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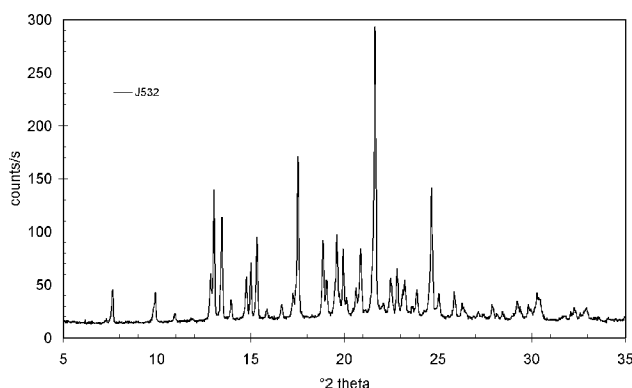
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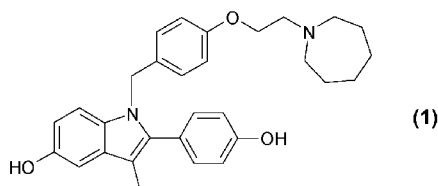
(54) Title: CRYSTALLINE COMPOUND OF 1-[4-(2-AZEPAN-1-YLETHOXY)BENZYL]-2-(4-HYDROXYPHENYL)-3-METHYL-1H-INDOL-5-OL

Figure 1

Form A



(57) Abstract: The present invention relates to a crystalline compound of 1-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (INN: bazedoxifene) of formula (1) with an acid selected from the group consisting of propionic acid or nicotinic acid or a hydrate thereof, where the molar ratio of the compound of formula (1) to the acid is 1:0.9 to 1:1.1, and to a process for its preparation.



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Crystalline compound of 1-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol

- 5 The present invention relates to a crystalline compound of 1-[4-(2-azepan-1 -ylethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1 H-indol-5-ol (INN: bazedoxifene) with an acid selected from the group consisting of propionic acid or nicotinic acid or a hydrate thereof, and a process for its preparation.
- 10 Bazedoxifene belongs to the class of selective oestrogen receptor modulators (SERMs). Selective oestrogen receptor modulators (SERMs) are defined as substances that bind to the oestrogen receptor with high affinity and at the same have no significant binding activity with other nuclear receptors. In contrast to oestrogens, however, they lead in the various target tissues to "oestrogen-
- 15 agonistic" or "oestrogen-antagonistic" action. Bazedoxifene is effective in the prevention and treatment of osteoporosis and in particular of postmenopausal osteoporosis. A detailed description of its action can be found, for example, in Drugs of the Future, 2002, 27(2), 117-121 .
- 20 The preparation of bazedoxifen and its acetates is disclosed in US 5,998,402 and US 6,479,535. The preparation of bazedoxifene has also been described in J.Med.Chem. 2001 , 44, 1654-1657.
- Crystalline bazedoxifene acetate is disclosed in US 2005/0227965 A1. In particular,
- 25 two polymorphic forms of bazedoxifene acetate are described. However, according to the teaching of US 2005/0227965 A1 bazedoxifene acetate contains impurities and is unstable.
- According to the prior art, form B of bazedoxifene acetate is the thermodynamically
- 30 stable form while form A is kinetically stable. For this reason, the conditions for the

- 2 -

preparation of pure form A or pure form B are critical, in particular if the solvent used for crystallization is identical, as is described in US 7,683,051 and US 7,683,052.

WO 2009/012734 A2 discloses salts of bazedoxifene with polycarboxylic acids.

- 5 The undesired decomposition of bazedoxifene acetate is to be avoided by making available novel salts of bazedoxifene. No crystalline compounds containing bazedoxifene and propionic acid or nicotinic acid are disclosed in WO 2009/012734 A2 and US 2005/0227965 A1.

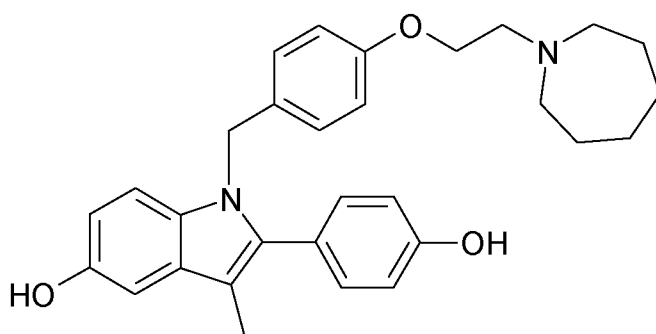
- 10 The use of a substance as a medicament necessitates a high substance quality of the pharmaceutically active substance. One of the most effective purification processes is crystallization. If a substance cannot be crystallized, it can be difficult to adhere to the internationally recognized quality criteria of the ICH (International Commission for Harmonization). In addition, amorphous substances are often
15 prone to easier decomposition, in particular to hydrolysis or oxidation, which can be caused by the higher free energy and by the typically larger surface area. To summarize, it can be stated that bazedoxifene and the forms thereof known up to now are difficult to purify and prone to decomposition.

