TREATMENT OF LIVER DISORDERS WITH A THR-β AGONIST

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to PCT/CN2021/130083, filed on November 11, 2021, and PCT/CN2022/097426 filed on 6/7/2022. The contents of the aforementioned patent applications are incorporated herein by reference in their entirety for all purposes.

FIELD OF THE INVENTION

[0002] This invention relates to methods and compositions for treating liver disorder in a patient.

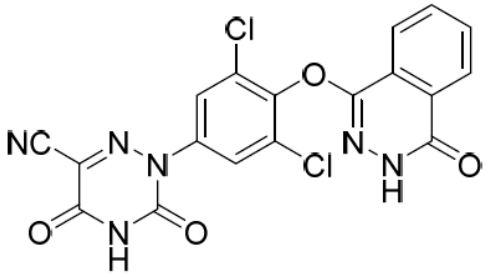
BACKGROUND

[0003] Fatty liver disease (FLD) encompasses a spectrum of disease states characterized by excessive accumulation of fat in the liver often accompanied with inflammation. FLD can lead to non-alcoholic fatty liver disease (NAFLD), which may be characterized by insulin resistance. If untreated, NAFLD can progress to a persistent inflammatory response or non-alcoholic steatohepatitis (NASH), progressive liver fibrosis, and eventually to cirrhosis. In Europe and the US, NAFLD is the second most common reason for liver transplantation. Accordingly, the need for treatment is urgent, but due to the lack of obvious symptoms to the patient, patients may lack the motivation to maintain treatment regimens, particularly burdensome treatment regimens, such as injected medicines, medications that are administered many times a day, or any that produce dangerous or irritating side effects. There is currently no approved treatment of NASH.

[0004] Thyroid hormone receptor-beta (THR-β) agonists have recently been investigated in the treatment of liver disease, including NASH. THR-β is the major form of THR in the liver and plays a key role in energy balance and metabolism of fatty acids and lipids, whereas THR-α predominates in the heart and is responsible for most of the unwanted cardiovascular effects of thyroid hormone stimulation. A significant problem to overcome involves developing a THR-β agonist for treating NASH that will not produce undesirable side effects associated with THR-α agonism.

BRIEF SUMMARY

[0004a] In an aspect of the present disclosure, there is provided a use of a compound of formula:



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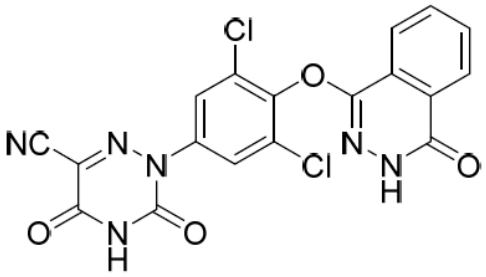
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a patient in need thereof, wherein the compound or a pharmaceutically acceptable salt thereof is to be orally administered to the patient once daily at a dose of from about 0.5 mg to about 25 mg.

[0004b] In another aspect of the present disclosure, there is provided a use of a compound of formula:



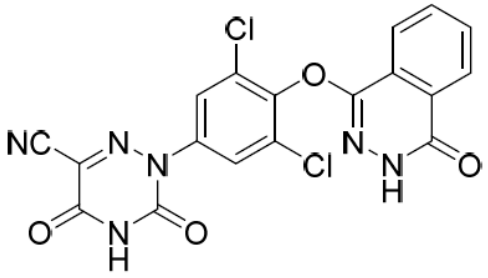
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a patient in need thereof, wherein the compound or a pharmaceutically acceptable salt thereof is to be orally administered to the patient to obtain a steady state area under the curve from zero to infinity ($AUC_{0-\infty}$) of:

(i) from about 2,500 ng*h/mL to about 50,000 ng*h/mL;

(ii) from about 5,000 ng*h/mL to about 50,000 ng*h/mL; and/or

(iii) from about 5,000 ng*h/mL to about 25,000 ng*h/mL.

[0004c] In a further aspect of the present disclosure, there is provided a crystalline potassium salt of a compound of formula:



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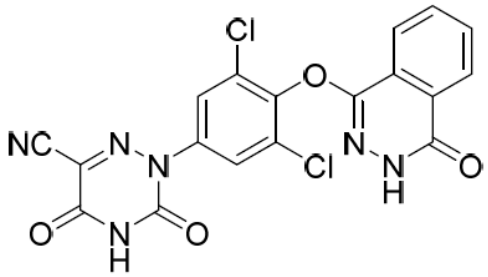
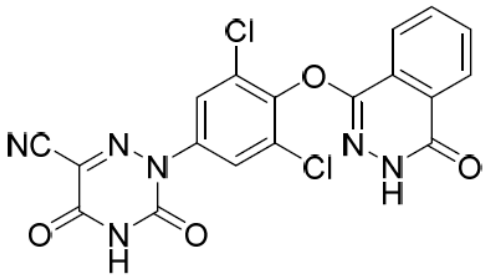
[0004d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein.

