

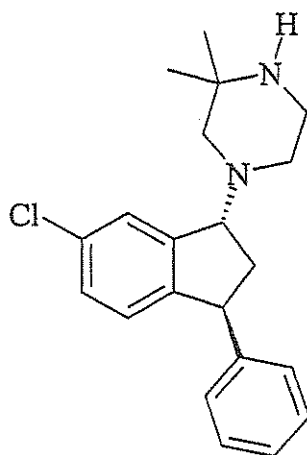
## CRYSTALLINE BASE OF

## TRANS-1-((1R, 3S) - 6- CHLORO-3 - PHENYLINDAN-1-YL) -3 , 3-DIMETHYLPIPERAZINE

The present invention relates to crystalline base of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine, formulations of said base, the use of said base in the preparation of a salt of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine, formulations of such salt and the medical use of said base or salt, in particular for treatment of schizophrenia or other diseases involving psychotic symptoms.

## BACKGROUND OF THE INVENTION

The compound, which is the subject of the present invention (Compound I, *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine) has the general formula (I).



(I)

Compound I and salts thereof, including a fumarate salt and a maleate salt, are described in PCT/DK04/000546 (WO05/016901).

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As described in PCT/DK04/000546 the inventors have found that Compound I displays high affinity for dopamine (DA) D1 receptors, DA D2 receptors and for  $\alpha_1$  adrenoceptors. Furthermore, Compound I was found to be an antagonist at dopamine D1 and D2 receptors, and at serotonin 5-HT<sub>2a</sub> receptors. As further described in PCT/DK04/000546, Compound I is a relatively weak inhibitor of CYP2D6 (i.e. reduced potential for drug to drug interaction) and has a relatively low effect on the QT interval in a rabbit model (i.e. reduced potential for introducing drug-induced QT interval prolongation and appearance of fatal cardiac arrhythmias, torsade de pointes (TdP), in humans). Additionally, the 5-HT<sub>2</sub> antagonistic

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activity of Compound I suggests that Compound I may have a relatively low risk of extrapyramidal side effects.

The properties outlined above, e.g. binding assays (including alfa1, DA D1 or D2 receptors),  
5 efficacy assays (including DA D1 or D2, or serotonin 5-HT<sub>2A</sub> receptors), CYP2D6 inhibition and QT-interval may be determined as described in PCT/DK04/000546, cf. in particular the "Example" section page 19-24 in the application text as filed for PCT/DK04/000546.

Further, the inventors have found that Compound I did not induce dystonia when tested in  
10 pigs sensitized to haloperidol, indicating that Compound I does not possess EPS (extrapyramidal symptoms) response/liability in humans.

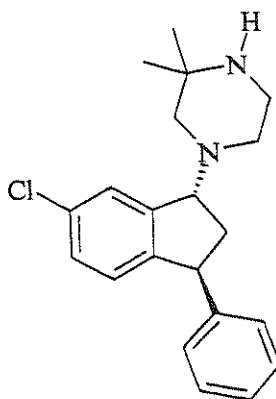
PCT/DK04/000546 describes the following medical uses of Compound I: a disease in the central nervous system, including psychosis, in particular schizophrenia (e.g. positive,  
15 negative, and/ or depressive symptoms) or other diseases involving psychotic symptoms, such as, e.g., Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder as well other psychotic disorders or diseases that present with psychotic symptoms, e.g. mania in bipolar disorder. Also described is the use of Compound I for treatment of anxiety disorders,  
20 affective disorders including depression, sleep disturbances, migraine, neuroleptic-induced parkinsonism, or cocaine abuse, nicotine abuse, alcohol abuse and other abuse disorders.

As indicated in PCT/DK04/000546 a group of compounds structurally related to Compound I, i.e. *trans* isomers of 3-aryl-1-(1-piperaziny)indanes substituted in the 2- and/or 3-position  
25 of the piperazine ring, has been described in EP 638 073; Bøgesø et al. in J. Med. Chem., 1995, 38, 4380-4392 and Klaus P. Bøgesø in "Drug Hunting, the Medicinal Chemistry of 1-Piperazino-3-phenylindans and Related Compounds", 1998, ISBN 87-88085-10-4I. For example, an enantiomeric pure compound corresponding to formula (I) but differing in that it has an *N*-methyl group instead of an *N*-hydrogen on the piperazine has been disclosed in  
30 Bøgesø et al. in J. Med. Chem., 1995, 38, 4380-4392, see table 5, compound (-)-38.

None of the above references apart from PCT/DK04/000546 disclose the specific enantiomeric form above (Compound I) or medical use thereof. The trans isomer in the form of the racemate of Compound I is only indirectly disclosed as an intermediate in the synthesis of compound 38 in Bøgesø et al. in J. Med. Chem., 1995, 38, 4380-4392 while medical use of Compound I or its corresponding racemate is not described. Compound I as an intermediate is disclosed in PCT/DK04/000545 (WO05/016900).

### SUMMARY

In a first aspect, there is provided a crystalline base of the compound of formula (I), Compound I, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine,



(I)

characterised by an X-Ray powder diffractogram obtained using  $\text{CuK}\alpha_1$  radiation ( $\lambda=1.5406$  Å), that exhibits peaks at the following  $2\theta$ -angles: 6.1, 11.1, 12.1, 16.2, 16.8, 18.3, 18.6, 20.0.

