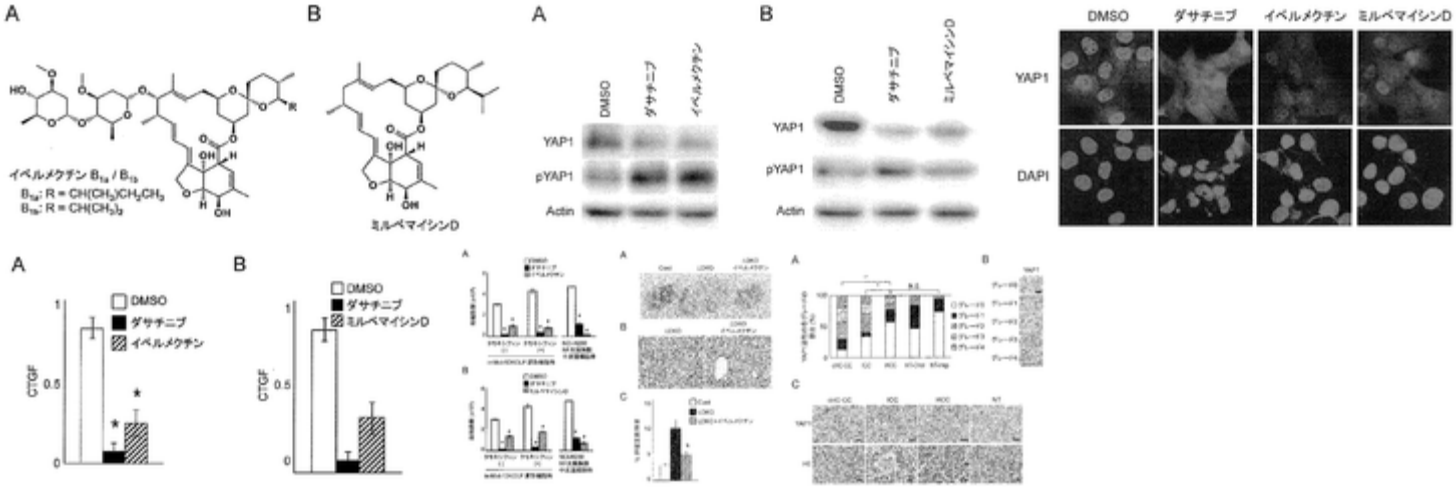
Anticancer agent containing ivermectin or milbemycin d as active ingredient

Abstract

Provided is an anticancer agent that acts on the Hippo pathway. This agent is for treating or preventing a cancer involving an abnormality in the Hippo pathway, and includes ivermectin or milbemycin D as an active ingredient.

Images (7)



Classifications

A61K31/7048 Compounds having saccharide radicals and heterocyclic rings having oxygen as a ring hetero atom, e.g. leucoglucosan, hesperidin, erythromycin, nystatin, digitoxin or digoxin

WO2016076359A1

WIPO (PCT)

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Worldwide applications
2014 JP 2015 WO

Application PCT/JP2015/081741 events

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Publication of WO2016076359A1

Description

Anticancer agent containing ivermectin or milbemycin D as active ingredient

The present invention relates to a preventive or therapeutic agent for cancer having an abnormality in the Hippo pathway.

Hippo pathway is a kinase pathway involved in organ size and cancer onset / progression control. In the inactivated state of the Hippo pathway, the downstream transcriptional coupling factor YAP1 (YES-related protein 1) / TAZ (transcriptional coupling factor having a PDZ-binding motif that is a paralog of YAP1) is mainly the transcription factor TEAD (TEA domain family). Cell proliferation is promoted by binding and inducing expression of target genes involved in cell proliferation and cell division. On the other hand, when the Hippo pathway is activated by cell adhesion or stress stimulation, it phosphorylates YAP1 / TAZ through two kinase cascades, MST kinase (mammalian Ste20-like kinase) and LATS kinase (large tumor suppressor kinase). As a result, it is excluded from the nucleus and leads to protein breakdown, thereby negatively controlling cell proliferation.

