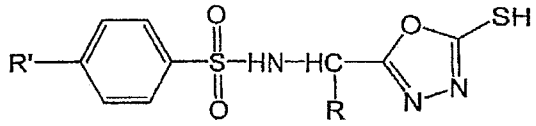
[chemical formula 1]



[0006]

(wherein, R represents CH_2Ph, and R' represents Me). However, the compound (4a-e) is a production intermediate for obtaining the 5-benzylthio-1,3,4-oxadiazole derivatives as an objective compound having an anti-HIV activity. Non-Patent Document 11 does not disclose a physiological activity of the compound (4a-e), and does not suggest an RNR inhibition activity and antitumor effects of the compound (4a-e).

[PRIOR ART DOCUMENT]

[NON-PATENT DOCUMENT]

[0007]

[Non-Patent Document 1] Annu. Rev. Biochem. 67, 71-98. (1998)
[Non-Patent Document 2] J. Biol. Chem. 245, 5228-5233. (1970)
[Non-Patent Document 3] Nat. Commun. 5, 3128 doi: 10.1038 / ncomms 4128 (2014)
[Non-Patent Document 4] Clin. Sci. 124, 567-578. (2013)
[Non-Patent Document 5] Expert. Opin. Ther. Targets 17, 1423 - 1437 (2013)
[Non-Patent Document 6] Biochem. Pharmacol. 59, 983-991 (2000)
[Non-Patent Document 7] Biochem. Pharmacol. 78, 1178- 11 85 (2009)
[Non-Patent Document 8] Cancer Res. 54, 3686-3691 (1994)
[Non-Patent Document 9] Pharmacol. Rev. 57, 547-583 (2005)
[Non-Patent Document 10] Future Oncol. 8, 145-150 (2012)
[Non-Patent Document 11] J. Enzym. Inhib. Med. Chem. 26, 5, 668 - 680 (2011)

[SUMMARY OF THE INVENTION]

[PROBLEMS TO BE SOLVED BY THE INVENTION]

[0008]

An object of the present invention is to provide a novel compound which selectively and strongly inhibits RNR and is useful as an antitumor agent and a therapeutic agent for other diseases involving RNR.

[MEANS TO BE SOLVED BY THE INVENTION]

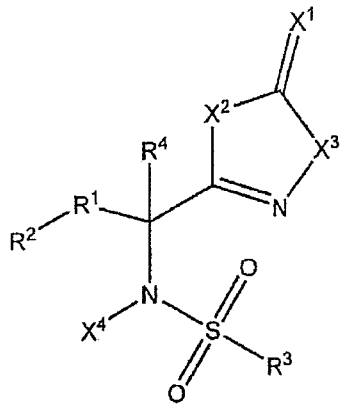
[0009]

As a result of extensive studies to solve the above-mentioned problems, the inventors of the present invention have found that a group of compounds having a sulfonamide structure represented by the following formula (I) has excellent RNR inhibitory activity, and is useful as an antitumor agent etc., and completed the present invention.

[0009a]

In one aspect, the present invention provides a compound represented by the following formula (I):

[Formula 1]



(I)

wherein X^1 represents an oxygen atom or a sulfur atom;

X^2 represents an oxygen atom or -NH-;

X^3 represents -NH- or an oxygen atom;

X^4 represents a hydrogen atom or a C1-C6 alkyl group;

R^1 represents $-C(R^{11})(R^{12})-$ or $-C(=CH_2)-$;

R^{11} and R^{12} are the same or different and represent a hydrogen atom, a halogen atom, or a hydroxy group, or a C1-C6 alkyl group, alternatively may be taken together with the carbon atoms to which R^{11} and R^{12} are attached to form a saturated hydrocarbon ring having 3 to 8 carbon atoms;

R^2 represents a C6-C14 aromatic hydrocarbon group or a 9 or 10 membered fully unsaturated heterocyclic group,

wherein R^2 may have substituents, and when R^2 has two substituents on carbon atoms which are adjacent to each other on the aromatic hydrocarbon ring, the substituents may be fused together with carbon atoms to which the substituents bind to form a saturated or partially unsaturated 4-8 membered hydrocarbon ring or heterocyclic ring, either of which may have substituents,

