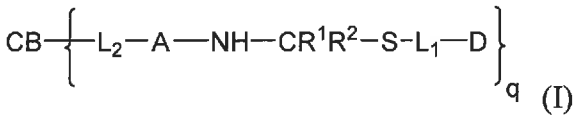
CLAIMS

1. A cell-binding agent-cytotoxic agent conjugate represented by the following formula:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

CB is a cell-binding agent;

L_2 is absent or a spacer;

A is an amino acid residue or a peptide comprising 2 to 20 amino acid residues;

R^1 and R^2 are each independently H or a C_{1-3}alkyl;

L_1 is a spacer;

D-L_1-SH is a cytotoxic agent; and

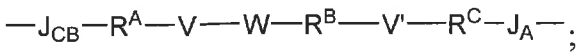
q is an integer from 1 to 20.

2. The conjugate of claim 1, wherein one of R^1 and R^2 is H, and the other one is Me, or R^1 and R^2 are both H.

3. The conjugate of claim 1 or 2, wherein L_1 is –L_1'–C(=O)-; and L_1' is an alkylene or a cycloalkylene, wherein the –C(=O)- moiety in L_1 is connected to D.

4. The conjugate of claim 3, wherein L_1 is –CR^3R^4-$(CH_2)_{1-8}$-C(=O)-; R^3 and R^4 are each independently H or Me.

5. The conjugate of any one of claims 1-4, wherein L_2 is represented by the following structural formula:



;

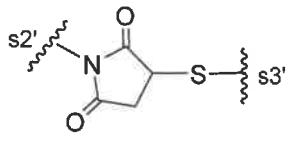
wherein:

R^A is an alkylene, a cycloalkylalkylene or an arylene;

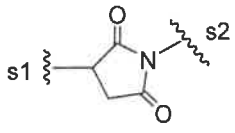
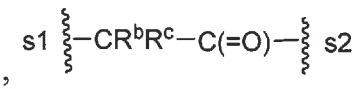
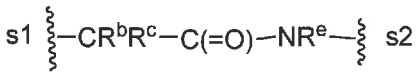
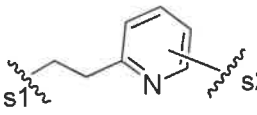
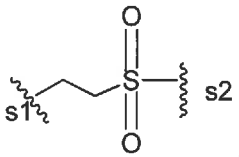
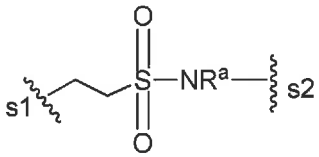
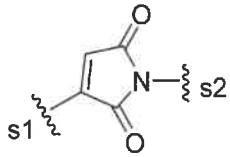
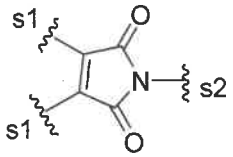
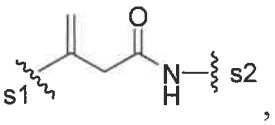
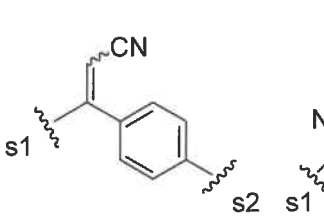
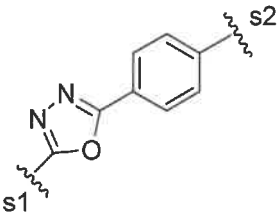
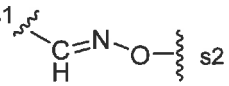
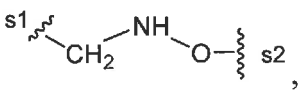
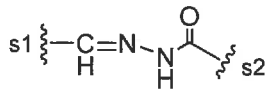
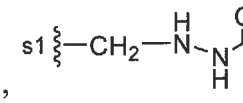
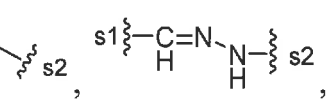
R^B and R^C are each independently absent, an alkylene, a cyclalkylene, or an arylene;

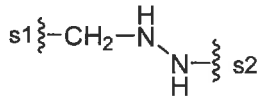
V and V' are each independently -$(O\text{-}CH_2\text{-}CH_2)_p$-, or -$(CH_2\text{-}CH_2\text{-}O)_p$-;

p is 0 or an integer from 1 to 10;

W is absent,  , or ,

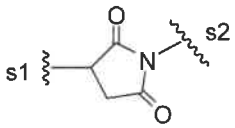
wherein s2' indicates the site connected to V, R^A or J_{CB} and s3' indicates the site connected to R^B, V', R^C or J_A;

J_{CB} is -C(=O)-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ;  ,  ,  ,  ,  ,

or  , wherein s1 indicates the site connected to the cell-binding agent CB and s2 indicates the site connected to R^A;

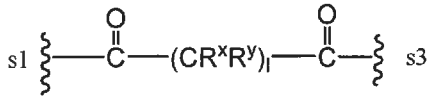
R^a, R^b, R^c, and R^e, for each occurrence, are independently H or an alkyl; and

J_A is -C(=O)-.

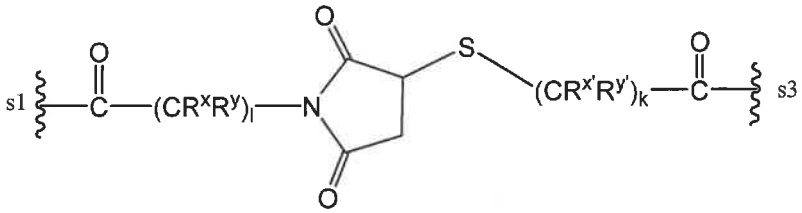
6. The conjugate of claim 5, wherein J_{CB} is -C(=O)- or  .

7. The conjugate of claim 5 ot 6, wherein L_2 is represented by the following

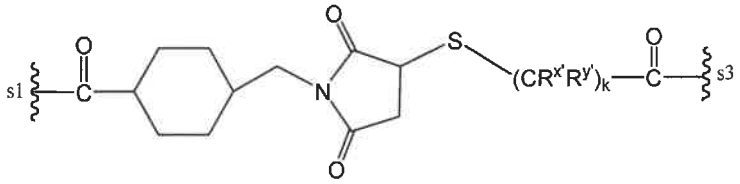
structural formulas:



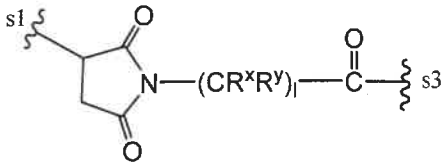
(L2a);



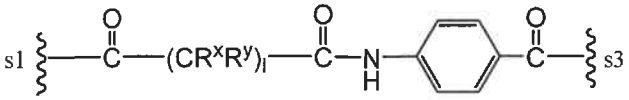
(L2b);



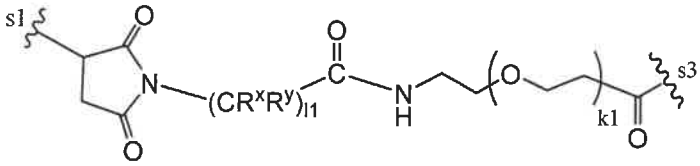
(L2c);



(L2d);



(L2e); or



(L2f);

wherein:

R^x, R^y, $R^{x'}$ and $R^{y'}$, for each occurrence, are independently H, -OH, halogen, -O-(C_{1-4} alkyl), -SO_3H, -$NR_{40}R_{41}R_{42}^+$, or a C_{1-4} alkyl optionally substituted with -OH, halogen, SO_3H or $NR_{40}R_{41}R_{42}^+$, wherein R_{40}, R_{41} and R_{42} are each independently H or a C_{1-4} alkyl;

l and k are each independently an integer from 1 to 10;

s1 indicates the site connected to the cell-binding agent CB and s3 indicates the site connected to the A group;

l1 are each an integer from 2 to 6; and

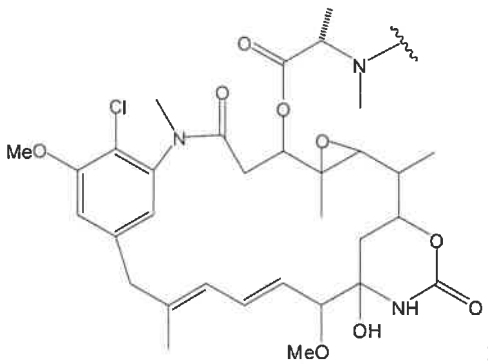
k1 is an integer from 1 to 5.

8. The conjugate of claim 7, wherein R^x, R^y, $R^{x'}$ and $R^{y'}$ are all H; and l and k are each independently an integer an integer from 2 to 6.

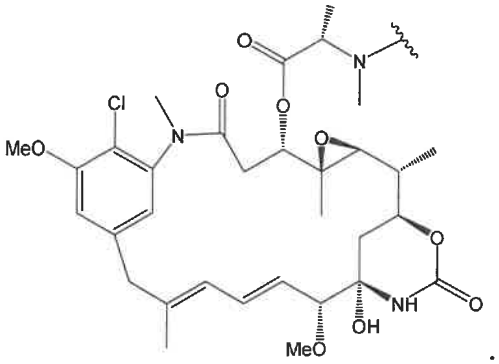
9. The conjugate of any one of claims 1-8, wherein A is a peptide cleavable by a protease expressed in tumor tissue.

10. The conjugate of any one of claims 1-8, wherein A is selected from the group consisting of Gly-Gly-Gly, Ala-Val, Val-Ala, D-Val-Ala, Val-Cit, D-Val-Cit, Val-Lys, Phe-Lys, Lys-Lys, Ala-Lys, Phe-Cit, Leu-Cit, Ile-Cit, Phe-Ala, Phe-N^9-tosyl-Arg, Phe-N^9-nitro-Arg, Phe-Phe-Lys, D-Phe-Phe-Lys, Gly-Phe-Lys, Leu-Ala-Leu, Ile-Ala-Leu, Val-Ala-Val, Ala-Ala-Ala, D-Ala-Ala-Ala, Ala-D-Ala-Ala, Ala-Ala-D-Ala, Ala-Leu-Ala-Leu (SEQ ID NO: 1), β-Ala-Leu-Ala-Leu (SEQ ID NO: 2), Gly-Phe-Leu-Gly (SEQ ID NO: 3), Val-Arg, Arg-Arg, Val-D-Cit, Val-D-Lys, Val-D-Arg, D-Val-Cit, D-Val-Lys, D-Val-Arg, D-Val-D-Cit, D-Val-D-Lys, D-Val-D-Arg, D-Arg-D-Arg, Ala-Ala, Ala-D-Ala, D-Ala-Ala, D-Ala-D-Ala, Ala-Met, Gln-Val, Asn-Ala, Gln-Phe, Gln-Ala, D-Ala-Pro, and D-Ala-tBu-Gly, wherein the first amino acid in each peptide is connected to L_2 group and the last amino acid in each peptide is connected to –NH-CR^1R^2-S-L_1-D.

