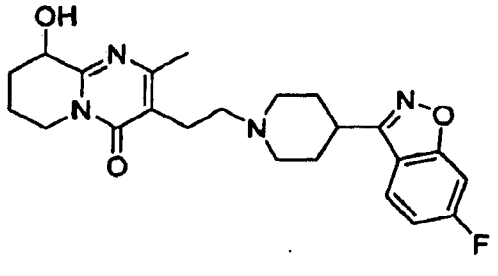
Field of Invention:

The present invention relates to the process for synthesis of paliperidone in high yield and purity. More specifically, the present invention relates to an improved process for preparation of paliperidone wherein the intermediate prepared *in situ* is directly converted into paliperiodone. In another embodiment the intermediates are isolated and further converted to paliperidone.

Background of Invention:

Paliperidone, also known as 9-hydroxyrisperidone, is an atypical antipsychotic developed by Janssen Pharmaceutica. Chemically, paliperidone is the primary active metabolite of the older atypical antipsychotic risperidone (paliperidone is 9-hydroxyrisperidone, i.e. risperidone with an extra hydroxyl group). It is indicated for the acute and maintenance treatment of schizophrenia.

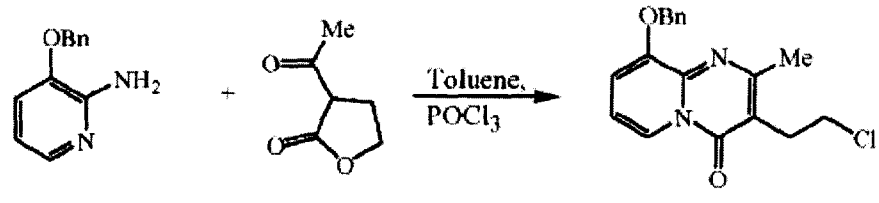
IUPAC name for paliperidone is 3-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-7-hydroxy-4-methyl-l,5-diazabicyclo[4,4,0]deca-3,5-dien-2-one or 3-(2-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-yl)ethyl)-9-hydroxy-2-methyl-2,3,6,7,8,9-hexahydropyrido [1,2-a]pyrinidin-4-one and has a chemical structure as given below:



Formula I

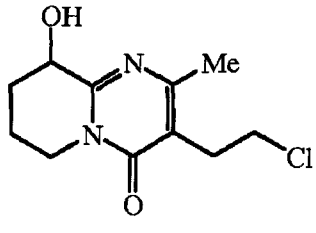
Paliperidone was first disclosed in EP0368388 (EP '388) (corresponding to US5158952) assigned to Janssen Pharmaceutica N. V. The said patent discloses and claims paliperidone in a markush claim as a part of 3-piperidinyl-1,2-benzisoxazoles group of compounds. EP '388 patent also discloses a process for preparation of above mentioned compounds.

The process as exemplified in EP '388 comprises reacting 2-amino-3-benzoxypyridine (Formula II) with 2-acetyl-4-butyrolactone (Formula III) in presence of phosphoryl trichloride in toluene. The reaction mixture was stirred along with a first portion of 2-acetyl-4-butyrolactone at 50°C and subsequently for 5 hours at 90°C after addition of second potion of 2-acetyl-4-butyrolactone. This stage of reaction yields an intermediate compound namely 3-(2-chloroethyl)-2-methyl-9-(phenylmethoxy)-4H-pyrido[1,2-a]-pyrimidin-4-one (Formula IV). The yield of this stage of about 62.3% of compound of Formula IV



Formula II Formula III Formula IV

In the next stage, the compound of formula IV is hydrogenated over Pd/C catalyst in presence of methanol to yield a compound of formula V



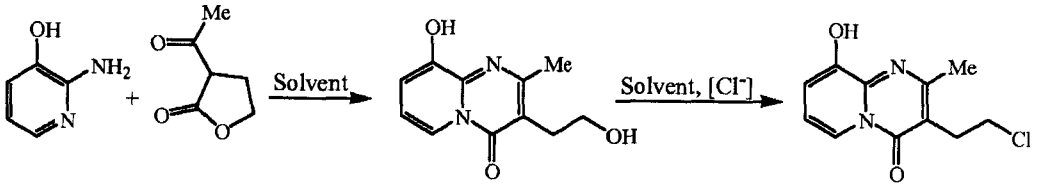
Formula V

The compound of Formula V is further condensed with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole monohydrochloride to yield the final product namely, paliperidone (formula I).

