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(54) Title: TREATMENT FOR NONALCOHOLIC STEATOHEPATITIS AND FIBROSIS

(57) Abstract: The present invention provides a method for treating nonalcoholic steatohepatitis comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6- (4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a patient.

Treatment for Nonalcoholic Steatohepatitis and Fibrosis

Nonalcoholic steatohepatitis is a liver disease with an etiological constellation characterized by macrovesicular hepatic steatosis, inflammation hepatocyte ballooning and fibrosis. Nonalcoholic steatohepatitis occurs in people who drink little or no alcohol and is often comorbid with obesity, type II diabetes, elevated levels of cholesterol, and triglycerides. Nonalcoholic steatohepatitis may lead to cirrhosis and liver failure. It has been established that patients with nonalcoholic steatohepatitis are more likely to develop cirrhosis, and have a higher risk of cardiovascular mortality, and hepatocyte carcinoma. This non-alcoholic, non-viral cirrhosis is, in fact, among the top causes of liver transplantation.

Nonalcoholic steatohepatitis is a progressive disease characterized by the development of liver fibrosis. The stage of disease can be defined, for example, by the nonalcoholic steatohepatitis CRN (Clinical Research Network) fibrosis staging which measures the amount and pattern of nonalcoholic steatohepatitis fibrosis, as well as parenchymal architectural remodeling in a patient. Nonalcoholic steatohepatitis is typically diagnosed in a human patient using liver biopsy.

Currently, there is no approved pharmaceutical medicament specifically for the treatment of nonalcoholic steatohepatitis. Current nonalcoholic steatohepatitis patient recommendations include weight loss, diet, and exercise. There is a need for pharmaceutical medicaments to offer additional treatment options for patients suffering from nonalcoholic steatohepatitis.

The present invention provides a pharmaceutical treatment for nonalcoholic steatohepatitis comprising administering an effective amount of the compound, (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol to a patient.

The compound, (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, is disclosed in WO 2011/123372 as Example 20a. Compounds of WO 2011/123372 are stated to be agonists of the cannabinoid receptor 2 (CB2 receptor) *in vitro* and useful for treatment or prevention of pain.

The present invention provides a method for treating nonalcoholic steatohepatitis, comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-

(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a patient.

The present invention provides a method for treating nonalcoholic steatohepatitis and fibrosis, comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a patient.

The present invention provides a method for treating nonalcoholic steatohepatitis, comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol to a patient.

The present invention provides the compound (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or pharmaceutically acceptable salt thereof, for use in treating nonalcoholic steatohepatitis in a patient.

The present invention provides the compound (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or pharmaceutically acceptable salt thereof, for use in treating nonalcoholic steatohepatitis and fibrosis in a patient.

The present invention provides the compound (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, for use in treating nonalcoholic steatohepatitis in a patient.

The present invention provides the compound (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or pharmaceutically acceptable salt thereof, for use in treating hepatic fibrosis in a mammal.

The present invention provides a pharmaceutical composition for use in the treatment of nonalcoholic steatohepatitis comprising (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol , or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

The present invention provides a pharmaceutical composition for use in the treatment of nonalcoholic steatohepatitis and fibrosis comprising (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

The present invention provides the use of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of nonalcoholic steatohepatitis.

The present invention provides the use of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of nonalcoholic steatohepatitis and fibrosis.

The present invention provides the use of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of hepatic fibrosis.

The present invention provides a method for treating hepatic fibrosis, comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a mammal.

Figure 1 illustrates the liver excision used in the pathological analysis for the 3H-Z mouse model for nonalcoholic steatohepatitis and fibrosis.

Figure 2 represents the decrease in perisinusoidal fibrosis when (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, is dosed at 3 and 10 mg/kg in the 3H-Z mouse model for nonalcoholic steatohepatitis and fibrosis .

Figure 3 represents the decrease in portal fibrosis when (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, is dosed at 3 and 10 mg/kg in the 3H-Z mouse model for nonalcoholic steatohepatitisand fibrosis.

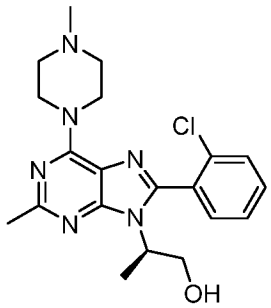
Figure 4 represents the results from the nonalcoholic steatohepatitis and fibrosis development model in high fat diet fed LDLr-/- Leiden Mice showing decrease in fibrosis by pathological scoring with 30 mg/kg (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol.

