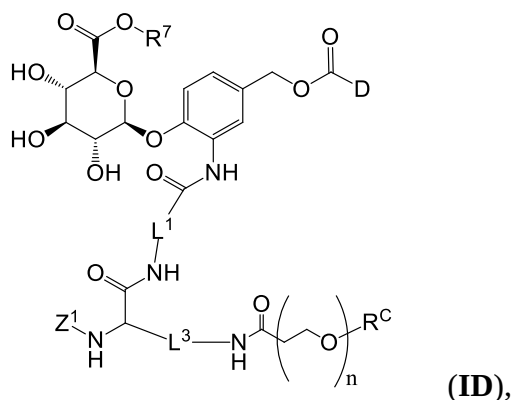


CLAIMS

WHAT IS CLAIMED IS:

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



or a salt thereof,

wherein D is an auristatin Drug Unit,

each of L¹ and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

R⁷ is optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so-OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group;

Z¹ is a first suitable amino protecting group;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the step of:

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



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

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



or a salt thereof,

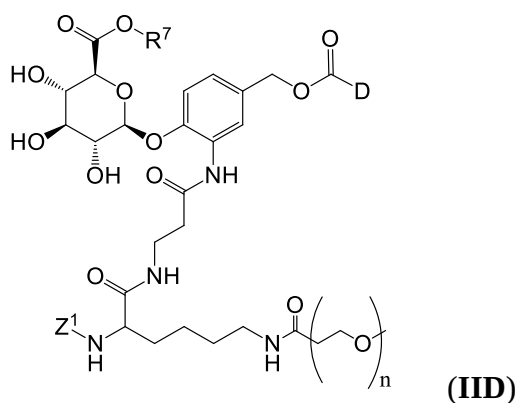
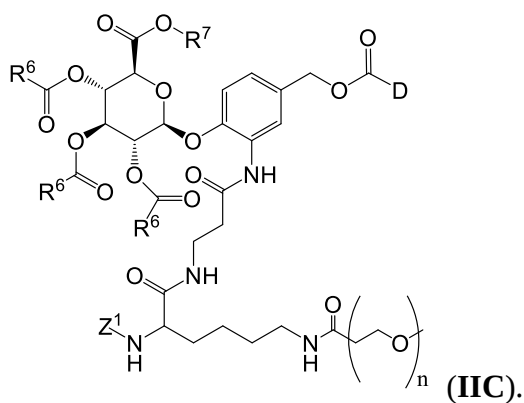
wherein D is an auristatin Drug Unit,

each of L¹ and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

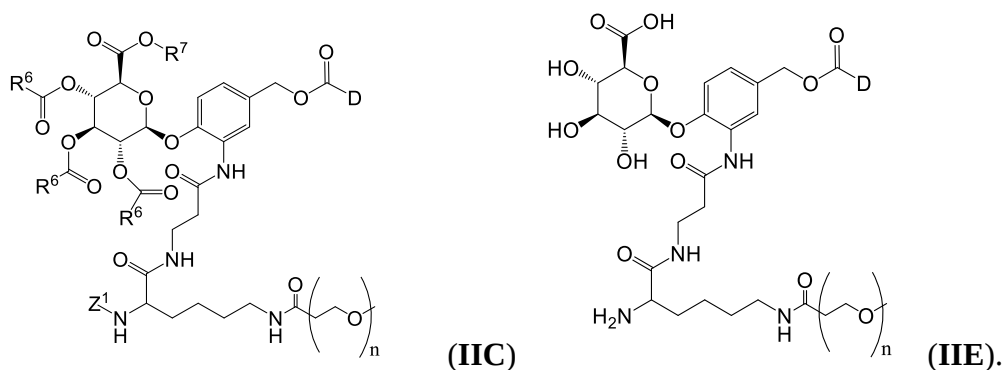
R⁷ is optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so—OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group;

R^C is a PEG Capping Unit; and
subscript n ranges from 2 to 24,
the method comprising step (c) of claim 1, further comprising the subsequent step of:
(d) contacting the product of step (c) with a first deprotecting agent, wherein said first deprotecting agent contacting removes the Z^1 amino and carboxylic acid protecting groups to provide the Formula **IE** Drug Linker intermediate compound.

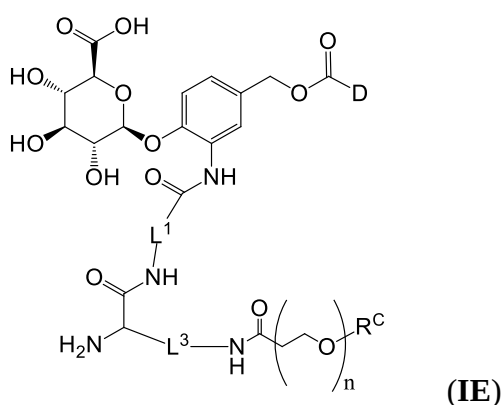
3. The method of claim 1, wherein the Formula **IC** and Formula **ID** Drug Linker intermediate compounds have the structures of Formula **IIC** and Formula **IID**:



4. The method of claim 2, wherein the Formula **IC** and Formula **IE** Drug Linker intermediate compounds, or salts thereof, have the structures of Formula **IIC** and Formula **IIE**:



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



or a salt thereof,

wherein D is an auristatin Drug Unit,

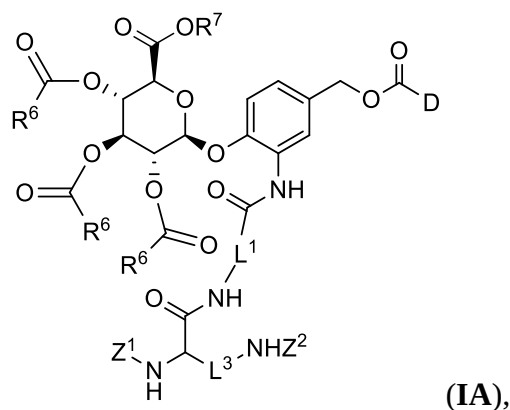
each of L^1 and L^3 is independently selected from the group consisting of optionally substituted C_1 - C_{20} alkylene, optionally substituted C_4 - C_{20} heteroalkylene, optionally substituted C_3 - C_8 carbocyclo, optionally substituted C_6 - C_{10} arylene, optionally substituted C_5 - C_{10} heteroarylene and optionally substituted C_3 - C_8 heterocyclo;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising the steps of claim 2, further comprising prior to steps (c) and (d) the steps of:

(a) contacting a Drug Linker intermediate of Formula **IA** with a second deprotecting agent, wherein the Formula **IA** Drug Linker intermediate compound has the structure of:



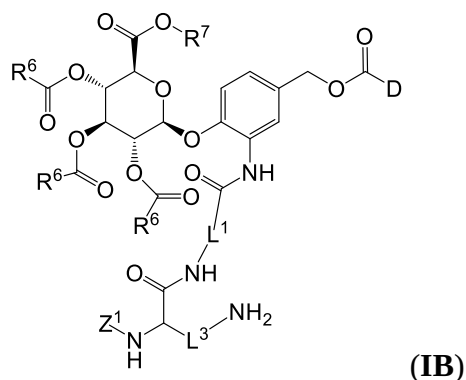
or a salt thereof, wherein

each of R^6 and R^7 is independently optionally substituted C_1 - C_8 alkyl, optionally substituted C_6 - C_{10} arylene or optionally substituted C_5 - C_{10} heteroarylene so that $R^6C(=O)-$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-OR^7$ provides an ester functional group that is a suitable carboxylic acid protecting group;

each of Z^1 and Z^2 is independently a first and second suitable amino protecting group, respectively; and

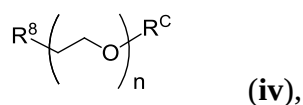
the remaining variable groups are as previously defined,

wherein said second deprotecting agent contacting selectively removes the Z^2 amino protecting group to provide a Drug Linker intermediate compound of Formula **IB**:



or a salt thereof, wherein the variable groups are as previously defined;

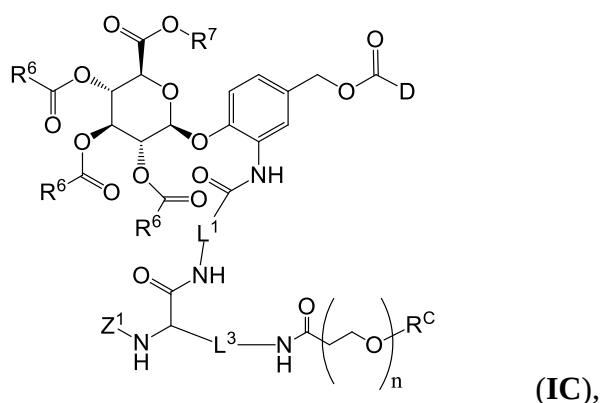
(b) contacting the Formula **IB** compound in a suitable solvent with a compound of Formula **iv**:



wherein R^8 is an activated ester group; and the remaining variable groups are as previously defined, or

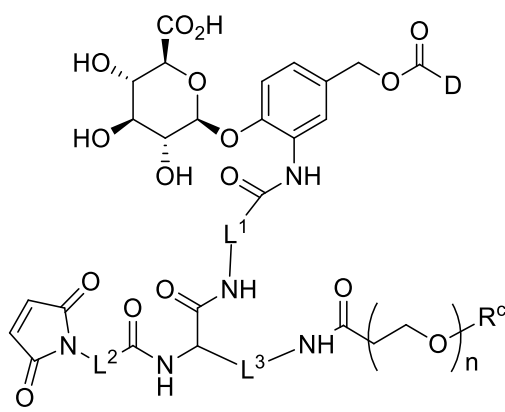
(b') contacting the Formula **IB** Drug Linker intermediate compound in a suitable solvent with a Formula **iv** compound in which R^8 is $-COOH$ and the remaining variable

groups are as previously defined in the presence of a first activating agent, wherein said contacting step (b) or (b') provides the Formula **IC** Drug Linker intermediate compound of:



or a salt thereof, wherein the variable groups are as previously defined.

6. A method for preparing a Drug Linker compound or intermediate thereof of Formula **I**:



or a salt thereof,

wherein D is an auristatin Drug Unit,

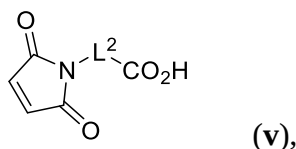
each of L¹, L², and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

R^C is a PEG Capping Unit; and

subscript n ranges from 2 to 24,

the method comprising steps (a)-(d) of claim 5, followed by the step of:

(e) contacting the Formula **IE** Drug Linker intermediate compound in a suitable solvent with a compound of Formula **v**:

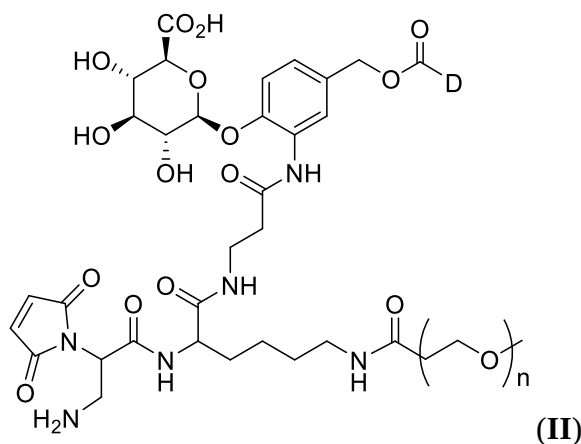


or a salt thereof, wherein L² is as previously defined, in the presence of a second activating agent; and

wherein said Formula **v** contacting provides the Formula **I** Drug Linker or Drug Linker intermediate compound or salt thereof.

7. The method of any one of claims **1-6** wherein each of L¹ and L³ is independently C₁-C₄ alkylene and L² is independently optionally substituted C₁-C₄ alkylene.

8. A method for preparing a Drug Linker compound of Formula **II**:



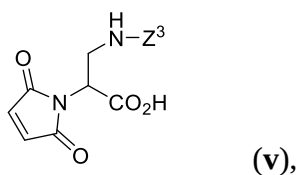
or a salt thereof,

wherein D is an auristatin Drug Unit; and

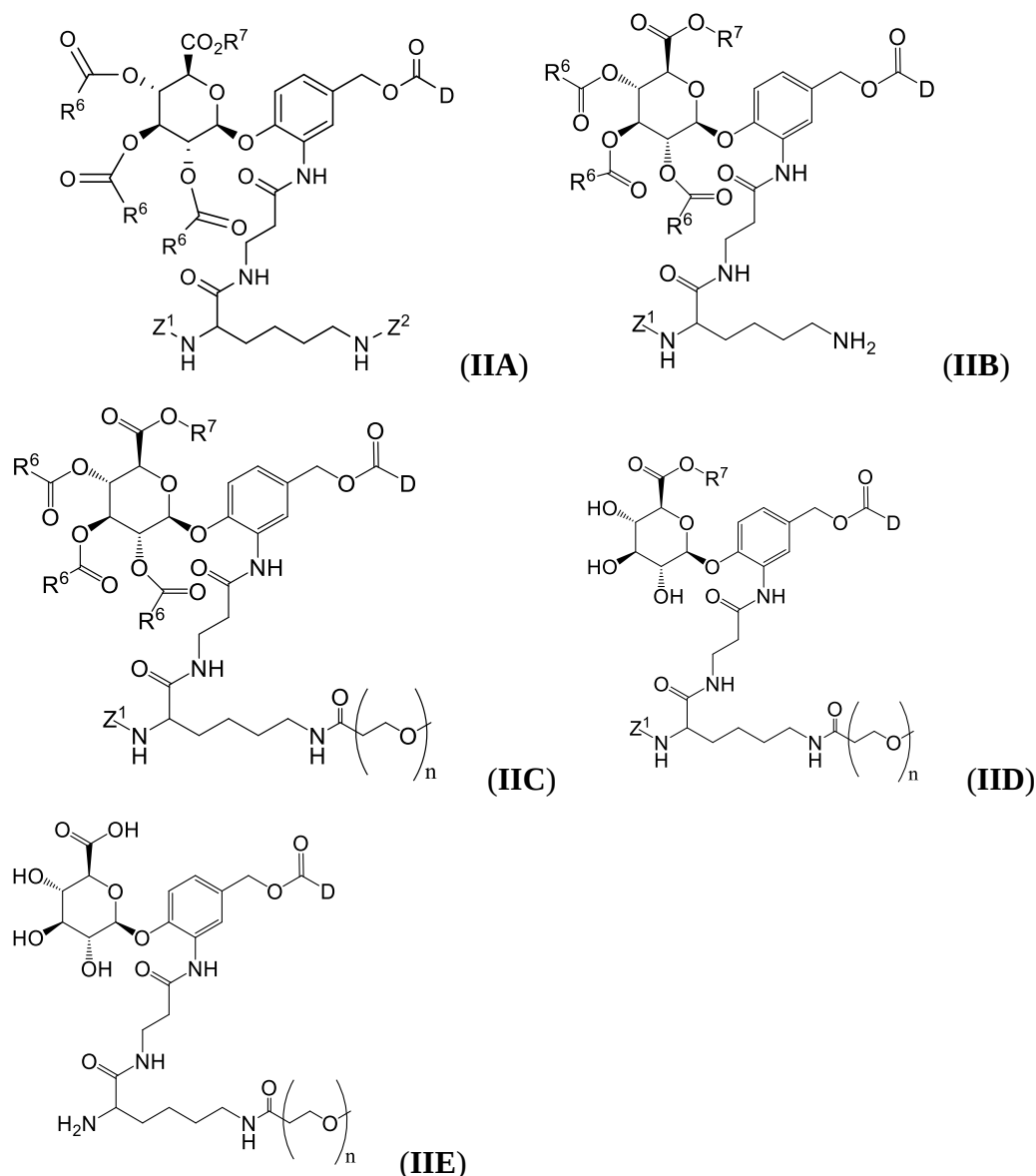
subscript n ranges from 2 to 24,

the method comprising steps (a)-(e) of claim **6**,

wherein the Formula **v** compound has the structure of:



and wherein the Formula **IA**, Formula **IB**, Formula **IC**, Formula **ID** and Formula **IE** Drug Linker intermediate compounds, optionally in salt form, have the structures of Formula **IIA**, Formula **IIB**, Formula **IIC**, Formula **IID**, Formula **IIE**, Formula **IIF**:



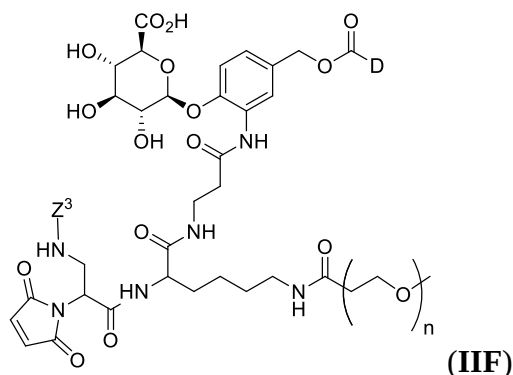
wherein

each of R^6 and R^7 is independently optionally substituted $\text{C}_1\text{-C}_8$ alkyl, optionally substituted $\text{C}_6\text{-C}_{10}$ arylene or optionally substituted $\text{C}_5\text{-C}_{10}$ heteroarylene so that $\text{R}^6\text{C(=O)-}$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-\text{OR}^7$ provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 , Z^2 and Z^3 are independently a first, second and third suitable amino protecting group, respectively, or

Z^1 and Z^2 are independently a first and second suitable amino protecting group, respectively and Z^3 is an acid-labile amino protecting group, or Z^1 and Z^2 are independently a first and second suitable amino protecting group, respectively, and Z^3 is $-C(=O)O-t-Bu$,

and wherein step (e) provides a Drug Linker intermediate compound of Formula **IIIF**:

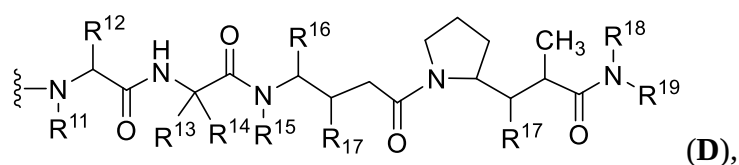


or a salt thereof,

the method further comprising the step of:

(f) contacting the Formula **IIIF** Drug Linker intermediate compound with a third deprotecting agent, wherein said contacting with the third deprotecting reagent removes the Z^3 amino protecting group whereby the Formula **II** Drug Linker compound or salt thereof is provided.

