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(54) **Title:** PROCESS FOR PREPARATION OF BOSENTAN MONOHYDRATE OF PHARMACEUTICAL PURITY

(57) **Abstract:** A process for the preparation of bosentan monohydrate of pharmaceutical purity is characterized by that crude bosentan is suspended in methyl alcohol / dichloromethane mixture at a volume ratio from 8:1 to 1:2, the mixture is stirred at room temperature, crystalline bosentan monohydrate is isolated, dried to constant weight and optionally crystallized to obtain appropriate crystal shape.



WO 2014/104904 A1

Process for preparation of bosentan monohydrate of pharmaceutical purity

Field of the invention

5 The present invention relates to the process for preparation of bosentan monohydrate of pharmaceutical purity.

Background of the invention

Bosentan, 4-*tert*-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]benzene-1-sulfonamide, is an orally active dual
10 endothelin-A and -B receptor (ETA/ETB) antagonist. Bosentan is indicated in Europe for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III (with efficacy shown in primary (idiopathic and heritable) PAH, PAH secondary to scleroderma without significant interstitial pulmonary disease, and PAH associated with congenital systemic-
15 to-pulmonary shunts and Eisenmenger's physiology), and also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease [Mealy, N. E. et al., Drugs Future 2001, 26, 1149; Thomson Reuters Cortellis].

Both bosentan as well as the syntheses thereof have been described in the
20 European Patent Application EP 0526708 A1. The key steps of one of the synthetic variants, depicted in Scheme 1 below, are the condensation of dichloropyrimidine derivative (1) and *tert*-butyl benzenesulfonamide (2) to block susceptible to substitution chlorine atom. The resulting monochloro derivative of N-pyrimidinesulfonamide (3) is subsequently transformed into bosentan due to condensation with ethylene glycol in the
25 presence of metallic sodium.

Numerous modifications of the aforementioned method have been disclosed in some publications and patent applications. Condensation of dichloropyrimidine derivative (1) and *tert*-butyl benzenesulfonamide (2) carried out in the presence of different bases, eg. K₂CO₃ and either BnNEt₃Cl or Bu₄NBr in toluene under reflux,
30 K₂CO₃ in the absence of phase transfer catalyst in toluene or MeCN, or in DMSO either

in the presence or absence of K_2CO_3 , have been disclosed in EP 0526708 A1. Substitution with ethylene glycol anion was also carried out by means of the bases such as NaOH in boiling THF, optionally in the presence of 18-crown-6, or *t*-BuONa, *t*-BuOK, NaOMe or NaH in THF under reflux.

5 One of the drawbacks of this synthetic approach is that said synthesis leads to the formation of abundant reaction by-products such as bis-sulfonamide derivative (6), i.e. the product of the reaction between two molecules of sulfonamidic derivative and one molecule of ethylene glycol. Said by-product, named 'dimer', is difficult to remove. In addition, following the synthetic pathway disclosed in EP 0526708 A1 (temperature
10 range between 100-110°C, excess of ethylene glycol, metallic sodium) bosentan of low chemical purity is obtained. According to the Inventors of International Patent Application published as WO 2009/004374, purity of synthesized bosentan was assessed at the level of barely 69-73%, and the attempts of its purification by means of column chromatography led to further decrease of total yield to 30-40%. Such a
15 dramatic yield drop under the employed conditions resulted from degradation of bosentan to the so called 'deshydroxyethyl bosentan' (7), the by-product which has been disclosed in WO 2009/093127 description.

Bosentan obtained according to the procedure disclosed in EP 0526708 A requires multiple and elaborate crystallization processes. Authors of "Research and
20 Development of a Second-Generation Process for Bosentan, an Endothelin Receptor Antagonist" in Org. Proc. Res. Dev., **2002**, 6 (2), 120-124 report, to decrease the amount of impurities, such as dimer and pyrimidinon to the level accepted for active pharmaceutical ingredient, three subsequent crystallizations are necessary to be carried out, two of them in methyl alcohol : isopropyl acetate and one in ethyl alcohol : water
25 mixtures. Unfortunately, none analytical data concerning reduction of impurities level can be found in the said publication. The authors claim, purity of the product obtained under disclosed protocol accounts for 99.3% (HPLC), except for identified impurities it contains also unidentified ones up to 0.2%. This purity is too low for the compound to be accepted as the active pharmaceutical ingredient.

30 According to European Medicines Agency guidelines (European Medicines Agency) authorized by International Conference on Harmonisation, Harmonised

Tripartite Guideline. Q3A(R2), Impurities in new drug substances, and Q3C(R4), Impurities: Guideline for Residual Solvents, approved in Geneva in 2006, active pharmaceutical ingredient must fall into line with the particular recommendations regarding purity, which means, the content of impurities and residual solvents cannot
5 exceed acceptable limits. For the pharmaceutical substances, which are not disclosed in monographs of European Pharmacopoeia, acceptable content of a single identified impurity is <0.15% and of an unidentified impurity is <0.10%.

In the International Patent Application WO 2009/093127 modified synthetic approach has been disclosed. To reduce the level of bosentan impurities, the substitution
10 of N-pyrimidinylsulfonamide monochloro derivative (3) with ethylene glycol was carried out in the presence of NaOH at 92-97°C for 5 h. This process yielded crude bosentan of as high purity as 99.11% (Impurity 7 – 0.35%, Impurity 6 – 0.2%). Owing to subsequent crystallization in methyl alcohol / ethyl acetate, bosentan of 99.94% purity was obtained. The main drawback of this methodology is low yield of the final
15 product in comparison with yield of the process disclosed in EP 0526708 A1. In addition, as has been reported in the International Patent Application WO 2011/024056, bosentan synthesized in the presence of sodium hydroxide contained higher amount of dimer (6) by-product, reaching up to 0.34%.

In the process described in WO 2010/032261, substitution reaction was carried
20 out under similar conditions to those revealed in EP 0526708 A1, except the amount of metallic sodium used was reduced from about 10 to 2.4 equivalents in relation to the amount of the substrate. The synthesis was performed at 100°C for 27-30 h to furnish the product of 95.66% purity. Subsequent crystallization in methyl alcohol / isopropyl acetate mixture (1:1) yielded bosentan of 97.8% purity, and the subsequent
25 crystallization in ethyl alcohol / water mixture yielded the product of 99.13% purity. The level of impurities in such a way purified compound still exceeds limits acceptable for pharmaceutical substance.

Bosentan purification to remove the aforementioned impurities is also the subject of International Patent Application published as WO 2011/021216. Said process
30 comprises multiple crystallization of crude bosentan in the mixtures of solvents including, among others, methyl alcohol / ethyl acetate, and methyl alcohol / ethyl

acetate / water. The final product of 99.85% purity is obtained, but in only 40% yield of crystallization process.

According to the alternate approach, referred to as second generation synthesis, bosentan is obtained by condensation of N-pyrimidinylsulfonamide monochloro derivative (3) with *tert*-butyl ethylene glycol ether in the presence of NaOH in toluene, followed by treatment of *tert*-butyl bosentan ether, as an intermediate, with formic acid at 85-90°C in toluene and subsequent hydrolysis of the formate derivative (NaOH in H₂O) (Org. Proc. Res. Dev., **2002**, 6 (2), 120–124).

In this process, after one crystallization in ethyl alcohol-water mixture, the final product is obtained in 99.7% yield, but deprotection of bosentan formate makes the total synthesis one step longer in comparison with the first generation one.

