DESCRIPTION

Title of Invention

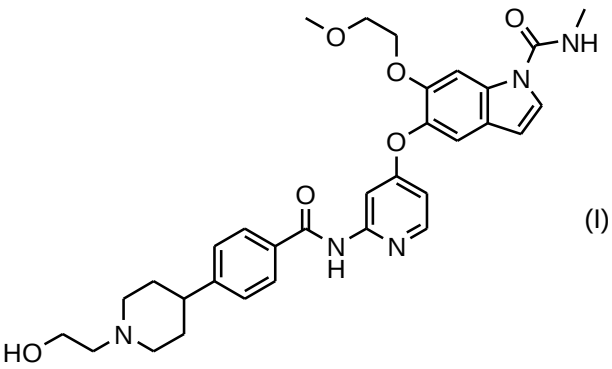
THERAPEUTIC AGENT FOR HEPATOCELLULAR CARCINOMA

Technical Field

[0001] The present invention relates to a therapeutic agent for hepatocellular carcinoma, comprising a monocyclic pyridine derivative having a fibroblast growth factor receptor (FGFR) inhibitory action or a pharmacologically acceptable salt thereof. More specifically, the present invention relates to a therapeutic agent for hepatocellular carcinoma, 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.

Background Art

[0002]



(I)

[0003] It has been reported that 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) is known as an inhibitor against FGFR1, FGFR2 or FGFR3, and has an inhibitory action on the cell proliferation of stomach cancer, lung cancer, bladder cancer, and endometrial cancer (Patent Literature 1). It has been reported that the above compound exerts a high therapeutic effect against bile duct cancer (Patent Literature 2) and breast cancer (Patent Literature 3). As the pharmacologically acceptable salt of the above compound, a succinate and a maleate are known (Patent Literature 4).

[0004] Hepatocellular carcinoma develops due to malignant transformation of liver cells following chronic hepatitis or liver cirrhosis. Examples of the causes of the development of hepatocellular carcinoma include excessive alcohol intake, excessive calorie intake, viral infection, and genetic predisposition.

Examples of the methods for treating hepatocellular carcinoma include surgical resection, cautery, hepatic artery embolization, and ethanol injection therapy. However, these treatment methods are limited to the use in a case where the area of development of hepatocellular carcinoma is narrow. In a case where many cancer foci are recognized, or in a case where many cancer foci are spread to other organs, chemotherapy is performed by transhepatic arterial infusion or systemic administration of an antitumor agent. As the drugs effective in the treatment of hepatocellular carcinoma, regorafenib, sorafenib (Non Patent Literatures 1 and 2) and the like are known, but such drugs often cause adverse drug reactions such as pneumonia, hypertension, and hand-foot syndrome, and therefore, further, the development of a novel drug is awaited.

Citation List

Patent Literature

[0005] Patent Literature 1: US 2014-0235614 A

Patent Literature 2: US 2018-0015079 A

Patent Literature 3: International Publication No. WO 2017/104739

Patent Literature 4: US 2017-0217935 A

Non Patent Literature

[0006] Non Patent Literature 1: Kim K. et al., Regorafenib in advanced hepatocellular carcinoma (HCC): considerations for treatment, Cancer Chemotherapy and Pharmacology, 80, 945-954, 2017

Non Patent Literature 2: Josep M. et al., Sorafenib in Advanced Hepatocellular Carcinoma, The New England Journal of Medicine, 359, 378-390, 2008

Summary of Invention

Technical Problem

[0007] An object of the present invention is to provide a novel therapeutic agent for hepatocellular carcinoma.

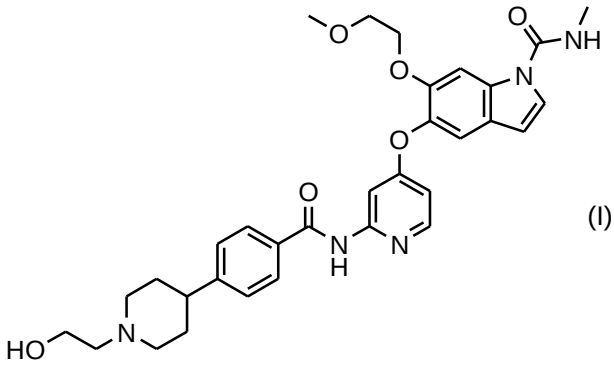
Solution to Problem

[0008] In view of the above circumstances, as a result of intensive studies, the present inventors have found that the compound represented by the above formula (I) exerts a high therapeutic effect against hepatocellular carcinoma, and thus have completed the present invention.

