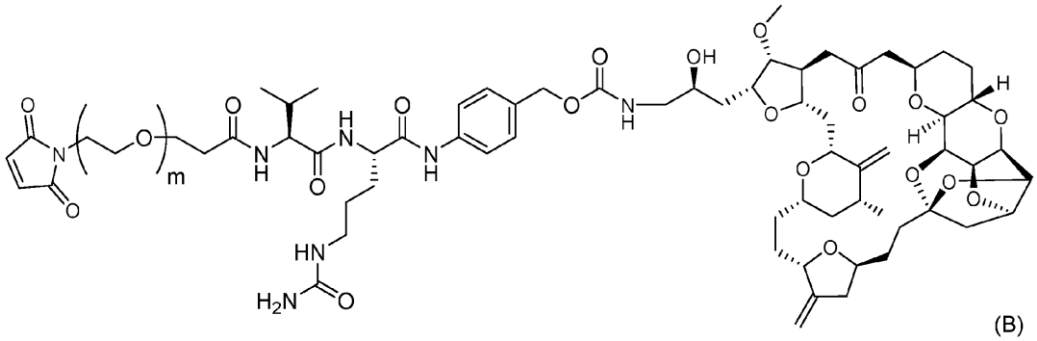
CLAIMS

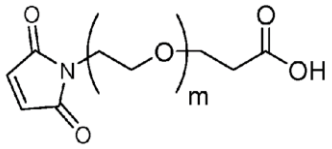
1. A method of producing a compound represented by Formula (B),



(B)

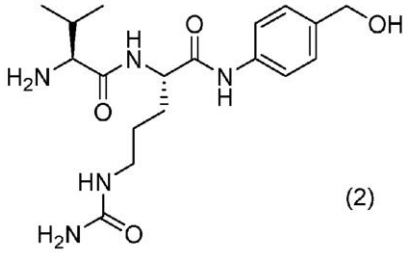
wherein m in Formula (B) is an integer from 1 to 10, the method comprising:

(i) reacting a compound of Formula (1):



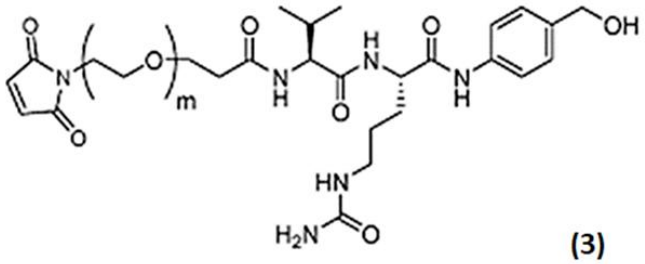
(1) ,

wherein m in Formula (1) is an integer from 1 to 10, with a compound of Formula (2):



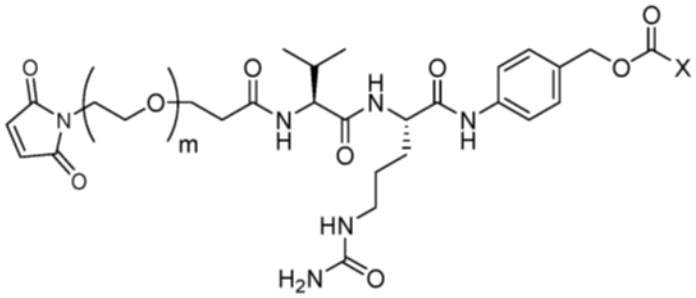
(2) ,

to produce a compound of Formula (3):



(3) ;

(ii) acylating a hydroxyl group in the compound on Formula (3) using an acylating agent, wherein m in Formula (3) is an integer from 1 to 10, and wherein the acylating agent comprises a phenoxy group or a nitrophenoxy group, thereby producing a compound represented by Formula (A),

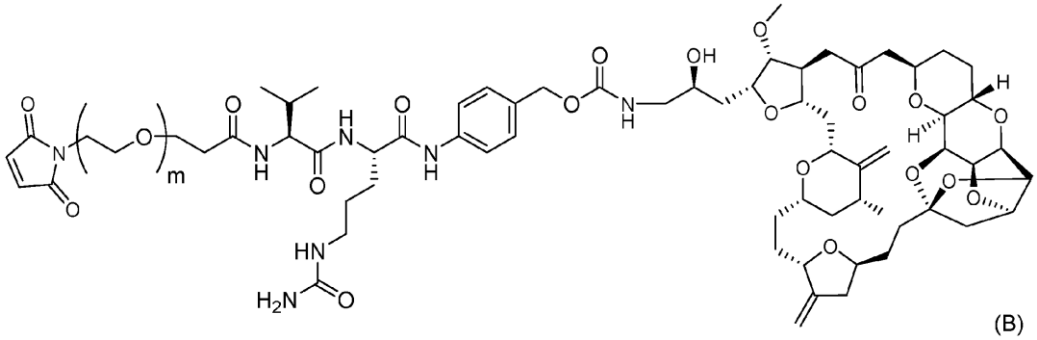


(A)

wherein m in Formula (A) is an integer from 1 to 10, and X in Formula (A) is a phenoxy group or a nitrophenoxy group; and

(iii) reacting a compound of Formula (A) with an eribulin or a salt thereof, thereby producing a compound represented by Formula (B).