9. The method of any one of claims **1-8**, wherein the auristatin Drug Unit (D) has the structure of:



wherein the wavy line indicates covalent bonding of D to the remainder of the Drug Linker or Drug Linker intermediate compound;

R^{11} is selected from the group consisting of H and C_1 - C_8 alkyl, in particular methyl,

R^{12} is selected from the group consisting of H, C_1 - C_8 alkyl, C_3 - C_8 carbocycle, aryl, C_1 - C_8 alkyl-aryl, C_1 - C_8 alkyl-(C_3 - C_8 carbocycle), C_3 - C_8 heterocycle, and C_1 - C_8 alkyl-(C_3 - C_8 heterocycle);

R^{13} is selected from the group consisting of H, C_1 - C_8 alkyl, C_3 - C_8 carbocycle, aryl, C_1 - C_8 alkyl-aryl, C_1 - C_8 alkyl-(C_3 - C_8 carbocycle), C_3 - C_8 heterocycle, and C_1 - C_8 alkyl-(C_3 - C_8 heterocycle);

R^{14} is selected from the group consisting of H and methyl;
 or R^{13} and R^{14} jointly form a carbocyclic ring and have the formula $-(CR^aR^b)_n-$ wherein R^a and R^b are independently selected from the group consisting of H, C₁-C₈ alkyl and C₃-C₈ carbocycle, and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R^{15} is selected from the group consisting of H and C₁-C₈ alkyl;

R^{16} is selected from the group consisting of H, C₁-C₈ alkyl, C₃-C₈ carbocycle, aryl, C₁-C₈ alkyl-aryl, C₁-C₈ alkyl-(C₃-C₈ carbocycle), C₃-C₈ heterocycle, and C₁-C₈ alkyl-(C₃-C₈ heterocycle);

each R^{17} is independently selected from the group consisting of H, OH, C₁-C₈ alkyl, C₃-C₈ carbocycle, and O-(C₁-C₈ alkyl);

R^{18} is selected from the group consisting of H and C₁-C₈ alkyl;

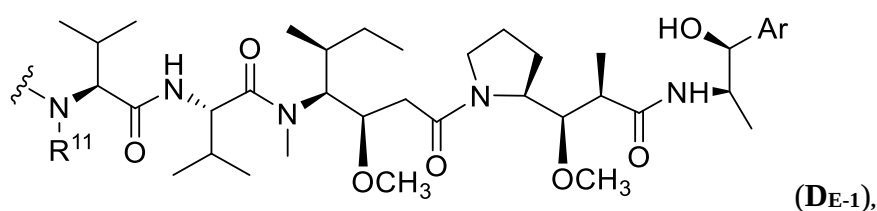
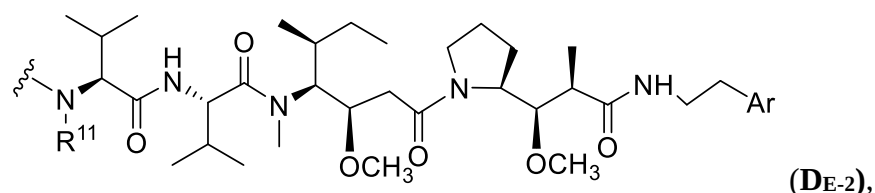
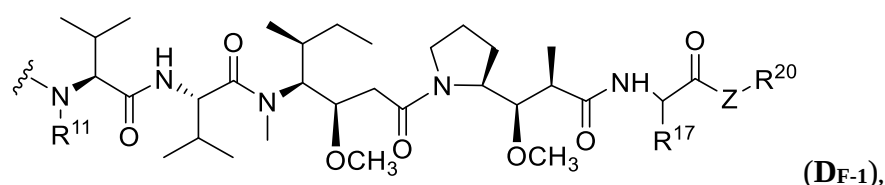
R^{19} is selected from the group consisting of $-C(R^{17})_2-C(R^{17})_2$ -aryl, $-C(R^{17})_2-C(R^{17})_2$ -(C₃-C₈ heterocycle), $-C(R^{17})_2-C(O)-ZR^{20}$, and $-C(R^{17})_2-C(R^{17})_2$ -(C₃-C₈ carbocycle);

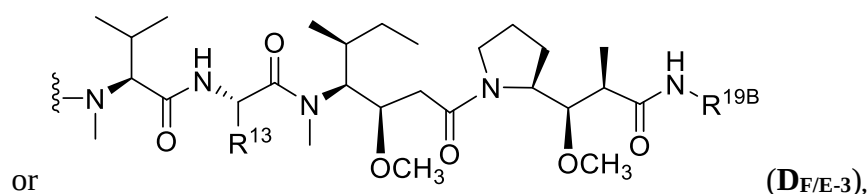
R^{20} is selected from the group consisting of H, C₁-C₈ alkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₅-C₁₀ heteroaryl and C₃-C₈ heterocyclyl;

Z is -O-, or -NH-, or

Z- is -O- and R^{20} is C₁-C₄ alkyl or Z is -NH- and R^{20} is optionally substituted phenyl or optionally substituted C₅-C₆ heteroaryl, or

the auristatin Drug Unit (D) has the structure of Formula **D_{E-1}**, **D_{E-2}**, **D_{F-1}** or **D_{F/E-3}**:

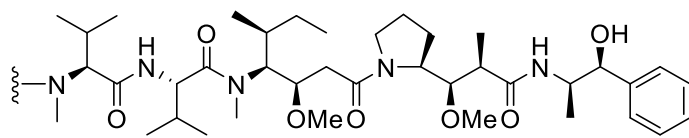




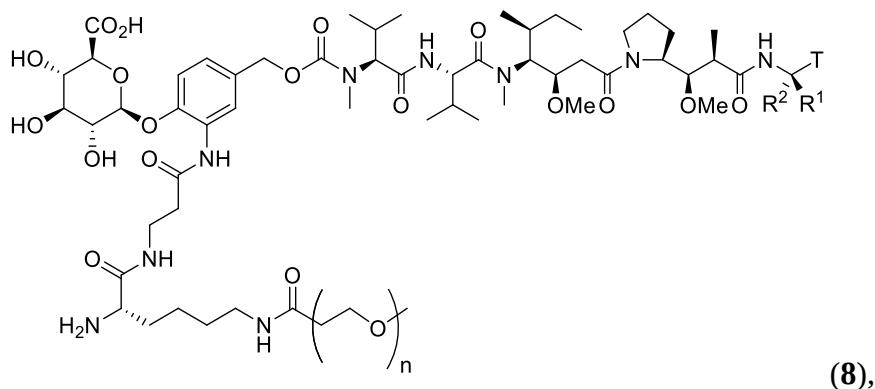
wherein R¹³ is isopropyl or –CH₂-CH(CH₃)₂; and

R^{19B} is –CH(CH₃)-CH(OH)Ph, –CH(CO₂H)CH₂Ph, –CH(CH₂Ph)-2-thiazole, –CH(CH₂Ph)-2-pyridyl, –CH(CO₂Me)-CH₂Ph, –CH(CO₂Me)-CH₂CH₂SCH₃, CH(CH₂CH₂SCH₃)C(=O)NH-3-quinolyl, or –CH(CH₂Ph)C(=O)NH-p-Cl-Ph;

Ar is optionally substituted C₆-C₁₀ aryl or optionally substituted C₃-C₈ heterocyclyl, in particular, or Ar is optionally substituted phenyl or optionally substituted 2-pyridyl, or the auristatin Drug Unit (D) has the structure of:



10. The method of claim 5, wherein the Formula **IE** Drug Linker intermediate has the structure of Formula **8**:



or a salt thereof, wherein

subscript n ranges from 2 to 24;

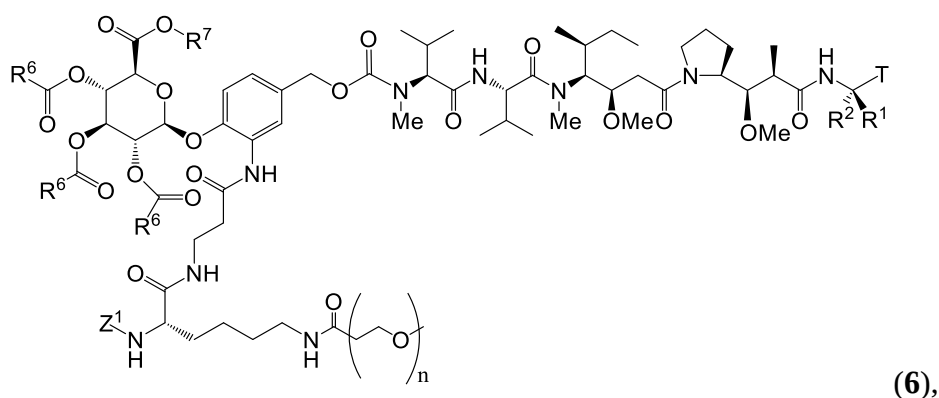
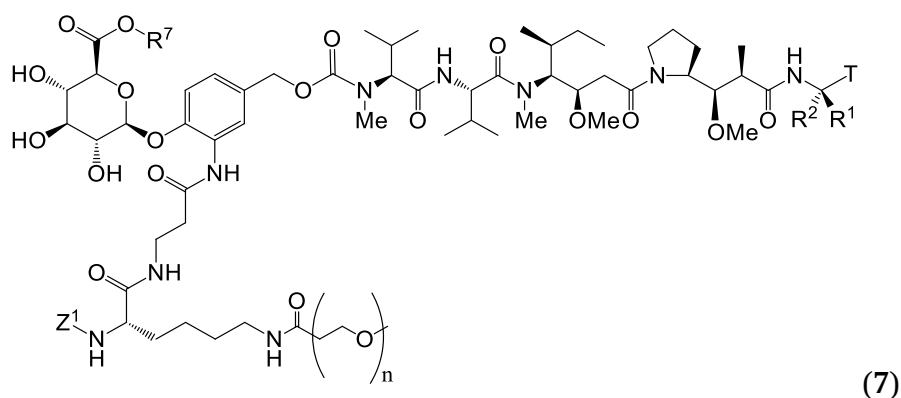
R¹ is H or C₁-C₄ alkyl;

R² is H, C₁-C₄ alkyl or –CH₂-R³;

R³ is C₆-C₁₀ aryl or C₃-C₈ heterocyclyl; and

T is selected from the group consisting of –CH(OR⁴)-R⁵ and –C(=O)-OR⁴, wherein R⁴ is H or C₁-C₄ alkyl; and R⁵ is C₆-C₁₀ aryl or C₃-C₆ heteroaryl,

wherein the Formula **IC** and Formula **ID** Drug Linker intermediate compounds, optionally in salt form, have the structures of Formula **6** and Formula **7**:



wherein

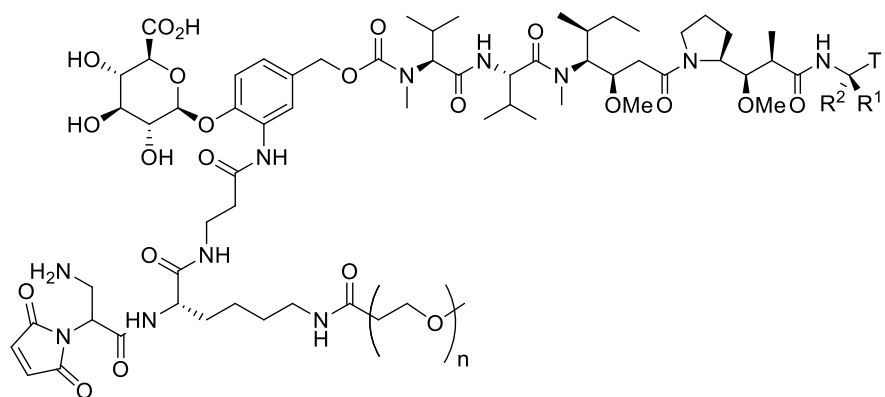
each of R^6 and R^7 is independently optionally substituted C_1 - C_8 alkyl, optionally substituted C_6 - C_{10} arylene or optionally substituted C_5 - C_{10} heteroarylene so that $R^6C(=O)-$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-OR^7$ provides an ester functional group that is a suitable carboxylic acid protecting group;

Z^1 is a first suitable amino protecting group; and the remaining variable groups are as previously defined in the claim, or

R^1 is H or methyl, R^2 is H, and T is $-\text{CH}(OR^4)-R^5$, wherein R^4 is H or methyl and R^5 is C_6 - C_{10} aryl, and the remaining variable groups are as previously defined in the claim, or

R^1 is methyl, R^2 is H, and T is $-\text{CH}(\text{OH})\text{Ph}$ and the remaining variable groups are as previously defined in the claim.

