The present invention concerns a process for the manufacture of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine.
**Purification of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl] piperazine**

**Field of the invention**

The present invention relates to production and purification of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine.

**Background**

The international patent applications published as WO 03/029232 and WO 2007/144005 disclose that the compound 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and salts thereof have affinity to the serotonin transporter and the serotonin receptors 3 and 1A (5-HT3 and 5-HT1A). This pharmacological profile makes the use of said compounds in the treatment of affective disorders, such as depression and anxiety, attractive. In fact, the compound is currently subjected to clinical trials in affective disorders.

The manufacture of pharmaceutical products is a highly regulated area with many guidelines and rules concerning quality/purity of active pharmaceutical ingredients (API). It is therefore a requirement that manufacturing routes ensure a high purity of final products, one approach towards this aim is to develop specific purification steps.

Crystallisation and re-crystallisation are well-known ways to provide purified compounds. The examples provided in WO 2007/144005 disclose that 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and salts thereof may be crystallised from solvents such as ethylacetate, ethylacetate/water, water and toluene.
Summary **of the invention**

The present inventors have found that including a step in the synthesis of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable salts thereof in which step 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine-HBr isopropanol solvate is prepared from 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine-HBr removes or reduces impurities and thus provides purified 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable salts thereof, e.g. the β-form of the HBr salt.

Hence, in one embodiment, the invention provides a process for the manufacture of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of achieving a solution by dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr salt in a solvent comprising more than 65% (v/v) isopropanol.

In one embodiment, the invention provides a process for the manufacture of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of precipitating 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate from a solvent comprising more than 65% (v/v) isopropanol.

In one embodiment, the invention relates to a process for the manufacture of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate in a solvent that does not form stable solvates with the compound.

In one embodiment, the invention provides a compound which is 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate.

**Figures**

Figure 1: XRPD of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, β-form

Figure 2: XRPD of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, isopropanol solvate

Figure 3: TGA and DSC thermograms of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate
Figure 4: 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-4-(2-piperazin-1-yl-phenyl)-piperazine
Figure 5: 1-[2-(5-chloro-2,4-dimethyl-phenylsulfanyl)phenyl]piperazine
Figure 6: 1-[2-(2,6-dimethylphenylsulfanyl)phenyl]piperazine

Detailed description of the invention

The present invention relates to a purification step which may be used in the manufacture of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine and pharmaceutically acceptable salts thereof. The molecular structure of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine is depicted below.

![Molecular structure of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine](image)

In particular, pharmaceutically acceptable salts are acid addition salts of acids that are non-toxic. Said salts include salts made from organic acids, such as maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylene salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citaconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Said salts may also be made from inorganic salts, such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Particular mention is made of salts made from lactic acid, methanesulfonic acid, maleic acid, fumaric acid, meso-tartaric acid, (+)-tartaric acid, (-)-tartaric acid, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphorous acid and nitric acid. Distinct mention is made of the hydrobromide salt.

As shown in WO 2007/144005, HBr salt crystals of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine are polymorphic and exist in (at least) three different forms, i.e. the cc, the β- and the γ-form - the alpha-, beta- and gamma-form. Judged from DSC and solubility data, the β-form is the most stable form, and it is characterised by XRPD.
reflections at approximately 6.86, 9.73, 13.78 and 14.62 (°2Θ). An XRPD pattern of the β-form is depicted in Figure 1. Please see example 1 for the preparation of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, β-form.

Manufacturing processes for the compound are disclosed in WO 03/029232 and WO 2007/144005. One manufacturing process exploits Buchwald palladium catalysis (see US 5,576,460) to prepare the N-aryl bond. In this process, 2,4-dimethylthiophenol, 2-bromo-l-iodobenzene and piperazine are mixed together with a palladium source and a phosphine ligand in a suitable solvent, e.g. toluene, at elevated pH. Other di-halogen benzenes may be used and the piperazine may be protected. Suitable palladium sources include Pd2dba3, Pddba2 and Pd(OAc)2. dba abbreviates dibenzylideneacetone. Particular mention is made of Pddba2. Suitable phosphine ligands include monodentate and bidentate ligands, such as racemic 2,2′-bis-diphenylphosphanyl-[1,1′]binaphtalenyl (rac-BINAP), 1,1′-bis(diphenylphosphino)ferrocene (DPPF), bis-(2-diphenylphosphinophenyl)ether (DPEphos), tri-t-butyl phosphine (Fu's salt), biphenvl-2-yl-di- t-butyl-phosphine, biphenvl-2-yl-dicyclohexyl-phosphine, (2′-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethyl-amine, [2′-(di-t-butyl-phosphanyl)-biphenyl-2-yl]-dimethyl-amine, and dicyclohexyl-(2′,4′,6′-tri-propyl-biphenyl-2-yl)-phosphane. Moreover, carbene ligands, such as e.g. 1,3-bis-(2,6-diisopropyl-phenyl)-3H-imidazol-l-ium; chloride may be used in stead of phosphine ligands.

