

(**XIII**);

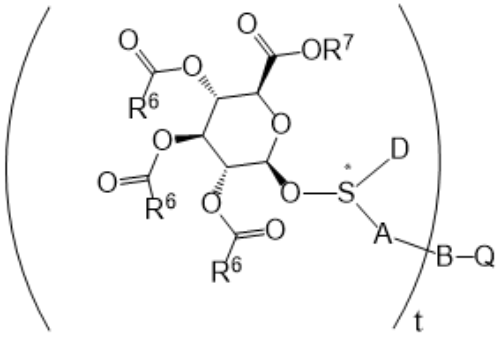
the wavy line indicates the point of attachment to A, and # indicates the point of attachment to the O atom connected to S*;

D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

T* is an oxygen, sulfur, or optionally substituted nitrogen atom from a hydroxyl, thiol or amine functional group of the DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

R^7 is C_1-C_8 alkyl or optionally substituted phenyl so that $–OR^7$ provides for an ester functional group that is a suitable carboxylic acid protecting group; and

subscript t is 1, 2, 3, or 4, the method comprising the step of: (c) contacting a compound of Formula **VIC** with a Grignard reagent or an alkoxy magnesium halide in a suitable alcohol-containing solvent, wherein the Formula **VIC** compound has the structure of:

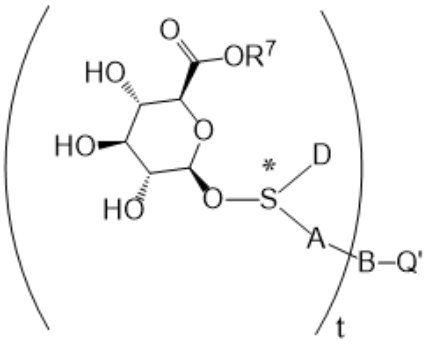


(**VIC**)

or a salt thereof, wherein each of R^6 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 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.

[0004b] In another aspect, the present disclosure refers to method for preparing a compound of Formula **VIIE**:

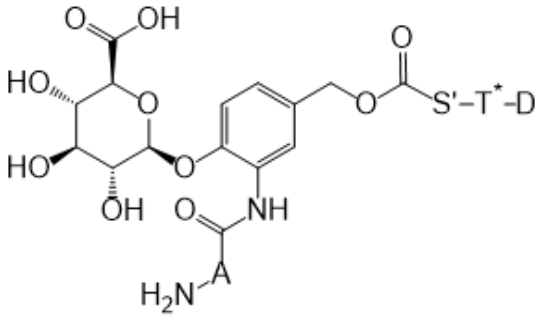
an ester functional group that is a suitable carboxylic acid protecting group; and the remaining variable groups are as previously defined for Formula **VIIE**, wherein said Grignard reagent or alkoxy magnesium halide contacting selectively removes the hydroxyl protecting groups to provide a compound of Formula **VIID**:



(**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 **VIIE** compound or its salt is obtained.

[0004c] In yet another aspect, the present disclosure refers to method for preparing a compound of Formula **IE**:

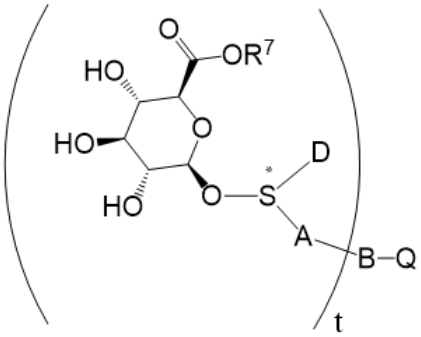


(**IE**)

or a salt thereof, wherein A is an optional Connector Unit; S' is absent or–NR^N-$C(R^1)(R^2)$-, wherein R^N, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or R^N 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; D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor having a hydroxyl, thiol, or amine functional group, wherein the functional group forms a covalent bond with S'; T* is the oxygen, sulfur, or optionally substituted nitrogen from said functional group; Z^1 is a first suitable amine protecting group; and R^7 is C_1-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,

WHAT IS CLAIMED IS:

1. A method for preparing a compound of Formula **VID**:



(**VID**)

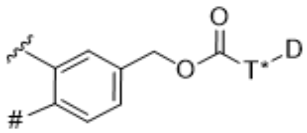
or a salt thereof, wherein

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

A is an optional Connector 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;

S* is a Self-Immolating Unit, wherein the S*-D has the structure of Formula **XIII**:



(**XIII**);

the wavy line indicates the point of attachment to A, and # indicates the point of attachment to the O atom connected to S*;

