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(54) Title: NOVEL MEDICAMENT FOR TREATING HEPATIC ENCEPHALOPATHY

(57) Abstract: The present invention relates to a medicament for treating and/or preventing hepatic encephalopathy, comprising a quinolone compound as an active ingredient.



WO 2021/161981 A1

Description

Title of Invention: NOVEL MEDICAMENT FOR TREATING HEPATIC ENCEPHALOPATHY

Technical Field

[0001] The present invention relates to a medicament for treating and/or preventing hepatic encephalopathy, in more detail, a medicament for treating and/or preventing hepatic encephalopathy, comprising a quinolone compound as an active ingredient.

Background Art

[0002] In hepatic encephalopathy, it is thought that neurological symptom is caused by hyperammonemia resulting from ammonia metabolic hypoactivity, and then encephalopathy develops.

[0003] In order to treat hepatic encephalopathy, a synthetic disaccharide (e.g. lactulose, etc.) as a medicament for treating hyperammonemia, or a low-absorbent antimicrobial (e.g. rifaximin, etc.) has been used (Non-Patent Literature 1). An antimicrobial, rifaximin has an action mechanism of decreasing enteric bacteria including ammonia-producing bacteria (Non-Patent Literatures 2 and 3), thereby the antimicrobial has been approved as a therapy for hyperammonemia in hepatic encephalopathy. Even using these medicaments, however, any complete therapy of hyperammonemia is not expected, thus it has been desired to develop a more potent medicament thereof than existing medicaments.

[0004] Patent Literature 1 discloses specific quinolone antimicrobials which exhibit the antibacterial activity against *Clostridium difficile* living in intestinal tract.

Citation List

Patent Literature

[0005] [PL 1] WO2013/029548

Non-Patent Literature

[0006] [NPL 1] Montagnese S, et al., Dig Liver Dis. 2019; 51: 190-205.

[NPL 2] Finegold SM, et al., Antimicrob Agents Chemother. 2009; 53: 281-6.

[NPL 3] J. M. Sierra, et al., Antimicrob Agents Chemother. 2001; 45: 643-644.

Summary of Invention

Technical Problem

[0007] The main purpose of the present invention is to provide a novel medicament for treating and/or preventing hepatic encephalopathy, which is more effective than existing medicaments.

Solution to Problem

- [0008] The present inventors have extensively studied and then have found that a known quinolone antimicrobial,
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid can lower the ammonia concentration in portal blood more than existing medicaments which have been approved as a therapy for hyperammonemia in hepatic encephalopathy, and it is effectable for treatment of hepatic encephalopathy. Based upon the new findings, the present invention has been completed.
- [0009] The present invention includes the following embodiments.
(Item 1)
A medicament for treating and/or preventing hepatic encephalopathy, comprising 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof as an active ingredient.
- [0010] (Item 2)
The medicament of Item 1, wherein the metabolite is
(2S,3S,4S,5R,6R)-6-((7-amino-5-cyanopyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carbonyl)oxo)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid,
7-(6-amino-5-carbamoylpyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, or ethyl
7-(6-amino-5-cyanopyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate.
- [0011] (Item 3)
The medicament of Item 1 or 2, which is for oral administration.
- [0012] (Item 4)
The medicament of any one of Items 1 - 3, wherein the daily dose of the active ingredient is 0.5 mg - 6000 mg.
- [0013] (Item 5)
A method for treating and/or preventing hepatic encephalopathy, comprising administering a therapeutically effective amount of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof as an active ingredient to a patient in need thereof.
- [0014] (Item 6)
Use of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof in the manufacture of a medicament for treating and/or preventing hepatic en-

cephalopathy.

[0015] (Item 7)

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof for use in treating and/or preventing hepatic encephalopathy.