Figure 5 represents the results from the nonalcoholic steatohepatitis and fibrosis development model in high fat diet fed LDLr-/- Leiden Mice showing decrease in fibrosis by Sirius red staining with 30 mg/kg (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol.

Figure 6 represents the results from the nonalcoholic steatohepatitis and fibrosis development model in high fat diet fed LDLr-/- Leiden Mice showing the total collagen content as determined by quantitative analysis of hydroxyproline in liver homogenates with 30 mg/kg (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol.

Figure 7 represents the reduced liver fibrosis from the CCl_4 mouse model with 30 mg/kg (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol.

The compound, (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol has the following structural formula:



.

The artisan can readily prepare the compound using the methods set forth in WO 2011/123372.

The term "treating" (or "treat" or "treatment") as used herein refers to restraining, slowing, or stopping the progression or alleviating the severity of the stated condition to be treated.

As used herein, the term "effective amount" refers to the amount or dose of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, which upon single or multiple dose administration to the patient, provides the desired effect in the patient. It will be understood that the amount of active agent actually administered will be determined by a physician, in light of the relevant circumstances.

As used herein, "patient" refers to a mammal in need of treatment for nonalcoholic steatohepatitis. In a preferred embodiment, the patient is a mammal.

In a preferred embodiment, "mammal" is a human. In a preferred embodiment the mammal is a human in need of treatment for nonalcoholic steatohepatitis and fibrosis.

(2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, is preferably formulated as a pharmaceutical composition administered by any route which makes the compound bioavailable. Most preferably, such composition is for oral administration. Such pharmaceutical compositions and processes for preparing the same are well known in the art. *See, e.g., Remington: The Science and Practice of Pharmacy* (D.B. Troy, Editor, 21st Edition, Lippincott, Williams & Wilkins, 2006).

Study of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, in Mouse Model of Nonalcoholic steatohepatitis and Fibrosis Induced by 3H Diet

Male C57BL/6N mice are fed with D09100301 diet (Research Diets, 40% fat, 2% cholesterol, 24% fructose, 3H diet) for 150 days. Each mouse is then singly housed after 5 days of acclimation period. Plasma alanine aminotransferase (ALT) and CK18 are measured. After one week of acclimation, the mice are randomized into groups (Table 1) by their ALT, CK18 and body weight. (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, is represented in Table 1 as LY3038404.

Table 1.

Group	Animal Number	Dietary Rx	Compound Rx	Dose (mg/kg)	Rx Time (week)
A	10	Chow	Vehicle	N/A	11
B	15	D09100301	Vehicle	N/A	11
C	15	D09100301	LY3038404	3	11
D	15	D09100301	LY3038404	10	11

Animals of each group (Table 1) are administrated either vehicle (0.5% Methylcellulose (MC) + 0.25% Tween 80 in distilled water) or 3 mg/kg or 10 mg/kg dose of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, once daily in a volume of 5 ml/kg for 11 weeks. Animals are sacrificed. Livers are excised according to Figure 1. Section 2 of the left and right lobes are fixed in

neutral buffered 10% formalin. H&E, Sirius red and Masson's Trichrome slides are prepared for pathological analysis.

All slides are examined microscopically with left lateral lobes oriented at the top of the slide (left by the label) and right lateral lobes at the bottom of the slide. Scores are based on the grading scheme and end-points as described below. Group means are then calculated for each individual end-point as well as overall sum score (total possible for sum = 20). The following endpoints are used to characterize the fast food model of nonalcoholic steatohepatitis in mice as modified from nonalcoholic steatohepatitis endpoints from Brunt, et al (1999, 2009), Charlton, et al (2011), Takahashi Y., et al (2012), Liedtke C., et al (2013), Starkel P. (2011), Riordan JD, et al (2014) as a modified Brunt score (NASH Activity Score):

Inflammation: Number of inflammatory foci per 10 fields on 20x magnification. Most often neutrophils but macrophages, lymphocytes, and eosinophils may also be present. Lipogranulomas reported as 'present' with no grade given.

