CLAIMS

1. An antibody-drug conjugate comprising an . antibody covalently attached to one or more drug moieties, the antibody-drug conjugate having Formula Ic:

$$Ab-\left(A_a-W_w-Y_y-D\right)_p \qquad \text{Ic}$$

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Ab is an antibody which binds to one or more tumor-associated antigens selected from the group consisting of:

BMPR1B i.e. bone morphogenetic protein receptor-type IB;

E16 i.e. LAT1, SLC7A5;

STEAP1 i.e. six transmembrane epithelial antigen of prostate;

0772P i.e. CA125, MUC16;

MPF i.e. MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin;

Napi3b i.e. NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b;

Sema 5b i.e. FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain,; seven thrombospondin repeats i.e. type 1 and type 1-like; transmembrane domain and short cytoplasmic domain, semaphorin 5B;

PSCA hlg i.e. 2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene;

ETBR i.e. Endothelin type B receptor;

MSG783 i.e. RNF124, hypothetical protein FLJ20315;

STEAP2 i.e. 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;

TrpM4 i.e. BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4;

CRIPTO i.e. CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor;

CD21 i.e. Complement receptor 2 or C3d/Epstein Barr virus receptor or Hs.73792 ;

CD79b i.e. immunoglobulin-associated beta, B29;

FcRH2 i.e. IFGP4, IRTA4; SPAP1A i.e. SH2 domain containing phosphatase anchor protein 1a; SPAP1B, SPAP1C;

HER2 ;

NCA ;

MDP ;

IL20Rα ;

Brevican ;

Ephb2R ;

ASLG659 ;

PSCA ;

GEDA ;

BAFF-R ;

CD22 ;

CD79a i.e..CD79A, CD79α, immunoglobulin-associated alpha;

CXCR5 i.e. Burkitt's lymphoma receptor 1;

HLA-DOB i.e. Beta subunit of MHC class II molecule Ia antigen that binds peptides and presents them to CD4+ T lymphocytes;

P2X5 i.e. Purinergic receptor P2X ligand-gated ion channel 5;

CD72 i.e. B-cell differentiation antigen CD72, Lyb-2;

LY64 i.e. Lymphocyte antigen 64 i.e. RP105; type I membrane protein of the leucine rich repeat family;

FCRH1 i.e. Fc receptor-like protein 1; and

IRTA2 i.e. Immunoglobulin superfamily receptor translocation associated 2,

A is a Stretcher unit,

a is 0 or 1,

each W is independently an Amino Acid unit,

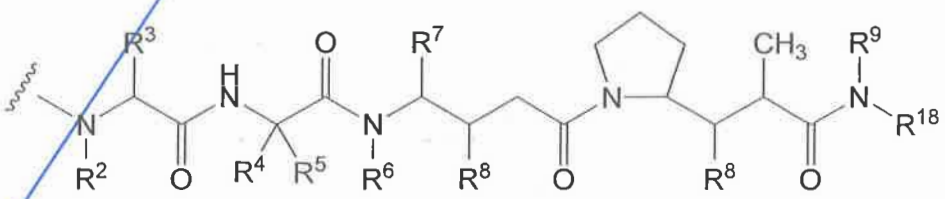
w is an integer ranging from 0 to 12,

Y is a Spacer unit, and

y is 0, 1 or 2,

p ranges from 1 to 20, and

D is a drug moiety having Formulae D_E:



D_E

wherein the wavy line of D_E indicates the covalent attachment site to A, W, or Y, and independently at each location:

R^2 is C_1-C_8 alkyl;

R^3 is C_1-C_8 alkyl;

R^4 is C_1-C_8 alkyl;

R^5 is H;

R^6 is C_1-C_8 alkyl;

R^7 is C_1-C_8 alkyl;

each R^8 is independently O-C_1-C_8 alkyl;

R^9 is H ; and

R^{18} is–$CH(CH_3)$-CH(OH)-phenyl.

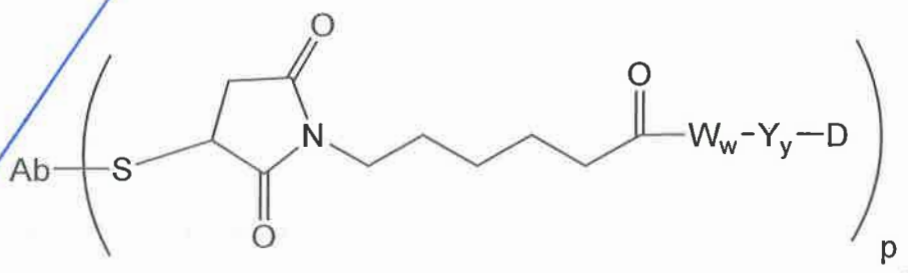
2. The antibody-drug conjugate of claim **1**, wherein the antibody is attached to the drug moiety through a cysteine residue of the antibody.

