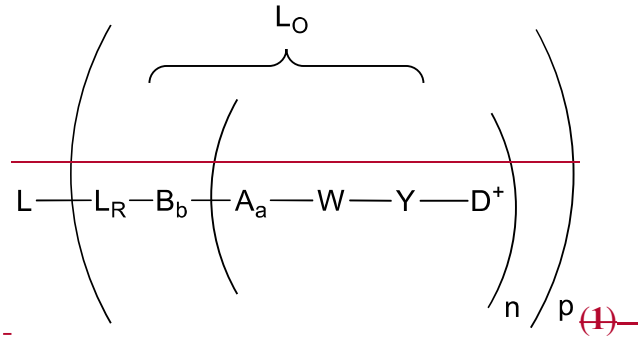
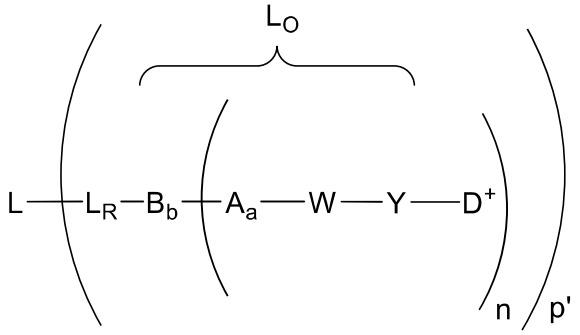
SUMMARY

[0005a] In one aspect, the present disclosure refers to a Ligand Drug Conjugate ~~composition~~ compound represented by Formula 1:



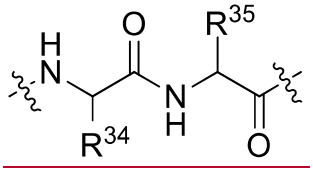
~~(1)~~



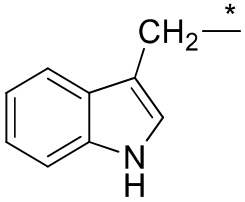
in salt form, particularly in pharmaceutically acceptable salt form, wherein

L is a Ligand Unit that is an antibody or an antigen binding fragment thereof;

W is from 1-12 independently selected amino acids and comprises a dipeptide having 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 site of covalent attachment to the dipeptide backbone; and

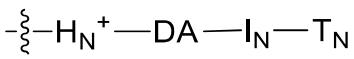
R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3NH(C=O)NH_2$, -$(CH_2)_3NH(C=NH)NH_2$, or -$(CH_2)_2CO_2H$; and

wherein the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to Y and the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment of the dipeptide to the remainder of the peptide sequence, or

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

Y is a self-immolative Spacer Unit comprising ~~comprised of~~ a PAB or PAB-type moiety;

D^+ is represented by the general structure of:

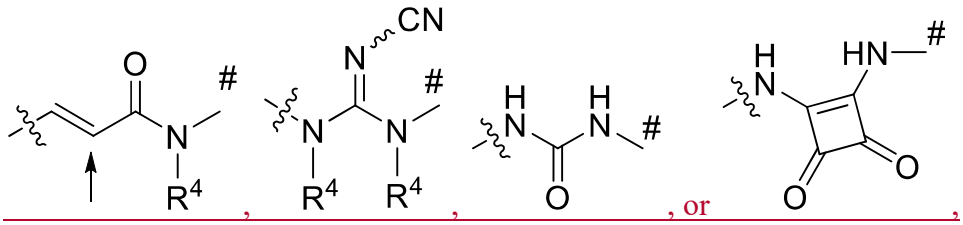


wherein:

H_N^+ is an optionally substituted C_5-C_{24} heteroaryl or partially unsaturated or partially aromatic optionally substituted C_9-C_{24} heterocyclyl comprising a 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system, a skeletal nitrogen atom of which is the site of quaternization to L_O, as indicated by the wavy line to H_N^+;

DA is a hydrogen bond donor or acceptor functional group that is ~~optionally cyclized with HN+~~ bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing partially unsaturated or heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system, with optional formal cyclization of DA back to an adjacent skeletal carbon atom of the 6-membered nitrogen-containing ring system through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted nitrogen, oxygen or sulfur atom resulting in a partially unsaturated, partially aromatic or fully aromatic 6,5- or 6,6-fused ring system, wherein said bonding of DA is in relation to a skeletal nitrogen atom of the 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system and wherein said formal cyclization to the adjacent carbon atom of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system substantially retains the hydrogen bonding ability of the donor or acceptor functional group of DA in absence of said cyclization;

wherein DA has the structure of:



or a salt thereof, wherein each R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

wherein said optional cyclization is to the indicated sp^2 carbon atom proximal to the carbonyl carbon through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom;

the wavy line indicates the site of covalent attachment to H_N^+; and

the pound sign (#) indicates the site of covalent attachment to I_N;

I_N is -X^1-$[C(=O)]_{0,1}$-, –X^1-$S(=O)_{1,2}$-, –X^2-C_6-C_{24} arylene-$[C(=O)]_{0,1}$-, –X^2-C_6-C_{24} arylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_6-C_{24} arylene-O-, -X^2-C_5-C_{24} heteroarylene-$[C(=O)_{0,1}]$-, –X^2-C_5-C_{24} heteroarylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_5-C_{24} heteroarylene-O- or -X^2-C_3-C_{20} heterocyclo-$[C(=O)_{0,1}]$-, wherein the arylene, heteroarylene and heterocyclo are optionally substituted;

X^1 is an optionally substituted C_5-C_7 alkylene;

X^2 is absent or is an optionally substituted C_1-C_4 alkylene;

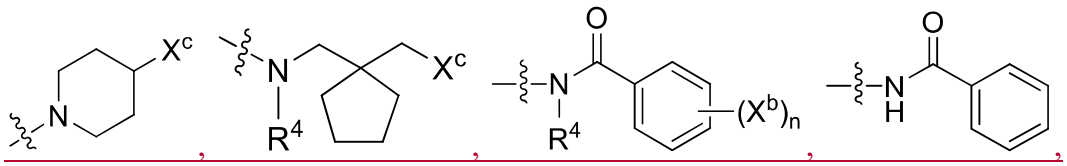
T_N is an optionally substituted amino-alcohol residue or a carboxylic acid-alcohol residue, the amino nitrogen or carbonyl carbon of which is bonded to I_N, or

T_N is an optionally substituted benzamide moiety, the amide nitrogen atom of which is bonded to I_N with optional cyclization of that atom back to I_N or to the remainder of T_N, or

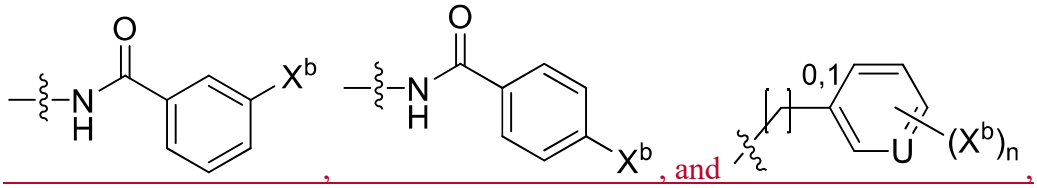
T_N is an optionally substituted C_6-C_{24} aryl, C_5-C_{24} heteroaryl or a combination thereof independently selected in the form of a biaryl, an aromatic atom of which is bonded to I_N or the remainder of T_N; and

wherein T_N or the remainder thereof is bond to I_N, wherein said remainder is an optionally substituted C_2-C_7 heteroalkylene or an optionally substituted C_5-C_6 heterocyclo; or

T_N is selected from the group consisting of:



,



, and ,

wherein X^b is $–NH_2$, –OH, halogen, or optionally substituted C_1-C_4 alkoxy or C_1-C_4 alkyl, X^C is hydrogen, halogen, -OH or C_1-C_4 alkoxy; R^4 is hydrogen or optionally substituted C_1-C_4 alkyl, subscript n is 0, 1 or 2, the phenyl optionally substituted by X^b is optionally fused to a 5- or 6-mebered heterocyclic or heteroaromatic ring system, U is $=C(R^{24})$- or =N-, R^{24} is hydrogen or X^b, and the wavy line indicates the site of covalent attachment to I_N or the remainder of T_N that is bonded to I_N, and the amide nitrogen atom of the benzamide moiety is the site of formal optional cyclization of T_N to I_N or the remainder of T_N that is bonded to I_N so that R^4 attached to that nitrogen atom is replaced by a bond;

wherein enzymatic action on W/W' of a drug linker moiety of a Ligand Drug Conjugate compound initiates release of the quaternized NAMPT Drug (D^+) Unit as a NAMPTi compound of formula H_N-D_A-I_N-T_N, wherein H_N is a NAMPT Head Unit that is a fully aromatic C_5-C_{24} or C_9-C_{24} heteroaryl, optionally substituted, comprising a 5- or 6-membered nitrogen-containing heteroaromatic ring system having the previously

quaternized skeletal nitrogen atom, and the other variable groups are as previously defined;

wherein H_N- or H_N-DA- of the NAMPTi compound is capable of interacting with enzymatically competent NAMPT homodimer at its nicotinamide binding site;

~~wherein the Ligand Drug Conjugate compound is represented by Formula 1 in which subscript p is replaced by subscript p';~~

L_R is a primary linker that interconnects the Ligand Unit and Drug Unit through L_O, wherein L_O is an optional secondary linker that is present;

subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B;

subscript n is 1, 2, 3 or 4;

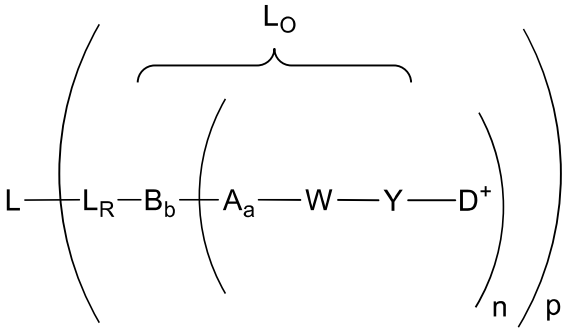
A is a first optional Stretcher;

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

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

~~subscript p is a number ranging from 1 to 24 and~~ subscript p' is an integer ranging from 1 to 24.

[0006] In one example, the disclosure refers to a Ligand Drug Conjugate compositions represented by Formula 1:



(Formula 1)

[0007] or a salt thereof, preferably a pharmaceutically acceptable salt thereof, wherein L is a Ligand Unit; W is a Peptide Cleavable Unit and Y is a self-immolative Spacer Unit comprised of a PAB or PAB-type moiety, or W-Y is replaced by a Glucuronide Unit of formula –Y(W'), wherein W' represents a carbohydrate moiety with glycosidic bonding to Y through an optionally substituted heteroatom, wherein Y is as previously defined; D^+ is a quaternized NAMPT Drug Unit covalently attached to the remainder of the Formula 1 composition structure through a quaternized skeletal aromatic nitrogen atom of an optionally substituted C_5-C_{24} heteroaryl, or a quaternized skeletal non-aromatic nitrogen atom of a partially unsaturated or partially aromatic optionally substituted C_9-C_{24} heterocyclyl,

[0008] wherein non-enzymatic or enzymatic action on W/W' of a drug linker moiety of a Ligand Drug Conjugate compound of the composition initiates release of the quaternized NAMPT Drug (D^+) Unit as a NAMPTi compound comprised of an optionally substituted C_5-C_{24} or C_9-C_{24} heteroaryl having a skeletal non-quaternized aromatic nitrogen atom corresponding to the previously quaternized skeletal nitrogen atom; and wherein the Ligand Drug Conjugate compound is represented by Formula 1 in which subscript p is replaced by p';

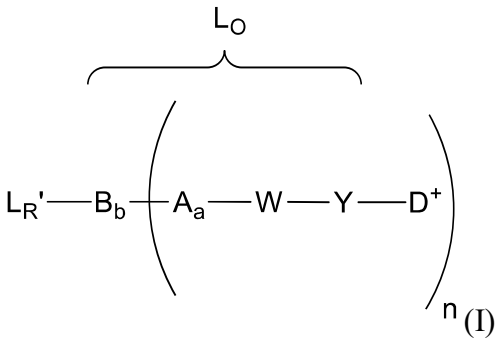
[0009] L_R in the Ligand Drug Conjugate is a primary linker that interconnects the Ligand Unit and quaternized Drug Unit through L_O, wherein L_O is an optional secondary linker that is present; subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B; subscript n is 1, 2, 3 or 4; A is an first optional Stretcher; B is a Branching Unit that is present, when subscript b is 1 and subscript n is 2, 3 or 4, or B is absent so that subscript b is 0, when subscript n is 1, wherein each of A and B is an independently selected single unit or is optionally comprised or consists of two, three or four independently selected subunits; and subscript p is a number ranging from 1 to 24 and subscript p' is an integer ranging from 1 to 24.

[0009a] In another aspect, the present disclosure refers to a formulation comprising a Ligand Drug Conjugate compound~~composition~~ as described herein, and one, two, three or more excipients, in particular, wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof, in particular, wherein the pharmaceutically acceptable formulation is a liquid formulated for intravenous injection and the pharmaceutically acceptable formulation precursor is a solid formulated for reconstitution as a solution for intravenous injection.

[0009b] In another aspect, the present disclosure refers to the use of a Ligand Drug Conjugate compound~~composition~~ as described herein, and one, two, three or more excipients, in the manufacture of a pharmaceutical formulation for treating a hyperproliferative disease or condition, in particular, wherein the hyperproliferative disease or condition is a cancer, more particularly, wherein the cancer is a leukemia or lymphoma, wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof, in particular, wherein the pharmaceutically acceptable formulation is a liquid suitable for intravenous injection to a subject and the pharmaceutically acceptable formulation precursor is a solid suitable for reconstitution as a solution for intravenous injection to a subject, and wherein the Ligand Drug Conjugate compound~~composition~~ is present in the formulation in an effective amount.

[0009c] In yet another aspect, the present disclosure refers to the use of an effective amount of a Ligand Drug Conjugate as described herein in the manufacture of a medicament for inhibiting the multiplication of a tumor cell or cancer cell *in vivo*, or causing apoptosis in a tumor or cancer cell *in vivo*, comprising that said cell is exposed with the Ligand Drug Conjugate.

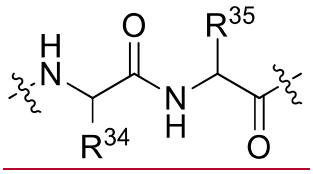
[0009d] In yet another aspect, the present disclosure refers to a Drug Linker Compound represented by Formula I:

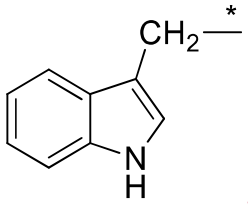


in salt form, particularly in pharmaceutically acceptable salt form, wherein

L_O, as indicated, is an optional linker that is present;

W is from 1-12 independently selected amino acids and comprises a dipeptide having 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 site of covalent attachment to the dipeptide backbone; and

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

wherein the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to Y and the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment of the dipeptide to the remainder of the peptide sequence, or

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

Y is a self-immolative Spacer Unit comprising ~~comprised of~~ a PAB or PAB-type moiety;

D^+ is

represented by the general structure of:



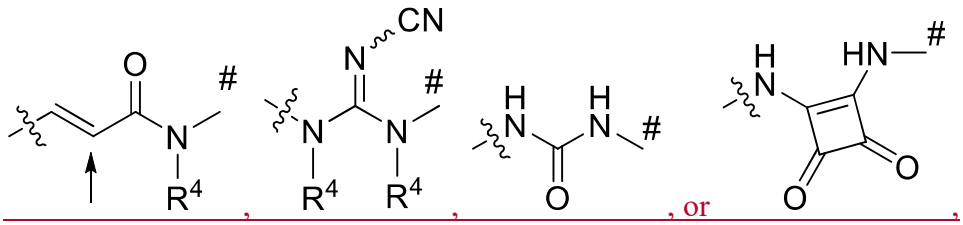
wherein:

H_N^+ is an optionally substituted C_5-C_{24} heteroaryl or partially unsaturated or partially aromatic optionally substituted C_9-C_{24} heterocyclyl comprising a 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system, a skeletal nitrogen atom of which is the site of quaternization to L_O, as indicated by the wavy line to H_N^+;

DA is a hydrogen bond donor or acceptor functional group that is ~~optionally cyclized with HN+~~bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing partially unsaturated or heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system, with optional formal cyclization of DA back to an adjacent skeletal carbon atom of the 6-membered nitrogen-containing ring system through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted nitrogen, oxygen or sulfur atom resulting in a partially unsaturated, partially aromatic or fully aromatic 6,5- or 6,6-fused

ring system, wherein said bonding of DA is in relation to a skeletal nitrogen atom of the 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system and wherein said formal cyclization to the adjacent carbon atom of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system substantially retains the hydrogen bonding ability of the donor or acceptor functional group of DA in absence of said cyclization;

wherein DA has the structure of:



, or , or salt thereof, wherein each R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

wherein said optional cyclization is to the indicated sp^2 carbon atom proximal to the carbonyl carbon through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom;

the wavy line indicates the site of covalent attachment to H_N^+; and

the pound sign (#) indicates the site of covalent attachment to I_N;

I_N is -X^1-$[C(=O)]_{0,1}$-, –X^1-$S(=O)_{1,2}$-, –X^2-C_6-C_{24} arylene-$[C(=O)]_{0,1}$-, –X^2-C_6-C_{24} arylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_6-C_{24} arylene-O-, -X^2-C_5-C_{24} heteroarylene-$[C(=O)_{0,1}]$-, –X^2-C_5-C_{24} heteroarylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_5-C_{24} heteroarylene-O- or -X^2-C_3-C_{20} heterocyclo-$[C(=O)_{0,1}]$-, wherein the arylene, heteroarylene and heterocyclo are optionally substituted;

X^1 is an optionally substituted C_5-C_7 alkylene;

X^2 is absent or is an optionally substituted C_1-C_4 alkylene;

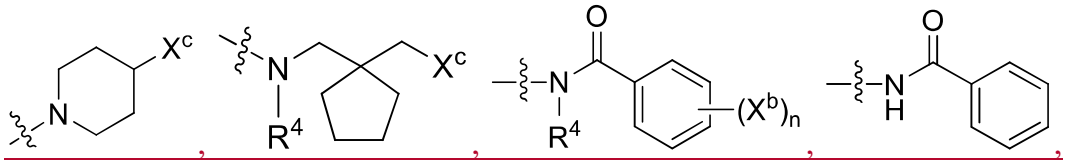
T_N is an optionally substituted amino-alcohol residue or a carboxylic acid-alcohol residue, the amino nitrogen or carbonyl carbon of which is bonded to I_N, or

T_N is an optionally substituted benzamide moiety, the amide nitrogen atom of which is bonded to I_N with optional cyclization of that atom back to I_N or to the remainder of T_N, or

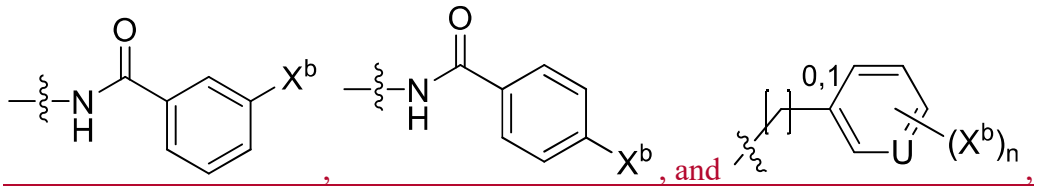
T_N is an optionally substituted C_6-C_{24} aryl, C_5-C_{24} heteroaryl or a combination thereof independently selected in the form of a biaryl, an aromatic atom of which is bonded to I_N or the remainder of T_N; and

wherein T_N or the remainder thereof is bond to I_N, wherein said remainder is an optionally substituted C_2-C_7 heteroalkylene or an optionally substituted C_5-C_6 heterocyclo; or

T_N is selected from the group consisting of:



,



, and ,

wherein X^b is $–NH_2$, –OH, halogen, or optionally substituted C_1-C_4 alkoxy or C_1-C_4 alkyl, X^C is hydrogen, halogen, -OH or C_1-C_4 alkoxy; R^4 is hydrogen or optionally substituted C_1-C_4 alkyl, subscript n is 0, 1 or 2, the phenyl optionally substituted by X^b is optionally fused to a 5- or 6-mebered heterocyclic or heteroaromatic ring system, U is $=C(R^{24})$- or =N-, R^{24} is hydrogen or X^b, and the wavy line indicates the site of covalent attachment to I_N or the remainder of T_N that is bonded to I_N, and the amide nitrogen atom of the benzamide moiety is the site of formal optional cyclization of T_N to I_N or the remainder of T_N that is bonded to I_N so that R^4 attached to that nitrogen atom is replaced by a bond;

wherein enzymatic action on W/W' of a drug linker moiety of a Ligand Drug Conjugate compound initiates release of the quaternized NAMPT Drug (D^+) Unit as a NAMPTi compound of formula H_N-D_A-I_N-T_N, wherein H_N is a NAMPT Head Unit that is a fully aromatic C_5-C_{24} or C_9-C_{24} heteroaryl, optionally substituted, comprising a 5- or 6-membered nitrogen-containing heteroaromatic ring system having the previously quaternized skeletal nitrogen atom, and the other variable groups are as previously defined;

L_R' is a primary linker having a functional group capable of forming a covalent bond to a targeting moiety that becomes the Ligand Unit of a Ligand Drug Conjugate compound of Formula I; ~~in which subscript p is replaced by subscript p', wherein the other variable groups are as defined for that formula.~~

subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B;

subscript n is 1, 2, 3 or 4;

A is a first optional Stretcher;

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

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

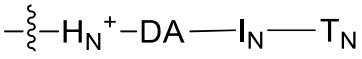
~~subscript p is a number ranging from 1 to 24 and subscript p' is an integer ranging from 1 to 24~~.

[0010] In some examples, the Ligand Unit of a Ligand Drug Conjugate composition or compound thereof is that of an antibody, thereby defining an Antibody Drug Conjugate (ADC) composition or compound, and the targeted moiety recognized by its targeting antibody Ligand Unit is an cell-surface antigen of abnormal cells, wherein the targeted antigen so bound from said recognition is capable of cellular internalization of a Ligand Drug Conjugate compound of the composition, wherein the antigen is typically present on the abnormal cells in greater copy number in comparison to that of normal cells distant from the site of the abnormal cells.

[0011] In other examples, the antibody Ligand Unit of a Ligand Drug Conjugate composition or compound thereof recognizes an antigen present within the vicinity of abnormal cells in which the antigen is typically present in greater copy number in comparison to that of normal cells distant from the site of the abnormal cells, wherein bonding to the targeted antigen culminates in release of the quaternized NAMPT Drug Unit as a NAMPTi compound in proximity to the abnormal cells, which is followed by entry of the NAMPTi compound from that release into the abnormal cells.

[0012] In any one of those examples, a quaternized NAMPT Drug Unit is released from a Ligand Drug Conjugate compound of the composition as a NAMPTi compound within abnormal cells, or is released in the vicinity of the abnormal cells targeted by the Ligand Drug Conjugate, so as to exert a therapeutic effect due intracellular inhibition of NAMPT in the abnormal cells.

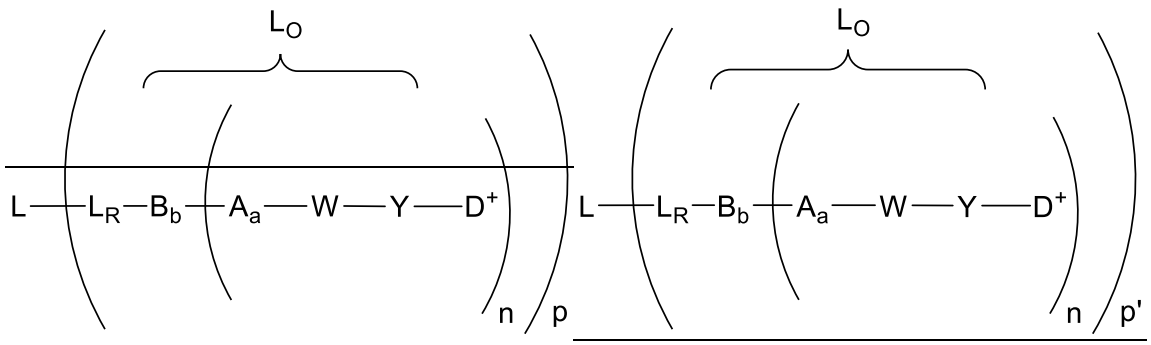
[0013] In some examples a quaternized NAMPT Drug Unit (D^+) is represented by the general structure of:



[0014] in salt form, preferably in pharmaceutically acceptable salt form, H_N^+ is a quaternized NAMPT Head Unit as the quaternized component of D^+ wherein the optionally substituted C_5-C_{24} heteroaryl or partially unsaturated or partially aromatic optionally substituted C_9-C_{24} heterocyclyl of that component is comprised of a 5- or 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system, a

WHAT IS CLAIMED IS:

1. A Ligand Drug Conjugate ~~composition~~ compound represented by Formula 1:

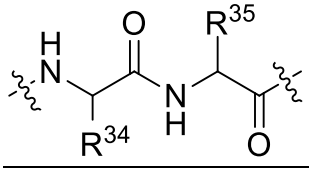


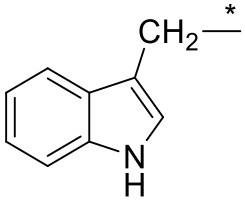
(**1**)

in salt form, particularly in pharmaceutically acceptable salt form, wherein

L is a Ligand Unit that is an antibody or an antigen binding fragment thereof;

W is from 1-12 independently selected amino acids and comprises a dipeptide having 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 site of covalent attachment to the dipeptide backbone; and

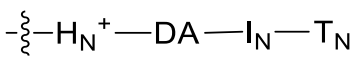
R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3$NH(C=O)NH_2, -$(CH_2)_3$NH(C=NH)NH_2, or -$(CH_2)_2CO_2H$; and

wherein the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to Y and the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment of the dipeptide to the remainder of the peptide sequence, or

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

Y is a self-immolative Spacer Unit ~~comprised of~~ comprising a PAB or PAB-type moiety;

D^+ is represented by the general structure of:

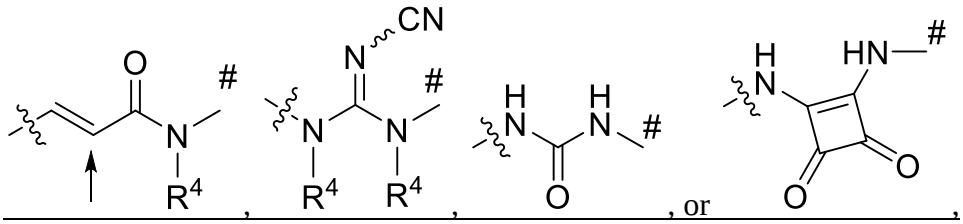


wherein:

H_N^+ is an optionally substituted C_5-C_{24} heteroaryl or partially unsaturated or partially aromatic optionally substituted C_9-C_{24} heterocyclyl comprising a 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system, a skeletal nitrogen atom of which is the site of quaternization to L_O, as indicated by the wavy line to H_N;

DA is a hydrogen bond donor or acceptor functional group that is ~~optionally cyclized with HN+~~ bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing partially unsaturated or heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system, with optional formal cyclization of DA back to an adjacent skeletal carbon atom of the 6-membered nitrogen-containing ring system through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted nitrogen, oxygen or sulfur atom resulting in a partially unsaturated, partially aromatic or fully aromatic 6,5- or 6,6-fused ring system, wherein said bonding of DA is in relation to a skeletal nitrogen atom of the 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system and wherein said formal cyclization to the adjacent carbon atom of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system substantially retains the hydrogen bonding ability of the donor or acceptor functional group of DA in absence of said cyclization;

wherein DA has the structure of:



or a salt thereof, wherein each R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

wherein said optional cyclization is to the indicated sp^2 carbon atom proximal to the carbonyl carbon through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom;

the wavy line indicates the site of covalent attachment to H_N^+; and

the pound sign (#) indicates the site of covalent attachment to I_N;

I_N is $-X^1-[C(=O)]_{0,1}-$, $-X^1-S(=O)_{1,2}-$, $-X^2-C_6-C_{24}$ arylene-$[C(=O)]_{0,1}-$, $-X^2-C_6-C_{24}$ arylene-$[S(=O)_{1,2}]_{0,1}$, $-X^2-C_6-C_{24}$ arylene-O-, $-X^2-C_5-C_{24}$ heteroarylene-$[C(=O)_{0,1}]-$, $-X^2-C_5-C_{24}$ heteroarylene-$[S(=O)_{1,2}]_{0,1}$, $-X^2-C_5-C_{24}$ heteroarylene-O- or $-X^2-C_3-C_{20}$ heterocyclo-$[C(=O)_{0,1}]-$, wherein the arylene, heteroarylene and heterocyclo are optionally substituted;

X^1 is an optionally substituted C_5-C_7 alkylene;

X^2 is absent or is an optionally substituted C_1-C_4 alkylene;

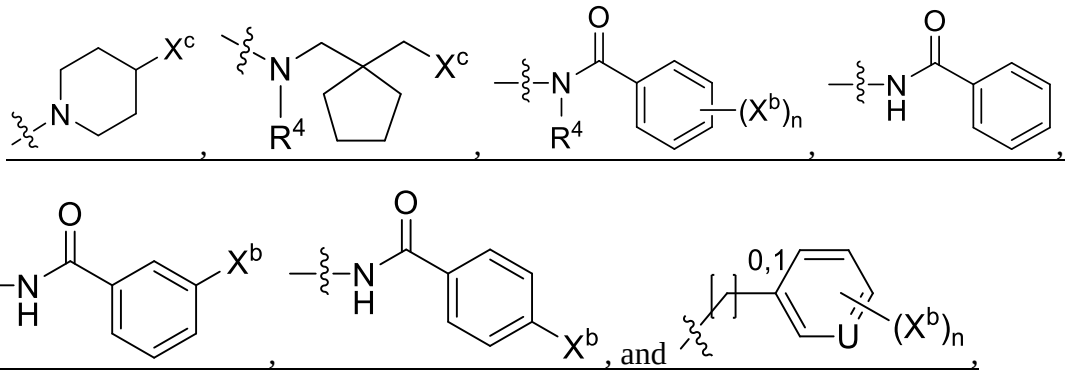
T_N is an optionally substituted amino-alcohol residue or a carboxylic acid-alcohol residue, the amino nitrogen or carbonyl carbon of which is bonded to I_N, or

T_N is an optionally substituted benzamide moiety, the amide nitrogen atom of which is bonded to I_N with optional cyclization of that atom back to I_N or to the remainder of T_N, or

T_N is an optionally substituted C_6-C_{24} aryl, C_5-C_{24} heteroaryl or a combination thereof independently selected in the form of a biaryl, an aromatic atom of which is bonded to I_N or the remainder of T_N; and

wherein T_N or the remainder thereof is bond to I_N, wherein said remainder is an optionally substituted C_2-C_7 heteroalkylene or an optionally substituted C_5-C_6 heterocyclo; or

T_N is selected from the group consisting of:



, , , , , , and ,

wherein X^b is $-NH_2$, –OH, halogen, or optionally substituted C_1-C_4 alkoxy or C_1-C_4 alkyl, X^C is hydrogen, halogen, -OH or C_1-C_4 alkoxy; R^4 is hydrogen or optionally substituted C_1-C_4 alkyl, subscript n is 0, 1 or 2, the phenyl optionally substituted by X^b is optionally fused to a 5- or 6-membered heterocyclic or heteroaromatic ring system, U is $=C(R^{24})-$ or =N-, R^{24} is hydrogen or X^b, and the wavy line indicates the site of covalent attachment to I_N or the remainder of T_N that is bonded to I_N, and the amide nitrogen atom of the benzamide moiety is the site of formal optional cyclization of T_N to I_N or the remainder of T_N that is bonded to I_N so that R^4 attached to that nitrogen atom is replaced by a bond;

wherein enzymatic action on W/W' of a drug linker moiety of a Ligand Drug Conjugate compound initiates release of the quaternized NAMPT Drug (D^+) Unit as a NAMPTi compound of formula H_N-D_A-I_N-T_N, wherein H_N is a NAMPT Head Unit that is a fully aromatic C_5-C_{24} or C_9-C_{24} heteroaryl, optionally substituted, comprising a 5- or 6-membered nitrogen-containing heteroaromatic ring system having the previously quaternized skeletal nitrogen atom, and the other variable groups are as previously defined;

wherein H_N- or H_N-DA- of the NAMPTi compound is capable of interacting with enzymatically competent NAMPT homodimer at its nicotinamide binding site;

~~wherein the Ligand Drug Conjugate compound is represented by Formula 1 in which subscript p is replaced by subscript p';~~

L_R is a primary linker that interconnects the Ligand Unit and Drug Unit through L_O, wherein L_O is an optional secondary linker that is present;

subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B;

subscript n is 1, 2, 3 or 4;

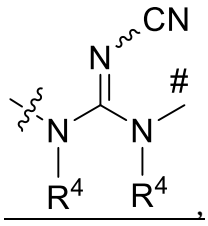
A is a first optional Stretcher;

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

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

~~subscript p is a number ranging from 1 to 24 and~~ subscript p' is an integer ranging from 1 to 24.

2. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein DA is ~~an optionally substituted amide functional group or bioisostere thereof, or wherein a skeletal nitrogen atom of the 5- or 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system of H_N^+ is quaternized~~



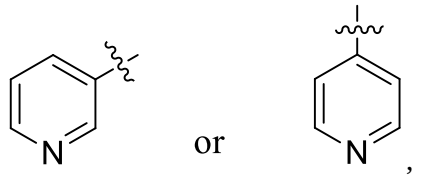
or a salt thereof, in particular a pharmaceutically acceptable salt, wherein each R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

the wavy line indicates the site of covalent attachment to H_N/H_N^+;and

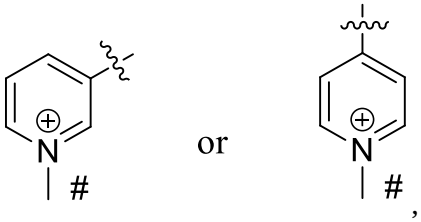
the pound sign (#) indicates the site of covalent attachment to I_N.

3. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein the 6-membered nitrogen-containing heteroaromatic ring system of H_N is that of pyridine with optional cyclization of DA back to the pyridine aromatic ring system through an introduced aromatic oxygen, sulfur or an optionally substituted nitrogen atom so that H_N contains a 6-5 fused aromatic ring system and H_N^+ is that Unit in which the pyridine aromatic ring system is quaternized at its skeletal nitrogen atom,

in particular, wherein H_N has the structure of:



or a salt thereof, in particular a pharmaceutically acceptable salt, and H_N^+ has the structure of:



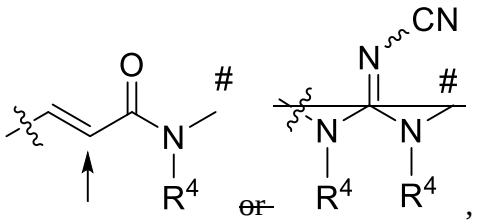
in salt form, in particular in pharmaceutically acceptable salt form, wherein

the pound sign (#) indicates the point of covalent attachment to L_O;

the wavy line indicates the site of covalent attachment to DA and an adjacent aromatic carbon atom thereto is the site of said optional formal cyclization by DA to H_N/H_N^+.

4. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein DA is an acrylamide DA Unit, optionally cyclized to an adjacent skeletal carbon atom of the nitrogen-

containing aromatic ring system of H_N/H_N^+ to which it is attached, ~~or is an amide bioisostere,~~ in particular having the structure of:



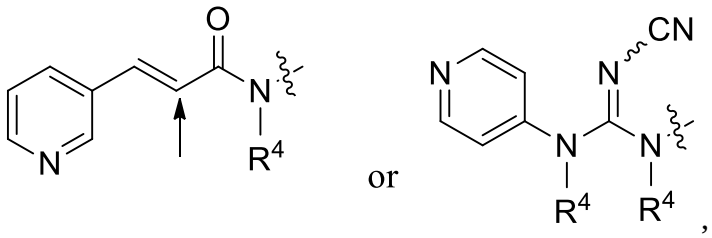
or a salt thereof, in particular a ~~pharmaceutical~~ pharmaceutically acceptable salt, wherein ~~each~~ R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

DA is optionally cyclized to H_N/H_N^+, wherein said cyclization is to the sp^2 carbon atom of the acrylamide DA Unit proximal to the carbonyl carbon (as indicated) through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom;

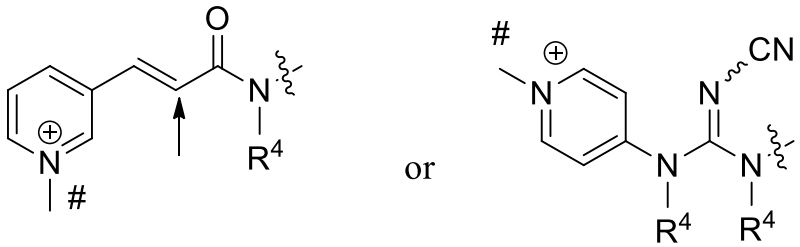
the wavy line indicates the site of covalent attachment to H_N/H_N^+, and the indicated carbon atom adjacent thereto is the site of said optional cyclization by the acrylamide DA; and

the pound sign (#) indicates the site of covalent attachment to I_N.

5. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein H_N-DA- is:



or a salt thereof, in particular a pharmaceutically acceptable salt, and H_N^+-DA has the structure of:



in salt form, in particular in pharmaceutically acceptable salt form, wherein

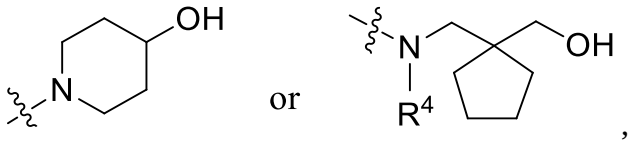
R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl; and

the pound sign (#) indicates the point of covalent attachment to L_O;

the wavy line indicates the site of covalent attachment to I_N, and

wherein the sp^2 carbon atom proximal to the carbonyl carbon is the site (as indicated) of optional cyclization to H_N/H_N^+ through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom.

6. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein T_N is an amino alcohol moiety having the structure of:



,

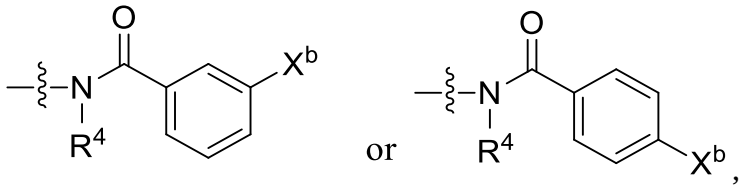
wherein

R^4 is hydrogen or optionally substituted C_1-C_4 alkyl; and

the wavy line indicates the site of covalent attachment to I_N,

or

wherein T_N is an optionally substituted benzamide moiety covalently attached to I_N or the remainder of T_N, through its amide nitrogen atom, in particular wherein the benzamide moiety has the structure of:



,

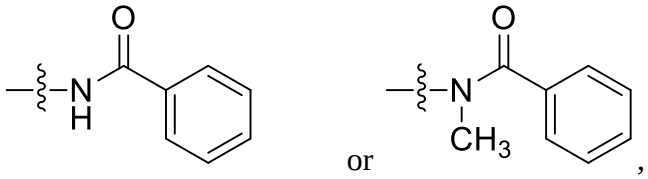
wherein X^b is –H, halogen, -OH, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 alkyl or $–NH_2$, optionally substituted;

R^4 is hydrogen or optionally substituted C_1-C_4 alkyl; and

the wavy line indicates the site of covalent attachment to I_N; and

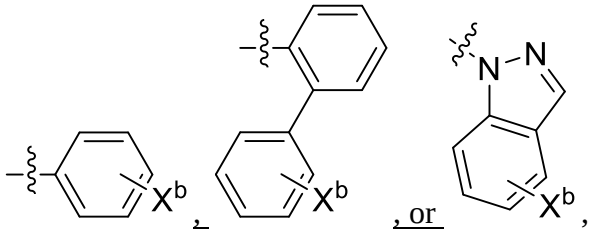
wherein the benzamide moiety is optionally cyclized to I_N wherein the amide nitrogen of the benzamide moiety is the site of said cyclization so that R^4 is replaced by a covalent bond,

more particularly wherein the benzamide moiety has the structure of:



or

wherein T_N is an optionally substituted (hetero)aryl or biaryl moiety, in particular having the structure of:

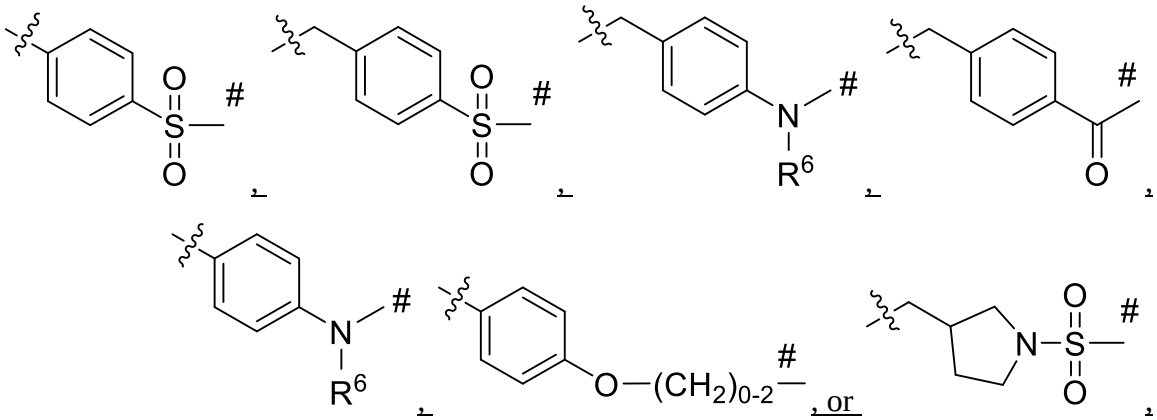


respectively, wherein

wherein X^b is –H, halogen, -OH, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 alkyl or $–NH_2$, optionally substituted;

the wavy line indicates the site of covalent attachment to I_N.

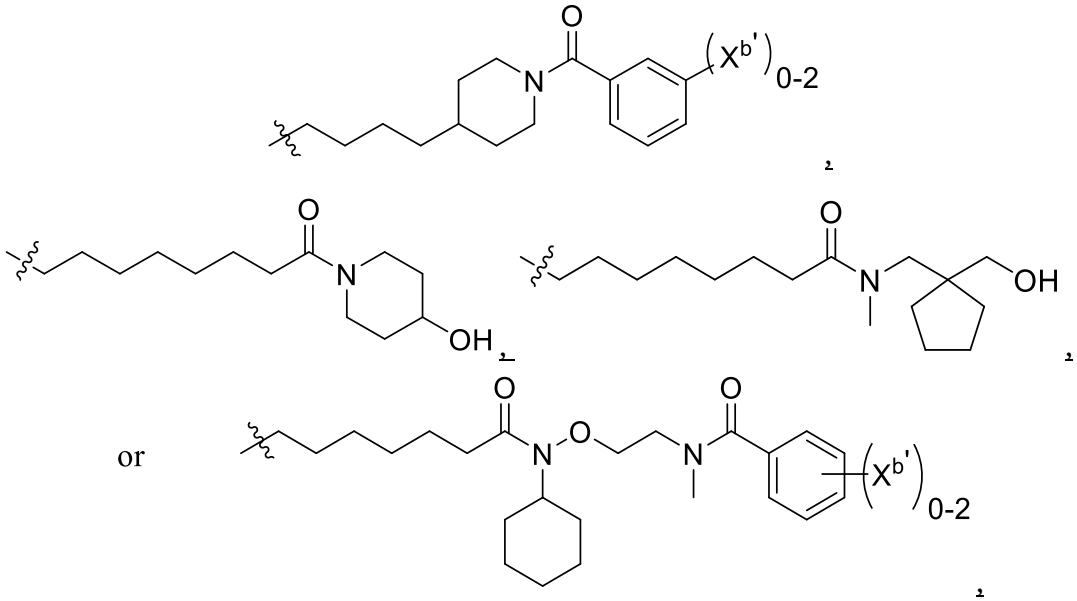
7. The Ligand Drug Conjugate ~~composition~~ compound of claim **6**, wherein I_N is $-CH_2-(CH_2)_{3-7}-CH_2-$, $-CH_2-(CH_2)_{3-7}-CH_2-O-$, $-CH_2-(CH_2)_{3-7}-C(=O)-$, $-CH_2-(CH_2)_{3-7}-S(=O)_2-$ or $-CH_2-(CH_2)_{3-7}-S(=O)-$, or wherein I_N has the structure of:



wherein the wavy line indicates the site of covalent attachment to DA and the pound sign (#) indicates the site of covalent attachment to T_N; and

R^6 is hydrogen, C_1-C_4 alkyl, -$CH_2CH=C(CH_3)_2$, or –CH_2-C≡CH.

8. The Ligand Drug Conjugate ~~composition~~ compound of claim **6**, wherein –I_N-T_N has the structure of:

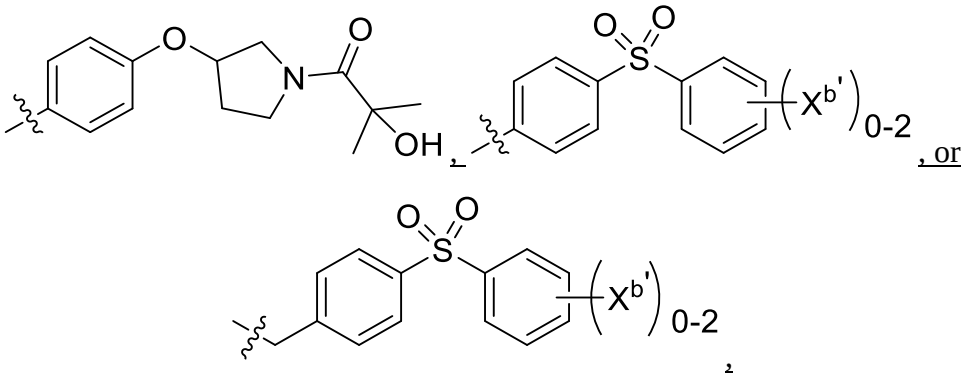


wherein

$X^{b'}$ when present is independently selected from the group consisting of halogen, -OH, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 alkyl and –NH_2, optionally substituted; and

the wavy line indicates the site of covalent attachment to DA, or

wherein –I_N-T_N has the structure of:

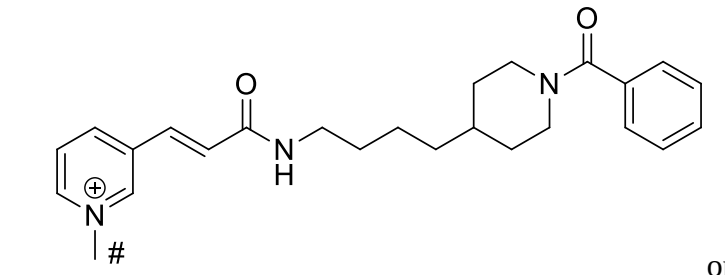


wherein

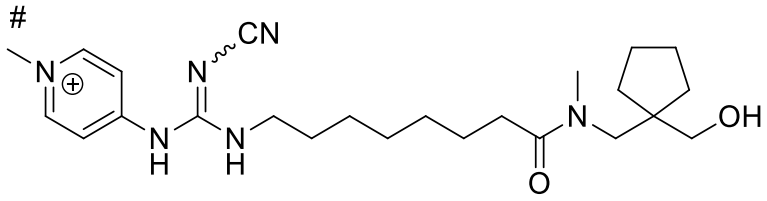
$X^{b'}$ if present is selected from the group consisting of, -OH and NH_2, optionally substituted, and halogen, provided that when subscript n is 2 one of X^b is –OH or -NH_2, optionally substituted, or halogen and the other is halogen; and

the wavy line indicates the site of covalent attachment to DA.

9. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein D^+ has the structure of:

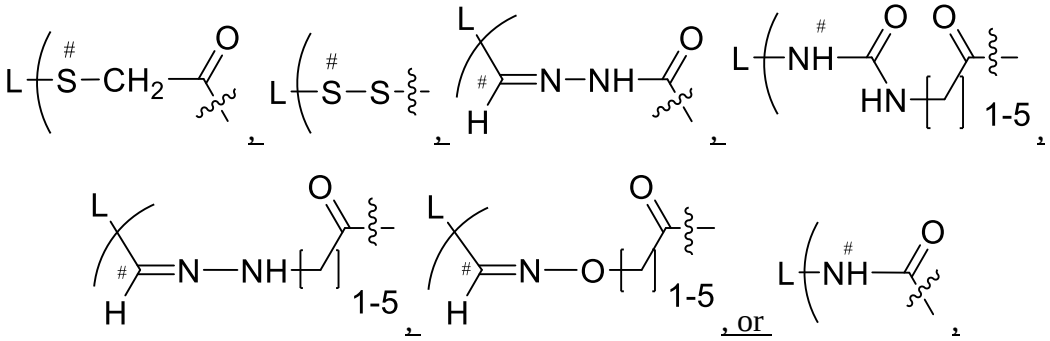


or



in salt form, in particular in pharmaceutically acceptable salt form, wherein the pound sign (#) indicates the site of quaternization by L_O.

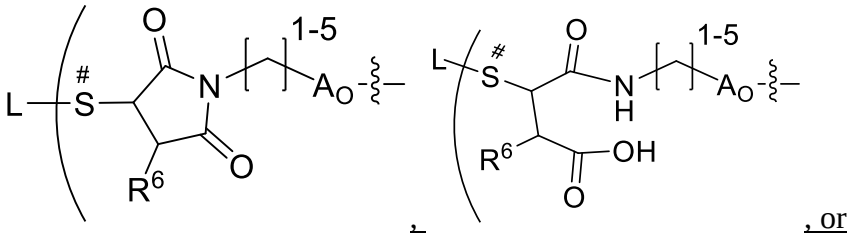
10. The Ligand Drug Conjugate ~~composition~~ compound of any one of claims **1** and **4** to **9**, wherein L-(L_R- has the structure of:

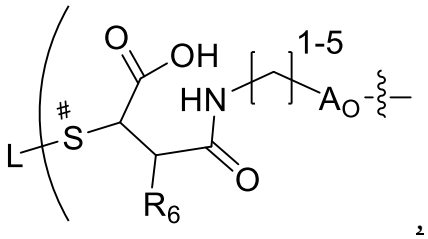


or a salt thereof, in particular a pharmaceutically acceptable salt, wherein

L is a Ligand Unit and the indicated (#) atom is from the Ligand Unit; and wherein the wavy line indicates the site of covalent attachment to the remainder of the Conjugate structure, or

wherein L-(L_R- has the structure of:





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

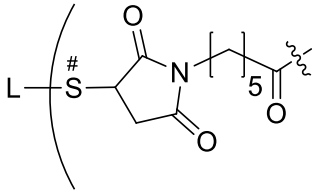
L is a Ligand Unit and the indicated (#) sulfur atom is from the Ligand Unit;

R^6 is hydrogen or an optionally substituted C_1-C_6 alkyl;

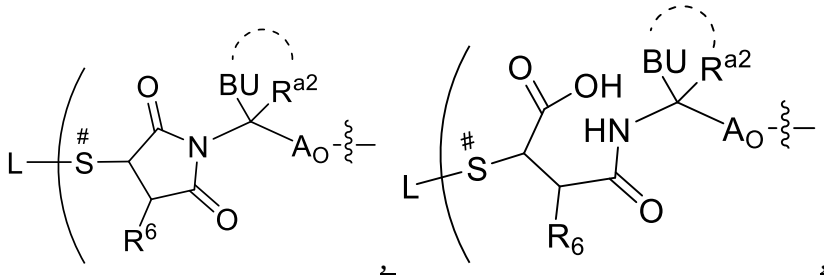
A_O is a second optional Stretcher Unit; and

the wavy line indicates the site of covalent attachment to the remainder of the Conjugate structure,

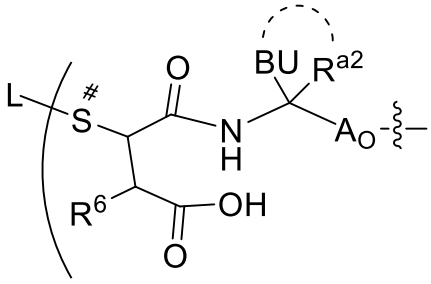
in particular having the structure of:



or wherein L-(L_R- has the structure of:



, , or



,

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

L is a Ligand Unit and the indicated (#) sulfur atom is from the Ligand Unit; and

R^6 is hydrogen or an optionally substituted C_1-C_6 alkyl;

A_O is a second optional Stretcher Unit;

BU is a Basic Unit;

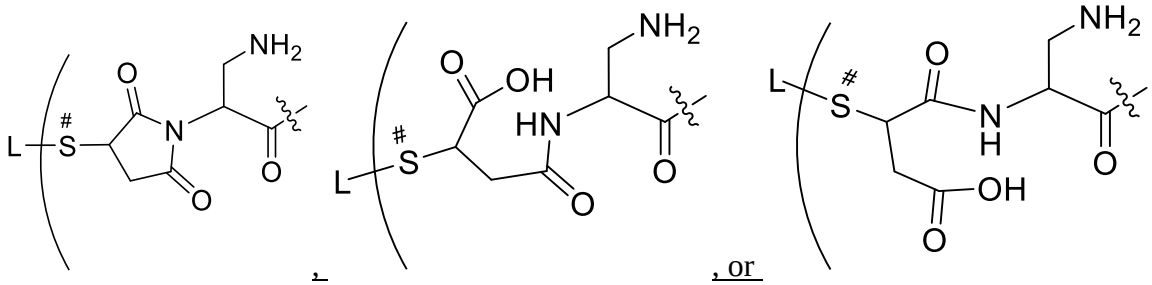
R^{a2} is an optionally substituted C_1-C_{12} alkyl;

the dotted curved line indicates optional cyclization so that in the absence of said cyclization BU is an acyclic Basic Unit or in the presence of said cyclization BU is a cyclized Basic Unit in which R^{a2} and BU together with the carbon atom to which both are attached, define an optionally substituted spiro C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group of BU,

wherein the basic nitrogen atom of the acyclic Basic Unit or 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; and

the wavy line indicates the site of covalent attachment to the remainder of the Conjugate structure,

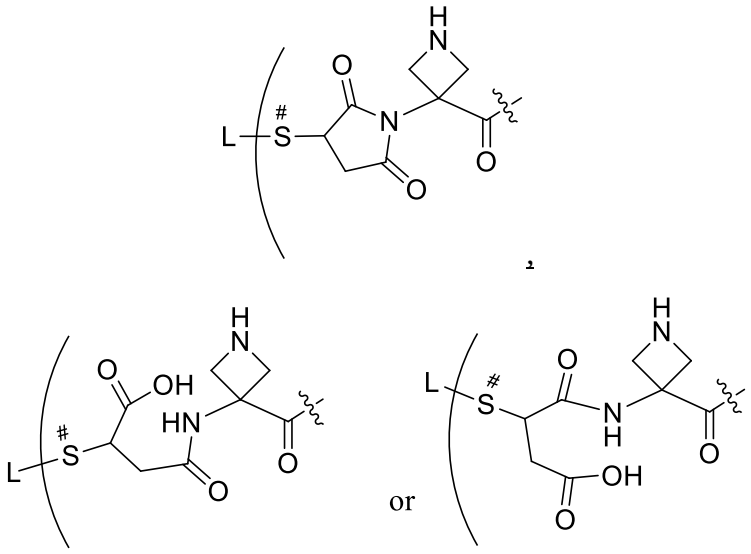
in particular having the structure of:



, or

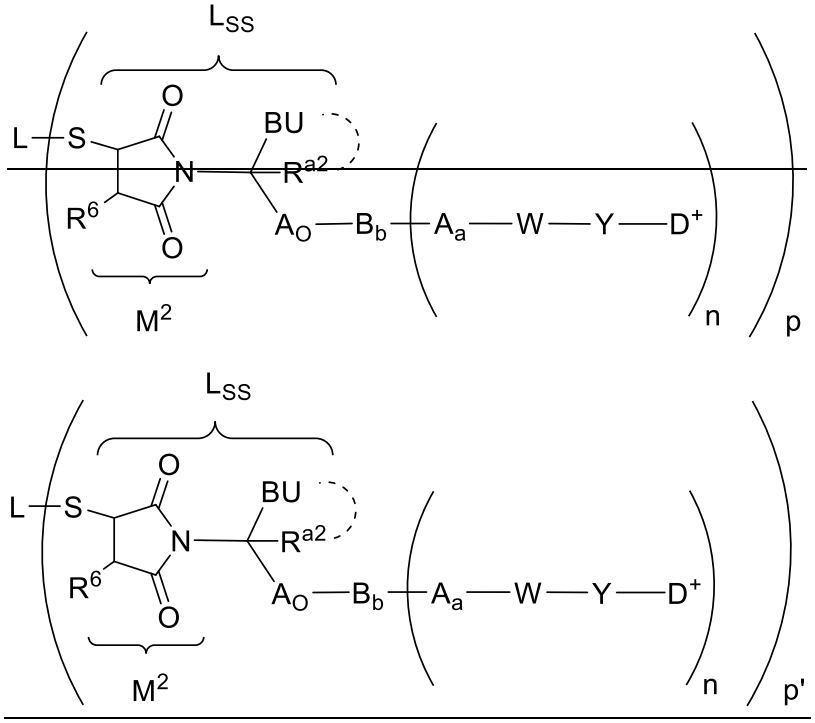
or a salt thereof, in particular a pharmaceutically acceptable salt, or

in particular having the structure of:

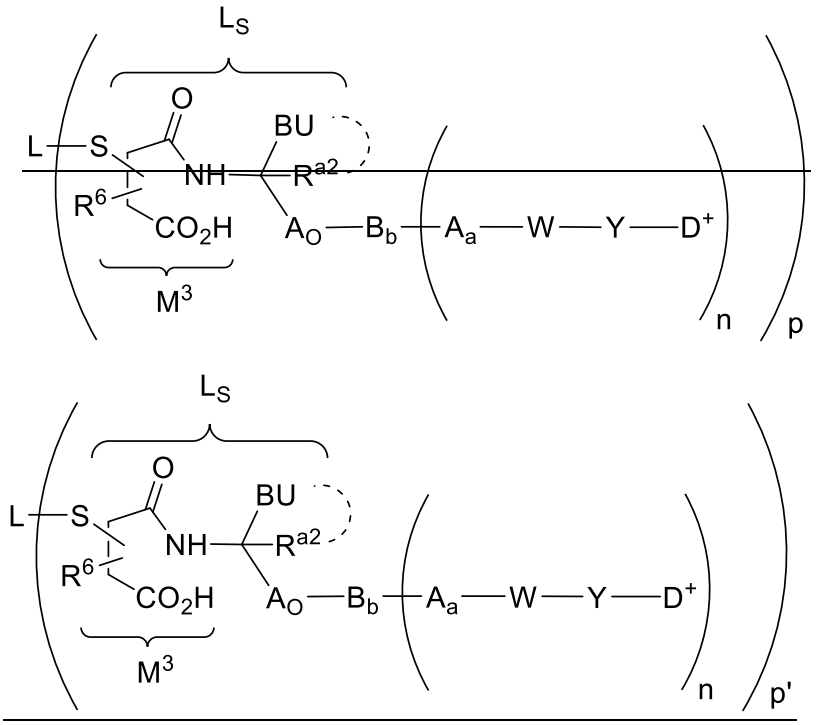


or a salt thereof, in particular a pharmaceutically acceptable salt.

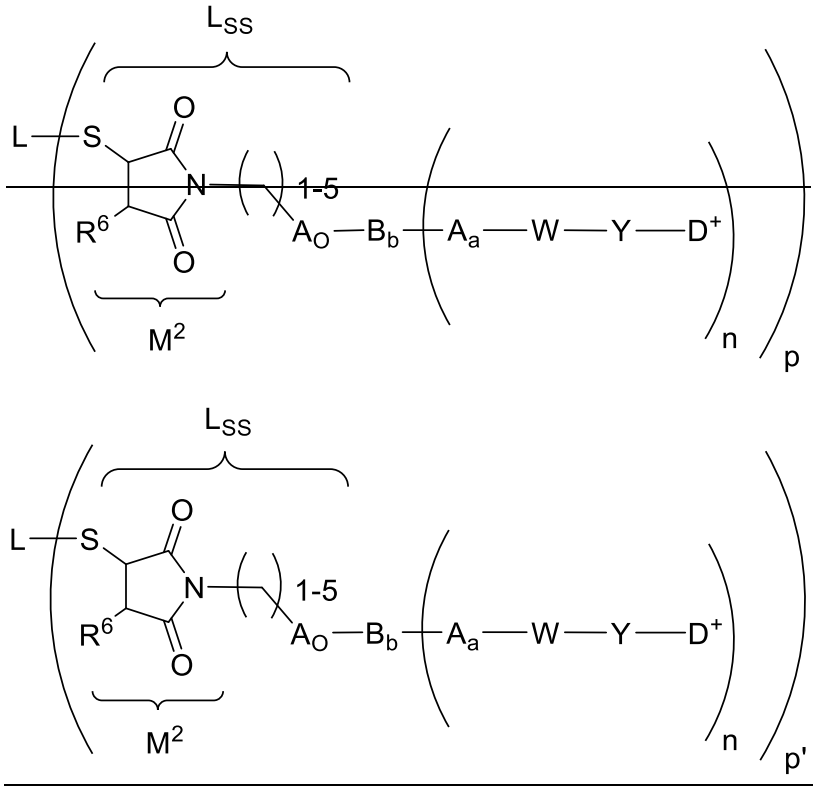
11. The Ligand Drug Conjugate ~~composition~~ compound of claim **10**, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of Formula 1a ~~and/~~or Formula 1b or is represented by the structure~~(s)~~ of Formula 1c ~~and/~~or Formula 1d:



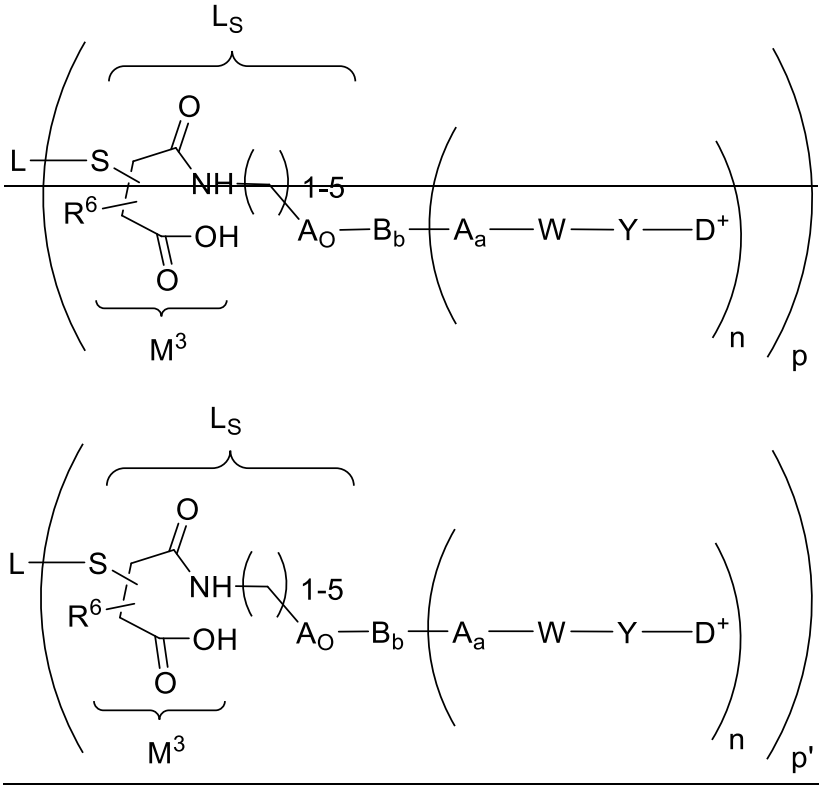
(Formula 1a)



(Formula 1b)



(Formula 1c)



(Formula 1d)

in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

L is a Ligand Unit;

S is a sulfur atom of the Ligand Unit, which in Formula 1b or Formula 1d is bonded to the carbon atom α or β to the carboxylic acid functional group of the indicated succinic acid amide (M^3) moiety;

R^6 is hydrogen or an optionally substituted C_1-C_6 alkyl, which in Formula 1b or Formula 1d is bonded to the saturated carbon atom adjacent to the carbon substituted by L-S-;

A_O is a second optional Stretcher Unit; and

W is from 1-12 independently selected amino acids, or

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

Y is a self-immolative Spacer Unit ~~comprised of~~ <u>comprising</u> a PAB or PAB-type moiety;

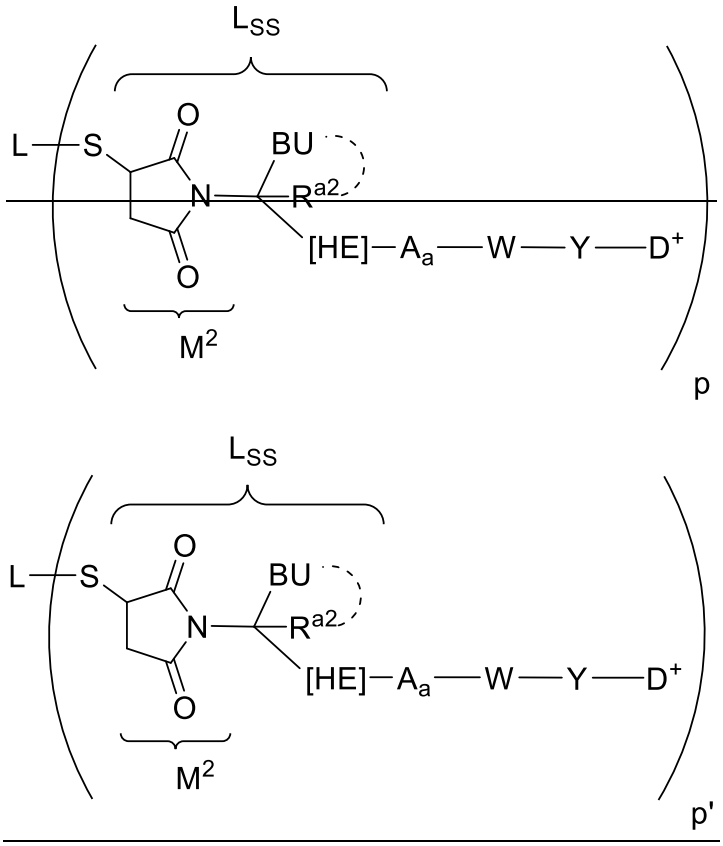
BU is a Basic Unit and R^{a2} is an optionally substituted C_1-C_{12} alkyl; and

the dotted curved line indicates optional cyclization so that in the absence of said cyclization BU is an acyclic Basic Unit or in the presence of said cyclization BU is a cyclized Basic Unit in which R^{a2} and BU together with the carbon atom to which both are attached, define an optionally substituted spiro C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group of BU,

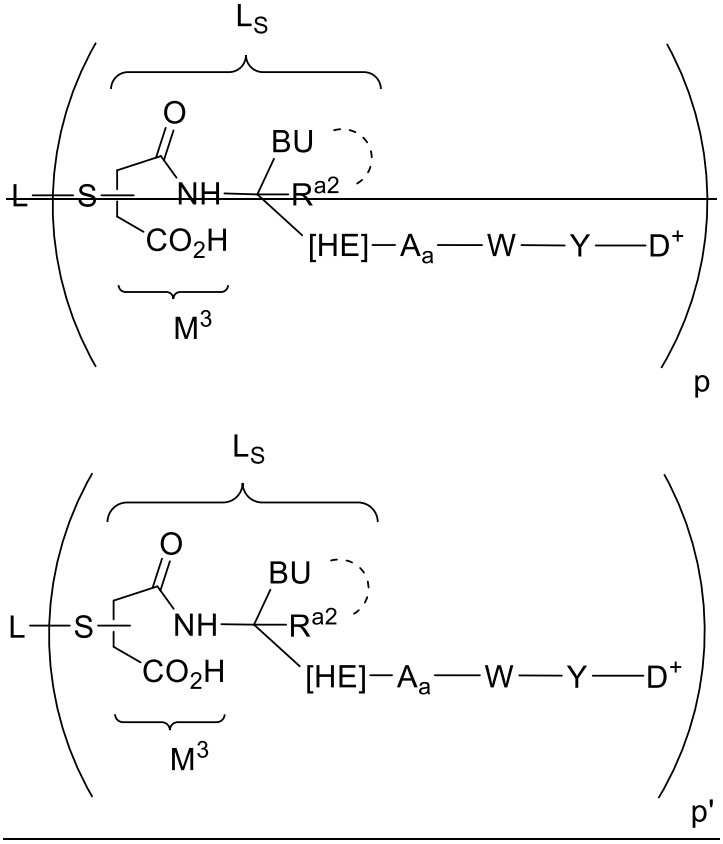
wherein the basic nitrogen atom of the acyclic Basic Unit or cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated, ~~and~~

~~wherein the Ligand Drug Conjugate compound is represented by Formula 1a, Formula 1b, Formula 1c or Formula 1d in which subscript p is replaced by subscript p',~~

in particular, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



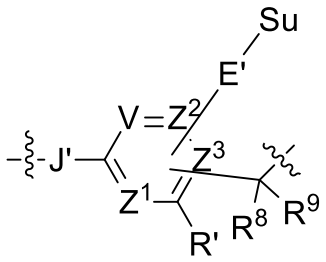
~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein [HE] as A_O is an optional Hydrolysis Enhancing Unit;

W is from 1-12 independently selected amino acids, and Y is a self-immolative Spacer Unit ~~comprised of~~ <u>comprising</u> a PAB or PAB-type moiety,

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



or a salt thereof, in particular a pharmaceutically acceptable salt, wherein Su is a carbohydrate moiety and -E'- represents an optionally substituted heteroatom of a glycosidic bond;

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

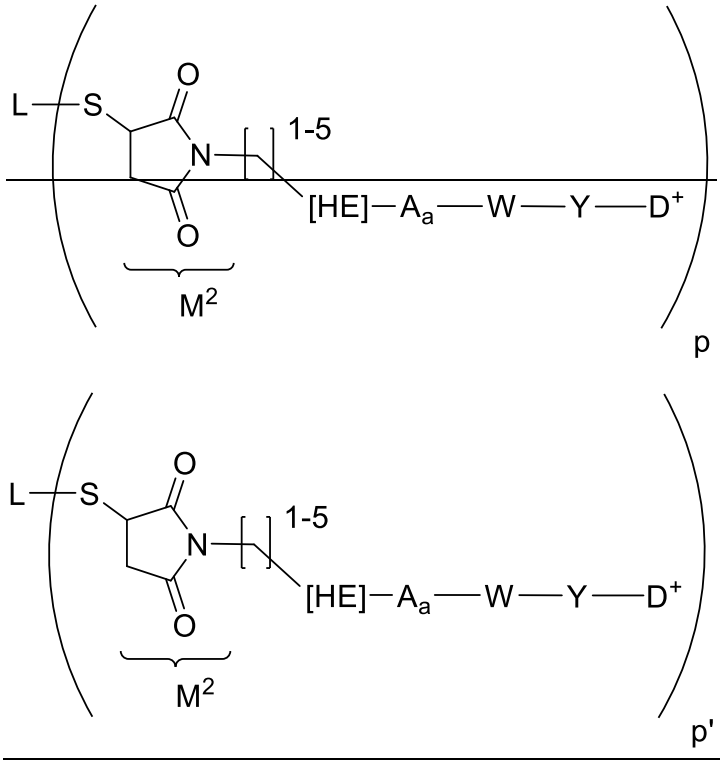
R^8 and R^9 together with the carbon atom to which both are attached define an optionally substituted C_5-C_{20} carbocyclo; and

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

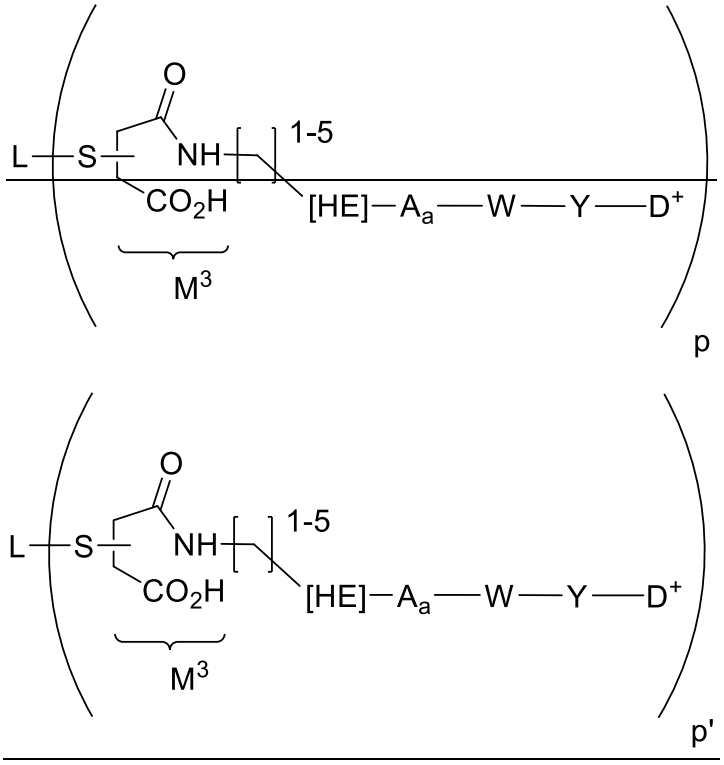
wherein the wavy line adjacent to J' indicates the site of covalent attachment of the Glucuronide Unit to A when subscript a is 1 or to the indicated L_{SS} or L_S primary linker when subscript a is 0; and the wavy line adjacent to the $–C(R^8)(R^9)$- moiety indicates the site of covalent attachment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

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or in particular wherein the ~~composition~~ <u>compound</u> is represented by the structure~~(s)~~ of:



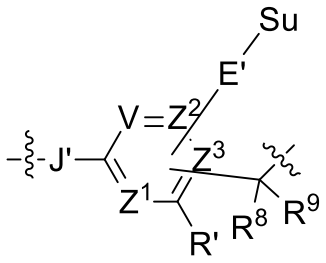
~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein [HE] as A_O is an optional Hydrolysis Enhancing Unit;

W is from 1-12 independently selected amino acids, and Y is a self-immolative Spacer Unit ~~comprised of~~ comprising a PAB or PAB-type moiety, or

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



in salt form, in particular in pharmaceutically acceptable salt, wherein Su is a carbohydrate moiety and -E'- represents an optionally substituted heteroatom of a glycosidic bond;

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

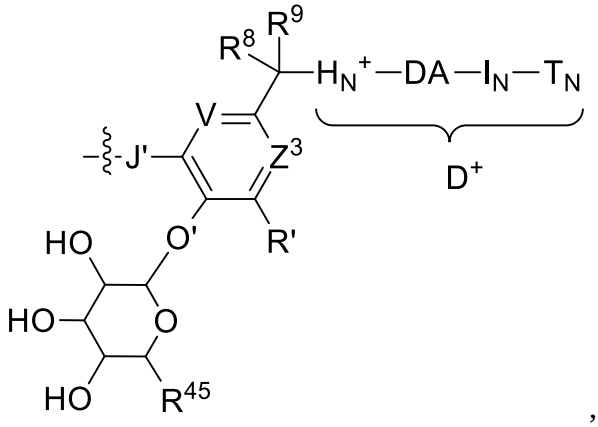
R^8 and R^9 together with the carbon atom to which both are attached define an optionally substituted C_5-C_{20} carbocyclo; and

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

wherein the wavy line adjacent to J' indicates the site 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 site of covalent attachment of the Glucuronide Unit D^+~~; and~~

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p'~~.

