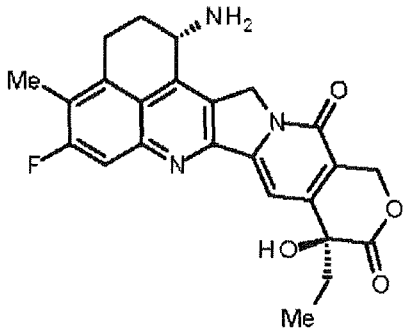
effect of the anti-HER3 antibody is expected, and a dose of the antitumor compound can be reduced compared to a case of administering the compound alone, and thus an influence of the antitumor compound on normal cells can be alleviated so that higher safety can be achieved.
In this connection, the inventors created a linker with a specific structure and succeeded in obtaining an antibody-drug conjugate in which the anti-HER3 antibody 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 invention.

[0013] Specifically, the present invention relates to the followings~~.~~: In one aspect, the present invention refers to an antibody-drug conjugate wherein an antitumor compound represented by the following formula

[Chem. 1]



is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

wherein, the anti-HER3 antibody is connected to the terminal of L^1,

the antitumor compound is connected to the carbonyl group of $-(CH_2)n^2-C(=O)-$ moiety or the C terminal of L^P, with the nitrogen atom of the amino group at position 1 as a 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,

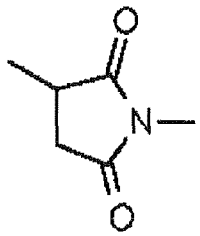
wherein n^4 represents an integer of 1 to 6,

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

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

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

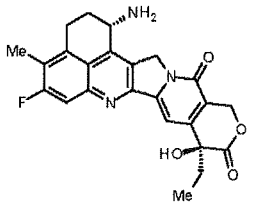
[Chem. 2]



which is connected to the anti-HER3 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.

In another aspect, the present invention refers to an antibody-drug conjugate wherein an antitumor compound represented by the following formula

[Chem. 5]



is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

wherein, the anti-HER3 antibody is connected to the terminal of L^1,

the antitumor compound is connected to the carbonyl group of $-(CH_2)n^2-C(=O)-$ moiety with the nitrogen atom of the amino group at position 1 as a 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,

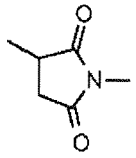
wherein n^4 represents an integer of 1 to 6,

L^P represents a tetrapeptide residue of -GGFG-,

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

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

[Chem. 6]



which is connected to the anti-HER3 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.

In another aspect, the present invention refers to a medicine comprising the antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof.

In one aspect, the present invention refers to an antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to claim 1, a salt thereof or a hydrate thereof. In one aspect, the present invention refers to the use of a antitumor medicine and/or anticancer medicine according to the present invention in the manufacture of a medicament for treating any disease selected from the group consisting of lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer,

rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, and penis cancer.

In still another aspect, the present invention refers to a pharmaceutical composition comprising the antibody-drug conjugate according to claim 1, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

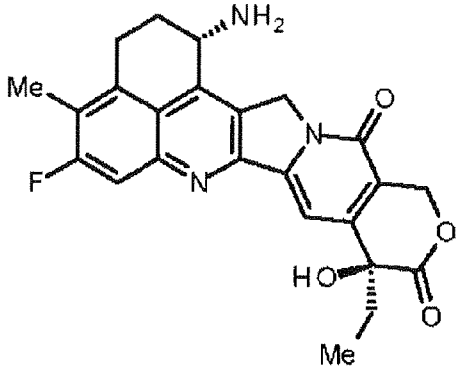
In one aspect, the present invention refers to the use of a pharmaceutical composition according to the present invention in the manufacture of a medicament for treating any disease selected from the group consisting of lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, and penis cancer.

In one aspect, the present invention refers to the use of an antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof in the manufacture of a medicament for treating tumor and/or cancer.

In still another aspect, the present invention refers to the use of a composition according to the present invention or medicine according to the present invention in the manufacture of a medicament for treating any disease selected from the group consisting of lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, and penis cancer.

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

[Chem. 2]



is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

[0014] Here, the anti-HER3 antibody is connected to the terminal of L^1, the antitumor compound is connected to the carbonyl group of $-(CH_2)n^2-C(=O)-$ moiety or the C terminal of L^P, with the nitrogen atom of the amino group at position 1 as a connecting position.