In particular, rac-BINAP is a useful ligand. Base is added to the reaction mixture to increase or elevate pH. In particular bases selected from NaO(t-Bu), KO(t-Bu) and Cs2COs are useful. Organic bases, such as 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) may be applied as well. Particular mention is made of NaO(t-Bu) and KO(t-Bu).

Alternatively, the thiophenol and the di-halogenbenzene may be reacted in a first step to achieve phenylsulfanyllphenyl, which may be isolated before further reaction with piperazine or protected piperazine to achieve the desired product.

In order to obtain a desired salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl)piperazine, the corresponding free base achieved in the above process may be reacted with an appropriate acid to precipitate the salt. In particular, aqueous hydrobromic acid may be used to precipitate 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr.
The present invention provides a purification process which can be used e.g. at this step of the manufacturing route. The process provides a highly purified end-product and, moreover, the process allows the use of starting materials of inferior purity. In summary, the HBr salt is dissolved in a solution comprising isopropanol from which solution the corresponding isopropanol solvate is precipitated. It is the experience of the inventors that isopropanol solvates are formed if the solution comprises more than 65% (v/v) isopropanol. The precipitation may be brought about by cooling. The isopropanol solvate is subsequently dissolved in a non-solvate forming solvent, and isopropanol and/or water may be removed or reduced, e.g. by distillation. Removing or reducing isopropanol may be used to increase yield. Finally, l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr is precipitated. The choice of solvent and conditions for the precipitation, e.g. temperature ramp, crystal seeding may be used to control the crystal form obtained. The term "non-solvate forming solvent" indicates a solvent, which does not take part in the formation of stable solvates of the l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr salt. Examples include water, THF (tetrahydrofuran), xylene, benzene, methanol, ethanol, acetone and toluene, and mixtures hereof. Particular mention is made of toluene mixed with water. Particular mention is made of mixtures comprising more than 80% toluene in water.

Purification by precipitation of corresponding solvates is unusual, and as discussed in Hilfiker, R. (editor). Polymorphism in the Pharmaceutical Industry. Wiley-VCH, 2006. p. 12-13.) such purification step is generally only recommended if the product to be purified is difficult to crystallise in a solvent-free form.

If a salt different from the HBr salt is desired, the purified HBr salt may be used as starting material in further processes in which the HBr salt is dissolved, the free base form is optionally obtained, and the desired salt is achieved by precipitation with an appropriate acid.

In one embodiment, the invention provides a process for the manufacture of l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of achieving a solution by dissolving l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr salt in a solvent comprising more than 65 %(v/v) isopropanol at elevated temperatures, such as reflux temperature. Alternatively, the temperature is not increased, and this will increase process time. In particular, said pharmaceutically acceptable salt is the HBr salt, β-form. In one embodiment, said solvent comprises more than 85% (v/v) isopropanol.
In one embodiment, the invention provides a process for the manufacture of \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine} \) or a pharmaceutically acceptable salt thereof comprising the step of precipitating \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate} \) from a solvent comprising more than 65 % (v/v) isopropanol, e.g. by cooling. In particular, said pharmaceutically acceptable salt is the HBr salt, \( \beta \)-form. In one embodiment, the solvent comprises more than 85 % (v/v) isopropanol.

In one embodiment, the invention provides a process for the manufacture of \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine} \) or a pharmaceutically acceptable salt thereof comprising the step of dissolving \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate} \) in a non-solvate forming solvent, followed by precipitation of \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr} \). In particular, said pharmaceutically acceptable salt is the HBr salt, such as the \( \beta \)-form.

