

## WHAT IS CLAIMED IS:

1. An antibody that specifically binds to the human Glypican-3 (GPC3) protein wherein the antibody comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO:1 and the three light chain CDRs of SEQ ID NO:2 wherein the CDRs are as defined by Kabat.
2. The antibody of claim 1 that is a humanized, chimeric or veneered antibody.
3. The antibody of any one of the preceding claims, comprising a mature heavy chain region having at least 80% sequence identity to SEQ ID NO:1 and a mature light chain variable region having at least 80% sequence identity to SEQ ID NO:2.
4. The antibody of any one of the preceding claims, which is a humanized antibody comprising a mature heavy chain variable region having at least 90% sequence identity with SEQ ID NO:1 and a mature light chain variable region having at least 90% sequence identity with SEQ ID NO:2.
5. The antibody of any one of the preceding claims, wherein the mature heavy chain variable region has at least 95% sequence identity with SEQ ID NO:1 and the mature light chain variable region has at least 95% sequence identity with SEQ ID NO:2.
6. The antibody of any one of the preceding claims, wherein H24 is occupied by V or A, H38 is occupied by Q, R or K, H48 is occupied by M or I, H66 is occupied by R or K, H67 is occupied by V or A, H69 is occupied by L, H71 is occupied by A, H73 is occupied by K or T, H93 is occupied by G or A, H94 is occupied by R and the following amino acid residues of the light chain are present: L45 is occupied by R or K, L46 is occupied by L or R, L105 is occupied by E or V, L106 is occupied by I or M; numbering is via the Kabat numbering system.
7. The antibody of any one of the preceding claims, wherein the following variable region frameworks positions are occupied as specified: H24 is occupied by V, H38 is occupied by Q, H48 is occupied by M, H66 is occupied by R, H67 is occupied by V, H69 is occupied by L, H71 is occupied by A, H73 is occupied by K, H93 is occupied by G, H94 is occupied by R; numbering is via the Kabat numbering system.

8. The antibody of any one of the preceding claims, wherein the following variable region frameworks positions are occupied as specified: L45 is occupied by R, L46 is occupied by L, L105 is occupied by E, L106 is occupied by I; numbering is via the Kabat numbering system.

9. The antibody of claim 1 that is HALA, HALB, HALC, HBLA, HBLB, HBLC, HBLD, HBLE, HBLB-Q, HBLB-V, HCLA, HCLB, HCLC, HDLA, HDLB and HDLC.

10. The antibody of any one of the preceding claims wherein the mature heavy chain variable region is fused to a heavy chain constant region and the mature light chain variable region is fused to a light chain constant region.

11. The antibody of claim 10, wherein the heavy chain constant region is a mutant form of a natural human constant region which has reduced binding to an Fc gamma receptor relative to the natural human constant region.

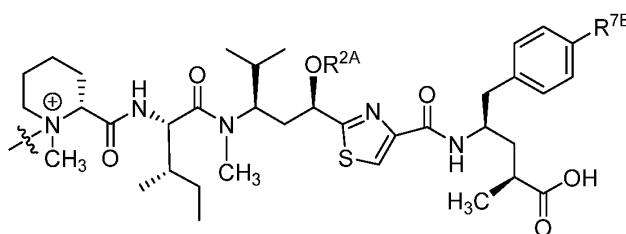
12. The antibody of claim 10, wherein the heavy chain constant region is of IgG1 isotype.

13. The antibody of claim 10, wherein the heavy chain constant region has an amino acid sequence comprising SEQ ID NO:5 or SEQ ID NO:6 and the light chain constant region has an amino acid sequence comprising SEQ ID NO:7.

14. The antibody of any one of the preceding claims, wherein the antibody is conjugated to a cytotoxic or cytostatic agent.

15. The antibody of claim 14 wherein the conjugated cytotoxic agent is a tubulysin.

16. The antibody of claim 14 wherein the conjugated cytotoxic agent is a conjugated tubulysin having the structure of:

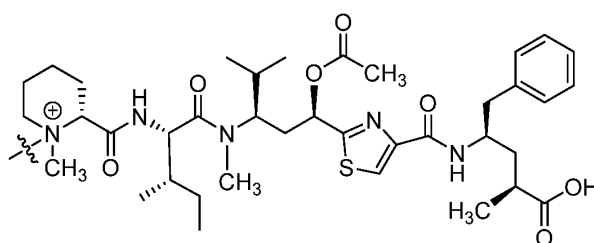


wherein the conjugated tubulysin is in salt form, in particular pharmaceutically acceptable salt form, or a solvate thereof, and wherein the wavy line indicates the site at which the tubulysin is conjugated to the antibody;

$R^{2A}$  is  $-C(=O)R^{2B}$  wherein  $R^{2B}$  is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or  $R^{2A}$  is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl; and

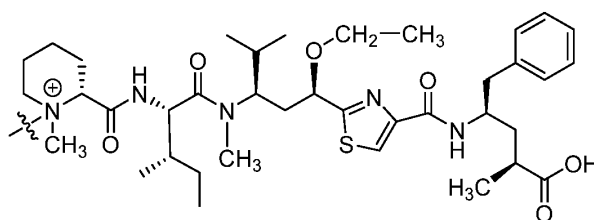
$R^{7B}$  is  $-H$  or  $-OH$ .

17. The antibody of claim 14 wherein the conjugated cytotoxic agent is a conjugated tubulysin having the structure of:



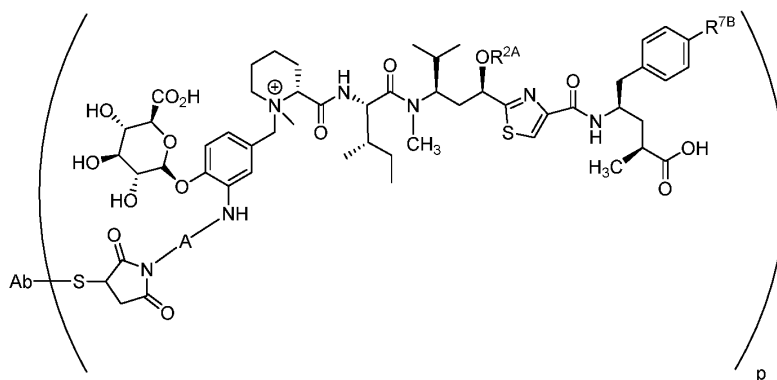
wherein the conjugated tubulysin is in salt form, in particular in pharmaceutically acceptable salt form, or a solvate thereof, and wherein the wavy line indicates the site at which the tubulysin is conjugated to the antibody.

18. The antibody of claim 14 wherein the conjugated cytotoxic agent is a conjugated tubulysin having the structure of:



wherein the conjugated tubulysin is in salt form, in particular in pharmaceutically acceptable salt form, or a solvate thereof, and wherein the wavy line indicates the site at which the tubulysin is conjugated to the antibody.