In the formula, 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,

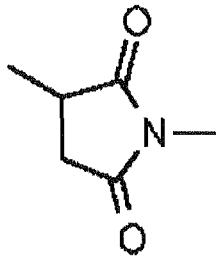
wherein n^4 represents an integer of 1 to 6,

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

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

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

[Chem. 3]



which is connected to the anti-HER3 antibody at position 3 thereof and is connected on the nitrogen atom at position 1 to a methylene group in the linker structure containing this structure.

[0015] The present ~~invention~~disclosure further relates to each of the followings.

[2] The antibody-drug conjugate according to [1], wherein the peptide residue of L^P is a peptide residue comprising an amino acid selected from phenylalanine, glycine, valine, lysine, citrulline, serine, glutamic acid, and aspartic acid.

[3] The antibody-drug conjugate according to [1] or [2], wherein L^P is a peptide residue selected from the following group

-GGF-,
-DGGF-,
-(D-)D-GGF-,
-EGGF-,
-GGFG-,
-SGGF-,
-KGGF-,
-DGGFG-,
-GGFGG-,
-DDGGFG-,
-KDGGFG-, and
-GGFGGGF-;
(wherein, "(D-)D" represents D-aspartic acid).

[4] The antibody-drug conjugate according to [1] or [2], wherein L^P is a peptide residue comprising 4 or 5 amino acids.

[5] The antibody-drug conjugate according to any one of [1] to [4], wherein L^P is -GGFG- or -DGGFG-.

[6] The antibody-drug conjugate according to any one of [1] to [4], wherein L^P is -GGFG-.

[0016]

[7] The antibody-drug conjugate according to any one of [1] to [6], wherein n^3 is an integer of 2 to 5 and L^2 is a single bond.

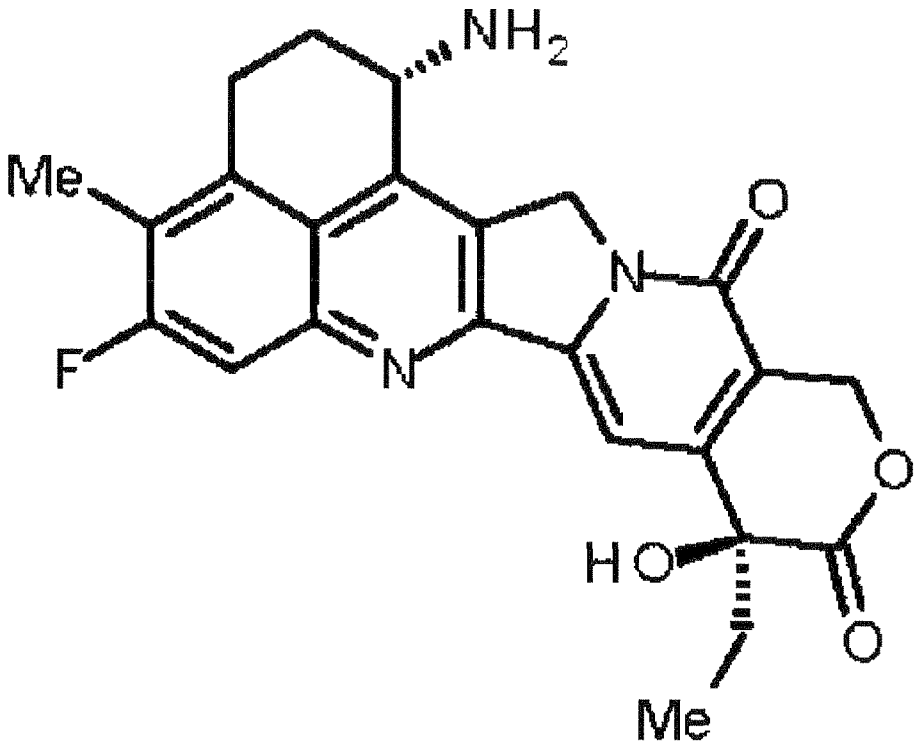
[8] The antibody-drug conjugate according to any one of [1] to [7], wherein the

Claims

[Claim 1]

An antibody-drug conjugate wherein an antitumor compound represented by the following formula

[Chem. 1]



is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

wherein, the anti-HER3 antibody is connected to the terminal of L^1,

the antitumor compound is connected to the carbonyl group of $-(CH_2)n^2-C(=O)-$ moiety or the C terminal of L^P, with the nitrogen atom of the amino group at position 1 as a connecting position,

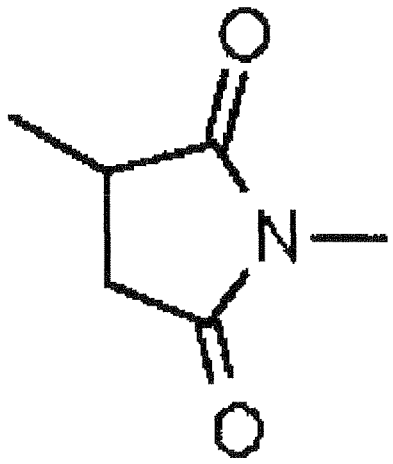
wherein, n^1 represents an integer of 0 to 6,

n^2 represents an integer of 0 to 5,

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

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,
-(Succinimid-3-yl-N)- has a structure represented by the following formula:
[Chem. 2]



which is connected to the anti-HER3 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.