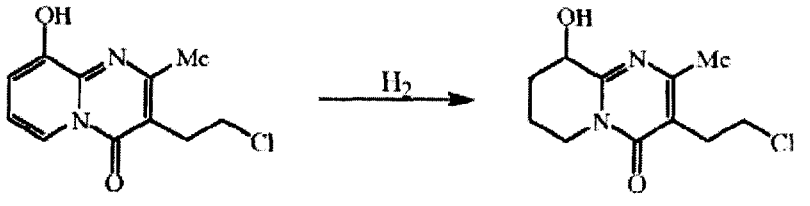
Further, according EP '388 the compound of Formula IV is purified by column chromatography over silica using a mixture of chloroform and diethylether. The mobile phase as used in EP '388 has an inherent risk of inflammability and toxicity. Since, the purification of compound of Formula IV is required to be done on column

chromatography this makes the process, as such, tedious and more time consuming and costly.

WO 2009/144288, a PCT International Application assigned to Inke S.A. discloses a two step process for obtaining 3-(2-chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one as below:



Formula VI Formula VII Formula VIII Formula IX



Formula IX Formula V

the compound obtained is subjected to hydrogenation to yield compound of Formula V and further condensing compound of Formula V with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole monohydrochloride, to obtain desired product. Since, this preparation involves a two-step process, the tediousness of process increases thereby decreasing economic viability.

WO 2008/021345, discloses a process for preparing paliperidone comprising condensation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]-pyrimidin-4-one with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole monohydrochloride in presence of an inorganic base. Furthermore, process as disclosed in WO '345 involves use of Phase Transfer Catalyst, which increases the overall reaction cost. Again the yield is low, about 58%.

Present inventors have devised a process for preparation of paliperidone, which involves minimal use of organic solvents as well as reduced work-up for purification, thereby making the process more economical as well as ecologically tolerant.

Summary of Invention:

The present invention provides an improved process of preparation of paliperidone in high yield and purity via *in situ* alkylation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-2,3,6,7,8,9-hexahydropyrido[1, 2-a]-pyrimidin-4-one (PLD-II) with 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole (Formula XI). In another embodiment the intermediates are isolated and further converted to paliperidone.

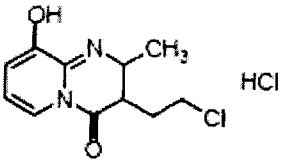
Description of Invention:

For the purpose of this invention, term "purifying" as described in the claims may be understood as related to the specific example as described in the specification.

It may further be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs.

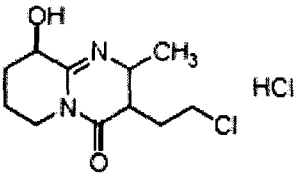
For the purpose of understanding this invention, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" or "using" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

For the purpose of current invention, the term "PLD-I HCl" denotes an intermediate formed, namely, 3-(2-chloroethyl)-9-hydroxy-[1,2-a]pyrimidin-4-one hydrochloride having following structure;



Formula IX

For the purpose of current invention, the term "PLD-II HCl" denotes an intermediate formed, namely, 3-(2-chloroethyl)-9-hydroxy-2-methyl-2,3,6,7,8,9-hexahydropyrido[1,2-a]pyrimidin-4-one hydrochloride having following structure;



Formula X

The present invention describes a process for preparation of paliperidone, which comprises the steps of:

(a) Condensing 2-amino-3-hydroxy pyridine (formula VII) with 2-acetyl butyrolactone (Formula VI) in presence of a chlorinating agent, PLD-I HCl (Formula IX);

(b) purifying PLD-I HCl as obtained in step (a) in acetone;

(c) purifying PLD-I HCl of step (b) in water;

(d) hydrogenating purified PLD-I HCl of step (c) dissolved in alcohol with hydrogen gas over 5-10% Pd/C optionally in presence of $ZnCl_2$ to obtain PLD-II HCl (Formula X);

(e) purifying PLD-II HCl as obtained in step (d) in ethyl acetate;

(f) *in situ* alkylation of PLD-II step (e) with 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole (Formula XI) to yield paliperidone in presence of a organic base, alkali metal iodide and lower alcohol; and

(g) isolating paliperidone obtained in step (f) in aqueous solvent system.