19. An anti-GPC3 antibody-drug conjugate compound having the formula



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

A is a Stretcher Unit;

$R^{2A}$  is  $-C(=O)R^{2B}$  wherein  $R^{2B}$  is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or  $R^{2A}$  is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl;

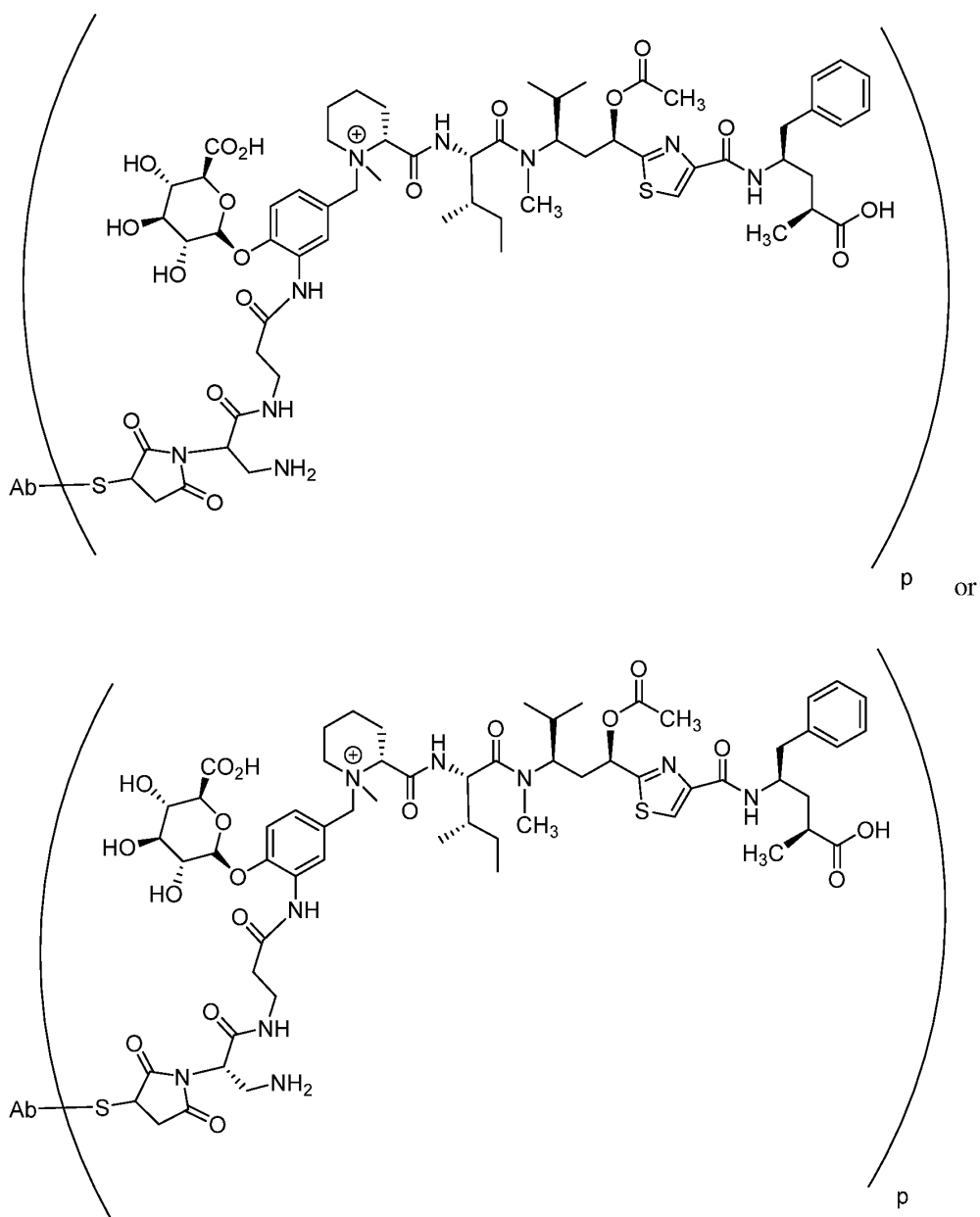
$R^{7B}$  is  $-H$  or  $-OH$ ;

Ab is an antibody as set forth in any of claims 1-16;

S is a sulfur atom from the antibody; and

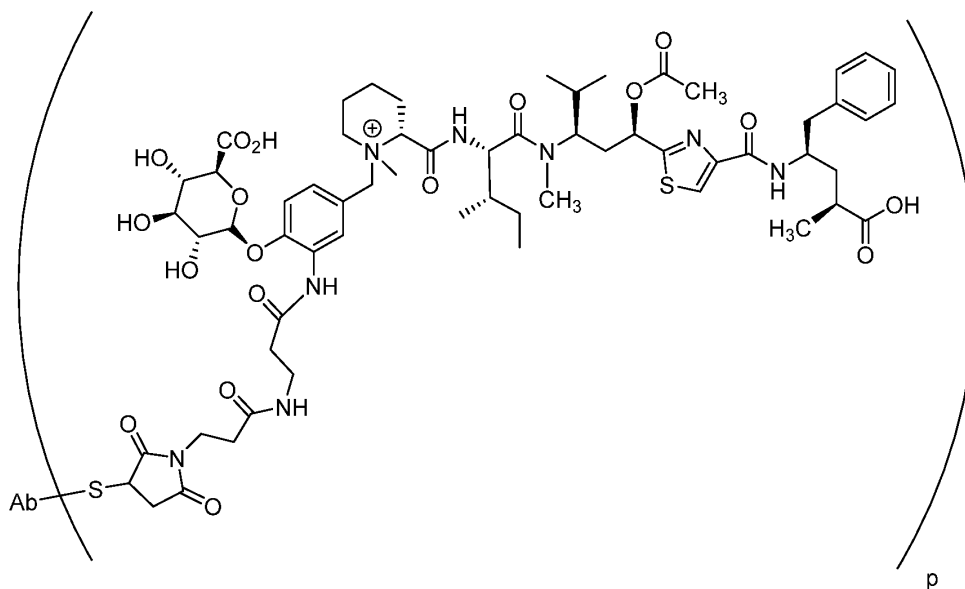
subscript p is an integer from 1 to 4.

20. The anti-GPC3 antibody-drug conjugate compound of claim 19, wherein the compound has the formula:



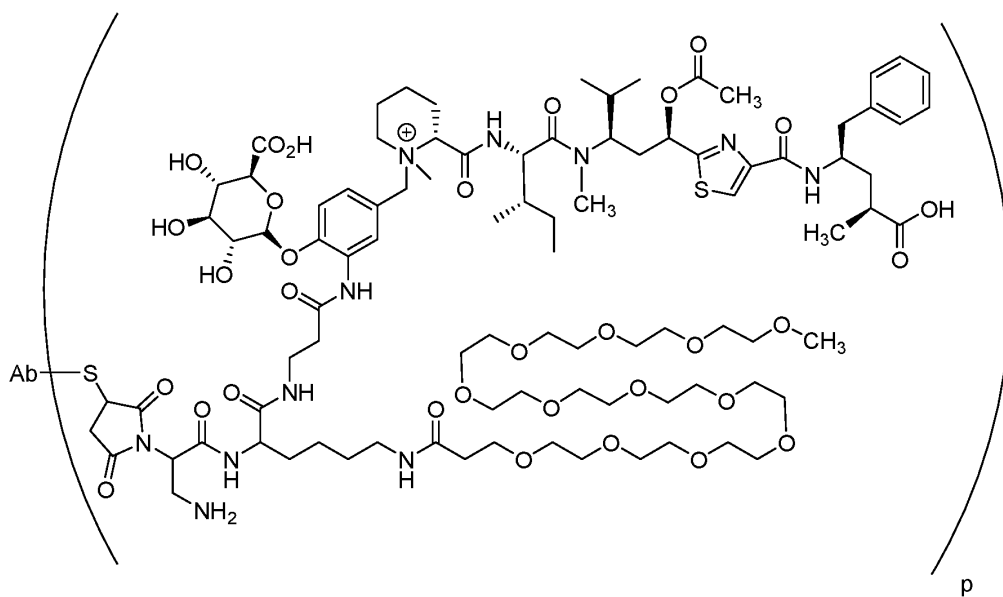
in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