In a second aspect, there is provided a pharmaceutical composition comprising the crystalline base as defined above.

In a third aspect, there is provided the use of the crystalline base as defined above, in the preparation of a medicament for the treatment of a disease selected from the group consisting of: diseases involving psychotic symptoms, schizophrenia, anxiety disorders, affective disorders, sleep disturbances, migraine, neuroleptic-induced parkinsonism, and abuse disorders.

In a fourth aspect, there is provided the use of the crystalline base as defined above in the preparation of a medicament for the treatment of a disease selected from the group consisting of: Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder, and mania in bipolar disorder.

In a fifth aspect, there is provided a method for preparing crystalline base of Compound I as defined above, characterised in that said crystalline Compound I is formed in a solvent.

In a sixth aspect, there is provided a method for the manufacturing of Compound I having the formula as defined above, comprising a step wherein Compound I is converted to a crystalline free base of Compound I.

In a seventh aspect, there is provided the free base of the compound of formula (I) [Compound I, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine] as defined above, in a solid form.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1: Shows an X-ray powder diffractogram of a crystalline free base of Compound I (obtained using CuK $\alpha_1$  radiation).

Figure 2: Shows a DSC thermogram of a crystalline free base of Compound

Further details for the figures are revealed in the Examples below.

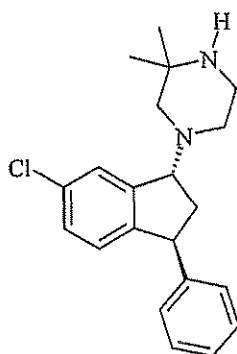
#### **DETAILED DESCRIPTION OF THE INVENTION**

By the methods disclosed in PCT/DK04/000546 Compound I was obtained as an oil. It has now been found that the free base of Compound I can be obtained as a crystalline product which is a favourable solid form of Compound I both for the manufacturing process (e.g. handling and processability properties in general are improved) and for pharmaceutical formulation (e.g. uniform physical and chemical properties of solids are required for formulation purposes).

Furthermore, it has been found that an efficient purification of Compound I may be obtained during the manufacture of Compound I by crystallisation of the base, and thereafter optionally forming a salt of the base. During the synthesis some *cis* diastereoisomer of Compound I (i.e. 1-((1*S*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine) may form as an impurity in the final product. The inventors have found that the final content of *cis*-isomer may be substantially reduced by precipitation of the crystalline base of Compound I. Furthermore, purification as regards other impurities, e.g. detected by HPLC, is significantly enhanced by crystallization of the free base (cf. Example 9 where other impurities than the *cis*-isomer are reduced from 10% to 1%.)

In contrast to this the inventors have found that it is difficult to obtain solid Compound I in the form of a salt suitable for pharmaceutical formulation, e.g. it has been difficult to prepare a salt of Compound I having a well defined stoichiometric ratio between the acid and Compound I, even upon recrystallisation, and/or which are not having organic solvents or water in the crystal.

Thus, the invention relates to crystalline base of Compound I (formula I below).



(I)

In further embodiments, the crystalline base of Compound I is characterised by one or more of:

- (i) an X-Ray powder diffractogram corresponding to that of Figure 1 as measured using  $\text{CuK}_{\alpha 1}$  radiation;
- (ii) an X-Ray powder diffractogram obtained using  $\text{CuK}_{\alpha 1}$  radiation ( $\lambda=1.5406 \text{ \AA}$ ) showing peaks at the following  $2\theta$ -angles: 6.1, 11.1, 12.1, 16.2, 16.8, 18.3, 18.6, 20.0;
- (iii) a DSC thermogram corresponding to that of Figure 2;
- (iv) a DSC trace showing an endotherm with onset about 91-93°C;
- (v) substantially anhydrous and/or solvent free;
- (vi) it has a purity of at least 90%, at least 95% or at least 98% as measured by HPLC (area).

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Described differently, the invention relates to the free base of the compound of formula (I) [Compound I, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine] in a solid form, preferably in a solid form comprising crystalline free base of Compound I, e.g. in a solid form that is at least 80% crystalline, at least 90 % crystalline, at least 95 % crystalline or at least 98 % crystalline. The following embodiments described below for "the crystalline base of Compound I", i.e. method of manufacturing, pharmaceutical compositions, medical

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uses, such as use of the free base of the invention in medicine, and methods of treatments is meant also to apply to the solid free base of the invention as further embodiments of the invention.

- 5 As used herein, the term "solid form" in connection with Compound I refers to any solid form of Compound I exemplified by crystalline form and amorphous solid form as well as mixtures thereof, in contrast, e.g., to Compound I in the form of an oil.

As used herein expressions like "characterized by the X-Ray powder diffractogram shown in Figure (1) as measured using  $\text{CuK}\alpha_1$ " mean the crystalline form of Compound I having an X-ray powder diffractogram substantially similar to Figure 1, i.e. exhibiting an X-ray powder diffraction pattern as exemplified in that Figure and measured under comparable conditions as described herein or by any comparable method using  $\text{CuK}\alpha_1$  radiation, such that margins of analytical variations are taken into consideration.