Grades 0-3

0 = no inflammatory foci present

1 = 1-2 foci per 20x field

2 = 2- $\leq$4 foci per 20x field

3 = > 4 foci per 20x field

Steatosis (macrovesicular vacuolation / steatosis): Large, discrete vacuoles that can be somewhat variable in size and distort hepatocytes. Zonal distribution or pattern is noted if a predominating pattern is present. Microvesicular vacuolation / steatosis is also graded similarly, but is not included in the overall sum NASH score.

Grades 0-3

0 = no macrovesicular vacuolation / steatosis observed

1 = $\leq$ 33 %

2 = 34% – 66%

3 = > 66%

Ballooning Degeneration: Hepatocytes that have lost normal integrity and should have lost cellular or nuclear detail. May have clearing within cytoplasm (but is not a vacuole)

or even be apoptosis / single cell necrosis. Disarray or disorganized hepatic cords may be observed as a result of this 'drop out' of cells.

Grades 0-3

0 = no degeneration observed

1 = ≤ 33 %

2 = 34% – 66%

3 = > 66%

Fibrosis: Accounting for zone location (specifically zone 3/perisinusoidal), and patterns of fibrosis, increase of connective tissue deposition, and architectural remodeling (progression).

- Perisinusoidal fibrosis (chicken wire fibrosis):

  Grades 0-3

  0 = no fibrosis observed

  1 = ≤ 33 %

  2 = 34% – 66%

  3 = > 66%

- Portal fibrosis:

  Grades 0-4

  0 = no fibrosis observed

  1 = expanded portal areas

  2 = periportal fibrosis

  3 = bridging fibrosis

  4 = cirrhosis

- Bridging fibrosis:

  Grades 0-4

  0 = no fibrosis observed

  1 = 1 focus

  2 = > 1 focus with no nodularity

  3 = bridging fibrosis with nodular remodeling

4 = cirrhosis

Pathological evaluation supports that (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, can be useful for treating nonalcoholic steatohepatitis. As represented by Figures 2 and 3, (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, decreases liver fibrosis at a dose of 3 and 10 mg/kg.

Nonalcoholic steatohepatitis and Fibrosis Development in High Fat Diet Fed LDLr-/- Leiden Mice

Male LDLr-/-.Leiden mice are fed a high fat diet (HFD) during a 20 week run-in period. After the run-in period mice are matched into 6 groups of 15 mice based on body weight (primary matching parameter), cholesterol, triglycerides, glucose and insulin measured at t=20 weeks. Obeticholic acid (OCA) is used as a positive control for this nonalcoholic steatohepatitis and fibrosis development model in high fat diet fed LDLr-/- Leiden Mice. OCA is a semi-synthetic bile acid analogue currently in clinical trials for use in the treatment of nonalcoholic steatohepatitis and used in these studies as a control. OCA has the chemical name 6α-ethyl-chenodeoxycholic acid and is known to be a highly potent farnesoid X receptor (FXR) agonist. The animals are then fed with high fed diet (HFD, control), 10 mg/kg/day of obeticholic acid (OCA, positive control) mixed in HFD, or 30 mg/kg/day (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, mixed in HFD. After 14 weeks of treatment, mice are sacrificed (un-fasted). The liver is isolated and total liver weight is determined. The medial lobe is isolated, fixed in formalin and embedded in paraffin for histological evaluation. Formalin-fixed and paraffin-embedded cross-sections (3 μm) are stained with haematoxylin and eosin and are scored blindly by a board-certified pathologist using an adapted grading method for human nonalcoholic steatohepatitis (Liang et al, PLoS ONE 2014). Briefly, two cross-sections/mouse are examined and the level of microvesicular and macrovesicular steatosis are determined relative to the liver area analyzed (expressed as a percentage). Hepatic inflammation is assessed by counting the number of inflammatory foci per field at a 100× magnification (view size 3.1 mm2) in five non-overlapping fields per specimen, expressed as total number of foci. Fibrosis is assessed histochemically by Picro-Sirius Red staining (Chroma, WALDECK-Gmbh, Münster,

Germany). The development of fibrosis is assessed by a pathologist to gain insight into the distribution pattern of the collagen and to quantify the percentage of pericellular fibrosis specifically. The total collagen content is determined by quantitative analysis of hydroxyproline in liver homogenate using a commercial colorimetric assay (QZBtotcol; Quickzyme Biosciences, Leiden, the Netherlands). (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, significantly reduces liver fibrosis and total collagen in the nonalcoholic steatohepatitis model at a 30 mg/kg /day food mixture dosing. Figures 4 and 5 represent the results from the nonalcoholic steatohepatitis and fibrosis development model in high fat diet fed LDLr-/- Leiden Mice showing decrease in fibrosis by pathological scoring with 30 mg/kg (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, .