- 20 The technical object of the present invention is the provision of crystalline compounds comprising bazedoxifene that have an advantageous property profile. In particular, these compounds should be easily obtainable, have good stability and be free of decomposition products. In addition, a process for the preparation of the aforementioned compounds should be made available.

25

The technical object of the present invention is achieved by a crystalline compound of 1-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1 H-indol-5-ol (INN: bazedoxifene) of formula 1

- 3 -



formula 1

with an acid selected from the group consisting of propionic acid or nicotinic acid or a hydrate thereof, where the molar ratio of the compound of formula 1 to the
5 acid is 1:0.9 to 1:1.1.

Surprisingly, the aforementioned compounds are easily obtainable and have good stability.

- 10 Surprisingly, the abovementioned acids and bazedoxifene form a crystalline compound having the molar ratio indicated above. In a preferred embodiment, the molar ratio of the compound of formula 1 and of the acid is 1:0.95 to 1:1.05 and most preferably 1:1.
- 15 Amorphous forms are generally characterized in that they show no sharp powder diffraction reflections. The powder diagram of amorphous forms has only a strongly increased background signal in the $2\theta^\circ$ region from about 10° to 30° . Mesomorphic forms are normally characterized in that they often only exhibit one or two, or no sharp powder diffraction reflections at all. Mixtures of amorphous
20 and crystalline phases especially exhibit only very weak powder diffraction reflections if the amorphous content is very high; for example 50% or higher.

X-ray powder diffraction is a widespread and recognized method for identification and characterization of molecular solids. Descriptions of this method are found
25 both in the European Pharmacopoeia and in the US Pharmacopeia as Method No. 941 "X-Ray Diffraction", or in "Polymorphism - In the Pharmaceutical Industry"

Chapter 6, Rolf Hilfiker, Editor Wiley-VCH Verlag, Weinheim, Germany, 2006.

Normally, x-ray powder diffraction is carried out using copper κ_α radiation, as was also the case here. D values in $\text{\AA}$ (d) and 2-theta (2Θ) values in angular degrees can be converted into one another by Bragg's equation as follows: $n\lambda = 2d\sin\theta$,

5 where n is an integer and λ is the wavelength of the x-ray radiation used in A. The data obtained from a powder diffraction measurement are signal intensity (in counts) as a function of the angle 2Θ as a measured variable. Furthermore, it is to be observed that measurements can be made both in reflection geometry, and in transmission geometry. The measurements mentioned here were carried out in
10 reflection geometry. While the position of the lines in angular degrees is not dependent on the geometry, the relative intensities, however, can change both due to the geometry, and due to the properties of the sample and the sample preparation. Therefore, the intensities indicated serve only as a qualitative feature. With measurements of this type, the measuring error is usually $\pm 0.2^\circ 2\Theta$. While
15 the measuring error for $^\circ 2\Theta$ over the entire measuring range is changed only slightly or not at all, on account of the abovementioned Bragg's equation the error in the d values is dependent on the angle. 2Θ angles and d values, however, are equivalent and, therefore, no measuring errors have been calculated for the d values, although one is present.

20

A special feature of the present invention here are crystalline compounds of bazedoxifene, which are emphasized by a high crystalline purity. The crystalline compounds of the present invention have sharp powder diffraction reflections and contain only small amorphous fractions.

25

Raman spectroscopy is a second very useful method for the identification and characterization of various forms of molecular solids. More detailed descriptions of the use of Raman spectroscopy for the purpose mentioned are found, for example, in "Polymorphism - In the Pharmaceutical Industry" Chapter 5, Rolf Hilfiker, Editor
30 Wiley-VCH Verlag, Weinheim, Germany, 2006. In measurements of this type the measuring error is customarily $\pm 1 \text{ cm}^{-1}$.

More preferably, the acid is propionic acid and the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as $2\theta \pm 0.2^\circ$ 2θ ($\text{Cu}_{K\alpha}$ radiation)) at 13.1° , 17.5° and 21.6° , which is designated below as form A. Form A preferably has at least one reflection 2θ at 7.7° , 13.1° , 13.5° , 15.3° , 17.5° , 18.9° , 19.6° , 21.6° and 24.7° . Figure 1 shows an X-ray powder diffractogram of form A.

Furthermore, form A is characterized in that it preferably has a characteristic Raman spectrum with spectral bands at 1615, 1587, 1562, 1474, 1426, 1346, 1276, 1171, 1126, 1084, 924, 796, 731, 641, 427, 354, 289 and 118 cm^{-1} (wavenumbers).

More preferably, the acid is nicotinic acid and the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as $2\theta \pm 0.2^\circ$ 2θ ($\text{Cu}_{K\alpha}$ radiation)) at 11.9° , 19.2° and 22.6° , which is designated below as form B. Preferably, form B has at least one reflection 2θ at 11.9° , 16.7° , 17.7° , 18.3° , 19.2° , 20.8° , 21.5° and 22.6° . Figure 2 shows an X-ray powder diffractogram of form B.

Furthermore, form B is characterized in that it preferably has a characteristic Raman spectrum with spectral bands at 1616, 1566, 1425, 1348, 1276, 1170, 1087, 1035, 925, 845, 796, 637, 419, 355 and 85 cm^{-1} (wavenumbers).