[Claim 2]

The antibody-drug conjugate according to claim 1, wherein the peptide residue of L^P is a peptide residue comprising an amino acid selected from phenylalanine, glycine, valine, lysine, citrulline, serine, glutamic acid, and aspartic acid.

[Claim 3]

The antibody-drug conjugate according to claim 2, wherein L^P is a peptide residue selected from the following group:
-GGF-,
-DGGF-,
-(D-)D-GGF-,
-EGGF-,
-GGFG-,

-SGGF-,
-KGGF-,
-DGGFG-,
-GGFGG-,
-DDGGFG-,
-KDGGFG-,
-GGFGGGF-;
wherein, "(D-)D" represents D-aspartic acid.

[Claim 4]
The antibody-drug conjugate according to claim 2, wherein L^P is a peptide residue comprising 4 or 5 amino acids.

[Claim 5]
The antibody-drug conjugate according to claim 4, wherein L^P is -GGFG- or -DGGFG-.

[Claim 6]
The antibody-drug conjugate according to claim 4, wherein L^P is -GGFG-.

[Claim 7]
The antibody-drug conjugate according to claim 1, wherein n^3 is an integer of 2 to 5 and L^2 is a single bond.

[Claim 8]
The antibody-drug conjugate according to claim 1, wherein n^3 is an integer of 2 to 5, L^2 is $-NH-(CH_2CH_2-O)n^4-CH_2CH_2-C(=O)-$, and n^4 is 2 or 4.

[Claim 9]
The antibody-drug conjugate according to claim 1, wherein the linker is $-L^1-L^2-L^P-NH-(CH_2)n^1-L^a-(CH_2)n^2-C(=O)-$.

[Claim 10]
The antibody-drug conjugate according to claim 9, wherein $-NH-(CH_2)n^1-L^a-(CH_2)n^2-C(=O)-$ is a partial structure having a chain length of 4 to 7 atoms.

[Claim 11]

The antibody-drug conjugate according to claim 9, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is a partial structure having a chain length of 5 or 6 atoms.

[Claim 12]

The antibody-drug conjugate according to claim 10, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is any one of the followings:

-NH-CH_2CH_2-C(=O)-,

-NH-$CH_2CH_2CH_2$-C(=O)-,

-NH-$CH_2CH_2CH_2CH_2$-C(=O)-,

-NH-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-,

-NH-CH_2-O-CH_2-C(=O)-,

-NH-CH_2CH_2-O-CH_2-C(=O)-.

[Claim 13]

The antibody-drug conjugate according to claim 12, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is any one of the followings:

-NH-$CH_2CH_2CH_2$-C(=O)-,

-NH-CH_2-O-CH_2-C(=O)-,

-NH-CH_2CH_2-O-CH_2-C(=O)-.

[Claim 14]

The antibody-drug conjugate according to claim 1, wherein the drug-linker structure moiety in which a drug is connected to -L^1-L^2-L^P-NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- or -L^1-L^2-L^P- is one drug-linker structure selected from the following group:

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

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

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-CH_2CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-(NH-DX),

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

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2CH_2-O-CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-(NH-DX),

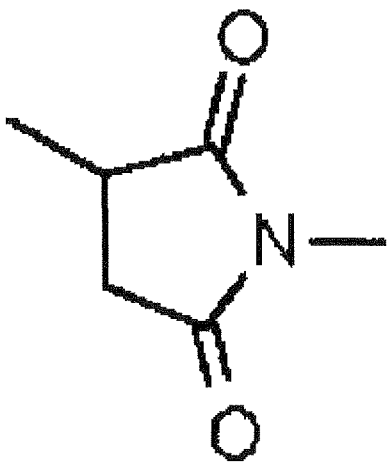
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-DGGFG-(NH-DX),

