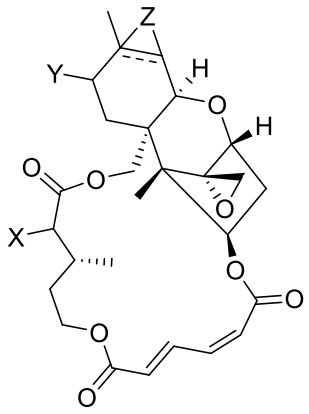
**[0008]** Furthermore, development of antivirals that utilize alternative mechanisms of action is critical for reducing the risk of viruses developing resistance to existing therapeutics. Utilization of ADCs containing a broad-spectrum payload may facilitate use of a broad range of antiviral antibodies which often lack sufficient neutralizing activity to be efficacious on their own. Thus, there is a continuing need for efficient, site-specific methods for treating viral infections.

## SUMMARY

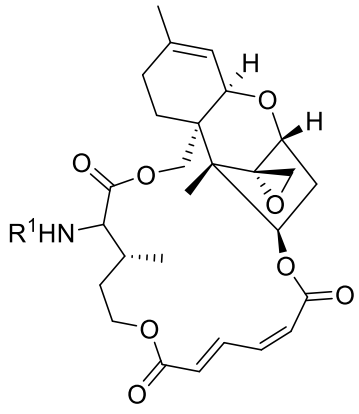
**[0009]** Provided herein are verrucarin A derivatives and ADCs thereof. In one example, the verrucarin A derivatives for use in the compositions and methods provided herein have Formula I:



**I**

**[0010]** or a pharmaceutically acceptable derivative thereof, wherein X, Y and Z are as defined elsewhere herein.

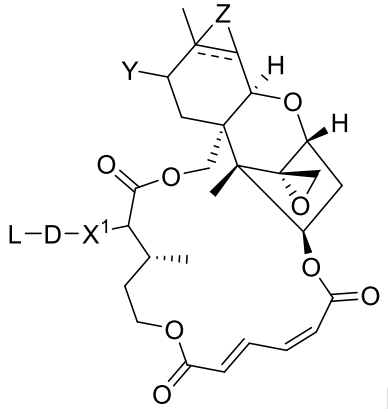
**[0011]** In another example, the verrucarin A derivatives for use in the compositions and methods provided herein have Formula II:



**II**

**[0012]** or a pharmaceutically acceptable derivative thereof, wherein $R^1$ is as defined elsewhere herein.

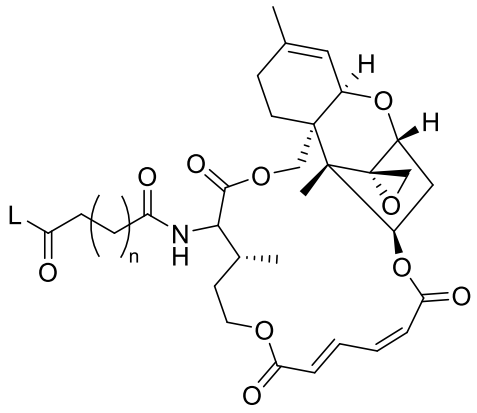
**[0013]** In another example, provided are linker-verrucarin A derivatives of Formula III for use in the compositions and methods provided herein:



**III**

**[0014]** or a pharmaceutically acceptable derivative thereof, wherein $X^1$, D, L, Y, and Z are as defined elsewhere herein.

**[0015]** In another example, provided are linker-verrucarin A derivatives of Formula IV for use in the compositions and methods provided herein:



**IV**

**[0016]** or a or a pharmaceutically acceptable derivative thereof, wherein L and n are as defined elsewhere herein.

**[0017]** In another example, provided are ADCs of Formula V for use in the compositions and methods provided herein:

**[0018]** $Z\text{-}(L\text{-}X)_v$ **V**

**[0019]** or a pharmaceutically acceptable derivative thereof, wherein:

**[0020]** Z is an anti-viral antigen-binding domain;

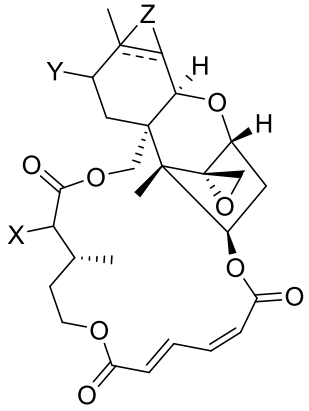
**[0021]** L is a linking group as defined elsewhere herein;

**[0022]** X is a verrucarin A derivative; and

**[0023]** v is an integer from 1 to 12.

**[0024]** In another example, the verrucarin A derivatives and ADCs thereof provided herein are useful in methods of treatment of viral diseases. In one example, the viral disease is influenza, COVID-19 or ebola.

**[0024a]** In an aspect, there is provided a compound of Formula I:



**I**

or a pharmaceutically acceptable salt thereof, wherein:

X is $NR^1R^2$, $OR^3$ or $SR^4$;

$R^1$ and $R^2$ are each independently H, alkyl, C(O)-alkylene-CO-W, C(O)-CH(V)-$CH_3$, $OR^5$ or $COR^6$, or together with the nitrogen atom to which they are attached form heterocycloalkyl or substituted heterocycloalkyl;

$R^3$ is alkyl;

$R^4$ is H, alkyl or $COR^8$;

$R^5$ is H or alkyl;

$R^6$ is $R^9$, -alkylene-COOH, $CH_2CH_2CH_2COOMe$, $CH_2CH_2CH_2CONHOH$, $CH_2CH_2CH_2CONHOMe$, $OR^{10}$ or $NR^{11}R^{12}$;

$R^7$-$R^9$ are each independently alkyl or aralkyl;

$R^{10}$-$R^{12}$ are each independently H, alkyl or aralkyl;

W is $OR^{13}$ or $NR^{14}R^{15}$;

V is $OR^{16}$ or $NR^{17}R^{18}$;

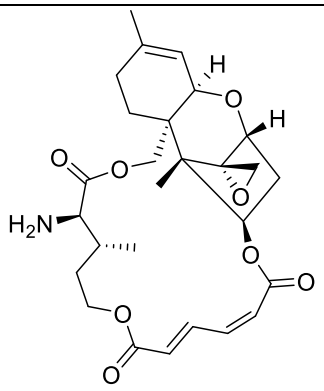
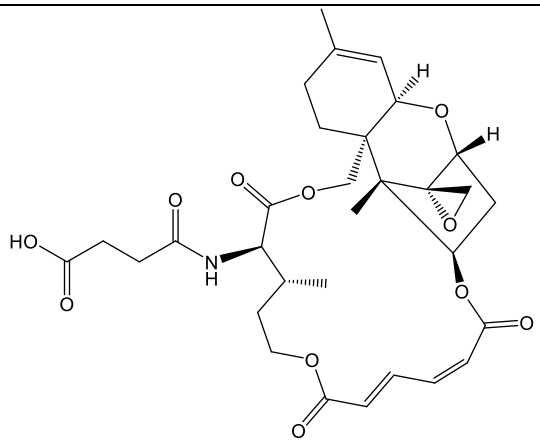
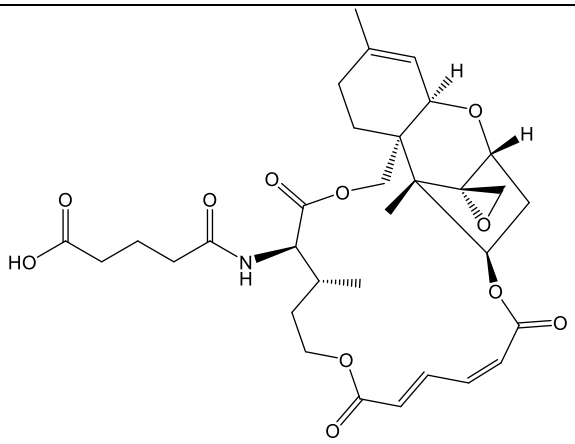
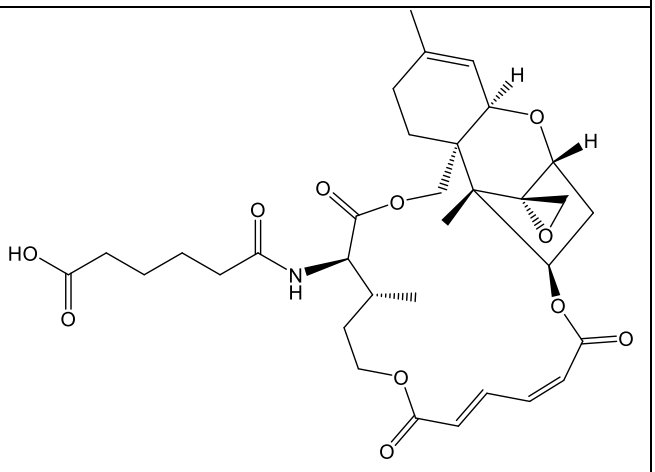
$R^{13}$ and $R^{16}$ are each independently H or alkyl;

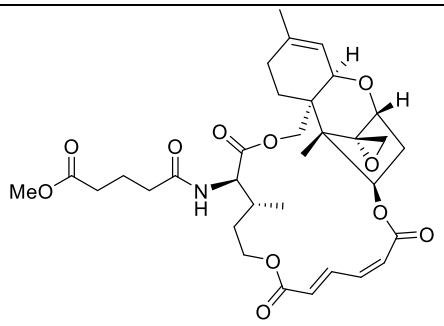
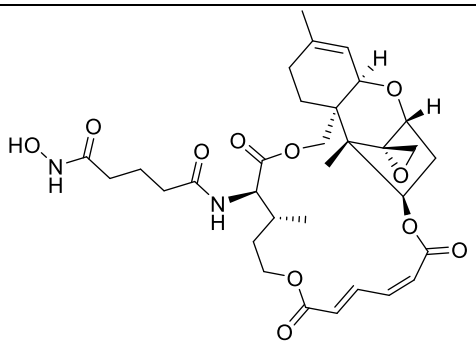
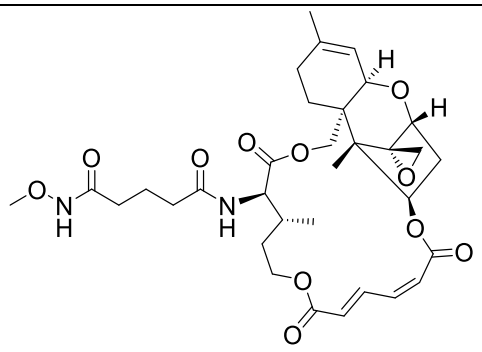
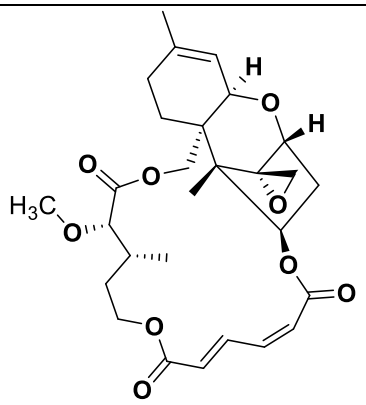
$R^{14}$, $R^{15}$, $R^{17}$ and $R^{18}$ are each independently H, alkyl, hydroxy or alkoxy;

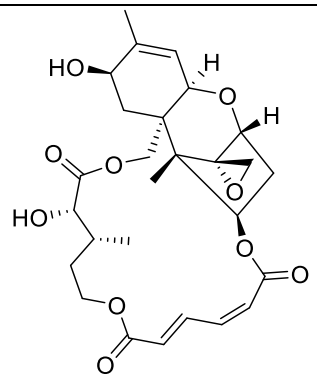
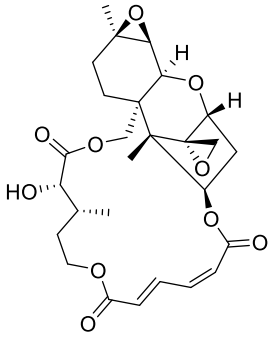
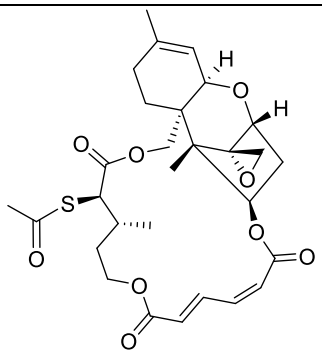
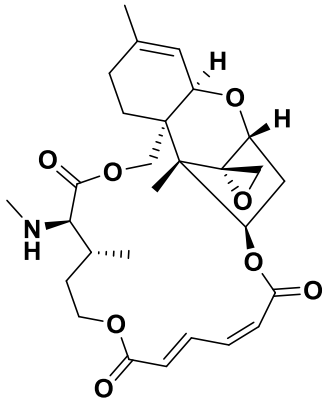
Y is H or OH; and

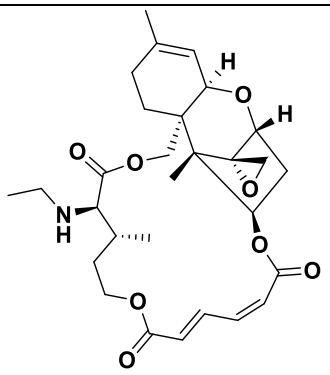
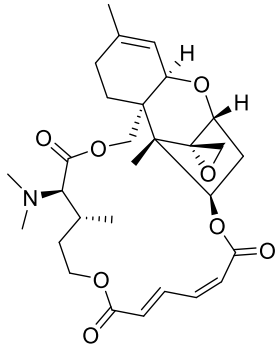
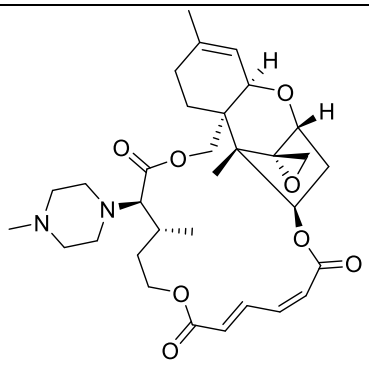
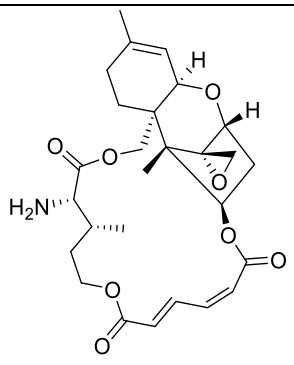
(i) Z is O and ⎓ is a single bond; or (ii) Z is absent and ⎓ is a double bond.