Thus, there is still a need in the art for a technological process based on simple and effective purification methods, which will provide bosentan of purity accepted by the demands approved for active pharmaceutical ingredients.

15 Description of the invention

The present invention relates to the process for preparation of bosentan of pharmaceutical purity due to purification of crude bosentan, obtained from dichloro pyrimidine in the two-step synthesis, comprising formation of N-pyrimidinylsulfonamide monochloro derivative, transforming the intermediate into bosentan in the reaction with ethylene glycol anion generated in presence of metallic sodium.

Crude bosentan, synthesized under said protocol, is contaminated with three main impurities of identified chemical structures. They are known as, 'deshydroxyethyl bosentan' (7), 'dimer' (6) and the substrate of the last synthetic step – N-pyrimidinylsulfonamide monochloro derivative (3). In particular, both first mentioned by-products appear to hamper purification of the final product and obtaining bosentan of pharmaceutical purity.

Excess of sodium, temperature and reaction time are the key reaction parameters, which quantitatively influence formation of the by-product (7). The impurity (7) is the degradation product of bosentan, which forms under basic

conditions. Sudden increase of this impurity is detected after completion of the reaction, when bosentan molecule decomposition occurs. The formation of the other impurity, ie. 'dimer', is influenced mainly by excess of glycol and sodium used in the reaction.

The term 'crude' when used herein, refers to bosentan of purity higher than 97%,
5 containing less than 1% of any single impurity assessed by HPLC analysis.

To obtain crude bosentan of the said purity profile, the reaction parameters such as the amount of metallic sodium, temperature and reaction time were optimized by means of HPLC monitoring of the last synthetic step. To find optimal reaction conditions, low level of the impurities as well as reaction time were mainly considered.

10 In the preferred embodiment of the invention, crude bosentan of demanded purity is obtained in the reaction of 4-(*tert*-butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidin]-4-yl)-benzenesulfonamide and sodium glycolate, which is generated from ethylene glycol and 10-fold molar excess of sodium, at 70-75°C for 3-5 h. More preferably, at first sodium glycolate is generated at room temperature, then 4-(*tert*-
15 butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidin]-4-yl)-benzenesulfonamide is added and the resulting mixture is heated at reaction temperature.

Process for preparation of bosentan monohydrate of pharmaceutical purity according to the present invention is characterized by that crude bosentan is suspended in methyl alcohol : dichloromethane mixture at volume ratio from 8:1 to 1:2, the
20 suspension is stirred at room temperature, crystalline bosentan monohydrate is isolated, dried to constant weight and optionally subjected to additional crystallization step to obtain appropriate crystal shape.

The term 'room temperature' relates to the temperature ranging from 15 to 30°C, for example from 20 to 25°C.

25 In the preferred embodiment of the invention, crude bosentan is suspended in methyl alcohol : dichloromethane mixture at volume ratio 5:1. Stirring the suspension, so called 'maceration' process, is continued at room temperature for 24 h.

The ratio of the solvents mixture volume in relation to the amount of crude bosentan subjected to maceration ranges from 2:1 to 10:1, preferably is about 6:1 (v/w),
30 which is far less in comparison with the amounts of solvents used under standard crystallization protocols.

Maceration process is carried out once or, preferably, twice.

The best mode of realization of the present invention involves the different variants.

According to one variant of the invention, crude bosentan as a solid is treated with previously prepared mixture of solvents.

5 According to another variant of the invention, crude bosentan as a solid is added into previously prepared mixture of solvents.

According to another variant of the invention, crude bosentan as a solid is treated with methyl alcohol, the resulting mixture is stirred for a short period of time, for example for ca. 1 h, to this mixture dichloromethane is added to obtain the mixture
10 of solvents of appropriate ratio, and then stirring is continued for a certain period of time, for example for ca. 23 h.

Bosentan, the reaction product of 4-(*tert*-butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidin]-4-yl)-benzenesulfonamide and sodium glycolate, crystallizes in form of monohydrate, forming monoclinic lattice system, with crystals
15 belonging to $P2_1/c$ space group. The basic parameters of bosentan monohydrate crystalline structure are collected in Table 1, and its crystalline structure is depicted on Fig. 2.

Table 1. X-ray structural data collected for bosentan monohydrate

Molecular formula	$C_{27}H_{29}N_5O_6S \cdot H_2O$
Molecular weight	569,63
Temperature of measurement, K	100(2)
Wave length, Å	0,71073
Lattice system	Monoclinic
Space group	$P 2_1/c$
Parameters of the unit cell, Å	$a = 12,3442(12); b = 15,1329(14);$ $c = 14,6450(14),$ $\alpha = \gamma = 90^\circ, \beta = 95,215(2)^\circ$

Unit cell volume, Å ³	2724,4(6)
Number of molecules in the unit cell, Z	4
Density (calculated), Mg/m ³	1,389

Bosentan monohydrate molecules are joined together, forming chains propagated along c axis. Water molecule is joined with two bosentan molecules through three hydrogen bonds: N(1)-H(1)...O(1S), O(1S)-H(1S)...N(5)#2, O(1S)-H(2S)...O(2). In two first mentioned bonds, water is the proton donor, but in the third one water is the proton acceptor. There are two other hydrogen bonds joining two bosentan molecules O(3)-H(3)...N(7)#1, O(3)-H(3)...N(5)#1, which are longer and account for respectively 3,3144(16) and 3,1354(15). The data of hydrogen bonding geometry are collected in Table 2.

Table 2. Hydrogen bounding geometry of bosentan monohydrate, (Å)

D-H...A	D-H	H...A	D...A	D-H...A
N(1)-H(1)...O(1S)	0,88	1.87	2.7226(15)	161.8
O(3)-H(3)...N(7)#1	0.84	2.49	3.3144(16)	166.8
O(3)-H(3)...N(5)#1	0.84	2.63	3.1354(15)	119.6
O(1S)-H(1S)...N(5)#2	0.824(9)	2.064(10)	2.8694(15)	165(2)
O(1S)-H(2S)...O(2)	0.820(9)	2.274(12)	3.0215(14)	151.8(19)

Symmetry code: #1 -x,-y+1,-z+1 #2 x,-y+1/2,z-1/2

It turned out that purification of crude bosentan by maceration according to the present invention does not affect crystalline structure of bosentan monohydrate, but it influences the shape of the obtained crystals.

The analysis of crystal shape and particle size distribution by laser diffraction technique proves that particles formed due to maceration of crude bosentan monohydrate in methyl alcohol / dichloromethane system tend to be smaller in size than

in case of crystallization under standard conditions in ethyl alcohol / water. The comparison analysis of volume particle size distribution is presented in Table 3.

Table 3. Volume particle size distribution of bosentan monohydrate

	d(0.1)	d(0.5)	d(0.9)	D[4,3]
Maceration: MeOH/CH ₂ Cl ₂	13.313	35.304	91.975	57,635
Crystallization: EtOH/water	26.825	148.246	346.191	169,940
Crystallization: EtOH/water	33.749	144.793	351.770	172,301

5

Particle size distribution of bosentan monohydrate obtained by the process according to the present invention is depicted on Fig. 4.

Bosentan monohydrate obtained by maceration has volume moment mean D[4,3] at range 50 - 60 μm , median particle size d(0.5) about 35 μm , wherein 10% of particles have diameter below 15 μm , and 90% below 100 μm .

