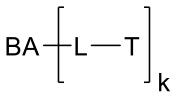
SUMMARY

[0006] Provided herein are compounds useful, for example, in anti-cancer and anti-angiogenesis treatments.

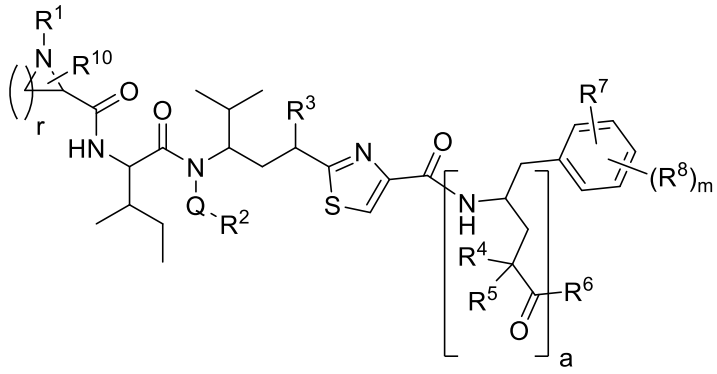
[0007] In one aspect, there is provided a compound having the following formula



or a pharmaceutically acceptable salt thereof, wherein

BA is a binding agent;

L is a linker covalently bound to **BA** and to **T**;

T is  wherein

R^{1} is a bond, hydrogen, C_1-C_{10} alkyl, a first *N*-terminal amino acid residue, a first amino acid residue, –C_1-C_{10} alkyl-N**R^{3a}R^{3b}**, or –C_1-C_{10} alkyl-OH;

R^{3} is hydroxyl, –O–, –O-C_1-C_5 alkyl, –OC(O)C_1-C_5 alkyl, –OC(O)N(H)C_1-C_{10} alkyl, –OC(O)N(H)C_1-C_{10} alkyl-N**R^{3a}R^{3b}**, –NHC(O)C_1-C_5 alkyl, or –OC(O)N(H)$(CH_2CH_2O)_{\mathbf{n}}C_1$-$C_{10}$ alkyl-N**R^{3a}R^{3b}**,

wherein **R^{3a}** and **R^{3b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{4} and **R^{5}** are, independently in each instance, hydrogen or C_1-C_5 alkyl;

R^{6} is –OH, –O–, –$NHNH_2$, –NHNH–, –$NHSO_2(CH_2)_{\mathbf{a1}}$-aryl-$(CH_2)_{\mathbf{a2}}$N**R^{6a}R^{6b}**,

wherein aryl is substituted or unsubstituted; and

R^{6a} and **R^{6b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{7} is, independently in each instance, hydrogen, –OH, –O–, halogen, or –N**R^{7a}R^{7b}**,

wherein $\mathbf{R^{7a}}$ and $\mathbf{R^{7b}}$ are, independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, –C(O)CH_2OH, –C(O)CH_2O–, a first *N*-terminal amino acid residue, a first amino acid residue, a first *N*-terminal peptide residue, a first peptide residue, –$CH_2CH_2NH_2$, and –CH_2CH_2NH–; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

$\mathbf{R^8}$ is, independently in each instance, hydrogen, –NH$\mathbf{R^9}$, or halogen,

wherein $\mathbf{R^9}$ is hydrogen, –C_1-C_5 alkyl, or –C(O)C_1-C_5 alkyl; and

m is one or two;

$\mathbf{R^{10}}$, when present, is -C_1-C_5 alkyl;

Q is –CH_2– or –O– wherein

$\mathbf{R^2}$ is alkyl, alkylene, alkynyl, alkynylene, a regioisomeric triazole, a regioisomeric triazolylene;

wherein said regioisomeric triazole or regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or acyl;

wherein **n** is an integer from one to ten;

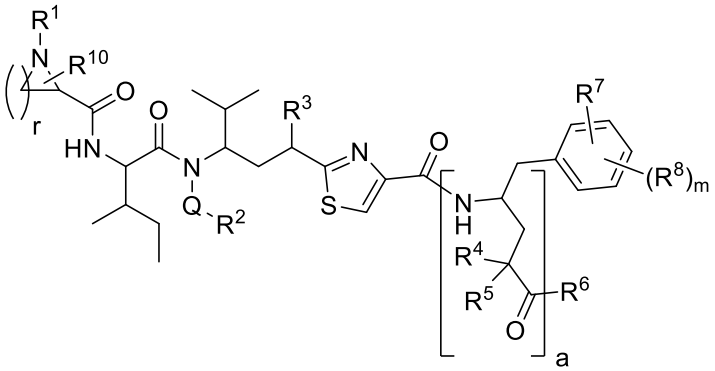
wherein **r** is an integer from one to six;

wherein **a**, **a1**, and, **a2** are, independently, zero or one; and

k is an integer from one to thirty;

wherein **T** is not compound **IVa**, **IVa'**, **IVb**, **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, **IVj**, **IVk**, **IVl**, **IVm**, **IVn**, **IVo**, **IVp**, **IVq**, **IVr**, **IVs**, **IVt**, **IVu**, **IVvA**, **IVvB**, **IVw**, **IVx**, **IVy**, **Va**, **Va'**, **Vb**, **Vc**, **Vd**, **Ve**, **Vf**, **Vg**, **Vh**, **Vi**, **Vj**, **Vk**, **VIa**, **IVb**, **VIc**, **VId**, **VIe**, **VIf**, **VIg**, **VIh**, **Vl**, **VIi**, **VII**, **VIII**, **IX**, **X**, **D-5a**, and **D-5c**, or a pharmaceutically acceptable salt thereof, covalently bound to **L**.

[0008] In another aspect, there is provided a compound having the structure of Formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

VIII, **IX**, **X**, **D-5a**, **D-5c**, Tubulysin A-I, U-X, or Z, Pretubulysin D, or N^{14}-desacetoxytubulysin H.

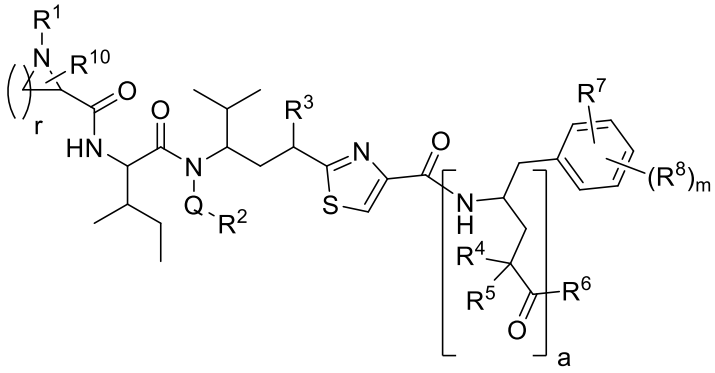
[0009] In another example, provided is a method for treating tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

[0010] In another aspect, provided is a linker-payload having the formula

L—T

or a pharmaceutically acceptable salt thereof, wherein

L is a linker covalently bound to **T**;

T is  wherein

R^1 is a bond, hydrogen, C_1-C_{10} alkyl, a first *N*-terminal amino acid residue, a first amino acid residue, –C_1-C_{10} alkyl-N**$R^{3a}R^{3b}$**, or –C_1-C_{10} alkyl-OH;

R^3 is hydroxyl, –O–, –O-C_1-C_5 alkyl, –OC(O)C_1-C_5 alkyl, –OC(O)N(H)C_1-C_{10} alkyl, –OC(O)N(H)C_1-C_{10} alkyl-N**$R^{3a}R^{3b}$**, –NHC(O)C_1-C_5 alkyl, or –OC(O)N(H)$(CH_2CH_2O)_n$$C_1$-$C_{10}$ alkyl-N**$R^{3a}R^{3b}$**,

wherein **R^{3a}** and **R^{3b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^4 and **R^5** are, independently in each instance, hydrogen or C_1-C_5 alkyl;

R^6 is –OH, –O–, –$NHNH_2$, –NHNH–, –$NHSO_2(CH_2)_{a1}$-aryl-$(CH_2)_{a2}$N**$R^{6a}R^{6b}$**,

wherein aryl is substituted or unsubstituted; and

R^{6a} and **R^{6b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^7 is, independently in each instance, hydrogen, –OH, –O–, halogen, or –N**$R^{7a}R^{7b}$**,

wherein **R^{7a}** and **R^{7b}** are, independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, –C(O)CH_2OH, –C(O)CH_2O–, a first *N*-terminal amino acid residue, a first amino acid residue, a first *N*-terminal peptide residue, a

first peptide residue, $–CH_2CH_2NH_2$, and $–CH_2CH_2NH–$; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^8 is, independently in each instance, hydrogen, –NH**R^9**, or halogen,

wherein **R^9** is hydrogen, $–C_1$-C_5 alkyl, or $–C(O)C_1$-C_5 alkyl; and

m is one or two;

R^{10}, when present, is -C_1-C_5 alkyl;

Q is $–CH_2–$ or –O– wherein

R^2 is alkyl, alkylene, alkynyl, alkynylene, a regioisomeric triazole, a regioisomeric triazolylene;

wherein said regioisomeric triazole or regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or acyl;

wherein **n** is an integer from one to ten;

wherein **r** is an integer from one to six;

wherein **a**, **a1**, and, **a2** are, independently, zero or one; and

wherein the linker-payload is not **LP1-IVa**, **LP2-Va**, **LP3-IVd**, **LP4-Ve**, **LP5-IVd**, **LP6-Vb**, **LP7-IVd**, **LP9-IVvB**, **LP10-VIh**, **LP11-IVvB**, **LP12-VIi**, **LP13-Ve**, **LP14-Ve**, **LP15-VIh**, **LP16-Ve**, **LP17-Ve**, **LP18-Ve**, **LP19-Ve**, **LP20-Ve**, **LP21-Ve**, **LP22-Ve**, **LP23-Vb**, **LP24-Vb**, **LP25-Ve**, and **LP26-Ve**, or a pharmaceutically acceptable salt thereof.

[0011] In another example, set forth herein is an antibody-drug conjugate including an antibody, or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof is conjugated to a compound as described herein.

[0012] In another example, set forth herein are methods for making the compounds, linker-payloads, or antibody-drug conjugates, and compositions described herein.

[0012a] In another aspect, there is provided a pharmaceutical composition comprising the compound as provided herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[0012b] In another aspect, there is provided the compound as provided herein for use in treating cancer or tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

[0012c] In another aspect, there is provided the compound as provided herein for use in treating cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small

cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

[0012d] In another aspect, there is provided use of the compound as provided herein in the manufacture of a medicament for the treatment of cancer.

[0012e] In another aspect, there is provided use of the compound as provided herein in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

[0012f] In another aspect, there is provided use of the compound as provided herein in the manufacture of a medicament for the treatment of tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

[0012g] In another aspect, there is provided the pharmaceutical composition as provided herein for use in treating cancer.

[0012h] In another aspect, there is provided the pharmaceutical composition as provided herein for use in treating cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial

cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

[0012i] In another aspect, there is provided the pharmaceutical composition as provided herein for use in treating tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

[0012j] In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of cancer.

[0012k] In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

BRIEF DESCRIPTIONS OF THE DRAWING

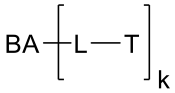
[0013] FIGS. 1-11, 12A, 12B, 13A, 13B, 14, 15A, 15B, 15C, and 16 show synthetic chemistry schemes for tubulyisin payloads, and tubulysin linker-payloads, wherein each are capable of conjugation to or conjugated to an antibody or antigen-binding fragment thereof.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0014] Provided herein are compounds, compositions, and methods useful for treating for example, cancer in a subject.

WHAT IS CLAIMED IS:

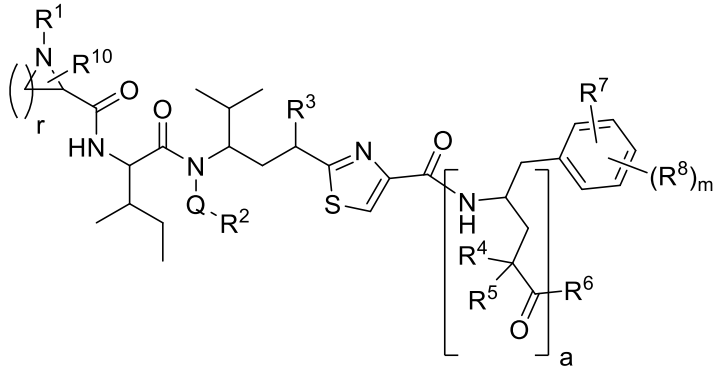
1. A compound having the following formula



or a pharmaceutically acceptable salt thereof, wherein

BA is a binding agent;

L is a linker covalently bound to **BA** and to **T**;

T is  wherein

R[1] is a bond, hydrogen, C_1-C_{10} alkyl, a first *N*-terminal amino acid residue, a first amino acid residue, –C_1-C_{10} alkyl-N**R[3a]R[3b]**, or –C_1-C_{10} alkyl-OH;

R[3] is hydroxyl, –O–, –O-C_1-C_5 alkyl, –OC(O)C_1-C_5 alkyl, –OC(O)N(H)C_1-C_{10} alkyl, –OC(O)N(H)C_1-C_{10} alkyl-N**R[3a]R[3b]**, –NHC(O)C_1-C_5 alkyl, or –OC(O)N(H)$(CH_2CH_2O)_{\mathbf{n}}C_1$-$C_{10}$ alkyl-N**R[3a]R[3b]**,

wherein **R[3a]** and **R[3b]** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R[4] and **R[5]** are, independently in each instance, hydrogen or C_1-C_5 alkyl;

R[6] is –OH, –O–, –$NHNH_2$, –NHNH–, –$NHSO_2(CH_2)_{\mathbf{a1}}$-aryl-$(CH_2)_{\mathbf{a2}}$N**R[6a]R[6b]**,

wherein aryl is substituted or unsubstituted; and

R[6a] and **R[6b]** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R[7] is, independently in each instance, hydrogen, –OH, –O–, halogen, or –N**R[7a]R[7b]**,

wherein **R[7a]** and **R[7b]** are, independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, –C(O)CH_2OH, –C(O)CH_2O–, a first *N*-terminal amino acid residue, a first amino acid residue, a first *N*-terminal peptide residue, a

first peptide residue, $–CH_2CH_2NH_2$, and $–CH_2CH_2NH–$; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^8 is, independently in each instance, hydrogen, $–NHR^9$, or halogen,

wherein **R^9** is hydrogen, $–C_1$-C_5 alkyl, or $–C(O)C_1$-C_5 alkyl; and

m is one or two;

R^{10}, when present, is $-C_1$-C_5 alkyl;

Q is $–CH_2–$ or –O– wherein

R^2 is alkyl, alkylene, alkynyl, alkynylene, a regioisomeric triazole, a regioisomeric triazolylene;

wherein said regioisomeric triazole or regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or acyl;

wherein **n** is an integer from one to ten;

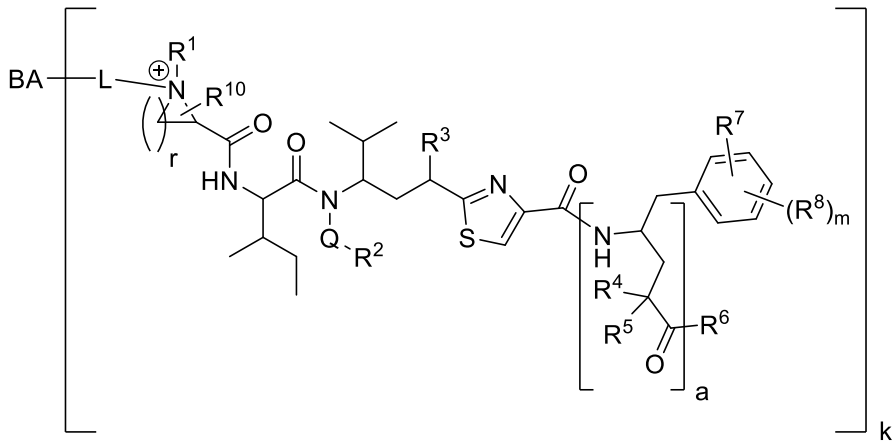
wherein **r** is an integer from one to six;

wherein **a**, **a1**, and, **a2** are, independently, zero or one; and

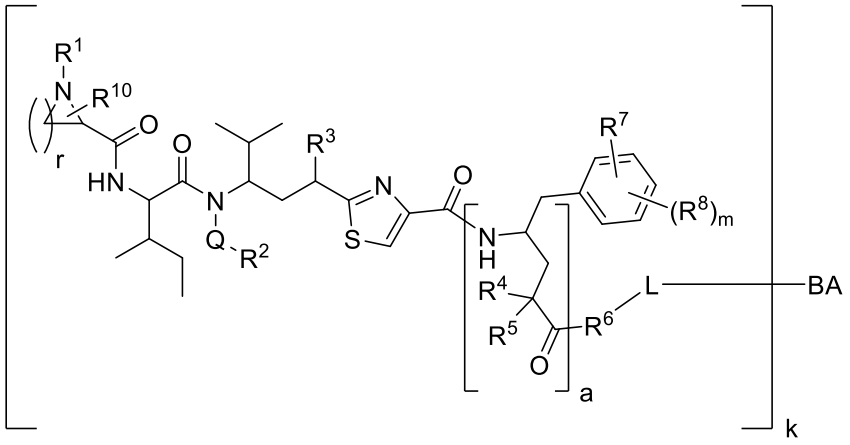
k is an integer from one to thirty;

wherein **T** is not compound **IVa**, **IVa'**, **IVb**, **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, **IVj**, **IVk**, **IVl**, **IVm**, **IVn**, **IVo**, **IVp**, **IVq**, **IVr**, **IVs**, **IVt**, **IVu**, **IVvA**, **IVvB**, **IVw**, **IVx**, **IVy**, **Va**, **Va'**, **Vb**, **Vc**, **Vd**, **Ve**, **Vf**, **Vg**, **Vh**, **Vi**, **Vj**, **Vk**, **VIa**, **IVb**, **VIc**, **VId**, **VIe**, **VIf**, **VIg**, **VIh**, **Vl**, **VIi**, **VII**, **VIII**, **IX**, **X**, **D-5a**, and **D-5c**, or a pharmaceutically acceptable salt thereof, covalently bound to **L**.

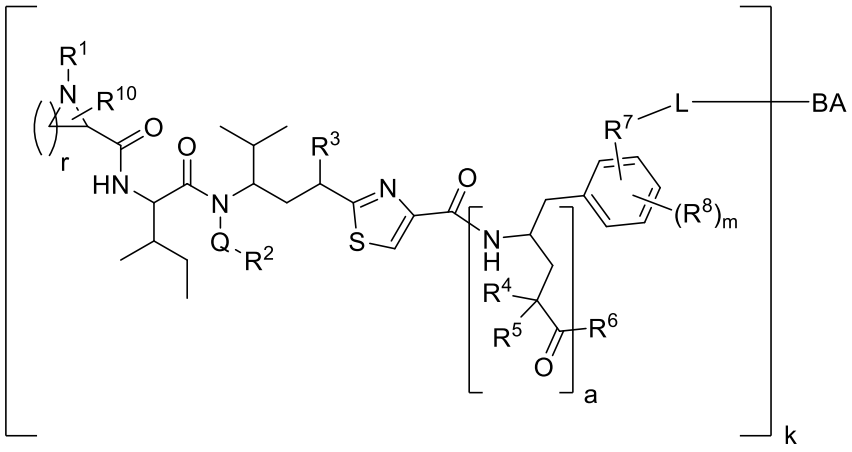
2. The compound of claim 1, having a Formula **A**, **B**, **C**, **D**, or **E**



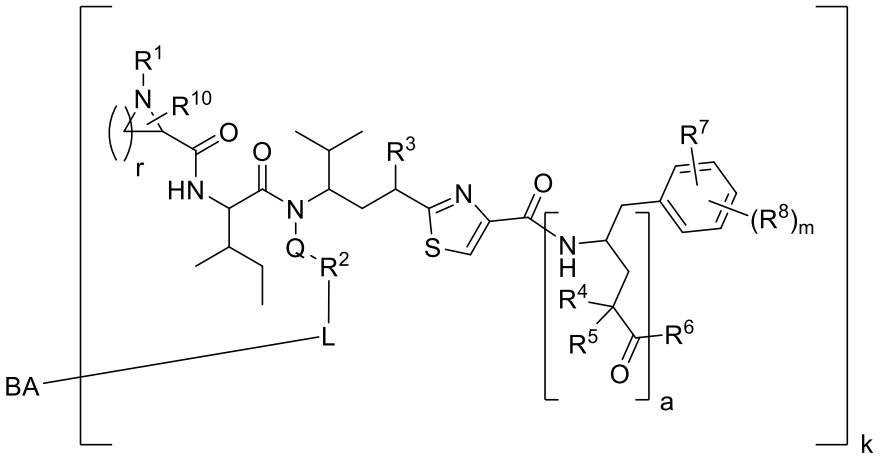
(**A**)



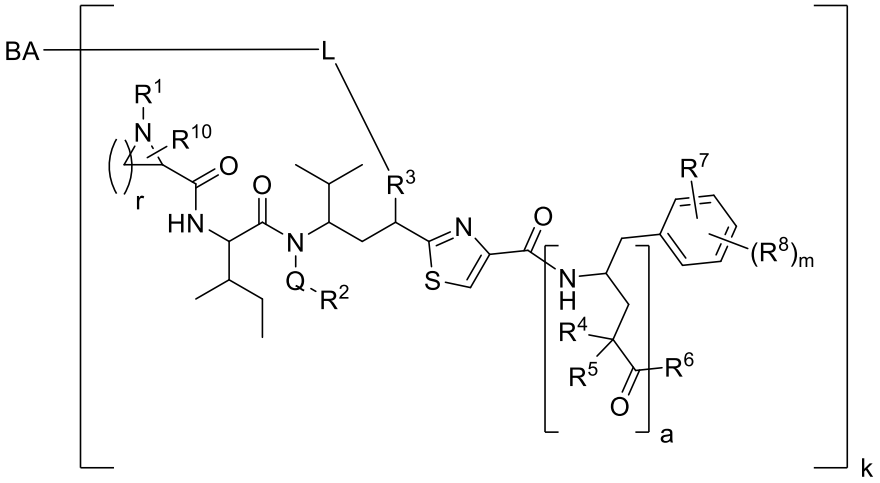
(**B**)



(**C**)



(**D**)



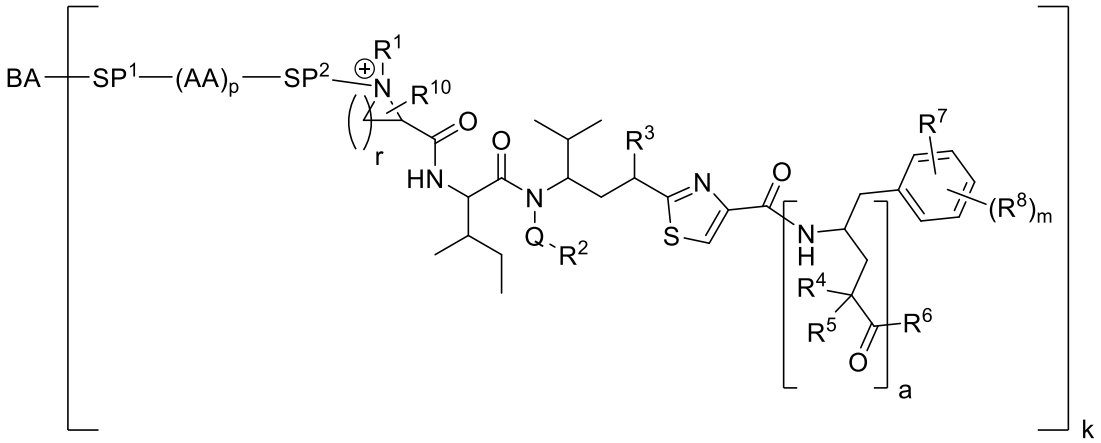
(**E**)

wherein **L** is a linker.

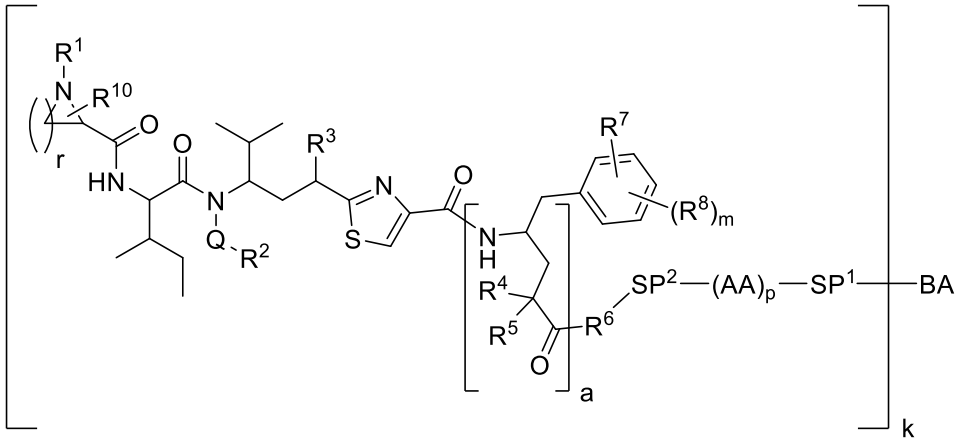
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^7}$ is, independently in each instance, hydrogen, –OH, –O–, halogen, or –N$\mathbf{R^{7a}R^{7b}}$,

wherein $\mathbf{R^{7a}}$ and $\mathbf{R^{7b}}$ are, independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, –C(O)CH_2OH, –C(O)CH_2O–, a first *N*-terminal amino acid residue, a first *N*-terminal peptide residue, –$CH_2CH_2NH_2$, and –CH_2CH_2NH–, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted.

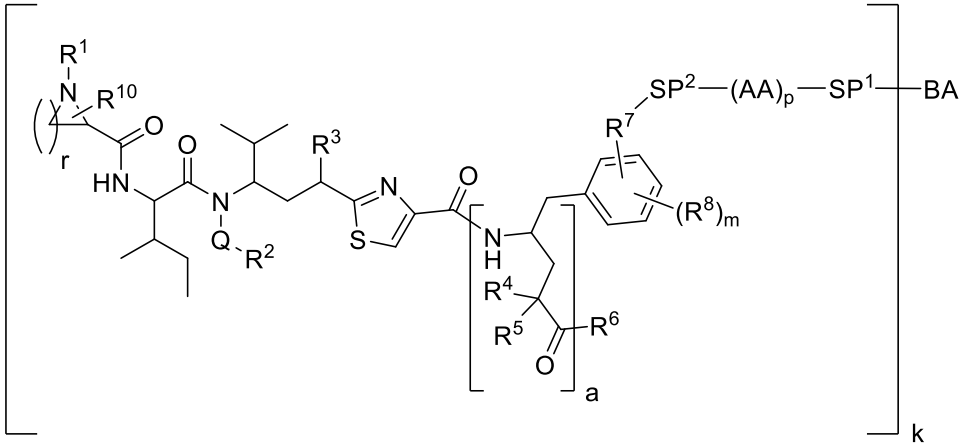
4. The compound of claim 2, wherein the compound is of the Formula **A'**, **B'**, **C'**, **D'**, or **E'**



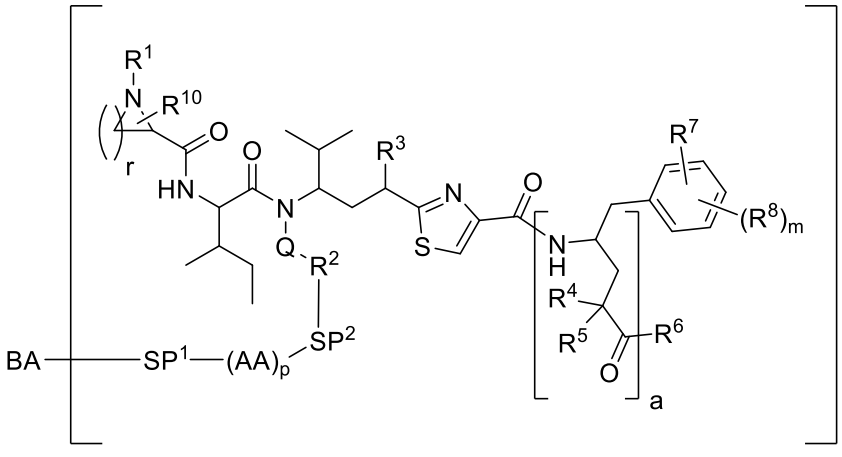
(**A'**)



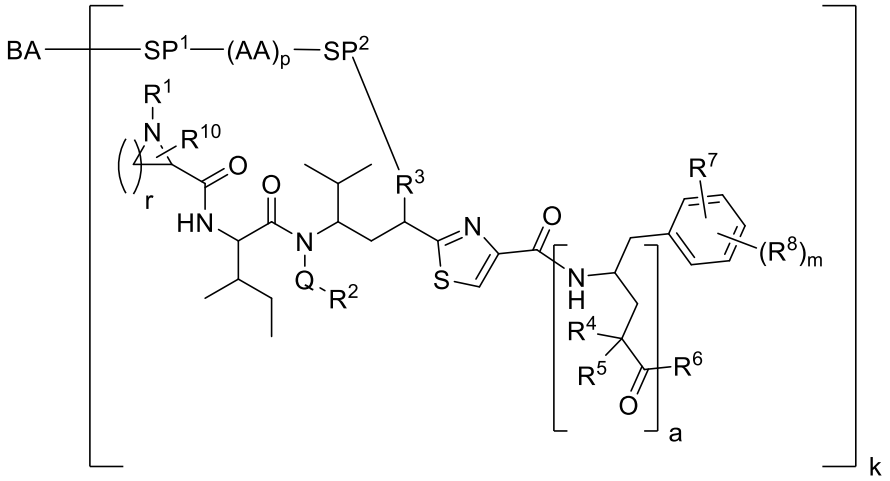
(**B'**)



(**C'**)



(**D'**)



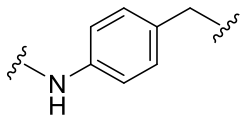
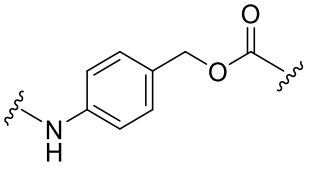
(**E'**)

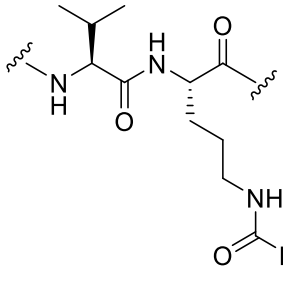
wherein **SP**^{1} and **SP**^{2}, when present, are spacer groups;

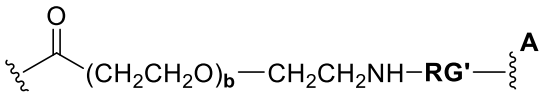
each **AA**, when present, is a second amino acid residue; and

p is an integer from zero to ten.

5. The compound of claim 4, wherein

the –**SP**^{2}– spacer, when present, is  or ;

the second –(**AA**)$_{\mathbf{p}}$– is ;

the –**SP**^{1}– spacer is ,

wherein **RG'** is a reactive group residue following reaction of a reactive group **RG** with a binding agent;

 is a bond, direct or indirect, to the binding agent; and

b is an integer from one to four.

6. The compound of claim 5, wherein the binding agent is an antibody modified with a primary amine compound according to the Formula H_2N-**LL**-**X**, wherein **LL** is a divalent linker selected from the group consisting of

a divalent polyethylene glycol (PEG) group;

$–(CH_2)_{\mathbf{n}}–$;

$–(CH_2CH_2O)_{\mathbf{n}}-(CH_2)_{\mathbf{p}}–$;

$–(CH_2)_{\mathbf{n}}-N(H)C(O)-(CH_2)_{\mathbf{m}}–$;

$–(CH_2CH_2O)_{\mathbf{n}}-N(H)C(O)-(CH_2CH_2O)_{\mathbf{m}}-(CH_2)_{\mathbf{p}}–$;

$–(CH_2)_{\mathbf{n}}-C(O)N(H)-(CH_2)_{\mathbf{m}}–$;

$–(CH_2CH_2O)_{\mathbf{n}}-C(O)N(H)-(CH_2CH_2O)_{\mathbf{m}}-(CH_2)_{\mathbf{p}}–$;

$–(CH_2)_{\mathbf{n}}-N(H)C(O)-(CH_2CH_2O)_{\mathbf{m}}-(CH_2)_{\mathbf{p}}–$;

$–(CH_2CH_2O)_{\mathbf{n}}-N(H)C(O)-(CH_2)_{\mathbf{m}}–$;

$–(CH_2)_{\mathbf{n}}-C(O)N(H)-(CH_2CH_2O)_{\mathbf{m}}-(CH_2)_{\mathbf{p}}–$; and

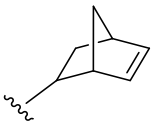
$–(CH_2CH_2O)_{\mathbf{n}}-C(O)N(H)-(CH_2)_{\mathbf{m}}–$,

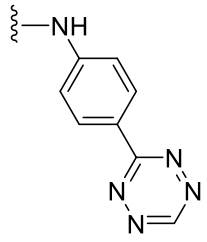
wherein

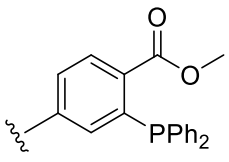
n is an integer selected from one to twelve;

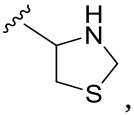
m is an integer selected from zero to twelve;

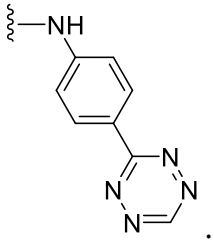
p is an integer selected from zero to two; and

X is selected from the group consisting of –SH, $–N_3$, –C≡CH, –C(O)H, tetrazole, 



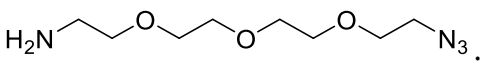
,


,


, and


.

7. The compound of claim 6, wherein the binding agent is an antibody modified with a primary amine according to the following formula



.

8. The compound of claim 4, wherein **Q** is –O–.

9. The compound of claim 4, wherein
Q is $–CH_2–$;
$\mathbf{R^1}$ is C_1-C_{10} alkyl;
$\mathbf{R^2}$ is alkyl;
$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;
$\mathbf{R^6}$ is –OH;
$\mathbf{R^{10}}$ is absent;
wherein **r** is four; and
wherein **a** is one.

10. The compound of claim 9, according to the structure of **C'**, or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen or fluoro.

12. The compound of claim 9, according to the structure of **E'**, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12, wherein $\mathbf{R^3}$ is $–OC(O)N(H)CH_2CH_2NH–$ or $–OC(O)N(H)CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2NH–$.

14. The compound of claim 4, wherein
Q is $–CH_2–$;
$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;
$\mathbf{R^2}$ is alkyl;
$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;
$\mathbf{R^6}$ is –OH;
wherein **r** is three or four; and
wherein **a** is one.

15. The compound of claim 14, according to the structure of **C'**, or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen.

17. The compound of claim 4, wherein

Q is $–CH_2–$;

$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;

$\mathbf{R^2}$ is alkyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;

$\mathbf{R^6}$ is –OH;

$\mathbf{R^{10}}$ is absent;

wherein **r** is four; and

wherein **a** is one.

18. The compound of claim 17, according to the structure of **C'**, or a pharmaceutically acceptable salt thereof.

19. The compound of claim 18, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen.

20. The compound of claim 4, wherein

Q is –O–;

$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;

$\mathbf{R^2}$ is alkyl or alkynyl;

$\mathbf{R^3}$ is hydroxyl or $–OC(O)C_1$-C_5 alkyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;

$\mathbf{R^6}$ is –OH;

$\mathbf{R^{10}}$, when present, is -C_1-C_5 alkyl;

wherein **r** is three or four; and

wherein **a** is one.

21. The compound of claim 20, according to the structure of **C'**, or a pharmaceutically acceptable salt thereof.

22. The compound of claim 21, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen.

23. The compound of claim 4, wherein

Q is $–CH_2–$ or –O–;

R[1] is C_1-C_{10} alkyl;

R[2] is alkyl or alkynyl;

R[4] and **R[5]** are C_1-C_5 alkyl;

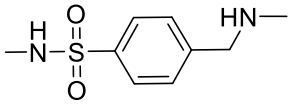
R[6] is $–NHSO_2(CH_2)_{a1}$-aryl-$(CH_2)_{a2}N\mathbf{R^{6a}R^{6b}}$;

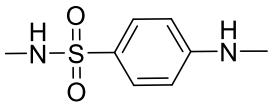
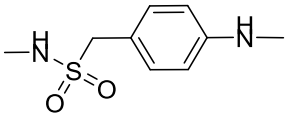
R[10] is absent;

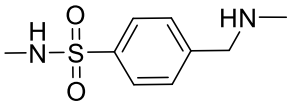
wherein **r** is four; and

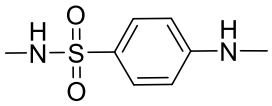
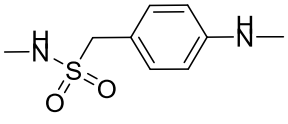
wherein **a**, **a1**, and, **a2** are, independently, zero or one.

