

TUBULYSINS AND PROTEIN-TUBULYSIN CONJUGATES

FIELD

[0001] Provided herein are novel tubulysins and protein conjugates thereof, and methods for treating a variety of diseases, disorders, and conditions including administering the tubulysins, and protein conjugates thereof.

BACKGROUND

[0002] While antibody-drug conjugates (ADCs) find increasing application in cancer treatment regimens, *de novo* or treatment-emergent resistance mechanisms could impair clinical benefit. Two resistance mechanisms that emerge under continuous ADC exposure *in vitro* include upregulation of transporters that confer multidrug resistance (MDR) and loss of cognate antigen expression. New technologies that circumvent these resistance mechanisms may serve to extend the utility of next generation ADCs.

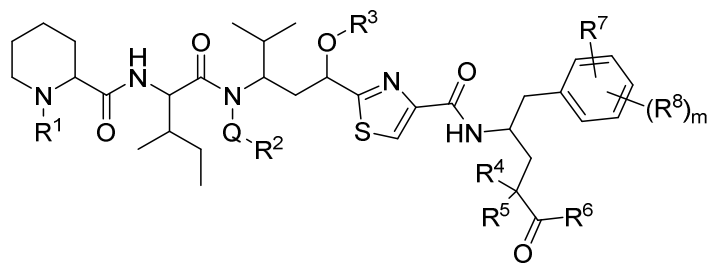
[0003] The tubulysins, first isolated from myxobacterial culture broth, are a group of extremely potent tubulin polymerization inhibitors that rapidly disintegrate the cytoskeleton of dividing cells and induce apoptosis. Tubulysins are comprised of *N*-methyl-D-pipecolinic acid (Mep), L-isoleucine (Ile), and tubuvaline (Tuv), which contains an unusual *N*,*O*-acetal and a secondary alcohol or acetoxy group. Tubulysins A, B, C, G, and I contain the C-terminal tubutyrosine (Tut) γ -amino acid, while D, E, F, and H instead have tubuphenylalanine (Tup) at this position (*Angew. Chem. Int. Ed. Engl.* 43, 4888–4892).

[0004] Tubulysins have emerged as promising anticancer leads due to their powerful activity in drug-resistant cells through a validated mechanism of action. The average cell growth inhibitory activity outperforms that of well-known epothilones, vinblastines, and taxols by 10-fold to more than 1000-fold, including activity against multi-drug resistant carcinoma (*Biochem. J.* 2006, 396, 235-242; *Nat. Prod. Rep.* 2015, 32, 654-662). Tubulysins have extremely potent antiproliferative activity against cancer cells, including multidrug resistant KB-V1 cervix carcinoma cells. (*Angew. Chem. Int. Ed.* **2004**, 43, 4888-4892; and *Biochemical Journal* **2006**, 396, 235-242).

SUMMARY

[0005] Provided herein are compounds useful, for example, in anti-cancer and anti-angiogenesis treatments.

[0006] In one aspect, the present disclosure refers to compounds having the structure of Formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH or -NHNH₂;

R⁷ is, independently in each instance, hydrogen, -OH, halogen, or -**NR^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** are independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, -NHR⁹, or halogen,

wherein **R⁹** is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R²** is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, -C₁-C₁₀ alkylene-(5-membered heteroaryl), -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, or C₁-C₃ hydroxyalkyl; or

when **Q** is -CH₂-, then **R²** is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl, -C₁-C₁₀ alkylene-(5-membered heteroaryl), -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, or C₁-C₃ hydroxyalkyl; and

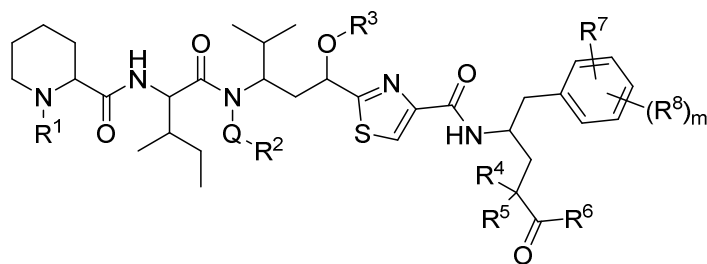
Q¹ is -CH₂- or -O-;

wherein said heteroaryl is unsubstituted or substituted with alkyl, aminoalkyl, hydroxylalkyl, carboxyalkyl, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro or amino; and

wherein **n** is an integer from one to five.

[0007] In one example, provided are compounds having the structure of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl; or, in certain examples, **R⁴** and **R⁵**, together with the carbon to which they are attached, form a 3-8 membered cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R⁶ is -OH or -NHNH₂; or, in certain examples, **R⁶** is -NHSO₂R⁶⁰, wherein **R⁶⁰** is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl;

R⁷ is, independently in each instance, hydrogen, -OH, halogen, or -NR^{7a}R^{7b},

wherein **R^{7a}** and **R^{7b}** 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;

R⁸ is, independently in each instance, hydrogen, deuterium, -NHR⁹, or halogen,

wherein **R⁹** is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is 1 or 2;

Q is -CH₂- or -O- wherein

when **Q** is $-\text{O}-$, then **R²** is $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkynyl,
 $-\text{C}_1\text{-C}_{10}$ alkylene-(5-membered heteroaryl), $-\text{C}_1\text{-C}_3$ alkylene-**Q¹**-(CH_2)_naryl, or $\text{C}_1\text{-C}_3$
hydroxyalkyl; or

when **Q** is $-\text{CH}_2-$, then **R²** is $\text{C}_5\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkynyl,
 $-\text{C}_1\text{-C}_{10}$ alkylene-(5-membered heteroaryl), $-\text{C}_1\text{-C}_3$ alkylene-**Q¹**-(CH_2)_naryl, or
 $\text{C}_1\text{-C}_3$ hydroxyalkyl; and

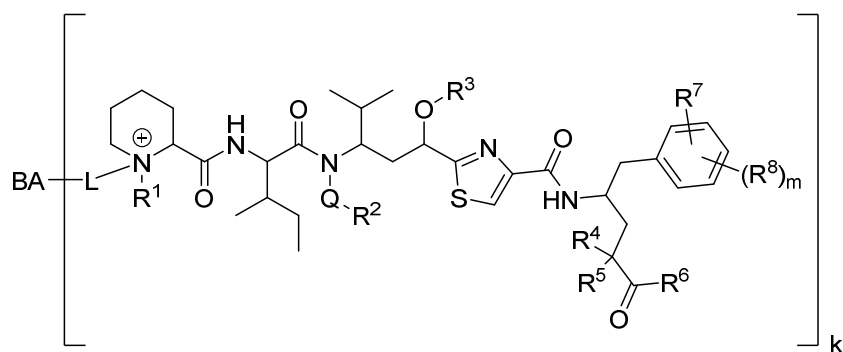
Q¹ is $-\text{CH}_2-$ or $-\text{O}-$;

wherein said heteroaryl is unsubstituted or substituted with alkyl, aminoalkyl, hydroxylalkyl,
carboxyalkyl, benzyl, or phenyl;

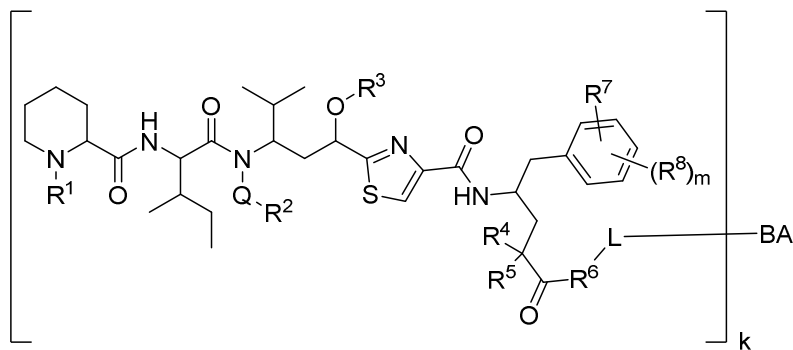
wherein said aryl is unsubstituted or substituted with nitro or amino; and

wherein **n** is an integer from 1 to 5.

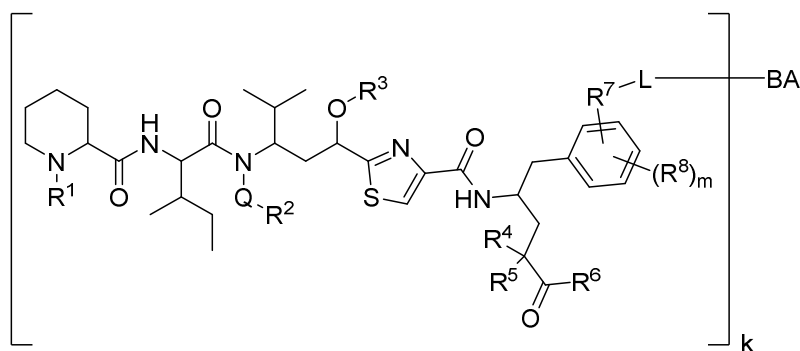
[0008] In another aspect, the present disclosure refers to a compound of Formula **A**, **B**, **C**,
or **D**



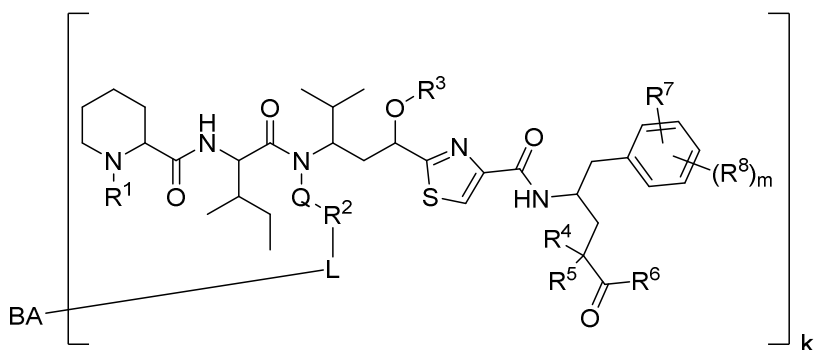
(A)



(B)



(C)



(D)

or a pharmaceutically acceptable salt thereof, wherein

L is a linker;

BA is a binding agent;

k is an integer from one to thirty;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -**NR^{7a}R^{7b}**,

wherein **R**^{7a} and **R**^{7b} are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, –NHR⁹, or halogen,

wherein **R**⁹ is hydrogen, –C₁-C₅ alkyl, or –C(O)C₁-C₅ alkyl; and

m is one or two;

Q is –CH₂– or –O– wherein

when **Q** is –O–, then **R**² is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenes, –C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric –C₁-C₁₀ alkylene-(5-membered heteroarylene), –C₁-C₃ alkylene–**Q**¹–(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; or

when **Q** is –CH₂–, then **R**² is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenes, –C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric –C₁-C₁₀ alkylene-(5-membered heteroarylene), –C₁-C₃ alkylene–**Q**¹–(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; and

Q¹ is –CH₂– or –O–;

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

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, –alkylene-NH–, hydroxyalkyl, –alkylene–O–, carboxyalkyl, –alkylene-COO–, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro, amino, or –NH–; and

wherein **n** is an integer from one to five.

[0009] In another example, provided is a compound of Formula **A**, **B**, **C**, or **D**:

or a pharmaceutically acceptable salt thereof, wherein

L is a linker;

BA is a binding agent;

k is an integer from 1 to 30;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-; or, in certain examples, **R⁶** is -NHSO₂**R⁶⁰**, wherein **R⁶⁰** is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, or divalent -alkylene-, -alkenylene-, -alkynylene-, -cycloalkylene-, -heterocycloalkylene-, -arylene-, -heteroarylene-, substituted -arylene-, or substituted -heteroarylene- when bonded to -**L**-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -**NR^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** 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, or divalent -alkylene-, -alkenylene-, -alkynylene-, -cycloalkylene-, -arylene-, -heteroarylene-, or -acylene- when bonded to -**L**-, wherein -alkylene-, -alkenylene-, -alkynylene-, -cycloalkylene-, -arylene-, -heteroarylene-, and -acylene- are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, -**NHR⁹**, or halogen,

wherein **R⁹** is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is 1 or 2;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R²** is C₁-C₁₀ alkyl, divalent -C₁-C₁₀ alkylene-, C₁-C₁₀ alkynyl, divalent -C₁-C₁₀ alkynylene-, a regioisomeric C₁-C₁₀ alkyl triazolyl, a regioisomeric divalent -C₁-C₁₀ alkyl triazolylene-, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric divalent -C₁-C₁₀ alkylene-(5-membered heteroarylene)-, -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, divalent -C₁-C₃ alkylene-**Q¹**-(CH₂)_narylene-, C₁-C₃ hydroxyalkyl, divalent -C₁-C₃ hydroxyalkylene-, C₁-C₁₀ alkylether, or divalent -C₁-C₁₀ alkylether-; or

when **Q** is $-\text{CH}_2-$, then **R**² is C₅-C₁₀ alkyl, divalent -C₅-C₁₀ alkylene-, C₁-C₁₀ alkynyl, divalent -C₁-C₁₀ alkynylene-, a regioisomeric C₁-C₁₀ alkyl triazolyl, a regioisomeric divalent -C₁-C₁₀ alkyl triazolylene-, $-\text{C}_1\text{-C}_{10}$ alkylene-(5-membered heteroaryl), a regioisomeric divalent $-\text{C}_1\text{-C}_{10}$ alkylene-(5-membered heteroarylene)-, $-\text{C}_1\text{-C}_3$ alkylene-**Q**¹-(CH₂)_naryl, divalent -C₁-C₃ alkylene-**Q**¹-(CH₂)_narylene-, C₁-C₃ hydroxyalkyl, divalent -C₁-C₃ hydroxyalkylene-, C₁-C₁₀ alkylether, or divalent -C₁-C₁₀ alkylether-; and

Q¹ is $-\text{CH}_2-$ or $-\text{O}-$;

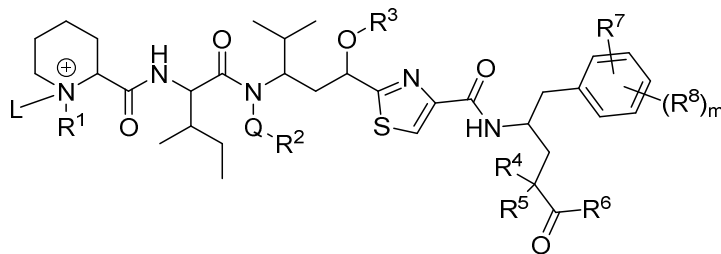
wherein said regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl;

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, $-\text{alkylene-NH}-$, hydroxylalkyl, $-\text{alkylene-O}-$, carboxyalkyl, $-\text{alkylene-COO}-$, benzyl, or phenyl;

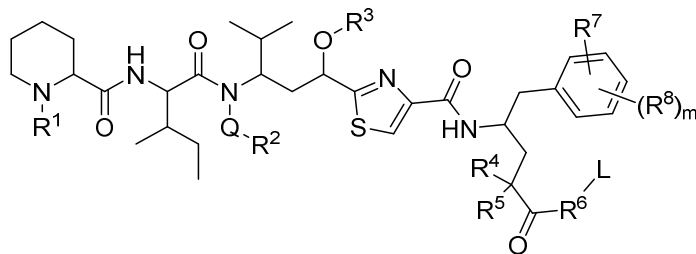
wherein said aryl is unsubstituted or substituted with nitro, amino, or $-\text{NH}-$; and

wherein **n** is an integer from 1 to 5.

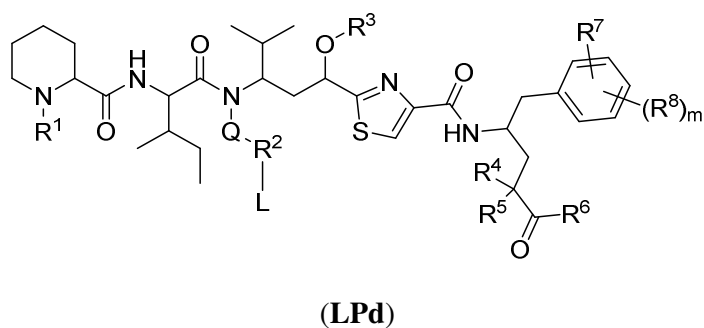
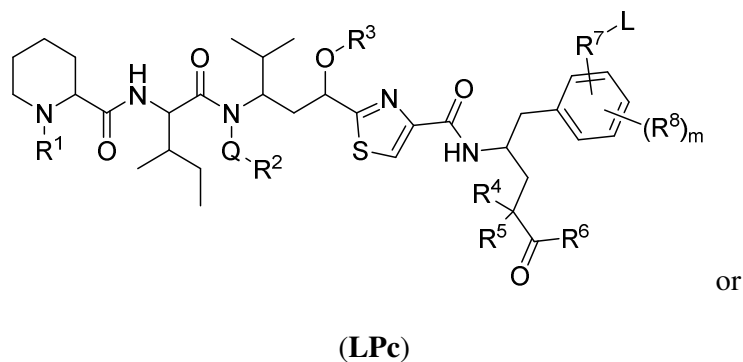
[0010] In one aspect, the present disclosure refers to a linker-payload of Formula **LPa**, **LPb**, **LPc**, or **LPd**:



(**LPa**)



(**LPb**)



or a pharmaceutically acceptable salt thereof, wherein

L is a linker;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -**NR^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, -NHR⁹, or halogen,

wherein **R⁹** is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

when **Q** is –O–, then **R²** is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylen, –C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric –C₁-C₁₀ alkylene-(5-membered heteroarylene), –C₁-C₃ alkylene–**Q¹**–(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; or

Q¹ is $-\text{CH}_2-$ or $-\text{O}-$;

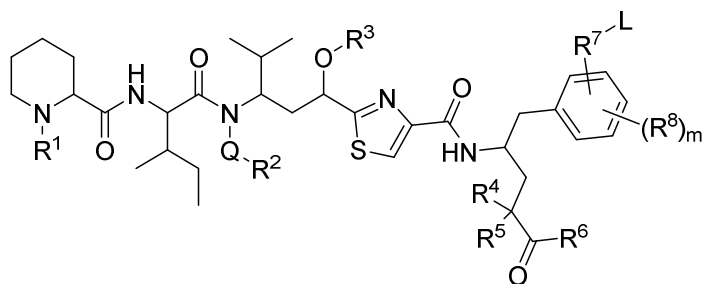
wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, -alkylene-NH-, hydroxylalkyl, -alkylene-O-, carboxyalkyl, -alkylene-COO-, benzyl, or phenyl;

wherein **n** is an integer from one to five.

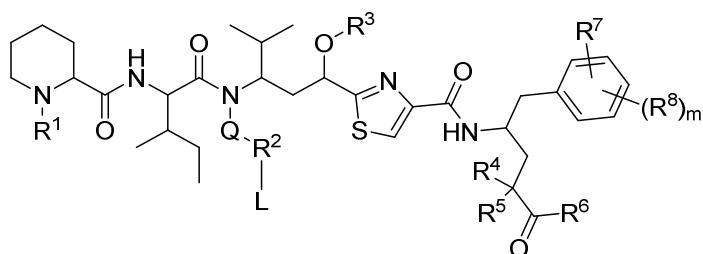
*N1CCCCC1C(=O)NC(=O)C(C)C(=O)N(C)C(C)C(C)OCc2cnc(C(=O)NCC(C)(C(=O)R6)C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5C6)cs2*N1CCCCC1C(=O)NC(=O)C(C)C(=O)N(C)C(C)COC2=NC(=C(C=C2)C(=O)NC(C)CC3=CC=C(C=C3)C(*)C(*)C4(C)C(=O)C(R6)C(L)C4)S

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(LPb)



(LPc)



(LPd)

or a pharmaceutically acceptable salt thereof, wherein

L is a linker;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-; or, in certain examples, **R⁶** is -NHSO₂**R⁶⁰**, wherein **R⁶⁰** is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, or divalent -alkylene-, -alkenylene-, -alkynylene-, -cycloalkylene-, -heterocycloalkylene-, -arylene-, -heteroarylene-, substituted -arylene-, or substituted -heteroarylene- when bonded to -**L**-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -**NR^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** 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, or divalent -alkylene-, -alkenylene-, -alkynylene-, -cycloalkylene-, -arylene-, -heteroarylene-, or -acylene- when bonded to -**L**-, wherein -alkylene-, -alkenylene-, -alkynylene-, -cycloalkylene-, -arylene-, -heteroarylene-, and -acylene- are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, –NHR⁹, or halogen,

wherein **R**⁹ is hydrogen, –C₁–C₅ alkyl, or –C(O)C₁–C₅ alkyl; and

m is 1 or 2;

Q is –CH₂– or –O– wherein

when **Q** is –O–, then **R**² is C₁–C₁₀ alkyl, divalent –C₁–C₁₀ alkylene-, C₁–C₁₀ alkynyl, divalent –C₁–C₁₀ alkynylene-, a regioisomeric C₁–C₁₀ alkyl triazolyl, a regioisomeric divalent –C₁–C₁₀ alkyl triazolylene-, –C₁–C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric divalent –C₁–C₁₀ alkylene-(5-membered heteroarylene)-, –C₁–C₃ alkylene–**Q**¹–(CH₂)_naryl, divalent –C₁–C₃ alkylene–**Q**¹–(CH₂)_narylene-, C₁–C₃ hydroxyalkyl, divalent –C₁–C₃ hydroxyalkylene-, C₁–C₁₀ alkylether, or divalent –C₁–C₁₀ alkylether-; or

when **Q** is –CH₂–, then **R**² is C₅–C₁₀ alkyl, divalent –C₅–C₁₀ alkylene-, C₁–C₁₀ alkynyl, divalent –C₁–C₁₀ alkynylene-, a regioisomeric C₁–C₁₀ alkyl triazolyl, a regioisomeric divalent –C₁–C₁₀ alkyl triazolylene-, –C₁–C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric divalent –C₁–C₁₀ alkylene-(5-membered heteroarylene)-, –C₁–C₃ alkylene–**Q**¹–(CH₂)_naryl, divalent –C₁–C₃ alkylene–**Q**¹–(CH₂)_narylene-, C₁–C₃ hydroxyalkyl, divalent –C₁–C₃ hydroxyalkylene-, C₁–C₁₀ alkylether, or divalent –C₁–C₁₀ alkylether-; and

Q¹ is –CH₂– or –O–;

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

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, –alkylene–NH–, hydroxylalkyl, –alkylene–O–, carboxyalkyl, –alkylene–COO–, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro, amino, or –NH–; and

wherein **n** is an integer from 1 to 5.

[0012] In another aspect, the present disclosure refers to 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.

[0013] In another example, set forth herein are methods for making the compounds, linker-payloads, or antibody-drug conjugates, and compositions described herein.

[0013a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable excipient, carrier, or diluent.

[0013b] In another aspect, the present disclosure refers to a compound or pharmaceutical composition as disclosed herein for use in therapy.

[0013c] In another aspect, the present disclosure refers to the use of a compound or pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject.

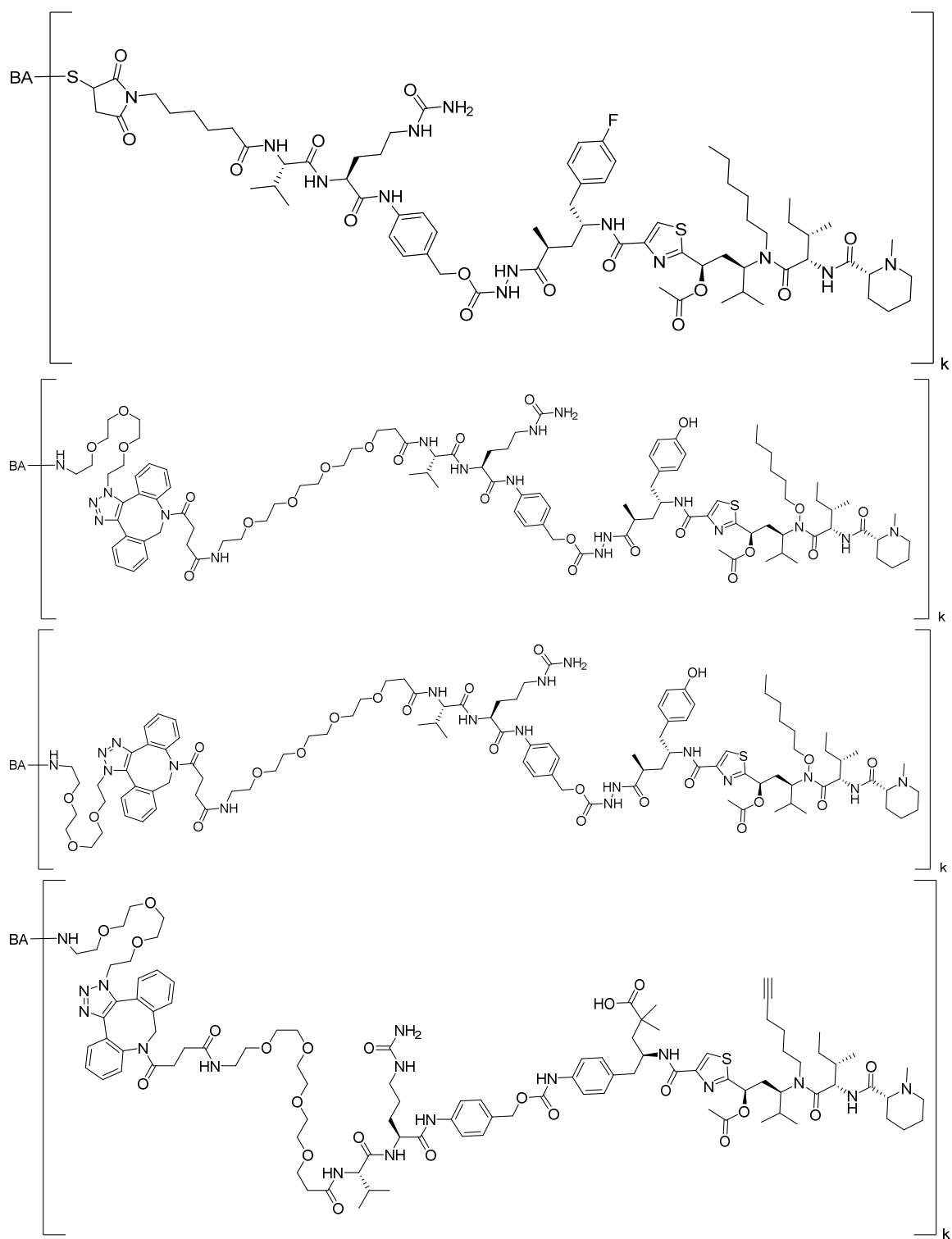
[0013d] In another aspect, the present disclosure refers to the use of of a compound or pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject comprising that an effective treatment amount of a compound or pharmaceutical composition of any of the preceding claims is to be administered to the subject, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostate 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.

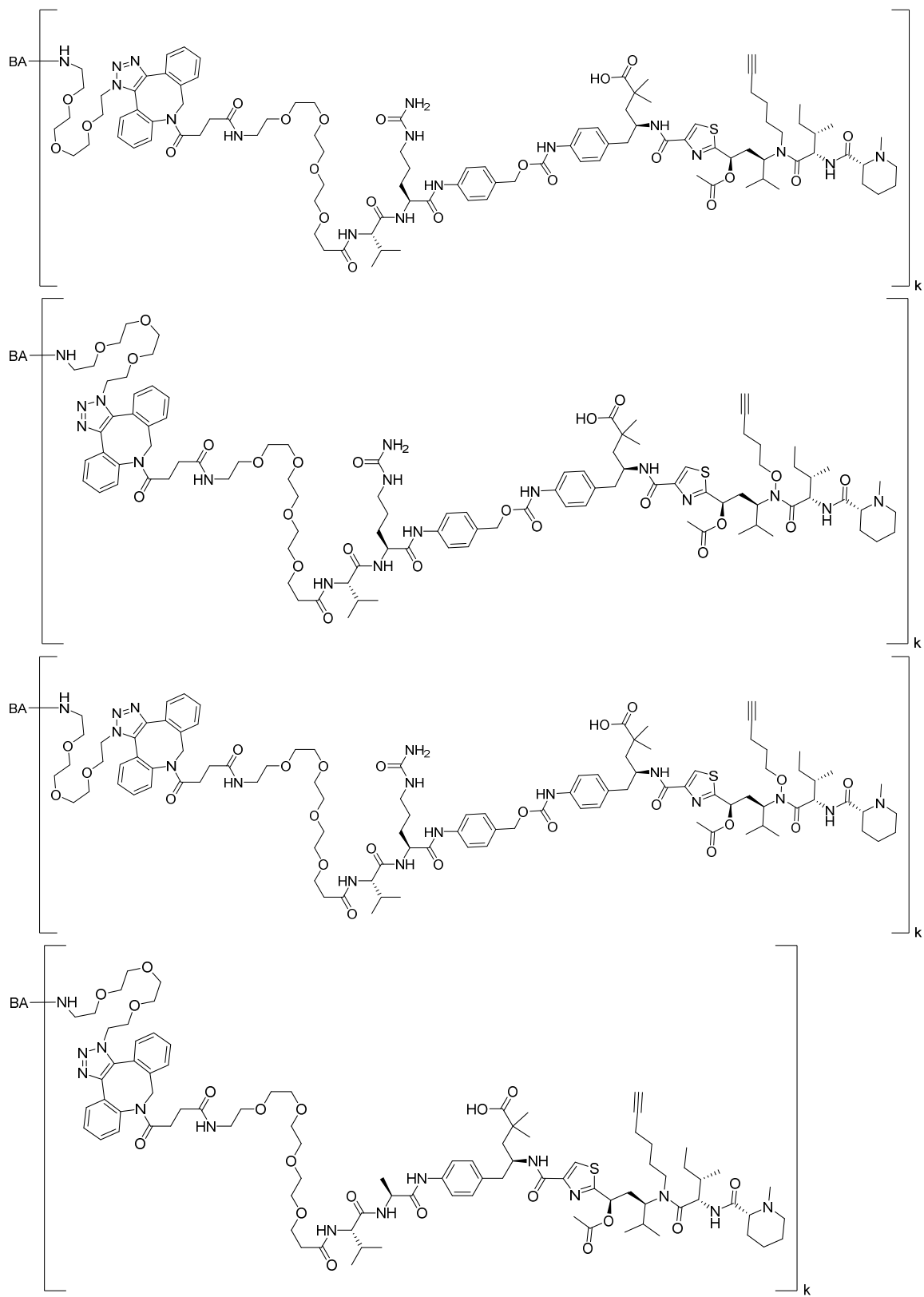
[0013e] In another aspect, the present disclosure refers to the use of a compound or pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating tumors that express an antigen selected from the group consisting of PRLR and STEAP2.

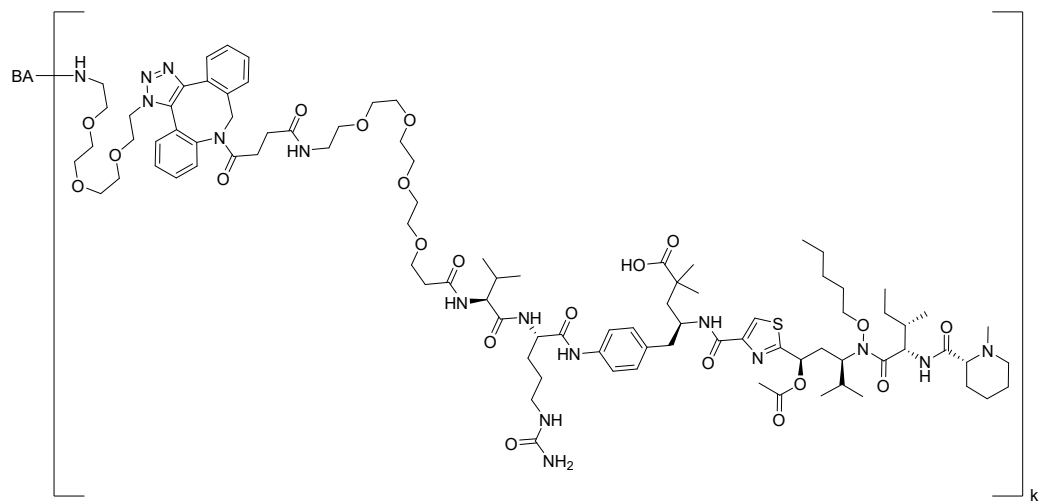
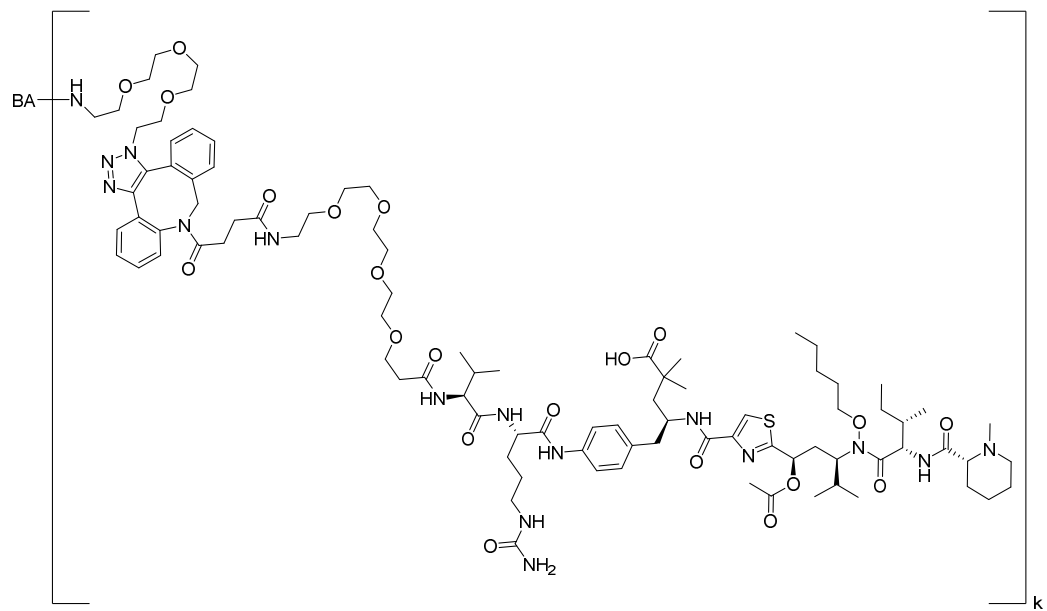
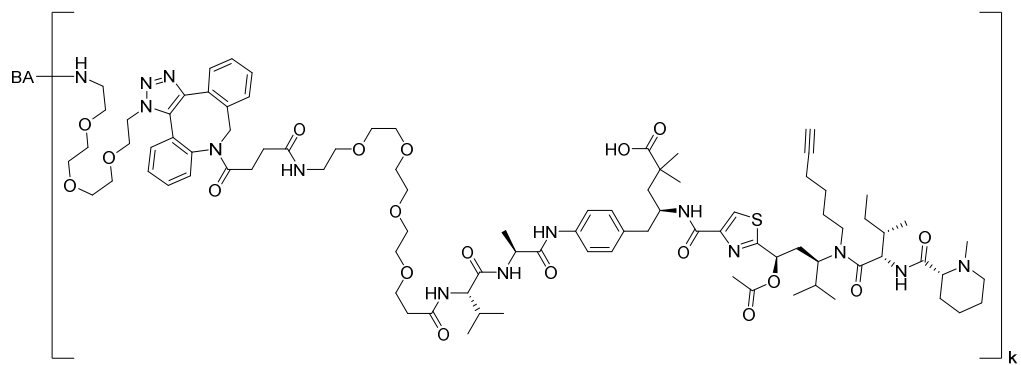
[0013f] In another aspect, the present disclosure refers to a linker-payload comprising the compound as disclosed herein bonded to a linker, wherein said linker comprises a moiety reactive with an antibody or antigen binding fragment thereof.

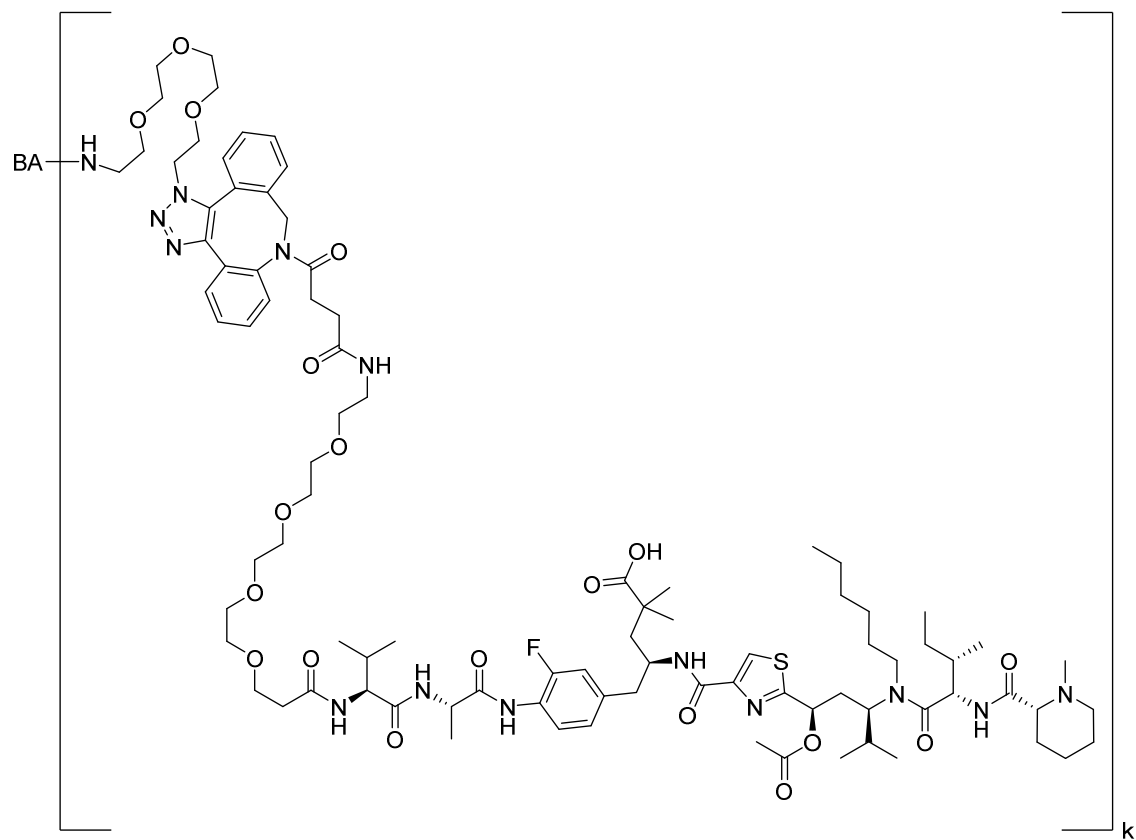
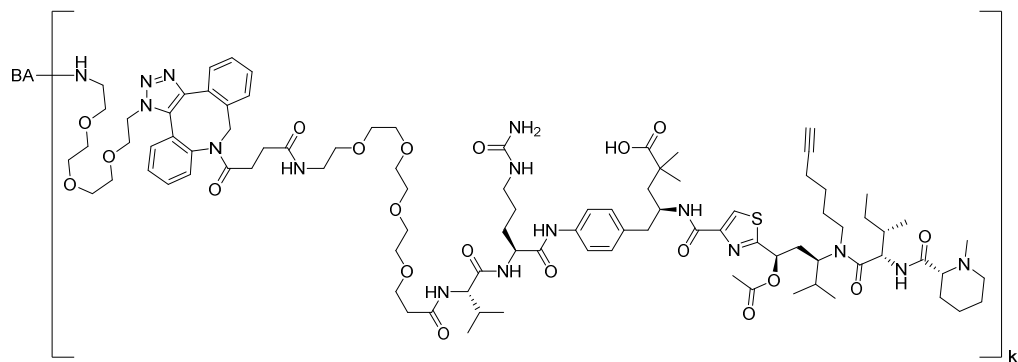
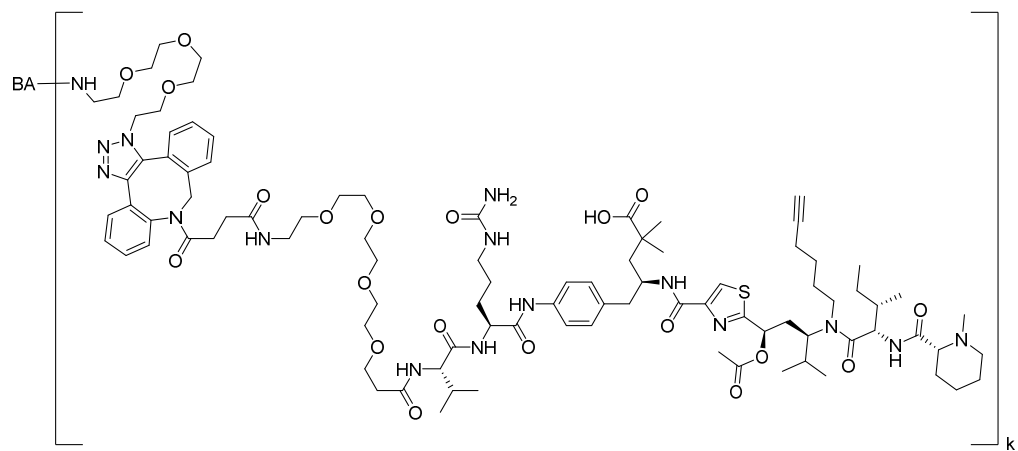
[0013g] In another aspect, the present disclosure refers to a method for preparing an antibody-drug conjugate comprising contacting a binding agent with a linker-payload as disclosed herein.

