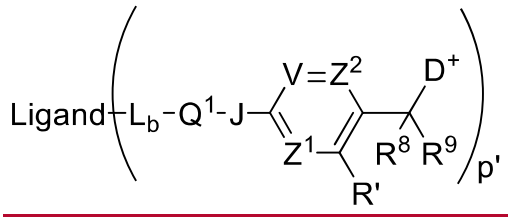
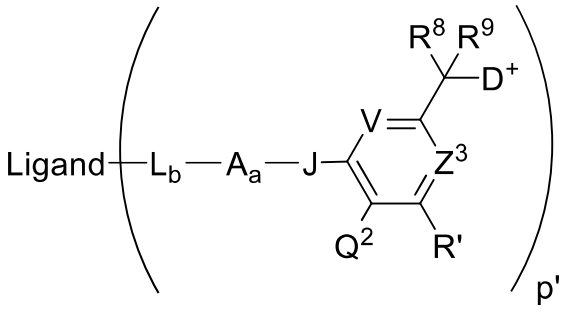
is a need in the art for LDCs that use the tertiary amine nitrogen as the site of conjugation in order to allow for release of fully active tertiary amine-containing drug at the targeted site of action. Even if reduced biological activity or changes in other pharmacological properties are tolerable through alteration of a tertiary amine-containing drug through removal of one of its nitrogen substituents, or when an alternative site of conjugation is available or can be introduced without serious consequences to desired biological activity, there remains a need in the art for the use of the tertiary amine nitrogen as the site of conjugation. That need exists since it is unpredictable as to which of the possible sites of conjugation that could be presented by a tertiary amine-containing drug will provide the most efficient release of the active drug and thus the most active LDC.

SUMMARY ~~OF THE INVENTION~~

[0005] In one aspect, the present disclosure provides a use of a composition in the manufacture of a medicament for treating cancer or an autoimmune disease, wherein the composition comprises a Ligand Drug Conjugate (LDC) compound represented by the structure of Formula 2A or Formula 3F:



(Formula 2A)



(Formula 3F)

or a pharmaceutically acceptable salt thereof, wherein

"Ligand" is a Ligand Unit (L), wherein L is from an antibody, thereby defining an antibody drug conjugate (ADC), wherein the antibody is capable of selective binding to an

antigen, wherein the antigen is an extracellularly accessible cell-surface protein or glycoprotein preferentially displayed by abnormal cells in comparison to normal cells, wherein the cells are mammalian cells of a subject intended for therapy and wherein the antigen is capable of cellular internalization upon said selective binding;

L_b is a ligand covalent binding moiety;

Q^1 is A_a-W, wherein A is an optional Stretcher Unit so that subscript a is 0 when A is absent or 1 when A is present and optionally comprises two, three, or four subunits;

Q^2 is W'-E-';

W and W' are Cleavable Units, wherein

W of Q^1 is comprises a peptide sequence selectively cleavable by a lysosomal protease in comparison to serum proteases;

W' of Q^2 is a carbohydrate moiety, wherein W'-E- of Q^2 provides a glycosidic bond to the carbohydrate moiety, wherein the glycosidic bond is cleavable by an intracellular glycosidase,

V, Z^1, Z^2, and Z^3 are each =CH-;

R', R^8, and R^9 are each hydrogen;

E is -O'-, wherein O' represents the oxygen atom of the glycosidic bond to the carbohydrate moiety;

J is -NH-;

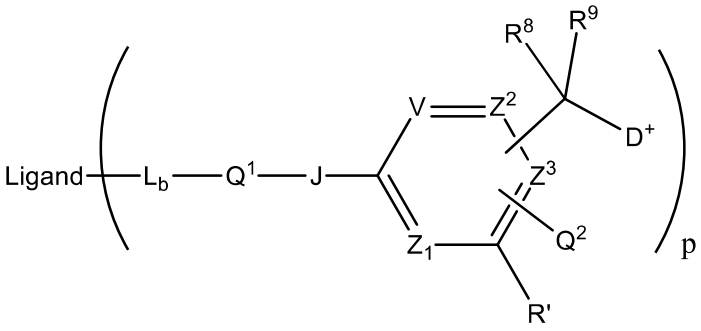
D^+ represents the structure of a quaternized tertiary amine-containing drug, wherein the tertiary amine-containing drug is quaternized at the nitrogen atom of its tertiary amine,

wherein the tertiary amine-containing drug (D) is a tertiary amine-containing tubulin disrupting agent; and

subscript p' is an integer ranging from 1 to 20; and

wherein said selective cleavage by the lysosomal protease or cleavage by the glycosidase initiates release of D from the Ligand Drug Conjugate compound.

Principle ~~embodiment~~examples of the ~~invention~~disclosure are Ligand Drug Conjugate (LDC) compositions, wherein a LDC composition is represented by the structure of Formula 1



(Formula 1)

,

[0006] wherein "Ligand" is from a targeting moiety, which selectively binds to a target moiety; L_b is a ligand covalent binding moiety; Q^1 is A_a-W_w, wherein A is an optional Stretcher unit, so that the subscript a is 0 when A is absent or a is 1 when A is present and is optionally comprised of two, three or four subunits; Q^2 is $W'_{w'}$-E-, wherein Q^2 when present is bonded to V, Z^1, Z^2 or Z^3; W_w and $W'_{w'}$ are Cleavable units; wherein W_w of Q^1 is capable of selective cleavage by a regulatory or intracellular protease in comparison to serum proteases, wherein the intracellular or regulatory protease may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells, or is capable of selective cleavage by a protease excreted in greater amounts by the targeted abnormal or other unwanted cells in comparison to normal cells, or is capable of cleavage by glutathione through disulfide exchange, or is more reactive to hydrolysis under lower pH conditions present in lysosomes in comparison to physiological

pH of serum, and W'-E of Q^2 provides a glycosidic bond cleavable by a glycosidase located intracellularly, wherein the glycosidase may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells, or is capable of selective cleavage by a glycosidase excreted in greater amounts by the targeted abnormal or other unwanted cells in comparison to normal cells, wherein the subscript w is 0 or 1 so that W is absent when w is 0 or W is present when w is 1, and w' is 0 or 1, wherein W'-E is absent when w' is 0 or W'-E is present when w' is 1, and wherein w + w' is 1 (i.e., one and only one of W, W' is present); V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, an electron donating group, -Q^2, or –C(R^8)(R^9)-D^+, wherein at least one of V, Z^1, Z^2 and Z^3 is =C(R^{24})- when w is 1 and at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})- when w' is 1,

[0007] provided that when w is 1, Q^2 is absent and one and only one R^{24} is –C(R^8)(R^9)-D^+ so that –C(R^8)(R^9)-D^+ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})- and the Q^1-J- and –C(R^8)(R^9)-D^+ substituents are *ortho* or *para* to each other,

[0008] provided that when w' is 1, one any only one R^{24} is –C(R^8)(R^9)-D^+ so that –C(R^8)(R^9)-D^+ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})- and one and only one other R^{24} is Q^2 so that Q^2 is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})-, and the Q^2 and –C(R^8)(R^9)-D^+ substituents are *ortho* or *para* to each other;

[0009] R^8 and R^9 independently are hydrogen, alkyl, alkenyl or alkynyl, optionally substituted, or aryl or heteroaryl, optionally substituted; E and J independently are –O-, -S- or –N(R^{33})-, wherein R^{33} is hydrogen or optionally substituted alkyl; R' is hydrogen or is halogen, -NO_2, -CN or other electron withdrawing group, or is an electron donating group; D^+ represents a structure of a quaternized tertiary amine-containing drug D; and p is an average drug loading having a number ranging from 1 to 24; wherein said protease cleavage, disulfide exchange, acid hydrolysis or glycosidase cleavage results in expulsion of D from an LDC of the LDC composition.

[0010] In some ~~aspect~~examples, the targeting moiety is an antibody, thereby defining an antibody drug conjugate (ADC), and the targeted moiety is an cell-surface antigen of targeted abnormal cells that is capable of cellular internalization of bound ADC, wherein the antigen is preferentially present on the abnormal cells in comparison to normal cells.

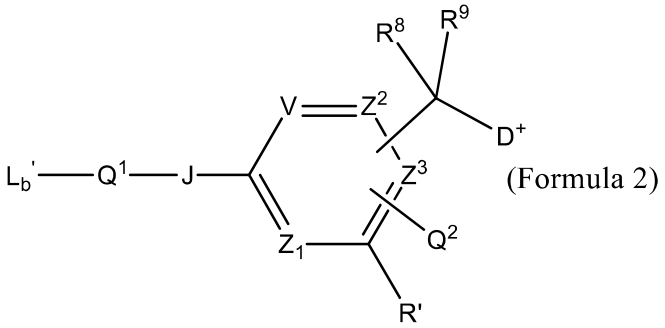
[0011] In some ~~aspect~~examples, W of Q^1 is comprised of a peptide moiety having a peptide bond to J that is selectively cleavable by an intracellular protease in comparison to serum proteases, wherein the intracellular protease may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells, and wherein action of the intracellular protease on W will cause release of a tertiary amine-containing drug (D) from the LDC. In other ~~aspect~~examples the peptide bond is cleavable by a protease that is excreted by abnormal cells to a greater extent than by normal cells.

[0012] In other ~~aspect~~examples W' is capable of selective cleavage by a regulatory protease in comparison to serum proteases, wherein the regulatory protease may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells.

[0013] In other ~~aspect~~examples W' is capable of selective cleavage by a lysosomal protease in comparison to serum proteases, wherein the lysosomal protease may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells.

[0014] In other ~~aspect~~examples, W' of Q^2 is a glycoside-bonded carbohydrate, wherein the glycoside bond in W'-E of Q^2 provides for a cleavage site for an intracellular glycosidase, wherein action of the glycosidase on W'-E causes release of tertiary amine-containing drug (D) from the LDC, wherein the glycosidase may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells, or is capable of selective cleavage by a glycosidase excreted in greater amounts by the targeted abnormal or other unwanted cells in comparison to normal cells.

[0015] Other principle ~~embodiment~~examples of the ~~invention~~disclosure provide for compounds having the structure of Formula 2:



(Formula 2)

,

[0016] wherein L_b' is a linker covalent binding precursor moiety; Q^1 is A_a-W_w, wherein A is an optional Stretcher unit, optionally comprised of two, three or four subunits, so that the subscript a is 0 or 1, wherein A is absent when a is 0 and A is present

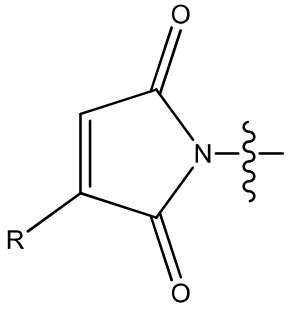
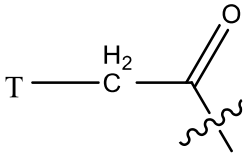
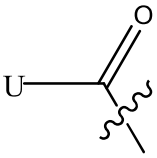
when a is 1; Q^2 is W'-E, wherein Q^2, when present, is bonded to V, Z^1, Z^2 or Z^3; W_w and $W'_{w'}$ are Cleavable units capable of cleavage in an LDC having a Formula I structure that

incorporates the structure of Formula 1 or Formula 2; wherein W_w of Q^1 is comprised of a peptide moiety having a peptide bond to J that is selectively cleavable by a regulatory or intracellular protease, which may or may not be more specific to abnormal or other unwanted cells in comparison to normal cells, or is selectively cleavable by a protease preferentially excreted by abnormal cells or unwanted cells in comparison to normal cells, or is comprised of a disulfide moiety that is cleavable by glutathione through disulfide exchange or is comprised of a hydrazone moiety that is more reactive to hydrolysis under lower pH conditions present in lysosomes in comparison to physiological pH of serum and W'-E of Q^2 provides a glycosidic bond cleavable by a glycosidase located intracellularly wherein the glycosidase may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells, or is capable of selective cleavage by a glycosidase excreted in greater amounts by the targeted abnormal or other unwanted cells in comparison to normal cells, wherein the subscript w is 0 or 1, wherein W is present when w is 1 or W is absent when w is 0, and w' is 0 or 1, wherein W'-E is absent when w' is 0 and W'-E is present when w' is 1, and wherein w + w' is 1 (i.e., one and only one W is present); V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or another electron withdrawing group, an electron donating group, -Q^2, or –C(R^8)(R^9)-D^+, provided that when w is 1, Q^2 is absent and one and only one R^{24} is –C(R^8)(R^9)-D^+ so that –C(R^8)(R^9)-D^+ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})- and the Q^1-J- and –C(R^8)(R^9)-D^+ substituents are *ortho* or *para* to each other, and provided that when w' is 1 one any only one R^{24} is –C(R^8)(R^9)-D^+ so that –C(R^8)(R^9)-D^+ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})- and one and only one other R^{24} is Q^2 so that Q^2 is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})-, and the Q^2 and –C(R^8)(R^9)-D^+ substituents are *ortho* or *para* to each other, R^8 and R^9 independently are hydrogen, alkyl, alkenyl or alkynyl, optionally substituted, or aryl or heteroaryl, optionally substituted; E and J independently are –O-, -S- or –N(R^{33})-, wherein R^{33} is hydrogen or optionally substituted alkyl; R' is hydrogen or is halogen, -NO_2, -CN or other electron withdrawing group, or is an electron donating group; and D^+ represents a structure of a quaternized tertiary amine-containing drug D, wherein said protease cleavage, disulfide exchange, acid hydrolysis or glycosidase cleavage results in expulsion of D from D^+ from an LDC prepared from a Formula 2 compound.

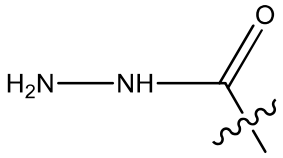
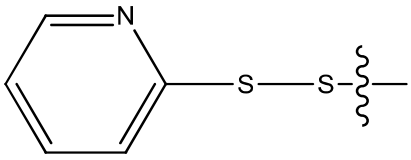
[0017] In some ~~aspect~~examples, the ~~invention~~disclosure provides for LDC conjugate compositions prepared from contacting a Formula 1 compound with a targeting moiety having a reactive

sulfhydryl, amino or aldehyde moiety under suitable conditions to effect condensation of the reactive moiety with an L_b' moiety of a Formula 2 compound, wherein L_b' is converted to L_b resulting from said contact.

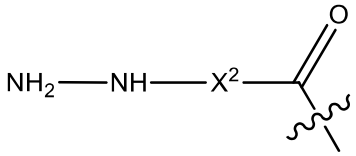
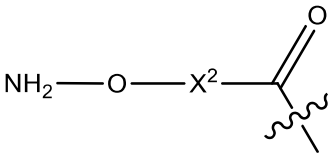
[0018] In some ~~aspect~~examples, L_b' has the structure of one of

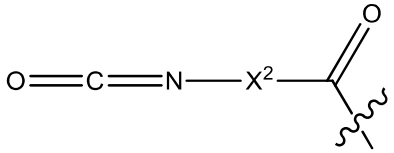
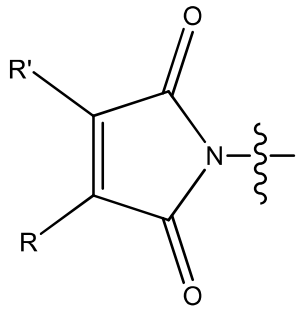
[0019]

[0020]

[0021]

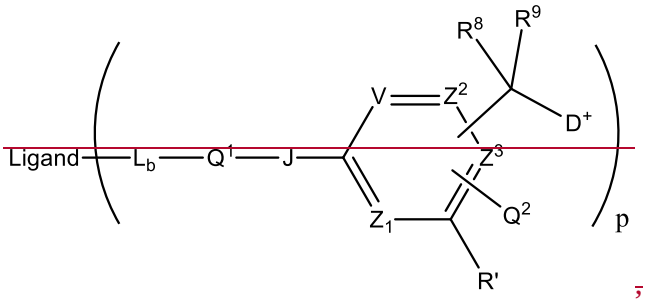
[0022] ,

[0023] wherein R is hydrogen or C_1-C_6 optionally substituted alkyl; R' is hydrogen or halogen or R and R' are independently selected halogen; T is –Cl, -Br, -I, -O-mesyl or –O-tosyl or other sulfonate leaving group; U is –F, –Cl, -Br, -I, -O-N-succinimide, -O-(4-nitrophenyl), -O-pentafluorophenyl, -O-tetrafluorophenyl or –O-C(=O)-OR^{57}; X^2 is C_{1-10} alkylene, C_3-C_8-carbocycle,-O-(C_1-C_6 alkyl), -arylene-, C_1-C_{10} alkylene-arylene, -arylene-C_1-C_{10} alkylene, -C_1-C_{10} alkylene-(C_3-C_6-carbocycle)-, -(C_3-C_8 carbocycle)-C_1-C_{10} alkylene-, C_3-C_8-heterocycle, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -C_3-C_8-heterocyclo)-C_1-C_{10} alkylene, -$(CH_2CH_2O)_u$, or –$CH_2CH_2O)_u$-CH_2-, wherein u is an integer ranging from 1 to 10 and R^{57} is C_1-C_6 alkyl or aryl.

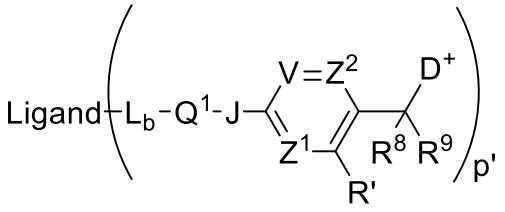
BRIEF DESCRIPTION OF THE DRAWINGS

WHAT IS CLAIMED IS:

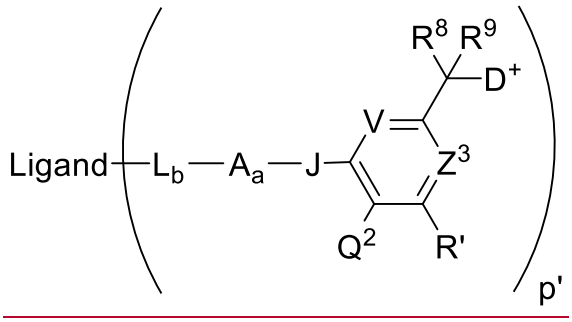
1. Use of a~~A Ligand Drug Conjugate (LDC)~~ composition in the manufacture of a medicament for treating cancer or an autoimmune disease, wherein the ~~LDC~~ composition comprises a Ligand Drug Conjugate (LDC) copound ~~is~~ represented by the structure of Formula ~~1~~2A or Formula 3F:



~~(Formula 1)~~



(Formula 2A)



(Formula 3F)

or a pharmaceutically acceptable salt thereof, wherein

~~LU is a Linker Unit;~~

"Ligand" is a Ligand Unit (L), ~~from a targeting moiety,~~ wherein L is from an antibody, thereby defining an antibody drug conjugate (ADC), wherein the antibody is capable of selective binding to an antigen, wherein the antigen is an extracellularly accessible cell-

surface protein or glycoprotein preferentially displayed by abnormal cells in comparison to normal cells, wherein the cells are mammalian cells of a subject intended for therapy and wherein the antigen is capable of cellular internalization upon said selective binding~~wherein L selectively binds to a target moiety~~;

L_b is a ligand covalent binding moiety;

Q^1 is A_a-W_{w}, wherein A is an optional Stretcher unit so that subscript a is 0 when A is absent or 1 when A is present and ~~is~~ optionally ~~comprised~~ comprises ~~of~~ two, three, or four subunits~~,~~;

Q^2 is W'$_{w'}$-E-~~', wherein Q^2, when present, is bonded to V, Z^1, Z^2 or Z^3~~;

W_{w} and $W'_{w'}$ are Cleavable ~~units~~Units, wherein

W_{w} of Q^1 comprises a peptide sequence ~~is capable of~~ selectively ~~cleavage~~ cleavable by a~~n~~ lysosomal ~~intracellular or regulatory~~ protease in comparison to serum proteases~~;, or by glutathione through disulfide exchange, or is more reactive to hydrolysis under lower pH (i.e., under more acidic) conditions present in lysosomes in comparison to physiological pH of serum,~~

W'~~-E~~ of Q^2 is a carbohydrate moiety, wherein W'-E- of Q^2 provides a glycosidic bond to the carbohydrate moiety, wherein the glycosidic bond is cleavable by an intracellular glycosidase ~~located intracellularly~~, ~~and~~

~~subscript w is 0 or 1 so that W is absent when w is 0 or W is present when w is 1, and subscript w' is 0 or 1, wherein W'-E is absent when w' is 0 or W'-E is present when w' is 1, and wherein w + w' is 1 (i.e., one and only one of W, W' is present);~~

V, Z^1, Z^2, and Z^3 are each =CH-; ~~=N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, $-NO_2$, -CN or other electron withdrawing group, an electron donating group, $-Q^2$, or $-C(R^8)(R^9)-D^+$, wherein at least one of V, Z^1, Z^2 and Z^3 is =C(R^{24})- when w is 1, and at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})- when w' is 1,~~

~~provided that when w is 1, Q^2 is absent and one and only one R^{24} is $-C(R^8)(R^9)-D^+$ so that $-C(R^8)(R^9)-D^+$ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})- and the Q^1-J- and $-C(R^8)(R^9)-D^+$ substituents are *ortho* or *para* to each other,~~

~~provided that when w' is 1, one any only one R^{24} is $-C(R^8)(R^9)-D^+$ so that $-C(R^8)(R^9)-D^+$ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is $=C(R^{24})-$ and one and only one other R^{24} is Q^2 so that Q^2 is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is $=C(R^{24})-$, and the Q^2 and $-C(R^8)(R^9)-D^+$ substituents are *ortho* or *para* to each other;~~

~~R^8 and R^9 independently are hydrogen, alkyl, alkenyl or alkynyl, optionally substituted, or aryl or heteroaryl, optionally substituted;~~

R', R^8, and R^9 are each ~~is~~ hydrogen ~~or is halogen, $-NO_2$, -CN or other electron withdrawing group, or is an electron donating group~~;

E ~~and J independently are~~is –O'-, ~~-S- or $-N(R^{33})-$,~~ wherein O' represents the oxygen atom of the glycosidic bond to the carbohydrate moiety~~R^{33} is hydrogen or optionally substituted alkyl~~;

J is -NH-;

D^+ represents a structure of a quaternized tertiary amine-containing drug; ~~and~~

~~subscript p is an average drug loading having a number ranging from 1 to 24; and~~

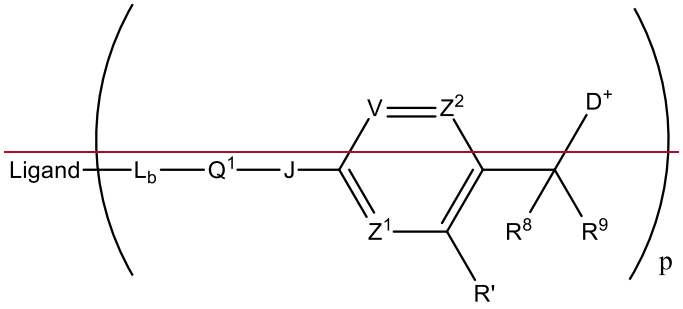
wherein ~~said protease cleavage, disulfide exchange, acid hydrolysis or glycosidase cleavage results in release of~~the tertiary amine-~~containind~~ containing drug is quaternized at the nitrogen atom of its tertiary amine,~~(D) from a Ligand Drug Conjugate compound of the composition.~~

wherein the tertiary amine-containing drug (D) is a tertiary amine-containing tubulin disrupting agent; and

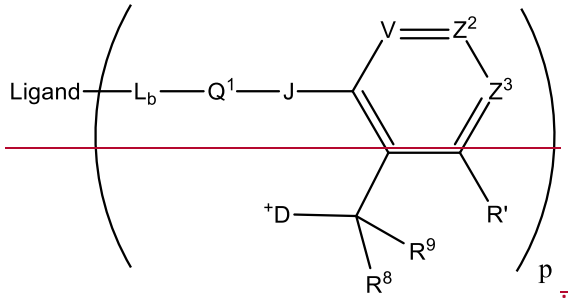
subscript p' is an integer ranging from 1 to 20; and

wherein said selective cleavage by the lysosomal protease or cleavage by the glycosidase initiates release of D from the Ligand Drug Conjugate compound.

~~**2.** The LDC composition of claim 1 wherein the structure of the composition is represented by the structure of Formula 2A or Formula 2B:~~

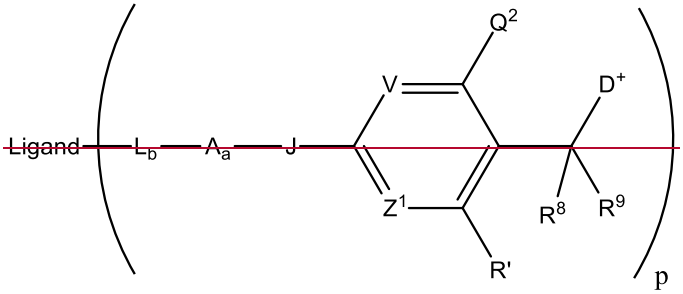


~~(Formula 2A)~~

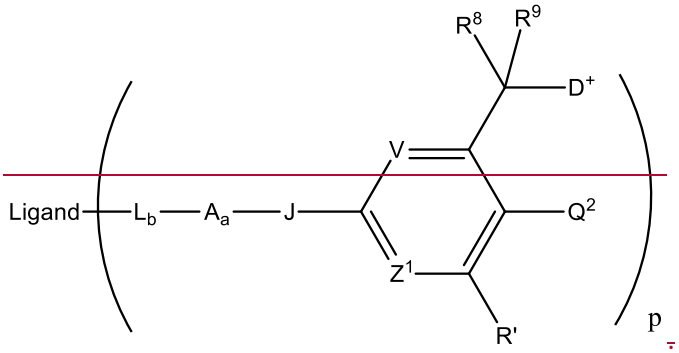


~~(Formula 2B)~~

~~**3.** The LDC composition of claim 1 wherein the structure of the composition is represented by the structure of Formula 3A or Formula 3B:~~

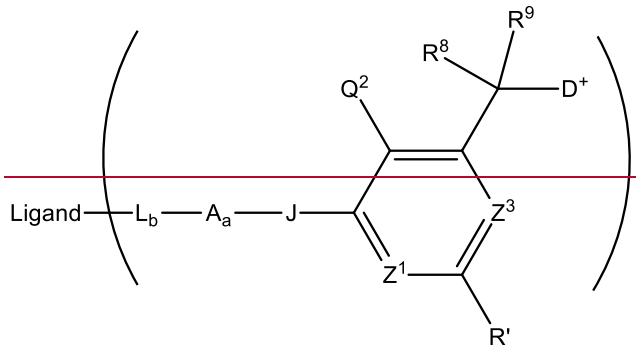


~~(Formula 3A)~~

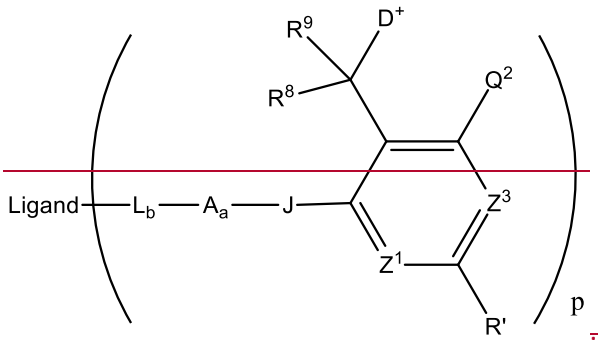


(Formula 3B)

4. The LDC composition of claim 1 wherein the composition is represented by the structure of Formula 3C or Formula 3D:

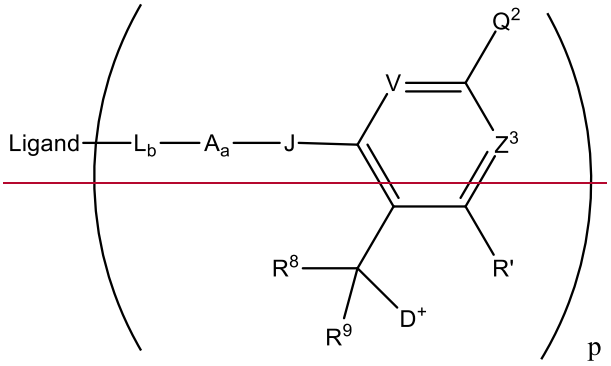


(Formula 3C)

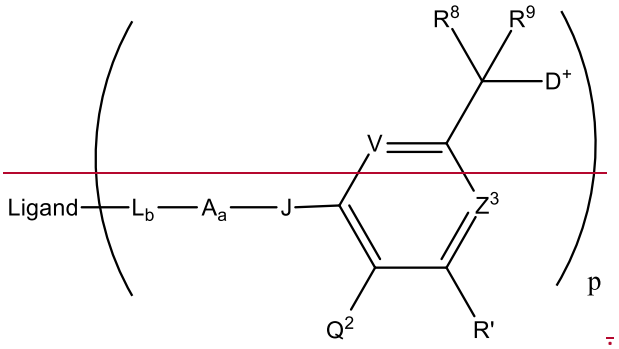


(Formula 3D)

5. The LDC composition of claim 1 wherein the structure of of the composition is represented by the structure of Formula 3E or Formula 3F:



~~(Formula 3E)~~



~~(Formula 3F)~~

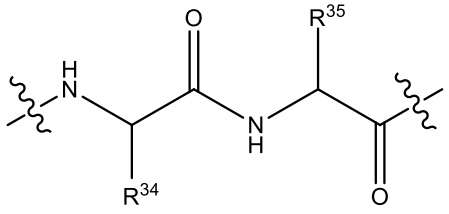
~~**6.** The LDC composition of any one of claims 1 to 5 wherein the targeting moiety is an antibody, thereby defining an antibody drug conjugate (ADC) wherein the targeted moiety of the antibody Ligand Unit is an accessible cell-surface antigen of targeted abnormal or other unwanted cells capable of cellular internalization of bound ADC, wherein the antigen is preferentially present on the abnormal or other unwanted cells in comparison to normal cells.~~

~~**7.** The LDC composition of any one of claims 1 to 5 wherein the targeting moiety is a ligand of an accessible cell-surface receptor and the targeted moiety is that cell-surface receptor, wherein the targeted receptor on abnormal cells is capable of cellular internalization of bound LDC, and wherein the receptor is preferentially present on the abnormal cells in comparison to normal cells.~~

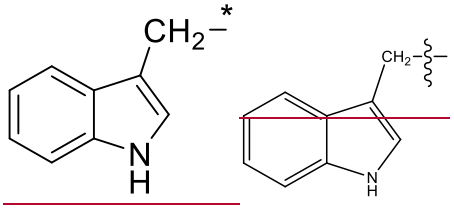
~~8~~2. The ~~LDC composition~~use of claim ~~6~~ 1, wherein W of Formula 2A ~~Q~~^{1} ~~is comprised or consists of a peptide moiety having~~ has a peptide bond to J that is selectively cleavable by ~~an~~ the lysosomal ~~intracellular or regulatory~~ protease and the carbohydrate moiety of Formula 3F is a glucuronic acid residue, wherein said cleavage by the intracellular glycosidase is by an intracellular glucuronidase~~in comparison to serum proteases wherein action of the regulatory protease on W causes release of tertiary amine-containing drug (D) from a Ligand Drug Conjugate compound of the composition~~.

