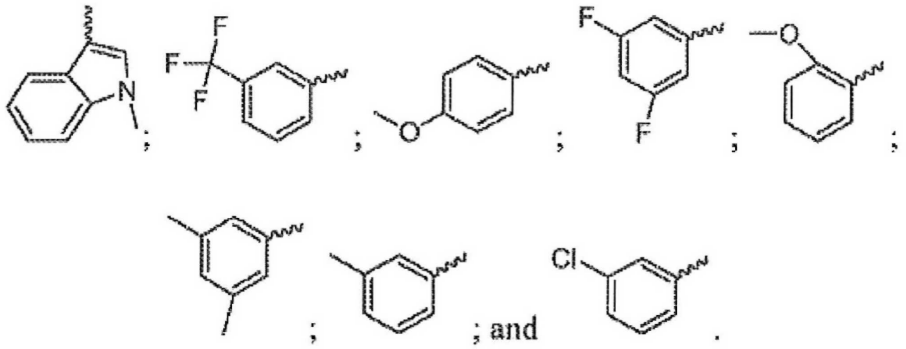


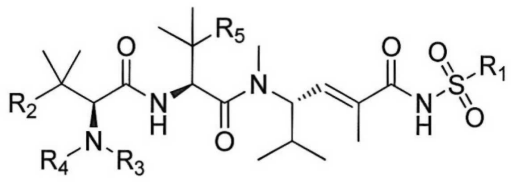
In another further embodiment, R_{27} is :



In another further embodiment, R_{16}, R_{17} and R_{18} are each methyl.

In another further embodiment, R_{16}, is H, R_{17} is methyl, and R_{18} is methyl.

In another embodiment, there is provided a compound having the following structure (I):



(I)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

R_2 is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

R_3 is selected from the group consisting of H and $C_{1\text{-}6}$alkyl;

R_4 is selected from the group consisting of H and $C_{1\text{-}6}$alkyl; and

R_5 is selected from the group consisting of $C_{1\text{-}6}$alkyl and -SH.

It is understood that any embodiment of the compounds of structure (Ib), as set forth above, and any specific substituent set forth herein for a R_{25}, R_{26}, R_{16}, R_{17}, R_{18}, R_{18} and R_{20} group in the compounds of structure (Ib), as set forth above, may be independently combined with other embodiments and/or substituents of compounds of structure (I) to form embodiments of the present disclosure not specifically set forth above. In addition, in the event that a list of substitutents is listed for any particular R_{25}, R_{26}, R_{16}, R_{17}, R_{18}, R_{18} and R_{20} in a particular embodiment and/or claim, it is understood that each individual substituent may be deleted from the particular embodiment and/or claim and that the remaining list of substituents will be considered to be within the scope of the present disclosure.

In one embodiment, the invention provides a method of making a compound having structure (I), (Ia) or (Ib).

In another embodiment, a pharmaceutical composition is provided comprising a compound having structure (I), (Ia) or (Ib), or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, a method of using a compound having structure (I), (Ia) or (Ib), or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof,

pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In one embodiment, compositions comprising biologically active compounds having structure or (I), (Ia) or (Ib), or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, linked directly or indirectly to a targeting moiety are provided.

In one embodiment, the invention provides compositions having the following structure:

(T)-(L)-(D)

(VI)

wherein (T) is a targeting moiety, (L) is an optional linker, and (D) is a compound having structure (I), (Ia) or (Ib), or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof. (D) is covalently attached to (L), if (L) is present, or (T), if (L) is not present.

In a particular embodiment, (D) is a compound having the structure (Ib).

In another embodiment, the invention provides a composition having the following structure:

(T)-(L)-(D)

(II)

wherein (T) is a targeting moiety, (L) is an optional linker, and (D) is a compound as described herein.

In one embodiment, the targeting moiety is an antibody. Accordingly, in one embodiment, antibody-drug conjugates (ADCs) comprising compounds having structure (I), (Ia) or (Ib), or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, are provided.

