In one aspect, the present disclosure is directed to a compound of Formula I:

T–L–P

I

wherein:

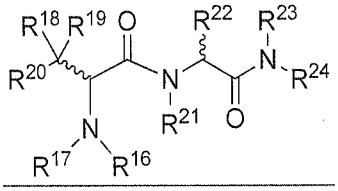
T is a targeting moiety comprising a VAR2CSA polypeptide, and

L–P is L^1–P^1 or L^2–P^2;

wherein:

L^1 is a linker, or L^1 is absent;

P^1 is a monovalent radical of a compound of Formula XIV



XIV

wherein:

R^{16} and R^{17} are each independently H or a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, and the carbon atoms are optionally substituted with: –OH, –I, –Br, –Cl, –F, –CN, $-CO_2H$, –CHO, –COSH, or $-NO_2$; or R^{17} and R^{20} are fused and form a ring;

R^{18} and R^{19} are independently selected from the group consisting of: H, R^{25}, and ArR^{25}–, or R^{18} and R^{19} are joined to form a ring, wherein the ring formed by joining R^{18} and R^{19} is a three to seven member non-aromatic cyclic skeleton within the definition of R^{25};

R^{20} is selected from the group consisting of: H, R^{25}, ArR^{25}–, and Ar; or R^{20} and R^{17} are fused and form a ring;

R^{21} is selected from the group consisting of: H, R^{25}, and ArR^{25}–;

R^{22} and R^{23} are independently selected from the group consisting of: H, R^{25}, and ArR^{25}–;

R^{24} is: $-Y-(CO)NHSO_2-R^{26}$;

R^{25} is a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, zero to four nitrogen atoms, zero to four oxygen atoms, and zero to four sulfur atoms, and

the carbon atoms are optionally substituted with: =O, =S, OH, $-OR^{28}$, $-O_2CR^{28}$, –SH, $-SR^{28}$, $-SOCR^{28}$, $-NH_2$, $-NHR^{28}$, $-N(R^{28})_2$, $-NHCOR^{28}$, $-NR^{28}COR^{28}$, –I, –Br, –Cl, –F, –CN, $-CO_2H$, $-CO_2R^{28}$, –CHO, $-COR^{28}$, $-CONH_2$, $-CONHR^{28}$, $-CON(R^{28})_2$, –COSH, $-COSR^{28}$, $-NO_2$, $-SO_3H$, $-SOR^{28}$, or $-SO_2R^{28}$, wherein R^{28} is a linear, branched or cyclic, one to ten carbon saturated or unsaturated alkyl group;

Y is a linear, saturated or unsaturated, one to six carbon alkyl group, optionally substituted with R^{25}, ArR^{25}–, or X;

X is selected from the group consisting of: –OH, $-OR^{25}$, =O, =S, $-O_2CR^{25}$, –SH, $-SR^{25}$, $-SOCR^{25}$, $-NH_2$, $-NHR^{25}$, $-N(R^{25})_2$, $-NHCOR^{25}$, $-NRCOR^{25}$, –I, –Br, –Cl, –F, –CN, $-CO_2H$, $-CO_2R^{25}$, –CHO, $-COR^{25}$, $-CONH_2$, $-CONHR^{25}$, $-CON(R^{25})_2$, –COSH, $-COSR^{25}$, $-NO_2$, $-SO_3H$, $-SOR^{25}$, and $-SO_2R^{25}$; and

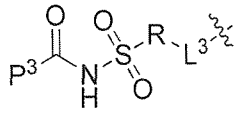
R^{26} is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl ~~and~~or optionally substituted heteroaryl; and

wherein:

L^2 is a linker;

P^2 is a cytotoxic compound; and

L^2–P^2 has the following structure (III):



III

wherein:

R is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is,

independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl, or R is absent;

P^3 is the remaining portion of compound P^2; and

L^3 is the remaining portion of linker L^2 or is absent.

In one aspect, the present disclosure is directed to a pharmaceutical composition comprising the compound as disclosed herein, and a pharmaceutically acceptable carrier, diluent or excipient.

In one aspect, the present disclosure is directed to a compound as disclosed herein or the pharmaceutical composition as disclosed herein for use in therapy.

In one aspect, the present disclosure is directed to the use of a compound as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a mammal, increasing survival of a mammal having cancer, or inhibiting tumor growth in a mammal.

In one aspect, the present disclosure is directed to the use of a compound as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of an indication selected from: cancer, arthritis, arthrosis, multiple sclerosis, neural damage, cartilage damage, and psoriasis.

CLAIMS

What is claimed is:

1. A compound of Formula I:

T–L–P

I

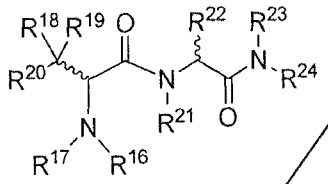
wherein:

T is a targeting moiety comprising a VAR2CSA polypeptide;

L–P is selected from: L^1–P^1 or L^2–P^2;

L^1 is a linker, or L^1 is absent;

P^1 is a monovalent radical of a compound of Formula XIV



XIV

wherein:

R^{16} and R^{17} are independently selected from the group consisting of: H and a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, and the carbon atoms are optionally substituted with: –OH, –I, –Br, –Cl, –F, –CN, $–CO_2H$, –CHO, –COSH, or $–NO_2$; or R^{17} and R^{20} are fused and form a ring;

R^{18} and R^{19} are independently selected from the group consisting of: H, R^{25}, and ArR^{25}–, or R^{18} and R^{19} are joined to form a ring;

R^{20} is selected from the group consisting of: H, R^{25}, ArR^{25}–, and Ar; or R^{20} and R^{17} are fused and form a ring;

R^{21} is selected from the group consisting of: H, R^{25}, and ArR^{25}–;

R^{22} and R^{23} are independently selected from the group consisting of: H, R^{25}, and ArR^{25}–;

R^{24} is: $–Y–(CO)NHSO_2–R^{26}$

R^{25} is defined as a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, zero to four nitrogen atoms, zero to four oxygen atoms, and zero to four sulfur atoms, and the carbon atoms are optionally substituted with: =O, =S, OH, $–OR^{28}$, $–O_2CR^{28}$, –SH, $–SR^{28}$, $–SOCR^{28}$, $–NH_2$, $–NHR^{28}$, $–N(R^{28})_2$, $–NHCOR^{28}$, $–NR^{28}COR^{28}$, –I, –Br, –Cl, –F, –CN, $–CO_2H$, $–CO_2R^{28}$, –CHO, $–COR^{28}$, $–CONH_2$, $–CONHR^{28}$, $–CON(R^{28})_2$,

–COSH, –$COSR^{28}$, -NO_2, -SO_3H, -SOR^{28}, -SO_2R^{28}, wherein R^{28} is a linear, branched or cyclic, one to ten carbon saturated or unsaturated alkyl group;

the ring formed by joining R^{18} and R^{19} is a three to seven member non-aromatic cyclic skeleton within the definition of R^{25},

Y is defined as a moiety selected from the group consisting of: a linear, saturated or unsaturated, one to six carbon alkyl group, optionally substituted with R^{25}, ArR^{25}–, or X; and,

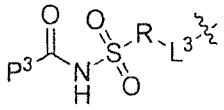
X is defined as a moiety selected from the group consisting of: –OH, –OR^{25}, =O, =S, –O_2CR^{25}, –SH, –SR^{25}, –$SOCR^{25}$, –NH_2, –NHR^{25}, –$N(R^{25})_2$, –$NHCOR^{25}$, –$NRCOR^{25}$, –I, –Br, –Cl, –F, –CN, –CO_2H, –CO_2R^{25}, –CHO, –COR^{25}, –$CONH_2$, –$CONHR^{25}$, –$CON(R^{25})_2$, –COSH, –$COSR^{25}$, –NO_2, –SO_3H, –SOR^{25}, and –SO_2R^{25};

R^{26} 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, –COR^{27}, –CSR^{27}, –OR^{27}, and –NHR^{27}, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl; and

L^2 is a linker;

P^2 is a biologically active compound; and

L^2–P^2 has the following structure (III):



III

wherein:

R is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, –COR^{27}, –CSR^{27}, –OR^{27}, and –NHR^{27}, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl, or R is absent;

P^3 is the remaining portion of compound P^2; and

L^3 is optionally the remaining portion of linker L^2.

2. The compound of claim 1, wherein said VAR2CSA polypeptide consists of a sequential amino acid sequence of

   a. ID1;

   b. DBL2Xb; and optionally

   c. ID2a.

3. The compound of claim 1, wherein said VAR2CSA polypeptide binds chondroitin sulfate A (CSA) on proteoglycans (CSPG) with an affinity as measured by a K_D lower than 100 nM, lower than 50 nM, lower than 10 nM, or lower than 5 nM.

4. The compound of any one of claims 1 to 3, wherein said VAR2CSA polypeptide comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from: 1-577 of SEQ ID NO:1; 1-592 of SEQ ID NO:3; 1-579 of SEQ ID NO:4; 1-576 of SEQ ID NO:5; 1-586 of SEQ ID NO:10; 1-579 of SEQ ID NO:11; 1-565 of SEQ ID NO:29; 1-584 of SEQ ID NO:34; 1-569 of SEQ ID NO:36; 1-575 of SEQ ID NO:37; 1-592 of SEQ ID NO:38; 1-603 of SEQ ID NO:41; 1-588 of SEQ ID NO:43; 1-565 of SEQ ID NO:44; 1-589 of SEQ ID NO:45; 1-573 of SEQ ID NO:48; 1-583 of SEQ ID NO:53; 1-569 of SEQ ID NO:54; 578-640 of SEQ ID NO:1; 593-656 of SEQ ID NO:3; 580-643 of SEQ ID NO:4; 577-640 of SEQ ID NO:5; 587-650 of SEQ ID NO:10; 580-643 of SEQ ID NO:11; 566-628 of SEQ ID NO:29; 585-647 of SEQ ID NO:34; 570-632 of SEQ ID NO:36; 576-639 of SEQ ID NO:37; 593-655 of SEQ ID NO:38; 604-667 of SEQ ID NO:41; 589-652 of SEQ ID NO:43; 30 566-628 of SEQ ID NO:44; 590-653 of SEQ ID NO:45; 574-637 of SEQ ID NO:48; 584-646 of SEQ ID NO:53; 570-632 of SEQ ID NO:54; SEQ ID NO:2; SEQ ID NO:6; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; SEQ ID NO:23; SEQ ID NO:24; SEQ ID NO:25; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:39; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:46; SEQ ID NO:47; SEQ ID NO:49; SEQ ID NO:50; SEQ ID NO:51; and SEQ ID NO:52.

5. The compound of any one of claims 1 to 4, wherein said VAR2CSA polypeptide consists of an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from: 1-577 of SEQ ID NO:1; 1-592 of SEQ ID NO:3; 1-579 of SEQ ID NO:4; 1-576 of SEQ ID NO:5; 1-586 of SEQ ID NO:10; 1-579 of SEQ ID NO:11; 1-565 of SEQ ID NO:29; 1-584 of SEQ ID NO:34; 1-569 of SEQ ID NO:36; 1-575 of SEQ ID NO:37; 1-592 of

SEQ ID NO:38; 1-603 of SEQ ID NO:41; 1-588 of SEQ ID NO:43; 1-565 of SEQ ID NO:44; 1-589 of SEQ ID NO:45; 1-573 of SEQ ID NO:48; 1-583 of SEQ ID NO:53; 1-569 of SEQ ID NO:54; SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:29; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:48; SEQ ID NO:53; and SEQ ID NO:54.

