FORM 2

THE PATENTS ACT 1970

(39 of 1970)

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The Patents [Amendment] Rules, 2006

COMPLETE SPECIFICATION

(*See* section 10; rule 13)

1. TITLE OF THE INVENTION

AN IMPROVED PROCESS FOR THE PREPARATION OF LUMATEPERONE OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS

2. APPLICANT

NAME : Alkem Laboratories Limited

NATIONALITY : Indian

ADDRESS : ALKEM HOUSE, SENAPATI BAPAT MARG, LOWER PAREL, MUMBAI – 400013

3. PREAMBLE TO THE DESCRIPTION

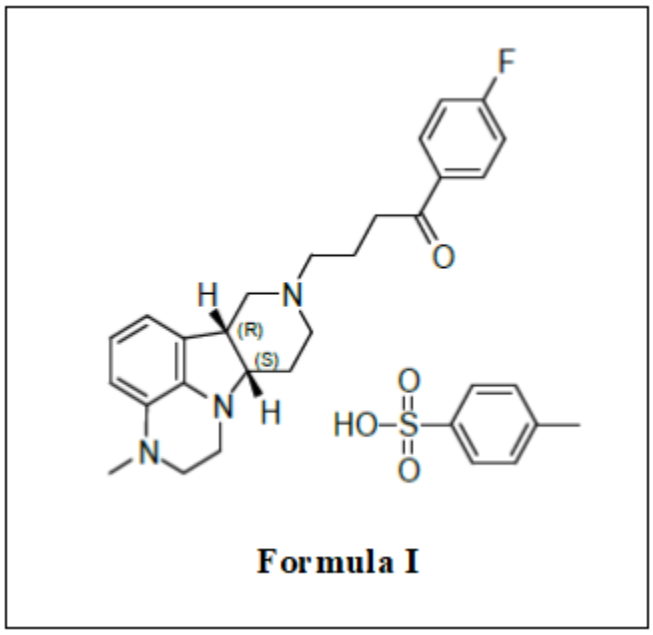
The following specification particularly describes the invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention provides an improved process for the preparation of Lumateperone or its pharmaceutically acceptable salts substantially free from process impurities. The present invention also provides a novel intermediate and its use in the preparation of Lumateperone or its pharmaceutically acceptable salts. The present invention further provides a process for preparation of a novel intermediate.

BACKGROUND OF THE INVENTION

Lumateperone tosylate salt is chemically, 4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3de]quinoxalin-8-yl)-1-(4-fluoro-phenyl)-butan-1-one-4-methylbenzenesulfonate. Its molecular formula is $C_{31}H_{36}FN_3O_4S$ and it has a molecular weight of 565.71 g/mol. Lumateperone tosylate is represented by the following structure:

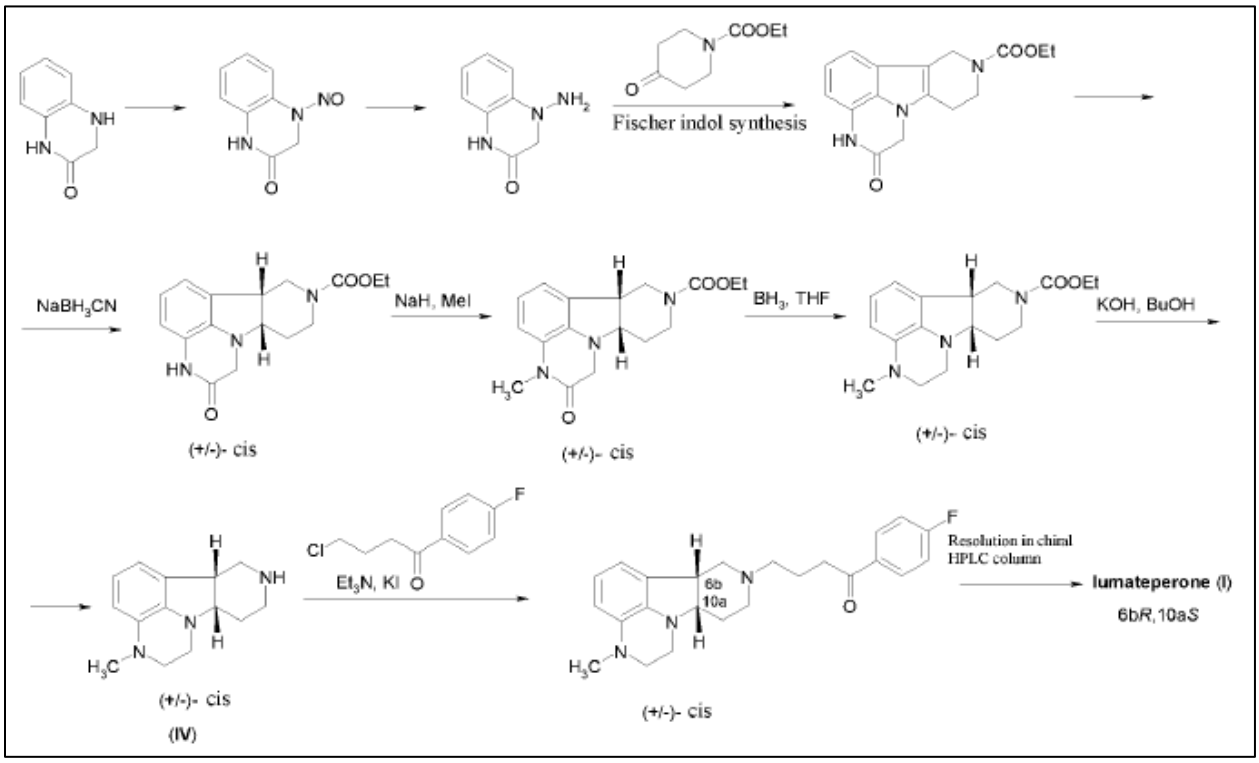


Formula I

Lumateperone Tosylate (ITI-007, trade name: Caplyta) is a new molecular entity atypical antipsychotic that has been approved by USFDA for the treatment of schizophrenia on 20th December 2019. Lumateperone Tosylate is also being developed for the treatment of sleep

disorders, depression, and other neuropsychiatric and neurological disorders. Lumateperone Tosylate appears to function as a serotonin 5HT2A and postsynaptic dopamine D2 receptor antagonist. In addition, Lumateperone Tosylate displays relatively high binding affinity for the serotonin transporter (SERT).

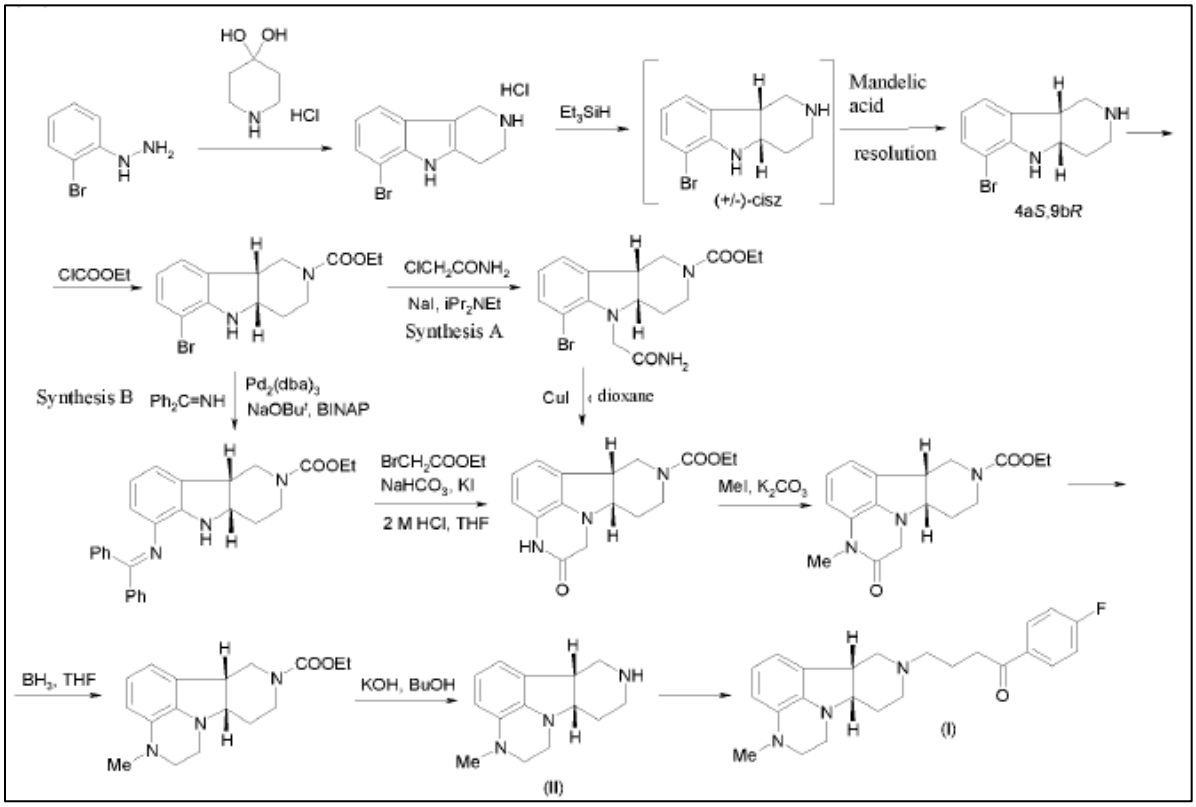
W02000077002 discloses the process for the preparation of a racemate containing Lumateperone and its enantiomer, then formula (I), Lumateperone is obtained by resolution the latter with chiral HPLC (Scheme 1).