3. The antibody-drug conjugate of claim **2**, wherein p is 1 to 4.

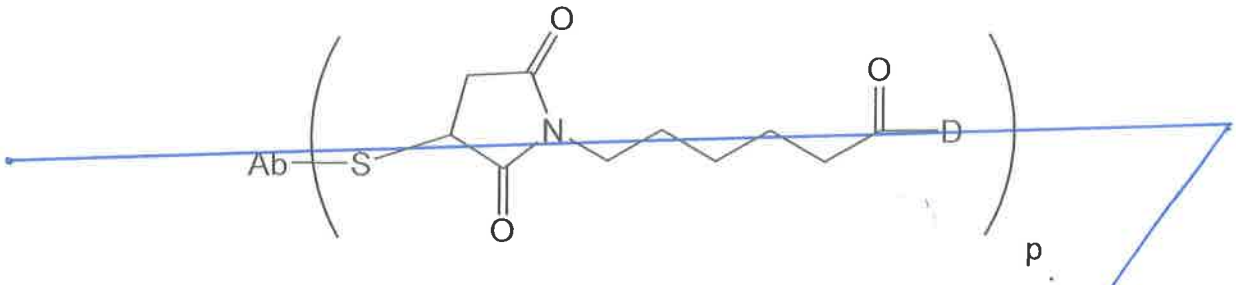
4. The antibody-drug conjugate of claim **1**, wherein p is 2 to 8.

5. The antibody-drug conjugate of claim **1**, wherein p is 2 to 5.

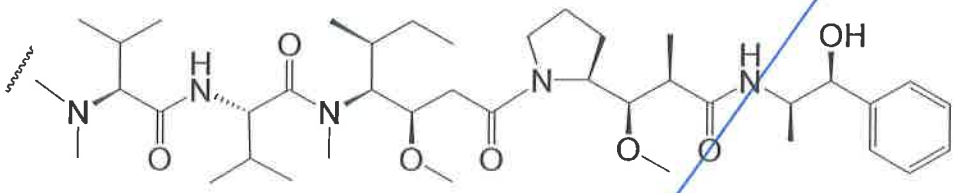
6. The antibody-drug conjugate of claim **2**, having the formula:



7. The antibody-drug conjugate of claim **6**, having the formula:

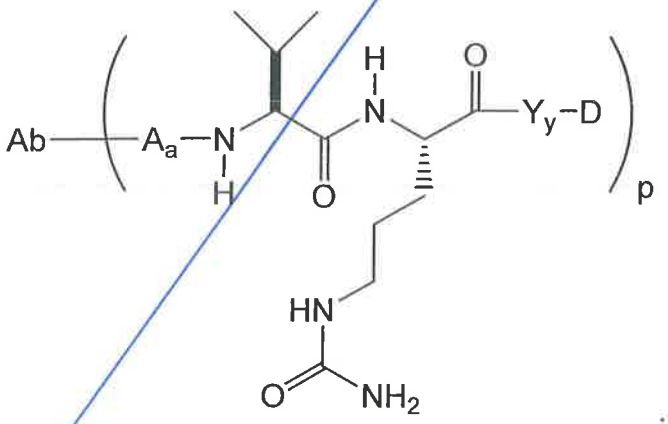


8. The antibody-drug conjugate of claim **7**, wherein D has the formula:

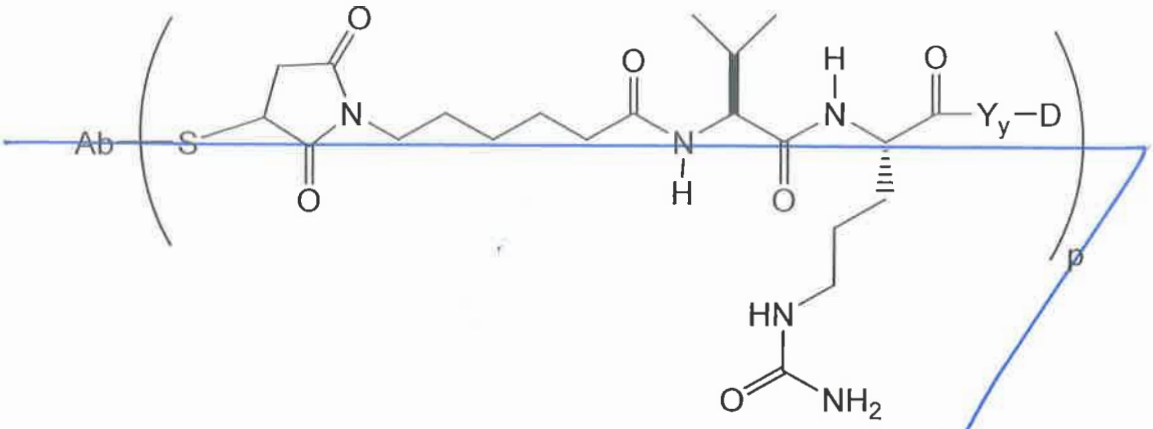


and pharmaceutically acceptable salts and solvates thereof.

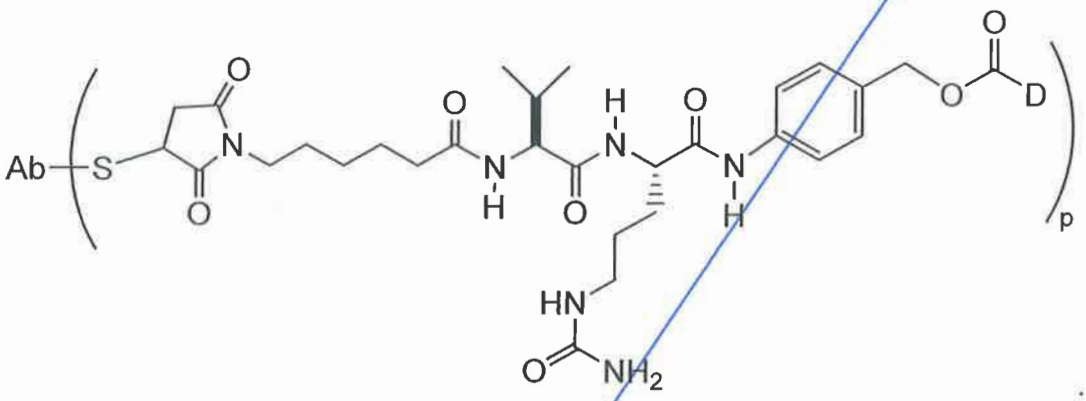
9. The antibody-drug conjugate of claim **1**, having the formula:



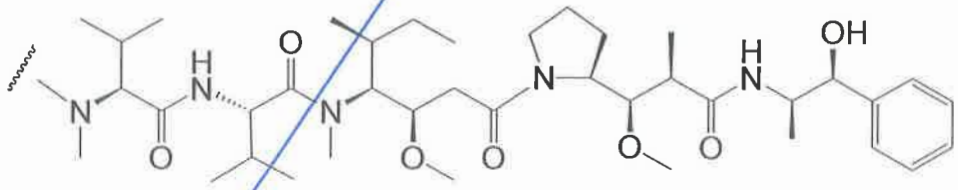
10. The antibody-drug conjugate of claim **9**, having the formula:



11. The antibody-drug conjugate of claim **10**, having the formula:



12. The antibody-drug conjugate of claim **11**, wherein Formula D_E has the formula:



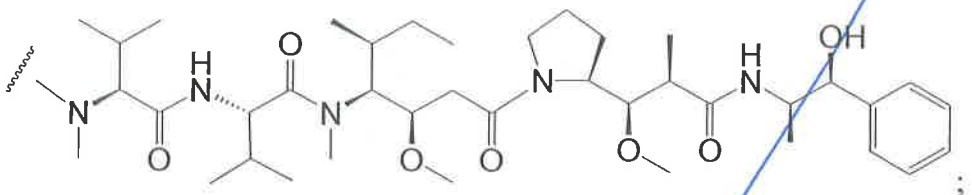
or a pharmaceutically acceptable salt or solvate thereof.

13. The antibody-drug conjugate of claim **1**, wherein w is an integer ranging from 2 to 12.

14. The antibody-drug conjugate of claim **1**, wherein w is 2.

15. The antibody-drug conjugate of claim 1, wherein W_w is -valine-citrulline-.

16. The antibody-drug conjugate of claim 1, wherein D is:



;

or a pharmaceutically acceptable salt or solvate thereof.

17. The antibody-drug conjugate of claim 1, wherein the antibody specifically binds to a HER2 receptor.

18. The antibody-drug conjugate of claim 17, which specifically binds to the extracellular domain of the HER2 receptor and inhibits growth of tumor cells which overexpress HER2 receptor.