[0009] That is, the present invention provides the following [1] to [10].

[1] A therapeutic agent for hepatocellular carcinoma, comprising a compound represented by

formula (I) or a pharmacologically acceptable salt thereof:



(I)

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

[3] A compound represented by formula (I) or a pharmacologically acceptable salt thereof, for use in treatment of hepatocellular carcinoma.

[4] A method for treating hepatocellular carcinoma, 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 hepatocellular carcinoma, comprising a compound represented by formula (I) or a pharmacologically acceptable salt thereof.

[6] A composition for treating hepatocellular carcinoma, 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 as above, wherein the hepatocellular carcinoma is metastatic hepatocellular carcinoma or recurrent hepatocellular carcinoma.

[8] The therapeutic agent, use, compound, method, or composition as above, wherein the hepatocellular carcinoma expresses an FGFR.

[9] The therapeutic agent, use, compound, method, or composition as above, wherein the FGFR is FGFR1, FGFR2, or FGFR3.

[10] The therapeutic agent, use, compound, method, or composition as above, wherein the pharmacologically acceptable salt of the compound represented by formula (I) is a sesquisuccinate.

Advantageous Effects of Invention

[0010] The compound represented by formula (I) may exert an effect of reducing a tumor volume against hepatocellular carcinoma.

Brief Description of Drawings

[0011] Figure 1 is a graph showing the results of Example 4. The ordinate shows the tumor volume, and the abscissa shows the days after administration.

Description of Embodiments

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

[0013] In the present specification, examples of the pharmacologically acceptable salt include a salt with an inorganic acid, a salt with an organic acid, and a salt with an acidic amino acid.

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

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

[0016] Preferable examples of the salt with an acidic amino acid include salts with aspartic acid and glutamic acid.

[0017] A preferable pharmacologically acceptable salt is a succinate or a maleate, and a more preferable salt is a succinate. In particular, it is preferable for the salt to be a sesquisuccinate.

[0018] The therapeutic agent for hepatocellular carcinoma according to the present invention can be administered orally in a form of a solid preparation such as a tablet, granules, fine particles, powder, or a capsule, a liquid, a jelly, a syrup, or the like. Further, the therapeutic agent for hepatocellular carcinoma according to the present invention may be administered parenterally in a form of an injection, a suppository, ointment, a cataplasm, or the like.

[0019] The therapeutic agent for hepatocellular carcinoma according to the present invention can be formulated by the method described in The Japanese Pharmacopoeia, Seventeenth Edition.

[0020] The dose of a compound represented by formula (I) or a pharmacologically acceptable salt thereof can be appropriately selected depending on the severity of symptoms, the age, sex, body weight, and differential sensitivity of a patient, the route of administration, the time of administration, the intervals of administration, the type of pharmaceutical

preparation, and the like. In general, in a case of oral administration to an adult (body weight: 60 kg), the dose is 100 μg to 10 g, preferably 500 μg to 10 g, and furthermore preferably 1 mg to 5 g, per day. This dose may be administered in 1 to 3 divided portions per day.

[0021] In the present specification, the hepatocellular carcinoma means a benign or malignant tumor developed in the liver cells. The hepatocellular carcinoma includes metastatic hepatocellular carcinoma in an organ tissue other than the liver, or recurrent hepatocellular carcinoma.

Examples

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

[0023] Production Example 1

By the method disclosed in the specification of US 2017-0217935 A, 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide sesquisuccinate (hereinafter, referred to as compound A) was produced.

[0024] Example 1: IC_{50} of compound A against proliferation of hepatocellular carcinoma cell line

As the human hepatocellular carcinoma cell line, SNU-398, Li-7, Hep3B2.1-7, and HuH-7 were used. In this regard, SNU-398, and Hep3B2.1-7 were obtained from American Type Culture Collection (ATCC), Li-7 was obtained from Cell Resource Center for Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University, and HuH-7 was obtained from JCRB Cell Bank, respectively.

For each cell line, maintenance culture was performed by using the following medium.

(1) SNU-398 and Li-7

An RPMI-1640 medium (Wako Pure Chemical Industries, Ltd.) containing 10% fetal bovine serum (FBS) and penicillin/streptomycin

(2) HuH-7

A DMEM-low glucose medium (Wako Pure Chemical Industries, Ltd.) containing 10% FBS and penicillin/streptomycin

(3) Hep3B2.1-7

An EMEM medium (Wako Pure Chemical Industries, Ltd.) containing 10% FBS

and penicillin/streptomycin

[0025] Into each well of a 96-well clear-bottom black plate (Corning Incorporated, catalog number: 3904), a suspension of each cell, which had been prepared to be 0.75 to 1.25×10^4 cells/mL, was added in an amount of 80 to 90 μL, and the cells were cultured overnight in a 5% CO_2 incubator (37°C). To the obtained cultured cells, a compound A diluted in each medium containing 10% FBS was added in an amount of 10 to 20 μL so that the mixture to be obtained was adjusted to be in a liquid amount of 100 μL, and then the obtained mixture was cultured for 6 days in a 5% CO_2 incubator (37°C).

