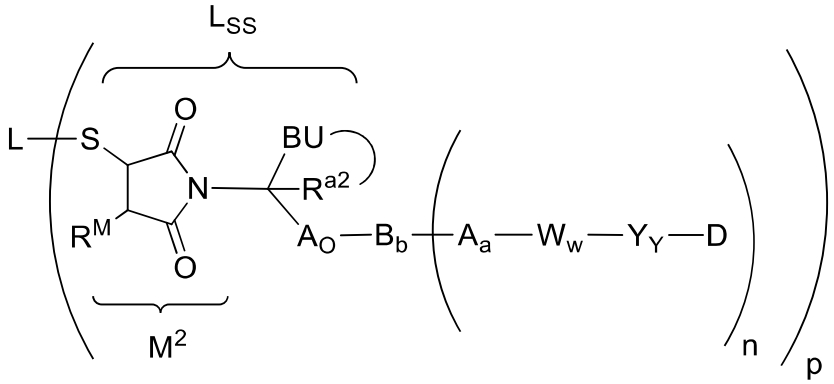
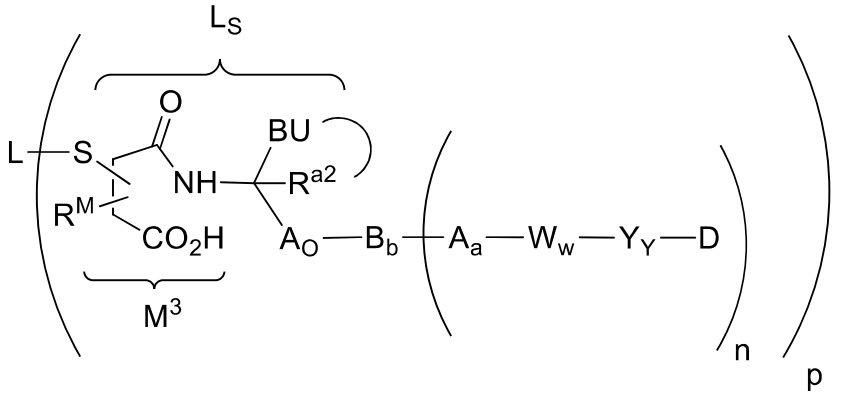
[0014a] In one aspect, there is provided a Ligand Drug Conjugate (LDC) composition, wherein the composition is represented by the structures of Formula 1 and/or Formula 2:



(Formula 1)



(Formula 2)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

S is a sulfur atom of the Ligand Unit;

R^M is hydrogen or an optionally substituted C_1-C_6 alkyl

subscript w is 0 or 1;

subscript y is 0, 1, or 2;

subscript n is 1, 2, 3 or 4;

subscript a is 0 or 1;

subscript b is 0 or 1,

provided that subscript b is 1 when subscript n is 2, 3 or 4; and subscript b is 0 when subscript n is 1;

A is a first Stretcher Unit;

A_O is a second optional Stretcher Unit;

B is an optional Branching Unit; and

wherein each of A, A_O and B is an independently selected single unit or is optionally comprised or consists of two, three or four independently selected subunits;

when subscript y is 0, Y is absent; when subscript y is 1, Y is a self-immolative spacer unit; and when subscript y is 2, Y_y is –Y-Y'-, wherein Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D^+);

subscript w is 0 or 1, wherein W is absent when subscript w is 0, or when subscript w is 1 then

W is a Peptide Cleavable Unit, or

W is a Glucuronide Unit of formula –Y(W')-, wherein W' represents a carbohydrate moiety with glycosidic bonding to Y through a optionally substituted heteroatom;

provided that Y bonded to W' is a self-immolative Spacer Unit;

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl group that together with the carbon atom to which both are attached, as represented by the solid curved line, define a cyclic Basic Unit having an optionally substituted C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group, an optionally substituted C_3-C_{20} carbocyclo with exocyclic substitution by an optionally substituted basic nitrogen atom of a basic secondary or tertiary amine functional group, or an optionally substituted C_3-C_{20} carbocyclo having exocyclic substitution by an optionally substituted C_1-C_{12} aminoalkyl in which the optionally substituted basic nitrogen atom of the amino moiety of the aminoalkyl is that of a primary, secondary or tertiary amine functional group, wherein the optionally substituted basic nitrogen atom of the exocyclic amine or aminoalkyl along with its optionally substituted alkyl moiety is attributable to BU, or

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl formally cyclized to the basic nitrogen atom of an acyclic Basic Unit of corresponding structure to Formula 1 and/or Formula 2 in which the solid curved lined between BU and R^{a2} is absent, or to a carbon atom of an optionally substituted C_1-C_{12} alkylene bearing that basic nitrogen atom, both of which comprise the acyclic Basic Unit, thus forming an optionally substituted C_3-C_{20} heterocyclo, which incorporates the basic nitrogen atom as a skeletal heteroatom, or an optionally substituted C_3-C_{20} carbocyclo substituted directly by the basic nitrogen atom, or substituted indirectly by the basic nitrogen atom through an optionally substituted C_1-C_{12} alkylene moiety remaining from said formal cyclization and whose structure is dependent on the site of cyclization, so in either instance a cyclic Basic Unit (cBU) is defined, as indicated by the solid curved line;

and

wherein the basic nitrogen atom of the cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated;

subscript p ranges from 1 to 24;

D is a Drug Unit, or

D is a quaternized Drug Unit represented as D^+ so that D^+ replaces D in Formula 1 and Formula 2 provided that subscript w is 1;

wherein if subscript w is 1, activation of the Glucuronide Unit by a glycosidase or activation of the Peptide Cleavable Unit by a protease within a compound of the Ligand Drug Conjugate composition initiates release of the Drug Unit or quaternized Drug Unit as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound,

or if subscript w is 0, a biologically active compound or derivative thereof is released from a Ligand Drug Conjugate compound of the composition on enzymatic or non-enzymatic cleavage of a bond within a drug linker moiety of the Conjugate compound that attaches Y_y-D to the indicated L_{SS} or L_S structure of that drug linker moiety; and

wherein the Ligand Drug Conjugate compound corresponds in structure to Formula 1 or Formula 2 in which p is replaced by p', wherein p' is an integer ranging from 1 to 24.

[0015] In some embodiments, A_O is present and is comprised or consists of a Hydrolysis Enhancing [HE] Unit and W is a Peptide Cleavable Unit and subscript y is 0, 1 or 2, or W is a Glucuronide Unit of structure –Y(W')-, so that subscript y is 1 or 2 in Formula 1, Formula 2, wherein Y is a self-immolative Spacer Unit and W' is a carbohydrate moiety (Su) with attachment to Y by glycosidic bonding through an optionally substituted heteroatom (E') wherein D/D^+ is attached directly to Y when subscript y is 1 or D is attached indirectly to Y through bonding to a second Spacer Unit designated Y' when subscript y is 2.

[0016] In some of those embodiments in which subscript y is 2, Y and Y' are both self-immolative Spacer Units, which undergo self-immolation upon enzymatic processing of the Peptide Cleavable Unit or Glucuronide Unit as, for example, when one self-immolative Spacer Unit (Y) is capable of 1,4- or 1,6-elimination and the other self-immolative Spacer Unit (Y') is a methylene carbamate unit or a carbamate functional group capable of CO_2 elimination as described herein.

[0017] In other embodiments, only one Y of Y_y undergoes self-immolation upon conditional enzymatic processing of the Peptide or Glucuronide Unit to release D, when

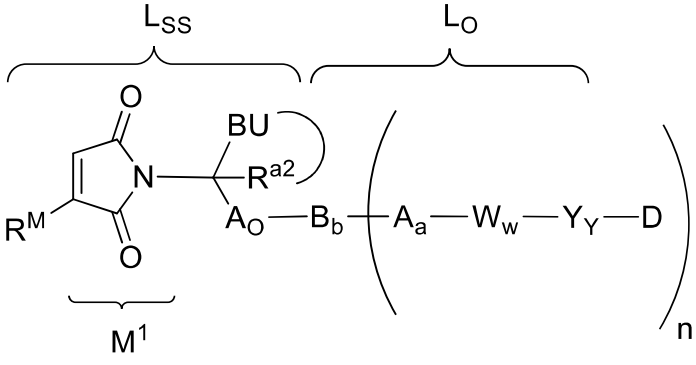
subscript y is 1, or to release Y'-D, when subscript y is 2, as a biologically active compound or derivative thereof, which sometimes are referred to as a drug compound or active drug moiety, respectively. In some of those embodiments Y' of –Y'-D also can undergo self-immolation to release D as a biologically active compound or derivative thereof. In still other embodiments, W is a Cleavable Unit that is not reliant upon enzymatic cleavage for release of the biologically active compound or derivative thereof and in some instances is acted upon non-enzymatically for that release.

[0018] In preferred embodiments, the functionality of BU in acyclic form to effect self-stabilization of a corresponding Ligand Drug Conjugate composition by conversion of Formula 1 to Formula 2 in which the curved dashed line is not present is substantially retained by cBU in a majority of compounds in the LDC composition of Formula 1 in which the curved dashed line is present.

[0019] In other preferred embodiments, the targeting moiety of the Ligand Drug Conjugate is that of an antibody, sometimes referred to as an antibody Ligand Unit, thereby defining an Antibody Drug Conjugate (ADC) composition, and the targeted moiety recognized by its antibody Ligand Unit is an cell-surface antigen of targeted abnormal cells or normal cells peculiar to and in the vicinity of the abnormal cells, wherein the antigen so bound from said recognition in some embodiments is capable of cellular internalization of a Conjugate compound of the ADC composition, wherein the antigen is preferentially present on the abnormal cells or nearby normal cells in comparison to normal cells distant from the abnormal cells.

[0020] In any one of those preferred embodiments, the released biologically active compound or derivative thereof exerts a therapeutic effect due to its biological activity at the desired site of action.

[0021] Other principle embodiments of the disclosure provide for compounds having the structure of Formula I:



(Formula I),

wherein L_{SS}, as indicated, is a self-stabilizing primary linker, $L_{O,}$ as indicated, is an optional secondary linker and wherein the variable groups of Formula I are as defined for Formula 1.

[0022] In any one of the above embodiments in which BU is cyclized to R^{a2} though its basic amine nitrogen so that a cyclized Basic Unit (cBU) having a skeletal secondary nitrogen atom is defined, the secondary amine functional group from cyclization to that heteroatom may be suitably protected or may be in protonated form. In any one of the above embodiments when BU is cyclized to R^{a2} though its basic nitrogen atom so that a cBU having a tertiary amine functional group is defined, that amine functional group may be in protonated form.

[0023] In any one of the above embodiments in which an acyclic Basic Unit (aBU) is formally cyclized to R^{a2} through its optionally substituted C_1-C_{12} alkyl moiety, that alkylene moiety is incorporated in whole or in part into an optionally substituted spiro C_3-C_{20} carbocyclo having substitution by a basic amine functional group attributable to aBU through its basic nitrogen atom, directly or indirectly through any intervening optionally substituted acyclic alkylene moiety remaining from said incorporation, wherein the basic amine nitrogen atom is that of a primary, secondary, or tertiary amine functional group, thus defining a cyclic Basic Unit (cBU) in which the degree of substitution of the basic amine nitrogen of that functional group prior to said formal cyclization is retained, wherein that basic amine functional group may be in protected or protonated form, dependent on the degree of substitution of its basic nitrogen atom.

[0024] In other embodiments, the disclosure provides for Ligand Drug Conjugate compositions prepared from contacting a Formula I compound with a targeting agent having a reactive thiol functional group under suitable conditions to effect condensation of a sulfur atom of that functional group with its maleimide moiety so as to provide a composition represented by the structure of Formula 1, which converts in whole or at least in part to Formula 2.

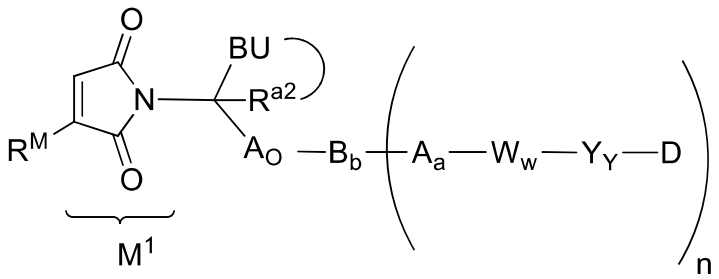
[0025a] In another aspect, there is provided a pharmaceutically acceptable formulation or precursor thereof comprising a Ligand Drug Conjugate composition disclosed herein and one, two, three or more excipients.

[0025b] In another aspect, there is provided use of a Ligand Drug Conjugate composition disclosed herein in the manufacture of a medicament for treating a hyperproliferative disease or condition in a patient having said disease or condition.

[0025c] In another aspect, there is provided use of a Ligand Drug Conjugate composition disclosed herein in the manufacture of a medicament for inhibiting the multiplication of an *in vitro* tumor cell or cancer cell, or causing apoptosis in an *in vitro* tumor or cancer cell.

[0025d] In another aspect, there is provided an *in vitro* 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 to an effective amount of a Ligand Drug Conjugate composition disclosed herein.

[0025e] In another aspect, there if provided a Drug Linker compound, wherein the compound has the structure of:



or a salt thereof, wherein

R^M is hydrogen or an optionally substituted C_1-C_6 alkyl;

subscript w is 0 or 1;

subscript y is 0, 1, or 2;

subscript n is 1, 2, 3 or 4;

subscript a is 0 or 1;

subscript b is 0 or 1,

provided that subscript b is 1 when subscript n is 2, 3 or 4 and subscript b is 0 when subscript n is 1;

A is a first Stretcher Unit;

A_O is a second optional Stretcher Unit;

B is an optional Branching Unit; and

wherein each of A, A_O and B is an independently selected single unit or is optionally comprised or consists of two, three or four independently selected subunits;

when subscript y is 0, Y is absent; when subscript y is 1, Y is a self-immolative spacer unit; and when subscript y is 2, Yy is Y-Y'-, wherein Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D+);

subscript w is 0 or 1, wherein W is absent when subscript w is 0, or when subscript w is 1 then

W is a Peptide Cleavable Unit, or

W is a Glucuronide Unit of formula –Y(W')-, wherein W' represents a carbohydrate moiety with glycosidic bonding to Y through a optionally substituted heteroatom;

provided that Y bonded to W' is a self-immolative Spacer Unit, and subscript y is 1 or 2;

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl group that together with the carbon atom to which both are attached, as represented by the solid curved line, define a cyclic Basic Unit having an optionally substituted C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group, an optionally substituted C_3-C_{20} carbocyclo with exocyclic substitution by an optionally substituted basic nitrogen of a basic secondary or tertiary amine functional group, or an optionally substituted C_3-C_{20} carbocyclo having exocyclic substitution by an optionally substituted C_1-C_{12} aminoalkyl in which the optionally substituted basic nitrogen atom of the amino moiety of the aminoalkyl is that of a primary, secondary or tertiary amine functional group, wherein the optionally substituted basic nitrogen atom of the exocyclic amine or aminoalkyl along with its optionally substituted alkyl moiety is attributable to BU, or

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl formally cyclized to the basic nitrogen atom of an acyclic Basic Unit of corresponding structure to Formula 1 and/or Formula 2 in which the solid curved lined between BU and R^{a2} is absent, or to a carbon atom of an optionally substituted C_1-C_{12} alkylene bearing that basic nitrogen atom, both of which comprise the acyclic Basic Unit, thus forming an optionally substituted C_3-C_{20} heterocyclo, which incorporates the basic nitrogen atom as a skeletal heteroatom, or an optionally substituted C_3-C_{20} carbocyclo substituted directly by the basic nitrogen atom, or substituted indirectly by the basic nitrogen atom through an optionally substituted C_1-C_{12} alkylene moiety remaining from said formal cyclization and whose structure is dependent on the site of cyclization, so in either instance a cyclic Basic Unit (cBU) is defined, as indicated by the solid curved line;

and

wherein the basic nitrogen atom of the cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated;

D is a Drug Unit, or

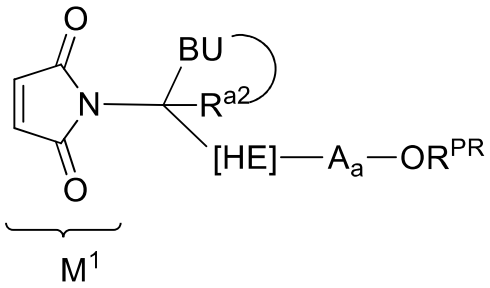
D is a quaternized Drug Unit represented as D^+ so that D^+ replaces D in Formula 1 and Formula 2, provided that subscript w is 1;

wherein if subscript w is 1, activation of the Glucuronide Unit by a glycosidase or activation of the Peptide Cleavable Unit by a protease initiates release of the Drug Unit or quaternized Drug Unit as a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound of a Ligand Drug Conjugate composition prepared from the Drug Linker compound,

or if subscript w is 0, a biologically active compound or derivative thereof is released from the Drug Linker compound or from a Ligand Drug Conjugate compound of a Ligand Drug Conjugate composition prepared from the Drug Linker compound on enzymatic or non-enzymatic cleavage of a bond between $–Y_y$-D of and the remainder of the Drug Linker compound or Ligand Drug Conjugate compound.

[0025f] In another aspect, there is provided a method of preparing a Ligand Drug Conjugate composition comprising the step of contacting a Drug Linker compound disclosed herein with a targeting agent having a reactive thiol functional group under conditions suitable for effecting Michael addition of the thiol to the indicated maleimide (M^1) moiety of the Drug Linker compound for incorporation of the targeting agent as a Ligand Unit in a Ligand Drug Conjugate compound of the composition.

[0025g] In another aspect, there is provided a compound having the structure of:



or a salt thereof, wherein

HE is –C(=O)-;

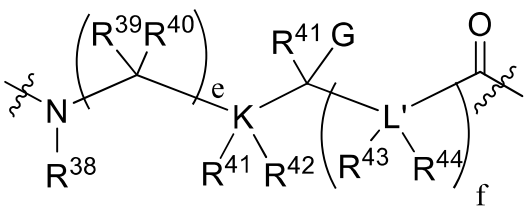
R^{PR} is H or a suitable carboxylic acid protecting group;

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl group that together with the carbon atom to which both are attached, as represented by the curved line, define an optionally substituted C_3-C_{20} heterocyclo having a skeletal secondary or tertiary basic nitrogen atom or a C_3-C_{20} carbocyclo having exocyclic substitution by a basic nitrogen atom of a primary, secondary or tertiary amine functional group or an

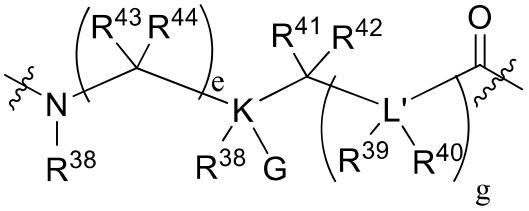
optionally substituted basic C_1-C_{12} aminoalkyl, wherein the basic nitrogen atom of the amine or aminoalkyl is attributable to BU, and is optionally protonated or protected by a suitable nitrogen-protecting group.

subscript a is 0 or 1;

A is absent when subscript a is 0, or when subscript a is 1 A has the structure of formula (3), formula (4), or formula (5):

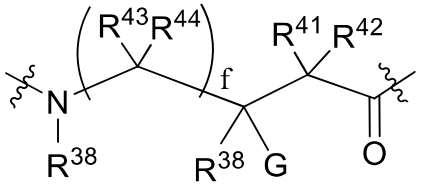


(3)



(4)

,



(5)

(3) (4)

wherein the wavy lines indicate covalent attachment within the 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, or

G is -N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is -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} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl, or

each L' in formula 4 is C, and in formula 3 or formula 4 R^{39}, R^{40} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{41}-R^{44} are as defined herein,

or K in formula 3 is C, and in formula 3 or formula 4 R^{41}, R^{42} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{39}, R^{40}, R^{43} and R^{44} are as defined herein,

or L' in formula 3 is C, and in formula 3 or formula 4 R^{43}, R^{44} together with the carbon atom to which both are attached define a C_3-C_6 cycloalkyl, and R^{39}-R^{42} are as defined herein,

or R^{40} and R^{41}together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39} and R^{42}- R^{44} as defined herein,

or R^{40} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{41}, R^{42}, and R^{44} are as defined herein,

or R^{41} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{40}, R^{42} and R^{44} and the remainder of R^{40}-R^{43} are as defined herein,

or

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

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1. Differential *in vitro* kinetics for Auristatin T Drug Unit release from Cysteine Drug Conjugates acting as surrogate Ligand Drug Conjugates of Formula 2, wherein release is initiated by exposure to the protease Cathepsin B, and wherein the Conjugates have a glu-dpr-Peptide Cleavable Unit, which is cleavable by the protease, and self-stabilized Linker Units comprised of an acyclic Basic Unit and succinic acid amide (M^3) moieties, the latter of which result from prior hydrolysis of the succinimide (M^2) moieties of their Formula 1 precursors, wherein the Conjugates differ in the stereochemical configuration of the carbon to which the acyclic Basic Unit is attached.

[0027] Figure 2. *Ex vivo* plasma stability of cAC10 Antibody Drug Conjugates having a MMAE Drug Unit (8-load) linked via protease-cleavable val-cit dipeptide having a self-stabilizing Linker Units comprised of a secondary Basic Unit cyclized as a secondary amine within a 4-membered (Conjugate B) or 6-membered (Conjugate C) heterocyclo in comparison to a cAC10 Antibody Drug Conjugate having the parent, acyclic Basic Unit (Conjugate A) or a related Antibody Drug Conjugate having no self-stabilizing Ligand Unit (Conjugate M).

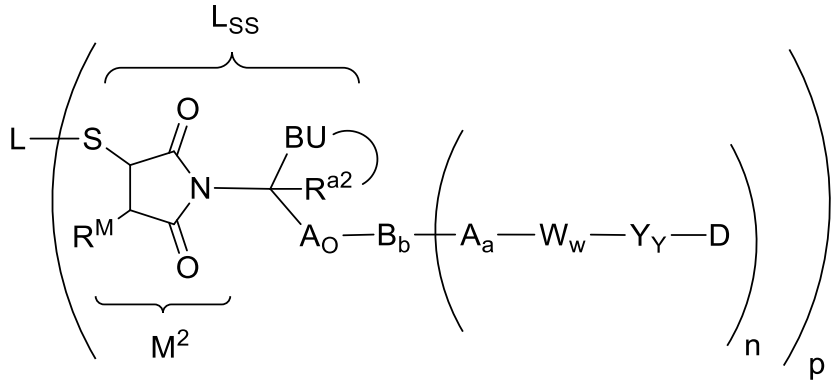
DETAILED DESCRIPTION OF THE INVENTION

[0028] Definitions

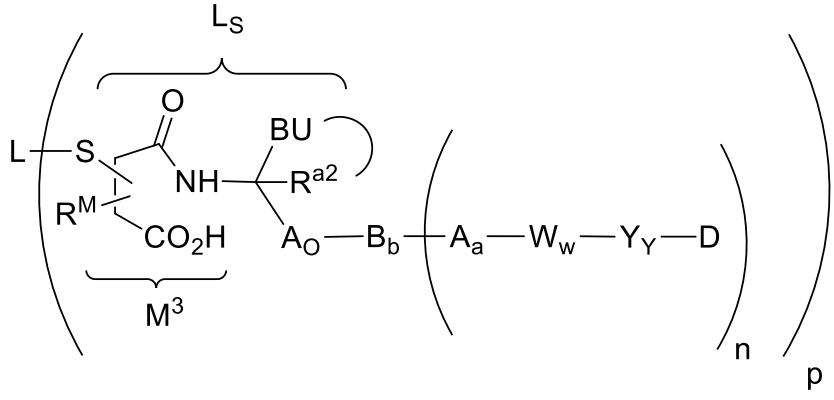
[0029] As used herein and unless otherwise stated or implied by context, terms that are used herein have the meanings defined below. Unless otherwise contraindicated or implied, e.g., by including mutually exclusive elements or options, in these definitions and throughout this specification, the terms "a" and "an" mean one or more and the term "or" means and/or where permitted by context. Thus, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

WHAT IS CLAIMED IS:

1. A Ligand Drug Conjugate (LDC) composition, wherein the composition is represented by the structures of Formula 1 and/or Formula 2:



(Formula 1)



(Formula 2)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

S is a sulfur atom of the Ligand Unit;

R^M is hydrogen or an optionally substituted C_1-C_6 alkyl;

subscript w is 0 or 1;

subscript y is 0, 1, or 2;

subscript n is 1, 2, 3 or 4;

subscript a is 0 or 1;

subscript b is 0 or 1,

provided that subscript b is 1 when subscript n is 2, 3 or 4; and subscript b is 0 when subscript n is 1;

A is a first Stretcher Unit;

A_O is a second optional Stretcher Unit;

B is an optional Branching Unit; and

wherein each of A, A_O and B is an independently selected single unit or is optionally comprised or consists of two, three or four independently selected subunits;

when subscript y is 0, Y is absent; when subscript y is 1, Y is a self-immolative spacer unit; and when subscript y is 2, Y_y is Y-Y'-, wherein Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D^+);

subscript w is 0 or 1, wherein W is absent when subscript w is 0, or when subscript w is 1 then

W is a Peptide Cleavable Unit, or

W is a Glucuronide Unit of formula –Y(W')-, wherein W' represents a carbohydrate moiety with glycosidic bonding to Y through a optionally substituted heteroatom;

provided that Y bonded to W' is a self-immolative Spacer Unit;

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl group that together with the carbon atom to which both are attached, as represented by the solid curved line, define a cyclic Basic Unit having an optionally substituted C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group, an optionally substituted C_3-C_{20} carbocyclo with exocyclic substitution by an optionally substituted basic nitrogen atom of a basic secondary or tertiary amine functional group, or an optionally substituted C_3-C_{20} carbocyclo having exocyclic substitution by an optionally substituted C_1-C_{12} aminoalkyl in which the optionally substituted basic nitrogen atom of the amino moiety of the aminoalkyl is that of a primary, secondary or tertiary amine functional group, wherein the optionally substituted basic nitrogen atom of the exocyclic amine or aminoalkyl along with its optionally substituted alkyl moiety is attributable to BU, or

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl formally cyclized to the basic nitrogen atom of an acyclic Basic Unit of corresponding structure to Formula 1 and/or Formula 2 in which the solid curved lined between BU and R^{a2} is absent, or to a carbon atom of an optionally substituted C_1-C_{12} alkylene bearing that basic nitrogen

atom, both of which comprise the acyclic Basic Unit, thus forming an optionally substituted C_3-C_{20} heterocyclo, which incorporates the basic nitrogen atom as a skeletal heteroatom, or an optionally substituted C_3-C_{20} carbocyclo substituted directly by the basic nitrogen atom, or substituted indirectly by the basic nitrogen atom through an optionally substituted C_1-C_{12} alkylene moiety remaining from said formal cyclization and whose structure is dependent on the site of cyclization, so in either instance a cyclic Basic Unit (cBU) is defined, as indicated by the solid curved line;

and

wherein the basic nitrogen atom of the cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated;

subscript p ranges from 1 to 24;

D is a Drug Unit, or

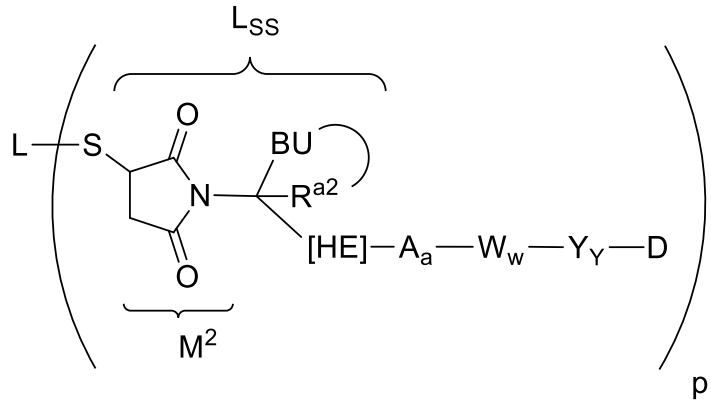
D is a quaternized Drug Unit represented as D^+ so that D^+ replaces D in Formula 1 and Formula 2 provided that subscript w is 1;

wherein if subscript w is 1, activation of the Glucuronide Unit by a glycosidase or activation of the Peptide Cleavable Unit by a protease within a compound of the Ligand Drug Conjugate composition initiates release of the Drug Unit or quaternized Drug Unit as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound,

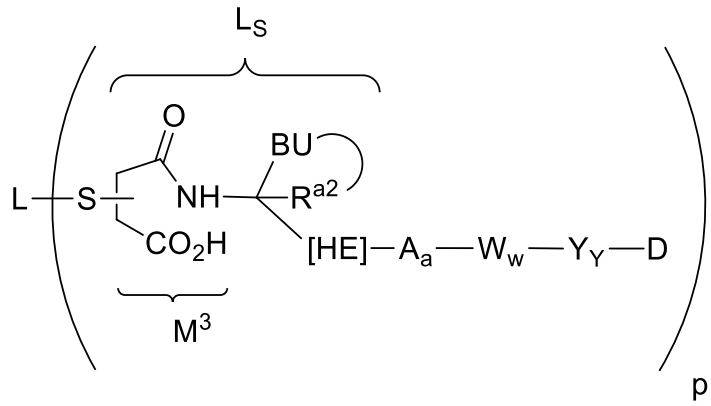
or if subscript w is 0, a biologically active compound or derivative thereof is released from a Ligand Drug Conjugate compound of the composition on enzymatic or non-enzymatic cleavage of a bond within a drug linker moiety of the Conjugate compound that attaches Y_y-D to the indicated L_{SS} or L_S structure of that drug linker moiety; and

wherein the Ligand Drug Conjugate compound corresponds in structure to Formula 1 or Formula 2 in which p is replaced by p', wherein p' is an integer ranging from 1 to 24.