Bosentan monohydrate of small particles size enhances its bioavailability *in vivo*, and also facilitates manufacturing process of solid dosage forms, allowing to avoid additional operations such as grinding or micronization of active pharmaceutical ingredient. Depending on a type of a dosage form to be produced, bosentan monohydrate purified by maceration can be optionally subjected to micronization. Both grinding and micronization techniques as well as crystal size analysis are well known to those skilled in the art. Upon grinding in a ball mill for instance, particles of size not smaller than 30-40 μm are usually obtained. When micronizing in a conical mill or in a mill with fluidal beads, in a ball mill, colloidal or jet mill or by spray drying, reduction of particle size to less than 10 μm can be achieved.

In the preferred variant of the invention, bosentan monohydrate of purity and particle size distribution meeting the requirements for active pharmaceutical ingredients is obtained directly by maceration, air drying to constant weight at room temperature, preferably at $22 \pm 2^\circ\text{C}$.

Optionally, if required, bosentan monohydrate can be crystallized in ethyl alcohol / water mixture. It has been proved experimentally that additional crystallization does not increase purity of the product, and only influences formation of crystals of different shape comparing with those obtained by maceration.

- 5 Bosentan monohydrate obtained by maceration according to the present invention is characterized by X-ray powder diffraction pattern (XRPD) measured on diffractometer equipped with the copper anode of $K\alpha \lambda = 1,54056 \text{ \AA}$ wave length, represented as relative intensities of diffraction peaks I/I_0 , diffraction angles 2θ and interplanar distances d , with scanning range from 3 to 40° , scanning rate $0,5^\circ/\text{min}$ and
- 10 step size $0,02^\circ$. The data are collected in Table 4.

Table 4. X-Ray powder diffraction pattern of bosentan monohydrate

$d [\text{\AA}]$	$2\theta [^\circ]$	$I/I_0 [\%]$
10.634	8.31	14
9.581	9.22	58
7.835	11.28	7
6.718	13.17	11
5.826	15.20	33
5.725	15.47	37
5.516	16.05	8
5.321	16.65	42
5.002	17.72	36
4.766	18.60	100
4.385	20.24	32
4.169	21.30	32
3.929	22.61	46
3.763	23.63	25

3.656	24.32	25
3.582	24.83	23
3.461	25.72	18
3.350	26.58	24
3.260	27.33	22
3.191	27.94	21

Exemplary XRPD pattern of bosentan monohydrate obtained according to the present invention is depicted on Fig. 5.

Infrared spectrum of bosentan monohydrate obtained according to the present invention, determined in KBr tablet, is depicted on Fig. 6.

On Fig. 7, TG curve obtained from thermogravimetric (TGA) analysis (TGA, full line) under dynamic heating regime ranging from 30°C to 180°C at heating rate 10°C/min, and SDTA curve (*Single Differential Thermal Analysis*, broken line) are depicted. On TGA the effect of mass loss at temperature range from 30°C to about 170°C is observed. Comparison of the effects shown on TGA and SDTA curves indicates, the first effect is attributed to evaporation of superficially absorbed solvent and the base line sloping down reflects melting and concomitant decomposition of the sample. Loss of mass accounts for about 3,13%, this result 3,31% was confirmed by coulometric titration with an oven evaporator and theoretical calculations of water content in the sample. Melting point 104,35°C was determined from SDTA curve.

The present invention provides the method for preparation of bosentan monohydrate in the stable crystalline form, having particles of relatively small diameters and narrow particle size distribution in one simple technological process. Bosentan monohydrate obtained according to the present invention has impurity profile that meets the standards established for active pharmaceutical ingredients. The advantage of purification by maceration in comparison with crystallization is significant reduction of solvents consumption, and thus diminished output of wastes.

The present invention is further illustrated by the following examples.

Examples

Analytical methods

➤ **Single-crystal X-ray diffraction**

5 Single-crystal structure was determined by X-ray diffraction technique using BRUKER KAPPA APEXII ULTRA diffractometer equipped with the rotating anode MoK α , ($\lambda = 0.71073$ Å, 50.0 kV, 22.0 mA), APEX-II CC detector, Oxford Cryostream cooler, at temperature 100 K. Indexing, integration and initial scaling was performed using *SAINT* and *SADABS* software. A single crystal was centered 50 mm from CCD
10 camera. 560 Frames were collected in 1° increment, at 20 s per frame exposure time. Crystal structure was elucidated and refined using SHELXS-97 software.

• **X-Ray powder diffraction (XRPD)**

15 X-Ray powder diffraction pattern was measured on Rigaku MiniFlex diffractometer, with the following parameters:

- Radiation: CuK α 1, $\lambda=1,54056$ Å
- Scanning range 2 θ : from 3 to 40°
- Step size: 0,02°
- 20 • Scanning rate: 0,5°/min
- Detector: scintillating counter.

• **Infrared spectroscopy (IR)**

25 IR spectra were performed in pressed KBr tablets, containing about 1,5 mg of tested substance and about 200 mg of KBr, on Nicolet Impact 410 spectrometer at measurement range from 4000 to 400 cm⁻¹ and 4 cm⁻¹ resolution.

• **Thermogravimetry (TGA)**

30

TGA measurements were performed in the furnace sample chamber TGA/SDTA851^e by Mettler Toledo, under following conditions:

Melting pot: aluminum, 40 μ L capacity,

Purge gas: N₂, flow rate 60 mL/min,

5 Measurement conditions: the samples were heated under dynamic regime ranging from 30 to 180 °C at heating rate 10 °C/min,

Samples preparation: the crystalline substances weighting from 5 to 10 mg were placed in the melting pots without prior preparation. The melting pots were air-tight pressed and punctured before the measurement. The empty
10 pot correction was included in the measurements.

On each thermogram the following curves are depicted: TGA (full line) and SDTA (broken line). TGA curve represents the changes of a sample mass as a function of temperature or time. On the differential SDTA curve the effects of solvent
15 evaporation and a substance melting are shown.

- **Microscopic and particle size analysis**

Particle size distribution was measured by laser diffraction method with particle
20 size distribution analyzer Mastersizer 2000, Malvern and dispersion adapter Hydro 2000S, Malvern. Microscopic visualization was performed with automated microscopic analyzer Morphologi G3s Malvern in diascope light.

Measurement conditions:

25 Measurement conditions:

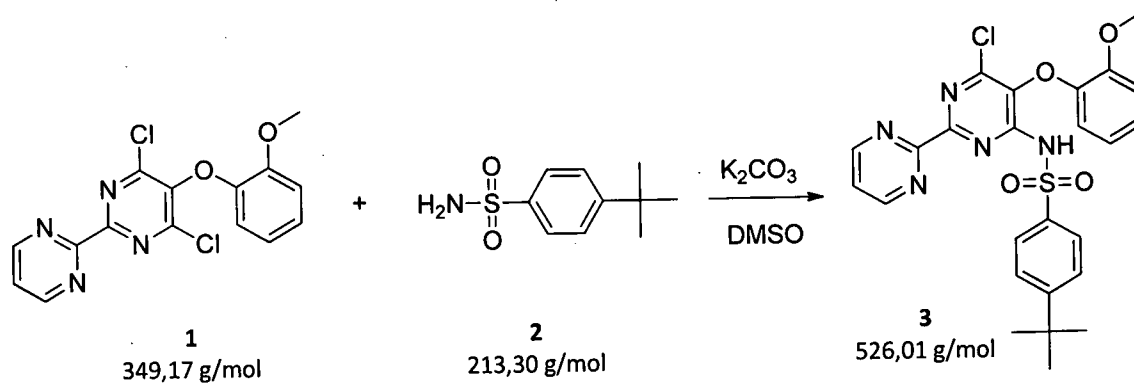
Laser diffractions

Device/dispersion adapter	Mastersizer 2000 / Hydro 2000S Malvern
Ultrasound (us)	0%

