

concentration from the concentration required for ensuring the original medicinal effects of MLN4924 has been identified (Non-patent Document 6). Further, since MLN4924 inhibits carbonic anhydrase II, which is highly expressed even in normal organs, such as red blood cells, kidneys, brain, and eyes, there is a concern that MLN4924 induces side effects, specifically, electrolyte abnormality, hypotonia bulbi, metabolic acidosis, polyuria, urinary calculus, and dysesthesia (Non-patent Document 8). Under such circumstances, a new NAE inhibitor that ensures NAE inhibitory activity, but that has a smaller carbonic anhydrase II inhibitory effect, has been desired.

Citation List

Patent Documents

[0005]

Patent Document 1: International Publication No. WO2006084281

Patent Document 2: International Publication No. WO2012061551

Non-patent Documents

[0006]

Non-patent Document 1: Nature Rev Mol Cell Biol, 2009, 10 (5): 319-31.

Non-patent Document 2: Genes & Cancer, 2010; 1 (7): 690-699

Non-patent Document 3: Journal of Cellular Physiology, 2000, 183, 10-17

Non-patent Document 4: Nature, 2009, 9; 458 (7239): 732-6

Non-patent Document 5: Mol Cancer Ther, 2014, 13 (6); 1-111625-1635

Non-patent Document 6: Mol Cancer Ther, 2012, 11 (4): 942-951

Non-patent Document 7: 9th International ISSX Meeting Abstract, p. 108

Non-patent Document 8: Israel Medical Association Journal, 2003, 5, April, 260-263

Summary of Invention

In Formula (A), preferable examples of the "C1-C6 alkoxy group that may have one or more of either halogen, C3-C7 saturated cycloalkyl group, or monocyclic or bicyclic unsaturated heterocycloalkyl group having at least one heteroatom selected from the group consisting of N, S, and O, as a substituent" represented by R₆ include methoxy group, difluoro methoxy group, trifluoro methoxy group, cyclopropyl methoxy group, 3-pyridyl methoxy group, pyrazol-1-ylmethoxy group, ethoxy group, 2,2,2-trifluoro ethoxy group, n-propoxy group, and isopropoxy group.

[0034]

In Formula (A), preferable examples of the "benzyloxy group that may have one or more carbamoyl groups as a substituent" represented by R₆ include benzyloxy group, and 3-carbamoyl benzyloxy group.

[0035]

In Formula (A), the mono- or di-(C1-C4 alkyl) amino group of the "mono- or di-(C1-C4 alkyl) amino group that may have one or more hydroxy group or phenyl group as a substituent" represented by R₆ refers to, among the above C1-C6 alkyl groups, an amino group monosubstituted or disubstituted with a C1-C4 alkyl group. Examples include methylamino group, ethylamino group, ~~dimethylamino group~~, diethylamino group, methylethylamino group, isopropylamino group, cyclobutylmethylamino group, and dimethylamino group. Preferably examples include methylamino group, ethylamino group, dimethylamino group, and isopropylamino group.

[0036]

In Formula (A), the "mono- or di-(C1-C4 alkyl) amino group that may have one or more hydroxy group or phenyl group as a substituent" represented by R₆ is preferably methylamino group, ethylamino group, isopropylamino group, hydroxyethylamino group, dimethylamino group, or phenylmethylamino group (benzylamino group).

[0037]

In Formula (A), the "C1-C6 alkoxy carbonyl group"

d]pyrimidin-5-yl]ethynyl]-3-ethoxy-5-fluoro-phenyl]morpholine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethoxy-4,6-
difluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
5 4-[4-[2-[4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidin-5-yl]ethynyl]-3,5-difluoro-phenyl]thio morpholine;
4-amino-5-[2-[2,6-difluoro-4-(3-hydroxy azetidin-1-
yl)phenyl]ethynyl]-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
10 [(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidine;
4-amino-5-[2-[4-(azetidin-1-yl)-2,6-difluoro-phenyl]ethynyl]-7-
| [~~(2R,3R,4S,5R)-3,4~~1R,2S,3R,4R)-2,3-dihydroxy-54-
[(sulfamoylamino)methyl]cyclopentyl]pyrrolo[2,3-d]pyrimidine;
15 4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethoxy-6-
fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-fluoro-6-
20 propoxy-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-[2-fluoro-6-
(2,2,2-trifluoro ethoxy)phenyl]ethynyl]pyrrolo[2,3-d]pyrimidine;
8-[2-[4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
25 | [~~(sulfamoylamino)methyl~~]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidin-5-yl]ethynyl]-7-fluoro-4-methyl-2,3-dihydro-1,4-
benzoxazine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-
30 ethylsulfanyl-6-fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine; 4-
amino-5-[2-[2-(cyclopropyl methoxy)-6-fluoro-phenyl]ethynyl]-7-
[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidine;
35 4-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-