D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

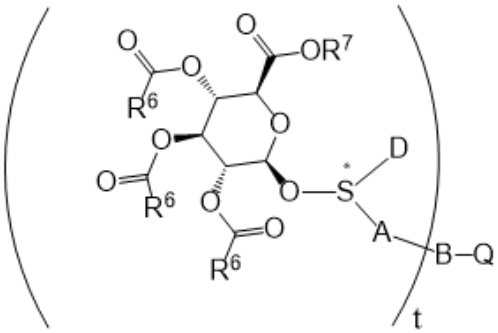
T* is an oxygen, sulfur, or optionally substituted nitrogen atom from a hydroxyl, thiol or amine functional group of the DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

R^7 is C_1-C_8 alkyl or optionally substituted phenyl so that $–OR^7$ provides for an ester functional group that is a suitable carboxylic acid protecting group; and

subscript t is 1, 2, 3, or 4,

the method comprising the step of:

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



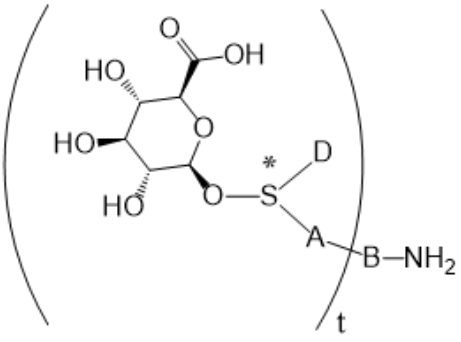
(**VIC**)

or a salt thereof, wherein

each of R^6 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 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 compound of Formula **VIIE**:



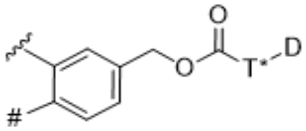
(**VIIE**)

or a salt thereof, wherein

A is an optional Connector 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;

S* is a Self-Immolating Unit, wherein the S*-D has the structure of Formula **XIII**:



(**XIII**);

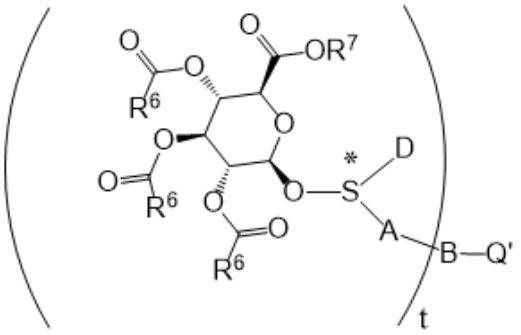
the wavy line indicates the point of attachment to A, and # indicates the point of attachment to the O atom connected to S*;

D is a Drug Unit incorporating a DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

T* is an oxygen, sulfur, or optionally substituted nitrogen atom from a hydroxyl, thiol or amine functional group of the DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

the method comprising the steps of:

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



(**VIIC**)

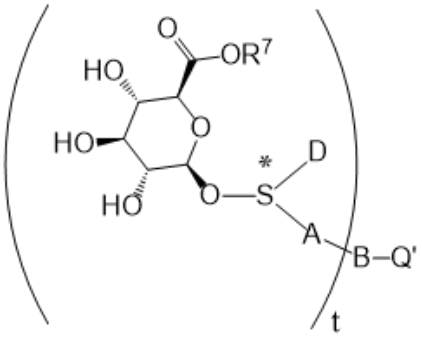
or a salt thereof, wherein

S*, D, A, B and subscript t are as defined for **VIC** and **VID** of claim 1;

Q’ is a suitably protected amino group;

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 for Formula **VIIE**,

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



(**VIID**)

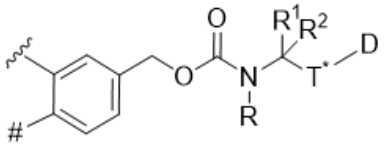
or a salt thereof, wherein the variable groups are as previously defined by Formula **VIIIC**; and

(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 **VIIE** compound or its salt is obtained.

3. The method of claim **1** or **2**, wherein

T* is an optionally substituted nitrogen atom from an amine functional group of the DNA minor groove binder, DNA damaging agent or DNA replication inhibitor that is capable of forming a carbamate functional group in Formula **XIII**.

