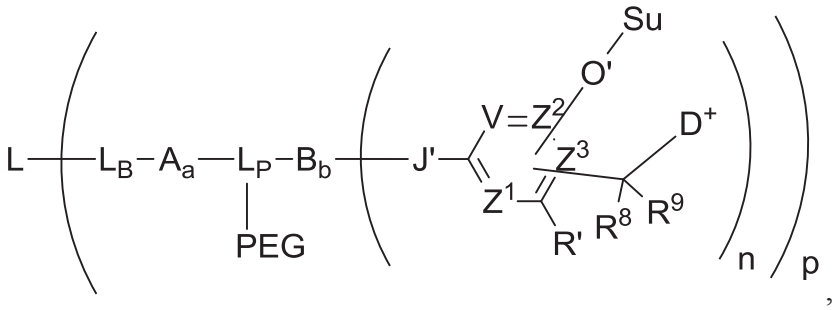
[0004] Because of the difficulty in incorporating a tubulysin compound into a LDC that will conditionally release that compound in unaltered form so as to retain its cytotoxic activity, there is a need in the art for such conjugates that use the tertiary amine nitrogen of a tubulysin's N-terminal component as the site of conjugation in order for release of fully active tubulysin compound at the targeted site of action. There is also a need to mask the hydrophobicity of a hydrophobic tubulysin compound within a LDC to allow for increased loading of the compound to the LDC's targeting Ligand Unit so as to increase the amount of tubulysin compound delivered to the desired site of action while diminishing aggregation resulting in elimination of the LDC and to rectify the loss of the acetate moiety in the tubuvaline (Tuv) component *in vivo*. Either event alone or in combination diminishes the efficacy of the administered LDC.

SUMMARY

[0005] Principle examples of the disclosure are Ligand Drug Conjugate (LDC) compositions, wherein a LDC composition is represented by the structure of Formula 1A

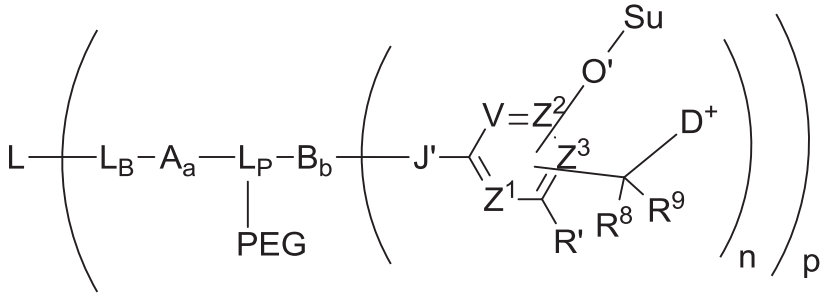


(Formula 1A)

[0006] wherein L is a Ligand Unit (L); L_B is a Ligand Covalent Binding Unit; L_P is a Parallel Connector Unit; PEG is a Polyethylene Glycol Unit; subscript a is 0 or 1; subscript b is 0 or 1; A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4); B is an Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A; subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 and subscript b is 0 or 1 so that B is A_O when subscript b is 1 and subscript n is 1; Su is a carbohydrate moiety; -O'- represents an

oxygen atom of an O-glycosidic bond cleavable by a glycosidase; -J'- represents a heteroatom, optionally substituted when nitrogen; 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, or -OCH_3 or other an electron donating group, -O'-Su, or –C(R^8)(R^9)-D^+, wherein at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})-, provided, 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 –O'-Su so that –O'-Su is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})-, and the –O'-Su 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; D^+ is a quaternized tubulysin Drug Unit; subscript p is a number ranging from 1 to 24; and wherein said glycosidase cleavage initiates release of a tubulysin therapeutic compound (D) from a Ligand Drug Conjugate compound of the composition.

[0006a] In one aspect, there is provided a Ligand Drug Conjugate composition wherein the composition is represented by the structure of Formula 1A:



(Formula 1A)

wherein

L is an antibody Ligand Unit, thereby defining an Antibody Drug Conjugate (ADC);

L_B is a Ligand Covalent Binding Unit;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscript a is 0 or 1;

subscript b is 0 or 1;

A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A;

wherein Ligand Covalent Binding Unit, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described

subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 and provided that B is A_O or is absent when subscript n is 1;

Su is a carbohydrate moiety as hereinbefore defined;

-O'- represents an oxygen atom of an O-glycosidic bond cleavable by a glycosidase;

-J'- represents a heteroatom, optionally substituted when nitrogen, from a functional group of B, when B is present, or L_B, when B is absent;

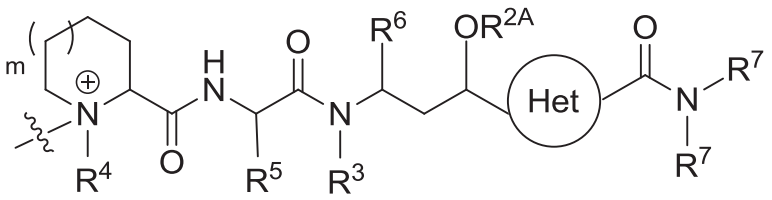
V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, or –OCH_3 or other electron donating group, -O'-Su, or –C(R^8)(R^9)-D^+, wherein at least at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})-,

provided, 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 one and only one other R^{24} is so that –O'-Su is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})-, and the –O'Su 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;

D^+ is a quaternized tubulysin Drug Unit having the structure of:



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

subscript m is 0 or 1;

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

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^5 and R^6 are optionally substituted alkyl;

one R^7 is an optionally substituted alkyl, an optionally substituted arylalkyl, optionally substituted heteroarylalkyl and the other R^7 is hydrogen or an optionally substituted alkyl; and

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

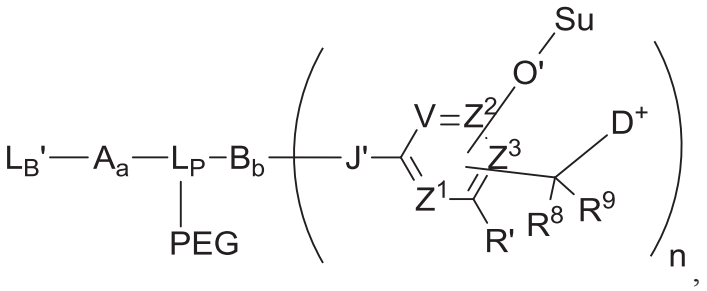
wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Ligand Drug Conjugate structure and wherein each optionally substituted alkyl is independently selected, and

wherein said glycosidase cleavage results in release of a tubulysin compound (D) from a Ligand Drug Conjugate compound of the composition,

wherein the Ligand Drug Conjugate compound has the structure of Formula IA in which subscript p is replaced by subscript p' wherein subscript p' is an integer ranging from 1 to 24.

[0007] In some examples, the Ligand Unit is that of an antibody, thereby defining an antibody drug conjugate (ADC) having an antibody Ligand Unit, and the targeted moiety to which the antibody Ligand Unit is capable of binding is an cell-surface antigen of targeted abnormal cells that is capable of cellular internalization of bound ADC.

[0008] Other principle examples of the disclosure provide for Drug Linker compounds having the structure of Formula IA:

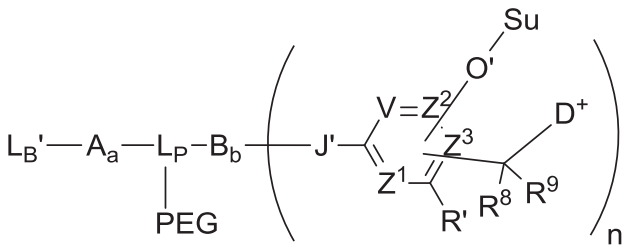


,

(Formula IA)

[0009] wherein L_B' is a Ligand Covalent Binding Unit precursor and the remaining variable groups are as defined for Formula 1A.

[0009a] In another aspect, there is provided a Drug Linker compound, wherein the compound has the structure of Formula IA:



(Formula IA)

wherein

L_B' is a Ligand Covalent Binding Unit precursor;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscript a is 0 or 1;

subscript b is 0 or 1;

A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A;

wherein Ligand Covalent Binding Unit precursor, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described

subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 and provided that B is A_O or is absent when subscript n is 1;

Su is a carbohydrate moiety as hereinbefore defined;

-O'- represents an oxygen atom of an O-glycosidic bond cleavable by a glycosidase;

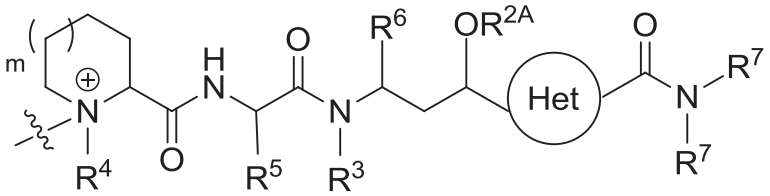
-J', optionally substituted -NH- or -J'- is -N(R^{33})-, wherein R^{33} is hydrogen or methyl, from a functional group of B, when B is present, or of L_P, when B is absent, V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, an electron donating group, -O'-Su, or –C(R^8)(R^9)-D^+, wherein at least at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})-,

provided, 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 so that –O'-Su is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})-, and the –O'Su 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;

D^+ is a quaternized tubulysin Drug Unit having the structure of:



wherein

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

subscript m is 0 or 1;

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

R^3 is hydrogen or optionally substituted alkyl;

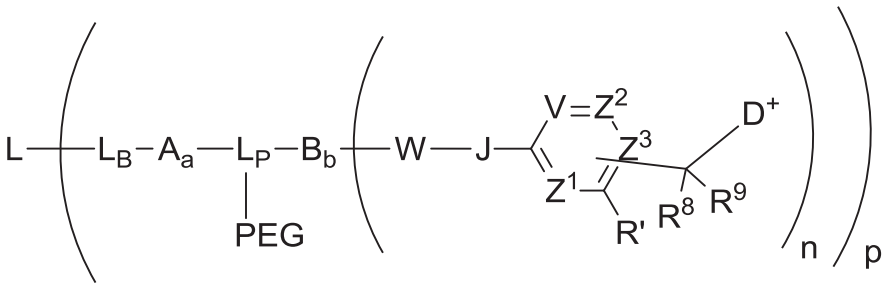
R^4, R^5 and R^6 are optionally substituted alkyl;

one R^7 is an optionally substituted alkyl, an optionally substituted arylalkyl, optionally substituted heteroarylalkyl and the other R^7 is hydrogen or an optionally substituted alkyl; and

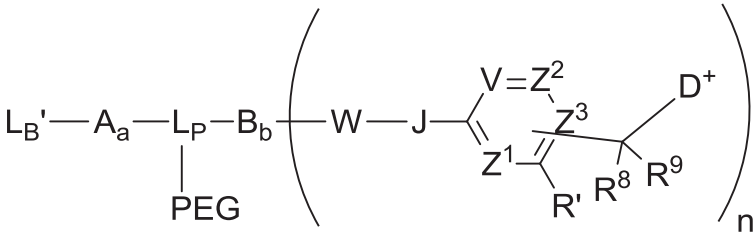
wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug Linker compound structure and wherein optionally substituted alkyl are independently selected; and

wherein said glycosidase cleavage results in release of tubulysin compound (D) from the Drug Linker compound or a Ligand Drug Conjugate compound prepared from the Linker Drug compound wherein the Ligand Drug Conjugate compound has the Formula 1A structure disclosed herein in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

[0010] In other principle examples the disclosure provide for Ligand Drug Conjugate compositions and Drug Linker compounds having the structures of Formula 1B and Formula IB, respectively:



(Formula 1B)

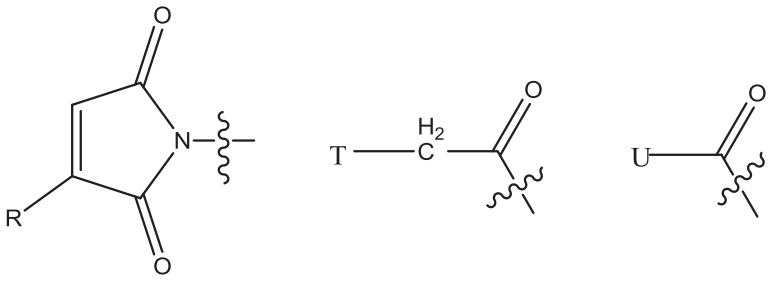


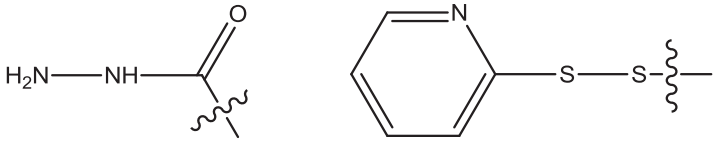
(Formula IB)

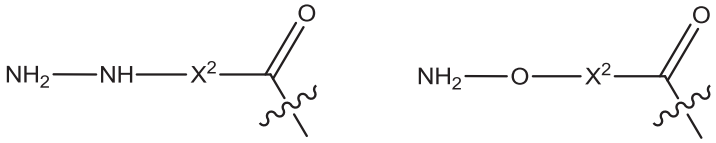
[0011] wherein V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, or -OCH_3 or other an electron donating group, or –C(R^8)(R^9)-D^+, wherein at least one of V, Z^1, and Z^3 is =C(R^{24})-, provided that 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, and Z^3 when that variable group is =C(R^{24})-, J represents a heteroatom, optionally substituted when nitrogen; R' is hydrogen or –OCH_3 or other electron donating group, W is a peptide comprised of an amino acid sequence covalently attached to J through an amide bond wherein that amide bond is cleavable by a protease and the other variable groups are as defined for Formula 1A and Formula IB; and wherein said protease cleavage initiates release of a tubulysin therapeutic compound (D) from a Ligand Drug Conjugate compound of the composition.

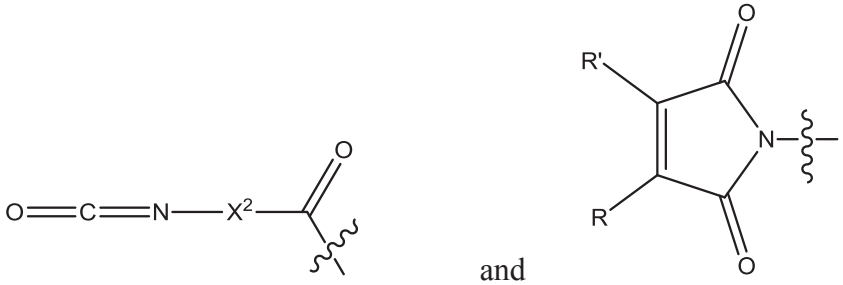
[0012] In some examples, the disclosure provides for LDC conjugate compositions prepared from contacting a Formula IA compound or Formula IB compound with a targeting moiety having a reactive sulfhydryl, amino or aldehyde moiety under suitable conditions to effect condensation of the reactive moiety with the L_B' moiety of the Formula I compound, wherein L_B' is converted to L_B covalently bonded to a Ligand Unit that corresponds to or incorporates the targeting agent as a result of said contact.

[0013] In some examples, L_B' has the structure of one of:

[0014] 

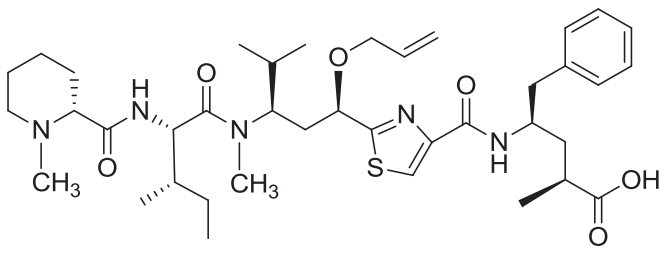
[0015] 

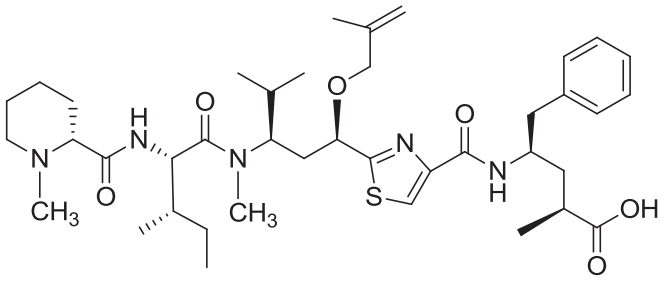
[0016] 

[0017]  and ,

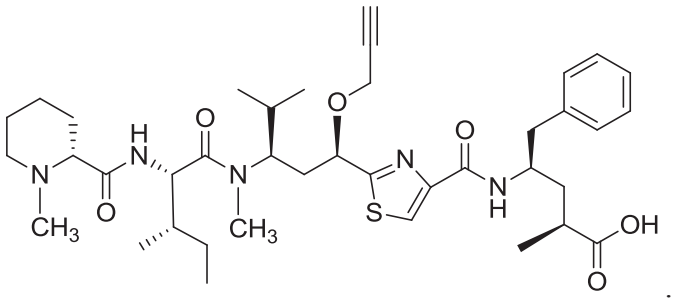
[0018] wherein R is hydrogen or C_1-C_6 optionally substituted alkyl; R' is hydrogen or halogen or R and R' are independently selected halogen; T is –Cl, -Br, -I, -O-mesyl or –O-tosyl or other sulfonate leaving group; U is –F, –Cl, -Br, -I, -O-N-succinimide, -O-(4-nitrophenyl), -O-pentafluorophenyl, -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.

[0018a] In another aspect, there is provided a tubulysin compound having the structure of:



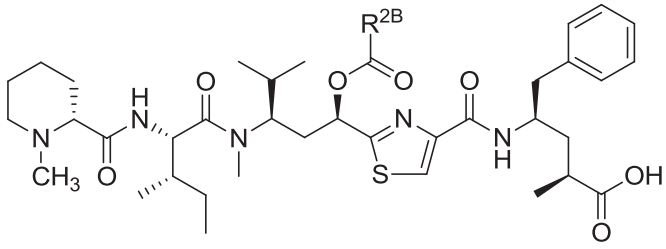


or

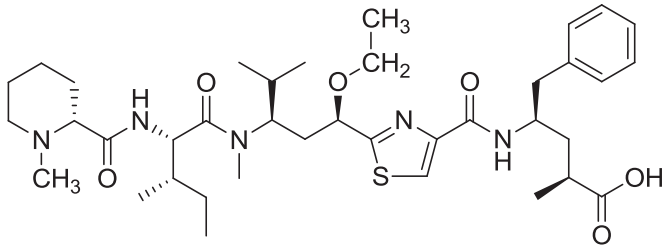


.

