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(71) Applicant (for all designated States except US): **CHIESI
FARMACEUTICI S. p. A.** [IT/IT]; Via palermo, 26/A,
43100 Parma (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PIGHI, Roberto**
[IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).
PIVETTI, Fausto [IT/IT]; Via Palermo, 26/A, I-43100
Parma (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Mi-
noja S.r.l., Via Rossini, 8, I-20122 Milan (IT).

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(54) Title: NOLOMIROLE HYDROCHLORIDE FORM I

(57) Abstract: Nolomirole hydrochloride in a highly purified crystalline polymorphic form I, the process for its preparation and pharmaceutical preparations thereof for the treatment of patients suffering of cardiovascular diseases such as congestive heart failure are described.

WO 2004/013083 A1

NOLOMIROLE HYDROCHLORIDE FORM I

The present invention relates to the pharmaceutical chemical compound nolomirole hydrochloride in a highly purified crystalline Form I, to the process for its preparation and isolation as well as to pharmaceutical preparations thereof for the treatment of patients suffering of cardiovascular diseases such as congestive heart failure.

In particular the present invention relates to a crystalline compound consisting of nolomirole hydrochloride polymorphic Form I of at least 95% by weight of chemical purity, preferably equal to or higher than 97%, more preferably 98% and of at least 90% w/w polymorphic purity, to the process for its preparation and isolation as well as to pharmaceutical preparations thereof for the treatment of patients suffering of cardiovascular diseases such as congestive heart failure.

(±)-5,6-diisobutyroyloxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride, (hereinafter indicated with its approved INN nolomirole hydrochloride) is a DA₂ dopaminergic receptor/ α_2 -adrenoceptor agonist, which has been claimed to be useful for the treatment of cardiovascular diseases (WO 96/29065) and in particular for the treatment of congestive heart failure.

Nolomirole hydrochloride is conveniently formulated in tablets for oral administration. The hydrochloride salt is particularly suitable for the preparation of tablets.

The daily dosage is comprised between 2.5 and 20 mg.

Nolomirole is a pro-drug which, after oral administration, is rapidly and completely converted, during absorption, by the esterases contained in the intestinal mucosa into its desesterified form, namely (±)-5,6-dihydroxy-2-methylaminotetralin, indicated hereinafter with the experimental code CHF 1024.

CHF 1024 also turned out to be one of the main occurring impurities and degradation products. Although the CHF 1024 is the active moiety, it is nevertheless important for pharmaceutical and therapeutic purposes that the drug product (nolomirole hydrochloride) is present in the formulation with
5 the highest as possible chemical purity.

Nolomirole has been first described as hydrobromide salt in GB 2,123,410 among a series of aminotetralin derivatives (tetralin is another name for 1,2,3,4-tetrahydro-naphthalene) and disclosed as potential antibronchospastic agents. In the description, an indication for the
10 preparation of the hydrobromide on a laboratory scale is provided in analogy to the pivaloyl derivative. Said procedure envisions precipitation from a mixture of ethyl ether and petroleum ether. The product has been characterised in terms of NMR spectrum in solution and melting point. The solvents used for its preparation cannot be utilised on an industrial scale;
15 moreover, although it is reported that the product is obtained as a white crystalline powder, once moving on a bigger scale, a significant percentage of amorphous is obtained.

EP 788472 in the name of the applicant and EP 534536 in the name of Zambon refer, respectively, to processes for the preparation of 5,6
20 dihydroxy-2-amino-tetralins and N-alkyl derivatives thereof and 5,6-dimethoxy-2-amino-tetralin as intermediates useful for obtaining pharmacologically active chemical compounds. In none of them processes for the preparation and isolation of acyl derivatives such as nolomirole are mentioned.

25 In a study presented as a poster at the XXth National Congress of AICAT (Rome, December 14-18, 1998), mainly aimed at investigating the thermal behaviour of nolomirole hydrochloride racemate (quoted with its experimental code CHF 1035) and its enantiomers, preliminary results about

its polymorphism were disclosed. In the poster it is stated that Form I can be obtained from acetone and ethanol after fast cooling, Form II from acetone after slow cooling and from III from methyl-ethyl-ketone. No details about the crystallisation conditions are reported nor on the process of preparation
5 of nolomirole hydrochloride.

In Giordano et al (*J Pharm Sci* 2001, 90(8), 1154-1163), the polymorphism of nolomirole hydrochloride has been thoroughly investigated. Thermal, spectroscopic, and X-ray diffraction analysis confirms that three differing crystal forms by recrystallization procedures
10 from common organic solvents can be obtained.

Taddei et al [*Biopolymers (Biospectroscopy)* 2002, 67, 289-293] used vibrational spectroscopy coupled with thermogravimetry and differential scanning calorimetry to investigate the possible presence of different polymorphic forms of CHF 1035 and their relative stability. Crystallized
15 CHF 1035 was obtained from an acetone solution by fast crystallization as α -form and from acetone solution by slow crystallization at a low cooling rate as β -form. According to the spectra, α and β -form in Taddei correspond to Form I and Form III in Giordano.

Recrystallizations have been performed in the prior art on a laboratory
20 scale and (in Giordano) according to the following procedures: 10 ml of the solvent under examination were saturated with the product, holding the temperature slightly below the boiling point. The hot suspension was then rapidly filtered into a flask maintained at room temperature (RT) or ice-cooled (IC). In all cases the filtrate was allowed to reach spontaneously RT
25 and to equilibrate overnight.

From ethanol and methanol as well as from methylethylketone, a single solid phase has been obtained whatever recrystallisation procedure is used; on the contrary, from acetone two solid phases were obtained depending on

the suspension was maintained at RT or IC. According to Giordano, Form I can be obtained from ethanol and methanol or acetone at room temperature, Form II from methylethylketone and Form III from acetone ice cooling.

We have now found that:

5 - Form I can be prepared in high chemical pure form by crystallization from acetone by ice cooling. It cannot be prepared by using ethanol/methanol since when operating on an industrial scale this kind of solvents can give rise to trans-esterification reactions and thus to significant amounts of de-esterified degradation products.

10 - Form II can be obtained from acetone at a temperature of about 20-25°C (room temperature), in any case not lower than 18°C;

 - Form III is obtained from methylethylketone.

Form II does not possess the chemical and physical stability characteristics required for a pharmaceutical product and is easily oxidised.

15 Moreover it has been found that Form II has not the desirable characteristics with respect to the manufacturing process since during isolation it is obtained as powder crystals that are indeed hardly filtered off to detriment of the product yield; moreover, said form strongly retains the solvent(s) of crystallisation so they cannot easily be dried.

20 The only form of nolomirole hydrochloride suitable as a medicament for pharmaceutical preparations is Form I. Accordingly, there is a need of a nolomirole hydrochloride Form I with high chemical and polymorphic purity and of a process for its preparation in order to fulfil the requirements described above.

25 In general terms, chemical purity is a very important issue for pharmaceutical products. Impurities should be kept as lowest as possible as they could be detrimental to the potency of the active ingredient and they could also be responsible of unwanted side effects.

