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(54) **Title**: PROCESS FOR PREPARING ASENAPINE AND SALTS OF INTERMEDIATES THEREOF

(57) **Abstract**: A process for preparing substantially pure trans-5-chloro-2-methyl-2,3,3a42b4etrahydro-lH-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (Asenapine) of formula (I) is provided. The salts of intermediates useful for preparing Asenapine of formula (I) i.e. 5-nitro-2-methyl-2,3,3a,12b-tetrahydro-lH-dibenz [2,3:6,7] oxepino [4,5-c]pyrrole of formula (VIII) and 5-amino-2-methyl-2,3,3a,12b-tetrahydro-lH-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole of formula (DC) are also provided.

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PROCESS FOR PREPARING ASENAPINE AND SALTS OF INTERMEDIATES THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of substantially pure trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (Asenapine) of formula (I). It also relates to novel salts of intermediates i.e. 5-nitro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole of formula (VIII) and 5-amino-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole of formula (IX) are useful for the preparation of substantially pure Asenapine of formula (I) and its pharmaceutically acceptable salts thereof.

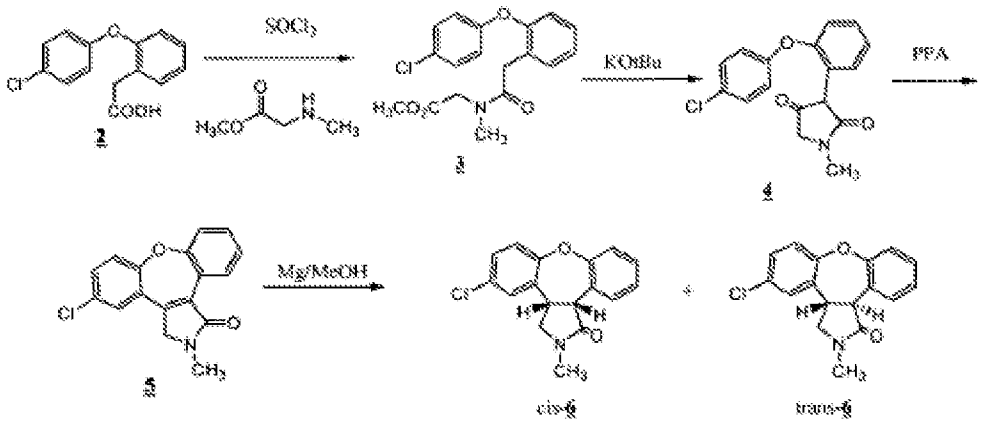
BACKGROUND OF THE INVENTION

Trans-5-chloro-2- methyl-2,3,3a,12b- tetrahydro-1H-dibenz[2,3:6,7] oxepino [4,5-c] - pyrrole, which is commonly known as asenapine, is a compound having CNS-depressant activity and having antihistamine and antiserotonin activities (U.S. Pat. No. 4,145,434 to van den Burg). The pharmacological profile of asenapine, its kinetics and metabolism, and the first safety and efficacy studies in human volunteers and in schizophrenic patients have been reviewed (De Boer et al., *Drugs of the Future,* 18(12), 1117-1123, 1993). It has been established that the maleate salt of asenapine, known as Org 5222, is a broad-spectrum, high potency serotonin, noradrenaline and dopamine antagonist.

Asenapine exhibits potential antipsychotic activity and may be useful in the treatment of depression (see international patent application WO 99/32108). A pharmaceutical preparation suitable for sublingual or buccal administration of asenapine maleate has been described in the international patent application WO 95/23600 (Akzo Nobel N.V.). A general methodology for the preparation of asenapine is disclosed in U.S. Pat. No.

4,145,434. Physical-chemical properties of the drug substance Org 5222 have been reported (Funke et al. *Arzneim. - Forsch/Drug.Res.* 40, 536-539, 1990). Additional synthetic methods for the preparation of Org 5222 and radiolabelled derivatives thereof have also been described (Vader et al., *J. Labelled Comp. Radiopharm.* 34, 845-869, 1994).

A general methodology for the preparation of asenapine is described in the US '434 patent, the disclosure of which is incorporated herein for reference. Following the generalized method given in US '434 patent, asenapine can be prepared by the method depicted in scheme-1, given below.



Scheme-I

For preparing Asenapine from the acid (2), the carboxyl group is first transformed into the corresponding acid chloride by treatment with thionylchloride. Coupling with sarcosinemethyl ester provides for an ester (3). Treatment of the ester (3) with potassium tert-butoxide in toluene yields the cyclic dione (4), which is subjected to further ring closure to an enamide (5) by treatment with polyphosphoric acid.

The step of reducing the enamide (5) with magnesium in methanol gave a mixture of cis and trans lactam (6). Both isomers must be separated by column chromatography. It appears that the formation of the cis-lactam (6) is predominant (approx. 4:1 cis/trans).

After separation, reduction of the cis or trans lactam (6) with LiAlH 4 /AlCl 3 finally furnished the cis amine (1a) or desired trans amine (Asenapine), respectively. Because the cis isomer is predominant, the synthesis is not optimal.

