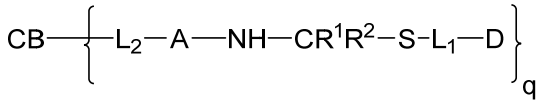
CLAIMS

1. An immunoconjugate represented by the following formula:

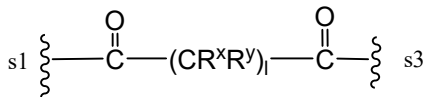


(I)

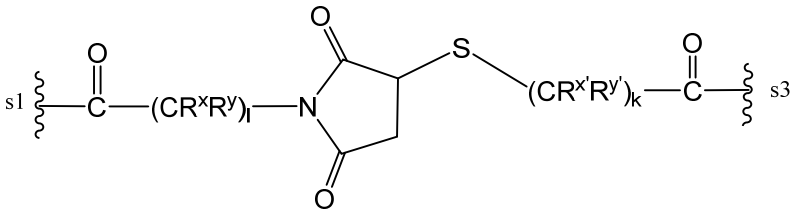
or a pharmaceutically acceptable salt thereof, wherein:

CB is an anti-ADAM9 antibody or ADAM9-binding fragment thereof;

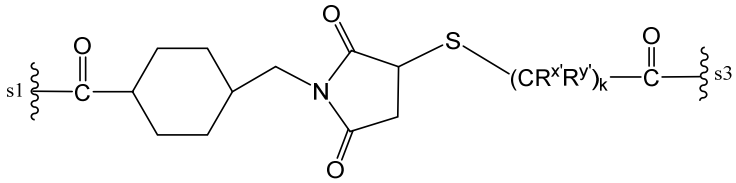
L_2 is represented by one of the following formula:



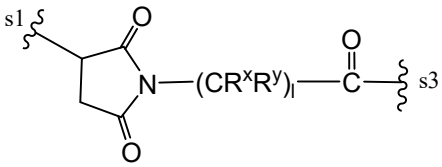
(L2a),



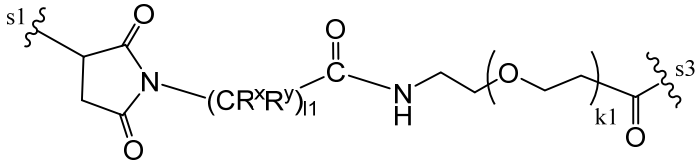
(L2b),



(L2c),



(L2d), or



(L2e);

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;

l1 is an integer from 2 to 5;

k1 is an integer from 1 to 5; and

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

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

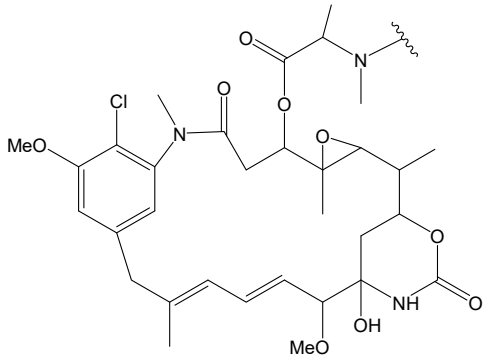
R^1 and R^2 are each independently H or a C_{1-3}alkyl;

L_1 is represented by the following formula:

$$-CR^3R^4-(CH_2)_{1-8}-C(=O)-$$

wherein R^3 and R^4 are each independently H or Me, and the –C(=O)- moiety in L_1 is connected to D;

D is represented by the following formula:



; and

q is an integer from 1 to 20.

2. The immunoconjugate of claim 1, 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.

3. The immunoconjugate of claim 1 or 2, wherein A is a peptide containing 2 to 5 amino acid residues.

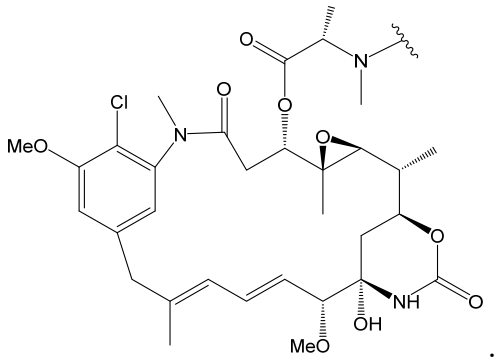
4. The immunoconjugate of claim 3, wherein A is selected from the group consisting of Gly-Gly-Gly, Ala-Val, Val-Ala, D-Val-Ala, Val-Cit, D-Val-Cit, Val-Lys, Phe-Lys, Lys-Lys, Ala-Lys, Phe-Cit, Leu-Cit, Ile-Cit, Phe-Ala, Phe-N^9-tosyl-Arg, Phe-N^9-nitro-Arg, Phe-Phe-Lys, D-Phe-Phe-Lys, Gly-Phe-Lys, Leu-Ala-Leu, 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: 144), β-Ala-Leu-Ala-Leu (SEQ ID NO: 145), Gly-Phe-Leu-Gly (SEQ ID NO: 146), 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 $–NH-CR^1R^2-S-L_1-D$.

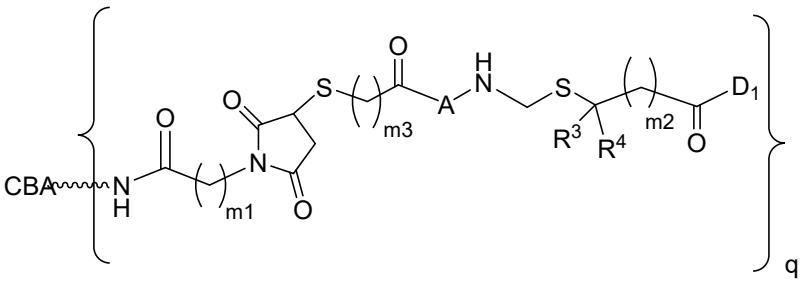
5. The immunoconjugate of any one of claims 1-4, wherein R^1 and R^2 are both H.

6. The immunoconjugate of any one of claims 1-5, wherein L_1 is $–(CH_2)_{4-6}-C(=O)-$.

7. The immunoconjugate of any one of claims 1-6, wherein D is represented by the following formula:



8. The immunoconjugate of any one of claims 1-7, wherein the immunoconjugate is represented by the following formula:



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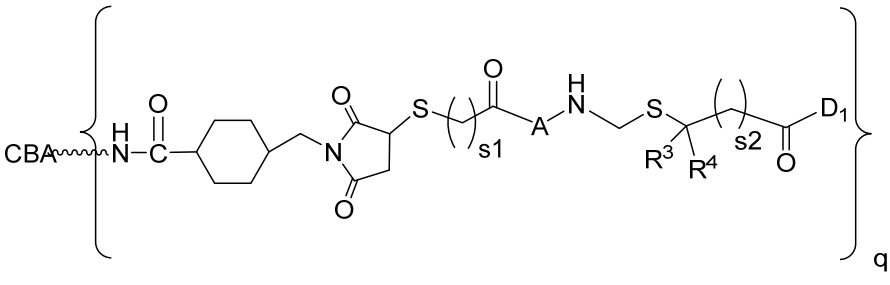
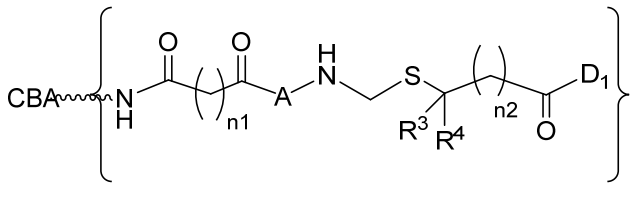
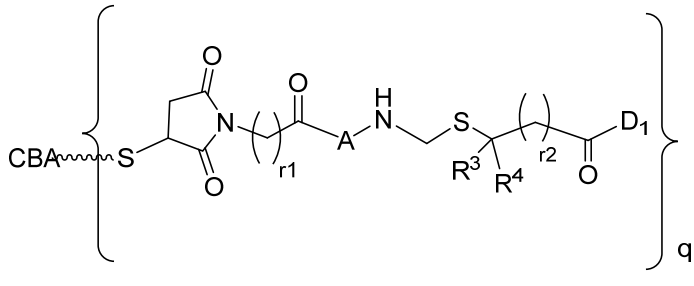


