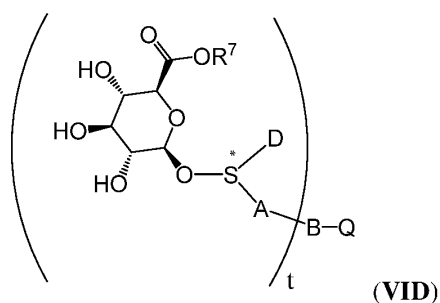


WHAT IS CLAIMED IS:

1. A method for preparing a Drug Linker compound intermediate of Formula VID:



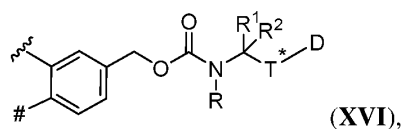
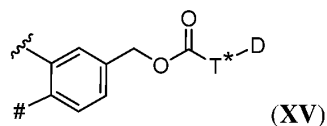
or a salt thereof, wherein

Q is an optionally protected functional group, preferably, hydroxyl, thiol or amine functional group;

A is a an optional Connector Unit;

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

S* is a Self-Immolating Unit, in particular having the structure of Formula XV or Formula XVI:



wherein the wavy line indicates the point of attachment to A, and # indicates the point of attachment to the glycosidic oxygen atom of the glucuronic acid moiety;

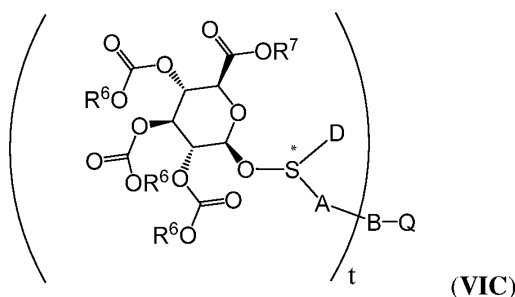
D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor having a functional group comprising heteroatom T*, wherein T* is oxygen, sulfur, or optionally substituted nitrogen, in particular D having an amine functional group capable of forming a carbamate functional group in Formula XV or a methylene carbamate functional group in Formula XVI;

R, R¹, and R² independently are hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆₋₁₄ aryl, or optionally substituted C-linked C₃-C₈ heteroaryl, or both R and R¹ together with the nitrogen and carbon atoms to which they are attached comprise an azetidiny, pyrrolodiny, piperidiny, or homopiperidiny moiety, in particular a pyrrolodiny or piperidiny moiety and R² is hydrogen;

R⁷ is C₁-C₈ alkyl or optionally substituted phenyl so that -OR⁷ provides for an ester functional group that is a suitable carboxylic acid protecting group; and subscript t is 0, 1, 2, 3, or 4,

the method comprising the step of:

(c) contacting a compound of Formula **VIC** with Grignard reagent or an alkoxy magnesium halide with either in a suitable alcohol-containing solvent, wherein the Formula **VIC** compound has the structure of:

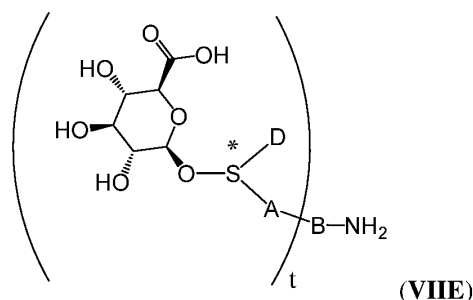


or a salt thereof, wherein

each of R⁶ is independently C₁-C₈ alkyl or optionally substituted phenyl such that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group; and the remaining variable groups are as previously defined,

wherein said Grignard reagent or alkoxy magnesium halide contacting selectively removes the hydroxyl protecting groups whereby the Formula **VID** compound or its salt is obtained.