R^3 represents a C6-C14 aromatic hydrocarbon group or a 5-10 membered fully unsaturated heterocyclic group,

wherein R^3 may have substituents, and when R^3 has two substituents on the carbon atoms which are adjacent to each other on the aromatic hydrocarbon ring, the substituents may be fused together with carbon atoms to which the substituents bind to form a saturated or partially unsaturated 4-8 membered hydrocarbon ring or heterocyclic ring, either of which may have substituents; and

R^4 represents a hydrogen atom or a C1-C6 alkyl group;

(with the proviso that X^1 is an oxygen atom when X^2 represents an oxygen atom, X^3 represents -NH-, X^4 represents a hydrogen atom, R^1 represents $-CH_2-$, R_2 represents a phenyl group, R^3 represents 4-methylphenyl group, and R^4 represents a hydrogen atom)

or a salt thereof.

In another aspect, the present invention provides a ribonucleotide reductase inhibitor or anti-tumor agent comprising the compound or a salt thereof as disclosed herein as an active ingredient.

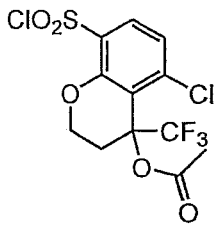
In another aspect, the present invention provides a medicament comprising the compound or a salt thereof as disclosed herein.

In yet another aspect, the present invention provides a pharmaceutical composition comprising the compound or a salt thereof as disclosed herein and a pharmaceutically acceptable carrier.

In yet another aspect, the present invention provides an anti-tumor agent for oral administration comprising the compound or a salt thereof as disclosed herein as an active ingredient.

In yet another aspect, the present invention provides the use of the compound or a salt thereof according to the present disclosure for manufacturing a ribonucleotide reductase inhibitor or pharmaceutical composition or an anti-tumor agent.

In yet another aspect, the present invention provides the use of the compound or a salt thereof as described herein for manufacturing an antitumor agent for oral administration.
In yet another aspect, the present invention refers to the compound or a salt thereof as decribed herein for use as a medicament.
In yet another aspect, the present invention provides the use of the compound or a salt thereof as described herein in the manufacture of a medicament for preventing and/or treating tumors
[0010]
The present disclosure provides the following: [1] to [33].
[1]
A compound represented by the following formula (I):
[0011]
[chemical formula 2]



[0189]

(Step 1) 8-bromo-5-chloro-4-(trifluoromethyl)chroman-4-ol

To a THF solution (4 mL) of 8-bromo-5-chloro-chromanon-4-one (398.2 mg), cesium fluoride (340.2 mg) and trifluoromethyltrimethylsilane (0.68 mL) were added at room temperature, and the reaction solution was stirred for 4 hours. An ammonium chloride aqueous solution (5 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate / hexane = 1/1 (15 mL). The organic layer was washed with saturated saline (10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexane / ethyl acetate) to obtain 8-bromo-5-chloro-4-(trifluoromethyl)chromanone-4-ol (139.2 mg).

(Step 2)

From 8-bromo-5-chloro-4-(trifluoromethyl)chroman-4-ol obtained from the above Step 1, the title compound was obtained according to the method of Reference Example E1 Step 2-4.

[0190]

Reference example E6 8-(chlorosulfonyl)-4-(trifluoromethyl)chroman-4-yl acetate

By using 8-bromo-chroman-4-one as a starting material, the title compound was obtained, according to the method of Reference Example E5 Steps 1 and 2.

Reference examples E2 to E4 and E7 to E34

According to the method of Reference Example E1 Steps 1-4, the compounds of Reference Examples E2 to E4 were synthesized. According to the method of Reference Examples E1 Step 3 and 4, the compounds of Reference Examples E7 to E32 were synthesized. According to the method of Reference Example E1 Step 2-4, the compounds of Reference Example E33 and E34 were synthesized. The compounds of Reference Examples E2 to E4 and E7 to E34, and the starting materials are listed in the following table.

purified by silica gel column chromatography (eluent: hexane / ethyl acetate) to obtain 1-(3-bromo-6-chloro-2-methoxyphenyl)ethanone (2.7 g).