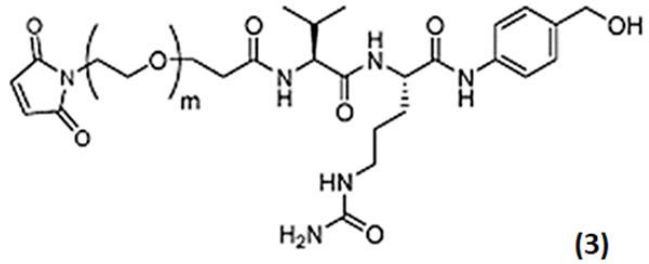
2. A method of producing a compound represented by Formula (B),



(B)

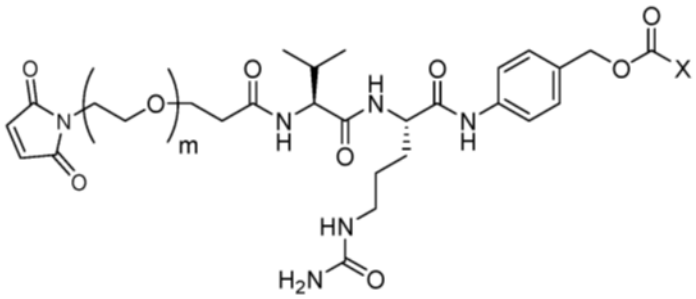
wherein m is an integer from 1 to 10, the method comprising:

preparing a mixture comprising: (a) an acylating agent which comprises a phenoxy group or a nitrophenoxy group, (b) a compound of Formula (3):



(3) , and (c) eribulin or a salt thereof;

acylating a hydroxyl group in the compound on Formula (3) using the acylating agent to provide a compound of Formula (A),



(A) ; and

reacting the compound of Formula (A) with the eribulin or a salt thereof, thereby producing the compound of Formula (B).

3. The method of claim 1 or claim 2, wherein the eribulin or the salt thereof is eribulin methanesulfonate.

4. The method of any one of claims 1 to 3, wherein the step of reacting a compound of Formula (A) with eribulin, or a salt thereof, is performed in the presence of a base.

5. The method of claim 4, wherein the base comprises: a tertiary amine or a nitrogen-containing aromatic compound.

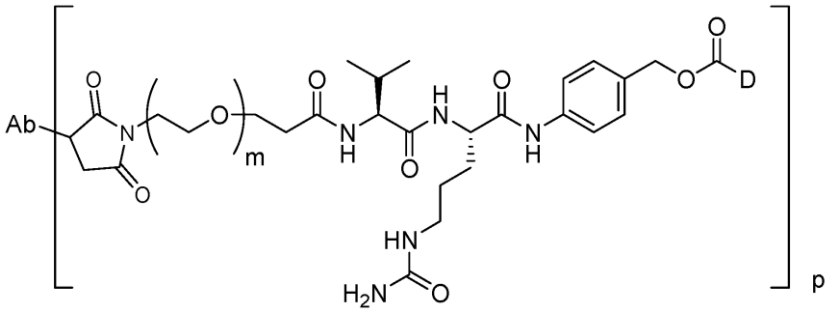
6. The method of claim 5, wherein the tertiary amine comprises triethylamine or N,N-diisopropylethylamine.

7. The method of claim 5, wherein the nitrogen-containing aromatic compound comprises pyridine or 2,6-lutidine.

8. The method according to any one of claims 1 to 7, wherein the acylating agent comprises: diphenyl carbonate, bis(4-nitrophenyl) carbonate, bis(2-nitrophenyl) carbonate, bis(3-nitrophenyl) carbonate, phenyl chloroformate, 4-nitrophenyl chloroformate, 2-nitrophenyl chloroformate, or 3-nitrophenyl chloroformate.

9. A method of producing an antibody-drug conjugate comprising reacting an antibody or antigen-binding fragment with the compound produced by the method according to any one of claims 1 to 8 under conditions that allow conjugation.

