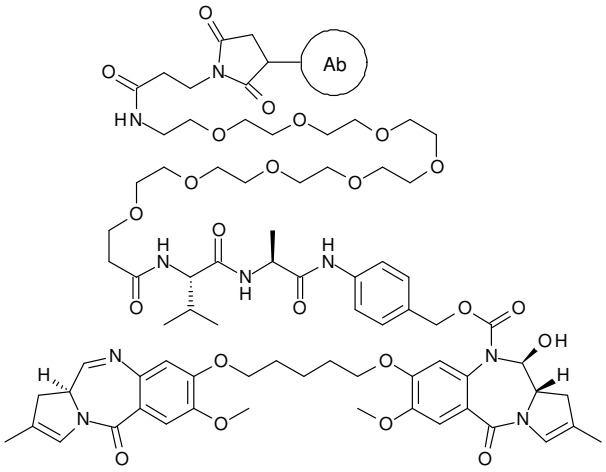
Maximal efficacy with minimal toxicity is sought thereby. Efforts to design and refine ADC have focused on the selectivity of monoclonal antibodies (mAbs) as well as drug mechanism of action, drug-linking, drug/antibody ratio (loading), and drug-releasing properties (Junutula, *et al*., 2008b Nature Biotech., 26(8):925-932; Dornan *et al* (2009) *Blood* 114(13):2721-2729; US 7521541; US 7723485; WO2009/052249; McDonagh (2006) Protein Eng. Design & Sel. 19(7): 299-307; Doronina *et al* (2006) Bioconj. Chem. 17:114-124; Erickson *et al* (2006) *Cancer Res.* 66(8):1-8; Sanderson *et al* (2005) *Clin. Cancer Res.* 11:843-852; Jeffrey *et al* (2005) *J. Med. Chem.* 48:1344-1358; Hamblett *et al* (2004) *Clin. Cancer Res.* 10:7063-7070). Drug moieties may impart their cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, proteasome and/or topoisomerase inhibition. Some cytotoxic drugs tend to be inactive or less active when conjugated to large antibodies or protein receptor ligands.

The present inventors have developed particular PBD dimer antibody conjugates.

Summary

In one aspect, the present disclosure refers to a conjugate of formula ConjE:



ConjE

wherein Ab is an antibody that binds to kidney associated antigen 1 (KAAG1), the antibody comprising

a VH domain comprising a VH CDR1 with the amino acid sequence of SEQ ID NO.5, a VH CDR2 with the amino acid sequence of SEQ ID NO.6, and a VH CDR3 with the amino acid sequence of SEQ ID NO.7; and a VL domain comprising a VL CDR1 with the amino acid sequence of SEQ ID NO.8, a VL CDR2 with the amino acid sequence of SEQ ID NO.9, and a VL CDR3 with the amino acid sequence of SEQ ID NO.10,

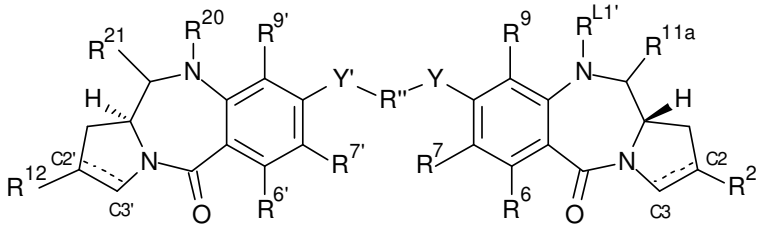
wherein the drug loading (p) is from 1 to 8.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the conjugate as disclosed herein and a pharmaceutically acceptable diluent, carrier or excipient.

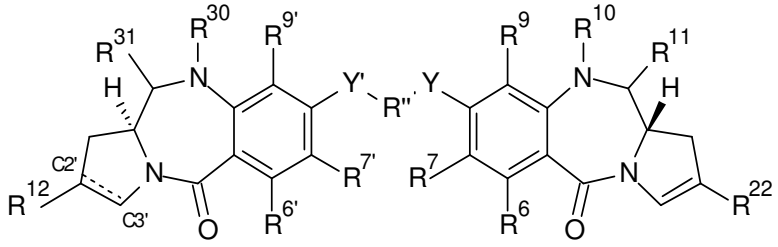
In another aspect, the present disclosure refers to the use of a conjugate as disclosed herein in the preparation of a medicament for the treatment of a kidney associated antigen 1 (KAAG1)-overexpressing cancer in a subject.