In another embodiment, there is provided a pharmaceutical composition comprising a compound as described herein, a composition as described herein, or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In one embodiment, the invention provides a method of making a composition having structure (VI).

In another embodiment, a pharmaceutical composition is provided comprising a composition having structure (VI), or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, a method of using a composition having structure (VI) in therapy is provided. In particular, the present disclosure provides a method of treating cancer in a mammal comprising administering to a mammal in need thereof an effective amount of a composition having structure (VI) or a pharmaceutical

composition comprising a composition having structure (VI) and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, the present disclosure provides a method of inhibiting tumor growth in a mammal comprising administering to a mammal in need thereof an effective amount of a composition having structure (VI) or a pharmaceutical composition comprising a composition having structure ('VI) and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, the present disclosure provides a method of killing cancer cells in vitro using a composition having structure (V1). In another embodiment, the present disclosure provides a method of killing cancer cells in vivo in a mammal, comprising administering to a mammal in need thereof an effective amount of a composition having structure (VI) or a phannaceutical composition comprising a composition having structure (VI) and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, the present disclosure provides a method of increasing the survival time of a mammal having cancer, comprising administering to a mammal in need thereof an effective amount of a composition having structure (VI) or a pharmaceutical composition comprising a composition having structure (VI) and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, there is provided use of a compound as described herein, a composition as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for inhibiting tumor growth in a mammal.

These and other aspects of the disclosure will be apparent upon reference to the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows summarized cytotoxicity data (EC_{50}) for each of Componds A-E for two cell lines (HCC1954 and Jurkat).

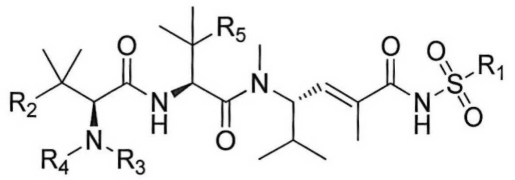
Figure 2 shows a cytotoxicity data plot for Compound A on two cell lines (HCC1954 and Jurkat).

Figure 3 shows a cytotoxicity data plot for Compound B on two cell lines (HCC1954 and Jurkat).

CLAIMS

What is claimed is:

1. A compound having the following structure (I):



(I)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

R_2 is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

R_3 is selected from the group consisting of H and $C_{1\text{-}6}$alkyl;

R_4 is selected from the group consisting of H and $C_{1\text{-}6}$alkyl; and

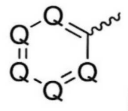
R_5 is selected from the group consisting of $C_{1\text{-}6}$alkyl and -SH.

2. The compound according to claim 1, wherein each optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl is, independently, optionally substituted with =O, =S, -OH, $-OR_6$, $-O_2CR_6$, -SH, $-SR_6$, $-SOCR_6$, $-NH_2$, $-N_3$, $-NHR_6$, $-N(R_6)_2$, $-NHCOR_6$, $-NR_6COR_6$, -I, -Br, -Cl, -F, -CN, $-CO_2H$, $-CO_2R_6$, -CHO, $-COR_6$, $-CONH_2$, $-CONHR_6$, $-CON(R_6)_2$, -COSH, $-COSR_6$, $-NO_2$, $-SO_3H$, $-SOR_6$ or $-SO_2R_6$, wherein each R_6 is, independently, alkyl optionally substituted with halogen, -OH or -SH.

3. The compound according to claim 1 or claim 2, wherein each optionally substituted aryl and optionally substituted heteroaryl is, independently, selected from the group consisting of

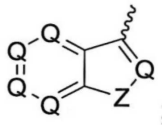
optionally substituted phenyl, optionally substituted naphthyl, optionally substituted anthracyl, optionally substituted phenanthryl, optionally substituted furyl, optionally substituted pyrrolyl, optionally substituted thiophenyl, optionally substituted benzofuryl, optionally substituted benzothiophenyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted imidazolyl, optionally substituted thiazolyl, optionally substituted oxazolyl, and optionally substituted pyridinyl.