2. A method for preparing a Drug Linker intermediate compound of Formula **VIII**:

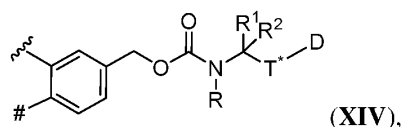
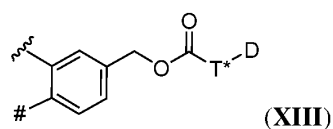


or a salt thereof, wherein

A is a an optional Connector Unit;

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

S* is a Self-Immolating Unit, in particular having the structure of Formula **XIII** or Formula **XIV**:

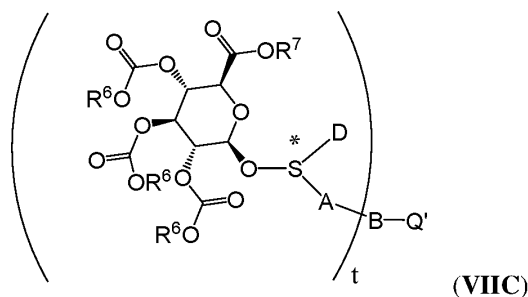


wherein the wavy line indicates the point of attachment to A, and # indicates the point of attachment to the glycosidic oxygen atom of the glucuronic acid moiety; and

D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor having a functional group comprising heteroatom T*, wherein T* is oxygen, sulfur, or optionally substituted nitrogen, in particular D having an amine functional group capable of forming a carbamate functional group in Formula **XIII** or a methylene carbamate functional group in Formula **XIV**,

the method comprising the steps of:

(c) contacting a compound of Formula **VIIIC** with a Grignard reagent or an alkoxy magnesium halide with either in a suitable an alcohol-containing solvent, wherein the Formula **VIIIC** compound has the structure of:



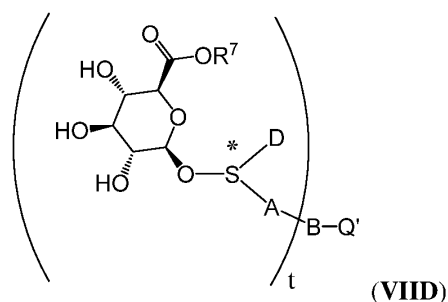
or a salt thereof, wherein

S*, D, A, B and subscript t are as defined for Formula **VIII** of claim 2;

Q' is a suitably protected amino group;

each of R⁶ and R⁷ is independently C₁-C₈ alkyl or optionally substituted phenyl such that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group and -OR⁷ provides for an ester functional group that is a suitable carboxylic acid protecting group; and the remaining variable groups are as previously defined,

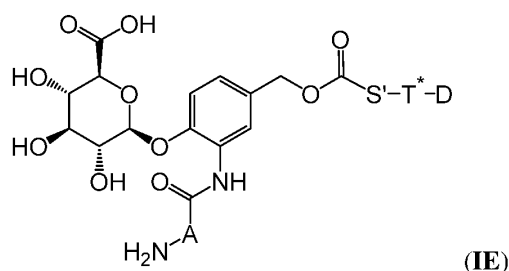
wherein said Grignard reagent or alkoxy magnesium halide contacting selectively removes the hydroxyl protecting groups to provide a compound of Formula **VIID**:



or a salt thereof, wherein the variable groups are as previously defined by Formula **VIIIC**; and

(d) contacting the Formula **VIID** compound with a first deprotecting agent, wherein said first deprotecting agent contacting removes the amine and carboxylic acid protecting groups whereby the Formula **VIII** compound or its salt is obtained.

