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 compound of Formula I:

T–L–P

I

wherein:

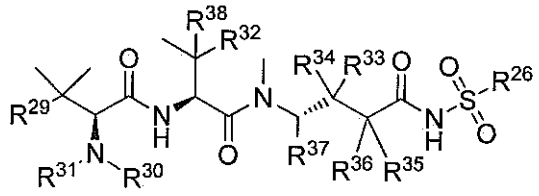
T is a targeting moiety comprising a VAR2CSA polypeptide, the VAR2CSA polypeptide comprising a sequential amino acid sequence of ID1 and DBL2Xb, and

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 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 and optionally substituted heteroaryl;

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

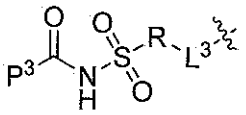
R^{37} is selected from the group consisting of H and C_{1-6} alkyl; or

wherein:

L^2 is a linker;

P^2 is a cytotoxic compound selected from a hemiasterlin, a hemiasterlin analog, a tubulysin, a tubulysin analog, an auristatin and an auristatin analog; 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 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

1. A compound of Formula I:

T–L–P

I

wherein:

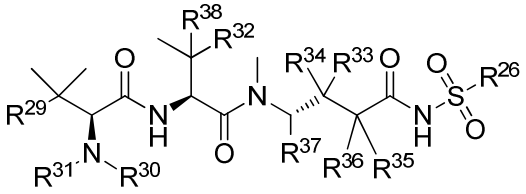
T is a targeting moiety comprising a VAR2CSA polypeptide, the VAR2CSA polypeptide comprising a sequential amino acid sequence of ID1 and DBL2Xb, and

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 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 and optionally substituted heteroaryl;

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 $C_{1\text{-}6}$ alkyl;

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

R^{32} and R^{38} are each independently selected from the group consisting of H, $C_{1\text{-}6}$ 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

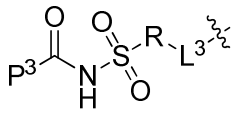
R^{37} is selected from the group consisting of H and C_{1-6} alkyl; or

wherein:

L^2 is a linker;

P^2 is a cytotoxic compound selected from a hemiasterlin, a hemiasterlin analog, a tubulysin, a tubulysin analog, an auristatin and an auristatin analog; 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 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;

b. DBL2Xb; and

c. ID2a.

3. The compound of claim 1 or 2, wherein the VAR2CSA polypeptide comprises a sequential amino acid sequence of DBL1-ID2a.

4. 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.

5. 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; ~~30~~ 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.

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; 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 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.

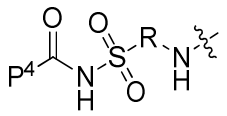
8. The compound of any one of claims 1 to 7, wherein said VAR2CSA polypeptide is a recombinant protein.

9. The compound of any one of claims 1 to 8, wherein said VAR2CSA polypeptide is non-glycosylated.

10. The compound of any one of claims 1 to 9, wherein L–P is L^2–P^2.

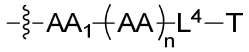
11. The compound of claim 10, wherein:

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 and optionally substituted heteroaryl,

each AA is independently an amino acid,

n is an integer from 0 to 25,

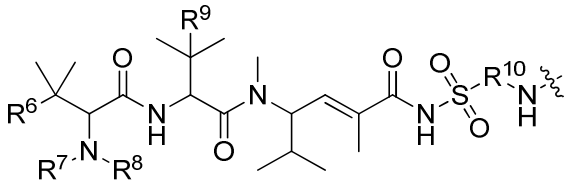
L^4 is optionally the remaining portion of linker L^2,

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.

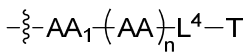
12. The compound of claim 11, wherein said cytotoxic compound is a hemiasterlin or an analog thereof; or an auristatin or an analog thereof.

