physicochemical, pharmacokinetic, pharmacological, and/or toxicological properties of ADCs to obtain ADCs having acceptable antigen binding properties, *in vivo* efficacy, therapeutic index, and/or stability.

SUMMARY

The present disclosure relates to antibody-drug conjugates (ADCs) wherein a linker drug is site-specifically conjugated to an antibody through an engineered cysteine at one or more specific positions of said antibody, and their use in the treatment of human solid tumours and haematological malignancies, in particular breast cancer, gastric cancer, colorectal cancer, urothelial cancer, ovarian cancer, uterine cancer, lung cancer, mesothelioma, liver cancer, pancreatic cancer, prostate cancer, and leukaemia.

In one aspect, the present disclosure refers to an antibody-drug conjugate compound wherein a linker drug is site-specifically conjugated to an antibody or antigen binding fragment thereof through an engineered cysteine at one or more positions of said antibody or antigen binding fragment thereof selected from heavy chain 41 according to Kabat numbering; light chain 40 according to Kabat numbering; and light chain 41 according to Kabat numbering. In another aspect, the present disclosure refers to the use of the compound as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of human solid tumours and haematological malignancies.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A. Identification of suitable linker drug conjugation positions in the Fab part of an antibody

Figure 1B. Docking of duocarmycin linker drug vc-*seco*-DUBA in the Fab cavity of an antibody (overlay of multiple vc-*seco*-DUBA dockings)

Figure 1C. Identification of suitable linker drug conjugation positions in the Fc part of an antibody

Figure 1D. Docking of duocarmycin linker drug vc-*seco*-DUBA in the Fc cavity of an antibody (overlay of multiple vc-*seco*-DUBA dockings)

Figure 2A. *In vivo* efficacy of engineered cysteine anti-PSMA (VH S41C) ADC (SYD1091) *versus* vehicle control, comparator engineered cysteine anti-PSMA (CH T120C) ADC (SYD1035), and non-engineered anti-PSMA (wild-type) wt ADC (SYD998) at 2 mg/kg each

CLAIMS

1. An antibody-drug conjugate compound wherein a linker drug is site-specifically conjugated to an antibody or antigen binding fragment thereof through an engineered cysteine at one or more positions of said antibody or antigen binding fragment thereof selected from

   heavy chain 41 according to Kabat numbering;

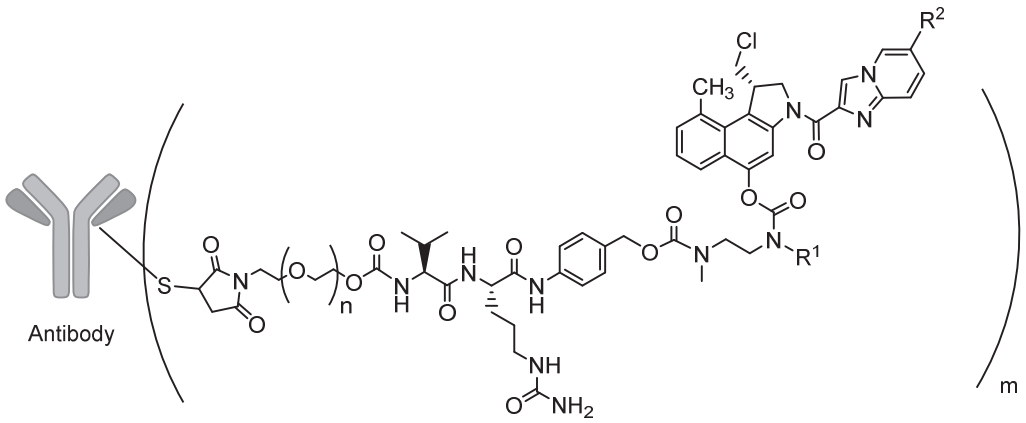
   light chain 40 according to Kabat numbering; and

   light chain 41 according to Kabat numbering.

2. The compound according to claim 1, further comprising an engineered cysteine at position 375 in the Fc part of said antibody or antigen binding fragment thereof according to Eu numbering.

3. The compound according to claim 1 or 2, wherein said linker drug comprises a duocarmycin derivative (with the proviso that the antibody-drug conjugate compound wherein a duocarmycin derivative is site-specifically conjugated to an antibody or antigen binding fragment thereof through an engineered cysteine in said antibody or antigen binding fragment thereof at heavy chain 41 according to Kabat numbering is disclaimed).

4. The compound according to claim 3 of the formula (I)



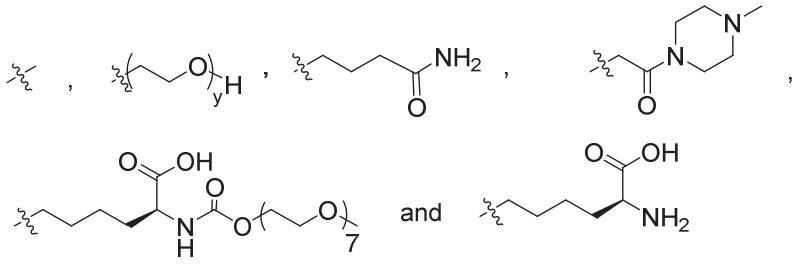
(I)

wherein

n is 0-3,

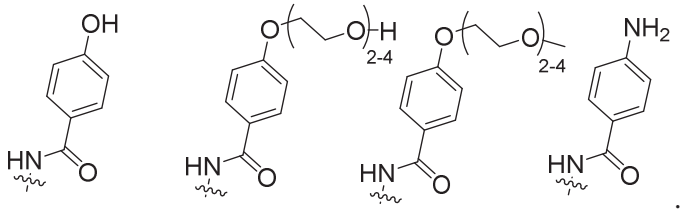
m represents an average DAR of from 1 to 6,

