DESCRIPTION

Title of Invention

THERAPEUTIC AGENT FOR BILE DUCT CANCER

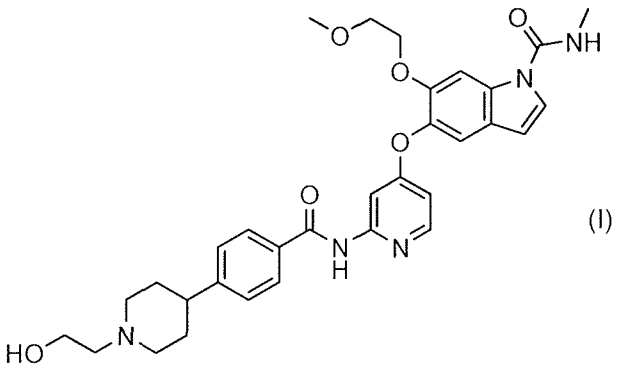
Technical Field

[0001] The present invention relates to a therapeutic agent for bile duct cancer comprising a monocyclic pyridine derivative or a pharmacologically acceptable salt thereof having an FGFR inhibitory activity.

Background Art

[0002] The compound represented by the formula (I) is known as 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide. It has been reported that the compound represented by the formula (I) has an inhibitory activity on fibroblast growth factor receptors (FGFRs) 1, 2 and 3 and has a cell growth suppressing activity in gastric cancer, lung cancer, bladder cancer and endometrial cancer (Patent Literature 1).

[0003] [Chemical Formula 1]



(I)

[0004] Bile duct cancer is low in incidence, but is known as a tumor with poor prognosis. The main therapeutic method for the bile duct cancer is surgical extirpation of the bile duct, but in many cases cancer cells cannot be completely removed. In such a case, a combined administration of gemcitabine and cisplatin is carried out after the surgery (Non Patent Literature 1).

Citation List

Patent Literature

[0005] Patent Literature 1: US 2014-235614

Non Patent Literature

[0006] Non Patent Literature 1: Celina Ang, "Role of the fibroblast growth factor receptor axis in cholangiocarcinoma", Journal of Gastroenterology and Hepatology, vol.30, p.1116-1122, 2015.

Summary of Invention

Technical Problem

[0007] However, a sufficient therapeutic activity cannot be obtained by the so far reported therapeutic agents for bile duct cancer.

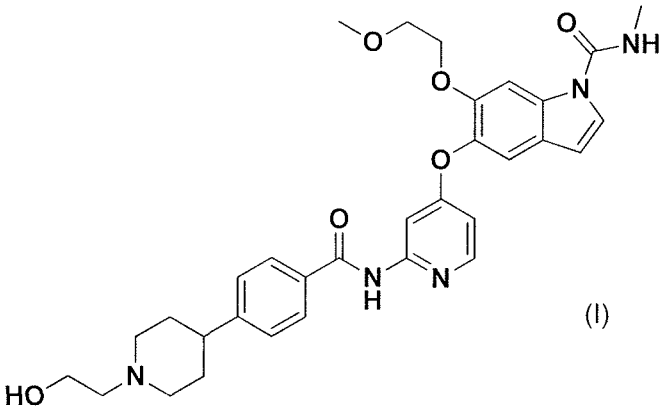
Solution to Problem

[0008] In view of such a situation, the present inventors have conducted intensive studies and as a result, have found that the compound represented by the formula (I) is effective for the treatment of bile duct cancer, and have completed the present invention.

[0009] That is, the present invention provides the following [1] to [12]:

[1] A therapeutic agent for bile duct 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 represented by the formula (I) or a pharmaceutically acceptable salt thereof.

[Chemical Formula 2]



(I)

[2] The therapeutic agent according to [1], wherein the bile duct cancer is intrahepatic bile duct cancer.

[3] A pharmaceutical composition for the treatment of bile duct 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 represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

[4] The pharmaceutical composition according to [3], wherein the bile duct cancer is intrahepatic bile duct cancer.

[5] A method for treating bile duct cancer, comprising administering to a patient a pharmacologically effective amount of 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 the formula (I) or a pharmaceutically acceptable salt thereof.

[6] The method according to [5], wherein the patient has been confirmed to have a gene encoding FGFR 2-fusion protein before the administration.

[7] The method according to [6], wherein the gene encoding the FGFR 2-fusion protein is FGFR2-AHCYL1, FGFR2-BICC1 type1, FGFR2-BICC1 type2, FGFR2-TXLNA or FGFR2-KCTD1.

[8] The method according to any one of [5] to [7], wherein the bile duct cancer is intrahepatic bile duct cancer.

[9] 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 the formula (I) or pharmaceutically acceptable salts thereof for the treatment of bile duct cancer.

[10] The compound or pharmaceutically acceptable salts thereof according to [9], wherein the bile duct cancer is intrahepatic bile duct cancer.

[11] Use of 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 the formula (I) or pharmaceutically acceptable salts thereof for the preparation of a therapeutic agent for bile duct cancer.

[12] The use according to [11], wherein the bile duct cancer is intrahepatic bile duct cancer.

Advantageous Effects of Invention

[0010] According to the present invention, the therapeutic agent which may

be effective for the treatment of bile duct cancer can be provided.

Brief Description of the Drawings

[0011] [Figure 1] Figure 1 is a schematic diagram illustrating structures of FGFR2-BICC1 type1 and type2 genes.

[Figure 2] Figure 2 is a diagram showing the results of Western blot analysis of proteins obtained by culturing mouse fibroblast cell line NIH3T3 transfected with various FGFR2 fusion genes.

[Figure 3] Figure 3 is a diagram showing the results of Western blot analysis of proteins obtained by culturing NIH3T3 cell line transfected with FGFR2 fusion genes.

[Figure 4] Figure 4 is a diagram showing the results of analysis of proteins obtained by culturing NIH3T3 cell line transfected with various FGFR2 fusion genes.

[Figure 5] Figure 5 is a diagram showing the activity of FGFR inhibitors on the growth capacity of NIH3T3 cell line transfected with FGFR2 fusion genes.

