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(54) Title: METHODS OF TREATING CANCER USING DIHYDROPYRIMIDIN-2-ONE COMPOUNDS

(57) Abstract: Provided is a therapeutic or prophylactic agent for cancer comprising 3- $\{(S)-4-[3\text{-chloro-4-}(3,3\text{-dimethyl-butyl})\text{-phenyl}]-5\text{-isopropyl-4-methyl-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl}\}$ -propionic acid or a pharmaceutically acceptable salt thereof or 3- $\{(S)-4-[4-((1R,2R)\text{-2-tert-butyl-cyclopropyl})\text{-3-chloro-phenyl}]-5\text{-isopropyl-4-methyl-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl}\}$ bicyclo[1.1.1]pentane-1-carboxylic acid or a pharmaceutically acceptable salt thereof.

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Description

Title of Invention: METHODS OF TREATING CANCER USING DIHYDROPYRIMIDIN-2-ONE COMPOUNDS

Technical Field

[0001] CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Appl. No. 62/965,254, filed January 24, 2020. The content of the prior application is incorporated by reference herein in its entirety.

[0002] TECHNICAL FIELD

The present invention pertains to medicinal use of 3-{(S)-4-[3-chloro-4-(3,3-dimethyl-butyl)-phenyl]-5-isopropyl-4-methyl-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl}-propionic acid or a pharmaceutically acceptable salt thereof and 3-{(S)-4-[4-((1R,2R)-2-tert-butyl-cyclopropyl)-3-chloro-phenyl]-5-isopropyl-4-methyl-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl}bicyclo[1.1.1]pentane-1-carboxylic acid or a pharmaceutically acceptable salt thereof as therapeutic agents or prophylactic agents for cancer.

Background Art

[0003] BACKGROUND

Cancer occurs when cells in the body grow out of control.

[0004] The pancreas is a gland located in the abdomen, between the stomach and the spine. Pancreatic cancer arises from cells within the pancreas. Pancreatic cancers are either exocrine or neuroendocrine cancers, depending on the type of cell from which they are derived. Pancreatic adenocarcinoma accounts for about 85% of all pancreatic cancers. Pancreatic adenocarcinoma has a poor prognosis, with 25% of patients surviving one year after diagnosis and 5% of patients living for five years after diagnosis.

[0005] Breast cancer is cancer that forms in the cells of the breasts. Breast cancers that start in the cells that line the ducts are called ductal cancers. Breast cancers that start in the lobules are called lobular cancers. Some breast cancers start in the stroma.

[0006] The liver is located in the right upper quadrant of the abdomen, below the diaphragm. Liver cancer, also known as hepatic cancer and primary hepatic cancer, is a cancer that starts in the liver. The leading causes of liver cancer are cirrhosis due to Hepatitis B, Hepatitis C, or alcohol.

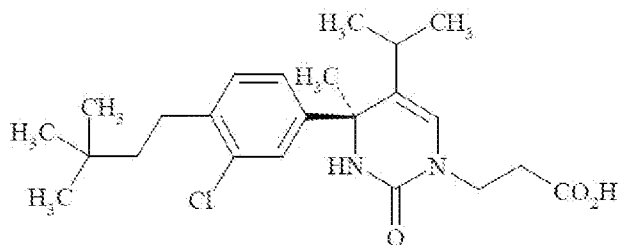
[0007] The prostate is located below the bladder and in front of the rectum. Prostate cancer begins when cells in the prostate gland grow out of control.

Summary of Invention

[0008] SUMMARY

The invention features a method of treating or preventing a pancreatic cancer in a human subject in need thereof by administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

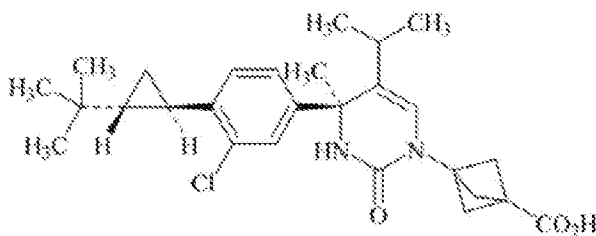
[Chem.1]



or a pharmaceutically acceptable salt thereof.

[0009] The invention also features a method of treating or preventing a pancreatic cancer in a human subject in need thereof by administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

[Chem.2]



or a pharmaceutically acceptable salt thereof.

[0010] In some embodiments of any of the preceding methods, the pancreatic cancer is an exocrine pancreatic cancer. In some instances, the exocrine pancreatic cancer is an adenocarcinoma (e.g., a ductal adenocarcinoma or an acinar adenocarcinoma). In some instances, the exocrine pancreatic cancer is an acinar cell carcinoma, an adenosquamous carcinoma, a colloid carcinoma, a hepatoid carcinoma, an intraductal papillary mucinous neoplasm, a mucinous cystic neoplasm, a pancreatic intraepithelial neoplasia, a pancreatoblastoma, a serous cystadenoma, a signet ring cell carcinoma, a solid-pseudopapillary neoplasm, an undifferentiated carcinoma, or an undifferentiated carcinoma with osteoclast-like giant cells.