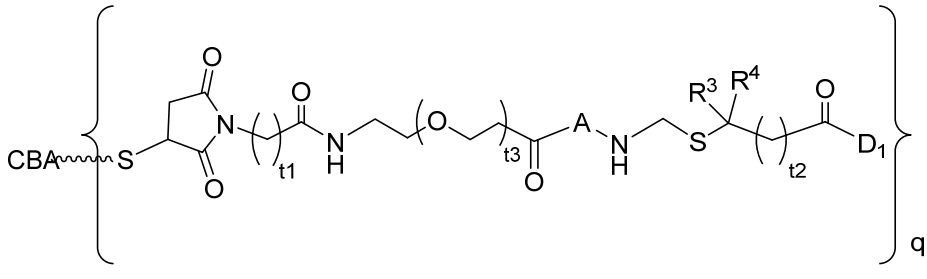
(Ib);



(Ic);



(Id); or



(Ie);

or a pharmaceutically acceptable salt thereof, wherein:

CBA–N(H)– is the anti-ADAM9 antibody or ADAM9-binding fragment thereof connected to the L_2 group through a Lys amine group;

CBA–S– is the anti-ADAM9 antibody or ADAM9-binding fragment thereof connected to the L_2 group through a Cys thiol group;

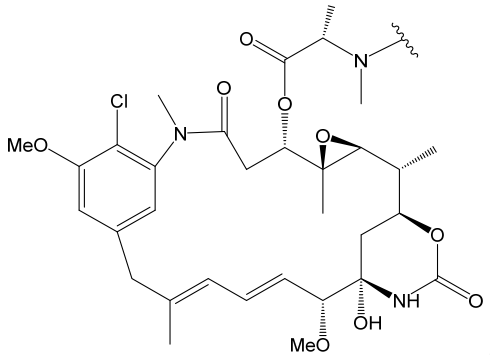
R^3 and R^4 are each independently H or Me;

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:



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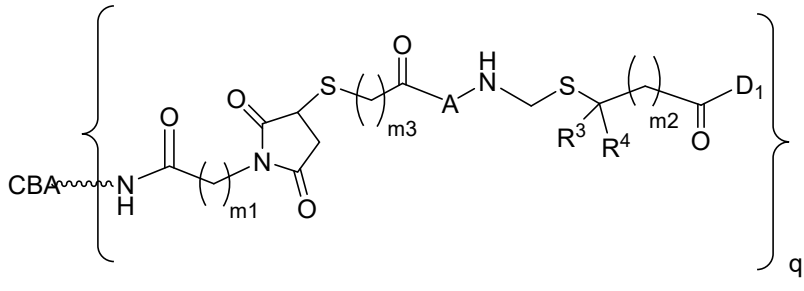
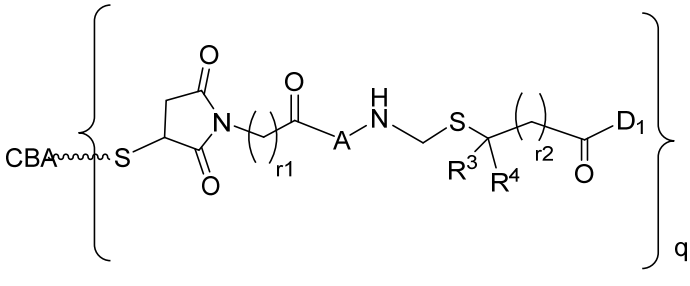
9. The immunoconjugate of claim 8, wherein the immunoconjugate is represented by the following formula:



(Ia), or



(Id);

wherein:

m1 and m3 are each independently an integer from 2 to 4;

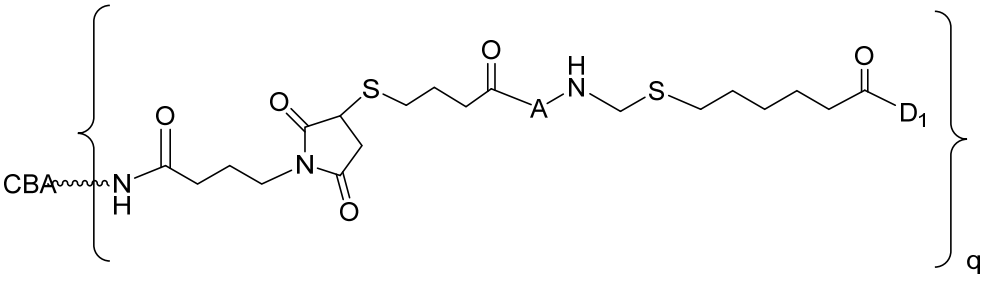
m2 is an integer from 2 to 5;

r1 is an integer from 2 to 6; and

r2 is an integer from 2 to 5.

