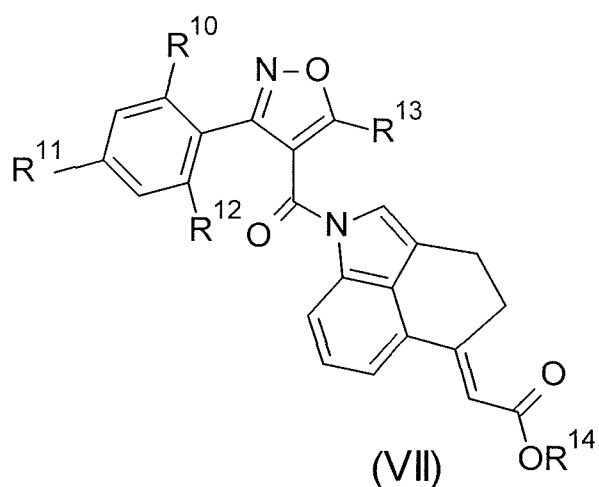


[Formula 8]



[0041]

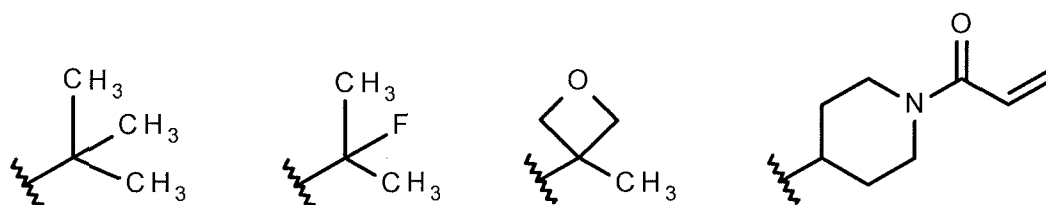
wherein

$R^{10}$ ,  $R^{11}$ , and  $R^{12}$  each independently represent a hydrogen atom or a halogen atom,

$R^{13}$  represents any of the following formulae:

[0042]

[Formula 9]



[0043]

$R^{14}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group.

[0044]

[9] A compound selected from the following group or a pharmaceutically acceptable salt thereof:

or a pharmaceutically acceptable salt thereof as an active ingredient.

[0050]

[15] A D-2-hydroxyglutarate production inhibitor comprising a compound according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof as an active ingredient.

[0051]

[16] A pharmaceutical composition comprising a compound according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof as an active ingredient.

[0052]

[17] An antitumor agent against a tumor having a isocitrate dehydrogenase 1 gene mutation, comprising a compound according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof as an active ingredient.

[0053]

[18] The antitumor agent according to [17], wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.

[0054]

[19] The compound according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof for use in a method for treating a tumor having a isocitrate dehydrogenase 1 gene mutation.

[0055]

[20] The compound according to [19] or a pharmaceutically acceptable salt thereof, wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.

[0056]

[21] Use of a compound according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the treatment of a tumor having a isocitrate dehydrogenase 1 gene mutation.

[0057]

[22] Use according to [21], wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell

lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.

[0058]

[23] A method for treating a tumor having a mutant isocitrate dehydrogenase 1 gene mutation, comprising administering a compound according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof.

[0059]

[24] A method for treating according to [23], wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.

[0060]

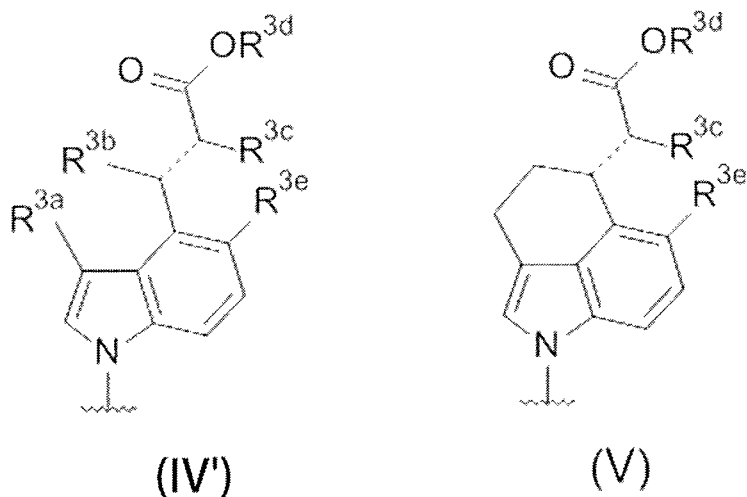
Compounds having an isoxazole skeleton have been reported so far as anti-inflammatory agents (Patent Reference 1), dopamine receptor subtype ligands (Patent Reference 2), immunosuppressants (Patent Reference 3), herbicides (Patent Reference 4), or heat shock protein inhibitors (Patent Reference 5). However, such a compound inhibiting the activity of mutant IDH protein has not yet been reported.

Advantageous Effects of Invention

$R^3$  preferably represents the following formula (IV')  
or (V):

[0086]

[Formula 13]



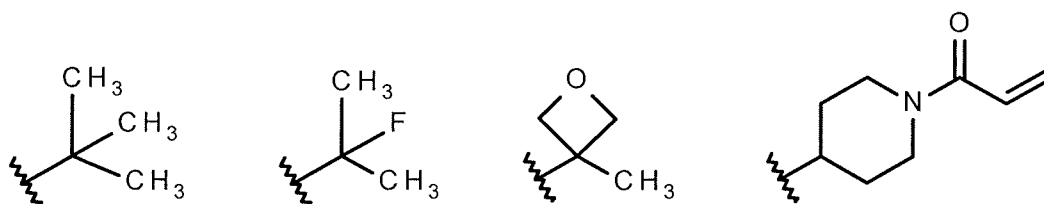
[0087]

In the formulae (IV) and (V),  
 $R^{3a}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group optionally substituted by 1 to 3 halogen atoms,  
 $R^{3b}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group,  
 $R^{3c}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group,  
 $R^{3d}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group,  
 $R^{3e}$  represents a hydrogen atom or a halogen atom, and  
the broken line represents a single bond or a double bond.