The aforementioned crystalline compounds and in particular forms A and B are non-hygroscopic. They, therefore, have an improved stability if they are stored in environments with a high atmospheric humidity. This is particularly advantageous if medicaments comprising the crystalline compound are administered in tropical and subtropical regions, as the medicaments thus exhibit good storage stability.

In addition, the forms A and B having a good polymorphic purity of preferably more than 90%, more preferably more than 95% and in particular of more than 99%, are obtained.

- 5 A further advantage is that the forms A and B are obtainable in high purity by crystallization from suitable solvents. Form A can be obtained, for example, in high purity by crystallization from ethanol, form B preferably by crystallization from ethyl acetate.
- 10 A further subject of the present invention is the aforementioned crystalline compound for use in the treatment of osteoporosis, in particular of postmenopausal osteoporosis. A medicament comprising the aforementioned crystalline compound is a further subject of the present invention.
- 15 In addition, the aforementioned crystalline compound can be used for production of a medicament for the treatment of osteoporosis, in particular of postmenopausal osteoporosis.

The formulations of the medicament comprise an effective proportion of crystalline
20 compound that is administered at a daily dose of 0.1 mg to 200 mg. Such a dose can be administered by means of any administration form that makes possible the entry of the active compound into the bloodstream, including oral administration, by means of implants, parenteral administration (including intravenous, intra-peritoneal and subcutaneous injection) and transdermal administration.

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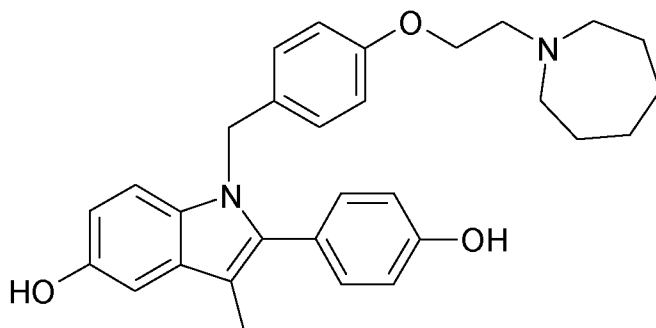
Oral formulations comprising the crystalline compound of the present invention contain any customarily used oral administration form such as tablets, capsules, juices, suspensions and solutions. Capsules or tablets can be produced with mixtures of other pharmaceutically active substances, inert fillers or diluents such
30 as pharmaceutically acceptable starches, sugars, artificial sweeteners, cellulose in powder form, gelatine, vegetable gum or the like.

Tablets comprising the crystalline compound of the present invention can be obtained by conventional pressing, wet granulation, dry granulation or using pharmaceutically acceptable diluents (fillers), binders, lubricants, disintegrants, suspending or stabilizing agents such as, for example, magnesium stearate, stearic acid, talc, sodium lauryl sulphate, microcrystalline cellulose, calcium carboxymethylcellulose, polyvinylpyrrolidone, gelatine, alginic acid, gum arabic, xanthan, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulphate, lactose, kaolin, mannitol, sodium chloride and/or powdered sugar.

Oral formulations can require a conventional release or a delayed release of active substance. Examples of pharmaceutical carriers for the production of formulations comprising the crystalline compound of the present invention include one or more fillers, disintegrants and lubricants. Preferred examples of formulations comprising the crystalline compound of the present invention are disclosed in US 2007/0048347.

A further subject of the present invention is a process for the preparation of the aforementioned compound, comprising the steps:

- a) preparation of a solution of 1-[4-(2-azepan-1-ylethoxy) benzyl] -2-(4-hydroxyphenyl)-3-methyl-1 H-indol-5-ol (INN: bazedoxifene) of formula 1



formula 1,

- b) addition of an acid selected from the group consisting of propionic acid or nicotinic acid to the solution of step a);
- c) optional concentration of the composition obtained according to step b) and/or optional addition of a suitable non-solvent for lowering the solubility of the crystalline compound and
- 5 d) separation of the solid obtained.

Preferably, the molar ratio of the dissolved compound of formula 1 in step a) to the acid in step b) is 1:0.9 to 1:1.1.

10

In a further preferred embodiment, the acid in step b) is added in solid form to the solution of step a) or the acid of step b) is added as a solution in a suitable solvent to the solution of step a).

- 15 The solvent of step a) and/or b) is preferably a low molecular weight and physiologically tolerable solvent and/or a physiologically tolerable alcohol, such as, for example, ethanol, isopropanol, 1-propanol, n-butanol, low molecular weight ketones, such as, for example, acetone, 2-butanone, methyl isobutyl ketone, acetates, e.g. ethyl formate, ethyl acetate, butyl acetate or isopropyl acetate, or
- 20 ethers, e.g. tert-butyl methyl ether, diethyl ether, diisopropyl ether or any desired mixtures thereof to be combined are employed. Particularly preferred for step a) and/or step b) are physiologically tolerable solvents in which the propionic acid or nicotinic acid is sufficiently soluble. Ethanol, 1-propanol, 2-propanol, THF, acetone, ethyl methyl ketone, water and mixtures thereof are preferred. Ethanol,
- 25 2-propanol, ethyl acetate, isopropyl acetate, acetone, ethyl methyl ketone are particularly preferred for step a) and ethanol, 2-propanol, acetone, ethyl methyl ketone and water for step b) .

