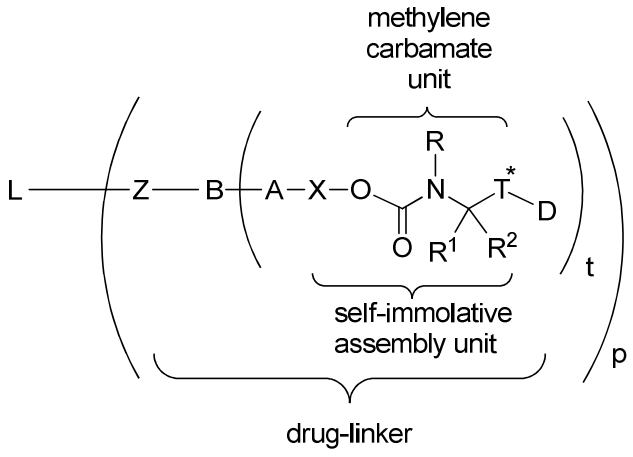
many aliphatic alcohol-containing drugs (see, for example, Toki, et al. *J. Org. Chem.* 2002, 67, 1866-1872). One reason for that may be due to the high pKa of aliphatic alcohol-containing drugs.

[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.

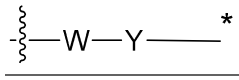
[0006a] In one aspect, the present disclosure provides a Ligand-Drug Conjugate compound, wherein the Ligand-Drug Conjugate compound has the structure of Formula II:



(II),

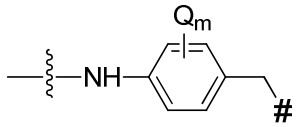
or a pharmaceutically acceptable salt thereof, wherein L is a Ligand Unit; Z is a Stretcher Unit comprising a thio-substituted succinimide or succinic acid-amide moiety; B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine 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):

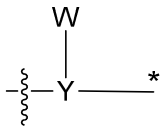


(i)

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:

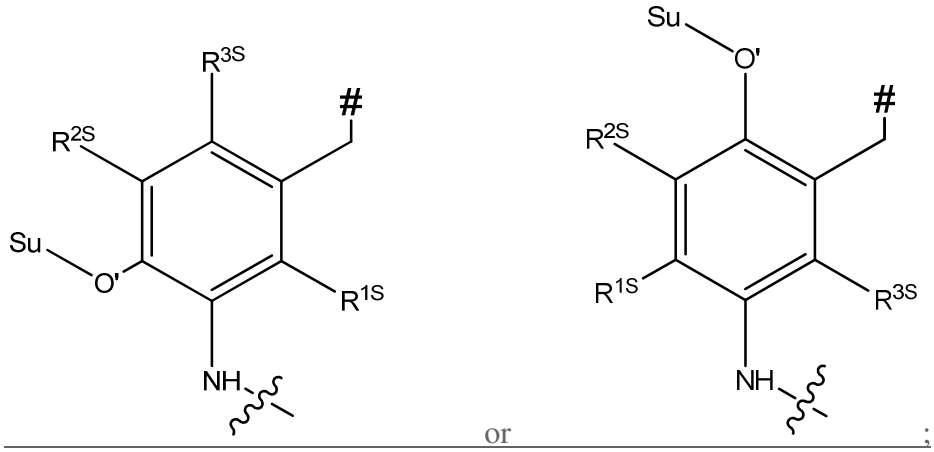


wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron 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:

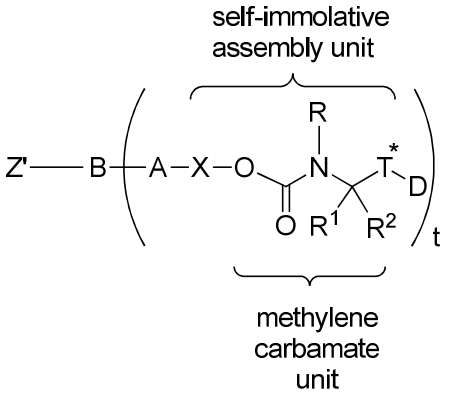


(XIXa) (XIXb)

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;~~, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase and results in release of D as free drug having said thiol or amine functional group~~; 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.