Hippo pathway genetically engineered mice develop cancer, and human cancer patients frequently have decreased expression of Hippo pathway molecules and gene mutations, and are known to correlate with cancer malignancy (non-patented) Document 1, Non-Patent Document 2).

For example, if YAP1 is overexpressed in mouse hepatocytes, the liver enlarges due to hyperplasia of hepatocytes and immature bile duct cells, and hepatocellular carcinoma develops. On the other hand, hepatocyte-specific YAP1 deficiency suppresses the decrease in hepatocytes and bile duct cells and the development of liver cancer. Moreover, when YAP1 is overexpressed in mouse keratinocytes, the number of epidermal stem cells / progenitor cells and keratinocytes increase and differentiation disorder, and squamous cell carcinoma develops. Furthermore, the inventors of the present invention found that mice that were completely defective in LAB kinase adapter molecule and core component MOB1 (Mps1 binder 1) of the Hippo pathway became embryonically lethal, and mice that were partially defective in MOB1 in all cases were external skin root sheaths. It has been reported that onset of cancer and loss of expression of MOB1 and activation of YAP1 are also observed in human outer hair root sheath cancer (Non-patent Document 3).

That is, the Hippo pathway is attracting attention as a new cancer suppression pathway. However, anticancer agents that act on the Hippo pathway have not been obtained so far.

Ivermectin is a chemical derivative of avermectin, a 16-membered macrolide produced by the actinomycete Streptomyces avermitilis, from a mixture of ivermectin B1a (22,23-dihydroavermectin B1a) and ivermectin B1b (22,23-dihydroavermectin B1b) (Patent Document 1). Ivermectin has been clinically used as an anthelmintic agent for human

