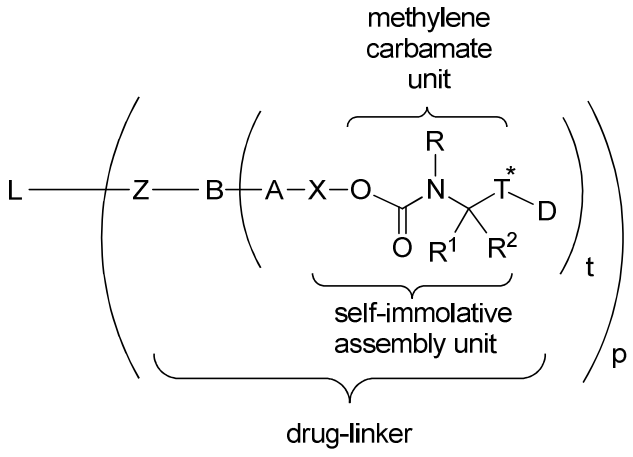
many aliphatic alcohol-containing drugs (see, for example, Toki, et al. *J. Org. Chem.* 2002, 67, 1866-1872). One reason for that may be due to the high pKa of aliphatic alcohol-containing drugs.

[0005] Therefore**,** a need exists for new linker technologies that can be used to attach drugs heretofore believed to be unsuitable for use as ADCs, and Ligand Drug Conjugates (LDCs) in general, including a need for more versatile methods for linking aromatic alcohol- and aliphatic alcohol-containing drugs to other targeting ligands in addition to antibodies. The present invention addresses those and other needs.

BRIEF SUMMARY

[0006] The disclosure provides *inter alia,* Ligand-Drug Conjugates, wherein the Ligand-Drug Conjugate is comprised of a Self-immolative Assembly Unit having a methylene carbamate unit for conjugation of a drug to a targeting ligand, methods of preparing and using them, and intermediates thereof. The Ligand-Drug Conjugates of the present disclosure are stable in circulation, yet capable of inflicting cell death once free drug is released from a Conjugate in the vicinity or within tumor cells.

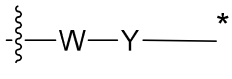
[0006a] In one aspect, the present disclosure provides a Ligand-Drug Conjugate compound, wherein the Ligand-Drug Conjugate compound has the structure of Formula II:



(II),

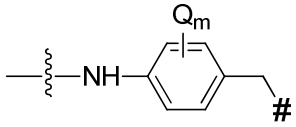
or a pharmaceutically acceptable salt thereof, wherein L is a Ligand Unit; Z is a Stretcher Unit comprising a thio-substituted succinimide or succinic acid-amide moiety; B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof; D is the Drug Unit having a thiol or amine functional group incorporated into the indicated methylene carbamate unit; T* is the sulfur or optionally substituted nitrogen atom from said functional group; X is the activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):

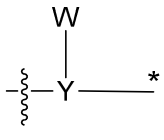


(i)

wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit; W is an Activation Unit; and Y is a self-immolative Spacer Unit, wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and the self-immolative Spacer Unit is a PAB group having the structure of:

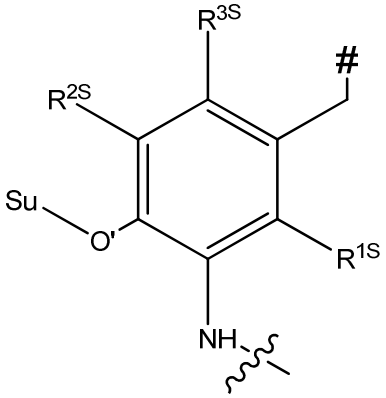


wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or the activateable self-immolative moiety is of formula (ii):

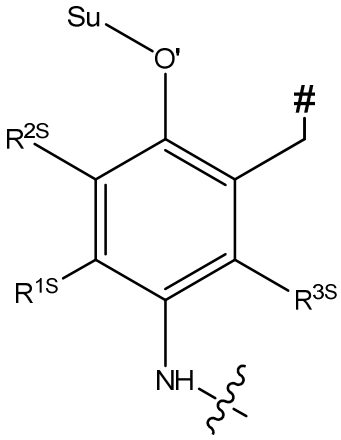


(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



or



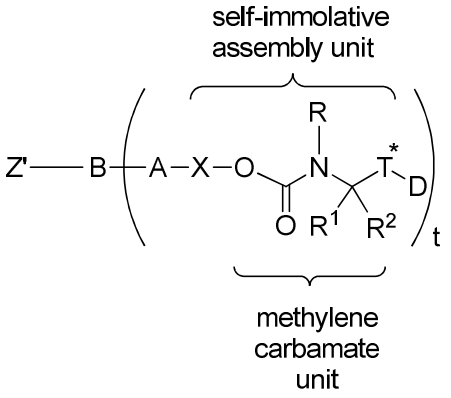
;

(XIXa) (XIXb)

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase; R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and $-NO_2$; the wavy line indicates the site of covalent attachment to the Stretcher Unit (Z), either directly or indirectly through the Connector Unit (A); and # indicates the site of attachment to the oxygen atom of the methylene carbamate unit;; R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety, and R^2 is hydrogen; subscript t ranges from 1 to 4; and subscript p is an integer ranging from 1 to 16.

[0006b] In another aspect, the present disclosure provides a Ligand-Drug Conjugate composition comprising a plurality of Conjugate compounds, wherein each independently has the structure of a Ligand-Drug Conjugate compound as described herein, wherein the integer range of subscript p is replaced by a number ranging from 1 to 16, and a pharmaceutically acceptable carrier.