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

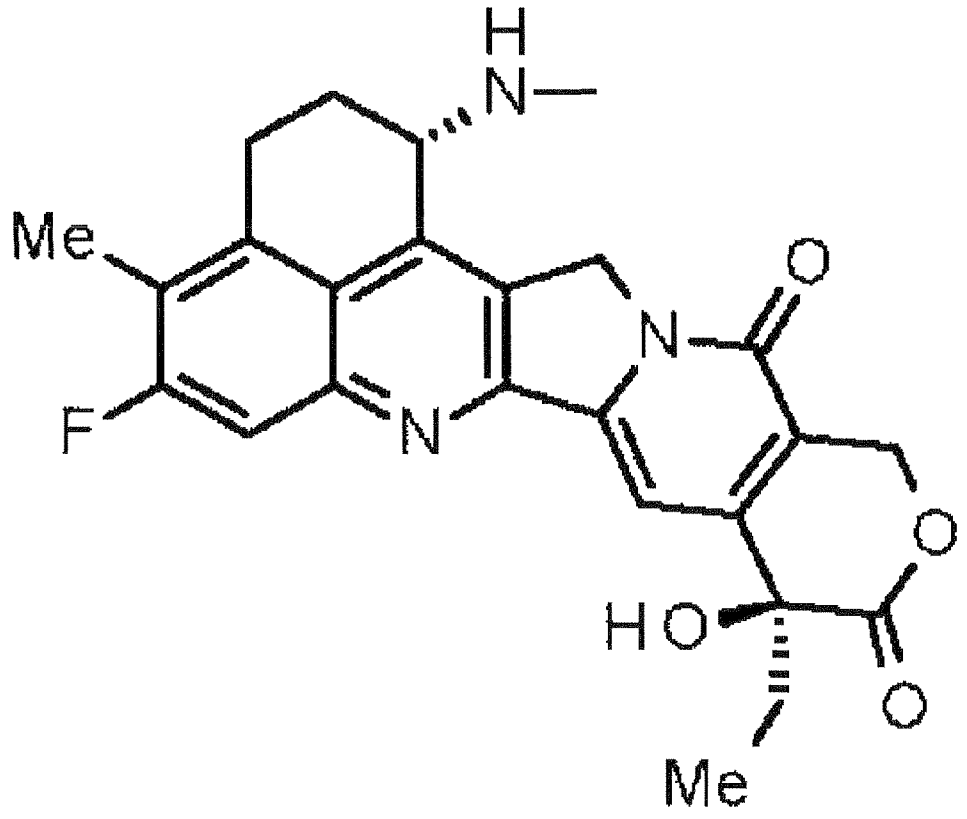
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-(NH-DX);

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

[Chem. 3]



which is connected to the anti-HER3 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, with the nitrogen atom of the amino group at position 1 being a connecting position,
[Chem. 4]



-GGFG- represents a tetrapeptide residue of -Gly-Gly-Phe-Gly- and
-DGGFG- represents a pentapeptide residue of
-Asp-Gly-Gly-Phe-Gly-.

[Claim 15]

The antibody-drug conjugate according to claim 14, wherein a drug-linker structure moiety is one drug-linker structure selected from the following group:
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

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

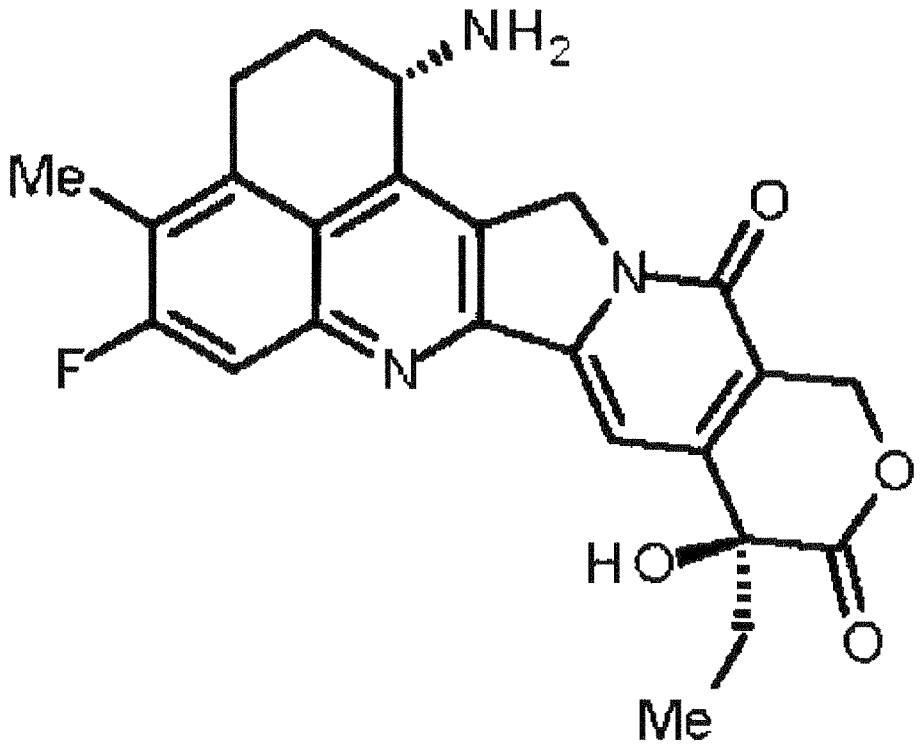
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-(NH-DX).