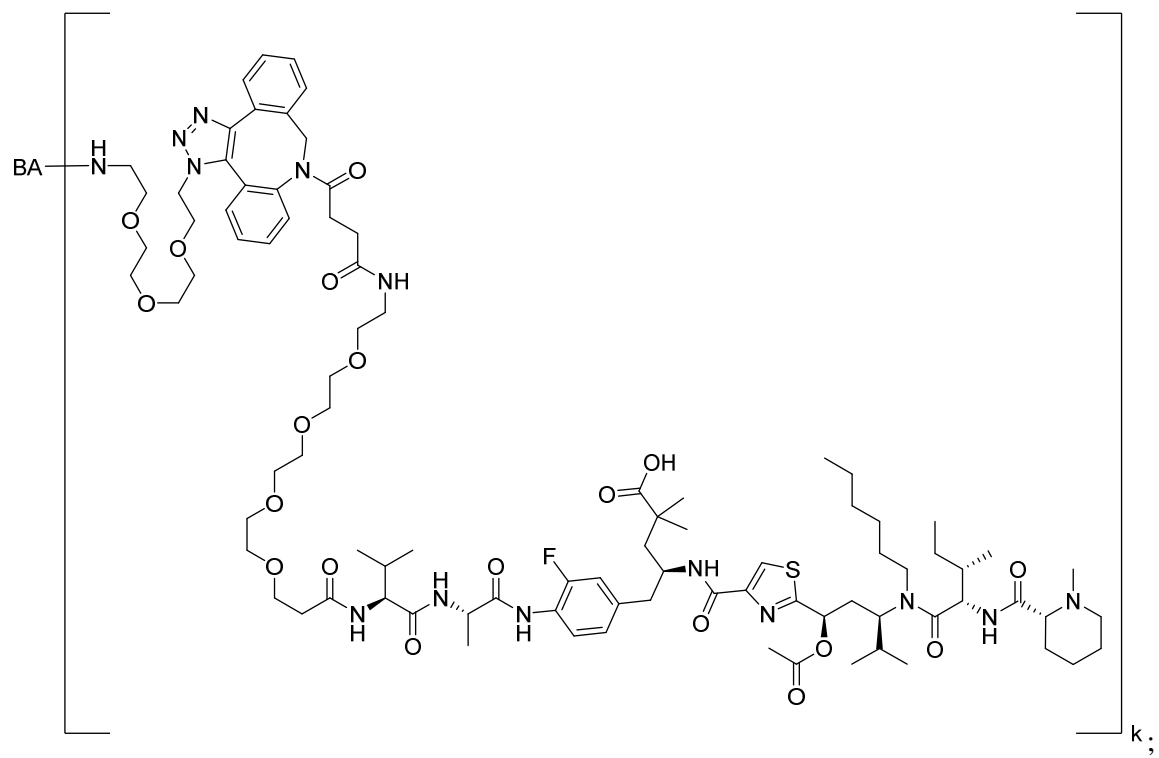
[0013h] In another aspect, the present disclosure refers to a compound selected from the group consisting of

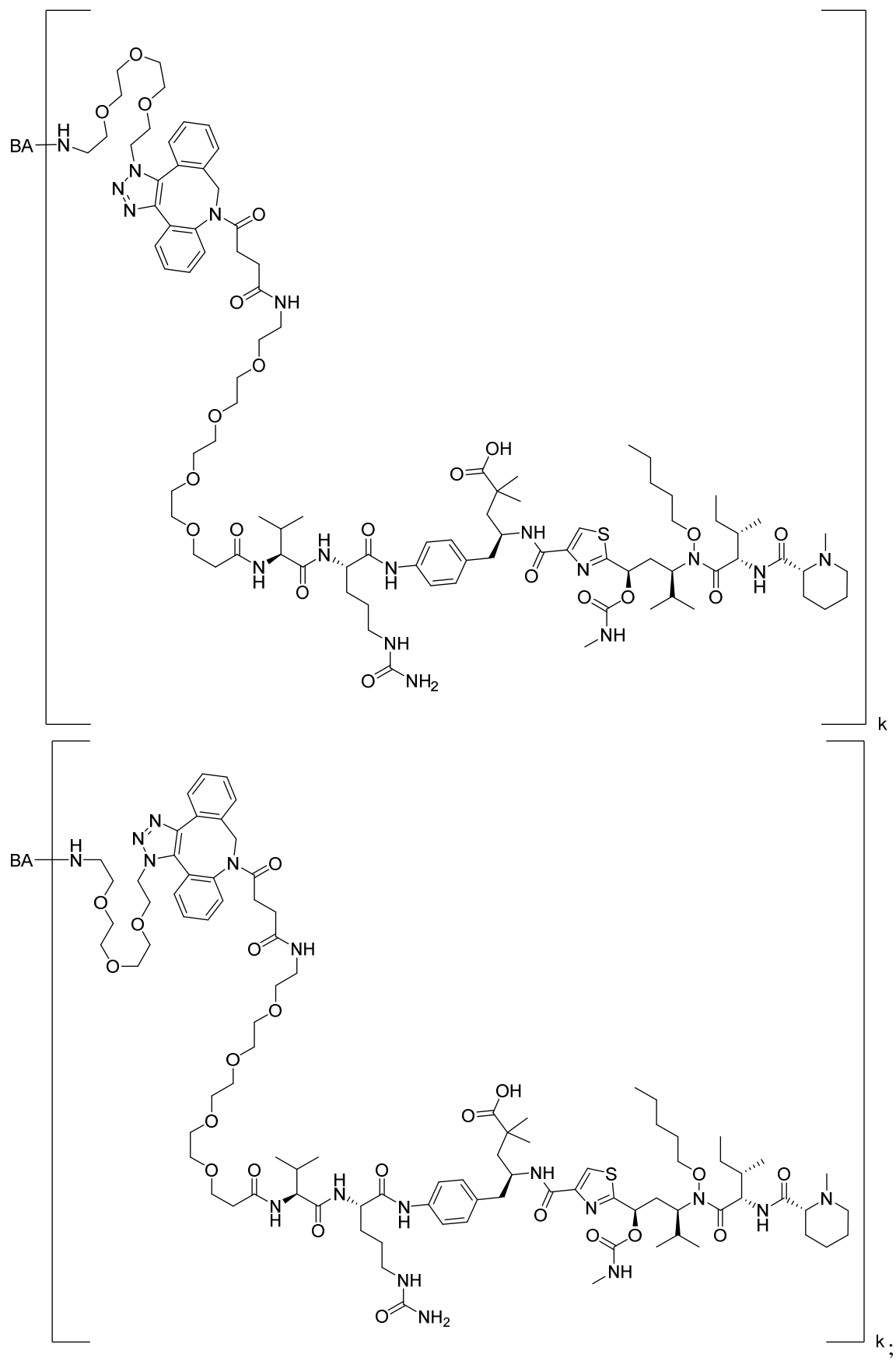


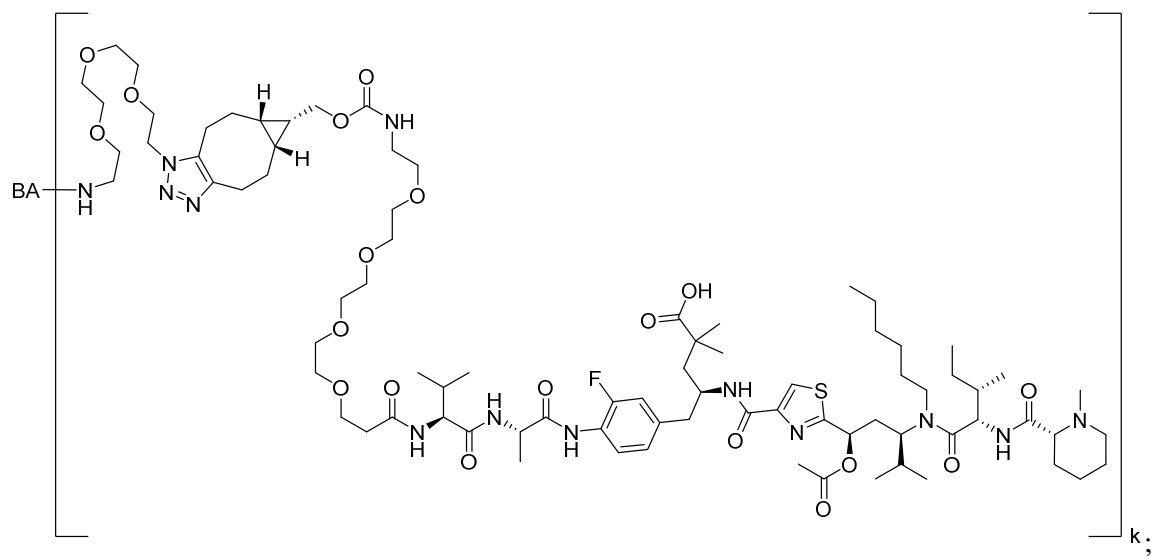






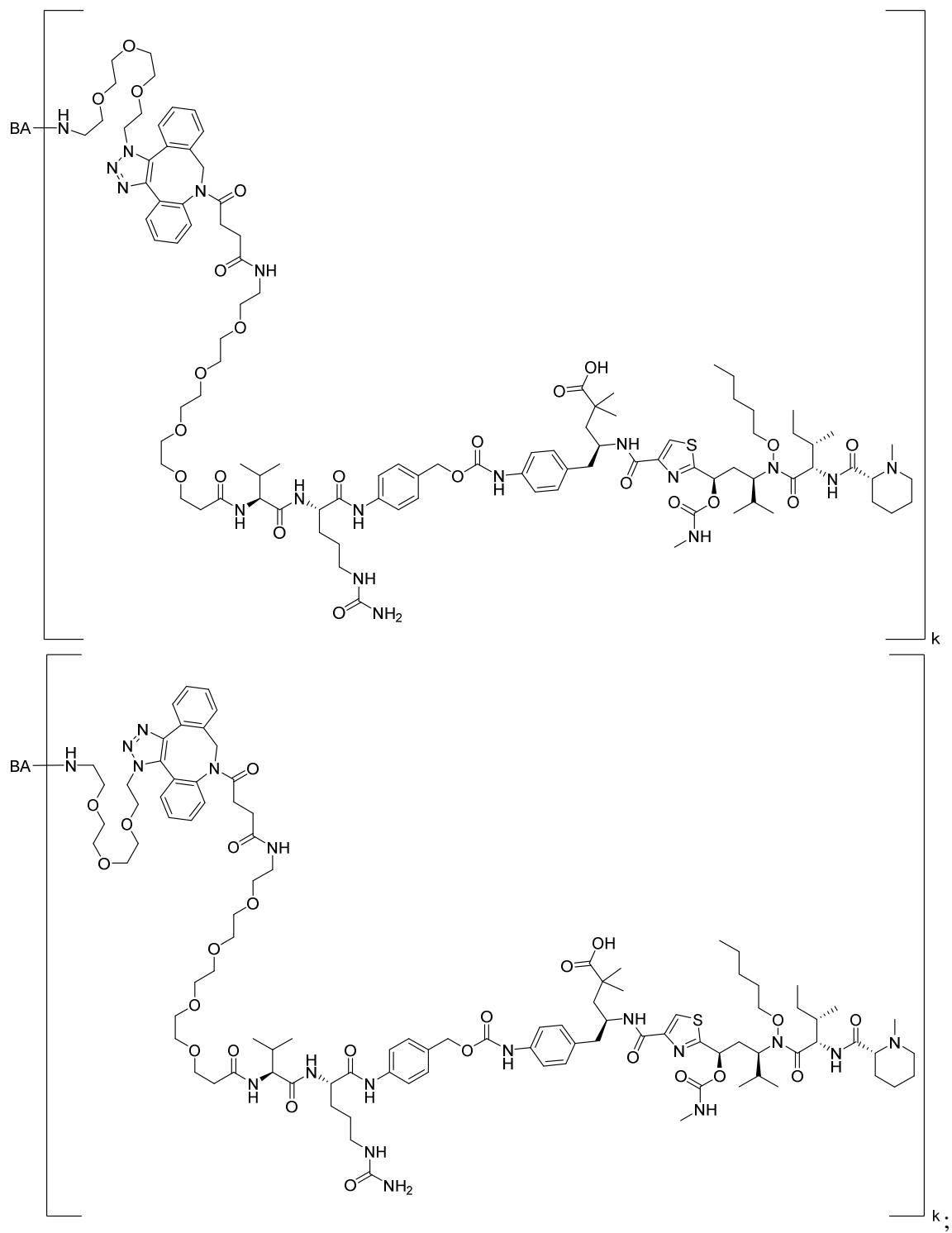




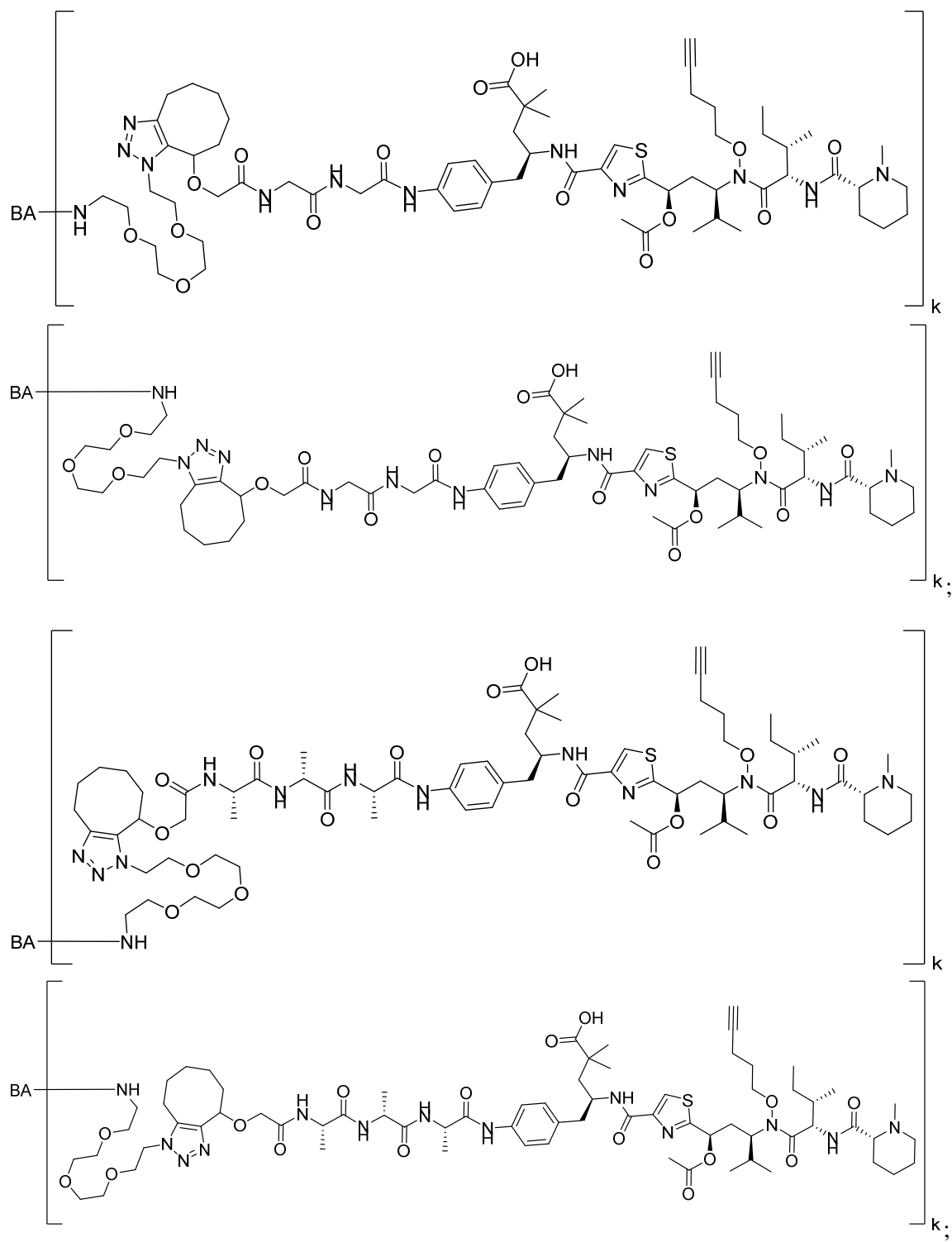


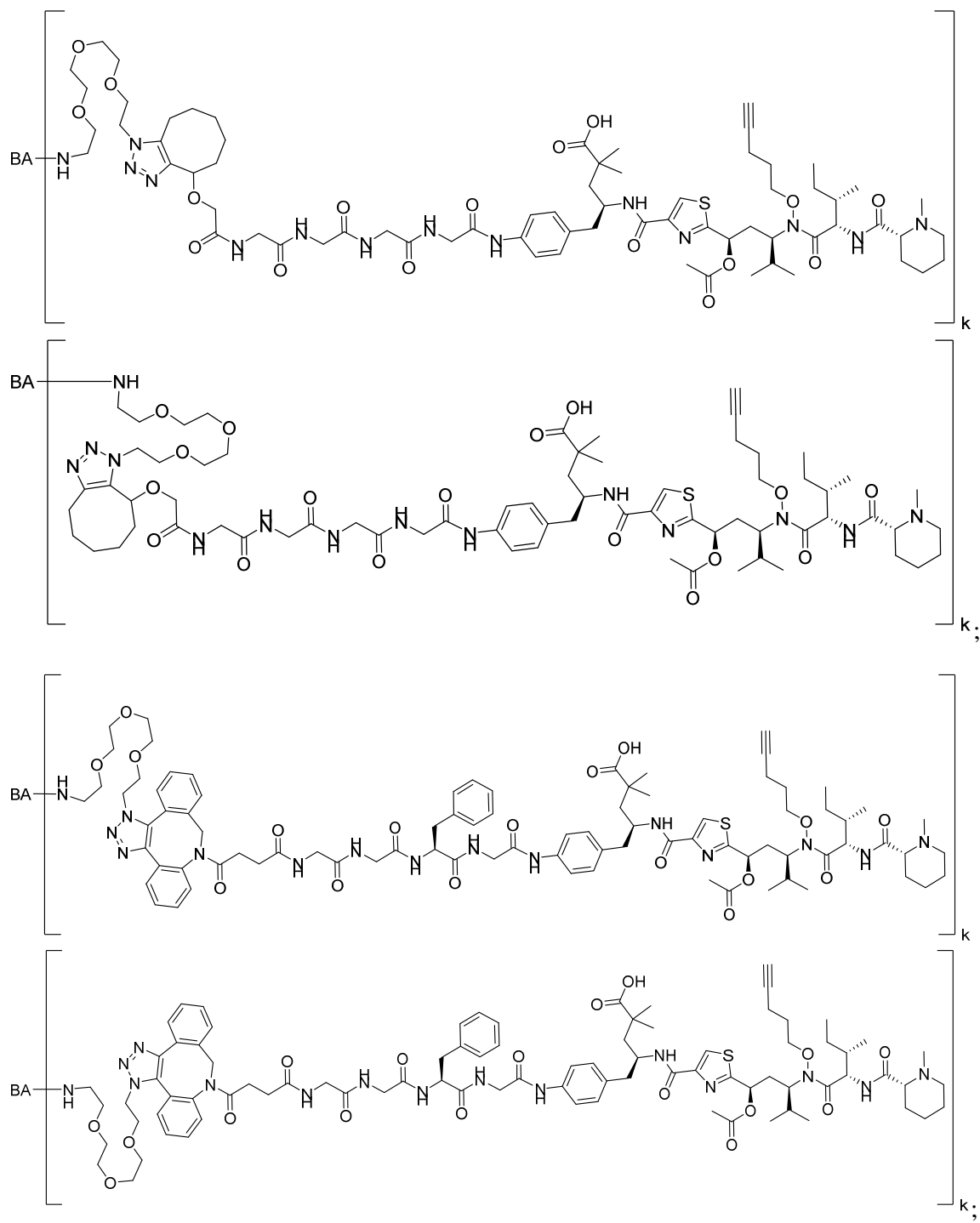


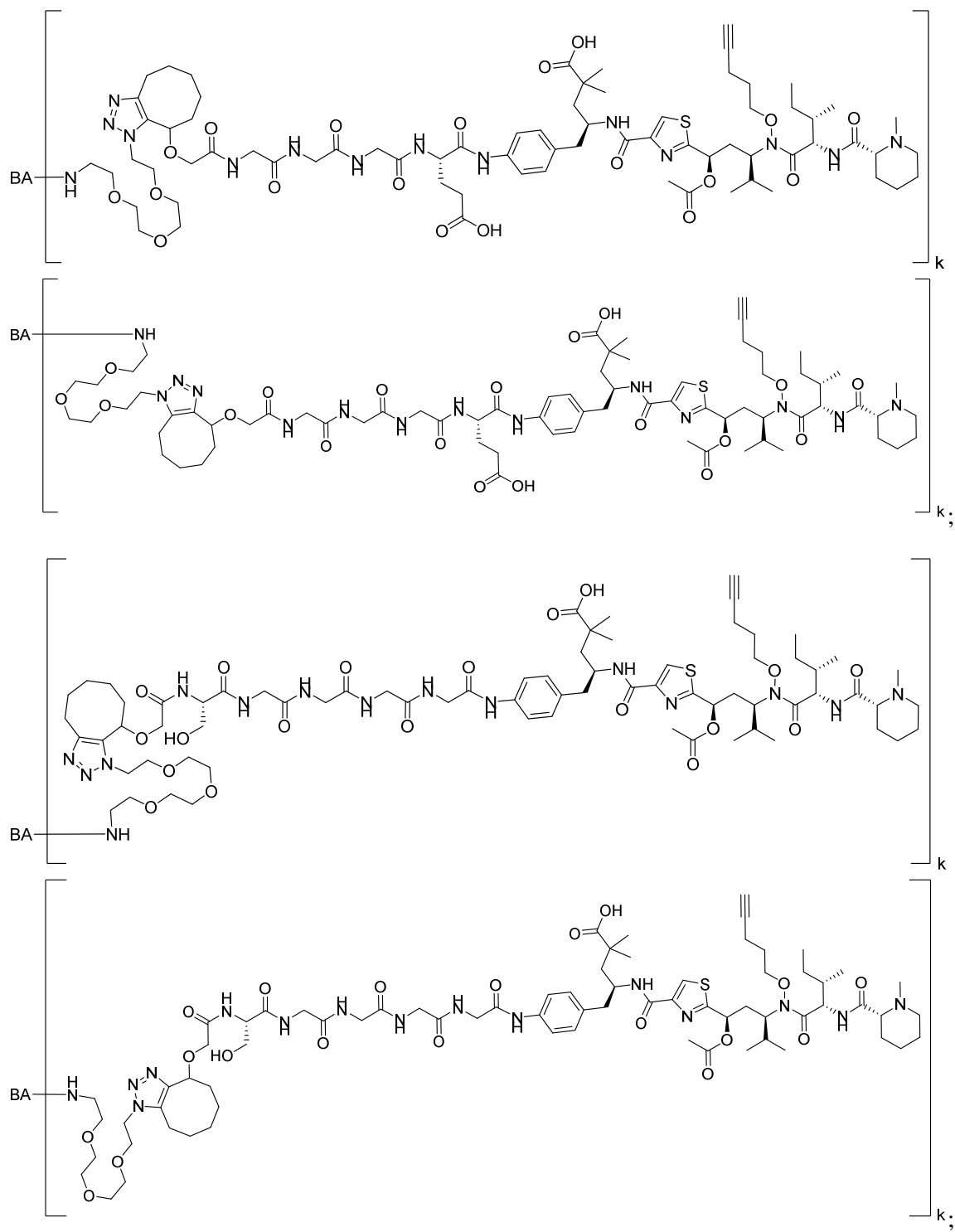


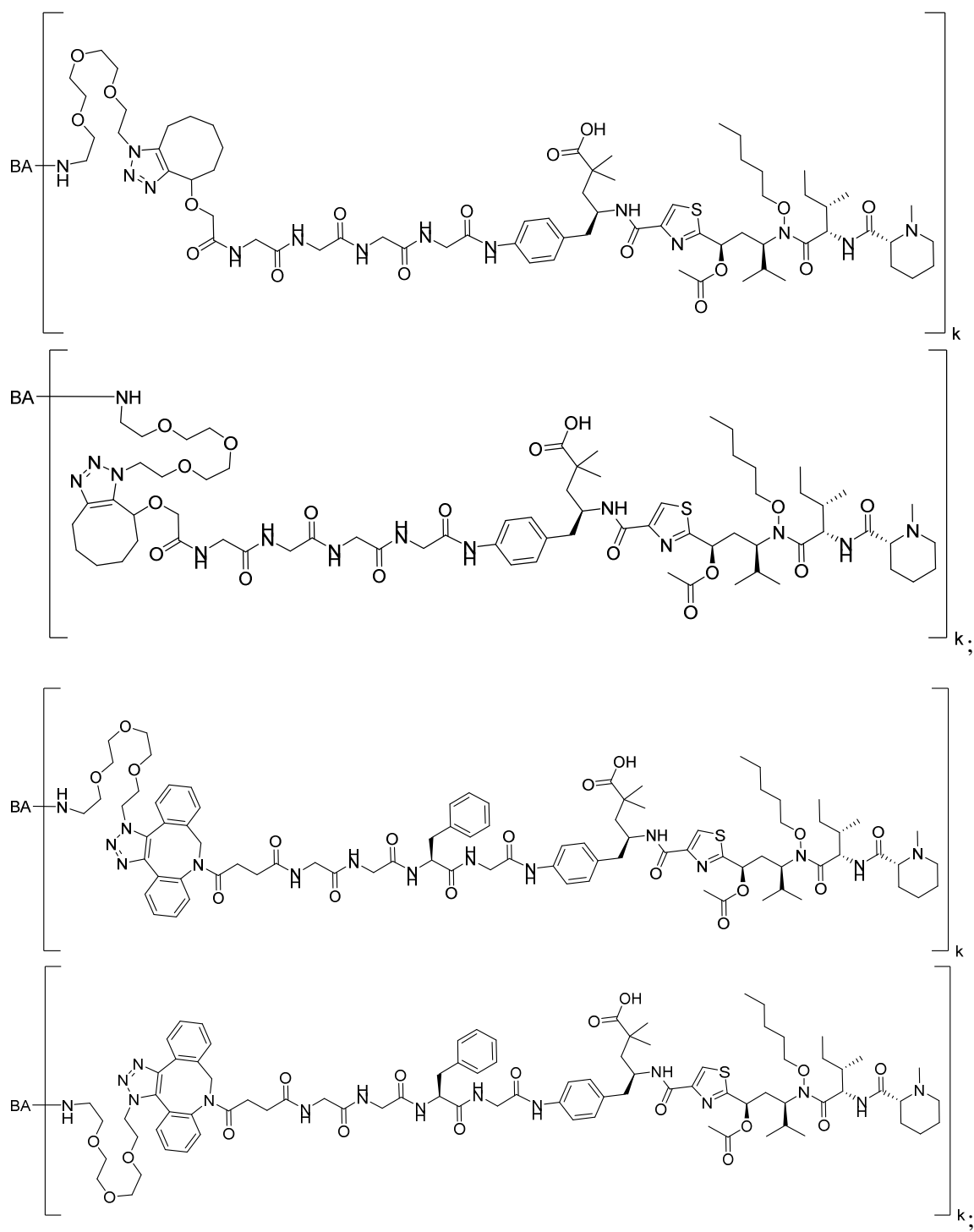


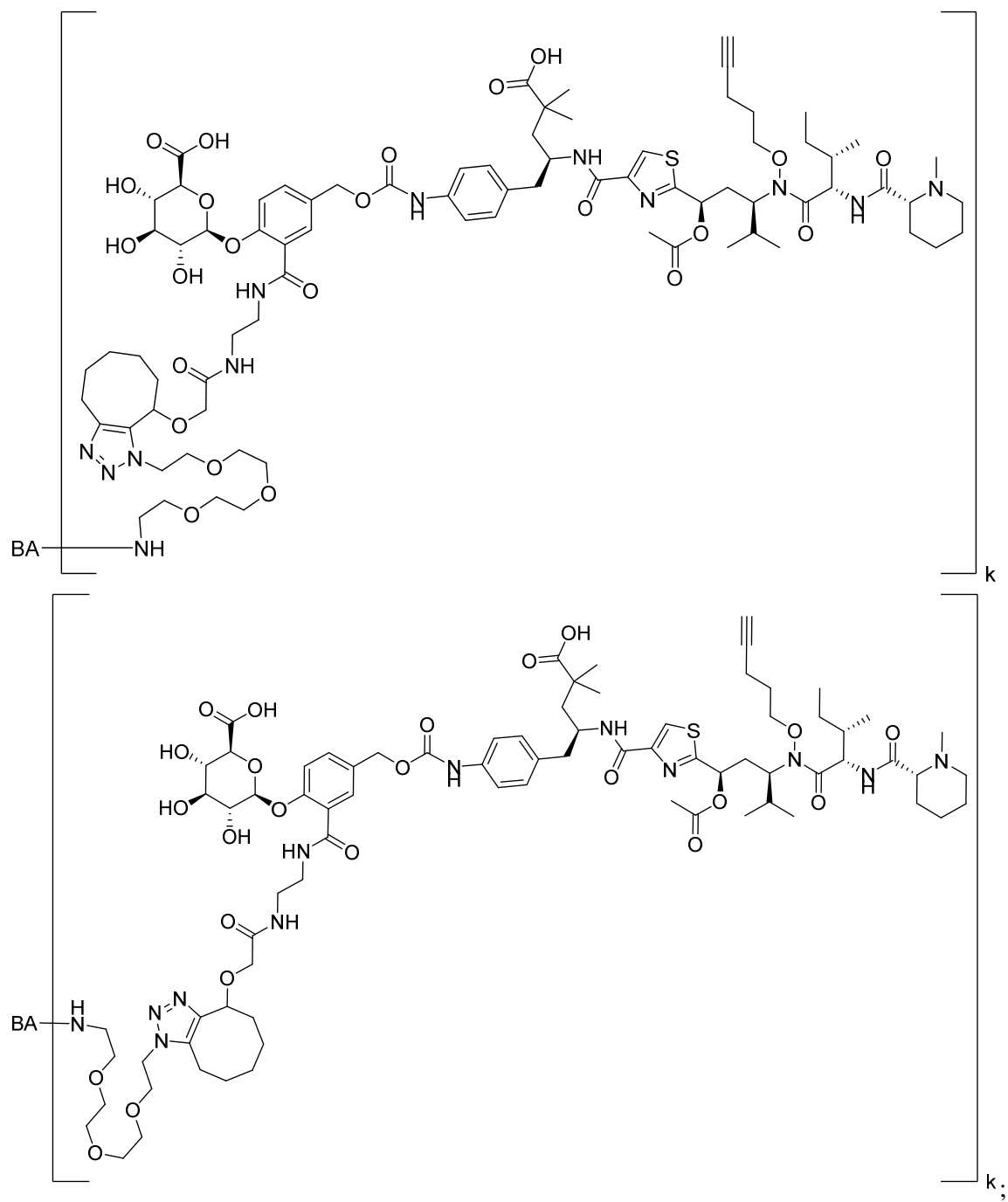


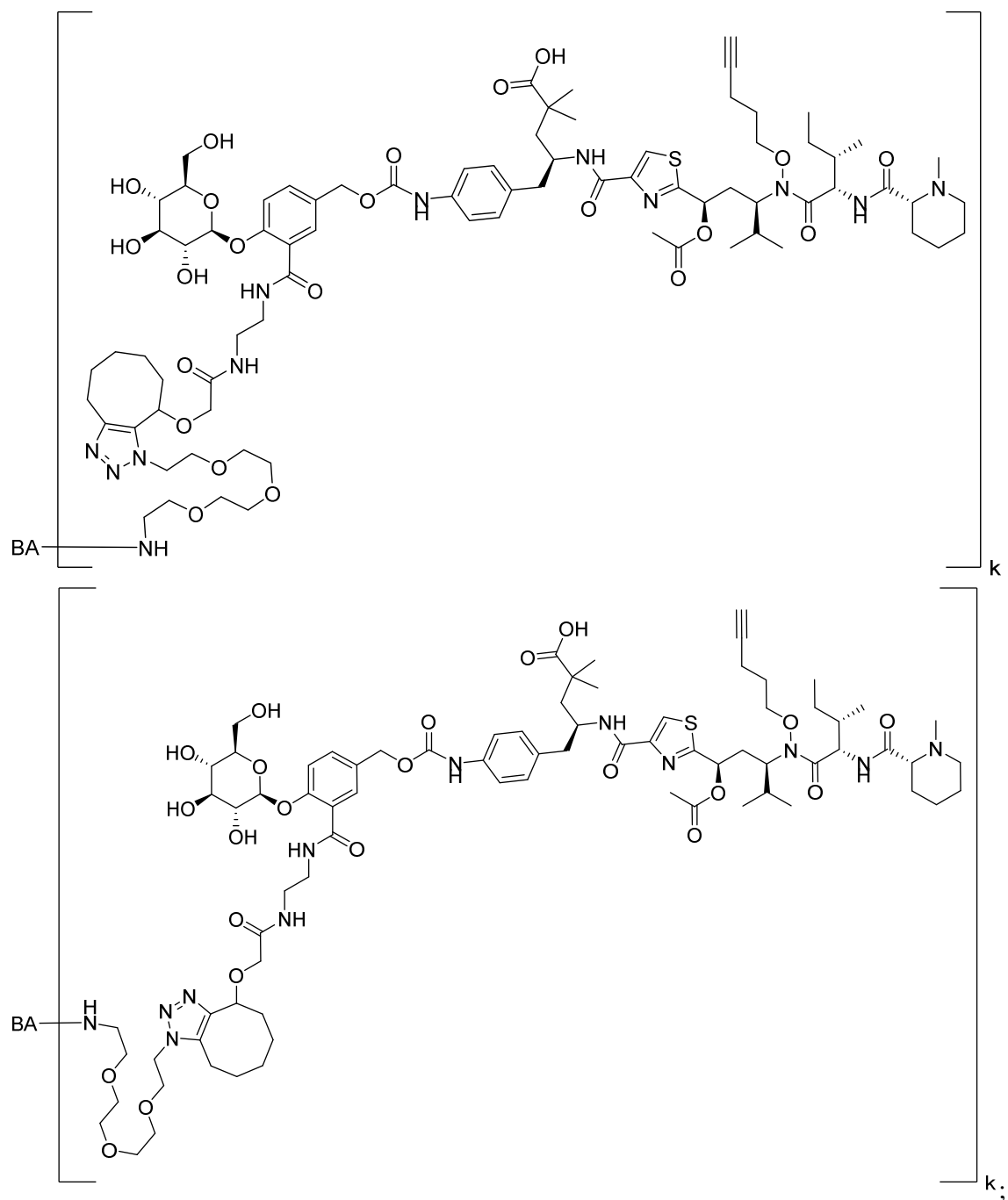






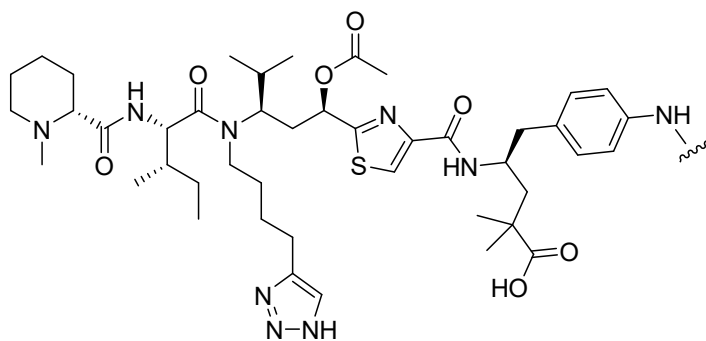
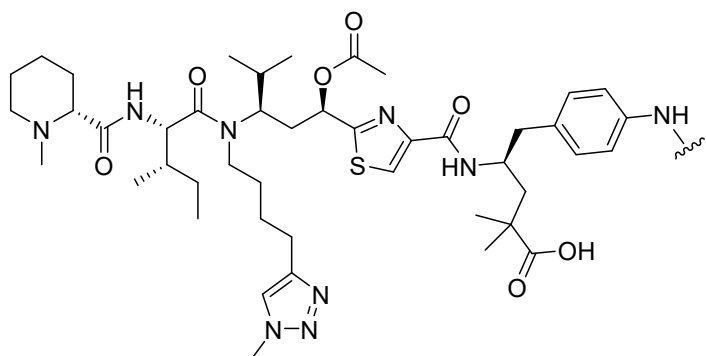
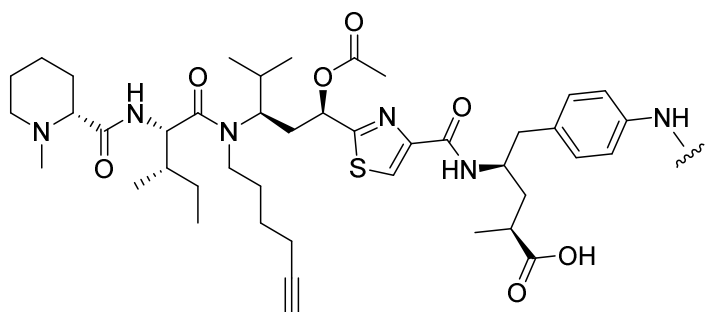
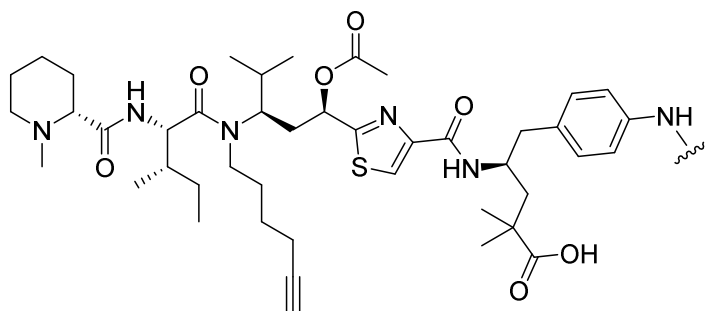