21. The anti-GPC3 antibody-drug conjugate compound of claim 19, wherein the compound has the formula:

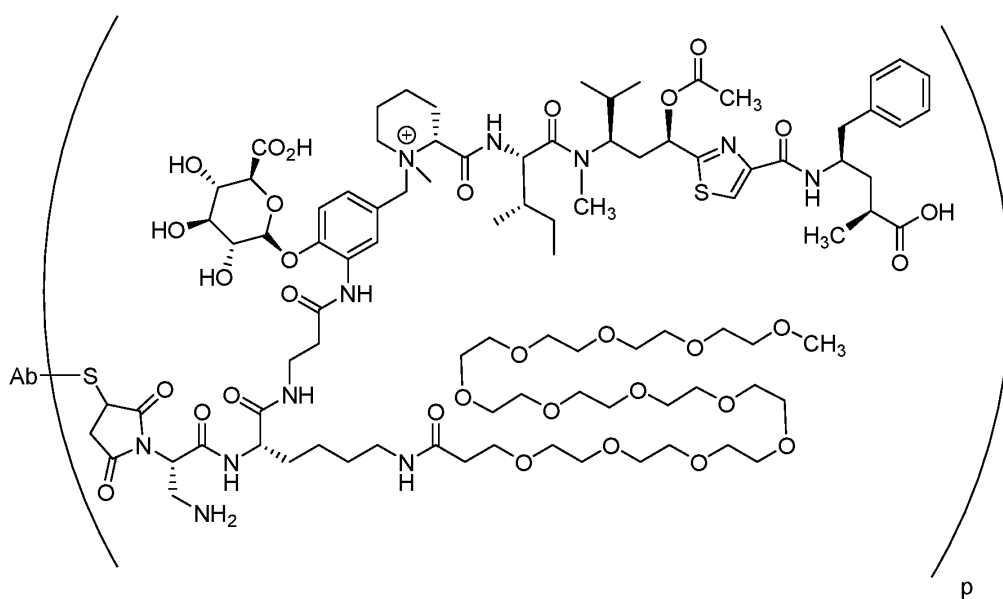


in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

22. The anti-GPC3 antibody-drug conjugate compound of claim 19, wherein the compound has the formula:



or



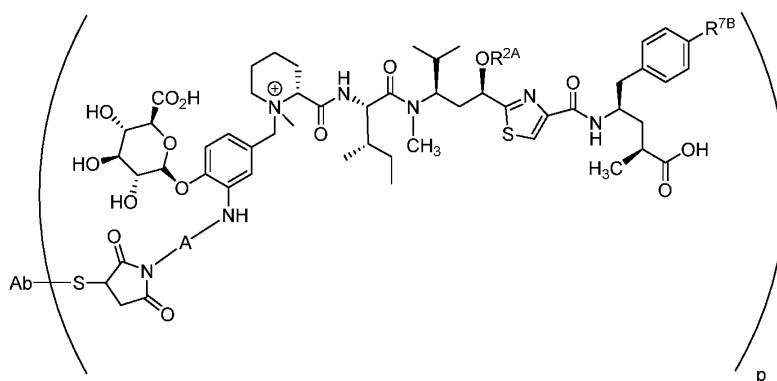
in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

23. The antibody-drug conjugate compound of any one of claims 19 to 22, wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab.

24. The antibody-drug conjugate compound of any one of claims 19 to 22, wherein attachment to Ab is via a sulfur atom or an engineered cysteine residue at position 239 of the heavy chain constant region, according to the EU index system of numbering.

25. The antibody-drug conjugate compound of any one of claims 19 to 22, wherein p is 2.

26. An antibody-drug conjugate composition comprising a population of anti-GPC3 antibody-drug conjugate compounds having the formula:



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

A is a Stretcher Unit;

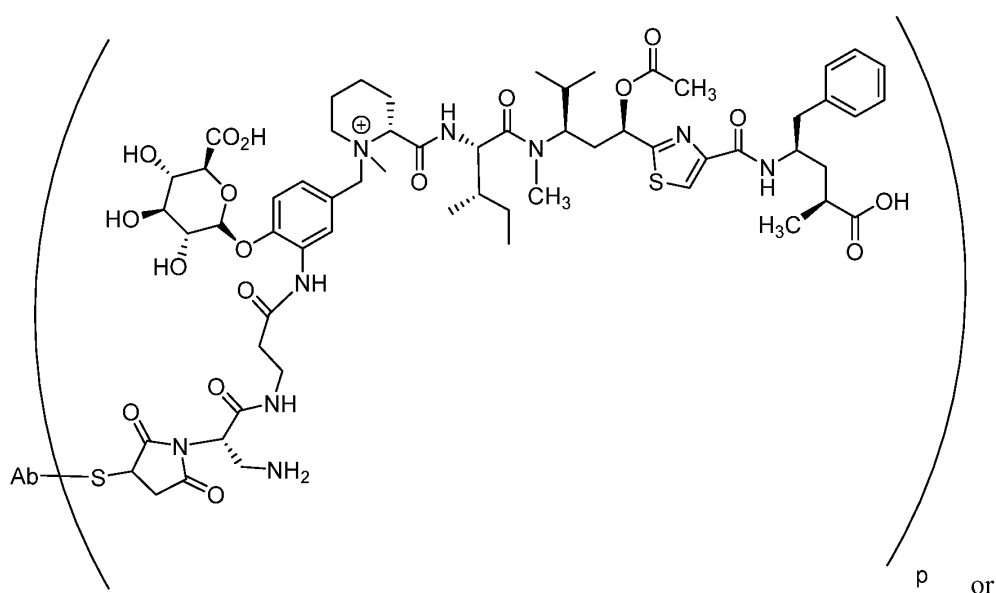
$R^{2A}$  is  $-C(=O)R^{2B}$  wherein  $R^{2B}$  is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or  $R^{2A}$  is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl;