12. The Ligand-Drug Conjugate ~~composition~~ compound of claim **11**, wherein W-Y is replaced by a Glucuronide Unit of formula –Y(W')- for which –Y(W')-D^+ has the structure of:



,

in salt form, in particular in pharmaceutically acceptable salt form, wherein

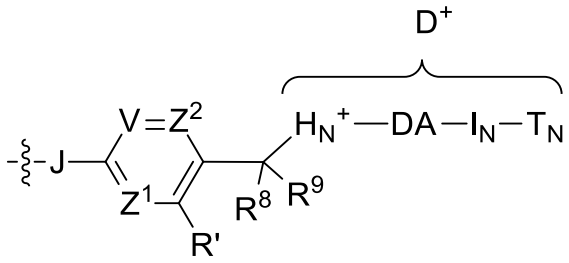
R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

wherein -O'- represents the oxygen heteroatom of an O-glycosidic bond,

or

wherein W is from 1-12 independently selected amino acids for which –Y-D^+ has the structure of:

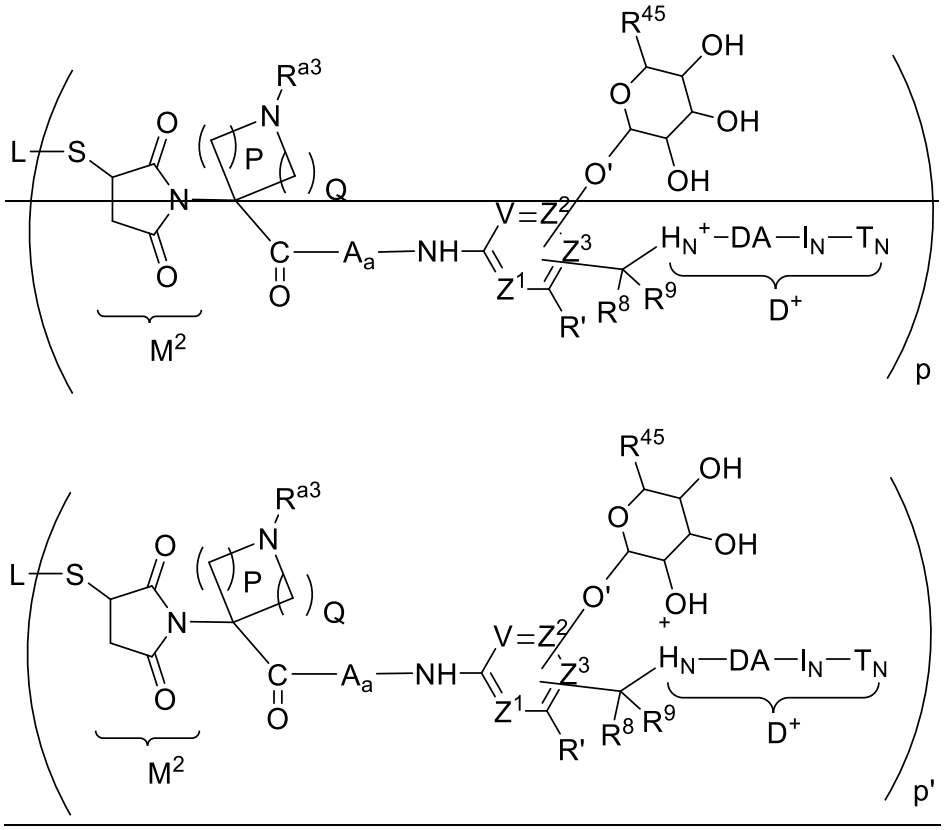


in salt form, in particular in pharmaceutically acceptable salt form, wherein

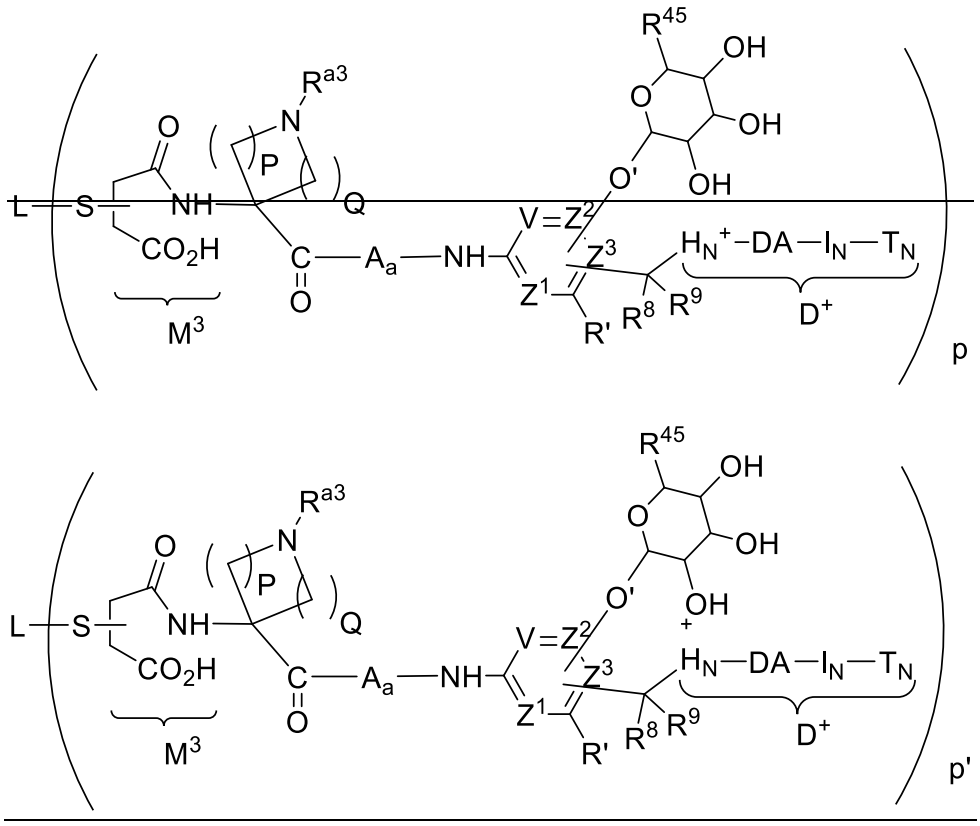
R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

J is an optionally substituted heteroatom bonded to W as indicated by the wavy line.

13. The Ligand Drug Conjugate ~~composition~~ compound of claim **11**, wherein W-Y is replaced by a Glucuronide Unit of formula –Y(W')-, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

subscript P is 1, 2 or 3;

subscript Q ranges from 1 to 6;

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

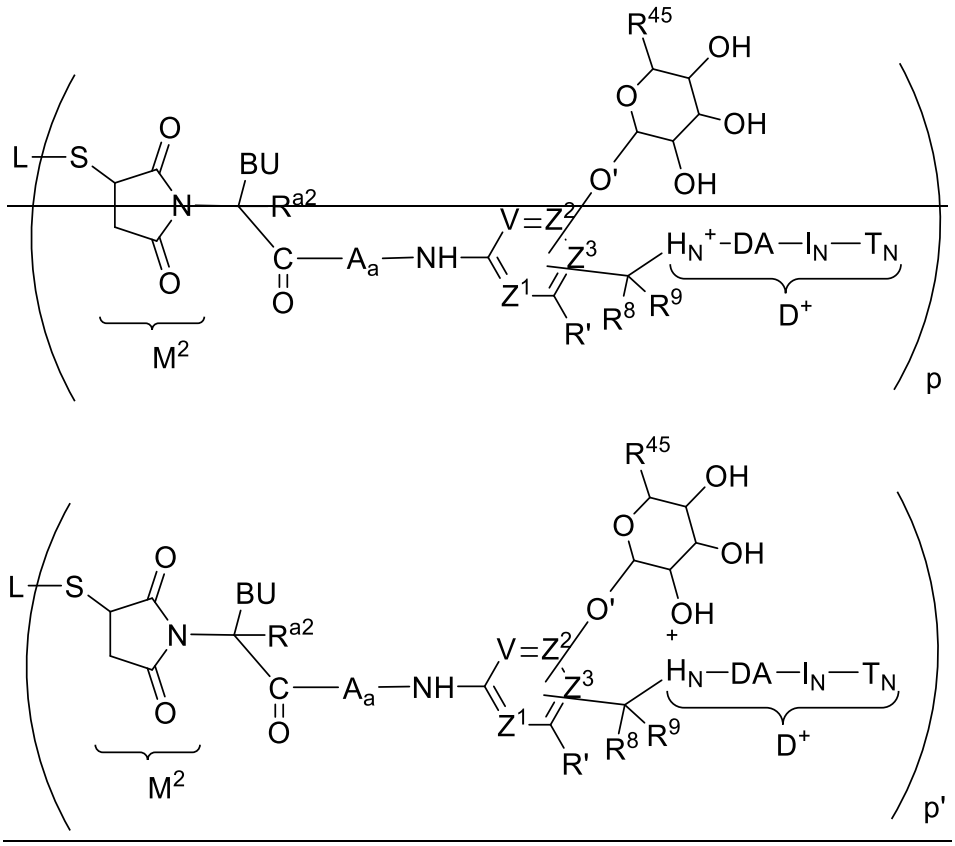
R^{a3} is –H, or optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{1-36}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, and R^{PEG2} is –H or C_1-C_4 alkyl; and

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

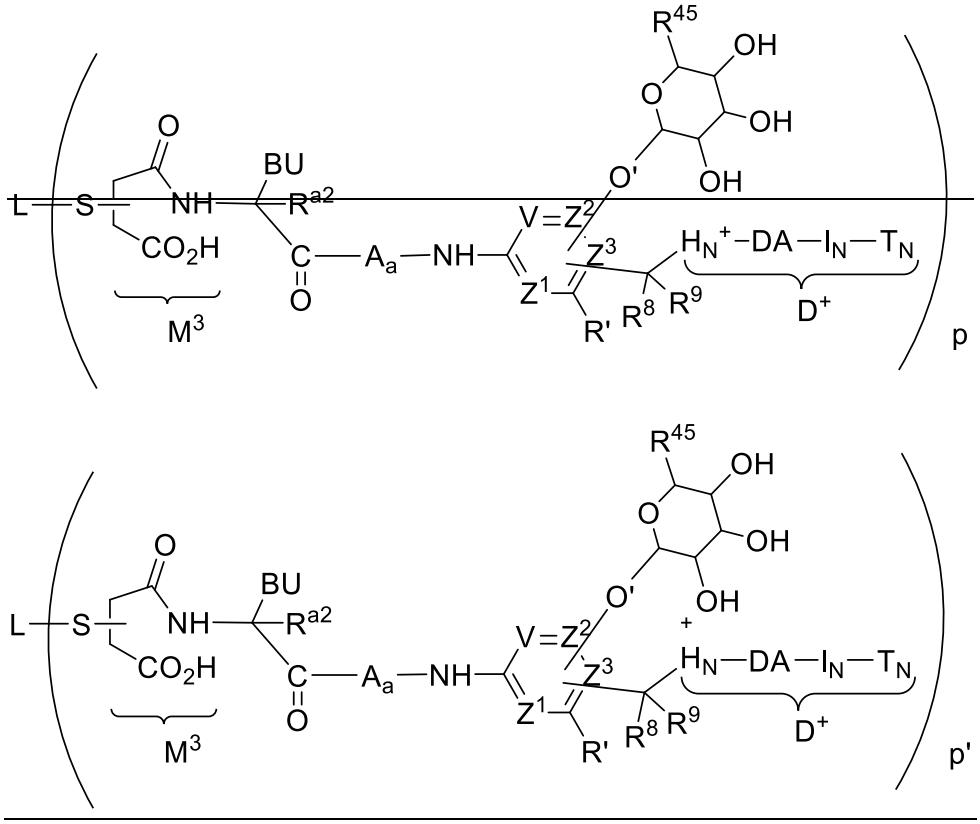
wherein -O'- represents the oxygen heteroatom of an O-glycosidic bond,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



and/or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

R^{a2} is hydrogen or C_1-C_6 alkyl;

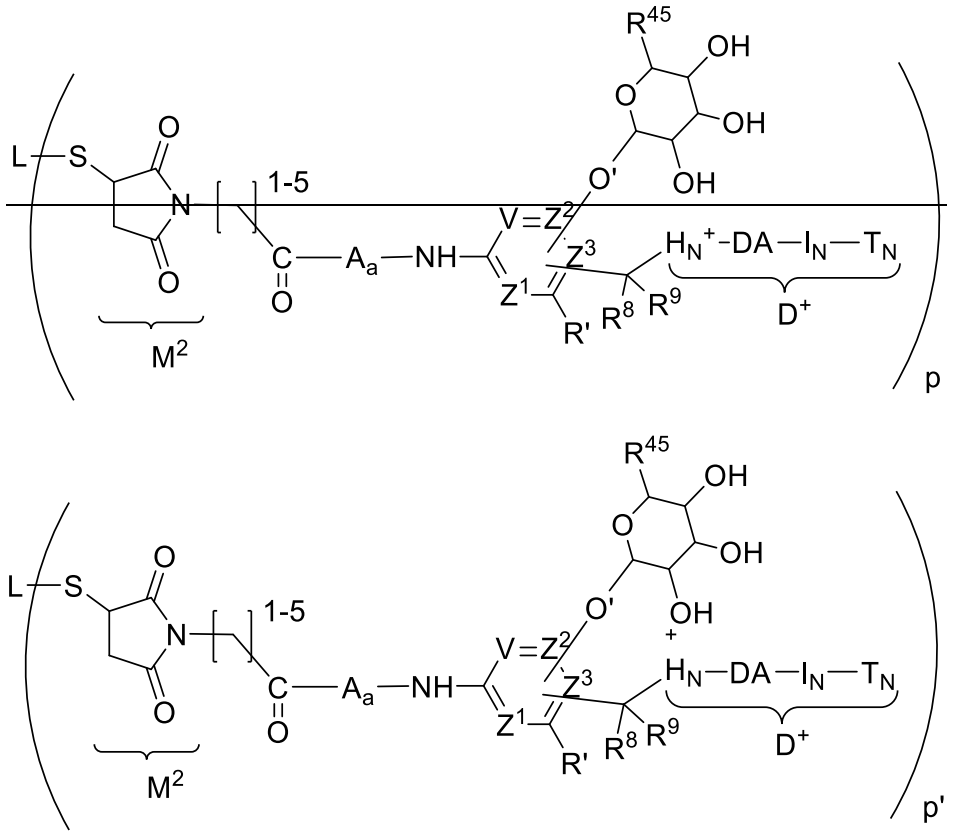
BU has the structure of $–[C(R^{a1})(R^{a1})]$-$[C(R^{a1})(R^{a1})]_{0-3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; R^{a3} independently are hydrogen, optionally substituted C_1-C_6 alkyl or R^{a3} together with the nitrogen atom to which both are attached define a C_3-C_6 heterocyclyl in which the basic nitrogen is a skeletal atom;

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

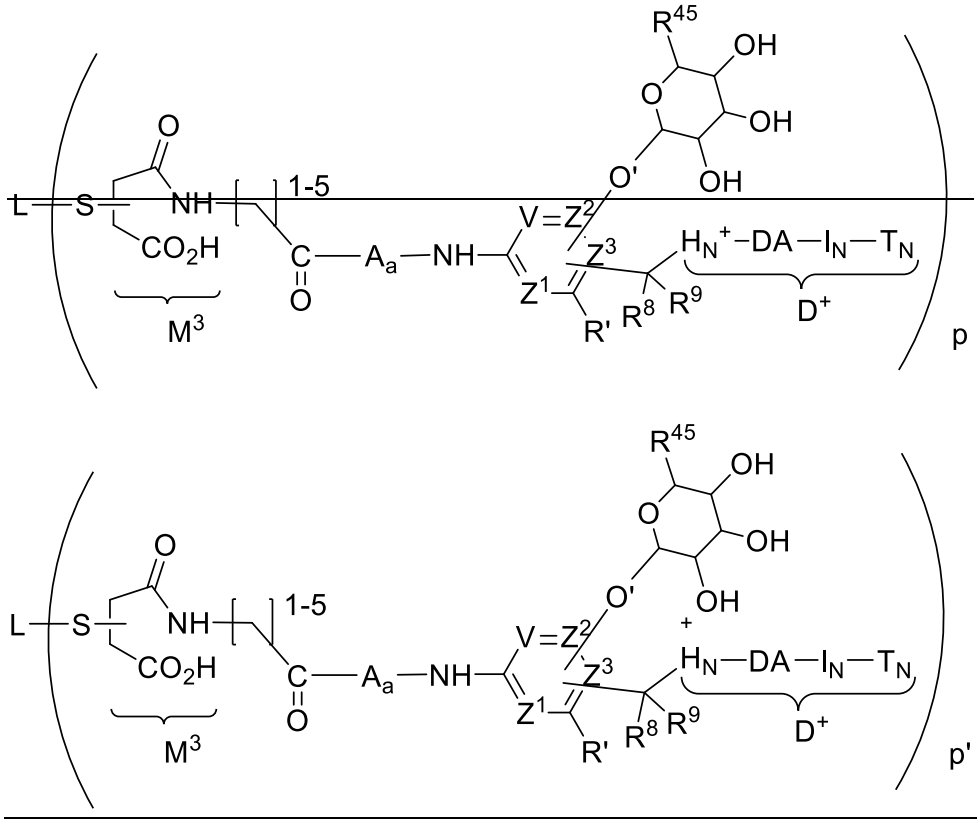
wherein -O'- represents the oxygen atom of an O-glycosidic bond,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ <u>compound</u> or compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

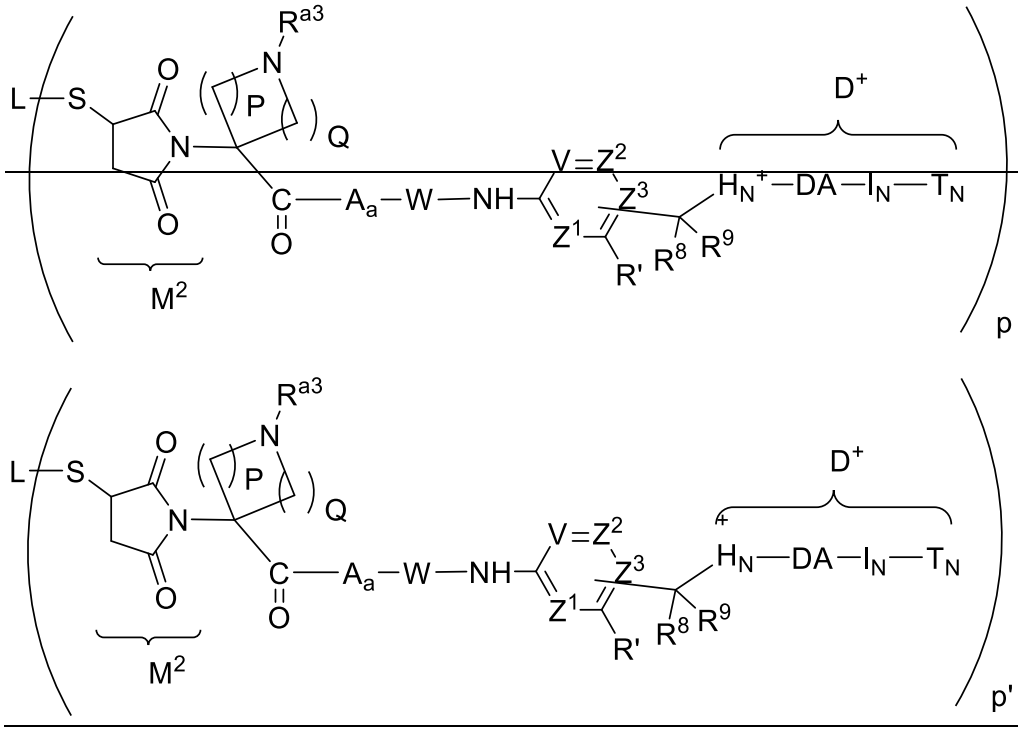
R^{45} is $–CH_2OH$ or $–CO_2H$;

R^{a2} is hydrogen or C_1-C_6 alkyl; and

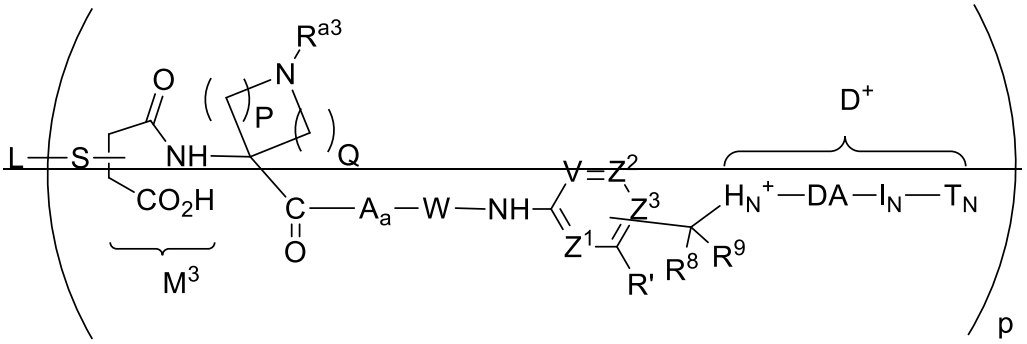
wherein -O'- represents the oxygen atom of an O-glycosidic bond,

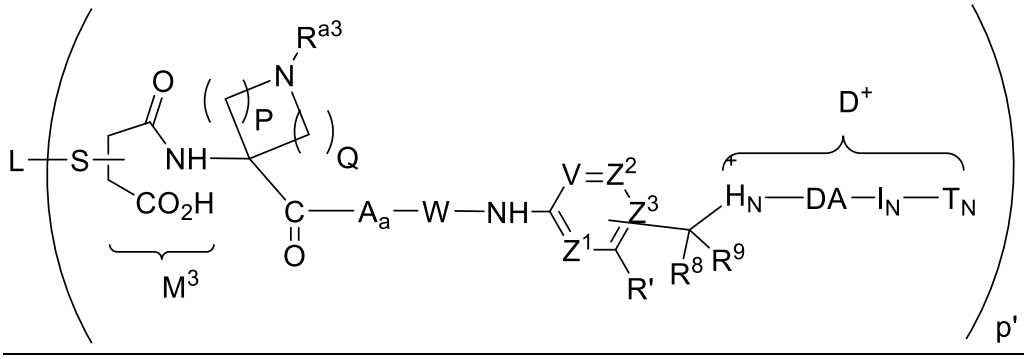
~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein W is from 1-12 independently selected amino acids and the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or





in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

subscript P is 1, 2 or 3;

subscript Q ranges from 1 to 6;

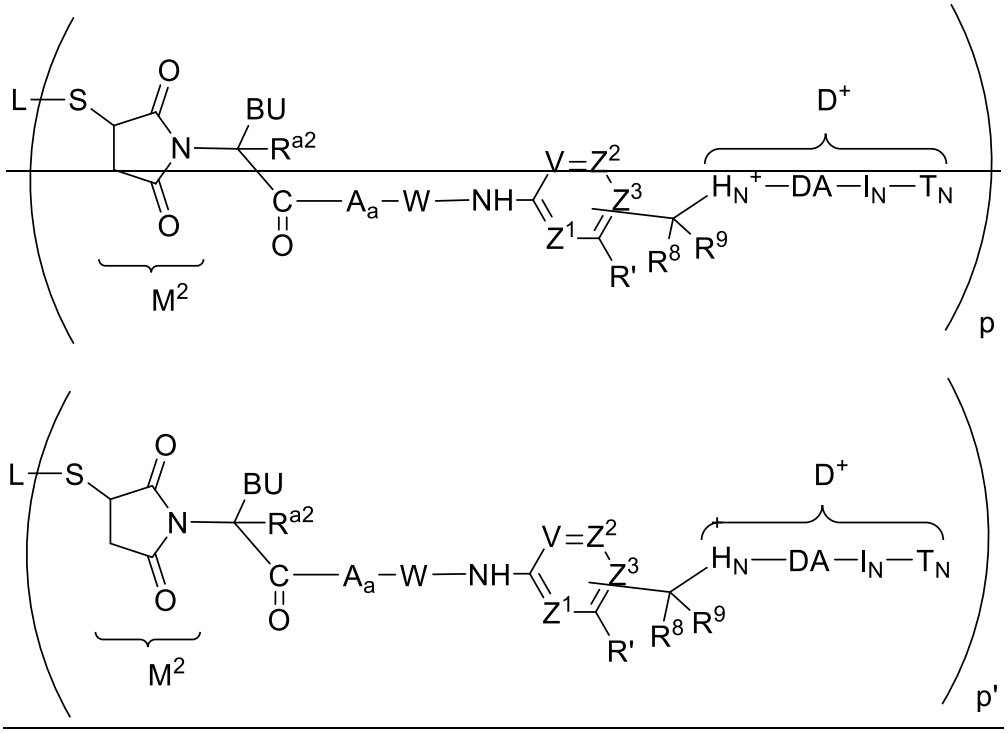
R’ is hydrogen or –OC_1-C_6 alkyl or other electron donating group;

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

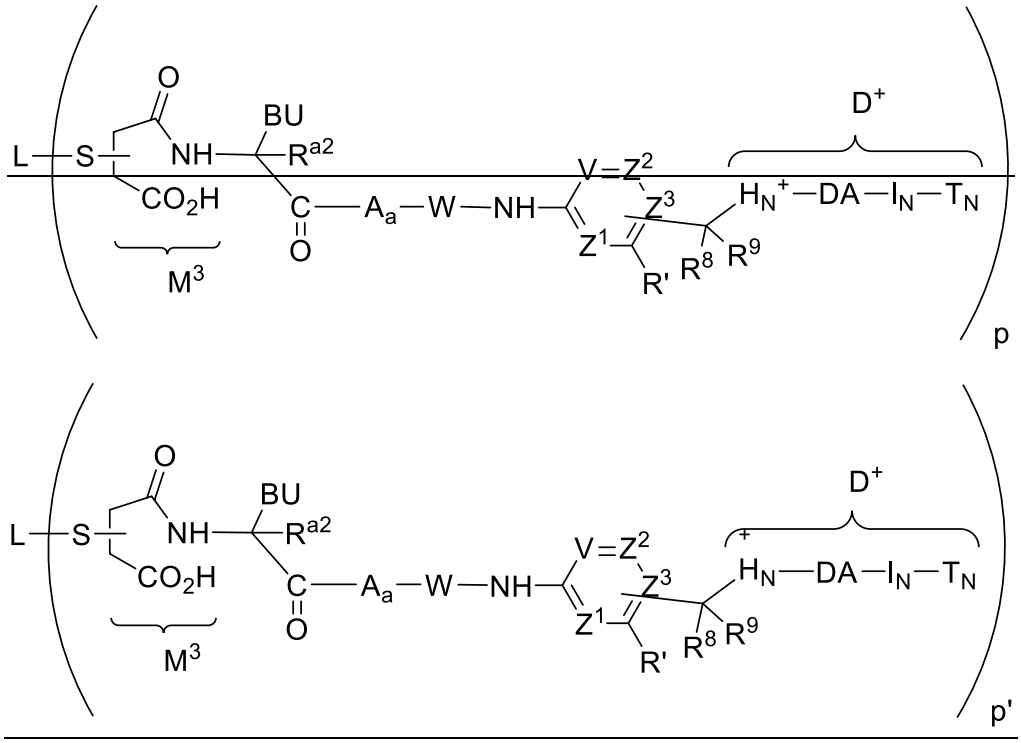
wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

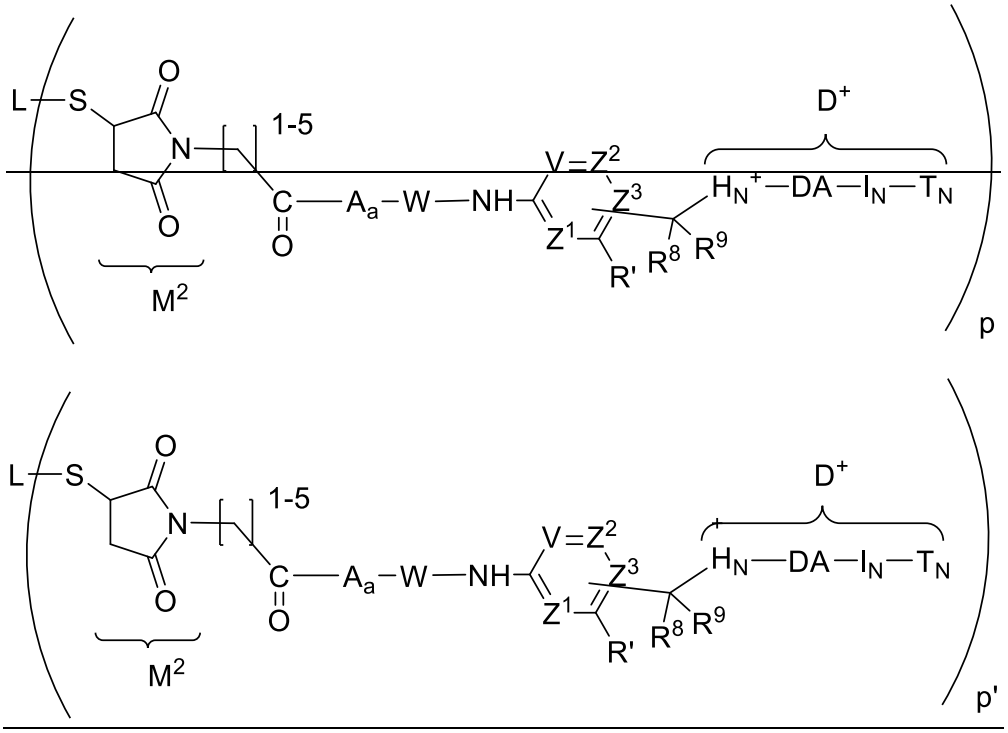
R^{a2} is hydrogen or C_1-C_6 alkyl;

BU has the structure of $–[C(R^{a1})(R^{a1})]$-$[C(R^{a1})(R^{a1})]_{0-3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl;

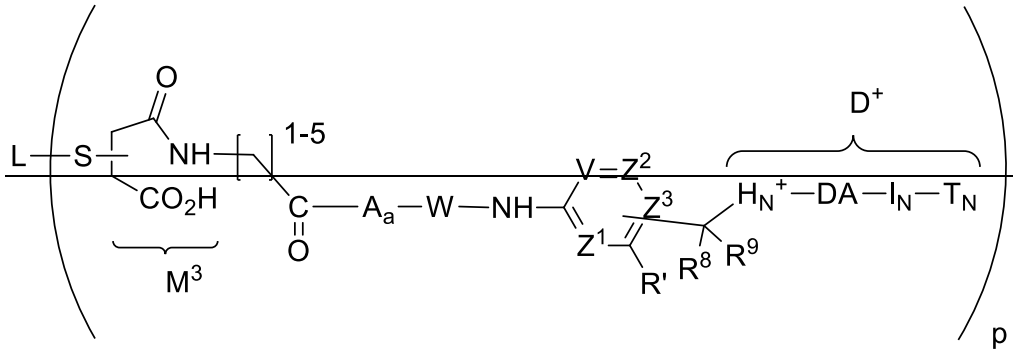
wherein the basic nitrogen atom of BU bonded to R^{a3} is optionally protonated;

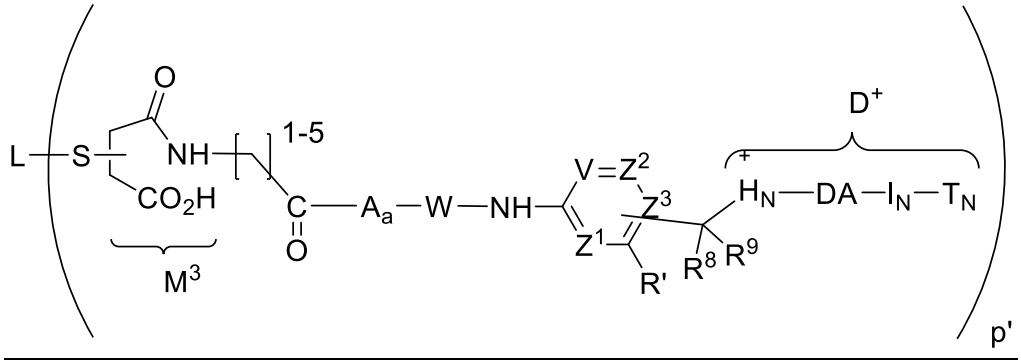
~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or





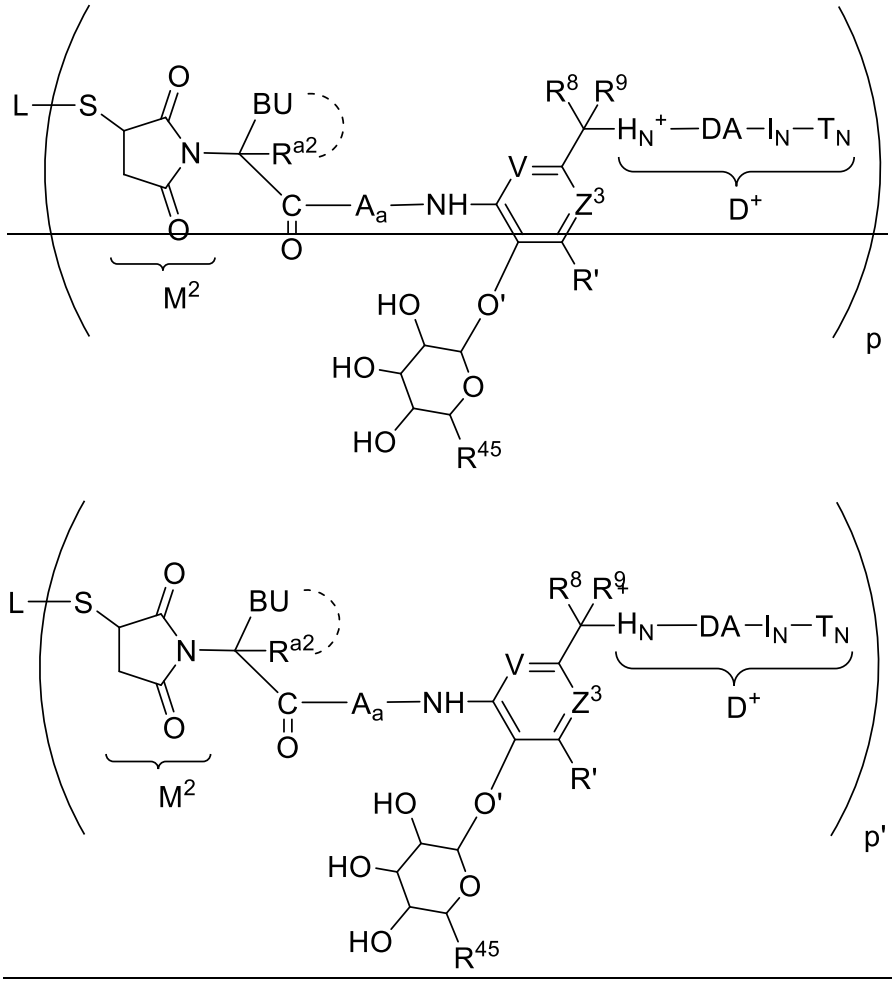
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R' is hydrogen or $-OC_1$-C_6 alkyl or other electron donating group;

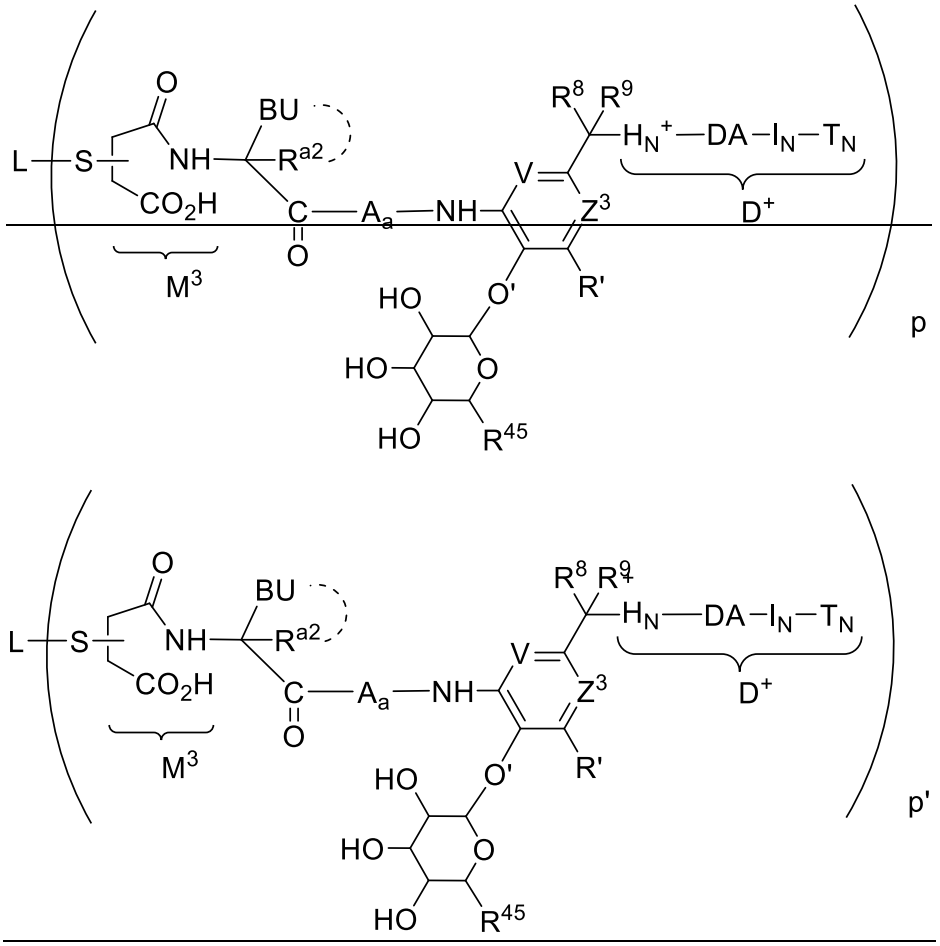
R^{a2} is hydrogen or C_1-C_6 alkyl,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p'.~~

in particular, W-Y is replaced by a Glucuronide Unit of formula –Y(W')-, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