intestinal fecal nematosis, “Stromectol (registered trademark)”.
Milbemycin D is a 16-membered macrolide produced by the actinomycete Streptomyces hygroscopicus subsp. Aureolacrimosus, and is known to be usable as an anthelmintic agent (Patent Document 2).
Ivermectin and milbemycin D are known to interact with glutamatergic chloride channels and γ-aminobutyric acid receptors present in invertebrate nerve and muscle cells.
JP 54-61198 A JP 56-32481 A
The present invention relates to providing an anticancer agent that acts on the Hippo pathway.
As a result of intensive studies, the present inventors have found that ivermectin and milbemycin D, which are known as anthelmintic agents, exhibit an excellent anticancer effect against cancers having an abnormality in the Hippo pathway. That is, the present invention is as follows.
[1] An agent for preventing or treating cancer having an abnormality in the Hippo pathway, comprising ivermectin or milbemycin D as an active ingredient.
[2] The preventive or therapeutic agent for cancer having an abnormality in the Hippo pathway according to [1], comprising milbemycin D as an active ingredient.
[3] The preventive or therapeutic agent for cancer according to [1] or [2] above, which acts on the Hippo pathway and suppresses the activity of YAP1 / TAZ.
[4] Cancers with abnormalities in the Hippo pathway are liver cancer, bile duct cancer, malignant mesothelioma, salivary gland cancer, esophageal cancer, oral cancer, stomach cancer, pancreatic cancer, cervical cancer, endometrial cancer, uterine sarcoma, bladder cancer, brain tumor The cancer preventive or therapeutic agent according to any one of [1] to [3] above, which is malignant bone tumor, myofibrosarcoma, rhabdomyosarcoma, non-melanoma skin cancer, or outer root sheath cancer.
This specification includes the disclosure of Japanese Patent Application No. 2014-228901, which is the basis of the priority of the present application.
According to the present invention, it is possible to provide an anticancer agent based on a new cancer inhibitory action, and not only an anticancer effect by a single agent therapy and a combination therapy with an existing anticancer agent but also a sufficient therapeutic effect can be obtained with an existing anticancer agent. Anticancer effects can also be expected for cases that did not exist.
Ivermectin is a diagram showing a chemical formula of (ivermectin B_{1a} and ivermectin $B_{1b)}$ and milbemycin D. It is a figure which shows the result of having detected the YAP1 protein (YAP1) and phosphorylated YAP1 protein (pYAP1) in the H1299 cell line treated with ivermectin or milbemycin D by Western blotting. It is a figure which shows the result of having detected the total amount of YAP1 protein (YAP1) in the H1299 cell strain treated with ivermectin or milbemycin D by immunofluorescence staining. It is a figure which shows the result of having detected the expression level of the YAP1 target gene (CTGF) in the H1299 cell line processed with ivermectin (FIG. 4A) or milbemycin D (FIG. 4B) by quantitative RT-PCR. It is a figure which shows the result of having processed the cell line which has abnormality in a Hippo pathway with ivermectin (FIG. 5A) or milbemycin D (FIG. 5B), and counting the number of cells. It is a figure which shows the result of a liver macroscopic analysis (A), histological analysis (B), and weight measurement (C) which administers ivermectin to the cancer model mouse which has abnormality in a Hippo path | route. It is a figure which shows YAP1 activation in human mixed liver cancer (cHC-CC) and intrahepatic cholangiocarcinoma (ICC). The histogram of FIG. 7A shows the grade (%) of YAP1 activation in cHC-CC, ICC, hepatocellular carcinoma (HCC), non-tumor healthy human bile duct cells (NT-Chol) and hepatocytes (NT-Hep). FIG. 7B shows a typical example of each grade. FIG. 7C shows YAP1 staining of mixed liver cancer (cHC-CC) (grade 3), intrahepatic cholangiocarcinoma (ICC) (grade 3), hepatocellular carcinoma (HCC) (grade 2) and non-tumor part (grade 0). A typical example of HE (hematoxylin and eosin) staining is shown.
Hereinafter, the present invention will be described in detail.
The present invention is a preventive or therapeutic agent for cancer comprising ivermectin or milbemycin D as an active ingredient.
Ivermectin is a chemical derivative of avermectin, a 16-membered ring macrolide produced by the actinomycete Streptomyces avermitilis, ivermectin B_{1a} (22,23-dihydroavermectin B_{1a}, $C_{48}H_{74}O_{14}$) and ivermectin B_{1b} (22, 23-dihydroavermectin B_{1b}, $C_{47}H_{72}O_{14}$).
Milbemycin D ($C_{33}H_{48}O_{7}$) is a 16-membered macrolide produced by the actinomycetes Streptomyces hygroscopicus subsp. Aureolacrimosus.
The chemical formulas of ivermectin (ivermectin B_{1a} and ivermectin B_{1b}) and milbemycin D are shown in FIG.
In the present invention, ivermectin and milbemycin D include salts or solvates of ivermectin and milbemycin D.

Examples of the salt preferably include a pharmaceutically acceptable salt that can be used as a medicine, including both salt hydrates and salt anhydrides, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; methyl Examples thereof include salts with organic bases such as amine, ethylamine and ethanolamine; salts with basic amino acids such as lysine and ornithine and ammonium salts. The salt may be an acid addition salt. Specific examples of such a salt include mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid; formic acid, Organic acids such as acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid And acid addition salts thereof. Furthermore, in the present invention, ivermectin and milbemycin D include various pharmaceutically acceptable solvates, crystal polymorphs, and the like such as hydrates of ivermectin and milbemycin D.

Specific examples of molecules involved in the mammalian Hippo pathway include MST1 / 2 (mammalian STE20-like protein 1/2) kinase, LATS1 / 2 (large tumor suppressor homolog 1/2) kinase and their core components of the Hippo pathway. Adapter molecules SAV1 (Salvador Homolog 1), MOB1 (Mps One Binder Kinase Activator 1), core core upstream molecule FAT4 (FAT tumor suppressor homolog 4), DCHS1 / 2 (Dachsous1 / 2), NF2 (neurofibromin -2), FRMD6 (FERM domain-containing 6), WWC1 (WW and C2 domain-containing 1; KIBRA) and RASSF1 / 5 (Ras association family member 1/5), and YAP1 (Yes-Associated Protein 1) / TAZ (transcriptional co-activator with PDZ binding binding) and TEAD1-4 (TEA domain domain 1-4).

