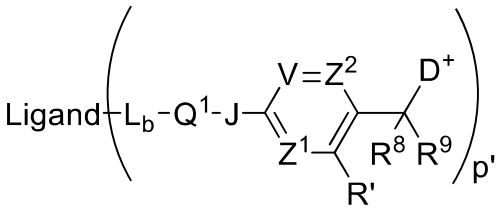
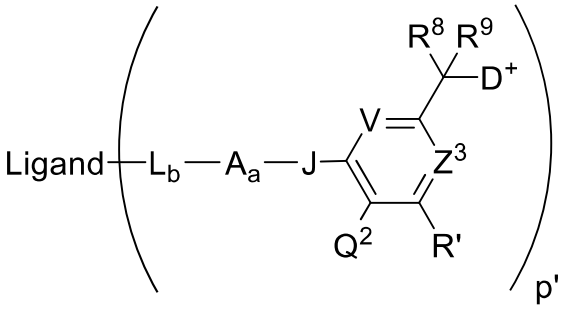
is a need in the art for LDCs that use the tertiary amine nitrogen as the site of conjugation in order to allow for release of fully active tertiary amine-containing drug at the targeted site of action. Even if reduced biological activity or changes in other pharmacological properties are tolerable through 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

[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-;

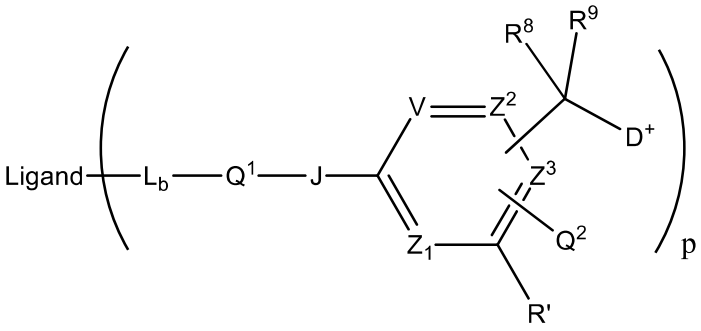
D^+ represents the structure of a quaternized tertiary amine-containing drug, wherein the tertiary amine-containing drug is quaternized at the nitrogen atom of its tertiary amine,

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 examples of the 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 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.

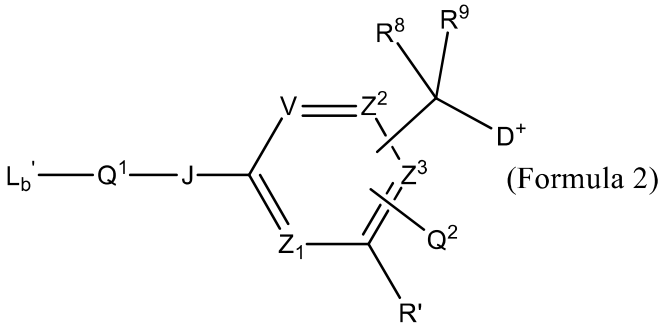
[0011] In some examples, W of Q^1 is comprised of a peptide moiety having a peptide bond to J that is selectively cleavable by an intracellular protease in comparison to serum proteases, wherein the intracellular protease may or may not be more specific to the targeted abnormal or other unwanted cells 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 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 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 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 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 examples of the 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

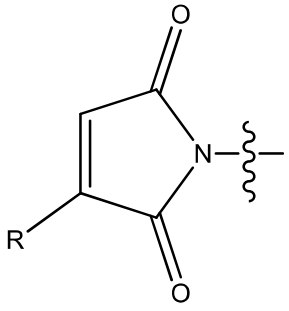
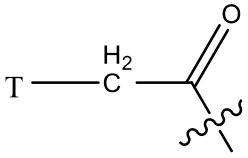
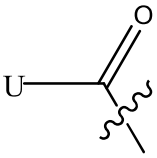
when a is 1; Q^2 is W'-E, wherein Q^2, when present, is bonded to V, Z^1, Z^2 or Z^3; W_w and $W'_{w'}$ are Cleavable units capable of cleavage in an LDC having a Formula I structure that

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.

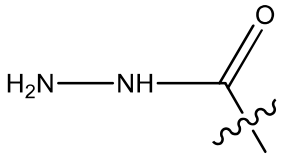
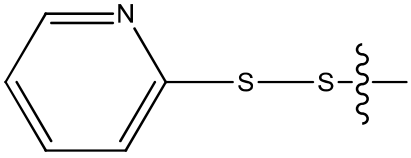
[0017] In some examples, the disclosure provides for LDC conjugate compositions prepared from contacting a Formula 1 compound with a targeting moiety having a reactive

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.