[0018b] In another aspect, there is provided a tubulysin compound having the structure of :



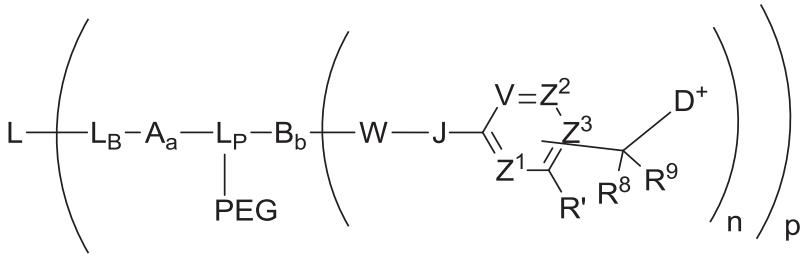
or



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

[0018c] In another aspect, there is provided a method of preparing a Drug Linker compound comprising the step of quaternizing a tubulysin compound disclosed herein with a Linker Unit precursor.

[0018d] In another aspect, there is provided a Ligand Drug Conjugate composition, wherein the composition is represented by the structure of Formula 1D:



(Formula 1D)

wherein

L is an antibody Ligand Unit, thereby defining an Antibody Drug Conjugate;

L_B is a Ligand Covalent Binding Unit;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscript a is 0 or 1;

subscript b is 0 or 1;

A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A;

wherein Ligand Covalent Binding Unit, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described;

subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 and provided that B is A_O or is absent when subscript n is 1;

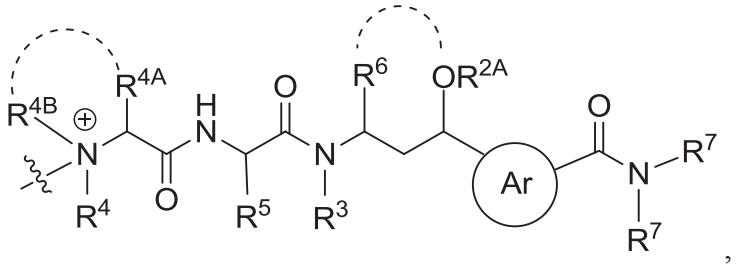
V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, or -OCH_3 or other an electron donating group, or –C(R^8)(R^9)-D^+, wherein at least one of V, Z^1, and Z^3 is =C(R^{24})-, provided that 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, and Z^3 when that variable group is =C(R^{24})- and provided that –J and -C(R^8)(R^9)-D^+ have relative substitution in the *para* or *ortho* positions;

R^8 and R^9 independently are hydrogen or optionally substituted C_1-C_6 alkyl;

R’ is hydrogen or –OCH_3 or other electron donating group;

subscript p is a number ranging from 1 to 24;

D+ is a quaternized tubulysinDrug Unit having the structure of



,

wherein the curved dashed lines indicate optional cyclizations;

R^{2A} is hydrogen or optionally substituted alkyl, or R^{2A} along with the oxygen atom to which it is attached defines an O-linked substituent other than –OH, or R^{2A} is absent when R^6 is bonded to that oxygen atom, as indicated by the curved dash line between R^6 and the oxygen atom, to define an oxygen-containing heterocycloalkyl;

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

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^5 and R^6 are optionally substituted alkyl, independently selected, or R^6 is bonded to the oxygen atom of the $–OR^{2A}$ moiety in which R^{2A} is absent and R^4 and R^5 are as previously defined;

R^{4a} is hydrogen or optionally substituted alkyl and R^{4B} is optionally substituted alkyl, or both together with the nitrogen to which they are attached, as indicated by the curved dotted line between R^{4A} and R^{4B}, define a quaternized nitrogen heterocycloalkyl, optionally substituted;

one R^7 is hydrogen or optionally substituted alkyl and the other R^7 is optionally substituted aralkyl or heteroaralkyl;

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug Linker compound structure and wherein optionally substituted alkyl are independently selected;

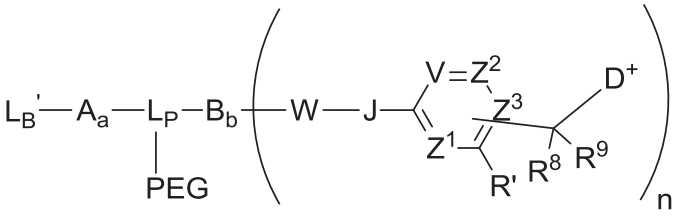
J is optionally substituted -NH-, or J is $–N(R^{33})-$, wherein R^{33} is hydrogen or methyl;

W is a peptide comprised of an amino acid sequence covalently attached to J through an amide bond wherein that amide bond is cleavable by a protease,

wherein said protease cleavage initiates release of a tubulysin compound (D) from a Ligand Drug Conjugate compound of the composition,

wherein the Ligand Drug Conjugate compound has the structure of Formula 1D in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

[0018e] In another aspect, there is provided a Drug Linker compound, wherein the compound is represented by the structure of:



wherein

L_B' is a Ligand Covalent Binding Unit precursor;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscripts a and b independently are 0 or 1;

subscript n is 1, 2, 3 or 4;

A is a first 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 independently selected subunits (A_1, A_2, A_3, A_4);

B is an Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or 1 when B is present and is optionally comprised of two, three or four subunits independently of A,

wherein subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 or b is 0 or 1 so that B is A_O when subscript n is 1;

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, or -OCH_3 or other an electron donating group, or –C(R^8)(R^9)-D^+, wherein at least one of V, Z^1, and Z^3 is =C(R^{24})-, provided that 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, and Z^3 when that variable group is =C(R^{24})-;

R' is hydrogen or –OCH_3 or other electron donating group;

D^+ is a quaternized tubulysin Drug Unit;

J is a heteroatom, optionall substituted when nitrogen, preferably J is –N(R^{33})-, wherein R^{33} is hydrogen or methyl;

W is a peptide comprised of an amino acid sequence covalently attached to J through an amide bond wherein that amide bond is cleavable by a protease, wherein said protease cleavage initiates release of a tubulysin compound (D) from the Drug Linker compound or a Ligand Drug Conjugate compound prepared from the Drug Linker compound, wherein the Ligand Drug Conjugate compound has the Formula 1D structure disclosed herein in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

[0018f] In another aspect, there is provided a formulation comprising a Ligand Drug Conjugate composition disclosed herein and one or more excipients.

[0018g] In another aspect, there is provided use of a Ligand Drug Conjugate disclosed herein in the manufacture of a medicament for treating a hyperproliferative disease or condition in a patient having said disease or condition.

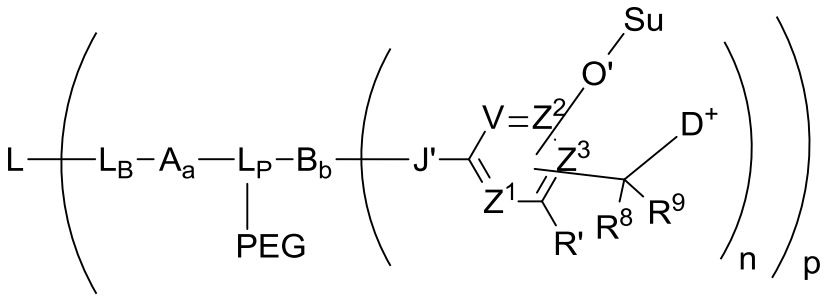
[0018h] In another aspect, there is provided a method of inhibiting the multiplication of a tumor cell or cancer cell, or causing apoptosis in a tumor or cancer cell, by exposing said cell in vitro with an effective amount of Ligand Drug Conjugate composition disclosed herein or of a tubulysin compound disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1. Mean tumor volume (mm^3) versus time (days) post-implant subsequent to treatment of $CD30^+$ L540cy Hodgkin lymphoma xenograft with DAR 4 quaternary amine-linked tubulysin antibody-drug conjugates having quaternized Tubulysin M Drug Units linked via a val-ala dipeptide (cAC10-**15**) protease-cleavable unit in comparison to conjugation via a β-glucuronidase-cleavable glucuronide unit (cAC10-**82**),

WHAT IS CLAIMED IS:

1. A Ligand Drug Conjugate composition wherein the composition is represented by the structure of Formula 1A:



(Formula 1A)

wherein

L is an antibody Ligand Unit, thereby defining an Antibody Drug Conjugate (ADC);

L_B is a Ligand Covalent Binding Unit;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscript a is 0 or 1;

subscript b is 0 or 1;

A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A

wherein Ligand Covalent Binding Unit, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described;

subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 and provided that B is A_O or is absent when subscript n is 1;

Su is a carbohydrate moiety as hereinbefore defined;

-O'- represents an oxygen atom of an O-glycosidic bond cleavable by a glycosidase;

-J'- represents optionally substituted -NH- from a functional group of B, when B is present, or L_B, when B is absent;

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, or –OCH_3 or other

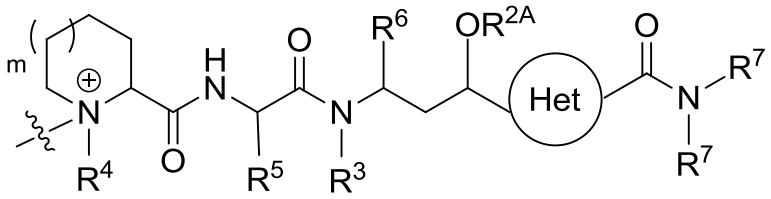
electron donating group, -O'-Su, or $-C(R^8)(R^9)-D^+$, wherein at least at least two of V, Z^1, Z^2 and Z^3 are $=C(R^{24})-$,

provided, 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 one and only one other R^{24} is so that –O'-Su is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is $=C(R^{24})-$, and the –O'Su 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;

D^+ is a quaternized tubulysin Drug Unit having the structure of:



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

subscript m is 0 or 1;

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

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^5 and R^6 are optionally substituted alkyl;

one R^7 is an optionally substituted alkyl, an optionally substituted arylalkyl, optionally substituted heteroarylalkyl and the other R^7 is hydrogen or an optionally substituted alkyl; and

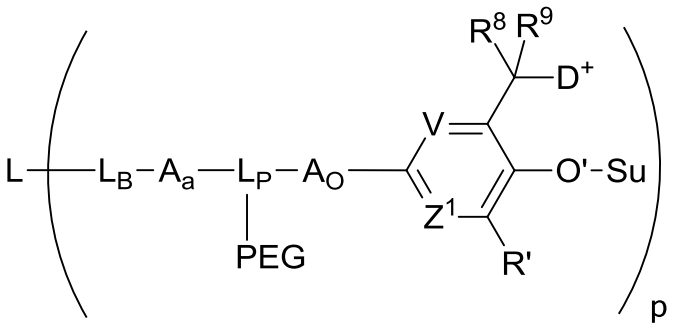
subscript p is a number ranging from 1 to 24; and

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Ligand Drug Conjugate structure and wherein each optionally substituted alkyl is independently selected, and

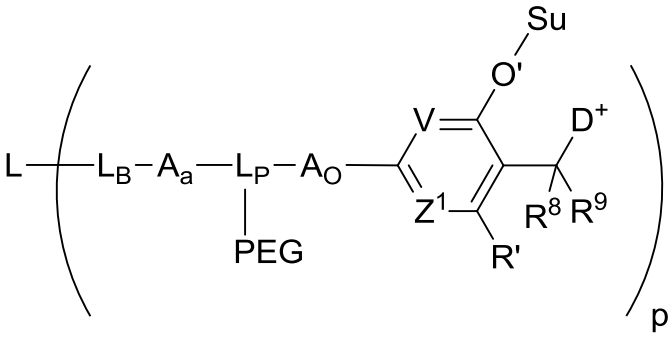
wherein said glycosidase cleavage results in release of a tubulysin compound (D) from a Ligand Drug Conjugate compound of the composition,

wherein the Ligand Drug Conjugate compound has the structure of Formula IA in which subscript p is replaced by subscript p' wherein subscript p' is an integer ranging from 1 to 24.

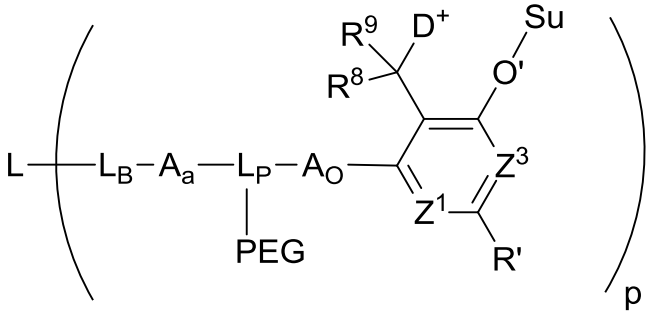
2. The Ligand Drug Conjugate composition of claim **1** wherein the composition of Formula 1A is represented by the structure of one of Formula 2A-2F:



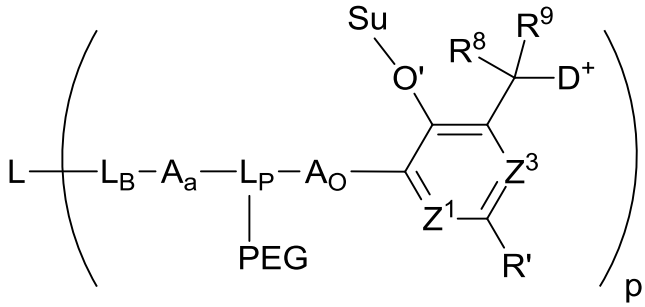
(Formula 2A)



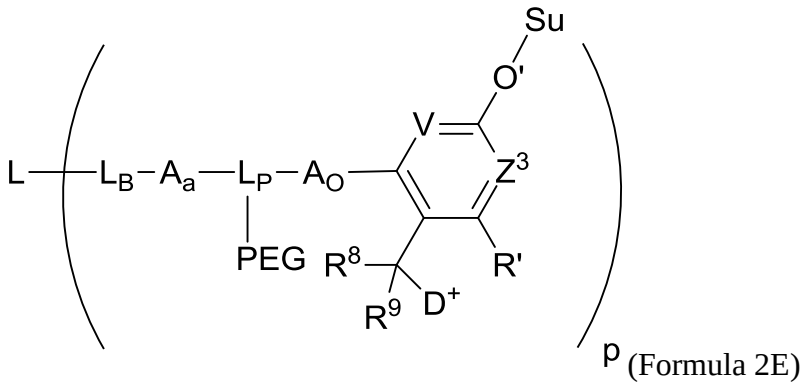
(Formula 2B)



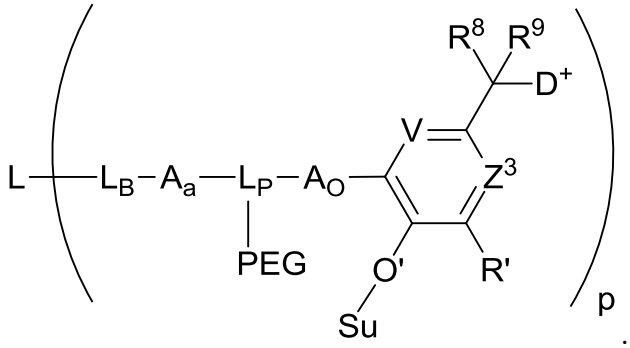
(Formula 2C)



(Formula 2D)



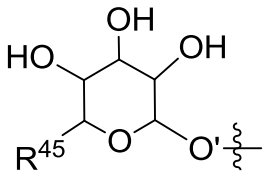
(Formula 2E)



(Formula 2F)

3. The Ligand Drug Conjugate composition of claim **1**, wherein the antibody Ligand Unit is capable of selectively binding to an accessible cell-surface antigen of abnormal cells, wherein the antigen is capable of cellular internalization of bound ADC and is preferentially present on the abnormal or other unwanted cells in comparison to normal cells.

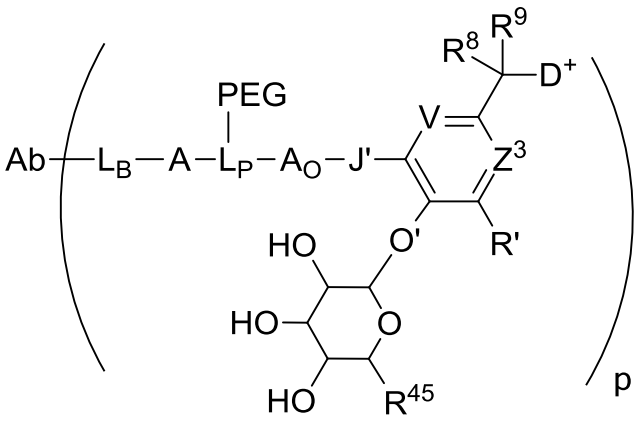
4. The Ligand Drug Conjugate composition of claim **2** wherein –O'-Su has the structure of Formula 3:



(Formula 3),

wherein the wavy line represents covalent bonding of O' to the remainder of the LDC structure; and R^{45} is $–CH_2OH$ or $–CO_2H$.

5. The Ligand Drug Conjugate composition of claim **2** wherein the composition is represented by the structure of Formula 4:



(Formula 4),

wherein

Ab is the antibody Ligand Unit;

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;

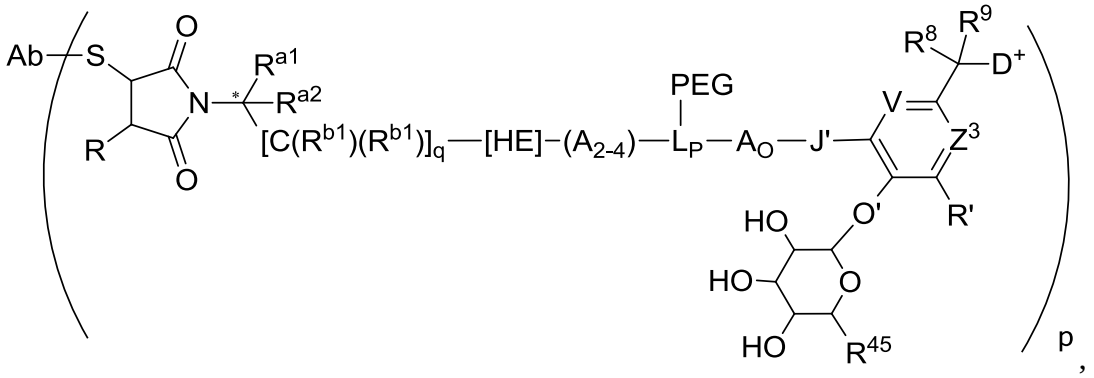
R^8 is hydrogen;

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 24.