In yet another aspect, the present disclosure refers to a conjugate as disclosed herein for use in therapy.

A first example of the present disclosure comprises a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:

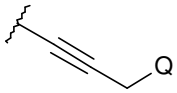


I



II

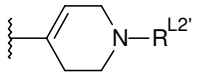
wherein:
L is an antibody (Ab) as defined below;
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;
(ib) C_{1-5} saturated aliphatic alkyl;
(ic) C_{3-6} saturated cycloalkyl;

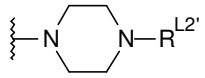


IIIc

(c)

where Q is selected from O-$R^{L2'}$, S-$R^{L2'}$ and NR^N-$R^{L2'}$, and R^N is selected from H, methyl and ethyl

X is selected from the group comprising: O-$R^{L2'}$, S-$R^{L2'}$, CO_2-$R^{L2'}$, CO-$R^{L2'}$, NH-C(=O)-$R^{L2'}$, NHNH-$R^{L2'}$, CONHNH-$R^{L2'}$, 

, 

, $NR^NR^{L2'}$, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;

$R^{L2'}$ is a linker for connection to the antibody (Ab);

R^{10} and R^{11} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

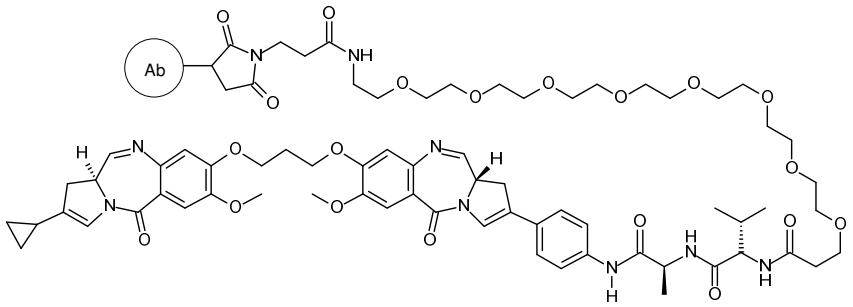
R^{10} is H and R^{11} is selected from OH, OR^A and SO_zM;

R^{30} and R^{31} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

R^{30} is H and R^{31} is selected from OH, OR^A and SO_zM.

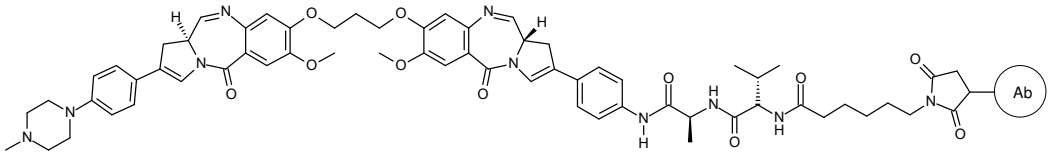
In some examples, the conjugate is not:

ConjA



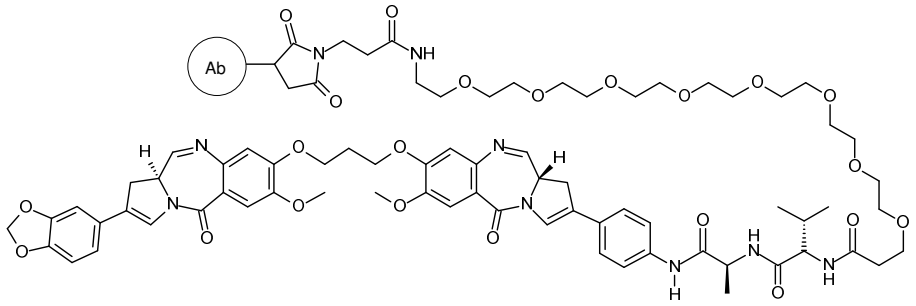
ConjA ;