10. The immunoconjugate of claim 8 or 9, 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.

11. The immunoconjugate of claim 8, wherein the immununoconjugate is represented by the following formula:



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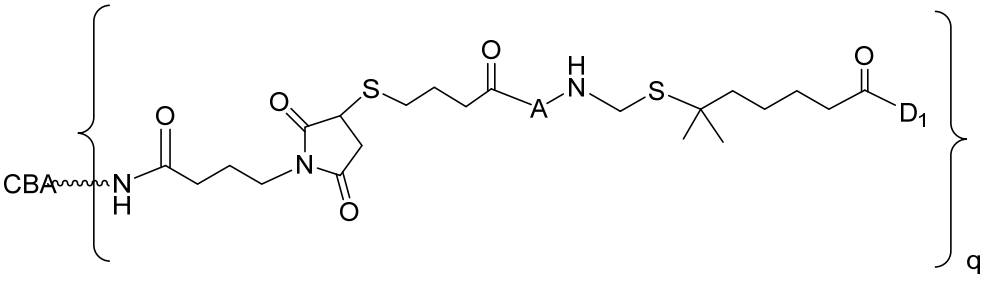
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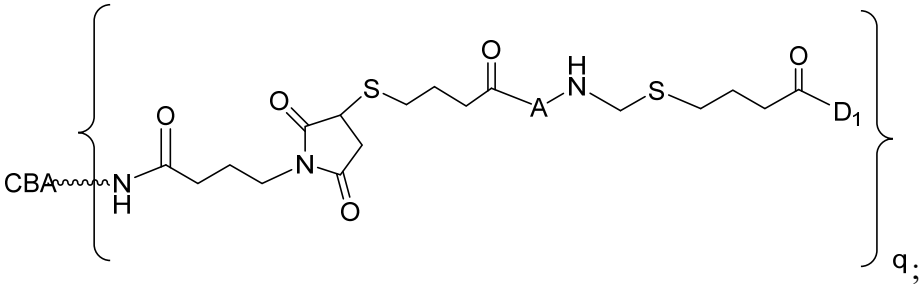
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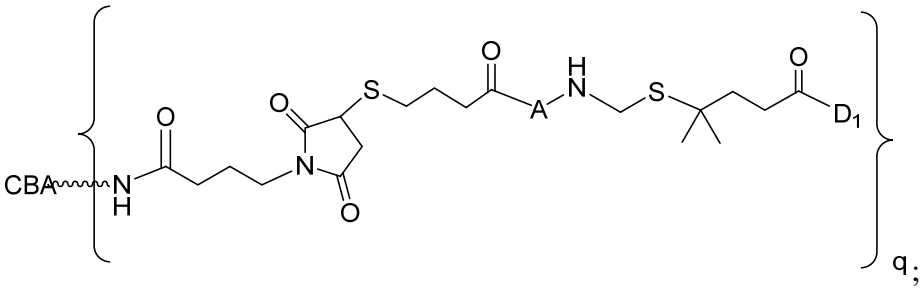
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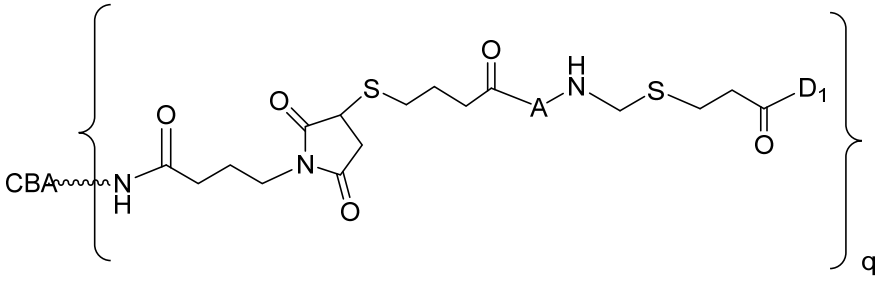
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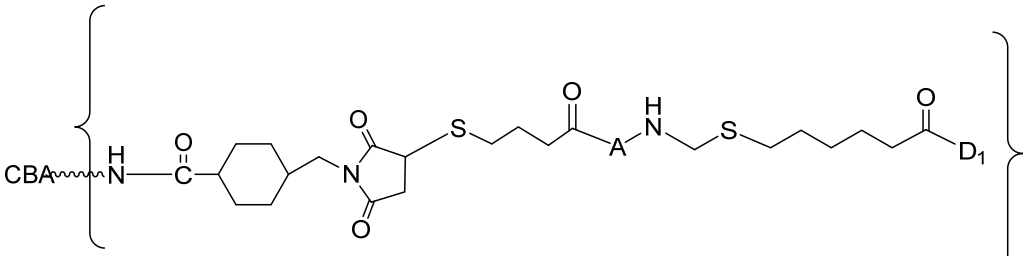
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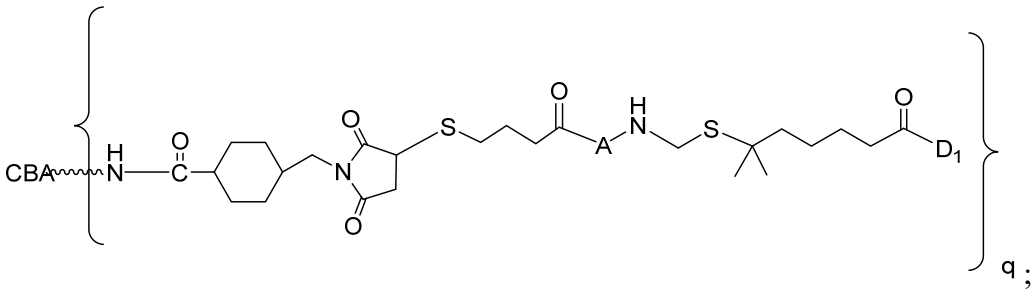
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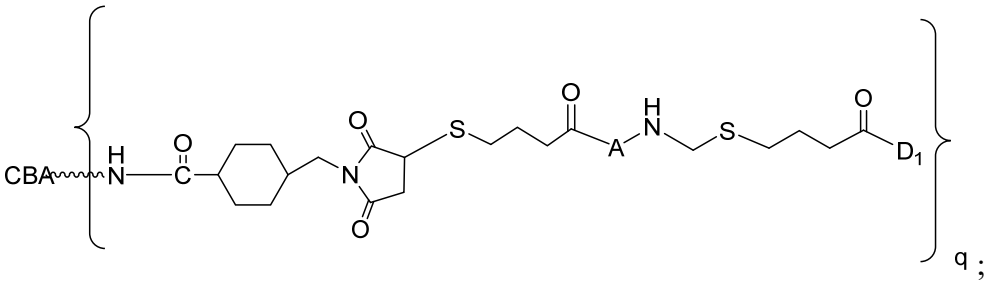
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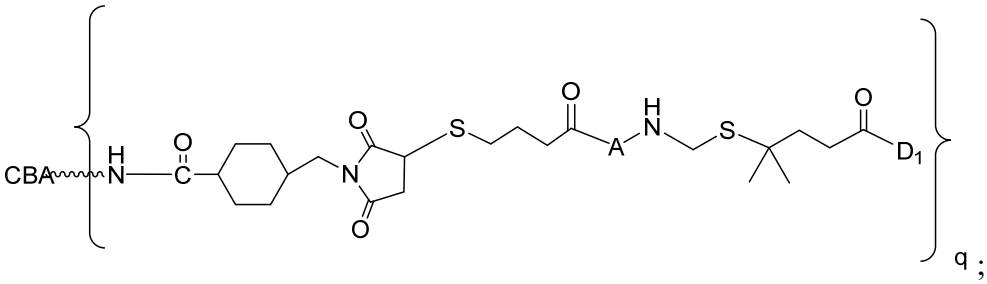
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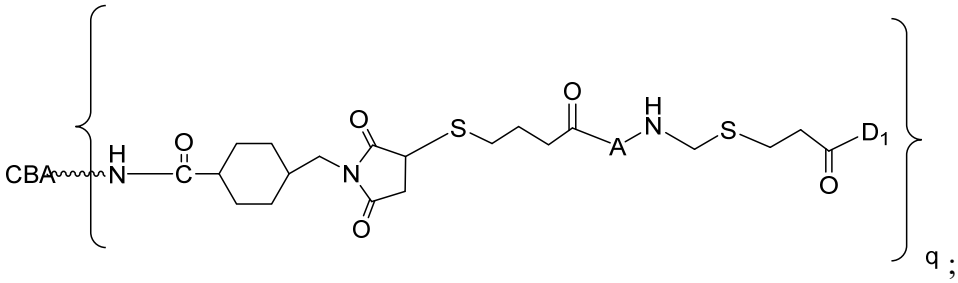
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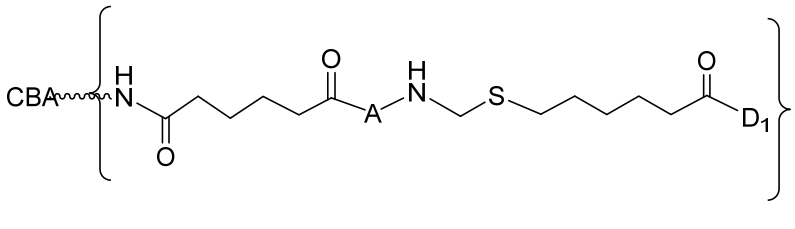
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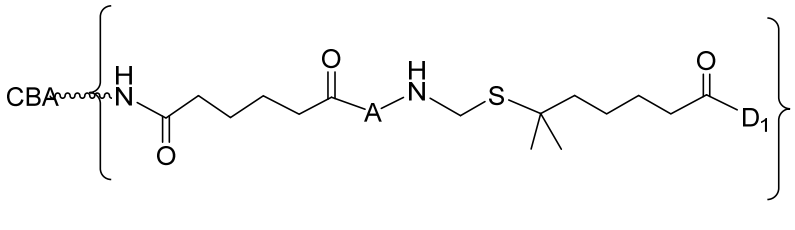
