wherein the antigen is an extracellularly accessible cell-surface protein or glycoprotein, or L is a ligand that specifically binds to an extracellularly accessible receptor,

wherein the receptor is capable of passive or facilitative transport of a Ligand Drug Conjugate compound bound to the receptor, and

wherein the cell-surface protein, glycoprotein, or receptor is characteristic of, or in greater abundance on, abnormal cells in comparison to normal cells, wherein the cells are mammalian cells;

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-;

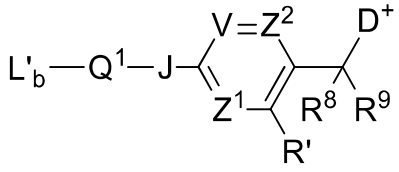
D^+ represents the structure of a quaternized tertiary amine-containing drug, wherein the tertiary amine-containing drug is covalently bonded to the -C(R8)(R9)- moiety through the quaternized tertiary amine,

wherein the tertiary amine-containing drug (D) is a tertiary amine-containing cytotoxic or cytostatic drug;

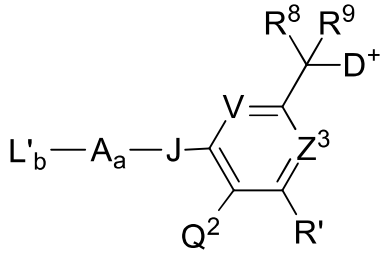
subscript p' is an integer ranging from 1 to 20; and

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

[0005a] In another aspect, the present disclosure provides a Drug-Linker compound, wherein the Drug Linker compound has the structure of Formula IIA or Formula IIIF:



(Formula IIA)



(Formula IIIF),

or a pharmaceutically acceptable salt thereof, wherein

L'$_b$ is a ligand covalent binding moiety precursor capable of forming a covalent bond to an antibody, a fragment of an antibody, or a ligand that specifically binds to an extracellularly accessible receptor so as to provide a Ligand Drug Conjugate (LDC) compound of Formula 2A or Formula 3F as described herein;

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;

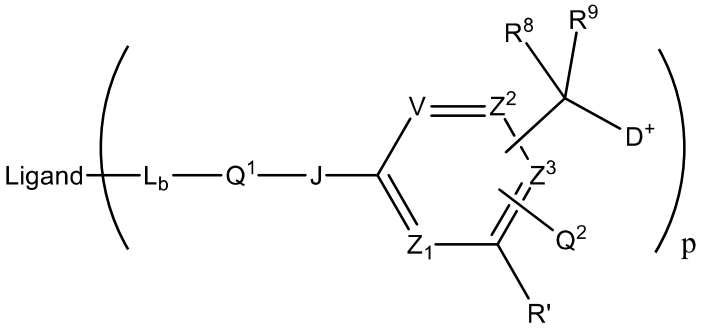
J is -NH-;

D^+ represents the structure of a quaternized tertiary amine-containing drug, wherein the tertiary amine-containing drug is covalently bonded to the -C(R8)(R9)- moiety through the quaternized tertiary amine,

wherein the tertiary amine-containing drug (D) is a tertiary amine-containing cytotoxic or cytostatic drug; and

wherein said selective cleavage by the lysosomal protease or cleavage by the intracellular glycosidase initiates release of D from the Drug-Linker compound, or from a Ligand Drug Conjugate compound as described herein, or an N-acetyl-cysteine Conjugate compound either of which being derived from the Drug-Linker compound.

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



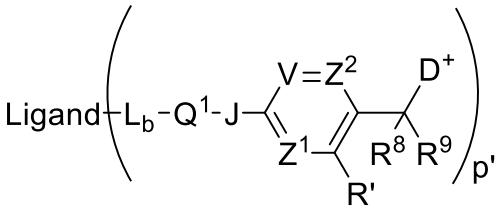
(Formula 1)

,

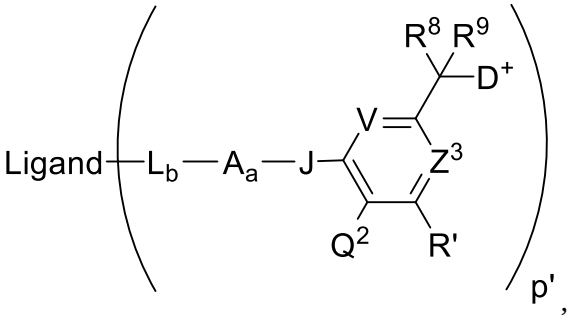
[0006] wherein "Ligand" is from a targeting moiety, which selectively binds to a target moiety; L_b is a ligand covalent binding moiety; Q^1 is A_a-W_w, wherein A is an optional Stretcher unit, so that the subscript a is 0 when A is absent or a is 1 when A is present and is optionally comprised of two, 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

CLAIMS

1. A pharmaceutical formulation comprising 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 an antibody or a fragment of an antibody, thereby defining an antibody drug conjugate (ADC), wherein the antibody or the fragment of the antibody is capable of selective binding to an antigen, provided that the antibody fragment has the requisite number of attachment sites for conjugation,

wherein the antigen is an extracellularly accessible cell-surface protein or glycoprotein, or L is a ligand that specifically binds to an extracellularly accessible receptor,

wherein the receptor is capable of passive or facilitative transport of a Ligand Drug Conjugate compound bound to the receptor, and

wherein the cell-surface protein, glycoprotein, or receptor is characteristic of, or in greater abundance on, abnormal cells in comparison to normal cells, wherein the cells are mammalian cells;

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 covalently bonded to the -C(R^8)(R^9)- moiety through the quaternized tertiary amine,

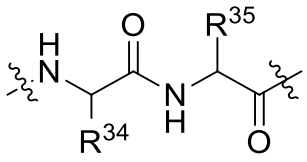
wherein the tertiary amine-containing drug (D) is a tertiary amine-containing cytotoxic or cytostatic drug;

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

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

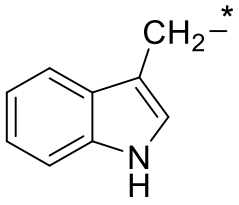
2. The pharmaceutical formulation of claim 1, wherein W of Formula 2A has a peptide bond to J that is selectively cleavable by the lysosomal protease and the carbohydrate moiety of Formula 3F is a glucuronic acid residue, wherein said cleavage by the intracellular glycosidase is by an intracellular glucuronidase.