ConjB



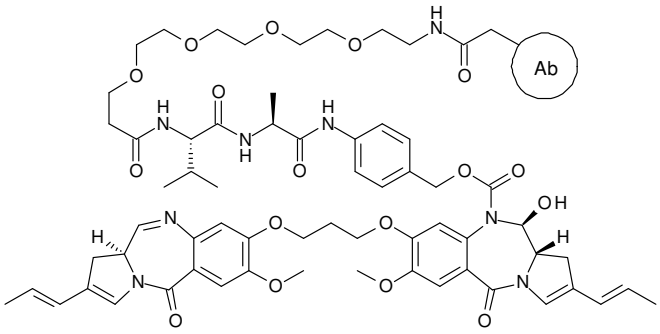
ConjB ;

ConjC:



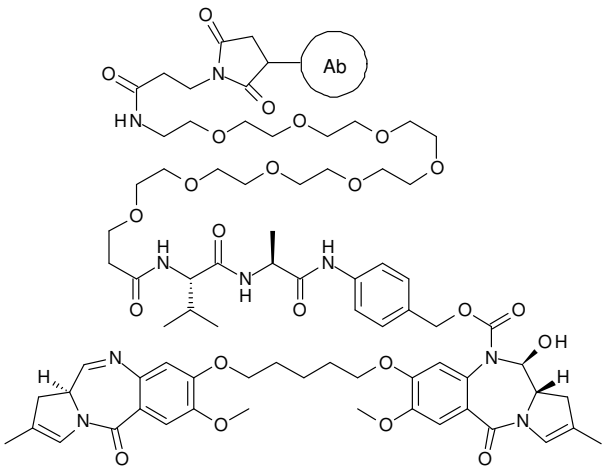
ConjC ;

ConjD



ConjD ; or

ConjE:



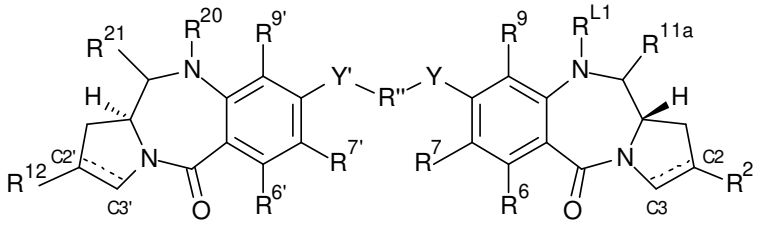
ConjE .

In other examples, it may be preferred that the conjugate is selected from a conjugate of formula ConjA, ConjB, ConjC, ConjD and ConjE.

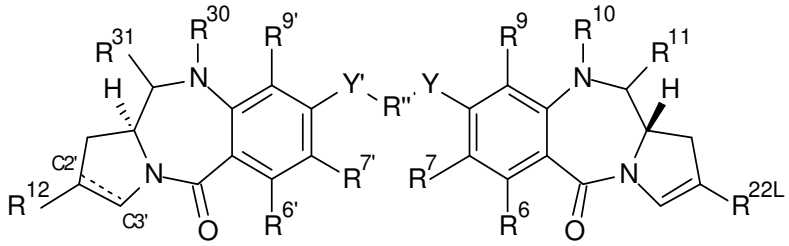
The subscript p in the formula I is an integer of from 1 to 20. Accordingly, the Conjugates comprise an antibody (Ab) as defined below covalently linked to at least one Drug unit by a Linker unit. The Ligand unit, described more fully below, is a targeting agent that binds to a target moiety. Accordingly, the present disclosure also provides methods for the treatment of, for example, various cancers and autoimmune disease. The drug loading is represented

by p, the number of drug molecules per antibody. Drug loading may range from 1 to 20 Drug units (D^L) per antibody. For compositions, p represents the average drug loading of the Conjugates in the composition, and p ranges from 1 to 20.