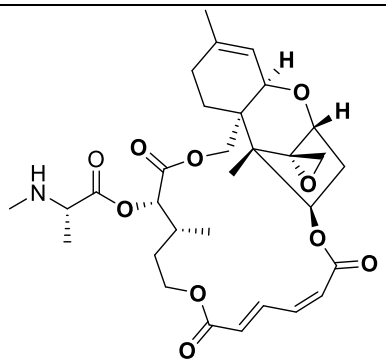
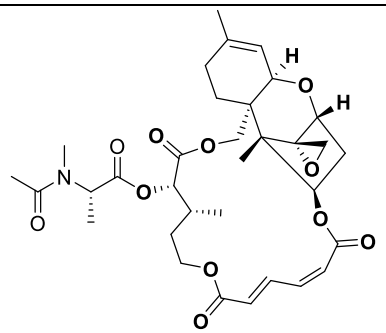
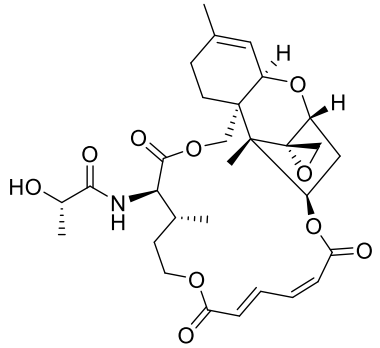
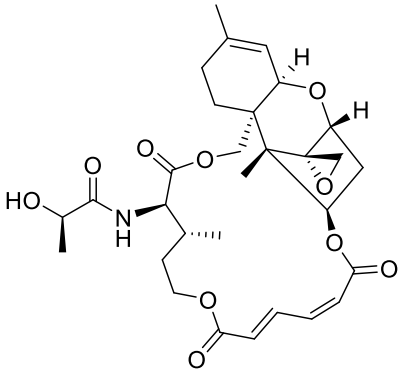
**[0024b]** In another aspect, there is provided a compound selected from:

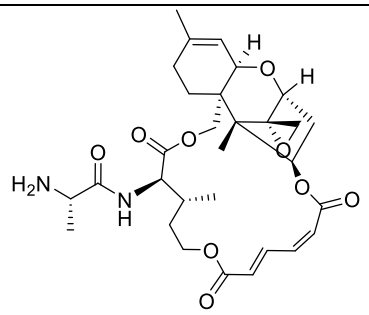
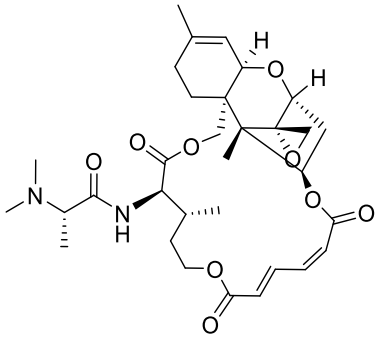
| Compound | Structure |
|---|---|
| **4**<br>(R)-amino-verrucarin A |  |
| **5** |  |
| **6** |  |
| **7** |  |

| Compound | Structure |
|---|---|
| **22** |  |
| **24** |  |
| **25** |  |
| **54** |  |

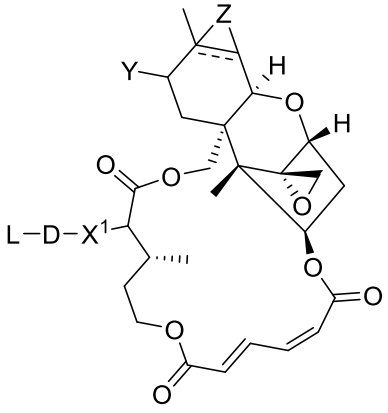
| Compound | Structure |
|---|---|
| **55** |  |
| **56** |  |
| **57** |  |
| **58** |  |

| Compound | Structure |
|---|---|
| **59** |  |
| **60** |  |
| **61** |  |
| **64** |  |

| Compound | Structure |
|---|---|
| **65** |  |
| **66** |  |
| **78** |  |
| **80** |  |

| Compound | Structure |
|---|---|
| **82** |  |
| **84** |  |

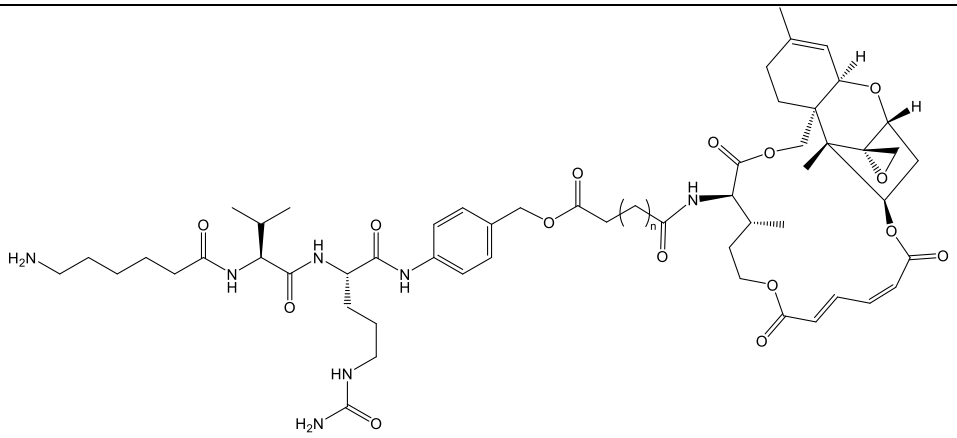
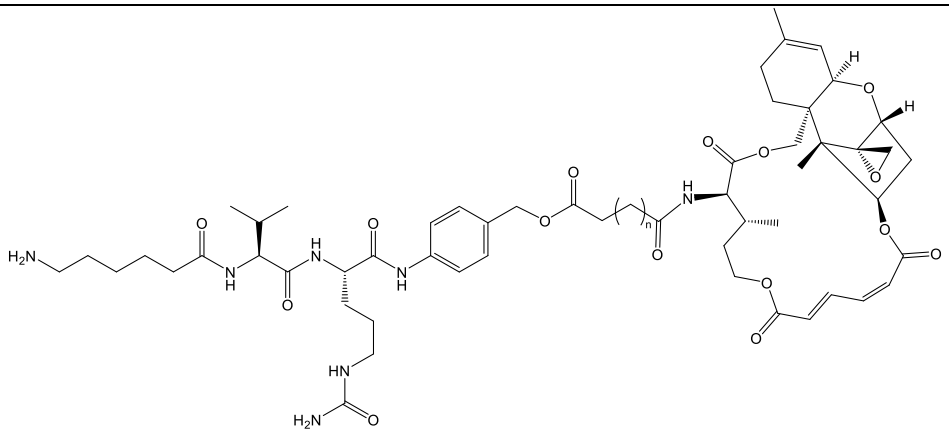
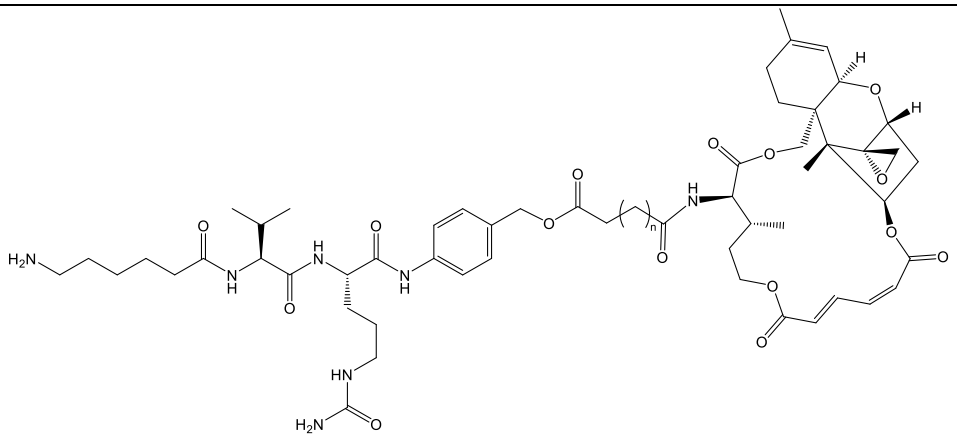
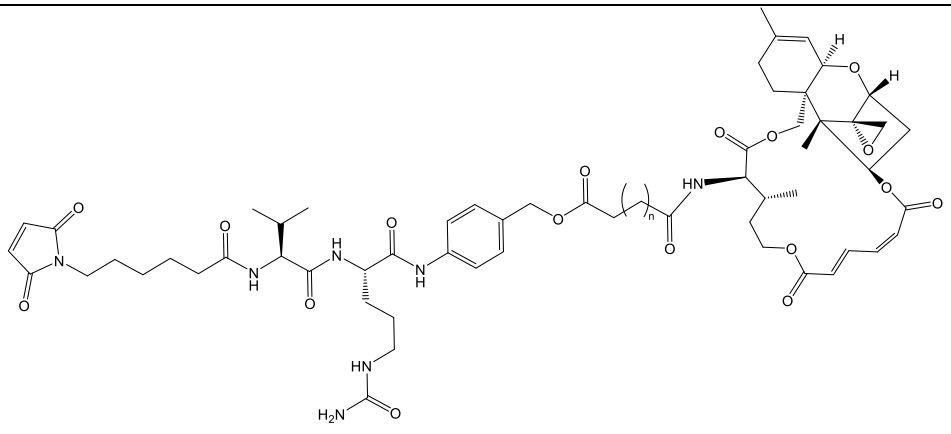
**[0024c]** In another aspect, there is provided a compound of Formula III:

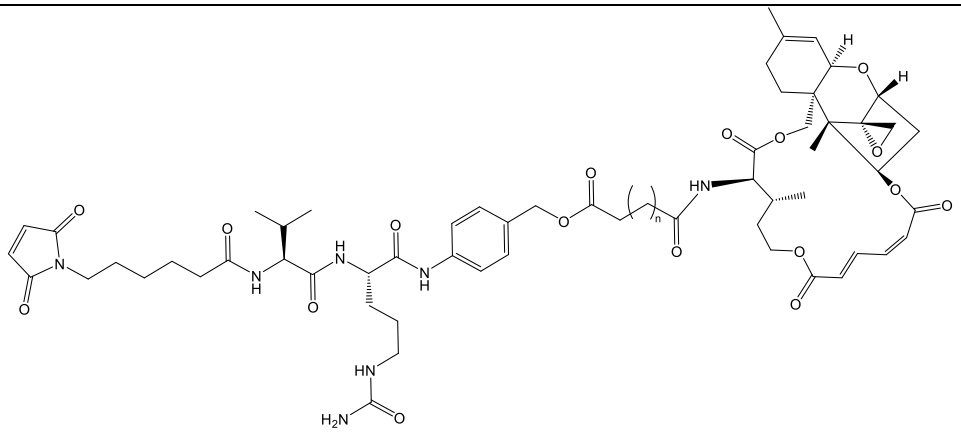
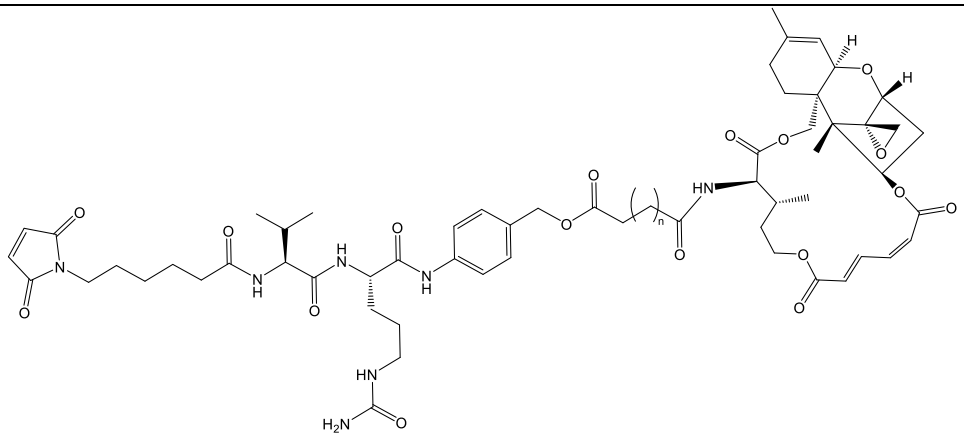
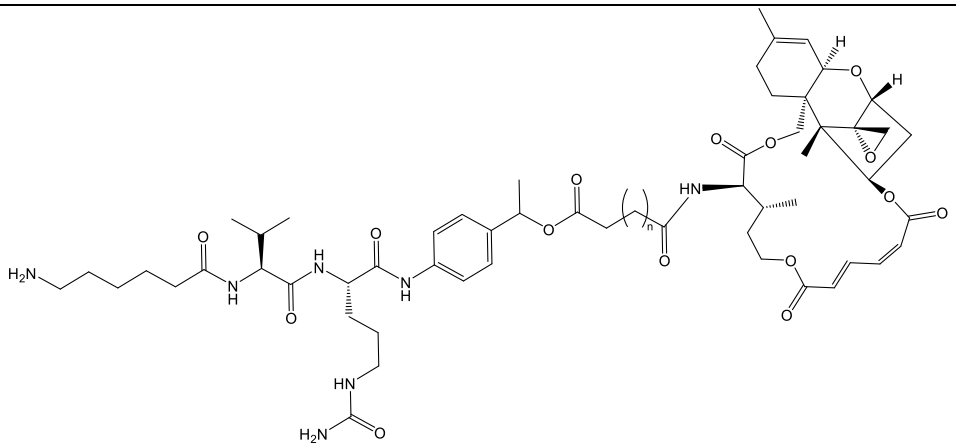
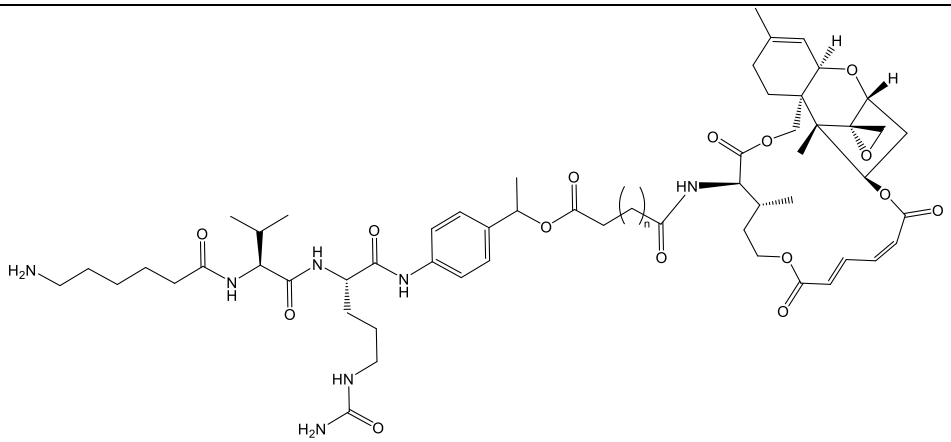


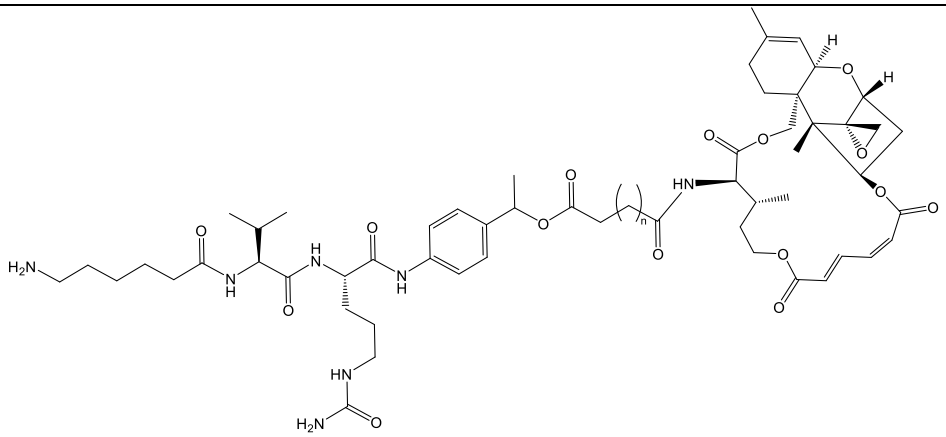
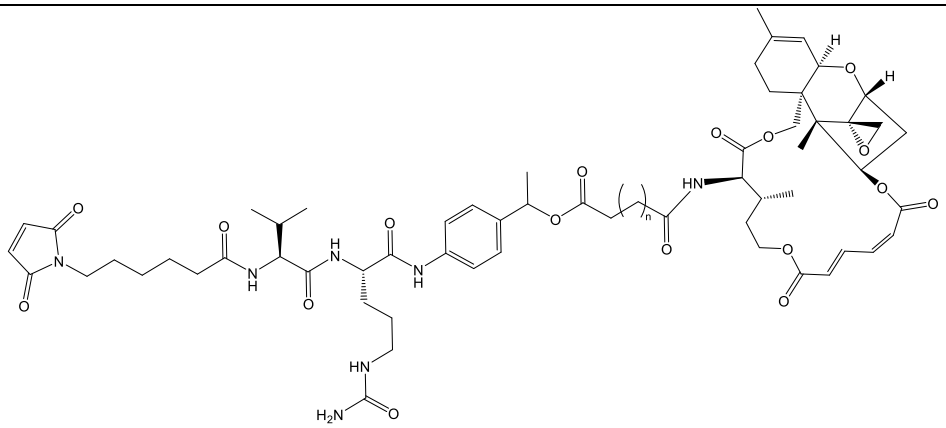
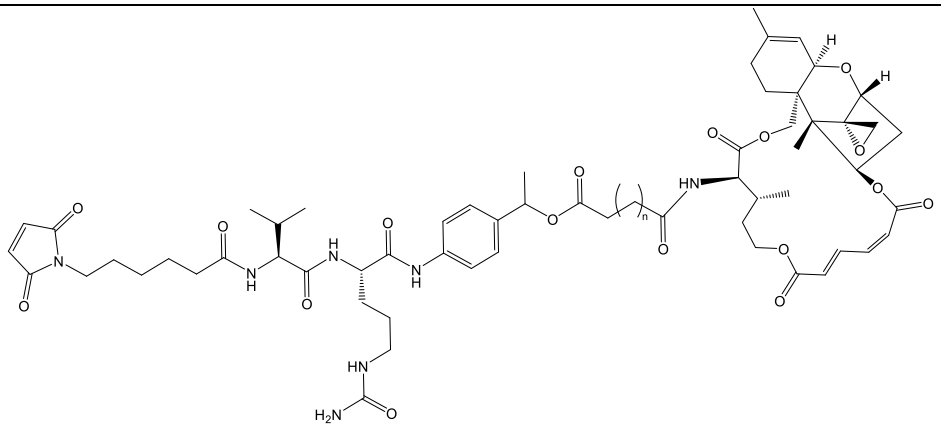
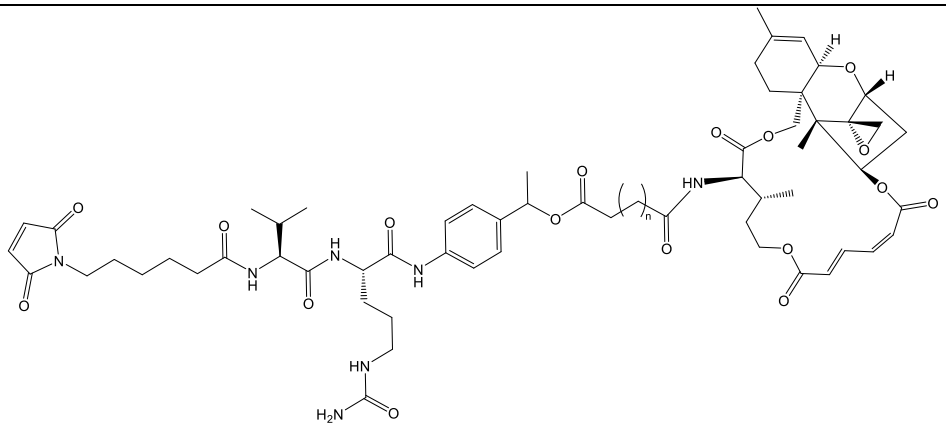
**III**