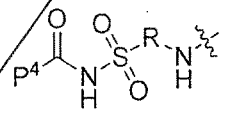
6. The compound of any one of claims 1 to 4, wherein said VAR2CSA polypeptide consists of an amino acid sequence having a length of less than 700 amino acids, less than 650 amino acids, less than 600 amino acids, or less than 570 amino acids.

7. The compound of any one of claims 1 to 6, wherein said VAR2CSA polypeptide has a molecular mass of less than about 100 kDa under non-reducing conditions on an SDS-PAGE, and/or wherein said VAR2CSA polypeptide is a recombinant protein, and/or wherein said VAR2CSA polypeptide is non-glycosylated.

8. The compound of any one of claims 1 to 7, wherein L–P is L^2–P^2.

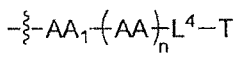
9. The compound of claim 8, wherein:

P^2 is a compound of Formula V:



V

L^2–T has the following structure (VI):



VI

wherein

P^4 is the remaining portion of compound P^2, wherein the –NH– group bonded to R in Formula V forms a peptide bond (JPB) with AA_1 in formula VI, wherein said JPB is enzymatically cleavable, wherein R is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl, , wherein each

AA is independently an amino acid, wherein n is an integer from 0 to 25, wherein L^4 is optionally the remaining portion of linker L^2, wherein T is said targeting moiety, and wherein AA_1–$(AA)_n$, taken together comprises an amino acid sequence capable of facilitating enyzmatic cleavage of said JPB.

10. The compound of claim 9, wherein AA_1–$(AA)_n$ is selected from: Phe-Lys, Val-Lys, Ala-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, and Phe-Arg.

11. The compound of any one of claims 8 to 10, wherein P^2 is a cytotoxic compound.

12. The compound of claim 11, wherein said cytotoxic compound is a microtubule disrupting peptide toxin.

13. The compound of claim 11, wherein said cytotoxic compound is selected from: hemiasterlin or an analog thereof; tubulysin or an analog thereof; and auristatin or an analog thereof.

14. The compound of claim 11, wherein said cytotoxic compound is selected from: calicheamycin, auristatin, doxorubicin, maytansinoid, taxol, ecteinascidin, geldanamycin, methotrexate Pseudomonas exotoxin A, diphtheria toxin, ricin toxin, pokeweed antiviral protein, saporin, gelonin, pyrrolobenzodiazepines (PBDs) and functional variants, fragments, and combinations thereof.

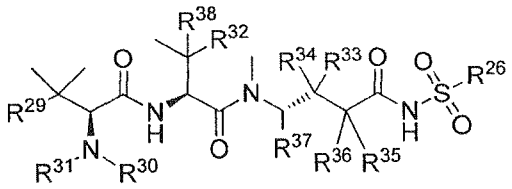
15. The compound of claim 11, wherein said cytotoxic payload is a synthetic chemotoxin not derived from a naturally occurring compound.

16. The compound of any one of claims 1 to 7, wherein L–P is L^1–P^1.

17. The compound of claim 16, wherein L^1 comprises: SPDP, SMCC, vcPABC, MCvcPABC, MTvc, ADvc, maleimide, NHS, biotin, streptavidin, NeutrAvidin, a glycoside, or a combination thereof.

18. The compound of claim 16, wherein L^1 is selected from: MTvc and ADvc; or L^1 is absent.

19. The compound of any one of claims 16 to 18, wherein P^1 is a monovalent radical of a compound of Formula XV:



XV

wherein:

R^{26} is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH;

R^{29} 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^{30} is selected from the group consisting of H and C_{1-6} alkyl;

R^{31} is selected from the group consisting of H and C_{1-6} alkyl;

R^{32} and R^{38} are independently selected from the group consisting of H, C_{1-6} alkyl and –SH, with the proviso that R^{32} and R^{38} cannot both be H;

R^{33}, R^{34}, R^{35} and R^{36} are independently H and C_{1-6} alkyl, at least one of R^{33} and R^{34} is H; or R^{34} and R^{35} form a double bond, R^{33} is H, and R^{36} is H or C_{1-6} alkyl; and

R^{37} is selected from the group consisting of H and C_{1-6} alkyl;

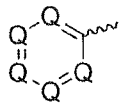
wherein each optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl is, independently, optionally substituted with =O, =S, –OH, $-OR^{27}$, $-O_2CR^{27}$, –SH, $-SR^{27}$, $-SOCR^{27}$, $-NH_2$, $-N_3$, $-NHR^{27}$, $-N(R^{27})_2$, $-NHCOR^{27}$, $-NR^{27}COR^{27}$, –I, –Br, –Cl, –F, –CN, $-CO_2H$, $-CO_2R^{27}$, –CHO, $-COR^{27}$, $-CONH_2$, $-CONHR^{27}$, $-CON(R^{27})_2$, –COSH, $-COSR^{27}$, $-NO_2$, $-SO_3H$, $-SOR^{27}$ or $-SO_2R^{27}$ wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH;

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

20. The compound of claim 19, 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.

21. The compound of claim 19, wherein R^{29} is selected from one of the following structures XVI, XVII, XVIII, and XIX:



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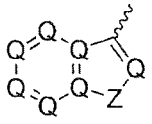
XVI



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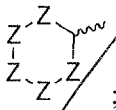
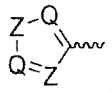
XVII



; and

XVIII



,

XIX

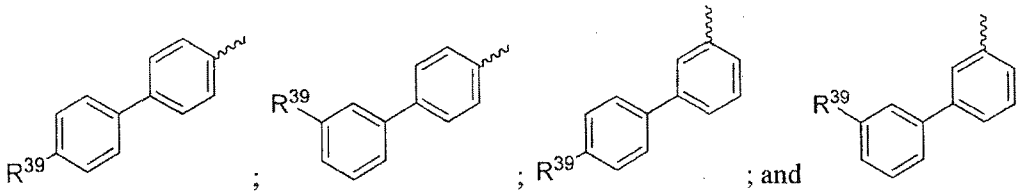
wherein:

Q is CR^{39} or N;

Z is $C(R^{39})_2$, NR^{39}, S, or O;

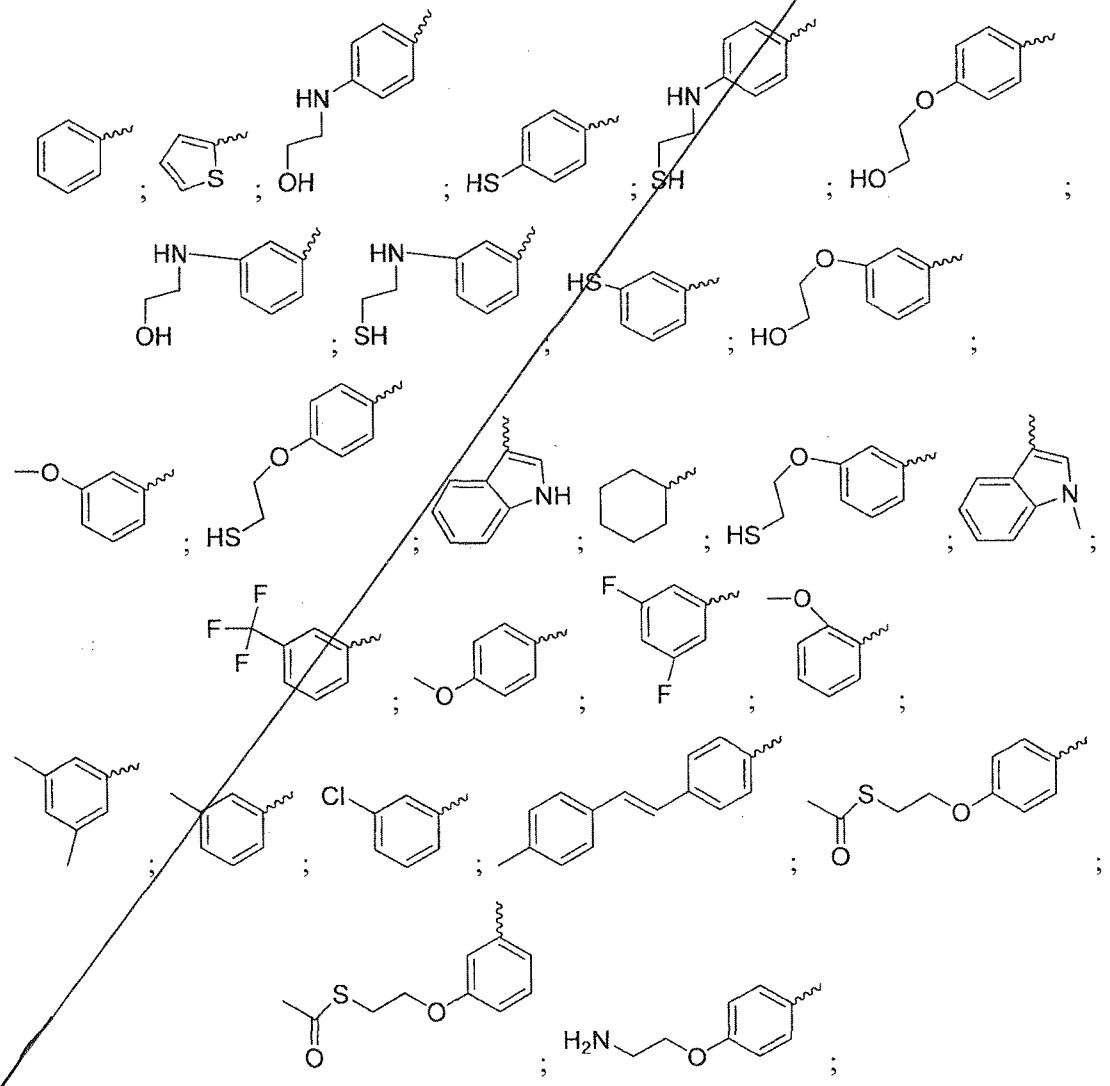
each R^{39} is, independently, selected from the group consisting of H, –OH, $-R^{27}$, $-OR^{27}$, $-O_2CR^{27}$, –SH, $-SR^{27}$, $-SOCR^{27}$, $-NH_2$, $-N_3$, $-NHR^{27}$, $-N(R^{27})_2$, $-NHCOR^{27}$, $-NR^{27}COR^{27}$, $-R^{27}NH_2$, –I, –Br, –Cl, –F, –CN, $-CO_2H$, $-CO_2R^{27}$, –CHO, $-COR^{27}$, $-CONH_2$, $-CONHR^{27}$, $-CON(R^{27})_2$, –COSH, $-COSR^{27}$, $-NO_2$, $-SO_3H$, $-SOR^{27}$, and $-SO_2R^{27}$, wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH.