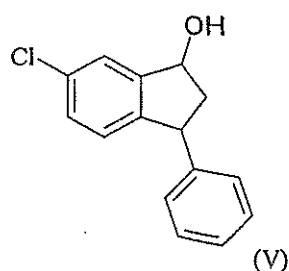
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That the crystalline base is substantially anhydrous and solvent free may e.g. be judged from TGA analysis, e.g. as described in the Examples herein.

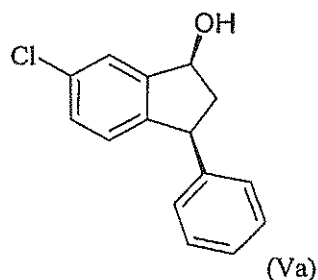
In one embodiment, the crystalline base of the invention is not a solvate, i.e. the crystalline base of the invention does not contain crystal bound solvent molecules.

The compound of formula (I) in racemic form may, e.g., be prepared analogously to the methods outlined in EP 638 073, and in Bøgesø et al. J. Med. Chem., 1995, 38, page 4380-4392 followed by optical resolution of the racemic compound by crystallisation of diastereomeric salts thereby obtaining the enantiomer of formula (I), i.e. Compound I. Alternatively, Compound I may be obtained by a method as described in the international patent application PCT/DK04/000546, i.e. from enantiomeric pure V, i.e. compound Va ((1S,3S)-6-chloro-3-phenylindan-1-ol, see below). Compound V has the following formula (V) with *cis* configuration:

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Compound Va has the following formula (Va), i.e. also with *cis* configuration:



As indicated above during the synthesis some *cis* diastereoisomer of Compound I is formed as an impurity. The *cis* form of Compound I may alternatively or additionally, e.g., be removed by precipitation of a suitable salt of the compound of formula Compound I, e.g. HCl or a salt of an organic acid, such as an organic diacid, e.g. a fumarate salt or a maleate salt of the compound of formula (I), optionally followed by one or more re-crystallisations.

Broadly speaking, the crystalline base of Compound I may be prepared by crystallising the base of Compound I from a solvent, i.e. a suitable single solvent or a suitable mixture of solvents. Accordingly, the term "a solvent" as used herein include both a single solvent or a mixture of different solvents. It is understood that the solvent may comprise water as the case may be, e.g. about 0-10% water. Compound I may be prepared using methods known in the art, such as those described herein.

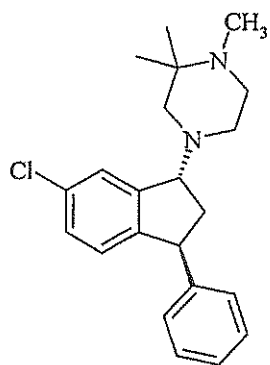
By way of general guidance, Compound I may be mixed with a suitable solvent which may be heated to facilitate the dissolution of Compound I. Preferred temperatures in this regard may range from about 30°C to the boiling point (i.e., the reflux temperature) of the solvent or solvent mixtures. More preferred temperatures may range from about 60°C to the boiling point of the solvent. The resulting mixture of solvent and Compound I may be cooled to initiate and/or continue crystallisation. The mixture is preferably cooled (i.e. including natural cooling to ambient temperature) to a temperature, which ranges from, e.g., about

minus 20°C to about 20°C, e.g. to ambient temperature. The precipitated solids may be isolated from the cooled mixture by for example filtration or centrifugation, and if necessary washed with a suitable solvent such as, but not limited to, the solvent employed for the crystallisation, and dried at ambient pressure or “in vacuo” at ambient or slightly elevated temperature, e.g. under a nitrogen purge. Seed crystals may be added to any crystallisation mixture to promote crystallisation.

Accordingly, the invention in a further aspect relates to a method for preparing crystalline base of Compound I in which method the crystalline base of Compound I is formed in a solvent, e.g. of ethyl acetate or heptane or a mixture hereof. In one embodiment, the crystalline base of Compound is prepared by crystallisation of the base of Compound I from a solvent, e.g. ethyl acetate or heptane or a mixture of these, and separating the solvent from the obtained crystalline base of Compound I.

The invention also relates to a method for the manufacturing of Compound I, characterised in that the base of Compound I is set free and precipitated to obtain the free base of Compound I in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt of Compound I. In one embodiment, the base of Compound I is set free from a crude salt or crude mixture of Compound I. The term crude mixture in this context means that the mixture comprises impurities, e.g. the diastereomer of Compound I and Compound V(a) and unreacted reactants, which it is desired to remove. The crude mixture may be separated directly from the reaction mixture, or the crude reaction mixture may have been subjected to some initial purification. Accordingly, the invention also relates to salts of Compound I obtained by a process comprising the steps of: (i) crystallising the base of Compound I, and (ii) forming a salt from the base, which salt is also termed “a salt of the invention”.