3. A method for preparing a Drug Linker intermediate compound of Formula **IE**:



or a salt thereof, wherein

A is an optional Connector Unit;

S' is absent or $\text{-NR}^N\text{-C(R}^1\text{)(R}^2\text{)-}$, wherein R^N , R^1 and R^2 independently are hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_6\text{-C}_{14}$ aryl, or optionally substituted C-linked $\text{C}_3\text{-C}_8$ heteroaryl, or R^N and R^1 together with the nitrogen and carbon atoms to which they are attached comprise an azetidiny, pyrrolodiny, piperidiny or homopiperidiny moiety, and R^2 is hydrogen;

D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor having a functional group, in particular, hydroxyl, thiol or amine functional group, wherein the functional group forms a covalent bond with S';

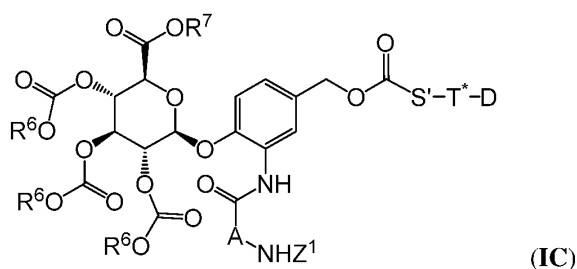
T* is a heteroatom from said functional group, in particular oxygen, sulfur, or optionally substituted nitrogen;

Z¹ is a first suitable amine protecting group; and

R⁷ is $\text{C}_1\text{-C}_8$ alkyl or optionally substituted phenyl such that -OR^7 provides for an ester functional group that is a suitable carboxylic acid protecting group,

the method comprising the steps of:

(c) contacting a compound of Formula **IC** with Grignard reagent or an alkoxy magnesium halide with either in a suitable an alcohol-containing solvent, wherein the Formula **IC** compound has the structure of:

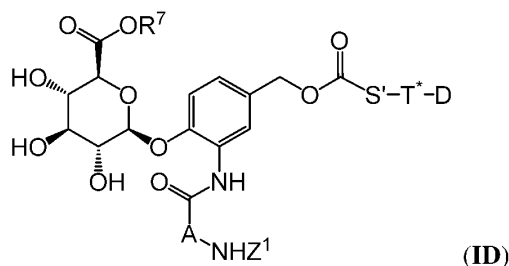


or a salt thereof, wherein

Z^1 is a first suitable amine protecting group; and

each of R^6 and R^7 is independently C_1 - C_8 alkyl or optionally substituted phenyl such that $R^6C(=O)-$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-OR^7$ provides for an ester functional group that is a suitable carboxylic acid protecting group; and the remaining variable groups are as previously defined by Formula **IE**,

wherein said Grignard reagent or alkoxy magnesium halide contacting selectively removes the hydroxyl protecting groups to provide a compound of Formula **ID**:



or a salt thereof, wherein the variable groups are as previously defined by Formula **IC**; and

(d) contacting the Formula **ID** compound with a first deprotecting agent, wherein said deprotecting agent contacting removes the amine and carboxylic acid protecting groups whereby the Formula **IE** compound or its salt is obtained.

4. The method of claim **1**, **2** or **3**, wherein the Grignard reagent has the formula of $R^{\#}MgX$ and the alkoxy magnesium halide has the formula of $R^{\#}OMgX$, wherein $R^{\#}$ is C_1 - C_5 alkyl and X is I, Br, or Cl.

5. The method of claim **4**, wherein the Grignard reagent is $MeMgI$ or $MeMgCl$.

6. The method of claim **5**, wherein the alkoxy magnesium halide is $MeOMgI$ or $MeOMgCl$.

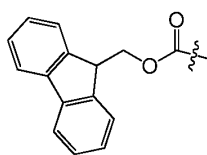
7. The method of any one of claims **1** to **6**, wherein the alcohol-containing solvent comprises a C_1 - C_4 alcohol.

8. The method of claim **7**, wherein the alcohol-containing solvent further comprises THF.

9. The method of claim 8, wherein the solvent is a 1:1 (v/v) mixture of methanol and THF.

10. The method claim 2, wherein the first deprotecting agent for removal of Z^1 is an aqueous-containing solution of LiOH.

