

ECTEINASCIDIN DERIVATIVE ANTIBODY DRUG CONJUGATES

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 63/480,285 filed January 17, 2023, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on January 10, 2024, is named 65657-702_601_SL.xml and is 20,721 bytes in size.

FIELD OF THE INVENTION

[0003] Provided herein are compounds, methods, and pharmaceutical compositions for use in the treatment of cancer. In certain embodiments, antibody drug conjugates that include ecteinascidin compounds are provided which display remarkable efficacy, pharmacokinetic parameters, selectivity, and safety for the treatment of, for example, cancer in a human.

BACKGROUND OF THE INVENTION

[0004] Antibody drug conjugates (ADCs) are a developing class of biopharmaceutical drugs that are designed for targeted therapy for treating cancer. In contrast to chemotherapy that lacks selectivity with respect to cancer cells, ADCs are designed to target and attack cancer cells while sparing healthy cells. ADCs accomplish selectivity by attaching a cytotoxic payload or drug to an antibody via a linker. ADCs leverage the antibody's binding selectivity to target delivery of the cytotoxic drug to an abnormal cell.

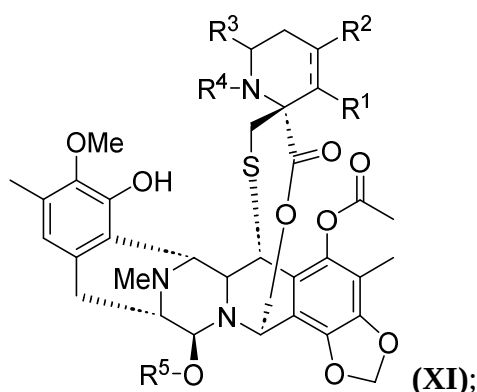
[0005] Ecteinascidins such as trabectedin and lurbinectedin are known to be cancer therapeutics. For example, lurbinectedin has been used to treat small cell lung cancer and trabectedin has been used to treat soft-tissue sarcoma and ovarian cancer. However, trabectedin and lurbinectedin are toxic even at a low concentration.

[0006] Accordingly, there is a continuing need for targeted treatments that can optimize an effective dose of ecteinascidin therapeutics.

SUMMARY

[0007] Provided herein are compounds, compositions and methods useful for treating proliferative disease in a subject.

[0008] In one example, provided herein are compounds according to Formula (XI), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



wherein:

R^1 and R^2 taken together to form an aromatic ring or bicyclic heteroaromatic ring;

wherein the aromatic ring and bicyclic heteroaromatic ring are optionally substituted with one to six substituents independently selected from the group consisting of C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, $-P(O)(OH)_2$, $-SH$, and $-SO_3H$;

R^3 is hydrogen or CH_2OR^6 ;

R^4 is H, C_{1-10} -alkyl, C_{6-10} -aryl, C_{3-10} -heterocycle, $C(O)R^8$, $C(O)OR^8$, $C(O)NHR^8$, SO_2R^8 , SO_2NHR^8 ; wherein the C_{1-10} -alkyl or C_{6-10} -aryl is optionally substituted with 1-3 substituents independently selected from the group consisting of $-OH$, $-F$, $-Cl$, $-Br$, $-C_{1-6}$ -alkyl, $-C_{3-6}$ -cycloalkyl, and $-C_{3-6}$ -heterocyclyl; or L^1

R^5 and R^6 are each independently selected from the group consisting of H, C_{1-10} -alkyl, C_{6-10} -aryl, phosphate, thiophosphate, phosphoramidate, $C(O)R^9$, $C(O)OR^9$, and $C(O)NHR^9$, SO_3H , SO_2R^9 , wherein the C_{1-10} -alkyl or C_{6-10} -aryl is optionally substituted with 1-3 substituents independently selected from the group consisting of $-OH$, $-F$, $-Cl$, $-Br$, optionally substituted $-C_{1-6}$ -alkyl, optionally substituted $-C_{3-6}$ -cycloalkyl, and optionally substituted $-C_{3-6}$ -heterocyclyl; or L^2

wherein the phosphate and thiophosphate of R^5 or R^6 are optionally substituted with one to six substituents independently, in each instance, selected from the group consisting of H, C_{1-6} -alkyl, C_{3-10} -cycloalkyl, (poly(ethylene) glycol)_y ([PEG]_y), C_{6-10} -aryl, and C_{5-10} -heteroaryl,

wherein C_{1-6} -alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, $-P(O)(OH)_2$, thiol, $-OH$, and $-SO_3H$; and

wherein the substituent on the phosphate and thiophosphate is optionally terminated with a protecting group;

wherein L^1 or L^2 is a reactive linker;

R^8 is selected from the group consisting of C_{1-6} -alkyl, C_{3-10} -cycloalkyl, $[PEG]_y$, C_{6-10} -aryl, and C_{6-10} -heteroaryl,

wherein C_{1-6} -alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, $-P(O)(OH)_2$, thiol, $-OH$, and $-SO_3H$;

R^9 is selected from the group consisting of C_{1-6} -alkyl, C_{3-10} -cycloalkyl, $[PEG]_y$, C_{6-10} -aryl, and C_{6-10} -heteroaryl,

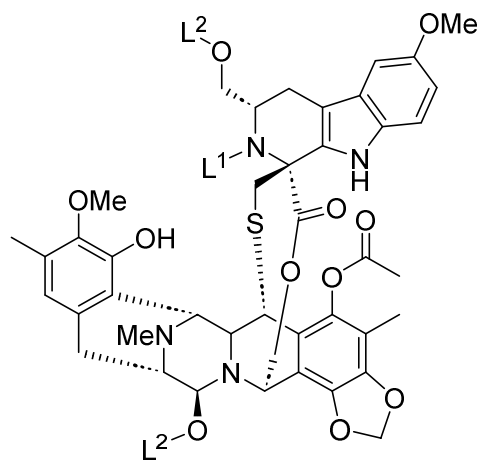
wherein C_{1-6} -alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, $-P(O)(OH)_2$, thiol, $-OH$, and $-SO_3H$;

wherein one of R^4 , R^5 , and R^6 is a linker to a reactive group R^{10} ; or is a linker to an antibody Ab;

wherein $\text{---}\text{||}$ is either a single or a double bond; and

wherein y is an integer selected from 0 to 32.

[0009] In certain examples, provided herein are compounds according to Formula (XII) or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof, comprising:



(XII);

wherein L^1 or one instance of L^2 is a reactive linker.

[0010] In certain examples, provided herein are compounds according to Formula (XIII), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof, comprising:

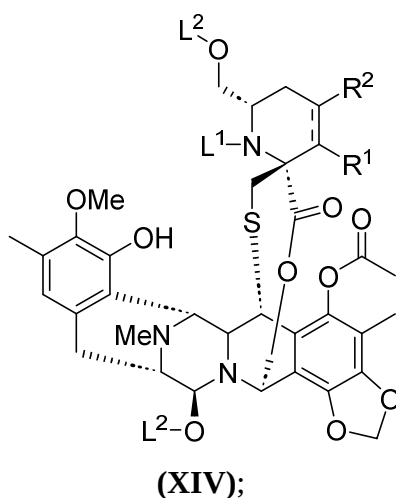
R^{11a} is selected from the group consisting of $[-NH]-(C_6H_4)-CH_2-O-$, $[-NH]-(C_6H_4)-CH_2-O-C(O)-$, $-O-(C_6H_4)-CH_2-O-C(O)-$, and $-O-(C_6H_4)-CH_2-O-$;

R^{11b} is $-(A_1)_{q-}$, wherein A_1 is an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

R^{11c} is $-(CH_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10; and

R^{11d} is selected from the group consisting of $-O-$ and $-NH-$.

[0011] In certain examples, provided herein are compounds according to Formula (XIV) or a pharmaceutically acceptable salt, ester, or tautomer thereof, comprising:



wherein R^1 and R^2 form at least one aromatic ring or bicyclic heteroaromatic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, $-P(O)(OH)_2$, thiol, and $-SO_3H$;

wherein --- is either a single or a double bond;

wherein L^1 or one instance of L^2 is a linker;

wherein L^1 is:

H;

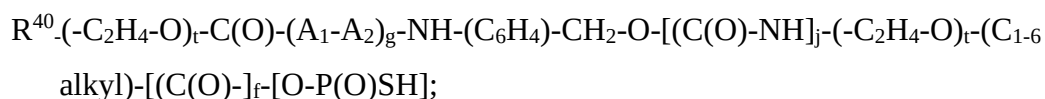
$R^{40}-(C_{1-6} \text{ alkyl})-[(C(O)-NH)]_b-(-C_2H_4-O)_c-(C_{1-6} \text{ alkyl})_e-[(C(O)-)]_f$; or

$R^{40}-(-C_2H_4-O)_c-C(O)-(A_1-A_2)_g-[-NH]_h-(C_6H_4)-CH_2-O-[(C(O)-NH)]_j-(-C_2H_4-O)_t-(C_{1-6} \text{ alkyl})-[(C(O)-)]_k$;

wherein L^2 is:

H;

$R^{40}-(C_{1-6} \text{ alkyl})-[(C(O)-NH)]_b-(-C_2H_4-O)_c-(C_{1-6} \text{ alkyl})-[(C(O)-NH)]_j-(-C_2H_4-O)_t-[O-P(O)SH]$; or



wherein one of L^1 or L^2 is not H;

wherein R^{40} is a reactive group;

wherein A_1 and A_2 are independently in each instance an amino acid;

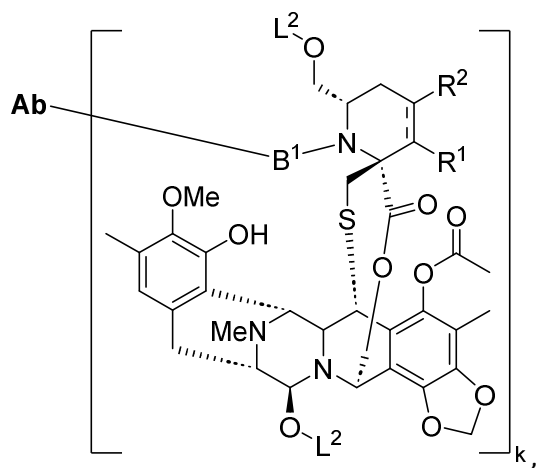
wherein subscript:

b and j are, independently in each instance, selected from 0 to 4;

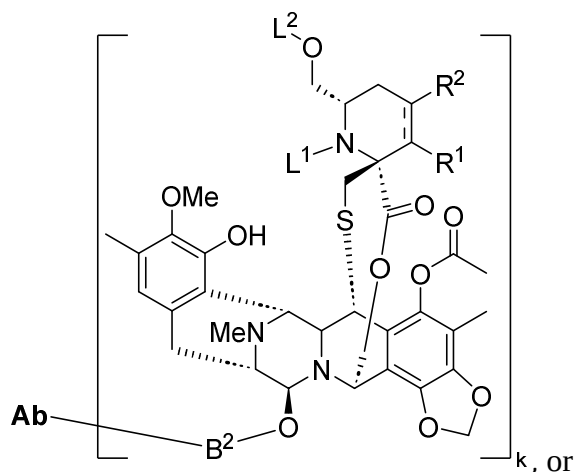
c and t are, independently in each instance, selected from 0 to 32;

e, f, g, h, and k, are, independently in each instance, 0 or 1.

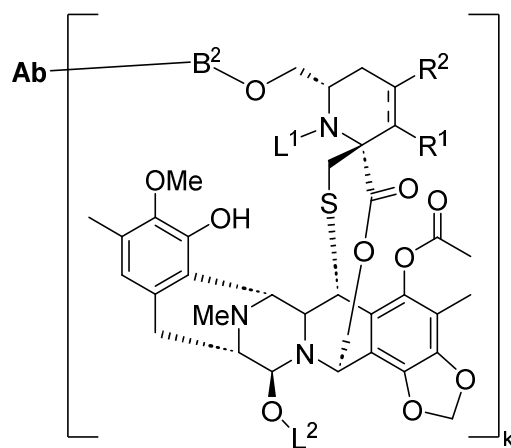
[0012] In certain examples, a compound of Formula (XVa), (XVb), or (XVc), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof, comprising:



(XVa)



(XVb)



(XVc)

wherein Ab is targeting agent;

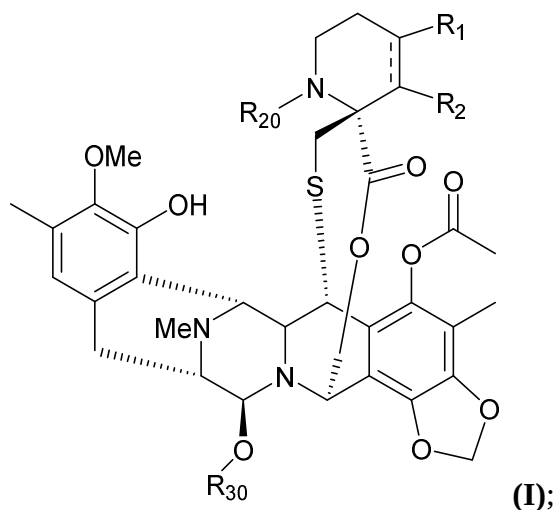
wherein subscript k is an integer from 1 to 10;

wherein R¹ and R² form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C₁₋₁₀-alkoxy, C₁₋₁₀-alkyl, amino, hydroxyl, halogen, nitro, -P(O)(OH)₂, thiol, and -SO₃H; and

wherein B¹ is a linker;

wherein B² is a linker.