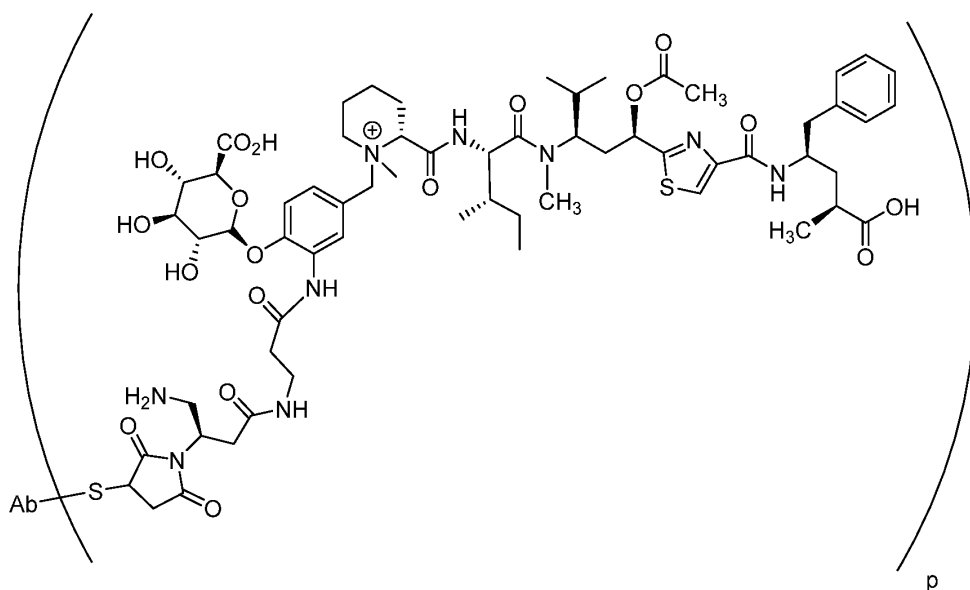
$R^{7B}$  is  $-H$  or  $-OH$ ;

Ab is an antibody as set forth in claim 1;

S is a sulfur atom from the antibody; and  
 subscript p is an integer from 1 to 4 for each antibody drug conjugate compound; and the  
 average drug loading of the composition is about 2.  
 and  
 the subscript p is an integer from 1 to 4; and the average drug load of the composition is  
 about 2.

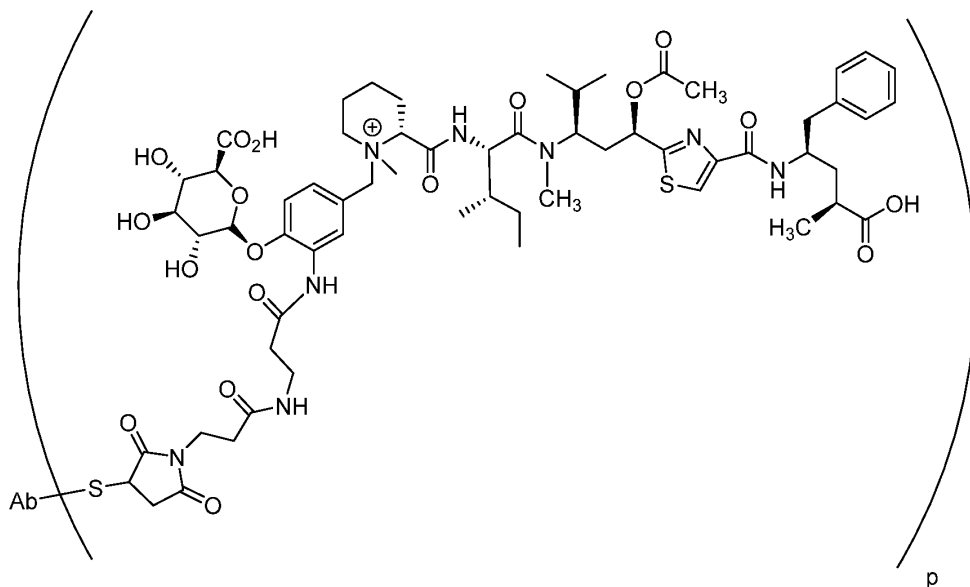
27. The antibody-drug conjugate composition of claim 26, wherein the  
 antibody-drug conjugate compounds have the formula of:





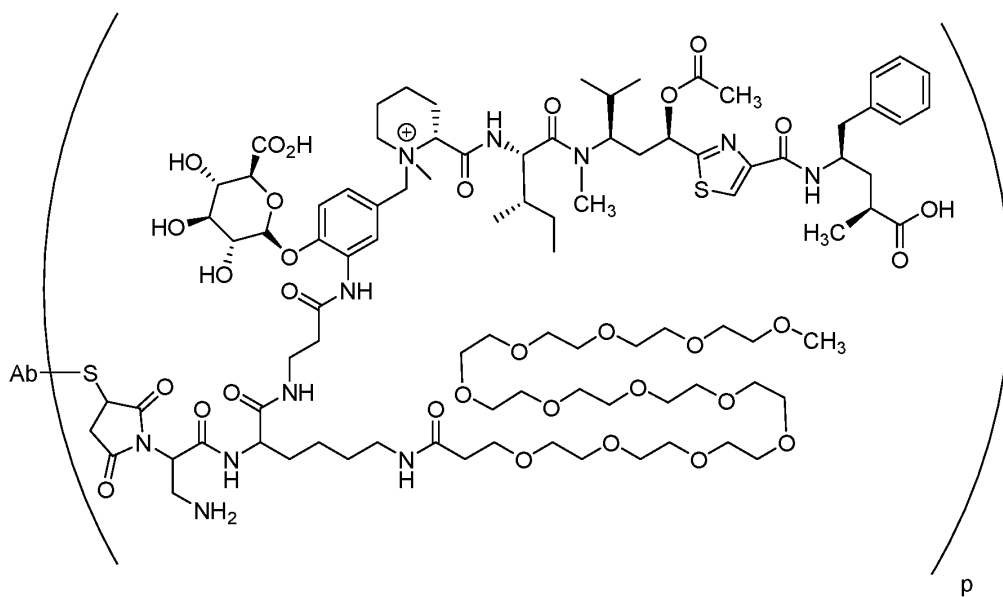
in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

28. The antibody-drug conjugate composition of claim 26, wherein the antibody-drug conjugate compounds have the formula of:

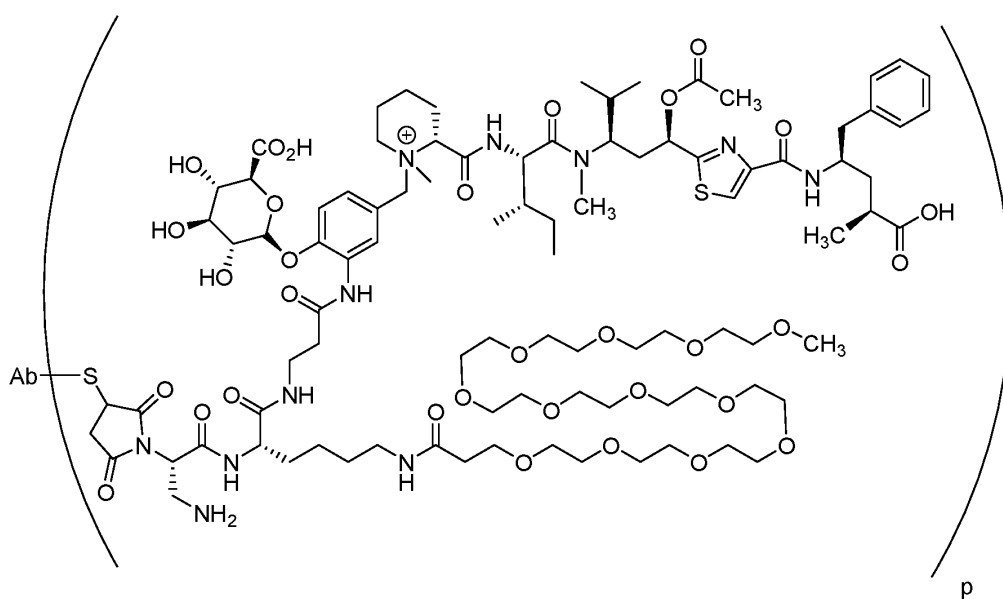


in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form.

