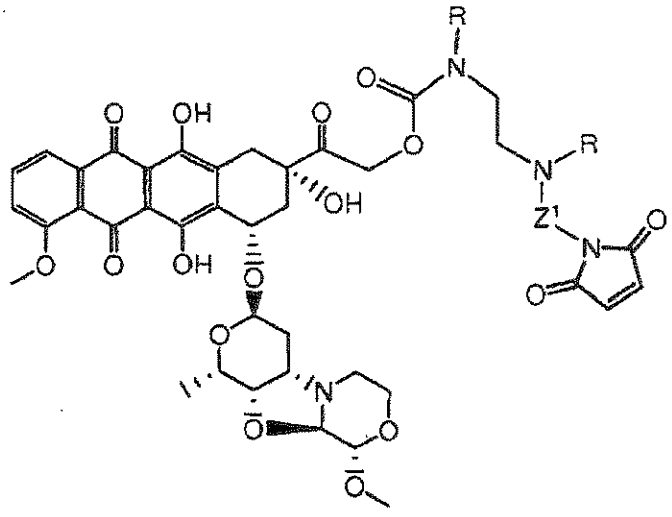
where Z is C_1-C_{12} alkylene,



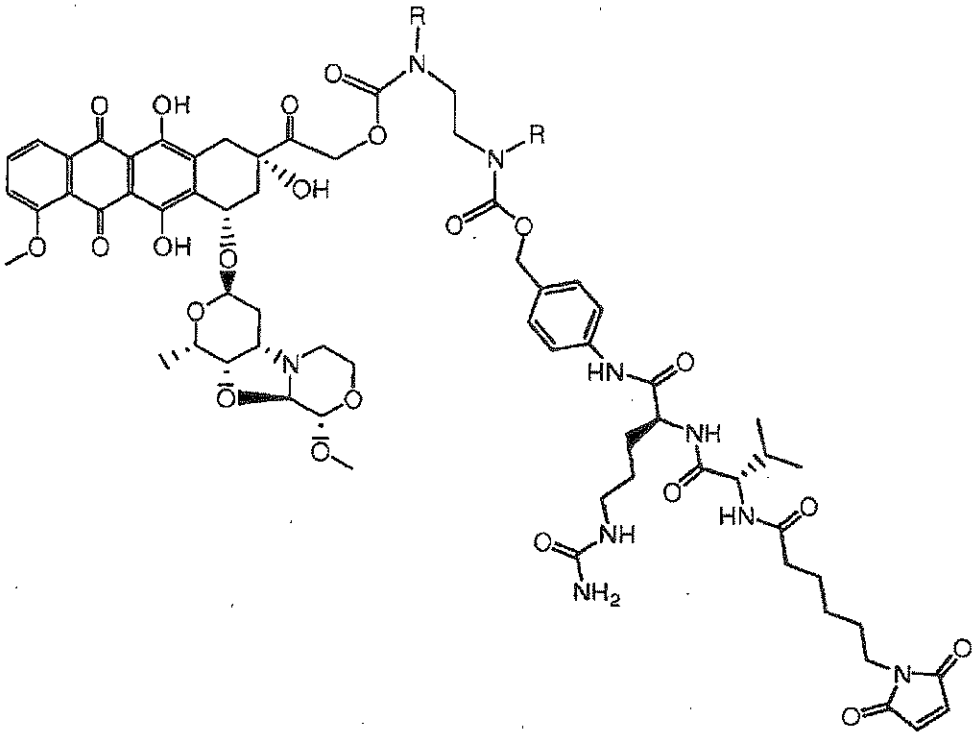








and



[0037] Also provided herein~~An aspect of the invention~~ is an antibody-drug conjugate (ADC) compound comprising an antibody covalently attached by a linker L and an optional spacer Z to one or more anthracycline derivative drug moieties D, the compound having formula (Ic)

$$Ab–(L–Z_m–D)_p \qquad (Ic)$$

or a pharmaceutically acceptable salt thereof, wherein p is an integer from 1 to 8.

[0037a] In one aspect, there is provided an antibody-drug conjugate compound comprising an antibody covalently attached by a linker L and an optional spacer Z to one or more anthracycline derivative drug moieties D, the compound having Formula **(Ic)**

$$Ab-(Z_m-L-D)_p \qquad Ic$$

or a pharmaceutically acceptable salt thereof, wherein:

Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(36):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008016Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

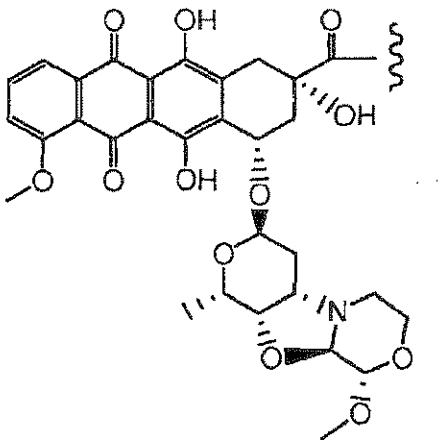
(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2); and

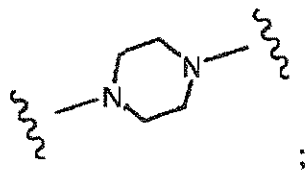
(36) TENB2 (putative transmembrane proteoglycan);

D is an anthracycline derivative selected from the structure:



where the wavy line indicates the attachment to L;

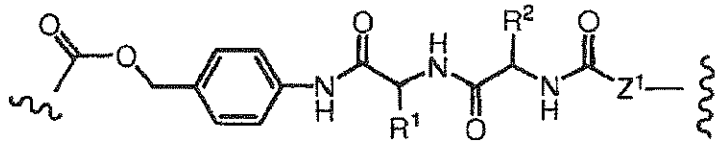
L is a linker selected from -N(R)-, -N(R)$_m$(C_1-C_{12} alkylene)-, -N(R)$_m$(C_2-C_8 alkenylene)-, -N(R)$_m$(C_2-C_8 alkynylene)-, -N(R)$_m$(CH_2CH_2O)$_n$-, and the structure:

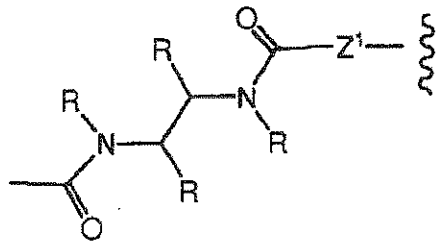


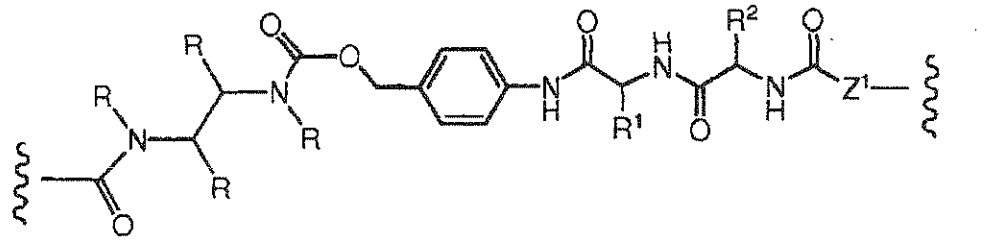
;

where the wavy lines indicate the attachments to D and Z; and

Z is an optional spacer selected from -$CH_2C(O)$-, -$CH_2C(O)NR(C_1$-C_{12} alkylene)-, and the structures:

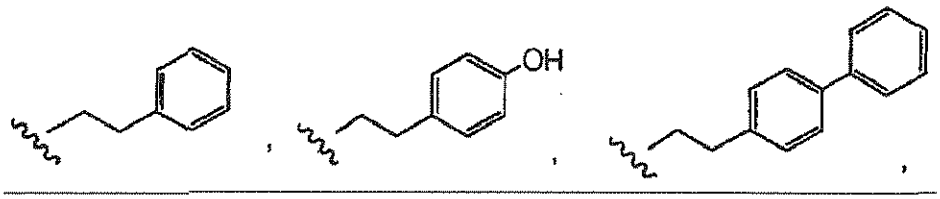


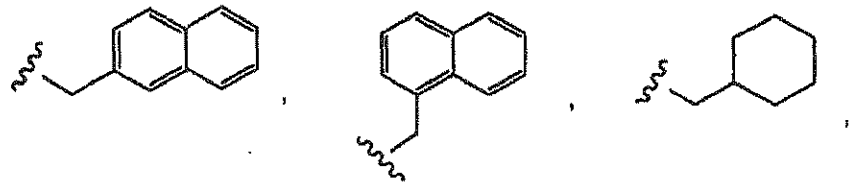


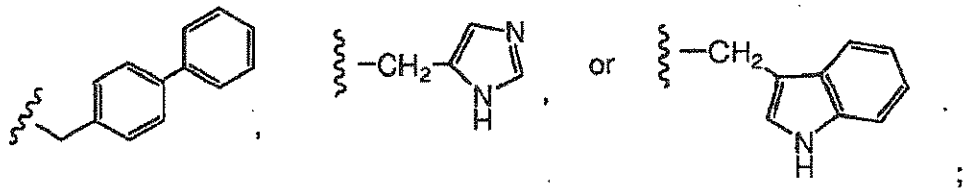


R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;

R^1 and R^2 are independently selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, -CH_2OH, -$CH(OH)CH_3$, -$CH_2CH_2SCH_3$,-CH_2CONH_2, -CH_2COOH, -$CH_2CH_2CONH_2$, -CH_2CH_2COOH, -$(CH_2)_3NHC(=NH)NH_2$,-$(CH_2)_3NH_2$, -$(CH_2)_3NHCOCH_3$, -$(CH_2)_3NHCHO$, -$(CH_2)_4NHC(=NH)NH_2$, -$(CH_2)_4NH_2$, -$(CH_2)_4NHCOCH_3$, -$(CH_2)_4NHCHO$, -$(CH_2)_3NHCONH_2$, -$(CH_2)_4NHCONH_2$,-$CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl, and the following structures:







;

Z^1 is selected from -(C_1-C_{12} alkylene)-, -(C_2-C_8 alkenylene)-, -(C_2-C_8alkynylene)-, and -$(CH_2CH_2O)_n$-.

m is 0 or 1;

n is 1 to 6; and

p is an integer from 1 to 8.

[0037b] In one aspect, there is provided a pharmaceutical composition comprising the antibody-drug conjugate compound as defined herein and a pharmaceutically acceptable diluent, carrier or excipient.

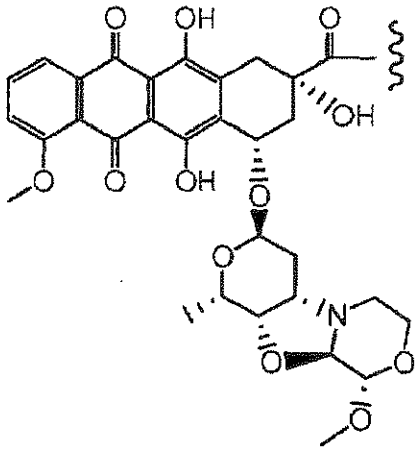
[0037c] In one aspect, there is provided the use of an antibody-drug conjugate compound as defined herein in the manufacture of a medicament for the treatment of cancer in a mammal.

[0037d] In one aspect, there is provided an antibody-drug conjugate compound as defined herein for use in a method for treating cancer.