[0012a] In an aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



(I);

wherein R¹ and R² form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C₁₋₁₀-alkoxy, C₁₋₁₀-alkyl, amino, hydroxyl, halogen, nitro, -P(O)(OH)₂, thiol, and -SO₃H;

wherein R²⁰ is either:

(a) selected from the group consisting of H, C₁₋₁₀-alkyl, C₆₋₁₀-aryl, C₃₋₁₀-heterocycle, C(O)R₅, C(O)OR₅, C(O)NHR₅, SO₂R₅, and SO₂NHR₅, wherein the C₁₋₁₀-alkyl and C₆₋₁₀-aryl are each, individually, substituted, or unsubstituted; or

(b) L¹, wherein L¹ is a reactive linker group;

wherein, R²⁰ is optionally substituted by 1-3 substituents, independently in each instance, selected from the group consisting of OH, F, Cl, Br, C₁₋₅-alkyl, C₃₋₆-cycloalkyl, and C₃₋₆-heterocycle;

wherein R³⁰ is either:

(c) selected from the group consisting of H, C₁₋₁₀-alkyl, C₆₋₁₀-aryl, phosphate, thiophosphate, phosphoramidate, C(O)R₆, C(O)OR₆, and C(O)NHR₆, sulfonyl, sulfonylamide, wherein the C₁₋₁₀-alkyl and C₆₋₁₀-aryl are each, individually, substituted, or unsubstituted; or

(d) L², wherein L² is a reactive linker group;

wherein the phosphate and thiophosphate are optionally substituted with one to two substituents independently, in each instance, selected from the group consisting of H, C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, (poly(ethylene) glycol)_y ([PEG]_y), C₆₋₁₀-aryl, and C₅₋₁₀-heteroaryl,

wherein C₁₋₆-alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, -P(O)(OH)₂, thiol, -OH, and -SO₃H; and

wherein the substituent on the phosphate and thiophosphate is optionally terminated with a protecting group;

wherein R⁵ and R⁶ are each, independently in each instance, selected from the group consisting of C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, [PEG]_y, C₆₋₁₀-aryl, and C₆₋₁₀-heteroaryl,

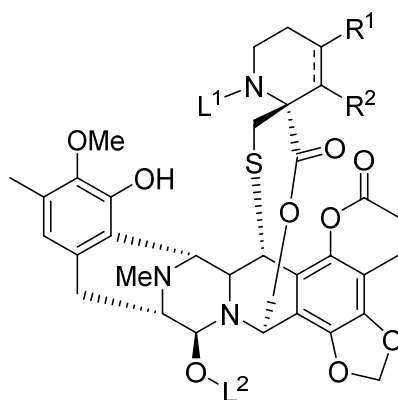
wherein C₁₋₆-alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, -P(O)(OH)₂, thiol, -OH, and -SO₃H;

wherein at least one of R²⁰ or R³⁰ is not H;

wherein $\begin{smallmatrix} | \\ | \\ | \end{smallmatrix}$ is either a single or a double bond; and

wherein subscript y is an integer selected from 0 to 32.

[0012b] In another aspect, provided herein is a compound of Formula (III), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



(III);

wherein R^1 and R^2 form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, $-P(O)(OH)_2$, thiol, and $-SO_3H$;

wherein $\text{---}\text{||}$ is either a single or a double bond;

wherein L^1 comprises at least one of the following:

- (a) $-H$, if L^2 is not H ;
- (b) $-CH_3$;
- (c) $-C_{2-8}$ -alkyl optionally substituted with at least one R^{10} ;
- (d) $-(C_{0-6}\text{-alkyl})-C_{3-10}$ -cycloalkyl optionally substituted with at least one R^{10} ;
- (e) $-(C_{0-6}\text{-alkyl})-C_{3-10}$ -heterocyclyl optionally substituted with at least one R^{10} , wherein the C_{3-10} -heterocyclyl optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;
- (f) $-(C_{0-6}\text{alkyl})$ -phenyl optionally substituted with at least one R^{10} ;
- (g) $-(C_{0-6}\text{alkyl})-C_{5-10}$ -heteroaryl optionally substituted with at least one R^{10} , wherein the C_{5-10} -heteroaryl optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

wherein R^{10} is $R^{10a}-R^{10b}$, wherein

R^{10a} is either absent or $-(CH_2)_e$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-\text{C}(\text{O})-\text{R}^{11}$;
- (ii) $-(\text{C}_2\text{H}_4-\text{O})_m-\text{R}^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-\text{NH}-\text{R}^{11}$;
- (iv) $-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (v) $-\text{C}(\text{O})-\text{NH}-\text{R}^{11}$;
- (vi) $-\text{C}(\text{O})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (vii) $-\text{C}(\text{O})-\text{NH}-\text{NH}-\text{R}^{11}$;
- (viii) $-\text{C}(\text{O})-\text{NHN}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (ix) $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{NH}-\text{R}^{11}$;
- (x) $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (xi) $-\text{CH}(\text{NH}_2)-\text{CO}-\text{R}^{11}$;
- (xii) $-\text{CH}(\text{NH}(\text{C}_{1-4}\text{-alkyl}))- \text{CO}-\text{R}^{11}$;
- (xiii) $-\text{CH}(\text{N}(\text{C}_{1-4}\text{-alkyl})_2)-\text{CO}-\text{R}^{11}$;
- (xiv) $-\text{CH}(\text{CO}-\text{R}^{11})-\text{NH}-\text{R}^{11}$;
- (xv) $-\text{CH}(\text{CO}-\text{R}^{11})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

R^{11a} is selected from the group consisting of $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$, $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, and $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$;

R^{11b} is $-(\text{A}_1)_{q-}$ or $-(\text{A}_1-\text{A}_2)_{q-}$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

R^{11c} is $-(\text{CH}_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10; and

R^{11d} is selected from the group consisting of $-\text{O}-$ and $-\text{NH}-$;

wherein L^2 comprises at least one of the following:

- (a) $-\text{H}$, if L^1 is not H ;
- (b) $-\text{PO}_3\text{H}-$;
- (c) $-\text{PO}_2\text{SH}-$;
- (d) $-\text{CH}_3$;
- (e) $-\text{C}_{2-8}\text{-alkyl}$ optionally substituted with at least one R^{10} ;
- (f) $-(\text{C}_{0-6}\text{-alkyl})-\text{C}_{3-10}\text{-cycloalkyl}$ optionally substituted with at least one R^{10} ;

- (g) $-(C_{0-6}\text{-alkyl})-C_{3-10}\text{-heterocyclyl}$ optionally substituted with at least one R^{10} , wherein the $C_{3-10}\text{-heterocyclyl}$ optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;
- (h) $-(C_{0-6}\text{alkyl})\text{-phenyl}$ optionally substituted with at least one R^{10} ;
- (j) $-(C_{0-6}\text{alkyl})-C_{5-10}\text{-heteroaryl}$ optionally substituted with at least one R^{10} , wherein the $C_{5-10}\text{-heteroaryl}$ optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

wherein R^{10} is $R^{10a}-R^{10b}$, wherein

R^{10a} is either absent or $-(CH_2)_e-$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-C(O)-R^{11}$;
- (ii) $-(C_2H_4-O)_m-R^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-NH-R^{11}$;
- (iv) $-N(C_{1-4}\text{-alkyl})-R^{11}$;
- (v) $-C(O)-NH-R^{11}$;
- (vi) $-C(O)-N(C_{1-4}\text{-alkyl})-R^{11}$;
- (vii) $-C(O)-NHNH-R^{11}$;
- (viii) $-C(O)-NHN(C_{1-4}\text{-alkyl})-R^{11}$;
- (ix) $-C(O)-N(C_{1-4}\text{-alkyl})NH-R^{11}$;
- (x) $-C(O)-N(C_{1-4}\text{-alkyl})N(C_{1-4}\text{alkyl})-R^{11}$;
- (xi) $-CH(NH_2)CO-R^{11}$;
- (xii) $-CH(NH(C_{1-4}\text{-alkyl}))CO-R^{11}$;
- (xiii) $-CH(N(C_{1-4}\text{-alkyl})_2)CO-R^{11}$;
- (xiv) $-CH(CO-R^{11})NH-R^{11}$;
- (xv) $-CH(CO-R^{11})N(C_{1-4}\text{-alkyl})-R^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

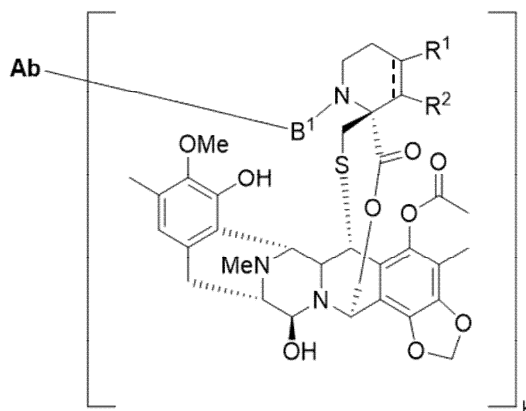
R^{11a} is selected from the group consisting of $[-NH]-(C_6H_4)-CH_2-O-$, $[-NH]-(C_6H_4)-CH_2-O-C(O)-$, $-O-(C_6H_4)-CH_2-O-C(O)-$, and $-O-(C_6H_4)-CH_2-O-$;

R^{11b} is $-(A_1)_q-$ or $-(A_1-A_2)_q-$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

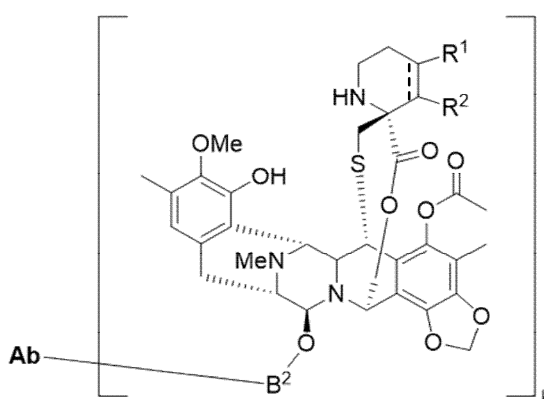
R^{11c} is $-(CH_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10; and

R^{11d} is selected from the group consisting of $-O-$ and $-NH-$.

[0012c] In another aspect, provided herein is a compound of Formula (Va) or (Vb), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



(Va)



(Vb)

wherein Ab is targeting agent, preferably an antibody, antibody fragment, protein, or peptide;

wherein subscript k is an integer from 1 to 10;

wherein R^1 and R^2 form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, $-P(O)(OH)_2$, thiol, and $-SO_3H$; and

wherein B^1 is a linker;

wherein B^2 is a linker.

[0012d] In another aspect, provided herein is a pharmaceutical composition comprising the compound as described herein and a pharmaceutically acceptable excipient.

[0013] One example provides a pharmaceutical composition comprising the compound of Formula (XI), (XII), (XIII), (XIV), (XVa), (XVb), (XVc), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable excipient.

[0014] One example provides a method of treating a disease or condition comprising administering the compound of Formula (XI), (XII), (XIII), (XIV), (XVa), (XVb), (XVc), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof.

[0014a] In another aspect, provided herein is a compound as described herein or the pharmaceutical composition as described herein for use in treating a disease or condition.

BRIEF DESCRIPTION OF THE DRAWINGS

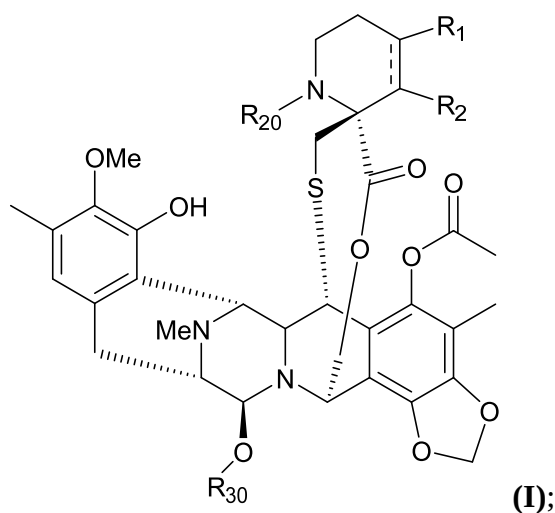
[0015] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0016] **FIG. 1** provides tumor volume measurements of female B-NDG mice subcutaneously injected with NCI-N87 cells and later dosed with either vehicle control (PBS) or 0.5 mg/kg bodyweight Trastuzumab-LD7.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



wherein R^1 and R^2 form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, - $P(O)(OH)_2$, thiol, and $-SO_3H$;

wherein R^{20} is either:

- (a) selected from the group consisting of H, C_{1-10} -alkyl, C_{6-10} -aryl, C_{3-10} -heterocycle, $C(O)R_5$, $C(O)OR_5$, $C(O)NHR_5$, SO_2R_5 , and SO_2NHR_5 , wherein the C_{1-10} -alkyl and C_{6-10} -aryl are each, individually, substituted, or unsubstituted; or

- (b) L^1 , wherein L^1 is a reactive linker group;

wherein, R^{20} is optionally substituted by 1-3 substituents, independently in each instance, selected from the group consisting of OH, F, Cl, Br, C_{1-5} -alkyl, C_{3-6} -cycloalkyl, and C_{3-6} -heterocycle;

wherein R^{30} is either:

- (c) selected from the group consisting of H, C_{1-10} -alkyl, C_{6-10} -aryl, phosphate, thiophosphate, phosphoramidate, $C(O)R_6$, $C(O)OR_6$, and $C(O)NHR_6$, sulfonyl, sulfonylamide, wherein the C_{1-10} -alkyl and C_{6-10} -aryl are each, individually, substituted, or unsubstituted; or

- (d) L^2 , wherein L^2 is a reactive linker group;

wherein the phosphate and thiophosphate are optionally substituted with one to two substituents independently, in each instance, selected from the group consisting of H, C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, (poly(ethylene) glycol)_y ([PEG]_y), C₆₋₁₀-aryl, and C₅₋₁₀-heteroaryl,

wherein C₁₋₆-alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, -P(O)(OH)₂, thiol, -OH, and -SO₃H; and

wherein the substituent on the phosphate and thiophosphate is optionally terminated with a protecting group;

wherein R⁵ and R⁶ are each, independently in each instance, selected from the group

consisting of C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, [PEG]_y, C₆₋₁₀-aryl, and C₆₋₁₀-heteroaryl,

wherein C₁₋₆-alkyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, propyl, fluoro, chloro, bromo, iodo, amino, nitro, -P(O)(OH)₂, thiol, -OH, and -SO₃H;

wherein at least one of R²⁰ or R³⁰ is not H;

wherein $\begin{array}{c} | \\ | \\ | \end{array}$ is either a single or a double bond; and

wherein subscript y is an integer selected from 0 to 32.