6. The Ligand Drug Conjugate composition of claim **5** wherein the composition is represented by the structure of Formula 6:



(Formula 6)

wherein

S is a sulfur atom of the antibody Ligand Unit (Ab);

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

A_{2-4} are independently selected optional subunits of A, wherein $–[C(R^{b1})(R^{b1})]_q$-[HE]- is A_1 when one or more such subunits are present;

R is hydrogen;

R' is hydrogen or an electron withdrawing group;

R^{a1} is hydrogen or a basic unit (BU) wherein BU is a Basic Unit having the structure of $–CH_2-N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} independently are hydrogen, methyl or ethyl or both together with the nitrogen atom to which they are attached define a 5- or 6-membered heterocycloalkyl, or one of R^{22}, R^{23} is hydrogen and the other is an acid labile carbamate protecting group;

R^{a2} is hydrogen;

subscript q 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^{45} is $–CO_2H$;

J' is –NH-;

V and Z^3 are =CH-;

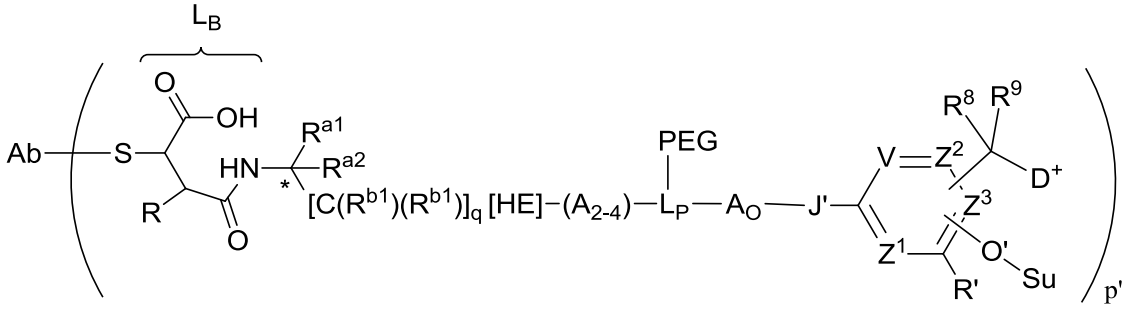
R^8 is hydrogen;

R^9 is hydrogen or methyl;

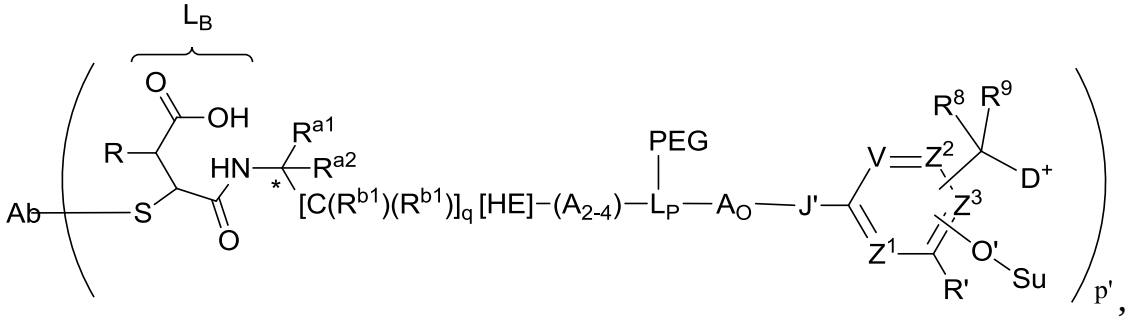
subscript p is a number ranging from 1 to 16; and

wherein the remaining variable groups are as defined for Formula 1A.

7. The Ligand Drug Conjugate composition of claim **1** wherein a compound thereof has the structure of Formula 9A or Formula 9B:



(Formula 9A)



(Formula 9B)

wherein

S is a sulfur atom of the antibody Ligand Unit (Ab);

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

A_{2-4} are independently selected optional subunits of A, wherein $–[C(R^{b1})(R^{b1})]_q$-[HE]- is A_1 when one or more such subunits are present;

R is hydrogen;

R' is hydrogen or an electron withdrawing group;

R^{a1} is –H or BU wherein BU is a Basic Unit having 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 basic nitrogen-containing 5- or 6-membered heterocycloalkyl, or one of R^{22}, R^{23} is hydrogen and the other is an acid labile protecting group;

R^{a2} is hydrogen;

subscript q 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)-;

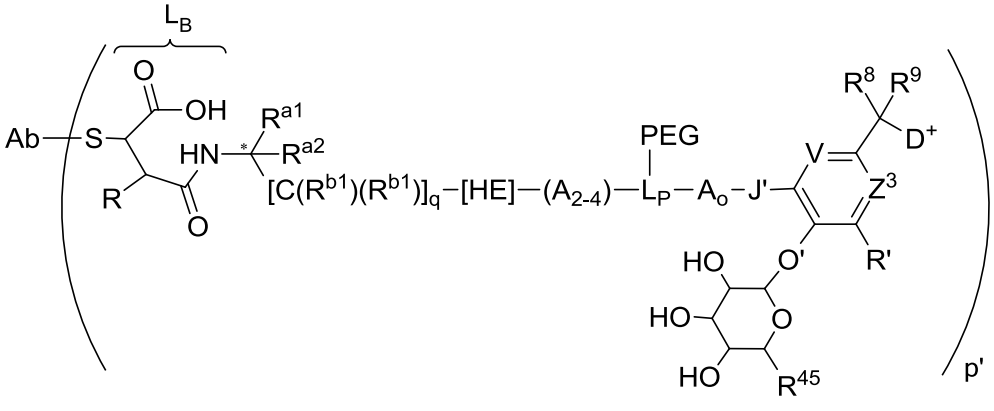
J'is –NH-;

R^8 and R^9 are independently –H or optionally substituted alkyl or both together along with the carbon atom to which they are attached define a cycloalkyl; and

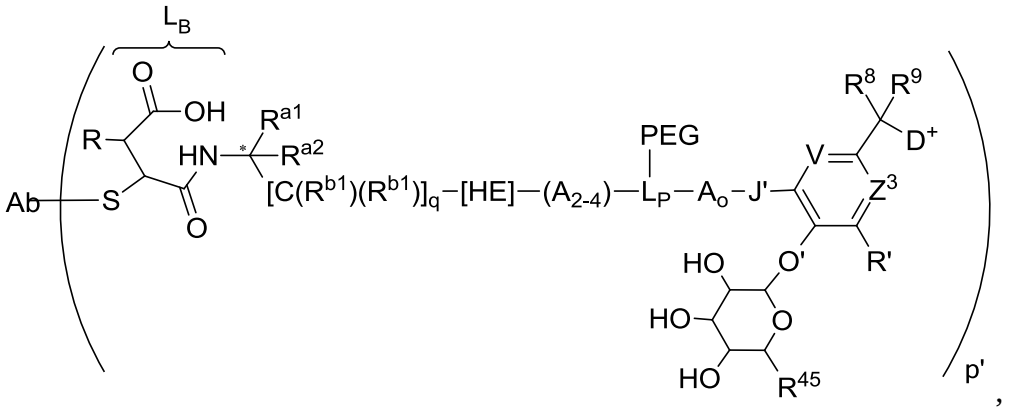
subscript p' is an integer ranging from 1 to 24; and

wherein the remaining variable groups are as defined for Formula 1A.

8. The Ligand Drug Conjugate composition of claim **7**, wherein a compound thereof has the structure of Formula 10A or Formula 10B:



(Formula 10A)



(Formula 10B)

wherein

R is hydrogen;

R' is hydrogen, -NO_2, –Cl or -F;

HE is –C(=O)-;

R^{45} is –CO_2H;

J' is –NH-;

V and Z^3 are each =CH_2-;

R^8 is hydrogen;

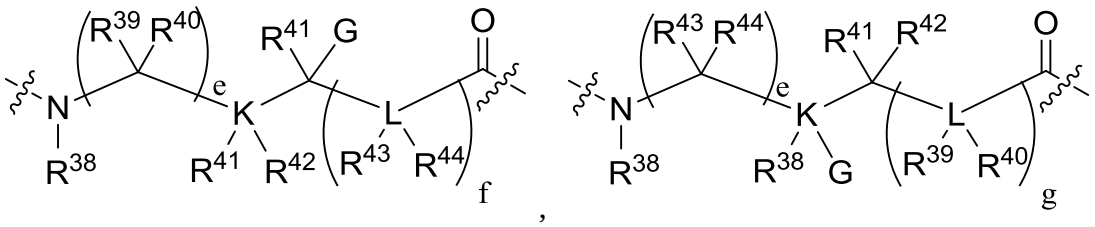
R^9 is hydrogen or methyl;

subscript p' is an integer ranging from 1 to 12; and

wherein the remaining variable groups are as defined for Formula 1A.

9. The Ligand Drug Conjugate composition, or compound thereof, of claim **6**, **7** or **8** 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 is chiral.

10. The Ligand Drug Conjugate composition of claim **1**, wherein A and A_O, independently has the structure of Formula 7 or Formula 8:



(Formula 7) (Formula 8)

wherein the wavy lines indicated covalent attachment within the Conjugate structure, wherein K and L independently are C, N, O or S, provided that when K or L is O or S, R^{41} and R^{42} to K or R^{43} and R^{44} to

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

wherein subscripts e and f are independently selected integers that range from 0 to 12, and subscript g is an integer ranging from 1 to 12:

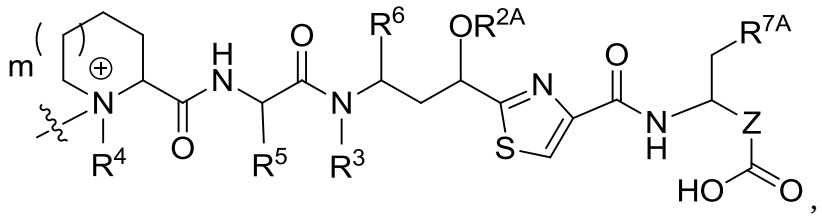
wherein G is hydrogen, optionally substituted C_1-C_6 alkyl, -OH, -OR^{PR}, -CO_2H, CO_2R^{PR}, wherein R^{PR} is a suitable protecting, -$N(R^{PR})(R^{PR})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or -$N(R^{45})(R^{46})$, wherein one of R^{45}, R^{46} is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C_1-C_6 alkyl;

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 aryl, or optionally substituted heteroaryl, or both R^{39}, R^{40} together with the carbon to which they are attached comprise a C_3-C_6 cycloalkyl, or R^{41}, R^{42} together with K to which they are attached when K is C,

or R^{43}, R^{44} together with L to which they are attached when L is a carbon atom comprise a C_3-C_6 cycloalkyl, or R^{40} and R^{41}, or R^{40} and R^{43}, or R^{41} and R^{43} to together with the carbon atom or heteroatom to which they are attached and the atoms intervening between those carbon atoms and/or heteroatoms comprise a 5- or 6-membered cycloalkyl or heterocycloalkyl, provided that when K is O or S, R^{41} and R^{42} are absent, when K is N, one of R^{41}, R^{42} is absent, when L is O or S, R^{43} and R^{44} are absent, and when L is N, one of R^{43}, R^{44} is absent, or

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

11. The Ligand Drug Conjugate composition of claim **1** wherein the quaternized tubulysin Drug Unit ($-D^+$) has the structure of:



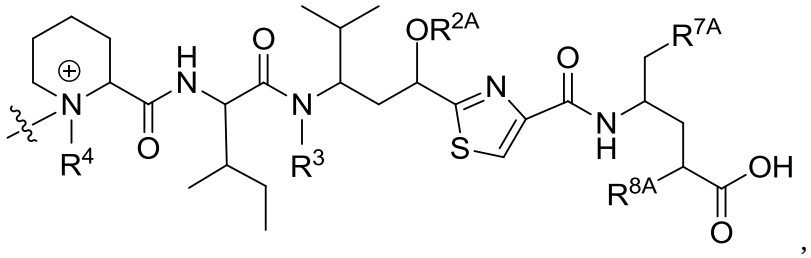
wherein

subscript m is 0 or 1;

Z is an optionally substituted alkylene or an optionally substituted alkenylene; and

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

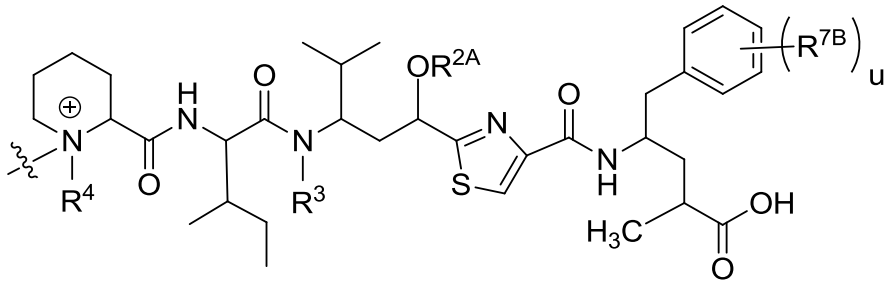
12. The Ligand Drug Conjugate composition of claim **11** wherein the quaternized tubulysin Drug Unit ($-D^+$) has the structure of:



,

wherein R^{7A} is optionally substituted phenyl and R^8 is hydrogen or methyl.

13. The Ligand Drug Conjugate composition of claim **12** wherein the quaternized tubulysin Drug Unit ($-D^+$) has the structure of:



,

wherein R^4 is methyl;

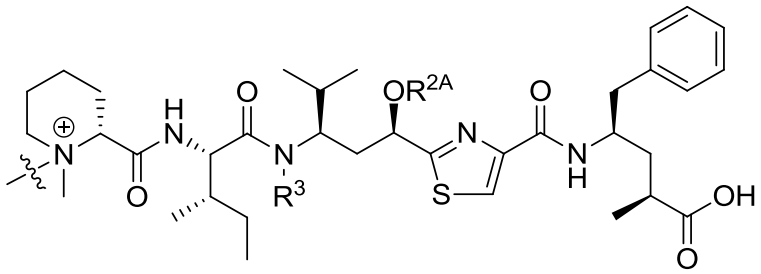
subscript u is 0, 1 or 2;

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

R^{2A} along with the oxygen atom to which it is attached is an O-linked substituent selected from the group consisting of $-OCH_2OCH_2R^{2B}$, $-OCH_2R^{2B}$, $-OC(O)R^{2B}$, $-CH_2OC(O)R^{2B}$, $-OC(O)N(R^{2B})(R^{2C})$, and $-OCH_2C(O)N(R^{2B})(R^{2C})$, wherein R^{2B} and R^{2C} are independently selected from the group consisting of H, C_1-C_6 alkyl and C_2-C_6 alkenyl; and

each R^{7B}, when present, independently is –OH or $-OCH_3$.

14. The Ligand Drug Conjugate composition, or compound thereof, of claim **13** wherein the quaternized tubulysin Drug Unit ($-D^+$) has the structure of:



.

15. The Ligand Drug Conjugate composition of claim **14** wherein R^{2A} is $-CH_2CH_3$.

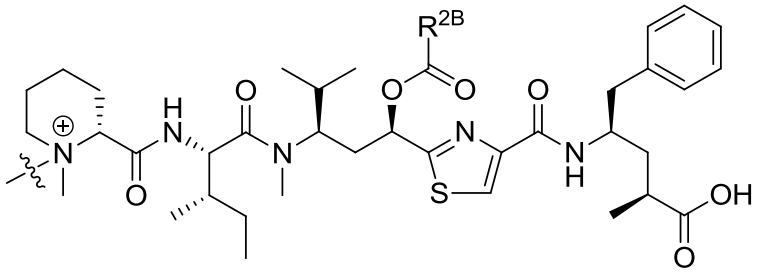
16. The Ligand Drug Conjugate composition of claim **14** wherein R^{2A} is $-CH_2-CH=CH_2$.

17. The Ligand Drug Conjugate composition, or compound thereof, of claim **13**, wherein

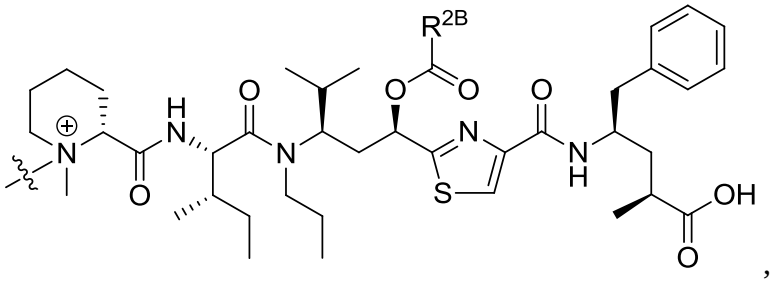
R^{2A} is $-CH_2CH_3$, $-CH_2-CH=CH_2$ or $-CH_2C(CH_3)=CH_2$, R^{2B} is $–CH_3$, R^3 is $–CH_3$ and subscript u is 0, or

R^{2A} is $-CH_2CH_3$ or $-CH_2-CH=CH_2$, or $-CH_2C(CH_3)=CH_2$, R^{2B} is $–CH_3$, R^3 is $–CH_3$ and subscript u is 1, wherein R^{7B} is -OH.

18. The Ligand Drug Conjugate composition , or compound thereof, of claim **13** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



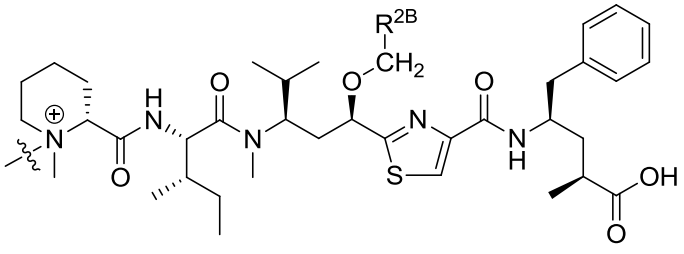
or



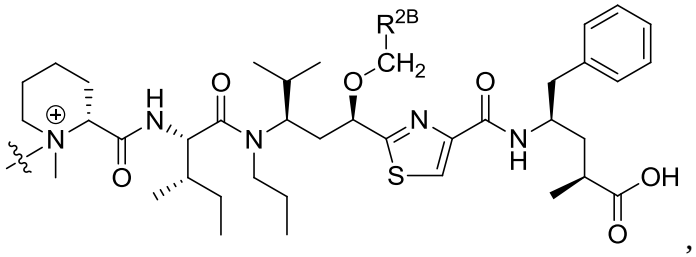
,

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

19. The Ligand Drug Conjugate composition of claim **13** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



or

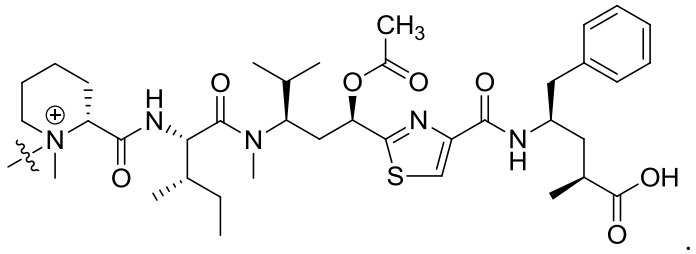


wherein

R^{2B} is hydrogen, methyl or $–OCH_3$, or

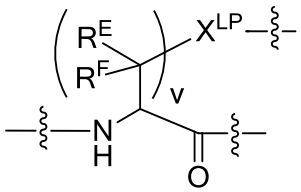
$-OCH_2R^{2B}$ is $–OCH_2CH=CH_2$ or $–OCH_2C(CH_3)=CH_2$.