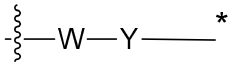
[0006c] In another aspect, the present disclosure provides a Drug-Linker compound having the structure of formula V:



(V)

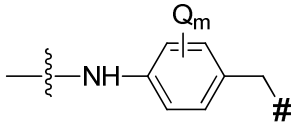
or a pharmaceutically acceptable salt thereof, wherein Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and comprises a maleimide functional group that provides for covalent attachment of a Ligand Unit to Z; B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof; D is a Drug Unit having a thiol or amine functional group that has been incorporated into the indicated methylene carbamate unit; T* is the sulfur or optionally substituted nitrogen atom from said functional group that becomes incorporated into the indicated methylene carbamate unit; R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen; X is an activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):

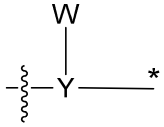


(i)

wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit; W is an Activation Unit; and Y is a self-immolative Spacer Unit, wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and the self-immolative Spacer Unit is a PAB group having the structure of:

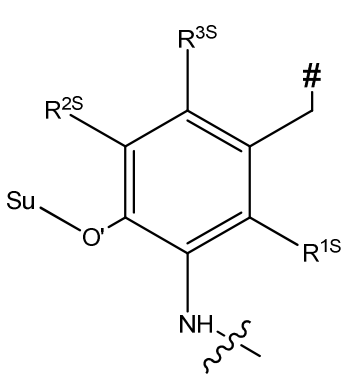


wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or the activateable self-immolative moiety is of formula (ii):

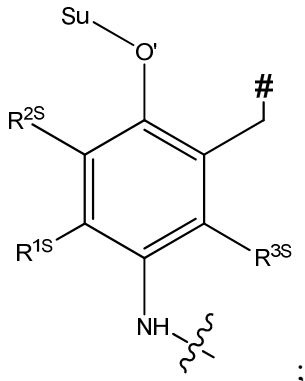


(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



or



;

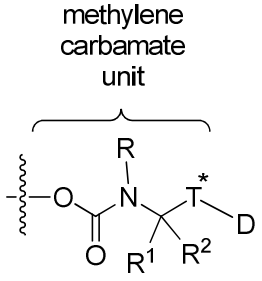
(XIXa) (XIXb)

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase; R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and -NO_2; the wavy line indicates the site of covalent attachment to the Stretcher Unit precursor (Z'), either directly or indirectly through the Connector Unit (A); and # indicates the site of attachment to the oxygen atom of the methylene carbamate unit; and subscript t ranges from 1 to 4.

[0006d]In another aspect, the present disclosure provides a method of preparing an Antibody Drug Conjugate compound as described herein, or a composition thereof as described herein, in which the Stretcher Unit (Z) comprises a succinimide moiety or a succinic acid-amide moiety; and wherein the Ligand Unit is an antibody, the method comprising the step of: contacting a Drug-Linker compound as described herein in which the Stretcher Unit precursor (Z') comprises a maleimide moiety with an antibody having a reactive cysteine thiol functional group obtained from interchain disulfide bond reduction and/or from an engineered cysteine residue, wherein said contacting converts Z' to Z by formation of a covalent bond between the reactive cysteine sulfur atom of the antibody and the succinimide moiety of Z, optionally followed by spontaneous hydrolysis of the succinimide moiety to an acid amide moiety, whereby the Antibody Drug Conjugate compound or composition thereof is obtained.

[0006e] In yet another aspect, the present disclosure provides use of a Ligand-Drug Conjugate compound as described herein, or a composition thereof as described herein for preparing a medicament. In another aspect, the present disclosure provides use of a Ligand-Drug Conjugate compound as described herein, or a composition thereof as described herein, in the manufacture of a medicament for treating a cancer.

[0007] In one principle example, a Ligand Drug Conjugate (LDC), or composition thereof, is comprised of a Ligand Unit, a Drug Unit and a Linker Unit that connects the Ligand Unit to the Drug Unit, wherein the Linker Unit is comprised of a Self-immolative Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety results in release of free drug from the LDC from self-immolation, and wherein the methylene carbamate unit is covalently attached to the Drug Unit and the activateable self-immolative moiety, wherein the methylene carbamate unit covalently attached to the Drug Unit is represented by the structure of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment of the methylene carbamate unit to an activateable self-immolative moiety (X);

D is a Drug Unit having a functional group (e.g., hydroxyl, thiol, amide or amine functional group) that has been incorporated into the methylene carbamate unit,

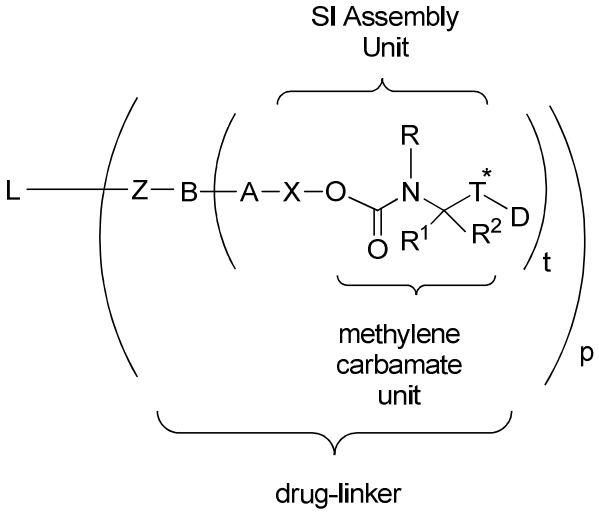
T* is a heteroatom from said functional group (e.g., oxygen, sulfur, optionally substituted nitrogen) that becomes incorporated into the methylene carbamate unit;

X is an activateable self-immolative moiety;

R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl,

or R and R^1 together with the nitrogen and carbon atoms to which they are attached comprise an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety, and R^2 is hydrogen.