19. The antibody-drug conjugate of claim 1, wherein the antibody is selected from the group consisting of a monoclonal antibody, a bispecific antibody, a chimeric antibody, a humanized antibody, and an antibody fragment.

20. The antibody-drug conjugate of claim 19, wherein the antibody fragment is a Fab fragment.

21. The antibody-drug conjugate of claim 19, wherein the humanized antibody is selected from the group consisting of huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8 i.e. trastuzumab.

22. The antibody-drug conjugate of claim 21, wherein the antibody is huMAb4D5-8 i.e. trastuzumab.

23. A pharmaceutical composition comprising an effective amount of the antibody-drug conjugate of any of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable diluent, carrier or excipient.

24. The pharmaceutical composition of claim 23, further comprising a therapeutically effective amount of chemotherapeutic agent selected from a tubulin-forming inhibitor, a topoisomerase inhibitor, and a DNA binder.

25. A use of the antibody-drug conjugate of any of claims **1-22**, in the manufacture of a medicament for treating cancer selected from the group consisting of a lymphoma, breast cancer, non-small cell lung cancer and kidney cancer.

26. The use of claim **25**, wherein the cancer is breast cancer.

27. The use of claim **25**, wherein the medicament further comprises an effective amount of an additional anticancer agent, an immunosuppressant agent or an anti-infectious agent.

28. The use of claim **25**, wherein the cancer is a lymphoma.

29. The use of claim **28**, wherein the lymphoma is a non-Hodgkin's Lymphoma.

30. A method of inhibiting cellular proliferation comprising:

exposing mammalian cells in a cell culture medium to the antibody-drug conjugate of any of claims **1-22**, and

measuring a cytotoxic activity of the antibody-drug conjugate,

whereby proliferation of the cells is inhibited.

31. The use of claim **25**, wherein the cancer is kidney cancer.

32. The use of claim **25**, wherein the antibody-drug conjugate specifically binds to a receptor encoded by an ErbB2 gene.

33. The use of claim **25**, wherein said antibody-drug conjugate is formulated with a pharmaceutically acceptable parenteral vehicle.

34. The use of claim **25**, wherein said antibody-drug conjugate is formulated in a unit dosage injectable form.

35. The use of claim 25, further comprising the administration of a second antibody which binds a tumor-associated antigen selected from:

BMPR1B i.e. bone morphogenetic protein receptor-type IB;

E16 i.e. LAT1, SLC7A5;

STEAP1 i.e. six transmembrane epithelial antigen of prostate;

0772P i.e. CA125, MUC16, Genbank accession no. AF361486;

MPF i.e. MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin;

Napi3b i.e. NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b

Sema 5b i.e. FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain,; seven thrombospondin repeats i.e. type 1 and type 1-like; transmembrane domain and short cytoplasmic domain, semaphorin 5B;

PSCA hlg i.e. 2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene;

ETBR i.e. Endothelin type B receptor;

MSG783 i.e. RNF124, hypothetical protein FLJ203153;

STEAP2 i.e. 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;

TrpM4 i.e. BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4;

CRIPTO i.e. CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor;

CD21 i.e. Complement receptor 2 or C3d/Epstein Barr virus receptor or Hs.73792;

CD79b i.e. immunoglobulin-associated beta, B29;

FcRH2 i.e. IFGP4, IRTA4; SPAP1A i.e. SH2 domain containing phosphatase anchor protein 1a; SPAP1B, SPAP1C;

HER2 ;

NCA ;

MDP ;

IL20Rα ;

Brevican ;

Ephb2R ;

ASLG659;

PSCA;

GEDA;

BAFF-R;

CD22 ;

CD79a i.e. CD79A, CD79α, immunoglobulin-associated alpha;

CXCR5 i.e. Burkitt's lymphoma receptor 1;

HLA-DOB i.e. Beta subunit of MHC class II molecule Ia antigen that binds peptides and presents them to CD4+ T lymphocytes;

P2X5 i.e. Purinergic receptor P2X ligand-gated ion channel 5;

CD72 i.e. B-cell differentiation antigen CD72, Lyb-2;

LY64 i.e. Lymphocyte antigen 64 i.e. RP105; type I membrane protein of the leucine rich repeat family;

FCRH1 i.e. Fc receptor-like protein 1; and

IRTA2 i.e. Immunoglobulin superfamily receptor translocation associated 2.