The invention also relates to a method for the manufacturing of the following compound of formula II [trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine; Compound II], or a salt thereof,



(II)

comprising the step of methylation at the secondary amine of Compound I to obtain the free base of Compound II, and alternatively precipitating said compound as a salt, wherein Compound I is produced according to a method of the invention as described herein, i.e. in particular comprising a step in which Compound I is converted to a crystalline free base of Compound I. The synthesis of Compound II from Compound I is described in WO05/016900. The salt of Compound II may, e.g., be a succinate or a malonate salt, e.g. a hydrogen succinate salt or a hydrogen malonate salt as described in WO05/016900. In further embodiments, Compound II or a salt thereof may subsequently be formulated into a pharmaceutical composition.

Thus, in further aspects the invention provides the following embodiments: crystalline base of Compound I obtainable, in particular obtained, by a method as described herein; a salt of Compound I obtainable, in particular obtained, by a method as described herein, e.g. a fumarate or a maleate or a hydrochloric salt of Compound I; a pharmaceutical composition comprising such base of Compound I or a salt of Compound I obtainable or obtained by a method of the invention; and the medical uses as described herein for these Compound I products.

The properties of Compound I indicate that it will be useful as a pharmaceutical. Accordingly, the present invention further relates to a pharmaceutical composition of the crystalline base of Compound I or a salt of the invention, together with, e.g., at least one pharmaceutically acceptable carrier, filler or diluent.

The invention also relates to the medical use of such crystalline base or salt of the invention and compositions, e.g. for the treatment of a disease in the central nervous system, including

psychosis, in particular schizophrenia or other diseases involving psychotic symptoms, such as, *e.g.*, Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder as well other psychotic disorders or diseases that present with psychotic symptoms, *e.g.* mania in bipolar disorder.

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The present invention also relates to use of the crystalline base of Compound I or a salt of the invention, for treatment of a disease selected from the group consisting of anxiety disorders, affective disorders including depression, sleep disturbances, migraine, neuroleptic-induced parkinsonism, cocaine abuse, nicotine abuse, alcohol abuse and other abuse disorders.

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In a preferred embodiment, the present invention relates to a method of treating Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder or mania in bipolar disorder, comprising administering a therapeutically effective amount of the crystalline base of Compound I or a salt of the invention.

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A further embodiment of the invention relates to a method of treating positive symptoms of schizophrenia comprising administering a therapeutically effective amount of the crystalline base of Compound I or a salt of the invention. Another embodiment of the invention relates to a method of treating negative symptoms of schizophrenia comprising administering a therapeutically effective amount of the crystalline base of Compound I or a salt of the invention. A further embodiment of the invention relates to a method of treating depressive symptoms of schizophrenia comprising administering a therapeutically effective amount of the crystalline base of Compound I or a salt of the invention. A further aspect of the invention relates to a method of treating mania and/or maintenance of bipolar disorder comprising administering a therapeutically effective amount of the crystalline base of Compound I or a salt of the invention.

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In the present context, in particular for the pharmaceutical uses, it is understood that when specifying the enantiomer form as done in formula (I) for Compound I, then the compound is relatively stereochemically pure, preferably the enantiomeric excess is of at least 60%, at

least 70%, and more preferably at least 80% (80% enantiomeric excess means that the ratio of I to its enantiomer is 90:10 in the mixture in question) at least 90%, at least 96%, or preferably at least 98%.

- 5 In a preferred embodiment, the diastereomeric excess of Compound I is at least 90% (90% diastereomeric excess means the ratio of Compound I to *cis*-1-((1*S*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine is 95:5), at least 95%, at least 97%, or at least 98%.
- 10 A further aspect of the invention relates to a method of treatment as described herein, wherein the patient treated with the crystalline base of Compound I or a salt of the invention is also treated with at least one other medicament. A particular relevant embodiment in this connection, is treatment with other medicaments being metabolised by CYP2D6 or at least having such potential. In a suitable embodiment, the other medicament is an antipsychotic.
- 15 Accordingly, one embodiment relates to the use of the crystalline base or a salt of the invention or pharmaceutical composition of the invention for treating a patient suffering from schizophrenia or other psychoses who is also treated with other medicament(s), e.g. where this other medicament is an antipsychotic.
- 20 In another embodiment, the invention relates to the use of the crystalline base of Compound I, a salt of the invention, or pharmaceutical composition of the invention for treating a patient suffering from schizophrenia or other psychoses who is a substance abuser, e.g. of alcohol or narcotics.
- 25 The crystalline base of the invention, or the salt of the invention, or pharmaceutical composition of the invention may be administered in any suitable way e.g. orally, buccal, sublingual or parenterally, and the compound or may be presented in any suitable form for such administration, e.g. orally in the form of tablets, capsules, powders, syrups, solutions or dispersions, or parenterally in the form of dispersions or solutions for injection. In one
- 30 embodiment, the crystalline base of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredient with ordinary adjuvants, fillers and diluents and subsequently compressing the mixture in a convenient tableting machine. Examples of adjuvants, fillers and diluents comprise microcrystalline cellulose, corn starch,  
5 potato starch, lactose, mannitol, sorbitol talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

In particular, the tablet formulations according to the invention may be prepared by direct  
10 compression of Compound I in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of Compound I, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

Solutions for injections may be prepared by solving the active ingredient and possible  
15 additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, solubilising agents, etc. Alternatively the crystalline free base may be dissolved in a digestible or non-digestible oil, mixtures hereof or similar, to prepare  
20 a intramuscular depot formulation capable of releasing the active ingredient over a prolong period of time.