Effect of Invention

[0016] The present compound can lower the ammonia concentration in portal blood, and further it has a potent lowering action on the ammonia concentration more than an existing medicament for treating hyperammonemia in hepatic encephalopathy, rifaximin. Thus, it is expected to a novel medicament for treating and/or preventing hepatic encephalopathy. Furthermore, the present compound is a poorly absorbable drug, and thereby it is distributed in a high concentration in the intestinal tract when it is orally administered, but it has low blood transferability. Thus, the present compound also has a merit, i.e., a low risk of generalized side effect, which is a problem in existing quinolone antibacterial agents.

Brief Description of Drawings

[0017] [fig.1]Fig. 1 shows the result of Test 1.

[fig.2]Fig. 2 shows the result of Test 2.

Description of Embodiments

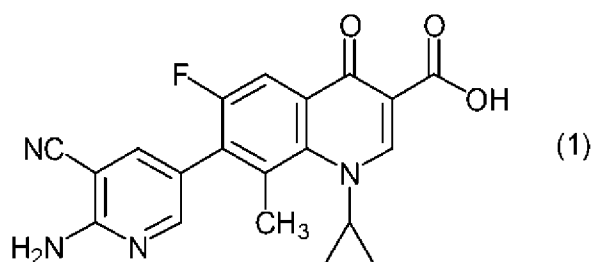
[0018] The present compound

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid has the structure of formula (1), which is disclosed as Compound number 2-18 in Patent Literature 1 that also discloses its process and its antibacterial activity for *Clostridium difficile*. And, the metabolites thereof are (2S,3S,4S,5R,6R)-6-((7-amino-5-cyanopyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carbonyl)oxo)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid,

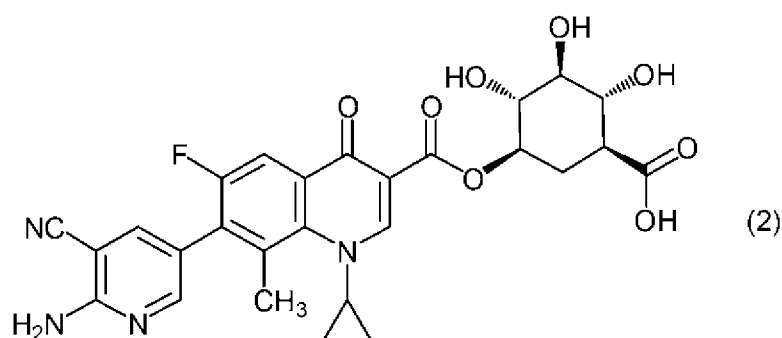
7-(6-amino-5-carbamoylpyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, and ethyl

7-(6-amino-5-cyanopyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate which have the following structures of formulae (2) - (4), respectively, which are included in the present compound.

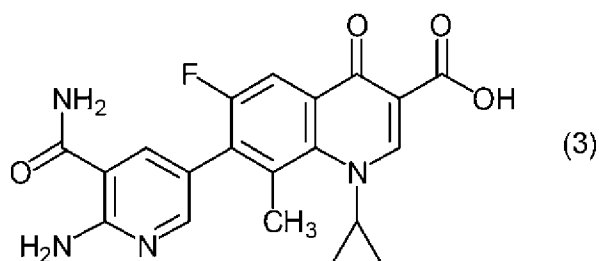
[Chem.1]



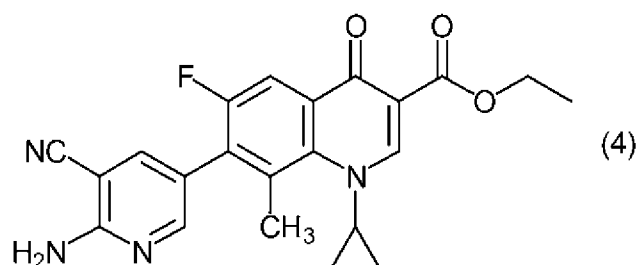
[Chem.2]



[Chem.3]



[Chem.4]



[0019] The compound of the present invention may be in the form of hydrate and/or solvate, and hence the present compound also encompasses a hydrate and/or solvate thereof.