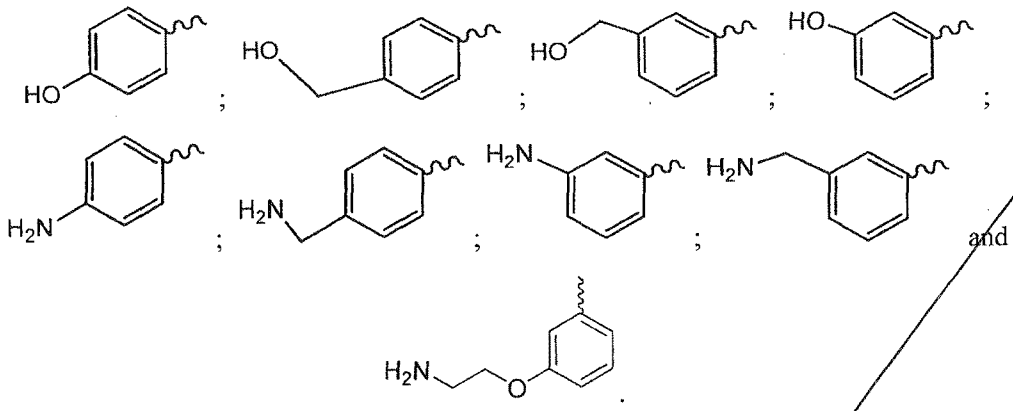
22. The compound of claim 19, wherein R^{29} is selected from the group consisting of:



wherein each R^{39} is, independently, selected from the group consisting of H, –OH, $-R^{27}$, $-OR^{27}$, $-O_2CR^{27}$, –SH, $-SR^{27}$, $-SOCR^{27}$, $-NH_2$, $-N_3$, $-NHR^{27}$, $-N(R^{27})_2$, $-NHCOR^{27}$, $-NR^{27}COR^{27}$, $-R^{27}NH_2$, –I, –Br, –Cl, –F, –CN, $-CO_2H$, $-CO_2R^{27}$, –CHO, $-COR^{27}$, $-CONH_2$, $-CONHR^{27}$, $-CON(R^{27})_2$, –COSH, $-COSR^{27}$, $-NO_2$, $-SO_3H$, $-SOR^{27}$, and $-SO_2R^{27}$, wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH.

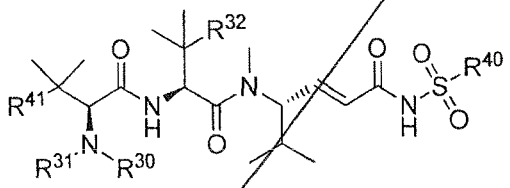
23. The compound of claim 19, wherein R^{29} is selected from the group consisting of:





24. The compound of any one of claims 19 to 23, wherein R^{30} is H or methyl, and R^{31}, R^{32}, and R^{38} are each methyl.

25. The compound of any one of claims 16 to 18, wherein P^1 is a monovalent radical of a compound of Formula XX:



XX

wherein:

R^{40} 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^{41} 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^{30} is selected from the group consisting of H and C_{1-6} alkyl;

R^{31} is selected from the group consisting of H and C_{1-6} alkyl; and

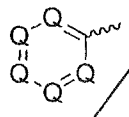
R^{32} is selected from the group consisting of C_{1-6} alkyl and –SH;

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, $-OR^{42}$, $-O_2CR^{42}$, –SH, $-SR^{42}$, $-SOCR^{42}$, $-NH_2$, $-N_3$, $-NHR^{42}$, $-N(R^{42})_2$, $-NHCOR^{42}$, $-NR^{42}COR^{42}$, –I, –Br, –Cl, –F, –CN, $-CO_2H$, $-CO_2R^{42}$, –CHO, $-COR^{42}$,

$-CONH_2$, $-CONHR^{42}$, $-CON(R^{42})_2$, $-COSH$, $-COSR^{42}$, $-NO_2$, $-SO_3H$, $-SOR^{42}$ or $-SO_2R^{42}$, wherein each R^{42} is, independently, alkyl optionally substituted with halogen, –OH or –SH; or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

26. The compound of claim 25, 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.

27. The compound of claim 25, wherein R^{41} is selected from one of the following structures XVI, XVII, XVIII, and XIX: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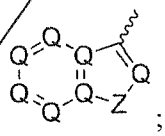
XVI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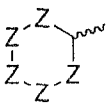
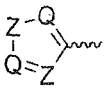
XVII


; and

XVIII


,

XIX

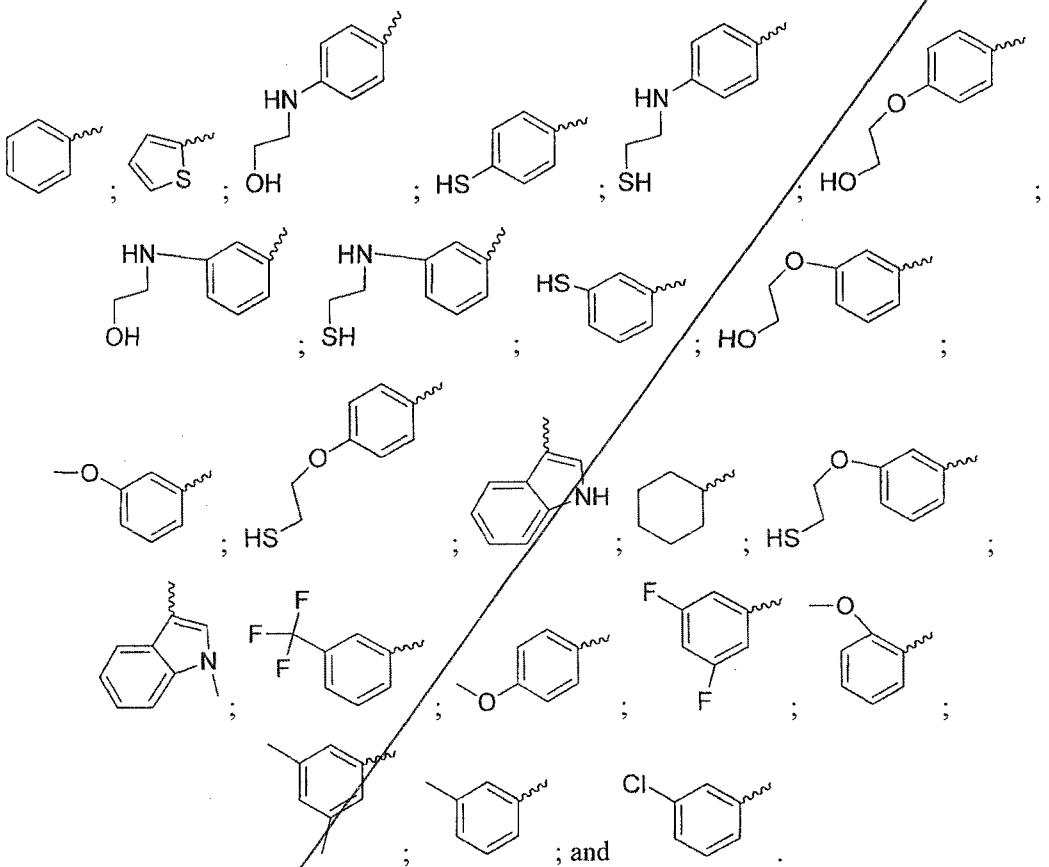
wherein:

Q is CR^{43} or N;

Z is $C(R^{43})_2$, NR^{43}, S, or O;

each R^{43} is, independently, selected from the group consisting of H, -OH, -OR^{42}, -O_2CR^{42}, -SH, -SR^{42}, -$SOCR^{42}$, -NH_2, -N_3, -NHR^{42}, -$N(R^{42})_2$, -$NHCOR^{42}$, -$NR^{42}COR^{42}$, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R^{42}, -CHO, -COR^{42}, -$CONH_2$, -$CONHR^{42}$, -$CON(R^{42})_2$, -COSH, -$COSR^{42}$, -NO_2, -SO_3H, -SOR^{42}, and -SO_2R^{42}, wherein each R^{42} is, independently, alkyl optionally substituted with halogen, -OH or -SH.

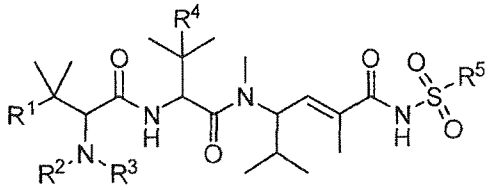
28. The compound of claim 25, wherein R^{41} is selected from the group consisting of:



; and .

29. The compound of claim 25, wherein R^{30} is H or methyl, and R^{31} and R^{32} are each methyl.

30. The compound of any one of claims 16 to 18 wherein P^1 is a monovalent radical of a compound of Formula II:



II

wherein:

R^1 is selected from: aryl, C_3-C_7 cycloalkyl, and heteroaryl, each of which is optionally substituted with one or more substituents selected from: C_1-C_4 acylthio, C_2-C_4 alkenyl, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy, amino, amino-C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl, hydroxyl, hydroxy-C_1-C_4 alkyl, and thio, wherein C_2-C_4 alkenyl, C_1-C_4 alkylamino and C_1-C_4 alkoxy are further optionally substituted with one substituent selected from C_1-C_4 alkylaryl, hydroxyl, and thio;

R^2 and R^3 are each independently selected from: H and C_1-C_6 alkyl;

R^4 is selected from the group consisting of C_1-C_6 alkyl and thio; and

R^5 is selected from: C_1-C_6 alkyl, aryl, aryl-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heteroaryl, and heterocyclyl, each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylamino, amino, amino-C_1-C_6 alkyl, amino-aryl, amino-C_3-C_7 cycloalkyl, aryl, carboxamide, carboxyl, C_3-C_7 cycloalkyl, cyano, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, halo, hydroxyl, nitro, thio, and thio-C_1-C_6 alkyl.

31. The compound of claim 30, wherein R^1 is selected from: is selected from: H, aryl, C_3-C_7 cycloalkyl, and heteroaryl, each of which is optionally substituted with one or more substituents selected from: C_1-C_4 acylthio, C_2-C_4 alkenyl, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy, amino, amino-C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl, hydroxyl, hydroxy-C_1-C_4 alkyl, and thio, wherein C_2-C_4 alkenyl, C_1-C_4 alkylamino and C_1-C_4 alkoxy are further optionally substituted with one substituent selected from *p*-tolyl, hydroxyl, and thio.

32. The compound of claim 30, wherein R^1 is selected from: H, 1*H*-indol-3-yl, 1-methyl-1*H*-indol-3-yl, 2-methoxyphenyl, 3-((2-hydroxyethyl)amino)phenyl, 3-((2-mercaptoethyl)amino)phenyl, 3-(2-(acetylthio)ethoxy)phenyl, 3-(2-hydroxyethoxy)phenyl, 3-(2-mercaptoethoxy)phenyl, 3-(4-methylstyryl)phenyl, 3-(aminomethyl)phenyl, 3-(hydroxymethyl)phenyl, 3-hydroxyphenyl, 3,5-difluorophenyl, 3,5-dimethylphenyl, 3-aminophenyl, 3-chlorophenyl, 3-mercaptophenyl, 3-methoxyphenyl, 3-trifluoromethylphenyl, 4-((2-hydroxyethyl)amino)phenyl, 4-((2-mercaptoethyl)amino)phenyl, 4-(2-(acetylthio)ethoxy)phenyl, 4-(2-aminoethoxy)phenyl, 4-(2-hydroxyethoxy)phenyl, 4-(2-mercaptoethoxy)phenyl, 4-(aminomethyl)phenyl, 4-(hydroxymethyl)phenyl, 4-aminophenyl, 4-hydroxyphenyl, 4-mercaptophenyl, 4-methoxyphenyl, cyclohexyl, thien-2-yl, *m*-tolyl, and phenyl.

