

Claims

[Claim 1]

A binding agent-drug conjugate comprising a binding agent and a payload, wherein the binding agent comprises:

- a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 9 or 10;
- a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 24 or 25;
- a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 34 or 35;
- a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 58 or 59;
- a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 70 or 71;
- a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 87 or 88; and

the binding agent is an antibody, or a binding fragment thereof, wherein the payload comprises a pyrrolobenzodiazepine toxin and a linking group; and wherein the pyrrolobenzodiazepine toxin is covalently linked to the linking group, the linking group is covalently linked to the binding agent, and the binding agent specifically binds to an extracellular domain of mesenchymal epithelial transition factor (cMET).

[Claim 2]

A binding agent-drug conjugate comprising a binding agent and a payload, wherein the binding agent comprises

- a heavy chain variable region comprising an amino acid sequence selected from SEQ ID NOs: 105, 106, 107 and 108, and
- a light chain variable region comprising an amino acid sequence selected from SEQ ID NOs: 46, 47, 48 and 49,

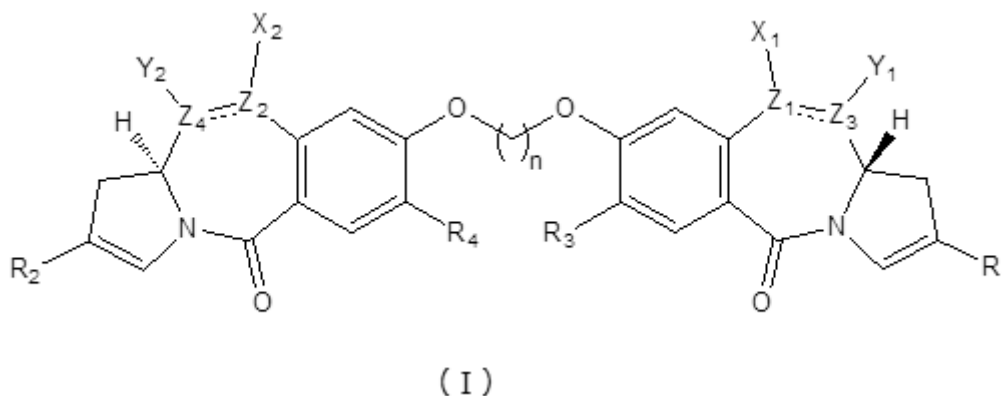
wherein the payload comprises a pyrrolobenzodiazepine toxin and a linking group; and wherein the pyrrolobenzodiazepine toxin is covalently linked to the linking group, the linking group is covalently linked to the binding agent, and the binding agent specifically binds to an extracellular domain of mesenchymal epithelial transition factor (cMET).

[Claim 3]

The binding agent-drug conjugate of claim 2, wherein the light chain sequence comprises SEQ ID NO: 47 and the heavy chain sequence comprises SEQ ID NO: 108.

[Claim 4]

The binding agent-drug conjugate of any one of claims 1-3, wherein the pyrrolobenzodiazepine toxin comprises the structure of chemical formula I:



wherein

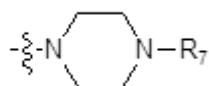
Z_1 and Z_2 are both N;

Z_3 and Z_4 are both C;

the double-dash lines ----- represent a single bond or a double bond;

n is 1 to 10; each of R_3 and R_4 are independently H, or a C_{1-4} alkoxy; and each of R_1 and R_2 are independently selected from the group consisting of H, C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{2-5} alkenyl, and a phenyl substituted with R_5 ,

wherein R_5 is selected from the group consisting of $-\text{NH}_2$, $-\text{NHR}_6$, and a piperazinyl substituted with R_7 having the structure



wherein R_6 comprises the linking group, and R_7 is H, or a C_{1-5} alkyl;

X_1 is null, a protecting group, or comprises the linking group; X_2 is null, a protecting group, or comprises the linking group; only one of X_1 , X_2 , R_1 , and R_2 comprises the linking group; and each of Y_1 and Y_2 are independently either null, OH, or SO_3H ; provided that:

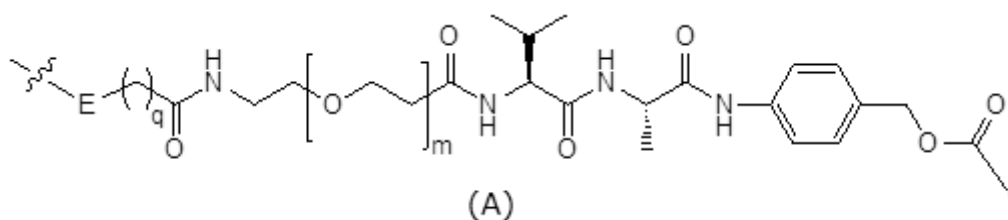
- (i) when X_1 comprises the linking group, $Z_1\text{-----}Z_3$ is N-C,
- (ii) when X_2 comprises the linking group, $Z_2\text{-----}Z_4$ is N-C,
- (iii) when X_1 comprises the protecting group, $Z_1\text{-----}Z_3$ is N-C, and
- (iv) when X_2 comprises the protecting group, $Z_2\text{-----}Z_4$ is N-C,

wherein null indicates the absence of the moiety or the presence of one or more hydrogens

to complete a required valency.

[Claim 5]

The binding agent-drug conjugate of any one of claims 1-4, wherein the linking group comprises the structure of chemical formula A:

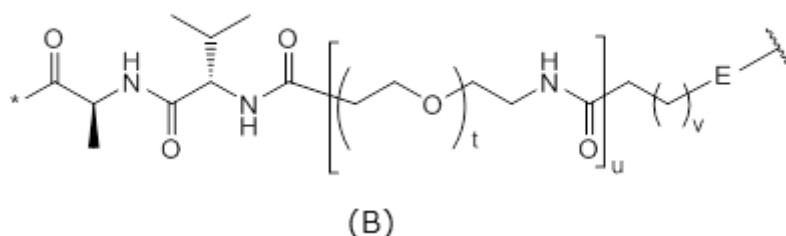


wherein

the asterisk indicates the point of attachment to the pyrrolobenzodiazepine toxin;
the wavy line indicates the point of attachment to the binding agent; m is 1 to 20; q is 0 to 10; and E is a connecting group.

[Claim 6]

The binding agent-drug conjugate of any one of claims 1-4, wherein the linking group comprises the structure of chemical formula B:

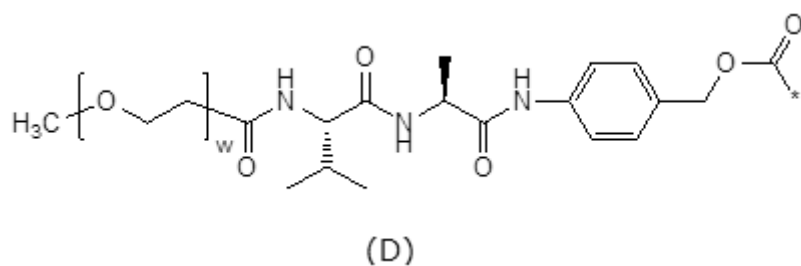


wherein

the asterisk indicates the point of attachment to the pyrrolobenzodiazepine toxin; the wavy line indicates the point of attachment to the binding agent; E is a connecting group; v is 0 to 10; and u is 0 or 1; wherein when u is 1, t is 1 to 10.