- [(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethoxy-4,6-difluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-5-[2-[2,6-difluoro-4-(3-hydroxy azetidin-1-yl)phenyl]ethynyl]-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
- 5 [(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-d]pyrimidine;
4-amino-5-[2-[4-(azetidin-1-yl)-2,6-difluoro-phenyl]ethynyl]-7-
[~~(2R,3R,4S,5R)-3,4~~(1R,2S,3R,4R)-2,3-dihydroxy-5]-
[(sulfamoylamino)methyl]cyclopentyl]pyrrolo[2,3-d]pyrimidine;
- 10 4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethoxy-6-fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-fluoro-6-
- 15 propoxy-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
8-[2-[4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-d]pyrimidin-5-yl]ethynyl]-7-fluoro-4-methyl-2,3-dihydro-1,4-benzoxazine;
- 20 4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethylsulfanyl-6-fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-5-[2-[2-(cyclopropyl methoxy)-6-fluoro-phenyl]ethynyl]-7-
[(2R,3R,4S,5R)-3,4-dihydroxy-5-
- 25 [(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-d]pyrimidine;
4-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-
[(sulfamoylamino)methyl]cyclopentyl]-5-[2-(2-fluoro-6-methylsulfanyl-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
- 30 8-[2-[4-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-
[(sulfamoylamino)methyl]cyclopentyl]pyrrolo[2,3-d]pyrimidin-5-yl]ethynyl]-7-fluoro-4-methyl-2,3-dihydro-1,4-benzoxazine;
4-amino-7-[(1R,4R,5S)-4,5-dihydroxy-3-
[(sulfamoylamino)methyl]cyclopent-2-en-1-yl]-5-[2-(2-ethoxy-6-
- 35 fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;

difluorophenyl)piperidin-3-ol

The title compound was obtained as in step 1 of Example 23, except that (R)-piperidin-3-ol was used in place of morpholine.

5 [0315]

¹H-NMR (CDCl₃) δ: 6.39 (2H, d, J = 11.0 Hz), 3.91-3.84 (1H, m), 3.49 (1H, dd, J = 12.5, 3.3 Hz), 3.38 (1H, s), 3.33-3.27 (1H, m), 3.12-3.01 (2H, m), 1.98-1.85 (2H, m), 1.80 (1H, d, J = 6.2 Hz), 1.69-1.60 (1H, m). LCMS (ESI) m/z 238 [M+H]⁺

10 Step 2: Synthesis of example compound 40

The title compound was obtained as in Example 1, except that (3R)-1-(4-ethynyl-3,5-difluorophenyl)piperidin-3-ol was used in place of 2-ethynyl-1,3-difluorobenzene.

[0316]

15 ¹H-NMR (DMSO-D₆) δ: 8.17 (1H, s), 7.86 (1H, s), 7.36-7.32 (1H, m), 6.72 (2H, d, J = 12.1 Hz), 6.59 (2H, s), 5.92 (1H, d, J = 7.0 Hz), 5.38 (1H, d, J = 6.6 Hz), 5.22 (1H, d, J = 4.4 Hz), 4.86 (1H, d, J = 4.4 Hz), 4.57 (1H, dd, J = 12.3, 6.8 Hz), 4.11-4.08 (1H, m), 4.06-4.03 (1H, m), 3.68-3.50 (3H, m), 3.23-3.18 (1H, m), 3.15-
20 3.07 (1H, m), 3.01-2.94 (1H, m), 2.84 (1H, dd, J = 12.6, 8.6 Hz), 1.89-1.83 (1H, m), 1.75-1.69 (1H, m), 1.47-1.37 (2H, m). LCMS (ESI) m/z 580 [M+H]⁺.