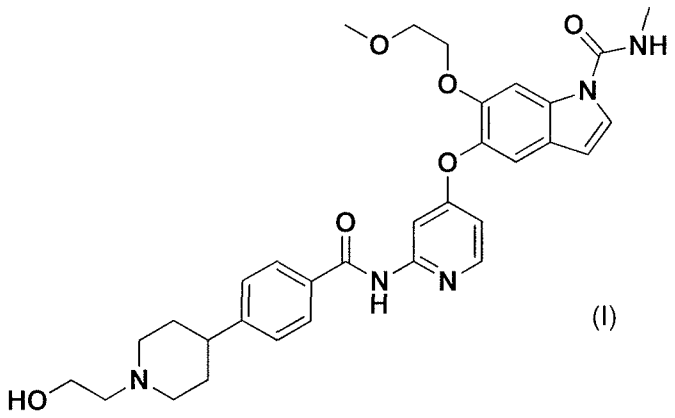
[Figure 6] Figure 6 is a graph showing the activity of FGFR inhibitors on the growth capacity of NIH3T3 cell line transfected with FGFR2 fusion genes.

[Figure 7] Figure 7 is a diagram showing the activity of FGFR inhibitors on the growth capacity of NIH3T3 cell line transfected with FGFR2 fusion genes.

Description of Embodiments

[0012] One embodiment of the present invention is a therapeutic agent for bile duct 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 represented by the formula (I) or a pharmaceutically acceptable salt thereof.

[Chemical Formula 3]



(I)

[0013] In the present specification, examples of pharmacologically acceptable salts may include salts with inorganic acids, salts with organic acids or salts with acidic amino acids.

[0014] Suitable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid.

[0015] Suitable examples of salts with organic acids include salts with carboxylic acids such as acetic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, lactic acid, stearic acid and benzoic acid, and salts with sulfonic acids such as methanesulfonic acid, ethanesulfonic acid and p-toluenesulfonic acid.

[0016] Suitable examples of salts with acidic amino acids include salts with aspartic acid and glutamic acid.

[0017] A preferred pharmacologically acceptable salt is a succinate or maleate, and a more preferred salt is a succinate. As the pharmacologically acceptable salt, a salt containing succinic acid 1.5 times on a mass basis more than the compound represented by the formula (I) (1.5 succinate) is particularly preferable.

[0018] The compound represented by the formula (I) or pharmacologically acceptable salts thereof according to the present invention can be produced by the process described in the Patent Literature 1.

[0019] In the present specification, the term "biliary duct" is used synonymously with "biliary tract". That is, bile duct cancer refers to intrahepatic bile duct cancer, extrahepatic bile duct cancer, cystic duct cancer, gallbladder cancer or duodenum papilla cancer. The bile duct cancer also

include these cancers metastasized to sites other than the bile duct. The therapeutic agent for bile duct cancer of the present invention is particularly effective against intrahepatic bile duct cancer.

[0020] The therapeutic agent for bile duct cancer of the present invention may be in the form of a preparation for oral administration, for example, a solid preparation such as a tablet, a granule, a subtle granule, a powder or a capsule, or a solution, a jelly or a syrup. The therapeutic agent for bile duct cancer of the present invention may also be in the form of a preparation for parenteral administration such as an injection, a suppository, an ointment or a cataplasm.

[0021] When preparing the preparation for oral administration, a pharmaceutically acceptable carrier such as an excipient, a binder, a disintegrator, a lubricant and a colorant may be added as appropriate to the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof. The preparation such as a tablet, a granule, a powder and a capsule may also be coated as appropriate.

[0022] When preparing an injection (such as for intravenous administration, intramuscular administration, subcutaneous administration or intraperitoneal administration), a pharmaceutically acceptable carrier such as a pH adjuster, a buffer, a suspending agent, a solubilizing agent, an antioxidant, a preservative (an antiseptic agent) or an isotonizing agent may be added as appropriate to the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof, and then the injection may be prepared by the conventional method. The injection may also be lyophilized to provide a lyophilized preparation which is dissolved before use.

[0023] When preparing an external preparation, a base material may be added to the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof, and the above-mentioned pharmaceutically acceptable carrier such as a preservative, an stabilizer, a pH adjuster, an antioxidant or a colorant may be then added thereto as appropriate, and thereafter, for example, a transdermal preparation (such as an ointment or a patch), an eye dropper, a nasal preparation, or a suppository may be prepared by the conventional method.

[0024] Examples of base materials which can be used include various materials usually used in pharmaceuticals, quasi drugs, cosmetics and the like.

[0025] The therapeutic agent for bile duct cancer of the present invention can be prepared with the compound represented by the formula (I) or a pharmacologically acceptable salt thereof according to the method described in the Japanese Pharmacopoeia 16th edition.

[0026] The dosage of the compound represented by the formula (I) or a pharmacologically acceptable salt thereof in the therapeutic agent for bile duct cancer of the present invention can be appropriately selected depending on the severity of the symptoms, the age, sex, body weight and differential sensitivity of the patient, the method of administration, time of administration, interval of administration, the type of pharmaceutical preparation, and the like. The therapeutic agent for bile duct cancer of the present invention, when administered orally, can be administered so that the dosage of the compound represented by the formula (I) or a pharmacologically acceptable salt thereof is 100 μg to 10 g per day, preferably 500 μg to 10 g per day, more preferably 1 mg to 5 g per day for an adult (body weight: 60kg). The therapeutic agent for bile duct cancer of the present invention can be administered in 1 to 3 divided portions daily.

[0027] According to the present invention, a method for treating bile duct cancer, comprising administering to a patient the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof can be provided. It is preferable that the subject for administration is a patient with bile duct cancer, it is more preferable that the subject is a patient with intrahepatic bile duct cancer, and it is particularly preferable that the subject is a patient with bile duct cancer having a gene encoding FGFR 2-fusion protein (FGFR2 fusion gene).

[0028] The FGFR2 fusion gene refers to a gene in which the FGFR2 and a particular other gene are fused, and examples of the FGFR2 fusion gene include FGFR2-BICC1 type1, FGFR2-BICC1 type2 (SEQ ID NO: 5), FGFR2-TXLNA (SEQ ID NO: 1), FGFR2-AHCYL1, FGFR2-CCDC6, FGFR2-KCTD1 (SEQ ID NO: 3), FGFR2-MGEA5, FGFR2-TACC3, FGFR2-PPHLN1, FGFR2-KIAA1598, FGFR2-CCAR1, FGFR2-NOL4 and

FGFR2-PARK2. Herein, as shown in Figure 1, FGFR2-BICC1 type1 refers to a gene having FGFR2 fused to the 5' terminal side of KHKH sequence of BICC1 gene, while FGFR2-BICC1 type2 refers to a gene having FGFR2 fused to the 5' terminal side of SAM region (sterile α motif) of BICC1 gene. FGFR2-BICC1 type1 encodes a peptide consisting of 1,574 amino acids, whereas FGFR2-BICC1 type2 encodes a peptide consisting of 835 amino acids (SEQ ID NO: 6). BICC1 type1 was also referred to as BICC1 until BICC1 type2 was discovered.

