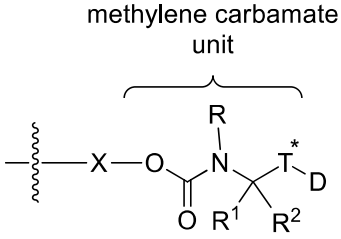
many aliphatic alcohol-containing drugs (see, for example, Toki, et al. *J. Org. Chem.* 2002, 67, 1866-1872). One reason for that may be due to the high pKa of aliphatic alcohol-containing drugs.

[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 refers to a Ligand-Drug Conjugate compound comprising a Ligand Unit, a Drug Unit and a Linker Unit, wherein the Linker Unit comprises a Self-immolative (SI) Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety wherein the methylene carbamate unit is covalently attached to the Drug Unit, and wherein the SI Assembly Unit covalently attached to the Drug Unit is represented by the structure of formula SI:



(SI)

or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment to the remainder of the Linker Unit;

D is the Drug Unit having an aromatic hydroxyl functional group that has been incorporated into the methylene carbamate unit; T* is the oxygen atom from said functional group that becomes incorporated into the indicated methylene carbamate unit;

X is the activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase;

R is hydrogen, optionally substituted C_1-C_6 alkyl that is optionally a Basic Unit, optionally substituted C_{6-14} aryl that is optionally a Basic Unit, or optionally substituted C-linked C_3-C_8 heteroaryl that is optionally a Basic Unit,

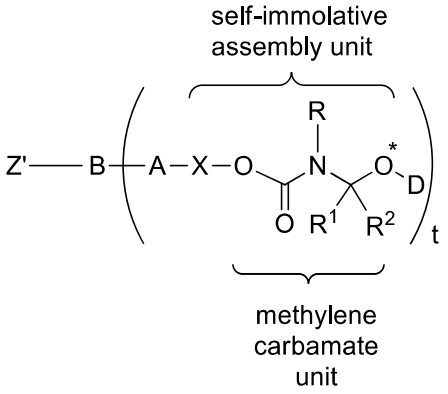
R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or

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; and

wherein activation of the activateable self-immolative moiety (X) results in release of free drug having the formula of D-T*H.

[0006b] In another aspect, the present disclosure refers to a Drug-Linker compound, wherein the Drug-Linker compound comprises a Drug Unit and a Linker Unit, wherein the Linker Unit comprises a Self-Immolative Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety wherein the Drug Unit is covalently attached to the methylene carbamate unit,

wherein the Drug-Linker compound has the structure of:



,

or a pharmaceutically acceptable salt thereof; wherein

D is a Drug Unit having an aromatic hydroxyl functional group that has been incorporated into the indicated methylene carbamate unit;

O* is the oxygen atom from said functional group that becomes incorporated into the indicated methylene carbamate unit;

R is hydrogen, optionally substituted C_1-C_6 alkyl that is optionally a Basic Unit, optionally substituted C_{6-14} aryl that is optionally a Basic Unit, or optionally substituted C-linked C_3-C_8 heteroaryl that is optionally a Basic Unit,

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 comprise an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen;

X is an activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase;

Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) of a Ligand Drug Conjugate compound as described herein and comprises a functional group that provides for covalent attachment of a Ligand Unit to Z;

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; and

wherein activation of the activateable self-immolative moiety (X) results in release of free drug having the formula of D-T^*H.

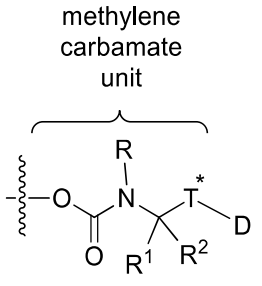
[0006c] In another aspect, the present disclosure refers to a method of preparing an Antibody Drug Conjugate compound as described herein, in which the Stretcher Unit (Z) comprises a succinimide moiety or an succinic acid-amide moiety; and wherein the Ligand Unit is an antibody, the method comprising the step of:

contacting a Drug Linker compound as described herein in which the Stretcher Unit precursor (Z') is comprised of a maleimide moeity 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 of Z, optionally followed by spontaneous hydrolysis of the succinimide moiety to an acid amide moiety, whereby the Antibody Drug Conjugate compound is obtained.

[0006d] In yet another aspect, the present disclosure refers to the Ligand-Drug Conjugate compound as described herein for use as a medicament. In yet another aspect, the present disclosure refers to use of a Ligand-Drug Conjugate compound as described herein in the manufacture of a medicament for the treatment of 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;

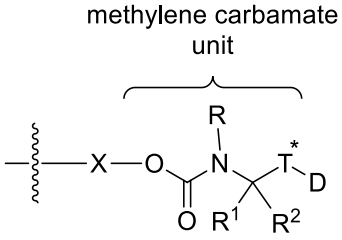
R, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{6-14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl,

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:

CLAIMS

1. A Ligand-Drug Conjugate compound comprising a Ligand Unit, a Drug Unit and a Linker Unit, wherein the Linker Unit comprises a Self-immolative (SI) Assembly Unit having a methylene carbamate unit and an activateable self-immolative moiety wherein the methylene carbamate unit is covalently attached to the Drug Unit, and wherein the SI Assembly Unit covalently attached to the Drug Unit is represented by the structure of formula SI:



(SI)

or a pharmaceutically acceptable salt thereof, wherein

the wavy line indicates covalent attachment to the remainder of the Linker Unit;

D is the Drug Unit having an aromatic hydroxyl functional group that has been incorporated into the methylene carbamate unit;

T* is the oxygen atom from said functional group that becomes incorporated into the indicated methylene carbamate unit;

X is the activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase;

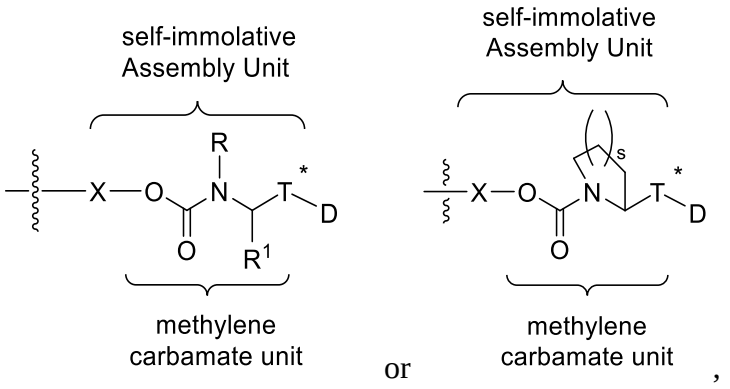
R is hydrogen, optionally substituted C_1-C_6 alkyl that is optionally a Basic Unit, optionally substituted C_{6-14} aryl that is optionally a Basic Unit, or optionally substituted C-linked C_3-C_8 heteroaryl that is optionally a Basic Unit,

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; and

wherein activation of the activateable self-immolative moiety (X) results in release of free drug having the formula of D-T^*H.