[Claim 7]

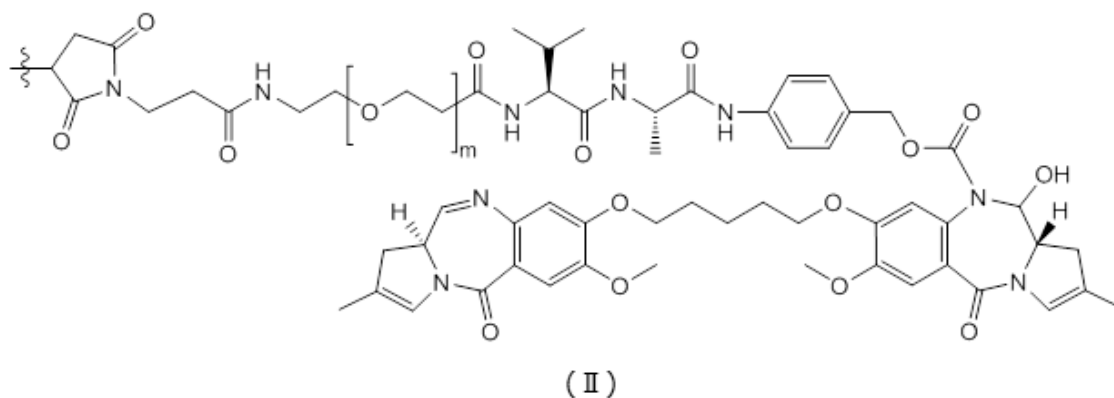
The binding agent-drug conjugate of any one of claims 4-6, wherein the protecting group has the following structure D:



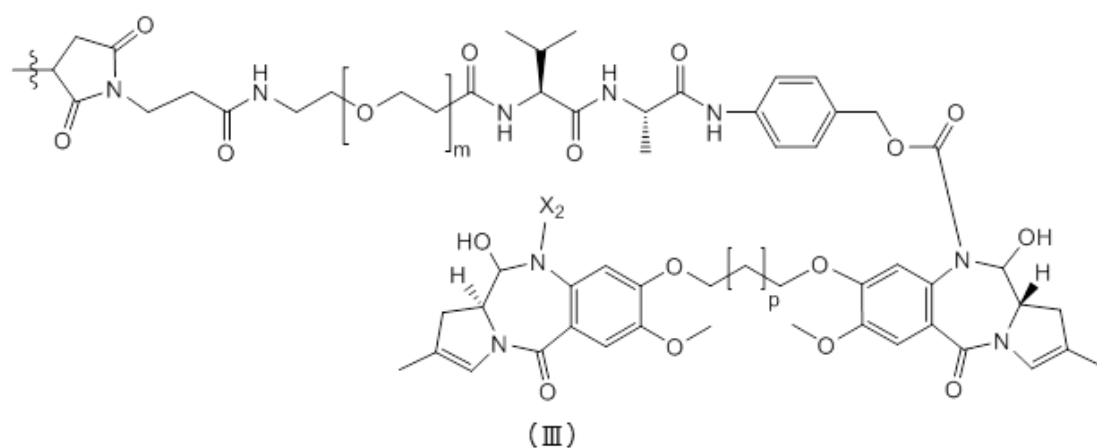
wherein the asterisk indicates the point of attachment to the pyrrolobenzodiazepine toxin; and w is 1 to 5.

[Claim 8]

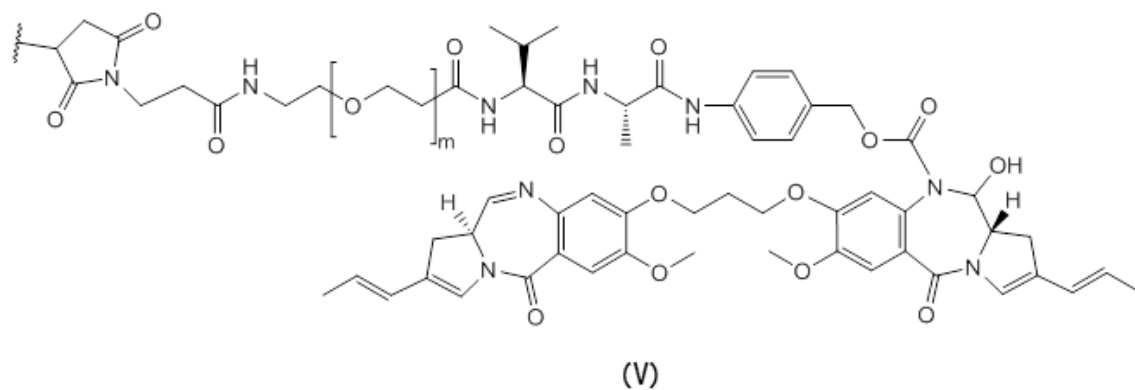
The binding agent-drug conjugate of any one of claims 1-4, wherein the payload comprises a structure selected from the group consisting of