[0037e] In one aspect, there is provided a method of making an antibody-drug conjugate compound comprising reacting an anthracycline derivative and an antibody Ab to form the antibody-drug conjugate compound, wherein the anthracycline derivative has Formula (IIc):

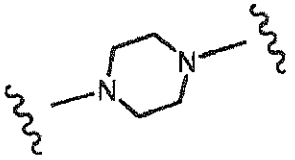
Ant-L-$(Z)_m$-X (IIc)

where Ant is selected from the structure:



where the wavy line indicates the attachment to L;

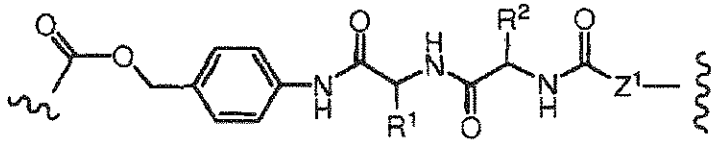
L is a linker selected from -N(R)-, -N(R)$_m$(C_1-C_{12} alkylene)-, -N(R)$_m$(C_2-C_8 alkenylene)-, -N(R)$_m$(C_2-C_8 alkynylene)-, -N(R)$_m$(CH_2CH_2O)$_n$-, and the structure:

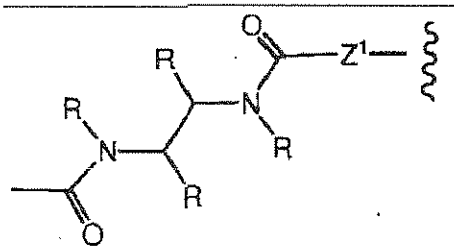


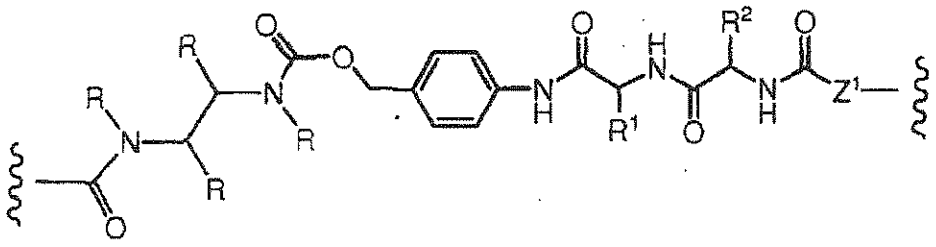
;

where the wavy lines indicate the attachments to Ant and Z; and

Z is an optional spacer selected from -$CH_2C(O)$-, -$CH_2C(O)NR$(C_1-C_{12} alkylene)-, and the structures:







X is a reactive functional group selected from maleimide, thiol, amino, bromide, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;

R^1 and R^2 are independently selected from an amino acid side chain;

Z^1 is selected from -(C_1-C_{12} alkylene)-, -(C_2-C_8 alkenylene)-, -(C_2-C_8 alkynylene)-, and -(CH_2CH_2O)$_n$-,

m is 0 or 1; and n is 1 to 6;

the antibody-drug conjugate has formula Ic:

$$Ab-(Z_m-L-D)_p \qquad \textbf{Ic}$$

wherein D is Ant;
where Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(36):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008016Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell-activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2); and

(36) TENB2 (putative transmembrane proteoglycan); and

p is an integer from 1 to 8.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Figure 1 shows in a graph form the stability of the compound 2 shown in Table 1 at pH 5.2 wherein in (Y) axis there is the percentage amount of the compound of the formula (IIA) as defined below, and in (X) axis the time in hours. This graph demonstrates the acid-sensitivity of the acetalic bound of the invention as indicated by the increased release of the free compound of the formula (IIA) from the conjugate under acid pH.

[0039] Figure 2 shows an exemplary process to prepare Formula Ia compounds by reacting anthracycline derivative Formula II with vinyl ether compounds (X) or (IX) to give acetal compound (XI), hydrolysis to a carboxy compound (XII), and activation to form an N-hydroxy succinimide (NHS) ester (XIII), ready for conjugation with a carrier compound.

[0040] Figure 3a shows an exemplary process to prepare Formula Ia compounds by reaction of activated N-hydroxy succinimide (NHS) ester (XIII) with amino-thiol reagent (XXI) to give XXII which can be reacted with pyridyl-disulfide carrier (T) intermediate (VI) to give disulfide linked anthracycline derivative conjugate (Ia), or reacted with maleimide

CLAIMS

1. An anthracycline derivative conjugate of formula (I) or formula (I')

$$[Ant\text{-}L\text{-}Z\text{-}]_m\text{-}T \quad (I)$$

$$Ant\text{-}L\text{-}Z\text{-}Q \quad (I')$$

or a pharmaceutical acceptable salt thereof, wherein

Ant is an anthracycline derivative residue,

L is a linker,

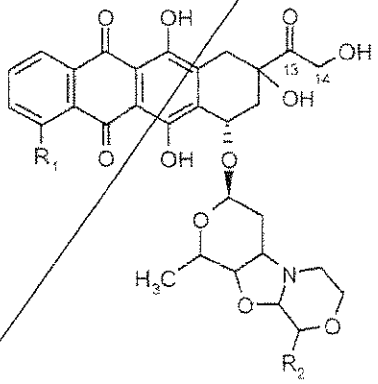
Z is a spacer.

m is an integer of from 1 to 30.

T is a carrier selected from protein, peptide, monoclonal or polyclonal antibody or a chemically modified derivative thereof suitable to be attached to the [Ant-L-Z-] moiety or moieties, or a polymeric carrier, and

Q is a hydrogen atom, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl or benzyl group;

and the Ant can be released to give an anthracycline derivative of formula (II)



(II)

wherein R_1 is a hydrogen atom, hydroxy or methoxy group and R_2 is a C_1-C_5 alkoxy group, or a pharmaceutically acceptable salt thereof.

2. An anthracycline derivative conjugate of formula (I) or formula (I') or a pharmaceutical acceptable salt thereof, according to Claim 1, wherein the spacer Z is selected from

a) –NH-,

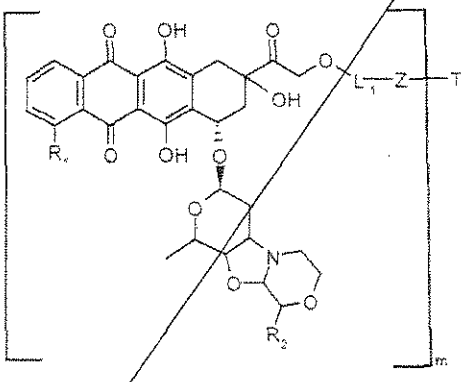
b) -S-,

c) aminoalkylene, thioalkylene, aminocycloalkylene or thiocycloalkylene bearing a further thiol or amino group or a carboxylic residue, or

d) a peptidic residue which is able to tether the L_1 linker to the T carrier by forming amide bonds or disulfide bonds.

3. An anthracycline derivative conjugate of formula (I) or a pharmaceutical acceptable salt thereof according to Claim 1, wherein the carrier T is selected from a polyclonal antibody or fragment thereof comprising an antigen binding site which is capable of binding to a tumor associated antigen: a monoclonal antibody or fragment thereof comprising an antigen binding site which is capable of binding to an antigen preferentially or selectively expressed on tumor cell populations: a natural or recombinant peptide or protein which is capable of preferentially or selectively binding to a tumor cell; or a chemically modified derivative thereof suitable to be attached to the [Ant-L_1-Z-] moiety or moieties, or a natural or synthetic polymeric carrier.

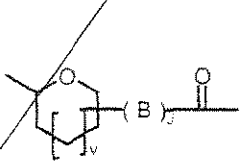
4. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 1 is of formula (Ia)



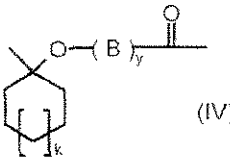
(Ia)

wherein:

R_1, R_2, Z, m and T are as defined in Claim 1, and L_1 is a linker of formula (III) or (IV)



(III)



(IV)

wherein B is a C_1-C_6 alkylene moiety optionally heteroatom interrupted, and v, j, k and y are independently 0 or 1; and the Ant is tether to the linker L_1 through an acetalic bond to the primary alcohol at the C-14 of the formula (II).

5. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 4 wherein the spacer Z is selected from:

i) -NH- so $[-Z-]_m$-T is derived from a carrier of the formula T-$[NH_2]_m$;

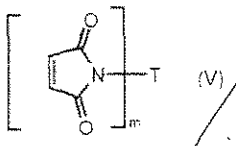
ii) –S- so $[-Z-]_m$-T is derived from a carrier of the formula T-$[SH]_m$;

iii) -NH-*D*-NH-CO- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-NH- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group so $[-Z-]_m$-T is derived from a carrier of formula T-$[COOH]_m$;

iv) –NH-*D*-CO-NH- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-CO- is a peptide residue constituted from 1 to 4 amino acids having at least one free carboxylic group so $[-Z-]_m$-T is derived from a carrier of formula T-$[NH_2]_m$;

v) –NH-*D*-N=CH- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene and -*D*-N- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group so $[-Z-]_m$-T is derived from a carrier of formula T-$[CHO]_m$;

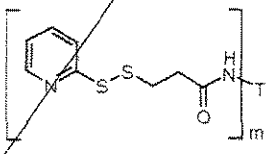
vi) -NH-*D*-S-CH- wherein -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group so $[-Z-]_m$-T is derived from a carrier derivative of formula (V):



(V)

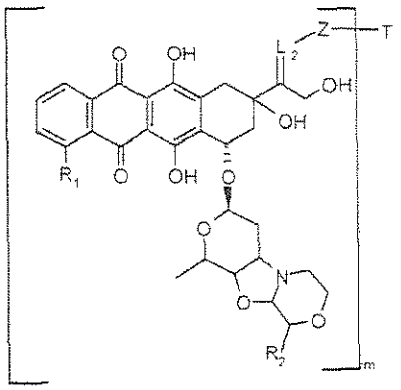
; and

vii) -NH-*D*-S-S- wherein is -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group so $[-Z-]_m$-T is derived from a carrier derivative of formula (VI):



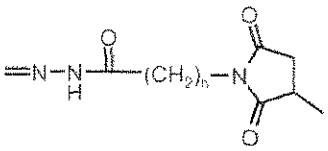
(VI)

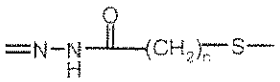
6. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 1 is of formula (Ib):



(Ib)

wherein R_1 and R_2, Z, m and T are as defined in Claim 1 and L_2 is a linker of formula (VII) or (VIII):


(VII)


(VIII)

wherein n is an integer from 1 to 9.

7. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 6 wherein

L_2 is a linker of formula (VII) as defined in Claim 6 and Z is selected from:

i) -NH- so $[-Z-]_m$-T is derived from a carrier of the formula T-$[NH_2]_m$;

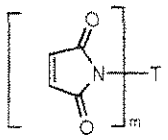
ii) –S- so $[-Z-]_m$-T is derived from a carrier of the formula T-$[SH]_m$;

iii) -NH-*D*-NH-CO- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-NH- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group so $[-Z-]_m$-T is derived from a carrier of formula T-$[COOH]_m$;

iv) –NH-*D*-CO-NH- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-CO- is a peptide residue constituted from 1 to 4 amino acids having at least one free carboxylic group so $[-Z-]_m$-T is derived from a carrier of formula T-$[NH_2]_m$;

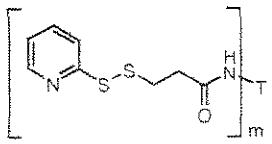
v) –NH-*D*-N=CH- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-N- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group so $[-Z-]_m$-T is derived from a carrier of formula T-$[CHO]_m$;

vi) -NH-*D*-S-CH- wherein -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group so $[-Z-]_m$-T is derived from a carrier derivative of formula (V):


(V)

;

vii) -NH-*D*-S-S- wherein is -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group so $[-Z-]_m$-T is derived from a carrier derivative of formula (VI):



(VI)

viii) -S-*D*-NH-CO- wherein -*D*-NH- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group;

ix) –S-*D*-CO-NH- wherein - -*D*-CO- is a peptide residue constituted from 1 to 4 amino acids having at least one free carboxylic group;

x) –S-*D*-N=C- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-N- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group;

xi) S-*D*-S-CH- wherein -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group; and

xii) -S-*D*-S-S- wherein -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group.

8. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 6 wherein

L_2 is a linker of formula (VIII) as defined in Claim 6 and Z is selected from:

i) –S- so $[-Z-]_m$-T is derived from a carrier of the formula $T-[SH]_m$:

ii) -S-*D*-NH-CO- wherein -*D*-NH- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group;

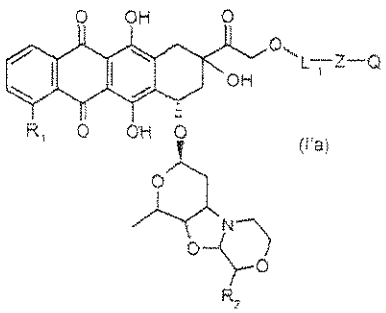
iii) –S-*D*-CO-NH- wherein - -*D*-CO- is a peptide residue constituted from 1 to 4 amino acids having at least one free carboxylic group;

iv) –S-*D*-N=C- wherein –*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-N- is a peptide residue constituted from 1 to 4 amino acids having at least one free amino group;

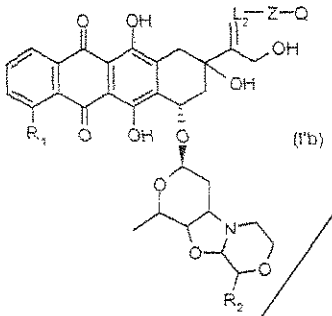
v) S-*D*-S-CH- wherein -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group; and

vi) -S-*D*-S-S- wherein -*D*- is a C_1-C_6 alkylene, C_3-C_6 cycloalkylene or -*D*-S- is a peptide residue constituted from 1 to 4 amino acids having at least one free thiol group.

9. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 1 is of formula (I'a) or (I'b):



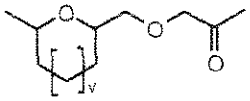
(I'a)



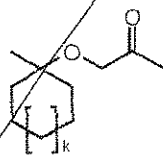
(I'b)

wherein L_1 L_2, R_1 and R_2 are as defined in claim 4 and 6, Z is -NH- or a peptic residue constituted from 1 to 3 amino acids and Q is hydrogen atom, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl or benzyl group.

10. The anthracycline derivative conjugates or a pharmaceutical acceptable salt thereof according to Claim 1 wherein L is of formula (IIIa) or (IVa)

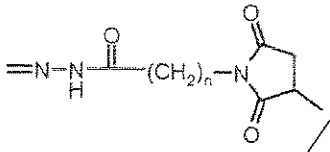


(IIIa)

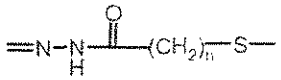


(IVa)

wherein v and k are independently 0 or 1; or L is of formula (VII) or (VIII)



(VII)



(VIII)

wherein n is an integer from 2 to 5.

11. The polymeric carrier according to Claim 3 is polylysine, polyglutamic acid, polyaspartic acid and analogues or derivatives thereof, dextran, polymeric carbohydrate and analogues or derivatives thereof; or synthetic copolymers derived from N-(2-hydroxypropyl)methacrylamide (HPMA).

12. The antibody according to Claim 3 is anti T-cell antibody T101 Royston, anti CD5 antibody OKT1 (Ortho) ATCC CRL 8000, anti CD20 antibody IgG1 ibritumomab, anti CD33 antibody huCD33, anti transferring receptor antibody OKT9 (Ortho) ATCC CRL 8021, anti melanoma antibody MAb 9.2.27, anti carcinoma markers antibody which is selected from the group consisting of anti-CEA 1116 NS-3d ATCC CRL 8019, anti alpha-fetoprotein OM 3-1.1 ATCC HB 134, 791T/36 Embleton, and B 72.3, anti ovarian carcinoma antibody OVB 3 ATCC HB 9147, anti breast carcinoma antibody, anti bladder carcinoma 1G3.10, anti CanAg antibody huC242 antibody, or anti prostate antibody MLN591.

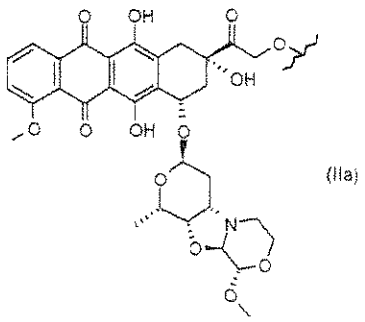
13. The peptide or protein according to Claim 3 is FGF, EGF, PDGF, TGF-ALPHA, ALPHA -MS, Interleukines, Interferones, TNF, melanotropin (MSH), or Mcm2.

14. The carrier T-$[CHO]_m$ according to Claim 5 is derived from polyclonal or monoclonal antibodies having the carbohydrate moiety, preferentially located in the Fc region, selectively oxidized to aldehyde groups by means of chemical or enzymatic methods.

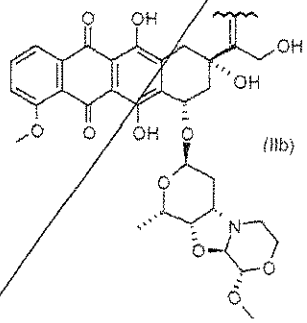
15. The anthracycline derivative conjugates according to Claim 1 are selected from compounds wherein

Formula I is $[Ant\text{-}L\text{-}Z\text{-}]_m$ –T, and Formula (I') is Ant-L-Z-*Q*;

Ant is a formula (IIa) or (IIb);

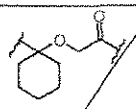
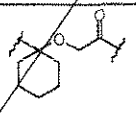
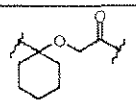
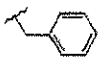
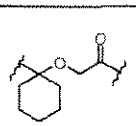
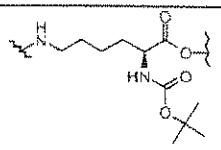
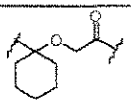
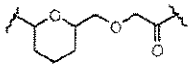


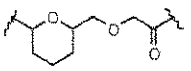
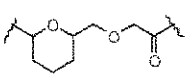
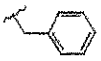
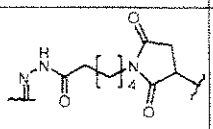
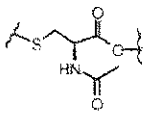
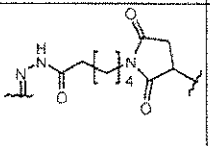
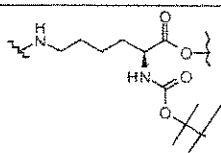
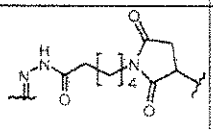
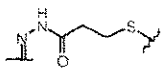
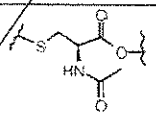
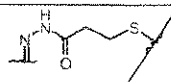
(IIa)



(IIb)

and L, Z m, Q and T are as defined below:

Comp	Formula	Ant	L	Z	m	Q	T
1	I'	IIa		-NH-	1	H	-
2	I'	IIa		-NH-	1	CH_3	-
3	I'	IIa		-NH-	1		-
4	I'	IIa			1	H	-
5	I	IIa		-NH-	6	-	Mcm2
6	I'	IIa		-NH-	1	H	-

7	I`	IIa		-NH-	1	CH_3	-
8	I`	IIa		-NH-	1		-
9	I`	IIb			1	H	-
10	I`	IIb			1	H	-
11	I	IIb		NH	6	-	Mcm2
12	I`	IIb			1	H	-
13	I	IIb		S	1	-	Mcm2
14	I	IIb		NH	6	-	Mcm2

16. The anthracycline derivative conjugates according to Claim 1 is selected from the group consisting of

2-[(1-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}cyclohexyl)oxy]acetamide,

N-methyl-2-[(1-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}cyclohexyl)oxy]acetamide,

N-benzyl-2-[(1-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-

pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}cyclohexyl)oxy]acetamide,

N^2-(*tert*-butoxycarbonyl)-N^6-{[(1-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}cyclohexyl)oxy]acetyl}-L-lysine,

N-methyl-2-[(6-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}tetrahydro-2*H*-pyran-2-yl)methoxy]acetamide,

2-[(6-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}tetrahydro-2*H*-pyran-2-yl)methoxy]acetamide,

N-benzyl-2-[(6-{2-oxo-2-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethoxy}tetrahydro-2*H*-pyran-2-yl)methoxy]acetamide,

N-acetyl-*S*-(1-{6-[(2*E*)-2-{2-hydroxy-1-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethylidene}hydrazinyl]-6-oxohexyl}-2,5-dioxopyrrolidin-3-yl)-L-cysteine,

N^2-(*tert*-butoxycarbonyl)-N^6-(1-{6-[(2*E*)-2-{2-hydroxy-1-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethylidene}hydrazinyl]-6-oxohexyl}-2,5-dioxopyrrolidin-3-yl)-L-lysine, and

N-acetyl-3-({3-[(2*E*)-2-{2-hydroxy-1-[(2*S*,4*S*)-2,5,12-trihydroxy-7-methoxy-4-{[(1*S*,3*R*,4a*S*,9*S*,9a*R*,10a*S*)-9-methoxy-1-methyloctahydro-1*H*-pyrano[4',3':4,5][1,3]oxazolo[2,3-*c*][1,4]oxazin-3-yl]oxy}-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethylidene}hydrazinyl]-3-oxopropyl}disulfanyl)-L-alanine.

17. A pharmaceutical composition comprising an anthracycline derivative conjugate or a pharmaceutically acceptable salt thereof according to Claim 1 and a pharmaceutically acceptable excipient, carrier or diluent.

18. A method of treating cancer or cellular proliferation disorders comprising administering to a patient in need thereof a therapeutically effective amount of an anthracycline derivative conjugate or a pharmaceutically acceptable salt thereof according to Claim 1, or a pharmaceutical composition according to Claim 17.

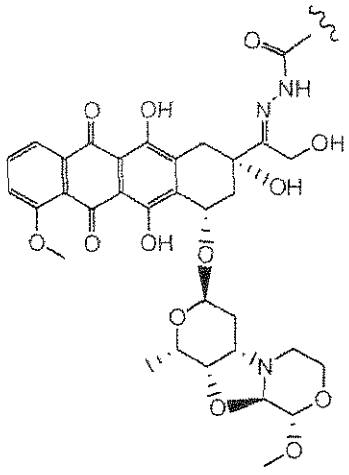
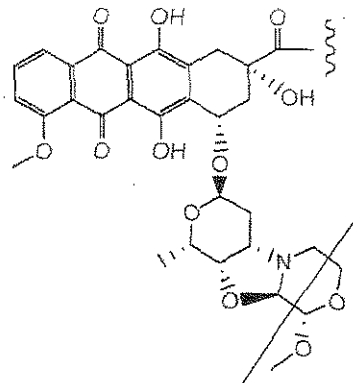
19. The cancer according to Claim 18 is carcinoma which is selected from the group consisting of bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin: squamous cell carcinoma; hematopoietic tumors of lymphoid lineage which is selected from the group consisting of leukaemia, acute lymphocytic leukaemia, acute lymphoblastic leukaemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage which is selected from the group consisting of acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukaemia; tumors of mesenchymal origin which is selected from the group consisting of fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system which is selected from the group consisting of astrocytoma neuroblastoma, glioma and schwannomas; melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer or Kaposi's sarcoma.