33. The compound of any one of claims 30 to 32, wherein R^2 is H, or methyl.

34. The compound of any one of claims 30 to 33 wherein R^3 is methyl.

35. The compound of any one of claims 30 to 34, wherein R^4 is methyl.

36. The compound of any one of claims 30 to 35, wherein R^5 is selected from: C_1-C_6 alkyl, aryl, aryl-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heteroaryl, and heterocyclyl, each optionally substituted with one or more substituents selected from: 1-aminocyclopropyl, 4-aminophenyl, amino, aminomethyl, bromo, *tert*-butyl, carboxamide, carboxyl, chloro, cyano, cyclopentyl, ethyl, fluoro, hydroxy, isopropyl, methoxy, methyl, nitro, phenyl, pyridin-3-yl, thio, thiomethyl, trifluoromethoxy, and trifluoromethyl.

37. The compound of any one of claims 30 to 35, wherein R^5 is selected from: 4-aminobenzyl, 4-(aminomethyl)benzyl, 4-(aminomethyl)phenyl, 4-aminophenyl, benzyl, 3-mercaptopropyl, 2-mercaptoethyl, 4-(mercaptomethyl)phenyl, *p*-tolyl, methyl, 2,4,6-trimethylphenyl, 4-(trifluoromethoxy)phenyl, 2,4,6-triisopropylphenyl, 4-*tert*-butylphenyl, 4-chlorophenyl, 3-cyanophenyl, 2-nitrophenyl, 4-methoxy-2-nitrophenyl, 4-aminocarbonyl-2-nitrophenyl, 4-methoxyphenyl, 4-aminophenyl, phenyl, 2-fluorobenzyl, piperidin-1-yl, *o*-tolyl, 4-bromophenyl, naphthalen-2-yl, 4-methoxycarbonylphenyl, 2-(trifluoromethyl)benzyl, hexan-2-yl, 2-methoxyethyl, cyclopentylmethyl, cyclohexyl, pyridin-3-ylmethyl, 4-carboxyphenyl, 3-aminophenyl, pyridin-3-yl, thien-2-yl, 4-hydroxyphenyl, 4-(1-aminocyclopropyl)benzyl, 4-(1-aminocyclopropyl)phenyl, 2-methylbenzyl, 4-nitrobenzyl, 4-chlorobenzyl, phenethyl, 4-bromobenzyl, 4-cyanobenzyl, 3-nitrobenzyl, 4-*tert*-butylbenzyl, 2-nitrobenzyl, 4-nitrophenethyl, 2-chloro-3-methoxycarbonylphenyl, 2-aminophenyl, [1,1'-biphenyl]-4-yl, 4'-amino-[1,1'-biphenyl]-4-yl, 4-fluorobenzyl, 3-(trifluoromethyl)benzyl, 3-(trifluoromethoxy)benzyl, 3,4-dichlorobenzyl, 2-cyanobenzyl, 3-chlorobenzyl, 4-amino-2-ethylphenyl, 4-amino-3-(trifluoromethoxy)phenyl, 4-amino-2,3-dimethylphenyl, 4-amino-5,6,7,8-tetrahydronaphthalen-1-yl, 4-amino-3-methylphenyl, 4-amino-3-fluorophenyl, 4-amino-3-ethylphenyl, and 4-amino-3-(trifluoromethyl)phenyl.

38. A pharmaceutical composition comprising the compound of any one of claims 1 to 37, and a pharmaceutically acceptable carrier, diluent or excipient.

39. A method of treating cancer in a mammal, or increasing survival of a mammal having cancer, or inhibiting tumor growth in a mammal, comprising administering to a mammal in need thereof an effective amount of the compound of any one of claims 1 to 37 or the pharmaceutical composition of claim 38.

40. The method of claim 39, wherein said cancer is selected from: carcinomas, sarcomas, hematopoietic cancers, and tumors of neuroepithelial tissue.

41. The compound of any one of claims 1 to 37 or the pharmaceutical composition of claim 38, for use in a method of treatment of the human or animal body by therapy.

42. The compound of any one of claims 1 to 37 or the pharmaceutical composition of claim 38, for use in treating cancer in a mammal, or for use in increasing survival of a mammal having cancer, or for use in inhibiting tumor growth in a mammal.

43. The compound or the pharmaceutical composition of claim 42, wherein said cancer is selected from: carcinomas, sarcomas, hematopoietic cancers, and tumors of neuroepithelial tissue.

44. Use of the compound of any one of claims 1 to 37, in the manufacture of a medicament for treating cancer in a mammal, or for increasing survival of a mammal having cancer, or for inhibiting tumor growth in a mammal.

45. The use of claim 44, wherein said cancer is selected from: carcinomas, sarcomas, hematopoietic cancers, and tumors of neuroepithelial tissue.

46. A pharmaceutical composition comprising the compound of any one of claims 8 to 10, and a pharmaceutically acceptable carrier, diluent or excipient.

47. A method of treating an indication selected from: cancer, arthritis, arthrosis, multiple sclerosis, neural damage, cartilage damage, and psoriasis in a mammal comprising administering to a mammal in need thereof an effective amount of the compound of any one of claims 8 to 10 or the pharmaceutical composition of claim 46.

48. The compound of any one of claims 8 to 10 or the pharmaceutical composition of claim 46, for use in a method of treatment of the human or animal body by therapy

49. The compound of any one of claims 8 to 10 or the pharmaceutical composition of claim 46, for use in a method of treatment of an indication selected from: cancer, arthritis, arthrosis, multiple sclerosis, neural damage, cartilage damage, and psoriasis.

50. Use of the compound of any one of claims 8 to 10, in the manufacture of a medicament for treating an indication selected from: cancer, arthritis, arthrosis, multiple sclerosis, neural damage, cartilage damage, and psoriasis.

CLAIMS

1. A compound of Formula I:

T–L–P

I

wherein:

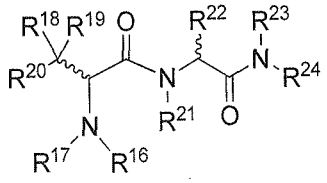
T is a targeting moiety comprising a VAR2CSA polypeptide, and

L–P is L^1–P^1 or L^2–P^2;

wherein:

L^1 is a linker, or L^1 is absent;

P^1 is a monovalent radical of a compound of Formula XIV



XIV

wherein:

R^{16} and R^{17} are each independently H or a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, and the carbon atoms are optionally substituted with: –OH, –I, –Br, –Cl, –F, –CN, $–CO_2H$, –CHO, –COSH, or $–NO_2$; or R^{17} and R^{20} are fused and form a ring;

R^{18} and R^{19} are independently selected from the group consisting of: H, R^{25}, and ArR^{25}–, or R^{18} and R^{19} are joined to form a ring, wherein the ring formed by joining R^{18} and R^{19} is a three to seven member non-aromatic cyclic skeleton within the definition of R^{25};

R^{20} is selected from the group consisting of: H, R^{25}, ArR^{25}–, and Ar; or R^{20} and R^{17} are fused and form a ring;

R^{21} is selected from the group consisting of: H, R^{25}, and ArR^{25}–;

R^{22} and R^{23} are independently selected from the group consisting of: H, R^{25}, and ArR^{25}–;

R^{24} is: –Y–(CO)$NHSO_2$–R^{26};

R^{25} is a saturated or unsaturated moiety having a linear, branched, or non-aromatic cyclic skeleton containing one to ten carbon atoms, zero to four nitrogen atoms, zero to four oxygen atoms, and zero to four sulfur atoms, and the carbon atoms are optionally substituted with: =O, =S, OH, $–OR^{28}$, $–O_2CR^{28}$, –SH, $–SR^{28}$, $–SOCR^{28}$, $–NH_2$, $–NHR^{28}$, $–N(R^{28})_2$, $–NHCOR^{28}$, $–NR^{28}COR^{28}$, –I, –Br, –Cl, –F, –CN, $–CO_2H$, $–CO_2R^{28}$, –CHO, $–COR^{28}$, $–CONH_2$, $–CONHR^{28}$, $–CON(R^{28})_2$, –COSH, $–COSR^{28}$, $-NO_2$, $-SO_3H$, $-SOR^{28}$, or $-SO_2R^{28}$, wherein R^{28} is a linear, branched or cyclic, one to ten carbon saturated or unsaturated alkyl group;

Y is a linear, saturated or unsaturated, one to six carbon alkyl group, optionally substituted with R^{25}, ArR^{25}–, or X;

X is selected from the group consisting of: –OH, $–OR^{25}$, =O, =S, $–O_2CR^{25}$, –SH, $–SR^{25}$, $–SOCR^{25}$, $–NH_2$, $–NHR^{25}$, $–N(R^{25})_2$, $–NHCOR^{25}$, $–NRCOR^{25}$, –I, –Br, –Cl, –F, –CN, $–CO_2H$, $–CO_2R^{25}$, –CHO, $–COR^{25}$, $–CONH_2$, $–CONHR^{25}$, $–CON(R^{25})_2$, –COSH, $–COSR^{25}$, $–NO_2$, $–SO_3H$, $–SOR^{25}$, and $–SO_2R^{25}$; and

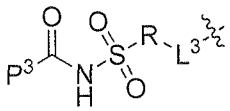
R^{26} is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl, $–COR^{27}$, $–CSR^{27}$, $–OR^{27}$, and $–NHR^{27}$, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl ~~and~~or optionally substituted heteroaryl; and

wherein:

L^2 is a linker;

P^2 is a cytotoxic compound; and

L^2–P^2 has the following structure (III):



III

wherein:

R is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl, or R is absent;

P^3 is the remaining portion of compound P^2; and

L^3 is the remaining portion of linker L^2 or is absent.

2. The compound of claim 1, wherein said VAR2CSA polypeptide comprises a sequential amino acid sequence of

a. ID1; and

b. DBL2Xb.

3. The compound of claim 1, wherein said VAR2CSA polypeptide comprises a sequential amino acid sequence of:

a. ID1;

b. DBL2Xb; and

c. ID2a.

4. The compound of claim 3, wherein the VAR2CSA polypeptide further comprises an amino acid sequence at the N- or C- terminus of 100 amino acids or less derived from a part of SEQ ID NO: 55 or SEQ ID NO: 56, wherein said part is not 1D1, DBL2Xb or ID2a.

5. The compound of claim 1, wherein said VAR2CSA polypeptide binds chondroitin sulfate A (CSA) on proteoglycans (CSPG) with an affinity as measured by a K_D lower than 100 nM.

6. The compound of claim 1, wherein said VAR2CSA polypeptide comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from: amino acids 1-577 of SEQ ID NO:1; amino acids 1-592 of SEQ ID NO:3; amino acids 1-579 of SEQ ID NO:4; amino acids 1-576 of SEQ ID NO:5; amino acids 1-586 of SEQ ID NO:10; amino acids 1-579 of SEQ ID NO:11; amino acids 1-565 of SEQ ID NO:29; amino acids 1-584 of SEQ ID NO:34; amino acids 1-569 of SEQ ID NO:36; amino acids 1-575 of SEQ ID NO:37; amino acids 1-592 of SEQ ID NO:38; amino acids 1-603 of SEQ ID NO:41; amino acids 1-588 of SEQ ID NO:43; amino acids 1-565 of SEQ ID NO:44; amino acids 1-589 of SEQ ID NO:45; amino acids 1-573 of SEQ ID NO:48; amino acids 1-583 of SEQ ID NO:53; amino acids 1-569 of SEQ ID NO:54; amino acids 578-640 of SEQ ID NO:1; amino acids 593-656 of SEQ ID NO:3; amino acids 580-643 of SEQ ID NO:4; amino acids 577-640 of SEQ ID NO:5; amino acids 587-650 of SEQ ID NO:10; amino acids 580-643 of SEQ ID NO:11; amino acids 566-628 of SEQ ID NO:29; amino acids 585-647 of SEQ ID NO:34; amino acids 570-632 of SEQ ID NO:36; amino acids 576-639 of SEQ ID NO:37; amino acids 593-655 of SEQ ID NO:38; amino acids 604-667 of SEQ ID NO:41; amino acids 589-652 of SEQ ID NO:43; amino acids 566-628 of SEQ ID NO:44; amino acids 590-653 of SEQ ID NO:45; amino acids 574-637 of SEQ ID NO:48; amino acids 584-646 of SEQ ID NO:53; amino acids 570-632 of SEQ ID NO:54; SEQ ID NO:2; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; SEQ ID NO:23; SEQ ID NO:24; SEQ ID NO:25; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:39; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:46; SEQ ID NO:47; SEQ ID NO:49; SEQ ID NO:50; SEQ ID NO:51; SEQ ID NO:52; SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:4; SEQ ID

NO:5; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:29; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:48; SEQ ID NO:53; and SEQ ID NO:54.

