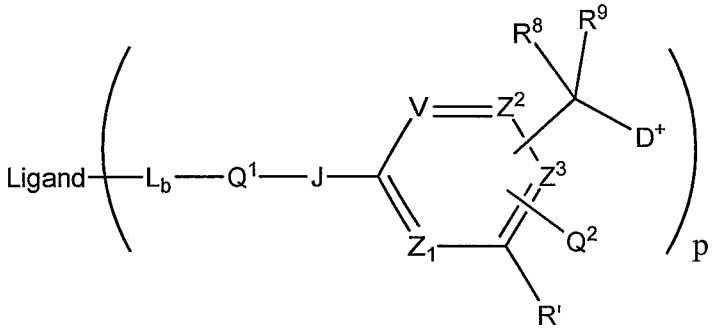
is a need in the art for LDCs that use the tertiary amine nitrogen as the site of conjugation in order to allow for release of fully active tertiary amine-containing drug at the targeted site of action. Even if reduced biological activity or changes in other pharmacological properties are tolerable through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

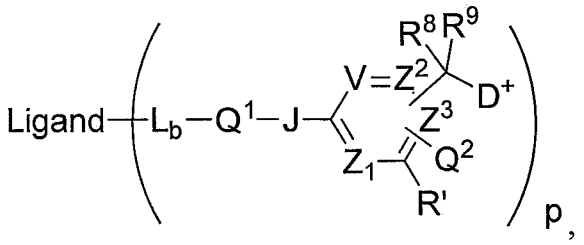
pH of serum, and W'-E of Q^2 provides a glycosidic bond cleavable by a glycosidase located intracellularly, wherein the glycosidase may or may not be more specific to the targeted abnormal or other unwanted cells in comparison to normal cells, or is capable of selective cleavage by a glycosidase excreted 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.

[0009a] In one aspect, there is provided a Ligand Drug Conjugate (LDC) composition, wherein the LDC composition is represented by the structure of Formula 1:



(Formula 1)

wherein

"Ligand" is a Ligand Unit (L), wherein L is an antibody or fragment thereof, 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;

L_b is a primary linker;

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 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 subscript w is 0 or W is present when subscript w is 1, and subscript w' is 0 or 1, wherein W'-E is absent when subscript w' is 0 or W'-E is present when subscript w' is 1, and wherein w + w' is 1 so that 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 subscript 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 subscript 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 subscript 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;

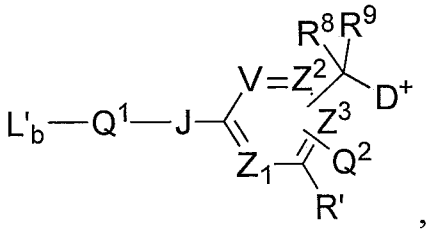
E and J independently are –O-, -S- or –$N(R^{33})$-, wherein R^{33} is hydrogen or optionally substituted alkyl;

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

subscript p is 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 tertiary amine-containing drug (D) from a Ligand Drug Conjugate compound of the composition.

[0009b] In another aspect, ther eis provided a Drug-Linker compound, wherein the Drug Linker 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 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 subscript w is 0 or W is present when subscript w is 1, and subscript subscript w' is 0 or 1, wherein W'-E is absent when subscript w' is 0 or W'-E is present when subscript w' is 1, and wherein w + w' is 1 so that 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 subscript w is 1, and at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})- when subscript w' is 1,

provided that when subscript 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 subscript w' is 1, one 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

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..

[0010] In some embodiments, 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.

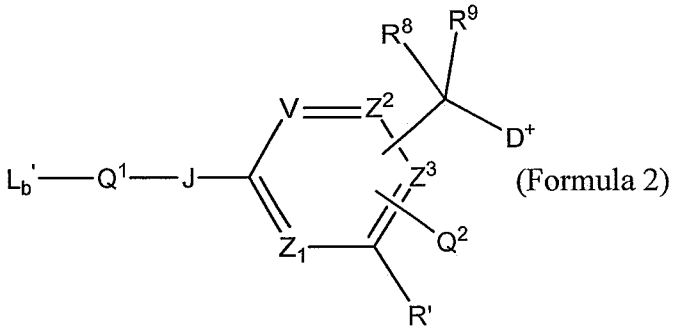
[0011] In some embodiments, W of Q^1 is comprised of a peptide moiety having a peptide bond to J that is selectively cleavable by an intracellular protease in comparison to serum proteases, wherein the intracellular protease may or may not be more specific to the targeted abnormal or other unwanted cells 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 embodiments 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 embodiments 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 embodiments 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 embodiments, 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 embodiments of the disclosure provide for compounds having the structure of Formula 2:



(Formula 2)

,

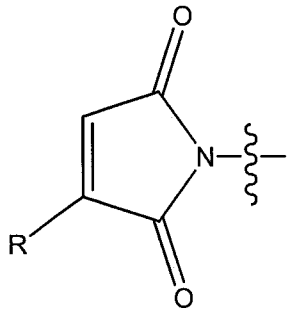
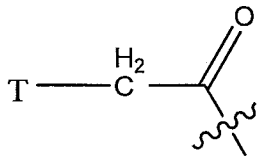
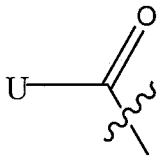
[0016] wherein L_b' is a linker covalent binding precursor moiety; Q^1 is A_a-W_w, wherein A is an optional Stretcher unit, optionally comprised of two, three or four subunits, so that the subscript a is 0 or 1, wherein A is absent when a is 0 and A is present when a is 1; Q^2 is W'-E, wherein Q^2, when 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.

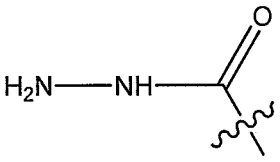
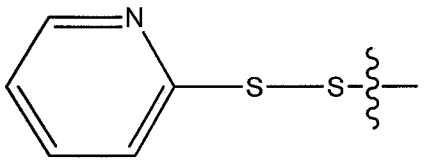
[0017] In some embodiments, the disclosure provides for LDC conjugate compositions prepared from contacting a Formula 1 compound with a targeting moiety having a reactive

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.

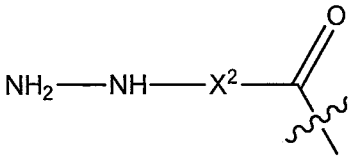
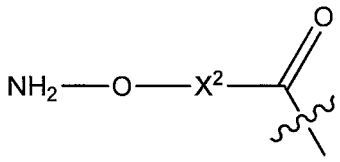
[0018] In some embodiments, L_b' has the structure of one of

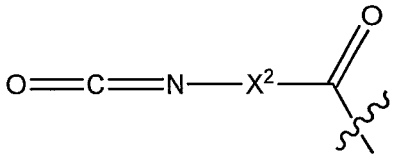
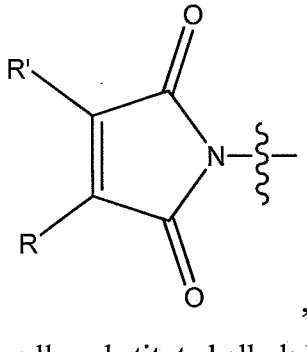
[0019]

[0020]

[0021]

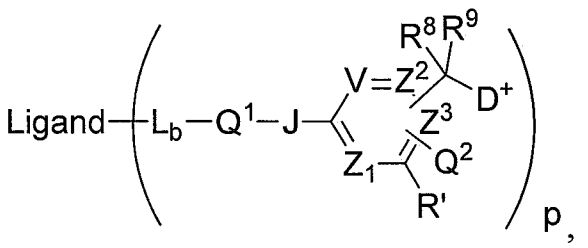
[0022]

[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. A Ligand Drug Conjugate (LDC) composition, wherein the LDC composition is represented by the structure of Formula 1:



(Formula 1)

wherein

"Ligand" is a Ligand Unit (L), wherein L is an antibody or fragment thereof, 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;

L_b is a primary linker;

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;

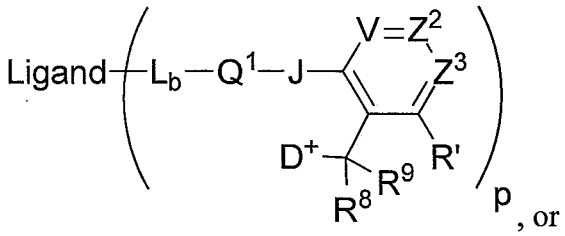
W_w and $W'_{w'}$ are Cleavable units, wherein