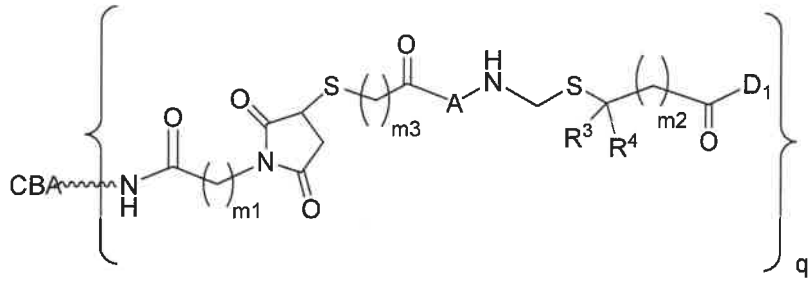
11. The conjugate of any one of claims 1-10, wherein D is represented by the following formula:



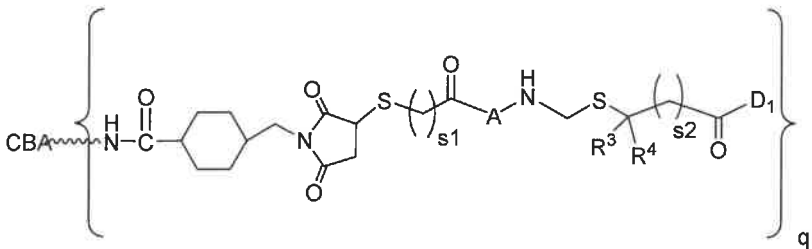
; or



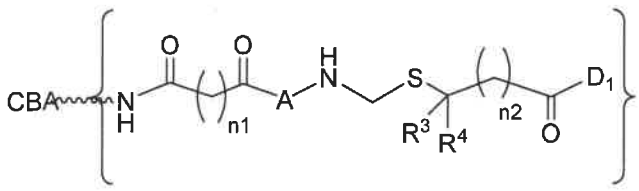
12. The conjugate of any one of claims 1-11, wherein the conjugate is represented by the following formula:



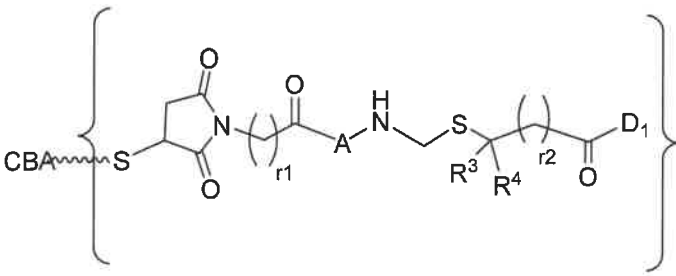
q;



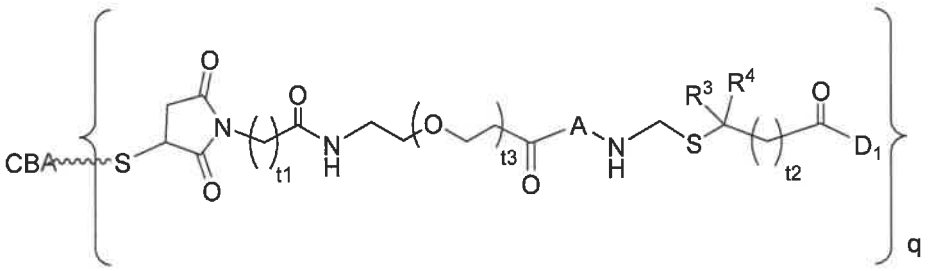
q;



q;



q; or



or a pharmaceutically acceptable salt thereof, wherein:

CBA—N(H)— is the cell-binding agent connected to the L_2 group through a Lys amine group;

CBA—S— is the cell-binding agent connected to the L_2 group through a Cys thiol group;

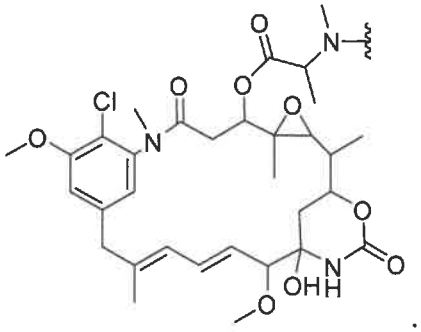
R^3 and R^4 are each independently H or Me;

m1, m3, n1, r1, s1 and t1 are each independently an integer from 1 to 6;

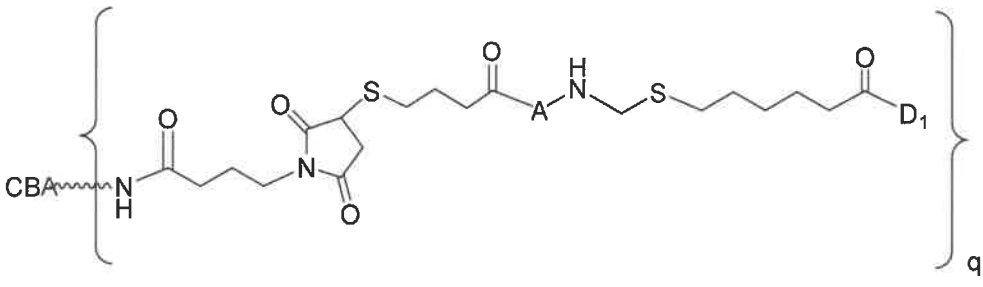
m2, n2, r2, s2 and t2 are each independently an integer from 1 to 7;

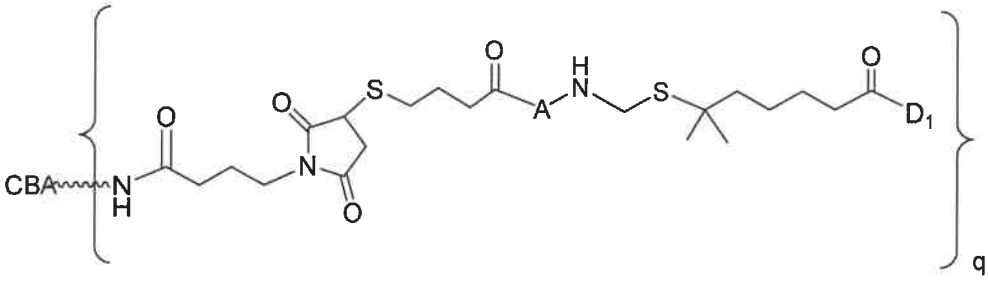
t3 is an integer from 1 to 12;

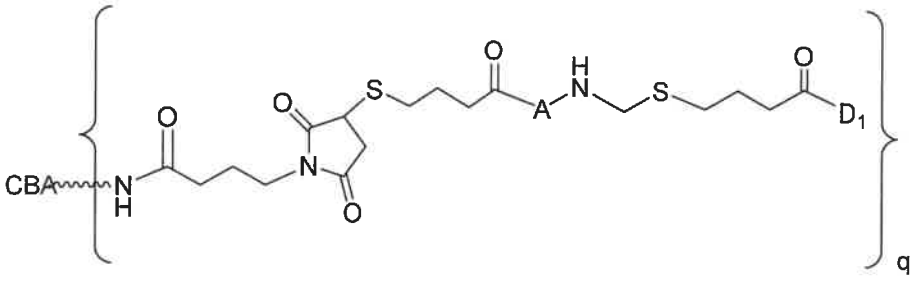
D_1 is represented by the following formula:

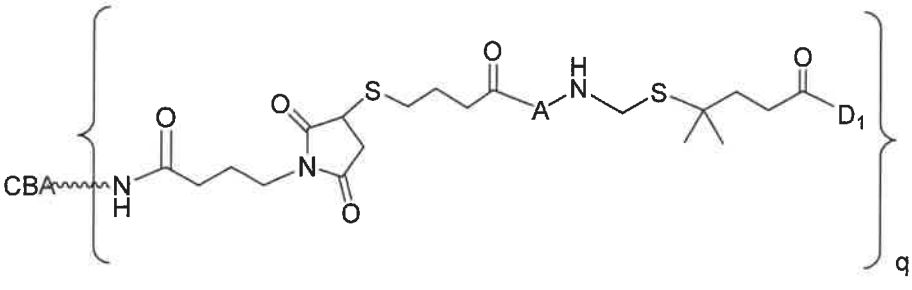


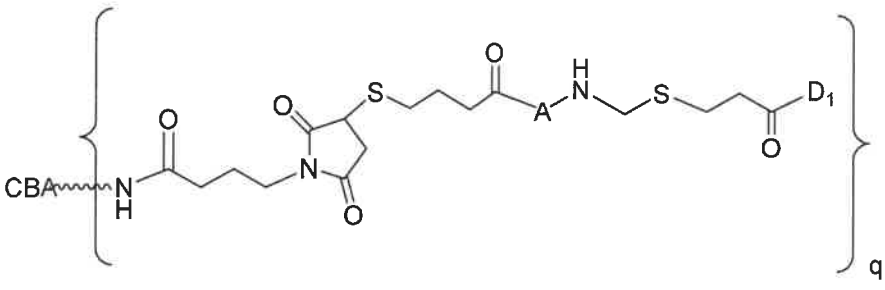
13. The conjugate of claim 12, wherein the conjugate is represented by the following formula:

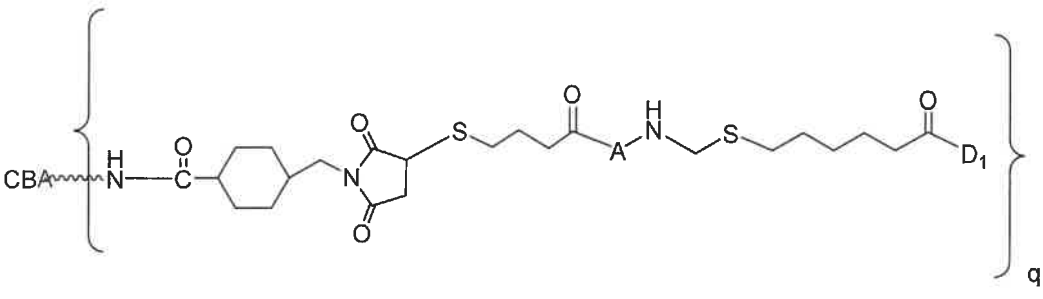


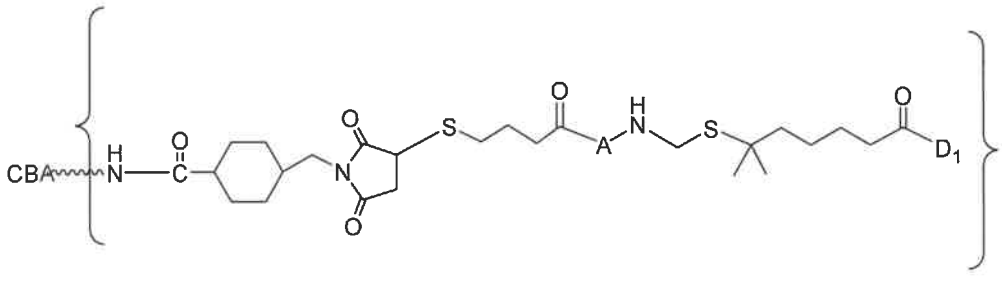

CBA
N
H
O
O
N
O
S
O
A
H
N
S
O
D1
q;

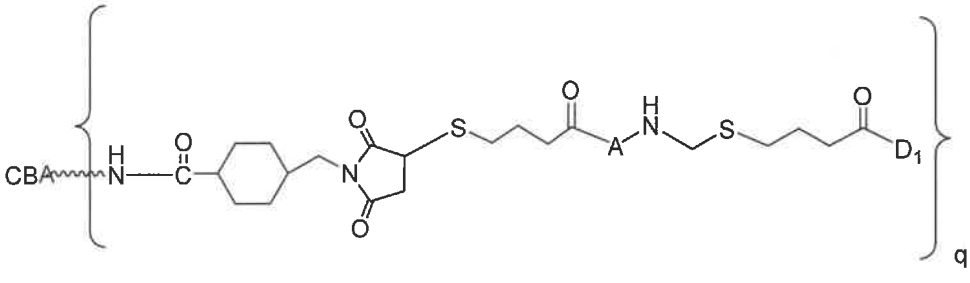

CBA
N
H
O
O
N
O
S
O
A
H
N
S
O
D1
q;

