ANTI-NTB-A ANTIBODIES AND RELATED COMPOSITIONS AND METHODS

SEQUENCE LISTING

[0001] A sequence listing designated NTBA-00303PR_ST25.txt, and has a size of 29 kilobytes, is incorporated by reference.

BACKGROUND

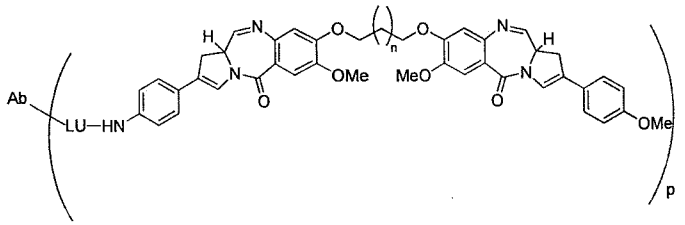
[0002] NTB-A, a single-pass type I membrane glycoprotein also referred to as SLAMF6, is an immunoglobulin superfamily (Ig-SF) member belonging to the CD2/SLAM subfamily. *See, e.g.*, Bottino *et al.*, *J. Exp. Med.* 194:235-246, 2001. NTB-A is characterized, in its extracellular portion, by an N-terminal V-type domain followed by a C2-type domain, while the intracytoplasmic portion contains three tyrosine-based motifs: two immunoreceptor tyrosine-based switch motifs (ITSM; TxYxxV/I) and a classical immunoreceptor tyrosine-based inhibition motif (ITIM; I/V/L/SxYxxL). *See id.* Through its ITSM motifs, NTB-A associates with the SH2 domain of the SLAM-associated protein SH2D1A and the related Ewing's sarcoma activated transcript (EAT) 2. *See* Bottino *et al.*, *supra*; Falco *et al.*, *Eur. J. Immunol.* 34:1663–1672, 2004; Flaig *et al.*, *J. Immunol.* 172:6524–6527, 2004.

[0003] NTB-A is expressed on natural killer (NK) cells, NK-like T-cells, T-cells, monocytes, dendritic cells, B-cells, and eosinophils. *See* Salort JD. *et al., Immunology Letters* 129-136, 2011; Matesanz-Isabel *et al., Immunology Letters* 104-112, 2011; Munitz *et al., Journal of Immunology* 174:110-118, 2005; Bottino *et al., Journal of Experimental Medicine* 194(3):235-246; 2001. NTB-A can function through homotypic interactions (*i.e.*, as a self-ligand), and has been shown to act as a positive regulator of NK cell functions via signaling, inducing NK cell cytotoxicity. *See, e.g.*, *See* Bottino *et al.*, *supra*; Falco *et al.*, *supra*; Flaig *et al.*, *supra.* NTB-A has also been shown to be expressed on B-cells from chronic lymphocytic leukemia (CLL) and B-cell lymphoma patients. *See* Korver *et al.*, *British Journal of Haematology* 137:307-318, 2007.

SUMMARY

[0003a] In one aspect, there is provided an antibody that specifically binds to the human NTB-A protein wherein the antibody comprises the three heavy chain complementarity determining regions of SEQ ID NO:3 and the 3 light chain complementarity determining regions (CDRs) of SEQ ID NO:13 wherein the CDRs are as defined by Kabat or IMGT. [0003b] In another aspect, there is provided a nucleic acid encoding the mature heavy chain variable region and the mature light chain variable region as described herein.

[0003c] In another aspect, there is provided an anti-NTBA antibody-drug conjugate compound having the formula



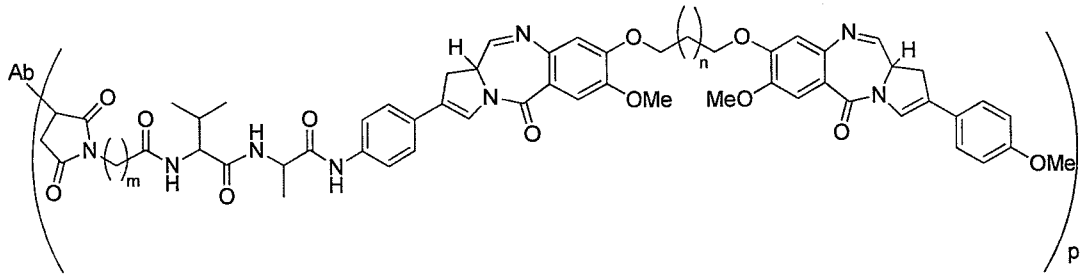
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 or 3;