4. The method of claim **1** or **2**, wherein the Self-Immolating Unit has the structure of Formula **XIV**:



(**XIV**),

wherein

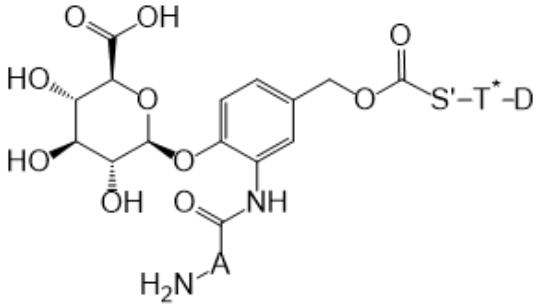
T* is an oxygen, sulfur, or optionally substituted nitrogen atom from a hydroxyl, thiol or amine functional group of the DNA minor groove binder, DNA damaging agent or DNA replication inhibitor;

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 a pyrrolodinyl or piperidinyl moiety and R^2 is hydrogen; and

the wavy line indicates the point of attachment to A, and # indicates the point of attachment to the O atom connected to S*.

5. A method for preparing a compound of Formula **IE**:



(**IE**)

or a salt thereof, wherein

A is an optional Connector Unit;

S’ is absent or $–NR^N-C(R^1)(R^2)-$, wherein R^N, R^1 and R^2 independently are hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{14} aryl, or optionally substituted C-linked C_3-C_8 heteroaryl, or R^N 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;

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

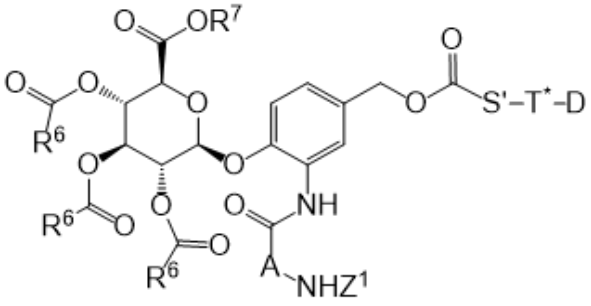
T* is the oxygen, sulfur, or optionally substituted nitrogen from said functional group;

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

R^7 is C_1-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 a Grignard reagent or an alkoxy magnesium halide in a suitable an alcohol-containing solvent, wherein the Formula **IC** compound has the structure of:



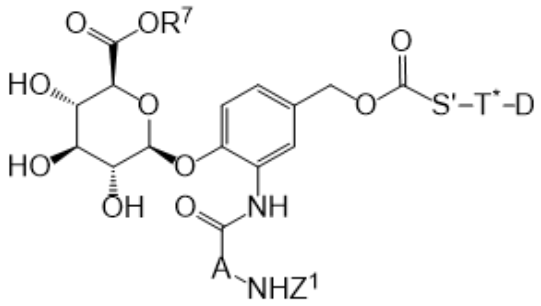
(**IC**)

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**:



(**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.

6. The method of claim **1**, **2**, or **5**, wherein the Grignard reagent has the formula of R^gMgX and the alkoxy magnesium halide has the formula of R^gOMgX, wherein R^g is C_1-C_5 alkyl and X is I, Br, or Cl.

7. The method of claim **6**, wherein the Grignard reagent is MeMgI or MeMgCl.

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

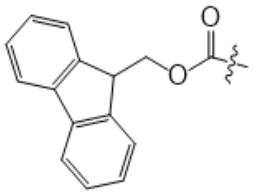
9. The method of claim **1**, **2**, or **5**, wherein the Grignard reagent is MeMgI, the alkoxy magnesium halide is MeOMgI or MeOMgCl and the suitable alcohol-containing solvent comprises a C_1-C_4 alcohol.

10. The method of claim **1**, **2**, or **5**, wherein when the Grignard reagent is in the suitable alcohol-containing solvent, the suitable alcohol-containing solvent further comprises THF.

11. The method of claim **10**, wherein when the Grignard reagent is in the suitable alcohol-containing solvent, the suitable alcohol-containing solvent is a 1:1 (v/v) mixture of methanol and THF.

12. The method of claim **5**, wherein the first deprotecting agent for removal of Z^1 is an aqueous-containing solution of LiOH.

13. The method of claim **5**, wherein Z^1 has the formula of:

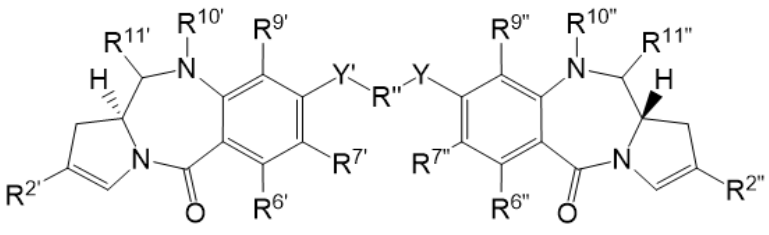


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14. The method of claim **5**, wherein said Grignard reagent or alkoxy magnesium halide contacting and said deprotecting agent contacting to remove Z^1 are done sequentially in one pot.