According to the pharmaceutical guideline ICH Q1A "Stability Testing of new Active Substances (and Medicinal Products)" of October 1993, a 5% change in assay of the active ingredient from its initial value does not meet the criteria of acceptance.

5 In the case of the product of the invention, the main occurring impurities are the monoester 5(6)-isobutyroyloxy-2-methylamino-1,2,3,4-tetrahydro-naphthalene (CHF 2101) hydrochloride and the free cathecol derivative (CHF 1024) hydrochloride which, during storage, is easily oxidized to quinonic derivatives as evidenced by the slight coloring of the
10 product.

High crystallinity is another important issue as amorphous or prevalently amorphous compounds are not suitable for pharmaceutical use due to the fact that potential crystallisation during handling and storage is always present. Such crystallization, in turn, can be responsible for
15 phenomena such as post- compression hardening of tablets (Elamin et al Int J Pharm 1994, 108, 729-752). Moreover amorphous or partially amorphous materials absorb water in larger amounts than crystalline ones (Hancock et al. J. Pharm. Sci. 1997, 86, 1-12); so formulations containing active ingredients such as nolomirole hydrochloride, whose chemical stability is
20 particularly sensitive to the humidity content due to the presence of ester bonds which can be subjected to hydrolysis reactions, could face stability problems during long term storage.

Polymorphic purity is a further important issue since different polymorphs have different physical properties which in turn can affect both
25 stability and bioavailability. Among others, it has been reported that different physical forms (e.g. polymorphs) can have different hydrolysis and rate profiles (Waterman K et al *Pharm Dev Tech* 2002, 7, 113-146) so that the stability of molecules such as nolomirole hydrochloride could be

dramatically affected by the polymorphic purity.

The process for the preparation of nolomirole hydrochloride Form I needs to be suitable for operating on an industrial scale and the crystallization solvent(s) should be readily and almost completely removable. Moreover, the product should be in a form that is readily filtered off and easily dried.

Finally, it has been found that it is highly advantageous to obtain a product with a particle size less than 400 μm , preferably less than 300 μm , and more preferably between 100 and 300 μm . Said particle size is optimal for having either good flowability characteristics and an homogenous distribution of the active ingredient in the preparation of pharmaceutical solid dosage forms and especially tablets.

It has also been found that a solid material with a particle size of about or higher than 400 μm is easily oxidized.

OBJECT OF THE INVENTION

It is a first object of the invention to provide nolomirole hydrochloride of at least 95% chemical purity. It is a further object of the invention to provide nolomirole hydrochloride polymorphic Form I of at least 95%, preferably 97%, more preferably of at least 98% chemical purity. In a preferred embodiment of the invention it is provided nolomirole hydrochloride Form I of at least 97%, preferably of at least 98% chemical purity containing an amount equal or less than 0.3% by weight of 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydro-naphthalene (CHF 1024) hydrochloride and/or a content of 5(6)-isobutyroyloxy-2-methylamino-1,2,3,4-tetrahydro-naphthalene (CHF 2101) hydrochloride equal to or less than 1.0% by weight.

Advantageously, nolomirole hydrochloride Form I (also referred to as drug product) will have a polymorphic purity of at least 90%, preferably of at least 95%.

Form I and Form II according to the invention are identified from the Raman spectra and the powder X-ray diffraction pattern reported in Figures 1,2,3,4 respectively.

The present invention also provides a manufacturing process, which
5 can be applied on an industrial scale for preparing nolomirole hydrochloride of at least 95% chemical purity. Said process comprises the steps of:

- i) reacting ($\pm$) 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydro-naphthalene (CHF 1024) hydrochloride with isobutyryl chloride optionally in the presence of a suitable solvent to yield raw nolomirole;
- 10 ii) removing any volatile substance from the raw reaction product and dissolving the oily residue with an organic solvent;
- iii) precipitating nolomirole as hydrochloride salt from the solution by adding hydrochloric acid;

wherein the organic solvent of step ii) is an ether solvent, preferably
15 isopropyl ether or mixtures thereof with non-alcoholic solvents and step iii) is carried out by bubbling gaseous hydrochloric acid to avoid the use of water which might favour the hydrolysis of the ester bonds.

The synthesis of 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydro-naphthalene (CHF 1024) hydrochloride is described in EP 788472.

20 The conversion of CHF 1024 hydrochloride into its isobutyryl ester is effected by reaction with isobutyryl chloride, using a suitable solvent. The elimination of the solvent excess from the reaction raw product leads to the formation of an oily mass. It has been found that nolomirole can be precipitated as hydrochloride from its oily mass by addition of gaseous
25 hydrochloric acid in the presence of an ether solvent. It has been found in this respect that, among the possible ether solvents, isopropyl ether is particularly suitable. In fact in the presence of another widely used ether solvent, i.e methyl-*tert*-butyl ether, nolomirole might experience a

significant degradation to the monoester (CHF 2101) and free cathecol (CHF 1024) hydrochloride derivatives. We have indeed found that methanol can form due to the degradation of methyl *tert*-butyl ether in acidic environment: the formed methanol reacts with nolomirole by parasitic trans-
5 esterification giving rise to the two aforementioned degradation products.

Although raw nolomirole hydrochloride is further subjected to a purification step by crystallization, nevertheless the amount of the above mentioned impurities should be maintained as low as possible since they are difficult to be completely eliminated from the finished product due to their
10 close structural similarity.

A further object of the invention is a purification process of nolomirole hydrochloride to obtain the Form I characterized by high crystallinity as well as high chemical and polymorphic purity, at the same time fulfilling the other desirable features described above.

15 There is so provided a process for the (re)-crystallization of nolomirole hydrochloride by dissolving the product in a non alcoholic solvent with a boiling point lower than 70°C, preferably lower than 60°C, then cooling the solution to a temperature lower than 20°C, preferably lower than 18°C, more preferably equal to or lower than 5°C at a speed higher than 1°C/min.

20 In fact it has been found that a crystalline nolomirole hydrochloride Form I of a highly chemical and polymorphic purity, can only be obtained using a non alcoholic solvent with a boiling point lower than 70°C, preferably lower than 60°C and after cooling the solution of raw nolomirole to a temperature lower than 20°C, preferably equal to or lower than 18°C,
25 more preferably equal to or lower than 15°C, even more preferably equal to or lower than 5°C, at a speed higher than 1°C/min.

The preferred non alcoholic solvent is acetone. Contrary to the teaching of the prior art when the crystallization from acetone is carried out

at room temperature, at about 20°-25°C and in any case at a temperature higher than 18°C, it predominantly gives rise to the form II, which is unsuitable for pharmaceutical utilization.

Although nolomirole hydrochloride polymorphic Form I can be
5 obtained from ethanol and methanol as well, such solvents, as reported above, are not suitable as they give rise to trans-esterification reactions and thus to significant amounts of the de-esterified degradation products mentioned above, namely CHF 2101 hydrochloride and CHF 1024 hydrochloride.

10 The re-crystallization process of the invention, instead, allows to obtain predominantly polymorph I of nolomirole hydrochloride with a polymorphic purity of at least 90%, preferably of at least 95%, in a highly crystalline form with a very high chemical purity, higher than 95%, preferably 97%, more preferably 98%.