$R^3$  more preferably represents any of the following  
formulae:

[0088]

[Formula 14]



[0097]

and  $R^{14}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group.

A compound represented by the general formula (I) is particularly preferably any compound selected from the following group:

[0098]

(2E)-3-(1-{[5-(3-methyloxetan-3-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-1H-indol-4-yl)prop-2-enoic acid

(2E)-3-(1-{[5-(2-fluoropropan-2-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-3-methyl-1H-indol-4-yl)prop-2-enoic acid

(2E)-3-(1-{[5-(tert-butyl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-1H-indol-4-yl)prop-2-enoic acid

(2E)-3-(1-{[3-(2,4-dichloro-6-fluorophenyl)-5-(2-fluoropropan-2-yl)-1,2-oxazol-4-yl]carbonyl}-3-methyl-1H-indol-4-yl)prop-2-enoic acid

(2E)-3-(1-{[3-(2,4-dichlorophenyl)-5-(2-fluoropropan-2-yl)-1,2-oxazol-4-yl]carbonyl}-3-methyl-1H-indol-4-yl)prop-2-enoic acid

Next, a typical method for producing a compound represented by the general formula (I) will be described. The compound of the present invention can be produced by various production methods. The production methods shown below are given for illustrative purposes. It should be understood that the present invention is not limited by these examples. The compound represented by the general formula (I) and intermediates for production thereof can be produced through the use of various reactions known in the art as described below. In this respect, functional groups in starting materials or intermediates may be protected with appropriate protective groups. Examples of such functional groups can include a hydroxy group, a carboxy group, and an amino group. For the types of their protective groups as well as conditions for the introduction and removal of these protective groups, see those described in, for example, Protective Groups in Organic Synthesis (T.W. Greene and P.G.M. Wuts, John Wiley & Sons, Inc., New York, 2006).

[0130]

[Production method 1]

Among the compounds represented by formula (I), compound 1a given below can be produced by, for example, the following reaction scheme:

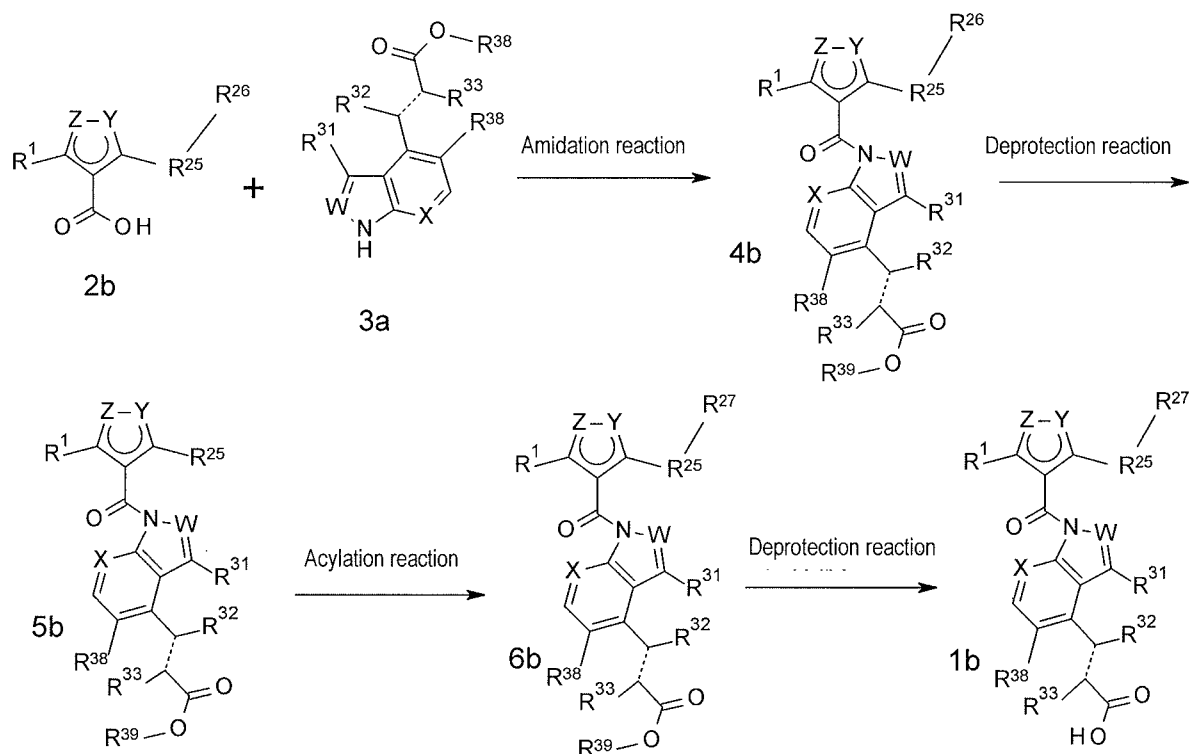
[0131]

[Formula 19]

Among the compounds represented by formula (I), compound 1b given below can be produced by, for example, the following reaction scheme:

[0139]

[Formula 20]



[0140]

In the scheme,  $R^1$ ,  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$ ,  $R^{38}$ ,  $W$ ,  $X$ ,  $Y$ , and  $Z$  are as defined above. In the scheme, the broken line represents a single bond or a double bond.  $R^{39}$  represents a protective group for a carboxy group.