13. The compound of claim 10, 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, and optionally substituted heteroaryl;

each AA is independently an amino acid;

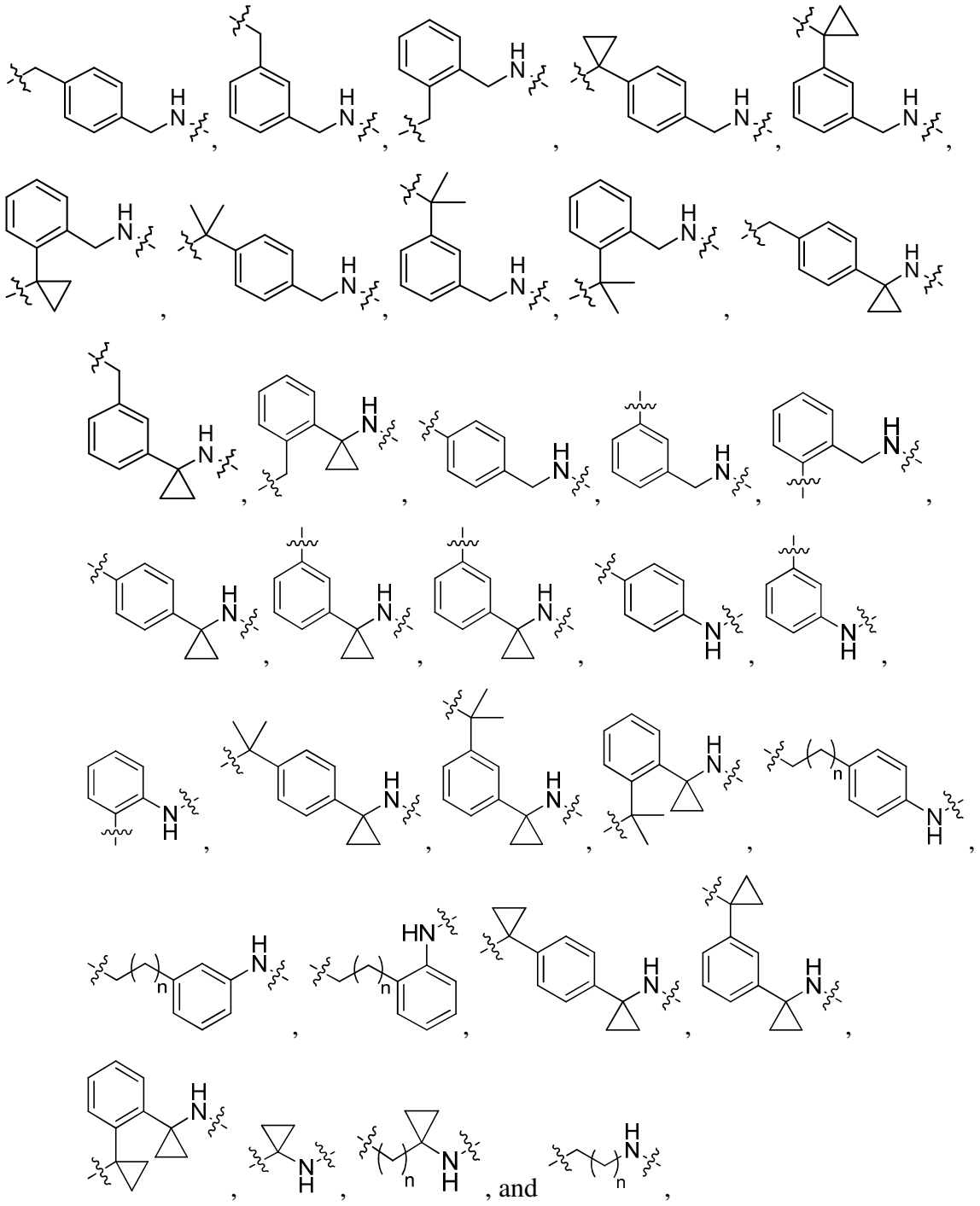
n is an integer from 0 to 25;

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

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.

14. The compound of claim 13, wherein –R^{10}–NH– of Formula X is selected from:



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

15. The compound of any one of claims 11 to 14, 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.

16. The compound of any one of claims 11 to 15, wherein L^4 comprises repeating alkoxy units, a diacid amide, a diacid ester, or a combination thereof.