In one embodiment, the invention provides a process for the manufacture of \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine} \) or a pharmaceutically acceptable salt thereof, and in particular the HBr salt, \( \beta \)-form comprising the step of

a) achieving a solution by dissolving \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr} \) in a solvent comprising more than 65 % (v/v), such as more than 85% (v/v) isopropanol, e.g. at elevated temperatures, such as reflux temperature;

b) precipitating \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr,} \) isopropanol solvate from said achieved solution, e.g. by cooling;

c) dissolving \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr,} \) isopropanol solvate in a non-solvate forming solvent; in particular, the non-solvate forming solvent comprises more than 80% toluene, such as more than 90%; and

d) precipitating \( \text{I-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr} \) from the solution obtained in c), e.g. by cooling.

If the HBr salt used in a) contains a large amount of impurities, it may be beneficial to re-dissolve the isopropanol solvate obtained in b) in a solvent comprising more than 65% isopropanol followed by precipitation as described in b).

In one embodiment, the invention relates to a product directly obtained by one of the processes described above.
In one embodiment, the invention relates to a process of removing or reducing an impurity from solid 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr salt or a solution of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, the process comprising the steps of:

a) mixing a solvent comprising more than 65% (v/v), such as more than 85% (v/v) isopropanol with solid 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr or with a solution of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, HBr as the case may be, e.g. followed by heating as appropriate, to achieve a solution of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr;

b) cooling said achieved solution to precipitate 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate;

c) dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate in a non-solvate forming solvent; and

d) precipitating 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr from the solution obtained in c), e.g. by cooling.

In particular, the non-solvate forming solvent used in c) is selected from water, THF, xylene, benzene, methanol, ethanol, acetone and toluene, and mixtures hereof. Particular mention is made of toluene mixed with water, in particular comprising more than 80% (v/v), such as more than 90% (v/v) toluene.

Examples of such impurities include palladium (Pd), 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-4-(2-piperazin-1-yl-phenyl)-piperazine (compound 1), 1-[2-(5-chloro-2,4-dimethyl-phenylsulfanyl) phenyl]piperazine (compound 2), 1-[2-(2,6-dimethylphenylsulfanyl)phenyl]piperazine (compound 3), and 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr tert-butanol solvate - see also Fig. 4-6.

Palladium is an impurity caused by the use of Pd catalysts. "Pd" or "palladium" is intended to indicate all Pd containing compounds. Compound 1 is an impurity generated when the Pd catalysed N-aryl bond formation takes place at both piperazine nitrogens. Compounds 2 and 3 are impurities carried over from the 2,4-dimethyliophenol raw material which may be contaminated with the corresponding 5-chloro or 2,5-dimethyl compounds. The tert-butanol solvate may be formed to due to the use of sodium tert-butoxide in the reaction.

To further illustrate the invention, the following description may be helpful. 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr (A) is charged to a reactor. Isopropanol
(10-15 L/kg A) and water (0.3 - 1.0 L/kg A) is added and agitation is started. The mixture is heated to reflux and all the 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr salt is dissolved. The solution is cooled to <20°C, and the crystals (isopropanol solvate) are filtered and washed twice with isopropanol (2.4 - 2.6 L/kg A, in total). The wet filter cake is recharged to the reactor and toluene (4 - 6 L/kg A) is added. The isopropanol/water from the wet filter cake is azeotropically distilled off and the toluene lost in the distillation is added together with water (0.2 - 0.3 x A). The mixture is heated to reflux and all the 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr is dissolved. The solution is cooled to <20°C, and the crystals are filtered and washed twice with toluene (1.0 - 4.0 L/kg A, in total). The crystals are dried at elevated temperature, e.g. 60°C and vacuum. The β-form of the 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr is obtained.

As shown in example 5, the purification process of the present invention is superior to equivalent re-crystallisation processes in that more impurities are reduced or removed. Hence, the purification process of the present invention is endowed with unique and unforeseeable qualities.

As illustrated above, 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr isopropanol solvate is useful in process steps for the purification of 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine and pharmaceutically acceptable salts thereof.

Thus, in one embodiment, the invention relates to a liquid solution comprising 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine in more than 65% (v/v) isopropanol.

In one embodiment, the invention relates to 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr isopropanol solvate.

In one embodiment, the invention relates to 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr isopropanol solvate with XRPD reflections at approximately 6.44, 8.13, 8.77, 10.41 (°2θ), e.g. with an XRPD patterns as depicted in Figure 2.