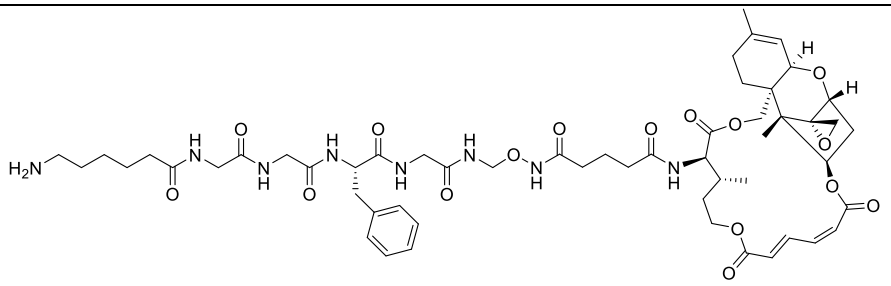
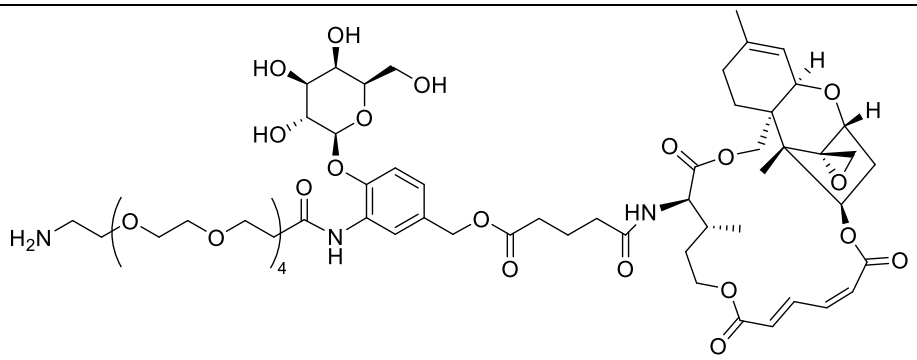
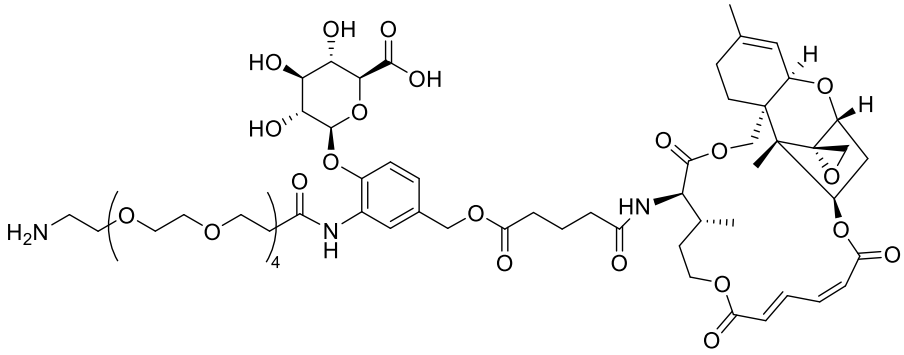
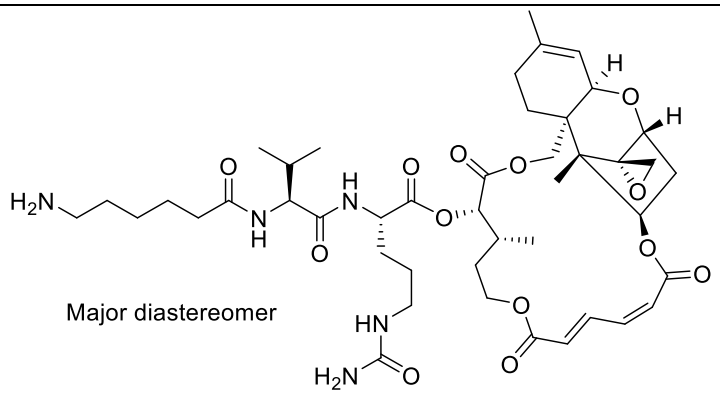
or a pharmaceutically acceptable derivative thereof, wherein $X^1$ is NH; D is absent or is -C(O)-$(CH_2)_{2-5}$-C(O)- or -O-NH-C(O)-$(CH_2)_{2-5}$-C(O)-; L is a linking group; Y is H or OH; and (i) Z is O and ⎓ is a single bond; or (ii) Z is absent and ⎓ is a double bond.

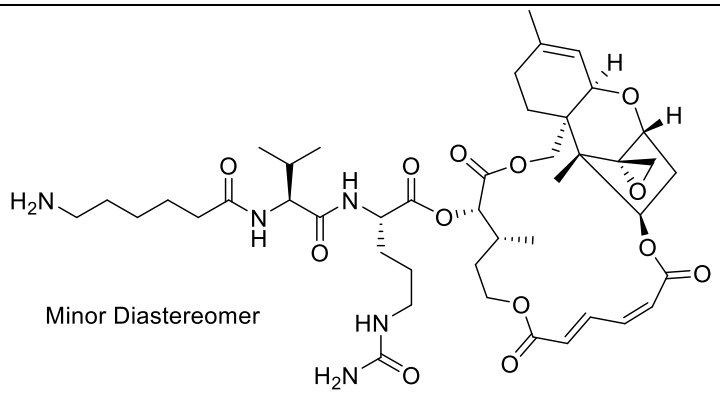
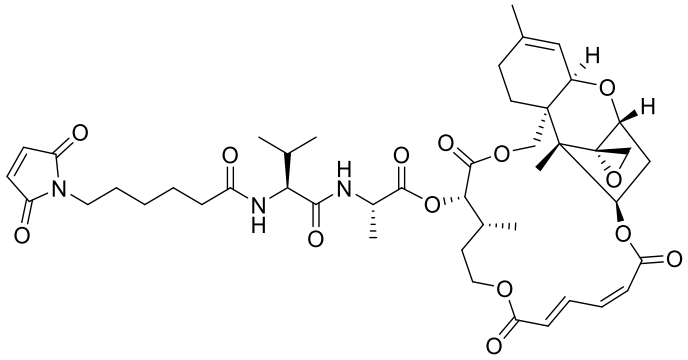
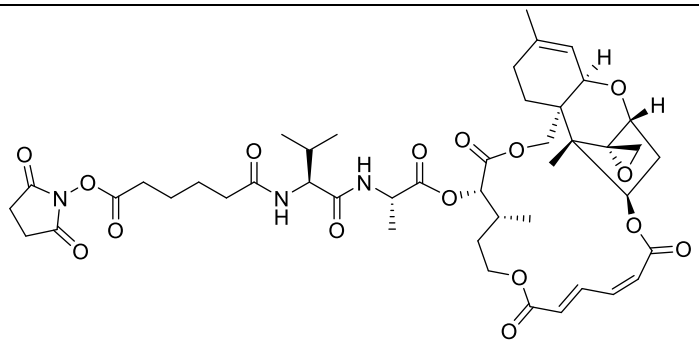
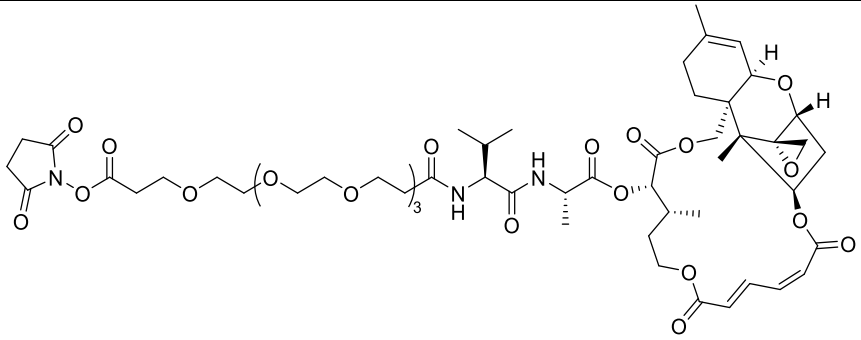
**[0024d]** In another aspect, there is provided a compound selected from:

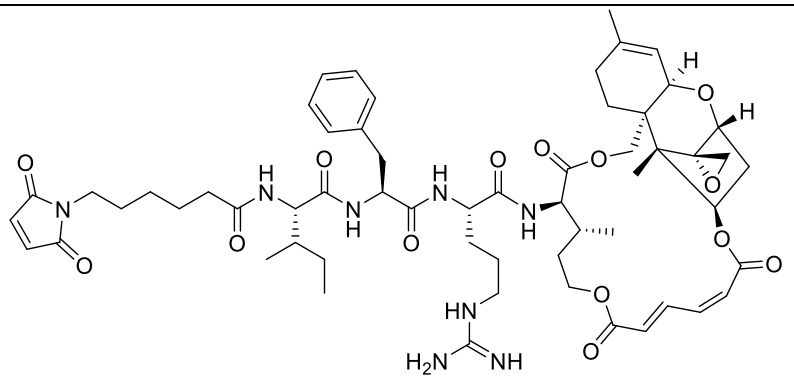
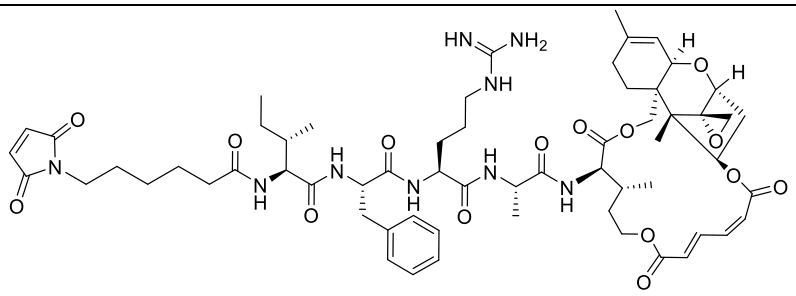
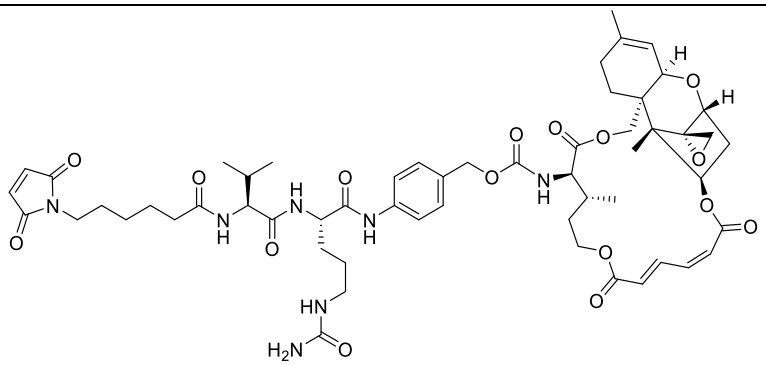
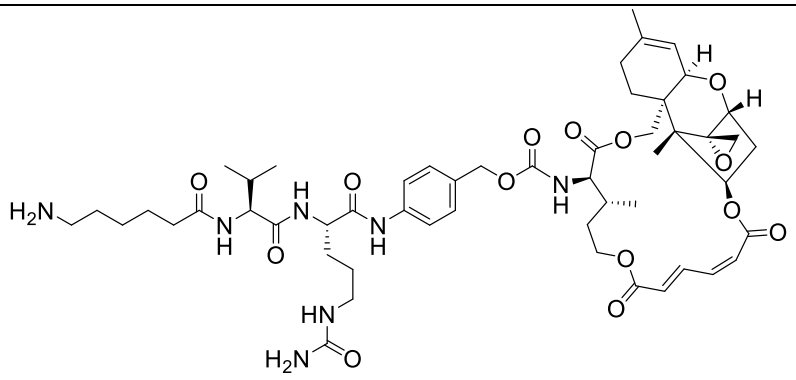
| Compound | Structure |
|---|---|
| **10a** (n = 1) |  |
| **10b** (n = 2) |  |
| **10c** (n = 3) |  |
| **12a** (n = 1) |  |

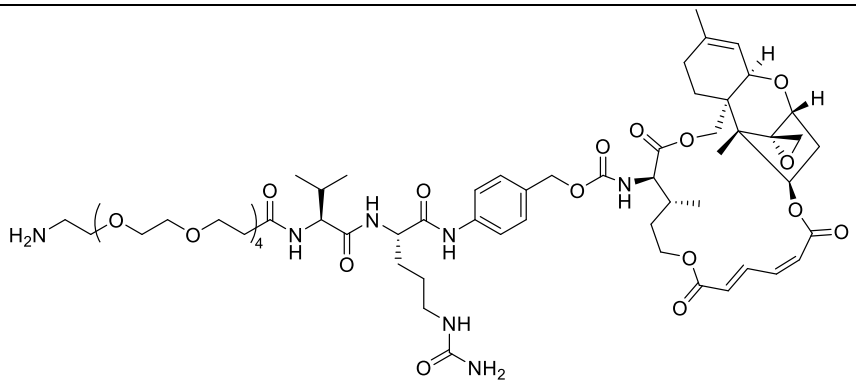
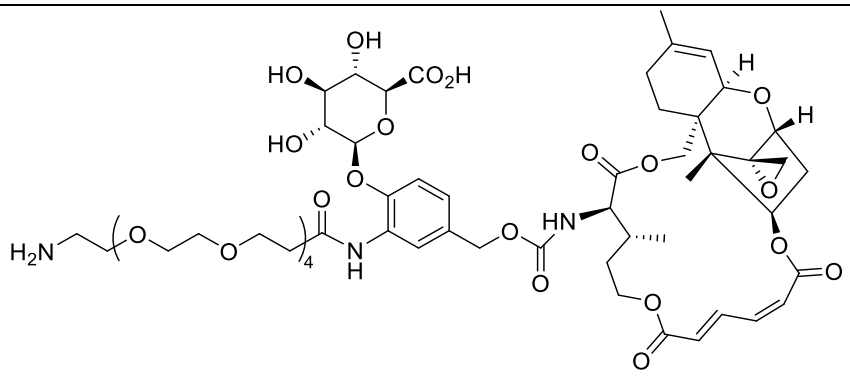
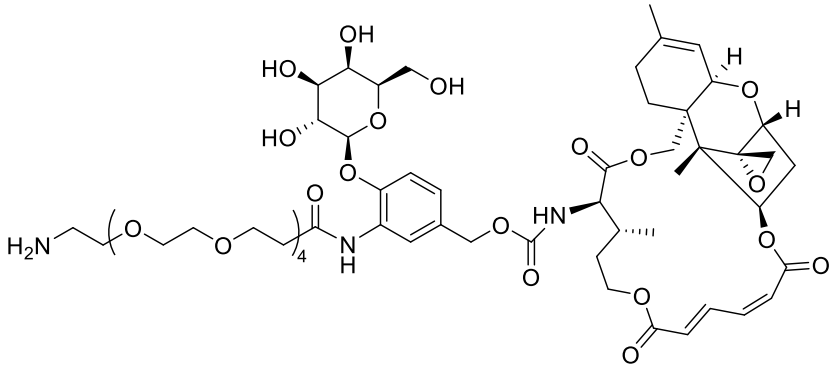
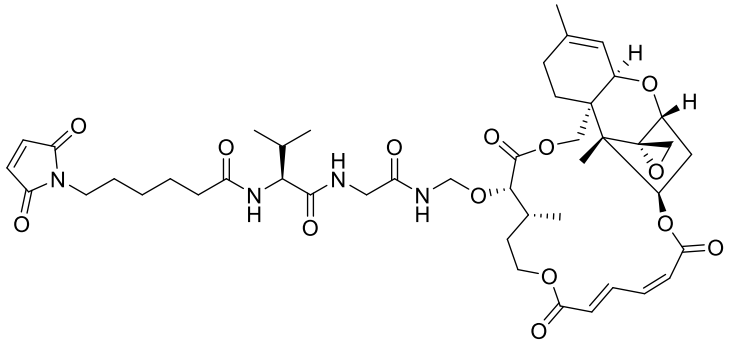
| Compound | Structure |
|---|---|
| **12b** (n = 2) |  |
| **12c** (n = 3) |  |
| **19a** (n = 1) |  |
| **19b** (n = 2) |  |