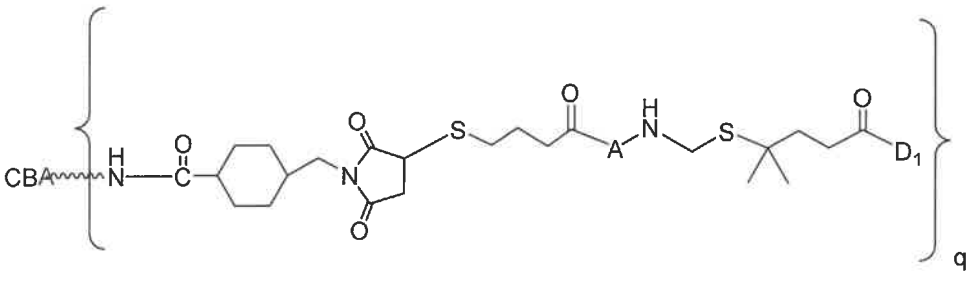

CBA
N
H
O
O
N
O
S
O
A
H
N
S
O
D1
q;

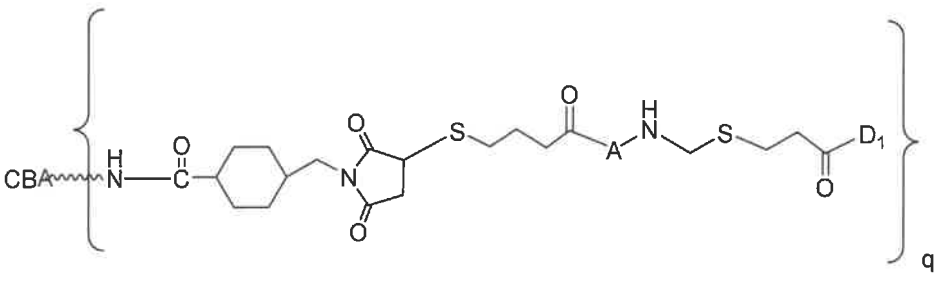

CBA
N
H
O
O
N
O
S
O
A
H
N
S
D1
O
q;

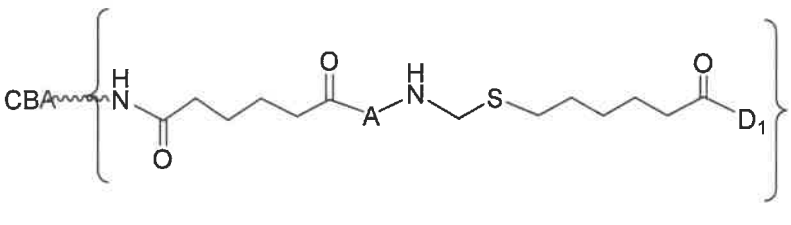

CBA
H
N
O
C
O
N
O
S
O
A
H
N
S
O
D1
q;

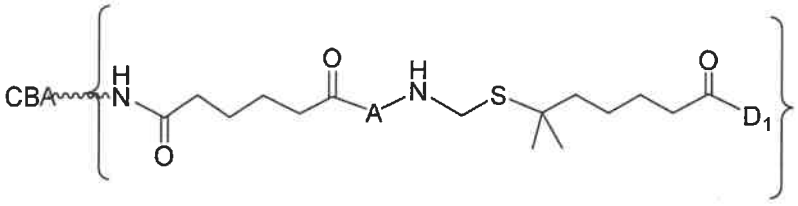

CBA
H
N
O
C
O
N
O
O
S
O
A
H
N
S
O
D1
q ;

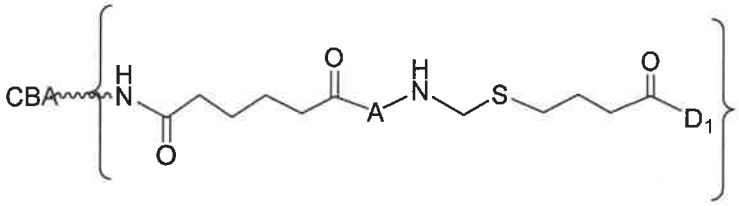

CBA
H
N
O
C
O
N
O
O
S
O
A
H
N
S
O
D1
q ;

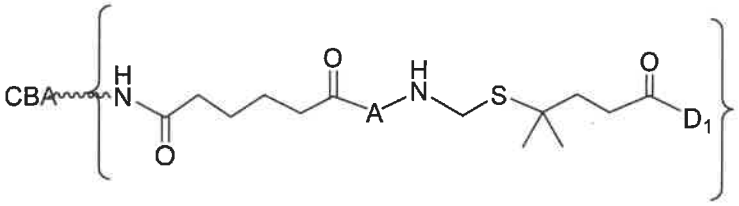

CBA
H
N
O
C
O
N
O
O
S
O
A
H
N
S
O
D1
q ;

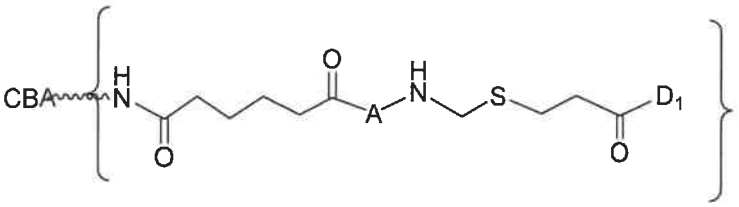

CBA
H
N
O
C
O
N
O
O
S
O
A
H
N
S
D1
O
q ;

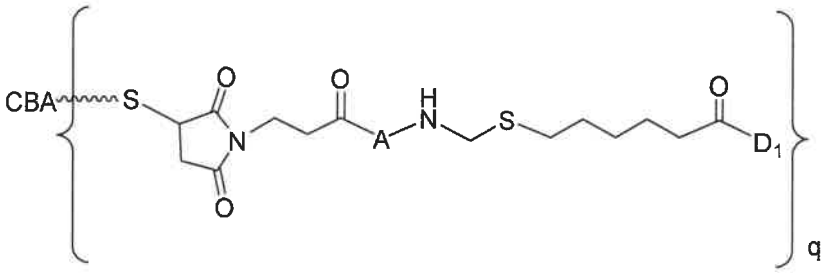

CBA
H
N
O
O
A
H
N
S
O
D1
q ;

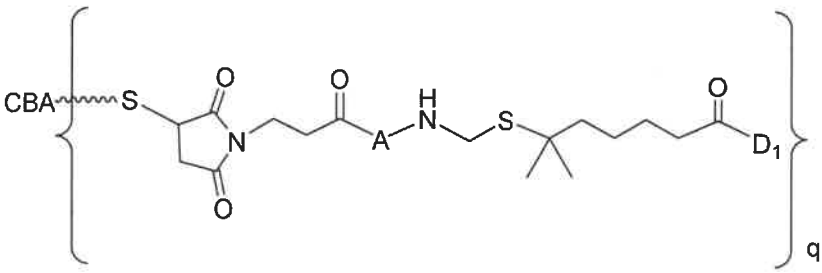

CBA
H
N
O
A
H
N
S
O
D1
q;

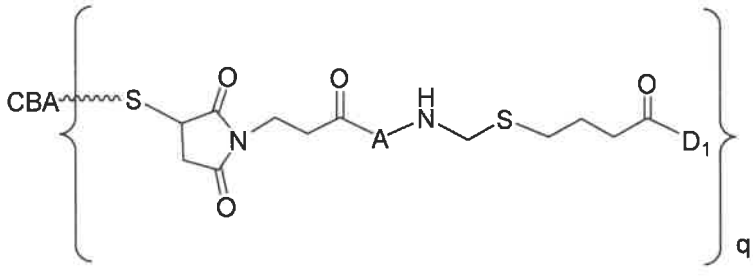

CBA
H
N
O
A
H
N
S
O
D1
q;

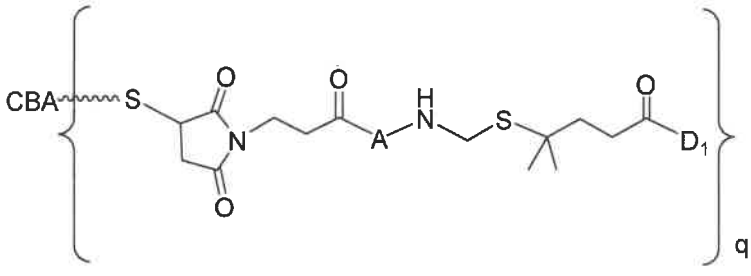

CBA
H
N
O
A
H
N
S
O
D1
q;

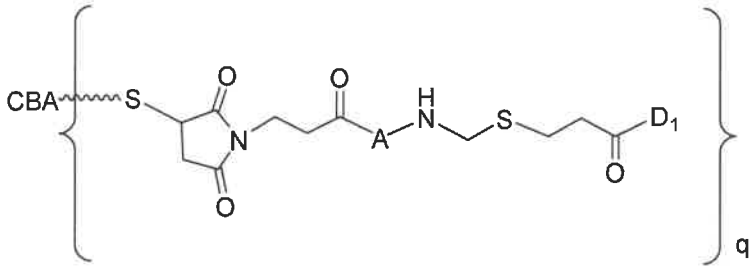

CBA
H
N
O
A
H
N
S
D1
O
q;

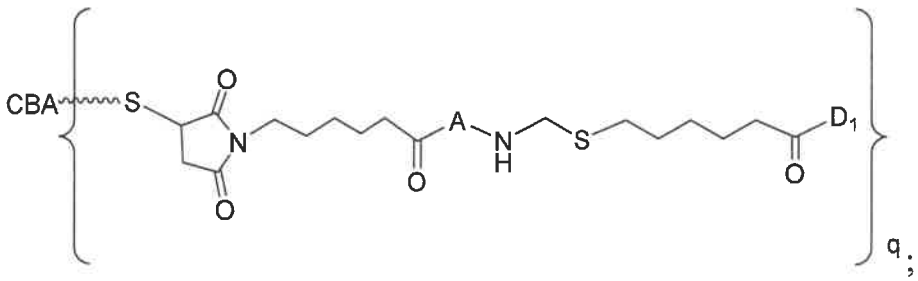

CBA
S
O
O
N
O
A
H
N
S
O
D1
q;

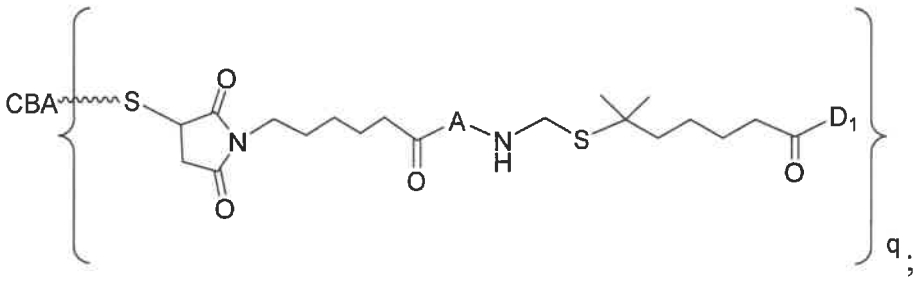

CBA
S
O
O
N
O
A
H
N
S
O
D1
q;