Figure 6 represents the total collagen content as determined by quantitative analysis of hydroxyproline in liver homogenates with 30 mg/kg (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol.

Study of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol in the CCl_4 induced Liver Fibrosis Model in BALB/c Mice

Female, 7-8 week old, BALB/c mice are acclimated for no less than 7 days. After the acclimation period, 15 untreated mice are allocated as sham or control group. Other mice are administered CCl_4 for a total period of 6 weeks to establish liver fibrosis. The CCl_4 is injected intraperitoneally (i.p.) at 1 mL/kg (4 mL/kg of 25% CCl_4 in olive oil), twice per week for a total period of 6 weeks except the sham control group. The CCl_4 treated mice are randomly grouped (n=15) and for treatment with vehicle (0.5% HEC (hydroxy ethyl cellulose)/ 0.25% tween80) or test compound (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, (30 mg/kg, QD (4 times a day), p.o. (orally)) coinciding with the beginning of CCl_4 administration and to continue throughout the entire study. Animals are sacrificed at 6 weeks. Liver tissue is flushed with ice-cold PBS (phosphate buffered saline), blotted briefly on paper towel, and weighed. Liver tissue is dissected into pieces and is fixed with 10% buffered neutral formalin for histopathology and immunohistochemistry (IHC) analysis, and then they are embedded in paraffin. Thin sections (4 μm) are deparaffinized and stains prepared using

picro-Sirius red for 15 min at room temperature. Sections on the slides are dehydrated in 95% and 100% ethanol and in xylene, and are mounted with mounting medium. The liver fibrosis tissue and the total liver tissue are measured using Picrosirius Red stained sections. Histomorphometry are performed using an OsteoMeasure image analysis software program (OsteoMetrics, Inc., Atlanta, GA) interfaced with an Olympus light/epifluorescent microscope and video subsystem. The histomorphometrist is blinded as to specimen identity when performing measurements. Liver tissue is flushed with ice-cold PBS (phosphate buffered saline), blotted briefly on paper towel, and weighed. Liver tissue is dissected into pieces and is fixed with 10% buffered neutral formalin for histopathology and immunohistochemistry (IHC) analysis, and then they are embedded in paraffin. Thin sections (4 μm) are deparaffinized and stains prepared using picro-Sirius red for 15 min at room temperature. Sections on the slides are dehydrated in 95% and 100% ethanol and in xylene, and are mounted with mounting medium. The liver fibrosis tissue and the total liver tissue are measured using Picrosirius Red stained sections. Histomorphometry are performed using an OsteoMeasure image analysis software program (OsteoMetrics, Inc., Atlanta, GA) interfaced with an Olympus light/epifluorescent microscope and video subsystem. The histomorphometrist is blinded as to specimen identity when performing measurements. As represented by Figure 7, (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol statistically significantly reduces % liver fibrosis in the CCl_4 mouse model at a dose of 30 mg/kg.

WE CLAIM:

1. A method for treating nonalcoholic steatohepatitis, comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a patient.

2. The method of Claim 1 wherein (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, is the free base.

3. The method as claimed by either of Claims 1 or 2 wherein the patient is a mammal.

4. The method as claimed by any one of Claims 1 to 3 wherein the patient is a human.

5. A method for treating nonalcoholic steatohepatitis and fibrosis, comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a patient.

6. The method of Claim 5 wherein (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, is the free base.

7. A method for treating hepatic fibrosis comprising administering an effective amount of (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, to a mammal.

8. (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic steatohepatitis.

9. (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol for use according to Claim 8.

10. (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic steatohepatitis and fibrosis.

11. (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, for use in the treatment of hepatic fibrosis.