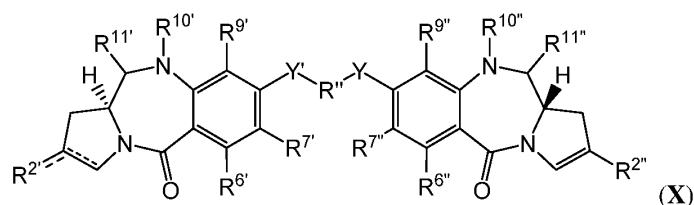
11. The method of any one of claims 2 to 10, wherein Z^1 has the formula:



12. The method of any one of embodiments 1 to 11, wherein said Grignard reagent or alkoxy magnesium halide contacting and said deprotecting agent contacting to remove Z^1 are done sequentially in one pot.

13. The method of any one of claims 1 to 12, wherein D is a PBD Drug Unit.

14. The method of claim 13, wherein the PBD Drug Unit has the structure of Formula X:

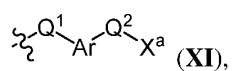


or a salt thereof,

wherein:

the dotted lines represent a tautomeric double bond;

$R^{2''}$ is of formula XI:



wherein the wavy line indicates the site of covalent attachment to the Formula X structure;

Ar is an optionally substituted C₅₋₇ arylene;

X^a is from a reactive or activateable group for covalent attachment to a Linker Unit or precursor thereof, wherein X^a is selected from the group comprising: -O-, -S-, -C(O)O-, -C(O)-, -NHC(O)-, and -N(R^N)-, wherein R^N is H or C₁-C₄ alkyl, and (C₂H₄O)_mCH₃, where subscript m is 1, 2 or 3;

and either:

(i) Q¹ is a single bond; and Q² is a single bond or -Z-(CH₂)_n-, wherein Z is selected from the group consisting of a single bond, O, S, and NH; and subscript n is 1, 2 or 3, or

(ii) Q¹ is -CH=CH-, and Q² is a single bond; and

R^{2'} is a optionally substituted C₁-C₄ alkyl or a C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the group consisting of halo, nitro, cyano, C₁-C₆ ether, C₁-C₇ alkyl, C₃-C₇ heterocyclyl and bis-oxy-C₁-C₃ alkylene, in particular by one such substituent, wherein the dotted lines indicate a single bond to R^{2'}, or

R^{2'} an optionally substituted C₁-C₄ alkenylene, wherein the dotted lines indicate a double bond to R^{2'};

R^{6''} and R^{9''} are independently selected from the group consisting of H, R, OH, OR, SH, SR, NH₂, NHR, NRR', nitro, Me₃Sn and halo;

R^{7''} is selected from the group consisting of H, R, OH, OR, SH, SR, NH₂, NHR, NRR', nitro, Me₃Sn and halo; and

R and R' are independently selected from the group consisting of optionally substituted C₁-C₁₂ alkyl, optionally substituted C₃-C₂₀ heterocyclyl and optionally substituted C₅-C₂₀ aryl;

and either:

(a) R^{10''} is H, and R^{11''} is OH or OR^A, wherein R^A is C₁-C₄ alkyl, or

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

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

(d) R^{10'}, R^{11'} and R^{10''} are each H and R^{11''} is SO_zM, or R^{10'} and R^{11'} are each H and R^{10''} and R^{11''} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound, or R^{10''}, R^{11''} and R^{10'} are each H and R^{11'} is SO_zM, or R^{10''} and R^{11''} are each H and R^{10'} and R^{11'} form a nitrogen-carbon double bond between the nitrogen and

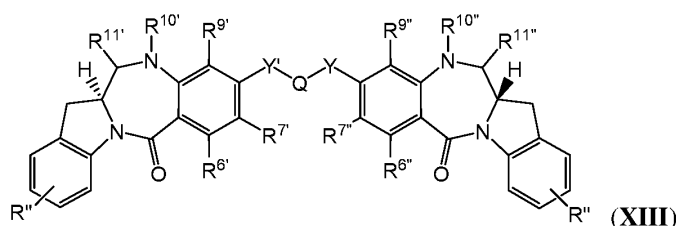
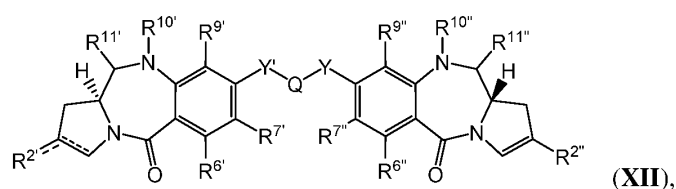
carbon atoms to which they are bound; wherein subscript z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation; and

