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.

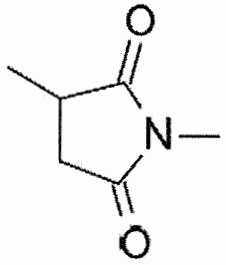
In this connection, the inventors created a linker with a specific structure and succeeded in obtaining an antibody-drug conjugate in which the anti-TROP2 antibody and exatecan are conjugated to each other via the linker, and confirmed an excellent antitumor effect exhibited by the conjugate to thereby complete the present invention.

[0014]

Specifically, the present invention relates to the followings.

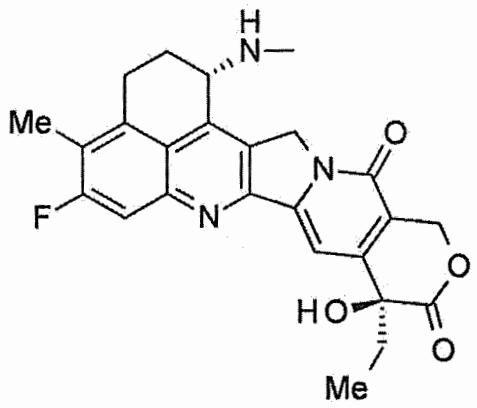
In one aspect, an antibody-drug conjugate wherein a drug-linker structure represented by the following formula is conjugated to an anti-TROP2 antibody, -(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX), wherein -(Succinimid-3-yl-N)- has a structure represented by the following formula:

[Formula 1]



which is connected to the anti-TROP2 antibody at position 3 thereof via a thioeter bond and and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1, and -(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.

[Formula 2]



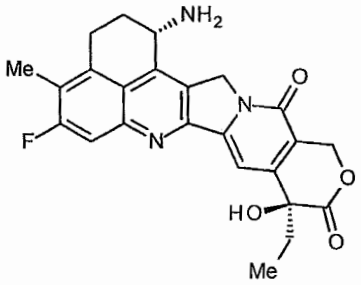
wherein the nitrogen atom of the amino group at position 1 is a connecting position. In another aspect, the present invention refers to a medicine comprising the antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof. In still another aspect, the present invention refers to an antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof.

In yet another aspect, the present invention refers to an antitumor drug and/or anticancer drug medicine comprising the antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof in the manufacture of a medicament for treating 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, cervical cancer, head and neck cancer, or esophageal cancer. In yet another aspect, the present invention refers to a pharmaceutical composition comprising the antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient. In another aspect, the present invention refers to a pharmaceutical composition comprising the antibody-drug conjugate according to the present invention, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient in the manufacture of a medicament for treating 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, cervical cancer, head and neck cancer, or esophageal cancer. Also described herein is the following:

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

[Formula 2]



is conjugated to an anti-TROP2 antibody by a thioether bond which is formed at a disulfide bond moiety present in a hinge part of the anti-TROP2 antibody via a linker having a structure represented by the following formula:

[0016]

The present disclosure further describes 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-;

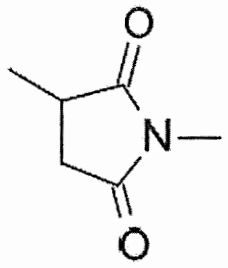
wherein "(D-)D" represents D-aspartic acid.

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

[Claims]

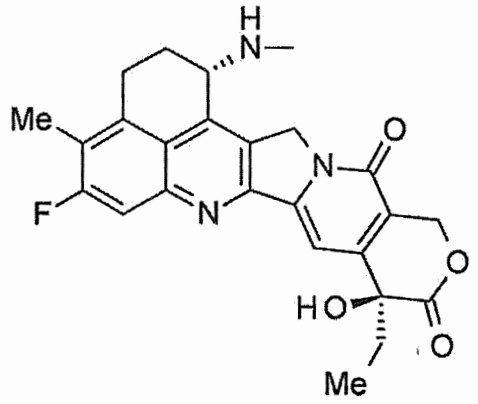
1. An antibody-drug conjugate wherein a drug-linker structure represented by the following formula is conjugated to an anti-TROP2 antibody, -(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX), wherein -(Succinimid-3-yl-N)- has a structure represented by the following formula:

[Formula 1]



which is connected to the anti-TROP2 antibody at position 3 thereof via a thioeter bond and and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1, and -(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.

[Formula 2]



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

2. The antibody-drug conjugate according to claim 1, wherein the anti-TROP2 antibody comprises CDRH1 consisting of the amino acid sequence of SEQ ID NO: 23, CDRH2 consisting of the amino acid sequence of SEQ ID NO: 24 and CDRH3 consisting of the amino acid sequence of SEQ ID NO: 25 in its heavy chain variable region and CDRL1 consisting of the amino acid sequence of SEQ ID NO: 26, CDRL2 consisting of the amino acid sequence of SEQ ID NO: 27 and CDRL3 consisting of the amino acid sequence of SEQ ID NO: 28 in its light chain variable region.

3. The antibody-drug conjugate according to claim 1, wherein the anti-TROP2 antibody comprises a heavy chain and a light chain selected from the group; a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQID NO: 12 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 18,a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 14 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 SEQ ID NO: 18, a heavy chain variable region consisting of the amino acid sequence of positions of 20 to 140 of SEQ ID NO: 14 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 20, and a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 16 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 22.

4. The antibody-drug conjugate according to claim 1, wherein the anti-TROP2 antibody comprises a heavy chain and a light chain selected from the group; a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 12

and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 18, a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 14 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 18,a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 14 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 20, and a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 16 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 22.

5. The antibody-drug conjugate according to claim 3, wherein the anti-TROP2 antibody comprises a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 12 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 18.

6. The antibody-drug conjugate according to claim 4, wherein the anti-TROP2 antibody comprises a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 12 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 18.

7. The antibody-drug conjugate according to claim 4, wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

8. The antibody-drug conjugate according to claim 6, wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

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

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

11. A medicine comprising the antibody-drug conjugate according to any one of claims 1 to 10, a salt thereof or a hydrate thereof.

12. An antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to any one of claims 1 to 10, a salt thereof or a hydrate thereof.

13. Use of an antitumor drug and/or anticancer drug medicine comprising the antibody-drug conjugate according to any one of claims 1 to 10, a salt thereof or a hydrate thereof in the manufacture of a medicament for treating 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, cervical cancer, head and neck cancer, or esophageal cancer.

14. A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1 to 10, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

15. Use of a pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1 to 10, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient in the manufacture of a medicament for treating 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, cervical cancer, head and neck cancer, or esophageal cancer.