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



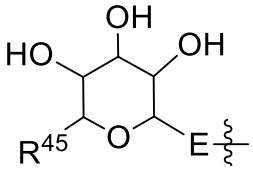
(Formula 6),

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:

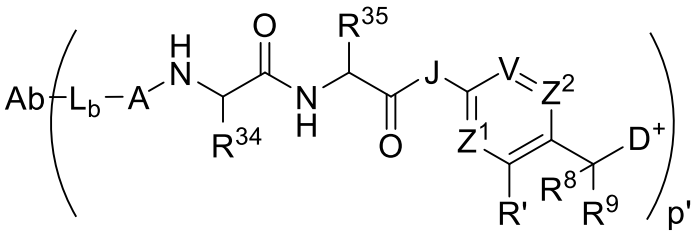
 (Formula 7),

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 pharmaceutical formulation 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 $-CH(OH)CH_3$;

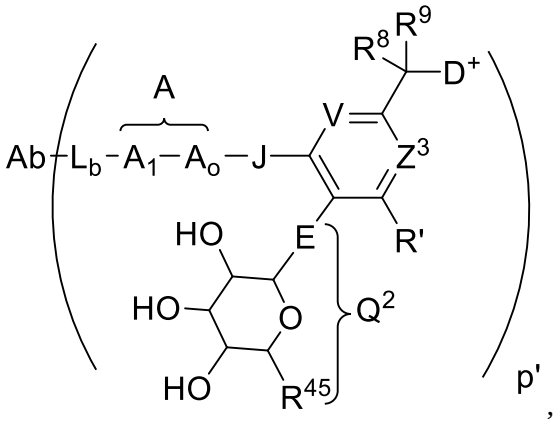
R^{35} is methyl, $-(CH_2)_3NH(C=O)NH_2$, or $-(CH_2)_2CO_2H$;

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-;

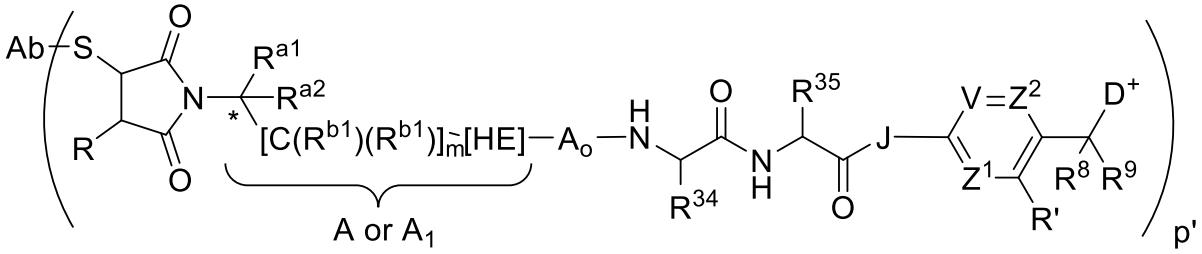
V and Z^3 are each =CH-;

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 pharmaceutical formulation 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;

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), 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 $-CH(OH)CH_3$;

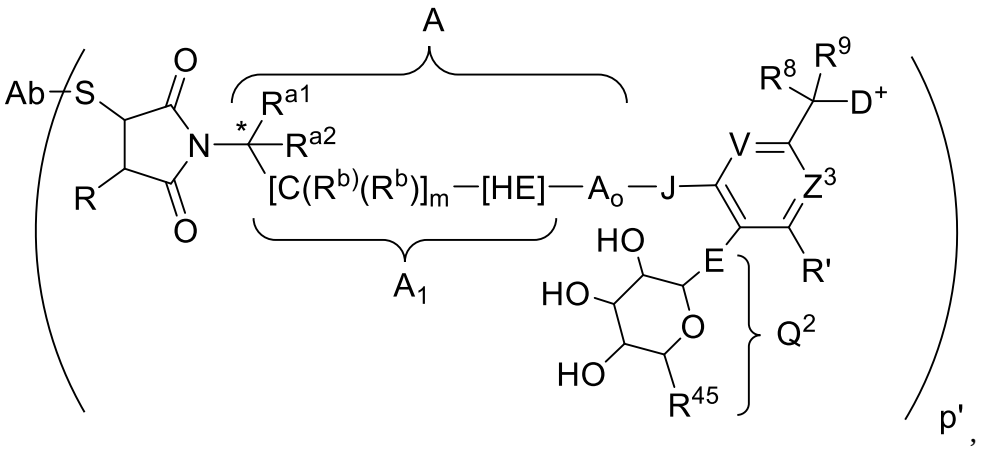
R^{35} is $–(CH_2)_3NH(C=O)NH_2$ or $–(CH_2)_2CO_2H$;

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;

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) 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} independently is hydrogen or optionally substituted C_1-C_6 alkyl;

HE is absent or is –C(=O)-;

R^{45} is $–CO_2H$;

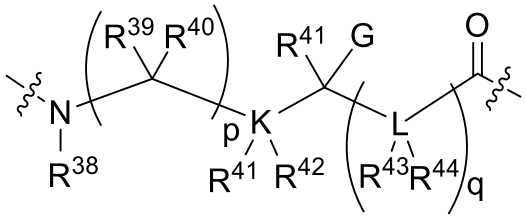
E is –O'-;

J is –NH-;

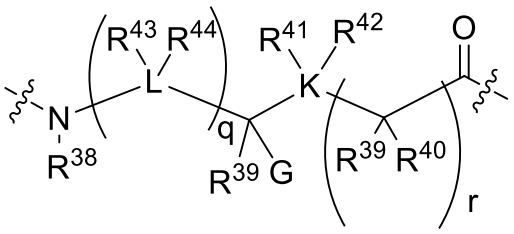
R', R^8, and R^9 are each hydrogen; and

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

6. The pharmaceutical formulation 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 each of subscript p and r is an integer ranging from 1 to 12;

