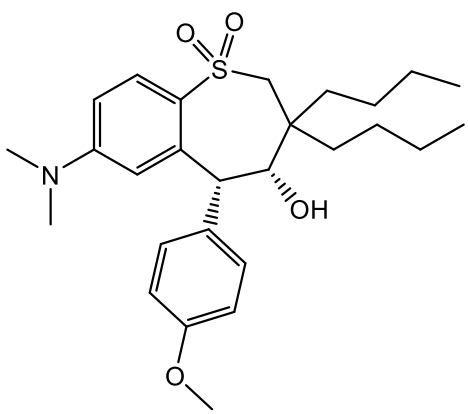
[0006] Thus, there is a need for a novel process of making highly pure maralixibat from highly pure and crystalline compounds there are starting materials or intermediates in order to minimize formations of impurities. Embodiments of the present disclosure are directed to this and other considerations.

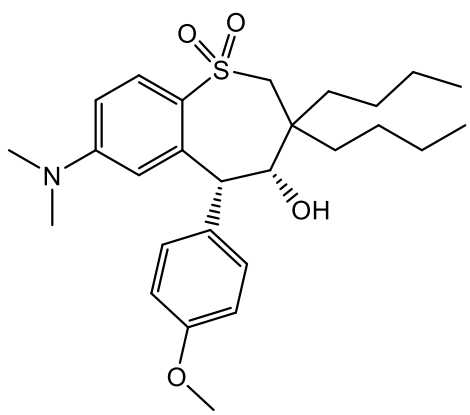
SUMMARY

[0007] Various non-limiting examples of the disclosure are described below.

[0008] Provided herein is a crystalline form of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula I), which is Form A.



(Formula I)

[0008a] In an aspect of the present disclosure, there is provided a crystalline form of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula I)  , which is Form A, characterized by an X-ray powder diffraction diffractogram (XRPD) having a signal of at least three peaks in 2Θ values

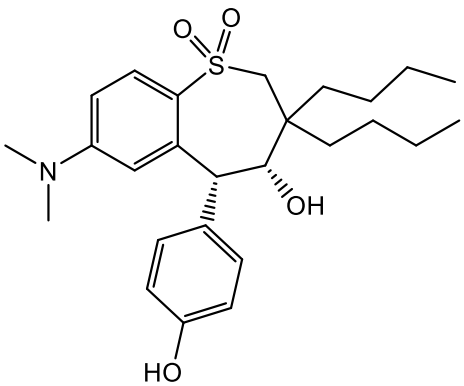
chosen from 4.7 ± 0.2, 6.6 ± 0.2, 9.3 ± 0.2, 10.4 ± 0.2, 13.3 ± 0.2, 16.8 ± 0.2, 19.3 ± 0.2, and 23.4 ± 0.2.

[0008b] In another aspect of the present disclosure, there is provided a process of preparing the crystalline Form A as disclosed herein, said process comprising (a) mixing the compound of Formula I with a solvent.

[0009] Also provided herein is a crystalline form of Formula I, which is Form B.

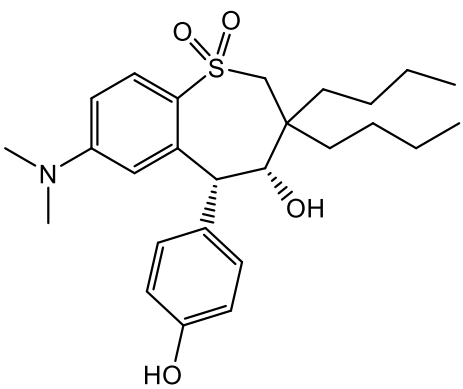
[0010] Also provided herein is a highly pure compound of Formula I, wherein the purity of the compound of Formula I is at least about 95%.

[0011] Also provided herein is a crystalline form of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula II), which is Form X.