In addition, the compound of the present invention in which any one or more ^1H atoms are replaced by ^2H (D) atoms is also within the scope of the present invention.

There may exist a polymorphism in a crystal of the compound of the present invention or a pharmaceutically acceptable salt thereof, and hence such crystal polymorphism is also within the scope of the present invention.

- [0020] The "pharmaceutically acceptable salt" includes, as an acid addition salt, a salt with inorganic acid such as hydrochloride, hydrobromide, hydroiodide, sulfate, perchlorate, and phosphate; a salt with organic acid such as oxalate, malonate, maleate, fumarate, lactate, malate, citrate, tartrate, benzoate, trifluoroacetate, acetate, methanesulfonate, p-toluenesulfonate, and trifluoromethanesulfonate; and a salt with amino acid such as glutamate and aspartate; and as a salt with a base, an alkali metal salt such as sodium salt and potassium salt; alkaline-earth metal salt such as calcium salt; and an ammonium salt.
- [0021] In hepatic encephalopathy of the present invention, it is thought that neurological symptom is caused by hyperammonemia, and then encephalopathy develops. The symptom is in broad range from asymptomatic state to comatose state, which includes reversal of sleep rhythm, disorientation, flapping tremor, excited state, delirium, unconsciousness, and coma. The cause of hyperammonemia includes severe hepatic dysfunction such as fulminant hepatitis and cirrhosis, urea cycle deficiency such as urea cycle disorder, portosystemic shunt, urease-producing bacteria infection, and a combination thereof.
- [0022] The present compound may be administered via any route selected from oral administration, parenteral administration and rectal administration. The daily dose depends on the compound, administration route, condition of patient, age of patient, etc. In case of oral administration, for example, it may be generally administered in a dose of about 0.01 mg - about 100 mg, preferably about 0.05 mg - about 50 mg, more preferably about 0.1 mg - about 20 mg, even more preferably about 1 mg - about 10 mg, per kg of human or mammal's body weight, in one to several portions. For example, the daily dose of human includes about 0.5 mg - about 6000 mg, preferably about 3 mg - about 3000 mg, more preferably about 6 mg - about 1200 mg, even more preferably about 60 mg - about 600 mg.
- [0023] The dosage form in the present invention includes tablet, capsule, granule, powder, syrup, suspension, injection, suppository, eyedrop, ointment, liniment, patch, and inhalant. These dosage forms can be prepared in a conventional manner. If the dosage form is a liquid one, it may be a formulation to prepare a solution or suspension in use by mixing it with water, appropriate water-solution, or other appropriate solvent. The tablet and the granule may be coated in a well-known manner. The dosage form may be prepared in known manner with pharmaceutically acceptable additives.
- The additives used herein include, according to the intended use, excipients, disintegrating agents, binders, fluidizer, lubricants, coating agents, colorants, solubilizers, solubilizing agents, thickeners, dispersants, stabilizing agents, sweeteners, and flavors. For example, they include lactose, mannitol, calcium hydrogen phosphate, micro-crystalline cellulose, low-substituted hydroxypropylcellulose, cornstarch, partly prege-

latinized starch, carmellose calcium, croscarmellose sodium, crospovidone, sodium starch glycolate, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, light anhydrous silicic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, polyethylene glycol, propylene glycol, titanium oxide, talc, iron sesquioxide, and yellow ferric oxide.

[0024] In case that the present compound is formulated into a single dosage form, the dosage form may include the present compound in 0.1 - 85 % (w/w) per the whole composition, but the present invention is not limited thereto. Preferably, it is 10 - 70 % (w/w) per the whole composition.

[0025] In addition, the present compound may be used in combination with another drug or as a combination with another drug in order to enhance the effect and/or relieve side effects. The other drug which can be used in combination includes, for example, rifaximin, lactulose, and lactitol.