15 Advantageously, the above mentioned (re)-crystallization process gives rise to particles with an inherent particle size optimal for nolomirole hydrochloride to be conveniently formulated in tablets for oral administration. The particles of the active ingredient are uniformly incorporated in the mixture before tableting by simple mixing so avoiding
20 any further treatment such as milling which may disturb their crystallinity.

The present invention also provides a process for the conversion of Form II of nolomirole hydrochloride to Form I.

The process can be carried out using similar conditions of (re)crystallisation as those described above which give purified Form I.
25 According to this way, Form II is dissolved in a non alcoholic solvent having a boiling point lower than 70°C, preferably lower than 60°C, by warming, then cooled at a temperature lower than 20°C, preferably lower than 18°C, more preferably lower than 15°C till complete crystallisation.

The preferred non alcoholic solvent is acetone. In order to speed up the process, the solution may be seeded with few crystals of Form I prior to the initiation of product crystallisation. Alternatively, the process can be carried out by: i) suspending Form II in a non alcoholic solvent having a boiling
5 point lower than 70°C, preferably lower than 60°C, such as acetone, in the presence of Form I; ii) keeping the suspension under stirring at a temperature lower than 20°C, preferably of about 10°C for several hours, preferably for at least ten hours, then filtering the resulting product. In a preferred embodiment the suspension has been stirred for 30 hours.

10 A particular object of the present invention is the use of nolomirole hydrochloride Form I of at least 95%, preferably 97%, more preferably 98% chemical purity as a medicament for the preparation of pharmaceutical compositions for the treatment of patients suffering from cardiovascular diseases, in particular congestive heart failure.

15 A further object of the invention are pharmaceutical compositions, in form of tablets for oral administration, further comprising pharmaceutically acceptable excipients, advantageously containing between 2.5 mg and 10 mg of the active ingredient per unit dose, preferably 2.5 mg or 5 mg per unit dose.

20 DETAILED DESCRIPTION OF THE INVENTION

The characteristics of the process for the preparation of nolomirole hydrochloride and nolomirole hydrochloride Form I and the features of the product obtained will be more apparent from the following detailed description.

25 The synthesis of nolomirole hydrochloride is carried out by conversion of 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride into its 5,6-diisobutyryl ester by reaction with isobutyryl chloride, using a suitable solvent, followed by the elimination of the solvent excess from

the reaction raw product till an oily mixture is obtained. The term suitable solvent means any volatile polar acidic solvent, preferably halogenated acetic acid. The preferred one is trifluoroacetic acid.

Advantageously, nolomirole is precipitated as hydrochloride from the
5 oily mixture by bubbling gaseous hydrochloric acid in the presence of an ether solvent. Preferably, gaseous hydrochloric acid is bubbled for at least 15 minutes, more preferably for 60 minutes keeping the temperature under 20°C, then optionally lowering the temperature to about 10°C and then to about 5°C.

10 As an ether solvent, isopropyl ether, ethyl ether, dioxane, tetrahydrofurane, 2-methoxyethyl ether and 2-ethoxyethyl ether can be advantageously used. Preferably, pure isopropyl ether or mixtures thereof with other non alcoholic solvents such as acetone and toluene, preferably in a ratio comprised between 10:1 to 3:1 v/v are used. More preferably, a
15 mixture of isopropyl ether: acetone in a ratio 5:1 is used.

Advantageously the process of (re)-crystallization for the preparation of nolomirole hydrochloride Form I starting from either raw nolomirole hydrochloride or nolomirole hydrochloride Form II is carried out as follows: i) dissolving in a suitable flask the product in a non alcoholic
20 solvent having a boiling point lower than 70°C, preferably lower than 60°C such as acetone at a temperature from about 30°C to reflux temperature, preferably at 50°C; ii) cooling the solution, preferably under stirring, by standard methods and/or by concentration under vacuum to a temperature lower than 20°C, preferably lower than 18°C, more preferably lower than
25 15°C, even more preferably lower than or equal to 5°C at a speed higher than 1°C/min, preferably equal to or higher than 2°C/min. Although theoretically suitable halogenated solvents such as chloroform are to be avoided for environmental reasons.

The amount of solvent is at least 3 part by volume per part of product. Higher amounts of solvents and generally up to 10 parts by volume can be used. Amounts higher than 10 volumes are not useful from an economical point of view because large size apparatus would be necessary. The most
5 preferred solvent is acetone.

The flask will be advantageously maintained at 5°C and the precipitation will typically be accomplished within 5 hours. However the time required will vary depending on such factors such as total volume of solution, size of batch and presence or absence of stirring. Methods known
10 in the art may be used to enhance any aspect of the process. For example, as reported above for crystallization of Form I starting from Form II, the solution may be seeded with few crystals of Form I prior to the initiation of product crystallisation; nolomirole hydrochloride Form I can be collected by any standard method known in the art such as by filtration, filtration under
15 vacuum, or decantation and drying.

Nolomirole hydrochloride Form I obtained by the process of the invention has a chemical purity, as determined by HPLC of at least 95% by weight, preferably of at least 97%, more preferably equal to or higher than 98%, with a melting range of 198-206°C as determined by Differential
20 Scanning Calorimetry (DSC). The main impurities are detected: the content of CHF 1024 hydrochloride is less or equal than 0.3% by weight and/or the content of CHF 2101 hydrochloride is less or equal than 1.0% by weight.

Accordingly, it is provided a method of testing the chemical purity of a sample of nolomirole hydrochloride Form I or a pharmaceutical dosage form
25 comprising nolomirole hydrochloride Form I assaying it for the presence of said derivatives.

The drug product and the pharmaceutical dosage form may be analyzed for purity or stability to degradation by a conventional analytical technique

and preferably by high performance liquid chromatography (HPLC).

The analytical testing will confirm that the main impurities or degradation products CHF 1024 hydrochloride and CHF 2101 hydrochloride are present at the above defined levels.

5 Advantageously, the polymorphic purity and the degree of crystallinity are both higher than 90% by weight, preferably higher than 95% as determined by powder X-ray diffraction. The crystal structure of nolomirole hydrochloride Form I has been determined. Unique indexing and lattice parameters values ($a=29.73(2)$ Å, $b=7.748(5)$ Å, $c=18.479(13)$ Å and
10 $\beta=104.901(9)^\circ$) were obtained from single crystal X-ray experiments performed on small ($0.19 \times 0.15 \times 0.06$ mm) specimen selected from the crystalline powder. The observation of systematic absences gave monoclinic C2/c space group and eight closely packed molecules in the unit cell.

Advantageously, at least 95% of the particles of nolomirole
15 hydrochloride Form I has a diameter lower than 400 µm, preferably equal to or lower than 300 µm, more preferably comprised between 100 and 300 µm, as determined by laser diffraction (Malvern).