The daily dose of the compound of formula (I) above, calculated as the free base, is suitably between 1.0 and 160 mg/day, more suitable between 1 and 100 mg, e.g. preferably between  
25 2 and 55 mg.

As indicated above the invention in particular relates to:

- crystalline base of Compound I
- a salt of the invention, i.e. a salt of compound I prepared from the crystalline base of  
30 Compound I ;
- a pharmaceutical compositions as described herein comprising the crystalline base Compound I or a salt of the invention;

- a medical use as described herein for Compound I;

wherein Compound I is having an enantiomeric excess of at least 60% (60% enantiomeric excess means that the ratio of Compound I to its enantiomer is 80:20 in the mixture in question), at least 70%, at least 80%, at least 85%, at least 90%, at least 96%, preferably at least 98%.

One embodiment relates to crystalline base of Compound I, or a salt of the invention or pharmaceutical composition of the invention and the uses as described herein, wherein Compound I is having a diastereomeric excess of at least 10% (10% diastereomeric excess means that the ratio of Compound I to the *cis*-(1*S*,3*S*) diastereoisomer is 55:45 in the mixture in question), at least 25%, at least 50%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, preferably at least 98%.

The term "treatment" in connection with a disease as used herein also includes prevention as the case may be. The term "disease" as used herein also includes a disorder as the case may be.

The invention will be illustrated in the following non-limiting examples.

## EXAMPLES

### ANALYTICAL METHODS

The enantiomeric excess of Compound (Va) in Example 1 is determined by chiral HPLC using a CHIRALCEL® OD column, 0.46cm ID X 25 cm L, 10µm at 40°C. n-Hexan/ethanol 95:5 (vol/vol) is used as mobile phase at a flow rate of 1.0 ml/min, detection is performed using a UV detector at 220nm.

The enantiomeric excess of Compound (I) may be determined by fused silica capillary electrophoresis (CE) using the following conditions: Capillar: 50µm ID X 48.5 cm L, run buffer: 1.25mM β cyclo dextrin in 25mM sodium dihydrogen phosphate, pH 1.5, voltage: 16kV, temperature: 22°C, injection: 40mbar for 4 seconds, detection: column diode array detection 195nm, sample concentration: 500µg/ml. In this system, Compound I has a

retention time of approximately 10 min, and the other enantiomer has a retention time of approximately 11 min.

<sup>1</sup>H NMR spectra is recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) is used as solvents, and tetramethylsilane (TMS) is used as internal reference standard.

The purity of Compound I is determined by HPLC (e.g. also the cis/trans ratio) using a Luna C18(2) 150\*4.6 mm (3µm) column at 40°C. The mobile phase is phosphate buffer pH7.4/acetonitril 40/60, run time 60min, and after 32 min a gradient of acetonitril/water 90/10 is applied. Detection is performed using a UV detector at 220nm.

The cis/trans ratio of Compound I and key intermediates may also be determined using <sup>1</sup>H NMR as described in, e.g., Bøgesø *et al.*, *J. Med. Chem.* **1995**, 38, 4380-4392 (page 4388, right column).. Generally, a content of approximately 1% of the undesired isomer can be detected by NMR. 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 were measured on a PANalytical X'Pert PRO X-Ray Diffractometer using CuK<sub>α1</sub> radiation. The samples were measured in reflection mode in the 2θ-range 5-40° using an X'celerator detector.

Optical rotation is measured on a polarimeter, Perkin Elmer model 241.

## SYNTHESIS

### Example 1 Synthesis of (1S,3S)-6-chloro-3-phenylindan-1-ol (Va) by use of chiral chromatography

Racemic *cis*-6-chloro-3-phenylindan-1-ol (V) (prepared as described in PCT/DK04/000546, i.e. adapting the method described in Bøgesø *et al.* *J. Med. Chem.* **1995**, 38, 4380-4392 using ethanol as solvent, and performing the reaction at approximately 0 °C) (492 grams) is

resolved by preparative chromatography, using a CHIRALPAK® AD column, 10cm ID X 50cm L, 10µm at 40 °C. Methanol is used as mobile phase at a flow rate of 190 ml/min, detection is performed using a UV detector at 287nm. The racemic alcohol (V) is injected as a 50,000 ppm solution in methanol; 90 ml is injected with intervals of 28 min. All the  
5 fractions, which contain the title compound with more than 98% enantiomeric excess, are combined and evaporated to dryness using a rotary evaporator, followed by drying in vacuo at 40°C. Yield 220 grams as a solid. Elemental analysis and NMR conform to the structure, the enantiomeric excess is higher than 98% according to chiral HPLC,  $[\alpha]_D^{20} +44.5^\circ$  (c=1.0, methanol).