$R^{25}$  represents a 4- to 6-membered aliphatic heterocyclic group having one nitrogen atom in the ring.

The 4- to 6-membered aliphatic heterocyclic ring is bonded to  $R^{26}$  via the nitrogen atom on the ring. This 4- to 6-membered aliphatic heterocyclic ring optionally has

The conversion of compound 2b to compound 4b can be carried out by a general coupling reaction similar to the method described above in (1) of [Production method 1].

[0144]

(2) Conversion of compound 4b to compound 5b

When  $R^{26}$  is a 2-nitrophenylsulfonyl group or the like, the conversion of compound 4b to compound 5b can be carried out by treatment with an appropriate base (e.g., potassium carbonate or cesium carbonate) and a thiol derivative (e.g., benzenethiol) in an appropriate solvent that has no adverse effect on the reaction (e.g., acetonitrile, N,N-dimethylformamide, or a mixed solvent thereof) at  $-30^{\circ}\text{C}$  to the boiling point of the solvent used in the reaction, preferably  $-20^{\circ}\text{C}$  to room temperature. The reaction time is preferably 10 minutes to 72 hours, more preferably 30 minutes to 24 hours.

[0145]

(3) Conversion of compound 5b to compound 6b

The conversion of compound 5b to compound 6b can be carried out by the reaction of the compound 5b with a carboxylic acid halide or a sulfonic acid halide in the presence of an appropriate base (e.g., an organic base such as triethylamine, N,N-di(propan-2-yl)ethylamine, 4-dimethylaminopyridine, N-methylmorpholine, pyridine, 2,6-lutidine, or diazabicyclo[5.4.0]undec-7-ene, or an inorganic base such as potassium carbonate, sodium carbonate, or sodium bicarbonate) in an appropriate

reaction time is preferably 10 minutes to 72 hours, more preferably 30 minutes to 24 hours.

[0150]

(2) Conversion of compound 7b to compound 1b

The conversion of compound 7b to compound 1b can be carried out by a Schotten-Baumann reaction. Specifically, the conversion can be carried out by reaction with a carboxylic acid halide or a sulfonic acid halide under two-layer system conditions using an appropriate solvent that has no adverse effect on the reaction (e.g., dichloromethane or chloroform) and an aqueous solution of a base such as sodium bicarbonate or sodium hydroxide. The reaction temperature is preferably 0°C to room temperature. The reaction time is preferably 10 minutes to 72 hours, more preferably 30 minutes to 24 hours.

[0151]

[Production method 4]

Among the compounds represented by formula (I), compound 1c given below can be produced by, for example, the following reaction scheme:

[0152]

[Formula 22]

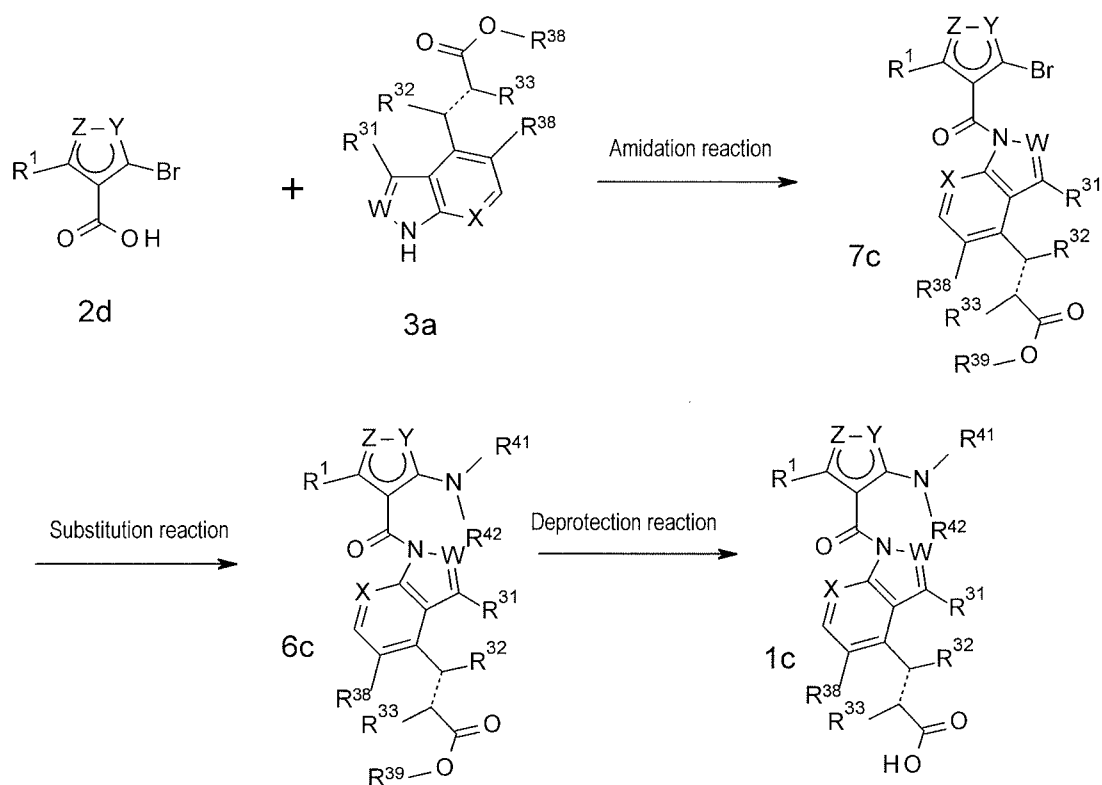
[0158]

[Production method 5]

Among the compounds represented by formula (I), compound 1c given below can also be produced by, for example, the following reaction scheme:

[0159]

[Formula 23]



[0160]

In the scheme,  $R^1$ ,  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$ ,  $R^{38}$ ,  $W$ ,  $X$ ,  $Y$ , and  $Z$  are as defined above. In the scheme, the broken line represents a single bond or a double bond.  $R^{39}$  represents a protective group for a carboxy group.