Whether or not the cancer is a cancer having an abnormality in the Hippo pathway is the above-mentioned MST1 / 2 kinase, LATS1 / 2 kinase and their adapter molecules SAV1, MOB1, and molecules upstream of the core component in cancer cells. This can be determined by checking whether there is an abnormality in FAT4, DCHS1 / 2, NF2, FRMD6, WWC1, RASSF1 / 5, and the like. Confirmation of abnormality of these molecules can be performed by measuring the expression level and activity of these molecules. For example, the expressed protein may be quantified by a method such as ELISA, the phosphorylation may be quantified by a Western method, or the gene transcription amount may be measured by a PCR method.

Cancers with abnormalities in the Hippo pathway include liver cancer, bile duct cancer, malignant mesothelioma, salivary gland cancer, esophageal cancer, oral cancer, stomach cancer, pancreatic cancer, cervical cancer, endometrial cancer, uterine sarcoma, bladder cancer, brain tumor, malignant bone Tumors, myofibrosarcomas, rhabdomyosarcomas, non-melanoma skin cancers, outer root sheath cancers, etc., and a preventive or therapeutic agent for cancer containing ivermectin or milbemycin D as an active ingredient is a prophylactic or therapeutic agent for these cancers Can be used as The cancers to be prevented or treated by the cancer preventive or therapeutic agent containing ivermectin or milbemycin D of the present invention include colon cancer, rectal cancer, lung cancer, glioblastoma, melanoma, urothelial cancer, prostate cancer Breast cancer, ovarian cancer, and NF2 abnormal schwannoma are excluded.

The cancer preventive or therapeutic agent containing ivermectin or milbemycin D of the present invention as an active ingredient may contain a pharmaceutically acceptable carrier or diluent. Carriers include, but are not limited to, physiological saline, phosphate buffered saline, phosphate buffered saline glucose solution, buffered saline, and the like. The administration route includes oral administration or parenteral administration such as intraoral, intratracheal, intrathoracic, intrarectal, intraperitoneal, subcutaneous, intramuscular and intravenous. Desirable is oral administration. As the dosage form, it can be administered in various forms such as capsules, tablets, granules, syrups, fine granules, sprays, emulsions, suppositories, injections, ointments, tapes. Agents and the like.

Liquid preparations such as emulsions and syrups include saccharides such as water, sucrose, sorbitol and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil and soybean oil; p-hydroxybenzoic acid Preservatives such as esters; flavors such as strawberry flavor and peppermint can be used as additives.

For capsules, tablets, powders, granules, fine granules, etc., excipients such as lactose, glucose, sucrose and mannitol; disintegrants such as starch and sodium alginate; lubricants such as magnesium stearate and talc; It can be produced using a binder such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin; a surfactant such as a fatty acid ester; a plasticizer such as glycerin as an additive.

Injections include sugars such as water, sucrose, sorbitol, xylose, trehalose, and fructose; sugar alcohols such as mannitol, xylitol, and sorbitol; buffers such as phosphate buffer, citrate buffer, and glutamate buffer; fatty acid esters A surfactant such as can be used as an additive.

The cancer preventive or therapeutic agent of the present invention may further contain a pH adjuster, antioxidant, stabilizer, preservative, thickener, chelating agent, humectant, colorant, isotonic agent, and the like. Good.

The dosage of the preventive or therapeutic agent for cancer of the present invention is not limited, but the properties such as the effectiveness of the components contained, the dosage form, the administration route, the type of disease, the

weight of the patient to be administered, the age, the medical condition, or the like It is appropriately selected according to the judgment of the doctor. For example, it is in the range of about 0.01 μg to about 100 mg, preferably about 0.1 μg to about 1 mg, per 1 kg body weight of the patient. The dose can be divided into 1 to several times a day, and may be intermittently administered once every several days or weeks.