LU is a cleavable Linker Unit;

Ab is an antibody as described herein;

the subscript p is an integer from 1 to 4, particularly wherein p is 2, particularly having the formula



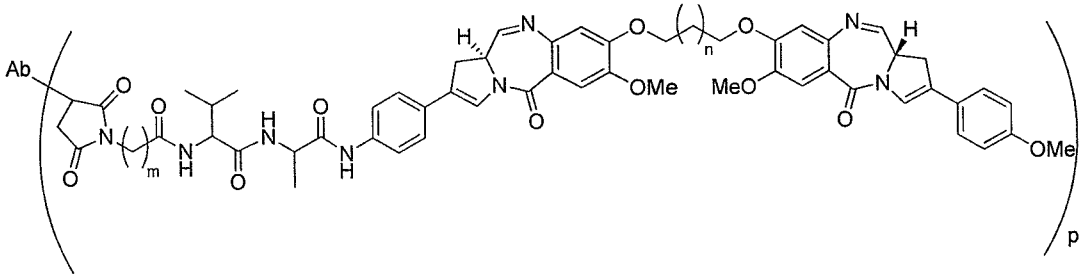
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 or 3;

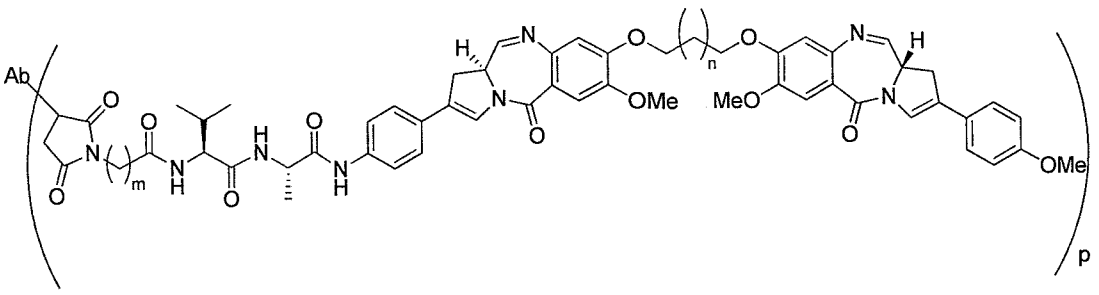
the subscript m is 2 to 5

Ab is an antibody as described herein;

the subscript p is an integer from 1 to 4, particularly having the formula:

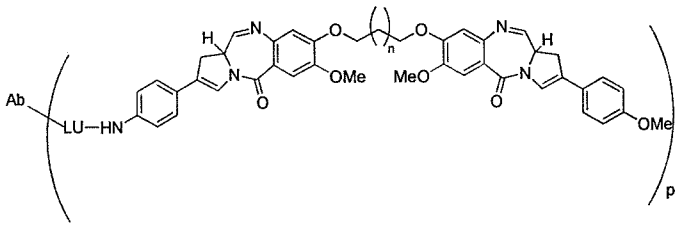


or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, or having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, particularly wherein n is 1, or wherein n is 3, and/or wherein m is 5, and/or wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab, and/or 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.

[0003d] In another aspect, there is provided an antibody-drug conjugate composition comprising a population of anti-NTB-A antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

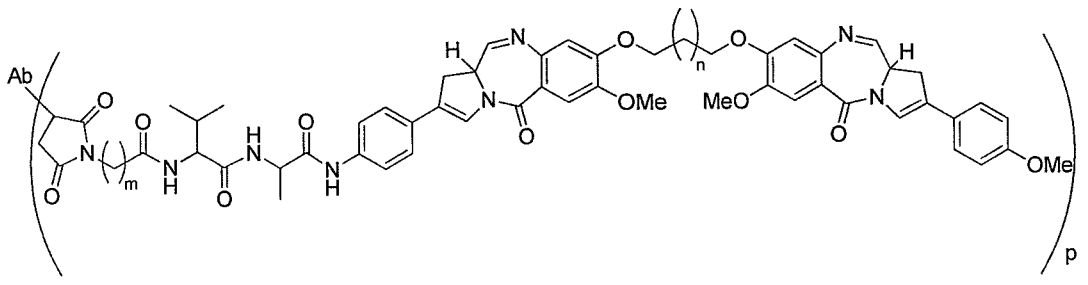
the subscript n is 1 to 3;