[0026] The number of cells in each well after the culture was calculated by measuring the intracellular ATP level with the emission intensity using CellTiter Glo-2.0 (Promega Corporation, catalog number: G9243).

CellTiter Glo-2.0 was added in an amount of 50 μL into each well, and the mixture was mixed for 10 minutes with a plate mixer. After that, the mixture was allowed to react at room temperature for 10 minutes, and then the luminescence was measured with Multilabel Reader (ARVO X4, PerkinElmer, Inc.) The luminescence value ratio in the presence of a compound A was determined, assuming that the luminescence value in a case where compound A had not added was set to 100% and the luminescence value in a well where cells had not been present was set to 0%. The concentration required for inhibiting the cell proliferation by 50% (IC_{50} value) of the test substance was calculated. The results are shown in Table 1.

[0027] [Table 1]

Name of cell	IC_{50} (nmol/L)
SNU-398	26
Hep3B2.1-7	77
HuH-7	249
Li-7	63

[0028] Example 2: Antitumor action of compound A against human hepatocellular carcinoma cell line (HuH-7)

Five nude mice (CAnN.Cg-Foxn1nu/CrlCrlj, female, CHARLES RIVER LABORATORIES JAPAN, INC.) were used in each group, and the antitumor effect in a case where compound A was administered was evaluated.

[0029] Human-derived hepatocellular carcinoma cell line HuH-7 (obtained from JCRB Cell Bank) cells were suspended in a DMEM medium (Wako Pure Chemical Industries, Ltd.) containing 10% bovine serum so that the concentration of the cells was 8.0×10^7

cells/mL. Into the suspension, Matrigel™ Matrix (Becton, Dickinson and Company, Japan) in the same volume as that of the suspension was added, and the obtained mixture was sufficiently mixed. The mixture in an amount of 0.1 mL was transplanted into the subcutaneous part in the right flank of each mouse, and the mouse was subjected to the antitumor effect evaluation.

[0030] On 11 days after the transplantation, the longest diameter and the short axis of the tumor were measured with an electronic digital caliper (Digimatic™ Caliper, Mitutoyo Corporation). The mice were divided into groups so that the average values of the tumor volumes in the respective groups were nearly equal to each other. In addition, the tumor volume was calculated in accordance with the following equation.

Tumor volume (mm^3) = longest diameter (mm) × short axis (mm) × short axis (mm) / 2

[0031] Compound A was dissolved in purified water so that the concentration of compound A was 2.5 mg/mL.

Compound A was administered to each of the mice in the respective groups at a dose of 50 mg/kg once daily for 5 days. After that, compound A was withdrawn for 2 days, and then administered orally for 3 days. In this regard, the volume to be administered was set to 20 mL/kg, and to the control group, purified water in the same volume was administered.

[0032] The measured values of the tumor volumes in the control group and the compound A administration group are shown in Table 2.

[0033] [Table 2]

Measurement date	Day 0	Day 3	Day 7	Day 10
Control group (mm^3)	147.3	500.7	1168.7	1767.0
Compound A group (mm^3)	148.1	409.2	939.9	1400.9

[0034] Example 3: Antitumor action of compound A against human hepatocellular carcinoma cell line (Hep3B2.1-7)

Five nude mice (CAnN.Cg-Foxn1nu/CrlCrlj, female, CHARLES RIVER LABORATORIES JAPAN, INC.) were used in each group, and the antitumor effect in a case where compound A was administered was evaluated.

[0035] Human-derived hepatocellular carcinoma cell line Hep3B2.1-7 (obtained from ATCC) cells were suspended in a Hank's Balanced Salt Solution (HBSS) so that the concentration of the cells was 4×10^7 cells/mL. Into the suspension, Matrigel™ Matrix (Becton, Dickinson and Company, Japan) in the same volume as that of the suspension was

added, and the obtained mixture was sufficiently mixed. The mixture in an amount of 0.1 mL was transplanted into the subcutaneous part in the right flank of each mouse, and the mouse was subjected to the antitumor effect evaluation.