20. The cellular proliferation disorders according to Claim 18 is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis.

21. An anthracycline derivative of formula (IIc)

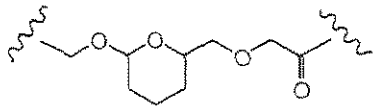
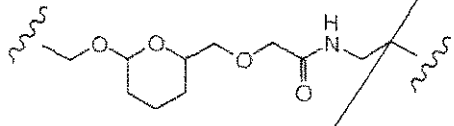
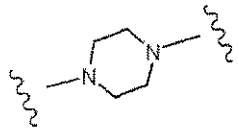
$$Ant{-}L{-}(Z)_m{-}X \qquad (IIc)$$

wherein Ant is selected from the structures:

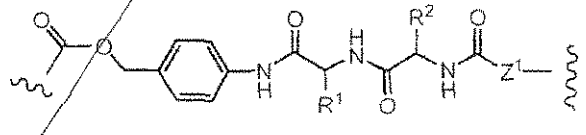
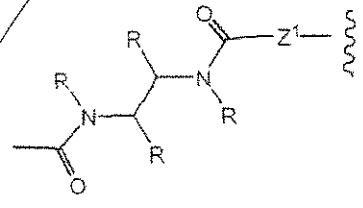
where the wavy line indicates the attachment to L;

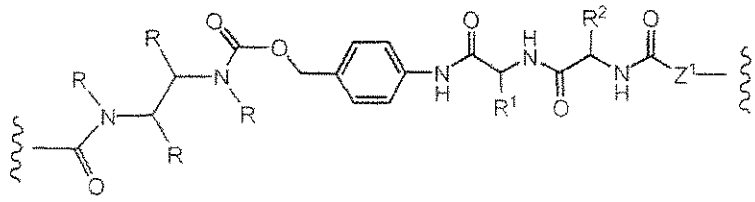
L is a linker selected from $-N(R)-$, $-N(R)_m(C_1-C_{12}$ alkylene$)-$, $-N(R)_m(C_2-C_8$ alkenylene$)-$, $-N(R)_m(C_2-C_8$ alkynylene$)-$, $-N(R)_m(CH_2CH_2O)_n-$, and the structures:

where the wavy lines indicate the attachments to Ant and Z; and

Z is an optional spacer selected from $-CH_2C(O)-$, $-CH_2C(O)NR(C_1-C_{12}$ alkylene$)-$, and the structures:



X is a reactive functional group selected from maleimide, thiol, amino, bromide, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

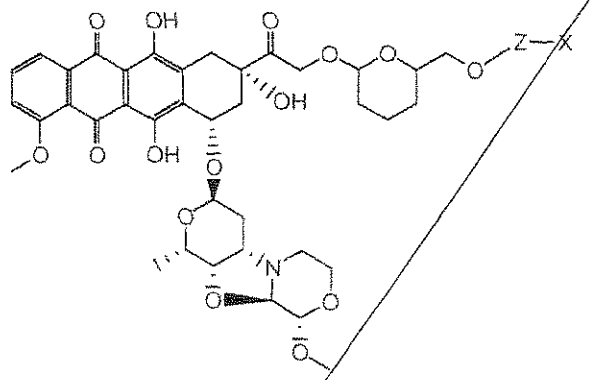
R is H, C_1–C_{12} alkyl, or C_6–C_{20} aryl;

R^1 and R^2 are independently selected from an amino acid side chain;

Z^1 is selected from –(C_1–C_{12} alkylene)–, –(C_2–C_8 alkenylene)–, –(C_2–C_8 alkynylene)–, and –$(CH_2CH_2O)_n$–.

m is 0 or 1; and n is 1 to 6.

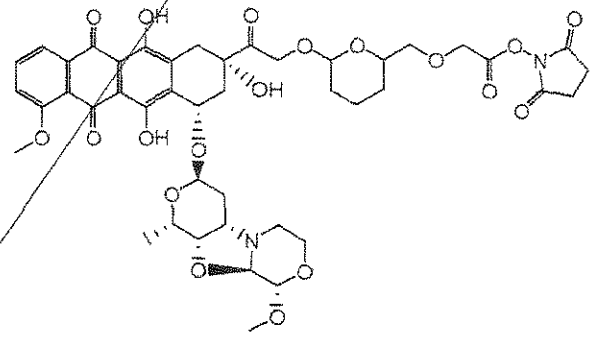
22. The anthracycline derivative of claim 21 selected from the structures:



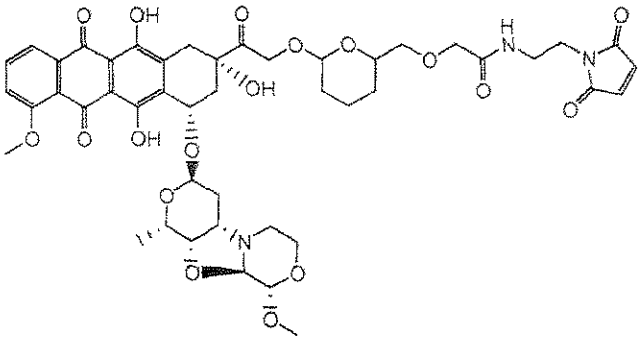
wherein Z–X is selected from:



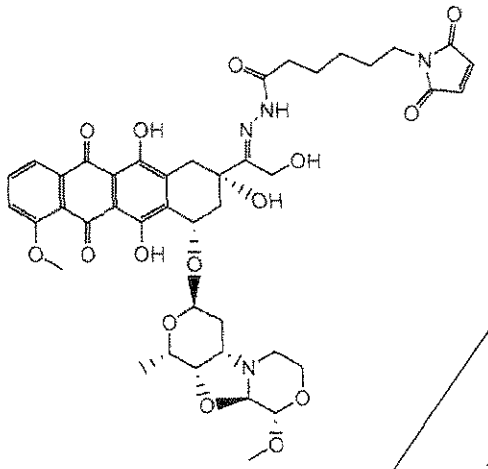
23. The anthracycline derivative of claim 22 having the structure:



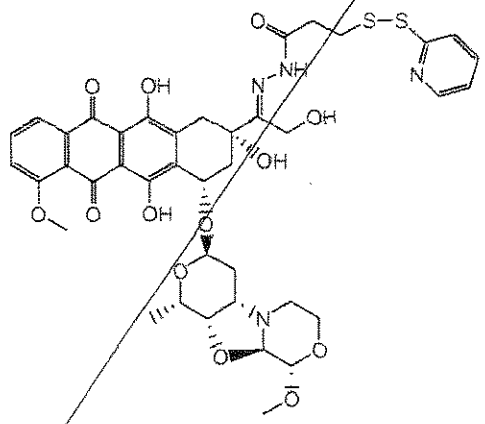
24. The anthracycline derivative of claim 22 having the structure:



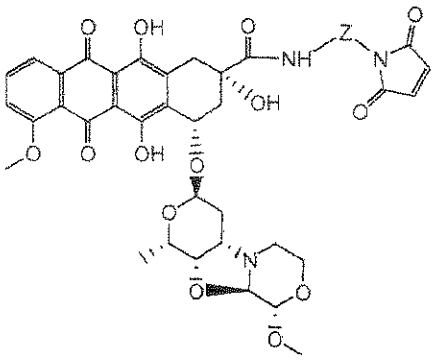
25. The anthracycline derivative of claim 21 having the structure:



26. The anthracycline derivative of claim 21 having the structure:

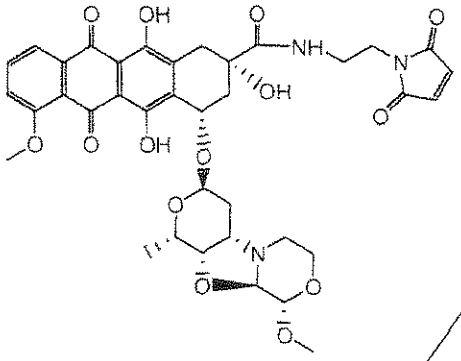


27. The anthracycline derivative of claim 21 having the structure:

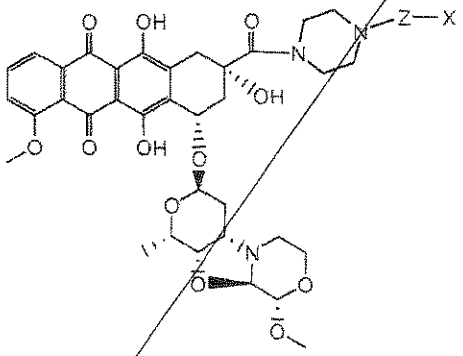


where Z is C_1–C_{12} alkylene.

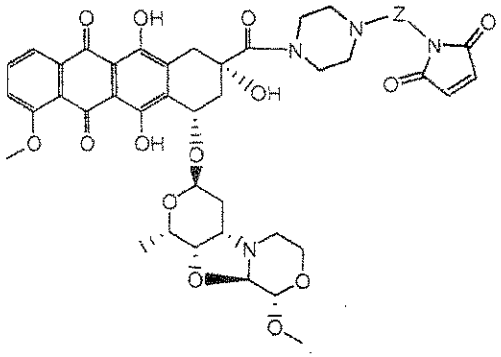
28. The anthracycline derivative of claim 27 having the structure:



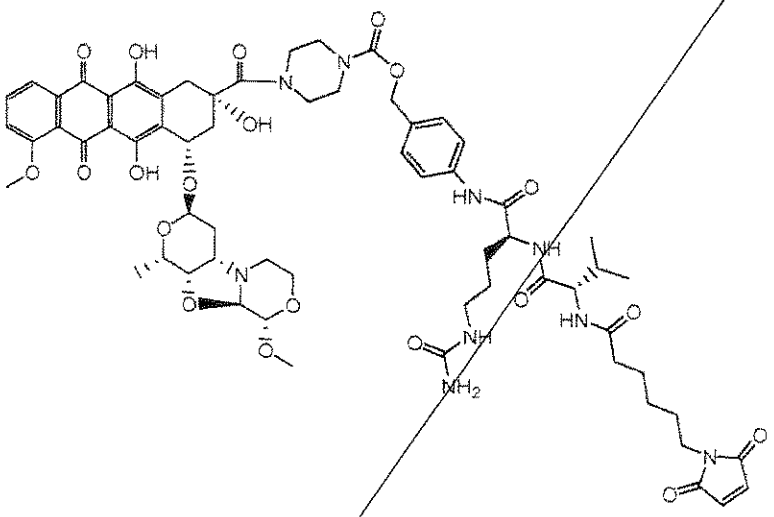
29. The anthracycline derivative of claim 21 having the structure:



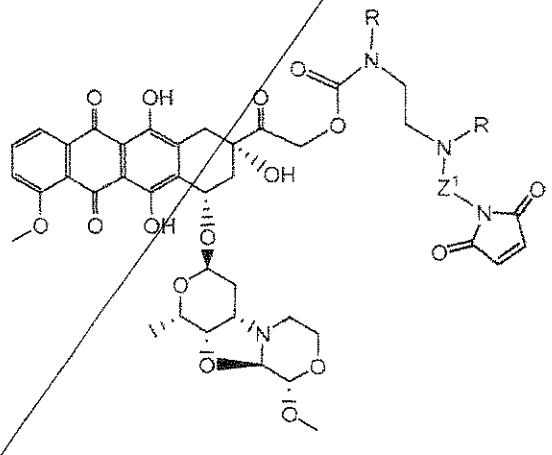
30. The anthracycline derivative of claim 29 having the structure:



31. The anthracycline derivative of claim 29 having the structure:

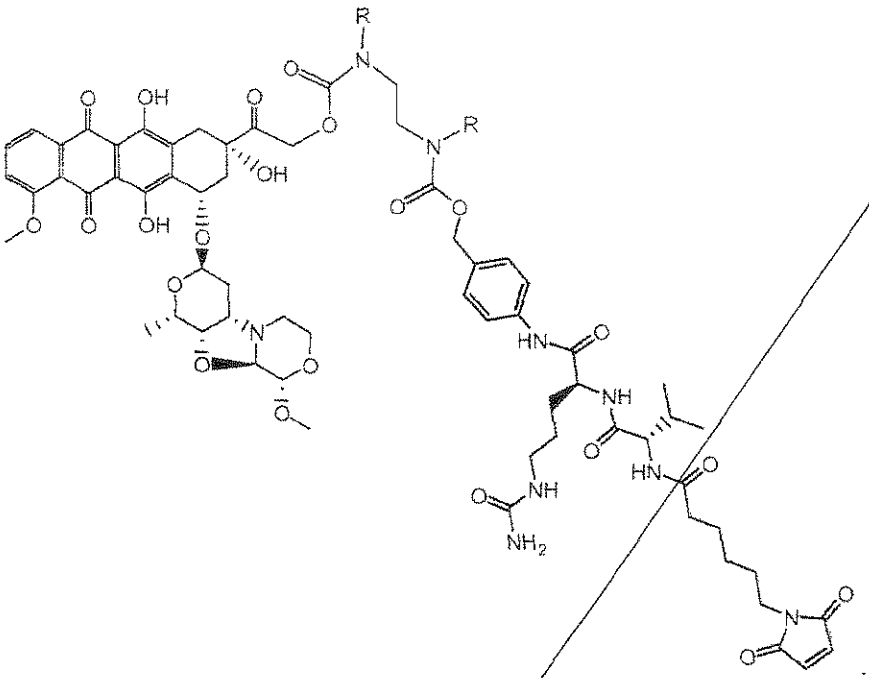


32. The anthracycline derivative of claim 29 selected from the structures:

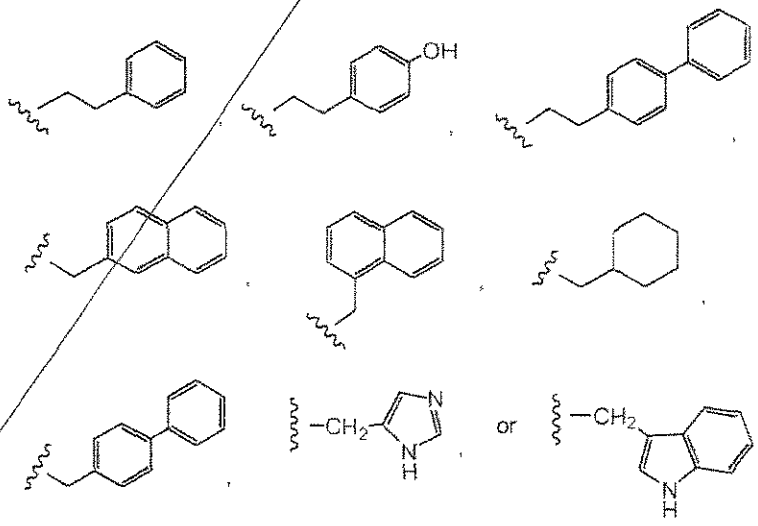


33. The anthracycline derivative of claim 32 wherein Z^1 is $-(C_1-C_{12}$ alkylene$)-$.

34. The anthracycline derivative of claim 32 having the structure:



35. The anthracycline derivative of claim 21 wherein R^1 and R^2 are independently selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, -CH_2OH, -$CH(OH)CH_3$, -$CH_2CH_2SCH_3$, -CH_2CONH_2, -CH_2COOH, -$CH_2CH_2CONH_2$, -CH_2CH_2COOH, -$(CH_2)_3NHC(=NH)NH_2$, -$(CH_2)_3NH_2$, -$(CH_2)_3NHCOCH_3$, -$(CH_2)_3NHCHO$, -$(CH_2)_4NHC(=NH)NH_2$, -$(CH_2)_4NH_2$, -$(CH_2)_4NHCOCH_3$, -$(CH_2)_4NHCHO$, -$(CH_2)_3NHCONH_2$, -$(CH_2)_4NHCONH_2$, -$CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl, and the following structures:



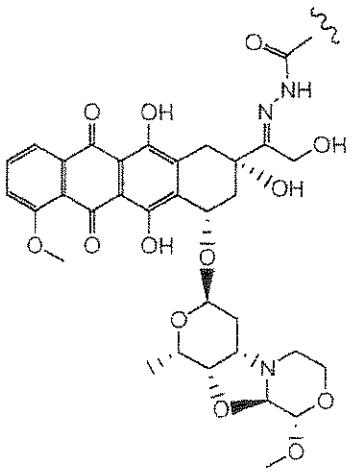
36. An antibody-drug conjugate compound comprising an antibody covalently attached by a linker L and an optional spacer Z to one or more anthracycline derivative drug moieties D, the compound having formula (**Ic**)

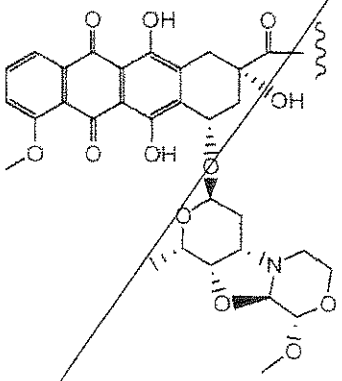
$$Ab-(L-Z_m-D)_p \qquad \textbf{Ic}$$

or a pharmaceutically acceptable salt thereof, wherein:

Ab is an antibody;

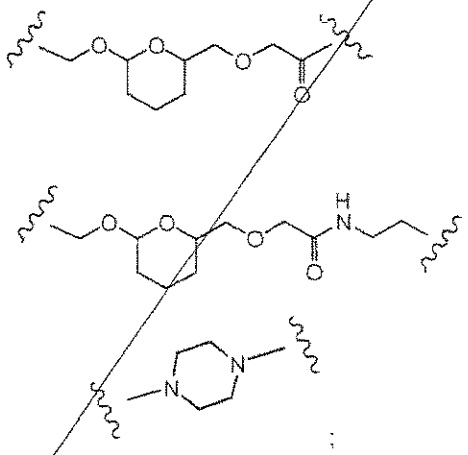
D is an anthracycline derivative selected from the structures:





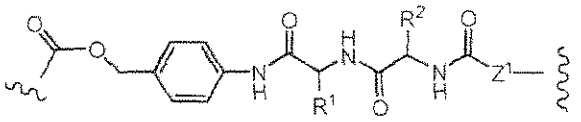
where the wavy line indicates the attachment to L;

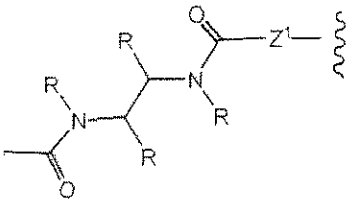
L is a linker selected from $-N(R)-$, $-N(R)_m(C_1-C_{12}\text{ alkylene})-$, $-N(R)_m(C_2-C_8\text{ alkenylene})-$, $-N(R)_m(C_2-C_8\text{ alkynylene})-$, $-N(R)_m(CH_2CH_2O)_n-$, and the structures:

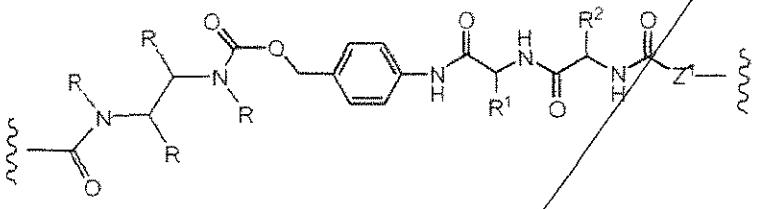


where the wavy lines indicate the attachments to D and Z; and

Z is an optional spacer selected from $-CH_2C(O)-$, $-CH_2C(O)NR(C_1-C_{12}$ alkylene$)-$, and the structures:







R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;

R^1 and R^2 are independently selected from an amino acid side chain;

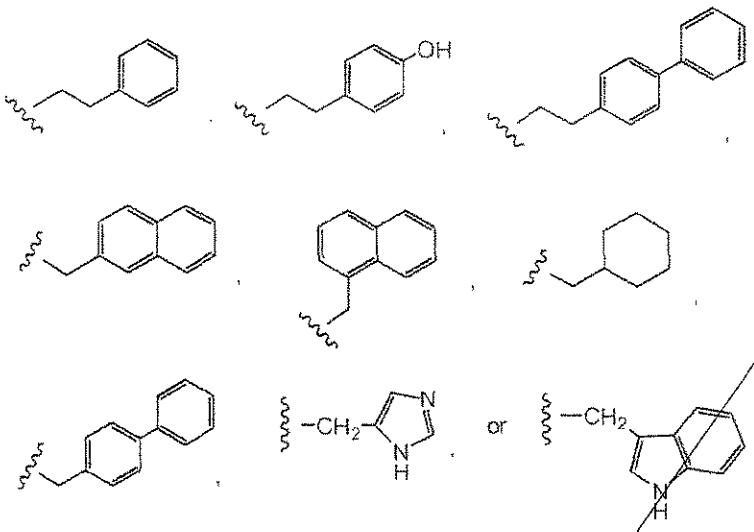
Z^1 is selected from $-(C_1-C_{12}$ alkylene$)-$, $-(C_2-C_8$ alkenylene$)-$, $-(C_2-C_8$ alkynylene$)-$, and $-(CH_2CH_2O)_n-$.

m is 0 or 1;

n is 1 to 6; and

p is an integer from 1 to 8.

37. The antibody-drug conjugate compound of claim 36 wherein R^1 and R^2 are independently selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH_2SCH_3$, $-CH_2CONH_2$, $-CH_2COOH$, $-CH_2CH_2CONH_2$, $-CH_2CH_2COOH$, $-(CH_2)_3NHC(=NH)NH_2$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCOCH_3$, $-(CH_2)_3NHCHO$, $-(CH_2)_4NHC(=NH)NH_2$, $-(CH_2)_4NH_2$, $-(CH_2)_4NHCOCH_3$, $-(CH_2)_4NHCHO$, $-(CH_2)_3NHCONH_2$, $-(CH_2)_4NHCONH_2$, $-CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl, and the following structures:



38. The antibody-drug conjugate compound of claim 36 wherein spacer Z comprises a para-aminobenzyloxycarbonyl (PAB) group.

39. The antibody-drug conjugate compound of claim 36 wherein linker–spacer unit L–Z comprises a maleimidocaproyl (MC) group.