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



and/or



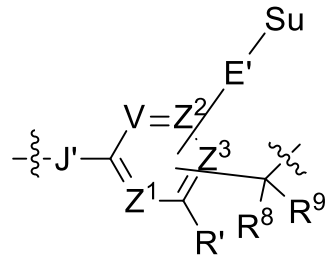
or pharmaceutically acceptable salt(s) thereof, wherein

[HE] as A_O is an optional Hydrolysis Enhancing Unit;

subscript w is 1;

W is Peptide Cleavable Unit, or

W is a Glucuronide Unit of formula –Y(W')- having the structure of:



wherein Su is a carbohydrate moiety and -E'- represents an optionally substituted heteroatom of an glycosidic bond cleavable by a glycosidase so that Su-E' is W' and the

remainder of the Glucuronide Unit structure is a self-immolative Spacer Unit bonded to W';

J' is an independently selected heteroatom, optionally substituted;

V, Z^1, Z^2 and Z^3 are independently =N- or =C(R^{24})-, wherein each R^{24} is independently selected from the group consisting of hydrogen and C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl, optionally substituted, and halogen, an electron withdrawing group, an electron donating group, -E'-Su, and –C(R^8)(R^9)-,

provided that one and only one –C(R^8)(R^9)- moiety and one and only one –E'-Su moiety is present,

wherein one of V, Z^1, Z^2 and Z^3 is =C(R^{24})- in which R^{24} is –C(R^8)(R^9)- and another of V, Z^1, Z^2 and Z^3 is =C(R^{24})- in which R^{24} is –E'-Su,

provided the –C(R^8)(R^9)- and –E'-Su moieties are *ortho* or *para* to each other;

R^8 and R^9 independently are hydrogen, or C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, optionally substituted, or C_6-C_{20} aryl or C_5-C_{20} heteroaryl, optionally substituted, or

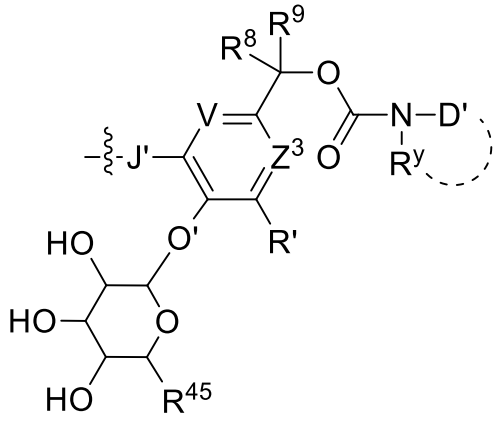
R^8 and R^9 together with the carbon atom to which both are attached define an optionally substituted C_5-C_{20} carbocyclo; and

R' is hydrogen or -NO_2, or other electron withdrawing group or –OC_1-C_6 alkyl, or other electron donating group; and

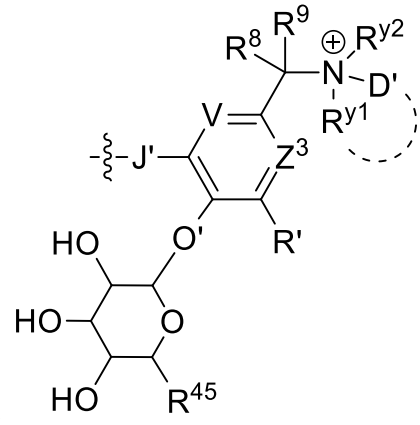
wherein glycosidase cleavage of the glycosidic bond within a compound of the Ligand Drug Conjugate composition initiates release of the Drug Unit or quaternized Drug Unit as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound;

wherein the wavy line adjacent to J' indicates the point of covalent attachment of the Glucuronide Unit to A when subscript a is 1 or to the indicated L_{SS} or L_S primary linker when subscript a is 0; and the wavy line adjacent to the –C(R^8)(R^9)- moiety indicates the point of covalent attachment of the Glucuronide Unit to Y' when subscript y is 2, or to D/D^+ when subscript y is 1.

3. The Ligand-Drug Conjugate composition of claim 2 wherein W is a Glucuronide Unit in which –W-Y_y-D and -W-D^+ have structures of:



and



,

respectively, or pharmaceutically acceptable salts thereof,

wherein the dotted curve line indicates optional cyclization of R^y or R^{y1} to D';

R^{45} is $–CH_2OH$ or $–CO_2H$;

-$N(R^Y)$D' and $–N^+(R^{y1})(R^{y2})$D' moieties, with or without cyclization, represent D and D^+, respectively, wherein D' is the remainder of D or D^+;

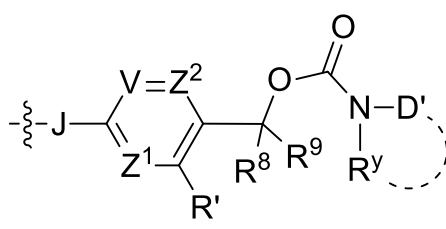
wherein R^y is hydrogen or optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or R^y is optionally substituted C_1-C_6 alkylene when cyclized to D';

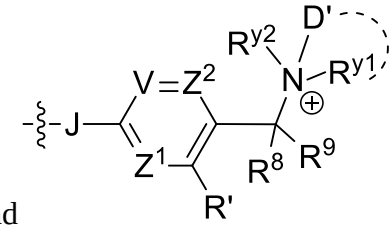
R^{y1} is optionally substituted C_1-C_6 alkyl, in absence of its cyclization within D^+, or R^{y1} is optionally substituted C_1-C_6 alkylene when cyclized within D^+;

R^{y2} is hydrogen or optionally substituted C_1-C_6 alkyl; and

wherein -O'- as E' represents the oxygen heteroatom of an O-glycosidic bond cleavable by a glycosidase, wherein said cleavage within a compound of the Ligand Drug Conjugate composition initiates release of D as a primary or secondary amine-containing biologically active compound or derivative thereof, or initiates release of D^+ as a tertiary amine-containing biologically active compound or derivative thereof from that Ligand Drug Conjugate compound.

4. The Ligand-Drug Conjugate composition of claim 2 wherein W is a Peptide Cleavable Unit and –Y_y-D – and -Y_y-D^+ have structures of:



and


,

respectively, or a pharmaceutically acceptable salt thereof, or in pharmaceutically acceptable salt form, wherein

-N(R^Y)D' and –N^+(R^{y1})(R^{y2})D' moieties represent D and D^+, respectively, wherein D' is the remainder of D or D^+, and wherein the dotted line indicates optional cyclization of R^y or R^{y1} to D'

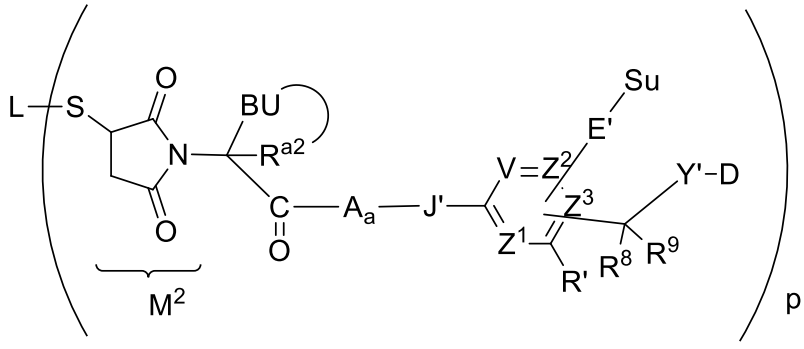
wherein R^y is hydrogen or R^y is optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or optionally substituted C_1-C_6 alkylene when cyclized to D';

R^{y1} is optionally substituted C_1-C_6 alkyl in absence of cyclization to D^+ or R^{y1} is optionally substituted C_1-C_6 alkylene when cyclized to D^+;

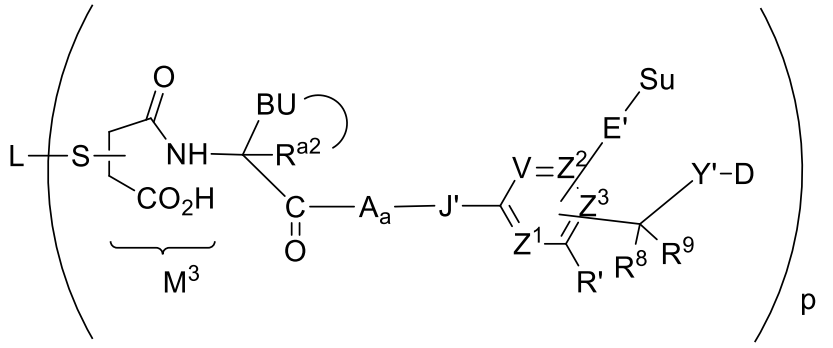
R^{y2} is optionally substituted C_1-C_6 alkyl;

J is an optionally substituted heteroatom bonded to W as indicated by the wavy line, wherein cleavage of that bond within a compound of the Ligand Drug Conjugate composition initiates release of D as a primary or secondary amine-containing biologically active compound or derivative thereof or initiates release of D^+ as a tertiary amine-containing biologically active compound or derivative thereof from that Ligand Drug Conjugate compound.

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



and/or



,

or pharmaceutically acceptable salt(s) thereof, wherein

Su is a carbohydrate moiety;

E' is an independently selected heteroatom, optionally substituted, of an glycosidic bond cleavable by a glycosidase;

J' represents an independently selected heteroatom, optionally substituted;

Y' is absent or Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D^+);

V, Z^1, Z^2 and Z^3 independently are =N- or =C(R^{24})-, wherein each R^{24} is independently selected from the group consisting of hydrogen and C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, halogen, an electron withdrawing group, an electron donating group, -E'-Su, –C(R^8)(R^9)-Y'-D and –C(R^8)(R^9)-D^+,

provided that one and only one of –C(R^8)(R^9)-Y'-D and –C(R^8)(R^9)-D^+ moieties and one and only one –E'-Su moiety is present;

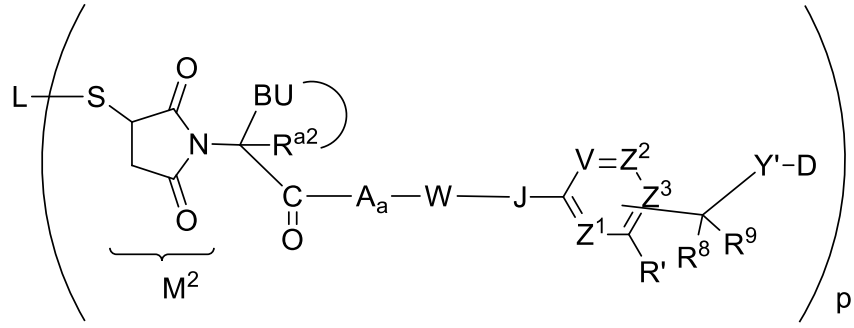
wherein one of V, Z^1, Z^2 and Z^3 is =C(R^{24})-, in which R^{24} is –C(R^8)(R^9)-Y'-D or –C(R^8)(R^9)-D^+ and another of V, Z^1, Z^2 and Z^3 is =C(R^{24})-, in which R^{24} is –E'-Su, provided the –E'-Su and –C(R^8)(R^9)-Y'-D or –C(R^8)(R^9)-D^+ moieties are *ortho* or *para* to each other;

R^8 and R^9 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, or C_5-C_{10} aryl or C_5-C_{10} heteroaryl, optionally substituted or R^8 and R^9 together with the carbon atom to which both are attached define an optionally substituted C_5-C_6 carbocyclo; and

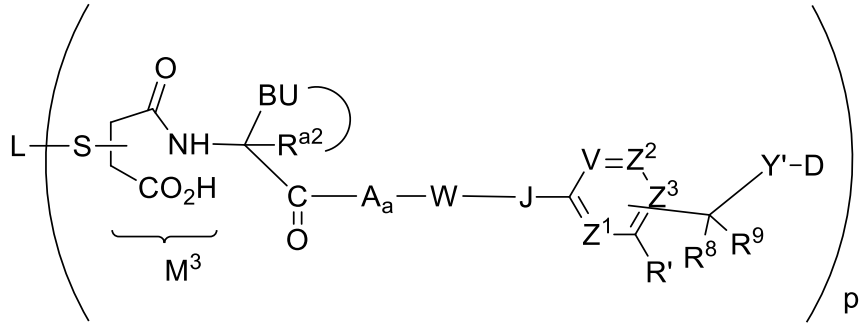
wherein glycosidase cleavage of the glycosidic bond within a compound of the Ligand Drug Conjugate composition initiates release of D/D^+ as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound,

or

wherein the composition is represented by the structure of:



and/or



,

or pharmaceutically acceptable salt(s) thereof, wherein

J is a heteroatom, optionally substituted;

Y' is absent or Y' is –O-C(=O)-, provided that –Y'- is absent when D is a quaternized Drug Unit (D^+);

W is a Peptide Cleavable Unit;

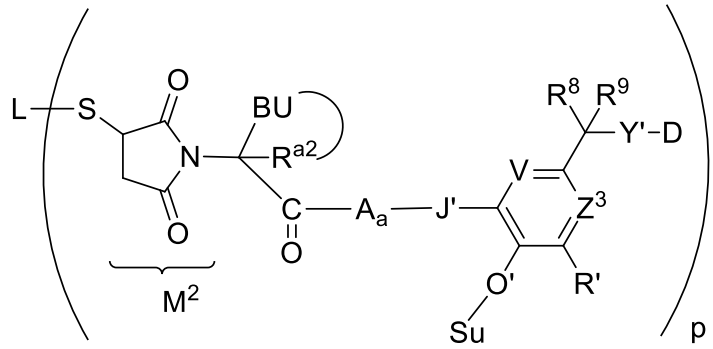
V, Z^1, Z^2 and Z^3 are independently =N- or =C(R^{24})-, wherein each R^{24} is independently selected from the group consisting of hydrogen and C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, halogen, an electron withdrawing group, an electron donating group,–C(R^8)(R^9)-Y'-D and –C(R^8)(R^9)-D^+, provided that one and only one of –C(R^8)(R^9)-Y'-D and –C(R^8)(R^9)-D^+ moieties is present,

wherein one of V, Z^1, Z^2 and Z^3 is $=C(R^{24})$-, in which R^{24} is $–C(R^8)(R^9)$-Y'-D or $–C(R^8)(R^9)$-D^+, provided the $–C(R^8)(R^9)$-Y'-D or $–C(R^8)(R^9)$-D^+ moiety is *ortho* or *para* to J;

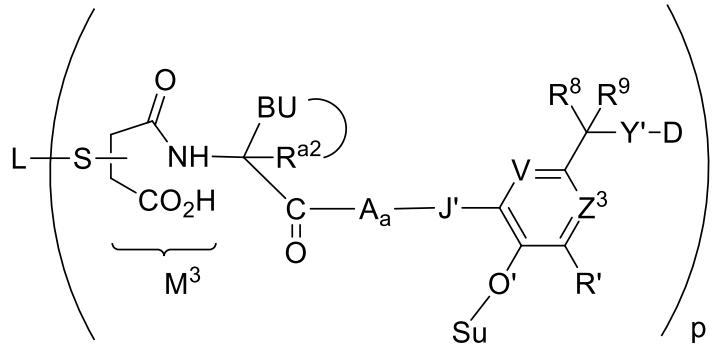
R^8 and R^9 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, or C_5-C_{10} aryl or C_5-C_{10} heteroaryl, optionally substituted, or R^8 and R^9 together with the carbon atom to which both are attached define an optionally substituted C_5-C_6 carbocyclo;

wherein protease action on W results in cleavage of the W-J bond within a compound of the Ligand Drug Conjugate composition so as to initiate release of D/D^+ as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound.

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



and/or

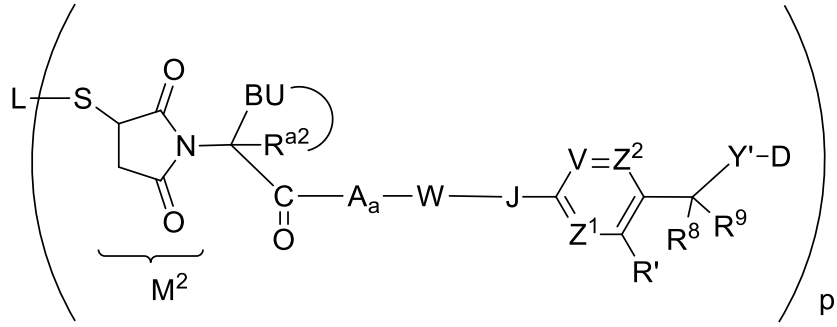


or pharmaceutically acceptable salt(s) thereof, wherein

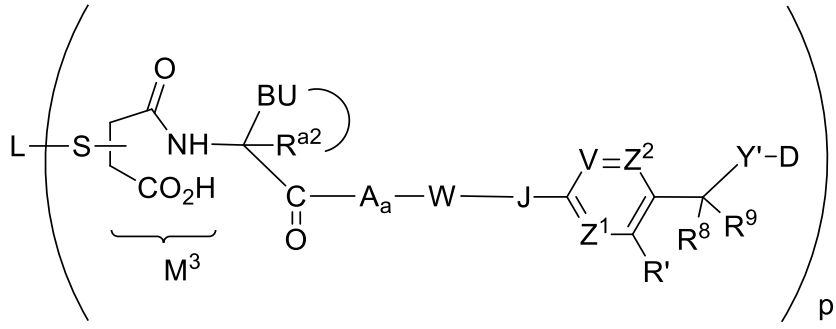
-O'- represents the oxygen heteroatom of an O-glycosidic bond cleavable by a glycosidase,

or

wherein the composition is represented by the structure of:

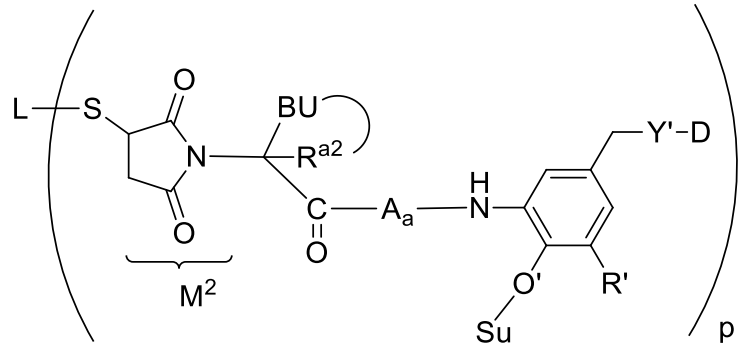


and/or

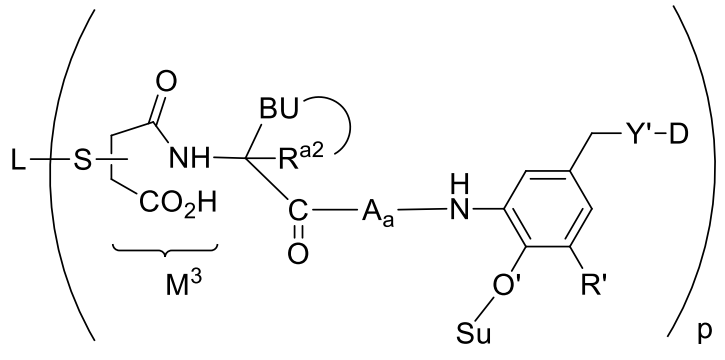


or pharmaceutically acceptable salt(s) thereof.

7. The Ligand-Drug Conjugate composition of claim 6, wherein the composition is represented by the structure of:



and/or

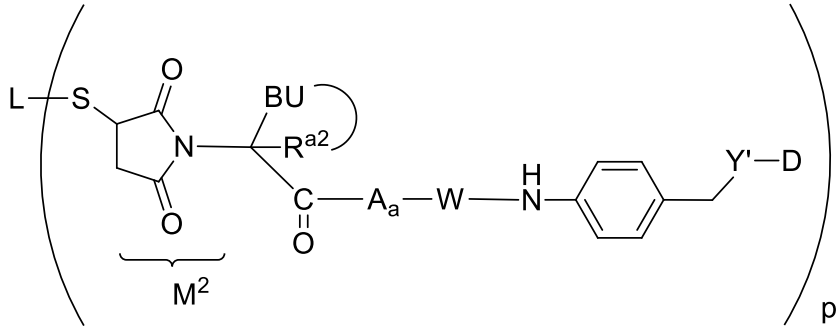


or pharmaceutically acceptable salt(s) thereof, wherein

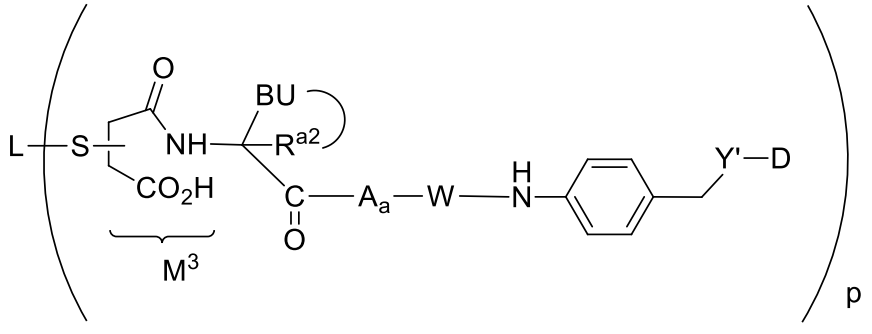
R' is hydrogen or $-NO_2$,

or

wherein the composition is represented by the structure of:



and/or

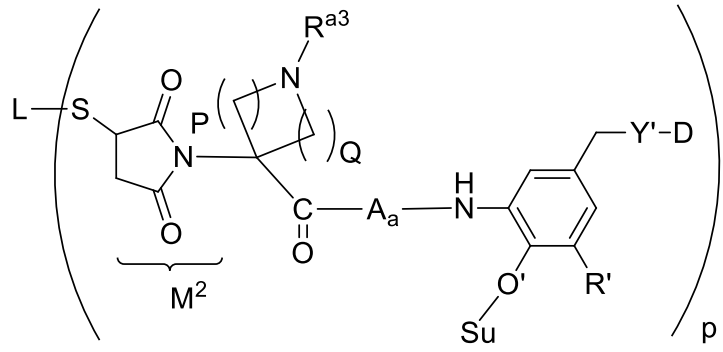


or pharmaceutically acceptable salt(s) thereof

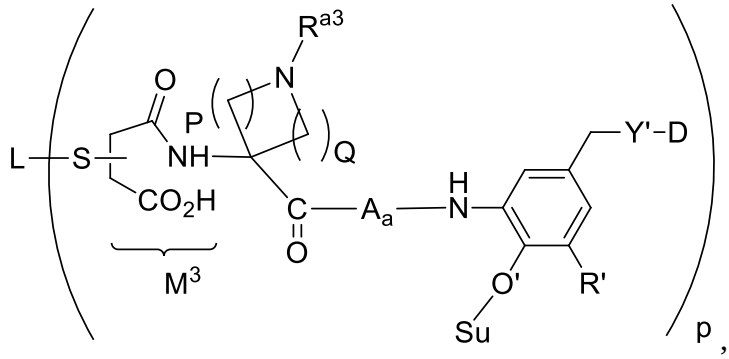
8. The Ligand-Drug Conjugate composition of claim 1, wherein BU and R^{a2} together with the carbon atom to which both are attached, define an optionally substituted C_3-C_8 heterocyclo having a skeletal secondary or tertiary basic nitrogen atom, wherein the

skeletal basic nitrogen atom is attributable to BU, wherein the basic nitrogen atom is optionally protonated.

9. The Ligand-Drug Conjugate composition of claim 7, wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript P is 1 or 2;

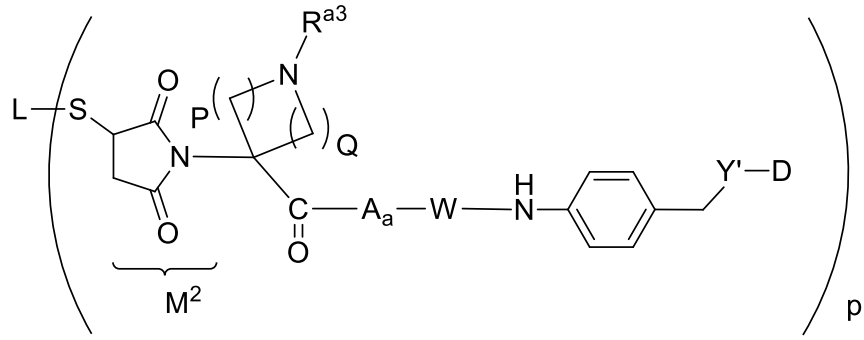
subscript Q ranges from 1 to 6; and

wherein R^{a3} is –H, C_1-C_6 alkyl, -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36; and

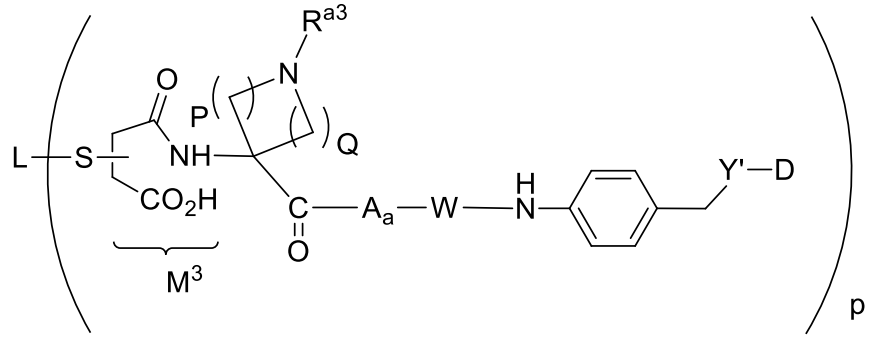
wherein the basic nitrogen bonded to R^{a3} is optionally protonated,

or

wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript p is 1 or 2;

subscript Q ranges from 1 to 6; and

R^{a3} is –H, C_1-C_6 alkyl, -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

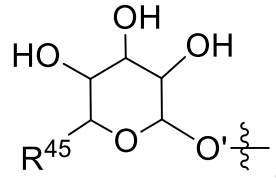
wherein the basic nitrogen bonded to R^{a3} is optionally protonated.

10. The Ligand-Drug Conjugate composition of claim 9, wherein subscript P is 1 and subscript Q is 1, 2 or 3 or subscript P is 2 and Q is 1 or 2.

11. The Ligand-Drug Conjugate composition of claim 10, wherein subscript P is 1, subscript Q is 1.

12. The Ligand-Drug Conjugate composition of claim 1 wherein BU and R^{a2} together with the carbon atom to which both are attached define an optionally substituted C_3-C_8 carbocyclo having exocyclic substitution by a primary, secondary or tertiary amine or by an optionally substituted C_1-C_6-aminoalkyl, wherein the basic nitrogen atom of the amine or aminoalkyl is attributable to BU and is optionally protonated.

13. The Ligand-Drug Conjugate composition of claim 6, wherein –E'-Su has the structure of:

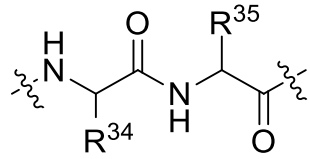


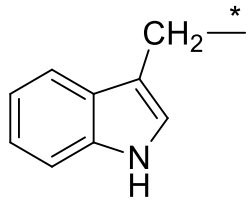
,

wherein the wavy line represents covalent bonding of O' to the remainder of the structure representing the Ligand-Drug Conjugate composition; and R^{45} is $–CH_2OH$ or $–CO_2H$, or a pharmaceutically acceptable salt thereof.

14. The Ligand-Drug Conjugate composition of claim 6, wherein W is a Peptide Cleavable Unit comprised of a dipeptide wherein the C-terminus of the dipeptide is covalently bonded to J wherein the dipeptide provides for a recognition site for a regulatory or lysosomal protease for cleavage by said protease of the W-J bond within a compound of the Ligand Drug Conjugate composition so as to initiate release of D or D^+ as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound.