[0004e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising, a compound of formula:



or a pharmaceutically acceptable salt thereof and sodium lauryl sulfate.

[0004f] In another aspect of the present disclosure, there is provided a crystalline potassium salt of a compound of formula:



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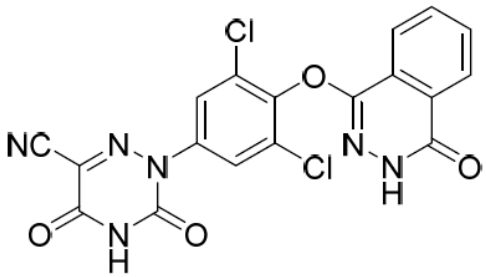
having an XRPD spectrum substantially as shown in FIG. 16.

[0004g] In a further aspect of the present disclosure, there is provided a crystalline potassium salt of a compound of formula:



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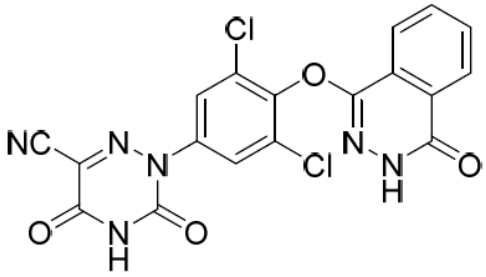
having an XRPD spectrum comprising peaks at angles 2-theta of 6.78±0.20, 11.35±0.20, and 20.51±0.20 degrees.

[0004h] In another aspect of the present disclosure, there is provided a crystalline sodium salt of a compound of formula:



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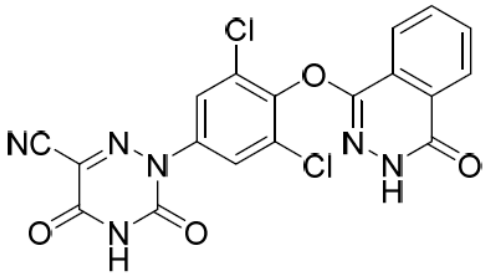
having an XRPD spectrum substantially as shown in FIG. 18.

[0004i] In a further aspect of the present disclosure, there is provided a crystalline sodium salt of a compound of formula:



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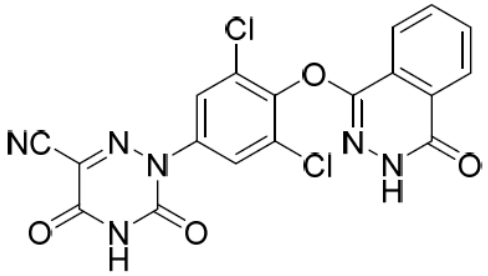
having an XRPD spectrum comprising peaks at angles 2-theta of 5.51±0.20, 8.47±0.20, and 16.57±0.20 degrees.

[0005] Provided herein are methods and compositions for treating a liver disorder in a patient in need thereof. The methods comprise administering to the patient the thyroid

hormone receptor beta (THR-β) agonist referred to herein as Compound 1, or a pharmaceutically acceptable salt thereof.



Compound 1

Compound 1, which has the chemical name 2-(3,5-dichloro-4-((4-oxo-3,4-dihydrophthalazin-1-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-nitrile, was described in US Patent No. 11,084,802, which is incorporated herein by reference in its entirety.

[0006] Inventors have discovered that Compound 1 or a pharmaceutically acceptable thereof, can be administered to patients suffering from liver disorders at surprisingly low doses while still maintaining the desired level of efficacy. As a result, Compound 1 can be used to treat liver disorders without the undesirable side effects generally associated with THR agonism.

[0007] In some examples of the disclosure, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered to patients orally once daily at doses as low as 1 mg or less and still sufficiently reduce amine oxidase activity and reduce lymphocyte adhesion and transmigration. For example, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of from about 1 mg to about 60 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of from about 0.5 mg to about 25 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of from about 1 mg to about 15 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of from about 3 mg to about 10 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 1 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 3 mg. In some examples,

Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 4 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 5 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 6 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 10 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 15 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 20 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 30 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 50 mg. In some examples, Compound 1, or a pharmaceutically acceptable salt thereof, can be administered orally once daily to a patient with a liver disorder (e.g. NASH) at a dose of about 60 mg.

[0008] In another example, the disclosure provide methods of treating or preventing NASH in a patient in need thereof, said method comprising administering to the patient a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof. In one example, the patient in need thereof is a patient that suffers from fatty liver disease such as NAFLD. In another example, the patient in need thereof is a patient that suffers from metabolic syndrome.