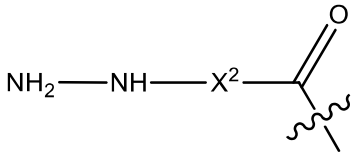
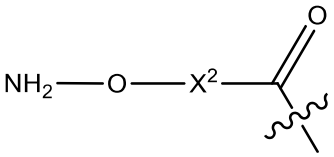
[0018] In some examples, L_b' has the structure of one of

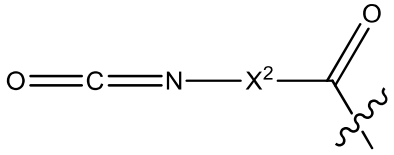
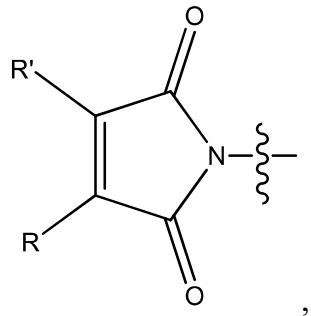
[0019]

[0020]

[0021]

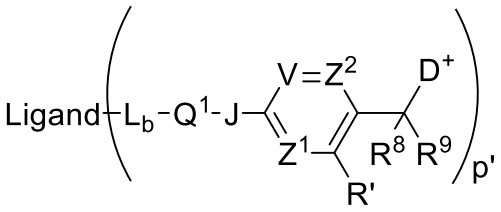
[0022] ,

[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.

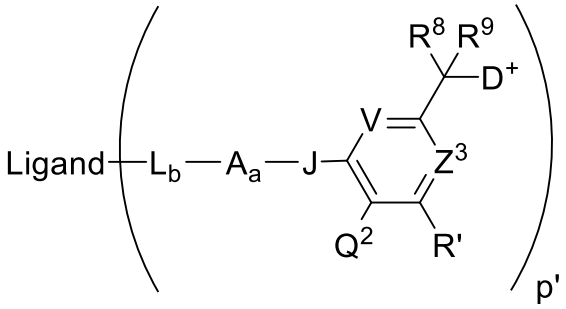
BRIEF DESCRIPTION OF THE DRAWINGS

WHAT IS CLAIMED IS:

1. Use of a 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,

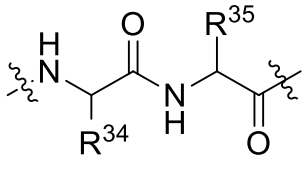
wherein the tertiary amine-containing drug (D) is a tertiary amine-containing tubulin disrupting agent; and

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.

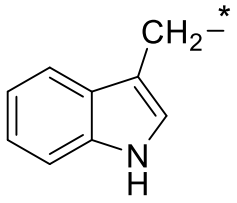
2. The use of claim 1, wherein W of Formula 2A has a peptide bond to J that is selectively cleavable by the lysosomal protease and the carbohydrate moiety of Formula 3F is a glucuronic acid residue, wherein said cleavage by the intracellular glycosidase is by an intracellular glucuronidase.

3. The use of claim 1, wherein W of Formula 2A is a dipeptide moiety having the structure of Formula 6:



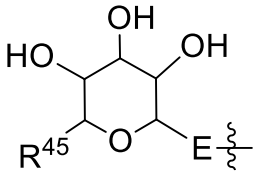
(Formula 6),

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 line to the dipeptide's C-terminus indicates covalent bonding to J of the arylene moiety of Formula 2A and the wavy line to the dipeptide's N-terminus indicates covalent bonding 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 protease, and

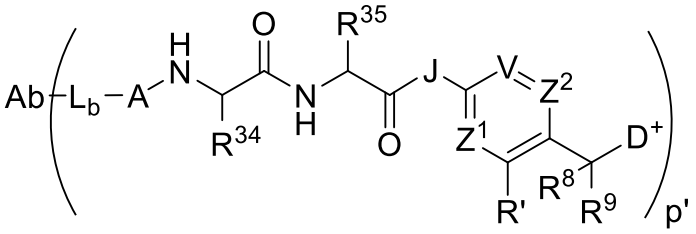
wherein W'-E of Formula 3F has the structure of Formula 7:

 (Formula 7),

wherein the wavy line represents E bonded to the arylene moiety of Formula 3F, wherein E is –O'-; and

R^{45} is $–CH_2OH$ or $–CO_2H$.