15. The Ligand-Drug Conjugate composition of claim 14 wherein the dipeptide of W has the structure of:



wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH_3 or has the structure of , wherein the asterisk indicates the point of covalent attachment to the dipeptide backbone; and

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

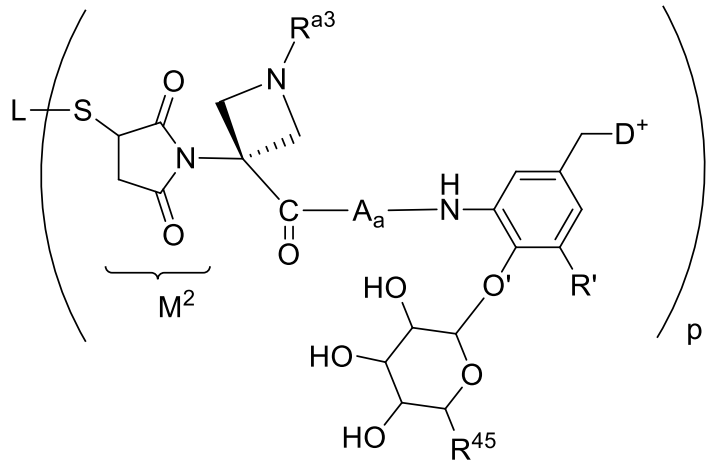
R^{35} is –$(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=NH)NH_2$, or -$(CH_2)_2CO_2H$, or a pharmaceutically acceptable salt thereof; and

wherein the wavy lines indicate the points of covalent attachment of the dipeptide into the structure representing the Ligand-Drug Conjugate composition.

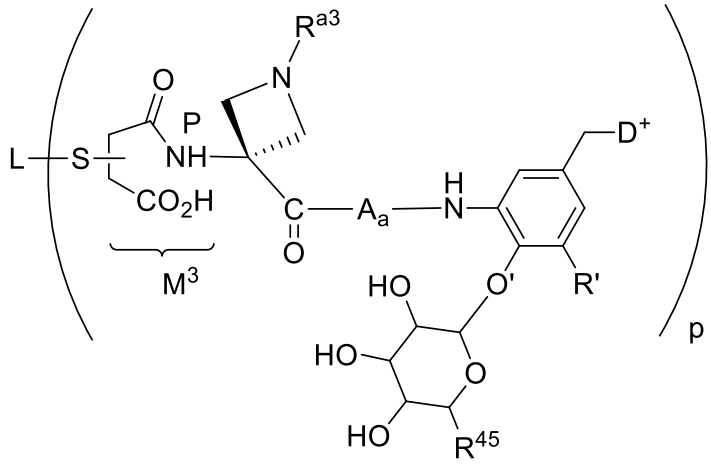
16. The Ligand-Drug Conjugate composition of claim 15 wherein the dipeptide of W is selected from the group consisting of -Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, -Val-Cit-, -Phe-Cit-, -Leu-Cit-, -Ile-Cit-, -Phe-Arg-, -Trp-Cit- and pharmaceutically acceptable salts thereof, wherein Cit is citrulline.

17. The Ligand-Drug Conjugate composition of claim 5 wherein D is a quaternized Drug Unit (D^+), Y' is absent and subscript y is 1 wherein Y bonded to D^+ is a self-immolative Spacer Unit.

18. The Ligand-Drug Conjugate composition of claim 17, wherein the composition is represented by the structure of:



and/or



in pharmaceutically acceptable salt form(s), wherein

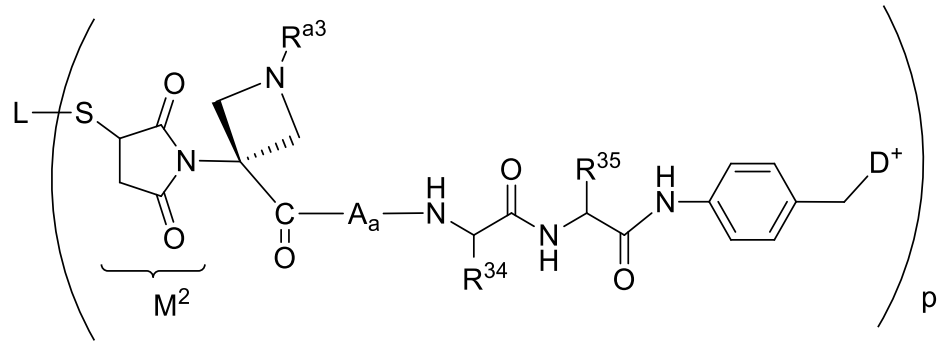
wherein R^{a3} is –H, C_1-C_6 alkyl, -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

R' is hydrogen or $–NO_2$; and

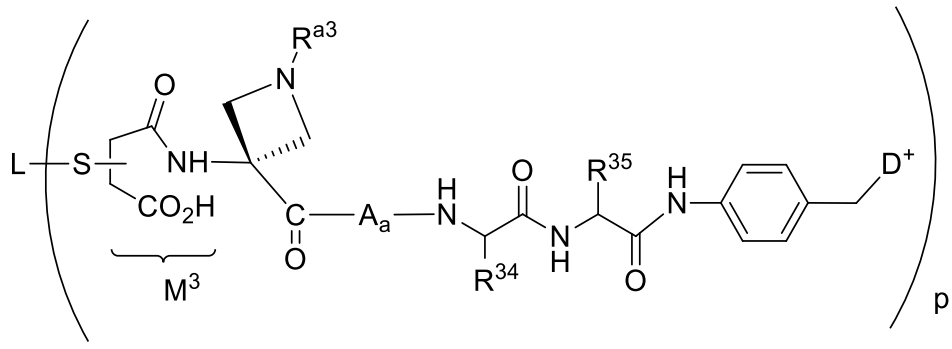
R^{45} is $–CH_2OH$ or $–CO_2H$,

or

the composition is represented by the structure of:



and/or



in pharmaceutically acceptable salt form(s), wherein

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

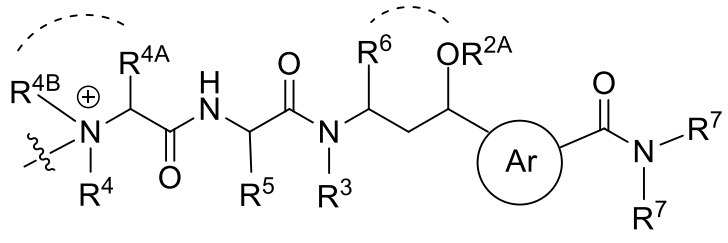
R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated.

19. The Ligand-Drug Conjugate composition of claim 18 wherein the released tertiary amine-containing biologically active compound or derivative thereof is a tubulysin compound thereby defining D^+ as a quaternized tubulysin Drug Unit.

20. The Ligand-Drug Conjugate composition of claim 1 wherein the quaternized Drug Unit –D^+ is a quaternized tubulysin Drug Unit having the structure of:



in pharmaceutically acceptable salt form, wherein

R^{2A} is hydrogen or optionally substituted C_1-C_{12} 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, thereby defining an oxygen-containing C_5-C_6-heterocyclo;

the circled Ar moiety 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 C_1-C_{12} alkyl;

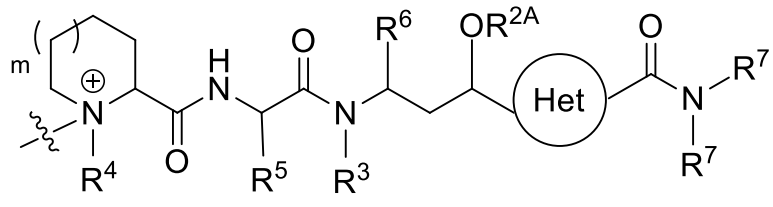
R^4, R^5 and R^6 are optionally substituted C_1-C_{12} alkyl, independently selected, or R^6 is bonded to the oxygen atom of the –OR^{2A} moiety in which R^{2A} is absent and R^4 and R^5 are as previously defined;

R^{4A} is hydrogen or optionally substituted C_1-C_{12} alkyl and R^{4B} is optionally substituted C_1-C_{12} 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-containing C_3-C_8 heterocyclyl, optionally substituted;

one R^7 is hydrogen or optionally substituted C_1-C_{12} alkyl and the other R^7 is optionally substituted (C_6-C_{20} aryl)-C_1-C_{12} alkyl- or (C_5-C_{20} heteroaryl)-C_1-C_{12} alkyl-;

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

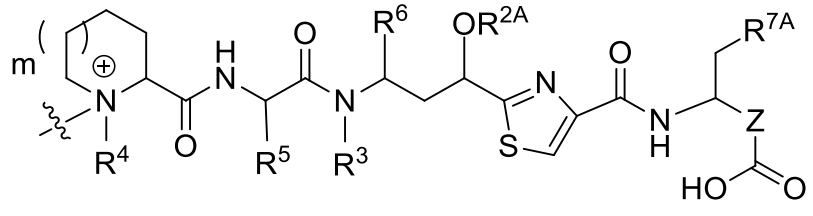
21. The Ligand-Drug Conjugate composition of claim 20 wherein D^+ has the structure of:



in pharmaceutically acceptable salt form, wherein

subscript m is 0 or 1.

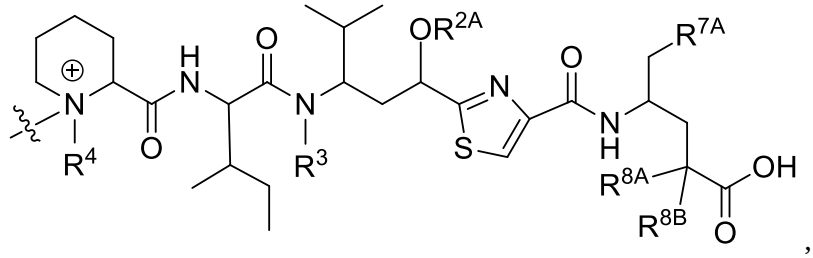
22. The Ligand-Drug Conjugate composition of claim 21 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



in pharmaceutically acceptable salt form, wherein

Z is an optionally substituted C_1-C_6 alkylene or an optionally substituted C_2-C_6 alkenylene; and R^{7A} is optionally substituted C_6-C_{10} aryl or optionally substituted C_5-C_{10} heteroaryl.

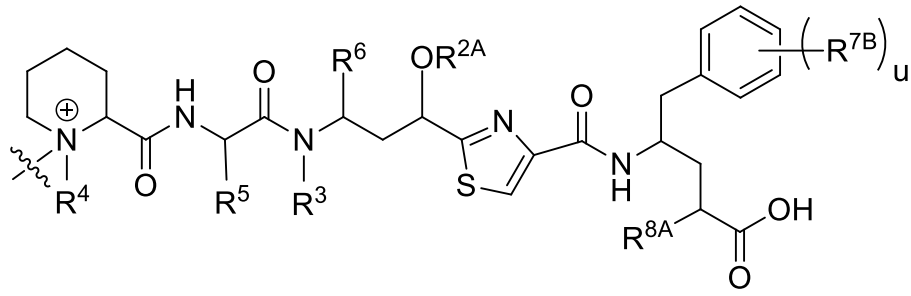
23. The Ligand-Drug Conjugate composition of claim 22 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



in pharmaceutically acceptable salt form, wherein R^{7A} is optionally substituted phenyl and R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen and

optionally substituted C_1-C_6 alkyl, or R^{8A} and R^{8B} together with the carbon atom to which both are attached define an optionally substituted C_3-C_6 carbocyclo.

24. The Ligand-Drug Conjugate composition of claim 23 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



in pharmaceutically acceptable salt form, wherein

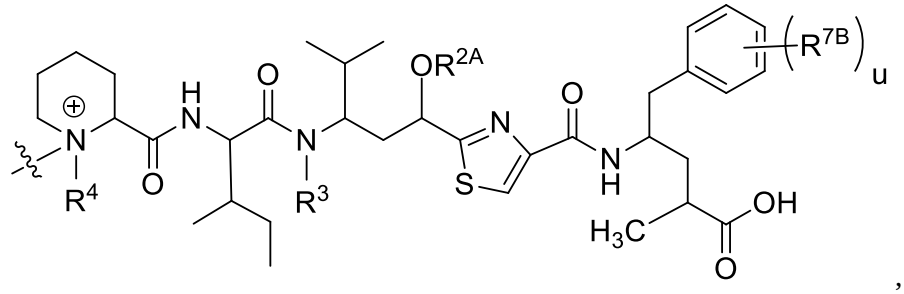
R^5 and R^6 are independently selected alkyl side chain residues of natural hydrophobic amino acids;

subscript u, indicating the number of R^{7B} substituents, is 0, 1, 2 or 3;

each R^{7B}, when present, is an independently selected O-linked substituent; and

R^{8A} is hydrogen or optionally substituted C_1-C_4 alkyl.

25. The Ligand-Drug Conjugate composition of claim 24 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



,

in pharmaceutically acceptable salt form, 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, wherein the C_1-C_6 alkyl of R^{3B} is independently selected from the C_1-C_6 alkyl of 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 $-OCH_2OCH_2R^{2B}$, $-OCH_2R^{2B}$, $-OC(O)R^{2B}$, $-OCH_2OC(O)R^{2B}$, $-OC(O)N(R^{2B})(R^{2C})$, 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 $–OCH_3$.

26. The Ligand-Drug Conjugate composition of claim 20 wherein R^{2A} is $-CH_2CH_3$ or $-CH_2-CH=CH_2$.

27. The Ligand-Drug Conjugate composition of claim 25 wherein

$-OR^{2A}$ is $-OCH_2CH_3$, $-OCH_2-CH=CH_2$, $-OCH_2C(CH_3)=CH_2$, or $-OC(O)CH_3$,

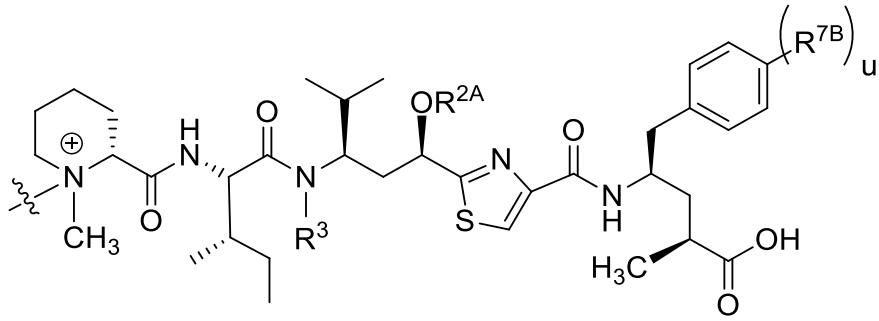
R^3 is $–CH_3$; and

R^{7B} is –OH or is absent;

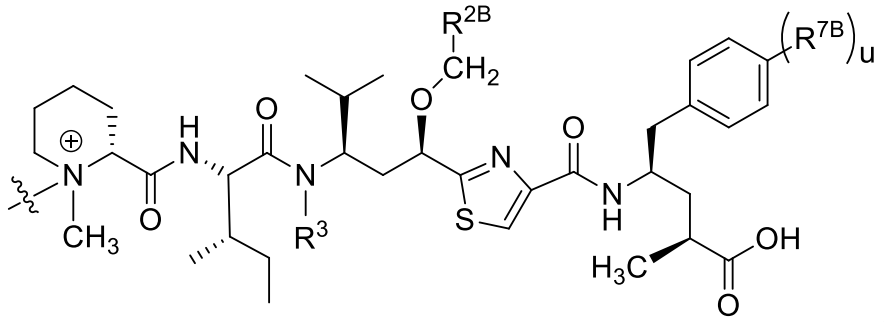
subscript u is 0 or 1, wherein

R^{7B} is –OH when subscript u is 1, and R^{7B} is absent when subscript u is 0.

28. The Ligand-Drug Conjugate composition of claim 25 wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of:



or



,

in pharmaceutically acceptable salt form, wherein

R^{2A} is -C(O)R^{2B}, -C(O)NHR^{2D}, or –CH_2C(O)R^{2D}

R^{2B} is H, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R^{2D} is –H, C_1-C_4 alkyl or C_2-C_4 alkenyl;

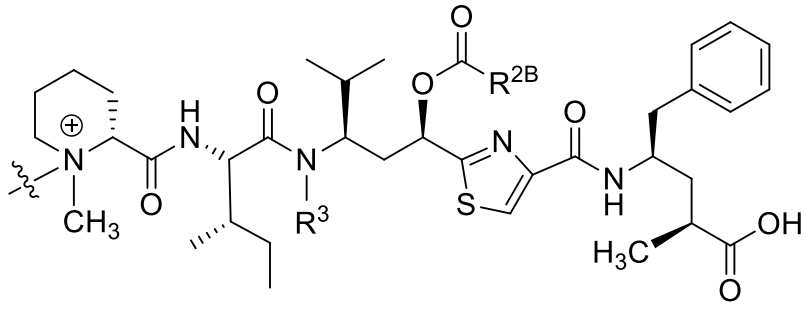
R^3 is methyl, ethyl or propyl;

R^{7B} is –OH or is absent; and

subscript u is 0 or 1, wherein

R^{7B} is –OH when subscript u is 1, and R^{7B} is absent when subscript u is 0.

29. The Ligand-Drug Conjugate composition of claim 28 wherein the quaternized tubulysin Drug Unit –D^+ has the structure of:



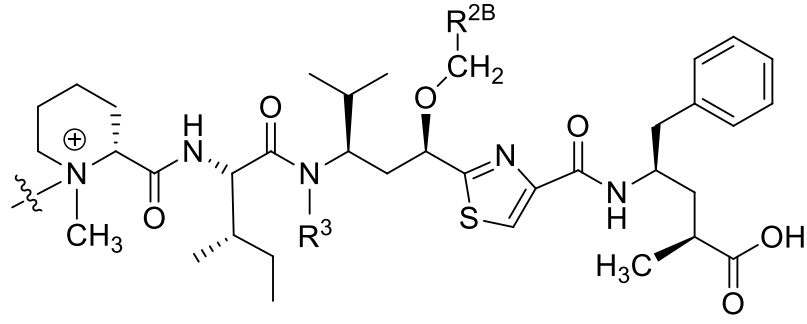
,

in pharmaceutically acceptable salt form, wherein

R^{2B} is a methyl, ethyl, propyl or a branched C_3-C_6 alkyl or is methyl, ethyl, propyl, iso-propyl, 3-methyl-prop-1-yl, 3,3-dimethyl-prop-1-yl, or vinyl.

30. The Ligand-Drug Conjugate composition of claim 29 wherein R^{2B} is –CH_3 and R^3 is –CH_3.

31. The Ligand-Drug Conjugate composition of claim 28 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:

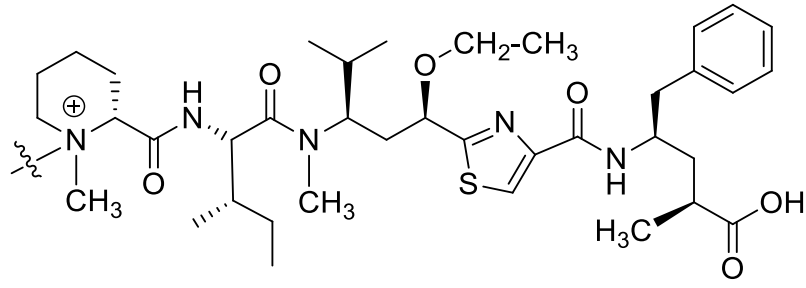


,

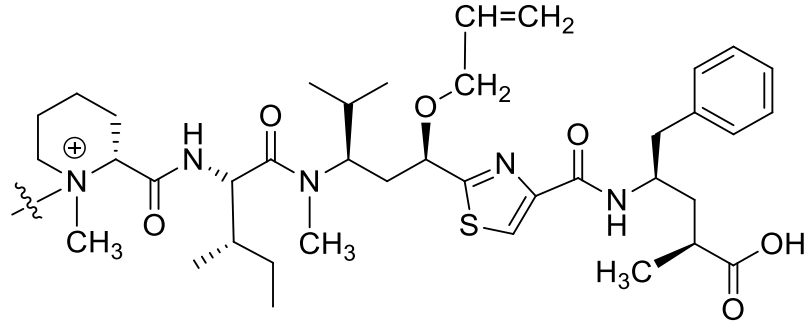
in pharmaceutically acceptable salt form, wherein

R^{2B} is –H, methyl, ethyl, vinyl or $-C(=CH_2)CH_3$.

32. The Ligand-Drug Conjugate composition of claim 31 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



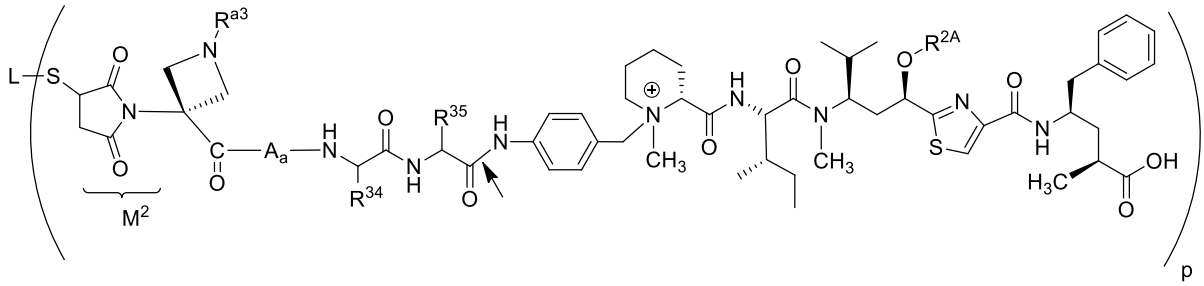
or



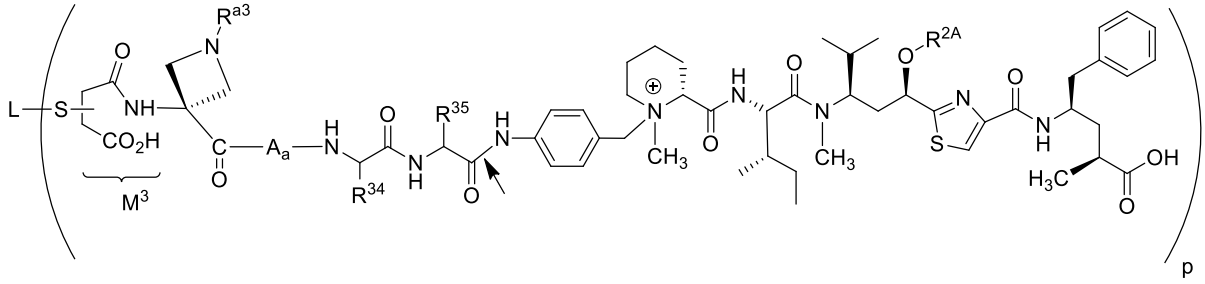
.

in pharmaceutically acceptable salt form.

33. The Ligand-Drug Conjugate composition of claim 23 wherein the composition is represented by the structure of:



and/or



in pharmaceutically acceptable salt form(s), wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H or C_1-C_4 alkyl;

R^{2A} is $–C(=O)CH_3$, $–CH_2CH_3$, $–CH_2CH=CH_2$ or $–CH_2C(=CH_2)CH_3$;

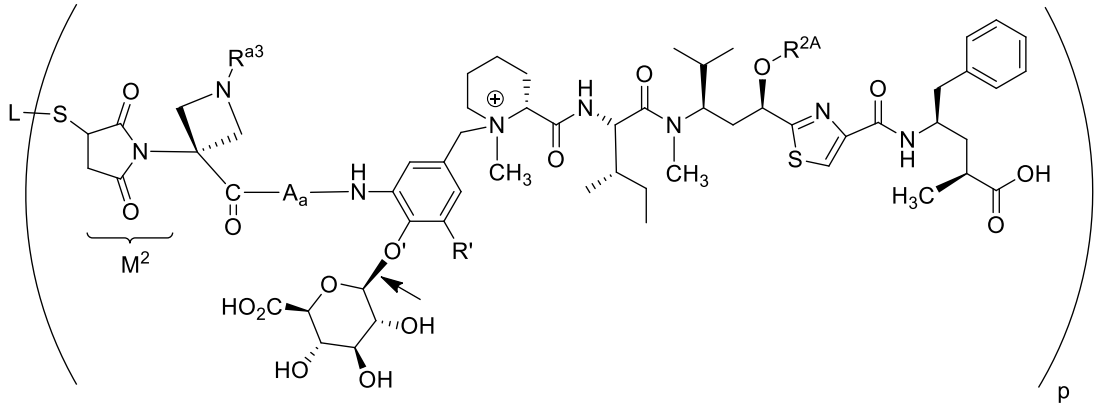
R^{34} is isopropyl;

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

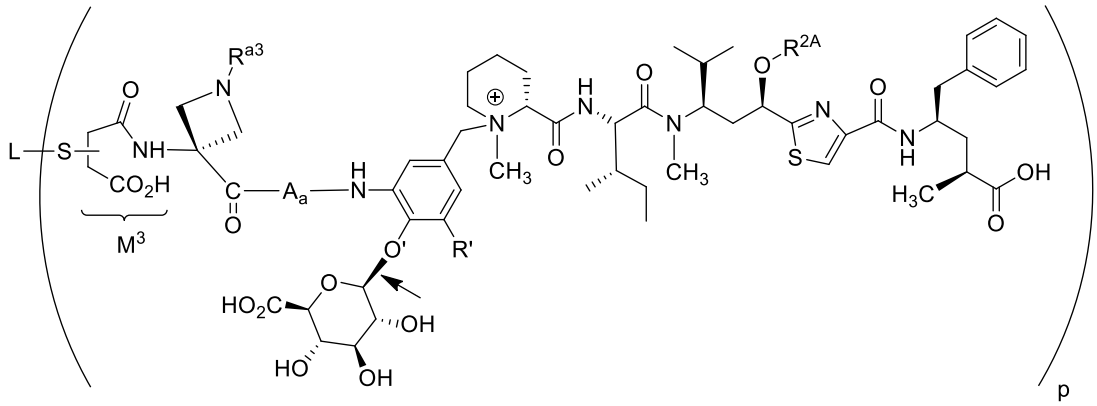
wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated,

or

wherein the composition is represented by the structure of:



and/or



in pharmaceutically acceptable salt form(s), wherein

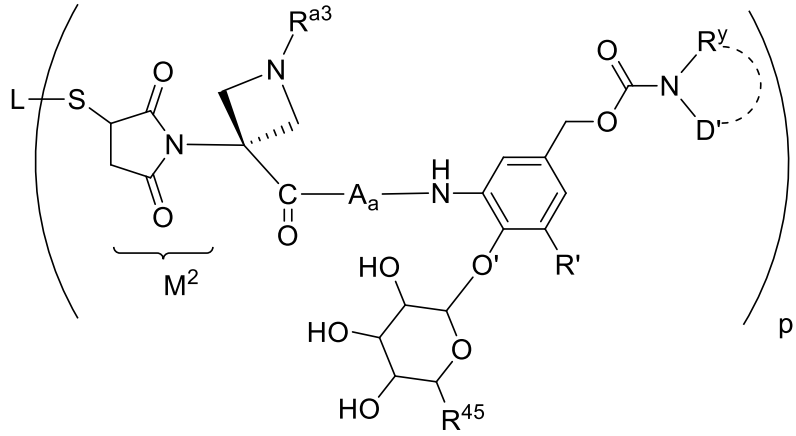
subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H or C_1-C_4 alkyl;

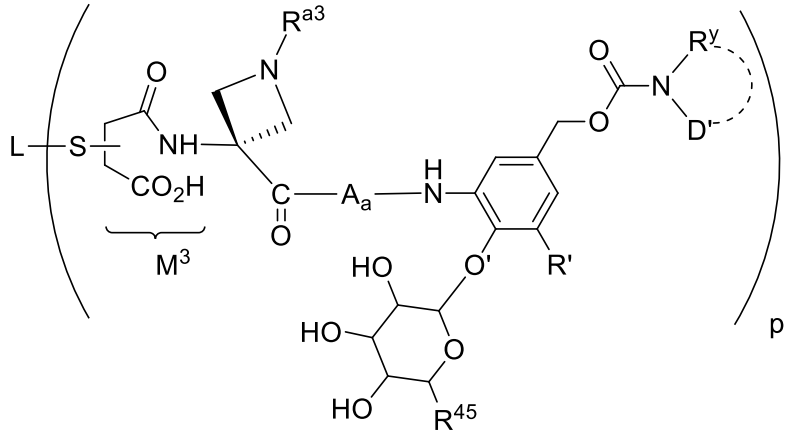
R^{2A} is $–C(=O)CH_3$, $–CH_2CH_3$, $–CH_2CH=CH_2$ or $–CH_2C(=CH_2)CH_3$; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated.