[0008] In some of those examples, a Ligand Drug Conjugate, or composition thereof, having the methylene carbamate unit of formula I is represented by the structure of formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

B is an optional Branching Unit and is present when t is greater than 1 and is absent when t is 1;

A is an optional Connector Unit;

X is an activateable self-immolative moiety;

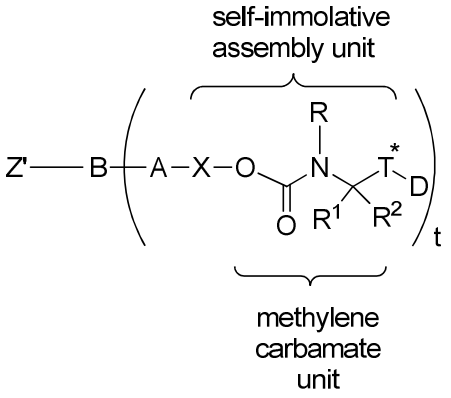
the subscript t ranges from 1 to 4;

the subscript p is an integer (for an individual LDC) or a number (for a population of LDCs in a LDC composition) ranging from 1 to 16; and

and D, T*, R, R^1 and R^2 are as defined in formula I.

[0009] Other principle examples are Drug-Linker Compounds useful as intermediates for preparing Ligand-Drug Conjugates, wherein the Drug-Linker Compound is comprised of a Drug Unit and a Linker Unit, wherein the Linker Unit is comprised of a Stretcher Unit precursor (Z') capable of forming a covalent bond to a targeting ligand that provides for a Ligand Unit, a Self-immolative Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety in a LDC in which the Drug-Linker Compound is incorporated results in release of free drug from the LDC by self-immolation, and wherein the methylene carbamate unit is covalently attached to the Drug Unit and the activateable self-immolative moiety.

[0010] In some of those examples the Drug-Linker Compound having the methylene carbamate unit of formula I has the structure of formula V:



(V)

or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and is comprised of a functional group that provides for covalent attachment of a Ligand Unit to Z;

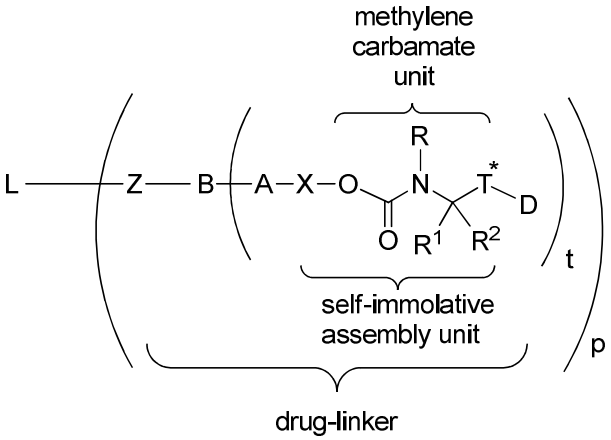
and B, A, X, R, R^1, R^2, T*, D, and the subscript t are as defined for Formula (II).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 demonstrates the stability *ex vivo* in rat and mouse plasma of an ADC composition having an average drug loading of 4 in which the ADCs of the composition are comprised of a methylene alkoxy carbamate unit (MAC unit) that incorporates the oxygen heteroatom from the hydroxyl functional group of Auristatin E.

WHAT IS CLAIMED IS:

1. A Ligand-Drug Conjugate compound, wherein the Ligand-Drug Conjugate compound has the structure of Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit comprising a thio-substituted succinimide or succinic acid-amide moiety;

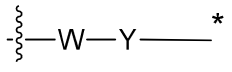
B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof;

D is the Drug Unit having a thiol or amine functional group incorporated into the indicated methylene carbamate unit;

T* is the sulfur or optionally substituted nitrogen atom from said functional group;

X is the activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):



(i)

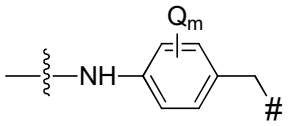
wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and

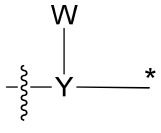
the self-immolative Spacer Unit is a PAB group having the structure of:



wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and

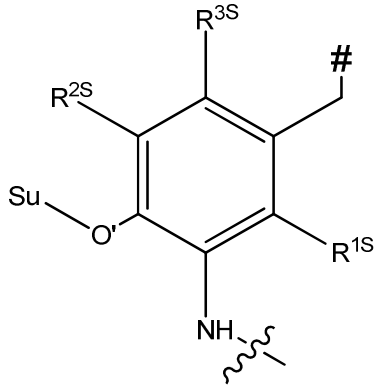
Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or

the activateable self-immolative moiety is of formula (ii):

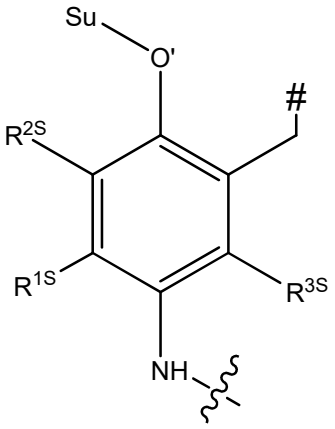


(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



or



;

(XIXa) (XIXb)

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase;

R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and $-NO_2$;

the wavy line indicates the site of covalent attachment to the Stretcher Unit (Z), either directly or indirectly through the Connector Unit (A); and

# indicates the site of attachment to the oxygen atom of the methylene carbamate unit;

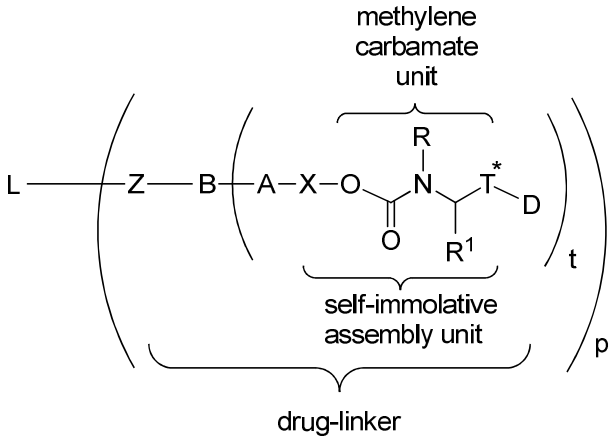
R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or

both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety, and R^2 is hydrogen;