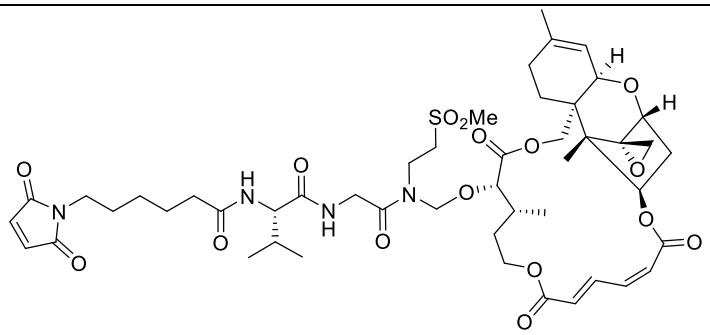
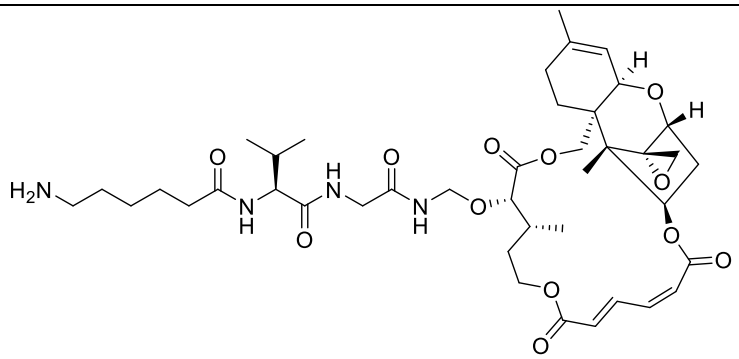
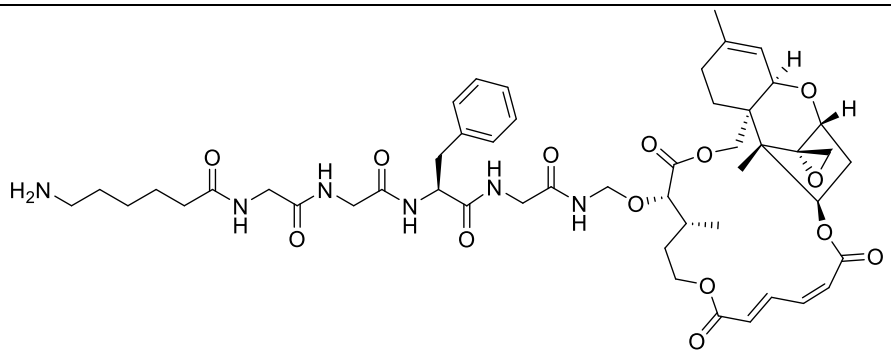
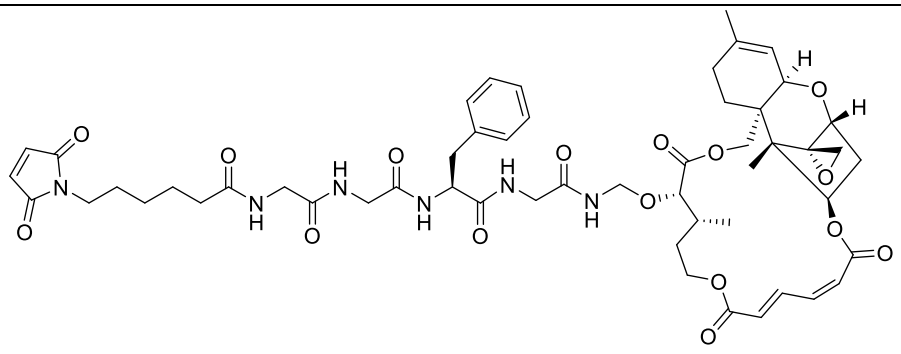
| Compound | Structure |
|---|---|
| **19c** (n = 3) |  |
| **21a** (n = 1) |  |
| **21b** (n = 2) |  |
| **21c** (n = 3) |  |

| Compound | Structure |
|---|---|
| **37** |  |
| **46** |  |
| **53** |  |
| **70a** |  Major diastereomer |

| Compound | Structure |
|---|---|
| **70b** |   |
| **74** |  |
| **75** |  |
| **76** |  |

| Compound | Structure |
|---|---|
| **88** |  |
| **91** |  |
| **97** |  |
| **95** |  |

| Compound | Structure |
|---|---|
| **101** |  |
| **106** |  |
| **109** |  |
| **114** |  |

| Compound | Structure |
|---|---|
| 118 |  |
| 121 |  |
| 124 |  |
| 126 |  |

**[0024e]** In another aspect, there is provided a compound of Formula V:

$Z\text{-}(L\text{-}X)_v$ **V**

or a pharmaceutically acceptable derivative thereof, wherein:

Z is an anti-influenza antigen-binding domain, an anti-SARS-CoV-2 antigen-binding domain, or an anti-ebola virus antigen-binding domain;

L is a linking group;

X is a residue from conjugation reaction between a linking group (L) and a compound as defined above; or

-L-X is a residue from conjugation reaction between Z and a compound as defined above; and

v is an integer from 1 to 12.

**[0024f]** In another aspect, there is provided a pharmaceutical composition, comprising a compound as defined above and a pharmaceutically acceptable carrier.

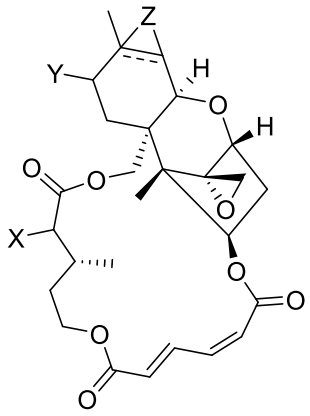
**[0024g]** In another aspect, there is provided a use of a compound as defined above or the composition as defined above in the manufacture of a medicament for treating influenza infection in a subject.

**[0024h]** In another aspect, there is provided a use of a compound as defined above or the composition as defined above in the manufacture of a medicament for treating SARS-CoV-2 infection in a subject.

**[0024i]** In another aspect, there is provided a use of a compound as defined above or the composition as defined above in the manufacture of a medicament for treating ebola infection in a subject.

**WHAT IS CLAIMED IS:**

1. A compound of Formula I:



**I**

or a pharmaceutically acceptable salt thereof, wherein:

X is $NR^1R^2$, $OR^3$ or $SR^4$;

$R^1$ and $R^2$ are each independently H, alkyl, C(O)-alkylene-CO-W, C(O)-CH(V)-$CH_3$, $OR^5$ or $COR^6$, or together with the nitrogen atom to which they are attached form heterocycloalkyl or substituted heterocycloalkyl;

$R^3$ is alkyl;

$R^4$ is H, alkyl or $COR^8$;

$R^5$ is H or alkyl;

$R^6$ is $R^9$, -alkylene-COOH, $CH_2CH_2CH_2COOMe$, $CH_2CH_2CH_2CONHOH$, $CH_2CH_2CH_2CONHOMe$, $OR^{10}$ or $NR^{11}R^{12}$;

$R^7$-$R^9$ are each independently alkyl or aralkyl;

$R^{10}$-$R^{12}$ are each independently H, alkyl or aralkyl;

W is $OR^{13}$ or $NR^{14}R^{15}$;

V is $OR^{16}$ or $NR^{17}R^{18}$;

$R^{13}$ and $R^{16}$ are each independently H or alkyl;

$R^{14}$, $R^{15}$, $R^{17}$ and $R^{18}$ are each independently H, alkyl, hydroxy or alkoxy;

Y is H or OH; and

(i) Z is O and ⎓ is a single bond; or (ii) Z is absent and ⎓ is a double bond.

2. The compound of claim 1, wherein $R^1$ and $R^2$ are each independently H, methyl, ethyl, C(O)-($C_{2\text{-}4}$alkylene)-CO-W where W is $OR^{13}$ or $NR^{14}R^{15}$, or C(O)-CH(V)-$CH_3$ where V is $OR^{16}$ or $NR^{17}R^{18}$, or together with the nitrogen atom to which they are attached form piperazinyl; $R^{13}$ and $R^{16}$ are each independently H or methyl; and $R^{14}$, $R^{15}$, $R^{17}$ and $R^{18}$ are each independently H, methyl, hydroxy or methoxy.

3. The compound of any one of claims 1-2, wherein $R^1$ is H, methyl, ethyl, $C(O)CH_2CH_2COOH$, $C(O)CH_2CH_2CH_2COOH$, $C(O)CH_2CH_2CH_2CH_2COOH$, $C(O)CH_2CH_2CH_2COOMe$, $C(O)CH_2CH_2CH_2CONHOH$, $C(O)CH_2CH_2CH_2CONHOMe$, C(O)-

$CH(OH)$-$CH_3$, $C(O)$-$CH(NH_2)$-$CH_3$ or $C(O)$-$CH(NMe_2)$-$CH_3$; and $R^2$ is H or methyl; or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached form 4-methyl-1-piperazinyl.

4. The compound of claim 1, wherein $R^3$ is methyl.

5. The compound of claim 1, wherein $R^6$ is $CH_2CH_2COOH$, $CH_2CH_2CH_2COOH$, $CH_2CH_2CH_2CH_2COOH$, $CH_2CH_2CH_2COOMe$, $CH_2CH_2CH_2CONHOH$ or $CH_2CH_2CH_2CONHOMe$.

6. The compound of claim 1, wherein $R^7$ and $R^8$ are each independently methyl.

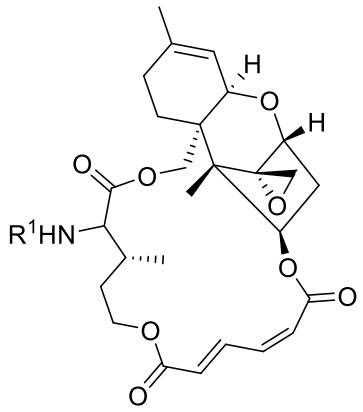
7. The compound of claim 1, wherein $R^{10}$-$R^{12}$ are each independently H or methyl.

8. The compound of any one of claims 1-7, wherein Y is H, Z is absent and ⎓ is a double bond.

9. The compound of any one of claims 1-7, wherein Y is OH, Z is absent and ⎓ is a double bond.

10. The compound of any one of claims 1-7, wherein Y is H, Z is O and ⎓ is a single bond.

11. The compound of claim 1 having Formula II:




**II**

or a pharmaceutically acceptable derivative thereof, wherein:

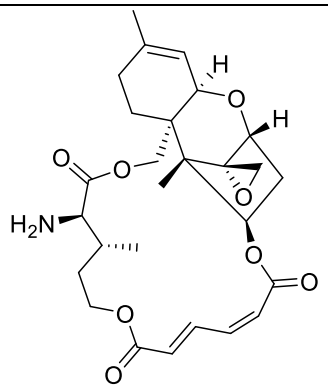
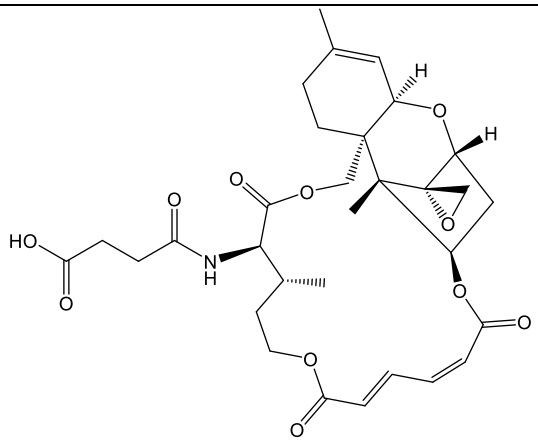
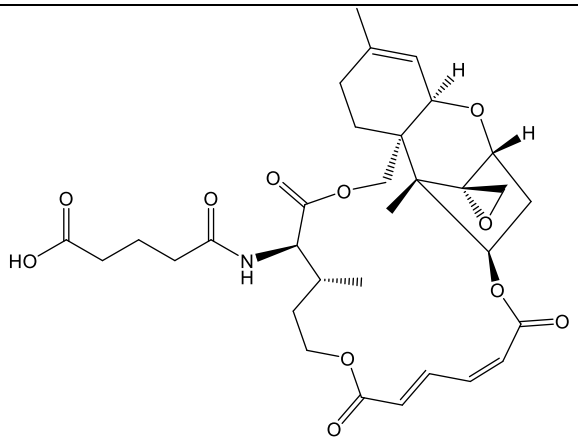
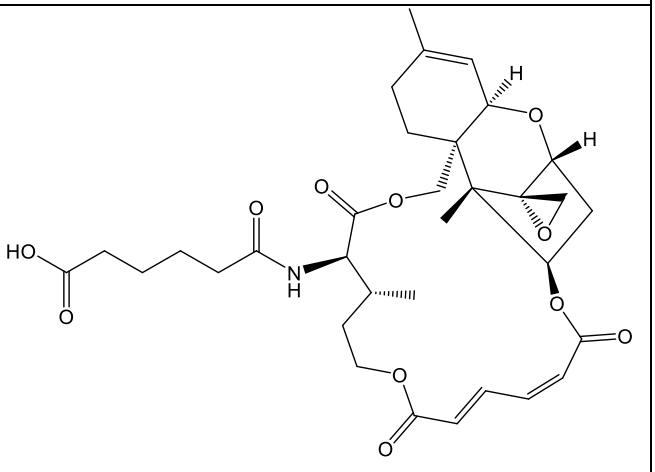
$R^1$ is H or -$COR^6$; and

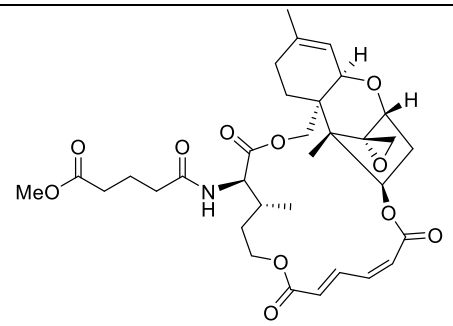
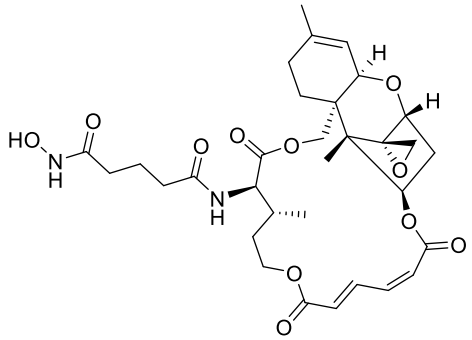
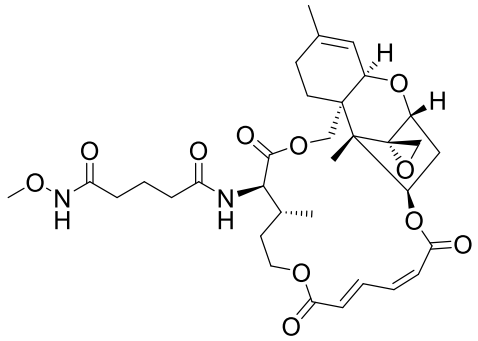
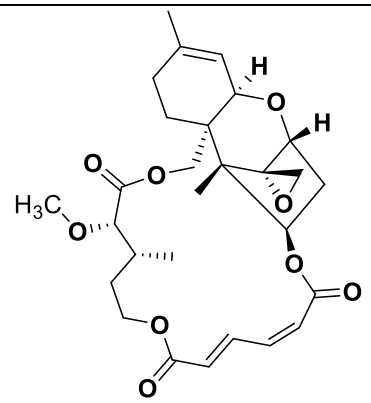
$R^6$ is -alkylene-COOH.