In another embodiment, the present invention provides preparation of paliperidone comprising:

(a) Condensing 2-amino-3-hydroxy pyridine (formula VII) with 2-acetyl butyrolactone (Formula VI) in presence of a chlorinating agent, to yield 3-(2-chloroethyl)-9-

hydroxy-2-methyl-2,3-dihydropyrido[1,2-a]pyrimidin-4-one hydrochloride (PLD-I HCl)(Formula X);

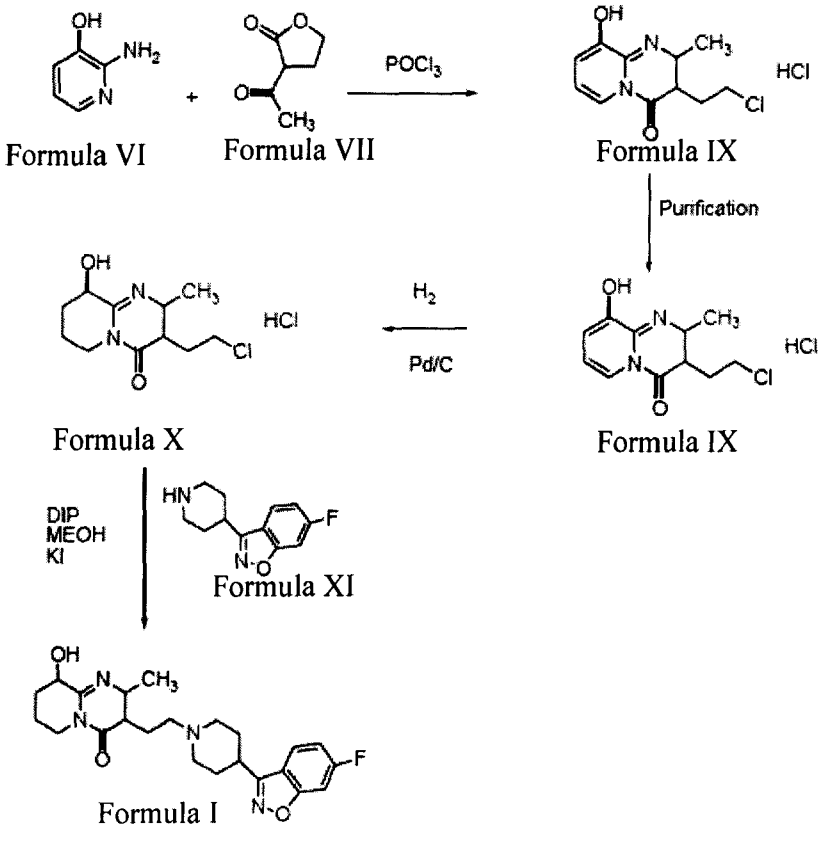
(b) purifying PLD-I HCl as obtained in step (a) in acetone;

(c) purifying PLD-I HCl of step (b) in water;

(d) hydrogenating purified PLD-I HCl of step (c) dissolved in C1 – C4 alcohol with hydrogen gas over 5-10% Pd/C, optionally in presence of $ZnCl_2$, and adding 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole (Formula XI) in presence of diisopropyl ethyl amine, potassium iodide and C1 – C4 alcohol to yield paliperidone (Formula I); and

(e) isolating paliperidone obtained in step (d) from aqueous solvent system.

The process for current invention can be shown schematically as below



The first stage comprises condensation of compounds of Formula VI and Formula VII in presence of a chlorinating agent, to yield PLD-I. HCl The said chlorinating agent is selected form those known in the prior art. The reaction is preferably carried out in absence of solvent.

Accordingly, the process of present invention comprises condensing 2-amino-3-hydroxy pyridine of formula I with 2-acetyl butyrolactone in presence of an chlorinating agent phosphorous oxychloride, in a reaction vessel at a temperature in range of 5 - 10°C. The reaction is further heated to a temperature of 65 - 75°C for 8 – 9 hours, till TLC indicates completion of reaction to obtain PLD-I HCl.