Form I of nolomirole hydrochloride produced according to the process of the invention can be characterised by its Raman spectrum and its X-ray
20 powder diffraction (XRD) pattern (Figs 1 and 2). The FT-Raman spectrum, obtained by simply packing the powder into a cup, shows the following main peaks in the $3500-700$ cm⁻¹ range (accuracy ± 1 cm⁻¹):

2937 cm⁻¹ (vs); 1771 (s); 1614 (s); 1588 (s); 1446 (s); 1426 (s); 1302
(s); 1274 (m); 1221 (m); 1255 (m); 1098 (br, m); 1009 (w); 966 (w); 856 (s);
25 818 (m)

Legend: vs = very strong; s = strong; m = medium; w = weak; br = broad

The interplanar distances and relative peak intensities (in brackets) of

the powder XRD pattern are reported as follows (depending on the packing conditions, the relative intensities can change):

14.35 d/Å (64); 8.93 (18); 8.63 (6); 7.46 (34); 7.19 (100); 7.13 (5);
7.04 (3); 6.46 (19); 5.55 (6); 5.40 (12); 4.82 (4); 4.66 (3); 4.62 (7); 4.52
5 (11); 4.27 (18); 4.07 (5); 3.90 (3); 3.80 (28); 3.60 (6); 3.55 (3); 3.24 (4);
2.86 (3).

For comparison Figures 3 and 4 show the Raman and XRD fingerprints of Form II.

The following examples better illustrate the invention.

10 **EXAMPLES**

Example 1 - Process for obtaining (±)-5,6-diisobutyroyloxy-2-methylamino-tetralin hydrochloride (nolomirole hydrochloride) starting from (±) 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydro-naphthalene (CHF 1024) hydrochloride.

15 Slowly add, in 2 hours, a molar excess of isobutyryl chloride to a suspension of CHF1024 hydrochloride in trifluoroacetic acid, always keeping temperature at $25 \pm 2^\circ\text{C}$.

Then heat the solution to $85 \pm 2^\circ\text{C}$ for 1 hour, thus obtaining a full dissolution.

20 Cool to $50 \pm 5^\circ\text{C}$, distil the maximum part of trifluoroacetic acid under vacuum and add toluene to the oily residue: then, distil again to oil.

Repeat three times both addition and distillation of toluene, then dissolve the oily residue in a mixture of isopropyl ether: acetone 5:1 v/v. Let gaseous hydrochloric acid bubbling for 60 minutes keeping temperature
25 under 20°C .

Raw nolomirole hydrochloride precipitates as a white crystalline solid and the suspension is kept at $10 \pm 2^\circ\text{C}$ for three hours, then at $5 \pm 3^\circ\text{C}$ for further five hours and finally centrifuged. The obtained raw nolomirole

hydrochloride is dried under vacuum at $60 \pm 2^\circ\text{C}$.

The purity of the compound obtained is about 95% both upon ^1H NMR and HPLC analysis.

^1H NMR ($\text{CH}_3\text{OH}-d_4$, ppm): 1.28 (d, 6H); 1.35 (2 x d, 6H); 1.82 (m, 1H), 2.30 (m, 1H); 2.6-3.0 (m, 5H); 2.80 (s, 3H); 3.30 (dd, 1H); 3.48 (m, 1H), 7.0-7.2 (AB syst, 2H).

^{13}C NMR ($\text{CH}_3\text{OH}-d_4$, ppm): 19.3; 19.4; 22.9; 25.6; 30.9; 32.2; 35.0; 55.9; 122.5; 128.2; 130.5; 132.4; 141.6; 142.5; 175.5; 176.6.

Legend: d = doublet; dd= doublets of doublet; m = mutiplet; s = single

10 Example 2 – Process for obtaining nolomirole hydrochloride Form I starting from raw nolomirole hydrochloride

Raw nolomirole hydrochloride is purified by crystallisation on acetone. The solid substance is dissolved in 10 volumes of solvent at 50°C , filtered, then the limpid solution is cooled to a temperature of 5°C upon concentration under vacuum at a speed of $2^\circ\text{C}/\text{min}$. The temperature is kept for five hours at $5 \pm 2^\circ\text{C}$, then centrifuged. The solid is dried under vacuum, at $60 \pm 2^\circ\text{C}$.

Assay = 99.1% (HPLC); melting range = $199-202^\circ\text{C}$ (DSC).

Operating in the same conditions as described in Example 2 nolomirole hydrochloride Form I can be obtained starting from nolomirole hydrochloride Form II as such or in presence of Form I.

25 Example 3 - The crystal structure of nolomirole hydrochloride Form I has been determined. Unique indexing and lattice parameters values ($a=29.73(2)$ Å, $b=7.748(5)$ Å, $c=18.479(13)$ Å and $\beta=104.901(9)^\circ$; cell volume= $4113(5)$ Å³) were obtained from single crystal X-ray experiments performed at ambient temperature $T=293(2)$ on a small specimen ($0.19 \times 0.15 \times 0.06$ mm) selected from the crystalline powder on a Bruker diffractometer using molibdenum $K\alpha$ radiation (0.7107 Å). The observation of systematic

absences gave monoclinic C2/c space group and eight closely packed molecules in the unit cell. The bond distances and angles are reported in Table 1 and the structure of the molecule is reported in Figure 5, wherein the thermal vibration ellipsoid of all non-hydrogen atoms is indicated.

5

Table 1

Bond lengths (Å)		Bond Angles (°)	
O1-C6	1.3858(135)	C18-C17-C19	111.52(3)
O1-C16	1.3548(176)	C18-C17-C16	114.08(4)
O2-C5	1.4193(146)	C19-C17-C16	109.24(4)
O2-C12	1.3660(176)	C11-N1-C2	114.62(4)
O3-C12	1.2058(177)	C15-C13-C14	113.29(4)
O4-C16	1.1860(179)	C15-C13-C12	113.25(4)
N1-C2	1.4990(124)	C14-C13-C12	107.65(3)
N1-C11	1.4877(145)	C5-O2-C12	117.94(4)
C1-C2	1.5230(160)	C6-O1-C16	117.62(5)
C1-C9	1.5165(148)	O2-C5-C6	119.59(4)
C2-C3	1.5214(157)	O2-C5-C10	117.64(4)
C4-C3	1.5171(146)	C6-C5-C10	122.44(4)
C4-C10	1.5032(163)	O1-C6-C5	119.36(4)
C5-C6	1.4065(172)	O1-C6-C7	122.14(4)
C5-C10	1.3851(159)	C5-C6-C7	118.49(4)
C6-C7	1.3489(189)	C10-C4-C3	112.09(4)
C8-C7	1.3743(161)	O4-C16-C17	125.03(4)
C8-C9	1.3962(166)	O4-C16-O1	123.28(5)
C10-C9	1.3765(175)	C17-C16-O1	111.69(4)
C13-C12	1.4968(215)	C5-C10-C4	118.54(4)
C14-C13	1.4792(225)	C5-C10-C9	118.03(4)
C15-C13	1.4239(230)	C4-C10-C9	123.35(4)
C17-C16	1.4701(192)	O3-C12-C13	125.69(4)
C18-C17	1.4956(236)	O3-C12-O2	122.85(5)
C19-C17	1.5379(244)	C13-C12-O2	111.39(4)
		C2-C1-C9	109.41(4)
		N1-C2-C1	109.69(4)
		N1-C2-C3	108.59(4)
		C1-C2-C3	110.44(3)
		C4-C3-C2	111.09(4)
		C9-C8-C7	122.02(4)
		C10-C9-C1	122.16(4)
		C10-C9-C8	118.99(4)
		C1-C9-C8	118.83(4)
		C6-C7-C8	119.87(4)