$R^{41}$  and  $R^{42}$  each independently represent a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group, or  $R^{41}$  and  $R^{42}$  optionally

[0163]

Compound 2d, which is a starting material for production, can be synthesized according to a method described in the Reference Examples.

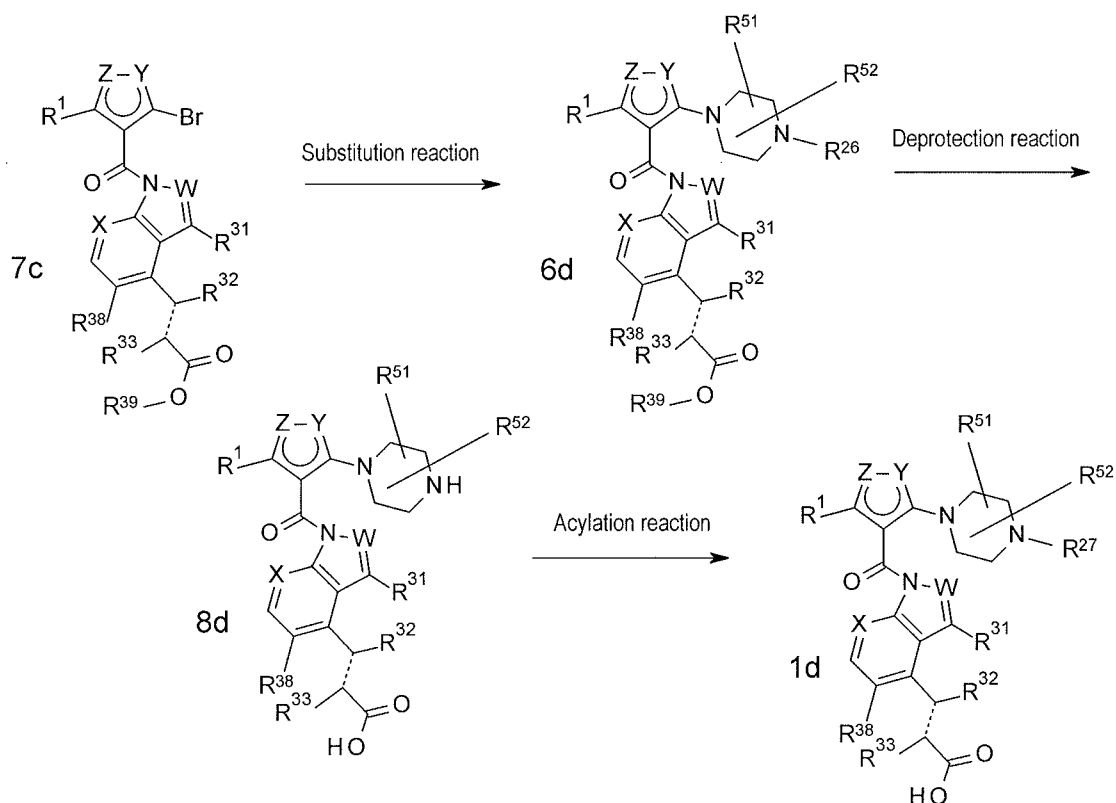
[0164]

[Production method 6]

Among the compounds represented by formula (I), compound 1d given below can be produced by, for example, the following reaction scheme:

[0165]

[Formula 24]



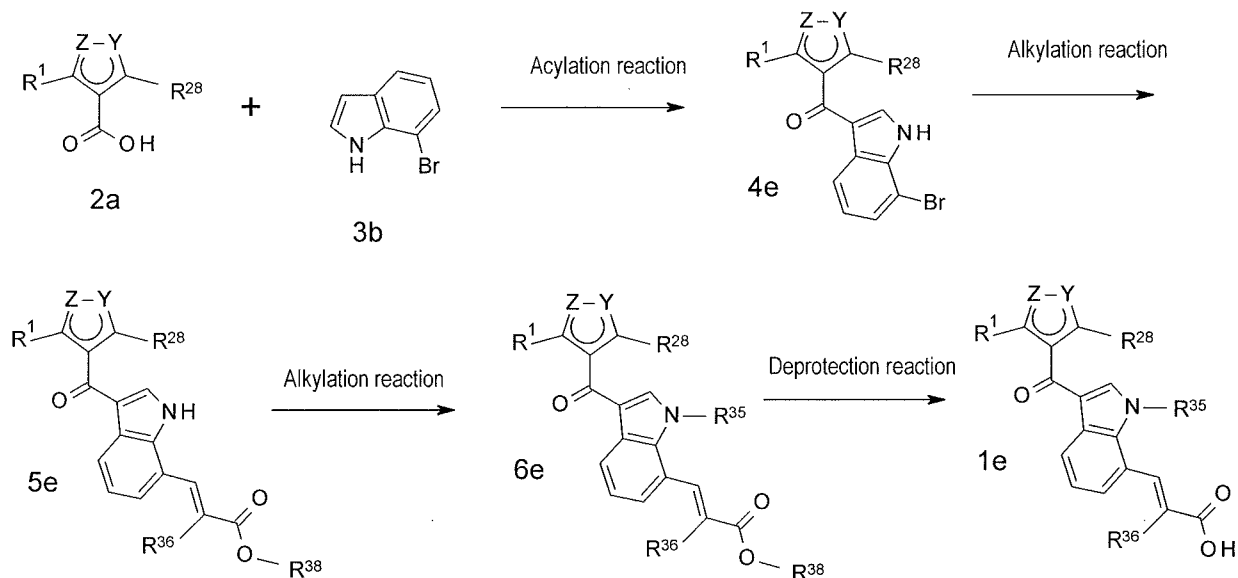
[0166]