[0317]

Example 41

25 1-[4-[2-[4-amino-7-[(2R,3R,4S,5R)]-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidin-5-yl]ethynyl]-3,5-difluoro-phenyl]pyrrolidine-3-
carboxylic acid

Step 1: Synthesis of 1-(4-ethynyl-3,5-difluorophenyl)pyrrolidine-
30 3-carboxylic acid

The title compound was obtained as in step 1 of Example 23, except that pyrrolidine-3-carboxylic acid was used in place of morpholine.

[0318]

35 ¹H-NMR (CDCl₃) δ: 6.06 (2H, d, J = 10.3 Hz), 3.61-3.52 (2H, m), 3.46-3.25 (4H, m), 2.38-2.33 (2H, m). LCMS (ESI) m/z 252 [M+H]⁺

Hz), 3.25-3.18 (1H, m), 3.14-3.07 (1H, m), 2.44 (4H, t, J = 5.9 Hz). LCMS (ESI) m/z 578 [M+H]⁺.

[0323]

Example 43

5 4-Amino-5-[2-[4-(azetidin-1-yl)-2,6-difluoro-phenyl]ethynyl]-7-
[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]cyclopentyl]tetrahydrofuran-2-
yl]pyrrolo[2,3-d]pyrimidine

Step 1: Synthesis of 1-(4-ethynyl-3,5-difluorophenyl)azetidine

10 The title compound was obtained as in step 1 of Example
23, except that azetidine was used in place of morpholine.

[0324]

¹H-NMR (CDCl₃) δ: 5.86 (2H, d, J = 9.5 Hz), 3.93-3.89 (4H, m),
3.37 (1H, s), 2.45-2.37 (2H, m). LCMS (ESI) m/z 194 [M+H]⁺

15 Step 2: Synthesis of example compound 43

The title compound was obtained as in step 4 of Example
1, except that 1-(4-ethynyl-3,5-difluorophenyl)azetidine was used
in place of 2-ethynyl-1,3-difluorobenzene.

[0325]

20 ¹H-NMR (DMSO-D₆) δ: 8.17 (1H, s), 7.85 (1H, s), 7.36-7.33 (1H, m),
6.60 (2H, s), 6.20 (2H, d, J = 9.9 Hz), 5.91 (1H, d, J = 7.0 Hz),
5.38 (1H, d, J = 6.6 Hz), 5.22 (1H, d, J = 4.4 Hz), 4.57 (1H, q,
J = 6.2 Hz), 4.11-4.07 (1H, m), 4.05-4.03 (1H, m), 3.91 (4H, t, J
= 7.3 Hz), 3.25-3.17 (1H, m), 3.14-3.07 (1H, m), 2.37-2.30 (2H,
25 m). LCMS (ESI) m/z 536 [M+H]⁺.

[0326]

Example 44

4-Amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-
30 pyridyl)ethynyl]pyrrolo[2,3-d]pyrimidine

The title compound was obtained as in step 4 of Example
1, except that 2-ethynylpyridine was used in place of 2-ethynyl-
1,3-difluorobenzene.

[0327]

35 ¹H-NMR (DMSO-D₆) δ: 8.12 (1H, s), 7.90 (1H, s), 7.78 (1H, t, J =
7.6 Hz), 7.60 (1H, d, J = 7.6 Hz), 7.33 (1H, dd, J = 7.6, 5.1 Hz),

7.5 Hz), 7.74-7.68 (2H, m), 7.52 (1H, dt, J = 1.4, 7.5 Hz), 7.29 (1H, m), 6.53 (2H, s), 5.87 (1H, d, J = 6.8 Hz), 5.40 (1H, brs), 5.23 (1H, brs), 4.53 (1H, t, J = 5.5 Hz), 4.04 (2H, dd, J = 5.5, 2.7 Hz), 4.01-3.98 (2H, brm), 3.19-3.03 (2H, m). LCMS (ESI) m/z
5 470 [M+H]⁺.

[0338]

Example 50

4-Amino-5-(3-cyclohexylpropyn-1-ynyl)-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-d]pyrimidine
10

The title compound was obtained as in step 4 of Example 1, except that prop-2-yn-1-yl cyclohexane was used in place of 2-ethynyl-1,3-difluorobenzene.