[0011] In some embodiments of any of the preceding methods, the pancreatic cancer is a pancreatic neuroendocrine tumor. In some instances, the pancreatic neuroendocrine tumor is an insulinoma or a glucagonoma.

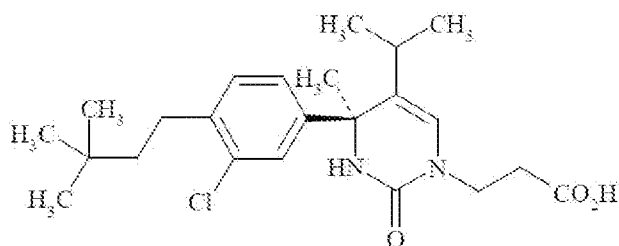
[0012] In some embodiments of any of the preceding methods, the compound or pharmaceutically acceptable salt thereof is administered orally.

[0013] In some embodiments of any of the preceding methods, the compound or pharma-

ceutically acceptable salt thereof is administered in combination with a second agent. In some instances, the second agent is gemcitabine. In some instances, gemcitabine is administered intravenously. In some instances, the compound or pharmaceutically acceptable salt thereof is administered orally and gemcitabine is administered intravenously. In some instances, gemcitabine is administered orally. In some instances, the compound or pharmaceutically acceptable salt thereof is administered orally and gemcitabine is administered orally. In some instances, the second agent is erlotinib, nab-paclitaxel, FOLFIRINOX, or TS-1.

[0014] The invention also features a method of treating or preventing a cancer in a human subject in need thereof by administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

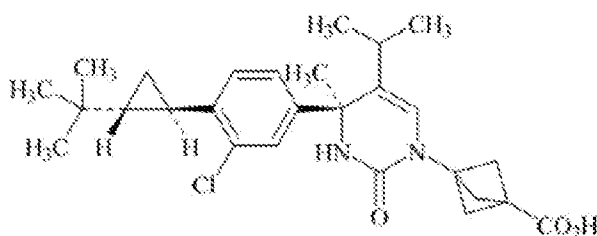
[Chem.3]



or a pharmaceutically acceptable salt thereof, wherein the cancer is a breast cancer, a liver cancer, a prostate cancer, a lung cancer, or a leukemia.

[0015] The invention also features a method of treating or preventing a cancer in a human subject in need thereof by administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

[Chem.4]



or a pharmaceutically acceptable salt thereof, wherein the cancer is a breast cancer, a liver cancer, a prostate cancer, a lung cancer, or a leukemia.

[0016] In some embodiments, the breast cancer is triple-negative breast cancer.

[0017] In some embodiments, the liver cancer is associated with hepatitis B virus or hepatitis C virus infection.

[0018] In some embodiments, the prostate cancer is castration-resistant prostate cancer.

[0019] In some embodiments, the lung cancer is small cell lung cancer.

[0020] In some embodiments, the lung cancer is non-small cell lung cancer.

- [0021] In some embodiments, the leukemia is acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, or chronic myelogenous leukemia.
- [0022] In some embodiments of any of the preceding methods, the compound or pharmaceutically acceptable salt thereof is administered orally.
- [0023] In some embodiments of any of the preceding methods, the compound or pharmaceutically acceptable salt thereof is administered in combination with a second agent.

Description of Embodiments

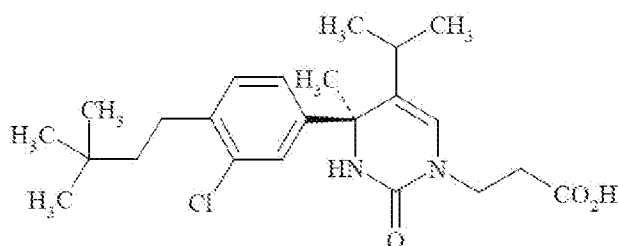
- [0024] DETAILED DESCRIPTION

Compound A, Compound B, and Pharmaceutically Acceptable Salts

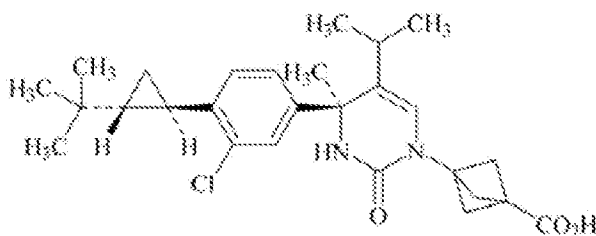
"Compound A" is

3-{(S)-4-[3-chloro-4-(3,3-dimethyl-butyl)-phenyl]-5-isopropyl-4-methyl-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl}-propionic acid, and is represented by the following formula:

[Chem.5]



- [0025] "Compound B" is
- 3-{(S)-4-[4-((1R,2R)-2-tert-butyl-cyclopropyl)-3-chloro-phenyl]-5-isopropyl-4-methyl-2-oxo-3,4-dihydro-2H-pyrimidin-1-yl}bicyclo[1.1.1]pentane-1-carboxylic acid, and is represented by the following formula:
- [Chem.6]



- [0026] Compound A and pharmaceutically acceptable salts thereof can be produced using a known method, such as a method described in US Patent number 10,196,363, the content of which is incorporated herein for reference.
- [0027] Compound B and pharmaceutically acceptable salts thereof can be produced using a known method, such as a method described in US published application number

2019/0300488, the content of which is incorporated herein for reference.