34. The Ligand-Drug Conjugate composition of claim 9 wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, C_1-C_6 alkyl, -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

R' is hydrogen or $–NO_2$;

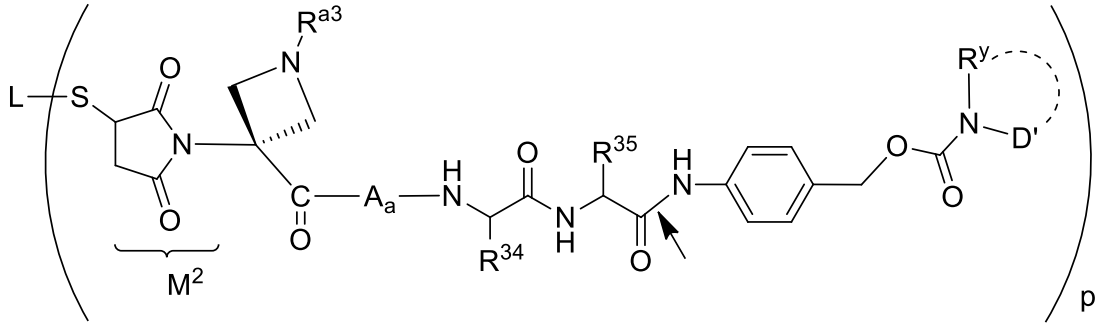
R^{45} is $–CH_2OH$ or $–CO_2H$;

-N(R^y)D' represents D, wherein D' is the remainder of D, and wherein the dotted line indicates optional cyclization of R^y to D', wherein R^y is hydrogen or optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or R^y is optionally substituted C_1-C_6 alkylene when cyclized to D';

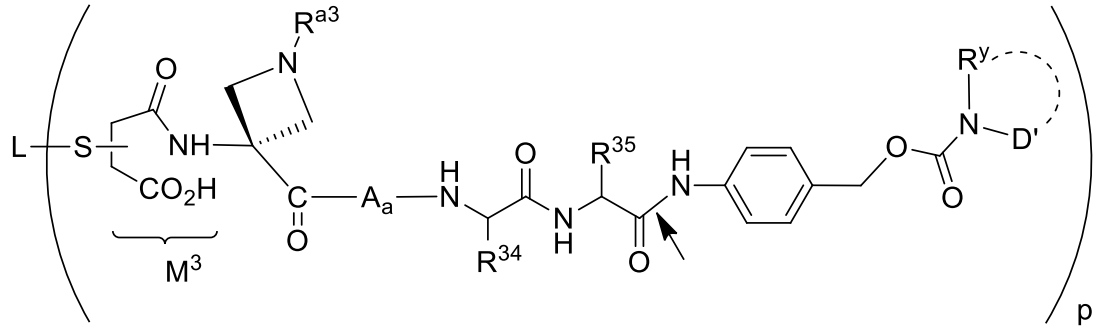
wherein -O'- represents the oxygen heteroatom of an O-glycosidic bond cleavable by a glycosidase, wherein said cleavage within a compound of the Ligand Drug Conjugate composition initiates release of D as a primary or secondary amine-containing biologically active compound or derivative thereof from that Ligand Drug Conjugate compound,

or

wherein the composition is represented by:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, C_1-C_6 alkyl, -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

R^{34} is methyl or isopropyl;

R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=O)NH_2$, -$(CH_2)_3NH(C=NH)NH_2$, or , -$(CH_2)_2CO_2H$;

-N(R^y)D' represents -D having covalent attachment to the remainder of the composition structure, wherein D' is the remainder of D, and wherein the dotted line

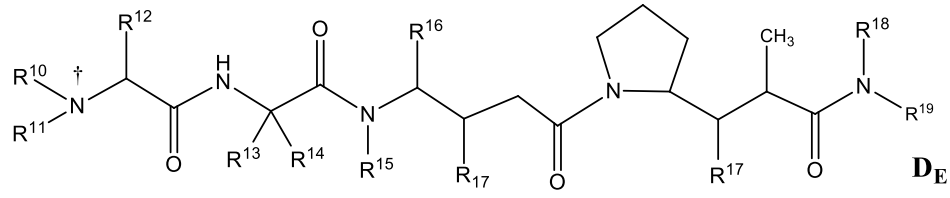
indicates optional cyclization of R^y to D', wherein R^y is hydrogen or optionally substituted C_1-C_6 alkyl in absence of cyclization to D', or R^y is optionally substituted C_1-C_6 alkylene when cyclized to D'; and

wherein protease cleavage of the indicated bond within a compound of the Ligand Drug Conjugate composition initiates release of D as a primary or secondary amine-containing biologically active compound or derivative thereof from that Ligand Drug Conjugate compound.

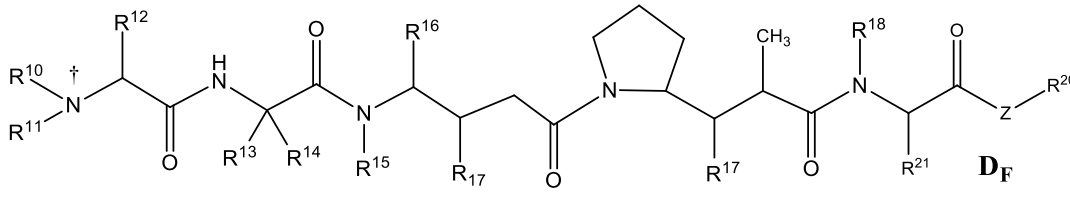
35. The Ligand-Drug Conjugate composition of 18, wherein the released tertiary amine-containing biologically active compound or derivative thereof from D thereby defining D^+ as a quaternized auristatin Drug Unit.

36. The Ligand-Drug Conjugate composition of 34, wherein the released primary or secondary amine-containing biologically active compound or derivative thereof from D is an auristatin drug compound thereby defining D as an auristatin Drug Unit.

37. The Ligand-Drug Conjugate composition of claim 35 or 36, wherein the auristatin drug compound released from –D or -D^+ has the structure of:



D_E



D_F

or a pharmaceutically acceptable salt thereof or in a pharmaceutically acceptable salt form, wherein

the dagger indicates the site of covalent attachment of the nitrogen atom that provides a carbamate functional group, wherein –OC(=O)- of that functional group is Y', on incorporation of the auristatin drug compound as -D into a Ligand Drug Conjugate compound of the composition in which subscript y is 2, or results in a quaternary amine nitrogen on incorporation of the auristatin drug compound as $-D^+$ into a Ligand Drug Conjugate compound of the composition in which subscript y is 1;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen and C_1-C_8 alkyl, provided that one of R^{10}, R^{11} is hydrogen when the auristatin drug compound is incorporated into the as -D and neither of R^{10}, R^{11} is hydrogen when the auristatin drug compound is incorporated as $–D^+$:

R^{12} is hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{24} aryl, -X^1-C_6-C_{24} aryl, -X^1-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl or -X^1-(C_3-C_8 heterocyclyl);

R^{13} is hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{24} aryl, -X^1- C_6-C_{24} aryl, -X^1-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl and -X^1-(C_3-C_8 heterocyclyl);

R^{14} is hydrogen or methyl, or

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

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

R^{16} is hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{24} aryl, -C_6-C_{24}-X^1-aryl, -X^1-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl and -X^1-(C_3-C_8 heterocyclyl);

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

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

R^{19} is $–C(R^{19A})_2–C(R^{19A})_2–$ C_6-C_{24} aryl, $–C(R^{19A})_2–C(R^{19A})_2–$($C_3$-$C_8$ heterocyclyl) or $–C(R^{19A})_2–C(R^{19A})_2–$($C_3$-$C_8$ carbocyclyl), wherein C_6-C_{24} aryl and C_3-C_8 heterocyclyl are optionally substituted;

R^{19A} independently are hydrogen, optionally substituted C_1-C_8 alkyl, -OH or optionally substituted –O-C_1-C_8 alkyl;

R^{20} is hydrogen or C_1-C_{20} alkyl, C_6-C_{24} aryl or C_3-C_8 heterocyclyl, optionally substituted, or -$(R^{47}O)_m$-R^{48}, or -$(R^{47}O)_m$-$CH(R^{49})_2$;

R^{21} is -C_1-C_8 alkylene-(C_6-C_{24} aryl) or -C_1-C_8 alkylene-(C_5-C_{24} heteroaryl), optionally substituted, or C_1-C_8 hydroxylalkyl, or optionally substituted C_3-C_8 heterocyclyl;

Z is O, S, NH, or NR^{46};

R^{46} is optionally substituted C_1-C_8 alkyl;

subscript m is an integer ranging from 1-1000;

R^{47} is C_2-C_8 alkyl;

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

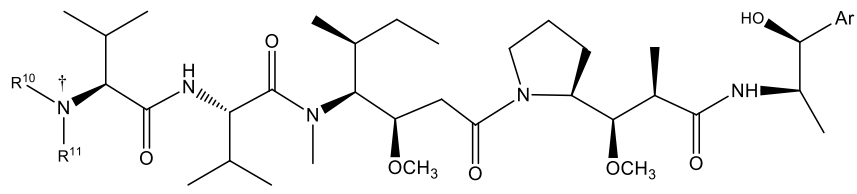
R^{49} independently are -COOH, $-(CH_2)_n$-$N(R^{50})_2$, $-(CH_2)_n$-SO_3H, or $-(CH_2)_n$-SO_3-C_1-C_8 alkyl;

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

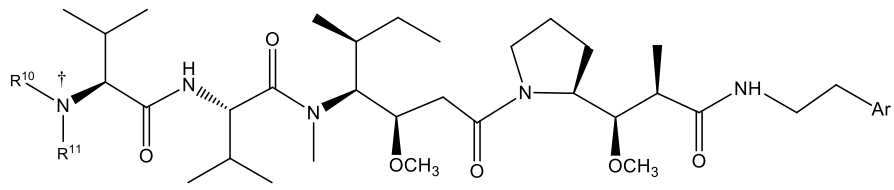
subscript n is an integer ranging from 0 to 6; and

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

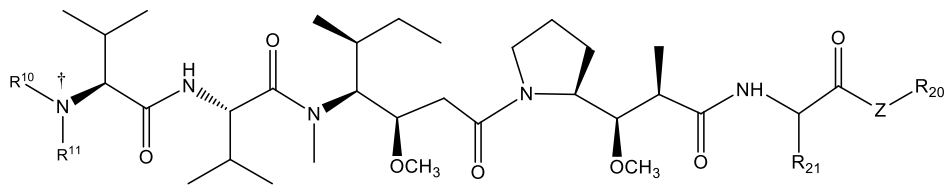
38. The Ligand-Drug Conjugate composition of claim 37, wherein the auristatin drug compound has the structure of Formula D_{E-1}, Formula D_{E-2} or Formula D_{F-1}:



D_{E-1}



D_{E-2},



D_{F-1}

or a pharmaceutically acceptable salt thereof or in a pharmaceutically acceptable salt form, wherein

Ar in Formula D_{E-1} or Formula D_{E-2} is C_6-C_{10} aryl or C_5-C_{10} heteroaryl, and in Formula D_{F-1}, Z is –O-, or –NH-;

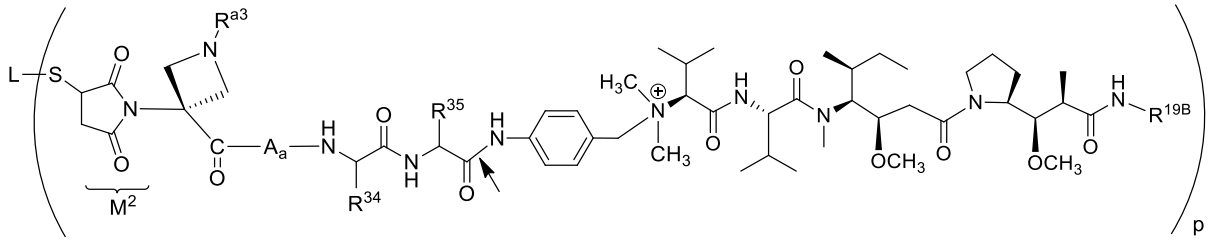
R^{20} is hydrogen or C_1-C_6 alkyl, C_6-C_{10} aryl or C_5-C_{10} heteroaryl, optionally substituted; and

R^{21} is C_1-C_6 alkyl, -C_1-C_6 alkylene-(C_6-C_{10} aryl) or -C_1-C_6 alkylene-(C_5-C_{10} heteroaryl), optionally substituted.

39. The Ligand-Drug Conjugate composition of claim 35 wherein the released auristatin drug compound incorporated as an auristatin quaternized Drug Unit (D^+) is Auristatin E, Auristatin PE, Auristatin PHE, Auristatin PYE, Auristatin EFP, Auristatin EB and Auristatin EVB.

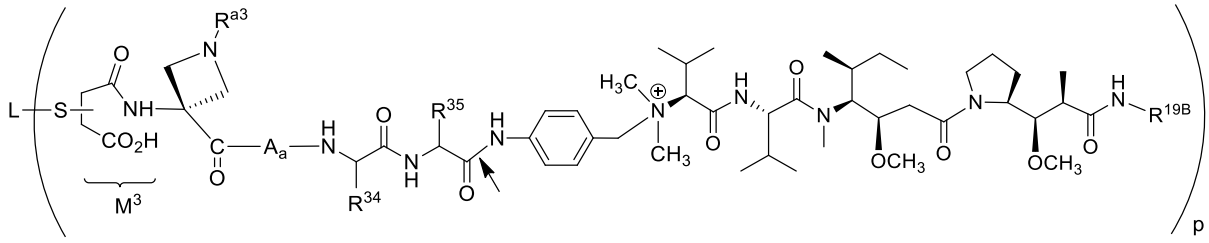
40. The Ligand-Drug Conjugate composition of claim 36 wherein the released auristatin drug compound incorporated into –D of a Ligand Drug Conjugate compound of the composition is monomethylauristatin E (MMAE) or monomethylauristatin F (MMAF), with covalent attachment of D through a carbamate functional group so that –OC(=O)- of that functional group is Y' wherein subscript y is 2.

41. The Ligand-Drug Conjugate composition of claim 35 wherein the composition is represented by the structure of:



.

and/or



in pharmaceutically acceptable salt form(s), wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

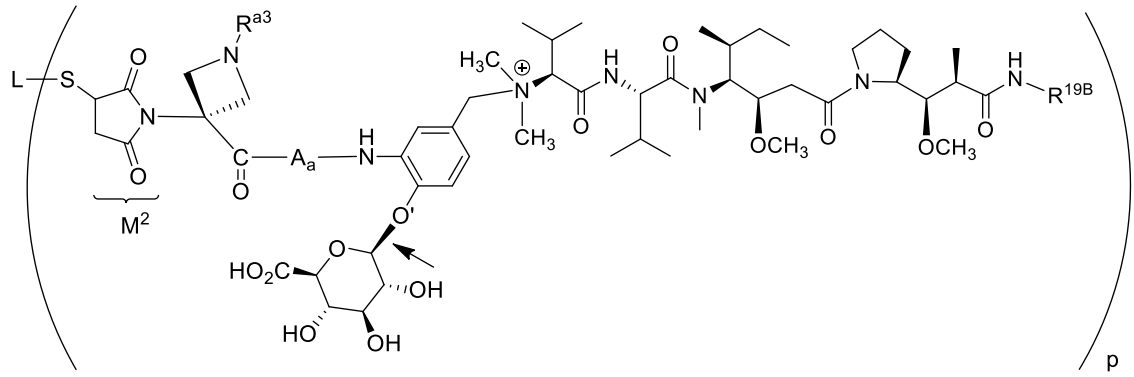
R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen bonded to R^{a3} is optionally protonated;

R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph;

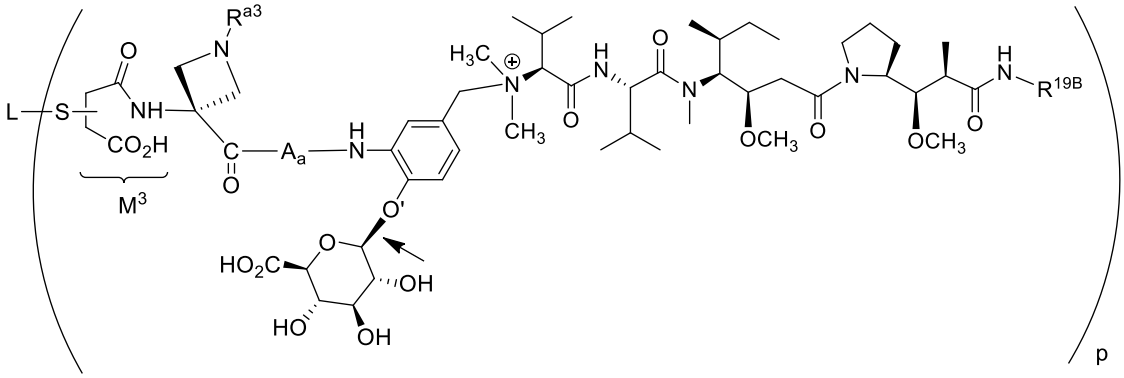
R^{34} is isopropyl and R^{35} is methyl or -$(CH_2)_3NH(C{=}O)NH_2$,

or

wherein the composition is represented by the structure of:



and/or



in a pharmaceutically acceptable salt form(s),wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue; and

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

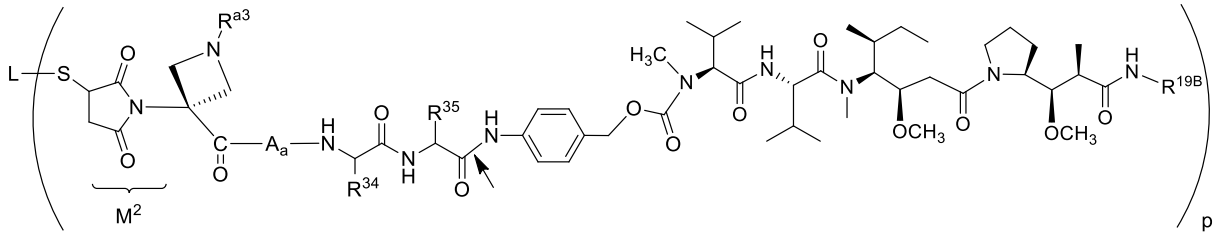
R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

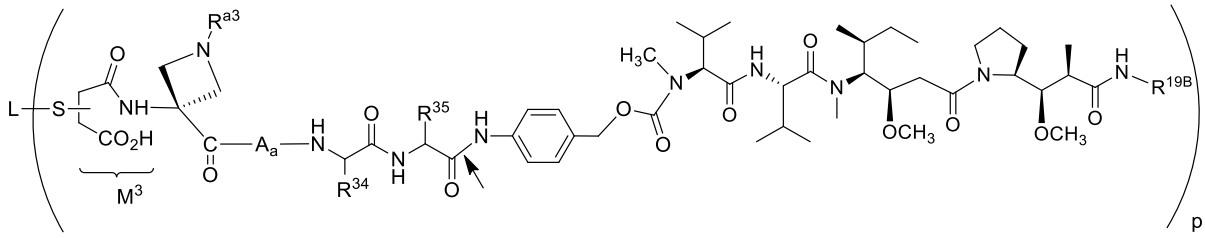
subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated.

42. The Ligand-Drug Conjugate composition of claim 36 wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript a is 1 so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

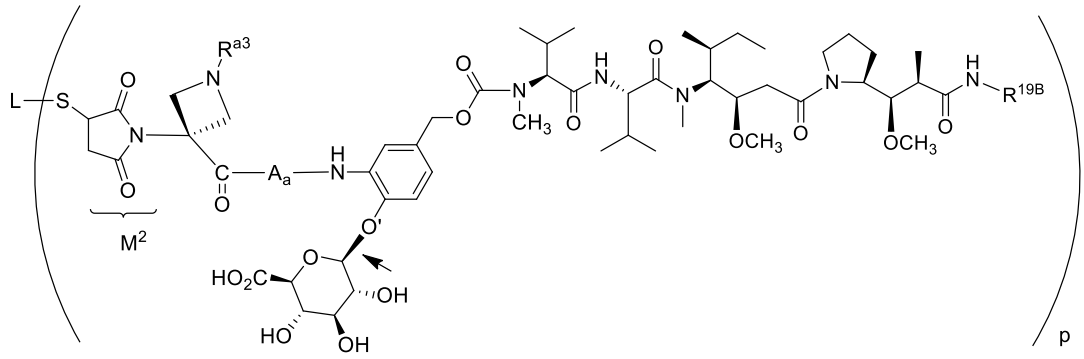
R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph;

R^{34} is isopropyl; and

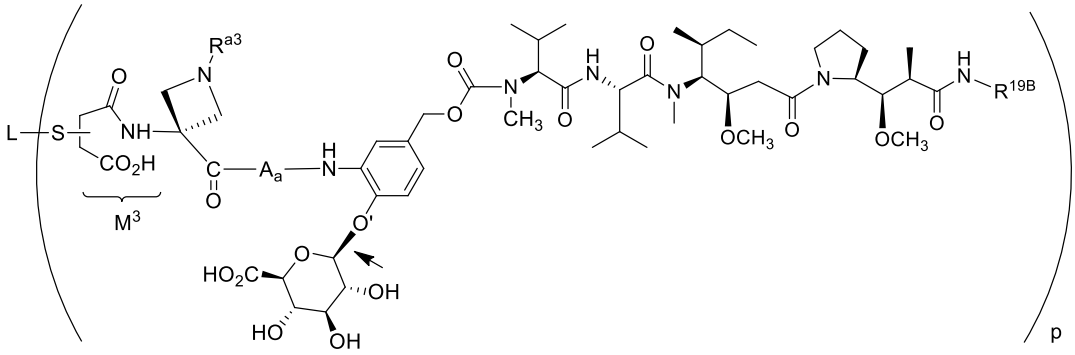
R^{35} is methyl or -$(CH_2)_3NH(C{=}O)NH_2$,

or

wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen bonded to R^{a3} is optionally protonated; and

R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph.

43. The Ligand-Drug Conjugate composition of claim 1,

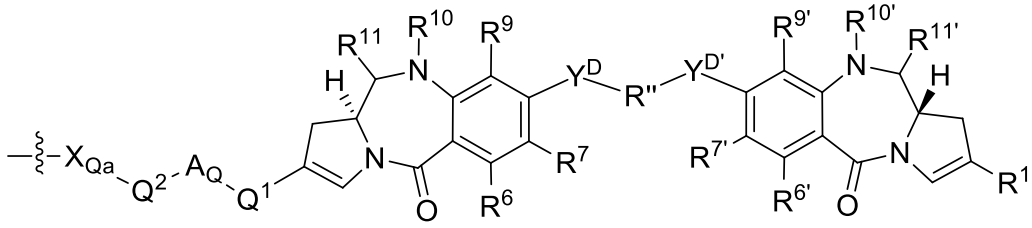
wherein subscript w is 1;

subscript y is 1 or 2, wherein

Y attached to W is a self-immolative Spacer Unit; and

D is that of a PBD dimer, thereby defining a PBD Drug Unit.

44. The Ligand-Drug Conjugate composition of claim 43 wherein the PBD Drug Unit has the structure of:



or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates the point of covalent attachment of the PBD Drug Unit to the remainder of composition structure;

A_Q is phenylene or C_5-C_7 heteroarylene, optionally substituted;

X_{Qa} is selected from the group consisting of -O-, -S-, -C(=O)O-, -C(=O)-, -NH(C=O)-, and -N(R^N)-, wherein R^N is selected from the group consisting of H, C_1-C_4 alkyl and $(C_2H_4O)_{n'}$-CH_3, wherein subscript n' ranges from 1 to 36, and either:

(i) Q^1 is a single bond, and Q^2 is selected from the group consisting of a single bond and -Z-$(CH_2)_n$-, wherein Z is selected from the group consisting of a single bond, O, S and NH, and subscript n ranges from 1 to 3, or

(ii) Q^1 is -CH=CH-, and Q^2 is a single bond;

R^{12} is C_6-C_{10} aryl or C_5-C_{10} heteroaryl;

R^6 and R^9 are independently selected from the group consisting of H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro and halo;

R^7 is selected from the group consisting of H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro and halo;

R and R' are independently selected from the group consisting of optionally substituted C_1-C_{12} alkyl, C_3-C_{20} heterocyclyl, C_6-C_{24} aryl and C_5-C_{24} heteroaryl; and

either:

(a) R^{10} is H, and R^{11} is OH or OR^A, wherein R^A is C_1-C_4 alkyl,

(b) R^{10} and R^{11} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are attached, or

(c) R^{10} is H and R^{11} is SO_zM, wherein subscript z is 2 or 3 and M is a monovalent cation;

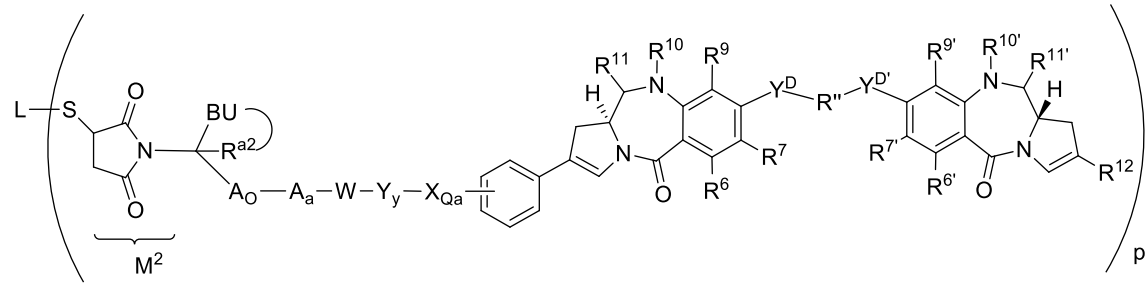
R″ is C_3-C_{12} alkylene, the carbon chain of which is optionally interrupted by one, two or three heteroatoms selected from the group consisting of O, S and NH, and/or by an aromatic ring;

Y^D is selected from the group consisting of O, S and NH;

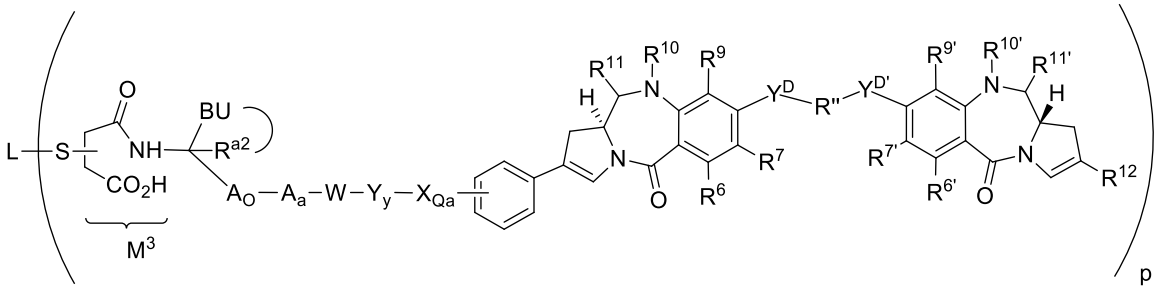
$R^{6'}$, $R^{7'}$, $R^{9'}$, and $Y^{D'}$ are independently selected from the same groups as R^6, R^7, R^9, and Y^D, respectively, and $R^{10'}$ and $R^{11'}$ are selected independently from the same groups as R^{10} and R^{11}, respectively, provided if R^{11} and $R^{11'}$ are each SO_zM, each M is an independently selected monovalent cation or together represents a divalent cation; and

wherein optional substitution is by one, two or three substituents independently selected from the group consisting of halo, nitro, cyano, -OR, C_1-C_7 alkyl, C_3-C_7 heterocyclyl, dimethyl-aminopropyloxy, piperazinyl and bis-oxy-C_1-C_3 alkylene, wherein R is as previously defined.