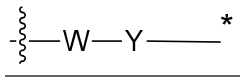
[0006c] In another aspect, the present disclosure provides a Drug-Linker compound having the structure of formula V:



(V)

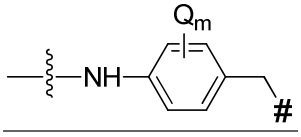
or a pharmaceutically acceptable salt thereof, wherein Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) and comprises a maleimide functional group that provides for covalent attachment of a Ligand Unit to Z; B is an optional Branching Unit comprising one or more natural or non-natural amino acid, 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):

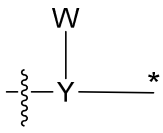


(i)

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:

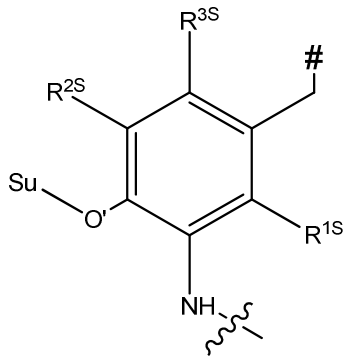


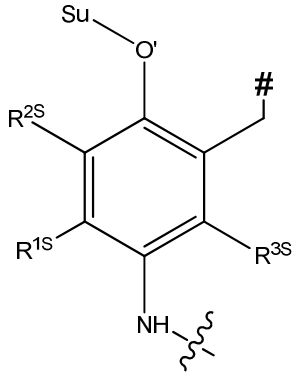
wherein the wavy line indicates the site of covalent attachment to the Activation Unit and the hashtag (#) indicates the site of covalent attachment to the benzylic carbon atom of the PAB group to the methylene carbamate unit; and Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron 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 ;

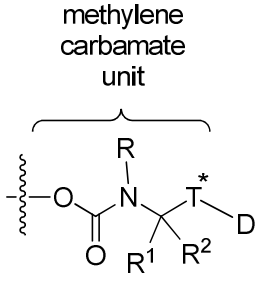
(XIXa) (XIXb)

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;~~, wherein activation is by a protease or a glucosidase; B is an optional Branching Unit that is present when subscript t is greater than 1 and is absent when subscript t is 1; A is an optional Connector 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~~n~~ 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 ~~moeity~~ 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 ~~moeity~~ 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,

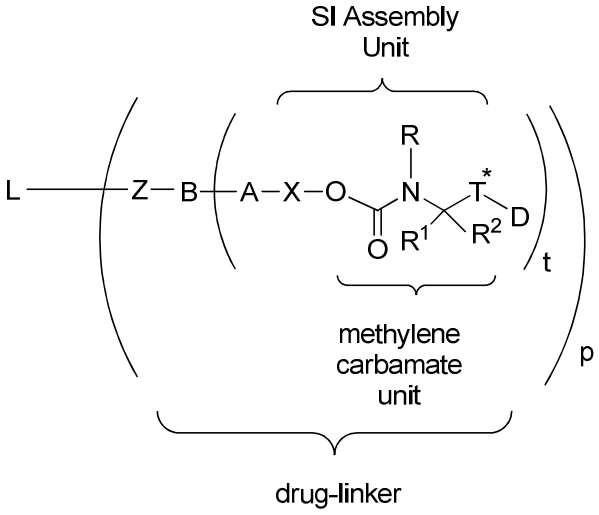
T* is a heteroatom from said functional group (e.g., oxygen, sulfur, optionally substituted nitrogen) that becomes incorporated into the methylene carbamate unit;

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;

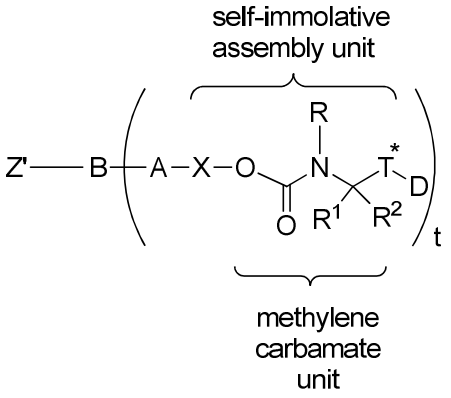
the subscript t ranges from 1 to 4;

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;

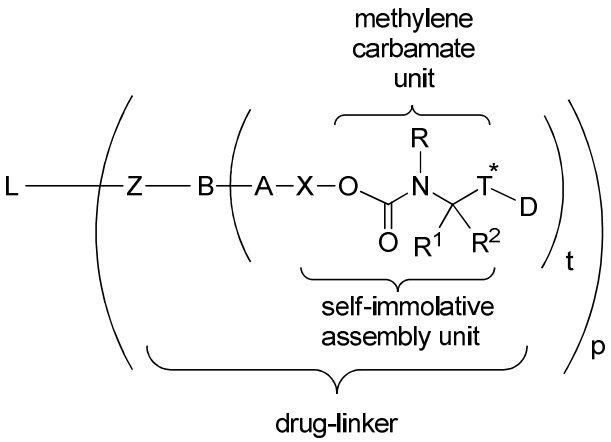
and B, A, X, R, R^1, R^2, T*, D, and the subscript t are as defined for Formula (II).

