[NPL 5] Kumazawa, E., Tohgo, A., Exp. Opin. Invest. Drugs (1998) 7, 625-632.
[NPL 6] Mitsui, I., et al., Jpn J. Cancer Res. (1995) 86, 776-786.
[NPL 7] Takiguchi, S., et al., Jpn J. Cancer Res. (1997) 88, 760-769.
[NPL 8] Joto, N. et al., Int J Cancer (1997) 72, 680-686.
[NPL 9] Kumazawa, E. et al., Cancer Chemother. Pharmacol. (1998) 42, 210-220.
[NPL 10] De Jager, R., et al., Ann N Y Acad Sci (2000) 922, 260-273.
[NPL 11] Inoue, K. et al. Polymer Drugs in the Clinical Stage, Edited by Maeda et al., (2003) 145-153.
[NPL 12] Kumazawa, E. et al., Cancer Sci (2004) 95, 168-175.
[NPL 13] Soepenberg, O. et al., Clinical Cancer Research, (2005) 11, 703-711.
[NPL 14] Wente M. N. et al., Investigational New Drugs (2005) 23, 339-347.
[NPL 15] Plowman, et al., Proc. Natl. Acad. Sci. U.S.A. (1990) 87, 4905-4909.
[NPL 16] Kraus et al., Proc. Natl. Acad. Sci. U.S.A. (1989) 86, 9193-9197.
[NPL 17] Kraus et al., Proc. Natl. Acad. Sci. U.S.A. (1993) 90, 2900-2094.
[NPL 18] Alimandi et al., Oncogene (1995) 10, 1813-1821.
[NPL 19] DeFazio et al., Int. J. Cancer (2000) 87, 487-498.
[NPL 20] Nadiu et al., Br. J. Cancer (1998) 78, 1385-1390.

[**SUMMARY**]

[Technical Problem]

[0011] With regard to the treatment of tumor using an antibody, an insufficient antitumor effect may be observed even when the antibody recognizes an antigen and binds to tumor cells, and thus a more effective antitumor antibody is sometimes needed. Further, many antitumor low-molecular-weight compounds have a problem in safety like side effect and toxicity even the compounds have an excellent antitumor effect. As such, it remains as a subject to achieve a superior therapeutic effect by further enhancing the safety. Thus, an object of the present invention is to provide an antitumor drug having an excellent therapeutic effect, which is excellent in terms of antitumor effect and safety.

[Solution to Problem]

[0012] The inventors thought that, since the anti-HER3 antibody is an antibody capable of targeting tumor cells, that is, it is an antibody having a property of recognizing tumor cells, a property of binding to tumor cells, a property of internalizing in tumor cells, a cytocidal activity against tumor cells, or the like, when exatecan as an antitumor compound is converted into an antibody-drug conjugate by conjugation to the antibody via a linker structure moiety, the antitumor compound can be more surely delivered to tumor cells to specifically exhibit the antitumor effect of the compound in tumor cells, and thus the antitumor effect can be surely exhibited and also an enhanced cytocidal

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.

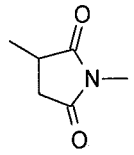
[0013] Specifically, the present invention relates to the following: in one aspect, the present invention refers to an antibody-drug conjugate wherein a drug-linker structure represented by the following formula is conjugated to an anti-HER3 antibody,

-(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:

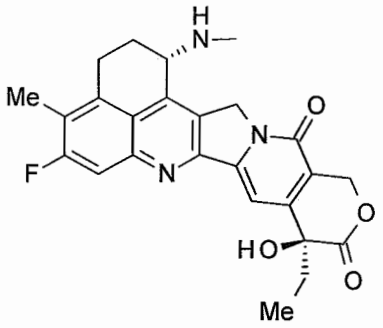
[Formula 1]



which is connected to the anti-HER3 antibody at position 3 thereof via a thioether bond 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]



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 yet 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 the use of 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 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, 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.

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 yet another aspect, the present invention refers to the use of 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, 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.

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 yet 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 yet another invention, the present invention refers to the Use of a pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 9 to 13, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically

acceptable formulation ingredient or the 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, 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.

Claims

[Claim 1]

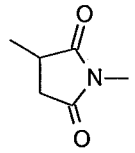
An antibody-drug conjugate wherein a drug-linker structure represented by the following formula is conjugated to an anti-HER3 antibody,

-(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:

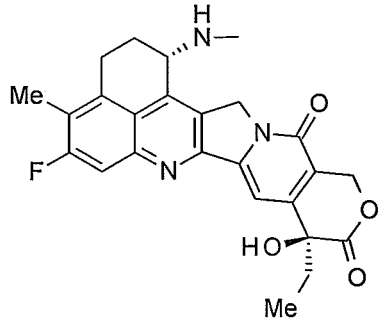
[Formula 1]



which is connected to the anti-HER3 antibody at position 3 thereof via a thioether bond 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]



[Claim 2]

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

[Claim 3]

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

[Claim 4]

A medicine comprising the antibody-drug conjugate according to any one of claims 1 to 3, a salt thereof or a hydrate thereof.

[Claim 5]

An antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to any one of claims 1 to 3, a salt thereof or a hydrate thereof.

[Claim 6]

Use of an antitumor medicine and/or anticancer medicine comprising the antibody-drug conjugate according to any one of claims 1 to 3, 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, 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 7]

A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1 to 3, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

[Claim 8]

Use of a pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 1 to 3, 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, 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 9]

The antibody-drug conjugate according to any one of claims 1 to 3, wherein the anti-HER3 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 10]

The antibody-drug conjugate according to any one of claims 1 to 3 and 9, wherein the anti-HER3 antibody comprises the heavy chain variable region and the light chain variable region of U1-49, U1-53, U1-59, U1-7 or U1-9 on the heavy and light chains, respectively.

[Claim 11]

The antibody-drug conjugate according to any one of claims 1 to 3, 9 and 10, wherein the anti-HER3 antibody comprises the amino acid sequences represented by SEQ ID No: 42 and 44, SEQ ID No: 54 and 56, SEQ ID No: 70 and 72, SEQ ID No: 92 and 94, or, SEQ ID No: 96 and 98, in the heavy and light chains, respectively.

[Claim 12]

The antibody-drug conjugate according to any one of claims 1 to 3 and 9 to 11, wherein the anti-HER3 antibody comprises the amino acid sequences represented by SEQ ID No: 583 and 584 in the heavy and light chains, respectively.

[Claim 13]

The antibody-drug conjugate according to claim 12, wherein the anti-HER3 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[Claim 14]

A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 9 to 13, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient.

[Claim 15]

A medicine comprising the antibody-drug conjugate according to any one of claims 9 to 13, a salt thereof or a hydrate thereof.

[Claim 16]

Use of a pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 9 to 13, a salt thereof or a hydrate thereof as an active ingredient, and a pharmaceutically acceptable formulation ingredient or the medicine comprising the antibody-drug conjugate according to any one of claims 9 to 13, 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, 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.