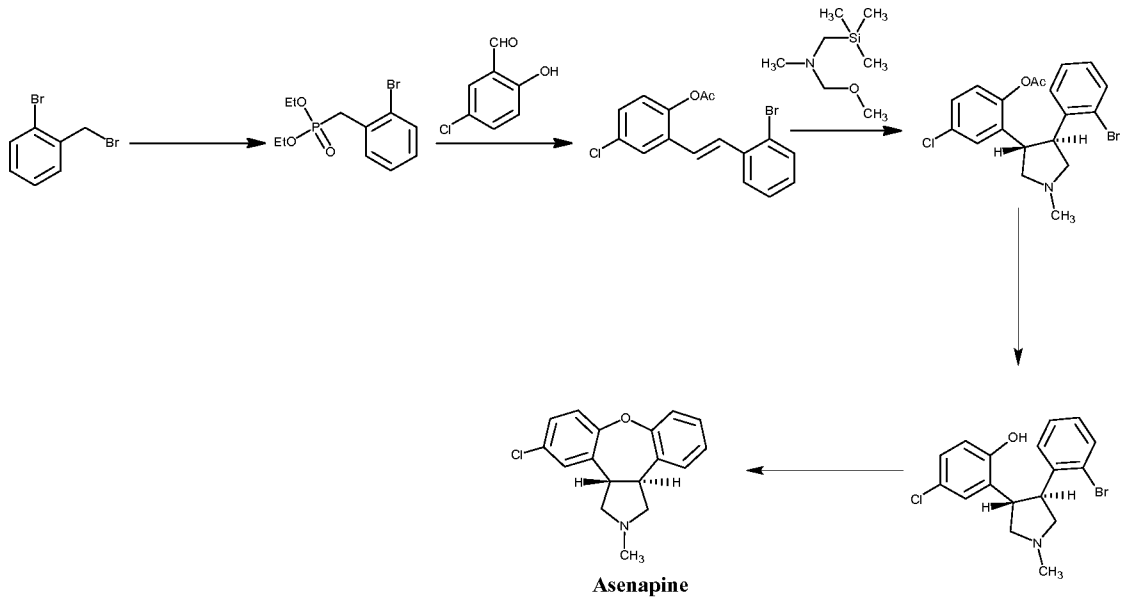
It seems from the disclosure that this reaction exhibits good yields, but it also predominantly provides the unwanted process impurities and cis-isomer of the compound (6a) upon subsequent work up, which leads consequently to the cis- asenapine (1a).

Additional synthetic methods for the preparation of asenapine or salts thereof are known from WO 2006/106136, WO 1998/54186 and EP 0,569,096 patent applications. Vader et al. (Labelled Comp. Radiopharm., 34(9), 845-869, 1994) discloses synthetic methods for the preparation of radiolabelled ORG 5222 and derivatives thereof. Orthorhombic crystal form of asenapine maleate is disclosed in WO 2006/106135.

A method of preparation of (5-chloro-2-phenoxyphenyl) acetic acid has been disclosed by J. Med. Chem. 25, 855 (1982). The method employed is Willegerodt-Kindler reaction whose synthetic utility is seriously limited by the necessity of elevated reaction temperature and use of frequently high pressure. The yield of the acid obtained by the method is less (46%) that is not commercially viable for pharmaceutical industries. A generalized method for one step synthesis of methyl (monosubstituted)arylacetates from acetophenones is disclosed in Synthesis 126-127 (1981). According to this disclosure, tor example, when a mixture of acetophenone, methanol and boron trifluoride etherate is added in one lot to a stirred suspension of lead(IV) acetate in benzene at room temperature, it leads to the formation of methyl phenyl acetate in good yields. This article does not disclose preparatory methods for the phenoxyphenyl acetic acid compounds of the present invention, particularly (disubstituted)phenylacetates, more particularly (5-chloro-2-phenoxyphenyl)acetic acid or esters thereof and their further conversion to asenapine or salts thereof.

U.S. Pat. No. 7750167 discloses process for the preparation of Asenapine. This process involves the preparation of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:

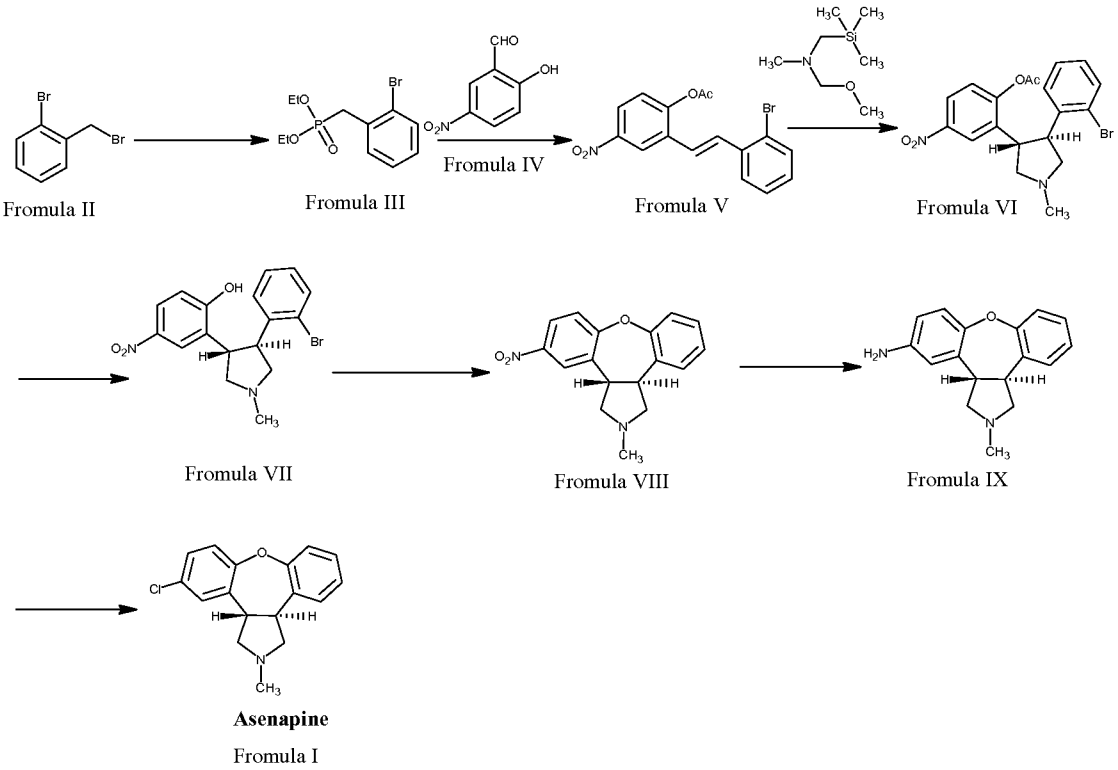
6,7]oxepino[4,5-c]pyrrole characterised in that an E-stilbene derivative is reacted with an azomethine ylide to provide a trans-pyrrolidine derivative is treated under conditions which effect an intramolecular ring closure reaction to produce trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino-[4,5-c]pyrrole.