~~**9.** The LDC composition of claim 6 wherein W' of Q^{2} is a glycoside-bonded carbohydrate, wherein the glycoside bond W'-E of Q^{2} provides for a cleavage site for a glycosidase located intracellularly wherein action of the glycosidase on W'-E causes release of tertiary amine-containing drug (D) from a Ligand Drug Conjugate compound of the composition.~~

~~10~~3. The ~~LDC composition~~use of claim ~~8~~1 wherein the ~~peptide moiety of~~ W of Forumla 2A is ~~comprised or consists of~~ a dipeptide moiety having the structure of Formula 6:



(Formula 6),

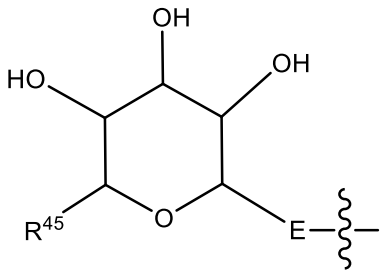
wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH$_3$, or has the structure of 

, wherein the asterisk indicates covalent bonding to the dipeptide backbone; and R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=O)NH_2$, -$(CH_2)_3NH(C=NH)NH_2$, or -$(CH_2)_2CO_2H$,

wherein the wavy ~~bond~~ line to the dipeptide's C-terminus indicates covalent bonding to J of the arylene moiety of Formula 2A ~~or 2B~~ and the wavy ~~bond~~ line to the dipeptide's N-

terminus indicates covalent bonding to ~~the remainder of W, if any such remainder is present, or to~~ A, or a subunit thereof, when subscript a is 1 or to L_b when subscript a is 0, and wherein the dipeptide's bond to J is selectively cleavable by the lysosomal ~~a intracellular or regulatory~~ protease~~.~~, and

~~**11**. The LDC composition of claim 9 wherein W' in Q^2 is a carbohydrate moiety that is glycoside-bonded to E, wherein the glycosidic bond is cleavable by a glycosidase located intracellularly, and~~ wherein W'-E of Formula 3F has the structure of Formula 7:



(Formula 7),

wherein the wavy line represents E bonded to the arylene moiety of Formula 3F~~one of V~~, ~~Z^1, Z^2, or Z^3 when that variable group is $=C(R^{24})$,~~

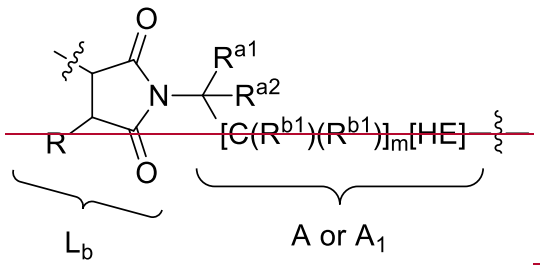
wherein E is –O'-~~, –S–, or –N(R^{33})–~~; ~~wherein R^{33} is hydrogen or methyl~~; and

wherein R^{45} is $–CH_2OH$ or $–CO_2H$.

~~**12**. The LDC composition of claim 1 wherein a is 1;~~

~~wherein L_b-A_a in Formula 1 is L_b-A when A_a is absent or L_b-A is L_b-A_1-A_O when A_O is present so that A becomes A_1-A_a~~

~~wherein L_b-A_a has the structure of Formula 8:~~



~~(Formula 8)~~

wherein

the -[C(R^{b1})(R^{b1})]$_m$-[HE]- moiety is A or A_1;

R and R^{a2} independently are hydrogen or methyl;

R^{a1} is hydrogen, methyl, ethyl or a Basic Unit (BU);

HE is an optional Hydrolysis Enhancer (HE) Unit;

subscript m is an integer ranging from 0 to 6;

each R^{b1} independently is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl, or two R^{b1} together with the carbon(s) to which they are attached comprise a C_3-C_6 cycloalkyl or one R^{b1} and HE together with the carbon to which they are attached comprise a 5- or 6-membered cycloalkyl or a 5- or 6-membered heterocycloalkyl and the other R^{b1} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl;

BU has the structure of -[C(R^1)(R^1)]-[C(R^2)(R^2)]$_n$-N(R^{22})(R^{23}),

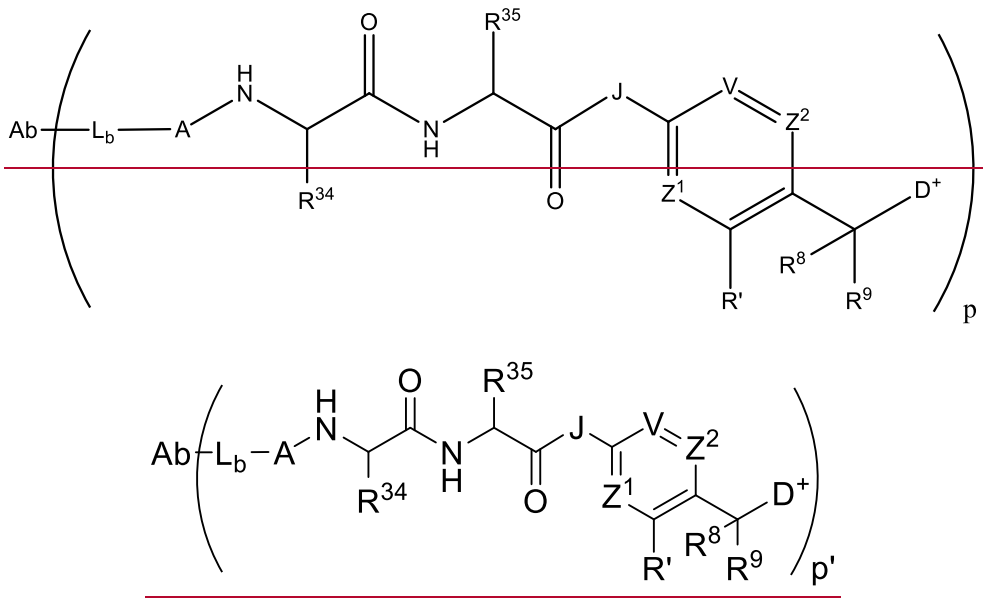
wherein subscript n is 0, 1, 2 or 3;

each R^1 independently is hydrogen or lower alkyl or two R^1 together with the carbon to which they are attached comprise a C_3-C_6 cycloalkyl, and each R^2 independently is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl, or two R^2 together with the carbon(s) to which they are attached and any intervening carbons define a C_3-C_6 cycloalkyl, or one R^1 and one R^2 together with the carbons to which they are attached and any intervening carbons comprise a 5- or 6-membered cycloalkyl and the remaining R^1 and R^2 are as defined;

R^{22} and R^{23} independently are hydrogen or optionally substituted C_1-C_6 alkyl or together with the nitrogen to which they are attached comprise a 5- or 6-membered heterocycloalkyl; and

wherein the wavy line to the succinimide ring of L_b indicates covalent bonding of sulfur derived from a sulfhydryl group of a targeting moiety and the other wavy line indicates covalent bonding of A (or A_1) to the remainder of the composition structure.

~~13~~4. The ~~LDC composition~~use of claim ~~10~~ 1, wherein Formula 2A ~~the structure of the composition~~ is represented by the structure of Formula 9:



(Formula 9)

wherein Ab is an antibody Ligand Unit;

R', R^8 and R^9 ~~is~~ are each hydrogen ~~or an electron donating group~~;

~~R^8 is hydrogen;~~

~~R^9 is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted phenyl;~~

R^{34} is methyl, isopropyl or -$CH(OH)CH_3$;

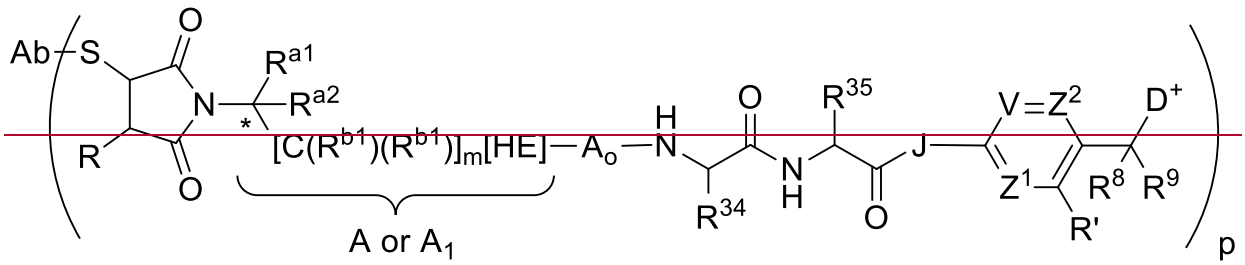
R^{35} is methyl, -$(CH_2)_3NH(C=O)NH_2$ or -$(CH_2)_2CO_2H$;

J is –N~~(R^{33})~~H-~~, wherein R^{33} is hydrogen or methyl~~; and

V, Z^2 and Z^1 ~~independently~~ are each =CH-, ~~or =N-.~~

and

~~**14.** The LDC composition of claim 13 wherein the structure of of the composition is represented by the structure of Formula 10:~~



~~(Formula 10)~~

~~wherein~~

~~S is a sulfur atom of an antibody Ligand Unit (Ab-);~~

~~the asterisk (*) designates chirality or absence thereof at the indicated carbon;~~

~~A_o is an optional subunit of A, wherein -[C(R^{b1})(R^{b1})]$_m$-[HE]- is A when A_o is absent and is A_1 when A_o is present so A becomes -A_1-A_o-;~~

~~R is -H;~~

~~R^{a1} is -H or a basic unit (BU), wherein BU has the structure of -CH_2-N(R^{22})(R^{23}), wherein R^{22} and R^{23} independently are hydrogen, methyl or ethyl or both together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;~~

~~R^{a2} is hydrogen;~~

~~subscript m is an integer ranging from 0 to 5 when HE is present or from 1 to 5 when HE is absent;~~

~~each R^{b1} independently is hydrogen or optionally substituted C_1-C_6 alkyl;~~

~~HE is absent or is -C(=O)-;~~

~~R^{34} is methyl, isopropyl or -CH(OH)CH_3;~~

~~R^{35} is -$(CH_2)_3$NH(C=O)NH_2, or -$(CH_2)_2$$CO_2$H;~~

~~J is -NH-;~~

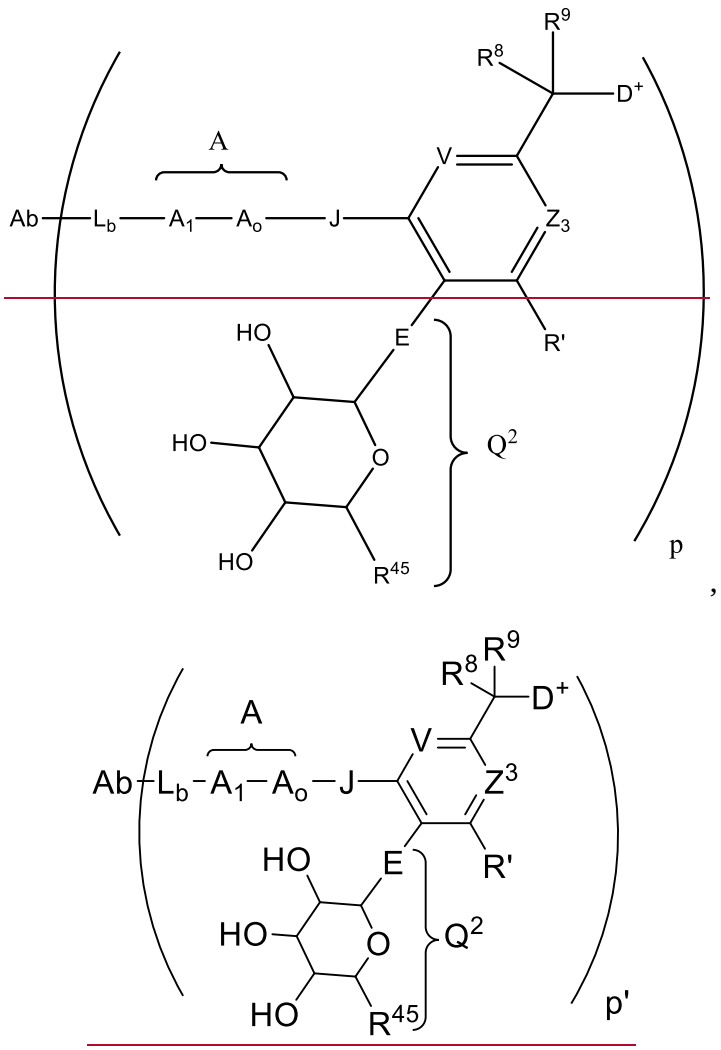
~~V, Z^1 and Z^2 are =CH_2-;~~

~~R' is hydrogen or an electron donating group;~~

~~R^8 is hydrogen; and~~

~~R^9 is hydrogen or methyl.~~

~~**15.** The LDC composition of claim 11 wherein~~ Formula 3F ~~the structure of the composition~~ is represented by the structure of Formula 11:



(Formula 11)

wherein

wherein Ab is an antibody Ligand Unit;

A_1 and A_o are independently selected subunits of A, wherein A_o is an optional subunit of A so that A_1 becomes A when A_o is absent and A is -A_1-A_o- when A_o is present;

E is –O- ~~or –NH-~~;

J is –N~~(R^{33})~~H-~~, wherein R^{33} is hydrogen or methyl~~;

V and Z^3 ~~independently~~ are each =CH- ~~or =N-~~;

R’, R^8 and R^9 ~~is~~ are each hydrogen ~~or an electron withdrawing group~~;

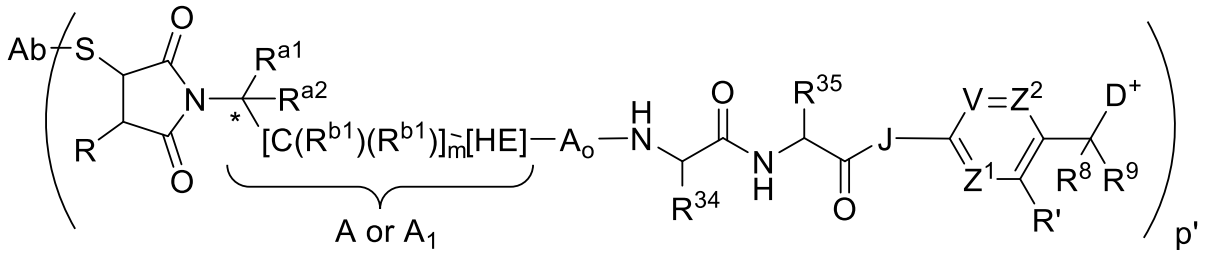
~~R^8 is hydrogen;~~

~~R^9 is hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted phenyl;~~

R^{45} is –CO_2H; and

subscript p’ is an integer ~~number~~ ranging from 1 to 8.

5. The use of claim 4, wherein Formula 2A is represented by the structure of Formula 10:



(Formula 10)

or a pharmaceutically acceptable salt thereof, wherein

S is a sulfur atom of the antibody Ligand Unit and the succinimide ring to which it is covalently attached is optionally in hydrolysed form;

the asterisk (*) designates chirality or absence thereof at the indicated carbon atom;

A_o is an optional subunit of A, wherein $–[C(R^{b1})(R^{b1})]_m$-[HE]- is A when A_o is absent and is A_1 when A_o is present so that A becomes $-A_1-A_o-$;

R is –H;

R^{a1} is –H or a basic unit (BU) in which the succinimide ring is in hydrolyzed form, wherein BU has the structure of $–CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} are each independently hydrogen, methyl, or ethyl, or both R^{22} and R^{23} together with the nitrogen atom to which they are attached define a 5- or 6-membered nitrogen-containing heterocycloalkyl;

R^{a2} is hydrogen;

subscript m is an integer ranging from 0 to 4;

each R^{b1} is hydrogen;

HE is –C(=O)-;

R^{34} is methyl, isopropyl, or $-CH(OH)CH_3$;

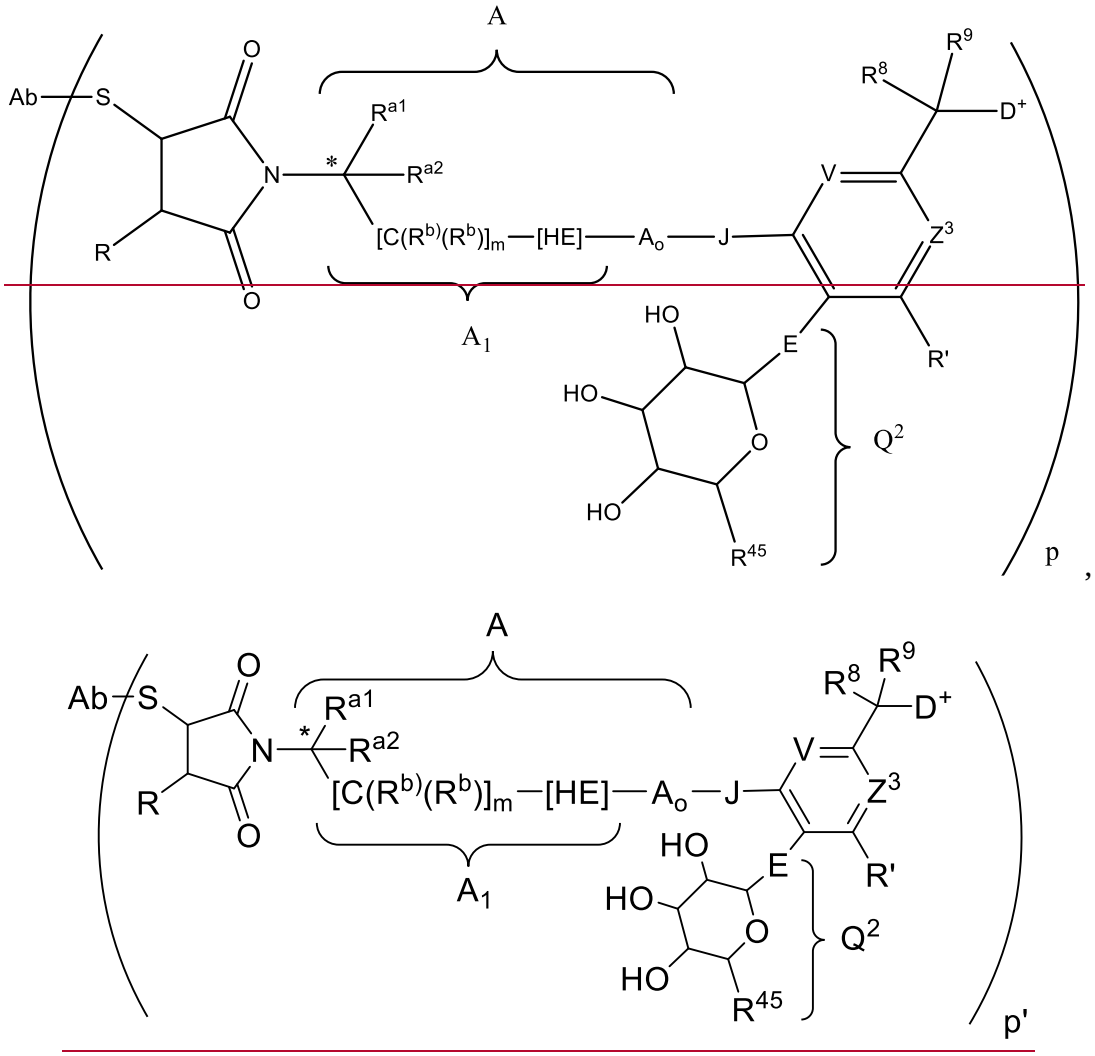
R^{35} is $–(CH_2)_3NH(C=O)NH_2$ or $–(CH_2)_2CO_2H$;

J is –NH-; and

R’, R^8, and R^9 are each hydrogen,

and

~~16. The LDC composition of claim 15~~ wherein Formula 3F ~~the structure of the composition~~ is represented by the structure of Formula 12:



(Formula 12)

or a pharmaceutically acceptable salt thereof, wherein

~~wherein~~ S is a sulfur atom of antibody Ligand Unit Ab and the succinimide ring to which it is covalently attached is optionally in hydrolysed form;

the asterisk (*) designates chirality or absence thereof at the indicated carbon;

A_1 and A_o are independently selected subunits of A, wherein A_o is an optional subunit of A, wherein–$[C(R^{b1})(R^{b1})]_m$-[HE]- is A when A_o is absent and is A_1 when A_o is present so that A becomes A_1-A_o~~;~~, wherein A_o when present corresponds in structure to an amine-containing acid bonded to J through the C-terminal carbonyl of the amine-containing acid;

R is hydrogen;

~~R' is hydrogen or an electron withdrawing group;~~

R^{a1} is hydrogen or a basic unit (BU) in which the succinimide ring is in hydrolyzed form, wherein BU has the structure of $–CH_2$-$N(R^{22})(R^{23})$, or a acid addition salt thereof, wherein R^{22} and R^{23} are each independently ~~are~~ hydrogen, methyl or ethyl or both R^{22} and R^{23} together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;

R^{a2} is hydrogen;

subscript m is an integer ranging from 0 to 5 ~~when HE is present or 1 to 5 when HE is absent~~;

each R^{b1} independently is hydrogen or optionally substituted C_1-C_6 alkyl;

HE is absent or is –C(=O)-;

R^{45} is $–CO_2H$;

E is –O'-;

J is –NH-;

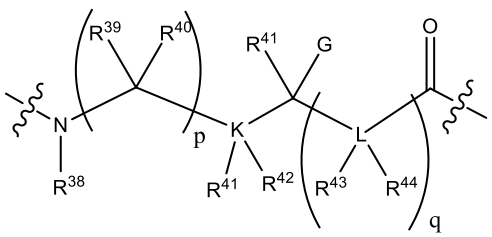
~~V and Z^3 are $=CH_2$-;~~

R', R^8, and R^9 is hydrogen;

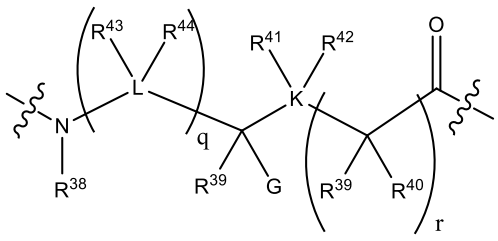
~~R^9 is hydrogen or methyl;~~ and

subscript p' is an integer~~number~~ ranging from 1 to 8.

~~17~~6. The ~~LDC composition~~use of claim ~~1~~5 wherein A_o, when present, has the structure of Formula 13 or Formula 14:



(Formula 13)



(Formula 14)

wherein the wavy line to the carbonyl moiety of either structure represents the point of attachment of A_o to W and wherein the wavy line to the amino moiety of either structure represents the point of attachment of A_o to A_1,

wherein K and L independently are C, N, O or S, provided that when K or L is O or S, R^{41} and R^{42} to K or R^{43} and R^{44} to L are absent, and when K or L are N, one of R^{41}~~,~~ and R^{42} to K or one of R^{43}~~,~~ and R^{44} to L are absent, and provided that no two adjacent L are independently selected as N, O, or S;

wherein q is an integer ranging from 0 to 12, and r is an integer ranging from 1 to 12;

wherein G is hydrogen, optionally substituted C_1-C_6 alkyl, -OH, $-OR^G$, $-CO_2H$, CO_2R^G, wherein R^G is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl, ~~optionally substituted,~~ or R^{PR},

wherein R^{PR} is a suitable protecting group, $-NH_2$, or $-N(R^G)(R^{PG})$, wherein each R^G is independently optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl ~~selected is as previously defined~~ or both R^G together with the nitrogen to which they are attached comprises a 5- or 6-membered heterocycloalkyl or both R^G ~~R~~^{PR} together form a suitable protecting group;

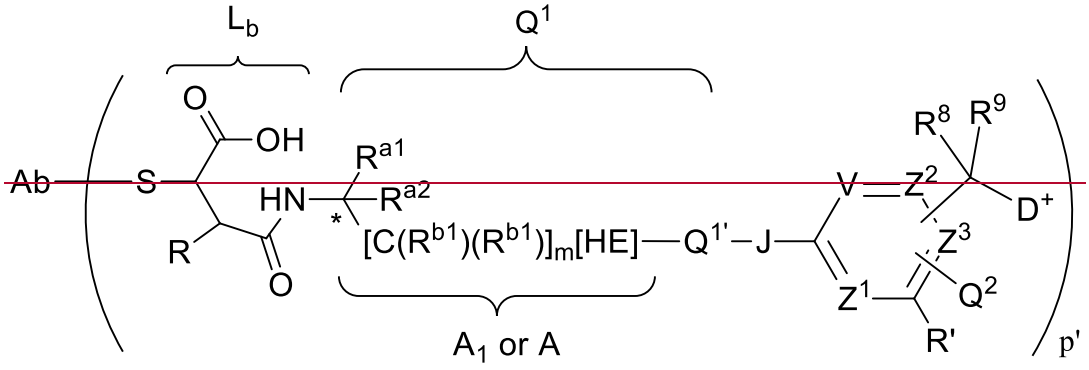
wherein R^{38} is hydrogen or optionally substituted C_1-C_6 alkyl;

each R^{39}-R^{44} is independently ~~are~~ hydrogen, optionally substituted C_1-C_6 alkyl, ~~optionally substituted,~~ or optionally substituted heteroaryl, or both R^{39}~~,~~ and R^{40} together with the carbon to which they are attached ~~comprise~~ define a C_3-C_6 cycloalkyl, or R^{41}~~,~~ and R^{42} together with K to which they are attached when K is C, or R^{43}~~,~~ and R^{44} together with L to which they are attached when L is C, ~~comprise~~ define a C_3-C_6 cycloalkyl, or R^{40} and R^{41}, or R^{40} and R^{43}, or R^{41} and R^{43} ~~to~~ together with the carbon or heteroatom to which they are attached and atoms intervening between those carbon and/or heteroatoms comprise a 5- or 6-membered cycloalkyl or heterocycloalkyl, or

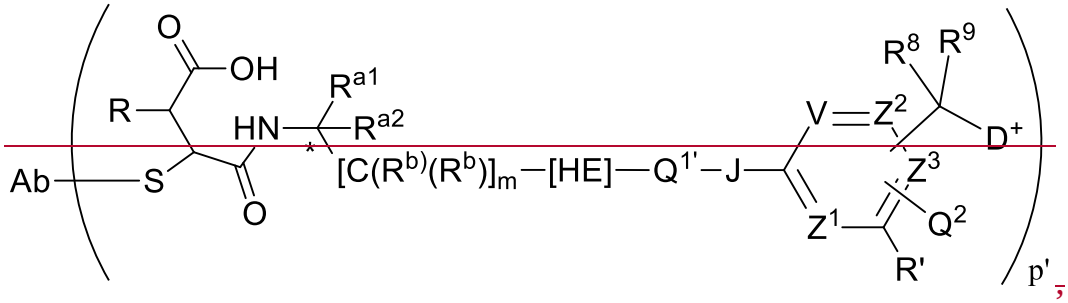
wherein A_o has a structure corresponding to alpha-amino, beta-amino or another amine-containing acid; and~~.~~

~~**18.** The LDC composition of claim 16~~ wherein the indicated starred (*) carbon is predominantly in the same absolute configuration as the alpha carbon of an **L**-amino acid when that indicated carbon has chirality.

19. The LDC composition of claim 6 wherein each Ligand Drug Conjugate compound of the composition is independently represented by the structure of Formula 16A or Formula 16B:



(Formula 16A)



(Formula 16B)

wherein Ab is a antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

$Q^{1'}$ is A_o-W_w, wherein A_o is an optional subunit of A so that $Q^{1'}$ is W_w when A_o is absent, or is A_o-W_W when A_o is present,

wherein $[C(R^b)(R^b)]_m$-[HE]- becomes A when A_o is absent or is A_1 when A_o is present, and

wherein subscript w is 1 when Q^2 is absent or w is 0 so that W is absent and Q^2 is present;

R is hydrogen;

~~R^{a1} is H or BU wherein BU has the structure of $-CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} independently are hydrogen or methyl or both together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;~~

~~R^{a2} is hydrogen;~~

~~subscript m is an integer ranging from 0 to 5 when HE is present or from 1 to 5 when HE is absent ;~~

~~each R^{b1} independently is hydrogen or optionally substituted C_1-C_6 alkyl;~~

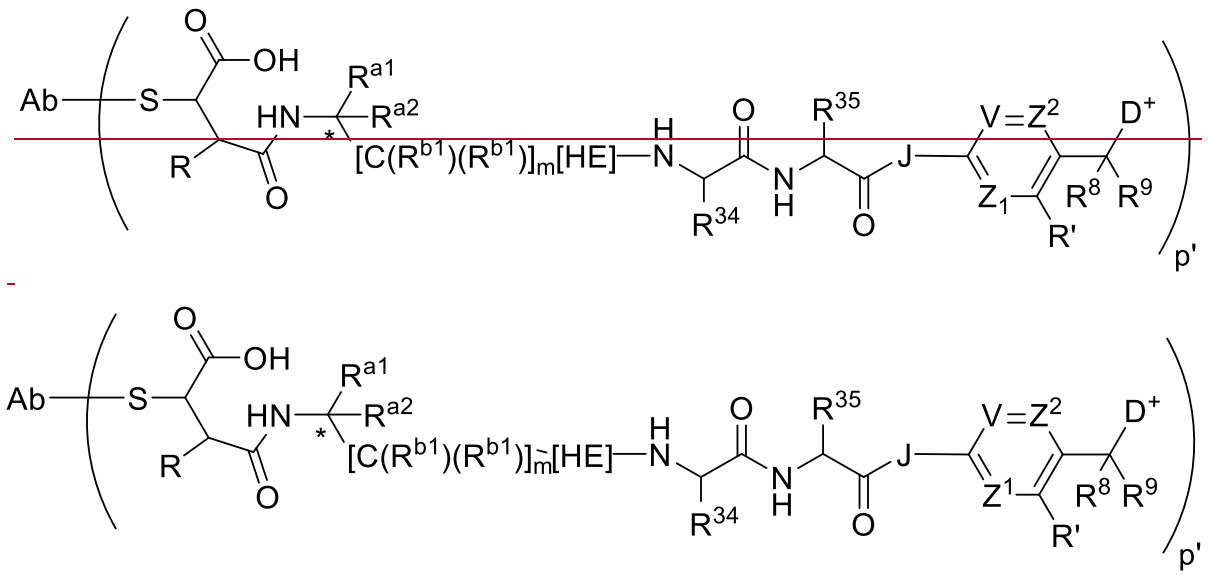
~~HE is absent or is C(=O) ;~~

~~J is O or NH ;~~

~~Q^2 when present is W-E, wherein E is O or NH ; and~~

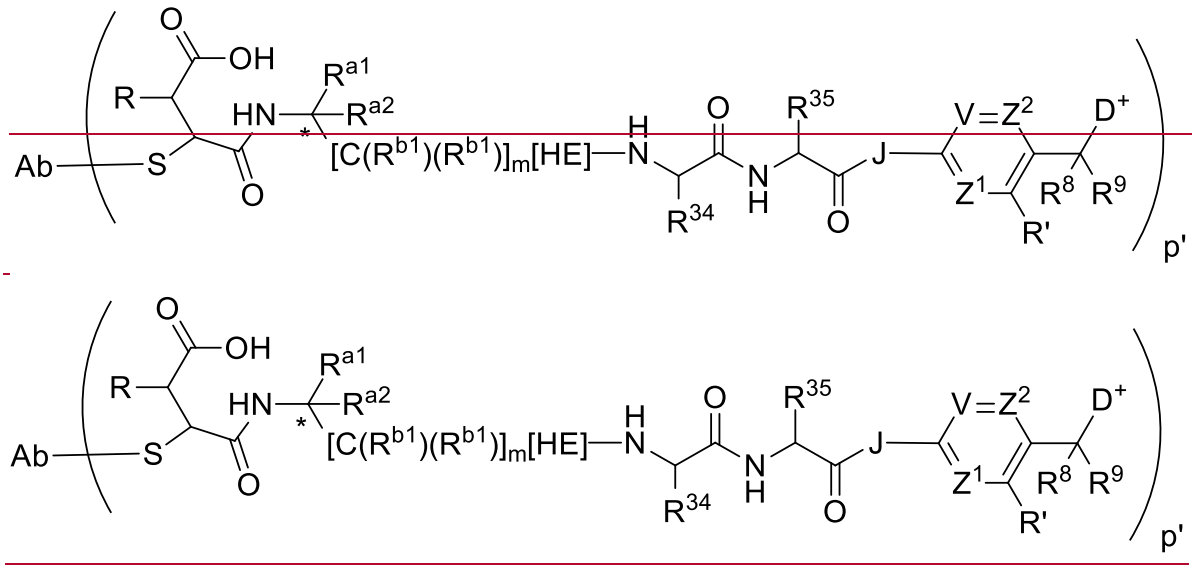
~~subscript p' is an integer ranging from 1 to 24.~~