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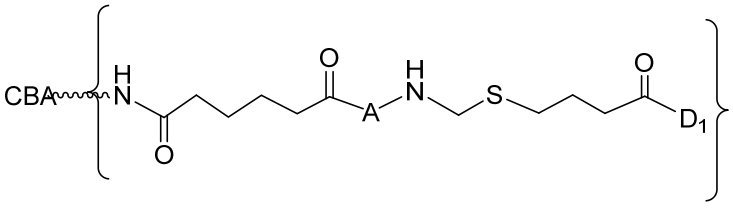
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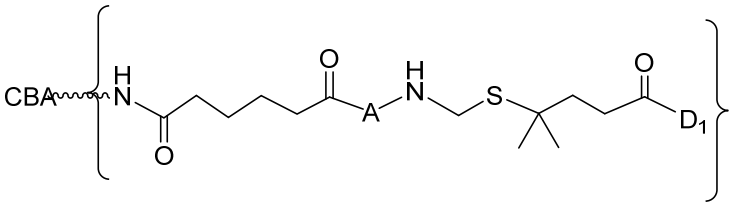
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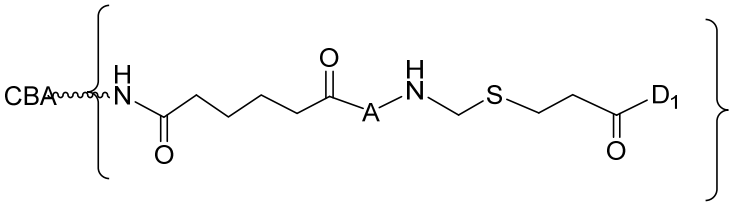
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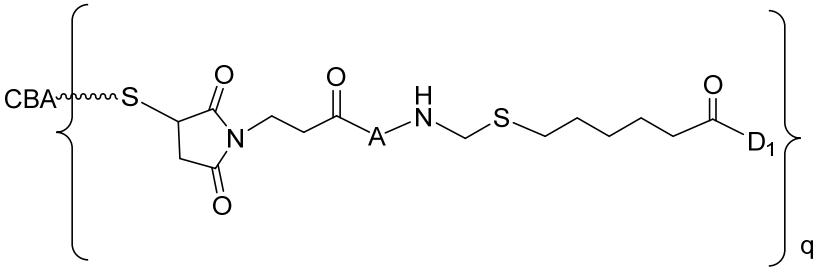
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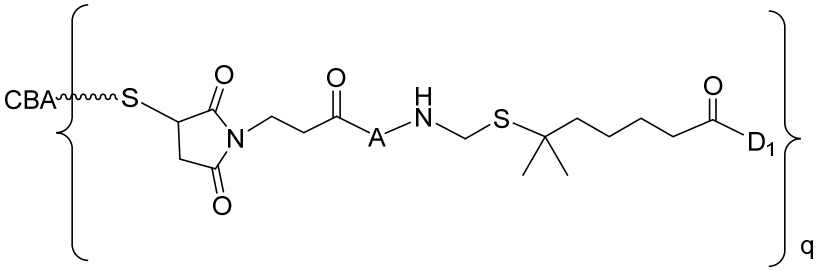
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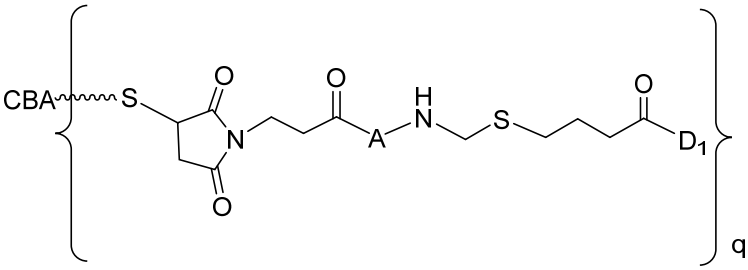
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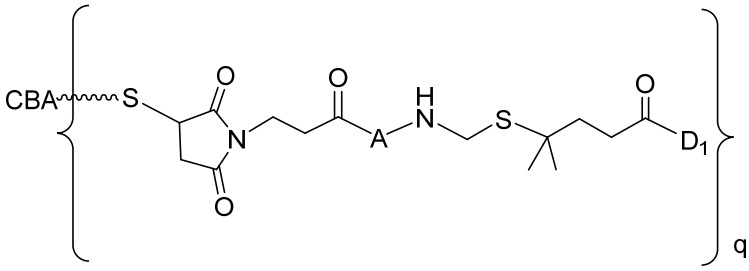
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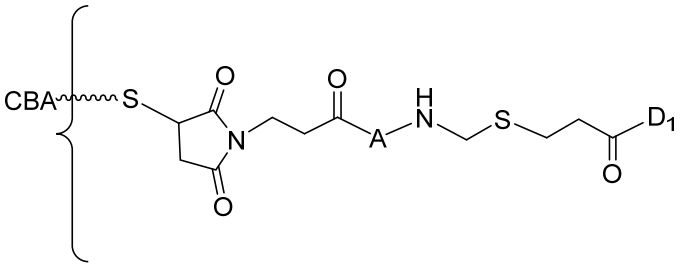
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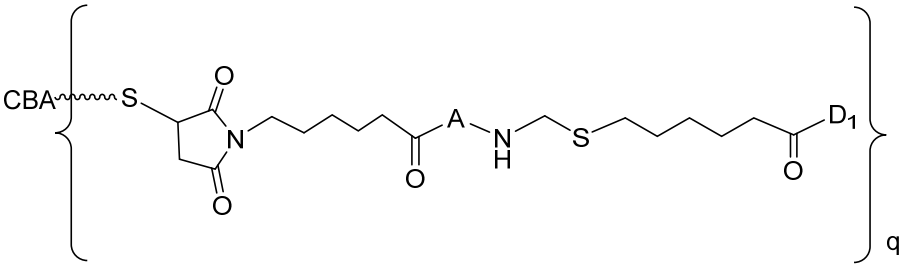
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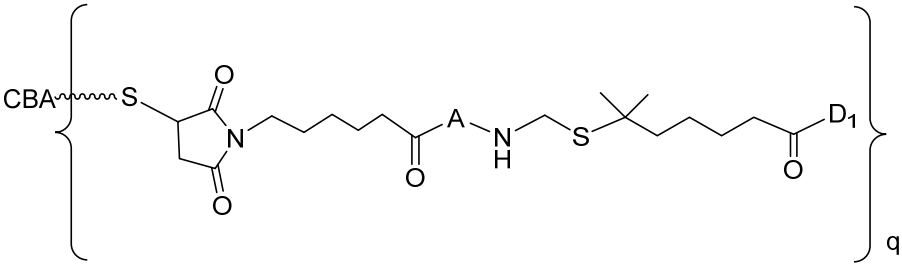
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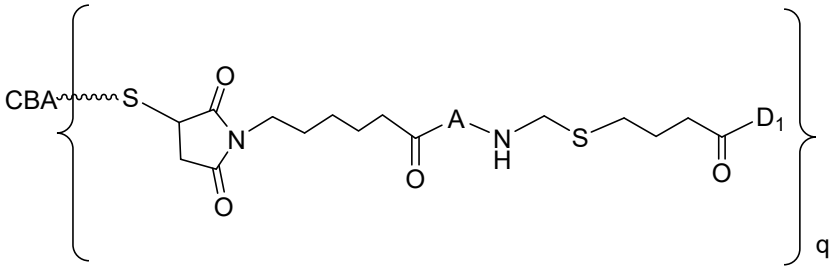
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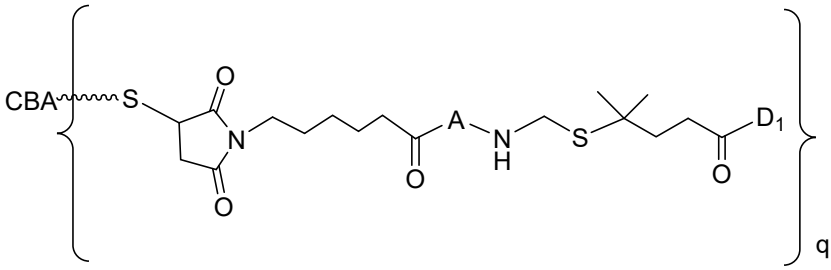
CBA
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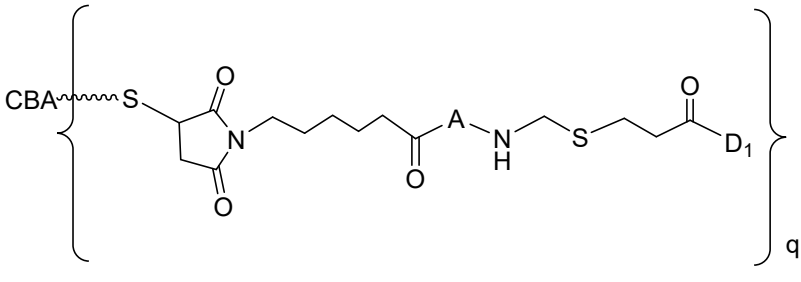