In the scheme,  $R^1$ ,  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$ ,  $R^{38}$ ,  $W$ ,  $X$ ,  $Y$ , and  $Z$  are as defined above. In the scheme, the broken line

Among the compounds represented by formula (I), compound 1e given below can be produced by, for example, the following reaction scheme:

[0170]

[Formula 25]



[0171]

In the scheme, R<sup>1</sup>, R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, R<sup>35</sup>, R<sup>36</sup>, Y, and Z are as defined above. R<sup>39</sup> represents a protective group for a carboxy group.

R<sup>28</sup> represents a C<sub>1</sub> to C<sub>6</sub> alkyl group optionally having 1 to 3 substituents independently selected from group B given below, a C<sub>3</sub> to C<sub>6</sub> cycloalkyl group optionally having 1 to 3 substituents independently selected from group C given below, or a 4- to 6-membered aliphatic heterocyclic group having one oxygen atom in the ring. The 4- to 6-membered aliphatic heterocyclic

an appropriate solvent that has no adverse effect on the reaction (e.g., N,N-dimethylformamide or tetrahydrofuran) or a mixed solvent thereof at -20°C to the boiling point of the solvent used in the reaction, preferably 0°C to room temperature. An excessive amount can be used as the amount of the base. The reaction time is preferably 1 hour to 72 hours, more preferably 8 hours to 24 hours.

[0176]

(4) Conversion of compound 6e to compound 1e

The conversion of compound 6e to compound 1e can be carried out by a general deprotection reaction similar to the method described above in (2) of [Production method 1].

[0177]

[Production method 8]

Among the compounds represented by formula (I), compound 1f given below can be produced by, for example, the following reaction scheme:

[0178]

[Formula 26]

chromatography (n-hexane/ethyl acetate) to obtain the title compound (490 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.52 (9H, s), 1.55 (9H, s), 2.95 (2H, t, J = 6.7 Hz), 3.43 (2H, t, J = 6.7 Hz), 6.44 (1H, s), 7.33 (1H, t, J = 7.9 Hz), 7.43-7.48 (2H, m), 8.33 (1H, d, J = 7.9 Hz).

[0414]

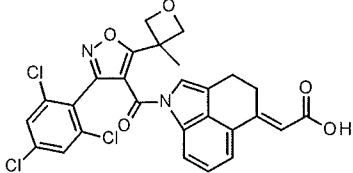
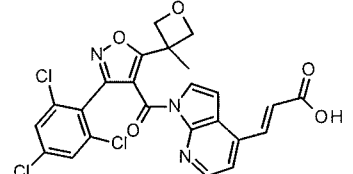
[Step 2] tert-Butyl (2E)-(3,4-dihydro-benzo[cd]indol-5(1H)-ylideneethanoate

To a mixed solution of the compound (490 mg) obtained in the preceding step 1 in tetrahydrofuran (1 ml) and methanol (3 ml), a 1 N aqueous sodium hydroxide solution (3 ml) was added at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with ethyl acetate, washed with 1 N hydrochloric acid, water, and saturated saline in this order and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue obtained was purified by silica gel column chromatography (n-hexane/ethyl acetate) to obtain the title compound (298 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.55 (9H, s), 2.98-3.03 (2H, m), 3.43-3.49 (2H, m), 6.45 (1H, t, J = 1.5 Hz), 6.94-6.95 (1H, m), 7.18 (1H, t, J = 7.9 Hz), 7.28-7.33 (2H, m), 7.93 (1H, brs).

[0415]

[Table 32]

