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(54) Titre : SEL DE SUCCINATE ET DE MALONATE DE TRANS-4-((1R,3S)-6-CHLORO-3-PHENYLINDAN-1-YL)-1,2,2-TRIMETHYLPIPERAZINE ET SON UTILISATION EN TANT QUE MEDICAMENT

(54) Title: SUCCINATE AND MALONATE SALT OF TRANS-4-(IR,3S)-6-CHLORO-3-PHENYLINDAN-1-YL)-1,2,2-TRIMETHYLPIPERAZINE AND THE USE AS A MEDICAMENT

(57) Abrégé/Abstract:
4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine hydrogen succinate or hydrogen malonate, pharmaceutical compositions containing these salts and the medical use thereof, including for the treatment of schizophrenia and other psychotic disorders. Also described are methods for the preparation of 4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine and medical uses thereof.

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ABSTRACT OF THE DISCLOSURE

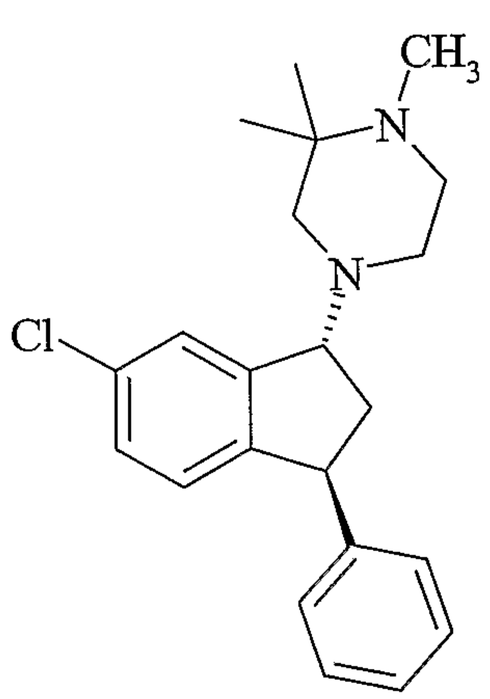
4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine hydrogen succinate or hydrogen malonate, pharmaceutical compositions containing these salts and the medical use thereof, including for the treatment of schizophrenia and other psychotic disorders. Also described are methods for the preparation of 4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine and medical uses thereof.

SUCCINATE AND MALONATE SALT OF TRANS-4-((*1R,3S*)-6-CHLORO-3-PHENYLINDAN-1-YL)-1,2,2-TRIMETHYLPIPERAZINE AND THE USE AS A MEDICAMENT

The present invention relates to 4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine, in particular the hydrogen succinate and the hydrogen malonate salts thereof, methods for the preparation of 4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazin and the salts thereof, pharmaceutical compositions containing these salts and the medical use thereof, including treatment of schizophrenia or other diseases involving psychotic symptoms.

BACKGROUND OF THE INVENTION

The compound, which is the subject of the present invention [4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine] has the general formula (I):



(I)

and is described generically in EP 638 073.

EP 638 073 covers a group of *trans* isomers of 3-aryl-1-(1-piperazinyl)indanes substituted in the 2- and/or 3-position of the piperazine ring. The compounds are described as having high affinity for dopamine D_1 and D_2 receptors and the 5-HT_2 receptor and are suggested to be useful for treatment of several diseases in the central nervous system, including schizophrenia. EP 638 073 does not disclose the specific enantiomeric form of the above compound of formula (I), only *trans* isomers in the form of racemates are described.

The enantiomer of formula (I) above has been described by Bøgesø et al. in J. Med. Chem., 1995, 38, page 4380-4392, in the form of the fumarate salt, see table 5, compound (-)-38. This publication concludes that the (-)-enantiomers of compound 38 is a potent D_1/D_2 antagonists showing some D_1 selectivity in vitro while in vivo it is equipotent as D_1 and D_2 antagonist. The compound is also described as a potent 5-HT_2 antagonist and as having high affinity for α_1 adrenoceptors. It is also mentioned that the compound does not induce catalepsy in rats.

The corresponding racemate as well as the fumarate salt of the above compound of formula (I) is also described by Klaus P. Bøgesø in "Drug Hunting, the Medicinal Chemistry of 1-Piperazino-3-phenylindans and Related Compounds", 1998, *ISBN 87-88085-10-4* (cf. *e.g.* compound 69 in table 3, p47 and in table 9A, p101).

Thus, the compound of formula (I) is a mixed D_1/D_2 antagonists, a 5-HT_2 antagonist and it has also affinity for α_1 adrenoceptors. In the following is outlined the possible linkage between different diseases and the dopamine D_1 and D_2 receptors, the 5-HT_2 receptors and the α_1 adrenoceptors, respectively.

The aetiology of schizophrenia is not known, but the dopamine hypothesis of schizophrenia (Carlsson, Am. J. *Psychiatry* **1978,** *135*, 164-173), formulated in the early 1960s, has provided a theoretical framework for understanding the biological mechanisms underlying this disorder. In its simplest form, the dopamine hypothesis states that schizophrenia is associated with a hyperdopaminergic state, a notion which is supported by the fact that all antipsychotic drugs on the market today exert some dopamine D_2 receptor antagonism (Seeman *Science and Medicine* **1995**, *2*, 28-37). However, whereas it is generally accepted that antagonism of dopamine D_2 receptors in the limbic regions of the brain plays a key role in the treatment of positive symptoms of schizophrenia, the blockade of D_2 receptors in striatal regions of the brain causes extrapyramidal symptoms (EPS). As described in EP 638 073 a profile of mixed dopamine D_1/D_2 receptor inhibition has been observed with some so-called "atypical" antipsychotic compounds, in particular with clozapine, used in treatment of schizophrenic patients.

Central α_1 antagonistic actions has also been suggested to contribute in improving antipsychotic properties (Millan *et al*, *JPET*, **2000**, *292*, 38-53).

Further, selective D_1 antagonists have been connected to treatment of sleep disorders and alcohol abuse (D.N.Eder, *Current Opinion in Investigational Drugs*, **2002** *3(2)*:284-288).

Dopamine may also play an important role in the etiology of affective disorders (P. Willner, *Brain. Res. Rev.* **1983**, *6*, 211-224, 225-236 and 237-246; J. Med. Chem., 1985, 28, 1817-1828).

In EP 638 073 is described how compounds having affinity for 5-HT_2 receptors, in particular 5-HT_2 receptors antagonists, have been suggested for treatment of different diseases, such as schizophrenia including the negative symptoms in schizophrenic patients, depression, anxiety, sleep disturbance, migraine attacks and neuroleptic-induced parkinsonism. 5-HT_2 receptor antagonism has also been suggested to reduce the incidence of extrapyramidal side effects induced by classical neuroleptics (Balsara et al. *Psychopharmacology* **1979**, *62*, 67-69).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Shows an X-ray powder diffractogram of the crystalline form alpha of the hydrogen succinate salt of Compound I (obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å))

Figure 2: Shows an X-ray powder diffractogram of the crystalline form beta of the hydrogen succinate salt of Compound I (obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å))

Figure 3: Shows an X-ray powder diffractogram of the hydrogen malonate salt of Compound I (obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å)).

DETAILED DESCRIPTION OF THE INVENTION

Salts of the invention

It has now been found that the aqueous solubility of the hydrogen succinate salt and of the hydrogen malonate salt of the compound of formula (I) is considerably larger than the aqueous solubility of the corresponding fumarate salt.

As used herein the term "hydrogen succinate" salt of the compound of formula (I) refers to the 1:1 salt of the compound of formula (I) and succinic acid.

As used herein the term "hydrogen malonate" salt of the compound of formula (I) refers to the 1:1 salt of the compound of formula (I) and malonic acid.

The hydrogen succinate salt was found to be more stable than the fumarate salt and than the hydrogen malonate salt and to be non-hygroscopic.

The hydrogen malonate salt of Compound I was found to have a stability similar to the fumarate salt when exposed to light and more stable when exposed to 60°C/80% relative humidity (RH), but less stable than the fumarate salt at 90°C. 90°C is however a very stressed condition, and does not necessarily relate to stability at normal conditions. The malonate absorbs gradually up to 1% of water when the relative humidity is raised to 95%, but with no hysterhesis. It is therefore considered as non-hygroscopic, but with good wetting properties, which indicates favourable dissolution properties.

The invention also covers crystalline salts of the invention, including, *e.g.* anhydrates hydrates, and solvates of the salts of the invention. By the term anhydrate is meant the salts of the invention containing no crystal bound water. By hydrates is meant the salts of the invention containing crystal bound water molecules. Hydrates are usually prepared by formation of the salt in presence of some water. By solvates is meant the salts of the invention containing crystal bound solvent molecules. Solvates are usually prepared by formation of the succinate salt in presence of the solvent. The solvent molecules in a single

solvate may be of one or two or more different solvents. A solvate may comprise water as one of two or more organic solvents or be only a non-water solvent.

One embodiment of the invention relates to the 1:1 salt of *trans*-4-((*1R,3S*)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine, i.e. of the compound of formula (I), and succinic acid in the form of a crystalline anhydrate.

The inventors have discovered 2 crystalline forms of the hydrogen succinate salt of Compound I (named alpha and beta).

Thus, one embodiment relates to a crystalline form of the hydrogen succinate salt of Compound I, which form is named alpha and characterized by one or more of:

(i) an X-Ray powder diffractogram as shown in Figure 1;

(ii) an X-Ray powder diffractogram pattern as illustrated in Table I obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) which shows main peaks at the 2θ-angles given;

(iii) having a DSC (Differential Scanning Calorimetry) trace which shows an endotherm with onset 139-141°C.

A further embodiment relates to a crystalline form of the hydrogen succinate salt of Compound I, which form is named beta and characterized by one or more of:

(i) an X-Ray powder diffractogram as shown in Figure 2;

(ii) an X-Ray powder diffractogram pattern as illustrated in Table I obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) which shows main peaks at the 2θ-angles given;

(iii) having a DSC trace which shows an endotherm with onset 135-138°C.

A further embodiment relates to a crystalline hydrogen malonate salt of Compound I characterized by one or more of:

(i) an X-Ray powder diffractogram as shown in Figure 3;

(ii) an X-Ray powder diffractogram pattern as illustrated in Table I obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) which shows main peaks at the 2θ-angles given.

Table I. Characteristic X-Ray powder diffractograms obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) of the crystal forms alpha and beta of the hydrogen succinate salt of Compound I, and of the crystalline hydrogen malonate salt of Compound I. Fig; cf. also Fig.

1, Fig. 2 and Fig. 3 providing a representative XRPD pattern of polymorphic form alpha and beta of the hydrogen succinate salt and of the malonate salt of Compound I, respectively.

Salt	**Characteristic reflexes - main peaks (expressed in degree of diffraction angle 2θ)**
Succinate, alpha	9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; 29.65
Succinate, beta	8.1; 10.5; 11.4; 14.0; 14.6; 15.6; 15.7; 16.2; 17.2; 17.5; 17.9; 18.4; 18.9; 19.2; 20.3; 21.0; 21.9; 22.5; 23.3; 26.3
Malonatet	8.3; 10.6; 11.5; 12.8; 14.2; 14.5; 14.7; 15.8; 16.5; 17.4; 17.6; 18.0; 18.6; 19.2; 21.2; 22.0; 22.9; 23.7; 24.7; 28.8

As used herein by expressions like "crystalline form of a specific salt of Compound I characterized by the X-Ray powder diffractogram shown in Figure (1)" is meant the crystalline form of salt of Compound I in question having an X-ray powder diffractogram substantially similar to Figure (1), i.e. exhibiting an X-ray powder diffraction pattern substantially as exemplified in that Figure and measured under comparable conditions as described herein or by any comparable method.

Generally, all data herein are understood to be approximate and subject to normal measurement error depending *e.g.* on the apparatus used and other parameters influencing peak positions and peak intensities.

The invention also relates to a solid hydrogen succinate salt of Compound I which solid salt consist mainly of the alpha form as compared to the total amount of the salt. In one embodiment, the term “mainly” means that the solid hydrogen succinate salt of Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline alpha form as compared to the total hydrogen succinate salt of Compound I present.

The invention also relates to a solid hydrogen succinate salt of Compound I which solid salt consist mainly of the beta form as compared to the total amount of the salt. In one embodiment, the term “mainly” means that the solid hydrogen succinate salt of Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline beta form as compared to the total hydrogen succinate salt of Compound I present.

The invention also relates to any mixtures of the crystalline forms of the hydrogen succinate salt of the invention, *e.g.* a mixture of the alpha and beta crystalline form of the hydrogen succinate salt of Compound I.

Preparation of the salts of the invention

The succinate salt according to the invention may be obtained by treatment of the free base of a compound of formula (I) with succinic acid in an inert solvent followed by precipitation, isolation and optionally recrystallization. If desired, the crystalline salt may thereafter be subjected to micronisation by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Precipitation of the succinate salt of the invention is preferably carried out by dissolving the free base of the compound of formula (I) in a suitable solvent, such as acetone or toluene, and thereafter mixing this solution to a suspension or solution of succinic acid in a suitable solvent, such as acetone, aqueous acetone or toluene. In one embodiment the solvent is a mixture of acetone and water, e.g. a mixture consisting essentially of acetone and about 2% to 10%, preferably about 5% water, based on the weight of the mixture. The resulting suspension may be heated or solvent may be added until all succinic acid has dissolved. The succinate salt of the compound of the invention is precipitated, preferably upon cooling of the solution. The succinate salt of the invention may optionally be recrystallised one or more times and isolated by filtration, washed, *e.g.* with acetone, and dried.

