

Specification

Title of the Invention: Salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine
Technical Field

[0001]

The present invention relates to a salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine, which is useful as an antitumor agent.

Background Art

[0002]

It is known that 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine (henceforth also referred to as "Compound A") has superior antitumor activity, and is useful as a therapeutic agent for tumors (Patent document 1). It is also known that Compound A shows potent antitumor activity even when it is orally administered to mice (Non-patent documents 1 and 2).

Prior art references

Patent document

[0003]

Patent document 1: International Patent Publication WO97/038001

Non-patent documents

[0004]

Non-patent document 1: Cancer Letters, Vol. 144, pp.177-182, 1999

Non-patent document 2: Oncology Reports, Vol. 9, pp.1319-1322, 2002

Summary of the Invention

Object to be Achieved by the Invention

[0005]

Compound A suffers from low water solubility, and therefore it is necessary to improve the solubility for use as a medicament for humans. Compound A also suffers from poor flowability and tableting property, and therefore it has a problem concerning pharmaceutical manufacturing using it.

Thus, there is highly desired Compound A showing high water solubility, superior storage stability, flowability, and/or tableting property.

Summary

[0005a]

In one aspect of the present disclosure, there is provided a method for preparing a crystal of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 19.8, 21.8, 27.5, 28.4, and 29.9 degrees in powder X-ray diffractometry, which comprises the step of converting 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine into the methanesulfonate thereof and crystallizing said salt.

[0005b]

In another aspect of the present disclosure, there is provided a use of a crystal of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 19.8, 21.8, 27.5, 28.4, and 29.9 degrees in powder X-ray diffractometry, in the manufacture of a medicament for treating a tumor in a subject.

[0005c]

In a further aspect of the present disclosure, there is provided a crystal of hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 9.2, 14.7, 15.7, 22.9, and 27.3 degrees in powder X-ray diffractometry.

[0005d]

In another aspect of the present disclosure, there is provided a pharmaceutical composition containing the crystal defined herein and a pharmaceutically acceptable additive.

[0005e]

In a further aspect of the present disclosure, there is provided a pharmaceutical composition defined herein, which is for use in a treatment of a tumor.

[0005f]

In another aspect of the present disclosure, there is provided a method for preparing the crystal defined herein, which comprises the step of converting 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine into the hydrochloride thereof and crystallizing said salt.

[0005g]

In a further aspect of the present disclosure, there is provided a use of the crystal defined herein, in the manufacture of a medicament for treating a tumor in a subject.

Means for Achieving the Object

[0006]

The inventors of the present invention conducted various researches under such

a situation as mentioned above. As a result, they found that a salt of Compound A has at least one or more of such characteristics as (1) it has superior antitumor activity, (2) it shows superior crystallinity, (3) it shows high water solubility, (4) it does not show deliquescent property, (5) it shows superior flowability, (6) it shows superior tableting property, (7) it can be manufactured with less environmental load, and (8) it can be manufactured in a large scale, and therefore it is useful as a bulk drug for medicaments, and thus they accomplished the present invention.

[0007]

The present invention provides the followings.

- [1] A pharmaceutically acceptable salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine.
- [2] The salt according to [1], which is a mineral acid salt or a sulfonate.
- [3] The salt according to [2], wherein the mineral acid salt is hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, or sulfate; and the sulfonate is methanesulfonate, benzenesulfonate, p-toluenesulfonate, mesitylenesulfonate, or naphthalenesulfonate.
- [4] The salt according to [2], wherein the mineral acid salt is hydrochloride, hydroiodide, nitrate, or sulfate; and the sulfonate is methanesulfonate.
- [5] The salt according to [2], wherein the mineral acid salt is hydrochloride; and the sulfonate is methanesulfonate.
- [6] A crystal of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 19.8, 21.8, 27.5, 28.4, and 29.9 degrees in powder X-ray diffractometry, or a crystal of hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 9.2, 14.7, 15.7, 22.9, and 27.3 degrees in powder X-ray diffractometry.
- [7] A pharmaceutical composition containing the salt according to any one of [1] to [5], or the crystal according to [6].
- [8] The pharmaceutical composition according to [7], which is for use in a treatment of a tumor.
- [9] A method for preparing the salt according to any one of [1] to [5], which comprises the step of converting 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine into a pharmaceutically acceptable salt thereof.