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

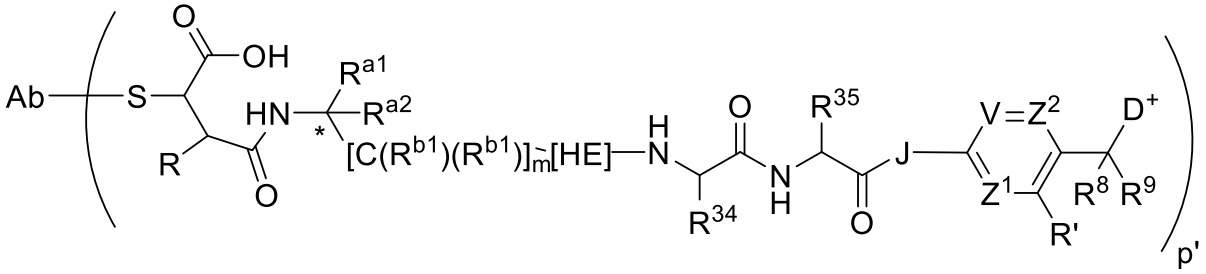
wherein R^{PR} is a suitable protecting group, $-NH_2$, or $-N(R^G)(R^G)$, wherein each R^G is independently selected optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or both R^G together with the nitrogen atom to which they are attached define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

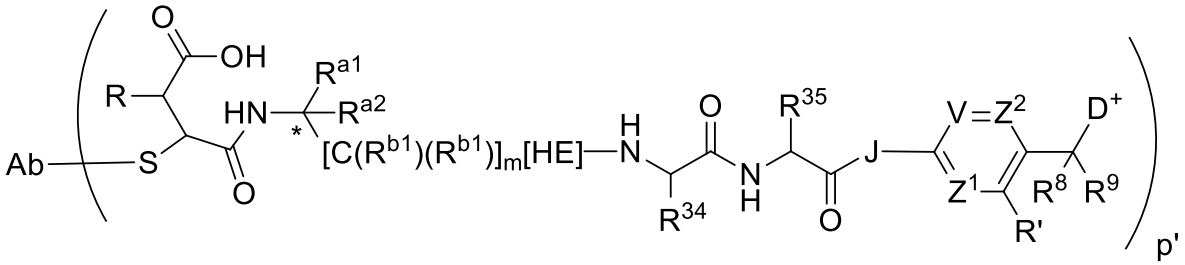
wherein the indicated starred (*) carbon atom is predominantly in the same absolute configuration as the alpha carbon atom of an **L**-amino acid when that indicated carbon atom has chirality.

7. The pharmaceutical formulation 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;

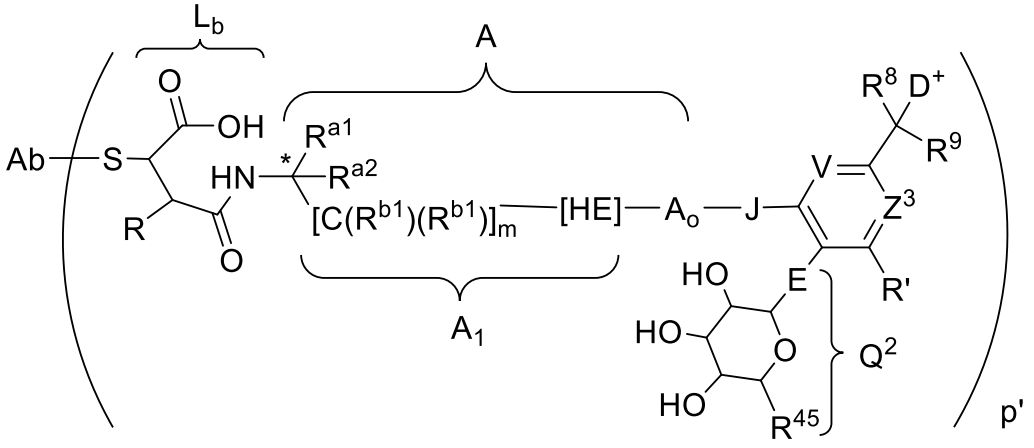
V, Z^1, and Z^2 are each =CH-;

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

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

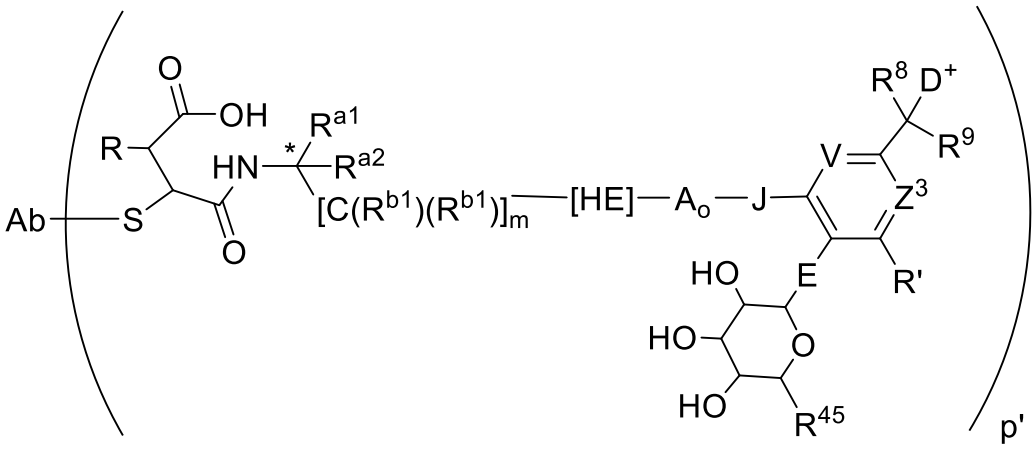
or

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'-;

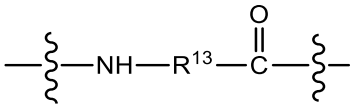
J is –NH-;

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 pharmaceutical formulation of claim 7, wherein A_O, when present, has the structure of:



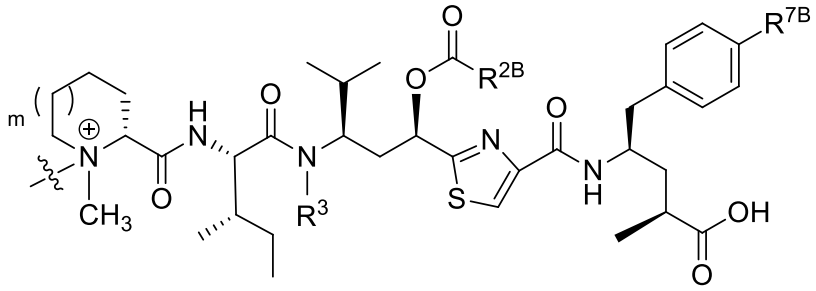
wherein R^{13} is -C_1-C_{10} alkylene-, -C_3-C_8 carbocyclo-, -arylene-, -C_1-C_{30} heteroalkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 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 pharmaceutical formulation of claim 1, wherein $–D^+$ is a quaternized tertiary amine-containing tubulin disrupting agent.