~~20~~7. The ~~LDC composition~~use of claim ~~19~~ 1, wherein each Ligand Drug Conjugate compound ~~of the composition~~ has the structure of Formula 17A or Formula 17B:



(Formula 17A)

or



(Formula 17B)

or a pharmaceutically acceptable salt thereof, wherein

Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

the asterisk (*) designates chirality or absence thereof at the indicated carbon atom;

~~wherein~~ J is –NH-;

R is hydrogen;

R^{a1} is a Basic Unit (BU), wherein BU has the structure of $–CH_2$-$N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} are each independently hydrogen or methyl, or both R^{22} and R^{23} together with the nitrogen atom to which they are attached define a 5- or 6-membered nitrogen-containing heterocycloalkyl;

R^{a2} is hydrogen;

subscript m is an integer ranging from 0 to 4;

each R^{b1} is hydrogen;

HE is–C(=O)-;

R^{34} is methyl, isopropyl, or -$CH(OH)CH_3$;

R^{35} is $–(CH_2)_3NH(C=O)NH_2$ or $–(CH_2)_2CO_2H$;

J is–NH;

V, Z^1, and Z^2 are each =CH-;

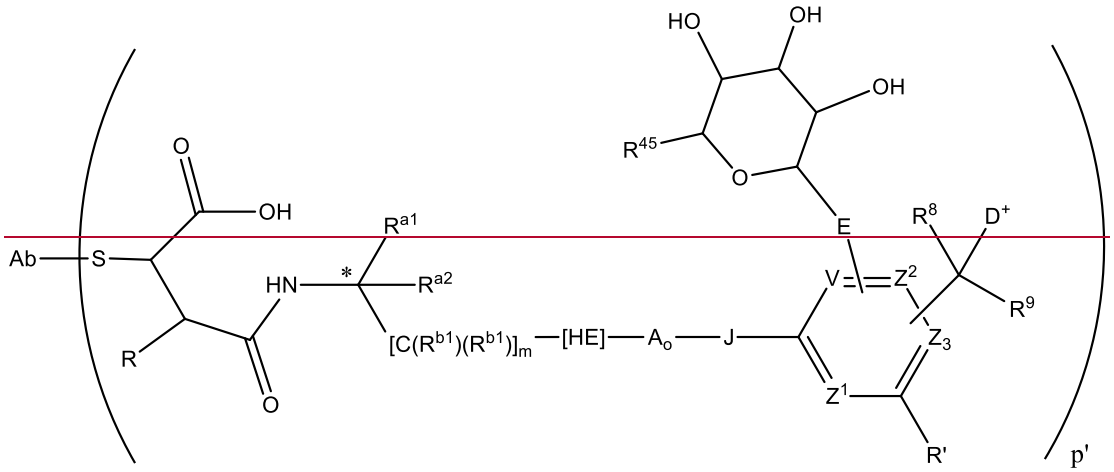
R’, R^8 , and R^9 are each ~~is~~ hydrogen;

~~R^9 is hydrogen or methyl~~; and

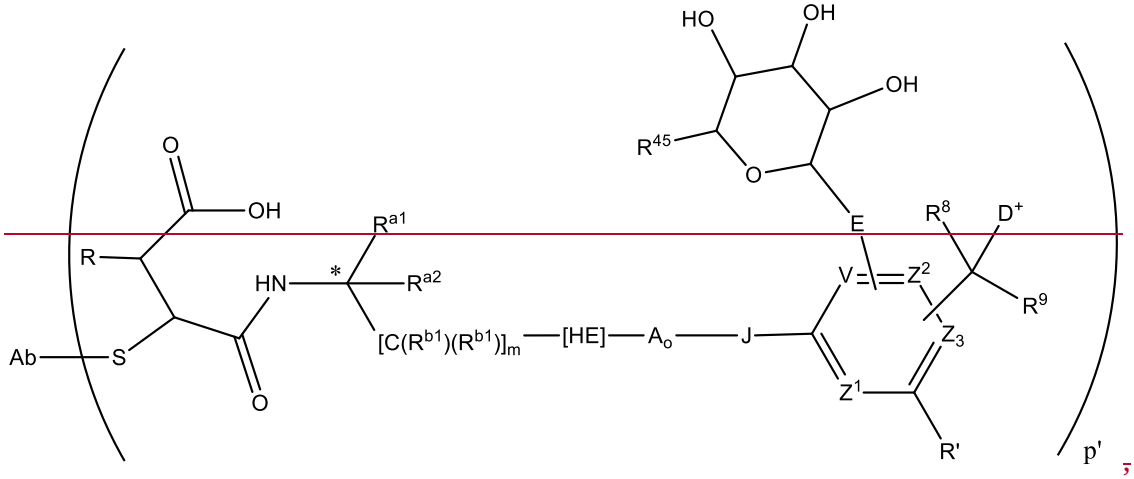
subscript p’ is an integer ranging from 1 to 8.

or

21. The LDC composition of claim 19 wherein each Ligand Drug Conjugate compound of the composition has the structure of Formula 18A or Formula 18B:



(Formula 18A)



(Formula 18B)

wherein A_o is an optional subunit of A, whereinthe $-[C(R^{b1})(R^{b1})]_m-[HE]-$ moiety is A when A_o is absent or the moiety is A_1 when A_o is present so that A becomes $-A_1-A_O-$;

R is H;

~~R^{a1} is H or a Basic Unit (BU), wherein BU has the structure of $-CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} independently are hydrogen or methyl or R^{22} both together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;~~

~~R^{a2} is hydrogen;~~

~~subscript m is an integer ranging from 0 to 5 when HE is present or 1 to 5 when HE is absent;~~

~~each R^{b1} independently is hydrogen or optionally substituted C_1-C_6 alkyl;~~

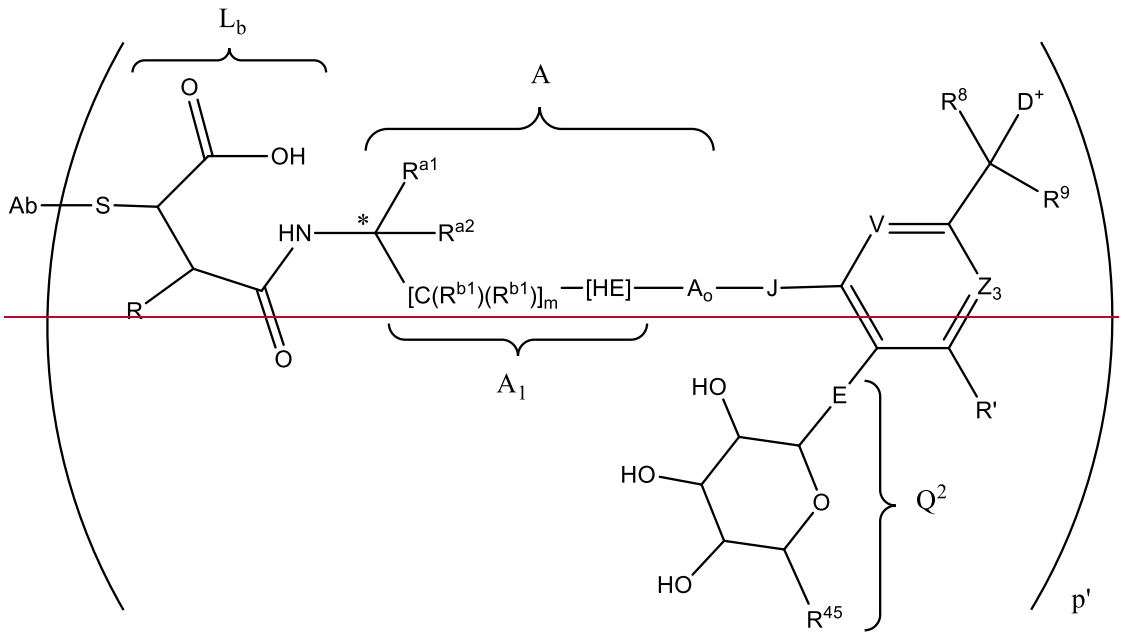
~~HE is absent or is $-C(=O)-$; and~~

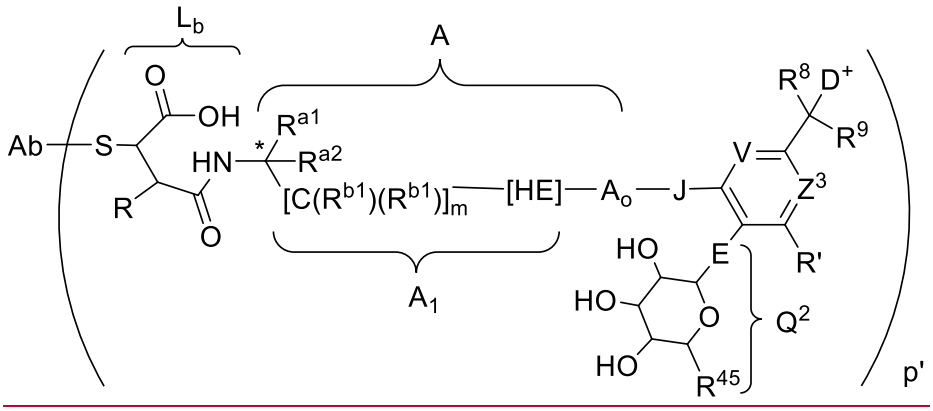
~~R^8 is hydrogen;~~

~~R^9 is hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted phenyl; and~~

~~subscript p' is an integer ranging from 1 to 24.~~

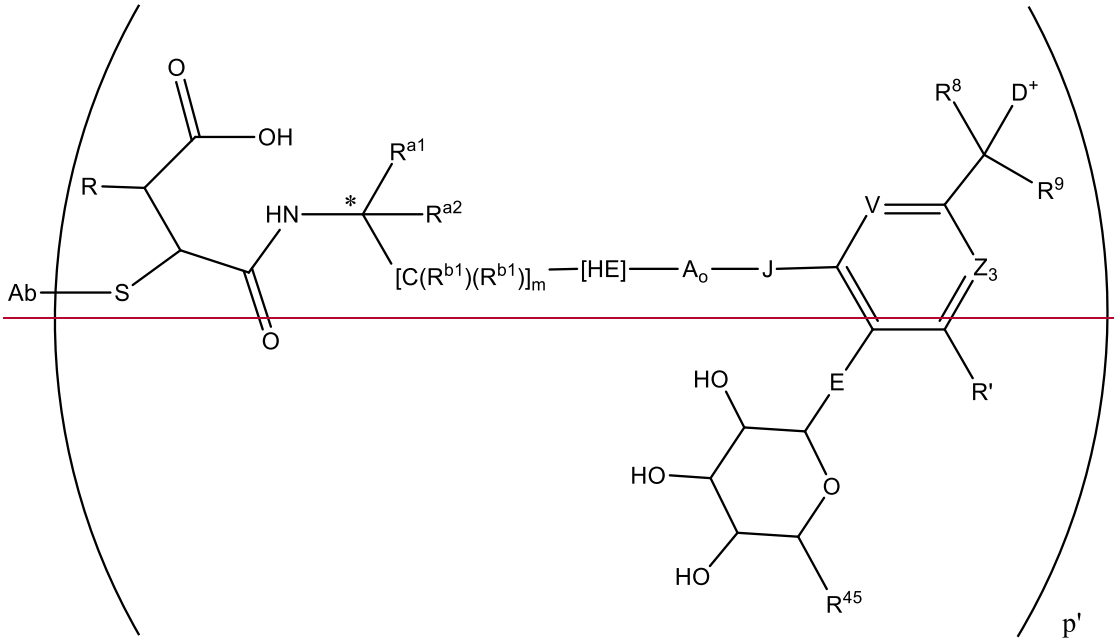
~~**22**. The LDC composition of claim 21~~ wherein ~~each~~ the Ligand Drug Conjugate compound ~~of the composition~~ has the structure of Formula 19A or Formula 19B:

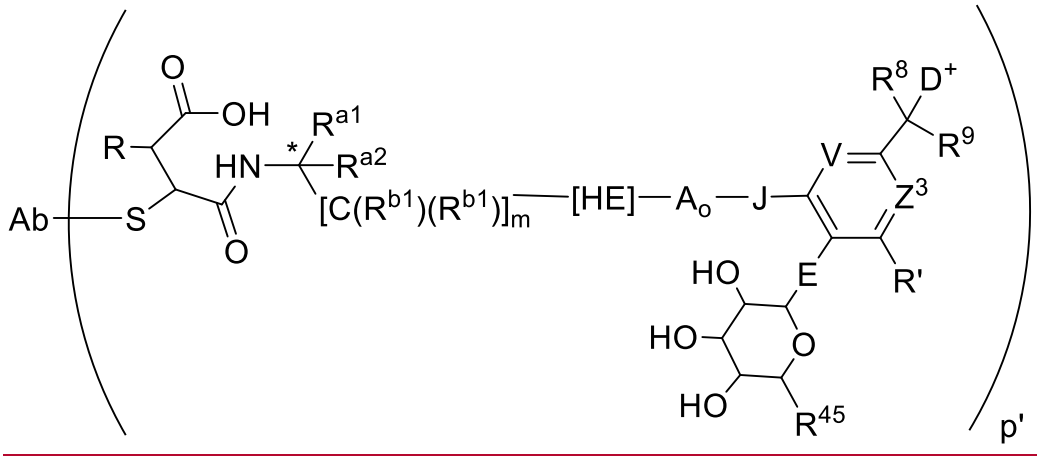




(Formula 19A)

or





(Formula 19B)

or a pharmaceutically acceptable salt thereof, wherein

Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

the asterisk (*) designates chirality or absence thereof at the indicated carbon atom;

A_O is an optional subunit of A, wherein the $–[C(R^{b1})(R^{b1})]_m$-[HE]- moiety is A when A_O is absent or the moiety is A_1 when A_O is present so that A becomes $-A_1-A_O-$;

R is –H~~hydrogen~~;

R^{a1} is ~~hydrogen or~~ a Basic Unit (BU), wherein BU has the structure of $–CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} are each independently ~~are~~ hydrogen or methyl, or R^{22} and R^{23} both together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;

R^{a2} is hydrogen;

subscript m is an integer ranging from 0 to ~~5~~ 4~~when HE is present or 1 to 5 when HE is absent~~;

each R^{b1} ~~independently~~ is hydrogen ~~or optionally substituted C_1-C_6 alkyl;~~

HE ~~is absent or~~ is –C(=O)-;

R^{45} is $–CO_2H$;

E is –O’-;

J is –NH-;

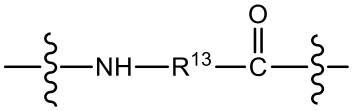
V and Z^3 ~~is~~ are each =CH-;~~=CH_2-;~~

R', R^8 and R^9 are each ~~is~~ hydrogen; and

~~R^9 is hydrogen or methyl~~

subscript p' is and integer ranging from 1 to 8.

~~23~~**8**. The ~~LDC composition~~use of claim ~~22~~ 7, A_O, when present, has the structure of:



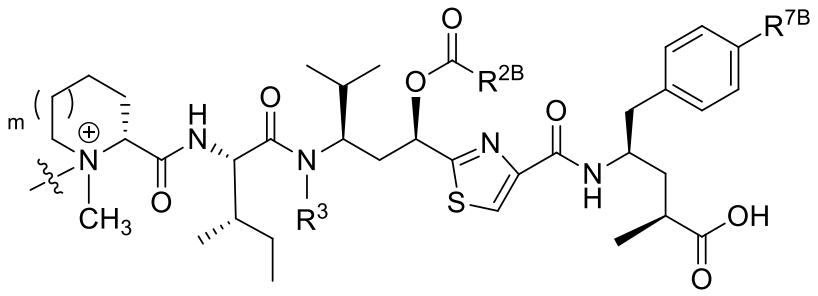
wherein R^{13} is -C_1-C_{10} alkylene-, -C_3-C_8 carbocyclo-, -arylene-, -C_1-C_{30} heteroalkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, -$(CH_2CH_2O)_{1-10}(-CH_2)_{1-3}$-, or -$(CH_2CH_2NH)_{1-10}(-CH_2)_{1-3}$-,

or wherein A_O has a structure corresponding to alpha-amino or beta-amino acid; and

wherein the indicated starred (*) carbon atom of Formula 17A, Formula 17B, Formula 19A, or Formula 19B is predominantly in the same absolute configuration as the alpha carbon of an **L**-amino acid when that indicated carbon has~~is~~ chirality.

~~24~~**9.** The ~~LDC composition~~use of ~~any one of~~ claim~~s~~ 1~~-23~~, wherein $–D^+$ is a quaternized tertiary amine-containing tubulin disrupting agent.

10. The use of claim 9, wherein the quaternized tertiary amine-containing tubulin disrupting agent $–D^+$ is a quaternized tubulysin Drug Unit having the structure of:



or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment of $–D^+$ to the benzylic carbon atom of the -$C(R^8)(R^9)$- moiety of Formula 2A or Formula 3F;

subscript m is 1;

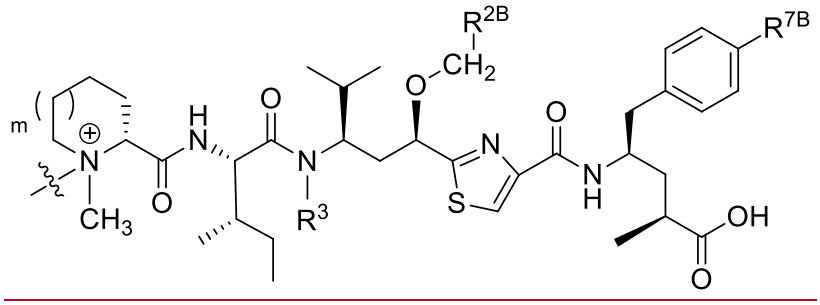
-OC(O)R^{2B} is –OC(O)CH_3, -OC(O)CH_2CH_3, -OC(O)$CH(CH_3)_2$, -OC(O)$C(CH_3)_3$, or –OC(O)$CH=CH_2$;

R^3 is methyl, ethyl, or propyl; and

R^{7B} is hydrogen or –OH,

or

–D^+ has the structure of:



or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment of –D^+ to the benzylic carbon atom of the -$C(R^8)(R^9)$- moiety Formula 2A or Formula 3F;

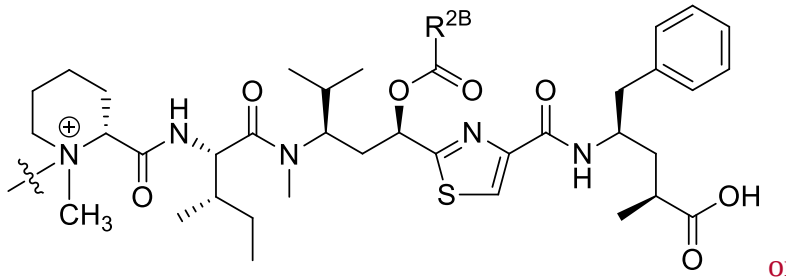
subscript m is 1;

–OCH_2R^{2B} is –OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, or –OCH_2OCH_3;

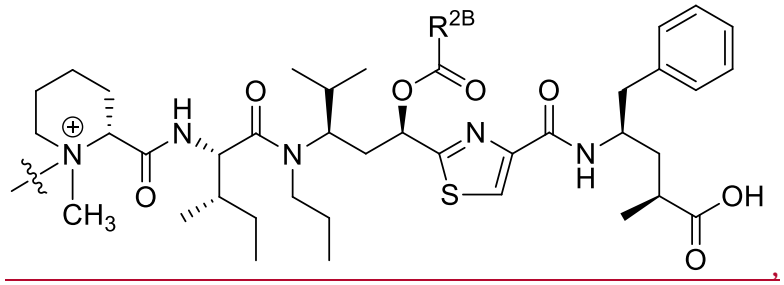
R^3 is methyl, ethyl, or propyl; and

R^{7B} is hydrogen or –OH.

11. The use of claim 10, wherein the quaternized tubulysin Drug Unit–D^+ has the structure of:



or



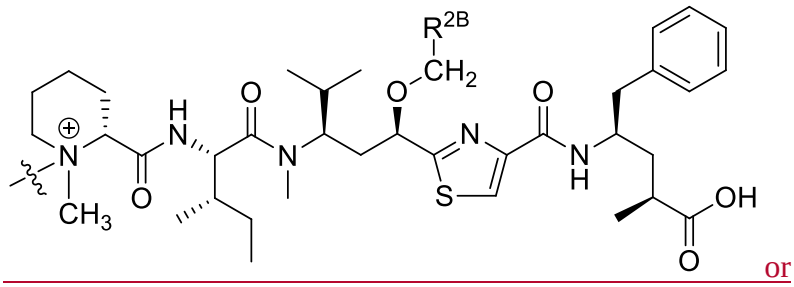
,

or a pharmaceutically acceptable salt thereof, wherein

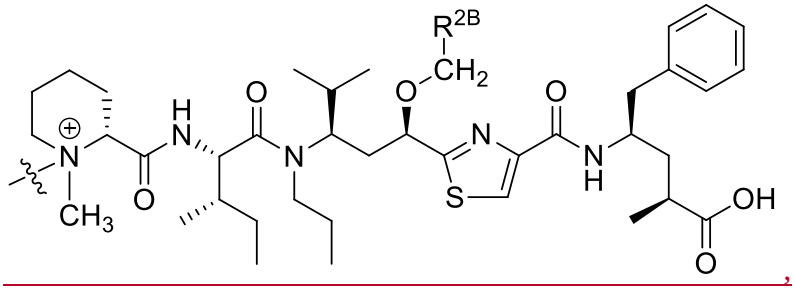
subscript m is 1;

R^{2B} is $–CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, or $-CH_2C(CH_3)_3$, or

$–D^+$ has the structure of:



or



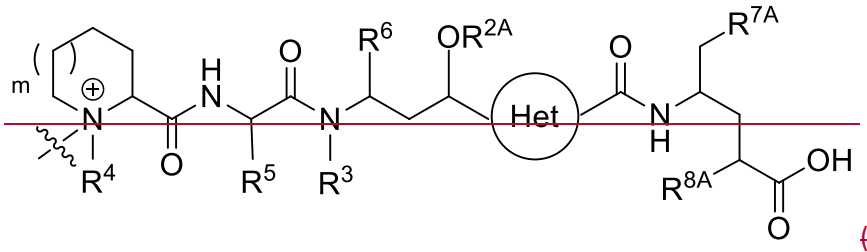
,

or a pharmaceutically acceptable salt thereof, wherein

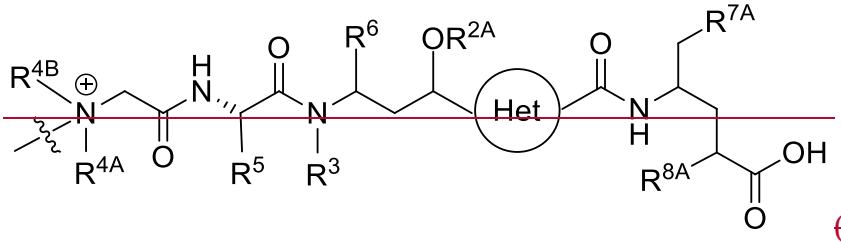
R^{2B} is hydrogen, methyl, or $–OCH_3$ so that $-OCH_2R^{2B}$ is a methyl, ethyl, or methoxymethyl ether O-linked substituent.

~~**25.** The LDC composition of claim 24 wherein the quaternized tubulin disrupting Drug Unit $–D^+$ is a quaternized tubulysin Drug Unit.~~

~~**26.** The LDC composition of claim 25 wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of Formula D_{G-1}' or Formula D_{H-1}':~~



(Formula D_{G-1})



(Formula D_{H-1})

wherein the circle represents an 5-membered nitrogen-heteroaryl and wherein the indicated required substituents to that heteroaryl are in a 1,3-relationship with each other with optional substitution at the remaining positions;

R^{2A} is hydrogen or optionally substituted alkyl or R^{2A} along with the oxygen atom to which it is attached defines an O-linked substituent other than -OH;

R^{3} is hydrogen or optionally substituted alkyl;

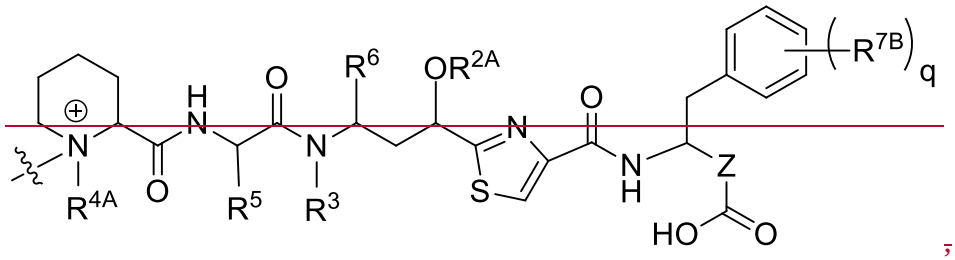
R^{4}, R^{4A}, R^{4B}, R^{5} and R^{6} are optionally substituted alkyl, independently selected;

R^{7A} is optionally substituted aryl or optionally substituted heteroaryl; and

R^{8A} is hydrogen or optionally substituted alkyl,

wherein the wavy line indicates covalent bonding of D^{+} to the remainder of the composition structure.

27. The LDC composition of claim 26 wherein the quaternized tubulysin Drug Unit D^{+} has the structure of:



,

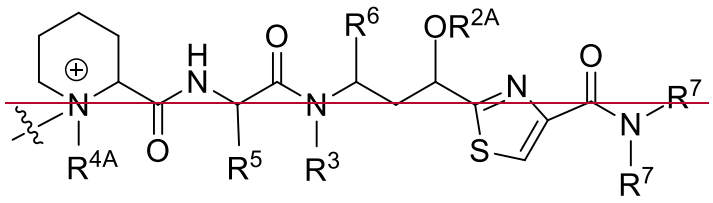
wherein Z is an optionally substituted lower alkylene or an optionally substituted lower alkenylene;

subscript q, indicating the number of R^{7B} substituents, is 1, 2 or 3;

wherein each R^{7B} is independently selected from the group consisting of hydrogen and an O-linked substituent; and

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the composition structure.

28. The LDC composition of claim 26 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



wherein R^{2A} is hydrogen or optionally substituted C_1-C_6 alkyl or R^2 along with the oxygen atom to which it is attached defines an O-linked substituent other than -OH;

R^3 is optionally substituted C_1-C_6 alkyl;

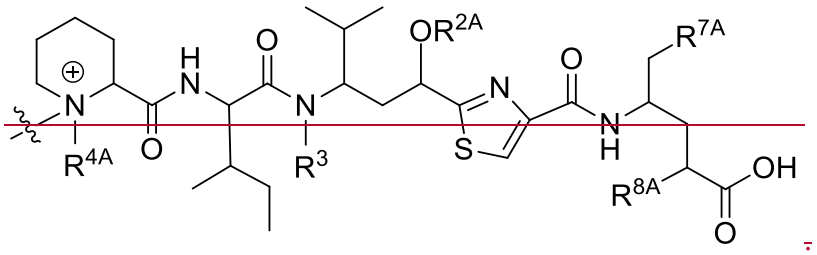
R^5 and R^6 are the side chain residues of natural hydrophobic amino acids;

$N(R^7)(R^7)$ is -NH(C_1-C_6 alkyl) or -NH-N(C_1-C_6 alkyl)$_2$, wherein one and only one C_1-C_6 alkyl is optionally substituted by CO_2H, or an ester thereof, or by an optionally substituted phenyl; and

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the composition structure.

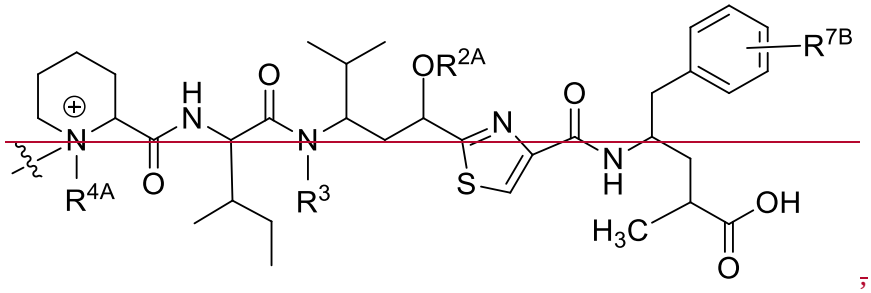
29. The LDC composition of claim 28 wherein $N(R^7)(R^7)$ is selected from the group consisting of -NH(CH_3), -$NHCH_2CH_2Ph$, and -$NHCH_2$-CO_2H, -$NHCH_2CH_2CO_2H$ and -$NHCH_2CH_2CH_2CO_2H$.

30. The LDC composition of claim 27 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



31. The LDC composition of any one of claims 26-30 wherein the O-linked substituent –OR^{2A} is other than –OH (i.e., R^{2A} is not hydrogen).

32. The LDC composition of claim 30 wherein the quaternized tubulysin Drug Unit –D^+ has the structure of:



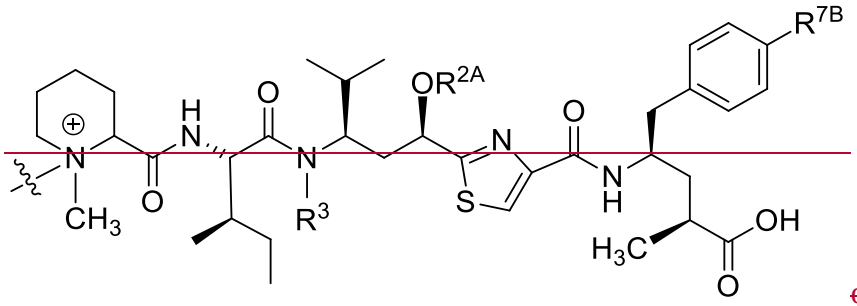
wherein R^{4A} is methyl;

R^3 is H, methyl, ethyl, propyl, -CH_2-$OC(O)R^{3A}$, -CH2$CH(R^{3B})C(O)R^{3A}$ or –$CH(R^{3B})C(O)NHR^{3A}$, wherein R^{3A} is C_1-C_6 alkyl and R^{3B} is H or C_1-C_6 alkyl, independently selected from R^{3A}; and

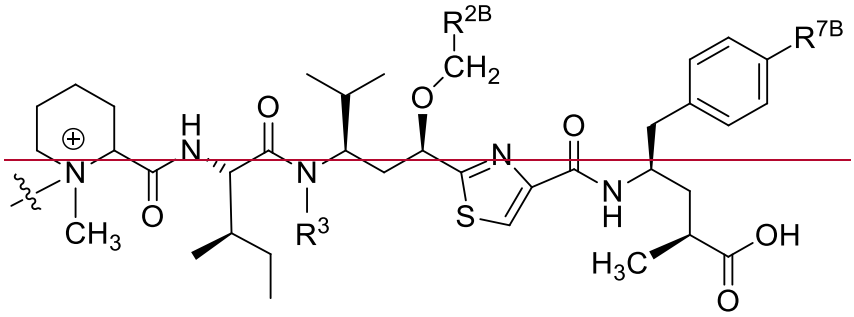
–OR^{2A} is an O-linked substituent selected from the group consisting of –OR^{2B}, –$OC(O)R^{2B}$ or –$OC(O)N(R^{2B})(R^{2C})$, wherein R^{2B} and R^{2C} is independently selected from the group consisting of H, C_1-C_6 alkyl and C_2-C_6 alkenyl; and

R^{7B} is hydrogen or –OH.

