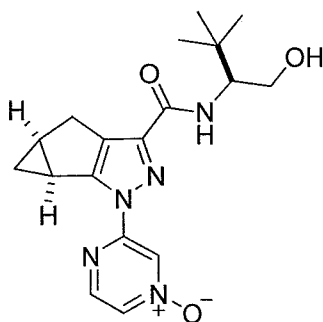


in a variety of peripheral tissues and cells (Matsuda, L. A. *et al.* (1990) *Nature* 346:561-564). In contrast, CB₂ is expressed predominantly, although not exclusively, in non-neural tissues, *e.g.* in hematopoietic cells, endothelial cells, osteoblasts, osteoclasts, the endocrine pancreas, and cancerous cell lines (Munro, S. *et al.* (1993) *Nature* 365:61-65; and as reviewed in Pacher, P. *et al.* (2006) *Pharmacol. Rev.* 58(3): 389-462). As such, CB₁ is believed to be primarily responsible for mediating the psychotropic effects of cannabinoids on the body, whereas CB₂ is believed to be primarily responsible for most of their non-neural effects.

SUMMARY

- 10 Disclosed are crystalline forms of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 1):



- Disclosed is an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide (Compound 1). In one aspect, there is provided an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.
- 20 In another aspect, there is provided a process for preparing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide comprising the steps of:
- 1) crystallizing (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide from a crystallizing mixture to obtain a crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide insaid crystallizing mixture, wherein said crystallizing mixture comprises acetonitrile and water; and
 - 2) isolating said crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide from said crystallizing mixture to obtain said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-

1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.

Disclosed is an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide prepared by a process as described herein.

In another aspect, there is provided a process for preparing a pharmaceutical composition comprising the steps of:

1) preparing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein; and

2) admixing said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide with a pharmaceutically acceptable carrier.

In another aspect, there is provided a process for preparing a dosage form comprising the steps of:

1) preparing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein; and

2) admixing said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide with a pharmaceutically acceptable carrier.

Disclosed are compositions comprising an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein. In another aspect, there is provided a composition comprising an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein.

Disclosed are compositions comprising an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, and a pharmaceutically acceptable carrier. In another aspect, there is provided a pharmaceutical composition comprising an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, and a pharmaceutically acceptable carrier.

In another aspect, there is provided a unit dosage form comprising an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-

cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, and a pharmaceutically acceptable carrier.

Disclosed are processes of making a composition comprising mixing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-

5 cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, with a pharmaceutically acceptable carrier. In another aspect, there is provided a process of making a pharmaceutical composition comprising admixing an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-
10 amide as described herein with a pharmaceutically acceptable carrier.

In another aspect, there is provided a process of making a unit dosage form comprising admixing an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein with a pharmaceutically
15 acceptable carrier; and subdividing the admixture into unit dosage forms, each of which comprises a therapeutically effective amount of the anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.

Disclosed are methods for the treatment of a cannabinoid receptor-mediated disorder in an
20 individual, comprising administering to the individual in need thereof, a therapeutically effective amount of an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein or a pharmaceutical composition thereof.

Disclosed are methods for the treatment of a CB₂ receptor-mediated disorder in an individual,
25 comprising administering to the individual in need thereof, a therapeutically effective amount of an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein or a pharmaceutical composition thereof.

Disclosed is the use of an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-
30 1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, in the manufacture of a medicament for the treatment of a cannabinoid receptor-mediated disorder.

Disclosed is the use of an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-

carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, in the manufacture of a medicament for the treatment of a CB₂ receptor-mediated disorder.

In another aspect, there is provided use of a therapeutically effective amount of an anhydrous non-solvated crystalline form as described herein in the manufacture of a medicament for the treatment of pain in an individual.

In another aspect, there is provided use of a therapeutically effective amount of an anhydrous non-solvated crystalline form as described herein in the manufacture of a medicament for the treatment of pain in an individual; wherein said pain is associated with one or more disorders selected from the group consisting of: bone pain, joint pain, muscle pain, dental pain, migraine pain, headache pain, inflammatory pain, neuropathic pain, pain that occurs as an adverse effect of a therapeutic, osteoarthritis pain, cancer pain, multiple sclerosis pain, allergic reactions, nephritic syndrome, scleroderma, thyroiditis, diabetic neuropathy, fibromyalgia, HIV related-neuropathy, sciatica, and an autoimmune condition.

