DESCRIPTION

Title of Invention

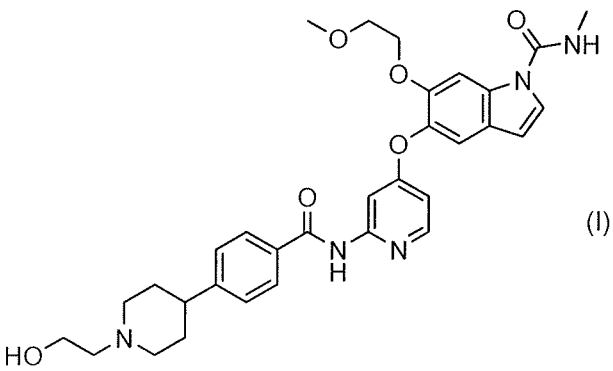
THERAPEUTIC AGENT FOR BREAST CANCER

Technical Field

[0001] The present invention relates to a therapeutic agent for breast cancer, comprising a monocyclic pyridine derivative having an FGFR inhibitory action or a pharmacologically acceptable salt thereof. The present invention relates more specifically to a therapeutic agent for breast cancer, comprising 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridine-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide or a pharmacologically acceptable salt thereof.

Background Art

[0002]



(I)

[0003] 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide represented by formula (I) has been known as an inhibitor against fibroblast growth factor receptors (FGFR) 1, 2, and 3, and a report (Patent Literature 1) shows that this compound exerts a gastric cancer, lung cancer, bladder cancer, and endometrial cancer cell proliferation inhibitory action.

[0004] Breast cancer is grouped according to the presence or absence of expression of an estrogen receptor, a progesterone receptor, and a HER2 receptor. Drug therapy corresponding to each type can be provided as well as a surgical removal of an affected site. Unfortunately, even such therapeutic intervention results in a decrease in 5-year survival rate depending on the stage of breast cancer. In the case of breast cancer called a triple negative type where any of the above receptors are not expressed, in particular, administration of an anti-cancer drug such as taxane often exerts an insufficient effect (Non Patent Literature 1). Meanwhile, an FGFR inhibitor is reportedly effective in breast cancer treatment (Non Patent

Literature 2).

Citation List

Patent Literature

[0005] Patent Literature 1: U.S. Patent Application Publication No. 2014 -235614

Non Patent Literature

[0006] Non Patent Literature 1: Foulkes *et al.*, "Triple-Negative Breast Cancer", The New England Journal of Medicine., 363, 1938-1948, 2010.

Non Patent Literature 2: Koziczak *et al.*, "Blocking of FGFR signaling inhibits breast cancer cell proliferation through downregulation of D-type cyclins", Oncogene., 23, 3501-3508, 2004.

Summary of Invention

Technical Problem

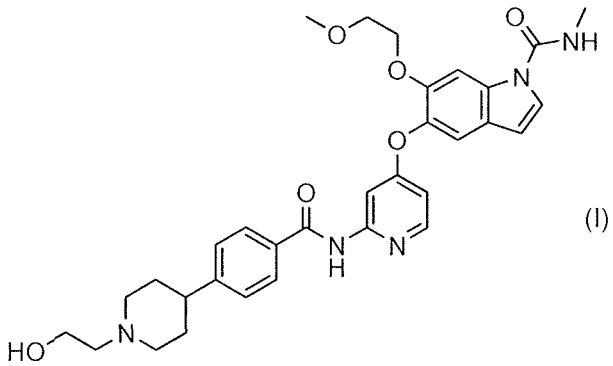
[0007] It is an objective of the present invention to provide a novel therapeutic agent for breast cancer.

Solution to Problem

[0008] In view of such situations, the present inventors have conducted intensive research and, as a result, have found that a compound represented by formula (I) elicits a marked anti-breast cancer therapeutic benefit. Then, the present invention has been completed.

[0009] Specifically, the present invention provides the following items [1] to [9].

