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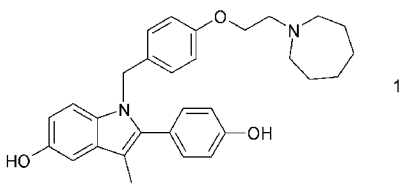
[Continued on next page]

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



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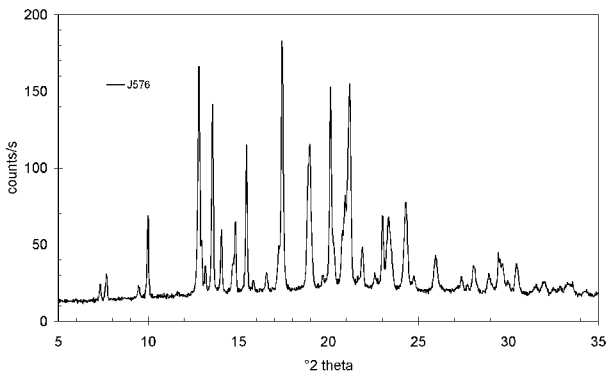
(57) **Abstract:** The present invention relates to a crystalline compound of l-[4-(2-azepan-l-ylethoxy)benzyl] -2-(4-hydroxyphenyl)-3-methyl-lH-indol-5-ol (INN: bazedoxifene) of formula 1 with lactic acid or a hydrate thereof, where the molar ratio of the compound of the formula 1 to lactic acid is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

Figure 1
Form A



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Crystalline compound of 1-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1 H-indol-5-ol and lactic acid

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 lactic acid or a hydrate thereof, and a process for its preparation.

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-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 .

The preparation of bazedoxifen and its acetates is disclosed in US 5,998,402 and 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 A 1. In particular, two polymorphic forms of bazedoxifene acetate are described. However, according to the teaching of US 2005/0227965 A 1 bazedoxifene acetate contains impurities and is unstable.

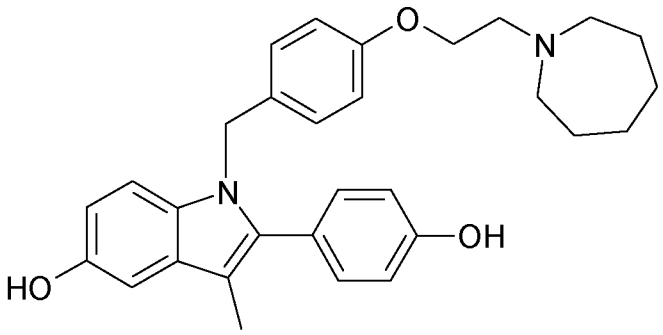
According to the prior art, form B of bazedoxifene acetate is the thermodynamically stable form while form A is kinetically stable. For this reason, the conditions for the preparation of pure form A or pure form B are critical, in particular if the solvent used for crystallization is identical, as is described in US 7,683,051 and US 7,683,052.

WO 2009/012734 A2 discloses salts of bazedoxifene with polycarboxylic acids. The undesired decomposition of bazedoxifene acetate is to be avoided by making available novel salts of bazedoxifene. No crystalline compounds containing bazedoxifene and lactic acid are disclosed in WO 2009/012734 A2 and US 2005/0227965 A1.

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 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.

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.

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-1H-indol-5-ol (INN: bazedoxifene) of formula 1



formula 1

with lactic 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.

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

Surprisingly, lactic acid 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 lactic acid is 1:0.95 to 1:1.05 and most preferably 1:1.

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 2Θ° 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 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 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 K_α radiation, as was also the case here. D values in Å (d) and 2-theta (2Θ) values in angular degrees can be converted into one another by Bragg's equation as follows: $n\lambda = 2d\sin\theta$, where n is an integer and λ is the wavelength of the X-ray radiation used in Å. 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 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 ±0.2° 2Θ. While the measuring error for ° 2Θ 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.

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.

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 Wiley-VCH Verlag, Weinheim, Germany, 2006. In measurements of this type the measuring error is customarily $\pm 1\ cm^{-1}$.