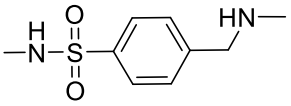
24. The compound of claim 23, according to the structure of **B'**, or a pharmaceutically acceptable salt thereof.

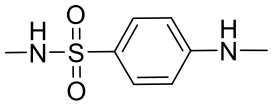
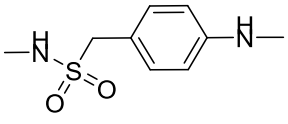
25. The compound of claim 24, wherein **R[6]** is ,

, or .

26. The compound of claim 24, wherein **a** is zero; and **R[6]** is ,

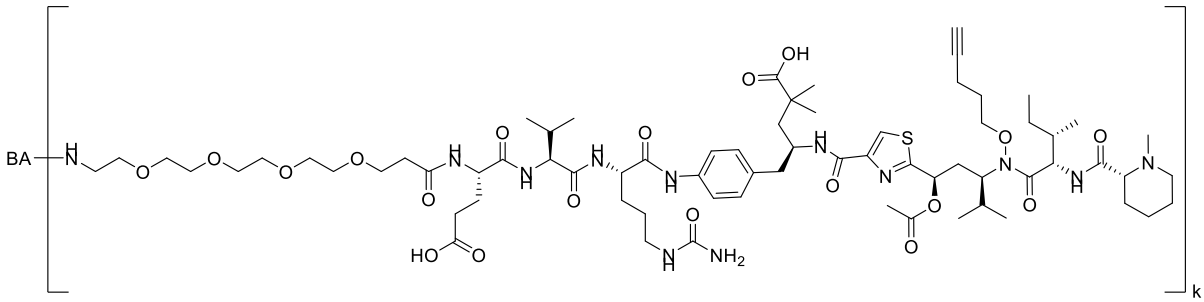
, or .

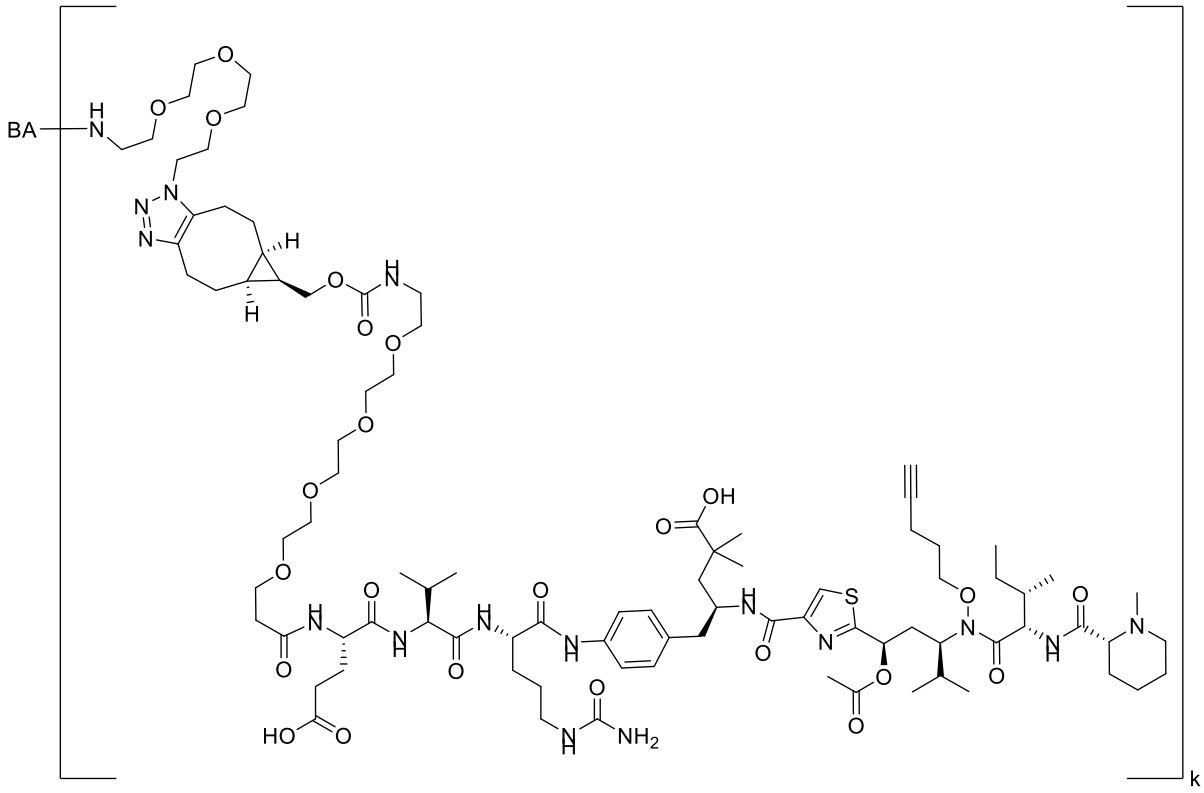
27. The compound of claim 24, wherein **a** is one; and **R[6]** is ,

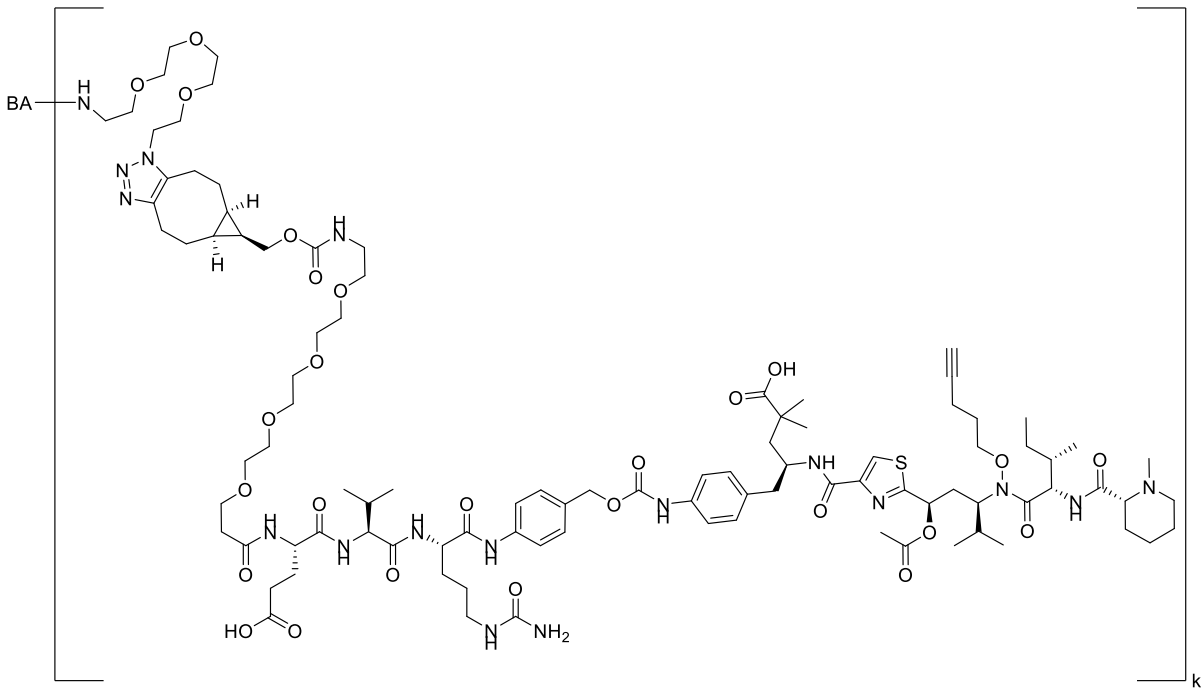
, or .

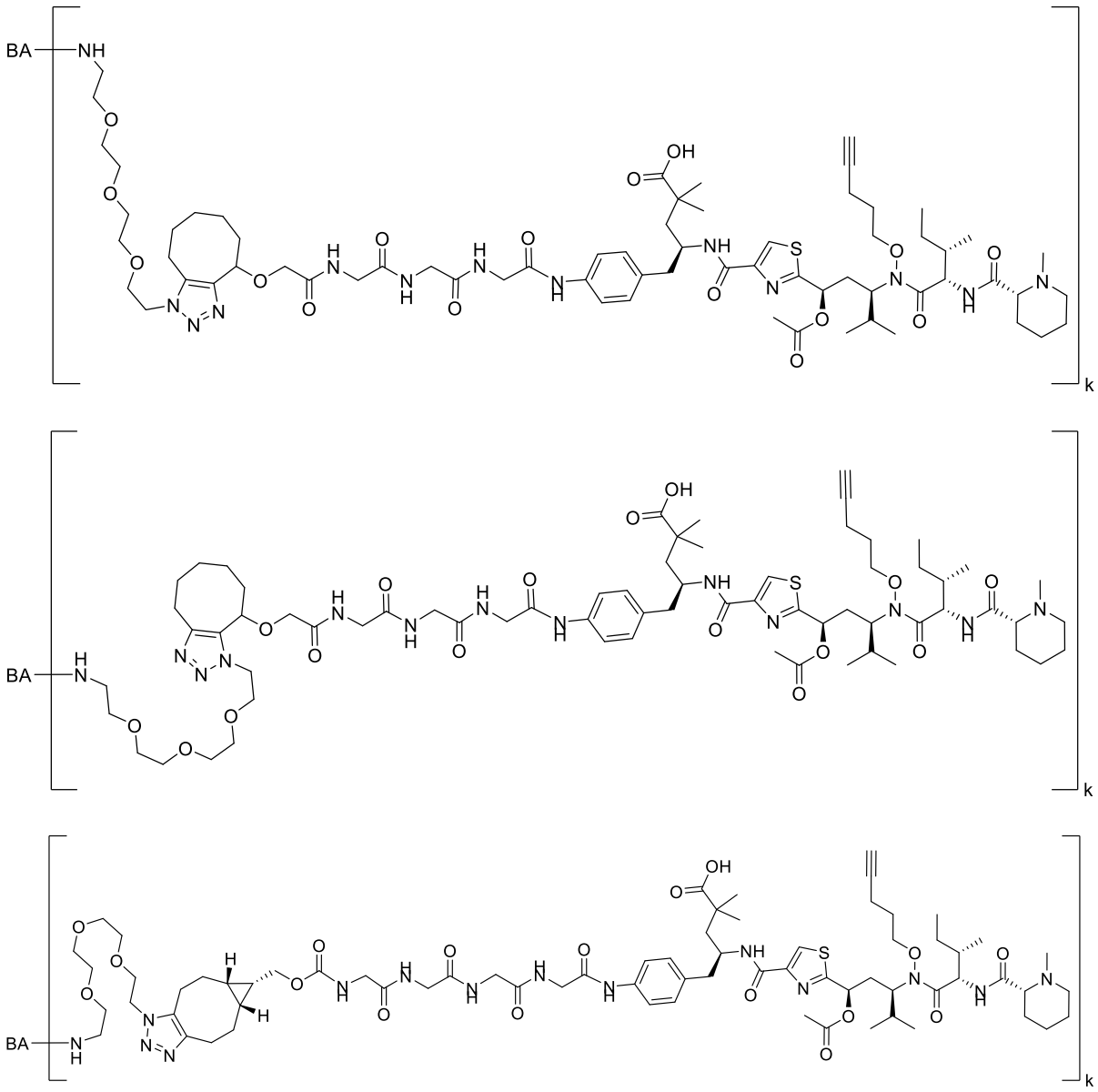
28. The compound of claim 21, wherein **R[7]** is –O–; and **R[8]** is hydrogen.

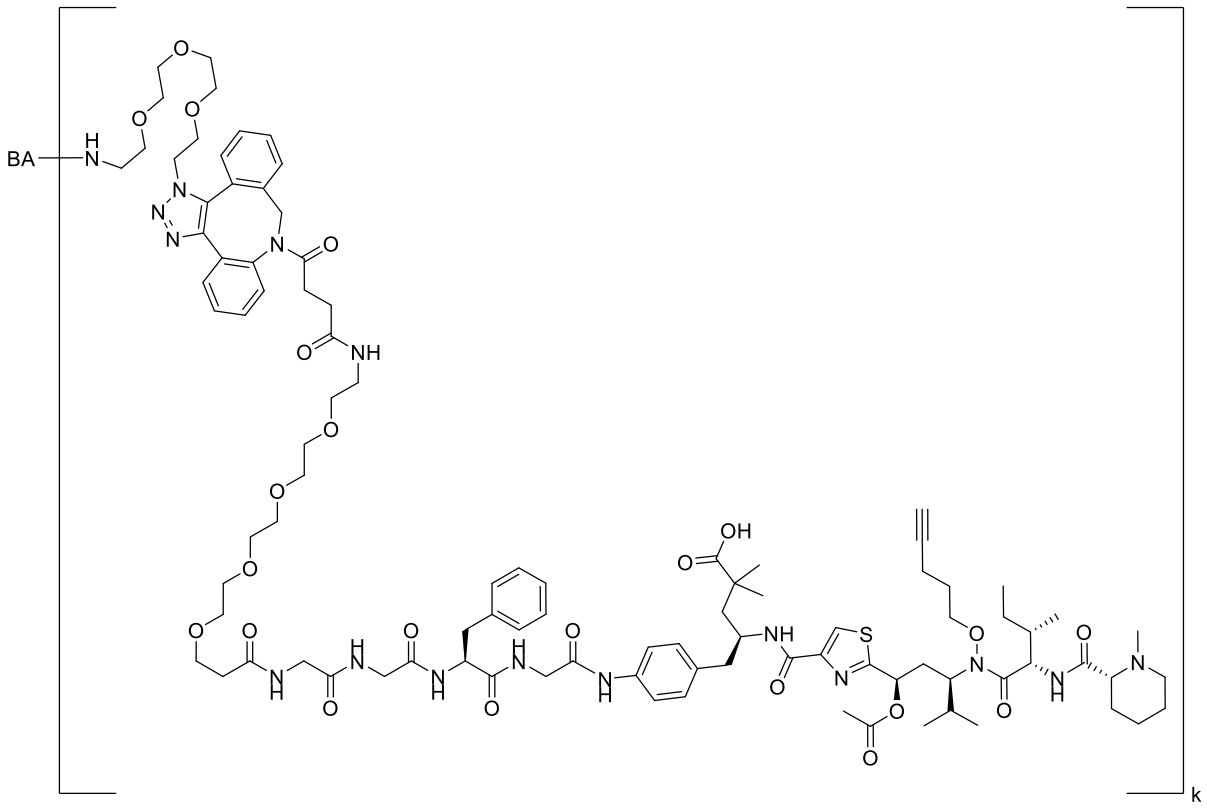
29. The compound of claim 4, selected from the group consisting of