Scheme 1

The key step is the reaction between (6bR,10aS)-2,3,6b,7,8,9,10,10a-Octahydro-3-methyl-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline **(Formula IV)** and 4-chloro-4′-fluoro-butyrophenone. The powdered potassium hydroxide is added to a stirred solution of ethyl (6bR, 10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3′,4′:4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (4.52 g, 15.0 mmol) in warm 1-butanol to give compound of formula IV. This overall synthesis pathway was later published in a scientific journal (J. Med. Chem. 2014, 57, 2670).

W02008112280 discloses two methods for the production of formula (I) optically active Lumateperone (Scheme 2). An early intermediate is resolved which does not contain the quinoxaline structural part. Two methods are disclosed for constructing this latter part (pathways A and B). Among the described synthesis pathways only pathway A was shown with examples. Pathway B was only described in examples in the aforementioned scientific article for the synthesis of the racemic cis compound, in other words leaving out the resolution steps.



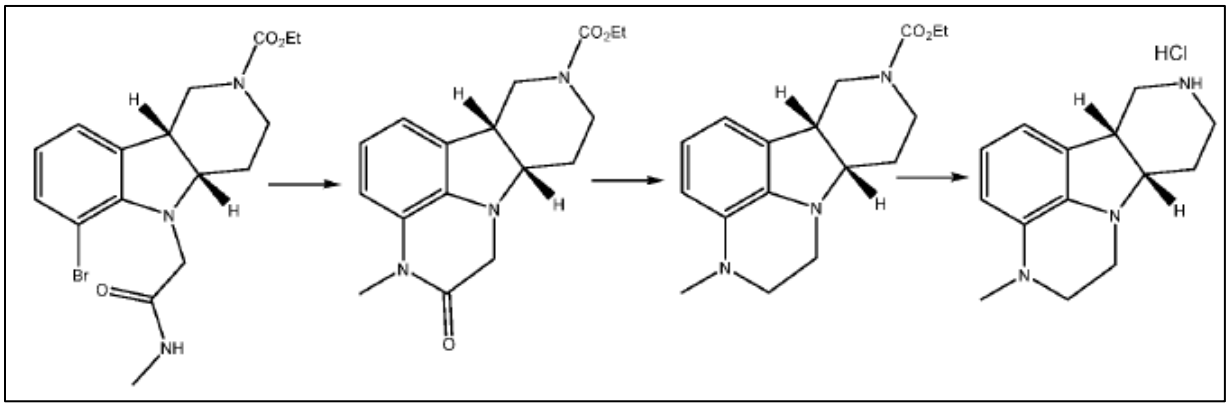
Scheme 2

W02008112280 discloses the advantages of the synthesis of Lumateperone over the synthetic pathway described in WO'002. The advantage is that the amount of material loss is reduced with the resolution after the second step.

WO2023195027A1 discloses process for the resolution of advanced amine intermediate using a chiral acid in a solvent to provide corresponding diastereomeric salt.

However, the major drawback associated with the above processes is that the compound of formula IV/II is obtained as a viscous liquid not in a solid form. Moreover, the above processes are lengthy, difficult to reproduce and contain steps that are less suited for upscaling.

WO2019241278 discloses preparation of Lumateperone from the reaction of (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3',4':4,5]pyrrolo[l,2,3-de]quinoxaline monohydrochloride salt and 4-chloro-4′-fluoro-butyrophenone. In the given publication, the (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3',4':4,5]pyrrolo[l,2,3-de]quinoxaline (Free base) is converted into monohydrochloride salt in order to get solid, crystallized product. The reaction scheme is as follows in scheme 3:



Scheme 3

WO2019102240 and CN112062767 provides the preparation of Lumateperone from the reaction of (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3',4':4,5]pyrrolo[l,2,3-de]quinoxaline dihydrochloride salt and 4-chloro-4′-fluoro-butyrophenone.

The advantage of the above processes over the W0'002 and W0'280 is that obtaining the key intermediate (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3',4':4,5]pyrrolo[l,2,3-de]quinoxaline in solid form instead of viscous liquid. However, the yield of the Lumateperone using HCl salt of the free base is very low. Moreover, synthesis of hydrochloride salt creates the risk of corrosion of manufacturing reactor and equipment, less than optimal solubility due to the risk of salting out and the potential for poor stability. The overall synthetic process become tedious.

The present inventors circumvented the above drawbacks and provides a novel intermediate and its use in the manufacturing of Lumateperone or its pharmaceutically acceptable salts substantially free from process impurities.

Therefore, the objective of the present invention is to provide a safe, environmental friendly, cost effective and commercially viable process for the preparation of oxalic acid salt of (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3',4':4,5]pyrrolo[l,2,3-de]quinoxaline and Lumateperone or its pharmaceutically acceptable salts of formula (I) with high yield and purity.

OBJECTIVES OF THE INVENTION

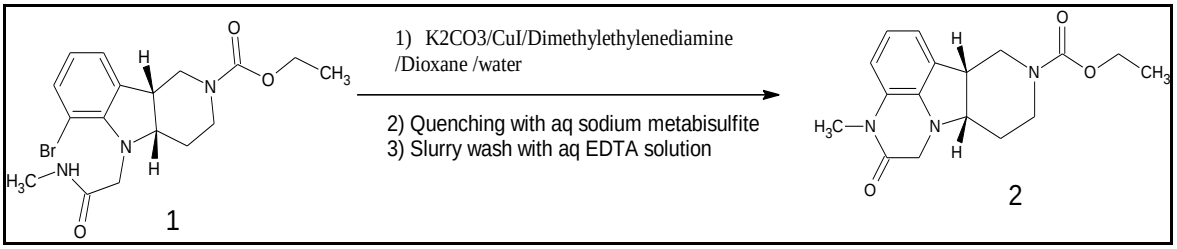
The main aspect of the present invention is to provide an improved process for the preparation of Lumateperone or its pharmaceutically acceptable salts using a novel intermediate.

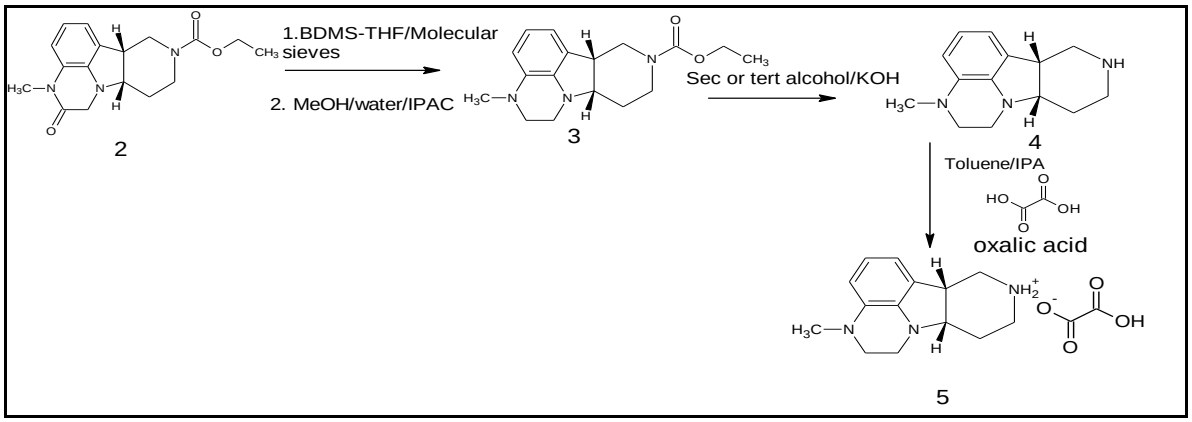
Another aspect of the present invention is to provide an improved process of the preparation of a novel intermediate.