[Claim 16]

An antibody-drug conjugate wherein an antitumor compound represented by the following formula

[Chem. 5]



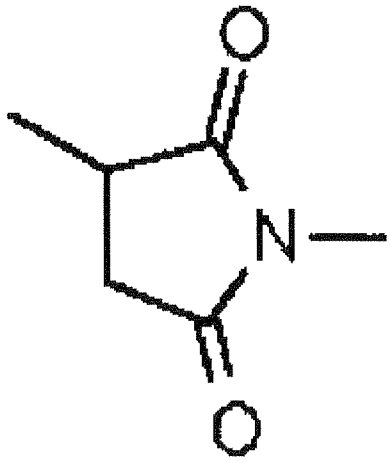
is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

wherein, the anti-HER3 antibody is connected to the terminal of L^1,

the antitumor compound is connected to the carbonyl group of -$(CH_2)n^2$-C(=O)- moiety with the nitrogen atom of the amino group at position 1 as a 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 tetrapeptide residue of -GGFG-,
L^a represents -O- or a single bond,
-(Succinimid-3-yl-N)- has a structure represented by the following formula:
[Chem. 6]



which is connected to the anti-HER3 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.

[Claim 17]

The antibody-drug conjugate according to claim 16, wherein n^1 is 3, n^2 is 0, n^3 is 2, L^2 is -NH-$(CH_2CH_2$-O$)n^4$-CH_2CH_2-C(=O)-, n^4 is 2, and L^a is a single bond, or
n^1 is 1, n^2 is 1, n^3 is 5, L^2 is a single bond, and L^a is -O-, or
n^1 is 2, n^2 is 1, n^3 is 5, L^2 is a single bond, and L^a is -O-.

[Claim 18]

The antibody-drug conjugate according to claim 16, wherein n^3 is 2 or 5 and L^2 is a single bond.

[Claim 19]

The antibody-drug conjugate according to claim 16, wherein n^3 is 2 or 5, L^2 is -NH-$(CH_2CH_2-O)n^4$-CH_2CH_2-C(=O)-, and n^4 is 2 or 4.

[Claim 20]

The antibody-drug conjugate according to claim 16, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is any one of the followings:

-NH-$CH_2CH_2CH_2$-C(=O)-,

-NH-CH_2-O-CH_2-C(=O)-,

-NH-CH_2CH_2-O-CH_2-C(=O)-.

[Claim 21]

The antibody-drug conjugate according to claim 1, wherein an average number of units of the selected one drug-linker structure conjugated per antibody is in a range of from 1 to 10.

[Claim 22]

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

[Claim 23]

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

[Claim 24]

A medicine comprising the antibody-drug conjugate according to claim 1, a salt thereof or a hydrate thereof.

[Claim 25]

An antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to claim 1, a salt thereof or a hydrate thereof.

[Claim 26]

Use of a antitumor medicine and/or anticancer medicine according to claim 25 in the manufacture of a medicament for treating any disease selected from the group consisting of lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, and penis cancer.

[Claim 27]

A pharmaceutical composition comprising the antibody-drug conjugate according to claim 1, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

[Claim 28]

Use of a pharmaceutical composition according to claim 27 in the manufacture of a medicament for treating any disease selected from the group consisting of lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, and penis cancer.

[Claim 29]

Use of an antibody-drug conjugate according to claim 1, a salt thereof or a hydrate thereof in the manufacture of a medicament for treating tumor and/or cancer.

[Claim 30]

The medicine according to claim 24, the antitumor medicine and/or anticancer medicine according to claim 25, the pharmaceutical composition according to claim 27, or the use according to claim 26 or 28 or 29, which is to be used in administration in combination with an additional medicine.

[Claim 31]

The pharmaceutical composition according to claim 27, further comprising even an additional medicine as an active ingredient.