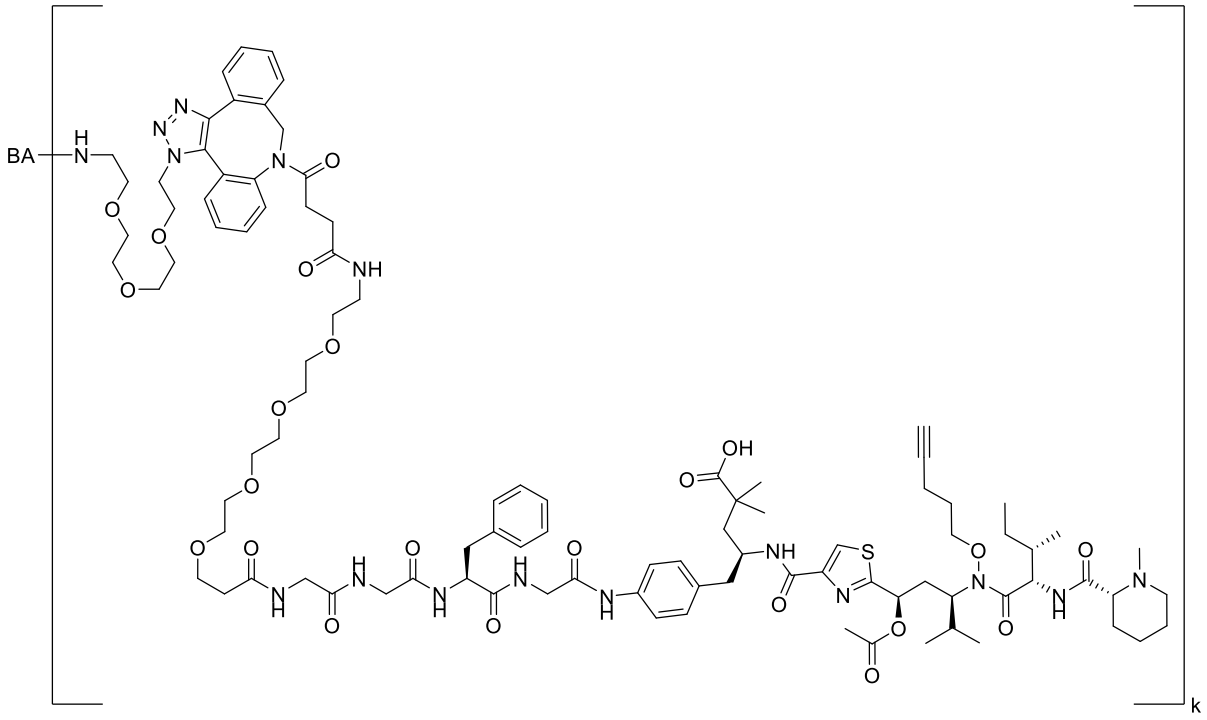

BA
OH
HO
NH2
k

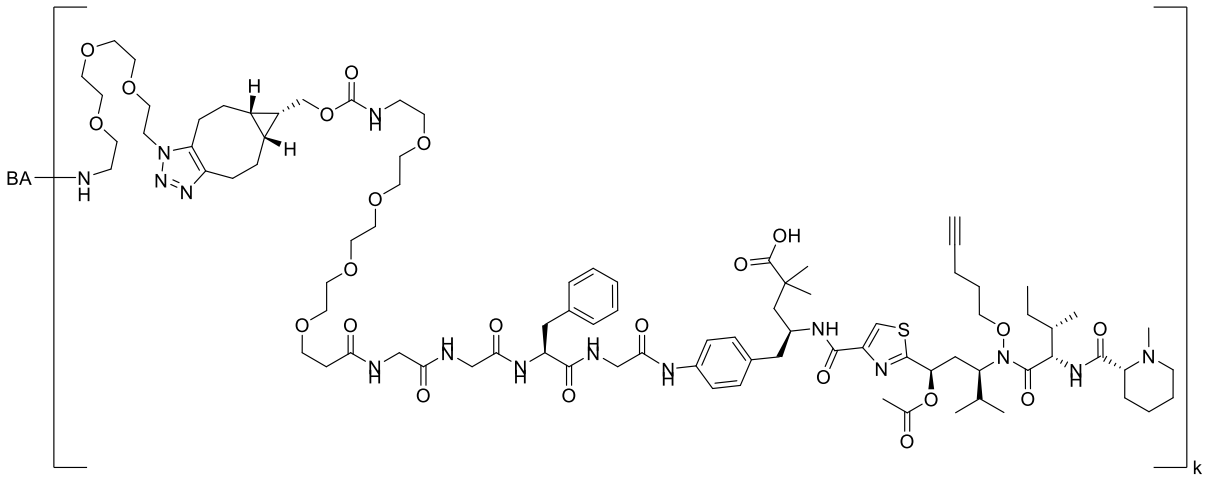

BA
OH
HO
NH2
k

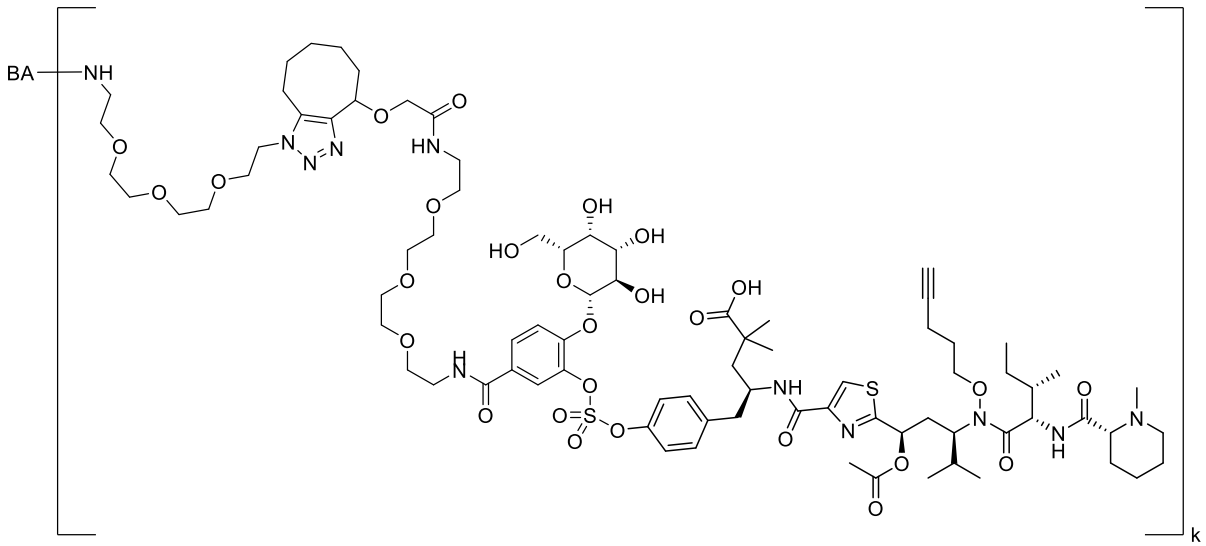

BA
OH
HO
NH2
k

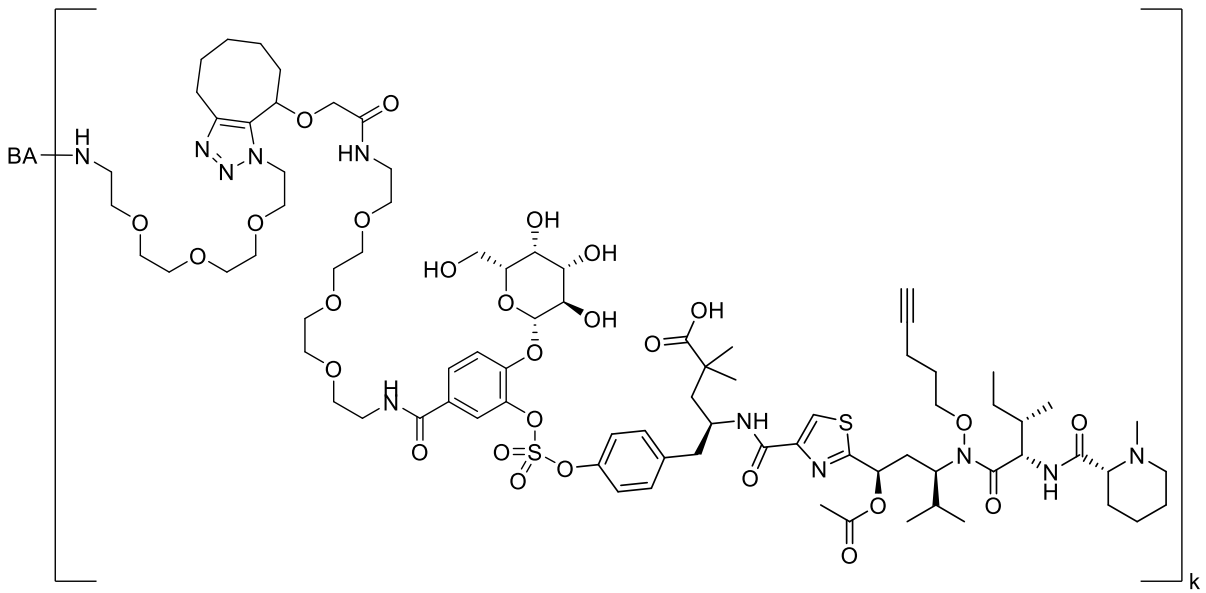


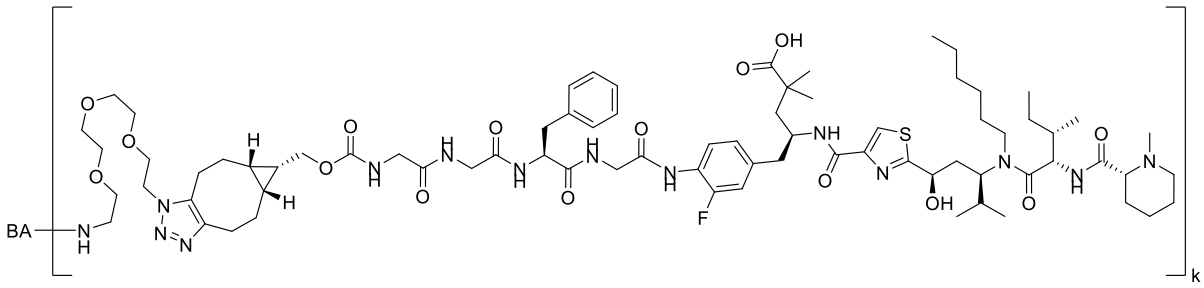


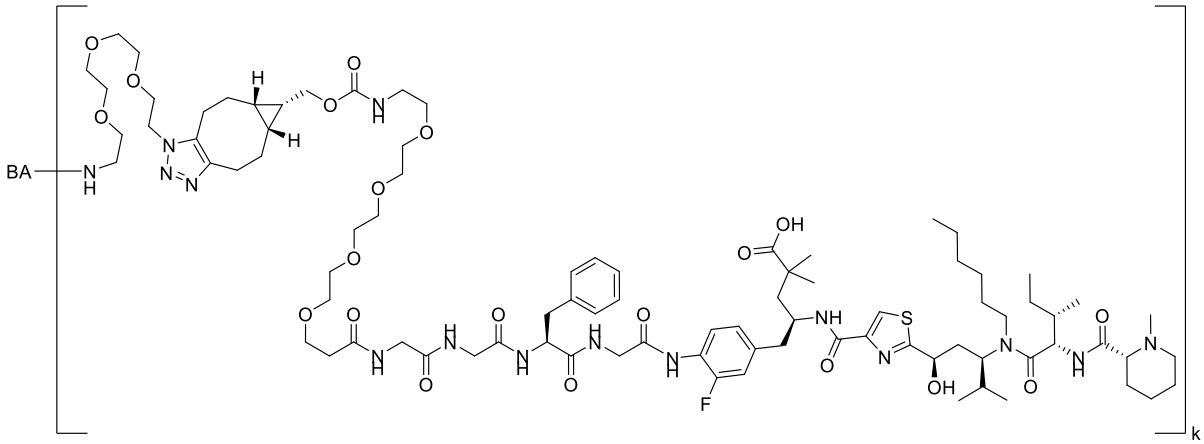


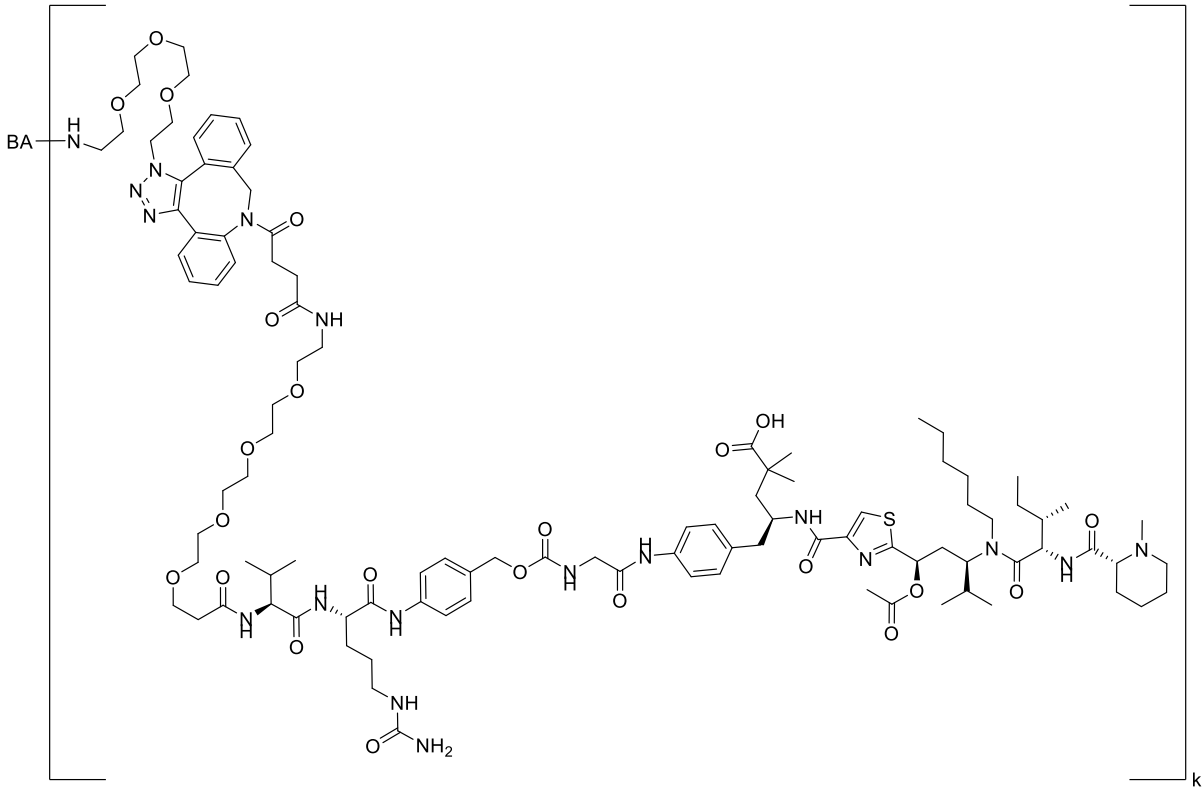


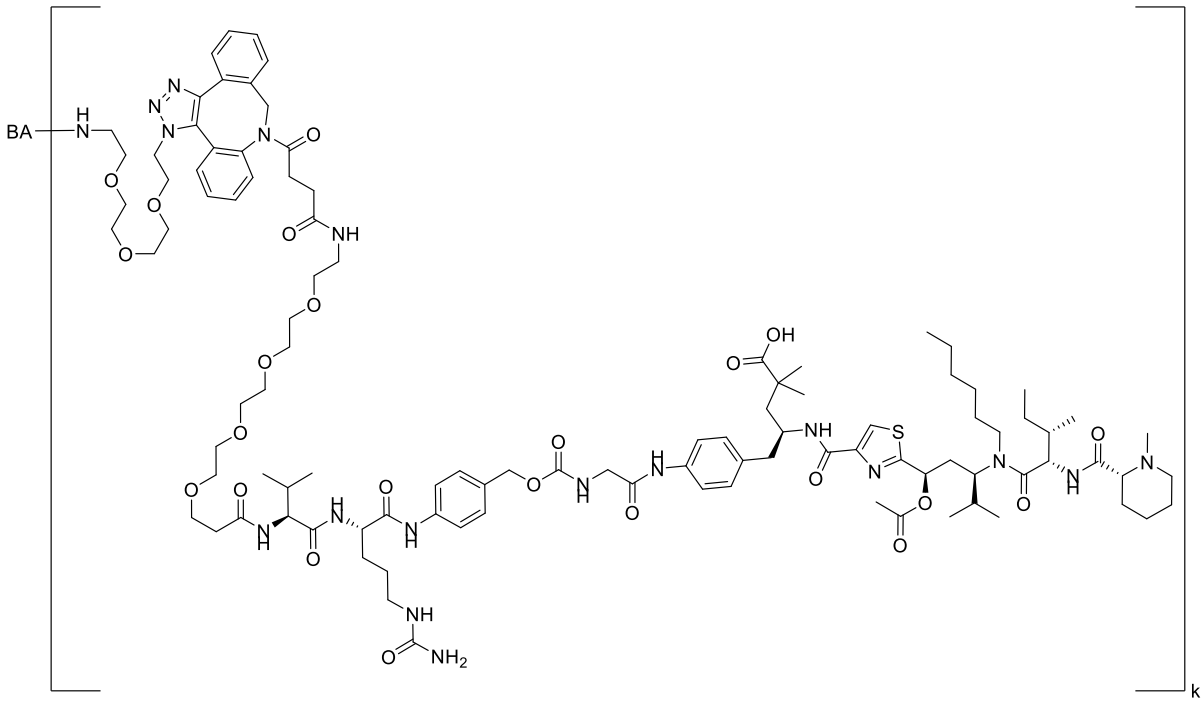


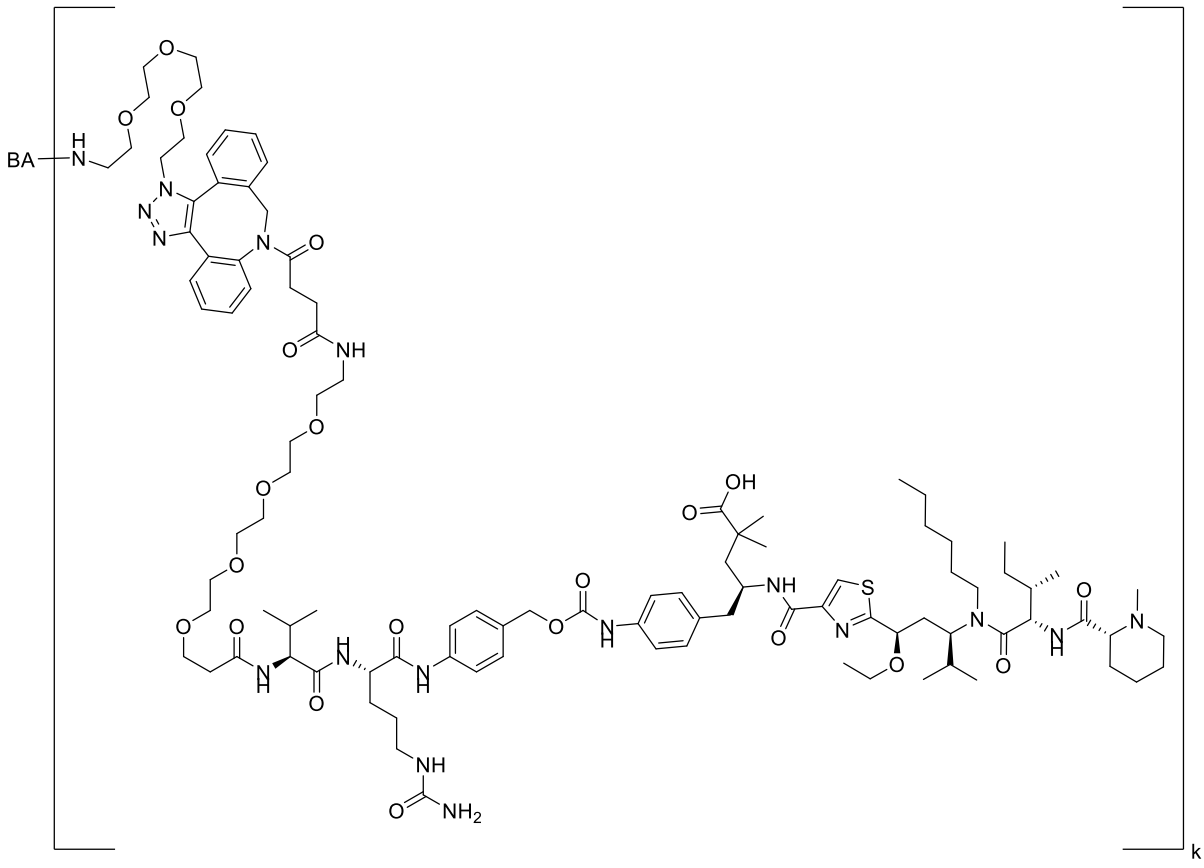


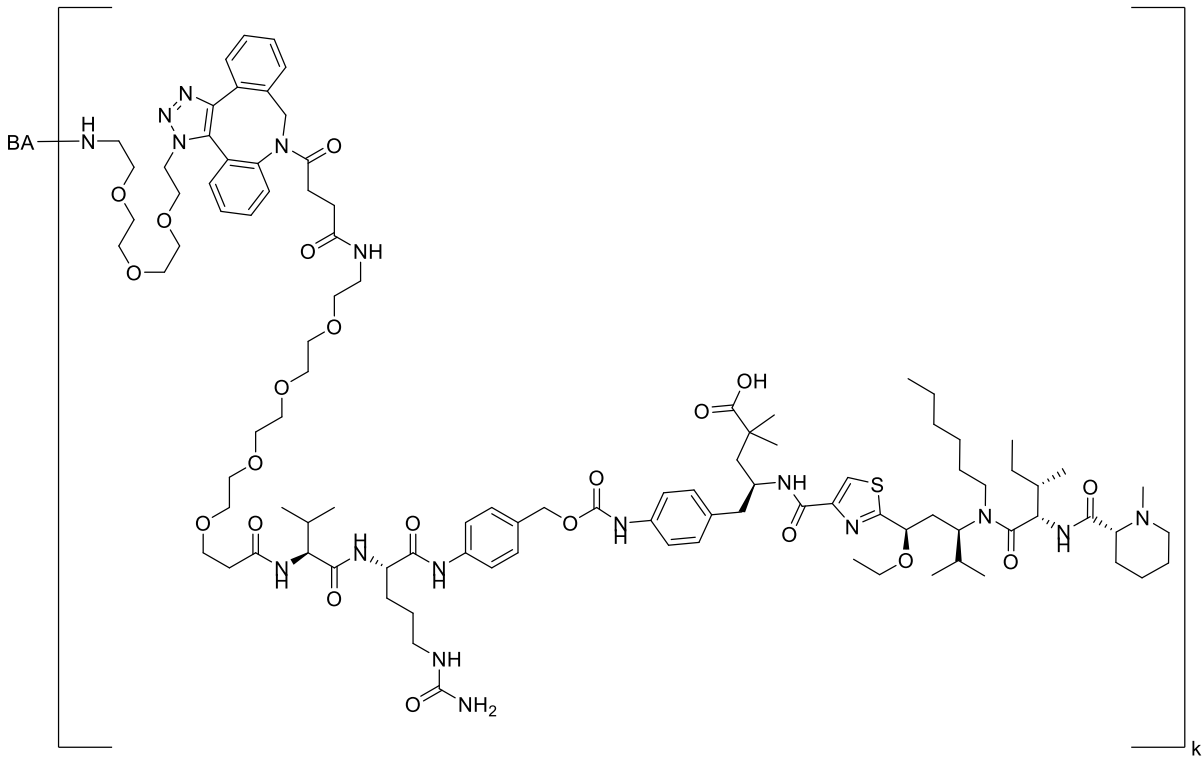

BA
k

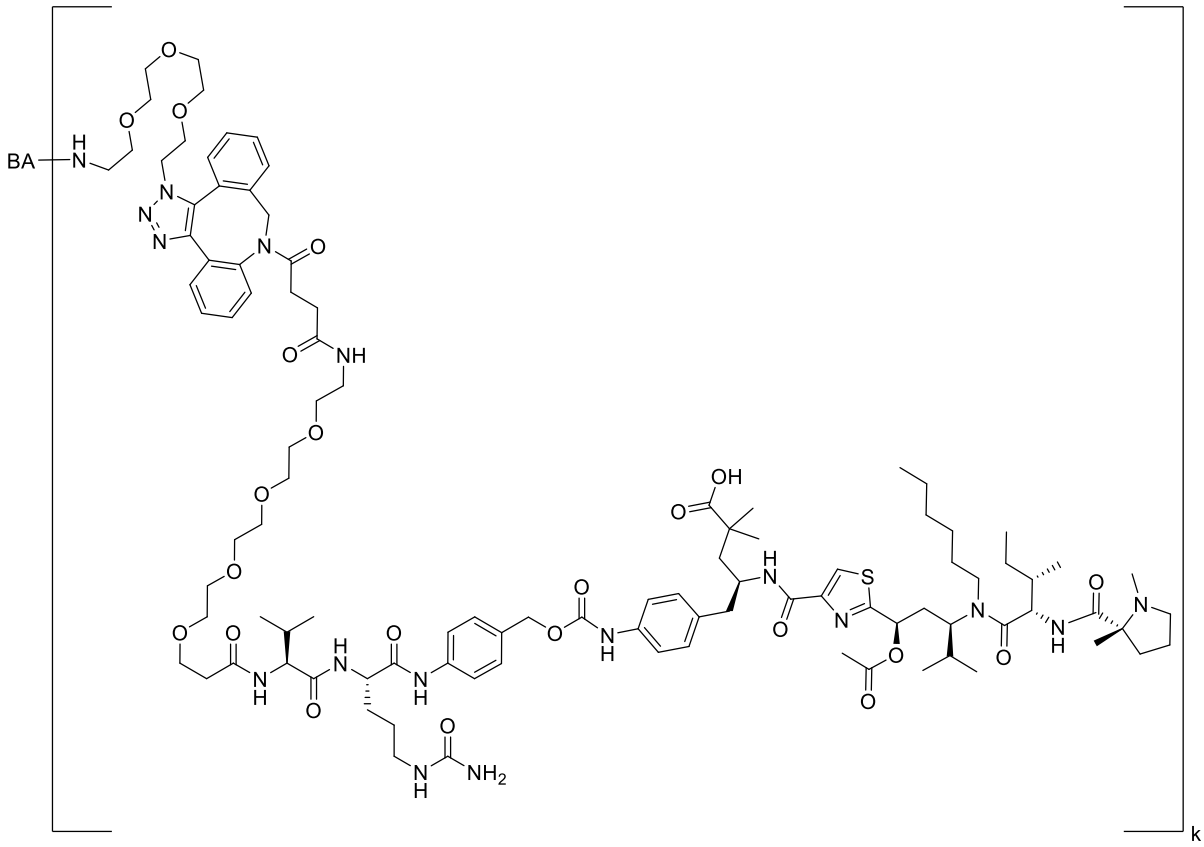

BA
k

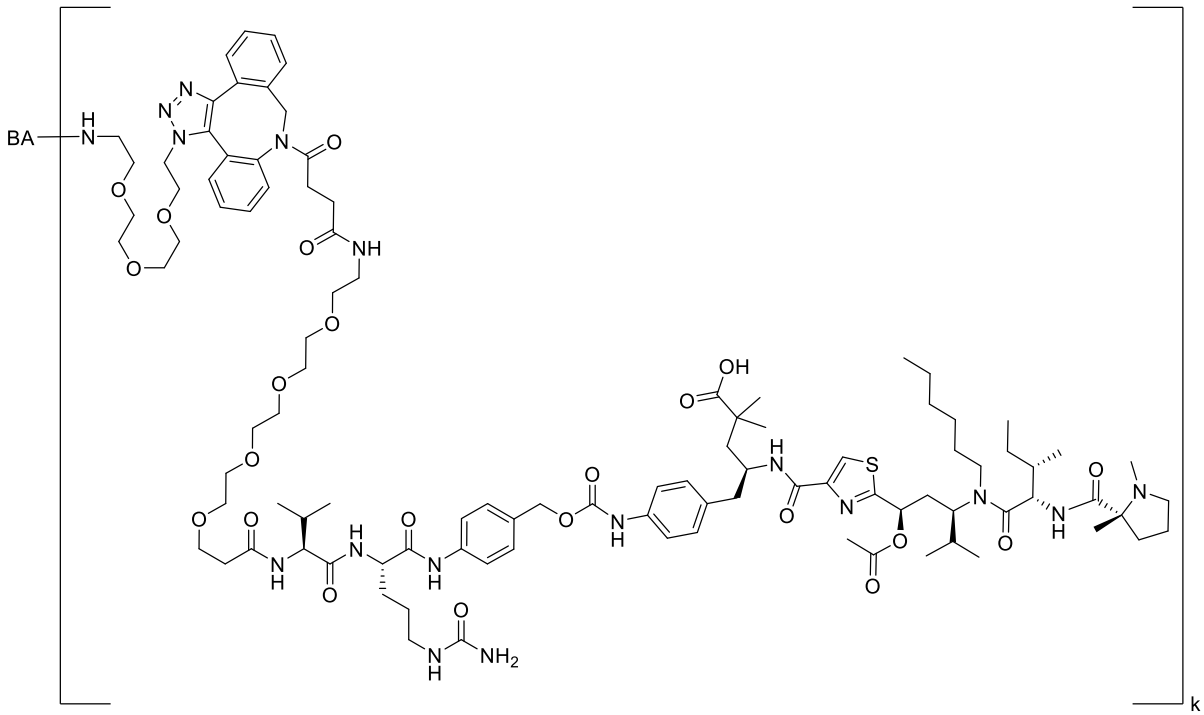

BA
k

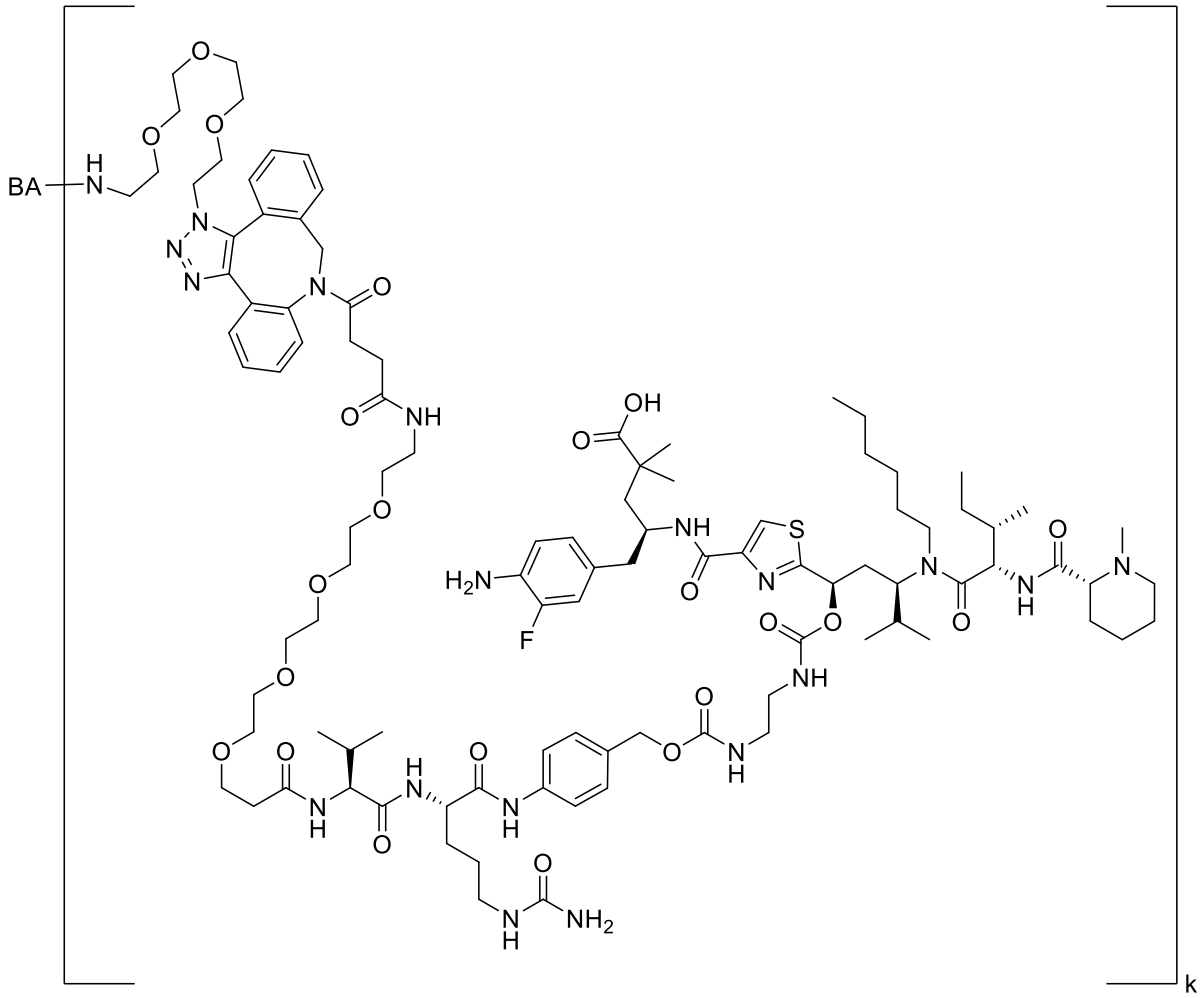


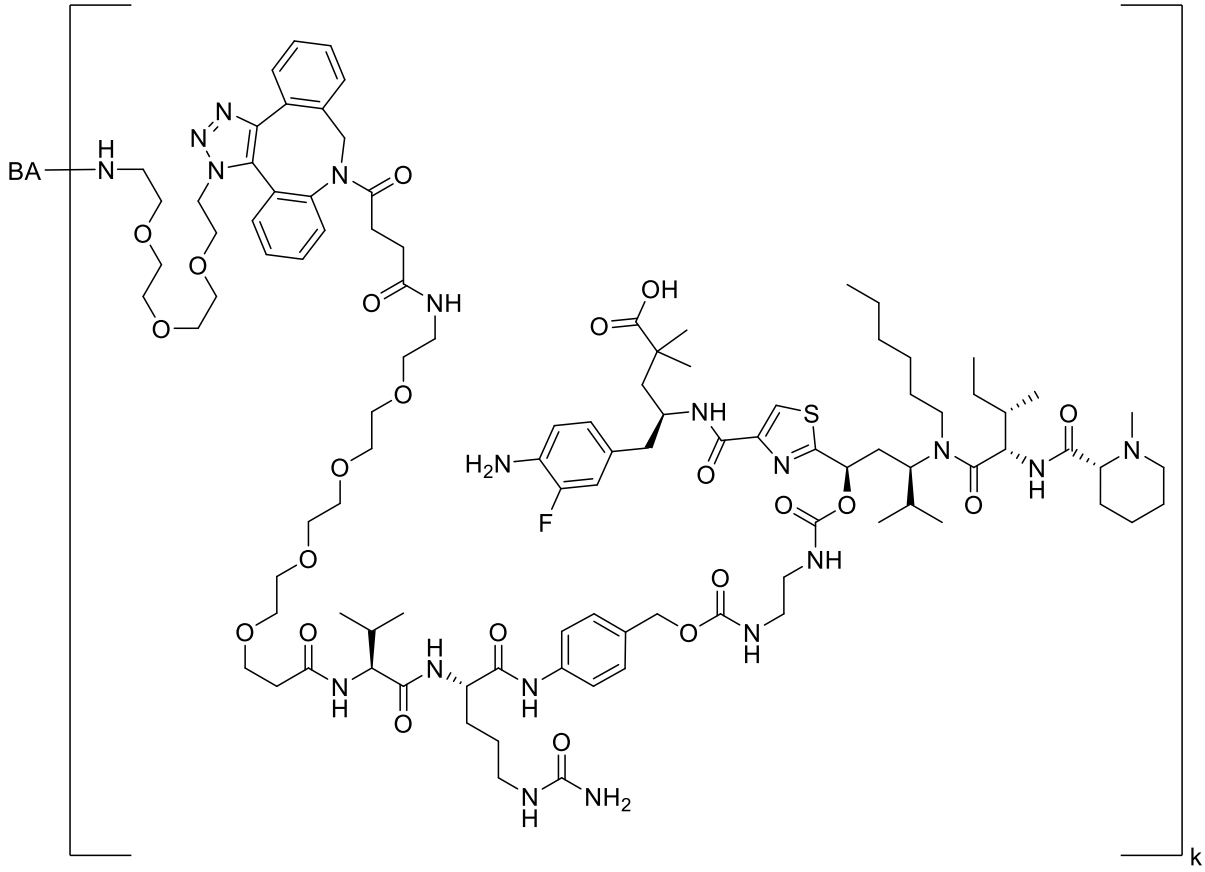


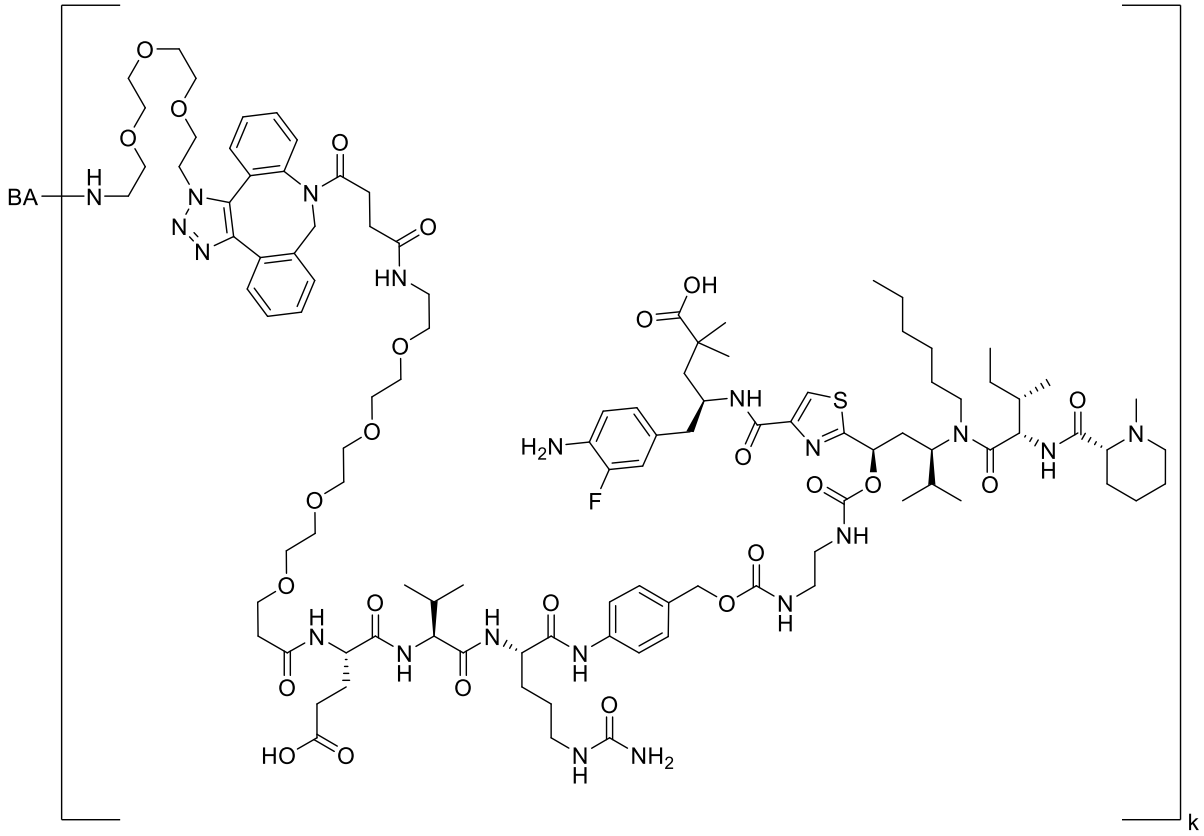


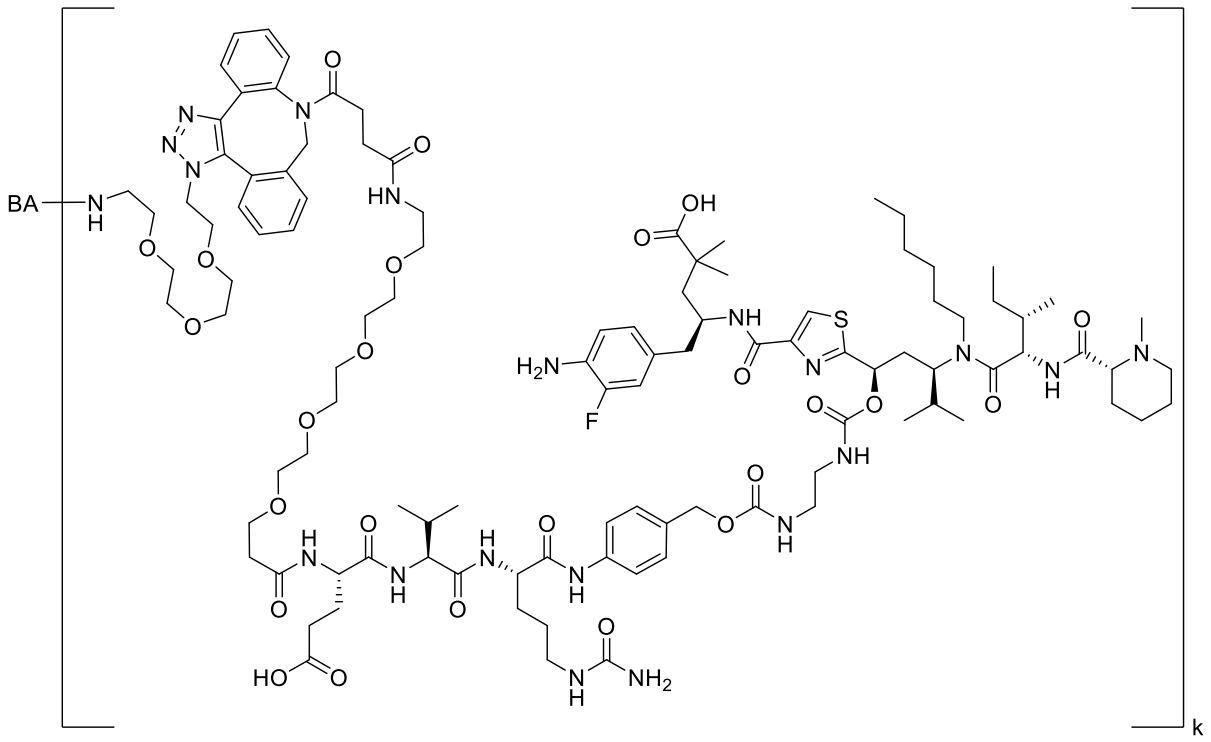


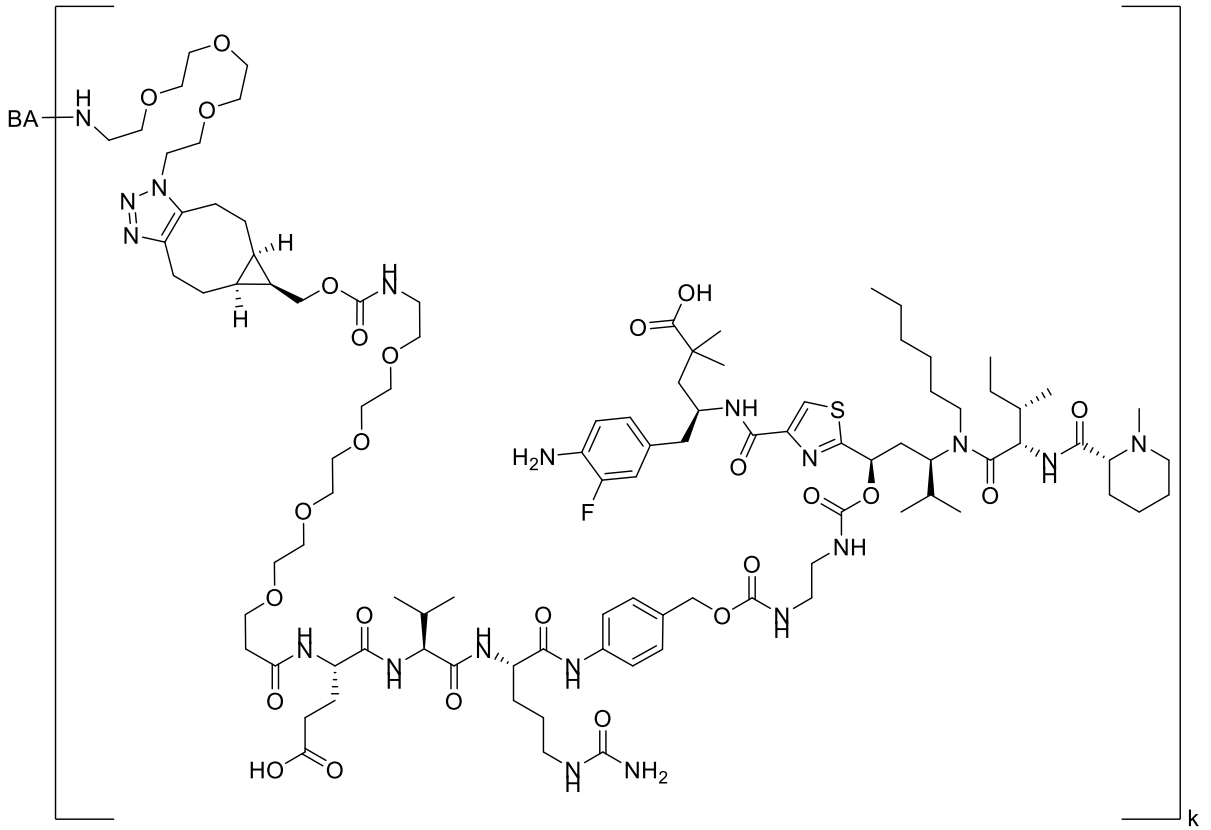


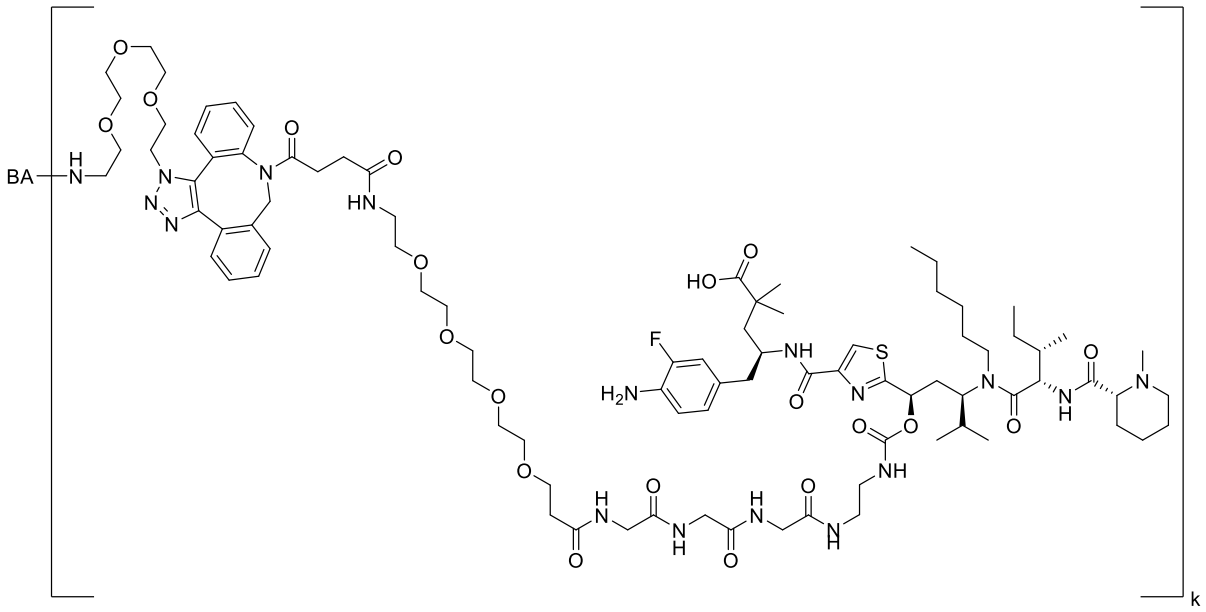


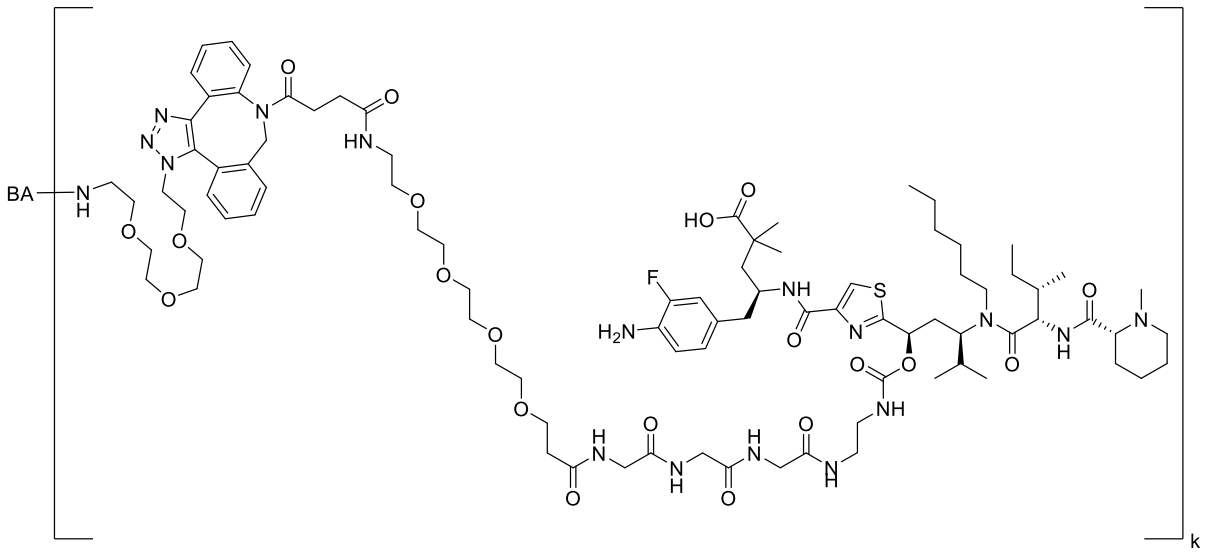


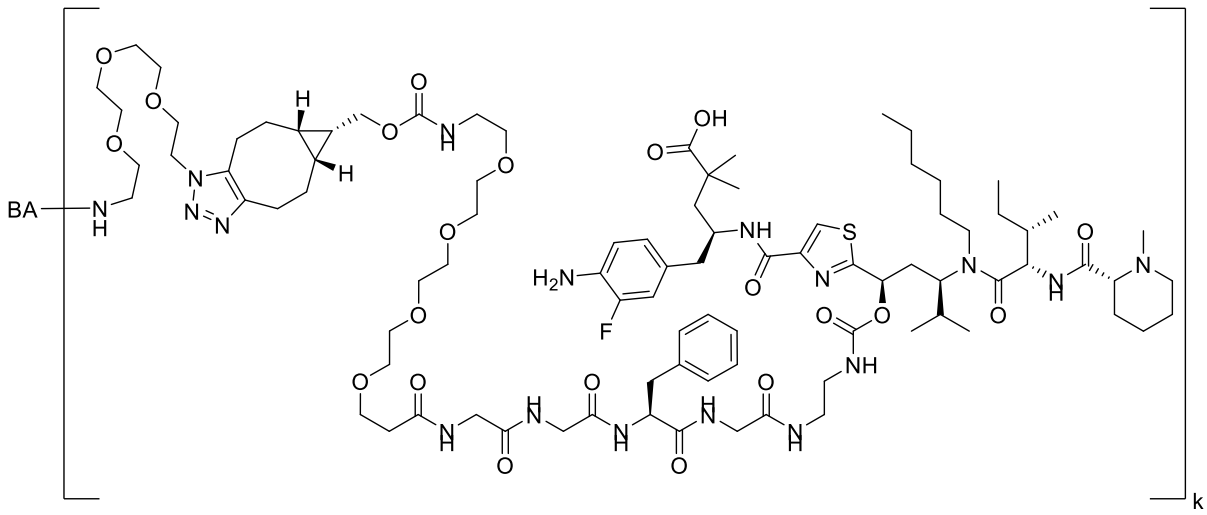


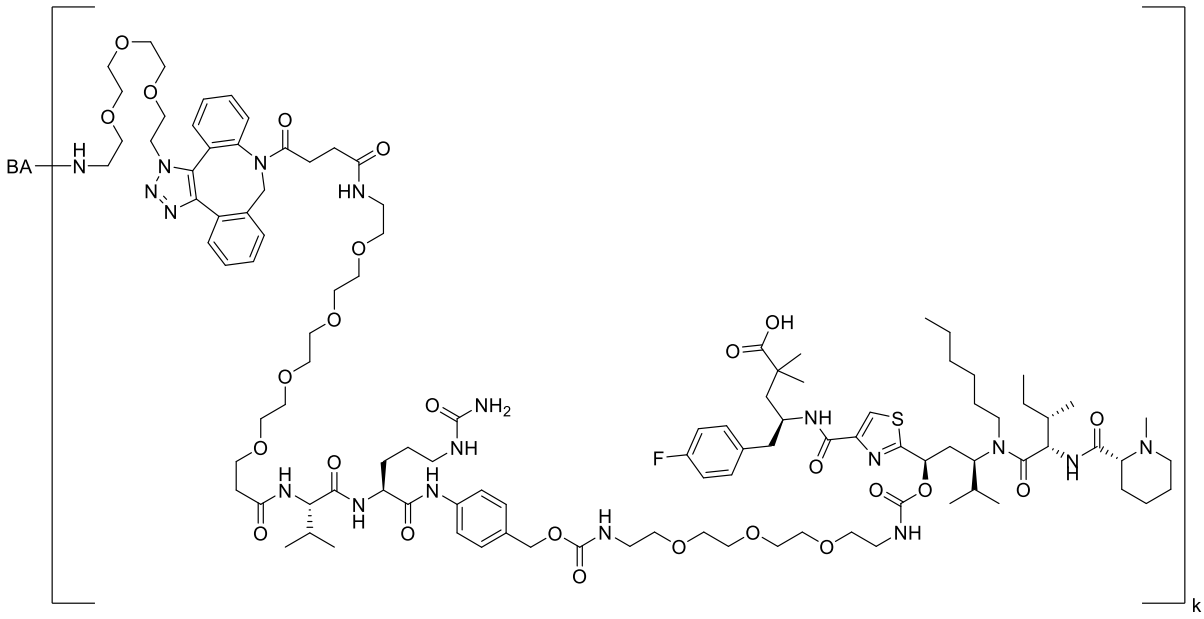


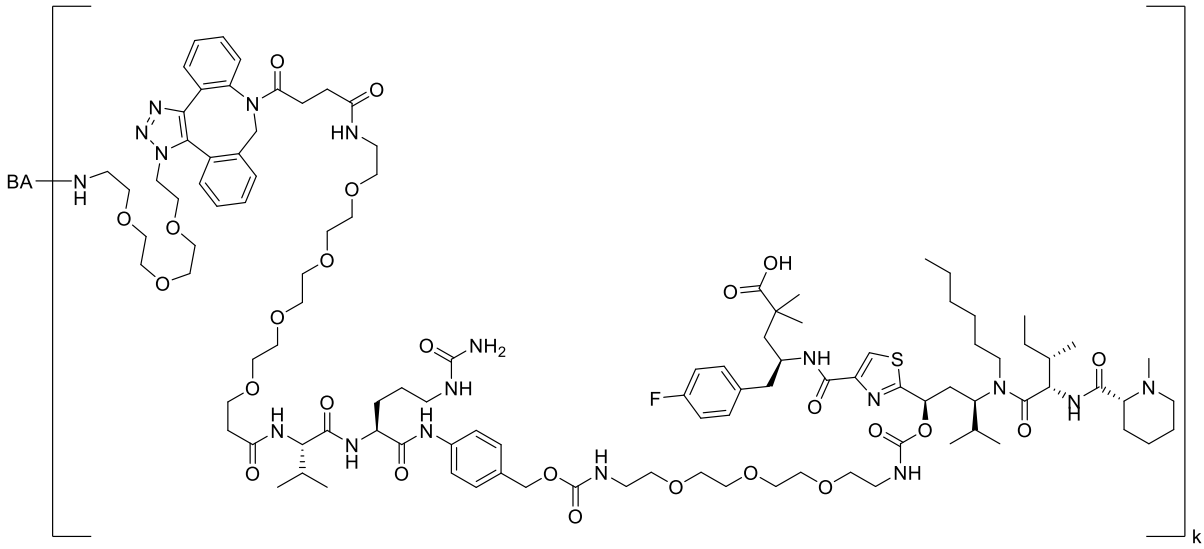


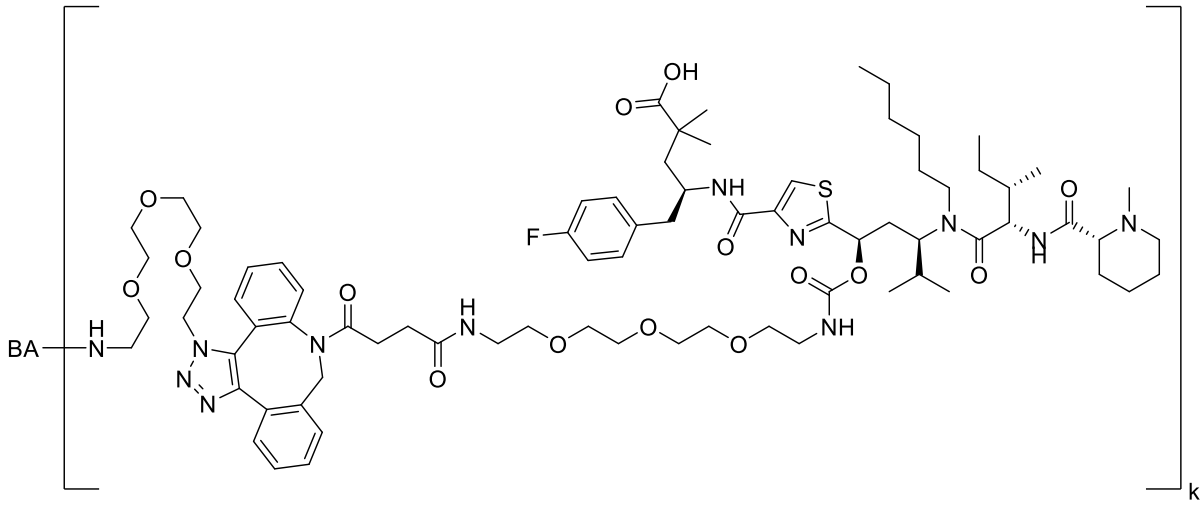


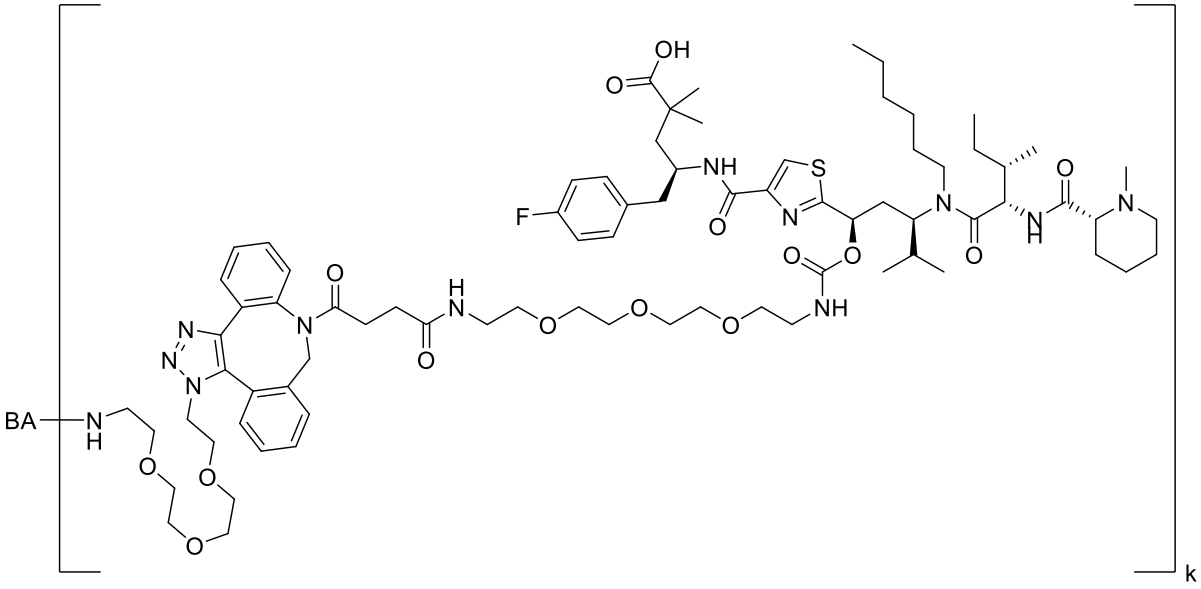


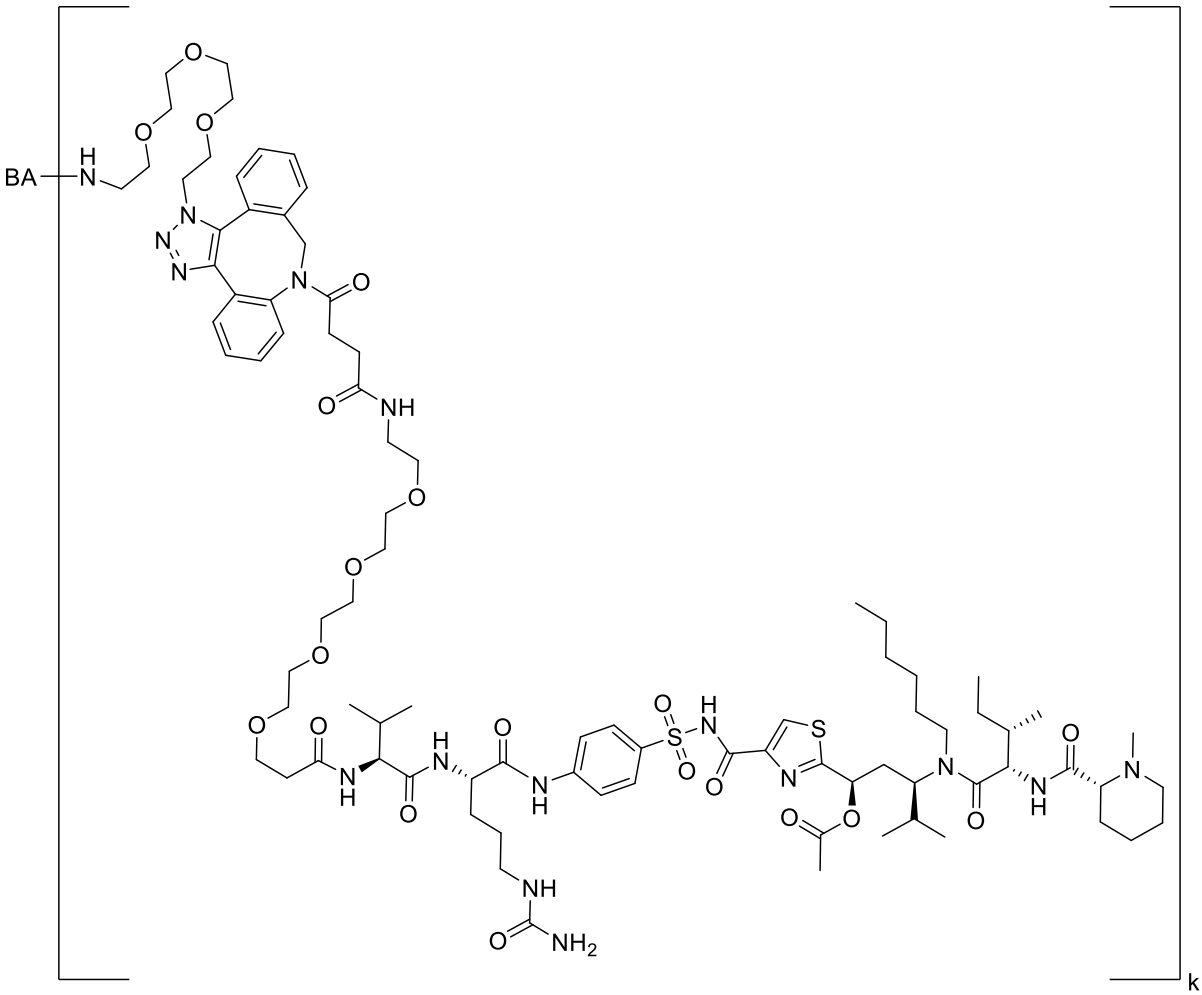


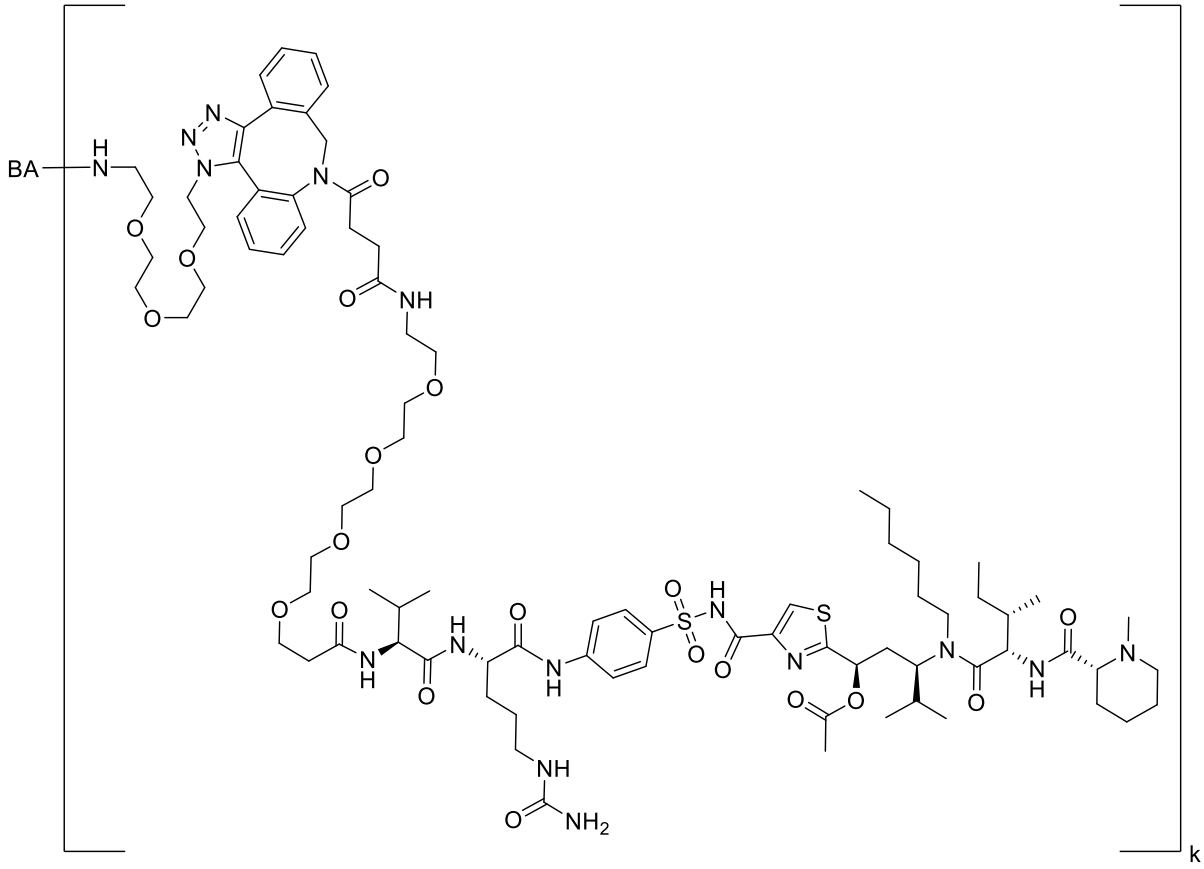


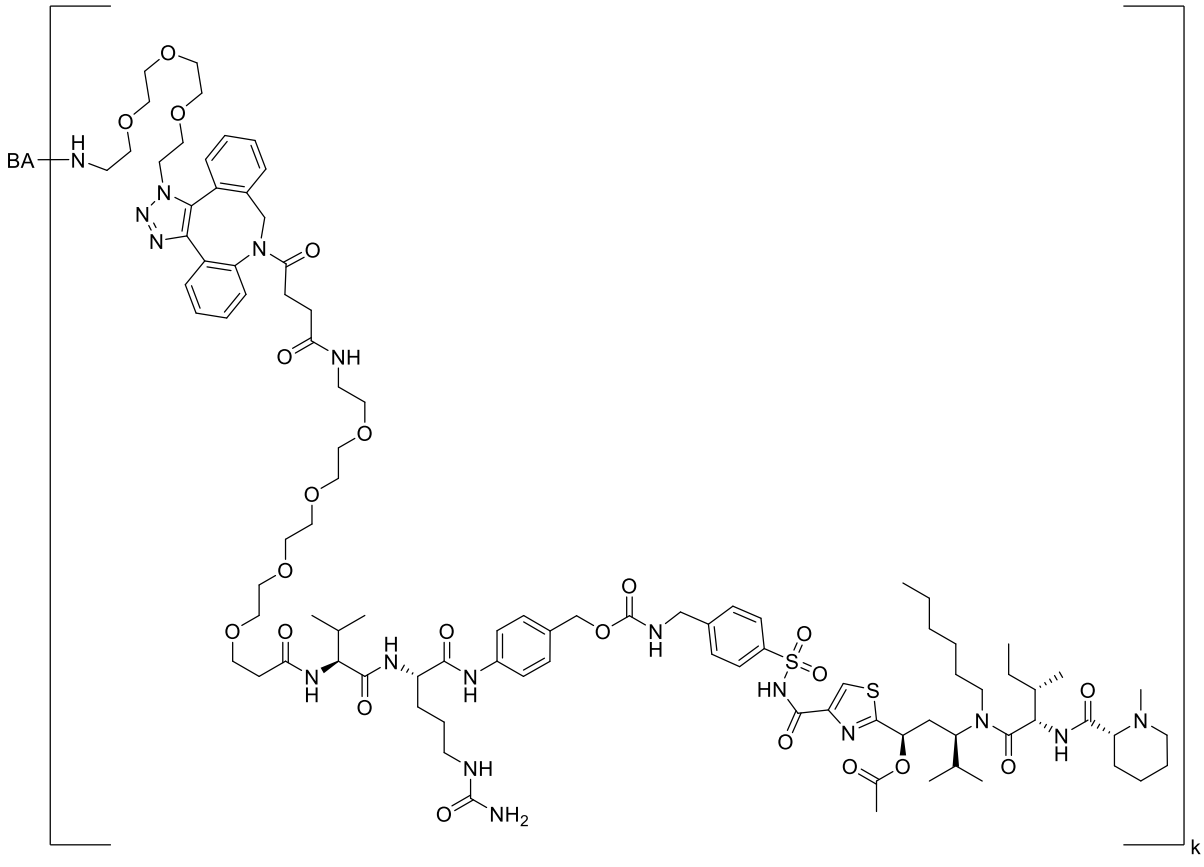


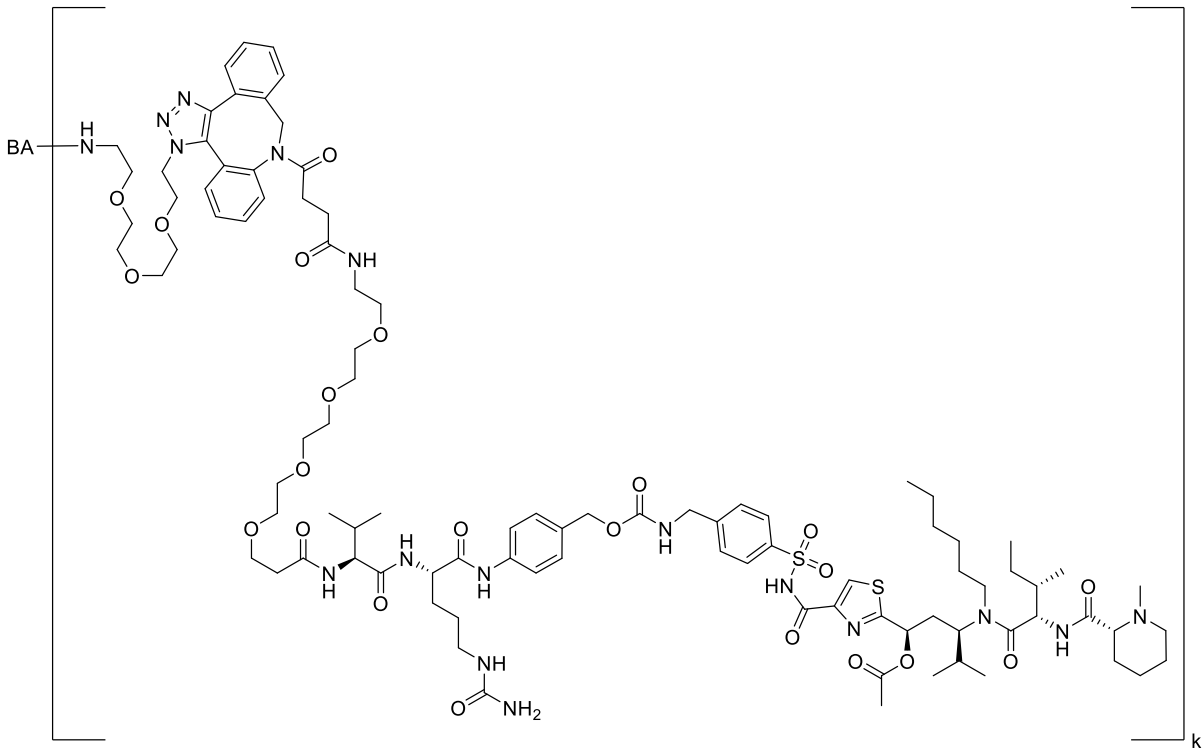


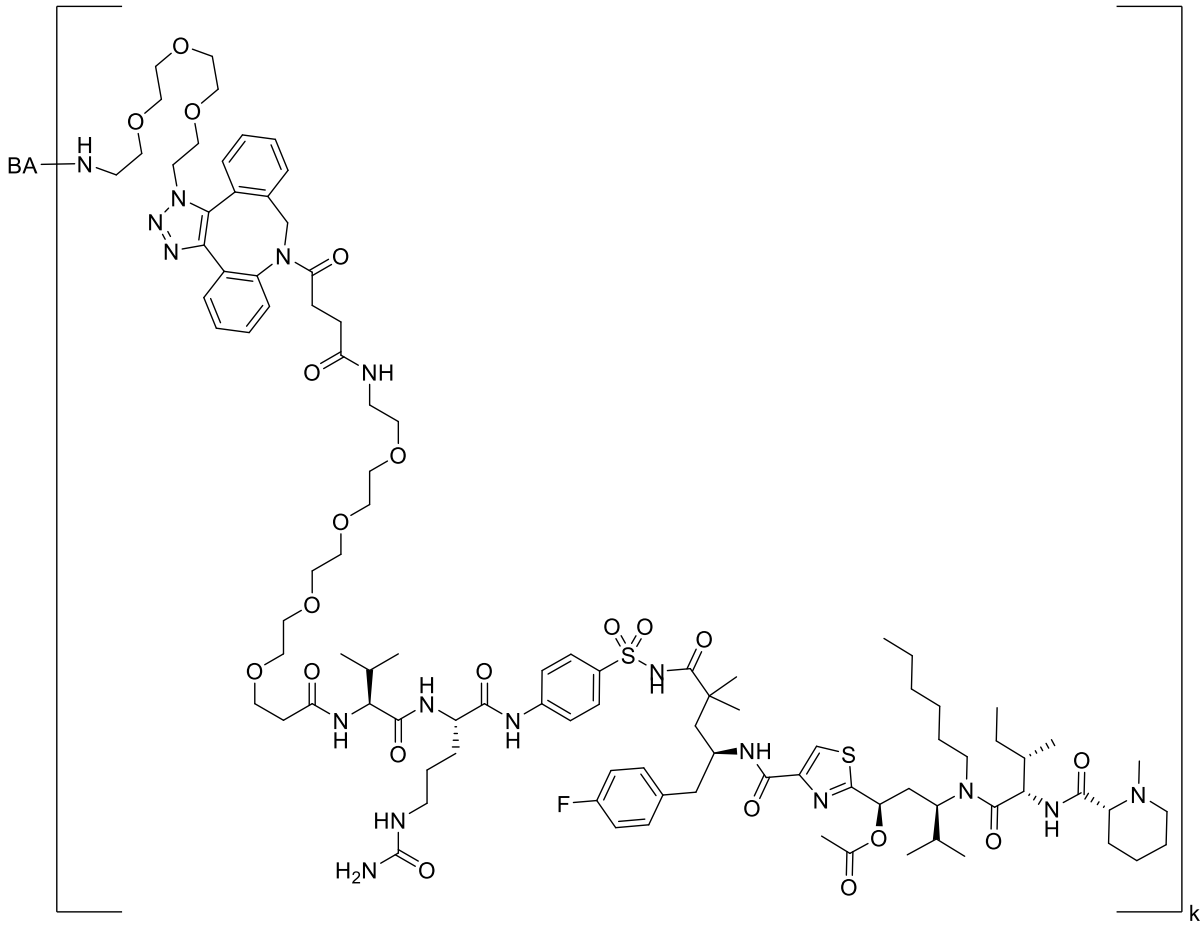