33. The LDC composition of claim 31 wherein the quaternized tubulysin Drug Unit –D^+ has the structure of:



or ,



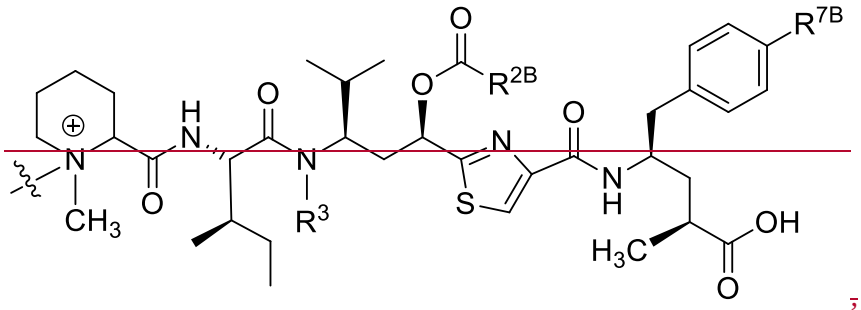
wherein R^{2A} and R^3 are independently selected from the group consisting of methyl, ethyl, propyl and iso-propyl;

R^{2B} is methyl, ethyl, propyl and iso-propyl or OR^{2A} is as previously defined;

R^3 is methyl, ethyl or propyl; and

R^{7B} is hydrogen or OH.

34. The LDC composition of claim 31 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



;

R^{2B} is methyl, ethyl, propyl, iso-propyl, 3-methyl-prop-1-yl, 3,3-dimethyl-prop-1-yl, or vinyl;

R^3 is methyl, ethyl or propyl; and

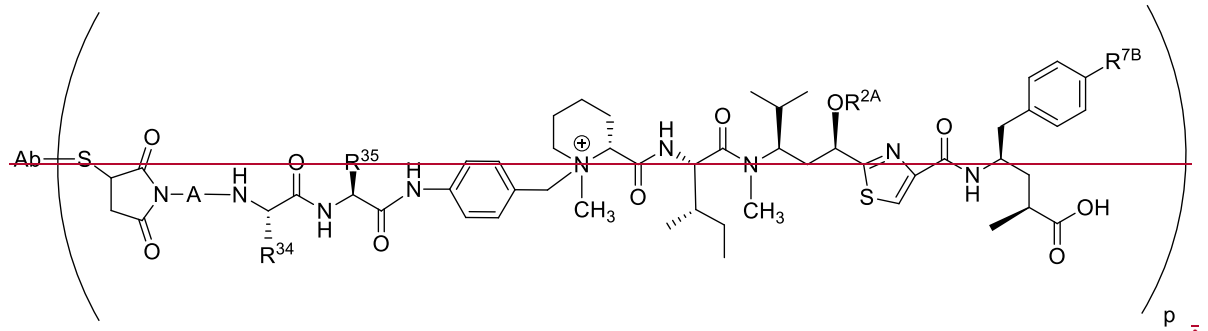
R^{7B} is hydrogen or OH.

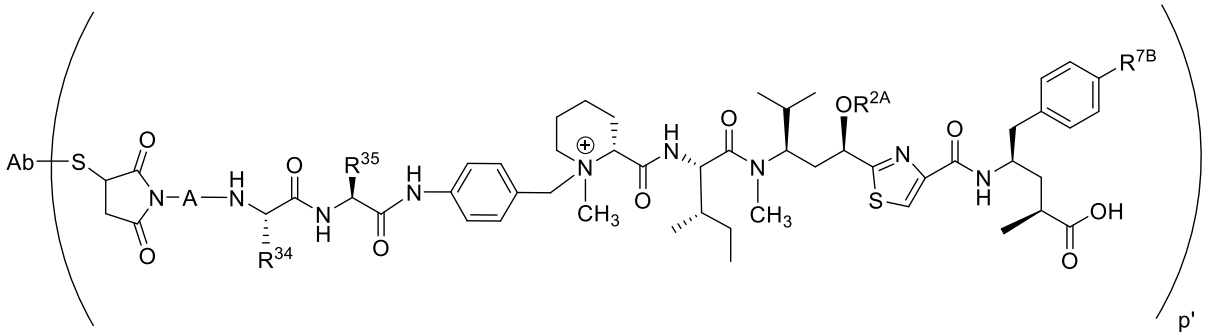
~~35. The LDC composition of claim 34 wherein R^{2B} is $-CH_3$, R^3 is $-CH_3$ and R^{7B} is H or $-OH$.~~

~~36. The LDC composition of any one of claims 26 to 32, wherein R^{2A} is $-CH_2CH3$,.~~

~~37. The LDC composition of claim 33 or 34 wherein R^{2B} is $-CH_3$, R^3 is $-CH_3$ and R^{7B} is H or $-OH$.~~

~~38~~12. The ~~LDC composition~~use of claim 1 wherein ~~thecomposition~~Formula 2A is represented by the structure of:





or a pharmaceutically acceptable salt thereof, wherein

wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit and the succinimide ring to which it is covalently attached is optionally in hydrolysed form;

R^{34} is isopropyl and R^{35} is $–CH_3$, isopropyl, $–CH_2CH_2CH_2NH(C=O)NH_2$, or $–CH_2CH_2CO_2H$;

R^{7B} is hydrogen or –OH;

~~R^{2A} is C_1-C_6 alkyl, C_2-C_6 alkenyl, $-OCH_2OR^{2B}$, $-C(=O)R^{2B}$ or $-C(=O)NHR^{2B}$, wherein R^{2B} is hydrogen, or C_1-C_6 alkyl; and~~

~~subscript p is anumber ranging from 1 to 8~~.

~~**39.** The LDC composition of claim 38 wherein~~

~~R^{34} is isopropyl and R^{35} is $-CH_3$, or $-CH_2CH_2CH_2NH(C=O)NH_2$;~~

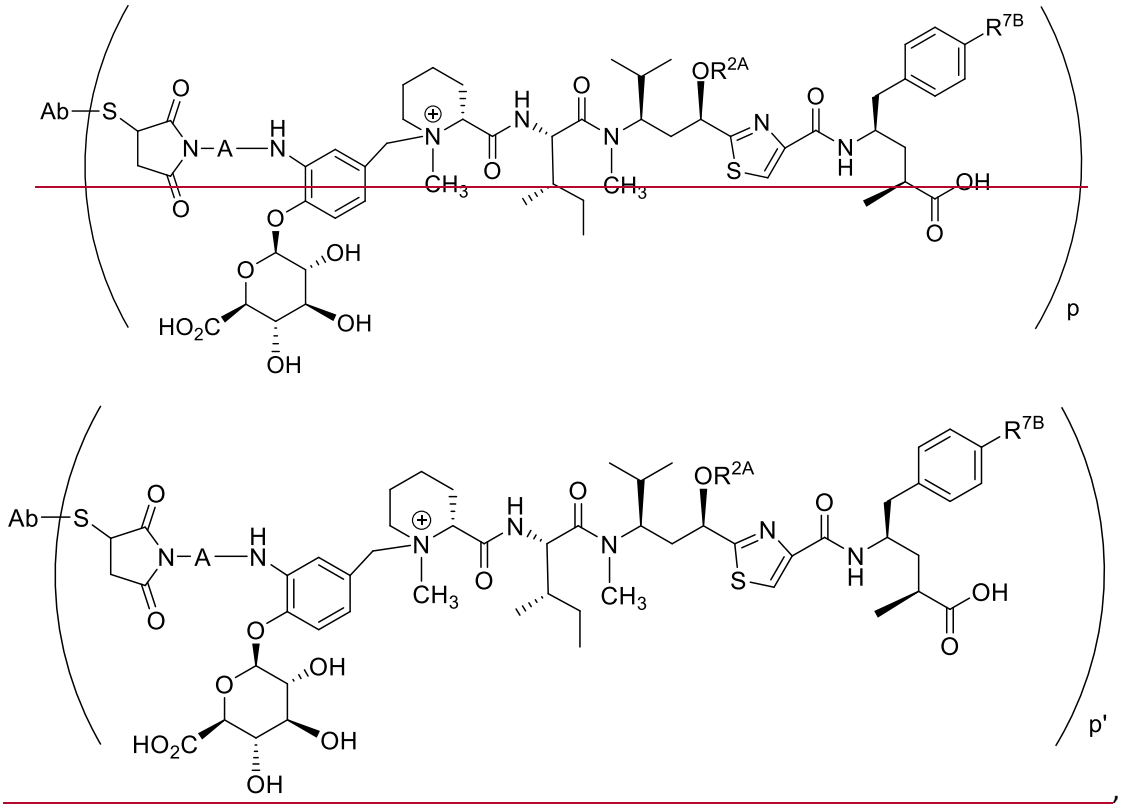
R^{7B} is hydrogen or –OH;

R^{2A} is lower alkyl, or –C(=O)R^{2B} ~~or $-C(=O)NHR^{2B}$~~, wherein R^{2B} is lower alkyl; and

subscript p' is an integer ~~number~~ ranging from 1 to 8~~.~~; and

A is $–CH_2(CH_2)_4(C=O)-$ or $–CH_2(CH_2)_4(C=O)NHCH_2CH_2(C=O)-$, and

~~**40.** The LDC composition of claim 1~~ wherein Formula 3F ~~the composition~~ is represented by the structure of:



,

or a pharmaceutically acceptable salt thereof, wherein

wherein Ab is an antibody Ligand Unit and the succinimide ring to which it is covalently attached is optionally in hydrolysed form;

S is a sulfur atom of the antibody Ligand Unit;

R^{7B} is hydrogen or –OH;

R^{2A} is C_1-C_6 alkyl, $-OCH_2OR^{2B}$, $-C(=O)R^{2B}$ ~~or $-C(=O)NHR^{2B}$~~, wherein R^{2B} is C_1-C_6 alkyl or C_2-C_6 alkenyl; and

subscript p' is an integer ~~number~~ ranging from 1 to 8.

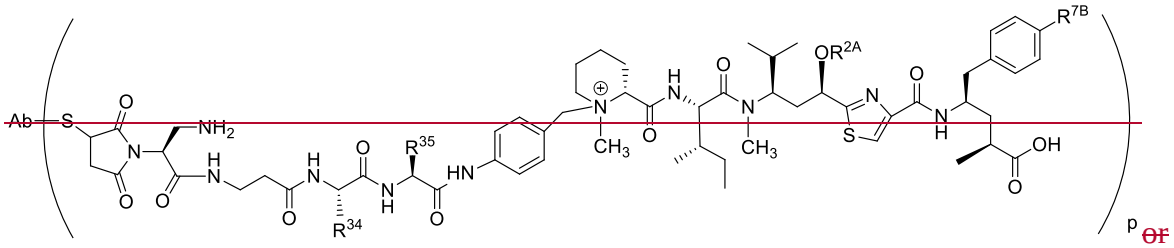
~~**41.** The LDC composition of claim 40 wherein~~

~~R^{7B} is hydrogen or –OH;~~

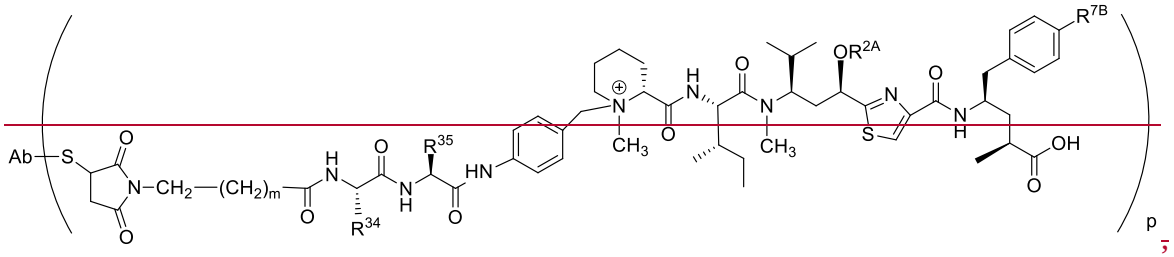
~~R^{2A} is lower alkyl, $-C(=O)R^{2B}$ or $-C(=O)NHR^{2B}$, wherein R^{2B} is lower alkyl; and~~

~~subscript p is a number ranging from 1 to 8.~~

~~**42.** The LDC composition of claim 38 wherein the structure of the composition is represented by the structure of:~~



~~or~~



~~;~~

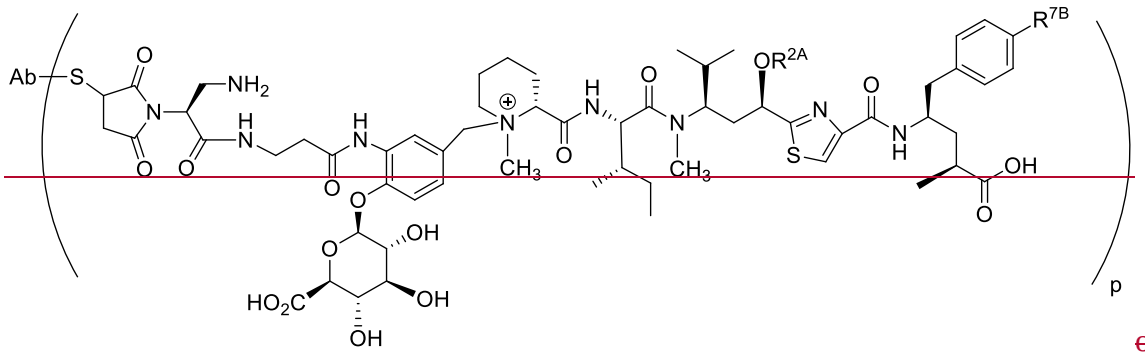
~~wherein Ab is an antibody Ligand Unit;~~

~~S is a sulfur atom of the antibody Ligand Unit;~~

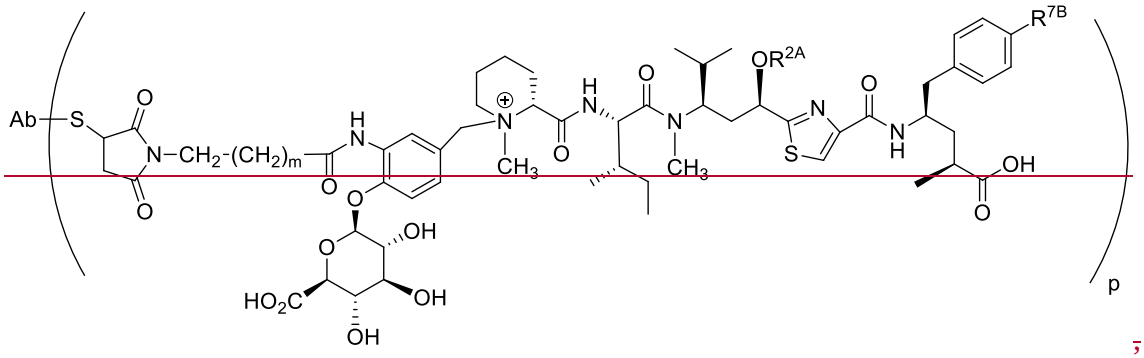
~~subscript p is an number ranging from 1 to 8; and~~

~~subscript m is 4.~~

43. The LDC composition of claim 40 wherein the structure of the composition is represented by the structure of:



or



;

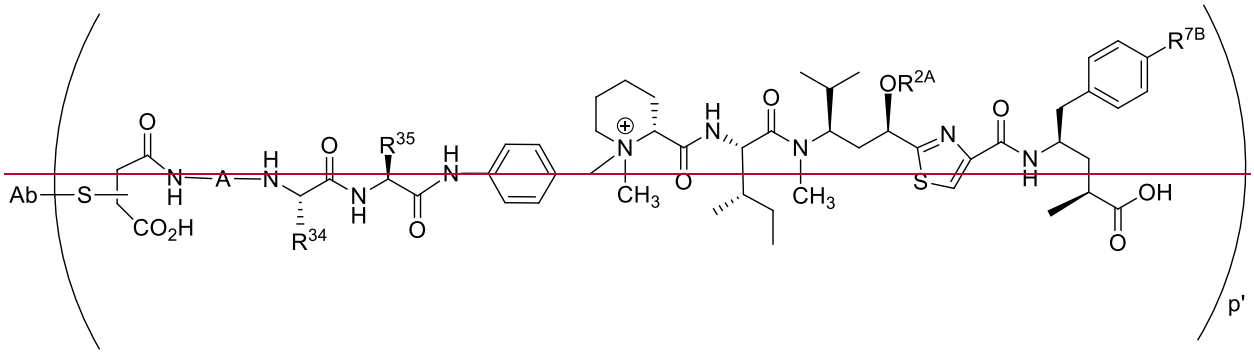
wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

subscript p is an number ranging from 1 to 8; and

subscript m is 4.

44. The LDC composition of claim 1 wherein each Ligand Drug Conjugate compound of the composition is represented by the structure of:



wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

the Ab-S- moiety is bonded to the carbon α or β to the carboxylic acid;

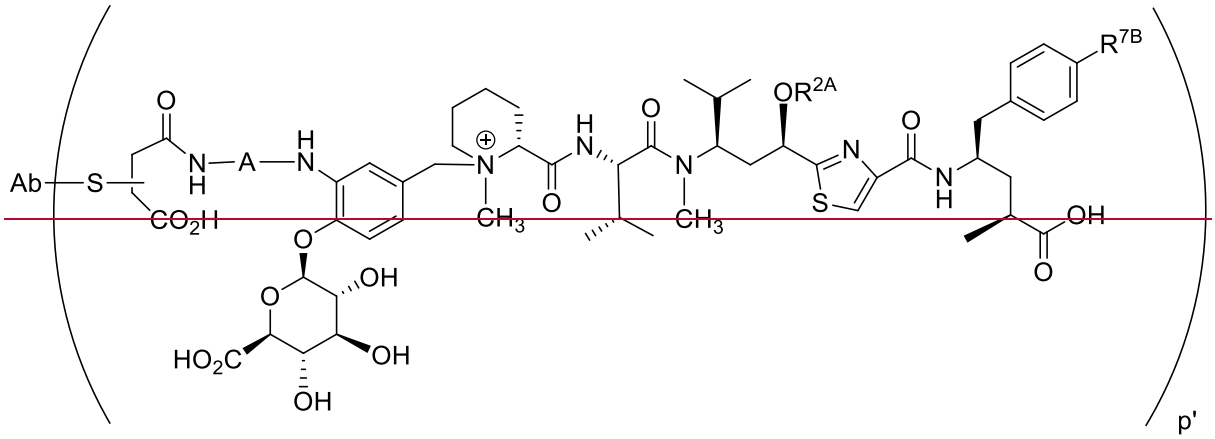
R^{34} is isopropyl and R^{35} is CH_3 or $CH_2CH_2CH_2NH(C=O)NH_2$;

R^{7B} is hydrogen or OH;

R^{2A} is lower alkyl, $C(=O)R^{2B}$ or $C(=O)NHR^{2B}$, wherein R^{2B} is lower alkyl; and

subscript p' is an integer ranging from 1 to 8.

45. The LDC composition of claim 1 wherein each Ligand Drug Conjugate compound of the composition is represented by the structure of:



wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

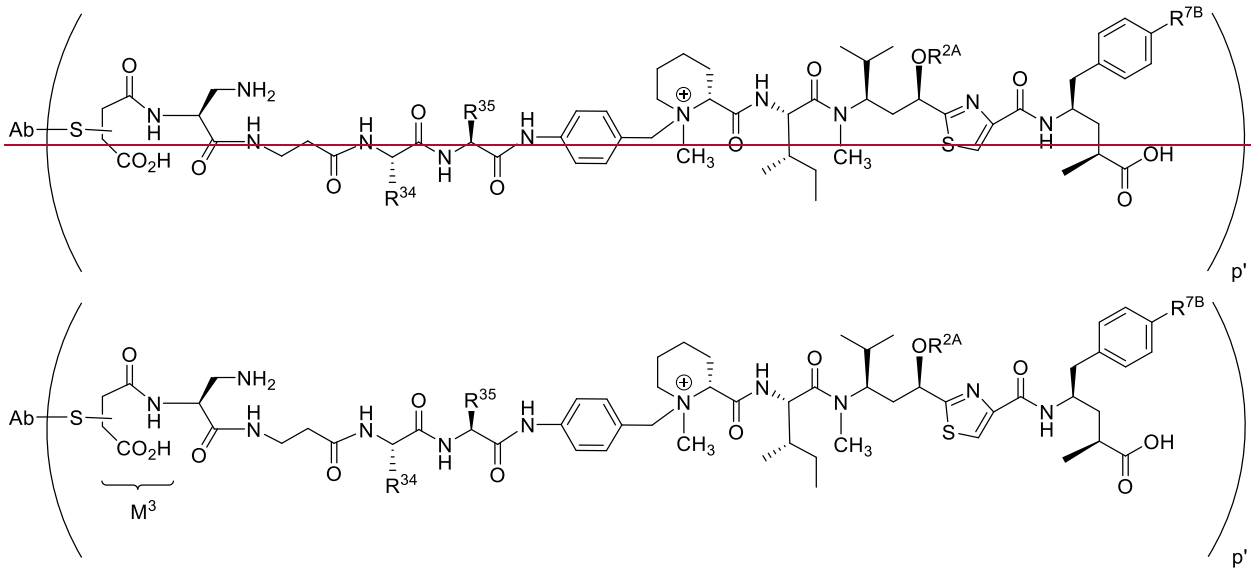
the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;

R^{7B} is hydrogen or OH;

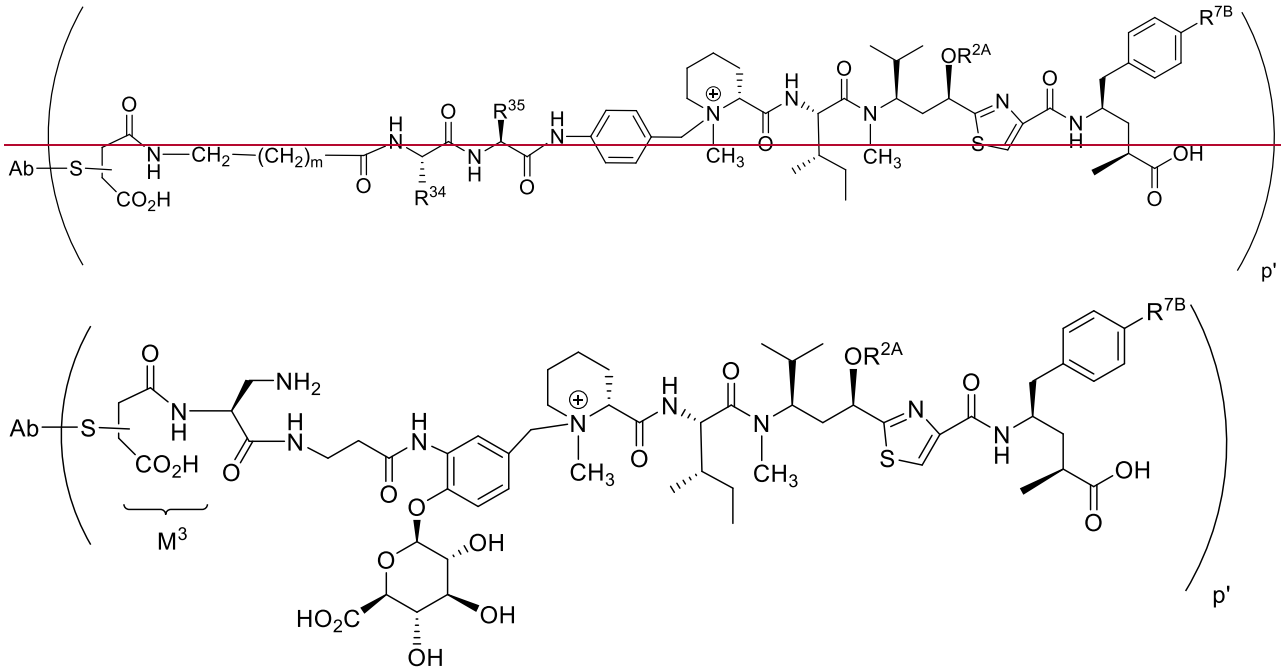
R^{2A} is lower alkyl, $C(=O)R^{2B}$ or $C(=O)NHR^{2B}$, wherein R^{2B} is lower alkyl;

~~and subscript 'p' is an integer ranging from 1 to 8.~~

~~46~~13. The ~~LDC composition~~use of claim ~~44~~ 1, wherein ~~each~~ the Ligand Drug Conjugate compound ~~of the composition~~ is represented by the structure of:



or



or a pharmaceutically acceptable salt thereof, wherein

wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;

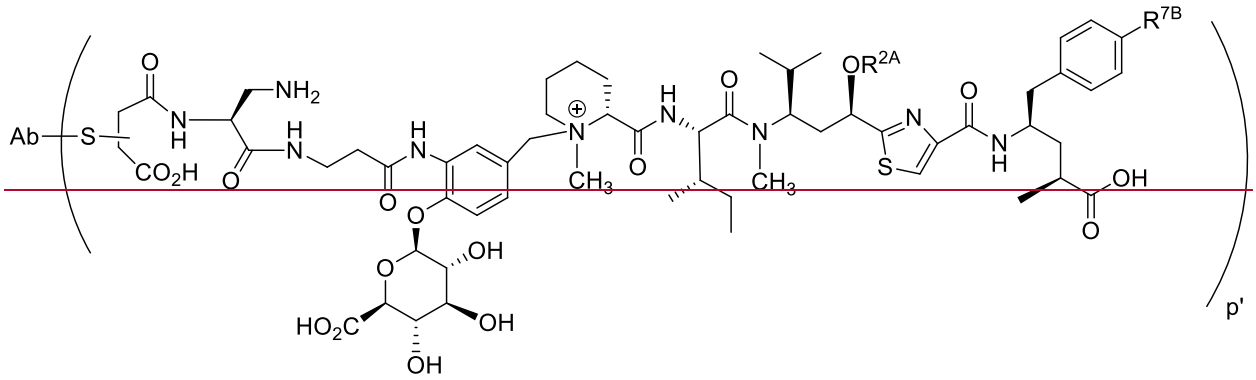
subscript p' is an integer ranging from 1 to 8; ~~and~~

~~subscript m is 4~~

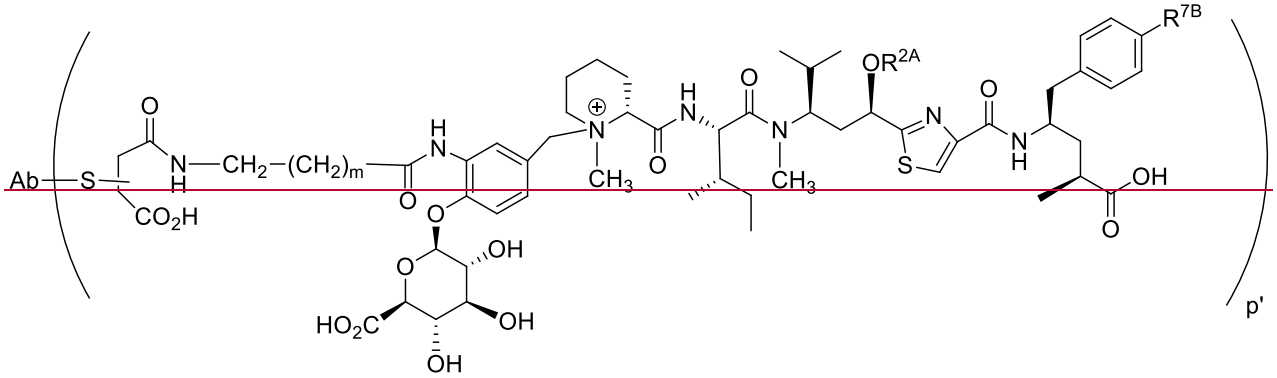
R^{7B} substituent is hydrogen or –OH;

R^{34} is isopropyl and R^{35} is $–CH_3$, isopropyl, $–CH_2CH_2CH_2NH(C=O)NH_2$, or $–CH_2CH_2CO_2H$; and~~.~~

~~**47.** The LDC composition of claim 45 wherein each Ligand Drug Conjugate compound of the composition is represented by the structure of:~~



~~or~~



~~wherein Ab is an antibody Ligand Unit;~~

~~S is a sulfur atom of the antibody Ligand Unit;~~

~~the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;~~

~~subscript p' is an integer ranging from 1 to 8; and~~

~~subscript m is 4.~~

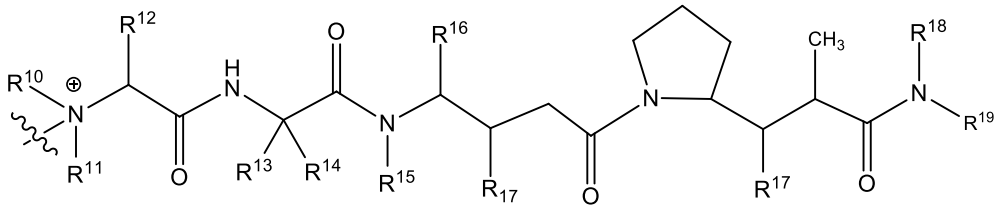
~~**48**. The LDC composition of any one of claims 37-40, 43 and 44 wherein A is $-CH_2(CH_2)_4(C=O)-$ or $-CH_2(CH_2)_4(C=O)NHCH_2CH_2(C=O)-$.~~

~~**49**. The LDC composition of any one of claims 38-48 wherein~~ R^{2A} is $-C(O)CH_3$, methyl, ethyl, or propyl.