- In steps a) and b), the two components can be dissolved both in identical and in
- 30 different solvents, and both in identical and in different concentrations. It is also possible to employ in each case two or more solvents in step a) and/or step b).

In step c), seed crystals of the desired form can preferably be added. In step c), it is further preferred that the suspension obtained is stirred at a suitable temperature. Preferably, this temperature is in the range from 5°C to 50°C.

5

Further, in steps a) and b) the crystallization temperature, or the reaching of saturation with respect to the desired salt, can be modulated by the choice of various combinations of the solvents and concentrations such that the desired salt is obtained in high yield and high purity.

10

By physiologically tolerable, it is meant that the solvents come under the ICH (International Commission for Harmonization) guideline Q3C, Class 3. The steps a) and b) in the sequence can be exchanged.

15 Preferably, the acid is propionic acid or nicotinic acid and the compound of formula 1 in step a) is introduced in a solution comprising ethanol, ethyl acetate and/or isopropanol. It is further preferred that in step b) ethanol and/or isopropanol is employed as a solvent. More preferably, in step b) comprising propionic acid or nicotinic acid and ethanol, ethyl acetate and/or isopropanol is
20 added as a solvent.

Using propionic acid and ethanol as a solvent, form A is preferably obtained. The use of nicotinic acid and of ethyl acetate as a solvent preferably causes the formation of form B.

25

A further subject of the present invention is the use of the aforementioned crystalline compounds for the preparation of further crystalline compounds comprising bazedoxifene and acids other than propionic acid or nicotinic acid. This is based on the fact that the crystalline compounds of the present invention are easily obtainable
30 in high purity.

Thus, for example, the aforementioned crystalline compound of the present invention can be dissolved in a suitable solvent and subsequently an acid other than propionic acid or nicotinic acid, such as, for example, acetic acid, is added. Crystallization and isolation of the bazedoxifene salt preferably follows. All
5 processes can be used here that are described for the crystalline compound of the present invention. Accordingly, for example, acetates of bazedoxifene can easily be obtained. The instability of pure bazedoxifene described in the prior art, thus, no longer has any influence on the purity of bazedoxifene acetate.

10 Examples

X-ray powder diffraction

Powder diffractograms were measured on a Bruker D8 Advance powder diffractometer with a goniometer radius of 217.5 mm using copper K α radiation. This apparatus operates in reflection Bragg-Brentano geometry at an anode voltage of
15 40 kV and a current of 40 mA, a variable divergence shutter being used. The Bruker D8 apparatus is equipped with a LynxEye detector, the active observation window being adjusted to 3°. The step width was 0.02° and the equivalent accumulation time 37 seconds per step. The samples were prepared without further treatment on circular silicon single crystal carriers with a depth of 0.1 mm
20 and a diameter of 12 mm. The samples were rotated during the measurement at 0.5 rotations per second. The measuring error is approximately $\pm 0.1^\circ 2\theta$.

Raman spectroscopy

Fourier transform Raman spectroscopy was carried out using a Bruker RFS1 00,
25 which for excitation has an Nd:YAG laser with a wavelength of 1064 nm. The laser power used was 300 mW. The apparatus used was equipped with a liquid nitrogen-cooled germanium detector. About 3 mg of the test sample are pressed in a small aluminium carrier and this carrier is inserted into the spectrometer measuring chamber. For recording spectra, 64 accumulations were measured with
30 a resolution of 2.0 cm⁻¹ in the range from 100-3500 cm⁻¹ wavenumbers. The

measurement error is approximately $\pm 1 \text{ cm}^{-1}$.

Water vapour adsorption measurements

Dynamic water vapour adsorption measurements (DVS) were carried out using an SPS1 1-100 η apparatus, manufactured by the company "Projekt Messtechnik" in Ulm, Germany. For this, about 20 mg of the sample were weighed into an aluminium carrier and this was inserted into the measuring chamber of the apparatus. The sample was then exposed according to a defined program to previously chosen preset relative humidities, the mass change being determined over time. The following measuring programme was used: 50% r.h. constant for two hours, then change of the relative humidity to 0% r.h., subsequent change of the relative humidity to 96% r.h., constant 96% r.h. for four hours, and then change of the relative humidity to 50% r.h. and then constant 50% r.h. for one hour. The change rates set were in each case 5% per hour.

¹H-NMR spectroscopy

¹H-NMR spectroscopy was carried out on a Bruker DPX300 apparatus.