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

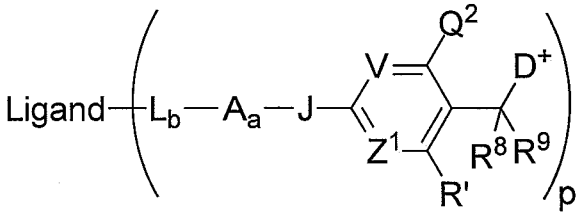
V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing



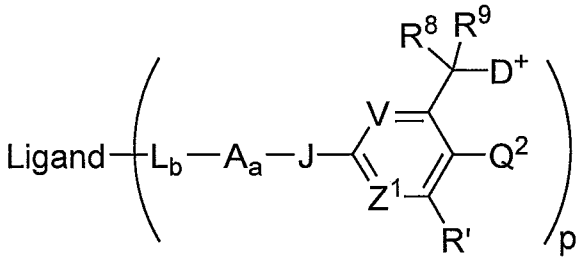
, or

(Formula 2B)

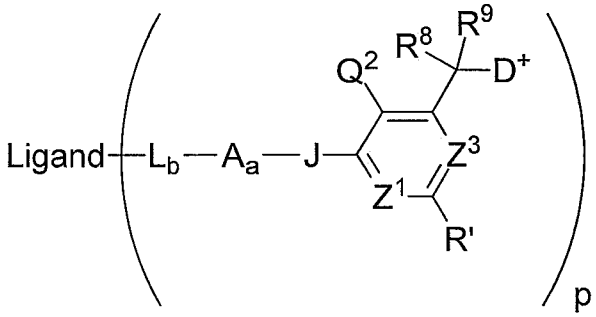
wherein the structure of the composition is represented by the structure of Formula 3A, Formula 3B, Formula 3C, Formula 3D, Formula 3E, or Formula 3F:



(Formula 3A)

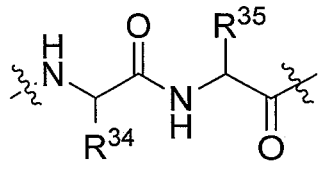


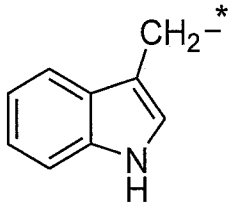
(Formula 3B)



(Formula 3C)

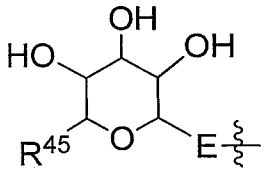
4. The LDC composition of claim 3, wherein the peptide moiety of W is comprised or consists of a dipeptide moiety having the structure of Formula 6:


(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, -$(CH_2)_3$NH(C=O)NH_2, -$(CH_2)_3$NH(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 2A or 2B 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 subscript a is 0, and wherein the dipeptide's bond to J is cleavable by an intracellular or regulatory protease, and

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 has the structure of Formula 7:


(Formula 7),

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.

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

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

R' is hydrogen or an electron withdrawing group;

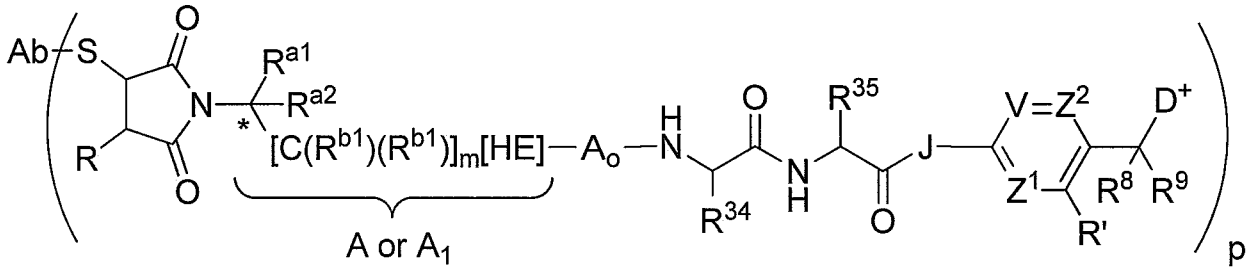
R^8 is hydrogen;

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

R^{45} is $–CO_2H$; and

subscript p is a number ranging from 1 to 8.