10. A method of producing an antibody-drug conjugate represented by Formula (I),



(I)

,

wherein

Ab is an antibody or an antigen-binding fragment thereof,

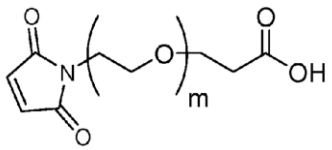
D is eribulin,

m is an integer from 1 to 10, and

p is an integer from 1 to 8,

the method comprising:

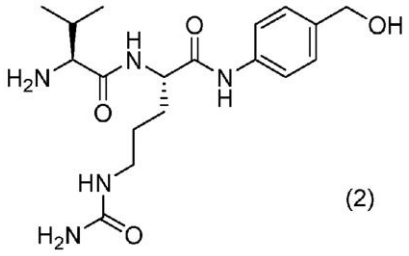
(i) reacting a compound of Formula (1):



(1)

,

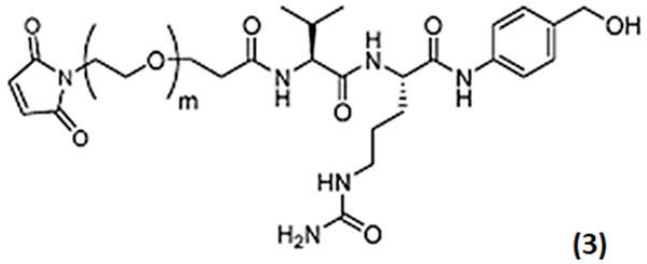
wherein m in Formula (1) is an integer from 1 to 10, with a compound of Formula (2):



(2)

,

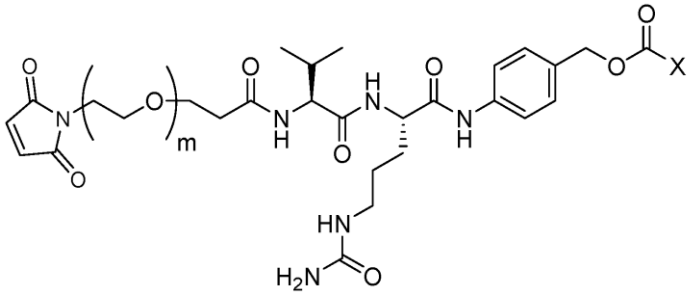
to produce a compound of Formula (3):



(3)

;

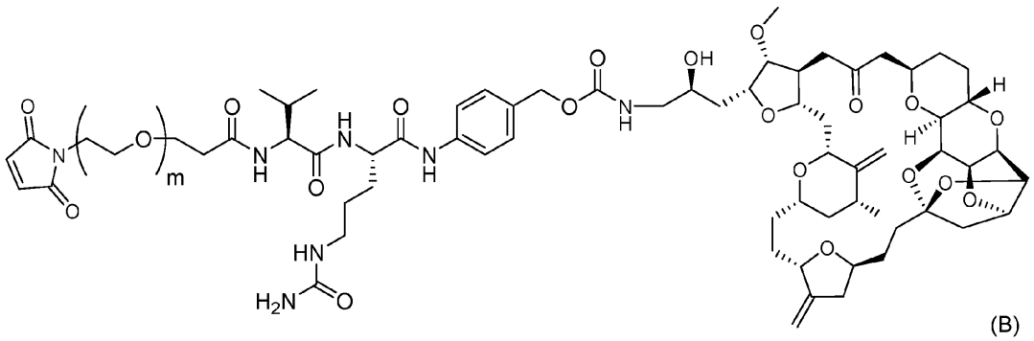
(ii) acylating a hydroxyl group in the compound on Formula (3) using an acylating agent, wherein m in Formula (3) is an integer from 1 to 10, and wherein the acylating agent comprises a phenoxy group or a nitrophenoxy group, thereby producing a compound represented by Formula (A),



(A)

wherein m in Formula (A) is an integer from 1 to 10, and X in Formula (A) is a phenoxy group or a nitrophenoxy group;

(iii) reacting eribulin or a salt thereof with the compound represented by Formula (A) to obtain a compound represented by Formula (B),



(B)

wherein m in Formula (B) is an integer from 1 to 10; and

(iv) reacting the compound represented by Formula (B) with an antibody or an antigen-binding fragment thereof to obtain the antibody-drug conjugate represented by Formula (I).