2. The Ligand-Drug Conjugate compound of claim **1**, wherein the SI Assembly Unit covalently attached to the Drug Unit is represented by the structure of:

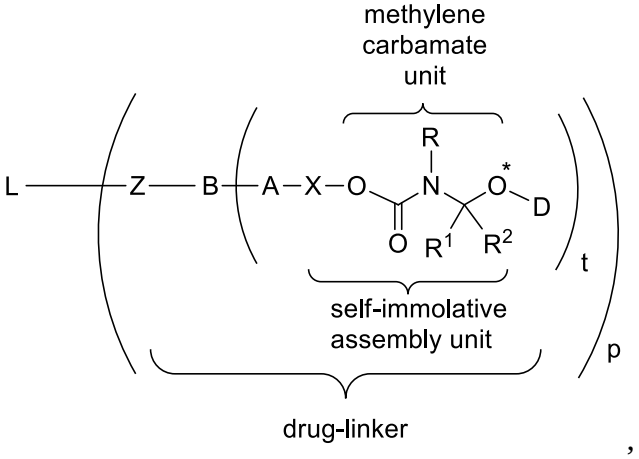


,

or a pharmaceutically acceptable salt thereof, wherein subscript s is 0, 1, 2 or 3 to define an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety.

3. The Ligand-Drug Conjugate compound of claim **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 **1**, wherein the Ligand-Drug Conjugate compound has the structure of:



,

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

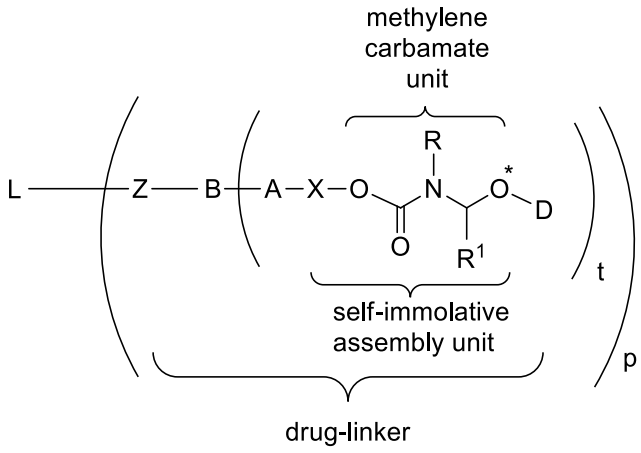
B is an optional Branching Unit and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit;

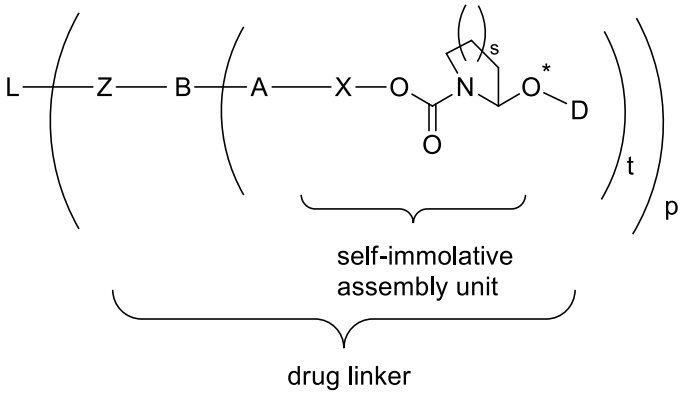
subscript t ranges from 1 to 4; and

subscript p is an integer ranging from 1 to 16.

5. The Ligand-Drug Conjugate compound of claim **4**, wherein the Ligand-Drug Conjugate compound has the structure of:



,



,

or a pharmaceutically acceptable salt thereof, wherein

R and R^1 independently are hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; and

subscript s is 1 or 2.

6. The Ligand-Drug Conjugate compound of claim 4, wherein R and R^1 are independently hydrogen, optionally substituted C_{1-4} alkyl or optionally substituted phenyl.

7. The Ligand-Drug Conjugate Compound of claim **5**, wherein R is a saturated C_{1-6} alkyl, optionally substituted with a basic group.

8. The Ligand-Drug Conjugate compound of any one of claims **1-5**, wherein R is a Basic Unit wherein the basic functional group of the Basic Unit is an amine or a nitrogen-containing 3, 4, 5, or 6 membered heterocycle that is C-linked or N-linked and is optionally substituted.

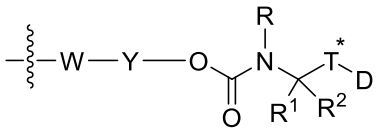
9. The Ligand-Drug Conjugate compound of claim **8**, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.

10. The Ligand-Drug Conjugate compound of claim **8**, 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.

11. The Ligand-Drug Conjugate compound of claim **8**, 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.

12. The Ligand-Drug Conjugate compound of any one of claims **1-11**, wherein R^1 is hydrogen.

13. The Ligand-Drug Conjugate compound of claim **1**, wherein its SI Assembly Unit covalently attached to the Drug Unit is represented by the structure of:



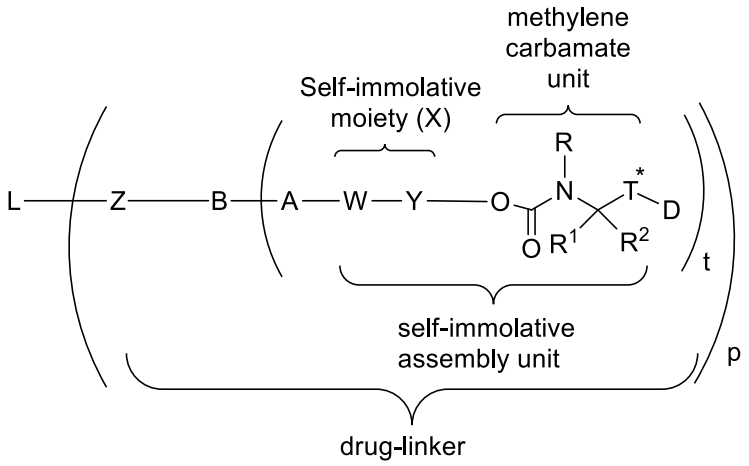
wherein

W is an Activation Unit; and

Y is a self-immolative Spacer Unit,

wherein enzymatic cleavage of W results in release of free drug.