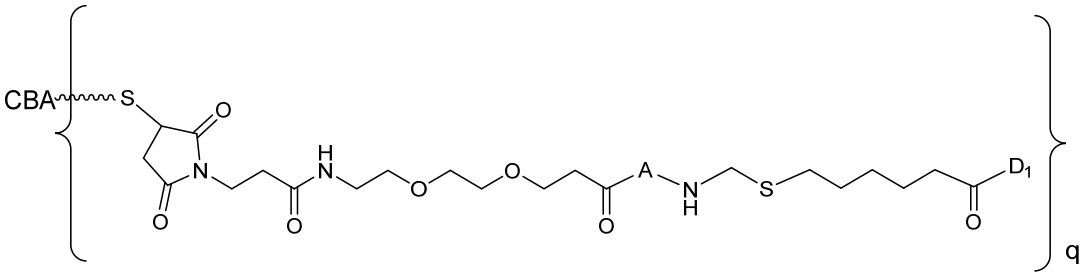

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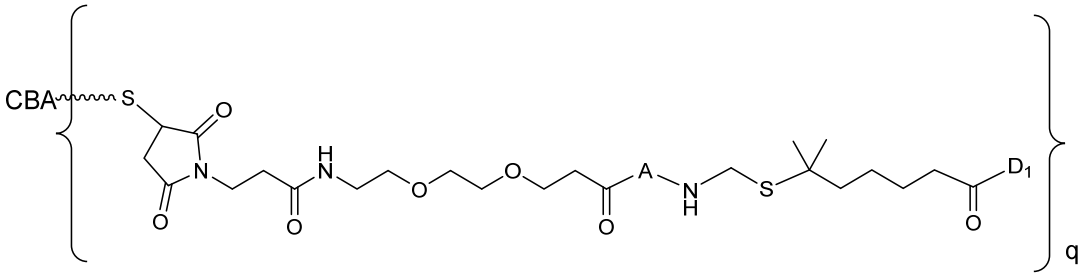

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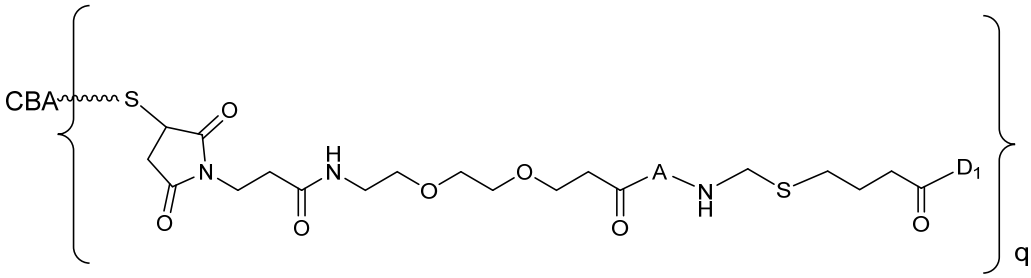

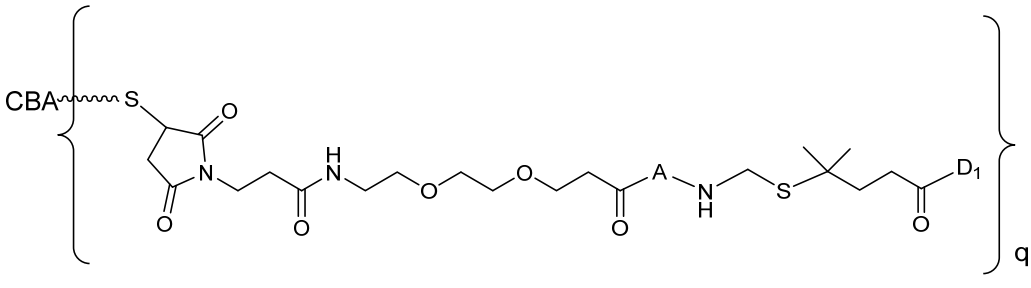

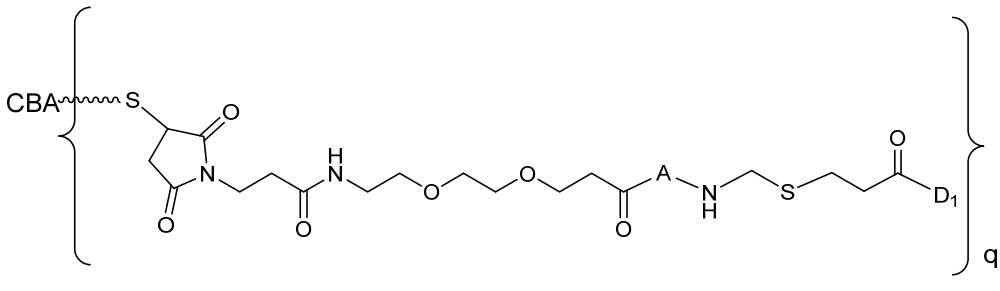

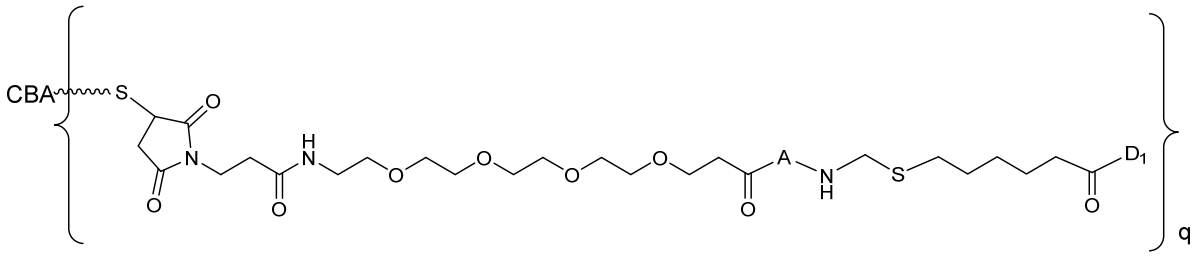

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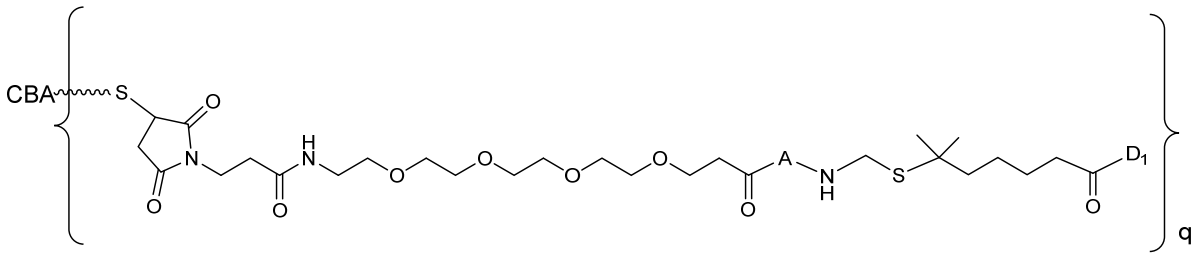

