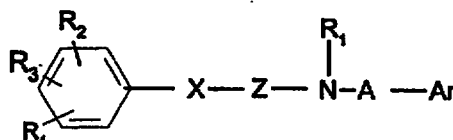


POLYMORPHIC N-[3-[[2-(3,4-DIMETHOXYPHENYL) ETHYL] AMINO] PROPYL] -4-NITRO BENZAMIDE HYDROCHLORIDE

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

- 5 International Patent Application, Publication Number WO 96/13479 discloses certain compounds of formula (A):



(A)

- 10 or a salt thereof, or a solvate thereof, characterised in that:
 Ar represents substituted or unsubstituted aryl, wherein the optional substituents are selected from alkyl, hydroxy or alkoxy or, if attached to adjacent carbon atoms any two substituents together with the carbon atoms to which they are attached may form a fused heterocyclic ring of five to six atoms wherein one, two or three of the said atoms are
 15 oxygen or nitrogen;
 A represents a C₁₋₄ n-alkylene group wherein each carbon is optionally substituted by 1 or 2 C₁₋₆ alkyl groups;
 R₁ represents hydrogen, alkyl, alkenyl or cycloalkyl;
 one or two of the group of R₂, R₃ and R₄ represents nitro the remaining members of the
 20 group of R₂, R₃ and R₄ represent hydrogen;
 X represents a -CO-NH- moiety; and
 Z represents C₂₋₄ n-alkylene group wherein each carbon is optionally substituted by 1 or 2 C₁₋₆ alkyl groups.

- Example 2 of WO 96/13479 is the hydrochloride salt, N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride (hereinafter also referred to as 'the Hydrochloride'), the disclosed melting point of which is 141-2°C.

- It has now been discovered that N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride exists in a novel polymorphic form which form is particularly suitable for bulk preparation and handling
 30 and is also indicated to have superior formulation properties. This novel polymorphic form can be prepared by an efficient, economic and reproducible process particularly suited to large scale preparation.

- The novel polymorphic form also has useful pharmaceutical properties and is considered to be a useful anti-arrhythmic agent having combined Class III/Class IV anti-arrhythmic properties, therefore showing an improved pharmacological profile over pure
 35 class III anti-arrhythmic agents, in particular showing a low proarrhythmic potential,

readily restoring the contractile function of the ischaemic myocardium. It is considered to be particularly useful for the treatment of atrial or ventricular cardiac arrhythmias.

Accordingly, the present invention provides a novel polymorphic form of N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride

5 (hereinafter also referred to as 'Compound (I)') characterised in that it:

- (i) provides a solid state nuclear magnetic resonance spectrum containing chemical shifts substantially as represented in Table I; and/or
- (ii) provides an X-ray powder refraction (XRPD) pattern substantially as represented in Table II; and/or

10 (iii) provides an infra red spectrum substantially as illustrated in Figure (I).

The present invention encompasses Compound (I) isolated in a purified form or in an impure form, such as when admixed with other materials, for example the known form of the Hydrochloride or any other material.

Preferably, Compound (I) is in a purified form, especially a crystalline form.

15 The invention also provides a process for preparing the novel polymorphic form of N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride, characterised in that N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride is crystallized from acetonitrile and thereafter the acetonitrile removed from the product.

20 Preferably the acetonitrile is removed by drying, suitably in vacuo.

The crystals are preferably dried at an elevated temperature, for example at 60°C and over an extended period, usually greater than 12 hours for example 36 hours.

Crystallisation and any recrystallisation is generally carried out at low to ambient temperature, suitably at ambient temperature.

25 Suitably the Hydrochloride is dissolved in acetonitrile at an elevated temperature, for example the reflux temperature of the solvent. Conveniently, crystallisation is initiated by allowing the solution to cool to ambient temperature.

In a preferred form of the process, Compound (I) is prepared from a solution of the Hydrochloride in acetonitrile at an elevated temperature such as 60°C, allowing the product to crystallise on cooling and thereafter drying the resulting product in vacuo at 60°C. Purification of Compound (I) is also suitably effected by recrystallization of impure Compound (I) using this last mentioned procedure.

30 The Hydrochloride is prepared according to known procedures such as those disclosed in WO 96/13479. The disclosures of WO 96/13479 are incorporated herein by reference.