Preferably the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as 2Θ ± 0.2° 2Θ ($Cu_{K\alpha}$ radiation)) at 12.8°, 13.6°, 17.4°, 20.1° and 21.2°, which is designated below as form A. Form A preferably has at least one reflection 2Θ at 10.0°, 12.8°, 13.6°, 15.5°, 17.4°, 19.0°, 20.1°, 21.2° and 24.3°. Figure 1 shows an X-ray powder diffractogram of form A.

In a further preferred embodiment, form A comprises L-lactic acid, D-lactic acid or racemic lactic acid, particular preference being given to L-lactic acid.

More preferably, the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as 2Θ ± 0.2° 2Θ ($Cu_{K\alpha}$ radiation)) at 12.4°, 15.9°, 18.5° and 20.4°, which is designated below as form B. Preferably, form B has at least one reflection 2Θ at 9.4°, 12.4°, 15.2°, 15.9°, 18.5°, 18.7°, 20.4°, 21.4° and 29.5°. Figure 2 shows an X-ray powder diffractogram of form B.

Furthermore, form B preferably has a characteristic Raman spectrum with spectral bands at 3056, 1612, 1568, 1471, 1422, 1358, 1276, 1173, 1087, 923, 843, 820, 798, 707, 634, 417, 352 and 286 cm^{-1} (wavenumbers).

In a more preferred embodiment, form B comprises L-lactic acid, D-lactic acid or racemic lactic acid, particular preference being given to L-lactic acid.

More preferably the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as 2Θ ± 0.2° 2Θ ($Cu_{K\alpha}$ radiation)) at 21.0°, 23.3° and 24.1°, which is designated below as form C. Preferably, form C has at least one reflection 2Θ at 10.0°, 12.8°, 15.5°, 17.4°, 18.8°, 21.0°, 23.3° and 24.1°. Figure 3 shows an X-ray powder diffractogram of form C. In a more preferred embodiment, form C comprises L-lactic acid, D-lactic acid or racemic lactic acid, particular preference being given to L-lactic acid.

The aforementioned crystalline compounds comprising lactic acid and in particular

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

A further advantage is that the forms A, B and C 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. Form C is obtainable easily by crystallization from isopropanol.

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.

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 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, intraperitoneal and subcutaneous injection) and transdermal administration.

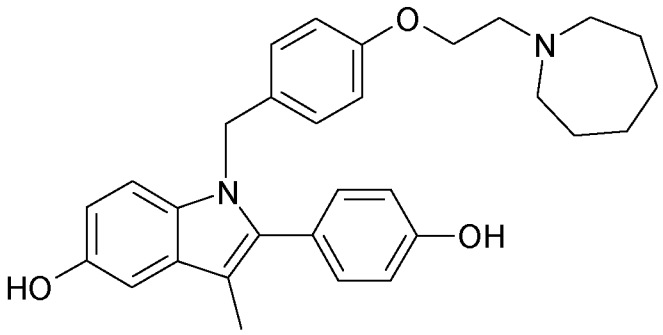
Oral formulations comprising the crystalline compound of the present invention contain any customarily used oral administration form such as tablets, capsules, juices, suspensions, and solutions. Capsules or tablets can be produced with mixtures of other pharmaceutically active substances, inert fillers or diluents such 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 carboxy-methylcellulose, polyvinylpyrollidone, 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-hydroxy-phenyl)-3-methyl-1 H-indol-5-ol (INN: bazedoxifene) of formula 1



formula 1,

b) addition of lactic 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.

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

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).

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 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 lactic acid is sufficiently soluble. Ethanol, 1-propanol, 2-propanol, THF, acetone, ethyl methyl ketone, water and mixtures thereof are preferred. Ethanol, 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 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.

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.

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.

In a more preferred embodiment, the acid is L-lactic acid, D-lactic acid or racemic lactic acid, particular preference being given to L-lactic acid.

Preferably 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) a solution comprising lactic acid and ethanol, ethyl acetate and/or isopropanol is added as a solvent. Preferably, the form A, B or C is thus obtained.

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

preferably leads to form C.

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 Kα radiation. This apparatus operates in reflection Bragg-Brentano geometry at an anode voltage of 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 and a diameter of 12 mm. The samples were rotated during the measurement at 0.5 rotations per second. The measuring error is approximately ±0.1° 2Θ.

Raman spectroscopy

Fourier transform Raman spectroscopy was carried out using a Bruker RFS100, 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 a resolution of 2.0 cm^{-1} in the range from 100-3500 cm^{-1} wavenumbers. The measurement error is approximately ±1 cm^{-1}.