[0029] As the patient with bile duct cancer, the patient having FGFR2-AHCYL1, FGFR2-BICC1 type1, FGFR2-BICC1 type2, FGFR2-TXLNA or FGFR2-KCTD1 is preferable, the patient having FGFR2-BICC1 type2, FGFR2-TXLNA or FGFR2-KCTD1 is more preferable, and the patient with FGFR2-BICC1 type2 is particularly preferable.

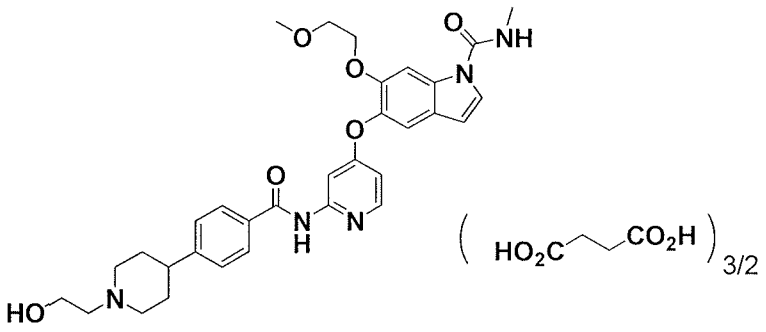
[0030] Before administering the therapeutic agent for bile duct cancer of the present invention, it may be diagnosed whether the subject to be administered has the FGFR2 fusion gene. The method for diagnosing the presence or absence of the FGFR2 fusion gene may be a genetic diagnosis commonly used.

Examples

[0031] The present invention will be described in greater detail by the following examples.

[0032] Production Example 1: Production 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 also referred to as Compound A)

[Chemical Formula 4]



2.93 g of 5-((2-(4-(1-(2-hydroxyethyl)piperidin-4-yl)benzamide)pyridin-4-yl)oxy)-6-(2-methoxyethoxy)-N-methyl-1H-indole-1-carboxamide was weighed out in an eggplant flask, 60 mL of ethanol was added thereto, and the reaction mixture was heated to 70°C while stirring in an oil bath to dissolve it. Succinic acid (1.23 g) was added, then the heating of the oil bath was stopped, and the reaction mixture was slowly cooled. The reaction mixture was stirred at room temperature for about 2 hours, and further stirred at 5°C for one hour. The resulting solid was collected by filtration to obtain Compound A (3.70 g).

^{1}H-NMR Spectrum (600MHz, 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 (100MHz, 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.

[0033] Construction of the FGFR2 fusion genes

cDNAs of three types of FGFR2 fusion genes (FGFR2-BICC1 type2 (SEQ ID NO: 5), FGFR2-TXLNA (SEQ ID NO: 1), FGFR2-KCTD1 (SEQ ID NO: 3)) were prepared from cancer tissues from a patient with biliary tract cancer, respectively. A nucleotide sequence encoding a FLAG epitope tag was ligated to the N-terminal of the resulting cDNA of each FGFR2 fusion gene in accordance with the reading frame of translation, and cloned in a

pMXs retrovirus vector to construct a retrovirus. Herein, the above ligated FGFR2 fusion gene is also referred to as "wild-type FGFR2 fusion gene". The peptide sequence of the FLAG epitope tag is H_2N-DYKDDDDK-COOH (molecular weight: 1,012Da).

Herein, the polynucleotide sequences of each cDNA of FGFR2, TXLNA and KCTD1 correspond to SEQ ID NOs: 7, 9 and 11, respectively, and the sequences of the peptides encoded by FGFR2, TXLNA and KCTD1 correspond to SEQ ID NOs: 8, 10 and 12, respectively.

[0034] Next, a retrovirus having the wild-type FGFR2 fusion gene in which two amino acids in the region encoding FGFR2 kinase were further mutated was constructed. The mutation means that the tyrosine which is a residue at position 568 was replaced by phenylalanine (Y568F) and the tyrosine which is a residue at position 569 was replaced by phenylalanine (Y569F). Herein, the gene obtained by subjecting the wild-type FGFR2 fusion gene to the above-mentioned mutation is also referred to as "KD mutant FGFR2 fusion gene"

[0035] Each of these retroviruses was infected to a mouse immortalized fibroblast cell line NIH3T3 cell to transfect the wild-type FGFR2 fusion gene or the KD mutant FGFR2 fusion gene into the cell, to obtain a cell line stably expressing the protein encoded by each fusion gene.

cDNA cloning:

pMXs vector (CellBiolabs), Plat-Eretrovirus packaging cell line (CellBiolabs)

[0036] Test Example 1: Immunoblot analysis

First, the wild-type FGFR2 fusion gene or KD mutant FGFR2 fusion gene was transfected into the mouse fibroblast cell line NIH3T3 using the retrovirus, and the obtained cell line was cultured in a liquid culture medium. The cultured cell line was subjected to serum starvation, and then treated with a culture medium containing an FGFR inhibitor before extracting the total proteins. Herein, the protein encoded by FGFR2-BICC1 type2, the protein encoded by FGFR2-TXLNA and the protein encoded by FGFR2-KCTD1 are shown in SEQ ID NOs: 6, 2 and 4, respectively.

[0037] For the obtained total proteins, the downstream signal of the fusion gene was analyzed by Western blot analysis using various antibodies.

Apparatus:
WesternBreeze chemilumiscent immunodetection kit (Lifetechnologies)
FGFR inhibitors:
BGJ398 (S2183, Selleck Chemicals), stored in 10 mM DMSO solution
PD173074 (S1264, Selleck Chemicals), stored in 10 mM DMSO solution
Compound A (stored in 20 mM DMSO solution)
Antibodies:
FLAG (#635691, Clontech Laboratories, Inc.)
phospho FGFR-Y653/654 (#3476, Cell Signaling Technology Japan, K.K.)
phospho AKT1-S473 (#4060, Cell Signaling Technology Japan, K.K.)
AKT-pan (#4691, Cell Signaling Technology Japan, K.K.)
phospho STAT3-Y705 (#9145, Cell Signaling Technology Japan, K.K.)
STAT3 (#610189, Becton Dickinson and Company)
phospho MAPK-T202/Y204 (#9106, Cell Signaling Technology Japan, K.K.)
MAPK (#4695, Cell Signaling Technology Japan, K.K.)
beta-actin (#A5441, Sigma-Aldrich Co. LLC).
Antibody array:
PathScan RTK signaling antibody array (Chemiluminescent Readout) (#7982, Cell Signaling Technology Japan, K.K.)