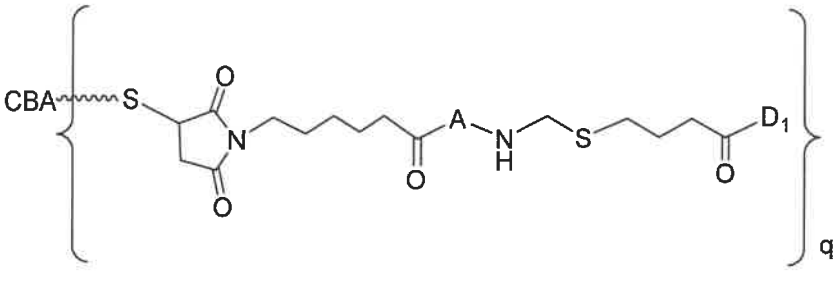

CBA
S
O
O
N
O
A
H
N
S
O
D1
q;

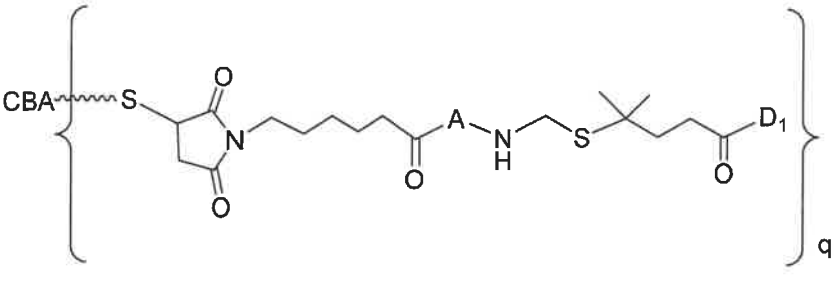

CBA
S
O
O
N
O
A
H
N
S
O
D1
q; or

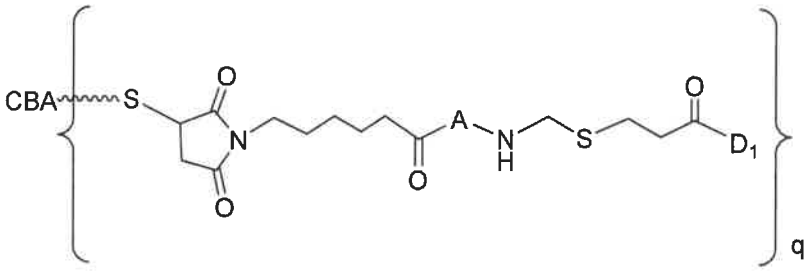

CBA
S
O
O
N
O
A
H
N
S
D1
O
q;

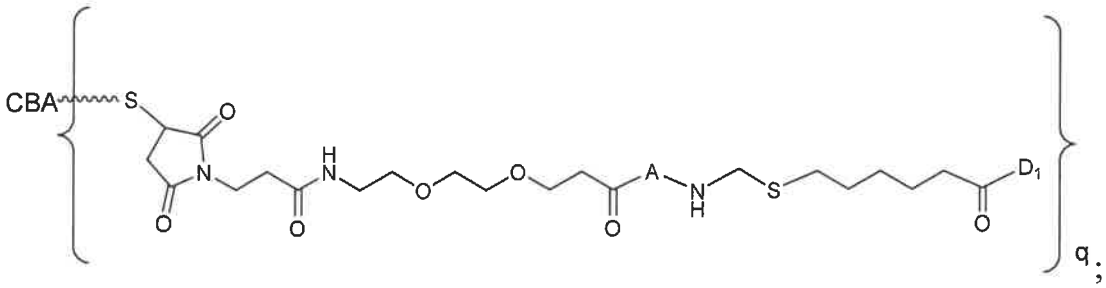

CBA
S
O
N
O
A
N
H
S
D1
O
q;

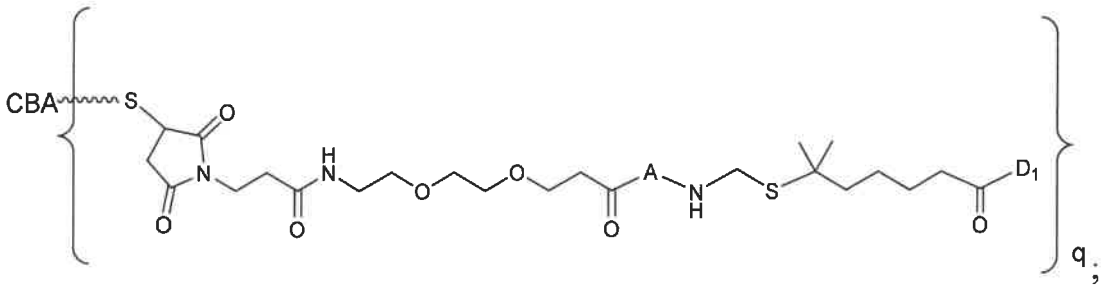

CBA
S
O
N
O
A
N
H
S
D1
O
q;

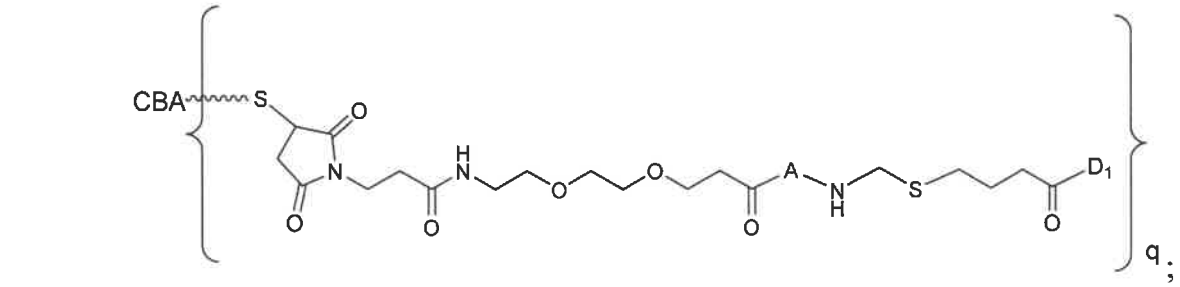

CBA
S
O
N
O
O
A
N
H
S
O
D1
q;

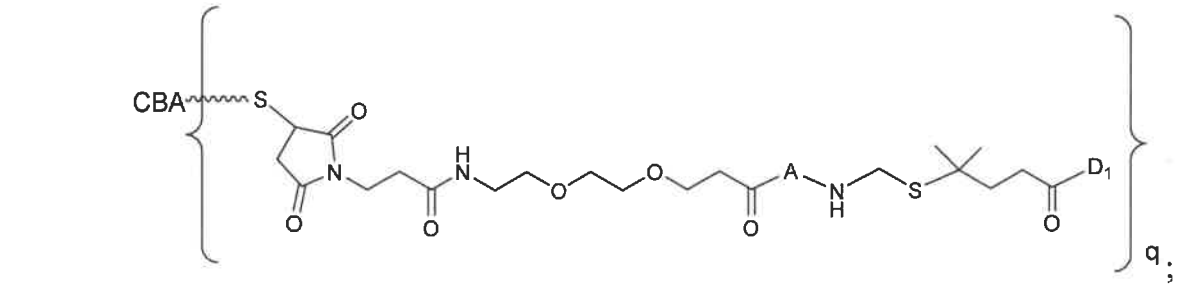

CBA
S
O
N
O
O
A
N
H
S
O
D1
q;

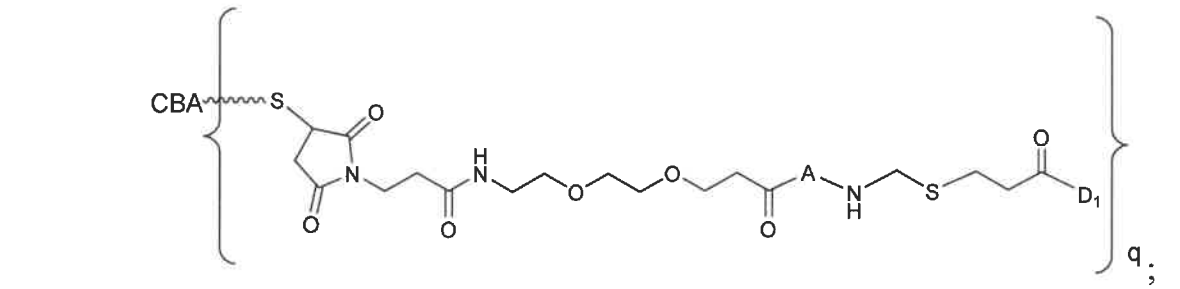

CBA
S
O
N
O
O
A
N
H
S
O
D1
q;

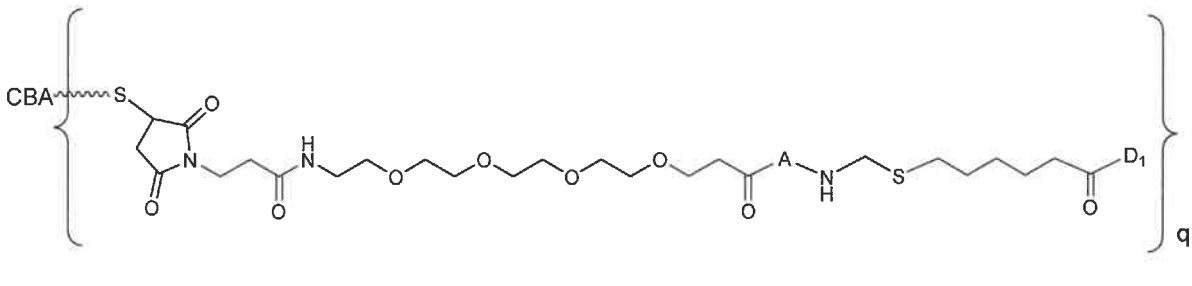

CBA
S
O
N
O
O
H
N
O
O
O
A
N
H
S
O
D1
q;

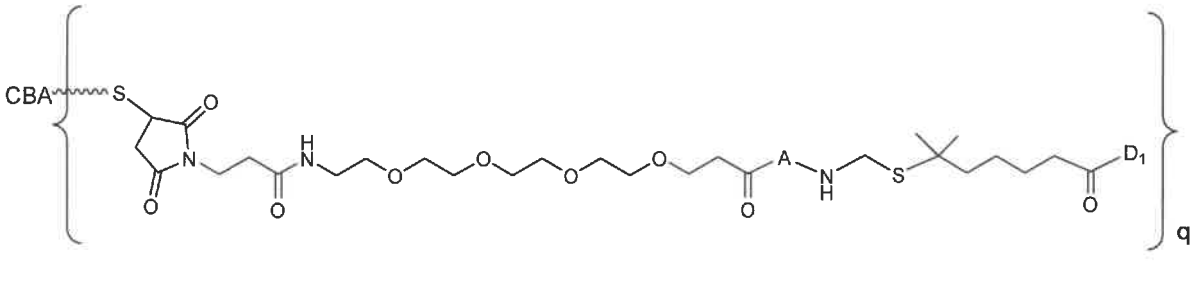

CBA
S
O
N
O
O
H
N
O
O
O
A
N
H
S
O
D1
q;

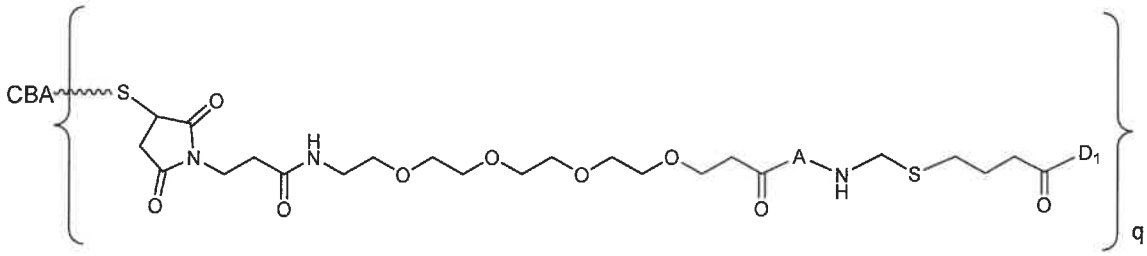

CBA
S
O
N
O
H
N
O
O
O
A
N
H
S
D1
O
q;