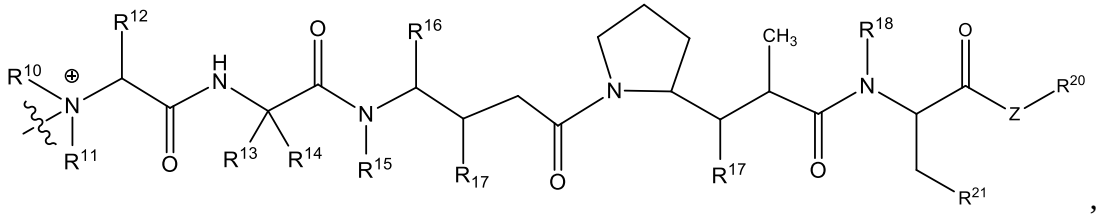
~~**50.** The LDC composition of claim 1 wherein $-D^+$ is a quaternized auristatin Drug Unit or a quaternized dolastatin Drug Unit.~~

~~**51**~~**14**. The ~~LDC composition~~use of claim ~~51~~ 1 wherein the quaternized tertiary amine-containing tubulin disrupting agent $-D^+$ is a ~~dolastatin Drug Unit is~~ quaternized dolastatin 10 or quaternized dolastatin 15, or~~.~~

~~**52.** The LDC composition of claim 50 wherein the~~ a quaternized auristatin ~~Drug unit $-D^+$ has~~ having the structure of D_E' or D_F':



(D_E'),



(D_F'),

or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment of $-D^+$ to the benzylic carbon atom of the $-C(R^8)(R^9)-$ moiety of Formula 2A or Formula 2F;

~~wherein~~ R^{10} and R^{11} are each independently C_1-C_8 alkyl;

R^{12} is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, aryl, -X^1-aryl, -X^1-(C_3-C_8 cycloalkyl), C_3-C_8 heterocycle, or -X^1-(C_3-C_8 heterocycle);

R^{13} is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, aryl, -X^1-aryl, -X^1-(C_3-C_8 cycloalkyl), C_3-C_8 heterocycle, or ~~and~~ -X^1-(C_3-C_8 heterocycle);

R^{14} is hydrogen or methyl;

or R^{13} and R^{14} taken together with the carbon to which they are attached comprise a C_3-C_8 cycloalkyl;

R^{15} is hydrogen or C_1-C_8 alkyl;

R^{16} is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, aryl, -X^1-aryl, -X^1-(C_3-C_8 cycloalkyl), C_3-C_8 heterocycle, or ~~and~~ -X^1-(C_3-C_8 heterocycle);

each R^{17} is independently ~~are~~ hydrogen, -OH, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or ~~and~~ O-(C_1-C_8 alkyl);

each R^{18} is independently ~~are~~ hydrogen or C_1-C_8 alkyl;

R^{19} is –$C(R^{19A})_2$–$C(R^{19A})_2$–aryl, –$C(R^{19A})_2$–$C(R^{19A})_2$–(C_3-C_8 heterocycle), or –$C(R^{19A})_2$–$C(R^{19A})_2$–(C_3-C_8 cycloalkyl)~~; , R^{21} is aryl or C_3-C_8 heterocycle;~~ wherein R^{19A} is hydrogen, C_1-C_8 alkyl, or –OH;

R^{20} is hydrogen, C_1-C_{20} alkyl, aryl, C_3-C_8 heterocycle, -$(R^{47}O)_m$-R^{48}, and -$(R^{47}O)_m$-$CH(R^{49})_2$;

R^{21} is aryl or C_3-C_8 heterocycle;

subscript m is an integer ranging from 1-1000;

R^{47} is C_2-C_8 alkyl;

R^{48} is hydrogen or C_1-C_8 alkyl;

each R^{49} is independently ~~are~~ -COOH, –$(CH_2)_n$-$N(R^{50})_2$, –$(CH_2)_n$-SO_3H, or –$(CH_2)_n$-SO_3-C_1-C_8 alkyl;

each R^{50} is independently ~~are~~ C_1-C_8 alkyl, or –$(CH_2)_n$-COOH;

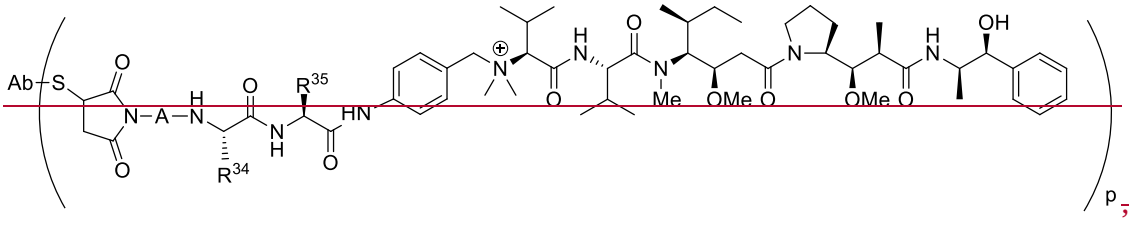
Z is O, S, NH, or NR^{46}, wherein R^{46} is C_1-C_8 alkyl;

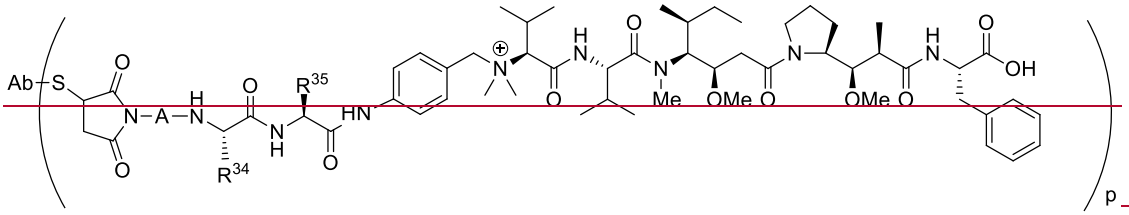
X^1 is C_1-C_{10} alkylene; and

subscript n is an integer ranging from 0 to 6~~;~~

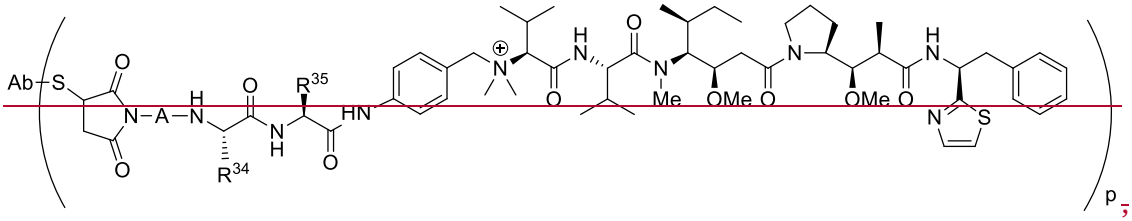
~~wherein the wavy line indicates covalent bonding of D^+ to the remainder of the composition structure~~.

53. The LDC composition of claim 52 wherein the composition is represented by the structure of





or



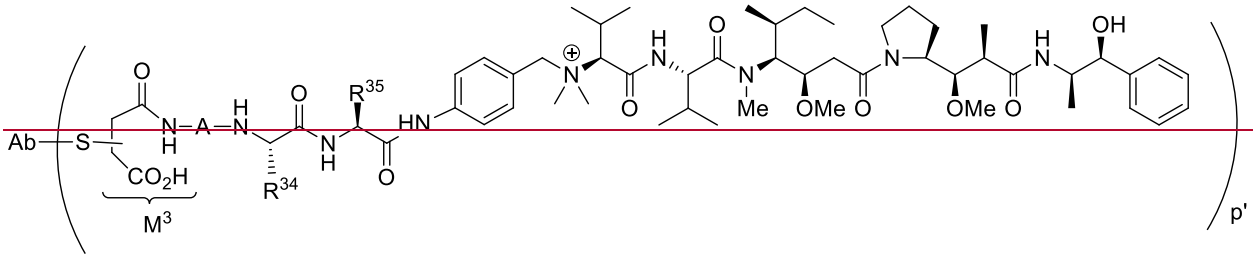
wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

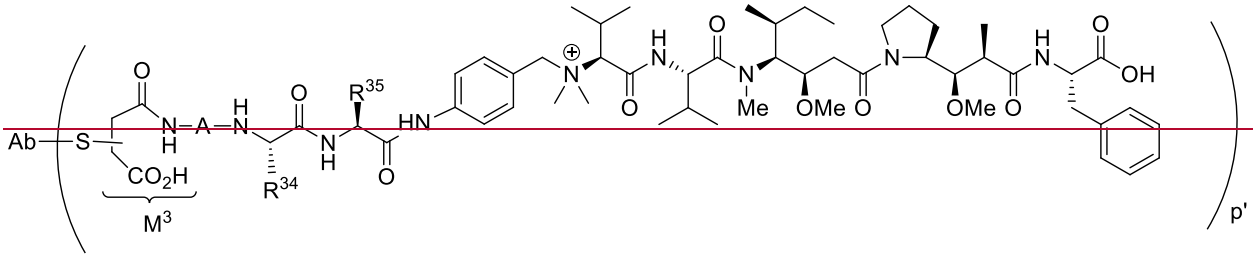
R^{34} is isopropyl and R^{35} is CH_3 or $CH_2CH_2CH_2NH(C{=}O)NH_2$; and

subscript p is a number ranging from 1 to 8.

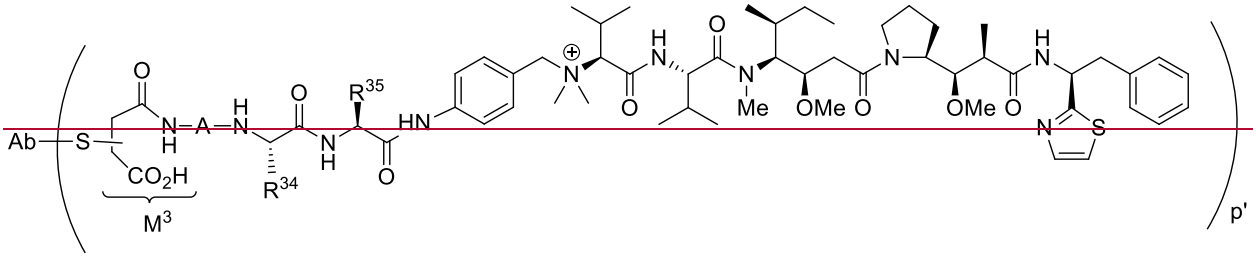
54. The LDC composition of claim 52 wherein each Ligand Drug Conjugate compound of the composition is represented by the structure of:



,



or



;

wherein Ab is an antibody Ligand Unit;

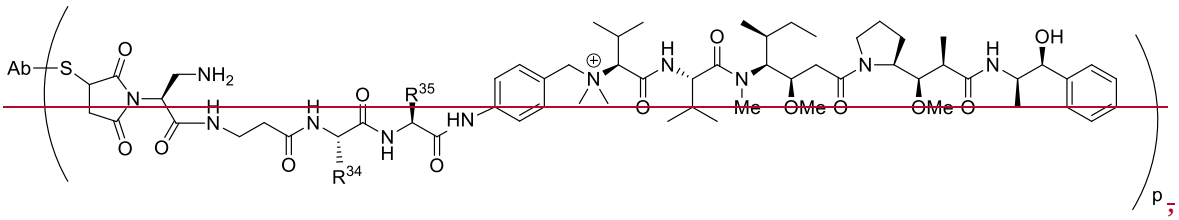
S is a sulfur atom of the antibody Ligand Unit;

the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;

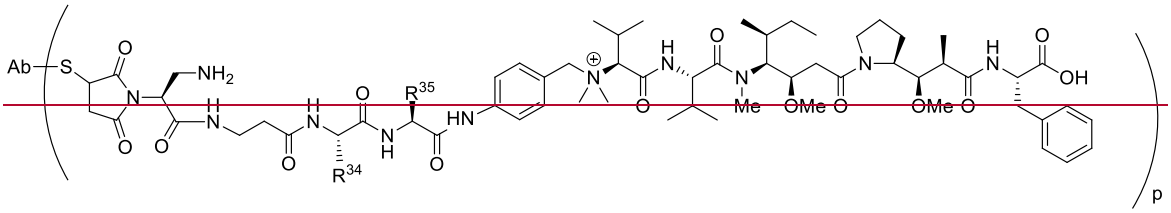
R^{34} is isopropyl and R^{35} is CH_3 or $CH_2CH_2CH_2NH(C{=}O)NH_2$;

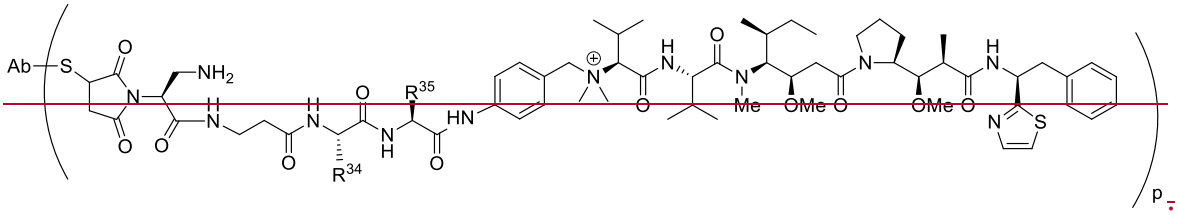
and subscript p' is an integer ranging from 1 to 8.

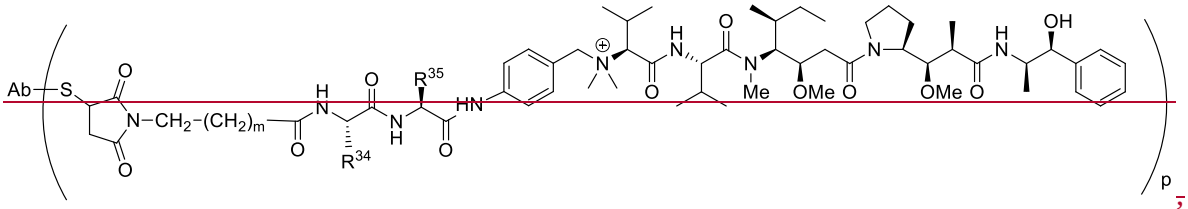
55. The LDC composition of claim 53 wherein the composition is represented by the structure of:

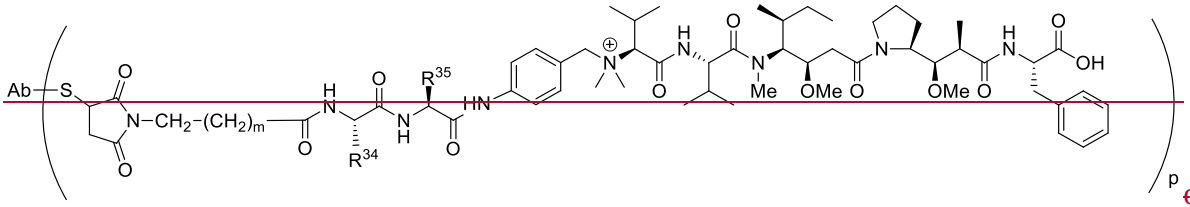


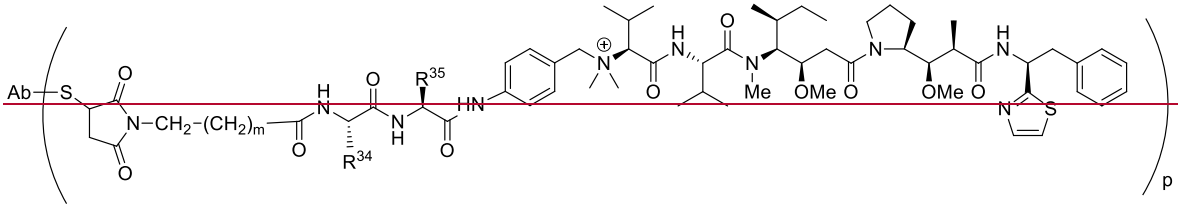
;











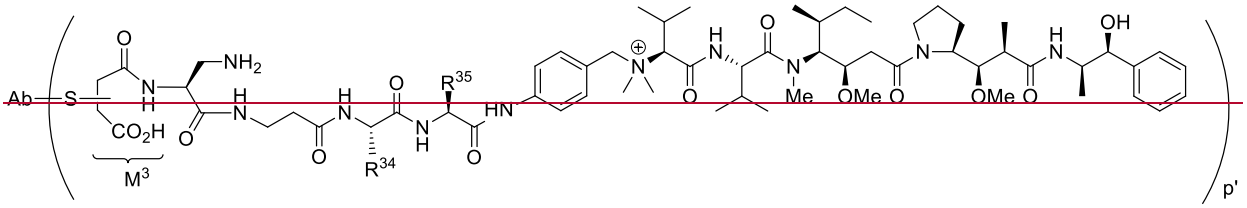
~~wherein Ab is an antibody Ligand Unit;~~

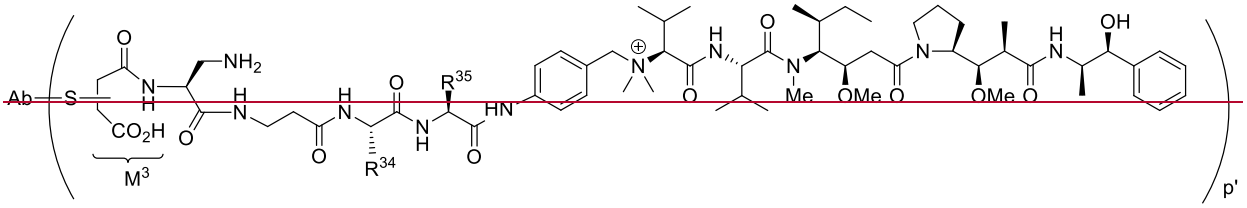
~~S is a sulfur atom of the antibody Ligand Unit;~~

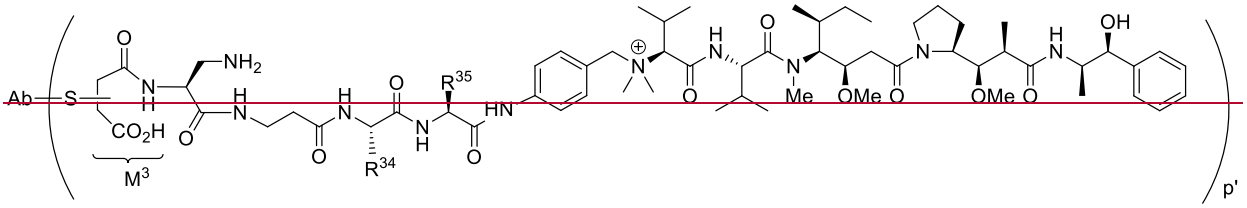
~~supbscript p is an number ranging from 1 to 8; and~~

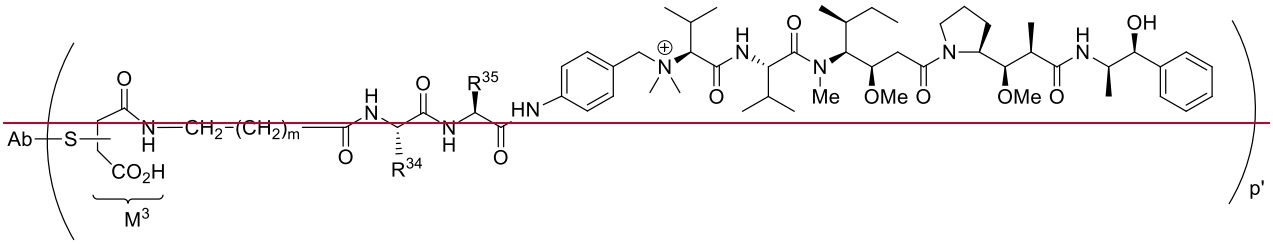
~~subscript m is 4.~~

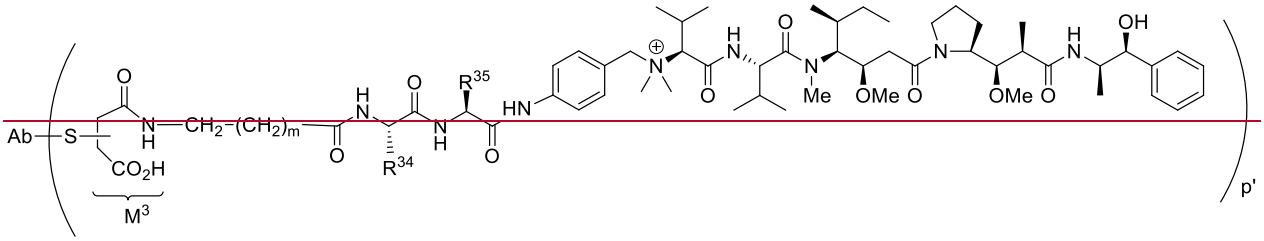
~~**56**. The LDC composition of claim 53 wherein each Ligand Drug Conjugate compound of the composition is represented by the structure of:~~



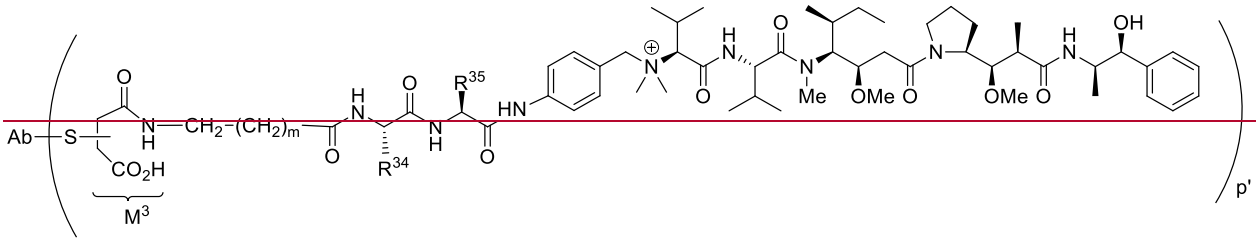








or



wherein Ab is an antibody Ligand Unit;

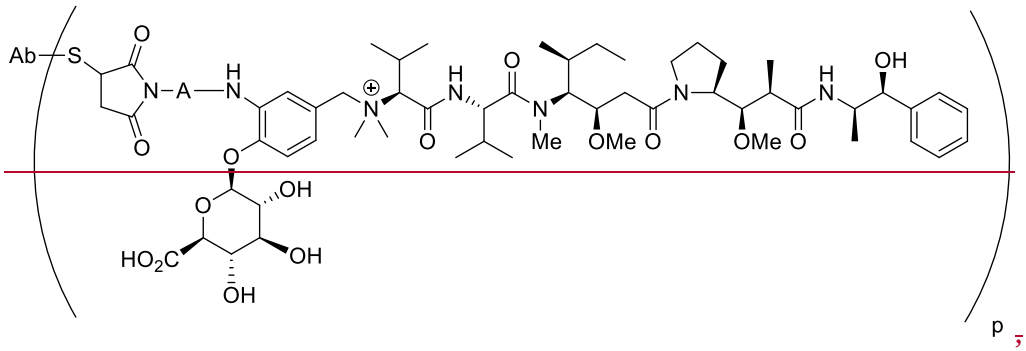
S is a sulfur atom of the antibody Ligand Unit;

~~the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;~~

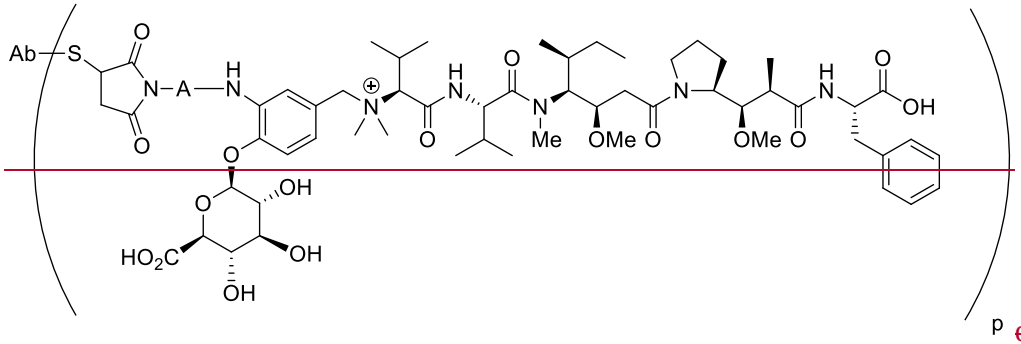
~~supbscript p' is an integer ranging from 1 to 8; and~~

~~subscript m is 4.~~

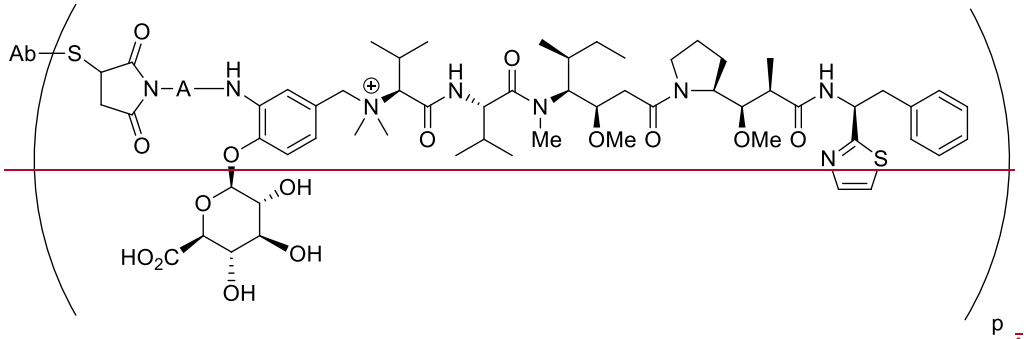
~~57. The LDC composition of claim 52 wherein the structure of the composition is represented by the structure of:~~



~~,~~



~~or~~



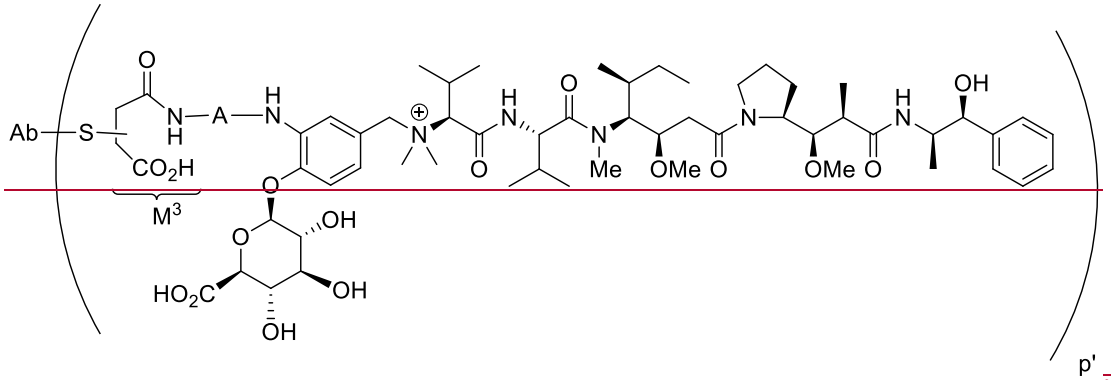
~~,~~

~~wherein Ab is an antibody Ligand Unit;~~

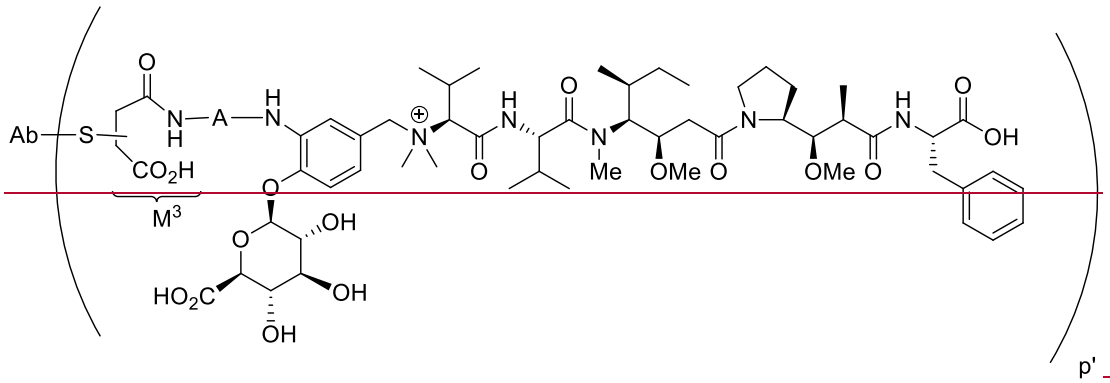
~~S is a sulfur atom of the antibody Ligand Unit; and~~

~~subscript p is an number ranging from 1 to 8.~~

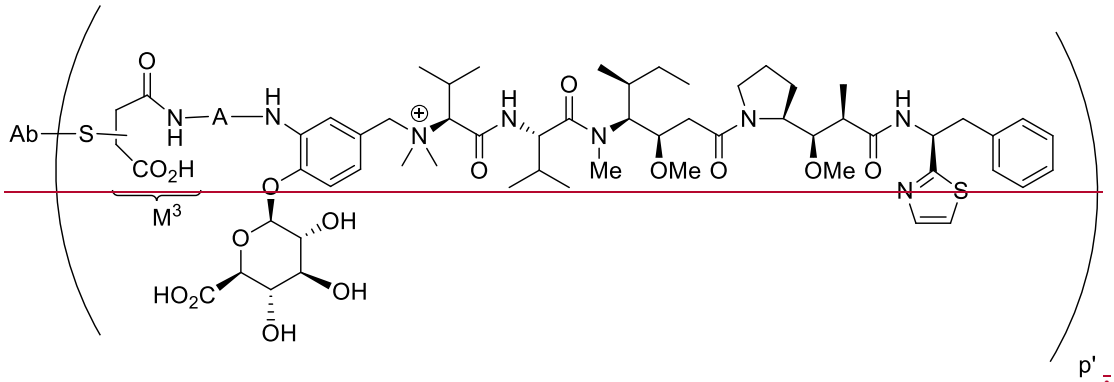
58. The LDC composition of claim 52 wherein each Ligand Drug Conjugate compound of the composition is represented by the structure of:



p' ;



p' or



p' ;

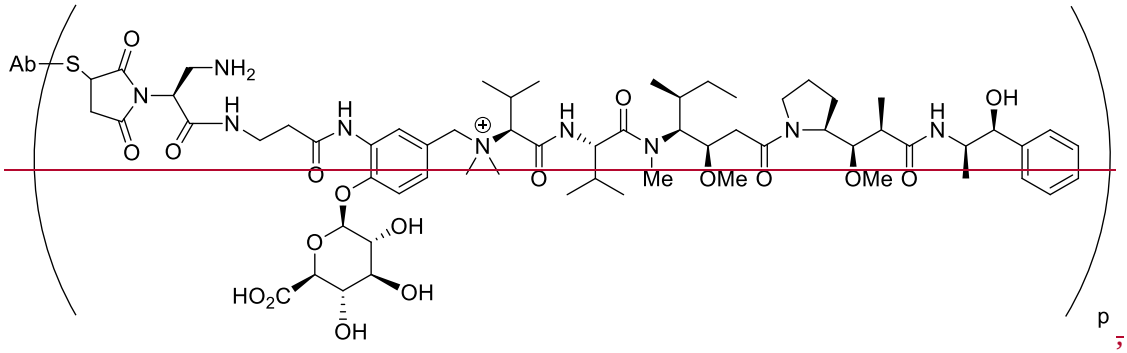
wherein Ab is an antibody Ligand Unit;

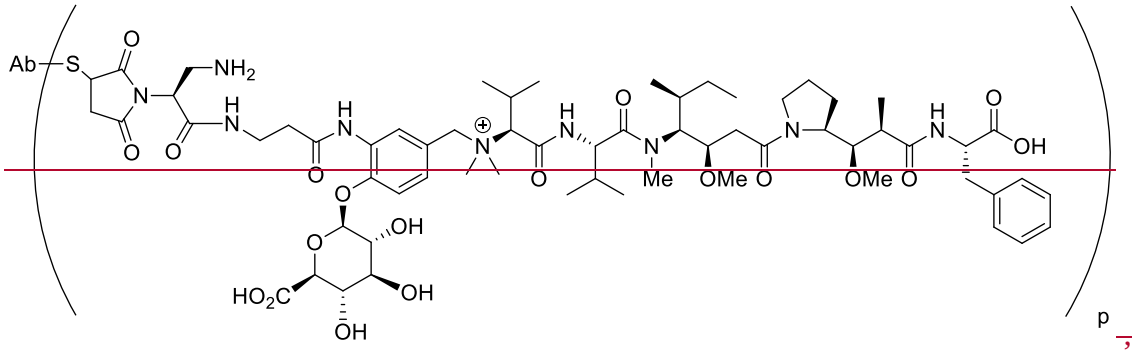
S is a sulfur atom of the antibody Ligand Unit;

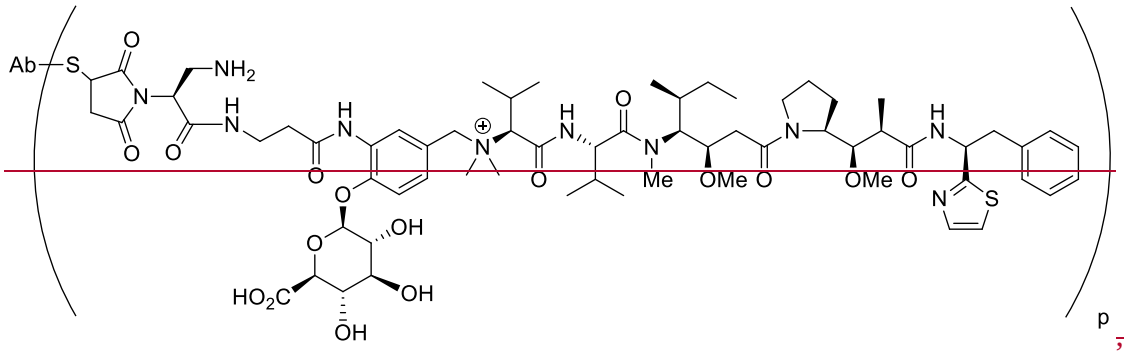
the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid; and

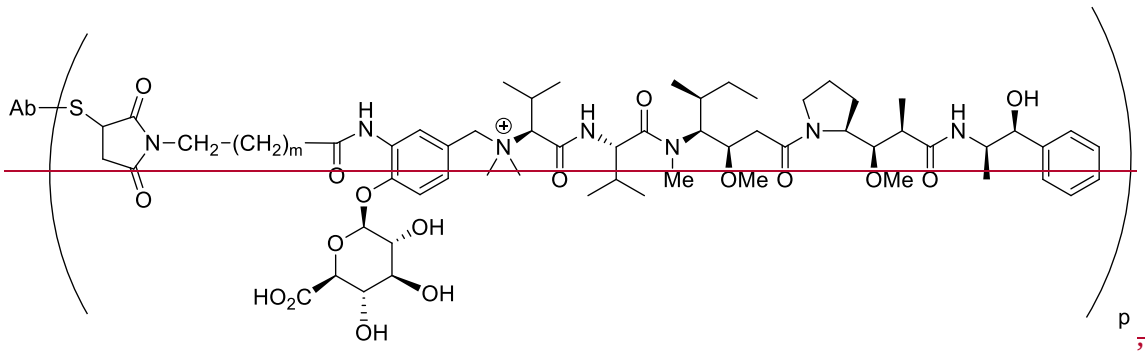
subscript p' is an integer ranging from 1 to 8.