Examples

[0026] The present invention is explained in more detail in the following by referring to Tests, however, the scope of the present invention is not limited thereto.

[0027] The influence of the present compound on the ammonia concentration in portal blood was studied below with rats. The present compound used herein (hereinafter, referred to as "test substance") and the reference drug were gained as shown below.

Test substance

[1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid]: gained from Otsuka Pharmaceutical Co., Ltd.

Reference drug (rifaximin): gained from Sigma-Aldrich.

[0028] Test 1. Influence of the test substance on the ammonia concentration in portal blood

Hyperammonemia is thought to be one of the major factors causing impaired consciousness in hepatic encephalopathy. Ammonia produced from food by metabolic activity of enteric bacteria is absorbed in intestinal tract, and then transported to liver via portal vein. The present test was done for the purpose of studying the action of the test substance on the ammonia concentration in portal blood of a normal rat.

[0029] (Preparation of administration sample)

The test substance was suspended in 5 % gum arabic, and then the suspension was diluted to prepare each suspension of three concentrations (0.02 mg/mL, 0.2 mg/mL, and 2 mg/mL) before using.

[0030] (Test method)

Normal male SD rats were separated based on their weights into each group shown in the table below. Each administration sample shown in the table below was orally administered to the rats in each administration group once a day. The day when the first

administration was done was set as the initial day (0 day). On the 1st, 3rd, and 5th days, each 8 rats were taken out from each group, the portal blood was collected from each rat, and the ammonia concentrations in each collected blood were analyzed by dry chemistry technology. In the collection of portal blood, it is necessary to serve one rat for one analysis, and it is impossible to collect blood from the same one rat more than once all through the test. Thus, the ammonia concentration on 0 day which was supposed to be the reference in each group was not analyzed, but instead, the ammonia concentration in portal blood on 0 day was assumed to be the same among each group because the grouping was done based on their weights, and the test was implemented under the assumption.

Administration group	Administration sample
Control group	5 % gum arabic
0.1 mg/kg group	0.02 mg/mL suspension
1 mg/kg group	0.2 mg/mL suspension
10 mg/kg group	2 mg/mL suspension

[0031] (Result)

The analyzed ammonia concentrations in portal blood of the 8 rats were calculated to obtain their average for each group and each analysis day, and the summarized result is shown in Figure 1. The test substance administration groups of 1 mg/kg or more showed significant lowering-action on the ammonia concentration in portal blood, compared with the control group.

[0032] Test 2. Comparison of the influence on the ammonia concentration in portal blood between the test substance and the reference drug

The present test substance and an existing antibiotic rifaximin that has been used in the treatment of hyperammonemia in hepatic encephalopathy were evaluated through the method shown in the above Test 1 about the lowering-action on the ammonia concentration in portal blood, and the actions were compared each other.

[0033] (Preparation of administration sample)

The test substance or rifaximin was suspended in 5 % gum arabic, and then the suspension was diluted to prepare each suspension of 2 mg/mL before using.

[0034] (Test method)

Normal male SD rats were separated based on their weights into each group shown in the table below. Each administration sample shown in the table below was administered to each administration group once a day. The day when the first administration was done was set as the initial day (0 day). On the 5th, 7th, and 10th days, each 5 rats were taken out from each group, the portal blood was collected from each rat, and the ammonia concentrations in each collected blood were analyzed by dry chemistry technology. In the collection of portal blood, it is necessary to serve one rat

for one analysis, and it is impossible to collect blood from the same one rat more than once all through the test. Thus, the ammonia concentration on 0 day which was supposed to be the reference in each group was not analyzed, but instead, the ammonia concentration in portal blood on 0 day was assumed to be the same among each group because the grouping was done based on their weights, and the test was implemented under the assumption.