[0214]

(Step 2) 2-(3-bromo-6-chloro-2-methoxyphenyl)propan-2-yl acetate

From 1-(3-bromo-6-chloro-2-methoxyphenyl)ethanone obtained in the above Step 1, 2-(3-bromo-6-chloro-2-methoxyphenyl)propan-2-yl acetate was obtained according to the method of Reference Example E1 Steps 1 and 2.

[0215]

(Step 3)

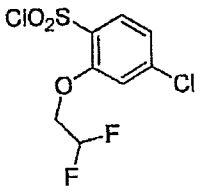
From the 2-(3-bromo-6-chloro-2-methoxyphenyl)propan-2-yl acetate (500 mg) obtained in the above Step 2, the title compound was obtained according to the method of Reference Examples E1 steps 3 and 4.

[0216]

Reference Example E47 4-Chloro-2-(2,2-difluoroethoxy)benzene-1-sulfonyl chloride

[0217]

[Formula 25]



[0218]

(Step 1) 1-bromo-4-chloro-2-(2,2-difluoroethoxy)benzene

To a DMF solution (5 mL) of 2-bromo-5-chlorophenol (244mg), potassium carbonate (325 mg) and 2,2-difluoroethyl 4-methylbenzenesulfonate (320 mg) were added, and the reaction solution was stirred for 3 hours at 95 °C. The reaction solution was added to an aqueous sodium hydroxide solution (1 M, 20 mL) and extracted with toluene / ethyl acetate = 1/1 (20 mL). The organic layer was washed with saturated saline (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate) to obtain 1-bromo-4-chloro-2-(2,2-difluoroethoxy)benzene (315 mg).

[0219]

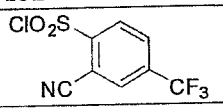
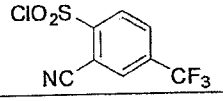
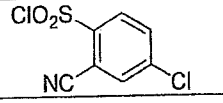
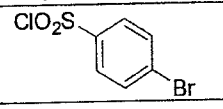
(Step 2)

The title compound was synthesized from 1-bromo-4-chloro-2-(2,2-difluoroethoxy)benzene obtained in the above Step 1 according to the method of Reference Examples E1 Steps 3 and 4.

[0220]

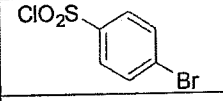
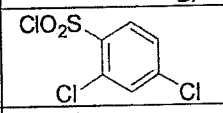
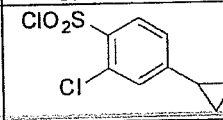
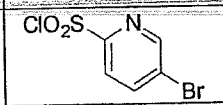
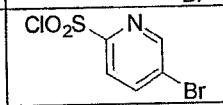
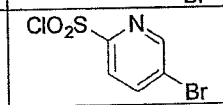
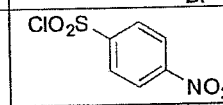
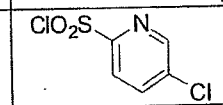
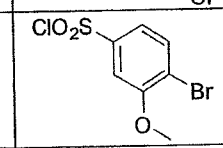
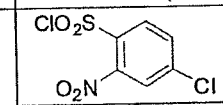
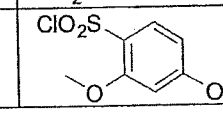
Reference examples E48 and E49

According to the methods of Reference Example E47 Step 1 and Reference Example E1 Steps 3 and 4, the compounds of Reference Examples E48 and 49 shown below were synthesized. However, regarding Reference Example 48, sodium chlorodifluoroacetate was used instead of 2,2-difluoroethyl 4-methylbenzenesulfonate.

			terephthalamide
40	Reference Example D1	Reference Example E32	2-chloro-5-(N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)isonicotinamide
41	Reference Example D1		2-(N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)-5-(trifluoromethyl)benzamide
42	Reference Example D5		2-(N-((1S,2R)-2-(3-bromo-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)-5-(trifluoromethyl)benzamide
43	Reference Example D44		5-chloro-2-[[(1S,2R)-3,3,3-trideuterio-2-(6-fluoro-2,3-dimethylphenyl)-1-(2-oxo-3H-1,3,4-oxadiazol-5-yl)propyl]sulfamoyl]benzamide
44	Reference Example D11		4-bromo-N-((1S,2R)-2-(naphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide

[0336]

[Table 7-5]

Example	Starting Material	ArSO2Cl	Name of the Synthesized Compound
45	Reference Example D27		N-((1S,2R)-2-(benzo[b]thiophen-4-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-bromobenzenesulfonamide
46	Reference Example D11		2,4-dichloro-N-((1S,2R)-2-(naphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide
47	Reference Example D21		2-chloro-4-cyclopropyl-N-((1S,2R)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-(5,6,7,8-tetrahydronaphthalen-1-yl)propyl)benzenesulfonamide
48	Reference Example D51		5-bromo-N-((1S)-2-(3-methyl-2,3-dihydro-1 H-inden-4-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)pyridine-2-sulfonamide
49	Reference Example D22		N-((1S,2R)-2-(9H-fluoren-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-5-bromopyridine-2-sulfonamide
50	Reference Example D23		N-((1S,2R)-2-(9H-fluoren-4-yl)-1-(5-oxo-4,5-dihydro- 1,3,4-oxadiazol-2-yl)propyl)-5-bromopyridine-2-sulfonamide
51	Reference Example D11		N-((1S,2R)-2-(naphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-nitrobenzene sulfonamide
52	Reference Example D21		5-chloro-N-((1S,2R)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-(5,6,7,8-tetrahydronaphthalen- 1-yl)propyl)pyridine-2-sulfonamide
53	Reference Example D21		4-bromo-3-methoxy-N-((1S,2R)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-(5,6,7,8-tetrahydronaphthalen- 1-yl)propyl)benzene sulfonamide
54	Reference Example D21		4-chloro-2-nitro-N-((1S,2R)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-(5,6,7,8-tetrahydronaphthalen- 1-yl)propyl)benzene sulfonamide
55	Reference Example D21		2,4-dimethoxy-N-((1S,2R)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-(5,6,7,8-tetrahydronaphthalen- 1-yl)propyl)benzene sulfonamide

methoxybenzenesulfonamide (5.6 mg) obtained from Example 290, DAST (10 μL) was added, and the mixture was stirred at room temperature for 2 hours. Saturated aqueous sodium hydrogen carbonate solution (5.0 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate / hexane = 1/1 (10 mL). The organic layer was washed with saturated saline (5.0 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (water / acetonitrile) to obtain the title compound as a diastereomeric mixture.

[0425]

Example 292

5-chloro-4-fluoro-N-((1S,2R)-2-(2-fluoronaphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)chroman-8-sulfonamide

[0426]

From 5-chloro-N-((1S,2R)-2-(2-fluoronaphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-hydroxychroman-8-sulfonamide (13 mg) obtained in Example 233, according to the method of Example 291, the title compound was obtained as a 1: 1 diastereomeric mixture.

[0427]

Example 293

5-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-6-(2,2,2-trifluoroacetyl)pyridine-2-sulfonamide

[0428]

From 5-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-sulfonamide (15.6 mg) obtained in Example 221, according to the method of Reference Example E46 Step 1, the title compound was obtained.

[0429]

Example 294

3-acetyl-4-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-2-methoxybenzenesulfonamide

[0430]

From 4-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-3-(1-hydroxyethyl)-2-methoxybenzenesulfonamide obtained in Example 204, the title compound was obtained according to the method of Reference Example E46 Step 1.

[0431]

Example 295

5-chloro-N-((1S,2R)-2-(2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-2H-chromene-8-sulfonamide

[0432]

(Step 1)

From (2S,3R)-2-amino-3-(2,3-dimethylphenyl)butanoic acid (58 mg) obtained in Reference Example D6 and 5-chloro-4-oxochroman-8-sulfonyl chloride (88 mg) obtained in Reference Example E7, in accordance with the procedures of Example 1 Steps 1 and 2, 5-chloro-N-((1S,2R)-2-(2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-oxochroman-8-sulfonamide (63.4 mg) was obtained.