The present invention will be specifically described with reference to the following examples, but the present invention is not limited to these examples.

Example 1: High-throughput screening of compounds that inhibit the transcriptional activity of the Hippo pathway

Carcinogenesis due to Hippo pathway disruption increases the activity of the downstream transcriptional coupling factor YAP1 / TAZ and the transcription factor TEAD to which YAP1 / TAZ binds. It is caused by activation of transcription of the target gene. Therefore, inhibitors of YAP1 / TAZ were selected by high-throughput screening.

As a reporter gene that can detect the transcriptional activity of the Hippo pathway with high sensitivity, the TEAD-binding sequence of the connective tissue growth factor (CTGF), which is the target gene of the transcription factor TEAD to which YAP1 / TAZ binds, is subjected to repetitive / base addition, and luciferase A linked reporter gene was constructed. Establish human stable cell lines in which the reporter gene is introduced into human non-small cell lung cancer cell line H1299 and human mammary epithelial cell line MCF10A, seed 1,000 cells per well in a 384-well microplate, and culture overnight in a CO_2 incubator did. Next, 1,282 kinds of isolated natural compound libraries and 10,240 kinds of synthetic compound libraries held by the National Institute of Advanced Industrial Science and Technology are dispensed to the microplate so that the final concentrations are 10 μM and 25 μM, respectively. , 24 hours after treatment, Picker Gene (registered trademark) Brillien Star LT Luminescent Reagent Kit (Manufacturer Code: 207-15373, Toyo B-Net Co., Ltd.) and Cell Counting Kit-8 (Manufacturer Code: CK04, Dojin Chemical Laboratory Co., Ltd.)) Was used to measure the luciferase activity and cell viability / cytotoxicity of the reporter gene-introduced cells. A compound that significantly suppressed the luciferase activity of the reporter gene-introduced cells and did not show cytotoxicity was used as a hit compound for high-throughput screening.

As a result, ivermectin and milbemycin D were obtained as compounds that inhibit the function of YAP1 / TAZ.

Example 2: Inhibition of YAP1 / TAZ activity The inhibitory effect of YAP1 / TAZ activity by the compound obtained in Example 1 was examined using Western blotting, immunofluorescence staining, and quantitative RT-PCR.

H1299 cell line, a human non-small cell lung cancer cell line, was treated with ivermectin (final concentration 10 μM) or milbemycin D (final concentration 10 μM) for 24 hours, and anti-YAP1 protein antibody and anti-phosphorylated YAP1 protein antibody (CST Japan) as primary antibodies), And using a horseradish peroxidase (HRP) labeled antibody as a secondary antibody, the amount of YAP1 protein (YAP1) and the amount of phosphorylated YAP1 protein (pYAP1) were detected by Western blotting (FIG. 2). . Detection of β-actin with anti-β-actin antibody (Sigma Aldrich) was used as a loading control. As shown in FIG. 2, treatment with ivermectin or milbemycin D resulted in a decrease in the amount of YAP1 protein and an increase in the amount of inactivated phosphorylated YAP1 protein.

Immunofluorescence staining was performed according to a conventional method. The H1299 cell line was seeded on a coverslip, treated with ivermectin (final concentration 10 μM) or milbemycin D (final concentration 10 μM) for 24 hours, added with 4% paraformaldehyde, and fixed at room temperature for 5 minutes. Anti-YAP1 antibody was used as the primary antibody, and immunostaining was performed using a fluorescently labeled secondary antibody to detect the total amount of YAP1 protein (FIG. 3). Cell nuclei were stained with DAPI. As shown in FIG. 3, the expression level of YAP1 protein decreased by ivermectin or milbemycin D treatment.