11. The method of claim **8**, wherein the Formula **II** Drug Linker compound has the structure of Formula **10**:



(10),

or a salt thereof, wherein

subscript n ranges from 2 to 24;

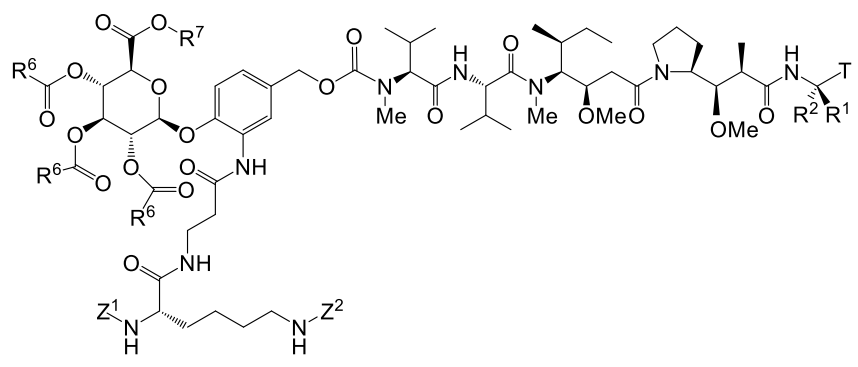
R¹ is H or C₁-C₄ alkyl;

R² is H, C₁-C₄ alkyl or -CH₂-R³;

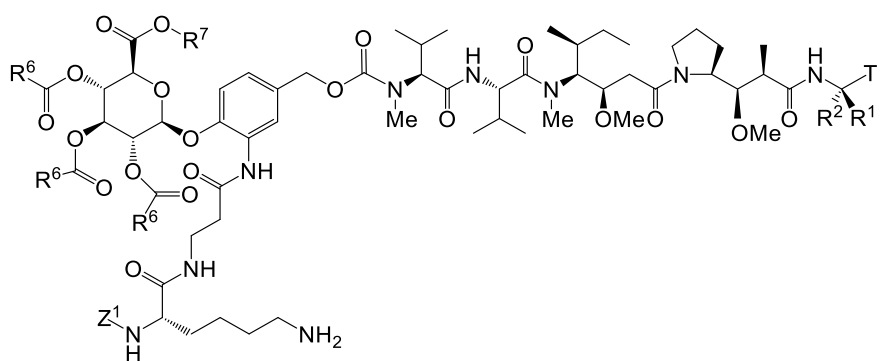
R³ is C₆-C₁₀ aryl or C₃-C₈ heterocyclyl; and

T is selected from the group consisting of -CH(OR⁴)-R⁵ and -C(=O)-OR⁴, wherein R⁴ is H or C₁-C₄ alkyl; and R⁵ is C₆-C₁₀ aryl or C₃-C₆ heteroaryl; and

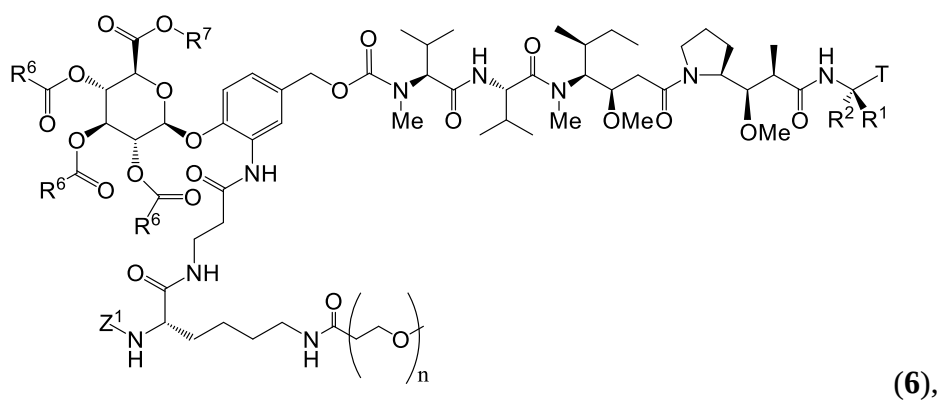
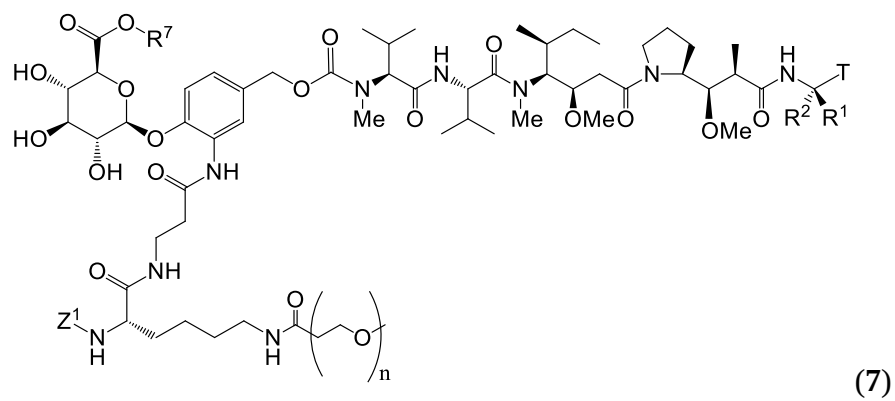
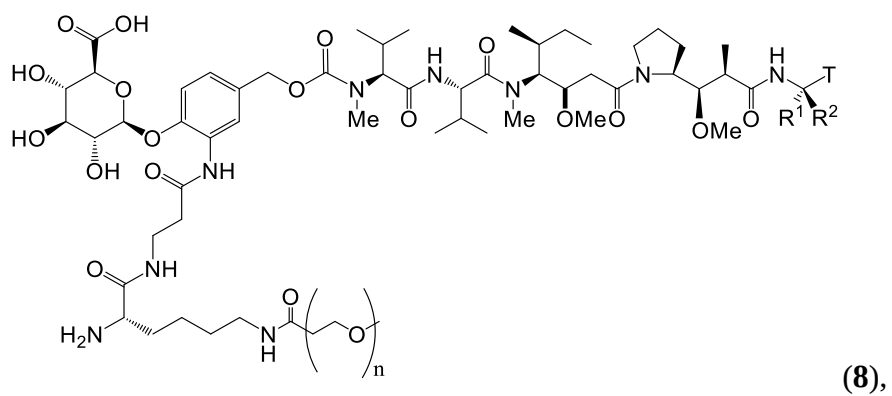
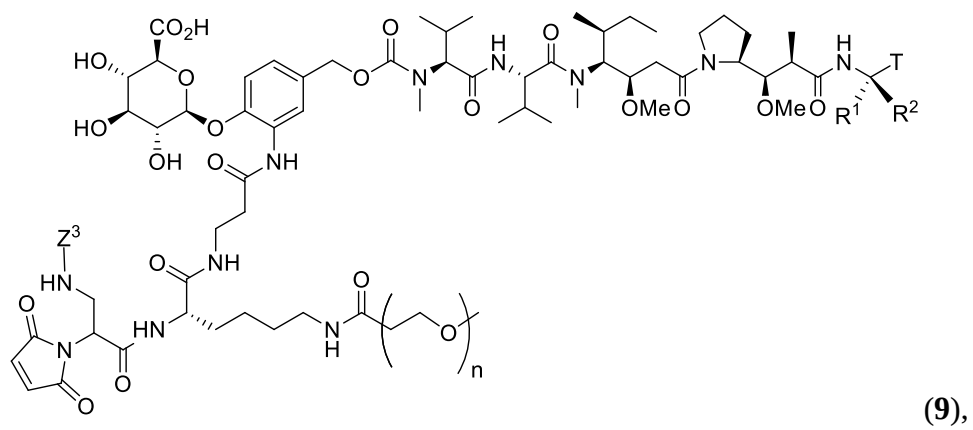
wherein the Drug Linker intermediate compounds, optionally in salt form, of Formula **IIA**, Formula **IIB**, Formula **IIC**, Formula **IID**, Formula **IIE** and Formula **IIF** have the structures of Formula **4**, Formula **5**, Formula **6**, Formula **7**, Formula **8**, and Formula **9**, respectively:



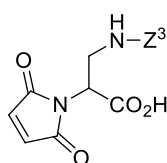
(4)



(5),



and the Formula **v** compound has the structure of:



or salt thereof, wherein

each of R⁶ and R⁷ is independently optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group and -OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group; and

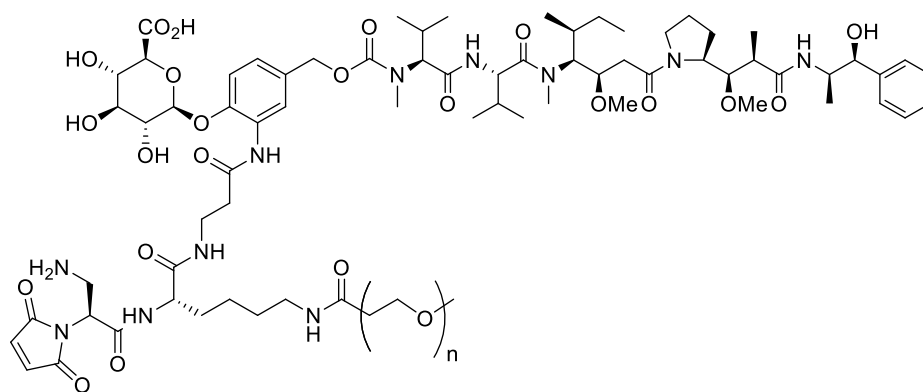
Z¹, Z² and Z³ are independently a suitable amino protecting group, or

R¹ is H or methyl, R² is H, and T is -CH(OR⁴)-R⁵, wherein R⁴ is H or methyl and R⁵ is C₆-C₁₀ aryl, and the remaining variable groups are as previously defined in the claim, or

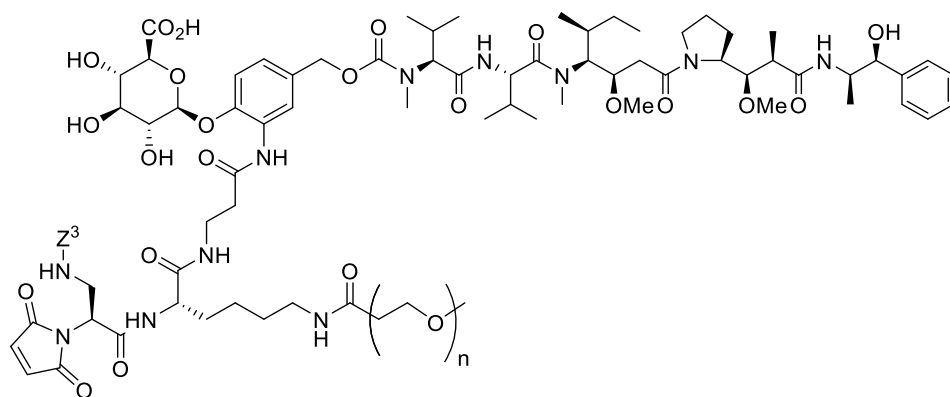
R¹ is methyl, R² is H, and T is -CH(OH)Ph, and the remaining variable groups are as previously defined in the claim.

12. The method of any one of claims **1-11**, wherein Z¹ is Fmoc, or the method of any one of claims **6-11**, wherein Z¹ is Fmoc and/or Z² is optionally substituted trityl, or Z¹ is Fmoc and Z² is 4-methoxy-trityl (MMT).

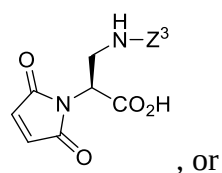
13. The method of claim **11**, wherein the Formula **10** Drug linker compound has the structure of:



the Formula **9** Drug Linker intermediate and Formula **v** compounds, or salts thereof, have structures of:

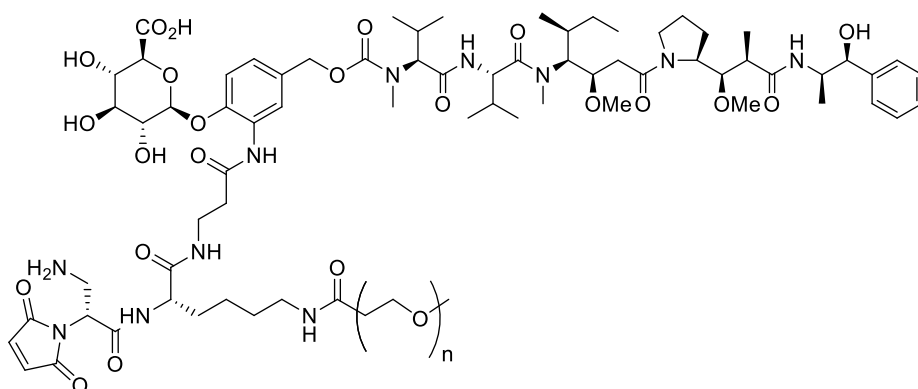


and



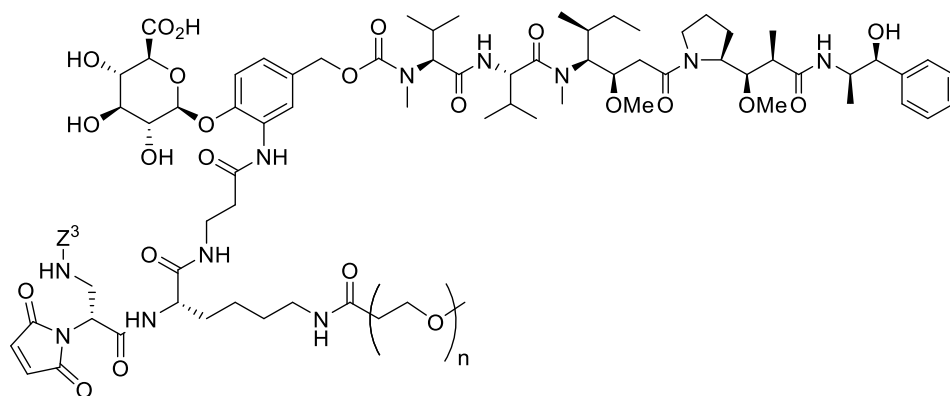
, or

the Formula **10** Drug Linker compound has the structure of:

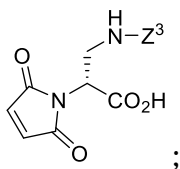


,

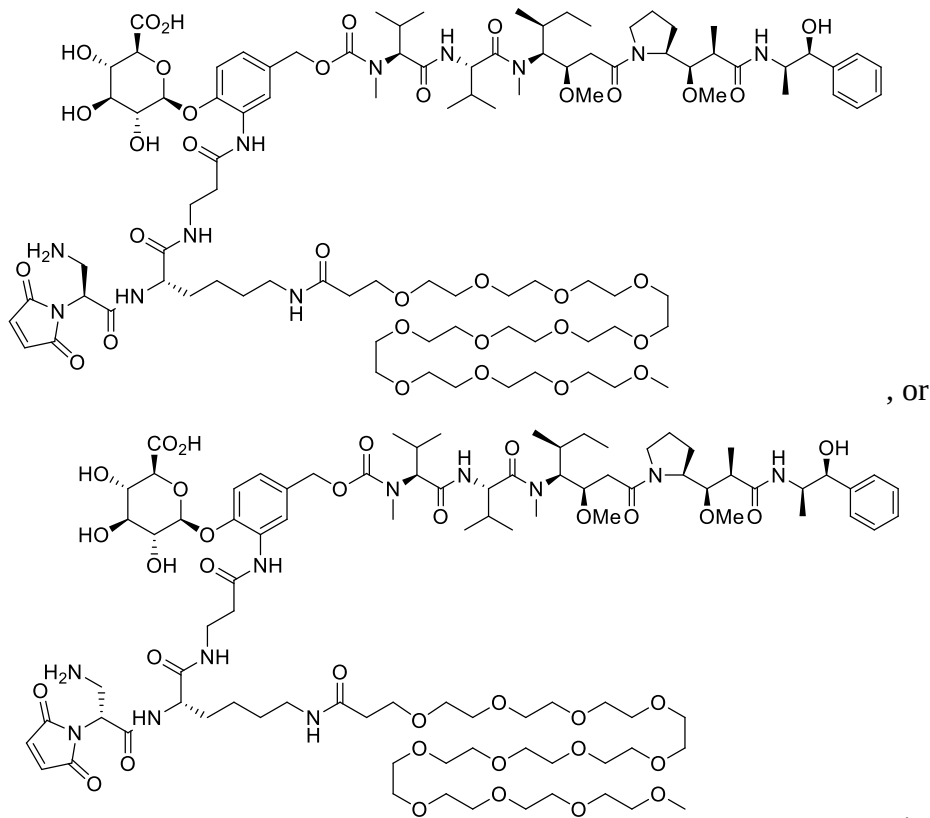
or a salt thereof, wherein the Formula **9** Drug Linker intermediate and Formula **v** compounds, optionally in salt form, have the structures of:



and



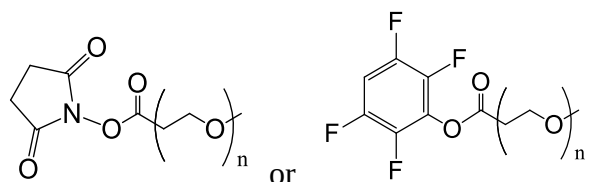
and wherein the other Drug Linker intermediate compounds of Formula **4**, Formula **5**, Formula **6**, Formula **7** and Formula **8** are those of claim **22**,
or the Formula **10** Drug Linker compound has the structure of:



14. The method of claim **13**, wherein Z^3 is $-\text{C}(=\text{O})\text{O}-t\text{-Bu}$ and/or R^6 and R^7 are independently $\text{C}_1\text{-C}_4$ alkyl, or

Z^3 is $-\text{C}(=\text{O})\text{O}-t\text{-Bu}$; and R^6 and R^7 are independently methyl or ethyl, or R^6 and R^7 are each methyl.

15. The method of any one of claims **6-14**, wherein the Formula **iv** compound has the structure of:



16. The method of any one of claims **1-14**, wherein subscript n ranges from 8 to 16, or wherein subscript n is 12.

17. The method of any one of claims **6-16**, wherein the second or third deprotecting agent for removal of Z^2 or Z^3 is an aqueous-containing acid solution having a pK_a ranging from 0-3, or

the aqueous-containing acid solution is that of or is an aqueous solution of trifluoroacetic acid or trichloroacetic acid.