[0008]

The present invention further provides the followings.

A salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine having an antitumor activity.

Use of a salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine for manufacture of an antitumor agent or manufacture of a medicament for use in a treatment of a tumor.

A method for a treatment of a tumor, which comprises the step of administrating a salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine to an object.

A salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine for use in a method for a treatment of a tumor.

Effect of the Invention

[0009]

The salt of the present invention has at least one or more of such characteristics as (1) it has superior antitumor activity, (2) it shows superior crystallinity, (3) it shows high water solubility, (4) it does not show deliquescent property, (5) it shows superior flowability, (6) it shows superior tableting property, (7) it can be manufactured with less environmental load, and (8) it can be manufactured in a large scale, and therefore it is useful as a bulk drug for medicaments.

The salt of the present invention shows, in particular, superior water solubility.

The salt of the present invention does not show deliquescent property, and shows, in particular, superior storage stability.

Brief Description of the Drawings

[0010]

Fig. 1 shows the result of infrared absorption spectrometry of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine.

Fig. 2 shows a powder X-ray diffraction spectrum of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine.

Fig. 3 shows the result of infrared absorption spectrometry of hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine.

Fig. 4 shows a powder X-ray diffraction spectrum of hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine.

Modes for Carrying out the Invention

[0011]

Hereafter, the present invention will be explained in detail. In the present invention, the values accompanied by "%" are used on the mass basis, unless specifically indicated, and the ranges indicated with "-" are ranges including the values on both sides of "-", unless specifically indicated.

[0012]

The present invention provides a pharmaceutically acceptable salt of Compound A. Examples of the pharmaceutically acceptable salt include a mineral acid salt, an organic carboxylate, and a sulfonate. Preferred examples of the salt include a mineral acid salt and a sulfonate.

[0013]

Examples of the mineral acid salt include, for example, hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, and sulfate, hydrochloride, hydroiodide, nitrate, and sulfate are preferred, and hydrochloride is more preferred. Examples of the organic carboxylate include, for example, formate, acetate, citrate, oxalate, fumarate, maleate, succinate, malate, tartrate, aspartate, trichloroacetate, and trifluoroacetate. Examples of the sulfonate include, for example, methanesulfonate, benzenesulfonate, p-toluenesulfonate, mesitylenesulfonate, and naphthalenesulfonate, and methanesulfonate is preferred.

[0014]

The salt of the present invention may be an anhydride, a hydrate, or a solvate. When the term "salt" is simply used in the present invention, it may be in the form of anhydride, hydrate, or solvate. As for the term "anhydride" used in the present invention, it refers to the salt in a state that it is not hydrate nor solvate, and even a substance that originally does not form hydrate nor solvate is also included in the "anhydride" referred to in the present invention, so long as it does not have crystal water, hydrating water, or interacting solvent. The anhydride may also be called "anhydrate." When the salt is a hydrate, the molecular number of hydrating water is not particularly limited, and it may be monohydrate, dihydrate, or the like. Examples of the solvate include, for example, methanol solvate, ethanol solvate, propanol solvate, and 2-propanol solvate.

[0015]

Particularly preferred specific examples of the salt of the present invention are the followings:

methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine;
hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine;
1/2 sulfate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine;
nitrate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine; and
hydroiodide of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine; as well as
anhydrides of the aforementioned salts.

[0016]

The salt of the present invention may be in the form of a crystal. One of the preferred embodiments of the present invention is a crystal of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 19.8, 21.8, 27.5, 28.4, and 29.9 degrees in powder X-ray diffractometry. Another preferred example is a crystal of hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 9.2, 14.7, 15.7, 22.9, and 27.3 degrees in powder X-ray diffractometry.