It is noted that a further benefit of using 1-(2,4-dimethylphenylsulfanyl)phenyl)piperazine·HBr isopropanol solvate relates to its process properties. The solvate is not static and it is easy to handle on the filters.

All references cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent
permitted by law), regardless of any separately provided incorporation of particular documents made elsewhere herein.

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. For example, the phrase "the compound" is to be understood as referring to various compounds of the invention or particular described aspect, unless otherwise indicated.

Unless otherwise indicated, all exact values provided herein are representative of corresponding approximate values (e.g., all exact exemplary values provided with respect to a particular factor or measurement can be considered to also provide a corresponding approximate measurement, modified by "about," where appropriate).

The description herein of any aspect or aspect of the invention using terms such as "comprising", "having," "including," or "containing" with reference to an element or elements is intended to provide support for a similar aspect or aspect of the invention that "consists of, "consists essentially of, "or "substantially comprises" that particular element or elements, unless otherwise stated or clearly contradicted by context (e.g., a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

Examples

Analytical methods

$^1$H NMR spectra are recorded at 500.13 MHz on a Bruker Avance DRX500 instrument.

Dimethyl sulfoxide (99.8% D) is used as solvent, and tetramethylsilane (TMS) is used as internal reference standard.
The melting points are measured using Differential Scanning Calorimetry (DSC). The equipment is a TA-Instruments DSC-Q1000 calibrated at 5°/min to give the melting point as onset value. About 2 mg of sample is heated 5°/min in a loosely closed pan under nitrogen flow.

Thermo gravimetric analysis (TGA) used for estimation of solvent/water content of dried material is performed using a TA-instruments TGA-Q500. 1-10 mg sample is heated 10°/min in an open pan under nitrogen flow.

X-Ray powder diffractograms (XRPD) were measured on a PANalytical X’Pert PRO X-Ray Diffractometer using CuKα radiation. The samples were measured in reflection mode in the 2θ-range 5-40° using an X’celerator detector. Diffraction data are indicated ± 0.1 (°2θ).

The purity of l-(2,4-dimethylphenylsulfanyl)phenyllpiperazine-HBr was determined using a gradient reverse-phase HPLC method applying a Luna Phenyl hexyl column, 150*4.6 mm, 3 μm particle size. Mobile phases consisted of purified water and acetonitrile acidified with trifluoroacetic acid. Flow rate 1.0 mL/min, column oven 40°C, injection volume 50 μL. Peak areas were quantified with UV detection at 226 nM.

Pd was quantitatively analysed using a Varian Vista PRO ICP-OES (inductively coupled plasma atomic emission spectroscopy). Wavelengths: 340.458 nm, 342.122 nm, 360.955 nm.

Example 1. Preparation of l-(2,4-dimethylphenylsulfanyl)phenyllpiperazine-HBr, β-form—see example 4c of WO 2007/144005

49.5 gram of l-[2-(2,4-Dimethylphenylsulfanyl)-phenyl]piperazine colourless oil was dissolved in 500 mL ethyl acetate and added 18.5 mL 48 %-wt HBr (aq). This addition caused formation of a thick slurry which was stirred over night at room temperature. Filtration and drying in vacuum (50 °C) over night produced the product in 29.6 gram as white solid (47 %).

NMR complies with structure. Elemental analysis: 56.86%C, 7.35%N, 6.24%H (Theory for 1:1 salt: 56.99%C, 7.39%N, 6.1 1%H)

Example 2. Characterization of l-(2,4-dimethylphenylsulfanyl)phenyllpiperazine-HBr, β-form—see example 4d of WO 2007/144005
The beta form of the hydrobromide, as prepared in example 1 is crystalline (XRPD) - see Figure 1. It has a melting point of -231 °C. It absorbs about 0.6% of water when exposed to high relative humidity and has a solubility of 1.2 mg/mL in water.

Example 3. Preparation of L-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr, isopropanol solvate

L-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr (25 g) was heated in isopropanol (250 mL) resulting in a thick suspension, additional isopropanol (25 mL) and water (25 mL) were added and the suspension was heated to reflux to give a solution. The solution was blank filtered, cooled on an ice bath and filtered. The resultant product was dried under vacuum at 50 °C.