Asenapine

Scheme-II

IN 3008/MUM/2011 Indian patent application filled by the Applicatn discloses process for the preparation of Asenapine. This process involves the preparation of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (Asenapine) of formula (I). It also relates to novel intermediates i.e. 2-[(*E*)-2-(2-bromophenyl)ethenyl]-4-nitrophenyl acetate of formula (V), 2-[(3*S*,4*S*)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenyl acetate of formula (VI), 2-[(3*S*,4*S*)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenol of formula (VII), 5-nitro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole of formula (VIII) and 5-amino-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole of formula (IX).



Scheme-III

There is a need for synthetic procedures for the preparation of asenapine which can reliably be carried out on an industrial scale.

When reproducing the procedure of U.S. Pat. No. 4,145,434, WO 2006/106136, WO 1998/54186 and EP 0,569,096 patent applications. Vader et al. (Labelled Comp. Radiopharm., 34(9), 845-869, 1994) we found out, that the intermediate compounds as prepared by this method required subsequent chromatographic purification as it was an oily substance with a relatively high content of process impurities. It is difficult to manage to find a solvent that would enable purification of this substance by crystallization.

However, the method in accordance with the prior art does not make it possible to prepare Asenapine maleate with high purity, which is required in the case of a pharmaceutical substance, and in a yield acceptable in the industrial scale. The reason is

mainly low purity of the intermediate products, which are moreover produced in forms requiring complicated purification with the use of chromatographic methods.

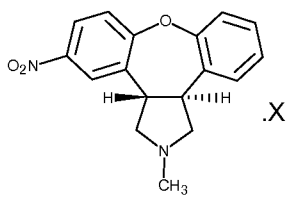
Several methods for the preparation of Asenapine maleate have been described. Like any synthetic compound, Asenapine maleate can contain process impurities, unreacted starting materials, chemical derivatives of impurities contained in starting materials, synthetic by-products, and degradation products. It is also known in the art that impurities present in an active pharmaceutical ingredient ("API") may arise from degradation of the API, for example, during storage or during the manufacturing process, including the chemical synthesis.

While developing a process for the preparation of Asenapine maleate, present inventors serendipitously found an improved process for the preparation of highly pure Asenapine maleate which minimizes process impurity.

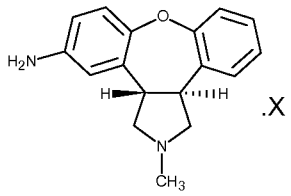
OBJECT OF THE INVENTION

Therefore, it is an object of the invention to provide novel process for the preparation of substantially pure trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (Asenapine maleate)

Another object of the invention to provide novel salts of intermediates 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa) and 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) are useful for the preparation of Asenapine maleate of formula (I)



Fromula VIIIa



Fromula IXa

Wherein X represent salts of inorganic or organic acids selected form the group of such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

Yet another object of the invention is to provide a process for the preparation of novel salts of intermediates 5-nitro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole of formula (VIIIa) and 5-amino-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino[4,5-c]pyrrole of formula (IXa) are useful for the preparation of Asenapine of formula (I)

SUMMARY OF THE INVENTION

An aspect of the present invention is related to process for the preparation of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino[4,5-c]pyrrole (Formula I) comprising:

a) reacting E-stilbene derivative 2-[(*E*)-2-(2-bromophenyl)ethenyl]-4-nitrophenyl acetate of formula (V) with N-methoxymetlyl-N-trimethylsilylmethyl-N-methylamine of formula X to obtain compound of formula VI;

b) compound of formula (VI) is treated with alcoholic solvent and base such as sodium hydroxide or potassium hydroxide to obtain compound of formula (VII);

c) intermolecular ring closure of compound of formula (VII) in presence of copper or copper (I) salts or with Copper(II) salts and solvent to obtain trans-5-nitro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino-[4,5-c]pyrrole compound of formula (VIII);

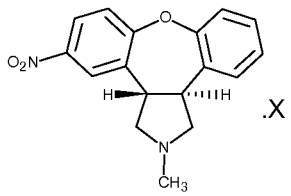
d) compound of formula (VIII) is treated with acid to obtain compound of formula (VIIIa);

e) compound of formula (VIIIa) is reduced to compound of formula (IX);

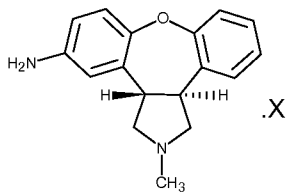
f) compound of formula (IX) is treated with acid to obtain compound of formula (IXa);

g) chlorination of compound of formula (IXa) to obtain Asenapine of formula (I).