[1] A therapeutic agent for breast cancer, comprising a compound represented by formula (I):



(I)

or a pharmacologically acceptable salt thereof.

[2] Use of a compound represented by formula (I) or a pharmacologically acceptable salt thereof for breast cancer treatment.

[3] A compound represented by formula (I) or a pharmacologically acceptable salt thereof for use in the treatment of breast cancer.

[4] A method of treating breast cancer comprising administering a compound represented by formula (I) or a pharmacologically acceptable salt thereof to a patient in need thereof.

[5] A composition for treating breast cancer comprising a compound represented by formula (I) or a pharmacologically acceptable salt thereof.

[6] A composition for treating breast cancer comprising a compound represented by formula (I) or a pharmacologically acceptable salt thereof and an excipient.

[7] The therapeutic agent, use, compound, method, or composition according to any one of the above items, wherein the breast cancer is locally advanced breast cancer, metastatic breast cancer, or recurrent breast cancer.

[8] The therapeutic agent, use, compound, method, or composition according to any one of the above items, wherein the breast cancer expresses an FGFR.

[9] The therapeutic agent, use, compound, method, or composition according to any one of the above items, wherein the FGFR is FGFR1, FGFR2, or FGFR3.

Advantageous Effects of Invention

[0010] The compound represented by formula (I) may exert an anti-breast cancer effect of reducing a tumor volume.

Brief Description of Drawings

[0011] Figure 1 is a graph showing changes in tumor volume over time after initiation of drug administration.

Figure 2 is a graph showing changes in body weight over time after initiation of drug administration.

Description of Embodiments

[0012] A compound represented by formula (I) or a pharmacologically acceptable salt thereof according to the present invention may be produced by the method described in Patent Literature 1.

[0013] As used herein, examples of the pharmacologically acceptable salt include a salt of an inorganic acid, a salt of an organic acid, and a salt of an acidic amino acid.

[0014] Preferable examples of the salt of the inorganic acid include salts of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc.

[0015] Preferable examples of the salt of the organic acid include salts of acetic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, lactic acid, stearic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, etc.

[0016] Preferable examples of the salt of acidic amino acid include salts of aspartic acid,

glutamic acid, etc.

[0017] The preferable pharmacologically acceptable salt is a succinate or a maleate. The more preferable salt is a succinate. Particularly preferred is a 1.5 succinate.

[0018] The therapeutic agent for breast cancer according to the present invention may be orally administered in the form of a solid preparation, such as a tablet, granules, fine particles, powder, and a capsule, or a liquid, jelly, syrup, etc. Also, the therapeutic agent for tumor according to the present invention may be parenterally administered in the form of an injection, a suppository, ointment, a cataplasm, etc.

[0019] The therapeutic agent for breast cancer according to the present invention may be formulated by the protocol described in the Japanese pharmacopoeia, 16th edition.

[0020] The dose of a compound represented by formula (I) or a pharmacologically acceptable salt thereof may be suitably selected depending on the degree of a symptom, the age, sex, body weight, and a sensitivity difference of a patient, an administration route, dosing timing, a dosing interval, the kind of a pharmaceutical preparation, etc. When the compound is orally administered to an adult (the body weight: 60 kg), the daily dose is usually from 100 μg to 10 g, preferably from 500 μg to 10 g, and more preferably from 1 mg to 5 g. This dose may be administered while being divided into 1 to 3 times a day.

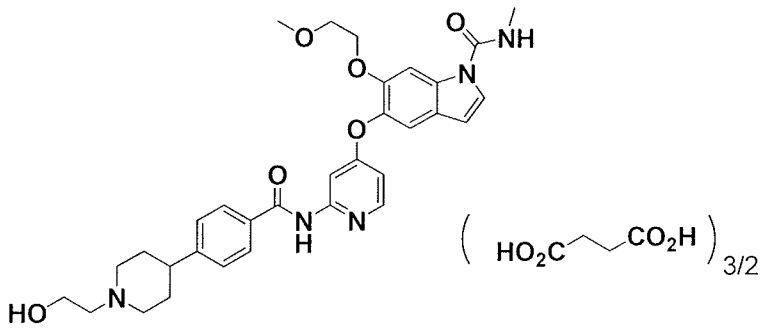
[0021] As used herein, the breast cancer means benign or malignant tumor developed in the mammary gland (breast ducts, lobules). The breast cancer includes locally advanced breast cancer, metastatic breast cancer, and recurrent breast cancer.