18. The method of any one of claims **1-17**, wherein the Grignard reagent in a suitable alcohol-containing solvent has the formula of R^gMgX and the alkoxy magnesium halide in a suitable alcohol-containing has the formula of R^gOMgX , wherein R^g is C_1 - C_4 alkyl or phenyl; and X is I, Br, or Cl, or

the Grignard reagent in a suitable alcohol-containing solvent is $MeMgI$ or $MeMgCl$, the alkoxy magnesium halide is $MeOMgI$ or $MeOMgCl$ and the alcohol-containing solvent comprises a C_1 - C_4 alcohol, or the alcohol-containing solvent is a 1:1 (v/v) mixture of methanol and THF.

19. The method any one of claims **1-18**, wherein the first deprotecting agent for removal of Z^1 is an aqueous-containing solution of $LiOH$.

20. The method of any one of claims **6-19**, wherein the first activating agent for said Formula **iv** contacting is a solution of:

N -(3-Dimethylaminopropyl)- N' -ethylcarbodiimide hydrochloride ($EDC \cdot HCl$),

2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ),

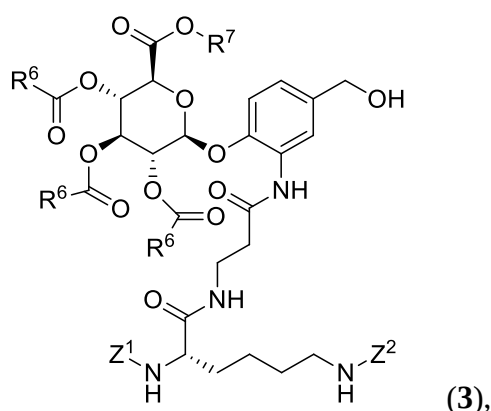
(1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU),

N -(3-Dimethylaminopropyl)- N' -ethylcarbodiimide hydrochloride/ N -Hydroxysuccinimide,

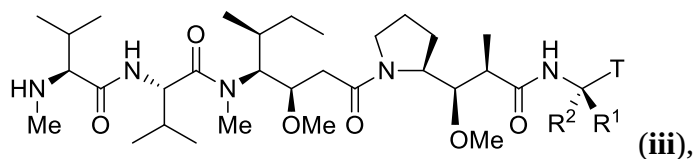
O -(7-Azabenzotriazol-1-yl)- N,N,N',N' -tetramethyluronium hexafluorophosphate

(HATU),
 Diphenyl phosphoryl azide (DPPA),
 Chloro-N,N,N',N'-bis(tetramethylene)formamidinium tetrafluoroborate,
 Fluoro-N,N,N',N'-bis(tetramethylene)formamidinium hexafluorophosphate,
 N,N'-Dicyclohexylcarbodiimide,
 N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride,
 1,1'-Carbonyldiimidazole,
 2-Chloro-1,3-dimethylimidazolidinium tetrafluoroborate,
 (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate,
 O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate,
 2-Chloro-1-methylpyridinium iodide, or
 Propylphosphonic anhydride, or
 the first activating agent for said Formula **iv** contacting is a solution of EDC·HCl, EEDQ or COMU, or a solution of COMU.

21. The method of claim **11**, wherein the Drug Linker intermediate compound of Formula **4** or salt thereof is prepared by the method comprising the step of:
 contacting a compound of Formula **3** having the structure of:



or a salt thereof, in a suitable solvent with a auristatin compound of Formula **iii** having the structure of:



in the presence of a carbamate coupling agent, or
 a solution of phosgene, trichloromethyl chloroformate (Diphosgene) and
 bis(trichloromethyl) carbonate (Triphosgene), 1,1'-Carbonyldiimidazole (CDI), or 1,1'-

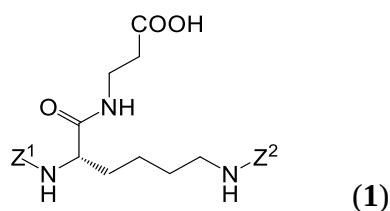
Carbonyl-di-(1,2,4-triazole) (CDT), or a solution of 1,1'-carbonyl-di-(1,2,4-triazole) (CDT),

wherein said Formula 3 contacting provides the Formula 4 Drug Linker intermediate compound or salt thereof.

22. The method of claim 21, wherein the Formula 3 compound is prepared by a method comprising the step of:

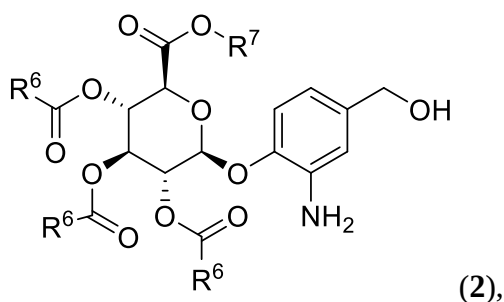
contacting a Parallel Connector Unit precursor (L_P') of Formula 1, or salt thereof, and a compound of Formula 2 in a suitable solvent in the presence of a claim 32 activating agent,

wherein the Formula 1 L_P' compound has the structure of:



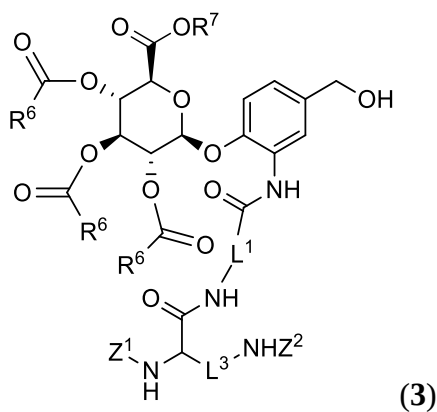
or a salt thereof, wherein each of Z^1 and Z^2 is independently a suitable amino protecting group; and

the Formula 2 compound has the structure of:



wherein said contacting provides the Formula 3 compound or salt thereof.

23. A compound of Formula 3 having the structure of:



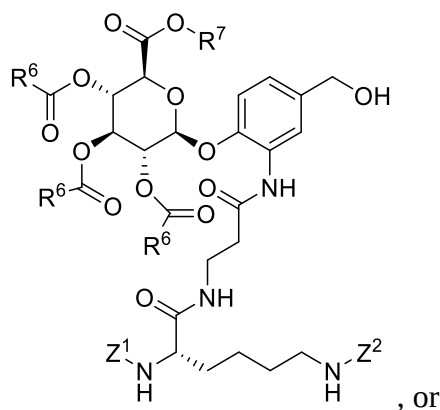
or a salt thereof, wherein

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1 - C_{20} alkylene, optionally substituted C_4 - C_{20} heteroalkylene, optionally substituted C_3 - C_8 carbocyclo, optionally substituted C_6 - C_{10} arylene, optionally substituted C_5 - C_{10} heteroarylene and optionally substituted C_3 - C_8 heterocyclo, or L^1 and L^3 independently are C_1 - C_4 alkylene;

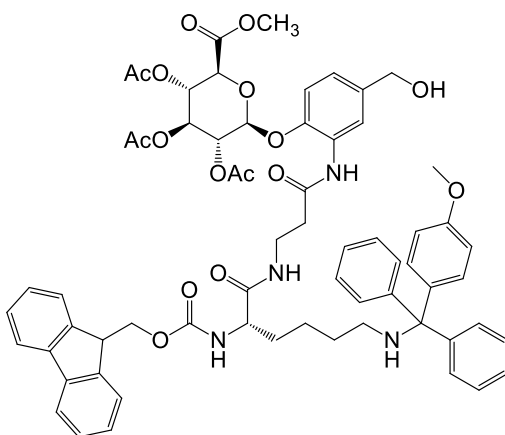
each of R^6 and R^7 is independently optionally substituted C_1 - C_8 alkyl, optionally substituted C_6 - C_{10} arylene or optionally substituted C_5 - C_{10} heteroarylene so that $R^6C(=O)-$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-OR^7$ provides an ester functional group that is a suitable carboxylic acid protecting group,

or each R^6 is C_1 - C_4 alkyl or optionally substituted phenyl and/or R^7 is methyl or ethyl or R^6 and R^7 are each methyl and the remaining variable groups are as defined in the claim; and

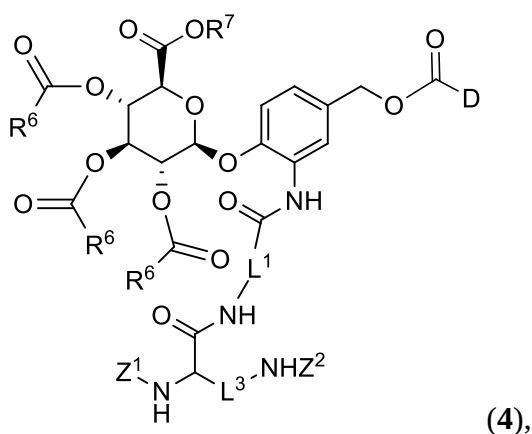
Z^1 and Z^2 independently are a first and second suitable amino protecting group, or Formula 3 has the structure of:



the Formula 3 compound has the structure of:



24. A Drug Linker intermediate compound having the structure of Formula 4 of:



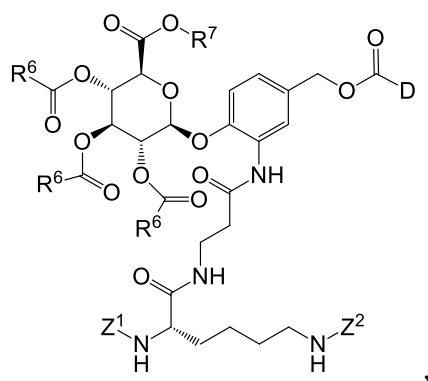
or a salt thereof, wherein

D is an auristatin Drug Unit;

L^1 and L^3 are independently selected from the group consisting of optionally substituted C_1 - C_{20} alkylene, optionally substituted C_4 - C_{20} heteroalkylene, optionally substituted C_3 - C_8 carbocyclo, optionally substituted C_6 - C_{10} arylene, optionally substituted C_5 - C_{10} heteroarylene and optionally substituted C_3 - C_8 heterocyclo;

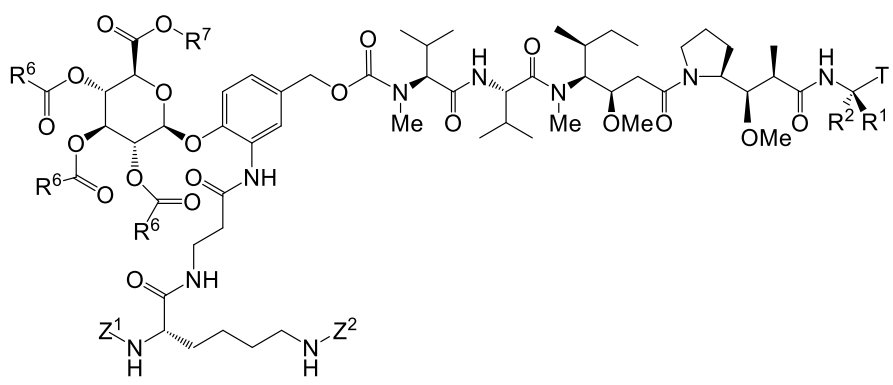
each of R^6 and R^7 is independently optionally substituted C_1 - C_8 alkyl, optionally substituted C_6 - C_{10} arylene or optionally substituted C_5 - C_{10} heteroarylene so that $R^6C(=O)-$ provides for an ester functional group that is a suitable hydroxyl protecting group and $-OR^7$ provides an ester functional group that is a suitable carboxylic acid protecting group; and

Z^1 and Z^2 independently are a first and second suitable amino protecting group, or the Formula 4 compound, or salt thereof, has the structure of:



wherein Z^2 is MMTr, or

the Formula 4 Drug Linker intermediate compound, optionally in salt form, has the structure of:



wherein

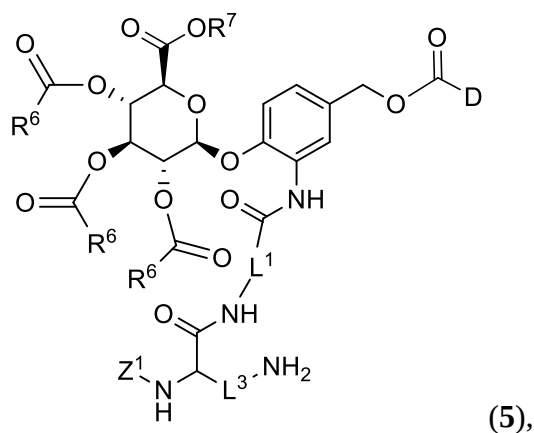
R^1 is H or C_1 - C_4 alkyl;

R^2 is H, C_1 - C_4 alkyl, or $-\text{CH}_2\text{-R}^3$;

R^3 is C_6 - C_{10} aryl or C_3 - C_8 heterocyclyl; and

T is selected from the group consisting of $-\text{CH}(\text{OR}^4)\text{-R}^5$ and $-\text{C}(=\text{O})\text{-OR}^4$, wherein R^4 is H, C_1 - C_4 alkyl and R^5 is C_6 - C_{10} aryl or C_3 - C_6 heteroaryl.

25. A Drug Linker intermediate compound, wherein the Drug Linker intermediate compound has the structure of Formula 5 of:



or a salt thereof, wherein

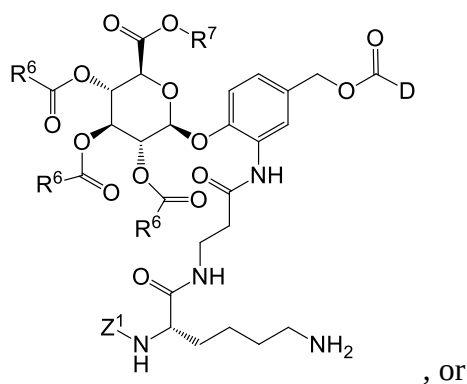
D is an auristatin Drug Unit;

L¹ and L³ are independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

each of R⁶ and R⁷ is independently optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so that R⁶C(=O)- provides for an ester functional group that is a suitable hydroxyl protecting group and – OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group; and

Z¹ is a first suitable amino protecting group,

or the Formula 5 Drug Linker intermediate compound, optionally in salt form, has the structure of:



the Formula 5 Drug Linker intermediate compound, optionally in salt form, has the structure of:



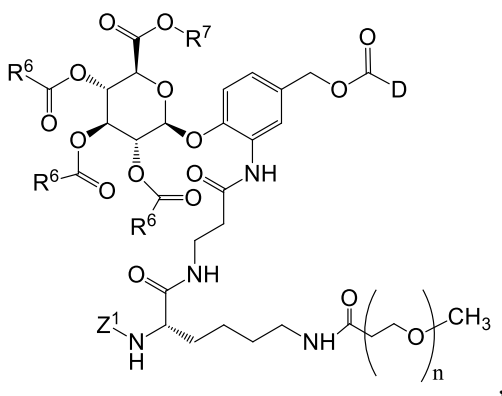
T is selected from the group consisting of $-\text{CH}(\text{OR}^4)\text{-R}^5$ and $-\text{C}(=\text{O})\text{-OR}^4$, wherein R^4 is H, $\text{C}_1\text{-C}_4$ alkyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_3\text{-C}_6$ heteroaryl.