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### Example 2    Synthesis of (1S,3S)-3,5-dichloro-1-phenylindan

*Cis*-(1S,3S)-6-chloro-3-phenylindan-1-ol (Va) (204 grams) obtained as described in Example 1 is dissolved in THF (1500ml) and cooled to -5°C. Thionyl chloride (119 grams) is added dropwise as a solution in THF (500 ml) over a period of 1 h. The mixture is stirred  
15 at room temperature over night. Ice (100 g) is added to the reaction mixture. When the ice has melted the water phase (A) and the organic phase (B) are separated, and the organic phase B is washed twice with aqueous saturated sodium bicarbonate (200 ml). The aqueous sodium bicarbonate phases are combined with water phase A, adjusted to pH 9 with sodium hydroxide (28%), and used to wash the organic phase B once again. The resulting aqueous  
20 phase (C) and the organic phase B are separated, and the aqueous phase C is extracted with ethyl acetate. The ethyl acetate phase is combined with the organic phase B, dried with magnesium sulphate, and evaporated to dryness using a rotary evaporator, giving the title compound as an oil. Yield 240 grams, which is used directly in the example 5a. *Cis/trans* ratio 77:23 according to NMR.

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### Example 3    Synthesis of 3,3-dimethylpiperazin-2-one

Potassium carbonate (390 grams) and ethylene diamine (1001 grams) are stirred with toluene (1.50 l). A solution of ethyl 2-bromoisobutyrate (500 grams) in toluene (750 ml) is added. The suspension is heated to reflux over night, and filtered. The filter cake is washed  
30 with toluene (500 ml). The combined filtrates (volume 4.0 l) are heated on a water bath and distilled at 0.3 atm. using a Claisen apparatus; first 1200 ml distillate is collected at 35 °C (the temperature in the mixture is 75 °C). More toluene is added (600 ml), and another 1200

ml distillate is collected at 76 °C (the temperature in the mixture is 80 °C). Toluene (750 ml) is added again, and 1100 ml of distillate is collected at 66 °C (temperature in the mixture 71 °C). The mixture is stirred on an ice bath and inoculated, whereby the product precipitates. The product is isolated by filtration, washed with toluene, and dried over night in a vacuum oven at 50 °C. Yield 171 g (52%) of 3,3-dimethylpiperazin-2-one. NMR consistent with structure.

#### Example 4 Synthesis of 2,2-dimethylpiperazine

A mixture of 3,3-dimethylpiperazin-2-one (8.28 kg, 64.6 mol, large scale preparation analogous to the preparation described in to Example 3) and tetrahydrofuran (THF) (60 kg) is heated to 50-60 °C giving a slightly unclear solution. THF (50 kg) is stirred under nitrogen, and LiAlH<sub>4</sub> (250 g, in a soluble plastic bag) is added, which gives a slow evolution of gas. After gas evolution has ceased, more LiAlH<sub>4</sub> is added (a total of 3.0 kg, 79.1 mol, is used), and the temperature rises from 22 °C to 50 °C because of an exotherm. The solution of 3,3-dimethylpiperazin-2-one is added slowly over 2 hours at 41-59 °C. The suspension is stirred for another hour at 59 °C (jacket temperature 60 °C). The mixture is cooled, and water (3 l) is added over two hours, keeping the temperature below 25 °C (it is necessary to cool with a jacket temperature of 0 °C). Then aqueous sodium hydroxide (15%, 3.50 kg) is added over 20 minutes at 23 °C, cooling necessary. More water (9 l) is added over half an hour (cooling necessary), and the mixture is stirred over night under nitrogen. Filter agent Celite (4 kg) is added, and the mixture is filtered. The filter cake is washed with THF (40 kg). The combined filtrates are concentrated in the reactor until the temperature in the reactor is 70 °C (distillation temperature 66 °C) at 800 mbar. The remanence (12.8 kg) is further concentrated on a rotary evaporator to approximately 10 l. Finally, the mixture is fractionally distilled at atmospheric pressure, and the product is collected at 163-4 °C. Yield 5.3 kg (72%). NMR complies with the structure.

#### Example 5a Synthesis of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium (Compound I) hydrogen maleate salt

*Cis*-(1*S*,3*S*)-3,5-dichloro-1-phenylindan (240 g) is dissolved in butan-2-one (1800 ml). Potassium carbonate (272 g) and 2,2-dimethyl piperazine (prepared as described in Example 4) (113 g) are added and the mixture is heated at reflux temperature for 40 h. To the reaction

mixture is added diethyl ether (2 l) and hydrochloric acid (1M, 6 l). The phases are separated, and pH in the water phase is lowered from 8 to 1 with concentrated hydrochloric acid. The water phase is used to wash the organic phase once again in order to ensure, that all product is in the water phase. Sodium hydroxide (28%) is added to the water phase until  
5 pH is 10, and the water phase is extracted twice with diethyl ether (2 l). The diethyl ether extracts are combined, dried with sodium sulphate, and evaporated to dryness using a rotary evaporator. Yield 251 grams of free base of Compound I as an oil. *Cis/trans* ratio, 18: 82 according to NMR. The crude oil (ca. 20 grams) was further purified by flash chromatography on silicagel (eluent: ethyl acetate/ethanol/triethylamine 90:5:5) followed by  
10 evaporation to dryness on a rotary evaporator. Yield 12 grams of free base of Compound I as an oil (*cis/trans* ratio, 10:90 according to NMR).