20. The Ligand Drug Conjugate composition of claim **13** wherein the quaternized tubulysin Drug Unit $–D^+$ is that of tubulysin M, which has the structure of:

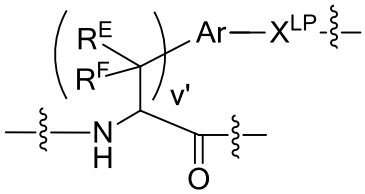


21. The Ligand Drug Conjugate composition of claim **1** wherein L_P is a aminoalkanedioic acid, a diaminoalkanoic acid, a sulfur-substituted alkanedioic acid, a sulfur-substituted aminoalkanoic acid, a diaminoalkanol, an aminoalkanediol, a hydroxyl substituted alkanedioic acid, a hydroxyl substituted aminoalkanoic acid or a sulfur-substituted aminoalkanol residue, optionally substituted, wherein the sulfur substituent is in reduced or oxidized form, or L_P is an amino acid residue of lysine, arginine, asparagine, glutamine, ornithine, citrulline, cysteine, homocysteine, penicillamine, threonine, serine, glutamic acid, aspartic acid, tyrosine, histidine or tryptophan, wherein the amino acid is in the **D**- or **L**-configuration.

22. The Ligand Drug Conjugate composition of claim **21** wherein the aminoalkanedioic acid, diaminoalkanoic acid, sulfur-substituted aminoalkanoic acid or hydroxyl substituted aminoalkanoic acid residue has the structure of Formula A or Formula B:



(Formula A)



(Formula B)

wherein

subscript v is an integer ranging from 1 to 4;

subscript v' is an integer ranging from 0 to 4;

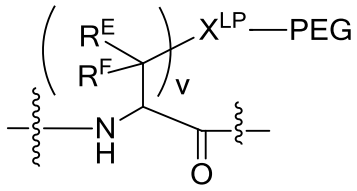
X^{LP} is selected from the group consisting of –O-, -NR^{LP}-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)N(R^{LP})-, -N(R^{LP})C(=O)N(R^{LP})-, and -N(R^{LP})C(=NR^{LP})N(R^{LP})- wherein each R^{LP} is independently selected from the group consisting of hydrogen and optionally substituted alkyl or two of R^{LP} together along with their intervening atoms define an optionally substituted heterocycloalkyl and any remaining R^{LP} are as previously defined;

Ar is an arylene or heteroarylene, optionally substituted;

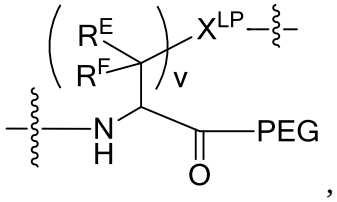
each R^E and R^F is independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, or R^E and R^F together with the same carbon to which they are attached, or R^E and R^F from adjacent carbons together with these carbons, define an optionally substituted cycloalkyl with any remaining R^E and R^F substituents are as previously defined; and

wherein the wavy lines indicate covalent attachments of the Formula A or Formula B structure within the Conjugate structure.

23. The Ligand Drug Conjugate composition of claim **1** wherein -L_P(PEG)- has the structure of Formula A1 or A2:



(Formula A1)



,

(Formula A2)

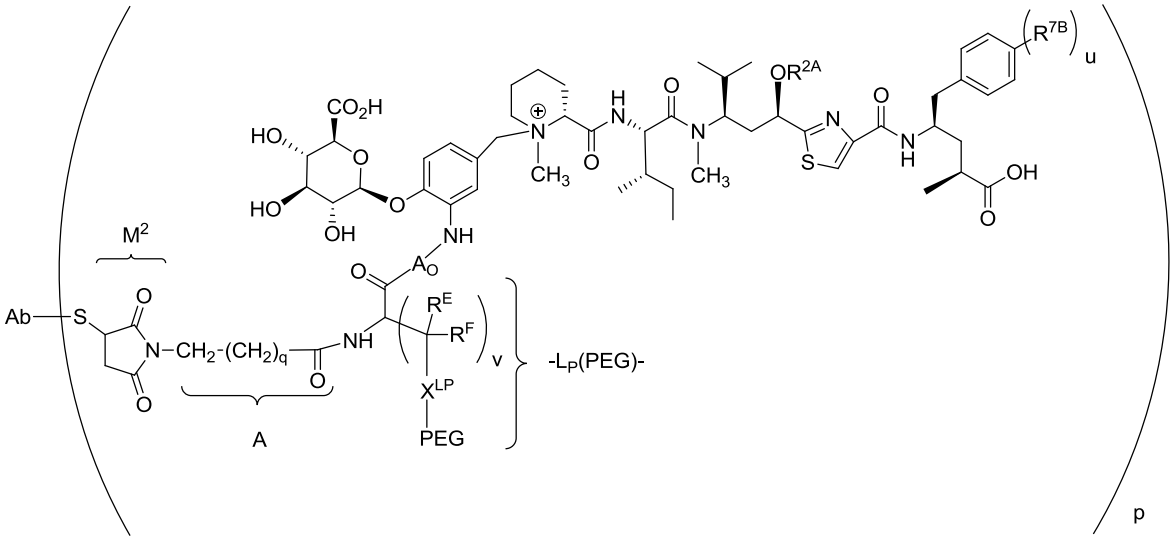
wherein

X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-;

R^E and R^F are independently selected from the group consisting of -H, and -C_1-C_4 alkyl; and

wherein the wavy line indicates covalent attachment of Formula A1 or Formula A2 within the Conjugate structure.

24. The Ligand Drug Conjugate composition of claim **1** wherein the composition is represented by the structure of:



wherein

Ab is the antibody Ligand Unit;

S is a sulfur atom of the antibody Ligand Unit;

R^{2A} is saturated C_1-C_4 alkyl, unsaturated C_2-C_4 alkyl, –C(=O)R^{2B}, wherein R^{2B} is C_1-C_4 alkyl;

A_O is absent or is an amine-containing acid residue;

subscript p is a number ranging from 1 to 8;

subscript q is an integer ranging from 1 to 4;

subscript u is 0 or 1;

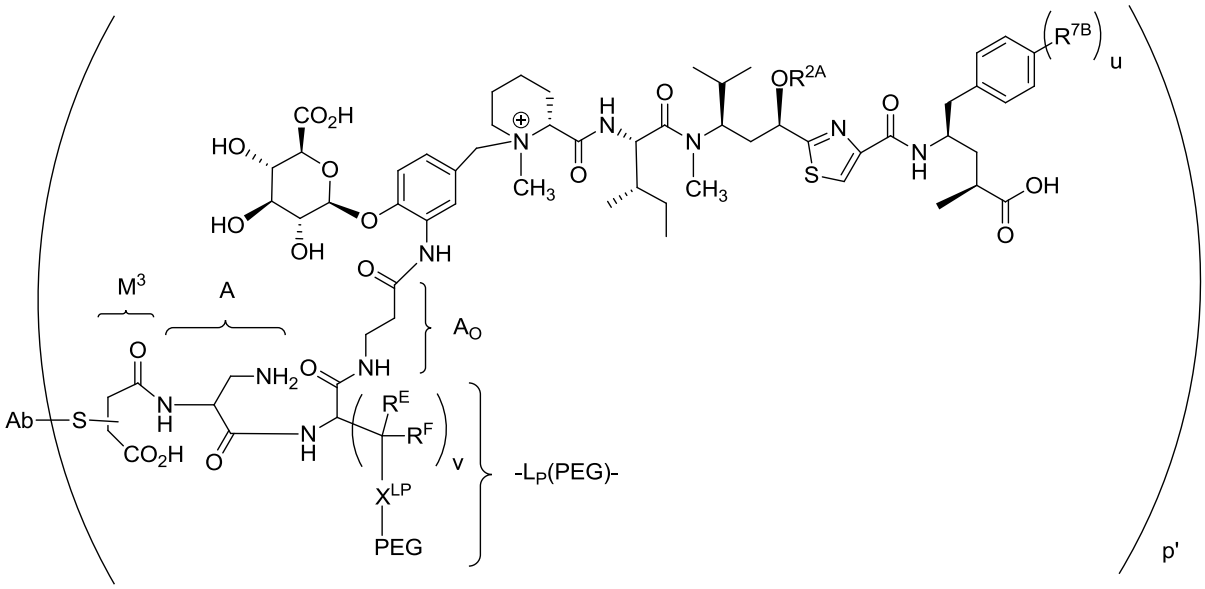
subscript v is an integer ranging from 1 to 4;

R^{7B}, when present, is –OH;

X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-; and

R^E and R^F are independently selected from the group consisting of -H, and C_1-C_4 alkyl.

25. The Ligand Drug Conjugate composition of claim **1** wherein a compound thereof is represented by the structure of:



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 indicated M^3 carboxylic acid;

R^{2A} is saturated C_1-C_4 alkyl, unsaturated C_2-C_4 alkyl, or –C(=O)R^{2B}, wherein R^{2B} is C_1-C_4 alkyl;

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

subscript q is an integer ranging from 1 to 4;

subscript u is 0 or 1;

subscript v is an integer ranging from 1 to 4;

R^{7B}, when present, is –OH;

X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-; and

R^E and R^F are independently selected from the group consisting of -H, and C_1-C_4 alkyl.

26. The Ligand Drug Conjugate composition, or compound thereof, of claim **24** or **25**, wherein R^{2A} is saturated C_1-C_4 alkyl or unsaturated C_3-C_4 alkyl, wherein saturated C_1-C_4 alkyl is -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$ and unsaturated C_3-C_4 alkyl is –$CH_2CH{=}CH_2$ or –$CH(CH_3)CH{=}CH_2$.

27. The Ligand Drug Conjugate composition, or compound thereof, of claim **24** or **25** wherein R^{2A} is –$C(O)CH_3$.

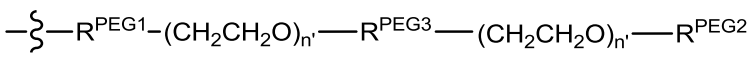
28. The Ligand Drug Conjugate composition, or compound thereof, of claim **24** or **25** wherein R^{2A} is -CH_2CH_3.

29. The Ligand Drug Conjugate composition, or compound thereof, of claim **24** or **25** wherein R^{2A} is –$CH_2CH{=}CH_2$.

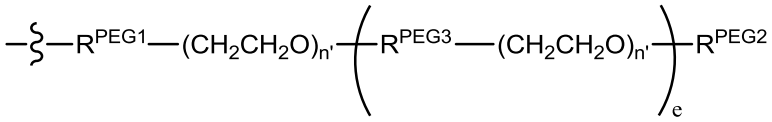
30. The Ligand Drug Conjugate composition of claim **1** wherein the PEG Unit has the structure selected from the group consisting of:



,



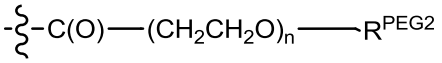
, and



wherein the wavy line indicates site of attachment to X^{LP} of the Parallel Connector Unit (L_P),
R^{PEG1} is an optional PEG Attachment Unit,
R^{PEG2} is a PEG Capping Unit;
R^{PEG3} is a PEG Coupling Unit;
subscript n ranges from 8 to 72;
each subscript n' is independently selected from 1 to 72; and
subscript e ranges from 2 to 5

provided that the PEG Unit contains at least 8 and no more than 72 ethylene glycol subunits.

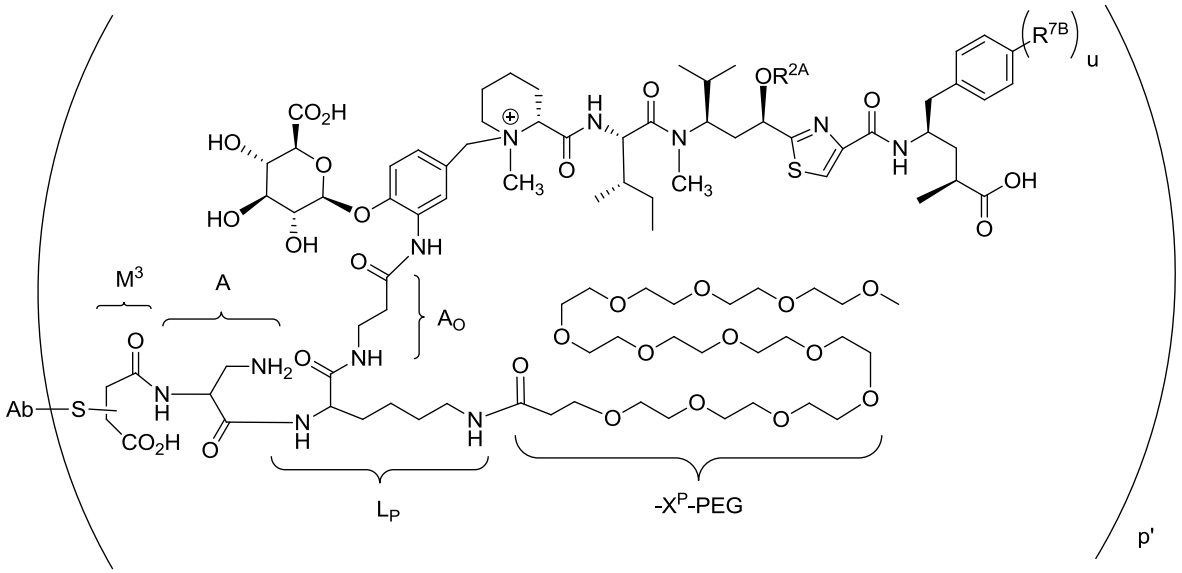
31. The Ligand Drug Conjugate composition, or compound thereof, of claim **24** or **25** wherein $–X^{LP}$-PEG has the structure of:



.

32. The Ligand Drug Conjugate composition, or a compound thereof, of claim **31** wherein subscript n is 12 and R^{PEG2} is hydrogen or $–CH_3$.

33. The Ligand Drug Conjugate composition of claim **1** wherein a compound thereof is represented by the structure of:



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 indicated M^3 carboxylic acid;

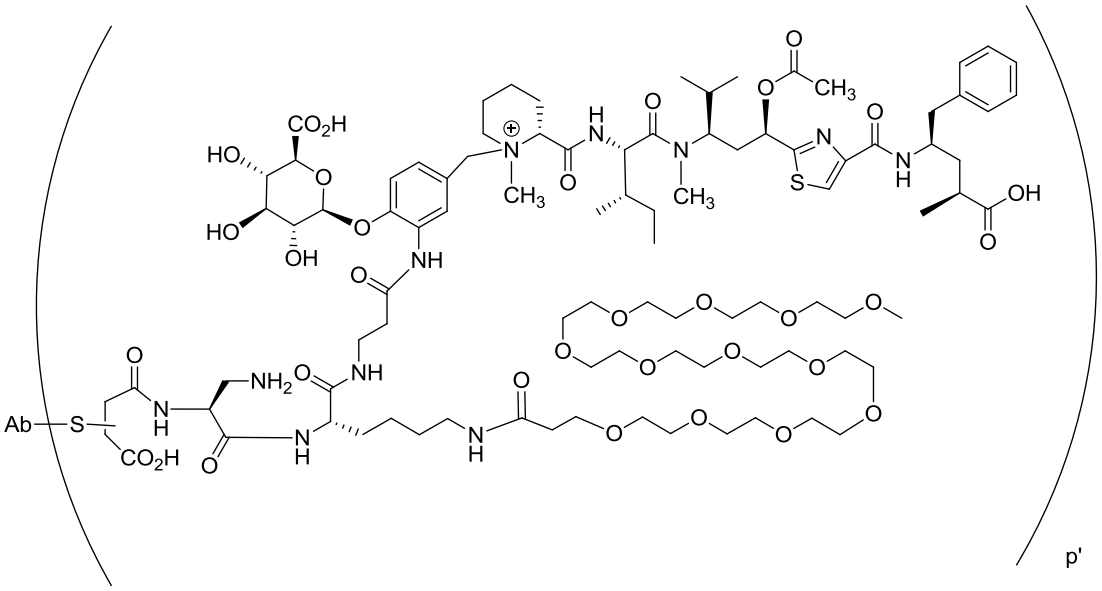
subscript p' is an integer ranging from 1 to 8;

subscript u is 0 or 1;

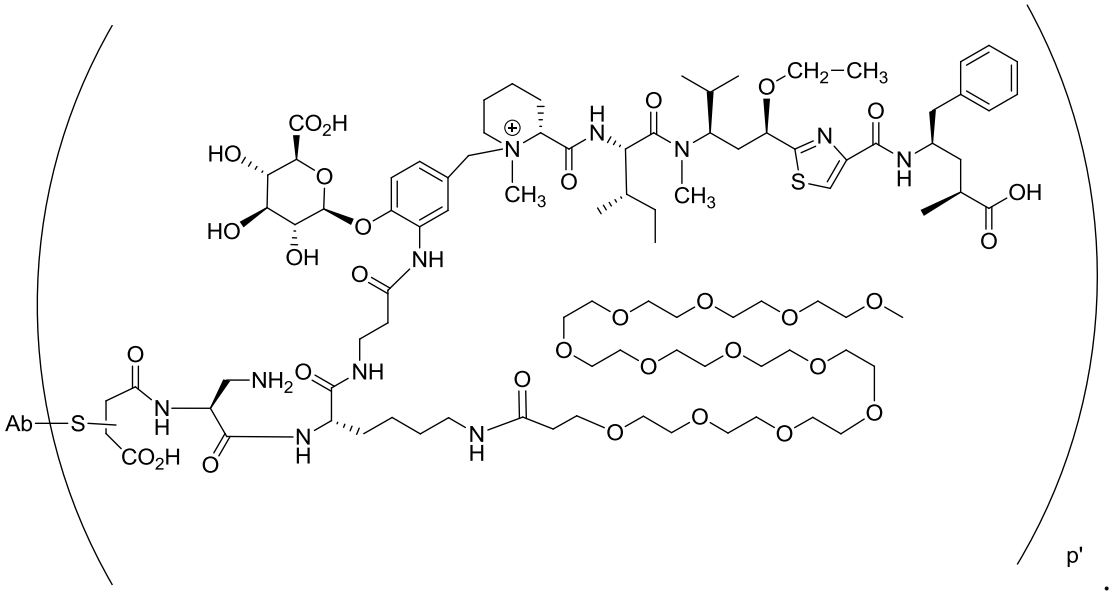
R^{7B}, when present, is –OH; and

R^{2A} along with the oxygen atom to which it is attached is $–OC(O)CH_3$, $-CH_2CH_3$ or $–CH_2CH=CH_2$.