36. The use of claim **35**, wherein said second antibody is conjugated with a cytotoxic agent.

37. The use of claim **25**, further comprising an additional chemotherapeutic agent.

38. An article of manufacture comprising:

an antibody-drug conjugate of any of claims **1-22**,

a container; and

a package insert or label indicating that the antibody-drug conjugate can be used for the detection of cancer cells.

39. The article of manufacture of claim **38**, wherein the cells are breast tumor cells.

40. The article of manufacture of claim **38**, wherein the detection is determined by measuring levels of tumor-associated antigen-encoding nucleic acid by fluorescent *in situ* hybridization.

41. The article of manufacture of claim **38**, wherein the detection is determined by immunohistochemistry.

42. An article of manufacture comprising:

an antibody-drug conjugate of any of claims **1-22**;

a container; and

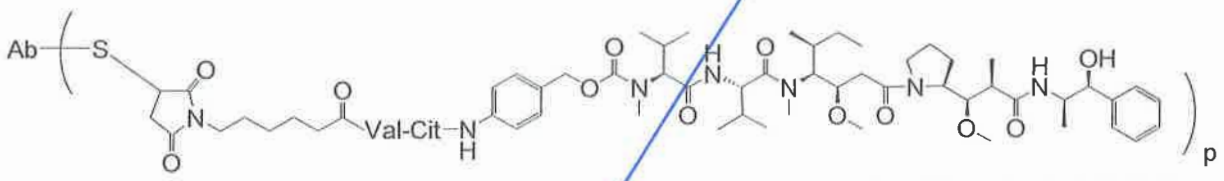
a package insert or label indicating that the antibody-drug conjugate can be used to treat cancer.

43. The article of manufacture of claim **38**, wherein said package insert or label indicates that the antibody-drug conjugate can be used to treat cancer characterized by the overexpression of an ErbB2 receptor.

44. The article of manufacture of claim **38**, wherein the cancer is breast cancer.

45. The use of claim **25**, wherein the cancer is further characterized by the overexpression of an ErbB2 (HER2) receptor and does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody.

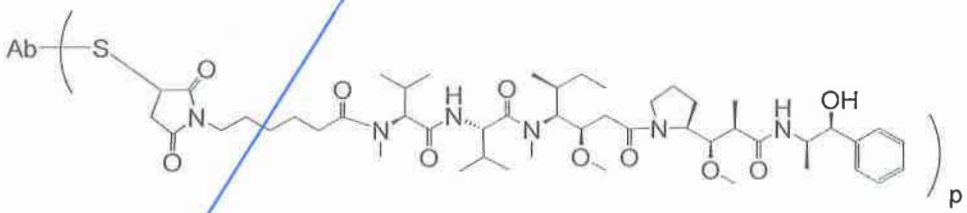
46. The antibody-drug conjugate of claim **1**, having the formula:



Ab-MC-vc-PAB-MMAE;

or a pharmaceutically acceptable salt thereof, wherein Val is valine, and Cit is citrulline.

47. The antibody-drug conjugate of claim **1**, having the formula:



Ab-MC-MMAE.

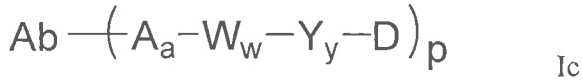
48. The use of an antibody-drug conjugate of any one of claims **1-22**, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament to treat a hematopoietic cancer.

49. The use of claim 48, wherein the hematopoietic cancer is Non-Hodgkins lymphoma.

[CLAIMS]

[Claim 1] A composition for treating cancer comprising an antibody-drug conjugate compound comprising an antibody covalently attached to one or more drug moieties, the compound having Formula Ic:

[Chemical formula 56]



Ic

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Ab is an antibody which binds to one or more tumor-associated antigens selected from (3)-(6), (9), (15), (17), (22), (24), (27), and (35):

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(9) ETBR (Endothelin type B receptor);

(15) CD79b (IGb (immunoglobulin-associated beta), B29);

(17) HER2;

(22) Ephb2R;

(24) PSCA;

(27) CD22; and

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2),

A is a Stretcher unit,

a is 0 or 1,

each W is independently an Amino Acid unit,

w is an integer ranging from 0 to 12,

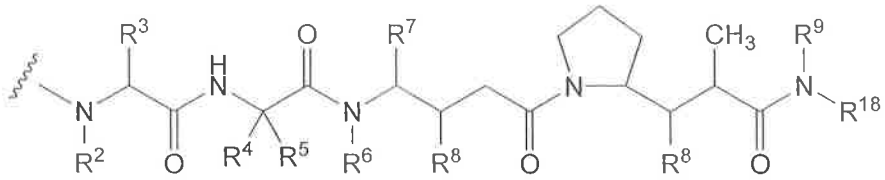
Y is a Spacer unit, and

y is 0, 1 or 2,

p ranges from 2 to 5, and

D has Formula D_E:

[Chemical formula 58]



D_E

wherein the wavy line of D_E indicates the covalent attachment site to A, W, or Y, and independently at each location:

R^2 is selected from H and C_1-C_8 alkyl;

R^3 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^4 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

R^5 is selected from H and methyl;

or R^4 and R^5 jointly form a carbocyclic ring and have the formula $-(CR^aR^b)_n-$ wherein R^a and R^b are independently selected from the group consisting of H, C_1-C_8 alkyl and C_3-C_8 carbocycle and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R^6 is selected from H and C_1-C_8 alkyl;

R^7 is selected from H, C_1-C_8 alkyl, C_3-C_8 carbocycle, aryl, C_1-C_8 alkyl-aryl, C_1-C_8 alkyl-(C_3-C_8 carbocycle), C_3-C_8 heterocycle and C_1-C_8 alkyl-(C_3-C_8 heterocycle);

each R^8 is independently selected from the group consisting of H, OH, C_1-C_8 alkyl, C_3-C_8 carbocycle and O-(C_1-C_8 alkyl);

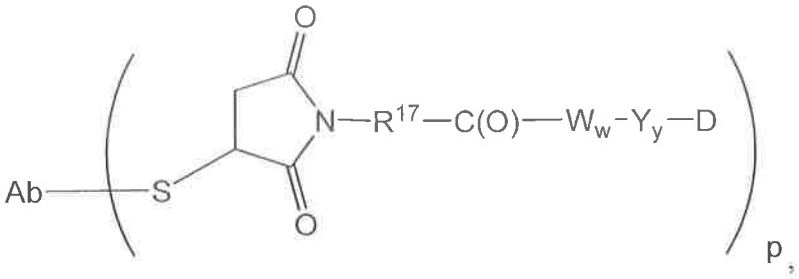
R^9 is selected from H and C_1-C_8 alkyl; and

R^{18} is selected from $-C(R^8)_2-C(R^8)_2-$aryl, $-C(R^8)_2-C(R^8)_2-(C_3$-C_8 heterocycle), and $-C(R^8)_2-C(R^8)_2-(C_3$-C_8 carbocycle).

[Claim 2] The composition of claim 1, wherein the antibody is attached to the drug moiety through a cysteine residue of the antibody.

[Claim 3] The composition of claim 1 wherein the antibody-drug conjugate compound has the formula:

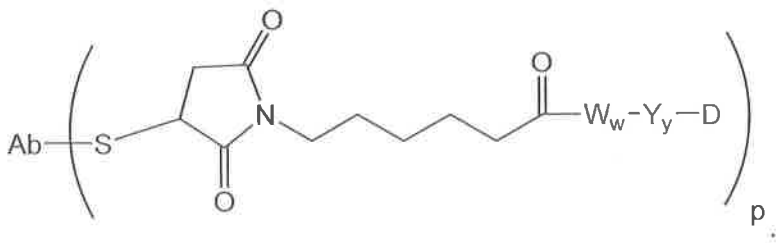
[Chemical formula 58A]



wherein Ab is an antibody and R^{17} is selected from the group consisting of -C_1-C_{10} alkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, -$(CH_2CH_2O)_r$-, and -$(CH_2CH_2O)_r$-CH_2-; and r is an integer ranging from 1 to 10.

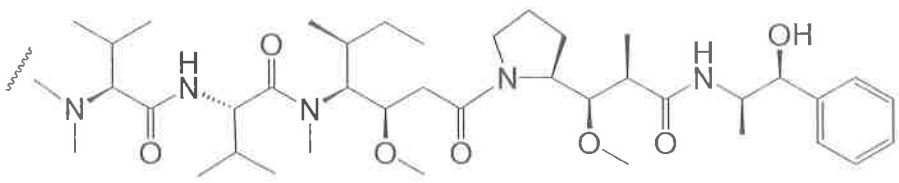
[Claim 4] The composition of claim 1 wherein the antibody-drug conjugate compound has the formula:

[Chemical formula 60A]