(Formula II)

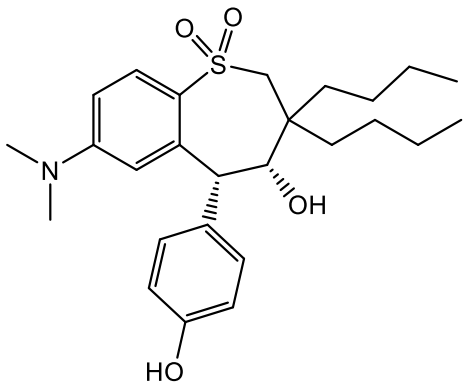
[00011a] In a further aspect of the present disclosure, there is provided a crystalline form of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula II)



(Formula II), which is Form X, characterized by an X-ray powder diffractogram (XRPD) having a signal of at least nine peaks in 2Θ values chosen from 5.0 ± 0.2, 8.7 ± 0.2, 10.0 ± 0.2, 12.5 ± 0.2, 13.3 ± 0.2, 14.9 ± 0.2, 15.8 ± 0.2, 17.0 ± 0.2, 17.8 ± 0.2, 19.3 ± 0.2, 19.9 ± 0.2, 21.7 ± 0.2, 22.6 ± 0.2, 23.2 ± 0.2, 24.5 ± 0.2, 24.9 ± 0.2, 25.8 ± 0.2, 26.4 ± 0.2, 28.0 ± 0.2, and 29.4 ± 0.2.

[0012] Also provided herein is a highly pure compound of Formula II, wherein the purity of the compound of Formula II is at least about 95%.

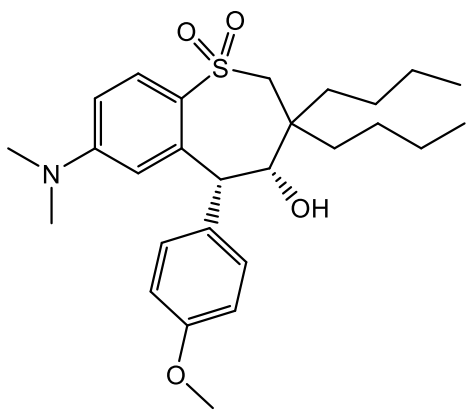
[00012a] In another aspect of the present disclosure, there is provided a highly pure compound (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula II)



(Formula II), wherein the purity of the compound of Formula II is at least about 95%.

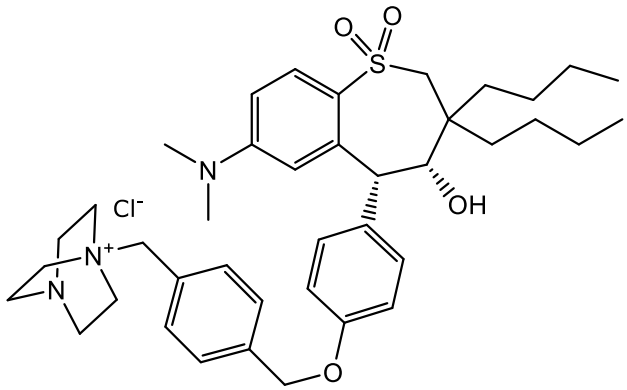
[00012b] In a further aspect of the present disclosure, there is provided a process of preparing the highly pure compound of Formula II as disclosed herein, wherein said process comprises contacting a highly pure compound

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-



tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula I) with DL-methionine to form a mixture, wherein the highly pure compound of Formula I has a purity of at least 95%.

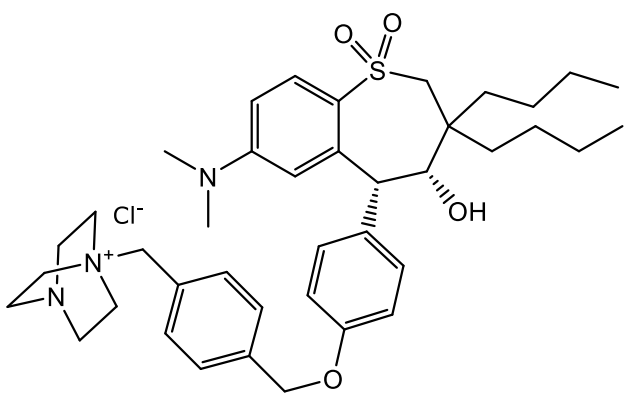
[0013] Also provided herein is an amorphous form of 1-(4-((4-((4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b]thiepin-5-yl)phenoxy)methyl)benzyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (Formula III)



(Formula III) characterized by at least about 80% amorphous content, wherein the amorphous form is characterized by an XRPD pattern substantially similar to that in FIG. 9.