The oil is dissolved in ethanol (100 ml), and to this solution is added a solution of maleic acid in ethanol to pH 3. The resulting mixture is stirred at room temperature for 16 hours, and the formed precipitate is collected by filtration. The volume of ethanol is reduced and  
15 another batch of precipitate is collected. Yield 3.5 gram solid, i.e. Compound I hydrogen maleate salt (no *cis* isomer is detected according to NMR) of the title compound. Enantiomeric excess according to CE is >99%. Melting point 175-178 °C. NMR complies with the structure.

20 **Example 5b Synthesis of trans-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium (Compound I) hydrogen chloride salt**

*Cis-(1S,3S)*-3,5-dichloro-1-phenylindan (large scale preparation analogous to the preparation described in example 2) (50.9 kg) is dissolved in MIBK (248 kg). Potassium carbonate (56.8 kg) and 2,2-dimethyl piperazine (29.6 kg) are added and the mixture is heated to 100°C  
25 temperature for 8 hour. The reaction mixture is cooled to room temperature before insoluble inorganic material is removed by filtration. The filtrate is subsequent washed with water (520 l), the phases are separated and pH of the organic phase is adjusted to a value between 3 – 6 by slow addition of hydrogen chloride (15,4 kg 37% aqueous solution), during the addition the product separates. The product is filtered on a nutsche, and the filter cake is  
30 washed by MIBK (100 kg) and cyclohexane (80kg). The product is dried at 50°C and 0.05bar for 12 hours.

Yield: 40 kg. Compound I (no *cis*-isomer is detected according to NMR-analysis).

Enantiomeric excess according to CE is > 99%. NMR spectrum complies with the structure.

**Example 6a Synthesis of the free base of Compound I from a hydrogen maleate salt**

5 A mixture of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium hydrogen maleate (9.9 grams), concentrated aqueous ammonia (100 ml), brine (150 ml) and ethyl acetate (250 ml) is stirred at room temperature for 30 min. The phases are separated, and the aqueous phase is extracted with ethyl acetate once more. The combined organic phases are washed with brine, dried over magnesium sulphate, filtered and evaporated to  
10 dryness in vacuo. Yield 7.5 grams of Compound I as an oil, which may solidify on standing. NMR complies with the structure.

**Example 6b Synthesis of the free base of Compound I from a hydrogen chloride salt**

The free base of Compound I was prepared as described in example 6a by the use of *trans*-1-  
15 ((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium hydrogen chloride as substitute for *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium hydrogen maleate.

Yield of Compound I was 9.0 grams starting from 10.2 grams of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium hydrochloride.

20

**Example 7a Preparation of crystalline base of Compound I from 6a**

Compound I (9.0 grams obtained as described in Example 6a) was dissolved in ethyl acetate (30 ml), and heptane (75 ml) was subsequently added to the solution. The solution was left with stirring for 4-16 hours. In some cases crystallisation was observed, and the crystalline  
25 material was collected by filtration. In other cases, crystallisation was not observed, and a part of the solvent was removed by distillation. The distillation was stopped when distillation temperature changed from the boiling point of ethyl acetate to the boiling point of heptane. The remaining solution was left to cool to room temperature at ambient temperature and prior to filtration on a water/ice bath. The crystallisation could be initiated  
30 by scratching with a glass spatula or by seeding. The crystalline Compound I was isolated by filtration. Yield 6,8 grams (74 %). NMR complies with the structure. Melting point: 92.4°C (DSC onset temperature), enantiomeric excess according to CE is > 99%.

**Example 7b Preparation of crystalline base of Compound I from 6b**

Prepared as described in example 7a starting with 9.0 grams of crude base. Yield 6,8 grams. Melting point 92.3 °C (DSC onset temperature) and enantiomeric excess determined by CE is > 99%.

**Example 8 Characterisation of the crystalline base of Compound I**

The crystalline base of Compound I obtained by a method as described in Example 7a and 7b had the X-ray powder diffractogram (XRPD) shown in Figure 1 and was characterized by the following reflections (peaks) in the X-Ray powder diffractogram as measured using CuK $\alpha_1$  radiation at 2-theta angles: 6.1, 11.1, 12.1, 16.2, 16.8, 18.3, 18.6, 20.0.

The crystalline base further had a DSC thermogram corresponding to that of Figure 2 and a DSC trace showing an endotherm with onset about 91-93°C.

The crystalline based obtained was anhydrous and solvent free as judged from TGA analysis.

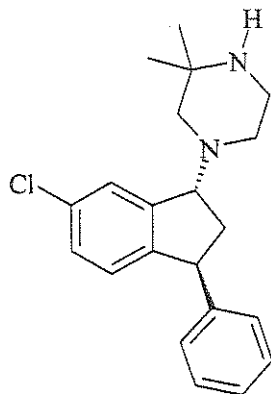
**Example 9 Preparation of crystalline base of Compound I from crude Compound I from Example 5a**

Compound I (2.0 grams of crude oil obtained as described in Example 5a, purity as determined by HPLC: 73% area, *cis/trans* ratio of 17/73) was dissolved in ethyl acetate (5 ml), and heptane (10 ml) was subsequently added to the solution. A part of the solvent was removed by distillation, and the remaining solution was added a spatula of crystalline Compound I (obtained from 7a or 7b). The resulting mixture was left at ambient temperature for 16 hours. The crystalline Compound I was isolated by filtration.