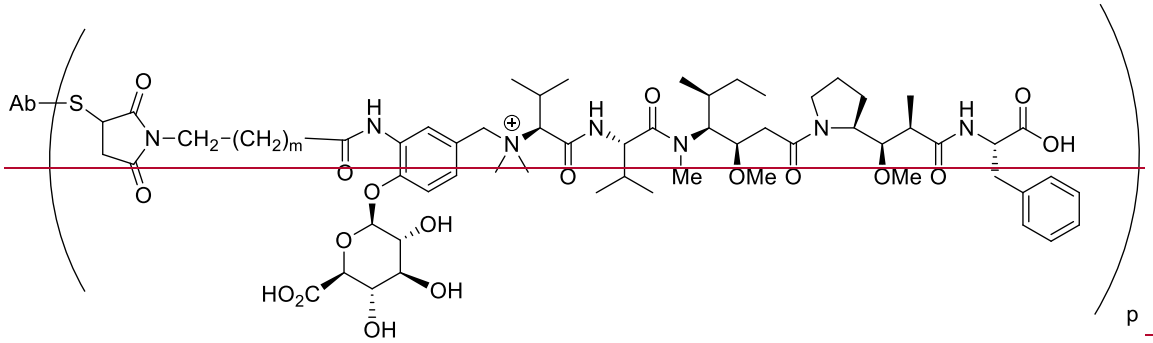
59. The LDC composition of claim 57 wherein the structure of the Formula 1 composition is represented by the structure of:



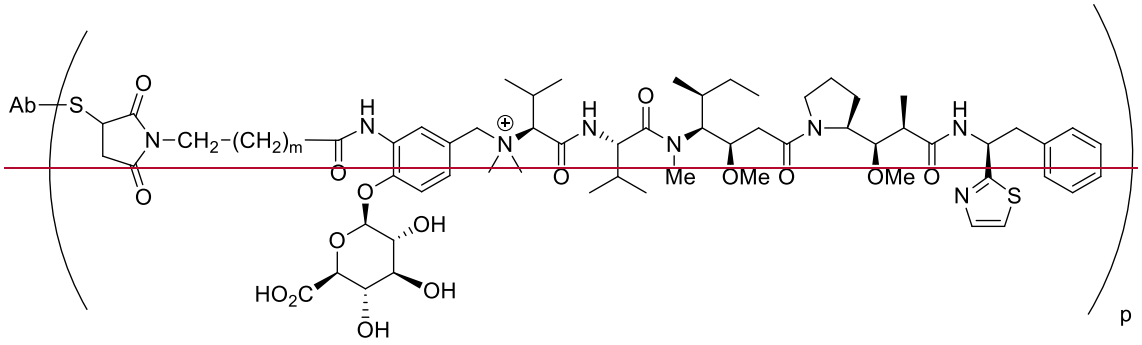








~~or~~

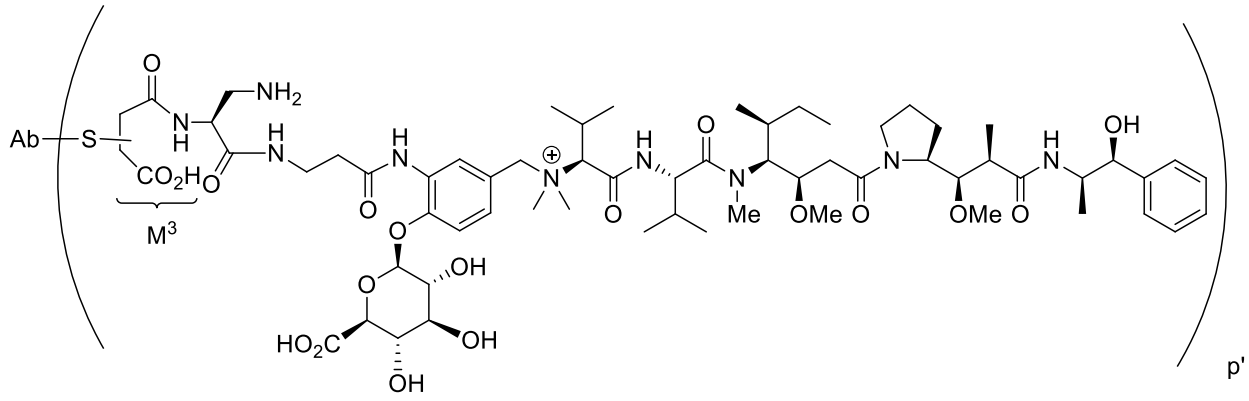


~~wherein Ab is an antibody Ligand Unit;~~

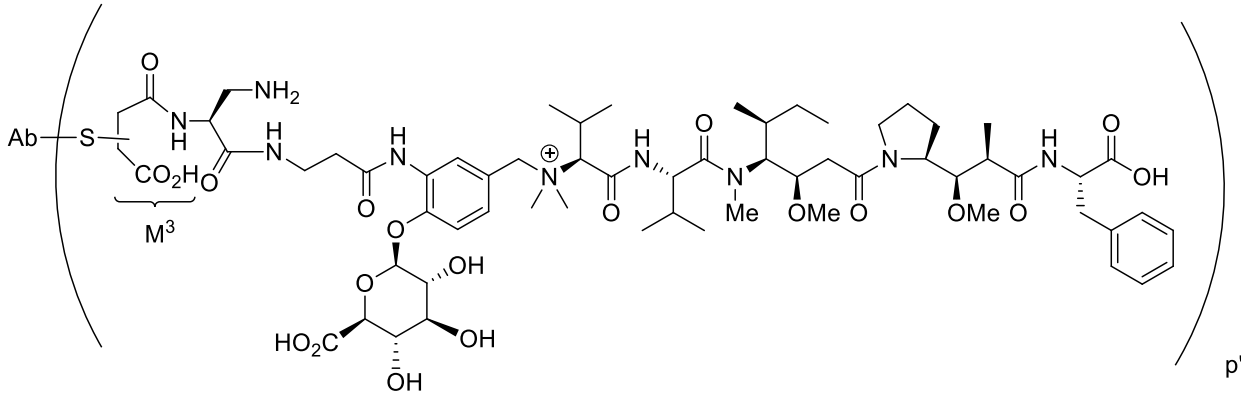
~~S is a sulfur atom of the antibody Ligand Unit;~~

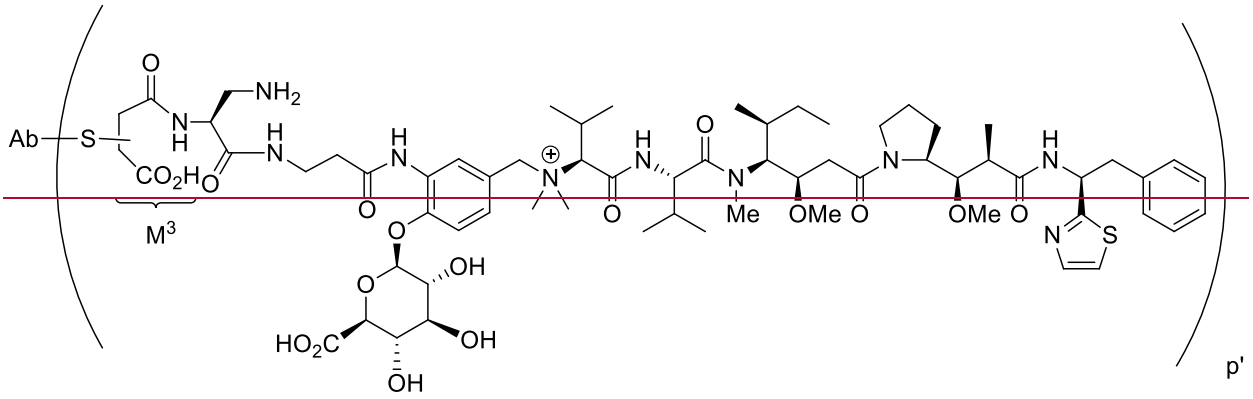
~~and subscript p is a number ranging from 1 to 8.~~

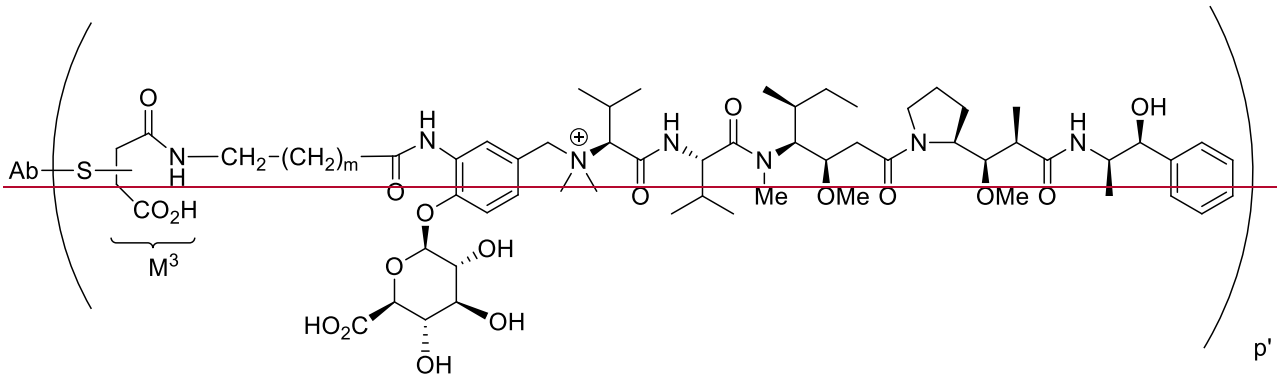
~~60~~**15**. The ~~LDC composition~~use of claim ~~58~~ 14, wherein each Ligand Drug Conjugate compound ~~of the composition~~ is represented by ~~the structure of~~:

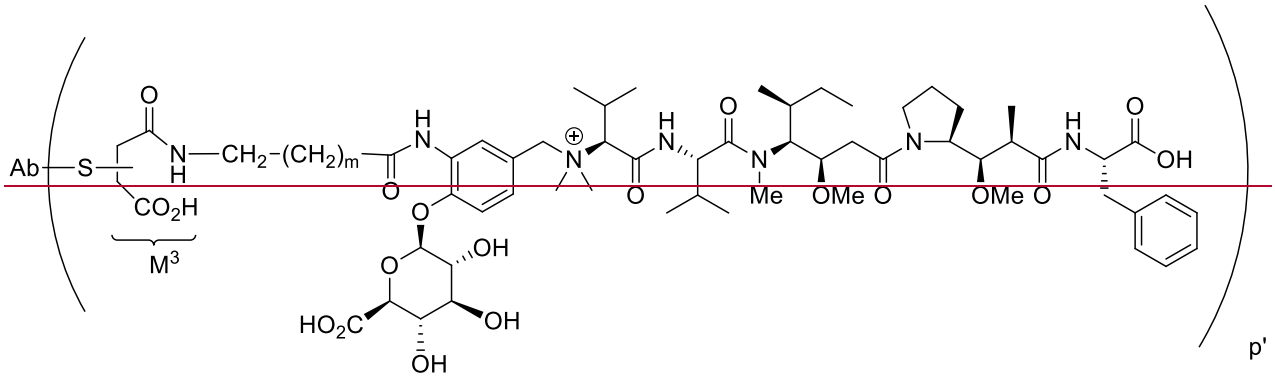


or

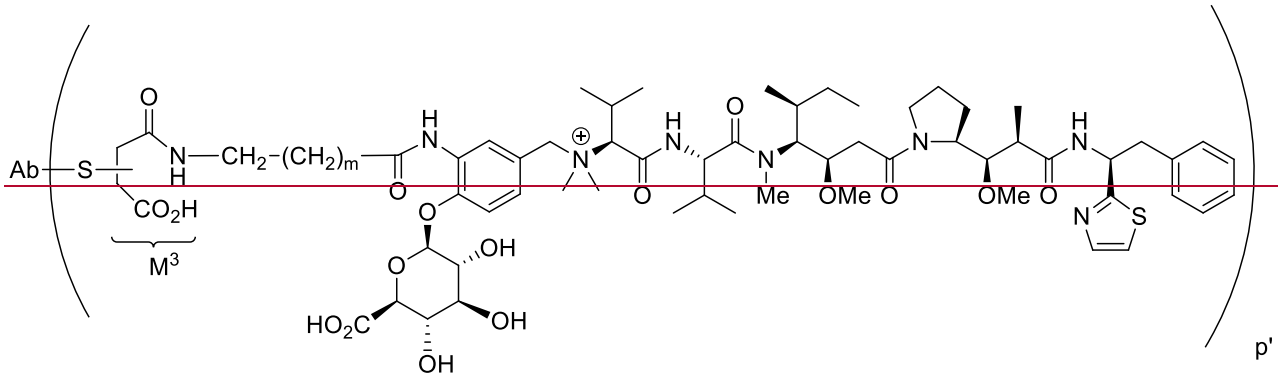

Ab
S
M3
NH2
CO2H
HO2C
OH
Me
OMe
p'


Ab
S
M3
NH2
CO2H
HO2C
OH
Me
OMe
N
S
p'


Ab
S
M3
CH2-(CH2)m
CO2H
HO2C
OH
Me
OMe
p'



or



or a pharmaceutically acceptable salt thereof, wherein

wherein Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid; and

subscript p' is an integer ranging from 1 to 8.

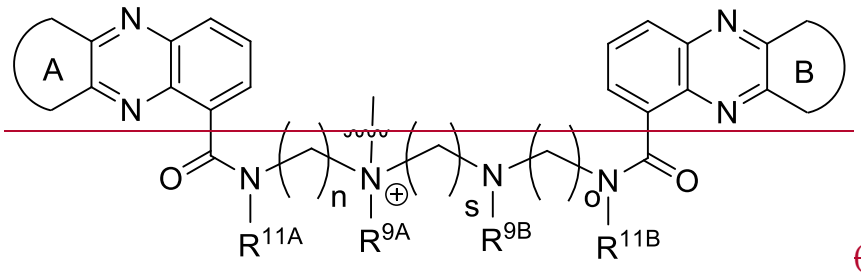
16. The use of any one of claims 5-8, 13, and 15, wherein the sulfur atom is from a cysteine residue of a reduced interchain disulfide bond of the antibody.

17. The use of claim 16, wherein the antibody is a monoclonal antibody.

18. The use of claim 17, wherein the monoclonal antibody is a chimeric antibody or a humanized antibody.

~~**61.** The LDC composition of claim 1 wherein D^+ is a quaternized phenazine dimer~~

62. The LDC composition of claim 61 wherein the quaternized phenazine dimer D^+ has the structure of D_I':



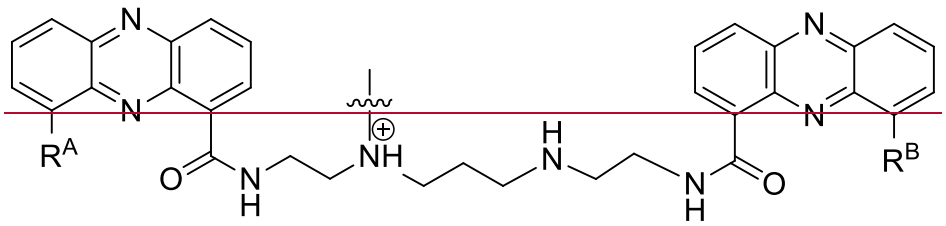
(D_I'),

wherein Ring A and Ring B are independently selected aryl or heteroaryl, optionally substituted on Ring A with one, two or three R^A substituents and/or optionally substituted on Ring B with one, two or three R^B substituents, fused to the phenazine ring systems wherein one phenazine ring system is optionally substituted with one, two or three independently selected R^C substituents and the other phenazine ring is optionally substituted with one, two or three independently selected R^D substituents, wherein R^A, R^B, R^C and R^D, when present, are, are independently halogen, optionally substituted alkyl or an O-linked substituent;

R^{9A} and R^{9B} are independently selected optional substituted alkyl or taken together with the nitrogen atoms to which they are attached and the intervening carbon atoms between these nitrogen comprise a heterocycloalkyl ring system and wherein n, s and o are independently integers ranging from 2 to 4;

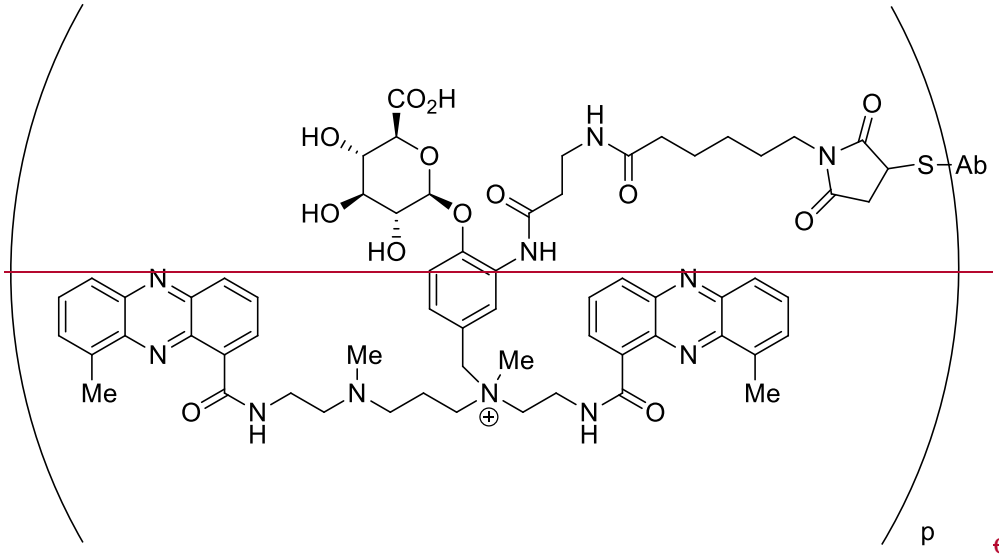
wherein the wavy line to N^+ indicates covalent bonding of D^+ to the remainder of the composition structure.

63. The LDC composition of claim 62 wherein quaternized phenazine dimer D^+ has the structure of

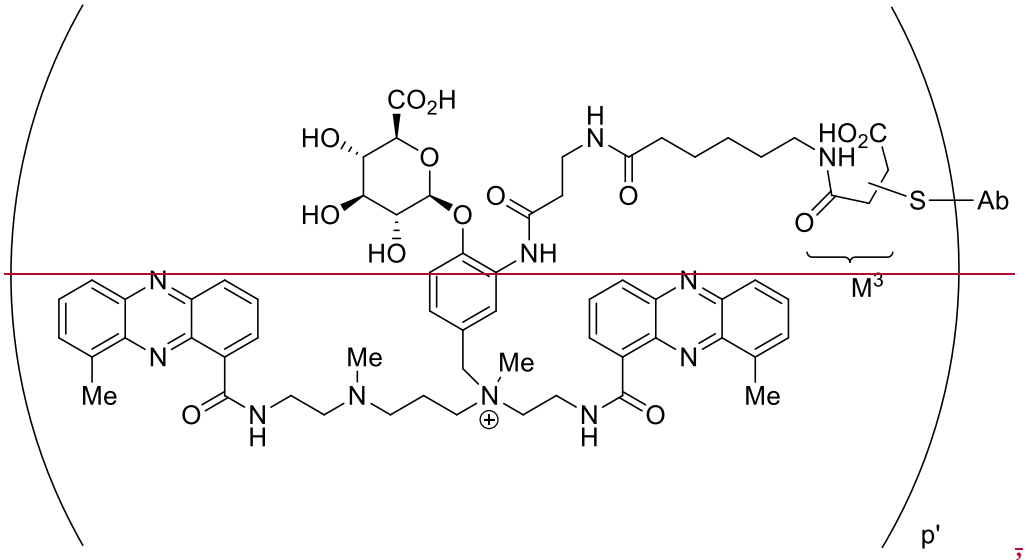


wherein R^A and R^B are present and are lower alkyl.

64. The LDC composition of claim 62 wherein the structure of the Formula 1 composition, or each LDC compound of the composition is represented by the structure of:



p or



p' ;

respectively, wherein

Ab is an antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

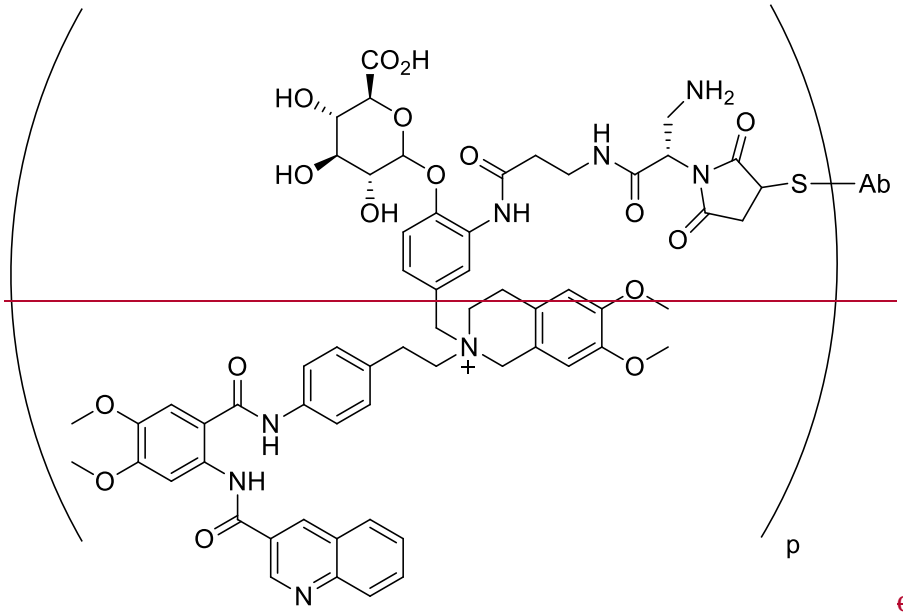
the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;

subscript p is a number ranging from 1 to 24; and

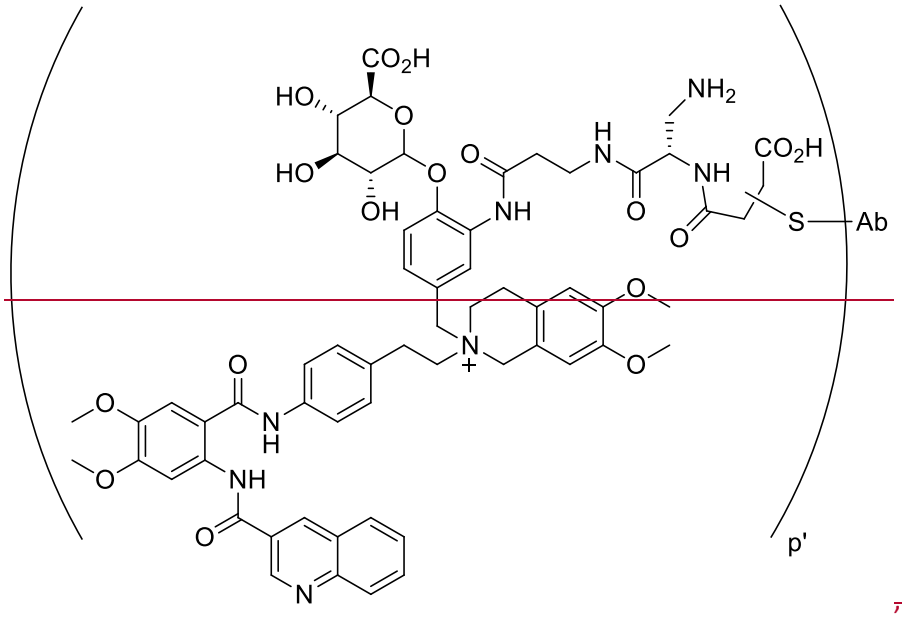
subscript p' is an integer from 1 to 24.

65. The LDC composition of claim 1 wherein D^+ is a quaternized MDR inhibitor having a isoquinoline substructure.

66. The LDC composition of claim 65 wherein the structure of the composition, or each Ligand Drug Conjugate compound of the composition is represented by the structure of:



or



, respectively, wherein

Ab is an antibody Ligand Unit;

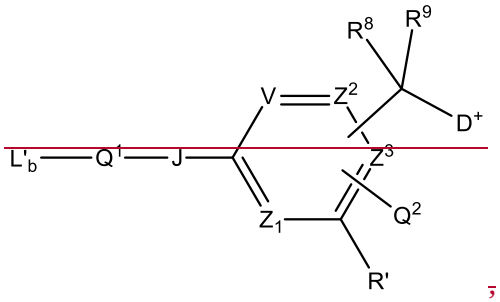
S is a sulfur atom of the antibody Ligand Unit;

the Ab-S- moiety is bonded to the carbon α or β to the M^3 carboxylic acid;

subscript p is a number ranging from 1 to 24; and

subscript p' is an integer ranging from 1 to 24.

67. A Drug-Linker compound wherein the compound has the structure of Formula I:



;

(Formula I)

wherein

L'_b is a ligand covalent binding moiety precursor;

Q^1 is A_a-W_w, wherein A is an optional Stretcher unit so that subscript a is 0 when A is absent or 1 when A is present and is optionally comprised of two, three or four subunits,;

Q^2 is $W'_{w'}$-E-, wherein Q^2, when present, is bonded to V, Z^1, Z^2 or Z^3;

W_w and $W'_{w'}$ are Cleavable units, wherein

W_w of Q^1 is capable of selective cleavage by an intracellular or regulatory protease in comparison to serum proteases, or by glutathione through disulfide exchange, or is more reactive to hydrolysis under lower pH (i.e., under more acidic) conditions present in lysosomes in comparison to physiological pH of serum,

W'-E of Q^2 provides a glycosidic bond cleavable by a glycosidase located intracellularly, and

subscript w is 0 or 1 so that W is absent when w is 0 or W is present when w is 1, and subscript w' is 0 or 1, wherein W'-E is absent when w' is 0 or W'-E is present when w' is 1, and wherein w + w' is 1 (i.e., one and only one of W, W' is present);

V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, $-NO_2$, -CN or other electron withdrawing group, an electron donating group,

~~$-Q^2$-, or $-C(R^8)(R^9)-D^+$, wherein at least one of V, Z^1, Z^2 and Z^3 is $=C(R^{24})-$ when w is 1, and at least two of V, Z^1, Z^2 and Z^3 are $=C(R^{24})-$ when w' is 1,~~

~~provided that when w is 1, Q^2 is absent and one and only one R^{24} is $-C(R^8)(R^9)-D^+$ so that $-C(R^8)(R^9)-D^+$ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is $=C(R^{24})-$ and the Q^1-J- and $-C(R^8)(R^9)-D^+$ substituents are *ortho* or *para* to each other,~~

~~provided that when w' is 1, one any only one R^{24} is $-C(R^8)(R^9)-D^+$ so that $-C(R^8)(R^9)-D^+$ is bonded to one of V, Z^1, Z^2, Z^3 when that variable group is $=C(R^{24})-$ and one and only one other R^{24} is Q^2 so that Q^2 is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is $=C(R^{24})-$, and the Q^2 and $-C(R^8)(R^9)-D^+$ substituents are *ortho* or *para* to each other;~~

~~R^8 and R^9 independently are hydrogen, alkyl, alkenyl or alkynyl, optionally substituted, or aryl or heteroaryl, optionally substituted;~~

~~R' is hydrogen or is halogen, $-NO_2$, -CN or other electron withdrawing group, or is an electron donating group;~~

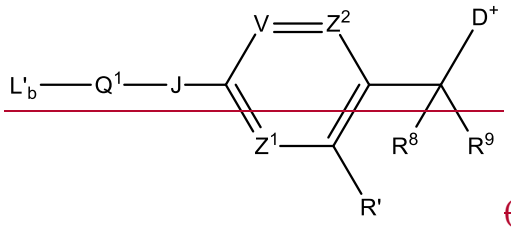
~~E and J independently are $-O-$, $-S-$ or $-N(R^{33})-$, wherein R^{33} is hydrogen or optionally substituted alkyl;~~

~~D^+ represents a structure of a quaternized tertiary amine-containing drug; and~~

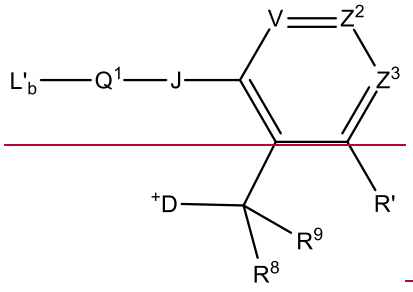
~~subscript p is a number ranging from 1 to 24; and~~

~~wherein said protease cleavage, disulfide exchange, acid hydrolysis or glycosidase cleavage results in expulsion of free tertiary amine-containing drug (D) from the Drug-Linker Compound, or a Ligand-Drug Conjugate compound or N-acetyl-cysteine Conjugate derived therefrom.~~

~~**68.** The Drug Linker compound of claim 67 wherein the compound has the structure of Formula IIA or Formula IIB:~~

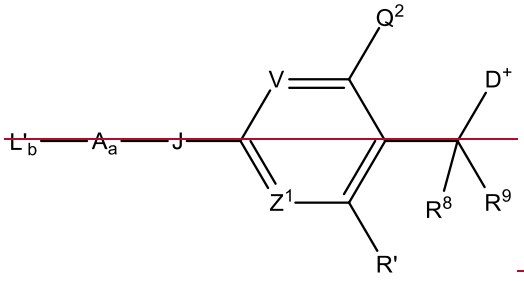


~~(Formula IIA)~~

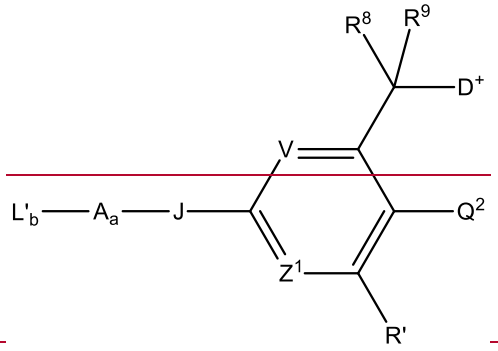


(Formula IIB).