R'' is a C₃₋₁₂ alkylene group, the carbon chain of which is optionally interrupted by one or more heteroatoms, in particular by one of O, S or NR^{N2} (where R^{N2} is H or C₁₋₄ alkyl), and/or by aromatic rings, in particular by one of benzene or pyridine;

Y and Y' are selected from the group consisting of O, S, and NH;

R^{6'}, R^{7'}, R^{9'} are selected from the same groups as R^{6''}, R^{7''} and R^{9''}, respectively, and for (a), (b) and (c) R^{10'} and R^{11'} are the same as R^{10''} and R^{11''}, respectively, and if R^{11'} and R^{11''} are SO_zM, each M is either a monovalent pharmaceutically acceptable cation or together represent a divalent pharmaceutically acceptable cation.

15. The method of claim **13**, wherein the PBD Drug Unit has the structure of Formula **XII** or Formula **XIII**:

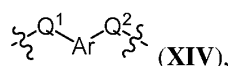


or a salt thereof,

wherein:

the dotted lines indicate a tautomeric double bond;

Q is of formula **XIV**:



wherein the wavy lines indicate the sites of covalent attachment to Y' and Y in either orientation;

Ar is a C₅₋₇ arylene group substituted by X^a and is otherwise optionally substituted, wherein X^a is from a reactive or activateable group for covalent attachment to a Linker Unit or precursor thereof, wherein X^a is selected from the group comprising: -O-, -S-, -C(O)O-, -

C(O)-, -NHC(O)-, and -N(R^N)-, wherein R^N is H or C₁-C₄ alkyl, and (C₂H₄O)_mCH₃, where subscript m is 1, 2 or 3;

and either:

(i) Q¹ is a single bond; and Q² is a single bond or -(CH₂)_n-, wherein subscript n is 1, 2 or 3, or

(ii) Q¹ is -CH=CH-, and Q² is a single bond or -CH=CH-; and

R^{2'} is a optionally substituted C₁-C₄ alkyl or a C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the group consisting of halo, nitro, cyano, C₁-C₆ ether, C₁-C₇ alkyl, C₃-C₇ heterocyclyl and bis-oxy-C₁-C₃ alkylene, in particular by one such substituent, wherein the dotted lines indicate a single bond to R^{2'}, or

R^{2'} an optionally substituted C₁-C₄ alkenylene wherein the dotted lines indicate a double bond to R^{2'};

R^{2''} is an optionally substituted C₁-C₄ alkyl or a C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the group consisting of halo, nitro, cyano, C₁-C₆ ether, C₁-C₇ alkyl, C₃-C₇ heterocyclyl and bis-oxy-C₁-C₃ alkylene, in particular by one such substituent;

R^{6''} and R^{9''} are independently selected from the group consisting of H, R, OH, OR, SH, SR, NH₂, NHR, NRR', nitro, Me₃Sn and halo;

R^{7''} is selected from the group consisting of H, R, OH, OR, SH, SR, NH₂, NHR, NRR', nitro, Me₃Sn and halo; and

R and R' are independently selected from the group consisting of optionally substituted C₁-C₁₂ alkyl, optionally substituted C₃-C₂₀ heterocyclyl and optionally substituted C₅-C₂₀ aryl;

and either:

(a) R^{10''} is H, and R^{11''} is OH or OR^A, wherein R^A is C₁-C₄ alkyl, or

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

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

(d) R^{10'.}, R^{11'.} and R^{10''.} are each H and R^{11''.} is SO_zM, or R^{10'.} and R^{11'.} are each H and R^{10''.} and R^{11''.} form a nitrogen-carbon double bond between the nitrogen and carbon atoms to which they are bound, or R^{10''.}, R^{11''.} and R^{10'.} are each H and R^{11'.} is SO_zM, or R^{10''.} and R^{11''.} are each H and R^{10'.} and R^{11'.} form a nitrogen-carbon double bond between the nitrogen and

carbon atoms to which they are bound; wherein subscript z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation; and

Y and Y' are selected from the group consisting of O, S, and NH;

R'' represents one or more optional substituents; and

R^{6'}, R^{7'}, R^{9'} are selected from the same groups as R^{6''}, R^{7''} and R^{9''}, respectively, and for (a), (b) and (c) R^{10'} and R^{11'} are the same as R^{10''} and R^{11''}, respectively, and if R^{11''} and R^{11'} are SO_zM, each M is either a monovalent pharmaceutically acceptable cation or together represent a divalent pharmaceutically acceptable cation.

16. The method of claim **14** or **15**, wherein R^{7''} is selected from the group consisting of H, OH and OR.

17. The method of claim **14** or **15**, wherein R^{7''} is a C₁₋₄ alkyloxy group.

18. The method of claim **14** or **15**, wherein R^{7''} is -OCH₃.

19. The method of any one of claims **14** to **18**, wherein Y and Y' are O.

20. The method of any one of claims **14** to **19**, wherein R^{9''} is H.

21. The method of any one of claim **14** to **20**, wherein R^{6''} is selected from the group consisting of H and halo.

22. The method of claim **14**, wherein Ar is phenylene; X^a is selected from the group consisting of -O-, -S- and -NH-; and Q¹ is a single bond.

23. The method of claim **15**, wherein Ar is phenylene, X^a is selected from the group consisting of -O-, -S-, and -NH-, Q¹ -CH₂- and Q₂ is -CH₂-.

24. The method of claim **22** or **23**, wherein X^a is NH.

25. The method of claim **14**, wherein Q¹ is a single bond and Q² is a single bond.

26. The method of claim any one of claims **14** to **25**, wherein the dotted lines indicate a single bond to $R^{2'}$, wherein $R^{2'}$ is a C_{5-7} aryl group optionally substituted by one or more substituents selected from the group consisting of halo, nitro, cyano, C_{1-7} alkoxy, C_{5-20} aryloxy, C_{3-20} heterocycloxy, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy- C_{1-3} alkylene wherein the C_{1-7} alkoxy group is optionally substituted by an amino group, and if the C_{3-7} heterocyclyl group is a C_6 nitrogen containing heterocyclyl group, it is optionally substituted by a C_{1-4} alkyl group.

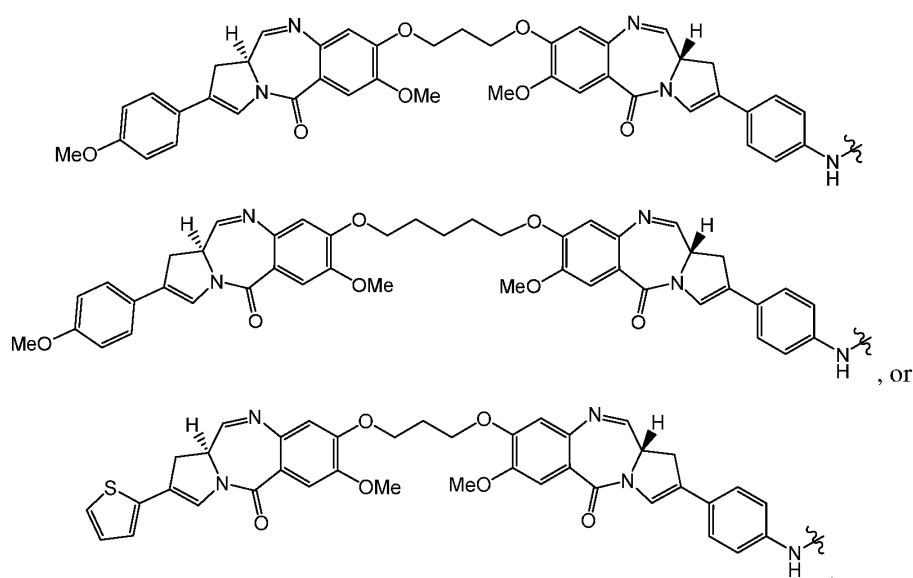
27. The method of claim **26**, wherein the optionally substituted C_{5-7} aryl is optionally substituted phenyl.