Examples

[0022] Hereinafter, the present invention is further described in detail by referring to Examples.

[0023] Production Example 1

Production of a salt of 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide 1.5 succinate (hereinafter, sometimes referred to as compound A).



2.93 g of 5-({2-[({4-[1-(2-hydroxyethyl)piperidin-4-yl]phenyl}carbonyl)amino]pyridin-4-yl}oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide was weighed in a recovery flask, 60 mL of ethanol was added, and the mixture was heated and stirred at 70°C in an oil bath to be dissolved. Succinic acid (1.23 g) was added, then turned off the oil bath and gradually cooled. The mixture was stirred at room temperature for 2 hours, and further stirred at 5°C for 1 hour. The solid was collected by filtration to obtain the title compound (3.70 g).

^{1}H-NMR Spectrum (600 MHz, CD_3OD) δ (ppm): 1.96-2.10 (4H, m), 2.52 (6H, s), 2.93 (1H, m), 2.96 (3H, s), 3.01 (2H, m), 3.16 (2H, t, J=5.4 Hz), 3.22 (3H, s), 3.56 (2H, t, J=4.7 Hz), 3.61 (2H, m), 3.87 (2H, t, J=5.4 Hz), 4.14 (2H, t, J=4.6 Hz), 6.61 (1H, d, J=3.6 Hz), 6.68 (1H, dd, J=5.8, 2.3 Hz), 7.37 (1H, s), 7.42 (2H, d, J=8.3 Hz), 7.58 (1H, d, J=3.6 Hz), 7.73 (1H, d, J=2.2 Hz), 7.88 (2H, d, J=8.3 Hz), 8.08 (1H, s), 8.15 (1H, d, J=5.8 Hz).

^{13}C-NMR Spectrum (100 MHz, solid state) δ(ppm): 27.1, 28.3, 29.7, 34.8, 38.0, 41.3, 54.0, 57.3, 59.7, 60.9, 72.1, 72.5, 103.3, 104.2, 108.5, 116.9, 126.9, 128.6, 134.5, 136.7, 140.7, 149.4, 151.3, 155.1, 169.5, 170.1, 175.6, 179.9, 183.7.

[0024] Example 1: Growth Inhibitory Action of Compound A on Human Breast Cancer Cell Line (MFM223).

Four nude mice (BALB/cAJcl-nu/nu, female, CLEA Japan, Inc.) per group were used to evaluate an anti-tumor effect when compound A was administered.

A human-derived breast cancer cell line MFM223 (ECACC) was subjected to preparatory conditioning. The MFM223 cells were suspended at a concentration of 2×10^8 cells/mL in HBSS (Wako Pure Chemical Industries, Ltd.). To the resulting suspension was added an equal volume of Matrigel™ matrix (Becton, Dickinson and Company, Japan), and the mixture was mixed sufficiently. Then, 0.1 mL of the mixture was subcutaneously transplanted into the right flank of each nude mouse (CAnN.Cg-Foxn1nu/CrlCrlj, female, Charles River Laboratories International, Inc.). During rearing, β-estradiol (Wako Pure

Chemical Industries, Ltd.) prepared at a final concentration of 2.5 μg/mL in drinking water was orally administered. 46 Days after the transplantation, a tumor formed was resected and cut into small pieces. HBSS containing Type I collagenase (SIGMA) at a final concentration of 380 units/mL and Deoxyribonuclease I (SIGMA) at a final concentration of 160 K units/mL was added thereto, and the mixture was stirred at 37°C. After the mixture was made to pass through a 100-μm cell strainer (Falcon(Registered Trademark)) and centrifuged to collect the cells, those cells were cultured in 10% bovine serum-containing EMEM culture medium.