[0339]

15 ¹H-NMR (DMSO-D₆) δ: 8.05 (1H, s), 7.56 (1H, s), 7.27 (1H, dd, J = 7.5, 4.1 Hz), 6.51 (2H, s), 5.79 (1H, d, J = 6.8 Hz), 4.46 (1H, dd, J = 6.8, 5.5 Hz), 4.01 (1H, dd, J = 5.5, 2.1 Hz), 3.97-3.94 (1H, brm), 3.17-2.99 (2H, m), 2.32 (2H, d, J = 6.2 Hz), 1.76-1.72 (2H, brm), 1.65-1.60 (2H, brm), 1.58-1.54 (1H, brm), 1.49-1.41
20 (1H, brm), 1.23-0.93 (5H, m). LCMS (ESI) m/z 465 [M+H]⁺.

[0340]

Example 51

4-Amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-fluoro-6-methoxy-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine
25

Step 1: Synthesis of 2-ethynyl-1-fluoro-3-methoxybenzene

2-Fluoro-6-methoxybenzaldehyde (2.0 g, 13 mmol) was dissolved in methanol (20 mL). Then, potassium carbonate (3.6 g, 26 mmol) was added thereto at room temperature, and dimethyl(1-diazo-2-oxopropyl)phosphonate (2.3 mL, 16 mmol) was added thereto
30 under ice-cooling, followed by stirring under ice-cooling for 1 hour and at room temperature for another 1 hour. The reaction solution was partitioned with the addition of ethyl acetate, a saturated aqueous sodium hydrogen carbonate solution, and water,
35 and the organic layer was washed with saturated saline. After

pyrrolo[2,3-d]pyrimidine, obtained in step 35 of Example 93 was dissolved in tetrahydrofuran (950 mL), and a tetrabutylammonium fluoride solution (1 M tetrahydrofuran solution, 180 mL) was added thereto at room temperature, followed by stirring at room temperature for 1 hour. The resulting mixture was partitioned in an ice bath with the addition of ethyl acetate (500 mL), water (500 mL), and a saturated sodium bicarbonate solution (300 mL), and the aqueous layer was extracted with ethyl acetate (500 mL). The organic layer was washed with saturated saline (500 mL), and dried over sodium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by silica gel column chromatography (developing solvent: ethyl acetate/hexane), thereby obtaining the title compound (70 g, two steps: 86%) as a light-green amorphous substance.

[0495]

¹H-NMR (CDCl₃) δ: 8.62 (1H, s), 7.48 (1H, s), 5.05-4.99 (1H, m), 4.91 (1H, t, J = 6.5 Hz), 4.71-4.68 (1H, m), 3.89-3.85 (1H, m), 3.82-3.78 (1H, m), 2.50-2.45 (2H, m), 2.31-2.27 (1H, m), 1.90-1.88 (1H, m), 1.59 (3H, s), 1.31 (3H, s). LCMS (ESI) m/z 450

[M+H]⁺

Step 7: Synthesis of ((3aR,4R,6R,6aS)-6-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methanol

((3aR,4R,6R,6aS)-6-(4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydro-3aH-

cyclopenta[d][1,3]dioxol-4-yl)methanol (70 g) was dissolved in 1,4-dioxane (350 mL), and 28% aqueous ammonia (350 mL) was added thereto at room temperature, followed by stirring at 100°C overnight in a pressure-resistant container. After the solvent was distilled off under reduced pressure, the resulting product was suspended in water (700 mL), followed by stirring at room temperature overnight. The precipitate was collected by filtration and washed with water (420 mL), followed by drying to give the title compound (67 g, 99%) as a light-brown powder.

[0496]

7.67-7.46 (3H, m), 6.59 (1H, dd, J = 7.7, 6.2 Hz), 4.62-4.59 (1H, m), 4.18-4.15 (1H, m), 3.41-3.34 (2H, m), 2.77 (1H, ddd, J = 13.9, 7.7, 6.2 Hz), 2.45 (1H, ddd, J = 13.9, 6.2, 2.9 Hz). LCMS (ESI) m/z 479 [M+H]⁺.