The invention also relates to a method for the preparation of the crystalline beta form of the hydrogen succinate salt of Compound I, which method comprises leaving an aqueous solution of hydrogen succinate salt of Compound I for slow evaporation of the solvent at ambient conditions.

The malonate salt may be obtained using analogous procedures. Accordingly, the malonate salt according to the invention may be obtained by treatment of the free base of a compound of formula (I) with malonic acid in an inert solvent followed by precipitation, isolation and optionally recrystallisation. If desired, the crystalline salt may thereafter be subjected to micronisation by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Precipitation of malonate salt of the invention is preferably carried out by dissolving the free base of the compound of formula (I) in a suitable solvent, *e.g.* 2-propanol, and thereafter mixing this solution to a suspension or solution of malonic acid in a suitable solvent, *e.g.* 2-

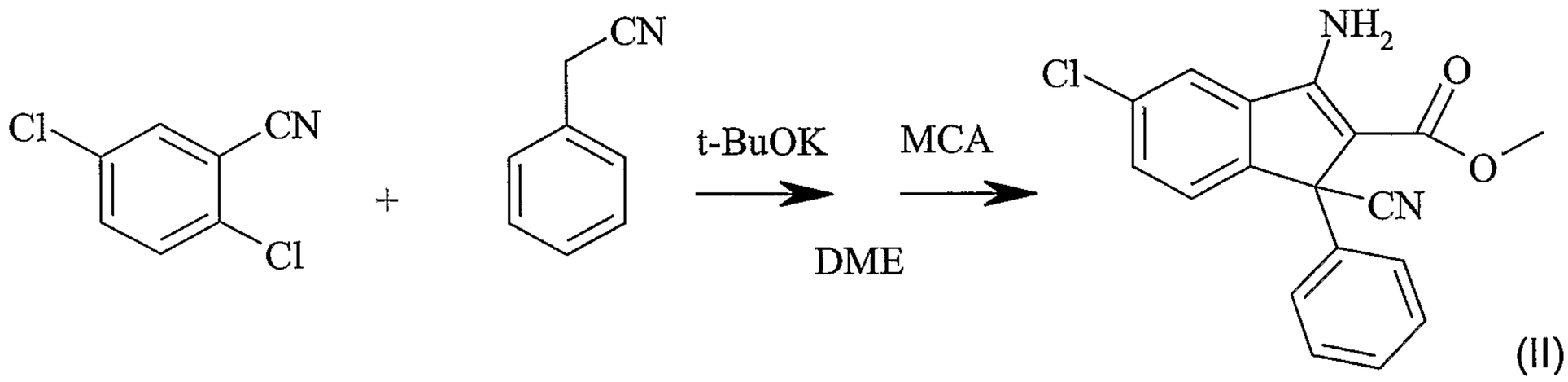
propanol. The suspension may be heated until all malonic acid has dissolved. The malonate salt of the compound of the invention precipitated, preferably upon cooling of the solution. The malonate salt of the invention may optionally be recrystallised one or more times and isolated by filtration, washed, *e.g.* in 2-propanol, and dried.

Preparation of the compound of formula (I)

The compound of formula (I) in racemic form may be prepared as described in EP 638 073, and in Bøgesø et al. J. Med. Chem., 1995, 38, page 4380-4392, it is described how optical resolution of the racemic compound may be accomplished by crystallisation of diastereomeric salts thereby obtaining the enantiomer of formula (I).

The present inventors have now developed an improved route of synthesis in which the enantiomer of formula (I) is obtained via a synthetic sequence starting from enantiomeric pure V, i.e. compound Va'((*1S,3S*)-6-chloro-3-phenylindan-1-ol, see below). Thus, in this process, the intermediate of formula V is resolved, *e.g.* by chiral chromatography or enzymatically, to obtain the enantiomer of formula Va. This new route of synthesis to obtain the compound of formula (I) is much more efficient than the above mentioned crystallisation of diastereomeric salts of the final product I. In particular the yield of the resolution is substantially higher in this new method (45% relative to the amount of racemic starting material, *i.e.* maximum theoretical yield is 50%) as compared to the yield (22% relative to the amount of racemic starting material, *i.e.* maximum theoretical yield is 50%) for the resolution of the final product I by crystallisation of diastereomeric salts. Another advantage of this invention is that the enantiomeric purity of (I) is higher (higher than 99%ee) when synthesised according to the invention as compared to the synthesis using crystallisation of diastereomeric salts (95.4%ee). Furthermore, the resolution of an intermediate instead of the final product gives a much more efficient synthesis, as only the right enantiomer is used in the subsequent steps, giving *e.g.* higher volume yields and less consumption of reagents.

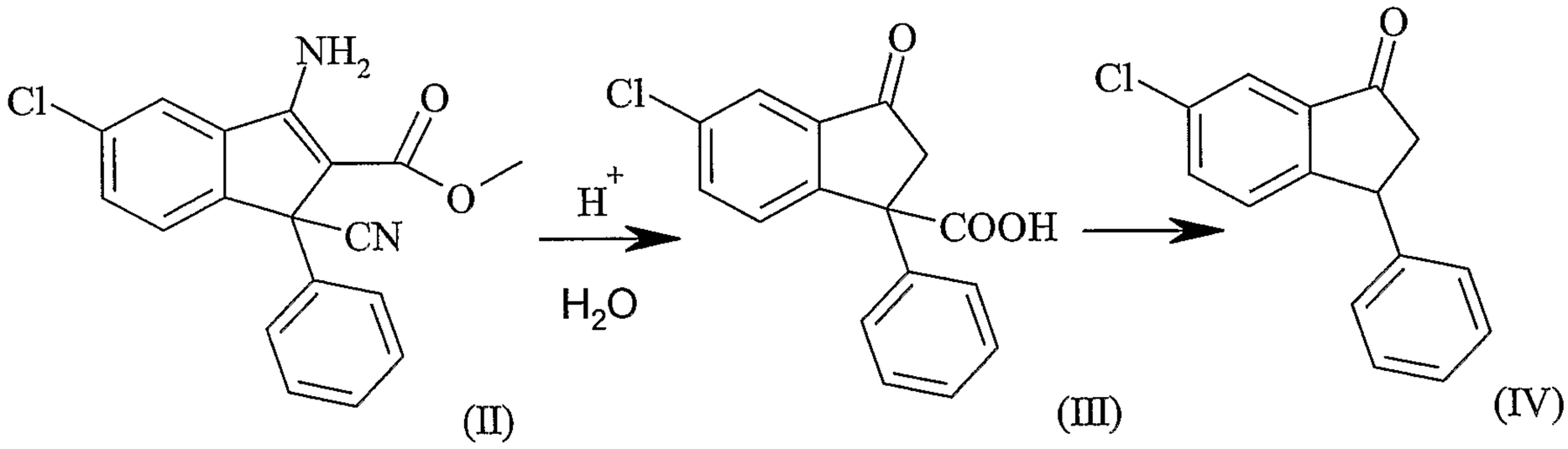
Accordingly, the enantiomer of formula (I) may be obtained by a process involving the following steps:



(II)

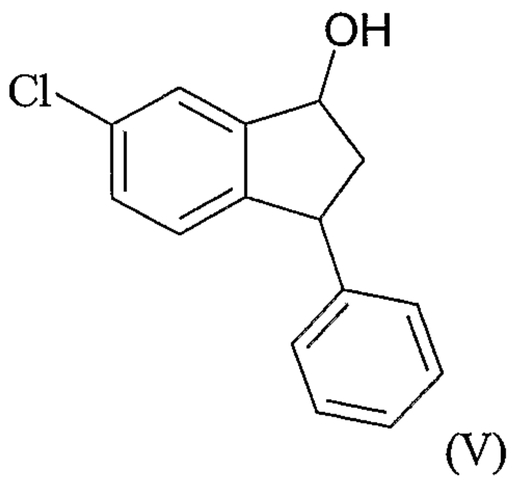
Benzyl cyanide is reacted with 2,5-dichlorobenzonitril in the presence of a base, suitably potassium tert-butoxide (t-BuOK) in a suitable solvent such as dimethyl ether (DME), further reaction with methyl chloro acetate (MCA) leads to spontaneous ring closure and one pot formation of the compound of formula (II).

The compound of formula (II) is then subjected to acidic hydrolysis to form a compound of formula (III), suitably by heating in a mixture of acetic acid, sulphuric acid and water, and thereafter decarboxylation by heating the compound of formula (III) in a suitable solvent, such as toluene with triethyl amine or N-methyl pyrrolidone, to form a compound of formula (IV).



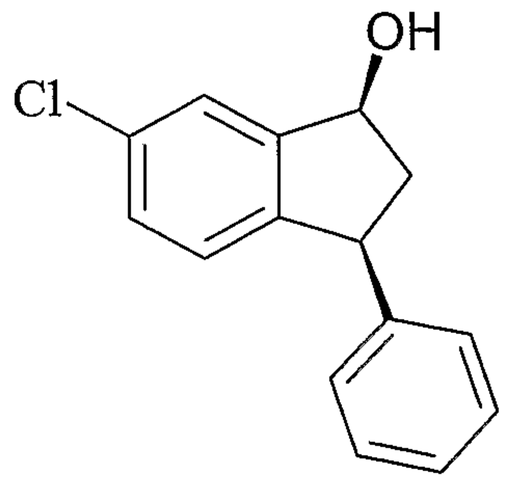
(II) (III) (IV)

The compound of formula (IV) is then reduced, suitably with $NaBH_4$ in a solvent such as an alcohol, *e.g.* ethanol or *iso*-propanol, and preferably at a temperature in the range of –30° to +30°C, *e.g.* below 30 °C, below 20 °C, below 10 °C, or preferably below 5 °C, to form a compound of formula (V) with *cis* configuration:



(V)

The compound of formula (V) is resolved to achieve the desired enantiomer (formula Va), i.e. also with *cis* configuration ((*1S,3S*)-6-chloro-3-phenylindan-1-ol):



(Va)

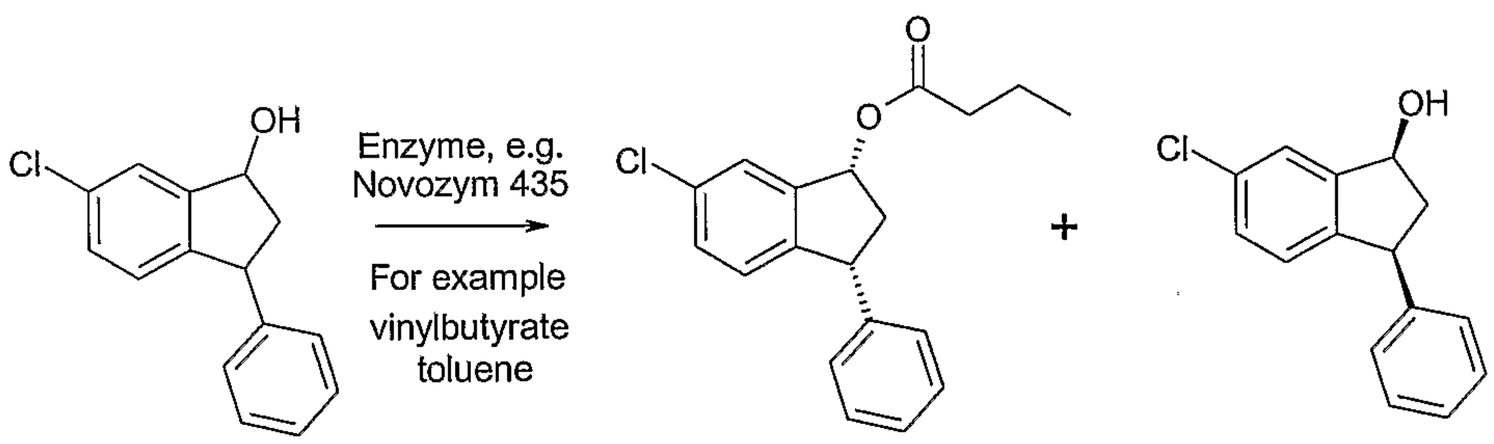
The resolution of (V) to (Va) may, *e.g.*, be performed using chiral chromatography, preferably liquid chromatography, suitably on a chiral column of silicagel coated with a chiral polymer, *e.g.* a modified amylose, preferably amylose tris-(3,5-dimethylphenylcarbamate) coated on silicagel. A suitable solvent is used for the chiral liquid chromatography, such as, *e.g.* an alcohol, a nitrile, an ether, or an alkane, or mixtures thereof, suitably ethanol, methanol, iso-propanol, acetonitrile, or methyl tert-butyl ether or mixtures thereof, preferably methanol or acetonitrile. The chiral liquid chromatography can be scaled up using suitable technologies, *e.g.* simulated moving bead technology (SMB).

Alternatively, the compound of formula (V) is resolved to achieve Compound Va by enzymatic resolution. It has been found that enantiomerically pure Compound Va, or acylated derivatives thereof, may be prepared by enzymatic enantioselective acylation of the hydroxyl group in racemic Compound V to obtain Compound Va or an acylated derivative thereof with high optical purity. Alternatively, enantiomerically pure Compound Va may also be obtained by a process comprising converting racemic Compound V to a

corresponding ester in the hydroxyl position followed by an enzymatic enantioselective deacylation. Use of enzymatic enantioselective deacylation has been reported for other compounds.