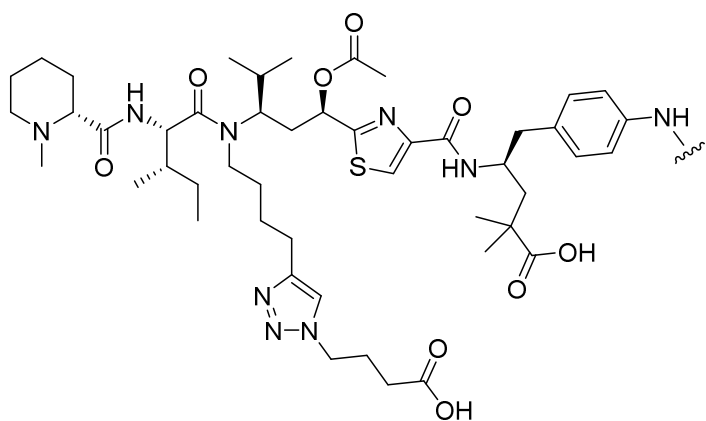
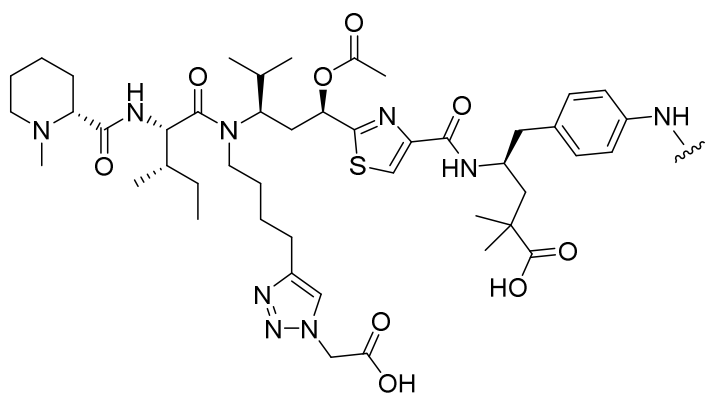
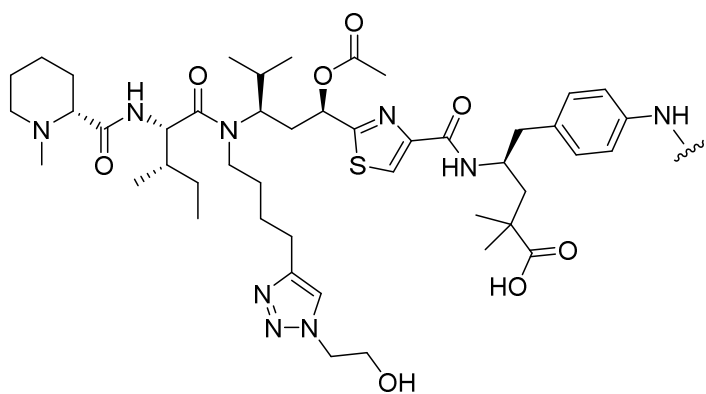
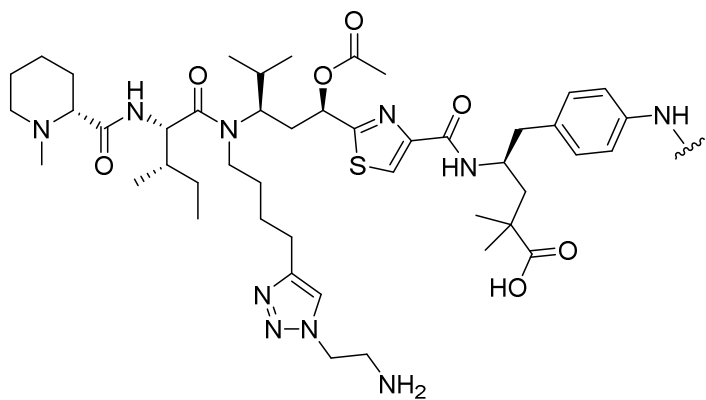


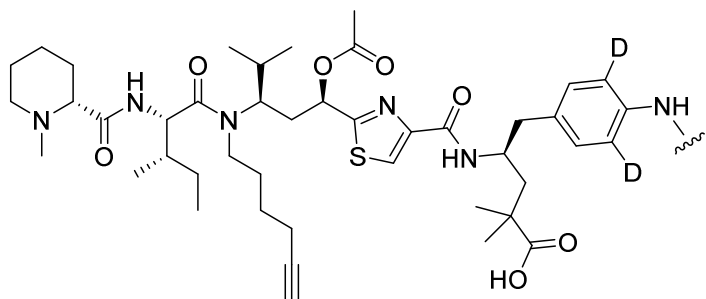
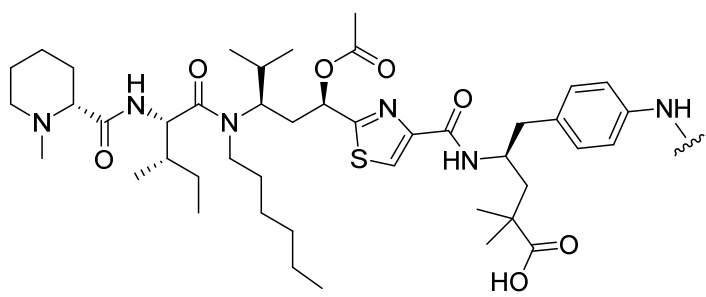
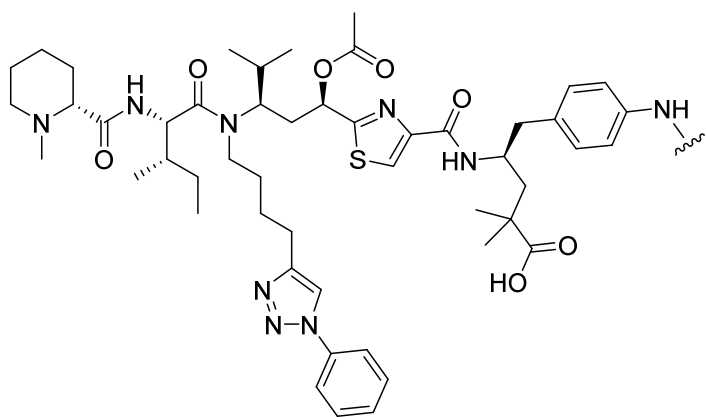
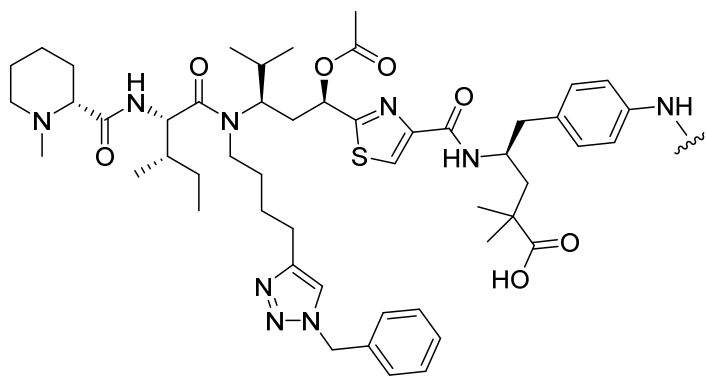


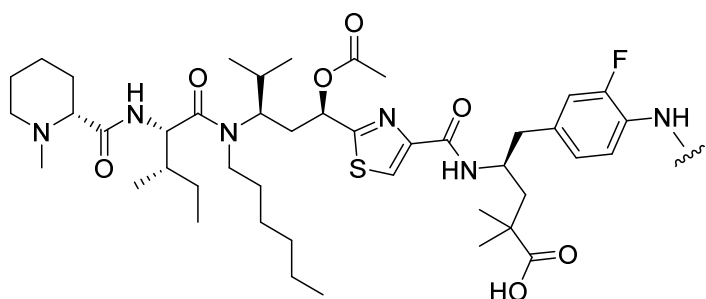
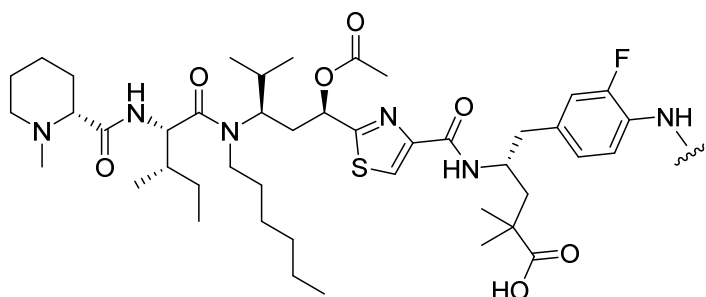
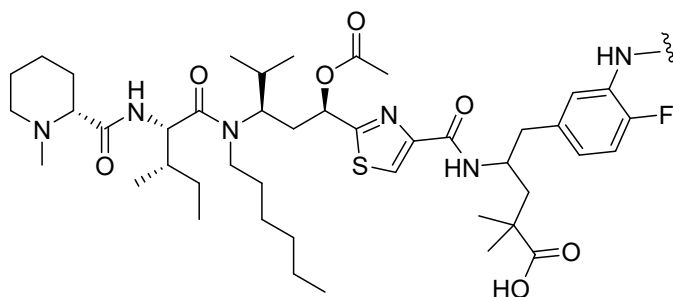
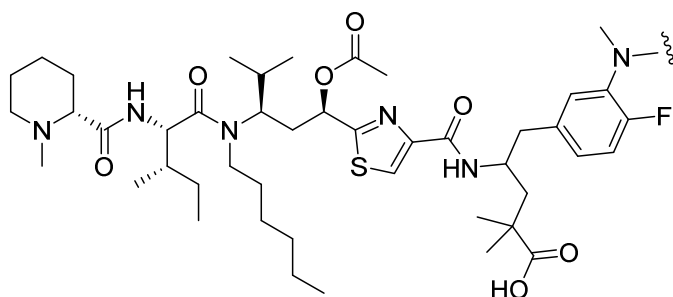
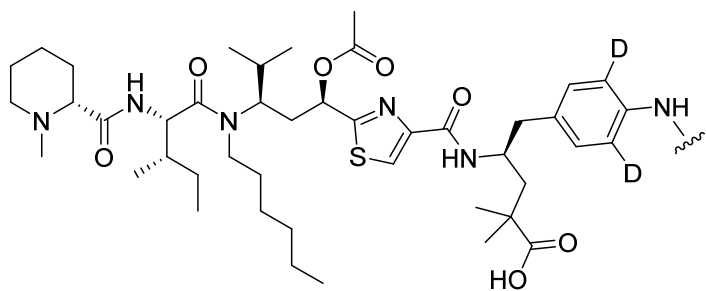
wherein **BA** is a binding agent; and **k** is one, two, three or four.

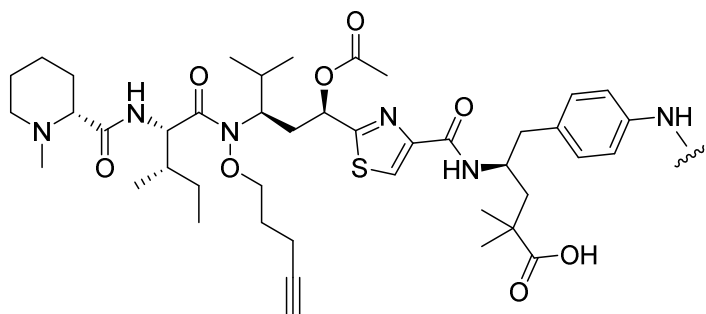
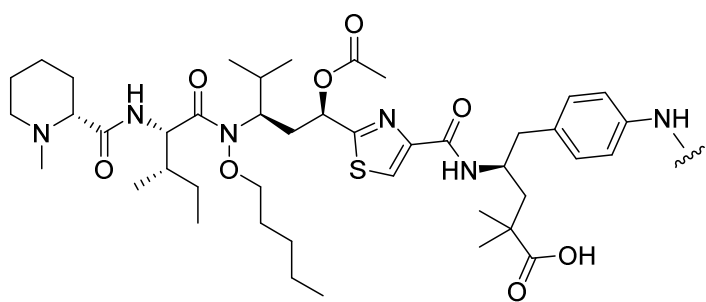
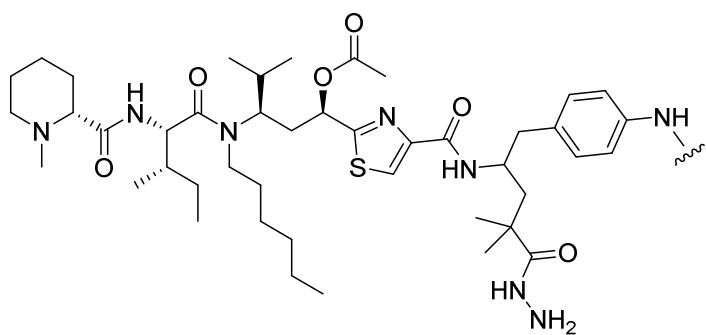
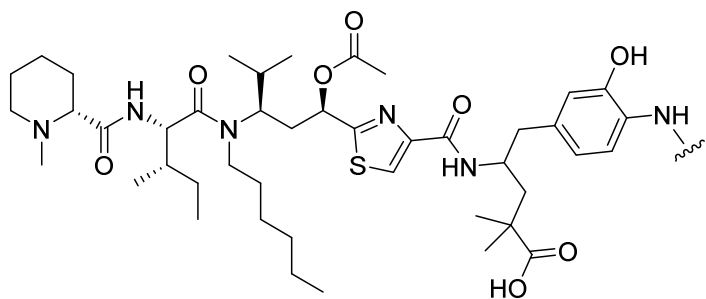
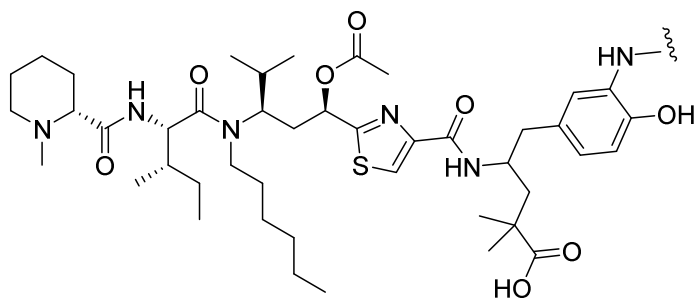
[0013i] In another aspect, the present disclosure refers to an antibody-drug conjugate comprising an antibody or antigen-binding fragment thereof conjugated to a compound as disclosed herein selected from the group consisting of

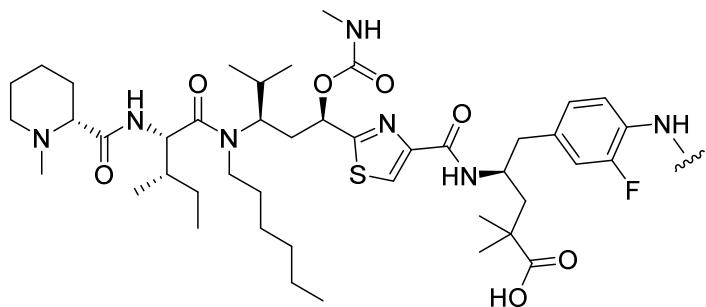
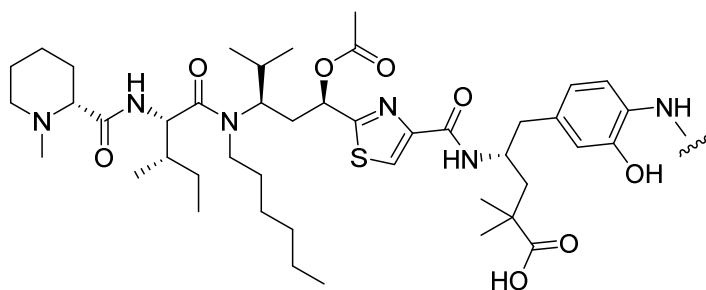
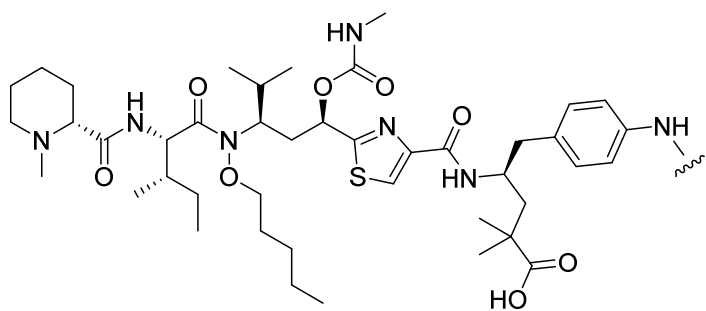
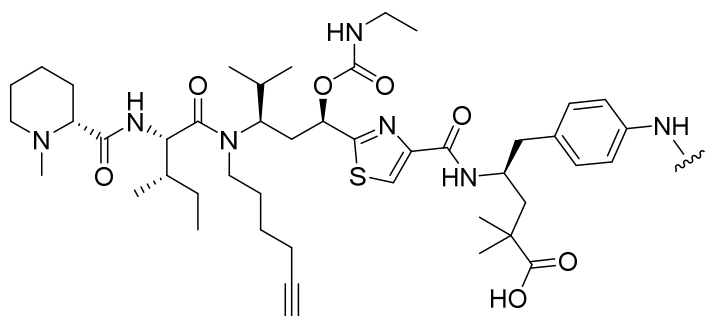
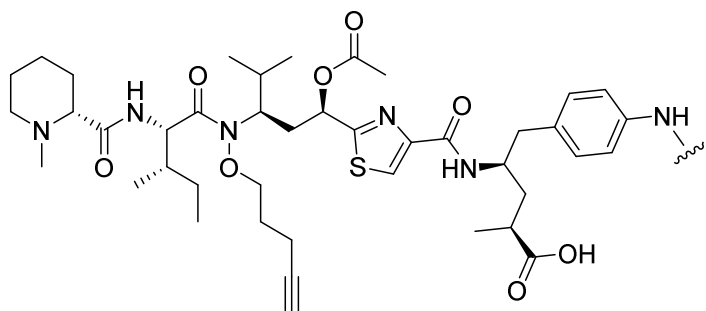


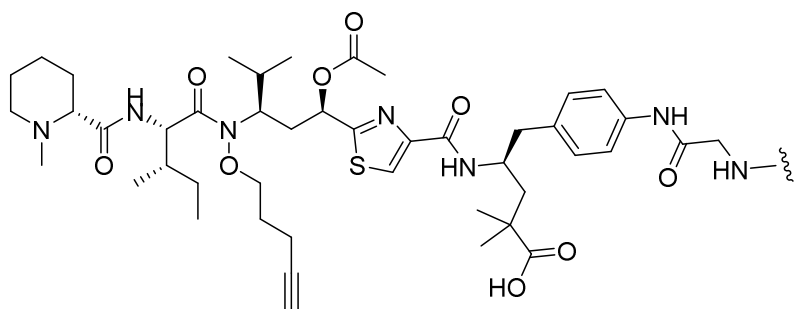






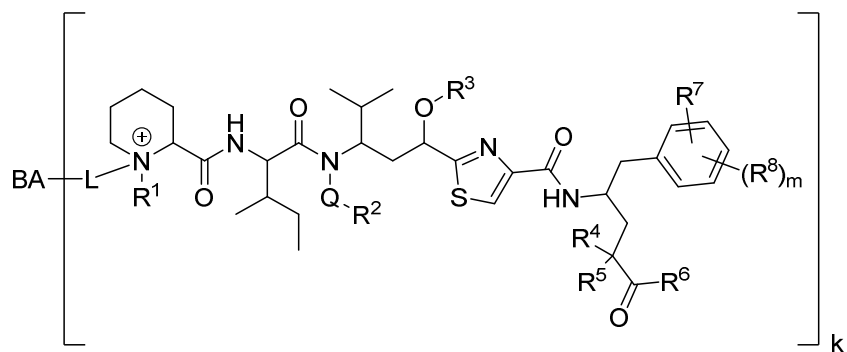




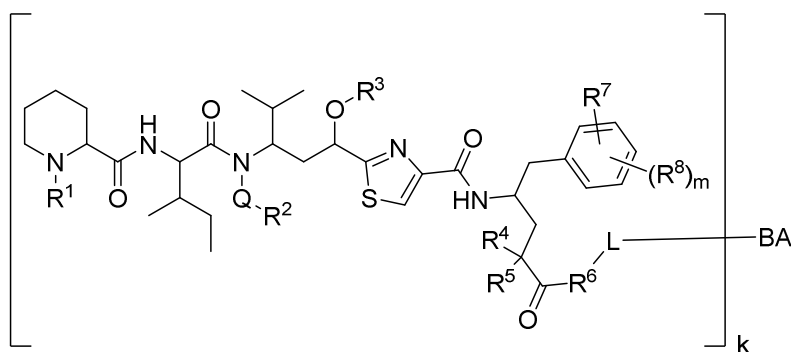
[illegible]

WHAT IS CLAIMED IS:

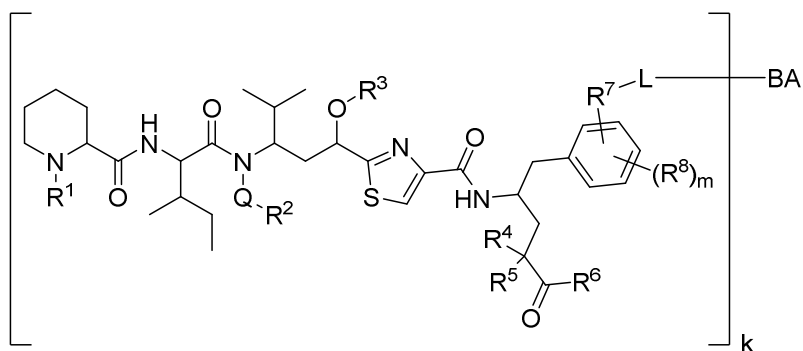
1. A compound of Formula A, B, C, or D



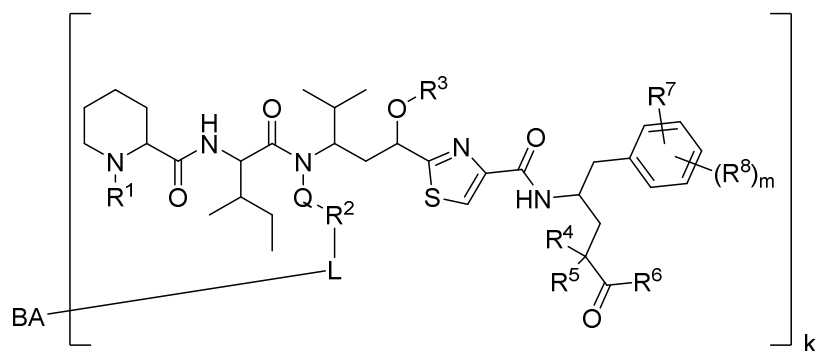
(A)



(B)



(C)



(D)

or a pharmaceutically acceptable salt thereof, wherein

L is a linker;

BA is a binding agent;

k is an integer from one to thirty;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -NR^{7a}R^{7b},

wherein **R^{7a}** and **R^{7b}** are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, -NHR⁹, or halogen,

wherein **R⁹** is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R²** is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenyl, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric -C₁-C₁₀ alkylene-(5-membered heteroarylene), -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; or

when **Q** is -CH₂-, then **R²** is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenyl, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric -C₁-C₁₀ alkylene-(5-membered heteroarylene), -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; and

Q¹ is -CH₂- or -O-;

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

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, –alkylene-NH–, hydroxylalkyl, –alkylene-O–, carboxyalkyl, –alkylene-COO–, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro, amino, or –NH–; and

wherein **n** is an integer from one to five.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein **L** is a linker;

BA is a binding agent;

k is an integer from one to thirty;

R¹ is C₁-C₁₀ alkyl;

R³ is –C(O)C₁-C₅ alkyl, –C(O)N(H)C₁-C₁₀ alkyl, or –(C₁-C₁₀ alkylene)-NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is –OH, –O–, –NHNH₂, or –NHNH–;

R⁷ is, independently in each instance, hydrogen, –OH, –O–, halogen, or –NR^{7a}R^{7b},

wherein **R^{7a}** and **R^{7b}** 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;

R⁸ is, independently in each instance, hydrogen, deuterium, –NHR⁹, or halogen,

wherein **R⁹** is hydrogen, –C₁-C₅ alkyl, or –C(O)C₁-C₅ alkyl; and

m is one or two;

Q is –CH₂– or –O– wherein

when **Q** is –O–, then **R²** is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenyl, –C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric –C₁-C₁₀ alkylene-(5-membered heteroarylene), –C₁-C₃ alkylene–Q¹–(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; or

when **Q** is –CH₂–, then **R²** is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenyl, –C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric –C₁-C₁₀ alkylene-(5-membered heteroarylene), –C₁-C₃ alkylene–Q¹–(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; and

Q¹ is –CH₂– or –O–;

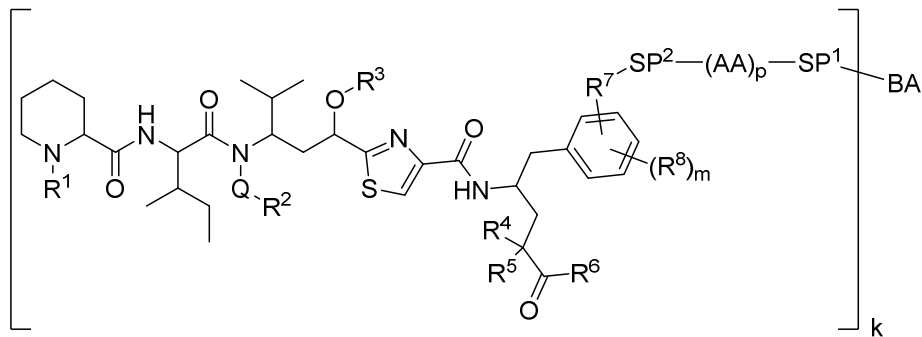
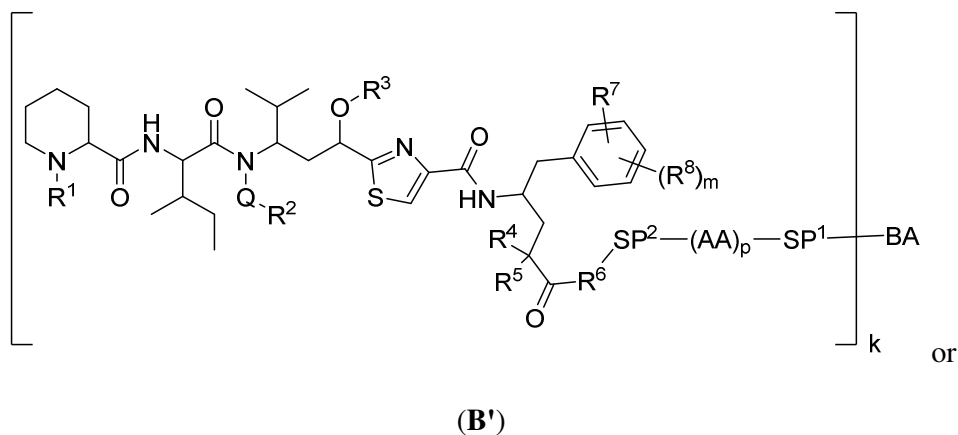
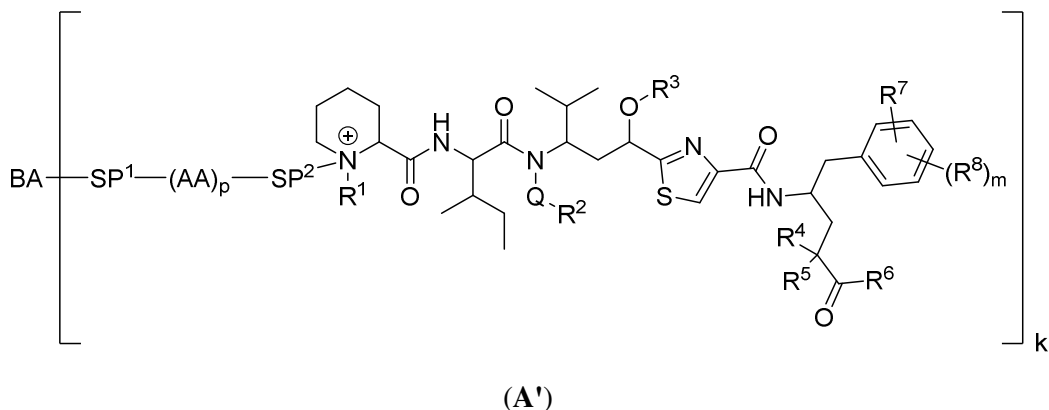
wherein said regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl;

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, -alkylene-NH-, hydroxylalkyl, -alkylene-O-, carboxyalkyl, -alkylene-COO-, benzyl, or phenyl;

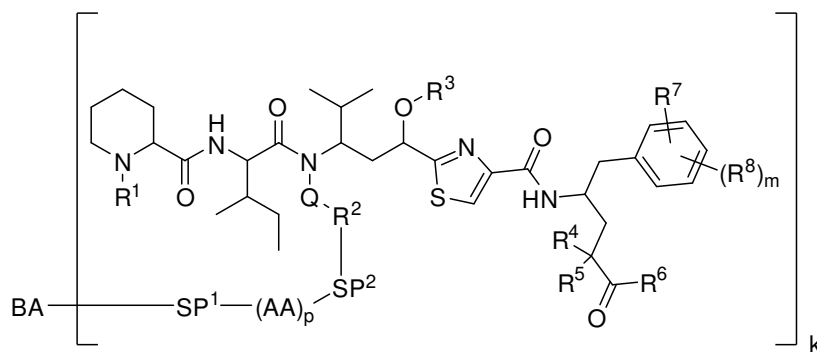
wherein said aryl is unsubstituted or substituted with nitro, amino, or -NH-; and

wherein **n** is an integer from one to five.

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



(C')



(D')

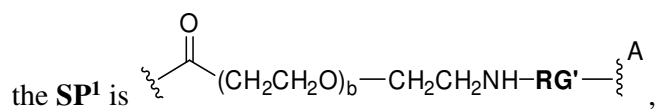
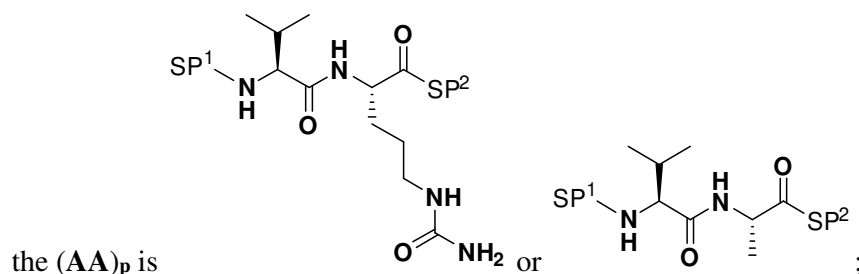
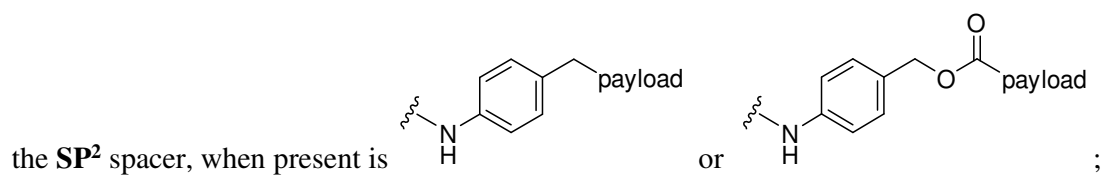
or a pharmaceutically acceptable salt or prodrug thereof, wherein

SP¹ and **SP²**, when present, are spacer groups;

each **AA** is an amino acid; and

p is an integer from one to ten.

4. A compound of claim 3, wherein



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

---^{A} is a bond, direct or indirect, to the binding agent; and

b is an integer from one to four.

5. A compound of any one of claim 1-4, 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;
- $-(CH_2)_n-$;
- $-(CH_2CH_2O)_n-(CH_2)_p-$;
- $-(CH_2)_n-N(H)C(O)-(CH_2)_m-$;
- $-(CH_2CH_2O)_n-N(H)C(O)-(CH_2CH_2O)_m-(CH_2)_p-$;
- $-(CH_2)_n-C(O)N(H)-(CH_2)_m-$;
- $-(CH_2CH_2O)_n-C(O)N(H)-(CH_2CH_2O)_m-(CH_2)_p-$;
- $-(CH_2)_n-N(H)C(O)-(CH_2CH_2O)_m-(CH_2)_p-$;
- $-(CH_2CH_2O)_n-N(H)C(O)-(CH_2)_m-$;
- $-(CH_2)_n-C(O)N(H)-(CH_2CH_2O)_m-(CH_2)_p-$; and
- $-(CH_2CH_2O)_n-C(O)N(H)-(CH_2)_m-$,

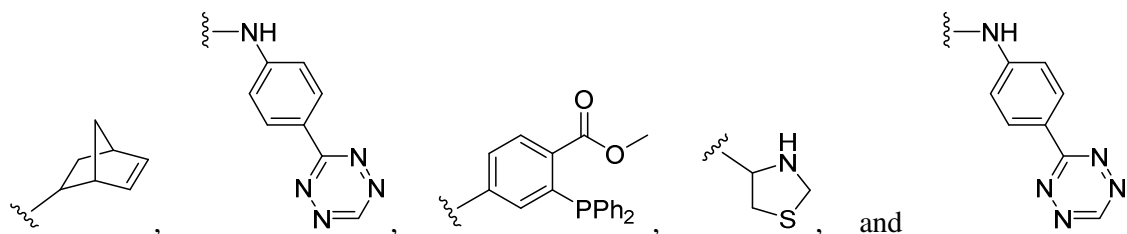
wherein

n is an integer selected from one to twelve;

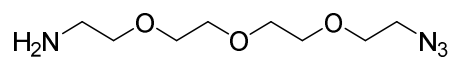
m is an integer selected from zero to twelve;

p is an integer selected from zero to two; and

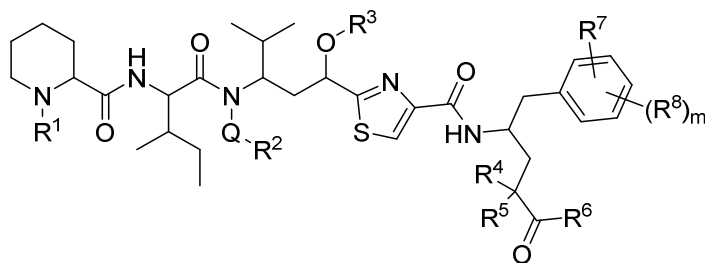
X is selected from the group consisting of $-SH$, $-N_3$, $-C\equiv CH$, $-C(O)H$, tetrazole,



6. The compound of claim 5, wherein the binding agent is an antibody modified with a primary amine according to the following formula



7. A compound having the structure of Formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR^{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;

R⁴ and **R⁵** are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH or -NHNH₂;

R⁷ is, independently in each instance, hydrogen, -OH, halogen, or -**NR^{7a}R^{7b}**,

wherein **R^{7a}** and **R^{7b}** are independently in each instance, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, -NHR⁹, or halogen,

wherein **R⁹** is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R²** is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl,

-C₁-C₁₀ alkylene-(5-membered heteroaryl), -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, or

C₁-C₃ hydroxyalkyl; or

when **Q** is -CH₂-, then **R²** is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl,

-C₁-C₁₀ alkylene-(5-membered heteroaryl), -C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl, or

C₁-C₃ hydroxyalkyl; and

Q¹ is -CH₂- or -O-;

wherein said heteroaryl is unsubstituted or substituted with alkyl, aminoalkyl, hydroxylalkyl, carboxyalkyl, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro or amino; and

wherein **n** is an integer from one to five.

8. The compound of claim 7, wherein

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-NR^{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;

R⁴ and **R**⁵ are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH or -NHNH₂;

R⁷ is, independently in each instance, hydrogen, -OH, halogen, or -NR^{7a}R^{7b},

wherein **R**^{7a} and **R**^{7b} 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;

R⁸ is, independently in each instance, hydrogen, deuterium, -NHR⁹, or halogen,

wherein **R**⁹ is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R**² is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl,

-C₁-C₁₀ alkylene-(5-membered heteroaryl), -C₁-C₃ alkylene-Q¹-(CH₂)_naryl, or C₁-C₃ hydroxyalkyl; or

when **Q** is -CH₂-, then **R**² is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl,

-C₁-C₁₀ alkylene-(5-membered heteroaryl), -C₁-C₃ alkylene-Q¹-(CH₂)_naryl, or C₁-C₃ hydroxyalkyl; and

Q¹ is -CH₂- or -O-;

wherein said heteroaryl is unsubstituted or substituted with alkyl, aminoalkyl, hydroxylalkyl, carboxyalkyl, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro or amino; and

wherein **n** is an integer from one to five.

9. The compound of claim 7, wherein

Q is -CH₂-;

R² is C₅-C₁₀ alkyl;

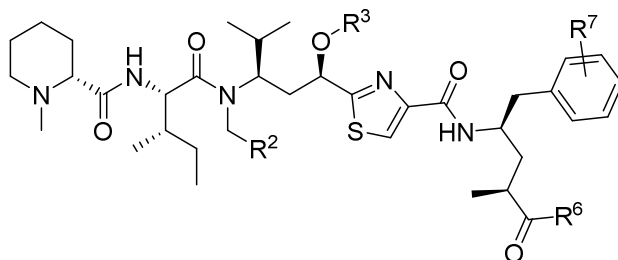
R³ is -C(O)C₁-C₅ alkyl;

R⁴ is hydrogen;

R⁵ is C₁-C₅ alkyl; and

R⁷ is halogen.

