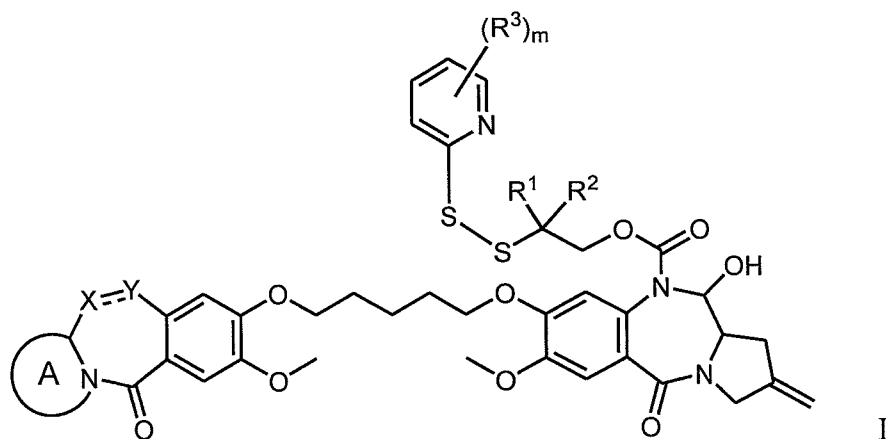


Pyrrolobenzodiazepine compounds can be employed as prodrugs by protecting them at the N10 position with a nitrogen protecting group, such as carbamate, which is removable *in vivo* (WO 2000/12507; WO 2005/023814). The protecting groups are removable from the N10 position of the PBD moiety to leave an N10-C11 imine bond. A range of protecting groups is described, including groups that can be cleaved by the action of enzymes.

Antibody-drug conjugates where the pyrrolobenzodiazepine (PBD) dimer is linked through the N10 position to an antibody specific for a tumor-associated antigen have in vitro and in vivo efficacy against tumor cells (WO 2011/130598). Antibody-drug conjugates with PBD dimer drug moieties having linker groups for connection to a cell binding agent, such as an antibody, via the bridge ("tether") linking the monomer PBD units of the dimer have been described (WO 2007/085930). Antibody-drug conjugates with PBD dimer drug moieties having amide and amine groups in the B ring at N10-C11 position have been described (WO 2014/096368; WO 2013/177481; WO 2012/112708). Antibody drug conjugates comprising dialkylator pyrrolobenzodiazepine (PBD) dimer drug moieties linked at the N10 of the PBD by a disulfide linkage to antibodies have been described (WO2013/055987; Gregson et al. (2001) J. Med. Chem. 44:1161-1174).

SUMMARY

The disclosure includes a linker-drug intermediate of Formula I:



wherein $X=Y$ is selected from CH_2-CH_2 , $CH=CH$, $C(=O)-NH$, or CH_2-NH ;

A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, C_1-C_6 alkyl, or $=C(R)_2$ where R is independently selected from H, F, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

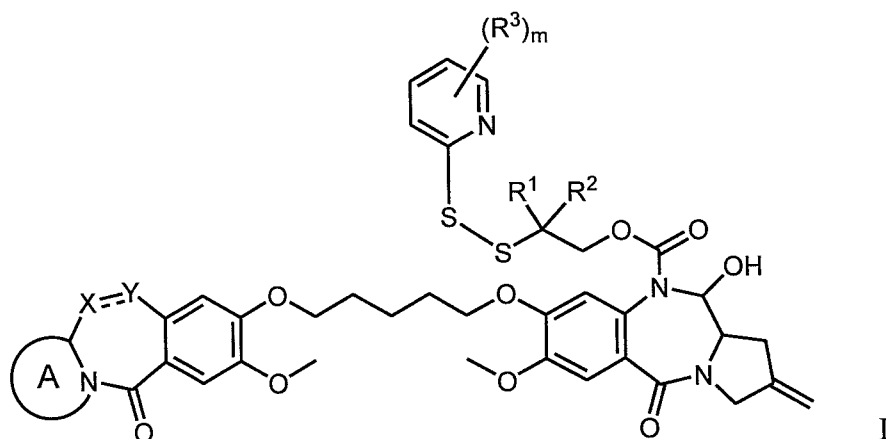
R^1 and R^2 are independently selected from H or C_1-C_6 alkyl, or R^1 and R^2 form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

R^3 is independently selected from NO_2 , Cl, F, CN, CO_2H or Br; and

m is 0, 1 or 2.

The disclosure includes monoalkylator pyrrolobenzodiazepine drug moieties covalently attached to antibodies by a disulfide linker to form antibody-drug conjugate (ADC) compounds with therapeutic or diagnostic applications.

In one aspect, there is provided a linker-drug intermediate of Formula I:



wherein $X=Y$ is selected from $\text{CH}_2\text{--CH}_2$, CH=CH , C(=O)--NH , or $\text{CH}_2\text{--NH}$;

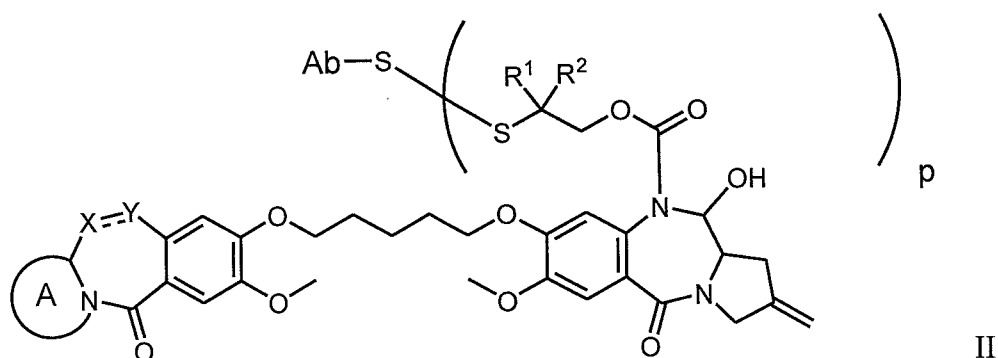
A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, $\text{C}_1\text{--C}_6$ alkyl, or =C(R)_2 where R is independently selected from H, F, $\text{C}_1\text{--C}_6$ alkyl, or $\text{C}_1\text{--C}_6$ fluoroalkyl;

R^1 and R^2 are independently selected from H or $\text{C}_1\text{--C}_6$ alkyl, or R^1 and R^2 form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

R^3 is independently selected from NO_2 , Cl, F, CN, CO_2H or Br; and

m is 1 or 2.