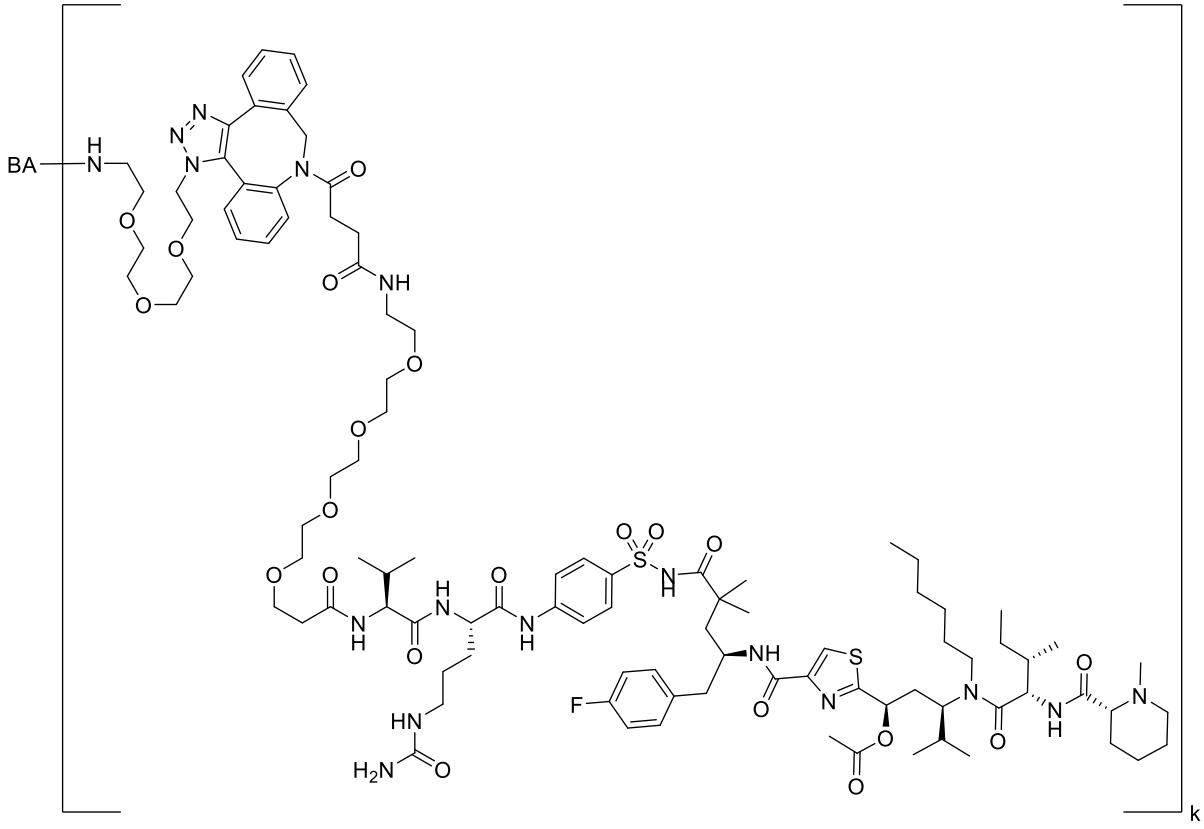


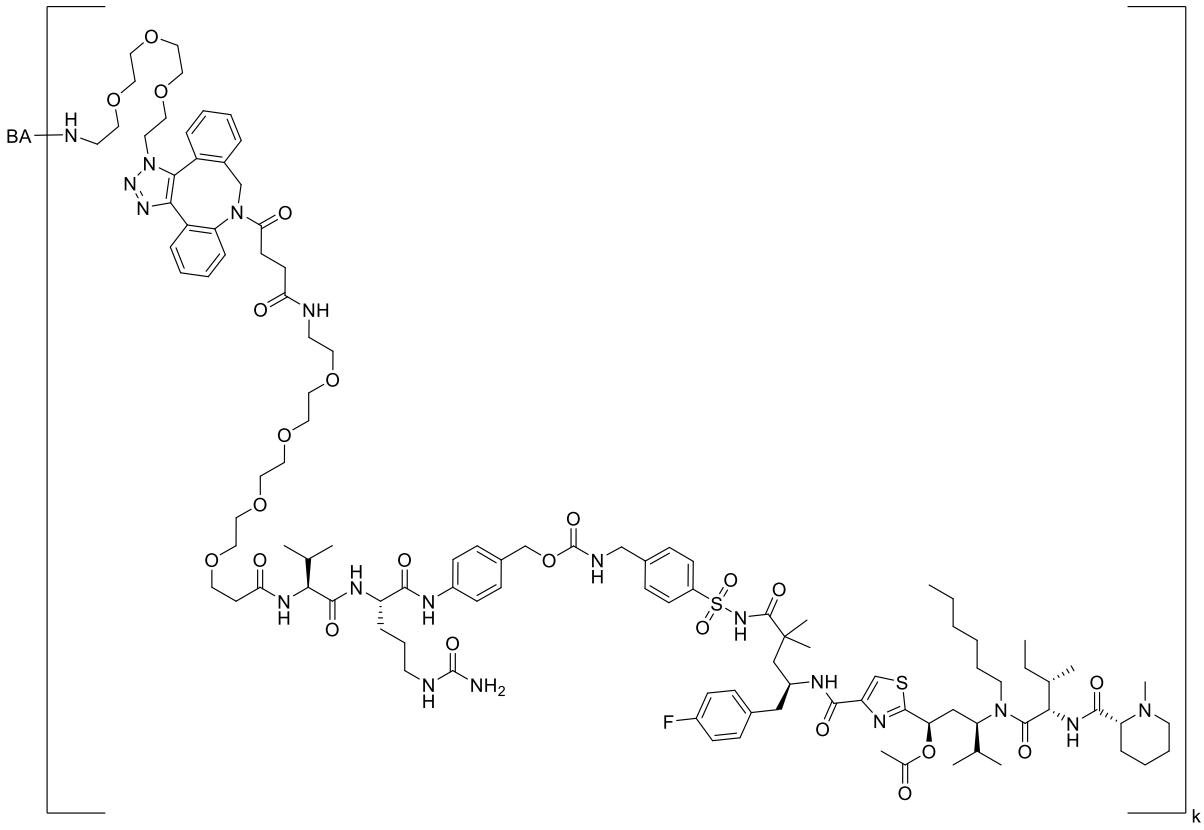


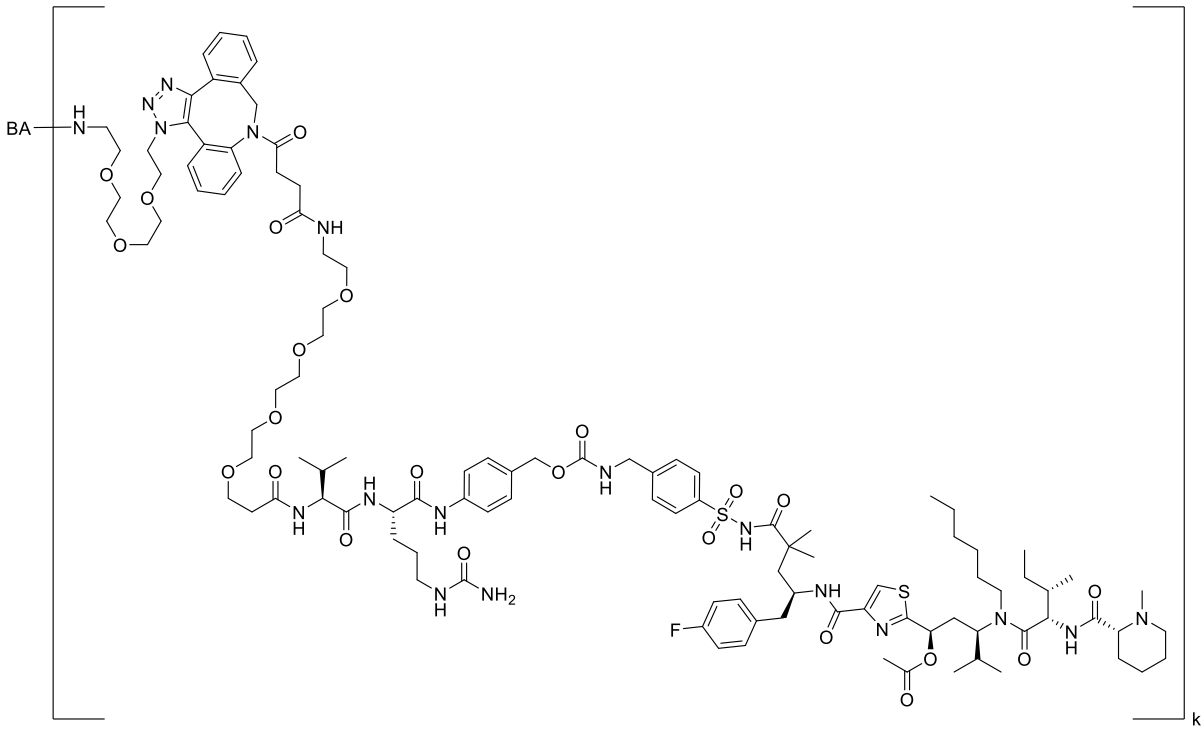


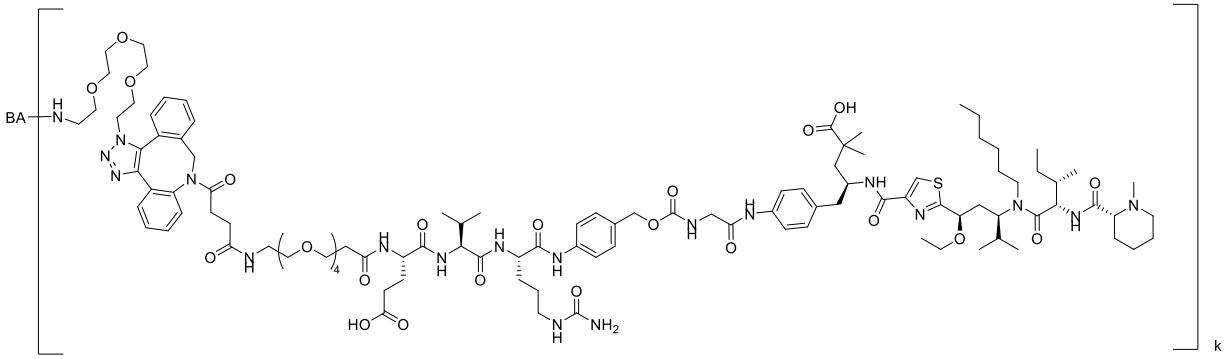




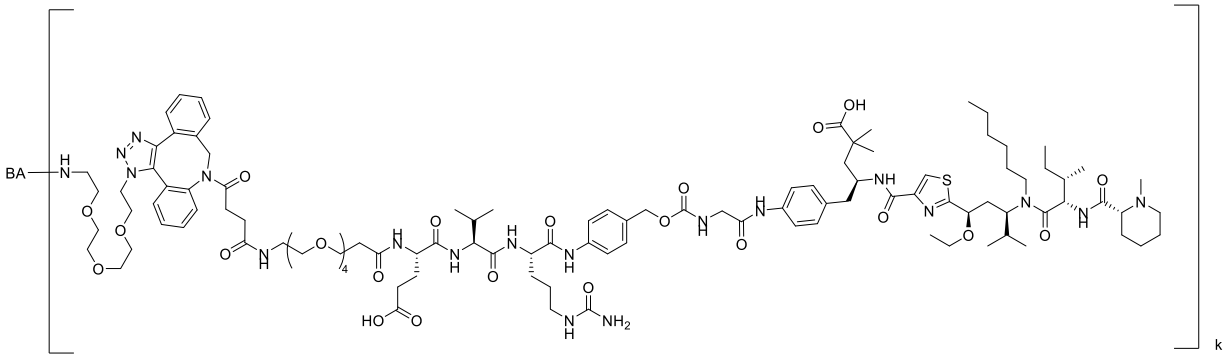

BA
k


BA
k





and



or a pharmaceutically acceptable salt thereof,

wherein **BA** is a binding agent; and **k** is one, two, three, or four.

30. The compound of claim 29, wherein **BA** is an antibody or antigen-binding fragment thereof.

31. The compound of claim 29, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least one glutamine residue used for conjugation.

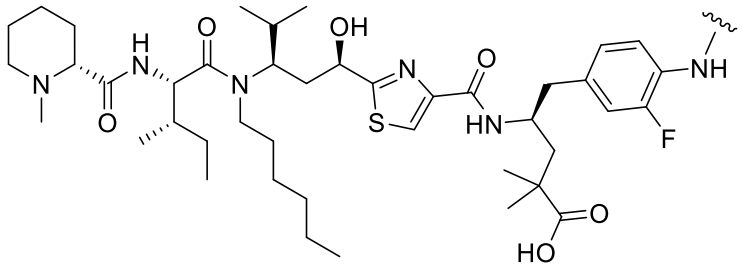
32. The compound of claim 29, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least two glutamine residues used for conjugation.

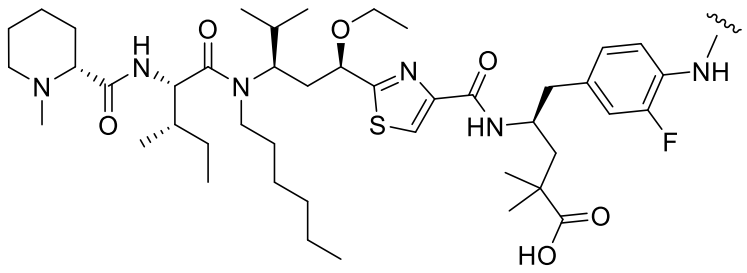
33. The compound of claim 29, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least four glutamine residues used for conjugation.

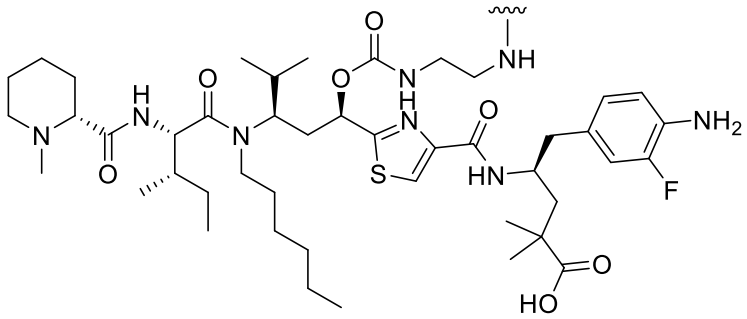
34. The compound of claim 33, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof wherein conjugation is at two Q295 residues; and **k** is two.

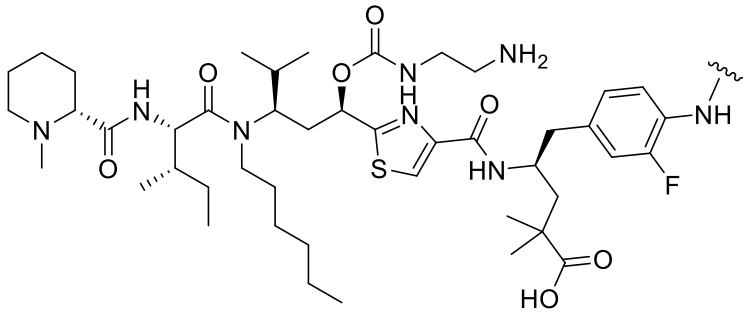
35. The compound of claim 33, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof wherein conjugation is at two Q295 residues and two N297Q residues; and **k** is four.