[0017]

The results of the powder X-ray diffractometry of the crystal of the hydrochloride and the crystal of the methanesulfonate are shown in Figs. 1 and 2.

[0018]

Diffraction angles at which a crystal shows characteristic peaks in powder X-ray diffractometry may vary depending on the measurement conditions. In general, 2θ may include an error in the range of ± 0.2 degree. Therefore, "diffraction angle of X degrees as 2θ " referred to in the present invention means a "diffraction angle of ((X - 0.2) to (X + 0.2)) degrees as 2θ ", unless specifically indicated. Accordingly, not only a crystal showing characteristic peaks in powder X-ray diffractometry at diffraction angles completely agreeing with the defined angles, but also a crystal showing characteristic peaks at diffraction angles agreeing with the defined angles with an error in the range of ± 0.2 degree falls within the scope of the present invention.

[0019]

Hereafter, the method for preparing the salt of the present invention will be explained. Compound A can be prepared by the method described in Patent document

1 or Journal of Organic Chemistry, Vol. 64, pp.7912-7920, 1999. A salt of Compound A, and a hydrate or a solvate thereof can be prepared by a combination of known methods, and they can be prepared by, for example, the following preparation methods.
[0020]

A salt of Compound A can be prepared by suspending Compound A in a poor solvent, adding an acid to dissolve the compound, and then removing the solvent, or adding a solvent in which the dissolved salt of Compound A is insoluble to deposit the salt. More specifically, a salt of Compound A can be prepared by suspending Compound A in water, adding an acid to dissolve the compound, and then evaporating the water. Alternatively, a salt of Compound A can be produced by suspending Compound A in water, adding an acid to dissolve the compound, and then adding acetone to deposit the salt.

[0021]

Examples of the poor solvent include, for example, water, acetone, acetonitrile, ethyl acetate, isopropyl acetate, methanol, ethanol, propanol, and 2-propanol, and these may be used as a mixture. The amount of the poor solvent to be used is 2.5- to 120-fold amount, preferably 5- to 60-fold amount, more preferably 10- to 30-fold amount, relative to Compound A (v/w). The amount of the acid to be used is, although it depends on type of the acid, 0.5 to 4.0 equivalents, preferably 1.0 to 2.0 equivalents, more preferably 1.0 to 1.5 equivalents, of Compound A.

Examples of the solvent in which the salt is insoluble include, for example, acetone, isopropyl acetate, ethanol, propanol, and 2-propanol, and these may be used as a mixture. The amount of the solvent in which the salt is insoluble to be used is 2.5- to 120-fold amount, preferably 5- to 60-fold amount, more preferably 10- to 30-fold amount, relative to Compound A (v/w).

[0022]

The salt provided by the present invention shows superior solubility, physical and chemical stabilities (deliquescent property, efflorescent property, vaporization property, evaporation property, solidification property, coagulation property, change with light, change of color, decomposition, generation of insoluble matter), and manufacturability (ease of handling in manufacture), and thus it is useful as a bulk drug for medicaments.

[0023]

The salt of Compound A of the present invention can be used as an antitumor agent, or an active ingredient of a pharmaceutical composition. In the present invention, the term "treatment" includes prophylactic treatment and therapeutic treatment.

[0024]

The pharmaceutical composition of the present invention can be used for a treatment of a tumor. The pharmaceutical composition of the present invention can be effectively used for a treatment of tumors of various types, including melanoma, hepatoma, neuroglioma, neuroblastoma, sarcoma, tumors of lung, colon, udder, bladder, ovary, testis, prostate gland, cervical part, pancreas, stomach, small intestine, and other organs. Among various kinds of the salts of Compound A, only one kind may be used for the pharmaceutical composition of the present invention, or two or more kinds of the salts may be contained. The pharmaceutical composition of the present invention may be used in combination with other therapeutic drugs containing a known antitumor agent conventionally used in this field.