Example 1: Preparation of the crystalline compound comprising bazedoxifene and propionic acid (form A)

4.0 ml of ethyl acetate, 4.0 ml of ethanol and 0.5 ml of propionic acid are added to 280 mg of amorphous bazedoxifene acetate. The mixture is heated to 40°C and the solvents are removed to dryness using a stream of nitrogen. The residue is taken up in 3.0 ml of ethanol and the mixture is stirred overnight at room temperature. The solid obtained is filtered off and dried in vacuo for three hours. The X-ray powder diffractogram of the crystalline solid is indicated in Figure 1 (Form A). The reflections indicated in Table 1 are seen.

According to ¹H-NMR spectrum, the ratio of bazedoxifene to propionic acid is approximately 1:1. A thermogravimetric analysis shows a weight loss of the

product of 0.3% when it is heated to 150°C at 10 K/min. This confirms the very good drying properties of the form A obtained.

Table 1: Reflections of form A in °2 θ and d values

Pos. [° 2 θ]	d values [Å]	Qualitative intensity
7.7	11.6	w
9.9	8.9	w
11.0	8.1	vw
12.9	6.9	w
13.1	6.8	s
13.5	6.6	s
13.9	6.3	w
14.8	5.99	m
15.0	5.90	m
15.3	5.77	m
15.9	5.58	vw
16.7	5.32	vw
17.2	5.14	vw
17.5	5.05	s
18.9	4.70	m
19.1	4.65	w
19.6	4.53	m
19.6	4.53	m
19.9	4.45	m
20.1	4.41	vw
20.6	4.30	w
20.9	4.25	m
21.6	4.11	vs
22.5	3.95	m

Pos. [$^{\circ}$ 2 θ]	d values [Å]	Qualitative intensity
22.8	3.90	m
23.2	3.83	w
24.7	3.61	s
25.0	3.55	w
25.9	3.44	w
26.3	3.38	w

Form A has a Raman spectrum as indicated in Figure 3. It shows the bands indicated in Table 2.

Table 2: Raman spectral bands of form A

Wavenumber [cm ⁻¹]	Intensities (qualitative)
1615	vs
1587	m
1562	s
1474	m
1426	m
1346	m
1276	m
1171	w
1126	w
1084	s
924	m
796	m
731	w
641	m
427	m
354	m

Wavenumber [cm ⁻¹]	Intensities (qualitative)
289	w
118	s

Where: vs = very strong intensity, s = strong intensity, m = medium intensity,
w = weak intensity.

Example 2: Preparation of the crystalline compound comprising bazedoxifene and
5 nicotinic acid (Form B)

2.5 ml of a 0.1 M solution of nicotinic acid in ethanol and 5.6 ml of a 0.45 M solution
of nicotinic acid in THF are added to 230 mg of amorphous bazedoxifene acetate in
2.0 ml of THF. The solvent is removed to dryness using a stream of nitrogen and
10 the residue is taken up in 4.0 ml THF. The solvent is again removed to dryness
using a stream of nitrogen. The residue is taken up in 2.0 ml of ethyl acetate and
stirred at room temperature until a suspension is obtained. Under the light
microscope, it appears that the solid obtained is crystalline. The solid obtained is
filtered off and dried at room temperature in vacuo. The X-ray powder diagram of
15 the crystalline solid is indicated in Figure 2 (Form B). It shows the reflections
indicated in Table 3.

According to ¹H-NMR spectrum, the ratio of bazedoxifene to nicotinic acid is
approximately 1:1.

20

Table 3: Reflections of Form B in ° 2Θ and d values

Pos. [° 2Θ]	d values [Å]	Qualitative intensity
6.1	14.4	vw
7.5	11.7	w
9.9	8.9	w
10.1	8.7	w
10.7	8.3	w

Pos. [$^{\circ}$ 2 θ]	d values [Å]	Qualitative intensity
11.9	7.5	vs
13.2	6.7	m
13.5	6.5	m
14.0	6.3	m
15.9	5.58	m
16.7	5.32	s
17.7	5.00	m
18.3	4.84	s
18.7	4.74	m
19.2	4.62	vs
20.3	4.37	m
20.8	4.28	s
21.5	4.13	m
22.6	3.94	s
23.4	3.81	w
24.2	3.68	w
25.9	3.43	w
26.3	3.39	m
27.1	3.29	w

Form B has a Raman spectrum as indicated in Figure 4. It shows the bands indicated in Table 4.

Table 4: Raman spectral bands of Form B

Wavenumber [cm^{-1}]	Intensities (qualitative)
1616	s
1566	s
1425	m
1348	m
1276	w

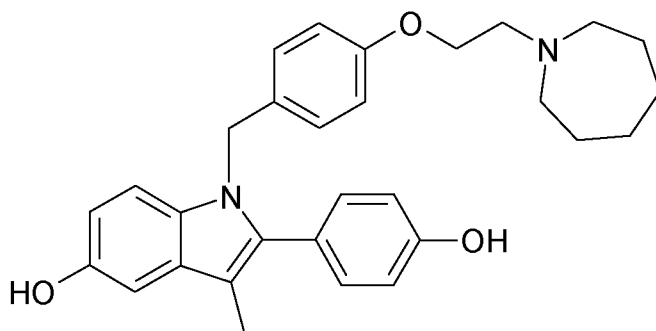
Wavenumber [cm ⁻¹]	Intensities (qualitative)
1170	w
1087	m
1035	m
925	m
845	m
796	m
637	m
419	w
355	w
85	vs

Where: vs = very strong intensity, s = strong intensity, m = medium intensity, w = weak intensity.