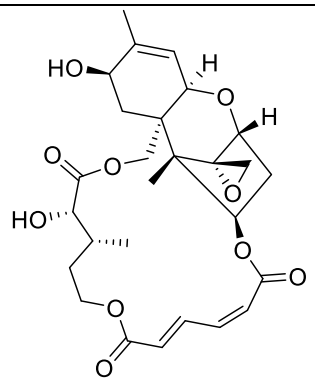
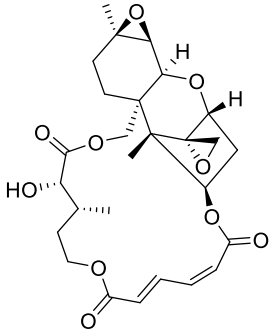
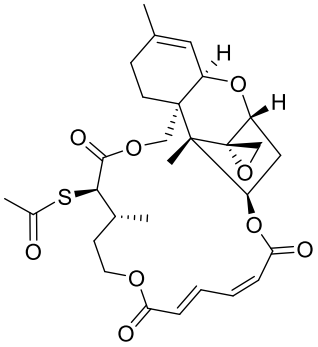
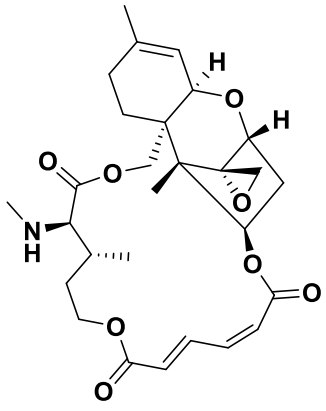
12. The compound of claim 11, wherein $R^1$ is -$COR^6$.

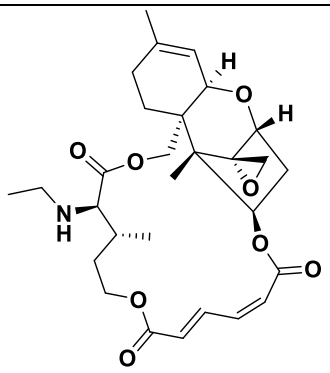
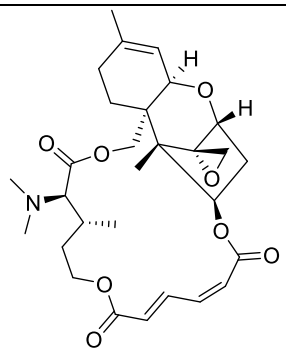
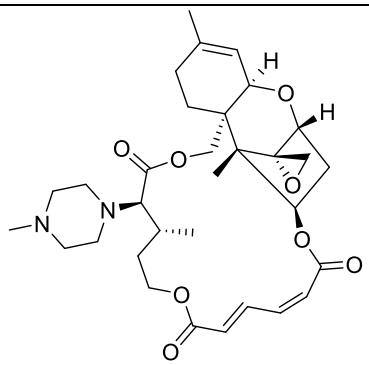
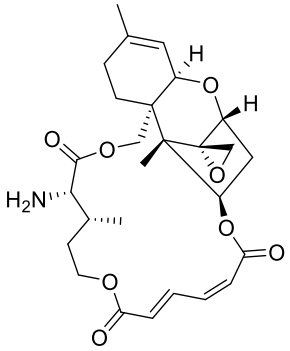
13. The compound of claim 11 or 12, wherein $R^6$ is $–(CR^{21}R^{22})_mCOOH$, where $R^{21}$ and $R^{22}$ are each independently H or alkyl; and m is an integer from 0-6.

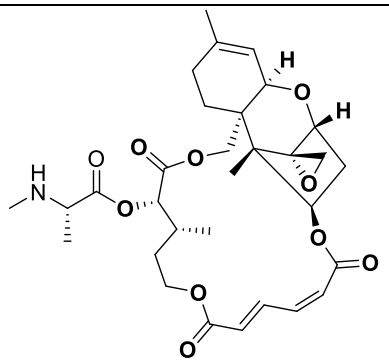
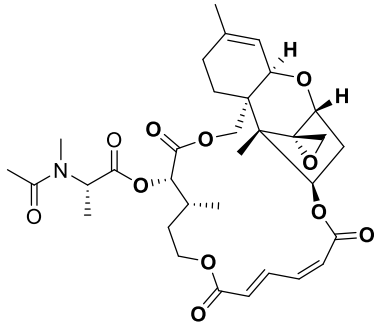
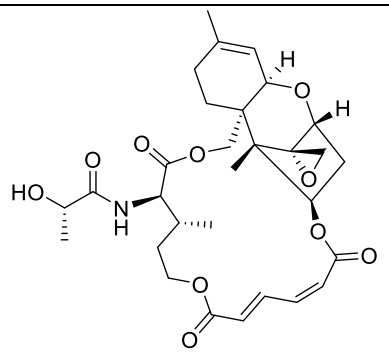
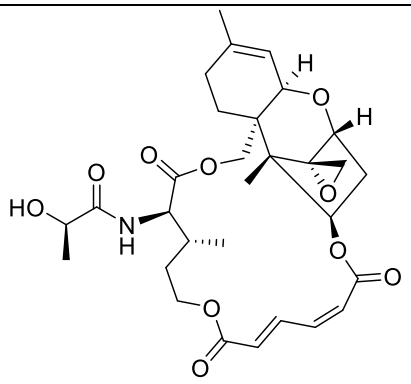
14. A compound selected from:

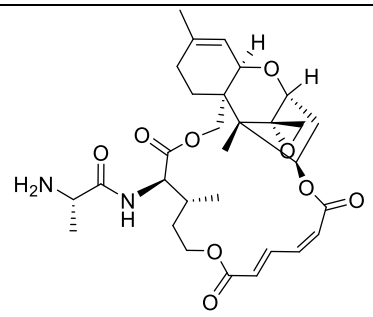
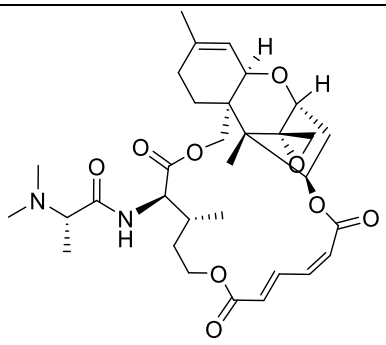
| Compound | Structure |
|---|---|
| **4**<br>(R)-amino-verrucarin A |  |
| **5** |  |
| **6** |  |
| **7** |  |

| Compound | Structure |
|---|---|
| **22** |  |
| **24** |  |
| **25** |  |
| **54** |  |

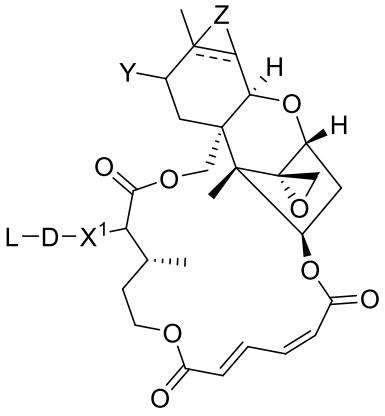
| Compound | Structure |
|---|---|
| **55** |  |
| **56** |  |
| **57** |  |
| **58** |  |

| Compound | Structure |
|---|---|
| **59** |  |
| **60** |  |
| **61** |  |
| **64** |  |

| Compound | Structure |
|---|---|
| **65** |  |
| **66** |  |
| **78** |  |
| **80** |  |

| Compound | Structure |
|---|---|
| **82** |  |
| **84** |  |

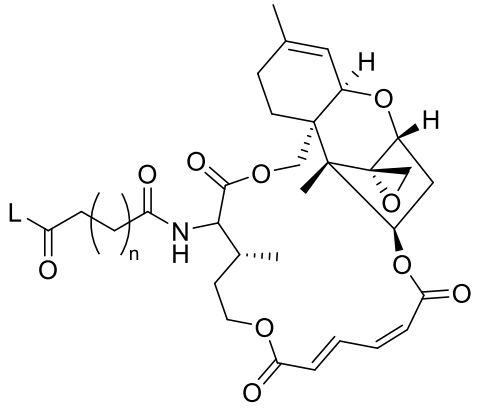
15. A compound of Formula III:



**III**

or a pharmaceutically acceptable derivative thereof, wherein $X^1$ is NH; D is absent or is -C(O)-$(CH_2)_{2\text{-}5}$-C(O)- or -O-NH-C(O)-$(CH_2)_{2\text{-}5}$-C(O)-; L is a linking group; Y is H or OH; and (i) Z is O and ⁻⁻⁻ is a single bond; or (ii) Z is absent and ⁻⁻⁻ is a double bond.

16. A compound of claim 15 that has Formula IV:



**IV**

or a pharmaceutically acceptable derivative thereof, wherein L is a linking group and n is an integer from 1 to 4.

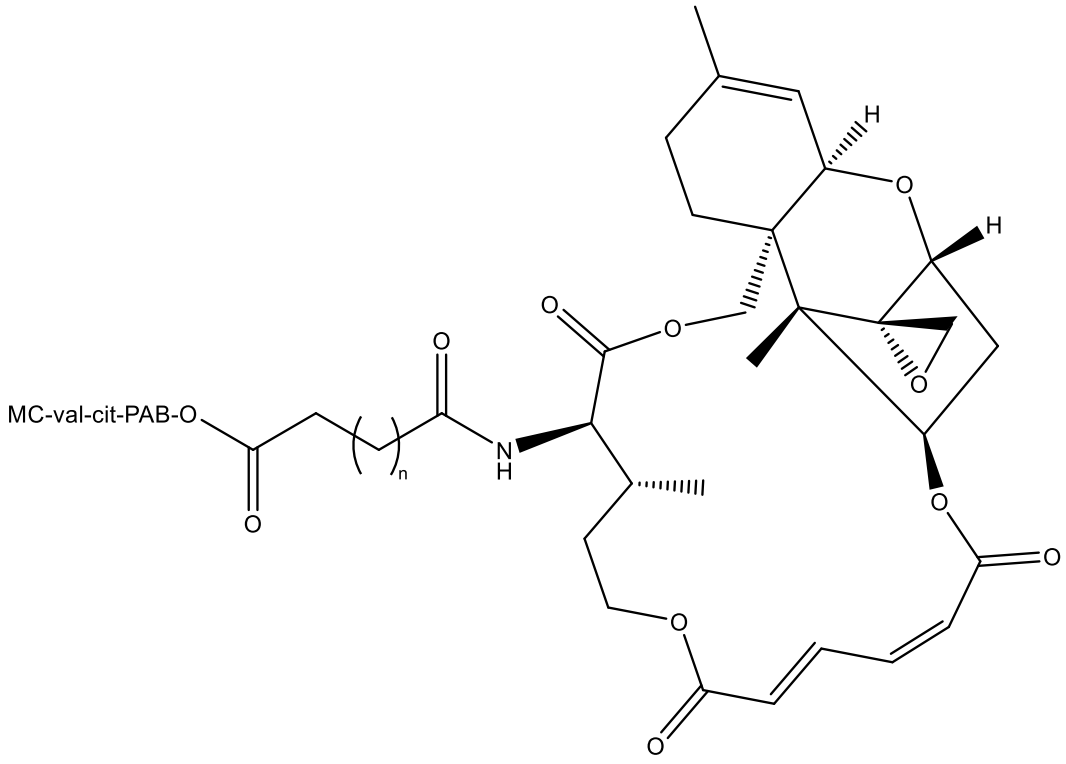
17. The compound of claim 16, wherein n is 1, 2 or 3.

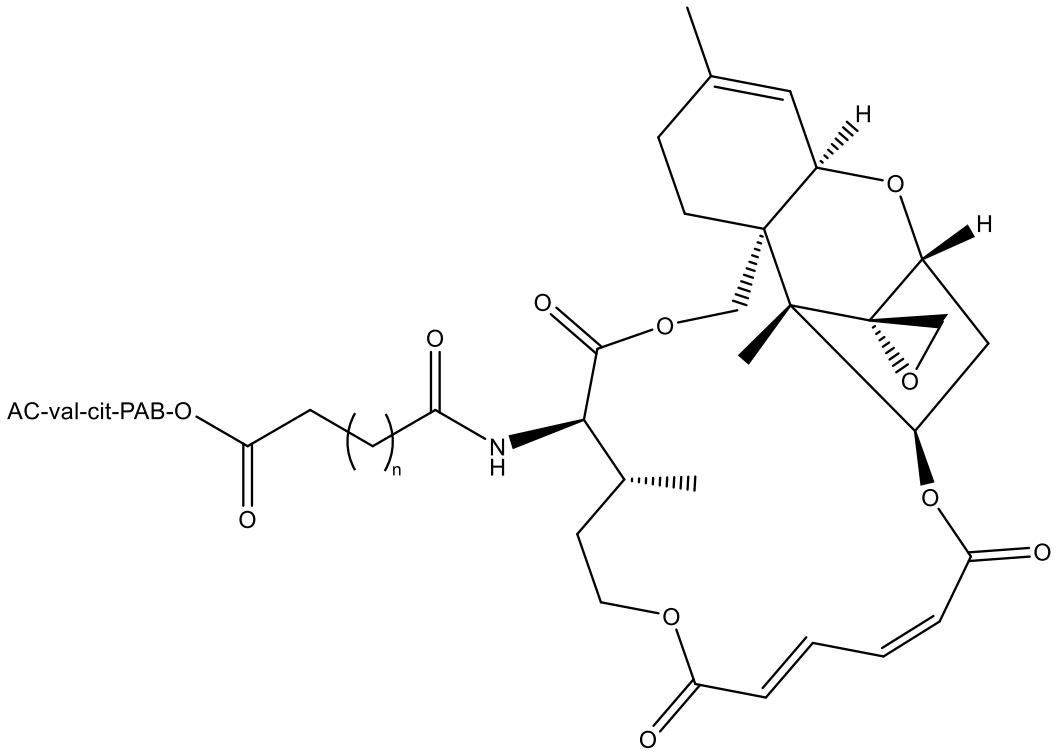
18. The compound of any one of claims 15-17, wherein L is a cleavable linker.

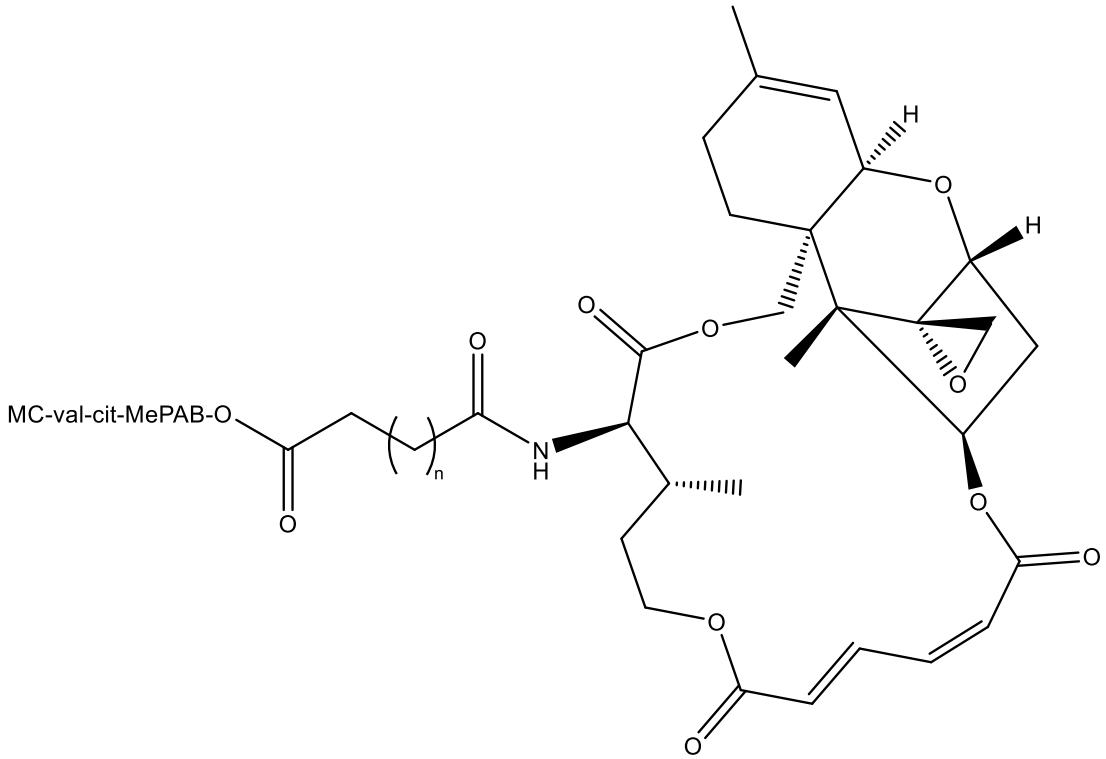
19. The compound of any one of claims 15-18, wherein L is an acid-labile linker, a hydrolysis-labile linker, an enzymatically cleavable linker, a reduction labile linker, or a self-immolative linker.