LU is a cleavable Linker Unit;

Ab is an antibody as described herein; and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

[0003e] In another aspect, there is provided a pharmaceutical composition comprising a population of anti-NTB-A antibody-drug conjugate molecules having the formula:



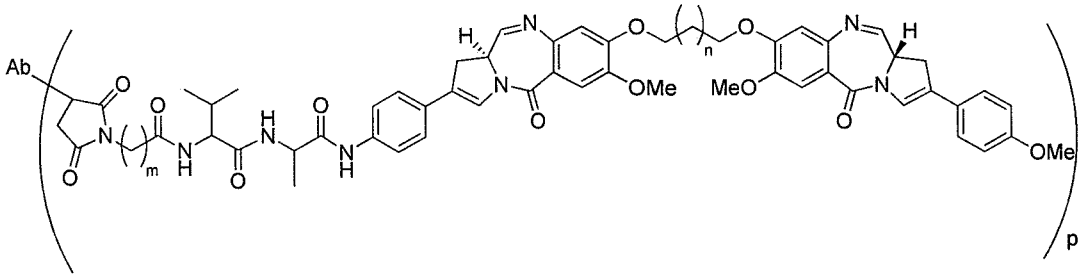
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 to 3;

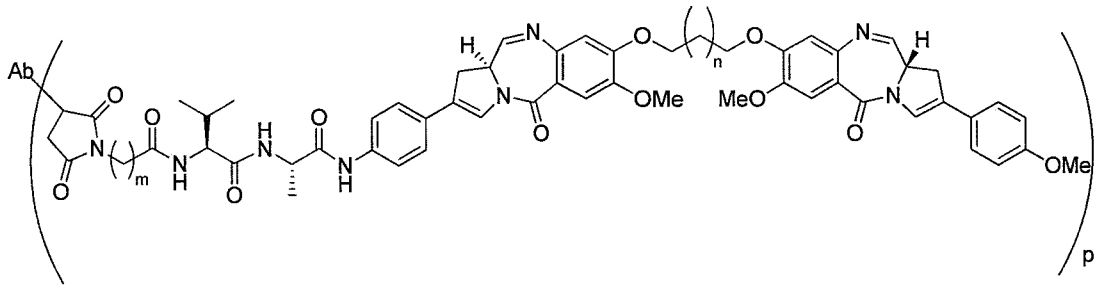
the subscript m is 2 to 5

Ab is an antibody as described herein; and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2; and a pharmaceutically acceptable carrier, particularly wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, or wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, and/or wherein n is 1, or 3, and/or wherein m is 5, and/or wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab, and/or 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

[0003f] In another aspect, there is provided a composition as described herein for use in the treatment of a cancer that expresses NTB-A in a patient, particularly wherein the cancer is a multiple myeloma, non-Hodgkin lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia, primary amyloidosis, Waldenström's macroglobulinemia, or monoclonal gammopathy of undetermined significance (MGUS), particularly wherein the cancer is a T-cell lymphoma.

[0003g] In another aspect, there is provided a composition as described herein for use in the treatment of an autoimmune disease in a patient.

[0003h] In another aspect, there is provided a pharmaceutical composition comprising an antibody as described herein; and a pharmaceutically acceptable carrier.

WHAT IS CLAIMED IS:

1. An antibody that specifically binds to the human NTB-A protein wherein the antibody comprises the three heavy chain complementarity determining regions of SEQ ID NO:3 and the 3 light chain complementarity determining regions (CDRs) of SEQ ID NO:13 wherein the CDRs are as defined by Kabat or IMGT.