12. A pharmaceutical composition for use in the treatment of nonalcoholic steatohepatitis comprising (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

13. A pharmaceutical composition for use in the treatment of nonalcoholic steatohepatitis and fibrosis comprising (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

14. A pharmaceutical composition for use in the treatment of hepatic fibrosis comprising (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

FIG. 1/7

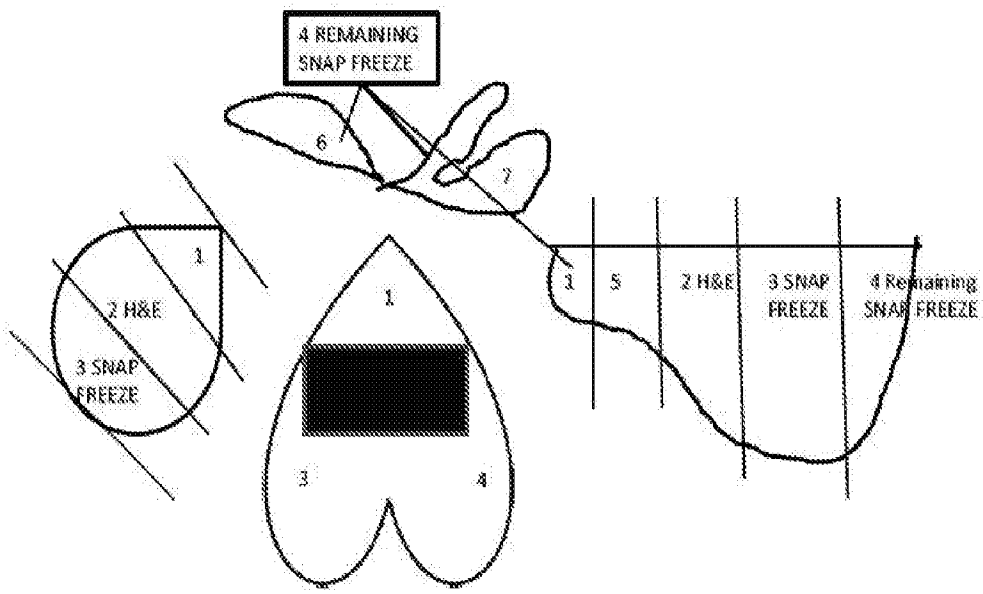
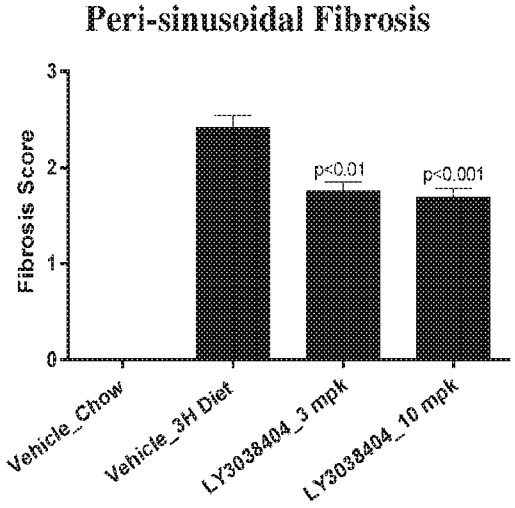
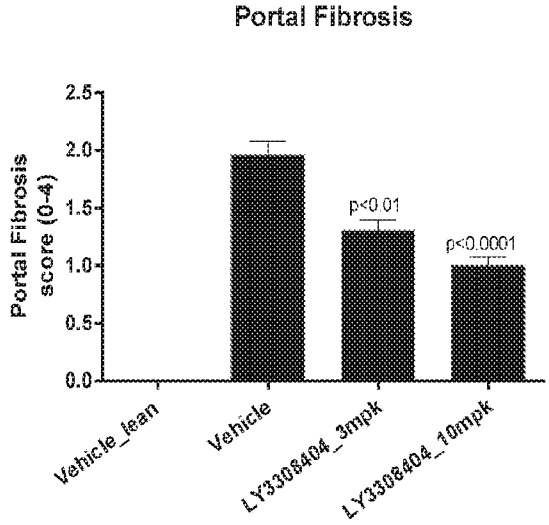