45. The Ligand-Drug Conjugate composition of claim 44, wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

A, if present, is an alpha-amino, beta-amino or another amine-containing acid residue;

W is a Peptide Cleavable Unit; and

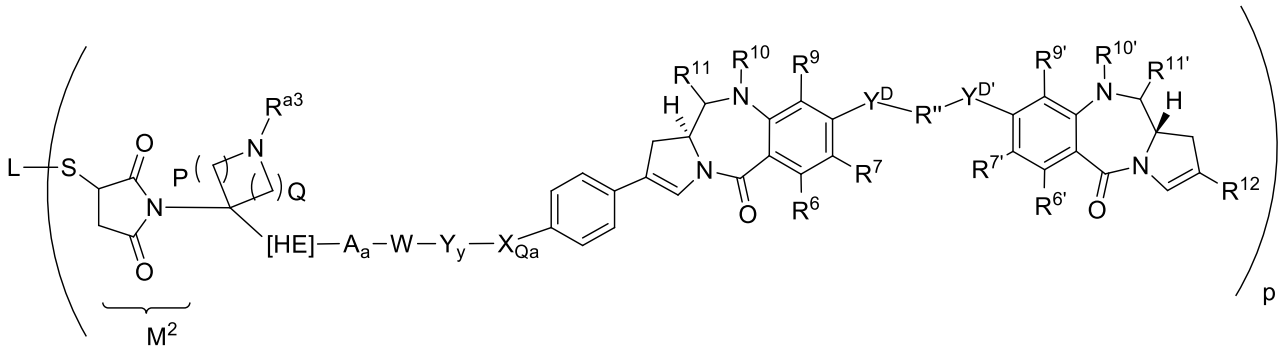
subscript y is 1 or 2, wherein Y bonded to W is a self-immolative Spacer Unit,

wherein the bond between W and that self-immolative Spacer Unit in a compound of the Ligand Drug Conjugate composition is cleavable by a protease to initiate release of the PBD Drug Unit as a PBD dimer from that Ligand Drug Conjugate compound,

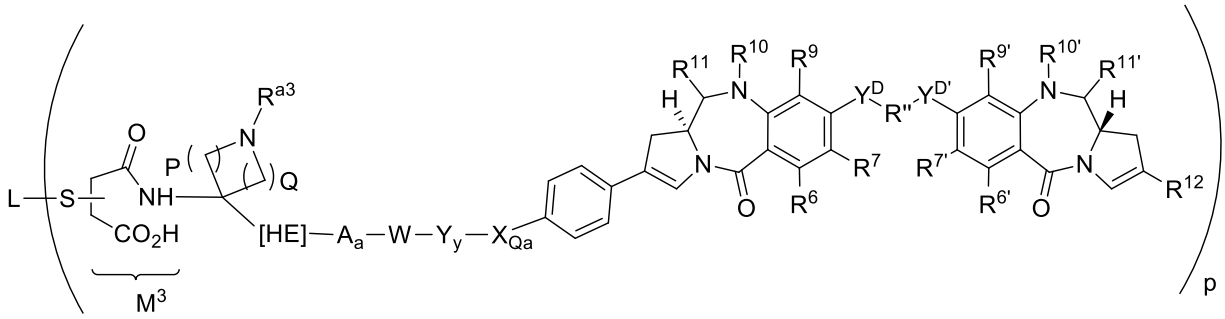
or subscript y is 0, wherein W is bonded to X_{QA},

wherein the bond between W and X_{QA} in a compound of the Ligand Drug Conjugate composition is cleavable by a protease to initiate release of the PBD Drug Unit as a PBD dimer from that Ligand Drug Conjugate compound.

46. The Ligand-Drug Conjugate composition of claim 45 wherein the composition is represented by the structure of:



and/or



or pharmaceutically acceptable salt(s) thereof, wherein

subscript P is 1 or 2;

subscript Q ranges from 1 to 6; and

X_{Qa} is –NH-;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2},;

R^{PEG1} is C_1-C_4 alkylene;

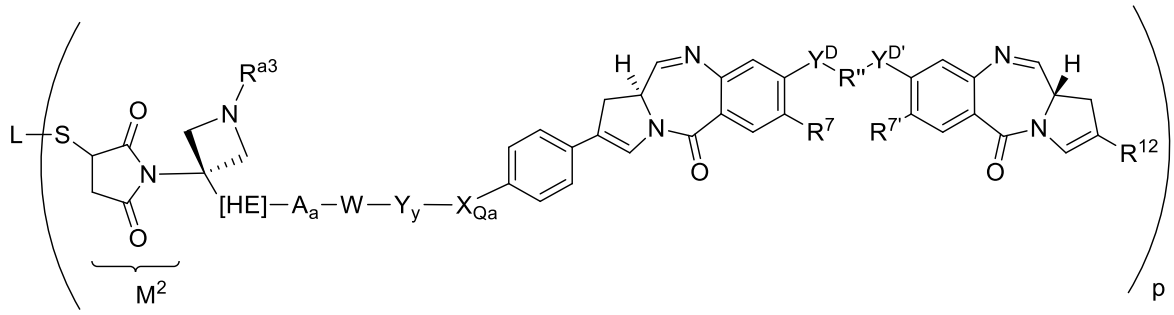
R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

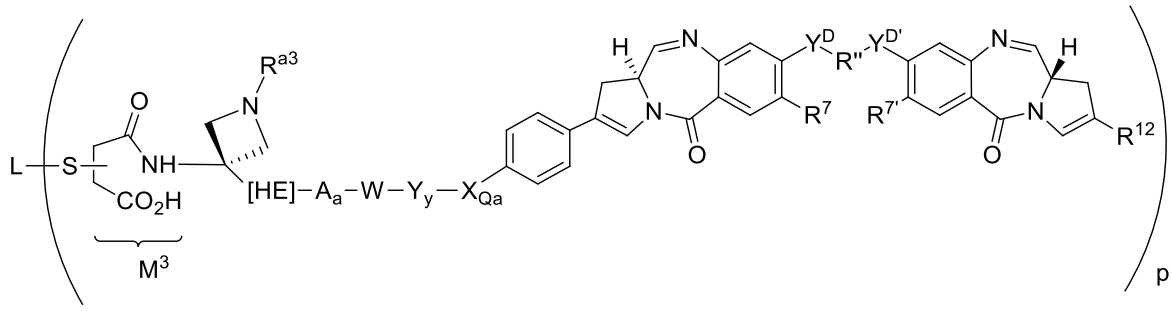
wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated.

47. The Ligand-Drug Conjugate composition of claim 46, wherein subscript P is 1, subscript Q is 1.

48. The Ligand-Drug Conjugate composition of claim 47, wherein the composition is represented by the structure of:



and/or



,

or pharmaceutically acceptable salt(s) thereof, wherein

X_{Qa} is –NH-;

R^{a3} is –H, C_1-C_4 alkyl or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

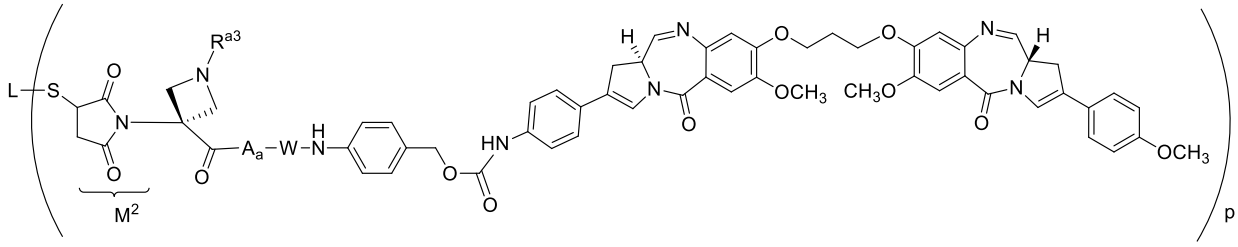
R^{PEG1} is –CH_2- or –CH_2CH_2-;

R^{PEG2} is –H, -CH_3 or -CH_2CH_3;

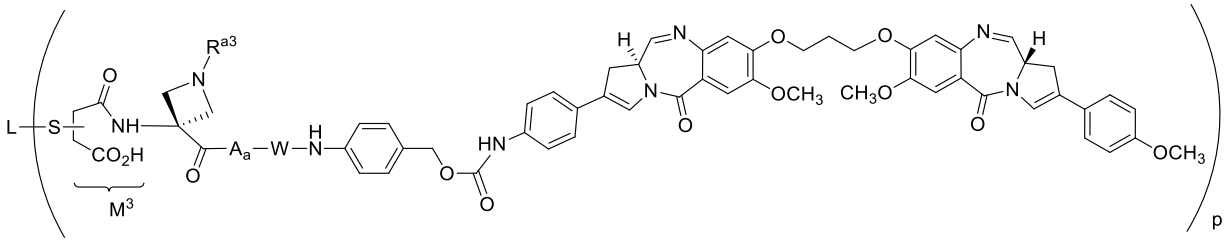
subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated.

49. The Ligand-Drug Conjugate composition of claim 48, wherein the composition is represented by the structure of:



and/or

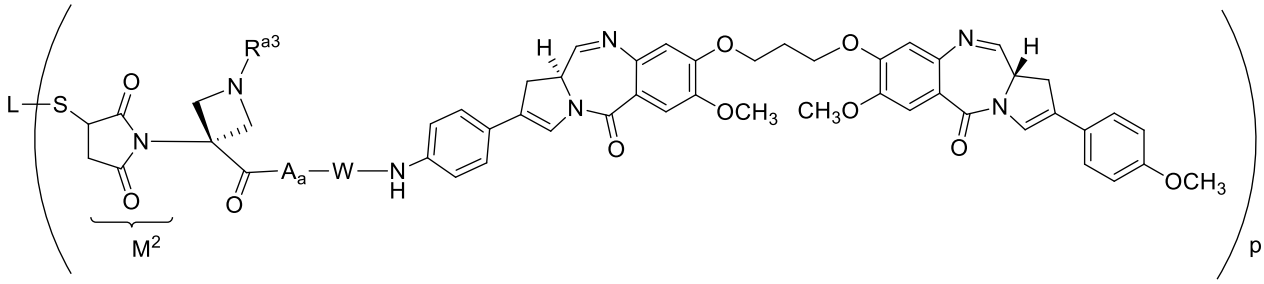


or pharmaceutically acceptable salt(s) thereof, wherein

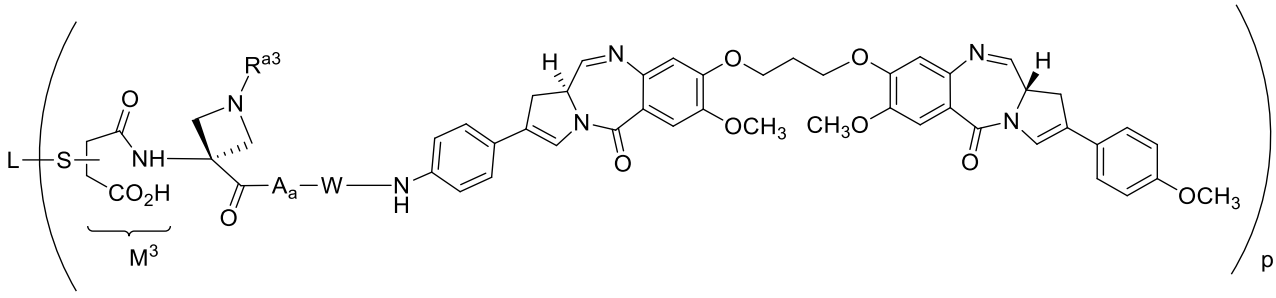
R^{a3} is –H, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated,

or

wherein the composition is represented by the structure of:



and/or

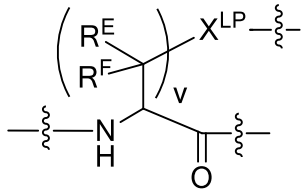


or pharmaceutically acceptable salt(s) thereof, wherein

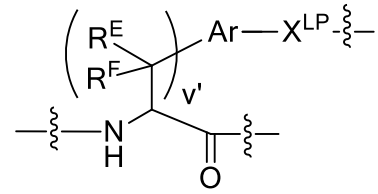
R^{a3} is –H, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated.

50. The Ligand-Drug Conjugate composition of claim 1, wherein if D/D^+, is that of a biologically active compound or derivative thereof, wherein that compound or its derivative is hydrophobic or has a SlogP < 0, then A or a subunit thereof is $–L^P(PEG)-$;

wherein $–L^P-$ or a subunit thereof has the structure of Formula L^P-1 or L^P-2:



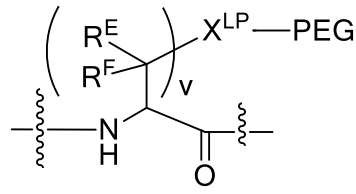
(Formula L^P-1)



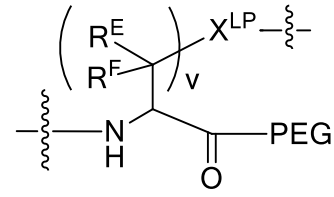
(Formula L^P-2)

or

wherein $-L^P(PEG)-$ or a PEG-containing subunit thereof has the structure of Formula L^P-3 or Formula L^P-4:



(Formula L^P-3)



(Formula L^P-4),

wherein subscript v is an integer ranging from 1 to 4;

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

X^{LP} is provided by a natural or un-natural amino acid side chain or 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 $-N(R^{LP})C(=NR^{LP})N(R^{LP})-$, or C_3-C_8 heterocyclo;

wherein each R^{LP} is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6 alkyl, or two of R^{LP} together along with the carbons atoms to which they are attached and their intervening atoms define a C_5-C_6 heterocyclo and any remaining R^{LP} are as previously defined;

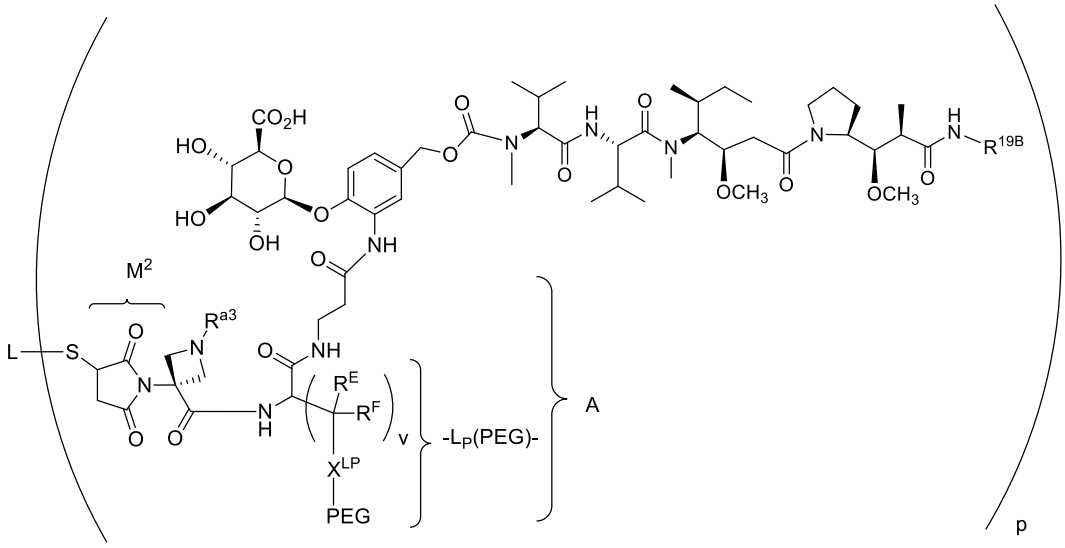
Ar is a C_6-C_{10} arylene or a C_5-C_{10} heteroarylene, optionally substituted;

each R^E and R^F is independently selected from the group consisting of -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkylene, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene,

or R^E and R^F together with the carbon atom to which both are attached defines an optionally substituted C_3-C_6 carbocyclo, or R^E and R^F from adjacent carbon atoms together with these atoms and any intervening carbon atoms defines an optionally substituted C_5-C_6 carbocyclo with any remaining R^E and R^F as previously defined;

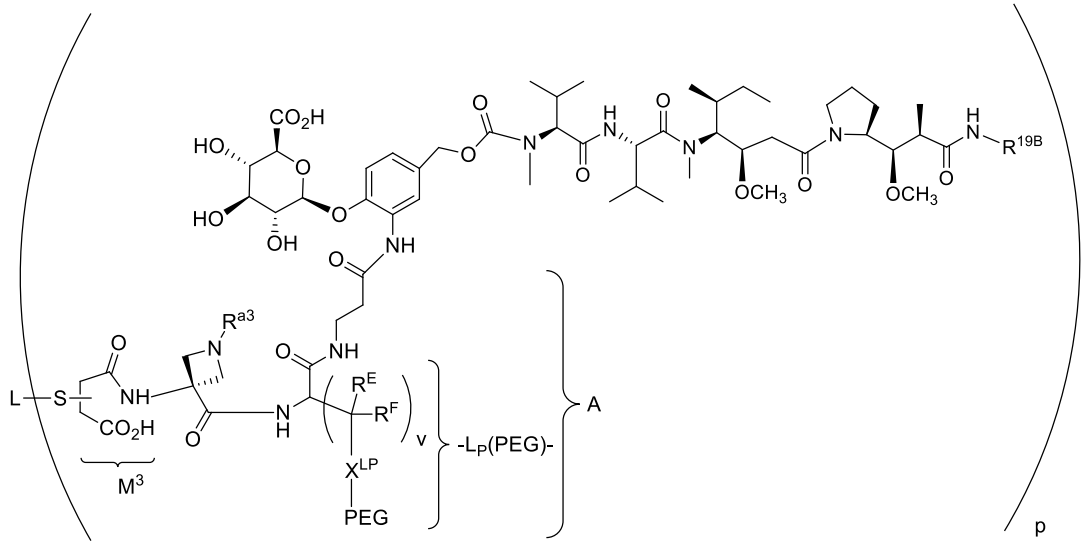
wherein one of the wavy lines indicate the point of covalent attachment of a PEG Unit and the other two wavy lines indicates covalent attachment of Formula L^P-1 or Formula L^P-2 within the structure representing the Ligand Drug Conjugate composition.

51. The Ligand-Drug Conjugate composition of claim 50 wherein the composition is represented by the structure of Formula 1a or Formula 2a:



(Formula 1a)

and/or



(Formula 2a)

or pharmaceutically acceptable salt(s) thereof, wherein

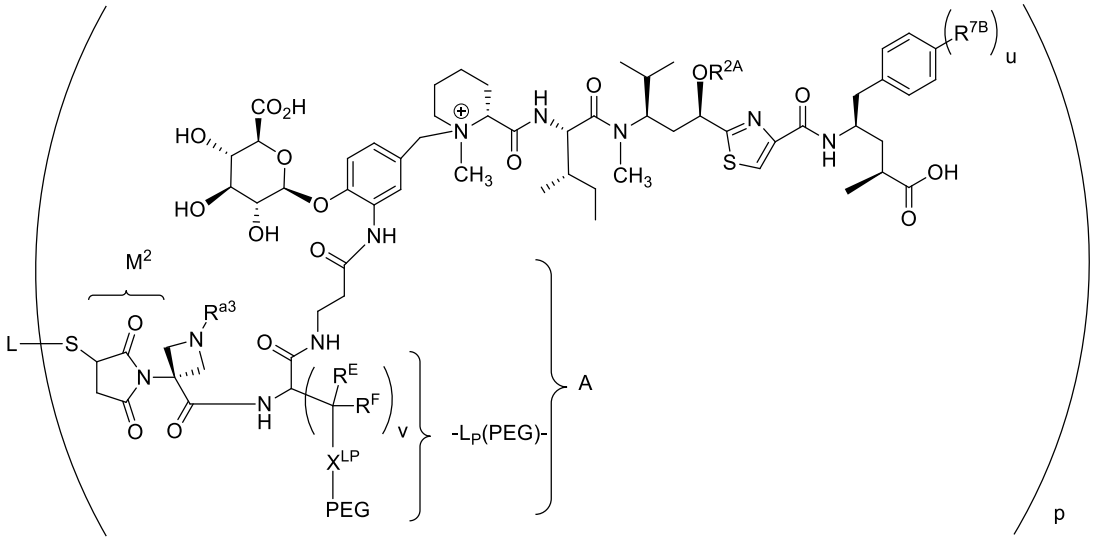
R^{a3} is –H, optionally substituted C_1-C_6 alkyl or optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

R^{19B} is –CH(CH_3)-CH(OH)-Ph, –CH(CO_2H)-CH(OH)-CH_3, or –CH(CO_2H)-CH_2Ph;

S is a sulfur atom of the Ligand Unit, wherein that sulfur atom in Formula 2a is bonded the carbon α or β to the carboxylic acid functional group of the indicated succinic acid amide (M^3) moiety,

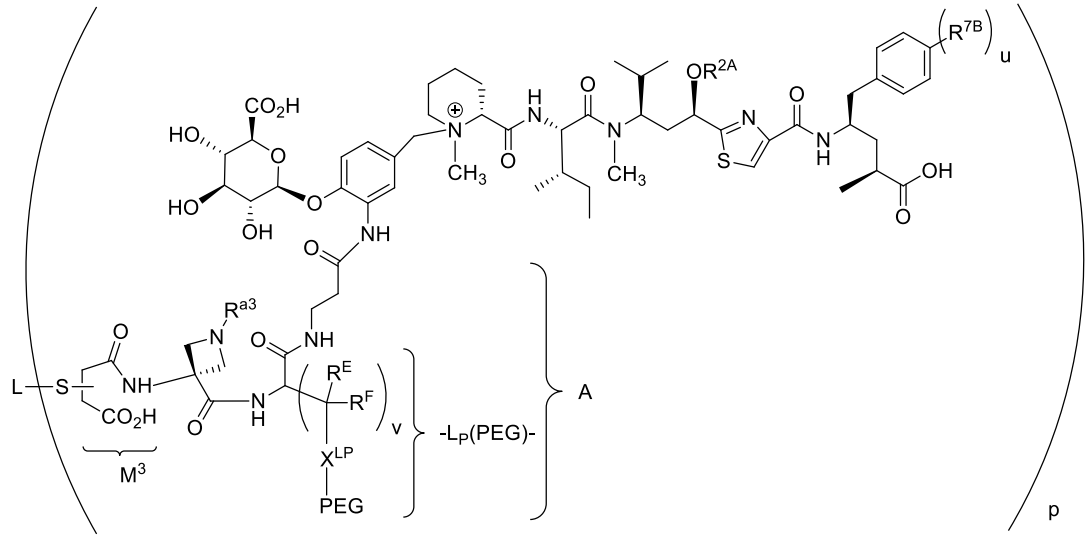
or

wherein the composition is represented by the structure of Formula 1b or Formula 2b:



(Formula 1b)

and/or



(Formula 2b)

or pharmaceutically acceptable salt(s) thereof, wherein

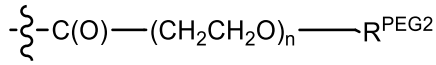
R^{2A} is $–C(=O)CH_3$, $–CH_2CH_3$, $–CH_2CH=CH_2$ or $–CH_2C(=CH_2)CH_3$;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl or optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

subscript u is 0 or 1; and

R^{7B} is –OH when subscript u is 1 or is absent when subscript u is 0.

52. The Ligand-Drug Conjugate composition of claim 51 wherein $-X^{LP}$-PEG has the structure of:



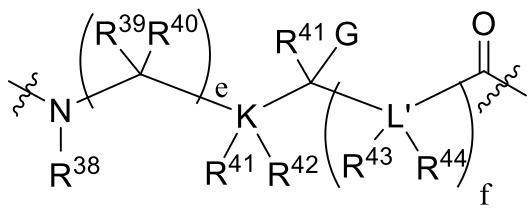
,

wherein R^{PEG2} is a PEG Capping Unit; and

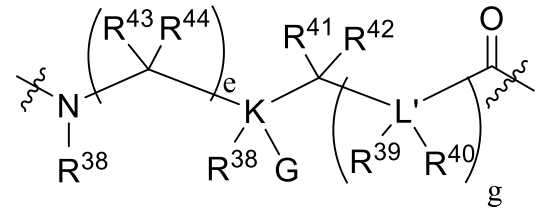
subscript n ranges from 2 to 72.

53. The Ligand-Drug Conjugate composition of claim 52 wherein subscript n is 12 and R^{PEG2} is hydrogen or $-CH_3$.

54. The Ligand-Drug Conjugate composition of claim 1 wherein A or a subunit thereof has the structure of formula (3),formula (4), or formula (5):

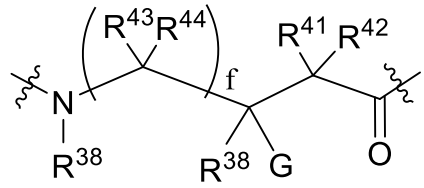


(3)



(4)

,



(5)

or a pharmaceutically acceptable salt thereof, wherein

the wavy lines indicated covalent attachment within the composition 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, or

G is $-N(R^{PR})(R^{PR})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is -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} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl, or

L' in formula 4 is C, and in formula 3 or formula 4 R^{39}, R^{40} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{41}-R^{44} are as defined herein

or K in formula 4 is C, and in formula 3 or formula 4 R^{41}, R^{42} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{39}, R^{40}, R^{43} and R^{44} are as defined herein,

or L' in formula 3 is C, and in formula 3 or formula 4 R^{43}, R^{44} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{39}-R^{42} are as defined herein,

or R^{40} and R^{41} together with the carbon atom(s) and/or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{42}-R^{44} are as defined herein,

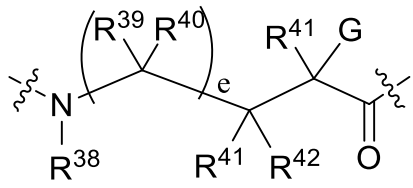
or R^{40} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{41}, R^{42}, and R^{44} are as defined herein,

or R^{41} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{40}, R^{42} and R^{44} and the remainder of R^{40}-R^{43} are as defined herein,

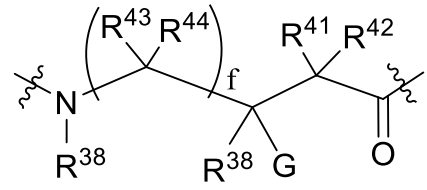
or

A or a subunit thereof is an alpha-amino, beta-amino or another amine-containing acid residue.

55. The Ligand-Drug Conjugate composition of claim 54 wherein A or a subunit thereof has the structure of formula (3a) or formula (5):



(3a),



(5),

or a pharmaceutically acceptable salt thereof, wherein

subscript e and f are independently 0 or 1,

or

A or a subunit thereof is an alpha-amino or beta-amino acid residue.

56. The Ligand-Drug Conjugate composition of claim 1 wherein the Ligand Unit is an antibody Ligand Unit, thereby defining an antibody drug conjugate (ADC), wherein the moiety targeted by the antibody Ligand Unit is an accessible cell-surface antigen of abnormal cells, wherein the targeted antigen is capable of cellular internalization of bound ADC and is present in greater copy number on the abnormal cells in comparison to normal cells distant from the site of the abnormal cells.

57. The Ligand-Drug Conjugate composition of claim 56 wherein the targeting agent is an antibody, thereby defining an antibody drug conjugate (ADC), wherein the targeted moiety of the antibody Ligand Unit is an accessible cell-surface antigen of a vascular epithelial cell in the vicinity of abnormal cells, wherein said antigen is capable of cellular internalization of bound ADC and is present in greater copy number on said cells in comparison to normal epithelial cells distant from the site of the abnormal cells.

58. The Ligand Drug Conjugate composition of claim 57 wherein subscript p is about 2, about 4, or about 8.

59. The Ligand Drug Conjugate composition of claim 58 wherein the Ligand Unit is that of an antibody or antigen-binding fragment thereof, thereby defining an antibody Ligand Unit, wherein the sulfur atom of the antibody Ligand Unit bonded to the succinic acid (M^2) moiety or succinic acid amide (M^3) moiety is that of a cysteine residue of the antibody or antigen-binding fragment thereof.

60. A pharmaceutically acceptable formulation or precursor thereof comprising a Ligand Drug Conjugate composition of claim 1 and one, two, three or more excipients.

61. The pharmaceutically acceptable formulation of claim 60, wherein the pharmaceutically acceptable formulation is a liquid suitable for intravenous injection to a subject or the pharmaceutically acceptable formulation precursor is a solid suitable for reconstitution as a solution for intravenous injection to a subject.

62. The pharmaceutically acceptable formulation of claim 61 wherein the Ligand Drug Conjugate composition is present in the formulation in an effective amount for treatment of a hyperproliferative disease or condition.

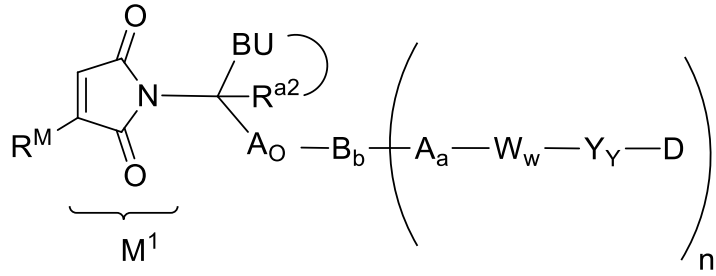
63. Use of a Ligand Drug Conjugate composition of claim 1 in the manufacture of a medicament for treating a hyperproliferative disease or condition in a patient having said disease or condition.

64. The use of claim 63 wherein the hyperproliferative disease or condition is a cancer.

65. The use of claim 64 wherein the cancer is a leukemia or lymphoma.

66. An *in vitro* 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 to an effective amount of a Ligand Drug Conjugate composition of claim 1.