6. The LDC composition of claim 5, wherein the structure of the composition is represented by Formula 10:



(Formula 10)

wherein

S is a sulfur atom of the antibody Ligand Unit;

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), in which the succinimide ring is in hydrolyzed form, 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 define 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 -$(CH_2)_3NH(C=O)NH_2$, or -$(CH_2)_2CO_2H$;

J is –NH-;

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

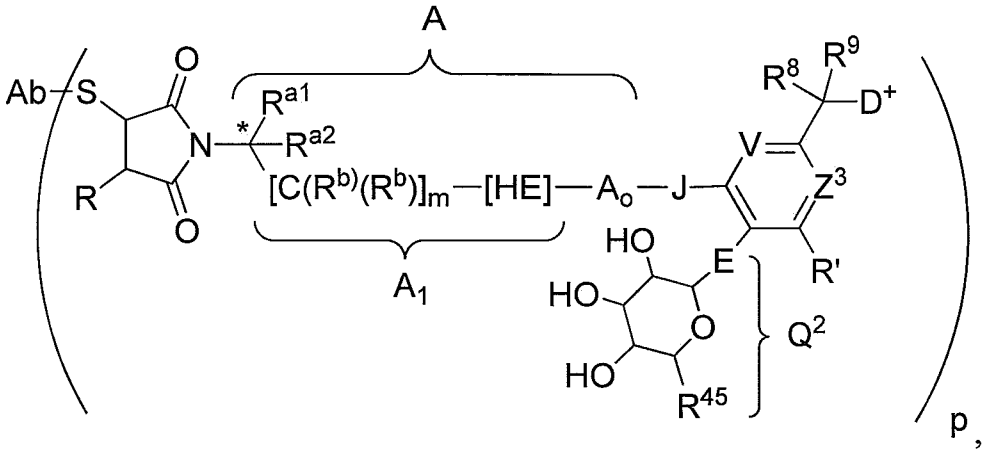
R' is hydrogen or an electron donating group;

R^8 is hydrogen; and

R^9 is hydrogen or methyl,

or

wherein the structure of the composition is represented by Formula 12:



(Formula 12)

wherein

S is a sulfur atom of the antibody Ligand Unit;

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' 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 an acid addition salt thereof, wherein R^{22} and R^{23} independently are

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

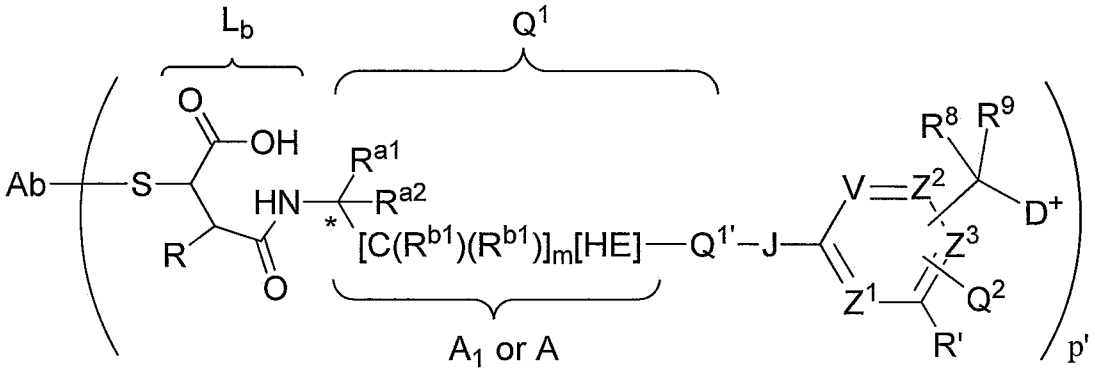
wherein R^{PR} is a suitable protecting group, -NH_2, or -$N(R^G)(R^{PG})$, wherein R^G independently selected is as previously defined or both R^G together with the nitrogen atom to which they are attached define a 5- or 6-membered heterocycloalkyl or both R^{PR} together form a suitable protecting 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, optionally substituted, or optionally substituted heteroaryl, or both R^{39}, R^{40} together with the carbon to which they are attached define 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, 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