[0028] The term "pharmaceutically acceptable salt" may be any salts without excess toxicity known in the art. Specifically, it includes, for example, salts with inorganic acids, salts with organic acids, salts with inorganic bases, and salts with organic bases. Various forms of pharmaceutically acceptable salts are well known in the art and are listed, for example, in the following references:

(a) Berge et al., *J. Pharm. Sci.*, 66, p1-19 (1977);

(b) Stahl et al., "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" (Wiley-VCH, Weinheim, Germany, 2002);

(c) Paulekuhn et al., *J. Med. Chem.*, 50, p6665-6672 (2007).

[0029] According to known methods, Compound A or Compound B may be reacted with an inorganic acid, organic acid, inorganic base, or organic base to give each pharmaceutically acceptable salt thereof.

[0030] Such salts with inorganic acids include, for example, salts with hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, phosphoric acid, and sulfuric acid. Preferable salts include salts with hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, and hydrobromic acid.

[0031] Such salts with organic acids include, for example, salts with acetic acid, adipic acid, alginic acid, 4-aminosalicylic acid, anhydromethylenecitric acid, benzoic acid, benzenesulfonic acid, camphor acid, camphor-10-sulfonic acid, carbonic acid, citric acid, edetic acid, ethane-1,2-disulfonic acid, dodecylsulfonic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glucuronic acid, glucoheptonic acid, glycolylarsanilic acid, hydroxynaphthoic acid, 2-hydroxy-1-ethanesulfonic acid, lactic acid, lactobionic acid, malic acid, maleic acid, mandelic acid, methanesulfonic acid, methylsulfuric acid, methylnitric acid, methylenebis(salicylic acid), galactaric acid, naphthalene-2-sulfonic acid, 2-naphthoic acid, 1,5-naphthalenedisulfonic acid, oleic acid, oxalic acid, pamoic acid, pantothenic acid, pectic acid, picric acid, propionic acid, polygalacturonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, teoclic acid, thiocyanic acid, trifluoroacetic acid, p-toluenesulfonic acid, undecanoic acid, asparaginic acid, and glutamic acid. Preferable salts include salts with oxalic acid, maleic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, benzoic acid, glucuronic acid, oleic acid, pamoic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and 2-hydroxy-1-ethanesulfonic acid.

[0032] Such salts with inorganic bases include, for example, salts with lithium, sodium, potassium, magnesium, calcium, barium, aluminum, zinc, bismuth, and ammonium. Preferable salts include salts with sodium, potassium, calcium, magnesium, and zinc.

[0033] Such salts with organic bases include, for example, salts with arecoline, betaine,

choline, clemizole, ethylenediamine, N-methylglucamine, N-benzylphenethylamine, tris(hydroxymethyl)methylamine, arginine, and lysine. Preferable salts include salts with tris(hydroxymethyl)methylamine, N-methylglucamine, and lysine.

- [0034] Compound A or Compound B or a pharmaceutically acceptable salt thereof may exist in a solvate form.
- [0035] The term "solvate" means Compound A or Compound B or a pharmaceutically acceptable salt thereof coordinate with a solvent molecule and includes a hydrate. Such a solvate is preferably a pharmaceutically acceptable solvate and includes hydrates, ethanolates, and solvates with dimethylsulfoxide of Compound A or Compound B or a pharmaceutically acceptable salt thereof.
- [0036] Specifically, such a solvate includes a hemihydrate, monohydrate, dihydrate, or monoethanolate of Compound A or Compound B, or a monohydrate of a hydrochloride salt or a 2/3 ethanolate of a dihydrochloride salt of Compound A or Compound B.
- [0037] Compound A or Compound B or a pharmaceutically acceptable salt thereof may be labelled with an isotope atom such as ^2H , ^3H , ^{14}C , and ^{35}S .
- [0038] For example, any hydrogen atoms of Compound A or Compound B include protium ^1H (H), deuterium ^2H (D), and tritium ^3H (T).
- [0039] Compound A or Compound B, or a pharmaceutically acceptable salt thereof is preferably Compound A or Compound B, or a pharmaceutically acceptable salt thereof, substantially purified. More preferable one is Compound A or Compound B, or a pharmaceutically acceptable salt thereof, having 80% or more of purity.
- [0040] The therapeutic agent or prophylactic agent for pancreatic cancer of the present invention is produced, for example, according to a known method in the technical field of medicinal preparations by mixing Compound A or Compound B or a pharmaceutically acceptable salt thereof with a suitable amount of at least one kind of pharmaceutically acceptable carrier or the like as appropriate. The amount of Compound A or Compound B or a pharmaceutically acceptable salt thereof in said preparation differs according to the dosage form, dose, and the like, but is, for example, 0.1 to 100 wt % of the entire preparation.
- [0041] The therapeutic agent or prophylactic agent can be administered orally or parenterally. Oral administration or parenteral administration such as intravenous, intramuscular, subcutaneous, percutaneous, local, or rectal administration can be given as examples of dosage forms. Tablets, capsules, granules, powders, troches, syrups, emulsions, suspensions, and the like can be given as examples of dosage forms that are appropriate for oral administration, and external preparations, suppositories, injections, eye drops, eye ointments, patches, gels, implants, nasal preparations, or pulmonary preparations can be given as examples of dosage forms that are appropriate for parenteral administration. These can be prepared according to known methods in the

technical field of medicinal preparations.