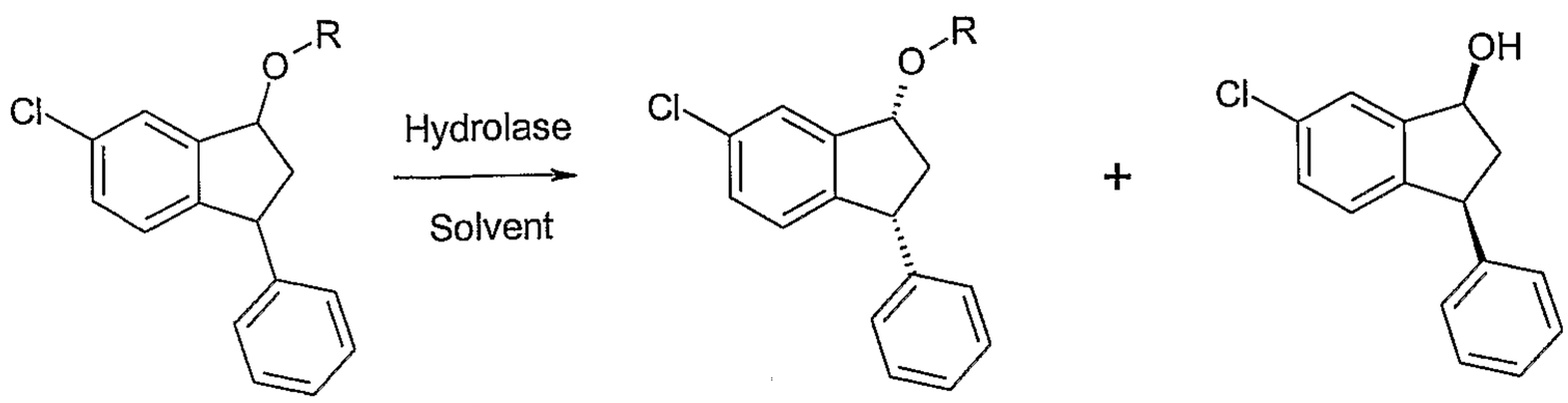
Accordingly, The resolution of Compound V to Compound Va may be performed by selective enzymatic acylation. Selective enzymatic acylation means that the enzymatic acylation is preferentially effective for conversion of one of the *cis*- enantiomers of the compound of formula Compound V leaving the other *cis*-enantiomer of Compound V as unconverted in the reaction mixture.

Alternatively, The resolution of Compound V to Compound Va may be performed by selective enzymatic deacylation. Selective enzymatic deacylation means that the enzymatic deacylation is preferentially effective for conversion of one of the esters of compound of formula (V), leaving the other *cis*-enantiomer of esters of a compound of formula (V) as unconverted in the reaction mixture.



V Va

Suitable esters (Vb) of the compound of formula (V) are ester such as acetate, propionate, butyrate, valerate, hexanoate, benzoate, laurate, isobutyrate, 2-methylbutyrate, 3-methylbutyrate, pivalate, 2-methylvalerate, 3-methylvalerate, 4-methylvalerate



Vb (1R,3R) Va

wherein R, *e.g.*, is acetate, propionate, butyrate, valerate, hexanoate, benzoate, laurate, isobutyrate, 2-methylbutyrate, 3-methylbutyrate, pivalate, 2-methylvalerate, 3-methylvalerate, 4-methylvalerate.

Thus, one embodiment relates to a process for the preparation of the (S, S)- or (R, R)-enantiomer of the compound of formula V (i.e. with *cis* configuration) comprising:

a) subjecting a racemic Compound V to enantioselective enzymatic acylation using an acylating agent, or

b) subjecting a racemic Compound Vb to entantioselective enzymatic deacylation to form a mixture of deacylated Compound Va.

Enantioselective enzymatic *acylation* means that the enzymatic acylation is preferentially effective for conversion of one of the enantiomers of a compound of formula (V) preferentially leaving the other enantiomer of the compound of formula (V) unconverted in the reaction mixture. Enantioselective enzymatic *deacylation* means that the enzymatic deacylation is preferentially effective for conversion of one of the enantiomers of a compound of formula (Vb), preferentially leaving the other enantiomer of the compound of formula (Vb) unconverted in the reaction mixture.

The mixtures obtained by the enzymatic resolution may not be entirely pure, *e.g.* they may contain a smaller amount of the other enantiomer in addition to a larger amount of the desired enantiomer (Va). The composition mixture obtained after acylation or deacylation according to the invention depend, i.a., on the specific hydrolase used and the conditions under which the reaction is carried out. Characteristic of the enzymatic acylation/deacylation according to the invention is that a considerably larger portion of one enantiomer is converted than of the other. The enantioselective *acylation* according to the invention thus results in a mixture containing preferentially the compound of formula (Vb) in the (R, R -form and the compound of formula (Va) in the (S, S)-form, or it may result in a mixture containing preferentially the compound of formula (Vb) in the (S, S)-form and the compound of formula (Va) in the (R, R)-form. Likewise, the enantioselective enzymatic *deacylation* may result in a mixture containing preferentially the compound of formula (Vb) in the (S, S)-form and the compound of formula (V) in the (R, R)-form, or it may result in a

mixture containing preferentially the compound of formula (Va) in the (R, R)-form and the compound of formula (Va) in the (S, S)-form. The optical purity of the Va obtained by the optical resolution method of the present invention is usually at least 90% ee., preferably at least 95% ee., more preferably at least 97% ee and most preferably at least 98% ee. However, lower values for the optical purity are acceptable.

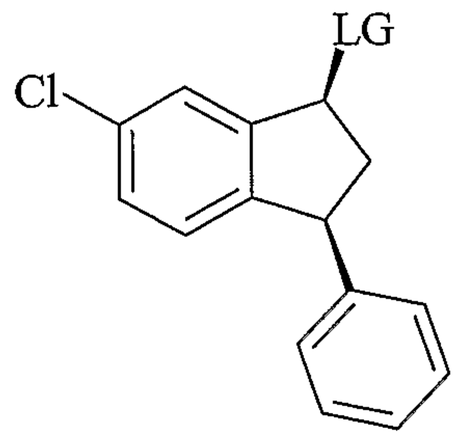
According to the invention, enantioselective enzymatic *acylation* is carried out under conditions substantially suppressing hydrolysis. Hydrolysis, which is the reverse reaction of the acylation reaction, takes place if water is present in the reaction system. Thus, enantioselective enzymatic acylation is preferably carried out in a water-free organic solvent or almost anhydrous organic solvent (enzymes normally require the presence of some water to be active). Suitable solvents include hydrocarbons such as hexane, heptane, benzene and toluene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxane, tert-butyl methyl ether and dimethoxyethane; ketones such as acetone, diethyl ketone, butanon, and methyl ethyl ketone; esters such as methyl acetate, ethyl acetate, ethyl butyrate, vinyl butyrate and ethyl benzoate; halogenated hydrocarbons such as methylene chloride, chloroform and 1,1,1-trichloroethane; secondary and tertiary alcohols, such as tert-butanol; nitrogen-containing solvents such as dimethylformamide, acetoamide, formamide, acetonitrile and propionitrile; and aprotic polar solvents such as dimethylsulfoxide, N-methylpyrrolidone and hexamethylphosphorous triamide. Preferred organic solvents for enzymatic acylation are organic solvents such as toluene, hexane, heptane, dioxane and tetrahydrofuran (THF).

Suitable irreversible *acyldonors* are, *e.g.*, acyldonors such as vinyl-esters, 2-propenyl-esters or 2,2,2-trihalid-ethyl-esters.

Enantioselective enzymatic *deacylation* is preferably carried out in water or a mixture of water and an organic solvent, suitable in presence of a buffer. Suitable organic solvents, *e.g.*, are solvents miscible with water such as alcohols, acetonitrile, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), 1,4-dioxane, DME and diglyme.

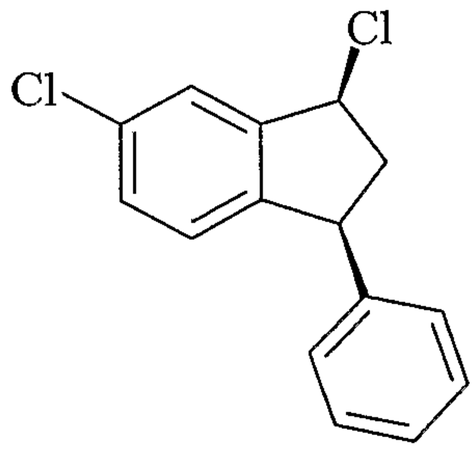
It has been found that enzymatic acylation according to the invention may be carried out using Novozym 435 (Candida Antarctica lipase B, from Novozymes A/S, Fluka Cat.-No. 73940). In general, the enzymatic acylation or deacylation according to the invention is preferably carried out using a lipase, an esterase, an acylase or a protease. The enzymes useful according to the invention are such enzymes capable of performing R-selective acylation or S-selective acylation of the hydroxy group in the racemic compound of formula (V) or such enzymes which are capable of performing R-selective deacylation or S-selective deacylation of the acyl group in the racemic compound of formula (Vb). In particular immobilized forms of the enzyme, including Cross-Linked Enzyme Crystal (CLEC) are useful according to the invention. A preferred embodiment relates to use of a lipase for carrying out the enzymatic resolution of Compound V. The most preferred lipase is Candida antarctica lipase (Fluka Cat.-No. 62299); Pseudomonas cepacia lipase (Fluka Cat.-No. 62309); Novozym CALB L (Candida antarctica lipase B) (Novozymes A/S); Novozym 435 (Candida antarctica lipase B) (Novozymes A/S); or Lipozyme TL IM (Thermomyces lanuginosus lipase) (Novozymes A/S), preferably in immobilized form.

The alcohol group of the *cis*-alcohol of formula (Va) is converted to a suitable leaving group, such as, *e.g.*, a halogen, *e.g.* Cl or Br, preferably Cl, or a sulphonate, *e.g.* mesylate or tosylate, suitably by reaction with an agent, such as thionyl chloride, mesyl chloride or tosyl chloride, in an inert solvent, *e.g.* an ether, suitably tetrahydrofuran. The resulting compound has formula (VI), where LG is the leaving group:



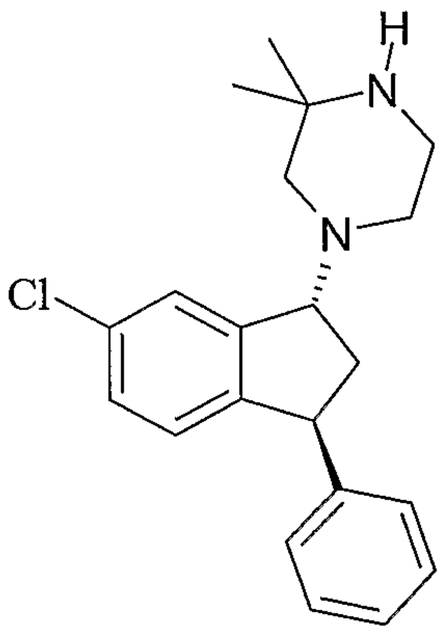
(VI)

In a preferred embodiment, LG is Cl, i.e. the cis-chloride of formula (VIa):



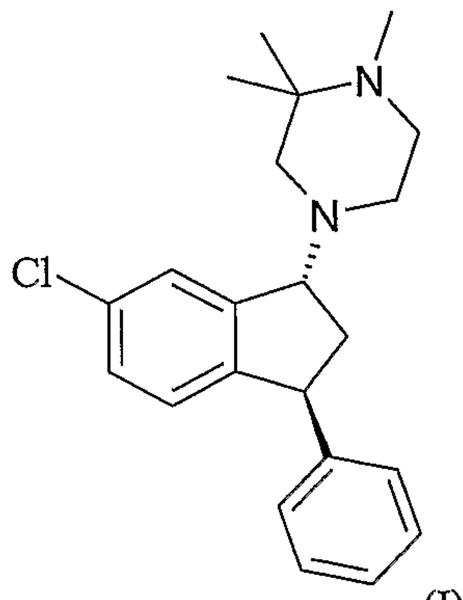
(VIa)

Compound VI, *e.g.* with LG as chloro, is then reacted with 2,2-dimethylpiperazine in a suitable solvent, *e.g.* a ketone such as, *e.g.*, methyl isobutyl ketone or methyl ethyl ketone, preferably methyl isobutyl ketone in presence of a base, such as *e.g.*, potassium carbonate. The resulting compound of formula (VII):



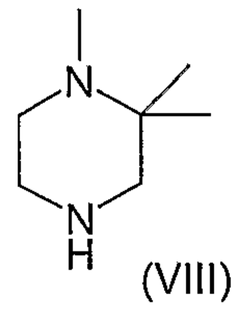
(VII)

is methylated at the secondary amine functionality (suitably by reductive amination using suitable agents, such as, *e.g.*, formaldehyde, paraformaldehyde, trioxane, or diethoxy methane (DEM)) to obtain the free base of a compound of formula (I).

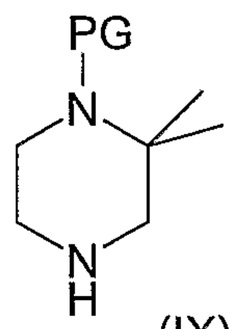


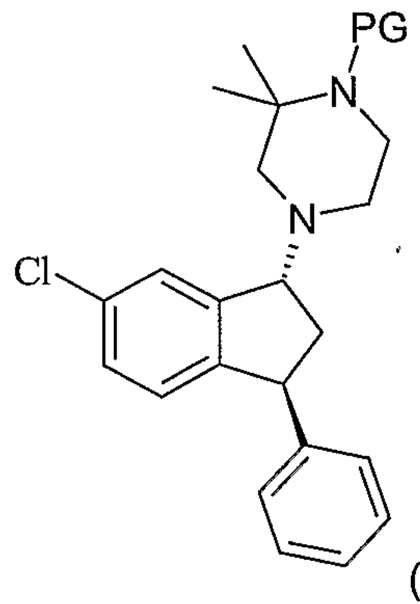
(I)

Alternatively, the methyl group may be introduced directly by use of 1,2,2-trimethyl piperazine (Formula VIII below) instead of 2,2-dimethyl piperazine when reacting with Compound VI, e.g. where LG is Cl, thereby shortening the synthesis by one step.