69. The The Drug Linker compound of claim 67 wherein the compound has the structure of Formula IIIA or Formula IIIB:

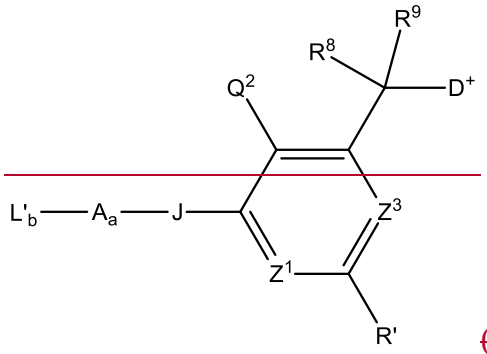


(Formula IIIA)

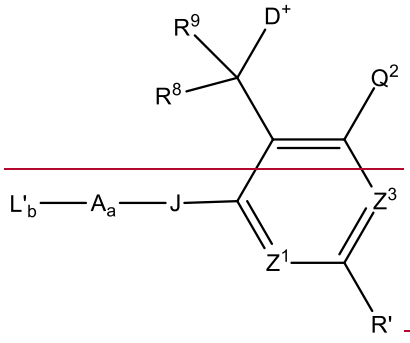


(Formula IIIB).

70. The Drug Linker compound of claim 1 wherein the compound has the structure of Formula IIIC or Formula IIID:

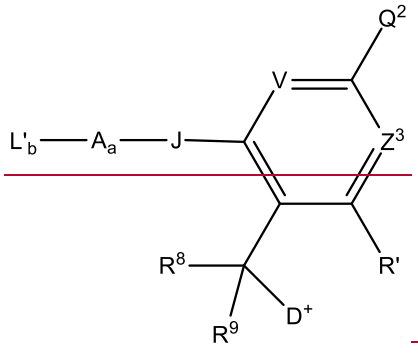


~~(Formula IIIC)~~

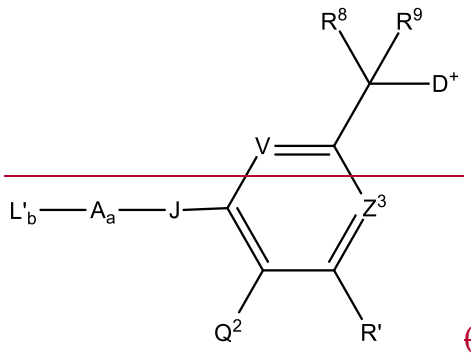


~~(Formula IIID).~~

~~**71.** The Drug Linker compound of claim 1 wherein the compound has the structure of Formula IIIE or Formula IIIC:~~

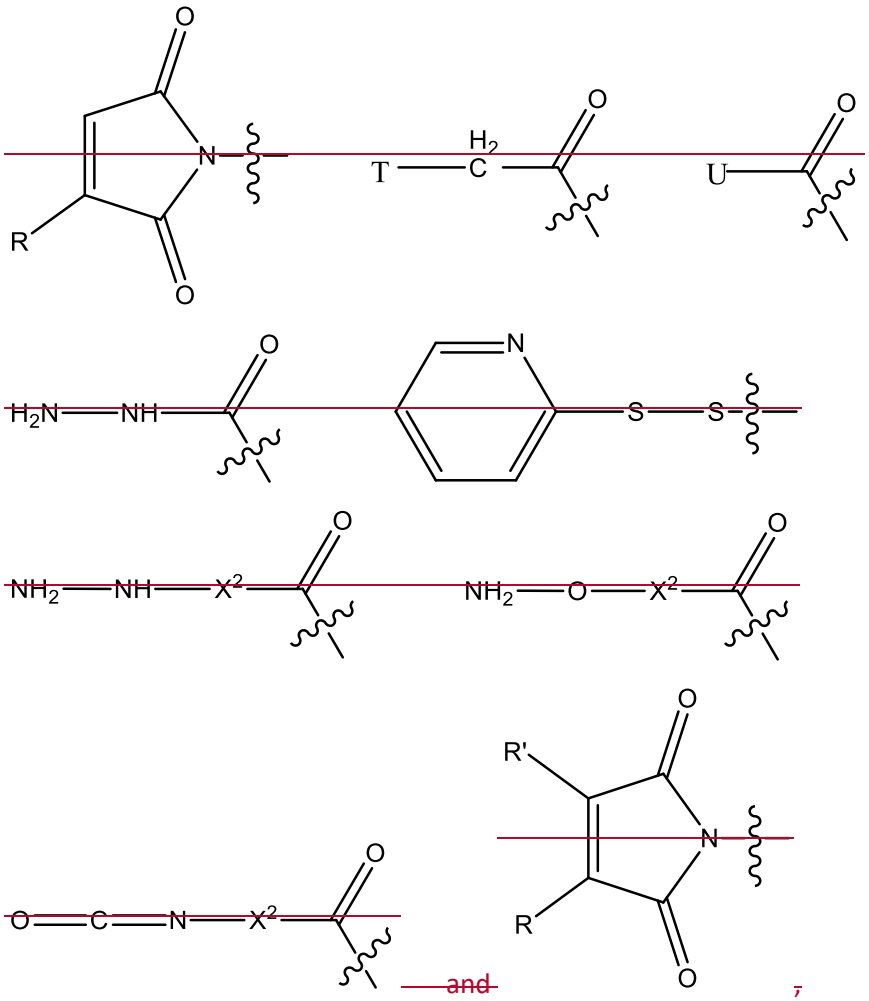


~~(Formula IIIE)~~



(Formula IIIF).

72. The Drug-Linker compound of any one of claims 1 to 5 wherein L_b' has a structure selected from the group consisting of:



and

,

wherein R is hydrogen or C_1-C_6 optionally substituted alkyl;

R' is hydrogen or halogen or R and R' are independently selected halogen;

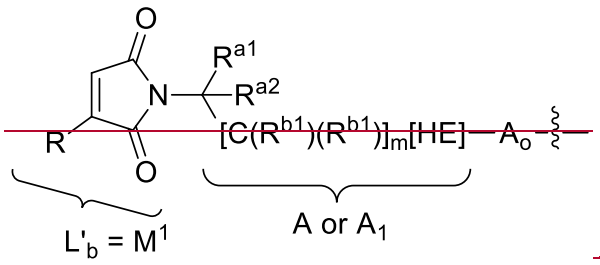
T is –Cl, –Br, –I, –O-mesyl or –O-tosyl or other sulfonate leaving group;

U is –F, –Cl, -Br, -I, -O-N-succinimide, -O-(4-nitrophenyl), -O-pentafluorophenyl, -O-tetrafluorophenyl or –O-C(=O)-OR^{57}; and

X^2 is C_1-$_{10}$ alkylene, C_3-C_8-carbocycle, O-(C_1-C_6 alkyl), -arylene-, C_1-C_{10} alkylene-arylene, -arylene-C_1-C_{10} alkylene, -C_1-C_{10} alkylene-(C_3-C_6-carbocycle)-, -(C_3-C_8 carbocycle)-C_1-C_{10} alkylene-, C_3-C_8-heterocycle, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -C_3-C_8-heterocyclo)-C_1-C_{10} alkylene, -$(CH_2CH_2O)_u$, or -$CH_2CH_2O)_u$-CH_2-, wherein subscript u is an integer ranging from 1 to 10 and R^{57} is C_1-C_6 alkyl or aryl.

73. The Drug-Linker compound of claim 67, wherein subscript a is 1 so that A in Q^1 is bonded to L'$_b$ of Formula I and Lb'-A is of genereal formula M^1-A_1-A_O-, wherein M^1 is a maleimide moiety and A_O is an optional subunit of A so that A is of two subunits when A_O is present or is a single unit when A_O is absent.

74. The Drug-Linker compound of claim 73 wherein M^1-A^1-A_O- has the structure of Formula VIII:



(Formula VIII)

wherein

A_O is an optional subunit of A, wherein -$[C(R^{b1})(R^{b1})]_m$-[HE]- is A when A_O is absent and is A_1 when A_o is present so that A becomes -A_1-A_o-;

R and R^{a2} independently are hydrogen or methyl;

R^{a1} is hydrogen, methyl, ethyl or a Basic Unit (BU);

HE is an optional Hydrolysis Enhancer (HE) unit;

m is an integer ranging from 0 to 6;

each R^{b1} independently is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl, or two R^{b1} together with the carbon(s) to which they are attached comprise a C_3-C_6 cycloalkyl or one R^{b1} and HE together with the carbon to which they are attached comprise a 5- or 6-membered cycloalkyl or a 5- or 6-membered heterocycloalkyl and the other R^{b1} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl;

BU has the structure of $-[C(R^1)(R^1)]-[C(R^2)(R^2)]_n-N(R^{22})(R^{23})$, or an acid addition salt thereof,

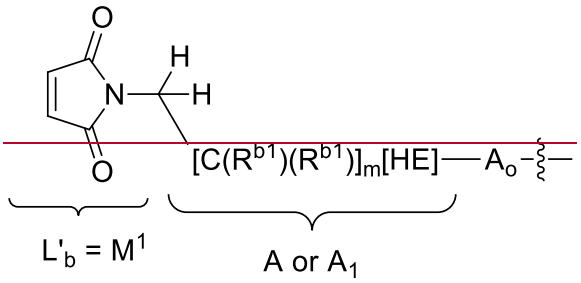
wherein subscript n is 0, 1, 2 or 3;

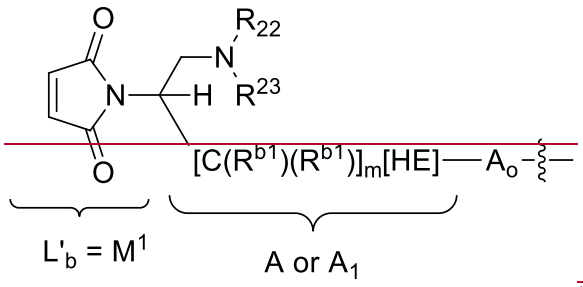
each R^1 independently is hydrogen or lower alkyl or two R^1 together with the carbon to which they are attached comprise a C_3-C_6 cycloalkyl, and each R^2 independently is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl, or two R^2 together with the carbon(s) to which they are attached and any intervening carbons define a C_3-C_6 cycloalkyl, or one R^1 and one R^2 together with the carbons to which they are attached and any intervening carbons comprise a 5- or 6-membered cycloalkyl and the remaining R^1 and R^2 are as defined;

R^{22} and R^{23} independently are hydrogen or optionally substituted C_1-C_6 alkyl or together with the nitrogen to which they are attached comprise a 5- or 6-membered heterocycloalkyl; and

the wavy line indicates covalent bonding of A (or A_O) to the remainder of the Formula VIII structure.

75. The Drug-Linker compound of claim 73 wherein M^1-A^1-A_O- of Formula I has the structure of

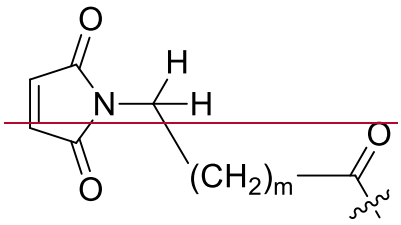




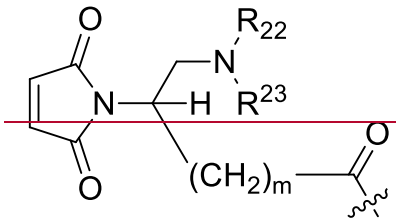
, or an acid addition salt thereof,

wherein R^{22} and R^{23} are each hydrogen or one of R^{22}, R^{23} is hydrogen and the other is an acid labile carbamate protecting group; and subscript m is an integer ranging from 0 to 4.

76. The Drug-Linker compound of claim 75 wherein M^1-A_1-A_O- of Formula I has the structure of:



;



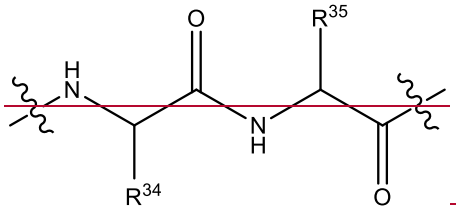
or an acid addition salt therof,

wherein subscript m is 0 or 4 and R^{22} abd R^{23} are each hydrogen or one of R^{22}, R^{23} is hydrogen and the other is –C(O)Ot-Bu.

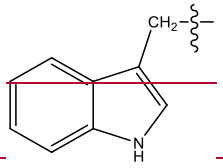
77. The Drug-Linker compound of claim 67 wherein W of Q^1 is comprised or consists of a peptide moiety having a peptide bond to J that is selectively cleavable by an intracellular or regulatory protease in comparison to serum proteases wherein action of the regulatory protease on W causes release of free tertiary amine-containing drug (D) from the Drug-Linker Compound or a Ligand Drug Conjugate compound or N-acetyl-cysteine Conjugate derived therefrom.

78. The Drug-Linker compound of claim 67 wherein W' of Q^2 is a glycoside-bonded carbohydrate, wherein the glycoside bond W'-E of Q^2 provides for a cleavage site for a glycosidase located intracellularly wherein action of the glycosidase on W'-E causes release of tertiary amine-containing drug (D) from the Drug-Linker Compound or a Ligand Drug Conjugate compound or N-acetyl-cysteine Conjugate derived therefrom.

79. The Drug-Linker compound of claim 77 wherein the peptide moiety of W is comprised or consists of a dipeptide moiety having the structure of Formula VI:

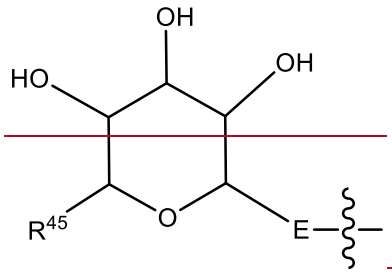


(Formula VI),

wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, $-CH(OH)CH_3$ or has the structure of  and R^{35} is methyl, $-(CH_2)_4-NH_2$, $-(CH_2)_3NH(C{=}O)NH_2$, $-(CH_2)_3NH(C{=}NH)NH_2$, or $-(CH_2)_2CO_2H$,

wherein the wavy bond to the dipeptide's C-terminus indicates covalent bonding to J of the arylene moiety of Formula IIA or IIB and the wavy bond to the dipeptide's N-terminus indicates covalent bonding to the remainder of W, if any such remainder is present, or to A, or a subunit thereof, when subscript a is 1 or to L_b when a is 0, and wherein the dipeptide's bond to J is cleavable by a intracellular or regulatory protease.

80. The Drug-Linker compound of claim 79 wherein W' in Q^2 is a carbohydrate moiety that is glycoside-bonded to E, wherein the glycosidic bond is cleavable by an intracellular glycosidase, and wherein W'-E has the structure of Formula VII:

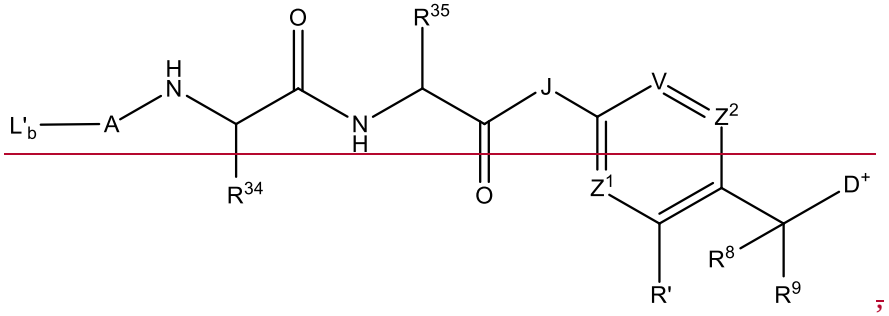


(Formula VII),

wherein the wavy line represents E bonded to one of V, Z^1, Z^2, or Z^3 when that variable group is $=C(R^{24})$, wherein E is -O-, -S-, or $-N(R^{33})-$, wherein R^{33} is hydrogen or methyl; and

wherein R^{45} is $-CH_2OH$ or $-CO_2H$.

81. The Drug-Linker compound of claim 79 wherein the compound has the structure of Formula IX:



,

(Formula IX)

wherein R' is hydrogen or an electron-donating group;

R^8 is hydrogen;

R^9 is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted phenyl;

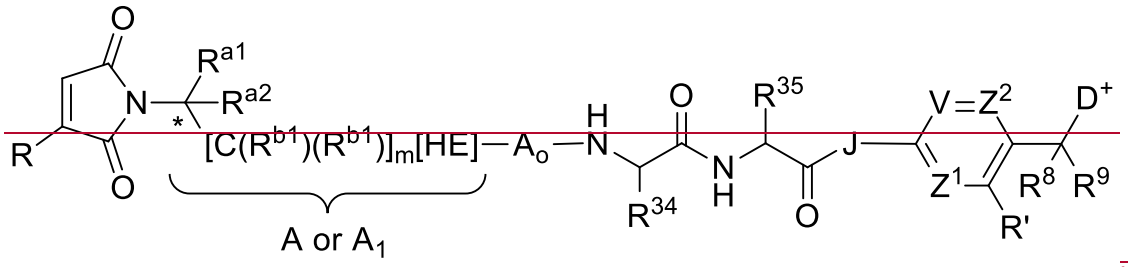
R^{34} is methyl, isopropyl or $-CH(OH)CH_3$;

R^{35} is methyl, $-(CH_2)_3NH(C=O)NH_2$ or $-(CH_2)_2CO_2H$;

J is $-N(R^{33})-$, wherein R^{33} is hydrogen or methyl; and

V and Z^1 independently are $=CH-$ or $=N-$.

82. The Drug-Linker compound of claim 80 wherein the compound has the structure of Formula X:



;

~~(Formula X)~~

~~wherein~~

~~the asterisk (*) designates chirality or absence thereof at the indicated carbon;~~

~~A_O is an optional subunit of A, wherein $-[C(R^{b1})(R^{b1})]_m-[HE]-$ is A when A_o is absent and is A_1 when A_O is present so A becomes A_1-A_O;~~

~~R is –H;~~

~~R^{a1} is –H or a Basic Unit (BU), wherein BU has the structure of $-CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} independently are hydrogen, methyl or ethyl or both together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;~~

~~R^{a2} is hydrogen;~~

~~subscript m is an integer ranging from 0 to 4;~~

~~each R^{b1} independently is hydrogen or optionally substituted C_1-C_6 alkyl;~~

~~HE is absent or is –C(=O)–;~~

~~R^{34} is methyl, isopropyl or $-CH(OH)CH_3$;~~

~~R^{35} is $-(CH_2)_3NH(C=O)NH_2$, or $-(CH_2)_2CO_2H$;~~

~~J is –NH–;~~

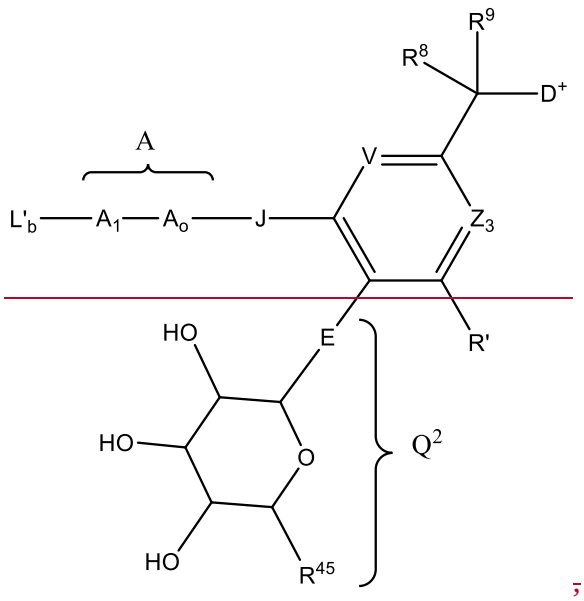
~~V, Z^1 and Z^2 are $=CH_2$–;~~

~~R' is hydrogen or an electron donating group;~~

~~R^8 is hydrogen; and~~

~~R^9 is hydrogen or methyl.~~

~~**83.** The Drug-Linker compound of claim 79 wherein the compound has the structure of Formula XI:~~



;

~~(Formula XI)~~

~~wherein~~

~~A_1 and A_O are independently selected subunits of A, wherein A_O is an optional subunit of A (i.e., A_1 becomes A when A_O is absent and A is $-A_1-A_O-$ when A_O is present);~~

~~E is –O– or –NH–;~~

~~J is –N(R^{33})–, wherein R^{33} is hydrogen or methyl;~~

~~V and Z^3 independently are =CH– or =N–;~~

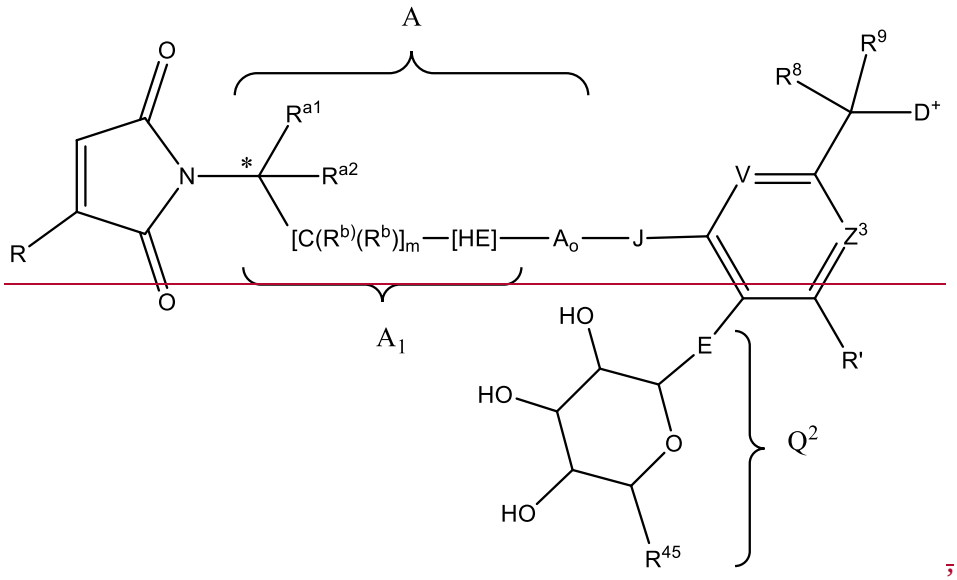
~~R' is hydrogen or an electron withdrawing group;~~

~~R^8 is hydrogen;~~

~~R^9 is hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted phenyl; and~~

~~R^{45} is –CO_2H or –CH_2OH.~~

~~**84**. The Drug-Linker compound of claim 83 wherein the compound has the structure of Formula XII:~~



(Formula XII)

wherein

the asterisk (*) designates chirality or absence thereof at the indicated carbon;

A_1 and A_O are independently selected subunits of A, wherein A_o is an optional subunit of A, wherein $-[C(R^{b1})(R^{b1})]_m$-[HE]- is A when A_o is absent and is A_1 when A_O is present so that A becomes A_1-A_O; wherein A_O when present corresponds in structure to an amine-containing acid bonded to J through the C-terminal carbonyl of the amine-containing acid;

R is hydrogen;

R' is hydrogen or an electron withdrawing group;

R^{a1} is hydrogen or a basic unit (BU) wherein BU has the structure of $-CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} independently are hydrogen, methyl or ethyl or both together with the nitrogen atom to which they are attached comprise a 5- or 6-membered heterocycloalkyl;

R^{a2} is hydrogen;

subscript m is an integer ranging from 1 to 5;

each R^{b1} independently is hydrogen or optionally substituted C_1-C_6 alkyl;

HE is absent or is $-C(=O)-$;

R^{45} is $-CO_2H$ or $-CH_2OH$;

E is $-O-$;

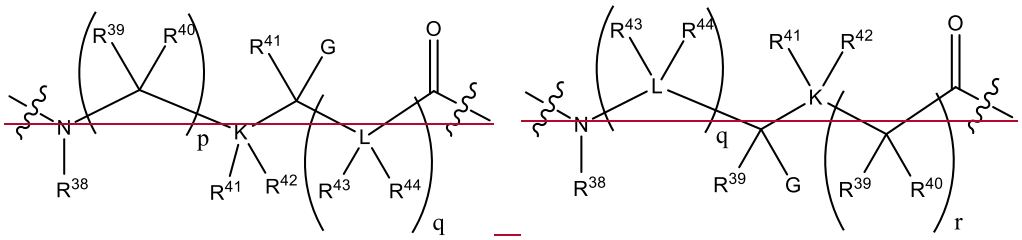
J is $-NH-$;

V and Z^3 are $=CH_2$-;

R^8 is hydrogen; and

R^9 is hydrogen or methyl.

85. The Drug-Linker compound of claim 81 wherein A_O, when present, has the structure of Formula XIII or Formula XIV:



(Formula XIII) (Formula XIV)

wherein the wavy line to the carbonyl moiety of either structure represents the point of attachment of A_O to W and wherein the wavy line to the amino moiety of either structure represents the point of attachment of A_e to A_1;

wherein K and L independently are C, N, O or S, provided that when K or L is O or S, R^{41} and R^{42} to K or R^{43} and R^{44} to L are absent, and when K or L are N, one of R^{41}, R^{42} to K or one of R^{43}, R^{44} to L are absent, and provided that no two adjacent L are independently selected as N, O, or S;

wherein subscript q is an integer ranging from 0 to 12, and subsript r is an integer ranging from 1 to 12;

wherein G is hydrogen, optionally substituted C_1-C_6 alkyl, -OH, $-OR^G$, $-CO_2H$, CO_2R^G, wherein R^G is C_1-C_6 alkyl, aryl or heteroaryl, optionally substituted, or R^{PR}, wherein R^{PR} is a suitable protecting group, $-NH_2$, or $-N(R^G)(R^{PG})$, wherein R^G independently selected is as previously defined or both R^G together with the nitrogen to which they are attached comprises a 5- or 6-membered heterocycloalkyl or both R^{PR} together form a suitable protecting group;

wherein R^{38} is hydrogen or optionally substituted C_1-C_6 alkyl; R^{39}-R^{44} independently are hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted heteroaryl, or both R^{39}, R^{40} together with the carbon to which they are attached comprise a C_3-C_6 cycloalkyl, or R^{41}, R^{42} together with K to which they are attached when K is C, or R^{43}, R^{44} together with L to which they are attached when L is C, comprise a C_3-C_6 cycloalkyl, or R^{40} and R^{41}, or R^{40} and R^{43}, or R^{41} and R^{43} together with the

carbon or heteroatom to which they are attached and atoms intervening between those carbon and/or heteroatoms comprise a 5- or 6-membered cycloalkyl or heterocycloalkyl, or

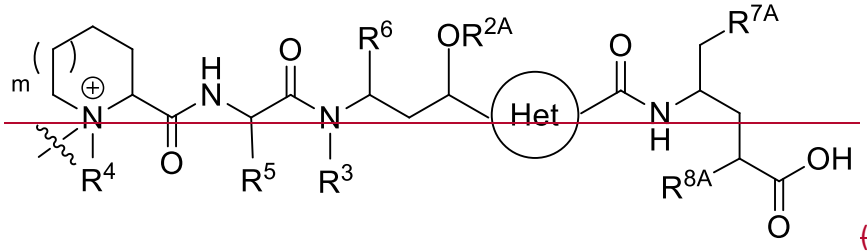
wherein A_o has a structure corresponding to alpha-amino, beta-amino or another amine-containing acid.

86. The Drug-Linker compound of claim 84 wherein the indicated starred (*) carbon is predominantly in the same absolute configuration as the alpha carbon of an **L**-amino acid when that indicated carbon has chirality.

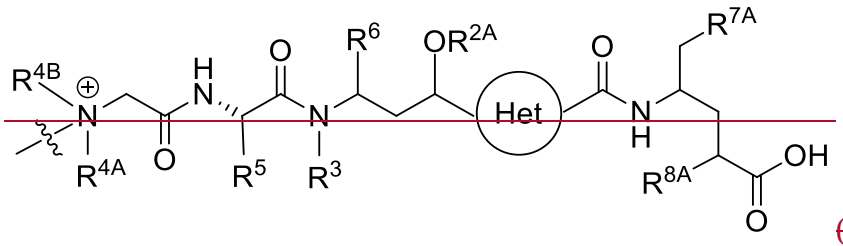
87. The Drug-Linker compound of any one of claims 69-86 wherein D^+ is a quaternized tertiary amine-containing tubulin disrupting agent.

88. The Drug-Linker compound of claim 87 wherein the quaternized tubulin disrupting agent D^+ is a quaternized tubulysin Drug Unit.

89. The Drug-Linker compound of claim 88 wherein the quaternized tubulysin Drug Unit D^+ has the structure of Formula D_{G-1}' or Formula D_{H-1}':



(Formula D_{G-1}')



(Formula D_{H-1}')

wherein the circle represents a 5-membered nitrogen-heteroaryl and wherein the indicated required substituents to that heteroaryl are in a 1,3-relationship with each other with optional substitution at the remaining positions;

R^{2A} is hydrogen or optionally substituted alkyl or R^{2A} along with the oxygen atom to which it is attached defines an O-linked substituent other than -OH;

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^{4A}, R^{4B}, R^5 and R^6 are optionally substituted alkyl, independently selected;

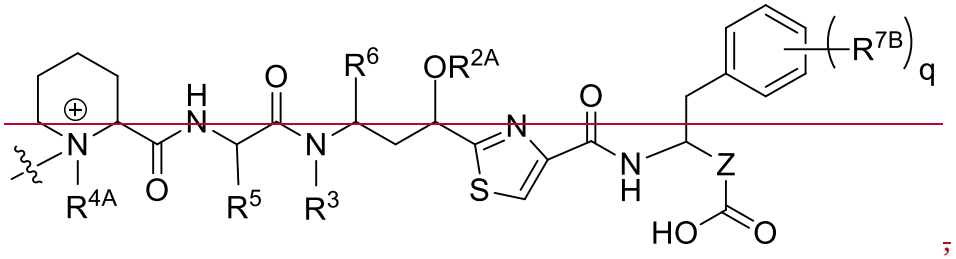
R^{7A} is optionally substituted aryl or optionally substituted heteroaryl;

R^{8A} is hydrogen or optionally substituted alkyl;

and subscript m is 0 or 1,

wherein the wavy line indicates covalent bonding of D^+ to LU'.

90. The Drug-Linker compound of claim 88 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



;

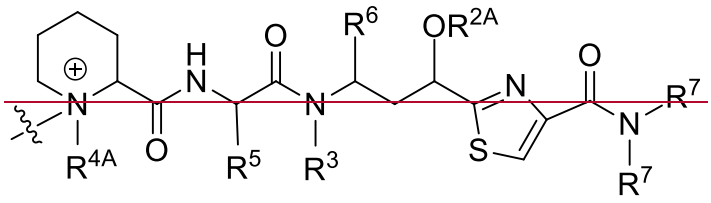
wherein Z is an optionally substituted lower alkylene or an optionally substituted lower alkenylene;

subscript q, indicating the number of R^{7B} substituent, is 1, 2 or 3;

each R^{7B} is independently selected from hydrogen and an O-linked substituent; and

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug-Linker compound.