Another aspect of the invention is related to the invention to provide novel salts of intermediates 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa) and 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) are useful for the preparation of Asenapine salts of formula (I)



Fromula VIIIa



Fromula IXa

Wherein X represent salts of inorganic or organic acids selected form the group of such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric

acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

Yet another aspect of the invention is related to the process for preparing novel salts of intermediates 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole (VIIIa) and 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa).

The fumaric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

The maleic acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

The hydrochloric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

The p-toluenesulfonic acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

The tartaric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

The fumaric acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

The maleic acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

The hydrochloric acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

The p-toluenesulfonic acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

The tartaric acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

Yet another aspect of the invention is related to the process for Asenapine comprising steps of:

a) reducing fumaric acid salts of trans-5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa) in the presence of reducing agent and solvent to obtain trans-5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IX);
b) treating trans-5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IX) with fumaric acid to obtain fumaric acid salts of trans-5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa);
c) chlorination of fumaric acid salts of trans-5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) to obtain Asenapine of formula (I).

DETAILS DESCRIPTION OF THE INVENTION

Here the term “crystallizing” means crystallizing compounds using methods known in the art. For example either reducing the volume of the solvent with respect to solute or decreasing the temperature of the solution or using both so as to crystallize the compound.

The term "treating" as used hereinabove refers to suspending, dissolving or mixing and contacting or reacting of product with solvent or reagents followed by isolating product by removal of reagents and solvents.

The term "triturating" as used hereinabove refers to suspending product in solvent and stirring for period of time sufficient for surface contact of solid with solvent and then filtering the compound from the mixture.

The term "acid" as used hereinabove used for acid addition salts refers of inorganic or organic acids selected form the group of such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

In the preferred embodiment of the invention relates to a process for the large-scale industrial preparation of the substantially pure trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino[4,5-c]pyrrole maleate (Asenapine maleate)

In the preferred embodiment of the present invention provides a process for the preparation of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino[4,5-c]pyrrole (Formula I) comprising:

a) reacting E-stilbene derivative 2-[(*E*)-2-(2-bromophenyl)ethenyl]-4-nitrophenyl acetate of formula (V) with N-methoxymetlyl-N-trimethylsilylmethyl-N-methylamine of formula (X) to obtain compound of formula (VI);
b) compound of formula (VI) is treated with alcoholic solvent and base such as sodium hydroxide or potassium hydroxide to obtain compound of formula (VII);
c) intermolecular ring closure of compound of formula (VII) in presence of copper or copper (I) salts or with Copper(II) salts and solvent to obtain trans-5-nitro-2-

methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino-[4,5-c]pyrrole compound of formula (VIII);

d) compound of formula (VIII) is treated with acid to obtain compound of formula (VIIIa);

e) compound of formula (VIIIa) is reduced to compound of formula (IX);

f) compound of formula (IX) is treated with acid to obtain compound of formula (IXa);

g) chlorination of compound of formula (IXa) to obtain Asenapine of formula (I).

Throughout this disclosure, compounds represented by structural formula having a pair of bold and hashed wedged bonds, as shown, e.g., in the formula of compounds (I) and (VIII), refer to the "trans" diastereoisomer. Each of the compounds may exist as a single enantiomer having the absolute stereochemical configuration indicated by the wedged bonds, or having the opposite absolute configuration, or as a mixture of enantiomers (e.g., racemate) having the relative stereochemical configuration indicated by the wedged bonds.

In a first reaction step of the process of the invention, an E-stilbene derivative of Formula (V) is reacted in a N-methoxymetlyl-N-trimethylsilylmethyl-N-methylamine to provide a trans-pyrrolidine derivative of Formula (VI). It is thought that the reaction proceeds in a concerted manner in which all bonds are created simultaneously. Consequently, the stereochemistry is conserved in the product. When the reaction is started with an E-stilbene derivative, the trans pyrrolidine ring is formed exclusively. The stereoselectivity of the dipolar addition step in the process of the invention represents a large advantage with respect to the good overall yield of the process.

In the second step of the process, 2-[(3*S*,4*S*)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenyl acetate of formula (VI) is treated with alcoholic solvent and base such as sodium hydroxide or potassium hydroxide to obtain 2-[(3*S*,4*S*)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenol of formula (VII).

In the third step of the process, the trans-pyrrolidine derivative 2-[(3*S*,4*S*)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenol of formula (VII) is treated under conditions which effect an intramolecular ring closure reaction to produce trans-5-nitro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3: 6,7]oxepino-[4,5-c]pyrrole of Formula (VIII).

The intramolecular ring closure reaction to form the 7-membered oxepine ring of asenapine can be performed with an Ullmann-type reaction, i.e. treatment of a compound of Formula (IIIa) in a solvent with copper(0) powder, with a copper(I) salt or with a copper (II) salt in the presence of a base at elevated temperatures (Ma,D., Cai,Q., *Organic Letters,* 5, 3799-3802, 2003; Buck, E., et. al, *Organic Letters* 4, 1623-1626, 202; Sawyer, J. S., *Tetrahedron* 5045-5065, 2002). An additive, such as N,N-dimethylglycine, N-methylglycine, 2,2,4,4-tetramethyl-3,5-heptanedione (TMHD) or 8-hydroxyquinoline, may be used to increase the solubility of the copper ions. Suitable bases include Cs_2CO_3, K_2CO_3, pyridine, NaOH, KOH or CsF. Useful copper sources include Cu-powder, CuI, CuBr, CuCl, $Cu(CO)_3$ (copper(II)carbonate, $Cu(OAc)_2$ (copper(II)acetate), $Cu(OTf)_2$ (copper(II)trifluoromethanesulfonate), Cu_2O or $CuSO_4$.