4. The use of claim 1, wherein Formula 2A is represented by the structure of Formula 9:



(Formula 9)

wherein

Ab is an antibody Ligand Unit;

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

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

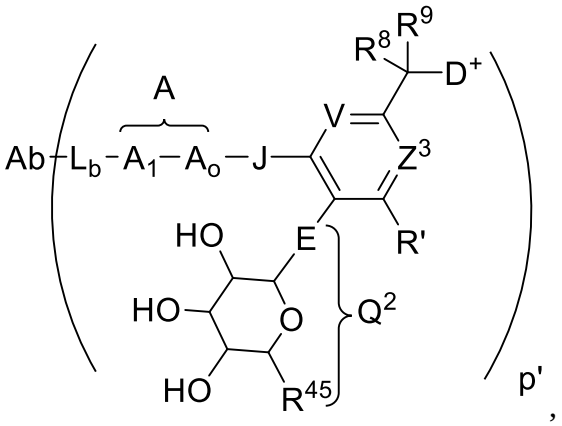
R^{35} is methyl, -$(CH_2)_3NH(C=O)NH_2$ or -$(CH_2)_2CO_2H$;

J is –NH-; and

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

and

Formula 3F is represented by the structure of Formula 11:



(Formula 11)

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'-;

J is –NH-;

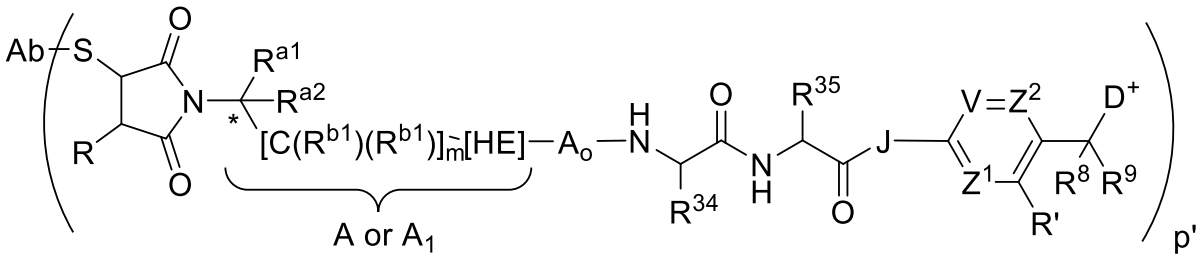
V and Z^3 are each =CH-;

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

R^{45} is –CO_2H; and

subscript p' is an integer 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 $-CH(OH)CH_3$;

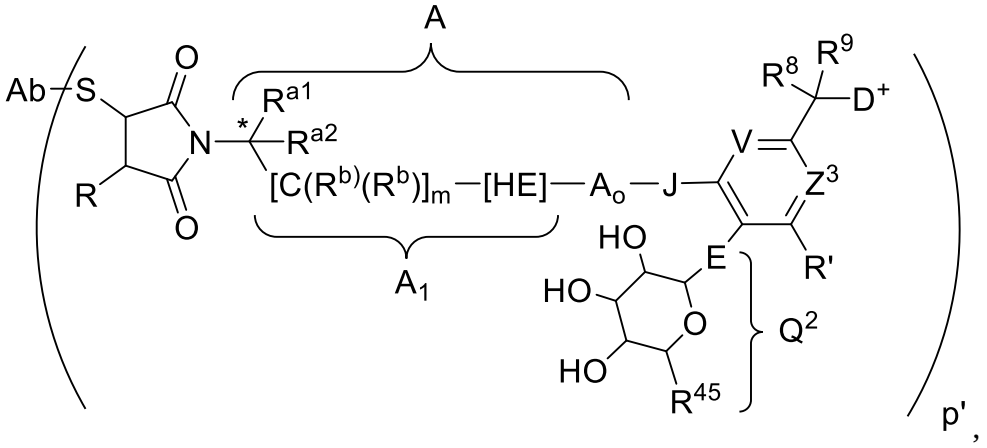
R^{35} is $–(CH_2)_3NH(C=O)NH_2$ or $–(CH_2)_2CO_2H$;

J is –NH-; and

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

and

wherein Formula 3F is represented by the structure of Formula 12:



(Formula 12)

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_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^{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 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 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 $–CO_2H$;

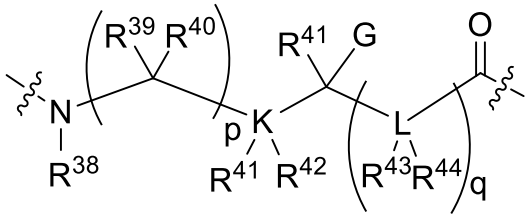
E is –O'-;

J is –NH-;

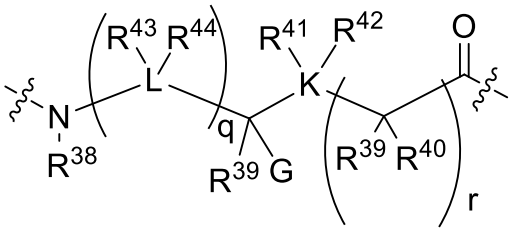
R', R^8, and R^9 are each hydrogen; and

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

6. The use of claim 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 is N, one of R^{41} and R^{42} to K or one of R^{43} and R^{44} to L is 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 subscript 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, or -CO_2R^G, wherein R^G is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^{PR},