7. The compound of claim 1, wherein said VAR2CSA polypeptide comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from: amino acids 1-577 of SEQ ID NO:1; amino acids 1-592 of SEQ ID NO:3; amino acids 1-579 of SEQ ID NO:4; amino acids 1-576 of SEQ ID NO:5; amino acids 1-586 of SEQ ID NO:10; amino acids 1-579 of SEQ ID NO:11; amino acids 1-565 of SEQ ID NO:29; amino acids 1-584 of SEQ ID NO:34; amino acids 1-569 of SEQ ID NO:36; amino acids 1-575 of SEQ ID NO:37; amino acids 1-592 of SEQ ID NO:38; amino acids 1-603 of SEQ ID NO:41; amino acids 1-588 of SEQ ID NO:43; amino acids 1-565 of SEQ ID NO:44; amino acids 1-589 of SEQ ID NO:45; amino acids 1-573 of SEQ ID NO:48; amino acids 1-583 of SEQ ID NO:53; amino acids 1-569 of SEQ ID NO:54; SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:29; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:48; SEQ ID NO:53; and SEQ ID NO:54.

8. The compound of any one of claims 1 to 5, wherein said VAR2CSA polypeptide consists of an amino acid sequence having a length of less than 700 amino acids.

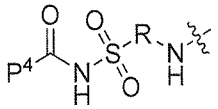
9. The compound of any one of claims 1 to 8, wherein said VAR2CSA polypeptide is a recombinant protein.

10. The compound of any one of claims 1 to 9, wherein said VAR2CSA polypeptide is non-glycosylated.

11. The compound of any one of claims 1 to 10, wherein L–P is L^2–P^2.

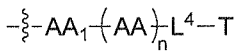
12. The compound of claim 11, wherein:

P^2 is a compound of Formula V:



V

L^2–T has the following structure (VI):



VI

wherein

P^4 is the remaining portion of compound P^2,

the –NH– group bonded to R in Formula V forms a peptide bond (JPB) with AA_1 in formula VI, wherein said JPB is enzymatically cleavable,

R is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is, independently, optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl ~~and~~ or optionally substituted heteroaryl,

each AA is independently an amino acid,

n is an integer from 0 to 25,

L^4 is optionally the remaining portion of linker L^2,

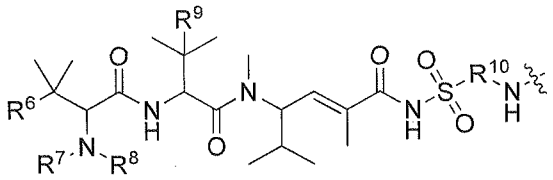
T is said targeting moiety, and

wherein AA_1–$(AA)_n$, taken together comprises an amino acid sequence capable of facilitating enyzmatic cleavage of said JPB.

13. The compound of claim 12, wherein said cytotoxic compound is a microtubule disrupting peptide toxin.

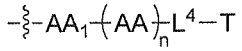
14. The compound of claim 13, wherein said cytotoxic compound is a hemiasterlin or an analog thereof; a tubulysin or an analog thereof; or an auristatin or an analog thereof.

15. The compound of claim 11, wherein P^2 has the following structure (X):



X

and L^2–T has the following structure (IV):



VI

wherein:

R^6 is selected from: aryl, C_3-C_7 cycloalkyl, and heteroaryl, each of which is optionally substituted with one or more substituents selected from: C_1-C_4 acylthio, C_2-C_4 alkenyl, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy, amino, amino-C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl, hydroxyl, hydroxy-C_1-C_4 alkyl, and thio, wherein C_2-C_4 alkenyl, C_1-C_4 alkylamino and C_1-C_4 alkoxy are further optionally substituted with one substituent selected from C_1-C_4 alkylaryl, hydroxyl, and thio;

R^7 and R^8 are each independently H or C_1-C_6 alkyl;

R^9 is C_1-C_6 alkyl or thio;

R^{10} is selected from optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is independently optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl; and

each AA is independently an amino acid;

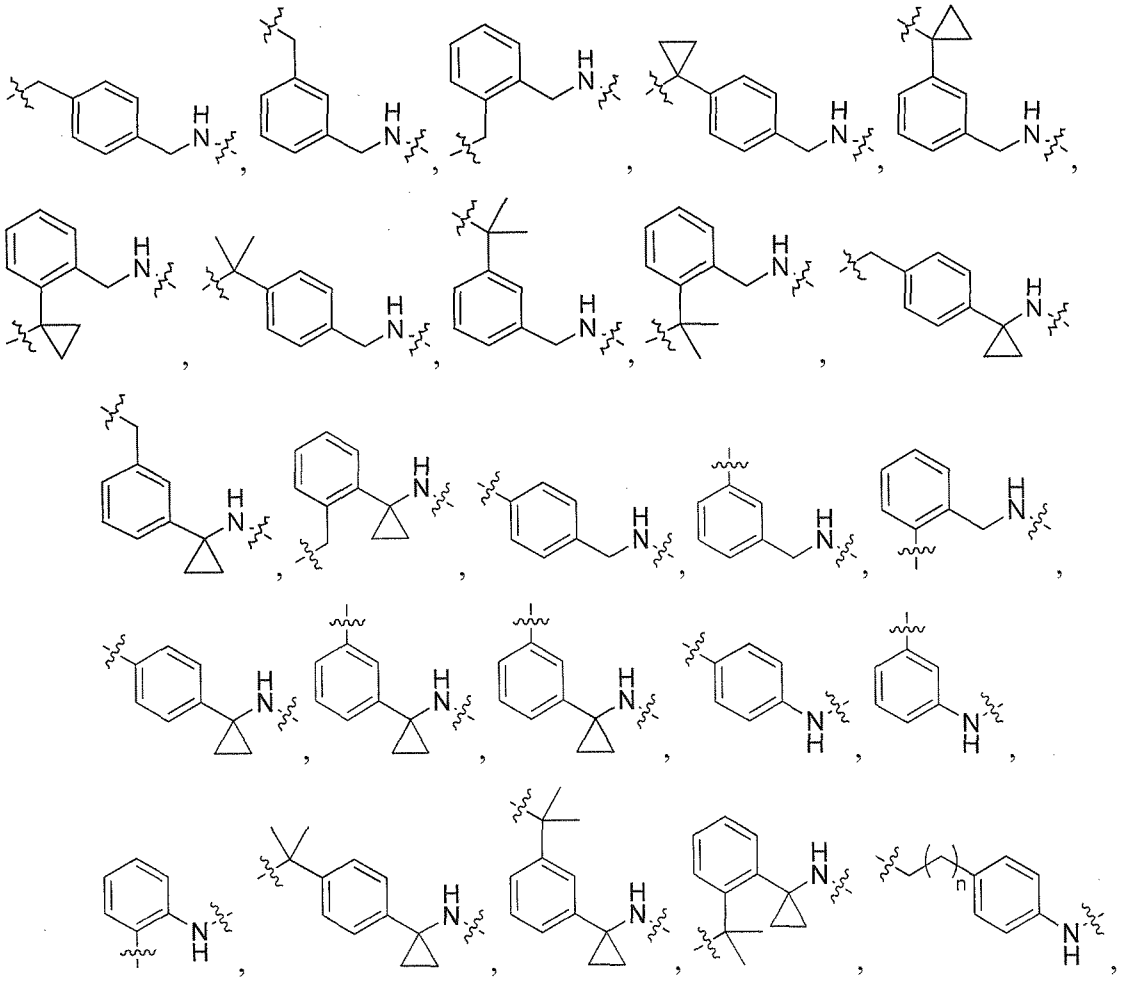
n is an integer from 0 to 25;

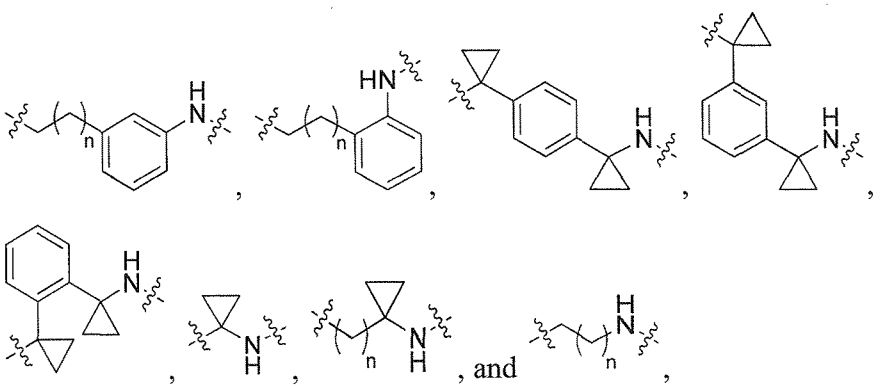
L^4 is the remaining portion of linker L^2 or is absent;

T is said targeting moiety;

wherein the –NH– group bonded to R^{10} in Formula X forms a junction peptide bond (JPB) with AA_1 in Formula VI, wherein the JPB is enzymatically cleavable, and wherein AA_1–$(AA)_n$, taken together comprises an amino acid sequence capable of facilitating enyzmatic cleavage of said JPB.

16. The compound of claim 15, wherein $–R^{10}–NH–$ of Formula X is selected from:





wherein each n is independently an integer from 0-10.

17. The compound of any one of claims 12 to 16, wherein AA_1–$(AA)_n$ is selected from: Phe-Lys, Val-Lys, Ala-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, (D)Phe-Phe-Lys and (D)Ala-Phe-Lys.

18. The compound of any one of claims 12 to 17, wherein L^4 comprises repeating alkoxy units, a diacid amide, a diacid ester, or a combination thereof.