Suitable conditions for complete conversion of a compound of 2-[(3*S*,4*S*)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenol of formula (VII) of Formula (VII) to trans-5-nitro -2-methyl-2,3,3a,12b -tetrahydro- 1H-dibenz [2,3:6,7]oxepino-[4,5-c] pyrrole of Formula (VIII) are the use of CuI, N,N-dimethylglycine and Cs_2CO_3. Solvents for use in the Ullman cyclisation reaction on an industrial scale are dimethylformamide (DMF), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), pyridine, dioxane, toluene, xylene, diethyleneglycoldimethylether (Diglyme), 2-methyltetrahydrofuran, and the like.

Preferred reaction conditions for the Ullman cyclisation reaction at industrial scale are the use of dimethylacetamide or mixtures thereof with toluene as the solvent system, the use of Cs_2CO_3, NaOH, KOH or K_2CO_3 as the base, and the use of dimethylglycine in combination with copper(I)iodide as the catalyst.

In the fourth step of the process the compound of formula (VIII), which is further reacted directly, according to the invention, optionally without being isolated, using the procedure described below, to obtain the compound of formula (VIIIa).

The compound of formula (VIII) is combined with solvent, preferably with halogenated hydrocarbons, or alcohols. More preferred is a solvent are such as methylene chloride, trichloroethylene or tetrachloroethylene or methanol or ethanol or propanol or isopropanol or butanol. If the resulting mixture is heated, a temperature of preferably about 25-50° C, preferably 30-40° C, particularly preferably 32-38° C is selected. Then acid is added. It is particularly preferable to use concentrated acid. Sufficient acid is added at constant temperature, with stirring, until the pH of the mixture obtained is less than 3, preferably less than 2, and particularly preferably is in the range between pH 0.6-1.3.

After the addition of the acid has ended the mixture obtained is stirred for a further period of at least 5 to 60 min (minutes), preferably at least 10 to 45 min, particularly preferably at least 20 to 30 min. During this time the solution is preferably maintained in one of the above-mentioned temperature ranges, while the temperature is particularly preferably kept constant. Then the resulting mixture is preferably cooled to a temperature in the range from 0 to 20° C., preferably 5 to 15° C., particularly preferably 7-13° C. and stirred at this temperature for a further period of at least 0.5 to 2 h (hours), preferably at least 0.75 to 1.5 h, particularly preferably at least 1 h.

The acid used to obtain an acid addition salt of compound of formula (VIII) may be for example an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or with an organic acid such as, for example, ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

The resulting suspension of compound of formula (VIIIa) in halogenated hydrocarbons, or alcohols is then freed from the solvent by centrifuging and the residue remaining is optionally washed with one of the above-mentioned halogenated hydrocarbons, or alcohols. The compound of formula (VIIIa) obtained is then dried in vacuo at a temperature of not more than 30-65° C., preferably not more than 50-60° C.

In the preferred embodiment of the present invention further relates to the acid salt of compound of formula (VIIIa)

Surprisingly it has been found that this salt of the compound of formula (VIII) is particularly easy to separate off, which makes it significantly simpler to isolate this intermediate product during reactions on an industrial scale. By ease of separation is meant, within the scope of the present invention, the ability to free the resulting crystalline product from the solvent by filtration, suction filtering, centrifuging or comparable methods of isolation. An improvement to the separation qualities has a direct effect on the throughput of the process and is therefore of exceptional importance, particularly when carrying out reactions on an industrial scale. The product, having better separation qualities, can be isolated faster, washed faster and better and hence dried faster as well.

In the fifth step of the process the compound of formula (IX) may be obtained from the compound of formula (VIIIa) using the following procedure.

In the preferred embodiment of the invention is related to the process for Asenapine wherein reducing trans-5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa) in the presence of reducing agent and solvent to obtain trans-5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IX).

In the sixth step of the process the compound of formula (IXa) may be obtained from the compound of formula (IX) using the following procedure.

The compound of formula (IX) is combined with solvent, preferably with halogenated hydrocarbons, or alcohols. More preferred is a solvent are such as methylene chloride, trichloroethylene or tetrachloroethylene or methanol or ethanol or propanol or isopropanol or butanol. Then acid is added. It is particularly preferable to use concentrated acid. Sufficient acid is added at constant temperature, with stirring, until the pH of the mixture obtained is less than 3, preferably less than 2, and particularly preferably is in the range between pH 0.6-1.3.

After the addition of the acid has ended the mixture obtained is stirred for a further period of at least 5 to 60 min (minutes), preferably at least 10 to 45 min, particularly preferably at least 20 to 30 min. During this time the solution is preferably maintained in one of the above-mentioned temperature ranges, while the temperature is particularly preferably kept constant. Then the resulting mixture is preferably cooled to a temperature in the range from 0 to 20° C., preferably 5 to 15° C., particularly preferably 7-13° C. and stirred at this temperature for a further period of at least 0.5 to 2 h (hours), preferably at least 0.75 to 1.5 h, particularly preferably at least 1 h.

The acid used to obtain an acid addition salt of compound of formula (IX) may be for example an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or with an organic acid such as, for example, ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

The resulting suspension of compound of formula (IXa) in halogenated hydrocarbons, or alcohols is then freed from the solvent by centrifuging and the residue remaining is optionally washed with one of the above-mentioned halogenated hydrocarbons, or

alcohols. The compound of formula (IXa) obtained is then dried in vacuo at a temperature of not more than 30-65° C., preferably not more than 50-60° C.