Claims

1. Crystalline compound of 1-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (INN: bazedoxifene) of formula 1

5



formula 1

with an acid selected from the group consisting of propionic acid or nicotinic acid or a hydrate thereof, where the molar ratio of the compound of formula 1 to the acid is 1:0.9 to 1:1.1.

10

2. The crystalline compound according to Claim 1, characterized in that the acid is propionic acid and the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as $2\theta \pm 0.2^\circ$ 2θ ($\text{Cu}_{K\alpha}$ radiation)) at 13.1° , 17.5° and 21.6° , which is designated below as form A.

15

3. The crystalline compound according to Claim 2, characterized in that it has at least one reflection 2θ at 7.7° , 13.1° , 13.5° , 15.3° , 17.5° , 18.9° , 19.6° , 21.6° and 24.7° .

20

4. The crystalline compound according to Claim 1, characterized in that the acid is nicotinic acid and the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as $2\theta \pm 0.2^\circ$ 2θ ($\text{Cu}_{K\alpha}$ radiation)) at 11.9° , 19.2° and 22.6° , which is designated below as Form B.

25

5. The crystalline compound according to Claim 4, characterized in that it has at least one reflection 2Θ at 11.9° , 16.7° , 17.7° , 18.3° , 19.2° , 20.8° , 21.5° and 22.6° .

5

6. The crystalline compound according to at least one of Claims 1 to 5 for use in the treatment of osteoporosis, in particular of postmenopausal osteoporosis.

- 10 7. A medicament comprising the crystalline compound according to at least one of Claims 1 to 5.

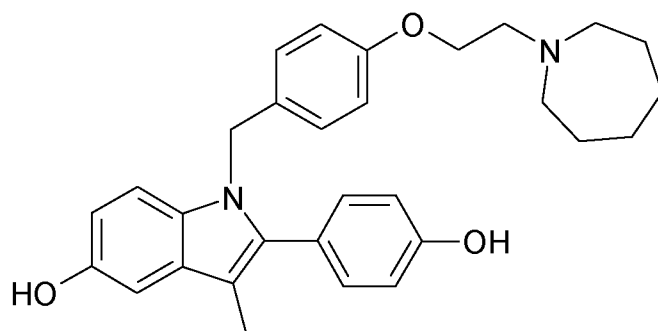
8. The use of the crystalline compound according to at least one of Claims 1 to 5 for the production of a medicament for the treatment of osteoporosis, in particular of postmenopausal osteoporosis.

15

9. Process for the preparation of the compound according to at least one of Claims 1 to 5 comprising the steps:

- a) preparation of a solution of 1-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (INN: bazedoxifene) of formula 1

20



formula 1,

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- b) addition of an acid selected from the group consisting of propionic or nicotinic acid to the solution of step a);

- c) optional concentration of the composition obtained according to step b) and/or optional addition of a suitable non-solvent for lowering the solubility of the crystalline compound and
- d) separation of the solid obtained.

5

10. The process according to Claim 9, characterized in that the molar ratio of the dissolved compound of formula 1 in step a) to the acid in step b) is 1:0.9 to 1:1.1.

10 11. The process according to Claim 9 or 10, characterized in that the acid in step b) is added in solid form to the solution of step a) or the acid of step b) is added to the solution of step a) as a solution in a suitable solvent.

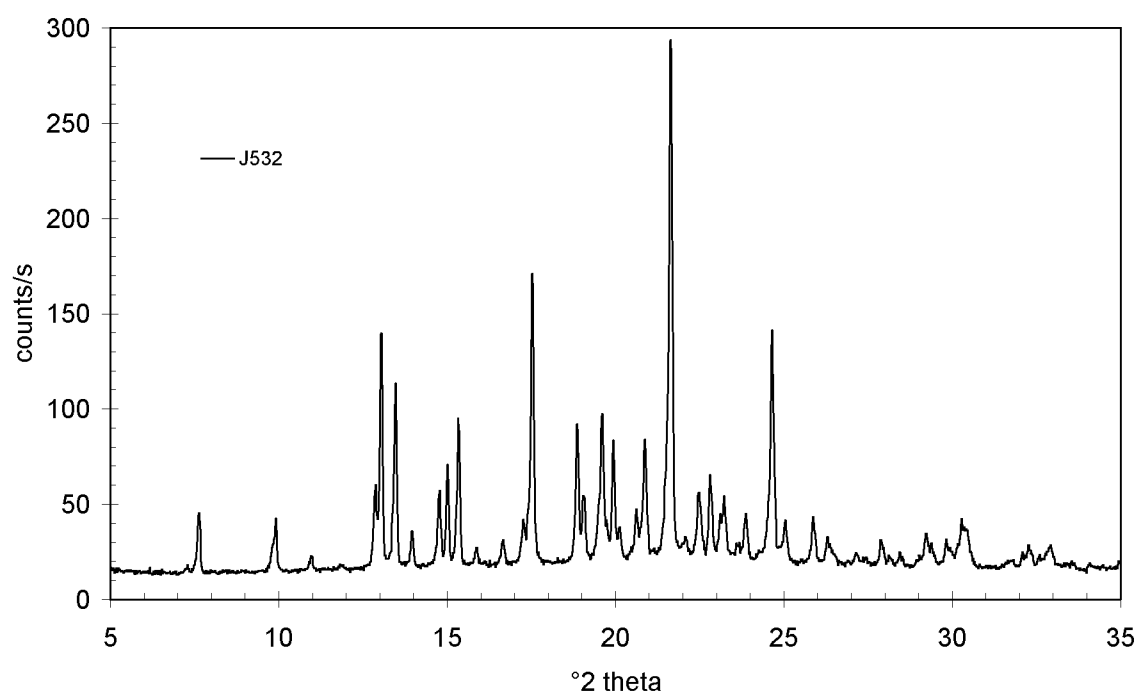
15 12. The process according to at least one of Claims 9 to 11, characterized in that the solvent of step a) and/or b) is a low molecular weight and physiologically tolerable solvent and/or a physiologically tolerable alcohol.