2. The compound of claim 1, wherein L¹ comprises at least one of (a)-(g) below, and/or wherein L² comprises at least one of (a)-(i) below:

(a) -H, wherein at least one of L¹ and L² is not H;

(b) -CH₃;

(c) -C₂₋₈-alkyl optionally substituted with at least one R¹⁰;

(d) -(C₀₋₆-alkyl)-C₃₋₁₀-cycloalkyl optionally substituted with at least one R¹⁰;

(e) -(C₀₋₆-alkyl)-C₃₋₁₀-heterocyclyl optionally substituted with at least one R¹⁰, wherein the C₃₋₁₀-heterocyclyl optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;

(f) -(C₀₋₆alkyl)-phenyl optionally substituted with at least one R¹⁰;

(g) -(C₀₋₆alkyl)-C₅₋₁₀-heteroaryl optionally substituted with at least one R¹⁰, wherein the C₅₋₁₀-heteroaryl optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

(h) -PO₃H- or -PO₃H₂; or

(i) $-\text{PO}_2\text{SH}-$ or $-\text{PO}_2\text{SH}_2$;

wherein R^{10} is $\text{R}^{10a}-\text{R}^{10b}$, wherein

R^{10a} is either absent or $-(\text{CH}_2)_e-$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-\text{C}(\text{O})-\text{R}^{11}$;
- (ii) $-(\text{C}_2\text{H}_4-\text{O})_m-\text{R}^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-\text{NH}-\text{R}^{11}$;
- (iv) $-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (v) $-\text{C}(\text{O})-\text{NH}-\text{R}^{11}$;
- (vi) $-\text{C}(\text{O})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (vii) $-\text{C}(\text{O})-\text{NH}-\text{NH}-\text{R}^{11}$;
- (viii) $-\text{C}(\text{O})-\text{NHN}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (ix) $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{NH}-\text{R}^{11}$;
- (x) $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (xi) $-\text{CH}(\text{NH}_2)-\text{CO}-\text{R}^{11}$;
- (xii) $-\text{CH}(\text{NH}(\text{C}_{1-4}\text{-alkyl}))- \text{CO}-\text{R}^{11}$;
- (xiii) $-\text{CH}(\text{N}(\text{C}_{1-4}\text{-alkyl})_2)-\text{CO}-\text{R}^{11}$;
- (xiv) $-\text{CH}(\text{CO}-\text{R}^{11})-\text{NH}-\text{R}^{11}$;
- (xv) $-\text{CH}(\text{CO}-\text{R}^{11})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

R^{11a} is selected from the group consisting of $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$, $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, and $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$;

R^{11b} is $-(\text{A}_1)_q-$ or $-(\text{A}_1-\text{A}_2)_q-$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

R^{11c} is $-(\text{CH}_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10; and

R^{11d} is selected from the group consisting of $-\text{O}-$ and $-\text{NH}-$, preferably wherein R^{11} is selected from:

$\text{R}^{11a}-\text{R}^{11b}-\text{R}^{11c}-\text{R}^{11d}$;

$R^{11b}-R^{11c}-R^{11d}$;

$R^{11c}-R^{11d}$; or

$R^{11a}-R^{11c}-R^{11d}$

and/or wherein R^{11} is terminated in a reactive group, R^{40} , wherein R^{40} is particularly maleimido.

3. The compound of claim 1 or 2, wherein L^1 comprises at least one of the bivalent structures (a)-(j) below, and/or wherein L^2 comprises at least one of the bivalent structures (a)-(l) below:

(a) $-C(O)-$;

(b) $-C(O)-NH-$;

(c) $-C(O)O-$;

(d) $-[(C(O)-NH)]_n-$;

(e) $-C(O)-$;

(f) $-(A_1-A_2)_d-$;

(g) $[-NH]-(C_6H_4)-CH_2-O-$, $[-NH]-(C_6H_4)-CH_2-O-C(O)-$, $-O-(C_6H_4)-CH_2-O-C(O)-$, or $-O-(C_6H_4)-CH_2-O-$;

(h) $-(C_{1-6}\text{-alkyl})-$;

(i) $-(C_2H_4-O)_r-$;

(j) $-(C_{1-6}\text{-alkyl})_p-$;

(k) $-PO_3H-$ or $-PO_3H_2$; or

(l) $-PO_2SH-$ or $-PO_2SH_2$;

wherein L^1 or L^2 are terminated in R^{40} , wherein R^{40} is a reactive group, particularly maleimido;

A_1 and A_2 are independent in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid;

wherein subscript:

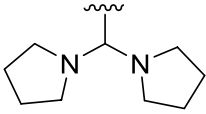
d is an integer selected from 0 to 1;

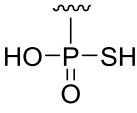
n is an integer selected from 0 to 4;

r is an integer selected from 0 to 32; and

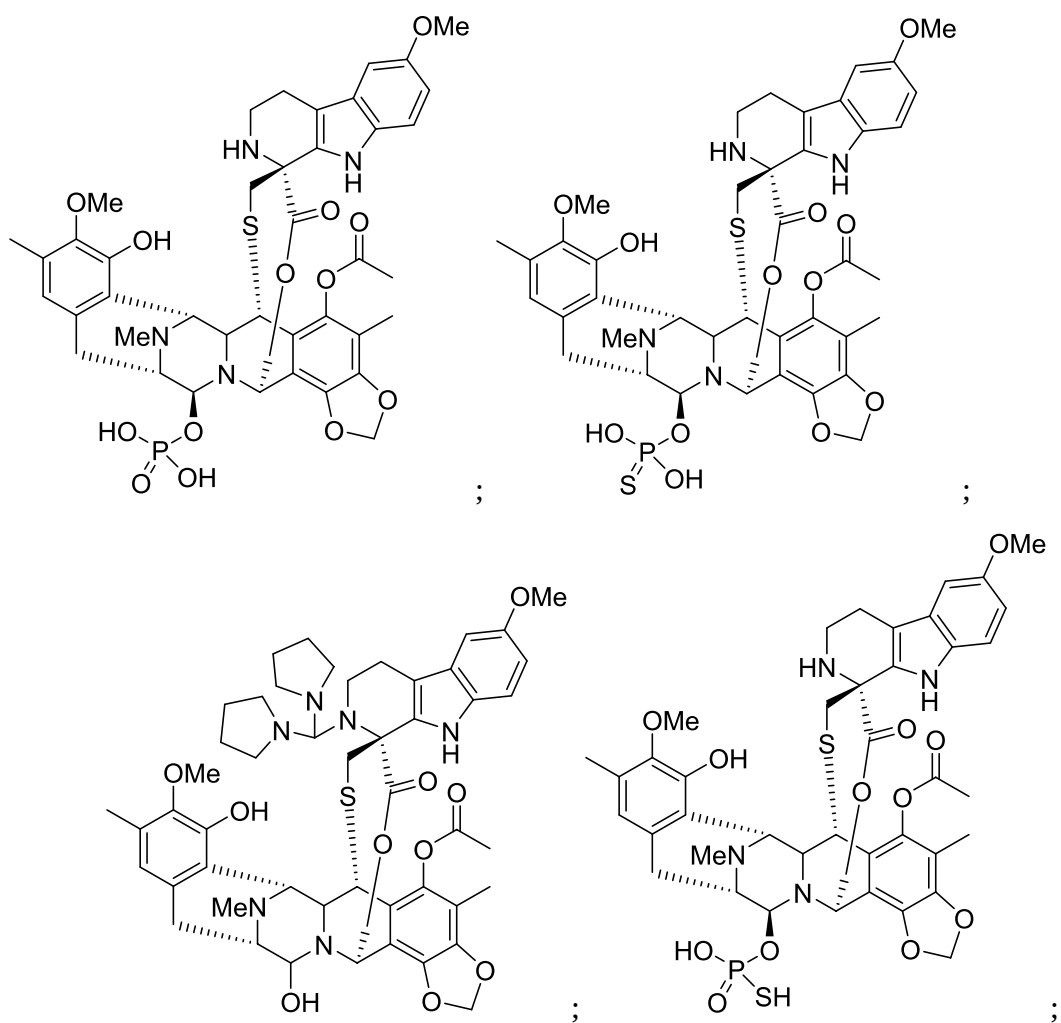
p is an integer 0 or 1.

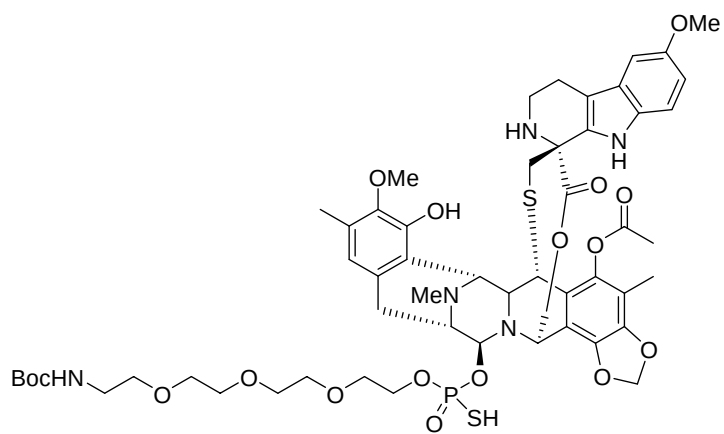
4. The compound of any one of claims 1-3,

wherein R²⁰ is , wherein  indicates a bond through which the illustrated substituent is bonded, and/or

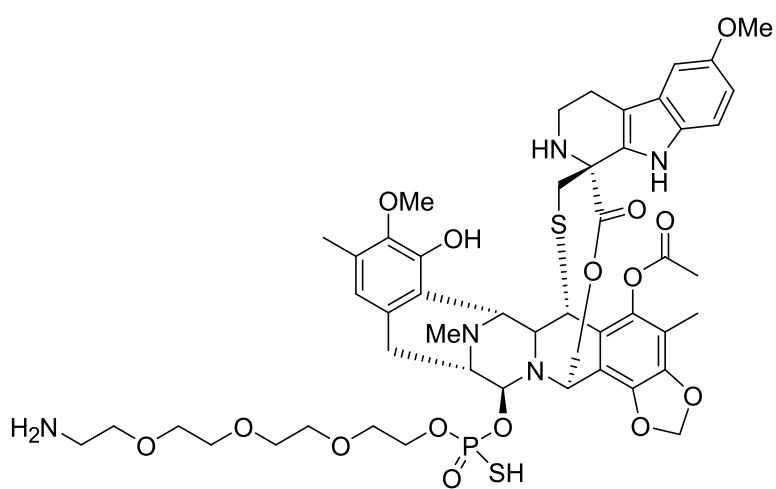
wherein R³⁰ is , wherein  indicates the bond through which the thiophosphate is bonded, and/or

wherein the compound is selected from

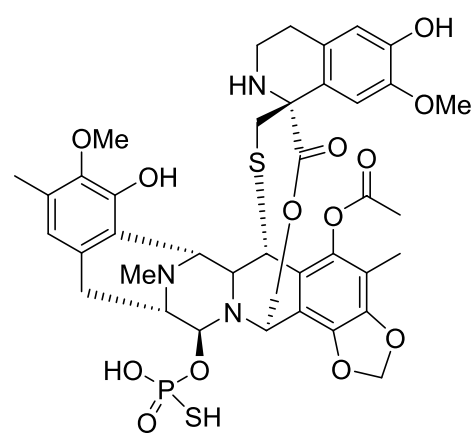




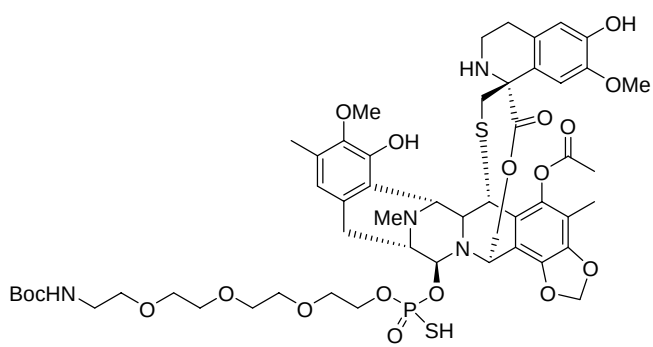
;



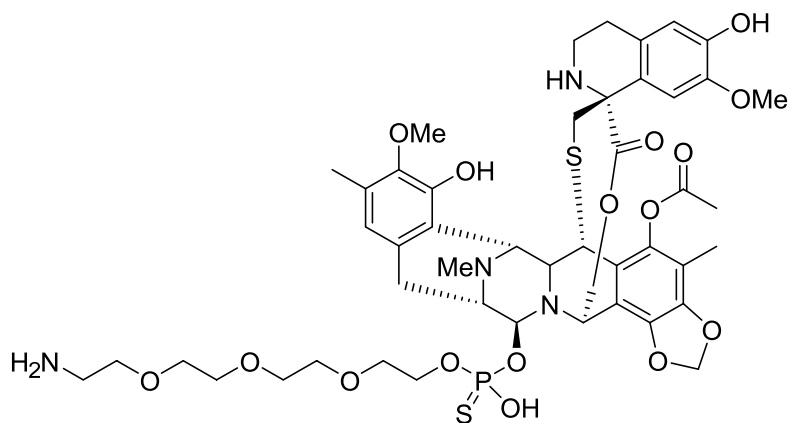
;



;

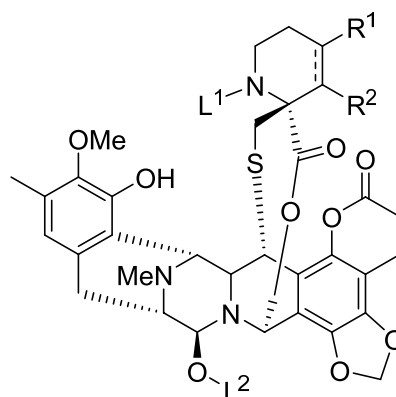


; or



.