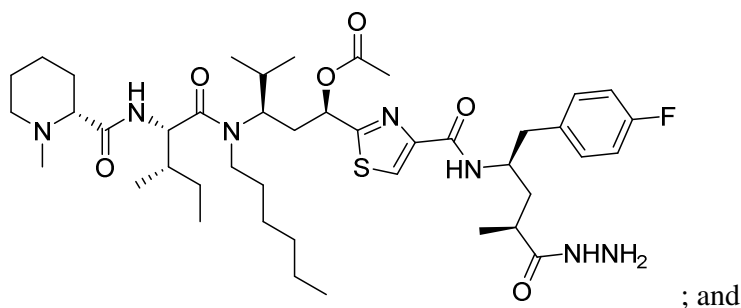
10. The compound of claim 9 according to the structure of Formula II



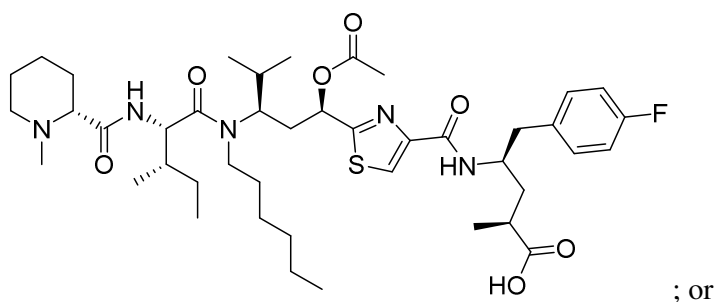
Formula II

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10 selected from the group consisting of



; and



; or

a pharmaceutically acceptable salt thereof.

12. The compound of claim 7, wherein

Q is -CH₂-;

R² is C₅-C₁₀ alkyl;

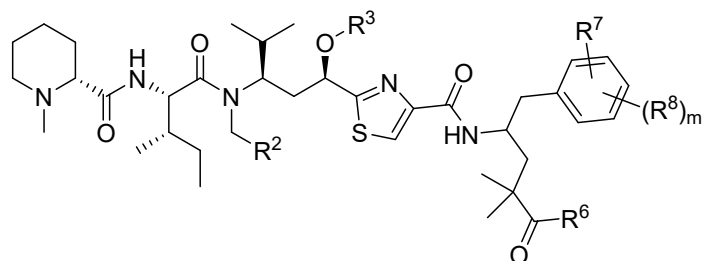
R³ is -C(O)C₁-C₅ alkyl;

R⁴ and **R⁵** are methyl;

R⁷ is -OH, halogen, or -NH₂;

R⁸ is, independently in each occurrence, hydrogen, deuterium, –NHR⁹, or halogen,
 wherein **R⁹** is hydrogen or –C₁–C₅ alkyl; and
m is one or two.

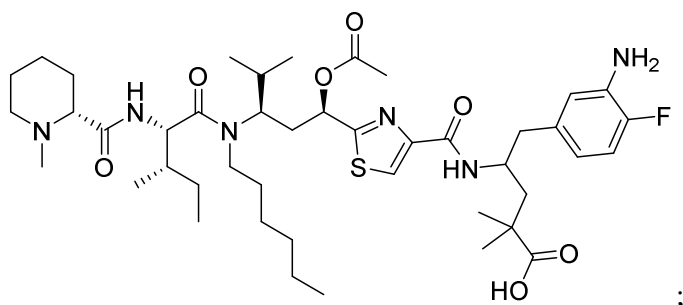
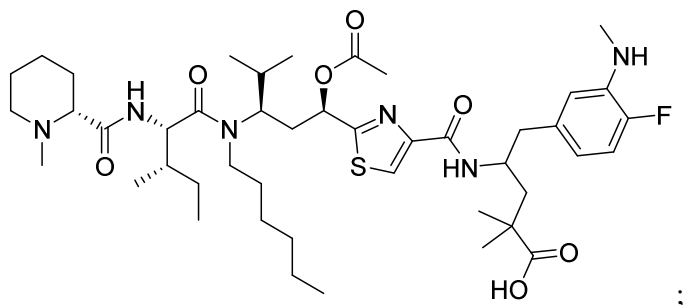
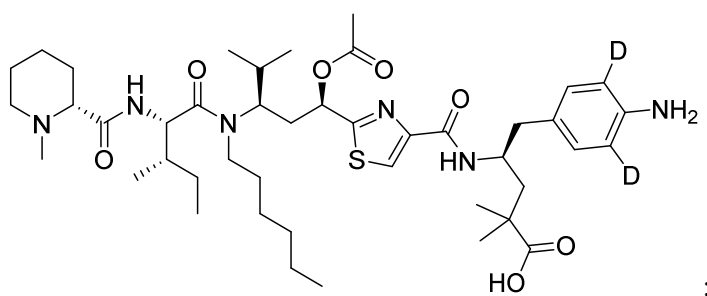
13. The compound of claim 12 according to the structure of Formula III

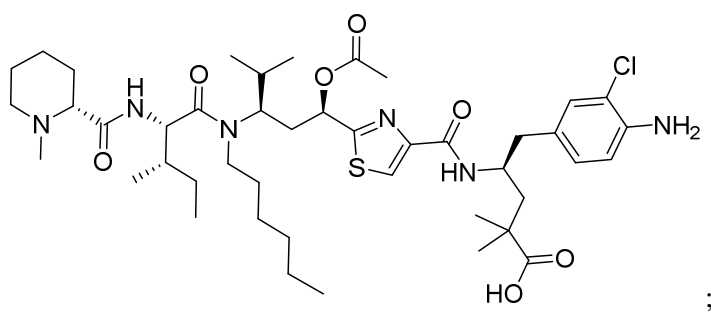
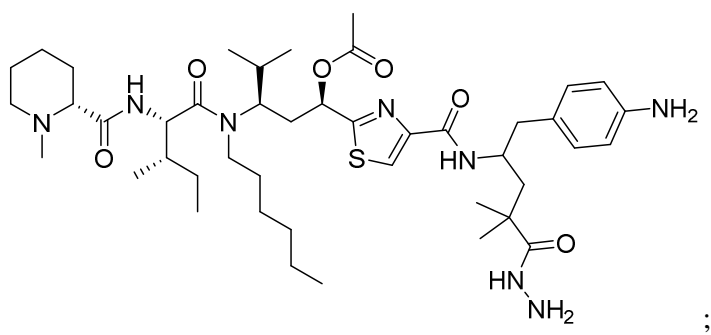
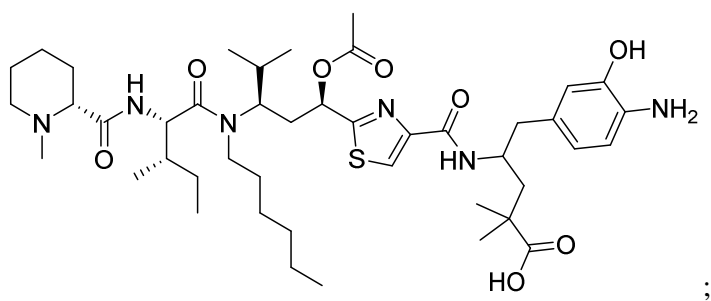
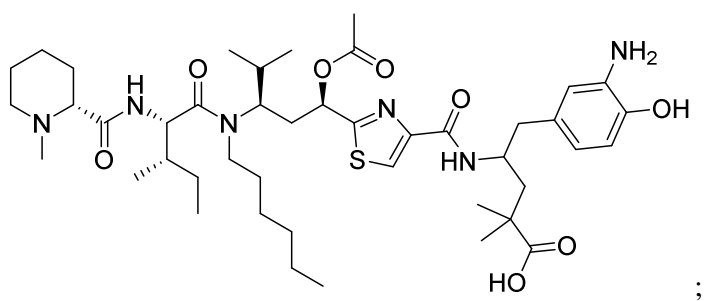
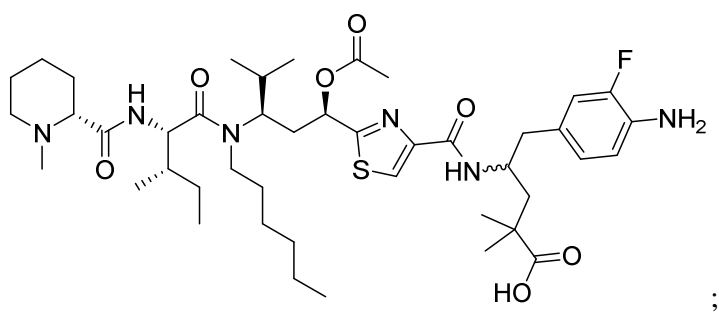


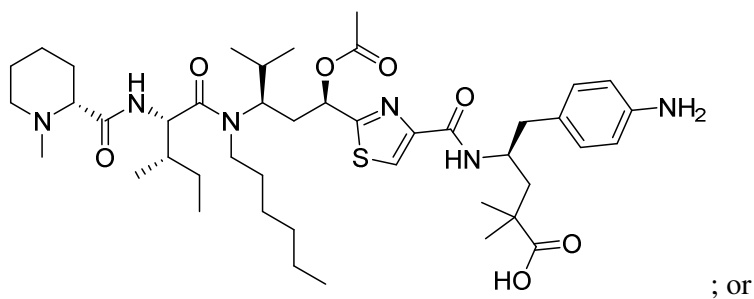
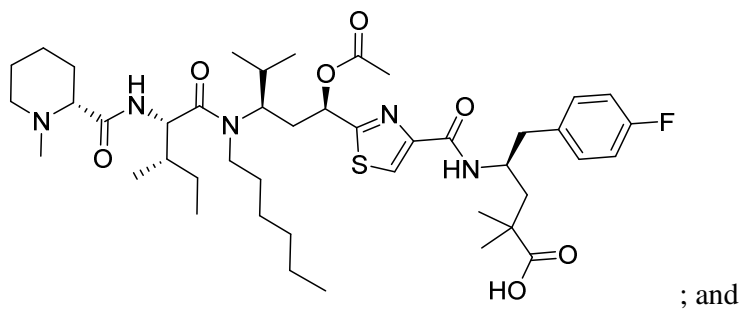
Formula III

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13 selected from the group consisting of







a pharmaceutically acceptable salt thereof.

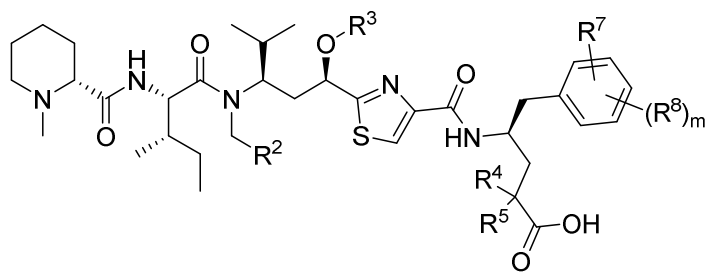
15. The compound of claim 7, wherein

Q is $-\text{CH}_2-$;

R² is C_1 - C_{10} alkynyl; and

R⁶ is $-\text{OH}$.

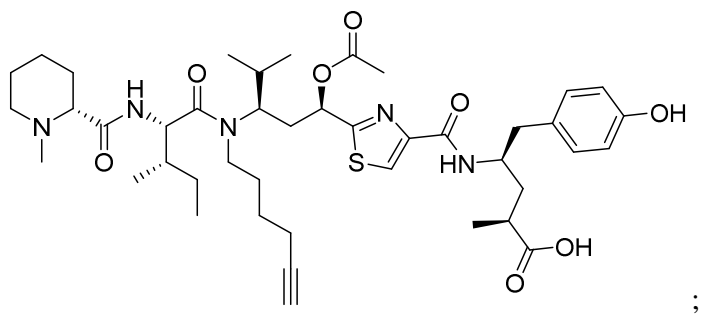
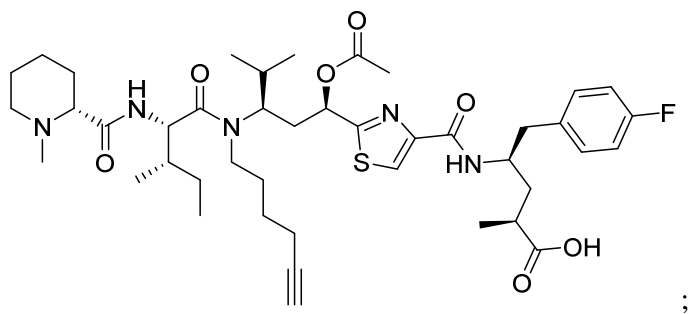
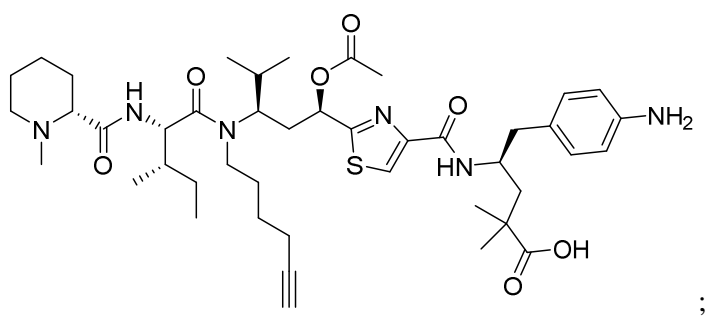
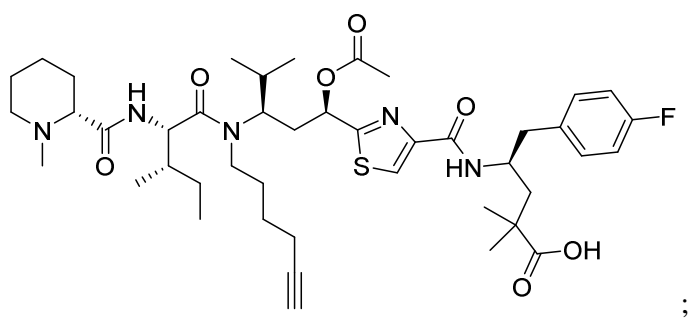
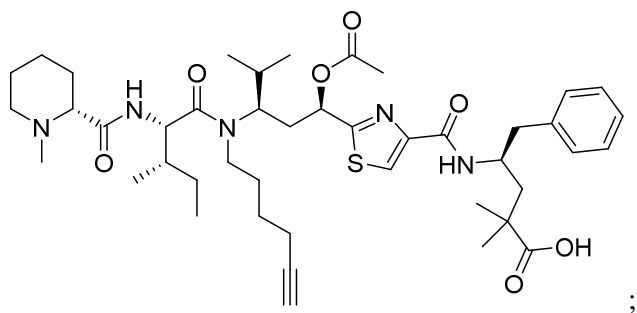
16. The compound of claim 15 according to the structure of Formula IV

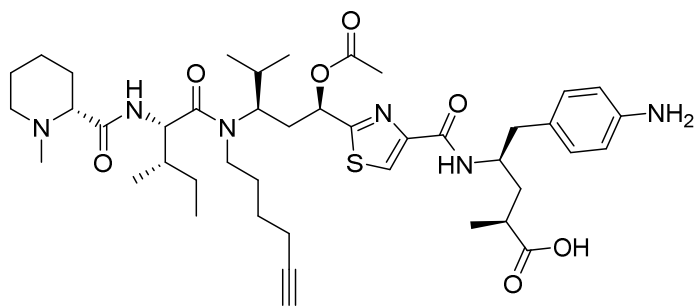


Formula IV

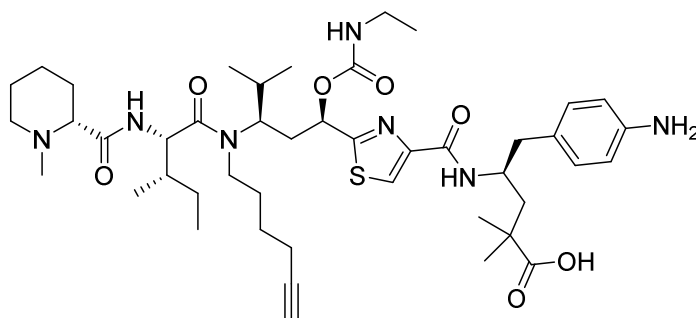
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 16 selected from the group consisting of

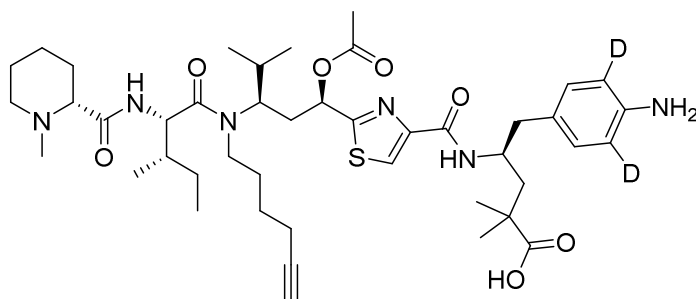




;



; and



; or

a pharmaceutically acceptable salt thereof.

18. The compound of claim 7, wherein

Q is $-\text{CH}_2-$;

R² is regioisomeric $-\text{C}_1-\text{C}_{10}$ alkylene-(5-membered heteroaryl), wherein said heteroaryl is unsubstituted or substituted with alkyl, aminoalkyl, hydroxylalkyl, carboxyalkyl, benzyl, or phenyl;

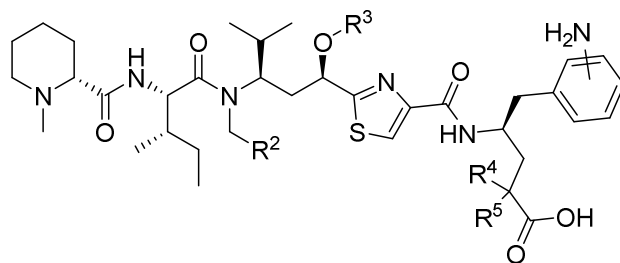
R³ is $-\text{C}(\text{O})\text{C}_1-\text{C}_5$ alkyl;

R⁴ and **R₅** are C_1-C_5 alkyl;

R⁶ is $-\text{OH}$; and

R⁷ is $-\text{NH}_2$.

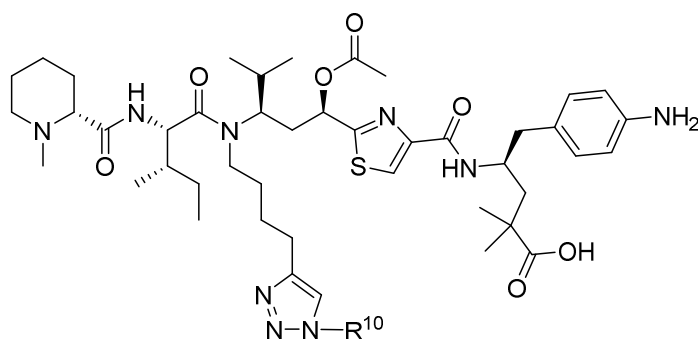
19. The compound of claim 18 according to the structure of Formula V



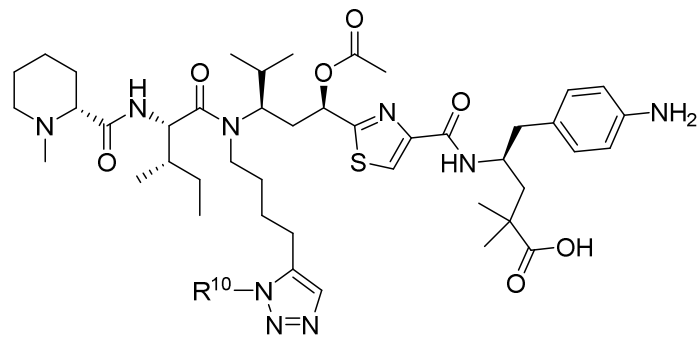
Formula V

or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19 according to the structure of Formula VI or VII



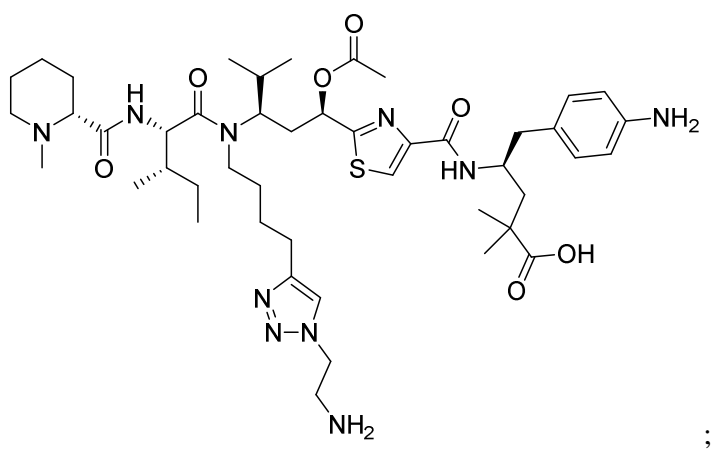
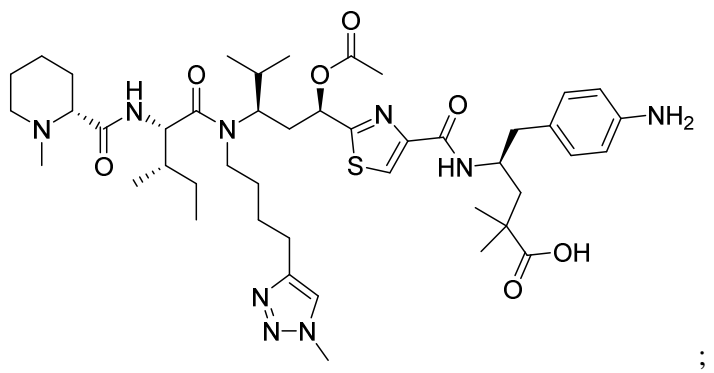
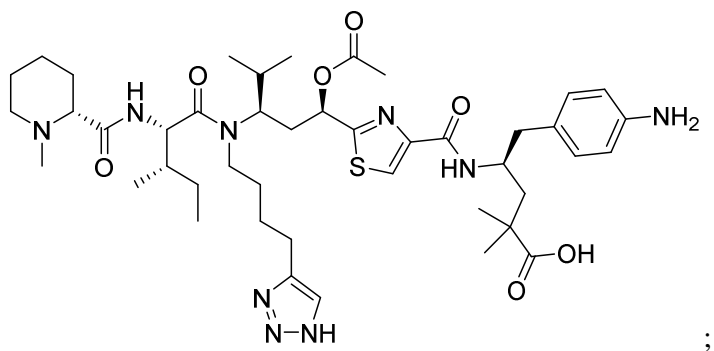
Formula VI

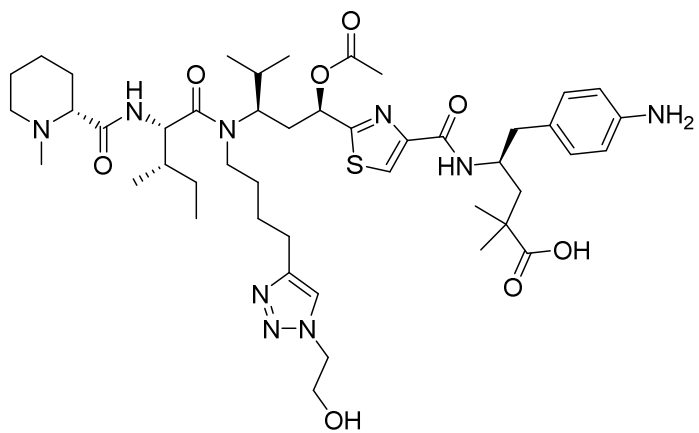


Formula VII

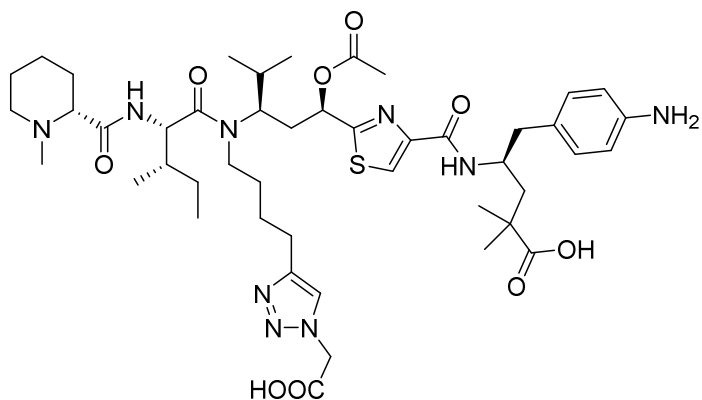
wherein **R¹⁰** is hydrogen, methyl, $-\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, benzyl, or phenyl; or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20 selected from the group consisting of

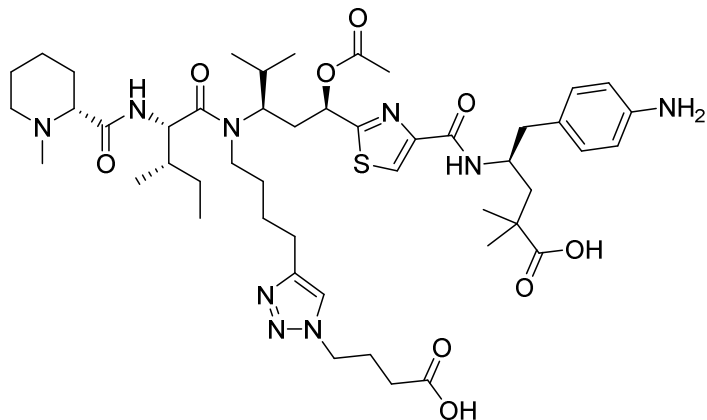




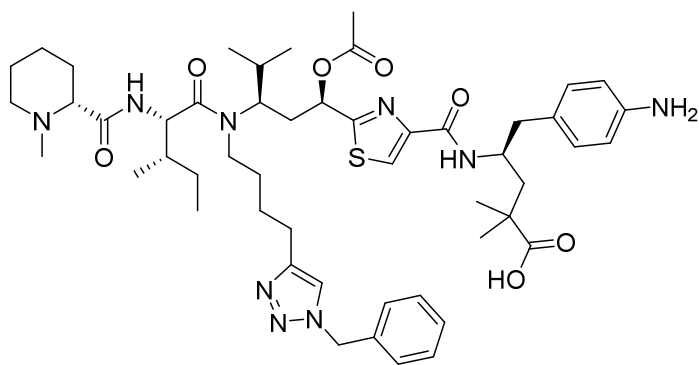
;



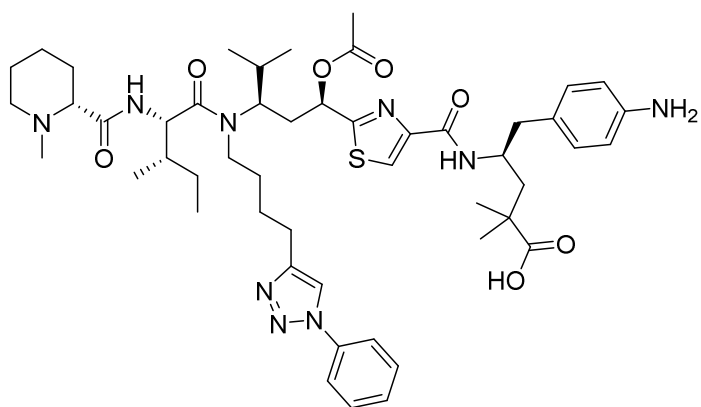
;



;



; and



; or

a regioisomer thereof; or

a pharmaceutically acceptable salt thereof.

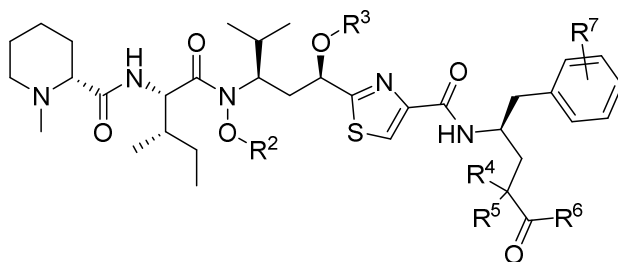
22. The compound of claim 7, wherein

Q is $-O-$;

R² is C_1-C_{10} alkyl; and

R⁷ is $-OH$ or $-NH_2$.

23. The compound of claim 22 according to the structure of Formula VIII

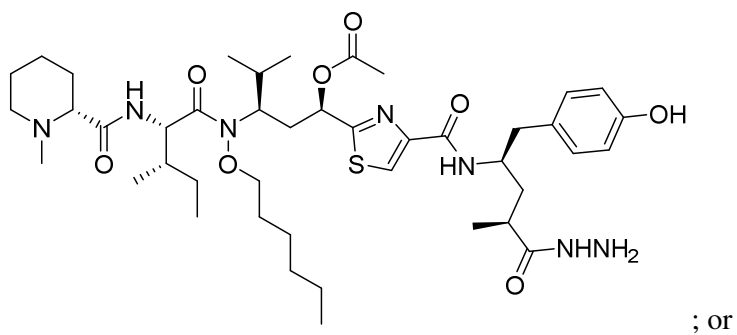
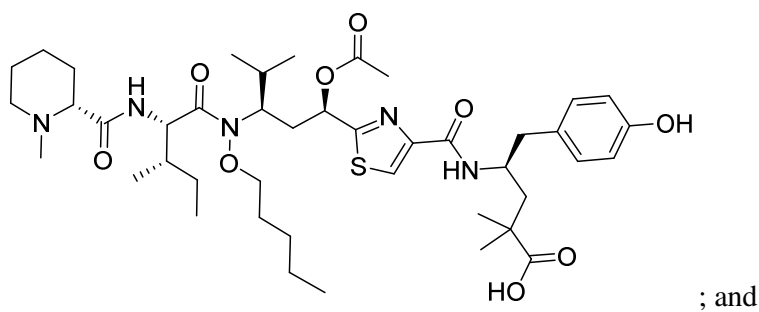
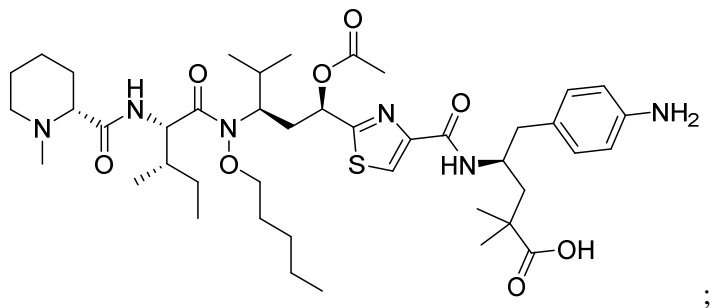
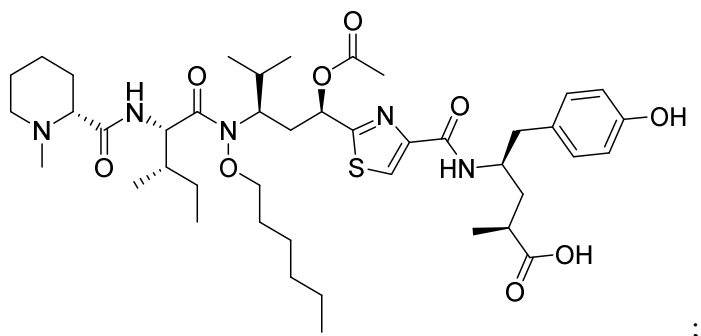


Formula VIII

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 23 wherein **R³** is $-C(O)Me$.

25. The compound of claim 24 selected from the group consisting of



a pharmaceutically acceptable salt thereof.

26. The compound of claim 23, wherein

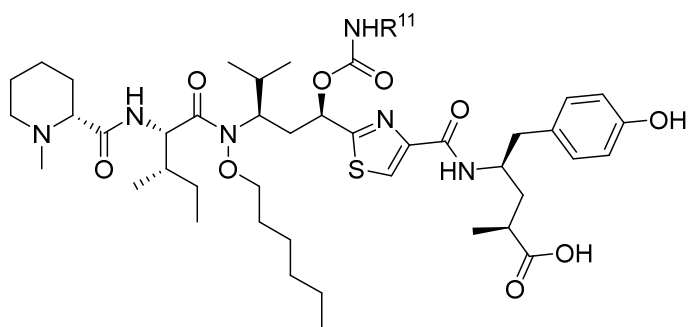
R³ is $-\text{C}(\text{O})\text{N}(\text{H})\text{C}_{1-10}$ alkyl;

R⁴ is hydrogen;

R⁵ is C_{1-5} alkyl; and

R⁶ and **R⁷** are $-\text{OH}$.

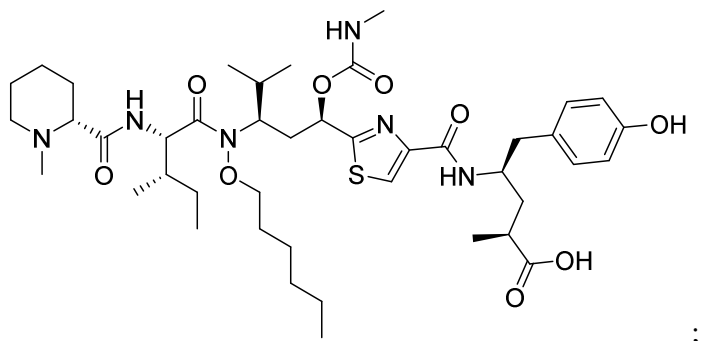
27. The compound of claim 26 having the structure of Formula IX



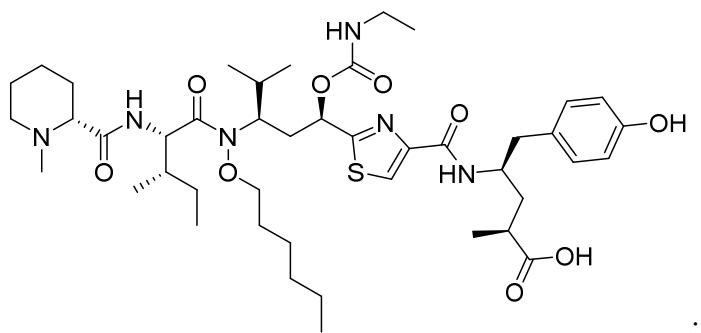
Formula IX

wherein **R¹¹** is C₁-C₁₀ alkyl; or
a pharmaceutically acceptable salt thereof.

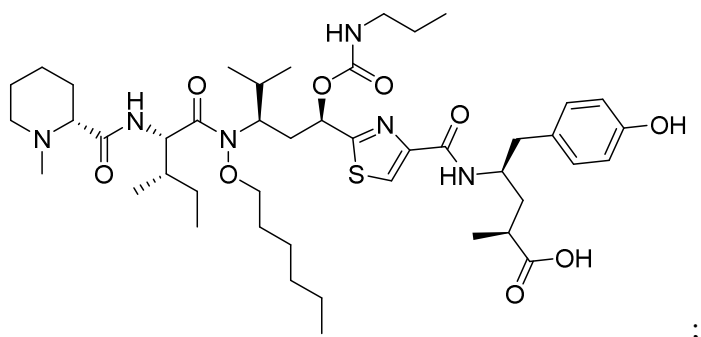
28. The compound of claim 27 selected from the group consisting of



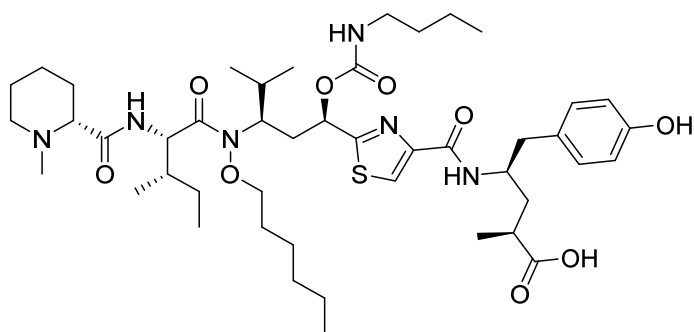
;



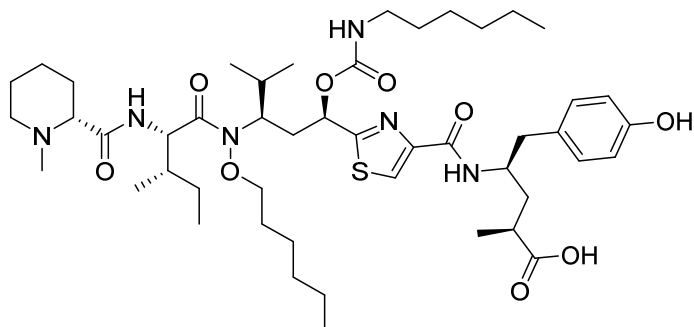
;



;



; and

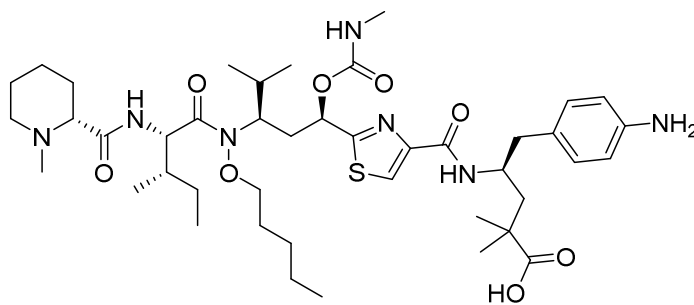


; or

a pharmaceutically acceptable salt thereof.

29. The compound of claim 23, wherein **R**₃ is $-\text{C}(\text{O})\text{N}(\text{H})\text{C}_1\text{-C}_{10}$ alkyl.

30. The compound of claim 29, wherein the compound is



or

a pharmaceutically acceptable salt thereof.

31. The compound of claim 7, wherein

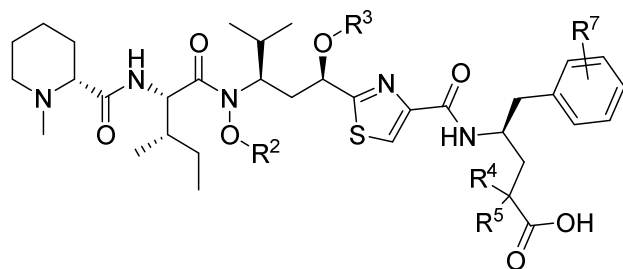
Q is $-\text{O}-$;

R² is $\text{C}_1\text{-C}_{10}$ alkynyl;

R³ is $-\text{C}(\text{O})\text{C}_1\text{-C}_5$ alkyl; and

R⁶ is $-\text{OH}$.