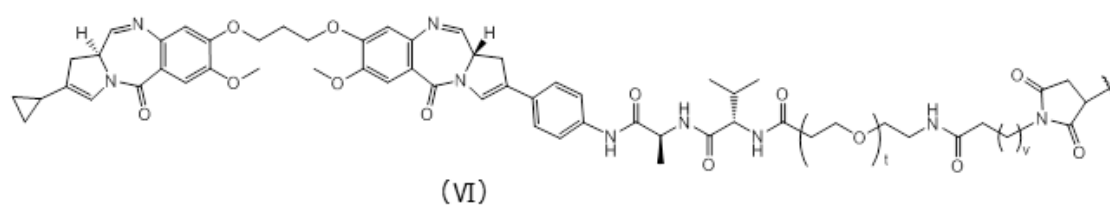
wherein m is 8;



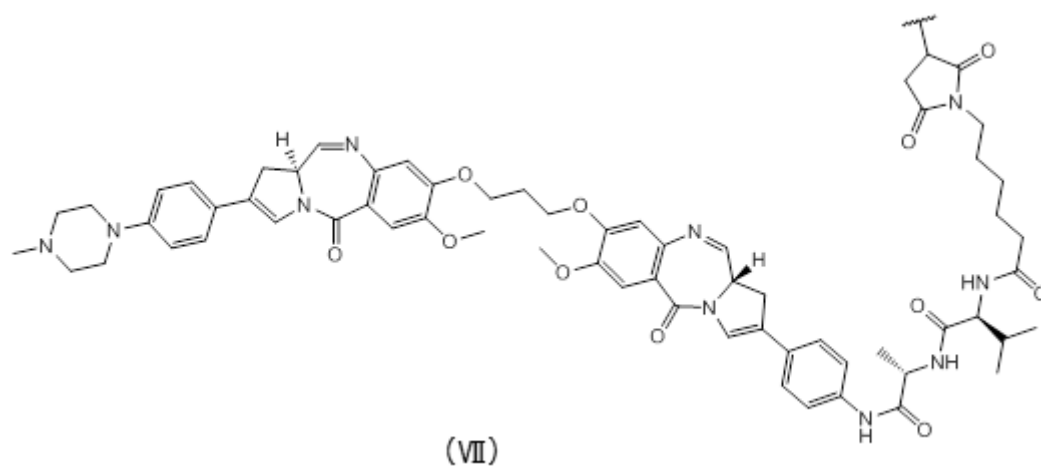
wherein m is 8, p is 3, and X₂ is a protecting group;



wherein m is 8;



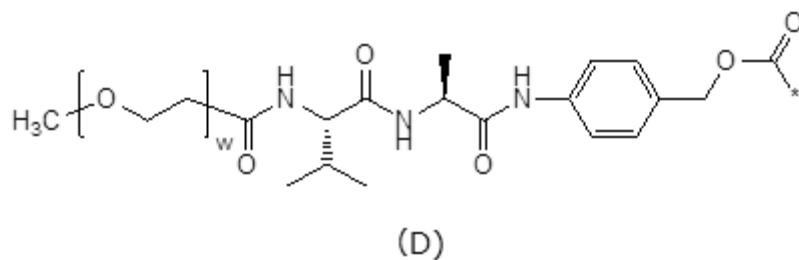
wherein t is 8, and v is 1; and



wherein the wavy line in formulae (II), (III), (IV), (V), (VI) and (VII) indicates the point of attachment to the binding agent.