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

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

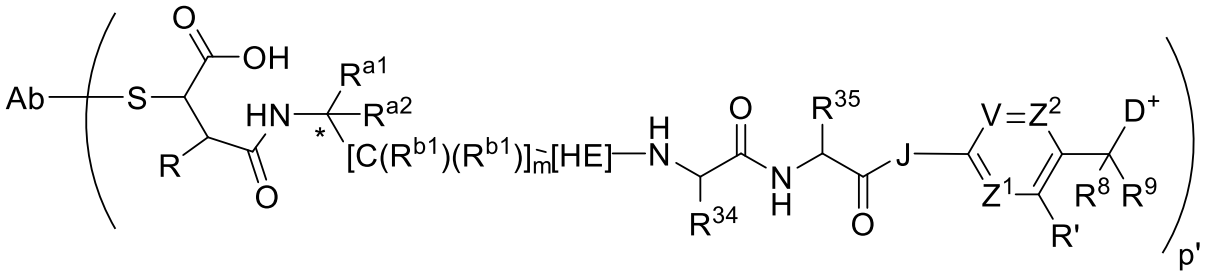
each R^{39}-R^{44} is independently hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted heteroaryl, or both R^{39} and R^{40} together with the carbon to which they are attached define a C_3-C_6 cycloalkyl, or R^{41} and R^{42} together with K to which they are attached when K is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

those carbon and/or heteroatoms define 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

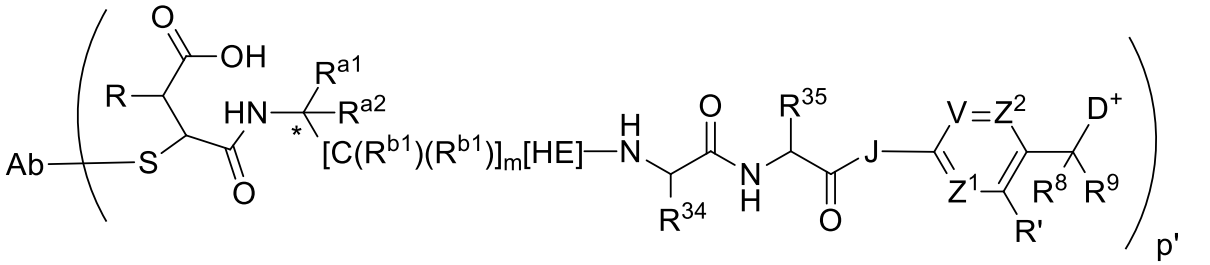
wherein the indicated starred (*) carbon atom is predominantly in the same absolute configuration as the alpha carbon atom of an **L**-amino acid when that indicated carbon atom has chirality.

7. The use of claim 1, wherein the Ligand Drug Conjugate compound 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;

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;

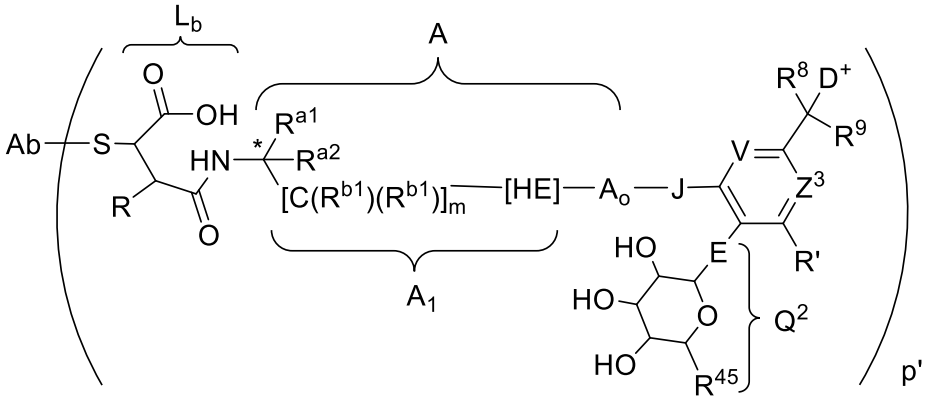
V, Z^1, and Z^2 are each =CH-;

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

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

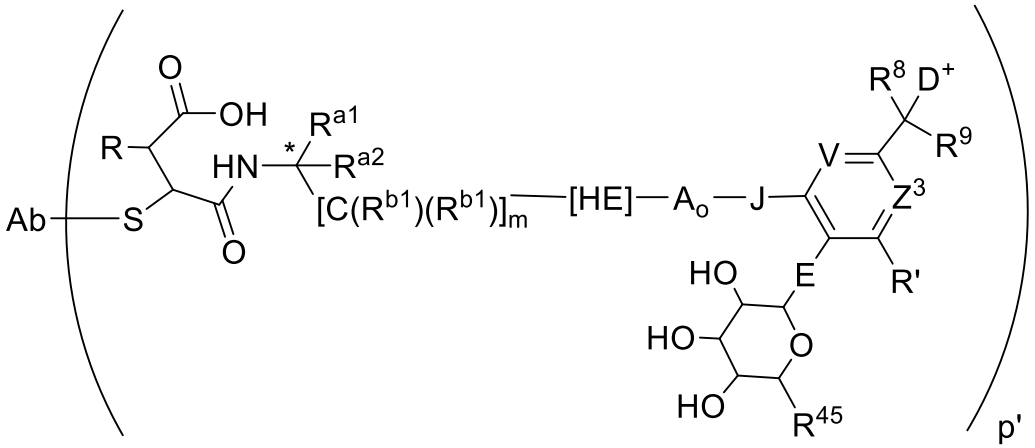
or

wherein the Ligand Drug Conjugate compound 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;