BU has the structure of $–[C(R^{a1})(R^{a1})]-[C(R^{a1})(R^{a1})]_{0-3}-N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; R^{a3} independently are hydrogen, optionally substituted C_1-C_6 alkyl or R^{a3} together with the nitrogen atom to which both are attached define a C_3-C_6 heterocyclyl in which the basic nitrogen is a skeletal atom;

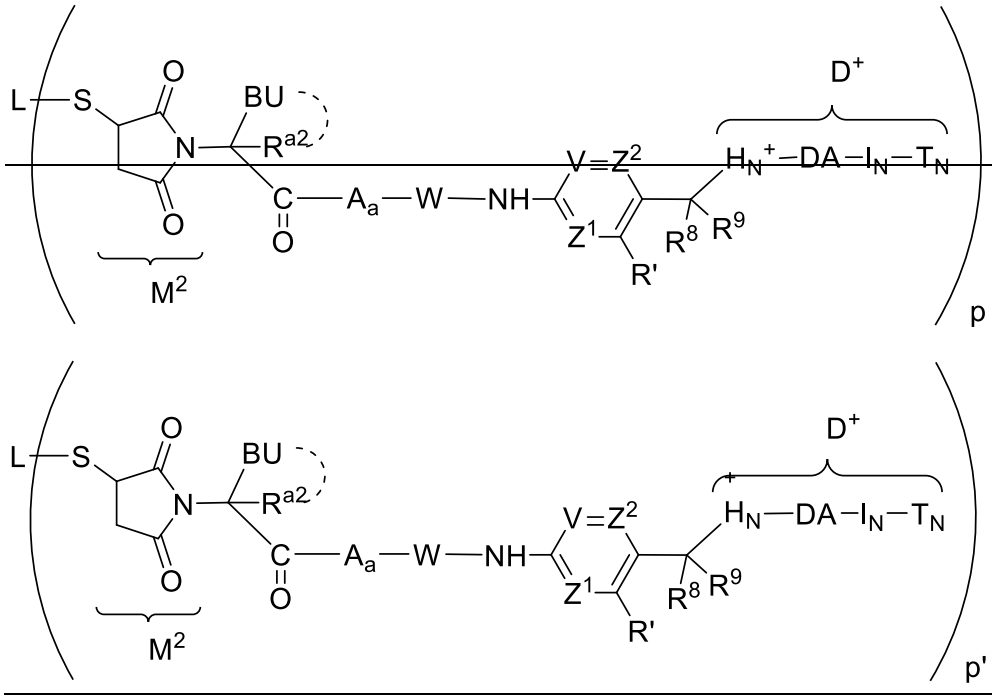
R^{a2} is hydrogen or C_1-C_6 alkyl, optionally cyclized to BU, as indicated by the dotted curved line, wherein one of R^{a1} or one of R^{a3} is replaced with a bond to a carbon atom of R^{a2} when R^{a2} is C_1-C_6 alkyl;

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

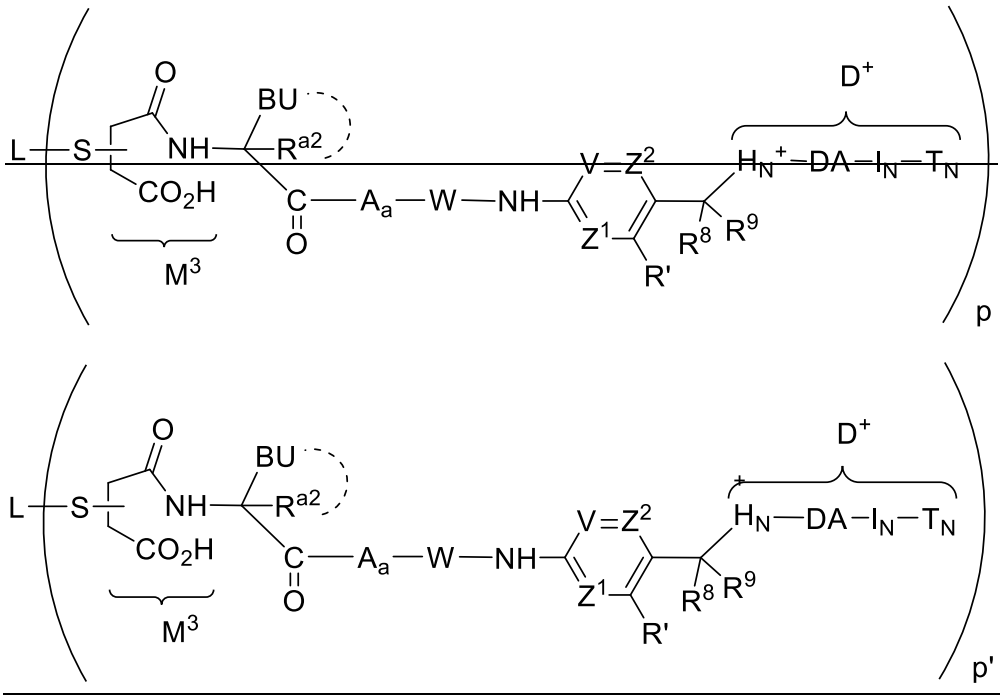
wherein -O'- represents the oxygen atom of an O-glycosidic bond,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or in particular W is from 1-12 independently selected amino acids and the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R’ is hydrogen or –OC_1-C_6 alkyl or other electron donating group;

R^{45} is –CH_2OH or –CO_2H;

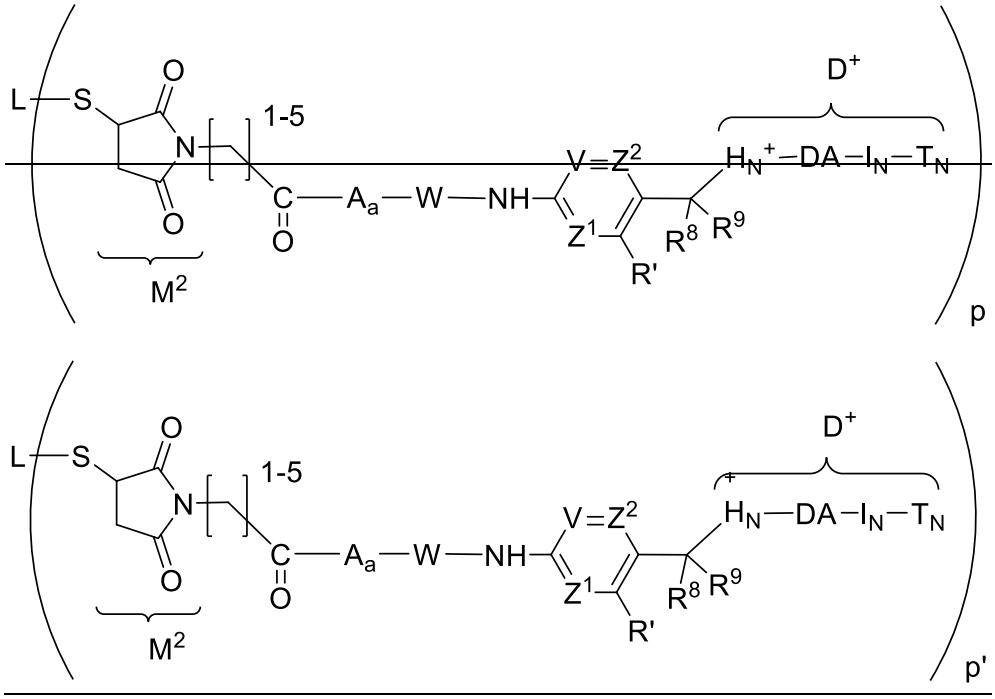
BU has the structure of –[$C(R^{a1})(R^{a1})$]-[$C(R^{a1})(R^{a1})]_{0\text{-}3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; R^{a3} independently are hydrogen, optionally substituted C_1-C_6 alkyl or R^{a3} together with the nitrogen atom to which both are attached define a C_3-C_6 heterocyclyl in which the basic nitrogen is a skeletal atom;

R^{a2} is hydrogen or C_1-C_6 alkyl, optionally cyclized to BU, as indicated by the dotted curved line, wherein one of R^{a1} or one of R^{a3} is replaced with a bond to a carbon atom of R^{a2} when R^{a2} is C_1-C_6 alkyl;

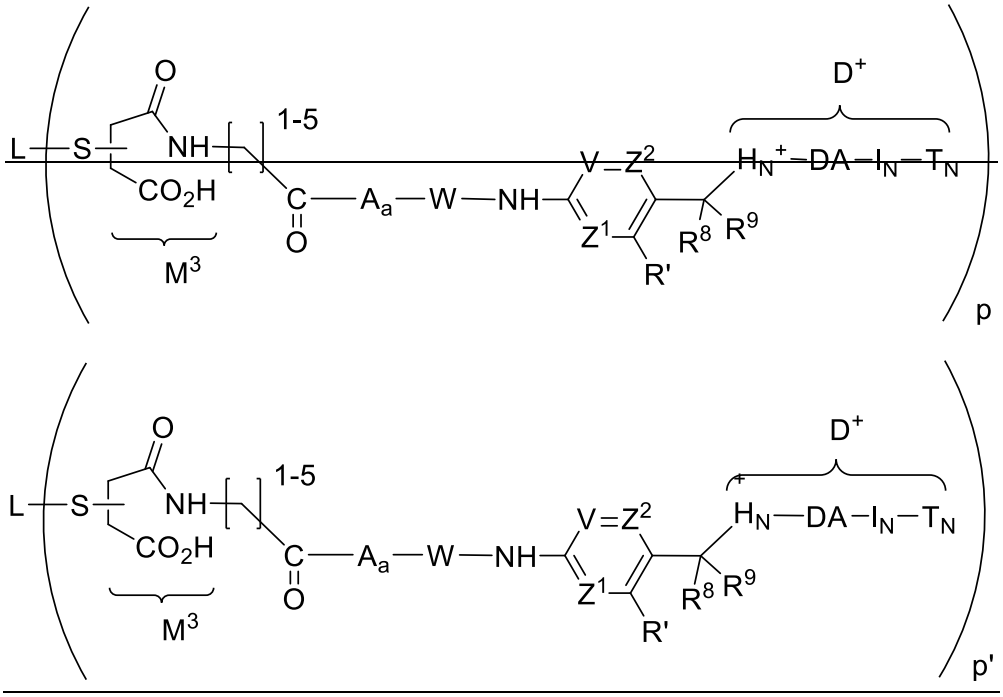
wherein the basic nitrogen atom of BU bonded to R^{a3} is optionally protonated; ~~and~~

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p’,~~

or, wherein the ~~composition~~ <u>compound</u> is represented by the structure~~(s)~~ of:



~~and/~~or



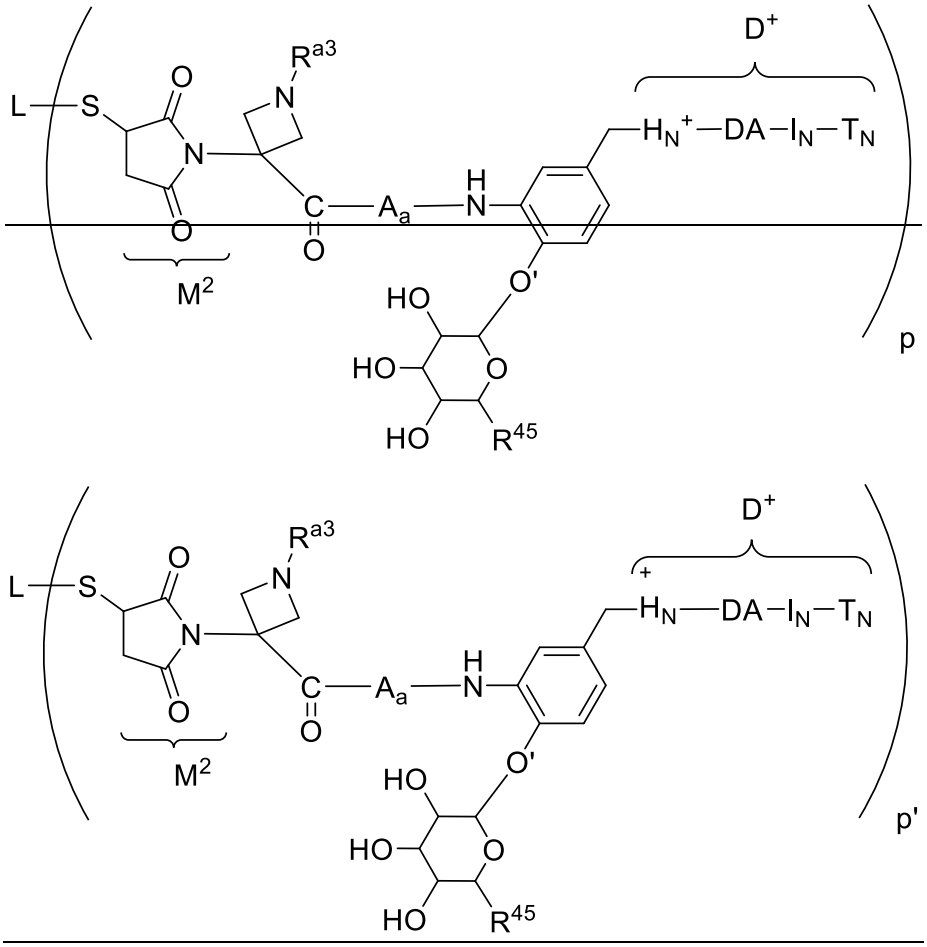
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

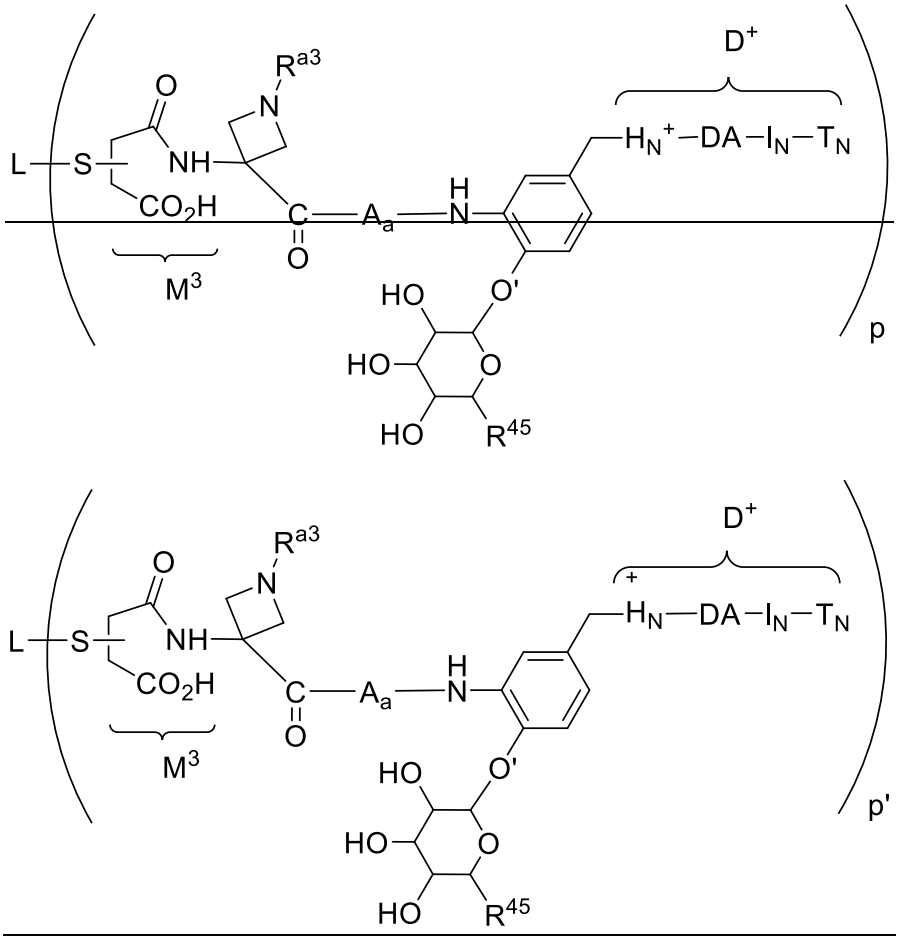
R^{45} is $–CH_2OH$ or $–CO_2H$~~,~~

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p'~~.

14. The Ligand-Drug Conjugate ~~composition~~ compound of claim **13**, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:


L
S
O
N
R^{a3}
N
C
O
A_a
H
N
D^+
H_N^+—DA—I_N—T_N
M^2
O'
HO
HO
HO
O
R^{45}
p
L
S
O
N
R^{a3}
N
C
O
A_a
H
N
D^+
+
H_N—DA—I_N—T_N
M^2
O'
HO
HO
HO
O
R^{45}
p'

~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

R^{45} is $–CH_2OH$ or $–CO_2H$;

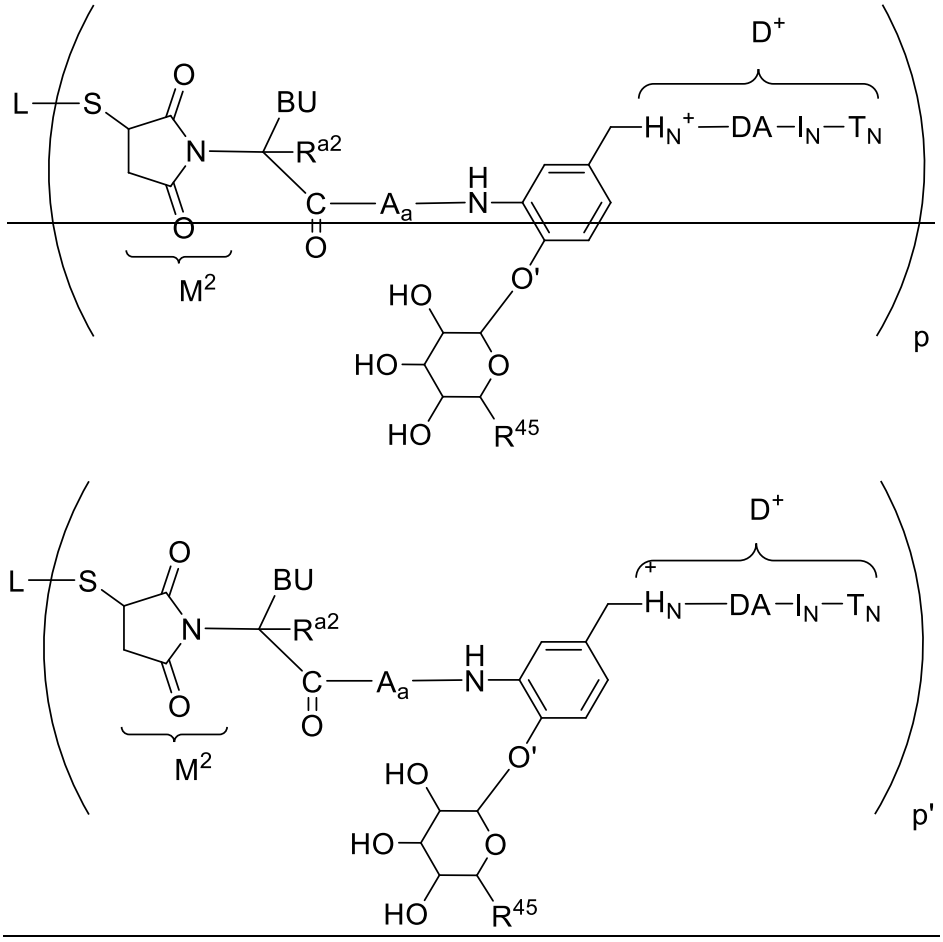
R^{a3} is –H, or optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{1-36}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, and R^{PEG2} is –H or C_1-C_4 alkyl; and

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

-O'- represents the oxygen atom of an O-glycosidic bond,

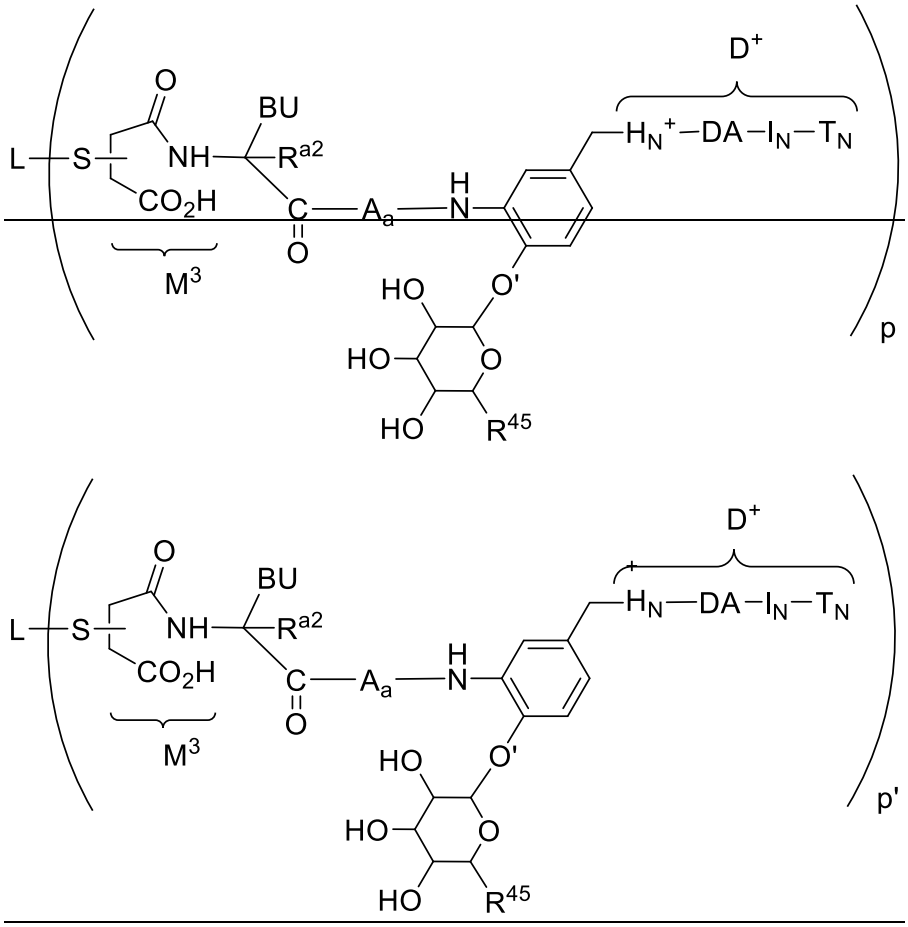
~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:


L
S
O
N
BU
R^{a2}
C
O
A_a
H
N
D^+
H_N^+—DA—I_N—T_N
M^2
O'
HO
HO
HO
O
R^{45}
p

L
S
O
N
BU
R^{a2}
C
O
A_a
H
N
D^+
H_N—DA—I_N—T_N
M^2
O'
HO
HO
HO
O
R^{45}
p'

~~and/~~or



or a ~~pharmaceutical~~ pharmaceutically acceptable salt thereof, wherein

R^{45} is $–CH_2OH$ or $–CO_2H$;

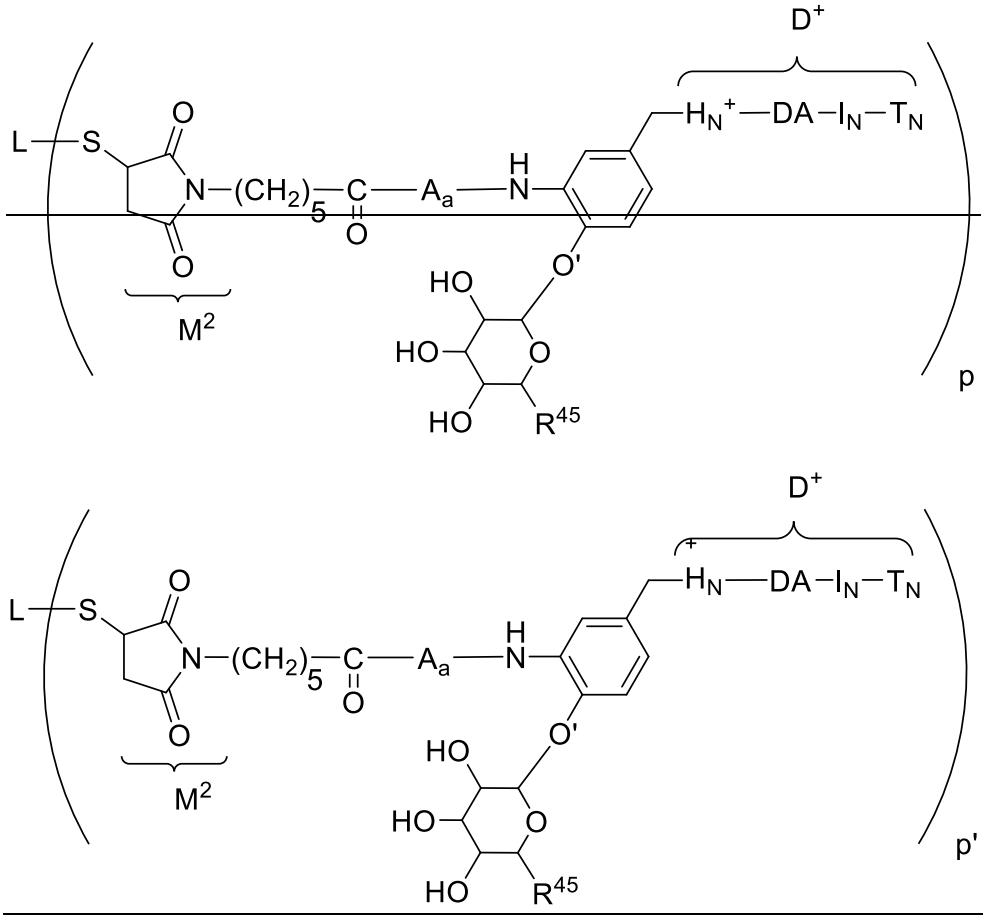
BU is $–CH_2$-NH_2, optionally protonated;

R^{a2} is hydrogen; and

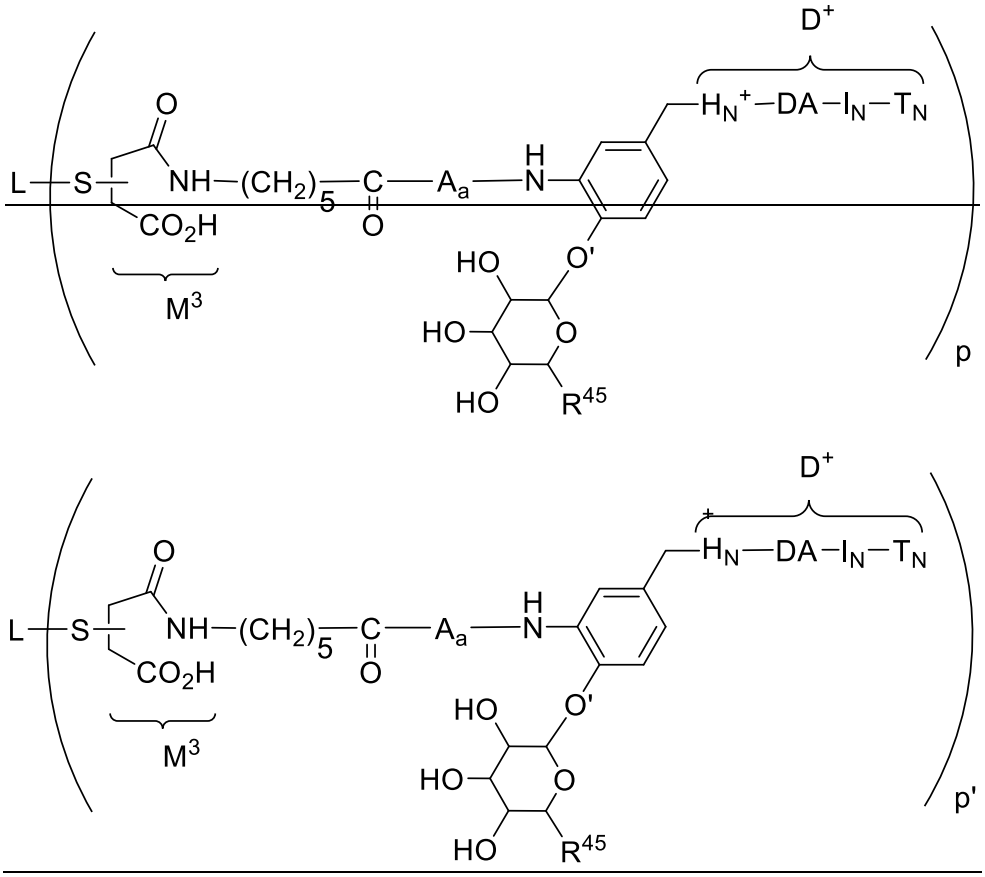
-O'- represents the oxygen atom of an O-glycosidic bond,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure of:


D+
L
S
O
N
(CH2)5
C
Aa
H
N
HN+
DA
IN
TN
O
M2
HO
HO
HO
O'
R45
p
D+
L
S
O
N
(CH2)5
C
Aa
H
N
HN
DA
IN
TN
O
M2
HO
HO
HO
O'
R45
p'

~~and/~~or



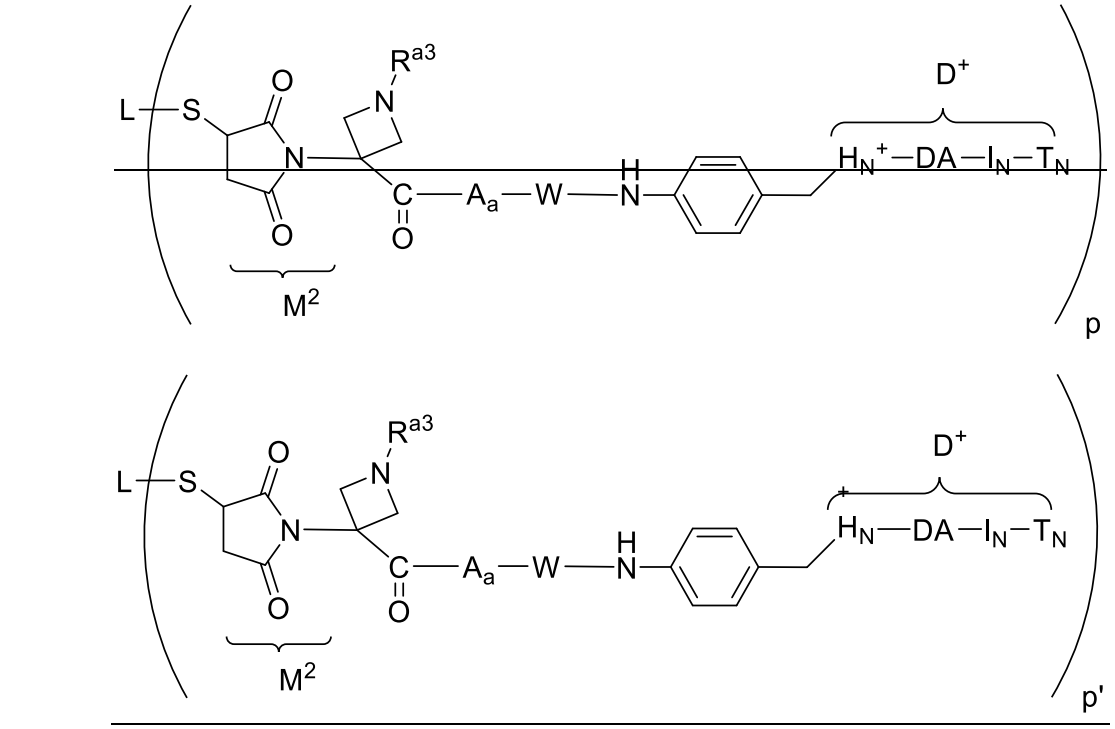
or a ~~pharmaceutical~~ pharmaceutically acceptable salt thereof, wherein

R^{45} is $–CH_2OH$ or $–CO_2H$; and

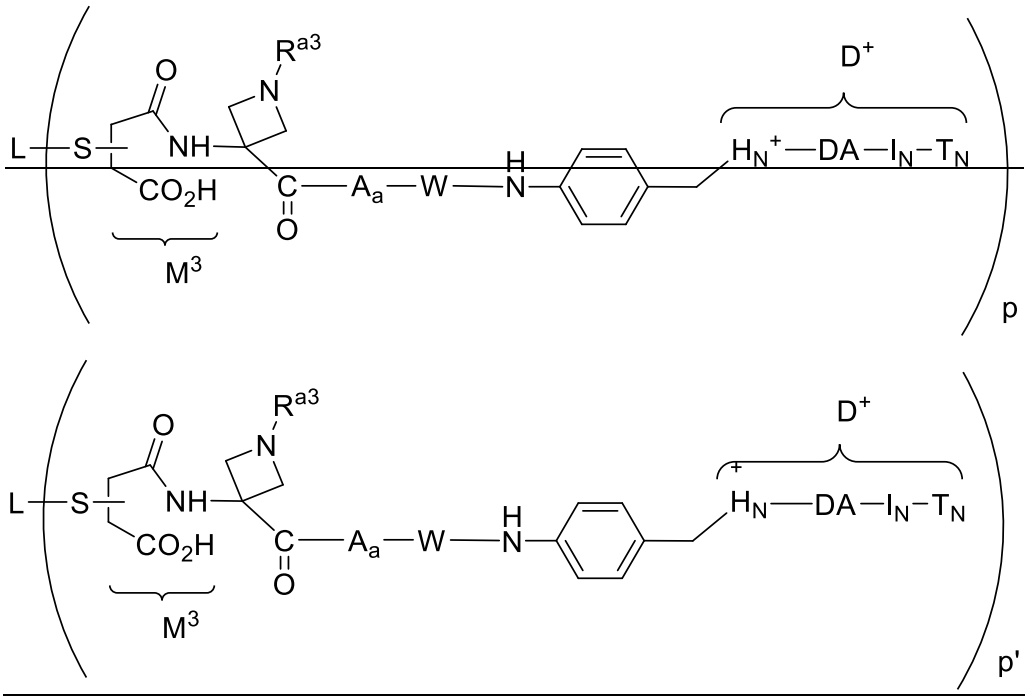
-O'- represents the oxygen atom of an O-glycosidic bond,

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



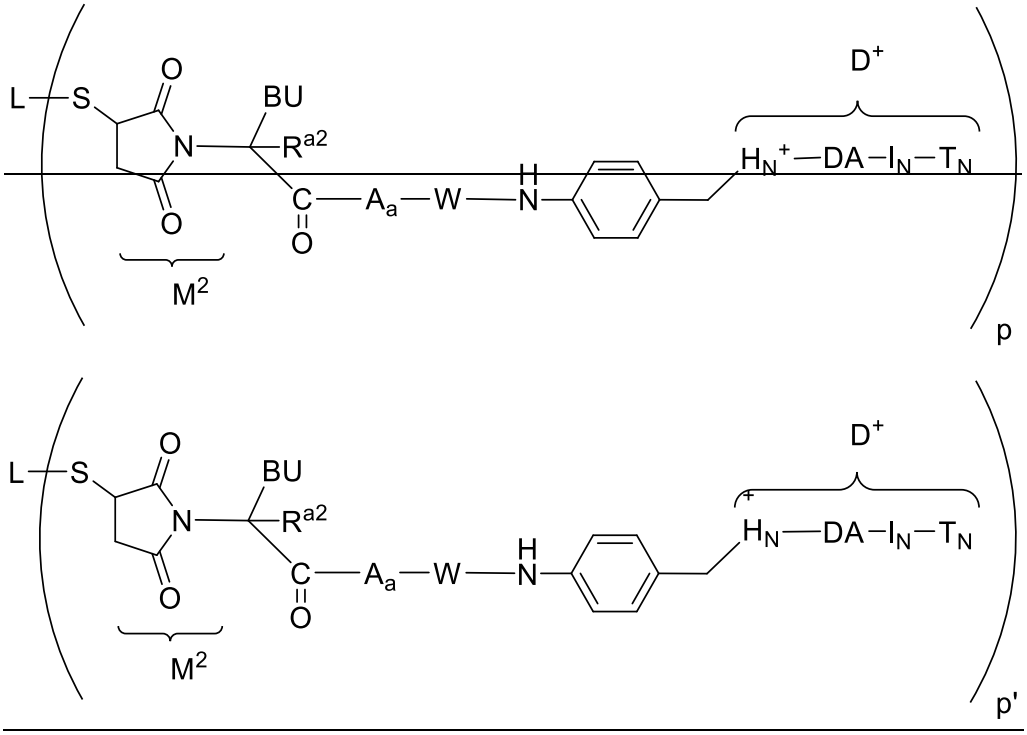
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein W is from 1-12 independently selected amino acids;

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

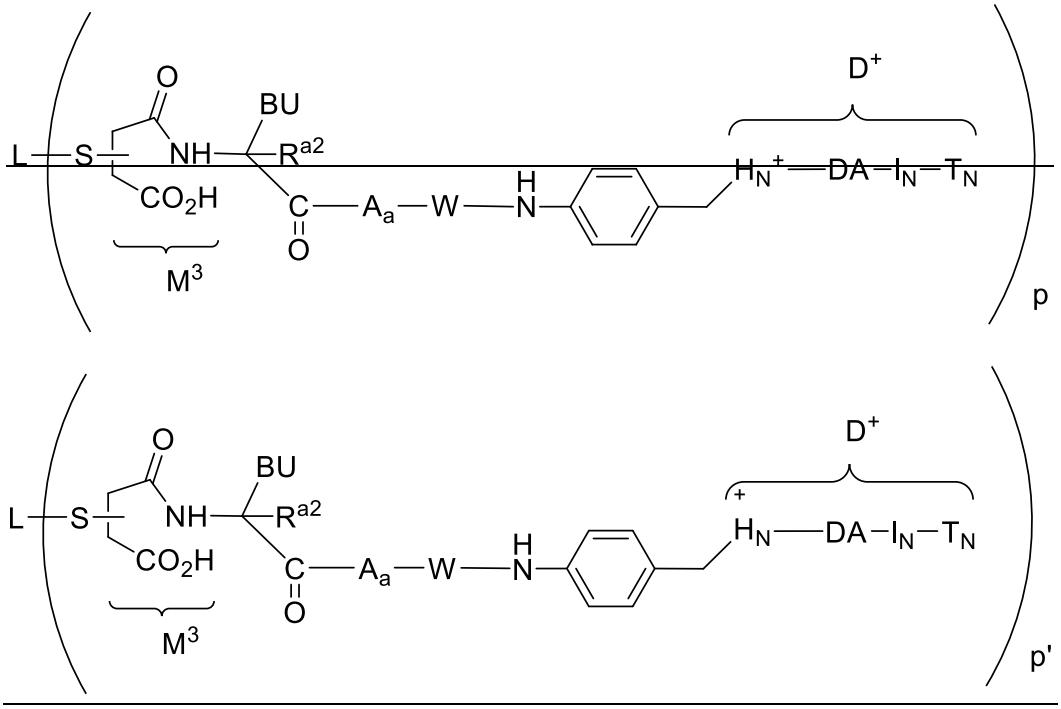
wherein the basic nitrogen atom bonded to R^{a3} is optionally protonated; ~~and~~