[0036] On 19 days after the transplantation, the longest diameter and the short axis of the tumor were measured with an electronic digital caliper (Digimatic™ Caliper, Mitutoyo Corporation). The mice were divided into groups so that the average values of the tumor volumes in the respective groups were substantially equal to each other. In addition, the tumor volume was calculated in accordance with the following equation.

Tumor volume (mm^3) = longest diameter (mm) × short axis (mm) × short axis (mm) / 2

[0037] Compound A was dissolved in purified water so that the concentration of compound A was 5 mg/mL.

Compound A was administered to each of the mice in the respective groups at a dose of 100 mg/kg once daily for 5 days. After that, compound A was withdrawn for 2 days, and then administered orally for 4 days. In this regard, the volume to be administered was set to 20 mL/kg, and to the control group, purified water in the same volume was administered.

[0038] The measured values of the tumor volumes in the control group and the compound A administration group are shown in Table 3.

[0039] [Table 3]

Measurement date	Day 0	Day 3	Day 7	Day 11
Control group (mm^3)	411.9	645.5	811.7	1040.0
Compound A group (mm^3)	417.4	504.0	630.4	862.3

[0040] Example 4: Antitumor action of compound A against human hepatocellular carcinoma cell line (SNU-398)

Five nude mice (CAnN.Cg-Foxn1nu/CrlCrlj, female, CHARLES RIVER LABORATORIES JAPAN, INC.) were used in each group, and the antitumor effect in a case where compound A was administered was evaluated.

[0041] Human-derived hepatocellular carcinoma cell line SNU-398 (obtained from ATCC) cells were suspended in a HBSS so that the concentration of the cells was 5×10^7 cells/mL. Into the suspension, Matrigel™ Matrix (Becton, Dickinson and Company, Japan) in the same volume as that of the suspension was added, and the obtained mixture was sufficiently mixed. The mixture in an amount of 0.1 mL was transplanted into the subcutaneous part in the right flank of each mouse, and the mouse was subjected to the

antitumor effect evaluation.

[0042] On 9 days after the transplantation, the longest diameter and the short axis of the tumor were measured with an electronic digital caliper (Digimatic™ Caliper, Mitutoyo Corporation). The mice were divided into groups so that the average values of the tumor volumes in the respective groups were nearly equal to each other. In addition, the tumor volume was calculated in accordance with the following equation.

Tumor volume (mm^3) = longest diameter (mm) × short axis (mm) × short axis (mm) / 2

[0043] Compound A was dissolved in purified water so that the concentration of compound A was 1.25 mg/kg or 2.5 mg/mL.

Compound A was administered orally to each of the mice in the respective groups at a dose of 25 mg/kg or 50 mg/kg once daily for 11 days. In this regard, the volume to be administered was set to 20 mL/kg. The control group was untreated.

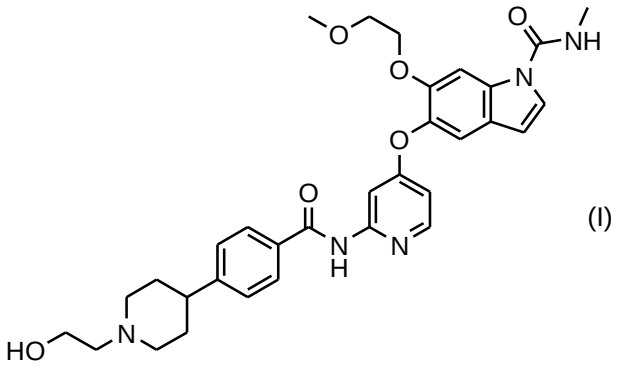
[0044] The measured values of the tumor volumes in the control group and compound A administration group are shown in Table 4 and Figure 1. The increase in the tumor volume was suppressed in a dose-dependent manner by the administration of compound A.

[0045] [Table 4]

Measurement date	Day 0	Day 4	Day 7	Day 11
Control group (mm^3)	154.5	566.0	1086.9	1868.0
Compound A at 25 mg/kg group (mm^3)	154.5	516.4	942.2	1280.1
Compound A at 50 mg/kg group (mm^3)	153.9	443.2	779.0	1066.1

CLAIMS

1. A therapeutic agent for hepatocellular carcinoma 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:



(I)

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2. The therapeutic agent for hepatocellular carcinoma according to claim 1, wherein the salt is a sesquisuccinate.

3. A pharmaceutical composition for treating hepatocellular carcinoma 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 for treating hepatocellular carcinoma according to claim 3, wherein the salt is a sesquisuccinate.