Water vapour adsorption measurements

Dynamic water vapour adsorption measurements (DVS) were carried out using an SPS11-100η 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.

^{1}H-NMR spectroscopy

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

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

279 mg of amorphous bazedoxifen acetate are dissolved in 4.0 ml of ethanol and initially charged. 10 ml of a 1M stock solution of L-lactic acid are prepared by adding ethanol to 906 mg of L-lactic acid up to a total volume of 10 ml. 1.0 ml of this stock solution is added to the solution comprising amorphous bazedoxifen acetate. The resulting solution is concentrated under nitrogen and, after complete removal of the solvent, the residue is taken up in ethanol and concentrated again. Subsequently, the residue is taken up with 3.0 ml of ethanol and the resulting solution is stirred at room temperature (22 ± 2°C). After stirring for 20 h, a suspension is obtained. The crystalline product thus obtained is filtered off and dried under air. According to ^{1}H-NMR, the bazedoxifene L-lactate salt was obtained, which is designated below as form A. The X-ray powder diagram is reproduced in Figure 1. It shows the reflections reported in Table 1.

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

Pos. [2Θ°]	d values [A]	Qualitative intensity
7.3	12.1	w
7.7	11.5	w
9.5	9.3	w

Pos. [2Θ°]	d values [A]	Qualitative intensity
10.0	8.9	m
12.8	7.0	vs
13.2	6.8	w
13.6	6.7	s
14.1	6.5	m
14.8	6.0	m
15.5	5.72	s
16.6	5.35	w
17.4	5.08	vs
19.0	4.67	s
20.1	4.40	vs
21.2	4.20	vs
21.9	4.08	w
23.0	3.86	m
23.4	3.81	m
24.3	3.66	m
26.0	3.42	w
28.1	3.18	w
29.0	3.08	w
29.5	3.02	w
30.5	2.93	w

Example 2: Preparation of the crystalline compound comprising bazedoxifene and lactic acid (form B)

20 ml of water and one equivalent of NaOH in the form of a 1M aqueous solution are added to 1.06 g of bazedoxifene acetate. The pH is adjusted to pH 11 by further addition of the 1M NaOH solution and the aqueous phase is extracted six times with 30 ml of CH_2Cl_2. The first three organic fractions are combined, filtered and concentrated to dryness in a rotary evaporator. The residue of about 400 mg to 500 mg

is taken up in 15 ml of ethyl acetate. 2.0 ml of the 1M L-lactic acid stock solution (Example 1) are added immediately to the solution thus obtained. The solution obtained is concentrated under nitrogen, dried, taken up in 3.0 ml of ethyl acetate and stirred at room temperature. About 10 mg of seed crystals of the form A from Example 1 are added and the suspension is exposed briefly to ultrasound in an ultrasound bath. The resulting suspension is stirred at room temperature for three days and a suspension of bazedoxifene lactate is obtained. The solid product is removed with a 0.45 µm filter and dried at room temperature. According to ^{1}H-NMR spectroscopy, the solid product has a stoichiometry of bazedoxifene to lactic acid of about 1:1, which is designated as form B. The X-ray powder diagram (form B) is reproduced in Figure 2. It shows the reflections reported in Table 2. The resulting crystals of the form B are subjected to a water vapour adsorption measurement, and the diagram shown in Figure 4 is obtained. The water absorption of the solid obtained is less than 0.3% with a relative humidity of 95%.

Table 2: Reflections of the form B in 2Θ° and d values

Pos. [2Θ°]	d values [A]	Qualitative intensity
7.0	12.6	vw
8.4	10.5	w
9.4	9.4	w
12.4	7.1	vs
12.8	6.9	vw
15.2	5.85	m
15.6	5.69	w
15.9	5.60	s
16.4	5.41	w
16.9	5.23	w
18.5	4.81	vs
18.7	4.76	s
18.9	4.70	w
20.1	4.41	m

Pos. [2Θ°]	d values [A]	Qualitative intensity
20.4	4.35	vs
21.4	4.16	m
21.6	4.11	s
22.8	3.89	m
23.1	3.85	w
23.4	3.80	w
24.9	3.58	m
25.4	3.51	w
26.2	3.39	w

The form B has a Raman spectrum as shown in Figure 5. It shows the bands listed in Table 3.