R^1 is selected from



y is 1-16, and

R^2 is selected from

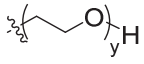


5. The compound according to claim 4, wherein

n is 0-1,

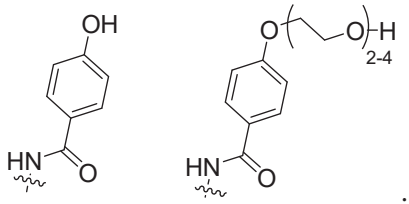
m represents an average DAR of from 1.5 to 2,

R^1 is

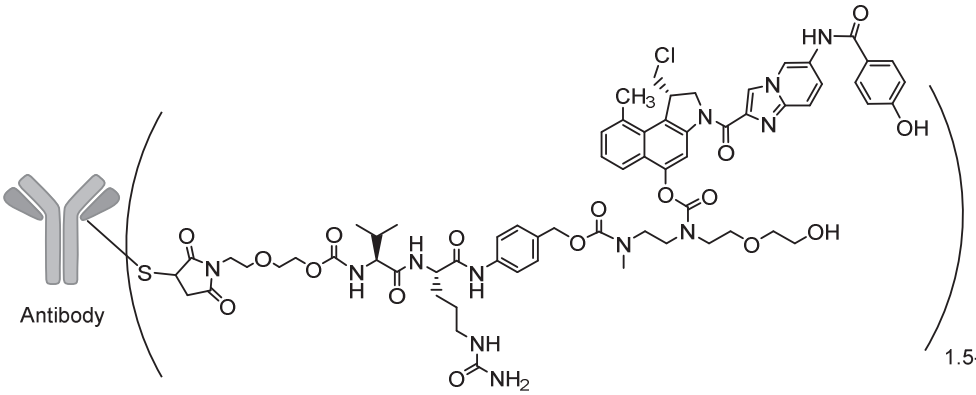


y is 1-4, and

R^2 is selected from



6. The compound according to claim 5 of the formula (II)



(II).

7. The compound according to any one of claims 1-6, wherein said antibody or antigen binding fragment thereof binds to an antigen target that is expressed in or on the cell membrane of a tumour cell and wherein said antibody or antigen binding fragment thereof is internalised by the cell after binding to said target.

8. The compound according to any one of claims 1-7, wherein said antibody is an anti-annexin A1 antibody, an anti-CD115 antibody, an anti-CD123 antibody, an anti-CLL-1 antibody, an anti-c-MET antibody, an anti-MUC1 antibody, an anti-PSMA antibody, an anti-5T4 antibody or an anti-TF antibody.

9. The compound according to any one of claims 1 to 8, wherein said antibody is an anti-PSMA monoclonal antibody or an anti-5T4 monoclonal antibody.

10. The compound according to claim 9, wherein said linker drug is conjugated at heavy chain variable region position 41 of said anti-PSMA antibody (with the proviso that the antibody-drug conjugate compound wherein a duocarmycin derivative is site-specifically conjugated to an antibody or antigen binding fragment thereof through an engineered cysteine in said antibody or antigen binding fragment thereof at heavy chain 41 according to Kabat numbering is disclaimed).

11. The compound according to claim 10, wherein the heavy chain of said anti-PSMA antibody comprises the amino acid sequence of SEQ ID NO:2 and the light chain of said anti-PSMA antibody comprises the amino acid sequence of SEQ ID NO:5.
12. The compound according to claim 9, wherein said linker drug is conjugated at heavy chain variable region position 41 of said anti-5T4 antibody (with the proviso that the antibody-drug conjugate compound wherein a duocarmycin derivative is site-specifically conjugated to an antibody or antigen binding fragment thereof through an engineered cysteine in said antibody or antigen binding fragment thereof at heavy chain 41 according to Kabat numbering is disclaimed).
13. The compound according to claim 12, wherein the heavy chain of said anti-5T4 antibody comprises the amino acid sequence of SEQ ID NO:8 and the light chain of said anti-5T4 antibody comprises the amino acid sequence of SEQ ID NO:11.
14. A pharmaceutical composition comprising a compound according to any one of claims 1-13 and one or more pharmaceutically acceptable excipients.
15. The pharmaceutical composition according to claim 14 in the form of a lyophilized powder.
16. The compound according to any one of claims 1-13 or the pharmaceutical composition according to claim 14 or 15 for use as a medicament.
17. Use of the compound according to any one of claims 1-13 or the pharmaceutical composition according to claim 14 or 15 in the manufacture of a medicament for the treatment of human solid tumours and haematological malignancies.
18. The use according to claim 17, wherein the human solid tumours are selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, urothelial cancer, ovarian cancer, uterine cancer, lung cancer, mesothelioma, liver cancer, pancreatic cancer, and prostate cancer.