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;

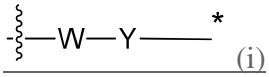
B is an optional Branching Unit comprising one or more natural or non-natural amino acid, amino alcohol, amino aldehyde, or polyamine residues or combinations thereof and is present when subscript t is greater than 1 and is absent when subscript t is 1;

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)

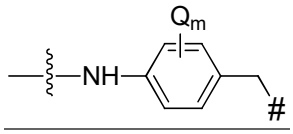
wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

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

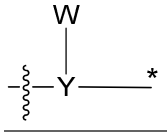
the self-immolative Spacer Unit is a PAB group having the structure of:



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

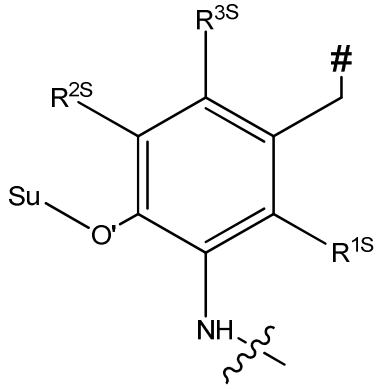
Q is independently -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), or other electron donating group and subscript m is 0, 1 or 2, or

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

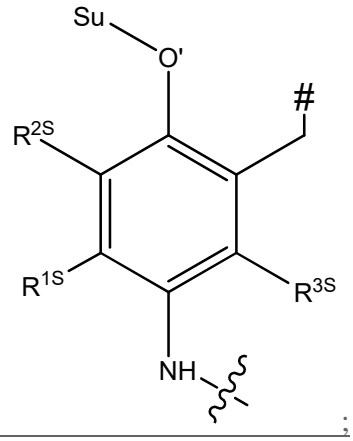


(ii)

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; ~~, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase and results in release of D as free drug having said thiol or amine functional group;~~

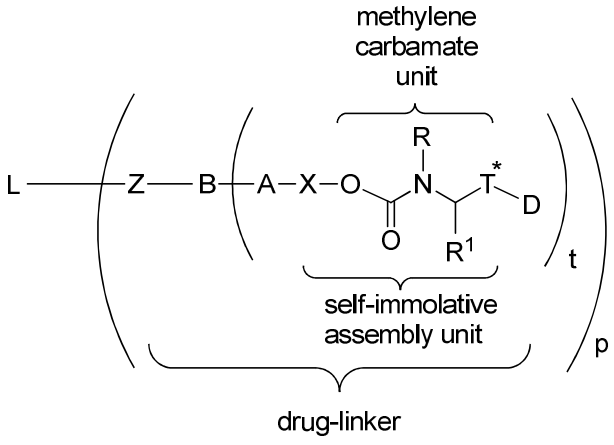
R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or

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;

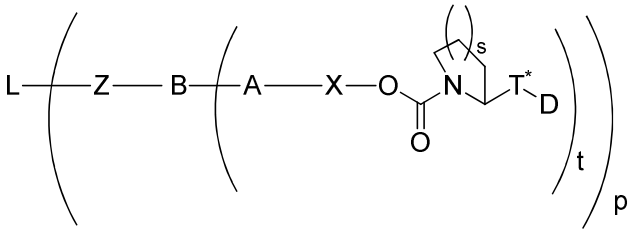
subscript t ranges from 1 to 4; and

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~~, and prodrug moieties~~.

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~~, and prodrug moieties~~.

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~~, and prodrug moieties~~.

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~~, and prodrug moieties~~.

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.

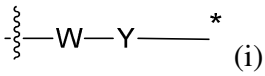
20. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the amine functional group is incorporated into the indicated methylene carbamate unit so that T* represents the nitrogen atom, optionally substituted, from that functional group.

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 ~~way~~ 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; ~~and wherein;~~

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.