5 [0591]

Example 126

4-[4-Amino-7-[(2R,4S,5R)-4-hydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidin-5-yl]-2-(o-tolyl)thiazole

10 The title compound was obtained as in Example 2, except that tert-butyl-N-[[(2R,3S,5R)-5-(4-amino-5-iodo-pyrrolo[2,3-d]pyrimidin-7-yl)-3-hydroxy-tetrahydrofuran-2-yl]methyl sulfamoyl]carbamate was used in place of tert-butyl N-(((3aR,4R,6R,6aR)-6-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)sulfamoyl carbamate.

15 [0592]

¹H-NMR (CD₃OD) δ: 8.37 (1H, s), 8.26 (1H, s), 8.15 (1H, s), 8.04-8.01 (1H, m), 7.66 (1H, d, J = 7.7 Hz), 7.49-7.35 (3H, m), 6.68 (1H, dd, J = 7.7, 6.2 Hz), 4.61-4.58 (1H, m), 4.16 (1H, dt, J = 5.9, 3.3 Hz), 3.44 (1H, dd, J = 13.6, 4.0 Hz), 3.39 (1H, dd, J = 13.6, 4.8 Hz), 2.72-2.65 (1H, m), 2.55 (3H, s), 2.47 (1H, ddd, J = 13.6, 6.2, 3.3 Hz). LCMS (ESI) m/z 502 [M+H]⁺.

[0593]

25 Example 127

4-Amino-5-[2-(2-ethoxy-6-fluoro-phenyl)ethynyl]-7-[(2R,4S,5R)-4-hydroxy-5-[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-d]pyrimidine

The title compound was obtained as in step 3 of Example 124, except that 1-ethoxy-2-ethynyl-3-fluorobenzene was used in place of 2-ethynyl-1,3-difluorobenzene.

30 [0594]

¹H-NMR (DMSO-D₆) δ: 8.17 (1H, s), 7.88 (1H, s), 7.37 (1H, ddd, J = 8.8, 8.4, 7.0 Hz), 7.19 (1H, dd, J = 7.0, 5.5 Hz), 6.97 (1H, d, J = 8.4 Hz), 6.91 (1H, t, J = 8.8 Hz), 6.57 (2H, s), 6.42 (1H, dd,

was determined as in Test Example 2, except that the cell lines, the culture plate, and the number of cells seeded per well were as shown in Table 19. For the culture plate, a 384-well plate (#3571, produced by Corning) was used.

5 [0674]

Table 20 below shows the results.

[0675]

Table 19

Cell Name	Origin	Obtained from	Plate	Seeding number (per 1 well) (cells/ μ L medium)
HCT116	Colon cancer	ATCC	384 wells	250 cells/20 μ L
Capan-1	Pancreatic cancer	ATCC	384 wells	500 cells/20 μ L
A-427	Lung cancer	ATCC	384 wells	250 cells/20 μ L
MDA-MB-453	Breast cancer	ATCC	384 wells	500 cells/20 μ L
LNCaP.FGC	Prostate cancer	Dainippon Pharmaceutical Co., Ltd. (currently Sumitomo Dainippon Pharma Co., Ltd./DS Pharma Biomedical Co., Ltd.)	384 wells	500 cells/20 μ L
SJCRH30	Osteo- and soft tissue sarcoma	ATCC	384 wells	250 cells/20 μ L
U266B1	Multiple myeloma	ATCC	384 wells	3000 cells/20 μ L
A-431	Skin cancer	ATCC	384 wells	400 cells/20 μ L
MV-4-11	Acute leukemia	ATCC	384 wells	400 cells/20 μ L
DB	B-cell lymphoma	ATCC	384 wells	1500 cells/20 μ L

10 [0676]

Table 20

	HCT116	Capan-1	A-427	MDA-MB-453	LNCaP.FGC
Examples	IC50 (μ M)	IC50 (μ M)	IC50 (μ M)	IC50 (μ M)	IC50 (μ M)
1	0.016	0.73	0.022	0.46	0.65
25	0.0064	0.38	0.0054	0.48	0.5
55	0.012	0.87	0.007	0.094	0.26
130	0.012	0.21	0.0064	0.032	0.46
29	0.014	0.56	0.049	0.64	0.28
122	0.018	0.89	0.022	0.076	0.51
64	0.014	1.2	0.091	0.14	0.68
Comp. Example	0.089	1.5	0.18	1.9	0.41