- [0042] Examples of a "pharmaceutically acceptable carrier" include various organic or inorganic carrier substances conventionally used as formulation materials, and examples include excipients, disintegrants, binders, fluidizers, lubricants, and the like for solid preparations; solvents, solubilizing agents, suspending agents, isotonicity agents, buffering agents, soothing agents, and the like for liquid preparations; and bases, emulsifiers, humectants, stabilizers, labilizing agents, dispersants, plasticizers, pH regulators, absorption promoters, gelling agents, antiseptics, fillers, solvents, solubilizers, suspending agents, and the like for semisolid preparations. It is also acceptable to use additives such as preservatives, antioxidants, colorants, sweetening agents, and the like as necessary.
- [0043] Examples of an "excipient" include lactose, sucrose, D-mannitol, D-sorbitol, cornstarch, dextrin, microcrystalline cellulose, crystalline cellulose, carmellose, carmellose calcium, sodium carboxymethyl starch, low-substituted hydroxypropylcellulose, gum arabic, and the like.
- [0044] Examples of a "disintegrant" include carmellose, carmellose calcium, carmellose sodium, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose, and the like.
- [0045] Examples of a "binder" include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, crystalline cellulose, sucrose, dextrin, starch, gelatin, carmellose sodium, gum arabic, and the like.
- [0046] Examples of a "fluidizer" include light anhydrous silicic acid, magnesium stearate, and the like.
- [0047] Examples of a "lubricant" include magnesium stearate, calcium stearate, talc, and the like.
- [0048] Examples of a "solvent" include purified water, ethanol, propylene glycol, macrogol, sesame oil, corn oil, olive oil, and the like.
- [0049] Examples of a "solubilizing agent" include propylene glycol, D-mannitol, benzyl benzoate, ethanol, triethanolamine, sodium carbonate, sodium citrate, and the like.
- [0050] Examples of a "suspending agent" include benzalkonium chloride, carmellose, hydroxypropylcellulose, propylene glycol, povidone, methylcellulose, glycerol monostearate, and the like.
- [0051] Examples of an "isotonic agent" include glucose, D-sorbitol, sodium chloride, D-mannitol, and the like.
- [0052] Examples of a "buffering agent" include sodium hydrogenphosphate, sodium acetate, sodium carbonate, sodium citrate, and the like.
- [0053] Examples of a "soothing agent" include benzyl alcohol and the like.

- [0054] Examples of a "base" include water, vegetable oils (olive oil, corn oil, peanut oil, sesame oil, castor oil, and the like), lower alcohols (ethanol, propanol, propylene glycol, 1,3-butylene glycol, phenol, and the like), higher fatty acids and esters thereof, waxes, higher alcohols, polyhydric alcohols, hydrocarbons (white petrolatum, liquid paraffin, paraffin, and the like), hydrophilic petrolatum, purified lanolin, absorptive ointments, hydrous lanolin, hydrophilic ointments, starches, pullulan, gum arabic, tragacanth gum, gelatins, dextran, cellulose derivatives (methyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and the like), synthetic polymers (carboxyvinyl polymer, sodium polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, and the like), propylene glycol, macrogol (Macrogol 200-600 and the like), and a combination of two or more kinds of these.
- [0055] Examples of a "preservative" include ethyl parahydroxybenzoate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, sorbic acid, and the like.
- [0056] Examples of an "antioxidant" include sodium sulfite, ascorbic acid, and the like.
- [0057] Examples of a "colorant" include food colorings (such as Food Red No. 2 or No. 3, or Food Yellow No. 4 or No. 5), β -carotene, and the like.
- [0058] Examples of a "sweetening agent" include saccharine sodium, dipotassium glycyrrhizinate, aspartame, and the like.
- [0059] Formulation examples for Compound A and Compound B include the following formulations. The present invention is not, however, limited by these formulation examples.
- Formulation Example 1: Production of a capsule
- 1) Compound A or Compound B 30 mg
 - 2) Microcrystalline cellulose 10 mg
 - 3) Lactose 19 mg
 - 4) Magnesium stearate 1 mg
- 1), 2), 3), and 4) are mixed and filled in a gelatin capsule.
- Formulation Example 2: Production of a tablet
- 1) Compound A or Compound B 10 g
 - 2) Lactose 50 g
 - 3) Corn starch 15 g
 - 4) Carmellose calcium 44 g
 - 5) Magnesium stearate 1 g
- [0060] The total amounts of 1), 2), and 3) and 30 g of 4) are kneaded with water, vacuum dried, and sieved. The sieved powder is mixed with 14 g of 4) and 1 g of 5), and the mixture is punched by means of a tableting machine. In this way, 1,000 tablets each containing 10 mg of Compound A or Compound B per tablet are obtained.
- [0061] Treatment or Prevention of Cancer

Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof can be used as an active ingredient of a therapeutic agent or prophylactic agent for cancer, such as pancreatic cancer, breast cancer, liver cancer, or prostate cancer.