29. The antibody-drug conjugate composition of claim 26, wherein the antibody-drug conjugate compounds have the formula of:



or



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

30. The antibody-drug conjugate composition of any one of claims 26 to 29, wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab.

31. The antibody-drug conjugate composition of any one of claims 26 to 29, wherein attachment to Ab is via a sulfur atom or an engineered cysteine residue at position 239 of the heavy chain constant region, according to the EU index system of numbering.

32. A method of treating a patient having a cancer that expresses GPC3, comprising administering to the patient an effective regimen of a composition of any one of the preceding claims.

33. The method of claim 32, wherein the cancer is a hepatocellular carcinoma (HCC), a lung carcinoma, Wilms tumor (nephroblastoma), an ovarian clear cell carcinoma, a colorectal carcinoma, or a sarcoma.

34. The method of claim 32, wherein the cancer is HCC.

35. A method of treating a patient having an autoimmune disease, comprising administering to the patient an effective regimen of a composition of any one of claims 1-32.

36. A pharmaceutical composition comprising an antibody of any of claims 1-35; and a pharmaceutically acceptable carrier.

37. The antibody of claim 1, wherein the three heavy chain CDRs are as set forth in SEQ ID NOs: 10, 11, and 12, and the three light chain CDRs are as set forth in SEQ ID NOs: 13, 14, and 15.

38. An antibody that specifically binds to the human GPC3 protein wherein the antibody comprises the three heavy chain CDRs as set forth in SEQ ID NOs: 10, 11, and 12, and the three light chain CDRs as set forth in SEQ ID NOs: 13, 14, and 15.

39. An isolated polynucleotide comprising a sequence encoding a heavy chain variable region comprising the three heavy chain CDRs as set forth in SEQ ID NO: 10, 11, and 12, and the three light chain CDRs as set forth in SEQ ID NO: 13, 14, and 15.

40. The polynucleotide of claim 39, comprising a mature heavy chain region having a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1 and a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 2.

41. An isolated vector comprising the polynucleotide of claim 39 or 40.

42. An isolated host cell comprising the vector of claim 41.

43. The host cell of claim 42, wherein the host cell is a CHO cell.

44. A method of making an anti-GPC3 antibody or antigen binding fragment thereof, wherein the method comprises:

- a) culturing the host cell of claim 42 under conditions suitable for expression of the polynucleotide encoding the antibody or antigen binding fragment thereof; and
- b) isolating the antibody or antigen binding fragment thereof.

45. The method of claim 44, wherein the host cell is a CHO cell.

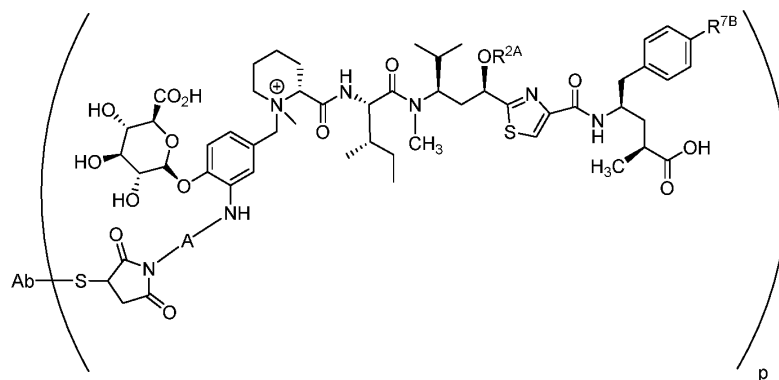
46. A method of making an anti-GPC3 antibody drug conjugate, wherein the method comprises:

- a) culturing the host cell of claim 42 under conditions suitable for expression of the polynucleotide encoding the antibody or antigen binding fragment thereof;
- b) isolating the antibody or antigen binding fragment thereof; and
- c) conjugating a cytotoxic agent to the antibody or antigen binding fragment thereof.

47. The method of claim 46, wherein the host cell is a CHO cell.

48. The method of claim 46, wherein the cytotoxic agent is a tubulysin.

49. A method of treating a patient having a cancer that expresses GPC3, comprising administering to the patient an effective regimen of a composition comprising a population of anti-GPC3 antibody-drug conjugate compounds having the formula:



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

A is a Stretcher Unit;

$R^{2A}$  is  $-C(=O)R^{2B}$  wherein  $R^{2B}$  is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or  $R^{2A}$  is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl;

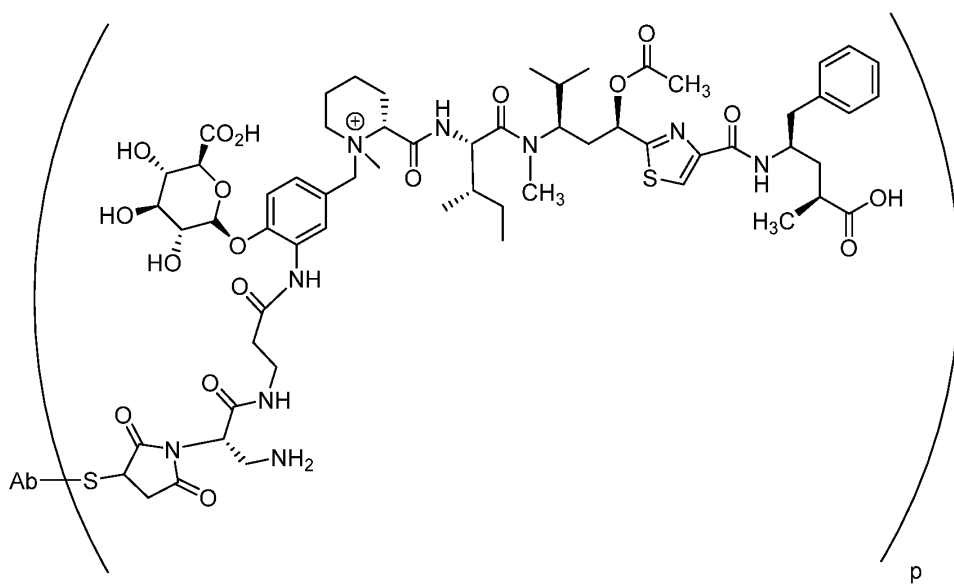
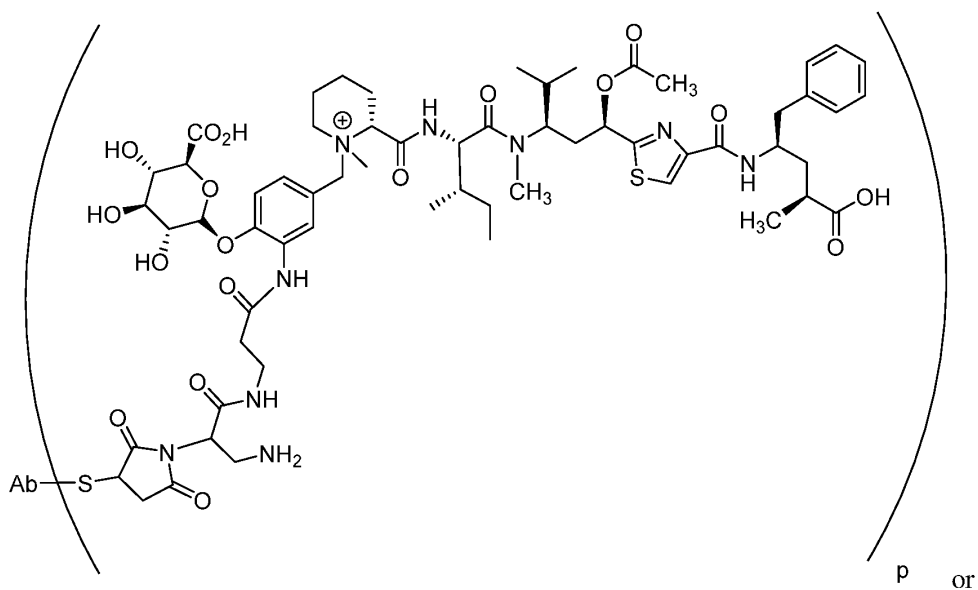
$R^{7B}$  is  $-H$  or  $-OH$ ;