5. A compound of Formula (III), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



(III);

wherein R^1 and R^2 form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, $-P(O)(OH)_2$, thiol, and $-SO_3H$;

wherein --- is either a single or a double bond;

wherein L^1 comprises at least one of the following:

- (a) $-H$, if L^2 is not H ;
- (b) $-CH_3$;
- (c) $-C_{2-8}$ -alkyl optionally substituted with at least one R^{10} ;
- (d) $-(C_{0-6}\text{-alkyl})-C_{3-10}$ -cycloalkyl optionally substituted with at least one R^{10} ;
- (e) $-(C_{0-6}\text{-alkyl})-C_{3-10}$ -heterocyclyl optionally substituted with at least one R^{10} , wherein the C_{3-10} -heterocyclyl optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;
- (f) $-(C_{0-6}\text{-alkyl})$ -phenyl optionally substituted with at least one R^{10} ;
- (g) $-(C_{0-6}\text{-alkyl})-C_{5-10}$ -heteroaryl optionally substituted with at least one R^{10} , wherein the C_{5-10} -heteroaryl optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

wherein R^{10} is $R^{10a}-R^{10b}$, wherein

R^{10a} is either absent or $-(CH_2)_e$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-\text{C}(\text{O})-\text{R}^{11}$;
- (ii) $-(\text{C}_2\text{H}_4-\text{O})_m-\text{R}^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-\text{NH}-\text{R}^{11}$;
- (iv) $-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (v) $-\text{C}(\text{O})-\text{NH}-\text{R}^{11}$;
- (vi) $-\text{C}(\text{O})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (vii) $-\text{C}(\text{O})-\text{NH}-\text{NH}-\text{R}^{11}$;
- (viii) $-\text{C}(\text{O})-\text{NHN}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;
- (ix) $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{NH}-\text{R}^{11}$;
- (x) $-\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{N}-(\text{C}_{1-4}\text{alkyl})-\text{R}^{11}$;
- (xi) $-\text{CH}(\text{NH}_2)-\text{CO}-\text{R}^{11}$;
- (xii) $-\text{CH}(\text{NH}(\text{C}_{1-4}\text{-alkyl}))- \text{CO}-\text{R}^{11}$;
- (xiii) $-\text{CH}(\text{N}(\text{C}_{1-4}\text{-alkyl})_2)-\text{CO}-\text{R}^{11}$;
- (xiv) $-\text{CH}(\text{CO}-\text{R}^{11})-\text{NH}-\text{R}^{11}$;
- (xv) $-\text{CH}(\text{CO}-\text{R}^{11})-\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

R^{11a} is selected from the group consisting of $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$, $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, and $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$;

R^{11b} is $-(\text{A}_1)_q-$ or $-(\text{A}_1-\text{A}_2)_q-$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

R^{11c} is $-(\text{CH}_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10; and

R^{11d} is selected from the group consisting of $-\text{O}-$ and $-\text{NH}-$;

wherein L^2 comprises at least one of the following:

- (a) $-\text{H}$, if L^1 is not H ;
- (b) $-\text{PO}_3\text{H}-$;
- (c) $-\text{PO}_2\text{SH}-$;
- (d) $-\text{CH}_3$;
- (e) $-\text{C}_{2-8}\text{-alkyl}$ optionally substituted with at least one R^{10} ;
- (f) $-(\text{C}_{0-6}\text{-alkyl})-\text{C}_{3-10}\text{-cycloalkyl}$ optionally substituted with at least one R^{10} ;

- (g) $-(C_{0-6}\text{-alkyl})-C_{3-10}\text{-heterocyclyl}$ optionally substituted with at least one R^{10} , wherein the $C_{3-10}\text{-heterocyclyl}$ optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;
- (h) $-(C_{0-6}\text{alkyl})\text{-phenyl}$ optionally substituted with at least one R^{10} ;
- (j) $-(C_{0-6}\text{alkyl})-C_{5-10}\text{-heteroaryl}$ optionally substituted with at least one R^{10} , wherein the $C_{5-10}\text{-heteroaryl}$ optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

wherein R^{10} is $R^{10a}\text{-}R^{10b}$, wherein

R^{10a} is either absent or $-(CH_2)_e\text{-}$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-\text{C}(\text{O})\text{-}R^{11}$;
- (ii) $-(C_2H_4\text{-O})_m\text{-}R^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-\text{NH}\text{-}R^{11}$;
- (iv) $-\text{N}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;
- (v) $-\text{C}(\text{O})\text{-NH}\text{-}R^{11}$;
- (vi) $-\text{C}(\text{O})\text{-N}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;
- (vii) $-\text{C}(\text{O})\text{-NHNH}\text{-}R^{11}$;
- (viii) $-\text{C}(\text{O})\text{-NHN}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;
- (ix) $-\text{C}(\text{O})\text{-N}(C_{1-4}\text{-alkyl})\text{NH}\text{-}R^{11}$;
- (x) $-\text{C}(\text{O})\text{-N}(C_1\text{-}C_4\text{-alkyl})\text{N}(C_{1-4}\text{alkyl})\text{-}R^{11}$;
- (xi) $-\text{CH}(\text{NH}_2)\text{CO}\text{-}R^{11}$;
- (xii) $-\text{CH}(\text{NH}(C_{1-4}\text{-alkyl}))\text{CO}\text{-}R^{11}$;
- (xiii) $-\text{CH}(\text{N}(C_{1-4}\text{-alkyl})_2)\text{CO}\text{-}R^{11}$;
- (xiv) $-\text{CH}(\text{CO}\text{-}R^{11})\text{NH}\text{-}R^{11}$;
- (xv) $-\text{CH}(\text{CO}\text{-}R^{11})\text{N}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

R^{11a} is selected from the group consisting of $[-\text{NH}]\text{-(C}_6\text{H}_4\text{)-CH}_2\text{-O-}$, $[-\text{NH}]\text{-(C}_6\text{H}_4\text{)-CH}_2\text{-O-C(O)-}$, $-\text{O-(C}_6\text{H}_4\text{)-CH}_2\text{-O-C(O)-}$, and $-\text{O-(C}_6\text{H}_4\text{)-CH}_2\text{-O-}$;

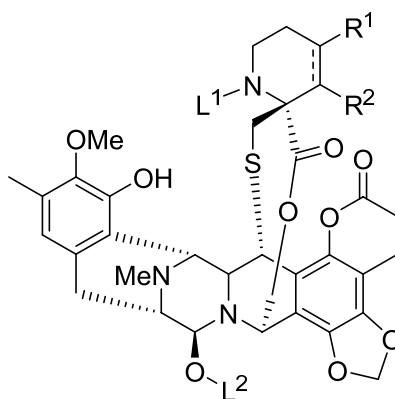
R^{11b} is $-(A_1)_{q-}$ or $-(A_1\text{-}A_2)_{q-}$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

R^{11c} is $-(CH_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10;

and

R^{11d} is selected from the group consisting of $-O-$ and $-NH-$.

6. The compound of claim 5, which is represented by Formula (IV) or a pharmaceutically acceptable salt, ester, or tautomer thereof:



(IV);

wherein R^1 and R^2 form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C_{1-10} -alkoxy, C_{1-10} -alkyl, amino, hydroxyl, halogen, nitro, $-P(O)(OH)_2$, thiol, and $-SO_3H$;

wherein $\parallel$ is either a single or a double bond;

wherein one of L^1 or L^2 is a linker;

wherein L^1 is:

H;

$R^{40}-(C_{1-6} \text{ alkyl})-[(C(O)-NH)_b-(-C_2H_4-O)_c-(C_{1-6} \text{ alkyl})_e-[(C(O)-)]_f$;

$R^{40}-(-C_2H_4-O)_c-C(O)-(A_1-A_2)_g-[-NH]_h-(C_6H_4)-CH_2-O-[(C(O)-NH)_j-(-C_2H_4-O)_t-(C_{1-6} \text{ alkyl})-[(C(O)-)]_k$; or

$R^{40}-(C_{1-6} \text{ alkyl})-C(O)-(A_1-A_2)_g-[-NH]_h-(C_6H_4)-CH_2-O-[(C(O)-NH)_j-]$;

wherein L^2 is:

H;

$R^{40}-(C_{1-6} \text{ alkyl})-[(C(O)-NH)_b-(-C_2H_4-O)_c-(C_{1-6} \text{ alkyl})-[(C(O)-NH)_j-(-C_2H_4-O)_t-[O-P(O)SH]]$; or

$R^{40}-(-C_2H_4-O)_t-C(O)-(A_1-A_2)_g-NH-(C_6H_4)-CH_2-O-[(C(O)-NH)_j-(-C_2H_4-O)_t-(C_{1-6} \text{ alkyl})-[(C(O)-)]_f-[O-P(O)SH]]$;

wherein one of L^1 or L^2 is not H;

wherein R^{40} is a reactive group, particularly maleimido;

wherein A_1 and A_2 are independently in each instance an amino acid;

wherein subscript:

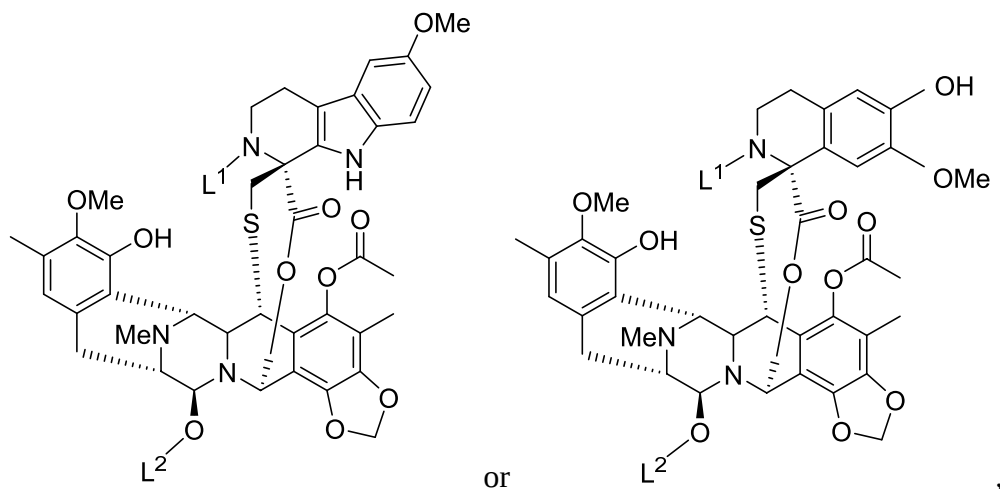
b and j are, independently in each instance, selected from 0 to 4;

c and t are, independently in each instance, selected from 0 to 32;

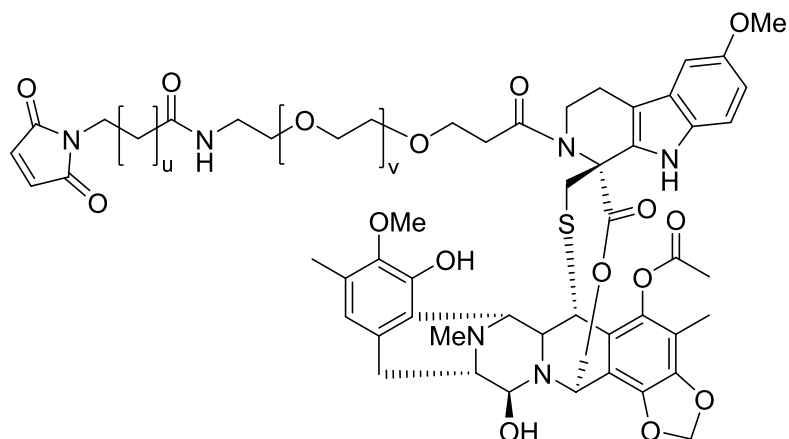
e, f, g, h, and k, are, independently in each instance, 0 or 1.

7. The compound of any one of claims 2-6, wherein R^{11b} is $-(A_1-A_2)_q$, wherein each occurrence of A_1-A_2 is independently: valine-citrulline, citrulline-valine, lysine-phenylalanine, phenylalanine-lysine, valine-asparagine, asparagine-valine, threonine-asparagine, asparagine-threonine, serine-asparagine, asparagine-serine, phenylalanine-asparagine, asparagine-phenylalanine, leucine-asparagine, asparagine-leucine, isoleucine-asparagine, asparagine-isoleucine, glycine-asparagine, asparagine-glycine, glutamic acid-asparagine, asparagine-glutamic acid, citrulline-asparagine, asparagine-citrulline, alanine-asparagine, or asparagine-alanine, preferably Val-Cit or Cit-Val.