35 As used herein, the term "cardiac arrhythmia" relates to any variation from the normal rhythm of heart beat, including, without limitation, sinus arrhythmia, premature

heartbeat, heartblock, fibrillation, flutter, tachycardia, paroxysmal tachycardia and premature ventricular contractions.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides Compound (I) for use as an active
5 therapeutic substance.

More particularly, the present invention provides Compound (I) for use in the treatment of and/or prophylaxis of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders.

Compound (I) may be administered per se or, preferably, as a pharmaceutical
10 composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising Compound (I) and a pharmaceutically acceptable carrier therefor.

Compound (I) is normally administered in unit dosage form.

An amount effective to treat the disorder hereinbefore described depends upon
15 such factors as the efficacy of a Compound (I) chosen, the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 500 mg for example 2 to 50 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 2,3,4,5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily
20 dose is normally in the range, for a 70 kg adult of 0.1 to 2500 mg, more usually 1 to 1000 mg, for example 1 to 200 mg, that is in the range of approximately 0.02 to 3 mg/kg/day, more usually 0.1 to 3 mg/kg/day, for example 0.15 to 2 mg/kg/day.

At the above described dosage range, no toxicological effects are indicated for the compounds of the invention.

25 In such treatment, the active compound may be administered by any suitable route, e.g. by the oral, parenteral or topical routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a human or veterinary pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

30 Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions,
35 since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting

agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

For topical administration, the composition may be in the form of a transdermal ointment or patch for systemic delivery of the compound and may be prepared in a conventional manner, for example, as described in the standard textbooks such as

'Dermatological Formulations' - B.W. Barry (Drugs and the Pharmaceutical Sciences - Dekker) or Harrys Cosmeticology (Leonard Hill Books).

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

- 5 As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

- 10 The present invention further provides a method for the treatment and/or prophylaxis of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Compound (I) to a human or non-human mammal in need thereof.

- 15 Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of arrhythmia and/or ischaemic arrhythmia disorders Compound (I) may be taken in doses, such as those described above.

- 20 Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of Compound (I) for the manufacture of a medicament for the treatment of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders.

- 25 No adverse toxicological effects are indicated when Compound (I) is administered in the above mentioned dosage ranges.

The following Examples illustrate the invention but do not limit it in any way.

Example 1**Preparation of a novel polymorphic form N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide, hydrochloride
5 (Compound (I))**

The Hydrochloride was prepared as disclosed in Example 2 of WO 96/13479.
173g of crude Hydrochloride was dissolved at reflux in 1.3 liter of acetonitrile.

- 10 The solution was then allowed to cool to room temperature over two hours during which time crystallisation occurred. The resulting crystals were filtered off, washed with acetonitrile (1L), dried under vacuum (0.5 Torr) at 60°C for 12 hours and then for a further period of 24 hours under the same conditions (0.5 Torr, 60°C) to afford 125.6 g of Compound (I) m.p. 156°C displaying by HPLC a main peak of 99.8% with the main
15 impurity < 0.1%. Total yield (synthesis + purification) 59.9%.

SPECTROSCOPIC DATA**(A) Solid State NMR**

The 90.55MHz ^{13}C CP-MAS NMR spectrum chemical shifts are tabulated in Table I. Data were recorded at ambient temperature and 10 kHz spinning frequency, on a Bruker AMX360WB spectrometer.

Table I
 C^{13} Chemical shifts (ppm)

28.8	33.4	36.0	49.1	54.6	57.6	107.2	112.7	120.5
126.3	127.9	131.7	137.3	146.8	148.9	164.5		

(B) X-Ray Powder Diffraction (XRPD)

A summary of the XRPD angles characteristic of the Compound (I) is given in Table II.