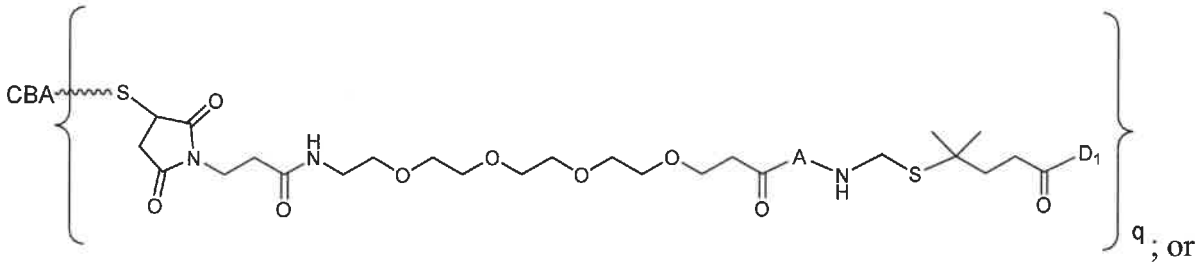

CBA
S
O
N
O
H
N
O
O
O
A
N
H
S
D1
O
q;


CBA
S
O
N
O
H
N
O
O
O
A
N
H
S
D1
O
q;

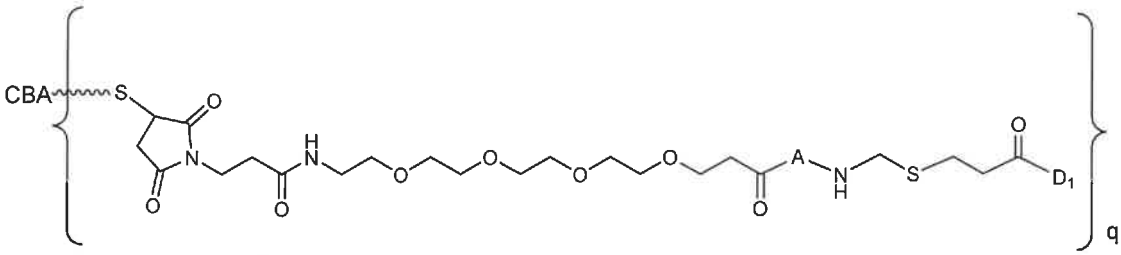

CBA
S
O
N
O
H
N
O
O
O
O
O
A
N
H
S
D1
O
q;


CBA
S
O
N
O
H
N
O
O
O
O
O
A
N
H
S
D1
O
q;





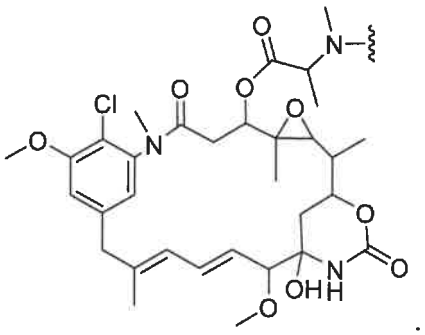
; or



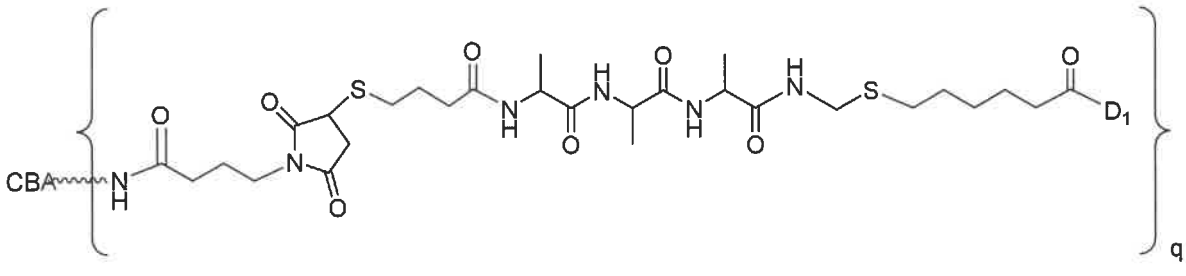
or a pharmaceutically acceptable salt thereof, wherein:

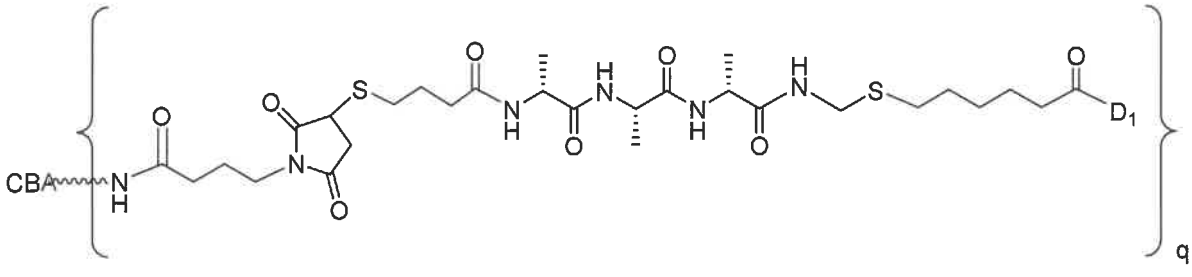
A is Ala-Ala-Ala, Ala-D-Ala-Ala, Ala-Ala, D-Ala-Ala, Val-Ala, D-Val-Ala, D-Ala-Pro, or D-Ala-tBu-Gly, and

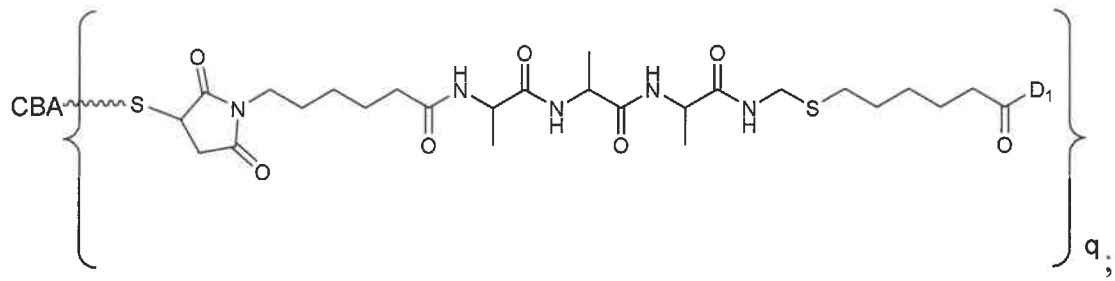
D_1 is represented by the following formula:

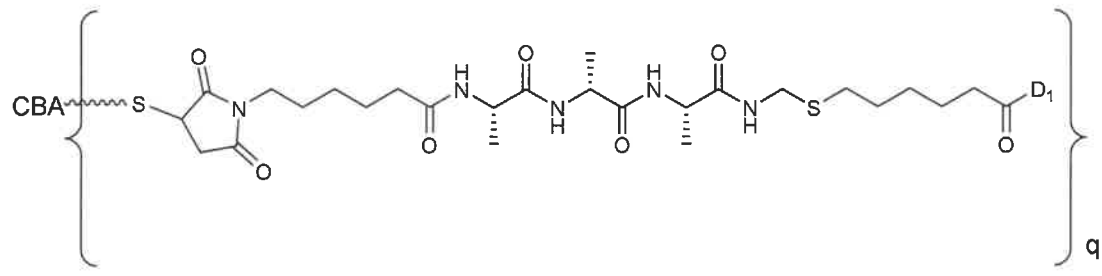


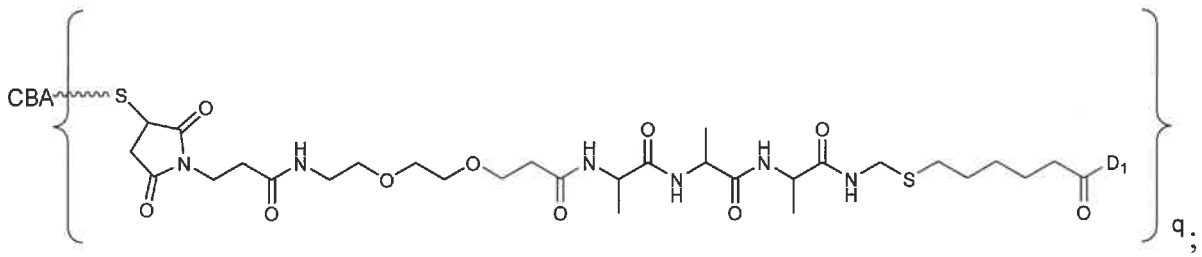
14. The conjugate of claim 13, wherein the conjugate is represented by the following formula:

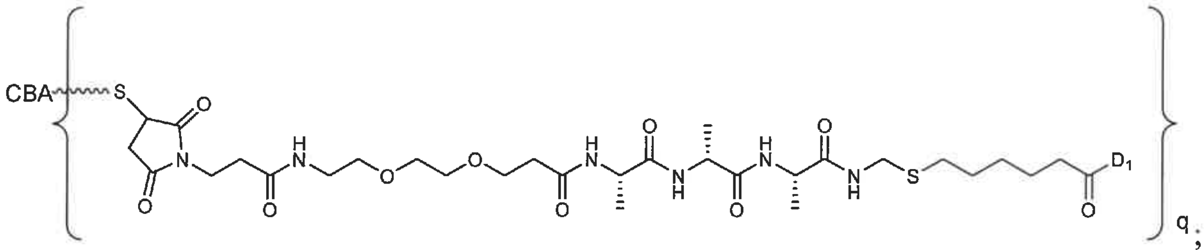

CBA
D1
q;


CBA
D1
q;

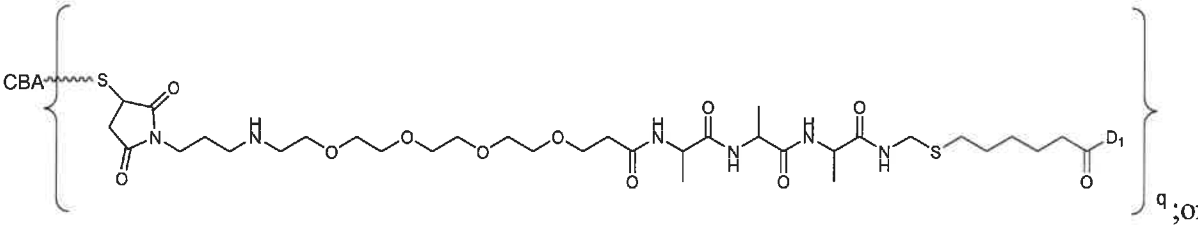

CBA
D1
q;


CBA
D1
q;

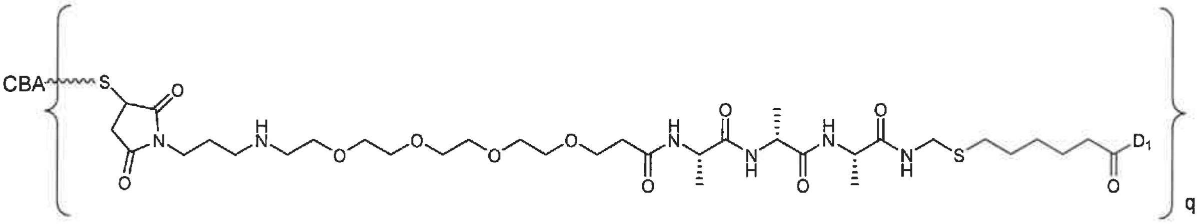

CBA
D1
q;