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 R^{22} and R^{23} both 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^{45} is $–CO_2H$;

E is –O'-;

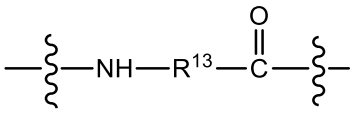
J is –NH-;

V and Z^3 are each =CH-;

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

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

8. The use of claim 7, wherein A_O, when present, has the structure of:



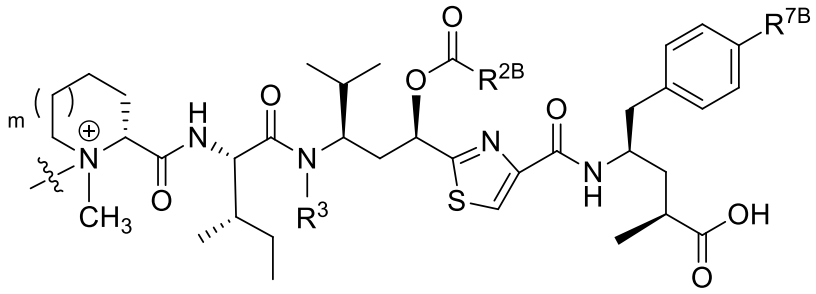
wherein R^{13} is $-C_1-C_{10}$ alkylene-, $-C_3-C_8$ carbocyclo-, -arylene-, $-C_1-C_{30}$ heteroalkylene-, $-C_3-C_8$ heterocyclo-, $-C_1-C_{10}$ alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, $-C_1-C_{10}$ alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, $-C_1-C_{10}$ 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 chirality.

9. The use of claim 1, 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;

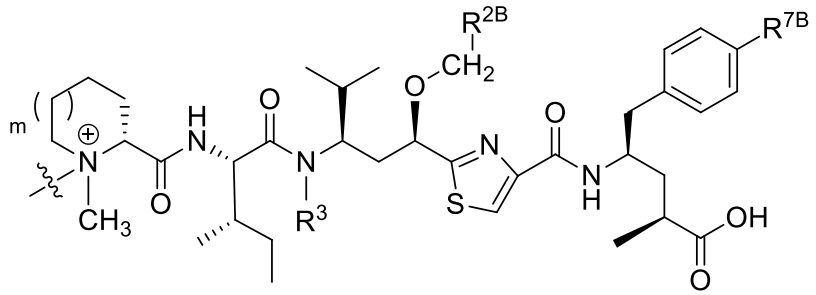
$-OC(O)R^{2B}$ is $–OC(O)CH_3$, $-OC(O)CH_2CH_3$, $-OC(O)CH(CH_3)_2$, $-OC(O)C(CH_3)_3$, or $–OC(O)CH=CH_2$;

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;

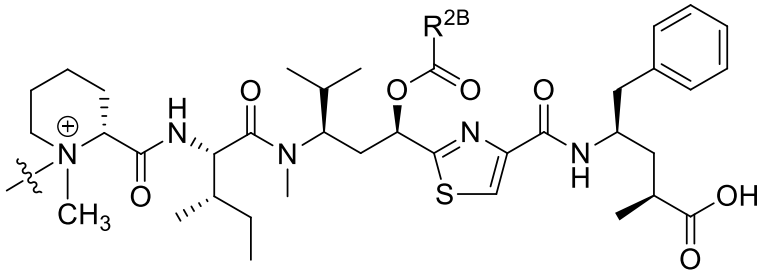
subscript m is 1;

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

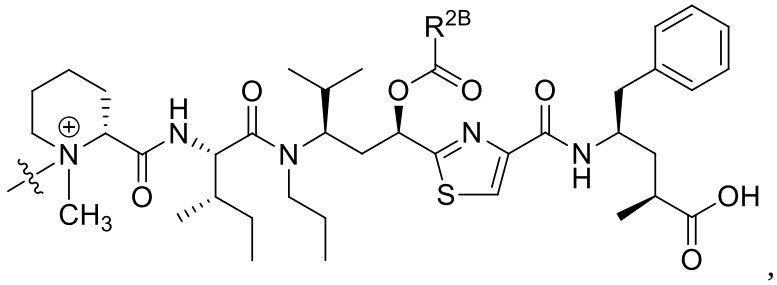
R^3 is methyl, ethyl, or propyl; and

R^{7B} is hydrogen or –OH.