Another embodiment of the disclosure is an antibody-drug conjugate compound of Formula II.



or a pharmaceutically acceptable salt thereof, wherein:

$X=Y$ is selected from $\text{CH}_2\text{--CH}_2$, $\text{CH}_2\text{--C(=O)}$, CH=CH , or $\text{CH}_2\text{--NH}$;

A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, C₁-C₆ alkyl, or =C(R)₂ where R is independently selected from H, F, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

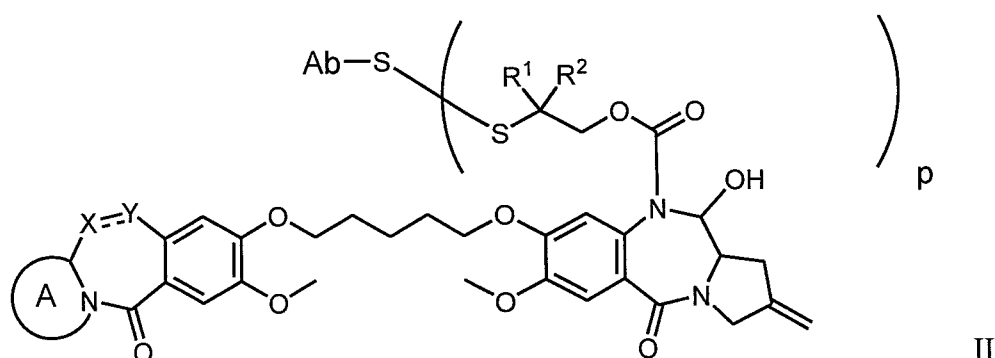
5 R¹ and R² are independently selected from H or C₁-C₆ alkyl, or R¹ and R² form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

p is an integer from 1 to 8; and

Ab is an antibody.

In another aspect, there is provided an antibody-drug conjugate compound of Formula

10 II.



or a pharmaceutically acceptable salt thereof, wherein:

X=Y is selected from CH₂-CH₂, CH=CH, C(=O)-NH and CH₂-NH;

15 A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, C₁-C₆ alkyl, or =C(R)₂ where R is independently selected from H, F, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

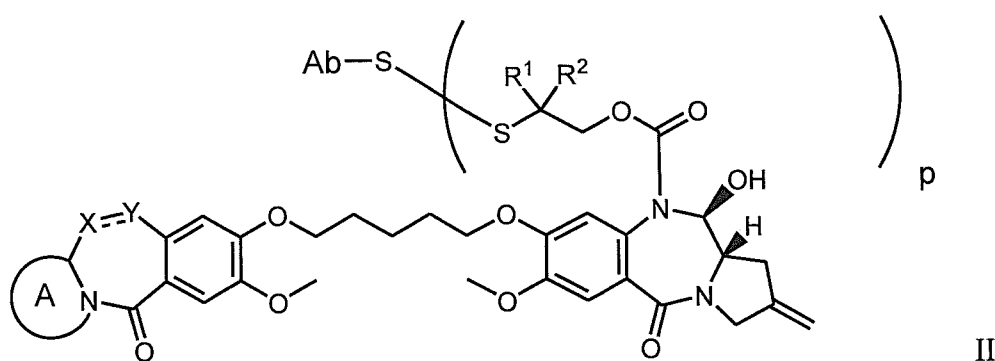
R¹ and R² are independently selected from H or C₁-C₆ alkyl, or R¹ and R² form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

p is an integer from 1 to 8; and

20 Ab is an antibody.

In another aspect, there is provided an antibody-drug conjugate compound of Formula

II.



or a pharmaceutically acceptable salt thereof, wherein:

X=Y is selected from CH₂-CH₂, CH=CH, C(=O)-NH and CH₂-NH;

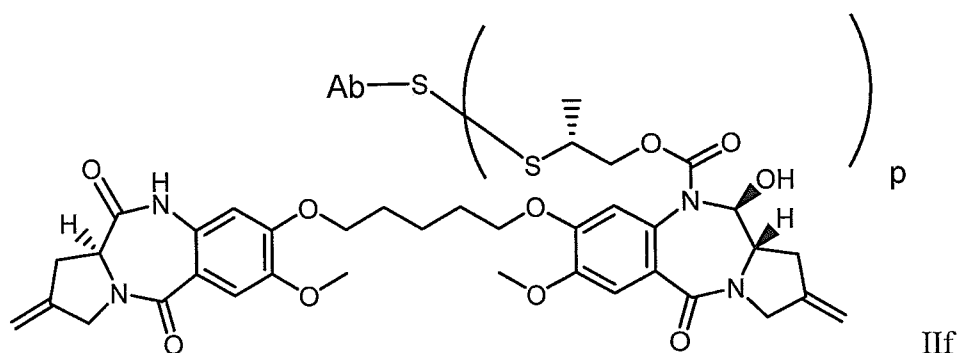
5 A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, C₁-C₆ alkyl, or =C(R)₂ where R is independently selected from H, F, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R¹ and R² are independently selected from H or C₁-C₆ alkyl, or R¹ and R² form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

10 p is an integer from 1 to 8; and

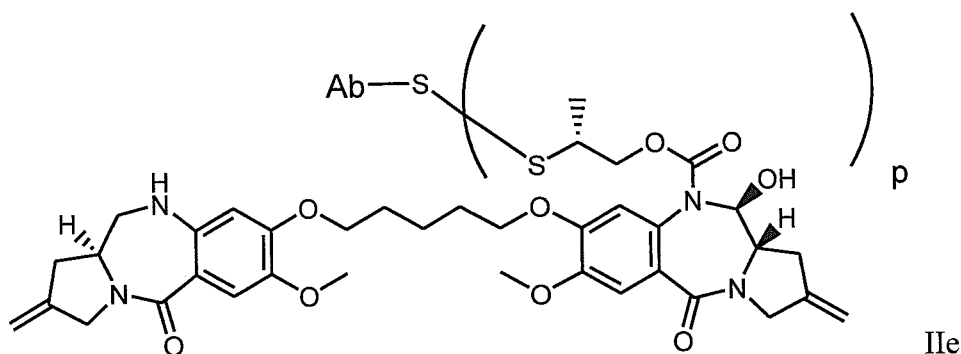
Ab is an anti-HER2 antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 19; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 20; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 21.

In another aspect, there is provided an antibody drug conjugate, or a pharmaceutically acceptable salt thereof, of Formula II_f



20 wherein Ab is a cysteine-engineered anti-HER2 antibody comprising LC K149C, and p is about 2.

In another aspect, there is provided an antibody drug conjugate of Formula IIe



wherein Ab is a cysteine-engineered anti-HER2 antibody, and p is about 2.