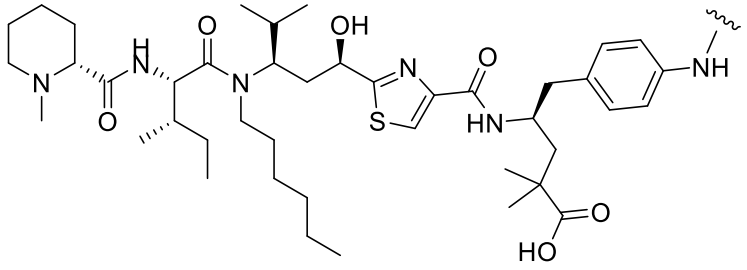
36. The compound of claim 1, wherein the compound is an antibody-drug conjugate comprising an antibody or antigen-binding fragment thereof conjugated to a compound selected from the group consisting of

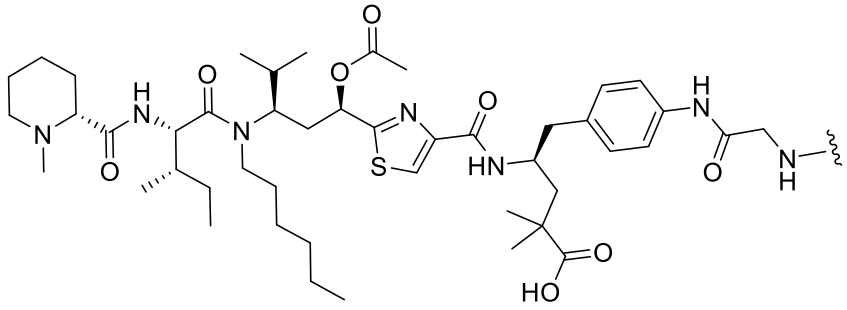


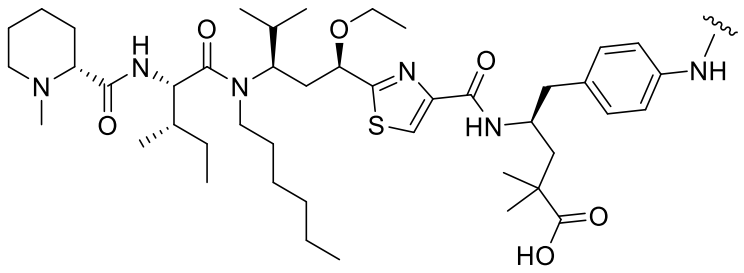


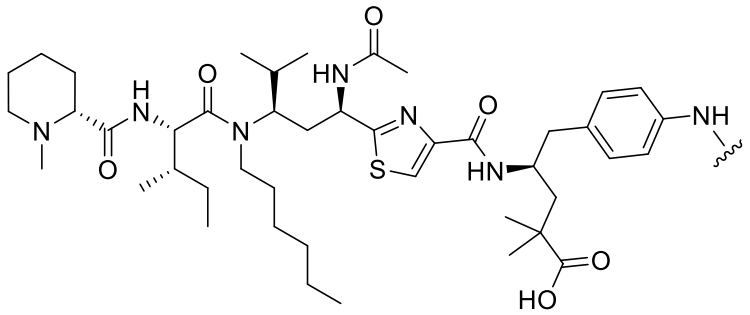


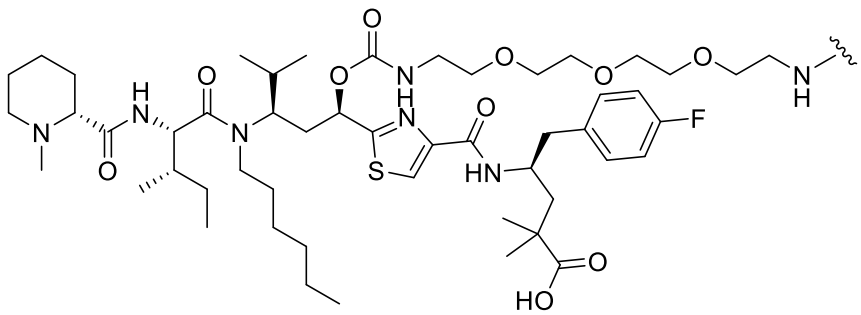


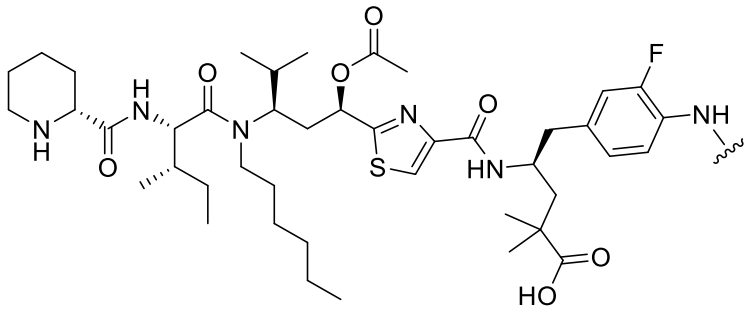


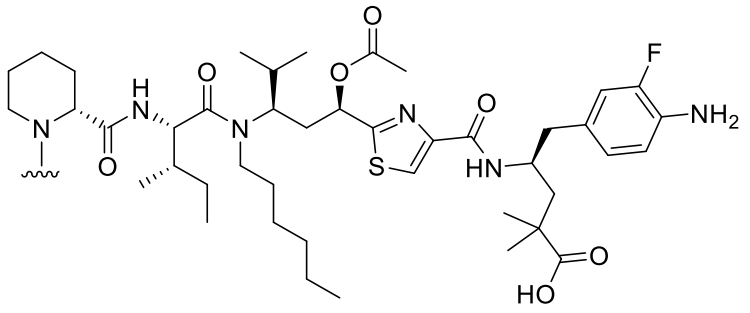


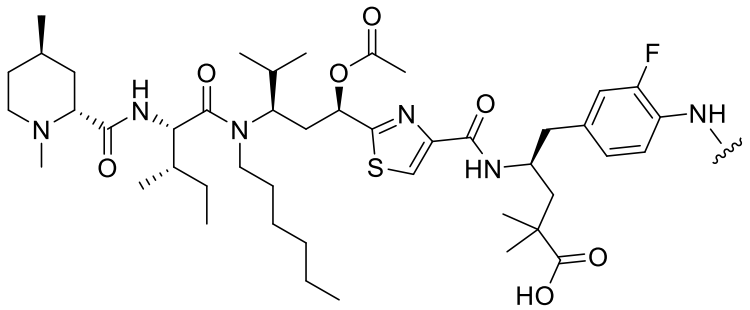


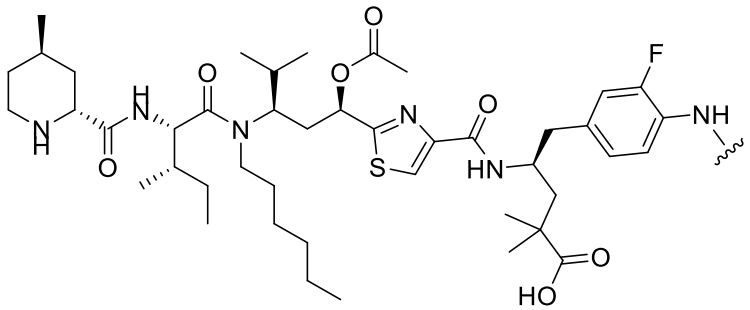


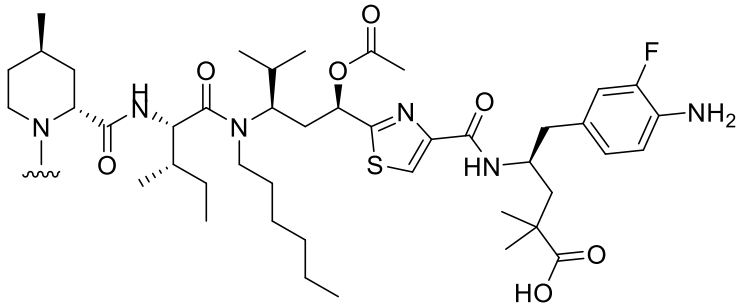


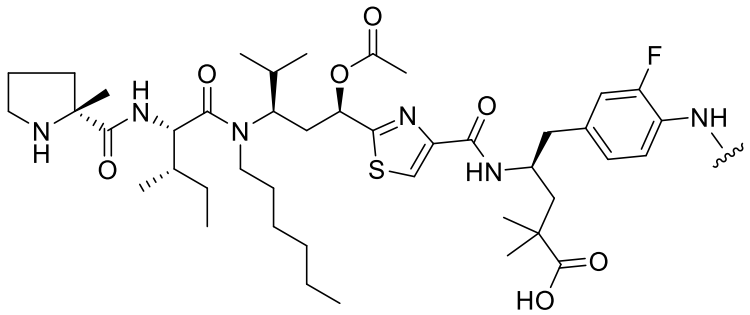


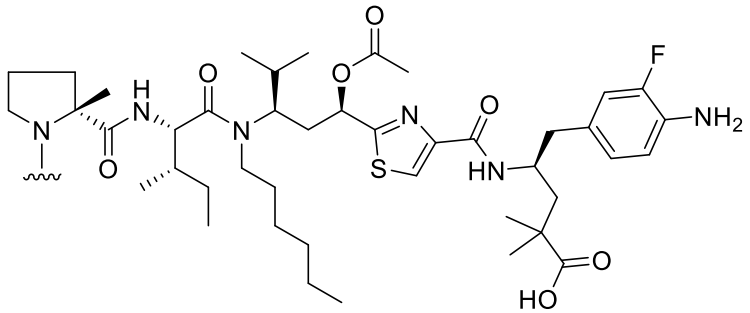


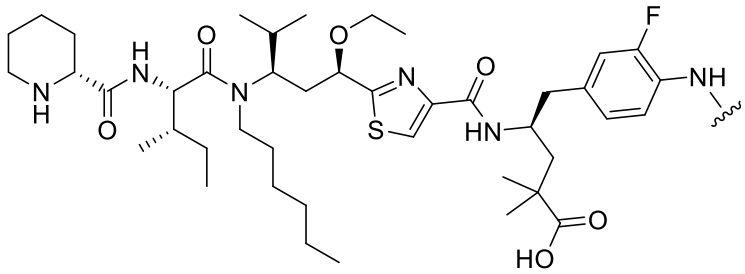


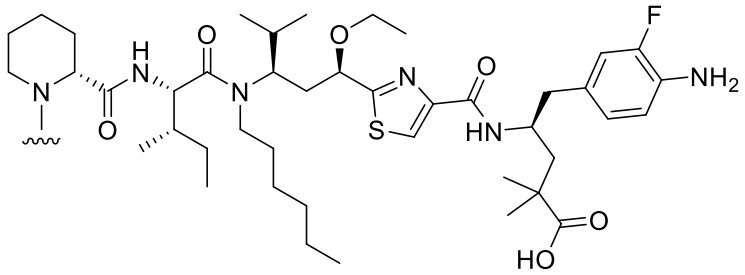


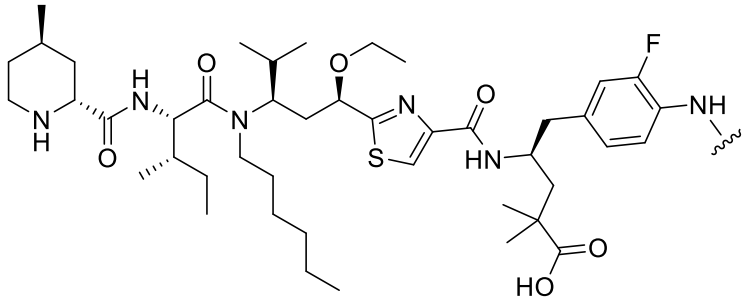


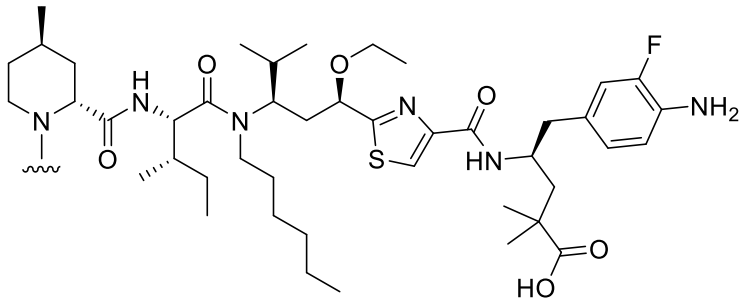


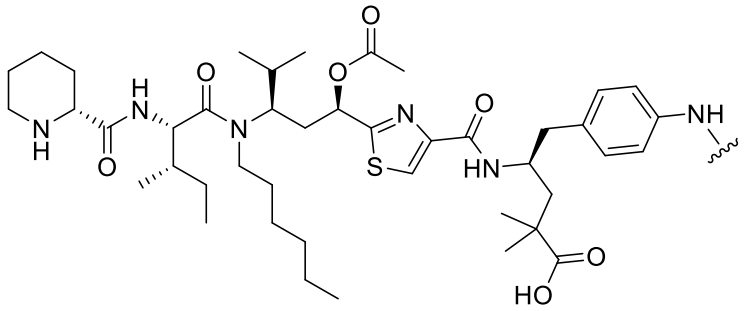


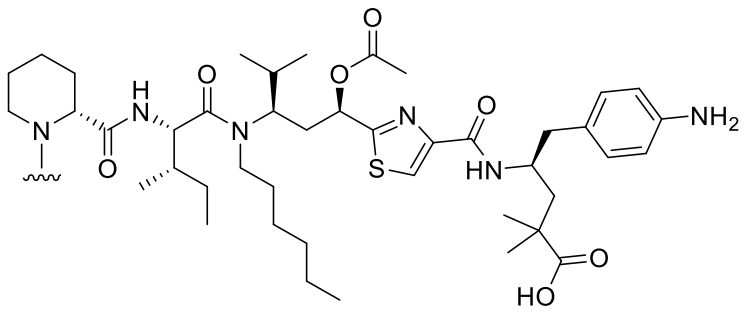


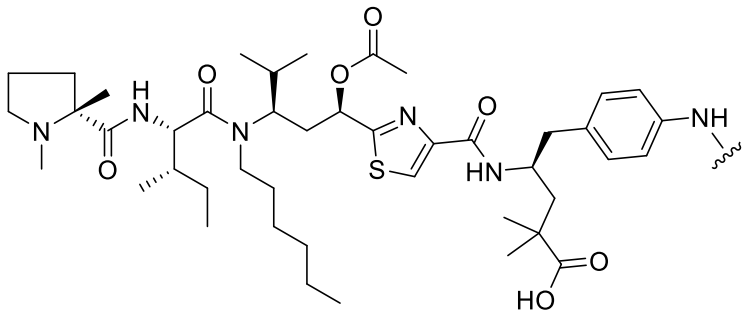


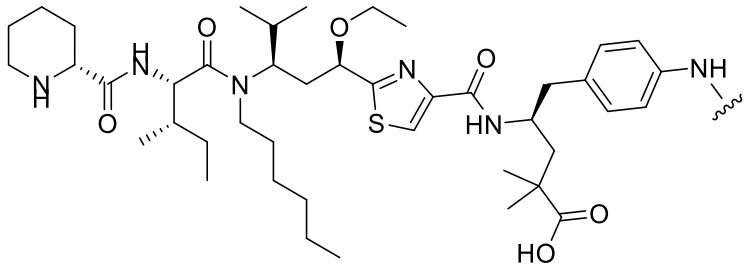


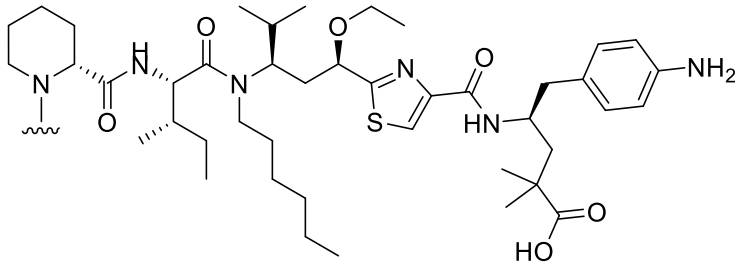


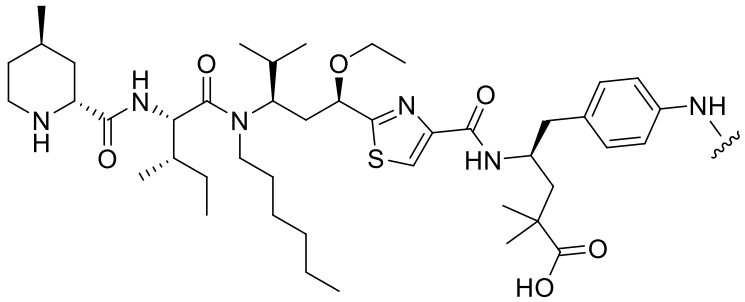


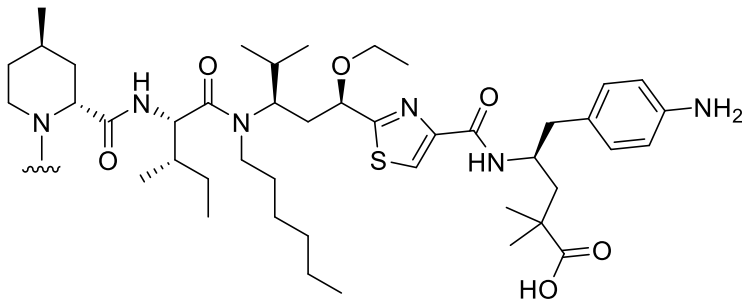


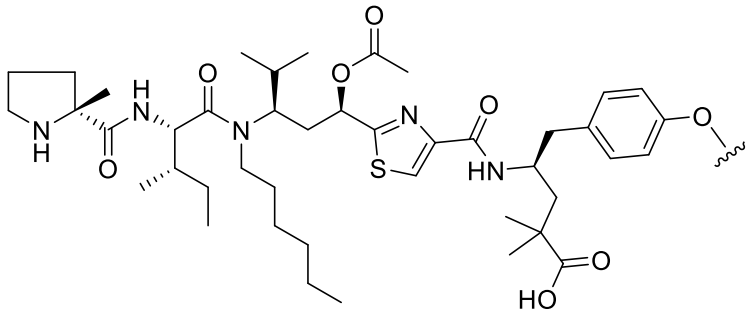


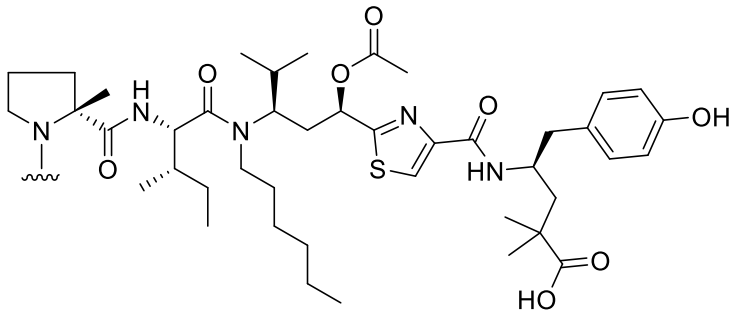


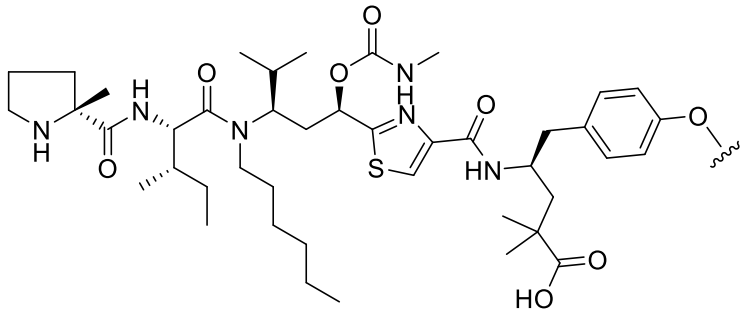


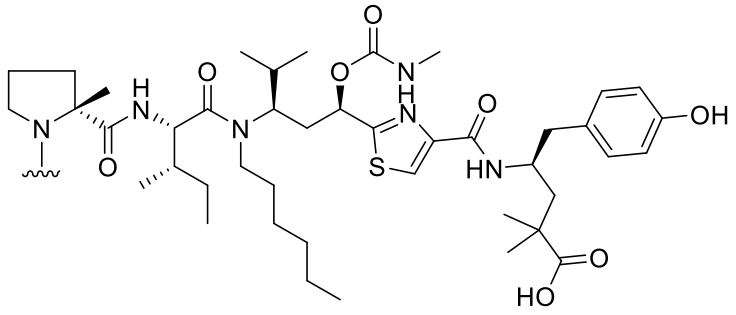


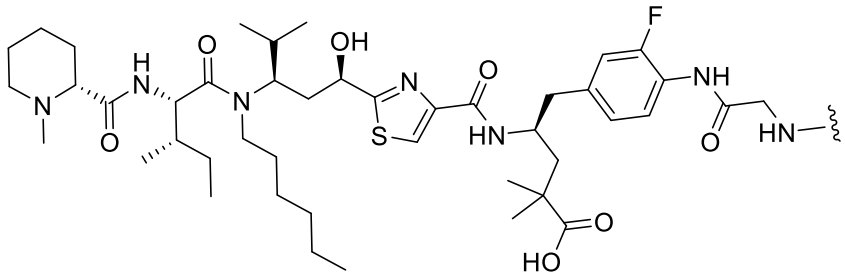


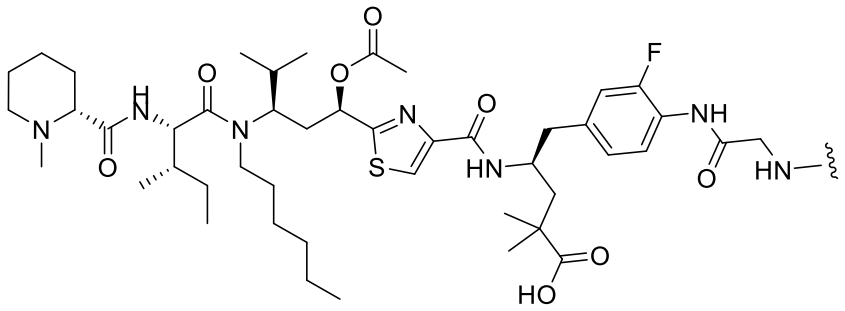


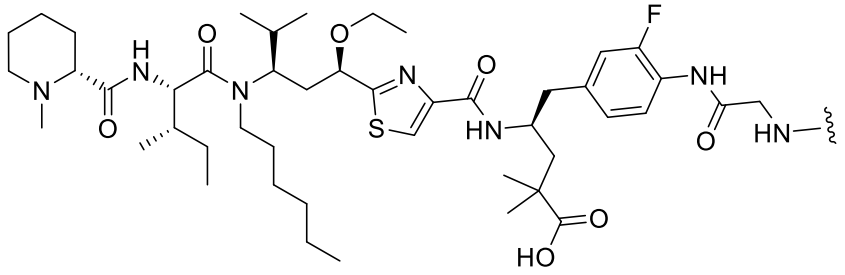


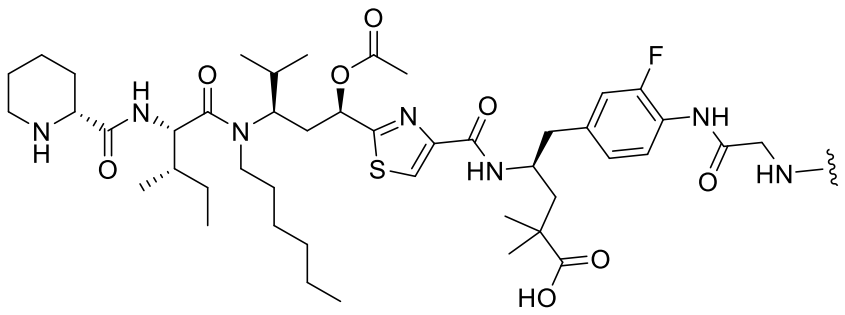


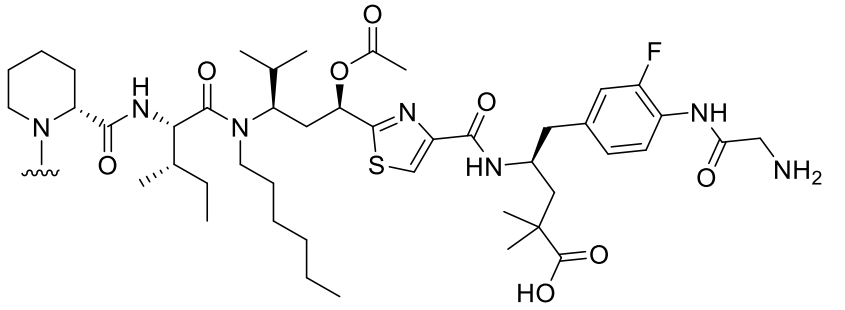


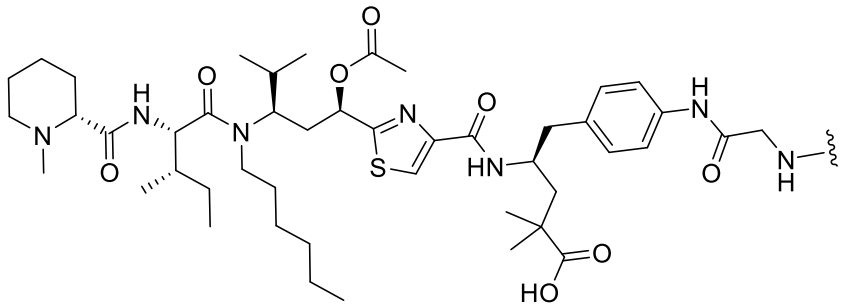


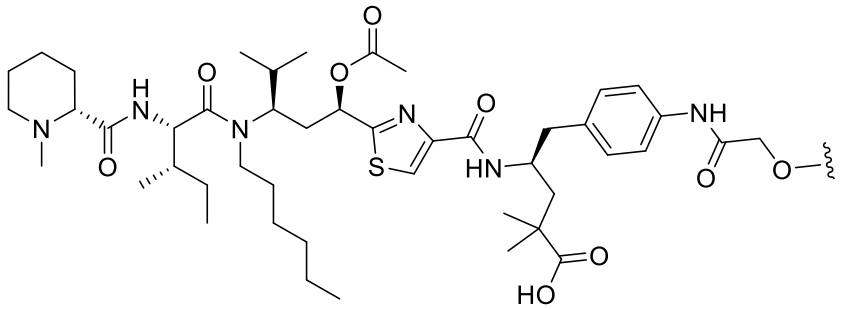


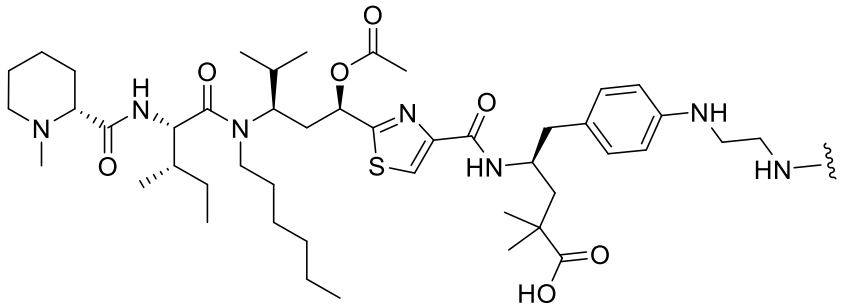


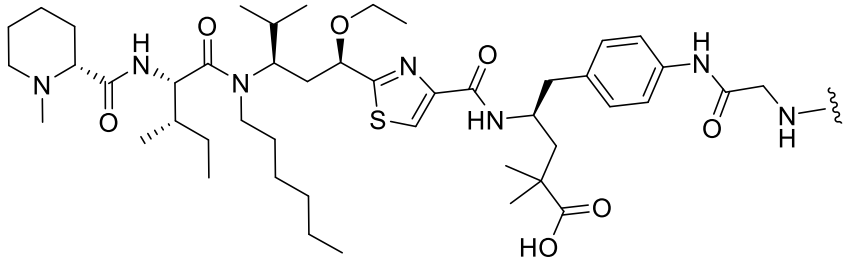


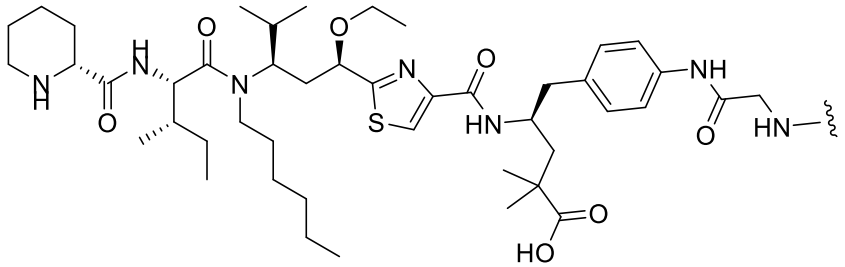


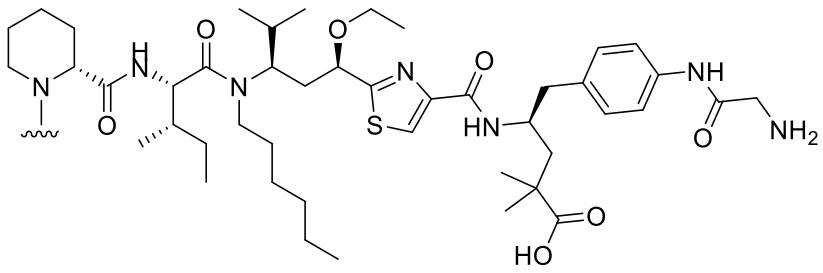


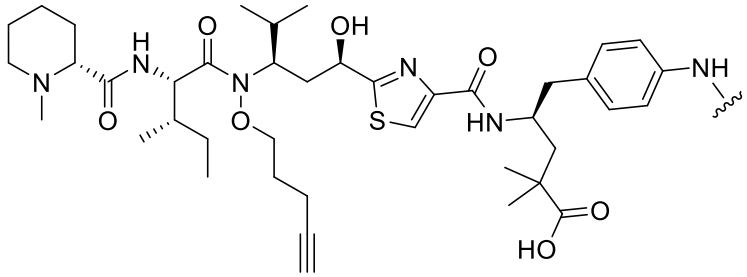


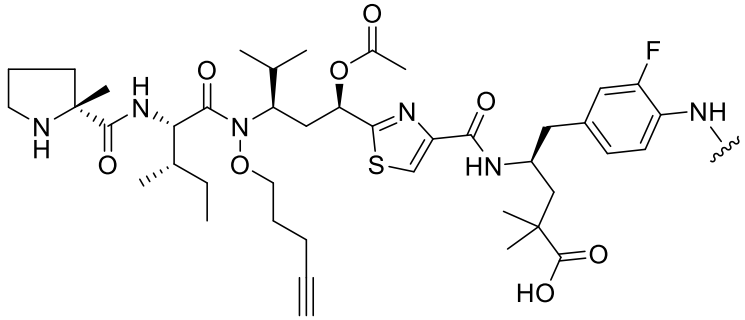


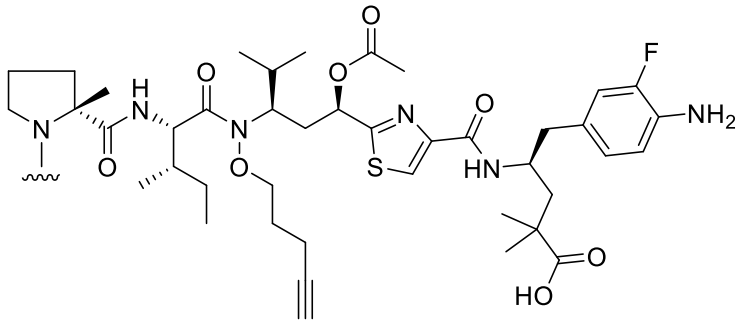


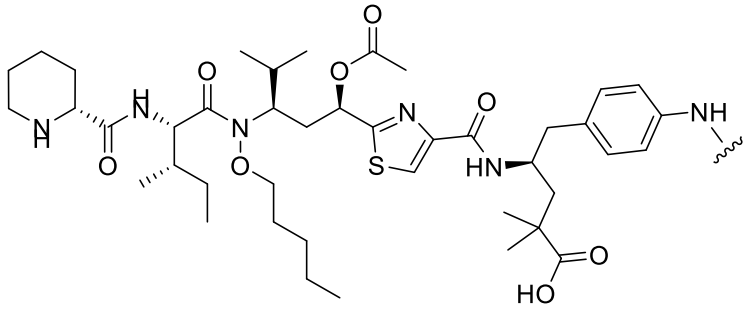


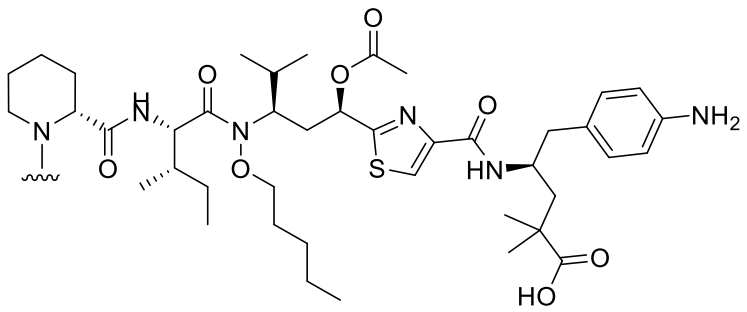


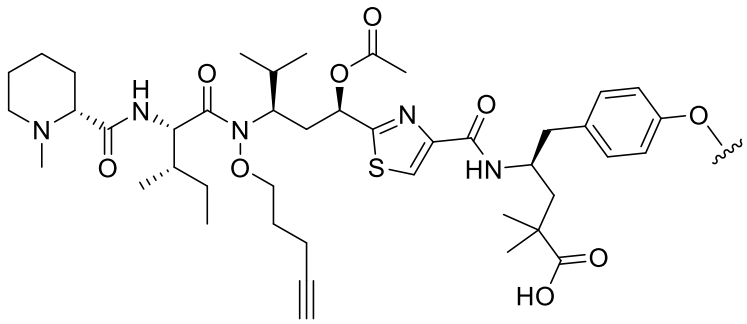


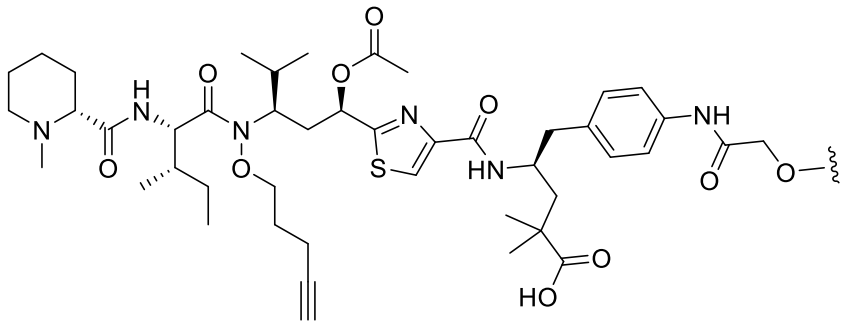


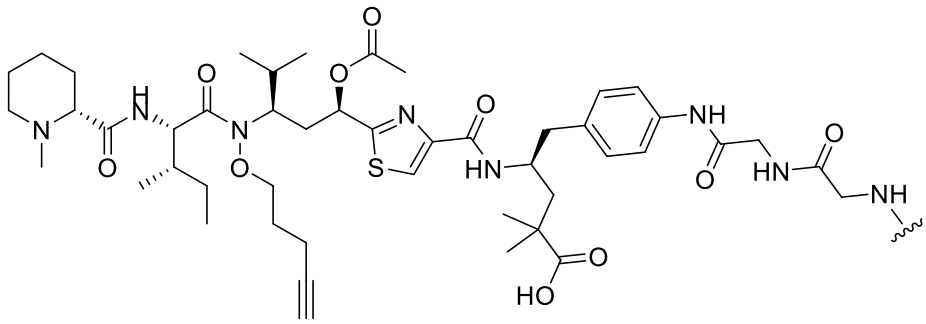


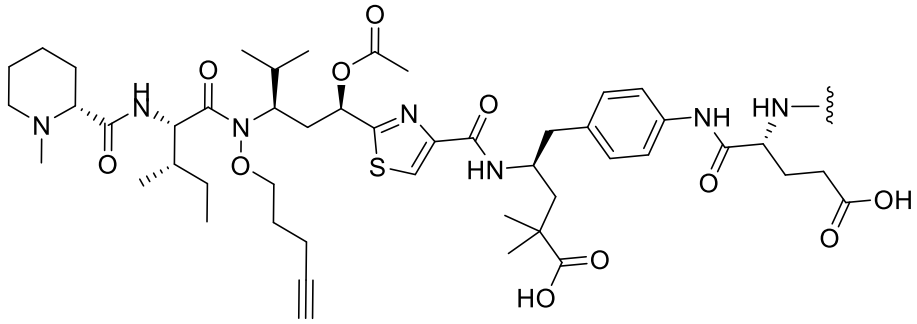


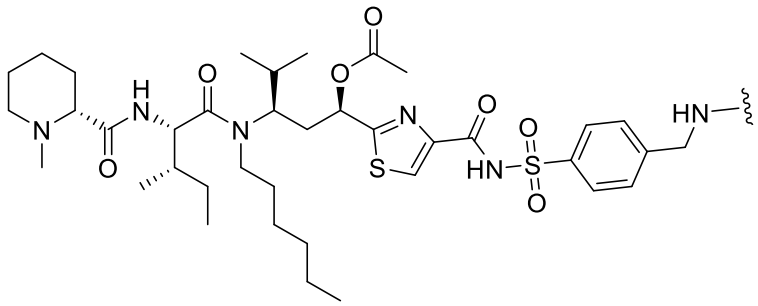


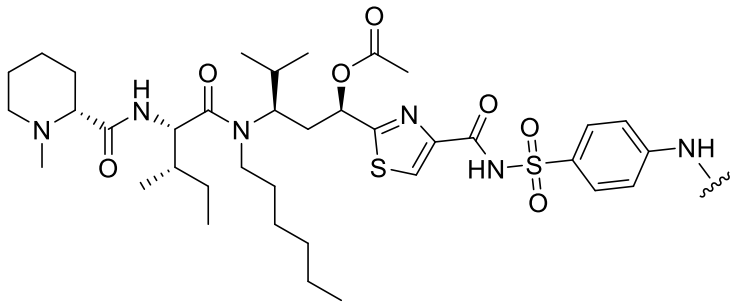


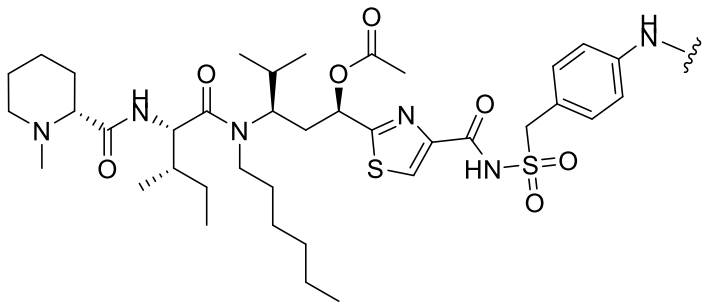


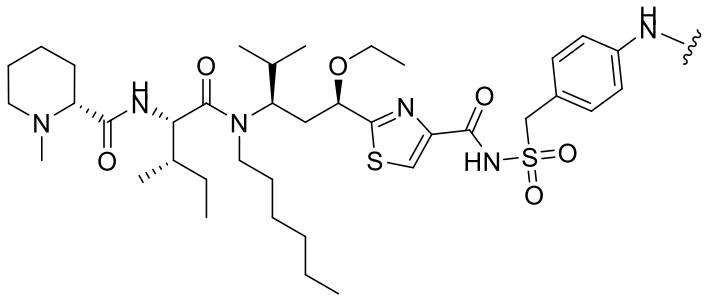


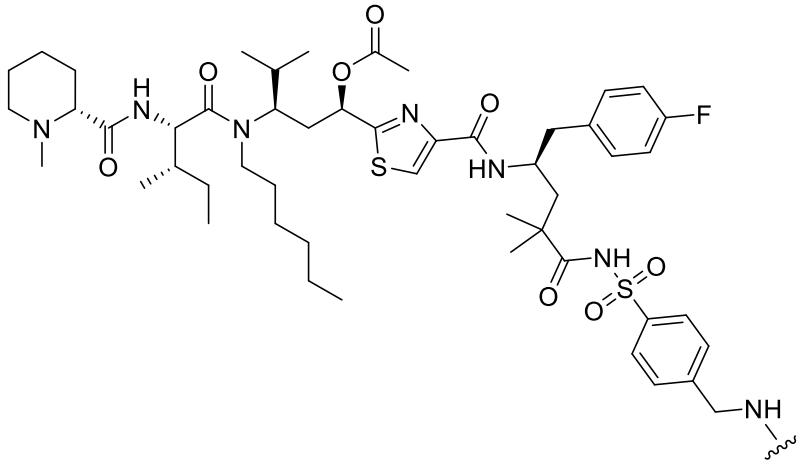


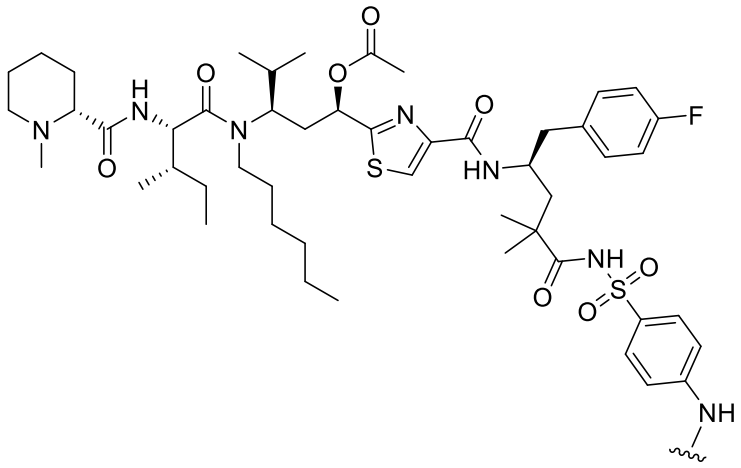


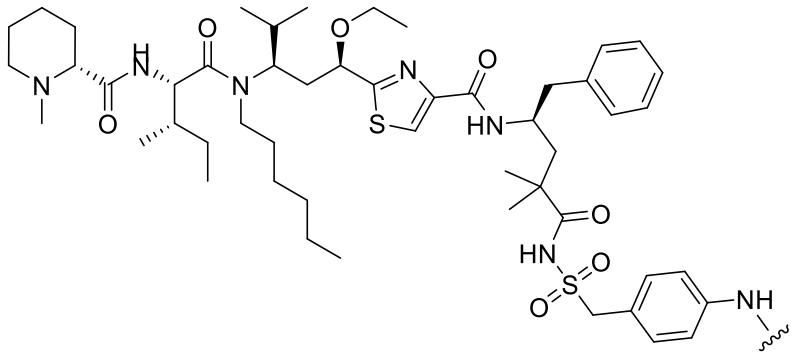




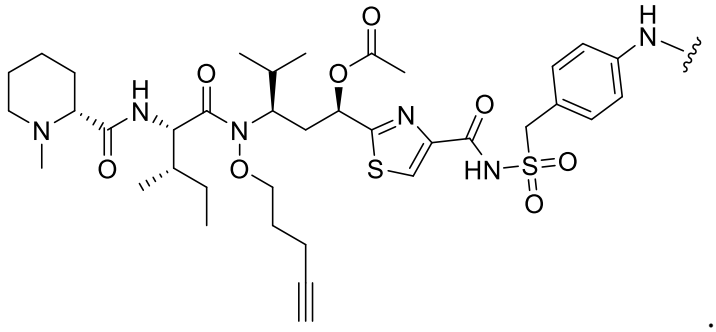








and



.

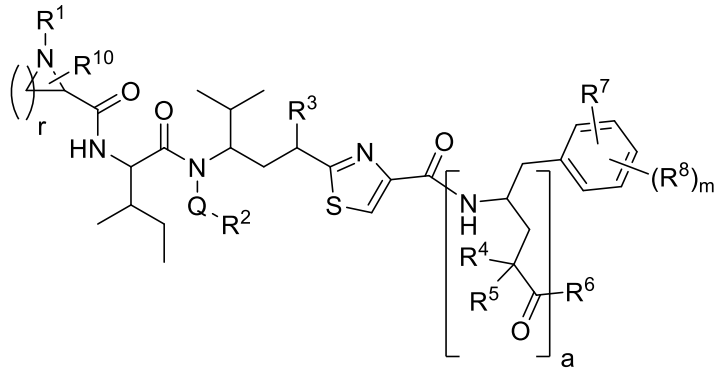
37. The compound of claim 29, wherein **BA** or the antibody or antigen-binding fragment thereof is selected from the group consisting of anti-MUC16, anti-PSMA, anti-EGFRvIII, anti-HER2, and anti-MET.

38. The compound of claim 29, wherein **BA** or the antibody or antigen-binding fragment thereof is anti-PRLR or anti-STEAP2.

39. The compound of claim 29, wherein **BA** or the antibody or antigen-binding fragment thereof binds to an antigen selected from the group consisting of lipoproteins; alpha1-

antitrypsin; a cytotoxic T-lymphocyte associated antigen (CTLA), such as CTLA-4 or CTLA4; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; protein A or D; fibroblast growth factor receptor 2 (FGFR2), EpCAM or Epcam, GD3, FLT3, PSCA, MUC1 or Muc1, MUC16 or Muc16, STEAP, STEAP2 or Steap-2, CEA, TENB2, EphA receptors, EphB receptors, folate receptor, FOLRI, mesothelin, cripto, alphavbeta6, VEGFR, EGFR, transferrin receptor, IRTA1, IRTA2, IRTA3, IRTA4, IRTA5; CD proteins such as CD2, CD3, CD4, CD5, CD6, CD8, CD11, CD14, CD19, CD20, CD21, CD22, CD25, CD26, CD28, CD30, CD33, CD36, CD37, CD38, CD40, CD44, CD52, CD55, CD56, CD59, CD70, CD79, CD80, CD81, CD103, CD105, CD134, CD137, CD138, CD152; erythropoietin; osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); T-cell receptors; surface membrane proteins; integrins, such as CD11a, CD11b, CD11c, CD18, an ICAM, VLA-4 and VCAM; a tumor associated antigen such as AFP, ALK, B7H4, BAGE proteins, β-catenin, brc-abl, BRCA1, BORIS, CA9 (carbonic anhydrase IX), caspase-8, CD123, CDK4, CLEC12A, c-kit, cMET, c-MET, MET, cyclin-B1, CYP1B1, EGFRvIII, endoglin, EphA2, ErbB2/Her2, ErbB3/Her3, ErbB4/Her4, ETV6-AML, Fra-1, FOLR1, GAGE proteins such as GAGE-1 and GAGE-2, GD2, GloboH, glypican-3, GM3, gp100, Her2 or HER2, HLA/B-raf, HLA/EBNA1, HLA/k-ras, HLA/MAGE-A3, hTERT, IGF1R, LGR5, LMP2, MAGE proteins such as MAGE-1, -2, -3, -4, -6, and -12, MART-1, ML-IAP, CA-125, MUM1, NA17, NGEP, NY-BR1, NY-BR62, NY-BR85, NY-ESO1, OX40, p15, p53, PAP, PAX3, PAX5, PCTA-1, PDGFR-α, PDGFR-β, PDGF-A, PDGF-B, PDGF-C, PDGF-D, PLAC1, PRLR, PRAME, PSGR, PSMA (FOLH1), RAGE proteins, Ras, RGS5, Rho, SART-1, SART-3, Steap-1, STn, survivin, TAG-72, TGF-β, TMPRSS2, Tn, TNFRSF17, TRP-1, TRP-2, tyrosinase, uroplakin-3, fragments of any of the above-listed polypeptides; cell-surface expressed antigens; molecules such as class A scavenger receptors including scavenger receptor A (SR-A), and other membrane proteins such as B7 family-related member including V-set and Ig domain-containing 4 (VSIG4), Colony stimulating factor 1 receptor (CSF1R), asialoglycoprotein receptor (ASGPR), and Amyloid beta precursor-like protein 2 (APLP-2); BCMA; SLAMF7; GPNMB; and UPK3A.