In the preferred embodiment of the present invention further relates to the acid salt of compound of formula (IXa)

Surprisingly it has been found that the salt of the compound of formula (IXa) is particularly easy to separate off, which makes it significantly simpler to isolate this intermediate product during reactions on an industrial scale. By ease of separation is meant, within the scope of the present invention, the ability to free the resulting crystalline product from the solvent by filtration, suction filtering, centrifuging or comparable methods of isolation. An improvement to the separation qualities has a direct effect on the throughput of the process and is therefore of exceptional importance, particularly when carrying out reactions on an industrial scale. The product, having better separation qualities, can be isolated faster, washed faster and better and hence dried faster as well.

In the seventh step of the process the Asenapine is obtained from the compound of formula (IXa) using the following procedure.

The process or present invention is related to chlorinating trans-5-amino -2-methyl-2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) to obtain Asenapine of formula (I).

In accordance with the present invention for chlorinating trans-5-amino -2-methyl-2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) with chlorine to produce the corresponding Asenapine of formula (I), in which formula (IXa) is chlorinated in a reaction medium consisting of nitrile solvent or alcohols in the presence of Cupric chloride which causes chlorination of the amine. Optionally, anhydrous conditions are required. An inert atmosphere, such as nitrogen, can be used to facilitate maintenance of substantially anhydrous reaction conditions. Atmospheric

pressure is generally used as hydrogen chloride is evolved. However, subatmospheric pressures can be used provided the overall temperature-pressure conditions do not cause the reaction media to boil and cool the media excessively.

A "nitrile solvent" is an organic solvent containing a cyano -(C≡N) bonded to another carbon atom. "Nitrile solvents" include, but are not limited to, tert-butyl nitrite, acetonitrile, propionitrile, C_{2-6}nitriles, or the like.

Cupric chloride employed in the process of the present invention is made present in the reaction system by adding thereto anhydrous cupric chloride, cupric chloride dihydrate, or a material which is converted to cupric chloride in hot aqueous hydrochloric acid, for example, cupric oxide, cupric sulfate, or cupric acetate or a material which is converted to cupric chloride by chlorine in the reaction solution, for example, cuprous oxide, cuprous chloride, or cuprous acetate.

The mixture obtained upon completion of the chlorination contains asenapine which may be isolated by ordinary isolating treatment. Asenapine may also be transformed in an acid addition salt. The isolated asenapine or its acid addition salt may be purified by ordinary purification means such as column chromatography or recrystallization, high vacuum distillation respectively.

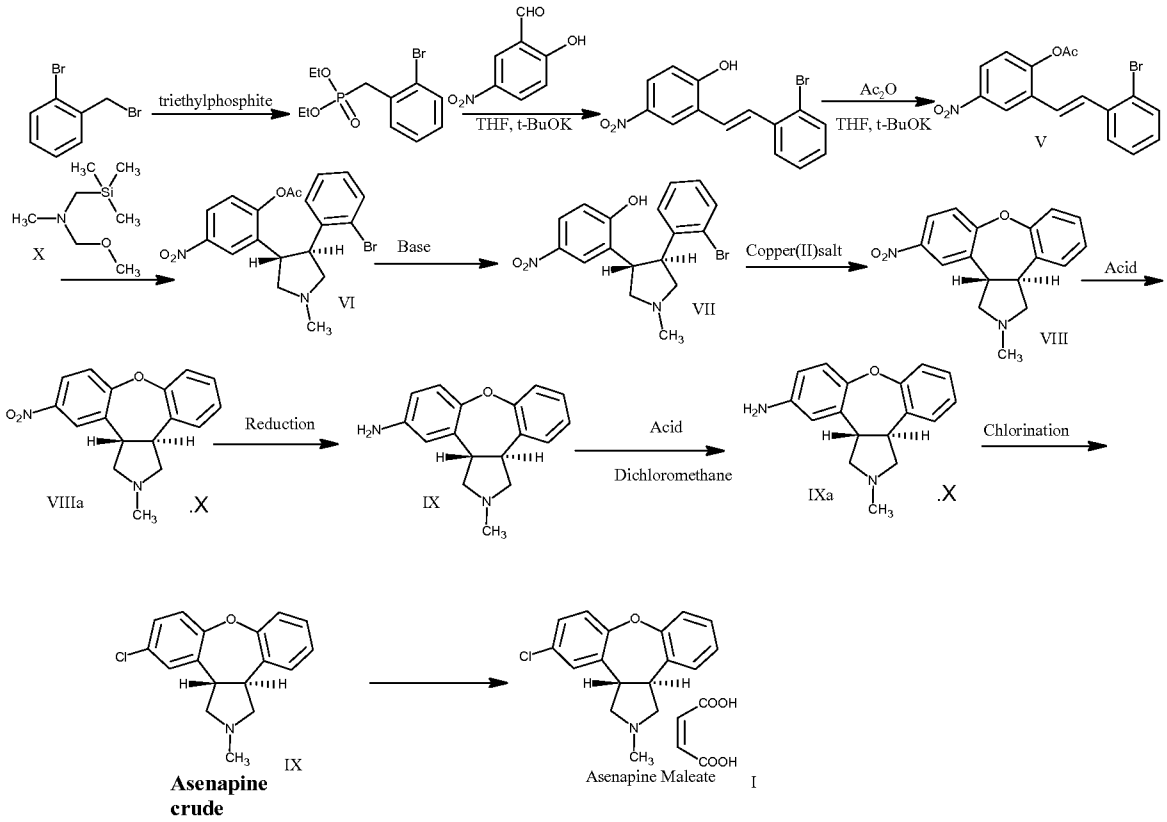
In the preferred embodiment of the present invention asenapine can be further purified via an acid addition salt thereof that, after being isolated and, optionally, purified is transformed again into asenapine by treatment with an organic or inorganic base. Asenapine isolated is combined with solvent, preferably with halogenated hydrocarbons, or alcohols. More preferred is a solvent are such as methylene chloride, trichloroethylene or tetrachloroethylene or methanol or ethanol or propanol or isopropanol or butanol and then acid is added, after the addition of the acid has ended the mixture obtained is stirred. The mixture obtained upon completion of the acid addition salt contains asenapine salt which may be isolated by ordinary isolating treatment. The salt of asenapine thus

obtained is further treated with organic or inorganic base to obtain pure free base of Asenapine.