(VIII)

Furthermore, the piperazine part of the molecule may be introduced by reacting Compound VI with a compound of formula (IX) below, where PG is a protecting group such as, but not restricted to, *e.g.* phenylmethoxycarbonyl (often called Cbz or Z), tert-butyloxycarbonyl (often called BOC), ethoxycarbonyl, or benzyl, thereby obtaining the compound of formula (X) below.


(IX)


(X)

After deprotection of the product to (VII), methylation as discussed above gives the final product, Compound I. Alternatively, the protecting group such as *e.g.* ethoxycarbonyl may be converted directly to a methyl group using a suitable reducing agent, *e.g.* lithium aluminium hydride.

During the synthesis some *cis* diastereoisomer of Compound I (*i.e.* 4-((1*S*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine) is formed as an impurity in the final product. This impurity is due mainly to the formation of some of the *trans* form of (VI) (*e.g.* (1*S*,3*R*)-3,5-dichloro-1-phenylindan when LG is Cl) in the step where Compound VI is formed. Therefore, the impurity can be minimized by crystallisation of the desired *cis* form of Compound VI, from the mixture of *trans* and *cis* (VI); in the case where LG is Cl in Compound VI this can be done by stirring the mixture with a suitable solvent, *e.g.* an alkane, such as heptane, whereby the desired *cis* form of VI precipitates and the undesired *trans* form of Compound VI goes into solution. The desired *cis* form of Compound VI (*e.g.* when LG is Cl) is isolated by filtration, washed with the solvent in question and dried.

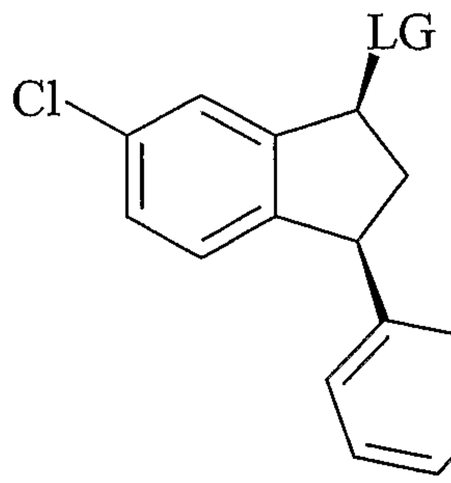
If the *cis* form of Compound VI is present in the batch of (VI) used in the synthesis of Compound VII, this will give raise to the formation of the *trans* form of Compound VII (*i.e.* 4-((1*S*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine) as an impurity in (VII); this gives a second option of avoiding the *cis* form of Compound I in the final product: It has been found that the *cis* form of Compound VII can be removed by precipitation of a suitable salt of the compound of formula Compound VII, *e.g.* a salt of an organic acid, such as an organic diacid, suitably the hydrogen fumarate salt or the hydrogen maleate salt of the compound of formula (VII), optionally followed by one more re-crystallisations.

Furthermore, it has been found that impurities in the form of *cis* diastereoisomer in (I) (*i.e.* 4-((1*S*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine) may effectively be removed by precipitation of a suitable salt of the compound of formula (I), *e.g.* a salt of an organic acid, such as an organic diacid, suitably a fumarate salt, *e.g.* the hydrogen fumarate salt of the compound of formula (I) optionally followed by one or more re-crystallisations.

The invention in further aspects also relates to the intermediates as described herein for the synthesis of the compound of formula (I), i.e. in particular the intermediates (Va), VI, e.g. VIa, and VII, or salts of Compound VII. In this context is understood that when specifying the stereoisomeric form, then the stereoisomer is the main constituent of the compound. In particular, when specifying the enantiomeric form, then the compound has an enantiomeric excess of the enantiomer in question.

Accordingly, one embodiment of the invention relates to the compound of formula (Va), preferably having an enantiomeric excess of at least 60% (60% enantiomeric excess means that the ratio of Va 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%. Furthermore, the diastereomeric excess of the compound is preferably at least 70% (70% diastereomeric excess means, that the ratio of Compound Va to (1R,3S)-6-chloro-3-phenylindan-1-ol is 85:15 in the mixture in question), at least 80%, at least 85%, at least 90%, or at least 95%. One embodiment relates to substantially pure Compound Va.

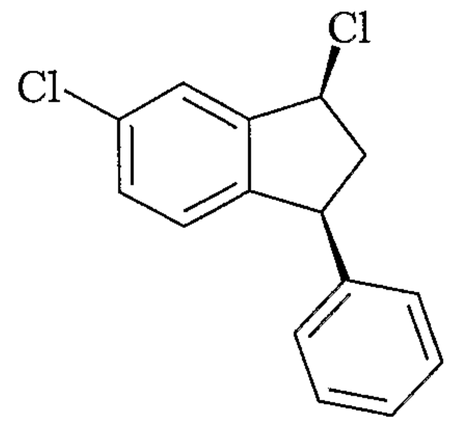
A further embodiment of the invention relates to the compound of formula (VI), preferably having an enantiomeric excess of at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 96%, preferably at least 98%,



(VI),

wherein LG is a potential leaving group, preferably selected from the group consisting of a halogen, *e.g.* chloride, or a sulphonate. One embodiment relates to the diastereomeric purity of Compound VI; *i.e.* the compound having a diasteromeric excess of preferably at least 10% (10% diastereomeric excess means that the ratio of Compound VI to the cis diastereoisomer (*e.g.* (1S,3R)-3,5-dichloro-1-phenylindan when LG=Cl) is 55:45 in the mixture in question), at least 25% or at least 50%. One embodiment, relates to substantially pure Compound VI.

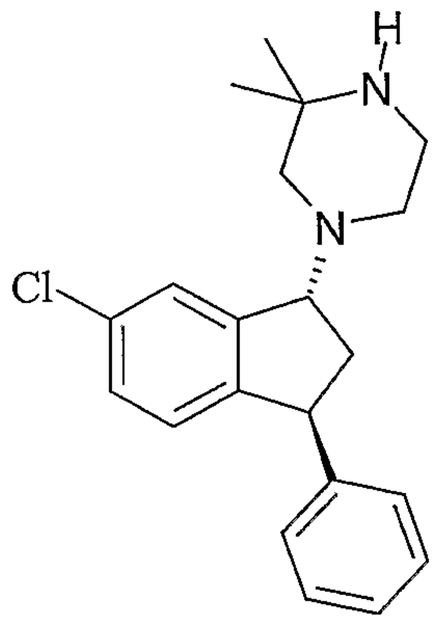
Accordingly, the invention also relates to a compound having the following formula (VIa),



(VIa)

preferably having an enantiomeric excess of at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 96%, preferably at least 98%. One embodiment relates to the diastereomeric purity of the compound, *i.e.* the compound having a diastereomeric excess of, preferably at least 10% (10% diastereomeric excess means that the ratio of the compound to the cis diastereoisomer, (1S,3R)-3,5-dichloro-1-phenylindan, is 55:45 in the mixture in question), at least 25% or at least 50%. One embodiment relates to substantially pure Compound VI where LG is Cl.

The invention also relates to a compound (VII) having the structure:



(VII),

preferably having an enantiomeric excess of at least 60% (60% enantiomeric excess means that the ratio of VII 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%, or a salt thereof, such as, *e.g.*, a fumarate salt, *e.g.* hydrogen fumarate, or a maleate salt, *e.g.* hydrogen maleate. One embodiment relates to the diastereomeric purity of the Compound VII, *i.e.* the compound having a diastereomeric excess of preferably at least 10% (10% diastereomeric excess means that the ratio of Compound VII to the cis-(*1S,3S*) 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%, at least 98%. One embodiment relates to substantially pure Compound VII or a salt thereof.

A further aspect relates to Compound I or a salt thereof, in particular the fumarate, malonate, or succinate salt, obtainable, in particular obtained, by a method of the invention as described herein.

A further aspect relates to Compound VII or a salt thereof, e.g. the fumarate salt, obtainable, in particular obtained, by a method of the invention as described herein.

Pharmaceutical use

The physical properties of the Compound I salts of the invention indicate that they will be particularly useful as a pharmaceutical.

Accordingly, the present invention further relates to a pharmaceutical composition of the succinate salt, in particular the hydrogen succinate salt as described herein (e.g. the alpha or beta form as described herein), or of the malonate salt, in particular the hydrogen malonate

salt, of the compound of formula (I). The invention also relates to the medical use of such salts and compositions, such as 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.

Additionally, the 5-HT_2 antagonistic activity of compound of the invention suggests that the compound may have a relatively low risk of extrapyramidal side effects.

The present invention also relates to use of the succinate or malonate salt of the invention, preferably the hydrogen succinate (*e.g.* the crystalline form alpha) or hydrogen malonate salt, of the compound of formula (I) 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.

In a broad aspect, 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 compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof.

As used herein the term "trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine", i.e. without any specific indication of the enantiomer form (*e.g.* using (+) and (-), or using the R/S-convention, is meant to refer to any enantiomeric form of this compound, i.e. either of the two enantiomers, 4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) or 4-((*1S,3R*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or to a mixture of the two, *e.g.* the racemic mixture. However, in this context preferably the content of the enantiomer corresponding to that of Compound I is at least 50%, i.e. at least as the racemic mixture, preferably Compound I is in enantiomeric excess.

In the present context for the pharmaceutical uses it is understood that when specifying the enantiomer form of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (*e.g.* as done in formula (I)), then the compound is relatively stereochemically pure as described above, preferably the enantiomeric excess is of 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%. In a preferred embodiment, the diastereomeric excess of Compound I is at least 90% (90% diastereomeric purity means the ratio of Compound I to *cis*-4-((1*S*,3*S*))-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine is 95:5), at least 95%, at least 97%, or at least 98%.

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 compound of formula (I) [i.e. 4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine] or a salt thereof.

One embodiment of the invention relates to a method of treating positive symptoms of schizophrenia, negative symptoms and depressive symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

A further embodiment of the invention relates to a method of treating positive symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

Another embodiment of the invention relates to a method of treating negative symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, or preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

A further embodiment of the invention relates to a method of treating depressive symptoms of
schizophrenia comprising administering a therapeutically effective amount of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment the hydrogen succinate or malonate salt of the compound of formula (I).

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 compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

A further aspect of the invention relates to a method of treating neuroleptic-induced parkinsonism comprising administering a therapeutically effective amount of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

The invention further relates to a method of treating substance abuse, *e.g.* nicotine, alcohol or cocaine abuse, comprising administering a therapeutically effective amount of the compound *trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof,

preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

A salt or a composition of the invention may be administered in any suitable way *e.g.* orally, buccal, sublingual or parenterally, and the salt may be presented in any suitable form for such administration, *e.g.* in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. In one embodiment, a salt of the invention are 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 tabletting machine. Examples of adjuvants, fillers and diluents comprise corn starch, lactose, 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.

Solutions for injections may be prepared by dissolving a salt of the invention and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, solubilising agents etc.

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 2 and 55, or between 3 and 55 mg.

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

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

EXAMPLES

COMPOUND PREPARATION

Analysis

The enantiomeric excess of compound (Va) in Example 1a 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.

HPLC analysis for conversion rate used for Examples 1b:

Column: A Lichrospher RP-8 column, 250 x 4 mm (5 µm particle size)

Eluent: Buffered MeOH/water prepared as follows: 1.1 ml Et_3N added to 150 ml water, 10% H_3PO_4(aq) is added to pH=7 and water is added to a total of 200 ml. The mixture is added to 1.8 L MeOH.

The enantiomeric excess of compound (Va) in example 1b is determined by chiral HPLC using a CHIRALPAK® AD column, 0.46cm ID X 25 cm L, 10µm at 21 °C. Heptane/ethanol/Diethylamine 89.9:10:0.1 (vol/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 is determined by fused silica capillary electrophoresis (CE) using the following conditions: Capillar: 50µm ID X 64.5 cm L, run buffer: 1.25mM β cyclo dextrin in 25mM sodium dihydrogen phosphate, pH 1.5, voltage: 16kV, temperature: 22 °C, injection: 50mbar for 5 seconds, detection: column diode array detection 192nm, sample concentration: 500µg/ml. In this system, Compound I has a retention time of approximately 33 min, and the other enantiomer has a retention time of approximately 35 min.

^{1}H NMR spectra are 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 *cis*/*trans* ratio of compounds I and VII is determined using ^{1}H NMR as described in Bøgesø *et al.*, *J. Med. Chem.* **1995**, *38*, 4380-4392 (page 4388, right column). The *cis*/*trans* ratio of compound VI is also determined by ^{1}H NMR in chloroform, using the integrals of the signal at 5.3 ppm for the *cis* isomer and the signal at 5.5 ppm for the *trans* isomer. Generally, a content of approximately 1% of the undesired isomer can be detected by NMR.

X-Ray powder diffractograms are recorded at a PANalytical X'Pert PRO X-Ray Diffractometer using $CuK_{\alpha 1}$ radiation. It is measured in reflection mode in the 2θ-range 5-40°.

The Melting points are measured using Differential Scanning Calorimetry (DSC). The equipment is a TA-Instruments DSC-2920 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.