CLAIMS

1. A compound which is ($\pm$)-5,6-diisobutyroyloxy-2-methylamino-tetralin (nolomirole) hydrochloride of at least 95% by weight chemical purity.
2. A process for preparing ($\pm$)-5,6-diisobutyroyloxy-2-methylamino-tetralin (nolomirole) hydrochloride which comprises the steps of:
 - i) reacting ($\pm$) 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride (CHF 1024) with isobutyroyl chloride optionally in the presence of a suitable solvent to yield raw nolomirole;
 - ii) removing any volatile substance from the raw reaction product and dissolving the oily residue with an organic solvent;
 - iii) precipitating nolomirole as hydrochloride salt from the solution by adding hydrochloric acid.
3. A process according to claim 2 wherein the step i) is carried out in the presence of a volatile polar acidic solvent.
4. A process according to claim 3 wherein the solvent is an halogenated acetic acid such as trifluoroacetic acid.
5. A process according to claim 2 wherein the organic solvent of step ii) is an ether solvent.
6. A process according to claim 5 wherein the ether solvent is selected from isopropyl ether, ethyl ether, dioxane, tetrahydrofuran, 2-methoxyethyl ether and 2-ethoxyethyl ether.
7. A process according to claims 5 and 6 wherein the ether solvent is isopropyl ether or mixtures thereof with a non-alcoholic solvent such as acetone or toluene.
8. A process according to claim 2 wherein step iii) is carried out by bubbling gaseous hydrochloric acid.
9. A process according to claims 2-8 to obtain nolomirole hydrochloride

of at least 95% chemical purity.

10. Crystalline nolomirole hydrochloride polymorphic Form I of at least 95% by weight chemical purity.

11. Nolomirole hydrochloride according to claim 10 characterized by a
5 melting range of 198-206°C.

12. Crystalline nolomirole hydrochloride according to claims 10 and 11 wherein the polymorphic purity and the crystallinity are of at least 90% by weight.

13. A process for preparing crystalline nolomirole hydrochloride Form I
10 by dissolving nolomirole hydrochloride in a non alcoholic solvent with a boiling point lower than 70°C then cooling the solution to a temperature lower than 20°C at a speed higher than 1°C/min.

14. A process according to claim 13 wherein the non alcoholic solvent is acetone and the product is dissolved in said solvent at a temperature from
15 about 30°C to reflux temperature.

15. A process according to claims 13-14 wherein the solution is cooled at a temperature lower than 15°C.

16. A process according to claims 13-15 wherein the solution is cooled at a temperature lower than 5°C at a speed equal or higher than 2°C/min.

20 17. A process for preparing a crystalline nolomirole hydrochloride Form I which comprises the step of dissolving nolomirole hydrochloride Form II in a non alcoholic solvent with a boiling point lower than 70°C, at a temperature from about 30°C to reflux temperature, then cooling the solution at a temperature lower than 20°C.

25 18. A process for preparing a crystalline nolomirole hydrochloride Form I which comprises the steps of: i) suspending nolomirole hydrochloride Form II in a non alcoholic solvent having a boiling point lower than 70°C in the presence of Form I; ii) keeping the suspension under stirring at a

temperature lower than 20°C, preferably 10°C, filtering the resulting product.

19. A process according to claims 17-18 wherein the non alcoholic solvent is acetone.

5 20. A process according to claims 13-19 for preparing crystalline nolomirole hydrochloride Form I of at least 95% by weight chemical purity.

21. A process according to claims 13-19 wherein the polymorphic purity and the crystallinity are higher than 90% by weight.

22. Crystalline nolomirole hydrochloride according to claims 10 and 11
10 having a content of 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride equal or less than 0.3% by weight and/or of 5(6)-isobutyryloxy- 2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride is equal to or less than 1.0% by weight.

23. A method of testing the purity of a sample of nolomirole
15 hydrochloride Form I or a pharmaceutical dosage form comprising nolomirole hydrochloride Form I, which method comprises assaying the said sample for the presence of 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride and/or 5(6)-isobutyryloxy- 2-methylamino-1,2,3,4-tetrahydronaphthalene hydrochloride.

20 24. Nolomirole hydrochloride Form I crystal having *inter alia* the following characteristic: $a=29.73(2) \text{ \AA}$, $b=7.748(5) \text{ \AA}$, $c=18.479(13) \text{ \AA}$ and $\beta=104.901(9)^\circ$.

25 25. Crystalline nolomirole hydrochloride Form I obtainable according to the process of claims 13-21 having *inter alia* the following characteristic FT-Raman spectrum peaks in the $3500\text{-}700 \text{ cm}^{-1}$ range:

2937 cm^{-1} (vs); 1771 (s); 1614 (s); 1588 (s); 1446 (s); 1426 (s); 1302 (s); 1274 (m); 1221 (m); 1255 (m); 1098 (br, m); 1009 (w); 966 (w); 856 (s); 818 (m),

and/or the following characteristic XRD peaks:

14.35 d/Å (64); 8.93 (18); 8.63 (6); 7.46 (34); 7.19 (100); 7.13 (5);
7.04 (3); 6.46 (19); 5.55 (6); 5.40 (12); 4.82 (4); 4.66 (3); 4.62 (7); 4.52
(11); 4.27 (18); 4.07 (5); 3.90 (3); 3.80 (28); 3.60 (6); 3.55 (3); 3.24 (4);
2.86 (3).

5 26. Crystalline nolomirole hydrochloride Form I according to any
preceding claim as a medicament for the preparation of pharmaceutical
compositions for the treatment of patients suffering from cardiovascular
diseases such as congestive heart failure.

27. Crystalline nolomirole hydrochloride Form I according to claim 26
10 wherein the 95% of the particles have a particle size of less than 300 µm.

28. A pharmaceutical composition comprising crystalline nolomirole
hydrochloride Form I according to claims 26 and 27 in combination with at
least one pharmaceutical acceptable excipient.

29. A pharmaceutical composition according to claim 28 in the form of
15 tablet for oral administration containing between 2.5 and 5 mg of
nolomirole hydrochloride per unit dose.