5

In an exemplary embodiment, the antibody binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(53):

- (1) BMPR1B (bone morphogenetic protein receptor-type IB);
- (2) E16 (LAT1, SLC7A5);
- 10 (3) STEAP1 (six transmembrane epithelial antigen of prostate);
- (4) MUC16 (0772P, CA125);
- (5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);
- (6) Napi2b (NAPI-3B, NPTIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

- (31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);
- (32) CD72 (B-cell differentiation antigen CD72, Lyb-2);
- (33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);
- 5 (34) FcRH1 (Fc receptor-like protein 1);
- (35) FcRH5 (IRTA2, Immunoglobulin superfamily receptor translocation associated 2);
- (36) TENB2 (putative transmembrane proteoglycan);
- (37) PMEL17 (silver homolog; SILV; D12S53E; PMEL17; SI; SIL);
- 10 (38) TMEFF1 (transmembrane protein with EGF-like and two follistatin-like domains 1; Tomoregulin-1);
- (39) GDNF-Ra1 (GDNF family receptor alpha 1; GFRA1; GDNFR; GDNFRA; RETL1; TRNR1; RET1L; GDNFR-alpha1; GFR-ALPHA-1);
- (40) Ly6E (lymphocyte antigen 6 complex, locus E; Ly67, RIG-E, SCA-2, TSA-1);
- 15 (41) TMEM46 (shisa homolog 2 (*Xenopus laevis*); SHISA2);
- (42) Ly6G6D (lymphocyte antigen 6 complex, locus G6D; Ly6-D, MEGT1);
- (43) LGR5 (leucine-rich repeat-containing G protein-coupled receptor 5; GPR49, GPR67);
- (44) RET (ret proto-oncogene; MEN2A; HSCR1; MEN2B; MTC1; PTC; CDHF12; Hs.168114; RET51; RET-ELE1);
- 20 (45) LY6K (lymphocyte antigen 6 complex, locus K; LY6K; HSJ001348; FLJ35226);
- (46) GPR19 (G protein-coupled receptor 19; Mm.4787);
- (47) GPR54 (KISS1 receptor; KISS1R; GPR54; HOT7T175; AXOR12);
- (48) ASPHD1 (aspartate beta-hydroxylase domain containing 1; LOC253982);
- 25 (49) Tyrosinase (TYR; OCA1A; OCA1A; tyrosinase; SHEP3);
- (50) TMEM118 (ring finger protein, transmembrane 2; RNFT2; FLJ14627);
- (51) GPR172A (G protein-coupled receptor 172A; GPCR41; FLJ11856; D15Ert747e);
- (52) CD33; or
- 30 (53) CLL-1.

In another aspect, there is provided a mixture of antibody-drug conjugate compounds, or pharmaceutically acceptable salts thereof, as disclosed herein, wherein the average drug loading per antibody, p, in the mixture of antibody-drug conjugate compounds is 2 to 5.

Another embodiment of the disclosure is a pharmaceutical composition comprising an antibody-drug conjugate compound of Formula II, and a pharmaceutically acceptable diluent, carrier or excipient.

In another aspect, there is provided a pharmaceutical composition comprising the antibody-drug conjugate compound disclosed herein and a pharmaceutically acceptable excipient.

In another aspect, there is provided a pharmaceutical composition comprising the antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, as disclosed herein and a pharmaceutically acceptable excipient.

Another embodiment of the disclosure is the use of an antibody-drug conjugate compound of Formula II in the manufacture of a medicament for the treatment of cancer in a mammal.

In another aspect, there is provided use of a therapeutically effective amount of the antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, in the manufacture of a medicament for treating cancer, wherein the cancer is a HER2-positive cancer.

Another embodiment of the disclosure is a method of treating cancer by administering to a patient a pharmaceutical composition comprising an antibody-drug conjugate compound of Formula II.

In another aspect, there is provided use of a therapeutically effective amount of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a HER2-positive cancer

Another embodiment of the disclosure is a method of making an antibody-drug conjugate compound of Formula II.

In another aspect, there is provided a method of making an antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, the method comprising reacting an antibody with a linker-drug intermediate of Formula I disclosed herein.

Another embodiment of the disclosure is an article of manufacture comprising a pharmaceutical composition comprising an antibody-drug conjugate compound of Formula II, a container, and a package insert or label indicating that the pharmaceutical composition can be used to treat cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows a plot of in vitro cell viability of BJAB cells treated with ADC-107, ADC-103, and non-target control ADC-108.

Figure 1B shows a plot of in vitro cell viability of WSU-DLCL2 cells treated with ADC-107, ADC-103 and non-target control ADC-108.

Figure 1C shows a plot of in vitro cell viability of Jurkat cells treated with ADC-107, ADC-103 and non-target control ADC-108.

Figure 1D shows a plot of in vitro cell viability of BJAB cells treated with ADC-101, ADC-113, ADC-103, ADC-111, and ADC-112.

Figure 1E shows a plot of in vitro cell viability of WSU-DLCL2 cells treated with ADC-101, ADC-113, ADC-103, ADC-111, and ADC-112.

Figure 1F shows a plot of in vitro cell viability of SK-BR-3 cells treated with ADC-108, ADC-102, ADC-203, ADC-201, and ADC-107.

Figure 1G shows a plot of in vitro cell viability of KPL-4 cells treated with ADC-108, ADC-102, ADC-203, ADC-201, and ADC-107.

Figure 2 shows the efficacy of antibody-drug conjugates in a plot of the *in vivo* fitted tumor volume change over time in the WSU-DLCL2 xenograft model in CB-17 Fox Chase SCID mice, dosed IV once with the following:

1) Vehicle (Histidine Buffer #8), 100 μ L

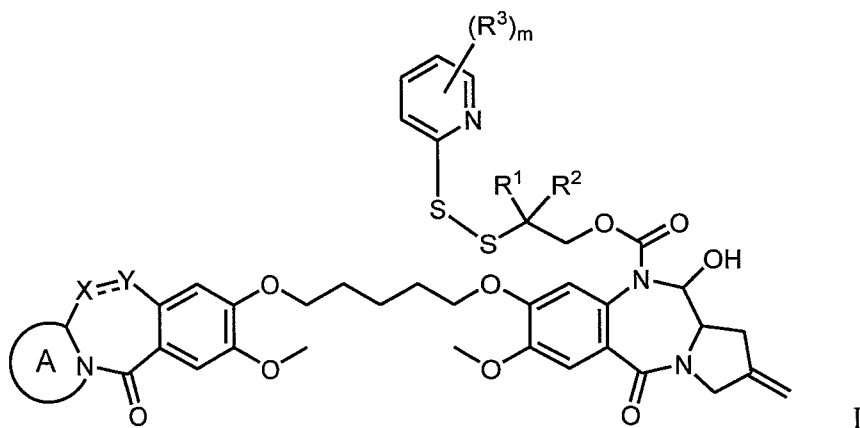
2) Thio Hu anti-CD22 10F4v3 LC K149C-(CLD-1), ADC-202, 0.5 mg/kg