[0014] Also provided herein is a process of making a highly pure compound of Formula III, said process comprising the step of converting a highly pure compound of Formula I to a highly pure compound of Formula II.

[00014a] In another aspect of the present disclosure, there is provided a process of making a highly pure compound 1-(4-((4-((4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b]thiepin-5-yl)phenoxy)methyl)benzyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (Formula III)



(Formula III), said process comprising the step of converting the crystalline Form A as disclosed herein to the crystalline Form X as disclosed herein, wherein the purity of the compound of Formula III is at least about 90%.

[0015] Also provided herein is a highly pure crystalline Form I, Form II, and/or amorphous form of Formula III, wherein the form of Formula III is prepared by a process comprising the step of converting a highly pure crystalline Form A of Formula I to a highly pure crystalline Form X of Formula II.

[0015a] In a further aspect of the present disclosure, there is provided a use of a highly pure crystalline Form II of the compound of Formula III made by the process as disclosed herein in the manufacture of a medicament for treating pruritus or cholestatic liver disease or condition.

[0016] These and other examples of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the invention, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Reference will now be made to the accompanying drawings, which are not necessarily drawn to scale, and which illustrate various implementations, aspects, and principles of the disclosed technology.

[0018] FIG. 1 is a XRPD plot of Form A of compound of Formula I.

[0019] FIG. 2 is a TGA/DSC plot of Form A of compound of Formula I.

[0020] FIG. 3 is a PLM image of Form A of compound of Formula I.

[0021] FIG. 4 is a XRPD plot of Form B of compound of Formula I.

[0022] FIG. 5 is a TGA plot of Form B of compound of Formula I.

[0023] FIG. 6 is a XRPD plot of Form X of compound of Formula II.

[0024] FIG. 7 is a TGA/DSC plot of Form X of compound of Formula II.

[0025] FIG. 8 is a PLM image of Form X of compound of Formula II.

[0026] FIG. 9 is a XRPD plot of amorphous form of compound of Formula III.

[0027] FIG. 10 is a DSC plot of amorphous form of compound of Formula III.

[0028] FIG. 11 is a XRPD plot of Form II of compound of Formula III in comparison to the reference.

[0029] FIG. 12 is a TGA/DSC plot of Form II of compound of Formula III.

[0030] FIG. 13 is a PLM image of Form II of compound of Formula III.

[0031] FIG. 14 is a XRPD plot of Form I of compound of Formula III.

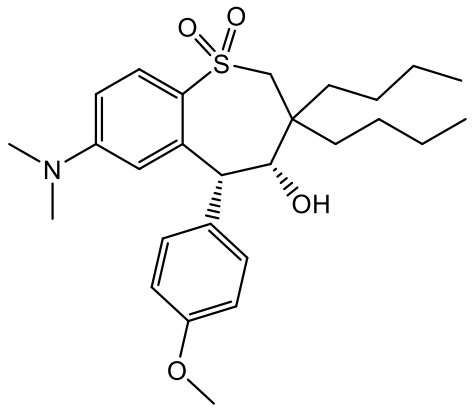
[0032] FIG. 15 is a TGA/DSC plot of Form I of compound of Formula III.

DETAILED DESCRIPTION

[0033] Detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely illustrative of the invention that may be embodied in various forms. In addition, each of the examples given in connection with the various embodiments of the invention is intended to be illustrative, and not restrictive. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present invention.

What is claimed is:

1. A crystalline form of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula I)



, which is Form A, characterized by an X-ray powder diffraction diffractogram (XRPD) having a signal of at least three peaks in 2Θ values chosen from 4.7 ± 0.2, 6.6 ± 0.2, 9.3 ± 0.2, 10.4 ± 0.2, 13.3 ± 0.2, 16.8 ± 0.2, 19.3 ± 0.2, and 23.4 ± 0.2.