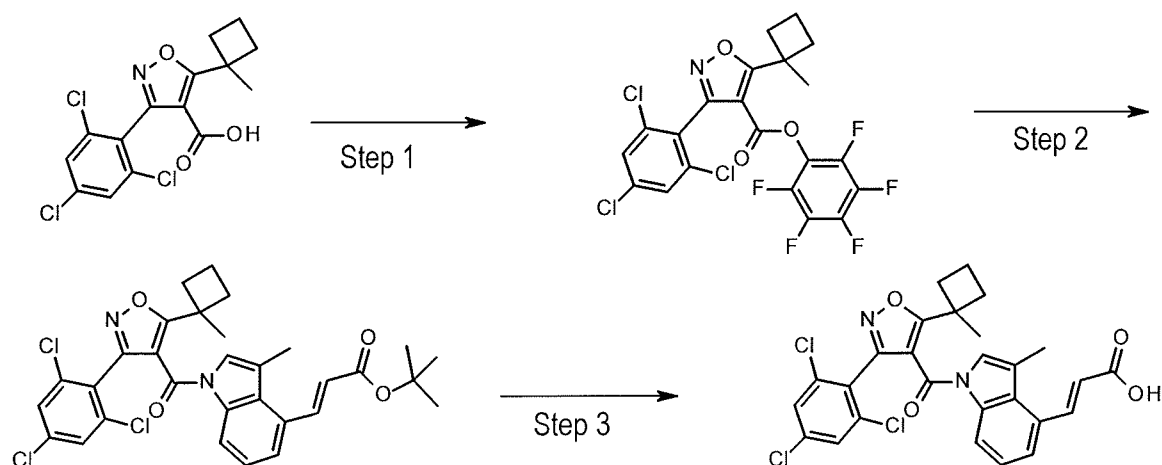
|   |              |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                           |
|---|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8 | X-11<br>E-17 | (2E)-[1-{[5-(3-Methyloxetan-3-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-3,4-dihydrobenzo[cd]indol-5(1H)-ylidene]ethanoic acid<br> | <sup>1</sup> H-NMR(CDCl <sub>3</sub> )δ:1.92(3H,s),2.76(2H,t,J=6.7Hz),3.37(2H,t,J=6.7Hz),4.62(2H,d,J=6.7Hz),5.13(2H,d,J=6.7Hz),6.53(1H,s),6.81(1H,s),7.31(2H,s),7.37(1H,t,J=7.9Hz),7.50(1H,d,J=7.9Hz),8.11(1H,d,J=7.9Hz).<br>MS(m/z):557(M+H) <sup>+</sup> .              |
| 9 | X-11<br>E-11 | (2E)-3-(1-{[5-(3-Methyloxetan-3-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)prop-2-enoic acid<br>    | <sup>1</sup> H-NMR(CDCl <sub>3</sub> )δ:1.78(3H,s),4.52(2H,d,J=6.0Hz),5.01(2H,d,J=6.0Hz),6.81(1H,d,J=15.7Hz),7.13(1H,d,J=4.2Hz),7.54(2H,s),7.58(1H,d,J=4.8Hz),7.78(1H,d,J=15.7Hz),7.90(1H,d,J=4.2Hz),8.25(1H,d,J=4.8Hz),12.86(1H,brs).<br>MS(m/z):532(M+H) <sup>+</sup> . |

[0445]

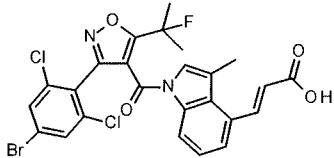
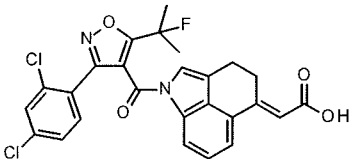
[Example 10] (2E)-3-(3-Methyl-1-{[5-(1-methylcyclobutyl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-1H-indol-4-yl)prop-2-enoic acid

[0446]

[Formula 68]

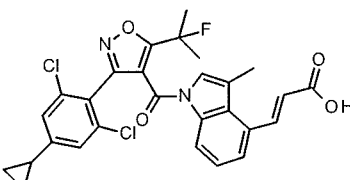


[Table 52]

|    |              |                                                                                                                                                                                                                                |                                                                                                                                                                                                                 |
|----|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 68 | X-49<br>E-8  | (2E)-3-(1-{[3-(4-Bromo-2,6-dichlorophenyl)-5-(2-fluoropropan-2-yl)-1,2-oxazol-4-yl]carbonyl}-3-methyl-1H-indol-4-yl)prop-2-enoic acid<br>     | <sup>1</sup> H-NMR(CDCl <sub>3</sub> )δ:1.88(6H,d,J=22.4Hz),2.42(3H,s),6.45(1H,d,J=15.7Hz),7.02(1H,s),7.36(1H,dd,J=7.9,3.9Hz),7.51(2H,s),7.58(1H,d,J=6.7Hz),8.43-8.52(2H,m).<br>MS(m/z):577(M-H) <sup>-</sup> . |
| 69 | X-22<br>E-17 | (2E)-[1-{[3-(2,4-Dichlorophenyl)-5-(2-fluoropropan-2-yl)-1,2-oxazol-4-yl]carbonyl}-3,4-dihydrobenzo[cd]indol-5(1H)-ylidene]ethanoic acid<br> | <sup>1</sup> H-NMR(CDCl <sub>3</sub> )δ:1.86(6H,d,J=21.8Hz),2.83-2.89(2H,m),3.39-3.45(2H,m),6.53(1H,s),7.24-7.39(5H,m),7.44(1H,d,J=7.9Hz),7.51(1H,d,J=7.9Hz).<br>MS(m/z):513(M+H) <sup>+</sup> .                |

[0477]

[Table 53]

|    |             |                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                 |
|----|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 70 | X-74<br>E-8 | (2E)-3-(1-{[3-(2,6-Dichloro-4-cyclopropylphenyl)-5-(2-fluoropropan-2-yl)-1,2-oxazol-4-yl]carbonyl}-3-methyl-1H-indol-4-yl)prop-2-enoic acid<br> | <sup>1</sup> H-NMR(CDCl <sub>3</sub> )δ:0.67(2H,dt,J=5.8,4.5Hz),1.02(2H,dt,J=7.4,5.5Hz),1.76-1.83(1H,m),1.88(6H,d,J=21.9Hz),2.40(3H,s),6.45(1H,d,J=15.8Hz),6.98(2H,s),7.04(1H,s),7.34(1H,dd,J=7.9,3.9Hz),7.57(1H,d,J=7.9Hz),8.46-8.51(2H,m).<br>MS(m/z):539(M-H) <sup>-</sup> . |
|----|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

[0478]

[Example 71] (2E)-3-(3-Cyclopropyl-1-{[5-(2-fluoropropan-2-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-1H-indol-4-yl)prop-2-enoic acid

[0479]

Chemical reaction scheme showing the synthesis of compound 10:

Step 1: Reaction of 2,4,6-trichloro-3-(2,2,2-trifluoroethylidene)-5-hydroxy-1,2,3,4-tetrahydropyridine with a brominated indole derivative to form an intermediate.