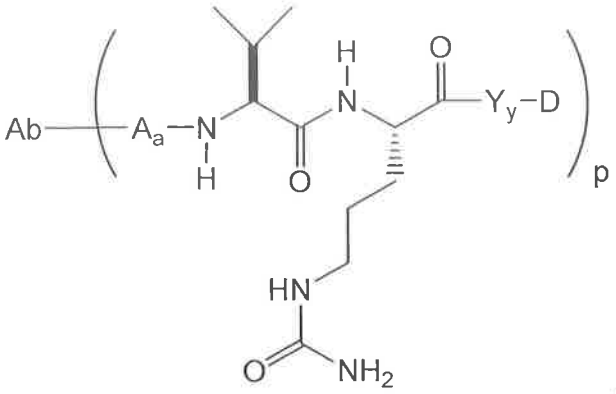
[Claim 5] The composition of claim 1 wherein Formula D_E has the formula:

[Chemical formula 62]



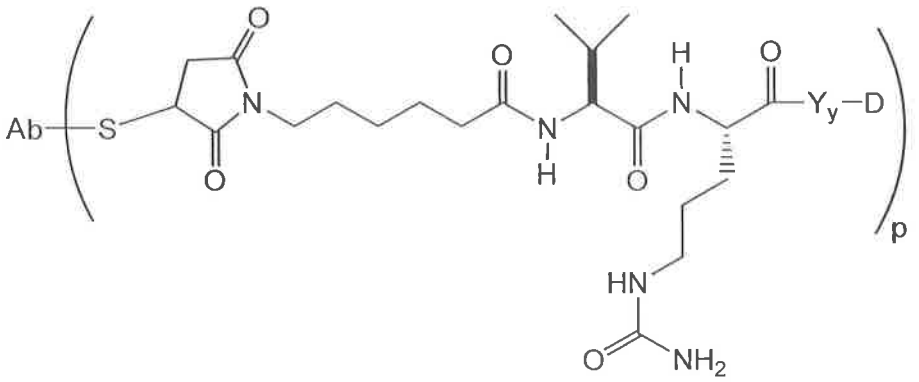
[Claim 6] The composition of claim 1 wherein the antibody-drug conjugate compound has the formula:

[Chemical formula 64]



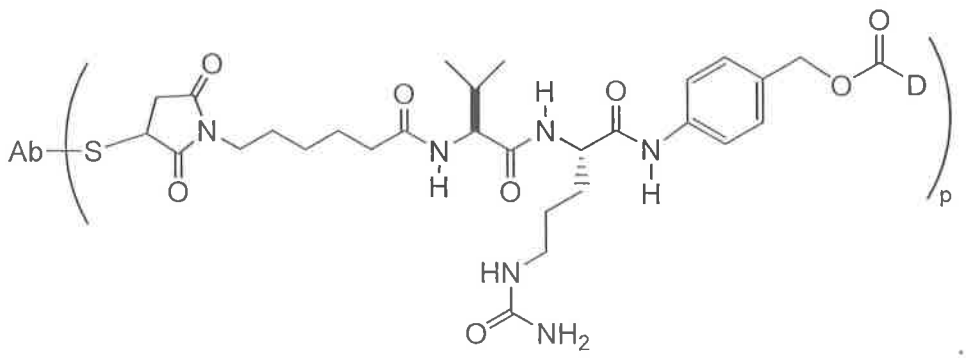
[Claim 7] The composition of claim 6 wherein the antibody-drug conjugate compound has the formula:

[Chemical formula 65]



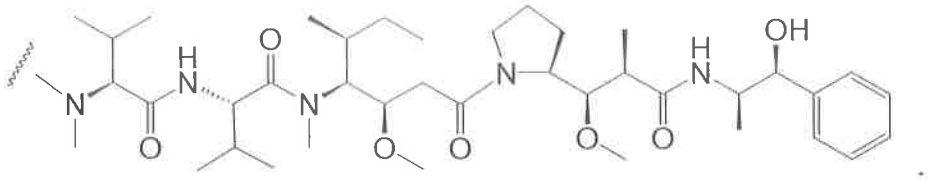
[Claim 8] The composition of claim 7 wherein the antibody-drug conjugate compound has the formula:

[Chemical formula 66]



[Claim 9] The composition of claim 8 wherein Formula D_E has the formula:

[Chemical formula 67]



[Claim 10] The composition of claim 1, wherein w is an integer ranging from 2 to 12.

[Claim 11] The composition of claim 1, wherein w is 2.

[Claim 12] The composition of claim 1, wherein W_w is -valine-citrulline-.

[Claim 13] The composition of claim 1, wherein the antibody is selected from the group consisting of a monoclonal antibody, a bispecific antibody, a chimeric antibody, a humanized antibody, and an antibody fragment.