26. A Drug Linker intermediate compound, wherein the Drug Linker intermediate compound has the structure of Formula **6** of:

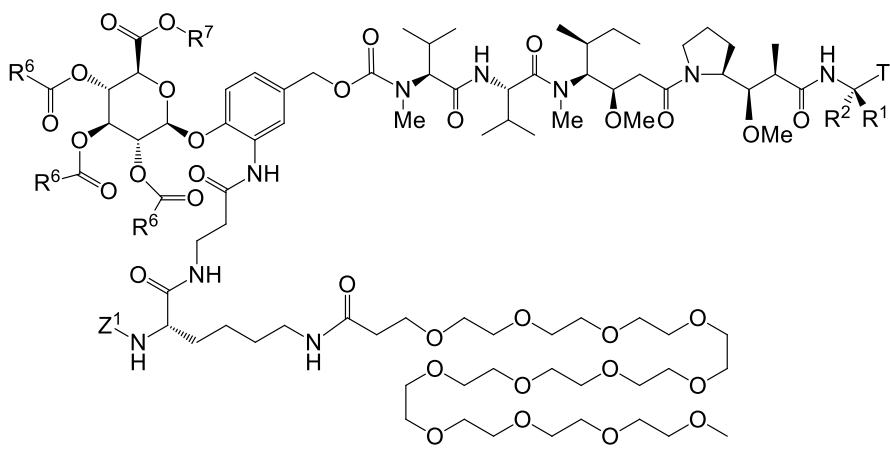


each of R⁶ and R⁷ is independently optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so that R⁶C(=O)-

provides for an ester functional group that is a suitable hydroxyl protecting group and –
OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group;
Z¹ is a first suitable amino protecting group;
R^C is a PEG Capping Unit; and
subscript n ranges from 1 to 24, or subscript n is 8 or 12, or
the Formula **6** Drug Linker intermediate compound, optionally in salt form, has the
structure of:



or the Formula 6 Drug Linker intermediate compound, optionally in salt form, has the structure of:



wherein

R¹ is H or C₁-C₄ alkyl;

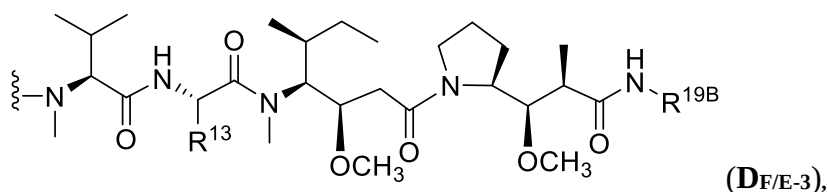
R² is H, C₁-C₄ alkyl, or -CH₂-R³;

R³ is C₆-C₁₀ aryl or C₃-C₈ heterocyclcyl; and

T is selected from the group consisting of $-\text{CH}(\text{OR}^4)-\text{R}^5$ and $-\text{C}(=\text{O})-\text{OR}^4$, wherein R^4 is H, $\text{C}_1\text{-C}_4$ alkyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_3\text{-C}_6$ heteroaryl.

27. The compound of any one of claims **24-26**, wherein the auristatin Drug Unit (D) has any one of the structures of claim **9**, or

wherein the auristatin Drug Unit (D) has the structure of Formula **D_{F/E-3}**:

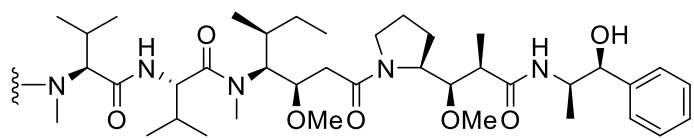


wherein

R^{13} is isopropyl or $-\text{CH}_2\text{-CH}(\text{CH}_3)_2$; and

R^{19B} is $-\text{CH}(\text{CH}_3)\text{-CH}(\text{OH})\text{Ph}$, $-\text{CH}(\text{CO}_2\text{H})\text{CH}_2\text{Ph}$, $-\text{CH}(\text{CH}_2\text{Ph})\text{-2-thiazole}$, $-\text{CH}(\text{CH}_2\text{Ph})\text{-2-pyridyl}$, $-\text{CH}(\text{CO}_2\text{Me})\text{-CH}_2\text{Ph}$, $-\text{CH}(\text{CO}_2\text{Me})\text{-CH}_2\text{CH}_2\text{SCH}_3$, $\text{CH}(\text{CH}_2\text{CH}_2\text{SCH}_3)\text{C}(=\text{O})\text{NH-3-quinolyl}$, or $-\text{CH}(\text{CH}_2\text{Ph})\text{C}(=\text{O})\text{NH-p-Cl-Ph}$, or

wherein the auristatin Drug Unit (D) has the structure of:

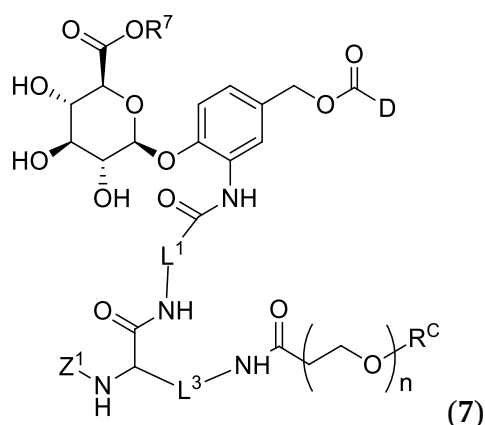


28. The Drug Linker intermediate compound of any one of claims **24-27** wherein each of R^6 and R^7 is independently $\text{C}_1\text{-C}_4$ alkyl, or each of R^6 and R^7 is methyl or each of R^6 and R^7 is ethyl.

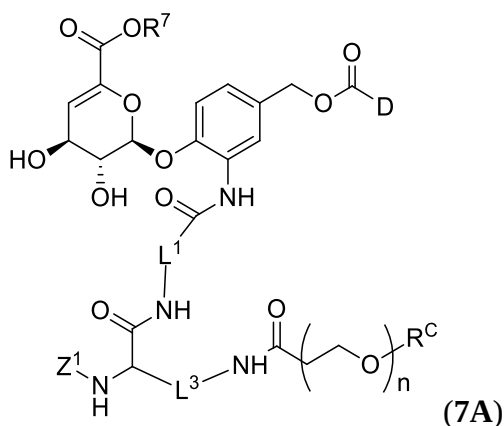
29. The Drug Linker intermediate compound of claim **24**, **25** or **26**, wherein R^1 is hydrogen or methyl; R^2 is hydrogen; and T is $-\text{CH}(\text{OR}^4)\text{-R}^5$; wherein R^4 is hydrogen or methyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl and Z^1 is Fmoc, or R^1 is methyl, R^2 is H, and T is $-\text{CH}(\text{OH})\text{-Ph}$, and Z^1 is Fmoc.

30. The Drug Linker intermediate compound of claim **24**, wherein the Formula **4** Drug Linker intermediate compound has the structure of:

33. A composition comprised of a Drug Linker intermediate compound of Formula 7 having the structure of:



or a salt thereof, and a compound of Formula 7A having the structure of:



or a salt thereof,

wherein in Formula 7 and Formula 7A:

D is an auristatin Drug Unit,

each of L¹ and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

R⁷ is optionally substituted C₁-C₈ alkyl, optionally substituted C₆-C₁₀ arylene or optionally substituted C₅-C₁₀ heteroarylene so-OR⁷ provides an ester functional group that is a suitable carboxylic acid protecting group, or R⁷ is methyl;

Z¹ is a first suitable amino protecting group;

R^C is a PEG Capping Unit; and

wherein the composition is comprised of no more than 5 wt.%, of the Formula **7A**

or the composition is comprised of:

a Drug Linker intermediate compound of Formula 7 and a compound of Formula 7A



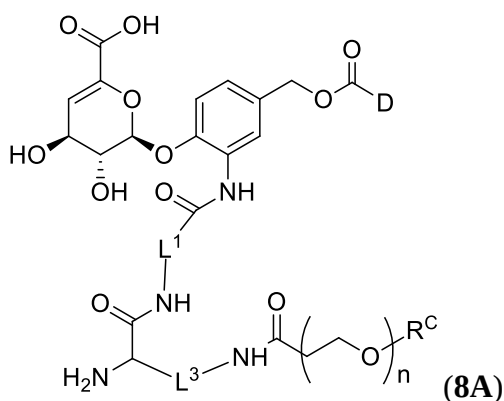
respectively, wherein Z¹ is Fmoc and subscript n is from 2 to 24, and

wherein the composition is comprised of no more than 5 wt.%, of the Formula **7A**

A composition comprised of a Drug Linker intermediate compound of Formula 8



or a salt thereof, and a compound of Formula **8A** having the structure of:



or a salt thereof,

wherein in Formula **8** and Formula **8A**:

D is an auristatin Drug Unit,

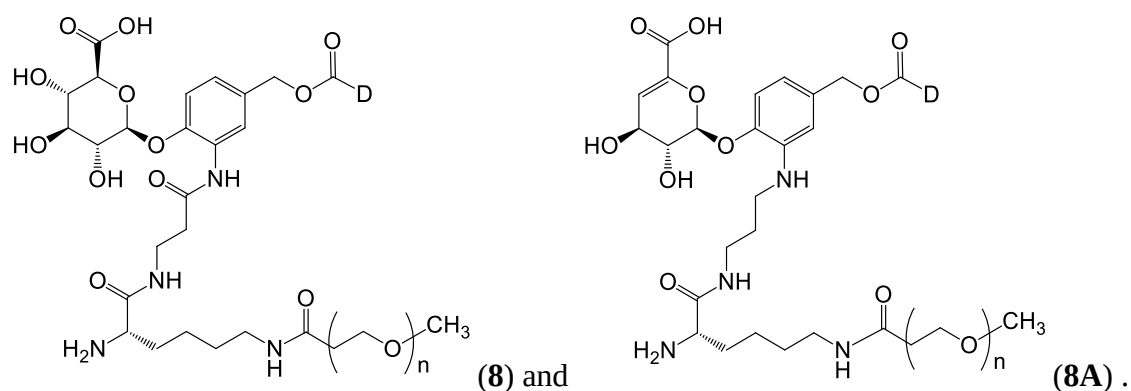
each of L¹ and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

R^C is a PEG Capping Unit; and

subscript n is from 2 to 24, and

wherein the composition is comprised of no more than about 5 wt.%, or no more than between 3 wt.% and 4 wt.%, of of the Formula **8A** compound, or

a composition comprised of a Drug Linker intermediate compound of Formula **8** and a compound of Formula **8A**, optionally in salt forms, having the structures of:

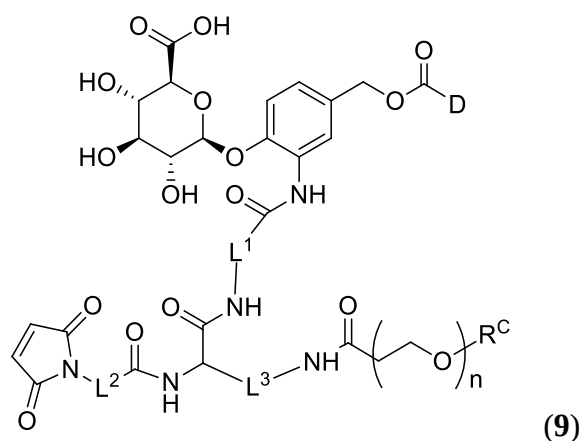


respectively, wherein

subscript n is from 2 to 24; and

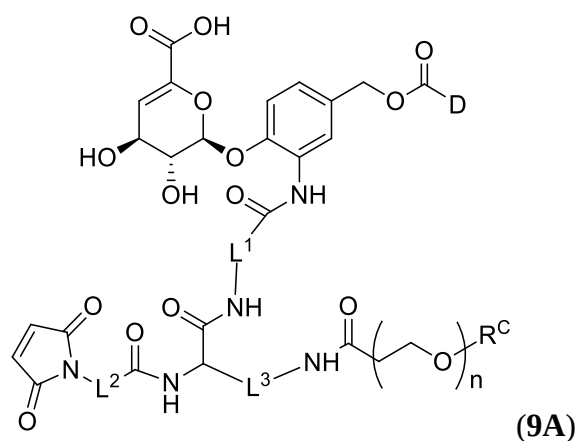
wherein the composition is comprised of no more than 5 wt.%, or no more than between 3 wt.% and 4 wt.%, of the Formula **8A** compound.

35. A composition comprised of a compound of Formula **9** having the structure of:



or a salt thereof, and

a compound of Formula **9A** having the structure of:



or a salt thereof,

wherein in Formula **9** and Formula **9A**:

D is an auristatin Drug Unit,

each of L¹, L² and L³ is independently selected from the group consisting of optionally substituted C₁-C₂₀ alkylene, optionally substituted C₄-C₂₀ heteroalkylene, optionally substituted C₃-C₈ carbocyclo, optionally substituted C₆-C₁₀ arylene, optionally substituted C₅-C₁₀ heteroarylene and optionally substituted C₃-C₈ heterocyclo;

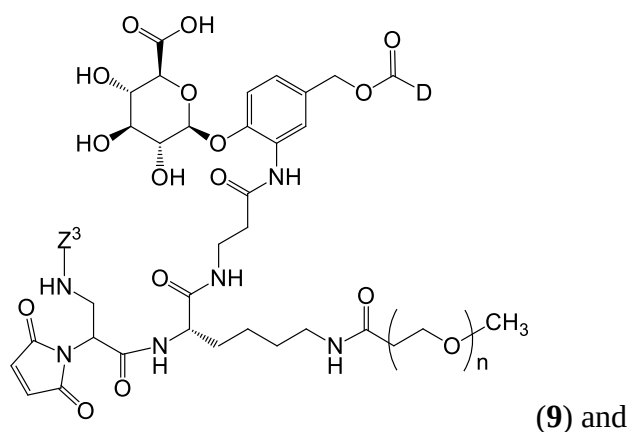
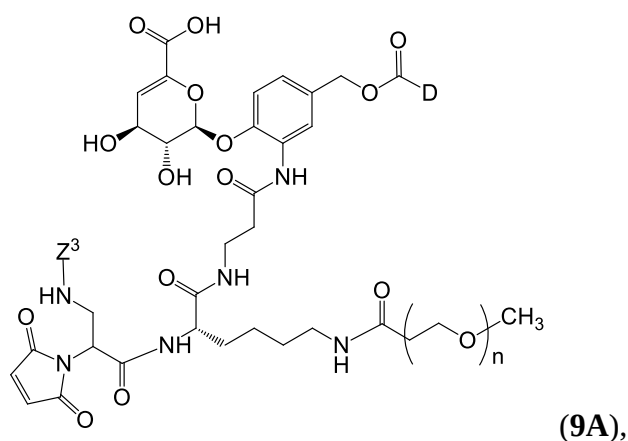
R^C is a PEG Capping Unit; and

subscript n is from 2 to 24,

wherein the composition is comprised of no more than 5 wt.% of the Formula **9A** compound

or

the composition is comprised of compound of the Formula **9** and a compound of Formula **9A**, optionally in salt forms, having the structures of:



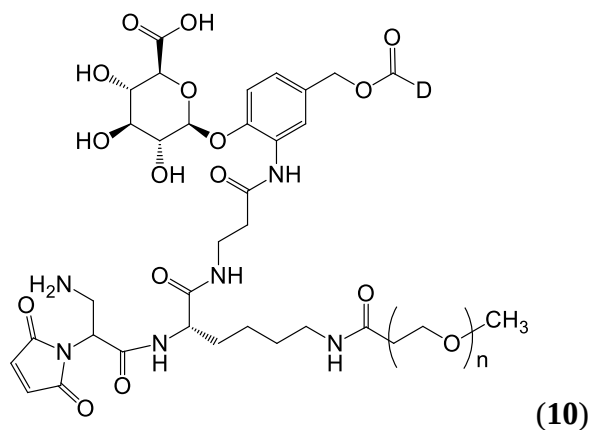
respectively, wherein

subscript n is from 2 to 24; and

Z^3 is a third amino protecting group that is acid-labile, or is of formula $-C(=O)O-R^8$, wherein R^8 is C_1 - C_4 alkyl or optionally substituted phenyl, and

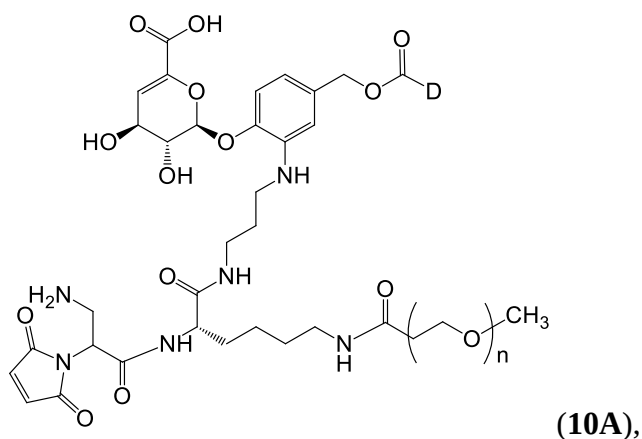
wherein the composition is comprised of no more than 5 wt.% of the Formula **9A** compound.