[0025]

The pharmaceutical composition of the present invention may usually contain additives used for drug manufacturing, such as excipient, binder, lubricant, disintegrating agent, colorant, corrigent, emulsifier, surfactant, dissolving aid, suspending agent, isotonic agent, buffering agent, preservative, anti-oxidant, stabilizer, and absorption enhancer.

[0026]

As for the administration route of the pharmaceutical composition of the present invention, examples of the administration method include, for example, intravenous, intraarterial, intrarectal, intraperitoneal, intramuscular, intratumorale and intracystic injections, oral administration, dermal administration, use of suppository, and the like. As for dose and administration frequency, for example, 0.01 to 1000 mg/kg per day of the salt of the present invention can be administered orally or parenterally (for example, injection, drip infusion, administration to rectal part, etc.) to an adult once a day, or several times a day with dividing the foregoing dose. Examples of the form of the pharmaceutical composition as a pharmaceutical preparation include tablet, capsule, powder, syrup, granule, pill, suspension, emulsion, solution, powdery preparation, suppository, eye drop, nose drop, ear drop, patch, ointment, and injection.

Examples

[0027]

In order to clarify usefulness of the compound of the present invention, the present invention will be explained with reference to the following test examples.

[0028]

Test Example 1: Antitumor activity

The compounds of Examples 1 and 2 were chosen as test compounds.

Compound A was chosen as a comparative compound.

Cells at the logarithmic phase were inoculated on a 96-well plate at a density of 1000 cells/well (BxPC-3, MIA PaCa-2) or 3000 cells/well (Capan-1), and cultured overnight at 37°C in a CO₂ incubator. On the next day, serially diluted solutions of each test compound were added, and culture was performed for 3 days in an incubator. After completion of the culture, by using a cell proliferation assay kit ATPlite (Perkin Elmer), and a plate reader Envision (Perkin Elmer), emission was measured. Concentrations of the test compounds providing 50% of cell proliferation inhibition (IC₅₀) were calculated by fitting using a sigmoid function. The solutions of the test compounds were prepared by diluting them with PBS (pH 7.4) at 10 mM, and further diluting the 10 mM solutions with PBS (pH 7.4), and used in the test.

The results are shown in Table 1.

[0029]

[Table 1]

Test compound	IC ₅₀ (nM)		
	BxPC-3	Capan-1	MIA PaCa-2
Example 1 (methanesulfonate)	45	36	373
Example 2 (hydrochloride)	41	31	417
Comparative compound	45	35	382

[0030]

The compounds of the present invention showed superior antitumor activity.

[0031]

Test Example 2: Solubility test

The compounds of Examples 1 to 5 were chosen as test compounds.

Compound A was chosen as a comparative compound.

Each of the test compounds and the comparative compound was added to water,

and the mixture was stirred at room temperature for 24 hours. The insoluble matter was removed by filtration using a membrane filter (0.2 μm). The filtrate was analyzed by high performance liquid chromatography (HPLC) to obtain the solubility.

The results are shown in Table 2.

[0032]

[Table 2]

Test compound	Solubility in water (mg/mL)
Example 1 (methanesulfonate)	79
Example 2 (hydrochloride)	67
Example 3 (1/2 sulfate)	35
Example 4 (nitrate)	45
Example 5 (hydroiodide)	128
Comparative compound	2

[0033]

The compounds of the present invention showed high solubility in water, i.e., superior solubility.

[0034]

Test Example 3: Stability test

The compounds of Examples 1 and 2 were chosen as test compounds.

The compounds of Examples 1 and 2 were stored for 2 weeks in an open state under conditions of 60°C and 75% relative humidity. The test compounds were macroscopically observed after the storage, and presence or absence of deliquescence was examined. As a result, the compounds of Examples 1 and 2 did not deliquesce, but were stable.

[0035]

The compounds of the present invention did not show deliquescent property, but showed superior stability.