4. The compound according to any one of claims 1 to 3, wherein R_2 is selected from one of the following structures (III), (IV), (V) and (VI):



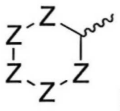
;

(III)



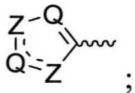
;

(IV)



; and

(V)



;

(VI)

wherein:

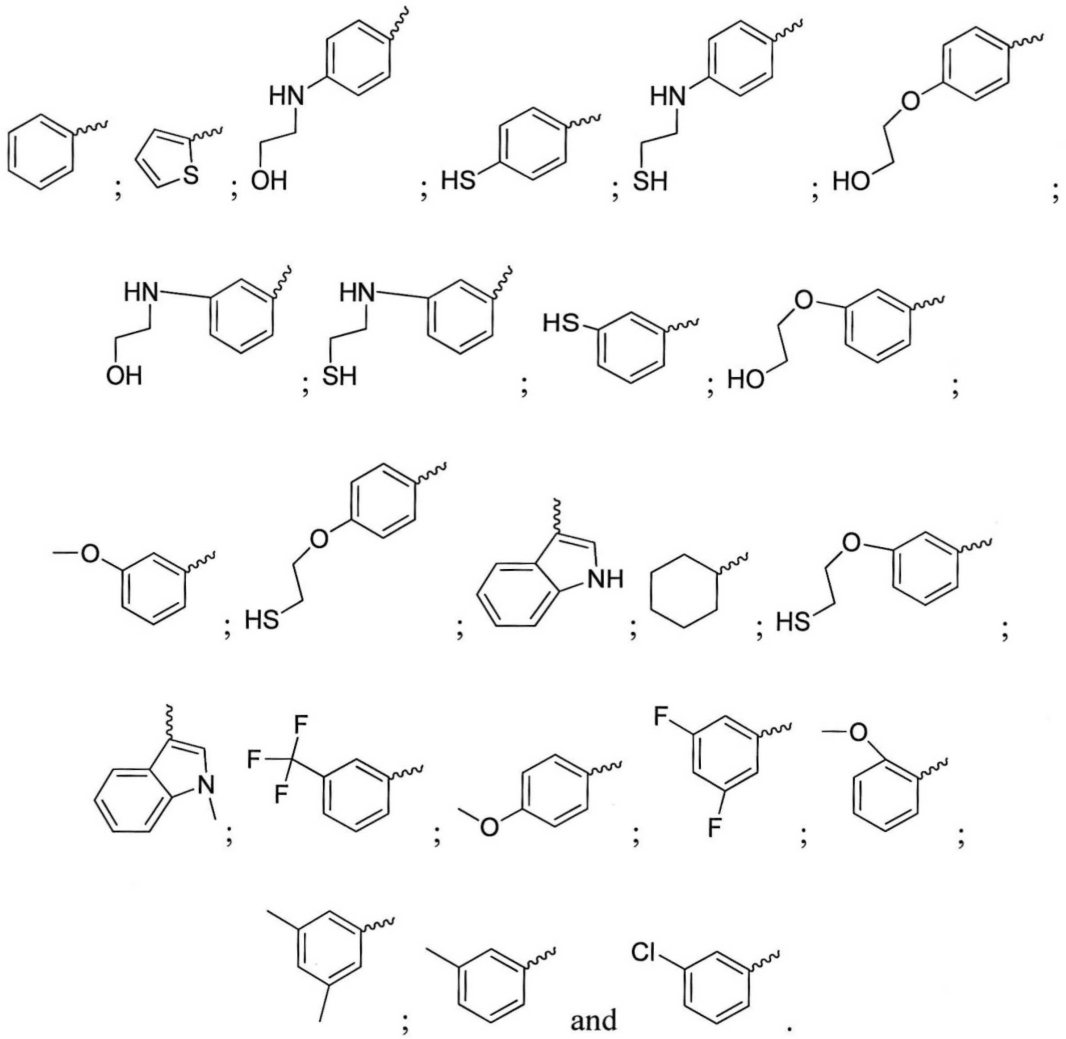
Q is CR_7 or N;