Step 2: Reaction of the intermediate with a cyclopropylmethyl ester to form another intermediate.

Step 3: Hydrolysis of the ester to yield the final product, 10.

[Step 1] tert-Butyl (2E)-3-(3-bromo-1-([5-(2-fluoropropan-2-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl)-1H-indol-4-yl)prop-2-enoate

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.55 (9H, s), 1.89 (6H, d, J = 21.8 Hz), 6.36 (1H, d, J = 15.7 Hz), 7.29-7.41 (4H, m), 7.57 (1H, d, J = 7.3 Hz), 8.43 (1H, d, J = 8.5 Hz), 8.88 (1H, d, J = 15.7 Hz).

[Step 2] tert-Butyl (2E)-3-(3-cyclopropyl-1-([5-(2-fluoropropan-2-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl))-1H-indol-4-yl)prop-2-enoate

The compound (1.50 g) obtained in the preceding step 1, cyclopropylboronic acid (0.216 g), tripotassium phosphate (1.45 g), tricyclohexylphosphine (0.128 g), and palladium acetate (51.3 mg) were suspended in toluene (30 ml) and water (0.1 ml), and the mixture was stirred at 90°C for 2 hours under a nitrogen atmosphere. After being allowed to cool, the reaction solution was diluted with ethyl acetate, washed with water and saturated saline in this order and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue obtained was purified by silica gel column chromatography (n-hexane/ethyl acetate) to obtain the title compound (863.9 mg), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.54-0.59 (2H, m), 1.01 (2H, dd, J = 8.2, 1.5 Hz), 1.54 (9H, s), 1.87 (6H, d, J = 21.2 Hz), 1.88-1.99 (0H, m), 6.38 (1H, d, J = 15.7 Hz), 6.87 (1H, s), 7.29-7.36 (3H, m), 7.56 (1H, d, J = 7.9 Hz), 8.40 (1H, d, J = 8.5 Hz), 8.74 (1H, d, J = 15.7 Hz). [0482]

[Step 3] (2E)-3-(3-Cyclopropyl-1-[[5-(2-fluoropropan-2-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl]-1H-indol-4-yl)prop-2-enoic acid

The title compound (547.0 mg) was obtained by the same method as in step 3 of Example 10 using the compound (863.9 mg) obtained in the preceding step 2.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.55-0.60 (2H, m), 1.01-1.05 (2H, m), 1.87 (6H, d, J = 21.8 Hz), 1.88-1.97 (7H, m), 6.46 (1H, d,

secreted into the supernatant. The virus-containing culture supernatant was centrifuged at 2000 rpm for 20 minutes, and the obtained centrifugation supernatant was used as a virus solution. 1200000 TF-1 cells were suspended in 6 mL of growth medium A and plated on a 10-cm plate (IWAKI, #3020-100). 4 mL of the virus solution mixed with Polybrene (Sigma-Aldrich Corp.) at a final concentration of 4  $\mu$ g/mL was added thereto. After the viral infection, IDH1R132H-expressing cells were selected in growth medium A containing 2  $\mu$ g/mL (final concentration) puromycin (Invitrogen Corp., #ant-pr) and subsequently cloned by the limiting dilution method to establish an IDH1R132H-expressing TF-1 cell line TF-1/IDH1R132H.

[0666]

40000 cells/190  $\mu$ L of TF-1/IDH1R132H cells in growth medium A were inoculated at 190  $\mu$ L/well to a 96-well plate (IWAKI, #3860-096). Then, 10  $\mu$ L of a solution of each compound diluted to a predetermined concentration with growth medium A was added to each well, and the cells were incubated at 37°C for 2 days under 5% CO<sub>2</sub>. After the incubation, 100  $\mu$ L of the culture supernatant was transferred from each well to a 96-well round-bottom plate (Corning Inc., #3799). The plate was centrifuged at 2000 rpm for 3 minutes, and then, 50  $\mu$ L of the supernatant in each well was dispensed to each 1.5-mL tube (Sarstedt K.K., #72.690.001S). 200  $\mu$ L of ethanol (Wako

[0680]

PLAT-E cells (kindly provided by professor Toshio Kitamura, The Institute of Medical Science, The University of Tokyo) were transfected with each of these 4 types of retrovirus vectors (pMy-NPMc-ires-EGFP, pGCDN-IDH1/R132H-ires-NGFR, pMSCV-DNMT3A/R882H, and pMSCV-FLT3/ITD) using GeneJuice (Merck KGaA). 48 hours later, 10 ml each of retrovirus-containing culture supernatants was recovered. 3.3 ml of a PEG concentrate (30% PEG-8000, 0.4 M NaCl, and 40 mM HEPES [pH 7.4]) was added thereto, and the mixture was left standing overnight at 4°C. The samples were centrifuged (1500 rpm x 45 minutes, 4°C) to prepare pellets. 50 ng/ml SCF, 10 ng/ml IL-3, and 10 ng/ml OSM were added to Stempro-34 solution (Invitrogen Corp.) (hereinafter, referred to as Stempro medium). The virus pellets were suspended in 200 µl of Stempro medium, and 100 µl each of the suspensions was dispensed, quickly frozen in liquid nitrogen and stored in a freezer of -80°C.

[0681]

Gene transduction and primary bone marrow transplantation were carried out as follows.