67. A Drug Linker compound, wherein the compound has the structure of:



or a salt thereof, wherein

R^M is hydrogen or an optionally substituted C_1-C_6 alkyl;

subscript w is 0 or 1;

subscript y is 0, 1, or 2;

subscript n is 1, 2, 3 or 4;

subscript a is 0 or 1;

subscript b is 0 or 1,

provided that subscript b is 1 when subscript n is 2, 3 or 4 and subscript b is 0 when subscript n is 1;

A is a first Stretcher Unit;

A_O is a second optional Stretcher Unit;

B is an optional Branching Unit; and

wherein each of A, A_O and B is an independently selected single unit or is optionally comprised or consists of two, three or four independently selected subunits;

when subscript y is 0, Y is absent; when subscript y is 1, Y is a self-immolative spacer unit; and when subscript y is 2, Yy is Y-Y'-, wherein Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D+);

subscript w is 0 or 1, wherein W is absent when subscript w is 0, or when subscript w is 1 then

W is a Peptide Cleavable Unit, or

W is a Glucuronide Unit of formula –Y(W')-, wherein W' represents a carbohydrate moiety with glycosidic bonding to Y through a optionally substituted heteroatom;

provided that Y bonded to W' is a self-immolative Spacer Unit, and subscript y is 1 or 2;

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl group that together with the carbon atom to which both are attached, as represented by the solid curved line, define a cyclic Basic Unit having an optionally substituted C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group, an optionally substituted C_3-C_{20} carbocyclo with exocyclic substitution by an optionally substituted basic nitrogen of a basic secondary or tertiary amine functional group, or an optionally substituted C_3-C_{20} carbocyclo having exocyclic substitution by an optionally substituted C_1-C_{12} aminoalkyl in which the optionally substituted basic nitrogen atom of the amino moiety of the aminoalkyl is that of a primary, secondary or tertiary amine functional group, wherein the optionally substituted basic nitrogen atom of the exocyclic amine or aminoalkyl along with its optionally substituted alkyl moiety is attributable to BU, or

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl formally cyclized to the basic nitrogen atom of an acyclic Basic Unit of corresponding structure to Formula 1 and/or Formula 2 in which the solid curved lined between BU and R^{a2} is absent, or to a carbon atom of an optionally substituted C_1-C_{12} alkylene bearing that basic nitrogen

atom, both of which comprise the acyclic Basic Unit, thus forming an optionally substituted C_3-C_{20} heterocyclo, which incorporates the basic nitrogen atom as a skeletal heteroatom, or an optionally substituted C_3-C_{20} carbocyclo substituted directly by the basic nitrogen atom, or substituted indirectly by the basic nitrogen atom through an optionally substituted C_1-C_{12} alkylene moiety remaining from said formal cyclization and whose structure is dependent on the site of cyclization, so in either instance a cyclic Basic Unit (cBU) is defined, as indicated by the solid curved line;

and

wherein the basic nitrogen atom of the cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated;

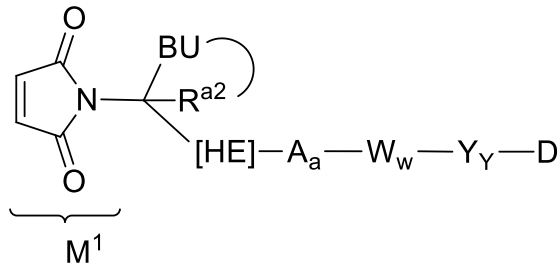
D is a Drug Unit, or

D is a quaternized Drug Unit represented as D^+ so that D^+ replaces D in Formula 1 and Formula 2, provided that subscript w is 1;

wherein if subscript w is 1, activation of the Glucuronide Unit by a glycosidase or activation of the Peptide Cleavable Unit by a protease initiates release of the Drug Unit or quaternized Drug Unit as a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound of a Ligand Drug Conjugate composition prepared from the Drug Linker compound,

or if subscript w is 0, a biologically active compound or derivative thereof is released from the Drug Linker compound or from a Ligand Drug Conjugate compound of a Ligand Drug Conjugate composition prepared from the Drug Linker compound on enzymatic or non-enzymatic cleavage of a bond between $–Y_y$-D of and the remainder of the Drug Linker compound or Ligand Drug Conjugate compound.

68. The Drug Linker compound of claim 67, wherein the compound has the structure of:



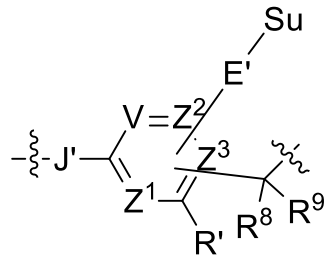
or a salt thereof, wherein

[HE] as A_O is an optional Hydrolysis Enhancing Unit;

subscript w is 1;

W is Peptide Cleavable Unit, or

W is a Glucuronide unit of formula –Y(W')- having the structure of:



wherein

wherein Su is a carbohydrate moiety and -E'- represents an optionally substituted heteroatom of an glycosidic bond cleavable by a glycosidase so that Su-E' is W' and the remainder of the Glucuronide Unit structure is a self-immolative Spacer Unit;

-J'- is an independently selected heteroatom, optionally substituted;

V, Z^1, Z^2 and Z^3 are independently =N- or =C(R^{24})-, wherein each R^{24} is independently selected from the group consisting of hydrogen and C_1-C_{12} alkyl, C_2-C_{12} alkenyl and C_2-C_{12} alkynyl, optionally substituted, halogen, an electron withdrawing group, an electron donating group, -E'-Su, and –C(R^8)(R^9)-, provided that one and only one –C(R^8)(R^9)- moiety and one and only one –E'-Su moiety is present, wherein

one of V, Z^1, Z^2 and Z^3 is =C(R^{24})- in which R^{24} is –C(R^8)(R^9)- and another of V, Z^1, Z^2 and Z^3 is =C(R^{24})- in which R^{24} is –E'-Su,

provided the –C(R^8)(R^9)- and –E'-Su moieties are *ortho* or *para* to each other;

R^8 and R^9 independently are hydrogen, or C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, optionally substituted, or C_6-C_{20} aryl or C_5-C_{20} heteroaryl, optionally substituted, or

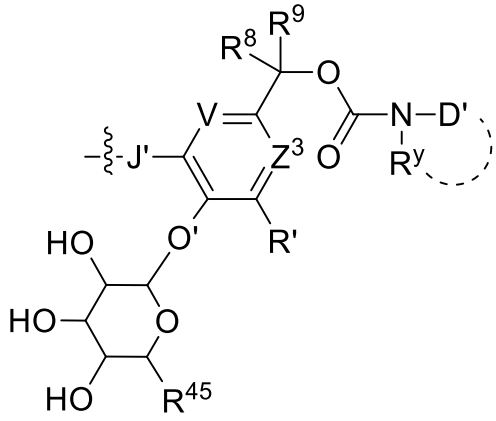
R^8 and R^9 together with the carbon atom to which both are attached define an optionally substituted C_5-C_{20} carbocyclo;

R' is hydrogen or -NO_2, or other electron withdrawing group or –OC_1-C_6 alkyl, or other electron donating group; and

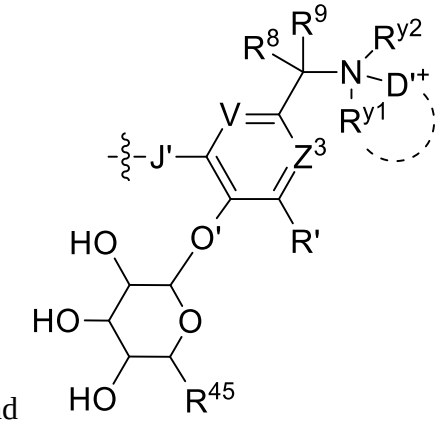
wherein glycosidase cleavage of the glycosidic bond initiates release of the Drug Unit or quaternized Drug Unit as a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound prepared from the Drug Linker compound;

wherein the wavy line adjacent to J' indicates the point of attachment of the Glucuronide Unit to A when subscript a is 1 or to the indicated L_{SS} or L_S primary linker when subscript a is 0; and the wavy line adjacent to the –C(R^8)(R^9)- moiety indicates the point of covalent attachment of the Glucuronide Unit to Y' when subscript y is 2, or to D/D^+ when subscript y is 1.

69. The Drug Linker compound of claim 68 wherein –W-Y_y-D and -W-D^+, in which W is a Glucuronide Unit, have structures of:



and



,

respectively, or a salt thereof, or in suitable salt form, wherein

the dotted curve line indicates optional cyclization of R^y or R^{y1} to D';

R^{45} is $–CH_2OH$ or $–CO_2H$;

$-N(R^Y)D'$ and $–N^+(R^{y1})(R^{y2})D'$ moieties, with or without cyclization, represent D and D^+, respectively, wherein D' is the remainder of D or D^+;

wherein R^y is hydrogen or optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or R^y is optionally substituted C_1-C_6 alkylene when cyclized to D';

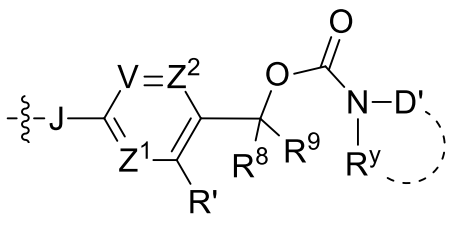
R^{y1} is optionally substituted C_1-C_6 alkyl, in absence of its cyclization within D^+, or R^{y1} is optionally substituted C_1-C_6 alkylene when cyclized within D^+;

R^{y2} is hydrogen or optionally substituted C_1-C_6 alkyl; and

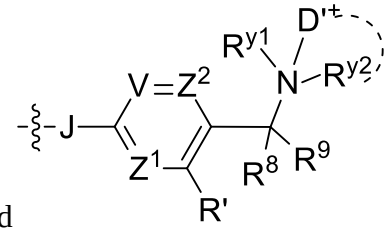
wherein -O'- as E' represents the oxygen heteroatom of an O-glycosidic bond cleavable by a glycosidase, wherein said cleavage initiates release of D as a primary or secondary amine-containing a biologically active compound or derivative thereof or initiates release of D^+ as a tertiary amine-containing biologically active compound or derivative thereof from the Drug Linker compound or Ligand Drug Conjugate compound prepared from the Drug Linker compound,

or

wherein $–W\text{-}Y_y\text{-}D$ and $-W\text{-}D^+$, in which W is a Peptide Cleavable Unit have structures of:



and



,

respectively, or a salt thereof, or in suitable salt form, wherein

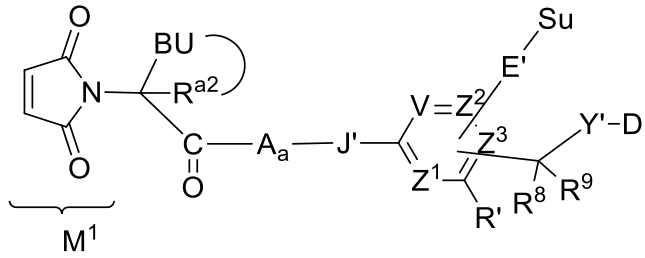
$-N(R^Y)D'$ and $-N(R^{y1})(R^{y2})D'^+$ moieties represent D and D^+, respectively, wherein D' and D'^+ are the remainder of D and D^+, and wherein the dotted line indicates optional cyclization of R^y or R^{y1} to D' or D'^+;

wherein R^y is hydrogen or R^y is optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or optionally substituted C_1-C_6 alkylene when cyclized to D';

R^{y1} is optionally substituted C_1-C_6 alkyl and R^{y2} is optionally substituted C_1-C_6 alkyl in absence of cyclization to D^+ or R^{y2} is optionally substituted C_1-C_6 alkylene when cyclized to D^+;

-J- is an optionally substituted heteroatom bonded to W as indicated by the adjacent wavy line, wherein cleavage of that bond initiates release of D as a primary or secondary amine-containing a biologically active compound or derivative thereof or initiates release of D^+ as a tertiary amine-containing a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound prepared from the Drug Linker compound.

70. The Drug Linker compound of claim 68, wherein the compound has the structure of:



or a salt thereof, wherein

Su is a carbohydrate moiety;

-E'- is an independently selected heteroatom, optionally substituted, of an glycosidic bond cleavable by a glycosidase;

-J'- represents an independently selected heteroatom, optionally substituted;

Y' is absent or Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D^+);

V, Z^1, Z^2 and Z^3 independently are =N- or =C(R^{24})-, wherein each R^{24} is independently selected from the group consisting of hydrogen and C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, halogen, an electron withdrawing group, an electron donating group, -E'-Su, –C(R^8)(R^9)-Y'-D and –C(R^8)(R^9)-D^+,

provided that one and only one of –C(R^8)(R^9)-Y'-D and –C(R^8)(R^9)-D^+ moieties and one and only one –E'-Su moiety is present;

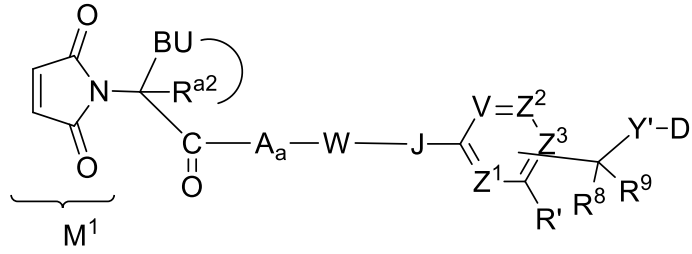
wherein one of V, Z^1, Z^2 and Z^3 is $=C(R^{24})$-, in which R^{24} is $-C(R^8)(R^9)$-Y'-D or $-C(R^8)(R^9)$-D^+ and another of V, Z^1, Z^2 and Z^3 is $=C(R^{24})$-, in which R^{24} is –E'-Su, provided the –E'-Su and $-C(R^8)(R^9)$-Y'-D or $-C(R^8)(R^9)$-D^+ moieties are *ortho* or *para* to each other;

R^8 and R^9 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, or C_5-C_{10} aryl or C_5-C_{10} heteroaryl, optionally substituted; and

wherein glycosidase cleavage of the glycosidic bond of the Drug Linker compound or a Ligand Drug Conjugate compound prepared from that Drug Linker compound initiates release of D/D^+ as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound,

or

wherein the compound has the structure of:



or a salt thereof, wherein

J represents a heteroatom, optionally substituted;

Y' is absent or Y' is –O-C(=O)-, provided that Y' is absent when D is a quaternized Drug Unit (D^+);

W is a Peptide Cleavable Unit;

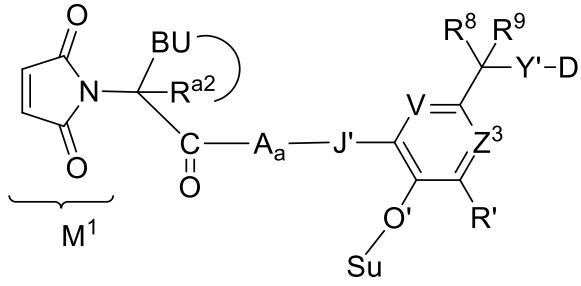
V, Z^1, Z^2 and Z^3 are independently =N- or $=C(R^{24})$-, wherein each R^{24} is independently selected from the group consisting of hydrogen and C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, halogen, an electron withdrawing group, an electron donating group, and $-C(R^8)(R^9)$-Y'-D, provided that one and only one $-C(R^8)(R^9)$-Y'-D moiety is present,

wherein one of V, Z^1, Z^2 and Z^3 is $=C(R^{24})$-, in which R^{24} is $-C(R^8)(R^9)$-Y'-D, provided the $-C(R^8)(R^9)$-Y'-D moiety is *ortho* or para to J';

R^8 and R^9 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl, optionally substituted, or C_5-C_{10} aryl or C_5-C_{10} heteroaryl, optionally substituted;

wherein protease action on W results in cleavage of the W-J' bond within the Drug Linker compound or a Ligand Drug Conjugate compound prepared from that Drug Linker compound so as to initiate release of D/D^+ as a biologically active compound or derivative thereof from that Ligand Drug Conjugate compound.

71. The Drug Linker compound of claim 70, wherein the compound has the structure of:

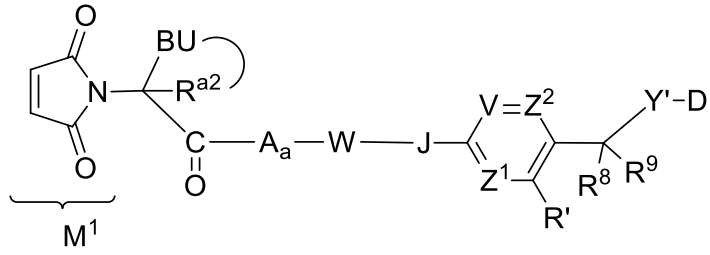


or a salt thereof, wherein

-O'- represents the oxygen heteroatom of an O-glycosidic bond cleavable by a glycosidase,

or

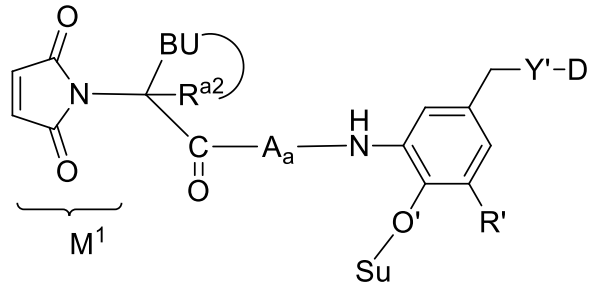
wherein the compound has the structure of:



,

or a salt thereof.

72. The Drug Linker compound of claim 71, wherein the compound has the structure of:

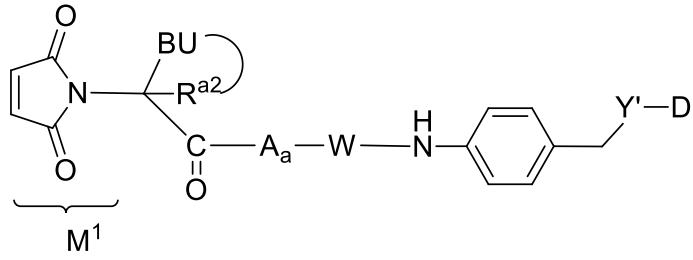


or a salt thereof, wherein

R' is hydrogen or $–NO_2$,

or

wherein the compound has the structure of:

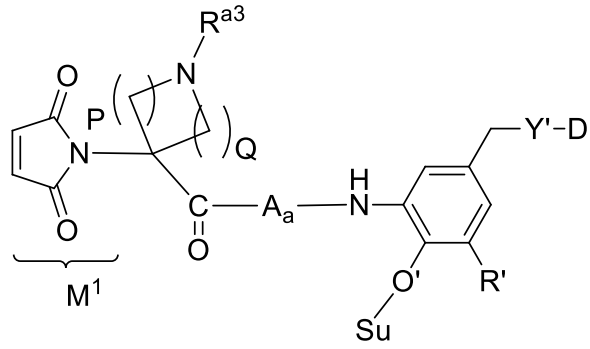


,

or a salt thereof.

73. The Drug Linker compound of claim 67, wherein BU and R^{a2} together with the carbon atom to which both are attached, define an optionally substituted C_3-C_8 heterocyclo having a skeletal secondary or tertiary basic nitrogen atom, wherein the skeletal basic nitrogen atom is attributable to BU, wherein the basic nitrogen is optionally protonated.

74. The Drug Linker compound of claim 71, wherein the compound has the structure of:



or a salt thereof, wherein

subscript P is 1 or 2;

subscript Q ranges from 1 to 6; and

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

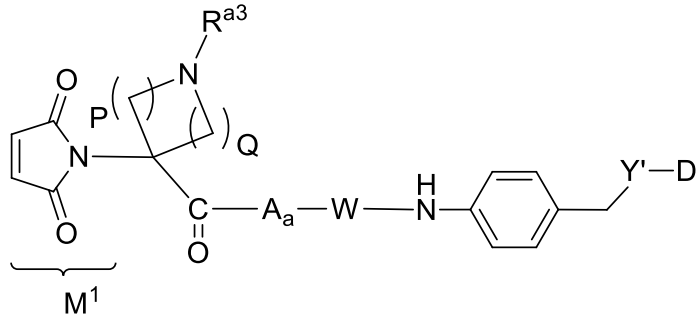
R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group,

or

wherein the compound has the structure of:



or a salt thereof, wherein

subscript P is 1 or 2;

subscript Q ranges from 1 to 6; and

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

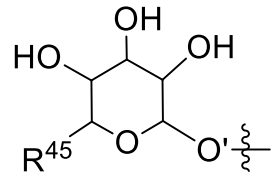
subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group.

75. The Drug Linker compound of claim 74, wherein subscript P is 1 and subscript Q is 1, 2 or 3 or subscript P is 2 and Q is 1 or 2.

76. The Drug Linker compound of claim 75, wherein subscript P is 1, subscript Q is 1.

77. The Drug Linker compound of claim 71, wherein –E'-Su has the structure of:

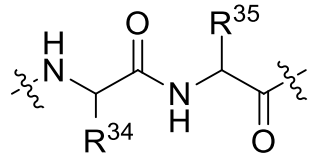


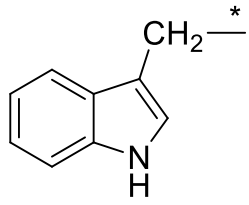
,

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

78. The Drug Linker compound of claim 71, wherein W is a Peptide Cleavable Unit comprised of a dipeptide wherein the C-terminus of the dipeptide is covalently bonded to J wherein the dipeptide provides for a recognition site for a regulatory or lysosomal protease for cleavage of the W-J bond by said protease thereby initiating release of D or D^+ as a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound prepared from the Drug Linker compound.

79. The Drug Linker compound of claim 78 wherein the dipeptide of W has the structure of:



wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH_3 or has the structure of , wherein the asterisk indicates the point of covalent attachment to the dipeptide backbone; and

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

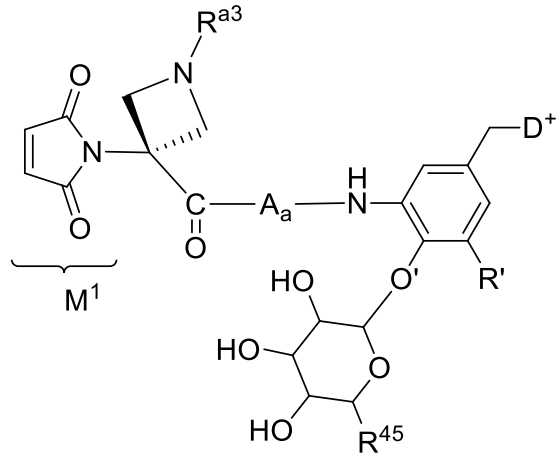
R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=O)NH_2$, -$(CH_2)_3NH(C=NH)NH_2$, or , -$(CH_2)_2CO_2H$, or a salt thereof; and

wherein the wavy line indicates the points of covalent attachment of the dipeptide into the Drug Linker compound.

80. The Drug Linker compound of claim 78 wherein the dipeptide of W selected from the group consisting of -Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, -Val-Cit-, -Phe-Cit-, -Leu-Cit-, -Ile-Cit-, -Phe-Arg-, and -Trp-Cit-, or a salt thereof, wherein Cit is citrulline.

81. The Drug Linker compound of claim 67 wherein D is a quaternized Drug Unit (–D^+), subscript y is 1 and Y' is absent, wherein said cleavage of the Peptide Cleavable Unit or Glucuronide Unit initiates release of D^+ as a tertiary amine-containing a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound prepared from the Drug Linker compound.

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



in suitable salt form, wherein

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or

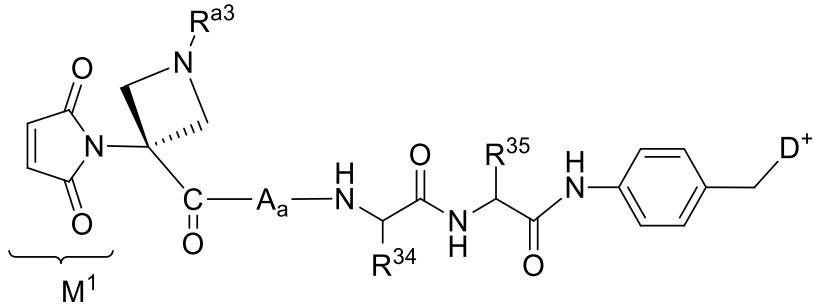
R^{a3} is a suitable nitrogen-protecting group;

R' is hydrogen or $–NO_2$; and

R^{45} is $–CH_2OH$ or $–CO_2H$,

or

wherein the compound has the structure of:



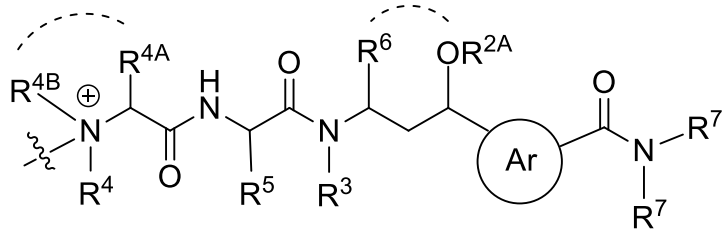
in suitable salt form, wherein

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or

R^{a3} is a suitable nitrogen-protecting group.

83. The Drug Linker compound of claim 81 wherein the released tertiary amine-containing biologically active compound or derivative thereof is a tubulysin compound thereby defining D^+ as a quaternized tubulysin Drug Unit.

84. The Drug Linker compound of claim 81 wherein the quaternized Drug Unit $–D^+$ is a quaternized tubulysin Drug Unit having the structure of:



,

in suitable salt form, wherein

R^{2A} is hydrogen or optionally substituted C_1-C_{12} 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, thereby defining an oxygen-containing C_5-C_6-heterocyclo;

the circled Ar moiety 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 C_1-C_{12} alkyl;

R^4, R^5 and R^6 are optionally substituted C_1-C_{12} 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;

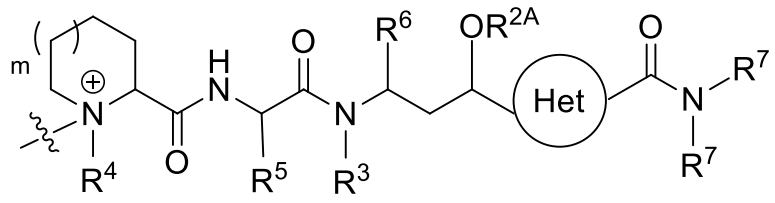
R^{4A} is hydrogen or optionally substituted C_1-C_{12} alkyl and R^{4B} is optionally substituted C_1-C_{12} alkyl, or both together with the nitrogen to which they are attached, as indicated by

the curved dotted line between R^{4A} and R^{4B}, define a quaternized nitrogen-containing C_3-C_8 heterocyclyl, optionally substituted;

one R^7 is hydrogen or optionally substituted C_1-C_{12} alkyl and the other R^7 is optionally substituted (C_6-C_{20} aryl)-C_1-C_{12} alkyl- or (C_5-C_{20} heteroaryl)-C_1-C_{12} alkyl-;

wherein the wavy line indicates the point of covalent attachment of D^+ to the remainder of the compound structure.

85. The Drug Linker compound of claim 84 wherein D^+ has the structure of:

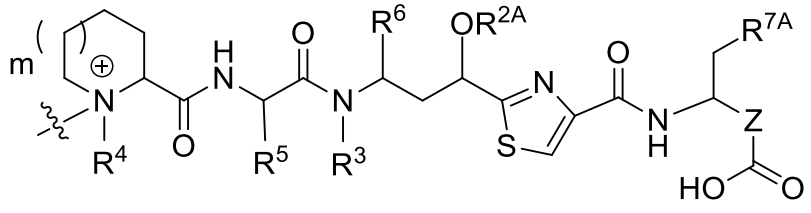


,

in suitable salt form, wherein

subscript m is 0 or 1.

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

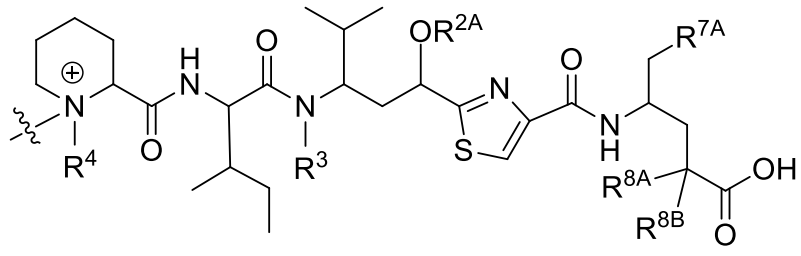


,

in suitable salt form, wherein

Z is an optionally substituted C_1-C_6 alkylene or an optionally substituted C_2-C_6 alkenylene; and R^{7A} is optionally substituted C_6-C_{10} aryl or optionally substituted C_5-C_{10} heteroaryl.