Synthesis of key starting material

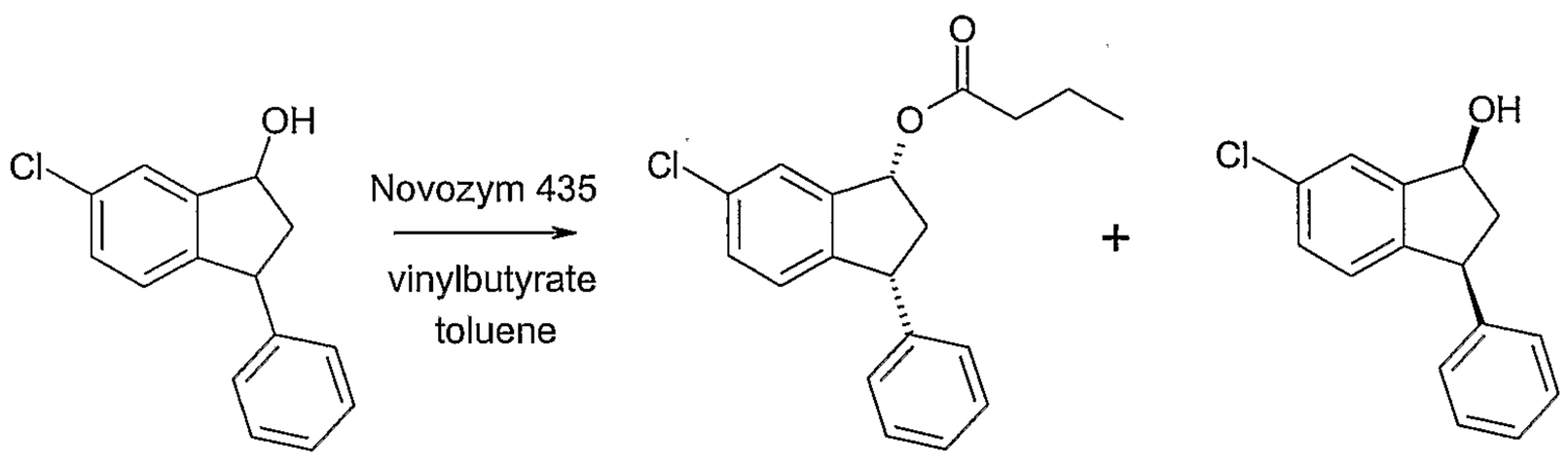
Compound V was synthesised from IV by reduction with sodium borohydride ($NaBH_4$) adapting a method described in Bøgesø *J. Med. Chem.* **1983**, *26*, 935, using ethanol as solvent, and performing the reaction at approximately 0 °C. Both compounds are described in Bøgesø *et al. J. Med. Chem.* **1995,** *38*, 4380-4392. Compound IV was synthesised from II using the general procedures described in Sommer et al., *J. Org. Chem.* **1990**, *55*, 4822, which also describes II and the synthesis thereof.

Example 1a 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) (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 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° (c=1.0, methanol).

Example 1b Synthesis of (1S,3S)-6-chloro-3-phenylindan-1-ol (Va) by use of enzymatic resolution



V Va

Compound V (5g, 20.4 mmol) is dissolved in 150 ml anhydrous toluene. 0.5 g Novozym 435 (Candida Antarctica lipase B) (Novozymes A/S, Fluka Cat.-No. 73940) is added followed by vinylbutyrate (13 ml, 102.2 mmol). The mixture is stirred using mechanical stirrer at 21 °C. After 1 day, an additional 0.5 g Novozym 435 is added. After 4 days at a conversion of 54%, the mixture is filtered and concentrated in vacuo to obtain an oil containing a mixture of (1R, 3R)-cis-6-chloro-3-phenylindan-1-ol-butyrate ester and desired compound Va with an enantiomeric excess of 99.2% (99.6% compound Va and 0.4% (1R, 3R)- cis-6-chloro-3-phenylindan-1-ol).

Synthesis of (I) and removal of the impurity in form of the *cis* diastereoisomer by precipitation of the hydrogen fumarate salt of (I)

Example 2 Synthesis of (1*S*,3*S*)-3,5-dichloro-1-phenylindan (VI, LG=Cl)

Cis-(1*S*,3*S*)-6-chloro-3-phenylindan-1-ol (Va) (204 grams) obtained as described in Example 1a 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 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 saturated sodium bicarbonate (200 ml). The 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 water phase (C) and the organic phase B are separated, and the water 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 5. *Cis/trans* ratio 77:23 according to NMR.

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 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) and tetrahydrofuran (THF) (60 kg) is heated to 50-60 °C. giving a slightly unclear solution. THF (50 kg) is stirred under nitrogen, and $LiAlH_4$ (250 g, in a soluble plastic bag, from Chemetall) is added, which gives a slow evolution of gas. After gas evolution has ceased, more $LiAlH_4$ 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 exoterm. 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 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™ (4kg) 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 rotavapor 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 5 Synthesis of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (VII)

Cis-(*1S,3S*)-3,5-dichloro-1-phenylindan (VI, LG=Cl) (240 g) is dissolved in butan-2-one (1800 ml). Potassium carbonate (272 g) and 2,2-dimethyl piperazine (prepared 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 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 the title compound as an oil, which is used directly in the next example. *Cis/trans* ratio, 82:18 according to NMR.

Example 6 Synthesis of *trans-4-((1R,3S)-6-chloro-3*-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen fumarate

Crude *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (VII) (250 grams) is mixed with formaldehyde (37% in water, 300 ml) and formic acid (366 grams), and the mixture is slowly heated to reflux. The mixture is stirred at reflux for 3.5 hours, and after cooling to room temperature, water (1200 ml) is added. The mixture is extracted twice with ether (1200 ml), and then the water phase is made alkaline by adding sodium hydroxide

(28%, approximately 500 ml). The water phase is extracted three times with ether (900 ml). The organic phases are combined and washed with brine (650 ml), and twice with water (500 ml). The organic phase is dried by sodium sulphate, filtered and evaporated to dryness on a rotary evaporator. Yield: 212 grams of *trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine free base (I) as an oil, with 19% of the cis diastereoisomer according to NMR. The compound is dissolved in 1-propanol (3.18 l) and the mixture is heated to 50°C, which gives a clear solution. Fumaric acid (69.3 grams) is added, giving a clear solution. The mixture is allowed to cool, whereby the title compound precipitates. The product is isolated by filtration, washed with 1-propanol, and dried "in vacuo" at 60°C. Yield: 182 grams, contains <1% of the cis diastereoisomer according to NMR. Elemental analysis and NMR conform to the structure. The enantiomeric excess is higher than 99% according to chiral capillary electrophoreses (CE). $[\alpha]_D^{20}$=-22.8° (c=1.0, methanol).

Liberation of the free amine of (I) from the hydrogen fumarate salt and reprecipitation as hydrogen succinate and hydrogen malonate salts

Example 7 Synthesis of 4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine free base (I)

Trans-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen fumarate (25.0 grams) is suspended in toluene (125 ml). Aqueous ammonia 25% (75 ml) is added. The three phases are stirred until all solids have disappeared. The organic phase is separated, and the aqueous phase is washed with toluene (25 ml). The combined toluene phases are washed with water (25 ml). The aqueous phase is discarded and the organic phase is dried by sodium sulphate sicc. (35 grams), the slurry is filtered and the filtrate is evaporated to dryness on a rotary evaporator, giving the title compound as an oil. The crude free base (15 grams) is used without further purification.

Example 8 Synthesis of *trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethyl-piperazinium (I) hydrogen succinate

Crude *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) (8,50 grams of oil) obtained as described in Example 7 is dissolved in acetone (30 ml). A suspension of succinic acid (3,25 grams) in acetone (32 ml) is prepared and the *trans*-4-

((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) solution is added, the succinic acid dissolves and shortly thereafter the *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen succinate precipitates. The suspension is cooled to 0°C for 90 minutes before the precipitate is isolated by centrifugation. The supernatant is discarded and the precipitate is washed with acetone (20 ml). The slurry is centrifuged and the supernatant is discarded and the precipitate is dried "in vacuo" at 50°C. Yield 8.56 grams.

When this procedure was performed for the first time the isolated product was the beta-form, following repetitions resulted in formation of the more stable alpha-form of Compound I hydrogen succinate.

Acetone in the above described experiment can be substituted by aqueous acetone (95%) also resulting I formation of the alpha-form of Compound I hydrogen succinate.

Differential Scanning Calorimetry (DSC) shows an endotherm with an onset temperature of 140 °C and a peak at 141 °C corresponding to the alpha form. XRPD diffractogram conforms with the alpha form.

Example 9 *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen malonate

Crude *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) (1.0 gram, 2.81 mmol, obtained as described in Example 7 is dissolved in 2-propanol (5 ml). A solution of malonic acid (0.291 grams, 2.46 mmol) in 2-propanol (5 ml) is prepared and the *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine solution is added, whereby the *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium hydrogen malonate precipitates. The suspension in cooled to room temperature before the precipitate is isolated by centrifugation. The supernatant is discarded and the precipitate is washed with 2-propanol (5 ml). The slurry is centrifuged and the supernatant is discarded and the precipitate is dried "in vacuo" at 50°C. Yield: 0.98 grams (84%). Elemental analysis conforms to the structure. The X-ray diffractogram conforms to the diffractogram of the hydrogen malonate as shown in figure 3.

Synthesis of (I), salt formation of (VII) in order to remove *cis* diastereoisomer of (VII), and formation of the hydrogen succinate salt from crude (I)

Example 10 Synthesis of *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium (VII) hydrogen maleate

Examples 2 and 5 are repeated, giving crude *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (VII) (ca. 20 grams) as an oil, which is further purified by flash chromatography on silicagel (eluent: ethyl acetate/ethanol/triethylamine 90:5:5) followed by evaporation to dryness on a rotary evaporator. Yield 12 grams of the title compound as an oil (*cis/trans* ratio, 90:10 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 another batch of precipitate is collected. Yield 3.5 gram solid of the title compound (no *cis* isomer is detected according to NMR) . Melting point 175-178 °C.

Example 11 *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (VII)

A mixture of trans-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium hydrogen maleate (VII) (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 dryness in vacuo. Yield 7.5 grams of oil.

Example 12 Preparation of *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine free base (I)

Trans-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (8.9 grams) (VII) is dissolved in formic acid (10.5 ml) and to the solution is added formaldehyde (10.5 ml). Heated to 60°C and kept at this temperature for 2½ hours. After cooling of the reaction mixture, water (50 ml) and hexane (50 ml) are added. Adjustment of pH with NaOH (27%, 33 ml) to pH > 12. The hexane phase is washed with aq. NaCl (20 ml) and water (20 ml).

Hexane is exchanged azeotropic with acetone (90 ml) and the mixture is concentrated. The crude free base in acetone (10 ml) is used without further purification.

Example 13 *Trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen succinate

Crude *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) in acetone solution (10 ml). A suspension of succinic acid (3.4 grams) in acetone (20 ml) is prepared and the *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) solution is added and the mixture is heated to reflux (55°C). The succinic acid dissolves and during cooling of the solution *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen succinate starts precipitating. Suspension left overnight to precipitate. *Trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium hydrogen succinate is isolated by filtration and washed with acetone (20 ml). The product is dried "in vacuo" at 60°C.

Yield: 7.9 grams.

Differential Scanning Calorimetry shows an endotherm with an onset temperature of 140 °C and a peak at 141 °C corresponding to the alpha form. XRPD diffractogram conforms with the alpha form. $[\alpha]_D^{20}$=-22.04° (c=1.0, methanol).

Synthesis of I using 1,2,2-trimethylpiperazine

Example 14 Synthesis of 3,3,4-trimethylpiperazin-2-one

3,3-dimethylpiperazin-2-one (50 grams) is suspended in 1,2-dimethoxyethane (DME) (150 ml) and potassium carbonate (70 grams) is added. Methyl iodide (66.4 grams) is added during half an hour, while the mixture is cooled slightly, allowing the temperature to reach 50 °C. The mixture is stirred 9 hours at an oil bath at 40-45 °C, and a sample is withdrawn for NMR, which indicates, that there is still 8% starting material left (singal at 2.8 ppm). More methyl iodide is added (4.6 grams), and the mixture is stirred for another 2½ hour at 40 °C, and a new NMR sample shows full conversion. The mixture is filtered, and the filter cake is washed with DME. The filtrate is evaporated to dryness giving 41 grams of the title compound. NMR complies with the structure.

Example 15 Synthesis of 1,2,2-trimethylpiperazine

A solution of lithium aluminium hydride in tetrahydrofuran (THF) (1.0 M, Aldrich cat. no. 21,277-6, 90 ml) is heated to 50 °C on an oil batch. Crude 3,3,4-trimethylpiperazin -2-one (10 g) is suspended in THF and is slowly added, giving evolution of gas. The resulting mixture is stirred at 45-56 °C for 4 hours, giving full conversion to the title compound according to NMR (no signal at 1.2 ppm from starting material). The mixture is cooled, and water (3.3 ml) is added, giving evolution of gas. Then a solution of sodium hydroxide in water (15%, 3.3 ml) is added, giving more gas, and finally water (10 ml) is added. The mixture is filtered, and the filter cake is washed with THF (100 ml). The filtrates are concentrated on a rotary evaporator (0.3 atm. and 60 °C in the water batch). The residue is dissolved in THF (200 ml) and dried with sodium sulphate, then the mixture is filtered, and the filtrate is concentrated on a rotary evaporator (0.2 atm and 60 °C in the water batch) giving 6.4 grams of the title compound. NMR complies with the structure, the substance contains some THF.

Example 16 Synthesis of *trans*-4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen fumarate from compound VI

Cis-(*1S,3S*)-3,5-dichloro-1-phenylindan (VI with LG=Cl) (17.8 grams) is coupled with distilled 1,2,2-trimethylpiperazine (VIII) (8.7 grams), using the procedure described in example 5. The raw product of the free amine (15.7 grams), containing 6% of the *cis* isomer, is used to form the hydrogen fumarate salt, using the procedure in example 6. Yield 15.7 grams of the title compound; NMR complies with the structure, no *cis* isomer is observed.