[0036]

Test Example 4: Flowability test

The compounds of Examples 1 and 2 were chosen as test compounds.

Compound A was chosen as a comparative compound.

Each of the test compounds and the comparative compound was sieved with

177 μm (80M) mesh to obtain a powdery sample. The obtained powdery sample was roughly filled in a glass measuring cylinder (10 cm^3), the upper surface of the powder layer was horizontally smoothened, and the value of the volume was read. The weight of the powdery sample was divided with the volume to obtain loose bulk density (g/cm^3).

Then, the glass measuring cylinder filled with the powdery sample was tapped by using a general powdery characteristic measuring apparatus (Powdertester Type PT-E, Hosokawa Micron CORP.). When the volume of the powder layer no longer changed, the value of the volume was read. The weight of the powdery sample was divided with the volume to obtain compacted bulk density (g/cm^3).

The compaction rate (%) was obtained in accordance with the following equation.

$$\text{Compaction rate (\%)} = [(\text{Compacted bulk density} - \text{Loose bulk density}) / \text{Compacted bulk density}] \times 100$$

The results are shown in Table 3.

[0037]

[Table 3]

Test compound	Compaction rate (%)
Example 1 (methanesulfonate)	18
Example 2 (hydrochloride)	21
Comparative compound	41

[0038]

The compounds of the present invention showed small compaction rates, and thus showed superior flowability. The compounds of the present invention showed superior physical properties.

[0039]

Test Example 5: Tableting property test

The compounds of Examples 1 and 2 were chosen as test compounds.

Compound A was chosen as a comparative compound.

Each of the test compounds and the comparative compound was sieved with 177 μm (80M) mesh to obtain a powdery sample. The obtained powdery sample was compression-molded by using a tableting machine (Tableting Machine HT-P18A, Hata Iron Works, Ltd.; tableting diameter, 6.5 mm; tableting pressure, 1000 kgf; tablet weight,

100 mg) to obtain tablets. The obtained tablets were macroscopically observed, and graded according to the following criteria.

5 Points: Surface has gloss.

4 Points: Surface is slightly roughened.

3 Points: Surface is roughened.

2 Points: Surface is slightly chipped.

1 Point: Surface is chipped.

0 Point: Tablets stick to pestle, and cannot be unstuck.

The tableting was performed five times, and averages of the scores of the tablets were calculated. The results are shown in Table 4.

[0040]

[Table 4]

Test compound	Score
Example 1 (methanesulfonate)	4.5
Example 2 (hydrochloride)	5.0
Comparative compound	1.0

[0041]

The compounds of the present invention showed high scores, and thus showed superior tableting property. The compounds of the present invention showed superior physical properties.

[0042]

Hereafter, the present invention will be explained with reference to examples. However, the present invention is not limited to these examples.

Moisture content was measured with a Karl Fischer moisture meter.

Infrared absorption spectrum was measured by the infrared absorption attenuated total reflectance spectroscopy (ATR method).

In the examples, the abbreviations have the following meanings.

Compound A: 1-(2-Deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine

DMSO-D₆: Heavy dimethyl sulfoxide

[0043]

Example 1

Compound A was prepared according to the method described in Journal of Organic Chemistry, Vol. 64, pp.7912-7920, 1999 (the same shall apply to the following

examples). Methanesulfonic acid (0.99 mL) was added to a suspension of Compound A (4.0 g) in water (73 mL), and the mixture was stirred at room temperature for 35 minutes. After dissolution was visually confirmed, the solvent was evaporated under reduced pressure. Acetone (75 mL) was added to the obtained residue, and the mixture was stirred at room temperature for 30 minutes. The solid matter was collected by filtration, washed with acetone, and air-dried to obtain methanesulfonate of Compound A (5.2 g) as a white solid. Moisture content: 1.3% (weight ratio).