8. The compound of any one of the preceding claims, wherein the compound is:



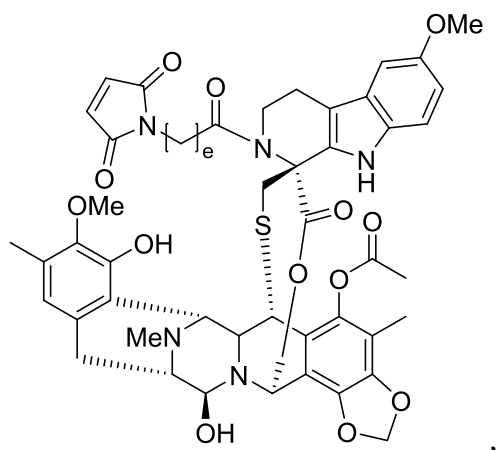
preferably wherein the compound is:



wherein subscript v is an integer from 1 to 32, particularly 1 to 14; and

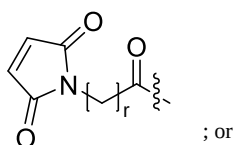
wherein subscript u is an integer from 0 to 11,

or

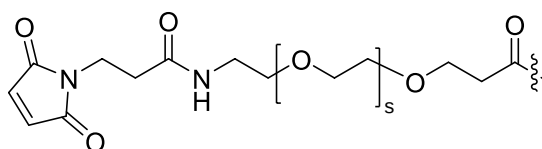


wherein subscript e is an integer selected from 1 to 6, particularly 1 to 4.

9. The compound of any one of the preceding claims, wherein L^1 is H or L^2 is H; and/or wherein at least one of L^1 or L^2 independently comprises:



; or

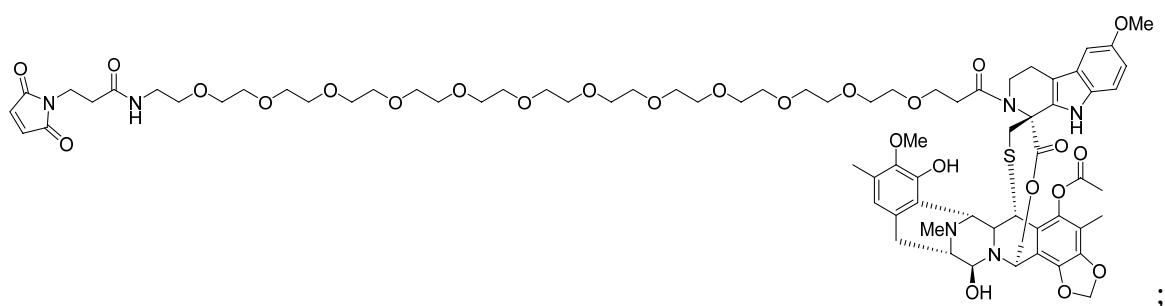
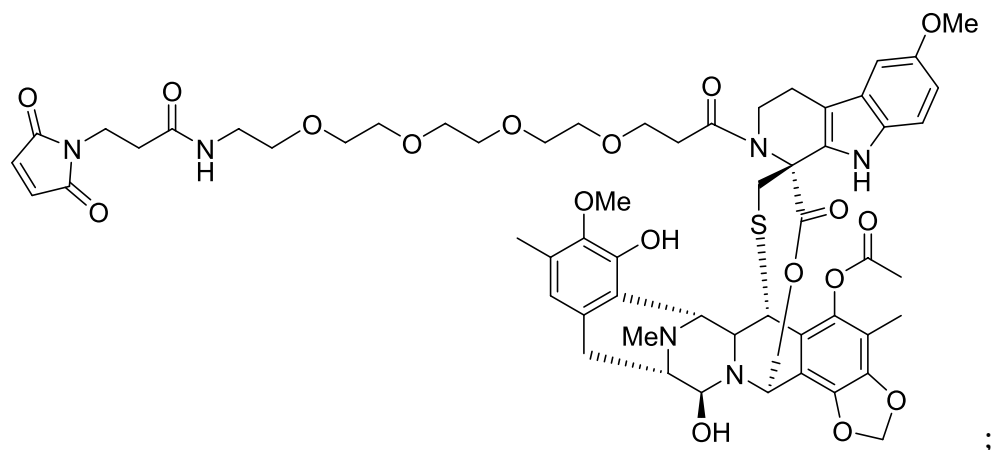
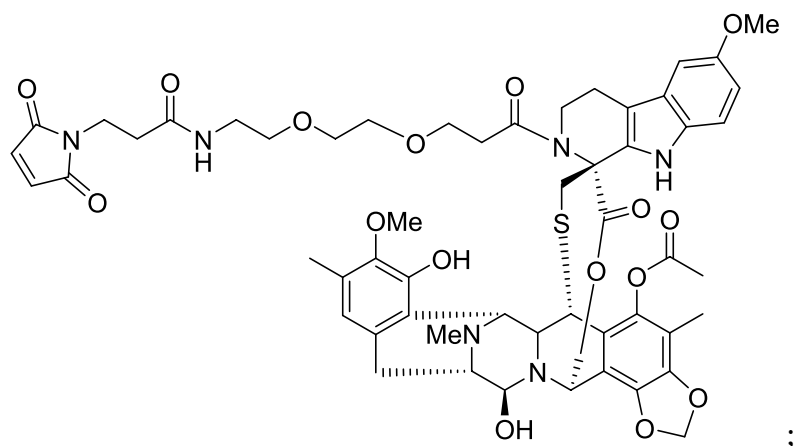


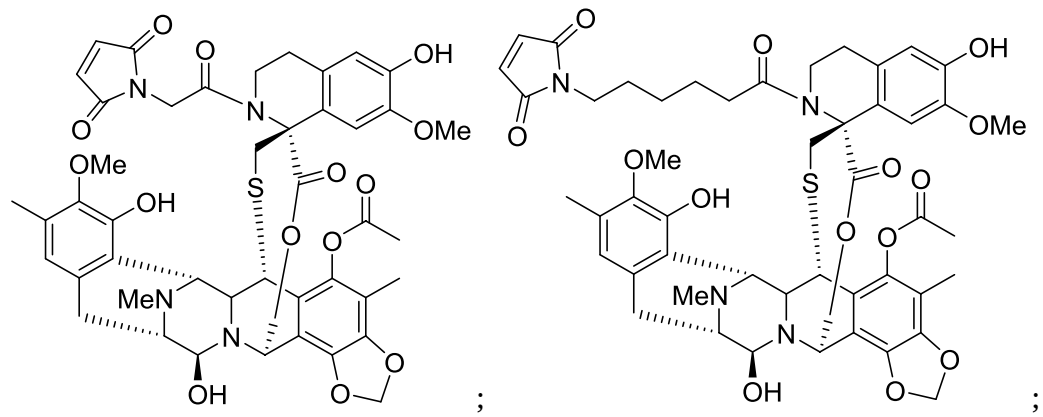
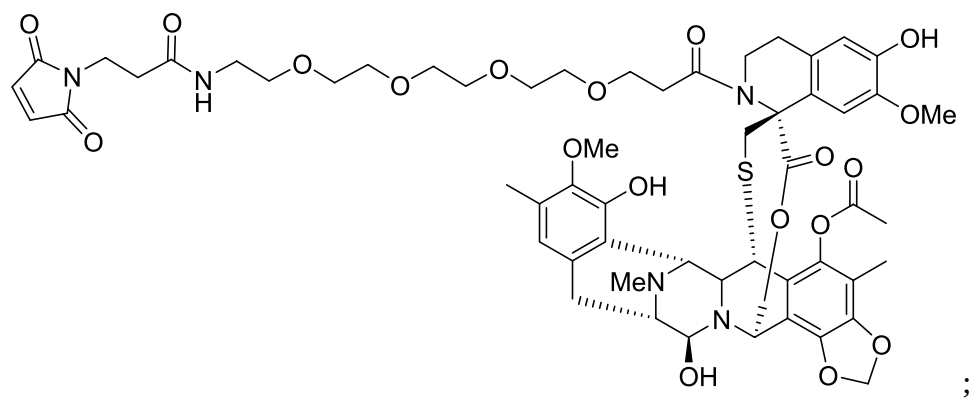
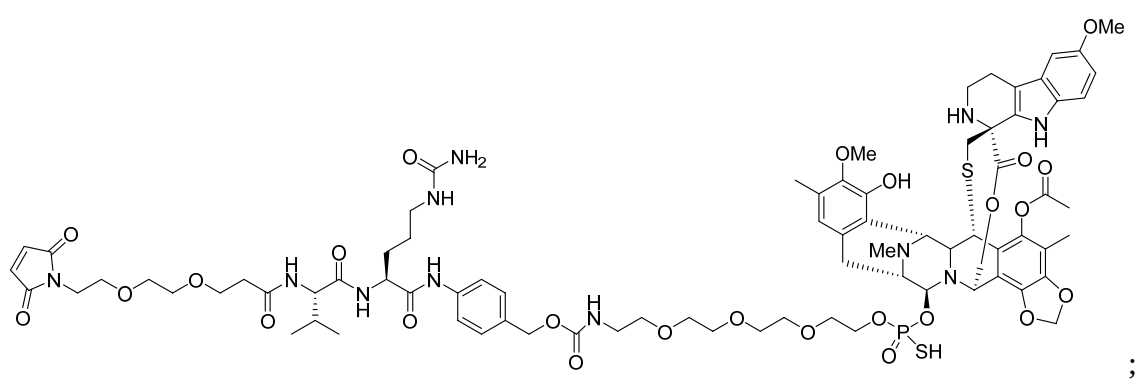
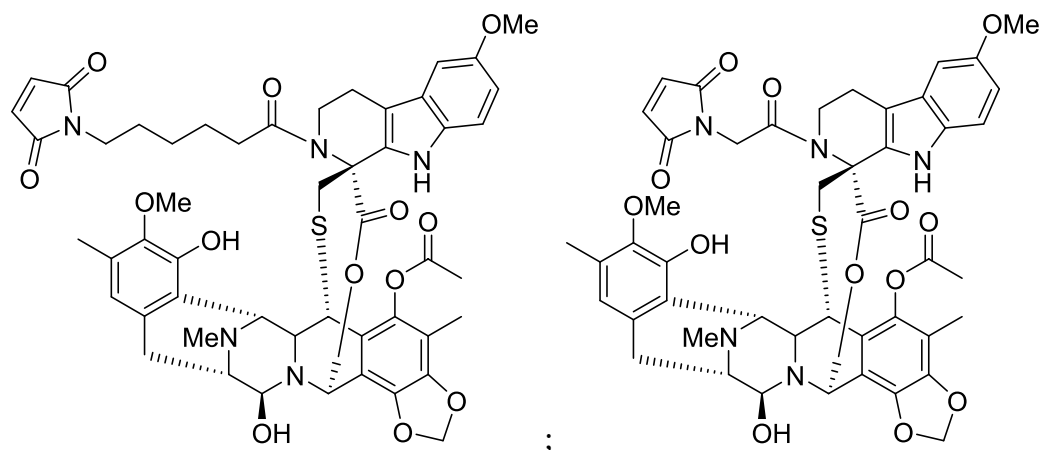
wherein  indicates the point of attachment to the compound of Formula (IV) or to a remaining portion of L¹ or L²;

wherein r is an integer selected from 1 to 12, particularly 2 to 12; and

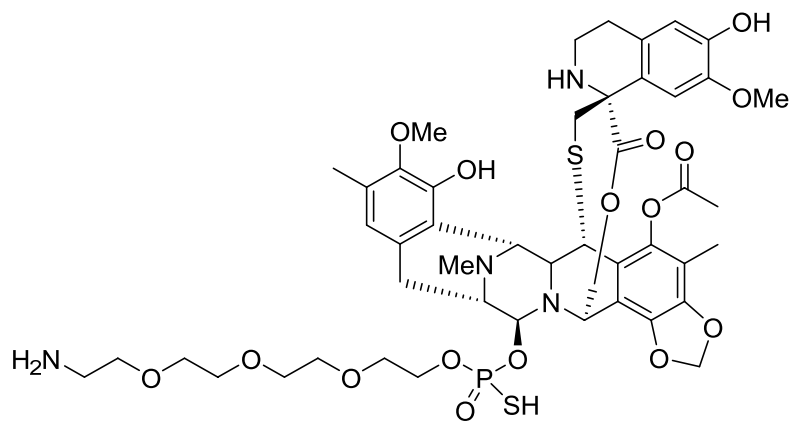
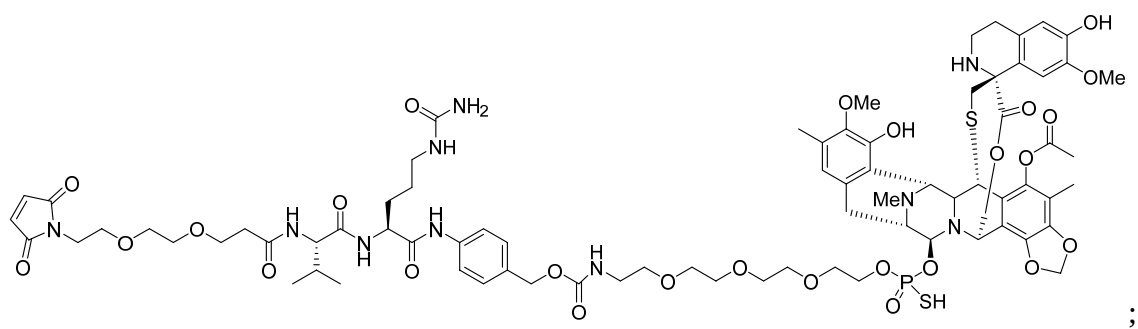
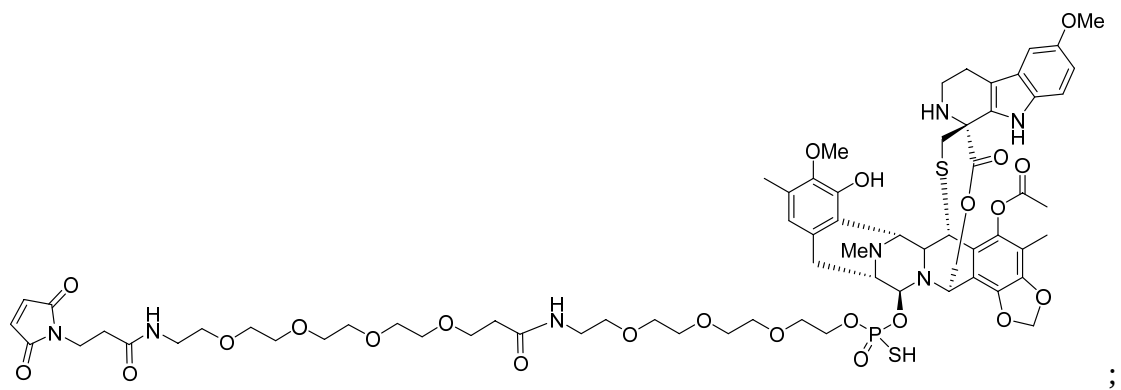
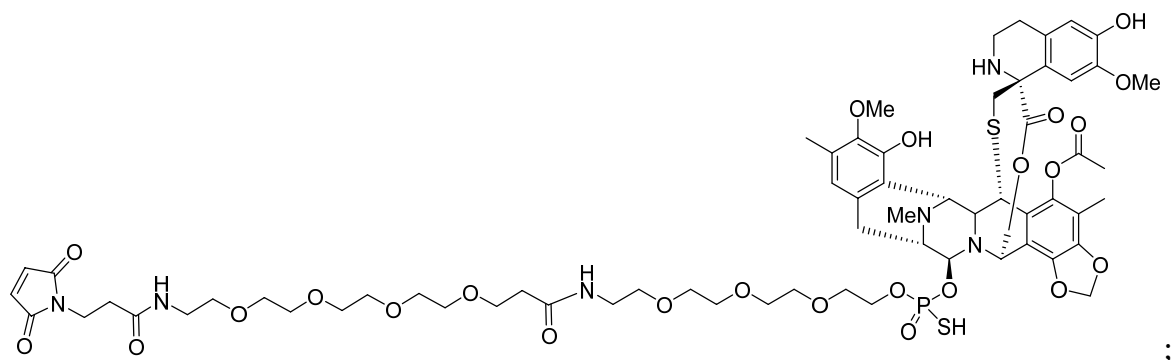
wherein s is an integer selected from 1 to 32, particularly 2 to 32.