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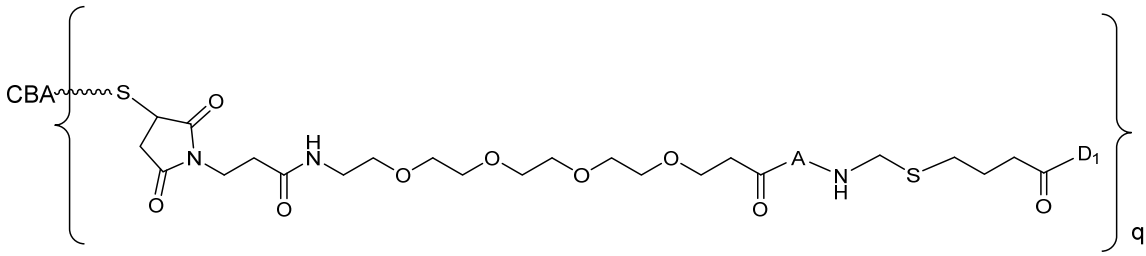
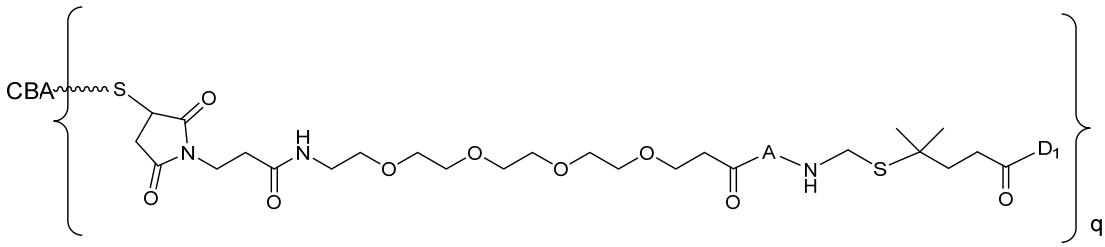
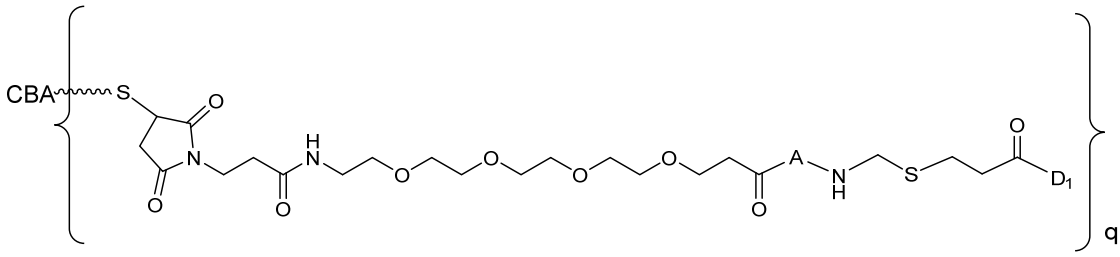




; or

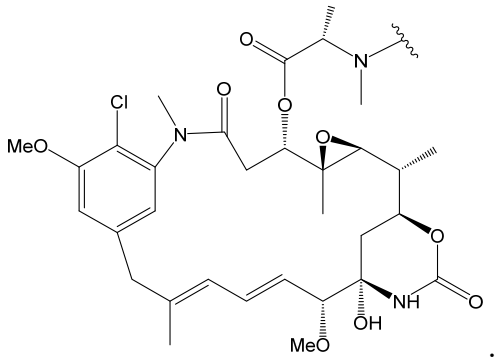


,

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:



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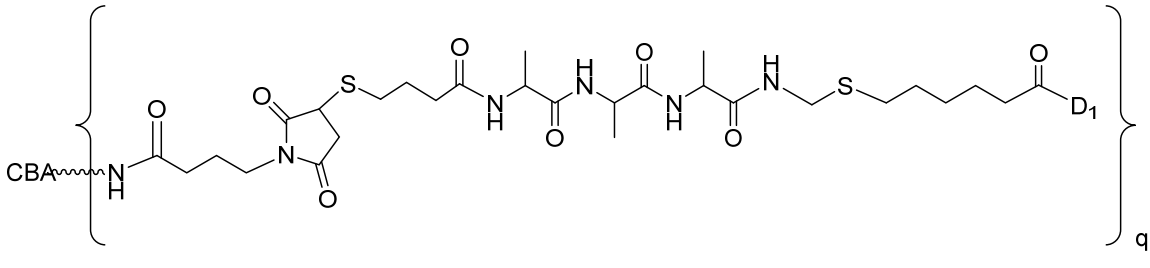
12. The immunoconjugate of claim 11, wherein the immunoconjugate is represented by the following formula:



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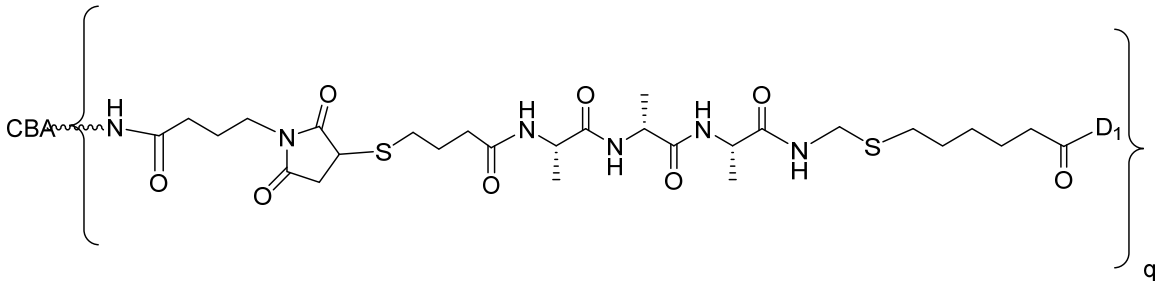

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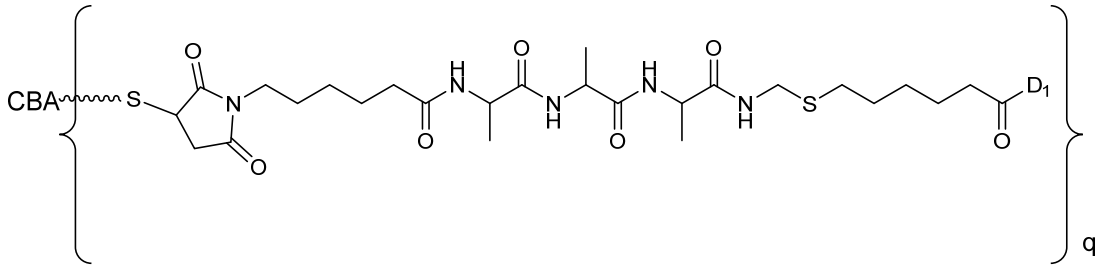
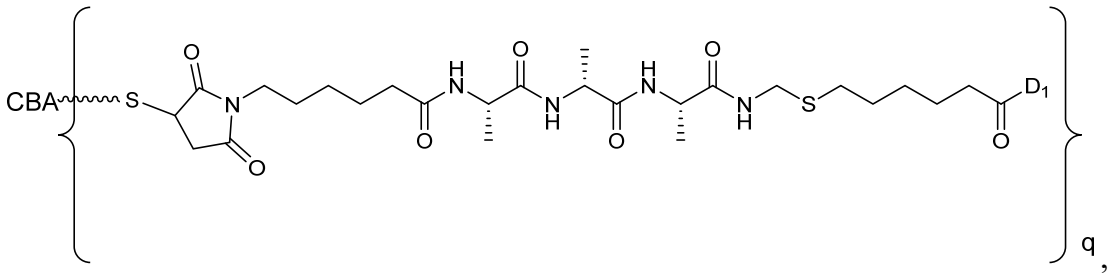
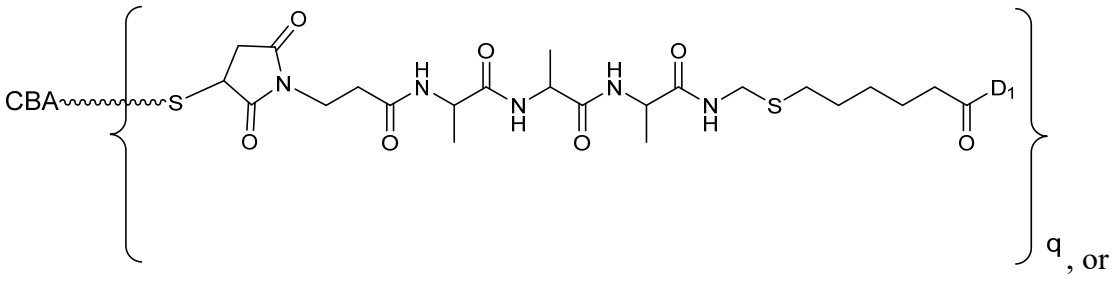
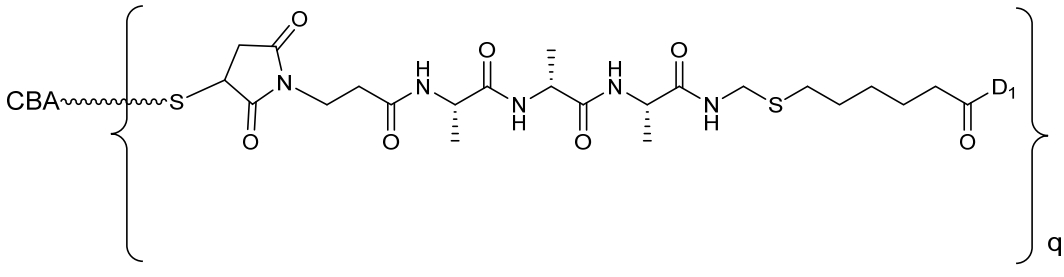