Synthesis of crystalline beta form of Compound I hydrogen succinate salt

Example 17 Synthesis of *trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethyl-piperazinium (I) hydrogen succinate, beta form

Compound I hydrogen succinate (50 mg) is suspended in of water (1 ml) and allowed to equilibrate for 3 days. Any undissolved material is removed by filtration. The beta -form of Compound I hydrogen succinate forms during the natural evaporation of the solvent. The beta form is analysed after full evaporation of the solvent by XRPD and DSC.

Analytical results: Differential Scanning Calorimetry (DSC) shows an endotherm with an onset temperature of 135.6°C and a peak at 137.5°C corresponding to the beta form. XRPD conforms with the beta-form.

CHARACTERISATION OF THE SALTS

Example 18 Solubility of the salts of the compound of formula (I)

The solubility of the salts in water was determined by adding an excess (50 mg) of salt to 2 ml of water. The suspensions were left at the rotarmix for at least 24 hours, and subsequently pH was measured and the concentration was determined by HPLC. The solid precipitate was isolated and left to dry in the laboratory. The results are summarized in table 1.

Table 1: Solubility of the salts in water at room temperature.

Sample	pH	Solubility(mg/ml)
Succinate 1:1 alpha	4.4	13
Malonate 1:1	3.9	15
Fumarate	3.8	1.5

Example 19 Stability of the salts of the compound of formula (I)

The stability of the salts was investigated under the following circumstances:

Heat, 60°C/80%RH: Samples were stored at 60°C with 80%RH for one week. Then they were dissolved and analysed by HPLC.

Heat, 90°C: Samples (~10 mg) were stored at 90°C in closed containers containing 1 droplet of water. Then they were dissolved and analysed by HPLC.

Light: Samples were placed in the light cabinet at 250 w/m^2 for 24 hours. Then they were dissolved and analysed by HPLC.

The area of peaks in the chromatograms besides the peaks corresponding to the substance or the acid was summarized. The succinate salt of the invention does not show any degradation at all.

Table 2

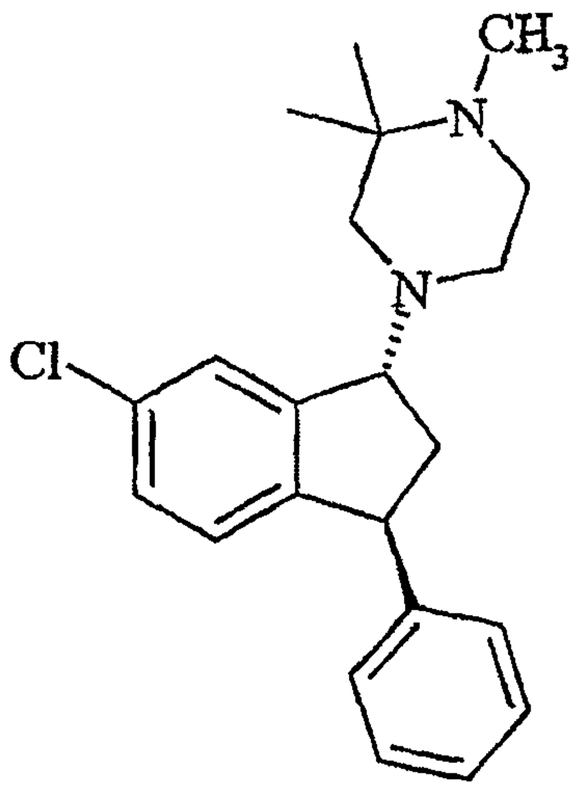
Sample	Sum of impurity peak area %		
	60°C/80%RH	90°C	Light
Malonate 1:1 alpha	0	6,19	0,06
Succinate 1:1	0	0	0
Fumarate	0,07	0,09	0,06

Example 20 The hygroscopicity of salts of the compound of formula (I)

The hygroscopicity of the fumarate salt, the succinate salt (the alpha form) and the malonate salt was investigated by Dynamic Vapour sorption (DVS). The fumarate and the succinate salts were found to be non-hygroscopic. The malonate absorbs gradually up to 1% of water when the relative humidity is raised to 95%, but with no hysteresis.

Claims

1. A succinate salt or a malonate salt of the compound of formula (I):



(I)

[*trans*-4-(1*R*,3*S*)-6-chloro-3-phenylindan-l-y1)-1,2,2-trimethylpiperazine].

2. The succinate salt according to claim 1, which is the hydrogen succinate salt of the compound of formula (I).

3. A crystalline hydrogen succinate salt of the compound of formula (I) as defined in claim 1.

4. The salt of claim 3, which crystal form is crystal form alpha.

5. The salt of claim 3 or 4, which crystal form is characterized by an X-Ray powder diffractogram corresponding to that of Figure 1.

6. The salt of any one of claims 3-5, which crystal form is characterized by an X-Ray powder diffractogram obtained, using $CuK_{\alpha 1}$ radiation with λ=1.5406 Å, showing peaks at the following 2θ-angles: 9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; and 29.65.

7. The salt of any one of claims 3-6, which crystal form is characterized by having a DSC trace showing an endotherm with an onset at about 139-141°C.

8. The malonate salt according to claim 1, which is the hydrogen malonate salt of the compound of formula (I).

9. A crystalline hydrogen malonate salt of the compound of formula (I) as defined in claim 1.

10. The crystalline salt of claim 9, which crystal form is characterized by an X-Ray powder diffractogram shown in Figure 3.

11. The crystalline salt of claim 9 or 10, which crystal form is characterized by an X-Ray powder diffractogram, obtained using $CuK_{\alpha 1}$ radiation with λ=1.5406 Å, showing peaks at the following 2θ-angles: 8.3; 10.6; 11.5; 12.8; 14.2; 14.5; 14.7; 15.8; 16.5; 17.4; 17.6; 18.0; 18.6; 19.2; 21.2; 22.0; 22.9; 23.7; 24.7; and 28.8.

12. A pharmaceutical composition comprising a salt according to any one of claims 1-11 together with at least one pharmaceutically acceptable carrier, filer or diluent.

13. The pharmaceutical composition of claim 12, wherein the content of said salt, calculated as the free base, is between 2 and 55 mg.

14. The pharmaceutical composition of claim 13, wherein the content of said salt, calculated as the free base, is about 3 mg.

15. A salt according to any one of claims 1-11 for use in medicine.

16. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of a disease involving psychotic symptoms.

17. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of anxiety disorders.

18. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of affective disorders.

19. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of sleep disturbances.

20. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of migraine.

21. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of neuroleptic-induced parkinsonism.

22. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of abuse disorders.

23. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of schizophrenia.

24. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of psychotic disorders.

25. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of Schizophreniform Disorder.

26. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of Schizoaffective Disorder.

27. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of Delusional Disorder.

28. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of Brief Psychotic Disorder.

29. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of Shared Psychotic Disorder.

30. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of mania in bipolar disorder.

31. Use of a salt according to any one of claims 1-11 in the preparation of a medicament for the treatment of positives symptoms, negative symptoms or depressive symptoms of schizophrenia, or a combination thereof.

32. Use of a salt according to any one of claims 1-11 for the treatment of a disease involving psychotic symptoms.

33. Use of a salt according to any one of claims 1-11 for the treatment of anxiety disorders.

34. Use of a salt according to any one of claims 1-11 for the treatment of affective disorders.

35. Use of a salt according to any one of claims 1-11 for the treatment of sleep disturbances.

36. Use of a salt according to any one of claims 1-11 for the treatment of migraine.

37. Use of a salt according to any one of claims 1-11 for the treatment of neuroleptic-induced parkinsonism.

38. Use of a salt according to any one of claims 1-11 for the treatment of abuse disorders.

39. Use of a salt according to any one of claims 1-11 for the treatment of schizophrenia.

40. Use of a salt according to any one of claims 1-11 for the treatment of psychotic disorders.

41. Use of a salt according to any one of claims 1-11 for the treatment of Schizophreniform Disorder.

42. Use of a salt according to any one of claims 1-11 for the treatment of Schizoaffective Disorder.

43. Use of a salt according to any one of claims 1-11 for the treatment of Delusional Disorder.

44. Use of a salt according to any one of claims 1-11 for the treatment of Brief Psychotic Disorder.

45. Use of a salt according to any one of claims 1-11 for the treatment of Shared Psychotic Disorder.

46. Use of a salt according to any one of claims 1-11 for the treatment of mania in bipolar disorder.

47. Use of a salt according to any one of claims 1-11 for the treatment of positives symptoms, negative symptoms or depressive symptoms of schizophrenia, or a combination thereof.

48. The use of claim 18 or 34, wherein the affective disorder is depression.

49. The use of claim 22 or 38, wherein the abuse disorder is cocaine abuse, nicotine abuse, or alcohol abuse.

50. The pharmaceutical composition of any one of claims 12-14 for the treatment of a disease involving psychotic symptoms.

51. The pharmaceutical composition of any one of claims 12-14 for the treatment of anxiety disorders.

52. The pharmaceutical composition of any one of claims 12-14 for the treatment of affective disorders.

53. The pharmaceutical composition of any one of claims 12-14 for the treatment of sleep disturbances.

54. The pharmaceutical composition of any one of claims 12-14 for the treatment of migraine.

55. The pharmaceutical composition of any one of claims 12-14 for the treatment of neuroleptic-induced parkinsonism.

56. The pharmaceutical composition of any one of claims 12-14 for the treatment of abuse disorders.

57. The pharmaceutical composition of any one of claims 12-14 for the treatment of schizophrenia.

58. The pharmaceutical composition of any one of claims 12-14 for the treatment of psychotic disorders.

59. The pharmaceutical composition of any one of claims 12-14 for the treatment of Schizophreniform Disorder.

60. The pharmaceutical composition of any one of claims 12-14 for the treatment of Schizoaffective Disorder.

61. The pharmaceutical composition of any one of claims 12-14 for the treatment of Delusional Disorder.

62. The pharmaceutical composition of any one of claims 12-14 for the treatment of Brief Psychotic Disorder.

63. The pharmaceutical composition of any one of claims 12-14 for the treatment of Shared Psychotic Disorder.

64. The pharmaceutical composition of any one of claims 12-14 for the treatment of mania in bipolar disorder.

65. The pharmaceutical composition of any one of claims 12-14 for the treatment of positives symptoms, negative symptoms or depressive symptoms of schizophrenia, or a combination thereof.

66. The pharmaceutical composition of claim 52, wherein the affective disorder is depression.

67. The pharmaceutical composition of claim 56, wherein the abuse disorder is cocaine abuse, nicotine abuse, or alcohol abuse.

68. The salt according to any one of claims 1-11 for the treatment of a disease involving psychotic symptoms.

69. The salt according to any one of claims 1-11 for the treatment of anxiety disorders.

70. The salt according to any one of claims 1-11 for the treatment of affective disorders.

71. The salt according to any one of claims 1-11 for the treatment of sleep disturbances.

72. The salt according to any one of claims 1-11 for the treatment of migraine.

73. The salt according to any one of claims 1-11 for the treatment of neuroleptic-induced parkinsonism.

74. The salt according to any one of claims 1-11 for the treatment of abuse disorders.

75. The salt according to any one of claims 1-11 for the treatment of schizophrenia.

76. The salt according to any one of claims 1-11 for the treatment of psychotic disorders.

77. The salt according to any one of claims 1-11 for the treatment of Schizophreniform Disorder.

78. The salt according to any one of claims 1-11 for the treatment of Schizoaffective Disorder.

79. The salt according to any one of claims 1-11 for the treatment of Delusional Disorder.

80. The salt according to any one of claims 1-11 for the treatment of Brief Psychotic Disorder.

81. The salt according to any one of claims 1-11 for the treatment of Shared Psychotic Disorder.

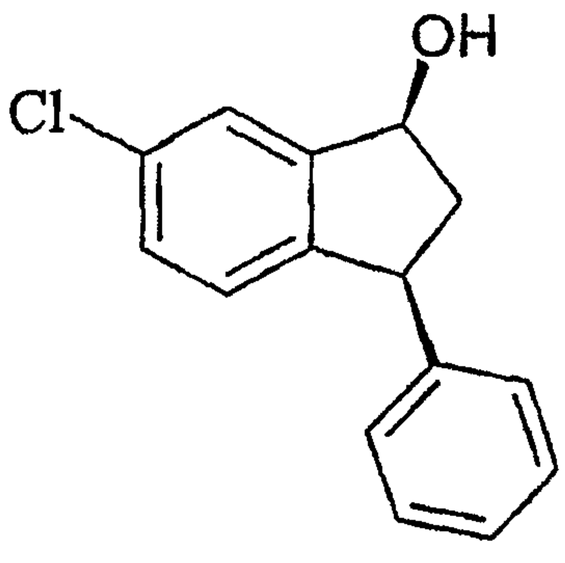
82. The salt according to any one of claims 1-11 for the treatment of mania in bipolar disorder.

83. The salt according to any one of claims 1-11 for the treatment of positives symptoms, negative symptoms or depressive symptoms of schizophrenia, or a combination thereof.