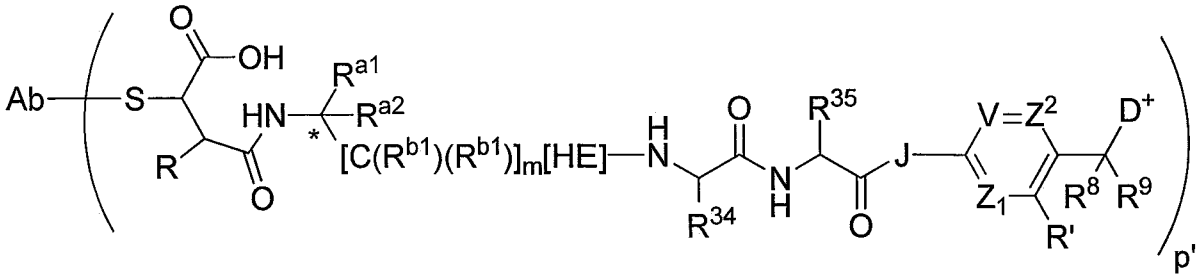
wherein the indicated starred (*) carbon is predominantly in the same absolute configuration as the alpha carbon of an L-amino acid when that indicated carbon has chirality.

8. The LDC composition of claim 3, wherein each Ligand Drug Conjugate compound of the composition independently has the structure of Formula 16A or Formula 16B:

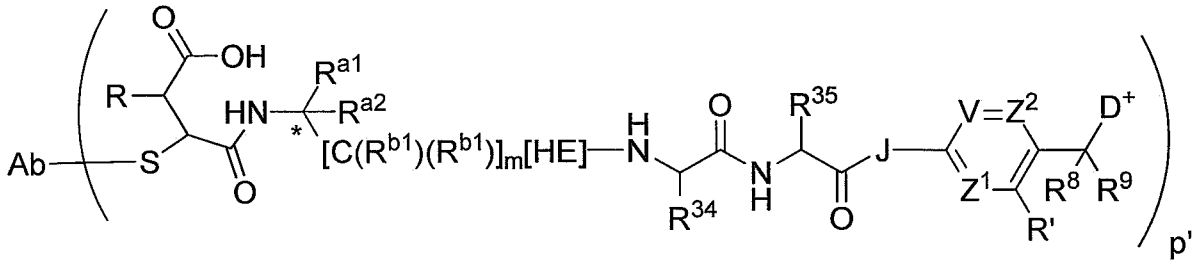


(Formula 16A)

9. The LDC composition of claim 8, wherein each Ligand Drug Conjugate compound of the composition independently has the structure of Formula 17A or Formula 17B:



(Formula 17A)



(Formula 17B)

wherein

J is –NH-;

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 define 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)-;

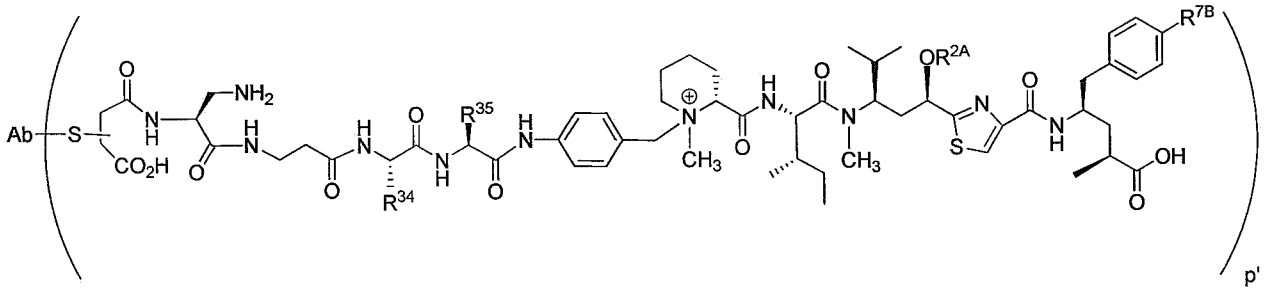
J is –O- or –NH;

one of V, Z^1 is $=C(R^{24})$-, wherein R^{24} is hydrogen, -Cl or $–NO_2$, and the other V, Z^1 and Z^2 are $=CH_2$-;