NMR complies with the structure. HPLC Purity (area%): 98%, Content of the *cis*-isomer: 1%. Enantiomeric excess according to CE is > 99%.

## CLAIMS

1. A crystalline base of the compound of formula (I), Compound I, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine,



(I)

characterised by an X-Ray powder diffractogram obtained using CuK $_{\alpha 1}$  radiation ( $\lambda=1.5406$  Å), that exhibits peaks at the following 2 $\theta$ -angles: 6.1, 11.1, 12.1, 16.2, 16.8, 18.3, 18.6, 20.0.

2. The crystalline base according to claim 1, characterized by having a DSC thermogram corresponding to that of Figure 2.
3. The crystalline base according to claim 1 or 2, characterized by having a DSC trace showing an endotherm with onset about 91-93°C.
4. The crystalline base according to any one of claims 1-3, which is anhydrous.
5. The crystalline base according to claim 4, which is solvent free.

6. The crystalline base according to any of claims 1-5, having a purity of at least 98% as measured by HPLC (area).
- 5 7. The crystalline base according to any one of claims 1-6, wherein the enantiomeric excess of Compound I is at least 98%.
8. The crystalline base according to any one of claims 1-7 for use in the medicine.
- 10 9. A pharmaceutical composition comprising the crystalline base according to any one of claims 1-7.
- 15 10. Use of the crystalline base according to any of claims 1-7, in the preparation of a medicament for the treatment of a disease selected from the group consisting of : diseases involving psychotic symptoms, schizophrenia, anxiety disorders, affective disorders, sleep disturbances, migraine, neuroleptic-induced parkinsonism, and abuse disorders.

11. Use according to claim 10, wherein said affective disorder is depression.
12. Use according to claim 10, wherein said abuse disorder is cocaine abuse, nicotine abuse or alcohol abuse.

5

13. Use according to claim 10 in the preparation of a medicament for the treatment of schizophrenia or other psychotic disorders.

10

14. Use according to claim 13 in the preparation of a medicament for the treatment of one or more of: positives symptoms, negative symptoms and depressive symptoms of schizophrenia.

15. Use of the crystalline base according to any one of claims 1-7 in the preparation of a medicament for the treatment of a disease selected from the group consisting of : Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder, and mania in bipolar disorder.

5

16. The use according to any one of claims 10-15 , wherein the treated patient is also under treatment with at least one other medicament.

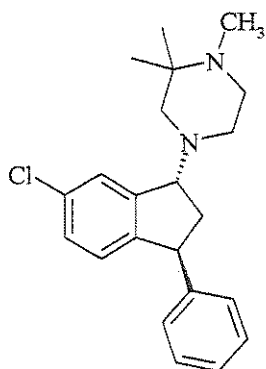
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17. A method for preparing crystalline base of Compound I as defined in claim 1, characterised in that said crystalline Compound I is formed in a solvent.

18. The method according to claim 17, wherein said solvent is ethyl acetate or heptane or a mixture thereof.

15

19. The method according to claim 17 or 18, comprising crystallising by precipitation the base of Compound I from the solvent, and separating the solvent from the obtained crystalline base of Compound I.
- 5 20. The method according to any one of claims 17-19, wherein said crystalline base of Compound I is as defined in any of claims 2-7.
21. Crystalline base of Compound I obtainable by the method according to any one of claims 17-19.
- 10 22. A method for the manufacturing of Compound I having the formula defined in claim 1, comprising a step wherein Compound I is converted to a crystalline free base of Compound I.
- 15 23. The method according to claim 22, further comprising converting the crystalline base of Compound I into a salt of Compound I.
24. The method according to claim 23, characterised in that the base of Compound I is set free and precipitated in crystalline form, and then converted to a salt of Compound I.
- 20 25. The method according to claim 24, wherein the precipitated base of Compound I in crystalline form is re-crystallised one or more times before being converted to a salt of Compound I.
- 25 26. The method of claim 24 or 25, wherein said base of Compound I is set free from a crude salt or crude mixture of Compound I.
27. The method according to any one of claims 22-26, wherein said crystalline base of Compound I is obtained according to the method of claim 17 or 18.
- 30 28. The method according to any one of claims 22-27, further comprising making a pharmaceutical composition comprising Compound I or a salt thereof.
- 35 29. The method according to any one of claims 22-27, further comprising the step of methylation at the secondary amine of Compound I to obtain the free base of the compound of formula II;



(II)

30. The method according to claim 29, wherein the compound of formula II is precipitated as a salt.

5

31. The method according to claim 30, wherein said salt is a succinate or a malonate salt of Compound II.

10

32. The method according to any one of claims 29-31, further comprising making a pharmaceutical composition comprising Compound II or a salt thereof.

33. The free base of the compound of formula (I) [Compound I, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine] as defined in claim 1, in a solid form.

15

34. The free base according to claim 33, wherein said solid comprises crystalline base of Compound I.