19. The compound of claim 12, wherein P^2 is a monovalent radical of one of the following compounds:

a) (S,E)-N-(3-Mercaptopropylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound A);

b) (S,E)-N-(2-Mercaptoethylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound B);

c) S,E)-N-(4-(Mercaptomethyl)phenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound C);

d) (S,E)-2,5-Dimethyl-N-tosyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound D);

e) (S,E)-2,5-dimethyl-N-(methylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound E);

f) (S,E)-N-(Mesitylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

g) (S,E)-2,5-Dimethyl-N-(4-(trifluoromethoxy)phenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

h) (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 (Compound 14);

i) (S,E)-2,5-Dimethyl-N-(2,4,6-triisopropylphenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

j) (S,E)-N-(4-tert-Butylphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

k) (S,E)-N-(4-Chlorophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

l) (S,E)-N-(3-Cyanophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

m) (S,E)-2,5-Dimethyl-N-(2-nitrophenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

n) (S,E)-N-(4-Methoxy-2-nitrophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

o) 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)-3-nitrobenzamide;

p) (S,E)-N-(4-Methoxyphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

q) (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 (Compound 23);

r) (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 (Compound 886);

s) (S,E)-2,5-Dimethyl-N-(phenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

t) (S,E)-N-(N-(2-Fluorobenzyl)sulfamoyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

u) (S,E)-2,5-Dimethyl-N-(piperidin-1-ylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

v) (S,E)-2,5-Dimethyl-N-(o-tolylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

w) (S,E)-N-(4-Bromophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

x) (S,E)-2,5-Dimethyl-N-(naphthalen-2-ylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

y) Methyl 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)benzoate;

z) (S,E)-2,5-Dimethyl-N-(N-(2-(trifluoromethyl)benzyl)sulfamoyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

aa) (4S,E)-N-(Hexan-2-ylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

bb) (S,E)-N-(2-Methoxyethylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

cc) (S,E)-N-(Cyclopentylmethylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

dd) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(4-cyanophenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

ee) (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;

ff) (S,E)-4-((S)-2-((S)-3-(4-Azidophenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-N-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

gg) (S,E)-4-((S)-2-((S)-3-(4-Aminophenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-N-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

hh) (S,E)-N-(Cyclohexylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ii) (S,E)-2,5-Dimethyl-N-(pyridin-3-ylmethylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

jj) 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)benzoic acid;

kk) (S,E)-2,5-Dimethyl-N-(3-(2,2,2-trifluoroacetamido)phenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ll) (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;

mm) (S,E)-2,5-Dimethyl-N-(pyridin-3-ylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

nn) (S,E)-2,5-Dimethyl-N-(thiophen-2-ylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

oo) (S,E)-N-(4-Hydroxyphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

pp) (S,E)-2,5-dimethyl-N-(4-(1-(2,2,2-trifluoroacetamido)cyclopropyl) phenylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

qq) (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;

rr) (S,E)-2,5-Dimethyl-N-(2-methylbenzylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ss) (S,E)-2,5-Dimethyl-N-(4-nitrobenzylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

tt) (S,E)-N-(4-Chlorobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

uu) (S,E)-2,5-Dimethyl-N-(phenethylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

vv) (S,E)-N-(4-Bromobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ww) (S,E)-N-(4-Cyanobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

xx) (S,E)-2,5-Dimethyl-N-(3-nitrobenzylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

yy) (S,E)-N-(4-tert-Butylbenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

zz) (S,E)-2,5-Dimethyl-N-(2-nitrobenzylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

aaa) (S,E)-2,5-Dimethyl-N-(4-nitrophenethylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

bbb) Methyl 4-Chloro-3-(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)benzoate;

ccc) (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;

ddd) (S,E)-N-(4-Aminobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

eee) (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;

fff) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(4-bromophenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

ggg) (S,E)-4-((S)-2-((S)-3-(4'-Acetylbiphenyl-4-yl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-N-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

hhh) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(4'-methoxybiphenyl-4-yl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

iii) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(biphenyl-4-yl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

jjj) (S,E)-N-(Benzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-(4-(4-methylstyryl)phenyl)butanamido)butanamido)hex-2-enamide;

kkk) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(4-methoxyphenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

lll) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((R)-3-(3-methoxyphenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

mmm) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(3-methoxyphenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

nnn) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-(4-(2-hydroxyethoxy)phenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

ooo) S-2-(4-((S)-4-((S)-1-(((S,E)-2,5-Dimethyl-6-oxo-6-(benzylsulfonamido)hex-4-en-3-yl)(methyl)amino)-3,3-dimethyl-1-oxobutan-2-ylamino)-2-methyl-3-(methylamino)-4-oxobutan-2-yl)phenoxy)ethyl ethanethioate;

ppp) (S,E)-4-((S)-2-((S)-3-(4-(2-Aminoethoxy)phenyl)-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-N-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

qqq) (S,E)-N-(2-Aminophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

rrr) (S,E)-N-(Biphenyl-4-ylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

sss) (S,E)-N-(4'-Aminobiphenyl-4-ylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ttt) (S,E)-N-(4-Fluorobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

uuu) (S,E)-2,5-Dimethyl-N-(3-(trifluoromethyl)benzylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

vvv) (S,E)-2,5-Dimethyl-N-(3-(trifluoromethoxy)benzylsulfonyl)-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

www) (S,E)-N-(3,4-Dichlorobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

xxx) (S,E)-N-(2-Cyanobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

yyy) (S,E)-N-(3-Chlorobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

zzz) (S,E)-N-(4-Amino-2-ethylphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

aaaa) (S,E)-N-(4-Amino-3-(trifluoromethoxy)phenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

bbbb) (S,E)-N-(4-Amino-2,3-dimethylphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

cccc) (S,E)-N-(4-Amino-5,6,7,8-tetrahydronaphthalen-1-ylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

dddd) (S,E)-N-(4-Amino-3-methylphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

eeee) (S,E)-N-(4-Amino-3-fluorophenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ffff) (S,E)-N-(4-Amino-3-ethylphenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

gggg) (S,E)-N-(4-Amino-3-(trifluoromethyl)phenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

hhhh) (S)-1-Isopropyl-N-((S)-1-(((S,E)-6-(3-mercaptopropylsulfonamido)-2,5-dimethyl-6-oxohex-4-en-3-yl)(methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)piperidine-2-carboxamide;

iiii) (S)-N-((S)-1-((S)-2-((E)-3-(3-Mercaptopropylsulfonamido)-2-methyl-3-oxoprop-1-enyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-methyl-2-(methylamino)-3-phenylbutanamide;

jjjj) (S)-N-((S)-1-(2-(3-(3-Mercaptopropylsulfonamido)-2-methyl-3-oxoprop-1-enyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-methyl-2-(methylamino)-3-phenylbutanamide;

kkkk) (S)-N-((S)-1-(2-(3-(4-(Mercaptomethyl)phenylsulfonamido)-2-methyl-3-oxoprop-1-enyl)piperidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-methyl-2-(methylamino)-3-phenylbutanamide;

llll) (R)-N-(Benzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hexanamide; or

mmmm) (S,E)-N-(Benzylsulfonyl)-4-((S)-2-((S)-3-cyclohexyl-3-methyl-2-(methylamino)butanamido)-N,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide.

20. The compound of claim 12, wherein P^2 is a monovalent radical of one of the following compounds:

a) (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 (Compound 886);

b) (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;

c) (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;

d) (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;

e) (S,E)-N-(4-Aminobenzylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide, or

f) (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.

21. The compound of claim 19 or 20, wherein AA_1–$(AA)_n$ is selected from: Phe-Lys, Val-Lys, Ala-Lys, Val-Cit, Phe-Cit, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Arg, (D)Phe-Phe-Lys and (D)Ala-Phe-Lys.

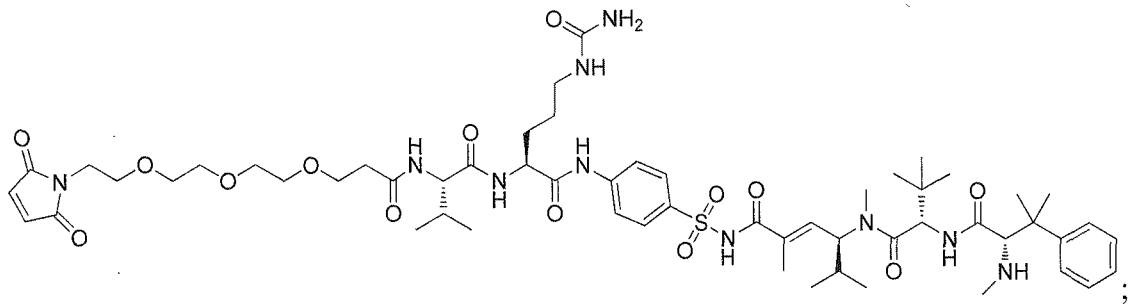
22. The compound of any one of claims 19 to 21, wherein L^4 comprises repeating alkoxy units, a diacid amide, a diacid ester, or a combination thereof.

23. The compound of claim 12, wherein L^2-P^2 is a monovalent radical of one of the following compounds:

a) (S,E)-N-(4-((S)-2-((S)-2-(6-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanamido)-3-methylbutanamido)-5-ureidopentanamido)phenylsulfonyl)-2,5-dimethyl-4-((S)-N,3,3-trimethyl-2-((S)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound N);

or

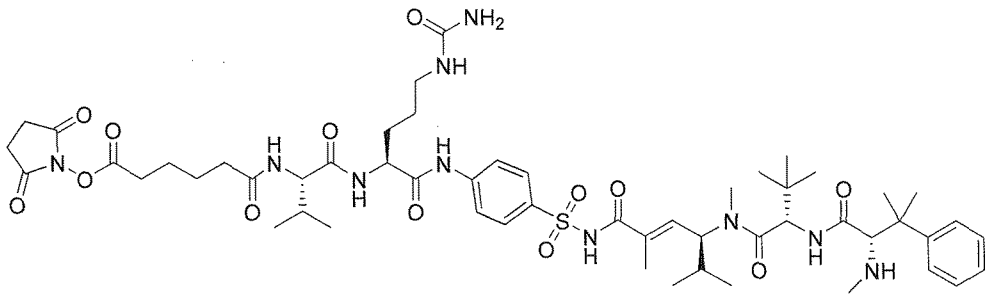
b) Compound O:



;

or

c) Compound KK:

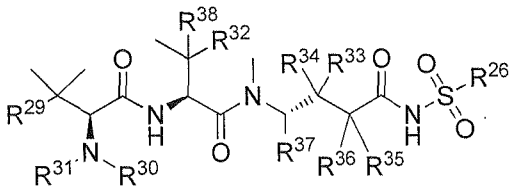


24. The compound of any one of claims 1 to 10, wherein L–P is L^1–P^1.

25. The compound of claim 24, wherein L^1 comprises: SPDP, SMCC, vcPABC, MCvcPABC, MTvc, ADvc, maleimide, NHS, biotin, streptavidin, NeutrAvidin, a glycoside, or a combination thereof.

26. The compound of claim 24, wherein L^1 comprises vcPABC, MCvcPABC, MTvc ~~and~~or ADvc.

27. The compound of any one of claims 24 to 26, wherein P^1 is a monovalent radical of a compound of Formula XV:



XV

wherein:

R^{26} is selected from the group consisting of optionally substituted alkyl, optionally substituted alkylamino, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-COR^{27}$, $-CSR^{27}$, $-OR^{27}$, and $-NHR^{27}$, wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH;

R^{29} 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^{30} is selected from the group consisting of H and C_{1-6} alkyl;

R^{31} is selected from the group consisting of H and C_{1-6} alkyl;

R^{32} and R^{38} are each independently selected from the group consisting of H, C_{1-6} alkyl and –SH, with the proviso that R^{32} and R^{38} cannot both be H;

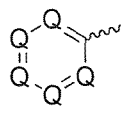
R^{33}, R^{34}, R^{35} and R^{36} are each independently H or C_{1-6} alkyl, wherein at least one of R^{33} and R^{34} is H; or R^{34} and R^{35} form a double bond, R^{33} is H, and R^{36} is H or C_{1-6} alkyl; and

R^{37} is selected from the group consisting of H and C_{1-6} alkyl;

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof.