A PW1710 X-ray powder diffractometer (Cu X-ray source) was used to generate the spectrum using the following acquisition conditions:

Tube anode:	Cu
Generator tension:	40 kV
Generator current:	30 mA
Start angle:	3.5 °2 θ
End angle:	35.0 °2 θ
Step size:	0.005 °2 θ
Time per step:	0.25 s

Table II

XRPD Diffraction Angles

Diffraction Angle

(°2 θ)

8.7

14.4

18.0

20.7

22.2

22.7

23.9

24.3

24.9

26.6

28.1

29.2

30.8

31.4

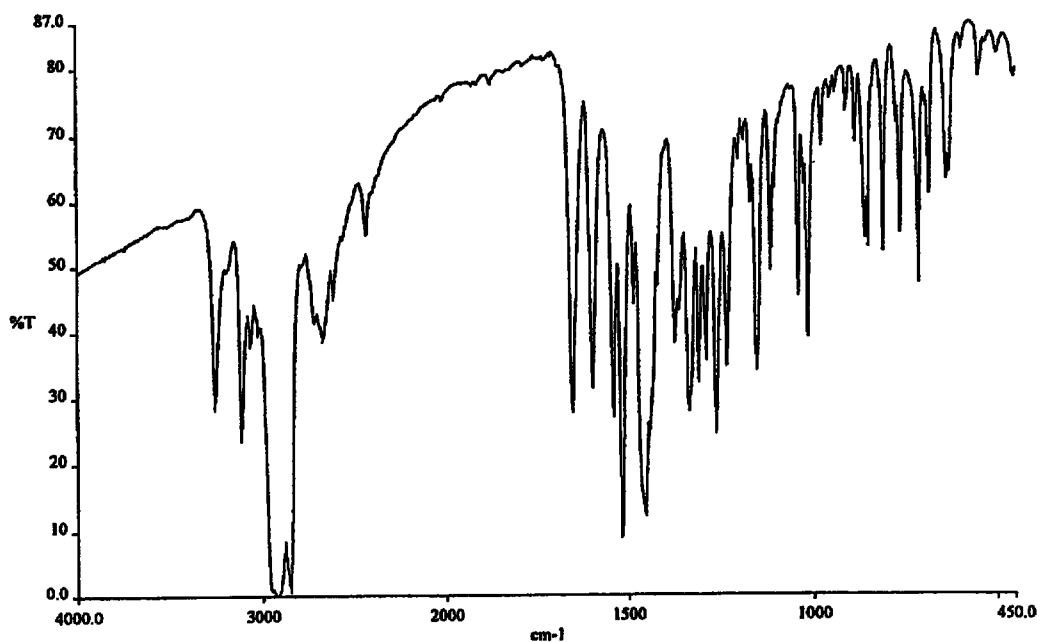
32.0

34.0

(C) Infra Red spectrum

The infrared absorption spectrum of a mineral oil dispersion of Compound (I) was obtained using a Perkin-Elmer PE2000 spectrometer at 2 cm⁻¹ resolution.

Figure (I)



CLAIMS

1. A novel polymorphic form of N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitro benzamide hydrochloride characterised in that it:
 - (i) provides a solid state nuclear magnetic resonance spectrum containing chemical shifts substantially as represented in Table I; and/or
 - (ii) provides an X-ray powder refraction (XRPD) pattern substantially as represented in Table II; and/or
 - (iii) provides an infra red spectrum substantially as illustrated in Figure (I).
2. The novel polymorph according to claim 1, in a purified form.
3. A process for preparing a novel polymorphic form of N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride, characterised in that N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride is crystallized from acetonitrile and thereafter the acetonitrile removed from the product.
4. A process according to claim 3, wherein the acetonitrile is removed by drying.
5. A process according to claim 3, or claim 4, wherein the final product is dried at an elevated temperature over an extended period of time.
6. A process according to any one of claims 3 to 5, wherein the novel polymorphic form is prepared from a solution of N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide hydrochloride in acetonitrile at 60°C, the product is allowed to crystallize on cooling and thereafter the resulting product is dried in vacuo at 60°C.
7. A pharmaceutical composition comprising the novel polymorphic form according to claim 1 and a pharmaceutically acceptable carrier therefor.
8. The present invention accordingly provides the novel polymorphic form according to claim 1, for use as an active therapeutic substance.
9. The novel polymorphic form according to claim 1, for use in the treatment of and/or prophylaxis of cardiac arrhythmia or ischaemic rhythm disorders.



11. A method for the treatment and/or prophylaxis of cardiac arrhythmia or ischaemic rhythm disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the novel polymorphic form according to claim 1, to a human or non-human mammal in need thereof.

12. A use of the novel polymorphic form according to claim 1, for the manufacture of a medicament for the treatment of cardiac arrhythmia or ischaemic rhythm disorders.