2. The antibody of claim 1, wherein the CDRs are as defined by IMGT, or wherein the CDRs are Kabat CDRs.

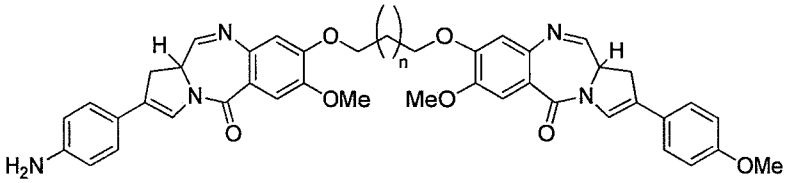
3. The antibody of claim 1 or 2 that is a humanized, chimeric or veneered antibody, or comprising a mature heavy chain region having at least 80% sequence identity to SEQ ID NO:8 and a mature light chain variable region having at least 80% sequence identity to SEQ ID NO:18, particularly which is a humanized antibody comprising a mature heavy chain variable region having at least 90% sequence identity with SEQ ID NO:8 and a mature light chain variable region having at least 90% sequence identity with SEQ ID NO:18, particularly wherein the mature heavy chain variable region has at least 95% sequence identity with SEQ ID NO:8 and the mature light chain variable region has at least 95% sequence identity with SEQ ID NO:18.

4. The antibody of claim 3 wherein H2 is occupied by I, H38 is occupied by R or K, H44 is occupied by D or G, H46 is occupied by K or E, H68 is occupied by V or A, H73 is occupied by K, H76 is occupied by N or S, H91 is occupied by Y or F, L1 is occupied by Q or E, L5 is occupied by S or T, L21 is occupied by M or L, L46 is occupied by P, L47 is occupied by W, L58 is occupied by V or I, and L71 is occupied by Y; numbering is via the Kabat numbering system, or wherein the following variable region frameworks positions are occupied as specified: H2 occupied by I, H38 occupied by R, H44 occupied by D, H46 occupied by K, H68 occupied by V, H73 occupied by K, H76 occupied by N, H91 occupied by Y, L1 occupied by Q, L5 occupied by S, L21 occupied by M, L46 occupied by P, L47 occupied by W, L58 occupied by V, L71 occupied by Y; numbering is via the Kabat numbering system, or wherein the following variable region frameworks positions are occupied as specified: H2 occupied by I, H44 occupied by D, H46 occupied by K, H73 occupied by K, H76 occupied by N, L1 occupied by Q, L5 occupied by S, L21 occupied by M, L46 occupied by P, L47 occupied by W, L58 occupied by V, L71 occupied by Y; numbering is via the Kabat numbering system.

5. 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, particularly wherein the heavy chain constant region is a mutant form of natural human constant region which has reduced binding to an Fcgamma receptor relative to the natural human constant region, or wherein the heavy chain constant region is of IgG1 isotype, or wherein the heavy chain constant region has an amino acid sequence comprising SEQ ID NO:29 or SEQ ID NO:30 and the light chain constant region has an amino acid sequence comprising SEQ ID NO:28, and/or having a dissociation constant for human or cynomolgus monkey NTB-A within a factor of 5 of that of 20F3.

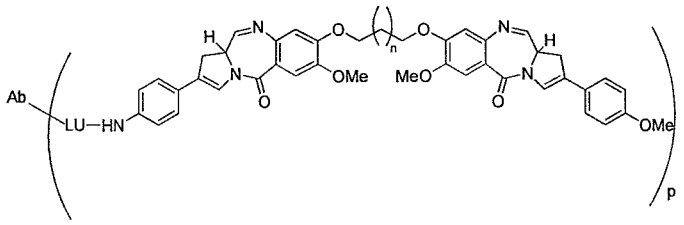
6. A nucleic acid encoding the mature heavy chain variable region and the mature light chain variable region as defined by any of claims 1-5.

7. The antibody of any one of claims 1-5, wherein the antibody is conjugated to a cytotoxic or cytostatic agent, particularly wherein the cytotoxic agent is a maytansinoid, auristatin, pyrrolo[1,4]benzodiazepine, indolinobenzodiazepine, or oxazolidinobenzodiazepine, particularly wherein the cytotoxic agent is



wherein the subscript n is 1 or 3; or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof.