Ab is an antibody as set forth in claim 1;

S is a sulfur atom from the antibody; and

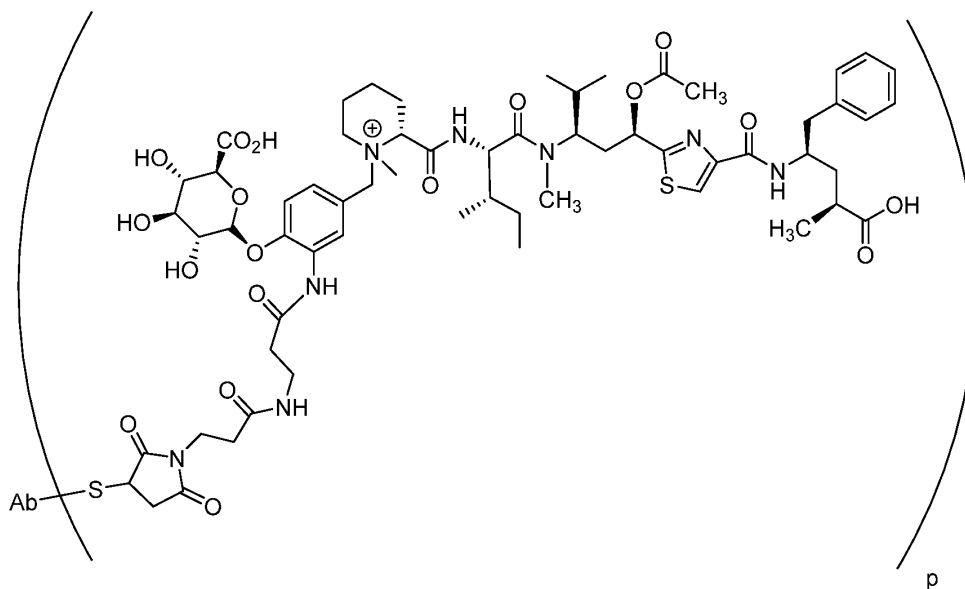
subscript p is an integer from 1 to 4 for each antibody drug conjugate compound; and the average drug loading of the composition is about 2.

50. The method of claim 49, wherein the antibody-drug conjugate compounds have the formula:



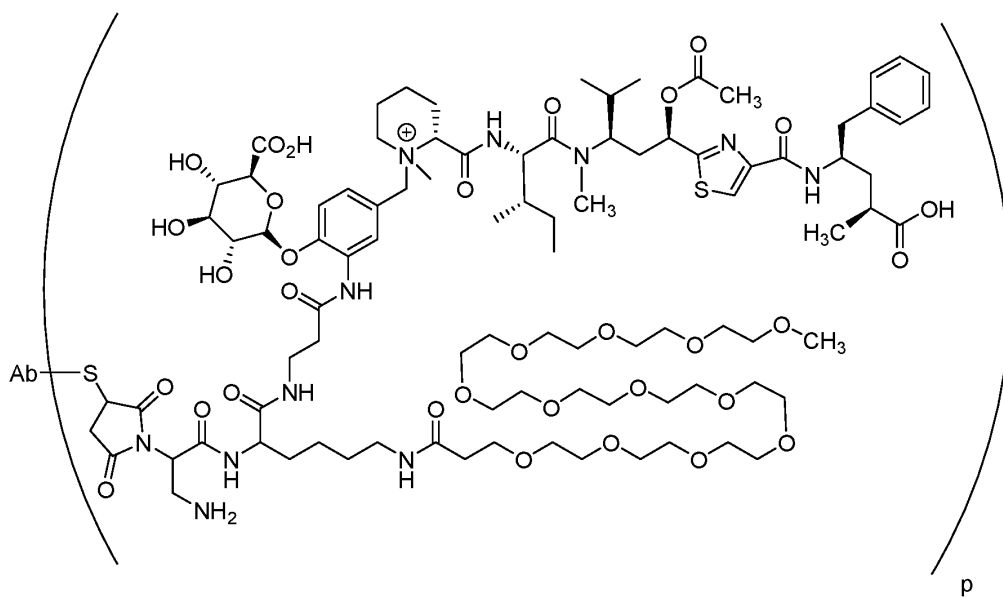
in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

51. The method of claim 49, wherein the antibody-drug conjugate compounds have the formula:

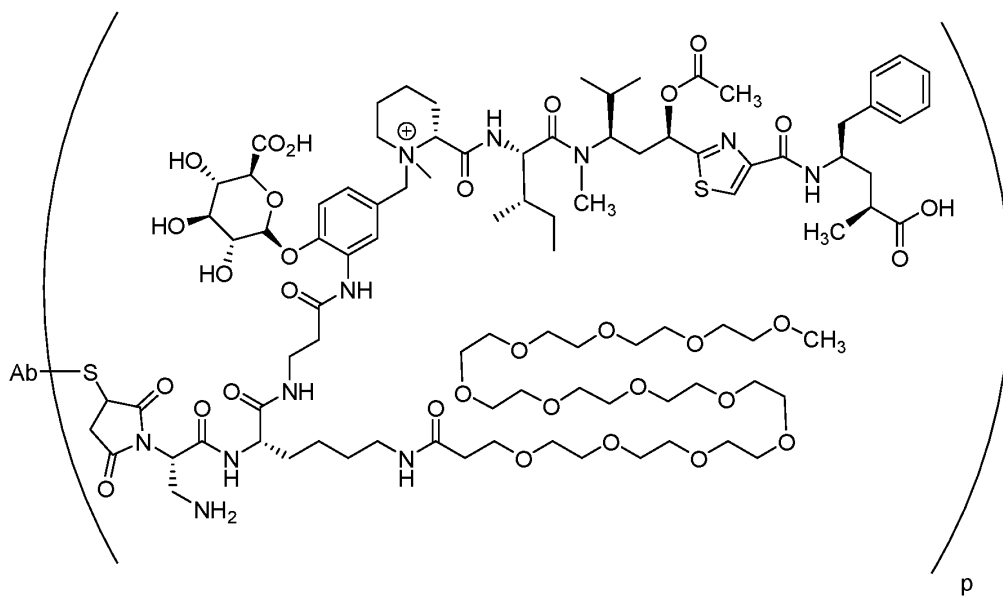


in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form.