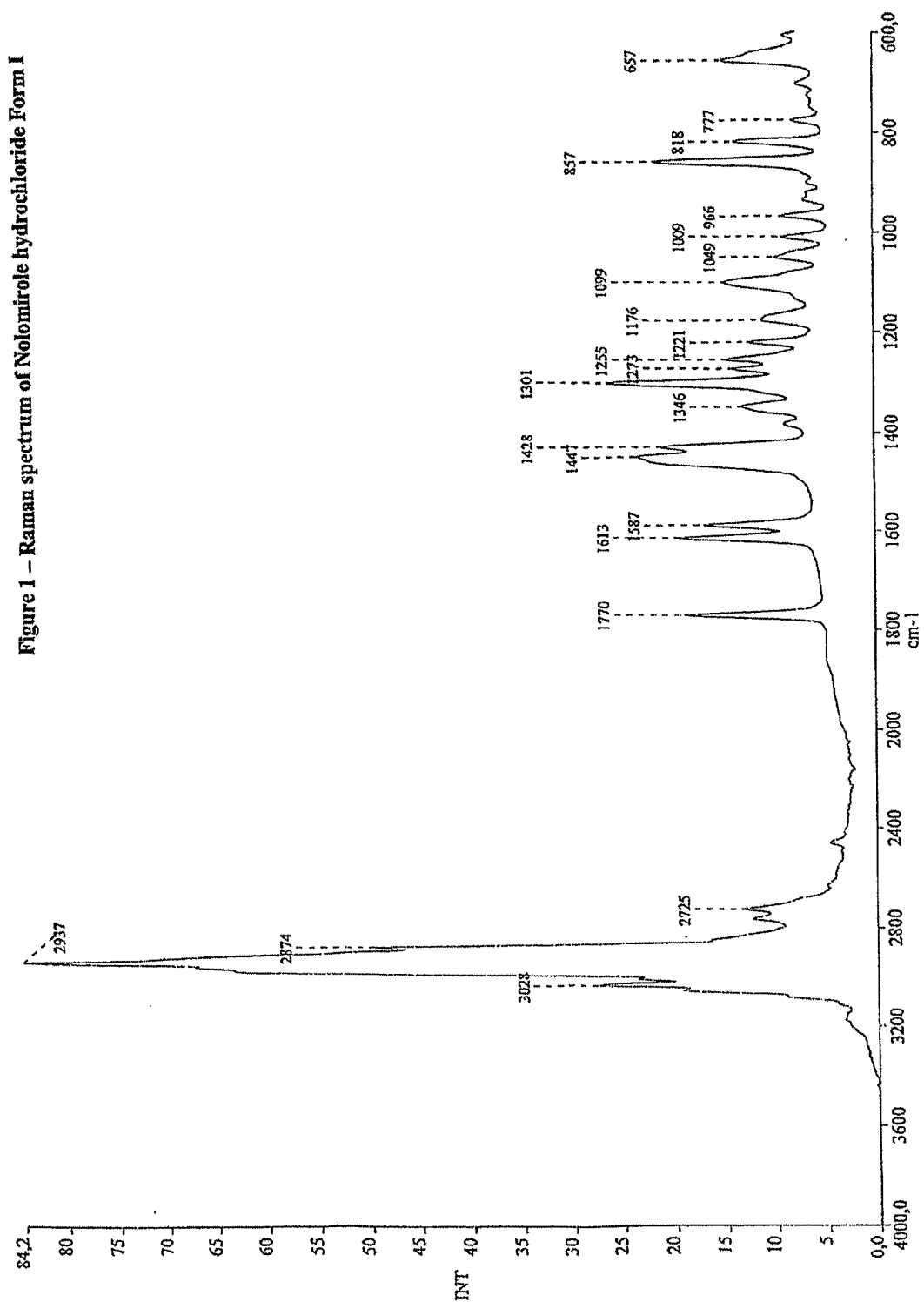
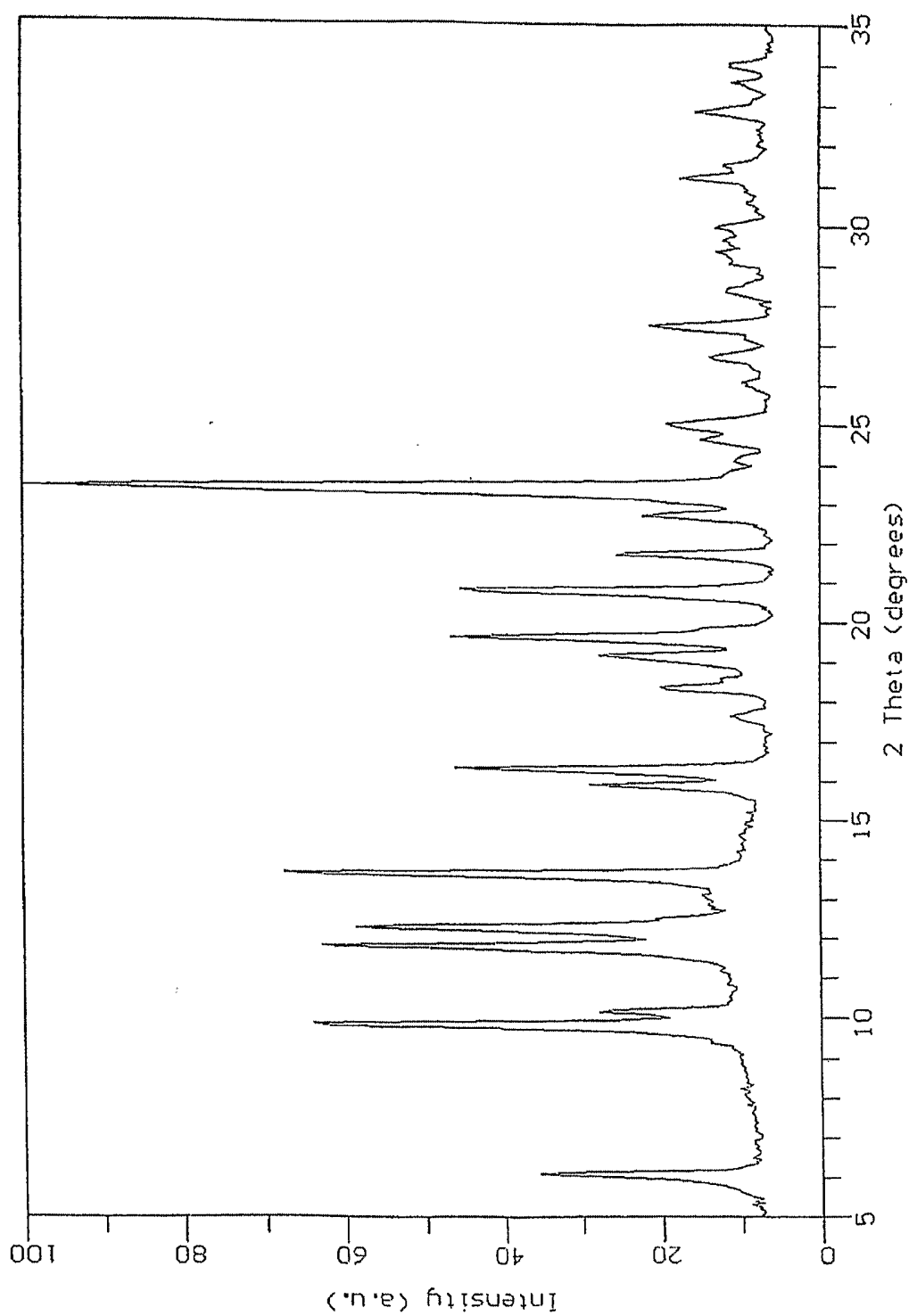