14. The Ligand-Drug Conjugate compound of claim **13**, wherein the Ligand-Drug Conjugate compound has the structure of:



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 subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit;

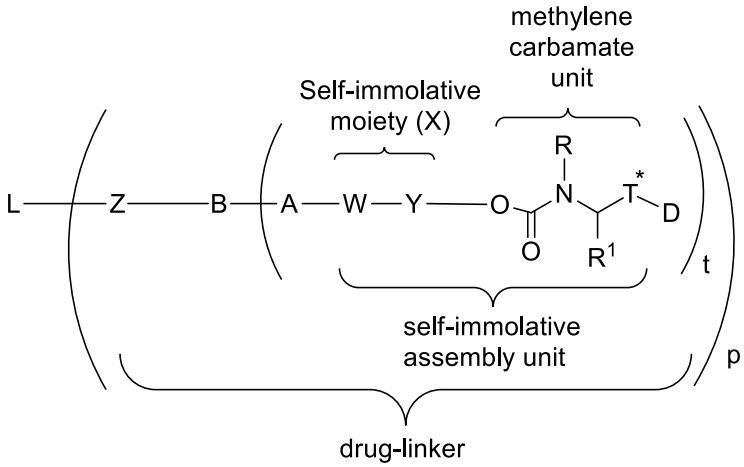
W is an Activation Unit;

Y is a self-immolative Spacer Unit;

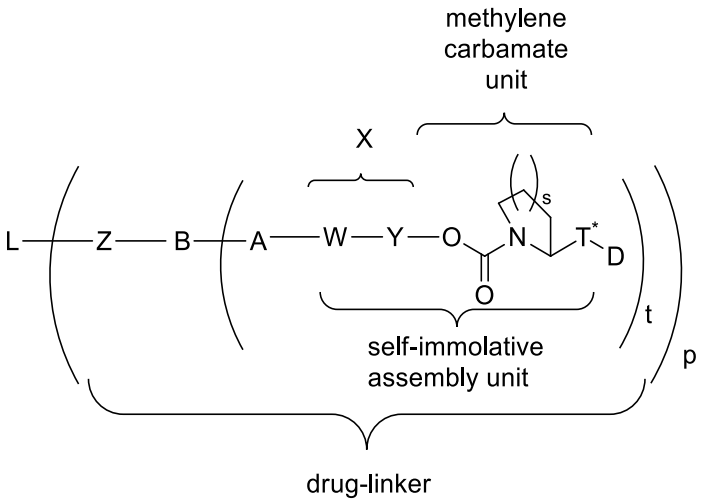
subscript t ranges from 1 to 4; and

subscript p is an integer ranging from 1 to 16.

15. The Ligand-Drug Conjugate compound of claim **14**, wherein the Ligand-Drug Conjugate compound has the structure of:



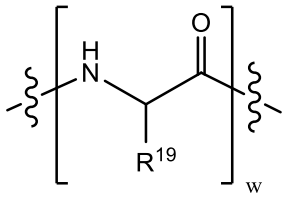
or



wherein R and R^1 independently are hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_{6-14} aryl; and

subscript s is 1 or 2.

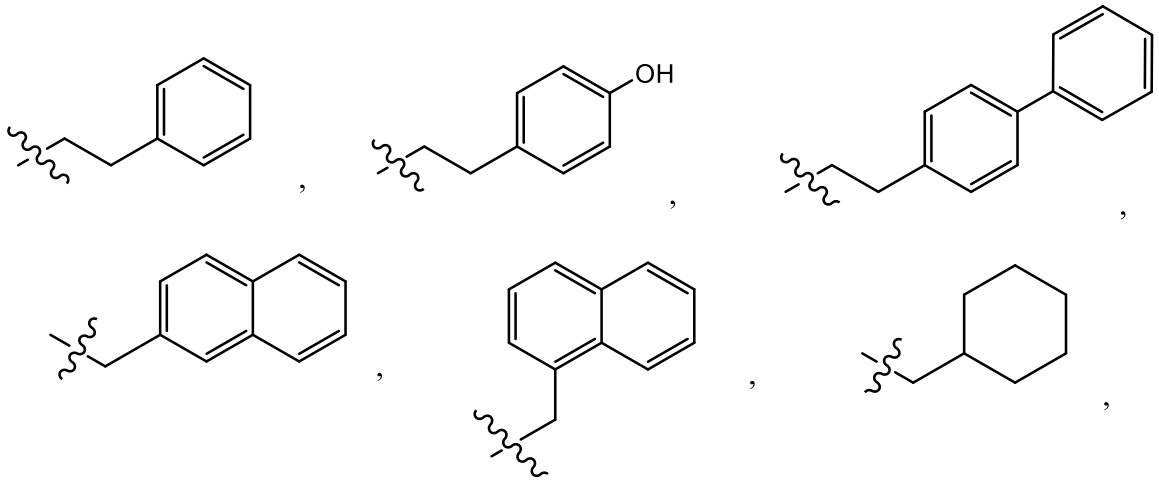
16. The Ligand-Drug Conjugate compound of claim **14** or **15**, wherein W has the formula of:



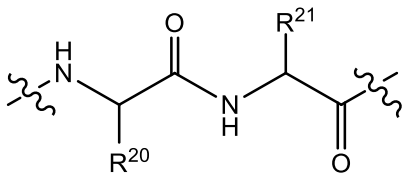
wherein, the wavy line adjacent to the carbonyl is attached to the self-immolative Spacer Unit and the other wavy line is attached to a Stretcher Unit (Z), directly or indirectly through an intervening Connector Unit (A), and/or Branching unit (B);

w is an integer ranging from 1 to 12;

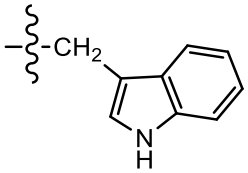
R^{19} is, in each instance, independently selected from the group consisting of hydrogen, methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, *p*-hydroxybenzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH_2SCH_3$, $-CH_2CONH_2$, $-CH_2COOH$, $-CH_2CH_2CONH_2$, $-CH_2CH_2COOH$, $-(CH_2)_3NHC(=NH)NH_2$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCOCH_3$, $-(CH_2)_3NHCHO$, $-(CH_2)_4NHC(=NH)NH_2$, $-(CH_2)_4NH_2$, $-(CH_2)_4NHCOCH_3$, $-(CH_2)_4NHCHO$, $-(CH_2)_3NHCONH_2$, $-(CH_2)_4NHCONH_2$, $-CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl,



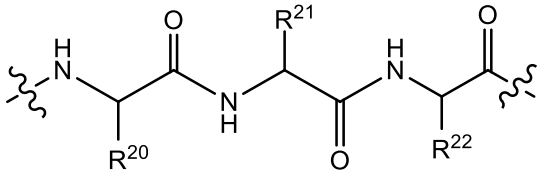
17. The Ligand-Drug Conjugate compound of claim **16**, wherein W has the formula of:



wherein R^{20} and R^{21} are as follows:

R^{20}	R^{21}
benzyl	$(CH_2)_4NH_2$
methyl	$(CH_2)_4NH_2$
isopropyl	$(CH_2)_4NH_2$
isopropyl	$(CH_2)_3NHCONH_2$
benzyl	$(CH_2)_3NHCONH_2$
isobutyl	$(CH_2)_3NHCONH_2$
sec-butyl	$(CH_2)_3NHCONH_2$
	$(CH_2)_3NHCONH_2$
benzyl	methyl
benzyl	$(CH_2)_3NHC(=NH)NH_2$.