36. A composition comprised of Drug Linker compound of Formula **10** having the structure of:



or a salt thereof,

and a compound of Formula **10A** having the structure of:



or a salt thereof, wherein in Formula **10** and Formula **10A**:

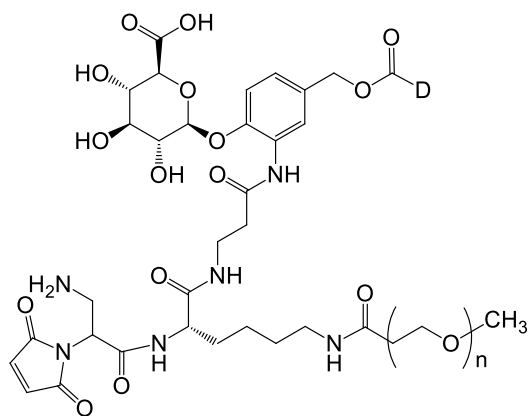
D is an auristatin Drug Unit; and

subscript n is from 2 to 24, and

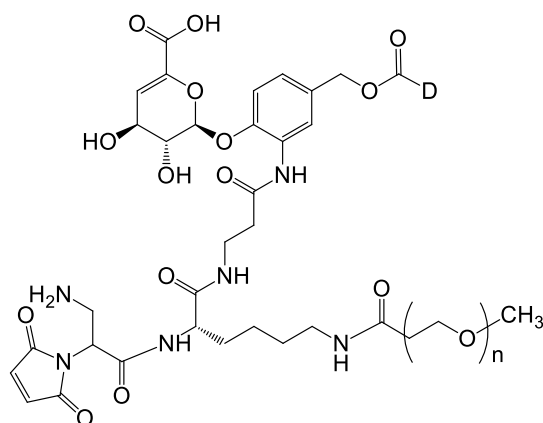
wherein the composition is comprised of no more than 5 wt.%, of the Formula **10A** compound,

or

a composition comprised of a Drug Linker compound of Formula **10** and a compound of Formula **10A**, optionally in salt forms, having the structures of:



(10) and

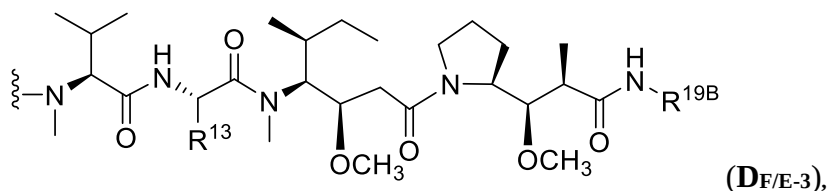


(10A)

respectively, wherein subscript n is from 2 to 24; and

wherein the composition is comprised of no more than 5 wt.%, of the Formula **10A** compound.

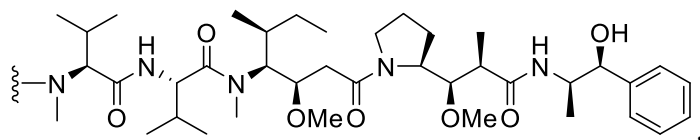
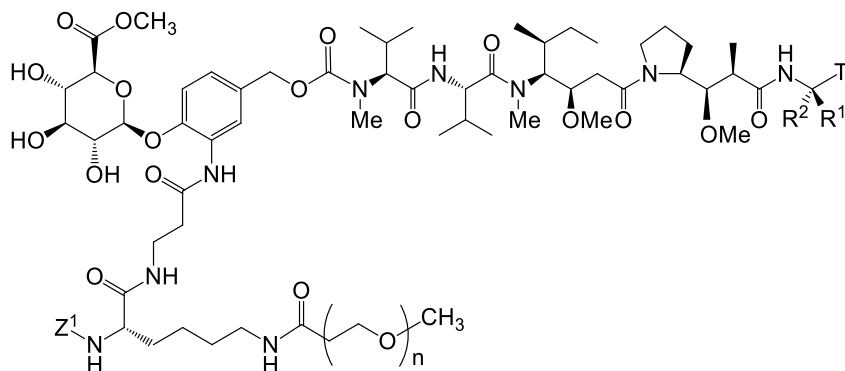
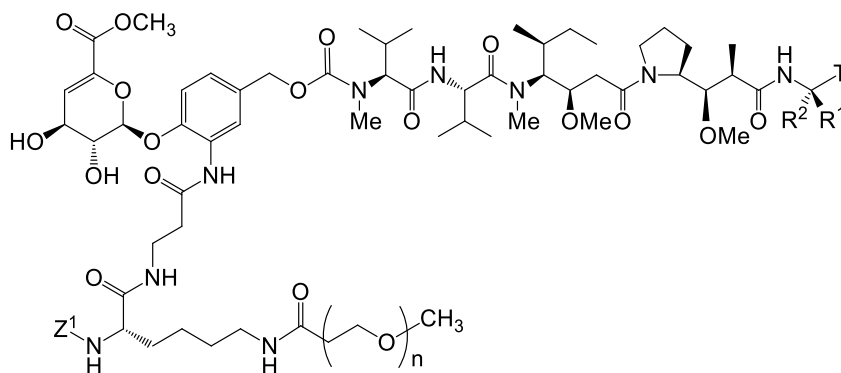
37. The composition of any one of claims **33-36**, wherein the auristatin Drug Unit (D) has any one of the structures of claim **9**, or the auristatin Drug Unit (D) has the structure of Formula **D_{F/E-3}**:



wherein

R^{13} is isopropyl or $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$; and

R^{19B} is $-\text{CH}(\text{CH}_3)-\text{CH}(\text{OH})\text{Ph}$, $-\text{CH}(\text{CO}_2\text{H})\text{CH}_2\text{Ph}$, $-\text{CH}(\text{CH}_2\text{Ph})$ -2-thiazole, $-\text{CH}(\text{CH}_2\text{Ph})$ -2-pyridyl, $-\text{CH}(\text{CO}_2\text{Me})-\text{CH}_2\text{Ph}$, $-\text{CH}(\text{CO}_2\text{Me})-\text{CH}_2\text{CH}_2\text{SCH}_3$, $\text{CH}(\text{CH}_2\text{CH}_2\text{SCH}_3)\text{C}(=\text{O})\text{NH}$ -3-quinolyl, or $-\text{CH}(\text{CH}_2\text{Ph})\text{C}(=\text{O})\text{NH}$ -p-Cl-Ph, or wherein the auristatin Drug Unit has the structure of:



Z¹ is FMOC;

R² is H, C₁-C₄ alkyl, or -CH₂-R³;

R³ is C₆-C₁₀ aryl or C₃-C₈ heterocyclcyl; and

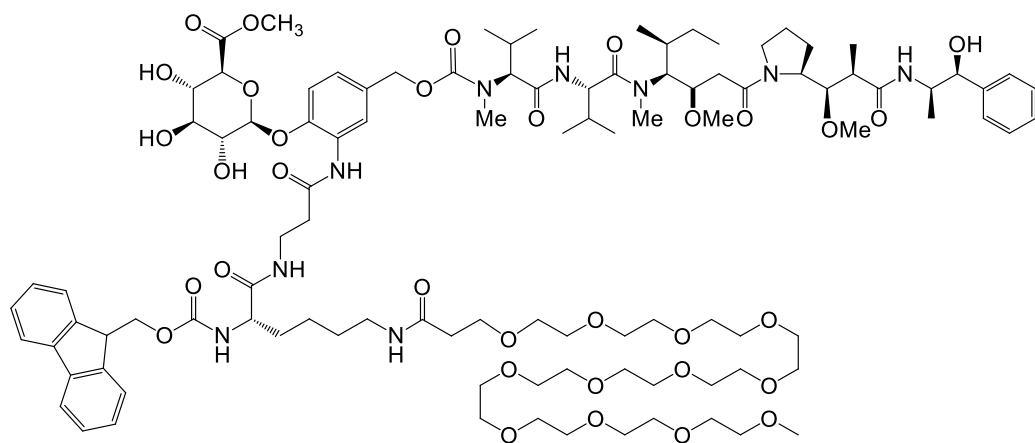
T is selected from the group consisting of $-\text{CH}(\text{OR}^4)-\text{R}^5$ and $-\text{C}(=\text{O})-\text{OR}^4$, wherein R^4 is H, $\text{C}_1\text{-C}_4$ alkyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_3\text{-C}_6$ heteroaryl, and

subscript n is from 2 to 24, or

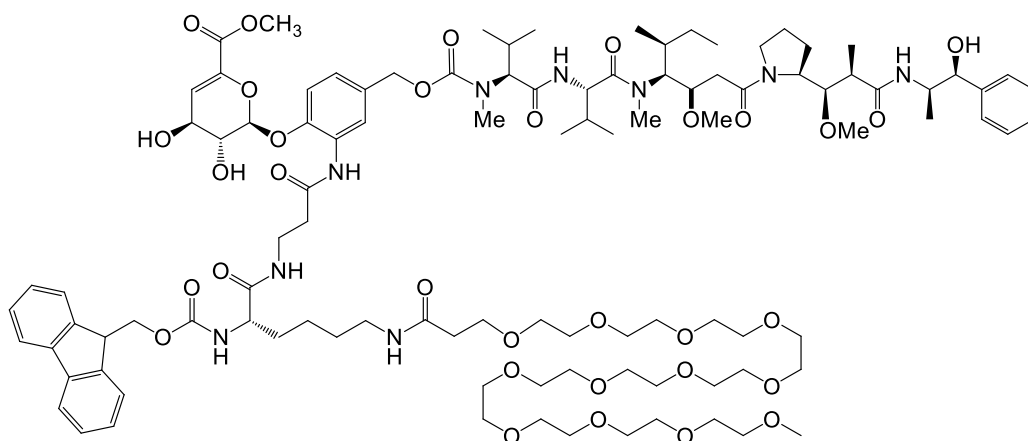
wherein in both structures R² is hydrogen; and T is—CH(OR⁴)-R⁵; wherein R⁴ is hydrogen or methyl and R⁵ is C₆-C₁₀ aryl, and the remaining variable groups are as defined in the claim, or

R² is H, and T is –CH(OH)–Ph and subscript n is 8 or 12; and the remaining variable groups are as previously defined by the claim, or

the Formula 7 Drug linker intermediate compound and the Formula 7A compound, optionally in salt forms, have the structures of:

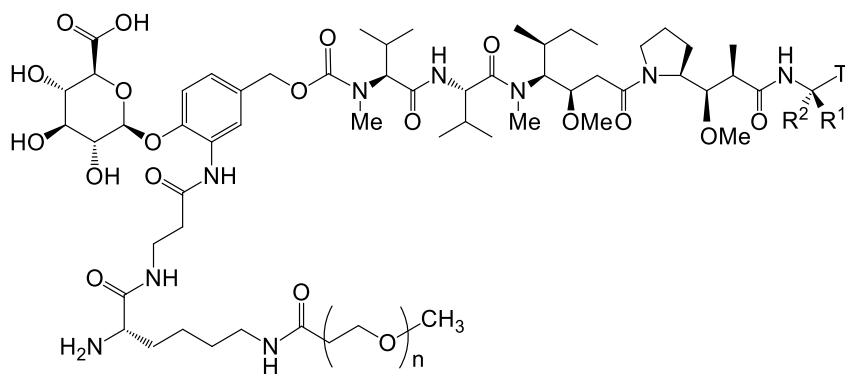


and

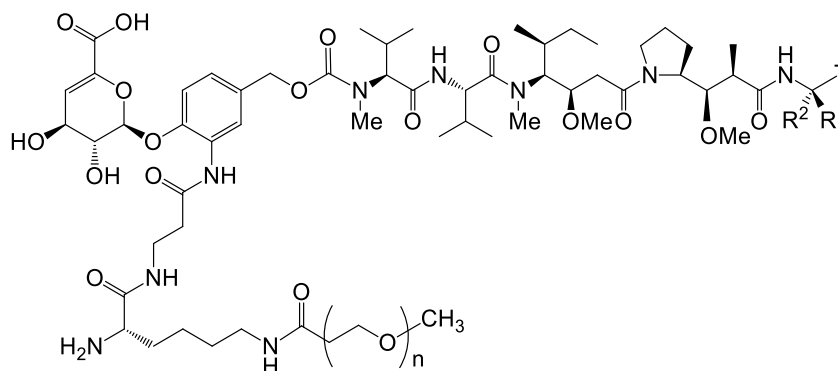


respectively.

39. The composition of claim **34**, wherein the Formula **8** Drug Linker intermediate compound and the Formula **8A** compound, optionally in salt forms, have the structures of:



and



respectively, wherein

R^1 is H or C₁-C₄ alkyl;

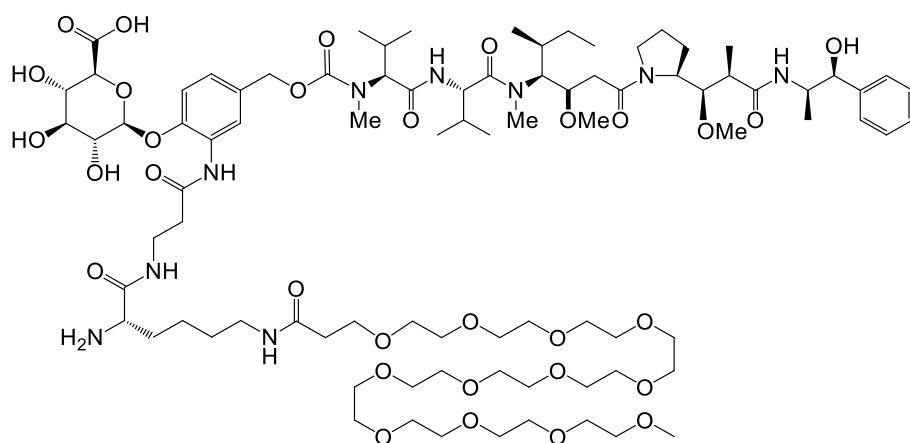
R^2 is H, C₁-C₄ alkyl, or $-\text{CH}_2\text{-R}^3$;

R^3 is C₆-C₁₀ aryl or C₃-C₈ heterocyclyl;

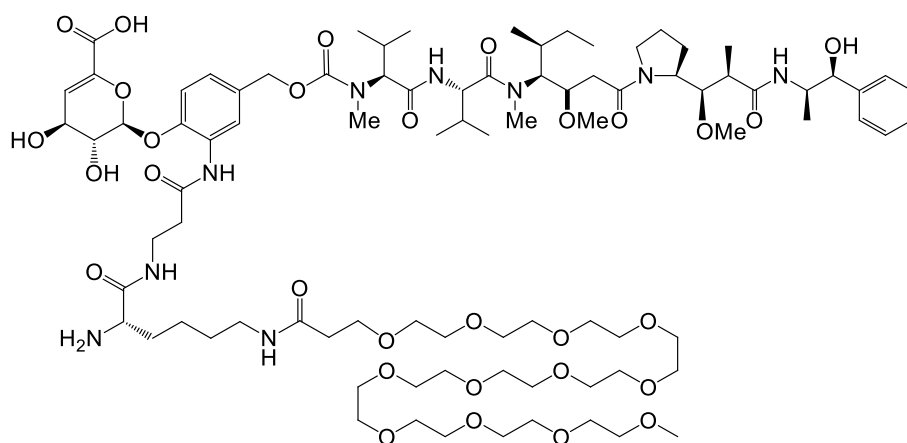
T is selected from the group consisting of $-\text{CH}(\text{OR}^4)\text{-R}^5$ and $-\text{C}(=\text{O})\text{-OR}^4$, wherein R^4 is H, C₁-C₄ alkyl and R^5 is C₆-C₁₀ aryl or C₃-C₆ heteroaryl, and subscript n ranges from 2 to 24, or

R^2 is hydrogen; and T is $-\text{CH}(\text{OR}^4)\text{-R}^5$; wherein R^4 is hydrogen or methyl and R^5 is C₆-C₁₀ aryl, or R^2 is H, and T is $-\text{CH}(\text{OH})\text{-Ph}$ and subscript n is 8 or 12, and the remaining variable groups are as defined in the claim, or

the Formula 8 Drug Linker intermediate compound and the Formula 8A compound, optionally in salt forms, have the structures of:

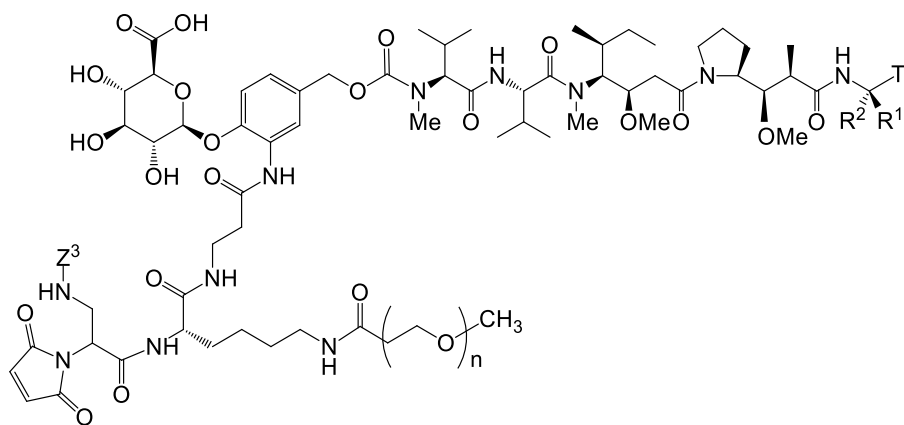


and

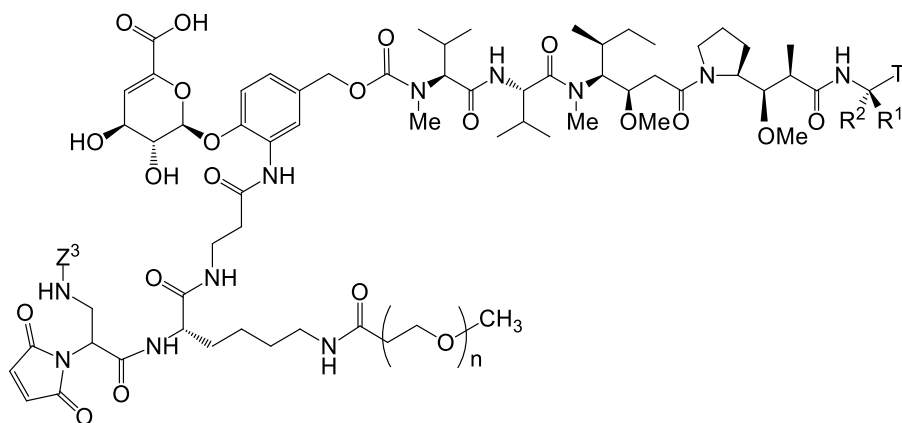


respectively.