Administration group	Administration sample
Control group	5 % gum arabic
10 mg/kg test substance administration group	2 mg/mL test substance suspension
10 mg/kg rifaximin administration group	2 mg/mL rifaximin suspension

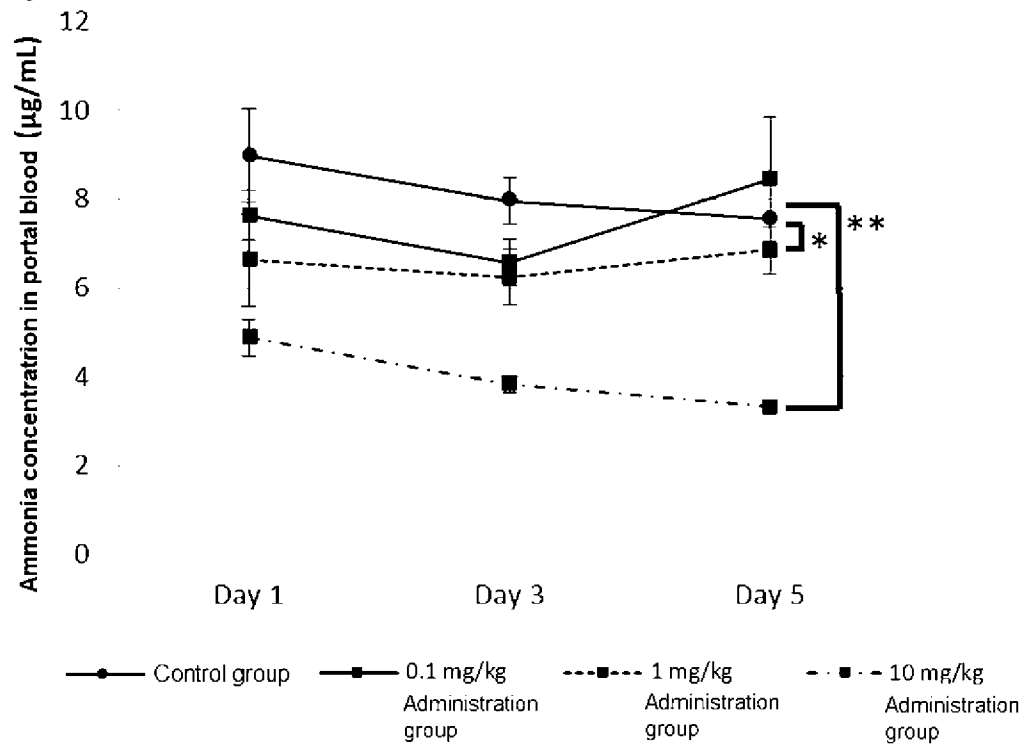
[0035] (Result)

The analyzed ammonia concentrations in portal blood of the 5 rats were calculated to obtain their average for each group and each measurement day, and the summarized result is shown in Figure 2. The test substance administration group and the rifaximin administration group showed significant lowering-action on the ammonia concentration in portal blood, compared with the control group. In addition, the test substance administration group showed significant lowering-action on the ammonia concentration in portal blood, compared with the rifaximin administration group.