[Claim 32]

The antibody-drug conjugate according to claim 1, wherein the antibody comprises the CDRH1 to CDRH3 and CDRL1 to CDRL3 of U1-49, U1-53, U1-59, U1-7 or U1-9 in the heavy and light chains, respectively.

[Claim 33]

The antibody-drug conjugate according to claim 1, wherein the antibody comprises the heavy chain variable region and the light chain variable chain of U1-49, U1-53, U1-59, U1-7 or U1-9 on the heavy and light chains, respectively.

[Claim 34]

The antibody-drug conjugate according to claim 1, wherein the antibody comprises the amino acid sequences represented by or comprising SEQ ID Nos: 42 and 33, SEQ ID Nos: 54 and 56, SEQ ID Nos: 70 and 72, SEQ ID Nos: 92 and 94, or, SEQ ID Nos: 96 and 98, in the heavy and light chains, respectively.

[Claim 35]

The antibody-drug conjugate according to claim 1, wherein the antibody comprises the amino acid sequences represented by or

comprising SEQ ID Nos: 583 (Figure 1) and 584 (Figure 2) in the heavy and light chains, respectively.

[Claim 36]

A pharmaceutical composition comprising the antibody-drug conjugate according to claim 32, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

[Claim 37]

A medicine comprising the antibody-drug conjugate according to claim 32, a salt thereof or a hydrate thereof.

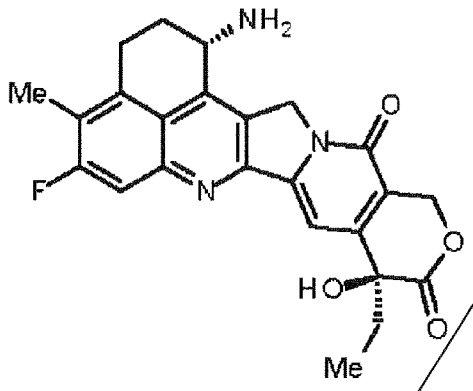
[Claim 38]

Use of a composition according to claim 36 or medicine according to claim 37 in the manufacture of a medicament for treating any disease selected from the group consisting of lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, and penis cancer.

Claims

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

[Chem.1]



is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

wherein, the anti-HER3 antibody is connected to the terminal of L^1,

the antitumor compound is connected to the carbonyl group of $-(CH_2)n^2-C(=O)-$ moiety or the C terminal of L^P, with the nitrogen atom of the amino group at position 1 as a 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,

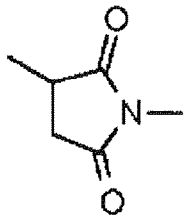
wherein n^4 represents an integer of 1 to 6,

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

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

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

[Chem.2]



which is connected to the anti-HER3 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.

[Claim 2] The antibody-drug conjugate according to claim 1, wherein the peptide residue of L^P is a peptide residue comprising an amino acid selected from phenylalanine, glycine, valine, lysine, citrulline, serine, glutamic acid, and aspartic acid.

[Claim 3] The antibody-drug conjugate according to claim 1 or 2, wherein L^P is a peptide residue selected from the following group:

-GGF-,
-DGGF-,
-(D-)D-GGF-,
-EGGF-,
-GGFG-,
-SGGF-,
-KGGF-,
-DGGFG-,
-GGFGG-,
-DDGGFG-,
-KDGGFG-,
-GGFGGGF-;

wherein, "(D-)D" represents D-aspartic acid.

[Claim 4] The antibody-drug conjugate according to claim 1 or 2, wherein L^P is a peptide residue comprising 4 or 5 amino acids.

[Claim 5] The antibody-drug conjugate according to any one of claims 1 to 4, wherein L^P is -GGFG- or -DGGFG-.

[Claim 6] The antibody-drug conjugate according to any one of claims 1 to 4, wherein L^P is -GGFG-.

[Claim 7] The antibody-drug conjugate according to any one of claims 1 to 6, wherein n^3 is an integer of 2 to 5 and L^2 is a single bond.

[Claim 8] The antibody-drug conjugate according to any one of claims 1 to 7, wherein the linker is -L^1-L^2-L^P-NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)-.

[Claim 9] The antibody-drug conjugate according to claim 8, wherein n^3 is an integer of 2 to 5, L^2 is -NH-$(CH_2CH_2$-O$)n^4$-CH_2CH_2-C(=O)-, and n^4 is 2 or 4.

[Claim 10] The antibody-drug conjugate according to claim 8 or 9, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is a partial structure having a chain length of 4 to 7 atoms.

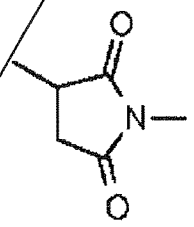
[Claim 11] The antibody-drug conjugate according to claim 8 or 9, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is a partial structure having a chain length of 5 or 6 atoms.