[0433]

(Step 2)

From 5-chloro-N-((1S,2R)-2-(2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-oxochroman-8-sulfonamide (63.4 mg) obtained from the Step 1 above, according to the method of Example 230 Step 2, 5-chloro-N-((1S,2R)-2-

-3-(6-fluoro-2,3-dimethylphenyl)butanoic acid (8.5 mg) obtained from the above Step 4, according to the method of Example 1 Step 2, 4-chloro-2-cyano-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-N-methylbenzenesulfonamide (6.0 mg) was obtained.

[0479]

(Step 6)

From 4-chloro-2-cyano-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-N-methylbenzenesulfonamide (6.0 mg) obtained from the above Step 5, according to the method of Example 1 Step 3, the title compound was obtained.

[0480]

Example 344

6-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4'-methoxy-[1,1'-biphenyl]-3-sulfonamide

Using 3-bromo-4-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide and (4-methoxyphenyl)boronic acid obtained from Example 325 step 1, the title compound was synthesized according to the method of Example 325 Step 2.

[0481]

Example 345

3-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)-2'-methoxy-[1,1'-biphenyl]-4-carboxamide

(Step 1)

From (2S,3R)-2-amino-3-(6-fluoro-2,3-dimethylphenyl)butanoic acid obtained from Reference Example D1 and 5-bromo-2-cyanobenzenesulfonyl chloride, according to the method of steps 1 and 2 of Example 1, 5-bromo-2-cyano-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide was synthesized.

(Step 2)

Using 5-bromo-2-cyano-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide obtained from the above Step 1 and 2-methoxyphenylboronic acid, according to the method of Example 325 Step 2 and Example 1 Step 3, the title compound was obtained.

[0482]

Example 346

4-(N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)-3-methoxybenzamide

From 4-cyano-N-((1S,2R)-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-2-methoxybenzenesulfonamide obtained in Example 342, the title compound was obtained according to the method of Example 1 Step 3.

[0483]

Example 347

4-(N-((1S,2R)-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)benzamide

From 4-cyano-N-((1S,2R)-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide obtained in Example 341, according to the method of Example 1 Step 3, the title compound was obtained.

[0484]

Example 348

4-bromo -N-((1S,2R)-2-(naphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)propyl)benzenesulfonamide

(Step 1)

Using (2S,3R)-2-amino-3-(naphthalen-1-yl)butanoic acid obtained in Reference Example D11 and 4-bromobenzenesulfonyl chloride, according to the method of Step 1 of Example 1, (2S,3R)-2-((4-bromophenyl)sulfonamido)-3-(naphthalen-1-yl)butanoic acid was obtained.

(Step 2)

To a DMF (2.5 ml) solution of (2S,3R)-2-((4-bromophenyl)sulfonamido)-3-(naphthalen-1-yl)butanoic acid (283 mg) obtained from the above Step 1, ammonium chloride (41 mg), HOBt (103 mg), triethylamine (0.264 ml) and WSC (146 mg) were added, and the reaction solution was stirred at room temperature for 3 hours. The reaction solution was added to water and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain (2S,3R)-2-((4-bromophenyl)sulfonamido)-3-(naphthalen-1-yl)butanamide as a crude product.

(Step 3)

To a DMF (2 ml) solution of (2S,3R)-2-((4-bromophenyl)sulfonamido)-3-(naphthalen-1-yl)butanamide obtained from the above Step 2, cyanuric chloride (59 mg) was added at 0 ° C, and the reaction solution was stirred at room temperature for 1 hour. The reaction solution was added to water and extracted with a mixed solvent of ethyl acetate / toluene. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate) to give 4-bromo-N-((1S,2R)-1-cyano-2-(naphthalen-1-yl)propyl)benzene sulfonamide (137 mg).

(Step 4)

To an ethanol (2 ml) solution of 4-bromo-N-((1S,2R)-1-cyano-2-(naphthalen-1-yl)propyl)benzenesulfonamide (137 mg) obtained from the above Step 3, water (0.66 ml) and a 50% aqueous solution of hydroxylamine (0.060 ml) were added, and the reaction solution was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, added to water and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give (2S,3R)-2-((4-bromophenyl)sulfonamido)-N-hydroxy-(3-naphthalen-1-yl)butanamide (130 mg) as a crude product.