Stirring speed	2100 rounds/min
Dispersion medium	Isooctanol
Single measurement time	0.5 s
Background measurement time	10 s
Refraction coefficient of tested particles	1.52
Refraction coefficient of dispersant	1.391
Absorption coefficient	0.01
Obscuration	5-25%

Microscopic analysis

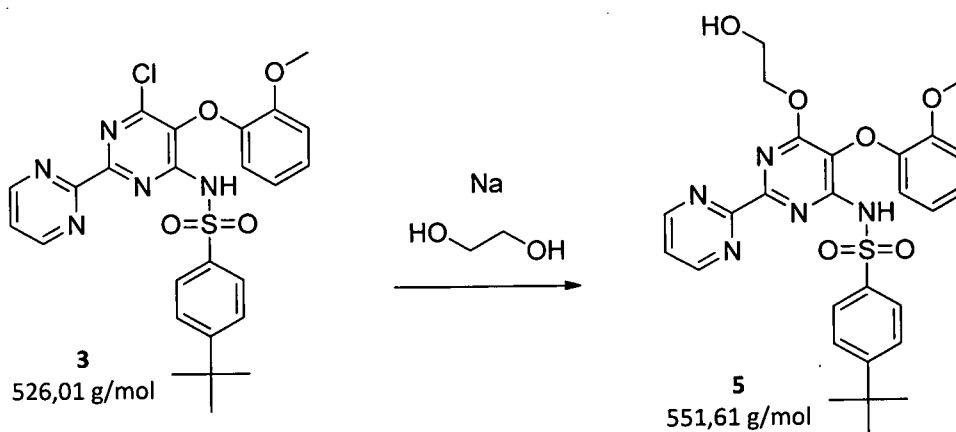
Device/dispersion adapter	Morphologi G3S / -, Malvern
Dispersion medium	Isooctan

Example 1
Synthesis of 4-(*tert*-butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidin]-4-yl)-benzenesulfonamide (3)


In a flask equipped with mechanical stirrer, thermometer, reflux condenser, dropping funnel and heating mantle, 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine **1** (105 g), 4-(*tert*-butyl)benzenesulfonamide **2** (64.1 g, 0.30 mol) in DMSO (525 mL) are placed. To this suspension potassium carbonate (83 g, 0.60 mol) is added. The resulting mixture is heated at 100 - 105°C for 3 - 4 h upon stirring. Reaction progress is monitored by HPLC. The solution is cooled down to 20 -25°C. Water (875 mL) is added dropwise within 10 - 15 min. and stirring is continued for 1 h. Precipitated solid is filtered off, washed with water (2 x 350 mL), then transferred into flask. After addition of water (800 mL) and concentrated hydrochloric acid (50 mL) the solution is stirred for 30 min. The precipitated solid is filtered off, washed with water (2 x 200 mL) and acetone (2 x 175 mL). The solid is dried at 40 ± 2°C for 16 - 24 h under atmospheric pressure. The product is obtained in 157.8 - 158.7 g (100%) yield as cream-colored solid.

15 Example 2

Synthesis of 4-(*tert*-butyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)benzenesulfonamide (5**)**



20

In a 6 L capacity flask equipped with mechanical stirrer, thermometer and reflux condenser ethylene glycol (2.325 L, 41.60 mol) is placed. Metallic sodium (67.8 g, 2.95 mol) is added portionwise upon stirring and maintaining temperature below 40°C. 4-(*tert*-Butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)-benzenesulfonamide (**3**) (155 g, 0.29 mol) obtained in the prior step is added. The

- mixture is heated at 70-75°C and stirred for 4 - 5 h. Reaction progress is monitored by HPLC. Heating is stopped and the solution is left to cool down to $22 \pm 2^\circ\text{C}$. The solution is transferred into separatory funnel, water (4 L) and acetic acid (320 mL) are added to adjust pH to 5. While stirring the solution for 30 min. suspension is formed.
- 5 Dichloromethane (1 L) is added and stirring is continued for 15 min. Organic phase is separated and water layer is extracted with dichloromethane (2 x 1 L). Combined organic extracts are condensed under vacuum evaporator. The product is obtained as pale yellow foam, which is dissolved in ethanol (500 mL) at 40 – 45 °C. The clear solution is transferred into 2 L capacity flask, equipped with mechanical stirrer and
- 10 dropping funnel. After addition of water (500 mL) within 15 min., the resulting mixture is stirred for 60 min. Precipitated solid is filtered off and washed with the mixture of ethanol : water 1:1 (2 x 100 mL). The solid is air dried to constant weight at $22 \pm 2^\circ\text{C}$. The product is obtained in 143.6 - 146.8 g (ca. 87%) yield.

15 **Example 3. Influence of reaction conditions on the level of crude bosentan purity**

An influence of reaction conditions on the crude bosentan purity was investigated. Synthesis was carried out under conditions described in Example 2.

No.	Conditions			Results (%, HPLC)		
	Na (eq.)	Temp.	Time (h)	Bosentan	Impurity 7	Impurity 3
1.	10	110-115	2.5	85.90	12.03	0.04
2.	10	100-110	1.5	92.51	4.90	0.03
3.	10	80-85	1.5	97.28	1.05	0.06
4.	10	70-75	4.5	97.71	0.36	0.54
5.	10	70-75	4	98.37	0.45	0.12
6.	2	100-110	24	93.33	2.70	1.96
7.	5	80-85	7	97.50	0.80	0.40

8.	5	70-75	24	97.70	0.90	0.05
9.	5	70-75	22	97.89	0.71	0.15

Example 4

Purification of 4-(*tert*-butyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)benzenesulfonamide (5)

A. First maceration in methanol : dichloromethane 5:1 (v/v) (previously prepared mixture of solvents is added to the solid)

In a 2 L capacity flask equipped with mechanical stirrer, 4-(*tert*-butyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)benzenesulfonamide **5** (146.0 g) obtained in prior step is placed. To this solid, previously prepared mixture of methanol : dichloromethane 5:1 (876 mL) is added. The resulting mixture is stirred at $22 \pm 2^\circ\text{C}$ for 24 h. Precipitated solid is filtered off and washed with methanol (2 x 40 mL). It is air dried at $22 \pm 2^\circ\text{C}$ to constant weight. The product is obtained in 115.1 – 128.5 g (79 – 88%) yield as fine-crystalline, yellowish solid.

B. Second maceration in methanol : dichloromethane 5:1 (v/v) (the solid is added into previously prepared solvents mixture)

Methanol (575 mL) and dichloromethane (115 mL) are placed in a 2 L capacity flask equipped with mechanical stirrer. 4-(*tert*-Butyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)benzenesulfonamide **5** (115.0 g) within 10 – 15 min. is added portionwise. The solution is stirred at $22 \pm 2^\circ\text{C}$ for 24 h. The solid is filtered off and washed with methanol (2 x 30 mL). The solid is air dried at $22 \pm 2^\circ\text{C}$ to constant weight. The product is obtained in 91.3 – 100.1 g (79 - 87%) yield as fine-crystalline, pale yellow solid.