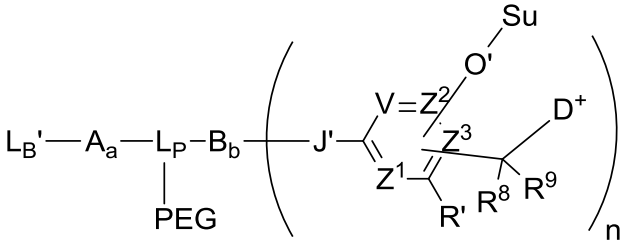
34. The Ligand Drug Conjugate composition of claim **33** wherein a compound thereof is represented by the structure of:



or



35. A Drug Linker compound, wherein the compound has the structure of Formula IA:



(Formula IA)

wherein

L_B' is a Ligand Covalent Binding Unit precursor;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscript a is 0 or 1;

subscript b is 0 or 1;

A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A

wherein Ligand Covalent Binding Unit precursor, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described;

subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching when subscript n is 2, 3 or 4 and provided that B is A_O or is absent when subscript n is 1;

Su is a carbohydrate moiety as hereinbefore defined;

-O'- represents an oxygen atom of an O-glycosidic bond cleavable by a glycosidase;

-J'- optionally substituted -NH- or -J'- is -N(R^{33})-, wherein R^{33} is hydrogen or methyl, from a functional group of B, when B is present, or of L_P, when B is absent;

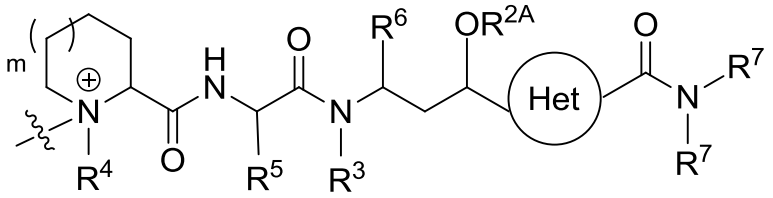
V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, an electron donating group, -O'-Su, or –C(R^8)(R^9)-D^+, wherein at least at least two of V, Z^1, Z^2 and Z^3 are =C(R^{24})-,

provided, 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 so that –O'-Su is bonded to another one of V, Z^1, Z^2, Z^3 when that variable group is =C(R^{24})-, and the –O'Su 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;

D^+ is a quaternized tubulysin Drug Unit having the structure of:



wherein

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

subscript m is 0 or 1;

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

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^5 and R^6 are optionally substituted alkyl;

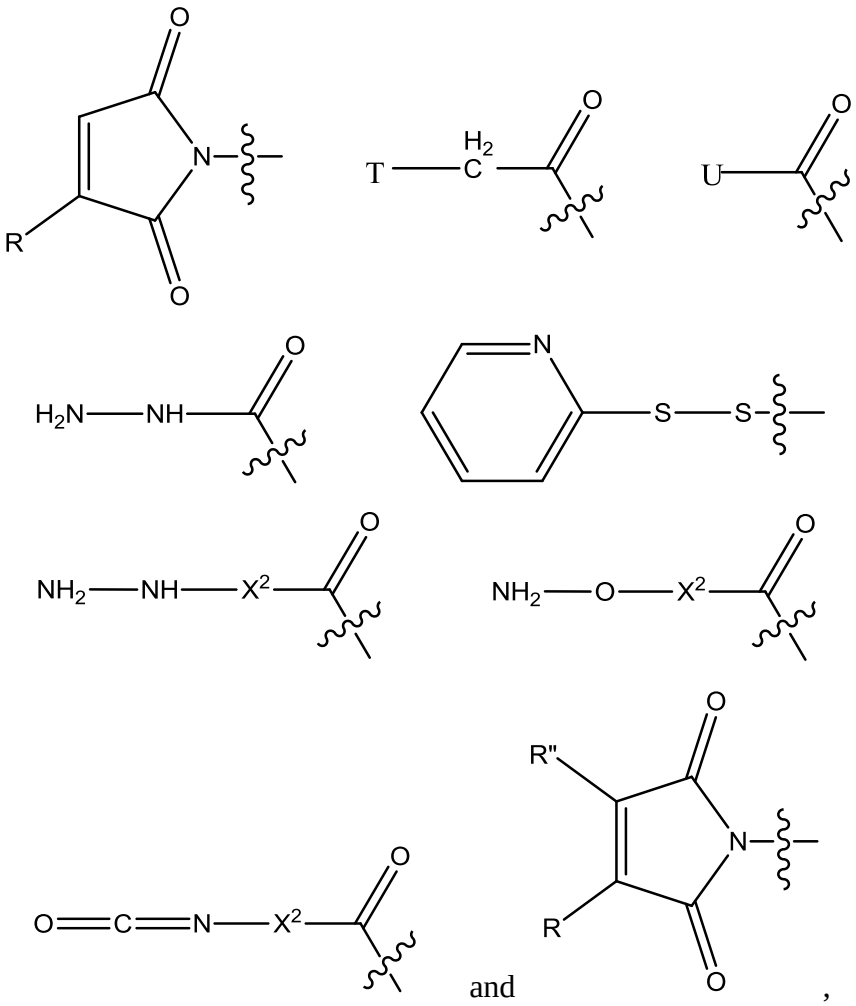
one R^7 is an optionally substituted alkyl, an optionally substituted arylalkyl, optionally substituted heteroarylalkyl and the other R^7 is hydrogen or an optionally substituted alkyl; and

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug Linker compound structure and wherein optionally substituted alkyl are independently selected; and

wherein said glycosidase cleavage results in release of tubulysin compound (D) from the Drug Linker compound or a Ligand Drug Conjugate compound prepared from the Linker Drug compound

wherein the Ligand Drug Conjugate compound has the Formula 1A structure of claim 1 in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

36. The Drug-Linker compound of claim **35** wherein L_B'- has a structure selected from the group consisting of:



,

wherein

R is hydrogen or C_1-C_6 optionally substituted alkyl;

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

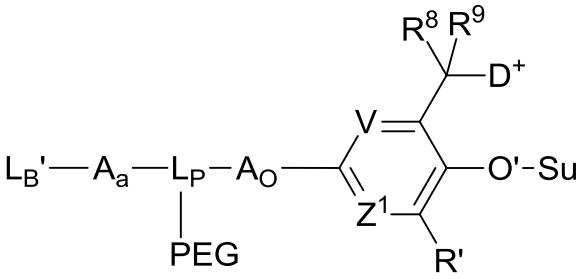
T is –Cl, -Br, -I, -O-mesyl or –O-tosyl or other sulfonate leaving group;

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

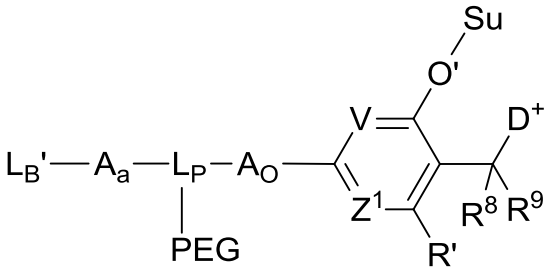
X^2 is C_1-$_{10}$ alkylene, C_3-C_8-carbocycle,-O-(C_1-C_6 alkyl), -arylene-, C_1-C_{10} alkylene-arylene, -arylene-C_1-C_{10} alkylene, -C_1-C_{10} alkylene-(C_3-C_6-carbocycle)-, -(C_3-C_8 carbocycle)-C_1-C_{10} alkylene-, C_3-C_8-heterocycle, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -C_3-C_8-heterocyclo)-C_1-C_{10} alkylene, -$(CH_2CH_2O)_u$,

or $–CH_2CH_2O)_u$-CH_2-, wherein subscript u is an integer ranging from 1 to 10 and R^{57} is C_1-C_6 alkyl or aryl.

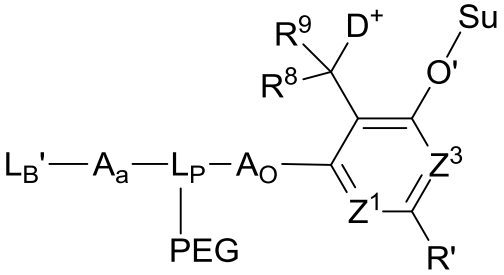
37. The Drug-Linker compound of claim **35** wherein the compound has the structure of one of Formula IIA-IIF:



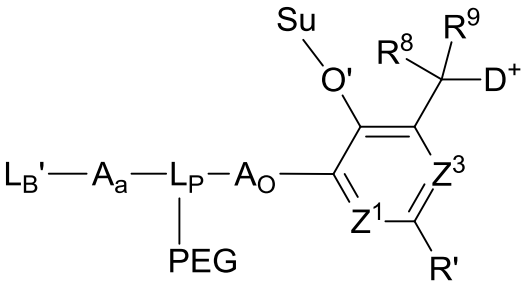
(Formula IIA)



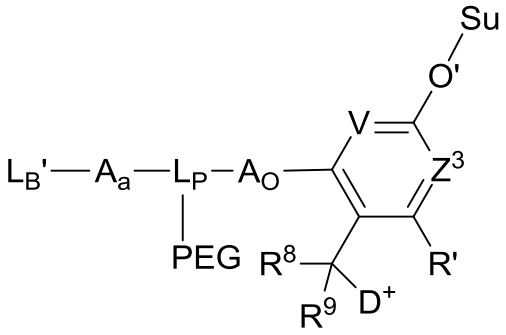
(Formula IIB)



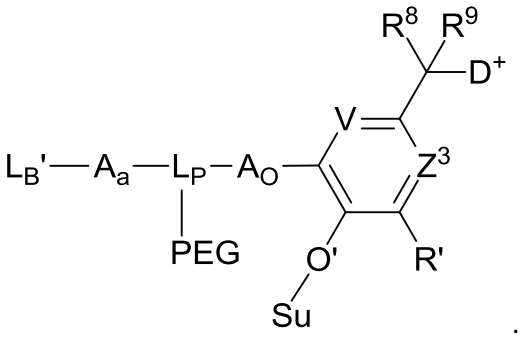
(Formula IIC)



(Formula IID)

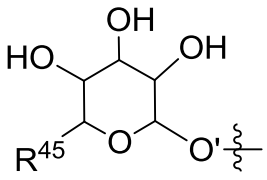


(Formula IIE)



(Formula IIF)

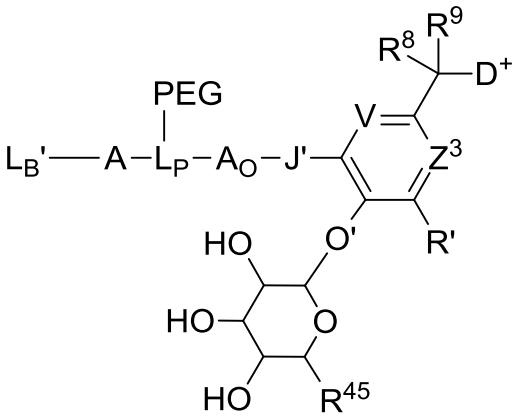
38. The Drug-Linker compound of claim **37** wherein –O'-Su has the structure of Formula 3:



(Formula 3),

wherein the wavy line represents covalent bonding of O' to the remainder of the Drug Linker compound structure; and R^{45} is $–CH_2OH$ or $–CO_2H$.

39. The Drug-Linker compound of claim **35** wherein the compound has the structure of Formula IV:



(Formula IV),

wherein

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

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

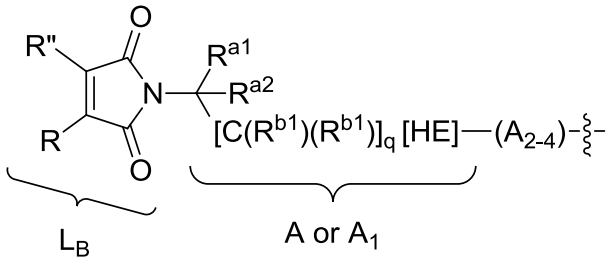
R’ is hydrogen or an electron withdrawing group;

R^8 is hydrogen;

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

R^{45} is $–CO_2H$.

40. The Drug-Linker compound of claim **35** wherein subscript a is 1; and L_B’-A- of Formula IA has the structure of Formula V:



(Formula V)

wherein

the -[C(R^{b1})(R^{b1})]$_q$-[HE]- moiety is A or A_1, wherein A_1 is a subunit of A;

A_{2-4} are optional subunits of A;

R is hydrogen, chloro or C_1-C_4 alkyl;

R” is hydrogen or chloro’

R^{a1} is hydrogen, optionally substituted alkyl or a Basic Unit (BU), optionally protected; and

R^{a2} is hydrogen or optionally substituted alkyl, or

R^{a1} and R^{a2} together with the carbon atom to which they are attached define a nitrogen-containing heterocycloalkyl;

HE is an optional Hydrolysis Enhancer (HE) Unit as hereinbefore described;

subscript q is an integer ranging from 0 to 6;

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

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

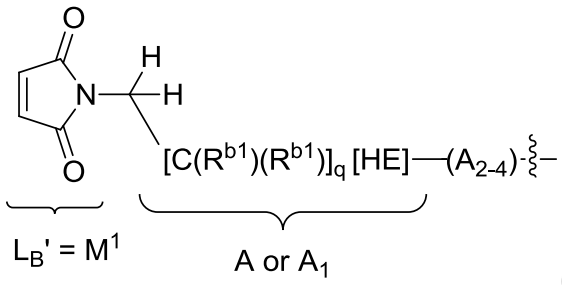
wherein subscript r is 0, 1, 2 or 3;

each R^1 independently is hydrogen or C_1-C_4 alkyl or two R^1 together with the carbon to which they are attached comprise a C_3-C_6 cycloalkyl, and each R^2 independently is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl or optionally substituted heteroaryl, or two R^2 together with the carbon(s) to which they are attached and any intervening carbons define a C_3-C_6 cycloalkyl, or one R^1 and one R^2 together with the carbons to which they are attached and any intervening carbons define a 5- or 6-membered cycloalkyl and the remaining R^1 and R^2 are as defined; and

R^{22} and R^{23} independently, hydrogen, optionally substituted C_1-C_6 alkyl, or an acid-labile protecting group, or together with the nitrogen to which they are attached define a 5- or 6-membered heterocycloalkyl, or one of R^{22}, R^{23} is hydrogen and the other is an acid labile protecting group; and

wherein the wavy line indicates the site of covalent attachment to the remainder of the Drug Linker compound structure.

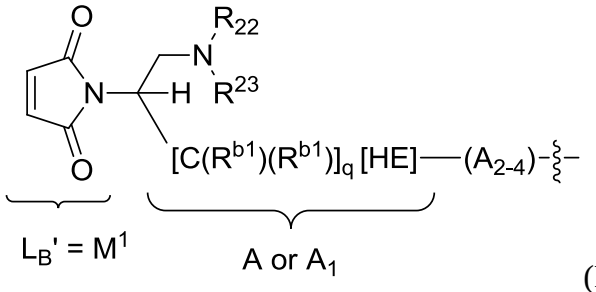
41. The Drug Linker compound of claim **40** wherein Formula V has the structure of Formula VA:



(Formula VA),

wherein subscript q is an integer ranging from 0 to 4.

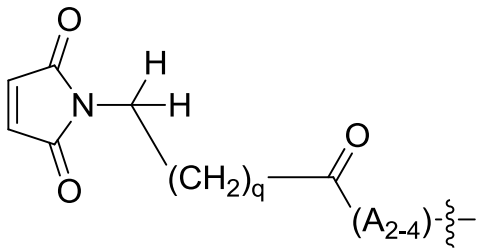
42. The Drug Linker compound of claim **40** wherein Formula V has the structure of Formula VB:



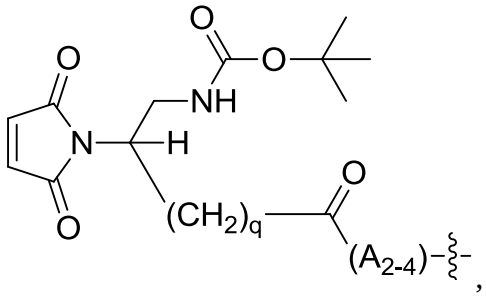
(Formula VB)

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

43. The Drug Linker compound of claim **41** or **42** wherein Formula VA or Formula VB has the structure of:



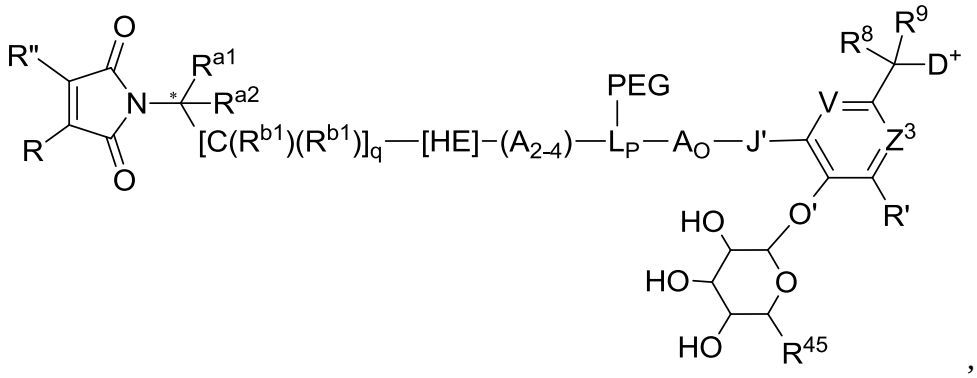
or



,

respectively.

44. The Drug Linker compound of claim **40** wherein the compound has the structure of Formula VI:



,

(Formula VI)

wherein

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

A_{2-4} are independently selected optional subunits of A, wherein $–[C(R^{b1})(R^{b1})]_q$-[HE]- is A_1 when one or more such subunits are present;

one of R and R" is hydrogen and the other is hydrogen or chloro;

R' is hydrogen or an electron withdrawing group;

R^{a1} is hydrogen or a basic unit (BU), optionally protected, having the structure of $–CH_2$-$N(R^{22})(R^{23})$, or an acid addition salt thereof, wherein R^{22} and R^{23} independently are hydrogen, methyl or ethyl or both together with the nitrogen atom to which they are attached define a 5- or 6-membered heterocycloalkyl, or one of R^{22}, R^{23} is hydrogen and the other is an acid labile carbamate protecting group;

R^{a2} is hydrogen;

subscript q 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^{45} is $–CO_2H$;

J' is –NH-;

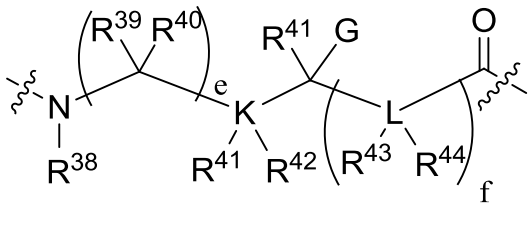
V and Z^3 are =CH-;

R^8 is hydrogen; and

R^9 is hydrogen or methyl.