[0038] The obtained results are shown in Figure 2. As shown in Figure 2, it was found that the phosphorylation of the MAPK gene (activation of the MAPK gene) occurred depending on the FGFR2 kinase activity. That is, the NIH3T3 cell transfected with the FGFR2 fusion gene had anchorage independent growth capacity. In Figure 2, "wild" means the wild-type FGFR2 fusion gene, and "KD" means the KD mutant FGFR2 fusion gene.

[0039] Next, the NIH3T3 cell line transfected with the FGFR2 fusion gene was subjected to Western blot analysis after adding the FGFR inhibitor to the cell line (the final concentration of the FGFR inhibitor: 0.2 μM or 0.5 μM) and extracting the total proteins similarly.

[0040] The obtained results are shown in Figure 3. As shown in Figure 3, by treatment with the FGFR inhibitor, phosphorylation of FGFR was suppressed, and the phosphorylation of MAPK was significantly suppressed. In Figure 3, "BG" refers to BGJ398, "PD" refers to PD173074, and "E9"

refers to Compound A. Specifically, for example, "BG-0.2" means that BGJ398 was added so that the final concentration was 0.2 μM.

[0041] Furthermore, the total proteins were similarly extracted from the NIH3T3 cell line not transfected with the FGFR2 fusion gene and from the NIH3T3 cell line transfected with the FGFR2-BICC1 type2, FGFR2-TXLNA or FGFR2-KCTD1. 90 μg of the total proteins extracted was used to analyze the expressed protein with the PathScan (R) array.

[0042] As shown in Figure 4, the phosphorylated Akt (pAkt-S473), phosphorylated MAPK (pMAPK-T202/Y204) and phosphorylated S6 ribosomal protein (pS6-S235/236) were detected.

[0043] Test Example 2: Colony formation assay

Using the following apparatus, the activity of FGFR inhibitors on the transformation capacity of FGFR2 fusion polypeptide was evaluated. That is, the NIH3T3 cell line transfected with the FGFR2 fusion gene was seeded in a soft agar culture medium (the concentration of agar in the culture medium: 4 mg/mL), and an FGFR inhibitor was added to the culture medium (the final concentration of the FGFR inhibitor: 0.2 μM), and the anchorage independent colony forming capacity was evaluated.

Apparatus:

CytoSelect 96-Well Cell Transformation Assay kit (CBA-130, CellBiolabs)

FGFR inhibitors:

BGJ398 (S2183, Selleck Chemicals), stored in 10 mM DMSO solution

PD173074 (S1264, Selleck Chemicals), stored in 10 mM DMSO solution

Compound A (stored in 20 mM DMSO solution)

[0044] The obtained results are shown in Figure 5 and Figure 6. As shown in Figure 5 and Figure 6, among the FGFR2 fusion genes, the anchorage independent growth of the NIH3T3 cells transfected with the FGFR2-TXLNA and FGFR2-KCTD1 was significantly suppressed by the addition of the FGFR inhibitor. On the other hand, the anchorage independent growth of the NIH3T3 cell transfected with FGFR2-BICC1 type2 was little suppressed when using BGJ398 or PD173074 as an FGFR inhibitor, while it was significantly suppressed when using Compound A as an FGFR inhibitor. In Figure 5 and Figure6, "BG" refers to BGJ398, "PD" refers to PD173074, and

"E9" refers to Compound A.

[0045] As shown in Figure 7, when BGJ398 or PD173074 was increased so that the final concentration was 1.0 μM, the anchorage independent growth was suppressed. In Figure 7, "BG" refers to BGJ398, and "PD" refers to PD173074.

[0046] Test Example 3: Calculation of IC_{50} values by Colony formation assay

Various NIH3T3 cell lines transfected with the FGFR2 fusion gene were cultured and maintained with D-MEM (Wako Pure Chemical Industries) culture medium containing 10% FBS and penicillin/streptomycin (Wako Pure Chemical Industries) in a 5% CO_2 incubator (37°C). To each well of a 96-well plate (Sumitomo Bakelite) was added 50 μL of D-MEM medium (SIGMA) (containing 10% FBS and penicillin/streptomycin) containing 0.66% agar culture medium (DIFCO Agar Noble, Japan Becton Dickinson). The cell suspension prepared so that the cell number was 4×10^4 cells/mL (prepared so that the cell number of FGFR2-TXLNA expressing cells was 8×10^4 cells/mL) was mixed with 0.66% agar medium solution in equal amounts, and the layers of 50 μL each of the resulting mixture were piled up and set by cooling at 4°C for about 30 minutes. After returning the plate to room temperature, layers of 50 μL each of 0.66% agar medium solution were further piled up. 50 μL of Compound A diluted with DMEM culture medium containing 10% FBS was added to each well, and cultured in the 5% CO_2 incubator (37°C) for 14 days. 10 μL of cytometry kit (Cell Counting Kit-8, DOJINDO LABORATORIES) was added to each well and cultured in the 5% CO_2 incubator (37°C) for 1 to 2 hours to result in color development. Absorbance at 450nm was measured by a multi-label reader (ARVO, PerkinElmer, Inc.). The absorbance in the presence of Compound A was determined assuming that the absorbance in the absence of Compound A was 100% and the absorbance of the well free of cells was 0%. The concentration of Compound A necessary to inhibit cell growth by 50% (IC_{50} value) was determined and shown in Table 1.

[0047] [Table 1]

Name of Cell Line	IC_{50} (nM)
FGFR2-BICC1 type2	17.3
FGFR2-TXLNA	1.3
FGFR2-KCTD1	5.0

[0048] Test Example 4: Antitumor activity in subcutaneously transplanted model mice

(1) Preparation of subcutaneously transplanted model mice

The NIH3T3 cell line transfected with each FGFR2 fusion gene (FGFR2-BICC1 type2, FGFR2-KCTD1, FGFR2-TXLNA) was cultured in DMEM culture media containing 10% FBS and penicillin/streptomycin.

D-PBS (-) (Wako Pure Chemical Industries) was added to the obtained culture media so that the cell number was 1×10^7 cells/mL to prepare each cell suspension.

100 μL each of these cell suspensions was transplanted subcutaneously in the right flank region of 7-week-old nude mice (strain: BALB/cAJcl-nu/nu, female, CLEA Japan, Inc.) to prepare FGFR2-BICC1 type2 transplant model mice, FGFR2-KCTD1 transplant model mice and FGFR2-TXLNA transplant model mice. Six days after the transplantation, the width and length of the tumor were measured with a digital caliper (trade name: Digimatic (TM) Caliper, Mitutoyo Corporation). The tumor volume was calculated based on the width and length of the tumor by the following calculation formula.