[0009] In one example, the disclosure provides methods of reducing hepatic inflammation in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof. The reduction of hepatic inflammation is characterized by reduced expression of inflammatory genes and markers of leukocyte activation in the liver. In some examples, hepatic inflammation is reduced without increasing the low-density lipoprotein cholesterol (LDL-C) levels in the blood of the patient.

[0010] In another example, the disclosure provides methods of treating a disease or condition characterized by fibrosis of the liver, comprising administering to the patient a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof. The reduction of fibrosis is characterized by histological improvement and reduced expression of pro-fibrotic genes in the liver. In some examples, hepatic fibrosis is reduced without increasing the low-density lipoprotein cholesterol (LDL-C) levels in the blood of the patient. In some examples, administration of Compound 1, or a pharmaceutically acceptable salt thereof, results in reduction of liver fibrosis and hepatic inflammation.

[0011] In some examples, the patient has a liver disorder and diabetes mellitus. In some examples, the patient has a liver disorder and a cardiovascular disorder. In some examples, the treatment period is the remaining lifespan of the patient. In some examples, the method does not comprise administering an antihistamine, an immunosuppressant, a steroid, rifampicin, an opioid antagonist, or a selective serotonin reuptake inhibitor (SSRI).

[0012] In some examples, Compound 1 is administered to the patient as a pharmaceutically acceptable salt. In some examples, the pharmaceutically acceptable salt is a potassium salt. In some examples, the pharmaceutically acceptable salt is a sodium salt.

[0013] The disclosure also provide novel compositions comprising Compound 1, or a pharmaceutically acceptable salt thereof. Compound 1 has very low aqueous solubility, even when administered in the salt form. It has been found that particular ionic surfactants can effectively solubilize Compound 1, and pharmaceutically salts thereof, with minimal or no degradation of the compound. In some examples, the ionic surfactant is sodium lauryl sulfate. In some such examples, the amount of SLS in the composition is from about 1% to about 8% by weight. In other such examples, the amount of SLS in the composition is about 5% by weight. In some examples, the pharmaceutical composition comprises the potassium salt of Compound 1 and SLS.

BRIEF DESCRIPTION OF THE FIGURES

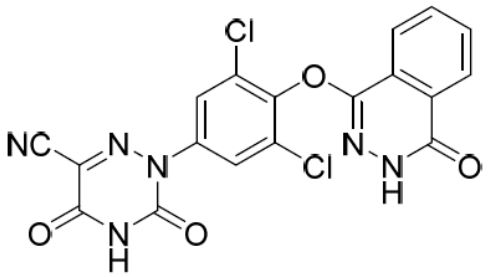
[0014] FIG. 1 shows the plasma concentration of compound 1 in patients up to 72 hours following administration of a single dose of compound 1.

[0015] FIG. 2 shows the area under the curve (AUC_{inf}) and maximum plasma concentration (C_{max}) of compound 1 in patients plotted against the administered dose.

CLAIMS

What is claimed is:

1. Use of a compound of formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a patient in need thereof, wherein the compound or a pharmaceutically acceptable salt thereof is to be orally administered to the patient once daily at a dose of from about 0.5 mg to about 25 mg.

2. The use of claim 1, wherein a dose of from about 1 mg to about 15 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once daily.

3 The use of claim 1, wherein a dose of from about 2 mg to about 10 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once daily.

4 The use of claim 1, wherein a dose of:

(i) about 1 mg;

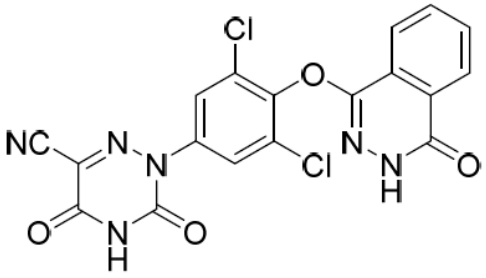
(ii) about 3 mg;

(iii) about 6 mg; or

(iv) about 10 mg,

of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once daily.

5. Use of a compound of formula:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a patient in need thereof, wherein the compound or a pharmaceutically acceptable salt thereof is to be orally administered to the patient to obtain a steady state area under the curve from zero to infinity ($AUC_{0-\infty}$) of:

(i) from about 2,500 ng*h/mL to about 50,000 ng*h/mL;

(ii) from about 5,000 ng*h/mL to about 50,000 ng*h/mL; and/or

(iii) from about 5,000 ng*h/mL to about 25,000 ng*h/mL.

6. The use of claim 5, wherein the compound is to be administered orally once daily.

7. The use of any one of claims 1 to 6, wherein the compound is to be administered as:

(i) a potassium salt; or

(ii) a sodium salt.

8. The use of any one of claims 1 to 7, wherein the compound is to be administered in a pharmaceutical composition comprising an ionic surfactant.