In another aspect, there is provided use of a therapeutically effective amount of an anhydrous non-solvated crystalline form as described herein in the manufacture of a medicament for the treatment of osteoporosis in an individual.

Disclosed is an anhydrous crystalline form of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, for use in a method of treatment of the human or animal body by therapy.

Disclosed is an anhydrous crystalline form of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, for use in a method of treatment of a cannabinoid receptor-mediated disorder.

Disclosed is an anhydrous crystalline form of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide as described herein, for use in a method of treatment of a CB₂ receptor-mediated disorder.

Disclosed are acetone solvates of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.

Disclosed are non-selective solvates of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.

Disclosed are ethyl acetate solvates of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.

Certain modulators of the cannabinoid receptor are described in PCT application

- 5 PCT/US2010/002360, filed 27 August 2010 (International Publication Number WO2011/025541), and in United States provisional applications 61/275,506, 61/396,588, and 61/400,146, each of which is incorporated herein by reference in its entirety. These and other embodiments of the disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

10

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a differential scanning calorimetry (DSC) thermogram for a sample containing a crystalline form of Compound **1** (CH₂Cl₂ solvate) and a thermogravimetric analysis (TGA) thermogram of a sample containing a crystalline form of Compound **1** (CH₂Cl₂ solvate).

- 15 **Figure 2** shows an overlay of a powder X-ray diffraction (PXRD) pattern for a sample containing a crystalline form of Compound **1** (CH₂Cl₂ solvate) obtained from recrystallization using CH₂Cl₂/hexane (Top Trace) and a powder X-ray diffraction (PXRD) pattern for a sample

CLAIMS

What is claimed is:

1. A process for preparing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide comprising the steps of:
 - 1) crystallizing (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide from a crystallizing mixture to obtain a crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide in said crystallizing mixture, wherein said crystallizing mixture comprises acetonitrile and water; and
 - 2) isolating said crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide from said crystallizing mixture to obtain said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.
2. The process according to claim 1, wherein said crystallizing is conducted at a temperature of about -5 °C to about 5 °C.
3. The process according to claim 1, wherein said crystallizing mixture is prepared by the steps of:
 - 1) dissolving (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide in acetonitrile and a first amount of water to form a first mixture; and
 - 2) adding a second amount of water to said first mixture to obtain said crystallizing mixture.
4. The process according to claim 3, wherein said dissolving is conducted at a temperature of about 58 °C to about 62 °C.
5. The process according to claim 3, wherein the molar ratio present in said first mixture between (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-

cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide, acetonitrile, and first amount water is about 1.0:9.2:37.0 to about 1.0:10.2:41.7.

- 5 6. The process according to claim 3, wherein said adding of said second amount of water to said first mixture is conducted at a rate that the temperature of the mixture of said second amount of water together with said first mixture is at about 25 °C to about 80 °C.
- 10 7. The process according to claim 3, wherein the molar ratio present in said crystallizing mixture between (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide, acetonitrile, and water in said crystallizing mixture is about 1.0:9.2:414.7 to about 1.0:10.2:458.3.
- 15 8. The process according to claim 3, wherein (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide prior to said dissolving step is selected from the group consisting of:
- 20 1) a dichloromethane solvate of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide;
- 2) an acetone solvate of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide;
- 25 3) a non-selective solvate of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide; and
- 4) an ethyl acetate solvate of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide; and
- 30 mixtures thereof.
- 35 9. The process according to claim 1, wherein said isolating comprises filtering said crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide from said crystallizing mixture.

10. The process according to claim 1, wherein said isolating comprises removing said crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide from said crystallizing mixture.
- 5 11. The process according to claim 1, further comprises the step of drying said crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide to obtain said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-10 1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.
12. The process according to claim 11, wherein said drying is conducted at a temperature of about 15 °C to about 80 °C.
- 15 13. The process according to claim 11, wherein said drying is conducted at a pressure of less than 760 mm Hg and a temperature of about 55 °C to about 65 °C.
14. The process according to claim 1, wherein after said isolating, said anhydrous 20 crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide has a chemical purity of about 98% or greater.
15. The process according to claim 1, wherein after said isolating, said anhydrous 25 crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide has an enantiomeric excess of about 98% or greater.
16. The process according to claim 1, wherein after said isolating, said anhydrous 30 crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide has a chemical purity of about 99% or greater and an enantiomeric excess of about 99% or greater.
- 35 17. A process for preparing a pharmaceutical composition comprising the steps of:

- 1) preparing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim 1; and
- 2) admixing said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide with a pharmaceutically acceptable carrier.
- 5
18. A process for preparing a dosage form comprising the steps of:
- 10 1) preparing an anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim 1; and
- 2) admixing said anhydrous crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide with a pharmaceutically acceptable carrier.
- 15
19. An anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.
- 20
20. The anhydrous non-solvated crystalline form according to claim 19, wherein said anhydrous crystalline form has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at $8.5^\circ \pm 0.2^\circ$, and $10.7^\circ \pm 0.2^\circ$.
- 25
21. The anhydrous non-solvated crystalline form according to claim 19, wherein said anhydrous crystalline form has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at $8.5^\circ \pm 0.2^\circ$, $10.7^\circ \pm 0.2^\circ$, and $16.9^\circ \pm 0.2^\circ$.
- 30
22. The anhydrous non-solvated crystalline form according to claim 19, wherein said anhydrous crystalline form has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at $8.5^\circ \pm 0.2^\circ$, $10.7^\circ \pm 0.2^\circ$, $16.9^\circ \pm 0.2^\circ$, $25.4^\circ \pm 0.2^\circ$, and $11.1^\circ \pm 0.2^\circ$.
- 35
23. The anhydrous non-solvated crystalline form according to claim 19, wherein said anhydrous crystalline form has a powder X-ray diffraction pattern comprising peaks, in

terms of 2θ , at $8.5^\circ \pm 0.2^\circ$, $10.7^\circ \pm 0.2^\circ$, $16.9^\circ \pm 0.2^\circ$, $25.4^\circ \pm 0.2^\circ$, $11.1^\circ \pm 0.2^\circ$, $9.8^\circ \pm 0.2^\circ$, and $17.4^\circ \pm 0.2^\circ$.

24. The anhydrous non-solvated crystalline form according to claim 19, wherein said
5 anhydrous crystalline form has a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 159.6 °C and about 169.6 °C.
25. The anhydrous non-solvated crystalline form according to claim 19, wherein said
10 anhydrous crystalline form has a thermogravimetric analysis profile showing about 0.5% weight loss below about 135 °C.
26. The anhydrous non-solvated crystalline form according to claim 19, wherein said
anhydrous crystalline form has:
- 15 1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ , at $8.5^\circ \pm 0.2^\circ$, and $10.7^\circ \pm 0.2^\circ$;
- 2) a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 159.6 °C and about 169.6 °C; and/or
- 20 3) a thermogravimetric analysis profile showing about 0.5% weight loss below about 135 °C.
27. A composition comprising an anhydrous non-solvated crystalline form of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim
25 19.
28. A pharmaceutical composition comprising an anhydrous non-solvated crystalline form of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim 19, and a pharmaceutically acceptable carrier.
30
29. A unit dosage form comprising an anhydrous non-solvated crystalline form of (1a*S*,5a*S*)-2-(4-oxy-pyrazin-2-yl)-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim 19, and a pharmaceutically acceptable carrier.
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30. A process of making a pharmaceutical composition comprising admixing an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim 19 with a pharmaceutically acceptable carrier.
31. A process of making a unit dosage form comprising admixing an anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide according to claim 19 with a pharmaceutically acceptable carrier; and subdividing the admixture into unit dosage forms, each of which comprises a therapeutically effective amount of the anhydrous non-solvated crystalline form of (1*aS*,5*aS*)-2-(4-oxy-pyrazin-2-yl)-1*a*,2,5,5*a*-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid ((*S*)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide.
32. Use of a therapeutically effective amount of an anhydrous non-solvated crystalline form according to claim 19 in the manufacture of a medicament for the treatment of pain in an individual.
33. Use of a therapeutically effective amount of an anhydrous non-solvated crystalline form according to claim 19 in the manufacture of a medicament for the treatment of pain in an individual; wherein said pain is associated with one or more disorders selected from the group consisting of: bone pain, joint pain, muscle pain, dental pain, migraine pain, headache pain, inflammatory pain, neuropathic pain, pain that occurs as an adverse effect of a therapeutic, osteoarthritis pain, cancer pain, multiple sclerosis pain, allergic reactions, nephritic syndrome, scleroderma, thyroiditis, diabetic neuropathy, fibromyalgia, HIV related-neuropathy, sciatica, and an autoimmune condition.
34. Use of a therapeutically effective amount of an anhydrous non-solvated crystalline form according to claim 19 in the manufacture of a medicament for the treatment of osteoporosis in an individual.