Table 3: Raman spectral bands of the form B

Wavenumber [cm^{-1}]	Relative intensity in % (rounded to whole numbers)
3056	5
1612	31
1568	14
1471	3
1422	8
1358	3
1276	4
1173	3
1087	8
923	4
843	2
820	2
798	5
707	2
634	3

Wavenumber [cm^{-1}]	Relative intensity in % (rounded to whole numbers)
417	3
352	2
286	2

Example 3: Preparation of the crystalline compound comprising bazedoxifene and lactic acid (form B)

6.0 ml of the 1M L-lactic acid stock solution (Example 1) in ethanol are added to a solution of 2.60 g of bazedoxifene in the form of its free base in 20 ml of ethanol. 30 mg of bazedoxifene L-lactate from Example 2 are added and a gentle nitrogen stream of about 20 ml/min is passed over the solution in a glass bottle until half of the solvent has been removed. 20 ml of heptane are added and the suspension obtained is stirred at room temperature overnight. The solid obtained is filtered off and dried at 40°C under reduced pressure for 3.5 hours. The solid product exhibits an X-ray powder diagram as shown in Figure 2. According to ^{1}H-NMR, the ratio of bazedoxifene to L-lactic acid in the solid obtained is 1:1. A thermogravimetric analysis shows a weight loss of the product of 0.12% when it is heated to 125°C at 10 K/min. This confirms the very good drying properties of the form B obtained, since the volatile components have already been removed after the brief drying time of 3.5 h at 40°C.

Example 4: Preparation of the crystalline compound comprising bazedoxifene and lactic acid (form C)

100 mg of bazedoxifene L-Lactate form B are dissolved in 3.5 ml of isopropanol at 65°C. The clear solution is cooled to 50°C within one hour and then to 10°C within two hours. The mixture is stirred overnight and a suspension is obtained. The solid is filtered off and dried at room temperature overnight. The X-ray powder diagram is shown in Figure 3 (form C). It shows the reflections reported in Table 4.

Table 4: Reflections of the form C in 2Θ° and d values

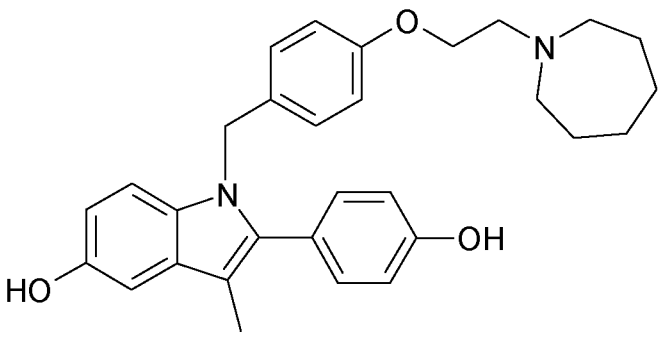
Pos. [2Θ°]	d values [A]	Qualitative intensity
7.4	12.0	w
7.7	11.5	vw
9.4	9.4	w
10.0	8.8	m
12.8	6.9	s
13.0	6.8	m
13.2	6.7	w
13.5	6.5	m
14.0	6.3	m
14.6	6.1	w
14.9	5.94	m
15.5	5.74	m
15.8	5.61	vw
16.5	5.36	vw
17.2	5.16	w
17.4	5.10	s
18.8	4.71	s
19.0	4.67	m
19.8	4.49	w
20.2	4.40	vs
21.0	4.23	vs
21.8	4.07	m
23.0	3.86	m
23.3	3.81	m
24.1	3.68	m
25.9	3.44	w
28.0	3.18	w
28.8	3.09	vw
29.4	3.03	w
29.5	3.02	w

Example 5: Preparation of the crystalline compound comprising bazedoxifene and lactic acid (form C)

The crystals obtained according to Example 4 are suspended in methyl ethyl ketone, the suspension obtained is stirred at room temperature for 40 hours and the solid is filtered off. The X-ray powder diagram of the solid corresponds to that of form C. A thermogravimetric analysis coupled to IR spectroscopy 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 C obtained.

Claims

1. 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



formula 1

with lactic acid or a hydrate thereof, where the molar ratio of the compound of formula 1 to lactic acid is 1:0.9 to 1:1.1.