Tumor volume (mm^3) = length (mm) × width (mm) × width (mm)/2

(2) Preparation of Compound A solution

Compound A was dissolved in water for injection and stored at 4°C under protection from light until just before administration. The solution was prepared so that the dosage of Compound A was 6.25, 12.5, 25 and 50 mg/kg when administered to a mouse at a dose of 20 mL/kg.

(3) Administration of drug solution

Based on the tumor volume on the first day of administration, the mice were grouped so that mean values of the tumor volume of the groups were nearly equal to each other. The number of mice per group was 5. The

Compound A solution was continuously administered orally to the mice in the Compound A administration group once a day at a dosage of 20 mL/kg. On the other hand, only the solvent (water for injection) was similarly administered to the mice in the control group. The Administration was carried out to FGFR2-BICC1 type2 or FGFR2-KCTD1 transplant model mice for 7 days and to FGFR2-TXLNA transplant model mice for 11 days.

On the first day and the last day of the administration, body weight was measured for each mice in the control group and the Compound A administration group. The ratio of the body weight on the last day to the body weight on the first day (relative body weight: RBW) was calculated. When the RBW of the Compound A administration group/the RBW of the control group was 0.9 or more, the dosage was judged as safe. The corresponding dosage was 6.25, 12.5, 25 and 50 mg/kg.

The tumor volume was also measured on the last day of administration. Percentage of the tumor volume of the mice in the Compound A administration group to the tumor volume of the mice in the control group (T/C) (%) was calculated.

[0049] The results of T/C (%) in each transplant model mice was shown in Table 2 to Table 4.

[Table 2]

FGFR2-BICC1 type 2 transplant model mice

Compound A	T/C (%)
6.25 mg/kg	80*
12.5 mg/kg	71**
25 mg/kg	68**
50 mg/kg	52**

Statistically significant *: $p<0.05$ **: $p<0.01$

[0050] [Table 3]

FGFR2-TXLNA transplant model mice

Compound A	T/C (%)
6.25 mg/kg	54**
12.5 mg/kg	43**
25 mg/kg	15**
50 mg/kg	6**

Statistically significant **: $p<0.01$

[0051] [Table 4]

FGFR2-KCTD1 transplant model mice

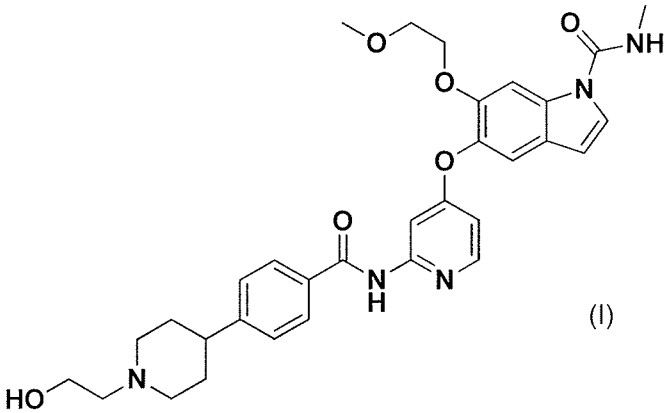
Compound A	T/C (%)
6.25 mg/kg	89
12.5 mg/kg	56
25 mg/kg	39*
50 mg/kg	19**

Statistically significant *: $p<0.05$ **: $p<0.01$

CLAIMS

1. A therapeutic agent for bile duct 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 represented by the formula (I) or a pharmaceutically acceptable salt thereof.

[Chemical Formula 1]

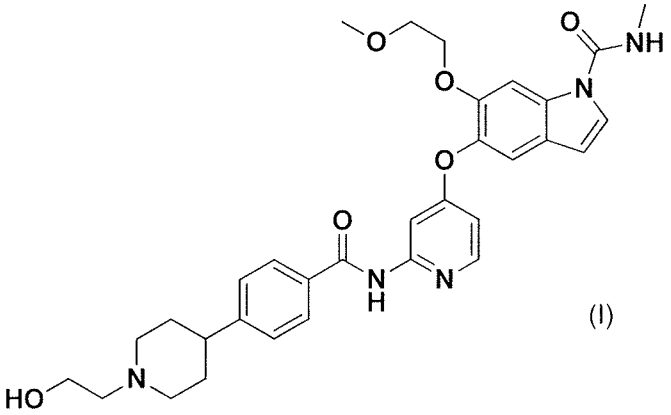


(I)

2. The therapeutic agent according to claim 1, wherein the bile duct cancer is intrahepatic bile duct cancer.

3. A pharmaceutical composition for the treatment of bile duct 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 represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

[Chemical Formula 2]



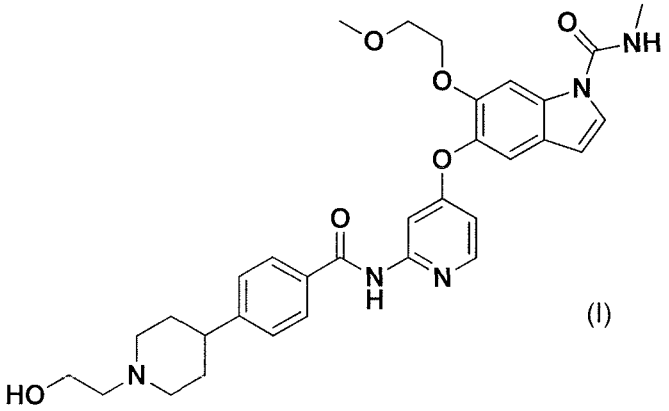
(I)

4. The pharmaceutical composition according to claim 3, wherein the

bile duct cancer is intrahepatic bile duct cancer.

5. A method for treating bile duct cancer, comprising administering to a patient a pharmacologically effective amount of 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 the formula (I) or a pharmaceutically acceptable salt thereof.

[Chemical Formula 3]



(I)

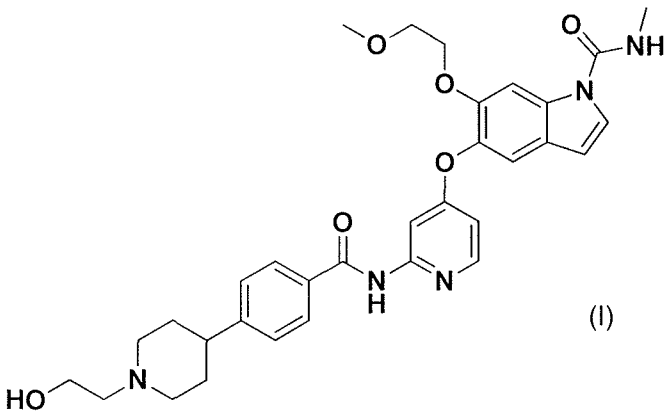
6. The method according to claim 5, characterized in that the patient has been confirmed to have a gene encoding FGFR 2-fusion protein before the administration.