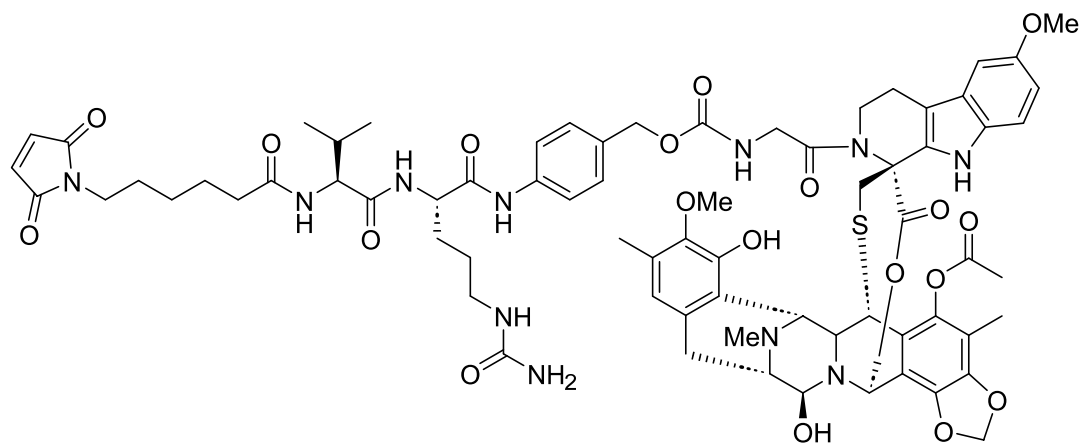
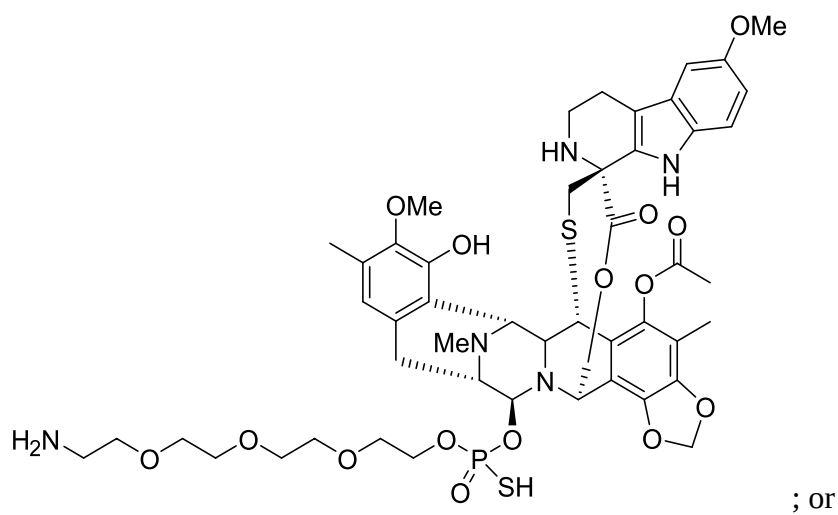
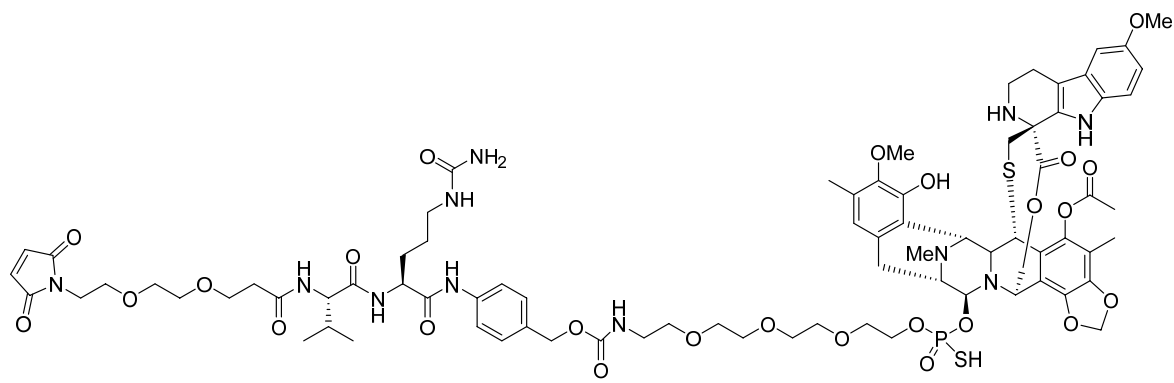
10. The compound of any one of the preceding claims, wherein the compound has the structure:



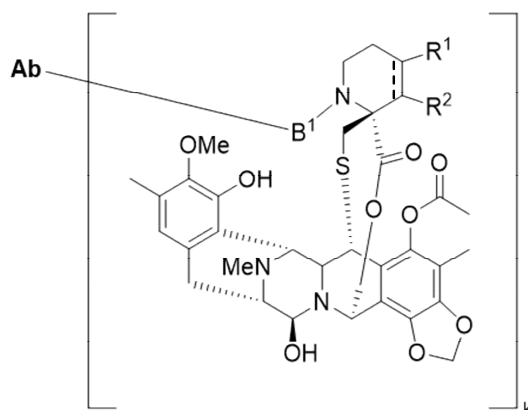




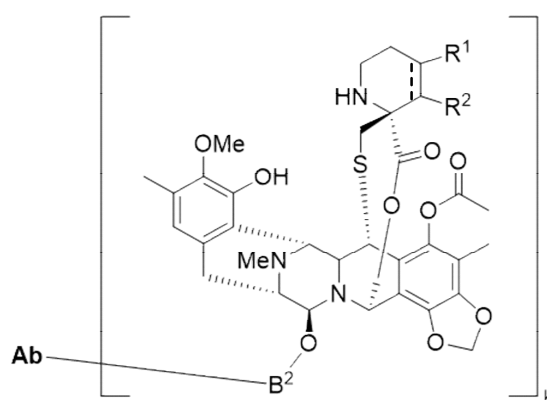




11. A compound of Formula (Va) or (Vb), or a pharmaceutically acceptable salt, ester, stereoisomer, or tautomer thereof:



(Va)



(Vb)

wherein Ab is targeting agent, preferably an antibody, antibody fragment, protein, or peptide;

wherein subscript k is an integer from 1 to 10;

wherein R¹ and R² form at least one aromatic ring or bicyclic heterocyclic ring, optionally substituted with one to six substituents, independently in each instance, selected from the group consisting of C₁₋₁₀-alkoxy, C₁₋₁₀-alkyl, amino, hydroxyl, halogen, nitro, -P(O)(OH)₂, thiol, and -SO₃H; and

wherein B¹ is a linker;

wherein B² is a linker.

12. The compound of claim 11, wherein

wherein B¹ comprises at least one of the following:

- (a) -H, if B² is not H;
- (b) -CH₃;
- (c) -C₂₋₈-alkyl optionally substituted with at least one R¹⁰;
- (d) -(C₀₋₆-alkyl)-C₃₋₁₀-cycloalkyl optionally substituted with at least one R¹⁰;

- (e) $-(C_{0-6}\text{-alkyl})-C_{3-10}\text{-heterocyclyl}$ optionally substituted with at least one R^{10} , wherein the $C_{3-10}\text{-heterocyclyl}$ optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;
- (f) $-(C_{0-6}\text{alkyl})\text{-phenyl}$ optionally substituted with at least one R^{10} ;
- (g) $-(C_{0-6}\text{alkyl})-C_{5-10}\text{-heteroaryl}$ optionally substituted with at least one R^{10} , wherein the $C_{5-10}\text{-heteroaryl}$ optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

wherein R^{10} is $R^{10a}\text{-}R^{10b}$, wherein

R^{10a} is either absent or $-(CH_2)_e$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-C(O)\text{-}R^{11}$;
- (ii) $-(C_2H_4\text{-}O)_m\text{-}R^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-\text{NH}\text{-}R^{11}$;
- (iv) $-\text{N}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;
- (v) $-C(O)\text{-NH}\text{-}R^{11}$;
- (vi) $-C(O)\text{-N}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;
- (vii) $-C(O)\text{-NH}\text{-NH}\text{-}R^{11}$;
- (viii) $-C(O)\text{-NHN}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;
- (ix) $-C(O)\text{N}(C_{1-4}\text{-alkyl})\text{-NH}\text{-}R^{11}$;
- (x) $-C(O)\text{N}(C_{1-4}\text{-alkyl})\text{-N}(C_{1-4}\text{alkyl})\text{-}R^{11}$;
- (xi) $-\text{CH}(\text{NH}_2)\text{-CO}\text{-}R^{11}$;
- (xii) $-\text{CH}(\text{NH}(C_{1-4}\text{-alkyl}))\text{-CO}\text{-}R^{11}$;
- (xiii) $-\text{CH}(\text{N}(C_{1-4}\text{-alkyl})_2)\text{-CO}\text{-}R^{11}$;
- (xiv) $-\text{CH}(\text{CO}\text{-}R^{11})\text{-NH}\text{-}R^{11}$;
- (xv) $-\text{CH}(\text{CO}\text{-}R^{11})\text{-N}(C_{1-4}\text{-alkyl})\text{-}R^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

R^{11a} is selected from the group consisting of $[-\text{NH}]\text{-(C}_6\text{H}_4\text{)-CH}_2\text{-O-}$, $[-\text{NH}]\text{-(C}_6\text{H}_4\text{)-CH}_2\text{-O-C(O)-}$, $-\text{O-(C}_6\text{H}_4\text{)-CH}_2\text{-O-C(O)-}$, and $-\text{O-(C}_6\text{H}_4\text{)-CH}_2\text{-O-}$;

R^{11b} is $-(A_1)_q\text{-}$ or $-(A_1\text{-}A_2)_q\text{-}$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

R^{11c} is $-(CH_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10;
and

R^{11d} is selected from the group consisting of $-O-$ and $-NH-$;

wherein B^2 comprises at least one of the following:

- (a) $-H$, if B^1 is not H ;
- (b) $-PO_3H-$;
- (c) $-PO_2SH-$;
- (d) $-CH_3$;
- (e) $-C_{2-8}$ -alkyl optionally substituted with at least one R^{10} ;
- (f) $-(C_{0-6}$ -alkyl)- C_{3-10} -cycloalkyl optionally substituted with at least one R^{10} ;
- (g) $-(C_{0-6}$ -alkyl)- C_{3-10} -heterocyclyl optionally substituted with at least one R^{10} , wherein the C_{3-10} -heterocyclyl optionally comprises 1-3 heteroatoms independently selected from the group consisting of N, O, and S;
- (h) $-(C_{0-6}$ alkyl)-phenyl optionally substituted with at least one R^{10} ;
- (j) $-(C_{0-6}$ alkyl)- C_{5-10} -heteroaryl optionally substituted with at least one R^{10} , wherein the C_{5-10} -heteroaryl optionally comprises 1-3 heteroatoms independently selected from the group N, O, and S;

wherein R^{10} is $R^{10a}-R^{10b}$, wherein

R^{10a} is either absent or $-(CH_2)_e-$, wherein e is independently in each instance, selected from 1-4;

R^{10b} is selected from the group consisting of:

- (i) $-C(O)-R^{11}$;
- (ii) $-(C_2H_4-O)_m-R^{11}$, wherein the subscript of m is an integer from 1-32;
- (iii) $-NH-R^{11}$;
- (iv) $-N(C_{1-4}$ -alkyl)- R^{11} ;
- (v) $-C(O)-NH-R^{11}$;
- (vi) $-C(O)-N(C_{1-4}$ -alkyl)- R^{11} ;
- (vii) $-C(O)-NHNH-R^{11}$;
- (viii) $-C(O)-NHN(C_{1-4}$ -alkyl)- R^{11} ;
- (ix) $-C(O)-N(C_{1-4}$ -alkyl)NH- R^{11} ;
- (x) $-C(O)-N(C_1-C_4$ -alkyl) $N(C_{1-4}$ alkyl)- R^{11} ;
- (xi) $-CH(NH_2)CO-R^{11}$;
- (xii) $-CH(NH(C_{1-4}$ -alkyl))CO- R^{11} ;