Quantitative RT-PCR was performed according to a standard method. H1299 cell line was treated with ivermectin (final concentration 10 μM) or milbemycin D (final concentration 10 μM) for 24 hours, RNA was extracted from the cells using RNAiso (Takara Bio Inc.), purified, and transcripter クリ first strand cDNA synthesis A reverse transcription reaction of 1 μg of total RNA was performed using a kit (Roche Diagnostics Inc.). Quantitative RT-PCR analysis was performed using the primers shown in Table 1, and the expression level of the target gene CTGF (connective tissue growth factor) downstream of YAP1 was detected (FIG. 4). As shown in FIG. 4, transcription of CTGF was suppressed by ivermectin or milbemycin D treatment.

Dasatinib (final concentration 5 μM) is an inhibitor of SRC family kinase YES and is known to inhibit the activity of YAP1 by controlling phosphorylation, and was used as a positive control.

プライマー	配列	
Human GAPDH Fw	gtg aag gtc gga gtc aac g	（配列番号１）
Human GAPDH Rv	tga ggt caa tga agg ggt c	（配列番号２）
Human CTGF Fw	ttg gcc cag acc caa cta tg	（配列番号３）
Human CTGF Rv	cag gag gcg ttg tca ttg gt	（配列番号４）

Treatment with ivermectin or milbemycin D resulted in a decrease in the amount of YAP1 protein and an increase in the amount of inactivated phosphorylated YAP1 protein, and the transcription of CTGF, a target gene downstream of the YAP1 protein, was suppressed.
It was suggested that ivermectin and milbemycin D act on the Hippo pathway and inhibit the function of YAP1 / TAZ.
Example 3: Cell growth inhibition The cell growth inhibition effect of the compound obtained in Example 1 was examined by counting the number of cells.
MOB1 is a core component of the Hippo pathway and strongly promotes the activity of LATS kinase as an adapter of LATS kinase. From the analysis of MOB1-deficient mice, it is known that cancer develops due to MOB1-deficiency.
As cell lines with mutations in the Hippo pathway, tamoxifen (Tamo) -inducible immortalized hepatic cell line (imMob1DKOLP) and NF2-deficient pleural mesothelioma cell line (NCI) in which YAP1 is constantly activated - H290), seed 1.5×10^4 cells per well in a 24-well plate, treat each cell with ivermectin or milbemycin D (both at a final concentration of 10 μM) for 3 days, and then add a 24-well plate per well. Cell proliferation was examined by seeding 1.5×10^4 cells and counting the number of cells. Tamoxifen was added 5 days before treatment with ivermectin or milbemycin D. Dasatinib (final concentration 0.5 μM) was used as a positive control. The results are shown in FIG.
As shown in FIG. 5, by treating a cell line having an abnormality in the Hippo pathway with ivermectin or milbemycin D, cell proliferation of the cell line was suppressed.
Example 4: Anticancer effect by in vivo administration The anticancer effect of the compound obtained in Example 1 was examined using a cancer model mouse having an abnormality in the Hippo pathway.
Mice deficient in Mob1 specifically (LDKO) were intraperitoneally administered with 2 mg / kg ivermectin or DMSO as a control for 5 days (4 to 8 days after birth). Analysis (FIG. 6A), histological analysis by hematoxylin and eosin staining (FIG. 6B), and weight measurement (FIG. 6C). In mice administered with ivermectin, the size and weight of the liver decreased as shown in FIGS. 6A and 6C, and proliferation of undifferentiated cholangiocyte-like cells around and inside the portal vein was suppressed as shown in FIG. 6B. It was. The weight was calculated as a ratio of liver weight to mouse body weight.
By administering ivermectin to a cancer model mouse having an abnormality in the Hippo pathway, hyperplasia of the liver and bile duct, which are precancerous lesions, was suppressed.
Reference example 1
Surgically excised mixed liver cancer (cHC-CC), intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) tissues were fixed with formalin and stained with anti-YAP1 antibody (Sigma) in a conventional manner . Non-tumor healthy human bile duct cells (NT-Chol) and hepatocytes (NT-Hep) were used as controls. The grade of activation of YAP1 was determined according to the criteria in Table 2. The results are shown in FIG.
As shown in FIG. 7A, YAP1 activation above grade 2 was 62%, 51% and 26 for mixed liver cancer (cHC-CC), intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC), respectively. It was 14% and 6% for non-tumor healthy human bile duct cells and hepatocytes, respectively. That is, YAP1 was remarkably activated in mixed liver cancer (cHC-CC) and intrahepatic cholangiocarcinoma (ICC). This result indicates that the onset of mixed liver cancer (cHC-CC) and intrahepatic cholangiocarcinoma (ICC) can be suppressed by suppressing the activity of YAP1 / TAZ, which is a transcriptional coupling factor downstream of the Hippo pathway.