52. The method of claim 49, wherein the antibody-drug conjugate compounds have the formula:



or

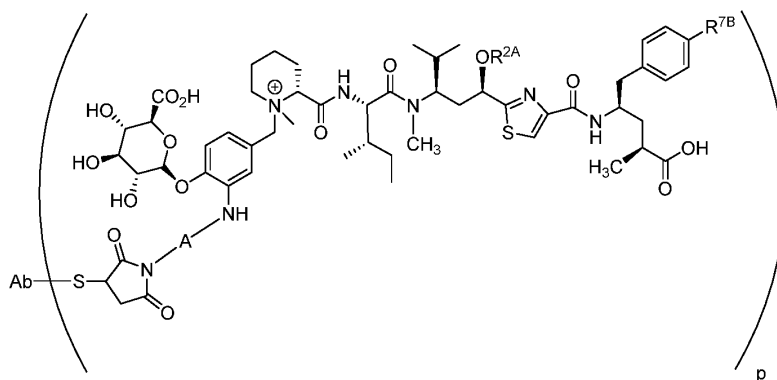


in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

53. The method of any one of claims 49 to 52, wherein the cancer is HCC, a lung carcinoma, Wilms tumor (nephroblastoma), an ovarian clear cell carcinoma, a colorectal carcinoma, or a sarcoma.

54. The method of claim 53, wherein the cancer is HCC.

55. A pharmaceutical composition comprising a population of anti-GPC3 antibody-drug conjugate compounds having the formula:



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

A is a Stretcher Unit;

$R^{2A}$  is  $-C(=O)R^{2B}$  wherein  $R^{2B}$  is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or  $R^{2A}$  is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl;

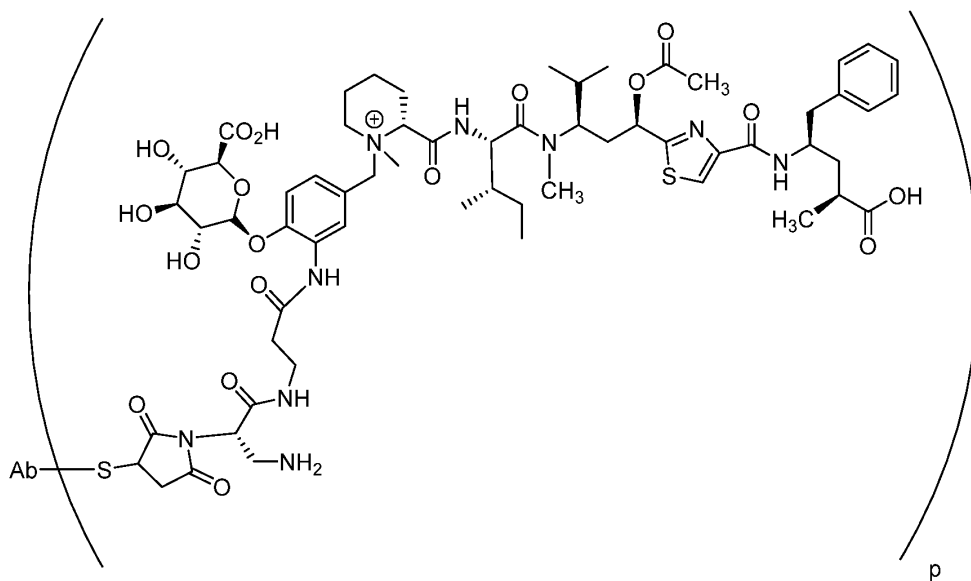
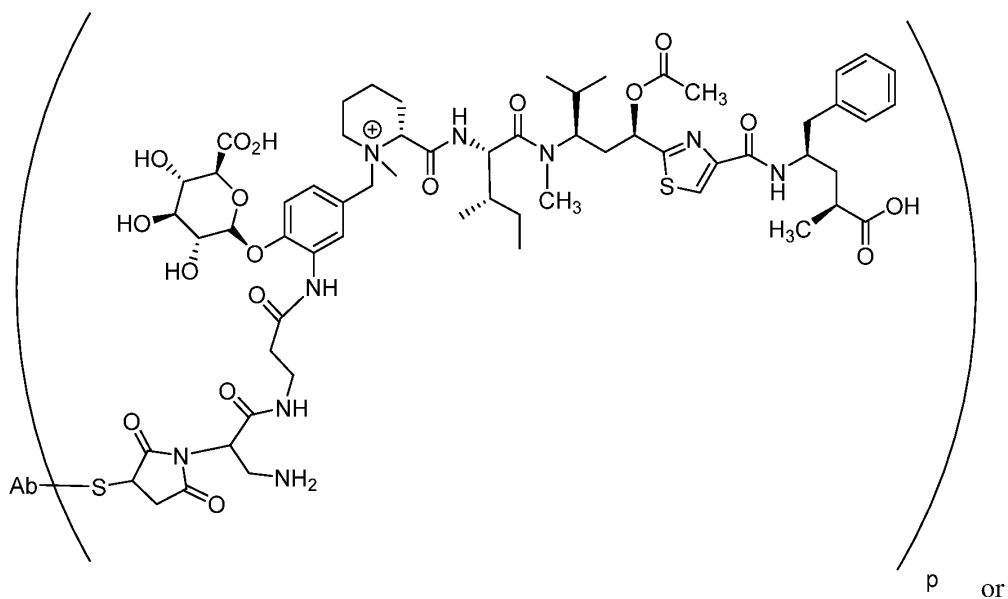
$R^{7B}$  is  $-H$  or  $-OH$ ;

Ab is an antibody comprising the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO:1 and the three light chain CDRs of SEQ ID NO:2 wherein the CDRs are as defined by Kabat;

S is a sulfur atom from the antibody; and

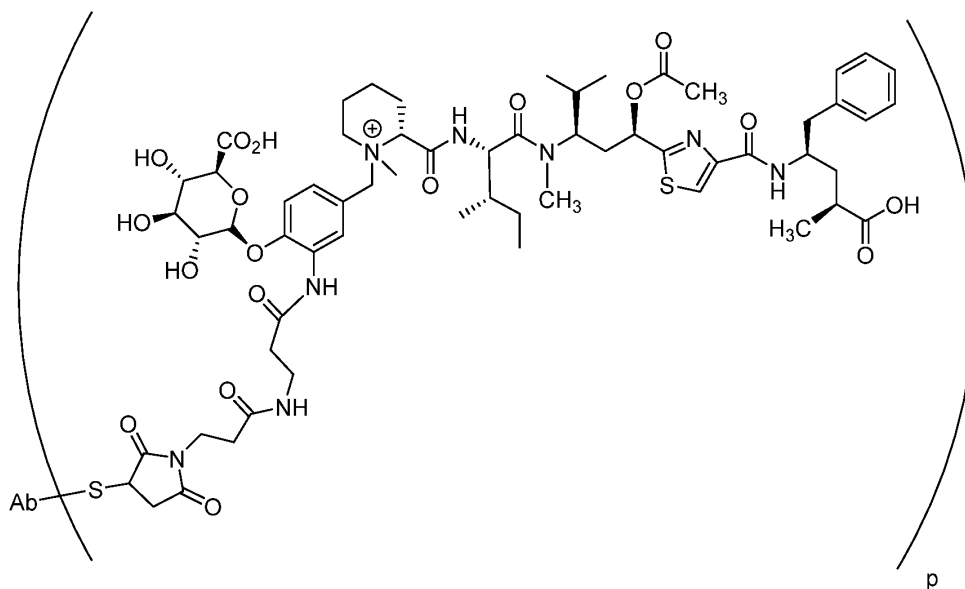
subscript p is 2.