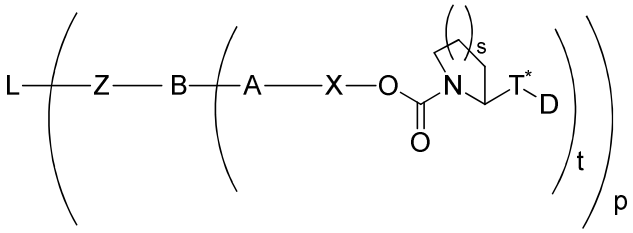
subscript t ranges from 1 to 4; and

subscript p is an integer ranging from 1 to 16.

2. The Ligand-Drug Conjugate compound of claim 1, wherein the Ligand-Drug Conjugate compound has the structure of Formula IIa or Formula IIb:



(IIa)



(IIb)

or a pharmaceutically acceptable salt thereof, wherein subscript s is 0, 1, 2, or 3.

3. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R and R^1 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl and optionally substituted C_{6-14} aryl; and subscript s is 0, 1, or 2.

4. The Ligand-Drug Conjugate compound of claim 3, wherein R^1 is not substituted.

5. The Ligand-Drug Conjugate compound of claim 3, wherein R^1 and R^2 are not substituted.

6. The Ligand-Drug Conjugate compound of claim 3, wherein R, R^1 and R^2 are not substituted.

7. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein optional substituents are independently selected from the group consisting of -X, $-R^{op}$, -OH, $-OR^{op}$, SR^{op}, $N(R^{op})_2$, $N(R^{op})_3$, $=NR^{op}$, CX_3, CN, NO_2, $-NR^{op}C(=O)R^{op}$, $-C(=O)R^{op}$, $-C(=O)N(R^{op})_2$, $-S(=O)_2R^{op}$, -

$S(=O)_2NR^{op}$, $-S(=O)R^{op}$, $-OP(=O)(OR^{op})_2$, $-P(=O)(OR^{op})_2$, $-PO_3^{=}$, PO_3H_2, $-C(=O)R^{op}$, $-C(=S)R^{op}$, $-CO_2R^{op}$, $-CO_2^{-}$, $-C(=S)OR^{op}$, $-C(=O)SR^{op}$, $-C(=S)SR^{op}$, $-C(=O)N(R^{op})_2$, $-C(=S)N(R^{op})_2$, and $-C(=NR^{op})N(R^{op})_2$, wherein each X is independently selected from the group consisting of a halogen: -F, -Cl, -Br, and -I; and each R^{op} is independently selected from the group consisting of hydrogen, $-C_1$-C_{20} alkyl, $-C_6$-C_{20} aryl, $-C_3$-C_{14} heterocycle, and protecting groups.

8. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein optional substituents are independently selected from the group consisting of -X, $-R^{op}$, -OH, $-OR^{op}$, $-SR^{op}$, $-N(R^{op})_2$, $N(R^{op})_3$, $=NR^{op}$, $-NR^{op}C(=O)R^{op}$, $-C(=O)R^{op}$, $-C(=O)N(R^{op})_2$, $-S(=O)_2R^{op}$, $-S(=O)_2NR^{op}$, $-S(=O)R^{op}$, $-C(=O)R^{op}$, $-C(=S)R^{op}$, $-C(=O)N(R^{op})_2$, $-C(=S)N(R^{op})_2$, and $-C(=NR^{op})N(R^{op})_2$, wherein X is independently selected from the group consisting of –F and-Cl; and each R^{op} is independently selected from the group consisting of hydrogen, $-C_1$-C_{20} alkyl, $-C_6$-C_{20} aryl, $-C_3$-C_{14} heterocycle, and protecting groups.

9. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein optional substituents are independently selected from the group consisting of -X, $-R^{op}$, -OH, $-OR^{op}$, $-N(R^{op})_2$, $-N(R^{op})_3$, $-NR^{op}C(=O)R^{op}$, $-C(=O)N(R^{op})_2$, $-S(=O)_2R^{op}$, $-S(=O)_2NR^{op}$, $-S(=O)R^{op}$, $-C(=O)R^{op}$, $-C(=O)N(R^{op})_2$, and $-C(=NR^{op})N(R^{op})_2$, wherein X is –F; and each R^{op} is independently selected from the group consisting of hydrogen, $-C_1$-C_{20} alkyl, $-C_6$-C_{20} aryl, $-C_3$-C_{14} heterocycle, and protecting groups.

10. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein an optional substituent is selected from the group consisting of $–N(R^{op})_2$, $-N^{+}(R^{op})_3$ and $-C(=NR^{op})N(R^{op})_2$ and acid addition salts thereof, wherein each R^{op} is independently selected from the group consisting of hydrogen, $-C_1$-C_{20} alkyl, $-C_6$-C_{20} aryl, $-C_3$-C_{14} heterocycle, and protecting groups.

11. The Ligand-Drug Conjugate compound of claim 3, wherein R is C_{1-6} alkyl, optionally substituted with a basic functional group.

12. The Ligand-Drug Conjugate compound of claim 3, wherein R is a saturated C_{1-6} alkyl, optionally substituted with a basic functional group.

13. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is a basic amine or basic nitrogen-containing 3-, 4-, 5-, or 6-membered heterocycle, wherein the heterocycle is C-linked or N-linked to 2-6 contiguous carbon atoms connecting the carbamate nitrogen of the indicated methylene carbamate unit to the basic functional group and is optionally substituted.

14. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.

15. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

16. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit, wherein, the basic functional group of the Basic Unit is $–NH_2$.

17. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

18. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2NH_2$.

19. The Ligand-Drug Conjugate compound of claim 18, wherein R^1 is hydrogen.

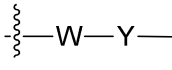
20. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the amine functional group is incorporated into the indicated methylene carbamate unit so that T* represents the nitrogen atom, optionally substituted, from that functional group.

21. The Ligand-Drug Conjugate compound of claim 20, wherein the amine functional group is that of an aliphatic amine-containing free drug.

22. The Ligand-Drug Conjugate compound of claim 20, wherein the amine functional group is that of an aromatic amine-containing free drug.

23. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein B is absent and subscript t is 1 or B is present and subscript t is 2.

24. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the structure of the activateable self-immolative moiety (X) is represented by formula (i):



(i)

wherein the wavy line indicates covalent attachment of W to A, B or Z depending on the presence or absence of A and/or B and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

W is an Activation Unit; and

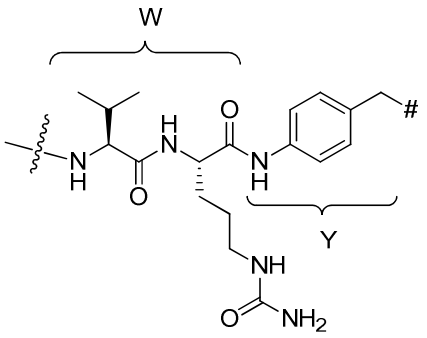
Y is a self-immolative Spacer Unit,

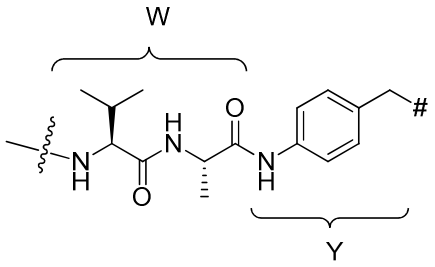
wherein activation of self-immolation of Y results in release of D as free drug.

25. The Ligand-Drug Conjugate compound of claim 24, wherein the tumor associated protease is cathepsin B.

26. The Ligand-Drug Conjugate compound of claim 24, wherein W is -Val-Cit-, -Phe-Lys-or –Val-Ala-.

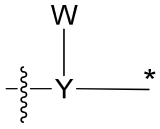
27. The Ligand-Drug Conjugate compound of claim 24, wherein –W-Y-is represented by the structure of:



or


wherein the wavy bond to the nitrogen of W indicates covalent linkage to Z, A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

28. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the structure of the activateable self-immolative moiety (X) is represented by formula (ii):



(ii)

wherein the wavy line indicates covalent attachment of Y to A, B or Z depending on the presence or absence of A and/or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate moiety;

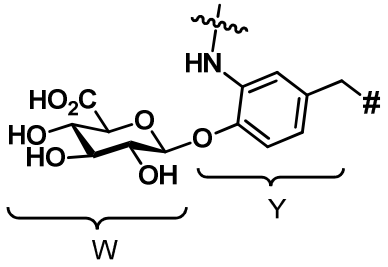
W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein activation of self-immolation of Y results in release of D as free drug.

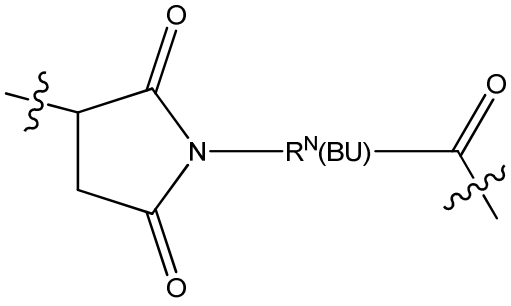
29. The Ligand-Drug Conjugate compound of claim 28, wherein the glycosidase is a glucuronidase.

30. The Ligand-Drug Conjugate compound of claim 28, wherein –Y(W)-is represented by the structure of:



wherein the wavy bond adjacent to the nitrogen of Y indicates covalent attachment of Y to Z, A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

31. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the Stretcher Unit (Z) comprises a succinimide moiety and is represented by the structure of formula **Xa':**



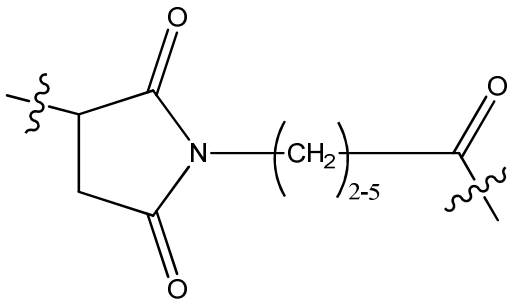
(**Xa'**)

wherein the wavy line adjacent to the succinimide ring system indicates covalent attachment to a sulfur atom of the Ligand Unit;

the wavy line adjacent to the carbonyl indicates covalent attachment to the remainder of the drug linker moiety;

and R^N is -C_2-C_5 alkylene, wherein the alkylene is optionally substituted by a Basic Unit (BU), wherein BU is $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^{op}$, or $–(CH_2)_xN(R^{op})_2$, wherein x is an integer ranging from 1-4; and R^{op} is C_{1-6} alkyl.

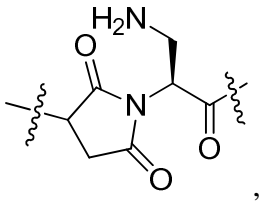
32. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure**:**



wherein the wavy line adjacent to the succinimide ring system indicates covalent attachment to a sulfur atom of the Ligand Unit, and

the wavy line adjacent to the carbonyl indicates covalent attachment to the remainder of the drug linker moiety.

33. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure of:

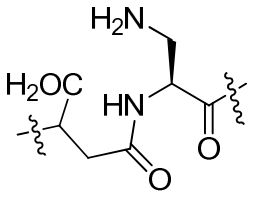


,

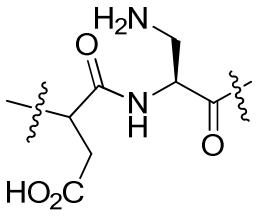
or an acid addition salt thereof,

or

wherein the Stretcher unit (Z) comprises a succinic acid-amide moiety and is represented by the structure of:



or



,

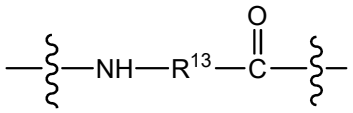
or an acid addition salt thereof;

and

wherein the wavy line adjacent to the carbonyl carbon indicates covalent attachment to the remainder of the drug linker moiety and the other wavy line indicates covalent attachment to a sulfur atom of the Ligand Unit.

34. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein a Connector Unit (A) is present.

35. The Ligand-Drug Conjugate compound of claim 34, wherein A is:

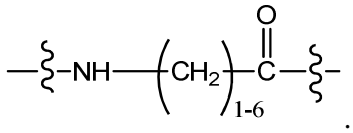


wherein the wavy line adjacent to the carbonyl indicates covalent attachment to the activateable self-immolative moiety X of the Self-immolative Assembly Unit, and

the other wavy line indicates covalent attachment to B, if present, or to Z if B is absent; and

R^{13} is -C_1-C_6 alkylene-, -C_3-C_8carbocyclo-, -arylene-, -C_1-C_{10} heteroalkylene-, -C_3-C_8heterocyclo-, -C_1-C_{10}alkylene-arylene-, -arylene-C_1-C_{10}alkylene-, -C_1-C_{10}alkylene-(C_3-C_8carbocyclo)-, -(C_3-C_8carbocyclo)-C_1-C_{10}alkylene-, -C_1-C_{10}alkylene-(C_3-C_8 heterocyclo)-, or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-.

36. The Ligand-Drug Conjugate compound of claim 35, wherein A has the formula



.

37. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein A is absent.

38. The Ligand-Drug Conjugate compound of claim 1, wherein p ranges from 1 to 10.

39. The Ligand-Drug Conjugate compound of claim 2, wherein p ranges from 1 to 8.

40. The Ligand-Drug Conjugate compound of claim 38 or 39, wherein the Ligand Unit is an antibody.

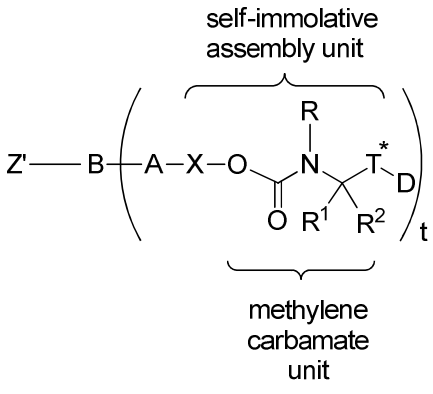
41. A Ligand-Drug Conjugate composition comprising a plurality of Conjugate compounds, wherein each independently has the structure of a Ligand-Drug Conjugate compound of claim 1, wherein the integer range of subscript p is replaced by a number ranging from 1 to 16, and a pharmaceutically acceptable carrier.

42. The Ligand-Drug Conjugate composition of claim 41, wherein the Stretcher Unit (Z) of each of the Conjugate compounds independently comprises a succinimide moiety or a succinic acid-amide moiety, wherein either moiety is attached to a sulfur atom of the Ligand Unit.

43. The Ligand-Drug Conjugate composition of claim 42, wherein there is-2 to 10 drug-linker moieties per Ligand Unit.

44. The Ligand-Drug Conjugate composition of claim 42, wherein there is 2 to 8 drug-linker moieties per Ligand Unit.

45. A Drug-Linker compound having the structure of formula V:



(V)

or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and comprises a maleimide functional group that provides for covalent attachment of a Ligand Unit to Z;

B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or diamino residues or combinations thereof;

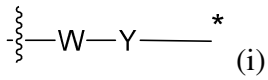
D is a Drug Unit having a thiol or amine functional group that has been incorporated into the indicated methylene carbamate unit;

T* is the sulfur or optionally substituted nitrogen atom from said functional group that becomes incorporated into the indicated methylene carbamate unit;

R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or

both R and R^1 together with the nitrogen and carbon atoms to which they are attached define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen;

X is an activateable self-immolative moiety, wherein the activateable self-immolative moiety is of formula (i):



(i)

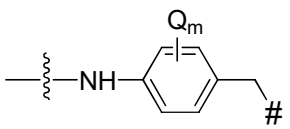
wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein the Activation Unit comprises a sequence of 1 to 12 amino acids having an amide linkage to the self-immolative Spacer Unit wherein the amide linkage is cleavable by the action of a tumor associated protease to initiate release of free drug, and

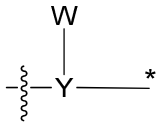
the self-immolative Spacer Unit is a PAB group having the structure of:



wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and

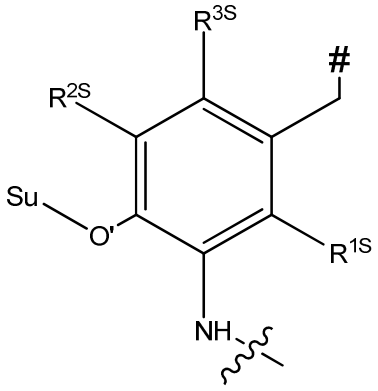
Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or

the activateable self-immolative moiety is of formula (ii):