;

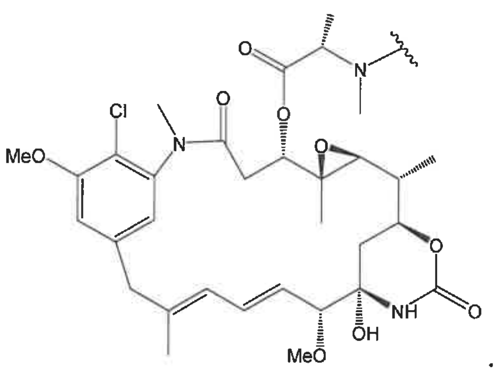


;or



,

wherein D_1 is represented by the following formula:



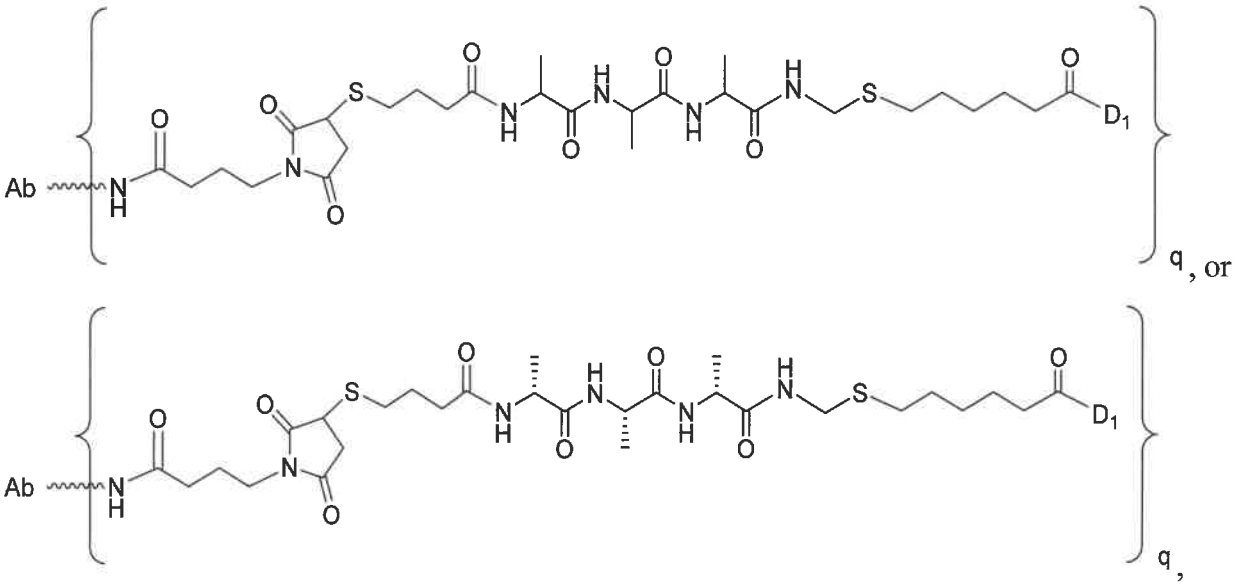
.

15. The conjugate of any one of claims 1-14, wherein, the cell-binding agent is an antibody or an antigen-binding fragment thereof, a single chain antibody, a single chain antibody fragment that specifically binds to a target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that specifically binds to a target cell, a chimeric antibody, a chimeric antibody fragment that specifically binds to a target cell, a domain antibody, a domain antibody fragment that specifically binds to a target cell, a probody, a nanobody, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, a nutrient-transport molecule, a Bicycles® peptide, or a pentarin.

16. The conjugate of claim 15, wherein the cell-binding agent is an antibody or an antigen-binding fragment thereof, a resurfaced antibody or a resurfaced antibody fragment thereof, a monoclonal antibody or a monoclonal antibody fragment thereof, a humanized antibody or a humanized antibody fragment thereof, a chimeric antibody or a chimeric antibody fragment thereof.

17. The conjugate of claim 15, wherein the cell-binding agent is an anti-folate receptor antibody or an antibody fragment thereof, an anti-EGFR antibody or an antibody fragment thereof, an anti-CD33 antibody or an antibody fragment thereof, an anti-CD19 antibody or an antibody fragment thereof, an anti-Muc1 antibody or an antibody fragment thereof, or an anti-CD37 antibody or an antibody fragment thereof, or an anti-CD123 antibody or an antibody fragment thereof.

18. The conjugate of claim 1, wherein the conjugate is represented by the following formula:



wherein Ab is an anti-folate receptor antibody; and q is an integer from 1 to 10.

19. The conjugate of claim 18, wherein the anti-folate receptor antibody comprises

(i) (a) a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 4; a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 5; and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 6; and (b) a light chain CDR1 having the amino acid sequence of SEQ ID NO: 7; a light chain CDR2 having the amino acid sequence of SEQ ID NO:

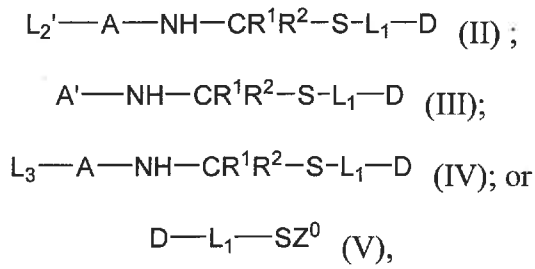
10; and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 9;

(ii) a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 14, and a light chain variable domain having the amino acid sequence of SEQ ID NO: 15 or SEQ ID NO: 16;

(iii) a heavy chain having the amino acid sequence of SEQ ID NO: 11, and a light chain having the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 13; or

(iv) a heavy chain that is encoded by the plasmid DNA having ATCC deposit no. PTA-10772 and a light chain that is encoded by the plasmid DNA having ATCC deposit no. PTA-10774.

20. A compound represented by the following formula:



$L_2'—A—NH—CR^1R^2—S-L_1—D$ (II);

$A'—NH—CR^1R^2—S-L_1—D$ (III);

$L_3—A—NH—CR^1R^2—S-L_1—D$ (IV); or

$D—L_1—SZ^0$ (V),

or a pharmaceutically acceptable salt thereof, wherein:

L_2' is absent or a spacer bearing a reactive moiety that can form a covalent bond with a cell-binding agent;

A is an amino acid or a peptide comprising 2 to 20 amino acids;

R^1 and R^2 are each independently H or a C_{1-3}alkyl;

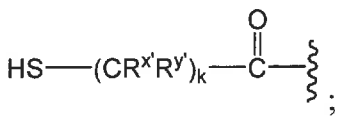
L_1 is a spacer;

D-L_1-SH is a cytotoxic agent; and

q is an integer from 1 to 20;

A' is an amino acid or a peptide comprising 2 to 20 amino acids;

L_3 is represented by the following formula:



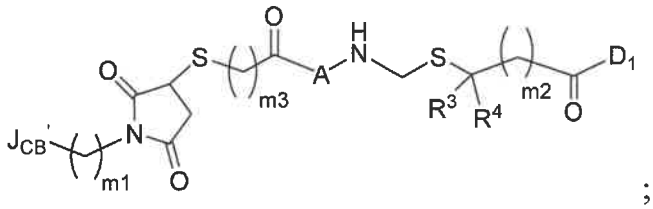
$HS—(CR^{x'}R^{y'})_k—C(=O)—\sim$;

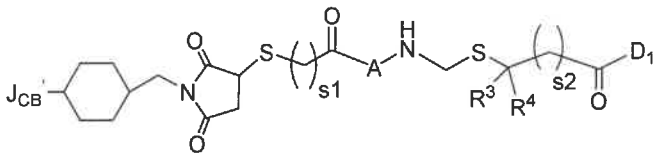
$R^{x'}$ and $R^{y'}$, for each occurrence, are independently H, -OH, halogen, -O-(C_{1-4} alkyl), -SO_3H, -$NR_{40}R_{41}R_{42}^+$, or a C_{1-4} alkyl optionally substituted with -OH, halogen, SO_3H or $NR_{40}R_{41}R_{42}^+$, wherein R_{40}, R_{41} and R_{42} are each independently H or a C_{1-4} alkyl;

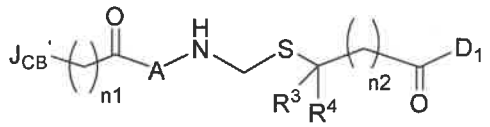
k is an integer from 1 to 10; and

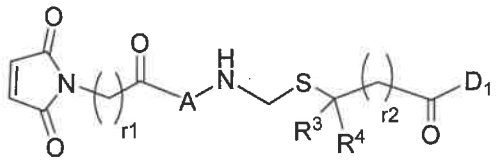
Z^0 is H or Me, provided when Z^0 is H, L_1 is not-C(=O)-$(CH_2)_q$- or –C(=O)-CH_2-CH_2–$C(CH_3)_2$-, wherein q is an integer from 1 to 3; and when Z^0 is Me, L_1 is not -C(=O)--$(CH_2)_2$- or –C(=O)-CH_2-CH_2–$C(CH_3)_2$-.

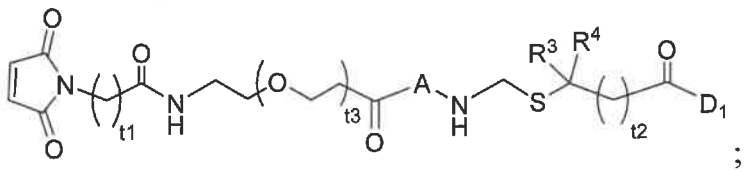
21. The compound of claim 20, wherein the compound is represented by the following formula:


;


;


;


; or


;

or a pharmaceutically acceptable salt thereof, wherein:

R^3 and R^4 are each independently H or Me;

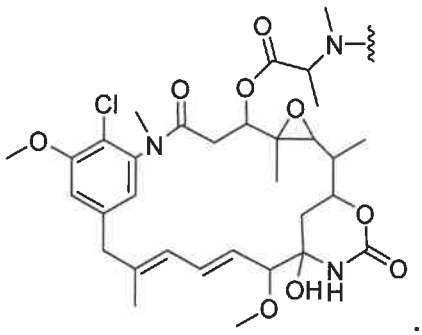
m1, m3, n1, r1, s1, and t1 are each independently an integer from 1 to 6;

m2, n2, r2, s2 and t2 are each independently an integer from 1 to 7;

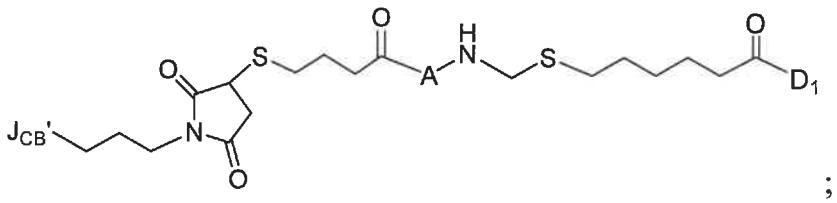
t3 is an integer from 1 to 12;

J_{CB}' is –C(=O)OH or –COE;