Example 4. Characterization of L-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr, isopropanol solvate

The isopropanol solvate, e.g. as prepared in example 3 is crystalline (XRPD) - see Figure 2. TGA shows that desolvation starts slowly at 80 °C, and the desolvation is complete at 120 °C. The weight loss was measured to 12.2%. DSC shows an endotherm corresponding to the desolvation. After desolvation, solvent free crystalline salt is formed which melts at 225 °C. This was shown to be the α-form (See WO 2007/144005 for definition of the cc. form) by XPRD on a heated sample. The α-form then partly recrystallizes into a form melting at 230 °C, probably the β-form. The TGA and DSC thermograms are shown in Figure 3.

Example 5. Purification of L-(2,4-dimethylphenylsulfanyl)phenyl piperazine-HBr

The starting material for both processes in this example was L-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr containing compound 1 (4.8 %), compound 2 (0.19 %) and compound 3 (0.18 %).

L-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr (33.1 Kg) in a mixture of isopropanol (412 L) and water (18L) was heated to reflux. The solution was cooled to 20 °C and isopropanol solvate of L-(2,4-dimethylphenylsulfanyl)phenylpiperazine was isolated by filtration and washed with isopropanol (82 L). The wet filter cake was dissolved in a mixture of isopropanol (353 L) and water (17 L) at reflux. The solution was cooled to 20 °C and
isopropanol solvate of l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine was isolated by filtration and washed with isopropanol (74 L). The wet filter cake was dissolved in a mixture of toluene (132 L) and water (13 L) at 80 °C and blank filtered. Water and isopropanol were distilled out of the reactor (55 L), distillation was stopped when distillate reached 102 °C. Water (7 L) was then added and the solution was cooled to 20 °C slowly. l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine-HBr was isolated by filtration, filter cake washed with toluene (77 L) and dried. The amounts of impurities were less than 0.05% of compound 1, less than 0.015% of compound 2 and less than 0.05% of compound 3.

For comparison, the starting material was also purified using the following method. 1 g l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine-HBr was heated to reflux in toluene (10 mL). Water (0.6 mL) was then added and the solution was heated to reflux to give a clear solution. This solution was allowed to cool to approximately 20 °C and then further cooled on an ice bath. l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine-HBr was isolated by filtration and dried in a vacuum oven to give (0.9 g).

The amounts of impurities were 4% of compound 1, 0.15% of compound 2 and 0.14% of compound 3.

Example 6. Purification of l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine-HBr

The l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine, HBr batch used in this example contained compound 1 (0.5 %).

114 kg of the HBr salt in a mixture of isopropanol (1424 L) and water (64 L) was heated to reflux. The solution was cooled and l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine-HBr isopropanol solvate was isolated by filtration. The solvate was dissolved in a mixture of toluene (513 L) and water (50 L) at 80 °C and blank filtered. Water and isopropanol were distilled out, and distillation was stopped when distillate reached 102 °C. Water (27 L) was added and the solution was cooled to 20 °C and l-(2,4-dimethylphenylsulfanyl)phenyl)piperazine-HBr was isolated by filtration. The filter cake was washed with toluene. Analysis of the final product showed less than 0.05% compound 1, and XRDP data confirmed that the β-form was obtained.
Example 7. Manufacture and purification of l-(2,4-dimethylphenylsulfanyl)phenyl 1-piperazine-HBr

Under a nitrogen atmosphere Pddba$_2$ (21 lmg, 0.367 mmol), BINAP (458 mg, 0.736 mmol), sodium tert-butoxide (26.0g), piperazine (27.5g) and toluene (185 mL) were stirred at room temperature for approx 30 minutes. To this mixture was added 1-bromo-2-iodobenzene (12 mL) and 2,4-dimethylthiophenol (12.3 mL) and the reaction mixture was stirred for approximately 60 minutes without heating. The reaction mixture was then heated at reflux for 5 hours, and then water (70 mL) was added followed by stirring for a further 5 minutes before the phases were separated (temperature above 60°C). The toluene phase was washed 2 times with a sodium chloride solution. To the warm toluene phase was added hydrobromic acid 48% (16.2g), seeding crystals (HBr β-form) were added and the solution was cooled. l-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr was isolated by filtration, and the filter cake was washed with toluene (160 mL) and water (190 mL). Analysis of a dried sample of filter cake showed 0.64% compound 1 and 70 ppm Pd. The wet filter cake was heated in isopropanol (345 mL) at reflux temperature and the hot solution was blank filtered. The clear solution was cooled to below room temperature, isopropanol solvate of l-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr was isolated by filtration, washed with isopropanol (40 mL) and dried under vacuum at 40°C. Analysis showed compound 1 (0.05%) and 2 ppm Pd.