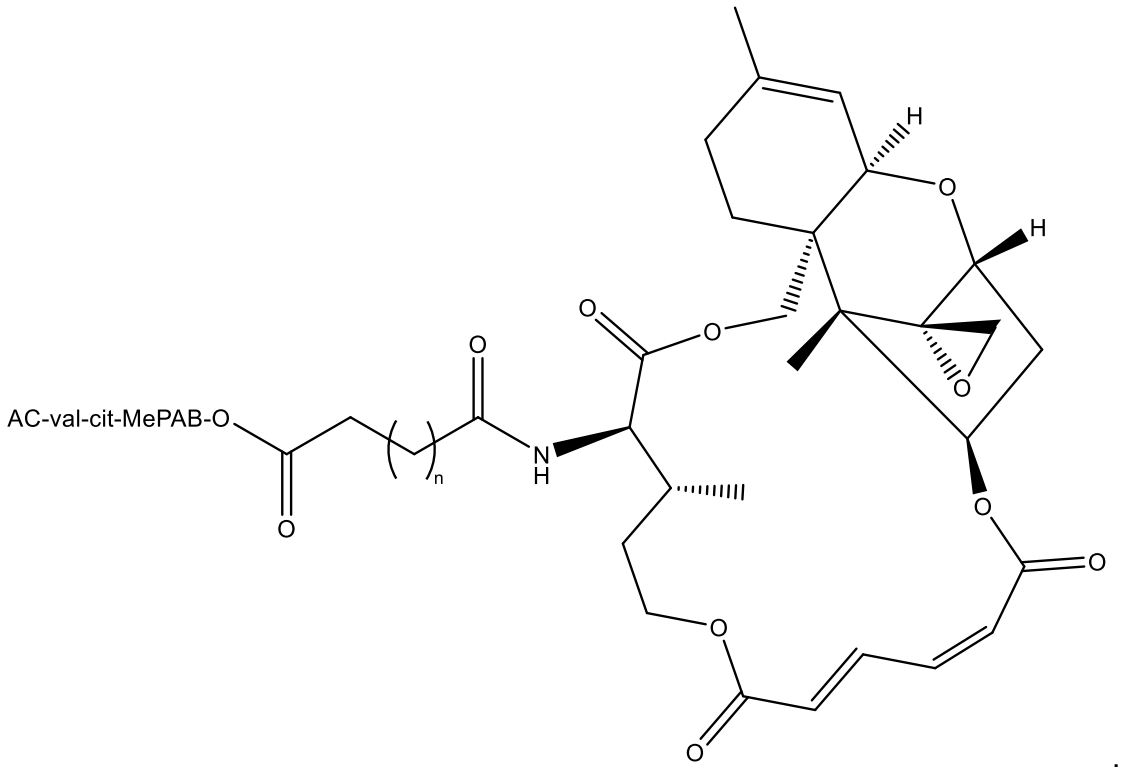
20. The compound of any one of claims 15-19, wherein L comprises or consists of val-cit-PAB, val-cit-MePAB (val-cit-(p-amino-α-benzyloxy)), AC (6-aminocaproyl), MC (6-maleimidocaproyl), MC-val-cit-PAB, AC-val-cit-PAB, MC-val-cit-MePAB, AC-val-cit-MePAB, or AC-GGFG-$CH_2$-.

21. The compound of any one of claims 15-20, having one of the formulae:



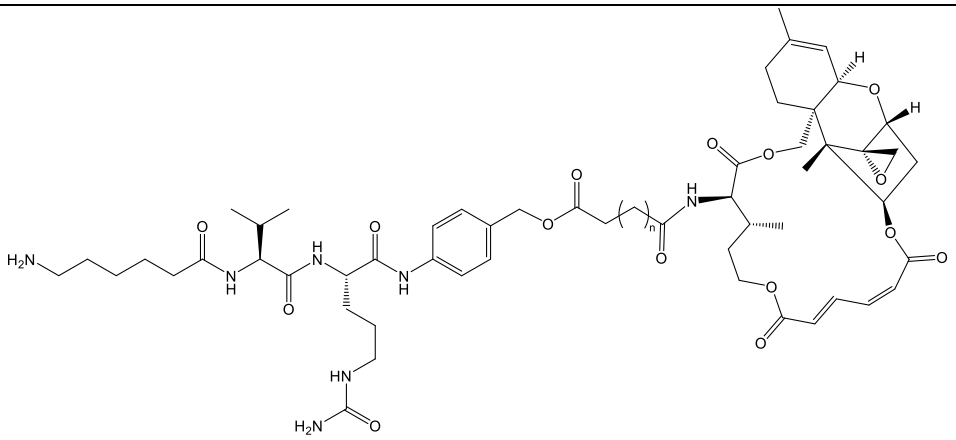

AC-val-cit-PAB-O
O
O
n
N
H
O
O
O
O
O
O
O
O
H
H
O

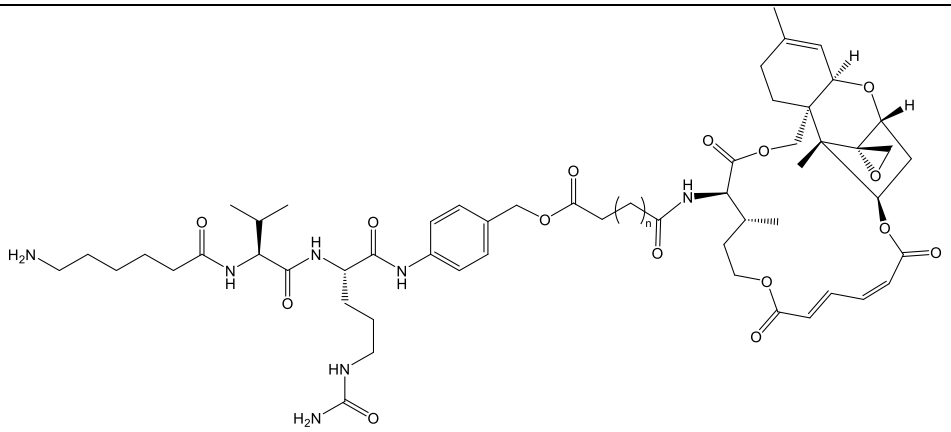
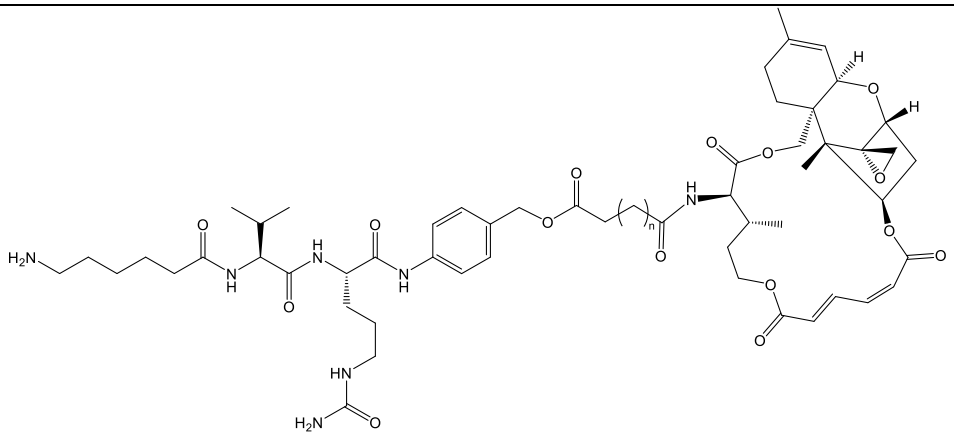
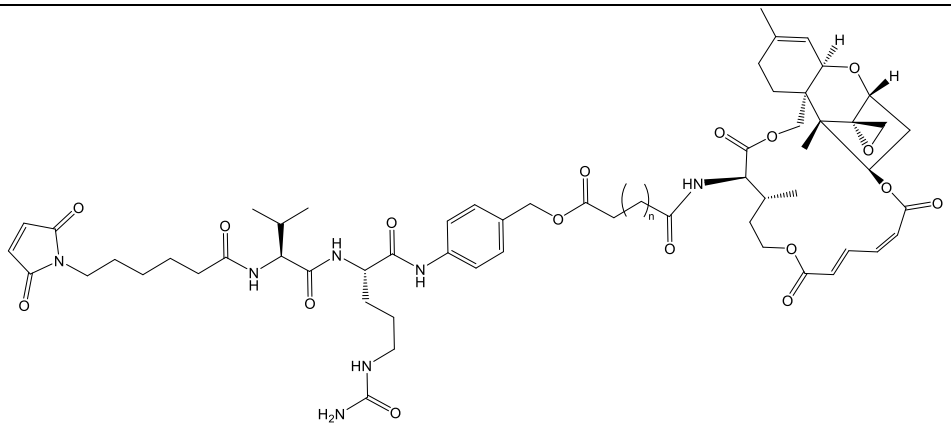
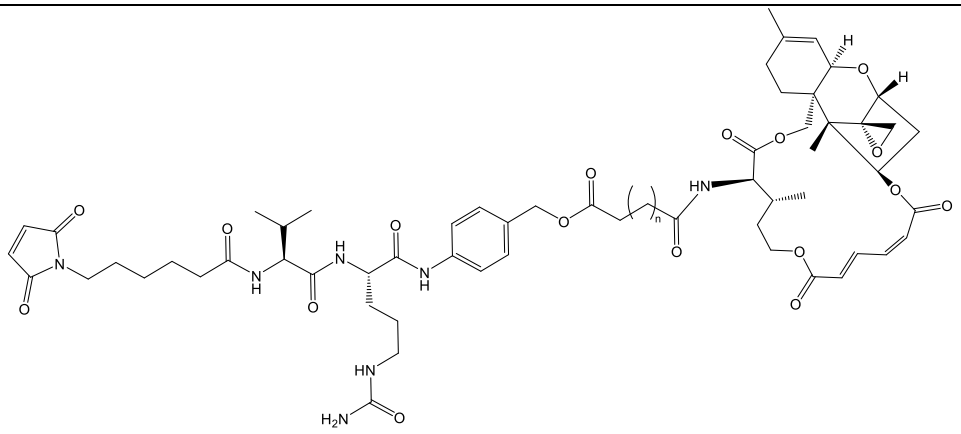

MC-val-cit-MePAB-O
O
O
n
N
H
O
O
O
O
O
O
O
O
H
H
O

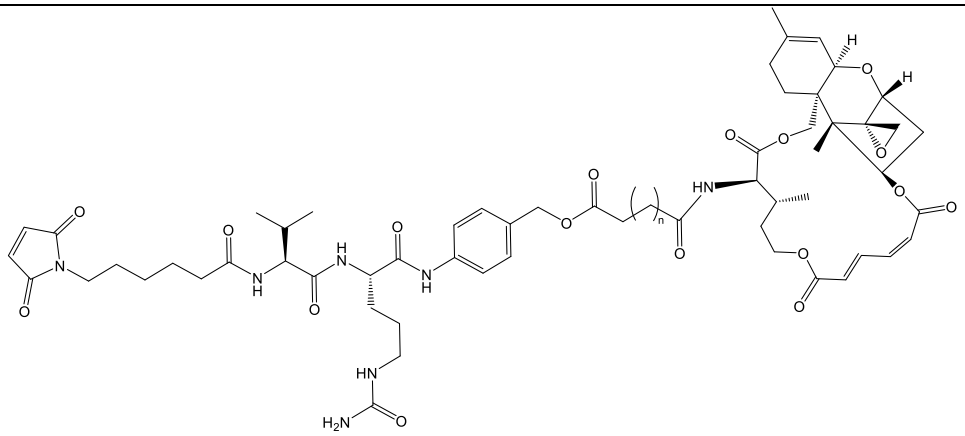
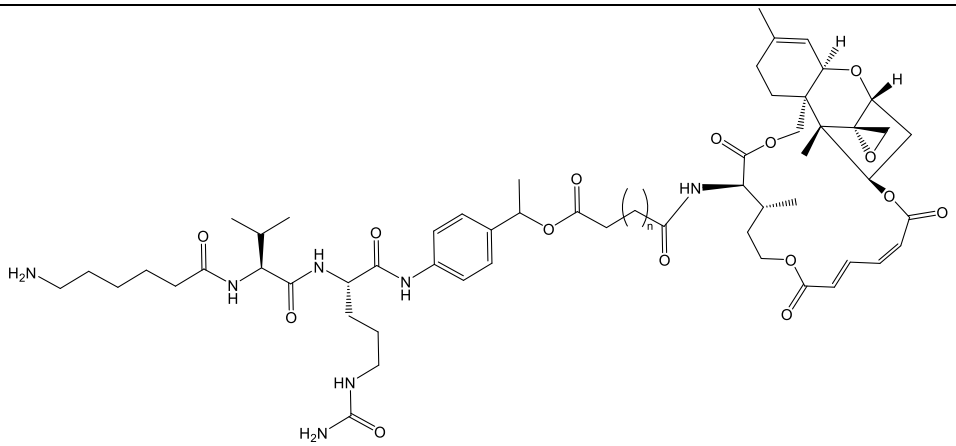
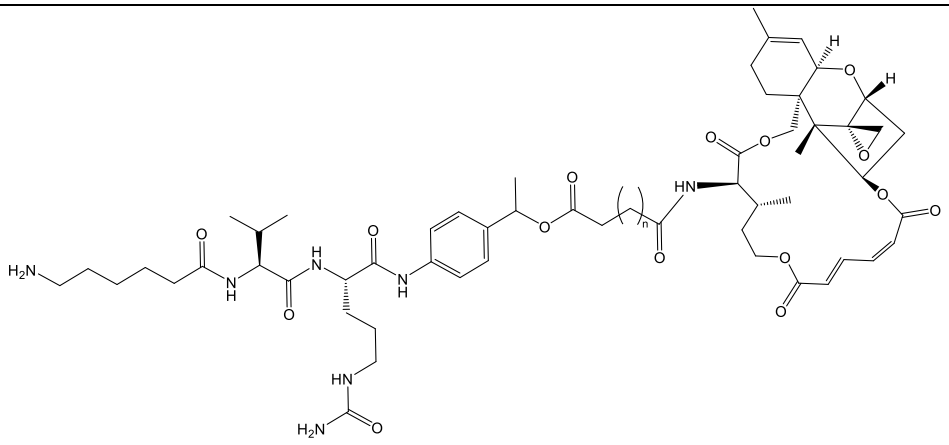
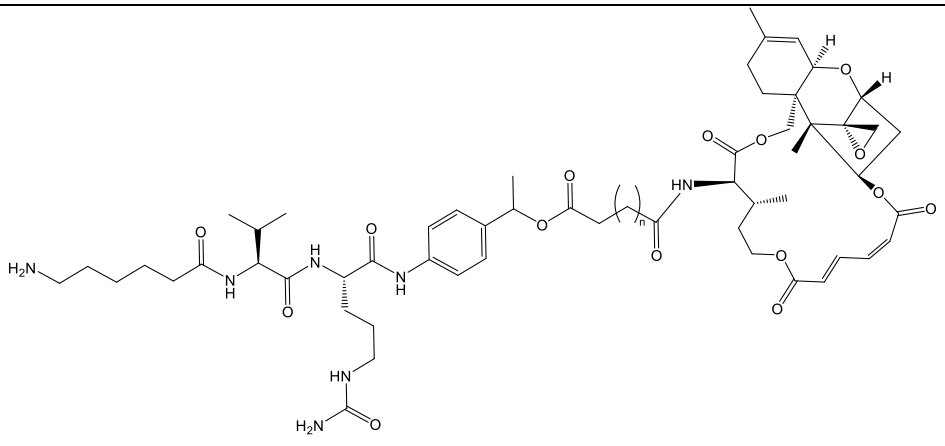