4 REMAINING SNAP FREEZE
6
7
1
2 H&E
3 SNAP FREEZE
1
3
4
1
5
2 H&E
3 SNAP FREEZE
4 Remaining SNAP FREEZE

FIG. 2/7



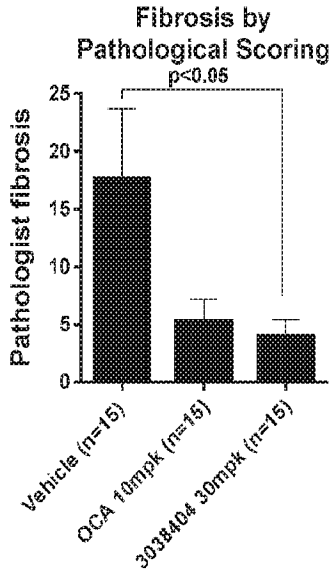
LY3038404: (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol,

FIG. 3/7



LY3038404: (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol,

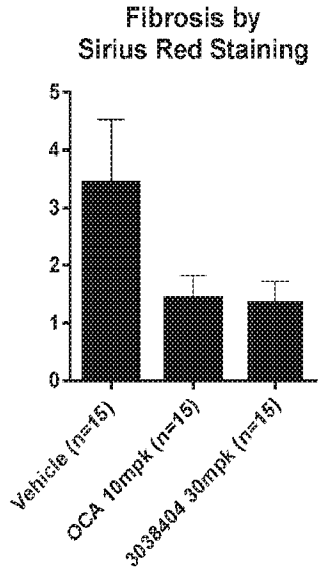
FIG. 4/7



OCA: Obeticholic acid

LY3038404: (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol

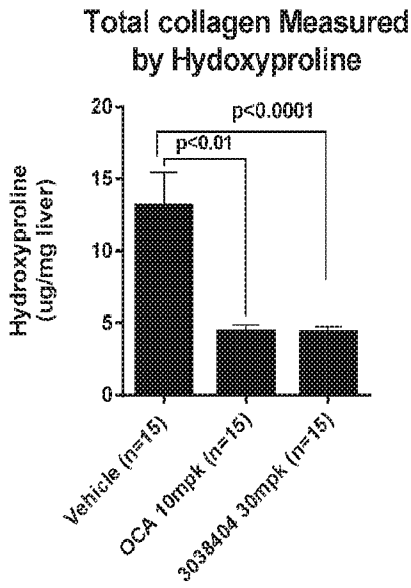
FIG. 5/7



OCA: Obeticholic acid

LY3038404: (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol

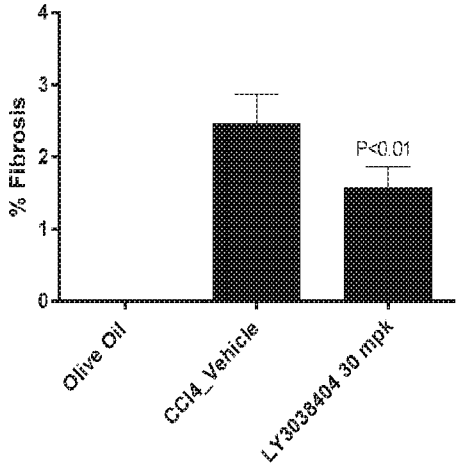
FIG. 6/7



OCA: Obeticholic acid

LY3038404: (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol

FIG. 7/7



LY3038404: (2R)-2-(8-(2-chlorophenyl)-2-methyl-6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propan-1-ol

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/027307

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/52 A61P3/00
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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/143448 A1 (GRENARD PASCALE [FR] ET AL) 30 June 2005 (2005-06-30) claims	1-14
Y	WO 2011/123372 A1 (LILLY CO ELI [US]; ASTLES PETER CHARLES [GB]; GUIDETTI ROSSELLA [GB];) 6 October 2011 (2011-10-06) cited in the application example 20	1-14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2017	23/06/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Zimmer, Barbara

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/027307

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIPING ZHANG ET AL: "Cannabinoid receptor 2 agonist attenuates pain related behavior in rats with chronic alcohol/high fat diet induced pancreatitis", MOLECULAR PAIN, BIOMED CENTRAL, LONDON, GB, vol. 10, no. 1, 17 November 2014 (2014-11-17), page 66, XP021203516, ISSN: 1744-8069, DOI: 10.1186/1744-8069-10-66 page 1 - page 2	1-14
A	MALLAT ARIANE ET AL: "Cannabinoid signaling and liver therapeutics", JOURNAL OF HEPATOLOGY, vol. 59, no. 4, 2013, pages 891-896, XP028731501, ISSN: 0168-8278, DOI: 10.1016/J.JHEP.2013.03.032 page 895	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/027307

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