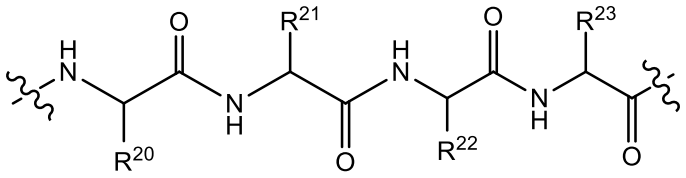
18. The Ligand-Drug Conjugate compound of claim **16**, wherein W has the formula of:



wherein R^{20}, R^{21} and R^{22} are as follows:

R^{20}	R^{21}	R^{22}
benzyl	benzyl	$(CH_2)_4NH_2$
isopropyl	benzyl	$(CH_2)_4NH_2$
H	benzyl	$(CH_2)_4NH_2$.

19. The Ligand-Drug Conjugate compound of claim **16**, wherein W has the formula of:

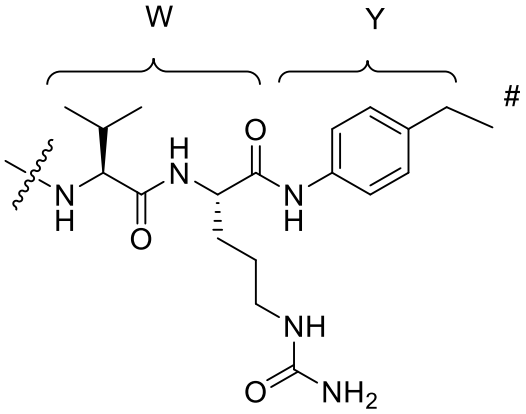


wherein R^{20}, R^{21}, R^{22} and R^{23} are as follows:

R^{20}	R^{21}	R^{22}	R^{23}
H	benzyl	isobutyl	H
methyl	isobutyl	methyl	isobutyl.

20. The Ligand-Drug Conjugate compound of claim **16**, wherein W is -Val-Cit-, -Phe-Lys- or –Val-Ala-.

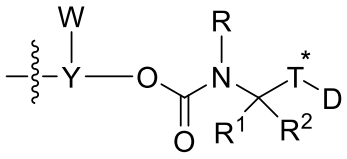
21. The Ligand-Drug Conjugate compound of claim **13**, **14** or **15**, wherein –W-Y- has the structure of:



wherein the wavy line indicates covalent attachment to a Stretcher Unit Z, either directly or indirectly through the Connector Unit (A) and/or Branching Unit (B); and

the hash mark (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit.

22. The Ligand-Drug Conjugate compound of claim **1**, wherein its SI Assembly Unit covalently attached to the Drug Unit is represented by the structure of:



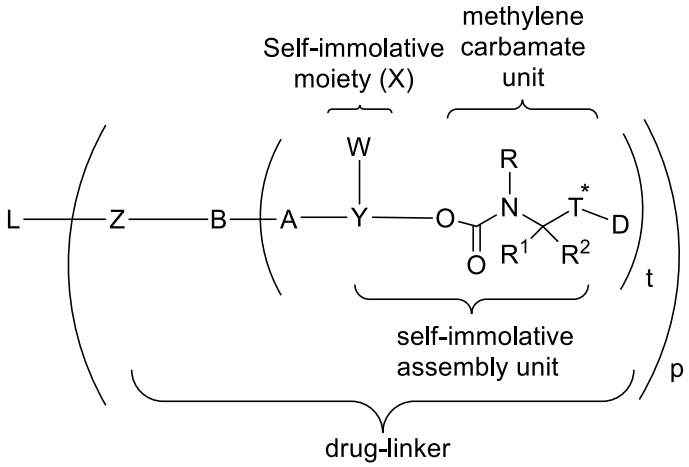
wherein W is an activation unit; and

Y is a self-immolative Spacer Unit,

wherein the activation unit is a sugar moiety attached to Y through a glycosidic bond so that –Y(W)- is a glycoside unit, wherein enzymatic cleavage of the glycosidic bond initiates self-immolation of Y to release free drug; and

wherein the wavy line indicates covalent attachment to a Stretcher Unit Z, either directly or indirectly through a Connector Unit (A) and/or Branching Unit (B).

23. The Ligand-Drug Conjugate compound of claim **22**, wherein the Ligand-Drug Conjugate compound has the structure of:



or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

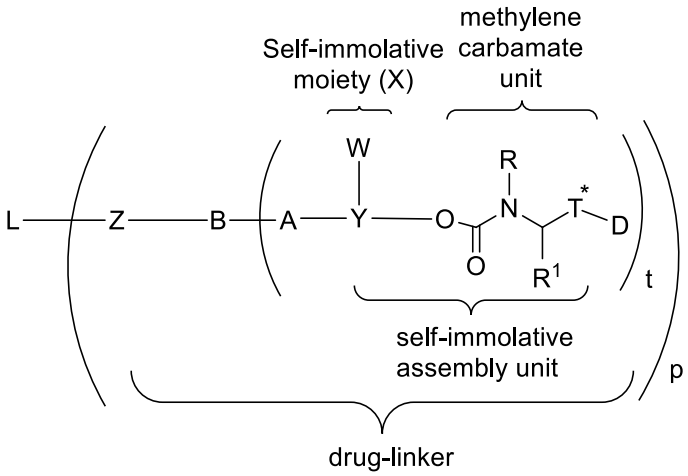
B is an optional Branching Unit and is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit;

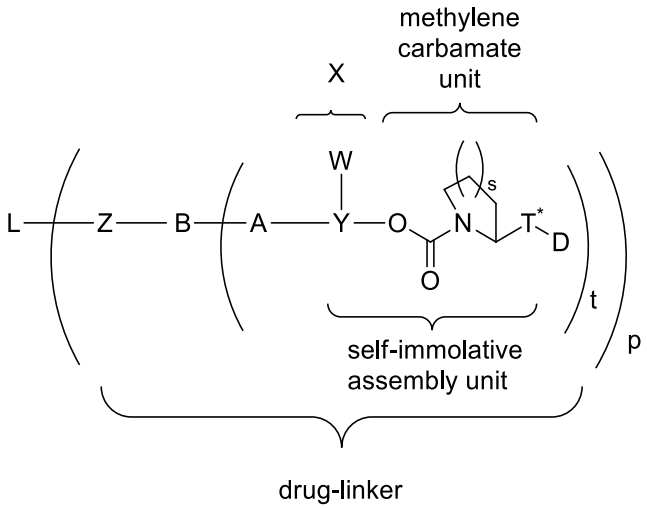
subscript t ranges from 1 to 4; and

subscript p is an integer ranging from 1 to 16.

24. The Ligand-Drug Conjugate compound of claim **23**, wherein the Ligand-Drug Conjugate compound has the structure of:



or



or a pharmaceutically acceptable salt thereof, wherein

R and R^1 independently are hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; and

subscript s is 1 or 2.

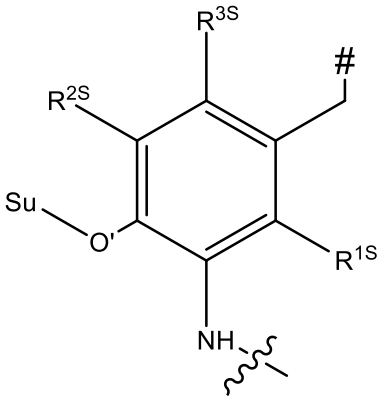
25. The Ligand-Drug Conjugate compound of claim **15** or **24**, wherein R and R^1 are independently hydrogen or optionally substituted C_1-C_4 alkyl.