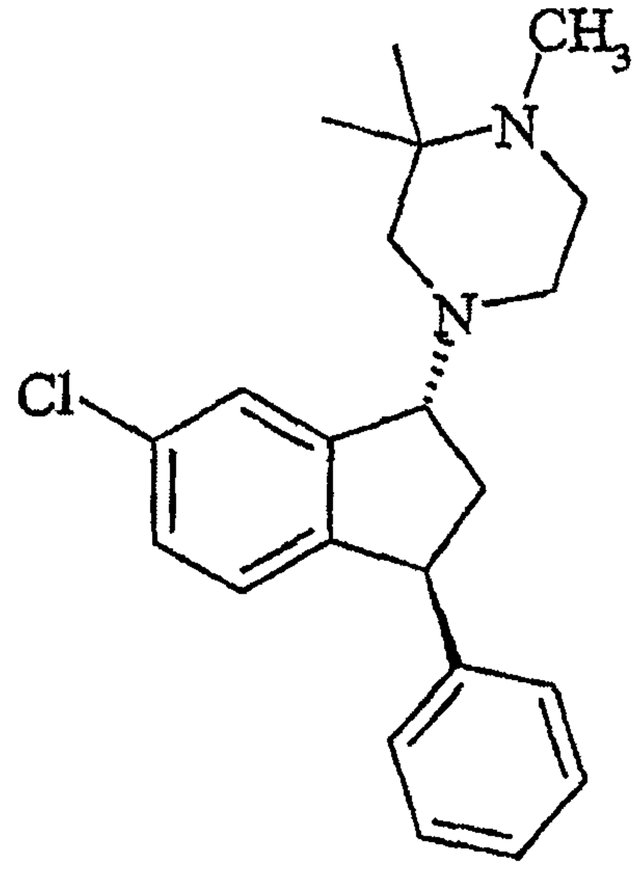
84. The salt of claim 70, wherein the affective disorder is depression.

85. The salt of claim 74, wherein the abuse disorder is cocaine abuse, nicotine abuse, or alcohol abuse.

86. A method for manufacturing 4-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (formula (I)) or a salt thereof, which method comprises conversion of the compound of formula (Va) in cis-configuration to the compound of formula (I), wherein formula (I) and (Va) are as follows:

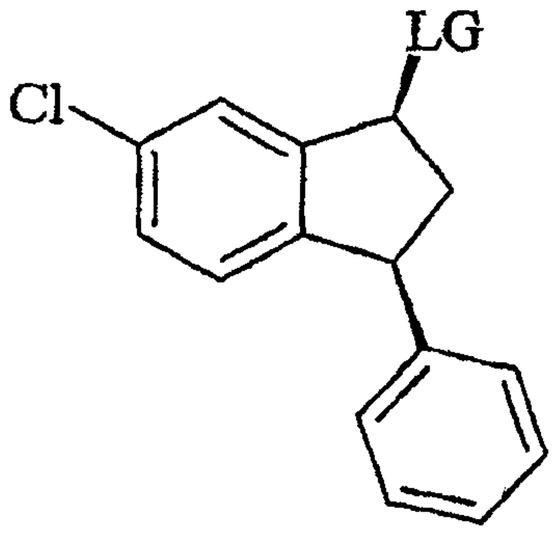


(Va) , and



(I) .

87. The method of claim 86, comprising conversion of the alcohol group of the *cis*-alcohol of formula (Va) to a suitable leaving group LG resulting in the compound of formula (VI):



(VI) .

88. The method of claim 87, wherein LG is a halogen or a sulphonate.

89. The method of claim 88, wherein LG is Cl or Br.

90. The method of claim 29, wherein LG is Cl.

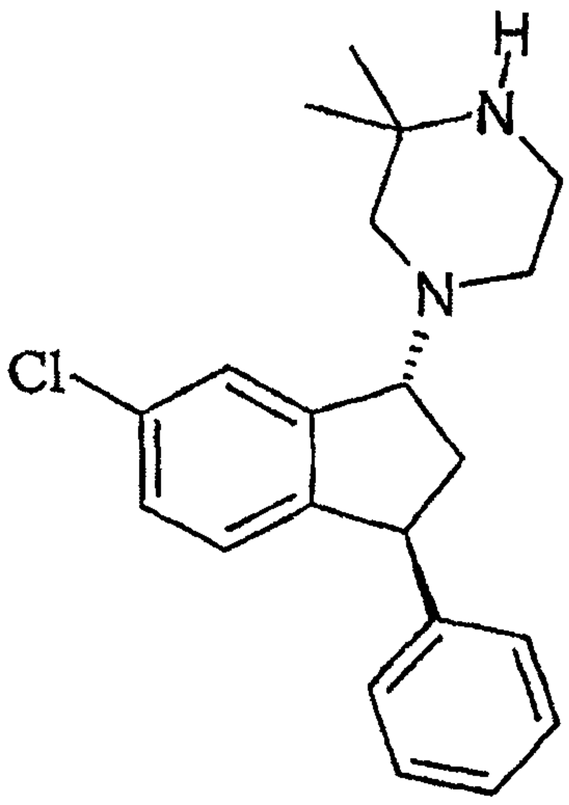
91. The method of any one of claims 86-90, wherein the compound of formula (VI) is precipitated from a suitable solvent.

92. The method of claim 91, wherein LG is a halogen and the solvent is an alkane.

93. The method of claim 92, wherein the alkane is heptane.

94. The method of claim 92 or 93, wherein the halogen is Cl.

95. The method of any one of claims 87-94, wherein the compound of formula (VI) is reacted with 2,2-dimethylpiperazine to obtain the compound of formula (VII):



(VII) .

96. The method of claim 95 comprising methylation at the secondary amine to obtain the free base of the compound of formula I.

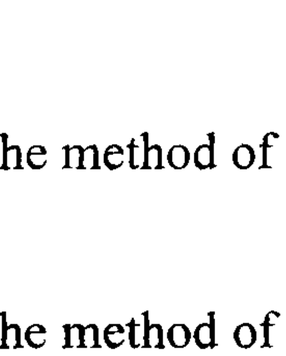
97. The method of claim 95 or 96, wherein the compound of formula (VII) is precipitated as a suitable salt.

98. The method of claim 97, wherein the formed salt is a salt of an organic acid.

99. The method of claim 98, wherein the organic acid is an organic diacid.

100. The method of any one of claims 97-99, wherein the formed salt is the hydrogen fumarate salt or the hydrogen maleate salt of the compound of formula (VII).

101. The method of any one of claims 87-94, wherein the compound of formula (VI) is reacted with 1,2,2- trimethylpiperazine (formula (VIII)) to obtain the free base of the compound of formula (I),

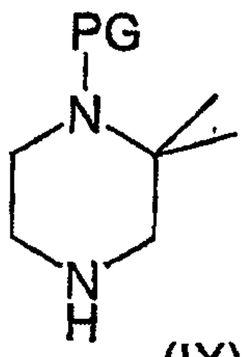


(VIII)

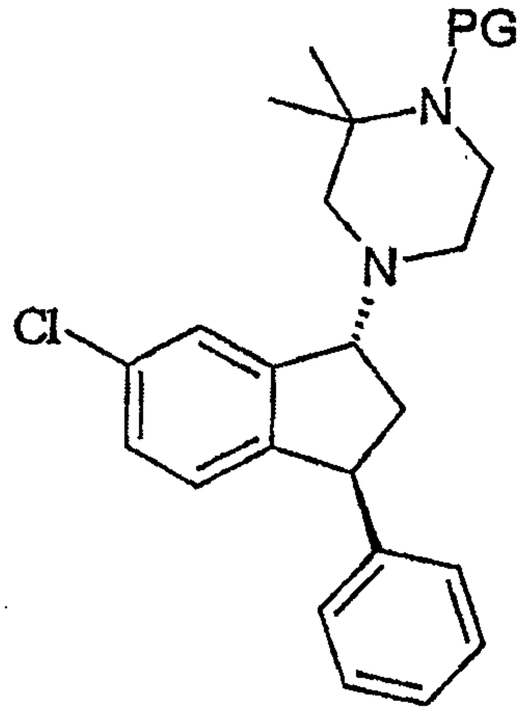
102. The method of any one of claims 88-96, comprising

- reacting the compound of formula (VI) with 1-protected 2,2-dimethylpiperazine (formula (IX)), wherein PG is a protection group, thereby obtaining a compound of formula (X); and
- deprotecting the compound of formula (X) to obtain the compound of formula (VII) or converting the compound of formula (X) directly to the compound of formula (I),

wherein the compounds of formulas (IX) and (X) are as follows:



(IX) , and

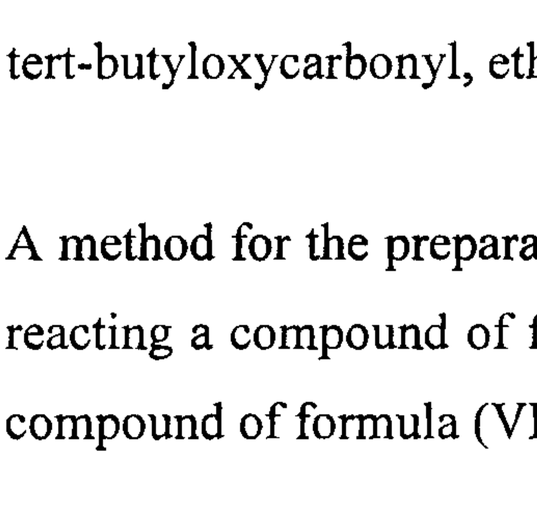


(X) .

103. The method of claim 102, wherein the protection group PG is phenylmethoxycarbonyl, tert-butyloxycarbonyl, ethoxycarbonyl, or benzyl.

104. A method for the preparation of the compound of formula (I) or a salt thereof comprising reacting a compound of formula (VIa) with 2,2-dimethylpiperazine thereby obtaining the compound of formula (VII), followed by methylation at the secondary amine.

105. A method for the preparation of a compound of formula (I) or a salt thereof comprising reacting a compound of formula (VIa)



(VIa)

with 2,2-dimethylpiperazine in presence of a base, followed by reductive amination with a suitable reagent, followed by isolation of the compound of formula (I) as the free base or as a salt thereof.

106. The method of claim 105, wherein the reagent is formaldehyde, paraformaldehyde, trioxane or diethoxymethane.

107. A method for manufacturing 4-((1*R*,3*S*)-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (formula (I)) or a salt thereof, which method comprises conversion of the compound of formula (VII) to the compound of formula (I0, wherein the compound of formula (VII) is as defined in claim 95.

108. The method of any one of claims 86-107, wherein the compound of formula (I) is precipitated as a suitable salt in order to remove undesired *cis* diastereoisomer.

109. The method of claim 108, wherein the formed salt is a salt of an organic acid.

110. The method of claim 109, wherein the organic acid is an organic diacid.

111. The method of any one of claims 108-110, wherein the formed salt is a hydrogen fumarate salt of the compound of formula (I).

112. The method of any one of claims 86-111, comprising preparing the succinate salt defined in any one of claims 1-7.

113. The method of claim 112, wherein the hydrogen succinate of the compound of formula (I) is prepared in a ketone solvent.

114. The method of claim 113, wherein the solvent is acetone.

115. The method of claim 114, wherein the acetone is aqueous acetone.

116. The method of any one of claims 86-111, comprising preparing the malonate salt defined in claim 1 or any one of claims 8-11.

117. The method of claim 116, wherein the hydrogen malonate of the compound of formula (I) is prepared in a in a alcohol solvent.

118. The method of claim 117, wherein the alcohol solvent is 2-propanol.

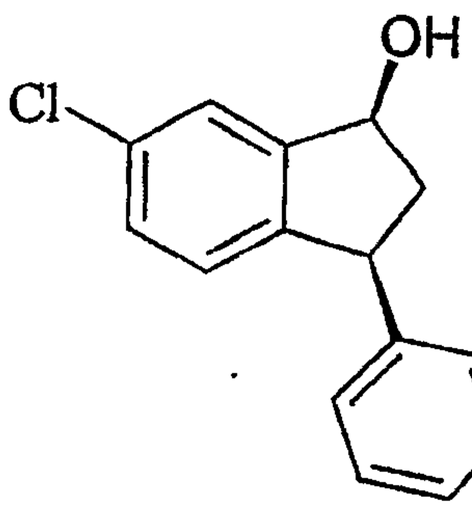
119. The method of any one of claims 86-118 comprising conversion of the free base of the compound of formula (I) to a salt as defined in any one of claims 1-14.

120. The method of any of claim 119, wherein the base of formula (I) obtained is first isolated as the fumarate salt thereof, which is optionally recrystallised one or more times, the fumarate salt is then treated with a base to liberate the free base of the compound of formula (I) which is then converted to the succinate or malonate salt thereof.

121. The method of any one of claims 86-119 followed by isolation of the compound of formula (I) as the free base or as a salt thereof.

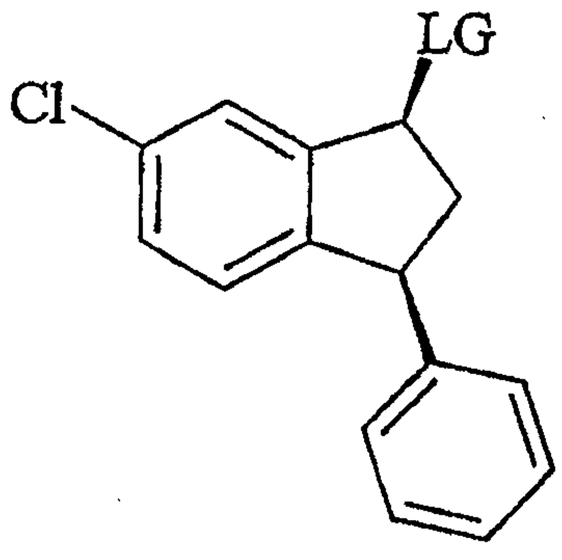
122. The method of claim 121, wherein the salt of the isolated compound of formula (I) is a succinate salt as defined in any one of claims 1-7 or a malonate salt as defined in any one of claims 8-11.