7. The method according to claim 6, wherein the gene encoding the FGFR 2-fusion protein is FGFR2-AHCYL1, FGFR2-BICC1 type1, FGFR2-BICC1 type2, FGFR2-TXLNA or FGFR2-KCTD1.

8. The method according to any one of claims 5 to 7, wherein the bile duct cancer is intrahepatic bile duct cancer.

9. 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 the formula (I) or a pharmaceutically acceptable salt thereof for the treatment of bile duct cancer.

[Chemical Formula 4]

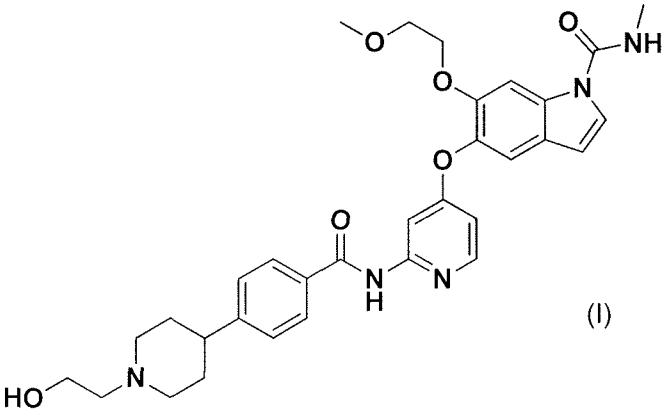


(I)

10. The compound or a pharmaceutically acceptable salt thereof according to claim 9, wherein the bile duct cancer is intrahepatic bile duct cancer.

11. Use of 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 the formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a therapeutic agent for bile duct cancer.

[Chemical Formula 5]



(I)

12. The use according to claim 11, wherein the bile duct cancer is intrahepatic bile duct cancer.

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35 40 45

Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys Phe Arg Cys
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Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu Lys Asn Gly
65 70 75 80

Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys Val Arg Asn
85 90 95

Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser Asp Lys Gly
100 105 110

Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile Asn His Thr
115 120 125

Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile Leu Gln
130 135 140

Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly Asp Val Glu
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Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Ile
165 170 175

Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp Gly Leu Pro
180 185 190

Tyr Leu Lys Val Leu Lys His Ser Gly Ile Asn Ser Ser Asn Ala Glu
195 200 205

Val Leu Ala Leu Phe Asn Val Thr Glu Ala Asp Ala Gly Glu Tyr Ile
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Cys Lys Val Ser Asn Tyr Ile Gly Gln Ala Asn Gln Ser Ala Trp Leu
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Thr Val Leu Pro Lys Gln Gln Ala Pro Gly Arg Glu Lys Glu Ile Thr
245 250 255

Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys Ile Gly Val Phe
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Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg Ile Thr Thr Arg
325 330 335

Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val Ser Glu Tyr
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Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp Lys Leu Thr
355 360 365

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370 375 380

Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys Glu Ala Val Thr Val
385 390 395 400

Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp Leu Ser Asp
405 410 415

Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn
420 425 430

Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val
435 440 445

Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Arg Ala
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Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn Arg Val Pro
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Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr Tyr Gln Leu
485 490 495

Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp
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Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val Met Lys Ile
515 520 525

Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp Tyr Tyr Lys
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Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala
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Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly
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Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly
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Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met
595 600 605

Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met Met Arg Asp
610 615 620

Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val
625 630 635 640

Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu Gly Ser Ser
645 650 655

Met Ser Leu Ser Arg Ser Asn Ser Arg Glu His Leu Gly Gly Gly Ser
660 665 670

Glu Ser Asp Asn Trp Arg Asp Arg Asn Gly Ile Gly Pro Gly Ser His
675 680 685

Ser Glu Phe Ala Ala Ser Ile Gly Ser Pro Lys Arg Lys Gln Asn Lys
690 695 700

Ser Thr Glu His Tyr Leu Ser Ser Ser Asn Tyr Met Asp Cys Ile Ser
705 710 715 720

Ser Leu Thr Gly Ser Asn Gly Cys Asn Leu Asn Ser Ser Phe Lys Gly
725 730 735

Ser Asp Leu Pro Glu Leu Phe Ser Lys Leu Gly Leu Gly Lys Tyr Thr
740 745 750

Asp Val Phe Gln Gln Gln Glu Ile Asp Leu Gln Thr Phe Leu Thr Leu
755 760 765

Thr Asp Gln Asp Leu Lys Glu Leu Gly Ile Thr Thr Phe Gly Ala Arg
770 775 780

Arg Lys Met Leu Leu Ala Ile Ser Glu Leu Asn Lys Asn Arg Arg Lys
785 790 795 800

Leu Phe Glu Ser Pro Asn Ala Arg Thr Ser Phe Leu Glu Gly Gly Ala
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Gly Arg Trp
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35 40 45

Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu
50 55 60

Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly
65 70 75 80

Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly
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Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr
100 105 110

Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile
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Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val
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Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu
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Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys
165 170 175

Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu
180 185 190

Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys
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Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser
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Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile
225 230 235 240

Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro
245 250 255

Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly
260 265 270

Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile
275 280 285

Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp
290 295 300

Gly Leu Pro Tyr Leu Lys Val Leu Lys His Ser Gly Ile Asn Ser Ser
305 310 315 320

Asn Ala Glu Val Leu Ala Leu Phe Asn Val Thr Glu Ala Asp Ala Gly
325 330 335

Glu Tyr Ile Cys Lys Val Ser Asn Tyr Ile Gly Gln Ala Asn Gln Ser
340 345 350

Ala Trp Leu Thr Val Leu Pro Lys Gln Gln Ala Pro Gly Arg Glu Lys
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Glu Ile Thr Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys Ile
370 375 380

Gly Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Leu Cys Arg
385 390 395 400

Met Lys Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala Val
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His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val Ser
420 425 430

Ala Glu Ser Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg Ile
435 440 445

Thr Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val
450 455 460

Ser Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp
465 470 475 480

Lys Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
485 490 495

Val Met Ala Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys Glu Ala
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Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp
515 520 525

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys
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His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro
545 550 555 560

Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr
565 570 575

Leu Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn
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Arg Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr
595 600 605