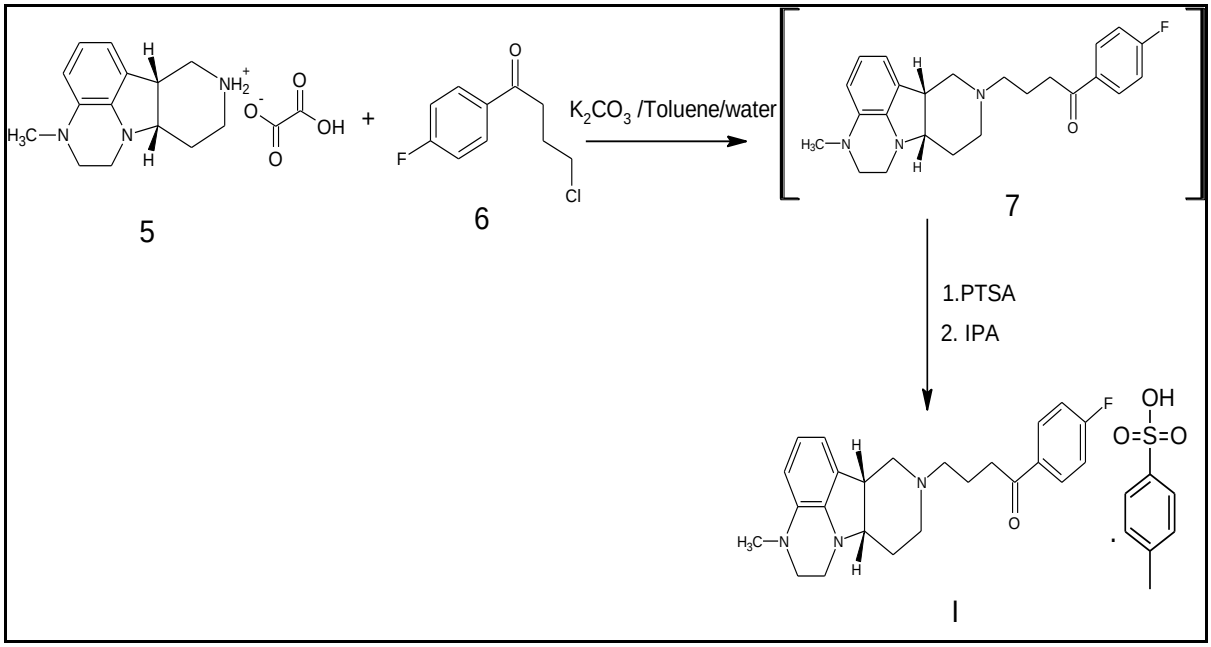
In another aspect of the present invention is to provide a scalable, cost effective and simple process to obtain a pure and high yield of Lumateperone or its pharmaceutically acceptable salts.

In another aspect of the present invention is to provide a process for the preparation of acid addition salt of Lumateperone of Formula I.

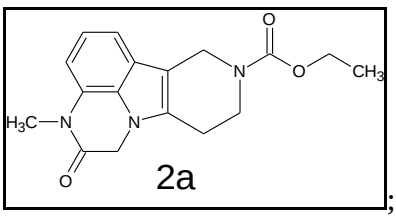
In another aspect of the present invention is to provide a process of preparing Lumateperone tosylate of formula **I** using novel intermediate of compound formula 5 comprising steps of:



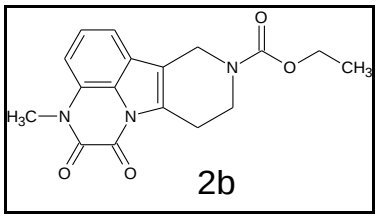


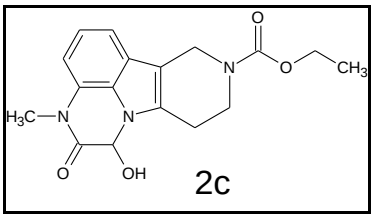


In another aspect of the present invention is to provide a process for preparation of Lumateperone tosylate of formula (**I**) free from impurities such as dehydro, oxo, hydroxy, dimer, cyclopropyl impurity, Dehydro impurity, N-oxide and nitrosamine of compound of formula 5 with a compound of formula (2a, 5a), (2b, 5b), (2c, 5c), (Ia), (Ib), (Ic) and (Id) respectively.

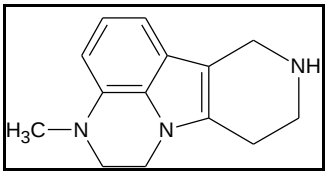


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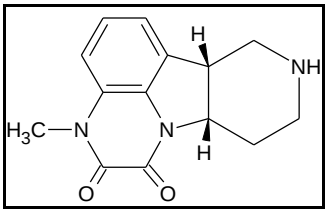




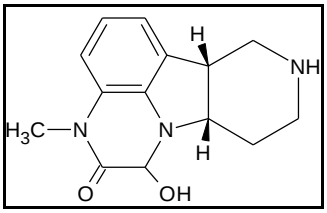
Structure of (5a)



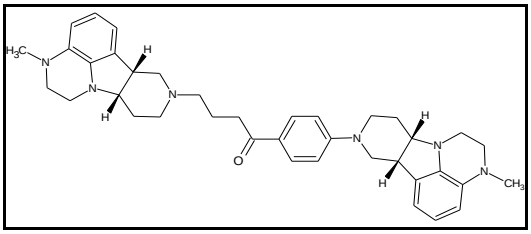
Structure of (5b)



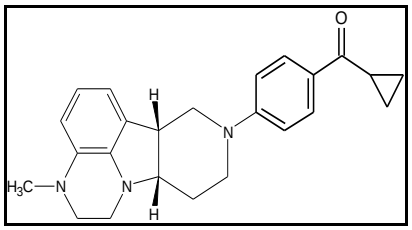
Structure of (5c)



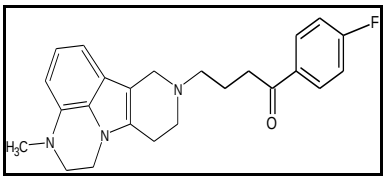
Structure (Ia)



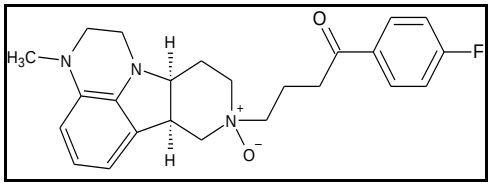
Structure (Ib)



Structure (Ic)



Structure (Id)



In another aspect of the present invention is to provide a pharmaceutical composition comprising solid form of Lumateperone or its pharmaceutically acceptable salts, wherein Lumateperone or its pharmaceutically acceptable salts is rendered more suitable for use in a pharmaceutical composition.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of Lumateperone or pharmaceutically acceptable salts thereof. The process of the present invention comprising following steps.

a. Compound with formula (1) is reacted with Dimethylethylenediamine in presence of cuprous iodide in an organic solvent and isolated as a compound of formula (2);

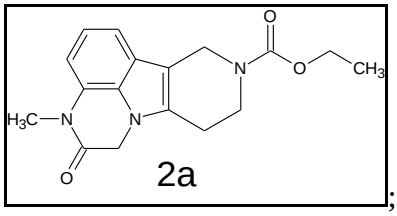
b. Reduction of compound (2) with borane dimethyl sulphide in an organic solvent to get the compound of formula (3). The compound of formula (3) undergoes hydrolysis with an inorganic

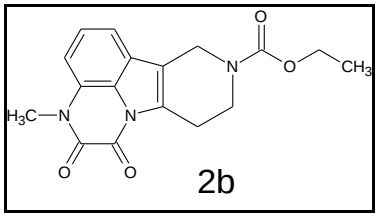
base in a secondary or tertiary alcohol to get compound of formula (4). The treatment of compound of formula (4) with an oxalic acid solution in an organic solvent to get compound of formula (5);

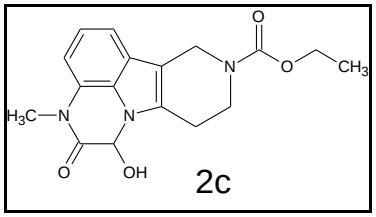
c. Reaction of compound of formula (5) with compound of formula (6) in presence of an inorganic base in presence of an organic solvent to get Lumateperone free base oil (7) *in situ*. The reaction of Lumateperone free base oil (7) with para toluene sulfonic acid in an alcoholic solvent by maintaining the pH 5.0 to 6.5 to get Lumateperone tosylate compound (I) as a crystalline solid.

In another aspect, the present invention provides a novel intermediate of compound of formula (5) and process for the preparation thereof. Further, present invention provides the use of a novel intermediate of compound of formula (5) for the preparation of Lumateperone and its pharmaceutically acceptable salts.