10. The pharmaceutical formulation 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;

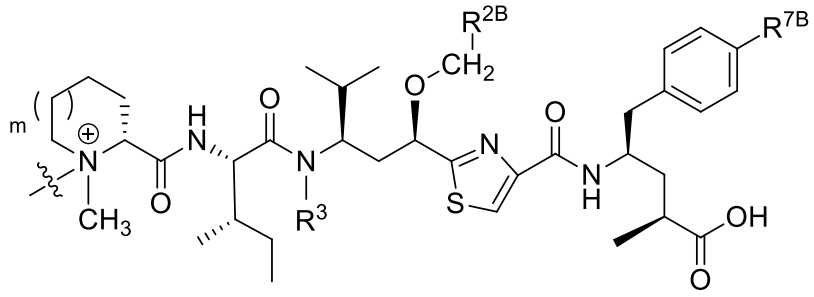
-$OC(O)R^{2B}$ is –$OC(O)CH_3$, -$OC(O)CH_2CH_3$, -$OC(O)CH(CH_3)_2$, -$OC(O)C(CH_3)_3$, or –$OC(O)CH=CH_2$;

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;

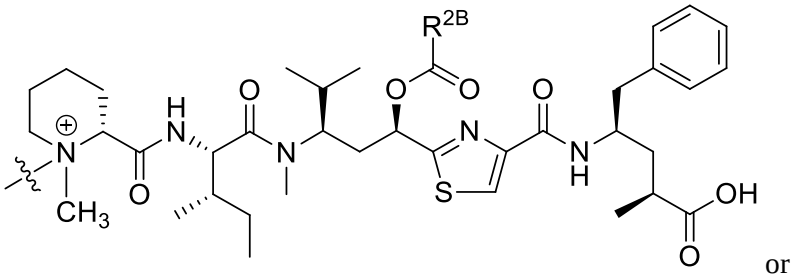
subscript m is 1;

$–OCH_2R^{2B}$ 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 pharmaceutical formulation of claim 10, wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of:



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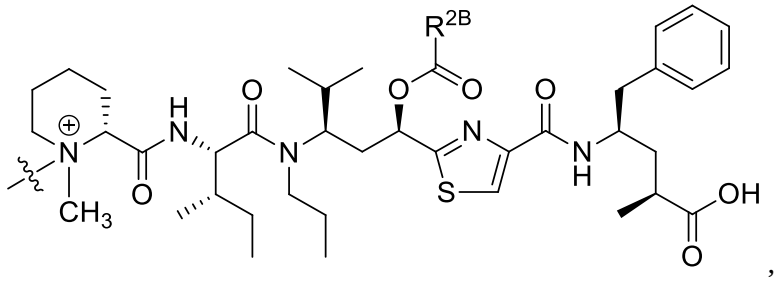


,

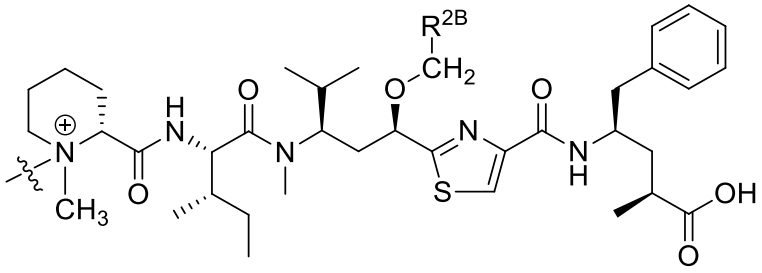
or a pharmaceutically acceptable salt thereof, wherein

subscript m is 1;

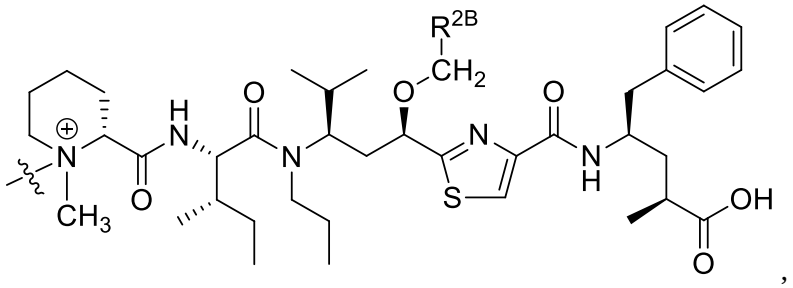
R^{2B} is $–CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, or $-CH_2C(CH_3)_3$,

or

$–D^+$ has the structure of:



or

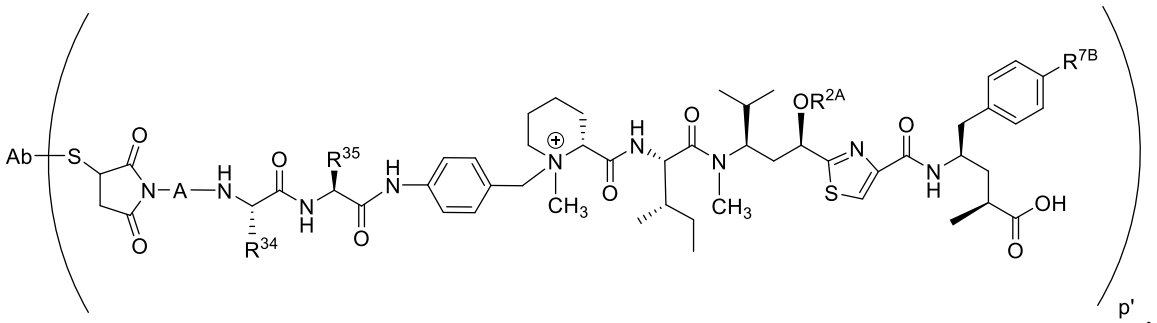


,

in pharmaceutically acceptable salt form, 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 pharmaceutical formulation of claim 1, wherein Formula 2A is represented by the structure of:



p' ,

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;