Tyr Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
610 615 620

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val
625 630 635 640

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp
645 650 655

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
660 665 670

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
675 680 685

Ser Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
690 695 700

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
705 710 715 720

His Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met
725 730 735

Met Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys
740 745 750

Gln Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu
755 760 765

Glu Tyr Leu Asp Leu Ser Gln Pro Leu Glu Gln Tyr Ser Pro Ser Tyr
770 775 780

Pro Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe Ser
785 790 795 800

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Ser Gln Ala Pro Arg Lys Pro Glu Gly Ala Gln Ala Arg Thr Ala Gln
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Ser Gly Ala Leu Arg Asp Val Ser Glu Glu Leu Ser Arg Gln Leu Glu
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Asp Ile Leu Ser Thr Tyr Cys Val Asp Asn Asn Gln Gly Gly Pro Gly
85 90 95

Glu Asp Gly Ala Gln Gly Glu Pro Ala Glu Pro Glu Asp Ala Glu Lys
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Ser Arg Thr Tyr Val Ala Arg Asn Gly Glu Pro Glu Pro Thr Pro Val
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Val Asn Gly Glu Lys Glu Pro Ser Lys Gly Asp Pro Asn Thr Glu Glu
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Ile Arg Gln Ser Asp Glu Val Gly Asp Arg Asp His Arg Arg Pro Gln
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Gln Thr Leu Asn Thr Leu Ser Thr Pro Glu Glu Lys Leu Ala Ala Leu
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Cys Lys Lys Tyr Ala Glu Leu Leu Glu Glu His Arg Asn Ser Gln Lys
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Gln Met Lys Leu Leu Gln Lys Lys Gln Ser Gln Leu Val Gln Glu Lys
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Asp His Leu Arg Gly Glu His Ser Lys Ala Val Leu Ala Arg Ser Lys
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Lys Met Thr Lys Lys Ile Lys Lys Leu Glu Lys Glu Thr Thr Met Tyr
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His Tyr Cys Ser Ala Gly Glu Glu Glu Glu Glu Glu Glu Glu Glu Asp
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Met Gly Leu Asp Trp Asp Glu Pro Leu Glu Pro Glu Asp Ser Ala Gly
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Glu Glu Leu Glu Pro Glu Pro Val His Met Ile Asn Met Asp Gln Ser
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Gln Arg Pro Glu Arg Ala Arg Leu Ser Glu Asn Thr Arg Leu Ala Thr
165 170 175

Arg Tyr Ala Val Arg Ile Phe Arg Glu Tyr Leu Ser Glu Lys Ala Gln
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Ser Pro Asp Phe Glu Thr Met Asp Lys Gly Ala Leu Cys Arg Val Leu
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Arg Ser Phe Tyr Ala Glu Ala Arg Ser Lys Ser Gly Gln Leu Tyr Ser
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Glu Pro Pro Tyr Cys Arg Thr Leu Asp Leu Thr Lys Asp Pro Glu Leu
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Arg Ser Ala Asn Leu Thr Leu Ala Ala Val Ile Arg Lys Leu Glu Glu
260 265 270

Gln Gly Ala Gly Pro Val Val Gln Lys Gln Ala Ile Thr Arg Ala Asp
275 280 285

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Gly Leu Leu Asn Lys Val Trp Phe Glu Thr Cys Met Tyr Phe Cys Thr
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325 330 335

Ala Met Asp Glu Asp Gly Arg Lys Phe Val Tyr Phe Lys Ser Leu Gly
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Pro Tyr His Lys Ser Arg Ser Ser Ser Trp Ser Lys Lys Arg Ala Glu
355 360 365

Ser Ser Asp Glu Glu Asn Leu Pro Arg Met Tyr Glu Thr Gly Thr Glu
370 375 380

Phe Cys Pro Tyr Ala Ser Phe Val Lys Tyr Leu Ser Lys Arg Asn Pro
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Leu Cys Lys Ala Phe Phe Gln Arg Pro Arg Asp His Cys Ser Glu Gly
405 410 415

Asp Val Thr Trp Tyr Glu Asn Lys Ala Ile Gly Lys Asn Leu Leu Gly
420 425 430

Thr Arg Met Gln Met Leu Ser Lys Ala Ala Lys Leu Ser Lys Thr Tyr
435 440 445

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Ala Gly Ile Gly Thr Lys Leu Gly Ser Pro Ala Pro Gln Gly Cys Tyr
465 470 475 480

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Thr His Pro Ser His His His Arg Pro Gln Pro Pro Ser Leu Gly Asn
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Thr Tyr Ile Leu Pro Lys Asp Ser Gln Val Gly Pro Asp Val Lys Ser
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Ile Val Ser Pro Ala Ile Val Ser Pro Thr Gln Asp Ser Arg Pro Asn
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Met Ser Arg Pro Leu Ile Thr Arg Ser Pro Ala Ser Pro Leu Asn Asn
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His Ile Asp Val Gly Gly His Met Tyr Thr Ser Ser Leu Ala Thr Leu
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Thr Lys Tyr Pro Glu Ser Arg Ile Gly Arg Leu Phe Asp Gly Thr Glu
660 665 670

Pro Ile Val Leu Asp Ser Leu Lys Gln His Tyr Phe Ile Asp Arg Asp
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725 730 735

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Val Arg Val Ala Pro Asp Leu Gly Glu Arg Ile Thr Leu Ser Gly Asp
755 760 765

Lys Ser Leu Ile Glu Glu Val Phe Pro Glu Ile Gly Asp Val Met Cys
770 775 780

Asn Ser Val Asn Ala Gly Trp Asn His Asp Ser Thr His Val Ile Arg
785 790 795 800

Phe Pro Leu Asn Gly Tyr Cys His Leu Asn Ser Val Gln Val Leu Glu
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Glu Arg Phe Arg Val Asp Arg Lys Lys Leu Glu Ala Met Leu Gln Ala
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Ala Ala Glu Gly Lys Gly Arg Ser Gly Glu Asp Phe Phe Gln Lys Ile
65 70 75 80

Met Glu Glu Thr Asn Thr Gln Ile Ala Trp Pro Ser Lys Leu Lys Ile
85 90 95

Gly Ala Lys Ser Lys Lys Asp Pro His Ile Lys Val Ser Gly Lys Lys
100 105 110

Glu Asp Val Lys Glu Ala Lys Glu Met Ile Met Ser Val Leu Asp Thr
115 120 125

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Lys Ser Asn Arg Val Thr Leu Lys Met Asp Val Ser His Thr Glu His
    130                 135                 140

Ser His Val Ile Gly Lys Gly Gly Asn Asn Ile Lys Lys Val Met Glu
145                 150                 155                 160

Glu Thr Gly Cys His Ile His Phe Pro Asp Ser Asn Arg Asn Asn Gln
                165                 170                 175

Ala Glu Lys Ser Asn Gln Val Ser Ile Ala Gly Gln Pro Ala Gly Val
            180                 185                 190