; or



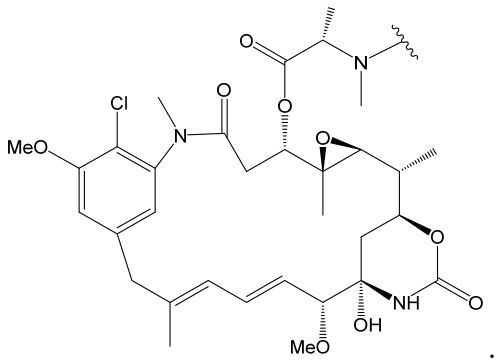


, or



;

wherein D_1 is represented by the following formula:



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13. The immunoconjugate of any one of claims 1-12, wherein the immunoconjugate comprises a humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof that specifically binds to human ADAM9 and cyno ADAM9 wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof is conjugated to the pharmacological agent.

14. The immunoconjugate of claim 13, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a CDR_H1 domain, a CDR_H2 domain, and a CDR_H3 domain and a CDR_L1 domain, a CDR_L2 domain, and a CDR_L3 domain having the sequences selected from the group consisting of:
(a) SEQ ID NOs: 8, 35, and 10 and SEQ ID NOs: 62, 13, 14, respectively;
(b) SEQ ID NOs: 8, 35, and 10 and SEQ ID NOs: 63, 13, 14, respectively;
(c) SEQ ID NOs: 8, 36, and 10 and SEQ ID NOs: 63, 13, 14, respectively; and
(d) SEQ ID NOs: 34, 36, and 10 and SEQ ID NO:64, 13, 65, respectively.

15. The immunoconjugate of claims 13 or 14, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having sequences that are at least 90%, at least 95%, or at least 99% identical to sequences selected from the group consisting of:
(a) SEQ ID NO:17 and SEQ ID NO:55, respectively;
(b) SEQ ID NO:17 and SEQ ID NO:56, respectively;
(c) SEQ ID NO:18 and SEQ ID NO:56, respectively; and
(d) SEQ ID NO:19 and SEQ ID NO:57, respectively.

16. The immunoconjugate of claim 15, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having the sequences selected from the group consisting of:
(a) SEQ ID NO:17 and SEQ ID NO:55, respectively;
(b) SEQ ID NO:17 and SEQ ID NO:56, respectively;
(c) SEQ ID NO:18 and SEQ ID NO:56, respectively; and
(d) SEQ ID NO:19 and SEQ ID NO:57, respectively.

17. The immunoconjugate of claim 13, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof is optimized to have at least a 100-fold enhancement in binding affinity to cyno ADAM9 and retains high affinity binding to human ADAM9 as compared to the chimeric or murine parental antibody.

18. The immunoconjugate of claim 17, wherein said anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a CDR_H1 domain, a CDR_H2 domain, and a CDR_H3 domain and a CDR_L1 domain, a CDR_L2 domain, and a CDR_L3 domain having the sequences selected from the group consisting of:
(a) SEQ ID NOs: 8, 35, and 37 and SEQ ID NOs: 62, 13, 14, respectively;
(b) SEQ ID NOs: 8, 35, and 38 and SEQ ID NOs: 62, 13, 14, respectively;
(c) SEQ ID NOs: 8, 35, and 39 and SEQ ID NOs: 62, 13, 14, respectively;
(d) SEQ ID NOs: 8, 35, and 40 and SEQ ID NOs: 62, 13, 14, respectively;
(e) SEQ ID NOs: 8, 35, and 41 and SEQ ID NOs: 62, 13, 14, respectively;
(f) SEQ ID NOs: 8, 35, and 42 and SEQ ID NOs: 62, 13, 14, respectively;
(g) SEQ ID NOs: 8, 35, and 43 and SEQ ID NOs: 62, 13, 14, respectively;
(h) SEQ ID NOs: 8, 35, and 44 and SEQ ID NOs: 62, 13, 14, respectively;
(i) SEQ ID NOs: 8, 35, and 45 and SEQ ID NOs: 62, 13, 14, respectively; and
(j) SEQ ID NOs: 8, 35, and 46 and SEQ ID NOs: 62, 13, 14, respectively.

19. The immunoconjugate of claim 18, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having sequences that are at least 90%, at least 95%, or at least 99% identical to sequences selected from the group consisting of:
(a) SEQ ID NO:20 and SEQ ID NO:55, respectively;
(b) SEQ ID NO:21 and SEQ ID NO:55, respectively;
(c) SEQ ID NO:22 and SEQ ID NO:55, respectively;
(d) SEQ ID NO:23 and SEQ ID NO:55, respectively;
(e) SEQ ID NO:24 and SEQ ID NO:55, respectively;
(f) SEQ ID NO:25 and SEQ ID NO:55, respectively;
(g) SEQ ID NO:26 and SEQ ID NO:55, respectively;
(h) SEQ ID NO:27 and SEQ ID NO:55, respectively;
(i) SEQ ID NO:28 and SEQ ID NO:55, respectively; and
(j) SEQ ID NO:29 and SEQ ID NO:55, respectively.

20. The immunoconjugate of claim 19, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having the sequences selected from the group consisting of:
(a) SEQ ID NO:20 and SEQ ID NO:55, respectively;
(b) SEQ ID NO:21 and SEQ ID NO:55, respectively;
(c) SEQ ID NO:22 and SEQ ID NO:55, respectively;
(d) SEQ ID NO:23 and SEQ ID NO:55, respectively;
(e) SEQ ID NO:24 and SEQ ID NO:55, respectively;
(f) SEQ ID NO:25 and SEQ ID NO:55, respectively;
(g) SEQ ID NO:26 and SEQ ID NO:55, respectively;
(h) SEQ ID NO:27 and SEQ ID NO:55, respectively;
(i) SEQ ID NO:28 and SEQ ID NO:55, respectively; and
(j) SEQ ID NO:29 and SEQ ID NO:55, respectively.

21. The immunoconjugate of any one of claims 13-20, wherein said humanized anti-ADAM9 antibody is a full length antibody comprising an Fc region.

22. The immunoconjugate of claim 21, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences selected from the group consisting of:
(a) SEQ ID NO:50 and SEQ ID NO:68, respectively;
(b) SEQ ID NO:51 and SEQ ID NO:68, respectively; and
(c) SEQ ID NO:52 and SEQ ID NO:68, respectively.

23. The immunoconjugate of any one of claims 13-22, wherein said Fc region is a variant Fc region that comprises:
(a) one or more amino acid modification(s) that reduces(s) the affinity of the variant Fc region for an FcγR selected from the group consisting of: L234A, L235A, and L234A and L235A; and/or
(b) an amino acid modification that introduces a cysteine residue at S442, wherein said numbering is that of the EU index as in Kabat; and/or
(c) one or more amino acid substitution(s) that extend(s) the half-life of the variant Fc region for FcRn selected from the group consisting of: M252Y, S254T, and T256E .