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



or



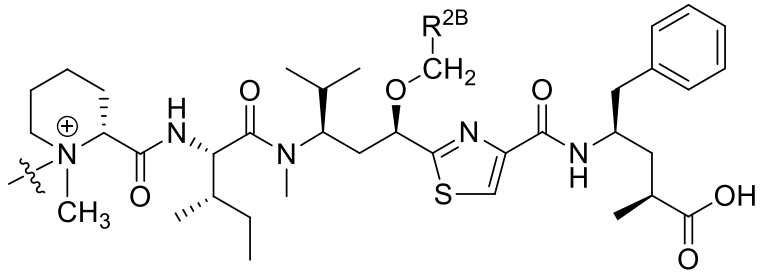
,

or a pharmaceutically acceptable salt thereof, wherein

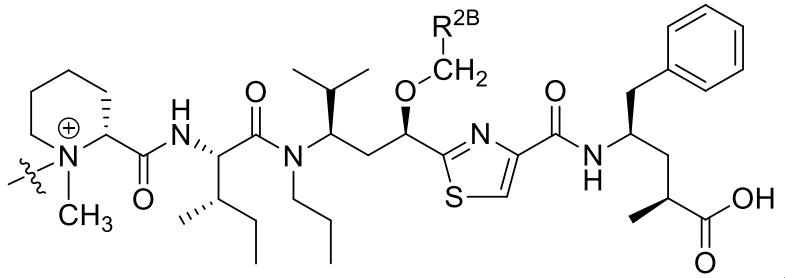
subscript m is 1;

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

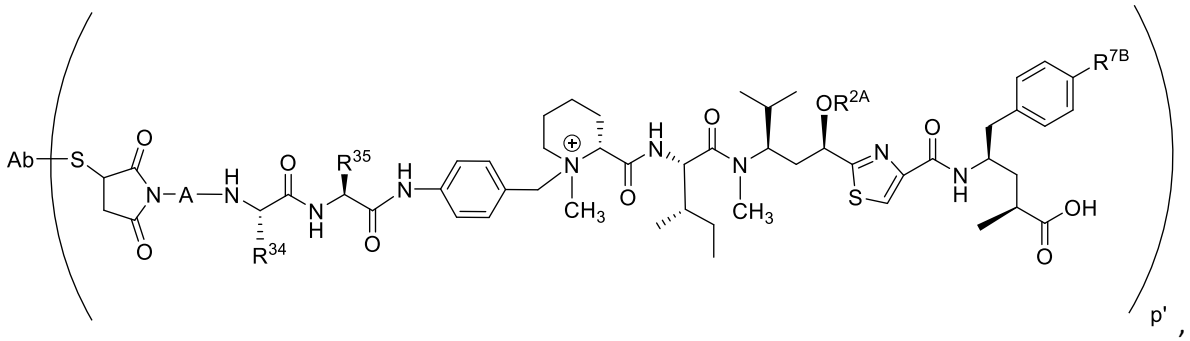


,

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.

12. The use of claim 1, wherein Formula 2A is represented by the structure of:



,

or a pharmaceutically acceptable salt thereof, 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;

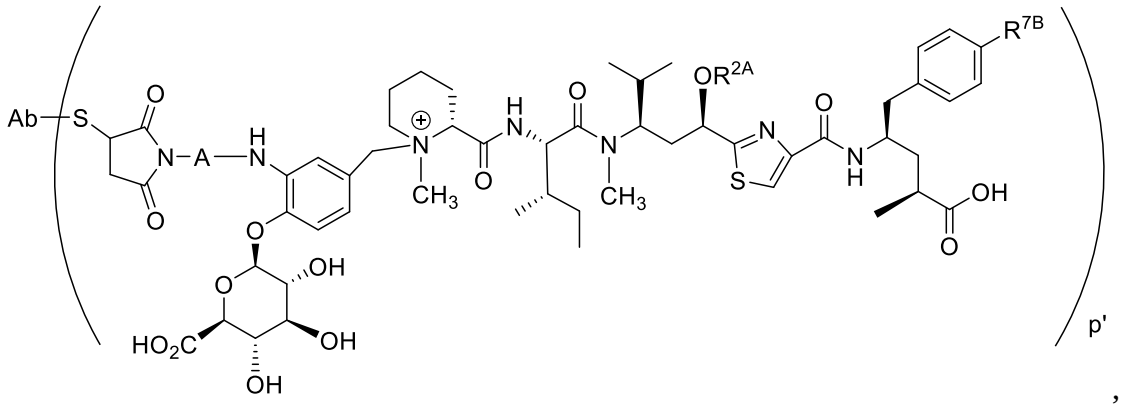
R^{2A} is lower alkyl or $–C(=O)R^{2B}$, wherein R^{2B} is lower alkyl;

subscript p' is an integer 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

wherein Formula 3F is represented by the structure of:



,

or a pharmaceutically acceptable salt thereof, 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;

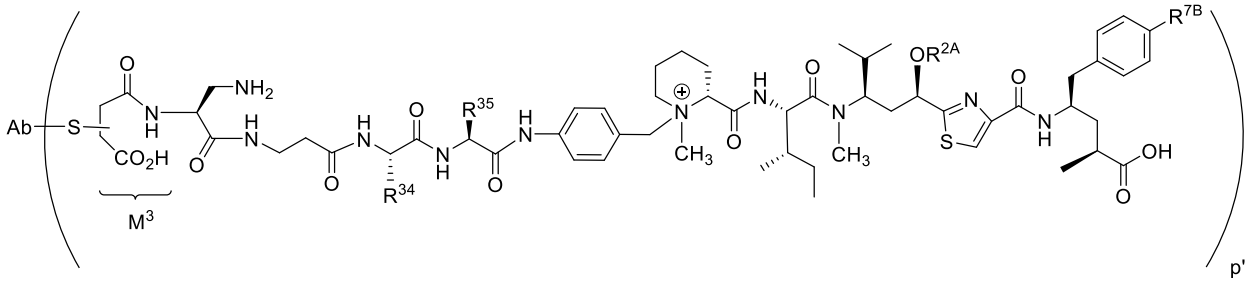
R^{7B} is hydrogen or –OH;

R^{2A} is C_1-C_6 alkyl, -CH_2OR^{2B}, or –C(=O)R^{2B}, wherein R^{2B} is C_1-C_6 alkyl or C_2-C_6 alkenyl;

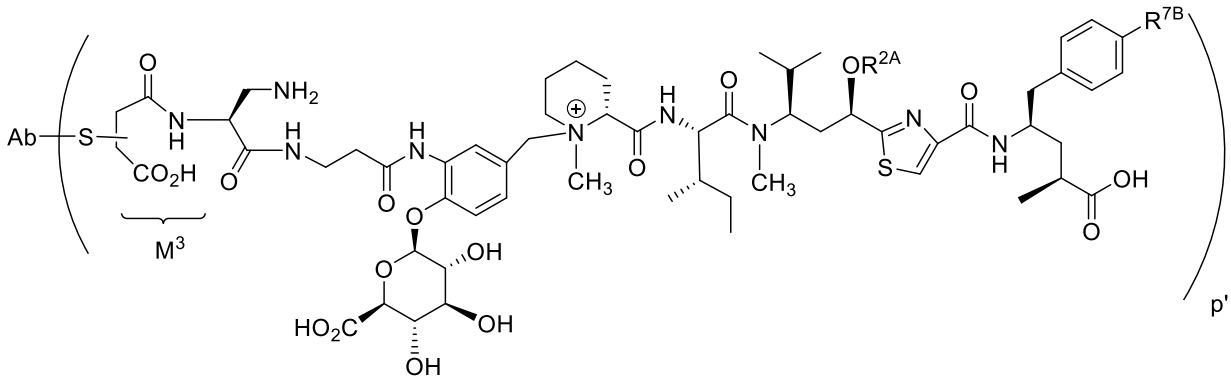
subscript p' is an integer ranging from 1 to 8; and

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

13. The use of claim 1, wherein the Ligand Drug Conjugate compound is represented by the structure of:



or



or a pharmaceutically acceptable salt thereof, 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;

R^{7B} is hydrogen or –OH;

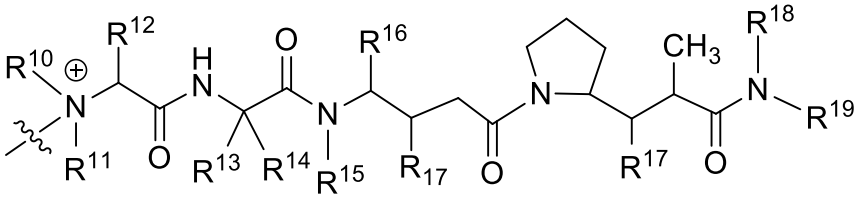
R^{34} is isopropyl and R^{35} is –CH_3, isopropyl, –$CH_2CH_2CH_2NH$(C=O)NH_2, or –$CH_2CH_2CO_2H$; and

R^{2A} is –C(O)CH_3, methyl, ethyl, or propyl.