[Claim 12] The antibody-drug conjugate according to claim 10 or 11, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is any one of the followings:
-NH-CH_2CH_2-C(=O)-,
-NH-$CH_2CH_2CH_2$-C(=O)-,
-NH-$CH_2CH_2CH_2CH_2$-C(=O)-,
-NH-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-,
-NH-CH_2-O-CH_2-C(=O)-,
-NH-CH_2CH_2-O-CH_2-C(=O)-.

[Claim 13] The antibody-drug conjugate according to claim 12, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is any one of the followings:
-NH-$CH_2CH_2CH_2$-C(=O)-,
-NH-CH_2-O-CH_2-C(=O)-,
-NH-CH_2CH_2-O-CH_2-C(=O)-.

[Claim 14] The antibody-drug conjugate according to claim 1, wherein the drug-linker structure moiety in which a drug is connected to -L^1-L^2-L^P-NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- or -L^1-L^2-L^P- is one drug-linker structure selected from the following group:
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-(NH-DX),

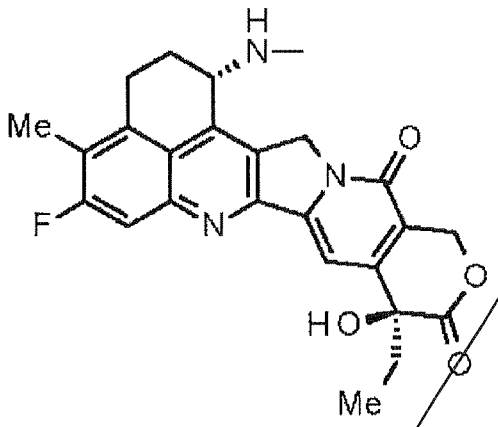
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-CH_2CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-$CH_2CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2CH_2-O-CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-CH_2CH_2-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-(NH-DX),
-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-DGGFG-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-(NH-DX),
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-(NH-DX);
wherein, -(Succinimid-3-yl-N)- has a structure represented by the following formula:
[Chem.3]



which is connected to the anti-HER3 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,

with the nitrogen atom of the amino group at position 1 being a connecting position,

[Chem.4]



-GGFG- represents a tetrapeptide residue of -Gly-Gly-Phe-Gly- and -DGGFG- represents a pentapeptide residue of -Asp-Gly-Gly-Phe-Gly-.

[Claim 15] The antibody-drug conjugate according to claim 14, wherein a drug-linker structure moiety is one drug-linker structure selected from the following group:

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

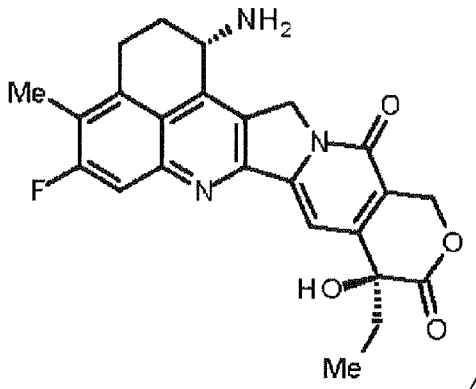
-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-(NH-DX),

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-DGGFG-(NH-DX).

[Claim 16] An antibody-drug conjugate wherein an antitumor compound represented by the following formula

[Chem.5]



is conjugated to an anti-HER3 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-HER3 antibody via a linker having a structure represented by the following formula:

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

wherein, the anti-HER3 antibody is connected to the terminal of L^1, the antitumor compound is connected to the carbonyl group of $-(CH_2)n^2-C(=O)-$ moiety,

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,

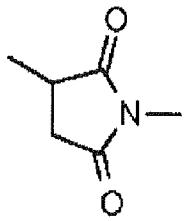
wherein n^4 represents an integer of 1 to 6,

L^P represents a tetrapeptide residue of -GGFG-,

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

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

[Chem.6]



which is connected to the anti-HER3 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.

[Claim 17] The antibody-drug conjugate according to claim 16, wherein n^1 is 3, n^2 is 0, n^3 is 2, L^2 is -NH-$(CH_2CH_2-O)n^4$-CH_2CH_2-C(=O)-, n^4 is 2, and L^a is a single bond, or
n^1 is 1, n^2 is 1, n^3 is 5, L^2 is a single bond, and L^a is -O-, or
n^1 is 2, n^2 is 1, n^3 is 5, L^2 is a single bond, and L^a is -O-.