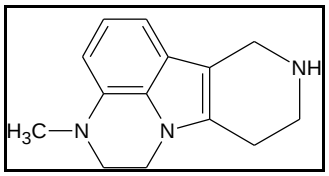
In another aspect, the present invention provides a process for the preparation of Lumateperone tosylate of compound of formula (I) free from process impurities such as dehydro, oxo, hydroxy, dimer, cyclo impurity, Dehydro impurity, N-oxide and nitrosamine with a compound of formula (2a, 5a), (2b, 5b), (2c, 5c), (Ia), (Ib), (Ic) and (Id) respectively.



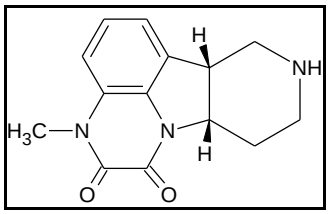
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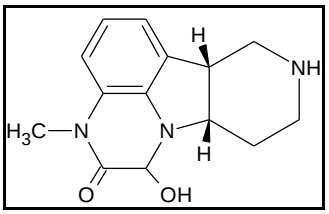
Structure of (5a)



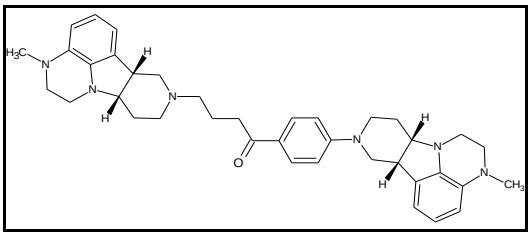
Structure of (5b)



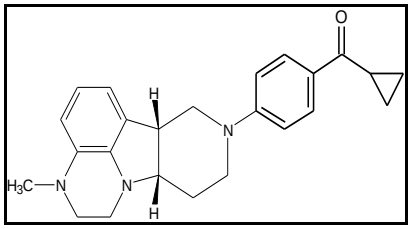
Structure of (5c)



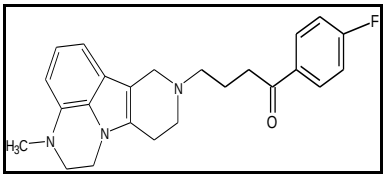
Structure (Ia)



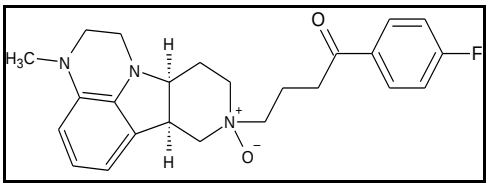
Structure (Ib)



Structure (Ic)



Structure (Id)



In another aspect, the present invention provides a pharmaceutical composition comprising solid form of Lumateperone or its pharmaceutically acceptable salts; wherein Lumateperone or its pharmaceutically acceptable salts is rendered more suitable for use in a pharmaceutical composition.

In another aspect, the present invention provides a pharmaceutical composition comprising solid form of Lumateperone or its pharmaceutically acceptable salts; wherein Lumateperone or its pharmaceutically acceptable salts is free from nitrosamine impurity.

BRIEF DESCRIPTION OF DRAWINGS OF THE INVENTION

Fig. I Illustrates the PXRD pattern of crystalline oxalate salt of compound of formula (5), a novel intermediate, obtained by process of Example 2.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides a process for the preparation of Lumateperone Tosylate using a novel intermediate comprising following steps;

a. Compound of formula (1) is reacted with dimethylethylenediamine in presence of cuprous iodide in an organic solvent followed by quenching of reaction mass in an aqueous sodium metabisulfite solution, filtration and washing of wet cake with EDTA solution to get compound of formula (2);

b. Reduction of compound (2) with borane dimethyl sulphide in THF to get compound of formula (3). The compound of formula (3) undergoes hydrolysis of compound with potassium hydroxide in a secondary or tertiary alcohol provides compound of formula (4). The treatment of compound of formula (4) with an oxalic acid in an organic acid to get compound of formula (5);

c. Reaction of compound of formula (5) with compound of formula (6) in presence of potassium carbonate in toluene provides Lumateperone free base oil (7) *in situ.* The reaction of Lumateperone free base oil (7) with para toluene sulfonic acid in an alcoholic solvent by maintaining the pH 5.0 to 6.5 gives Lumateperone tosylate salt (I) as a crystalline solid.

In one embodiment, the isolated Lumateperone tosylate salt (I) has a purity of at least 99.2% as measured by chiral HPLC.

In one another embodiment, the isolated Lumateperone tosylate salt (I) has a purity of at least 99.9% as measured by chiral HPLC.

In one embodiment, the isolated Lumateperone tosylate salt (I) has a purity of at least 99.9% as measured by chiral HPLC.

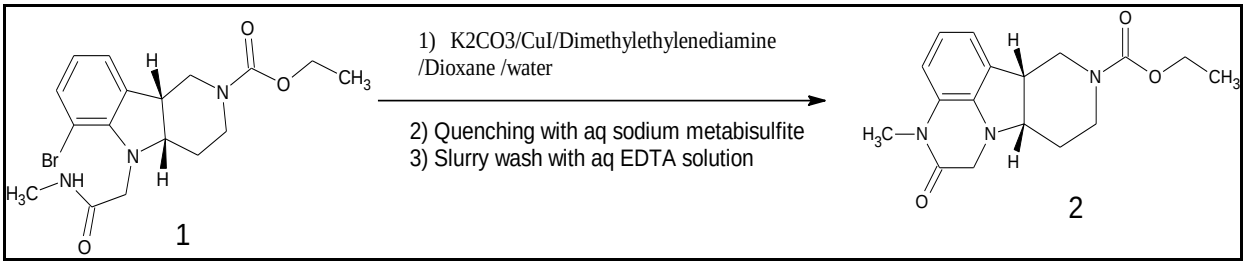
In one another embodiment, the isolated Lumateperone tosylate salt (I) has a purity of at least 99.9% as measured by chiral HPLC and wherein the content of impurity is less than 1%w/w.

In one embodiment, the isolated Lumateperone tosylate salt (I) has a purity of at least 99.9% as measured by chiral HPLC and wherein the content of nitrosamine impurity is less than 1%w/w.

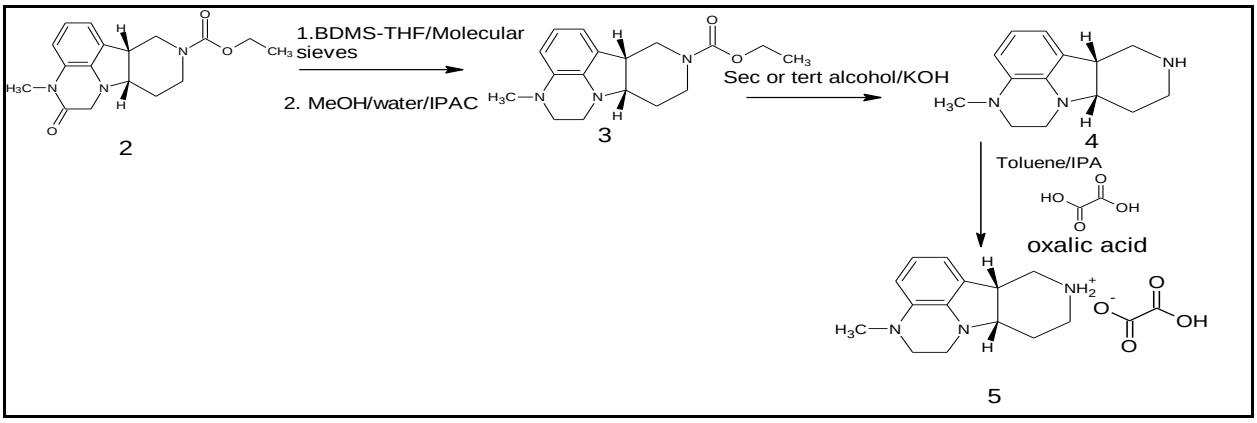
The process for the preparation of Lumateperone tosylate of the present invention is schematically represented in the scheme 4 below:

Scheme 4:

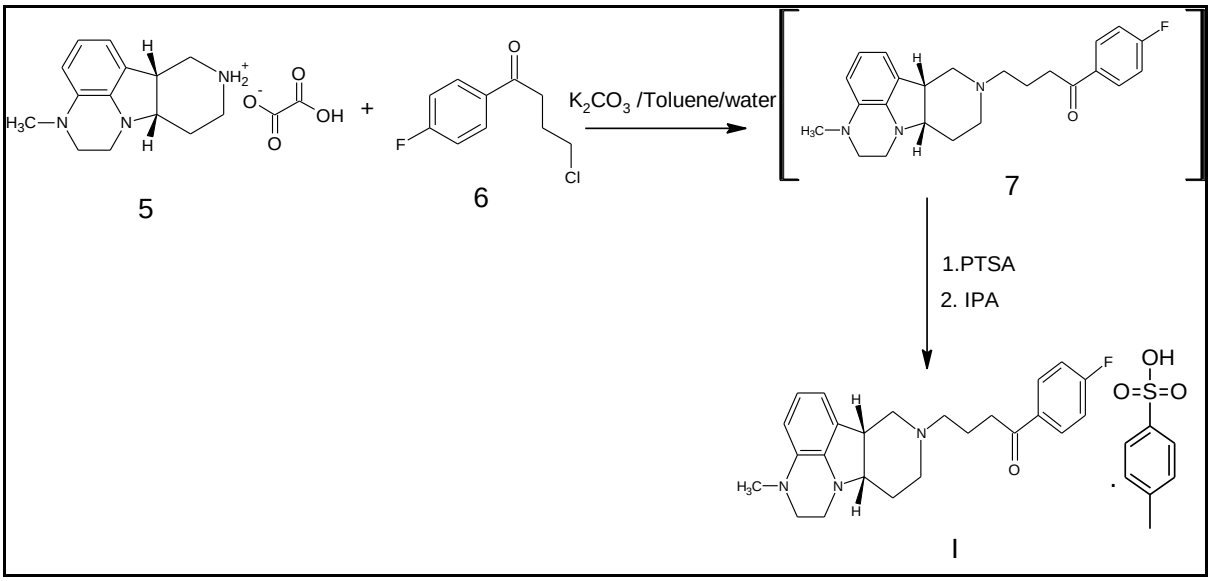
Step a)



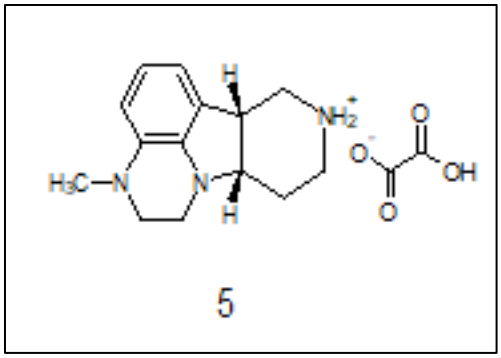
Step b)



Step c)



In an embodiment, the present invention provides a novel intermediate of formula (5) as represented below:



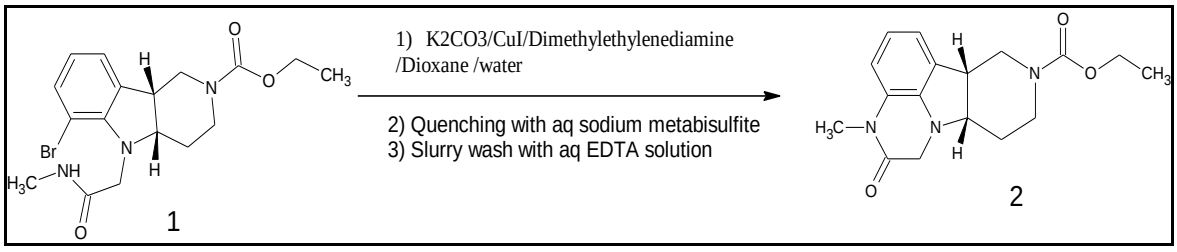
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In an embodiment, the present invention provides the use of the novel intermediate represented by compound of formula (5) for the preparation of Lumateperone Tosylate of formula I.

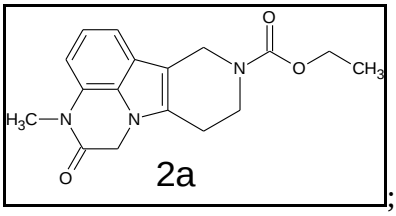
In another embodiment, the present invention provides a process for the preparation of Lumateperone tosylate of formula (I) free from process impurities comprising the following steps:

a. Compound of formula (1) is heated with dimethylethylenediamine in presence of cuprous iodide in dioxane followed by quenching of reaction mass was in an aqueous sodium metabisulfite solution, filtration and washing of wet cake with EDTA solution to get compound of formula (2) free from dehydro, oxo and hydroxy impurities with compound formula (2a), (2b) and (2c) respectively.

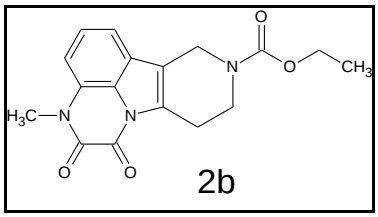
b.



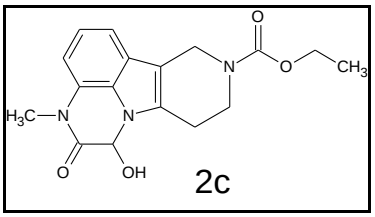
1 2



2a;

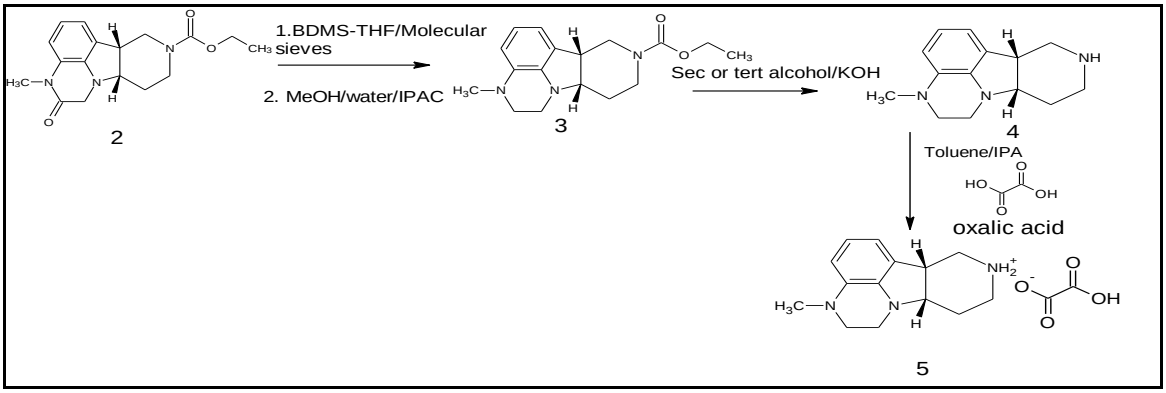


2b

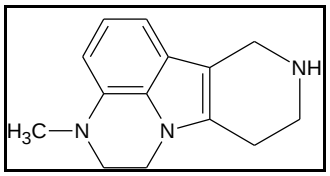


2c

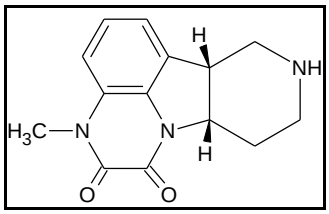
c. Reduction of compound (2) with borane dimethyl sulphide in THF to get compound of formula (3). The compound of formula (3) undergoes hydrolysis with potassium hydroxide in secondary or tertiary alcohol to get compound of formula (4). The treatment of compound of formula (4) with oxalic acid in IPA and toluene mixture to get compound of formula (5), free from dehydro, oxo and hydroxy impurities with compound formula (5a),5(b) and (5c) respectively.



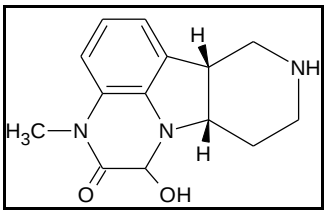
Structure of (5a)



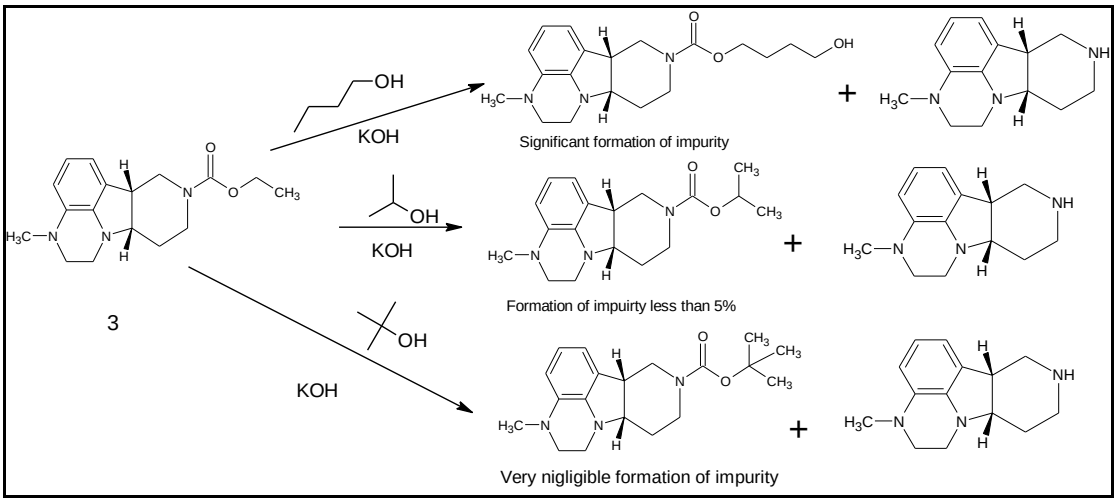
Structure of (5b)