17. The compound of claim 11, 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.

18. The compound of claim 11, 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.

19. The compound of claim 17 or 18, 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.

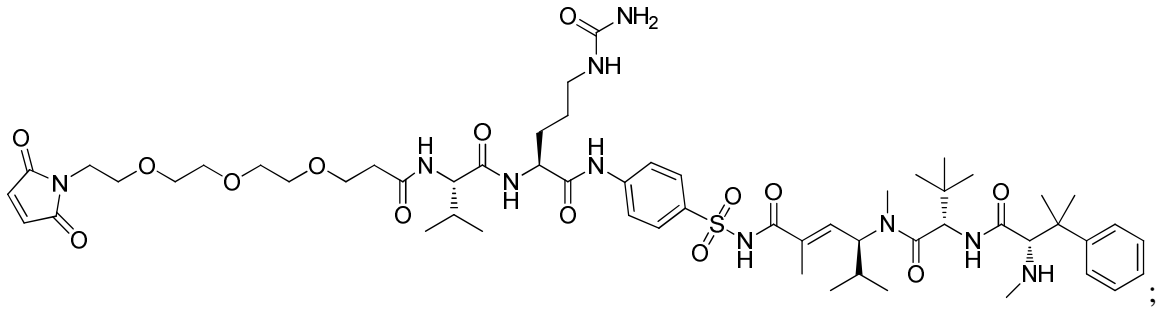
20. The compound of any one of claims 17 to 19, wherein L^4 comprises repeating alkoxy units, a diacid amide, a diacid ester, or a combination thereof.

21. The compound of claim 11, 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

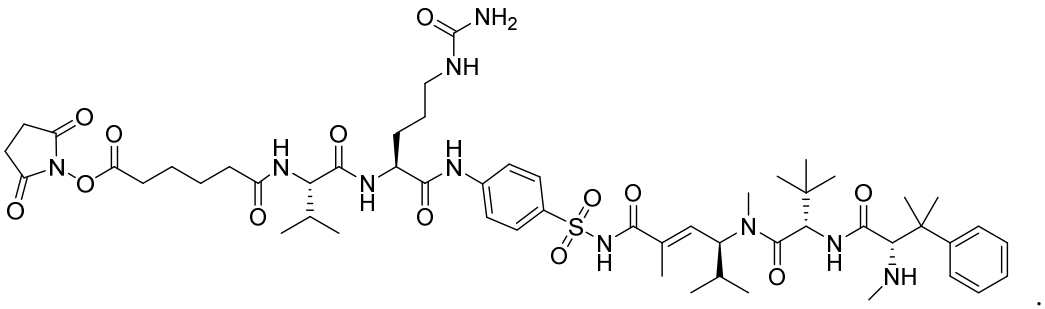
b) Compound O:



;

or

c) Compound KK:



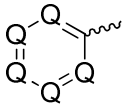
22. The compound of any one of claims 1 to 9, wherein L–P is L^1–P^1.

23. The compound of claim 22, wherein L^1 comprises: SPDP, SMCC, vcPABC, MCvcPABC, MTvc, ADvc, maleimide, NHS, biotin, streptavidin, NeutrAvidin, a glycoside, or a combination thereof.

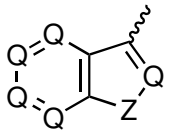
24. The compound of claim 22, wherein L^1 comprises vcPABC, MCvcPABC, MTvc or ADvc.

25. The compound of any one of claims 22 to 24, 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.

26. The compound of any one of claims 22 to 24, wherein R^{29} is selected from one of the following structures XVI, XVII, XVIII, and XIX:

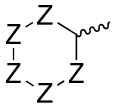

;

XVI



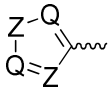
;

XVII



; and

XVIII



,

XIX

wherein:

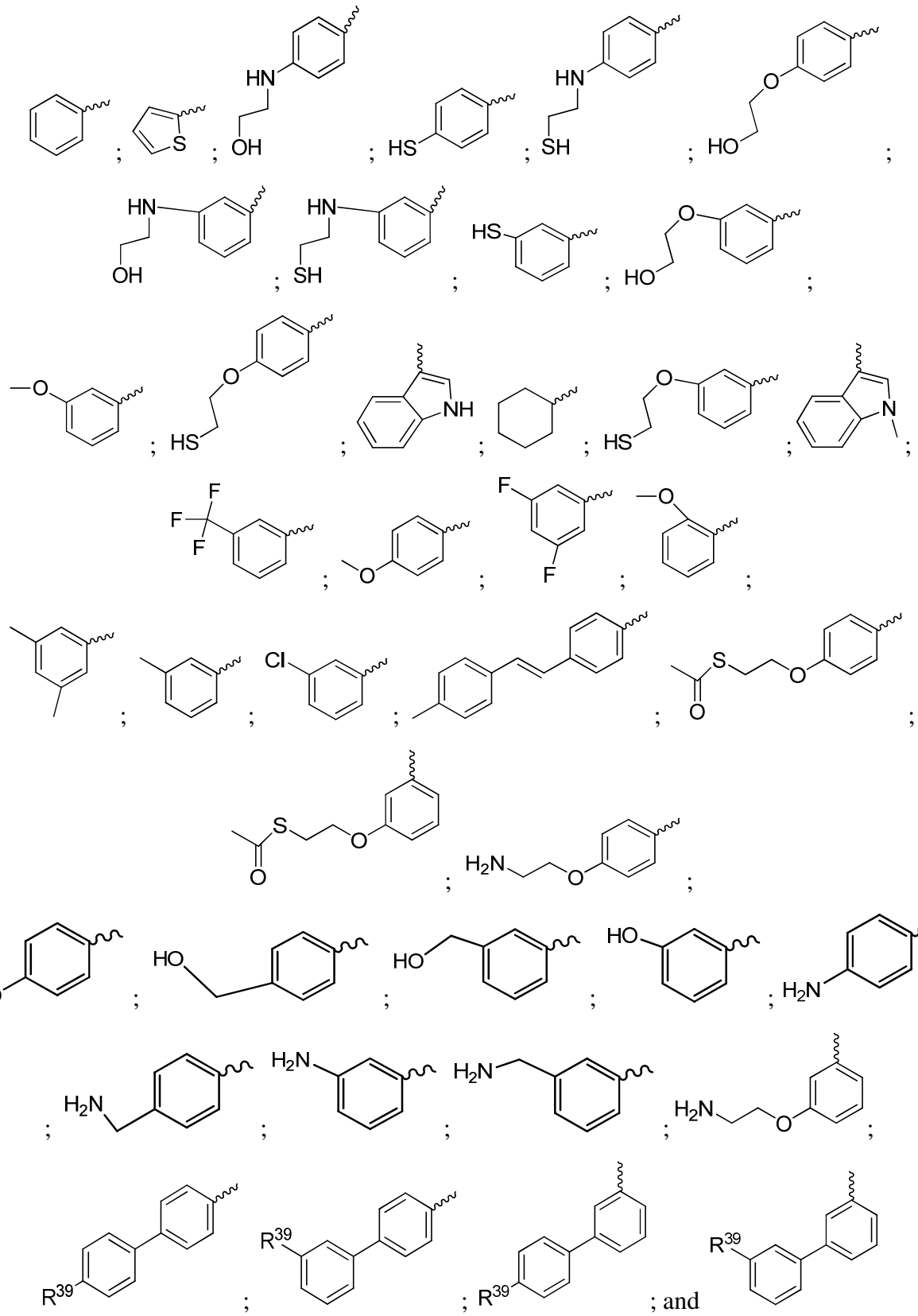
Q is CR^{39} or N;

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.

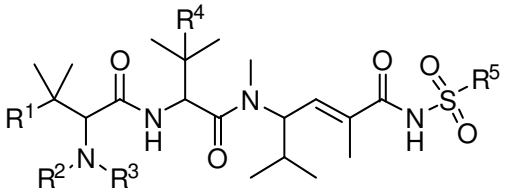
27. The compound of any one of claims 22 to 24, wherein R^{29} is selected from the group consisting of:


HN
OH
S
HS
SH
O
HO
NH
N
F
Cl
H2N
R39
; and

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.

28. The compound of any one of claims 22 to 27, wherein R^{30} is H or methyl, and R^{31}, R^{32}, and R^{38} are each methyl.

29. The compound of any one of claims 22 to 24, 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.

30. The compound of claim 29, 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.

31. The compound of claim 29 or 30, wherein R^2 is H, or methyl.

32. The compound of any one of claims 29 to 31, wherein R^3 is methyl.

33. The compound of any one of claims 29 to 32, wherein R^4 is methyl.

34. The compound of any one of claims 29 to 33, 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.

35. The compound of any one of claims 29 to 33, 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.

36. The compound of any one of claims 22 to 24, 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) (*R*)-*N*-(Benzylsulfonyl)-2,5-dimethyl-4-((*S*)-*N*,3,3-trimethyl-2-((*S*)-3-methyl-2-(methylamino)-3-phenylbutanamido)butanamido)hexanamide; or

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

37. The compound of any one of claims 22 to 24, 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.

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 compound of any one of claims 1 to 37 or the pharmaceutical composition of claim 38 for use in therapy.

40. Use of a compound of any one of claims 1 to 37 or the pharmaceutical composition of claim 38 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.

41. The use according to claim 40, wherein said cancer is a carcinoma, a sarcoma, a hematopoietic cancer, or a tumor of neuroepithelial tissue.

42. Use of a compound of any one of claims 1 to 37 or the pharmaceutical composition of claim 38 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.