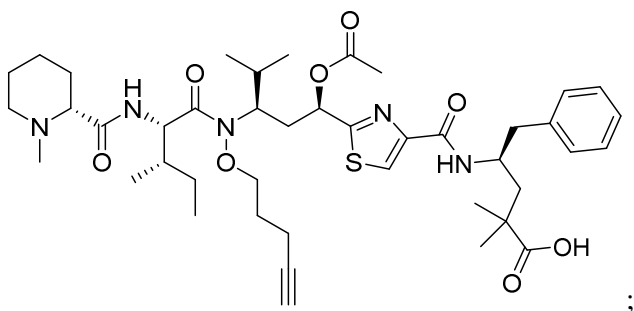
32. The compound of claim 31 according to the structure of Formula X



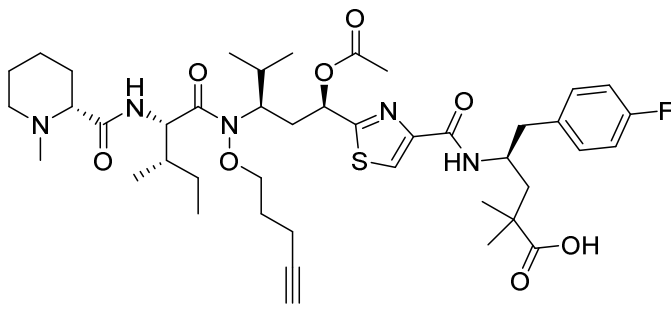
Formula X

or a pharmaceutically acceptable salt thereof.

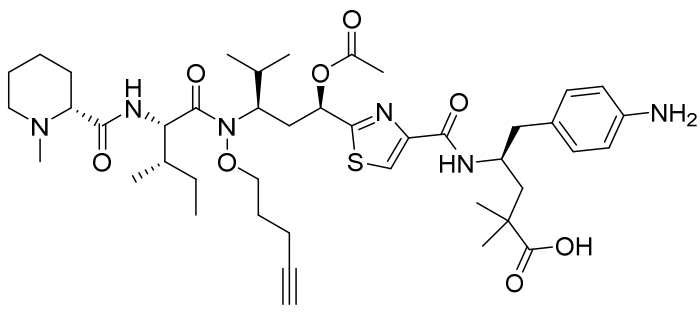
33. The compound of claim 32 selected from the group consisting of



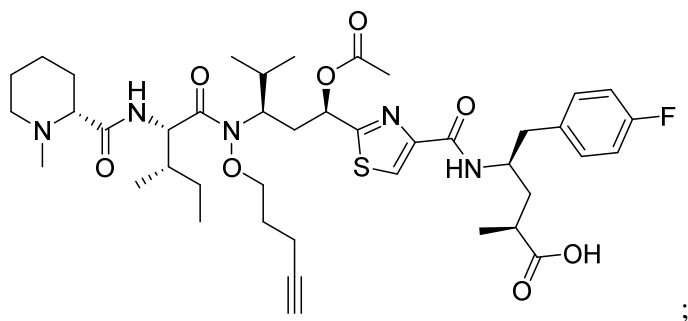
;



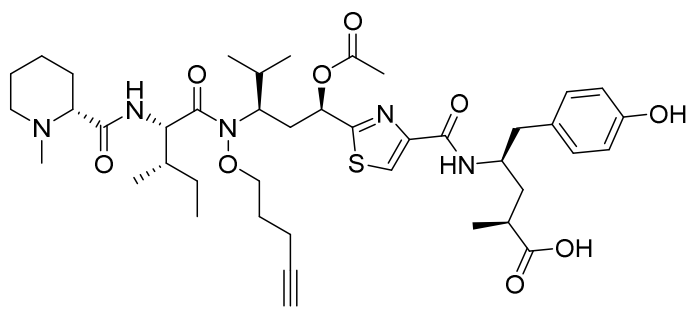
;



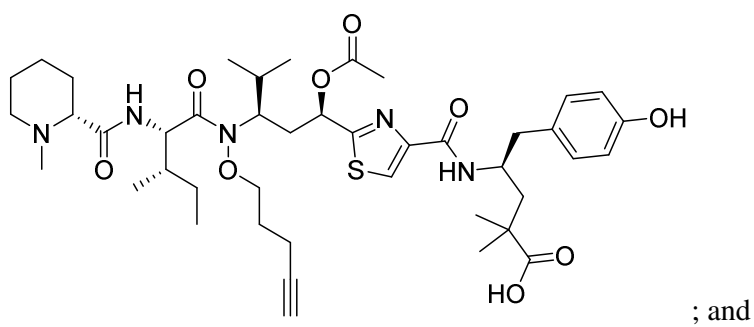
;



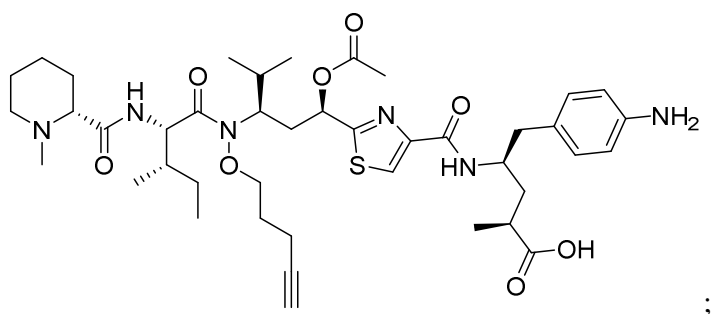
;



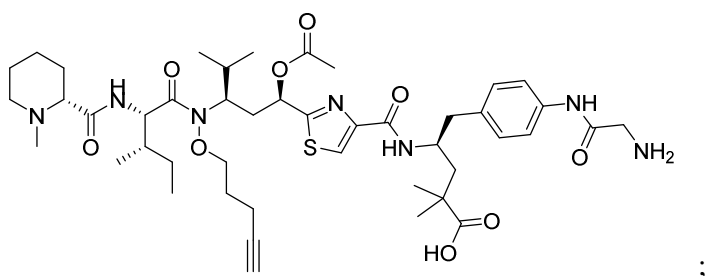
;



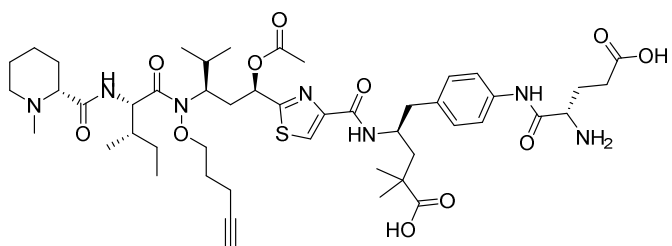
; and



;



;



; or

a pharmaceutically acceptable salt thereof.

34. The compound of claim 7, wherein

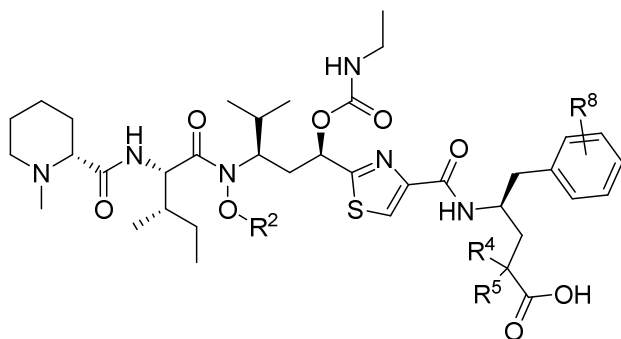
Q is $-O-$;

R² is C_1-C_{10} alkynyl;

R³ is $-C(O)N(H)C_1-C_{10}$ alkyl; and

R⁶ is $-OH$.

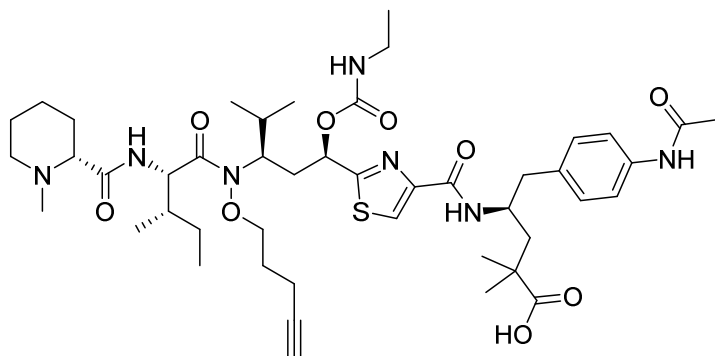
35. The compound of claim 34 according to the structure of Formula XI



Formula XI

or a pharmaceutically acceptable salt thereof.

36. The compound of claim 35, wherein the compound is



or

a pharmaceutically acceptable salt thereof.

37. The compound of claim 7, wherein

Q is -O-;

R² is C₁-C₃ alkylene-**Q¹**-(CH₂)_naryl; or C₁-C₃ hydroxyalkyl;

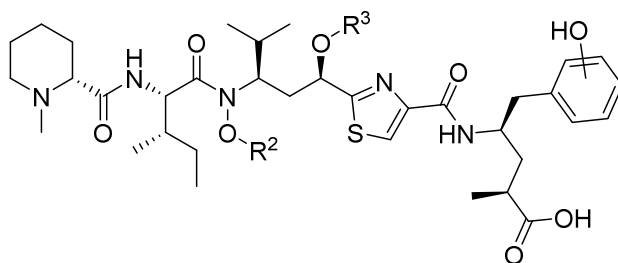
R³ is -C(O)C₁-C₅ alkyl;

R⁴ is hydrogen;

R⁵ is C₁-C₅ alkyl; and

R⁶ and **R⁷** is -OH.

38. The compound of claim 37 having the structure of Formula XII

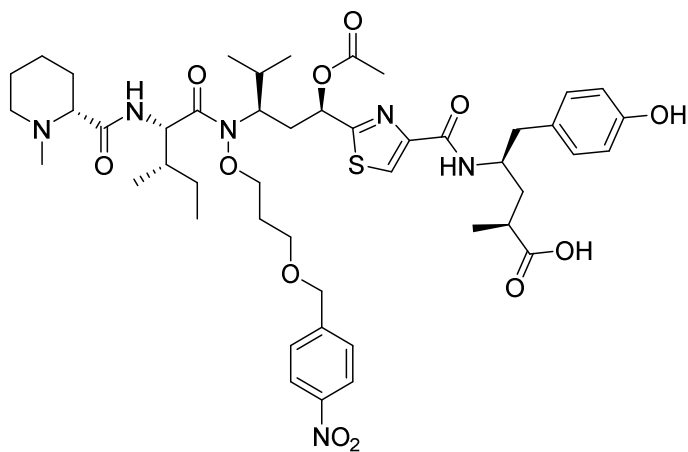


Formula XII

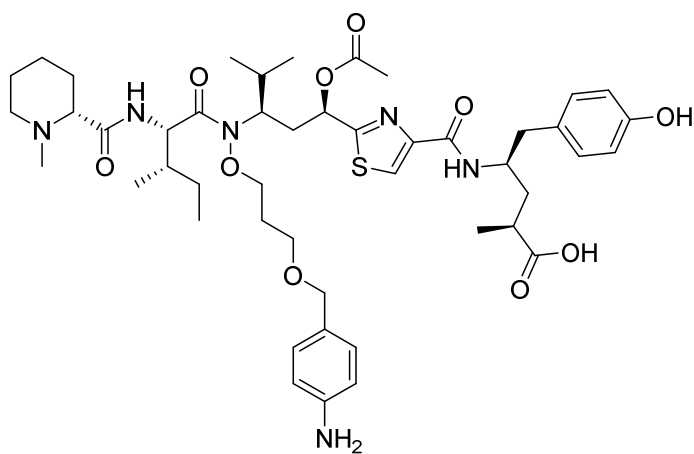
or a pharmaceutically acceptable salt thereof.

39. The compound of claim 38, wherein **R²** is C₁-C₃ alkylene-O-(CH₂)_naryl.

40. The compound of claim 39 selected from the group consisting of



and

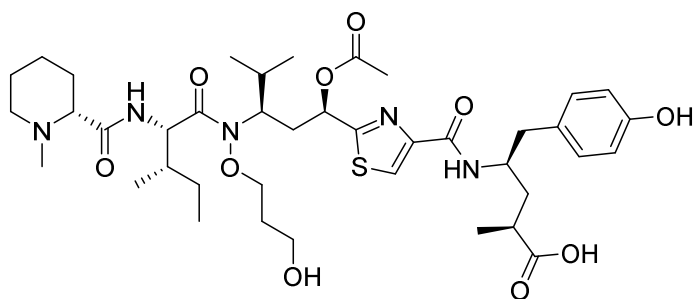


; or

a pharmaceutically acceptable salt thereof.

41. The compound of claim 38, wherein **R**² is C₁-C₃ hydroxyalkyl.

42. The compound of claim 41, wherein the compound is



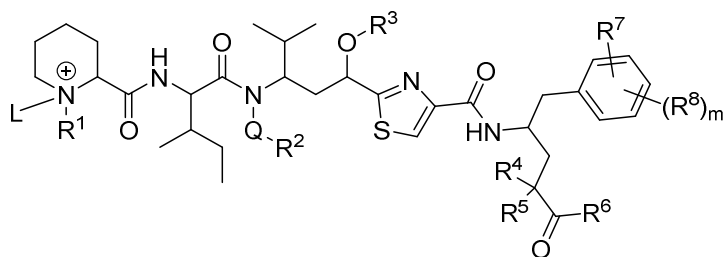
or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising the compound of any one of claims 1-2 or 7-42 and a pharmaceutically acceptable excipient, carrier, or diluent.
44. The compound or pharmaceutical composition comprising of any one of claims 1-2 or 7-43 for use in therapy.
45. Use of a compound or pharmaceutical composition comprising of any one of claims 1-2 or 7-43 in the manufacture of a medicament for treating cancer in a subject.
46. Use of a compound or pharmaceutical composition comprising of any one of claims 1-2 or 7-43 in the manufacture of a medicament for treating cancer in a subject comprising that an effective treatment amount of a compound or pharmaceutical composition of any of the preceding claims is to be administered to the subject, wherein the cancer is selected from the group consisting of renal cell carcinoma, pancreatic carcinoma, head and neck cancer, prostate cancer, castrate-resistant prostate 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.
47. Use of a compound or pharmaceutical composition comprising of any one of claims 1-2 or 7-43 in the manufacture of a medicament for treating tumors that express an antigen selected from the group consisting of PRLR and STEAP2.
48. An antibody-drug conjugate comprising an antibody, or antigen binding fragment thereof, wherein said antibody or antigen binding fragment thereof is conjugated to a compound of claims 7-42.

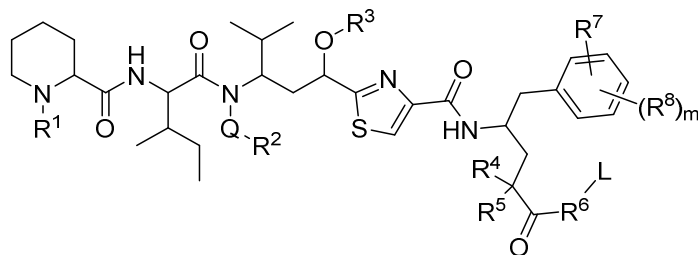
49. A linker-payload comprising the compound of any one of claims 7-42 bonded to a linker, wherein said linker comprises a moiety reactive with an antibody or antigen binding fragment thereof.

50. The linker-payload of claim 49, wherein the linker is bonded to the piperidine nitrogen, **R**², **R**⁶, or **R**⁷ of the compound of any one of claims 7-42.

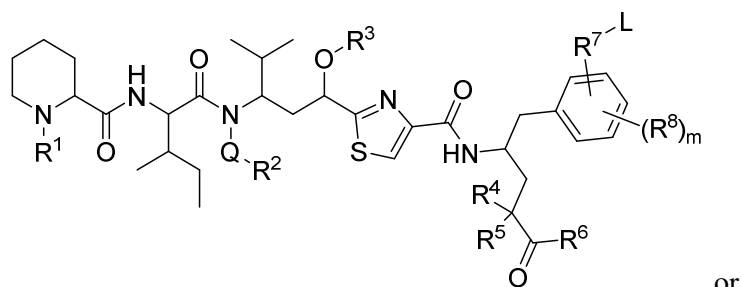
51. A linker-payload of Formula **LPa**, **LPb**, **LPc**, or **LPd**



(**LPa**)

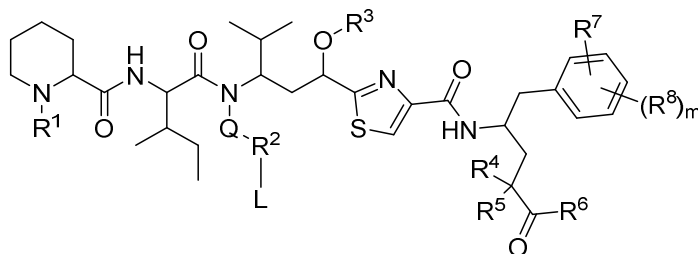


(**LPb**)



(**LPc**)

or



(LPd)

or a pharmaceutically acceptable salt thereof, wherein

L is a linker;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR**^{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;

R⁴ and **R**⁵ are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -**NR**^{7a}**R**^{7b},

wherein **R**^{7a} and **R**^{7b} are independently in each instance, a bond, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, acyl, and amino acid residue, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl are optionally substituted;

R⁸ is, independently in each instance, hydrogen, deuterium, -**NHR**⁹, or halogen,

wherein **R**⁹ is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R**² is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenes, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric -C₁-C₁₀ alkylene-(5-membered heteroarylene), -C₁-C₃ alkylene-**Q**¹-(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; or

when **Q** is -CH₂-, then **R**² is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylenes, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric -C₁-C₁₀ alkylene-(5-membered heteroarylene), -C₁-C₃ alkylene-**Q**¹-(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; and

Q¹ is -CH₂- or -O-;

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

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, -alkylene-NH-, hydroxyalkyl, -alkylene-O-, carboxyalkyl, -alkylene-COO-, benzyl, or phenyl;

wherein said aryl is unsubstituted or substituted with nitro, amino, or -NH-; and

wherein **n** is an integer from one to five.

52. The linker-payload of claim 51, or a pharmaceutically acceptable salt thereof, wherein **L** is a linker;

R¹ is C₁-C₁₀ alkyl;

R³ is -C(O)C₁-C₅ alkyl, -C(O)N(H)C₁-C₁₀ alkyl, or -(C₁-C₁₀ alkylene)-**NR**^{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;

R⁴ and **R**⁵ are, independently in each instance, hydrogen or C₁-C₅ alkyl;

R⁶ is -OH, -O-, -NHNH₂, or -NHNH-;

R⁷ is, independently in each instance, hydrogen, -OH, -O-, halogen, or -**NR**^{7a}**R**^{7b},

wherein **R**^{7a} and **R**^{7b} 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;

R⁸ is, independently in each instance, hydrogen, deuterium, -**NHR**⁹, or halogen,

wherein **R**⁹ is hydrogen, -C₁-C₅ alkyl, or -C(O)C₁-C₅ alkyl; and

m is one or two;

Q is -CH₂- or -O- wherein

when **Q** is -O-, then **R**² is C₁-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylene, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric -C₁-C₁₀ alkylene-(5-membered heteroarylene), -C₁-C₃ alkylene-**Q**¹-(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; or

when **Q** is -CH₂-, then **R**² is C₅-C₁₀ alkyl, C₁-C₁₀ alkynyl, a regioisomeric C₁-C₁₀ triazolylene, -C₁-C₁₀ alkylene-(5-membered heteroaryl), a regioisomeric -C₁-C₁₀ alkylene-(5-membered heteroarylene), -C₁-C₃ alkylene-**Q**¹-(CH₂)_naryl, C₁-C₃ hydroxyalkyl, or C₁-C₁₀ alkylether; and

Q¹ is -CH₂- or -O-;

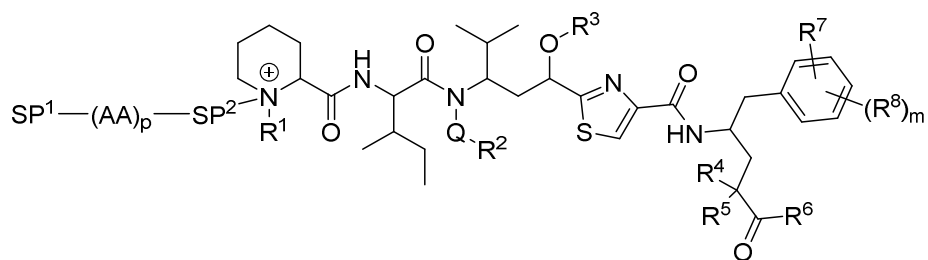
wherein said regioisomeric triazolylene is unsubstituted or substituted with alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and acyl;

wherein said heteroaryl or regioisomeric heteroarylene is unsubstituted or substituted with alkyl, aminoalkyl, -alkylene-NH-, hydroxyalkyl, -alkylene-O-, carboxyalkyl, -alkylene-COO-, benzyl, or phenyl;

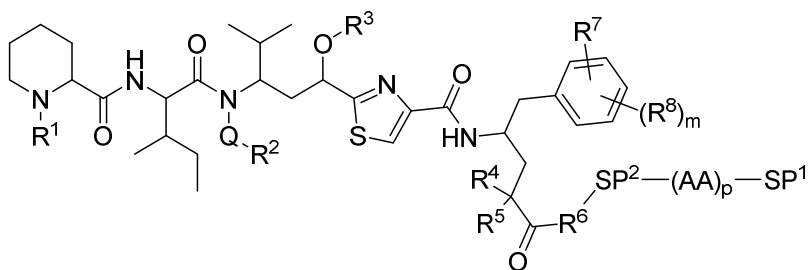
wherein said aryl is unsubstituted or substituted with nitro, amino, or -NH-; and

wherein **n** is an integer from one to five.

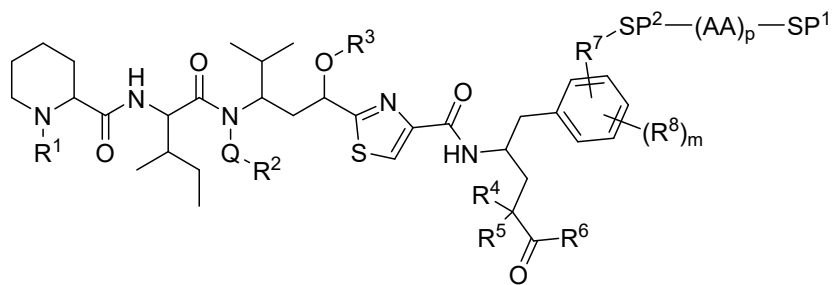
53. The linker payloads of claim 52, having the Formula **LPa'**, **LPb'**, **LPc'**, or **LPd'**



(**LPa'**)

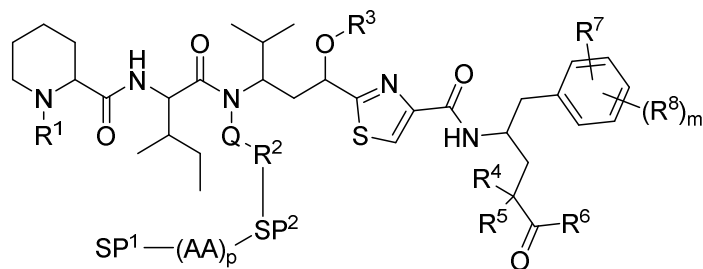


(**LPb'**)



(**LPc'**)

or



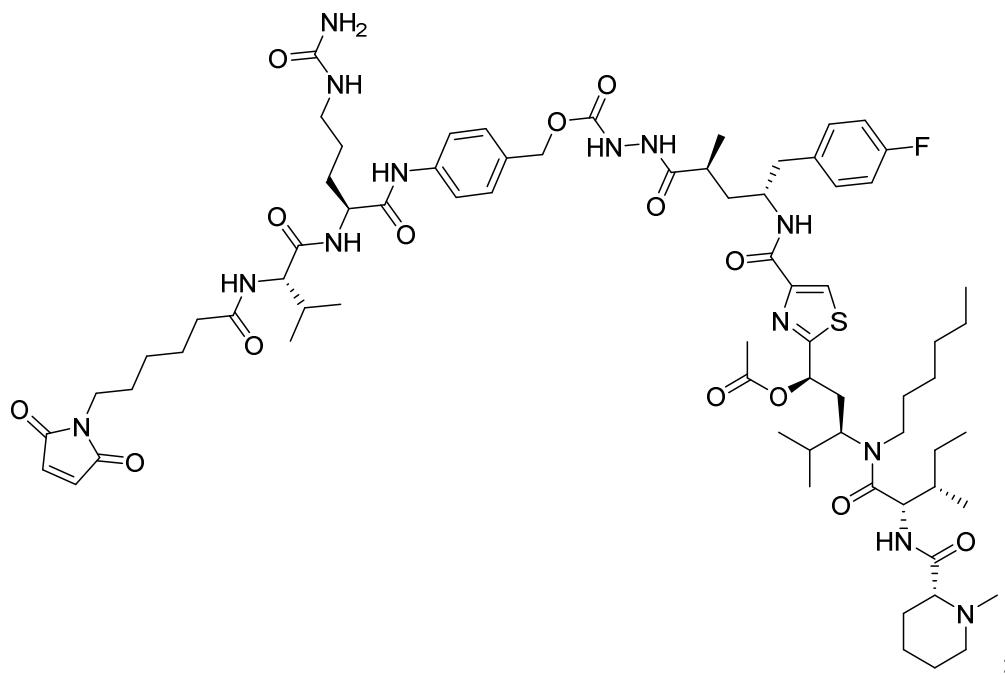
(**LPd'**)

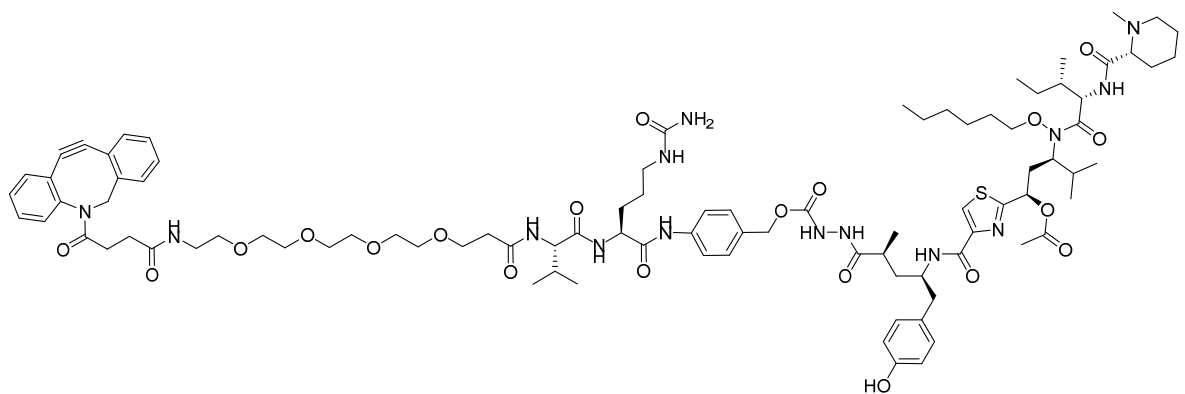
or a pharmaceutically acceptable salt thereof, wherein

SP¹ and **SP²**, when present, are spacer groups;

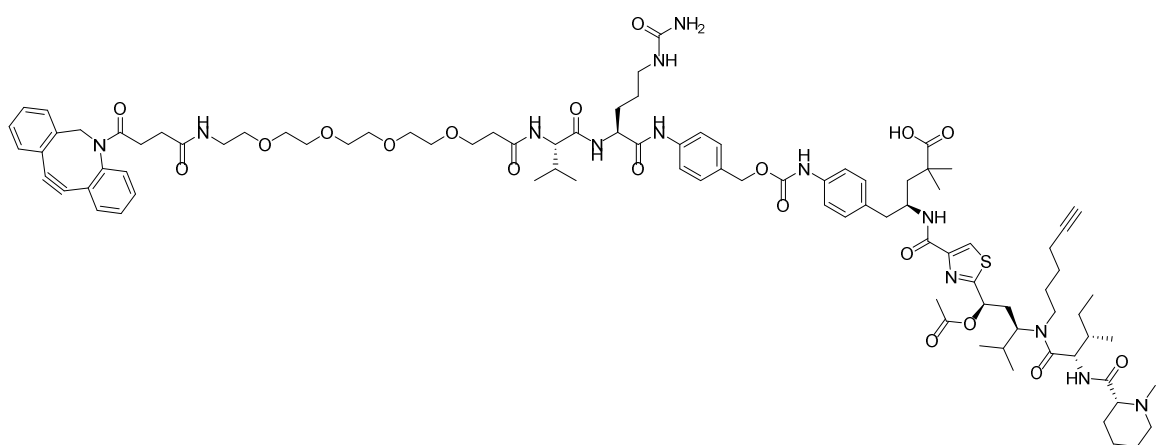
p is an integer from one to ten.

55. The linker-payload of claim 53, wherein the linker-payload is selected from the group consisting of

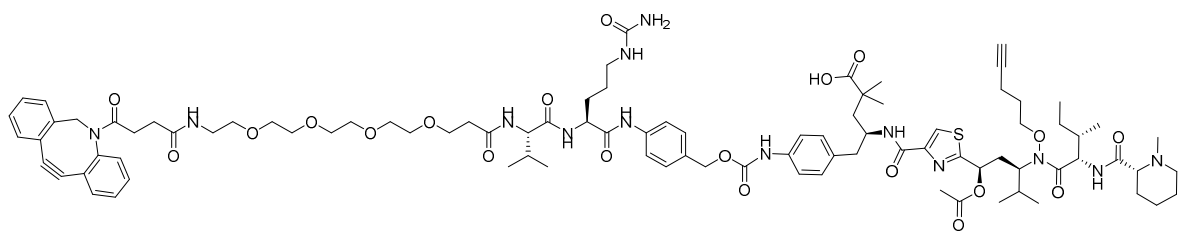




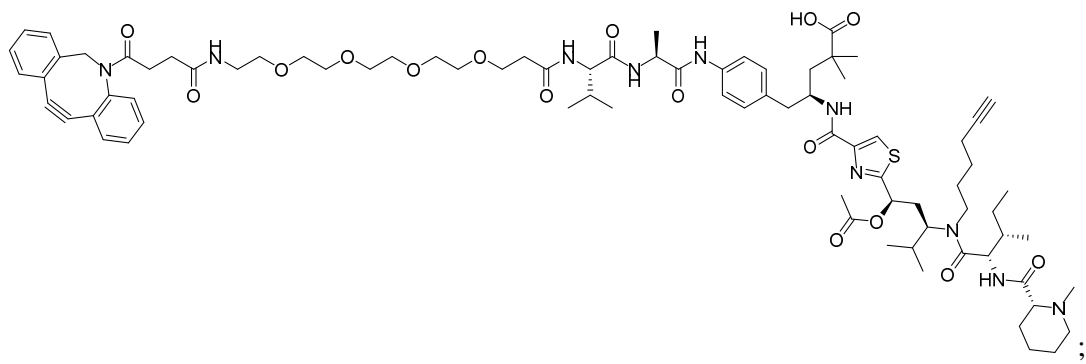
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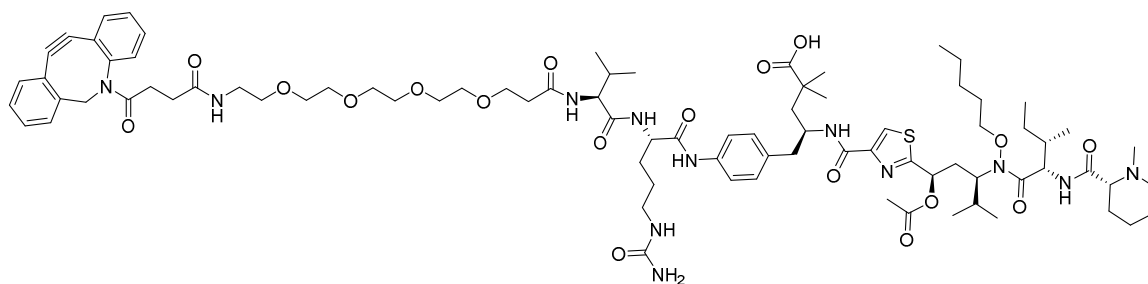


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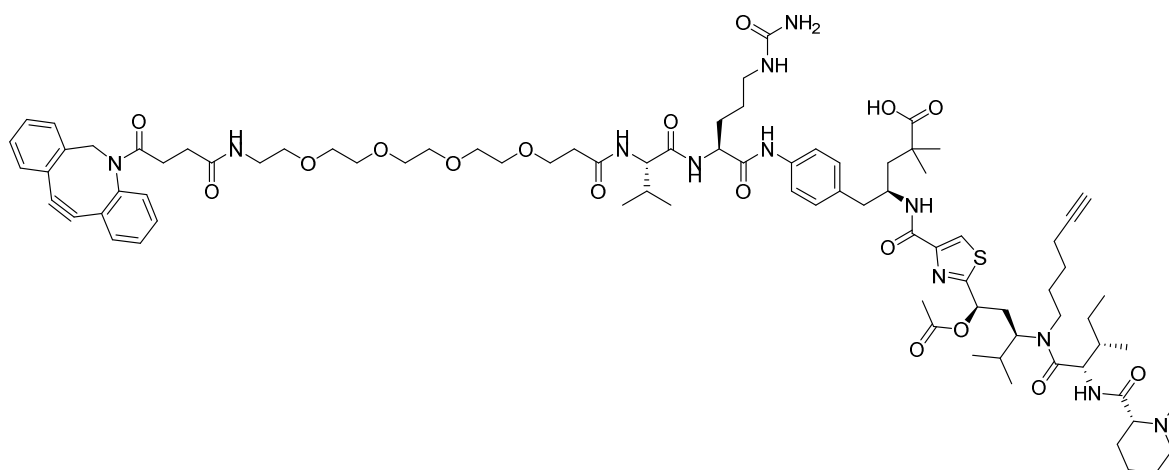


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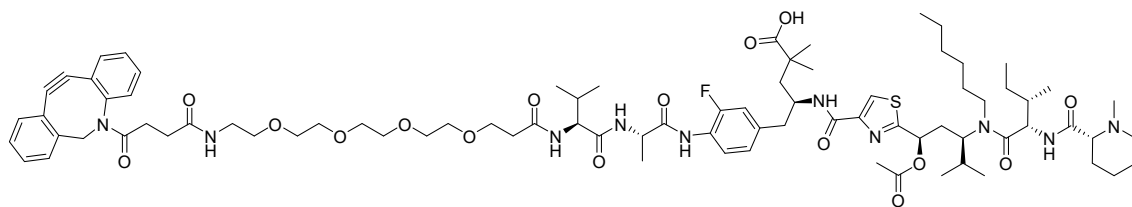