Claims

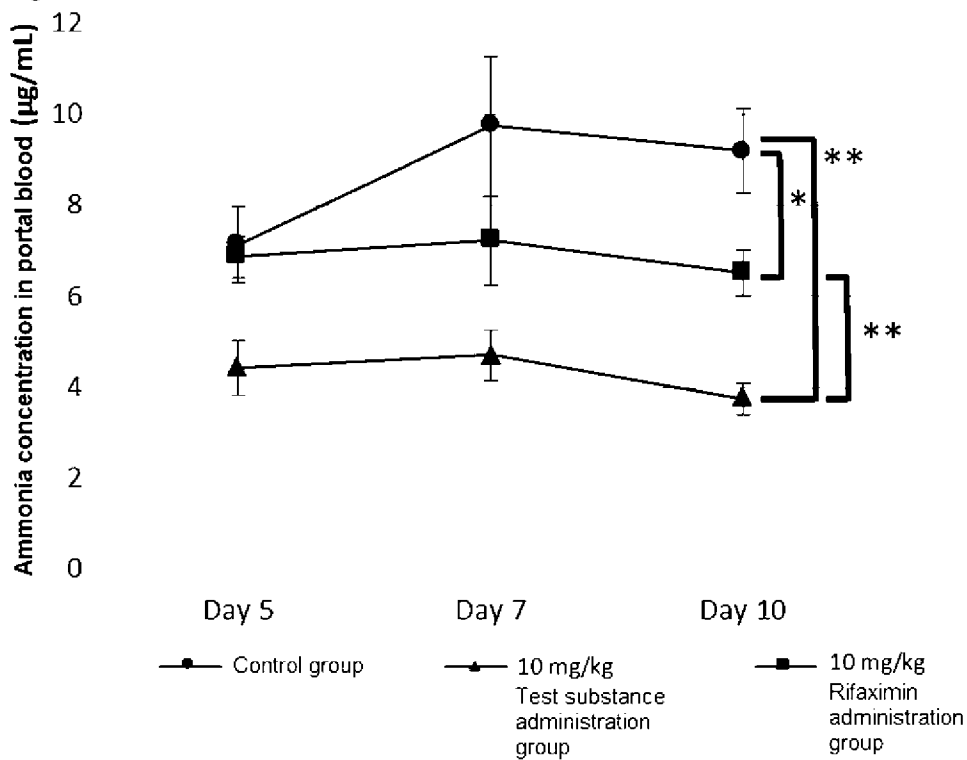
- [Claim 1] A medicament for treating and/or preventing hepatic encephalopathy, comprising
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof as an active ingredient.
- [Claim 2] The medicament of claim 1, wherein the metabolite is
(2S,3S,4S,5R,6R)-6-((7-amino-5-cyanopyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carbonyl)oxo)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid,
7-(6-amino-5-carbamoylpyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, or ethyl
7-(6-amino-5-cyanopyridin-3-yl)-1-cyclopropyl-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate.
- [Claim 3] The medicament of claim 1 or 2, which is for oral administration.
- [Claim 4] The medicament of any one of claims 1 - 3, wherein the daily dose of the active ingredient is 0.5 mg - 6000 mg.
- [Claim 5] A method for treating and/or preventing hepatic encephalopathy, comprising administering a therapeutically effective amount of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof as an active ingredient to a patient in need thereof.
- [Claim 6] Use of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof in the manufacture of a medicament for treating and/or preventing hepatic encephalopathy.
- [Claim 7] 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(2-amino-3-cyano-5-pyridyl)-4-oxo-3-quinoline-carboxylic acid or a pharmaceutically acceptable salt thereof or a metabolite thereof for use in treating and/or preventing hepatic encephalopathy.

[Fig. 1]



N = 8, $\pm$ SEM

[Fig. 2]



N = 5, $\pm$ SEM

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2021/004730

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4709 A61P1/16 A61P25/00
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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2013/029548 A1 (OTSUKA PHARMA CO LTD [JP]; ABUDUSAIMI MAMUTI [CN] ET AL.) 7 March 2013 (2013-03-07) cited in the application page 1, line 21 - page 2, line 3 page 105; compounds 2-18 ----- -/--	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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Date of the actual completion of the international search

26 April 2021

Date of mailing of the international search report

06/05/2021

Name and mailing address of the ISA/

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Authorized officer

Hoff, Philippe

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2021/004730

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BASS N M: "Review article: the current pharmacological therapies for hepatic encephalopathy", ALIMENTARY PHARMACOLOGY & THERAPEUTICS, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, GB, vol. 25, no. SUPPL 1, 1 February 2007 (2007-02-01), pages 23-31, XP002669397, ISSN: 0269-2813, DOI: 10.1111/J.1746-6342.2006.03218.X [retrieved on 2007-01-23] the whole document -----	1-7
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2021/004730

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