C. Crystallization in ethanol : water 1:1 (v/v).

4-(*tert*-Butyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)benzenesulfonamide **5** (91.0 g) in ethanol (260 mL) is placed in a 500 mL capacity

flask equipped with mechanical stirrer, reflux condenser and thermometer. The solution is heated at reflux, until the solid is completely dissolved. Hot solution is filtered, the residue is washed out from the flask with ethanol (2 x 20 mL). The solution is transferred into a 1 L capacity flask equipped with mechanical stirrer and dropping
 5 funnel. To the hot mixture water (300 mL) is added dropwise within 15 min., resulting solution is stirred at $22 \pm 2^\circ\text{C}$ for 2 h. Precipitated solid is filtered off and washed with ethanol : water 1:1 (2 x 40 mL). It is air dried at $22 \pm 2^\circ\text{C}$ to constant weight. The product is obtained in 87.4 - 90.1 g (96 - 99%) yield as white solid.

Bosentan [%]	Impurity 3 [%]	Impurity 6 [%]	Impurity 7 [%]	Yield [%]	Purification step
98.74	0.19	0.49	0.36	90	Crude bosentan
99.43	0.09	0.20	0.20	79	MeOH/CH ₂ Cl ₂ (1)
99.70	0.05	0.09	0.13	79	MeOH/CH ₂ Cl ₂ (2)
99.71	0.05	0.07	0.11	99	EtOH/water

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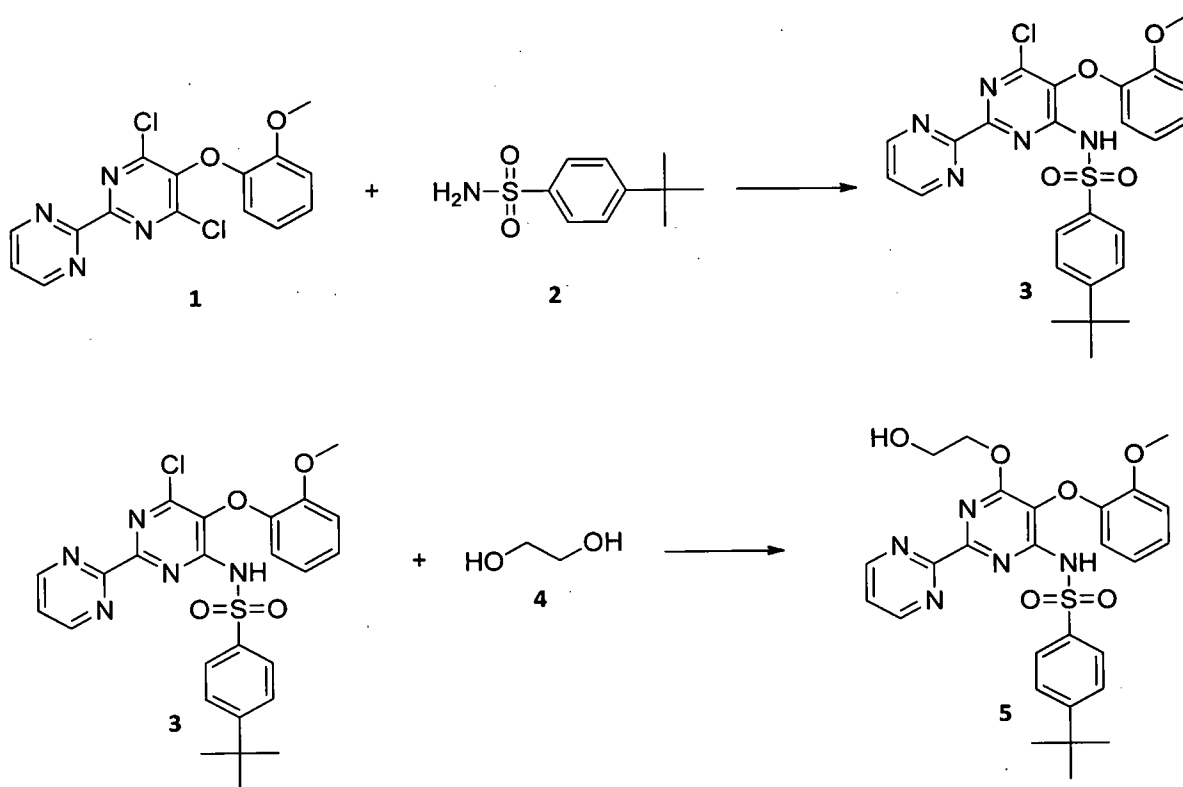
Claims

1. A process for the preparation of bosentan monohydrate of pharmaceutical purity, characterized by that crude bosentan is suspended in methyl alcohol /
5 dichloromethane mixture at a volume ratio from 8:1 to 1:2, the mixture is stirred at room temperature, crystalline bosentan monohydrate is isolated, dried to constant weight and optionally crystallized to obtain appropriate crystal shape.
2. The process according to claim 1 wherein the step of maceration is performed once or twice.
- 10 3. The process according to claim 1 wherein crude bosentan is suspended in methyl alcohol / dichloromethane mixture at volume ratio about 5:1.
4. The process according to claim 1 wherein the volume of solvents mixture in relation to crude bosentan weight is from 2:1 to 10:1 (v/w).
5. The process according to claim 4 wherein the volume of solvents mixture in
15 relation to crude bosentan weight is about 6:1 (v/w).
6. The process according to claim 1 wherein the mixture is stirred for ca. 24 h.
7. The process according to any one of claims 1-6 wherein crude bosentan as a solid is treated with the previously prepared mixture of solvents
- 20 8. The process according to any one of claims 1-6 wherein crude bosentan as a solid is added to the previously prepared solvents mixture.
8. The process according to any one of claims 1-6 wherein crude bosentan as a solid is treated with methyl alcohol, the resulting suspension is stirred for ca. 1 h, to this mixture dichloromethane is added to achieve said proportions of solvents and
25 stirring is continued for ca. 23 h.
9. The process according to any one of claims 1-8 wherein crude bosentan is obtained in the reaction of 4-(*tert*-butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)benzenesulfonamide and sodium glycolate generated using 10-fold molar excess of metallic sodium.
- 30 10. The process according to any one of claims 1-9 wherein crude bosentan is obtained in the reaction of 4-(*tert*-butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-

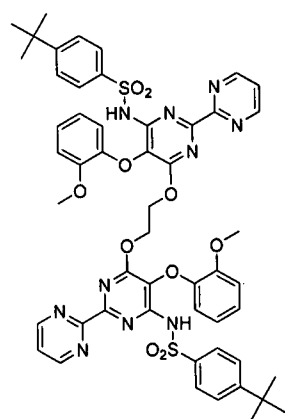
bipyrimidine]-4-yl)benzenesulfonamide and sodium glycolate carried out at 70-75°C for 3-5 h.

11. The process according to any one of claims 9 or 10 wherein sodium glycolate is generated at room temperature, then 4-(*tert*-butyl)-N-(6-chloro-5-(2-methoxyphenoxy)-[2,2'-bipyrimidine]-4-yl)-benzenesulfonamide is added and the resulting mixture is heated up to 70-75°C.