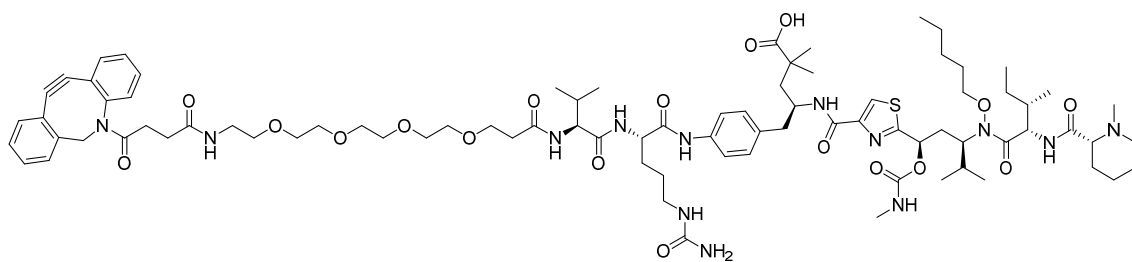
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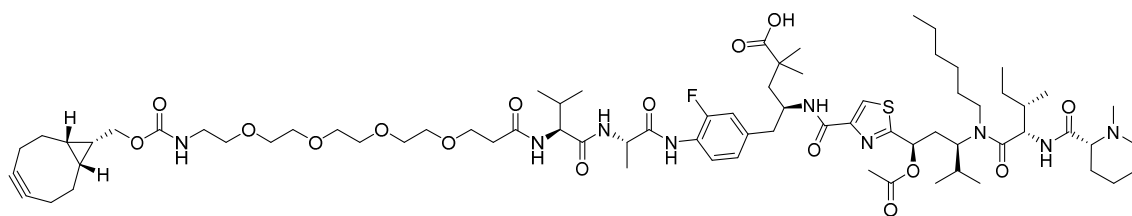
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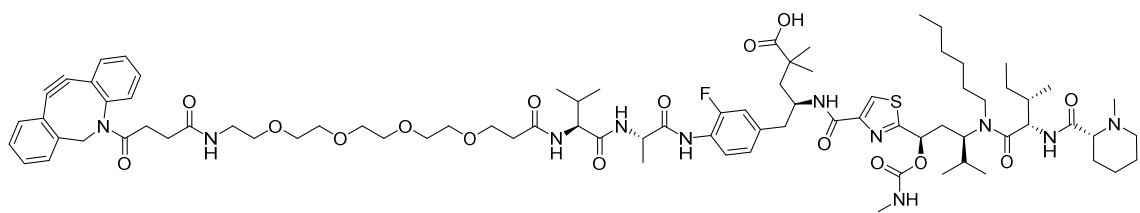
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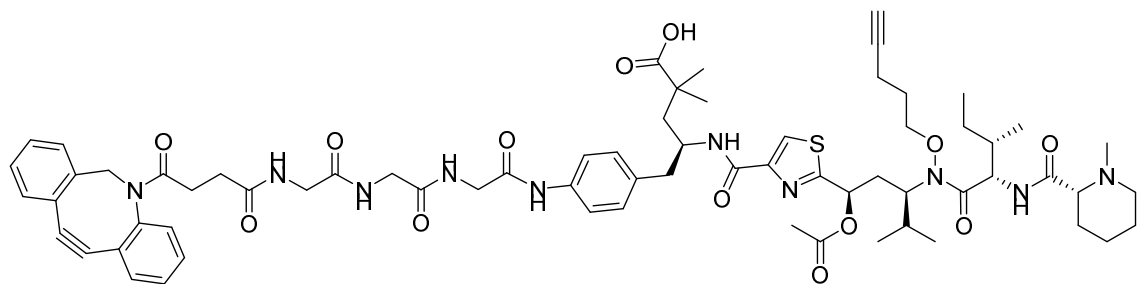
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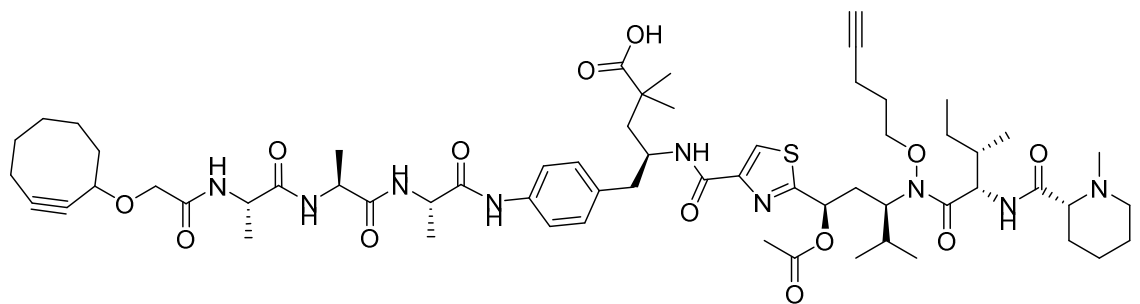
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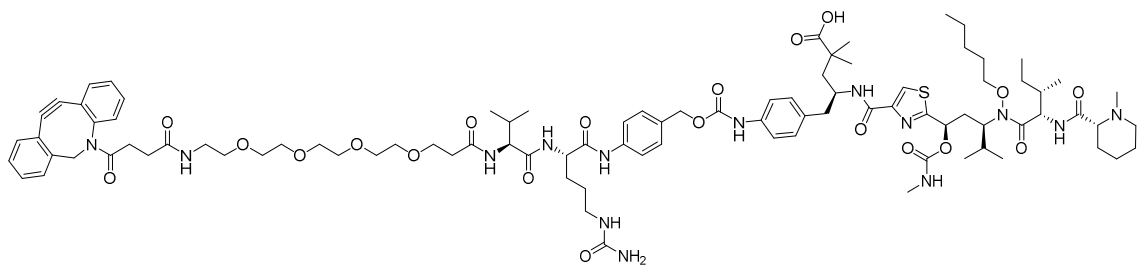
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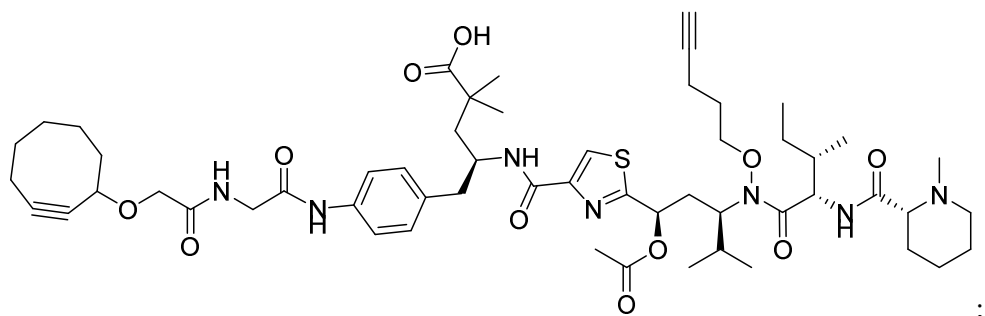
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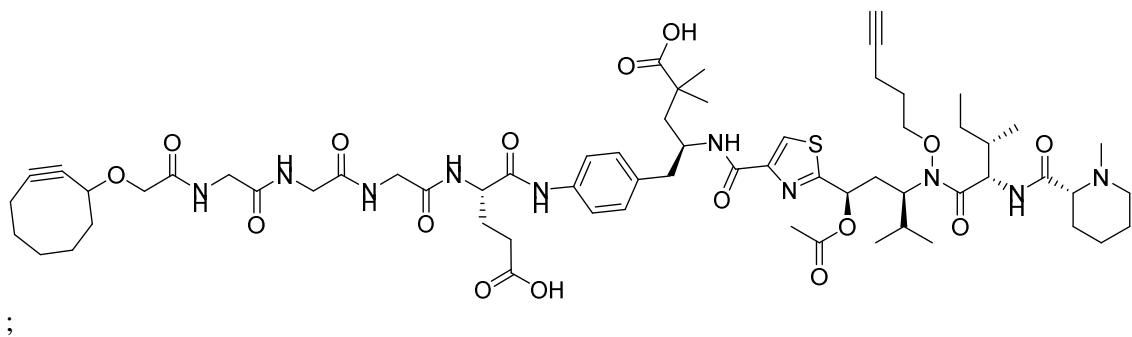
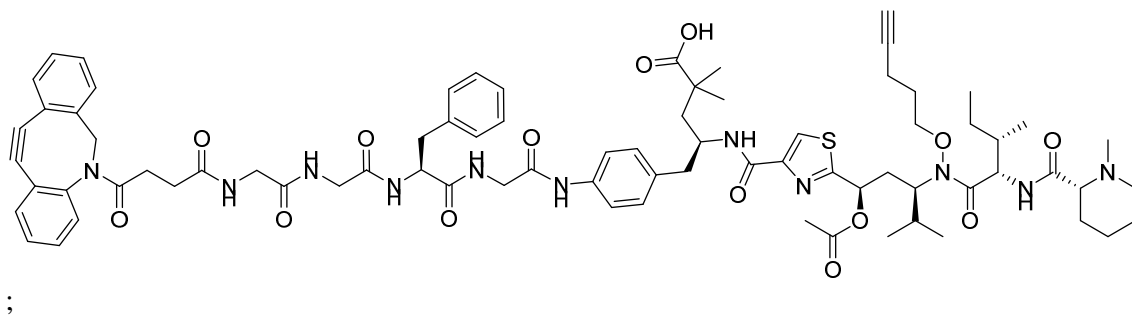
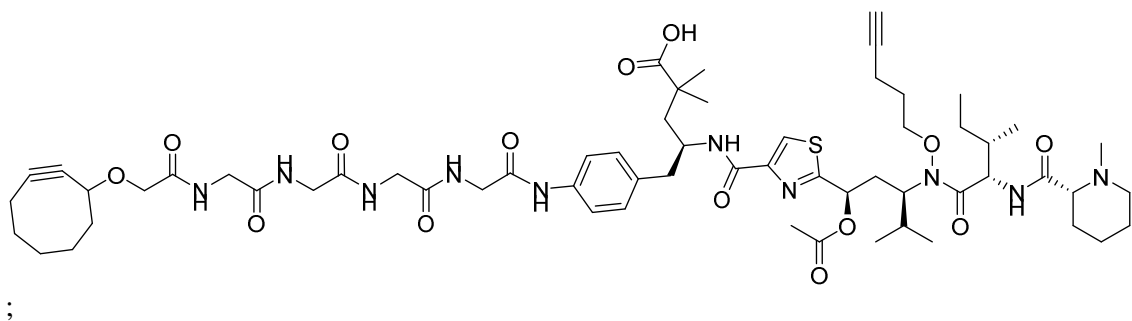
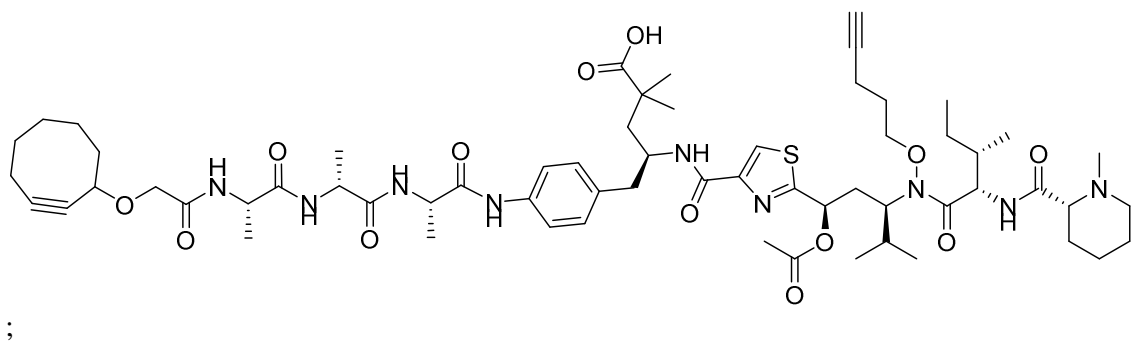
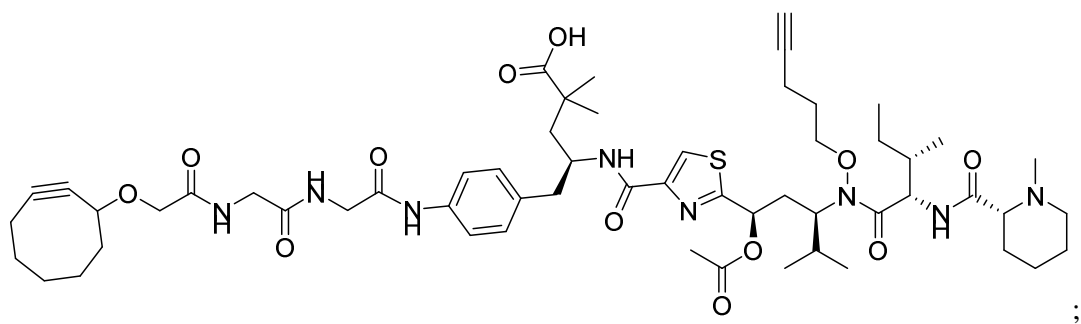
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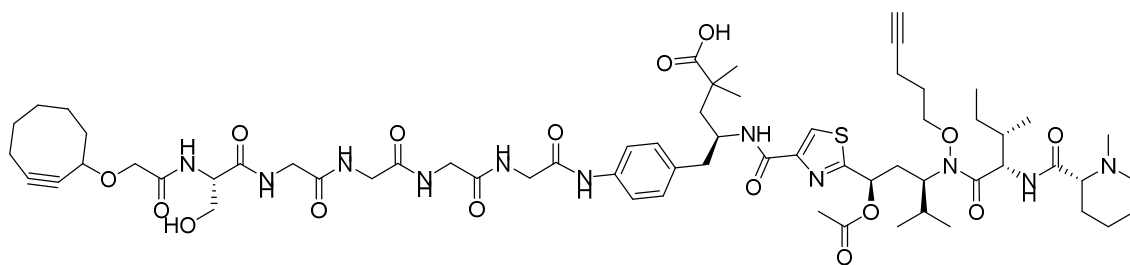


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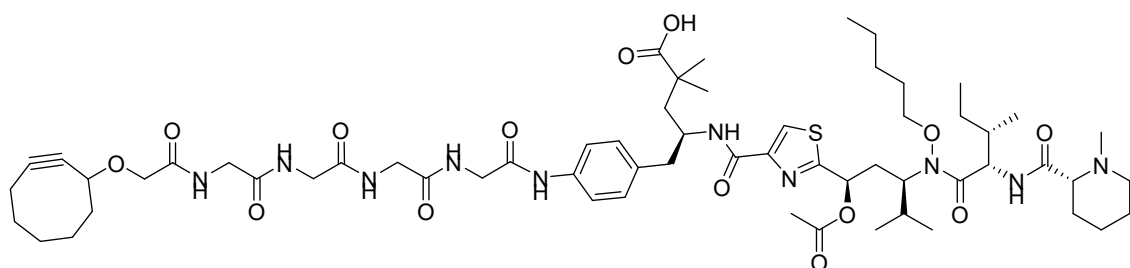


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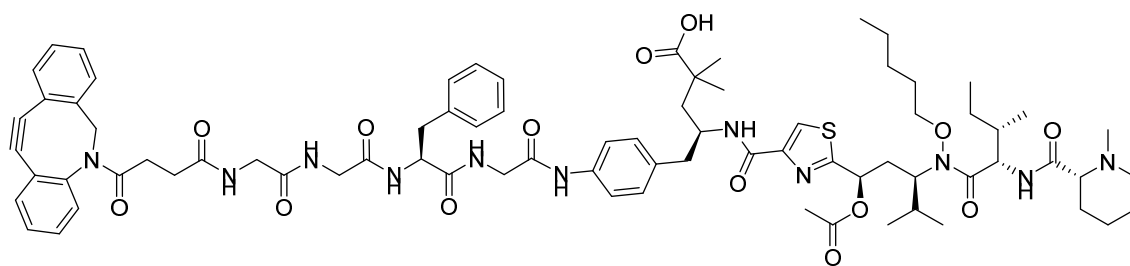




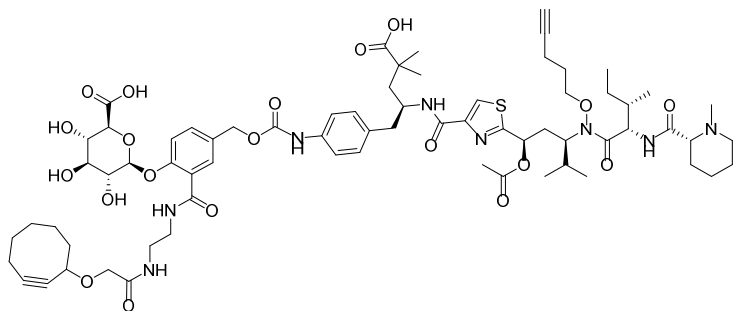
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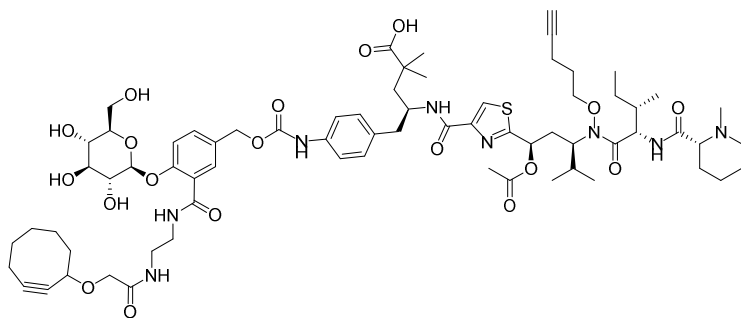
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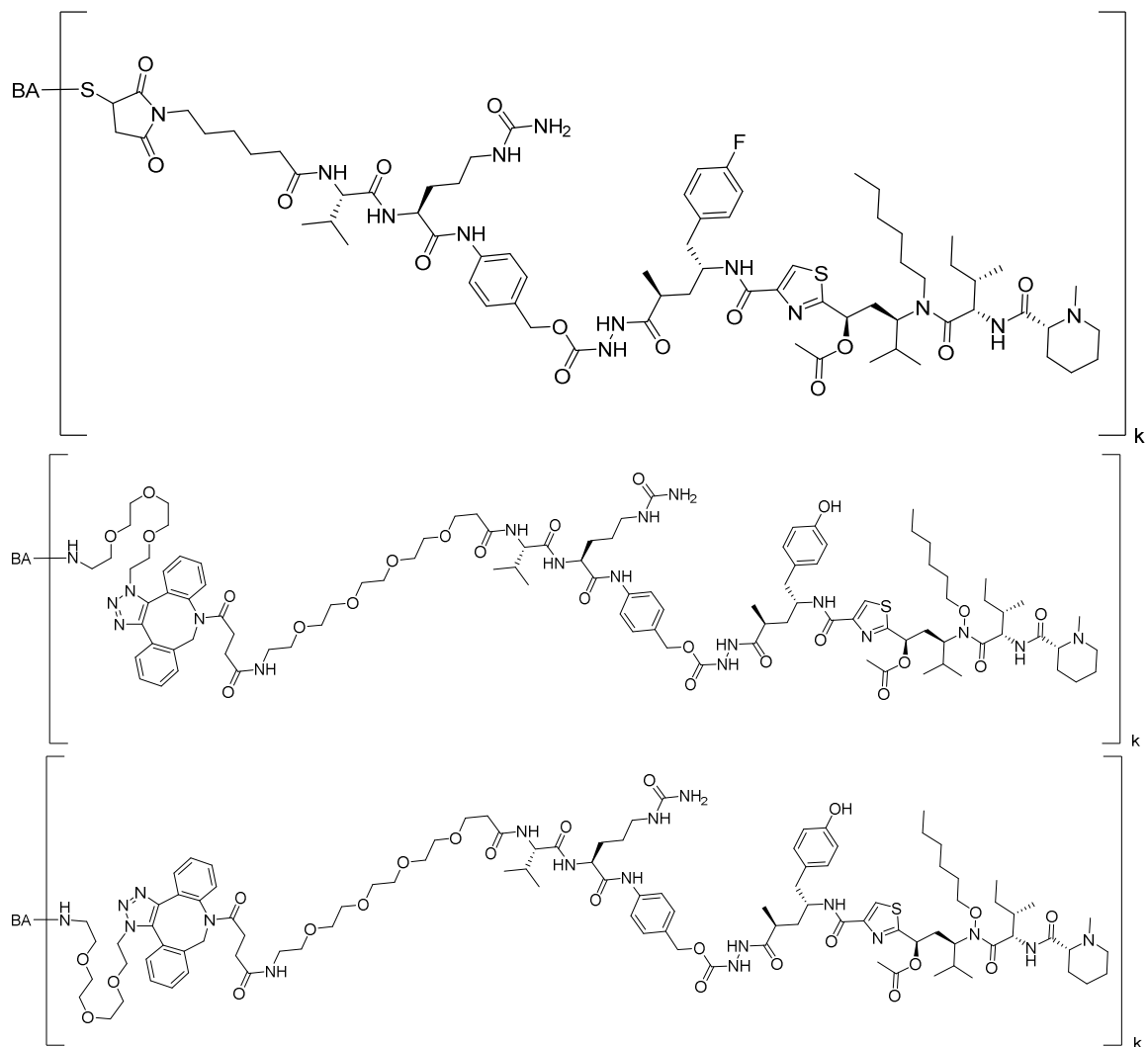
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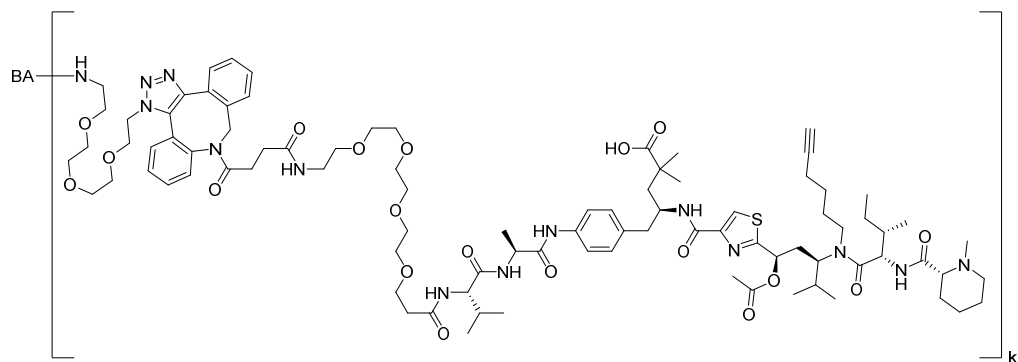
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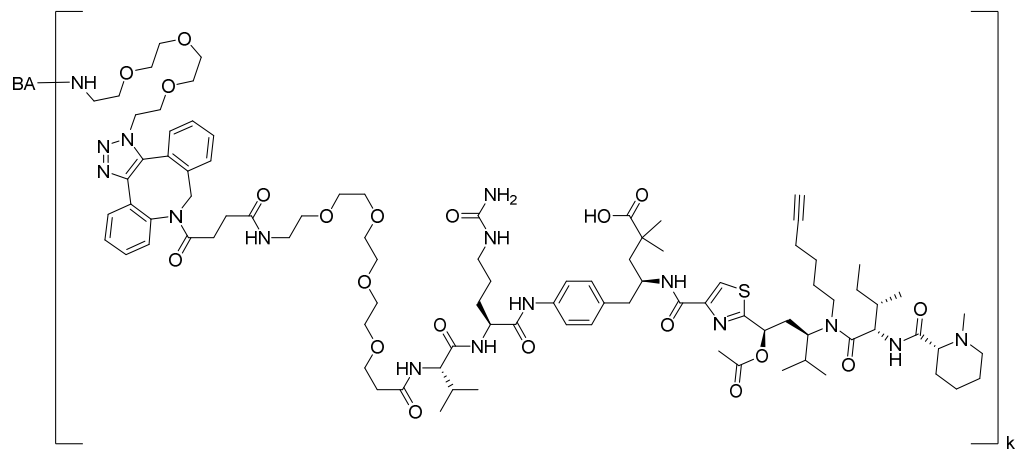
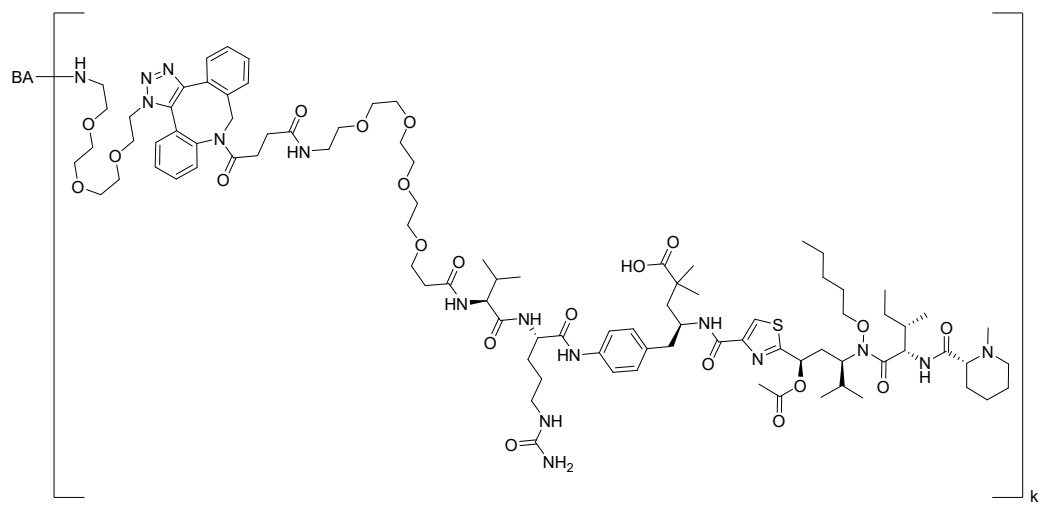
56. A method for preparing an antibody-drug conjugate comprising contacting a binding agent with a linker-payload of claim 54.

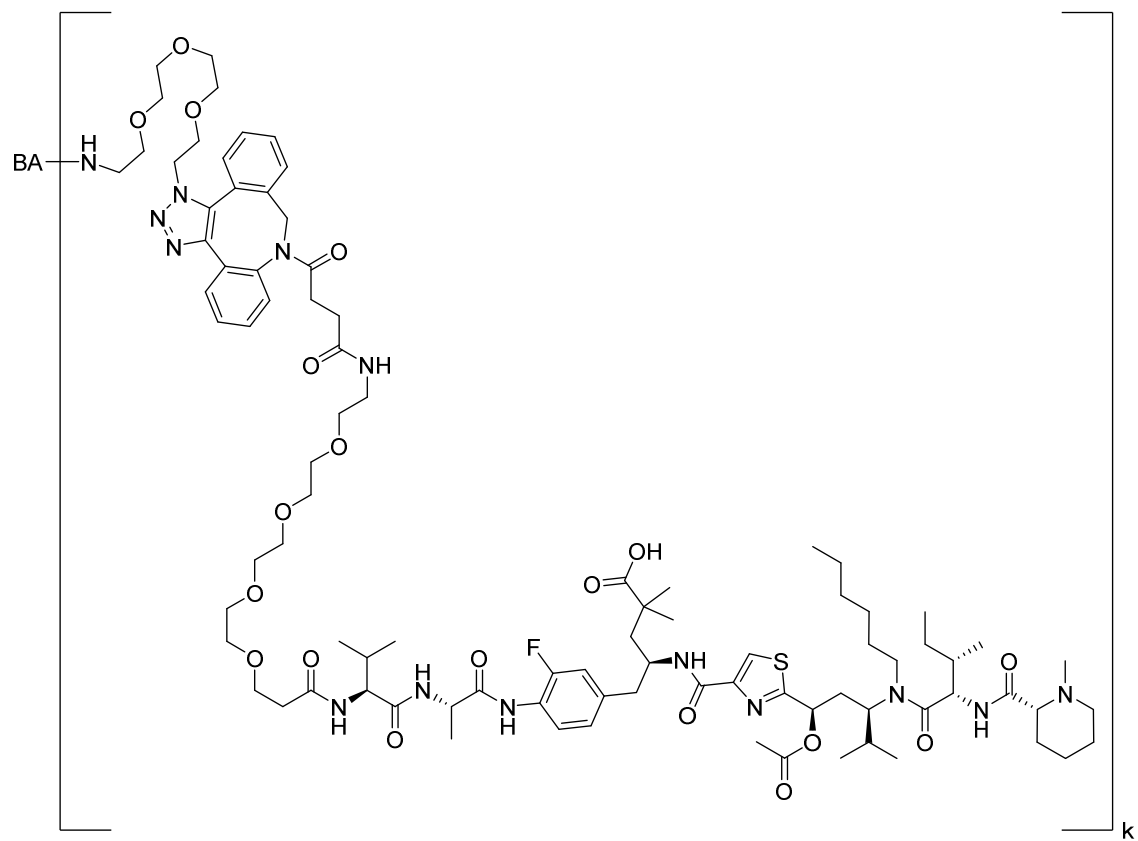
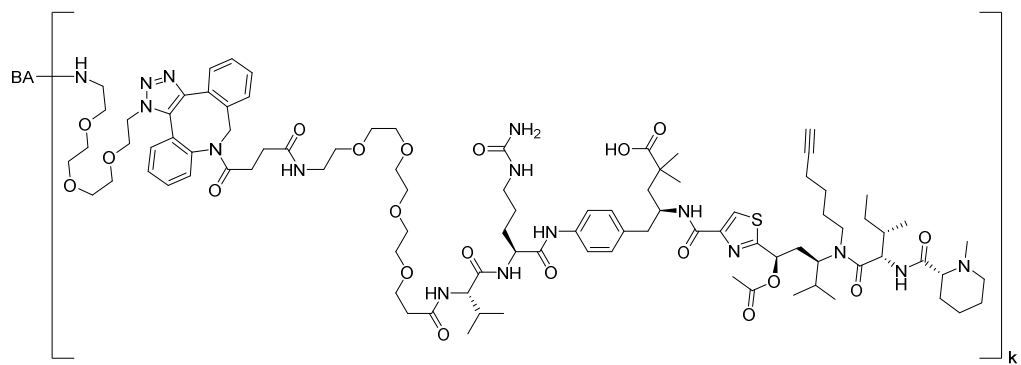
57. A compound selected from the group consisting of

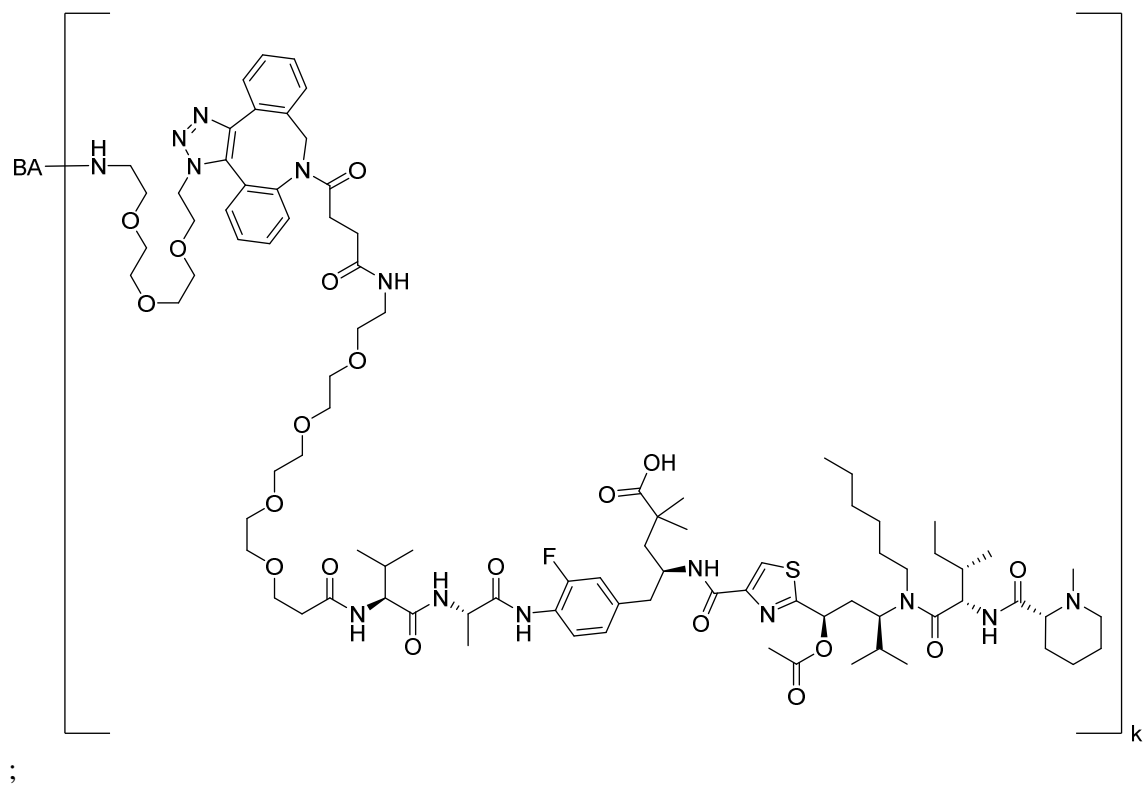


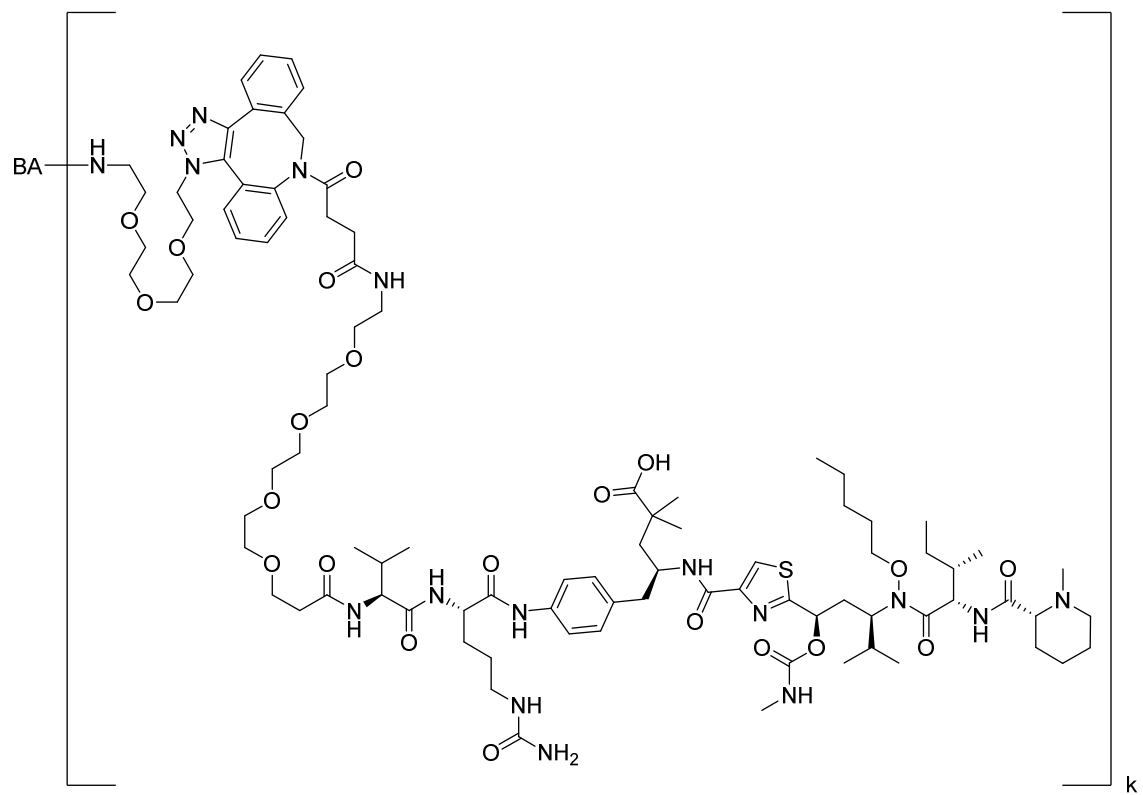
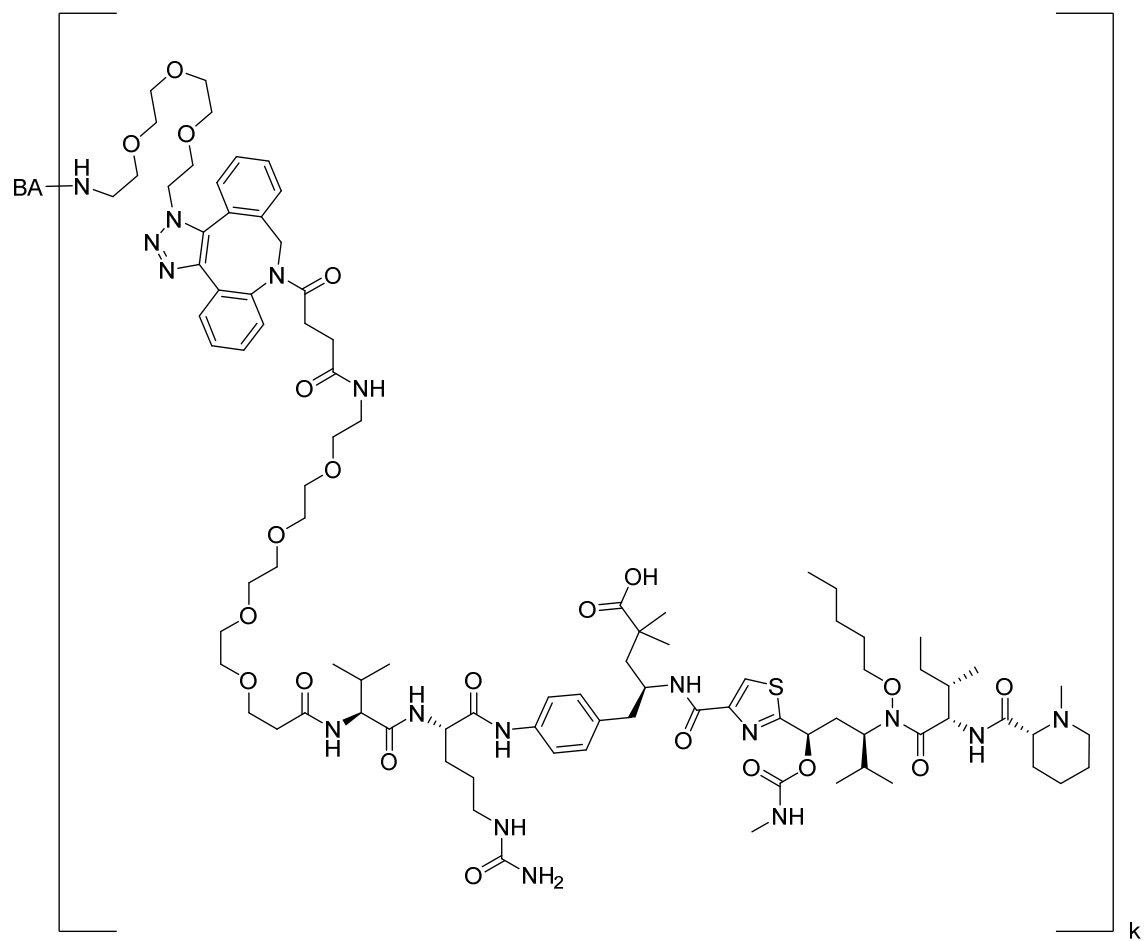