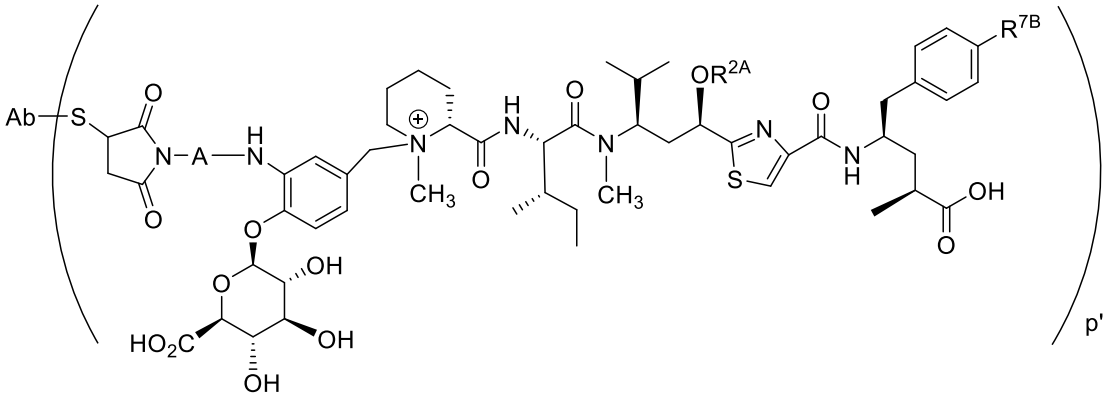
R^{2A} is lower alkyl or $–C(=O)R^{2B}$, wherein R^{2B} is lower alkyl;

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;

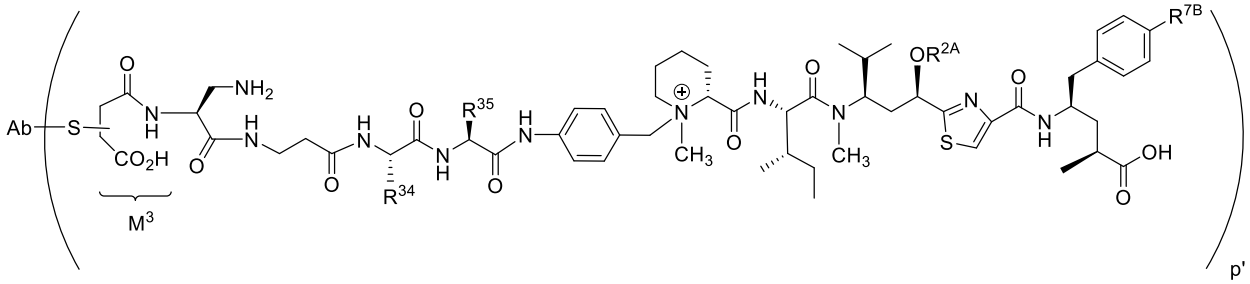
R^{7B} is hydrogen or –OH;

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;

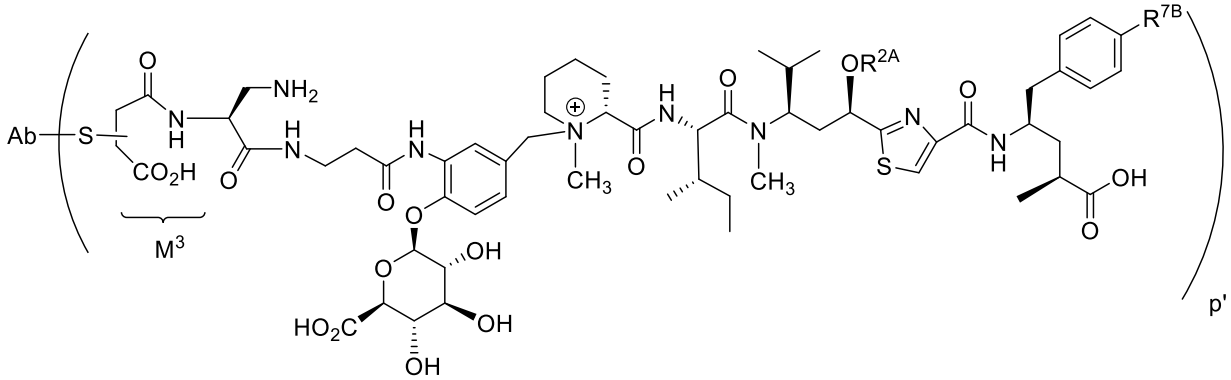
subscript p' is an integer ranging from 1 to 8; and

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

13. The pharmaceutical formulation 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 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 M^3 carboxylic acid;

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

R^{7B} is hydrogen or–OH;

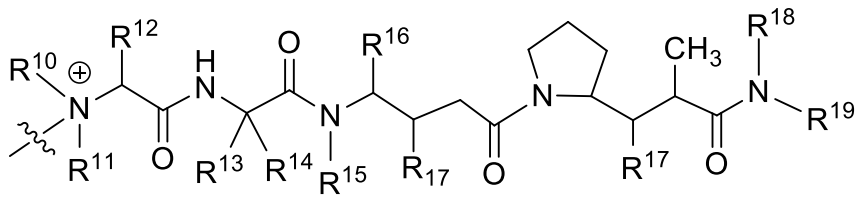
R^{34} is isopropyl and R^{35} is $–CH_3$, isopropyl, $–CH_2CH_2CH_2NH(C=O)NH_2$, or $–CH_2CH_2CO_2H$; and

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

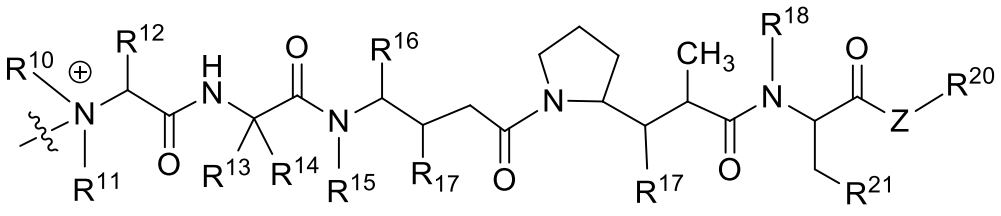
14. The pharmaceutical formulation of claim 9, wherein the quaternized tertiary amine-containing tubulin disrupting agent $–D^+$ is