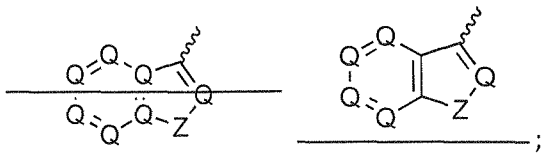
28. The compound of claim 27, wherein each optionally substituted aryl and optionally substituted heteroaryl is, independently, selected from the group consisting of optionally substituted phenyl, optionally substituted naphthyl, optionally substituted anthracyl, optionally substituted phenanthryl, optionally 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.

29. The compound of claim 27, wherein R^{29} is selected from one of the following structures XVI, XVII, XVIII, and XIX:

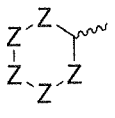


;

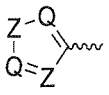
XVI



XVII

 ; and

XVIII

,

XIX

wherein:

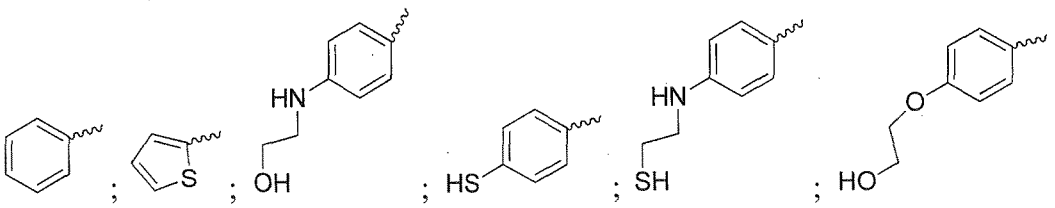
Q is CR^{39} or N;

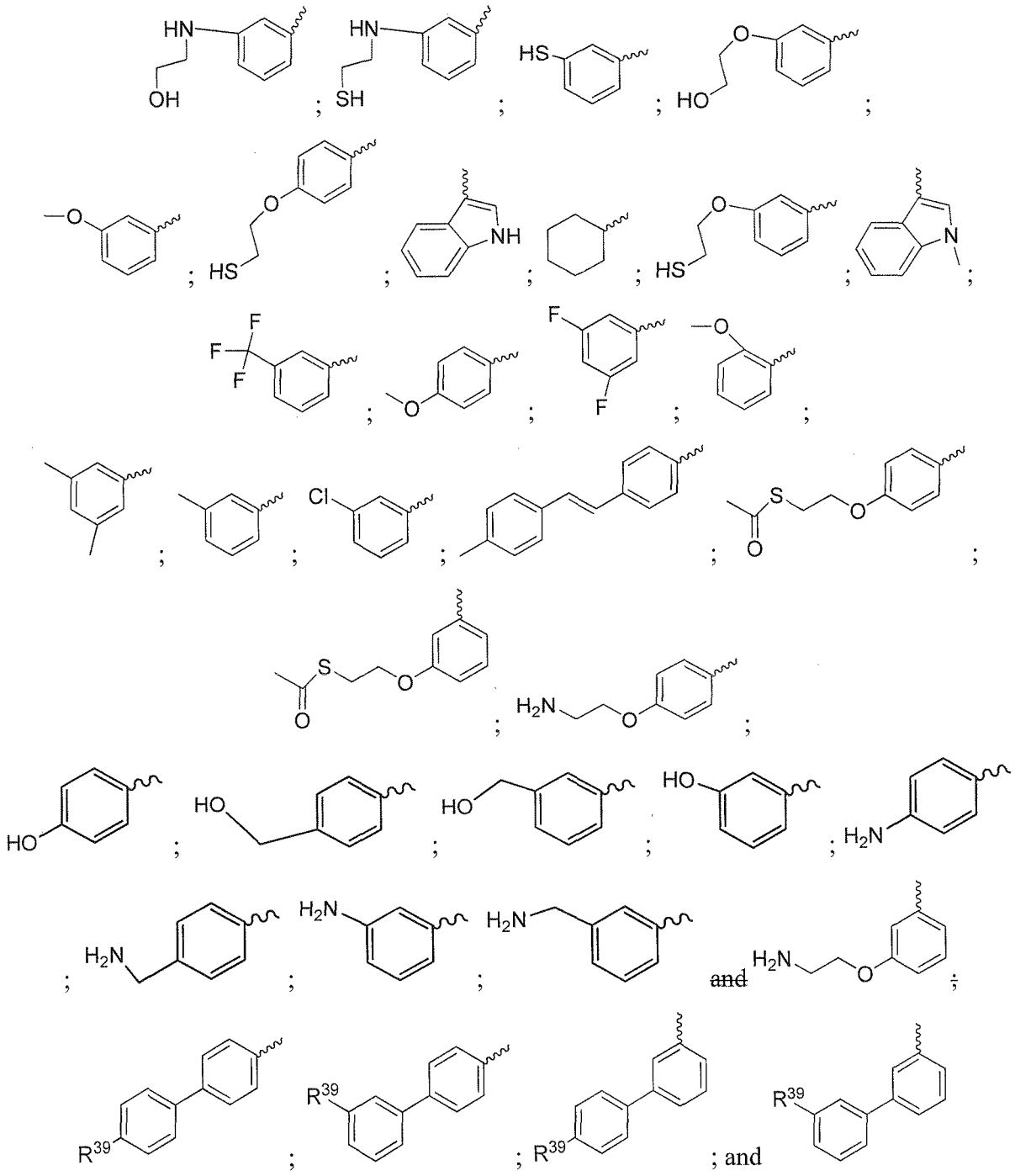
Z is $C(R^{39})_2$, NR^{39}, S, or O;

wherein in structure XIX, one instance of Z is CR^{39} or N, and the other instance is $(CR^{39})_2$, NR^{39}, S or O; and

each R^{39} is, independently, selected from the group consisting of H, –OH, $–R^{27}$, $–OR^{27}$, $–O_2CR^{27}$, –SH, $–SR^{27}$, $–SOCR^{27}$, $–NH_2$, $–N_3$, $–NHR^{27}$, $–N(R^{27})_2$, $–NHCOR^{27}$, $–NR^{27}COR^{27}$, $–R^{27}NH_2$, –I, –Br, –Cl, –F, –CN, $–CO_2H$, $–CO_2R^{27}$, –CHO, $–COR^{27}$, $–CONH_2$, $–CONHR^{27}$, $–CON(R^{27})_2$, –COSH, $–COSR^{27}$, $–NO_2$, $–SO_3H$, $–SOR^{27}$, and $–SO_2R^{27}$, wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH.

30. The compound of claim 27, wherein R^{29} is selected from the group consisting of:



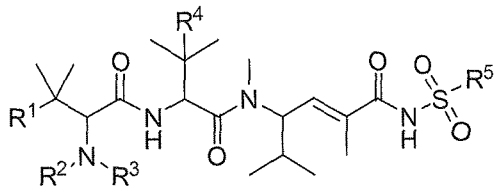


wherein each R^{39} is independently selected from the group consisting of H, –OH, $–R^{27}$, $–OR^{27}$, $–O_2CR^{27}$, –SH, $–SR^{27}$, $–SOCR^{27}$, $–NH_2$, $–N_3$, $–NHR^{27}$, $–N(R^{27})_2$, $–NHCOR^{27}$, $–NR^{27}COR^{27}$, $–R^{27}NH_2$, –I, –Br, –Cl, –F, –CN, $–CO_2H$, $–CO_2R^{27}$,

–CHO, –COR^{27}, –$CONH_2$, –$CONHR^{27}$, –$CON(R^{27})_2$, –COSH, –$COSR^{27}$, –NO_2, –SO_3H, –SOR^{27}, and –SO_2R^{27}, wherein each R^{27} is, independently, alkyl optionally substituted with halogen, –OH or –SH.

31. The compound of any one of claims 27 to 30, wherein R^{30} is H or methyl, and R^{31}, R^{32}, and R^{38} are each methyl.

32. The compound of any one of claims 24 to 26, wherein P^1 is a monovalent radical of a compound of Formula II:



II

wherein:

R^1 is selected from: aryl, C_3-C_7 cycloalkyl, and heteroaryl, each of which is optionally substituted with one or more substituents selected from: C_1-C_4 acylthio, C_2-C_4 alkenyl, C_1-C_4 alkyl, C_1-C_4 alkylamino, C_1-C_4 alkoxy, amino, amino-C_1-C_4 alkyl, halo, C_1-C_4 haloalkyl, hydroxyl, hydroxy-C_1-C_4 alkyl, and thio, wherein C_2-C_4 alkenyl, C_1-C_4 alkylamino and C_1-C_4 alkoxy are further optionally substituted with one substituent selected from C_1-C_4 alkylaryl, hydroxyl, and thio;

R^2 and R^3 are each independently H or C_1-C_6 alkyl;

R^4 is C_1-C_6 alkyl or thio; and

R^5 is selected from: C_1-C_6 alkyl, aryl, aryl-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heteroaryl, and heterocyclyl, each optionally substituted with one or more substituents selected from: C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkylamino, amino, amino-C_1-C_6 alkyl, amino-aryl, amino-C_3-C_7 cycloalkyl, aryl, carboxamide, carboxyl, C_3-C_7 cycloalkyl, cyano, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, halo, hydroxyl, nitro, thio, and thio-C_1-C_6 alkyl.

33. The compound of claim 32, wherein R^1 is selected from: 1*H*-indol-3-yl, 1-methyl-1*H*-indol-3-yl, 2-methoxyphenyl, 3-((2-hydroxyethyl)amino)phenyl, 3-((2-mercaptoethyl)amino)phenyl, 3-(2-(acetylthio)ethoxy)phenyl, 3-(2-hydroxyethoxy)phenyl, 3-(2-mercaptoethoxy)phenyl, 3-(4-methylstyryl)phenyl, 3-(aminomethyl)phenyl, 3-(hydroxymethyl)phenyl, 3-hydroxyphenyl, 3,5-difluorophenyl, 3,5-dimethylphenyl, 3-aminophenyl, 3-chlorophenyl, 3-mercaptophenyl, 3-methoxyphenyl, 3-trifluoromethylphenyl, 4-((2-hydroxyethyl)amino)phenyl, 4-((2-mercaptoethyl)amino)phenyl, 4-(2-(acetylthio)ethoxy)phenyl, 4-(2-aminoethoxy)phenyl, 4-(2-hydroxyethoxy)phenyl, 4-(2-mercaptoethoxy)phenyl, 4-(aminomethyl)phenyl, 4-(hydroxymethyl)phenyl, 4-aminophenyl, 4-hydroxyphenyl, 4-mercaptophenyl, 4-methoxyphenyl, cyclohexyl, thien-2-yl, *m*-tolyl, and phenyl.

34. The compound of claim 32 or 33, wherein R^2 is H, or methyl.

35. The compound of any one of claims 32 to 34, wherein R^3 is methyl.

36. The compound of any one of claims 32 to 35, wherein R^4 is methyl.

37. The compound of any one of claims 32 to 36, wherein R^5 is selected from: C_1-C_6 alkyl, aryl, aryl-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heteroaryl, and heterocyclyl, each optionally substituted with one or more substituents selected from: 1-aminocyclopropyl, 4-aminophenyl, amino, aminomethyl, bromo, *tert*-butyl, carboxamide, carboxyl, chloro, cyano, cyclopentyl, ethyl, fluoro, hydroxy, isopropyl, methoxy, methyl, nitro, phenyl, pyridin-3-yl, thio, thiomethyl, trifluoromethoxy, and trifluoromethyl.