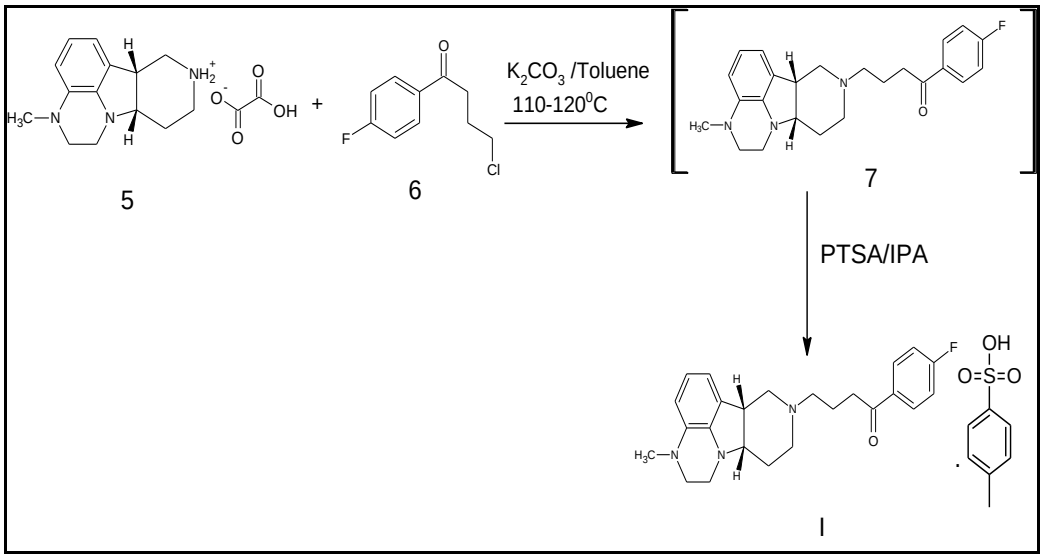
Structure of (5c)



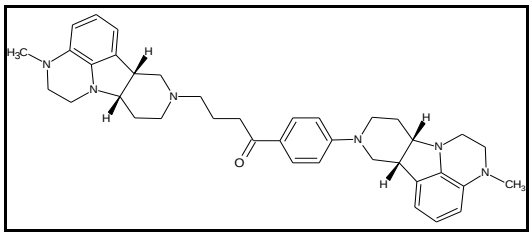
Secondary and tertiary alcohols are relatively less nucleophilic and therefore the formation of side product (Isopropyl and t-butyl carbamate impurity) is very less. Whereas the use of primary alcohol results in substantial amount of side product and therefore reaction is extremely slow and yields are inferior.



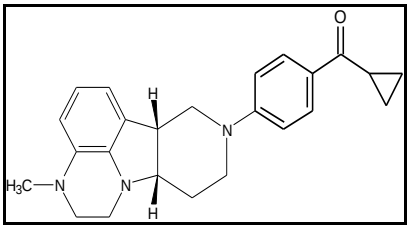
d. Reaction of compound of formula (5) free from process impurities with compound of formula (6) in presence of potassium carbonate in toluene to get Lumateperone free base oil (7) *in situ*. The reaction of Lumateperone free base oil (7) compound with para toluene sulfonic acid in alcoholic solvent by maintaining the pH 5.0 to 6.5 to get Lumateperone tosylate compound (I) free from impurities such as dimer impurity (Ia), cyclo impurity (Ib) Dehydro impurity (Ic), N-oxide (Id) with an amount less than 0.10%.



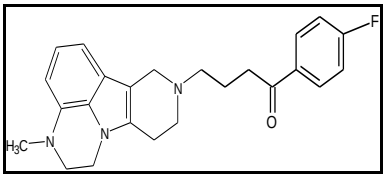
Structure (Ia)



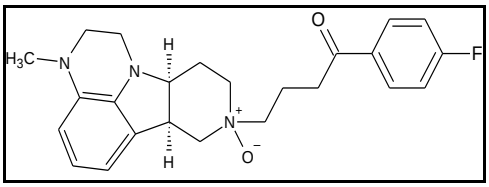
Structure (Ib)



Structure (Ic)



Structure (Id)



In an embodiment, wherein the step (a) can be carried out in the presence of an inorganic base which is selected from the group consisting of potassium carbonate, sodium carbonate, calcium carbonate and sodium bicarbonate and their mixtures.

In an embodiment, the step (a) can be carried out in the presence of an organic base which is selected from the group consisting of amines, wherein the amine is selected from the group comprising of Dimethylethylenediamine, dimethylamine, ethylene diamine, and isopropyl diamine and their mixtures.

In an embodiment, wherein the suitable solvent used in step (a) is an organic solvent, wherein the solvent is selected from the group comprising of an alcoholic solvent, an ester solvent, ketone solvent and mixtures thereof. In an embodiment, the solvent used in step (a) is selected from the group comprising of water, toluene, acetone, ethyl acetate, isopropyl acetate, chloroform, ethanol, acetonitrile, isopropyl alcohol, tert-butyl alcohol, n-butyl alcohol, methylene chloride, dimethylformamide, tetrahydrofuran, 1,4-dioxane, and mixtures thereof. Preferably, the suitable solvent is a mixture of 1,4-dioxane and water.

In an embodiment, wherein the suitable reducing agent used for the process for the preparation of compound of formula (3) in step (c) is selected from the group comprising of BDMS

(Bromodimethylsulfonium Bromide), BHT (Butylated hydroxytoluene) in presence of solvents such as THF, DMF, DMSO, and DME.

In an embodiment, wherein the suitable solvent used for the preparation of compound of formula (3) in step (c) is selected from the group comprising of tetrahydrofuran, methylene chloride, water, methanol, isopropyl acetate and pyridine and mixtures thereof.

In an embodiment, wherein the compound of formula (5) is isolated as acid addition salt, selected from Benzoic acid, oxalic acid and fumaric acid.

In an embodiment, wherein the suitable solvent used to prepare a novel intermediate of formula (5) in step (c) is an organic solvent selected from the group comprising of an alcoholic solvent, an ester solvent, ketone solvent, water and mixtures thereof. In an embodiment, wherein solvent is selected from the group comprising of methanol, ethanol, n-butanol, tert-butyl alcohol, iso-propyl alcohol, ethyl acetate, acetonitrile, methyl ethyl ketone, acetone, methylene chloride, dimethylformamide, tetrahydrofuran, toluene, dimethyl sulfoxide, cyclohexane, n-hexane, water and mixtures thereof.

In an embodiment, wherein the suitable solvent used for the preparation of compound formula (7) in step (d) is selected from an organic solvent. In an embodiment, wherein the organic solvent is selected from the group comprising of an alcoholic solvent, an ester solvent, ketone solvent, aromatic hydrocarbons and mixtures thereof. In an embodiment the suitable solvent is selected from the group comprising of water, toluene, ethanol, acetonitrile, isopropyl alcohol, tert-butyl alcohol, n-butanol, methylene chloride, dimethylformamide, tetrahydrofuran and mixtures thereof. Preferably, the suitable solvent is toluene.

In an embodiment, wherein the final product Lumateperone tosylate of formula I is isolated using a suitable solvent selected from the group comprising of methanol, ethanol, n-butanol, tert-butyl alcohol, isopropanol, ethyl acetate, acetonitrile, methyl ethyl ketone, Acetone, methylene chloride, dimethylformamide, tetrahydrofuran, toluene, dimethyl sulfoxide, cyclohexane, n-hexane and mixtures thereof.

Further, present invention provides a solid form of Lumateperone tosylate of formula I or pharmaceutically acceptable salt thereof with an improved physicochemical stability and dissolution characteristics.

Further, present invention provides a crystalline oxalate salt, a novel intermediate of formula (5). The crystalline form of compound of formula (5) has an x-ray powder diffraction pattern comprising characteristic peaks with degrees two-theta positions of about 5.240, 12.655, 12.860, 16.565, 16.906, 19.590, 21.655 and 25.041 (±0.2°).