l-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate (19.5g), toluene (100 mL) and water (5 mL) were heated to reflux temperature, and water and isopropanol were removed by distillation (23 mL). Toluene was added (23 mL) and the temperature increased to reflux temperature, whereafter water (10 mL) was added and the solution allowed to cool to room temperature. l-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr was isolated by filtration, washed with cooled toluene (70 mL) and dried at 50°C under vacuum. Analysis showed compound 1 under 0.05%, and 1 ppm Pd. XRDP data confirmed that the β-form was obtained.

Example 8. Manufacture and purification of l-(2,4-dimethylphenylsulfanyl)phenyl 1-piperazine-HBr
1000 g of Pddba$_2$, 3600 - 4600 g of BINAP, 270 - 310 kg sodium-ter$t$-butoxide, 360 - 420 kg piperazine and 1300 - 1500 L toluene are charged to a reactor, and the mixture is stirred for at least 30 minutes. 210 - 214 kg l-Br-2-iodobenzen and 99,5 - 100,5 kg 2,4-dimethylthiophenol are added and the resulting mixture is stirred for at least 60 min below 25°C. The temperature is increased to 80 -95°C for at least 13 hours. The mixture is cooled, 1000 - 1200 L water is added and the phases are separated. The toluene phase is washed several times with a total of 1070 - 1140 kg -15% NaCl. 126 - 128 kg HBr 48% and 40 - 46 L water are added and the mixture is heated until completely clear solution is obtained. Crude crystals of the title compound are obtained by cooling. The crystals are isolated by filtering, and the crystals are washed with 1000 - 1200 L toluene and with 400 - 700 L water. The filter cake is dissolved in 3063 - 3112 L isopropanol and the solution obtained is blank filtered. The solution is heated and 2470 - 2964 L is distilled off followed by the addition of 1457 - 1507 L isopropanol. Complete dissolution is obtained by heating, and crystals of the isopropanol solvate are obtained by cooling. The crystals are isolated by filtering followed by wash with 865 - 914 L isopropanol.

Add 200 kg of l-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr isopropanol solvate to 980 - 1020 L toluene and 48 - 52 L water. The crystals are dissolved heating and the solution is blank filtered. The solution is distilled until the vapour temperature is above 102°C, and toluene is added in an amount equal to the volume of the distillate. An additional 48 - 52 L water is added and the liquid is heated until complete dissolution. Crystallisation of l-(2,4-dimethylphenylsulfanyl)phenylpiperazine-HBr β form is obtained by cooling and seeding.
**Claims**

1. A process for the manufacture of l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of achieving a solution by dissolving l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr salt in a solvent comprising more than 65 % (v/v) isopropanol.

2. The process according to claim 1, wherein said pharmaceutically acceptable salt is the HBr salt.

3. The process according to claim 2, wherein said pharmaceutically acceptable salt is the HBr salt, β-form.

4. The process according to any of claims 1-3, wherein said solvent comprises more than 85% (v/v) isopropanol.

5. The process according to any of claims 1-4, which process comprises a subsequent step in which l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, isopropanol solvate is precipitated from said solution.

6. A process for the manufacture of l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of precipitating l-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate from a solvent comprising more than 65 % (v/v) isopropanol.

7. The process according to claim 6, wherein said pharmaceutically acceptable salt is the HBr salt.

8. The process according to claim 7, wherein said pharmaceutically acceptable salt is the HBr salt, β form.
9. The process according to any of claims 6-8, wherein said solvent comprises more than 85% (v/v) isopropanol.

10. A process for the manufacture of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salt thereof comprising the step of dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate, in a non-solvate forming solvent, followed by precipitation of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine-HBr.

11. The process according to claim 10, wherein said non-solvate forming solvent is selected from water, THF, xylene, benzene, methanol, ethanol, acetone and toluene, and mixtures thereof.