3) Thio Hu anti-CD22 10F4v3 LC K149C-(CLD-1), ADC-202, 2 mg/kg

4) Thio Hu anti-CD22 10F4v3 LC K149C-(LD-51), monoamide, ADC-103, 2 mg/kg

We Claim:

1. A linker-drug intermediate of Formula I:



wherein $X=Y$ is selected from $\text{CH}_2\text{-CH}_2$, CH=CH , C(=O)-NH , or $\text{CH}_2\text{-NH}$;

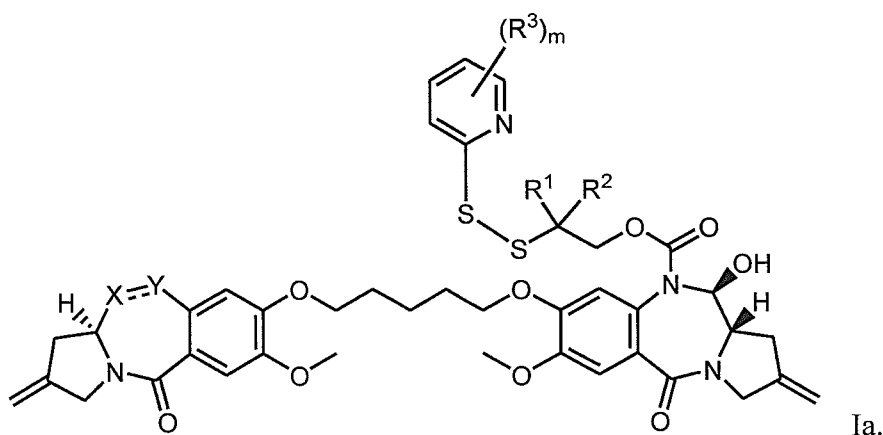
A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, $\text{C}_1\text{-C}_6$ alkyl, or =C(R)_2 where R is independently selected from H, F, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ fluoroalkyl;

R^1 and R^2 are independently selected from H or $\text{C}_1\text{-C}_6$ alkyl, or R^1 and R^2 form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

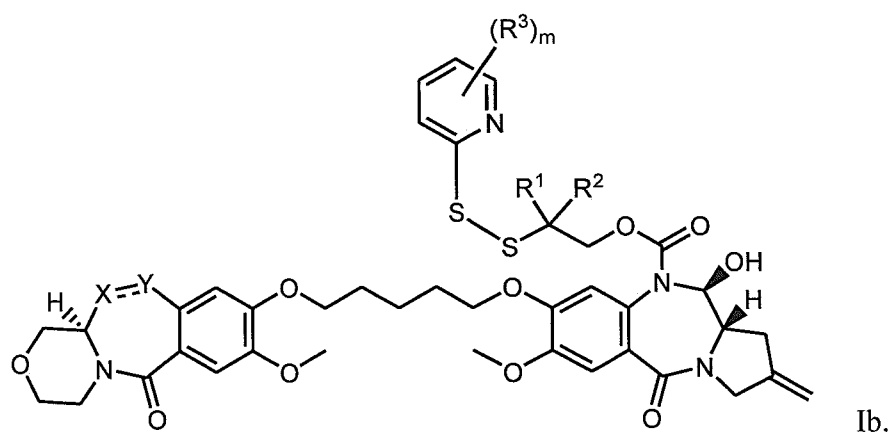
R^3 is independently selected from NO_2 , Cl, F, CN, CO_2H or Br; and

m is 1 or 2.

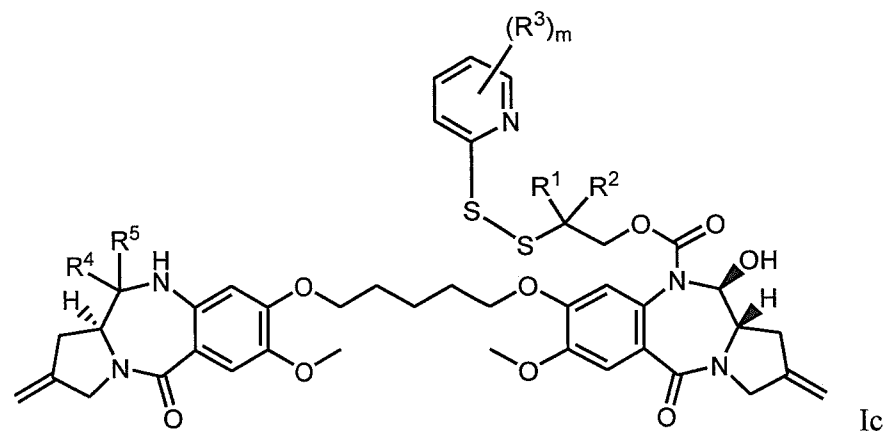
2. The linker-drug intermediate of claim 1 of Formula Ia:



3. The linker-drug intermediate of claim 1 of Formula Ib:

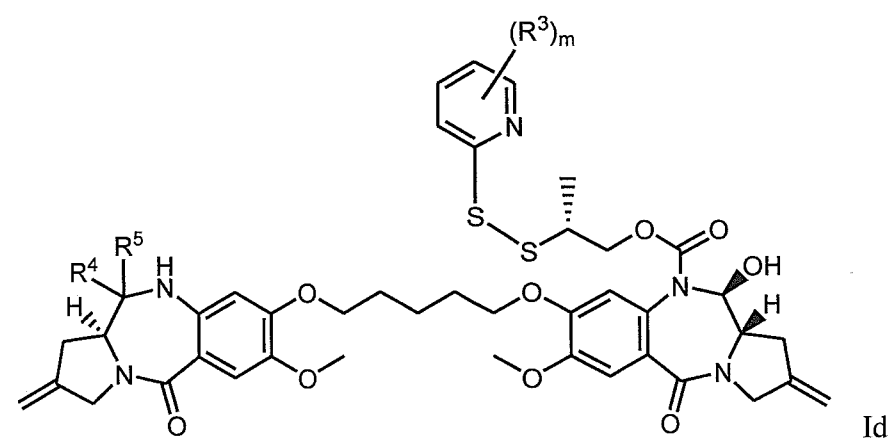


4. The linker-drug intermediate of claim 1 of Formula Ic:



wherein R^4 and R^5 are each H, or R^4 and R^5 are =O.