YAP1 活性グレードの決定

YAP1 活性のグレード 0-4 は 'Frequency Score' x 'Intensity Score' により決定した。

(i) 核中の染色細胞の%	Frequency Score
<5%	0
6-25%	1
26-50%	2
51-75%	3
>75%	4

(ii) 染色強度	Intensity Score
無染色	0
青白い	1
黄	2
褐色	3

'Frequency Score (i)' x 'Intensity Score (ii)'	グレード
0	0
1-3	1
4-6	2
7-9	3
10-12	4

Comparative Example 1: Hippo pathway transcription inhibitory activity by other milbemycins Other milbemycins (milbemycin A_1, milbemycin A_3 and nemadectin), which are analogs of milbemycin D, were used in the same manner as in Example 1. Using the luciferase activity of the reporter gene-introduced cells as an index, the transcription inhibitory activity of the Hippo pathway was examined (Table 3).

As a result, milbemycin A_1, milbemycin A_3 and nemadectin did not show strong inhibitory activity like milbemycin D obtained in the present invention. Surprisingly, it was clarified that milbemycin D exhibits the strongest inhibitory activity, even though the analogs have different effects on the Hippo pathway.

化合物名	ミルベマイシン A_1	ミルベマイシン A_3	ネマデクチン	ミルベマイシン D
Luc 活性 (%)	6.0	6.0	*	6.7

*:終濃度 10μMにおける阻害活性は認められなかった。

As a result, ivermectin and milbemycin D are useful as a preventive or therapeutic agent for cancers having an abnormality in the Hippo pathway.

Ivermectin and milbemycin D can be used as a preventive or therapeutic agent for cancers having an abnormality in the Hippo pathway.

1-4 Primers

All publications, patents and patent applications cited in this specification are incorporated herein by reference in their entirety.

Claims (4)

Hide Dependent

1. A preventive or therapeutic agent for cancer having an abnormality in the Hippo pathway, comprising ivermectin or milbemycin D as an active ingredient.
2. The preventive or therapeutic agent for cancer having an abnormality in the Hippo pathway according to claim 1, comprising milbemycin D as an active ingredient.
3. The cancer preventive or therapeutic agent according to claim 1 or 2, which acts on the Hippo pathway and suppresses the activity of YAP1 / TAZ.
4. Cancers with abnormal Hippo pathway are liver cancer, bile duct cancer, malignant mesothelioma, salivary gland cancer, esophageal cancer, oral cancer, stomach cancer, pancreatic cancer, cervical cancer, endometrial cancer, uterine sarcoma, bladder cancer, brain tumor, malignant bone The preventive or therapeutic agent for cancer according to any one of claims 1 to 3, which is a tumor, myofibrosarcoma, rhabdomyosarcoma, non-melanoma skin cancer, or outer root sheath cancer.