[0044]

¹H-NMR (DMSO-D₆) δ: 9.55 (1H, s), 8.56 (1H, s), 8.46 (1H, d, J=7.9Hz), 6.28 (1H, dd, J=10.6, 5.3Hz), 6.14 (1H, d, J=7.9Hz), 5.06 (1H, dt, J=50.2, 5.9Hz), 4.24-4.13 (1H, m), 3.80-3.61 (2H, m), 3.23 (1H, q, J=5.7Hz), 2.35 (3H, s)

[0045]

The result of infrared absorption spectrometry of the obtained crystal of the methanesulfonate of Compound A is shown in Fig. 1.

[0046]

Powder X-ray diffraction of the obtained crystal of the methanesulfonate of Compound A was measured.

Conditions of powder X-ray diffractometry:

X-ray used: CuKα

Applied voltage: 50 kV

Applied current: 280 mA

Scanning axis: 2θ

[0047]

The obtained powder X-ray diffraction spectrum is shown in Fig. 2 and Table 5.

[0048]

[Table 5]

2θ	d (Å)	Relative intensity (%)
16.514	5.368	9
18.431	4.814	10
18.699	4.746	9
19.770	4.491	31
21.817	4.074	27

24.428	3.644	17
27.455	3.249	26
28.388	3.144	100
29.895	2.989	33
34.322	2.613	12

[0049]

Example 2

Concentrated hydrochloric acid (1.31 mL) was added to a suspension of Compound A (4.0 g) in water (68 mL), and the mixture was stirred at room temperature for 1 hour. After dissolution was visually confirmed, the solvent was evaporated under reduced pressure. Acetone (68 mL) was added to the obtained residue, and the mixture was stirred at room temperature for 1 hour. The solid matter was collected by filtration, washed with acetone, and air-dried to obtain hydrochloride of Compound A (4.5 g) as a white solid. Moisture content: 0.9% (weight ratio).

[0050]

¹H-NMR (DMSO-D₆) δ: 9.80 (1H, s), 8.71 (1H, s), 8.47 (1H, d, J=7.9Hz), 6.27 (1H, dd, J=9.9, 5.3Hz), 6.21 (1H, d, J=7.9Hz), 5.07 (1H, dt, J=50.4, 6.1Hz), 4.22-4.14 (1H, m), 3.80-3.61 (2H, m), 3.23 (1H, q, J=5.7Hz)

[0051]

The result of infrared absorption spectrometry of the obtained crystal of the hydrochloride of Compound A is shown in Fig. 3.

[0052]

Powder X-ray diffraction of the obtained crystal of the hydrochloride of Compound A was measured. The measurement conditions were the same as those used in Example 1. The obtained powder X-ray diffraction spectrum is shown in Fig. 4 and Table 6.

[0053]

[Table 6]

2θ	d (Å)	Relative intensity (%)
9.172	9.642	64
13.299	6.658	30
14.704	6.025	92

15.713	5.640	53
18.458	4.807	26
22.879	3.887	100
27.261	3.271	86
34.336	2.612	34
34.677	2.587	23
37.031	2.428	34

[0054]

Example 3

Sulfuric acid (5 μ L) was added to a suspension of Compound A (50 mg) in water (1.0 mL), and the mixture was stirred at room temperature for 10 minutes. After dissolution was visually confirmed, the solvent was evaporated under reduced pressure. Acetone (1.0 mL) was added to the obtained residue. The solid matter was collected by filtration, and air-dried to obtain 1/2 sulfate of Compound A (50 mg) as a white solid.

[0055]

$^1\text{H-NMR}$ (D_2O) δ : 8.56 (1H, d, $J=8.6\text{Hz}$), 6.40 (1H, dd, $J=8.9, 5.6\text{Hz}$), 6.26 (1H, d, $J=7.9\text{Hz}$), 5.19 (1H, dt, $J=50.0, 6.3\text{Hz}$), 4.42-4.34 (1H, m), 3.94-3.84 (2H, m), 3.44 (1H, q, $J=5.5\text{Hz}$)

[0056]

Example 4

60% Nitric acid (0.014 mL) was added to a suspension of Compound A (50 mg) in water (1.0 mL), and the mixture was stirred at room temperature for 10 minutes. After dissolution was visually confirmed, the solvent was evaporated under reduced pressure. Acetone (1.0 mL) was added to the obtained residue. The solid matter was collected by filtration, and air-dried to obtain nitrate of Compound A (70 mg) as a white solid.