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

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;

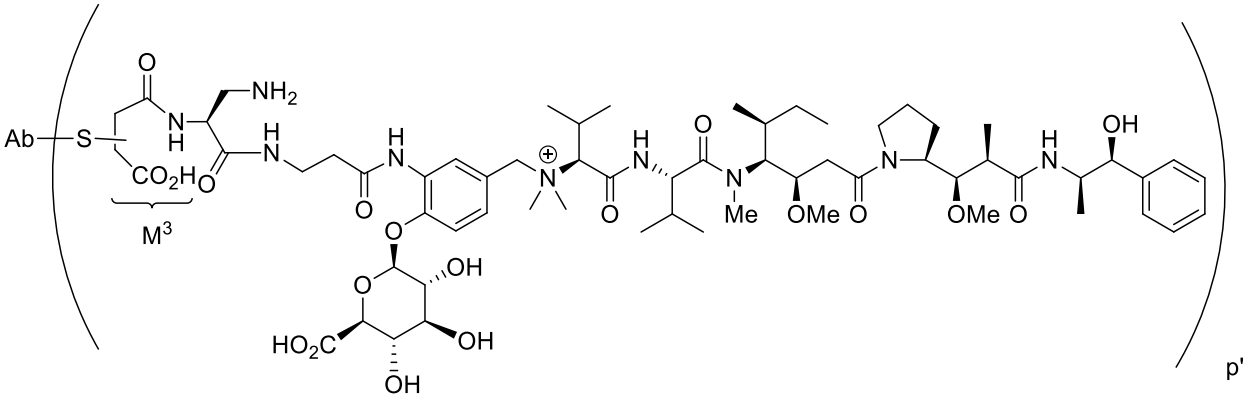
each R^{50} is independently C_1-C_8 alkyl or $-(CH_2)_n-COOH$;

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

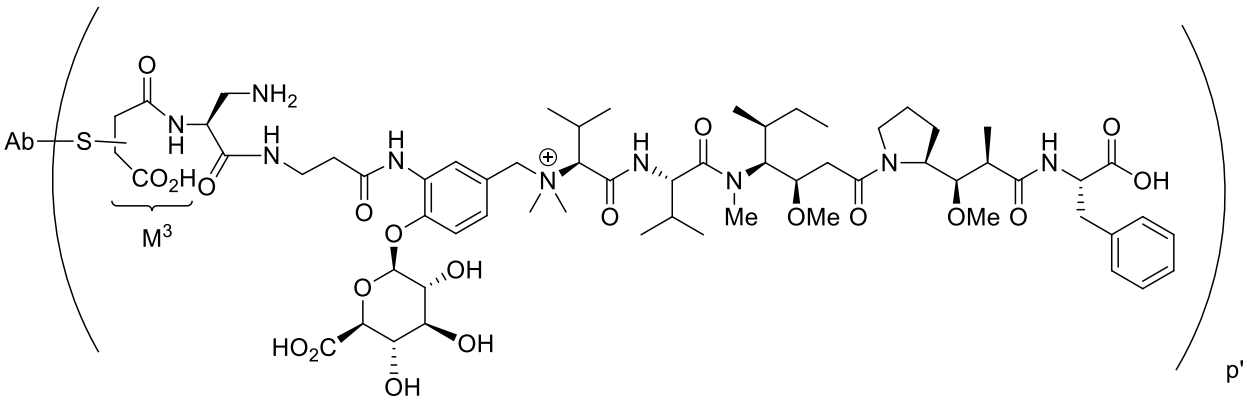
X^1 is C_1-C_{10} alkylene; and

subscript n is an integer ranging from 0 to 6.

15. The pharmaceutical formulation 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

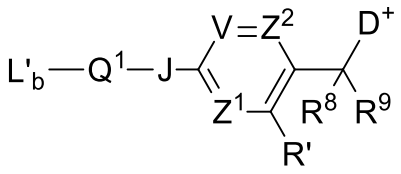
subscript p' is an integer ranging from 1 to 8.

16. The pharmaceutical formulation 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.

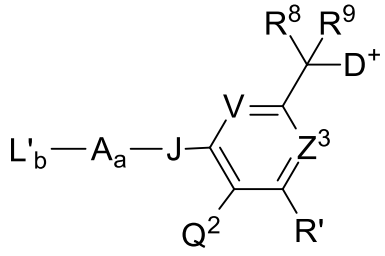
17. The pharmaceutical formulation of claim 16, wherein the antibody is a monoclonal antibody.

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

19. A Drug-Linker compound, wherein the Drug Linker compound has the structure of Formula IIA or Formula IIIF:



(Formula IIA)



(Formula IIIF),

or a pharmaceutically acceptable salt thereof, wherein

L'$_b$ is a ligand covalent binding moiety precursor capable of forming a covalent bond to an antibody, a fragment of an antibody, or a ligand that specifically binds to an extracellularly accessible receptor so as to provide a Ligand Drug Conjugate (LDC) compound of Formula 2A or Formula 3F of claim 1;

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;

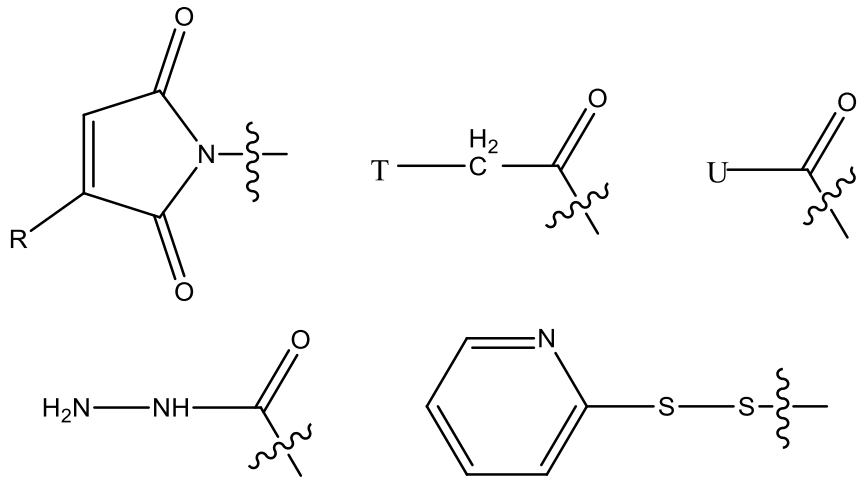
J is -NH-;