Patent Citations (2)

Publication number Priority date Publication date Assignee Title
WO2004006906A2 * 2002-07-15 2004-01-22 Combinatorx, Incorporated Methods for the treatment of neoplasms
JP2005508312A * 2001-07-23 2005-03-31 エピダウロス・バイオテクノロジー・アクチェンゲゼルシャフト Means and methods for improved cancer treatment based on MDR1
Family To Family Citations

* Cited by examiner, † Cited by third party

Non-Patent Citations (2)

Title
HASHIMOTO,HISASHI ET AL.: "Ivermectin inactivates the kinase PAK1 and blocks the PAK1-dependent growth of human ovarian cancer and NF2 tumor cell lines", DRUG DISCOVERIES & THERAPEUTICS, vol. 3, no. 6, 2009, pages 243 - 246, ISSN: 1881-7831 *
ROMANO, DAVID ET AL.: "Protein interaction swithces coordinate Raf-1 and MST2/Hippo signalling", NATURE CELL BIOLOGY, vol. 16, no. 7, 15 June 2014 (2014-06-15), pages 673 - 684, ISSN: 1465-7392 *

* Cited by examiner, † Cited by third party

Cited By (2)

Publication number Priority date Publication date Assignee Title
WO2019235569A1 * 2018-06-08 2019-12-12 日産化学株式会社 Kinase inhibitor
Family To Family Citations
WO2020013113A1 * 2018-07-10 2020-01-16 国立大学法人神戸大学 Non-human mammalian cancer model

* Cited by examiner, † Cited by third party, ‡ Family to family citation

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WO2017190077A1 2017-11-02 Ty-52156 compounds for the treatment of cancer
JP2013043862A 2013-03-04 Composition for treating prostatic cancer, and screening method of active ingredient in composition for treating prostatic cancer

Priority And Related Applications

Priority Applications (2)

Application Priority date Filing date Title
JP2014228901A 2014-11-11 2014-11-11 Anticancer agent comprising ivermectin or milbemycin d as active ingredient
JP2014-228901 2014-11-11

Legal Events

Date Code Title Description
2016-06-29 121 Ep: the epo has been informed by wipo that ep was designated in this application

Ref document number: 15858399

Country of ref document: EP

Kind code of ref document: A1

2017-05-11 NENP Non-entry into the national phase in:

Ref country code: DE

2017-12-06 122 Ep: pct application non-entry in european phase

Ref document number: 15858399

Country of ref document: EP

Kind code of ref document: A1

Concepts

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Name Image Sections Count Query match

22,23-dihydroavermectin B1a title,claims,abstract,description 47 0.000
Ivermectin title,claims,abstract,description 41 0.000
active ingredient title,claims,abstract,description 9 0.000
antineoplastic agent title,abstract,description 7 0.000
cancer claims,abstract,description 51 0.000
Hippo pathway claims,abstract,description 41 0.000
Milbemycin D claims,abstract,description 40 0.000
YAP1 claims,description 46 0.000
YAP1 claims,description 46 0.000
drug claims,description 18 0.000
preventive claims,description 16 0.000
effects claims,description 14 0.000
liver cancer claims,description 10 0.000
Neoplasm claims,description 6 0.000
root sheath claims,description 5 0.000
Malignant melanoma claims,description 4 0.000
Bile duct cancer claims,description 3 0.000
Bladder cancer claims,description 3 0.000
Bone and Bones claims,description 3 0.000
Brain Neoplasms claims,description 3 0.000
Cervix carcinoma claims,description 3 0.000
Endometrial cancer claims,description 3 0.000
Gastric cancer claims,description 3 0.000
Malignant Mesothelioma claims,description 3 0.000
Oesophageal carcinoma claims,description 3 0.000
Pancreatic Carcinoma claims,description 3 0.000
Salivary gland cancer claims,description 3 0.000
Sarcoma claims,description 3 0.000
cervical cancer claims,description 3 0.000
esophageal cancer claims,description 3 0.000
malignant claims,description 3 0.000
pancreatic cancer claims,description 3 0.000
rhabdomyosarcoma claims,description 3 0.000
stomach cancer claims,description 3 0.000
urinary bladder cancer claims,description 3 0.000
abnormal effect claims,description 2 0.000
chemical substances by application abstract,description 3 0.000
Show all concepts from the description section