Z is $C(R_7)_2$, NR_7, S, or O;

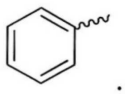
wherein in structure (VI), one instance of Z is CR_7 or N, and the other instance is $C(R_7)_2$, NR_7, S, or O;

each R_7 is, independently, selected from the group consisting of H, -OH, -OR_6, -O_2CR_6, -SH, -SR_6, -$SOCR_6$, -NH_2, -N_3, -NHR_6, -$N(R_6)_2$, -$NHCOR_6$, -NR_6COR_6, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R_6, -CHO, -COR_6, -$CONH_2$, -$CONHR_6$, -$CON(R_6)_2$, -COSH, -$COSR_6$, -NO_2, -SO_3H, -SOR_6 or -SO_2R_6, wherein each R_6 is, independently, alkyl optionally substituted with halogen, -OH or -SH.

5. The compound according to claim 4, wherein R_2 is selected from the group consisting of:



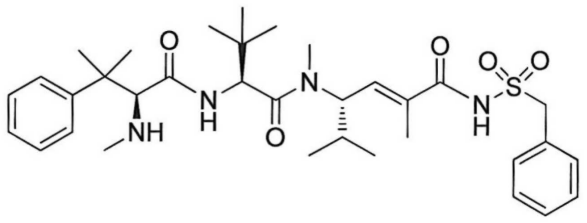
6. The compound according to claim 5, wherein R_2 is:



7. The compound according to any one of claims 1-6, wherein R_3, R_4 and R_5 are each methyl.

8. The compound according to any one of claims 1-6, wherein R_3 is H, R_4 is methyl, and R_5 is methyl.

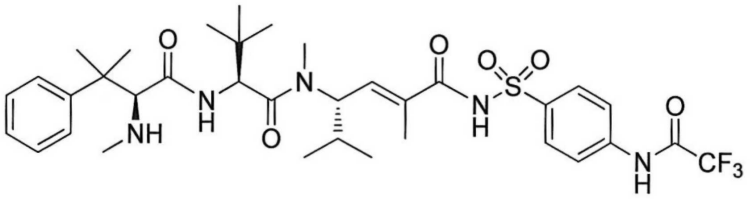
9. The compound according to claim 1, which is (S,E)-N-(benzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(14)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

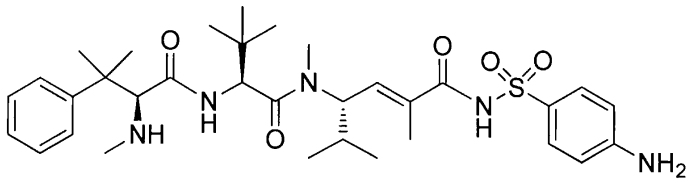
10. The compound according to claim 1, which is (S,E)-2,5-dimethyl-N-(4-(2,2,2-trifluoroacetamido)phenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(23)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

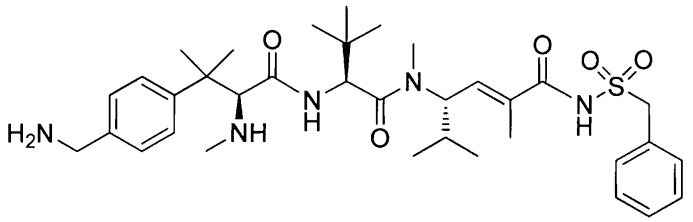
11. The compound according to claim 1, which is (S,E)-N-(4-aminophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(24)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

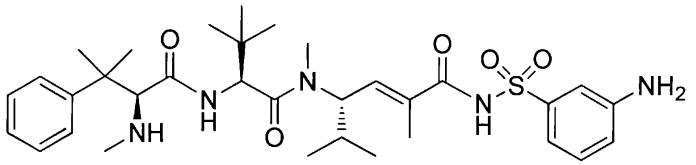
12. The compound according to claim 1, which is (S,E)-4-((S)-2-((S)-3-(4-(aminomethyl)phenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-N-(benzylsulfonyl)-2,5-dimethylhex-2-enamide, having the following structure:



(41)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

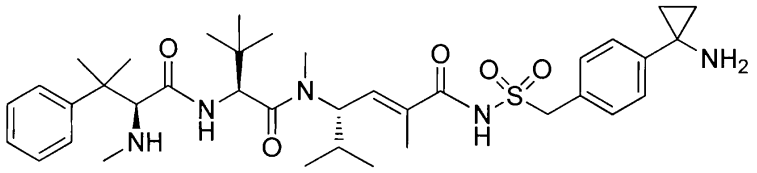
13. The compound according to claim 1, which is (S,E)-N-(3-aminophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(48)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

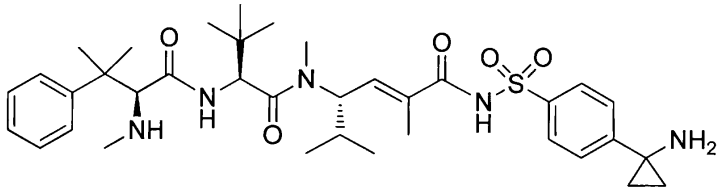
14. The compound according to claim 1, which is (S,E)-N-(4-(1-aminocyclopropyl)benzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(58)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

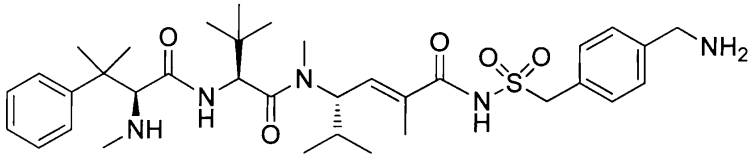
15. The compound according to claim 1, which is (S,E)-N-(4-(1-aminocyclopropyl)phenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(63)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

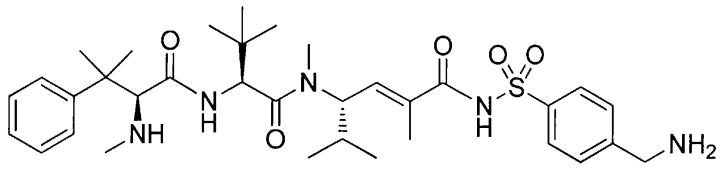
16. The compound according to claim 1, which is (S,E)-N-(4-(aminomethyl)benzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(77)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

17. The compound according to claim 1, which is (S,E)-N-(4-(aminomethyl)phenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, having the following structure:



(85)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

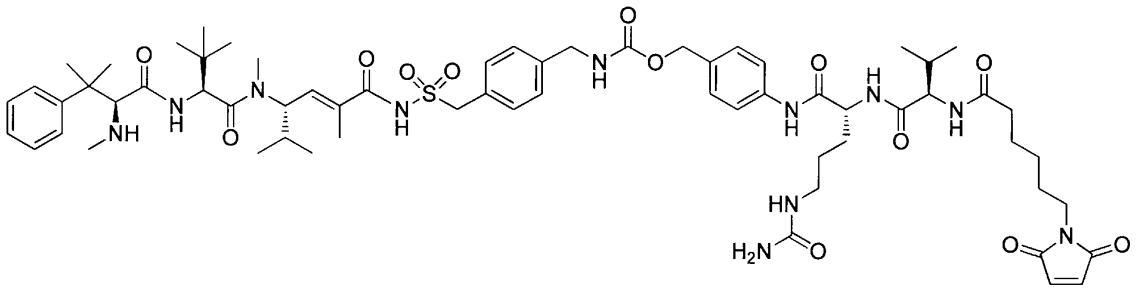
18. A composition having the following structure:

(T)-(L)-(D)

(II)

