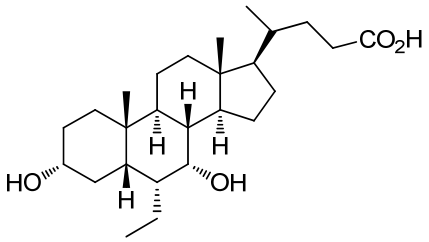
POLYMOPRHIC CRYSTALLINE FORMS OF OBETICHOLIC ACID

SUMMARY

The present disclosure relates to obeticholic acid, an agonist for FXR, processes of preparation for obeticholic acid, pharmaceutical formulations comprising obeticholic acid, and the therapeutic use of the same.



obeticholic acid
(also known as INT-747)

In one aspect of the present disclosure, there is provided a crystalline form of obeticholic acid characterized by an X-ray powder diffraction pattern comprising peaks at about 5.0 and 5.3 degrees 2-theta.

In another aspect of the present disclosure, there is provided a crystalline form of obeticholic acid, wherein the crystalline form is selected from the group consisting of D, F, G, and I.

The present disclosure also relates to a process for the preparation of obeticholic acid using crystalline obeticholic acid as a synthetic intermediate. The crystalline obeticholic acid is selected from the group consisting of Forms A, C, D, F, G, and I. The present disclosure further relates to a process for the selective preparation of crystalline obeticholic acid.

The present disclosure relates to a crystalline obeticholic acid Form A characterized by an X-ray diffraction pattern including characteristic peaks at about 5.0 and 5.3 degrees 2-Theta. The crystalline obeticholic acid Form A is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 41.

The present disclosure relates to a crystalline obeticholic acid Form C characterized by an X-ray diffraction pattern including characteristic peaks at about 4.2, 6.4, 9.5, 12.5, and 16.7 degrees 2-Theta. The crystalline obeticholic acid Form C is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 5 and further characterized by a Differential Scanning Calorimetry (DSC) thermogram having an endotherm value at about 98±2 ºC.

The present disclosure relates to a crystalline obeticholic acid Form D characterized by an X-ray diffraction pattern including characteristic peaks at about 4.4, 5.2, and 7.5 degrees 2-Theta. The crystalline obeticholic acid Form D is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 45.

The present disclosure relates to a crystalline obeticholic acid Form F characterized by an X-ray diffraction pattern including characteristic peaks at about 8.0,

13.2, and 13.8 degrees 2-Theta. The crystalline obeticholic acid Form F is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 49.

The present disclosure relates to a crystalline obeticholic acid Form G characterized by an X-ray diffraction pattern including characteristic peaks at about 12.9 and 13.4 degrees 2-Theta. The crystalline obeticholic acid Form G is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 53.

The present disclosure relates to a crystalline obeticholic acid Form I characterized by an X-ray diffraction pattern including a characteristic peak at about 7.2 degrees 2-Theta. The crystalline obeticholic acid Form I is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 57.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the step of converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid; and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-

cholan-24-oic acid methyl ester; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester; reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with CH_3OH and H_2SO_4 to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester; reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester; reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form A to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form A in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form C to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form C in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form D to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form D in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form F to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form F in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form G to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form G in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form I to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form I in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid is carried out at a temperature at about 85 ºC to about 110 ºC in a basic aqueous solution.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is carried out at a temperature at about 20 ºC to about 105 ºC and at a pressure at about 0.5

to about 5 bars. In a separate embodiment, the hydrogenation is performed at a temperature range from about 20 °C to about 105 °C, e.g. 30 °C, 40 °C, 50 °C, 60 °C, 70 °C, 80 °C, 90 °C, and 100 °C, as well as any increment in between. In another embodiment, the hydrogenation is performed at a pressure at about 0.5 bar to about 5.5 bar, e.g., 0.6 bar, 0.7 bar, 0.8 bar, 0.9 bar, 1.0 bar, 1.2 bar, 1.4 bar, 1.6 bar, 1.8 bar, 2.0 bar, 2.2 bar, 2.4 bar, 2.6 bar, 2.8 bar, 3.0 bar, 3.2 bar, 3.4 bar, 3.6 bar, 3.8 bar, 4.0 bar, 4.2 bar, 4.4 bar, 5.0 bar, 5.2 bar, 5.3 bar, and 5.4 bar, as well as any increment in between. The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid is carried out at a temperature at about 20 °C to about 60 °C.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with CH_3CHO to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at about -50 °C to about -70 °C in the presence of BF_3. In one embodiment, the reaction is carried out at a temperature range of below -60 °C to about -70 °C in the presence of BF_3. In one embodiment, the reaction is carried out at is carried out at an upper limit temperature of about -60 °C in the presence of BF_3.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at about -10 °C to about -30 °C.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with CH_3OH and H_2SO_4 to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution to a pH-range of about 9.5 to about 10.

The present disclosure relates to a obeticholic acid, or a pharmaceutically acceptable salt, solvate or amino acid conjugate thereof, having a potency of greater than about 98%, greater than about 98.5%, greater than about 99.0%, or greater than about 99.5%. The present disclosure relates to a pharmaceutical composition comprising

obeticholic acid Form 1 produced by a process of the disclosure and a pharmaceutically acceptable carrier.

The present disclosure relates to a method of treating or preventing an FXR mediated disease or condition in a subject comprise of administering an effective amount of obeticholic acid Form 1. The disease or condition is selected from biliary atresia, cholestatic liver disease, chronic liver disease, nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, primary biliary cirrhosis (PBC), liver damage due to progressive fibrosis, liver fibrosis, and cardiovascular diseases including atherosclerosis, arteriosclerosis, hypercholesterolemia, and hyperlipidemia. The present disclosure relates to a method for lowering triglycerides in a subject comprise of administering an effective amount of obeticholic acid Form 1.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a HPLC-UV/MS chromatogram of crude compound 5 of Step 4 of Example 1 injected at 1 mg/mL, injection volume 3µl. The chromatogram is obtained according to the method described in Example 2.

Figure 2 is a HPLC-UV/MS chromatogram of compound 5 of Step 4 of Example 1, purified reference injected at 1 mg/mL, injection volume 20 µL. The chromatogram is obtained according to the method described in Example 2.

Figure 3 is a UV chromatogram of crude compound 5 of step 4 of Example 1 using HPLC method. The chromatogram is obtained according to the method described in Example 2.

Figure 4A is an accurate ion trace of m/z 850.61914 ± 3ppm from the main peak fraction (RT 29.0 min) of compound 5 of Step 4 of Example 1, purely isolated with HPLC method (see Example 2).

Figure 4B is an accurate ion trace of m/z 850.61914 ± 3ppm from the minor peak fraction (RT 29.9 min) of compound 5 of Step 4 of Example 1, purely isolated with HPLC method (see Example 2).

Figure 4C is an accurate ion trace of m/z 850.61914 ± 3ppm from crude compound 5 of Step 4 of Example 1 (see Example 2).