20 13. The process according to at least one of Claims 9 to 12, characterized in that the acid is propionic or nicotinic acid and the compound of formula 1 in step a) is introduced in a solution comprising ethanol, ethyl acetate and/or isopropanol.

25 14. The process according to Claim 9, characterized in that in step b) a solution comprising propionic or nicotinic acid and ethanol, ethyl acetate and/or isopropanol is added as a solvent.

Figure 1

Form A



2 / 4

Figure 2

Form B

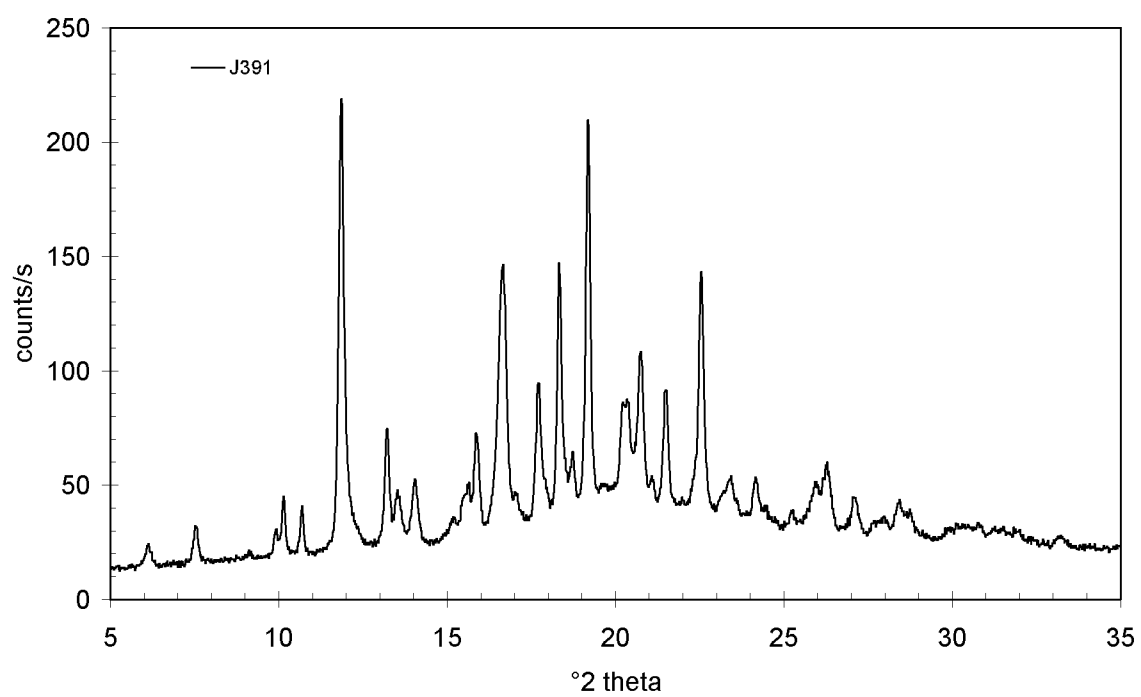


Figure 3

Main part of the Raman spectrum of form A (from 1800 - 200 cm^{-1})