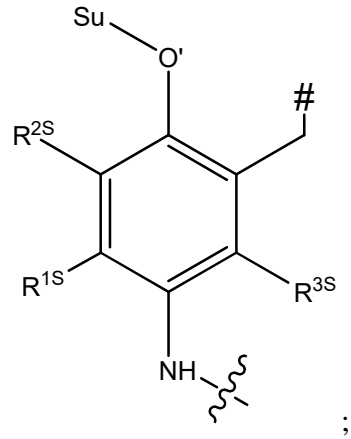
(ii)

wherein the wavy line indicates covalent attachment of Y to A, B, or Z, depending on the presence or absence of A or B, and the asterisk (*) indicates the site of covalent attachment of Y to the oxygen atom of the methylene carbamate unit, wherein formula (ii) is a Glucuronide Unit having the structure of formula XIXa or XIXb:



(XIXa)

or



(XIXb)

;

wherein Su is a Sugar moiety; -O'-represents the oxygen atom of glycosidic bond cleavable by a glycosidase;

R^{1S}, R^{2S} and R^{3S} are independently selected from the group consisting of hydrogen, halogen, -CN and -NO_2;

the wavy line indicates the site of covalent attachment to the Stretcher Unit precursor (Z'), either directly or indirectly through the Connector Unit (A); and

# indicates the site of attachment to the oxygen atom of the methylene carbamate unit; and

subscript t ranges from 1 to 4.

46. The Drug-Linker compound of claim 45, wherein R and R^1 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl and optionally substituted C_{6-14} aryl.

47. The Drug-Linker compound of claim 46, wherein R^1 is not substituted.

48. The Drug-Linker compound of claim 46, wherein R^1 and R^2 are not substituted.

49. The Drug-Linker compound of claim 45, wherein R, R^1 and R^2 are not substituted.

50. The Drug-Linker compound of claim 45, wherein optional substituents are independently selected from the group consisting of -X, -R^{op}, -OH, -OR^{op}, SR^{op}, $N(R^{op})_2$, $N(R^{op})_3$, =NR^{op}, CX_3, CN, NO_2, -$NR^{op}C(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, -$S(=O)_2R^{op}$, -$S(=O)_2NR^{op}$, -$S(=O)R^{op}$, -$OP(=O)(OR^{op})_2$, -$P(=O)(OR^{op})_2$, -$PO_3^{=}$, PO_3H_2, -$C(=O)R^{op}$, -$C(=S)R^{op}$, -CO_2R^{op}, -CO_2^{-}, -$C(=S)OR^{op}$, -$C(=O)SR^{op}$, -$C(=S)SR^{op}$, -$C(=O)N(R^{op})_2$, -$C(=S)N(R^{op})_2$, and -$C(=NR^{op})N(R^{op})_2$, wherein each X is independently selected from the group consisting of a halogen: -F, -Cl, -Br, and -I; and each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and protecting groups.

51. The Drug-Linker compound of claim 45, wherein optional substituents are independently selected from the group consisting of -X, -R^{op}, -OH, -OR^{op}, -SR^{op}, -$N(R^{op})_2$, $N(R^{op})_3$, =NR^{op}, -$NR^{op}C(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, -$S(=O)_2R^{op}$, -$S(=O)_2NR^{op}$, -$S(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=S)R^{op}$, -$C(=O)N(R^{op})_2$, -$C(=S)N(R^{op})_2$, and -$C(=NR^{op})N(R^{op})_2$, wherein X is independently selected from the group consisting of –F and-Cl; and each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and protecting groups.

52. The Drug-Linker compound of claim 45, wherein optional substituents are independently selected from the group consisting of -X, -R^{op}, -OH, -OR^{op}, -$N(R^{op})_2$, -$N(R^{op})_3$, -$NR^{op}C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, -$S(=O)_2R^{op}$, -$S(=O)_2NR^{op}$, -$S(=O)R^{op}$, -$C(=O)R^{op}$, -$C(=O)N(R^{op})_2$, and -$C(=NR^{op})N(R^{op})_2$, wherein X is –F; and each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and protecting groups.

53. The Drug-Linker compound of claim 45, wherein an optional substituent is selected from the group consisting of –$N(R^{op})_2$, -$N^+(R^{op})_3$ and -$C(=NR^{op})N(R^{op})_2$ and acid addition salts thereof, wherein each R^{op} is independently selected from the group consisting of hydrogen, -C_1-C_{20} alkyl, -C_6-C_{20} aryl, -C_3-C_{14} heterocycle, and protecting groups.

54. The Drug-Linker compound of claim 46, wherein R is C_{1-6} alkyl, optionally substituted with a basic functional group.

55. The Drug-Linker compound of claim 46, wherein R is a saturated C_{1-6} alkyl, optionally substituted with a basic functional group.

56. The Drug-Linker compound of claim 45, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is a basic amine or basic nitrogen-containing 3-, 4-, 5-, or 6-membered heterocycle, wherein the heterocycle is C-linked or N-linked to 2-6 contiguous carbon atoms connecting the carbamate nitrogen of the indicated methylene carbamate unit to the basic functional group and is optionally substituted.

57. The Drug-Linker compound of claim 45, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is –$N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.

58. The Drug-Linker compound of claim 45, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is –$N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

59. The Drug-Linker compound of claim 45, wherein R is a Basic Unit, wherein, the basic functional group of the Basic Unit is $–NH_2$.

60. The Drug-Linker compound of claim 45, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and methyl.

61. The Drug-Linker compound of claim 45, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2NH_2$.

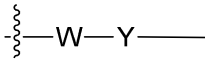
62. The Drug-Linker compound of claim 61, wherein R^1 is hydrogen.

63. The Drug-Linker compound of claim 45, wherein D is a Drug Unit corresponding to free drug having an amine functional group that has been incorporated into the methylene carbamate unit so that T* represents the nitrogen atom, optionally substituted, from that functional group.

64. The Drug-Linker compound of claim 45, wherein D is a Drug Unit corresponding to an aliphatic amine-containing free drug, wherein incorporation into the methylene carbamate unit of D is via the optionally substituted nitrogen atom of the aliphatic amine so that T* represents the nitrogen atom from that functional group.