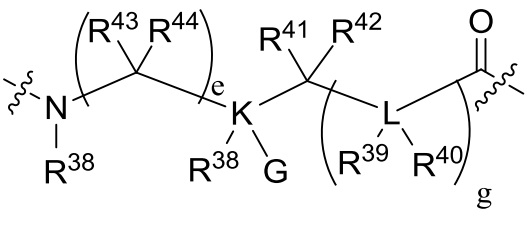
45. The Drug Linker compound of claim **44** wherein the indicated starred (*) carbon atom is predominantly in the same absolute configuration as the alpha carbon atom of an **L**-amino acid when that indicated carbon atom is chiral.

46. The Drug Linker compound of any one of claims **35** wherein A and A_O independently have the structure of Formula 7 or Formula 8:



(Formula 7)

,



(Formula 8)

wherein the wavy lines indicated covalent attachment within the remainder of the Drug Linker compound structure, wherein K and L independently are C, N, O or S, provided that when K or L is O or S, R^{41} and R^{42} to K or R^{43} and R^{44} to L are absent, and when K or L are N, one of R^{41}, R^{42} to K or one of R^{42}, R^{43} to L are absent, and provided that no two adjacent L are independently selected as N, O, or S;

wherein subscripts e and f are independently selected integers that range from 0 to 12, and subscript g is an integer ranging from 1 to 12;

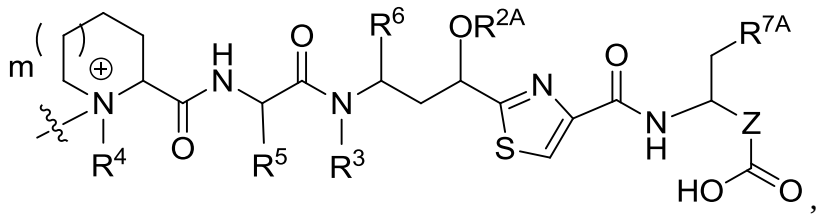
wherein G is hydrogen, optionally substituted C_1-C_6 alkyl, -OH, -OR^{PR}, -CO_2H, CO_2R^{PR}, wherein R^{PR} is a suitable protecting, -$N(R^{PR})(R^{PR})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or -$N(R^{45})(R^{46})$, wherein one of R^{45}, R^{46} is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C_1-C_6 alkyl;

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 aryl, or optionally substituted heteroaryl, or both R^{39}, R^{40} together with the carbon to which they are attached comprise a C_3-C_6 cycloalkyl, or R^{41}, R^{42} together with K to which they are attached when K is C,

or R^{43}, R^{44} together with L to which they are attached when L is a carbon atom comprise a C_3-C_6 cycloalkyl, or R^{40} and R^{41}, or R^{40} and R^{43}, or R^{41} and R^{43} to together with the carbon atom or heteroatom to which they are attached and the atoms intervening between those carbon atoms and/or heteroatoms comprise a 5- or 6-membered cycloalkyl or heterocycloalkyl, provided that when K is O or S, R^{41} and R^{42} are absent, when K is N, one of R^{41}, R^{42} is absent, when L is O or S, R^{43} and R^{44} are absent, and when L is N, one of R^{43}, R^{44} is absent, or

wherein A_O is an alpha-amino, beta-amino or another amine-containing acid residue.

47. The Drug Linker compound of any one of claims **35** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



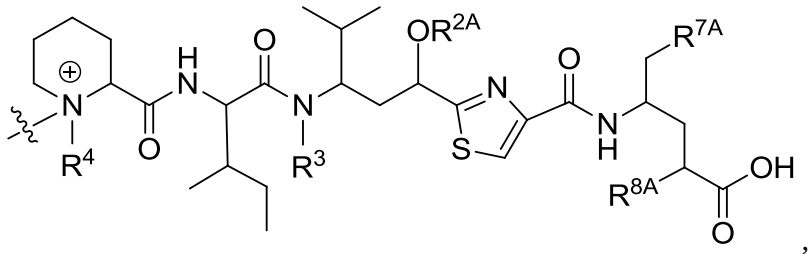
wherein

subscript m is 0 or 1;

Z is an optionally substituted alkylene or an optionally substituted alkenylene; and

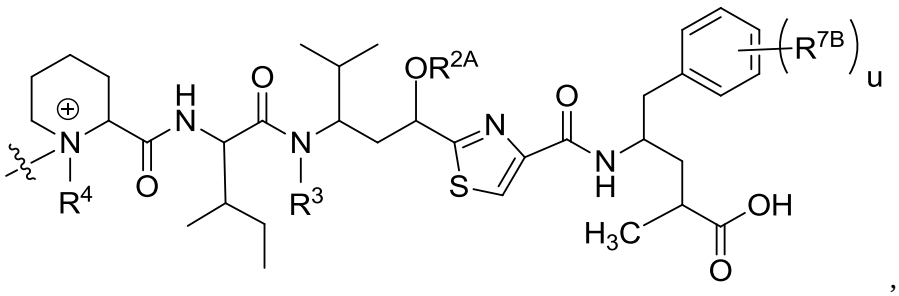
R^{7A} is optionally substituted aryl or optionally substituted heteroaryl.

48. The Drug Linker compound of claim **47** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



wherein R^{7A} is optionally substituted phenyl and R^8 is hydrogen or methyl.

49. The Drug Linker compound of claim **50** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



wherein

R^4 is methyl;

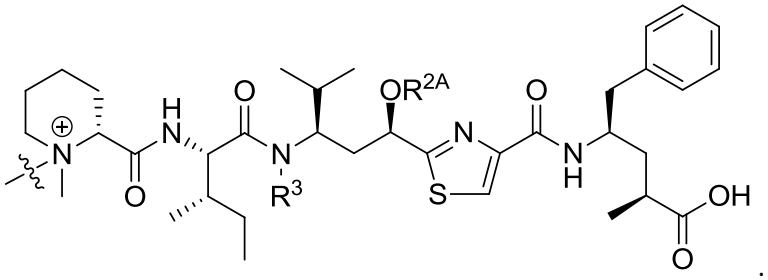
subscript u is 0, 1 or 2;

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

R^{2A} along with the oxygen atom to which it is attached is an O-linked substituent selected from the group consisting of -$OCH_2OCH_2R^{2B}$, -OCH_2R^{2B}, -$OC(O)R^{2B}$, -$CH_2OC(O)R^{2B}$, –$OC(O)N(R^{2B})(R^{2C})$, and –$OCH_2C(O)N(R^{2B})(R^{2C})$, wherein R^{2B} and R^{2C} are independently selected from the group consisting of H, C_1-C_6 alkyl and C_2-C_6 alkenyl; and

each R^{7B}, when present, independently is –OH or –OCH_3.

50. The Drug Linker compound of claim **49** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



.

51. The Drug Linker compound of claim **50** wherein R^{2A} is -CH_2CH_3.

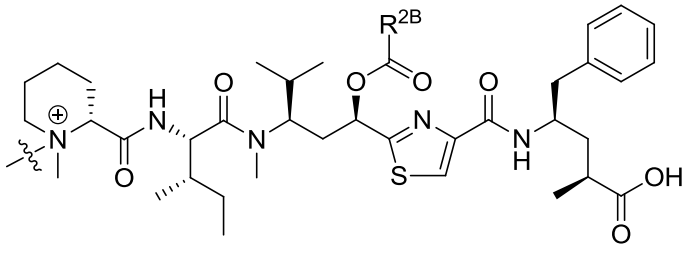
52. The Drug Linker compound of claim **50** wherein R^{2A} is -CH_2-CH=CH_2.

53. The Drug Linker compound of claim **49**, wherein

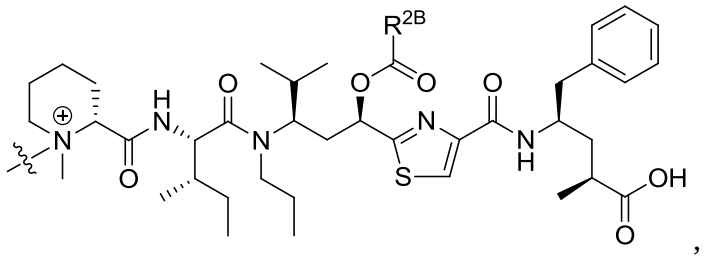
R^{2A} is -CH_2CH_3, -CH_2-CH=CH_2 or -$CH_2C(CH_3)$=CH_2, R^{2B} is –CH_3, R^3 is –CH_3 and subscript u is 0, or

R^{2A} is -CH_2CH_3 or -CH_2-CH=CH_2, or -$CH_2C(CH_3)$=CH_2, R^{2B} is –CH_3, R^3 is –CH_3 and subscript u is 1, wherein R^{7B} is -OH.

54. The Drug Linker compound of claim **49** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



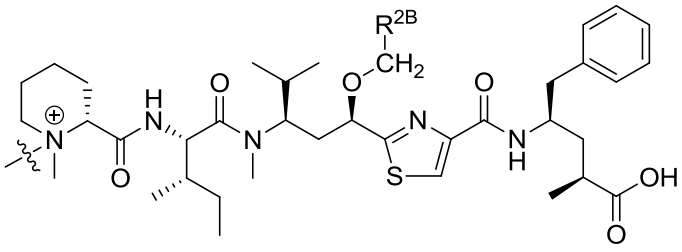
or



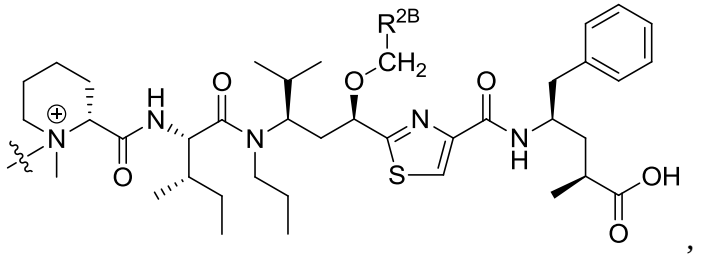
,

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

55. Drug Linker compound of claim **49**, wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



or



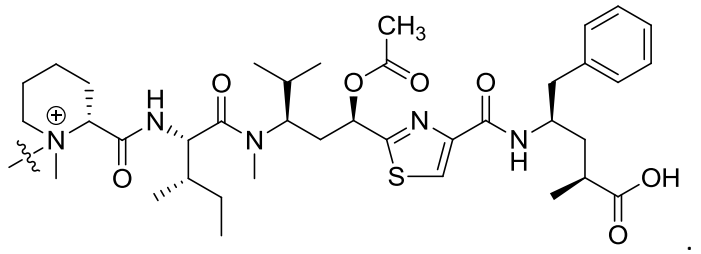
,

wherein

R^{2B} is hydrogen, methyl or $–OCH_3$, or

$-OCH_2R^{2B}$ is $–OCH_2CH=CH_2$ or $–OCH_2C(CH_3)=CH_2$.

56. The Drug Linker compound of claim **49**, wherein the quaternized tubulysin Drug Unit $–D^+$ is that of tubulysin M, for which the structure is:

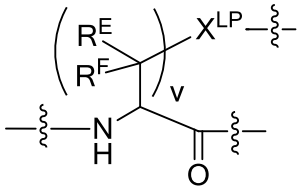


.

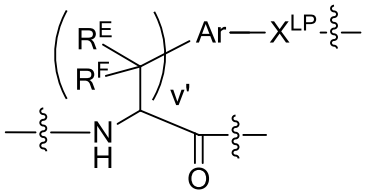
57. The Drug Linker compound of any one of claims **35** wherein L_P is a aminoalkanedioic acid, a diaminoalkanoic acid, a sulfur-substituted alkanedioic acid, a sulfur-substituted aminoalkanoic acid, a diaminoalkanol, an aminoalkanediol, a hydroxyl substituted alkanedioic acid, a hydroxyl substituted aminoalkanoic acid or a sulfur-substituted aminoalkanol residue, optionally substituted, wherein the

sulfur substituent is in reduced or oxidized form, or L_P is an amino acid residue of lysine, arginine, asparagine, glutamine, ornithine, citrulline, cysteine, homocysteine, penicillamine, threonine, serine, glutamic acid, aspartic acid, tyrosine, histidine or tryptophan, wherein the amino acid is in the **D**- or **L**-configuration.

58. The Drug Linker compound of claim **57** wherein the aminoalkanedioic acid, diaminoalkanoic acid, sulfur-substituted aminoalkanoic acid or hydroxyl substituted aminoalkanoic acid residue has the structure of Formula A or Formula B:



(Formula A)



(Formula B)

wherein

subscript v is an integer ranging from 1 to 4;

subscript v' is an integer ranging from 0 to 4;

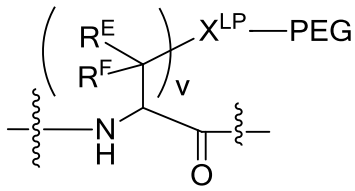
X^{LP} is selected from the group consisting of –O-, -NR^{LP}-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)N(R^{LP})-, -N(R^{LP})C(=O)N(R^{LP})-, and -N(R^{LP})C(=NR^{LP})N(R^{LP})- wherein each R^{LP} is independently selected from the group consisting of hydrogen and optionally substituted alkyl or two of R^{LP} together along with their intervening atoms define an optionally substituted heterocycloalkyl and any remaining R^{LP} are as previously defined;

Ar is an arylene or heteroarylene, optionally substituted;

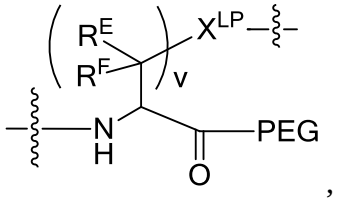
each R^E and R^F is independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, or R^E and R^F together with the same carbon to which they are attached, or R^E and R^F from adjacent carbons together with these carbons, defines a optionally substituted cycloalkyl with any remaining R^E and R^F substituents as previously defined; and

wherein the wavy lines indicate covalent attachments of the Formula A or Formula B structure within the Drug Linker compound structure.

59. The Drug Linker compound of any one of claims **35** wherein -L_P(PEG)- has the structure of Formula A1 or A2:



(Formula A1)



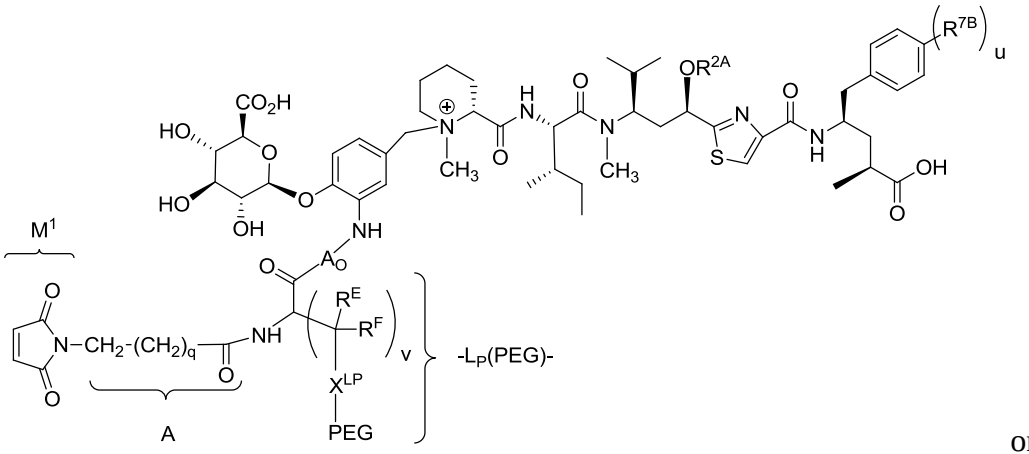
(Formula A2)

wherein X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-;

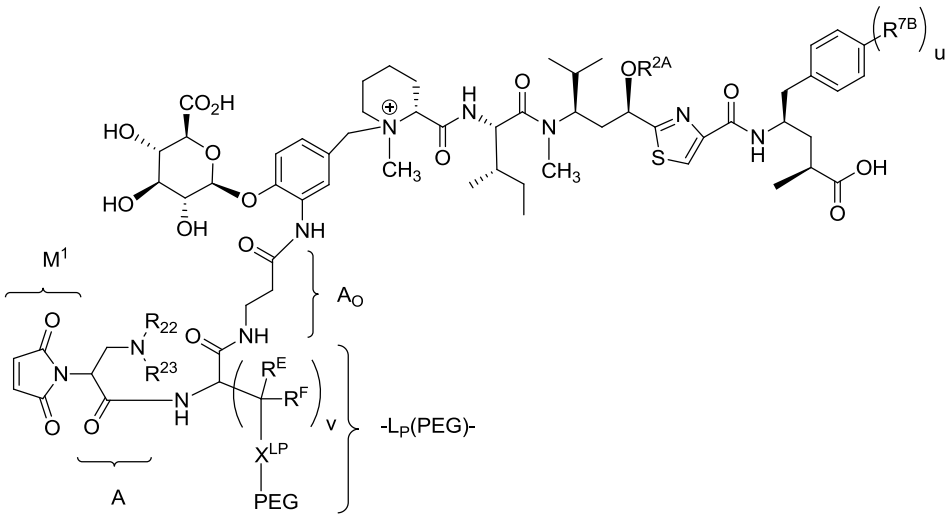
R^E and R^F are independently selected from the group consisting of -H, and -C_1-C_4 alkyl; and

wherein the wavy line indicates covalent attachment of Formula A1 or Formula A2 within the Drug Linker compound structure.

60. The Drug Linker compound of claim **35** wherein the compound is represented by the structure of:



or



wherein

R^{2A} is saturated C_1-C_4 alkyl, unsaturated C_2-C_4 alkyl, –C(=O)R^{2B}, wherein R^{2B} is C_1-C_4 alkyl;

A_O is absent or is an amine-containing acid residue;

subscript q is an integer ranging from 1 to 4;

subscript u is 0 or 1;

subscript v is an integer ranging from 1 to 4;

R^{7B}, when present, is –OH;

X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-;

R^E and R^F are independently selected from the group consisting of -H, and C_1-C_4 alkyl;

one of R^{22}, R^{23} is hydrogen and the other is an acid labile protecting group or R^{22} and R^{23} are each hydrogen with the nitrogen to which they are attached optionally protonated as an acid addition salt.

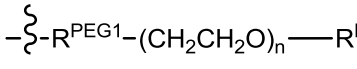
61. The Drug Linker compound of claim **60**, wherein R^{2A} is saturated C_1-C_4 alkyl or unsaturated C_3-C_4 alkyl, wherein saturated C_1-C_4 alkyl is -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$ and unsaturated C_3-C_4 alkyl is –$CH_2CH{=}CH_2$ or –$CH(CH_3)CH{=}CH_2$.