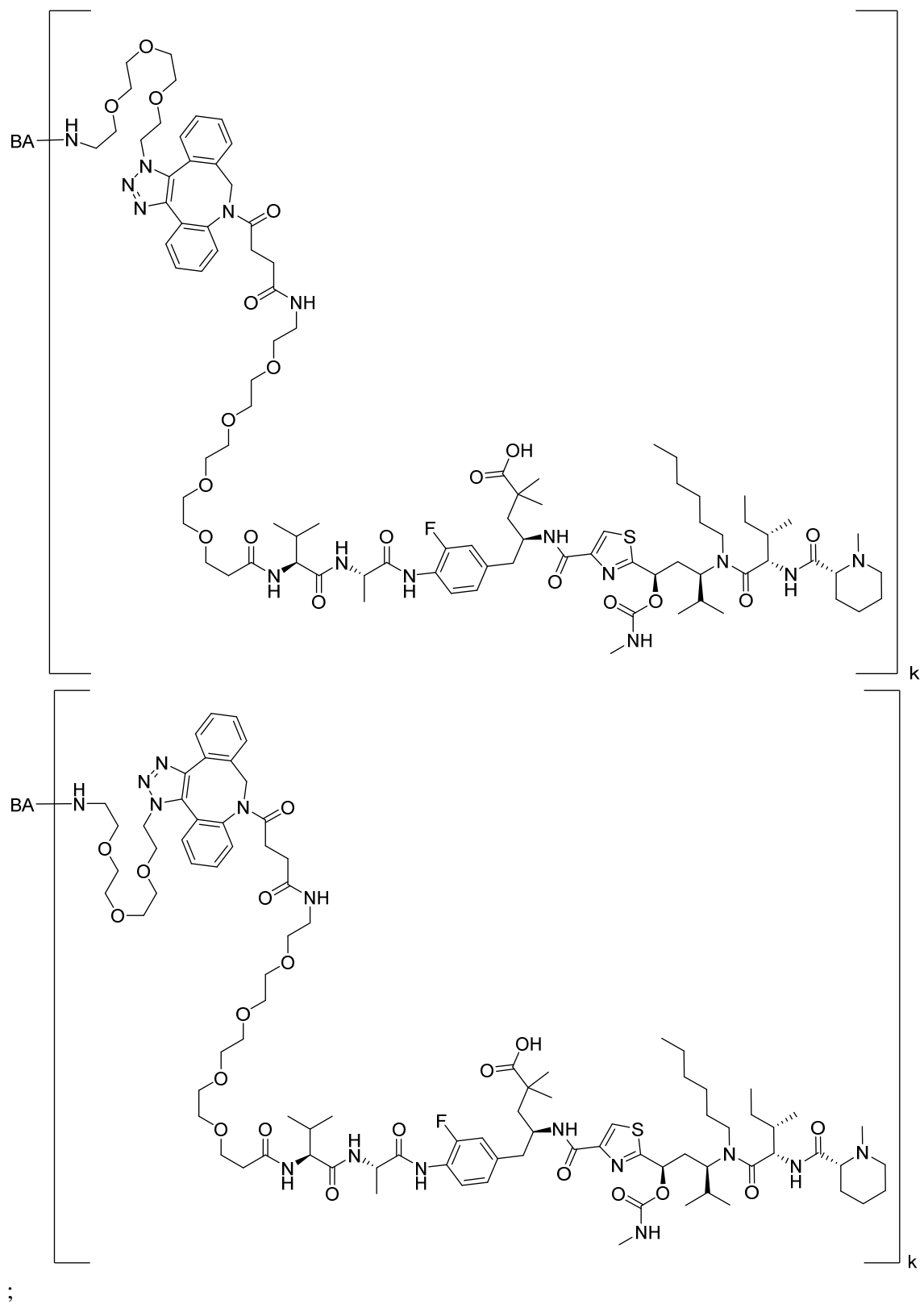


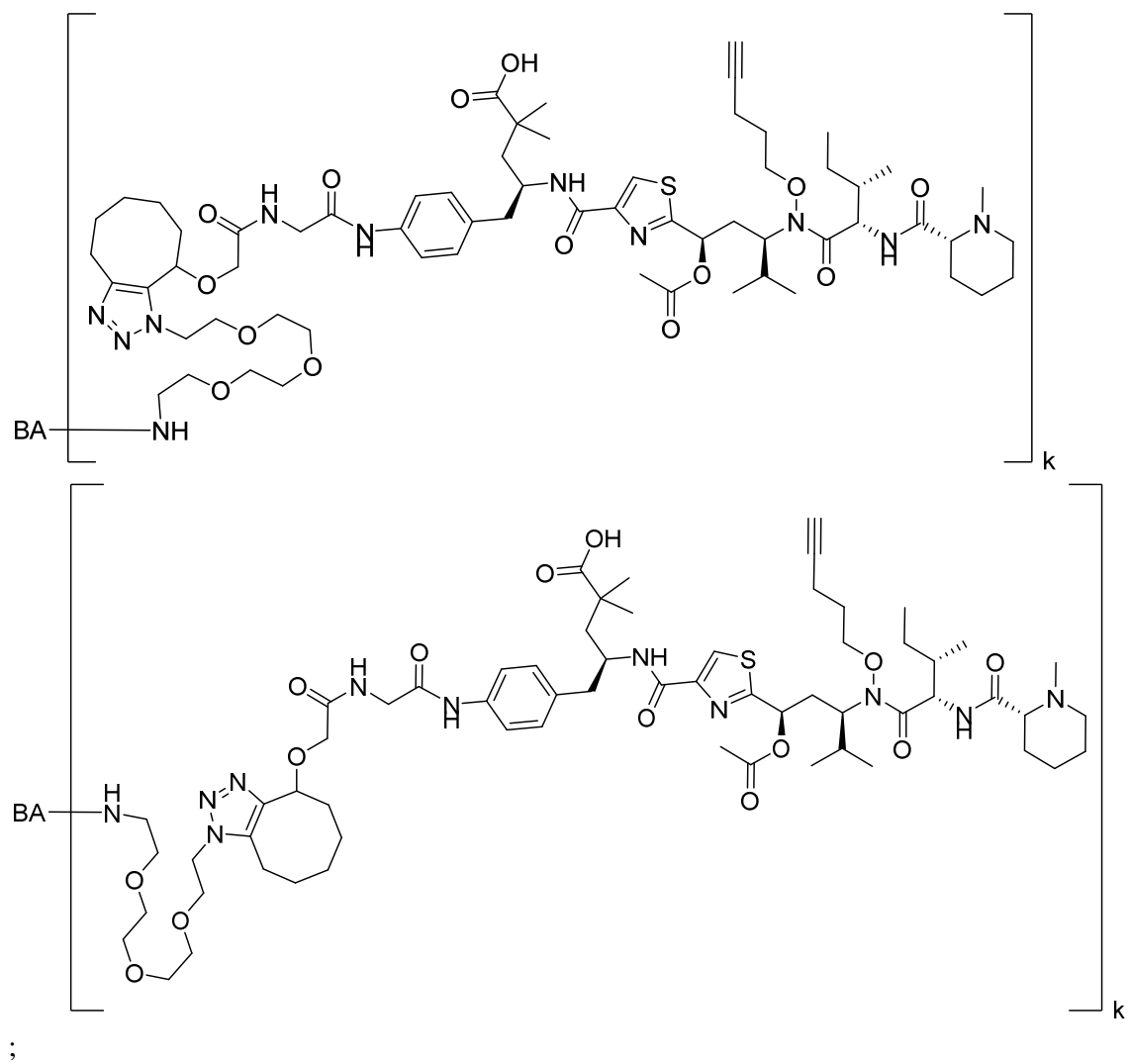


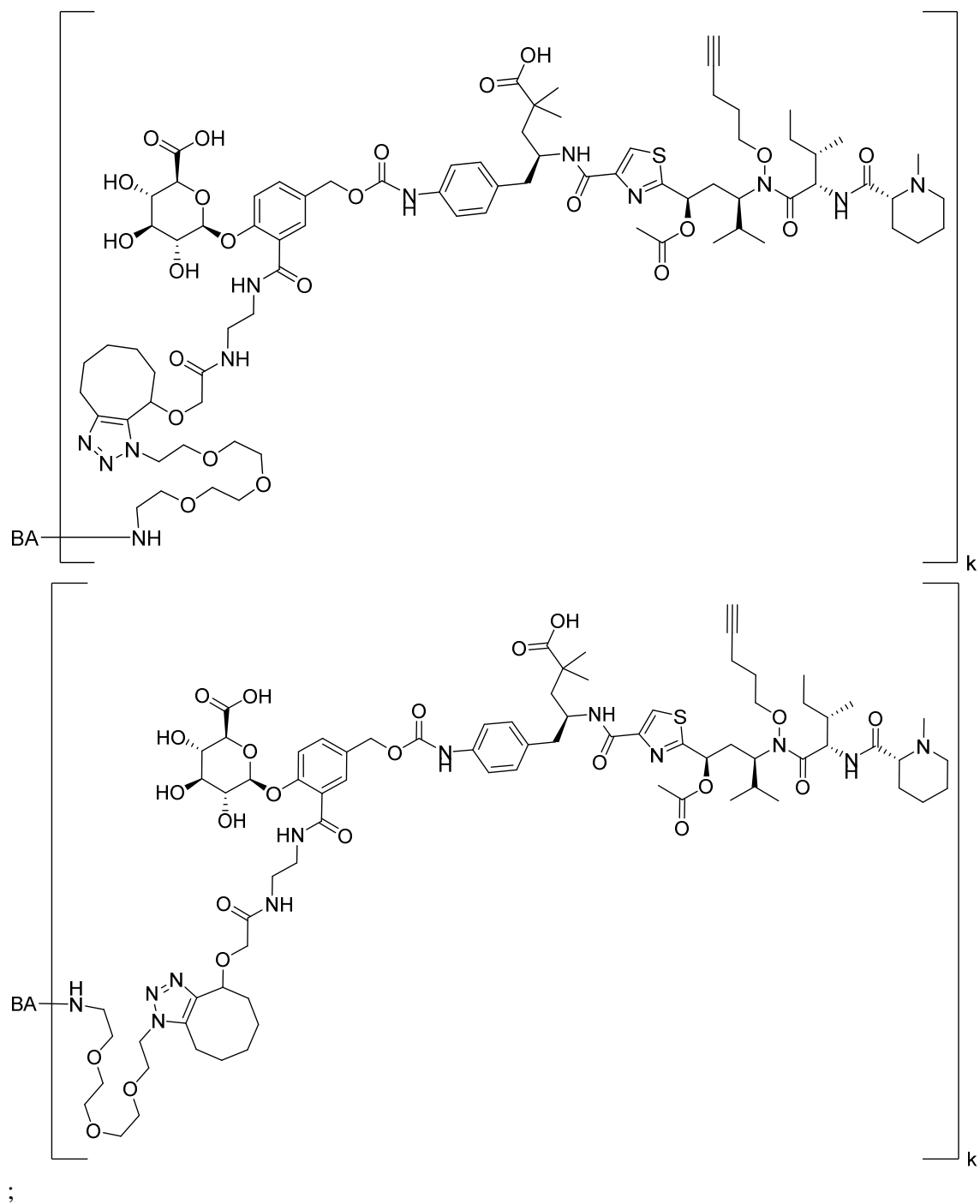


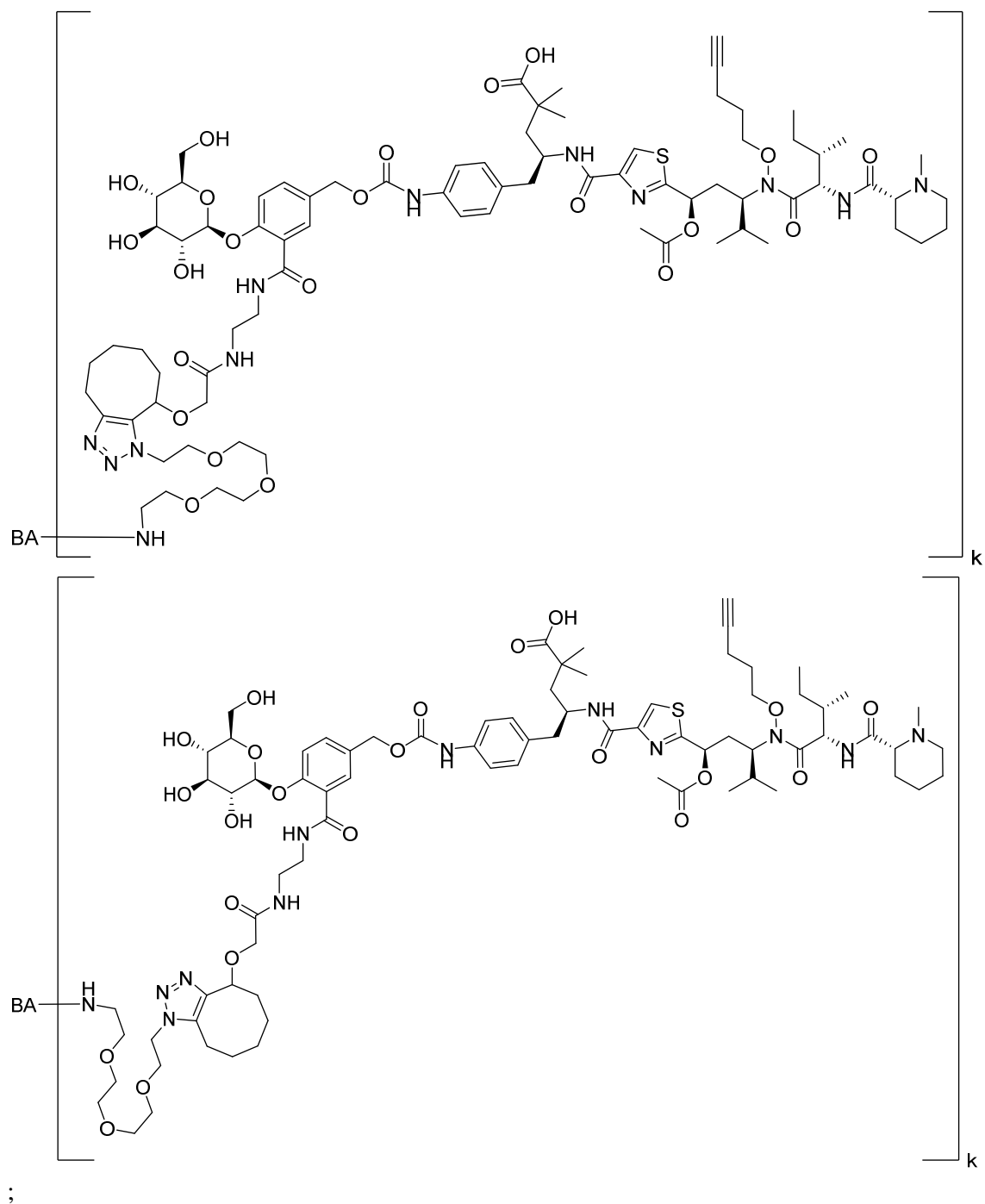








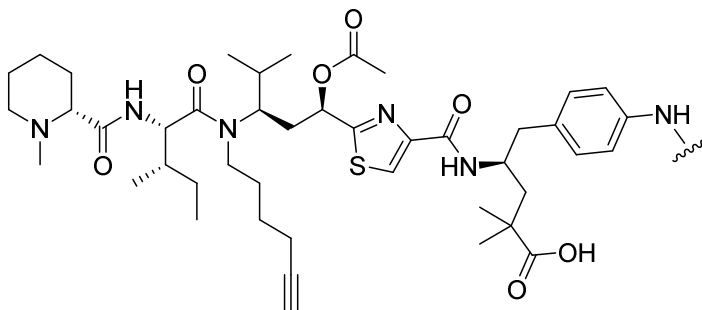


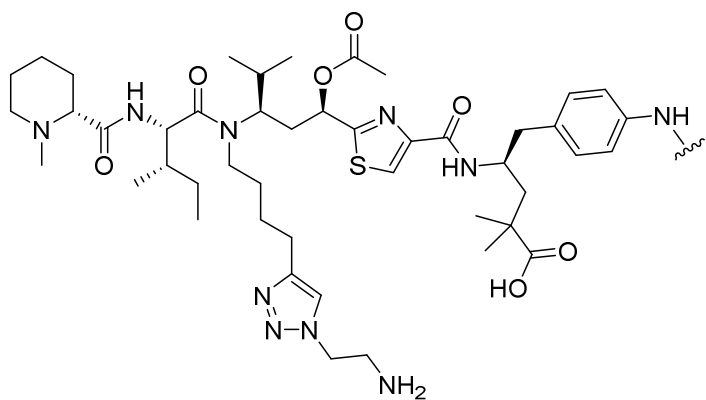
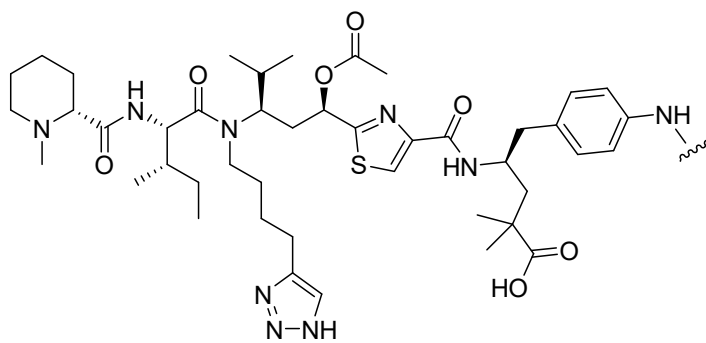
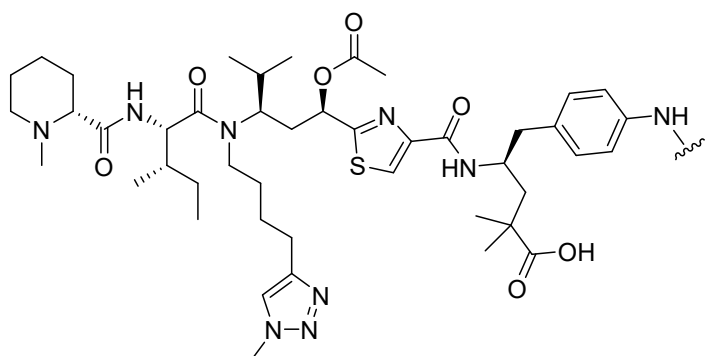
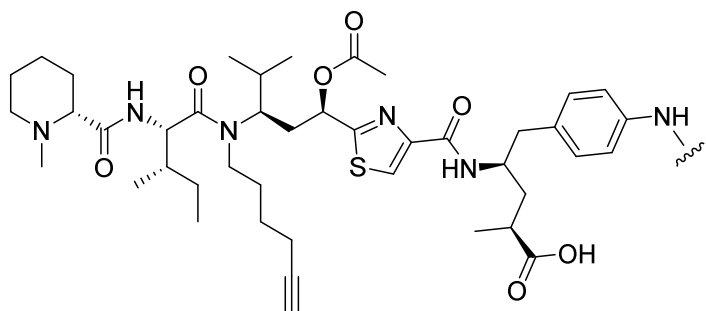


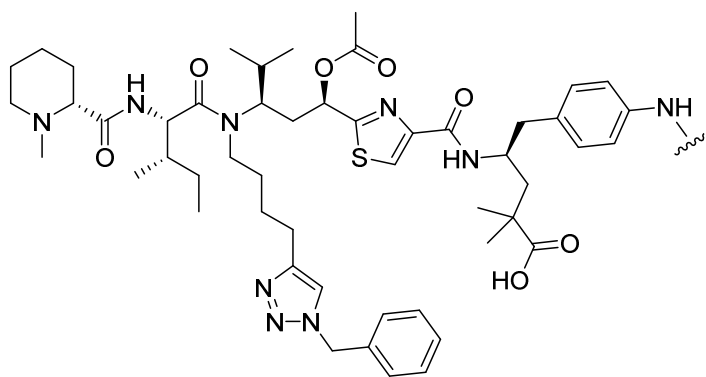
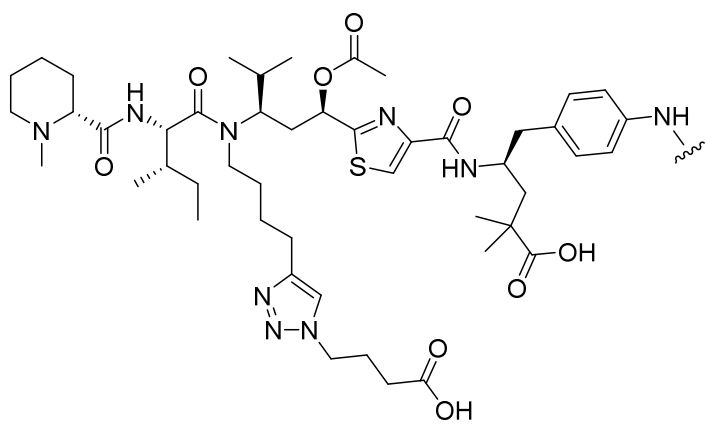
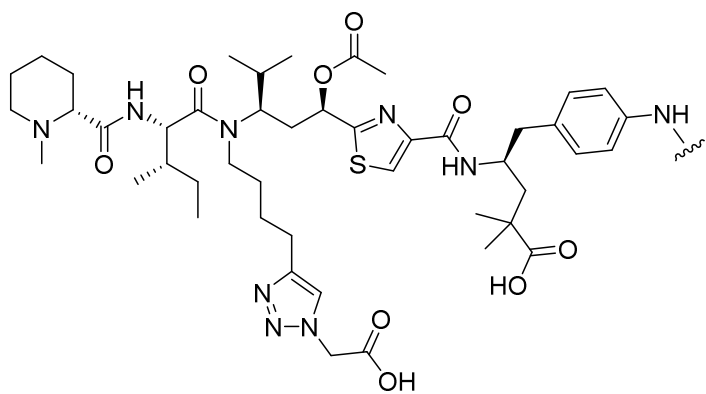
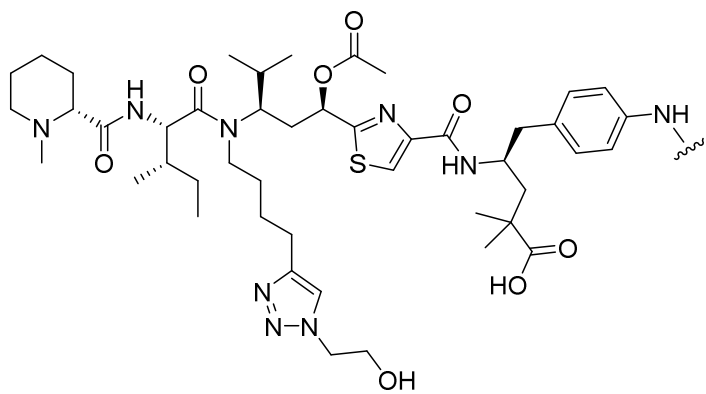
wherein **BA** is a binding agent; and **k** is one, two, three or four.

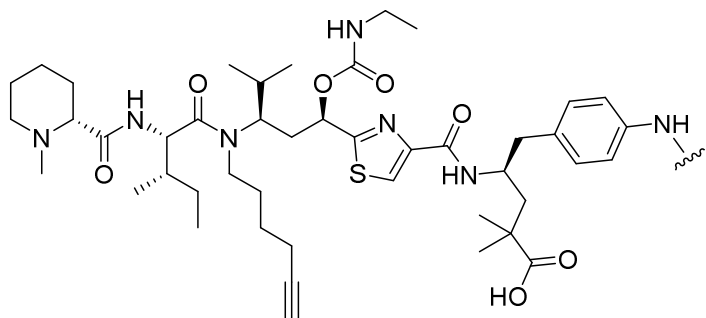
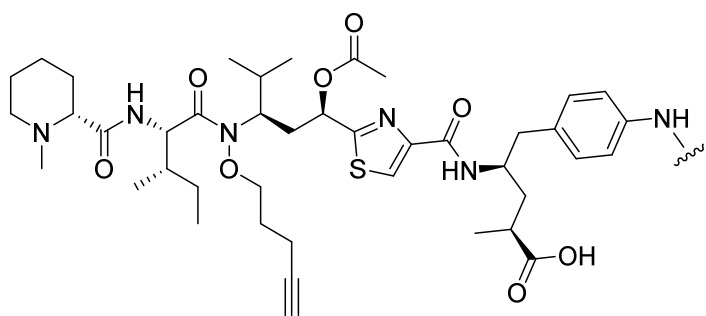
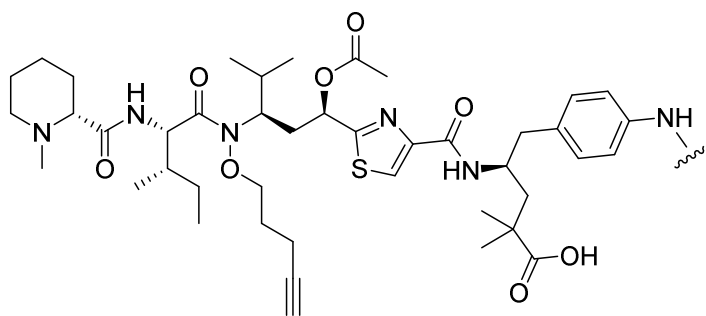
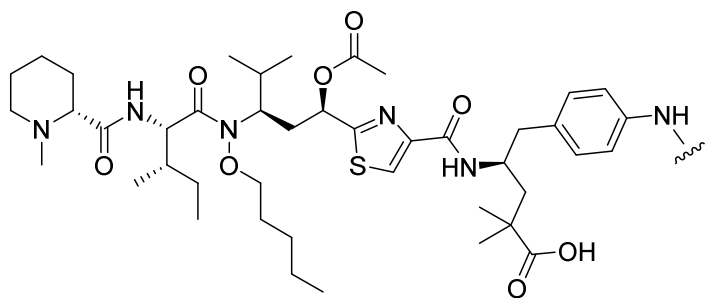
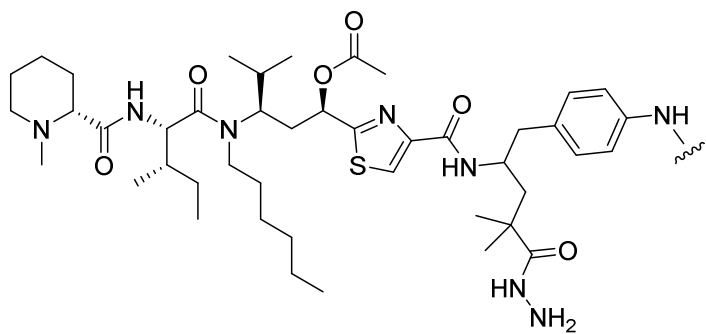
58. The compound of claim 57, wherein **BA** is an antibody or antigen-binding fragment thereof.

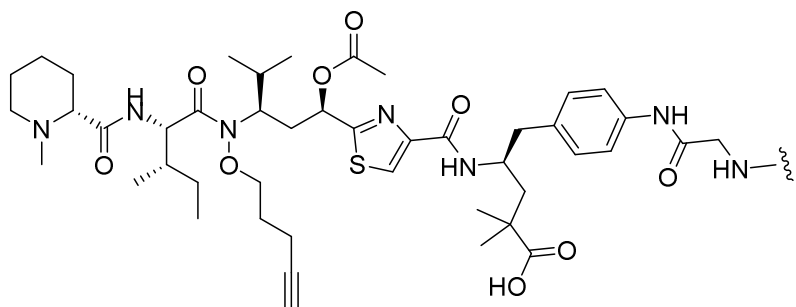
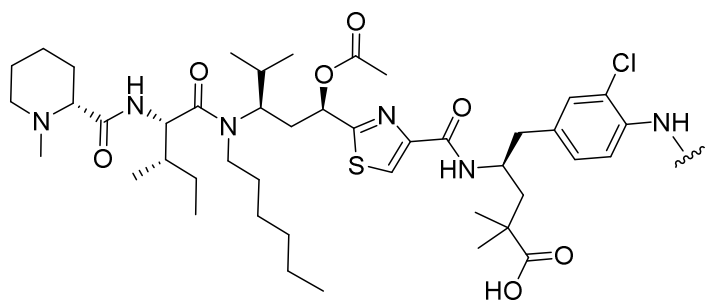
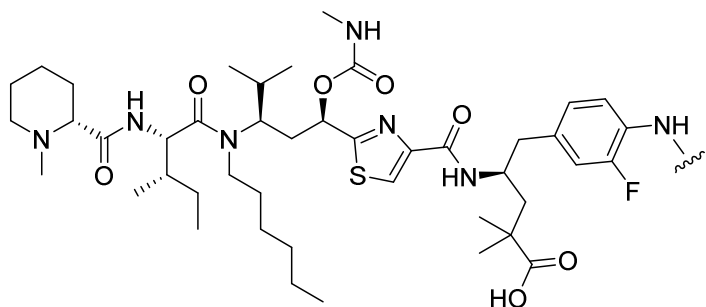
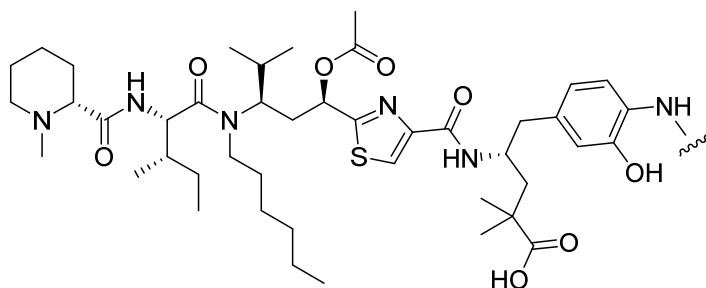
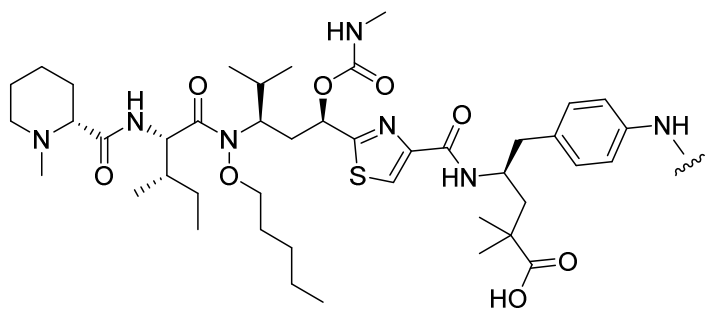
59. The compound of any one of claims 57 or 58, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least one glutamine residue used for conjugation.
60. The compound of any one of claims 57 or 58, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least two glutamine residues used for conjugation.
61. The compound of any one of claims 57 or 58, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof comprising at least four glutamine residues used for conjugation.
62. The compound of claim 61, wherein **BA** is a transglutaminase-modified antibody or antigen-binding fragment thereof wherein conjugation is at two Q295 residues; and **k** is two.
63. The compound of claim 61, 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.
64. An antibody-drug conjugate comprising an antibody or antigen-binding fragment thereof conjugated to a compound of claim 7 selected from the group consisting of



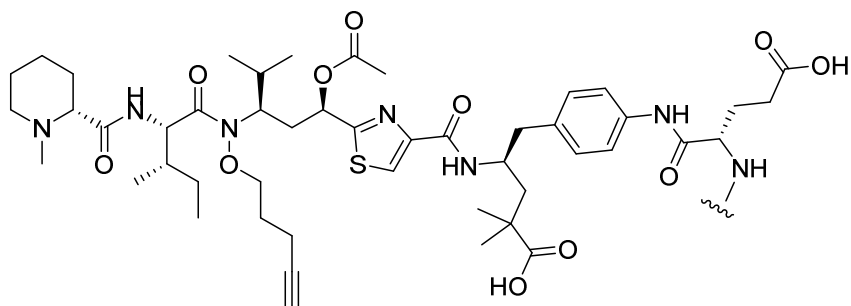






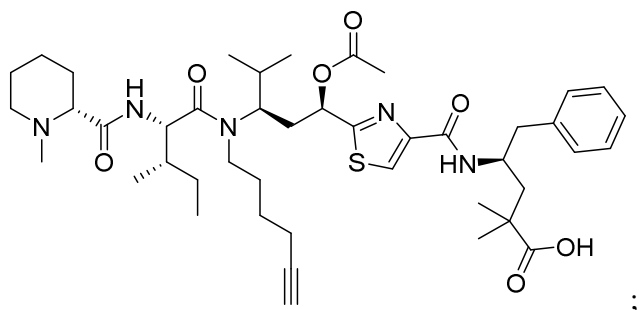
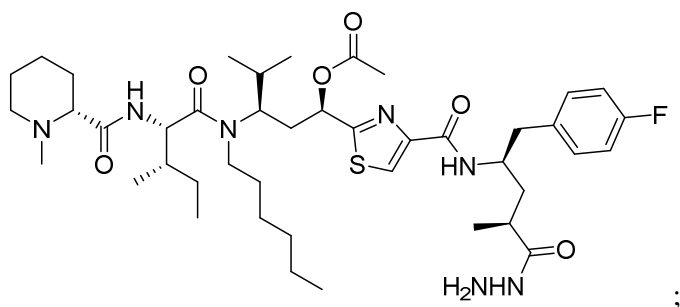
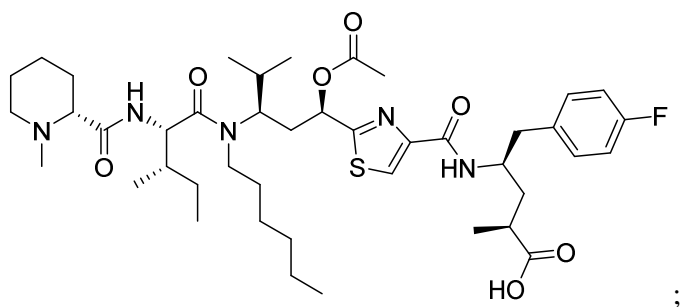


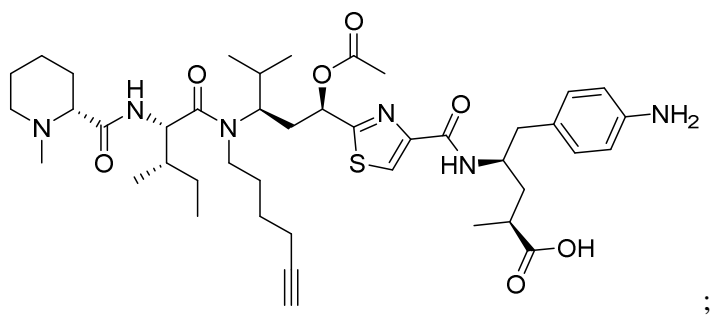
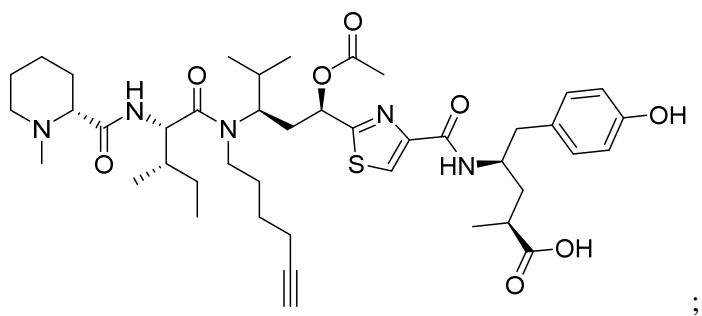
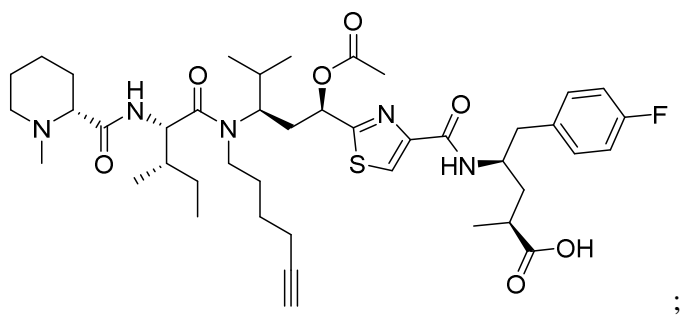
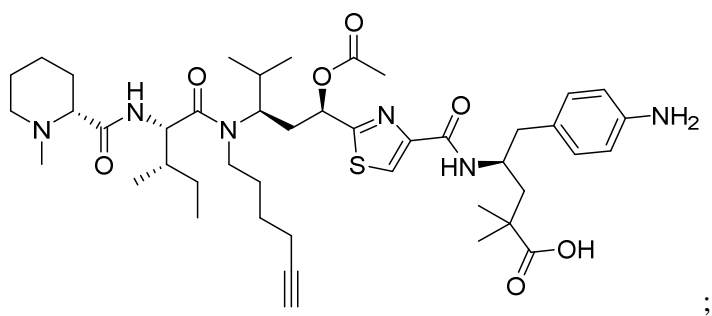
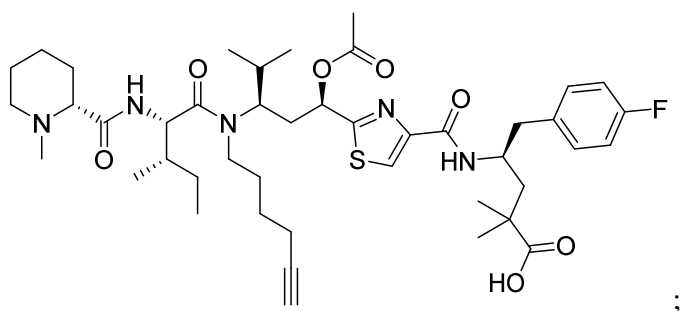
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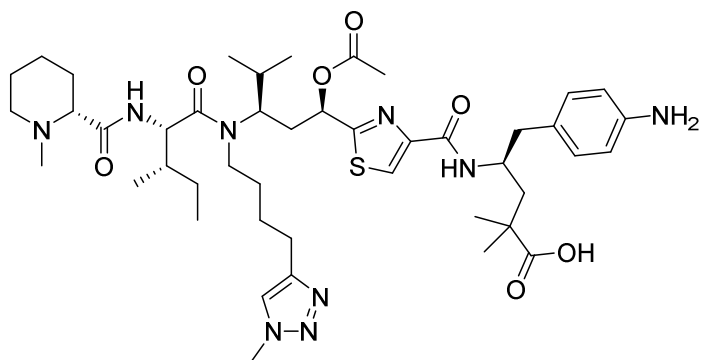


65. The compound of any one of claims 57-64, wherein **BA** or the antibody or antigen-binding fragment thereof is anti-PRLR or anti-STEAP2.