The acid used to obtain an acid addition salt of asenapine may be for example an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or with an organic acid such as, for example, ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, (−)-Diisopropyl D-tartrate, Di-1,4-toluoyl-D-tartaric acid, Dibenzoyl-D-tartaric acid, (4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-dimethanol, (4R,5R)-2,2-Dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol, (−)-2,3-O-Isopropylidene-1,1,4,4-tetraphenyl-L-threitol, (R,R)-(-)-Dimethyl-2,3-O-isopropylidene-L-tartrate, (+)-Diethyl L-tartrate, (+)-Dimethyl L-tartrate and methane sulfonic acid.

In the preferred embodiment of the present invention relates to process for the preparation of Asenapine Maleate. Pure asenapine is combined with solvent, preferably with halogenated hydrocarbons, or alcohols. More preferred is a solvent are such as methylene chloride, trichloroethylene or tetrachloroethylene or methanol or ethanol or propanol or isopropanol or butanol and then maleic acid is added, after the addition of the maleic acid has ended the mixture obtained is stirred. The mixture obtained upon completion of the acid addition salt contains asenapine maleate which may be isolated by ordinary isolating treatment.

The process for the preparation of Asenapine maleate depicts below in Scheme-IV:



Scheme-IV

The following Examples serve to illustrate a synthesis process carried out by way of example. They are intended solely as examples of possible procedures without restricting the invention to their contents.

Example 1: Preparation of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

To a mixture of 2-[(3S,4S)-4-(2-bromophenyl)-1-methylpyrrolidin-3-yl]-4-nitrophenol (100 gm) and toluene (800 ml) were added under a nitrogen atmosphere cesium carbonate (172.68 gm), N,N dimethylglycine (36.98 gm), N,N-dimethylacetamide (200 ml) and cuprous chloride (26.23 gm). The mixture was heated to reflux, stirred for 20-26 hours at reflux temperature and azeotropically reflux in dean stark column. The residue

was dissolved in toluene (100 ml) and washed twice with ammonia (50 ml) and with water (50 ml). The toluene layer was dried on magnesium sulphate and evaporated.

Example 2: Preparation of fumaric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

Fumaric acid (27.68 gm) was added to solution of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole in acetone (200ml) at 40-65°C. The mixture was stirred at 50-55°C temperature. The mixture was allowed to bring at room temperature stirred for 1 to 10 hours at room temperature. The obtained solid was than filtered, washed with isopropyl alcohol and dried.

Example 3: Preparation of Maleic acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

Maleic acid (27.68 gm) was added to solution of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole in acetone (200ml) at 40-65°C. The mixture was stirred at 50-55°C temperature. The mixture was allowed to bring at room temperature stirred for 1 to 10 hours at room temperature. The obtained solid was than filtered, washed with isopropyl alcohol and dried.

Example 3: Preparation of hydrochloric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole

Hydrochloric acid (420ml) was added to solution of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole in acetone (200ml) at 40-65°C. The mixture was stirred at 50-55°C temperature. The mixture was allowed to bring at room temperature stirred for 1 to 10 hours at room temperature. The obtained solid was than filtered, washed with isopropyl alcohol and dried.

Example 4: Preparation of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole (30gm) were dissolved in 600ml methanol and phosphorous acid and 24 gm of 10gm palladium on charcoal were added. The reaction mixture was refluxed for 1 hour, cooled to room temperature and filtered over hyflo. Aqueous sodium hydroxide was added and the mixture was extracted with ethyl acetate. The crude 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole was obtained in nearly quantitative yield (268 mg, 1.0 mmol) and used without further purification.

Example 5: Preparation of fumaric acid salts of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

Fumaric acid (27.68 gm) was added to solution of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole in acetone (200ml) at 40-65°C. The mixture was stirred at 50-55°C temperature. The mixture was allowed to bring at room temperature stirred for 1 to 10 hours at room temperature. The obtained solid was than filtered, washed with isopropyl alcohol and dried.

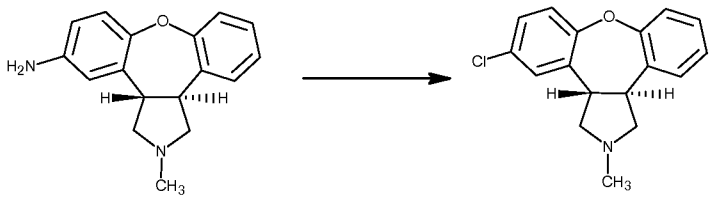
Example 6: Preparation of maleic acid salts of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

Maleic acid salts (27.68 gm) was added to solution of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole in acetone (200ml) at 40-65°C. The mixture was stirred at 50-55°C temperature. The mixture was allowed to bring at room temperature stirred for 1 to 10 hours at room temperature. The obtained solid was than filtered, washed with isopropyl alcohol and dried.

Example 7: Preparation of Hydrochloric acid salts of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

Hydrochloric acid (420ml) was added to solution of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole in acetone (200ml) at 40-65°C. The mixture was stirred at 50-55°C temperature. The mixture was allowed to bring at room temperature stirred for 1 to 10 hours at room temperature. The obtained solid was than filtered, washed with isopropyl alcohol and dried.