65. The Drug-Linker compound of claim 45, wherein D is a Drug Unit corresponding to an aromatic amine-containing free drug, wherein incorporation into the methylene carbamate unit of D is via the optionally substituted nitrogen atom of the aromatic amine so that T* represents the nitrogen atom from that functional group.

66. The Drug-Linker compound of claim 45, wherein the structure of the indicated activateable self-immolative moiety (X) is represented by formula (i):



(i)

wherein the wavy line indicates covalent attachment of W to A, B or Z depending on the presence or absence of A and/or B and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

W is an Activation Unit; and

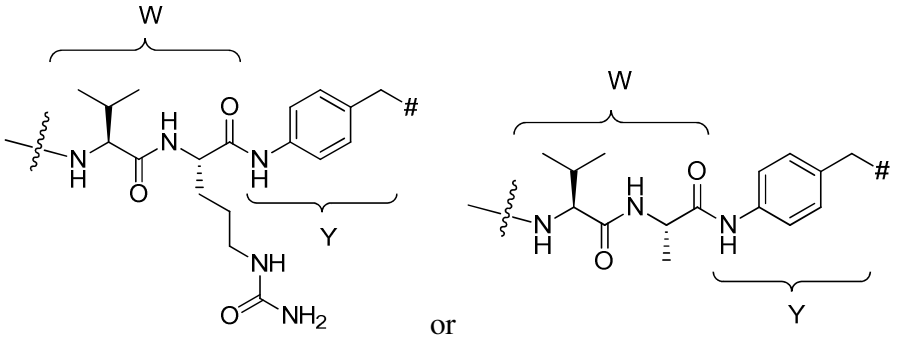
Y is a self-immolative Spacer Unit,

wherein activation of self-immolation of Y in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound results in release of D as free drug.

67. The Drug-Linker compound of claim 66, wherein the tumor associated protease is cathepsin B.

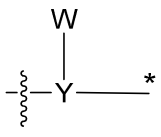
68. The Drug-Linker compound of claim 66, wherein W is -Val-Cit-, -Phe-Lys-or –Val-Ala-.

69. The Drug-Linker compound of claim 66, wherein –W-Y-is represented by the structure of:



wherein the wavy bond to the nitrogen of W indicates covalent linkage to Z, A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

70. The Drug-Linker compound of claim 45, wherein the structure of the activateable self-immolative moiety (X) is represented by formula (ii):



(ii)

wherein the wavy line indicates covalent attachment of Y to A, B or Z depending on the presence or absence of A and/or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate moiety;

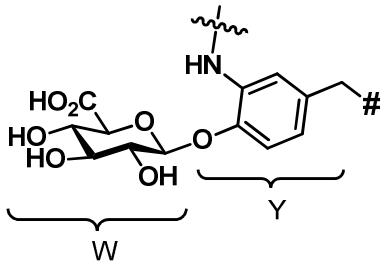
W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein activation of self-immolation of Y in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound results in release of D as free drug.

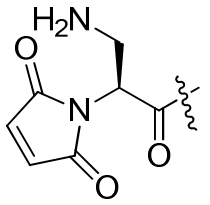
71. The Drug-Linker compound of claim 70, wherein the glycosidase is a glucuronidase.

72. The Drug-Linker compound of claim 70, wherein –Y(W)-is represented by the structure of:



wherein the wavy bond adjacent to the nitrogen of Y indicates covalent attachment to Z', A or B, depending on the presence or absence of A and/or B, and the hash mark (#) indicates covalent attachment of the benzylic carbon of Y to the oxygen atom of the methylene carbamate unit.

73. The Drug-Linker compound of claim 45, wherein Z' has the structure of:

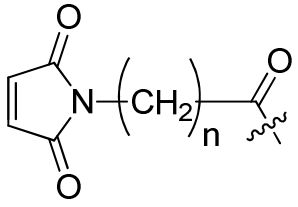


,

or an acid addition salt thereof,

or

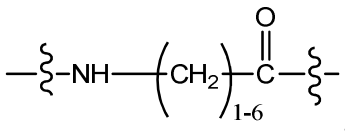
wherein Z' has the structure of:



and

wherein the wavy line adjacent to the carbonyl indicates covalent attachment of Z' to A, B or X, depending on the presence or absence of A and/or B.

74. The Drug-Linker compound of claim 45, wherein A is present and has the formula of:



.

75. The Drug-Linker compound of claim 45, wherein B is absent and subscript t is 1 or B is present and subscript t is 2.

76. A method of preparing an Antibody Drug Conjugate compound of claim 1 or 2, or a composition thereof of claim 42, in which the Stretcher Unit (Z) comprises a succinimide moiety or a succinic acid-amide moiety; and wherein the Ligand Unit is an antibody, the method comprising the step of:

contacting a Drug-Linker compound of claim 45 in which the Stretcher Unit precursor (Z') comprises a maleimide moiety with an antibody having a reactive cysteine thiol functional group obtained from interchain disulfide bond reduction and/or from an engineered cysteine residue,

wherein said contacting converts Z' to Z by formation of a covalent bond between the reactive cysteine sulfur atom of the antibody and the succinimide moiety of Z, optionally followed by spontaneous hydrolysis of the succinimide moiety to an acid amide moiety, whereby the Antibody Drug Conjugate compound or composition thereof is obtained.

77. The Ligand-Drug Conjugate compound of claim 1, wherein the Drug Unit is a cytotoxic drug.

78. Use of a Ligand-Drug Conjugate compound of claim 1, or a composition thereof of claim 41, for preparing a medicament.

79. Use of a Ligand-Drug Conjugate compound of claim 77, or a composition thereof of claim 41, in the manufacture of a medicament for treating a cancer.

80. The use according to claim 79, wherein the cancer is a hematological cancer.

81. The use according to claim 79, wherein the cancer is in the form of a solid tumor.