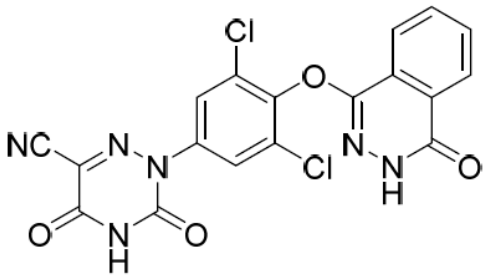
9. The use of claim 8, wherein the ionic surfactant is sodium lauryl sulfate.

10. The use of claim 9, wherein the sodium lauryl sulfate is present in the composition at from about 1% to about 8% by weight.

11. The use of claim 9, wherein the sodium lauryl sulfate is present in the composition at from about 1% to about 5% by weight.

12. The use of claim 9, wherein the sodium lauryl sulfate is present in the composition at about 5% by weight.

13. A crystalline potassium salt of a compound of formula:



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14. The crystalline potassium salt of claim 13 produced by the method of example 8.

15. A pharmaceutical composition comprising the compound of claim 13 or claim 14.

16. The pharmaceutical composition of claim 15, wherein the amount of the compound in the pharmaceutical composition is from about 1 mg to about 15 mg.

17. The pharmaceutical composition of claim 15, wherein the amount of the compound in the pharmaceutical composition is from about 2 mg to about 10 mg.

18. The pharmaceutical composition of claim 15, wherein the amount of the compound in the pharmaceutical composition is:

(i) about 1 mg;

(ii) about 3 mg;

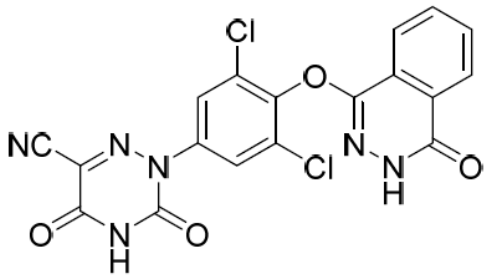
(iii) about 6 mg; or

(iv) about 10 mg.

19. The pharmaceutical composition of any one of claims 15 to 18, further comprising an ionic surfactant.

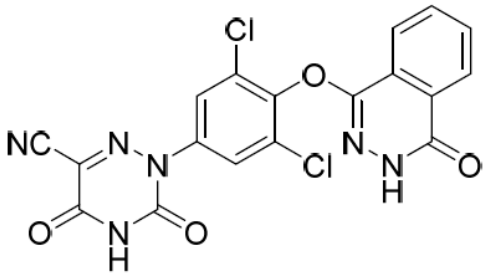
20. The pharmaceutical composition of claim 19, wherein the ionic surfactant is sodium lauryl sulfate.

21. A pharmaceutical composition comprising, a compound of formula:



or a pharmaceutically acceptable salt thereof and sodium lauryl sulfate.

22. A crystalline potassium salt of a compound of formula:



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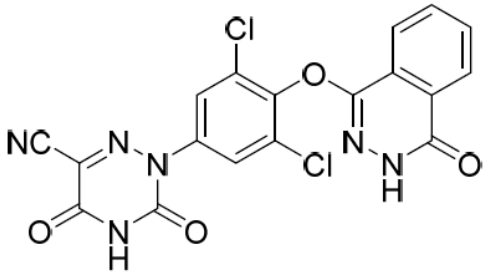
having an XRPD spectrum substantially as shown in FIG. 16.

23. A crystalline potassium salt of a compound of formula:



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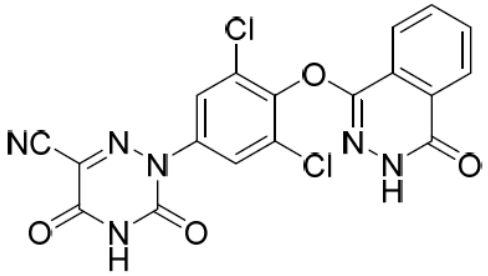
having an XRPD spectrum comprising peaks at angles 2-theta of 6.78±0.20, 11.35±0.20, and 20.51±0.20 degrees.

24. A crystalline sodium salt of a compound of formula:



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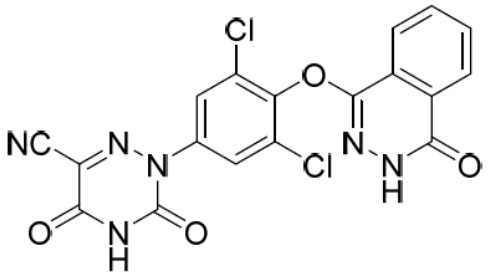
having an XRPD spectrum substantially as shown in FIG. 18.

25. A crystalline sodium salt of a compound of formula:



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having an XRPD spectrum comprising peaks at angles 2-theta of 5.51±0.20, 8.47±0.20, and 16.57±0.20 degrees.