40. A compound having the structure of Formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^{1} is hydrogen, C_1-C_{10} alkyl, a first *N*-terminal amino acid residue, –C_1-C_{10} alkyl-N**R^{3a}R^{3b}**, or –C_1-C_{10} alkyl-OH;

R^{3} is hydroxyl, –O-C_1-C_5 alkyl, –OC(O)C_1-C_5 alkyl, –OC(O)N(H)C_1-C_{10} alkyl, –OC(O)N(H)C_1-C_{10} alkyl-N**R^{3a}R^{3b}**, –NHC(O)C_1-C_5 alkyl, or –OC(O)N(H)$(CH_2CH_2O)_{\mathbf{n}}C_1$-$C_{10}$ alkyl-N**R^{3a}R^{3b}**,

wherein **R^{3a}** and **R^{3b}** are independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{4} and **R^{5}** are, independently in each instance, hydrogen or C_1-C_5 alkyl;

R^{6} is –OH, –$NHNH_2$, –$NHSO_2(CH_2)_{\mathbf{a1}}$-aryl-$(CH_2)_{\mathbf{a2}}$N**R^{6a}R^{6b}**,

wherein aryl is substituted or unsubstituted; and

R^{6a} and **R^{6b}** are independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{7} is, independently in each instance, hydrogen, –OH, halogen, or –N**R^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** are, independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, –C(O)CH_2OH, a first *N*-terminal amino acid residue, a first *N*-terminal peptide residue, and –$CH_2CH_2NH_2$; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{8} is, independently in each instance, hydrogen, –NH**R^{9}**, or halogen,

wherein **R^{9}** is hydrogen, –C_1-C_5 alkyl, or –C(O)C_1-C_5 alkyl; and

m is one or two;

R^{10}, when present, is -C_1-C_5 alkyl;

Q is –CH_2– or –O– wherein

R^2 is alkyl, alkynyl, or a regioisomeric triazole;

wherein said regioisomeric triazole is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl;

wherein **n** is an integer from one to ten;

wherein **r** is an integer from one to six;

wherein **a**, **a1**, and, **a2** are, independently, zero or one; and

wherein **T** is not compound **IVa**, **IVa'**, **IVb**, **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, **IVj**, **IVk**, **IVl**, **IVm**, **IVn**, **IVo**, **IVp**, **IVq**, **IVr**, **IVs**, **IVt**, **IVu**, **IVvA**, **IVvB**, **IVw**, **IVx**, **IVy**, **Va**, **Va'**, **Vb**, **Vc**, **Vd**, **Ve**, **Vf**, **Vg**, **Vh**, **Vi**, **Vj**, **Vk**, **VIa**, **IVb**, **VIc**, **VId**, **VIe**, **VIf**, **VIg**, **VIh**, **Vl**, **VIi**, **VII**, **VIII**, **IX**, **X**, **D-5a**, **D-5c**, Tubulysin A-I, U-X, or Z, Pretubulysin D, or N^{14}-desacetoxytubulysin H.

41. The compound of claim 40, wherein **r** is four.

42. The compound of claim 40, wherein

Q is $–CH_2–$;

R^1 is C_1-C_{10} alkyl;

R^2 is alkyl;

R^4 and **R^5** are C_1-C_5 alkyl;

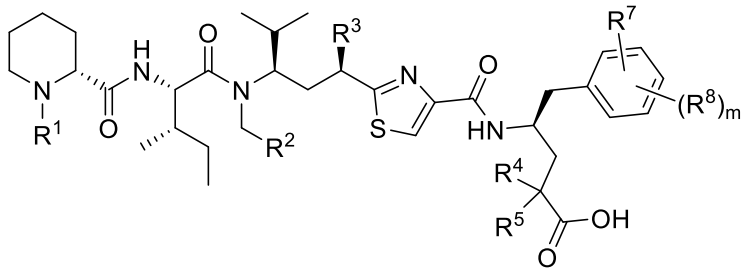
R^6 is –OH;

R^{10} is absent;

wherein **r** is four; and

wherein **a** is one.

43. The compound of claim 41, according to the structure of Formula II

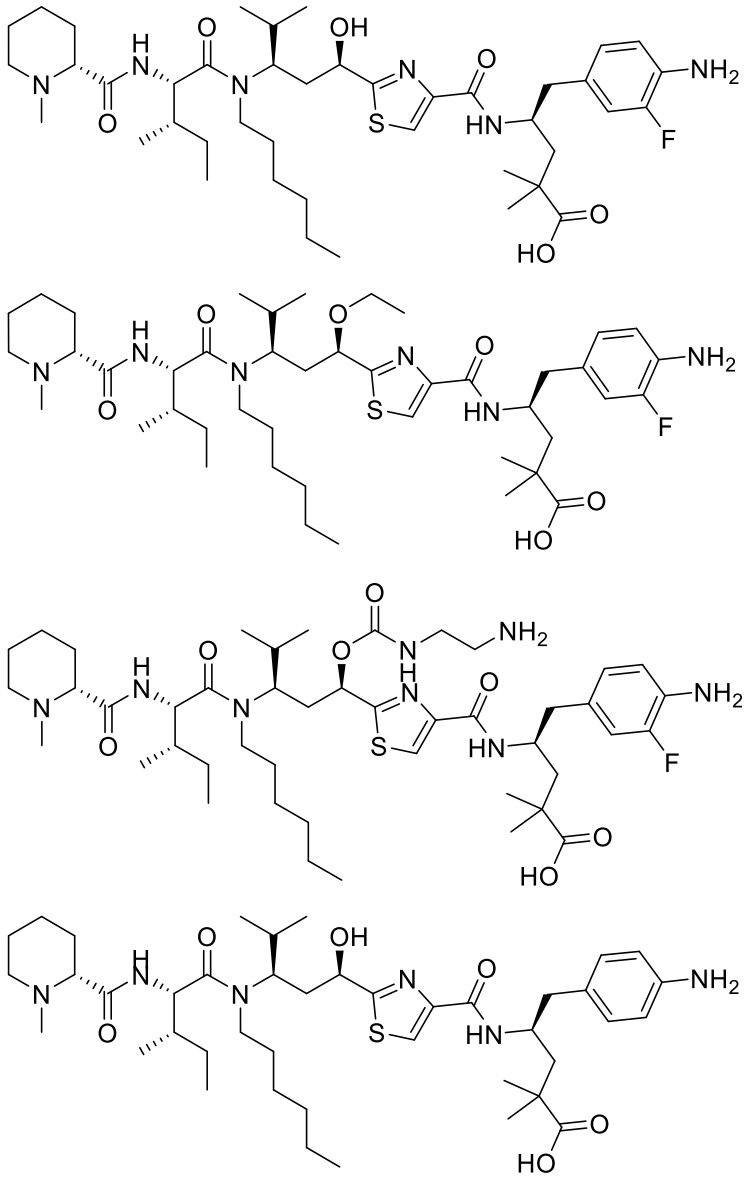


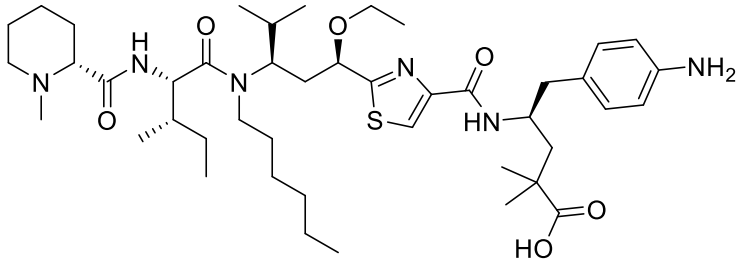
Formula II

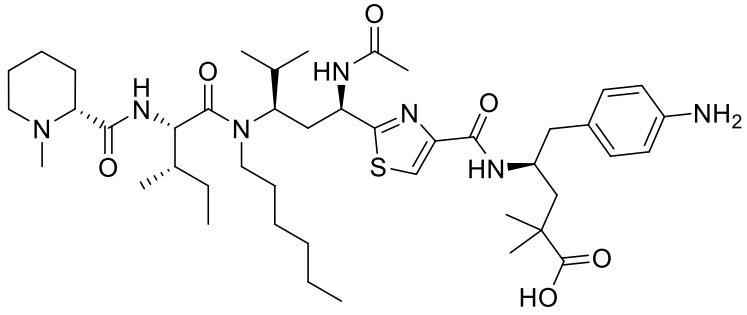
or a pharmaceutically acceptable salt thereof.

44. The compound of claim 43, wherein $\mathbf{R^3}$ is hydroxyl, –OEt, –OC(O)N(H)$CH_2CH_2NH_2$, –NHC(O)Me, or –OC(O)N(H)$CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$.

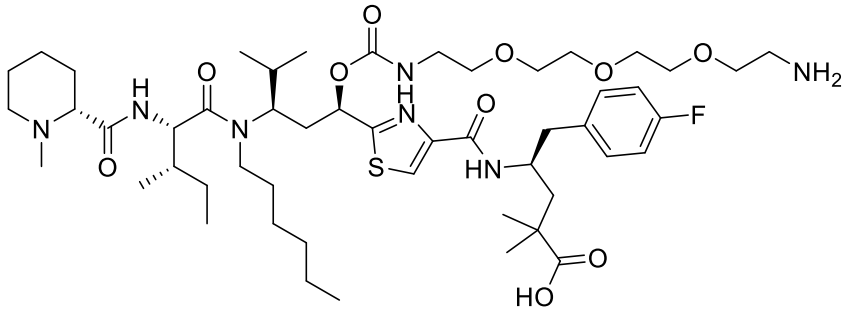
45. The compound of claim 43, selected from the group consisting of







and



or

a pharmaceutically acceptable salt thereof.

46. The compound of claim 40, wherein

Q is $–CH_2–$;

$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;

$\mathbf{R^2}$ is alkyl;

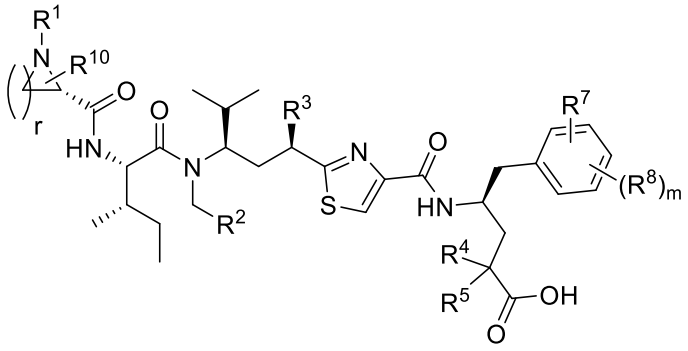
$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;

$\mathbf{R^6}$ is –OH;

wherein **r** is three or four; and

wherein **a** is one.

47. The compound of claim 46, according to the structure of Formula III

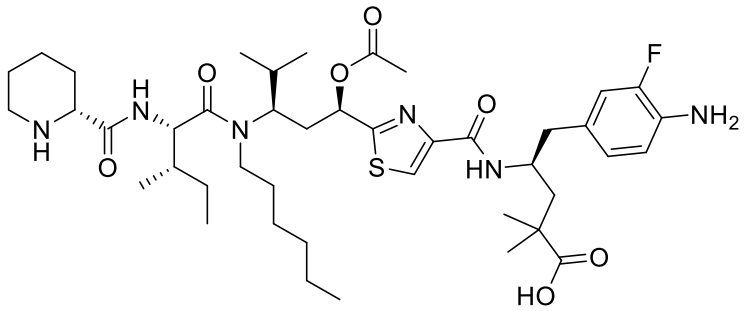


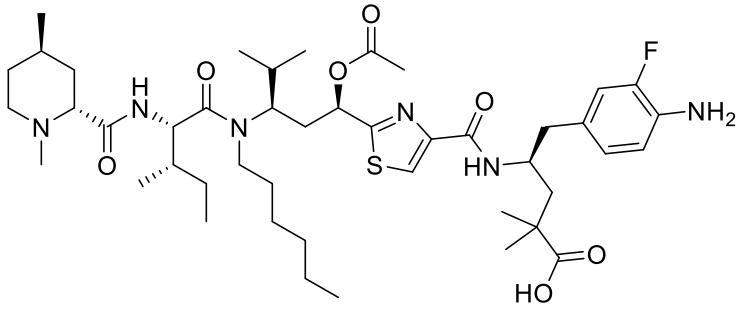
Formula III

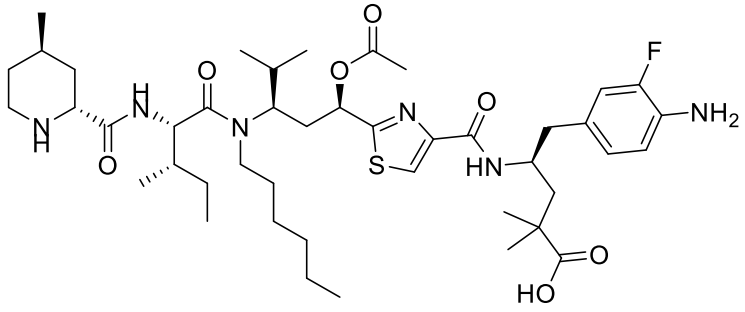
or a pharmaceutically acceptable salt thereof.

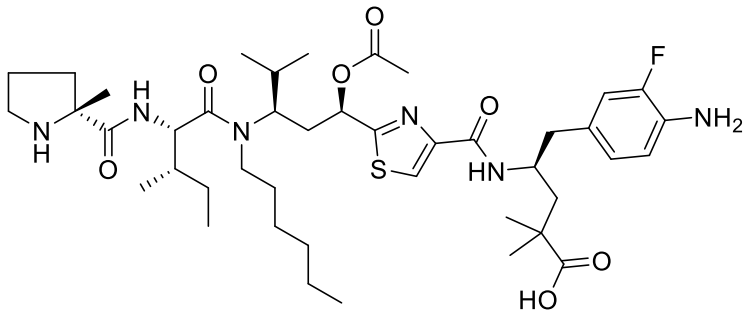
48. The compound of claim 47, wherein **R^1** is hydrogen or methyl; and **R^{10}** is methyl.

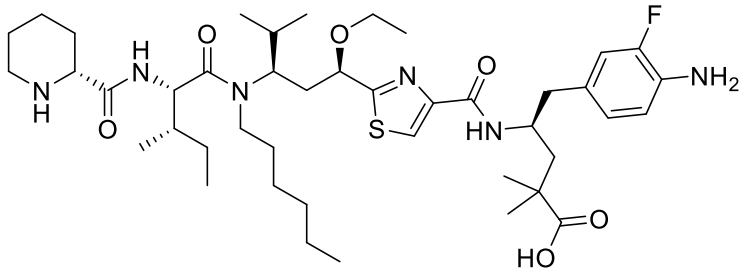
49. The compound of claim 47, selected from the group consisting of

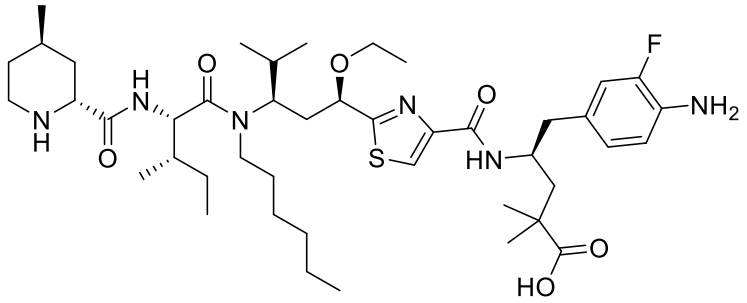


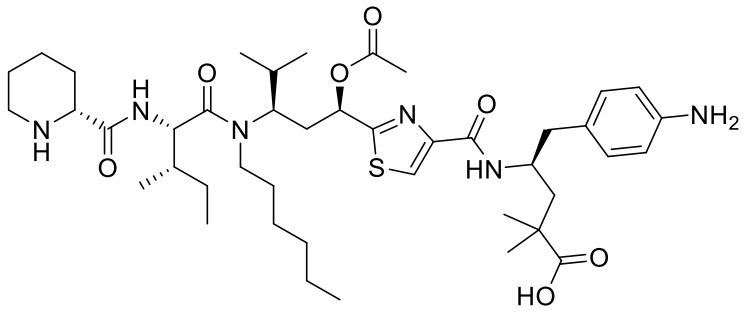


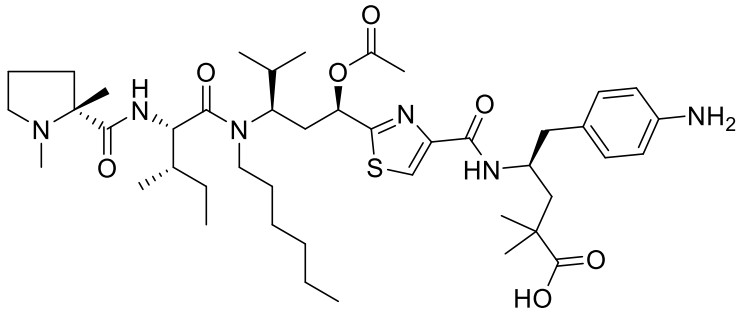


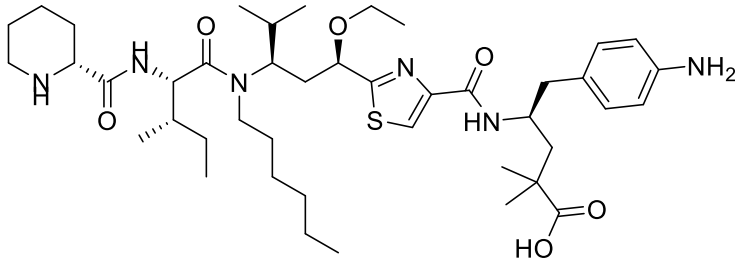


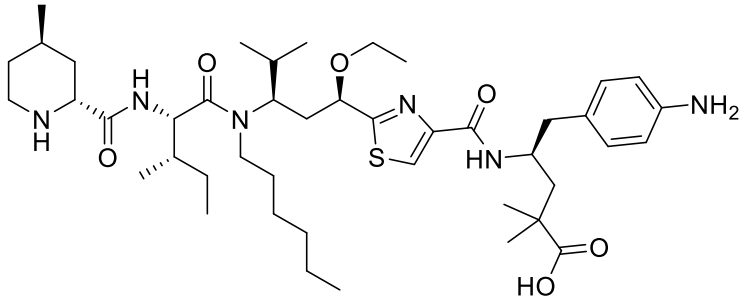


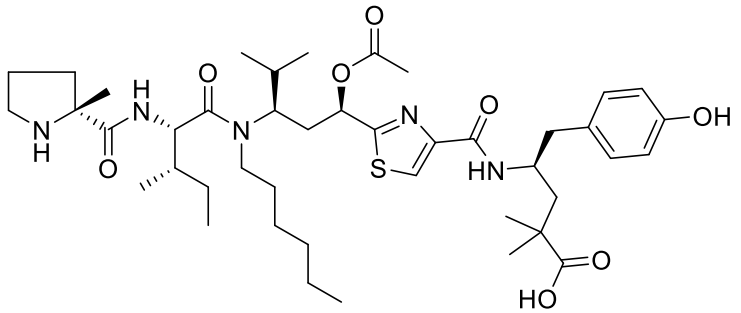




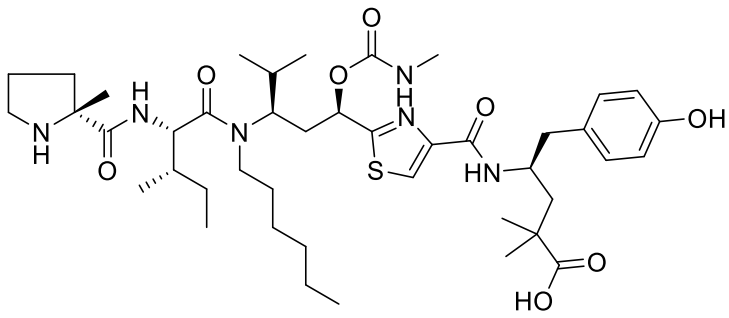








and



or

a pharmaceutically acceptable salt thereof.

50. The compound of claim 40, wherein

Q is –CH_2–;

$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;

$\mathbf{R^2}$ is alkyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;

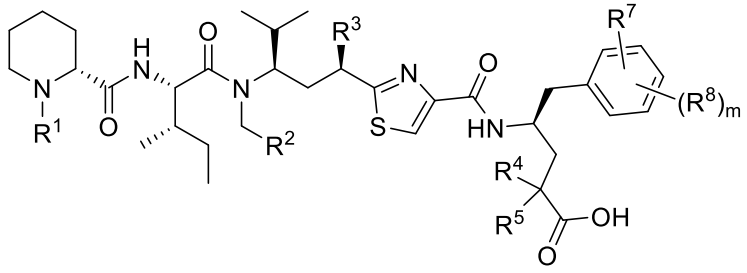
$\mathbf{R^6}$ is –OH;

$\mathbf{R^{10}}$ is absent;

wherein **r** is four; and

wherein **a** is one.

51. The compound of claim 50, according to the structure of Formula II

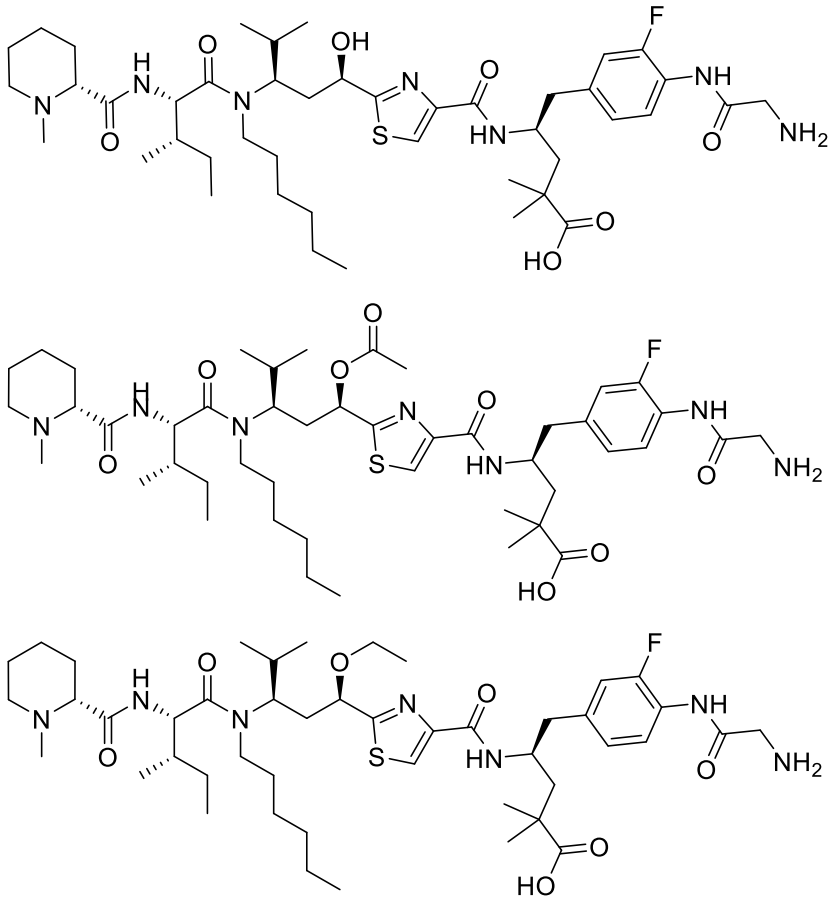


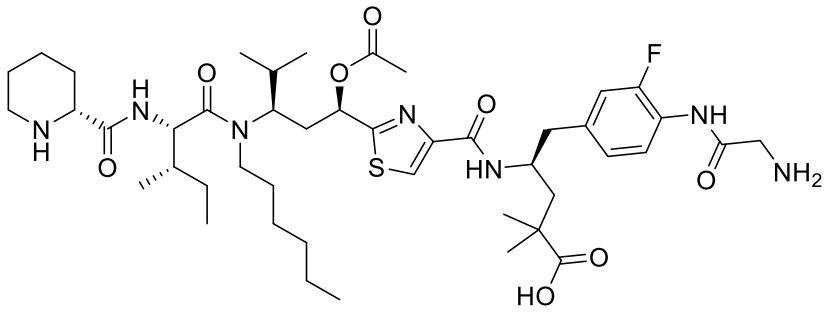
Formula II

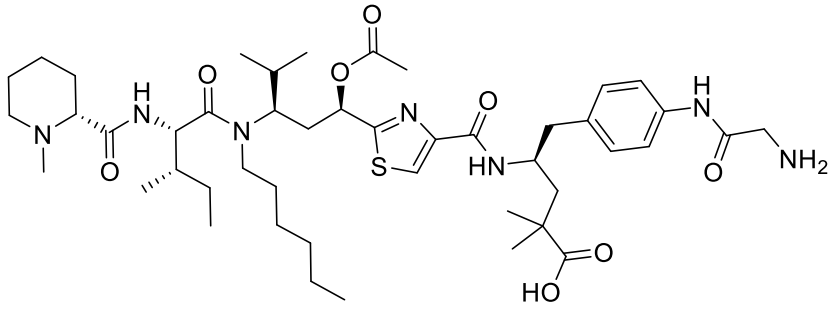
or a pharmaceutically acceptable salt thereof.