62. The Drug Linker compound of claim **60** wherein R^{2A} is –$C(O)CH_3$.

63. The Drug Linker compound of claim **60** wherein R^{2A} is -CH_2CH_3.

64. The Drug Linker compound of claim **60** wherein R^{2A} is –$CH_2CH{=}CH_2$.

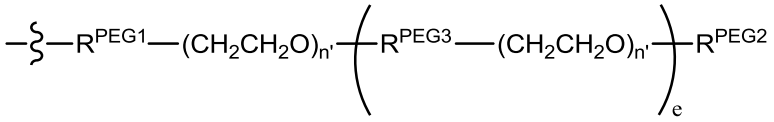
65. The Drug Linker compound of claim **35**, wherein PEG has the structure selected from the group consisting of:



,



, and



wherein the wavy line indicates site of attachment to X^{LP} of the Parallel Connector Unit (L_P),

R^{PEG1} is an optional PEG Attachment Unit,

R^{PEG2} is a PEG Capping Unit;

R^{PEG3} is a PEG Coupling Unit;

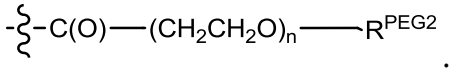
subscript n ranges from 8 to 72;

each subscript n' is independently selected from 1 to 72; and

subscript e ranges from 2 to 5,

provided that the PEG Unit contains at least 8 and no more than 72 ethylene glycol subunits.

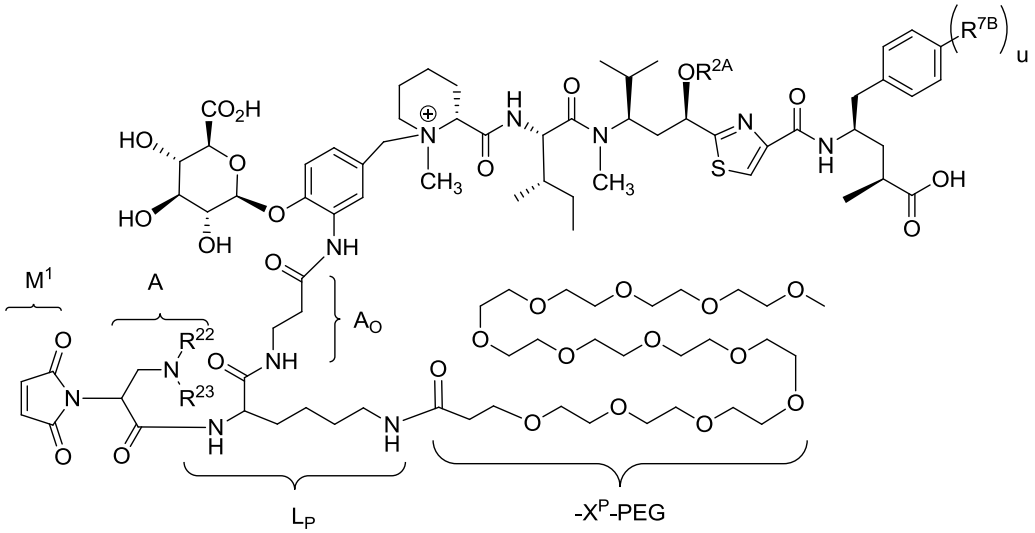
66. The Drug Linker compound of claim **60** wherein –X^{LP}-PEG has the structure of:



.

67. The Drug Linker compound of claim **66** wherein subscript n is 12 and R^{PEG2} is hydrogen or –CH_3.

68. The Drug Linker compound of claim **60** wherein the compound has the structure of:



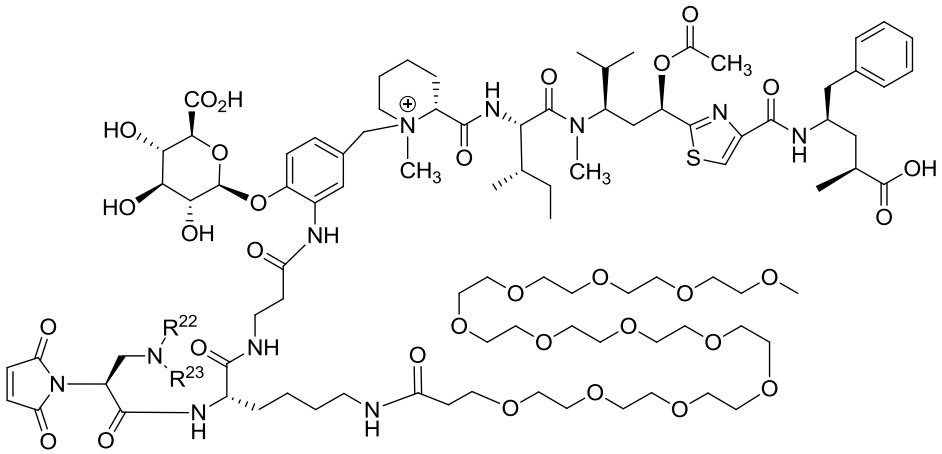
wherein

subscript u is 0 or 1;

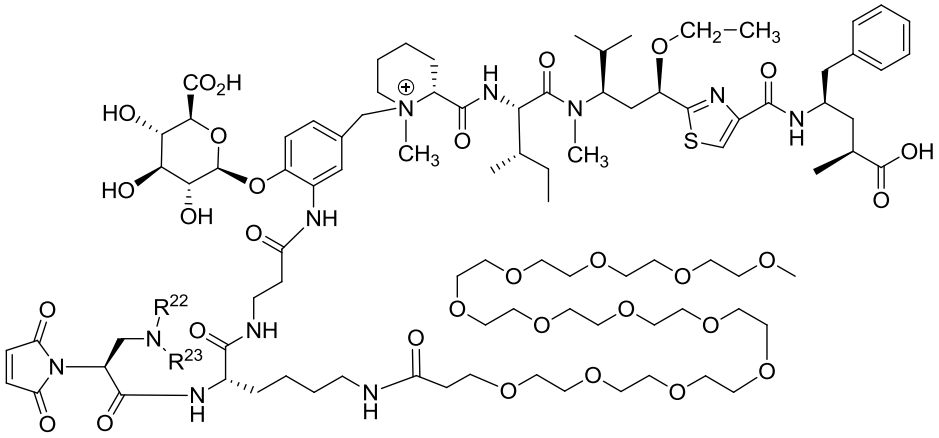
R^{7B}, when present, is –OH; and

R^{2A} along with the oxygen atom to which it is attached is –$OC(O)CH_3$, -CH_2CH_3 or –$CH_2CH{=}CH_2$.

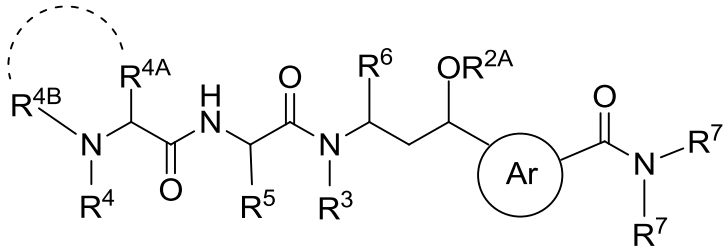
69. The Drug Linker compound of claim **68** wherein the compound has the structure of:



or



70. A tubulysin compound having the structure of:



wherein the curved dashed line indicates optional cyclization;

R^{2A} is unsaturated alkyl, optionally substituted;

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

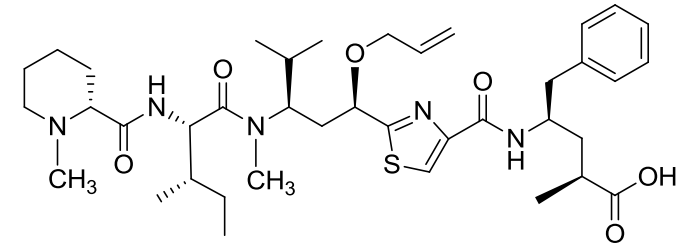
R^3 is hydrogen or optionally substituted alkyl;

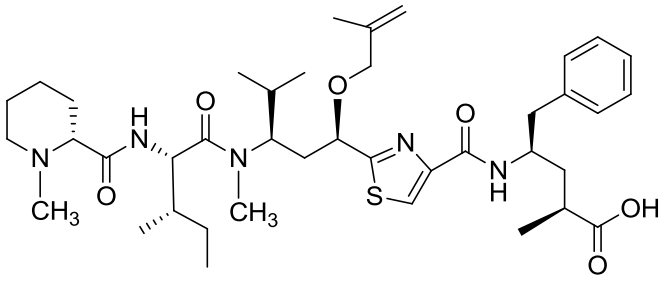
R^4, R^5 and R^6 are optionally substituted alkyl, independently selected;

R^{4a} is hydrogen or optionally substituted alkyl and R^{4B} is optionally substituted alkyl, or both together with the nitrogen to which they are attached, as indicated by the curved dashed line, define a quaternized nitrogen heterocycloalkyl, optionally substituted; and

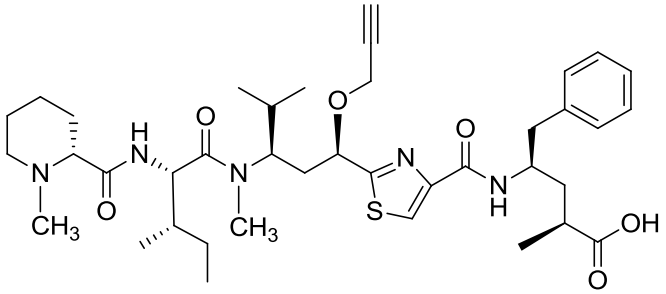
one R^7 is hydrogen or optionally substituted alkyl and the other R^7 is optionally substituted aralkyl or heteroaralkyl.

71. The tubulysin compound of claim **70**, wherein the compound has the structure of :





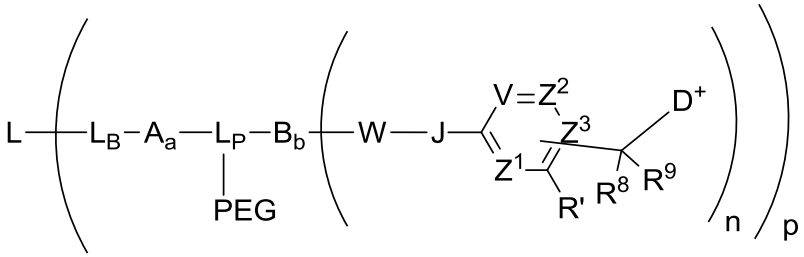
or



.

72. A method of preparing a Drug Linker compound comprising the step of quaternizing a tubulysin compound of claim **70** or **71** with a Linker Unit precursor.

73. A Ligand Drug Conjugate composition, wherein the composition is represented by the structure of Formula 1D:



(Formula 1D)

wherein

L is an antibody Ligand Unit, thereby defining an Antibody Drug Conjugate;

L_B is a Ligand Covalent Binding Unit;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscript a is 0 or 1;

subscript b is 0 or 1;

A is a first optional Stretcher Unit so that subscript a is 0 when A is absent or A is present so that subscript a is 1 and is optionally comprised of two, three or four independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or B is present so that subscript b is 1 and is optionally comprised of two, three or four subunits independently of A

wherein Ligand Covalent Binding Unit, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described;

subscript n is 1, 2, 3 or 4, provided that subscript b is 1 and B is a Branching Unit when subscript n is 2, 3 or 4 and provided that B is A_O or is absent when subscript n is 1;

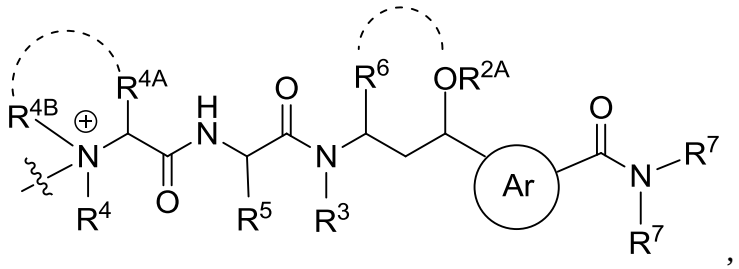
V, Z^1, Z^2 and Z^3 are =N- or =C(R^{24})-, wherein R^{24} is hydrogen or alkyl, alkenyl or alkynyl, optionally substituted, or halogen, -NO_2, -CN or other electron withdrawing group, or -OCH_3 or other an electron donating group, or –C(R^8)(R^9)-D^+, wherein at least one of V, Z^1, and Z^3 is =C(R^{24})-, provided that 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, and Z^3 when that variable group is =C(R^{24})- and provided that –J and -C(R^8)(R^9)-D^+ have relative substitution in the *para* or *ortho* positions;

R^8 and R^9 independently are hydrogen or optionally substituted C_1-C_6 alkyl;

R’ is hydrogen or –OCH_3 or other electron donating group;

subscript p is a number ranging from 1 to 24;

D+ is a quaternized tubulysin Drug Unit having the structure of:



,

wherein the curved dashed lines indicate optional cyclizations;

R^{2A} is hydrogen or optionally substituted alkyl, or R^{2A} along with the oxygen atom to which it is attached defines an O-linked substituent other than –OH, or R^{2A} is absent when R^6 is bonded to that oxygen atom, as indicated by the curved dash line between R^6 and the oxygen atom, to define an oxygen-containing heterocycloalkyl;

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

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^5 and R^6 are optionally substituted alkyl, independently selected, or R^6 is bonded to the oxygen atom of the $–OR^{2A}$ moiety in which R^{2A} is absent and R^4 and R^5 are as previously defined;

R^{4a} is hydrogen or optionally substituted alkyl and R^{4B} is optionally substituted alkyl, or both together with the nitrogen to which they are attached, as indicated by the curved dotted line between R^{4A} and R^{4B}, define a quaternized nitrogen heterocycloalkyl, optionally substituted;

one R^7 is hydrogen or optionally substituted alkyl and the other R^7 is optionally substituted aralkyl or heteroaralkyl;

wherein the wavy line indicates covalent bonding of D^+ to the remainder of the Drug Linker compound structure and wherein optionally substituted alkyl are independently selected;

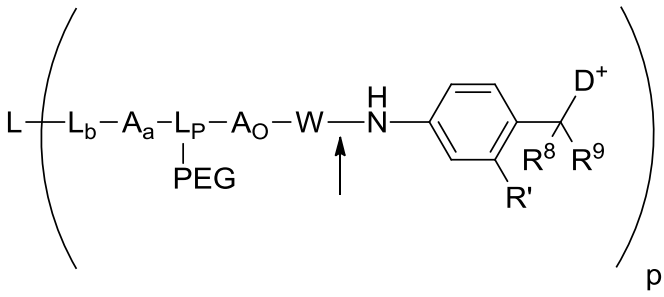
J is optionally substituted -NH-, or J is $–N(R^{33})-$, wherein R^{33} is hydrogen or methyl;

W is a peptide comprised of an amino acid sequence covalently attached to J through an amide bond wherein that amide bond is cleavable by a protease,

wherein said protease cleavage initiates release of a tubulysin compound (D) from a Ligand Drug Conjugate compound of the composition,

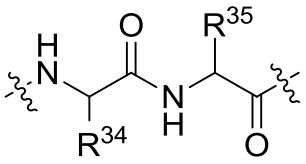
wherein the Ligand Drug Conjugate compound has the structure of Formula 1D in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

74. The Ligand Drug Conjugate composition of claim **73**, wherein the composition is represented by the structure of:

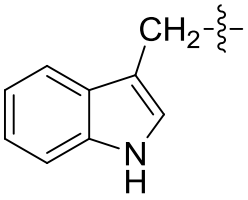


wherein W consists or is comprised of a dipeptide, wherein the dipeptide is at the distal end of W and the indicated bond is an amide bond specifically cleavable by an intracellular protease in comparison to freely circulating serum proteases.

75. The Ligand Drug Conjugate composition of claim **74**, wherein the dipeptide has the structure of;



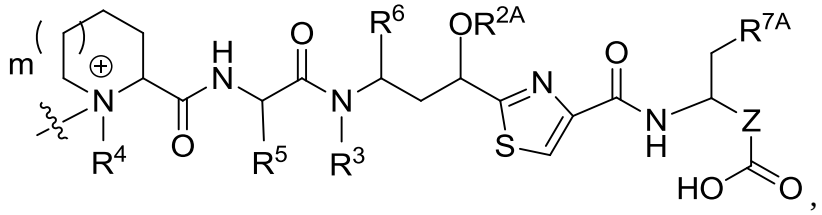
wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH_3 or has the structure of



; and

R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=O)NH_2$, $(CH_2)_3NH(C=NH)NH_2$, or -$(CH_2)_2CO_2H$, wherein the wavy line at the dipeptide N-terminus indicates covalent binding to A_O or L_P, depending on the presence or absence of A_O, respectively, and the wavy line at the dipeptide C-terminus indicates covalent binding to J.

76. The Ligand Drug Conjugate composition of claim **73**, **74** or **75** wherein the quaternized tubulysin Drug Unit (–D^+) has the structure of:



,

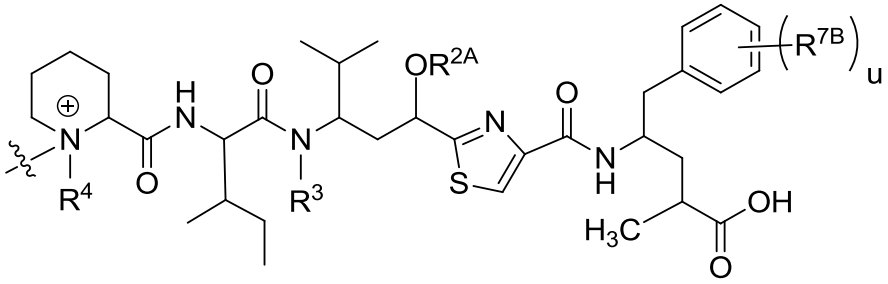
wherein

subscript m is 0 or 1;

Z is an optionally substituted alkylene or an optionally substituted alkenylene; and

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

77. The Ligand Drug Conjugate composition of claim **76** wherein the quaternized tubulysin Drug Unit –D^+ has the structure of:



,

wherein R^4 is methyl;

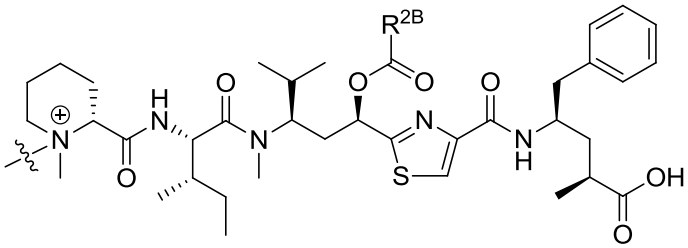
subscript u is 0, 1 or 2;

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

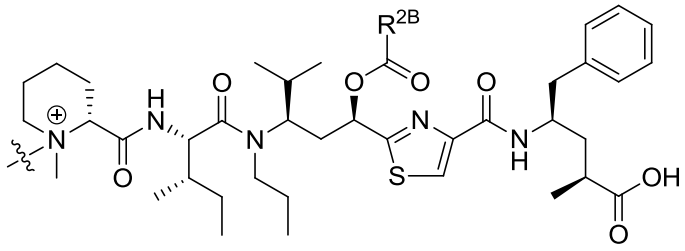
R^{2A} along with the oxygen atom to which it is attached is an O-linked substituent selected from the group consisting of -$OCH_2OCH_2R^{2B}$, -OCH_2R^{2B}, -OC(O)R^{2B}, -CH_2OC(O)R^{2B}, –OC(O)N(R^{2B})(R^{2C}), and –OCH_2C(O)N(R^{2B})(R^{2C}), wherein R^{2B} and R^{2C} are independently selected from the group consisting of H, C_1-C_6 alkyl and C_2-C_6 alkenyl; and

each R^{7B}, when present, independently is –OH or –OCH_3.