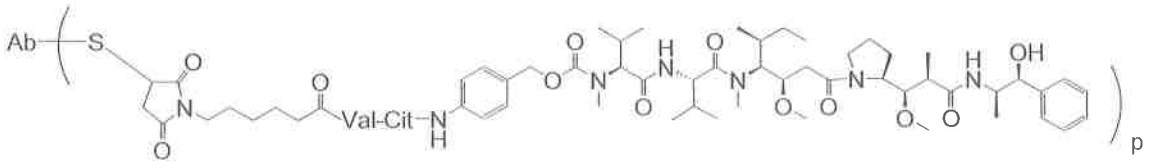
[Claim 14] The composition of claim 13, wherein the antibody fragment is a Fab fragment.

[Claim 15] The composition of claim 13, wherein the antibody is a humanized antibody selected from huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8 (trastuzumab).

[Claim 16] The composition of claim 15, wherein the antibody is huMAb4D5-8 (trastuzumab).

[Claim 17] The composition of claim 1 wherein the antibody-drug conjugate compound has the formula:

[Chemical formula 81A]



Ab-MC-vc-PAB-MMAE;

wherein Val is valine, and Cit is citrulline.

[Claim 18] The composition of claim 17, wherein the antibody is huMAb4D5-8 (trastuzumab).

[Claim 19] A pharmaceutical composition comprising an effective amount of the antibody-drug conjugate compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier or excipient.

[Claim 20] The pharmaceutical composition of claim 19 further comprising a therapeutically effective amount of chemotherapeutic agent selected from a tubulin-forming inhibitor, a topoisomerase inhibitor, and a DNA binder.

[Claim 21] A use of the antibody-drug conjugate compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, wherein the medicament is for treating cancer.

[Claim 22] The use of claim 21 wherein the cancer is selected from the group consisting of breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate, and bladder cancer.

[Claim 23] The use of claim 21 wherein the medicament further comprises an effective amount of an anticancer agent, or an immunosuppressant agent.

[Claim 24] The use of claim 21 wherein the amount of antibody-drug conjugate compound or a pharmaceutically acceptable salt thereof, is in the range of 0.1 to 10 mg/kg of patient weight.

[Claim 25] The use of claim 21 wherein the medicament is administered at about three week intervals.

[Claim 26] The use of claim 21 wherein said antibody-drug conjugate compound or a pharmaceutically acceptable salt thereof, is formulated with a pharmaceutically acceptable parenteral vehicle and is administered parenterally or formulated in a unit dosage injectable form.

[Claim 27] The use of claim 21 wherein said medicament is administered intravenously.

[Claim 28] The use of claim 21 wherein said medicament further comprises a second antibody which binds a tumor-associated antigen selected from (3)-(6), (9), (15), (17), (22), (24), (27), and (35).

[Claim 29] The use of claim 28 wherein said second antibody is conjugated with a cytotoxic agent.

[Claim 30] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (3) STEAP1.

[Claim 31] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (4) 0772P (CA125, MUC16).

[Claim 32] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (5) MPF.

[Claim 33] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (6) Napi3b.

[Claim 34] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (9) ETBR.

[Claim 35] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (15) CD79b.

[Claim 36] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (17) HER2.

[Claim 37] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (27) CD22.

[Claim 38] The composition of claim 1 wherein the antibody binds to tumor-associated antigen (35) IRTA2.

[Claim 39] The composition of any one of claims 1-18 wherein the cancer is selected from the group consisting of breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate, and bladder cancer.

[Claim 40] The composition of any one of claims 1-18 further comprising an effective amount of an anticancer agent, or an immunosuppressant agent.

[Claim 41] The composition of any one of claims 1-18 wherein the amount of antibody-drug conjugate compound or a pharmaceutically acceptable salt thereof, is in the range of 0.1 to 10 mg/kg of patient weight.

[Claim 42] The composition of any one of claims 1-18 wherein the composition is administered at about three week intervals.

[Claim 43] The composition of any one of claims 1-18 wherein said antibody-drug conjugate compound or a pharmaceutically acceptable salt thereof, is formulated with a pharmaceutically acceptable parenteral vehicle and is administered parenterally or formulated in a unit dosage injectable form.

[Claim 44] The composition of any one of claims 1-18 wherein said composition is administered intravenously.

[Claim 45] The composition of any one of claims 1-18 further comprising a second antibody which binds a tumor-associated antigen selected from (3)-(6), (9), (15), (17), (22), (24), (27), and (35).

[Claim 46] The composition of claim 45 wherein said second antibody is conjugated with a cytotoxic agent.