40. The composition of claim **35**, wherein the Formula **9** and Formula **9A** compound, optionally in salt forms, have the structures of:



and



wherein in both structures:

Z^3 is $-\text{C}(=\text{O})\text{O}-t\text{-Bu}$;

R^1 is H or $\text{C}_1\text{-C}_4$ alkyl;

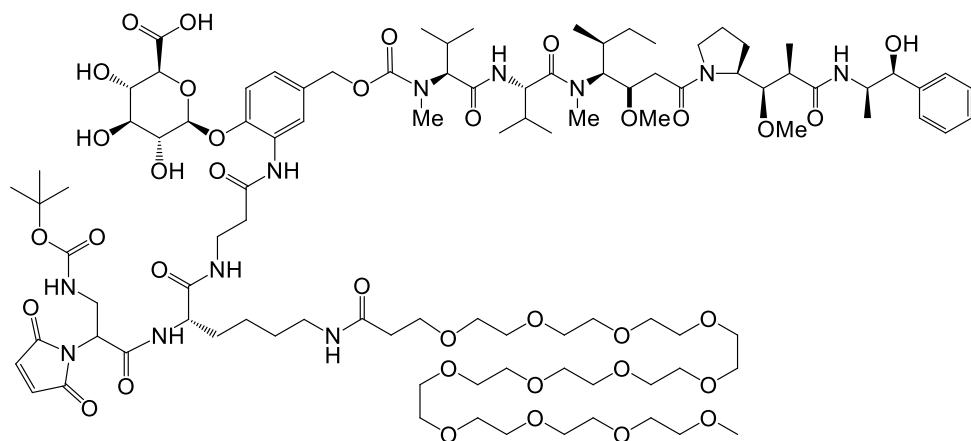
R^2 is H, $\text{C}_1\text{-C}_4$ alkyl, or $-\text{CH}_2\text{-R}^3$;

R^3 is $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_3\text{-C}_8$ heterocyclyl; and

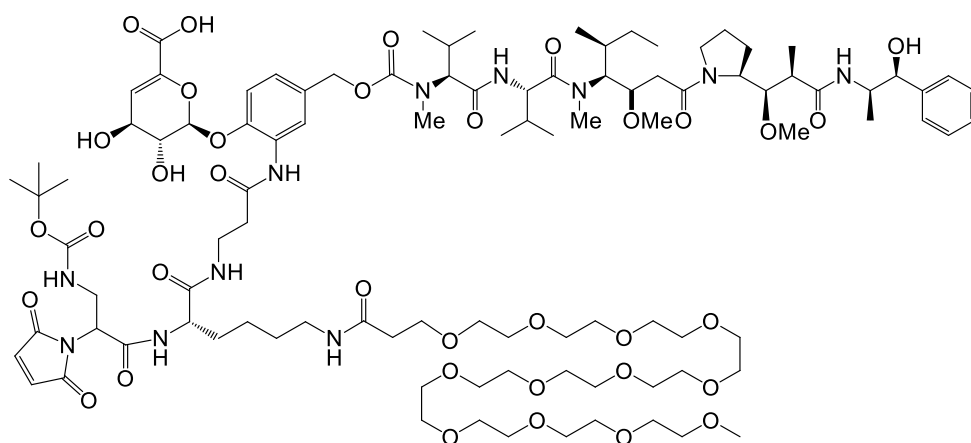
T is selected from the group consisting of $-\text{CH}(\text{OR}^4)\text{-R}^5$ and $-\text{C}(=\text{O})\text{-OR}^4$, wherein R^4 is H, $\text{C}_1\text{-C}_4$ alkyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_3\text{-C}_6$ heteroaryl, and

subscript n is from 2 to 24, or R^2 is hydrogen; and T is $-\text{CH}(\text{OR}^4)\text{-R}^5$; wherein R^4 is hydrogen or methyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl, more particularly R^2 is H, and T is $-\text{CH}(\text{OH})\text{-Ph}$, and/or subscript n is 8 or 12, and the remaining variable groups are as previously described, or

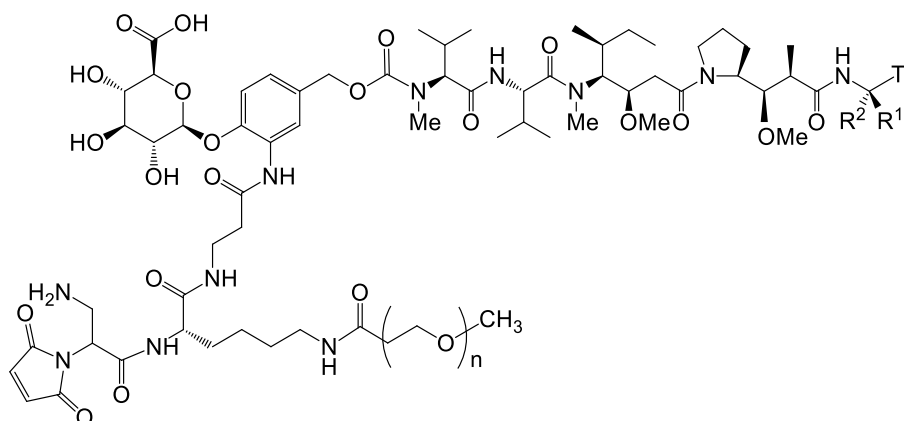
the Formula 9 Drug Linker intermediate compound and the Formula 9A compound, optionally in salt forms, have the structures of:



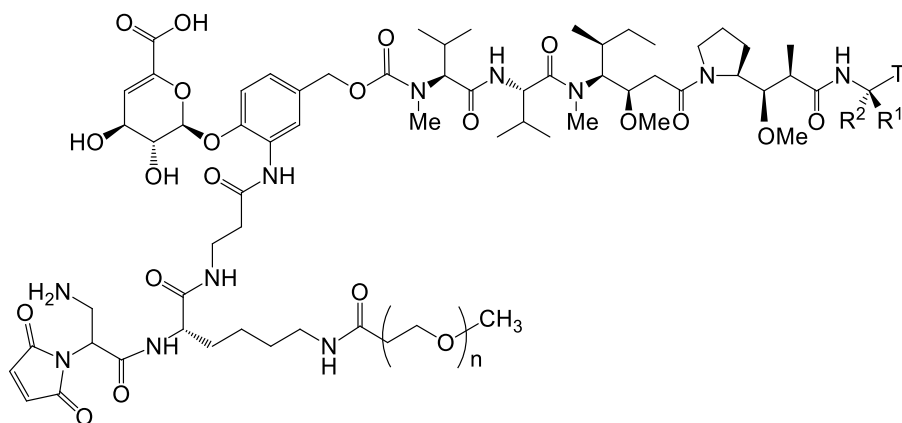
and



41. The composition of claim 36, wherein the Formula 10 Drug Linker compound and the Formula 10A compound, optionally in salt forms, have the structures of:



and



wherein

R¹ is H or C₁-C₄ alkyl;

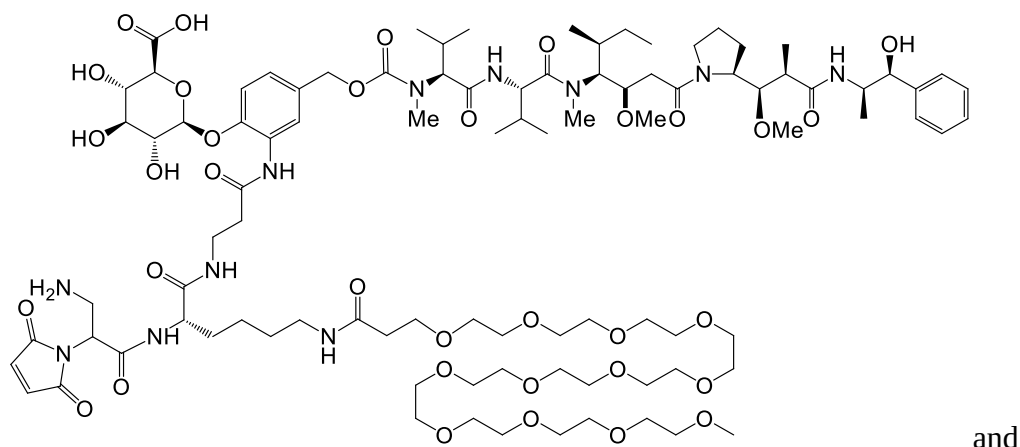
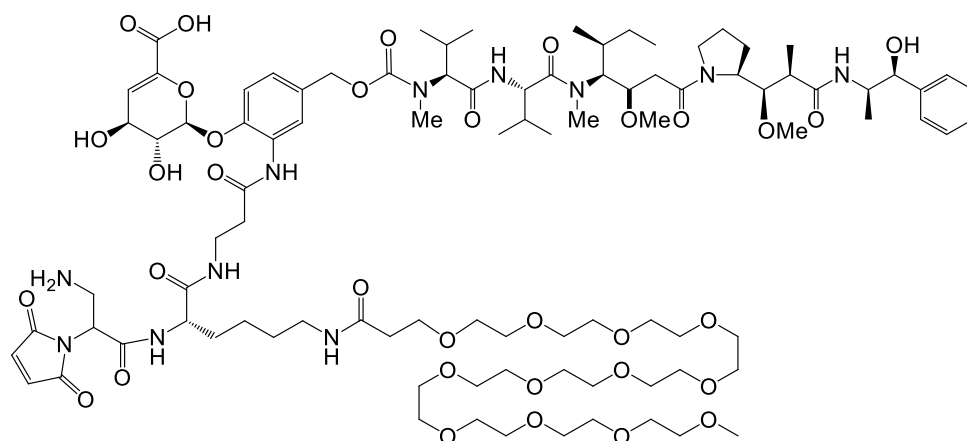
R² is H, C₁-C₄ alkyl, or -CH₂-R³;

R³ is C₆-C₁₀ aryl or C₃-C₈ heterocyclyl; and

T is selected from the group consisting of $-\text{CH}(\text{OR}^4)-\text{R}^5$ and $-\text{C}(=\text{O})-\text{OR}^4$, wherein R^4 is H, $\text{C}_1\text{-C}_4$ alkyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_3\text{-C}_6$ heteroaryl, and subscript n is from 2 to 24, or

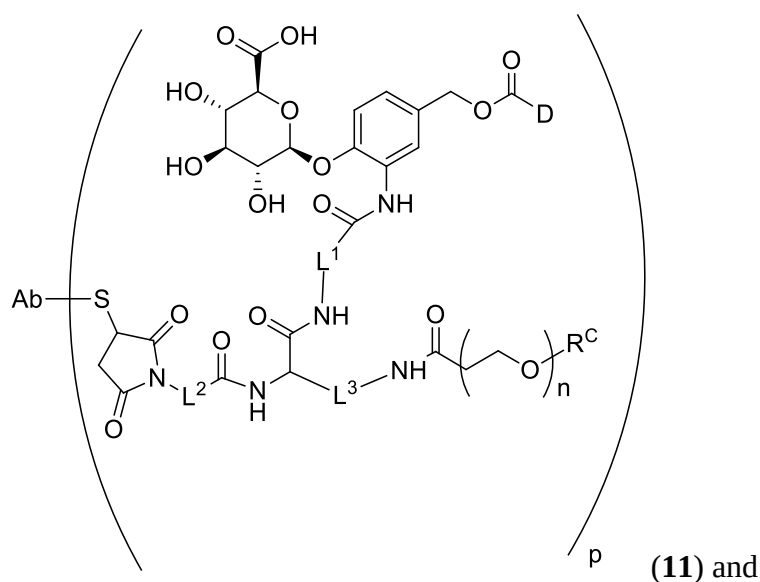
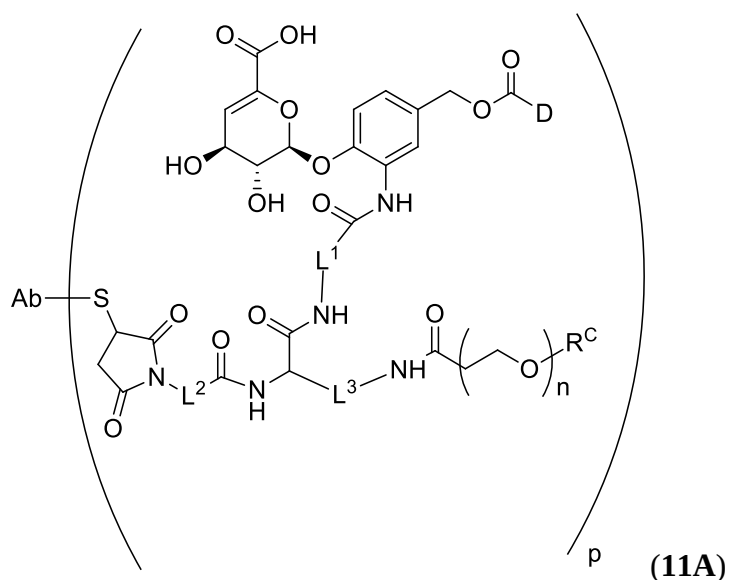
R^2 is hydrogen; and T is $-\text{CH}(\text{OR}^4)-\text{R}^5$; wherein R^4 is hydrogen or methyl and R^5 is $\text{C}_6\text{-C}_{10}$ aryl, R^2 is H, and T is $-\text{CH}(\text{OH})-\text{Ph}$ and subscript n is 8 or 12, and the remaining variable groups are as previously defined in the claim, or

the Formula **10** Drug Linker compound and the Formula **10A** compound, optionally in salt forms, have the structures of:



respectively.