2. The crystalline Form A according to claim 1, wherein the crystalline form is characterized by a melting point at about 133 °C to about 135 °C, or wherein the crystalline form is characterized by a DSC thermogram with an endotherm having an onset at about 130.8° C, a peak at about 134.7° C, and an exotherm at about 145° C.

3. The crystalline Form A according to any one of claims 1-2, wherein the crystalline form has no weight loss between about 25 °C to about 225 °C as measured by thermogravimetric analysis (TGA).

4. The crystalline Form A according to any one of claims 1-3, wherein the crystalline form comprises rod-shaped crystals as observed by polarized light microscopy.

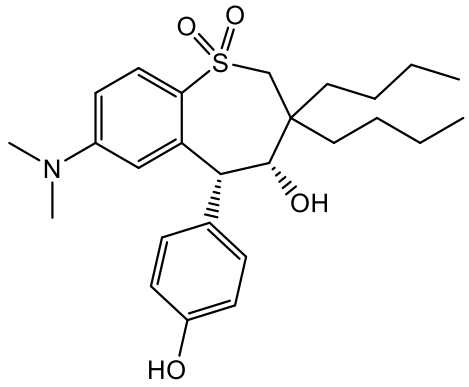
5. The crystalline Form A according to any one of claims 1-4, wherein at least about 95% of the crystalline form is the R,R stereoisomer.

6. The crystalline Form A according to any one of claims 1-5, wherein the purity of the compound of Formula I is at least about 95%.

7. A process of preparing the crystalline Form A according to any of claims 1-6, said process comprising (a) mixing the compound of Formula I with a solvent.

8. The process of claim 7, wherein step (a) further comprises obtaining a clear solution of the mixture, and the process further comprises (b) adding an antisolvent.

9. A crystalline form of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula II)



(Formula II), which is Form X, characterized by an X-ray powder diffractogram (XRPD) having a signal of at least nine peaks in 2Θ values chosen from 5.0 ± 0.2, 8.7 ± 0.2, 10.0 ± 0.2, 12.5 ± 0.2, 13.3 ± 0.2, 14.9 ± 0.2, 15.8 ± 0.2, 17.0 ± 0.2, 17.8 ± 0.2, 19.3 ± 0.2, 19.9 ± 0.2, 21.7 ± 0.2, 22.6 ± 0.2, 23.2 ± 0.2, 24.5 ± 0.2, 24.9 ± 0.2, 25.8 ± 0.2, 26.4 ± 0.2, 28.0 ± 0.2, and 29.4 ± 0.2.

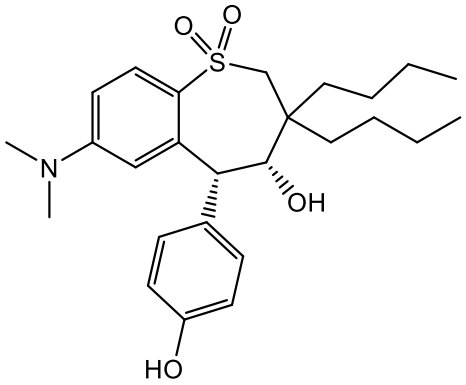
10. The crystalline Form X according to claim 9, wherein the crystalline form is characterized by a melting point at about 216.7 °C to about 217.7 °C, or wherein the crystalline form is characterized by a DSC thermogram with an endotherm having an onset at about 216.1 °C, a peak at about 217.2 °C, and an exotherm at about 218.3 °C.

11. The crystalline Form X according to any one of claims 9-10, wherein the crystalline form has less than about 0.1% weight loss between about 95.1 °C to about 200.0 °C as measured by thermogravimetric analysis (TGA).

12. The crystalline Form X according to any one of claims 9-11, wherein the crystalline form comprises rod-shaped crystals as observed by polarized light microscopy.