123. A compound having the structure:



(Va) .

124. A compound having the structure:



(VI),

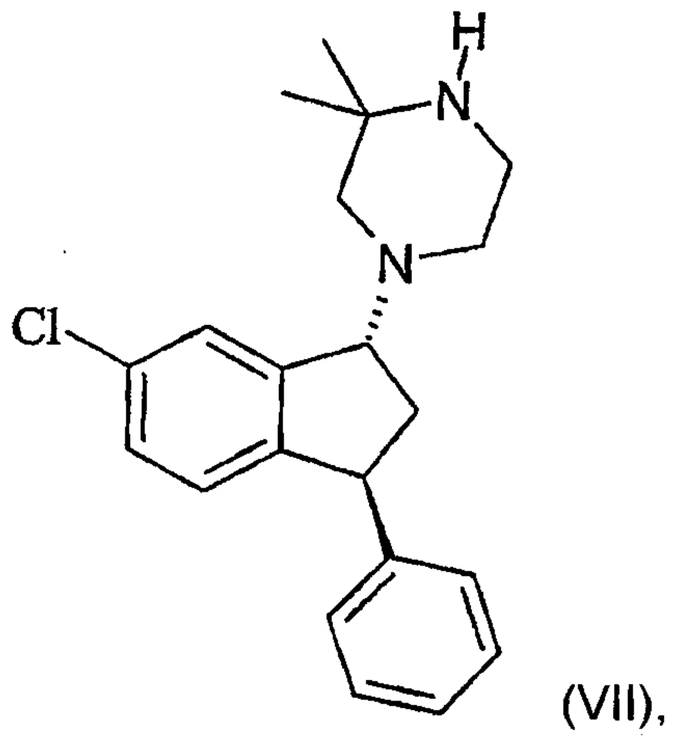
wherein LG is a potential leaving group.

125. The compound of claim 124, wherein LG is a halogen or a sulphonate.

126. The compound of claim 125, wherein LG is Br or Cl.

127. The compound of claim 126, wherein LG is Cl.

128. A compound having the structure:



(VII),

or a salt thereof.

129. A compound as defined in any one of claims 123-128, which compound has an enantiomeric excess of at least 80%.

130. The method of any one of claims 86-122, wherein the compound of formula (Va) is obtained by enzymatic resolution of the compound of formula (V).

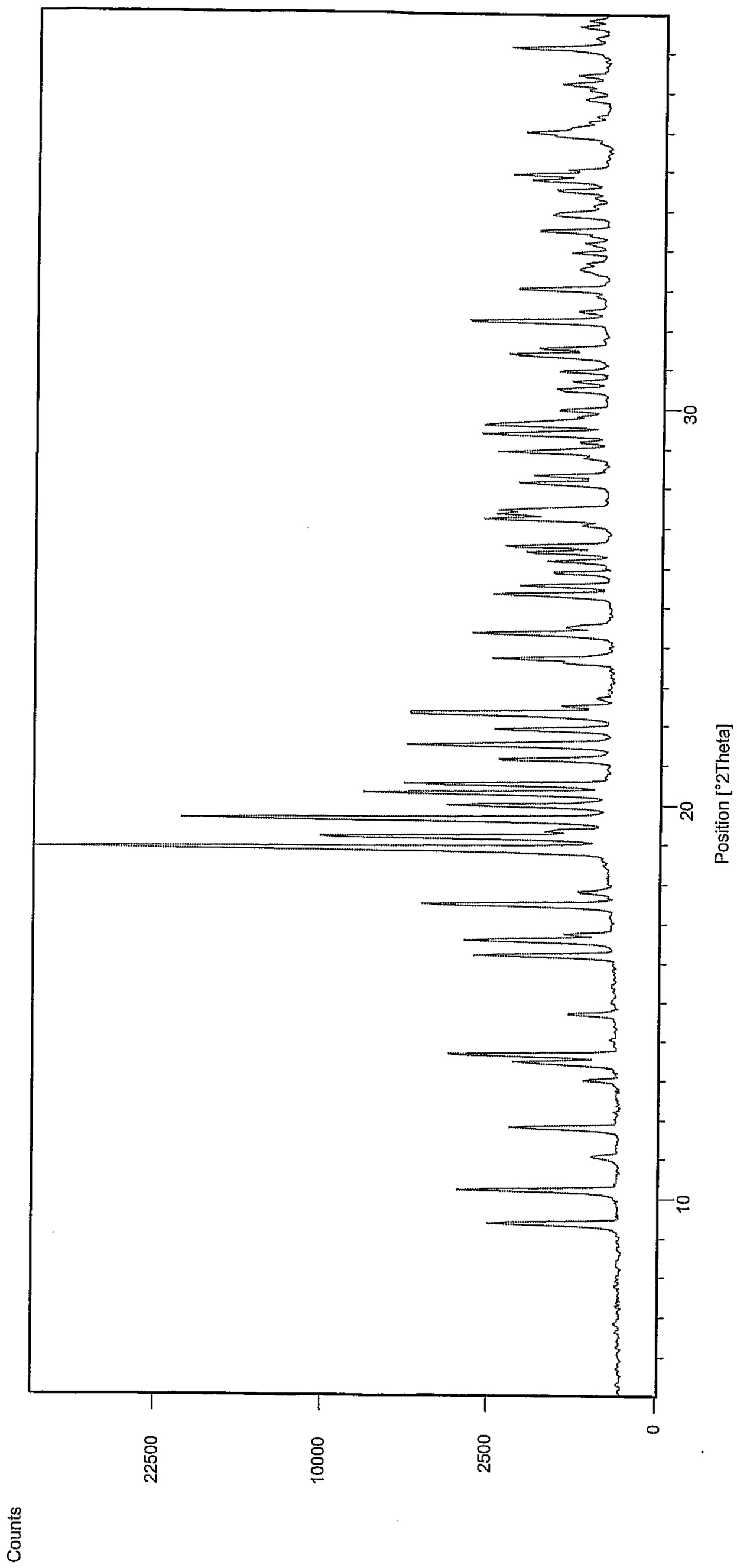


Fig. 1

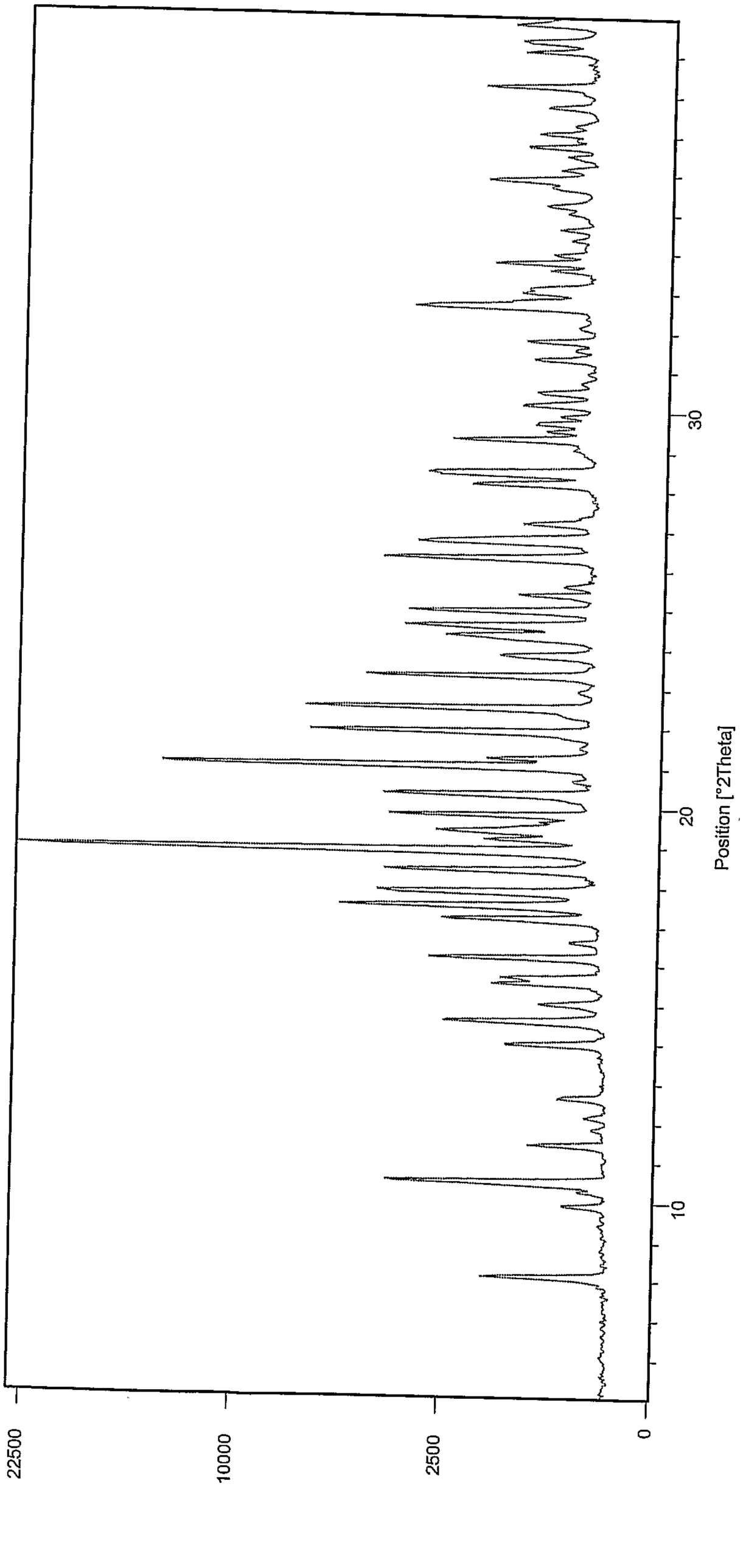


Fig. 2

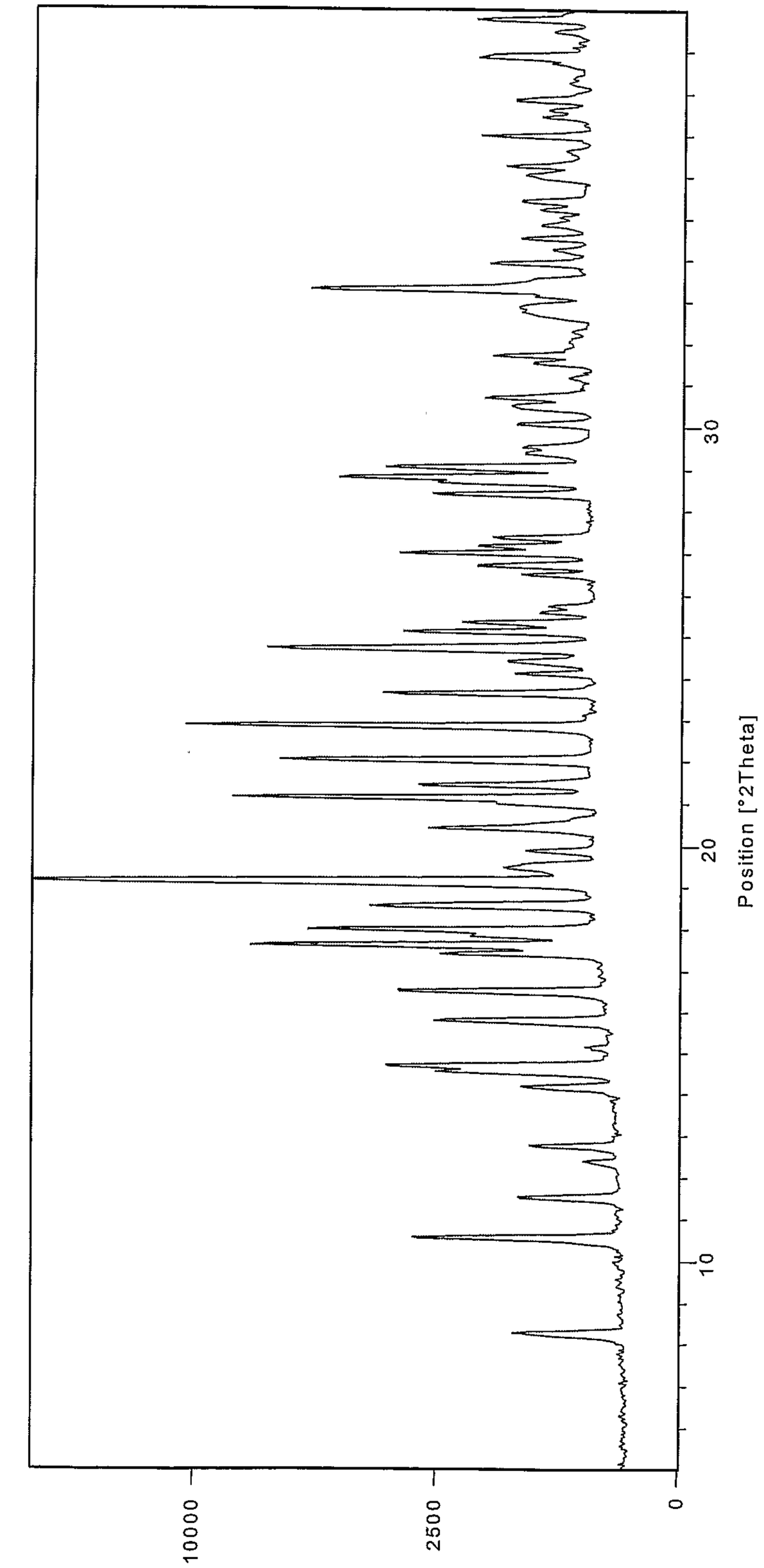


Fig. 3