40. The antibody-drug conjugate compound of claim 36 wherein Z comprises a valine-citrulline (vc) group.

41. The antibody-drug conjugate compound of claim 36 wherein Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(36):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2); and

(36) TENB2 (putative transmembrane proteoglycan).

42. The antibody-drug conjugate compound of claim 36 wherein Ab is a cysteine-engineered antibody.

43. The antibody-drug conjugate compound of claim 36 wherein Ab is an antibody which binds to an ErbB receptor.

44. The antibody-drug conjugate of claim 43 wherein Ab is trastuzumab.

45. The antibody-drug conjugate compound of claim 36 wherein p is 1, 2, 3, or 4.

46. The antibody-drug conjugate compound of claim 36 comprising a mixture of the antibody-drug conjugate compounds, wherein the average drug loading per antibody in the mixture of antibody-drug conjugate compounds is about 2 to about 5.

47. The antibody-drug conjugate compound of claim 46 wherein the average drug loading per antibody in the mixture of antibody-drug conjugate compounds is about 3 to about 4.

48. A pharmaceutical composition comprising the antibody-drug conjugate compound of claim 36 and a pharmaceutically acceptable diluent, carrier or excipient.

49. The pharmaceutical composition of claim 48 further comprising a therapeutically effective amount of a chemotherapeutic agent.

50. A method of treating cancer comprising administering to a patient the pharmaceutical composition of claim 48.

51. The method of claim 50 wherein the patient is administered a chemotherapeutic agent, in combination with the antibody-drug conjugate compound.

52. The use of an antibody-drug conjugate compound of claim 36 in the manufacture of a medicament for the treatment of cancer in a mammal.

53. The use of claim 52 wherein the mammal is human.

54. An article of manufacture comprising

an antibody-drug conjugate compound of claim 36;

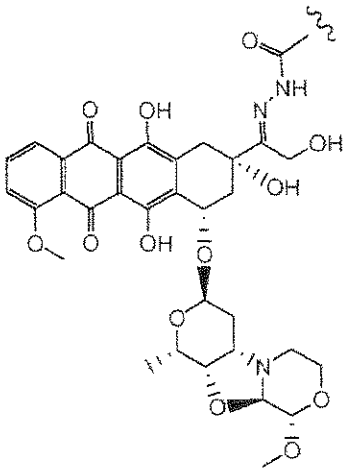
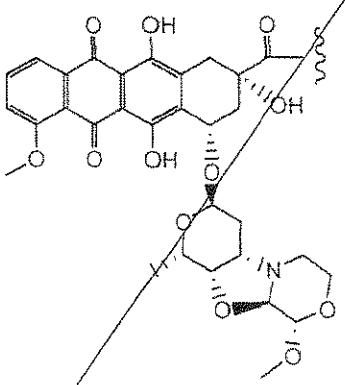
a container; and

a package insert or label indicating that the compound can be used to treat cancer.

55. A method of making an antibody-drug conjugate compound comprising reacting an anthracycline derivative and an antibody Ab to form the antibody-drug conjugate compound, wherein the anthracycline derivative has formula (IIc):

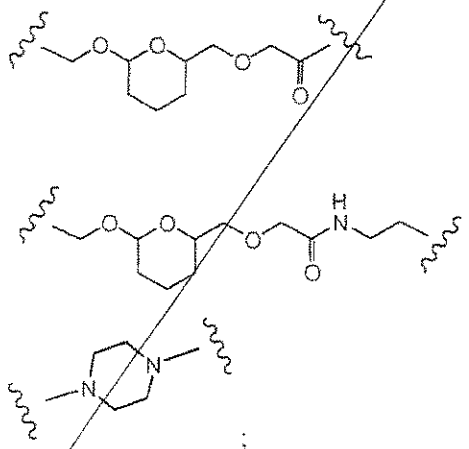
$$Ant–L–(Z)_m–X \qquad (IIc)$$

where Ant is selected from the structures:

where the wavy line indicates the attachment to L;

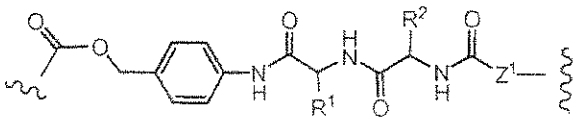
L is a linker selected from –N(R)–, $–N(R)_m(C_1–C_{12}$ alkylene)–, $–N(R)_m(C_2–C_8$ alkenylene)–, $–N(R)_m(C_2–C_8$ alkynylene)–, $–N(R)_m(CH_2CH_2O)_n–$, and the structures:

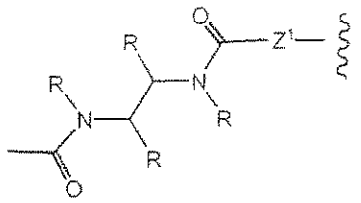


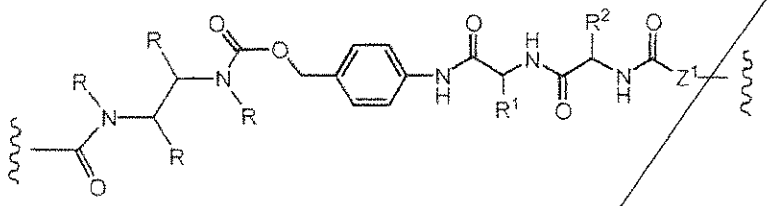
;

where the wavy lines indicate the attachments to Ant and Z; and

Z is an optional spacer selected from $–CH_2C(O)–$, $–CH_2C(O)NR(C_1–C_{12}$ alkylene)–, and the structures:







X is a reactive functional group selected from maleimide, thiol, amino, bromide, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

R is H, C_1–C_{12} alkyl, or C_6–C_{20} aryl;

R^1 and R^2 are independently selected from an amino acid side chain;

Z^1 is selected from –(C_1–C_{12} alkylene)–, –(C_2–C_8 alkenylene)–, –(C_2–C_8 alkynylene)–, and –$(CH_2CH_2O)_n$–,

m is 0 or 1; and n is 1 to 6;

the antibody-drug conjugate has formula Ic:

$$Ab–(L–Z_m–D)_p \qquad \textbf{Ic}$$

where Ab is an antibody; and

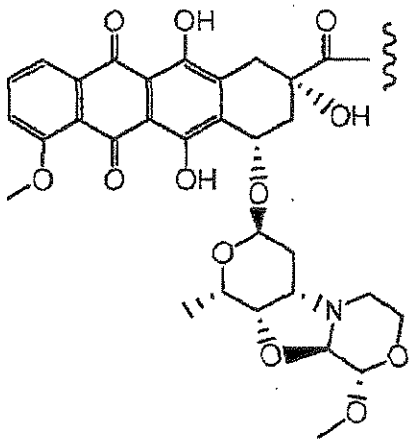
p is an integer from 1 to 8.

CLAIMS

1. An anthracycline derivative of Formula (IIc)

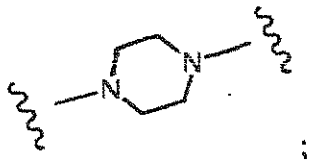
$$Ant\text{-}L\text{-}(Z)_m\text{-}X \qquad (IIc)$$

wherein Ant is selected from the structure:



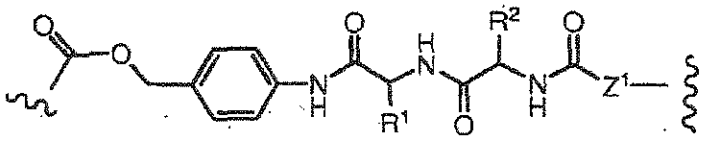
where the wavy line indicates the attachment to L;

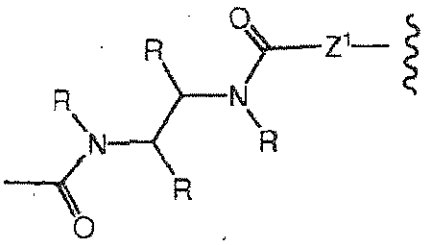
L is a linker selected from -N(R)-, -N(R)$_m$(C_1-C_{12} alkylene)-, -N(R)$_m$(C_2-C_8 alkenylene)-, -N(R)$_m$(C_2-C_8 alkynylene)-, -N(R)$_m$(CH_2CH_2O)$_n$-, and the structure:

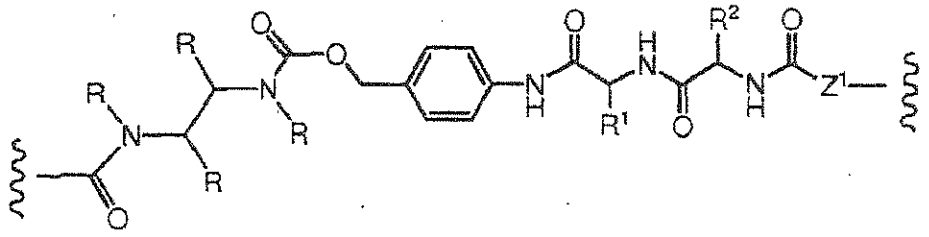


where the wavy lines indicate the attachments to Ant and Z; and

Z is an optional spacer selected from -$CH_2C(O)$-, -$CH_2C(O)NR(C_1$-C_{12} alkylene)-, and the structures:







X is a reactive functional group selected from maleimide, thiol, amino, bromide, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;

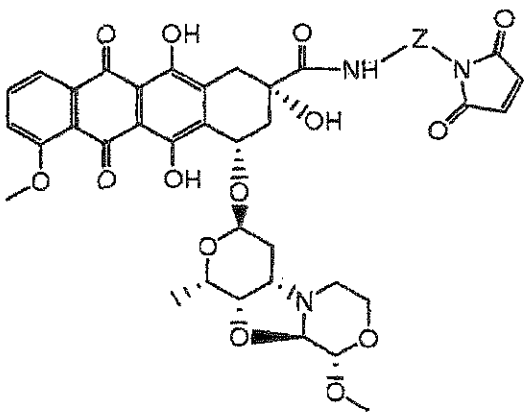
R^1 and R^2 are independently selected from an amino acid side chain;

Z^1 is selected from -(C_1-C_{12} alkylene)-, -(C_2-C_8 alkenylene)-, -(C_2-C_8alkynylene)-, and -$(CH_2CH_2O)_n$-;

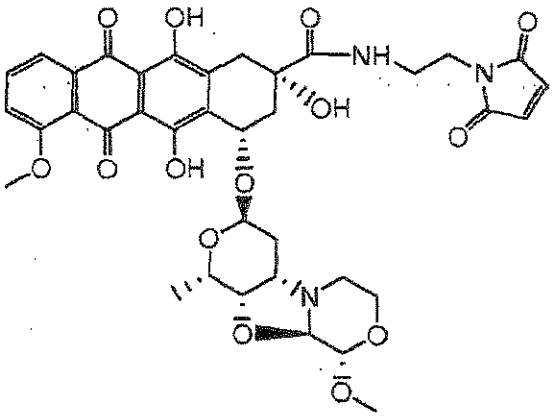
m is 0 or 1; and

n is 1 to 6;