15. The method of claim **1**, **2**, or **5**, wherein D is a PBD Drug Unit.

16. The method of claim **15**, wherein the PBD Drug Unit has the structure of Formula **X**:



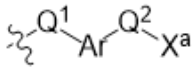
(**X**)

or a salt thereof,

wherein:

the dotted lines represent a tautomeric double bond;

$R^{2"}$ is of formula **XI**:

 (**XI**),

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

Ar is an optionally substituted C_{5-7} arylene;

X^a is from a reactive or activatable group for covalent attachment to Q^2, when Q^2 is other than a single bond or to S* or S' when Q^2 is a single bond, 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 C_1-C_4 alkyl, and $(C_2H_4O)_mCH_3$, where subscript m is 1, 2 or 3;

and either:

(i) Q^1 is a single bond; and Q^2 is a single bond or -Z-$(CH_2)_n$-, 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) Q^1 is -CH=CH-, and Q^2 is a single bond; and

$R^{2'}$ 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} heterocyclyoxy, C_1-C_6 ether, C_1-C_7 alkyl, C_3-C_7 heterocyclyl and bis-oxy-C_1-C_3 alkylene;

$R^{6"}$ and $R^{9"}$ are independently selected from the group consisting of H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;

$R^{7"}$ is selected from the group consisting of H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo; and

R and R' are independently selected from the group consisting of optionally substituted C_1-C_{12} alkyl, optionally substituted C_3-C_{20} heterocyclyl and optionally substituted C_5-C_{20} aryl;

and either:

(a) $R^{10"}$ is H, and $R^{11"}$ is OH or OR^A, wherein R^A is C_1-C_4 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

R″ is a C_{3-12} alkylene group, the carbon chain of which is optionally interrupted by one or more of O, S or NR^{N2} (where R^{N2} is H or C_1-C_4 alkyl), and/or 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 $R^{10'}$ 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.

17. The method of claim **16**, wherein $R^{7"}$ is selected from the group consisting of H, OH and OR.

18. The method of claim **16**, wherein $R^{7"}$ is a C_{1-4} alkyloxy group.

19. The method of claim **16**, wherein $R^{7"}$ is $–OCH_3$.

20. The method of claim **16**, wherein Y and Y' are O.

21. The method of claim **16**, wherein $R^{9"}$ is H.

22. The method of claim **16**, wherein $R^{6"}$ is selected from the group consisting of H and halo.

23. The method of claim **16**, wherein Ar is phenylene; X^a is selected from the group consisting of -O-, -S- and -NH-; and Q^1 is a single bond.

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

25. The method of claim **16**, wherein Q^1 is a single bond and Q^2 is a single bond.

26. The method of claim **16**, wherein $R^{2'}$ is a C_{5-7} aryl group optionally substituted by a C_{3-7} heterocyclyl 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.

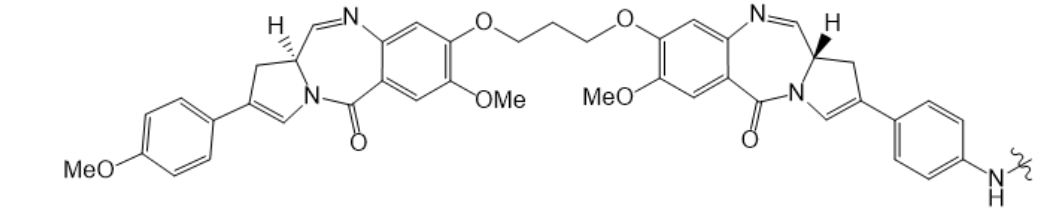
27. The method of claim **26**, wherein $R^{2'}$ is an optionally substituted C_{5-7} aryl group, wherein the optionally substituted C_{5-7} aryl group is optionally substituted phenyl.