24. The immunoconjugate of claim 18, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences selected from the group consisting of:

(a) SEQ ID NO:141 and SEQ ID NO:68, respectively;

(b) SEQ ID NO:142 and SEQ ID NO:68, respectively;

(c) SEQ ID NO:143 and SEQ ID NO:68, respectively;

(d) SEQ ID NO:151 and SEQ ID NO:68, respectively;

(e) SEQ ID NO:152 and SEQ ID NO:68, respectively;

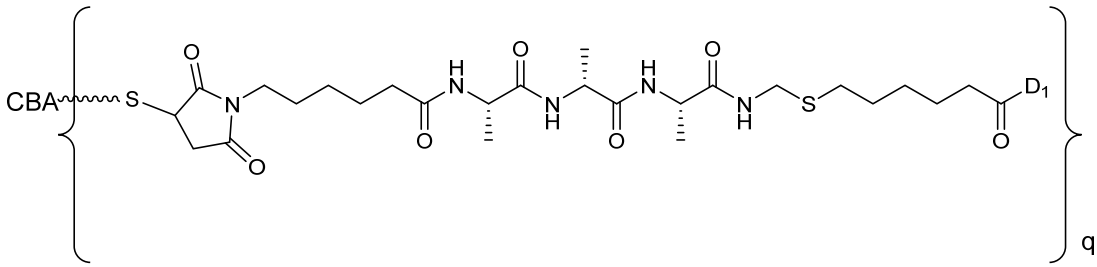
(f) SEQ ID NO:153 and SEQ ID NO:68, respectively; and

(g) SEQ ID NO:154 and SEQ ID NO:68, respectively.

25. The immunoconjugate of claim 24, wherein X in SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153 or SEQ ID NO:154 is lysine.

26. The immunoconjugate of claim 24, wherein X in SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153 or SEQ ID NO:154 is absent.

27. The immunoconjugate of claim 1, wherein the immunoconjugate is represented by the following formula:

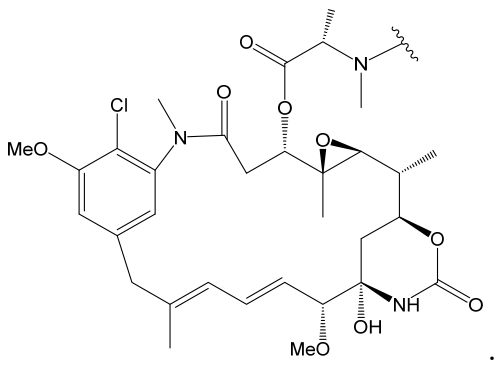


wherein:

CBA is a humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprising a CDR_H1 domain, a CDR_H2 domain, and a CDR_H3 domain and a CDR_L1 domain, a CDR_L2 domain, and a CDR_L3 domain having the sequences of SEQ ID NOs: 8, 35, and 45 and SEQ ID NOs: 62, 13, 14, respectively;

q is 1 or 2;

D_1 is represented by the following formula:



28. The immunoconjugate of claim 27, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having sequences of SEQ ID NO:28 and SEQ ID NO:55, respectively.

29. The immunoconjugate of claim 27, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences of SEQ ID NO:142 and SEQ ID NO:68, respectively.

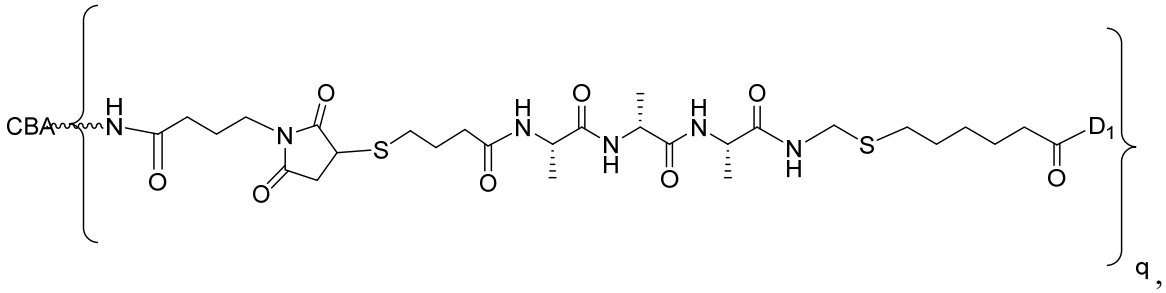
30. The immunoconjugate of claim 27, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences of SEQ ID NO:152 and SEQ ID NO:68, respectively.

31. The immunoconjugate of claim 29 or 30, wherein X in SEQ ID NO:142 or SEQ ID NO:152 is lysine.

32. The immunoconjugate of claim 29, wherein X in SEQ ID NO:142 is absent.

33. The immunoconjugate of claim 27, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences of SEQ ID NO:156 and SEQ ID NO:68, respectively.

34. The immunoconjugate of claim 1, wherein the immunoconjugate is represented by the following formula:

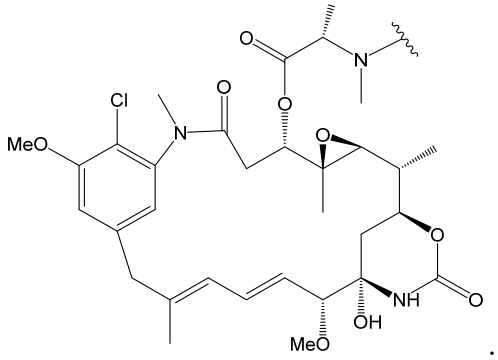


wherein:

CBA is an humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprising a CDR_H1 domain, a CDR_H2 domain, and a CDR_H3 domain and a CDR_L1 domain, a CDR_L2 domain, and a CDR_L3 domain having the sequences of SEQ ID NOs: 8, 35, and 45 and SEQ ID NOs: 62, 13, 14, respectively;

q is an integer from 1 or 10;

D_1 is represented by the following formula:



35. The immunoconjugate of claim 33, wherein said humanized anti-ADAM9 antibody or ADAM9-binding fragment thereof comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having sequences of SEQ ID NO:28 and SEQ ID NO:55, respectively.

36. The immunoconjugate of claim 35, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences of SEQ ID NO:52 and SEQ ID NO:68, respectively.

37. The immunoconjugate of claim 34, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences of SEQ ID NO:151 and SEQ ID NO:68, respectively.

38. The immunoconjugate of claim 36 or 37, wherein X in SEQ ID NO:52 or SEQ ID NO:151 is lysine.

39. The immunoconjugate of claim 36, wherein X in SEQ ID NO:52 is absent.

40. The immunoconjugate of claim 34, wherein said humanized anti-ADAM9 antibody comprises a heavy chain and a light chain having the sequences of SEQ ID NO:155 and SEQ ID NO:68, respectively.

41. A pharmaceutical composition comprising an effective amount of the immunoconjugate of any of claims 1-40 and a pharmaceutically acceptable carrier, excipient or diluent.

42. Use of the immunoconjugate of any one of claims 1-40 or the pharmaceutical composition of claim 41 in the preparation of a medicament for the treatment of a disease or condition associated with, or characterized by, the expression of ADAM9 in a subject.

43. The use of claim 42, wherein said disease or condition associated with, or characterized by, the expression of ADAM9 is cancer.

44. The use of claims 43, wherein said cancer is selected from the group consisting of non-small-cell lung cancer, colorectal cancer, bladder cancer, gastric cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, esophageal cancer, breast cancer, head and neck cancer, uterine cancer, ovarian cancer, liver cancer, cervical cancer, thyroid cancer, testicular cancer, myeloid cancer, melanoma, and lymphoid cancer.

45. The use of claim 44, wherein said non-small-cell lung cancer is squamous cell carcinoma, nonsquamous cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma.

46. The use of claim 44, wherein said colorectal cancer is adenocarcinoma, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, primary colorectal lymphoma, leiomyosarcoma, or squamous cell carcinoma.

47. The use of claim 42, wherein the medicament is for treating non-small-cell lung

cancer, gastric cancer, pancreatic cancer, triple negative breast cancer (TNBC) or colorectal cancer.