1/6

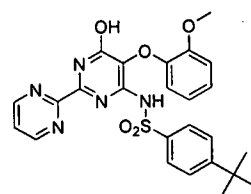


Scheme 1



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Bosentan dimer



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Deshydroxyethyl bosentan

2/6

5

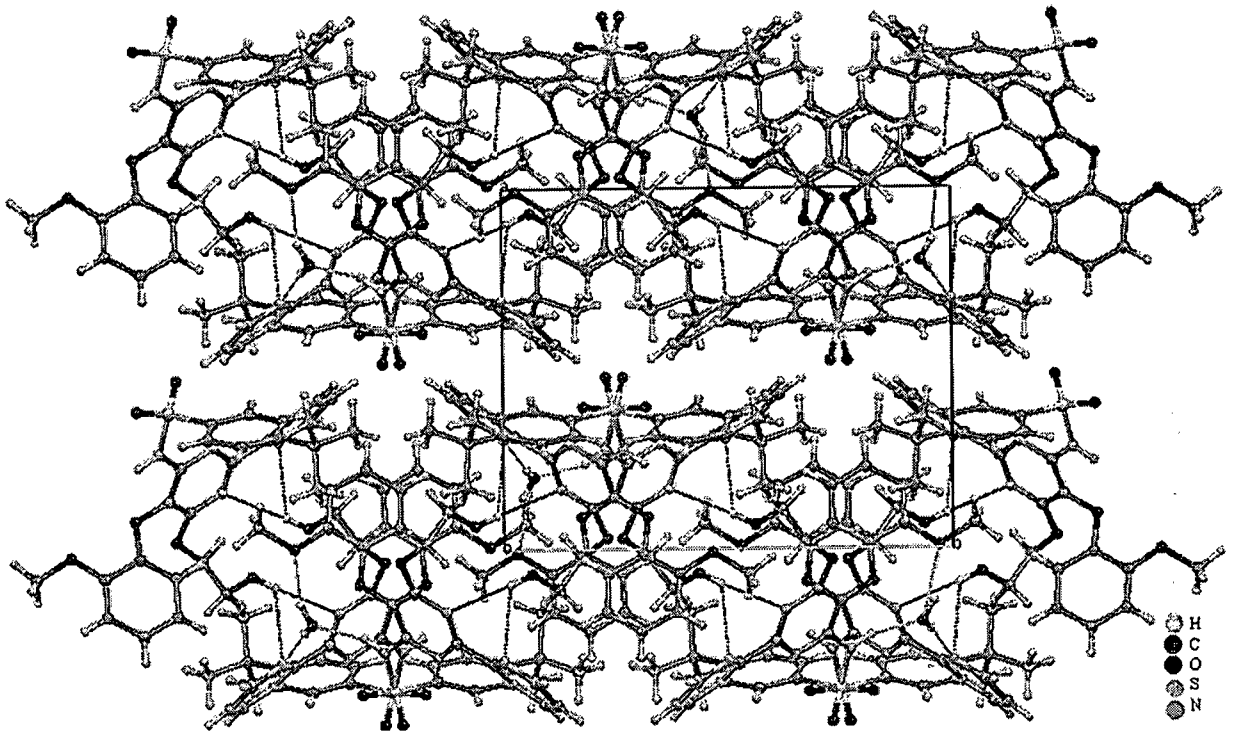


Fig. 2. Bosentan monohydrate chains propagating along the c axis

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3/6

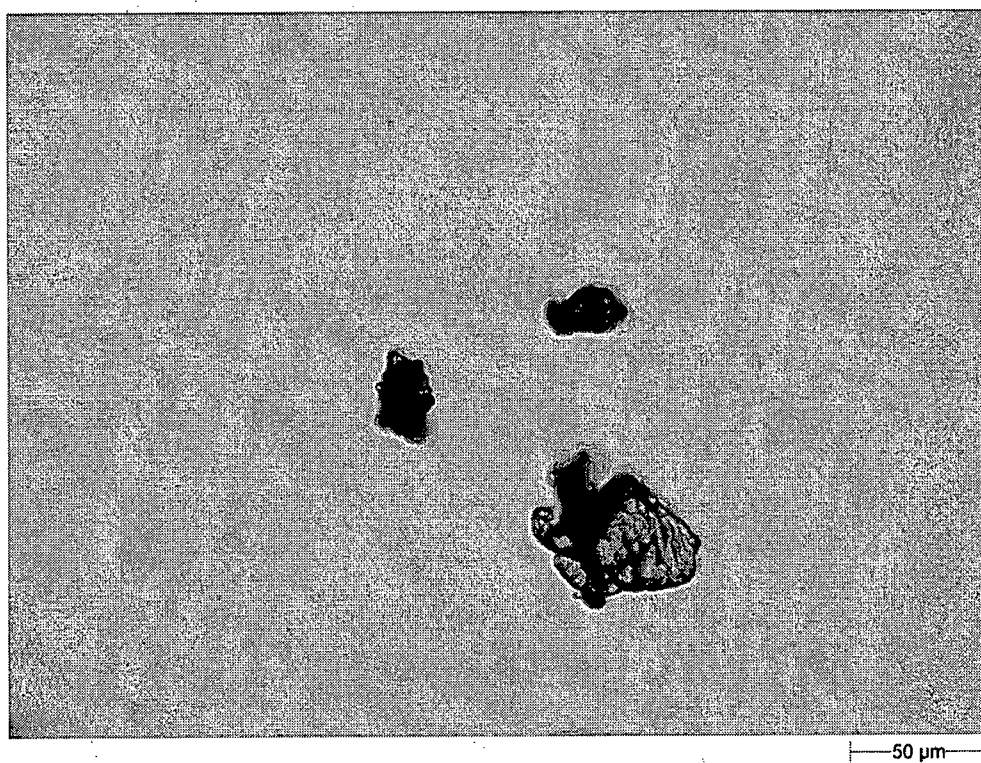
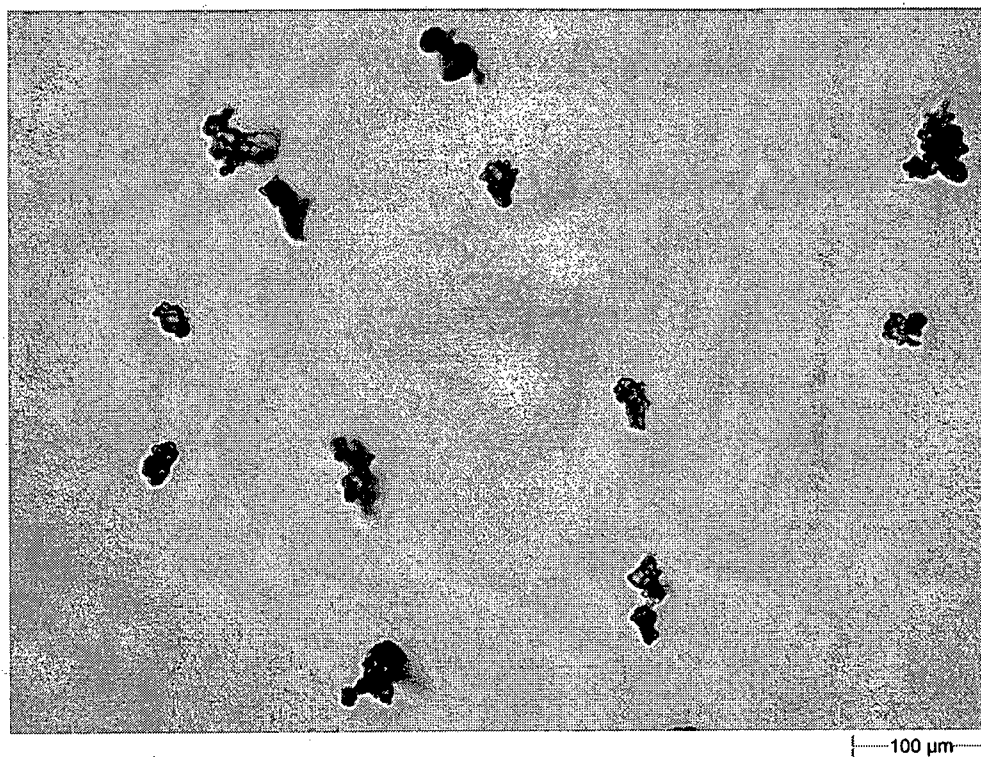
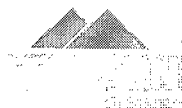