12. The process according to claim 11, wherein said non-solvate forming solvent comprises more than 80% toluene.

13. The process according to claim 10, wherein said pharmaceutically acceptable salt is the HBr salt.

14. The process according to claim 13, wherein said pharmaceutically acceptable salt is the HBr salt, β-form.

15. The process according to claim 1 comprising the step of
   a) achieving a solution by dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]-piperazine-HBr in a solvent comprising more than 65 % (v/v) isopropanol;
   b) precipitating 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, isopropanol solvate from said achieved solution;
   c) dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, isopropanol solvate in a non-solvate forming solvent; and
   d) precipitating 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr from the solution obtained in c)
16. The process according to claim 15, wherein said solvent in step a) comprises more than 85% (v/v) isopropanol, and said non-solvate forming solvent in step c) comprises more than 80% (v/v) toluene.

17. The process according to claim 15 or 16, wherein said pharmaceutically acceptable salt is the HBr salt.

18. The process according to claim 17, wherein said pharmaceutically acceptable salt is the HBr salt, β-form.

19. A process for removing or reducing an impurity from solid 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr or from a solution of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, the process comprising the steps of
   a) mixing a solvent comprising more than 65% (v/v) isopropanol with solid 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr or with a solution of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr to achieve a solution of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr; and
   b) cooling said achieved solution to precipitate 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine-HBr isopropanol solvate;
   c) dissolving 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr, isopropanol solvate in a non-solvate forming solvent; and
   d) precipitating 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr from the solution obtained in step c)

20. The process according to claim 19, wherein said impurity is selected from 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-4-(2-piperazin-l-yl-phenyl)-piperazine, or a salt thereof; 1-[2-(5-chloro-2,4-dimethyl-phenylsulfanyl)phenyl]piperazine, or a salt thereof; or palladium.

21. A liquid solution comprising -(2,4-dimethylphenylsulfanyl)phenyl]piperazine in more than 65% (v/v) isopropanol.
22. A compound which is 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine-HBr isopropanol solvate.

23. The compound according to claim 22, which compound has XRPD reflections at approximately 6.44, 8.13, 8.77, 10.41 (°2Θ).

24. The compound according to claim 23 having an XRPD as depicted in figure 2.
XRPD of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, HBr, β-form

Fig. 1
XRPD of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, HBr, isopropanol solvate

Fig. 2
TGA and DSC thermograms of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, HBr, isopropanol solvate

Fig. 3
1-[2-(2,4-dimethyl-phenylsulfonyl)-phenyl]-4-(2-piperazin-1-yl-phenyl)-piperazine

Fig. 4
1-
[2-(5-chloro-2,4-dimethyl-phenylsulfanyl)phenyl]piperazine
1-[2-(2,6-dimethylphenylsulfonyl)phenyl]piperazine

Fig. 6
**INTERNATIONAL SEARCH REPORT**

international application No
PCT/DK2010/050039

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**A. CLASSIFICATION OF SUBJECT MATTER**

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INV. C07D295/096
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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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C07D
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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No</th>
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**D. Further documents are listed in the continuation of Box C**

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**X** See patent family annex

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* Special categories of cited documents

**A** document defining the general state of the art which is not considered to be of particular relevance

**E** earlier document but published on or after the international filing date

**L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

**O** document referring to an oral disclosure, use exhibition or other means

**P** document published prior to the international filing date but later than the priority date claimed

**T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y** document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**S** document member of the same patent family

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**Date of the actual completion of the international search**

28 July 2010

**Date of mailing of the international search report**

11/08/2010

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Name and mailing address of the ISA

European Patent Office, P B 5818 Patentlaa ± 2
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Fax (+31-70) 340-3016

**Authorised officer**

Gavriliu, Daniel a
INTERNATIONAL SEARCH REPORT

Box No II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1) Claims Nos ______ because they relate to subject matter not required to be searched by this Authority namely

2) Claims Nos ______ because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

3) Claims Nos ______ because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1) As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2) As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of additional fees.

3) As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos ______

4) No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos ______

1-20, 22-24

Remark on Protest:

☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20, 22-24

   Further process for preparing
   1-[(2-[(2,4-di methyl phenyl sulfanyl)phenyl]piperazine] using
   as intermediate the corresponding hydrobromide isopropanol solvate

2. claim: 21

   Further compositions containing
   1-[(2-[(2,4-di methyl phenyl sulfanyl)phenyl]piperazine]
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