and exatecan are conjugated to each other via the linker, and confirmed an excellent antitumor effect exhibited by the conjugate to thereby complete the present disclosure.

[0014a] In one aspect, the present disclosure refers to a method for producing an antibody-drug conjugate, in which a drug-linker structure represented by the following formula is conjugated to an anti-HER2 antibody via a thioether bond,

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

comprising a step of

treating the anti-HER2 antibody in a reducing condition and thereafter

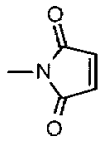
reacting the anti-HER2 antibody with a compound represented by the following formula:

(maleimid-N-yl)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

wherein,

(maleimid-N-yl)- is a group represented by the following formula:

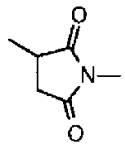
[Formula 1]



wherein the nitrogen atom is a connecting position,

-(Succinimid-3-yl-N)- has a structure represented by the following formula:

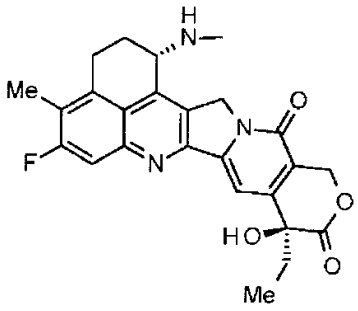
[Formula 2]



which is connected to the antibody at position 3 thereof and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1,

-(NH-DX) represents a group represented by the following formula:

[Formula 3]



wherein the nitrogen atom of the amino group at position 1 is a connecting position, and

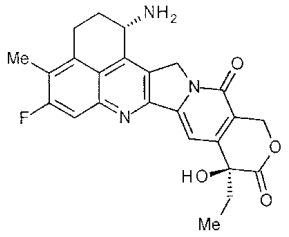
-GGFG- represents a tetrapeptide residue of -Gly-Gly-Phe-Gly-.

[0015]

Specifically, the present disclosure relates to the following.

[1] An antibody-drug conjugate wherein an antitumor compound represented by the following formula:

[Formula 2]



is conjugated to an anti-HER2 antibody via a linker having a structure represented by the following formula:

$-L^1-L^2-L^P-NH-(CH_2)n^1-L^a-(CH_2)n^2-C(=O)-$

via a thioether bond which is formed at a disulfide bond moiety present in the hinge part of the anti-HER2 antibody.

[0016]

Here, the anti-HER2 antibody is connected to the terminal L^1,

the antitumor compound is connected to the carbonyl group of the $-(CH_2)n^2-C(=O)-$ moiety with the nitrogen

atom of the amino group at position 1 as the connecting position,

wherein

n^1 represents an integer of 0 to 6,

n^2 represents an integer of 0 to 5,

L^1 represents -(Succinimid-3-yl-N)-$(CH_2)n^3$-C(=O)-,

wherein n^3 represents an integer of 2 to 8,

L^2 represents -NH-$(CH_2CH_2-O)n^4$-CH_2CH_2-C(=O)- or a single bond,

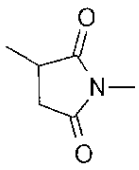
wherein n^4 represents an integer of 1 to 6,

L^P represents a peptide residue consisting of 2 to 7 amino acids,

L^a represents -O- or a single bond, and

-(Succinimid-3-yl-N)- has a structure represented by the following formula:

[Formula 3]



which is connected to the anti-HER2 antibody at position 3 thereof and is connected to the methylene group in the linker structure containing this structure on the nitrogen atom at position 1.

[0017]

The present disclosure further relates to each of the following.

Claims

[Claim 1]

A method for producing an antibody-drug conjugate, in which a drug-linker structure represented by the following formula is conjugated to an anti-HER2 antibody via a thioether bond,

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

comprising a step of

treating the anti-HER2 antibody in a reducing condition and thereafter

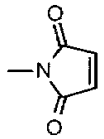
reacting the anti-HER2 antibody with a compound represented by the following formula:

(maleimid-N-yl)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX)

wherein,

(maleimid-N-yl)- is a group represented by the following formula:

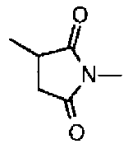
[Formula 1]



wherein the nitrogen atom is a connecting position,

-(Succinimid-3-yl-N)- has a structure represented by the following formula:

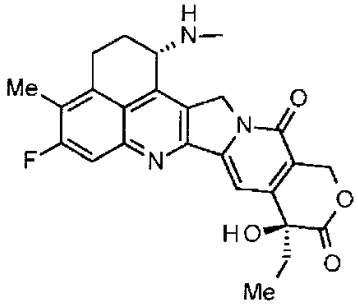
[Formula 2]



which is connected to the antibody at position 3 thereof and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1,

-(NH-DX) represents a group represented by the following formula:

[Formula 3]



wherein the nitrogen atom of the amino group at position 1 is a connecting position, and

-GGFG- represents a tetrapeptide residue of -Gly-Gly-Phe-Gly-.

[Claim 2]

The method according to claim 1, wherein an average number of units of the drug-linker structure conjugated per antibody is in a range of from 2 to 8.

[Claim 3]

The method according to claim 1, wherein an average number of units of the drug-linker structure conjugated per antibody is in a range of from 3 to 8.