91. The Drug-Linker compound of claim 89 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



wherein R^{2A} is hydrogen or optionally substituted C_1-C_6 alkyl or R^2 along with the oxygen atom to which it is attached defines an O-linked substituent other than -OH;

R^3 is optionally substituted C_1-C_6 alkyl;

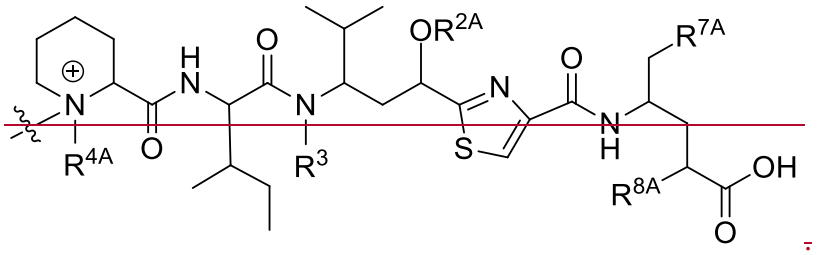
R^5 and R^6 are the side chain residues of natural hydrophobic amino acids;

$N(R^7)(R^7)$ is $-NH(C_1$-C_6 alkyl) or $-NH-N(C_1$-C_6 alkyl)$_2$, wherein one and only one C_1-C_6 alkyl is optionally substituted by $-CO_2H$, or an ester thereof, or by an optionally substituted phenyl; and

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug-Linker compound.

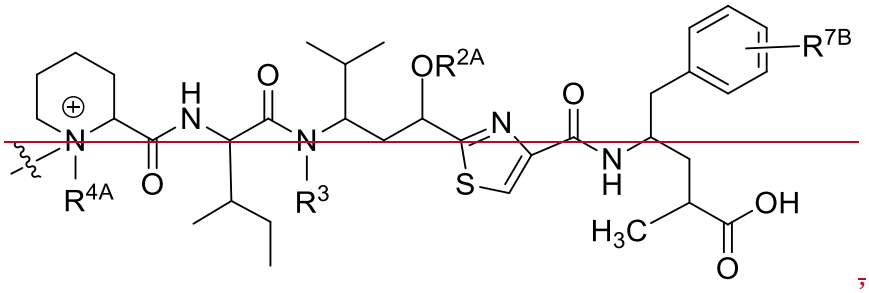
92. The Drug-Linker compound of claim 91 wherein $-N(R^7)(R^7)$ is selected from the group consisting of $-NH(CH_3)$, $-NHCH_2CH_2Ph$, and $-NHCH_2$-CO_2H, $-NHCH_2CH_2CO_2H$ and $-NHCH_2CH_2CH_2CO_2H$.

93. The Drug-Linker compound of claim 90 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



94. The Drug-Linker compound of any one of claims 89-93 wherein the O-linked substituent $-OR^{2A}$ is other than -OH (i.e., R^{2A} is not hydrogen).

95. The Drug-Linker compound of claim 93 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



;

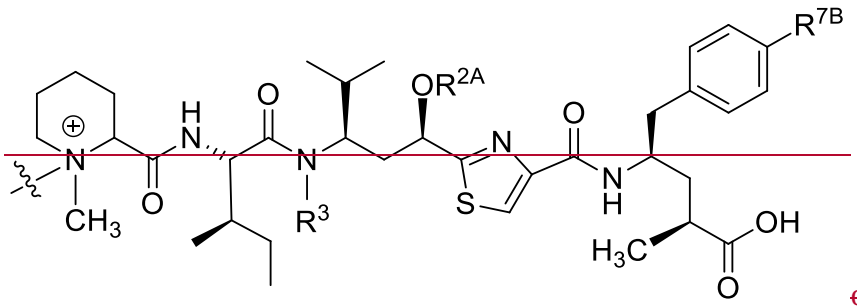
wherein R^{4A} is methyl;

R^3 is H, methyl, ethyl, propyl, $-CH_2-OC(O)R^{3A}$, $-CH_2CH(R^{3B})C(O)R^{3A}$ or $-CH(R^{3B})C(O)NHR^{3A}$, wherein R^{3A} is C_1-C_6 alkyl and R^{3B} is H or C_1-C_6 alkyl, independently selected from R^{3A}; and

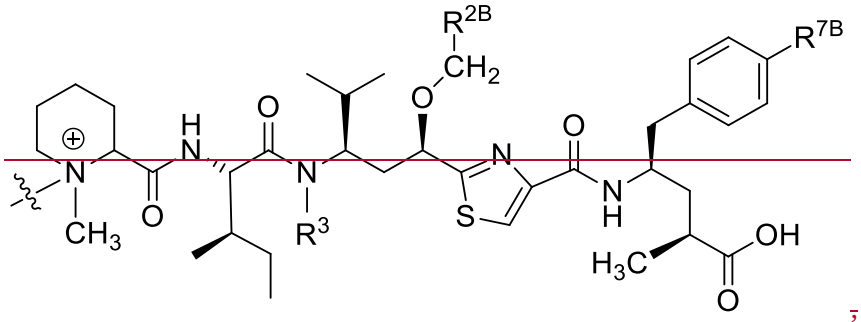
$-OR^{2A}$ is an O-linked substituent selected from the group consisting of $-OR^{2B}$, $-OC(O)R^{2B}$ or $-OC(O)N(R^{2B})(R^{2C})$, wherein R^{2B} and R^{2C} are independently selected from the group consisting of H, C_1-C_6 alkyl and C_2-C_6 alkenyl; and

R^{7B} is hydrogen or $-OH$.

96. The Drug-Linker compound of claim 95 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



or



;

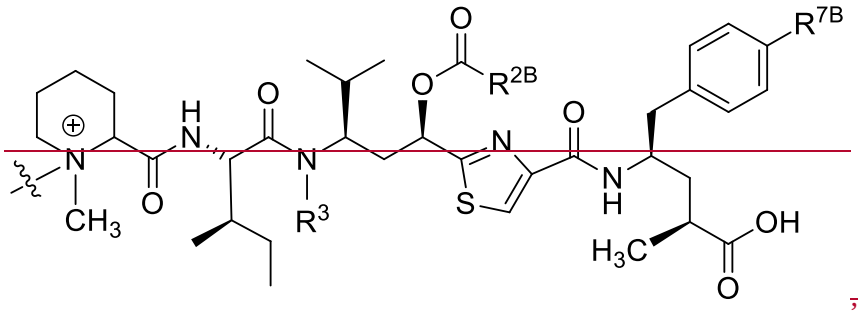
wherein R^{2A} and R^3 are independently selected from the group consisting of methyl, ethyl, propyl and iso-propyl;

R^{2B} is methyl, ethyl, propyl and iso-propyl or $-OR^{2A}$ is as previously defined;

R^3 is methyl, ethyl or propyl; and

R^{7B} is hydrogen or $-OH$.

97. The Drug-Linker compound of claim 95 wherein the quaternized tubulysin Drug Unit D^+ has the structure of:



;

wherein R^{2B} is methyl, ethyl, propyl, iso-propyl, 3-methyl-prop-1-yl, 3,3-dimethyl-prop-1-yl, or vinyl;

R^3 is methyl, ethyl or propyl; and

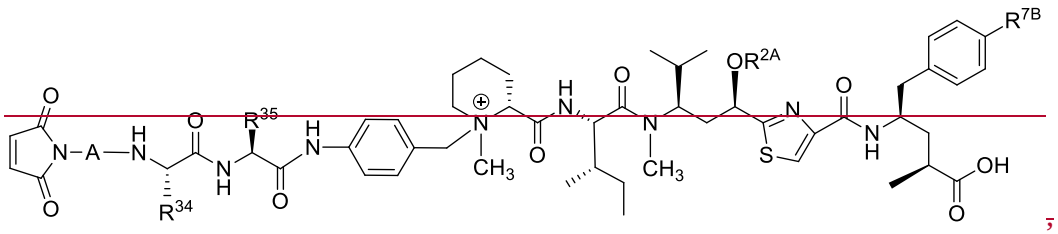
R^{7B} is hydrogen or $-OH$.

98. The Drug-Linker compound of claim 97 wherein R^{2B} is $-CH_3$, R^3 is $-CH_3$ and R^{7B} is H or $-OH$.

99. The Drug-Linker compound of any one of claims 89 to 96, wherein R^{2A} is $-CH_2CH_3$.

100. The Drug-Linker compound of claim 96 or 97 wherein R^{2B} is $-CH_3$, R^3 is $-CH_3$ and R^{7B} is H or $-OH$.

101. The Drug-Linker compound of claim 67 wherein the compound has the structure of:



;

wherein

R^{34} is isopropyl and R^{35} is CH_3, isopropyl, $CH_2CH_2CH_2NH(C=O)NH_2$ or $CH_2CH_2CO_2H$;

R^{7B} is hydrogen or OH; and

R^{2A} is C_1-C_6 alkyl, C_2-C_6 alkenyl, OCH_2OR^{2B}, $C(=O)R^{2B}$ or $C(=O)NHR^{2B}$, wherein R^{2B} is hydrogen, or C_1-C_6 alkyl.

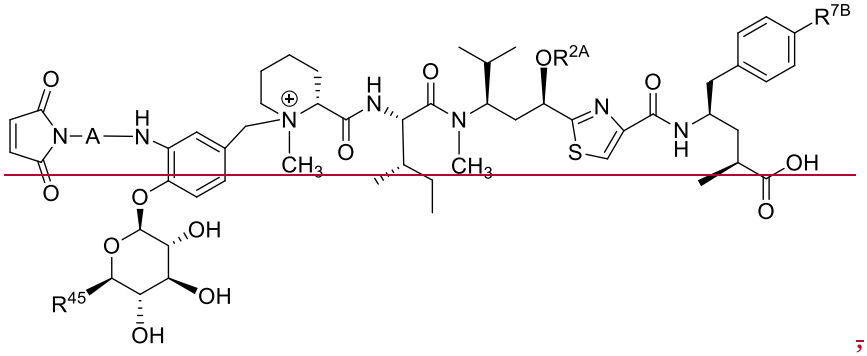
102. The Drug-Linker compound of claim 101 wherein

R^{34} is isopropyl and R^{35} is CH_3, or $CH_2CH_2CH_2NH(C=O)NH_2$;

R^{7B} is hydrogen or OH; and

R^{2A} is lower alkyl, $C(=O)R^{2B}$ or $C(=O)NHR^{2B}$, wherein R^{2B} is lower alkyl.

103. Drug-Linker compound of claim 67 wherein the compound has the structure of



;

wherein

R^{7B} is hydrogen or OH;

R^{2A} is C_1-C_6 alkyl, C_2-C_6 alkenyl, OCH_2OR^{2B}, $C(=O)R^{2B}$ or $C(=O)NHR^{2B}$, wherein R^{2B} is hydrogen, or C_1-C_6 alkyl; and

R^{45} is CO_2H or CH_2OH.

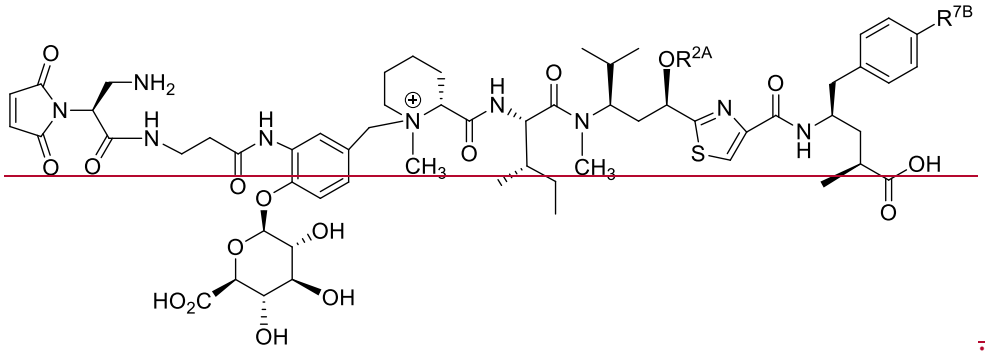
104. The Drug-Linker compound of claim 103 wherein

~~R^{34} is isopropyl and R^{35} is CH_3, or $CH_2CH_2CH_2NH(C=O)NH_2$;~~

~~R^{7B} is hydrogen or OH; and~~

~~R^{2A} is lower alkyl, $C(=O)R^{2B}$ or $C(=O)NHR^{2B}$, wherein R^{2B} is lower alkyl.~~

~~**105.** The Drug-Linker compound of claim 103 or 104 wherein the compound has the structure of~~



~~.~~

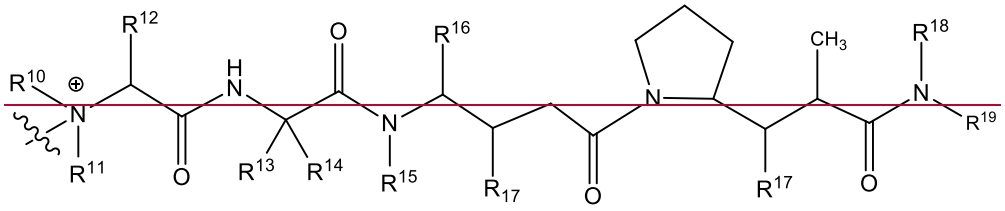
~~**106**. The Drug-Linker compound of any one of claims 81, 82 and 101-104wherein A or A_1-A_O- is $CH_2(CH_2)_4(C=O)$- or $CH_2(CH_2)_4(C=O)NHCH_2CH_2(C=O)$-.~~

~~**107**. The Drug-Linker compound of any one of claims 89-95 wherein R^{2A} is $C(O)CH_3$, methyl, ethyl or propyl.~~

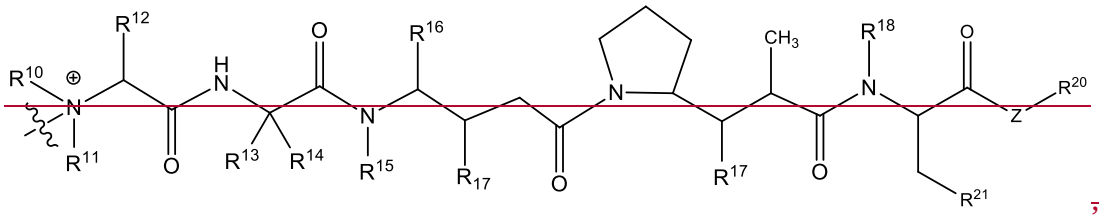
~~**108**. The Drug-Linker compound of claim 87 wherein the quaternized tubulin disrupting agent D^+ is a quaternized auristatin or dolastatin Drug Unit.~~

~~**109**. The Drug-Linker compound of claim **108** wherein the quaternized tubulin disrupting agent D^+ is quaternized dolastatin 10 or dolastatin 15.~~

~~**110.** The Drug-Linker compound of claim **108** wherein the quaternized auristatin Drug unit D^+ has the structure of D_E' or D_F':~~



(D$_E$')



(D$_F$')

wherein R^{10} and R^{11} are independently C_1-C_8 alkyl;

R^{12} is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, aryl, -X^1-aryl, -X^1-(C_3-C_8 cycloalkyl), C_3-C_8 heterocycle or -X^1-(C_3-C_8 heterocycle);

R^{13} is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, aryl, -X^1-aryl, -X^1-(C_3-C_8 cycloalkyl), C_3-C_8 heterocycle and -X^1-(C_3-C_8 heterocycle);

R^{14} is hydrogen or methyl;

or R^{13} and R^{14} taken together with the carbon to which they are attached comprise a C_3-C_8 cycloalkyl;

R^{15} is hydrogen or C_1-C_8 alkyl;

R^{16} is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, aryl, -X^1-aryl, -X^1-(C_3-C_8 cycloalkyl), C_3-C_8 heterocycle and -X^1-(C_3-C_8 heterocycle);

R^{17} independently are hydrogen, -OH, C_1-C_8 alkyl, C_3-C_8 cycloalkyl and O-(C_1-C_8 alkyl);

R^{18} is hydrogen or C_1-C_8 alkyl;

R^{19} is -$C(R^{19A})_2$-$C(R^{19A})_2$-aryl, -$C(R^{19A})_2$-$C(R^{19A})_2$-(C_3-C_8 heterocycle) or -$C(R^{19A})_2$-$C(R^{19A})_2$-(C_3-C_8 cycloalkyl); R^{21} is aryl or C_3-C_8 heterocycle; wherein R^{19A} is hydrogen, C_1-C_8 alkyl or -OH;

R^{20} is hydrogen, C_1-C_{20} alkyl, aryl, C_3-C_8 heterocycle, -$(R^{47}O)_m$-R^{48}, and -$(R^{47}O)_m$-$CH(R^{49})_2$;

subscript m is an integer ranging from 1-1000;

R^{47} is C_2-C_8 alkyl;

R^{48} is hydrogen or C_1-C_8 alkyl;

~~R^{49} independently are –COOH, $-(CH_2)_n-N(R^{50})_2$, $-(CH_2)_n-SO_3H$, or $-(CH_2)_n-SO_3-C_1-C_8$ alkyl;~~

~~R^{50} independently are C_1-C_8 alkyl, or $-(CH_2)_n-COOH$;~~

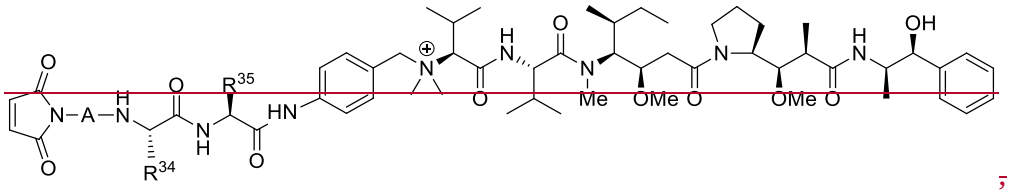
~~Z is O, S, NH, or NR^{46}, wherein R^{46} is C_1-C_8 alkyl;~~

~~X^1 is C_1-C_{10} alkylene; and~~

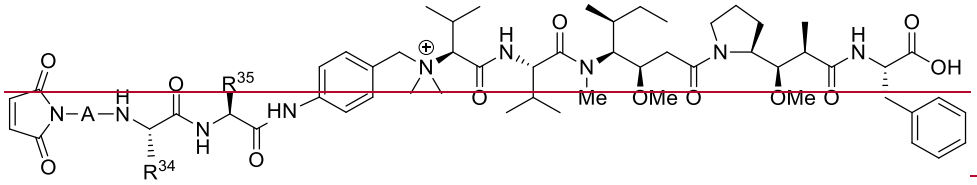
~~subscript n is an integer ranging from 0 to 6;~~

~~wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug-Linker compound.~~

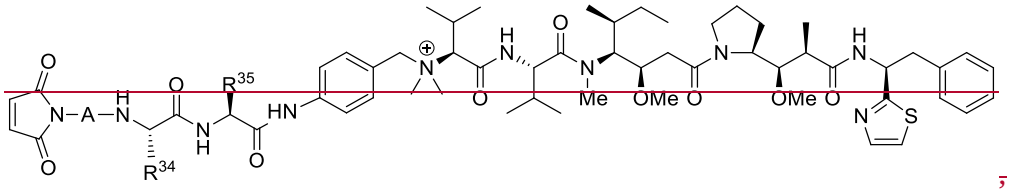
~~**111**. The Drug-Linker compound of claim 110 wherein the compound has the structure of:~~



;



~~or~~

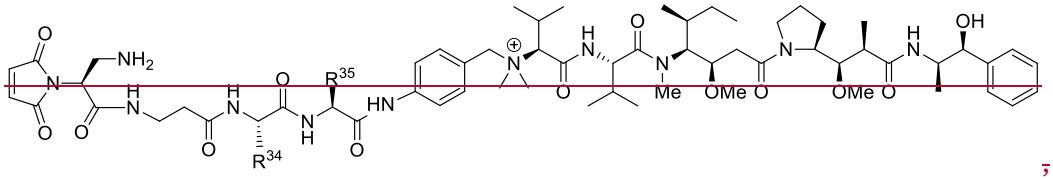


;

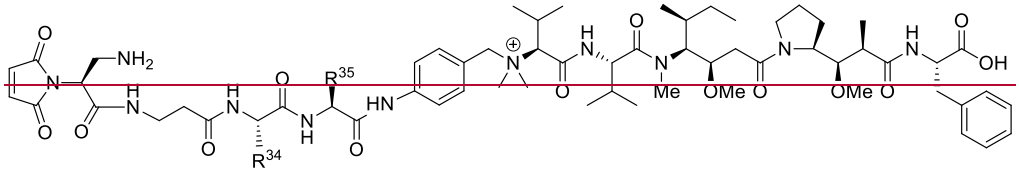
~~wherein~~

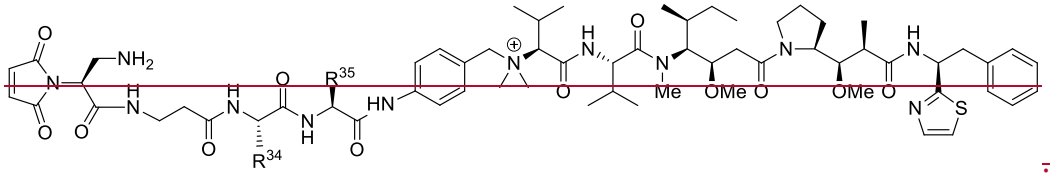
~~R^{34} is isopropyl and R^{35} is $-CH_3$, $-CH_2CH_2COOH$ or $-CH_2CH_2CH_2NH(C=O)NH_2$.~~

~~**112**. The Drug-Linker compound of claim 111 wherein the compound has the structure of:~~

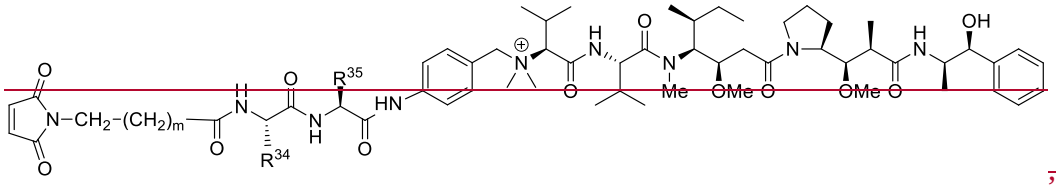


;

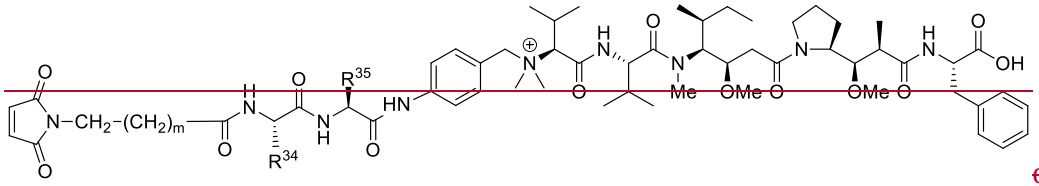




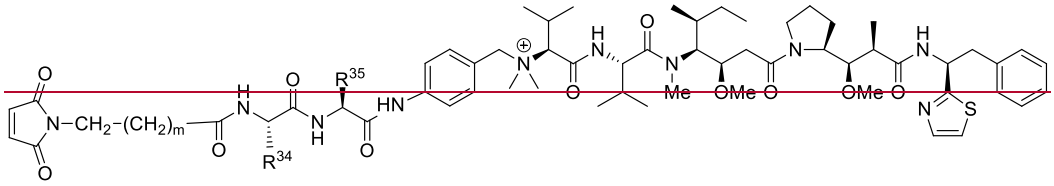
;



;

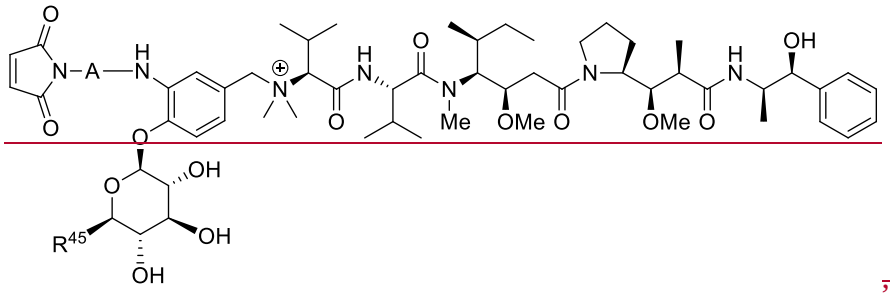


or

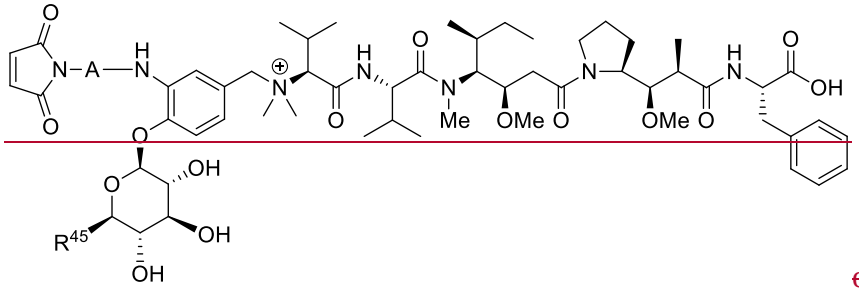


wherein the subscript m is 4.

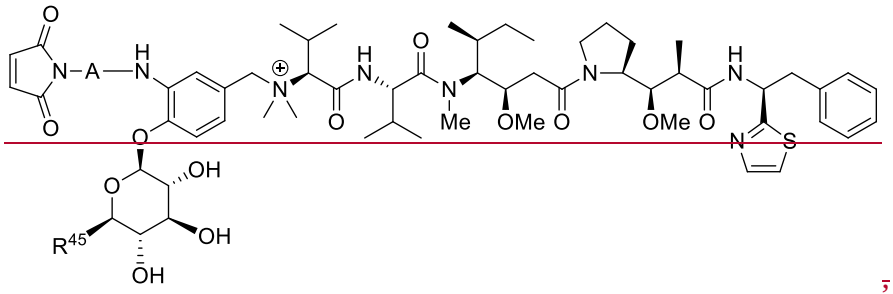
113. The Drug-Linker compound of claim 110 wherein the compound has the structure of:



;



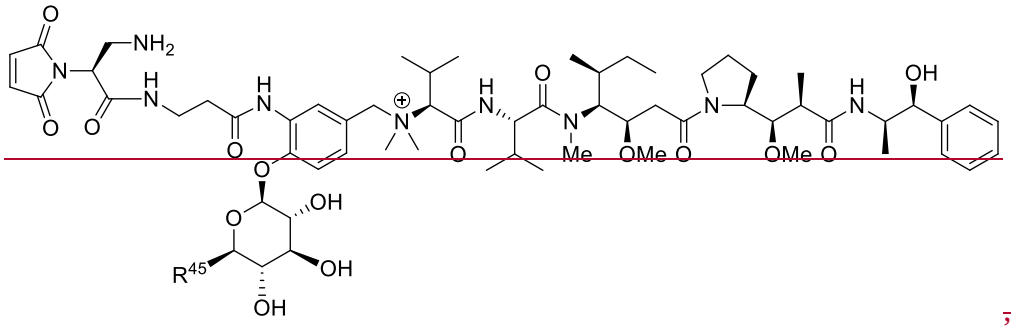
or



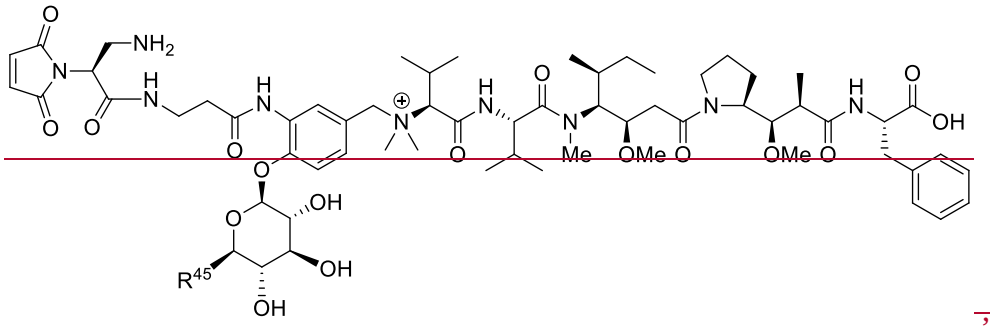
;

wherein R^{45} is CO_2H or CH_2OH.

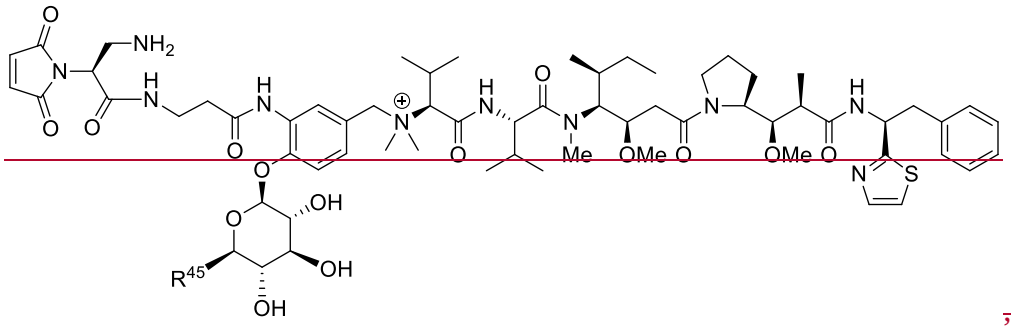
114. The Drug-Linker compound of claim 113 wherein the compound has the structure of:



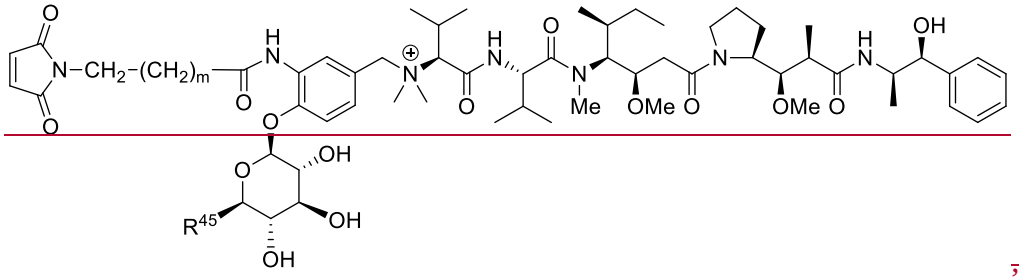
;



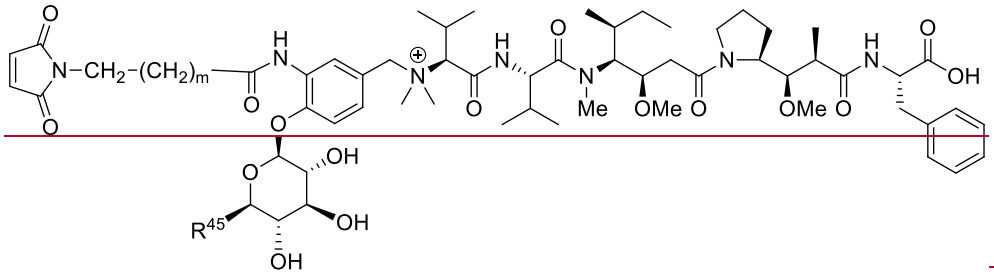
,



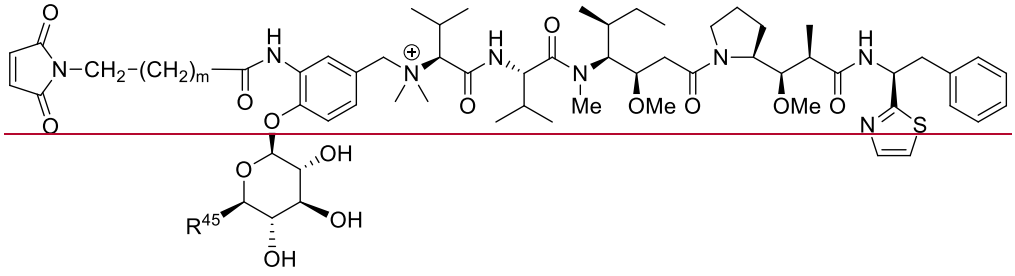
,



,



~~or~~



~~wherein R^{45} is $-CO_2H$ or $-CH_2OH$; and subscript m is 4.~~