56. The pharmaceutical composition of claim 55, wherein the antibody-drug conjugate compounds have the formula:



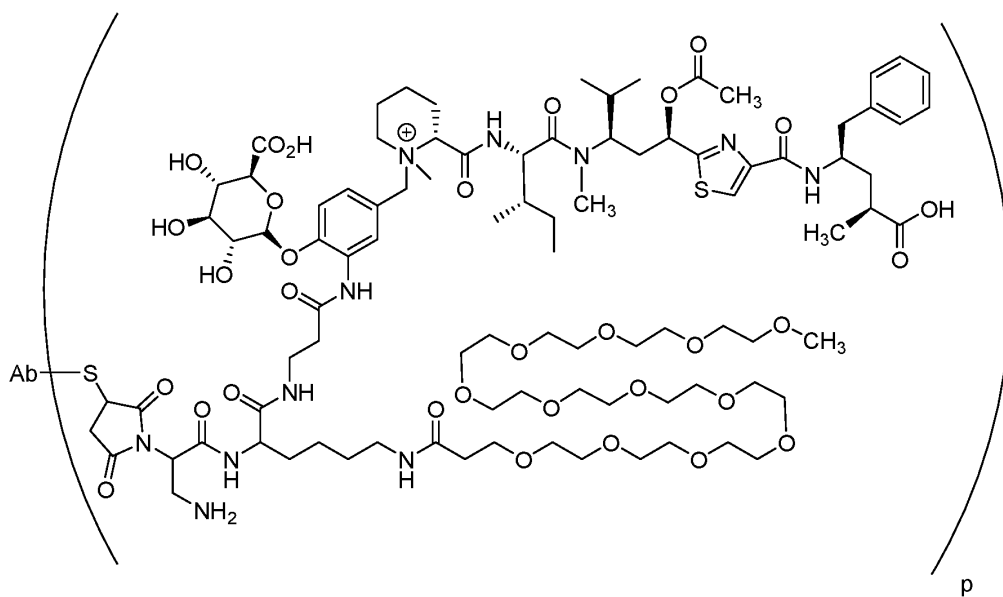
in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

57. The pharmaceutical composition of claim 55, wherein the antibody-drug conjugate compounds have the formula:

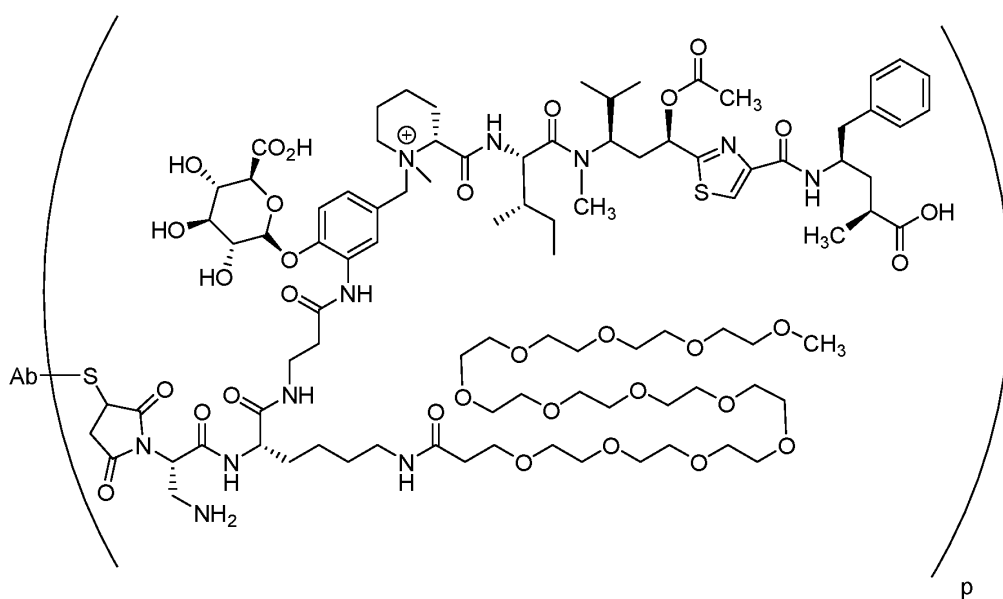


in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form.

58. The pharmaceutical composition of claim 55, wherein antibody-drug conjugate compounds have the formula:

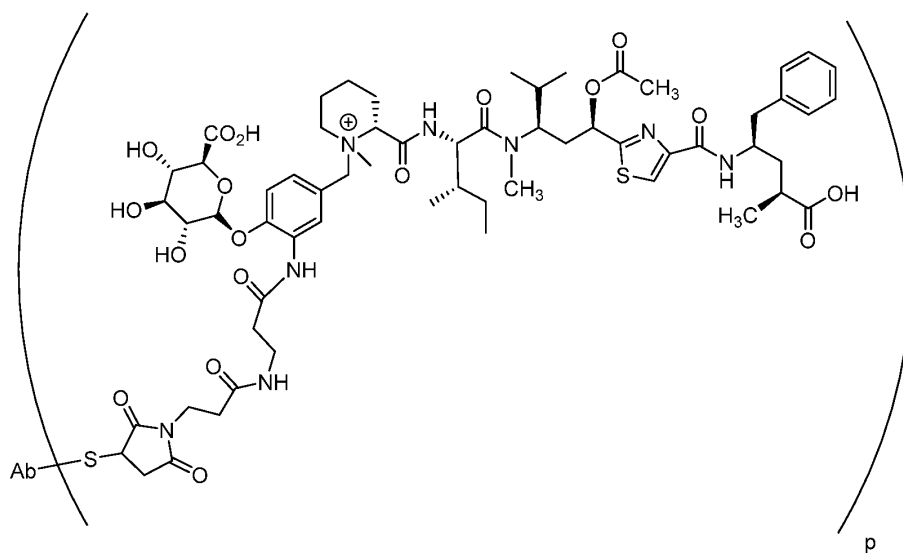


or



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having one of the formula above in which the thio-substituted succinimide is in hydrolyzed form.

59. A pharmaceutical composition comprising a population of anti-GPC3 antibody-drug conjugate compounds having the formula:



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

Ab is an antibody comprising the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO:1 and the three light chain CDRs of SEQ ID NO:2 wherein the CDRs are as defined by Kabat;

S is a sulfur atom from the antibody; and

subscript p is 2.