[0057]

$^1\text{H-NMR}$ (DMSO-D_6) δ : 9.50 (1H, s), 8.45 (1H, d, $J=7.9\text{Hz}$), 8.35 (1H, s), 6.29 (1H, dd, $J=10.6, 5.3\text{Hz}$), 6.13 (1H, d, $J=7.9\text{Hz}$), 5.06 (1H, dt, $J=50.2, 5.9\text{Hz}$), 4.22-4.14 (1H, m), 3.71 (2H, m), 3.24 (1H, q, $J=5.6\text{Hz}$)

[0058]

Example 5

57% Hydroiodic acid (0.025 mL) was added to a suspension of Compound A (50 mg) in water (1.0 mL), and the mixture was stirred at room temperature for 10 minutes. After dissolution was visually confirmed, the solvent was evaporated under reduced pressure. Acetone (1.0 mL) was added to the obtained residue. The solid matter was collected by filtration, and air-dried to obtain hydroiodide of Compound A (50 mg) as a white solid.

[0059]

¹H-NMR (DMSO-D₆) δ: 9.51 (1H, s), 8.45 (1H, d, J=7.9Hz), 8.38 (1H, s), 6.29 (1H, dd, J=10.6, 5.3Hz), 6.13 (1H, d, J=7.9Hz), 5.06 (1H, dt, J=50.2, 5.9Hz), 4.22-4.14 (1H, m), 3.71 (2H, m), 3.24 (1H, q, J=5.6Hz)

Industrial Applicability

[0060]

The salt of the present invention shows at least one or more of such characteristics as (1) it has superior antitumor activity, (2) it shows superior crystallinity, (3) it shows high water solubility, (4) it does not show deliquescent property, (5) it shows superior flowability, (6) it shows superior tableting property, (7) it can be manufactured with less environmental load, and (8) it can be manufactured in a large scale, and therefore it is useful as a bulk drug for medicaments.

Claims

1. A method for preparing a crystal of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 19.8, 21.8, 27.5, 28.4, and 29.9 degrees in powder X-ray diffractometry, which comprises the step of converting 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine into the methanesulfonate thereof and crystallizing said salt.

2. Use of a crystal of methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 19.8, 21.8, 27.5, 28.4, and 29.9 degrees in powder X-ray diffractometry, in the manufacture of a medicament for treating a tumor in a subject.

3. A crystal of hydrochloride of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine showing characteristic peaks at diffraction angles (2θ) of 9.2, 14.7, 15.7, 22.9, and 27.3 degrees in powder X-ray diffractometry.

4. A pharmaceutical composition containing the crystal according to claim 3 and a pharmaceutically acceptable additive.

5. The pharmaceutical composition according to claim 4, which is for use in a treatment of a tumor.

6. A method for preparing the crystal according to claim 3, which comprises the step of converting 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine into the hydrochloride thereof and crystallizing said salt.

7. Use of the crystal according to claim 3, in the manufacture of a medicament for treating a tumor in a subject.

Title of the Invention: Salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine

Abstract

A superior antitumor agent is provided. A salt of 1-(2-deoxy-2-fluoro-4-thio- β -D-arabinofuranosyl)cytosine shows at least one or more of such characteristics as (1) it has superior antitumor activity, (2) it shows superior crystallinity, (3) it shows high water solubility, (4) it does not show deliquescent property, (5) it shows superior flowability, (6) it shows superior tableting property, (7) it can be manufactured with less environmental load, and (8) it can be manufactured in a large scale, and therefore it is useful as a bulk drug for medicaments.

(Figure 1)