78. The Ligand Drug Conjugate composition of claim **77**, wherein the quaternized tubulysin Drug Unit has the structure of:



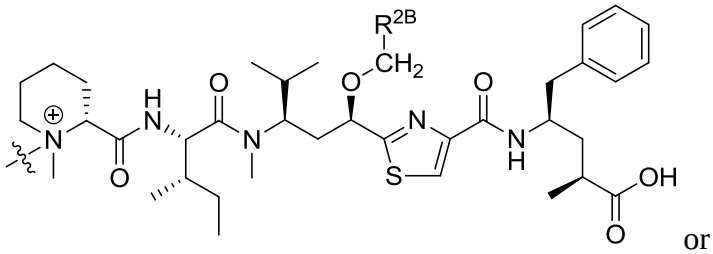
or



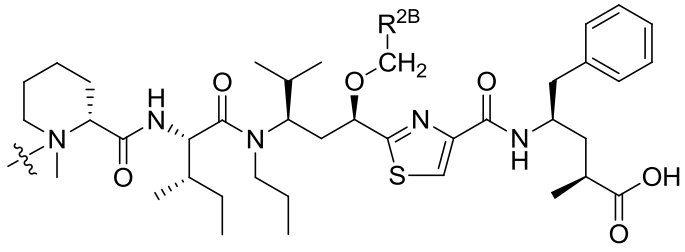
,

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

79. The Ligand Drug Conjugate composition of claim **78**, wherein the quaternized tubulysin Drug Unit has the structure of:



or

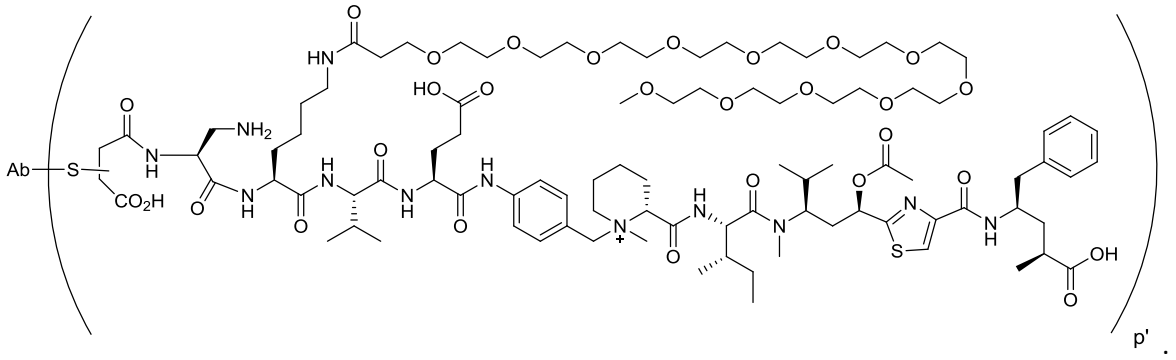


,

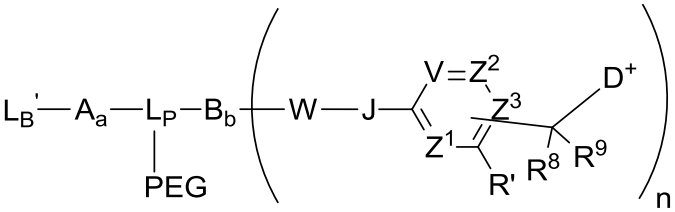
wherein R^{2B} is hydrogen, methyl or $–OCH_3$, or

$-OCH_2R^{2B}$ is $–OCH_2CH=CH_2$ or $–OCH_2C(CH_3)=CH_2$.

80. The Ligand Drug Conjugate composition of claim **73**, wherein a compound thereof is represented by the structure of:



81. A Drug Linker compound, wherein the compound is represented by the structure of:



wherein

L_B' is a Ligand Covalent Binding Unit precursor;

L_P is a Parallel Connector Unit;

PEG is a Polyethylene Glycol Unit;

subscripts a and b independently are 0 or 1;

subscript n is 1, 2, 3 or 4;

A is a first 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 independently selected subunits (A_1, A_2, A_3, A_4);

B is a Branching Unit or a second optional Stretcher Unit (A_O) so that subscript b is 0 when B is absent or 1 when B is present and is optionally comprised of two, three or four subunits independently of A,

wherein Ligand Covalent Binding Unit precursor, Parallel Connector Unit, Polyethylene Glycol Unit, Stretcher Unit and Branching Unit are as hereinbefore described;

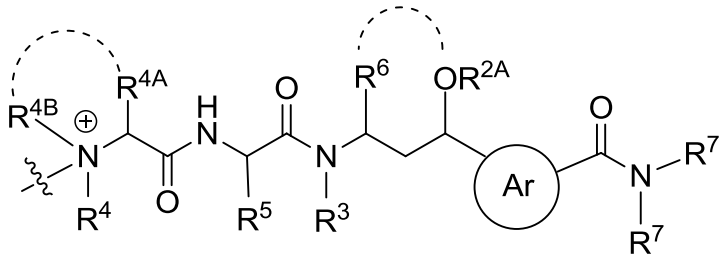
wherein subscript b is 1 and B is a Branching Unit when subscript n is 2, 3 or 4 or b is 0 or 1 so that B is A_O when subscript n is 1;

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, or -OCH_3 or other an electron donating group, or –C(R^8)(R^9)-D^+, wherein at least one of V, Z^1, and Z^3 is =C(R^{24})-, provided that 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, and Z^3 when that variable group is =C(R^{24})- and provided that –J and -C(R^8)(R^9)-D^+ have relative substitution in the *para* or *ortho* positions;

R^8 and R^9 independently are hydrogen or optionally substituted C_1-C_6 alkyl;

R' is hydrogen or –OCH_3 or other electron donating group;

D^+ is a quaternized tubulysin Drug Unit having the structure of:



,

wherein the curved dashed lines indicate optional cyclizations; R^{2A} is hydrogen or optionally substituted alkyl, or R^{2A} along with the oxygen atom to which it is attached defines an O-linked substituent other than –OH, or R^{2A} is absent when R^6 is bonded to that oxygen atom, as indicated by the curved dash line between R^6 and the oxygen atom, to define an oxygen-containing heterocycloalkyl;

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

R^3 is hydrogen or optionally substituted alkyl;

R^4, R^5 and R^6 are optionally substituted alkyl, independently selected, or R^6 is bonded to the oxygen atom of the –OR^{2A} moiety in which R^{2A} is absent and R^4 and R^5 are as previously defined;

R^{4a} is hydrogen or optionally substituted alkyl and R^{4B} is optionally substituted alkyl, or both together with the nitrogen to which they are attached, as indicated by the curved dotted line between R^{4A} and R^{4B}, define a quaternized nitrogen heterocycloalkyl, optionally substituted;

one R^7 is hydrogen or optionally substituted alkyl and the other R^7 is optionally substituted aralkyl or heteroaralkyl;

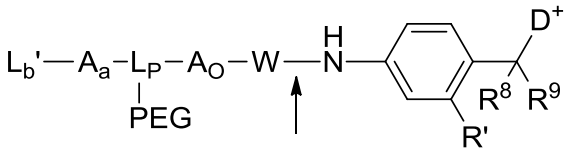
wherein the wavy line indicates covalent bonding of the D^+ structure to the remainder of the Drug Linker compound structure;

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

W is a peptide comprised of an amino acid sequence covalently attached to J through an amide bond wherein that amide bond is cleavable by a protease, wherein said protease cleavage initiates release of a tubulysin compound (D) from the Drug Linker compound or a Ligand Drug Conjugate compound

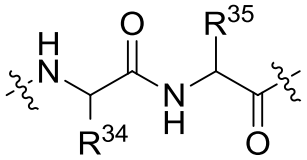
prepared from the Drug Linker compound, wherein the Ligand Drug Conjugate compound has the Formula 1D structure of claim 74 in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

82. The Drug Linker compound of claim **81**, wherein the compound is represented by the structure of:

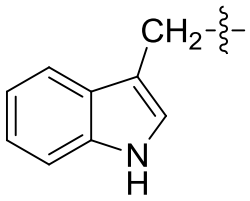


wherein W consists or is comprised of a dipeptide, wherein the dipeptide is at the distal end of W and the indicated bond is an amide bond specifically cleavable by an intracellular protease in comparison to freely circulating serum proteases.

83. The Drug Linker compound of claim **80**, wherein the dipeptide has the structure of;



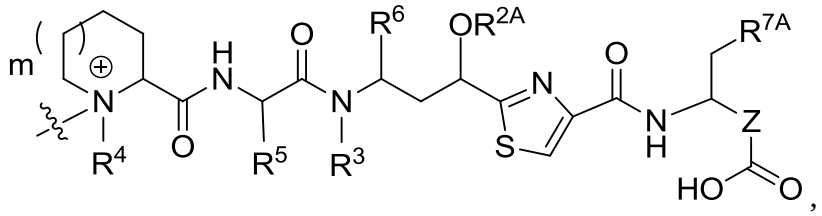
wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH_3 or has the structure of



; and

R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3$NH(C=O)NH_2, $(CH_2)_3$NH(C=NH)NH_2, or -$(CH_2)_2CO_2H$, wherein the wavy line at the dipeptide N-terminus indicates covalent binding to A_O or to L_B, depending on the presence or absence of A_O, respectively, and the wavy line at the dipeptide C-terminus indicates covalent binding to the nitrogen atom of said amide bond.

84. The Drug Linker compound of claim **81**, **82** or **83** wherein the quaternized tubulysin Drug Unit (–D^+) has the structure of:

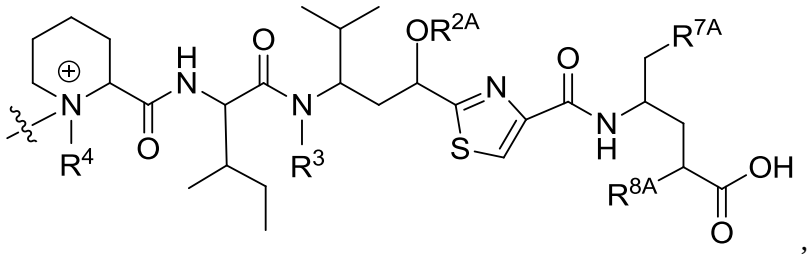


subscript m is 0 or 1;

Z is an optionally substituted alkylene or an optionally substituted alkenylene; and

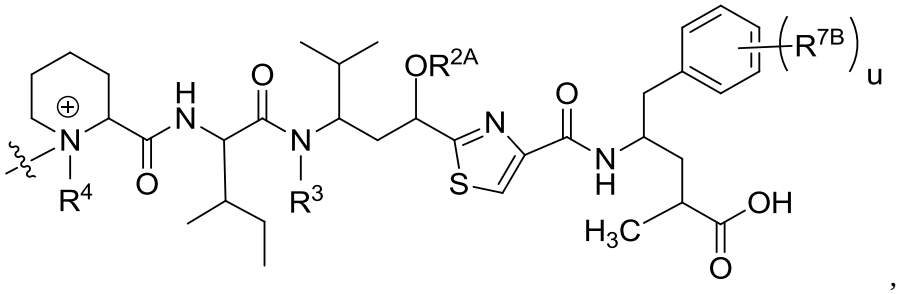
R^{7A} is optionally substituted aryl or optionally substituted heteroaryl.

85. The Drug Linker compound of claim **84** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



wherein R^{7A} is optionally substituted phenyl and R^8 is hydrogen or methyl.

86. The Drug Linker compound of claim **85** wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



wherein R^4 is methyl;

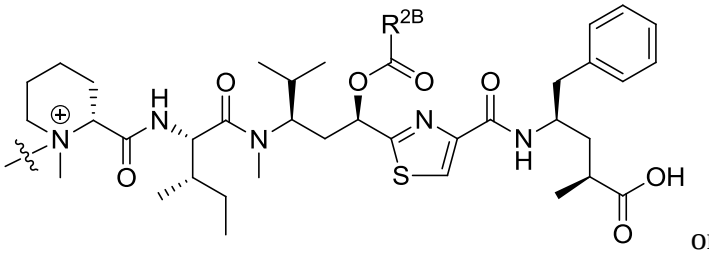
subscript u is 0, 1 or 2;

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

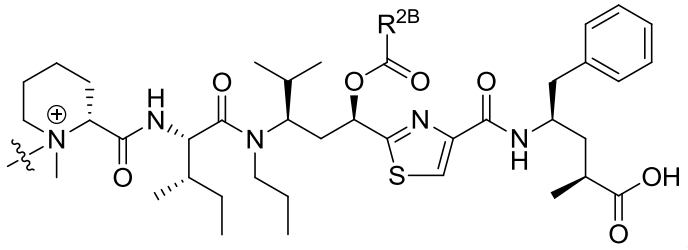
R^{2A} along with the oxygen atom to which it is attached is an O-linked substituent selected from the group consisting of $-OCH_2OCH_2R^{2B}$, $-OCH_2R^{2B}$, $-OC(O)R^{2B}$, $-CH_2OC(O)R^{2B}$, $–OC(O)N(R^{2B})(R^{2C})$, and $–OCH_2C(O)N(R^{2B})(R^{2C})$, wherein R^{2B} and R^{2C} are independently selected from the group consisting of H, C_1-C_6 alkyl and C_2-C_6 alkenyl; and

each R^{7B}, when present, independently is –OH or $–OCH_3$.

87. The Drug Linker compound of claim **86**, wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



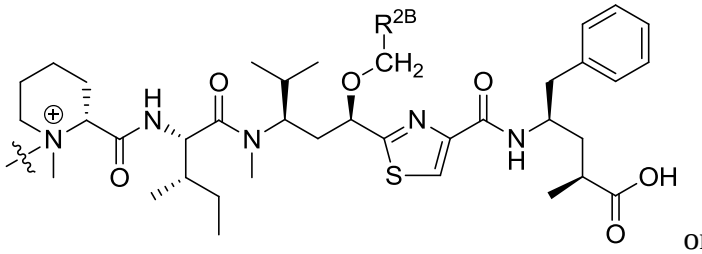
or



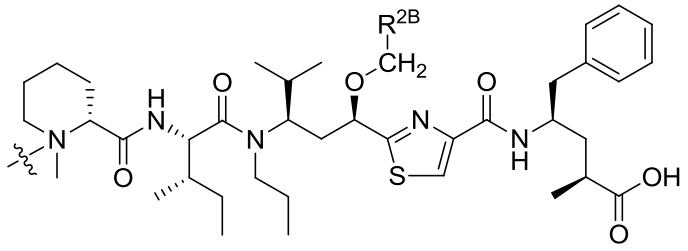
,

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

88. The Drug Linker compound of claim **86**, wherein the quaternized tubulysin Drug Unit ($–D^+$) has the structure of:



or

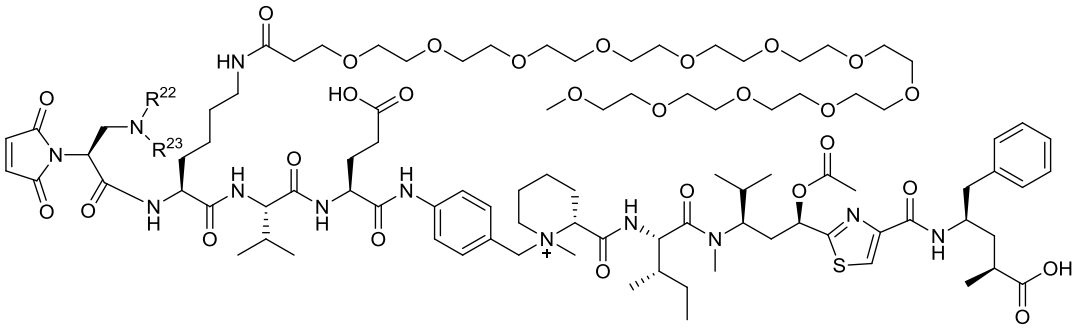


,

wherein R^{2B} is hydrogen, methyl or $–OCH_3$, or

$-OCH_2R^{2B}$ is $–OCH_2CH=CH_2$ or $–OCH_2C(CH_3)=CH_2$.

89. The Drug Linker compound of claim **81**, wherein the compound has the structure of:



wherein one of R^{22}, R^{23} is hydrogen and the other is an acid labile protecting group or R^{22} and R^{23} are each hydrogen with the nitrogen to which they are attached optionally protonated as an acid addition salt.

.

90. A formulation comprising a Ligand Drug Conjugate composition of claim **1** and one or more excipients.

91. The formulation of claim **90** wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof.

92. The formulation of claim **90** wherein the pharmaceutically acceptable formulation precursor is a solid suitable for reconstitution as a solution for intravenous injection to a subject.

93. The formulation of claim **90** wherein the pharmaceutically acceptable formulation is a liquid suitable for intravenous injection to a subject.

94. The formulation of claims **91**, **92** or **93** wherein the Ligand Drug Conjugate composition is present in the pharmaceutically acceptable formulation or precursor thereof in an effective amount for treatment of a hyperproliferative condition.

95. Use of a Ligand Drug Conjugate composition of claim **1** or claim **73** in the preparation of a medicant for the treatment of a hyperproliferative disease or condition.

96. The use according to claim **95** wherein the hyperproliferative disease or condition is a cancer.

97. The use according to claim **96** wherein the hyperproliferative disease or condition is a leukemia or a lymphoma.

` **98**. A method of inhibiting the multiplication of a tumor cell or cancer cell, or causing apoptosis in a tumor or cancer cell, by exposing said cell in vitro with an effective amount of Ligand Drug Conjugate composition of claim **1** or claim **73** or of a tubulysin compound of claim **70** ~~or **72**~~.