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

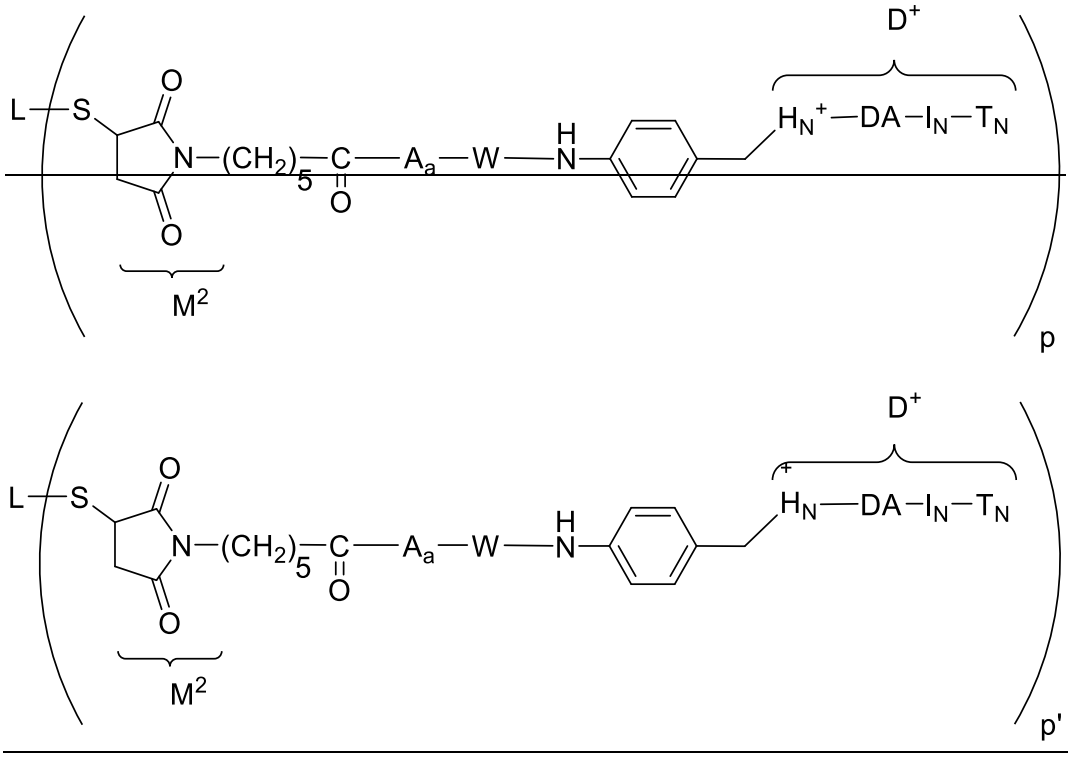
W is from 1-12 independently selected amino acids;

BU is $–CH_2\text{-}NH_2$, optionally protonated;

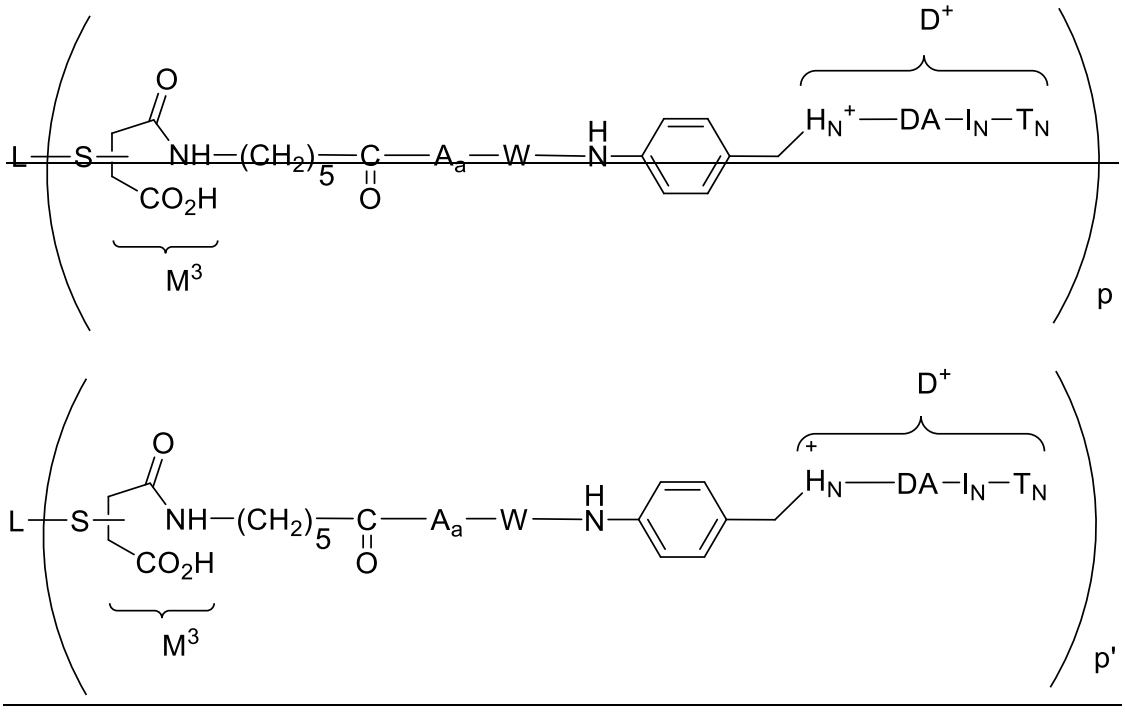
R^{a2} is hydrogen; ~~and~~

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p',~~

or wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or

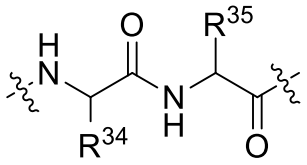


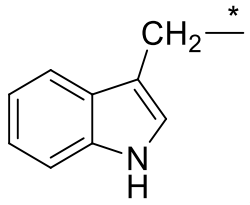
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

W is from 1-12 independently selected amino acids~~,~~

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition in which subscript p is replaced by subscript p'~~.

15. The Ligand-Drug Conjugate ~~composition~~ compound of claim **11** wherein W is a dipeptide having the structure of:



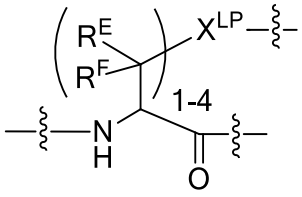
wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH_3 or has the structure of , wherein the asterisk indicates the site of covalent attachment to the dipeptide backbone; and

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

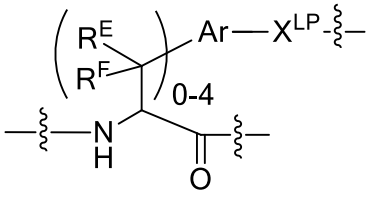
wherein the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to Y and the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment of the dipeptide to the remainder of the peptide sequence,

in particular wherein the dipeptide 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-, and -Trp-Cit-, wherein Cit is citrulline.

16. The Ligand-Drug Conjugate ~~composition~~ compound of claim **11**, wherein 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:



(L^P-1)



(L^P-2)

or a salt thereof, in particular ~~pharmaceutical~~ pharmaceutically acceptable salt, wherein

X^{LP} is selected from the group consisting of –O-, -NR^{LP}-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)N(R^{LP})-, -N(R^{LP})C(=O)N(R^{LP})-, -N(R^{LP})C(=NR^{LP})N(R^{LP})-, and 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;

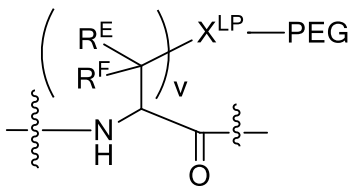
Ar is a C_6-C_{10} arylene or a C_5-C_{10} heteroarylene, optionally substituted;

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 and optionally substituted C_5-C_{10} heteroarylene,

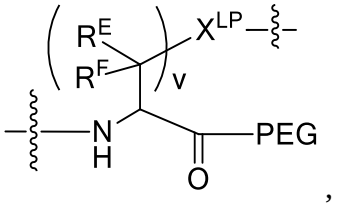
or R^E and R^F together with the carbon atom to which both are attached defines an optionally substituted spiro C_3-C_6 carbocyclo, or R^E and R^F from adjacent carbon atoms together with these atoms and any intervening carbon atoms defines an optionally substituted C_5-C_6 carbocyclo with any remaining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

wherein one of the wavy lines indicates the site of covalent attachment of a PEG Unit and the other wavy lines indicates covalent attachment of Formula L^P-1 or Formula L^P-2 within the structure representing the Ligand Drug Conjugate ~~composition~~ compound,

or wherein -L^P(PEG)- has the structure of Formula L^P-3 or Formula L^P-4:



(L^P-3)



(L^P-4)

or a salt thereof, in particular a ~~pharmaceutical~~ pharmaceutically acceptable salt, wherein

subscript v is an integer ranging from 1 to 4;

X^{LP} is selected from the group consisting of –O-, -NR^{LP}-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)N(R^{LP})-, -N(R^{LP})C(=O)N(R^{LP})-, -N(R^{LP})C(=NR^{LP})N(R^{LP})-, and 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 and 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 spiro 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, or

wherein the side chain of $–[C(R^E)(R^F)]_v$-X^{LP}- is provided by a natural or un-natural amino acid side chain; and

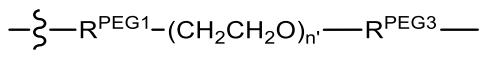
wherein one of the wavy lines indicate the site of covalent attachment of a PEG Unit and the other wavy lines indicates covalent attachment of Formula L^P-1 or Formula L^P-2 within the structure representing the Ligand Drug Conjugate ~~composition~~ compound,

in particular in any one of the above formula, R^E and R^F are independently selected from the group consisting of -H, and -C_1-C_4 alkyl and X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-;

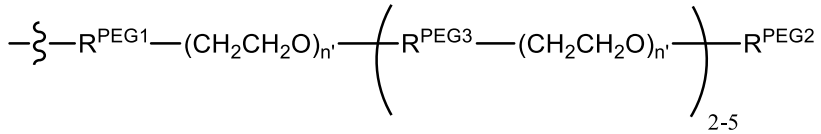
and in L^P-3 or L^P-4 PEG has the structure selected from the group consisting of:



,



, and



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

subscript n' independently ranges from 1 to 72;

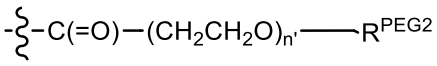
R^{PEG1} is an optional PEG Attachment Unit;

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

R^{PEG3} is an PEG Coupling Unit,

or

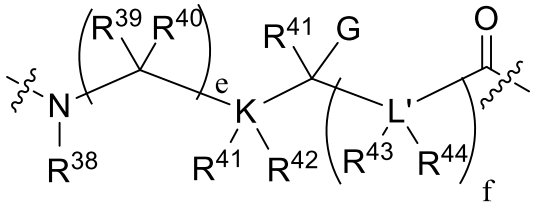
X^{LP}-PEG has the structure of:



,

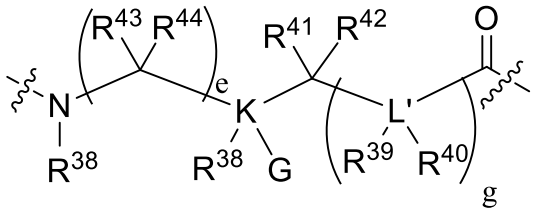
wherein subscript n' is 8, 12 or 24 and R^{PEG2} is H or $–CH_3$,

or A or a subunit thereof has the structure of formula (3) or formula (4):



f

,



g

(3) (4)

wherein the wavy lines indicated covalent attachment within the ~~composition~~ 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

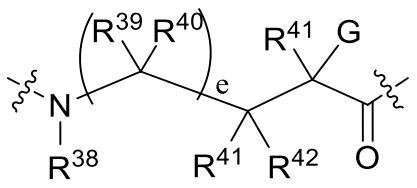
R^{39}, R^{40} together with the carbon atom to which both are attached, or R^{41}, R^{42} together with K to which both are attached when K is a carbon atom, define a C_3-C_6 carbocyclo, and R^{41}-R^{44} are as defined herein,

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

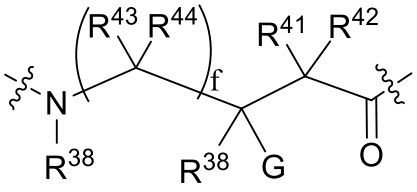
or R^{40} and R^{41}, or R^{40} and R^{43}, or R^{41} and R^{43} to together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{44} and the remainder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

provided that when K is O or S, R^{41} and R^{42} are absent, and when K is N, one of R^{41}, R^{42} is absent, and when L' is O or S, R^{43} and R^{44} are absent, and when L' is N, one of R^{43}, R^{44} is absent,

in particular having the formula of:



(3a),



(4a),

wherein subscript e and f are independently 0 or 1,

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

17. The Ligand-Drug Conjugate ~~composition~~ compound of claim **11**, wherein the Ligand Unit is an intact antibody or antigen binding fragment thereof, wherein the moiety targeted by the antibody Ligand Unit is an accessible cell-surface antigen of abnormal cells that is capable of cellular internalization when bound to ~~ADC~~ the Ligand Drug Conjugate compound ~~of the composition~~ and is present in greater copy number on the abnormal cells in comparison to normal cells distant from the site of the abnormal cells,

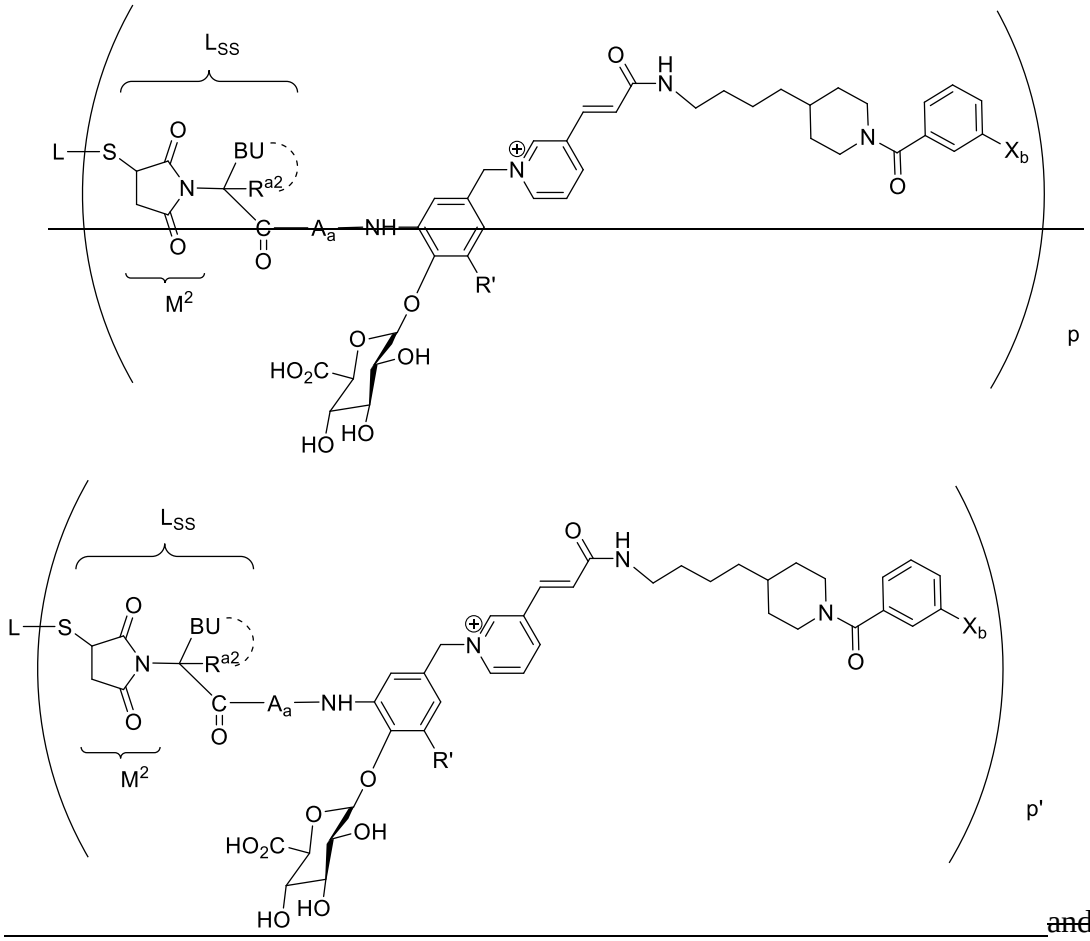
or wherein the Ligand Unit is a cognate ligand of an accessible cell-surface receptor on abnormal cell that is capable of cellular internalization when bound to a Ligand Drug Conjugate compound ~~of the composition~~, and wherein the receptor is present in greater copy number on the abnormal cells in comparison to normal cells,

or wherein the Ligand Unit is an antibody, thereby defining an antibody Ligand Unit of an antibody drug conjugate (ADC), wherein the moiety targeted by the antibody Ligand Unit is an accessible cell-surface antigen of a vascular epithelial cell in the vicinity of abnormal

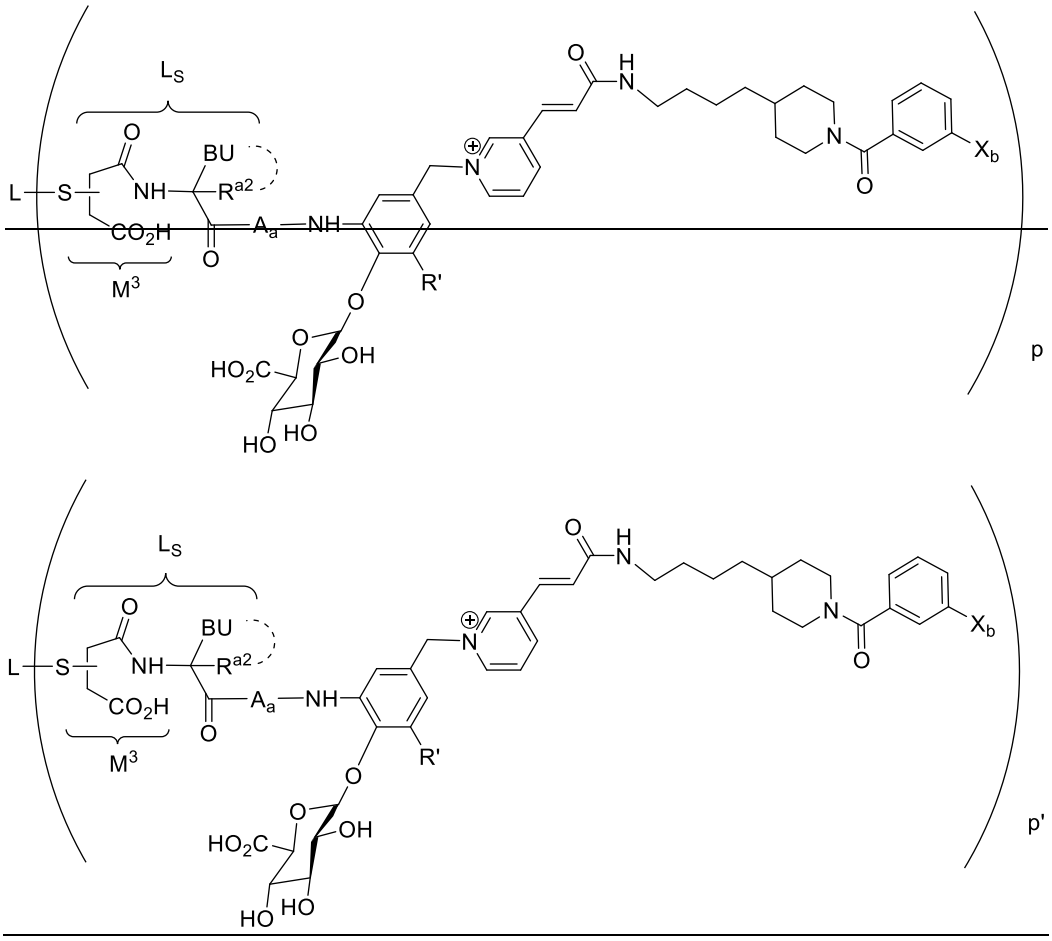
cells, wherein said antigen is capable of cellular internalization of bound ADC and is present in greater copy number on said cells in comparison to normal epithelial cells distant from the site of the abnormal cells.

18. The Ligand Drug Conjugate ~~composition~~ compound of claim **17**, wherein the Ligand Unit is an intact antibody and subscript p' is ~~about~~ 2, ~~about~~ 4, or ~~about~~ 8 and wherein each sulfur atom of the antibody Ligand Unit bonded to each succinic acid (M^2) moiety or succinic acid amide (M^3) moiety is that of a cysteine residue of the intact antibody or wherein each cysteine residue is an introduced cysteine residue in the heavy chain or light chain of the antibody or antigen binding-fragment thereof.

19. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

L is an antibody, thereby defining an antibody Ligand Unit of an antibody drug conjugate (ADC), and S is a sulfur atom of the antibody;

subscript a is 1 and A is an amino acid residue;

BU is an acyclic Basic Unit so that the dotted curve line is absent, and R^{a2} is hydrogen, or

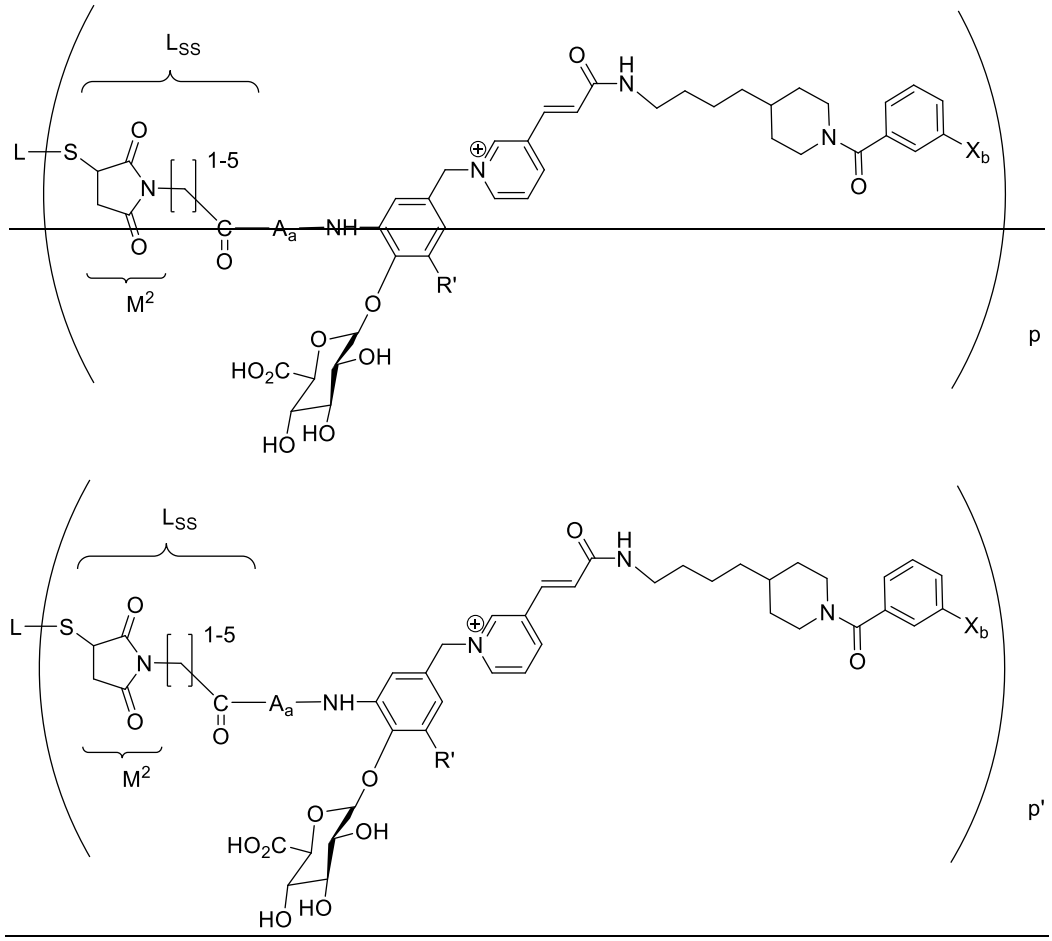
BU together with R^{a2} as C_1-C_6 alkyl and the carbon atom to which both are attached define a cyclic Basic Unit so that the dotted curved line is present; and

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$.

or

wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

L is an antibody, thereby defining an antibody Ligand Unit of an antibody drug conjugate (ADC), and S is a sulfur atom of the antibody;

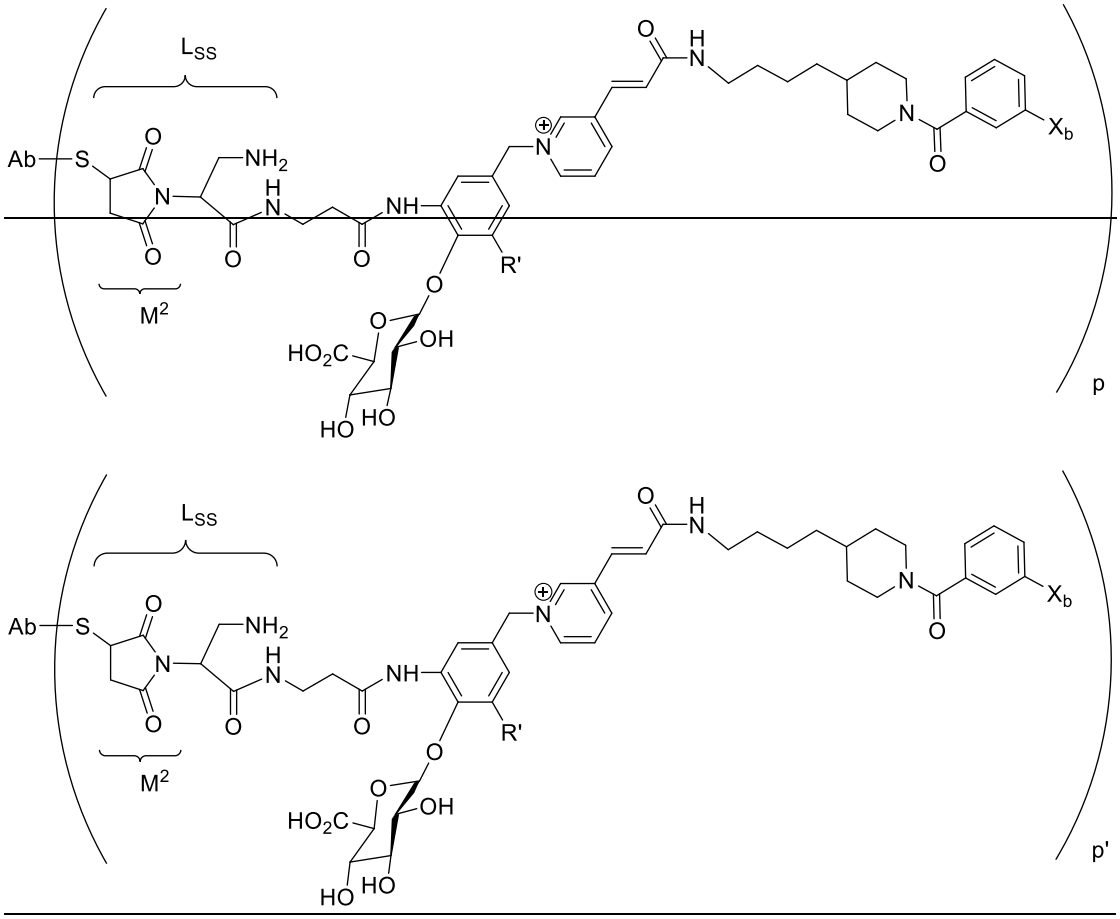
subscript a is 1 and A is an amino acid residue;

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$,

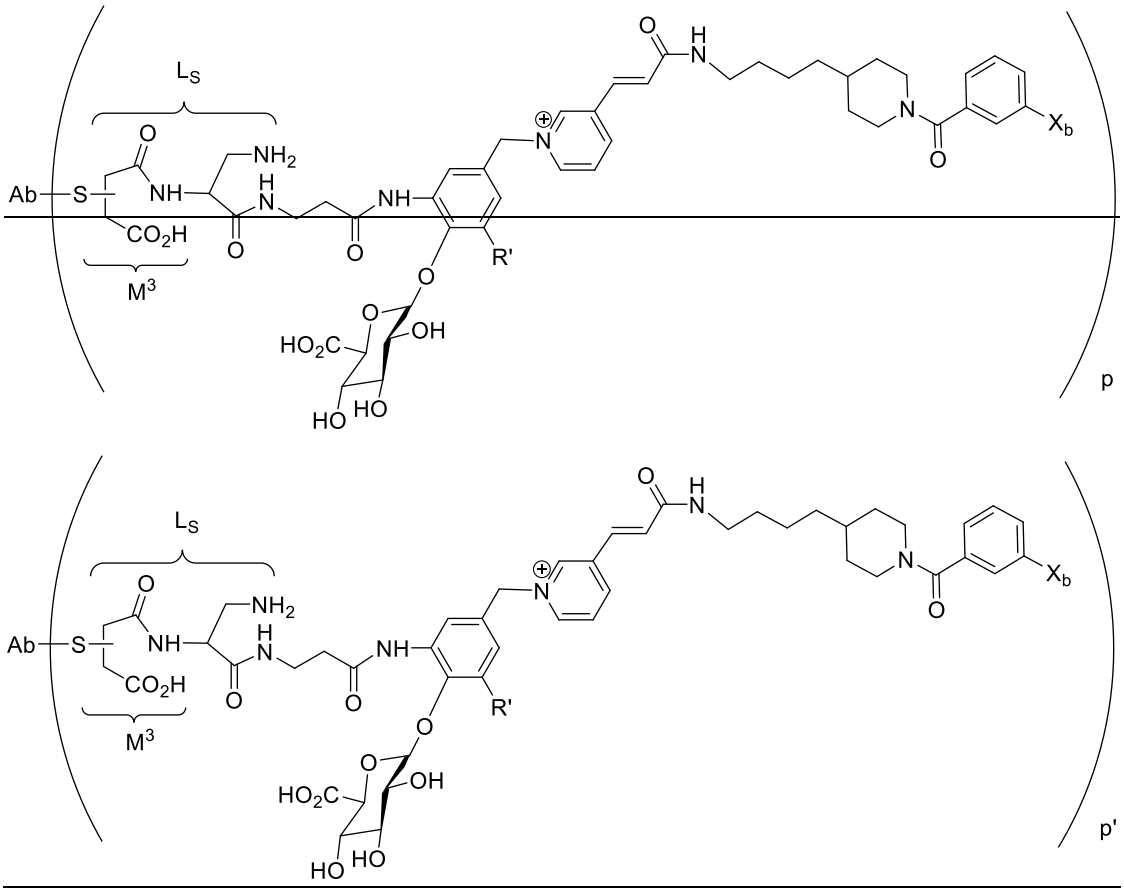
in particular

wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:


Ab
S
O
N
O
O
L_{SS}
M^2
NH_2
H
N
O
NH
O
O
R'
O
O
OH
HO_2C
HO
HO
O
H
N
N
X_b
O
p

Ab
S
O
N
O
O
L_{SS}
M^2
NH_2
H
N
O
NH
O
O
R'
O
O
OH
HO_2C
HO
HO
O
H
N
N
X_b
O
p'

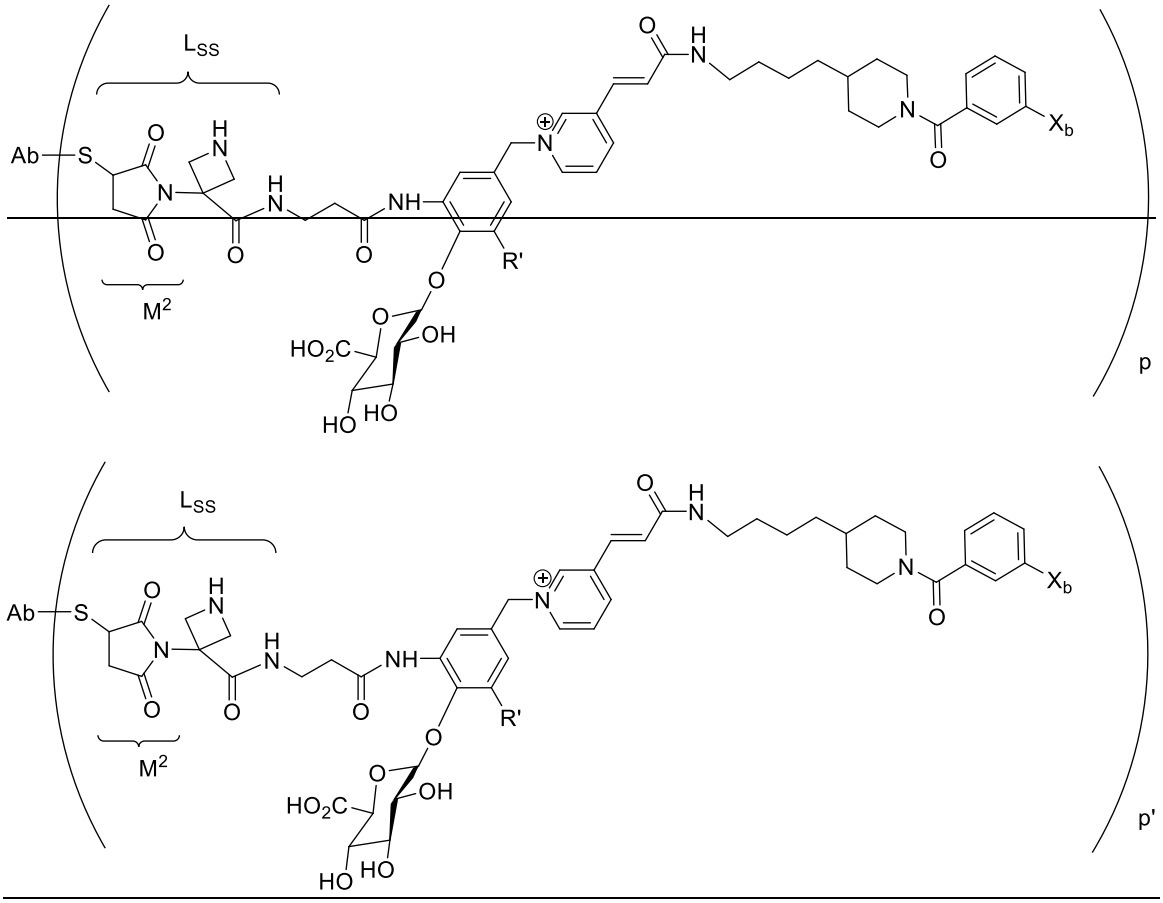
~~and/~~or



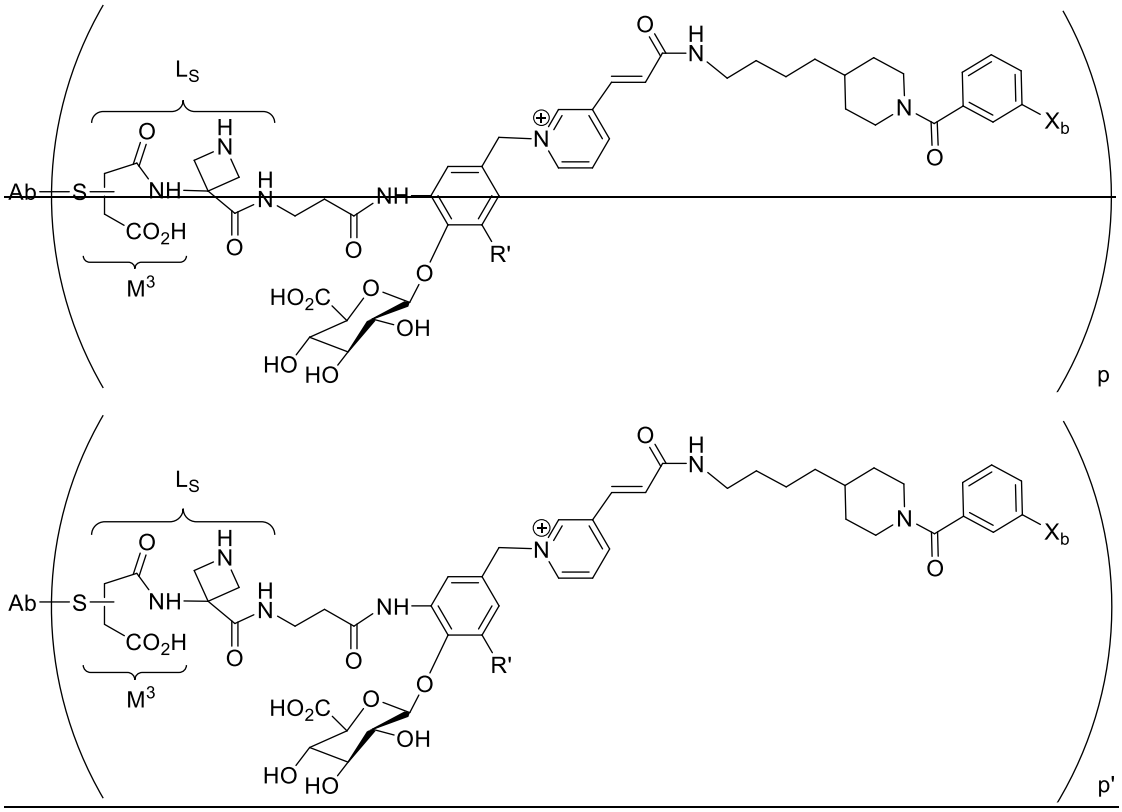
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein Ab is an antibody Ligand Unit; S is a sulfur atom of the antibody; and subscript p’ is ~~about~~ 8,

or in particular,

wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:

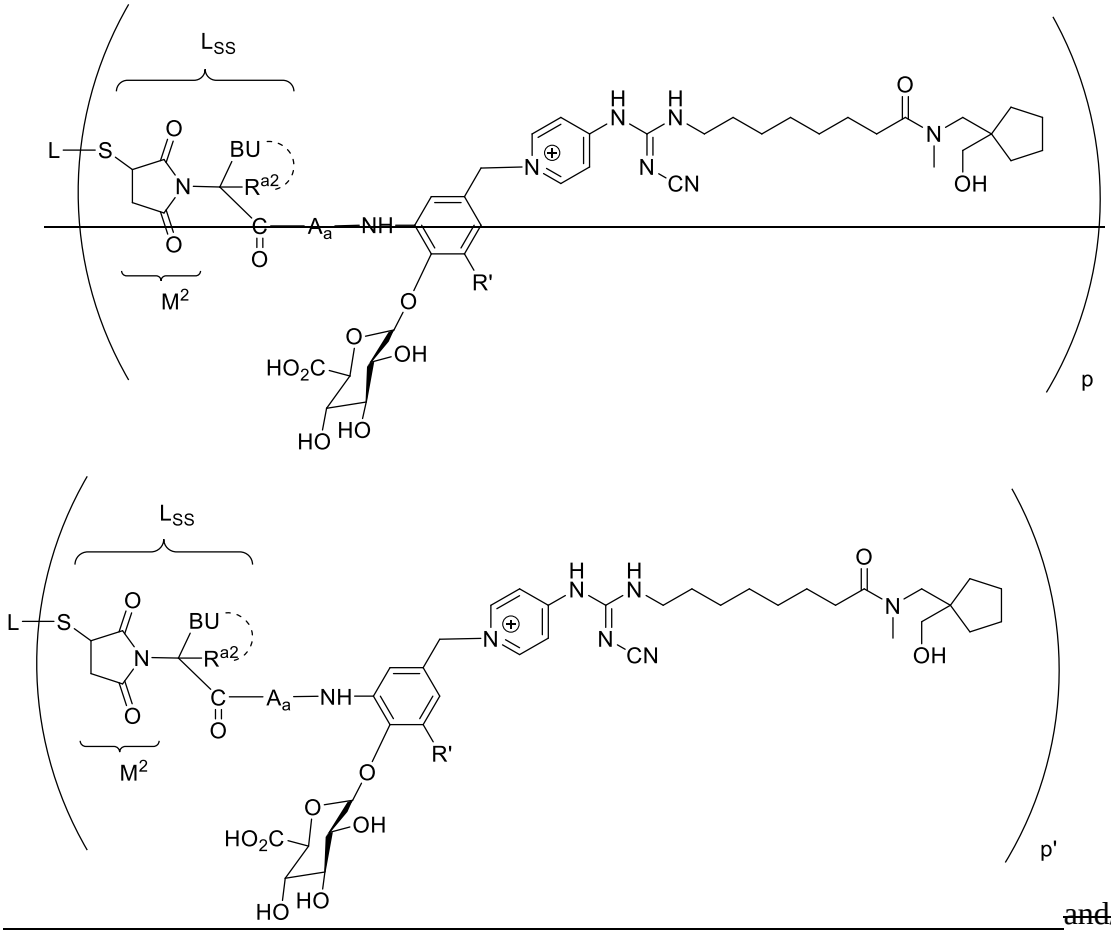


~~and/~~or

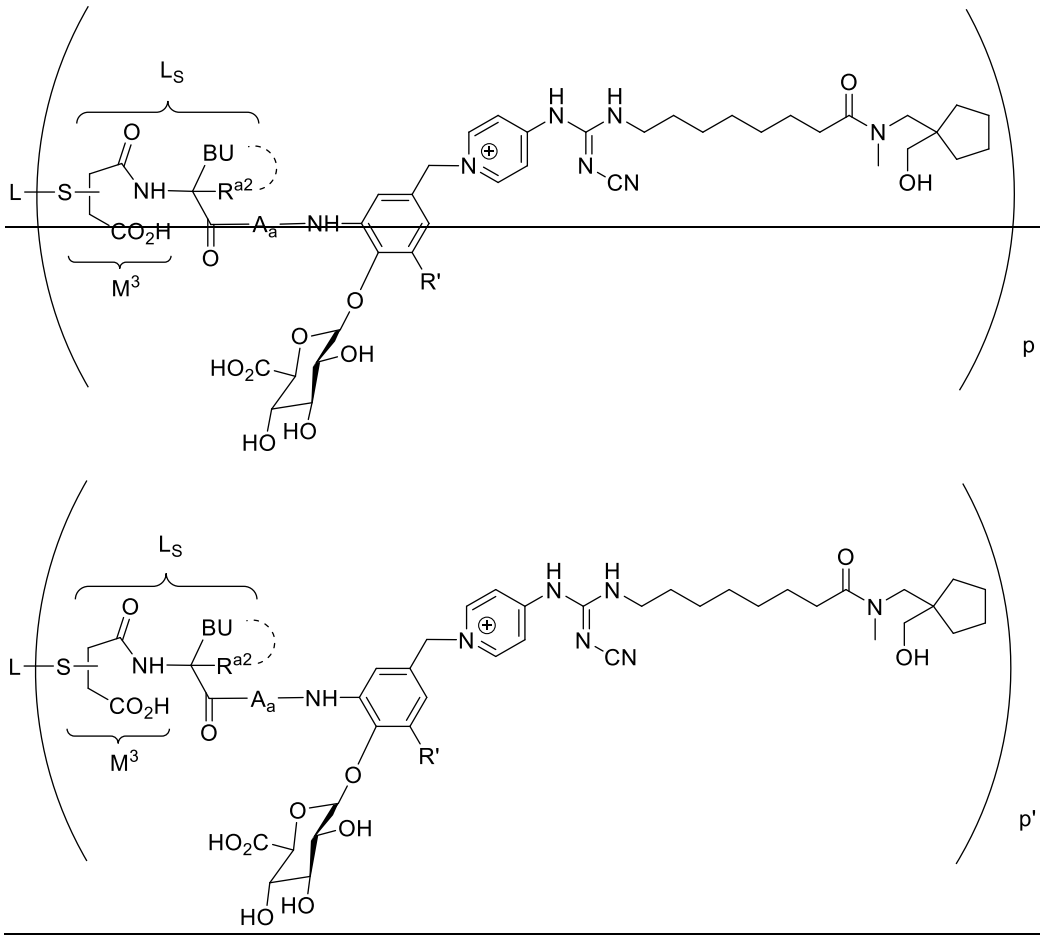


in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein Ab is an antibody Ligand Unit; S is a sulfur atom of the antibody; and subscript p’ is ~~about~~ 8.

20. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

L is an antibody, thereby defining an antibody Ligand Unit of an antibody drug conjugate (ADC), and S is a sulfur atom of the antibody;

subscript a is 1 and A is an amino acid residue;

BU is an acyclic Basic Unit so that the dotted curve line is absent, and R^{a2} is hydrogen, or

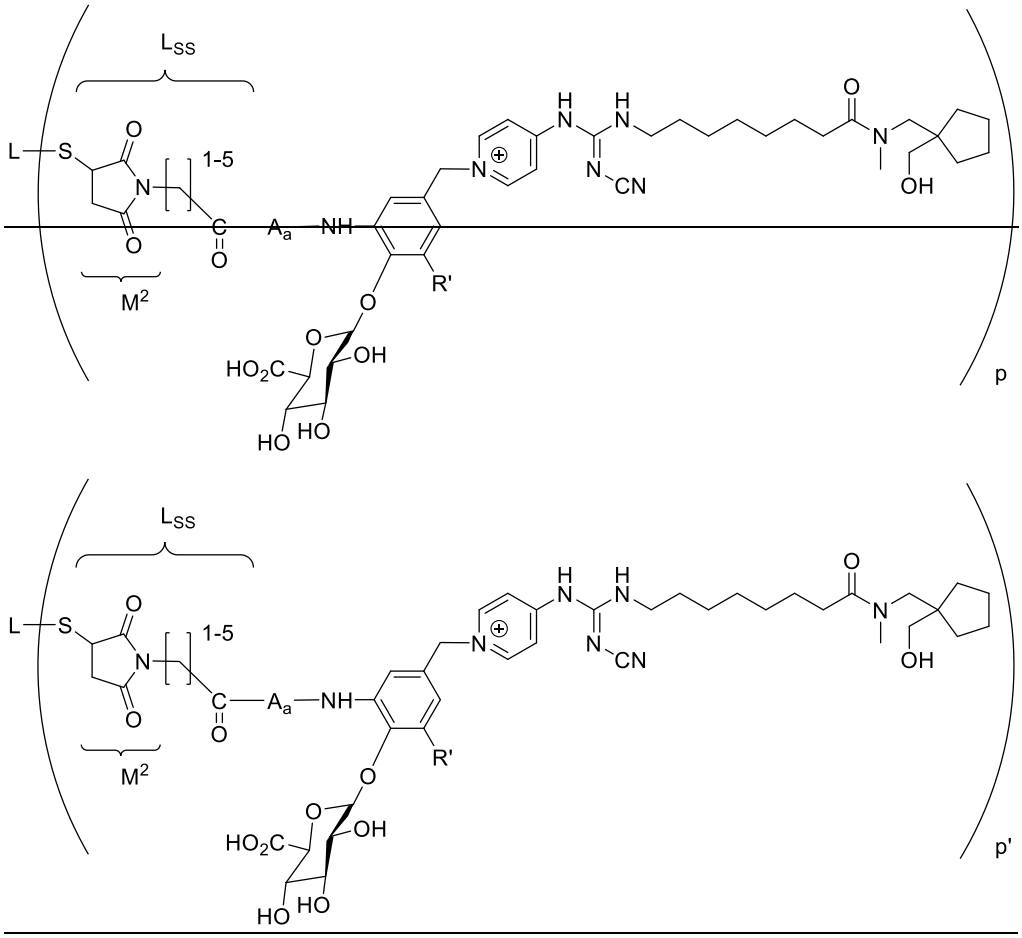
BU together with R^{a2} as C_1-C_6 alkyl and the carbon atom to which both are attached define a cyclic Basic Unit so that the dotted curved line is present; and

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$,

or

wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein

L is an antibody, thereby defining an antibody Ligand Unit of an antibody drug conjugate (ADC), and S is a sulfur atom of the antibody;

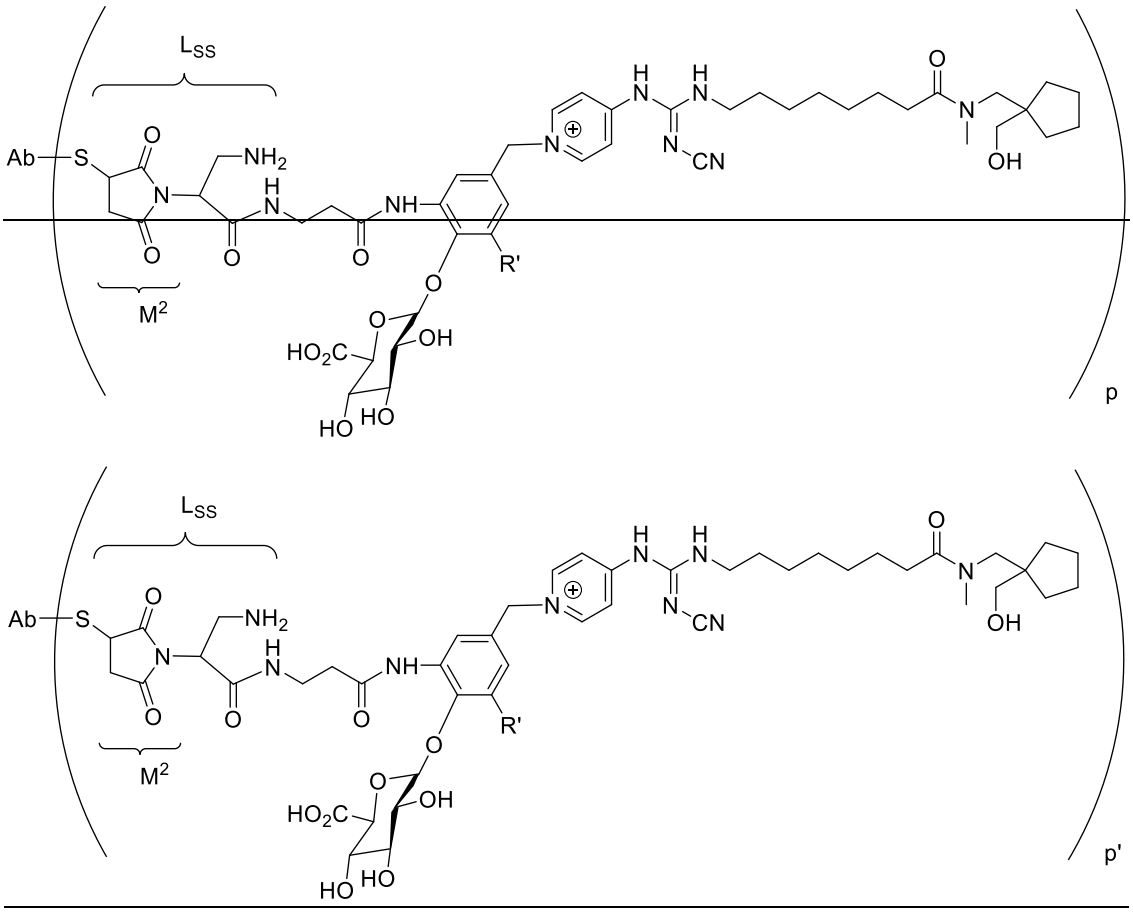
subscript a is 1 and A is an amino acid residue;

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$,

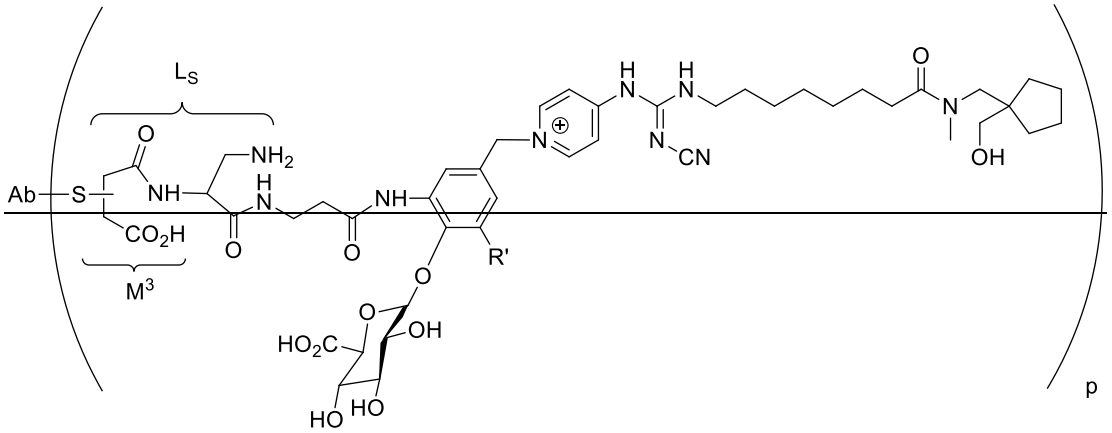
in particular

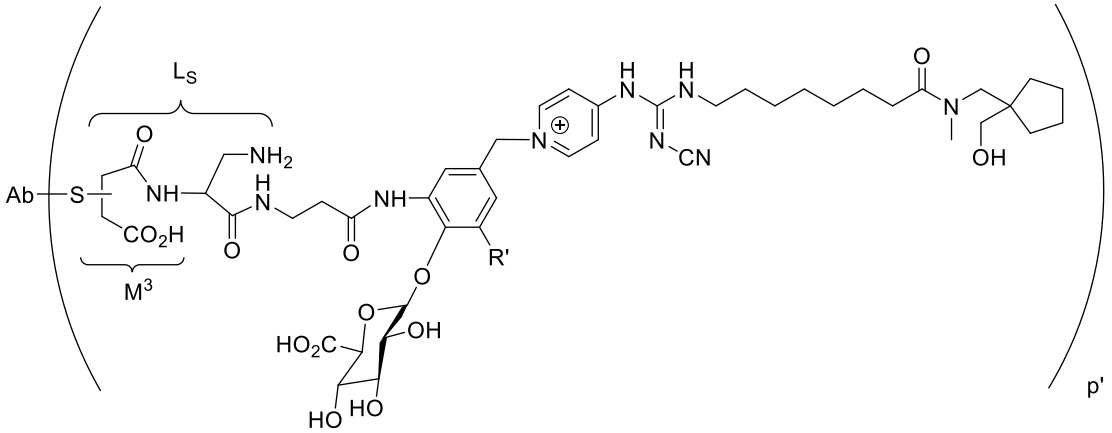
wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:


Ab
S
O
N
O
O
NH2
H
N
O
NH
O
M2
LSS
N
H
N
H
N
CN
O
N
OH
R'
O
O
HO2C
OH
HO
HO
p

Ab
S
O
N
O
O
NH2
H
N
O
NH
O
M2
LSS
N
H
N
H
N
CN
O
N
OH
R'
O
O
HO2C
OH
HO
HO
p'

~~and/~~or

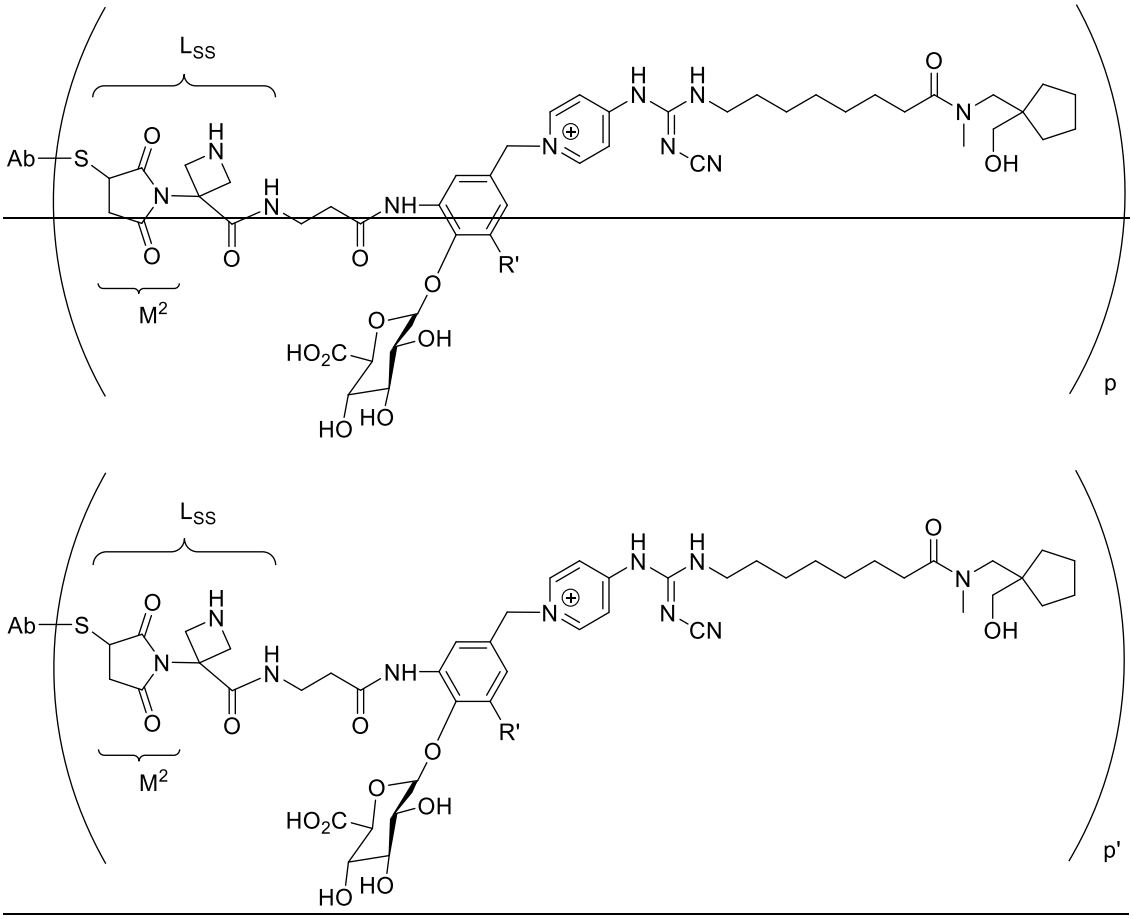




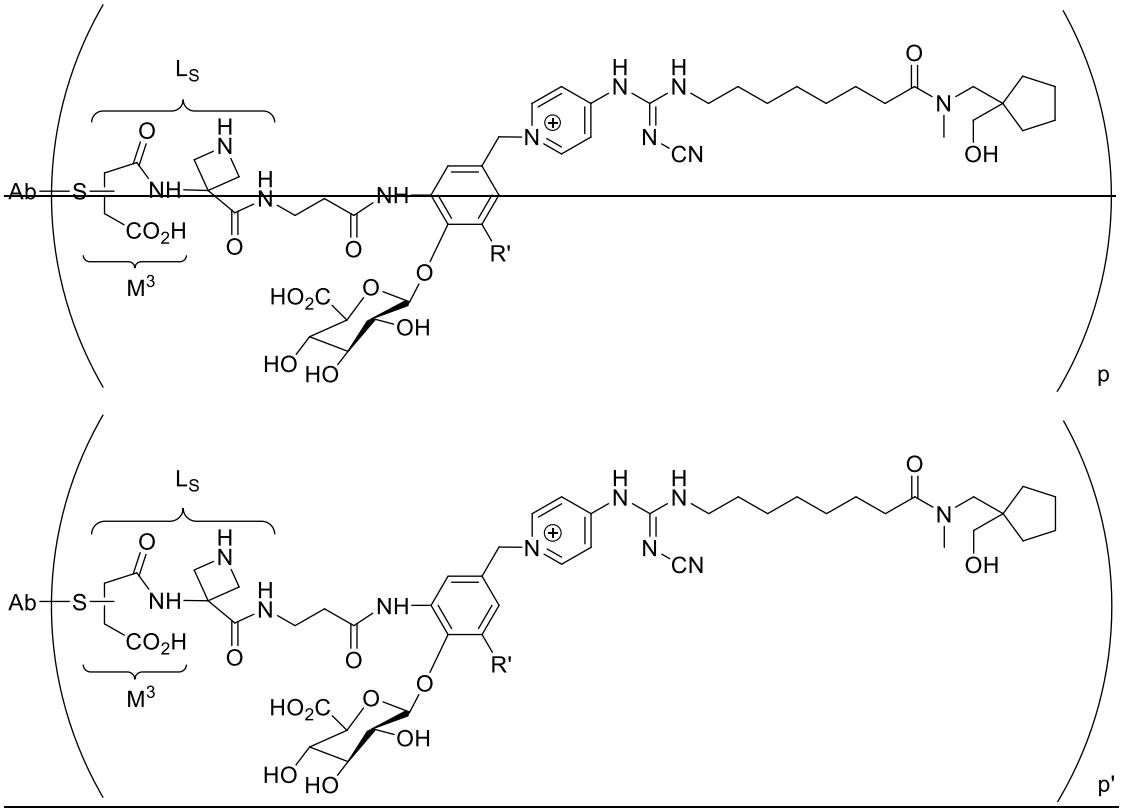
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein Ab is an antibody Ligand Unit; S is a sulfur atom of the antibody; and subscript p’ is ~~about~~ 8,

or in particular

wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:

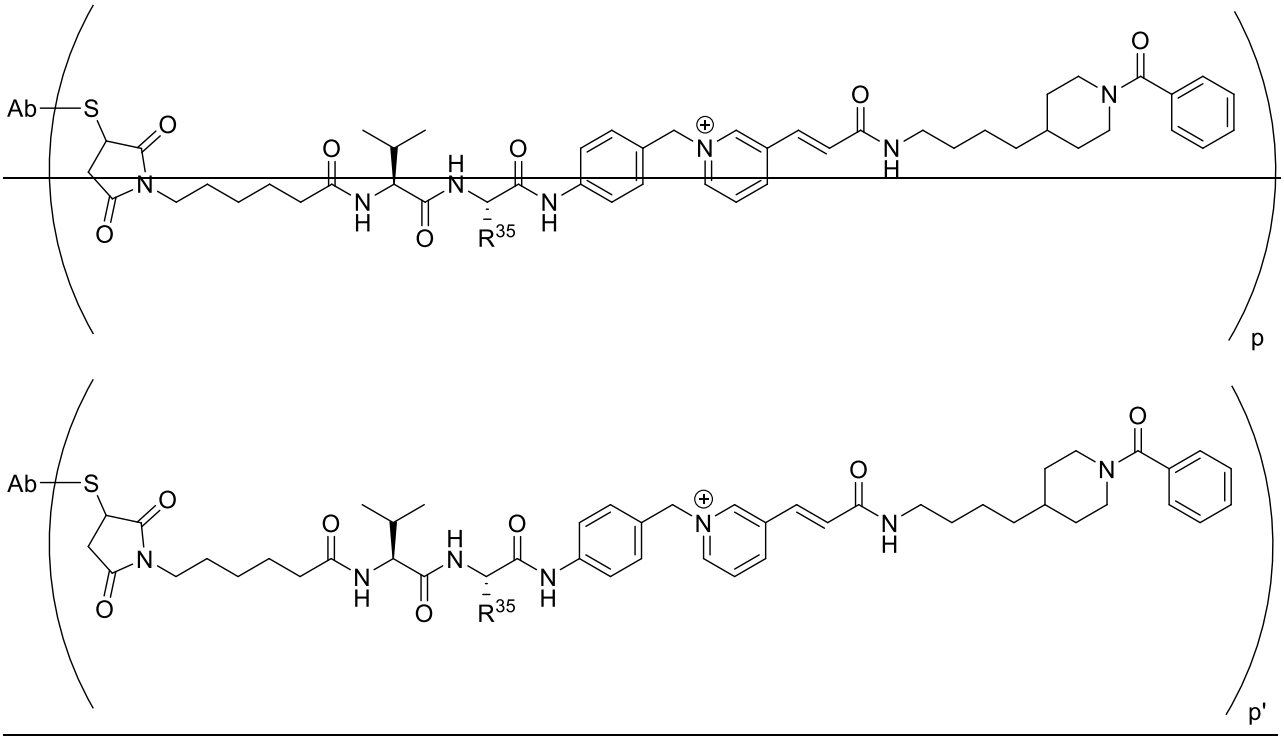

L_{SS}
Ab
S
M^2
HO_2C
HO
HO
OH
R'
p
L_{SS}
Ab
S
M^2
HO_2C
HO
HO
OH
R'
p'

~~and/~~or

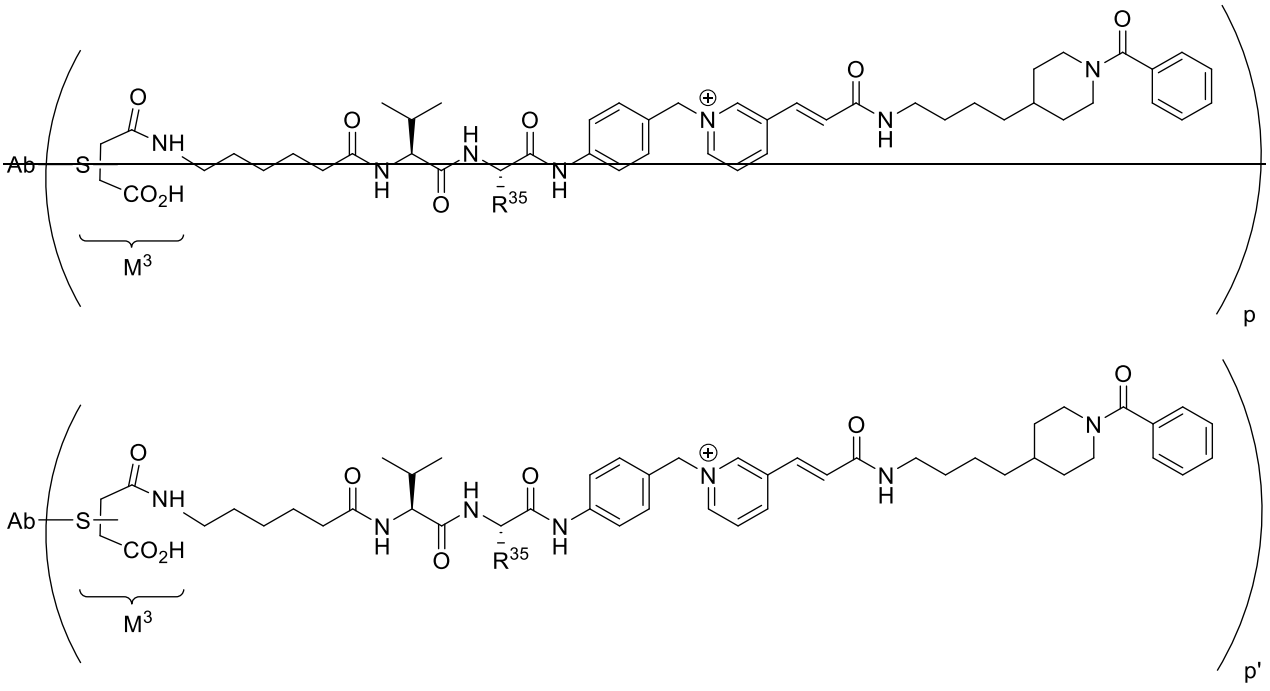

L_S
Ab
S
NH
CO_2H
M^3
HO_2C
HO
HO
OH
R'
p
L_S
Ab
S
NH
CO_2H
M^3
HO_2C
HO
HO
OH
R'
p'

in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein Ab is an antibody Ligand Unit; S is a sulfur atom of the antibody; and subscript p’ is ~~about~~ 8.

21. The Ligand Drug Conjugate ~~composition~~ compound of claim **1**, wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



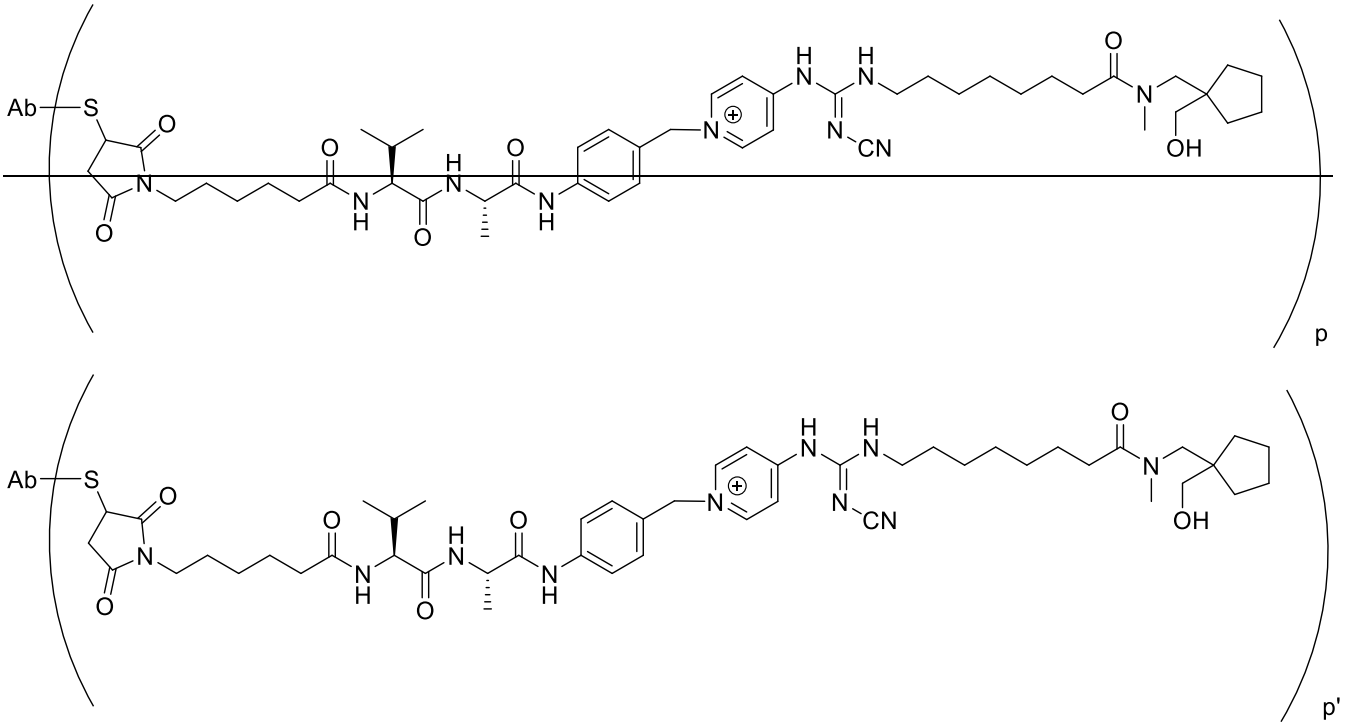
~~and/~~or



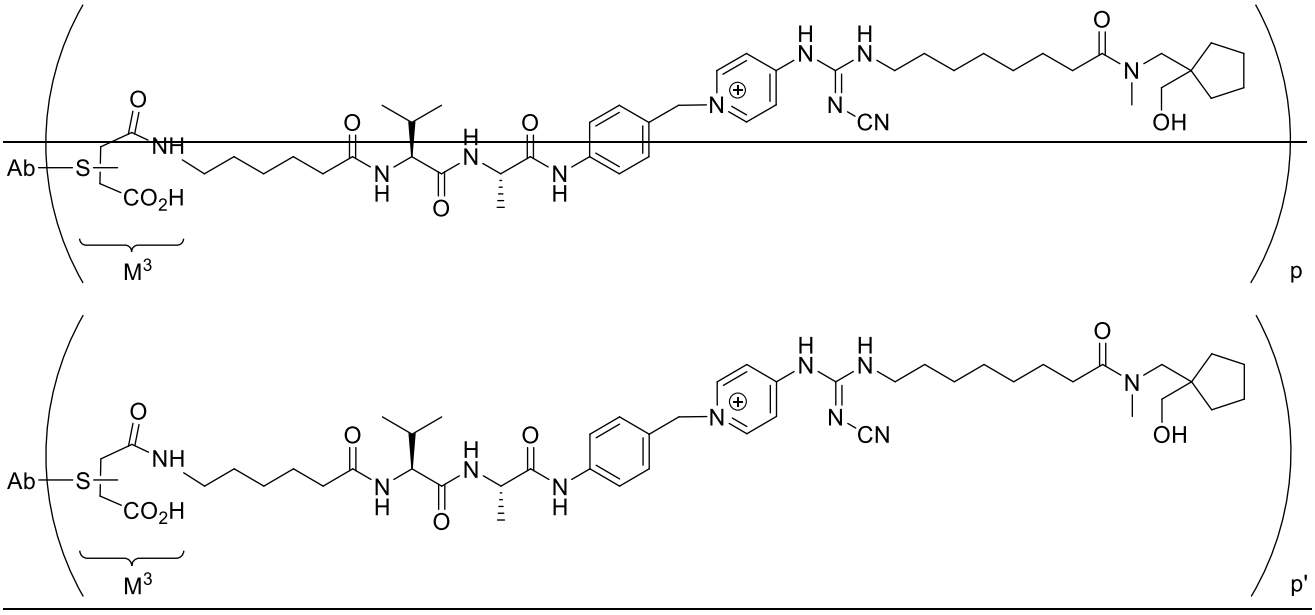
in salt form(s), in particular in pharmaceutically acceptable salt form(s), wherein Ab is an antibody Ligand Unit; S is a sulfur atom of the antibody; and subscript p’ is ~~about~~ 8,

or,

wherein the ~~composition~~ compound is represented by the structure~~(s)~~ of:



~~and/~~or



in ~~pharmaceutical~~ pharmaceutically acceptable salt form, wherein Ab is an antibody Ligand Unit; S is a sulfur atom of the antibody; and subscript p' is ~~about~~ 8.

22. A formulation comprising a Ligand Drug Conjugate ~~composition~~ compound of any one of claims **1** and **19-21**, and one, two, three or more excipients, in particular,

wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof, in particular, wherein the pharmaceutically acceptable formulation is a liquid formulated for intravenous injection and the pharmaceutically acceptable formulation precursor is a solid formulated for reconstitution as a solution for intravenous injection.

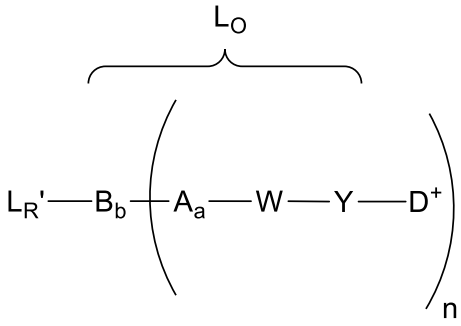
23. Use of a Ligand Drug Conjugate ~~composition~~ compound of any one of claims **1** and **19-21**, and one, two, three or more excipients, in the manufacture of a pharmaceutical formulation for treating a hyperproliferative disease or condition, in particular, wherein the hyperproliferative disease or condition is a cancer, more particularly, wherein the cancer is a leukemia or lymphoma,

wherein the formulation is a pharmaceutically acceptable formulation or a precursor thereof, in particular, wherein the pharmaceutically acceptable formulation is a liquid suitable for intravenous injection to a subject and the pharmaceutically acceptable formulation precursor is a solid suitable for reconstitution as a solution for intravenous injection to a subject, and

wherein the Ligand Drug Conjugate ~~composition~~ compound is present in the formulation in an effective amount.

24. Use of an effective amount of a Ligand Drug Conjugate of any one of claims **1** and **19-21** in the manufacture of a medicament for inhibiting the multiplication of a tumor cell or cancer cell *in vivo*, or causing apoptosis in a tumor or cancer cell *in vivo*, comprising that said cell is exposed with the Ligand Drug Conjugate.