[0025] The cells as so obtained were suspended at a concentration of 1.4×10^8 cells/mL in 10% bovine serum-containing EMEM culture medium (Wako Pure Chemical Industries, Ltd.). To the resulting suspension was added an equal volume of Matrigel™ matrix (Becton, Dickinson and Company, Japan), and the resulting mixture was mixed sufficiently. Next, 0.1 mL of the mixture was subcutaneously transplanted into the right flank of each mouse, and then, the anti-tumor effect was evaluated.

20 Days after the transplantation, an electronic digital caliper (Digimatic™ Caliper; Mitutoyo Corporation) was used to measure the long and short diameters of a tumor of interest. The mice were grouped such that each group had substantially the same average of the tumor volumes. Note that each tumor volume was calculated by using the following equation:

Tumor Volume (mm^3) = Long Diameter (mm) × Short Diameter (mm) × Short Diameter (mm) / 2.

[0026] Compound A as obtained in Production Example 1 was dissolved at a concentration of 0.625 mg/mL or 2.5 mg/mL in purified water.

Then, the solution was orally administered at a dose of 20 mL/kg, i.e., 12.5 mg/kg or 50 mg/kg, once a day for 12 days to the mice of each group. Purified water was administered at 20 mL/kg to the control group.

[0027] On day 3, 7, and 12 after initiation of the administration, the tumor volume of each mouse was measured. Table 1 and Figure 1 show the results. In addition, Table 2 and Figure 2 show changes in body weight over time.

[0028] [Table 1]

Changes in tumor volume over time (mm^3)

	Day 0	Day 3	Day 7	Day 12
Control group	156.6	159.7	175.5	208.4

Compound A	12.5 mg/kg	151.6	139.0	143.8	148.2
Compound A	50 mg/kg	151.6	112.8	99.3	87.2

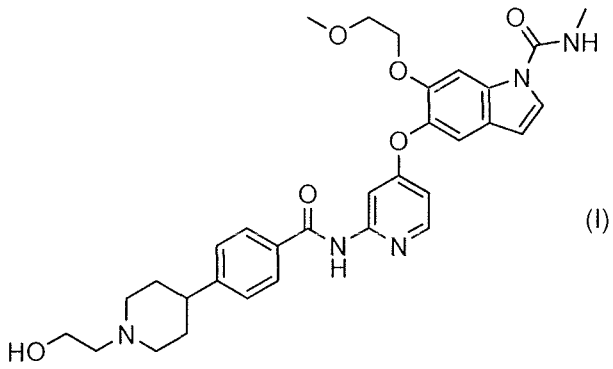
[0029] [Table 2]

Changes in body weight over time (g)

		Day 0	Day 3	Day 7	Day 12
Control group		21.6	20.7	21.0	20.3
Compound A	12.5 mg/kg	21.1	21.4	22.6	23.2
Compound A	50 mg/kg	21.5	22.8	23.8	24.0

CLAIMS

1. A therapeutic agent for breast cancer, comprising 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide:



(I)

or a pharmacologically acceptable salt thereof.

2. The therapeutic agent according to claim 1, wherein the salt is a 1.5 succinate.

3. A pharmaceutical composition for treating breast cancer, comprising 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide or a pharmacologically acceptable salt thereof.

4. The pharmaceutical composition according to claim 3, wherein the salt is a 1.5 succinate.

5. The therapeutic agent according to claim 1 or 2, wherein the breast cancer is locally advanced breast cancer, metastatic breast cancer, or recurrent breast cancer.

6. The pharmaceutical composition according to claim 3 or 4, wherein the breast cancer is locally advanced breast cancer, metastatic breast cancer, or recurrent breast cancer.