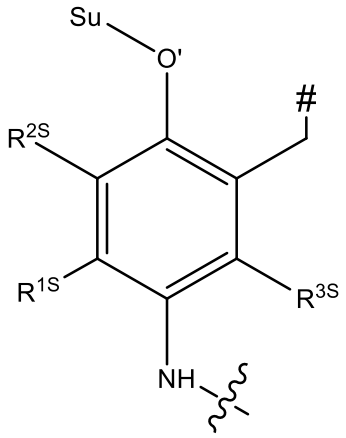
26. The Ligand-Drug Conjugate compound of claim **25**, wherein the optional substituents are independently selected from the group consisting of -X, -OH, -OR^{op}, -$N(R^{op})_2$, -$N(R^{op})_3$, -CX_3, -CN, -NO_2, -$S(=O)_2R^{op}$ and -$C(=NR^{op})N(R^{op})_2$, wherein each X is independently selected 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 and -C_1-C_{20} alkyl.

27. The Ligand-Drug Conjugate compound of claim **26**, wherein the optional substituent is selected from the group consisting of –$N(R^{op})_2$, -$N(R^{op})_3$, -$C(=NR)N(R^{op})_2$ and -$S(=O)_2R^{op}$.

28. The Ligand-Drug Conjugate compound of claim **15** or **24**, wherein R is a Basic Unit or a PEG Unit and R^1 is hydrogen.

29. The Ligand-Drug Conjugate compound of claim **22**, **23** or **24**, wherein the glycoside unit has the structure of:



or


;

wherein Su is the sugar moiety;

-O'- represents the oxygen atom of the glycosidic bond;

R^{1S}, R^{2S} and R^{3S} independently are hydrogen, halogen, -CN, or - NO_2.; and

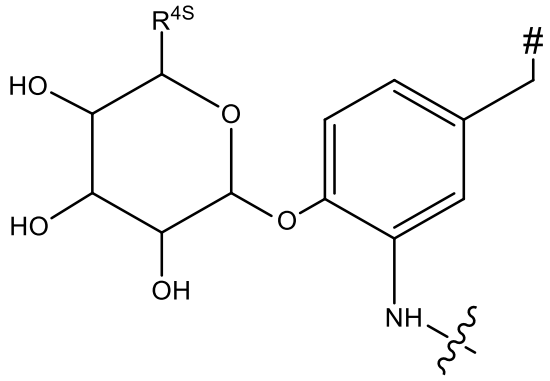
wherein the wavy line indicates covalent attachment to a Stretcher Unit (Z) either directly or indirectly through a Connector Unit (A) and/or Branching Unit (B);

and the hash mark (#) indicates covalent attachment to the methylene carbamate unit.

30. The Ligand-Drug Conjugate compound of claim **29**, wherein R^{1S}, R^{2S} and R^{3S} are each hydrogen.

31. The Ligand-Drug Conjugate compound of claim **29**, wherein R^{2S} is $-NO_2$, and R^{1S} and R^{3S} are each hydrogen.

32. The Ligand-Drug Conjugate compound of claim **29**, wherein the glycoside unit has the structure of:

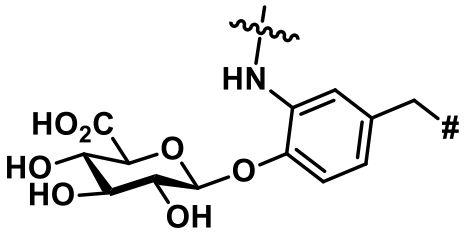


wherein R^{4S} is CH_2OH or $–CO_2H$;

the wavy line indicates covalent attachment to a Stretcher Unit (Z), either directly or indirectly through a Connector Unit (A) and/or Branching Unit (B); and

the hash mark (#) indicates covalent attachment to the methylene carbamate unit.

33. The Ligand-Drug Conjugate compound of claim **32**, wherein the glycoside unit is a Glucuronide Unit having the structure of:



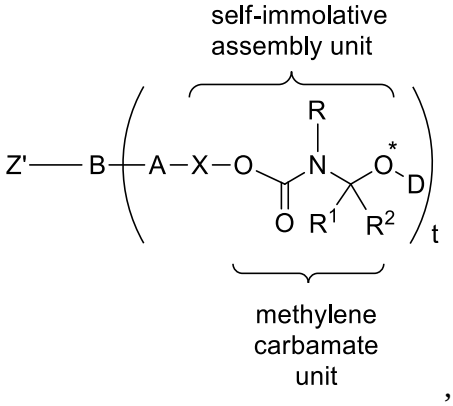
,

or pharmaceutically acceptable salt thereof.

34. A Drug-Linker compound, wherein the Drug-Linker compound comprises a Drug Unit and a Linker Unit, wherein the Linker Unit comprises a Self-Immolative Assembly Unit

having a methylene carbamate unit and an activateable self-immolative moiety wherein the Drug Unit is covalently attached to the methylene carbamate unit,

wherein the Drug-Linker compound has the structure of:



,

or a pharmaceutically acceptable salt thereof; wherein

D is a Drug Unit having an aromatic hydroxyl functional group that has been incorporated into the indicated methylene carbamate unit;

O* is the oxygen atom from said functional group that becomes incorporated into the indicated methylene carbamate unit;

R is hydrogen, optionally substituted C_1-C_6 alkyl that is optionally a Basic Unit, optionally substituted C_{6-14} aryl that is optionally a Basic Unit, or optionally substituted C-linked C_3-C_8 heteroaryl that is optionally a Basic Unit,

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 comprise an azetidinyl, pyrrolodinyl, piperidinyl or homopiperidinyl moiety and R^2 is hydrogen;

X is an activateable self-immolative moiety, wherein activation of the activateable self-immolative moiety is by a protease or a glucosidase;

Z' is a Stretcher Unit precursor to a Stretcher Unit (Z) of a Ligand-Drug Conjugate compound of claim **4** and comprises a functional group that provides for covalent attachment of a Ligand Unit to Z;

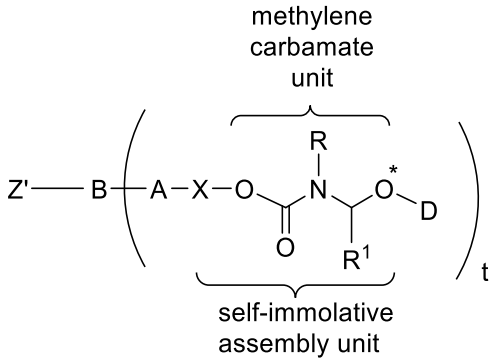
B is an optional Branching Unit that is present when subscript t is greater than 1 and is absent when subscript t is 1;

A is an optional Connector Unit; and

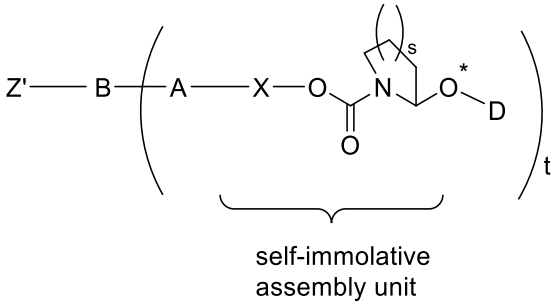
subscript t ranges from 1 to 4; and

wherein activation of the activateable self-immolative moiety (X) results in release of free drug having the formula of D-T*H.