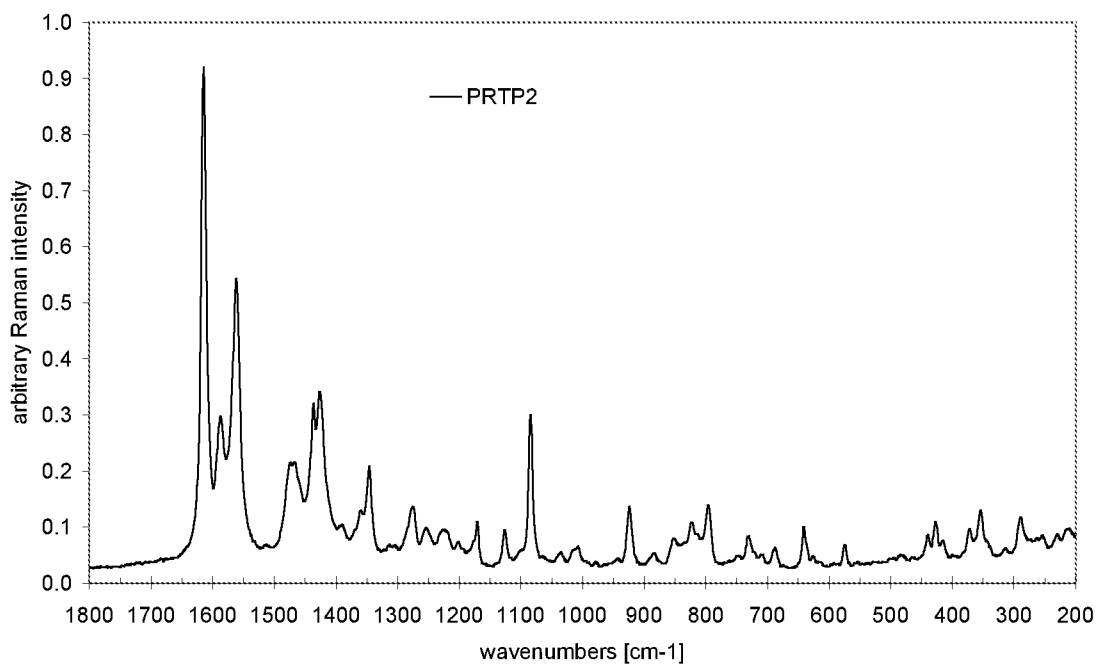
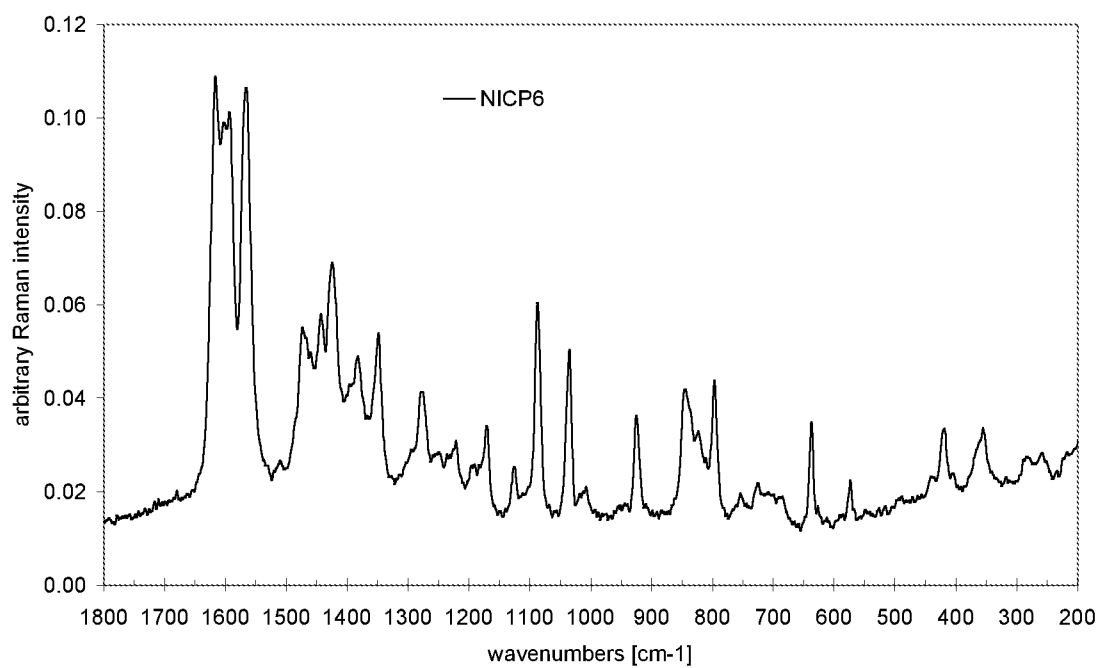


Figure 4

Main part of the Raman spectrum of form B (from 1800 - 200 cm^{-1})



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061840

A. CLASSIFICATION OF SUBJECT MATTER			
INV.	C07D209/32	C07D209/12	A61K31/403
	A61P5/24	A61P5/30	A61K31/404
			A61K31/55
ADD.			
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)			
C07D A61K			
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)			
EPO-Internal , CHEM ABS 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 2009/012734 A2 (ZENTIVA AS [CZ] ; JI RMAN JOSEF [CZ] ; RICHTER JINDRICH [CZ]) 29 January 2009 (2009-01-29) cited in the appli cation the whol e document & US 2010/240888 AI (JI RMAN JOSEF [CZ] ET AL) 23 September 2010 (2010-09-23) the whol e document -----		1-14
X	US 2005/227964 AI (FAWZI MAHDI B [US] ET AL) 13 October 2005 (2005-10-13) the whol e document -----		1-14
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Date of the actual completion of the international search		Date of mailing of the international search report	
11 August 2011		19/08/2011	
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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