Fig. 3. Microscopic imaging of bosentan monohydrate

4/6



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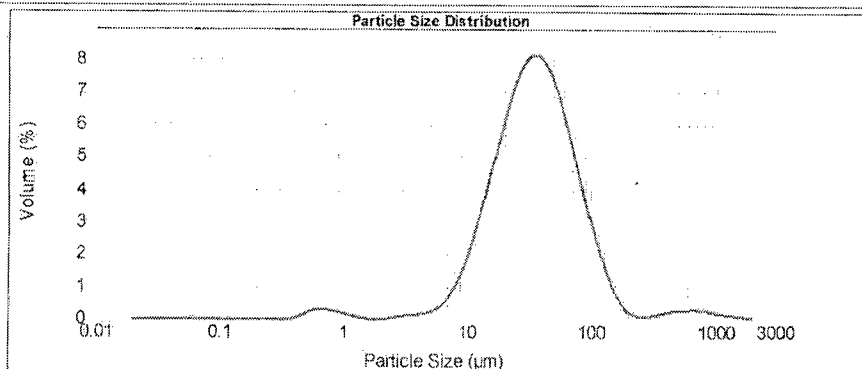


Result Analysis Report

Sample Name: BO 235-064-1wynik sredni
Sample Source & type: IF
Sample bulk lot ref:
SOP Name:
Measured by: IF
Result Source: Averaged
Measured: 13 kwietnia 2012 10:30:45
Analysed: 13 kwietnia 2012 10:30:46

Particle Name: 1.52/0.01	Accessory Name: Hydro 2000S (A)	Analysis model: General purpose	Sensitivity: Normal
Particle Rf: 1.520	Absorption: 0.01	Size range: 0.020 to 2000.000 μm	Obscuration: 6.70 %
Dispersant Name: Iso-Octane	Dispersant Rf: 1.391	Weighted Residual: 0.560 %	Result Emulation: Off
Concentration: 0.0234 %Vol	Span: 2.228	Uniformity: 1.04	Result units: Volume
Specific Surface Area: 0.337 m^2/g	Surface Weighted Mean D[3,2]: 17.762 μm	Vol. Weighted Mean D[4,3]: 57.635 μm	

d(0.1): 13.313 μm d(0.5): 35.384 μm d(0.9): 91.975 μm



BO 235-064-1wynik sredni, 13 kwietnia 2012 10:30:45

Size (μm)	Vol Under %	Size (μm)	Vol Under %	Size (μm)	Vol Under %	Size (μm)	Vol Under %	Size (μm)	Vol Under %	Size (μm)	Vol Under %
0.031	0.48	1.005	1.42	5.754	2.14	17.378	17.37	59.481	70.18	198.488	97.04
0.124	0.74	2.158	1.42	8.807	2.46	18.653	22.43	60.256	70.27	181.970	97.52
0.332	0.90	2.512	1.42	7.666	3.26	22.900	20.29	69.160	81.52	208.909	97.73
0.985	1.17	2.904	1.48	8.710	3.04	26.505	34.77	70.433	85.14	239.883	97.82
1.668	1.31	3.311	1.54	10.000	5.27	30.200	41.78	82.201	88.80	275.423	97.88
1.920	1.39	3.602	1.60	11.482	7.19	34.674	49.04	104.713	92.04	316.228	97.96
1.448	1.42	4.365	1.77	12.183	9.78	39.811	56.36	120.220	94.72	333.078	98.07
1.660	1.43	5.012	1.82	15.150	13.16	45.708	83.48	138.036	95.15	415.389	98.24

Operator notes: Average of 40 measurements from BO 235-064-1 *RO DISCUM*

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Mastersizer 2000 Ver. 5.01
 Serial Number: MAL1006422

File name: BO 235-064-1
 Record Number: 211
 13 April 2012 10:50:43

Fig. 4. Particle size distribution of bosentan monohydrate

5/6

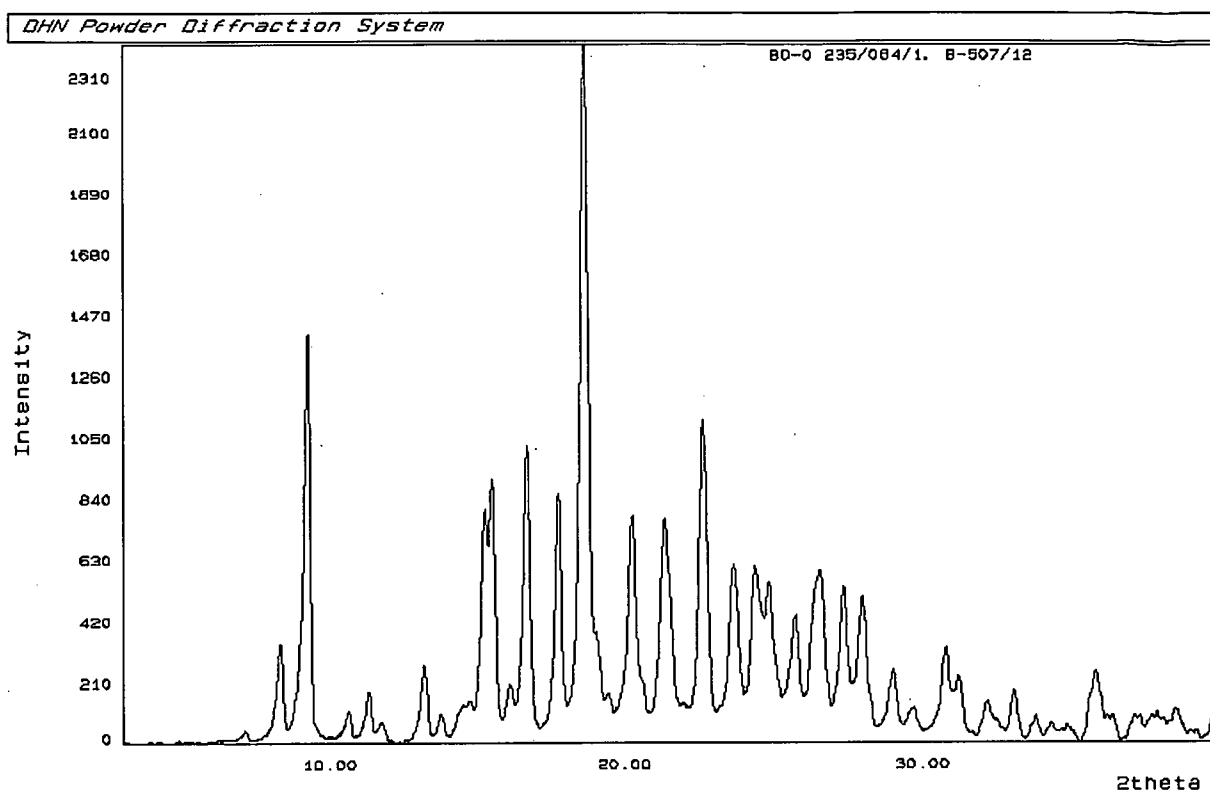
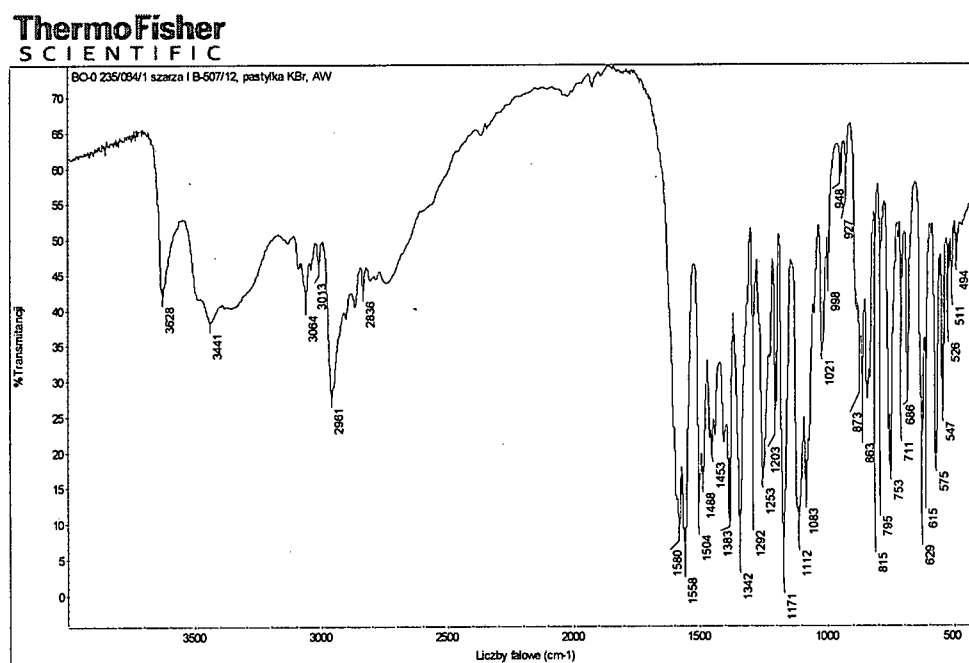