- [0062] The term "treating" used herein also includes ameliorating symptoms, preventing from becoming severe, maintaining remission, preventing exacerbation, and preventing relapse.
- [0063] The term "preventing" used herein means suppressing pathogenesis of symptoms.
- [0064] The term "pancreatic cancer" means a cancer arising from cells within the pancreas. The pancreas is a gland located in the abdomen, between the stomach and the spine. Pancreatic cancers are either exocrine or neuroendocrine cancers, depending on the type of cell from which they are derived. Examples of exocrine pancreatic cancers include adenocarcinoma (e.g., ductal adenocarcinoma and acinar adenocarcinoma), acinar cell carcinoma, adenosquamous carcinoma, colloid carcinoma, hepatoid carcinoma, intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, pancreatic intraepithelial neoplasia, pancreatoblastoma, serous cystadenoma, signet ring cell carcinoma, solid-pseudopapillary neoplasm, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells. Examples of pancreatic neuroendocrine tumors include insulinoma and glucagonoma.
- [0065] The term "breast cancer" means a cancer arising from cells within breast tissue. Breast cancer cells have receptors on their surface, in their cytoplasm, and in their nucleus. Breast cancer cells may or may not have one or more of the following three receptors: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Triple-negative breast cancer is negative for each of estrogen receptor, progesterone receptor, and HER2.
- [0066] The term "liver cancer" means a cancer arising from cells within the liver. The most common risk factor for liver cancer is chronic infection with hepatitis B virus or hepatitis C virus. These infections lead to cirrhosis of the liver. The most common types of liver cancer are hepatocellular carcinoma and cholangiocarcinoma.
- [0067] The term "prostate cancer" means a cancer arising from cells within the prostate gland. An example of prostate cancer includes castration-resistant prostate cancer. Most prostate cancers are adenocarcinomas. Other types of prostate cancer include small cell carcinomas, neuroendocrine tumors, transitional cell carcinomas, and sarcomas.
- [0068] The term "lung cancer" means a cancer arising from cells within the lung. Examples of lung cancer include small cell lung cancer and non-small cell lung cancer.
- [0069] The term "leukemia" means a cancer of the blood or bone marrow. Examples of leukemia include acute lymphocytic leukemia, acute myelogenous leukemia, chronic

lymphocytic leukemia, and chronic myelogenous leukemia.

- [0070] Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof can be used in combination (hereinafter also referred to as "concomitantly") with one or multiple other drugs (hereinafter also referred to as a "concomitant drug" or a "second agent") using a common practice employed in the medical field.
- [0071] Examples of a concomitant drug include Abraxane (nab-paclitaxel), Afinitor (Everolimus), Erlotinib Hydrochloride, Everolimus, 5-FU (Fluorouracil Injection), Fluorouracil Injection, Gemzar (Gemcitabine Hydrochloride), Irinotecan Hydrochloride Liposome, Mitomycin C, Onivyde (Irinotecan Hydrochloride Liposome), Paclitaxel Albumin-stabilized Nanoparticle Formulation, Sutent (Sunitinib Malate), Tarceva (Erlotinib Hydrochloride), FOLFIRINOX (Oxaliplatin, Fluorouracil, Leucovorin Calcium, and Irinotecan Hydrochloride combination), GEMCITABINE-CISPLATIN (Gemcitabine Hydrochloride and Cisplatin combination), GEMCITABINE-OXALIPLATIN (Gemcitabine Hydrochloride and Oxaliplatin combination), OFF (Oxaliplatin, Fluorouracil, and Leucovorin Calcium combination), and TS-1 (tegafur, gimeracil, and oteracil combination).
- [0072] Gemzar (Gemcitabine Hydrochloride) can be administered intravenously or orally. For intravenous administration, an exemplary dosing regimen is 1000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.
- [0073] The timing of administration of a drug comprising Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof and a concomitant drug is not limited, it is acceptable to administer these to an administration subject as a combination drug, and it is also acceptable to administer the two formulations either simultaneously or at a fixed interval. Furthermore, it is also acceptable to use the therapeutic agent or prophylactic agent of the present invention and a concomitant drug as a medication that is characterized in that the medication is a kit comprising said agent and concomitant drug. The dosage of a concomitant drug is acceptable as long as it is based on a dosage used in clinical practice, and the dosage can be appropriately selected according to the administration subject, disease, symptoms, dosage form, administration route, administration time, combination, and so on. The dosage form of a concomitant drug is not particularly limited, and is acceptable as long as a drug comprising Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof are combined with the concomitant drug.
- [0074] Examples of one embodiment of the present invention include a method for the treatment or prophylaxis of pancreatic cancer that comprises administering to a human

a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof.