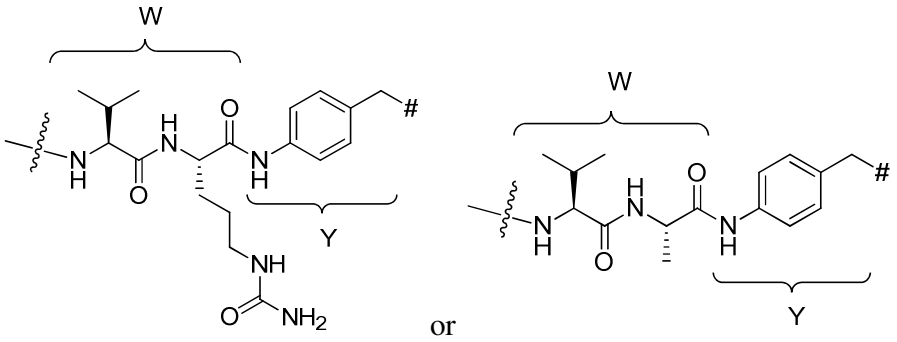
~~25. The Ligand-Drug Conjugate compound of claim 24, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y.~~

~~26. The Ligand-Drug Conjugate compound of claim 25, wherein enzymatic cleavage is by a tumor-associated protease.~~

~~27~~25. The Ligand-Drug Conjugate compound of claim ~~26~~24, wherein the tumor associated protease is cathepsin B.

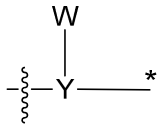
~~28~~26. The Ligand-Drug Conjugate compound of claim ~~26~~24, wherein W is -Val-Cit-, -Phe-Lys- or –Val-Ala-.

~~29~~27. The Ligand-Drug Conjugate compound of claim 24, 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.

~~30~~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~~, and wherein~~;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

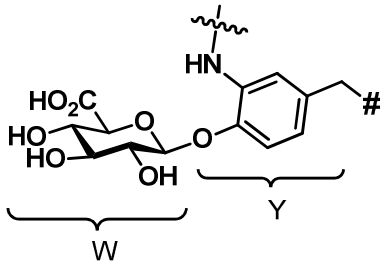
wherein activation of self-immolation of Y results in release of D as free drug.

~~31. The Ligand-Drug Conjugate compound of claim 30, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y, wherein enzymatic cleavage is by a glycosidase.~~

~~32~~29. The Ligand-Drug Conjugate compound of claim ~~31~~28, wherein the glycosidase is a glucuronidase.

~~33. The Ligand-Drug Conjugate compound of claim 30, wherein W is a sugar moiety connected to Y via a glycosidic bond capable of cleavable by a glycosidase for activation of self-immolation of Y.~~

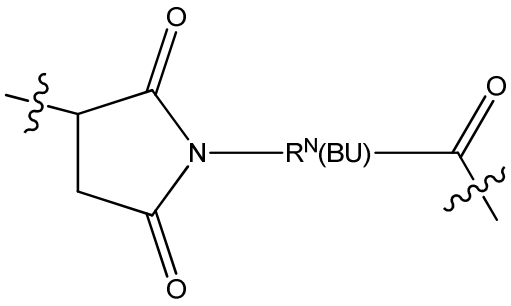
~~34~~30. The Ligand-Drug Conjugate compound of claim ~~33~~28, wherein –Y(W)-is represented by the structure of:



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.

~~35. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein the Stretcher Unit (Z) comprises a succinimide moiety or an succinic acid amide moiety, wherein that moiety is attached to a sulfur atom of the Ligand Unit.~~

~~36~~31. The Ligand-Drug Conjugate compound of claim ~~35~~1 or 2, wherein the Stretcher Unit (Z) comprises a succinimide moiety and is represented by the structure of formula **Xa':**



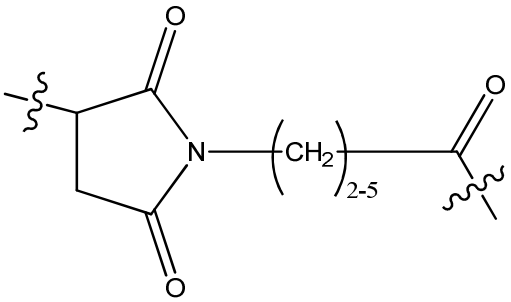
(**Xa')**

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.