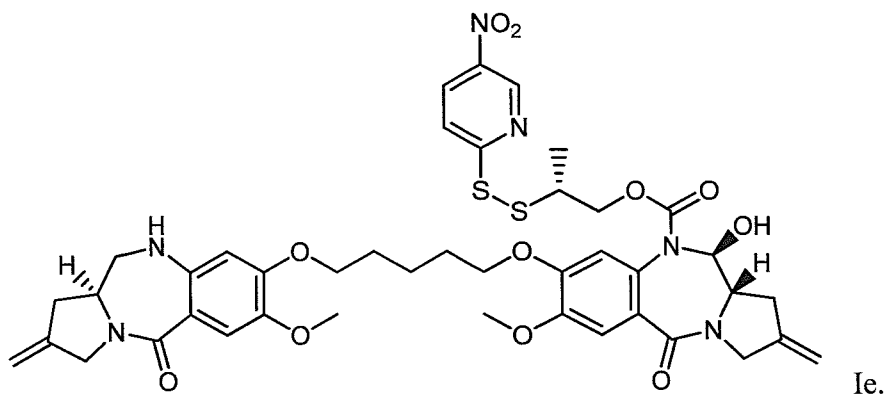
5. The linker-drug intermediate of claim 1 of Formula Id:



wherein R^4 and R^5 are each H, or R^4 and R^5 are =O.

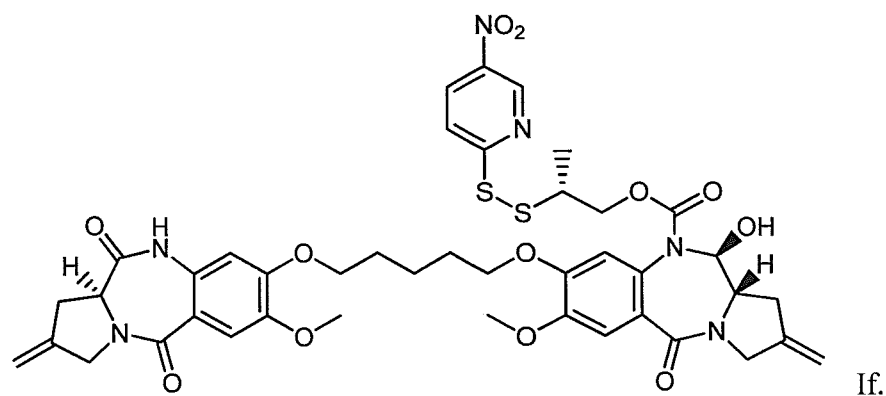
6. The linker-drug intermediate of claim 4 wherein R^4 and R^5 are each H.

7. The linker-drug intermediate of claim 1 of Formula Ie:



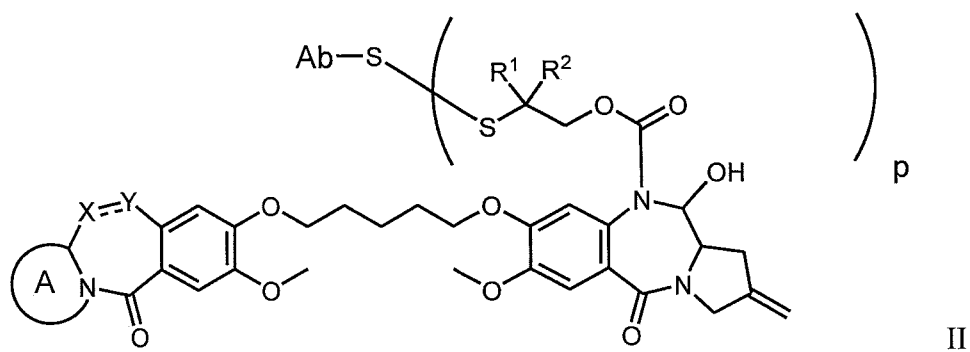
8. The linker-drug intermediate of claim 4 wherein R^4 and R^5 are =O.

9. The linker-drug intermediate of claim 1 of Formula If:



10. The linker-drug intermediate of claim 1 wherein R^1 and R^2 along with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring.

11. An antibody-drug conjugate compound of Formula II:



or a pharmaceutically acceptable salt thereof, wherein:

X=Y is selected from CH₂-CH₂, CH=CH, C(=O)-NH and CH₂-NH;

A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, C₁-C₆ alkyl, or =C(R)₂ where R is independently selected from H, F, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R¹ and R² are independently selected from H or C₁-C₆ alkyl, or R¹ and R² form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

p is an integer from 1 to 8; and

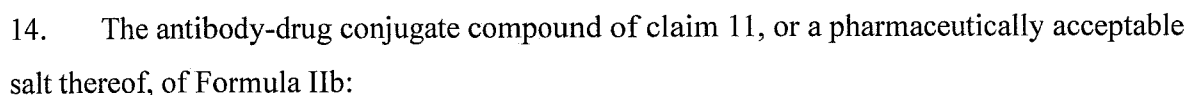
Ab is an antibody.

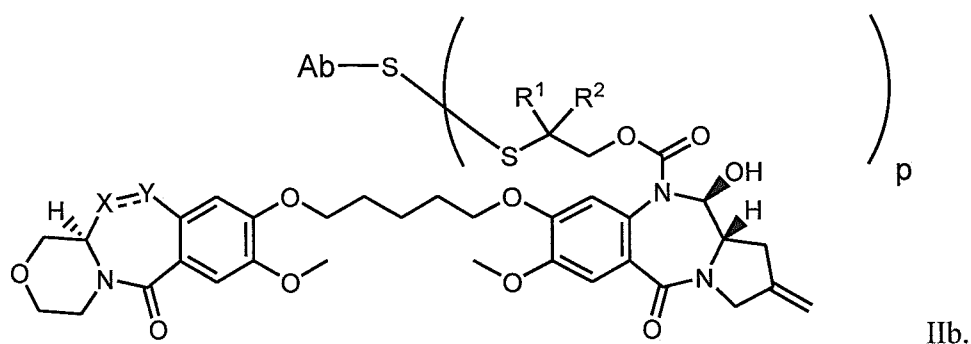
12. The antibody-drug conjugate compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(53):

- (1) BMPR1B (bone morphogenetic protein receptor-type IB);
- (2) E16 (LAT1, SLC7A5);
- (3) STEAP1 (six transmembrane epithelial antigen of prostate);
- (4) MUC16 (0772P, CA125);
- (5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);
- (6) Napi2b (NAPI-3B, NPTIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);
- (7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);
- (8) PSCA hlg (2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);
- (9) ETBR (Endothelin type B receptor);
- (10) MSG783 (RNF124, hypothetical protein FLJ20315);
- (11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);
- (12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