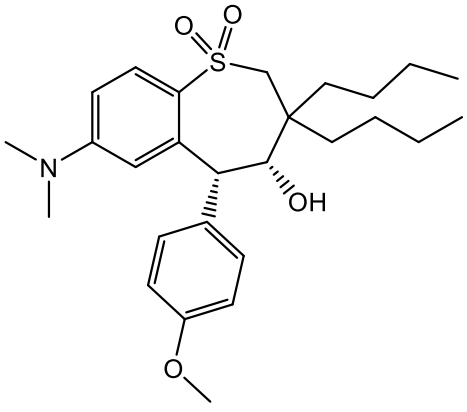
13. The crystalline Form X according to any one of claims 9-12, wherein at least about 95% of the crystalline form is the R,R stereoisomer.

14. A highly pure compound (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula II)



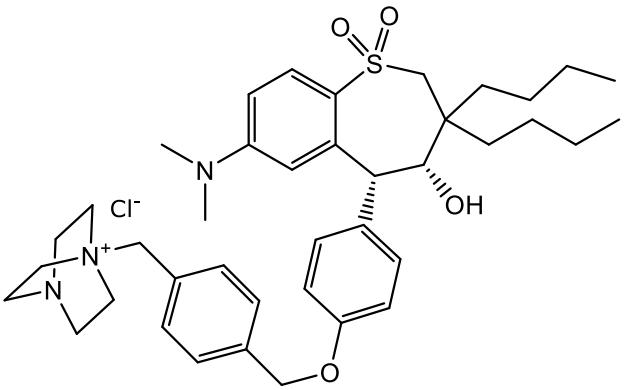
(Formula II), wherein the purity of the compound of Formula II is at least about 95%.

15. A process of preparing the highly pure compound of Formula II according to claim 14, wherein said process comprises contacting a highly pure compound (4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-



tetrahydrobenzo[b]thiepine 1,1-dioxide (Formula I) with DL-methionine to form a mixture, wherein the highly pure compound of Formula I has a purity of at least 95%.

16. A process of making a highly pure compound 1-(4-((4-((4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydrobenzo[b]thiepin-5-yl)phenoxy)methyl)benzyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (Formula III)



(Formula III), said process comprising the step of converting the crystalline Form A according to any one of claims 1-6 to the crystalline Form X according to any one of claims 9-13, wherein the purity of the compound of Formula III is at least about 90%.

17. The process of making the highly pure compound of Formula III according to claim 16, wherein the compound of Formula III is in crystalline Form.

18. The process of making the highly pure compound of Formula III according to claim 17, wherein the compound of Formula III is in crystalline Form I.

19. The process of making the highly pure compound of Formula III according to claim 17, wherein the compound of Formula III is in crystalline Form II.

20. Use of a highly pure crystalline Form II of the compound of Formula III made by the process according to claim 17 or 19 in the manufacture of a medicament for treating pruritus or cholestatic liver disease or condition.

21. The use of claim 20, wherein the cholestatic liver disease or condition is selected from the group consisting of obstructive cholestasis, non-obstructive cholestasis, extrahepatic cholestasis, intrahepatic cholestasis, primary intrahepatic cholestasis, secondary intrahepatic cholestasis, progressive familial intrahepatic cholestasis (PFIC), PFIC type 1, PFIC type 2, PFIC type 3, benign recurrent intrahepatic cholestasis (BRIC), BRIC type 1, BRIC type 2, BRIC type 3, total parenteral nutrition associated cholestasis, paraneoplastic cholestasis, Stauffer syndrome, intrahepatic cholestasis of pregnancy, contraceptive-associated cholestasis, drug-associated cholestasis, infection-associated cholestasis, Dubin-Johnson Syndrome, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), gallstone disease, Alagille syndrome, Dubin-Johnson Syndrome, biliary atresia, post-Kasai biliary atresia, post-liver transplantation biliary atresia, post-

liver transplantation cholestasis, post-liver transplantation associated liver disease, intestinal failure associated liver disease, bile acid mediated liver injury, MRP2 deficiency syndrome, and neonatal sclerosing cholangitis.

22. The use of any one of claims 20-21, wherein the pruritus is associated with Alagille syndrome (ALGS).

23. The use of any one of claims 20-22, wherein the compound of Formula III decreases pruritus.