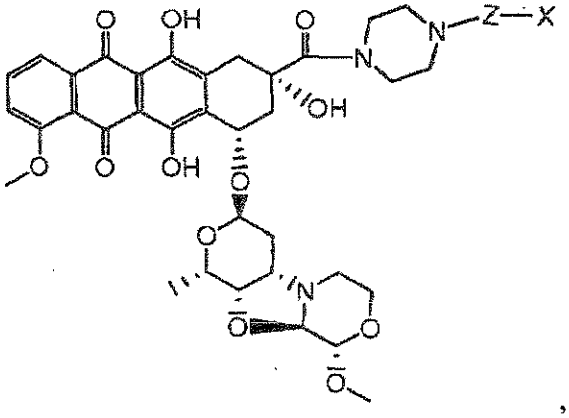
or wherein the anthracycline derivative is selected from the structures:



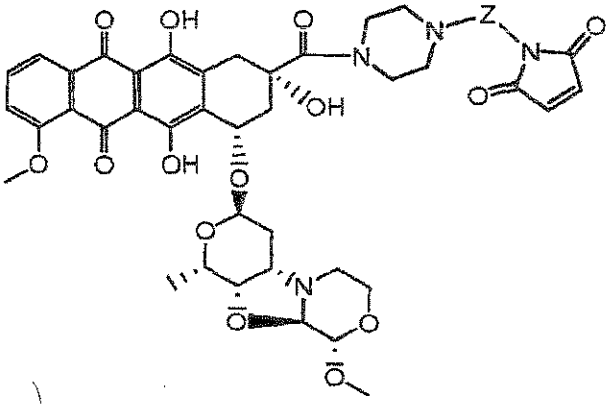
where Z is C_1-C_{12} alkylene,



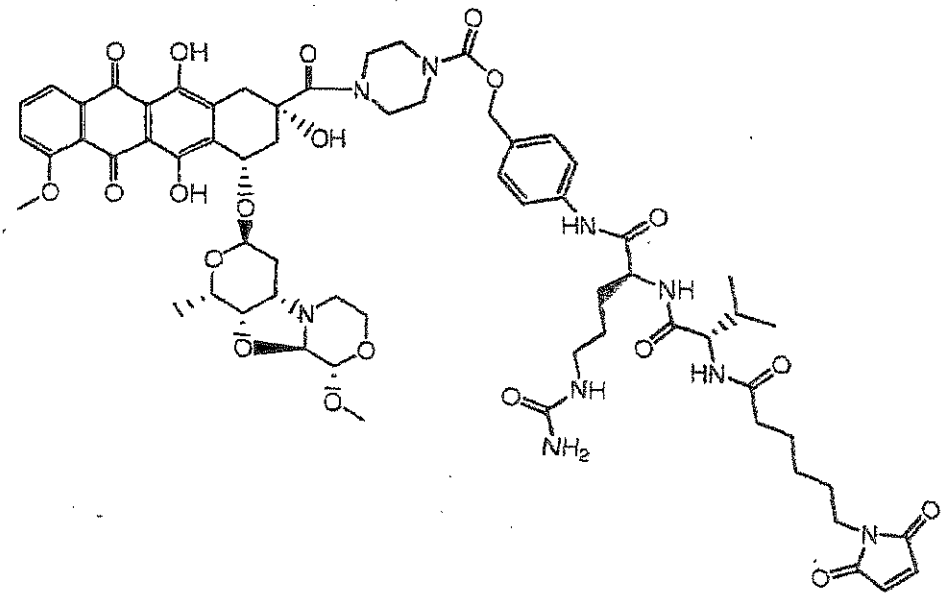
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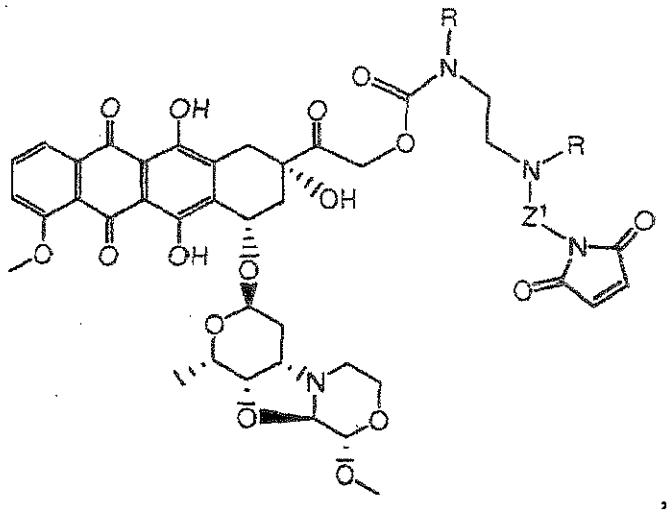


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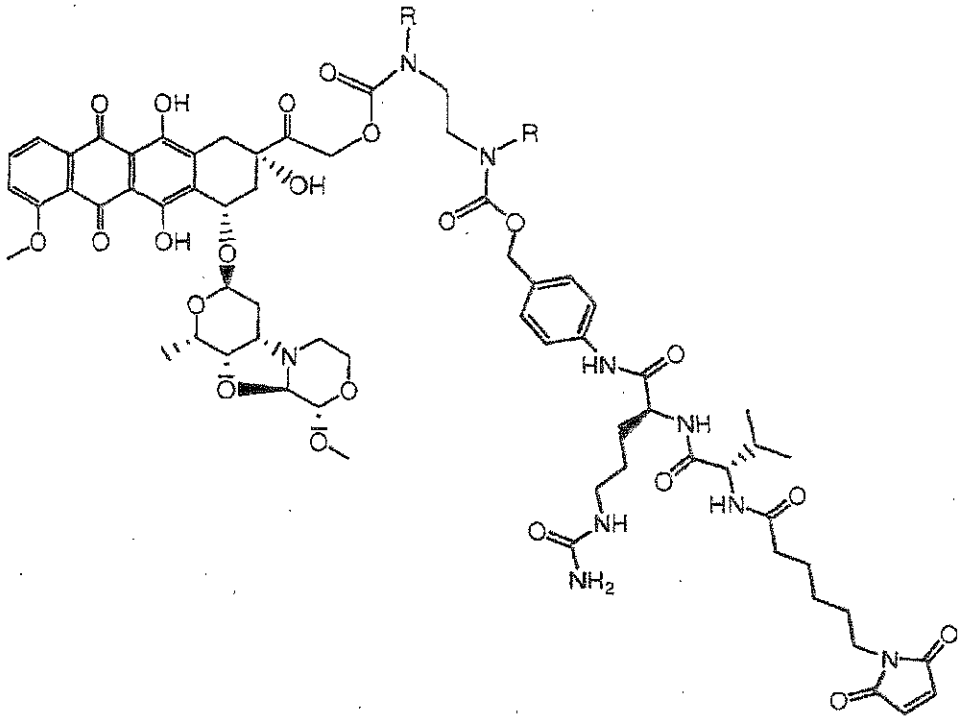


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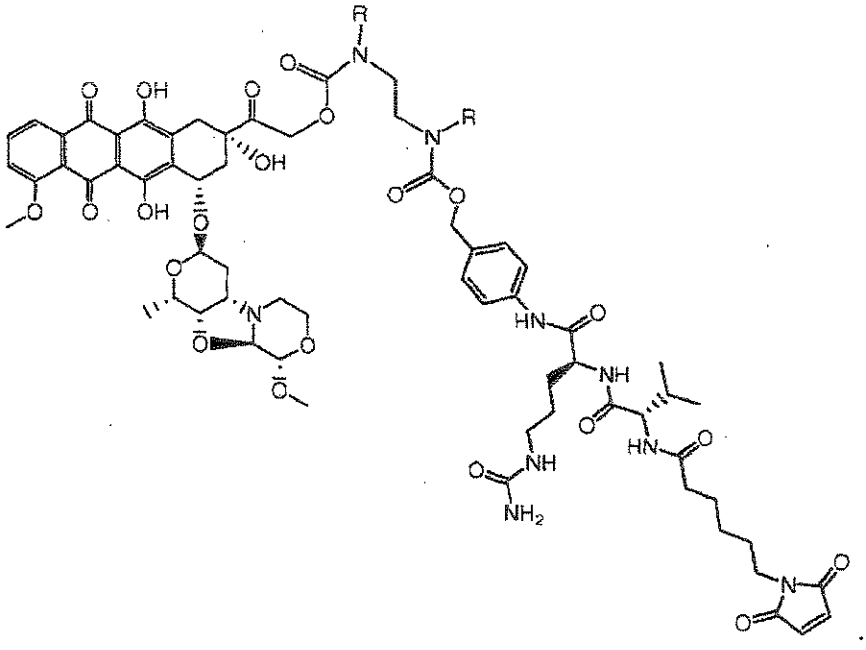


and

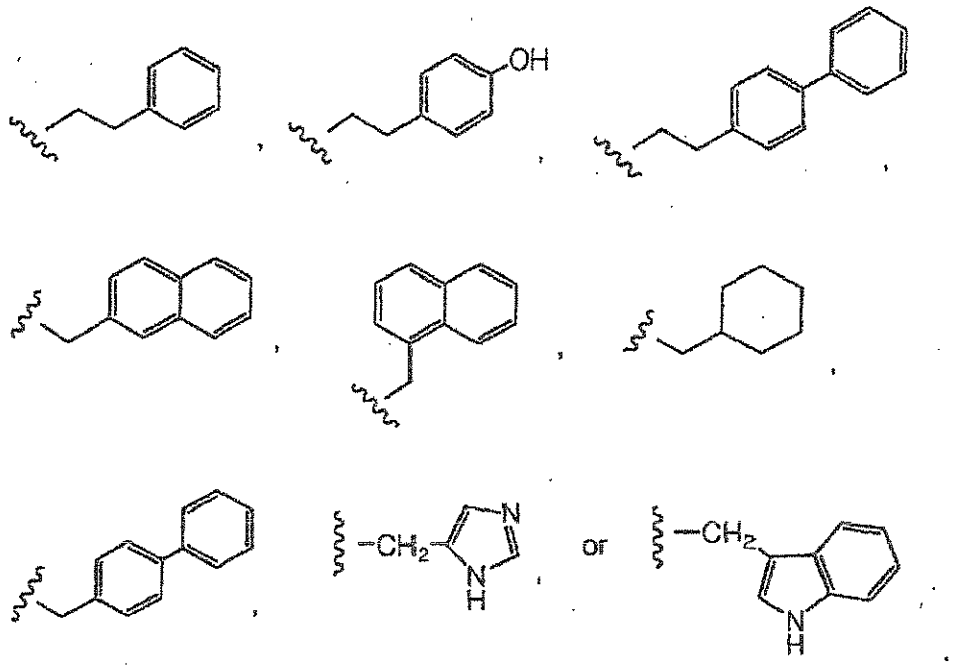


2. The anthracycline derivative of claim 1, wherein R is H or C_1-C_{12} alkyl.

3. The anthracycline derivative of claim 1, having the structure:



4. The anthracycline derivative according to claim 1,
wherein R^1 and R^2 are independently selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH_2SCH_3$, $-CH_2CONH_2$, $-CH_2COOH$, $-CH_2CH_2CONH_2$, $-CH_2CH_2COOH$, $-(CH_2)_3NHC(=NH)NH_2$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCOCH_3$, $-(CH_2)_3NHCHO$, $-(CH_2)_4NHC(=NH)NH_2$, $-(CH_2)_4NH_2$, $-(CH_2)_4NHCOCH_3$, $-(CH_2)_4NHCHO$, $-(CH_2)_3NHCONH_2$, $-(CH_2)_4NHCONH_2$, $-CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl, and the following structures:



5. An antibody-drug conjugate compound comprising an antibody covalently attached by a linker L and an optional spacer Z to one or more anthracycline derivative drug moieties D, the compound having Formula **(Ic)**

$$Ab\text{-}(Z_m\text{-}L\text{-}D)_p \qquad Ic$$

or a pharmaceutically acceptable salt thereof, wherein:

Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(36):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008016Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

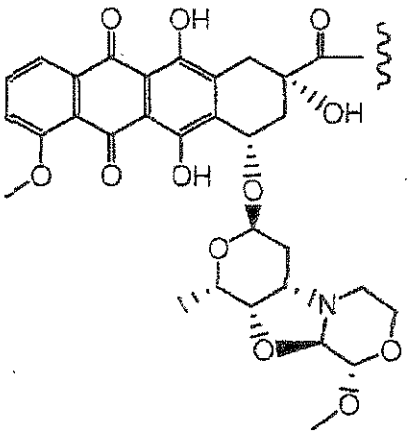
(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2); and

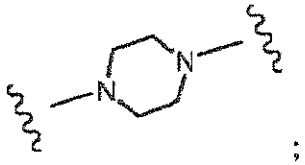
(36) TENB2 (putative transmembrane proteoglycan);

D is an anthracycline derivative selected from the structure:



where the wavy line indicates the attachment to L;

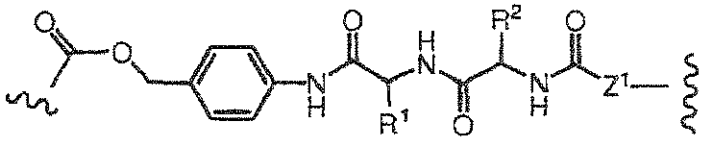
L is a linker selected from -N(R)-, -N(R)$_m$(C_1-C_{12} alkylene)-, -N(R)$_m$(C_2-C_8 alkenylene)-, -N(R)$_m$(C_2-C_8 alkynylene)-, -N(R)$_m$(CH_2CH_2O)$_n$-, and the structure:

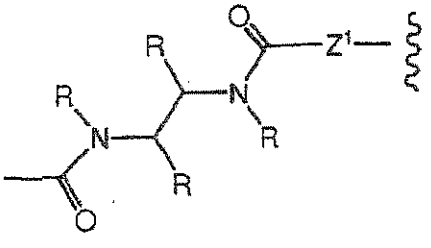


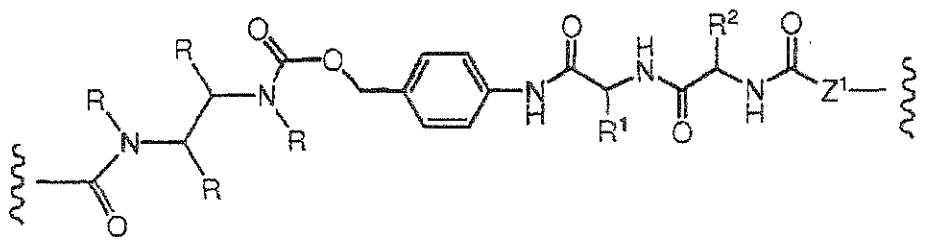
;

where the wavy lines indicate the attachments to D and Z; and

Z is an optional spacer selected from -$CH_2C(O)$-, -$CH_2C(O)NR$(C_1-C_{12} alkylene)-, and the structures:

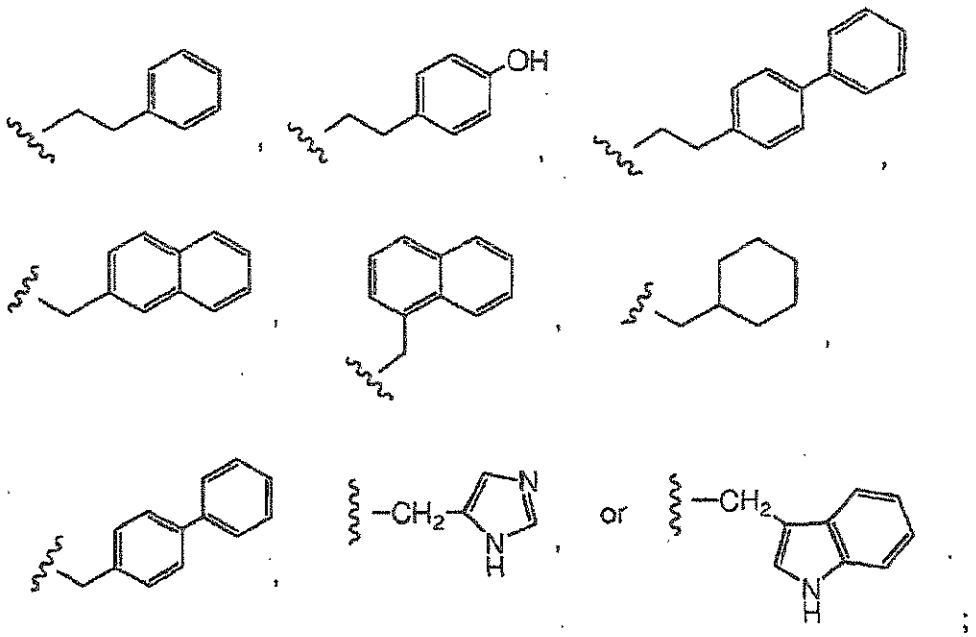






R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;

R^1 and R^2 are independently selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH_2SCH_3$,$-CH_2CONH_2$, $-CH_2COOH$, $-CH_2CH_2CONH_2$, $-CH_2CH_2COOH$, $-(CH_2)_3NHC(=NH)NH_2$,$-(CH_2)_3NH_2$, $-(CH_2)_3NHCOCH_3$, $-(CH_2)_3NHCHO$, $-(CH_2)_4NHC(=NH)NH_2$, $-(CH_2)_4NH_2$, $-(CH_2)_4NHCOCH_3$, $-(CH_2)_4NHCHO$, $-(CH_2)_3NHCONH_2$, $-(CH_2)_4NHCONH_2$,$-CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl, and the following structures:



Z^1 is selected from $-(C_1$-C_{12} alkylene)-, $-(C_2$-C_8 alkenylene)-, $-(C_2$-C_8alkynylene)-, and $-(CH_2CH_2O)_n$-,

m is 0 or 1;

n is 1 to 6; and

p is an integer from 1 to 8.

6. The antibody-drug conjugate compound according to claim 5, wherein:

spacer Z comprises a para-aminobenzyloxycarbonyl (PAB) group;

or Z comprises a valine-citrulline (vc) group.

7. The antibody-drug conjugate compound according to claim 5, wherein Ab is a cysteine-engineered antibody.

8. The antibody-drug conjugate compound according to claim 5, wherein Ab is an antibody which binds to an ErbB receptor.

9. The antibody-drug conjugate compound according to claim 8, wherein Ab is trastuzumab.

10. The antibody-drug conjugate compound according to claim 5, wherein p is 1, 2, 3, or 4.

11. The antibody-drug conjugate compound according to claim 5, comprising a mixture of the antibody-drug conjugate compounds, wherein the average drug loading per antibody in the mixture of antibody-drug conjugate compounds is about 2 to about 5.

12. A pharmaceutical composition comprising the antibody-drug conjugate compound according to any one of claims 5 to 11 and a pharmaceutically acceptable diluent, carrier or excipient.

13. The pharmaceutical composition of claim 12, further comprising a therapeutically effective amount of a chemotherapeutic agent.

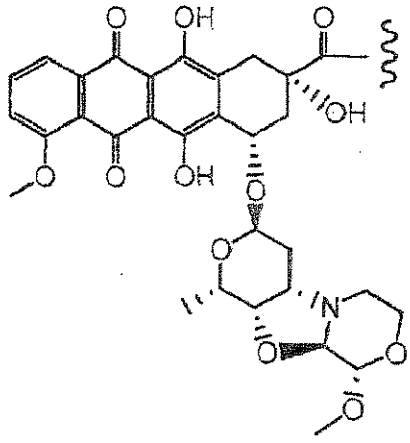
14. Use of an antibody-drug conjugate compound according to any one of claims 5 to 11 in the manufacture of a medicament for the treatment of cancer in a mammal.

15. An antibody-drug conjugate compound according to any one of claims 5 to 11 for use in a method for treating cancer.

16. A method of making an antibody-drug conjugate compound comprising reacting an anthracycline derivative and an antibody Ab to form the antibody-drug conjugate compound, wherein the anthracycline derivative has Formula (IIc):

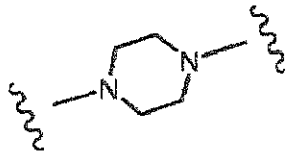
$$Ant\text{-}L\text{-}(Z)_m\text{-}X \qquad (IIc)$$

where Ant is selected from the structure:



where the wavy line indicates the attachment to L;

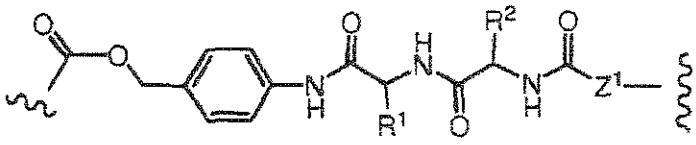
L is a linker selected from -N(R)-, -N(R)$_m$(C_1-C_{12} alkylene)-, -N(R)$_m$(C_2-C_8 alkenylene)-, -N(R)$_m$(C_2-C_8 alkynylene)-, -N(R)$_m$(CH_2CH_2O)$_n$-, and the structure:

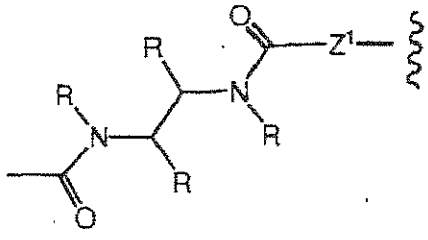


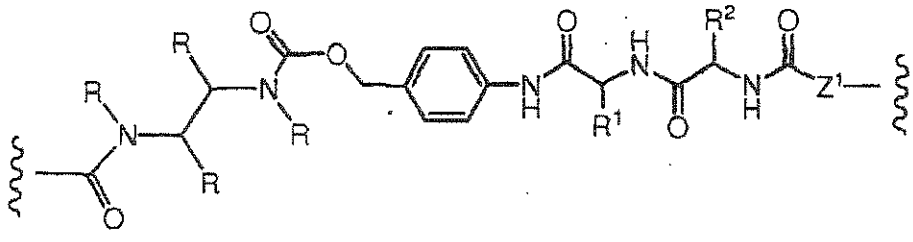
;

where the wavy lines indicate the attachments to Ant and Z; and

Z is an optional spacer selected from -$CH_2C(O)$-, -$CH_2C(O)NR(C_1$-C_{12} alkylene)-, and the structures:







X is a reactive functional group selected from maleimide, thiol, amino, bromide, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;
R is H, C_1-C_{12} alkyl, or C_6-C_{20} aryl;
R^1 and R^2 are independently selected from an amino acid side chain;
Z^1 is selected from -(C_1-C_{12} alkylene)-, -(C_2-C_8 alkenylene)-, -(C_2-C_8 alkynylene)-, and -$(CH_2CH_2O)_n$-,
m is 0 or 1; and n is 1 to 6;
the antibody-drug conjugate has formula Ic:

$$Ab\text{-}(Z_m\text{-}L\text{-}D)_p \qquad \text{Ic}$$

wherein D is Ant;
where Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(36):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008016Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell-activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2); and

(36) TENB2 (putative transmembrane proteoglycan); and

p is an integer from 1 to 8.