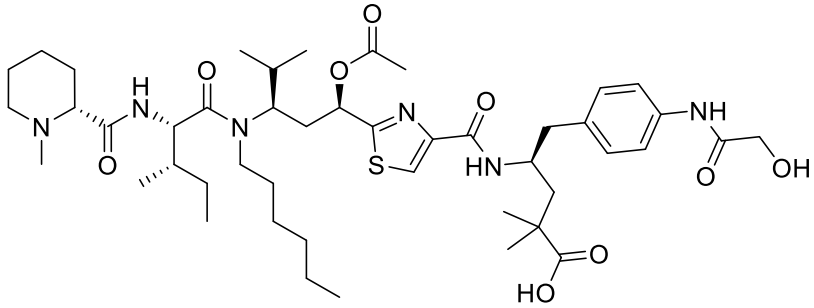
52. The compound of claim 51, wherein $\mathbf{R^7}$ is hydrogen, –N(H)C(O)CH_2NH_2, –N(H)C(O)CH_2OH, or –N(H)$CH_2CH_2NH_2$; and $\mathbf{R^8}$ is hydrogen or fluoro.

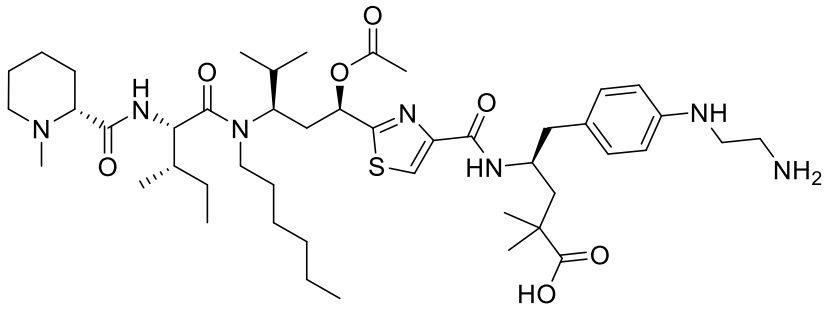
53. The compound of claim 51, selected from the group consisting of

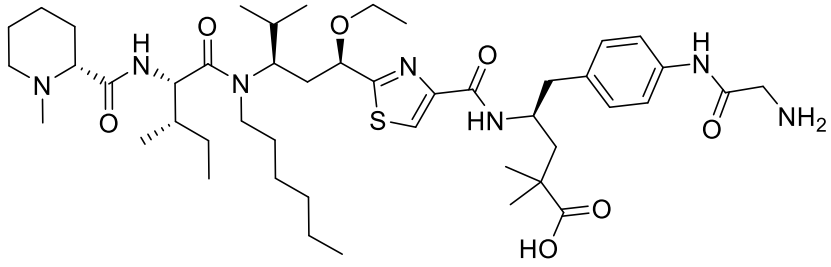




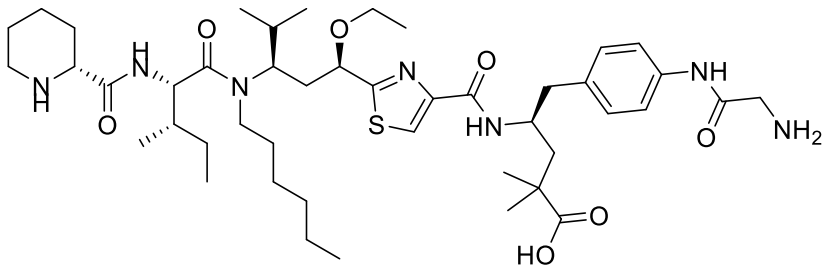








and



or

a pharmaceutically acceptable salt thereof.

54. The compound of claim 40, wherein

Q is –O–;

R^1 is hydrogen or C_1-C_{10} alkyl;

R^2 is alkyl or alkynyl;

R^3 is hydroxyl or –OC(O)C_1-C_5 alkyl;

R^4 and **R^5** are C_1-C_5 alkyl;

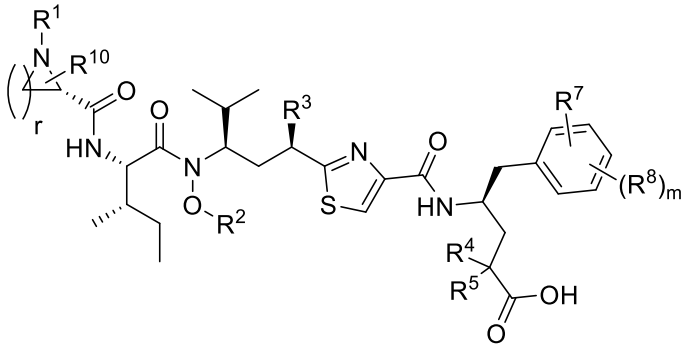
R^6 is –OH;

R^{10}, when present, is -C_1-C_5 alkyl;

wherein **r** is three or four; and

wherein **a** is one.

55. The compound of claim 54, according to the structure of Formula IV

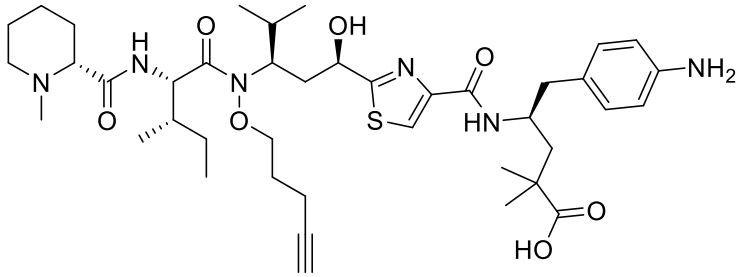


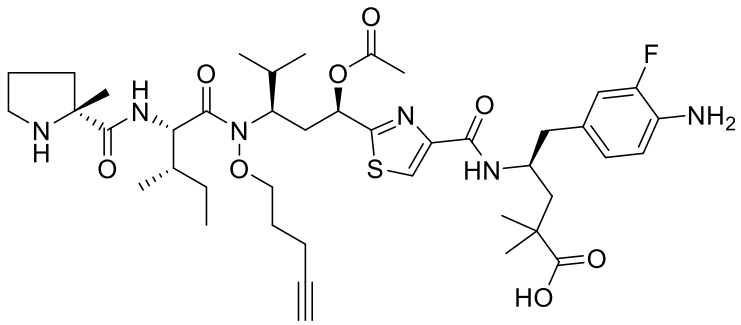
Formula IV

or a pharmaceutically acceptable salt thereof.

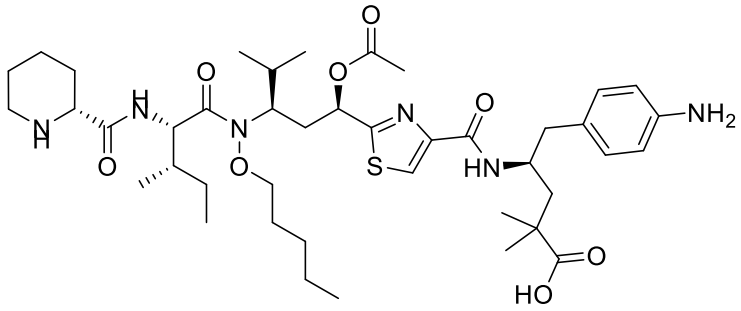
56. The compound of claim 54, wherein **R^7** is hydrogen or –NH_2; and **R^8** is hydrogen or fluoro.

57. The compound of claim 55, selected from the group consisting of





and



or

a pharmaceutically acceptable salt thereof.

58. The compound of claim 40, wherein

Q is –O–;

R[1] is C_1-C_{10} alkyl;

R[2] is alkynyl;

R[3] is –OC(O)C_1-C_5 alkyl;

R[4] and **R[5]** are C_1-C_5 alkyl;

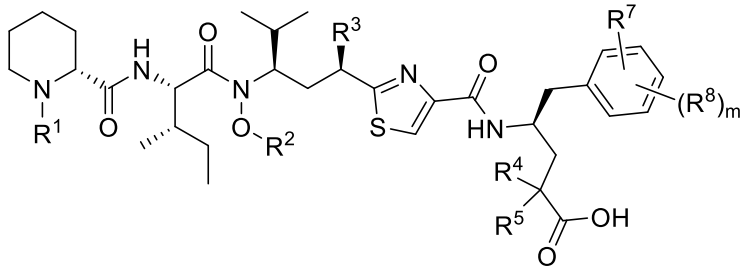
R[6] is –OH;

R[10] is absent;

wherein **r** is four; and

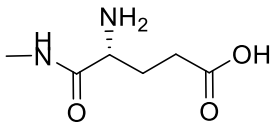
wherein **a** is one.

59. The compound of claim 58, according to the structure of Formula V

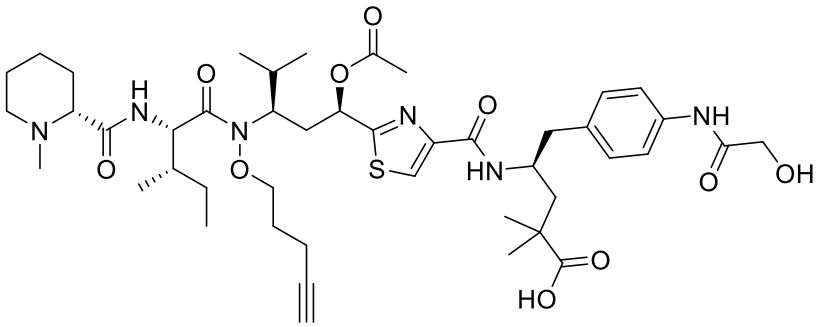


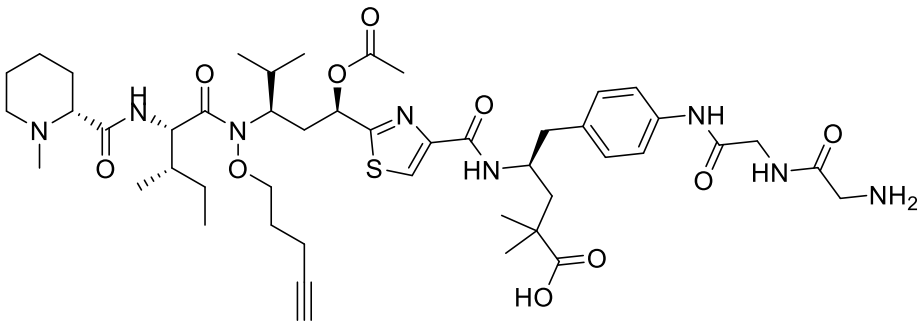
Formula V

or a pharmaceutically acceptable salt thereof.

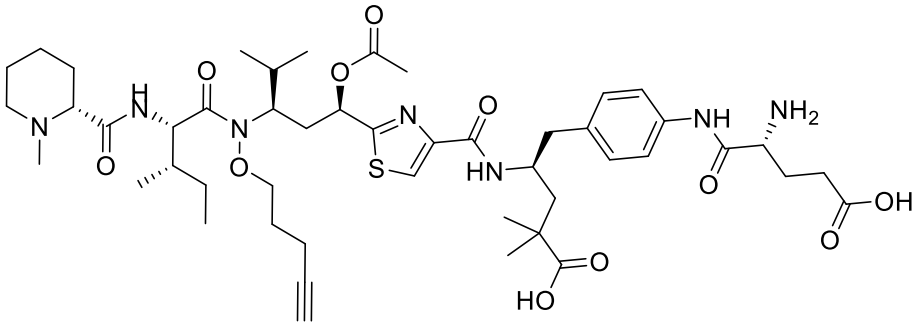
60. The compound of claim 59, wherein **R**^{7} is hydrogen or –N(H)C(O)CH$_2$OH, –N(H)C(O)CH$_2$NHC(O)CH$_2$NH$_2$, or  ; and **R**^{8} is hydrogen.

61. The compound of claim 59, selected from the group consisting of





and



or

a pharmaceutically acceptable salt thereof.

62. The compound of claim 40, wherein

Q is –CH_2– or –O–;

R^1 is C_1-C_{10} alkyl;

R^2 is alkyl or alkynyl;

R^4 and **R^5** are C_1-C_5 alkyl;

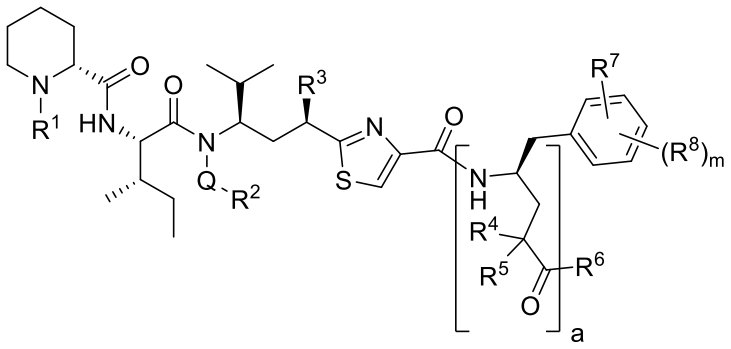
R^6 is –$NHSO_2(CH_2)_{a1}$-aryl-$(CH_2)_{a2}N$**$R^{6a}R^{6b}$**;

R^{10} is absent;

wherein **r** is four; and

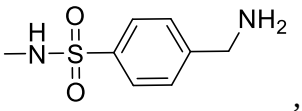
wherein **a**, **a1**, and, **a2** are, independently, zero or one.

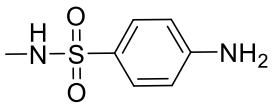
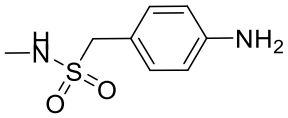
63. The compound of claim 62, according to the structure of Formula VI

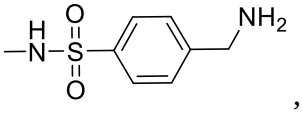


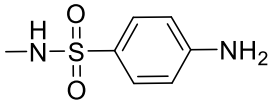
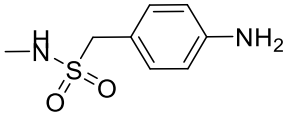
Formula VI

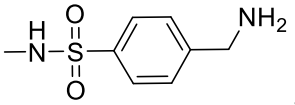
or a pharmaceutically acceptable salt thereof.

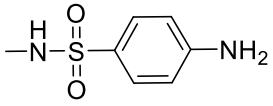
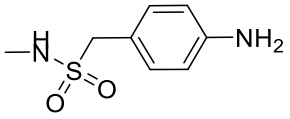
64. The compound of claim 63, wherein **R^6** is ,

, or .

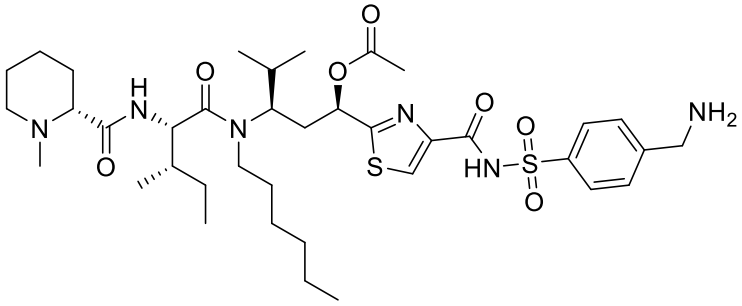
65. The compound of claim claim 63, wherein **a** is zero; and **R^6** is ,

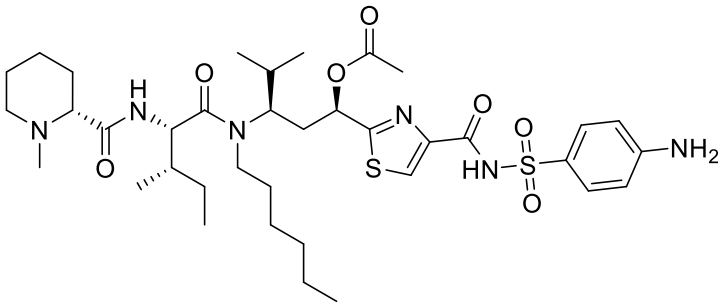
, or .

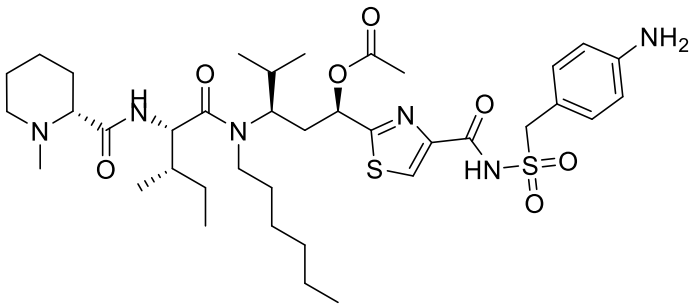
66. The compound of claim 63, wherein **a** is one; and $\mathbf{R^6}$ is ,

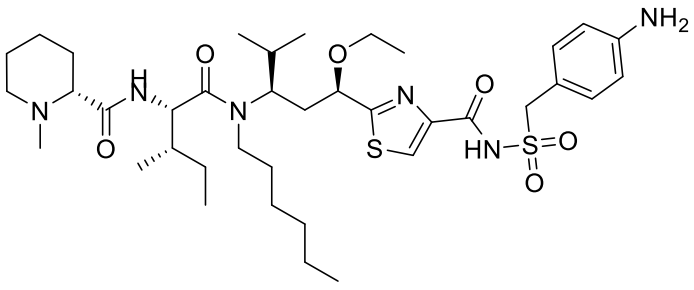
, or .

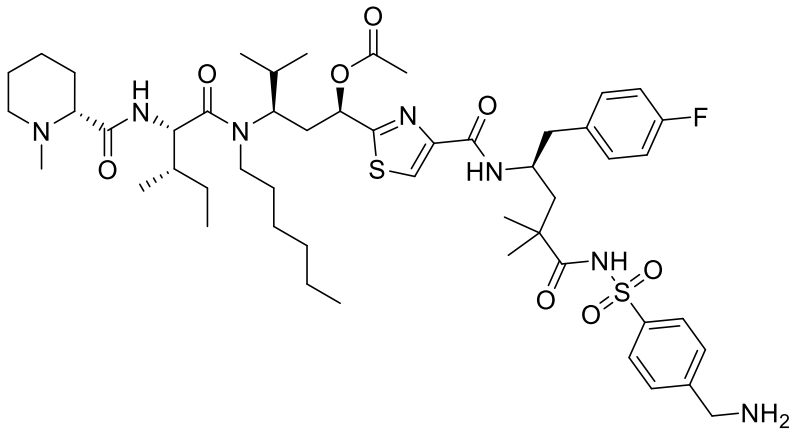
67. The compound of claim 63, selected from the group consisting of

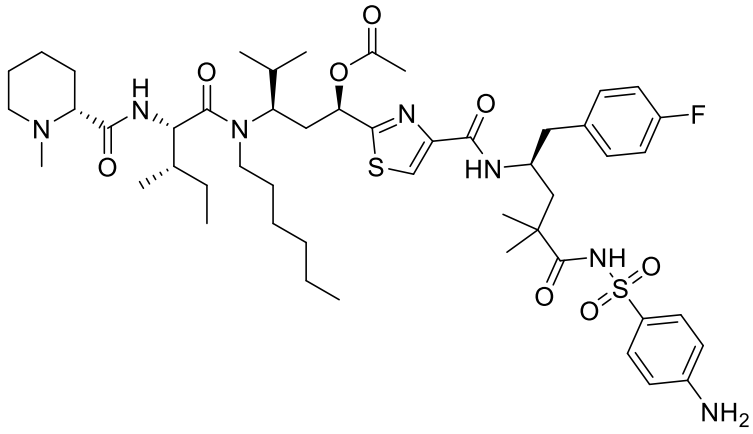


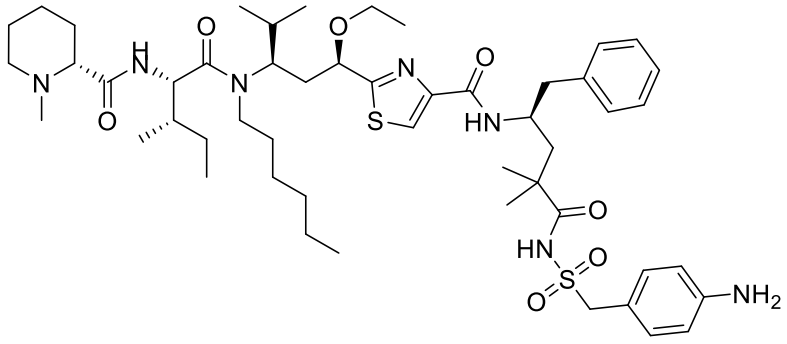




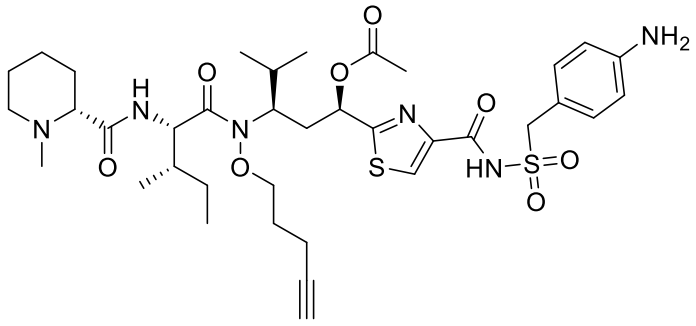








and



or

a pharmaceutically acceptable salt thereof.

68. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient, carrier, or diluent.

69. The compound of claim 1 or 40 for use in treating cancer or tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

70. The compound of claim 1 or 40 for use in treating cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

71. Use of the compound of claim 1 or 40 in the manufacture of a medicament for the treatment of cancer.

72. Use of the compound of claim 1 or 40 in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

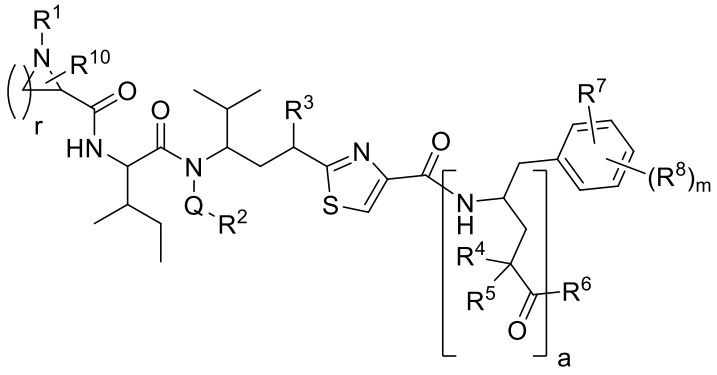
73. Use of the compound of claim 1 or 40 in the manufacture of a medicament for the treatment of tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

74. A linker-payload having the formula

L—T

or a pharmaceutically acceptable salt thereof, wherein

L is a linker covalently bound to **T**;

T is  wherein

R^{1} is a bond, hydrogen, C_1-C_{10} alkyl, a first *N*-terminal amino acid residue, a first amino acid residue, –C_1-C_{10} alkyl-N**R^{3a}R^{3b}**, or –C_1-C_{10} alkyl-OH;

R^{3} is hydroxyl, –O–, –O-C_1-C_5 alkyl, –OC(O)C_1-C_5 alkyl, –OC(O)N(H)C_1-C_{10} alkyl, –OC(O)N(H)C_1-C_{10} alkyl-N**R^{3a}R^{3b}**, –NHC(O)C_1-C_5 alkyl, or –OC(O)N(H)$(CH_2CH_2O)_{\mathbf{n}}C_1$-$C_{10}$ alkyl-N**R^{3a}R^{3b}**,

wherein **R^{3a}** and **R^{3b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{4} and **R^{5}** are, independently in each instance, hydrogen or C_1-C_5 alkyl;

R^{6} is –OH, –O–, $–NHNH_2$, –NHNH–, $–NHSO_2(CH_2)_{\mathbf{a1}}$-aryl-$(CH_2)_{\mathbf{a2}}$N**R^{6a}R^{6b}**,

wherein aryl is substituted or unsubstituted; and

R^{6a} and **R^{6b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^{7} is, independently in each instance, hydrogen, –OH, –O–, halogen, or –N**R^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** are, independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, $–C(O)CH_2OH$, $–C(O)CH_2O–$, a first *N*-

terminal amino acid residue, a first amino acid residue, a first *N*-terminal peptide residue, a first peptide residue, $–CH_2CH_2NH_2$, and $–CH_2CH_2NH–$; wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R^8 is, independently in each instance, hydrogen, $–NHR^9$, or halogen,

wherein **R^9** is hydrogen, $–C_1$-C_5 alkyl, or $–C(O)C_1$-C_5 alkyl; and

m is one or two;

R^{10}, when present, is $-C_1$-C_5 alkyl;

Q is $–CH_2–$ or –O– wherein

R^2 is alkyl, alkylene, alkynyl, alkynylene, a regioisomeric triazole, a regioisomeric triazolylene;

wherein said regioisomeric triazole or regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or acyl;

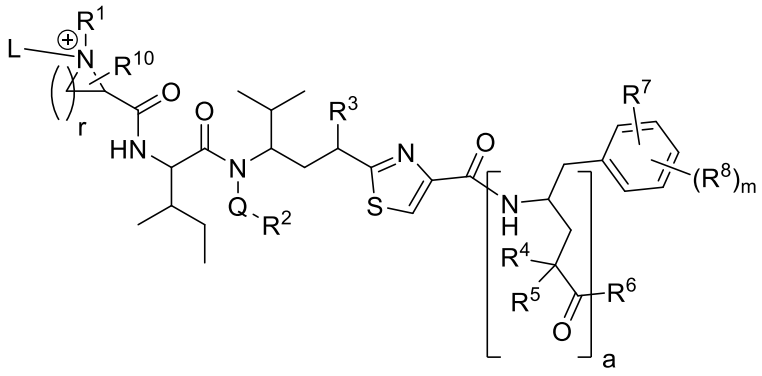
wherein **n** is an integer from one to ten;

wherein **r** is an integer from one to six;

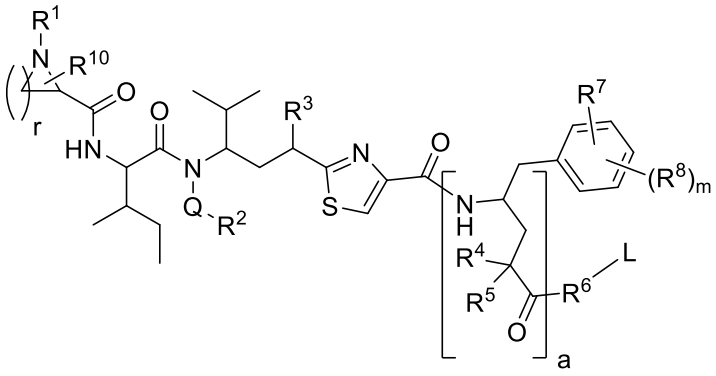
wherein **a**, **a1**, and, **a2** are, independently, zero or one; and

wherein the linker-payload is not **LP1-IVa**, **LP2-Va**, **LP3-IVd**, **LP4-Ve**, **LP5-IVd**, **LP6-Vb**, **LP7-IVd**, **LP9-IVvB**, **LP10-VIh**, **LP11-IVvB**, **LP12-VIi**, **LP13-Ve**, **LP14-Ve**, **LP15-VIh**, **LP16-Ve**, **LP17-Ve**, **LP18-Ve**, **LP19-Ve**, **LP20-Ve**, **LP21-Ve**, **LP22-Ve**, **LP23-Vb**, **LP24-Vb**, **LP25-Ve**, and **LP26-Ve**, or a pharmaceutically acceptable salt thereof.

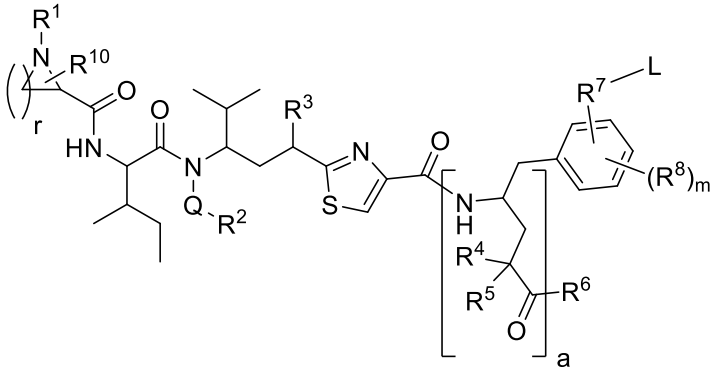
75. The linker-payload of claim 74, having a Formula **LPa**, **LPb**, **LPc**, **LPd**, or **LPe**



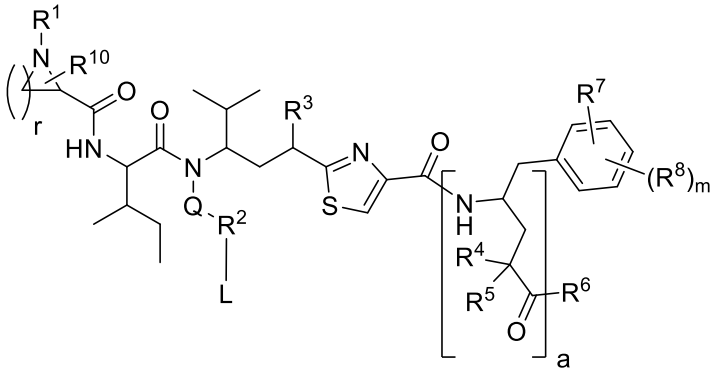
(**LPa**)



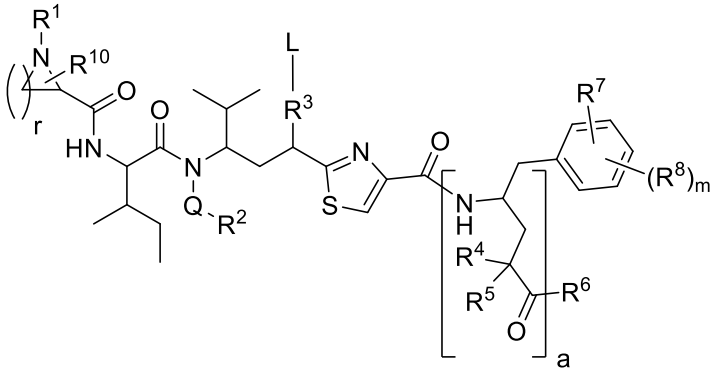
(**LPb**)



(**LPc**)



(**LPd**)



(**LPe**)

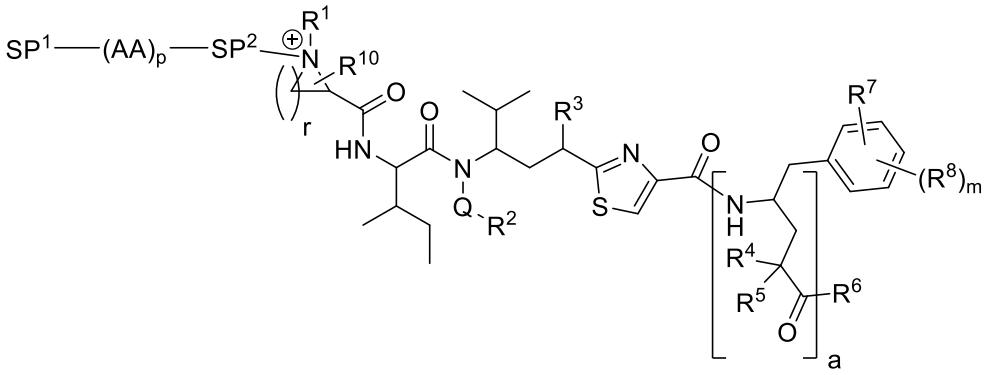
wherein **L** is a linker.

76. The linker-payload of claim 75, wherein

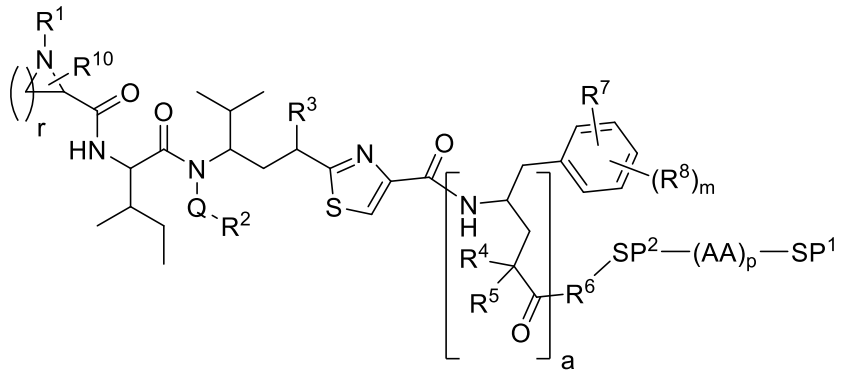
$\mathbf{R^7}$ is, independently in each instance, hydrogen, –OH, –O–, halogen, or –N$\mathbf{R^{7a}R^{7b}}$,

wherein $\mathbf{R^{7a}}$ and $\mathbf{R^{7b}}$ are, independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, –C(O)CH_2OH, –C(O)CH_2O–, a first *N*-terminal amino acid residue, a first *N*-terminal peptide residue, –$CH_2CH_2NH_2$, and –CH_2CH_2NH–, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted.

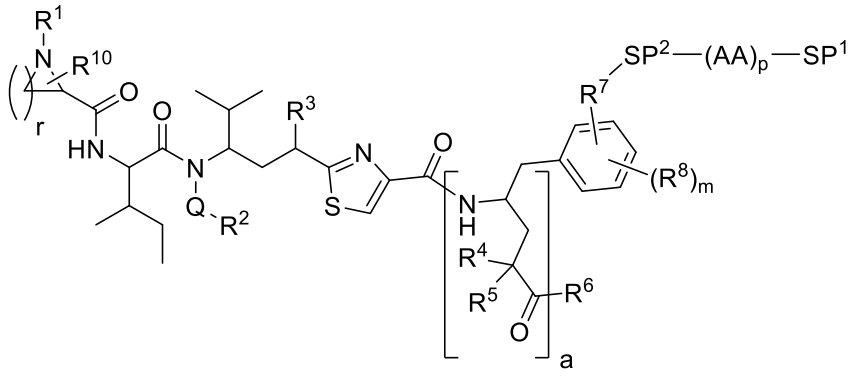
77. The linker-payload of claim 76, having the Formula **LPa'**, **LPb'**, **LPc'**, **LPd'**, or **LPe'**



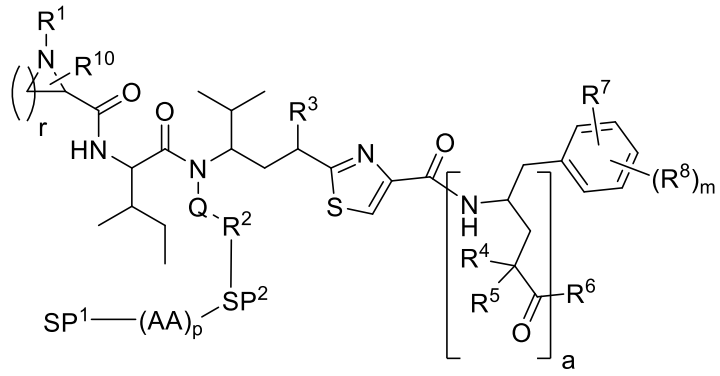
(**LPa'**)



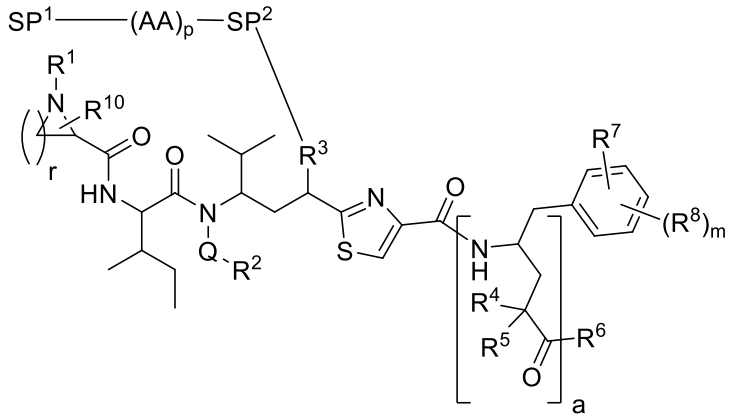
(**LPb'**)



(**LPc'**)



(**LPd'**)



(**LPe'**)

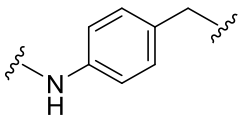
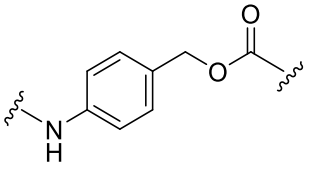
wherein

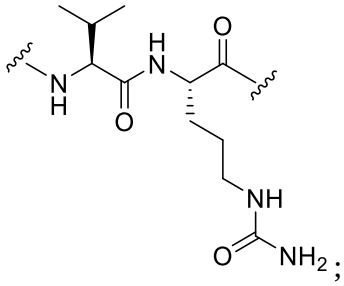
SP^1 and **SP^2**, when present, are spacer groups;

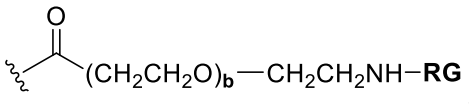
each **AA**, when present, is a second amino acid residue; and

p is an integer from zero to ten.