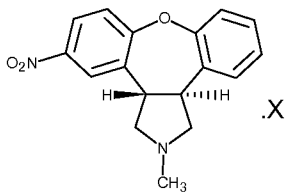
Example 8: Preparation of Asenapine Maleate



5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole (35gm) were dissolved in 200ml hydrochloric acid and cooled to 0°C. 10 gm sodium nitrite (27.93gm) was added and the mixture was stirred for 30 minutes at 0°C. A few milligrams of copper chloride (66.79gm) were added and the reaction mixture was stirred for 1 hour at room temperature. Volatiles were evaporated in a stream of dry nitrogen, aqueous ammonia solution was added and the aqueous slurry was extracted with ethyl acetate and ammonia solution. The resulting product was purified with cyclohexane and ethyl acetate. Further purification is of the residue on silica gel ethyl acetate in cyclohexane (35%) afforded pure asenapine. The asenapine (100gm) was dissolved in n-propanol/ n-butyl alcohol (300ml). To this solution was added a solution of maleic acid (41.62 gram) in n-propanol. The mixture was stirred the asenapine maleate was collected and dried under vacuum at 40° C.

We Claim,

1. The salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa)



Fromula VIIIa

Wherein X represent inorganic or organic acids salts

comprises:

a) The fumaric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole;

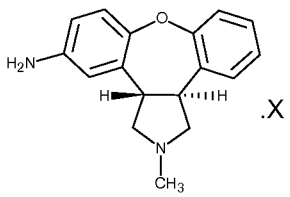
b) The maleic acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole;

c) The hydrochloric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole;

d) The p-toluenesulfonic acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole;

e) The tartaric acid salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole;

2. The salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa)



Fromula IXa

Wherein X represent inorganic or organic acids salts

comprises:

a) The fumaric acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

b) The maleic acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole
c) The hydrochloric acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole
d) The p-toluenesulfonic acid salts of 5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole
e) The tartaric acid salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole

3. A process for preparing salts of 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole comprising reacting 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole with inorganic or organic acids salts.

4. A process for preparing salts of 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole comprising reacting 5-amino -2-methyl-2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole with inorganic or organic acids salts.

5. A process for preparing salts according to claim 3 and 4 wherein salts is inorganic or organic acids selected form the group of such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

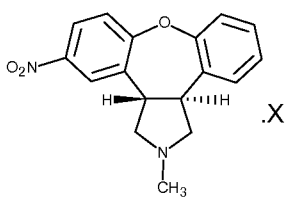
6. A process for preparing 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole fumaric acid salts comprising reacting 5-nitro -2-

methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole with fumaric acid.

7. A process for preparing 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole fumaric acid salts comprising reacting 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole with fumaric acid.

8. A process for Asenapine comprising steps of:
   a) reducing fumaric acid salts of trans-5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa) in the presence of reducing agent and solvent to obtain trans-5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IX);
   b) treating trans-5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IX) with fumaric acid to obtain fumaric acid salts of trans-5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa);
   c) chlorination of fumaric acid salts of trans-5-amino -2-methyl- 2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) to obtain Asenapine of formula (I).

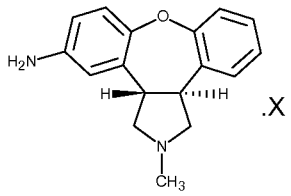
9. Use of salts of intermediates 5-nitro -2-methyl -2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole of formula (VIIIa) for the preparation of Asenapine



Fromula VIIIa

Wherein X represent salts of inorganic or organic acids selected form the group of such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

10. Use of salts of intermediates 5-amino -2-methyl- 2,3,3a,12b- tetrahydro-1H-dibenz [2,3:6,7] oxepino[4,5-c] pyrrole of formula (IXa) for the preparation of Asenapine



Fromula IXa

Wherein X represent salts of inorganic or organic acids selected form the group of such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, trifluoromethanesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, tetrakis(pentafluorophenyl)boric acid, and sulfuric acid, or ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, oxalic acid, and methane sulfonic acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/055026

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D491/-, C07D209/-, C07D207/-, C07D313/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases: WPI; EPODOC; STN; CNKI; CPRS; Keywords: asenapine, oxepino+, nitro, amino, salt, pyrrole+, maleate, CAS-RN: 65576-45-6, 135882-95-0, 1403259-30-2, 165890-03-9, 165890-04-0

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PA	WO 2013061247 A1 (ALEMBIC PHARMACEUTICALS LIMITED et al.), 02 May 2013(02.05.2013) see claims 1-9, description, pages 11-16	1-10
A	US 20080009619 A1 (N. V. ORGANON), 10 Jan. 2008(10.01.2008) see claims 1-9	1-10
A	US 20100234618 A1 (N. V. ORGANON), 16 Sept. 2010(16.09.2010) see claims 1-4, examples 1-6	1-10
A	US 4145434 A (AKZO INCORPORATED), 20 Mar. 1979(20.03.1979) see claims 1-35	1-10
A	WO 2008003460 A1 (N. V. ORGANON et al.), 10 Jan. 2008(10.01.2008) see claims 1-11	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 Sept. 2013(26.09.2013)	**07 Nov. 2013 (07.11.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WEN, Guoyong Telephone No. (86-10)82246762

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/055026

Continuation of "**CLASSIFICATION OF SUBJECT MATTER**"

C07D491/04 (2006.01) i

C07D209/58 (2006.01) i

C07D207/08 (2006.01) i

C07D313/14 (2006.01) i

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2013/055026

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INTERNATIONAL SEARCH REPORT
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International application No.
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