2. The crystalline compound according to Claim 1, characterized in that the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as 2Θ ± 0.2° 2Θ ($Cu_{K\alpha}$ radiation)) at 12.8°, 13.6°, 17.4°, 20.1° and 21.2°, which is designated below as form A.

3. The crystalline compound according to Claim 2, characterized in that it has at least one reflection 2Θ at 10.0°, 12.8°, 13.6°, 15.5°, 17.4°, 19.0°, 20.1°, 21.2° and 24.3°.

4. The crystalline compound according to Claim 1, characterized in that the compound has an X-ray powder diffractogram (XRPD) having at least one reflection (expressed as 2Θ ± 0.2° 2Θ ($Cu_{K\alpha}$ radiation)) at 12.4°, 15.9°, 18.5° and 20.4°, which is designated below as form B.

5. The crystalline compound according to Claim 4, characterized in that it has at least one reflection 2Θ at 9.4°, 12.4°, 15.2°, 15.9°, 18.5°, 18.7°, 20.4°, 21.4° and 29.5°.

6. The crystalline compound according to Claim 1, characterized in that the compound has an X-ray powder diffractogram (XRPD) with at least one reflection (expressed as 2Θ ± 0.2° 2Θ ($Cu_{K\alpha}$ radiation)) at 21.0°, 23.3° and 24.1°, which is designated below as form C.

7. The crystalline compound according to Claim 6, characterized in that it has at least one reflection 2Θ at 10.0°, 12.8°, 15.5°, 17.4°, 18.8°, 21.0°, 23.3° and 24.1°.

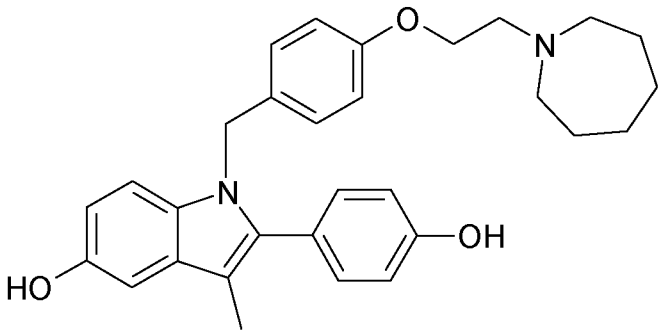
8. The crystalline compound according to at least one of Claims 1 to 7 for use in the treatment of osteoporosis, in particular of postmenopausal osteoporosis.

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

10. The use of the crystalline compound according to at least one of Claims 1 to 7 for the production of a medicament for the treatment of osteoporosis, in particular of postmenopausal osteoporosis.

11. Process for the preparation of the compound according to at least one of Claims 1 to 7 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



formula 1,

b) addition of lactic 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.

12. The process according to Claim 11, characterized in that the molar ratio of the dissolved compound of formula 1 in step a) to lactic acid in step b) is 1:0.9 to 1:1.1.

13. The process according to Claim 11 or 12, characterized in that lactic 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.

14. The process according to at least one of Claims 12 to 13, 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.

15. The process according to at least one of Claims 11 to 14, characterized in that the compound of formula 1 in step a) is introduced in a solution comprising ethanol, ethyl acetate and/or isopropanol.

16. The process according to Claim 15, characterized in that in step b) a solution comprising lactic acid and ethanol, ethyl acetate and/or isopropanol is added as a solvent.