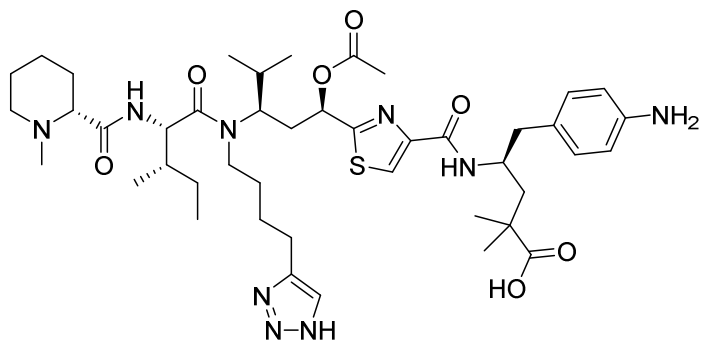
66. The compound of claim 7, wherein the compound is selected from the group consisting of



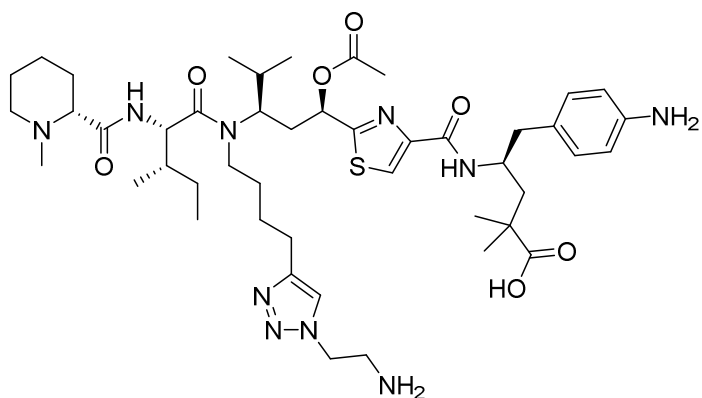




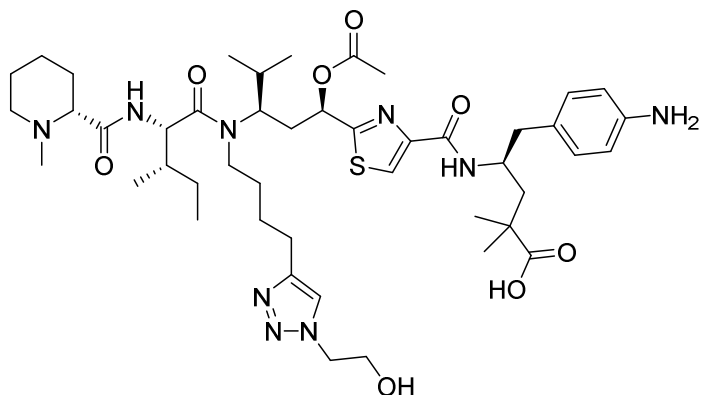
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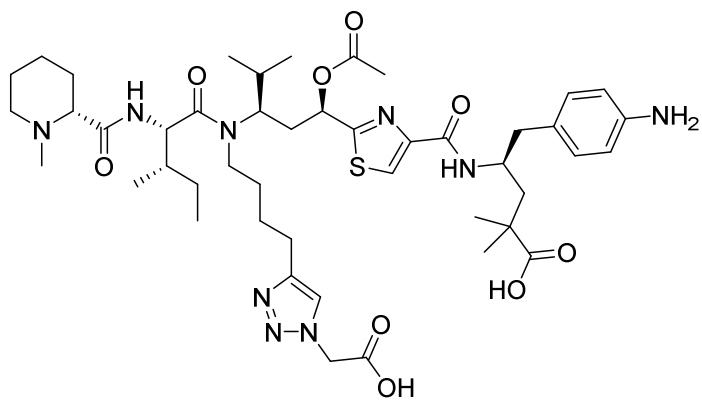
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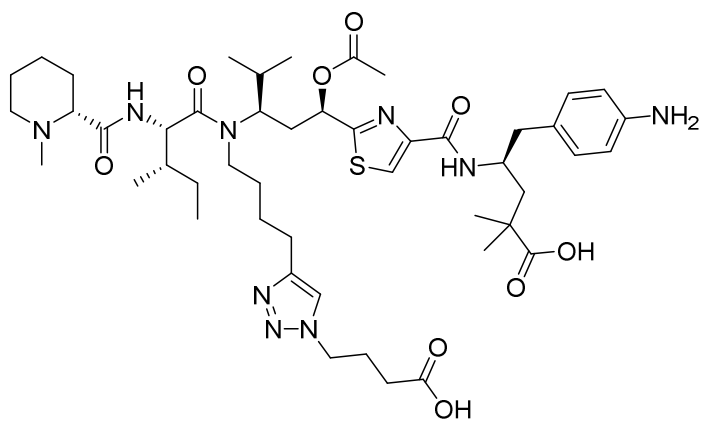
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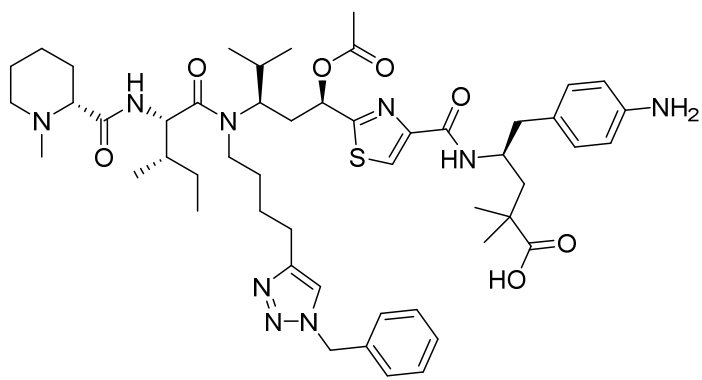
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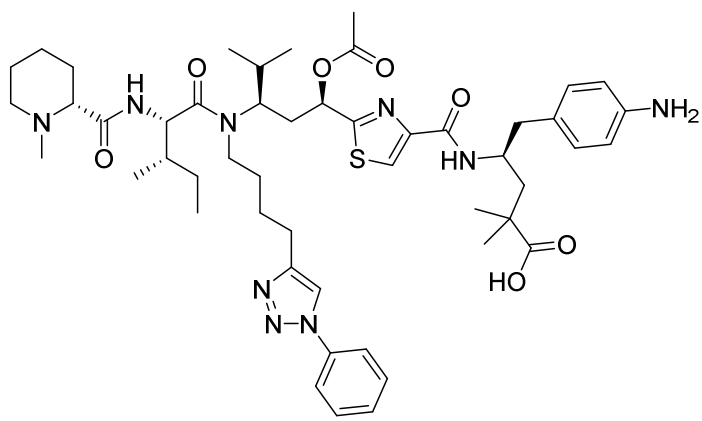
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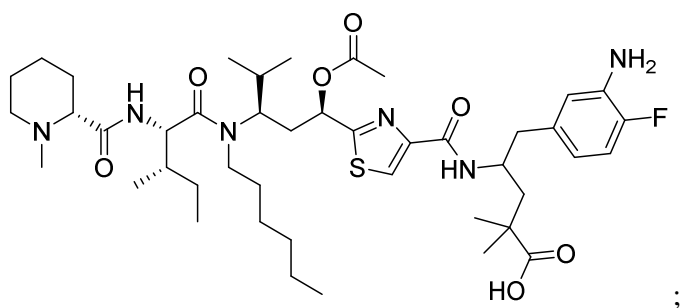
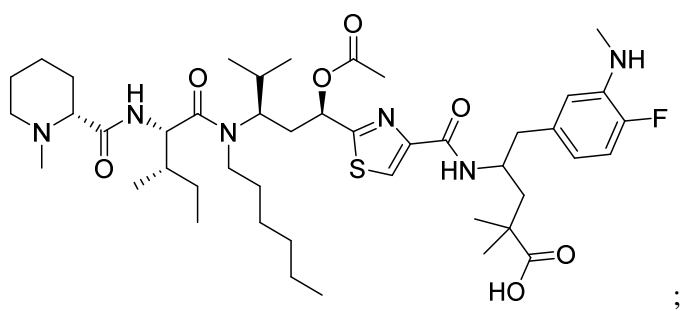
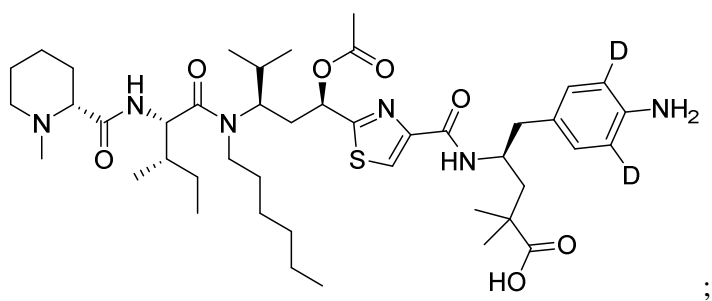
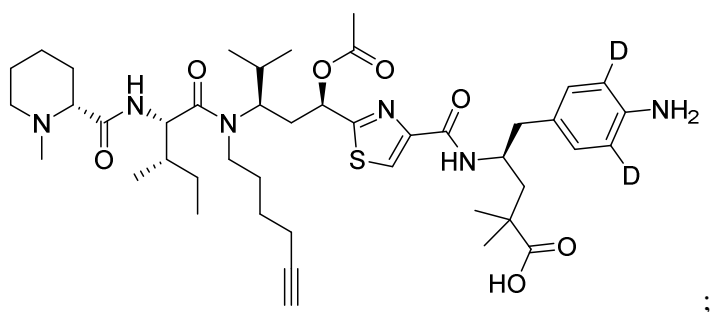
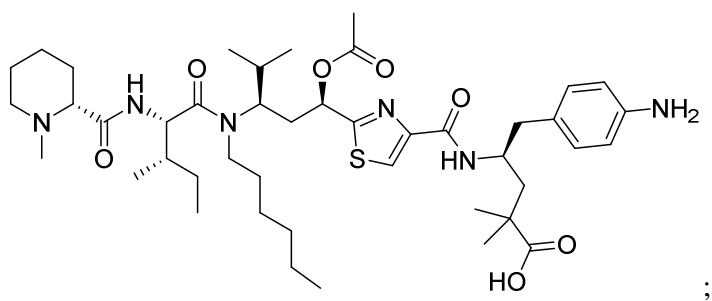
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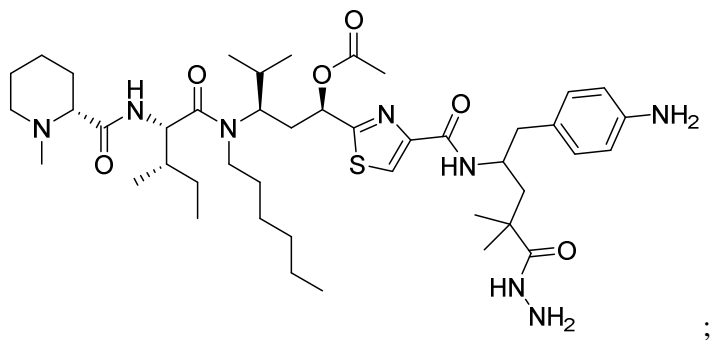
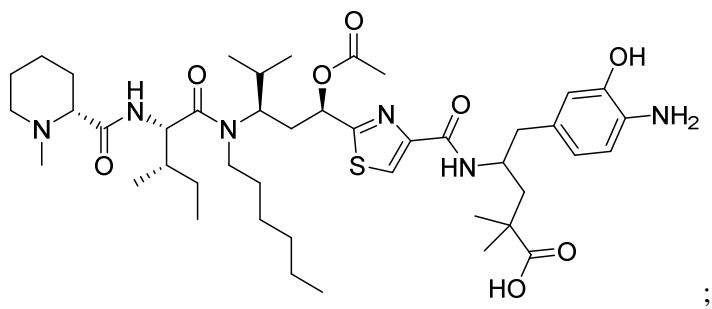
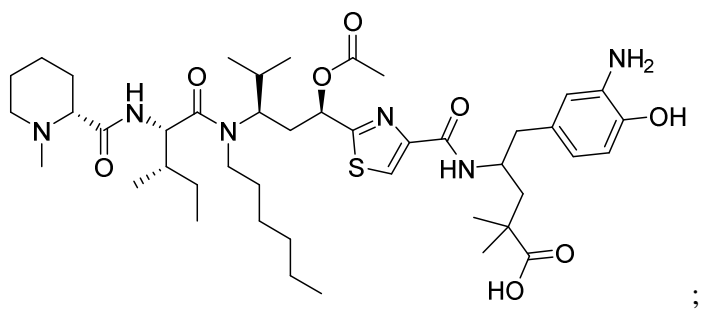
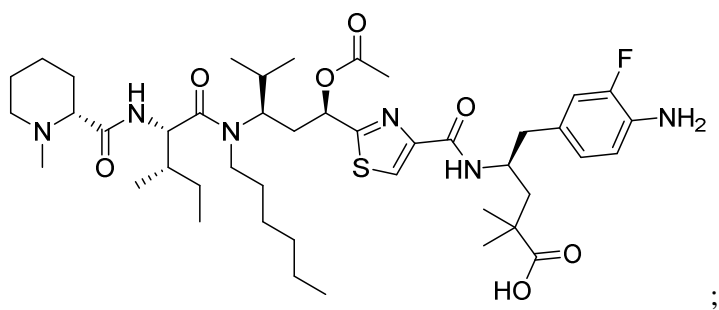
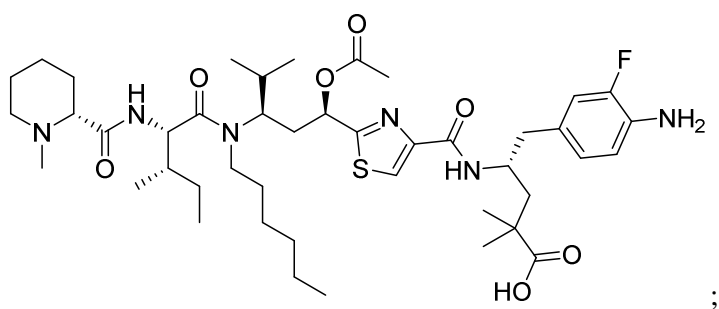


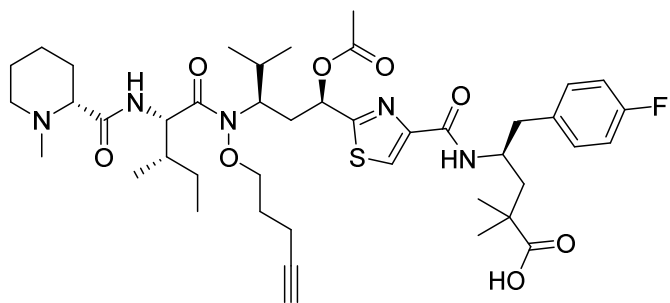
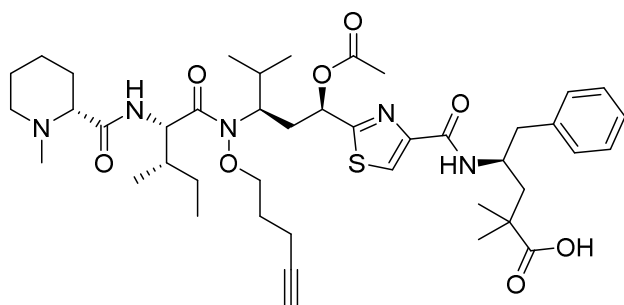
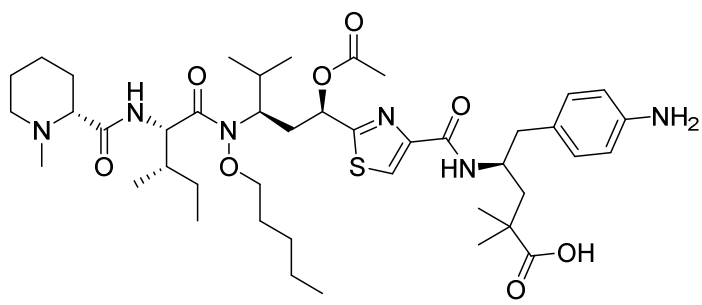
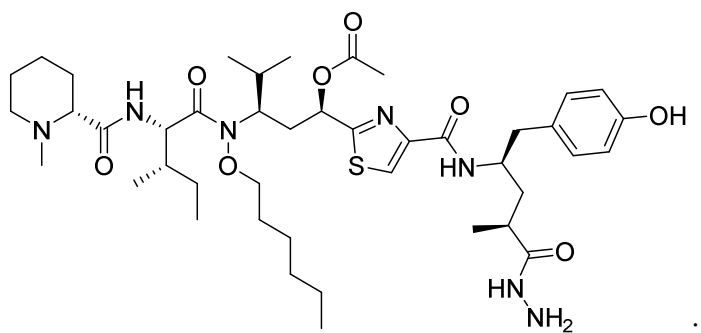
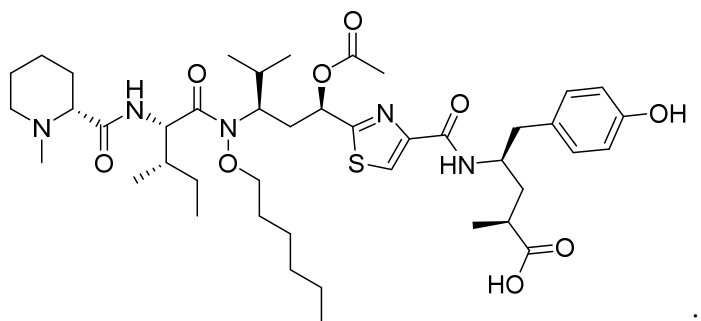
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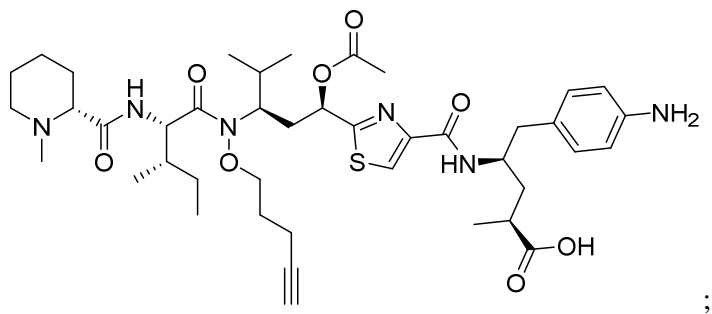
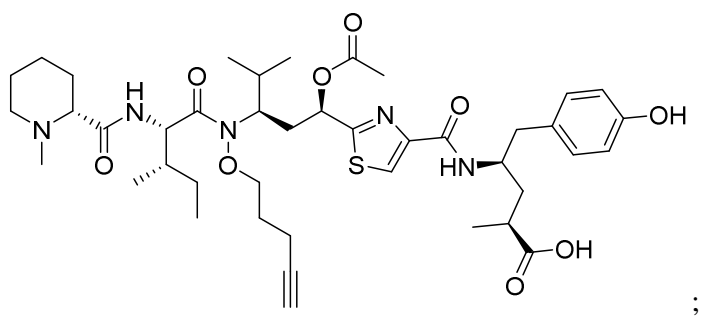
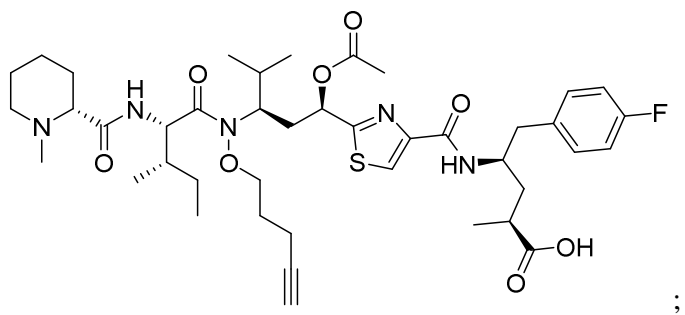
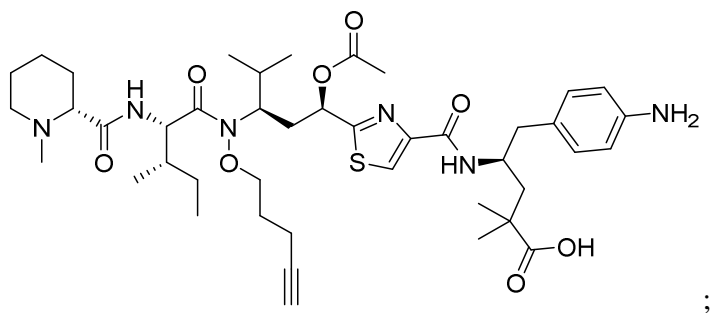


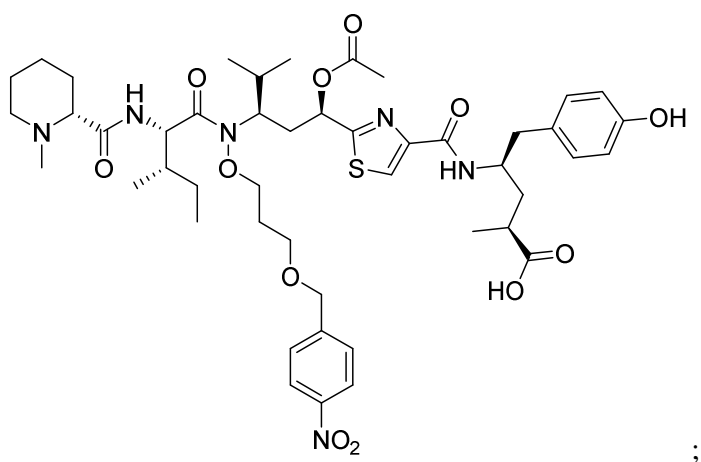
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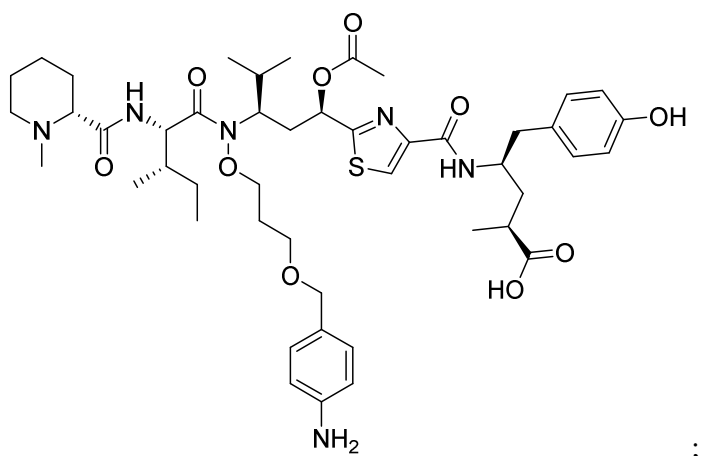




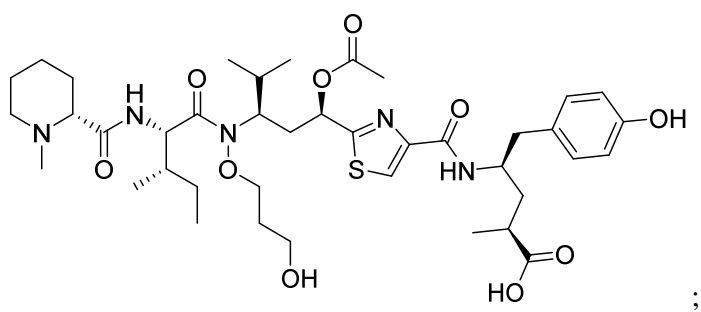




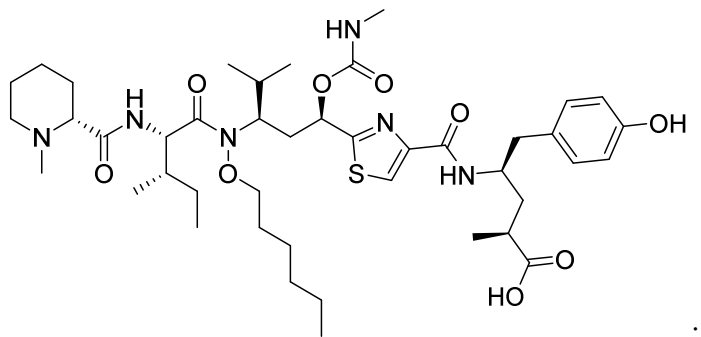
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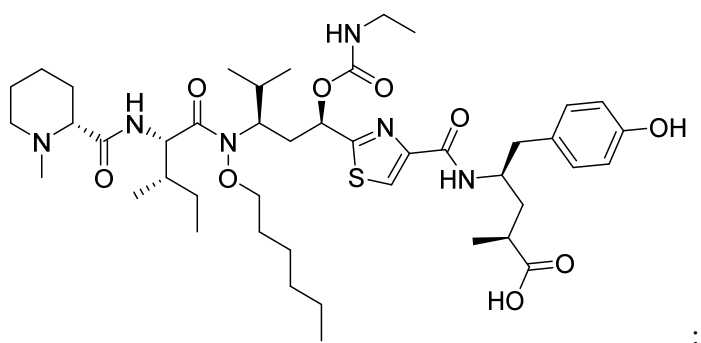
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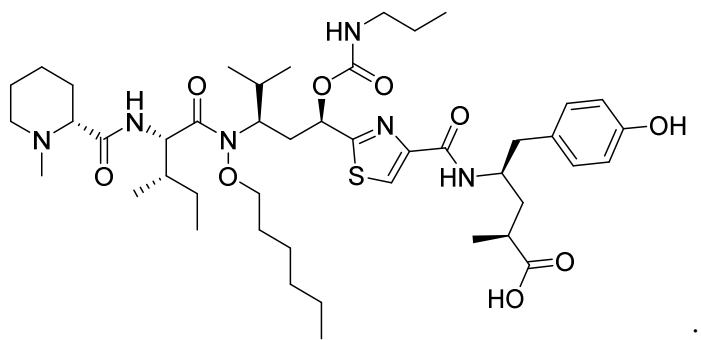
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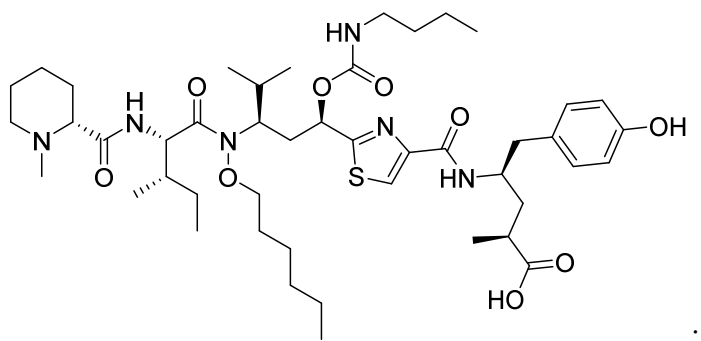
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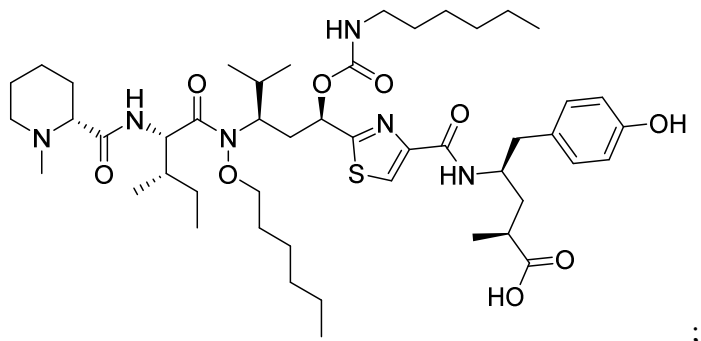
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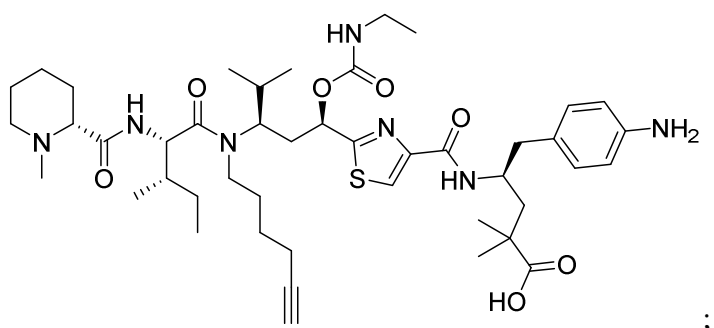
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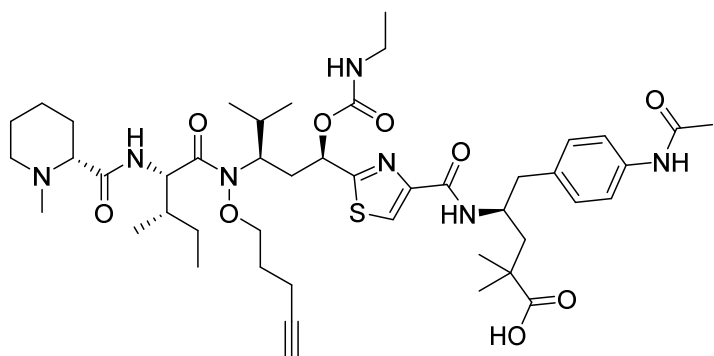
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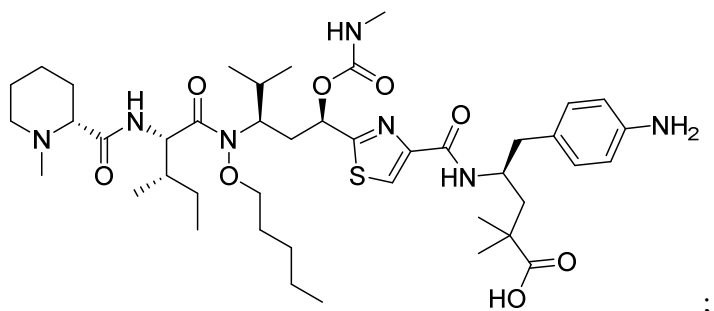
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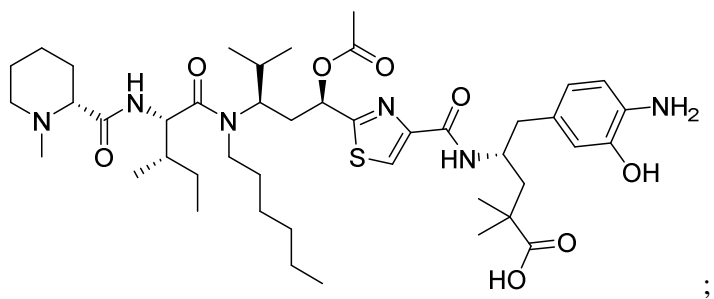
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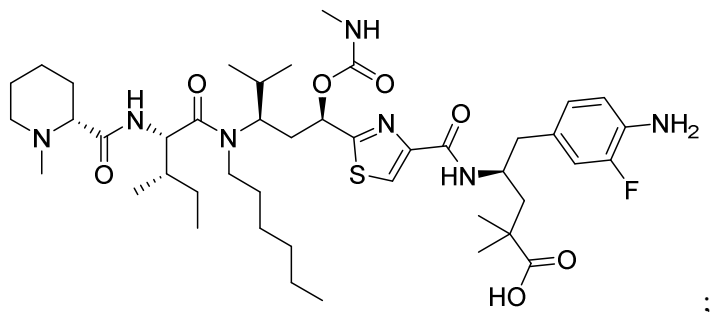
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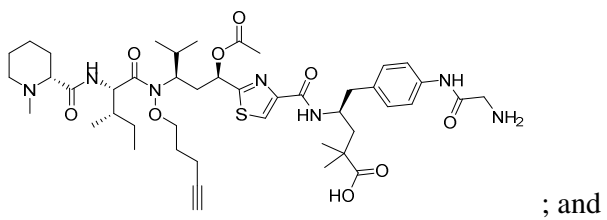
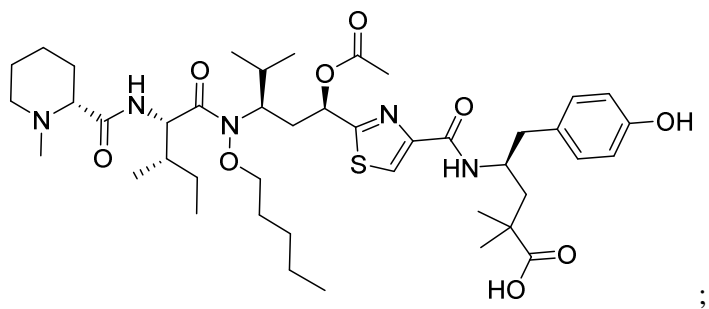
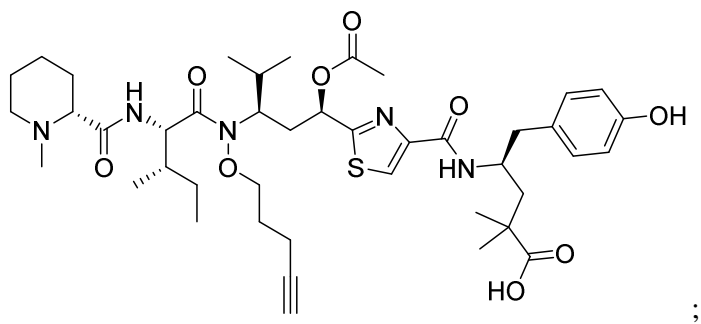
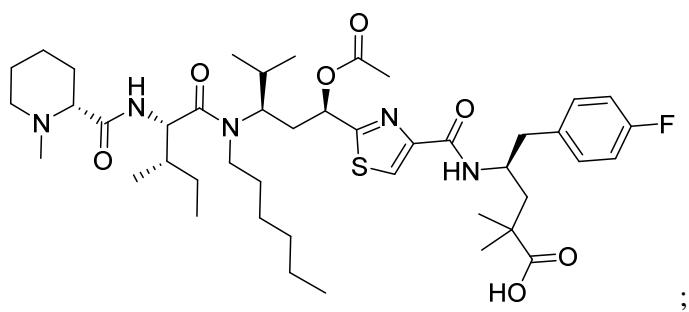
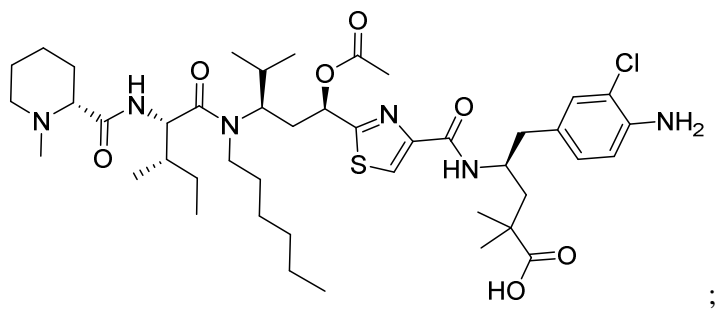
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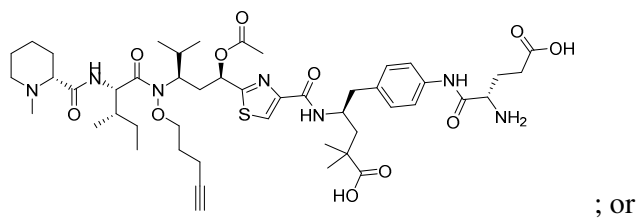


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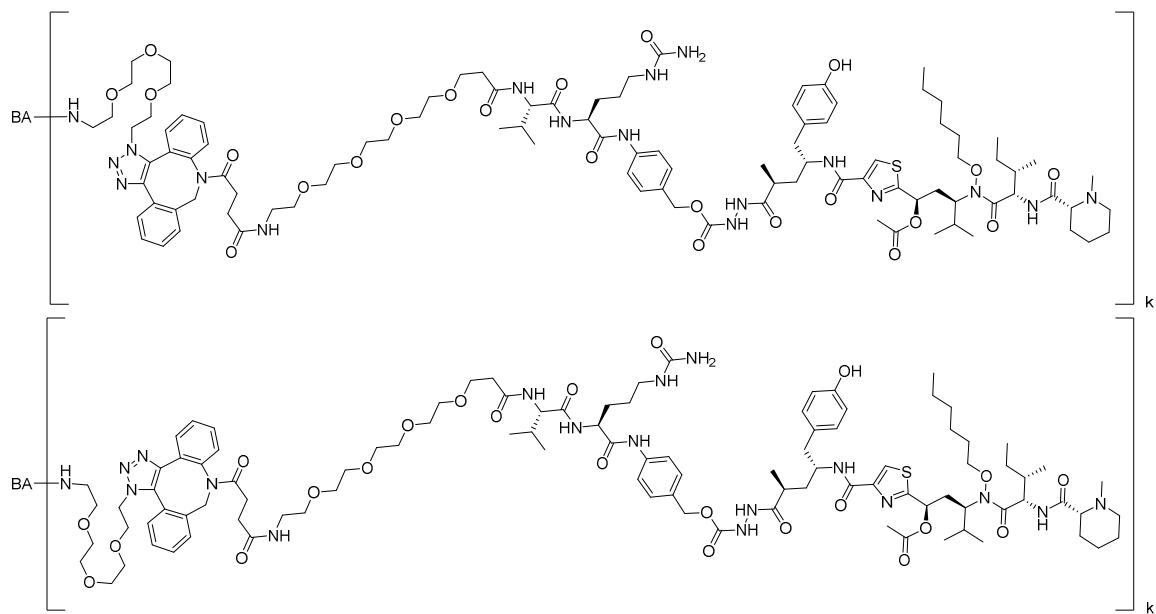
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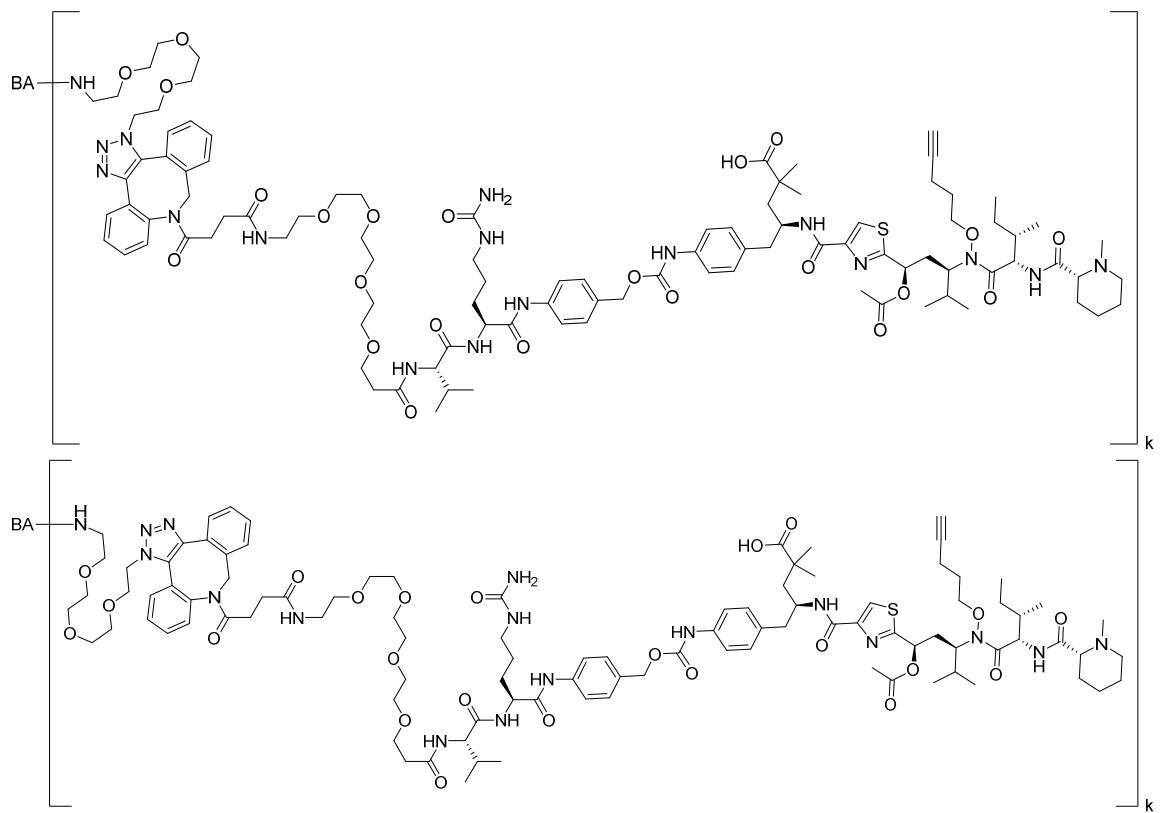
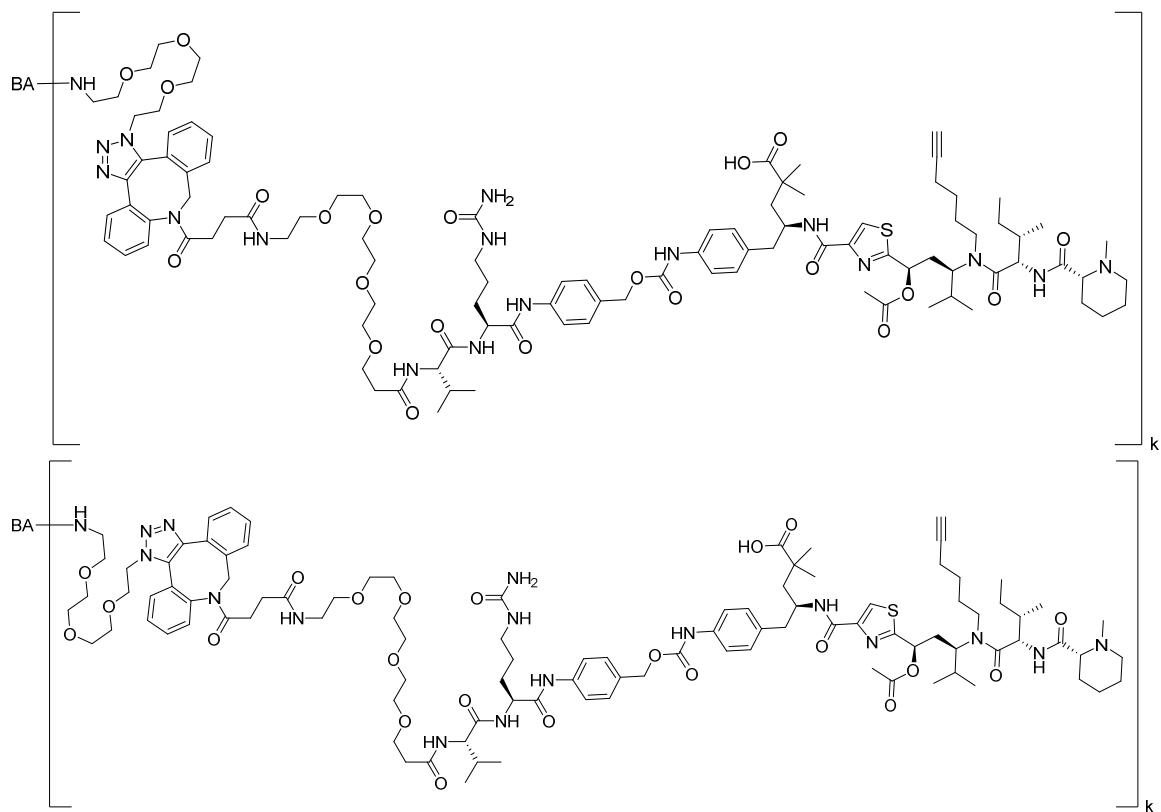




or a pharmaceutically acceptable salt thereof.

67. The compound of claim 1, selected from the group consisting of





and