Figure 2 -- XRD pattern of Nolomirole hydrochloride Form I



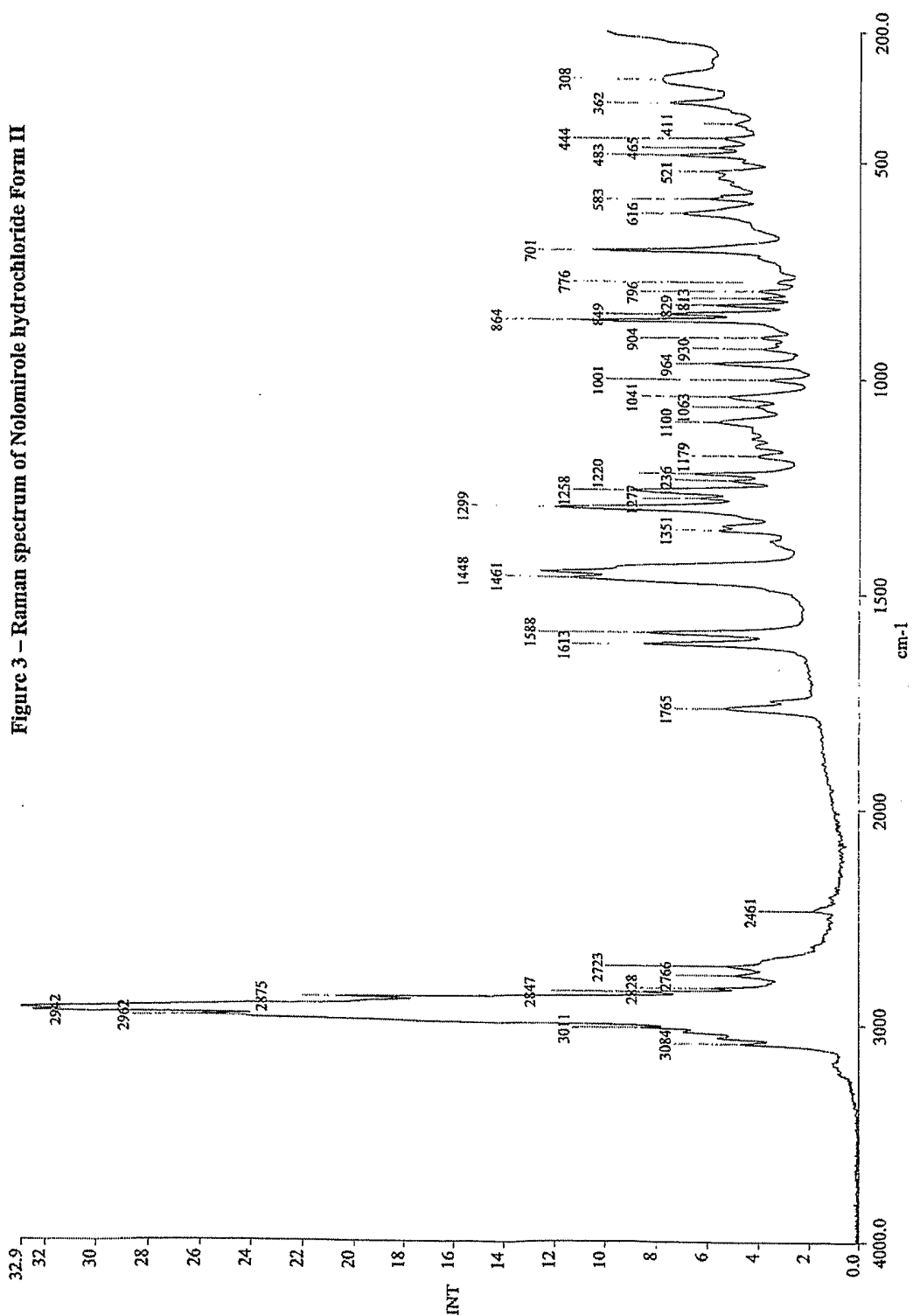


Figure 4:— XRD pattern of Nolomirole hydrochloride Form II

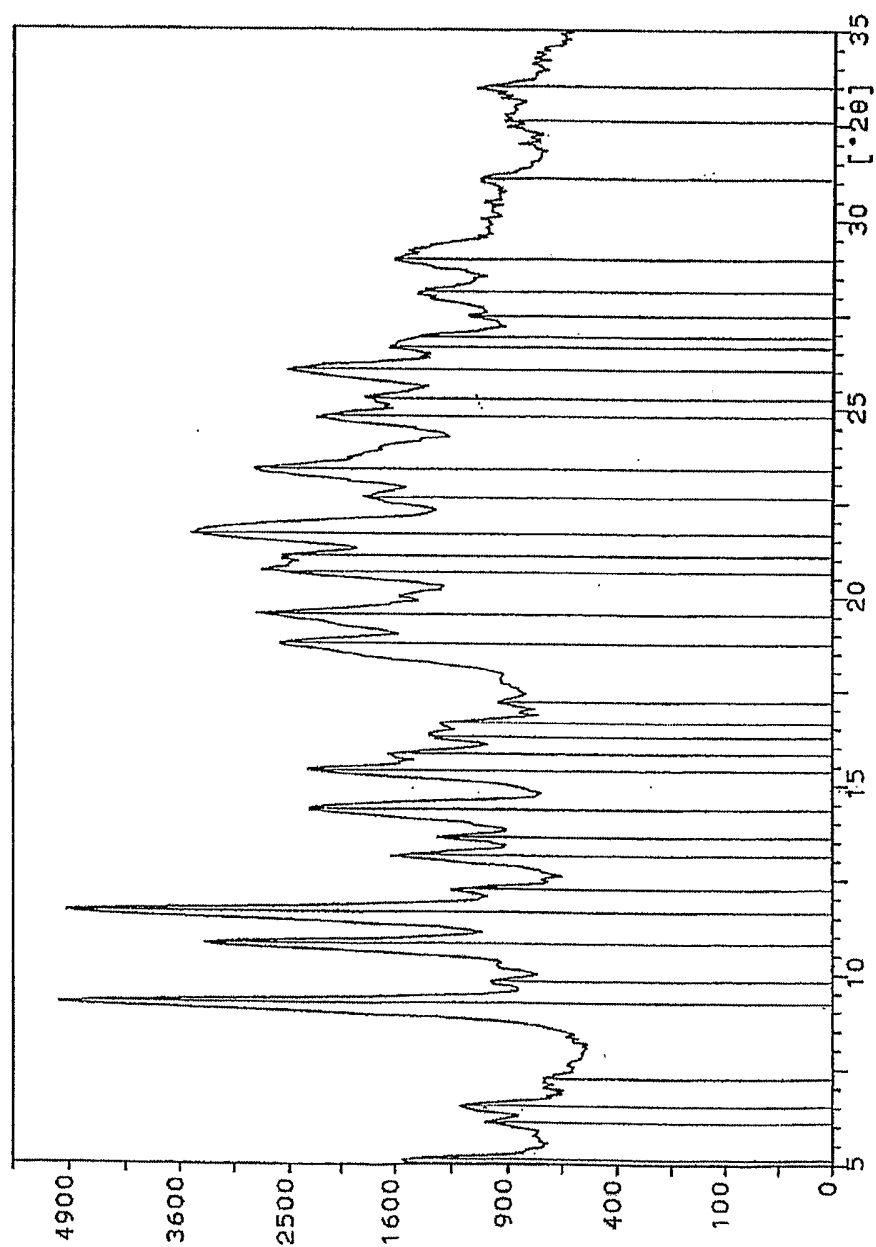
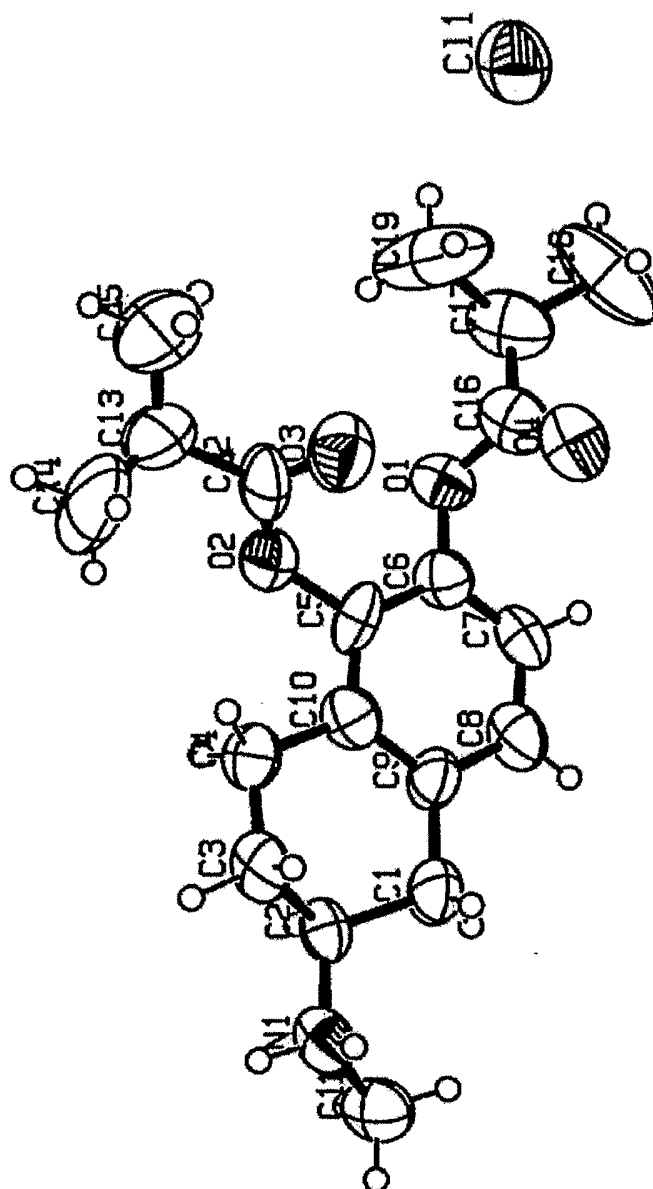


Fig. 5



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08078

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C213/10 C07C213/00 C07C215/64 A61K31/22 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EP0-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 85668 A (DEL CANALE MAURIZIO ;AMARI GABRIELE (IT); RONDELLI IVANO (IT); CHI) 15 November 2001 (2001-11-15) example 3 h) on p. 15 page 6, line 13-17 --- -/--	1-12,22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

25 November 2003

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Österle, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GIORDANO, FERDINANDO ET AL: "Polymorphism of rac-5,6-diisobutyryloxy-2-methylamino-1,2, 3,4-tetrahydro- naphthalene hydrochloride (CHF 1035). I. Thermal, spectroscopic, and X-ray diffraction properties" JOURNAL OF PHARMACEUTICAL SCIENCES (2001), 90(8), 1154-1163, XP002223546 cited in the application page 1156, column 2, paragraph 3 -page 1157, column 1, paragraph 4	10-12, 22-25
Y		26-29
A		13-21
X	MEALY, N. E. ET AL: "Nolomirole hydrochloride: treatment of heart failure dopamine D2 agonist.alpha.2-adrenoreceptor agonist CHF - 1035" DRUGS OF THE FUTURE (2001), 26(11), 1046-1051, XP009002202 page 1-2	1-9
X	WO 96 29065 A (UMILE ALBERTO ;CHIESI PAOLO (IT); BONGRANI STEFANO (IT); CHIESI FA) 26 September 1996 (1996-09-26) cited in the application claims; examples	1
Y	claims; examples	26-29
