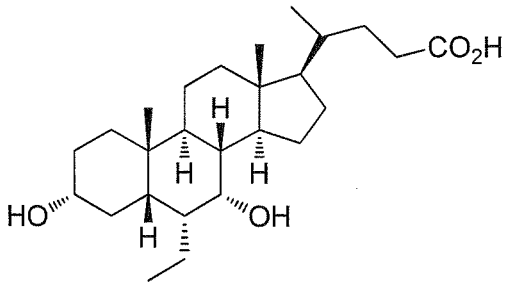
PREPARATION, USES AND SOLID FORMS OF OBETICHOLIC ACID

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~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)

The present ~~invention~~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 °C.

The present ~~invention~~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 ~~invention~~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 ~~invention~~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 ~~invention~~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 ~~invention~~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 ~~invention~~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 ~~invention~~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 ~~invention~~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 ~~invention~~disclosure relates to a process for preparing obeticholic acid Form 1, wherein in 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 °C to about 110 °C in a basic aqueous solution.

The present ~~invention~~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 100 °C to about 105 °C and at a pressure at about 4 to about 5 bars.

The present ~~invention~~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 ~~invention~~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.

The present ~~invention~~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 ~~invention~~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-value of about 6.5 to about 8.0.

The present ~~invention~~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 ~~invention~~disclosure relates to a pharmaceutical composition comprising obeticholic acid Form 1 produced by a process of the ~~invention~~disclosure and a pharmaceutically acceptable carrier.

The present ~~invention~~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, hypercholesteremia, and hyperlipidemia. The present ~~invention~~disclosure relates to a method for lowering triglycerides in a subject comprise of administering an effective amount of obeticholic acid Form 1.

In a first aspect of the present disclosure, there is provided 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.

In a second aspect of the present disclosure, there is provided a crystalline obeticholic acid Form C characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 5.

In a third aspect of the present disclosure, there is provided a crystalline obeticholic acid Form C characterized by a Differential Scanning Calorimetry (DSC) thermogram having an endotherm value at about 98±2 °C.

In a fourth aspect of the present disclosure, there is provided a process for preparing obeticholic acid Form 1, comprising a crystalline form of obeticholic acid as a synthetic intermediate.

In a fifth aspect of the present disclosure, there is provided a process for preparing obeticholic acid Form 1, comprising converting crystalline obeticholic acid to obeticholic acid Form 1.

In a sixth aspect of the present disclosure, there is provided a compound E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid produced by the process according to the fourth or fifth aspects, wherein the E/Z isomer ratio is greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 83%, greater than about 85%, greater than about 90%, greater than about 93%, greater than about 95%, or greater than about 99%.

In a seventh aspect of the present disclosure, there is provided a obeticholic acid, or a pharmaceutically acceptable salt, solvate or amino acid conjugate thereof, having a potency of greater than about 98%.

In an eighth aspect of the present disclosure, there is provided a crystalline obeticholic acid, or a pharmaceutically acceptable salt, solvate or amino acid conjugate thereof, wherein said crystalline obeticholic acid is Form C.

In a ninth aspect of the present disclosure, there is provided a pharmaceutical composition comprising obeticholic acid Form 1 produced by the process of any one of the fourth or fifth aspects and a pharmaceutically acceptable carrier.

In a tenth aspect of the present disclosure, there is provided a pharmaceutical composition comprising of crystalline obeticholic acid and a pharmaceutically acceptable carrier.

In a eleventh aspect of the present disclosure, there is provided a use of obeticholic acid Form 1 according to the seventh aspect, or produced by a process according to any one of the fourth or fifth aspects, or a pharmaceutical composition

according to the ninth aspect, for the manufacture of a medicament for the treatment or prevention of an FXR mediated disease or condition in a subject.

In a twelfth aspect of the present disclosure, there is provided a use of crystalline obeticholic acid according to any one of the first, second, third, or eighth aspects, or a pharmaceutical composition according to the tenth aspect, for the manufacture of a medicament for the treatment or prevention of an FXR mediated disease or condition in a subject.

In a thirteenth aspect of the present disclosure, there is provided a use of obeticholic acid Form 1 according to the seventh aspect, or produced by a process according to any one of the fourth or fifth aspects, or a pharmaceutical composition according to the ninth aspect, for the manufacture of a medicament for lowering triglycerides in a subject.

In a fourteenth aspect of the present disclosure, there is provided a use of crystalline obeticholic acid according to any one of the first, second, third, or eighth aspects, or a pharmaceutical composition according to the tenth aspect, for the manufacture of a medicament for lowering triglycerides in a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

97. The crystalline obeticholic acid Form C according to claim 96, wherein the total impurities is less than about 3.8 %.

98. The crystalline obeticholic acid Form C according to any one of claims 96-97, wherein the total impurities is less than about 3.6%.

99. A pharmaceutical composition comprising obeticholic acid Form 1 produced by the process of any one of claims 10-50 and a pharmaceutically acceptable carrier.

100. A pharmaceutical composition comprising of crystalline obeticholic acid and a pharmaceutically acceptable carrier.

101. The pharmaceutical composition according to claim 100, wherein the crystalline obeticholic acid is Form C.

102. Use of obeticholic acid Form 1 according to any one of claims 60-86, or produced by a process according to any one of claims 10-50, or a pharmaceutical composition according to claim 99, for the manufacture of a medicament for the treatment or prevention of~~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 according to any one of claims 60-86 or produced by a process according to any one of claims 10-50, or a pharmaceutical composition according to claim 99~~.

103. Use of crystalline obeticholic acid according to any one of claims 1-9 or 87-98, or a pharmaceutical composition according to any one of claims 100-101, for the manufacture of a medicament for the treatment or prevention of~~A method of treating or preventing~~ an FXR mediated disease or condition in a subject~~ comprise of administering an effective amount of crystalline obeticholic acid according to any one of claims 1-9 or 87-98 or a pharmaceutical composition according to any one of claims 100-101~~.

104. The ~~method~~ use according to any one of claims 102-103, wherein 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, hypercholesteremia, and hyperlipidemia.

105. Use of obeticholic acid Form 1 according to any one of claims 60-86, or produced by a process according to any one of claims 10-50, or a pharmaceutical composition according to claim 99, for the manufacture of a medicament for ~~A method for~~ lowering triglycerides in a subject ~~comprise of administering an effective amount of obeticholic acid Form 1 according to any one of claims 60-86 or produced by a process according to any one of claims 10-50, or a pharmaceutical composition according to claim 99~~.

106. Use of crystalline obeticholic acid according to any one of claims 1-9 or 87-98, or a pharmaceutical composition according to any one of claims 100-101, for the manufacture of a medicament for ~~A method for~~ lowering triglycerides in a subject ~~comprise of administering an effective amount of crystalline obeticholic acid according to any one of claims 1-9 or 87-98 or a pharmaceutical composition according to any one of claims 100-101~~.