78. The linker-payload of claim 77, wherein

the –**SP^{2}**– spacer, when present, is  or ;

the second –(**AA**)$_{\mathbf{p}}$– is ;

the –**SP^{1}**– spacer is ,

wherein **RG** is a reactive group; and

b is an integer from one to four.

79. The linker-payload of claim 77, wherein **Q** is –O–.

80. The linker-payload of claim 77, wherein

Q is –CH_2–;

R^{1} is C_1-C_{10} alkyl;

R^{2} is alkyl;

R^{4} and **R^{5}** are C_1-C_5 alkyl;

R^{6} is –OH;

R^{10} is absent;

wherein **r** is four; and

wherein **a** is one.

81. The linker-payload of claim 80, according to the structure of **LPc'**, or a pharmaceutically acceptable salt thereof.

82. The linker payload of claim 81, wherein **R^{7}** is –NH–; and **R^{8}** is hydrogen or fluoro.

83. The linker-payload of claim 80, according to the structure of **LPe'**, or a pharmaceutically acceptable salt thereof.

84. The linker payload of claim 83, wherein $\mathbf{R^3}$ is –OC(O)N(H)CH_2CH_2NH– or –OC(O)N(H)$CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$NH–.

85. The linker-payload of claim 77, wherein
Q is –CH_2–;
$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;
$\mathbf{R^2}$ is alkyl;
$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;
$\mathbf{R^6}$ is –OH;
wherein **r** is three or four; and
wherein **a** is one.

86. The linker-payload of claim 85, according to the structure of **LPc'**, or a pharmaceutically acceptable salt thereof.

87. The linker-payload of claim 86, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen.

88. The linker-payload of claim 77, wherein
Q is –CH_2–;
$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;
$\mathbf{R^2}$ is alkyl;
$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;
$\mathbf{R^6}$ is –OH;
$\mathbf{R^{10}}$ is absent;
wherein **r** is four; and
wherein **a** is one.

89. The linker-payload of claim 88, according to the structure of **LPc'**, or a pharmaceutically acceptable salt thereof.

90. The linker-payload of claim 89, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen.

91. The linker-payload of claim 77, wherein

Q is –O–;

$\mathbf{R^1}$ is hydrogen or C_1-C_{10} alkyl;

$\mathbf{R^2}$ is alkyl or alkynyl;

$\mathbf{R^3}$ is hydroxyl or –OC(O)C_1-C_5 alkyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;

$\mathbf{R^6}$ is –OH;

$\mathbf{R^{10}}$, when present, is -C_1-C_5 alkyl;

wherein **r** is three or four; and

wherein **a** is one.

92. The linker-payload of claim 91, according to the structure of **LPc'**, or a pharmaceutically acceptable salt thereof.

93. The linker-payload of claim 92, wherein $\mathbf{R^7}$ is –NH–; and $\mathbf{R^8}$ is hydrogen.

94. The linker-payload of claim 77, wherein

Q is –CH_2– or –O–;

$\mathbf{R^1}$ is C_1-C_{10} alkyl;

$\mathbf{R^2}$ is alkyl or alkynyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are C_1-C_5 alkyl;

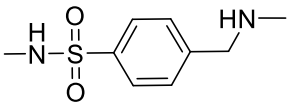
$\mathbf{R^6}$ is –NHSO_2(CH_2)$_{\mathbf{a1}}$-aryl-(CH_2)$_{\mathbf{a2}}$N$\mathbf{R^{6a}R^{6b}}$;

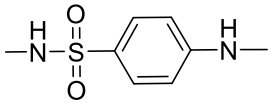
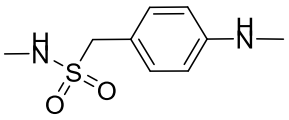
$\mathbf{R^{10}}$ is absent;

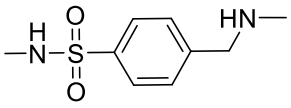
wherein **r** is four; and

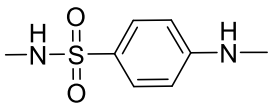
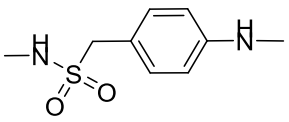
wherein **a**, **a1**, and, **a2** are, independently, zero or one.

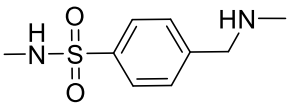
95. The linker-payload of claim 94, according to the structure of **LPb'**, or a pharmaceutically acceptable salt thereof.

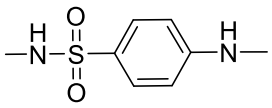
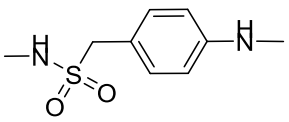
96. The linker-payload of claim 95, wherein **R**^{6} is ,

, or .

97. The linker-payload of claim 95, wherein **a** is zero; and **R**^{6} is ,

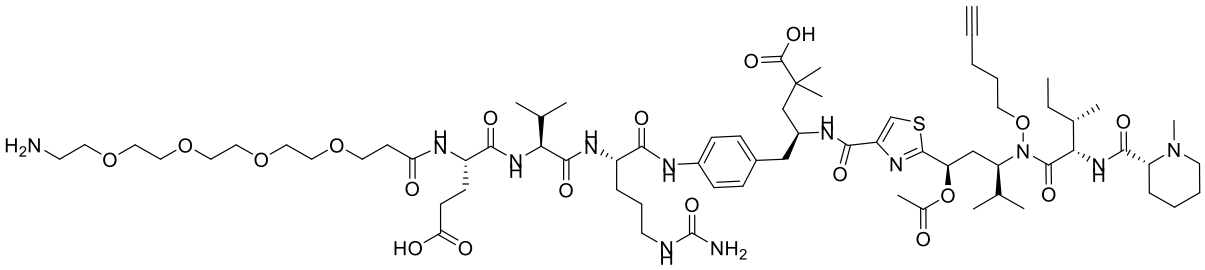
, or .

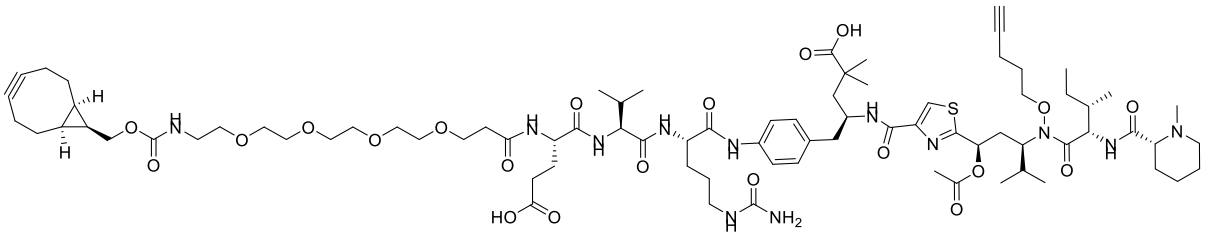
98. The linker-payload of claim 95, wherein **a** is one; and **R**^{6} is ,

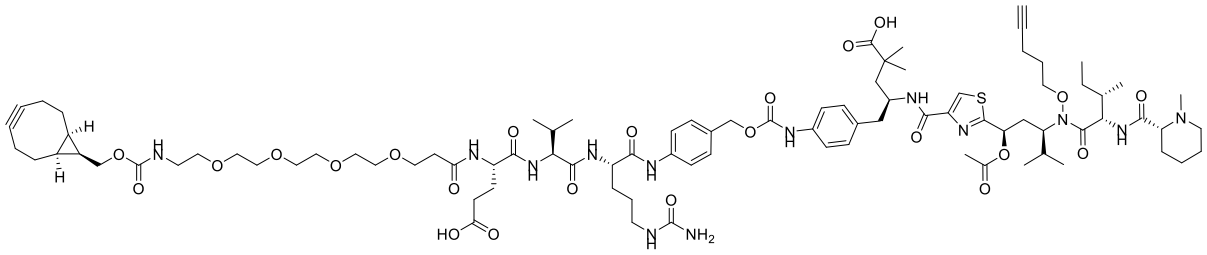
, or .

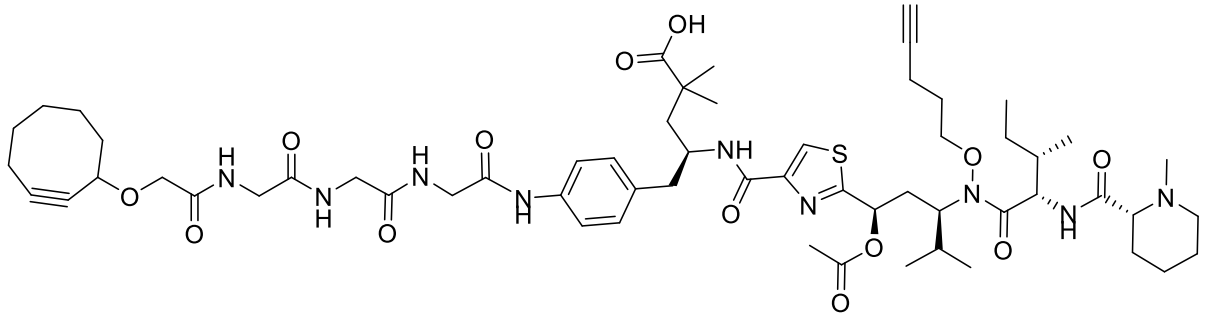
99. The linker-payload of claim 92, wherein **R**^{7} is –O–; and **R**^{8} is hydrogen.

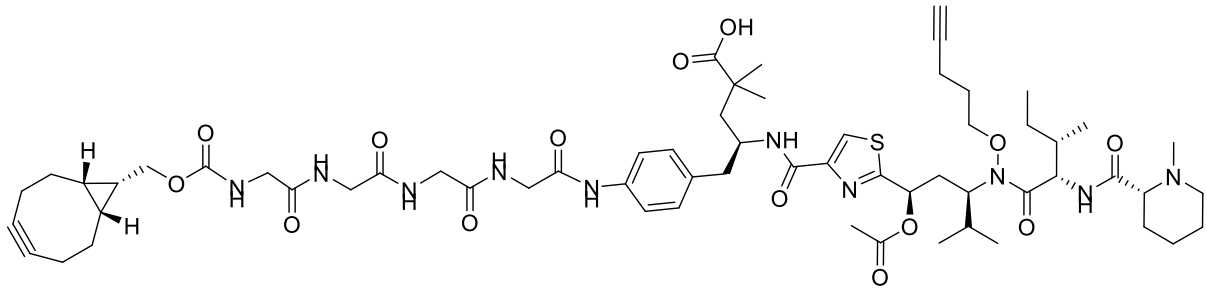
100. The linker-payload of claim 77, wherein the linker-payload is selected from the group consisting of

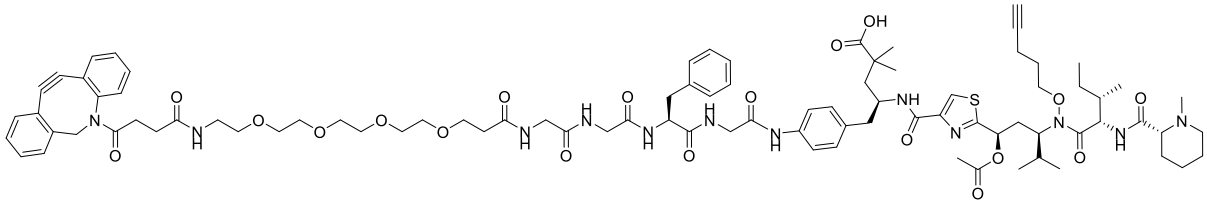


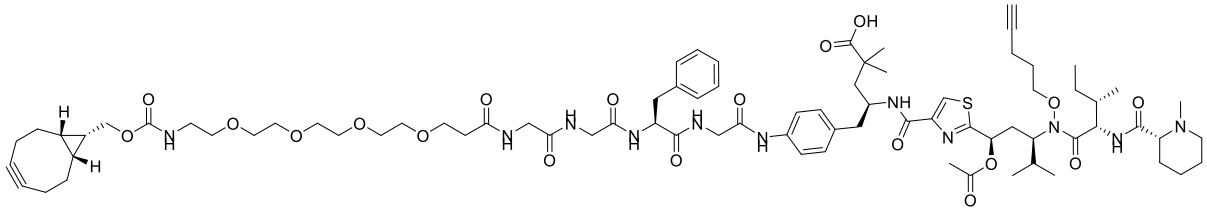


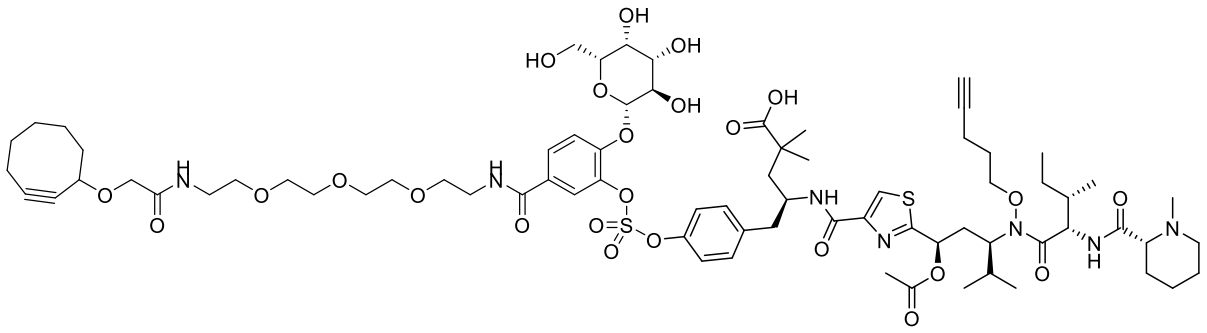


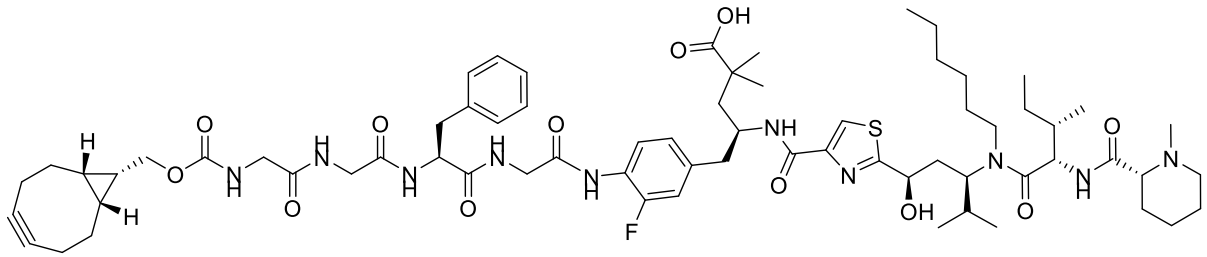


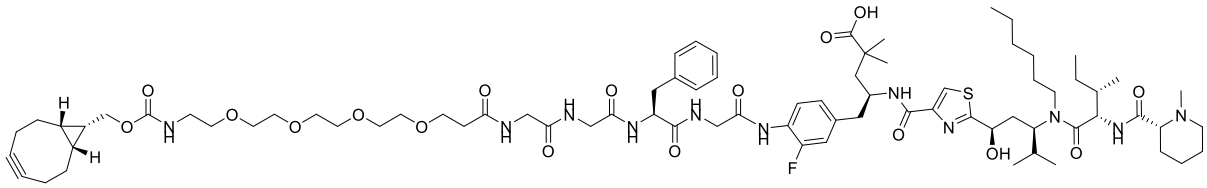


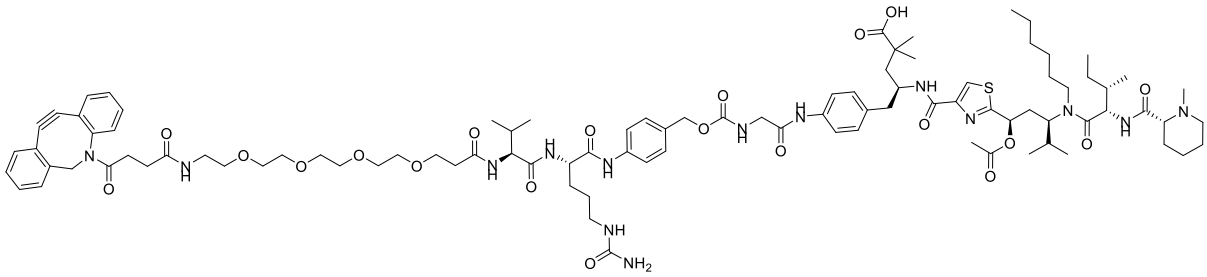


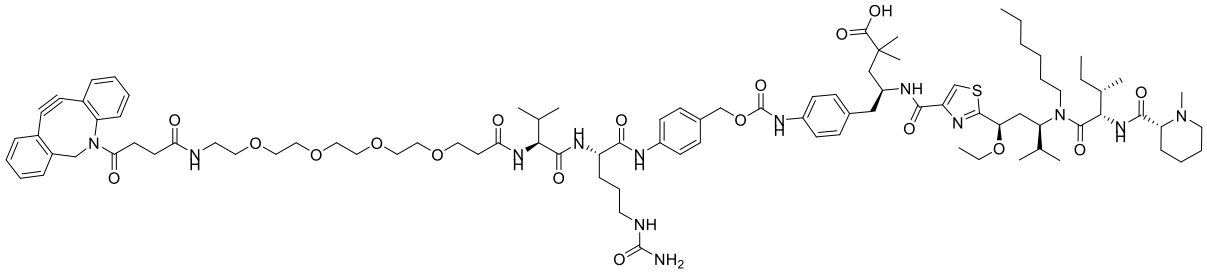


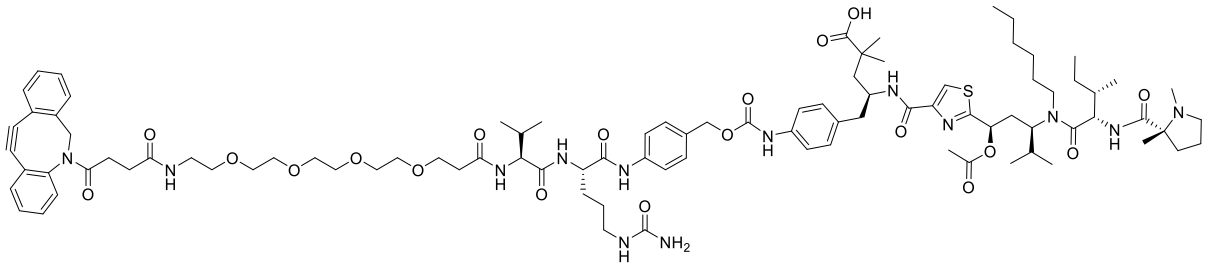


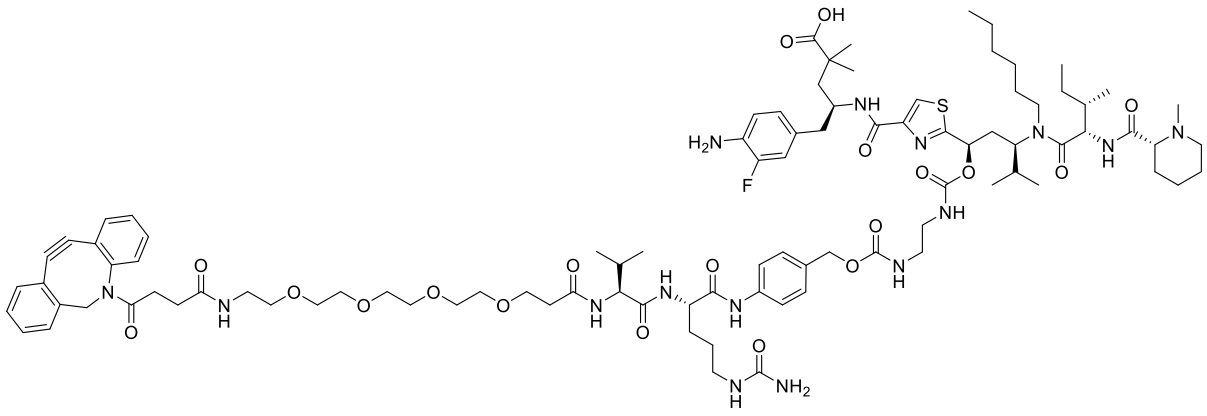


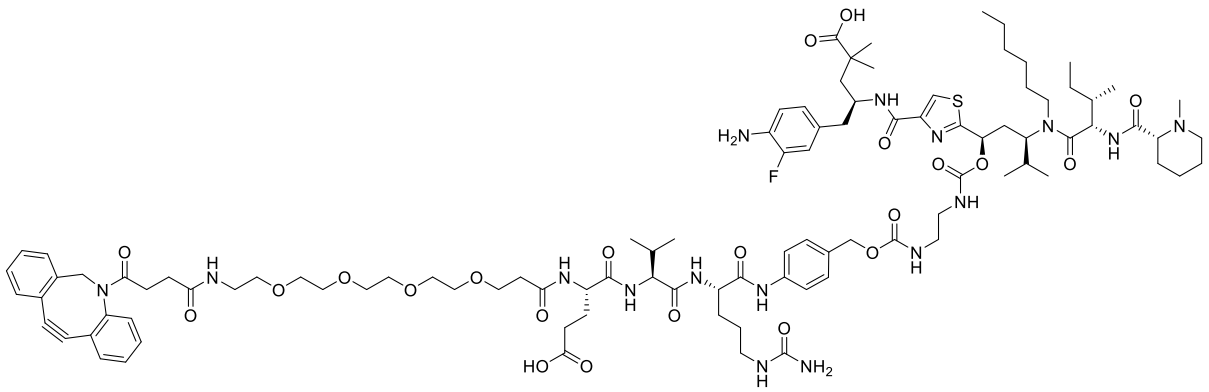


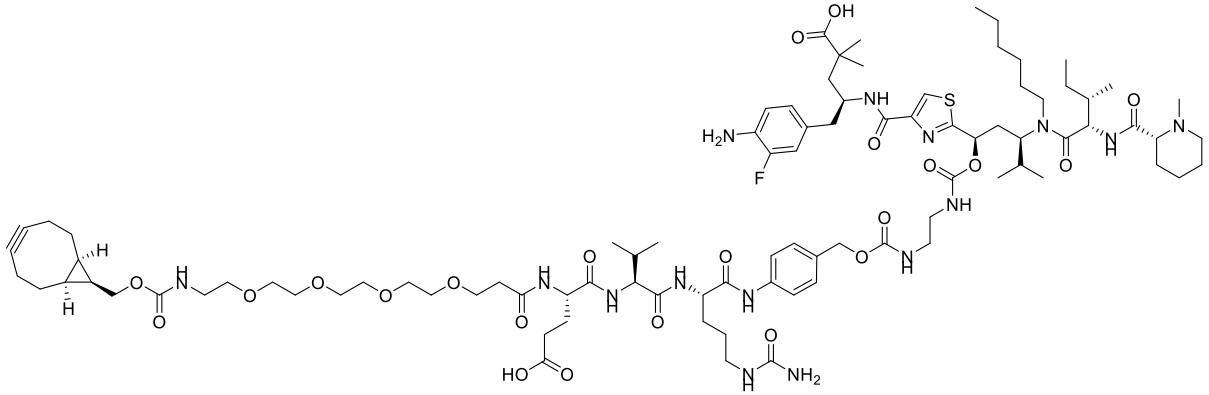


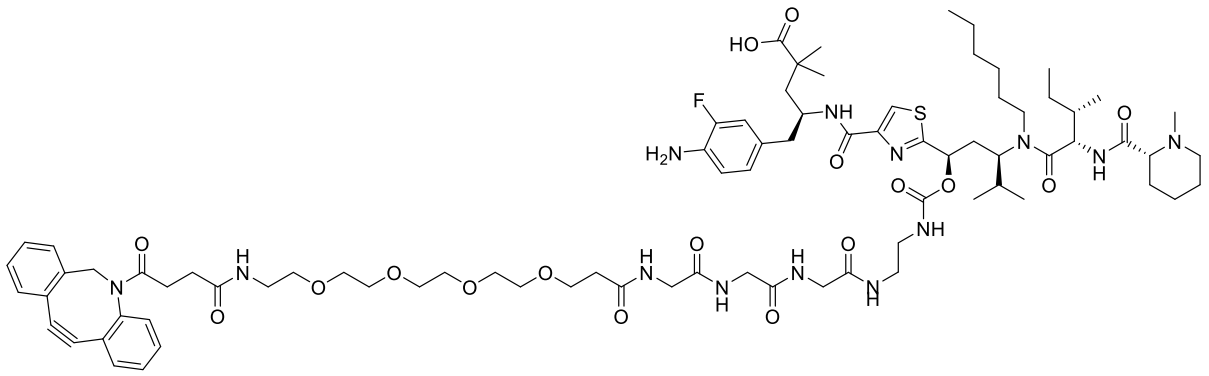


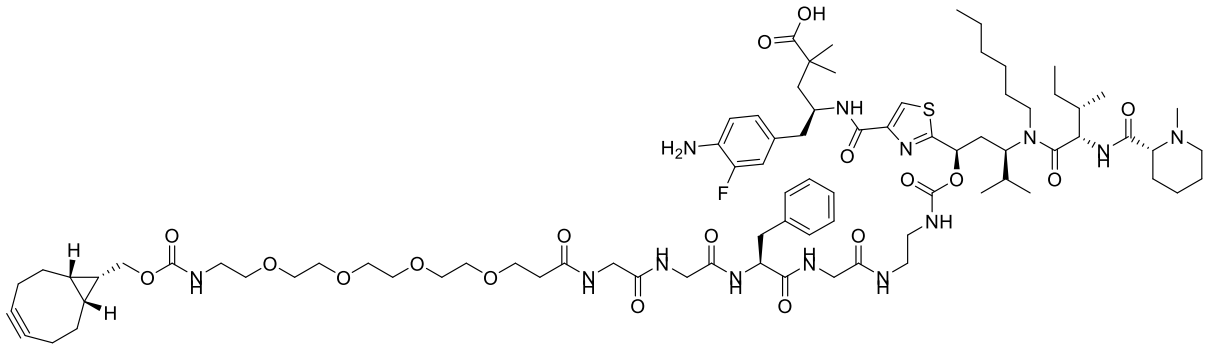


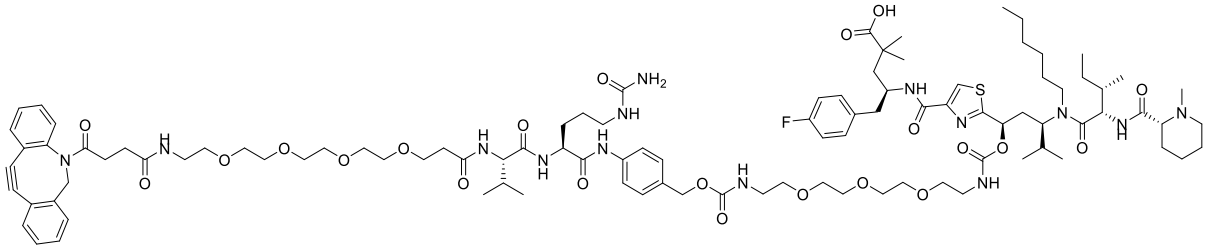


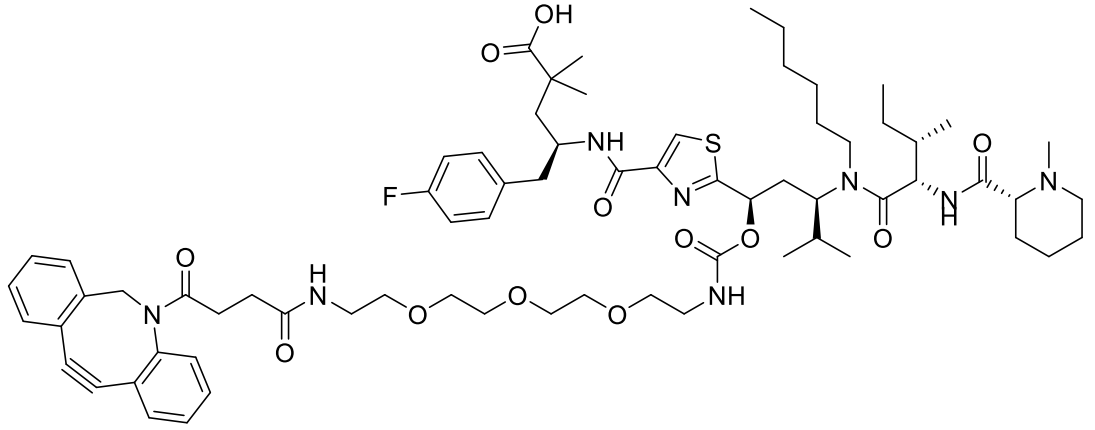


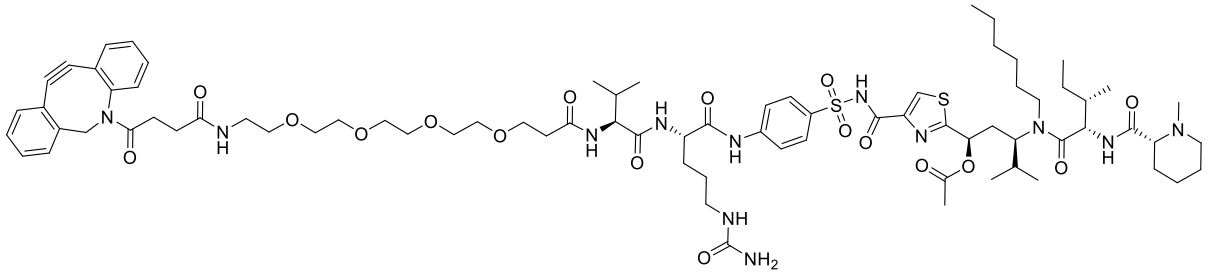


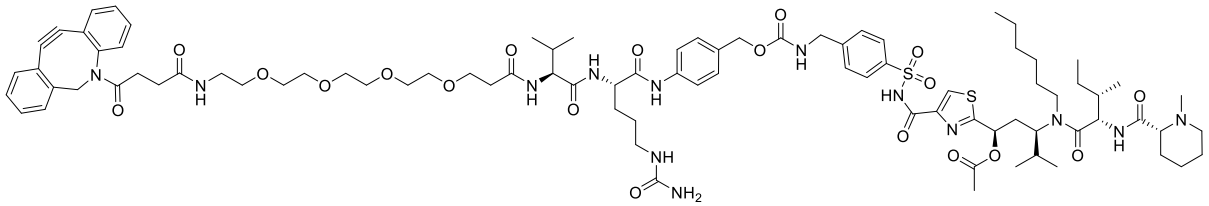


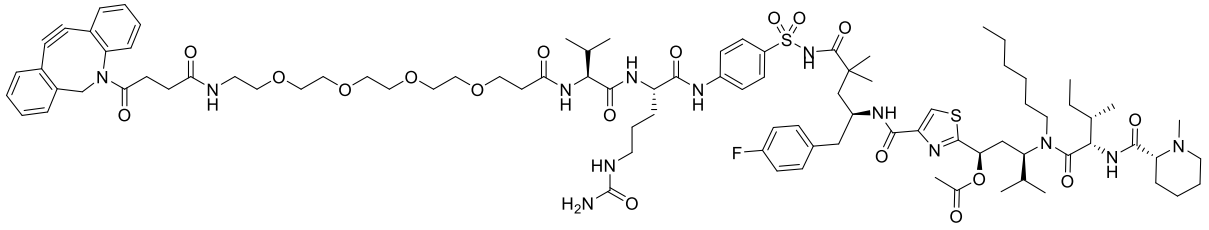


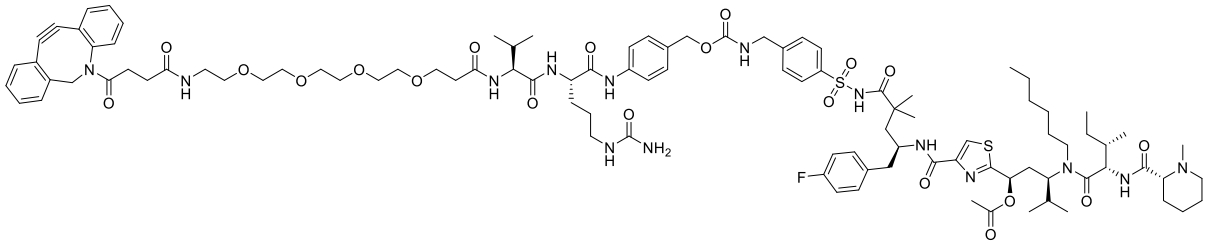


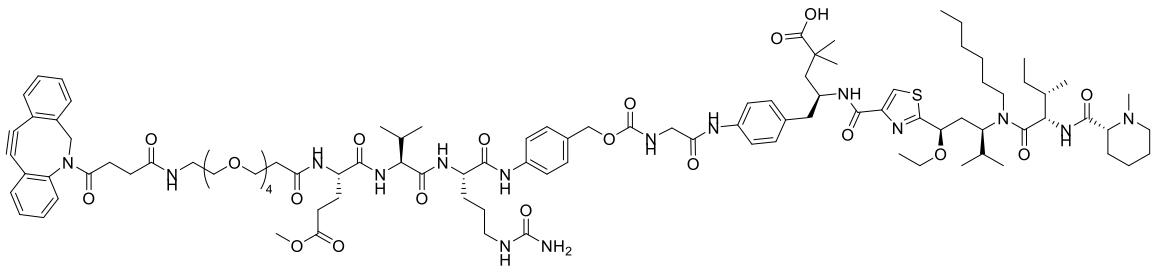




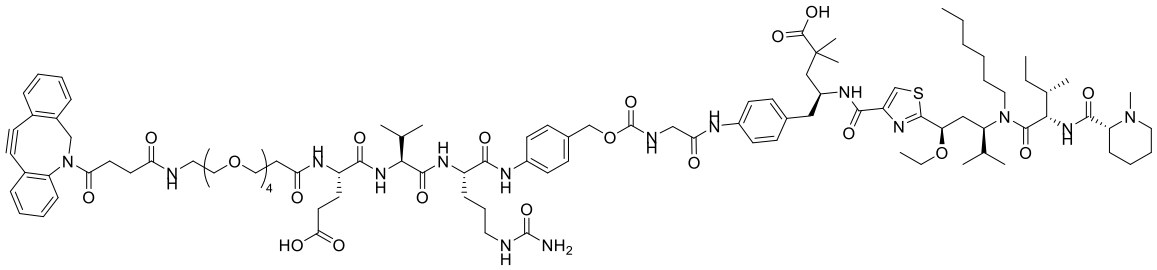








and



or a pharmaceutically acceptable salt thereof.

101. The pharmaceutical composition of claim 68 for use in treating cancer.

102. A pharmaceutical composition comprising the compound of claim 40 and a pharmaceutically acceptable excipient, carrier, or diluent.

103. The pharmaceutical composition of claim 102 for use in treating cancer.

104. The pharmaceutical composition of claim 68 for use in treating cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

105. The pharmaceutical composition of claim 102 for use in treating cancer, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung

cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

106. The pharmaceutical composition of claim 68 or 102 for use in treating tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

107. Use of the pharmaceutical composition of claim 68 or 102 in the manufacture of a medicament for the treatment of cancer.

108. The use of claim 107, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostrate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, mesothelioma, malignant mesothelioma, multiple myeloma, ovarian cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, breast cancer, PRLR positive (PRLR+) breast cancer, melanoma, acute myelogenous leukemia, adult T-cell leukemia, astrocytomas, bladder cancer, cervical cancer, cholangiocarcinoma, endometrial cancer, esophageal cancer, glioblastomata, Kaposi's sarcoma, kidney cancer, leiomyosarcomas, liver cancer, lymphomas, MFH/fibrosarcoma, nasopharyngeal cancer, rhabdomyosarcoma, colon cancer, stomach cancer, uterine cancer, residual cancer, and Wilms' tumor.

109. Use of the pharmaceutical composition of claim 68 or 102 in the manufacture of a medicament for the treatment of tumors that express an antigen selected from the group consisting of PRLR and STEAP2.