[0075] Examples of another embodiment of the present invention include a method for the treatment or prophylaxis of breast cancer (e.g., triple-negative breast cancer) that comprises administering to a human a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof.

[0076] Examples of another embodiment of the present invention include a method for the treatment or prophylaxis of liver cancer (e.g., liver cancer associated with hepatitis B virus or hepatitis C virus infection) that comprises administering to a human a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof.

[0077] Examples of another embodiment of the present invention include a method for the treatment or prophylaxis of prostate cancer that comprises administering to a human a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof.

[0078] Examples of another embodiment of the present invention include a method for the treatment or prophylaxis of lung cancer that comprises administering to a human a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof.

[0079] Examples of another embodiment of the present invention include a method for the treatment or prophylaxis of leukemia that comprises administering to a human a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof or Compound B or a pharmaceutically acceptable salt thereof.

[0080] In this specification, an "effective amount" signifies, for example, the amount of a medication or drug that elicits a biological or medical response in a tissue, system, or human. Furthermore, a "therapeutically effective amount" signifies an arbitrary amount that either produces a treatment, cure, prophylaxis, or improvement where cancer or a side effect is improved in comparison with a corresponding subject that has not received such an amount.

[0081] The present invention will be explained below in detail using examples of embodiment, but the present invention is not limited by these examples of embodiment.

[0082] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art can develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Examples

[0083] EXAMPLES

Example 1: Evaluation of the Effect of Compounds on Viability of Organoid Lines

The effect of three compounds on cell proliferation of three organoid lines was evaluated. The three test compounds evaluated were Compound A, Compound B, and gemcitabine. The organoid lines used are described in Table 1. The major reagents used are described in Table 2.

[Table 1]

Table 1: Organoid lines

No.	Organoid line name	Tissue Origin	Cell Culture Medium	Compound treatment time
1	PA2410	Pancreatic cancer	PATM	5 days
2	PA5389	Pancreatic cancer	PATM	5 days
3	PA6261	Pancreatic cancer	PATM	5 days

The cells were cultured in a 37°C incubator with 5% CO₂ and 95% air.

[Table 2]

Table 2: Reagents

Item	Supplier	Cat#
Advanced DMEM/F12	Life Technologies	12634028
DMEM	Hyclone	SH30243.01
Matrigel GFR, Phenol Red-free	Corning	356231
Organoid culture media PATM	Crownbio	
TrypLE™ Express	Life Technologies	12605010
CellTiter-Glo® 3D Cell Viability Assay	Promega	G9683
384-well Ultra-Low Attachment Microplate	Corning	4588
DMSO	Sigma	D2650
CD326 (EpCAM)	Biolegend	324220
CD133	Biolegend	372804
L/D	Invitrogen	65-0866-14

[0084] Gemcitabine was purchased from Selleck (Cat. no. S1714).

Staurosporine, a positive control, was purchased from Selleck (Cat. no. S1421).

[0085] The following equipment was used in the analysis:

EnVision Multi Label Reader 2104-0010A, PerkinElmer, Equip ID:TAREA0011;

CO₂ Water Jacketed Incubator, SANYO, Equip ID: TAINC0020;

Digital Dispenser, Tecan D300e; and
Multidrop Combi reagent dispenser, Thermofisher.

[0086] On Day -1, organoids were sheared to uniform sizes. The organoids were processed 1:1 using 50% Matrigel to define the size of the organoids to perform the screen.

[0087] On Day 0, organoids were seeded, as follows.

a) The organoids were collected from each well by adding 20 μ l 100x Dispase solution to each well from a 6-well plate, which contains 2 ml of organoid medium.

b) The plates were put back in the incubator, at 37°C for 30 minutes.

c) The organoids were collected from all wells and pipetted through a pre-wet 100 μ m filter into a 50 ml plastic tube.

d) Once all wells were filtered over 100 μ m filters, the flow through was filtered over a pre-wet 20 μ m filter.

e) The 20 μ m filter was inverted and the organoids were recovered in a new 50 ml tube.

f) The organoids were collected and resuspended in the corresponding culture media. The organoids were counted to determine the concentration.

g) The cell concentration was adjusted with culture medium to the proper concentration.

h) Matrigel was added to a final concentration of 5% v/v and the organoids suspension was kept on ice.

i) 40 μ L cell suspensions were added to a 384-well plate by Multidrop dispenser.

j) Screening plates were placed back into the incubator before adding compounds.

k) Compounds (Compound A, Compound B, and gemcitabine) were added and evaluated at each of the concentrations shown below.

[0088] For Compound A and Compound B, the top working concentration was 100 μ M, with 3.16-fold serial dilutions of each dose level, to achieve 9 dose levels, identified below as C1-C9.

[Table 3]

	C1	C2	C3	C4	C5	C6	C7	C8	C9
Concentration (μ M)	100.00	31.63	10.01	3.17	1.00	0.32	0.10	0.03	0.01

[0089] For gemcitabine, the top working concentration was 1 μ M, with 3.16-fold serial dilutions of each dose level, to achieve 9 dose levels, identified below as C1-C9.