38. The compound of any one of claims 32 to 36, wherein R^5 is selected from: 4-aminobenzyl, 4-(aminomethyl)benzyl, 4-(aminomethyl)phenyl, 4-aminophenyl, benzyl, 3-mercaptopropyl, 2-mercaptoethyl, 4-(mercaptomethyl)phenyl, *p*-tolyl, methyl, 2,4,6-trimethylphenyl, 4-(trifluoromethoxy)phenyl, 2,4,6-triisopropylphenyl,

4-*tert*-butylphenyl, 4-chlorophenyl, 3-cyanophenyl, 2-nitrophenyl, 4-methoxy-2-nitrophenyl, 4-aminocarbonyl-2-nitrophenyl, 4-methoxyphenyl, 4-aminophenyl, phenyl, 2-fluorobenzyl, piperidin-1-yl, *o*-tolyl, 4-bromophenyl, naphthalen-2-yl, 4-methoxycarbonyphenyl, 2-(trifluoromethyl)benzyl, hexan-2-yl, 2-methoxyethyl, cyclopentylmethyl, cyclohexyl, pyridin-3-ylmethyl, 4-carboxyphenyl, 3-aminophenyl, pyridin-3-yl, thien-2-yl, 4-hydroxyphenyl, 4-(1-aminocyclopropyl)benzyl, 4-(1-aminocyclopropyl)phenyl, 2-methylbenzyl, 4-nitrobenzyl, 4-chlorobenzyl, phenethyl, 4-bromobenzyl, 4-cyanobenzyl, 3-nitrobenzyl, 4-*tert*-butylbenzyl, 2-nitrobenzyl, 4-nitrophenethyl, 2-chloro-3-methoxycarbonylphenyl, 2-aminophenyl, [1,1'-biphenyl]-4-yl, 4'-amino-[1,1'-biphenyl]-4-yl, 4-fluorobenzyl, 3-(trifluoromethyl)benzyl, 3-(trifluoromethoxy)benzyl, 3,4-dichlorobenzyl, 2-cyanobenzyl, 3-chlorobenzyl, 4-amino-2-ethylphenyl, 4-amino-3-(trifluoromethoxy)phenyl, 4-amino-2,3-dimethylphenyl, 4-amino-5,6,7,8-tetrahydronaphthalen-1-yl, 4-amino-3-methylphenyl, 4-amino-3-fluorophenyl, 4-amino-3-ethylphenyl, and 4-amino-3-(trifluoromethyl)phenyl.

39. The compound of any one of claims 24 to 26, wherein P^1 is a monovalent radical of one of the following compounds:

a) (*S*,*E*)-*N*-(3-Mercaptopropylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound A);

b) (*S*,*E*)-*N*-(2-Mercaptoethylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound B);

c) *S*,*E*)-*N*-(4-(Mercaptomethyl)phenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound C);

d) (*S*,*E*)-2,5-Dimethyl-*N*-tosyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound D);

e) (*S*,*E*)-2,5-dimethyl-*N*-(methylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide (Compound E);

f) (*S*,*E*)-*N*-(Mesitylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

g) (*S*,*E*)-2,5-Dimethyl-*N*-(4-(trifluoromethoxy)phenylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

h) (*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 (Compound 14);

i) (*S*,*E*)-2,5-Dimethyl-*N*-(2,4,6-triisopropylphenylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

j) (*S*,*E*)-*N*-(4-*tert*-Butylphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

k) (*S*,*E*)-*N*-(4-Chlorophenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

l) (*S*,*E*)-*N*-(3-Cyanophenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

m) (*S*,*E*)-2,5-Dimethyl-*N*-(2-nitrophenylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

n) (*S*,*E*)-*N*-(4-Methoxy-2-nitrophenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

o) 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)-3-nitrobenzamide;

p) (*S*,*E*)-*N*-(4-Methoxyphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

q) (*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 (Compound 23);

r) (*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 (Compound 886);

s) (*S*,*E*)-2,5-Dimethyl-*N*-(phenylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

t) (*S*,*E*)-*N*-(*N*-(2-Fluorobenzyl)sulfamoyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

u) (*S*,*E*)-2,5-Dimethyl-*N*-(piperidin-1-ylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

v) (*S*,*E*)-2,5-Dimethyl-*N*-(o-tolylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

w) (*S*,*E*)-*N*-(4-Bromophenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

x) (*S*,*E*)-2,5-Dimethyl-*N*-(naphthalen-2-ylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

y) Methyl 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)benzoate;

z) (*S*,*E*)-2,5-Dimethyl-*N*-(*N*-(2-(trifluoromethyl)benzyl)sulfamoyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

aa) (4*S*,*E*)-*N*-(Hexan-2-ylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

bb) (*S*,*E*)-*N*-(2-Methoxyethylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

cc) (*S*,*E*)-*N*-(Cyclopentylmethylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

dd) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(4-cyanophenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

ee) (*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;

ff) (*S*,*E*)-4-((*S*)-2-((*S*)-3-(4-Azidophenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-*N*-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

gg) (*S*,*E*)-4-((*S*)-2-((*S*)-3-(4-Aminophenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-*N*-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

hh) (*S*,*E*)-*N*-(Cyclohexylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ii) (*S*,*E*)-2,5-Dimethyl-*N*-(pyridin-3-ylmethylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

jj) 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)benzoic acid;

kk) (*S*,*E*)-2,5-Dimethyl-*N*-(3-(2,2,2-trifluoroacetamido)phenylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ll) (*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;

mm) (*S*,*E*)-2,5-Dimethyl-*N*-(pyridin-3-ylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

nn) (*S*,*E*)-2,5-Dimethyl-*N*-(thiophen-2-ylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

oo) (*S*,*E*)-*N*-(4-Hydroxyphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

pp) (*S*,*E*)-2,5-dimethyl-*N*-(4-(1-(2,2,2-trifluoroacetamido)cyclopropyl) phenylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

qq) (*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;

rr) (*S*,*E*)-2,5-Dimethyl-*N*-(2-methylbenzylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ss) (*S*,*E*)-2,5-Dimethyl-*N*-(4-nitrobenzylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

tt) (*S*,*E*)-*N*-(4-Chlorobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

uu) (*S*,*E*)-2,5-Dimethyl-*N*-(phenethylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

vv) (*S*,*E*)-*N*-(4-Bromobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ww) (*S*,*E*)-*N*-(4-Cyanobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

xx) (*S*,*E*)-2,5-Dimethyl-*N*-(3-nitrobenzylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

yy) (*S*,*E*)-*N*-(4-*tert*-Butylbenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

zz) (*S*,*E*)-2,5-Dimethyl-*N*-(2-nitrobenzylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

aaa) (*S*,*E*)-2,5-Dimethyl-*N*-(4-nitrophenethylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

bbb) Methyl 4-Chloro-3-(*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)benzoate;

ccc) (*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;

ddd) (*S*,*E*)-*N*-(4-Aminobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

eee) (*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;

fff) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(4-bromophenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

ggg) (*S*,*E*)-4-((*S*)-2-((*S*)-3-(4'-Acetylbiphenyl-4-yl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-*N*-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

hhh) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(4'-methoxybiphenyl-4-yl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

iii) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(biphenyl-4-yl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

jjj) (*S*,*E*)-*N*-(Benzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-(4-(4-methylstyryl)phenyl)butanamido)butanamido)hex-2-enamide;

kkk) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(4-methoxyphenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

lll) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((R)-3-(3-methoxyphenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

mmm) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(3-methoxyphenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

nnn) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-(4-(2-hydroxyethoxy)phenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide;

ooo) *S*-2-(4-((*S*)-4-((*S*)-1-(((*S*,*E*)-2,5-Dimethyl-6-oxo-6-(benzylsulfonamido)hex-4-en-3-yl)(methyl)amino)-3,3-dimethyl-1-oxobutan-2-ylamino)-2-methyl-3-(methylamino)-4-oxobutan-2-yl)phenoxy)ethyl ethanethioate;

ppp) (*S*,*E*)-4-((*S*)-2-((*S*)-3-(4-(2-Aminoethoxy)phenyl)-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-*N*-(benzylsulfonyl)-2,5-dimethylhex-2-enamide;

qqq) (*S*,*E*)-*N*-(2-Aminophenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

rrr) (*S*,*E*)-*N*-(Biphenyl-4-ylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

sss) (*S*,*E*)-*N*-(4'-Aminobiphenyl-4-ylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ttt) (*S*,*E*)-*N*-(4-Fluorobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

uuu) (*S*,*E*)-2,5-Dimethyl-*N*-(3-(trifluoromethyl)benzylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

vvv) (*S*,*E*)-2,5-Dimethyl-*N*-(3-(trifluoromethoxy)benzylsulfonyl)-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

www) (*S*,*E*)-*N*-(3,4-Dichlorobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

xxx) (*S*,*E*)-*N*-(2-Cyanobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

yyy) (*S*,*E*)-*N*-(3-Chlorobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

zzz) (*S*,*E*)-*N*-(4-Amino-2-ethylphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

aaaa) (*S*,*E*)-*N*-(4-Amino-3-(trifluoromethoxy)phenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

bbbb) (*S*,*E*)-*N*-(4-Amino-2,3-dimethylphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

cccc) (*S*,*E*)-*N*-(4-Amino-5,6,7,8-tetrahydronaphthalen-1-ylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

dddd) (*S*,*E*)-*N*-(4-Amino-3-methylphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

eeee) (*S*,*E*)-*N*-(4-Amino-3-fluorophenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

ffff) (*S*,*E*)-*N*-(4-Amino-3-ethylphenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

gggg) (*S*,*E*)-*N*-(4-Amino-3-(trifluoromethyl)phenylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide;

hhhh) (*S*)-1-Isopropyl-*N*-((*S*)-1-(((*S*,*E*)-6-(3-mercaptopropylsulfonamido)-2,5-dimethyl-6-oxohex-4-en-3-yl)(methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)piperidine-2-carboxamide;

iiii) (*R*)-*N*-(Benzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hexanamide; or

jjjj) (*S*,*E*)-*N*-(Benzylsulfonyl)-4-((*S*)-2-((*S*)-3-cyclohexyl-3-methyl-2-(methylamino)butanamido)-*N*,3,3-trimethylbutanamido)-2,5-dimethylhex-2-enamide.

40. The compound of any one of claims 24 to 26, wherein P^1 is a monovalent radical of one of the following compounds:

a) (*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;

b) (*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;

c) (*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;

d) (*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, or

e) (*S*,*E*)-*N*-(4-Aminobenzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hex-2-enamide.

41. A pharmaceutical composition comprising the compound of any one of claims 1 to 40, and a pharmaceutically acceptable carrier, diluent or excipient.

42. A compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 for use in therapy.

43. Use of a compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 in the manufacture of a medicament for treating cancer in a mammal, increasing survival of a mammal having cancer, or inhibiting tumor growth in a mammal.

44. The use according to claim 43, wherein said cancer is a carcinoma, a sarcoma, a hematopoietic cancer, or a tumor of neuroepithelial tissue.

45. Use of a compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 in the manufacture of a medicament for the treatment of an indication selected from: cancer, arthritis, arthrosis, multiple sclerosis, neural damage, cartilage damage, and psoriasis.