8. An anti-NTBA antibody-drug conjugate compound having the formula



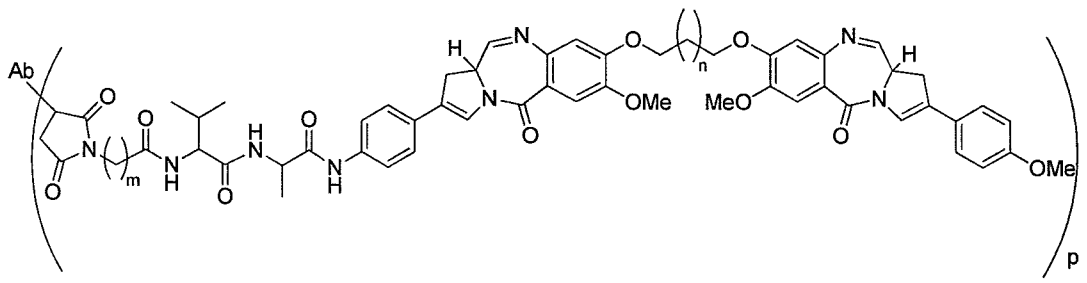
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 or 3;

LU is a cleavable Linker Unit;

Ab is an antibody as set forth in any one of claims 1 to 5;

the subscript p is an integer from 1 to 4, particularly wherein p is 2, particularly having the formula



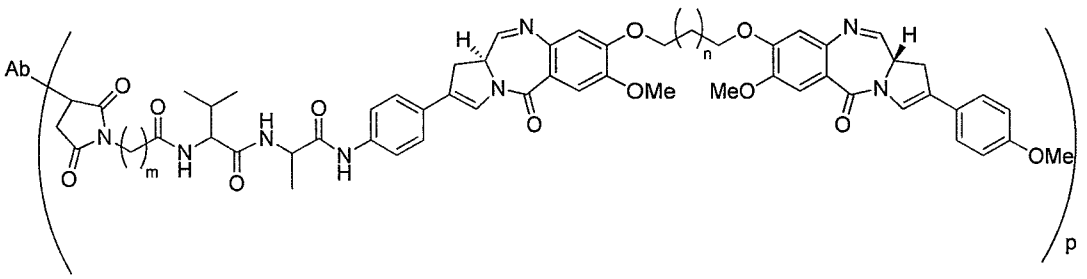
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 or 3;

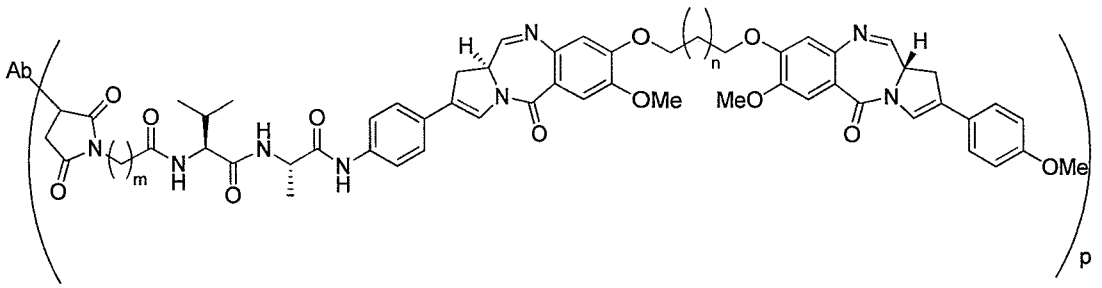
the subscript m is 2 to 5

Ab is an antibody as set forth in any one of claims 1 to 5;

the subscript p is an integer from 1 to 4, particularly having the formula:

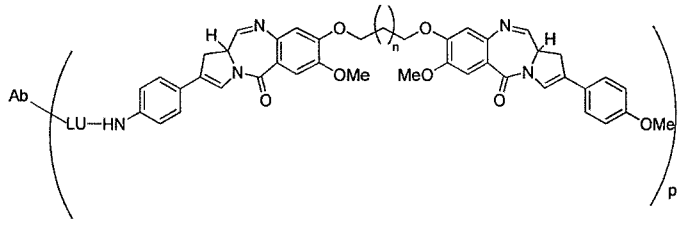


or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, or having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, particularly wherein n is 1, or wherein n is 3, and/or wherein m is 5, and/or wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab, and/or 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.