25. A Drug Linker Compound represented by Formula I:

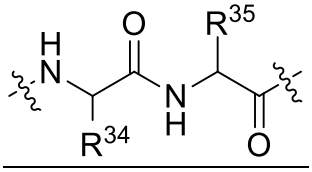


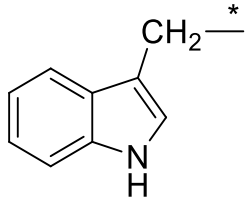
(I)

in salt form, particularly in pharmaceutically acceptable salt form, wherein

L_O, as indicated, is an optional linker that is present;

W is from 1-12 independently selected amino acids and comprises a dipeptide having 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 site of covalent attachment to the dipeptide backbone; and

R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3$NH(C=O)NH_2, -$(CH_2)_3$NH(C=NH)NH_2, or -$(CH_2)_2CO_2H$; and

wherein the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to Y and the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment of the dipeptide to the remainder of the peptide sequence, or

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

Y is a self-immolative Spacer Unit ~~comprised of~~ comprising a PAB or PAB-type moiety;

D^+ is represented by the general structure of:

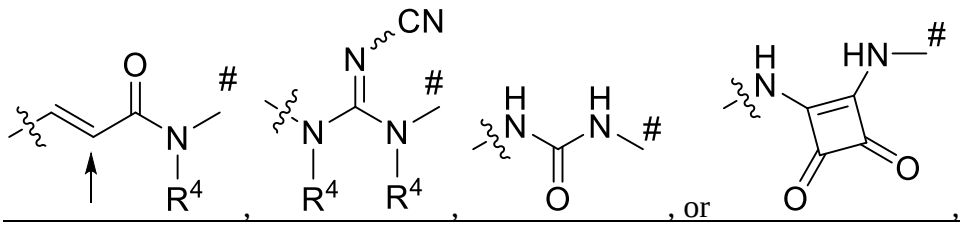


wherein:

H_N^+ is an optionally substituted C_5-C_{24} heteroaryl or partially unsaturated or partially aromatic optionally substituted C_9-C_{24} heterocyclyl comprising a 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system, a skeletal nitrogen atom of which is the site of quaternization to L_O, as indicated by the wavy line to H_N^+;

DA is a hydrogen bond donor or acceptor functional group that is ~~optionally cyclized with HN+~~ bonded to a carbon skeletal atom at position 2 or 3 of the 5-membered nitrogen-containing partially unsaturated or heteroaromatic ring system or at position 3 or 4 of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system, with optional formal cyclization of DA back to an adjacent skeletal carbon atom of the 6-membered nitrogen-containing ring system through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted nitrogen, oxygen or sulfur atom resulting in a partially unsaturated, partially aromatic or fully aromatic 6,5- or 6,6-fused ring system, wherein said bonding of DA is in relation to a skeletal nitrogen atom of the 5- or 6- membered nitrogen-containing partially unsaturated or heteroaromatic ring system and wherein said formal cyclization to the adjacent carbon atom of the 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system substantially retains the hydrogen bonding ability of the donor or acceptor functional group of DA in absence of said cyclization;

wherein DA has the structure of:



, or ,

or a salt thereof, wherein each R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

wherein said optional cyclization is to the indicated sp^2 carbon atom proximal to the carbonyl carbon through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom;

the wavy line indicates the site of covalent attachment to H_N^+; and

the pound sign (#) indicates the site of covalent attachment to I_N;

I_N is -X^1-$[C(=O)]_{0,1}$-, –X^1-$S(=O)_{1,2}$-, –X^2-C_6-C_{24} arylene-$[C(=O)]_{0,1}$-, –X^2-C_6-C_{24} arylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_6-C_{24} arylene-O-, -X^2-C_5-C_{24} heteroarylene-$[C(=O)_{0,1}]$-, –X^2-C_5-C_{24} heteroarylene-$[S(=O)_{1,2}]_{0,1}$, -X^2-C_5-C_{24} heteroarylene-O- or -X^2-C_3-C_{20} heterocyclo-$[C(=O)_{0,1}]$-, wherein the arylene, heteroarylene and heterocyclo are optionally substituted;

X^1 is an optionally substituted C_5-C_7 alkylene;

X^2 is absent or is an optionally substituted C_1-C_4 alkylene;

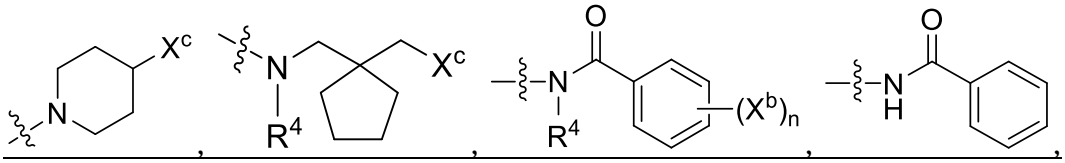
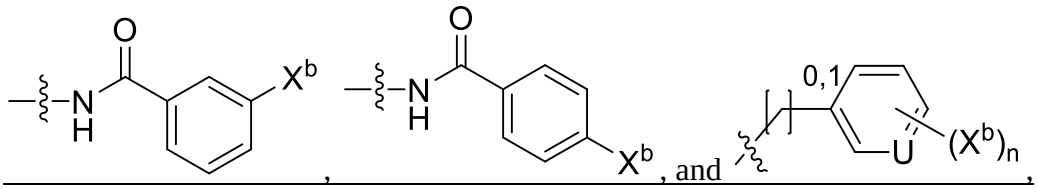
T_N is an optionally substituted amino-alcohol residue or a carboxylic acid-alcohol residue, the amino nitrogen or carbonyl carbon of which is bonded to I_N, or

T_N is an optionally substituted benzamide moiety, the amide nitrogen atom of which is bonded to I_N with optional cyclization of that atom back to I_N or to the remainder of T_N, or

T_N is an optionally substituted C_6-C_{24} aryl, C_5-C_{24} heteroaryl or a combination thereof independently selected in the form of a biaryl, an aromatic atom of which is bonded to I_N or the remainder of T_N; and

wherein T_N or the remainder thereof is bond to I_N, wherein said remainder is an optionally substituted C_2-C_7 heteroalkylene or an optionally substituted C_5-C_6 heterocyclo; or

T_N is selected from the group consisting of:

wherein X^b is $–NH_2$, –OH, halogen, or optionally substituted C_1-C_4 alkoxy or C_1-C_4 alkyl, X^C is hydrogen, halogen, -OH or C_1-C_4 alkoxy; R^4 is hydrogen or optionally substituted C_1-C_4 alkyl, subscript n is 0, 1 or 2, the phenyl optionally substituted by X^b is optionally fused to a 5- or 6-membered heterocyclic or heteroaromatic ring system, U is $=C(R^{24})-$ or =N-, R^{24} is hydrogen or X^b, and the wavy line indicates the site of covalent attachment to I_N or the remainder of T_N that is bonded to I_N, and the amide nitrogen atom of the benzamide moiety is the site of formal optional cyclization of T_N to I_N or the remainder of T_N that is bonded to I_N so that R^4 attached to that nitrogen atom is replaced by a bond;

wherein enzymatic action on W/W' of a drug linker moiety of a Ligand Drug Conjugate compound initiates release of the quaternized NAMPT Drug (D^+) Unit as a NAMPTi compound of formula H_N-D_A-I_N-T_N, wherein H_N is a NAMPT Head Unit that is a fully aromatic C_5-C_{24} or C_9-C_{24} heteroaryl, optionally substituted, comprising a 5- or 6-membered nitrogen-containing heteroaromatic ring system having the previously quaternized skeletal nitrogen atom, and the other variable groups are as previously defined;

L_R' is a primary linker having a functional group capable of forming a covalent bond to a targeting moiety that becomes the Ligand Unit of a Ligand Drug Conjugate compound of Formula I; ~~in which subscript p is replaced by subscript p', wherein the other variable groups are as defined for that formula.~~

subscripts a and b independently are 0 or 1, indicating the absence or presence, respectively, of A or B;

subscript n is 1, 2, 3 or 4;

A is a first optional Stretcher;

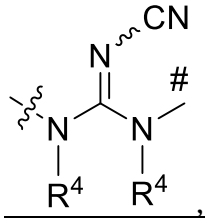
B is a Branching Unit, when subscript b is 1 and subscript n is 2, 3 or 4, or B is absent, so that subscript b is 0, when subscript n is 1,

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

~~subscript p is a number ranging from 1 to 24 and subscript p' is an integer ranging from 1 to 24~~.

26. The Drug Linker compound of claim **25**, wherein a skeletal aromatic nitrogen atom of H_N is quaternized to form H_N^+.

27. The Drug Linker compound of claim **25**, wherein DA is ~~an optionally substituted amide functional group or bioisostere thereof, or wherein a skeletal nitrogen atom of the 5- or 6-membered nitrogen-containing partially unsaturated or heteroaromatic ring system of H_N is quaternized to form H_N^+~~



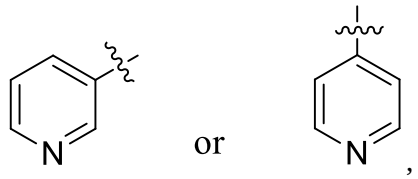
or a salt thereof, in particular a pharmaceutically acceptable salt, wherein each R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

the wavy line indicates the site of covalent attachment to H_N/H_N^+;and

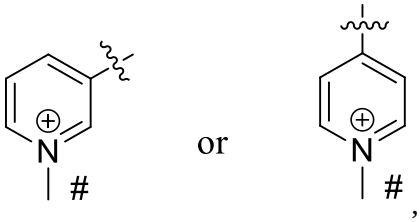
the pound sign (#) indicates the site of covalent attachment to I_N.

28. The Drug Linker compound of claim **25**, wherein the 6-membered nitrogen-containing heteroaromatic ring system of H_N is that of pyridine with optional cyclization of DA back to the pyridine aromatic ring system through an introduced aromatic oxygen, sulfur or an optionally substituted nitrogen atom so that H_N contains a 6-5 fused aromatic ring system and H_N^+ is that Unit in which the pyridine aromatic ring system is quaternized at its skeletal nitrogen atom,

in particular, wherein H_N has the structure of:



or a salt thereof, in particular a pharmaceutically acceptable salt, and H_N^+ has the structure of:

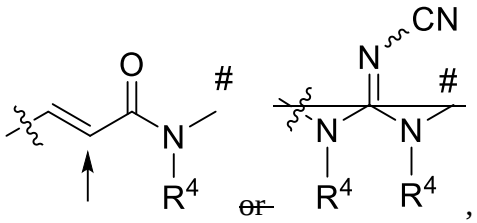


in salt form, in particular in pharmaceutically acceptable salt form, wherein

the pound sign (#) indicates the point of covalent attachment to L_O;

the wavy line indicates the site of covalent attachment to DA and an adjacent aromatic carbon atom thereto is the site of said optional formal cyclization by DA to H_N/H_N^+.

29. The Drug Linker compound of claim **25**, wherein DA is an acrylamide, optionally cyclized to an adjacent skeletal carbon atom of the nitrogen-containing aromatic ring system of H_N/H_N^+ to which it is attached, ~~or is an amide bioisostere, or~~ and DA has the structure of:



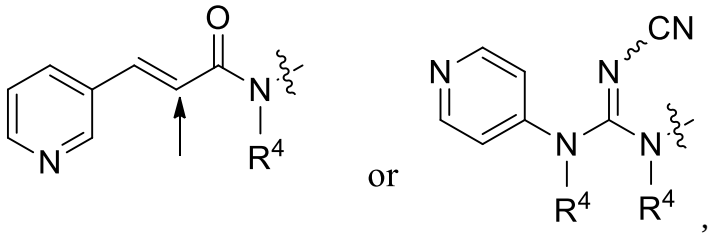
or a salt thereof, in particular a ~~pharmaceutical~~ pharmaceutically acceptable salt, wherein ~~each~~ R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl;

DA is optionally cyclized to H_N/H_N^+, wherein said cyclization is to the sp^2 carbon atom of the acrylamide proximal to the carbonyl carbon (as indicated) through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom;

the wavy line indicates the site of covalent attachment to H_N/H_N^+, and the indicated carbon atom adjacent thereto is the site of said optional cyclization by the acrylamide DA; and

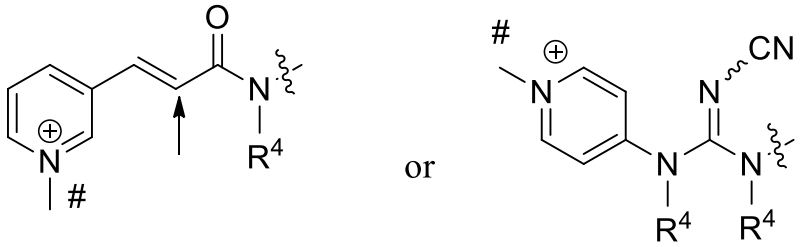
the pound sign (#) indicates the site of covalent attachment to I_N.

30. The Drug Linker compound of claim **25**, wherein H_N-DA- is



,

or a salt thereof, in particular a pharmaceutically acceptable salt, and H_N^+-DA has the structure of:



in salt form, in particular in pharmaceutically acceptable salt form, wherein

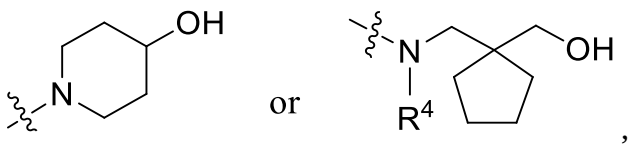
R^4 is independently selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl; and

the pound sign (#) indicates the point of covalent attachment to L_O;

the wavy line indicates the site of covalent attachment to I_N, and

wherein the sp^2 carbon atom proximal to the carbonyl carbon is the site (as indicated) of optional cyclization to H_N/H_N^+ through an introduced optionally substituted non-aromatic carbon atom or an optionally substituted aromatic heteroatom.

31. The Drug Linker compound of claim **25**, wherein T_N has the structure of:



,

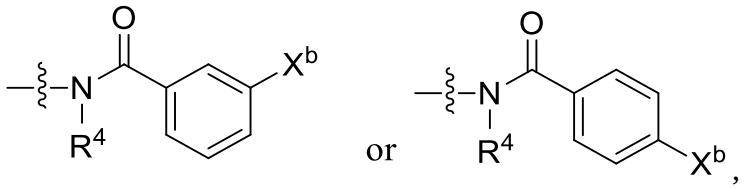
wherein

R^4 is hydrogen or optionally substituted C_1-C_4 alkyl; and

the wavy line indicates the site of covalent attachment to I_N,

or

wherein T_N is an optionally substituted benzamide moiety covalently attached to I_N or the remainder of T_N, through it amide nitrogen atom, in particular wherein the benzamide moiety has the structure of:



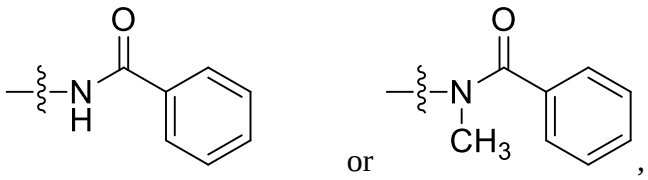
wherein X^b is –H, halogen, -OH, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 alkyl or $–NH_2$, optionally substituted;

R^4 is hydrogen or optionally substituted C_1-C_4 alkyl; and

the wavy line indicates the site of covalent attachment to I_N; and

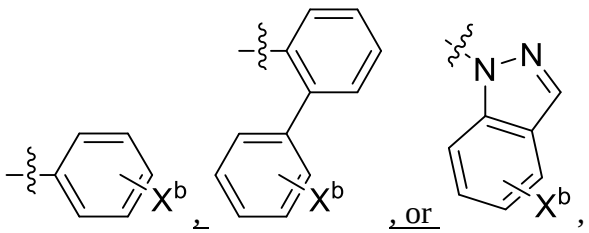
wherein the benzamide moiety is optionally cyclized to I_N wherein the amide nitrogen of the benzamide moiety is the site of said cyclization so that R^4 is replaced by a covalent bond,

more particularly wherein the benzamide moiety has the structure of:



or

wherein T_N is an optionally substituted (hetero)aryl or biaryl moiety, in particular having the structure of:

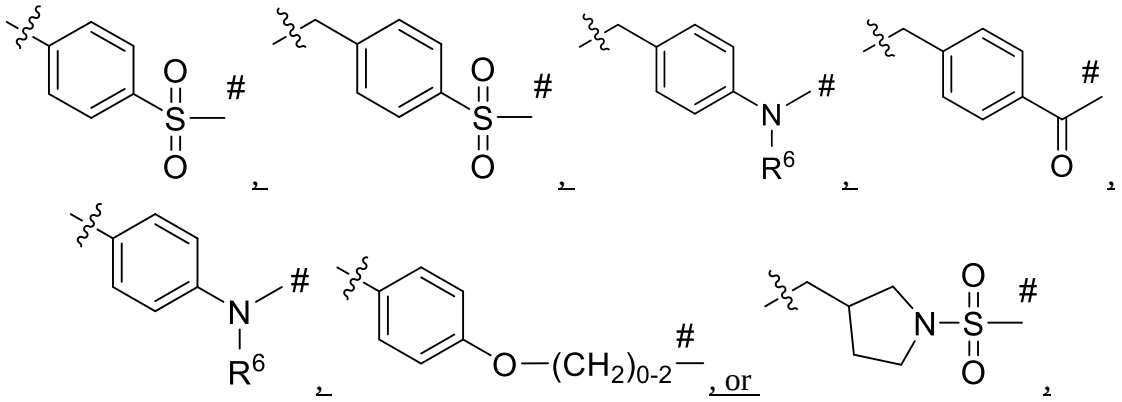


respectively, wherein

wherein X^b is –H, halogen, -OH, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 alkyl or $–NH_2$, optionally substituted;

the wavy line indicates the site of covalent attachment to I_N.

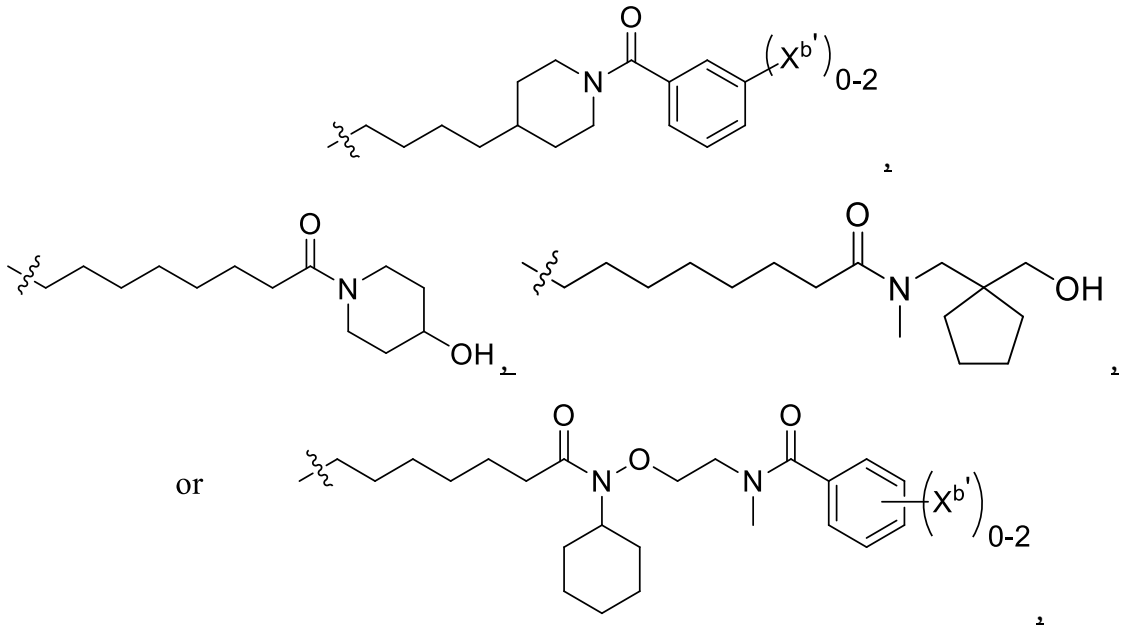
32. The Drug Linker compound of claim **25**, wherein I_N is $-CH_2-(CH_2)_{3-7}-CH_2-$, $-CH_2-(CH_2)_{3-7}-CH_2-O-$, $-CH_2-(CH_2)_{3-7}-C(=O)-$, $-CH_2-(CH_2)_{3-7}-S(=O)_2-$ or $-CH_2-(CH_2)_{3-7}-S(=O)-$, or wherein I_N has the structure of:



wherein the wavy line indicates the site of covalent attachment to DA and the pound sign (#) indicates the site of covalent attachment to T_N; and

R^6 is hydrogen, C_1-C_4 alkyl, $-CH_2CH=C(CH_3)_2$, or $–CH_2-C\equiv CH$.

33. The Drug Linker compound of claim **25**, wherein $–I_N-T_N$ has the structure of:

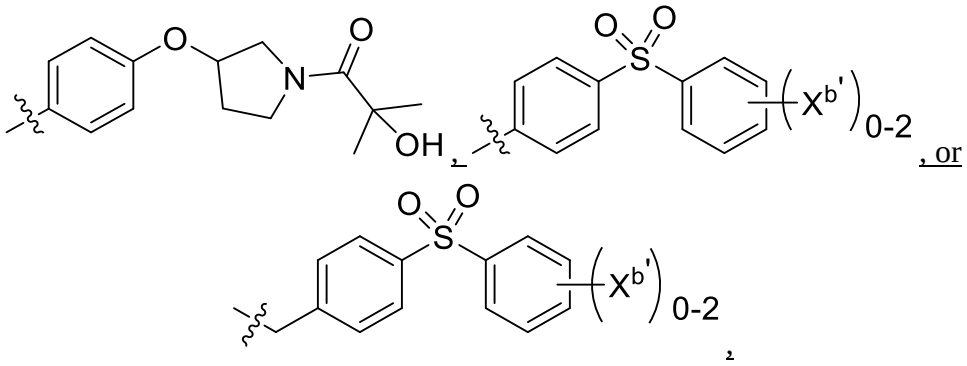


wherein

$X^{b'}$ when present is independently selected from the group consisting of halogen, -OH, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 alkyl and $–NH_2$, optionally substituted; and

the wavy line indicates the site of covalent attachment to DA, or

wherein $–I_N$-T_N has the structure of:

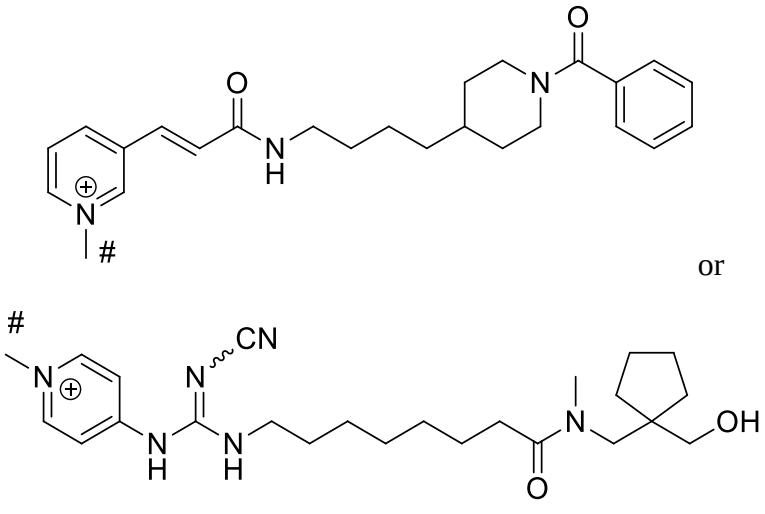


wherein

$X^{b'}$ if present is selected from the group consisting of, -OH and NH_2, optionally substituted, and halogen, provided that when subscript n is 2 one of X^b is –OH or -NH_2, optionally substituted, or halogen and the other is halogen; and

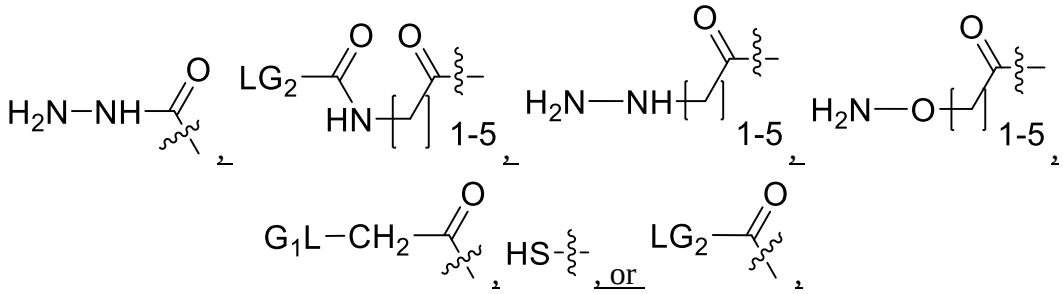
the wavy line indicates the site of covalent attachment to DA.

34. The Drug Linker compound of claim **25**, wherein D^+ has the structure of:



in salt form, in particular in pharmaceutically acceptable salt form, wherein the pound sign (#) indicates the site of quaternization by L_O.

35. The Drug Linker compound of any one of claims **25** to **34**, wherein L_R'- has the structure of:



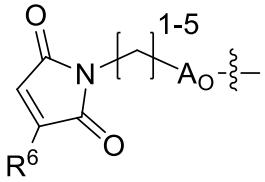
or a salt thereof, in particular a pharmaceutically acceptable salt, wherein

LG_1 is a leaving group for nucleophilic displacement by a targeting agent nucleophile;

LG_2 is a leaving group for amide bond formation to a targeting agent, or –OH to provide an activatable carboxylic acid for amide bond formation to a targeting agent; and

the wavy line indicates the site of covalent attachment to the remainder of the Drug Linker compound structure, or

wherein L_R'- has the structure of:



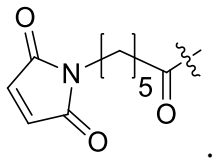
wherein

R^6 is hydrogen or an optionally substituted C_1-C_6 alkyl;

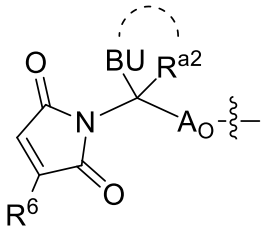
A_O is an second optional Stretcher Unit; and

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

in particular having the structure of :



or wherein L_R'- has the structure of:



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

R^6 is hydrogen or an optionally substituted C_1-C_6 alkyl;

A_O is a second optional Stretcher Unit;

BU is a Basic Unit;

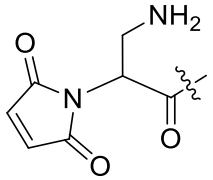
R^{a2} is an optionally substituted C_1-C_{12} alkyl;

the dotted curved line indicates optional cyclization so that in the absence of said cyclization BU is an acyclic Basic Unit or in the presence of said cyclization BU is a cyclized Basic Unit in which R^{a2} and BU together with the carbon atom to which both are attached, define an optionally substituted spiro C_3-C_{20} heterocyclo containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group of BU,

wherein the basic nitrogen atom of the acyclic Basic Unit or 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; and

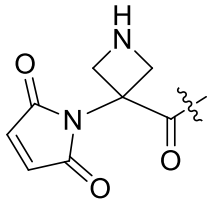
the wavy line indicates the site of covalent attachment to the remainder of the Drug Linker compound structure,

in particular having the structure of:



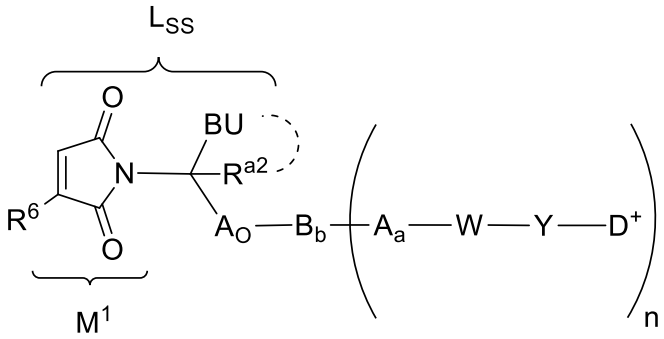
or a salt thereof, in particular, a pharmaceutically acceptable salt, or

in particular having the structure of:

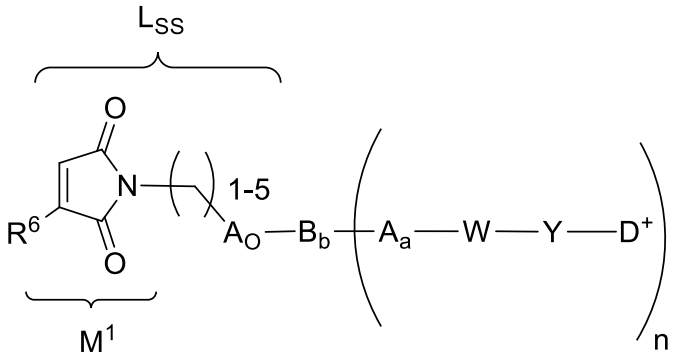


or a salt thereof, in particular, a pharmaceutically acceptable salt thereof.

36. The Drug Linker compound of claim **25,** wherein the compound is represented by the structure of Formula Ia or Formula Ib:



(Formula Ia)



(Formula Ib)

in salt form, in particular, in pharmaceutically acceptable salt form, wherein

R^6 is hydrogen or an optionally substituted C_1-C_6 alkyl;

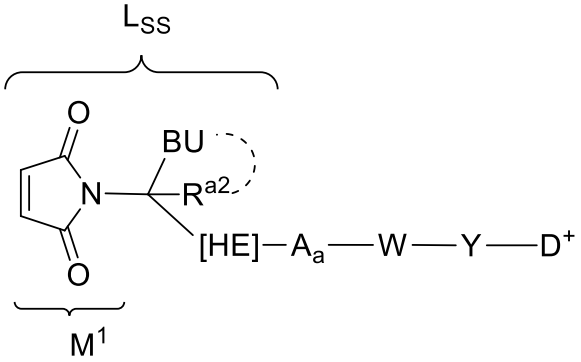
A_O is a second optional Stretcher Unit; and

W is from 1-12 independently selected amino acids, or

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

Y is a self-immolative Spacer Unit ~~comprised of~~ <u>comprising</u> a PAB or PAB-type moiety;

in particular, wherein the compound is represented by the structure of:

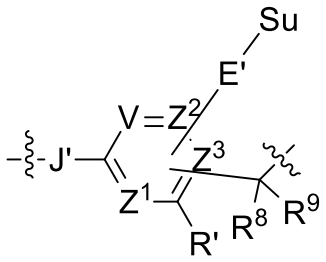


in salt form, in particular, in pharmaceutically acceptable salt form, wherein

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

W is from 1-12 independently selected amino acids, and Y is a self-immolative Spacer Unit ~~comprised of~~ comprising a PAB or PAB-type moiety, or

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



or a salt thereof, in particular a pharmaceutically acceptable salt, wherein Su is a carbohydrate moiety and -E'- represents an optionally substituted heteroatom of a glycosidic bond;

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

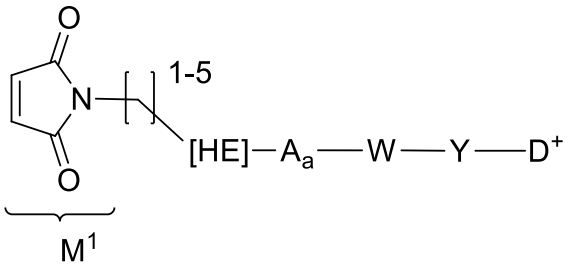
wherein the wavy line adjacent to J' indicates the site of covalent attachment of the Glucuronide Unit to A when subscript a is 1 or to the indicated L_{SS} or L_S primary linker when subscript a is 0; and the wavy line adjacent to the –$C(R^8)(R^9)$- moiety indicates the site of covalent attachment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

~~wherein the Ligand Drug Conjugate compound is of corresponding structure to the composition of Formula 1 in which subscript p is replaced by subscript p'; and~~

wherein the basic functional group of BU is optionally protonated, or the basic nitrogen atom thereof is optionally protected,

or,

wherein the compound is represented by the structure of:

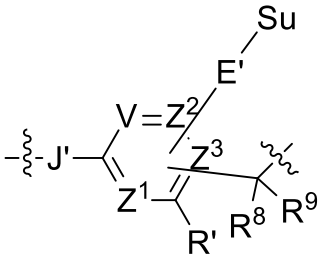


in salt form, in particular, in pharmaceutically acceptable salt form, wherein

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

W is from 1-12 independently selected amino acids, and Y is a self-immolative Spacer Unit ~~comprised of~~ <u>comprising</u> a PAB or PAB-type moiety, or

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



or a salt thereof, in particular a pharmaceutically acceptable salt, wherein Su is a carbohydrate moiety and -E'- represents an optionally substituted heteroatom of a glycosidic bond;

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;

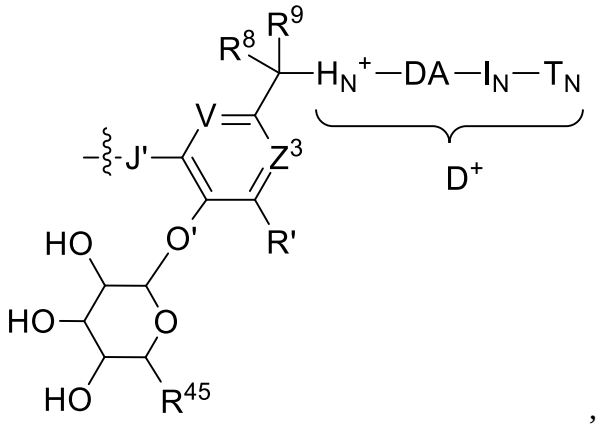
R^8 and R^9 independently are hydrogen, or C_1-C_{12} alkyl, C_2-C_{12} alkenyl or C_2-C_{12} alkynyl, optionally substituted, or C_6-C_{20} aryl or C_5-C_{20} heteroaryl, optionally substituted, or

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 the wavy line adjacent to J' indicates the site 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 site of covalent attachment of the Glucuronide Unit to D^+;

in particular W-Y is replaced by a Glucuronide Unit of formula –Y(W')- for which –Y(W')-D^+ has the structure of:



,

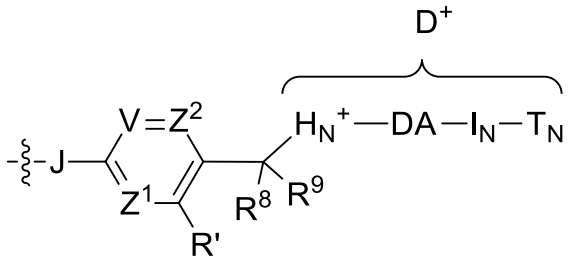
in salt form, particularly in pharmaceutically acceptable salt from, wherein

R’ is hydrogen or $–NO_2$ or other electron withdrawing group; and

R^{45} is $–CH_2OH$ or $–CO_2H$,

or

in particular W is from 1-12 independently selected amino acids for which $–Y\text{-}D^+$ has the structure of:

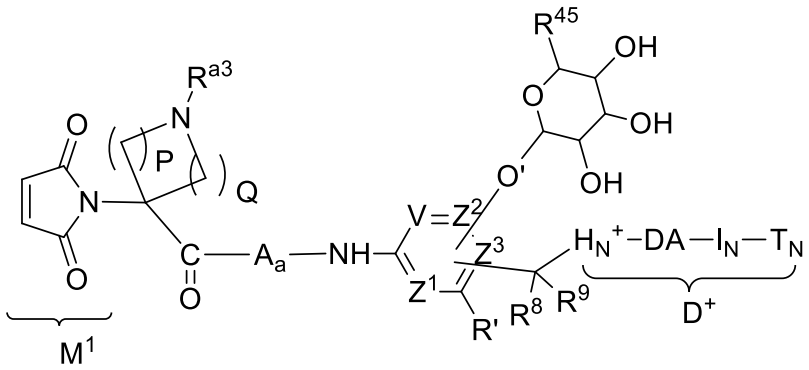


in salt form, in particular in ~~pharmaceutical~~ pharmaceutically acceptable salt form, wherein

R’ is hydrogen or $–OC_1\text{-}C_6$ alkyl or other electron donating group;

J is an optionally substituted heteroatom bonded to W as indicated by the wavy line.