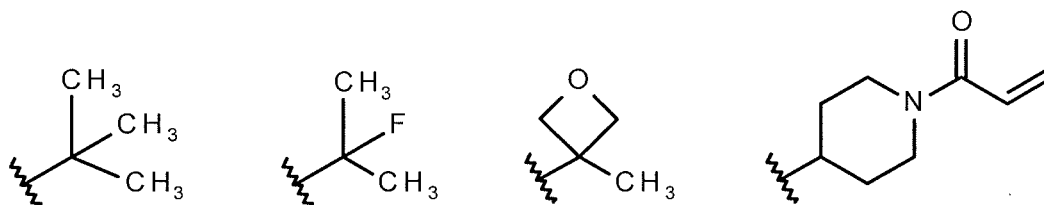
[0682]

Bone marrow cells were recovered from the lower limb of an 8-week-old NPM<sup>+/-</sup> mouse (TaconicArtemis GmbH). After hemolysis treatment, c-Kit<sup>+</sup> cells were recovered using CD117 MACS beads (Miltenyi Biotec K.K.).

A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein in the formula (I),

$R^2$  represents any of the following formulae:

[Formula 3]

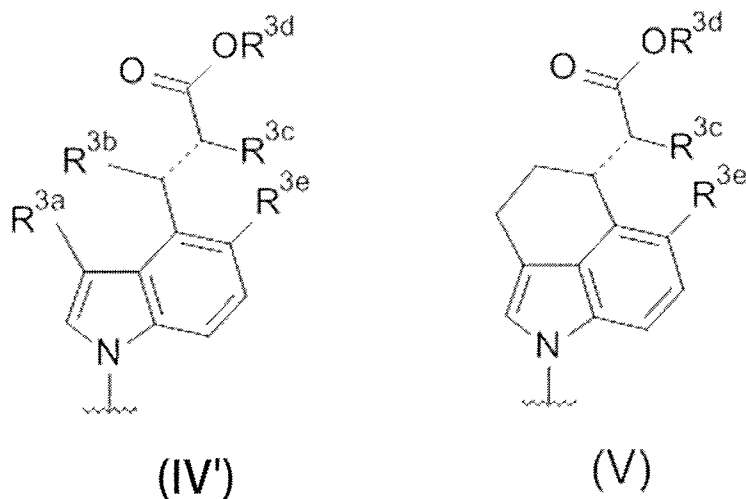


[Claim 5]

A compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein in the formula (I),

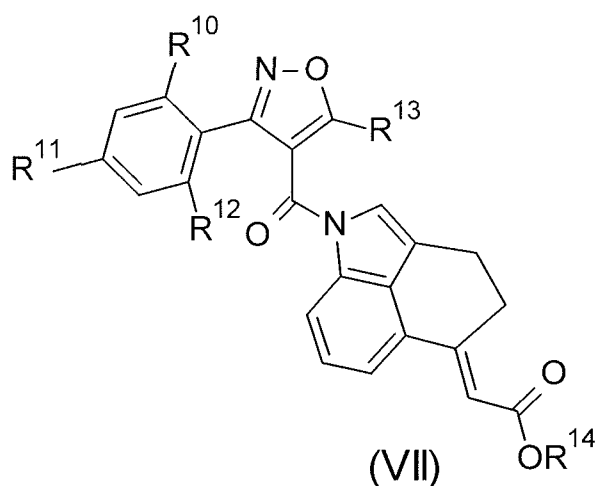
$R^3$  represents the following formula (IV') or (V):

[Formula 4]



wherein

$R^{3a}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group optionally substituted by 1 to 3 halogen atoms,

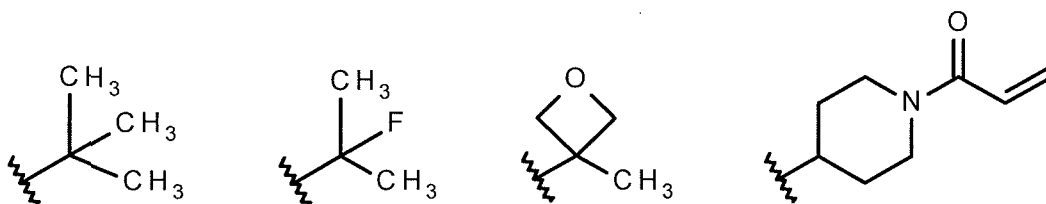


wherein

$R^{10}$ ,  $R^{11}$ , and  $R^{12}$  each independently represent a hydrogen atom or a halogen atom,

$R^{13}$  represents any of the following formulae:

[Formula 9]



and

$R^{14}$  represents a hydrogen atom or a  $C_1$  to  $C_6$  alkyl group.

[Claim 9]

A compound selected from the following group or a pharmaceutically acceptable salt thereof:

(2E)-3-(1-{[5-(3-methyloxetan-3-yl)-3-(2,4,6-trichlorophenyl)-1,2-oxazol-4-yl]carbonyl}-1H-indol-4-yl)prop-2-enoic acid

13 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 16]

A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 17]

An antitumor agent against a tumor having a isocitrate dehydrogenase 1 gene mutation, comprising a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 18]

An antitumor agent according to claim 17, wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.

[Claim 19]

A compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof for use in a method for treating a tumor having a isocitrate dehydrogenase 1 gene mutation.

[Claim 20]

A compound according to claim 19 or a pharmaceutically acceptable salt thereof, wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.

[Claim 21]

Use of a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the treatment of a tumor having a isocitrate dehydrogenase 1 gene mutation.

[Claim 22]

Use according to claim 21, wherein the tumor is brain tumor (including glioma), acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative tumor, peripheral T-cell lymphoma, chondrosarcoma, osteosarcoma, bile duct cancer, primitive neuroectodermal tumor, B-cell lymphoblastic lymphoma, malignant melanoma, prostate cancer, colorectal cancer, or thyroidal cancer.