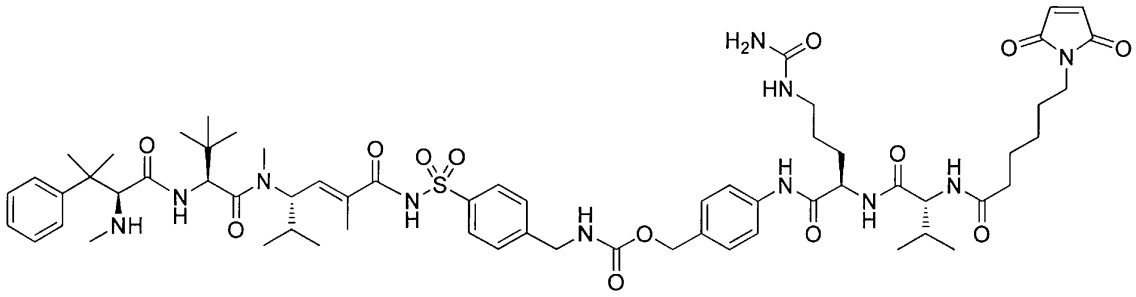
wherein (T) is a targeting moiety, (L) is an optional linker, and (D) is a compound according to any one of claims 1 to 9 and 11 to 17.

19. The composition according to claim 18, wherein (L-D) is MC-VC-PABC-77, having the following structure:



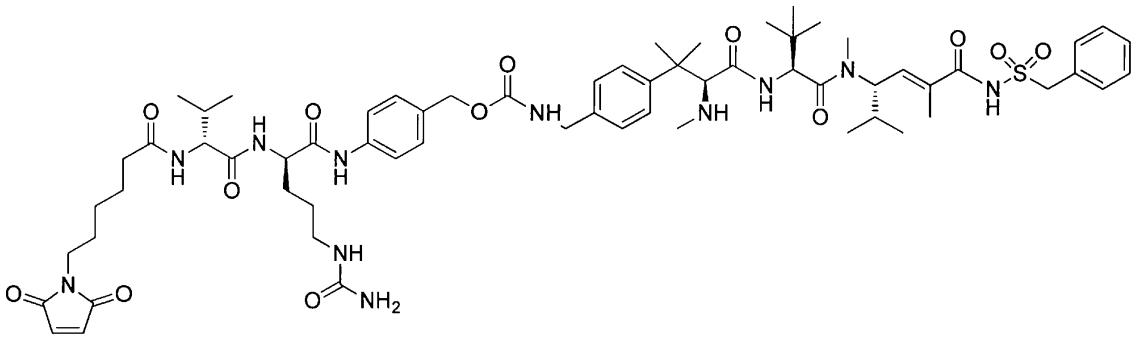
(119).

20. The composition according to claim 18, wherein (L-D) is 4-((R)-2-((R)-2-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl 4-(N-((S,E)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enoyl)sulfamoyl)benzylcarbamate (MC-VC-PABC-85), having the following structure:



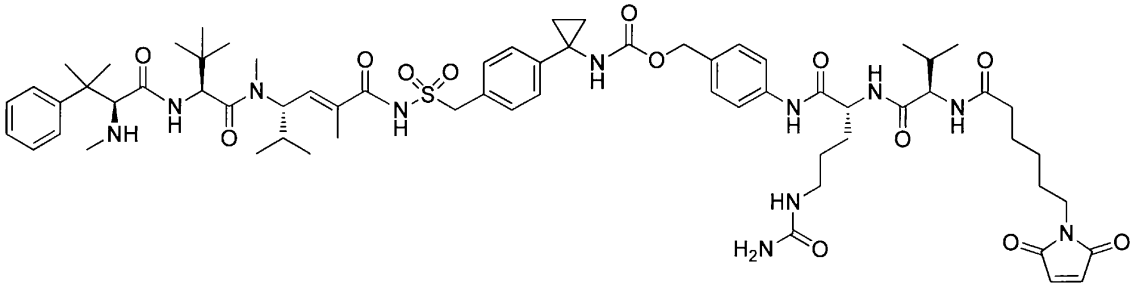
(120).