9. An antibody-drug conjugate composition comprising a population of anti-NTB-A antibody-drug conjugate molecules having the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

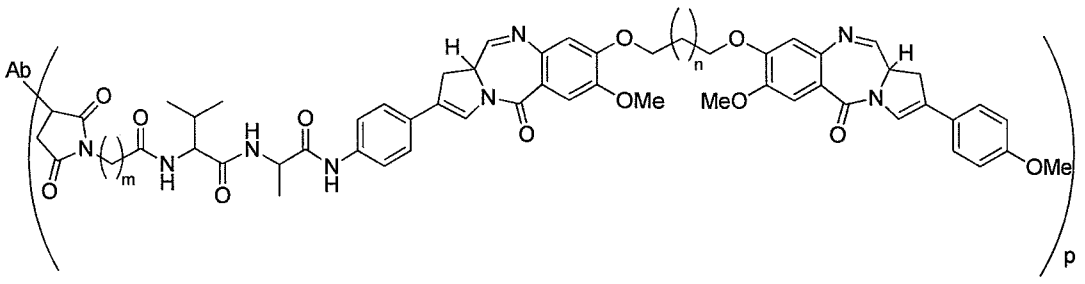
the subscript n is 1 to 3;

LU is a cleavable Linker Unit;

Ab is an antibody as set forth in any one of claims 1 to 5; and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

10. An antibody-drug conjugate composition of claim 9 comprising a population of anti-NTB-A antibody-drug conjugate molecules having the formula:



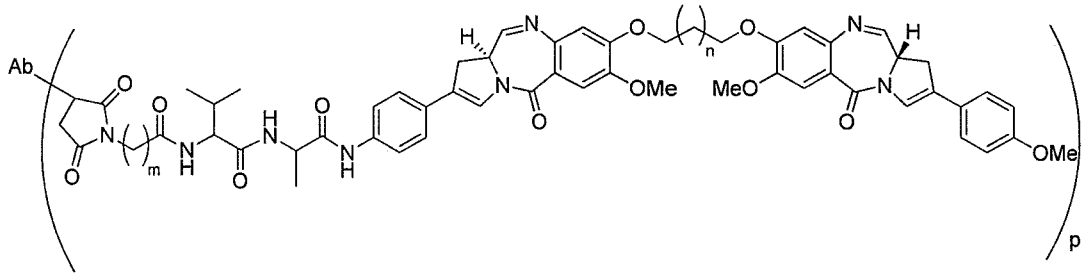
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 to 3;

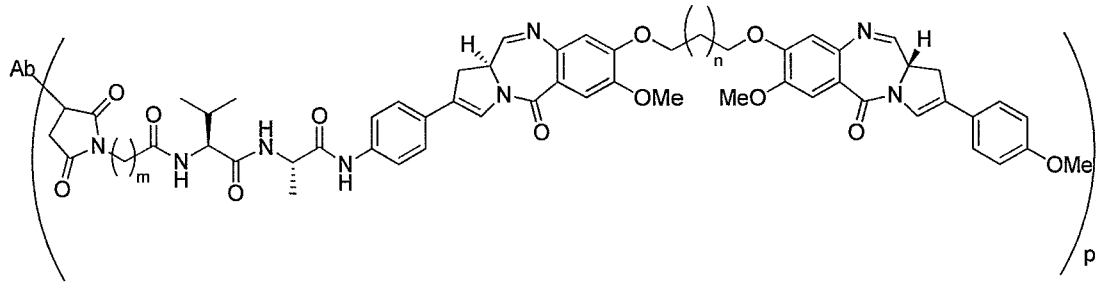
the subscript m is 2 to 5

Ab is an antibody as set forth in any one of claims 1 to 5; and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2, particularly wherein the antibody-drug conjugate molecules have the formula:



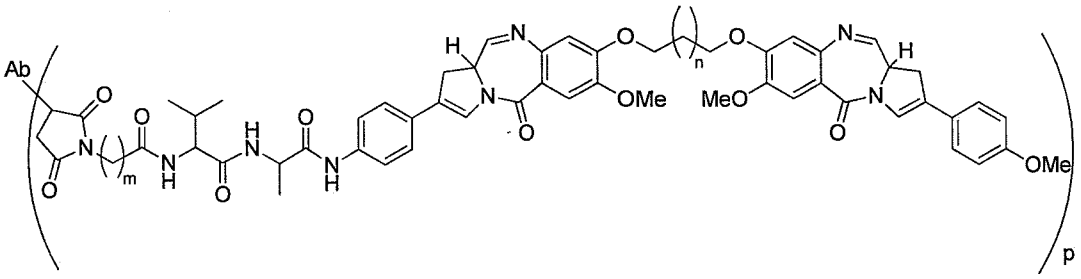
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, or wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, particularly wherein n is 1, or wherein n is 3, and/or wherein m is 5, and/or wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab, and/or 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.

11. A pharmaceutical composition comprising a population of anti-NTB-A antibody-drug conjugate molecules having the formula:



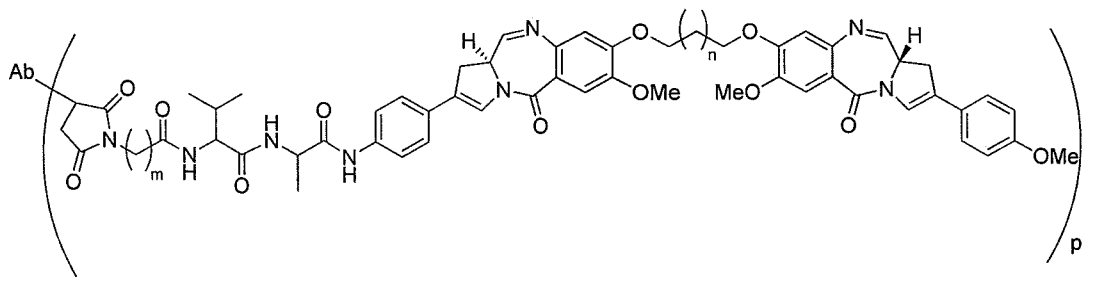
or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof; wherein

the subscript n is 1 to 3;

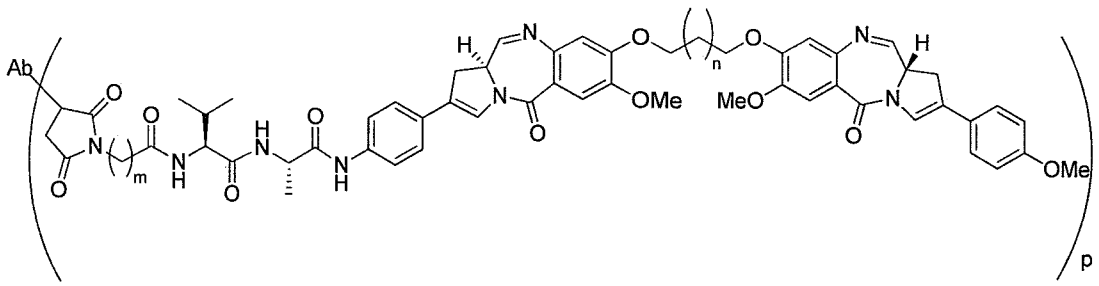
the subscript m is 2 to 5

Ab is an antibody as set forth in any one of claims 1 to 5; and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2; and a pharmaceutically acceptable carrier, particularly wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, or wherein the antibody-drug conjugate molecules have the formula:



or a pharmaceutically acceptable salt thereof, solvate thereof, or solvate of the salt thereof, and/or wherein n is 1, or 3, and/or wherein m is 5, and/or wherein attachment to Ab is via a sulfur atom of an engineered cysteine residue of Ab, and/or 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.

12. A composition of any of claims 9 to 11 for use in the treatment of a cancer that expresses NTB-A in a patient, particularly wherein the cancer is a multiple myeloma, non-Hodgkin lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia, primary amyloidosis, Waldenström's macroglobulinemia, or monoclonal gammopathy of undetermined significance (MGUS), particularly wherein the cancer is a T-cell lymphoma.

13. A composition of any of claims 9 to 11 for use in the treatment of an autoimmune disease in a patient.

14. A pharmaceutical composition comprising an antibody of any of claims 1-5; and a pharmaceutically acceptable carrier.