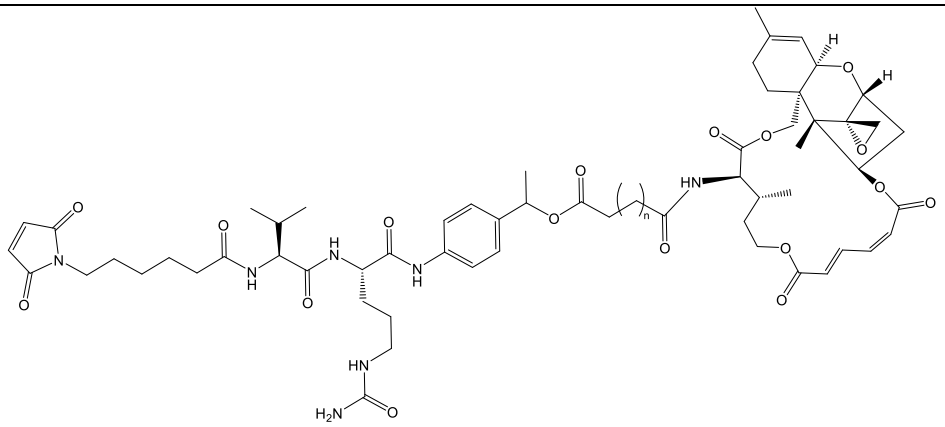
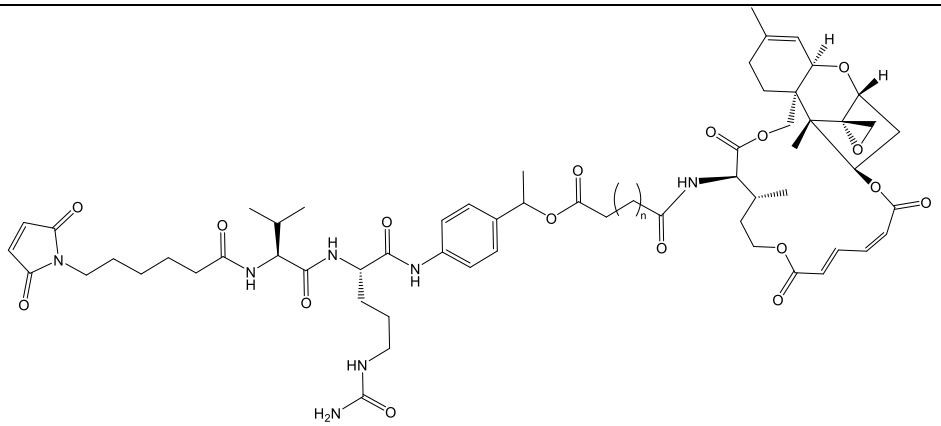
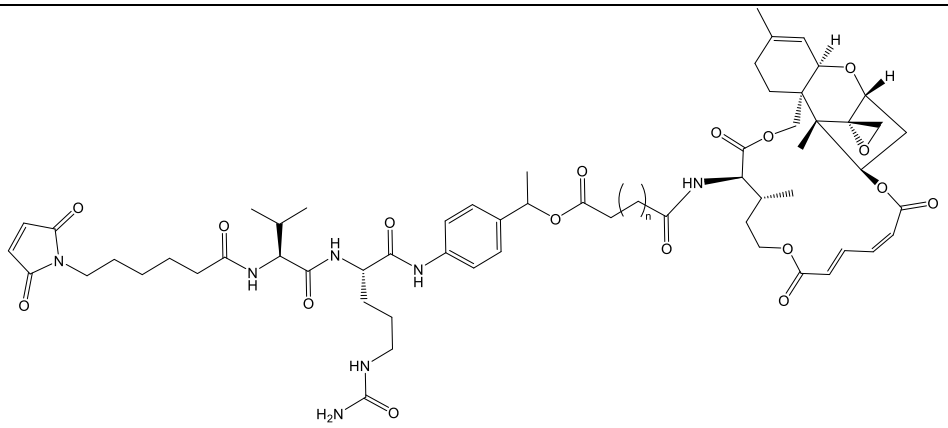
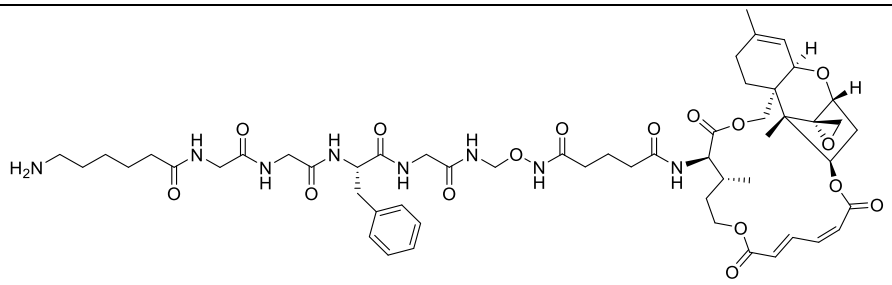

22. The compound of any one of claims 15-17, wherein L is a non-cleavable linker.

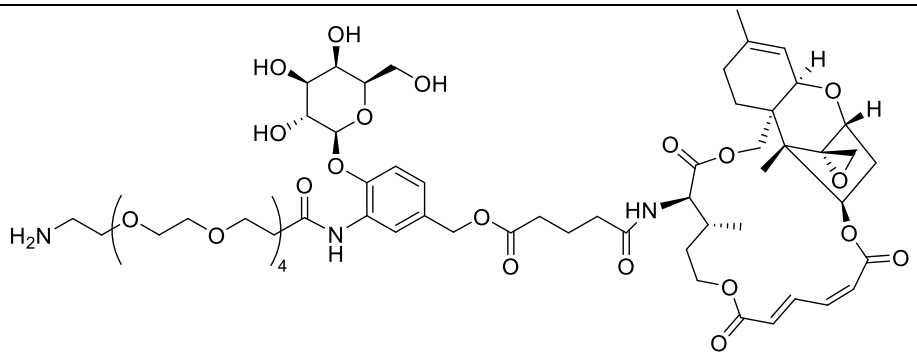
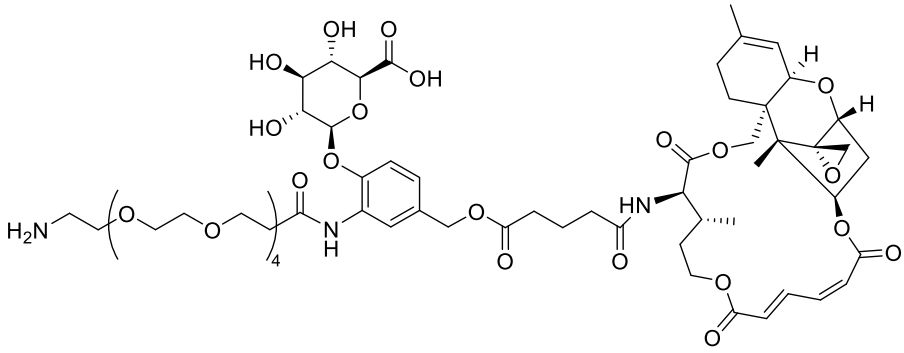
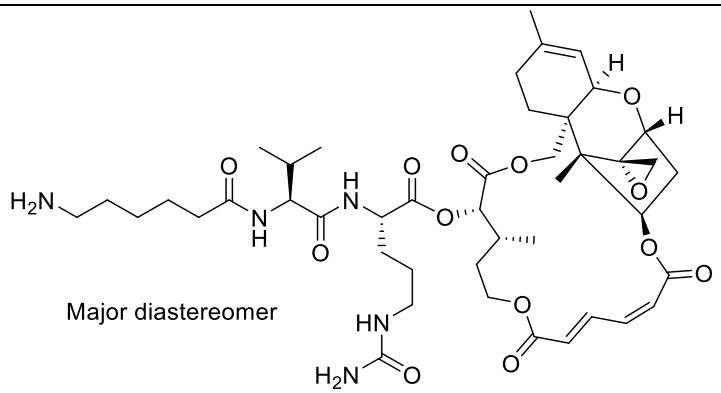
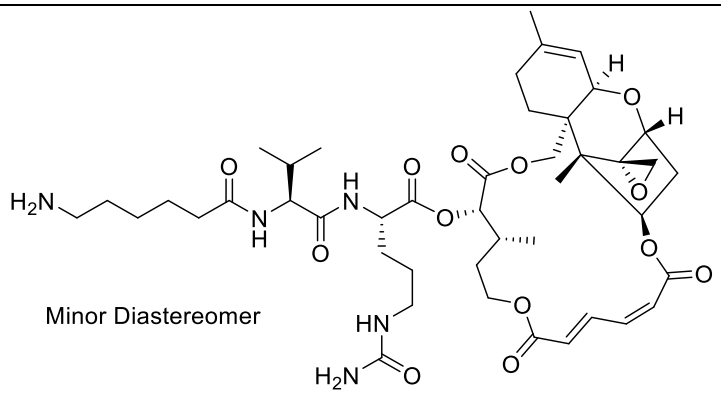
23. A compound selected from:

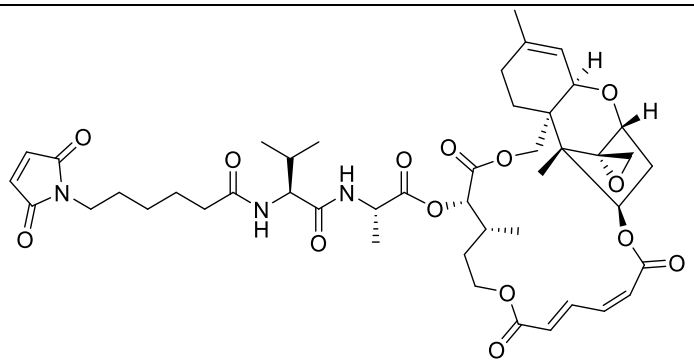
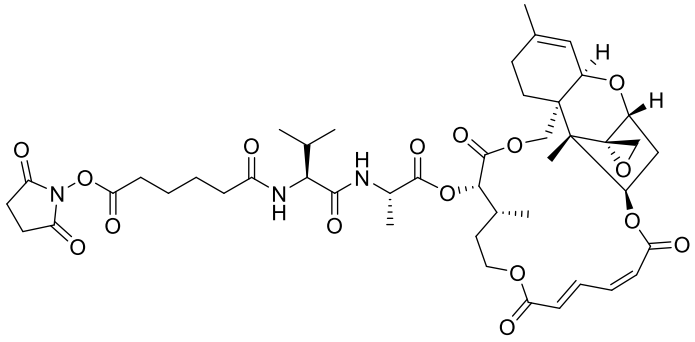
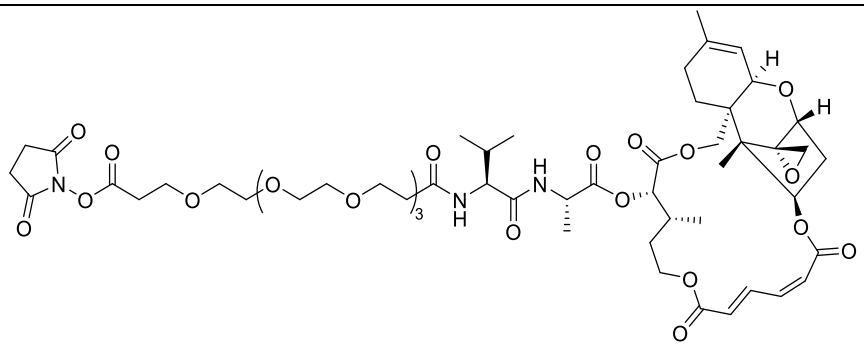
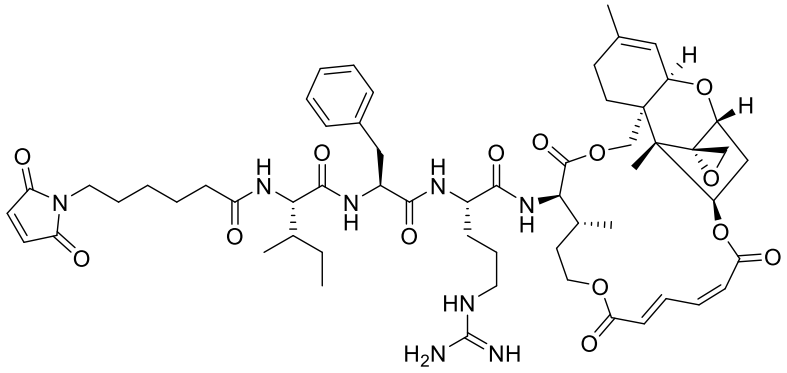
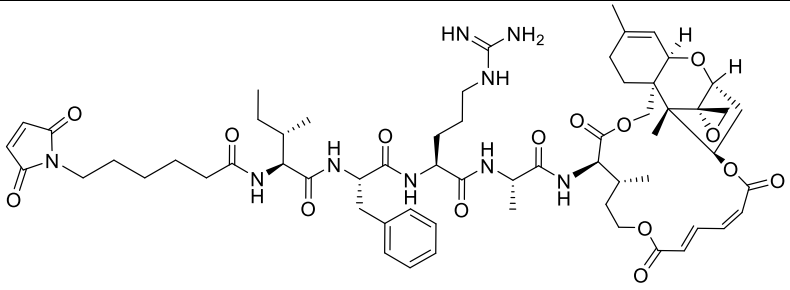
| Compound | Structure |
|---|---|
| **10a** (n = 1) |  |

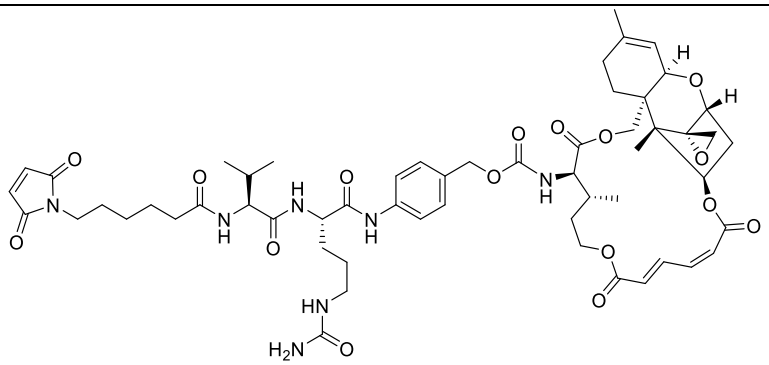
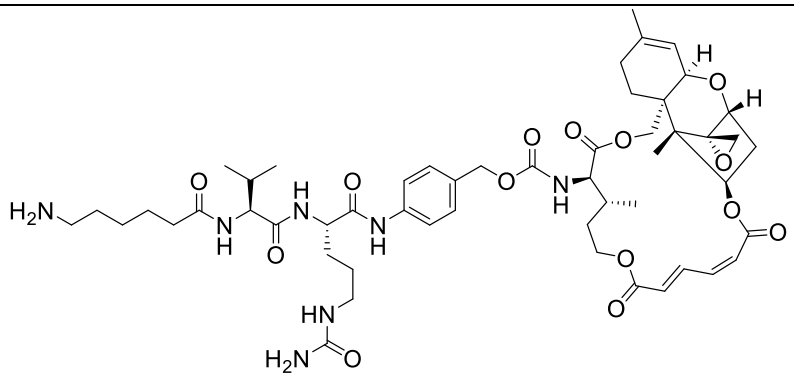
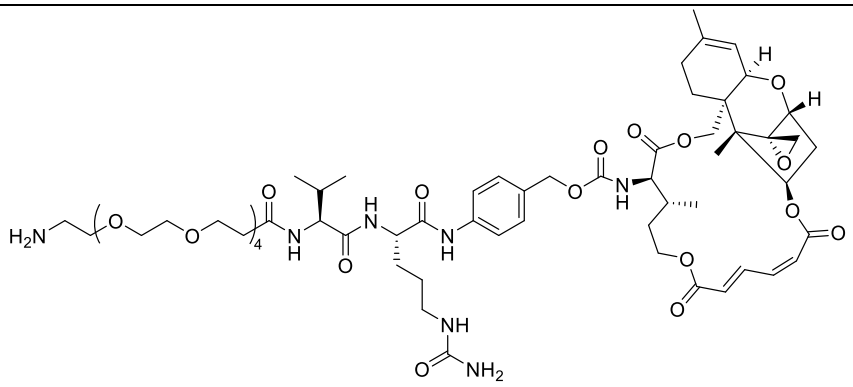
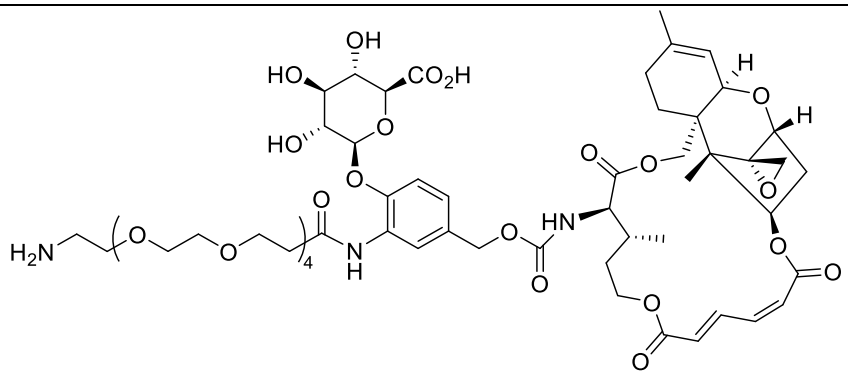
| Compound | Structure |
|---|---|
| **10b** (n = 2) |  |
| **10c** (n = 3) |  |
| **12a** (n = 1) |  |
| **12b** (n = 2) |  |