Further, present invention provides a crystalline form of Lumateperone tosylate of formula I or pharmaceutically acceptable salt thereof with an improved physicochemical stability and dissolution characteristics. The crystalline form having x-ray powder diffraction pattern shown in figure 1.

Further, present invention provides an amorphous form of Lumateperone tosylate of formula I or pharmaceutically acceptable salt thereof with an improved physicochemical stability and dissolution characteristics.

In an embodiment, the solid form of Lumateperone tosylate of formula I or pharmaceutically acceptable salt of the present invention can be used in the pharmaceutical composition.

The pharmaceutical excipient agents is selected from group of cellulose derivatives but not limited to croscarmellose sodium, micro crystalline cellulose (MCC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxymethylethylcellulose (HEMC), ethylcellulose (EC), methylcellulose (MC), cellulose esters, cellulose glycolate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, polymethylacrylate (HPMCP), hypromellose, vinylpyrrolidone, polyvinylpyrrolidone, mannitol, polyvinyl acetate phthalate, polyethylene glycol, copovidone and the like.

In one embodiment, the present invention provides pharmaceutical compositions comprising Lumateperone tosylate obtained by processes herein described, having a D90 particle size of less than about 250 microns, preferably less than about 150 microns, more preferably less than about 50 microns, still more preferably less than about 20 microns, still more preferably less than about 15 microns and most preferably less than about 10 microns.

In one embodiment, the present invention provides pharmaceutical compositions comprising Lumateperone tosylate obtained by the processes herein described, having a D50 particle size of less than about 250 microns, preferably less than about 150 microns, more preferably less than about 50 microns, still more preferably less than about 20 microns, still more preferably less than about 15 microns and most preferably less than about 10 microns.

In one embodiment, the present invention provides pharmaceutical compositions comprising Lumateperone tosylate obtained by the processes herein described, having D90 particle size less than 150 microns, D50 particle size of less than 75 microns and D10 particle size less than 35 microns.

The particle size disclosed herein can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state Lumateperone tosylate into any of the foregoing desired particle size range.

The examples that follow are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention.

EXAMPLES

Example 1: Preparation of compound of formula (2)

Reaction of compound of formula (1) [(4aS,9bR)-Ethyl 6-bromo-5-(2-(methylamino)-2-oxoethyl)-3,4,4a,5-tetrahydro-1H-pyrido[4,3-b] indole-2(9bH)-carboxylate] (100 g, 1 mole eq.) with Dimethylethylenediamine (13.35 g. 0.6 mole eq.) in presence of cuprous iodide (9.62 g, 0.2 mole eq.) in dioxane (500 ml ,5V) is carried out for 13-15 h at 98-105°C. After completion, the reaction mass is quenched with aqueous sodium metabisulfite (7.5g) in water (1500 ml. 15 v), followed by filtration and washing of wet cake with aq. 5% EDTA solution (15 V).

Output: 63 g; yield: 80%; HPLC purity: ≥ 99%

Experimental details of for compound with formula (2) are summarized below:

Experimental data summarized with quality profile and defined quenching process with aq. sodium metabisulfite for the removal of dehydro impurity and washing with aq. EDTA solution for the removal of metallic impurities to avoid the degradation of product during drying process.

Process details	**Sample details**	**Purity by HPLC (%, AUC)**		
		Formula (2)	**Formula (1)**	**Imp. @ RT 12.7 min (Dehydro Impurity)**
Reaction of KSM-1 with Dimethylethylenediamine in presence of CuI catalyst and K_2CO_3 in 1,4-dioxane	Reaction monitoring samples	95.69	0.71	1.79
Quenching with aqueous sodium metabisulfite solution followed by filtration	Wet cake sample analysis	99.00	ND	0.37
Wet cake drying at 30-40◦C	Dry solid analysis	93.95	ND	4.44
Reaction of KSM-1 with Dimethylethylenediamine in presence of CuI catalyst and K_2CO_3 in 1,4-dioxane	Reaction monitoring	93.97	0.04	1.36
Quenching with aqueous sodium metabisulfite solution followed by filtration	Wet cake analysis	99.24	ND	0.28
Wet cake slurry wash in aqueous EDTA solution	Wet cake analysis	99.67	ND	0.06

Drying	Dry solid analysis	99.70	ND	0.06

Example 2: Preparation of compound of formula (5)

Reaction of Lumateperone stage-1 (100 g 1 mole eq.) product with borane dimethyl sulphide (47.56 g, 1.5 mole eq.) in THF (500 mL, 5v) in presence of molecular sieves (25g, 0.25% w/w) is carried out at 50-70°C for 2-3 h followed by quenching the reaction mass with methanol (100 mL,1 V). The distillation of reaction mass carried out followed by addition of water (500 mL, 5V) and extraction in an isopropyl acetate with pH adjustment between 9-11 with an aqueous sodium hydroxide solution. The separation of isopropyl acetate layer followed by distillation and hydrolysis with potassium hydroxide (71 g, 4 moles eq.) in t-butanol (500 mL, 5V) at is carried out at 80-85 °C. Again, distillation is carried out followed by addition of water (500 mL, 5 V) and compound is extracted in toluene (1000 mL, 10V). Finally, addition of solution of oxalic acid dihydrate (44 g, 1.1 mole) in an isopropyl alcohol (400 mL ,4 V) at 25-30°C gives oxalate salt. Output: 90 g; yield: 79%; HPLC purity: 99 %.

Experimental details for synthesis of compound with formula (5) in different solvents with impurity profile summarized below.

Solvent	**Reaction. Time (h)**	**Reaction monitoring by HPLC (%AUC)**				**Purity by HPLC (%, AUC) Oxalate salt**		
		Formula (5)	**Formula (3)**	**n-butyl carbamate impurity**	**Isopropyl carbamate impurity**	**Formula (5)**	**Formula (3)**	**Ester Impurity**
n-butanol	10.0	76.34	0.06	19.64	ND	Salt was not prepared		
IPA	14	93.37	0.23	ND	4.56	98.15	ND	0.49
t-Butanol	10	96.28	0.02	ND	ND	97.23	ND	ND
t-Butanol	10.	97.72	0.03	ND	ND	99.22	ND	ND
t-Butanol	13	98.51	ND	ND	ND	99.04	ND	ND

Example 3: Lumateperone toylate compound with formula (I)

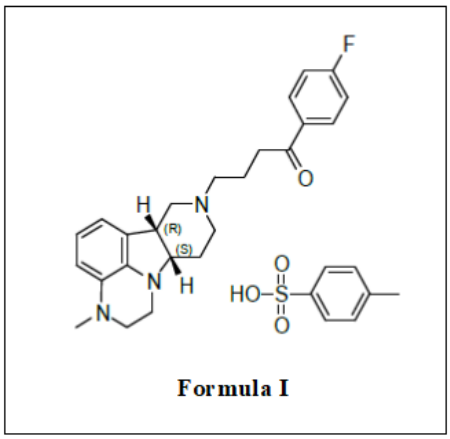
Reaction of oxalate salt of compound of formula (5) (100g ,1 mole eq.) free from process impurities with 4-chloro-1-(4-fluorophenyl) butan-1-one (200g, 3 mole eq) in presence of potassium carbonate (138 g, 4 mole eq) in toluene (1500 ml, 15 V) followed by acid-base extraction in water to get Lumateperone free base. Treatment of Lumateperone free base oil *in situ*

with para toluene sulfonic acid (53.6 g, 0.9 mole eq.) in isopropyl alcohol 10 V) by maintaining the pH between 5.0 to 6.5 gives Lumateperone tosylate isolated by filtration in solid form and dried.

Output: 125g; HPLC purity: ≥99.90%

We claim:

1] a process for the preparation of Lumateperone or pharmaceutically acceptable salt of compound of formula I,



Formula I

comprising the following steps.

a. Compound of formula (1) reacted with Dimethylethylenediamine in presence of cuprous iodide in an organic solvent and isolated as a compound of formula (2);
b. Reduction of compound (2) with borane dimethyl sulphide in an organic solvent to get the compound of formula (3). The compound of formula (3) undergoes hydrolysis with an inorganic base in a secondary or tertiary alcohol to get compound of formula (4). The treatment of compound of formula (4) with an oxalic acid solution in an organic solvent to get compound of formula (5);
c. Reaction of compound of formula (5) with compound of formula (6) in presence of an inorganic base in presence of an organic solvent to get Lumateperone free base oil (7) *in situ*. The reaction of Lumateperone free base oil (7) with para toluene sulfonic acid in an alcoholic solvent by maintaining the pH 5.0 to 6.5 to get Lumateperone tosylate compound (I) as a crystalline solid.

2] The process as claimed in claim 1, the step (a) can be carried out in the presence of an organic base which is selected from the group consisting of amines, wherein the amine is selected from the group comprising of Dimethylethylenediamine, dimethylamine, ethylene diamine, and isopropyl diamine and their mixtures.