[Claim 9]

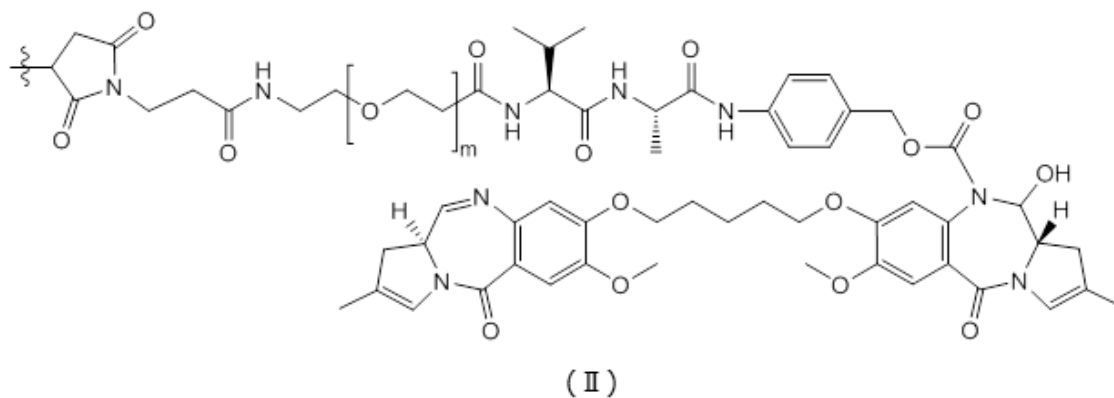
The binding agent-drug conjugate of claim 8, wherein the payload has the structure of formula (III) and the protecting group of X₂ has the structure (D):



wherein the asterisk indicates the point of attachment to the payload; and w is 1 to 5.

[Claim 10]

The binding agent-drug conjugate of claim 8, payload has the structure of formula (II):



wherein m is 8, the wavy line indicates the point of attachment to a thiol residue in the binding agent.

[Claim 11]

The binding agent-drug conjugate of any one of claims 1-10, wherein the binding agent binds specifically to a human cMET, monkey cMET or rat cMET.

[Claim 12]

The binding agent-drug conjugate of any one of claims 1-11, wherein the binding agent specifically binds to the extracellular domain of a cMET variant.

[Claim 13]

The binding agent-drug conjugate of any one of claims 1 to 12 for use in therapy.

[Claim 14]

Use of the binding agent-drug conjugate of any one of claims 1 to 12 in the manufacture of a medicament for the treatment of a subject having or suspected of having a cMET expressing neoplastic disorder or cancer.

[Claim 15]

The use of claim 13, wherein the cMET expressing neoplastic disorder or cancer comprises a carcinoma, sarcoma, neuroblastoma, glioblastoma, myeloma, lymphoma, melanoma or a solid or soft tissue tumor.

[Claim 16]

The use of claim 14, wherein the cMET expressing neoplastic disorder or cancer comprises a bladder cancer, breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, esophageal cancer, liver cancer, hepatocellular cancer, hypopharynx cancer, lung cancer, adenocarcinoma, ovarian cancer or renal cancer.

[Claim 17]

The use of claim 14 or 15, wherein the cMET expressing neoplastic disorder or cancer comprises a pancreatic adenocarcinoma, pancreatic neuroendocrine cancer, colorectal adenocarcinoma, small intestinal malignancy, cholangiocarcinoma, non-small cell lung cancer (NSCLC), thyroid carcinoma, esophageal or esophagogastric junction (EGJ) cancer, gastric adenocarcinoma, liver hepatocellular carcinoma, head and neck squamous carcinoma, female genital tract malignancy, breast carcinoma, triple negative breast cancer, lung small cell carcinoma, ovarian surface epithelial carcinoma, retroperitoneal or peritoneal sarcoma, prostatic adenocarcinoma, neuroendocrine tumor, gastrointestinal stromal tumor, glioblastoma or non-epithelial ovarian cancer.