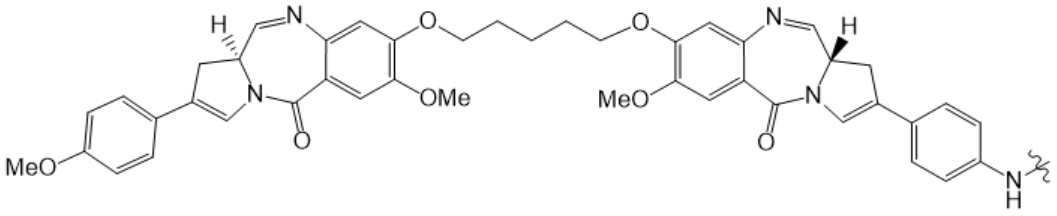
28. The method of claim **27**, wherein the optionally substituted C_{5-7} aryl group is phenyl having one to three substituents.

29. The method of claim **16**, wherein $R^{10"}$ and $R^{11"}$ form a nitrogen-carbon double bond.

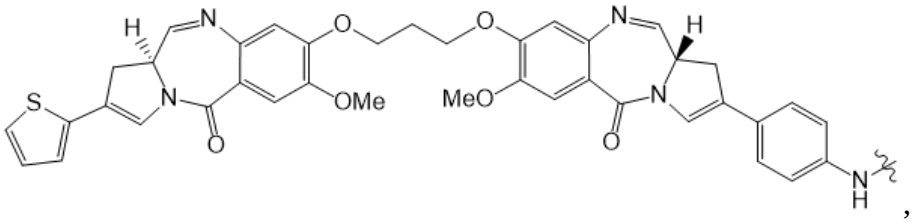
30. The method of claim **16**, wherein $R^{6'}$, $R^{7'}$, $R^{9'}$, and Y' are the same as $R^{6"}$, $R^{7"}$, $R^{9"}$, and Y respectively.

31. The method of claim **16**, wherein the PBD Drug Unit is:





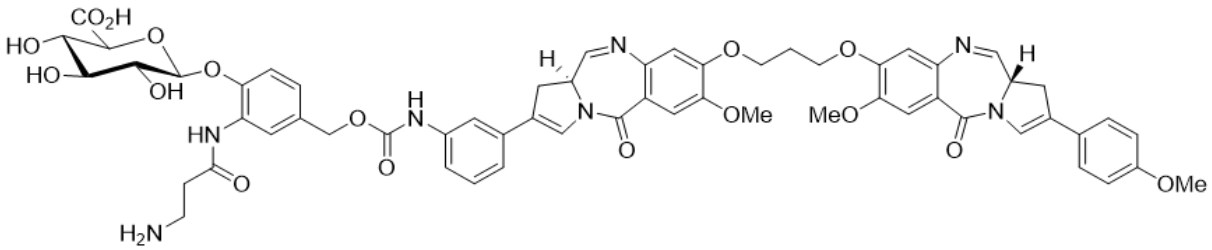
, or



,

or a salt thereof, wherein the wavy line indicates the point of covalent attachment to Q^2, S* or S' in the form of a carbamate functional group.

32. The method of claim **5**, wherein D is a PBD Drug Unit, in which the compound of Formula **IE** has the structure of:

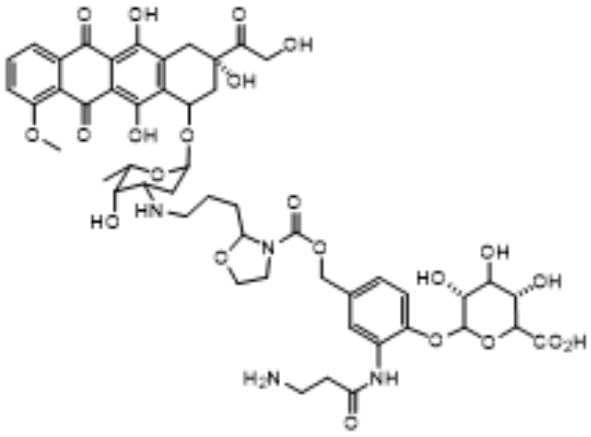


or a salt thereof.

33. The method of claim **1**, **2**, or **5**, wherein D is an anthracyclin Drug Unit.

34. The method of claim **33**, wherein the anthracyclin Drug Unit incorporates the structure of doxorubicin, idarubicin, daunorubicin, doxorubicin propyloxazoline (DPO) or cyanomorpholino-doxorubicin.

35. The method of claim **5**, wherein D is an anthracyclin Drug Unit in which the compound of Formula **IE** has the structure of:



or a salt thereof.

36. The method of claim **1**, **2**, or **5**, wherein D is a camptothecin Drug Unit.

37. The method of claim **1**, **2**, or **5**, wherein D is a duocarmycin Drug Unit.