[Claim 18] The antibody-drug conjugate according to claim 16 or 17, wherein n^3 is 2 or 5 and L^2 is a single bond.

[Claim 19] The antibody-drug conjugate according to claim 16 or 17, wherein n^3 is 2 or 5, L^2 is -NH-$(CH_2CH_2-O)n^4$-CH_2CH_2-C(=O)-, and n^4 is 2 or 4.

[Claim 20] The antibody-drug conjugate according to any one of claims 16 to 19, wherein -NH-$(CH_2)n^1$-L^a-$(CH_2)n^2$-C(=O)- is any one of the followings:
-NH-$CH_2CH_2CH_2$-C(=O)-,
-NH-CH_2-O-CH_2-C(=O)-,
-NH-CH_2CH_2-O-CH_2-C(=O)-.

[Claim 21] The antibody-drug conjugate according to any one of claims 1 to 20, wherein an average number of units of the selected one drug-linker structure conjugated per antibody is in a range of from 1 to 10.

[Claim 22] The antibody-drug conjugate according to any one of claims 1 to 20, wherein the average number of units of the selected one drug-linker structure conjugated per antibody is in a range of from 2 to 8.

[Claim 23] The antibody-drug conjugate according to any one of claims 1 to 20, wherein the average number of units of the selected one drug-linker structure conjugated per antibody is in a range of from 3 to 8.

[Claim 24] A medicine comprising the antibody-drug conjugate according to any one of claims 1 to 23, a salt thereof or a hydrate thereof.

[Claim 25] An antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to any one of claims 1 to 23, a salt thereof or a hydrate thereof.

[Claim 26] The antitumor medicine and/or anticancer medicine according to claim 25, which is applied to lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, stomach cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer,

vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, or penis cancer.

[Claim 27] A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1 to 23, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

[Claim 28] The pharmaceutical composition according to claim 27, which is applied to lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, stomach cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, or penis cancer.

[Claim 29] A method for treating tumor and/or cancer comprising administering the antibody-drug conjugate according to any one of claims 1 to 23, a salt thereof or a hydrate thereof.

[Claim 30] The medicine according to claim 24, the antitumor medicine and/or anticancer medicine according to claim 25 or 26, the pharmaceutical composition according to claim 27 or 28, or the treatment method according to claim 29, which is used in administration in combination with an additional medicine.

[Claim 31] The pharmaceutical composition according to claim 27 or 28, further comprising even an additional medicine as an active ingredient.

[Claim 32] The antibody-drug conjugate according to any one of claims 1 to 23, wherein the antibody comprises the CDRH1 to CDRH3 and CDRL1 to CDRL3 of U1-49, U1-53, U1-59, U1-7 or U1-9 in the heavy and light chains, respectively.

[Claim 33] The antibody-drug conjugate according to any one of claims 1 to 23 and 32, wherein the antibody comprises the heavy chain variable region and the light chain variable chain of U1-49, U1-53, U1-59, U1-7 or U1-9 on the heavy and light chains, respectively.

[Claim 34] The antibody-drug conjugate according to any one of claims 1 to 23, 32 and 33, wherein the antibody comprises the amino acid sequences represented by or comprising SEQ ID Nos: 42 and 33, SEQ ID Nos: 54

and 56, SEQ ID Nos: 70 and 72, SEQ ID Nos: 92 and 94, or, SEQ ID Nos: 96 and 98, in the heavy and light chains, respectively.

[Claim 35] The antibody-drug conjugate according to any one of claims 1 to 23 and 32 to 34, wherein the antibody comprises the amino acid sequences represented by or comprising SEQ ID Nos: 583 (Figure 1) and 584 (Figure 2) in the heavy and light chains, respectively.

[Claim 36] A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 32 to 35, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

[Claim 37] A medicine comprising the antibody-drug conjugate according to any one of claims 32 to 35, a salt thereof or a hydrate thereof.

[Claim 38] The composition according to claim 36 or medicine according to claim 37, which is applied to lung cancer, kidney cancer, urothelial cancer, colorectal cancer, prostate cancer, glioblastoma multiforme, ovarian cancer, pancreatic cancer, breast cancer, melanoma, liver cancer, bladder cancer, stomach cancer, gastrointestinal stromal tumor, cervical cancer, head and neck cancer, esophageal cancer, epidermoid cancer, peritoneal cancer, adult glioblastoma multiforme, hepatic cancer, hepatocellular carcinoma, colon cancer, rectal cancer, colon and rectal cancer, endometrial cancer, uterus cancer, salivary cancer, renal cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anus carcinoma, or penis cancer.