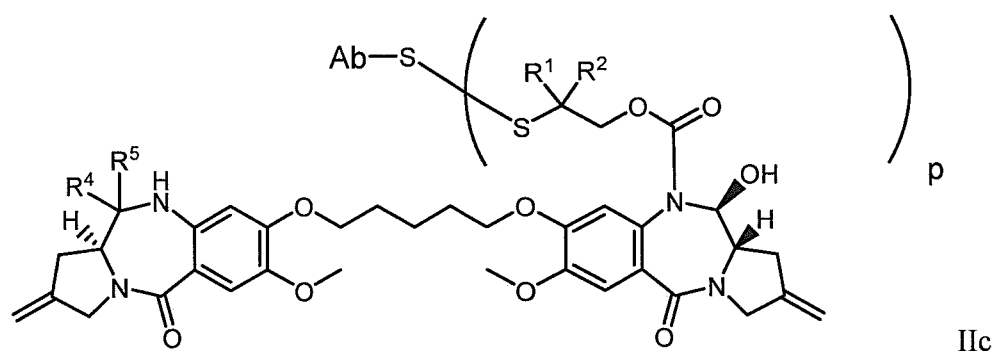
- (13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);
- (14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);
- (15) CD79b (CD79B, CD79 β , Igb (immunoglobulin-associated beta), B29);
- (16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C);
- (17) HER2;
- (18) NCA;
- (19) MDP;
- (20) IL20R α ;
- (21) Brevican;
- (22) EphB2R;
- (23) ASLG659;
- (24) PSCA;
- (25) GEDA;
- (26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);
- (27) CD22 (B-cell receptor CD22-B isoform);
- (28) CD79a (CD79A, CD79 α , immunoglobulin-associated alpha);
- (29) CXCR5 (Burkitt's lymphoma receptor 1);
- (30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));
- (31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);
- (32) CD72 (B-cell differentiation antigen CD72, Lyb-2);
- (33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);
- (34) FcRH1 (Fc receptor-like protein 1);
- (35) FcRH5 (IRTA2, Immunoglobulin superfamily receptor translocation associated 2);
- (36) TENB2 (putative transmembrane proteoglycan);
- (37) PMEL17 (silver homolog; SILV; D12S53E; PMEL17; SI; SIL);
- (38) TMEFF1 (transmembrane protein with EGF-like and two follistatin-like domains 1; Tomoregulin-1);

13. The antibody-drug conjugate compound of claim 11, or a pharmaceutically acceptable salt thereof, of Formula IIa:





15. The antibody-drug conjugate compound of claim 11, or a pharmaceutically acceptable salt thereof, of Formula IIc:

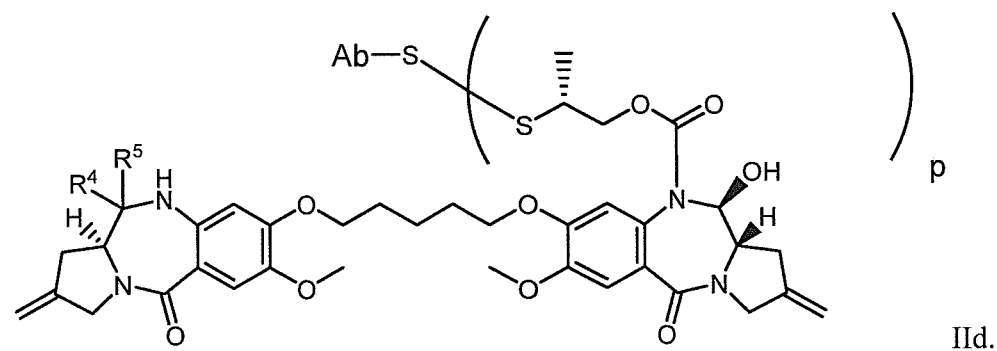


wherein R^4 and R^5 are each H, or R^4 and R^5 are =O.

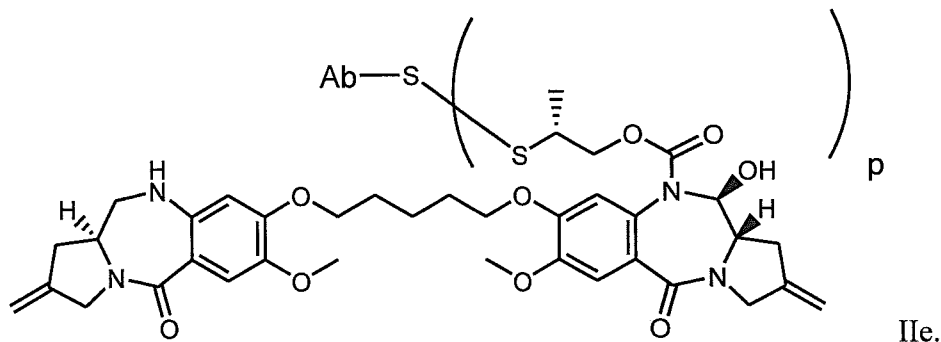
16. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 15 wherein R⁴ and R⁵ are each H.

17. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 15 wherein R⁴ and R⁵ are =O.

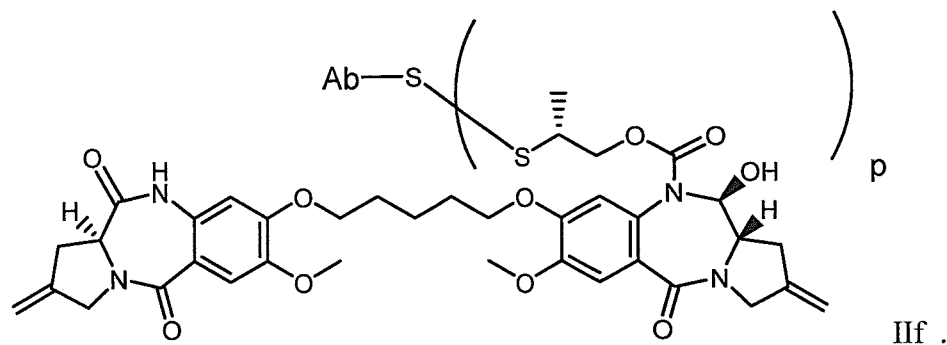
18. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 15 having Formula IIId:



19. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 15 having Formula IIe:



20. The antibody-drug conjugate compound of claim 15, or a pharmaceutically acceptable salt thereof, having Formula II:



21. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 11, wherein Ab is a cysteine-engineered antibody.

22. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 21, wherein the cysteine-engineered antibody comprises LC K149C or HC A118C as the site of drug conjugation.

23. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 11, wherein Ab is selected from anti-HER2, anti-CD22, anti-CD33, anti-Napi2b, or anti-CLL-1.

24. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 11, wherein p is 1, 2, 3, or 4.

25. A mixture of antibody-drug conjugate compounds, or pharmaceutically acceptable salts thereof, according to claim 11, wherein the average drug loading per antibody, p, in the mixture of antibody-drug conjugate compounds is 2 to 5.

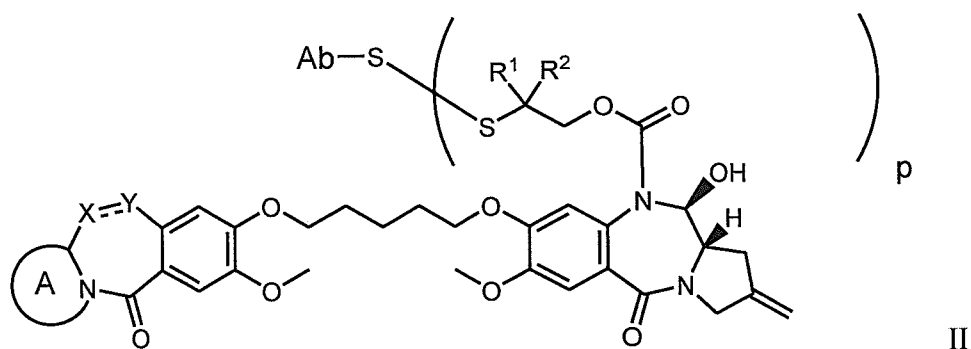
26. A pharmaceutical composition comprising the antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 11 and a pharmaceutically acceptable excipient.

27. Use of a therapeutically effective amount of the pharmaceutical composition of claim 26 in the manufacture of a medicament for treating a HER2-positive cancer.

28. The use of claim 27 wherein the patient is administered a chemotherapeutic agent, in combination with an antibody-drug conjugate according to claim 11, or a pharmaceutically acceptable salt thereof.

29. A method of making an antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 11, the method comprising reacting an antibody with a linker-drug intermediate of Formula I of claim 1.

30. An antibody-drug conjugate compound of Formula II.



or a pharmaceutically acceptable salt thereof, wherein:

X=Y is selected from CH₂-CH₂, CH=CH, C(=O)-NH and CH₂-NH;

A is a 5-membered or 6-membered heterocyclic ring, optionally substituted with a group selected from F, C₁-C₆ alkyl, or =C(R)₂ where R is independently selected from H, F, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R¹ and R² are independently selected from H or C₁-C₆ alkyl, or R¹ and R² form a 3, 4, 5, or 6-membered cycloalkyl or heterocyclyl group;

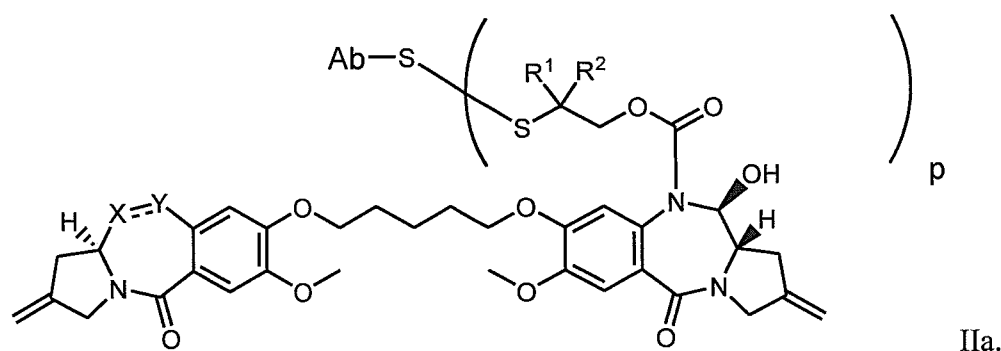
p is an integer from 1 to 8; and

Ab is an anti-HER2 antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1

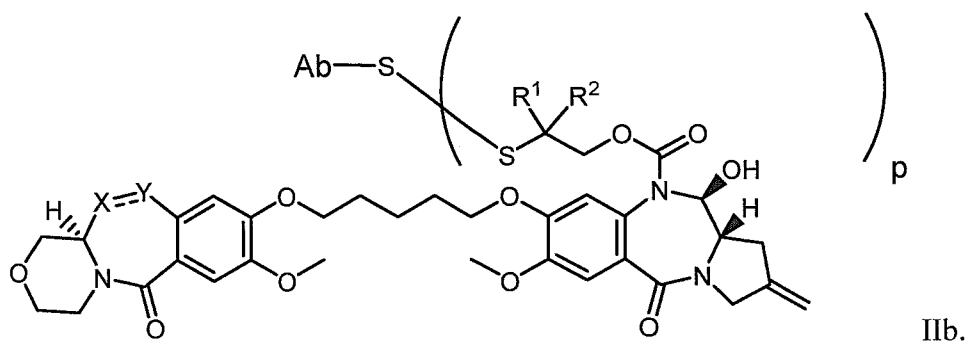
comprising the amino acid sequence of SEQ ID NO: 19; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 20; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 21.

31. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 30, wherein the anti-HER2 antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 17 and a heavy chain variable region comprising the sequence of SEQ ID NO: 18.

32. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 30 having Formula IIa:



33. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 30 having Formula IIb:



34. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 30 having Formula IIc:



wherein R^4 and R^5 are each H, or R^4 and R^5 are =O.

35. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 34 wherein R⁴ and R⁵ are each H.

36. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 34 wherein R⁴ and R⁵ are =O.

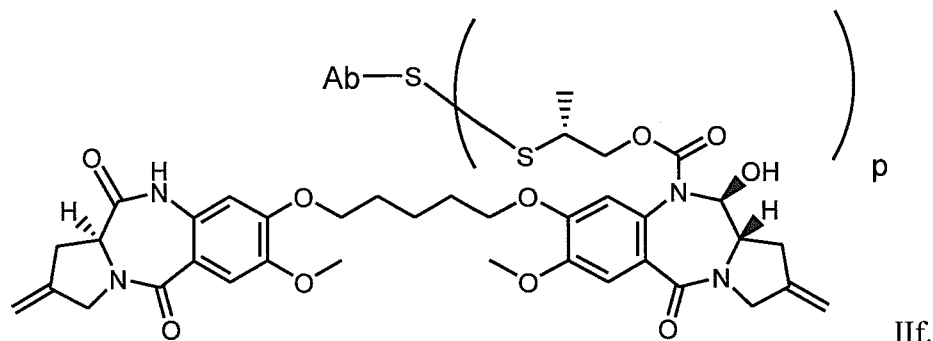
37. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 34 having Formula IIId:



38. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 34 having Formula IIe:



39. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 34 having Formula II*f*:



40. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 30, wherein the anti-HER2 antibody is a cysteine-engineered antibody.

41. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 40, wherein the cysteine-engineered antibody comprises LC K149C or HC A118C as the site of drug conjugation.

42. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 30, wherein *p* is 1, 2, 3, or 4.

43. A mixture of antibody-drug conjugate compounds, or pharmaceutically acceptable salts thereof, according to claim 30, wherein the average drug loading per antibody, *p*, in the mixture of antibody-drug conjugate compounds is 2 to 5.

44. A pharmaceutical composition comprising the antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 30 and a pharmaceutically acceptable excipient.

45. Use of a therapeutically effective amount of the antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 30 in the manufacture of a medicament for treating cancer, wherein the cancer is a HER2-positive cancer.

46. The use of claim 45, wherein the HER2-positive cancer is breast cancer or gastric cancer.

47. The use of claim 45, further comprising administering to a patient an additional therapeutic agent.

48. The use of claim 47, wherein the additional therapeutic agent is a chemotherapeutic agent.

49. The use of claim 47, wherein the additional therapeutic agent is an antibody or immunoconjugate that binds HER2.

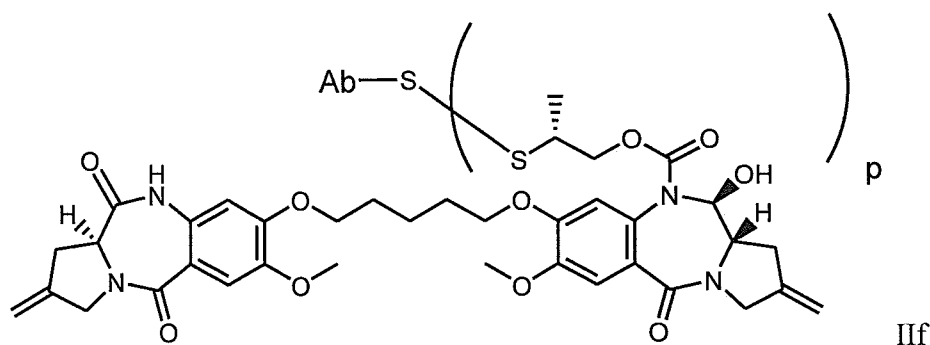
50. The use of claim 49, wherein the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to domain II of HER2, and/or (ii) an antibody or immunoconjugate that binds to domain IV or HER2.

51. The use of claim 47, wherein the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to epitope 2C4, and/or (ii) an antibody or immunoconjugate that binds to epitope 4D5.

52. The use of claim 49, wherein the additional therapeutic agent is selected from trastuzumab, trastuzumab-MCC-DM1 (T-DM1), or pertuzumab.

53. The use of claim 49, further comprising administering to the patient (1) trastuzumab or T-DM1, and (2) pertuzumab.

54. An antibody drug conjugate, or a pharmaceutically acceptable salt thereof, of Formula II f



wherein Ab is a cysteine-engineered anti-HER2 antibody comprising LC K149C, and p is about 2.

55. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 54, wherein Ab is an anti-HER2 antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence

of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 19; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 20; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 21.

56. The antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, of claim 54, wherein the anti-HER2 antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 17 and a heavy chain variable region comprising the sequence of SEQ ID NO: 18.

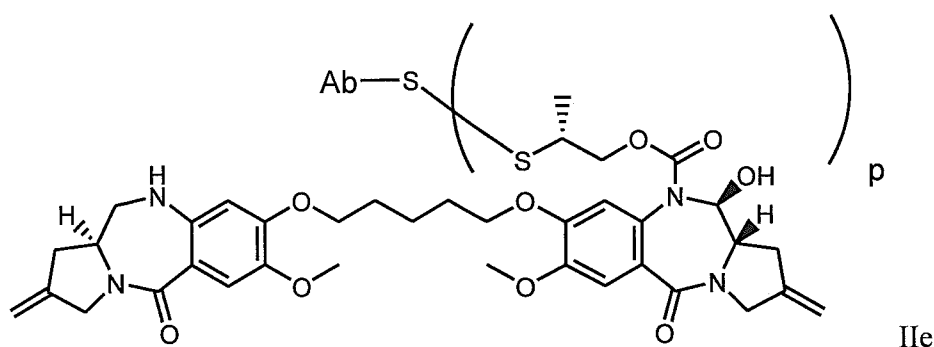
57. A pharmaceutical composition comprising the antibody-drug conjugate compound, or a pharmaceutically acceptable salt thereof, according to claim 54 to and a pharmaceutically acceptable excipient.

58. The antibody-drug conjugate compound of claim 54, wherein the anti-HER2 antibody comprises: (i) the heavy chain sequence of SEQ ID NO:26 and the light chain sequence of SEQ ID NO:30; or (ii) the heavy chain sequence of SEQ ID NO:31 and the light chain sequence of SEQ ID NO:25.

59. The antibody drug conjugate compound of claim 54 wherein p is about 2.

60. The antibody-drug conjugate compound of claim 54 wherein the cysteine-engineered antibody comprises K149C substitution in the light chain according to Kabat numbering; or A118C substitution in the heavy chain according to EU numbering as the site of drug conjugation.

61. An antibody drug conjugate of Formula IIe



wherein Ab is a cysteine-engineered anti-HER2 antibody, and p is about 2.

62. The antibody-drug conjugate compound of claim 61, wherein Ab is an anti-HER2 antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 19; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 20; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 21.

63. The antibody-drug conjugate compound of claim 61, wherein the anti-HER2 antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 17 and a heavy chain variable region comprising the sequence of SEQ ID NO: 18.

64. A pharmaceutical composition comprising the antibody-drug conjugate compound according to claim 61 and a pharmaceutically acceptable excipient.

65. The antibody-drug conjugate compound of claim 61, wherein the anti-HER2 antibody comprises: (i) the heavy chain sequence of SEQ ID NO:26 and the light chain sequence of SEQ ID NO:30; or (ii) the heavy chain sequence of SEQ ID NO:31 and the light chain sequence of SEQ ID NO:25.

66. The antibody drug conjugate compound of claim 61 wherein p is about 2.

67. The antibody-drug conjugate compound of claim 61 wherein the cysteine-engineered antibody comprises K149C substitution in the light chain according to Kabat numbering; or A118C substitution in the heavy chain according to EU numbering as the site of drug conjugation.