Crystalline phases of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide

The present invention relates to polymorphic forms and solvates of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide, processes for their preparation and their use, in particular for the preparation of medicaments.

SUMMARY

In a first aspect, there is provided the form of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide, which is a polymorph and has at least one property of

(a) characteristic reflections in an X-ray powder diffractogram using $CuK_{\alpha 1}$ radiation in transmission mode at a 2θ angle [°] of 6.7 ± 0.2, 13.2 ± 0.2, 17.6 ± 0.2, 19.1 ± 0.2, 20.0 ± 0.2, 21.4 ± 0.2, 22.5 ± 0.2; and

(b) characteristic signals in an FT (Fourier-Transformation) Raman spectrum using a near infrared laser (λ = 1064 nm) at 3050 ± 2 cm^{-1}, 2929 ± 2 cm^{-1}, 2887 ± 2 cm^{-1}, 1605 ± 2 cm^{-1}, 1293 ± 2 cm^{-1}, 1042 ± 2 cm^{-1}.

In a second aspect, there is provided a pharmaceutical composition comprising the polymorph of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide as defined above and one or more pharmaceutical acceptable excipients.

In a third aspect, there is provided the use of the polymorph of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide as defined above in the manufacture of a medicament.

In a fourth aspect, there is provided the use of the polymorph of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide as defined above for the manufacture of a medicament for the treatment of atrial arrhythmia or sleeping-related respiratory disorders.

In a fifth aspect, there is provided a process for the preparation of the polymorph of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide as defined above, comprising the steps of

(a) suspending 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide at room temperature in a solvent selected from the group consisting of methanol, ethanol, methanol/water, ethanol/water, methyl acetate, ethyl acetate, butyl acetate, methyl ethyl ketone, tetrahydrofuran, 1,4-dioxane, acetonitrile and methylene chloride to obtain a suspension;

(b) maintaining the suspension at room temperature to allow formation of the polymorph crystals;

(c) isolating the precipitate of the polymorph;

or

(a') suspending 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide at room temperature in a solvent selected from the group consisting of ethanol and isopropanol to obtain a suspension;

(b') maintaining the suspension at a temperature of 0 °C to 45 °C to allow formation of the polymorph crystals;

(c') isolating the precipitate of polymorph;

or

(a") suspending 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide at room temperature in acetone to obtain a suspension;

(b") maintaining the suspension at a temperature of 15 °C to 40 °C to allow formation of the polymorph crystals;

(c") isolating the precipitate of polymorph;

or

(a'") dissolving 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide in ethanol to obtain a solution;

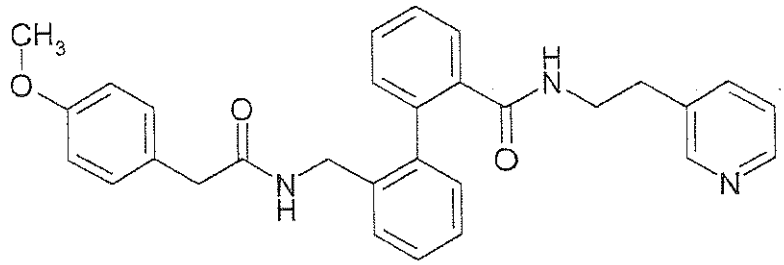
(b'") rapid cooling of the solution to a temperature of 0 °C;

(c'") isolating the precipitate of the polymorph.

In a sixth aspect, there is provided a process for the purification of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide comprising a crystallization step, wherein the polymorph, of 2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide as defined above is obtained.

DETAILED DESCRIPTION

2'-{[2-(4-Methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide of the formula I,



I

which is also designated as AVE0118 and herein is also abbreviated as "compound I", is a known pharmaceutical active compound which is described in WO 01/25189, US 6531495 and WO 2007/124849, for example. However, data concerning polymorphic forms, or crystalline forms, and solvates of said compound are not disclosed in the prior art.

Polymorphism is the ability of a single compound to exist in more than one form or crystal structure. Different polymorphs represent distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. A single compound may give rise to a variety of polymorphic forms wherein each form has different and distinct physical properties, such as different solubility profiles, different thermodynamic stability, different crystallization behavior, different filtrability, different melting point temperatures and/or different X-ray diffraction peaks. The difference in the physical properties of different polymorphic forms results from