(xiii) $-\text{CH}(\text{N}(\text{C}_{1-4}\text{-alkyl})_2)\text{CO}-\text{R}^{11}$;

(xiv) $-\text{CH}(\text{CO}-\text{R}^{11})\text{NH}-\text{R}^{11}$;

(xv) $-\text{CH}(\text{CO}-\text{R}^{11})\text{N}(\text{C}_{1-4}\text{-alkyl})-\text{R}^{11}$;

wherein R^{11} is selected from the group consisting of R^{11a} , R^{11b} , R^{11c} , R^{11d} , and combinations thereof; wherein

R^{11a} is selected from the group consisting of $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$, $[-\text{NH}]-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, and $-\text{O}-(\text{C}_6\text{H}_4)-\text{CH}_2-\text{O}-$;

R^{11b} is $-(\text{A}_1)_{\text{q}}-$ or $-(\text{A}_1-\text{A}_2)_{\text{q}}-$, wherein A_1 and A_2 are independently in each instance an amino acid, wherein the amino acid is selected from a natural amino acid or a non-natural amino acid, wherein subscript q is an integer selected from 1 to 6;

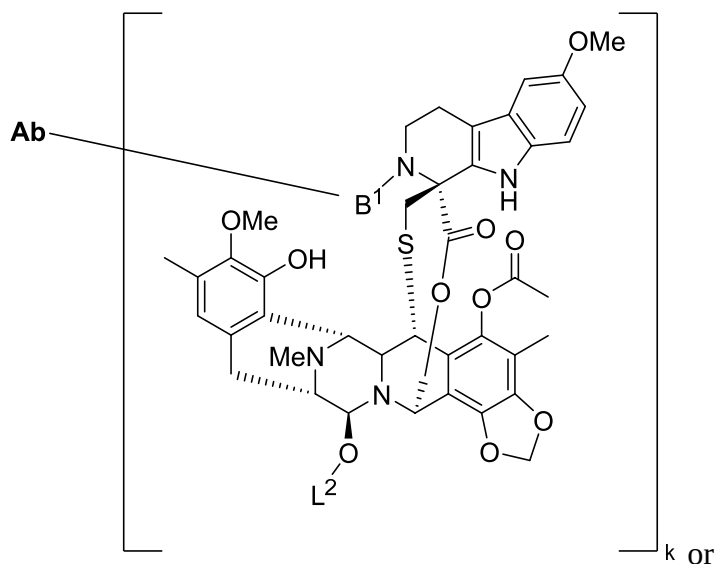
R^{11c} is $-(\text{CH}_2)_x-$, wherein the subscript of x is an integer selected from 1 to 10; and

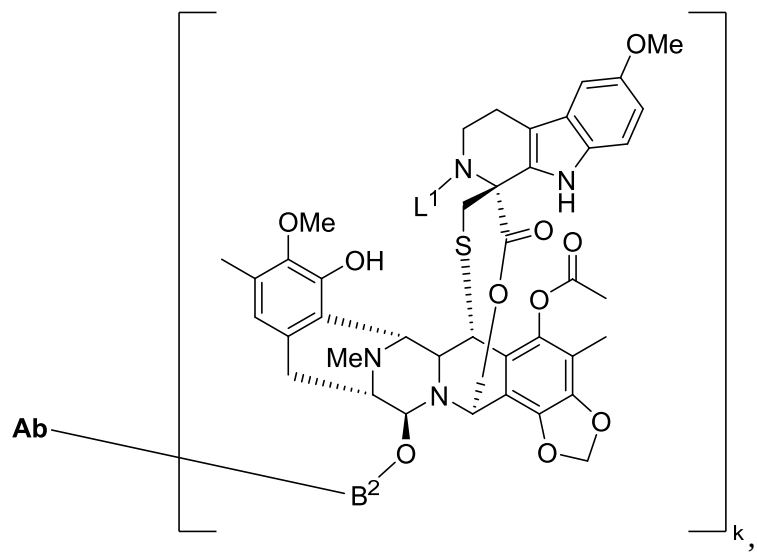
R^{11d} is selected from the group consisting of $-\text{O}-$ and $-\text{NH}-$; and

wherein one of B^1 or B^2 is not H; and

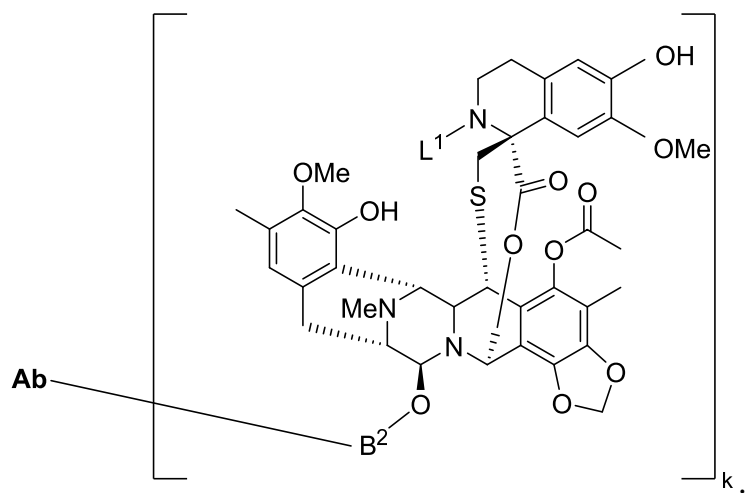
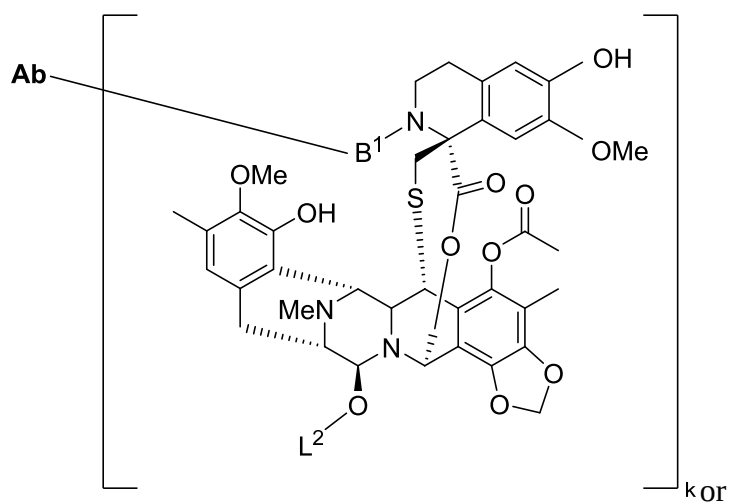
wherein one of B^1 or B^2 is bonded to Ab.

13. The compound of claim 11 or 12, wherein the compound is

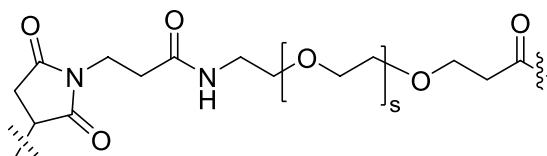




or wherein the compound is



14. The compound of any one of claim 11-13, wherein at least one of B^1 or B^2 independently comprises



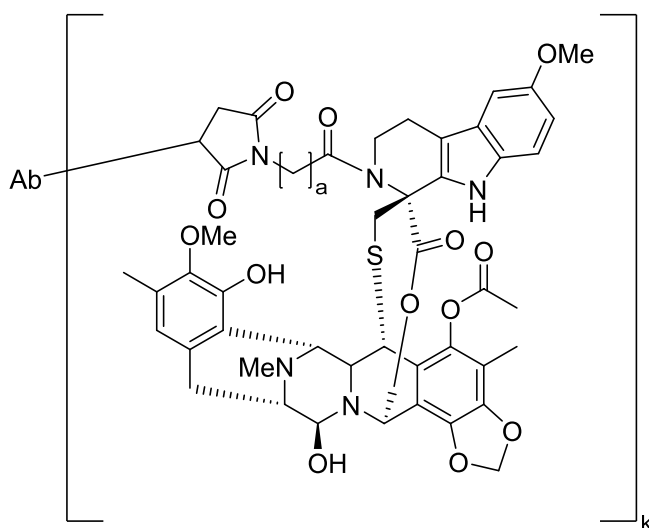
to a remaining portion of L^1 or L^2 ;

wherein  indicates the point of attachment to an antibody or antibody fragment;

wherein subscript r is an integer selected from 1 to 6, particularly 2 to 6; and

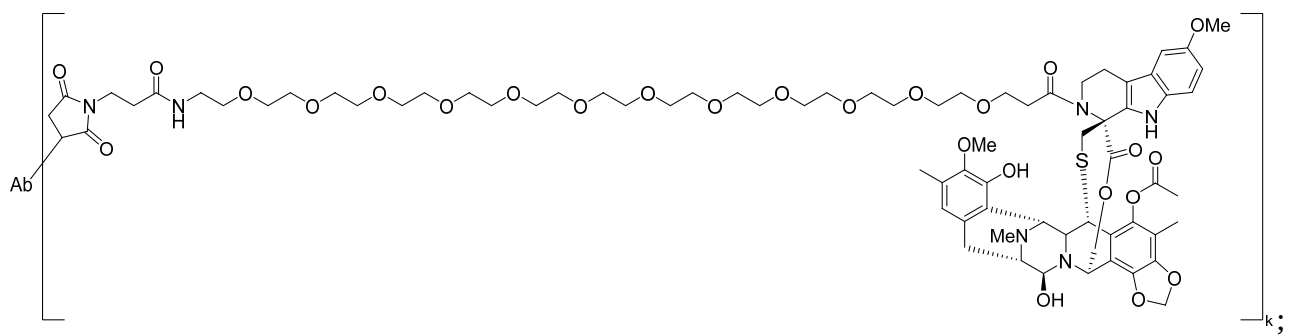
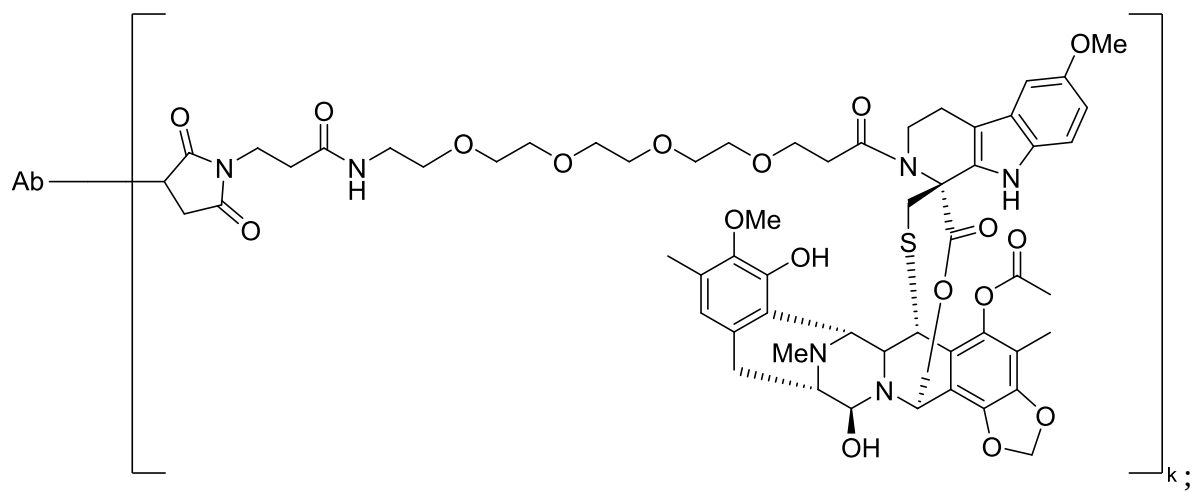
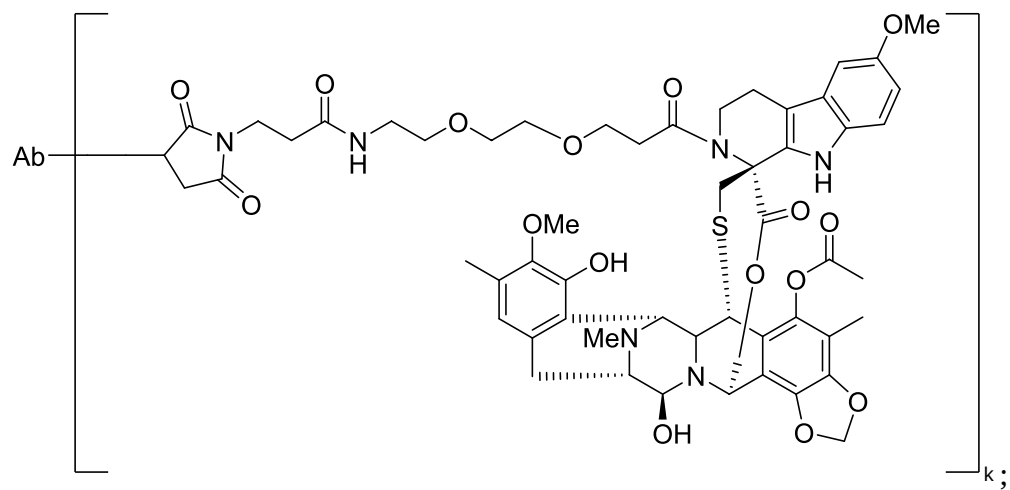
wherein subscript s is an integer selected from 2 to 14,