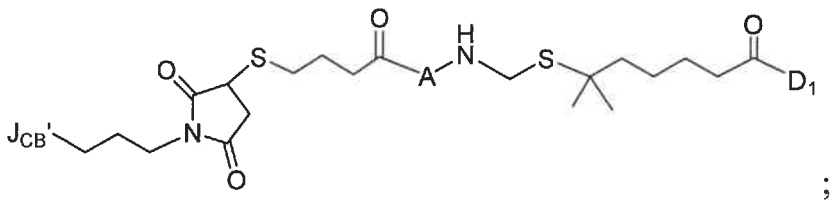
D_1 is represented by the following formula:



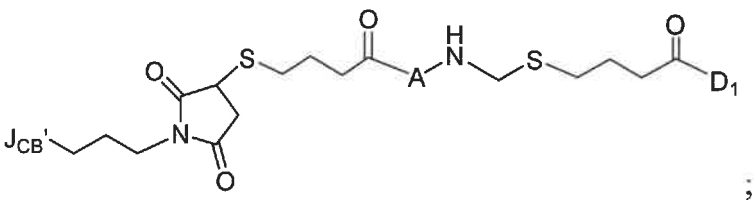
22. The compound of claim 21, wherein the compound is represented by the following formula:



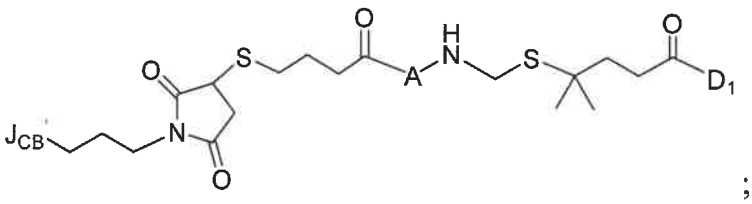
;



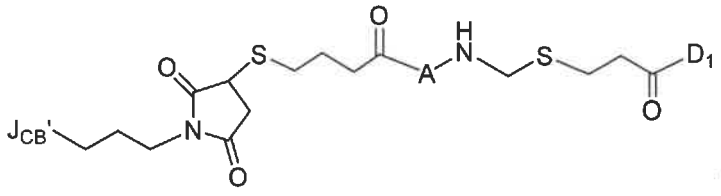
;



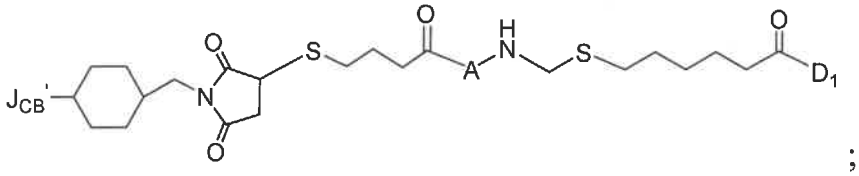
;



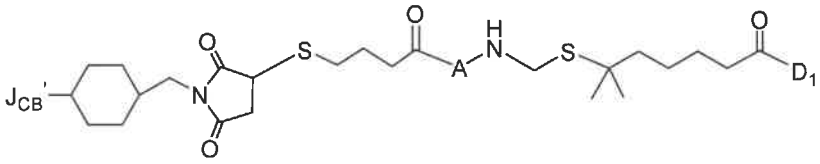
;



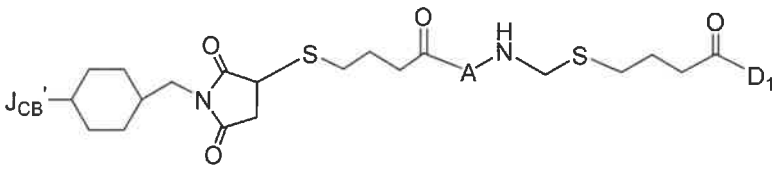
;



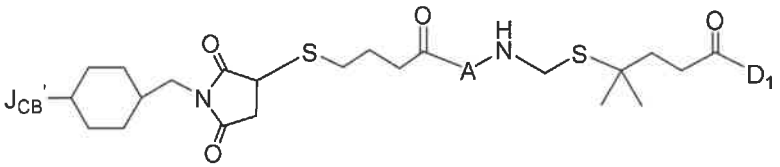
;



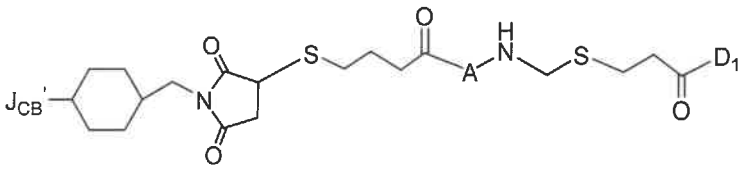
;



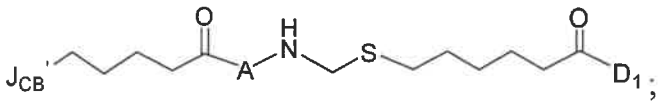
;



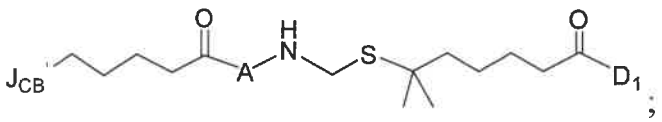
;



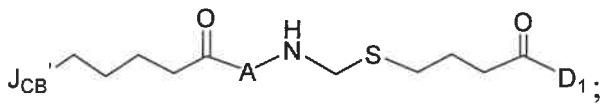
;

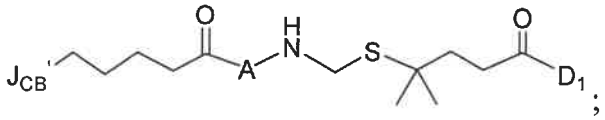


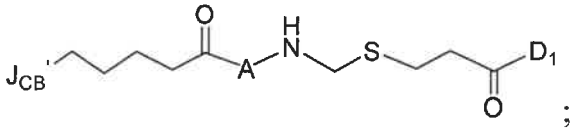
;

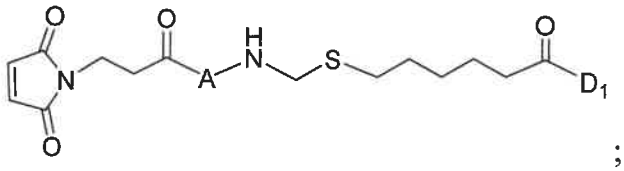


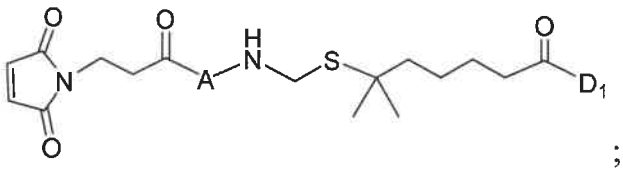
;

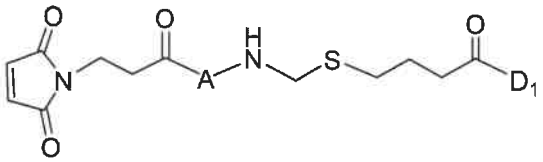

;

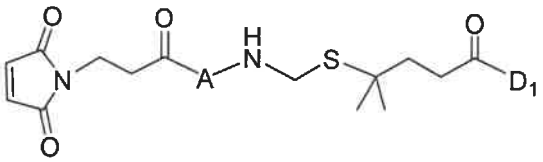

;

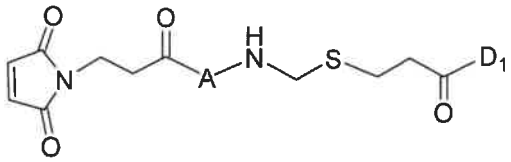

;

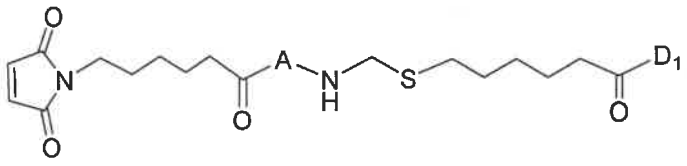

;

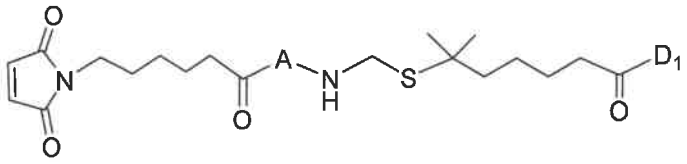

;

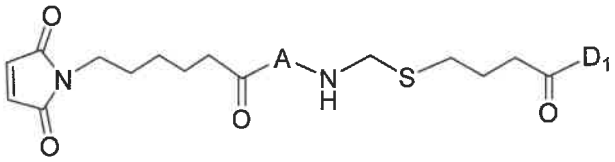

;

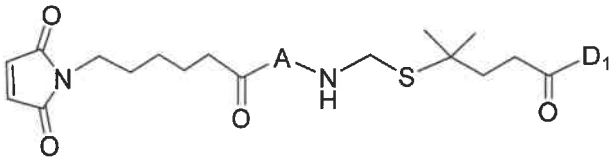

;

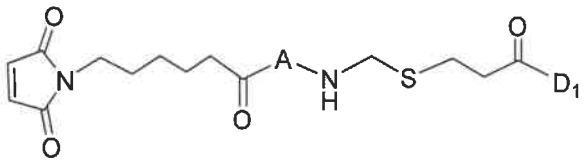

;

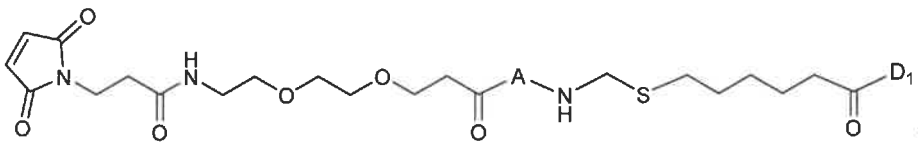

;

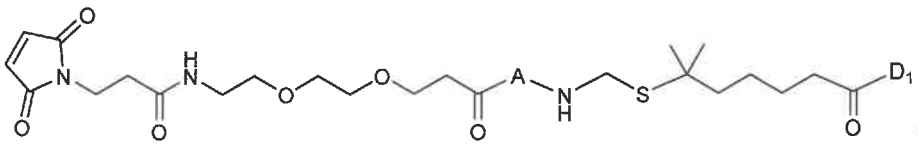

;

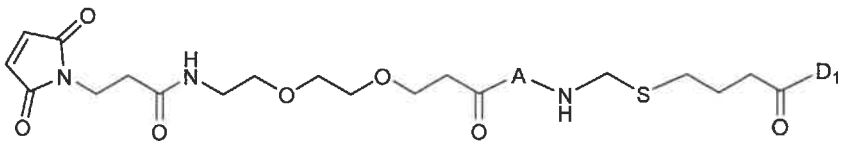

;

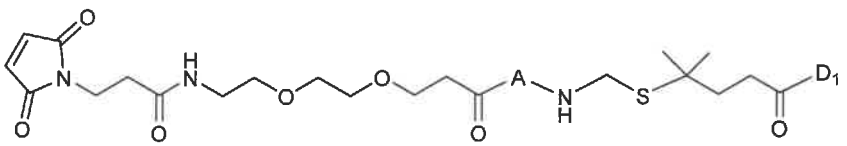

;

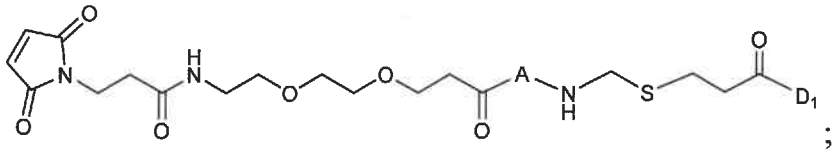

;