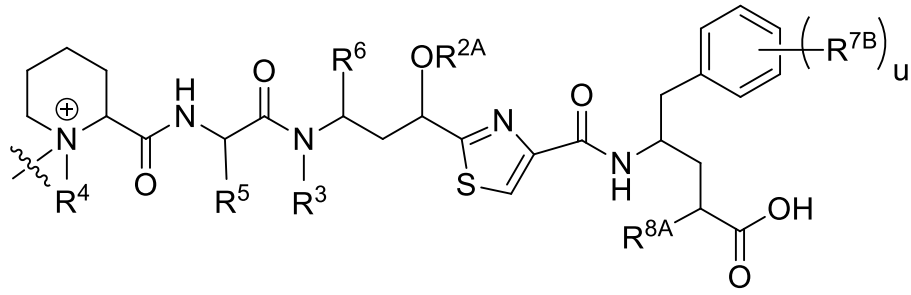
87. The Drug Linker compound of claim 86 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



in suitable salt form, wherein

R^{7A} is optionally substituted phenyl and R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6 alkyl or R^{8A} and R^{8B} together with the carbon atom to which both are attached define an optionally substituted C_3-C_6 carbocyclo.

88. The Drug Linker compound of claim 87 wherein the quaternized tubulysin Drug Unit $-D^+$ has the structure of:



in suitable salt form, wherein

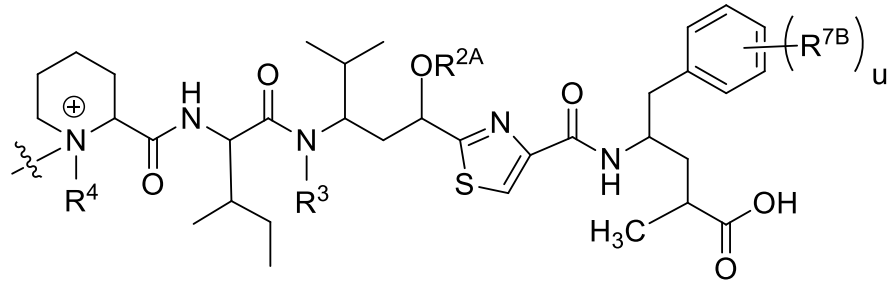
R^5 and R^6 are alkyl side chain residues of natural hydrophobic amino acids, independently selected;

subscript u, indicating the number of R^{7B} substituents, is 0, 1, 2 or 3;

each R^{7B}, when present, is an independently selected O-linked substituent; and

R^{8A} is hydrogen or optionally substituted C_1-C_4 alkyl.

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



,

in suitable salt form, 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;

R^{2A} along with the oxygen atom to which it is attached is an O-linked substituent selected from the group consisting of $-OCH_2OCH_2R^{2B}$, $-OCH_2R^{2B}$, $-OC(O)R^{2B}$, $-OCH_2OC(O)R^{2B}$, $-OC(O)N(R^{2B})(R^{2C})$, 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 $–OCH_3$.

90. The Drug Linker compound claim 84 wherein R^{2A} is $-CH_2CH_3$, or R^{2A} is $-CH_2-CH=CH_2$.

91. The Drug Linker compound of claim 89 wherein

$-OR^{2A}$ is $-OCH_2CH_3$, $-OCH_2-CH=CH_2$, $-OCH_2C(CH_3)=CH_2$ or $-OC(O)CH_3$;

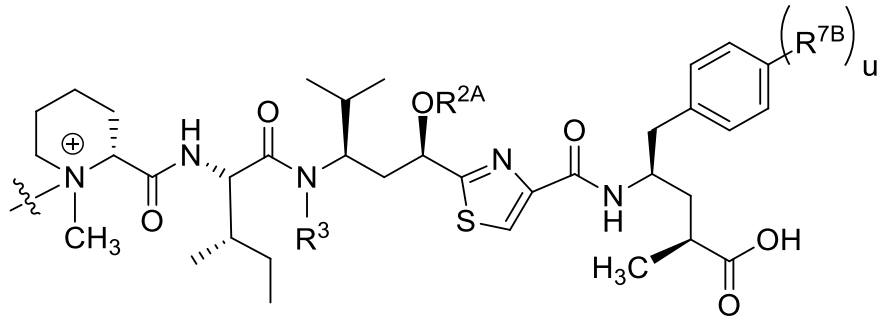
R^3 is $–CH_3$; and

R^{7B} is –OH or is absent;

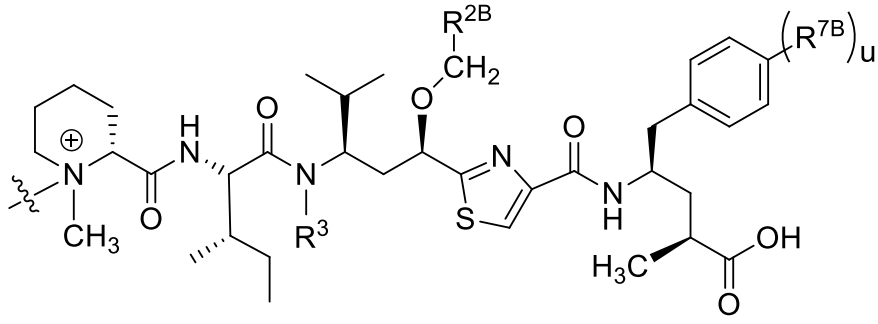
subscript u is 0 or 1, wherein

R^{7B} is –OH when subscript u is 1, and R^{7B} is absent when subscript u is 0.

92. The Drug Linker compound of claim 89 wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of:



or



in suitable salt form, wherein

R^{2A} is -C(O)R^{2B}, -C(O)NHR^{2D}, or –CH_2C(O)R^{2D}

R^{2B} is H, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R^{2D} is –H, C_1-C_4 alkyl or C_2-C_4 alkenyl;

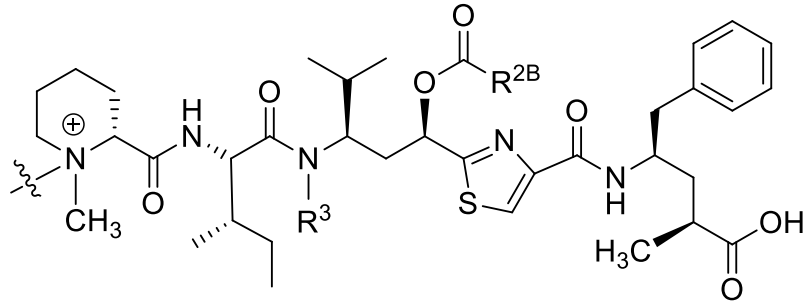
R^3 is methyl, ethyl or propyl;

R^{7B} is –OH or is absent;

subscript u is 0 or 1, wherein

R^{7B} is –OH when subscript u is 1, and R^{7B} is absent when subscript u is 0.

93. The Drug Linker compound of claim 92 wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of:

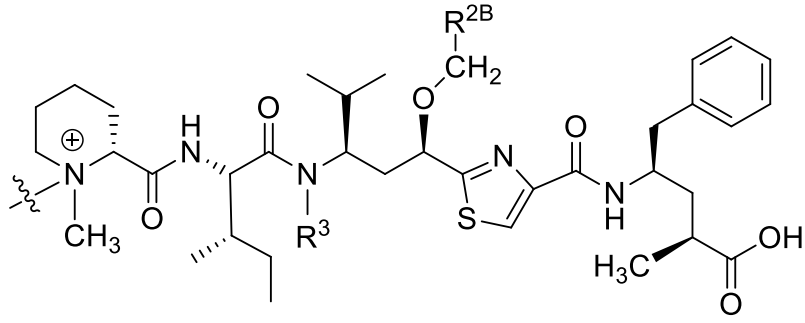


in suitable salt form, wherein

R^{2B} is a methyl, ethyl, propyl or a branched C_3-C_6 alkyl or is methyl, ethyl, propyl, iso-propyl, 3-methyl-prop-1-yl, 3,3-dimethyl-prop-1-yl, or vinyl.

94. The Drug Linker compound of claim 93 wherein R^{2B} is $–CH_3$ and R^3 is $–CH_3$.

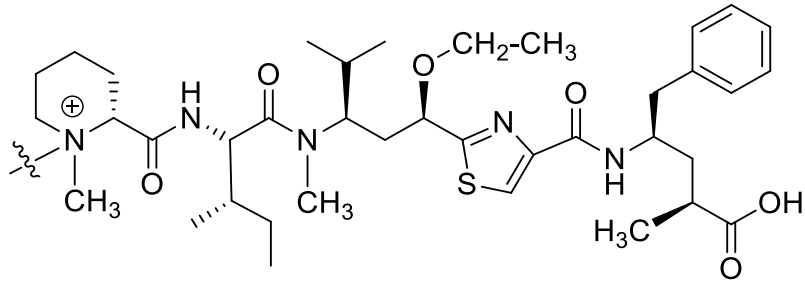
95. The Drug Linker compound of claim 92 wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of:



in suitable salt form, wherein

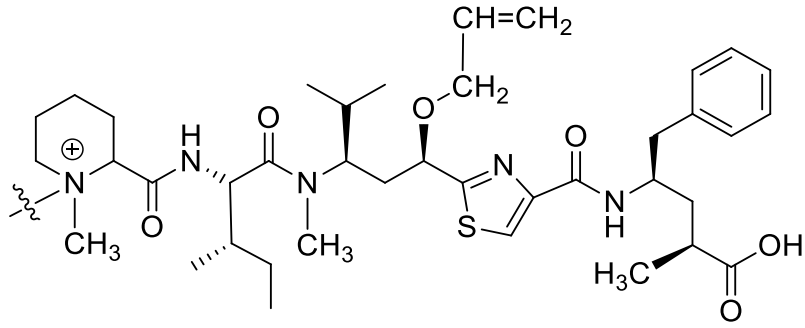
R^{2B} is –H, methyl, ethyl, vinyl or $-C(=CH_2)CH_3$.

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



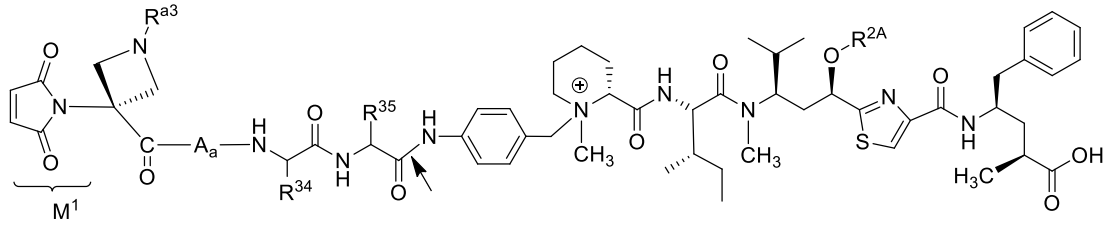
in suitable salt form, or

wherein the quaternized tubulysin Drug Unit $–D^+$ has the structure of:



in suitable salt form.

97. The Drug Linker compound of claim 92 wherein the compound has the structure of:



in suitable salt form, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, C_1-C_4 alkyl, or $-R^{PEG1}-O-(CH_2CH_2O)_{n'}-R^{PEG2}$;

R^{PEG1} is $–CH_2-$, $-CH_2CH_2-$;

R^{PEG2} is –H or $–CH_3$ or $–CH_2CH_3$;

subscript n' ranges from 1 to 36; and

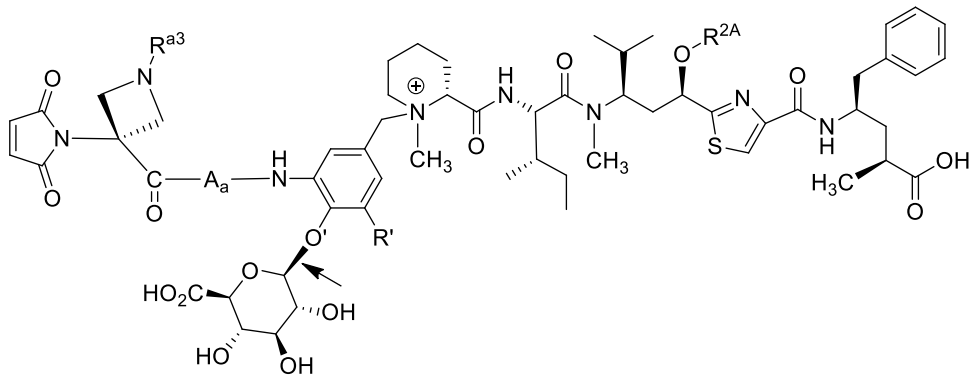
wherein the basic nitrogen bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group;

R^{2A} is $–C(=O)CH_3$, $–CH_2CH_3$, $–CH_2CH=CH_2$ or $–CH_2C(=CH_2)CH_3$; and

R^{34} is isopropyl, and R^{35} is methyl or $-(CH_2)_3NH(C=O)NH_2$,

or

wherein compound has the structure of:



in suitable salt form, wherein

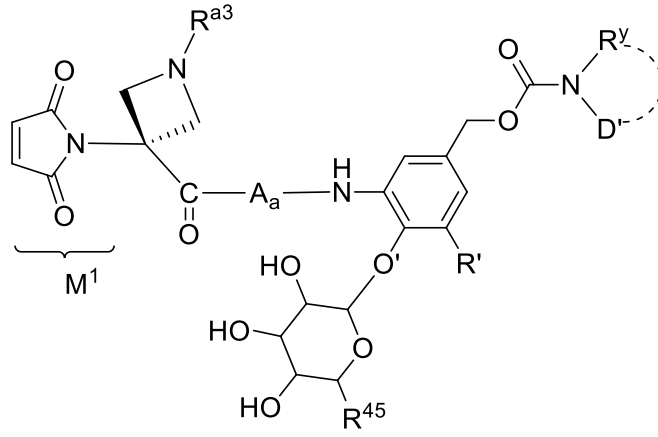
subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, C_1-C_4 alkyl, or $-R^{PEG1}-O-(CH_2CH_2O)_{n'}-R^{PEG2}$, wherein R^{PEG1} is $–CH_2-$ or $-CH_2CH_2-$; R^{PEG2} is –H, $–CH_3$ or $–CH_2CH_3$; and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or

R^{a3} is a suitable nitrogen-protecting group; and

R^{2A} is $–C(=O)CH_3$, $–CH_2CH_3$, $–CH_2CH=CH_2$ or $–CH_2C(=CH_2)CH_3$.

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



,

or a salt thereof, wherein

A, if present, is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated,

or R^{a3} is a suitable nitrogen-protecting group;

R' is hydrogen or $–NO_2$;

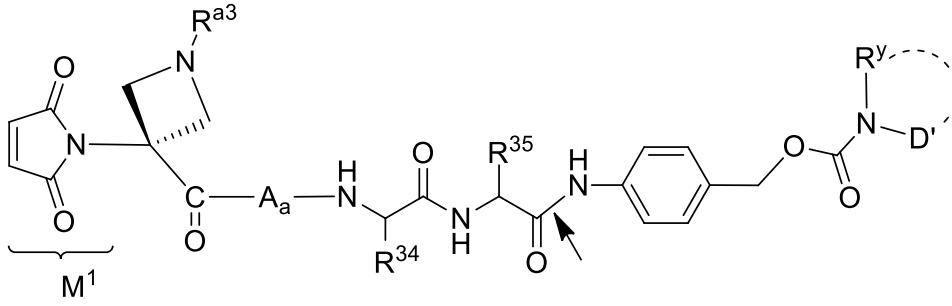
R^{45} is $–CH_2OH$ or $–CO_2H$;

-$N(R^y)$D' represents D, wherein D' is the remainder of D, and wherein the dotted line indicates optional cyclization of R^y to D', wherein R^y is hydrogen or optionally substituted C_1-C_6 alkyl in absence of cyclization to D' or R^y is optionally substituted C_1-C_6 alkylene when cyclized to D';

wherein -O'- represents the oxygen heteroatom of an O-glycosidic bond cleavable by a glycosidase, wherein said cleavage initiates release of D as a primary or secondary amine-containing a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound prepared from the Drug Linker compound,

or

wherein the compound has the structure of:



or a salt thereof, wherein

A, if present, is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, R^{PEG2} is –

H or C_1-C_4 alkyl, and subscript n' ranges from 1 to 36, wherein the basic nitrogen bonded to R^{a3} is optionally protonated, or

R^{a3} is a suitable nitrogen-protecting group;

R^{34} is methyl or isopropyl;

R^{35} is methyl, $–(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=O)NH_2$, -$(CH_2)_3NH(C=NH)NH_2$, or , -$(CH_2)_2CO_2H$;

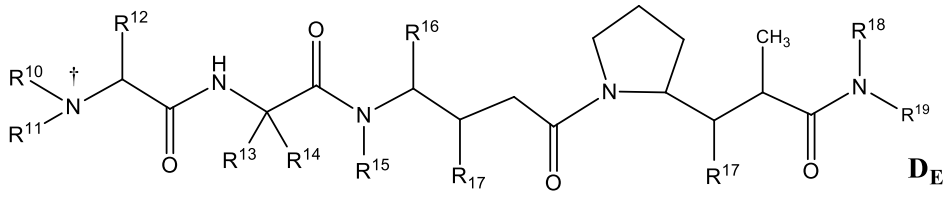
-$N(R^y)$D' represents -D having covalent attachment to the remainder of the composition structure, wherein D' is the remainder of D, and wherein the dotted line indicates optional cyclization of R^y to D', wherein R^y is hydrogen or optionally substituted C_1-C_6 alkyl in absence of cyclization to D', or R^y is optionally substituted C_1-C_6 alkylene when cyclized to D'; and

wherein protease cleavage of the indicated bond initiates release of D as a primary or secondary amine-containing a biologically active compound or derivative thereof from the Drug Linker compound or from a Ligand Drug Conjugate compound prepared from the Drug Linker compound.

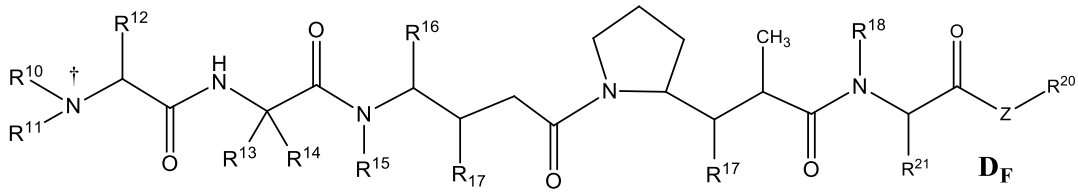
99. The Drug Linker compound of claim 82, wherein the released tertiary amine-containing drug compound from D^+ is an auristatin drug compound thereby defining D^+ as a quaternized auristatin Drug Unit.

100. The Drug Linker compound of claim 98, wherein the released primary or secondary amine-containing biologically active compound or derivative thereof from D, is an auristatin drug compound thereby defining D as an auristatin Drug Unit.

101. The Drug Linker compound of claim 99 or 100, wherein the auristatin drug compound released from –D or -D^+ has the structure of:



$\mathbf{D_E}$



$\mathbf{D_F}$

or a salt thereof or in suitable salt form, wherein

the dagger indicates the site of covalent attachment of the nitrogen atom that provides a carbamate functional group, wherein –OC(=O)- of that functional group is Y', on incorporation of the auristatin drug compound as -D into the Drug Linker in which subscript y is 2, or results in a quaternary amine nitrogen on incorporation of the auristatin drug compound as $-D^+$ into the Drug Linker compound in which subscript y is 1;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen and C_1-C_8 alkyl, provided that one of R^{10}, R^{11} is hydrogen when the auristatin drug compound is incorporated into the as -D and neither of R^{10}, R^{11} is hydrogen when the auristatin drug compound is incorporated as $–D^+$:

R^{12} is hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{24} aryl, -X^1-C_6-C_{24} aryl, -X^1-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl or -X^1-(C_3-C_8 heterocyclyl);

R^{13} is hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{24} aryl, -X^1- C_6-C_{24} aryl, -X^1-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl and -X^1-(C_3-C_8 heterocyclyl);

R^{14} is hydrogen or methyl, or

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

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

R^{16} is hydrogen, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{24} aryl, -C_6-C_{24}-X^1-aryl, -X^1-(C_3-C_8 carbocyclyl), C_3-C_8 heterocyclyl and -X^1-(C_3-C_8 heterocyclyl);

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

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

R^{19} is $–C(R^{19A})_2–C(R^{19A})_2–$ C_6-C_{24} aryl, $–C(R^{19A})_2–C(R^{19A})_2–$($C_3$-$C_8$ heterocyclyl) or $–C(R^{19A})_2–C(R^{19A})_2–$($C_3$-$C_8$ carbocyclyl), wherein C_6-C_{24} aryl and C_3-C_8 heterocyclyl are optionally substituted;

R^{19A} independently are hydrogen, optionally substituted C_1-C_8 alkyl, -OH or optionally substituted –O-C_1-C_8 alkyl;

R^{20} is hydrogen or C_1-C_{20} alkyl, C_6-C_{24} aryl or C_3-C_8 heterocyclyl, optionally substituted, or $-(R^{47}O)_m-R^{48}$, or $-(R^{47}O)_m-CH(R^{49})_2$;

R^{21} is -C_1-C_8 alkylene-(C_6-C_{24} aryl) or -C_1-C_8 alkylene-(C_5-C_{24} heteroaryl), optionally substituted, or C_1-C_8 hydroxylalkyl, or optionally substituted C_3-C_8 heterocyclyl;

Z is O, S, NH, or NR^{46};

R^{46} is optionally substituted C_1-C_8 alkyl;

subscript m is an integer ranging from 1-1000;

R^{47} is C_2-C_8 alkyl;

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

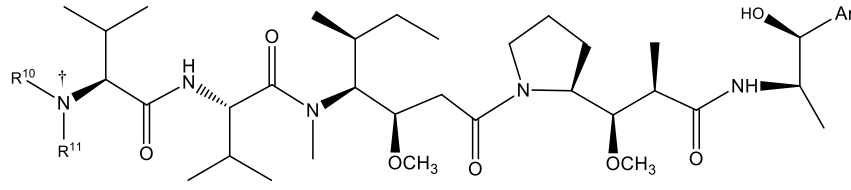
R^{49} independently are -COOH, $–(CH_2)_n-N(R^{50})_2$, $–(CH_2)_n-SO_3H$, or $–(CH_2)_n-SO_3-C_1$-C_8 alkyl;

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

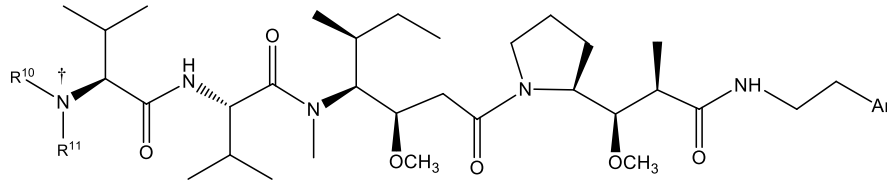
subscript n is an integer ranging from 0 to 6; and

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

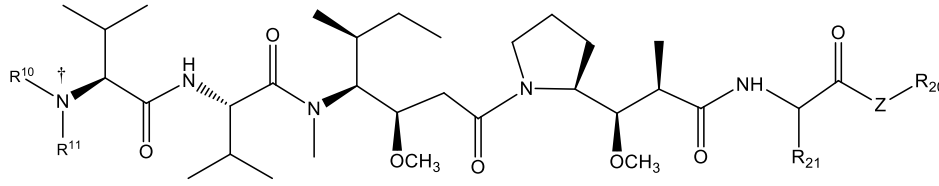
102. The Drug Linker compound of claim 101, wherein the auristatin drug compound has the structure of Formula D_{E-1}, Formula D_{E-2} or Formula D_{F-1}:



D_{E-1}



D_{E-2},



D_{F-1}

or a salt thereof or in suitable salt form, wherein

Ar in Formula D_{E-1} or Formula D_{E-2} is optionally substituted C_6-C_{10} aryl or optionally substituted C_5-C_{10} heteroaryl, and in Formula D_{F-1}, Z is –O-, or –NH-;

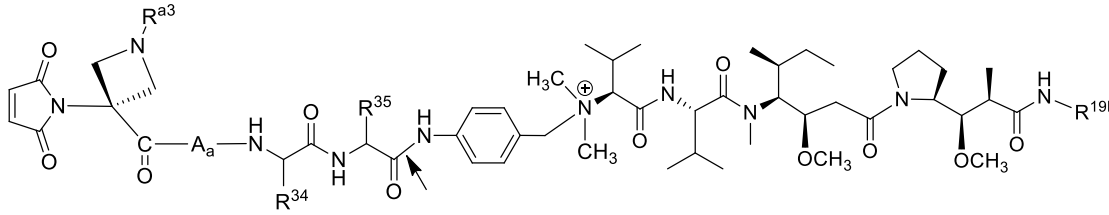
R^{20} is hydrogen, C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl or optionally substituted C_5-C_{10} heteroaryl; and

R^{21} is optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_6 alkylene-(C_6-C_{10} aryl) or optionally substituted -C_1-C_6 alkylene-(C_5-C_{10} heteroaryl).

103. The Drug Linker compound of claim 99 wherein the released auristatin drug compound incorporated as an auristatin quaternized Drug Unit (D^+) is Auristatin E, Auristatin PE, Auristatin PHE, Auristatin PYE, Auristatin EFP, Auristatin EB and Auristatin EVB.

104. The Drug Linker compound of claim 100 wherein the released auristatin drug compound incorporated into –D with covalent attachment through a carbamate functional group is monomethylauristatin E (MMAE) or monomethylauristatin F (MMAF).

105. The Drug Linker compound of claim 99 wherein the compound is represented by the structure of:



in suitable salt form, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkylene;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group;

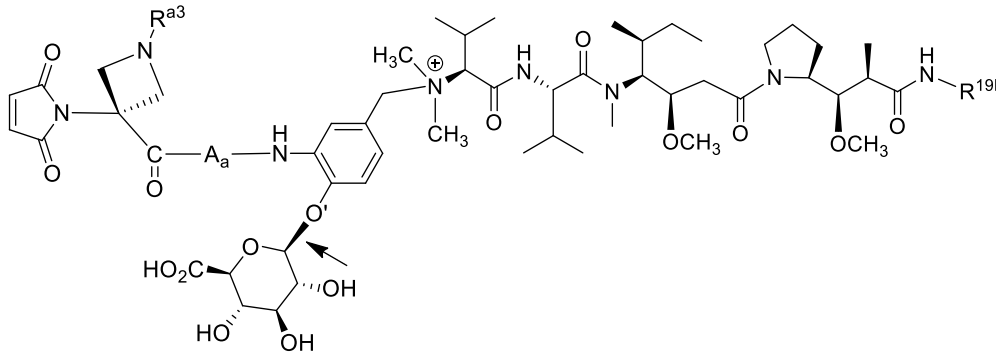
R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph;

R^{34} is isopropyl; and

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

or

wherein the compound has the structure of:



in suitable salt form, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue; and

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

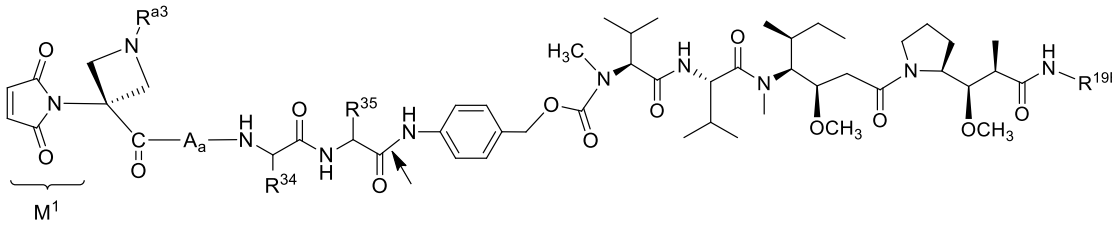
R^{PEG2} is –H or C_1-C_4 alkyl;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or

R^{a3} is a suitable nitrogen protecting group.

106. The Drug Linker compound of claim 100 wherein the compound has the structure of:



or a salt thereof, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

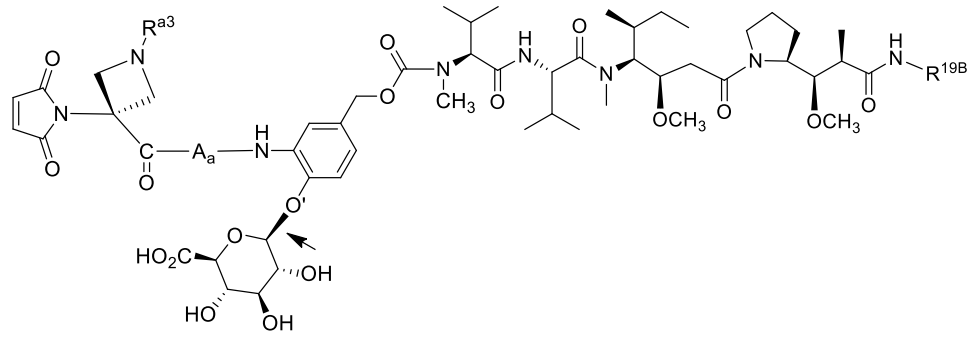
subscript n' ranges from 1 to 36; and wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group;

R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph; and

R^{34} is isopropyl and R^{35} is methyl or -$(CH_2)_3NH(C{=}O)NH_2$,

or

wherein the compound has the structure of:



or a salt thereof, wherein

subscript a is 1, so that A is present, wherein A is an alpha-amino, beta-amino or another amine-containing acid residue;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl; and

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group; and

R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph.