28. The method of claim **26**, wherein the optionally substituted C_{5-7} aryl is phenyl having one to three substituents.

29. The method of any one of claims **14** to **28**, wherein $R^{10''}$ and $R^{11''}$ form a nitrogen-carbon double bond.

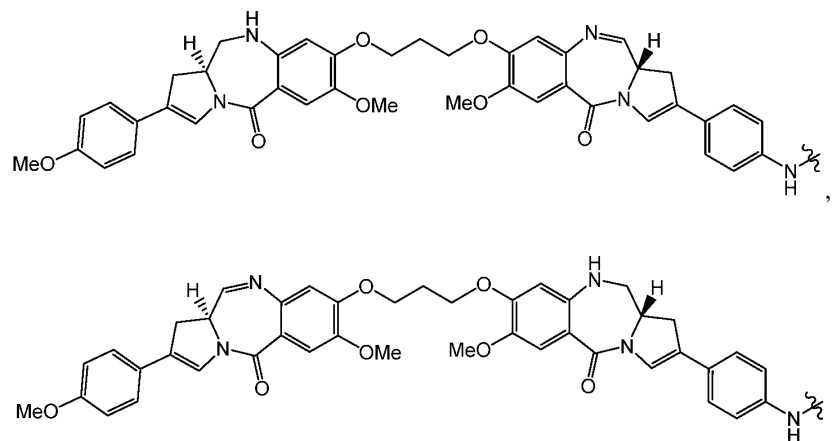
30. The method of claim any one of claims **14** to **29**, wherein $R^{6'}$, $R^{7'}$, $R^{9'}$, and Y' are the same as $R^{6''}$, $R^{7''}$, $R^{9''}$, and Y respectively.

31. The method of claim **14**, wherein the PBD Drug Unit is:



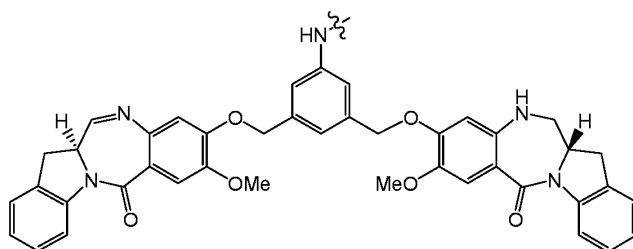
or a salt thereof, wherein the wavy line indicates the point of covalent attachment to S* in the form of a carbamate functional group.

32. The method of claim 14, wherein the PBD Drug Unit is:



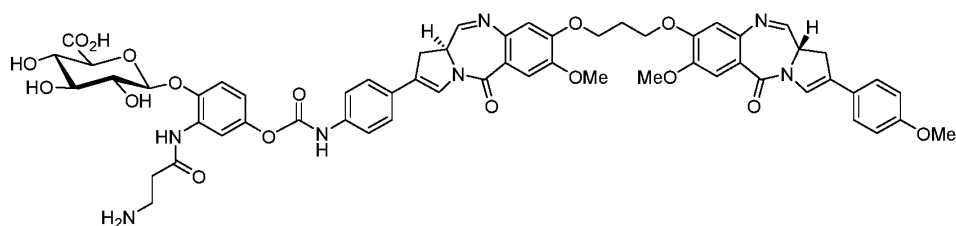
or a salt thereof, wherein the wavy line indicates the point of covalent attachment to S* in the form of a carbamate functional group.