Figure 1

Form A

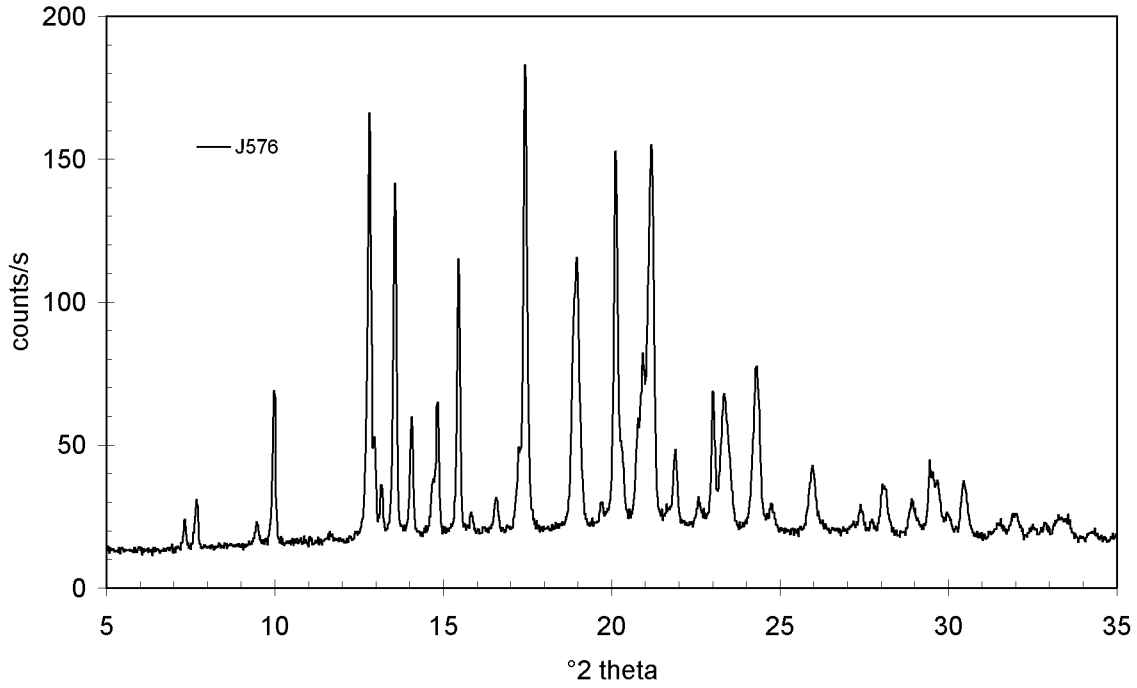


Figure 2

Form B

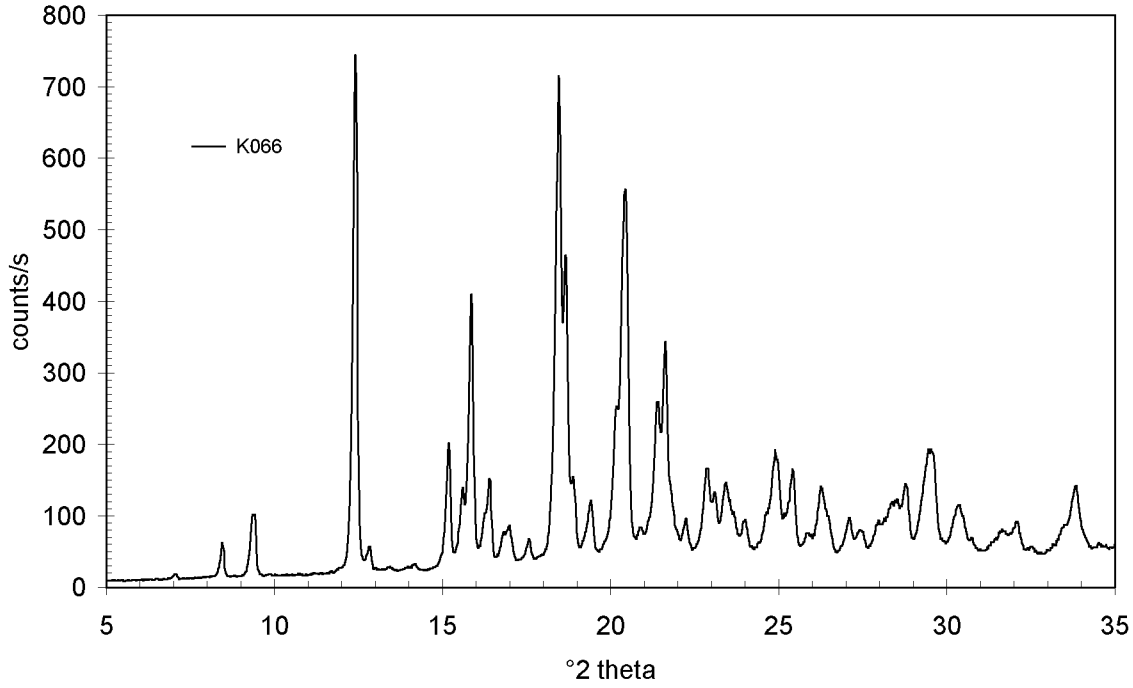


Figure 3

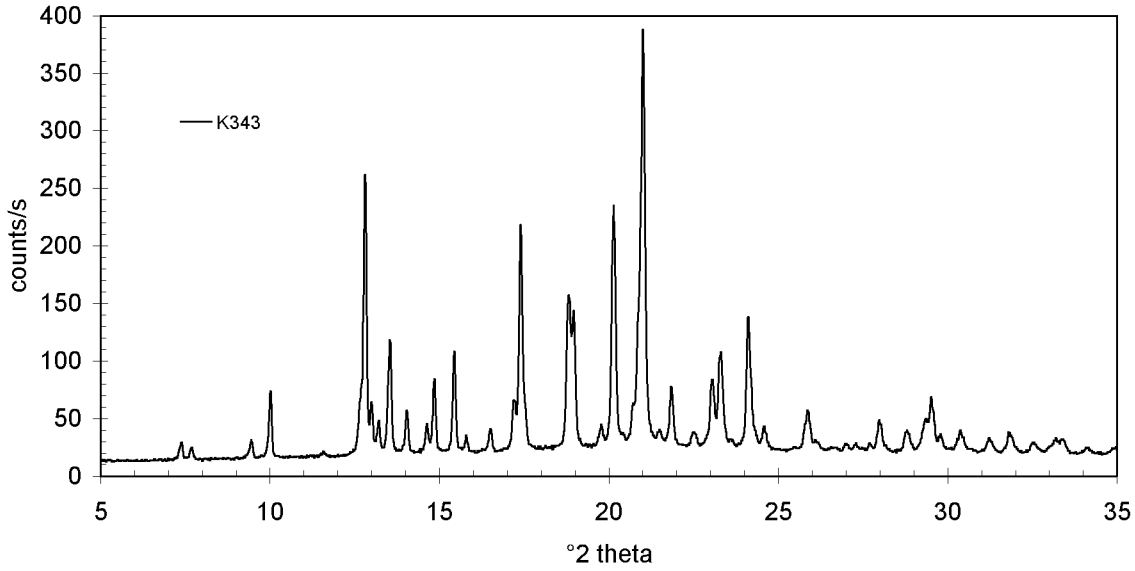


Figure 4

Form B: DVS

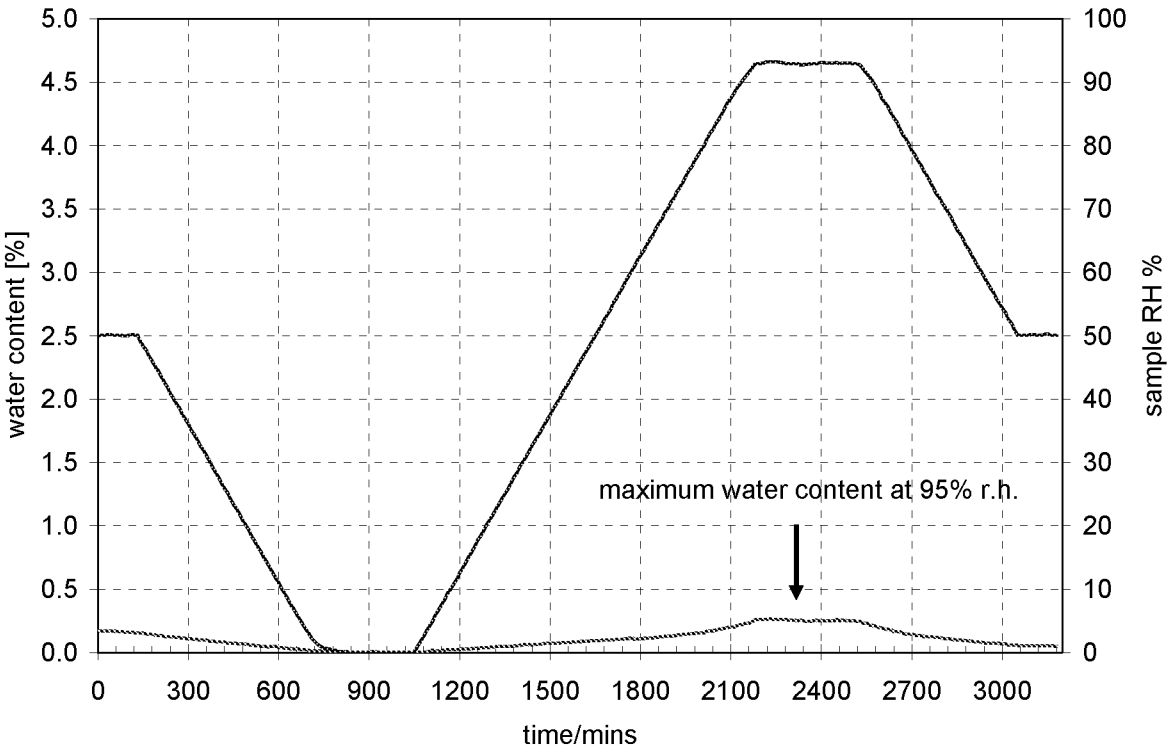
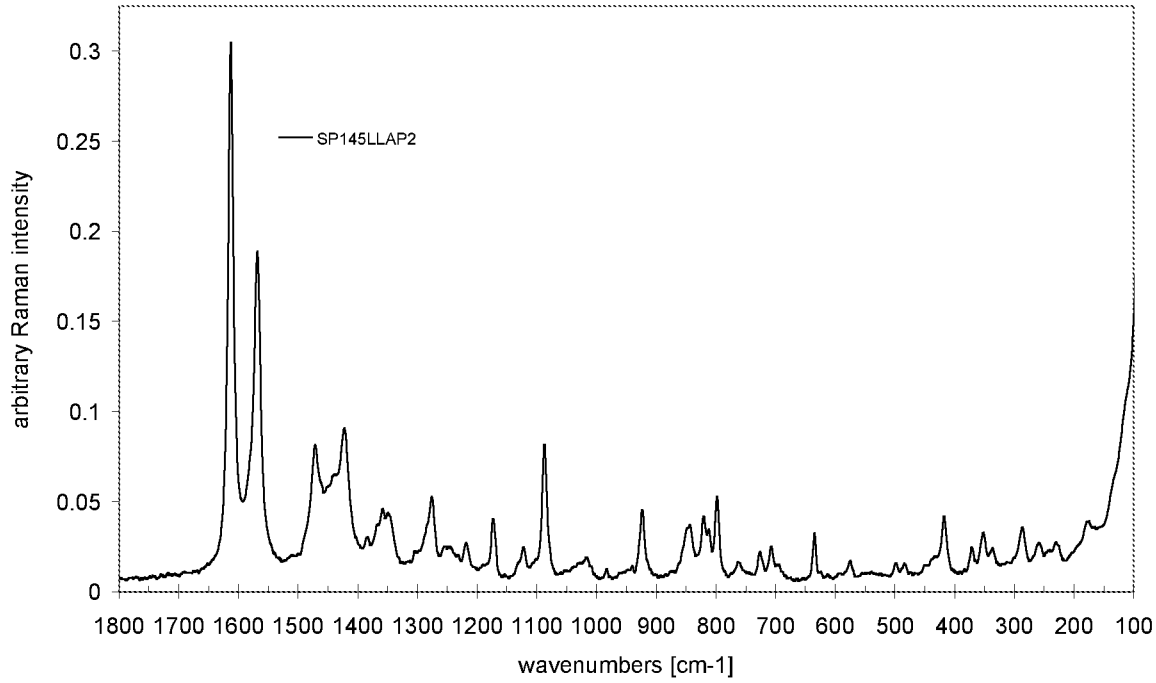


Figure 5

Main part of the Raman spectrum of form B (from 1800 - 100 cm^{-1})



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061838

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 A61K31/551 A61P19/10
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 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)
EPO-Internal , CHEM ABS Data, WPI Data, BEILSTEIN 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] ; JIRMAN JOSEF [CZ] ; RICHTER JINDRICH [CZ]) 29 January 2009 (2009-01-29) cited in the application examples 2-7 , 9 , 10 -----	1-16
X	WO 2006/104791 A1 (WYETH CORP [US] ; SHAH SYED [US] ; FAWZI MAHDI [US] ; DIORIO CHRISTOPHER) 5 October 2006 (2006-10-05) page 4 , paragraph 3 - paragraph 4 -----	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2011	22/09/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Mooren , Nicolai

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/061838

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