35. The Drug-Linker compound of claim **34**, wherein the Drug-Linker compound has the structure of:



,



,

or a pharmaceutically acceptable salt thereof, wherein

R and R^1 independently are hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; and

subscript s is 1 or 2.

36. The Drug-Linker compound of claim **35**, wherein R and R^1 are independently hydrogen, optionally substituted C_1-$_4$ alkyl or optionally substituted phenyl.

37. The Drug-Linker Compound of claim **35**, wherein R is a saturated C_{1-6} alkyl, optionally substituted with a basic group.

38. The Drug-Linker compound of claim **34** or **35**, wherein R is a Basic Unit, wherein the basic functional group of the Basic Unit is an amine or a nitrogen-containing 3-, 4-, 5-, or 6-membered heterocycle that is C-linked or N-linked and is optionally substituted.

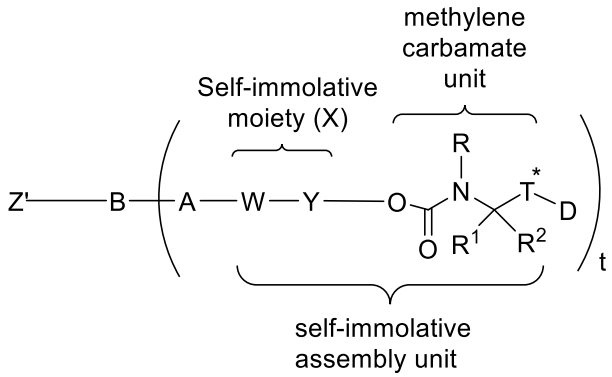
39. The Drug-Linker compound of claim **38**, wherein the basic functional group of the Basic Unit is $–N(R^{op})_2$, wherein R^{op} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.

40. The Drug-Linker compound of claim **38**, 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.

41. The Drug-Linker compound of claim **38**, 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.

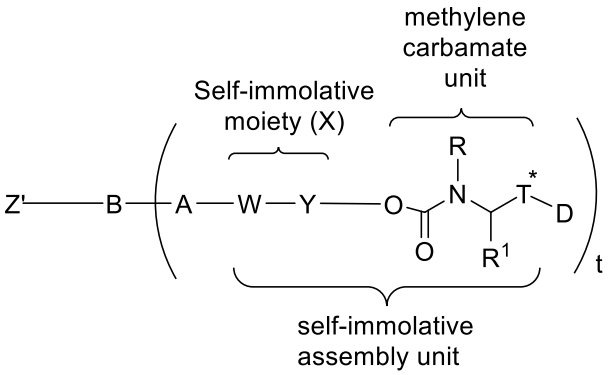
42. The Drug-Linker compound of any one of claims **34-41**, wherein R^1 is hydrogen.

43. The Drug-Linker compound of claim **34**, wherein the Drug-Linker compound has the structure of:

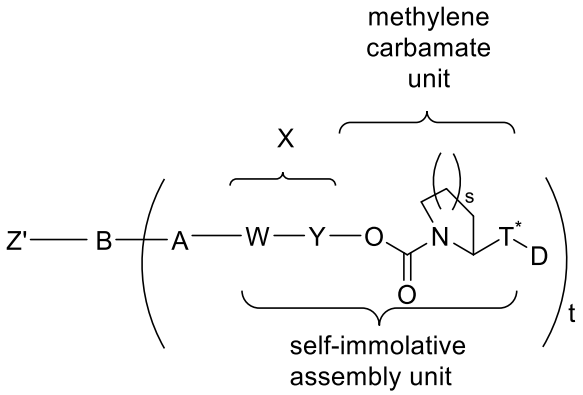


or a pharmaceutically acceptable salt thereof, wherein

44. The Drug-Linker compound of claim **43**, wherein the Drug-Linker compound has the structure of:



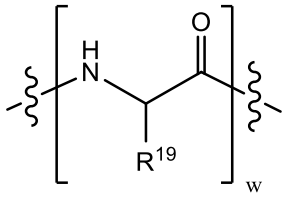
or



wherein R and R^1 independently are hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; and

subscript s is 1 or 2.

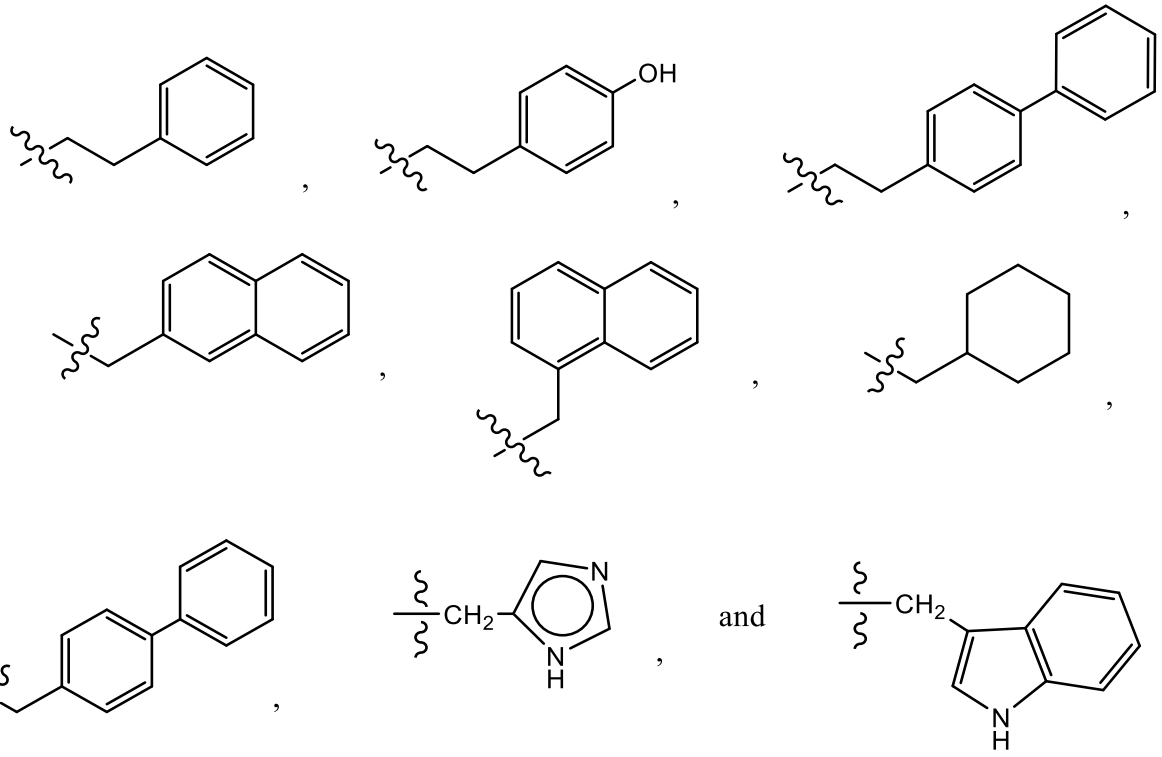
45. The Drug-Linker compound of claim **43** or **44**, wherein W has the formula of:



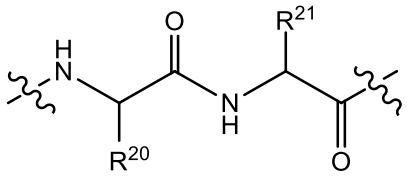
wherein, the wavy line adjacent to the carbonyl is attached to the self-immolative Spacer Unit and the other wavy line is attached to a Stretcher Unit (Z), directly or indirectly through an intervening Connector Unit (A), and/or Branching unit (B);

w is an integer ranging from 1 to 12;

R^{19} is, in each instance, independently selected from the group consisting of hydrogen, methyl, isopropyl, isobutyl, *sec*-butyl, benzyl, *p*-hydroxybenzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH_2SCH_3$, $-CH_2CONH_2$, $-CH_2COOH$, $-CH_2CH_2CONH_2$, $-CH_2CH_2COOH$, $-(CH_2)_3NHC(=NH)NH_2$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCOCH_3$, $-(CH_2)_3NHCHO$, $-(CH_2)_4NHC(=NH)NH_2$, $-(CH_2)_4NH_2$, $-(CH_2)_4NHCOCH_3$, $-(CH_2)_4NHCHO$, $-(CH_2)_3NHCONH_2$, $-(CH_2)_4NHCONH_2$, $-CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl,

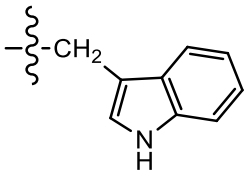


46. The Drug-Linker compound of claim **45**, wherein W has the formula of:

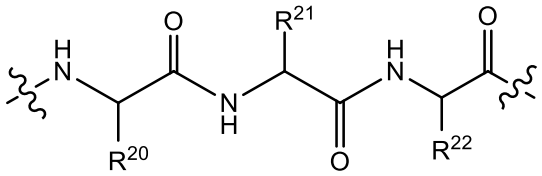


wherein R^{20} and R^{21} are as follows:

R^{20}	R^{21}

benzyl	$(CH_2)_4NH_2$
methyl	$(CH_2)_4NH_2$
isopropyl	$(CH_2)_4NH_2$
isopropyl	$(CH_2)_3NHCONH_2$
benzyl	$(CH_2)_3NHCONH_2$
isobutyl	$(CH_2)_3NHCONH_2$
sec-butyl	$(CH_2)_3NHCONH_2$
	$(CH_2)_3NHCONH_2$
benzyl	methyl
benzyl	$(CH_2)_3NHC(=NH)NH_2$.

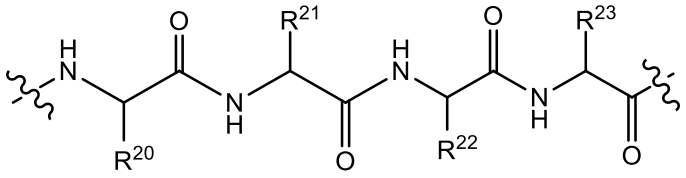
47. The Drug-Linker compound of claim **45**, wherein W has the formula of:



wherein R^{20}, R^{21} and R^{22} are as follows:

R^{20}	R^{21}	R^{22}
benzyl	benzyl	$(CH_2)_4NH_2$
isopropyl	benzyl	$(CH_2)_4NH_2$
H	benzyl	$(CH_2)_4NH_2$.

48. The Drug-Linker compound of claim **45**, wherein W has the formula of:

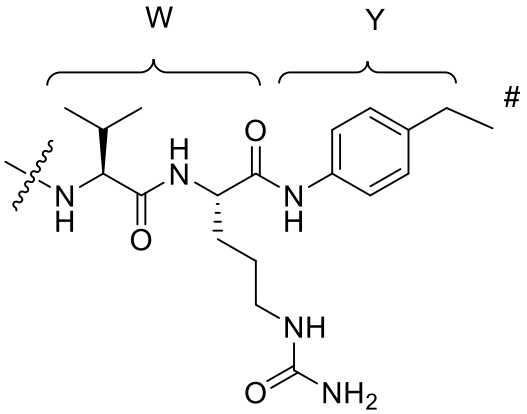


wherein R^{20}, R^{21}, R^{22} and R^{23} are as follows:

R^{20}	R^{21}	R^{22}	R^{23}
H	benzyl	isobutyl	H
methyl	isobutyl	methyl	isobutyl.

49. The Drug-Linker compound of claim **45**, wherein W is -Val-Cit-, -Phe-Lys- or –Val-Ala-.

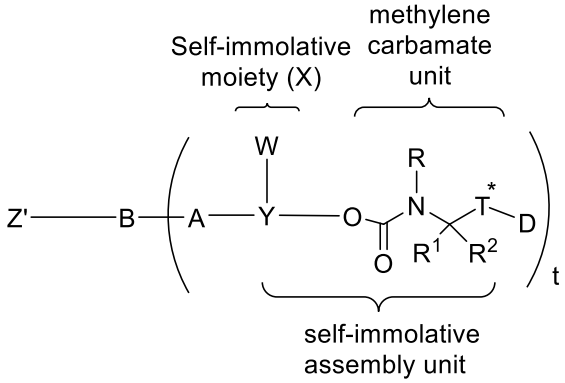
50. The Drug-Linker compound of claim **43** or **44**, wherein –W-Y- has the structure of:



wherein the wavy line indicates covalent attachment to a Stretcher Unit Z, either directly or indirectly through the Connector Unit (A) and/or Branching Unit (B); and

the hash mark (#) indicates covalent attachment of the benzylic carbon to the methylene carbamate unit.