11. The method according to claim 10, wherein:

(A) Ab comprises an antibody or antigen-binding fragment that binds folate receptor alpha (FRA), wherein the antibody or antigen-binding fragment comprises:

(i) three heavy chain CDR sequences represented by SEQ ID NO: 2 (HCDR1), SEQ ID NO: 3 (HCDR2), and SEQ ID NO: 4 (HCDR3), and three light chain CDR sequences represented by SEQ ID NO: 7 (LCDR1), SEQ ID NO: 8 (LCDR2), and SEQ ID NO: 9 (LCDR3) as defined by the Kabat numbering system,

(ii) three heavy chain CDR sequences represented by SEQ ID NO: 13 (HCDR1), SEQ ID NO: 14 (HCDR2), and SEQ ID NO: 15 (HCDR3), and three light chain CDR sequences represented by SEQ ID NO: 16 (LCDR1), SEQ ID NO: 17 (LCDR2), and SEQ ID NO: 18 (LCDR3) as defined by the IMGT numbering system,

(iii) a heavy chain comprising an amino acid sequence represented by SEQ ID NO: 1 and a light chain comprising an amino acid sequence represented by SEQ ID NO: 6, or

(iv) a heavy chain variable domain comprising an amino acid sequence represented by SEQ ID NO: 23 and a light chain variable domain comprising an amino acid sequence represented by SEQ ID NO: 24;

(B) Ab comprises an antibody or antigen-binding fragment that binds human

epidermal growth factor receptor two (HER2), wherein the antibody or antigen-binding fragment comprises:

(v) three heavy chain CDR sequences represented by SEQ ID NO: 71 (HCDR1), SEQ ID NO: 72 (HCDR2), and SEQ ID NO: 73 (HCDR3), and three light chain CDR sequences represented by SEQ ID NO: 74 (LCDR1), SEQ ID NO: 75 (LCDR2), and SEQ ID NO: 76 (LCDR3) as defined by the Kabat numbering system,

(vi) three heavy chain CDR sequences represented by SEQ ID NO: 191 (HCDR1), SEQ ID NO: 192 (HCDR2), and SEQ ID NO: 193 (HCDR3), and three light chain CDR sequences represented by SEQ ID NO: 194 (LCDR1), SEQ ID NO: 195 (LCDR2), and SEQ ID NO: 196 (LCDR3) as defined by the IMGT numbering system,

(vii) a heavy chain variable domain comprising an amino acid sequence represented by SEQ ID NO: 27 and a light chain variable domain comprising an amino acid sequence represented by SEQ ID NO: 28, or

(viii) a heavy chain comprising an amino acid sequence represented by SEQ ID NO: 307 or 347 and a light chain comprising an amino acid sequence represented by SEQ ID NO: 308; or

(C) Ab comprises an antibody or antigen-binding fragment that binds mesothelin, wherein the antibody or antigen-binding fragment comprises:

(ix) three heavy chain CDR sequences represented by SEQ ID NO: 65 (HCDR1), SEQ ID NO: 66 (HCDR2), and SEQ ID NO: 67 (HCDR3), and three light chain CDR sequences represented by SEQ ID NO: 68 (LCDR1), SEQ ID NO: 69 (LCDR2), and SEQ ID NO: 70 (LCDR3) as defined by the Kabat numbering system,

(x) three heavy chain CDR sequences represented by SEQ ID NO: 185 (HCDR1), SEQ ID NO: 186 (HCDR2), and SEQ ID NO: 187 (HCDR3), and three light chain CDR sequences represented by SEQ ID NO: 188 (LCDR1), SEQ ID NO: 189 (LCDR2), and SEQ ID NO: 190 (LCDR3) as defined by the IMGT numbering system,

(xi) a heavy chain variable domain comprising an amino acid sequence represented by SEQ ID NO: 25 and a light chain variable domain represented by SEQ ID NO: 26, or

(xii) a heavy chain comprising an amino acid sequence represented by SEQ ID NO: 305 and a light chain comprising an amino acid sequence represented by SEQ ID NO: 306.

12. The method according to claim 10 or claim 11, wherein p is 3 or 4.

13. The method according to any one of claims 10 to 12, wherein the eribulin or the salt thereof is eribulin methanesulfonate.

14. The method according to any one of claims 10 to 13, wherein the acylating agent comprises: diphenyl carbonate, bis(4-nitrophenyl) carbonate, bis(2-nitrophenyl) carbonate, bis(3-nitrophenyl) carbonate, phenyl chloroformate, 4-nitrophenyl chloroformate, 2-nitrophenyl chloroformate, or 3-nitrophenyl chloroformate.

15. Use of an antibody-drug conjugate produced by the method according to any one of claims 10 to 14 in the manufacture of a medicament for treating a cancer.

16. The use according to claim 15, wherein the cancer expresses folate receptor alpha (FRA), human epidermal growth factor receptor 2 (HER2), and/or mesothelin.