Fig. 5. X-ray powder diffraction pattern of bosentan monohydrate



5 Fig. 6. Infrared spectrum of bosentan monohydrate

6/6

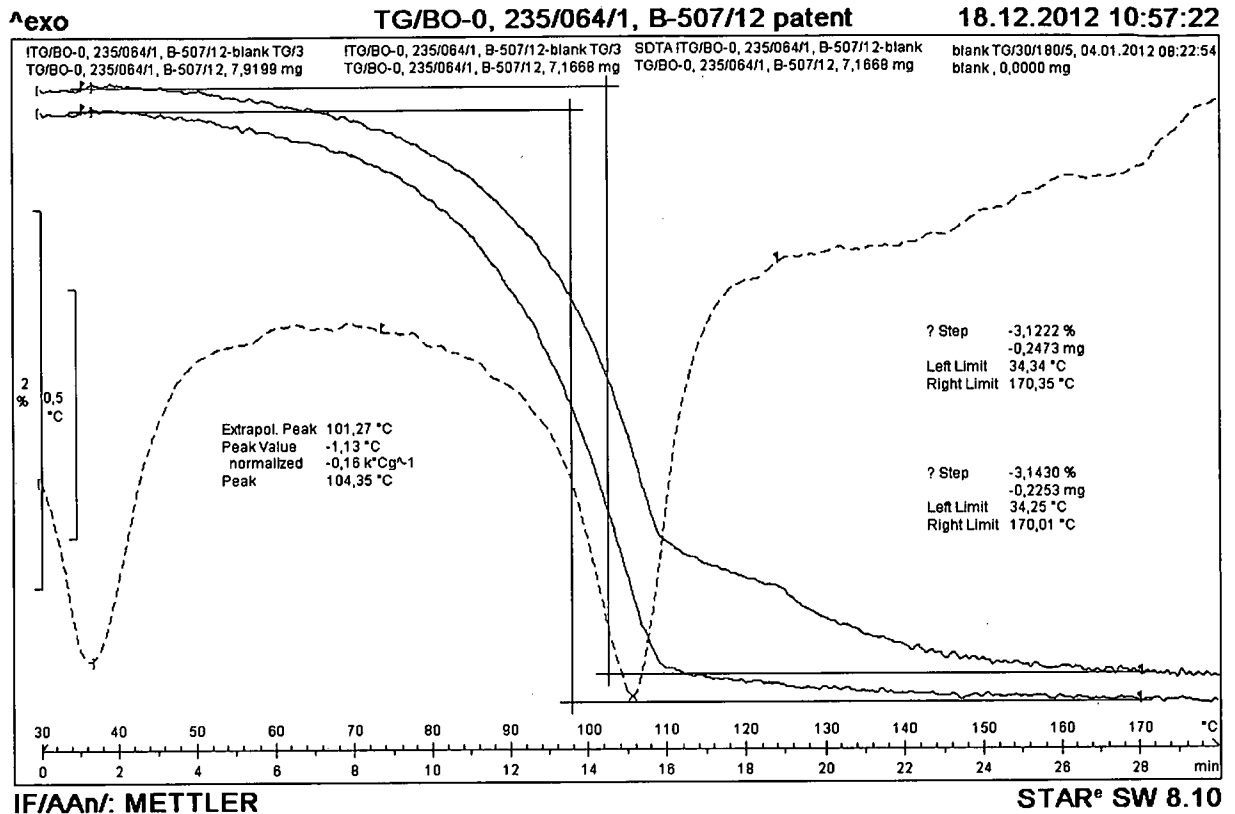


Fig. 7. Thermogravimetric analysis of bosentan monohydrate

INTERNATIONAL SEARCH REPORT

International application No

PCT/PL2013/000173

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D239/69 A61K31/506
 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

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/021216 A2 (MSN LAB LTD [IN]; SATYANARAYANA REDDY MANNE [IN]; ESWARAI AH SAJJA [IN]) 24 February 2011 (2011-02-24) cited in the application reference example 1, 2; examples 13-16 -----	1-11
A	WO 2009/093127 A2 (ACTAVIS GROUP PTC EHF [IS]; DIXIT GIRISH [IN]; GAIKWAD NANDKUMAR [IN];) 30 July 2009 (2009-07-30) cited in the application examples -----	1-11
A	WO 2009/053748 A2 (GENERICS UK LTD [GB]; MYLAN DEV CT PRIVATE LTD [IN]; GAITONDE ABHAY [I]) 30 April 2009 (2009-04-30) examples -----	1-11



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

28 March 2014

Date of mailing of the international search report

09/04/2014

Name and mailing address of the ISA/

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Authorized officer

Miniejew, Catherine

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/PL2013/000173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			US 2011021547 A1 27-01-2011
			WO 2009093127 A2 30-07-2009

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			CA 2703230 A1 30-04-2009
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			NZ 585438 A 28-09-2012
			NZ 600010 A 29-11-2013
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			WO 2009053748 A2 30-04-2009