A second example of the disclosure provides a method of making a conjugate according to the first example of the disclosure comprising conjugating a compound of formula I^L or II^L:

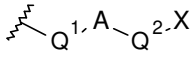


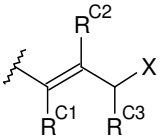
I^L



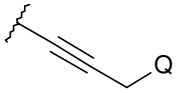
II^L

to the antibody (Ab) as defined below, wherein:
R^{L1} is a linker suitable for conjugation to the antibody (Ab);
R^{22L} is of formula $IIIa^L$, formula $IIIb^L$ or formula $IIIc^L$:

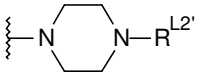
(a)  IIIa ;



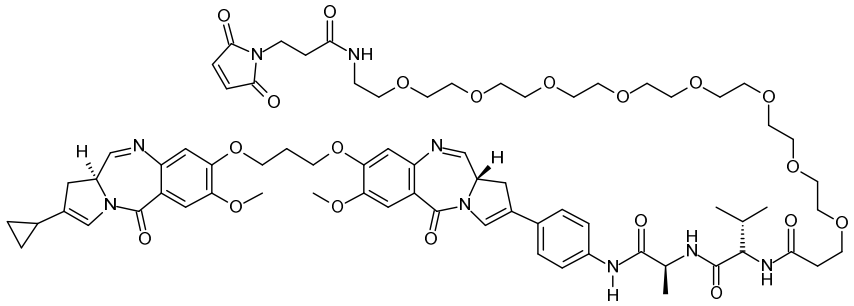
(b) IIIb ;



(c) IIIc

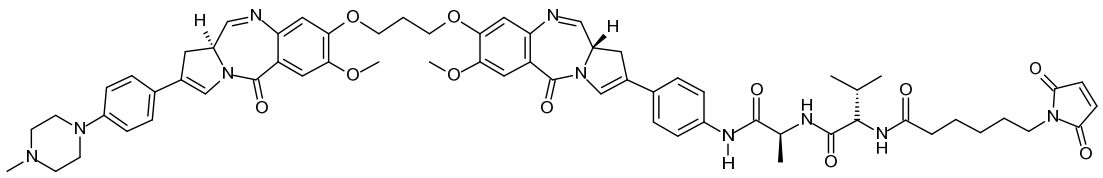
where Q^L is selected from O-R^{L2}, S-R^{L2} and NR^N-R^{L2}, and R^N is selected from H, methyl and ethyl
X^L is selected from the group comprising: O-R^{L2}, S-R^{L2}, CO_2-R^{L2}, CO-R^{L2}, N=C=O-R^{L2}, NHNH-R^{L2}, CONHNH-R^{L2}, , , NR^NR^L, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;
R^{L2} is a linker suitable for conjugation to the antibody (Ab);
and all the remaining groups are as defined in the first example.

Thus it may be preferred in the second example, that the disclosure provides a method of making a conjugate selected from the group consisting of ConjA, ConjB, ConjC, ConjD and ConjE comprising conjugating a compound which is selected respectively from A:



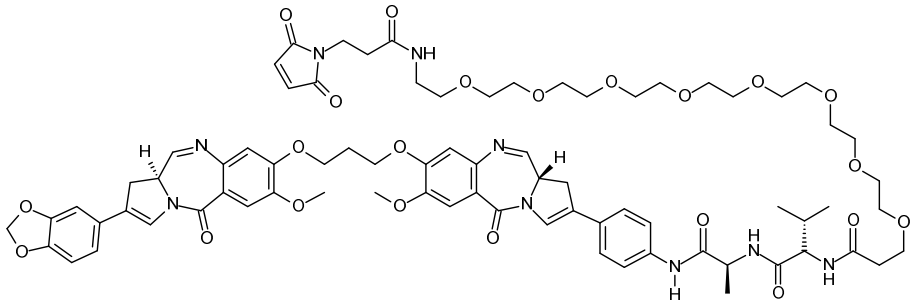
A

B:



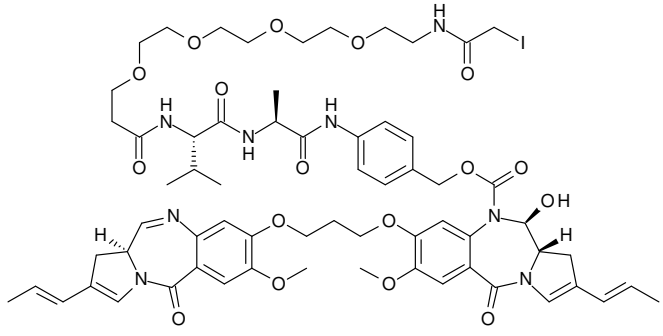
B

C:



C

D:

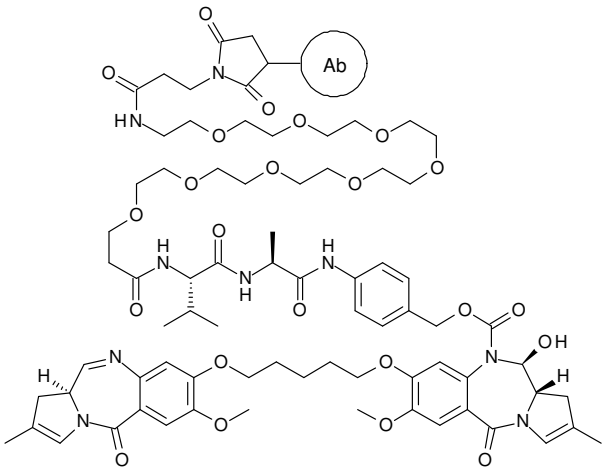


D

and E:

CLAIMS

1. A conjugate of formula ConjE:



ConjE

wherein Ab is an antibody that binds to kidney associated antigen 1 (KAAG1), the antibody comprising
a VH domain comprising a VH CDR1 with the amino acid sequence of SEQ ID NO.5, a VH CDR2 with the amino acid sequence of SEQ ID NO.6, and a VH CDR3 with the amino acid sequence of SEQ ID NO.7; and a VL domain comprising a VL CDR1 with the amino acid sequence of SEQ ID NO.8, a VL CDR2 with the amino acid sequence of SEQ ID NO.9, and a VL CDR3 with the amino acid sequence of SEQ ID NO.10,
wherein the drug loading (p) is from 1 to 8.

2. The conjugate according to claim 1, wherein the VH domain has the sequence according to SEQ ID NO. 1.

3. The conjugate according to claim 1 or 2, wherein the VL domain has the sequence according to SEQ ID NO. 2.

4. The conjugate according to any one of claims 1 to 3 wherein the antibody comprises a heavy chain having the sequence of SEQ ID NO. 3 or SEQ ID NO. 11.

5. The conjugate according to any one of the preceding claims, wherein the antibody comprises a light chain having the sequence of SEQ ID NO.4, SEQ ID NO.14, or SEQ ID NO.16.

6. The conjugate according to claim 5, wherein the antibody comprises a light chain having the amino acid sequence of SEQ ID NO.4.

7. The conjugate according to any one of the preceding claims, wherein the antibody is an intact antibody.

8. The conjugate according to any one of the preceding claims, wherein the antibody is a fully human monoclonal IgG1 antibody.

9. The conjugate according to claim 8, wherein the antibody is a fully human monoclonal IgG1,κ antibody.

10. The conjugate according to any one of the preceding claims, wherein the drug loading (p) is 1, 2, 3, or 4.

11. A pharmaceutical composition comprising the conjugate of any one of the preceding claims and a pharmaceutically acceptable diluent, carrier or excipient.

12. The pharmaceutical composition according to claim 11, comprising a mixture of antibody-drug conjugates, wherein the average drug loading per antibody in the mixture of antibody-drug conjugates is about 2 to about 5.

13. The pharmaceutical composition according to claim 11 or 12, further comprising a therapeutically effective amount of a chemotherapeutic agent.

14. Use of a conjugate according to any one of claims 1 to 10 in the preparation of a medicament for the treatment of a kidney associated antigen 1 (KAAG1)-overexpressing cancer in a subject.

15 . The use according to claim 14, wherein a therapeutically effective amount of a chemotherapeutic agent is to be further administered to the subject.

16 . The use according to claim 14 or 15, wherein the cancer is ovarian cancer, breast cancer, prostate cancer, or renal cancer.

17. A conjugate according to any one of claims 1 to 10 for use in therapy.