(Step 5)

To a DMF (1.0 ml) solution of (2S,3R)-2-((4-bromophenyl)sulfonamido)-N-hydroxy-3-(naphthalen-1-yl)butanamide (20 mg) obtained from the above Step 4, Pyridine (0.004 ml) and 2-ethylhexyl chloroformate (0.009 ml) were added, and the reaction solution was stirred at room temperature for 1 hour. Further, xylene was added, and the reaction solution was stirred overnight at 100 ° C. Water was added to the reaction solution, and the mixture was extracted with a mixed solvent of ethyl acetate / hexane. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography (eluent: hexane / ethyl acetate) to give the title compound (37 mg).

[0485]

Example 349

4-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)propyl)-2-methoxybenzenesulfonamide

(Step 1)

Using (2S,3R)-2-amino-3-(6-fluoro-2,3-dimethylphenyl)butanoic acid obtained in Reference Example D1 and 4-chloro-2-methoxybenzenesulfonyl chloride, according to the method of Example 1 Step 1, (2S,3R)-2-((4-chloro-2-methoxyphenyl)sulfonamido)-3-(6-fluoro-2,3-dimethylphenyl)butanoic acid was obtained.

(6) 5-chloro-2-(N-((1S,2R)-2-(3-ethyl-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)benzamide
(7) 5-chloro-2-(N-((1S,2R)-2-(3-chloro-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)benzamide
(8) 5-bromo-2-(N-((1S,2R)-2-(3-chloro-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)benzamide
(9) 2-(N-((1S,2R)-2-(3-bromo-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)-5-chloro-benzamide
(10) 5-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-6-(pyrrolidine-1-carbonyl)pyridine-2-sulfonamide
(11) 5-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-hydroxy-4-methyl-d3-chroman-8-sulfonamide
(12) 5-chloro-N-((1S,2R)-2-(3-chloro-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-hydroxy-4-methyl-chroman-8-sulfonamide
(13) N-((1S,2R)-2-(3-bromo-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-5-chloro-4-hydroxy-4-methyl-chroman-8-sulfonamide
(14) 5-chloro-N-((1S,2R)-2-(3-chloro-6-fluoro-2-methylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-hydroxy-4-methyl-d3-chroman-8-sulfonamide
(15) 5-chloro-N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-4-hydroxychroman-8-sulfonamide
(16) 3-chloro-6-(N-((1S,2R)-2-(6-fluoro-2,3-dimethylphenyl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)sulfamoyl)-N,N-dimethylpicolinamide
(17) 4-amino-2-methoxy-N-((1S,2R)-2-(8-methylnaphthalen-1-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)benzenesulfonamide
(18) 4-amino-N-((1S,2R)-2-(2,3-dihydro-1H-inden-4-yl)-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)propyl)-2-methoxybenzenesulfonamide, and
(19) 5-chloro-2-[[(1S,2R)-3,3,3-trideuterio-2-(6-fluoro-2,3-dimethylphenyl)-1-(2-oxo-3H-1,3,4-oxadiazol-5-yl)propyl]sulfamoyl]benzamide

Claim 19. A ribonucleotide reductase inhibitor or anti-tumor agent comprising the compound or a salt thereof according to any one of claims 1-18 as an active ingredient.

Claim 20. A medicament comprising the compound or a salt thereof according to any one of claims 1-18.

Claim 21. A pharmaceutical composition comprising the compound or a salt thereof according to any one of claims 1-18 and a pharmaceutically acceptable carrier.

Claim 22. An anti-tumor agent for oral administration comprising the compound or a salt thereof according to any one of claims 1-18 as an active ingredient.

Claim 23. Use of the compound or a salt thereof according to any one of claims 1-18 for manufacturing a ribonucleotide reductase inhibitor or pharmaceutical composition or an anti-tumor agent.

Claim 24. Use of the compound or a salt thereof according to any one of claims 1-18 for manufacturing an antitumor agent for oral administration.

Claim 25. The compound or a salt thereof according to any one of claims 1-18 for use as a medicament.

Claim 26. Use of the compound or a salt thereof according to any one of claims 1-18 in the manufacture of a medicament for preventing and/or treating tumors.