3] The process as claimed in claim 1, wherein the suitable solvent used in step (a) is an organic solvent, wherein the solvent is selected from the group comprising of an alcoholic solvent, an ester solvent, ketone solvent and mixtures thereof. the solvent used in step (a) is selected from the group comprising of water, toluene, acetone, ethyl acetate, isopropyl acetate, chloroform, ethanol, acetonitrile, isopropyl alcohol, tert-butyl alcohol, n-butyl alcohol, methylene chloride, dimethylformamide, tetrahydrofuran, 1,4-dioxane, and mixtures thereof. Preferably, the suitable solvent is a mixture of 1,4-dioxane and water.

4] The process as claimed in claim 1, wherein the suitable reducing agent used for the process for the preparation of compound of formula (3) in step (c) is selected from the group comprising of BDMS, BHT in presence of solvents such as THF, DMF, DMSO, and DME.

5] The process as claimed in claim 1, wherein the suitable solvent used for the preparation of compound of formula (3) in step (c) is selected from the group comprising of tetrahydrofuran, methylene chloride, water, methanol, isopropyl acetate and pyridine and mixtures thereof.
In an embodiment, wherein the compound of formula (5) is isolated as acid addition salt, selected from Benzoic acid, oxalic acid and fumaric acid.

6] The process as claimed in claim 1, wherein the suitable solvent used for the preparation of compound formula (7) in step (d) is selected from an organic solvent. wherein the organic solvent is selected from the group comprising of an alcoholic solvent, an ester solvent, ketone solvent, aromatic hydrocarbons and mixtures thereof. The suitable solvent is selected from the group comprising of water, toluene, ethanol, acetonitrile, isopropyl alcohol, tert-butyl alcohol, n-butanol, methylene chloride, dimethylformamide, tetrahydrofuran and mixtures thereof. Preferably, the suitable solvent is toluene.

7] The process as claimed in claim 1, wherein the final product Lumateperone tosylate of formula I is isolated using a suitable solvent selected from the group comprising of methanol, ethanol, n-butanol, tert-butyl alcohol, isopropanol, ethyl acetate, acetonitrile, methyl ethyl ketone, Acetone, methylene chloride, dimethylformamide, tetrahydrofuran, toluene, dimethyl sulfoxide, cyclohexane, n-hexane and mixtures thereof.

8] Pharmaceutical compositions comprising Lumateperone tosylate obtained by processes herein described, having a D90 particle size of less than about 250 microns, preferably less than about 150 microns, more preferably less than about 50 microns, still more preferably less than about 20 microns, still more preferably less than about 15 microns and most preferably less than about 10 microns.

9] The process as claimed in claim 1, the isolated Lumateperone tosylate salt (I), has a purity of at least 99.9% as measured by chiral HPLC and wherein the content of nitrosamine impurity is less than 1%w/w.

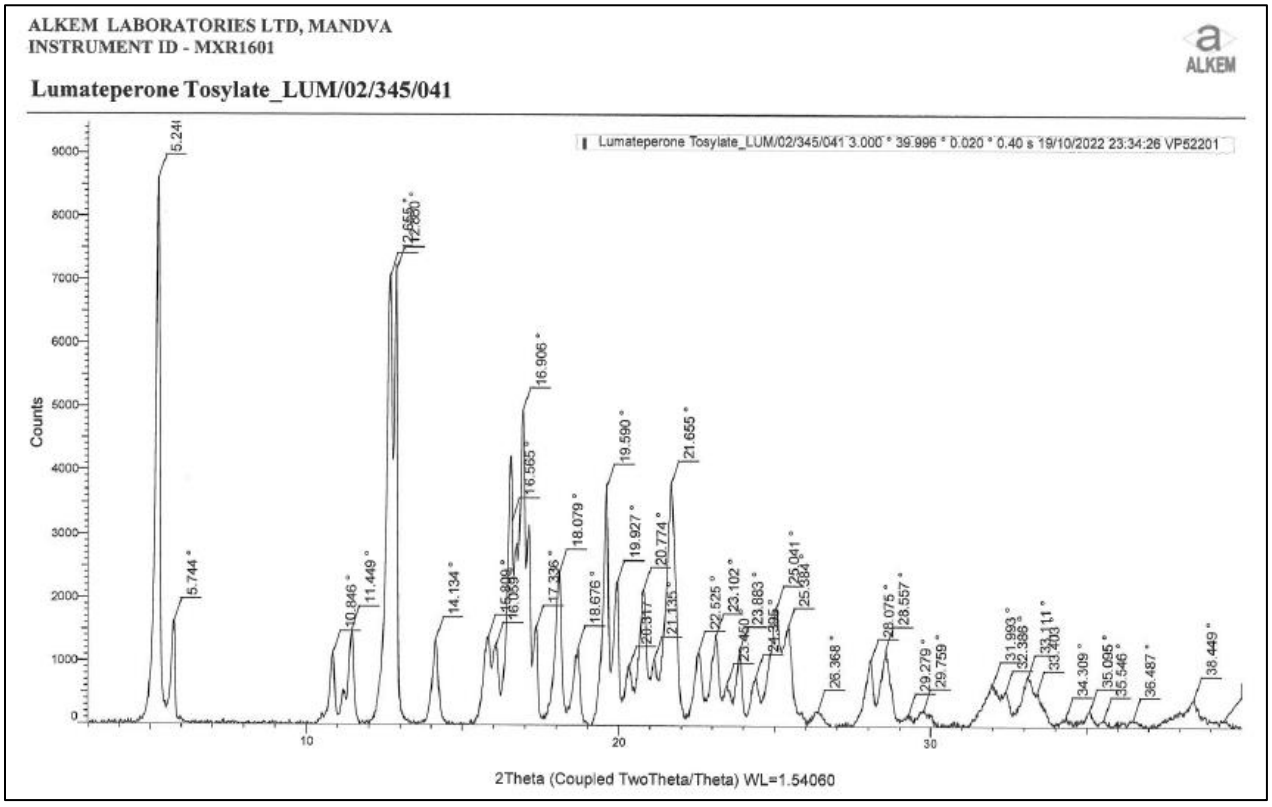
10] Pharmaceutical composition of Lumateperone tosylate salt with an one or more excipient wherein excipient is selected from group of cellulose derivatives but not limited to croscarmellose sodium, micro crystalline cellulose (MCC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxymethylethylcellulose (HEMC), ethylcellulose (EC), methylcellulose (MC), cellulose esters, cellulose glycolate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, polymethylacrylate (HPMCP), hypromellose, vinylpyrrolidone, polyvinylpyrrolidone, mannitol, polyvinyl acetate phthalate, polyethylene glycol, copovidone and the like.

Dated this on 07th day of November 2023

Thirupathi. B

Mr. Thirupathi Bendram
AVP & Head – IPR
Alkem Laboratories Limited

Fig.1 the PXRD pattern of crystalline oxalate salt, a novel intermediate, obtained by process of Example 2



Dated this 11 th day of **November, 2022**

Mr. Thirupathi Bendram

AVP & Head - IPR

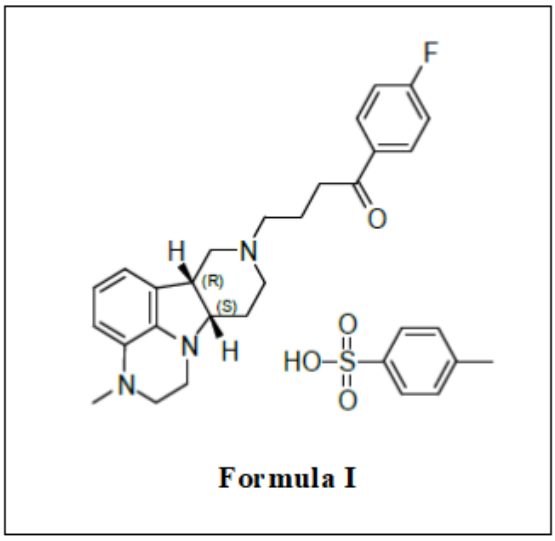
Alkem Laboratories Limited

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ABSTRACT

AN IMPROVED PROCESS FOR THE PREPARATION OF LUMATEPERONE OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS

The present invention provides an improved process for the preparation of Lumateperone or its pharmaceutically acceptable salts of formula I substantially free from organic impurities. More particularly, the present invention provides a novel intermediate of formula (5) and its use in the preparation of Lumateperone or its pharmaceutically acceptable salts of formula I. The present invention further provides a process for preparation of a novel intermediate of formula (5). Moreover, the present invention provides solid form of Lumateperone or its pharmaceutically acceptable salts of formula I and process thereof.



Formula I