107. The Drug Linker compound of claim 67, wherein

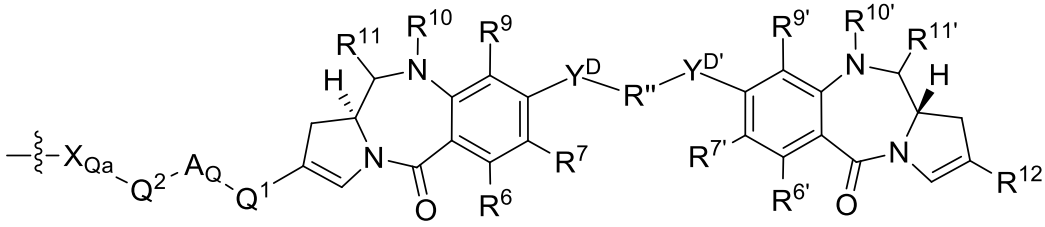
subscript w is 1;

subscript y is 1 or 2, wherein

Y attached to W is a self-immolative Spacer Unit; and

D is that of a PBD compound, thereby defining a PBD Drug Unit.

108. The Drug Linker compound of claim 107 wherein the PBD Drug Unit has the structure of:



or a salt thereof, wherein

the wavy line indicates covalent attachment of the PBD Drug Unit to the remainder of composition structure;

A_Q is a phenylene or C_5-C_7 heteroarylene, optionally substituted;

X_{Qa} is selected from the group consisting of -O-, -S-, -C(=O)O-, -C(=O)-, -NH(C=O)-, and -N(R^N)-, wherein R^N is selected from the group consisting of H, C_1-C_4 alkyl and $(C_2H_4O)_{n'}$-CH_3, wherein subscript n' ranges from 1 to 36, and either:

(i) Q^1 is a single bond, and Q^2 is selected from the group consisting of a single bond and -Z-$(CH_2)_n$-, wherein Z is selected from the group consisting of a single bond, O, S and NH and subscript n ranges from 1 to 3, or

(ii) Q^1 is -CH=CH-, and Q^2 is a single bond;

R^{12} is C_6-C_{10} aryl or C_5-C_{10} heteroaryl;

R^6 and R^9 are independently selected from the group consisting of H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro and halo;

R^7 is selected from the group consisting of H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro and halo;

R and R' are independently selected from the group consisting of optionally substituted C_1-C_{12} alkyl, C_3-C_{20} heterocyclyl, C_6-C_{20} aryl and C_5-C_{20} heteroaryl; and

either:

(a) R^{10} is H, and R^{11} is OH or OR^A, wherein R^A is C_1-C_4 alkyl,

(b) R^{10} and R^{11} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are attached, or

(c) R^{10} is H and R^{11} is SO_zM, where subscript z is 2 or 3 and M is a monovalent cation;

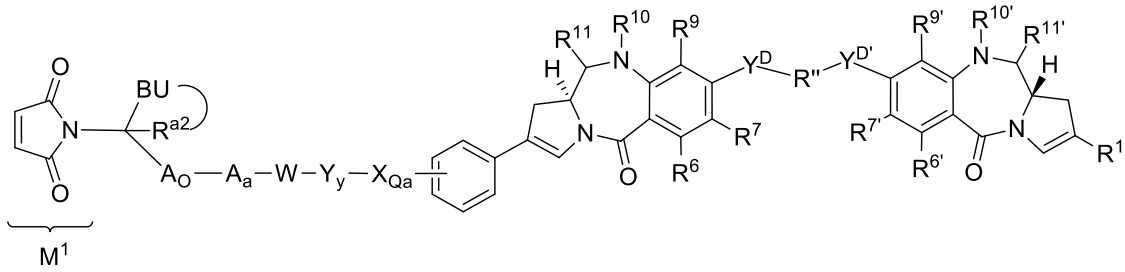
R″ is C_3-C_{12} alkylene, the carbon chain of which is optionally interrupted by one, two or three heteroatoms selected from the group consisting of O, S and NH, and/or by an aromatic ring;

Y^D is selected from the group consisting of O, S and NH;

$R^{6'}$, $R^{7'}$, $R^{9'}$, and $Y^{D'}$ are independently selected from the same groups as R^6, R^7, R^9, and Y^D, respectively, and $R^{10'}$ and $R^{11'}$ are selected independently from the same groups as R^{10} and R^{11}, respectively, provided if R^{11} and $R^{11'}$ are each SO_zM, each M is an independently selected monovalent cation or together represents a divalent cation; and

wherein optional substitution is by one, two or three substituents independently selected from the group consisting of halo, nitro, cyano, -OR, C_1-C_7 alkyl, C_3-C_7 heterocyclyl, dimethyl-aminopropyloxy, piperazinyl and bis-oxy-C_1-C_3 alkylene, wherein R is as previously defined.

109. The Drug Linker compound of claim 108, wherein the compound is represented by the structure of:



or a salt thereof, wherein

A, if present, is an alpha-amino, beta-amino or another amine-containing acid residue;

W is a Peptide Cleavable Unit; and

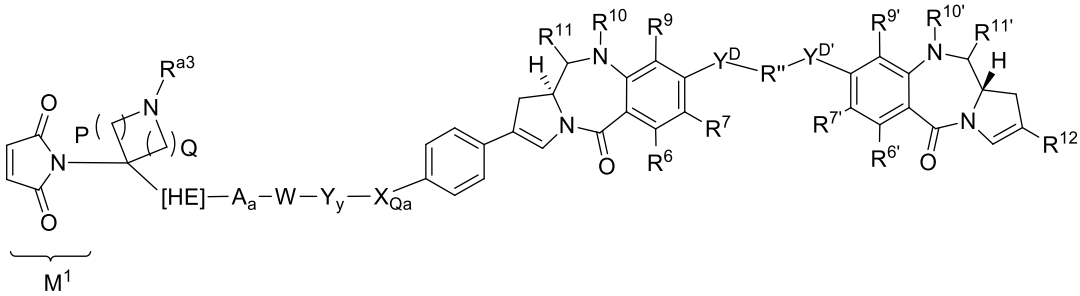
subscript y is 1 or 2, wherein Y bonded to W is a self-immolative Spacer Unit,

wherein the bond between W and that self-immolative Spacer Unit in the Drug Linker compound or a Ligand Drug Conjugate compound prepared from the Drug Linker compound is cleavable by a protease to initiate release of the PBD Drug Unit as a PBD dimer from that Drug Linker compound or Ligand Drug Conjugate compound, or

subscript y is 0, so that W is bonded to X_{QA},

wherein the bond between W and X_{QA} in the Drug Linker compound or a Ligand Drug Conjugate compound prepared from the Drug Linker compound is cleavable by a protease to initiate release of the PBD Drug Unit as a PBD dimer from that Drug Linker compound or Ligand Drug Conjugate compound.

110. The Drug Linker compound of claim 99 wherein the compound has the structure of:



or a salt thereof, wherein

subscript Q ranges from 1 to 6;

X_{Qa} is –NH-; and

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl) or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkyl;

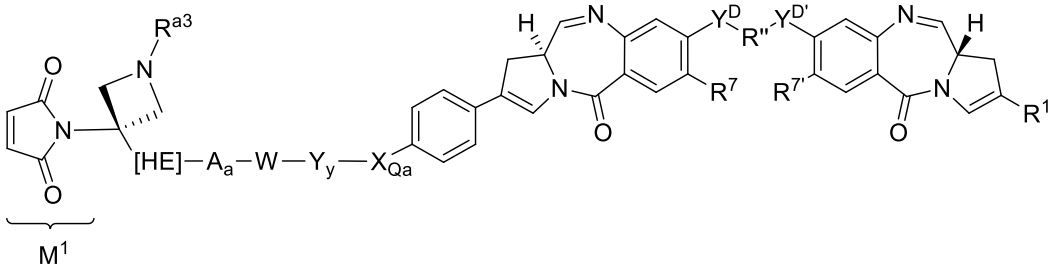
subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group.

111. The Drug Linker compound of claim 110, wherein subscript P is 1 and subscript Q is 1, 2 or 3 or subscript P is 2 and Q is 1 or 2.

112. The Drug Linker compound of claim 111, wherein subscript P is 1, subscript Q is 1.

113. The Drug Linker compound of claim 112, wherein the compound has the structure of:



or a salt thereof, wherein

X_{Qa} is –NH-;

R^{a3} is –H, C_1-C_4 alkyl or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

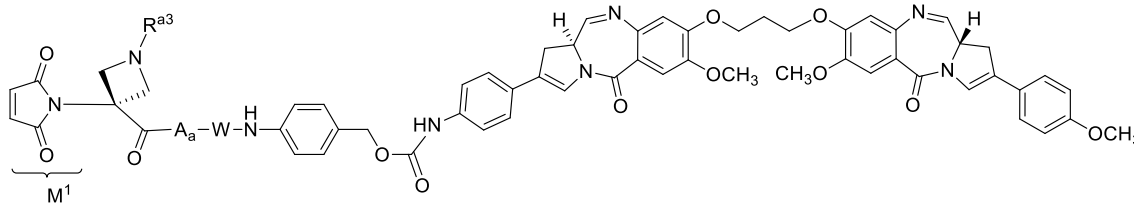
R^{PEG1} is –CH_2- or –CH_2CH_2-;

R^{PEG2} is –H, CH_3 or -CH_2CH_3;

subscript n' ranges from 1 to 36; and

wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or R^{a3} is a suitable nitrogen-protecting group.

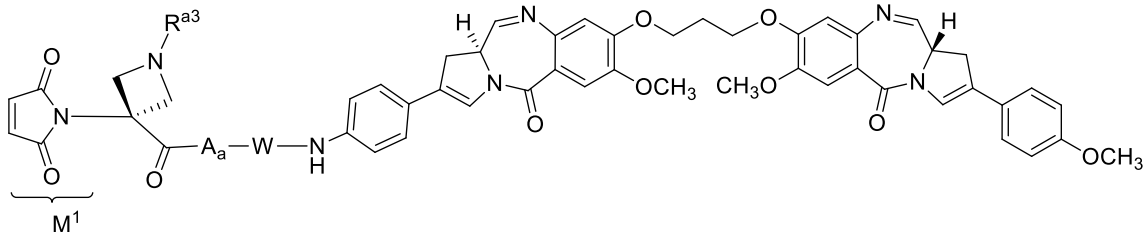
114. The Drug Linker compound of claim 113, wherein the compound has the structure of:



or a salt thereof, wherein

R^{a3} is –H, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated, or

wherein the compound has the structure of:



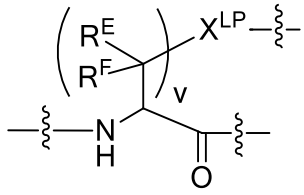
.

or a salt thereof, wherein

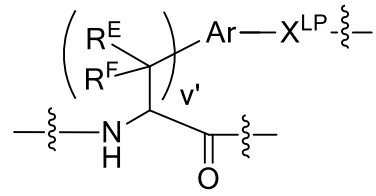
R^{a3} is –H, wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated,

115. The Drug Linker compound of claim 67, wherein if D, or D as D^+, is that of a biologically active compound or derivative thereof, wherein that compound or its derivative is hydrophobic or has a SlogP < 0, then A or a subunit thereof is $–L^P(PEG)-$, wherein L^P is a single unit or has 1, 2, 3 or 4 subunits;

wherein $–L^P-$ or a subunit thereof has the structure of Formula L^P-1 or L^P-2:



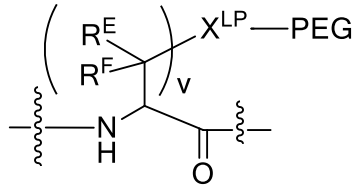
(Formula L^P-1)



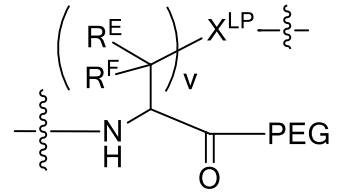
(Formula L^P-2),

or

wherein $–L^P(PEG)-$ or a PEG-containing subunit thereof has the structure of Formula L^P-3 or Formula L^P-4:



(Formula L^P-3)



(Formula L^P-4),

wherein subscript v is an integer ranging from 1 to 4;

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

X^{LP} is provided by a natural or un-natural amino acid side chain or 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 $-N(R^{LP})C(=NR^{LP})N(R^{LP})-$, or heterocyclo;

wherein each R^{LP} is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6 alkyl or two of R^{LP} together along with their intervening atoms define a C_5-C_6 heterocyclo and any remaining R^{LP} are as previously defined;

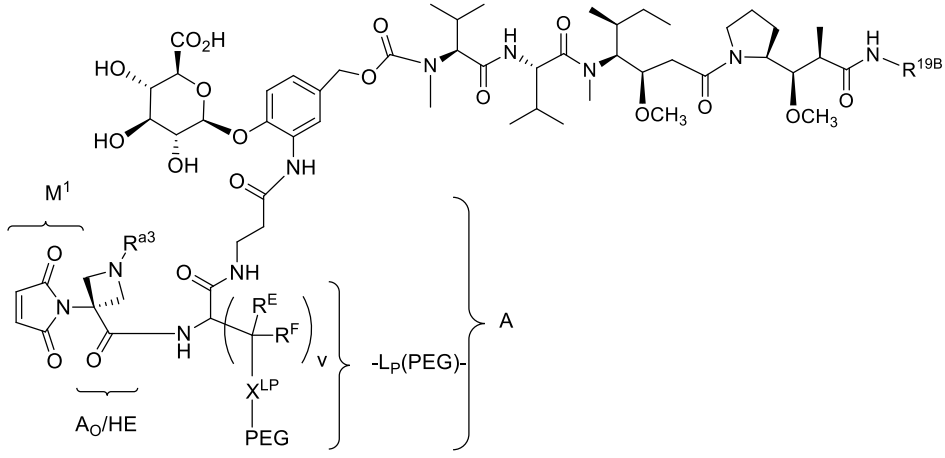
Ar is a C_6-C_{10} arylene or a C_5-C_{10} heteroarylene, optionally substituted;

each R^E and R^F is independently selected from the group consisting of -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkylene, optionally substituted C_6-C_{10} arylene or optionally substituted C_5-C_{10} heteroarylene,

or R^E and R^F together with the carbon atom to which both are attached defines an optionally substituted C_3-C_6 carbocyclo, or R^E and R^F from adjacent carbon atoms together with these atoms and any intervening carbon atoms defines an optionally substituted C_5-C_6 carbocyclo with any remaining R^E and R^F as previously defined;

wherein one of the wavy lines indicate the point of covalent attachment of a PEG Unit and the other two wavy lines indicates covalent attachment of Formula L^P-1 or Formula L^P-2 within the structure representing the Drug Linker compound.

116. The Drug Linker compound of claim 115 wherein the compound has the structure of:

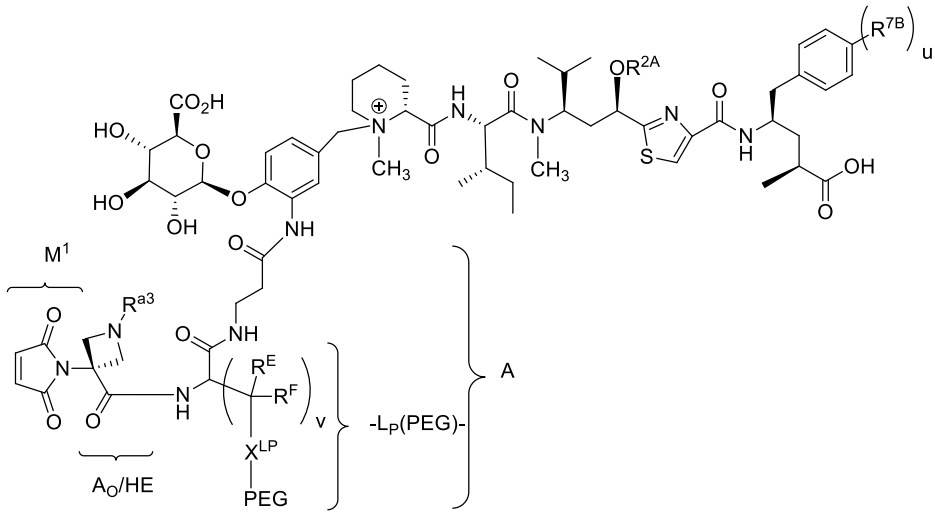


or a salt thereof, wherein

R^{a3} is –H, optionally substituted C_1-C_6 alkyl or optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), wherein the basic nitrogen bonded to R^{a3} is optionally protonated;

R^{19B} is –$CH(CH_3)$-CH(OH)-Ph, –$CH(CO_2H)$-CH(OH)-CH_3, or –$CH(CO_2H)$-CH_2Ph, or

wherein the compound has the structure of:



or a salt thereof, wherein

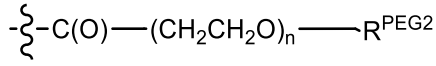
R^{2A} is $–C(=O)CH_3$, $–CH_2CH_3$, $–CH_2CH=CH_2$ or $–CH_2C(=CH_2)CH_3$;

R^{a3} is –H, optionally substituted C_1-C_6 alkyl or optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated;

subscript u is 0 or 1; and

R^{7B} is –OH when subscript u is 1 or is absent when subscript u is 0.

117. The Drug Linker compound of claim 116 wherein $–X^{LP}$-PEG has the structure of:

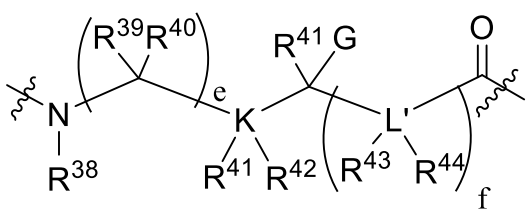


wherein R^{PEG2} is a PEG Capping Unit; and

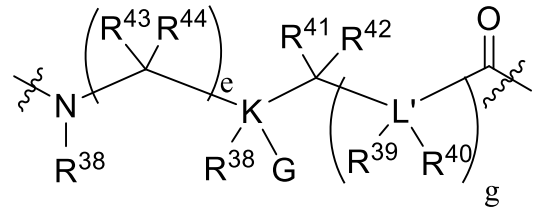
subscript n ranges from 2 to 72.

118. The Drug Linker compound of claim 117 wherein subscript n is 12 and R^{PEG2} is hydrogen or $–CH_3$.

119. The Drug Linker compound of claim 67 wherein Aor a subunit thereof has the structure of formula (3), formula (4), or formula (5):

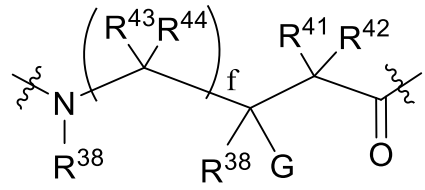


(3)



(4)

,



(5)

or a salt thereof, wherein

the wavy lines indicated covalent attachment within the composition 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, or

G is -$N(R^{PR})(R^{PR})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is -$N(R^{45})(R^{46})$, 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} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{24} aryl, and optionally substituted C_5-C_{24} heteroaryl, or

each L' in formula 4 is C, and in formula 3 or formula 4 R^{39}, R^{40} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo and R^{41}-R^{44} are as defined herein,

or K in formula 3 is C, and in formula 3 or formula 4 R^{41}, R^{42} together with K to which both are attached define a C_3-C_6 carbocyclo, and R^{39}, R^{40}, R^{43} and R^{44} are as defined herein,

or each L' in formula 3 is C, and in formula 3 or formula 4 R^{43}, R^{44} together with the carbon atom to which both are attached define a C_3-C_6 cycloalkyl, and R^{39}-R^{42} are as defined herein,

or R^{40} and R^{41} together with the carbon atom(s) and/or heteroatom(s) to which they are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39} and R^{42}-R^{44} are as defined herein,

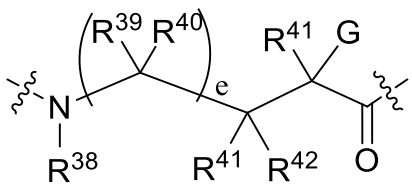
or R^{40} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{41}, R^{42}, and R^{44} are as defined herein,

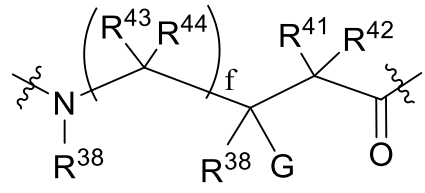
or R^{41} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{40}, R^{42} and R^{44} and the remainder of R^{40}-R^{43} are as defined herein,

or

A has a structure of an alpha-amino, beta-amino or another amine-containing acid residue.

120. The Drug Linker compound of claim 119, wherein A or a subunit thereof has the structure of formula (3a) or formula (5):



(3a),


(5),

or a salt thereof, wherein

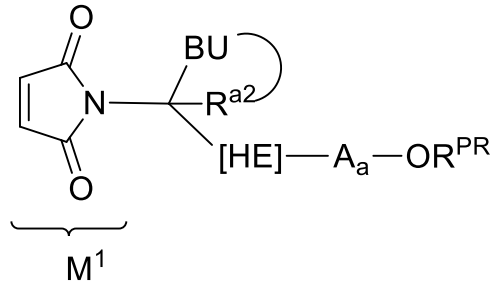
subscript e and f are independently 0 or 1,

or

A has a structure of an alpha-amino or beta-amino residue.

121. A method of preparing a Ligand Drug Conjugate composition comprising the step of contacting a Drug Linker compound of claim 67 with a targeting agent having a reactive thiol functional group under conditions suitable for effecting Michael addition of the thiol to the indicated maleimide (M^1) moiety of the Drug Linker compound for incorporation of the targeting agent as a Ligand Unit in a Ligand Drug Conjugate compound of the composition.

122. A compound having the structure of:



or a salt thereof, wherein

HE is –C(=O)-;

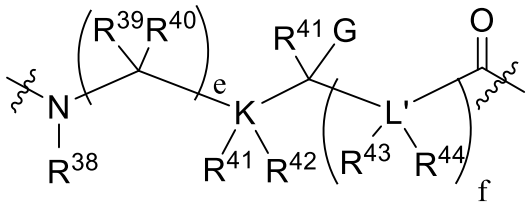
R^{PR} is H or a suitable carboxylic acid protecting group;

BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl group that together with the carbon atom to which both are attached, as represented by the curved line, define an optionally substituted C_3-C_{20} heterocyclo having a skeletal secondary or

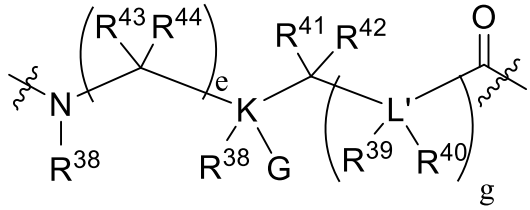
tertiary basic nitrogen atom or a C_3-C_{20} carbocyclo having exocyclic substitution by a basic nitrogen atom of a primary, secondary or tertiary amine functional group or an optionally substituted basic C_1-C_{12} aminoalkyl, wherein the basic nitrogen atom of the amine or aminoalkyl is attributable to BU, and is optionally protonated or protected by a suitable nitrogen-protecting group.

subscript a is 0 or 1;

A is absent when subscript a is 0, or when subscript a is 1 A has the structure of formula (3), formula (4), or formula (5):

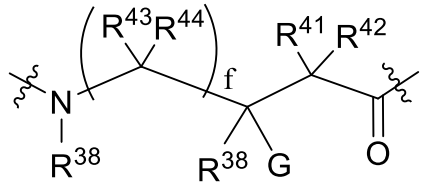


(3)



(4)

,



(5)

wherein the wavy lines indicate covalent attachment within the 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, or

G is -N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is -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} are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and optionally substituted heteroaryl, or

each L' in formula 4 is C, and in formula 3 or formula 4 R^{39}, R^{40} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{41}-R^{44} are as defined herein

or K in formula 3 is C, and in formula 3 or formula 4 R^{41}, R^{42} together with the carbon atom to which both are attached define a C_3-C_6 carbocyclo, and R^{39}, R^{40}, R^{43} and $R^{44}$are as defined herein,

or L' in formula 3 is C, and in formula 3 or formula 4 R^{43}, R^{44} together with the carbon atom to which both are attached define a C_3-C_6 cycloalkyl, and R^{39}-R^{42} are as defined herein,

or R^{40} and R^{41} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39} and R^{42}-R^{44} as defined herein,

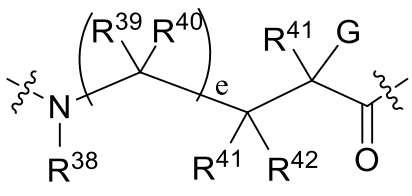
or R^{40} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{41}, R^{42}, and R^{44} are as defined herein,

or R^{41} and R^{43} together with the carbon atom(s) or heteroatom(s) to which both are attached and the atoms intervening between those carbon atom(s) and/or heteroatom(s) define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{40}, R^{42} and R^{44} and the remainder of R^{40}-R^{43} are as defined herein,

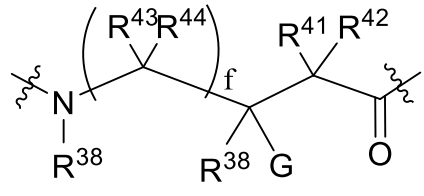
or

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

123. The compound of claim 122 wherein A or a subunit thereof has the structure of formula (3a) or formula (5):



(3a),



(5),

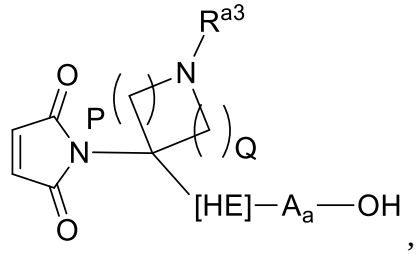
wherein subscript e and f are independently 0 or 1,

or

A is an alpha-amino or beta-amino acid residue.

124. The compound of claim 122 wherein BU and R^{a2} together with the carbon atom to which both are attached, define an optionally substituted C_4-C_6 heterocyclo having a skeletal secondary or tertiary basic nitrogen atom, wherein the basic nitrogen atom is attributable to BU and is optionally protonated or protected by a suitable nitrogen-protecting group.

125. The compound of claim 122, wherein the compound has the structure of:



,

or a salt thereof**,** wherein

subscript P is 1 or 2;

subscript Q ranges from 1 to 6; and

R^{a3} is –H, optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), an acid-labile nitrogen protecting group, or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

R^{PEG1} is C_1-C_4 alkylene;

R^{PEG2} is –H or C_1-C_4 alkylene;

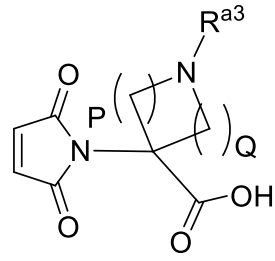
subscript n' ranges from 1 to 36; and

wherein the basic nitrogen bonded to R^{a3} is further optionally protonated, except when R^{a3} is an acid-labile nitrogen protecting group.

126. The compound of claim 125, wherein subscript P is 1 and subscript Q is 1, 2 or 3 or subscript P is 2 and Q is 1 or 2.

127. The compound of claim 126, wherein subscript P is 1, subscript Q is 1.

128. The compound of claim 122, wherein the compound has the structure of:



or a salt thereof,

wherein subscript P is 1 or 2 and subscript Q is 1 or 2; and

R^{a3} is H, C_1-C_4 alkyl, -CH_2Ph, -CH_2CH_2Ph or -R^{PEG1}-O-$(CH_2CH_2O)_{n'}$-R^{PEG2};

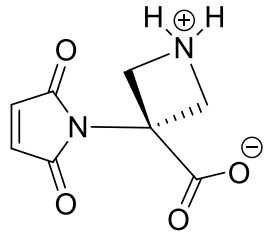
R^{PEG1} is –CH_2- or –CH_2CH_2-;

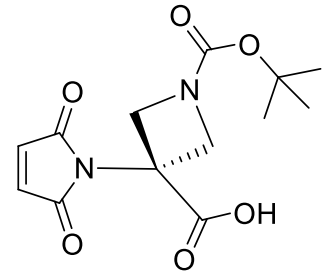
R^{PEG2} is –H, -CH_3 or –CH_2CH_3;

subscript n' ranges from 1 to 36; and

wherein phenyl is optionally substituted and the basic nitrogen bonded to R^{a3} is optionally protonated, or R^{a3} is –C(=O)-t-Bu (BOC).

129. The compound of 128 wherein the compound has the structure of:



or


.

130. Use of a Ligand Drug Conjugate composition of claim 1 in the manufacture of a medicament for inhibiting the multiplication of an *in vitro* tumor cell or cancer cell, or causing apoptosis in an *in vitro* tumor or cancer cell.