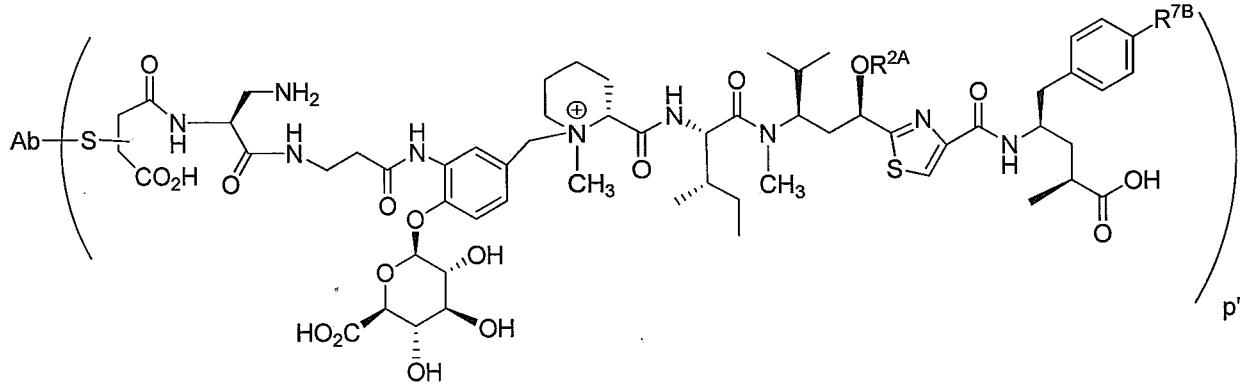
R^8 is hydrogen;

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

17. The LDC composition of claim 1, wherein the Ligand Drug Conjugate compounds of the composition are represented by the structure of:



or



wherein

Ab is the 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;

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

the R^{7B} substituent is absent, so that R^{7B} is replaced by hydrogen, or is –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.

18. The LDC composition of claim 11, wherein the quaternized tertiary amine-containing tubulin disrupting agent–D^+ is a

quaternized dolastatin 10 or quaternized dolastatin 15, or

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

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

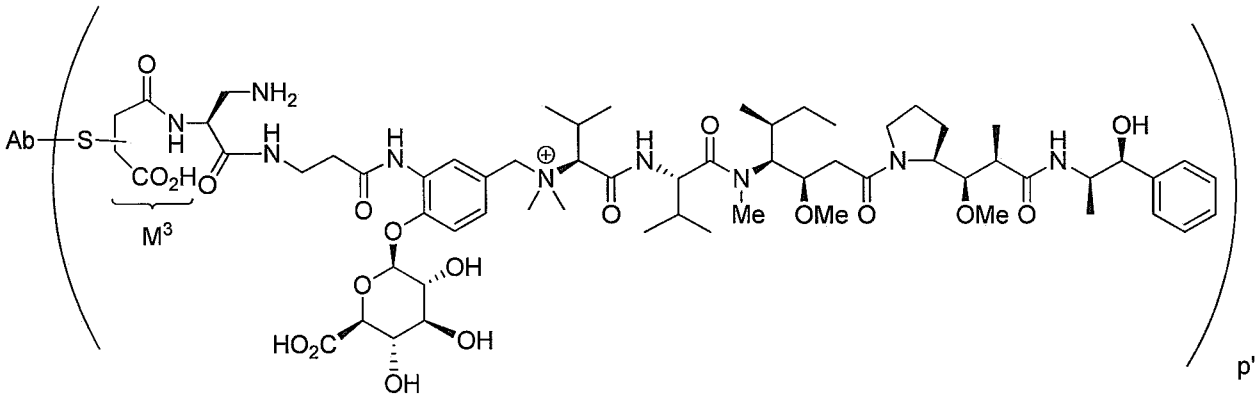
Z is O, S, NH, or NR^{46}, wherein R^{46} is C_1-C_8 alkyl;

