NOVEL FORMS OF CDDO METHYL ESTER

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims priority from US Provisional Application 60/955,939, filed August 15, 2007, incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Triterpenoids are biosynthesized in plants by the cyclization of squalene. Although candidates for medicinal use, these naturally occurring molecules display relatively weak biological activity. Accordingly, chemists have sought to synthesize analogues of enhanced potency (Honda *et al.*, 1997 & 1998).

[0003] Several synthetic analogs are reported to suppress the *de novo* formation of iNOS and COX-2 in macrophages that have been stimulated by IFN-γ or LPS (Suh *et al.*, 1998; Honda *et al.*, 2002). Another synthetic triterpenoid, 2-cyano-3,12-dioxoleana-1,9(11)-dien-28-oate (CDDO), exhibits anti-inflammatory and anti-proliferative activity (Honda *et al.*, 1998 & 2000).

[0004] Studying the methyl ester of CDDO, which is methyl 2-cyano-3,12-dioxoleana-1,9(11)-dien-28-oate (CDDO methyl ester), Bore *et al.* (2002) determined a crystal structure. In that form, which is hydrated, water coordinates interactions that engender a particular crystal packing and structure.

SUMMARY

[004a] In one aspect of the present disclosure, there is provided anhydrous, crystalline methyl 2-cyano-3,12-dioxoleana-1,9(11)-dien-28-oate (CDDO-methyl ester) characterized in that its X-ray powder diffractogram comprises peaks at 8.78° 2θ, 12.94° 2θ, 13.35° 2θ, 14.18° 2θ, and 17.4° 2θ±0.2° 2θ based upon data collected on a diffractometer with Cu K_α radiation.

[004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of the CDDO-methyl ester disclosed herein and one or more solid pharmaceutically acceptable carriers.

[004c] In a further aspect of the present disclosure, there is provided the CDDO-methyl ester disclosed herein for use in treating a chronic inflammatory condition in a subject suffering therefrom.

[004d] In another aspect of the present disclosure, there is provided a use of CDDO-methyl ester disclosed herein in the manufacture of a medicament for treating a chronic inflammatory condition in a subject suffering therefrom.

[004e] In a further aspect of the present disclosure, there is provided crystalline CDDO-methyl ester hemibenzenate, characterized in that its X-ray powder diffractogram comprises peaks at 9.25° 2θ, 14.17° 2θ, , 14.62° 2θ, 16.32°2θ, and 17.11° 2θ±0.2° 2θ based upon data collected on a diffractometer with Cu K_α radiation.

[0005] In one embodiment of the present disclosure, a non-hydrous crystalline form of CDDO methyl ester is provided. The non-hydrous crystal form preferably has a space group of $P4_3\ 2_12$ with unit cell dimensions of a=14.2Å, b=14.2Å, and c=81.6Å. The present disclosure also contemplates a pharmaceutical composition in solid dosage form, comprising (i) a therapeutically effective amount of a non-hydrous crystalline form of CDDO methyl ester with (ii) an edible carrier.

[0006] Additionally, the present disclosure is embodied in a glassy solid form of CDDO methyl ester, having an x-ray powder diffraction pattern with a halo peak at approximately 13.5 °2θ, as shown in Figure 2C, and a glass transition temperature (T_g). In particular

embodiments, the T_g can range from about 120°C to about 135°C. In other embodiments, the T_g ranges from about 125°C to about 130°C. The glassy solid form of CDDO-methyl ester can have a PDF spectrum with similar peaks to Figure 28 from about 5 Å to about 20 Å.

[0007] Furthermore, the present disclosure provides a pharmaceutical composition in solid dosage form, comprising (i) a therapeutically effective amount of a glassy solid form of CDDO methyl ester with (ii) an edible carrier. In this regard, the present disclosure contemplates a methodology for treating a cancer patient, comprising: administering such a pharmaceutical composition to a cancer patient. The present disclosure also contemplates administering the glassy form of CDDO-methyl ester in combination with another anti-cancer drug. For example, the anti-cancer drug may be gemcitabine and the cancer may be pancreatic cancer. The present disclosure encompasses as well a methodology for the treatment of diseases or disorders that involve acute or chronic oxidative stress and inflammation, particularly those characterized in part by overexpression of inducible nitric oxide synthase (iNOS) or inducible cyclooxygenase (COX-2).

[0008] In addition, the present disclosure is drawn to a dimethanol solvate form of CDDO-methyl ester, having an x-ray powder diffraction pattern with characteristic peaks as shown in Table 18 and a DSC pattern as shown in Figure 24. Pursuant to the present disclosure, the dimethanol solvate form may be used as an intermediate for the production of a glassy solid form of CDDO methyl ester. A method for the production of the glassy solid form of CDDO-methyl ester, via the dimethanol solvate form, comprises preparing a dimethanol solvate form of CDDO-methyl ester and drying the dimethanol solvate form.

[0009] In accordance with another embodiment, the present disclosure is drawn to a method of growing a crystal of CDDO methyl ester dimethanolate, comprising preparing a solution of purified CDDO methyl ester in warm anhydrous methanol, adding the warm solution to a vessel of chilled methanol, and filtering the resulting crystals.

[0010] In accordance with another embodiment, the present disclosure is drawn to a pharmaceutical composition comprising (i) a therapeutically effective amount of CDDO-methyl ester and (ii) an excipient that is a glass former, such that the composition has a T_g.

[0011] The excipient may be selected, for instance, from the group consisting of (A) a carbohydrate, carbohydrate derivative, or carbohydrate polymer, (B) a synthetic organic polymer, (C) an organic acid salt, (D) a protein, polypeptide, or peptide, and (E) a high

WHAT IS CLAIMED IS:

1. Anhydrous, crystalline methyl 2-cyano-3,12-dioxoleana-1,9(11)-dien-28-oate (CDDO-methyl ester) characterized in that its X-ray powder diffractogram comprises peaks at 8.78° 2θ, 12.94° 2θ, 13.35° 2θ, 14.18° 2θ, and 17.4° 2θ±0.2° 2θ based upon data collected on a diffractometer with Cu K_α radiation.

2. The CDDO-methyl ester according to claim 1, wherein the X-ray powder diffractogram is substantially as shown in FIG. 18.

3. The CDDO-methyl ester according to claim 1, further characterized in that its differential scanning calorimetry curve comprises a baseline shift at approximately 157° C. and an endotherm maximum at about 224° C.

4. The CDDO-methyl ester according to claim 3, wherein the differential scanning calorimetry curve is substantially as shown in FIG. 3.

5. A pharmaceutical composition comprising a therapeutically effective amount of the CDDO-methyl ester according to claim 1 and one or more solid pharmaceutically acceptable carriers.

6. The pharmaceutical composition according to claim 5, wherein the CDDO-methyl ester is micronized and the solid pharmaceutically acceptable carriers are edible carriers.

7. The CDDO-methyl ester according to claim 1 for use in treating a chronic inflammatory condition in a subject suffering therefrom.

8. Use of CDDO-methyl ester according to claim 1 in the manufacture of a medicament for treating a chronic inflammatory condition in a subject suffering therefrom.

9. Crystalline CDDO-methyl ester hemibenzenate, characterized in that its X-ray powder diffractogram comprises peaks at 9.25° 2θ, 14.17° 2θ, , 14.62° 2θ, 16.32°2θ, and 17.11° 2θ±0.2° 2θ based upon data collected on a diffractometer with Cu K_α radiation.

10. The crystalline CDDO-methyl ester hemibenzenate according to claim 9, further characterized in that it has a differential scanning calorimetry curve as substantially shown in FIG. 23.