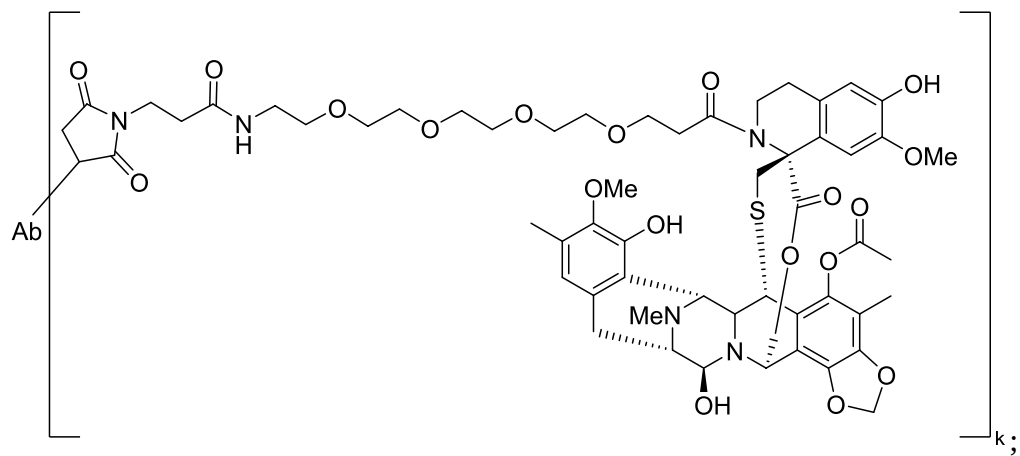
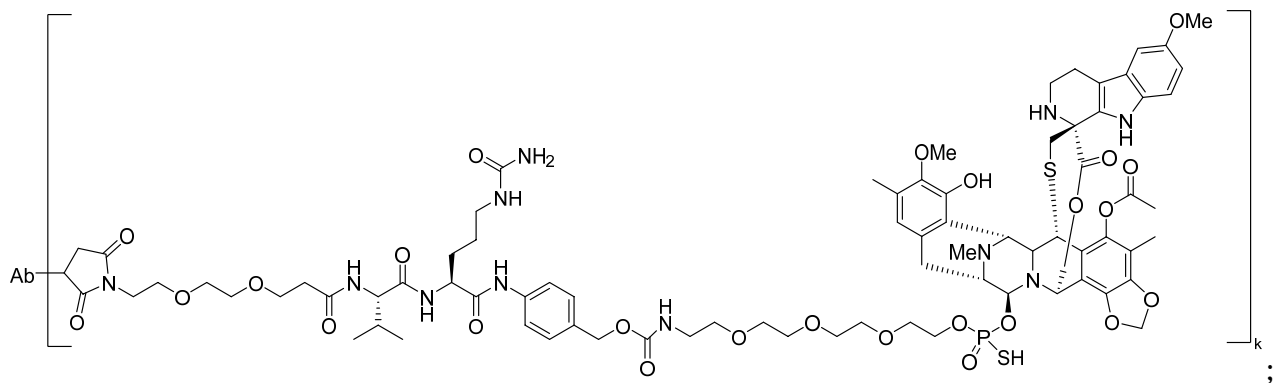
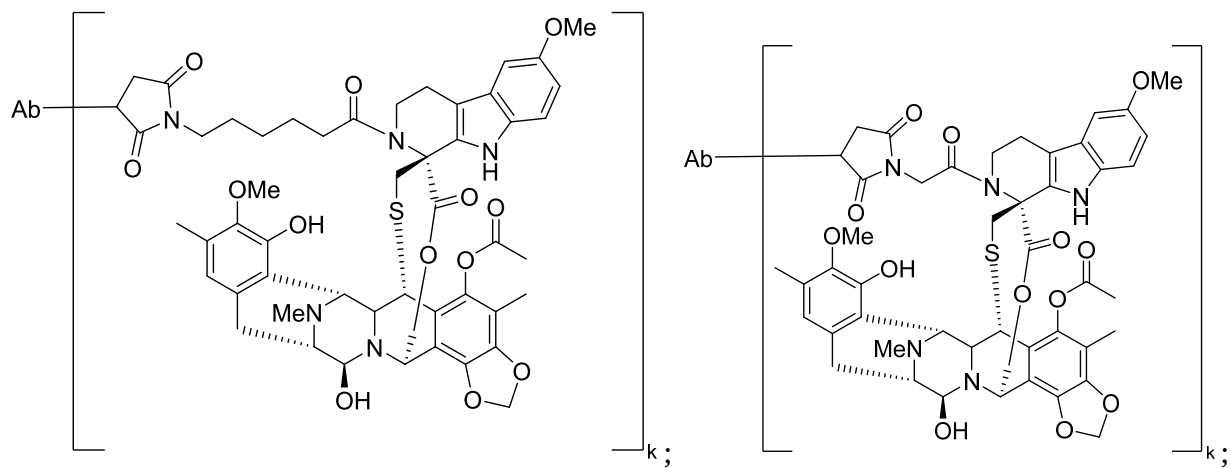
preferably wherein the compound is

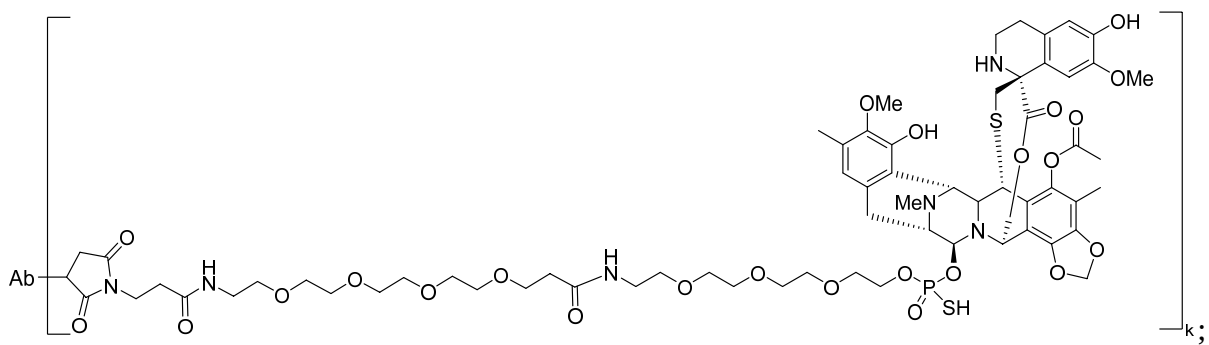
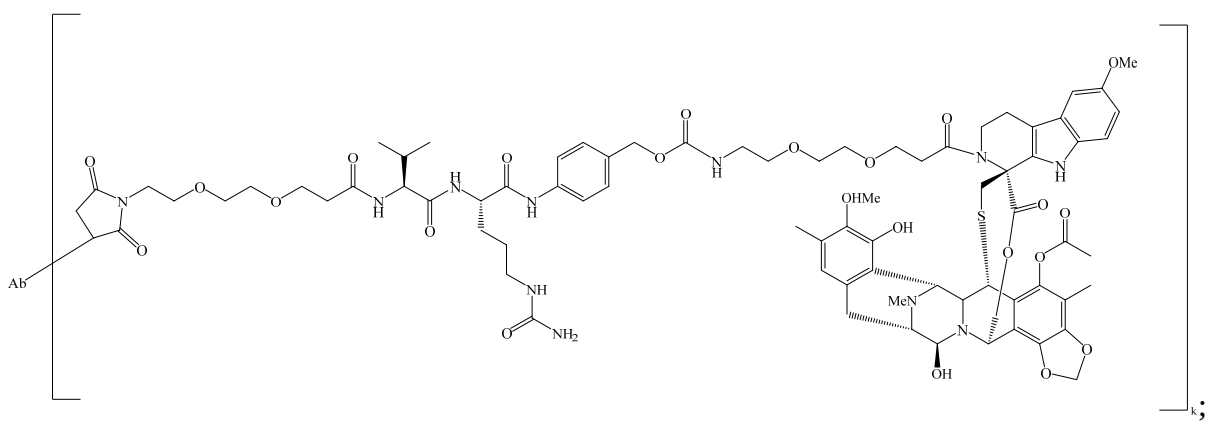
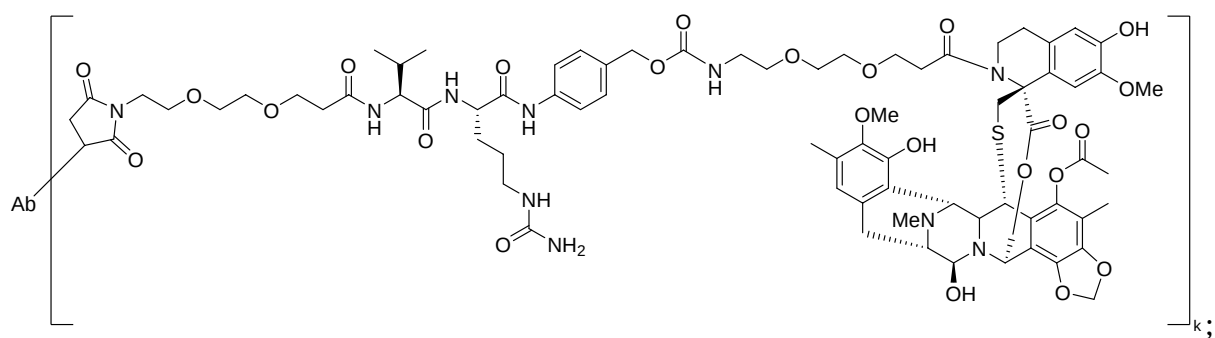
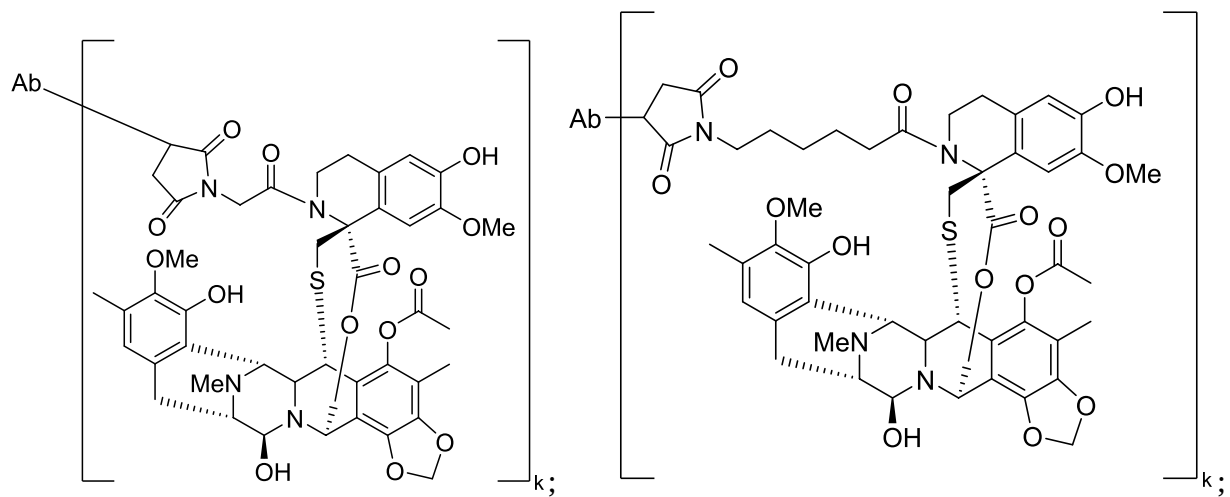


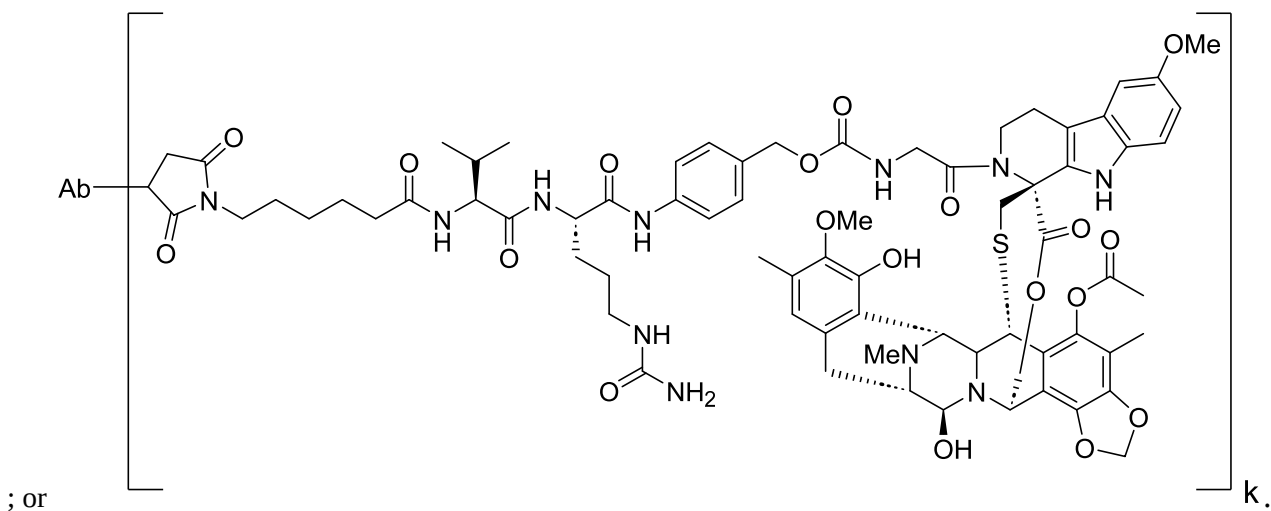
wherein a is an integer selected from 2 to 6.

15. The compound of any one of claims 11-14, wherein the compound is selected from









16. A pharmaceutical composition comprising the compound of any one of claims 1-4 or 11-15 and a pharmaceutically acceptable excipient.
17. A compound of any one of claims 1-4 or 11-15 or the pharmaceutical composition of claim 16 for use in treating a disease or condition.