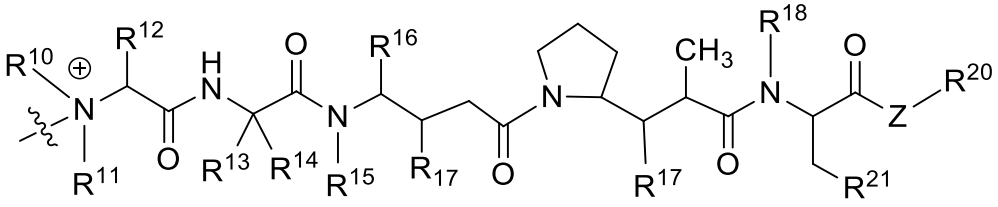
14. The use of claim 1, wherein the quaternized tertiary amine-containing tubulin disrupting agent $–D^+$ is

a quaternized dolastatin 10 or a quaternized dolastatin 15, or

a quaternized auristatin having the structure of D_E' or D_F':



(D_E'),



(D_F'),

or a pharmaceutically acceptable salt thereof, wherein, 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;

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 $-X^1$-(C_3-C_8 heterocycle);

R^{14} is hydrogen or methyl, or

R^{13} and R^{14} taken together with the carbon atom to which they are attached define 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 $-X^1$-(C_3-C_8 heterocycle);

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

each R^{18} is independently 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), 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}, or -$(R^{47}O)_m$-$CH(R^{49})_2$;

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

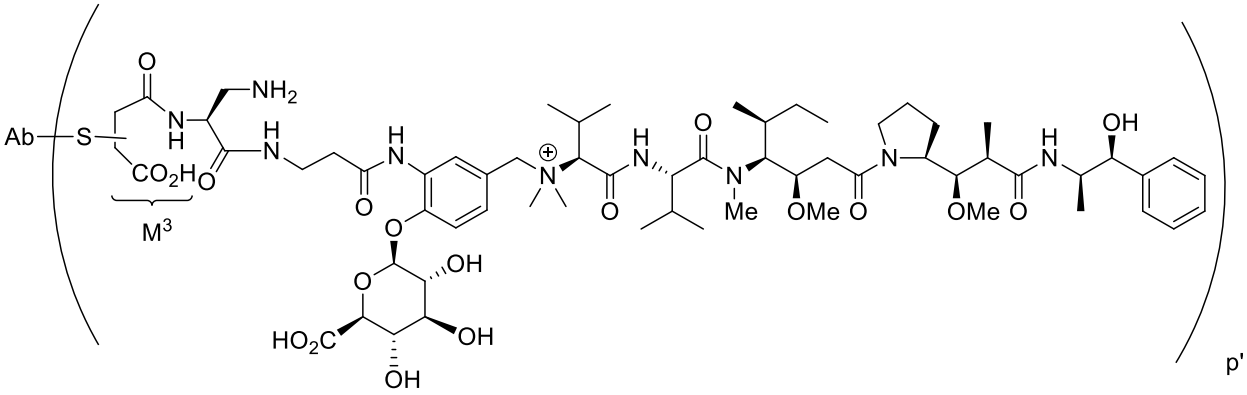
each R^{50} is independently C_1-C_8 alkyl or $–(CH_2)_n$-COOH;

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

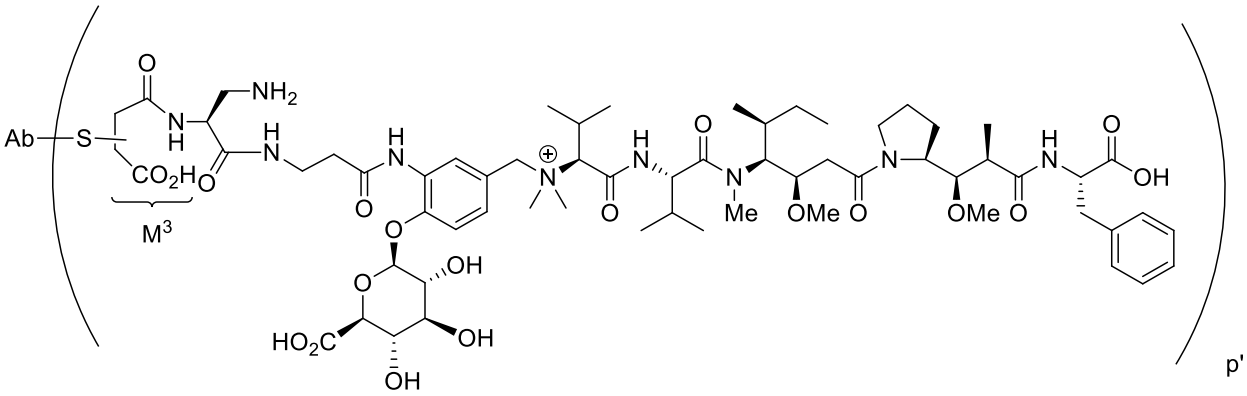
X^1 is C_1-C_{10} alkylene; and

subscript n is an integer ranging from 0 to 6.

15. The use of claim 14, wherein the Ligand Drug Conjugate compound is represented by:



or



or a pharmaceutically acceptable salt thereof, 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.