[Table 4]

	C1	C2	C3	C4	C5	C6	C7	C8	C9
Concentration (μ M)	1.00	0.316	0.100	0.032	0.010	0.0032	0.001	0.0003	0.0001

l) Screening plates were placed back into the incubator.

[0090] On Day 5, endpoint CellTiter-Glo (CTG) reading was performed. Assay plates were

read for luminescent CTG signal at the end of the assays. 40 μ L of CTG 3D per well was added by Multidrop dispenser, the contents were mixed for 5 minutes on the plate shaker, and the plates were incubated for 30 minutes at room temperature in the dark. Luminescent signal was read on an Envision plate reader.

[0091] Samples were processed as single cell suspensions and stained, followed by flow cytometry data acquisition and analysis. The final statistical analyses was performed on proportions of cells of interest (Table 3) of all cells of the population defined in a SSC-FSC plot.

[Table 5]

Table 3: Flow panel

Markers	Fluorochrome	Clone	Isotype
CD326 (EpCAM)	BV421	9C4	Mouse IgG2b, κ
CD133	PE	clone 7	Mouse IgG1, κ
L/D	Efluo506	NA	NA

[0092] In order to calculate absolute IC_{50} , a dose-response curve was fitted using nonlinear regression model with a sigmoidal dose response. The formula for calculating surviving rate is shown below.

The surviving rate (%) = $(Lum_{Test\ article} - Lum_{Medium\ control}) / (Lum_{None\ treated} - Lum_{Medium\ control}) \times 100\%$.

[0093] The IC_{50} and maximal inhibition of proliferation for each of the compounds, in each of the three organoid lines, is depicted in Table 4.

[0094]

[Table 6]

Table 4: Inhibition of Proliferation of Organoid Lines

Organoid Line	Compound	IC₅₀ (μM)	Maximal Inhibition (%)
PA2410	Compound A	35.8142	83.52
	Compound B	11.0358	99.66
	Gemcitabine	0.0105	99.58
	Staurosporine	<0.001	100.09
PA5389	Compound A	98.3732	54.27
	Compound B	25.7701	98.71
	Gemcitabine	0.0268	71.32
	Staurosporine	0.062	100.06
PA6261	Compound A	58.5117	104.3
	Compound B	22.1023	103.46
	Gemcitabine	0.0305	88.26
	Staurosporine	0.0366	107.25

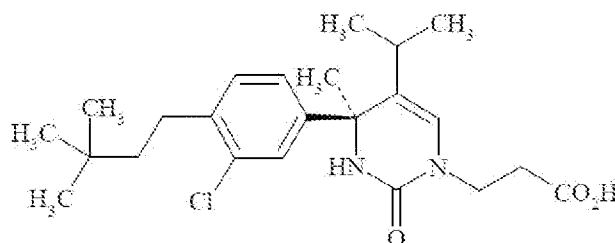
[0095] Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

Claims

[Claim 1] A method of treating or preventing a pancreatic cancer in a human subject in need thereof, comprising administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

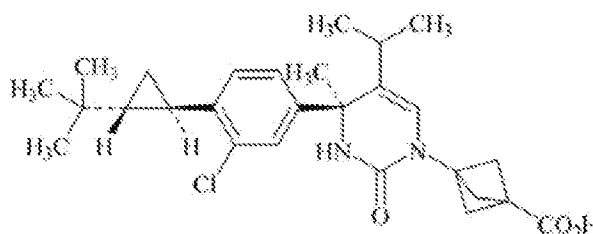
[Chem.1]



or a pharmaceutically acceptable salt thereof.

[Claim 2] A method of treating or preventing a pancreatic cancer in a human subject in need thereof, comprising administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

[Chem.2]



or a pharmaceutically acceptable salt thereof.

[Claim 3] The method of claim 1 or 2, wherein the pancreatic cancer is an exocrine pancreatic cancer.

[Claim 4] The method of claim 3, wherein the exocrine pancreatic cancer is an adenocarcinoma.

[Claim 5] The method of claim 4, wherein the adenocarcinoma is a ductal adenocarcinoma.

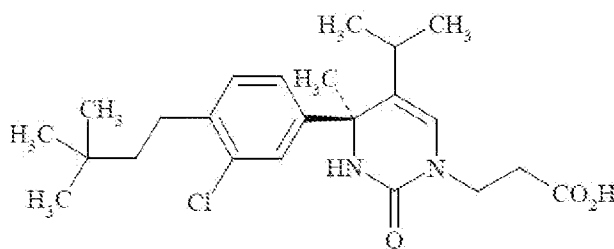
[Claim 6] The method of claim 4, wherein the adenocarcinoma is an acinar adenocarcinoma.

[Claim 7] The method of claim 3, wherein the exocrine pancreatic cancer is an acinar cell carcinoma, an adenosquamous carcinoma, a colloid carcinoma, a hepatoid carcinoma, an intraductal papillary mucinous neoplasm, a mucinous cystic neoplasm, a pancreatic intraepithelial

neoplasia, a pancreatoblastoma, a serous cystadenoma, a signet ring cell carcinoma, a solid-pseudopapillary neoplasm, an undifferentiated carcinoma, or an undifferentiated carcinoma with osteoclast-like giant cells.