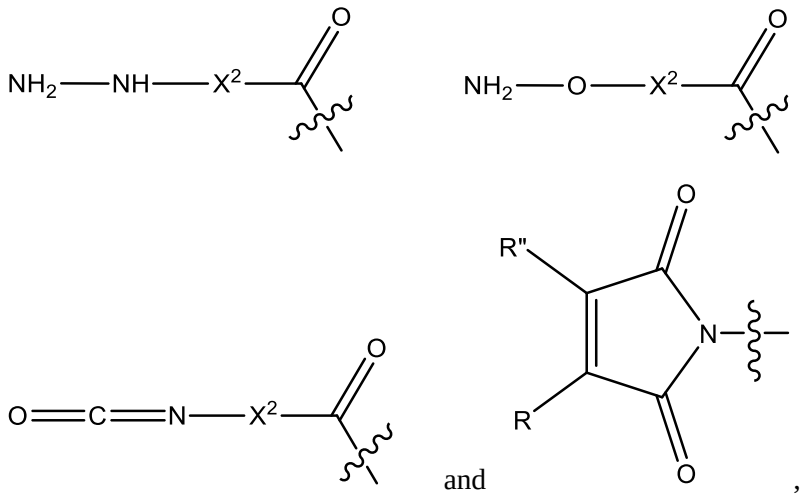
D^+ represents the structure of a quaternized tertiary amine-containing drug, wherein the tertiary amine-containing drug is covalently bonded to the -C(R^8)(R^9)- moiety through the quaternized tertiary amine,

wherein the tertiary amine-containing drug (D) is a tertiary amine-containing cytotoxic or cytostatic drug; and

wherein said selective cleavage by the lysosomal protease or cleavage by the intracellular glycosidase initiates release of D from the Drug-Linker compound, or from a Ligand Drug Conjugate compound of claim 1, or an N-acetyl-cysteine Conjugate compound either of which being derived from the Drug-Linker compound.

20. The Drug Linker compound of claim 19, wherein L'_b has a structure selected from the group consisting of:





wherein

the wavy line indicates covalent attachment to A if subscript a is 1 or to J when subscript a is 0;

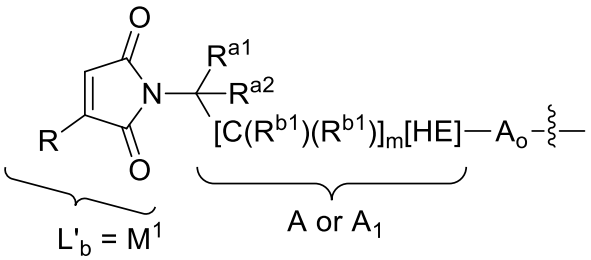
R and R" is hydrogen or -Cl;

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}, wherein R^{57} is C_1-C_6 alkyl or aryl; 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.

21. The Drug-Linker compound of claim 19, wherein subscript a is 1 so that A in Q^1 of Formula IIA or A of Q^2 in Formula IIIF is bonded to L'$_b$, wherein L_b'-A- is of general formula M^1-A_1-A_O-, 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} are each hydrogen;

R^{a1} is hydrogen, methyl, ethyl, or a Basic Unit (BU) having 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 is independently 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 is independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^2 together to the carbon(s) to which they are attached 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} are each independently 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 nitrogen-containing heterocycloalkyl, wherein the $–N(R^{22})(R^{23})$ moiety is optionally in the form of its acid addition salt;

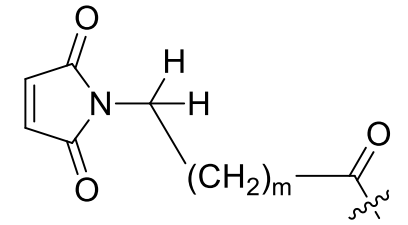
HE is -C(=O)-;

subscript m is an integer ranging from 0 to 4;

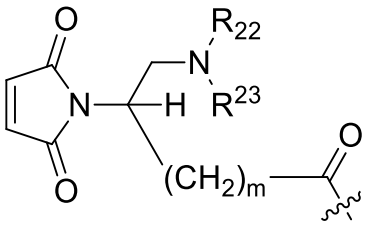
each R^{b1} is hydrogen; and

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

22. The Drug-Linker compound of claim 21, wherein M^1-A_1-A_O- of Formula VIII has the structure of



,



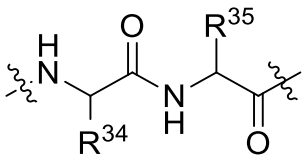
wherein

subscript m is 0 or 4; and

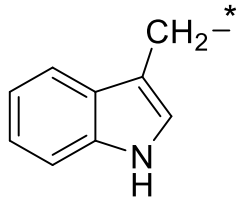
R^{22} and R^{23} are each hydrogen and the amine is in the form of its acid addition salt, or one of R^{22} and R^{23} is hydrogen and the other is –C(O)Ot-Bu.

23. The Drug Linker compound of claim 19, wherein W of Formula IIA has a peptide bond to J that is selectively cleavable by the lysosomal protease and the carbohydrate moiety of Formula IIIF is a glucuronic acid residue, wherein said cleavage by an intracellular glycosidase is by an intracellular glucuronidase.