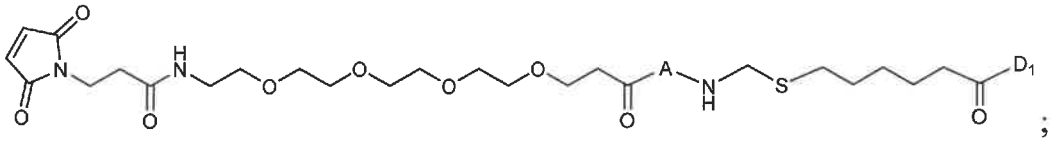

;

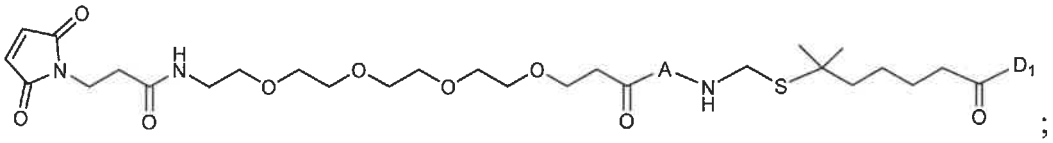

;

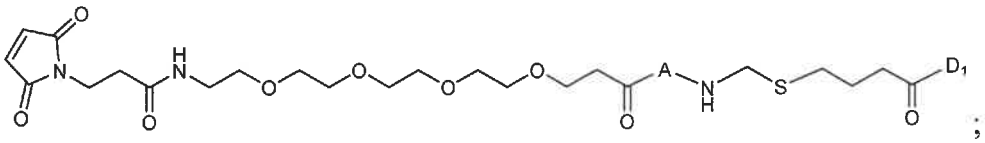

;

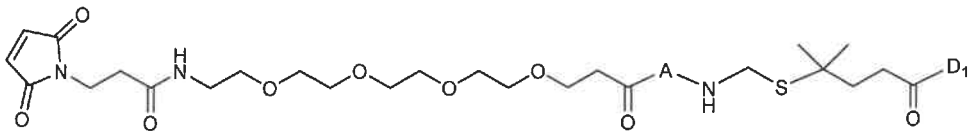

;

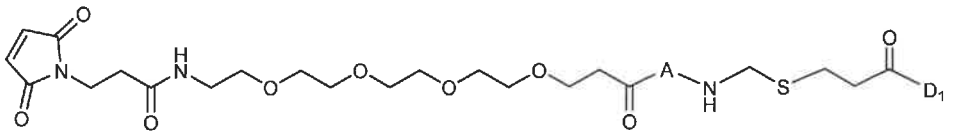

;


;


;


;


; or

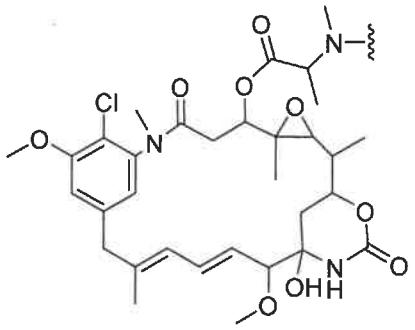


or a pharmaceutically acceptable salt thereof, wherein:

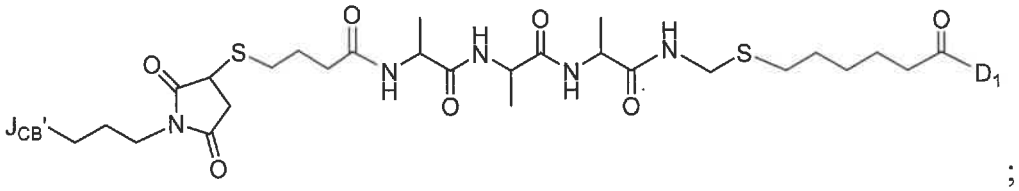
A is Ala-Ala-Ala, Ala-D-Ala-Ala, Ala-Ala, D-Ala-Ala, Val-Ala, D-Val-Ala, D-Ala-Pro, or D-Ala-tBu-Gly,

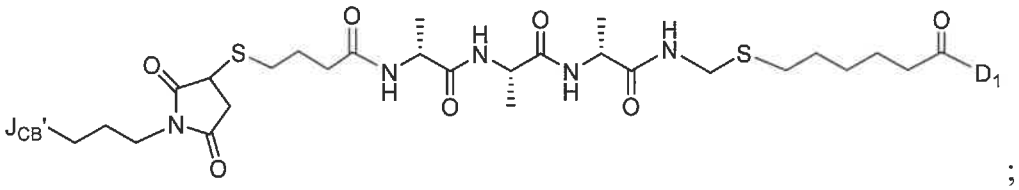
J_{CB}' is –C(=O)OH or –COE; and

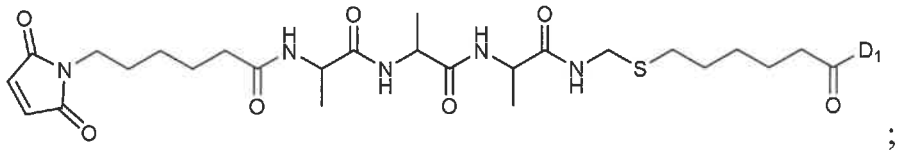
D_1 is represented by the following formula:

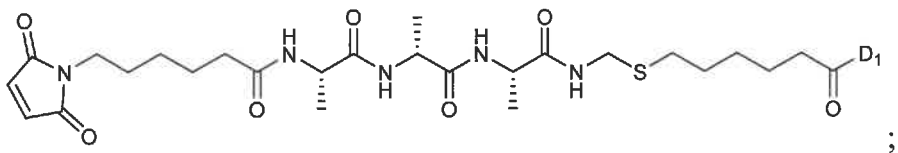

.

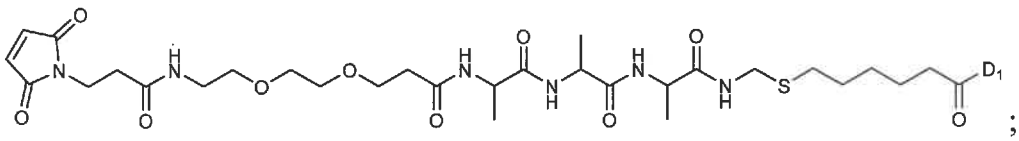
23. The compound of claim 22, wherein the compound is represented by the following formula:

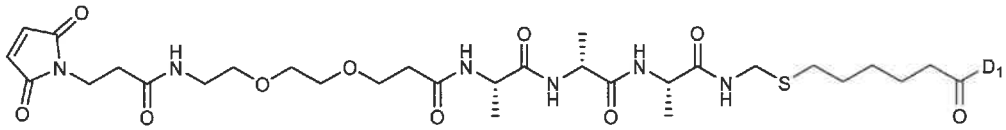

;

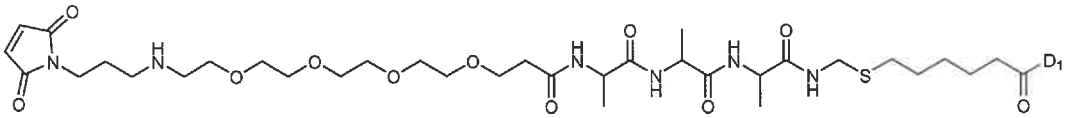

;

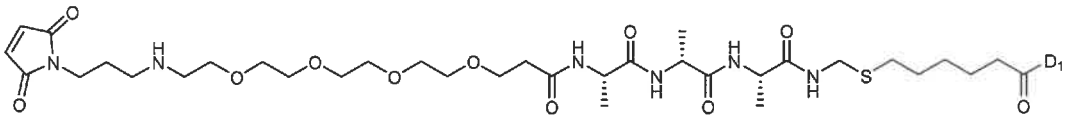

;


;

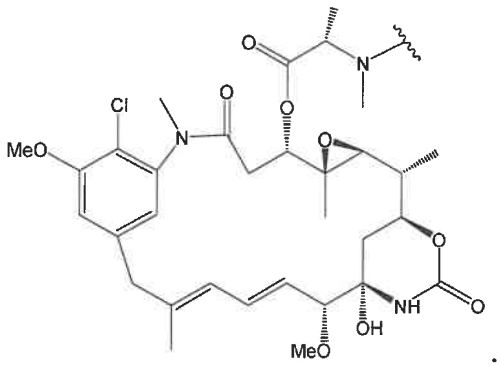

;


;


; or


,

wherein D_1 is represented by the following formula:



24. A pharmaceutical composition comprising the conjugate of any one of claims 1-19 and a pharmaceutically acceptable carrier.

25. Use of the conjugate of any one of claims 1-19 in the preparation of a medicament for inhibiting abnormal cell growth or treating a proliferative disorder in a mammal.

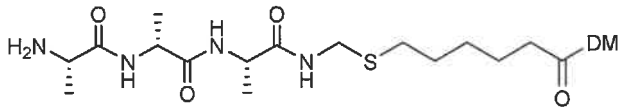
26. The use of claim 25, wherein the use is for treating a cancer; and wherein:

(i) the cancer is selected from renal cancer, breast cancer (e.g., triple-negative breast cancer (TNBC)), colon cancer, brain cancer, prostate cancer, endometrial cancer, cervical cancer, kidney cancer, pancreatic cancer, ovarian cancer (e.g., epithelial ovarian cancer), head and neck cancer, melanoma, colorectal cancer, gastric cancer, squamous cancer, lung cancer (e.g., non small-cell lung cancer and small-cell lung cancer), testicular cancer, choriocarcinoma, Merkel cell carcinoma, sarcoma (e.g., osteosarcoma, chondrosarcoma, liposarcoma, and leiomyosarcoma), glioblastoma, neuroblastoma, lymphoma (e.g., non-Hodgkin lymphoma), myelodysplastic syndrome (MDS), peritoneal cancer, fallopian tube cancer, uterine cancer or leukemia (e.g., acute myeloid leukemia (AML), acute monocytic leukemia, promyelocytic leukemia, eosinophilic leukemia, acute lymphoblastic leukemia (e.g., B-ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML));

(ii) the cancer is breast cancer, ovarian cancer or renal cancer; or

(iii) the cancer is cervical cancer, ovarian cancer, uterine cancer, endometrial cancer, or fallopian tube cancer.

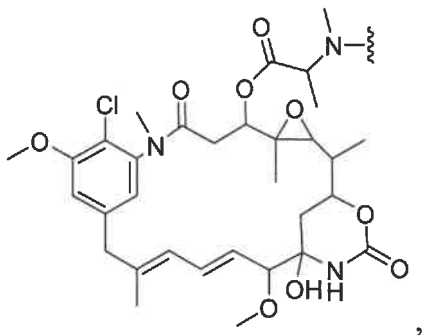
27. A compound of the following formula:



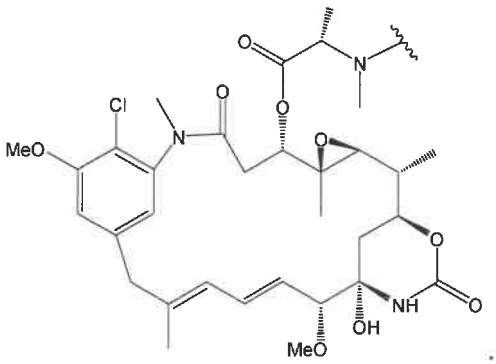
I-1a ,

or a pharmaceutically acceptable salt thereof, wherein:

DM is



, or



.