Glu Ser Ala Arg Val Arg Ile Arg Glu Leu Leu Pro Leu Val Leu Met
        195                 200                 205

Phe Glu Leu Pro Ile Ala Gly Ile Leu Gln Pro Val Pro Asp Pro Asn
    210                 215                 220

Ser Pro Ser Ile Gln His Ile Ser Gln Thr Tyr Asn Ile Ser Val Ser
225                 230                 235                 240

Phe Lys Gln Arg Ser Arg Met Tyr Gly Ala Thr Val Ile Val Arg Gly
                245                 250                 255

Ser Gln Asn Asn Thr Ser Ala Val Lys Glu Gly Thr Ala Met Leu Leu
            260                 265                 270

Glu His Leu Ala Gly Ser Leu Ala Ser Ala Ile Pro Val Ser Thr Gln
        275                 280                 285

Leu Asp Ile Ala Ala Gln His His Leu Phe Met Met Gly Arg Asn Gly
    290                 295                 300

Ser Asn Ile Lys His Ile Met Gln Arg Thr Gly Ala Gln Ile His Phe
305                 310                 315                 320

Pro Asp Pro Ser Asn Pro Gln Lys Lys Ser Thr Val Tyr Leu Gln Gly
                325                 330                 335

Thr Ile Glu Ser Val Cys Leu Ala Arg Gln Tyr Leu Met Gly Cys Leu
            340                 345                 350
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Pro Leu Val Leu Met Phe Asp Met Lys Glu Glu Ile Glu Val Asp Pro
355 360 365

Gln Phe Ile Ala Gln Leu Met Glu Gln Leu Asp Val Phe Ile Ser Ile
370 375 380

Lys Pro Lys Pro Lys Gln Pro Ser Lys Ser Val Ile Val Lys Ser Val
385 390 395 400

Glu Arg Asn Ala Leu Asn Met Tyr Glu Ala Arg Lys Cys Leu Leu Gly
405 410 415

Leu Glu Ser Ser Gly Val Thr Ile Ala Thr Ser Pro Ser Pro Ala Ser
420 425 430

Cys Pro Ala Gly Leu Ala Cys Pro Ser Leu Asp Ile Leu Ala Ser Ala
435 440 445

Gly Leu Gly Leu Thr Gly Leu Gly Leu Leu Gly Pro Thr Thr Leu Ser
450 455 460

Leu Asn Thr Ser Thr Thr Pro Asn Ser Leu Leu Asn Ala Leu Asn Ser
465 470 475 480

Ser Val Ser Pro Leu Gln Ser Pro Ser Ser Gly Thr Pro Ser Pro Thr
485 490 495

Leu Trp Ala Pro Pro Leu Ala Asn Thr Ser Ser Ala Thr Gly Phe Ser
500 505 510

Ala Ile Pro His Leu Met Ile Pro Ser Thr Ala Gln Ala Thr Leu Thr
515 520 525

Asn Ile Leu Leu Ser Gly Val Pro Thr Tyr Gly His Thr Ala Pro Ser
530 535 540

Pro Pro Pro Gly Leu Thr Pro Val Asp Val His Ile Asn Ser Met Gln
545 550 555 560

Thr Glu Gly Lys Lys Ile Ser Ala Ala Leu Asn Gly His Ala Gln Ser
565 570 575

Pro Asp Ile Lys Tyr Gly Ala Ile Ser Thr Ser Ser Leu Gly Glu Lys
580 585 590

Val Leu Ser Ala Asn His Gly Asp Pro Ser Ile Gln Thr Ser Gly Ser
595 600 605

Glu Gln Thr Ser Pro Lys Ser Ser Pro Thr Glu Gly Cys Asn Asp Ala
610 615 620

Phe Val Glu Val Gly Met Pro Arg Ser Pro Ser His Ser Gly Asn Ala
625 630 635 640

Gly Asp Leu Lys Gln Met Met Cys Pro Ser Lys Val Ser Cys Ala Lys
645 650 655

Arg Gln Thr Val Glu Leu Leu Gln Gly Thr Lys Asn Ser His Leu His
660 665 670

Ser Thr Asp Arg Leu Leu Ser Asp Pro Glu Leu Ser Ala Thr Glu Ser
675 680 685

Pro Leu Ala Asp Lys Lys Ala Pro Gly Ser Glu Arg Ala Ala Glu Arg
690 695 700

Ala Ala Ala Ala Gln Gln Asn Ser Glu Arg Ala His Leu Ala Pro Arg
705 710 715 720

Ser Ser Tyr Val Asn Met Gln Ala Phe Asp Tyr Glu Gln Lys Lys Leu
725 730 735

Leu Ala Thr Lys Ala Met Leu Lys Lys Pro Val Val Thr Glu Val Arg
740 745 750

Thr Pro Thr Asn Thr Trp Ser Gly Leu Gly Phe Ser Lys Ser Met Pro
755 760 765

Ala Glu Thr Ile Lys Glu Leu Arg Arg Ala Asn His Val Ser Tyr Lys
770 775 780

Pro Thr Met Thr Thr Thr Tyr Glu Gly Ser Ser Met Ser Leu Ser Arg
785 790 795 800

Ser Asn Ser Arg Glu His Leu Gly Gly Gly Ser Glu Ser Asp Asn Trp
805 810 815

Arg Asp Arg Asn Gly Ile Gly Pro Gly Ser His Ser Glu Phe Ala Ala
820 825 830

Ser Ile Gly Ser Pro Lys Arg Lys Gln Asn Lys Ser Thr Glu His Tyr
835 840 845

Leu Ser Ser Ser Asn Tyr Met Asp Cys Ile Ser Ser Leu Thr Gly Ser
850 855 860

Asn Gly Cys Asn Leu Asn Ser Ser Phe Lys Gly Ser Asp Leu Pro Glu
865 870 875 880

Leu Phe Ser Lys Leu Gly Leu Gly Lys Tyr Thr Asp Val Phe Gln Gln
885 890 895

Gln Glu Ile Asp Leu Gln Thr Phe Leu Thr Leu Thr Asp Gln Asp Leu
900 905 910

Lys Glu Leu Gly Ile Thr Thr Phe Gly Ala Arg Arg Lys Met Leu Leu
915 920 925

Ala Ile Ser Glu Leu Asn Lys Asn Arg Arg Lys Leu Phe Glu Ser Pro
930 935 940

Asn Ala Arg Thr Ser Phe Leu Glu Gly Gly Ala Ser Gly Arg Leu Pro
945 950 955 960

Arg Gln Tyr His Ser Asp Ile Ala Ser Val Ser Gly Arg Trp
965 970