X	TADDEI, PAOLA ET AL: "Vibrational study of polymorphism of tetralin derivative for treatment of cardiovascular diseases" BIOPOLYMERS (2002), VOLUME DATE 2001-2002, 61(3), 289-293, XP009002199 *the whole document*	1
Y	page 289, column 1	26-29
A	GB 2 123 410 A (CHIESI FARMA SPA) 1 February 1984 (1984-02-01) cited in the application claims; examples *the whole document*	1-9, 28, 29

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08078

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0185668 A	15-11-2001	IT MI20001053 A1	12-11-2001
		AU 7400001 A	20-11-2001
		BG 107259 A	31-07-2003
		CZ 20023718 A3	12-02-2003
		WO 0185668 A1	15-11-2001
		EP 1280759 A1	05-02-2003
		HU 0302027 A2	28-10-2003
		NO 20025393 A	13-01-2003
		SK 16052002 A3	04-03-2003
WO 9629065 A	26-09-1996	IT MI950532 A1	17-09-1996
		AT 218856 T	15-06-2002
		AU 702656 B2	25-02-1999
		AU 5107296 A	08-10-1996
		BR 9607996 A	23-06-1998
		CA 2215671 A1	26-09-1996
		CN 1181699 A ,B	13-05-1998
		CZ 9702866 A3	18-03-1998
		DE 69621786 D1	18-07-2002
		DE 69621786 T2	02-01-2003
		DK 814791 T3	07-10-2002
		EA 937 B1	26-06-2000
		EE 9700231 A	15-04-1998
		WO 9629065 A2	26-09-1996
		EP 1216702 A2	26-06-2002
		EP 0814791 A1	07-01-1998
		ES 2177769 T3	16-12-2002
		HK 1004802 A1	11-10-2002
		HU 9801686 A2	28-06-1999
		IL 117518 A	20-05-2001
		JP 11502211 T	23-02-1999
		LT 97147 A ,B	25-02-1998
		LV 11882 A	20-12-1997
		LV 11882 B	20-03-1998
		NO 974267 A	07-11-1997
		PL 322284 A1	19-01-1998
		PT 814791 T	31-10-2002
		SI 9620036 A ,B	28-02-1998
		SK 125497 A3	04-02-1998
		TR 9700963 T1	21-02-1998
		US 6013678 A	11-01-2000
		ZA 9602073 A	25-09-1996
GB 2123410 A	01-02-1984	IT 1218322 B	12-04-1990
		DE 3320936 A1	22-12-1983
		FR 2528422 A1	16-12-1983