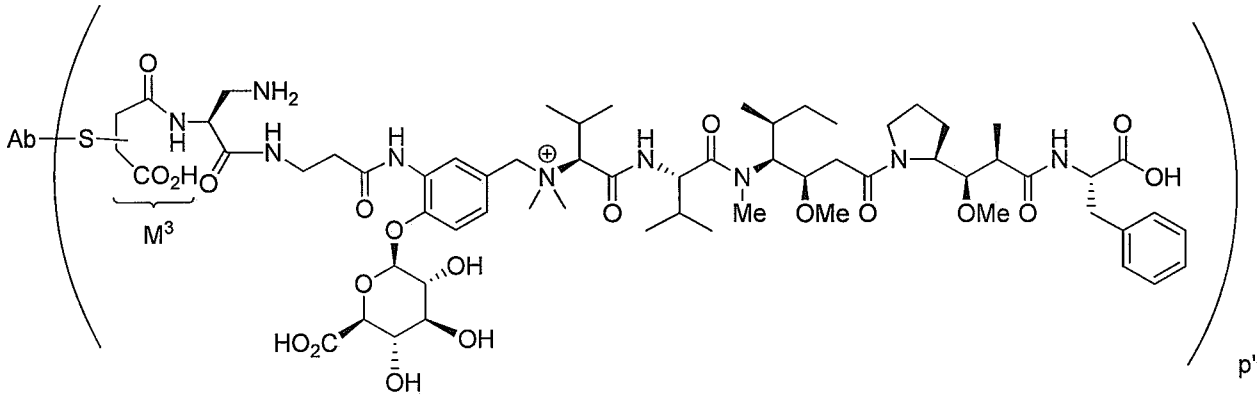
X^1 is C_1-C_{10} alkylene;

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

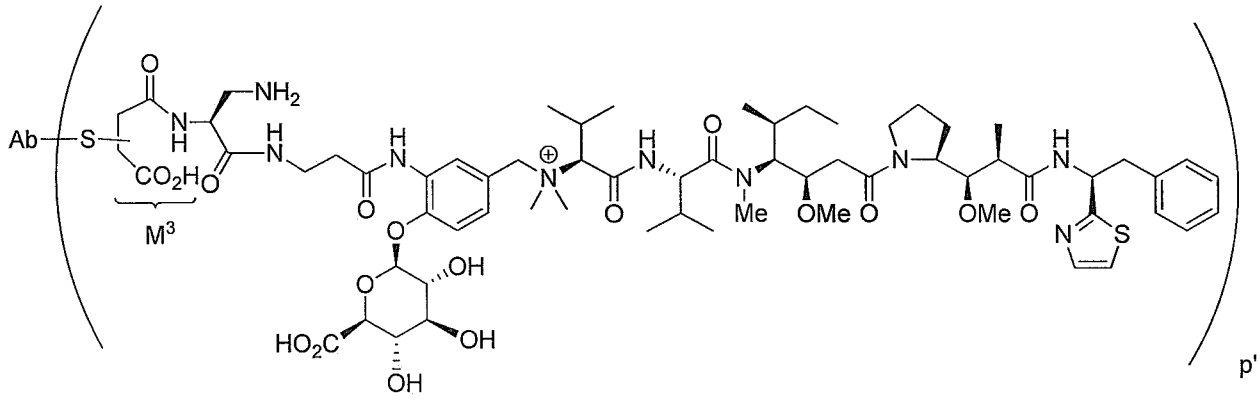
the wavy line indicates covalent bonding of D^+ to the remainder of the composition structure.

19. The LDC composition of claim 18 wherein the Ligand Drug Conjugate compounds of the composition are represented by the structure of:





or

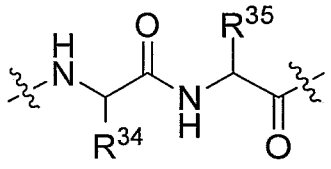


subscript m is 0 or 4; and

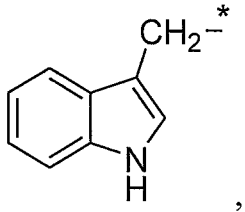
R^{22} and R^{23} are each hydrogen or one of R^{22}, R^{23} is hydrogen and the other is –C(O)Ot-Bu.

24. The Drug-Linker compound of claim 21, 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, or 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.

25. The Drug-Linker compound of claim 24, 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 

, 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 IIA or IIB and the wavy 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 cleavable by an intracellular or regulatory protease, and