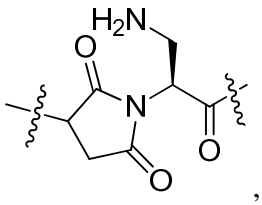
~~37~~32. The Ligand-Drug Conjugate compound of claim ~~35~~1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure**:**



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.

~~38~~33. The Ligand-Drug Conjugate compound of claim ~~35~~1 or 2, wherein the Stretcher unit (Z) comprises a succinimide moiety and is represented by the structure of:

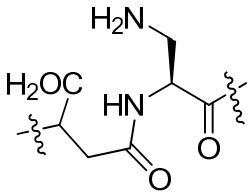


,

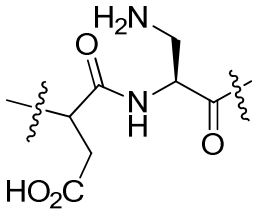
or an acid addition salt thereof,

or

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



or



,

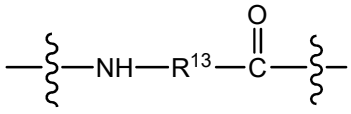
or an acid addition salt thereof;

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.

~~39~~34. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein a Connector Unit (A) is present.

~~40~~35. The Ligand-Drug Conjugate compound of claim ~~39~~34, wherein A is:

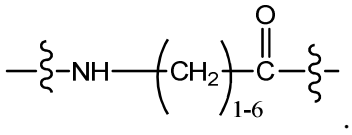


wherein the wavy line adjacent to the carbonyl indicates covalent attachment to the activateable self-immolative moiety X of the Self-immolative Assembly Unit, and

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-.

~~41~~36. The Ligand-Drug Conjugate compound of claim ~~40~~35, wherein A has the formula



.

~~42~~37. The Ligand-Drug Conjugate compound of claim 1 or 2, wherein A is absent.

~~43~~38. The Ligand-Drug Conjugate compound of claim 1, wherein p ranges from 1 to 10.

~~44~~39. The Ligand-Drug Conjugate compound of claim 2, wherein p ranges from 1 to 8.

~~45~~40. The Ligand-Drug Conjugate compound of claim ~~43 or 44~~38 or 39, wherein the Ligand Unit is an antibody.

~~46~~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.

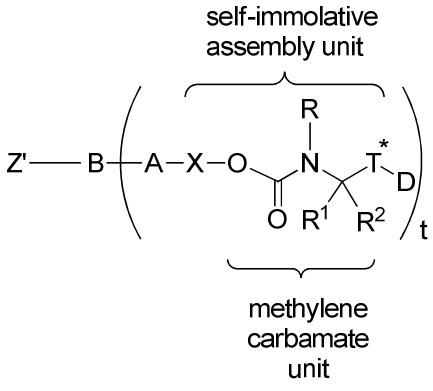
~~47~~42. The Ligand-Drug Conjugate composition of claim ~~46~~41, wherein the Stretcher Unit (Z) of each of the Conjugate compounds independently comprises a succinimide moiety or a

succinic acid-amide moiety, wherein either moiety is attached to a sulfur atom of the Ligand Unit.

~~48~~43. The Ligand-Drug Conjugate composition of claim ~~47~~42, wherein there is ~~an average of about~~ 2 to ~~about~~ 10 drug-linker moieties per Ligand Unit.

~~49~~44. The Ligand-Drug Conjugate composition of claim ~~47~~42, wherein there is ~~an average of about~~ 2 to ~~about~~ 8 drug-linker moieties per Ligand Unit.

~~50~~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;

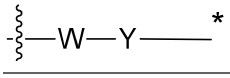
D is a Drug Unit having a thiol or amine functional group that has been incorporated into the indicated methylene carbamate unit;

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)

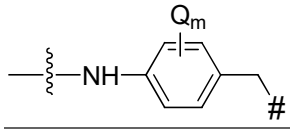
wherein the wavy line indicates covalent attachment of W to A, B, or Z depending on the presence or absence of A or B, and the asterisk (*) indicates covalent attachment of Y to the oxygen atom of the methylene carbamate unit;

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

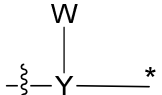
the self-immolative Spacer Unit is a PAB group having the structure of:



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

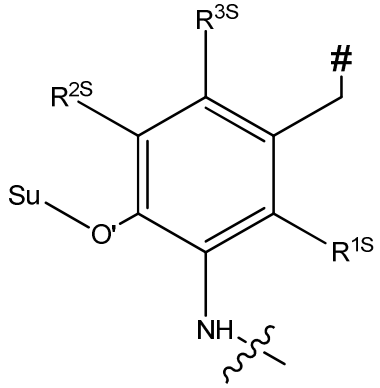
the activateable self-immolative moiety is of formula (ii):



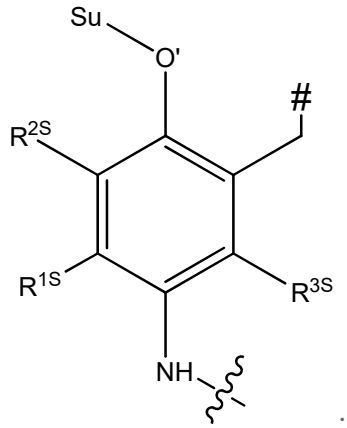
(ii)

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:



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;

~~, wherein activation is by a protease or a glucosidase;~~

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

~~A is an optional Connector Unit;~~ and

subscript t ranges from 1 to 4.

~~51~~46. The Drug-Linker compound of claim ~~50~~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.

~~52~~47. The Drug-Linker compound of claim ~~51~~46, wherein R^1 is not substituted.

~~53~~48. The Drug-Linker compound of claim ~~51~~46, wherein R^1 and R^2 are not substituted.

~~54~~49. The Drug-Linker compound of claim ~~50~~45, wherein R, R^1 and R^2 are not substituted.

~~55~~50. The Drug-Linker compound of claim ~~50~~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~~, and prodrug moieties~~.

~~56~~51. The Drug-Linker compound of claim ~~50~~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~~, and prodrug moieties~~.

~~57~~52. The Drug-Linker compound of claim ~~50~~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~~, and prodrug moieties~~.

~~58~~53. The Drug-Linker compound of claim ~~50~~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~~, and prodrug moieties~~.

~~59~~54. The Drug-Linker compound of claim ~~51~~46, wherein R is $C_{1\text{-}6}$ alkyl, optionally substituted with a basic functional group.

~~60~~55. The Drug-Linker compound of claim ~~51~~46, wherein R is a saturated $C_{1\text{-}6}$ alkyl, optionally substituted with a basic functional group.

~~61~~56. The Drug-Linker compound of claim ~~50~~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.

~~62~~57. The Drug-Linker compound of claim ~~50~~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 $C_{1\text{-}6}$ alkyl.

~~63~~58. The Drug-Linker compound of claim ~~50~~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.

~~64~~59. The Drug-Linker compound of claim ~~50~~45, wherein R is a Basic Unit, wherein, the basic functional group of the Basic Unit is $-NH_2$.

~~65~~60. The Drug-Linker compound of claim ~~50~~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.

~~66~~61. The Drug-Linker compound of claim ~~50~~45, wherein R is a Basic Unit, wherein the Basic Unit is $–CH_2CH_2NH_2$.

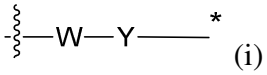
~~67~~62. The Drug-Linker compound of claim ~~66~~61, wherein R^1 is hydrogen.

~~68~~63. The Drug-Linker compound of claim ~~50~~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.

~~69~~64. The Drug-Linker compound of claim ~~50~~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.

~~70~~65. The Drug-Linker compound of claim ~~50~~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.

~~71~~66. The Drug-Linker compound of claim ~~50~~45, wherein the structure of the indicated activateable self-immolative moiety (X) is represented by formula (i):



(i)

wherein the ~~way~~ 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; ~~and wherein;~~

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.

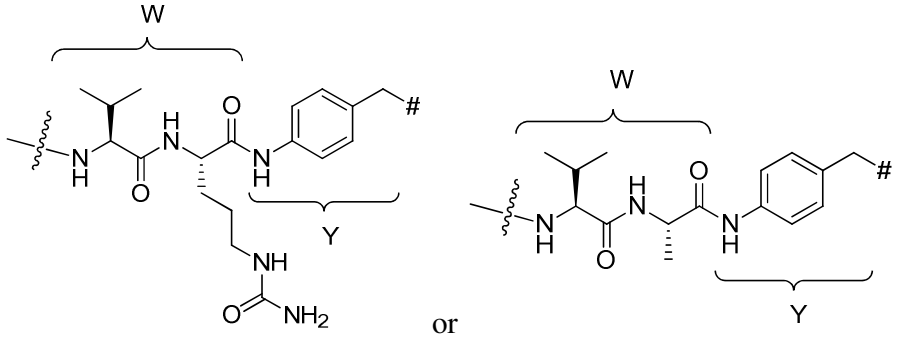
~~72. The Drug-Linker compound of claim 71, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y.~~

~~73. The Drug-Linker compound of claim 72, wherein enzymatic cleavage is by a tumor associated protease.~~

~~74~~67. The Drug-Linker compound of claim ~~73~~66, wherein the tumor associated protease is cathepsin B.