37. The Drug Linker compound of claim **36**, wherein W-Y is replaced by a Glucuronide Unit of formula –Y(W’)-, wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

subscript P is 1, 2 or 3;

subscript Q ranges from 1 to 6;

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

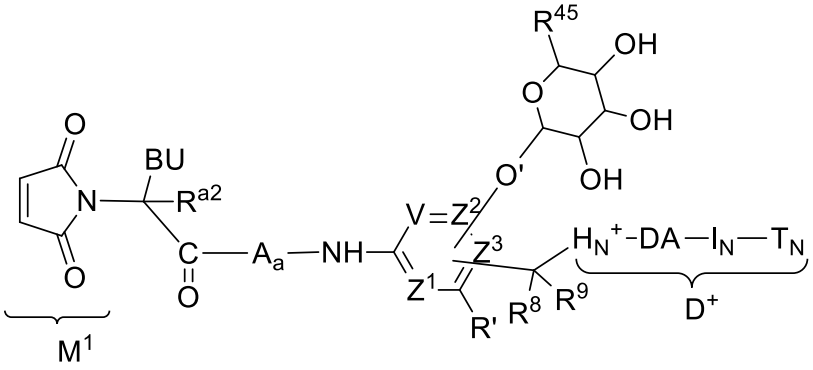
R^{a3} is –H, or optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{1-36}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, and R^{PEG2} is –H or C_1-C_4 alkyl; and

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

wherein -O'- represents the oxygen heteroatom of an O-glycosidic bond,

or

wherein the compound is represented by the structure of:



in salt form, particularly in pharmaceutically acceptable salt from, wherein

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

R^{a2} is hydrogen or C_1-C_6 alkyl;

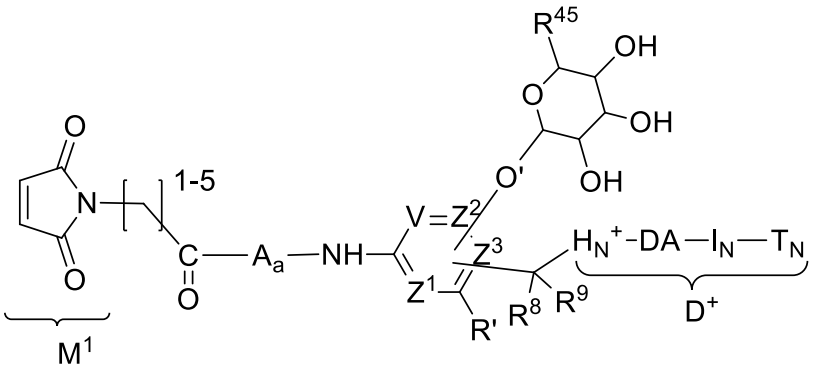
BU has the structure of $–[C(R^{a1})(R^{a1})]$-$[C(R^{a1})(R^{a1})]_{0-3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; R^{a3} independently are hydrogen, optionally substituted C_1-C_6 alkyl or R^{a3} together with the nitrogen atom to which both are attached define a C_3-C_6 heterocyclyl in which the basic nitrogen is a skeletal atom;

wherein the basic functional group of BU is optionally protonated, or the basic nitrogen atom thereof is optionally protected; and

wherein -O'- represents the oxygen atom of an O-glycosidic bond,

or

wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

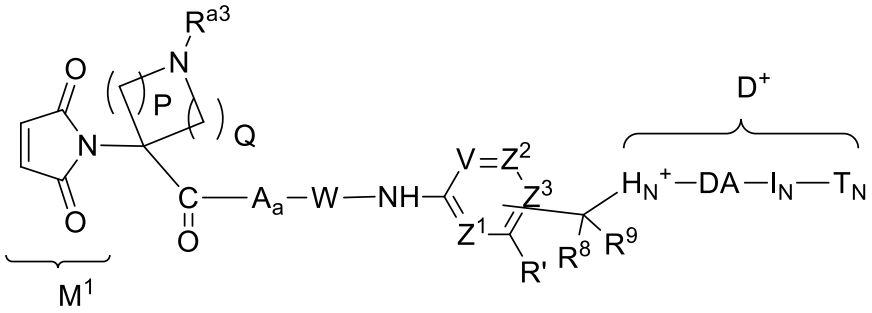
R^{45} is $–CH_2OH$ or $–CO_2H$;

R^{a2} is hydrogen or C_1-C_6 alkyl; and

wherein -O'- represents the oxygen atom of an O-glycosidic bond,

or

wherein W is from 1-12 independently selected amino acids and the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

subscript P is 1, 2 or 3;

subscript Q ranges from 1 to 6;

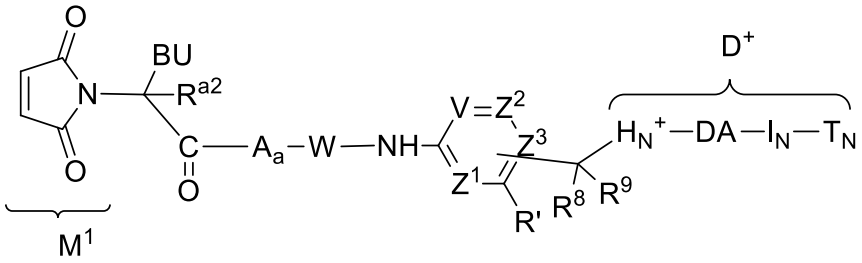
R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

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

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

or

wherein the compound is represented by the structure of:



in suitable salt form, wherein

R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

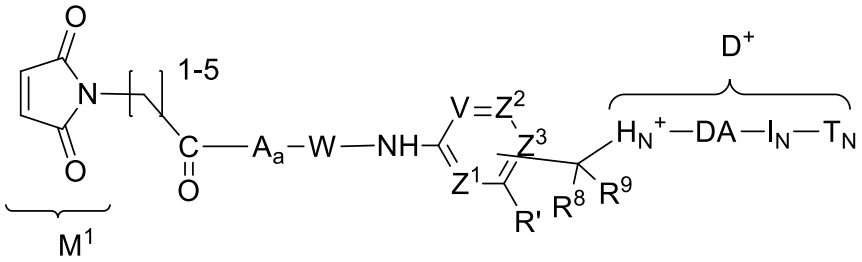
R^{a2} is hydrogen or C_1-C_6 alkyl;

BU has the structure of $–[C(R^{a1})(R^{a1})]$-$[C(R^{a1})(R^{a1})]_{0-3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; and

wherein the basic functional group of BU bonded is optionally protonated, or the basic nitrogen atom thereof is optionally protected;

or

wherein the compound is represented by the structure of:

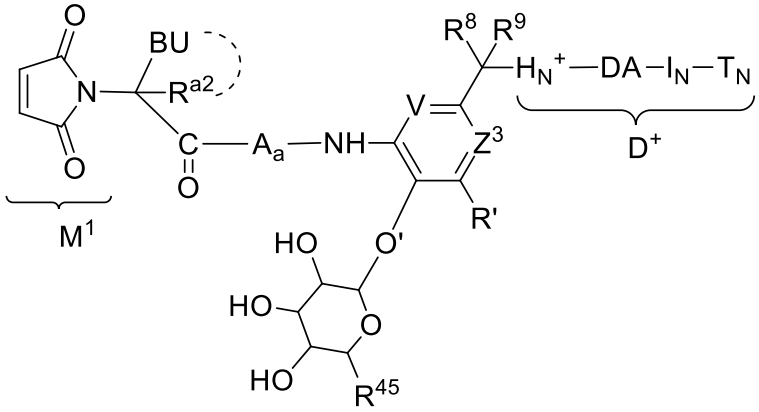


in suitable salt form, wherein

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

R^{a2} is hydrogen or C_1-C_6 alkyl.

38. The Drug Linker compound of claim **36**, wherein W-Y is replaced by a Glucuronide Unit of formula –Y(W')-, wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

R' is hydrogen or $–NO_2$ or other electron withdrawing group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

BU has the structure of $–[C(R^{a1})(R^{a1})]$-$[C(R^{a1})(R^{a1})]_{0-3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; R^{a3} independently are hydrogen, optionally substituted C_1-C_6

alkyl or R^{a3} together with the nitrogen atom to which both are attached define a C_3-C_6 heterocyclyl in which the basic nitrogen is a skeletal atom;

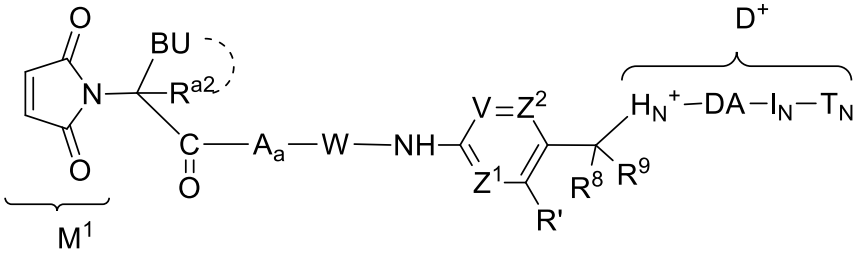
R^{a2} is hydrogen or C_1-C_6 alkyl, optionally cyclized to BU, as indicated by the dotted curved line, wherein one of R^{a1} or one of R^{a3} is replaced with a bond to a carbon atom of R^{a2} when R^{a2} is C_1-C_6 alkyl;

wherein the basic functional group of BU is optionally protonated, or the basic nitrogen atom thereof is optionally protected; and

wherein -O'- represents the oxygen atom of an O-glycosidic bond,

or

W is from 1-12 independently selected amino acids and the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

R^{45} is $–CH_2OH$ or $–CO_2H$;

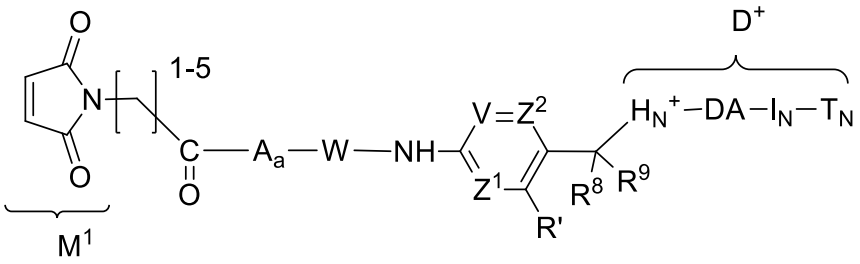
BU has the structure of $–[C(R^{a1})(R^{a1})]$-$[C(R^{a1})(R^{a1})]_{0-3}$-$N(R^{a3})(R^{a3})$, each R^{a1} independently is hydrogen or C_1-C_4 alkyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, (C_6-C_{10} aryl)-C_1-C_4 alkyl-, or (C_5-C_{10} heteroaryl)-C_1-C_4 alkyl-, optionally substituted, or two R^{a1} together with the carbon(s) to which they are attached and any intervening carbons define an optionally substituted C_3-C_6 cycloalkyl; R^{a3} independently are hydrogen, optionally substituted C_1-C_6 alkyl or R^{a3} together with the nitrogen atom to which both are attached define a C_3-C_6 heterocyclyl in which the basic nitrogen is a skeletal atom;

R^{a2} is hydrogen or C_1-C_6 alkyl, optionally cyclized to BU, as indicated by the dotted curved line, wherein one of R^{a1} or one of R^{a3} is replaced with a bond to a carbon atom of R^{a2} when R^{a2} is C_1-C_6 alkyl; and

wherein the basic functional group of BU is optionally protonated, or the basic nitrogen atom thereof is optionally protected;

or

wherein the compound is represented by the structure of:

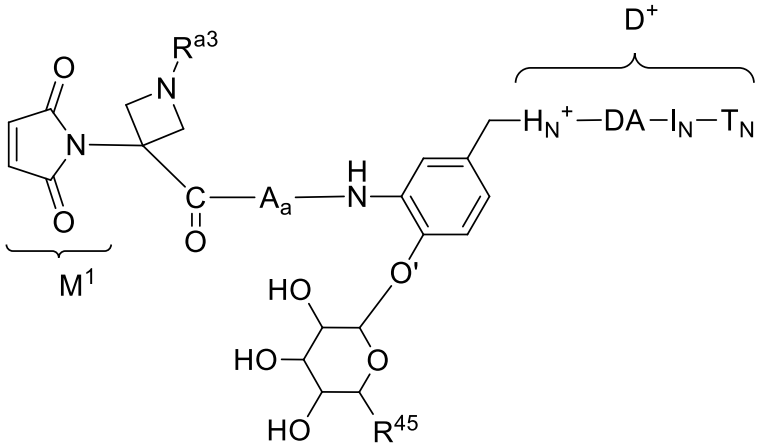


in salt form, in particular in pharmaceutically acceptable salt form, wherein

R' is hydrogen or $–OC_1$-C_6 alkyl or other electron donating group;

R^{45} is $–CH_2OH$ or $–CO_2H$,

in particular W-Y is replaced by a Glucuronide Unit of formula –Y(W')- and the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

R^{45} is $–CH_2OH$ or $–CO_2H$;

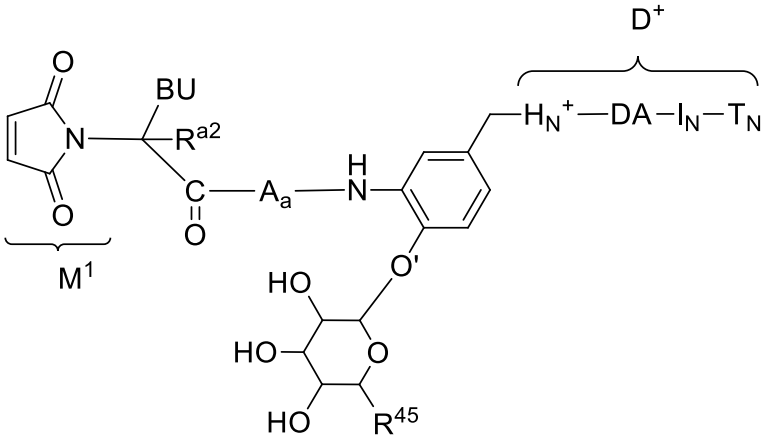
R^{a3} is –H, or optionally substituted C_1-C_6 alkyl, optionally substituted -C_1-C_4 alkylene-(C_6-C_{10} aryl), or -R^{PEG1}-O-$(CH_2CH_2O)_{1-36}$-R^{PEG2}, wherein R^{PEG1} is C_1-C_4 alkylene, and R^{PEG2} is –H or C_1-C_4 alkyl; and

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

-O'- represents the oxygen atom of an O-glycosidic bond,

or

wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from, wherein

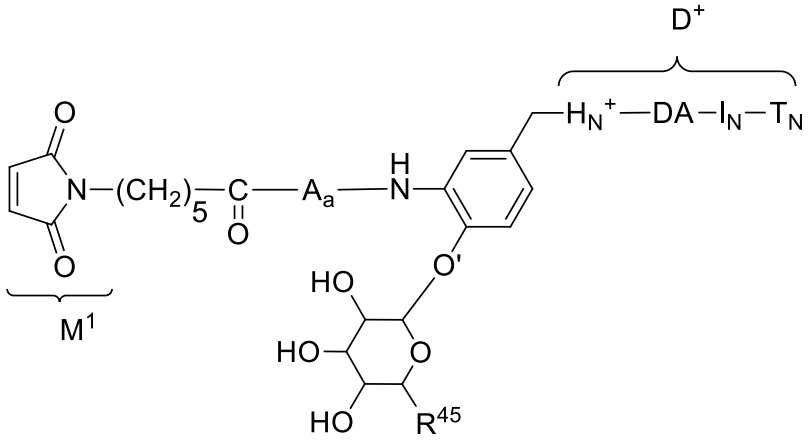
R^{45} is $–CH_2OH$ or $–CO_2H$;

BU is $–CH_2$-NH_2, optionally protonated, or the basic nitrogen atom thereof is optionally protected;

R^{a2} is hydrogen; and

-O'- represents the oxygen atom of an O-glycosidic bond,

or the compound is represented by the structure of:

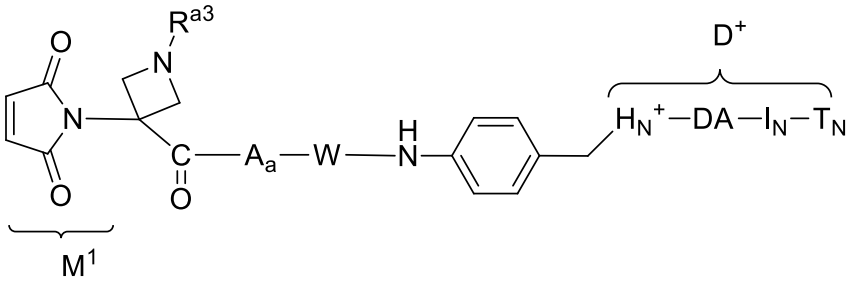


in salt form, in particular in pharmaceutically acceptable salt from, wherein

R^{45} is $–CH_2OH$ or $–CO_2H$; and

-O'- represents the oxygen atom of an O-glycosidic bond, or

W is from 1-12 independently selected amino acids and the compound is represented by the structure of:

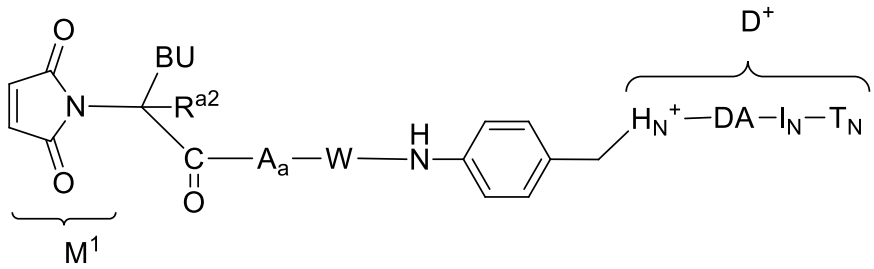


in salt form, in particular in pharmaceutically acceptable salt from, wherein

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

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

or is represented by the structure of:



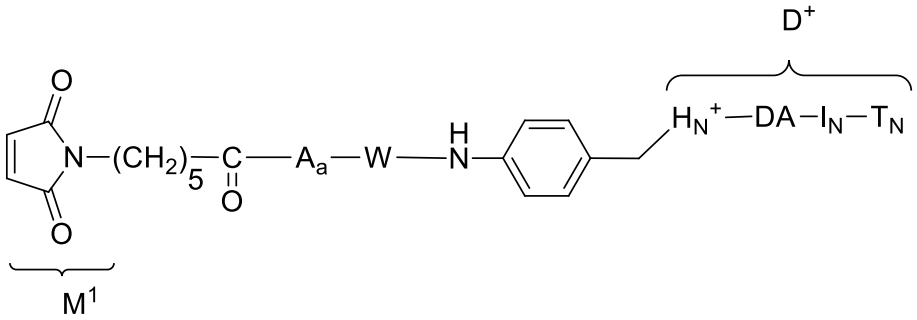
in salt form, in particular in pharmaceutically acceptable salt from, wherein

BU is –CH_2-NH_2, optionally protonated; and

R^{a2} is hydrogen;

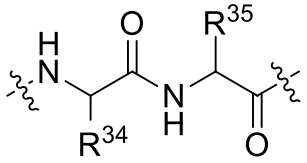
or

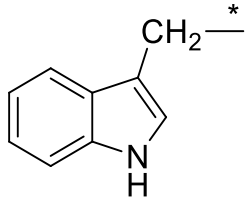
the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt from.

39. The Drug Linker compound of claim **36**, wherein W is a dipeptide having the structure of:



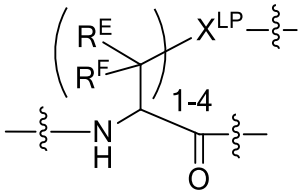
wherein R^{34} is benzyl, methyl, isopropyl, isobutyl, sec-butyl, -CH(OH)CH_3 or has the structure of , wherein the asterisk indicates the site of covalent attachment to the dipeptide backbone; and

R^{35} is methyl, –$(CH_2)_4$-NH_2, -$(CH_2)_3$NH(C=O)NH_2, -$(CH_2)_3$NH(C=NH)NH_2, or -$(CH_2)_2CO_2H$; and

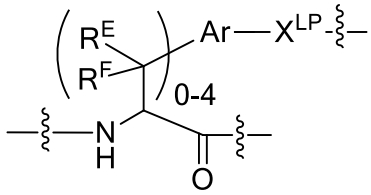
wherein the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to Y and the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment of the dipeptide to the remainder of the peptide sequence,

in particular wherein the dipeptide 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-, and -Trp-Cit-, wherein Cit is citrulline.

40. The Drug Linker compound of claim **36**, wherein 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:



(L^P-1)



(L^P-2)

or a salt thereof, in particular ~~pharmaceutical~~ pharmaceutically acceptable salt, wherein

X^{LP} is selected from the group consisting of –O-, -NR^{LP}-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)N(R^{LP})-, -N(R^{LP})C(=O)N(R^{LP})-, -N(R^{LP})C(=NR^{LP})N(R^{LP})-, and 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;

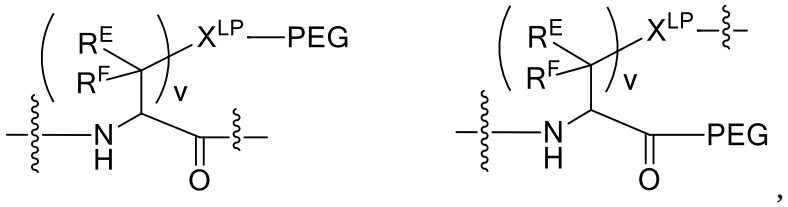
Ar is a C_6-C_{10} arylene or a C_5-C_{10} heteroarylene, optionally substituted;

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 and 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 spiro 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; and

wherein one of the wavy lines indicates the site of covalent attachment of a PEG Unit and the other wavy lines indicates covalent attachment of Formula L^P-1 or Formula L^P-2 within the structure representing the Ligand Drug Conjugate ~~composition~~ compound,

or wherein -L^P(PEG)- has the structure of Formula L^P-3 or Formula L^P-4:



(L^P-3) (L^P-4)

or a salt thereof, in particular a ~~pharmaceutical~~ pharmaceutically acceptable salt, wherein

subscript v is an integer ranging from 1 to 4;

X^{LP} is selected from the group consisting of –O-, -NR^{LP}-, -S-, -S(=O)-, -$S(=O)_2$-, -C(=O)-, -C(=O)N(R^{LP})-, -N(R^{LP})C(=O)N(R^{LP})-, -N(R^{LP})C(=NR^{LP})N(R^{LP})-, and 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 and 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 spiro 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, or

wherein the side chain of $–[C(R^E)(R^F)]_v$-X^{LP}- is provided by a natural or un-natural amino acid side chain; and

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

in particular in any one of the above formula, R^E and R^F are independently selected from the group consisting of -H, and -C_1-C_4 alkyl and X^{LP} is selected from the group consisting of –O-, -NH, -S- and -C(=O)-;

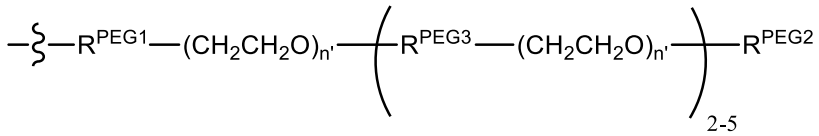
and in L^P-3 or L^P-4, PEG has the structure selected from the group consisting of:



,



, and



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

subscript n' independently ranges from 1 to 72;

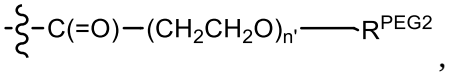
R^{PEG1} is an optional PEG Attachment Unit;

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

R^{PEG3} is an PEG Coupling Unit,

or

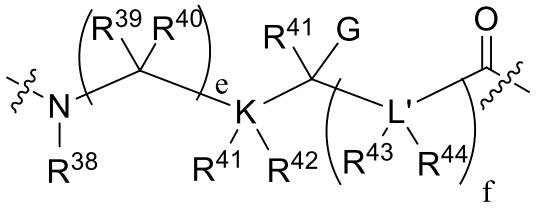
X^{LP}-PEG has the structure of:



,

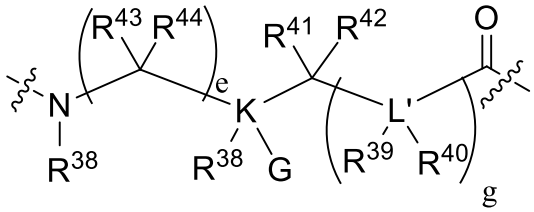
wherein subscript n' is 8, 12 or 24 and R^{PEG2} is H or $–CH_3$,

or A or a subunit thereof has the structure of formula (3) or formula (4):



f

,



g

(3) (4)

wherein the wavy lines indicated covalent attachment within the ~~composition~~ 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

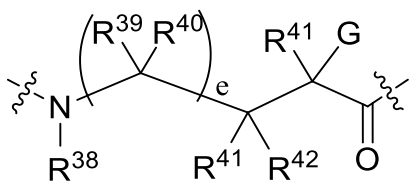
R^{39}, R^{40} together with the carbon atom to which both are attached, or R^{41}, R^{42} together with K to which both are attached when K is a carbon atom, define a C_3-C_6 carbocyclo, and R^{41}-R^{44} are as defined herein,

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

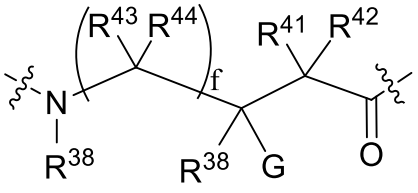
or R^{40} and R^{41}, or R^{40} and R^{43}, or R^{41} and R^{43} to together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C_5-C_6 carbocyclo or a C_5-C_6 heterocyclo, and R^{39}, R^{44} and the remainder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

provided that when K is O or S, R^{41} and R^{42} are absent, and when K is N, one of R^{41}, R^{42} is absent, and when L' is O or S, R^{43} and R^{44} are absent, and when L' is N, one of R^{43}, R^{44} is absent,

in particular having the formula of:



(3a),

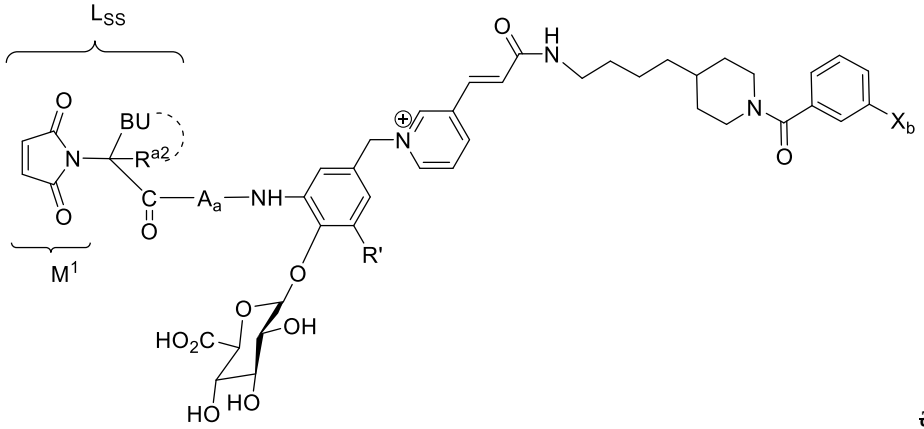


(4a),

wherein subscript e and f are independently 0 or 1,

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

41. The Drug Linker compound of claim **25**, wherein the ~~composition~~ compound is represented by the structure of:



~~and/~~or

in salt form, in particular in pharmaceutically acceptable salt form, wherein

subscript a is 1 and A is an amino acid residue;

BU is an acyclic Basic Unit so that the dotted curve line is absent, and R^{a2} is hydrogen, or

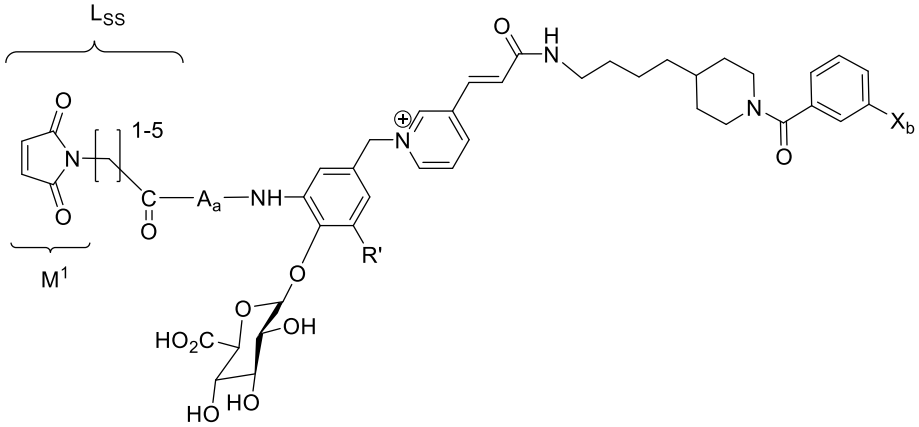
BU together with R^{a2} as C_1-C_6 alkyl and the carbon atom to which both are attached define a cyclic Basic Unit so that the dotted curved line is present; and

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$.

or

wherein the compound is represented by the structure~~(s)~~ of:



in salt form, in particular in pharmaceutically acceptable salt form, wherein

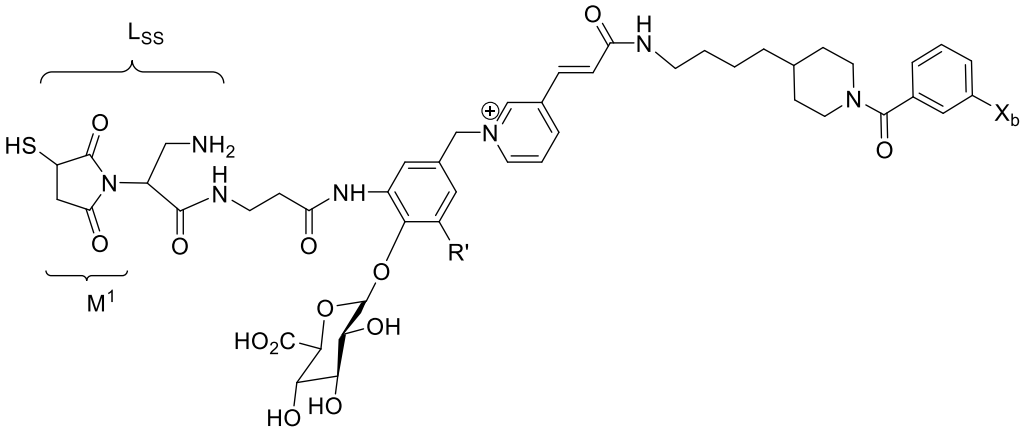
subscript a is 1 and A is an amino acid residue;

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$,

in particular

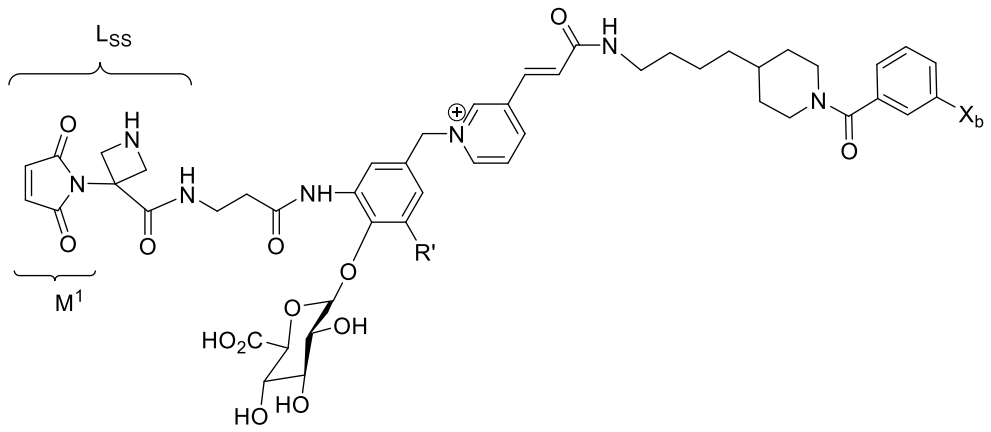
wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form,

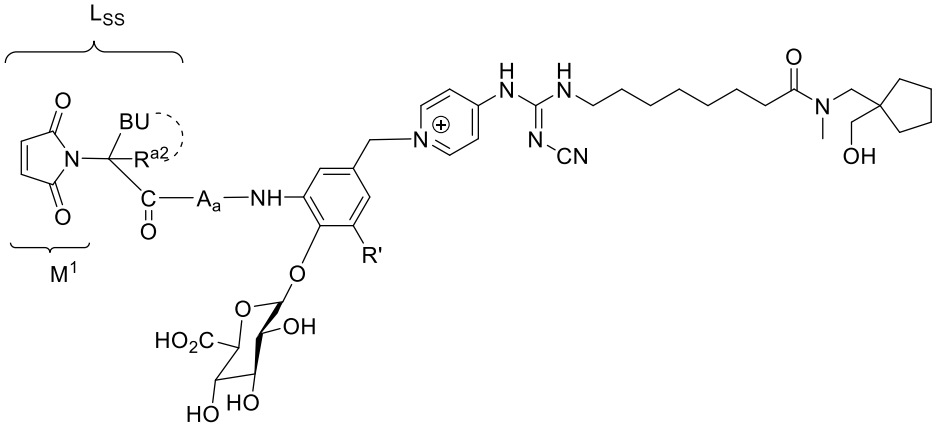
or in particular,

wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form.

42. The Drug Linker compound of claim **25**, wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form, wherein

subscript a is 1 and A is an amino acid residue;

BU is an acyclic Basic Unit so that the dotted curve line is absent, and R^{a2} is hydrogen, or

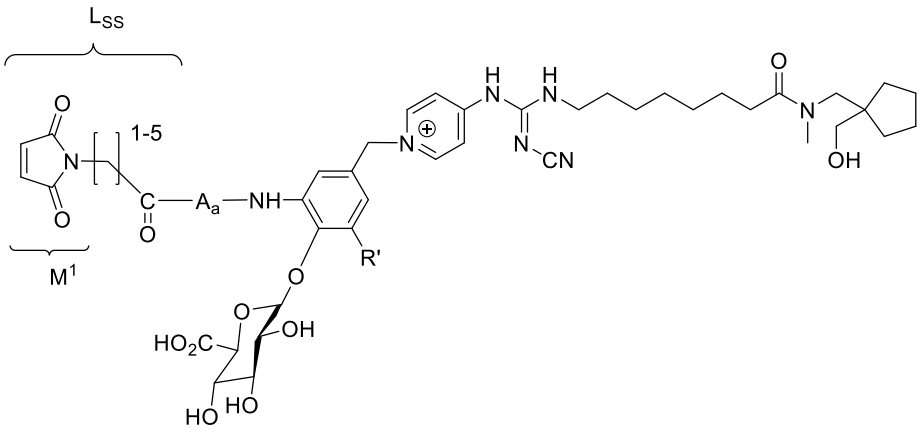
BU together with R^{a2} as C_1-C_6 alkyl and the carbon atom to which both are attached define a cyclic Basic Unit so that the dotted curved line is present; and

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$,

or

wherein the ~~composition~~ compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form, wherein

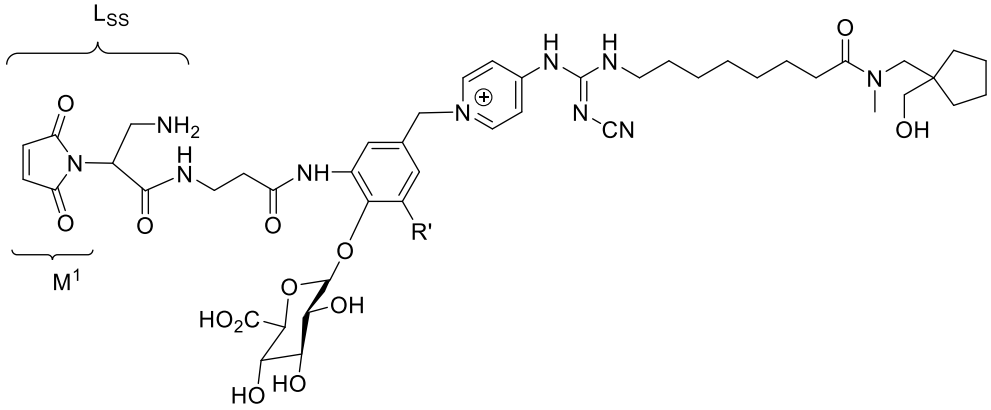
subscript a is 1 and A is an amino acid residue; and

R' is hydrogen or $–NO_2$; and

X^b is –H, -OH or $–NH_2$,

in particular

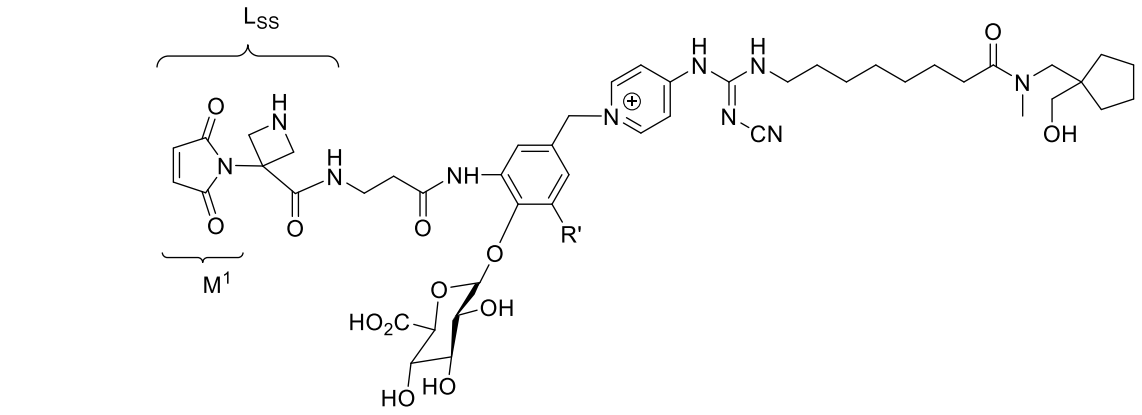
wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form,

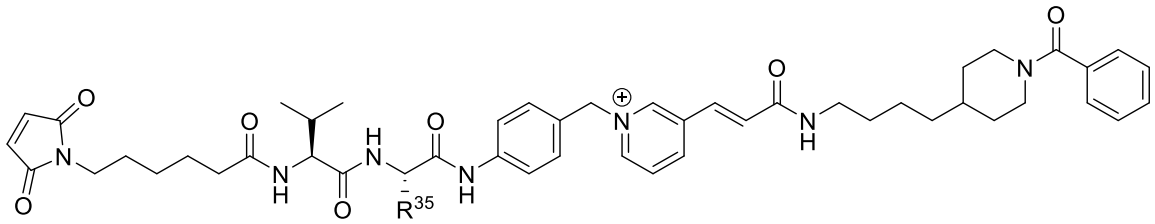
or in particular

wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form.

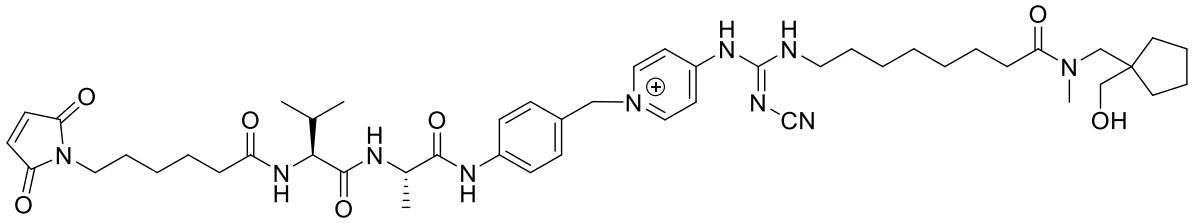
43. The Drug Linker compound of claim **25**, wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form,

or

wherein the compound is represented by the structure of:



in salt form, in particular in pharmaceutically acceptable salt form.