42. A composition comprising Antibody Drug Conjugates represented by Formula **11** and Formula **11A** having the structures of:



or pharmaceutically acceptable salts thereof, wherein in Formula 11 and Formula 11A:

Ab is an antibody;

S is a sulfur atom from the antibody;

D is an auristatin Drug Unit;

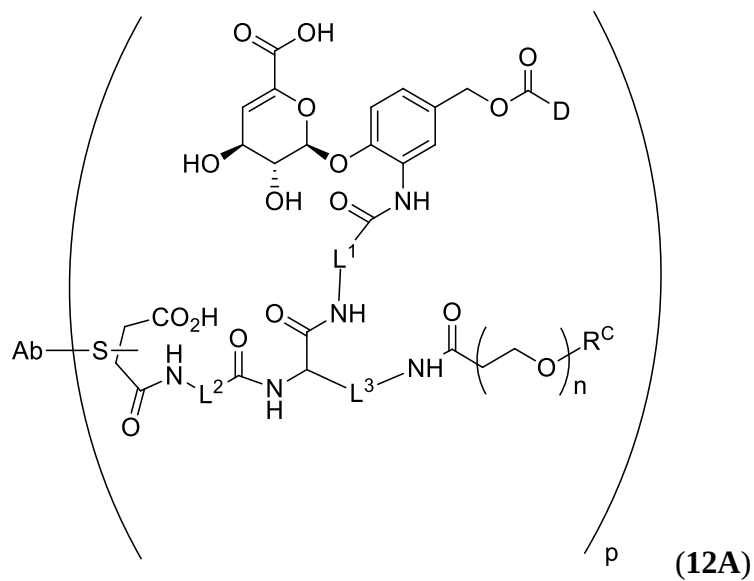
L^1 , L^2 and L^3 , independently are selected from the group consisting of optionally substituted C_1 - C_{20} alkylene, optionally substituted C_4 - C_{20} heteroalkylene, optionally substituted C_3 - C_8 carbocyclo, optionally substituted C_6 - C_{10} arylene, optionally substituted C_5 - C_{10} heteroarylene and optionally substituted C_3 - C_8 heterocyclo;

R^C is a PEG Capping Unit;

subscript n is from 2 to 24; and

wherein the composition contains no more than 5 wt.%, of Formula **11A** Antibody g Conjugate.

(12) and



S is a sulfur atom from the antibody;

the Ab-S- moiety is attached to the carbon atom α or β to the carboxylic acid functional group

D is an auristatin Drug Unit;

L^1 , L^2 and L^3 , independently are selected from the group consisting of optionally substituted C_1 - C_{20} alkylene, optionally substituted C_4 - C_{20} heteroalkylene, optionally substituted C_3 - C_8 carbocyclo, optionally substituted C_6 - C_{10} arylene, optionally substituted C_5 - C_{10} heteroarylene and optionally substituted C_3 - C_8 heterocyclo;

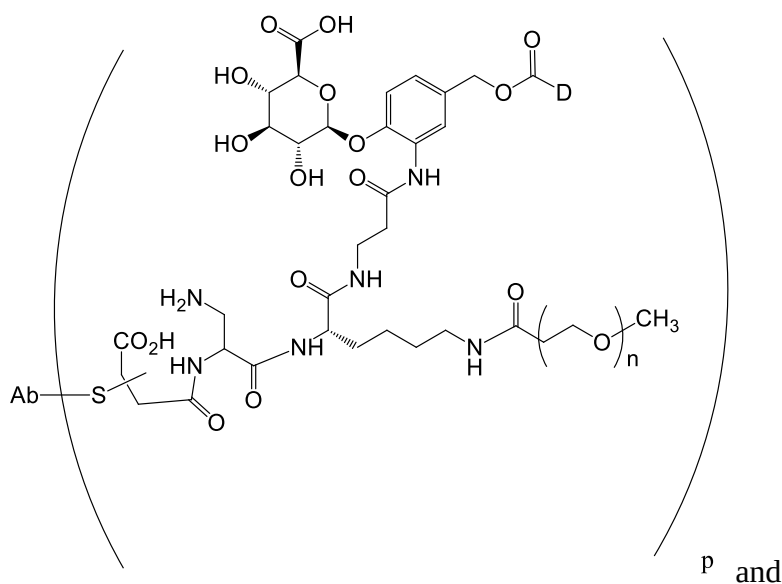
R^C is a PEG Capping Unit;

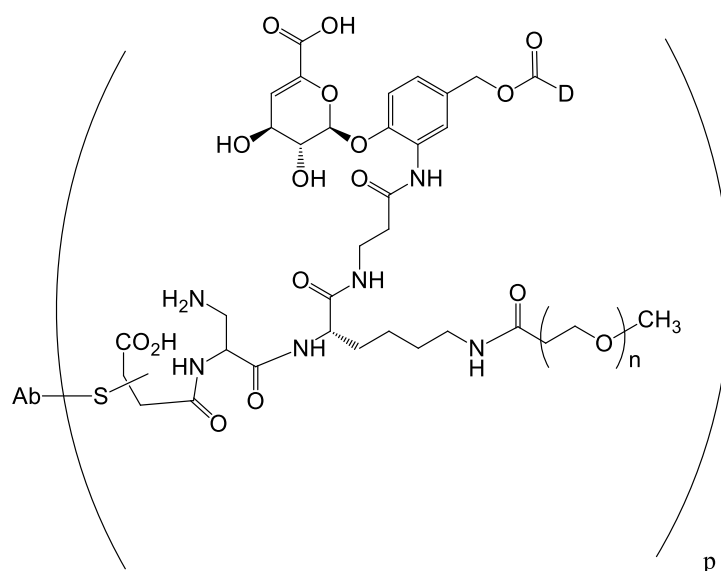
subscript n is from 2 to 24; and

subscript p is from about 1 to about 16,

wherein the composition contains no more than 5 wt.% Formula **12A** Antibody Drug Conjugate, or

the Formula **12** and Formula **12A** Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:





respectively, wherein Ab is an antibody;

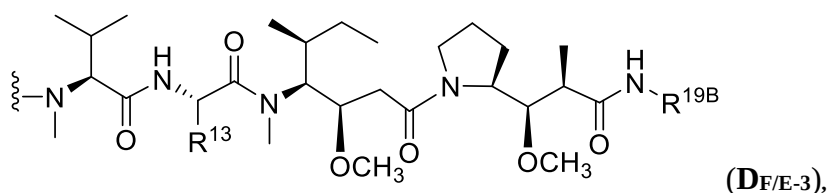
S is a sulfur atom from the antibody;

the Ab-S- moiety is attached to the carbon atom α or β to the carboxylic acid functional group; and

the remaining variable groups are as previously defined by the claim,

wherein the composition contains no more than 5 wt.% Formula **12A** Antibody Drug Conjugate.

44. The composition or compound of claim **42** or **43**, wherein the auristatin Drug Unit has the has any one of the structures of claim **9**, or wherein the auristatin Drug Unit has the structure of Formula **D_{F/E-3}**:

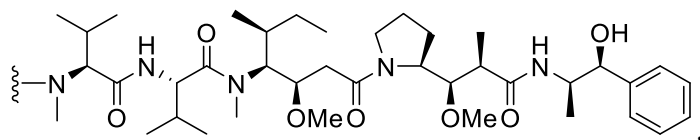


wherein

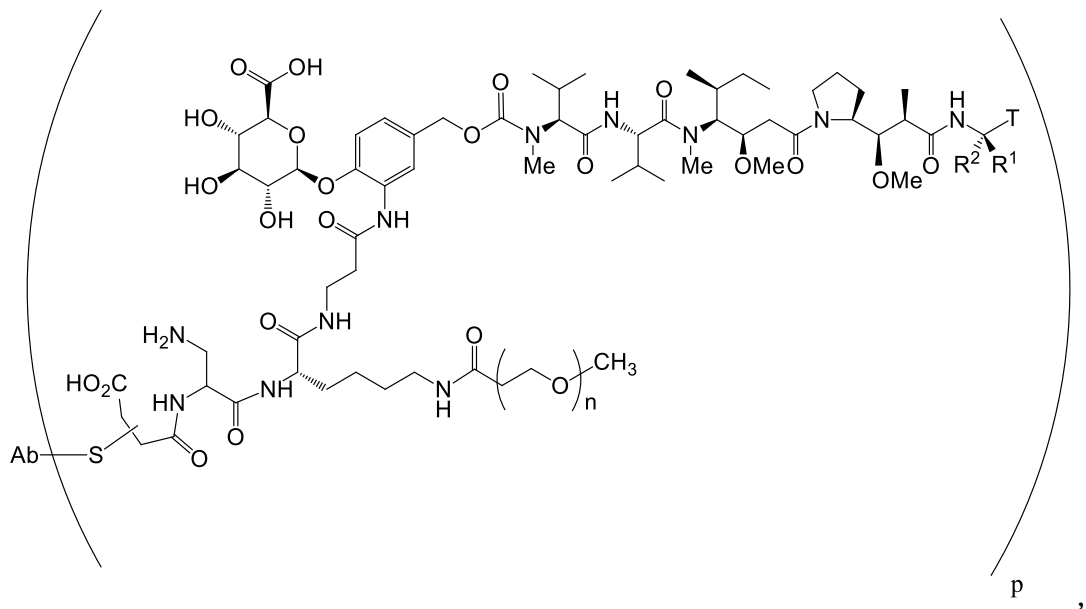
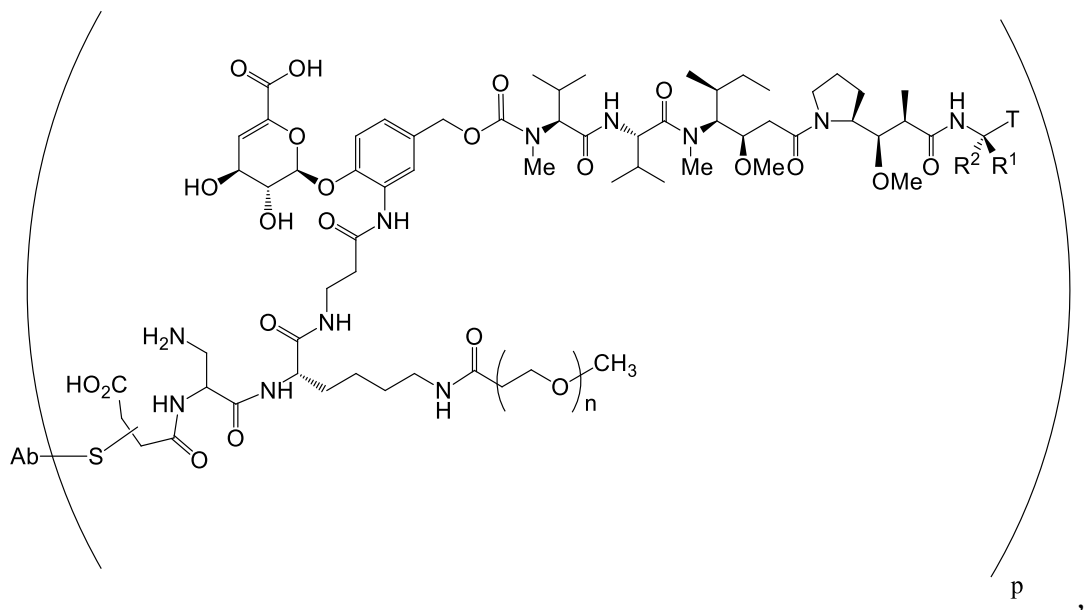
R^{13} is isopropyl or $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$; and

R^{19B} is $-\text{CH}(\text{CH}_3)-\text{CH}(\text{OH})\text{Ph}$, $-\text{CH}(\text{CO}_2\text{H})\text{CH}_2\text{Ph}$, $-\text{CH}(\text{CH}_2\text{Ph})-2\text{-thiazole}$, $-\text{CH}(\text{CH}_2\text{Ph})-2\text{-pyridyl}$, $-\text{CH}(\text{CO}_2\text{Me})-\text{CH}_2\text{Ph}$, $-\text{CH}(\text{CO}_2\text{Me})-\text{CH}_2\text{CH}_2\text{SCH}_3$, $\text{CH}(\text{CH}_2\text{CH}_2\text{SCH}_3)\text{C}(=\text{O})\text{NH}-3\text{-quinolyl}$, or $-\text{CH}(\text{CH}_2\text{Ph})\text{C}(=\text{O})\text{NH}-p\text{-Cl-Ph}$, or

wherein the auristatin Drug Unit has the structure of:

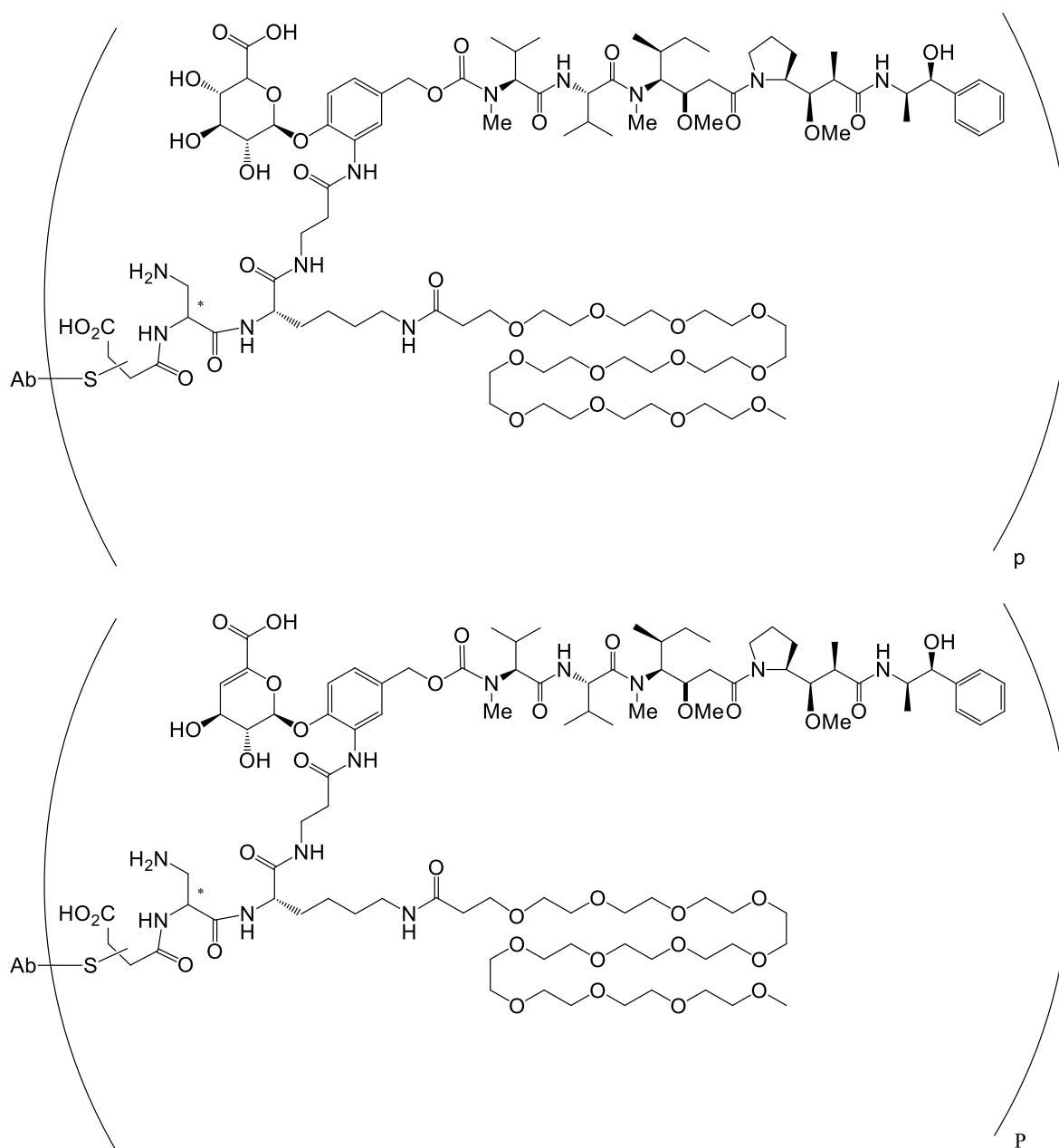


45. The composition of claim 43, wherein the Formula 12 and Formula 12A Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:



respectively, or

the Formula 12 and Formula 12A Antibody Drug Conjugates, optionally in pharmaceutically acceptable salt forms, have the structures of:



respectively, wherein the indicated carbon atom (*) is predominately in the S configuration, and subscript p is 8.

46. The composition of any one of claims **42-45**, wherein the antibody is capable of selectively binding to a tumor associated antigen.

47. The composition of claim **46**, wherein the tumor associated antigen is comprised of an extracellular domain of a cell-surface protein or glycoprotein to which the antibody is capable of binding, or

wherein the tumor associated antigen is comprised of an extracellular domain of a cell-surface glycoprotein that is capable of internalization upon binding by an Antibody Drug Conjugate compound of the composition.

48. Use of a composition of any one of claims **42-47**, in the manufacture of a medicament for the treatment of a haematological malignancy in a subject, or for treatment of a leukemia or lymphoma, or for treatment of a B-cell malignancy.