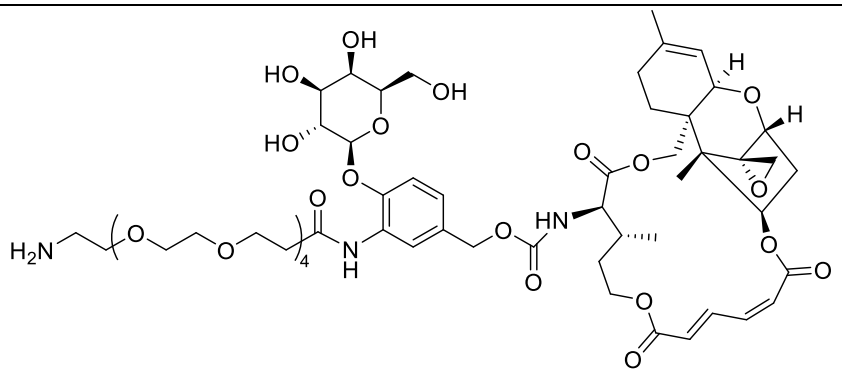
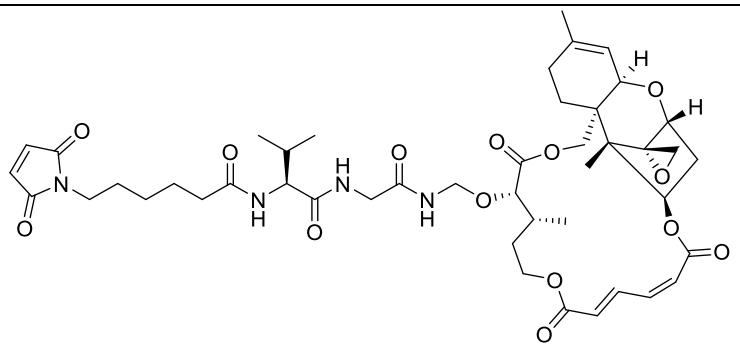
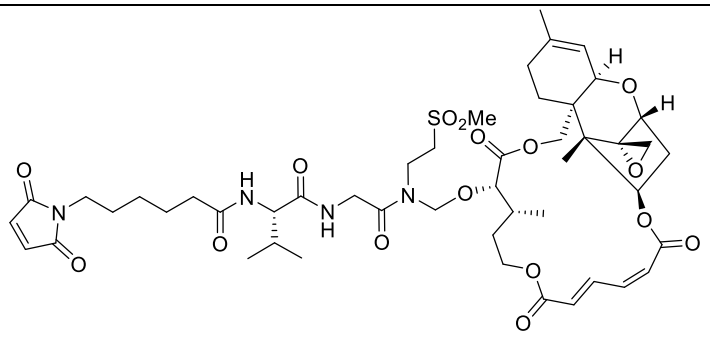
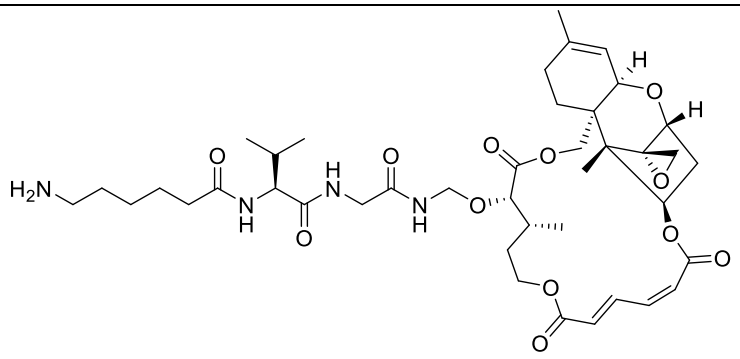
| Compound | Structure |
|---|---|
| **12c** (n = 3) |  |
| **19a** (n = 1) |  |
| **19b** (n = 2) |  |
| **19c** (n = 3) |  |

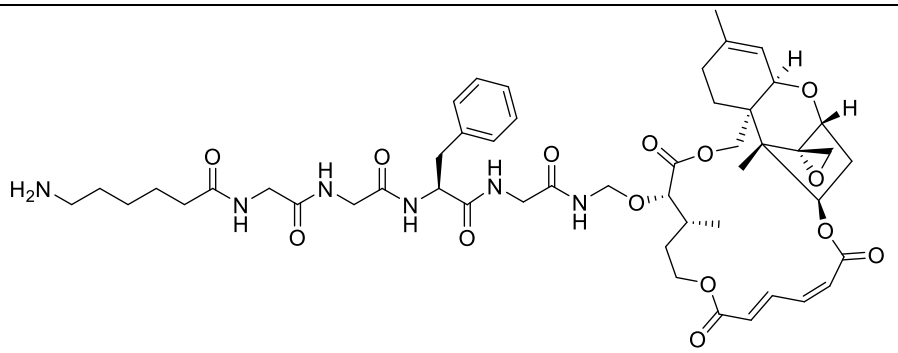
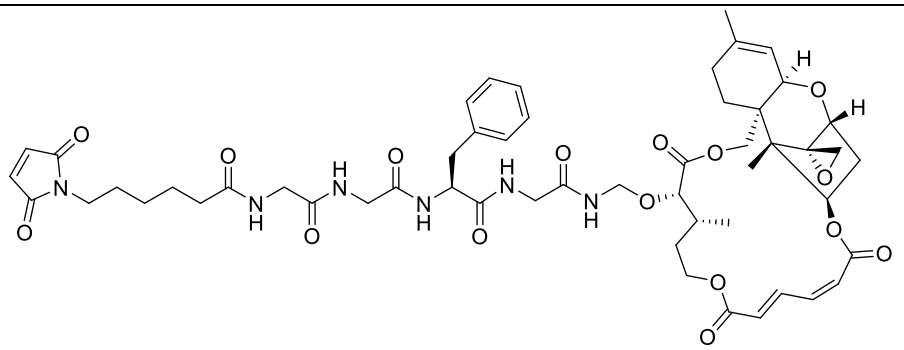
| Compound | Structure |
|---|---|
| **21a** (n = 1) |  |
| **21b** (n = 2) |  |
| **21c** (n = 3) |  |
| **37** |  |

| Compound | Structure |
|---|---|
| **46** |  |
| **53** |  |
| **70a** |  Major diastereomer |
| **70b** |  Minor Diastereomer |

| Compound | Structure |
|---|---|
| 74 |  |
| 75 |  |
| 76 |  |
| 88 |  |
| 91 |  |

| Compound | Structure |
|---|---|
| **97** |  |
| **95** |  |
| **101** |  |
| **106** |  |

| Compound | Structure |
|---|---|
| 109 |  |
| 114 |  |
| 118 |  |
| 121 |  |

| Compound | Structure |
|---|---|
| **124** |  |
| **126** |  |

24. A compound of Formula V:

$Z\text{-}(L\text{-}X)_v$ **V**

or a pharmaceutically acceptable derivative thereof, wherein:

Z is an anti-influenza antigen-binding domain, an anti-SARS-CoV-2 antigen-binding domain, or an anti-ebola virus antigen-binding domain;

L is a linking group;

X is a residue from conjugation reaction between a linking group (L) and a compound of any one of claims 1-23; or

-L-X is a residue from conjugation reaction between Z and a compound of any one of claims 15-23; and

v is an integer from 1 to 12.

25. The compound of claim 24, wherein v is an integer from 1 to 10, from 1 to 8, from 1 to 6, or from 1 to 4.

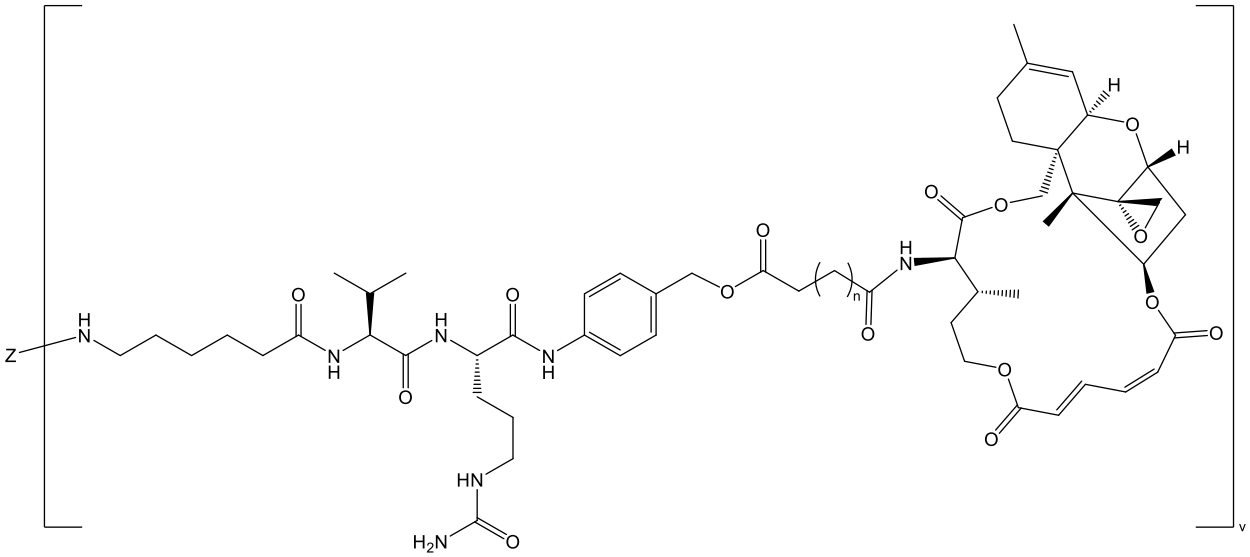
26. The compound of any one of claims 24-25, wherein v is 1, 2, 3, 4, 5, 6, 7 or 8.

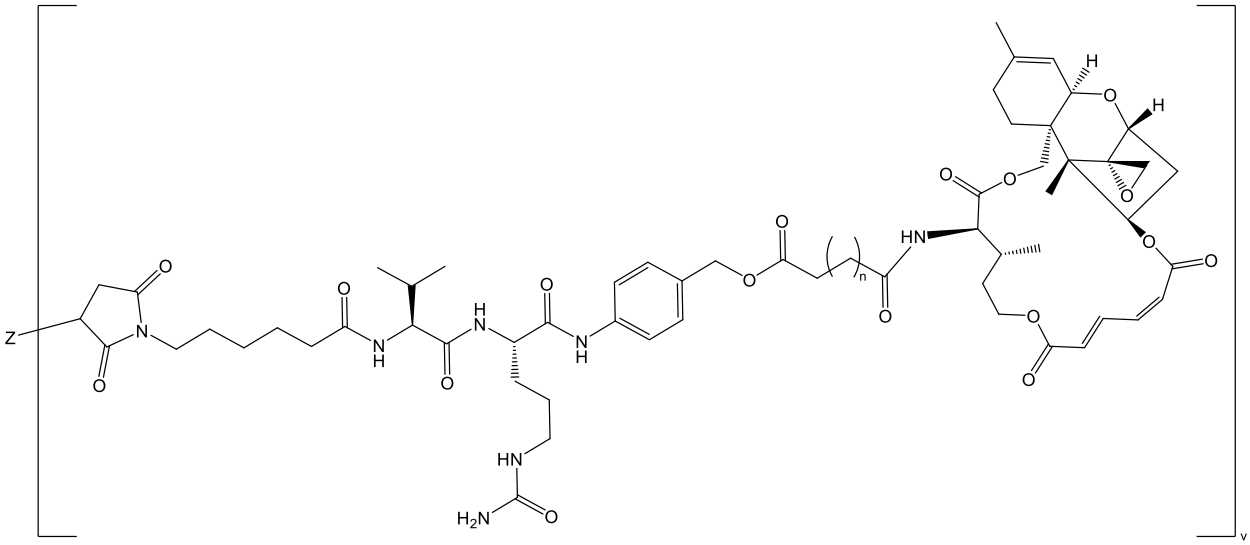
27. The compound of any one of claims 24-26, wherein Z comprises an antibody heavy chain and further includes a peptide tag at the C-terminus of the antibody heavy chain, wherein the peptide tag is ELQRP, LLQG, LLQGG, LLQLLQG, LLQYQG, LLQGA, LLQGSG, SLLQG, LQG, LLQLQ, LLQLLQ, LLQGR, LLQYQGA, LQGG, LGQG or LLQLLQGA.

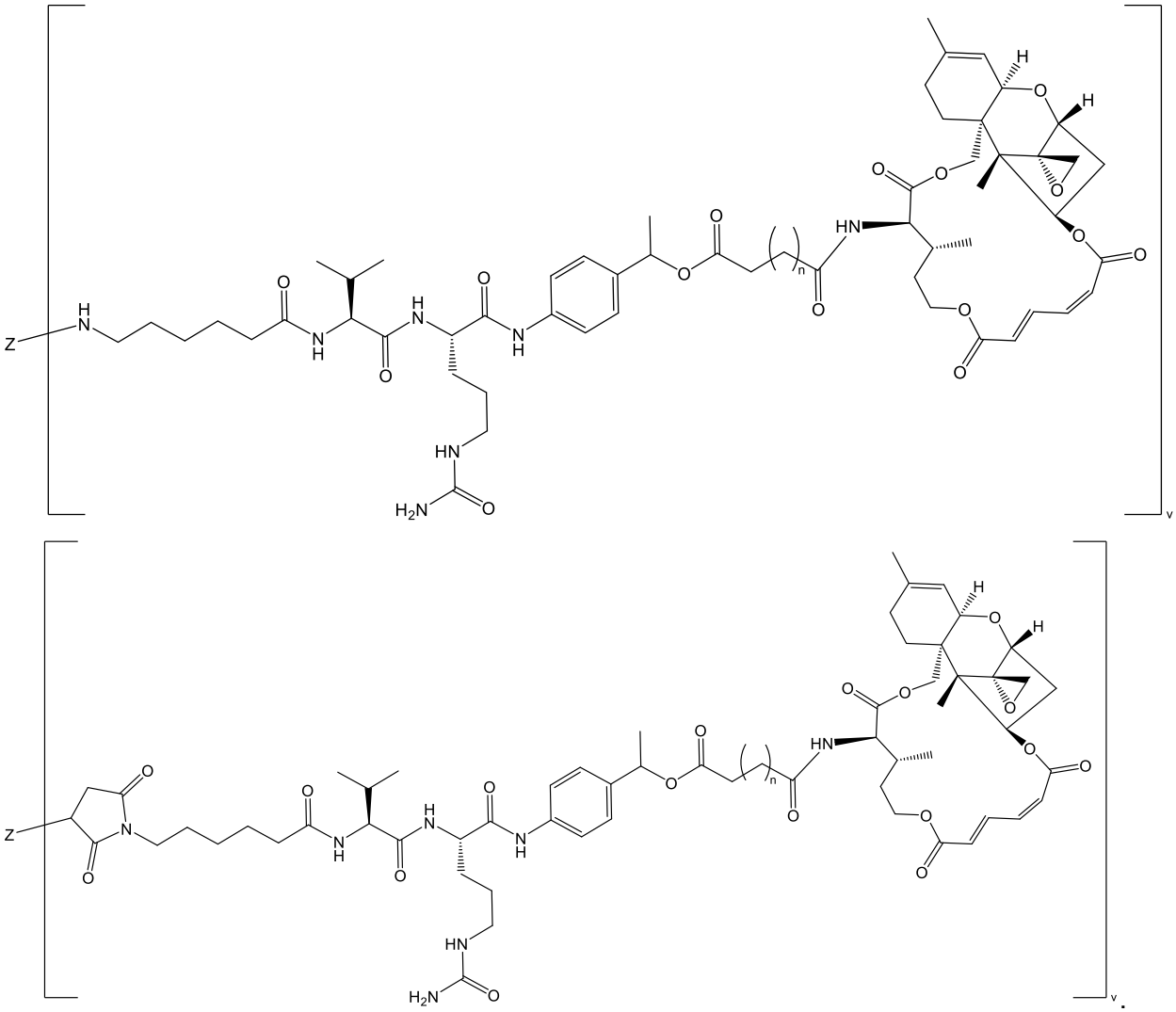
28. The compound of any one of claims 24-27, wherein Z comprises two antibody heavy chains and a peptide tag at the C-terminus of each antibody heavy chain.

29. The compound of any one of claims 27-28, wherein the peptide tag is the pentapeptide sequence LLQGA or ELQGP.

30. The compound of any one of claims 24-29, having one of the following formulae:







31. A pharmaceutical composition, comprising a compound of any one of claims 1-30 and a pharmaceutically acceptable carrier.

32. Use of a compound of any one of claims 1-30 or the composition of claim 31 in the manufacture of a medicament for treating influenza infection in a subject.

33. The use of claim 32, wherein the influenza is influenza A.

34. Use of a compound of any one of claims 1-30 or the composition of claim 31 in the manufacture of a medicament for treating SARS-CoV-2 infection in a subject.

35. The use of claim 34, wherein the SARS-CoV-2 is an omicron variant.

36. Use of a compound of any one of claims 1-30 or the composition of claim 31 in the manufacture of a medicament for treating ebola infection in a subject.