51. The Drug-Linker compound of claim **34**, wherein the Drug-Linker compound has the structure of:



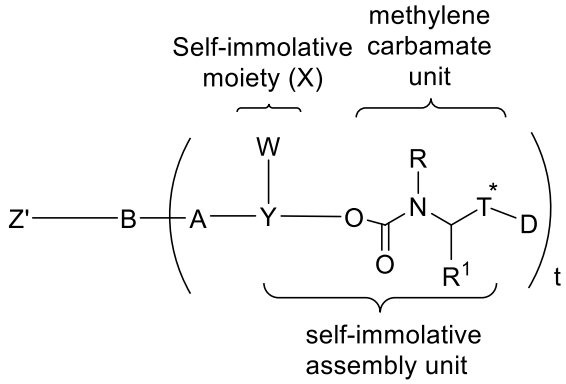
or a pharmaceutically acceptable salt thereof, wherein

W is an activation unit; and

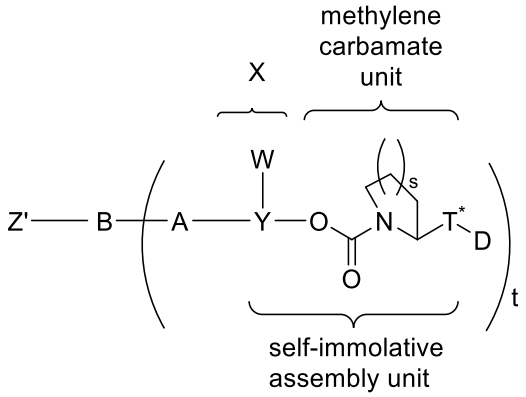
Y is a self-immolative Spacer Unit,

wherein the activation unit is a sugar moiety attached to Y through a glycosidic bond so that –Y(W)- is a glycoside unit, wherein enzymatic cleavage of the glycosidic bond initiates self-immolation of Y to release free drug

52. The Drug-Linker compound of claim **51**, wherein the Drug-Linker compound has the structure of:



or



or a pharmaceutically acceptable salt thereof, wherein

R and R^1 independently are hydrogen, optionally substituted C_1-C_6 alkyl or optionally substituted C_{6-14} aryl; and

subscript s is 1 or 2.

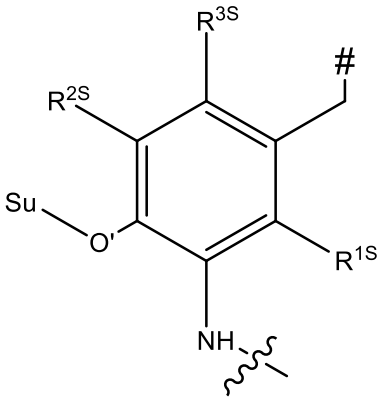
53. The Drug-Linker compound of claim **44** or **52**, wherein R and R^1 are independently hydrogen or optionally substituted C_1-C_4 alkyl.

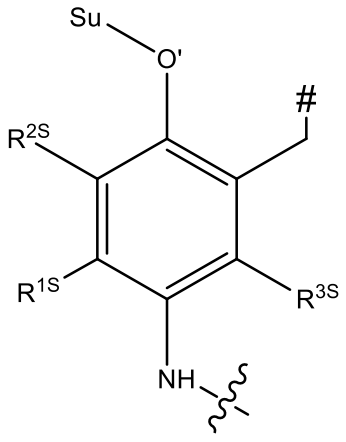
54. The Drug-Linker compound of claim **53**, wherein the optional substituents are independently selected from the group consisting of -X, -OH, -OR^{op}, -$N(R^{op})_2$, -$N(R^{op})_3$, -CX_3, -CN, -NO_2, -$S(=O)_2R^{op}$ and -$C(=NR^{op})N(R^{op})_2$, wherein each X is independently selected from the group consisting of a halogen: -F, -Cl, -Br, and -I; and each R^{op} is independently selected from the group consisting of hydrogen and -C_1- C_{20} alkyl.

55. The Drug-Linker compound of claim **54**, wherein the optional substituent is selected from the group consisting of –$N(R^{op})_2$, -$N(R^{op})_3$, -$C(=NR)N(R^{op})_2$ and -$S(=O)_2R^{op}$.

56. The Drug-Linker compound of claim **44** or **52**, wherein R is a Basic Unit or a PEG Unit and R^1 is hydrogen.

57. The Drug-Linker compound of claim **51** or **52**, wherein the glycoside unit has the structure of:



or


;

wherein Su is the sugar moiety;

O'- represents the oxygen atom of the glycosidic bond;

R^{1S}, R^{2S} and R^{3S} independently are hydrogen, halogen, -CN, or - NO_2.; and

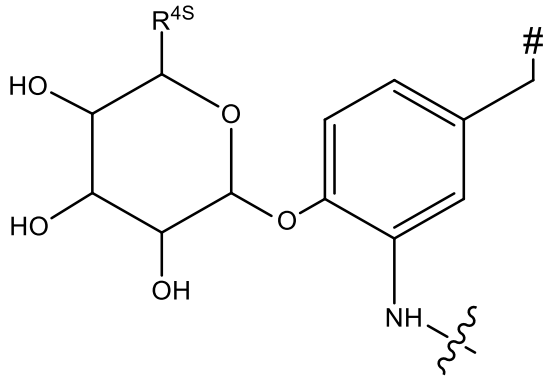
wherein the wavy line indicates covalent attachment to a Stretcher Unit (Z) either directly or indirectly through a Connector Unit (A) and/or Branching Unit (B);

and # indicates covalent attachment to the methylene carbamate unit.

58. The Drug-Linker compound of claim **57**, wherein R^{1S}, R^{2S} and R^{3S} are each hydrogen.

59. The Drug-Linker compound of claim **57**, wherein R^{2S} is $-NO_2$, and R^{1S} and R^{3S} are each hydrogen.

60. The Drug-Linker compound of claim **57**, wherein the glycoside unit has the structure of:

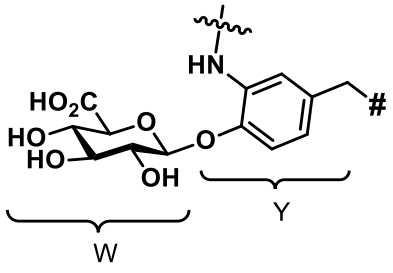


wherein R^{4S} is CH_2OH or $–CO_2H$;

the wavy line indicates covalent attachment to a Stretcher Unit (Z), either directly or indirectly through a Connector Unit (A) and/or Branching Unit (B); and

the hash mark (#) indicates covalent attachment to the methylene carbamate unit.

61. The Drug-Linker compound of claim 57, wherein the glycoside unit is a Glucuronide Unit having 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 methylene carbamate unit.

62. The Drug-Linker compound of any one of claims **34-61**, wherein Z' comprises a maleimide moiety.

63. A method of preparing an Antibody Drug Conjugate compound of claim **4**, in which the Stretcher Unit (Z) comprises a succinimide moiety or an 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 **62** in which the Stretcher Unit precursor (Z') comprises a maleimide moeity 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 of Z, optionally followed by spontaneous hydrolysis of the succinimide moiety to an acid amide moiety, whereby the Antibody Drug Conjugate compound is obtained.

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

65. The Ligand-Drug Conjugate compound of claim **1**, for use as a medicament.

66. Use of a Ligand-Drug Conjugate compound of claim **64** in the manufacture of a medicament for the treatment of a cancer.

67. The use according to claim **66**, wherein the cancer is a hematological cancer.

68. The use according to claim **67**, wherein the cancer is in the form of a solid tumor.