- [Claim 8] The method of claim 3, wherein the exocrine pancreatic cancer is an adenosquamous carcinoma.
- [Claim 9] The method of claim 3, wherein the exocrine pancreatic cancer is a pancreatic intraepithelial neoplasia.
- [Claim 10] The method of claim 1 or 2, wherein the pancreatic cancer is a pancreatic neuroendocrine tumor.
- [Claim 11] The method of claim 10, wherein the pancreatic neuroendocrine tumor is an insulinoma or a glucagonoma.
- [Claim 12] The method of any one of the preceding claims, wherein the compound or pharmaceutically acceptable salt thereof is administered orally.
- [Claim 13] The method of any one of the preceding claims, wherein the compound or pharmaceutically acceptable salt thereof is administered in combination with a second agent.
- [Claim 14] The method of claim 13, wherein the second agent is gemcitabine.
- [Claim 15] The method of claim 14, wherein gemcitabine is administered intravenously.
- [Claim 16] The method of claim 14, wherein the compound or pharmaceutically acceptable salt thereof is administered orally and gemcitabine is administered intravenously.
- [Claim 17] The method of claim 14, wherein gemcitabine is administered orally.
- [Claim 18] The method of claim 14, wherein the compound or pharmaceutically acceptable salt thereof is administered orally and gemcitabine is administered orally.
- [Claim 19] The method of claim 13, wherein the second agent is erlotinib, nab-paclitaxel, FOLFIRINOX, or TS-1.
- [Claim 20] A method of treating or preventing a cancer in a human subject in need thereof, comprising administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

[Chem.3]



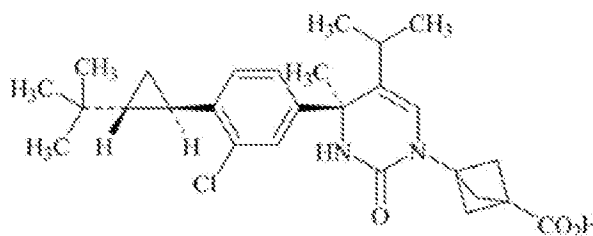
or a pharmaceutically acceptable salt thereof,

wherein the cancer is a breast cancer, a liver cancer, a prostate cancer, a lung cancer, or a leukemia.

[Claim 21]

A method of treating or preventing a cancer in a human subject in need thereof, comprising administering to the human subject a therapeutically effective amount of a compound represented by the following formula:

[Chem.4]



or a pharmaceutically acceptable salt thereof,

wherein the cancer is a breast cancer, a liver cancer, a prostate cancer, a lung cancer, or a leukemia.

[Claim 22]

The method of claim 20 or 21, wherein the breast cancer is triple-negative breast cancer.

[Claim 23]

The method of claim 20 or 21, wherein the liver cancer is associated with hepatitis B virus or hepatitis C virus infection.

[Claim 24]

The method of claim 20 or 21, wherein the prostate cancer is castration-resistant prostate cancer.

[Claim 25]

The method of claim 20 or 21, wherein the lung cancer is small cell lung cancer.

[Claim 26]

The method of claim 20 or 21, wherein the lung cancer is non-small cell lung cancer.

[Claim 27]

The method of claim 20 or 21, wherein the leukemia is acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, or chronic myelogenous leukemia.

[Claim 28]

The method of any one of claims 20 to 27, wherein the compound or

[Claim 29]

pharmaceutically acceptable salt thereof is administered orally.

The method of any one of claims 20 to 28, wherein the compound or pharmaceutically acceptable salt thereof is administered in combination with a second agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2021/002137

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/513 A61K31/337 A61K31/4745 A61K31/517 A61K31/519 A61K31/555 A61K31/7068 A61K45/06 A61P35/00 A61P35/02 ADD. According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, SCISEARCH, WPI Data														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>US 10 196 363 B2 (JAPAN TOBACCO INC [JP]) 5 February 2019 (2019-02-05) cited in the application claims; examples</td> <td>1-29</td> </tr> <tr> <td>X</td> <td>US 2019/300488 A1 (SAKAI TAKAYUKI [JP] ET AL) 3 October 2019 (2019-10-03) cited in the application</td> <td>21</td> </tr> <tr> <td>Y</td> <td>paragraph [0149]; claims; examples ----- -/--</td> <td>1-29</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	US 10 196 363 B2 (JAPAN TOBACCO INC [JP]) 5 February 2019 (2019-02-05) cited in the application claims; examples	1-29	X	US 2019/300488 A1 (SAKAI TAKAYUKI [JP] ET AL) 3 October 2019 (2019-10-03) cited in the application	21	Y	paragraph [0149]; claims; examples ----- -/--	1-29
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.														
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Date of the actual completion of the international search 23 April 2021		Date of mailing of the international search report 06/05/2021												
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Venturini, Francesca												

INTERNATIONAL SEARCH REPORT

International application No
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Information on patent family members

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