	SJCRH30	U266B1	A-431	MV-4-11	DB
Examples	IC50 (μ M)	IC50 (μ M)	IC50 (μ M)	IC50 (μ M)	IC50 (μ M)
1	>10	0.11	0.73	0.021	0.26
25	5.1	0.22	0.12	0.011	0.12
55	0.55	0.031	0.48	0.0067	0.061
130	0.17	0.024	0.16	0.025	0.13
29	6.6	0.42	0.56	0.02	0.15
122	0.13	0.27	1.6	0.038	0.12

A required amount of the test compound was weighed to prepare an administration solution. The compound of Example 1 was intravenously administered in an amount of 5 mL per 1 kg of body weight on days 1, 4, 8, and 11, and the compound of the Comparative Example was intravenously administered in an amount of 10 mL per 1 kg of body weight on days 1, 4, 8, and 11.

[0682]

Thereafter, the length and the width of the tumor and the body weight (BW_n) on day n were measured over time in the same manner, and the TV_n of each mouse was calculated. Further, the relative tumor volume (RTV_n) was calculated based on the TV_n of each mouse using the following equation (equation E); the treatment/control (T/C) value (%) was calculated based on the mean RTV_n of each drug administration group using the following equation (equation F); and the weight change rate (BWC_n) was calculated using the following equation (equation G).

[0683]

$RTV_n = TV_n / TV_1$ (equation E)

$T/C_n(\%) = (\text{mean RTV of each drug administration group on the last day of the test}) / (\text{mean RTV of the control group on the last day of the test}) \times 100$ (equation F)

$BWC_n(\%) = \frac{BW_n - BW_1}{BW_1} \times 100$ (equation G)

Figs. 1 and 2, and Table 21 below show the results.

[0684]

Table 21

Group	Dose (mg/kg/day)	Administration day	Number of mice	T/C15 (%)	BWC15 (%) Mean ±SD
Control	-	-	5	100	1.5 ±3.7
Comp. Example	120	1,4,8,11	5	36	-14.3 ±5.1
Example 1	50	1,4,8,11	5	23	-11.8 ±4.7

[0685]

An RTV₁₅ comparison using Dunnett's test revealed that the RTV of the example compound and the comparative example compound was significantly lower than that of the control. Further, a comparison using Aspin-Welch's t-test revealed that the RTV of Example 1 was significantly lower than that of the

- d]pyrimidine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethoxy-4,6-
difluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
5 4-amino-5-[2-[2,6-difluoro-4-(3-hydroxy azetidin-1-
yl)phenyl]ethynyl]-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidine;
10 4-amino-5-[2-[4-(azetidin-1-yl)-2,6-difluoro-phenyl]ethynyl]-7-
[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-
yl]cyclopentyl]pyrrolo[2,3-d]pyrimidine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-ethoxy-6-
15 fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-fluoro-6-
propoxy-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
8-[2-[4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
20 [(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidin-5-yl]ethynyl]-7-fluoro-4-methyl-2,3-dihydro-1,4-
benzoxazine;
4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]-5-[2-(2-
25 ethylsulfanyl-6-fluoro-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
4-amino-5-[2-[2-(cyclopropyl methoxy)-6-fluoro-phenyl]ethynyl]-7-
[(2R,3R,4S,5R)-3,4-dihydroxy-5-
[(sulfamoylamino)methyl]tetrahydrofuran-2-yl]pyrrolo[2,3-
d]pyrimidine;
30 4-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-
[(sulfamoylamino)methyl]cyclopentyl]-5-[2-(2-fluoro-6-
methylsulfanyl-phenyl)ethynyl]pyrrolo[2,3-d]pyrimidine;
8-[2-[4-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-
[(sulfamoylamino)methyl]cyclopentyl]pyrrolo[2,3-d]pyrimidin-5-
35 yl]ethynyl]-7-fluoro-4-methyl-2,3-dihydro-1,4-benzoxazine;
4-amino-7-[(1R,4R,5S)-4,5-dihydroxy-3-