24. The Drug Linker compound of claim 19, wherein W Formula IIA is a dipeptide moiety having the structure of Formula 6:



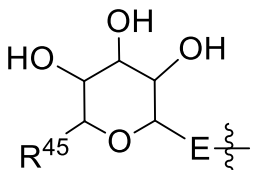
(Formula 6),

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, -$(CH_2)_3$NH(C=O)NH_2, -$(CH_2)_3$NH(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 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 IIIF has the structure of Formula 7:



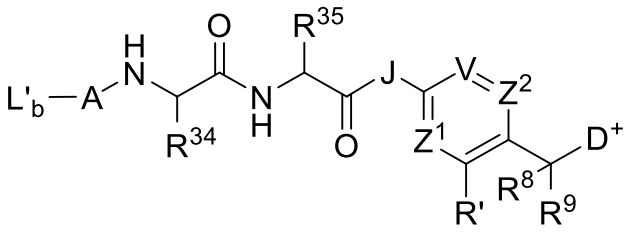
(Formula 7),

wherein the wavy line represents E bonded to the arylene moiety of Formula IIIF,

wherein E is –O'-; and

R^{45} is –CH_2OH or –CO_2H.

25. The Drug Linker compound of claim 19, wherein Formula IIA is represented by the structure of Formula IX:



(Formula IX)

wherein

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

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

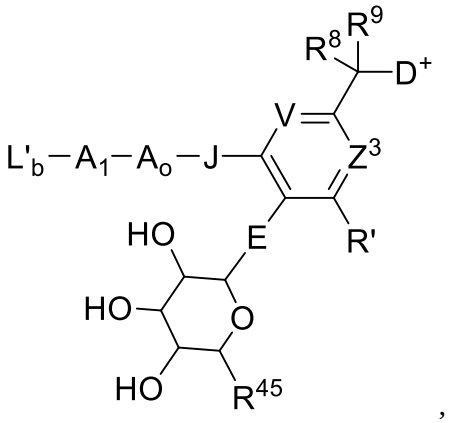
R^{35} is methyl, -$(CH_2)_3NH(C=O)NH_2$, or –$(CH_2)_2CO_2H$;

J is –NH-; and

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

and

Formula IIIF is represented by 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 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'-;

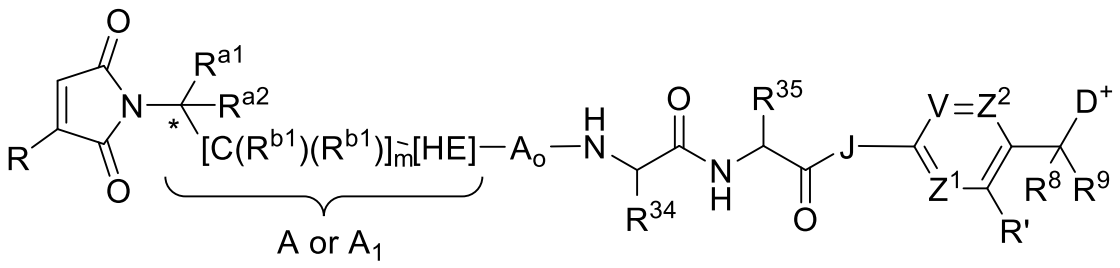
J is –NH-;

V and Z^3 are each =CH-;

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

R^{45} is –CO_2H.

26. The Drug Linker compound of claim 25, wherein Formula IIA is represented by the structure of Formula X:



(Formula X)

or a pharmaceutically acceptable salt thereof, wherein

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), 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 -$CH(OH)CH_3$;

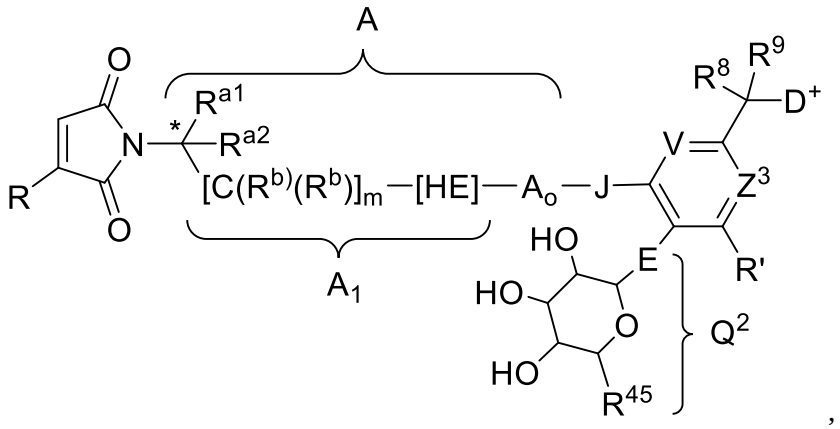
R^{35} is –$(CH_2)_3NH(C=O)NH_2$ or –$(CH_2)_2CO_2H$;

J is –NH-; and

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

and

wherein Formula IIIF is represented by the structure of Formula XII:



(Formula XII)

or a pharmaceutically acceptable salt thereof, wherein

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) 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} independently is hydrogen or optionally substituted C_1-C_6 alkyl;

HE is –C(=O)-;

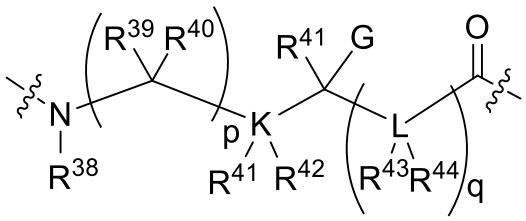
R^{45} is $–CO_2H$;

E is –O’-;

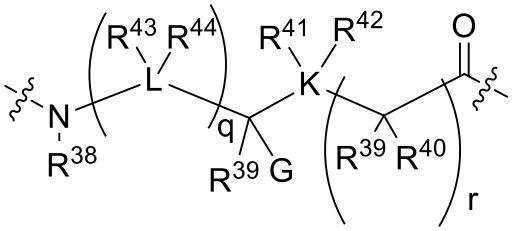
J is –NH-; and

R’, R^8, and R^9 are each hydrogen.

27. The Drug Linker compound of claim 26, 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_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 each of subscript p 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, 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},

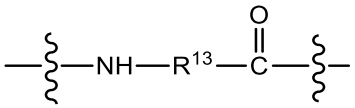
wherein R^{PR} is a suitable protecting group, -NH_2, or -$N(R^G)(R^G)$, wherein each R^G is independently optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or both R^G together with the nitrogen atom to which they are attached define a 5- or 6-membered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

28. The Drug Linker compound of claim 27, 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 X or Formula XII is predominantly in the same absolute configuration as the alpha carbon of an **L**-amino acid when that indicated carbon has chirality.