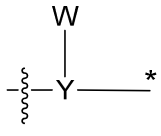
~~75~~68. The Drug-Linker compound of claim ~~71~~66, wherein W is -Val-Cit-, -Phe-Lys-or –Val-Ala-.

~~76~~69. The Drug-Linker compound of claim ~~71~~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.

~~77~~70. The Drug-Linker compound of claim ~~50~~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~~, and wherein~~;

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

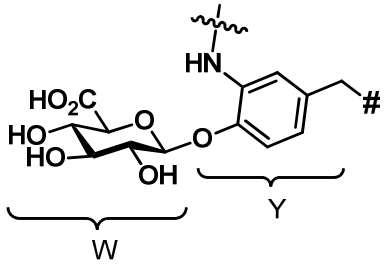
wherein activation of self-immolation of Y in the Drug-Linker compound or in a Ligand-Drug Conjugate prepared from the Drug-Linker compound results in release of D as free drug.

~~78. The Drug-Linker compound of claim 77, wherein activation for self-immolation of Y is by enzymatic cleavage of a covalent bond between W and Y, wherein enzymatic cleavage is by a glycosidase.~~

~~79~~71. The Drug-Linker compound of claim ~~78~~70, wherein the glycosidase is a glucuronidase.

~~80. The Drug-Linker compound of claim 77, wherein W is a sugar moiety connected to Y via a glycosidic bond capable of cleavable by a glycosidase for activation of self-immolation of Y.~~

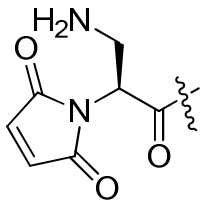
~~81~~72. The Drug-Linker compound of claim ~~80~~70, wherein –Y(W)-is represented by the structure of:



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.

~~82. The Drug-Linker compound of claim 50, wherein Z' comprises a maleimide moiety.~~

~~83~~73. The Drug-Linker compound of claim ~~50~~45, wherein Z' has the structure of:

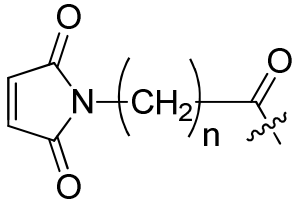


,

or an acid addition salt thereof,

or

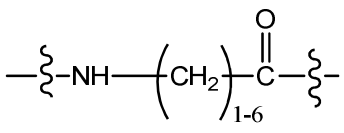
wherein Z' has the structure of:



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.

~~84~~74. The Drug-Linker compound of claim ~~50~~45, wherein A is present and has the formula of:



.

~~85~~75. The Drug-Linker compound of claim ~~50~~45, wherein B is absent and subscript t is 1 or B is present and subscript t is 2.

~~86~~76. A method of preparing an Antibody Drug Conjugate compound of claim ~~35~~1 or 2, or a composition thereof of claim ~~47~~42, in which the Stretcher Unit (Z) comprises a succinimide moiety or ~~an~~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 ~~82~~45 in which the Stretcher Unit precursor (Z') comprises a maleimide ~~moeity~~ 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 ~~moeity~~ 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.

~~87~~77. The Ligand-Drug Conjugate compound of claim 1, wherein the Drug Unit is a cytotoxic drug.

~~88~~78. Use of a Ligand-Drug Conjugate compound of claim 1, or a composition thereof of claim ~~46~~41, for preparing a medicament.

~~89~~79. Use of a Ligand-Drug Conjugate compound of claim ~~87~~77, or a composition thereof of claim ~~46~~41, in the manufacture of a medicament for treating a cancer.

~~90~~80. The use according to claim ~~89~~79, wherein the cancer is a hematological cancer.

~~91~~81. The use according to claim ~~89~~79, wherein the cancer is in the form of a solid tumor.