33. The method of claim 15, wherein the PBD Drug Unit is:



or a salt thereof, wherein the wavy line indicates the point of covalent attachment to S* in the form of a carbamate functional group.

34. The method of claim 3, wherein D is a PBD Drug Unit, in which the Drug Linker intermediate compound of Formula **1E** has the structure of:

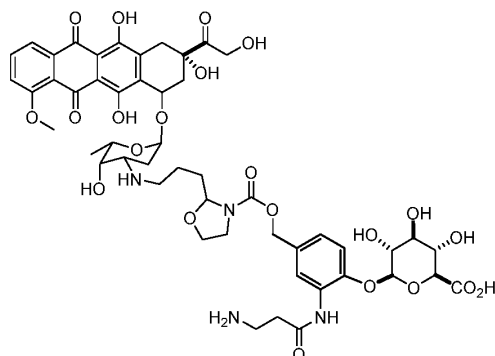


or a salt thereof.

35. The method of any one of claims **1** to **12**, wherein D is an anthracyclin Drug Unit.

36. The method of claim **35**, wherein the anthracyclin Drug Unit incorporates doxorubicin, idarubicin, daunorubicin, doxorubicin propyloxazoline (DPO) or cyanomorpholino-doxorubicin.

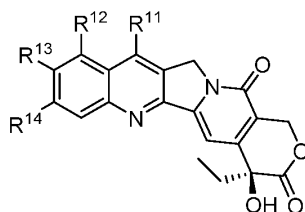
37. The method of claim **3**, wherein D is an anthracyclin Drug Unit in which the Drug Linker intermediate compound of Formula **IE** has the structure of:



or a salt thereof.

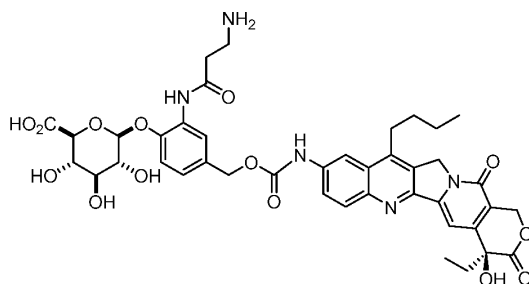
38. The method of any one of claims **1** to **12**, wherein D is an camptothecin Drug Unit

39. The method of claim **38**, wherein the camptothecin Drug Unit has the structure of:



or a lactone ring-opened form thereof, optionally in salt form, wherein one of R^{11} is n-butyl and one of R^{12} - R^{14} is $-NH_2$ and the other are hydrogen, or R^{12} is $-NH_2$ and R^{13} and R^{14} together are $-OCH_2O-$.

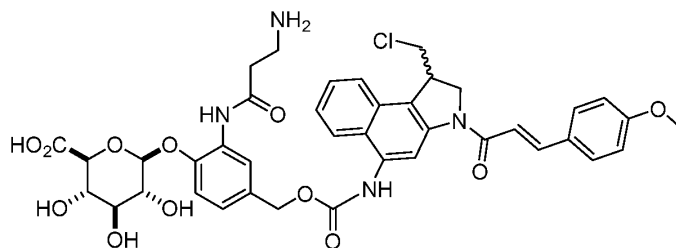
40. The method of claim **3**, wherein D is an camptothecin Drug Unit in which the Drug Linker intermediate compound of Formula **IE** has the structure of:



or a lactone ring-opened form thereof, optionally in salt form.

41. The method of any one of claims **1** to **12**, wherein D is an duocarmycin Drug Unit

42. The method of claim **3**, wherein D is an duocarmycin Drug Unit in which the Drug Linker intermediate compound of Formula **IE** has the structure of:



or a salt thereof.