21. The composition according to claim 18, wherein (L-D) is MC-VC-PABC-41, having the following structure:



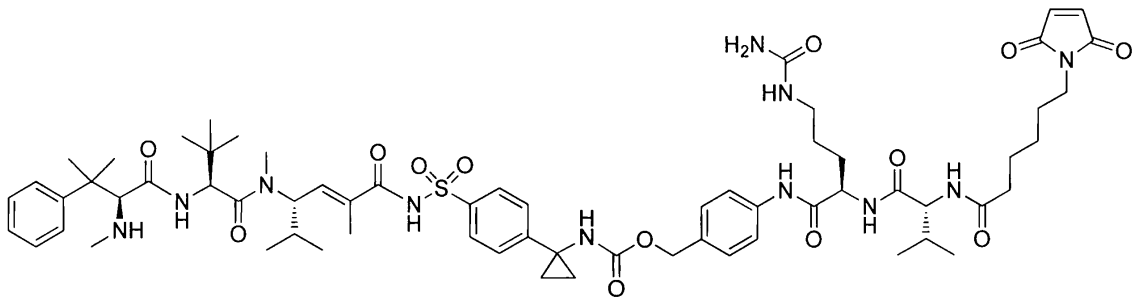
(122).

22. The composition according to claim 18, wherein (L-D) is MC-VC-PABC-58, having the following structure:



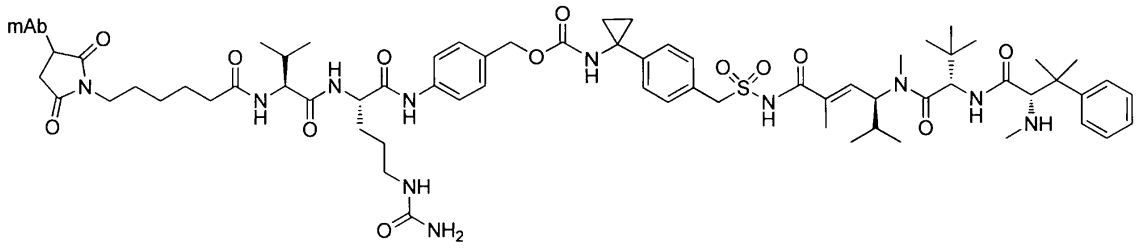
(158).

23. The composition according to claim 18, wherein (L-D) is MC-VC-PABC-63, having the following structure:



(159).

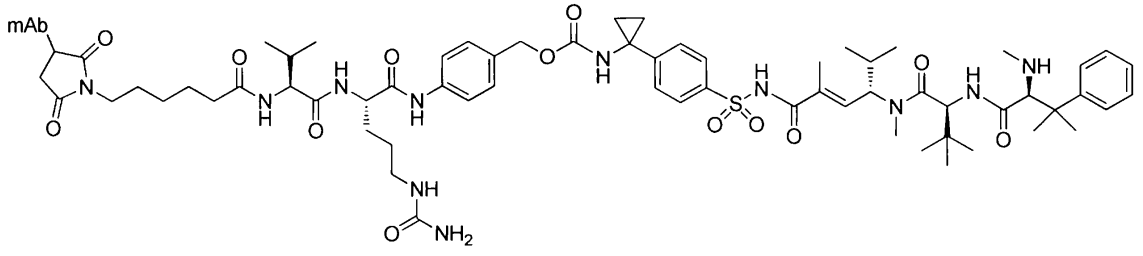
24. The composition according to claim 18, wherein (T-L-D) is mAb-MC-VC-PABC-58, having the following structure:



(155)

wherein mAb is trastuzumab.

25. The composition according to claim 18, wherein (T-L-D) is mAb-MC-VC-PABC-63, having the following structure:



(157)

wherein mAb is trastuzumab.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17, a composition according to any one of claims 18 to 25, or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

27. Use of a compound according to any one of claims 1 to 17, a composition according to any one of claims 18 to 25, or a pharmaceutical composition according to claim 26, in the manufacture of a medicament for inhibiting tumor growth in a mammal.