In preferred embodiment, PLD-I thus obtained is purified in presence of a solvent, followed by purification with water The said solvent is selected from acetone, ethyl methyl ketone, dimethyl ketone, etc.

In a preferred embodiment, purified PLD-I HCl thus obtained is dissolved in alcohol followed hydrogenation with hydrogen gas over 5-10% Pd/C and optionally in presence of $ZnCl_2$, to yield PLD-II HCl. The reaction is carried out at temperature in range of 25 – 50°C. After completion of reaction the catalyst is washed with methanol, distilling out methanol followed by addition of ethyl acetate and water. This is followed by adjusting the pH to 8-9 by addition of ammonia. To the separated organic layer is purged HCl gas till pH <2, to obtain HCl salt of PLD-II.

Alternately, Purified PLD-I HCl thus obtained is dissolved in alcohol and hydrogenated with hydrogen gas over 5-10% Pd/C and optionally in presence of $ZnCl_2$ is directly converted to paliperidone without isolation of PLD-II HCl.

Another preferred embodiment comprises *in situ* alkylation of PLD-II HCl with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (Formula XI) in presence of an organic base and alkali metal iodide and C1 – C4 alcohol to yield paliperidon. The organic base is selected from diisopropyl ethyl amine, triethyl amine, preferably diisopropyl ethyl amine (DIP).

In another embodiment, PLD-I HCl is converted to paliperidone directly by hydrogenating PLD-I HCl dissolved in alcohol and adding 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole HCl (Formula XI) in presence of a organic base and alkali metal iodide. The PLD-II thus obtained is further purified by in solvent selected form methyl acetate, ethyl acetate, alcohols, etc.

The paliperidone thus obtained is further isolated by solubilizing the mass in aqueous solvent system in presence of charcoal. The purity of paliperidone at the end of this stage is around 99.8%. The said aqueous solvent system consists of acetone and water.

Examples:

Example 1:

Synthesis of PLD-I HCl (Formula IX):

In 5 lit round bottom flask take 420 gm of 2-acetyl butyrolactone (Formula VII) and 2-amino-3-hydroxy pyridine are charged and maintained at room temperature. the mass is cooled to temperature of 5 – 10°C and slowly 2500 gm of $POCl_3$ is added in 2 – 2.5 Hrs at 10 – 15°C, reaction temperature is then allowed to rise till room temperature. The mass is then heated to a temperature of 70°C for 8 – 9 hrs. After completion, as checked by TLC, the reaction is quenched by adding 5kg of ice, and further cooled to 0 – 5°C. The mass is washed and filtered; residue obtained is washed with chilled water. The mass is dried at 70°C for 5 – 6 hrs. The end product of this reaction is 3-(2-chloroethyl)-9-hydroxy-2-methyl-2,3-dihydropyrido[1,2-a]pyrimidin-4-one hydrochloride, m. p. 206 – 208°C.
Yield: 95 – 97%.

1a. Purification of PLD-I in Acetone

100 gm of dried PLD-1 HCl along with 400 gm of acetone is charged in reaction vessel and the mass is heated to 50 -55°C for 1 hr. The mass is then cooled to room temperature and further chilled to 0°C, filtered and washed with chilled acetone. The end product of reaction is pure PLD-I HCl, m. p. 210 - 215°C. Dry wt 80 gm
Purity: 97%.

1b. Purification of PLD-I in water

100 gm of PLD-I HCl as obtained in example 1a is further dissolved in 250 ml of water at 60-70°C. Cool to 25-30 °C and keep for 30 min. Filter and dry 70 gm dry wt.
Purity: 98%.

Example 2:

Synthesis of PLD-II HCl (Formula X):

100gm of purified PLD-I HCl of Example 1 and 1000ml of methanol are charged in a 2 lit autoclave. 25gm of Pd/C 5 % is charged in reaction vessel and flushed with nitrogen thrice followed by flushing with hydrogen three times. Hydrogen is then passed at a pressure of 2 – 3 kg/cm^2. The reaction is carried out at temperature in range of 25 – 30°C for 4 – 5 hrs till completion as detected by HPLC (HPLC conversion 80%). Hydrogen gas is released and reaction mass is filtered under nitrogen atmosphere. The catalyst is filtered and washed with two volumes of 30ml methanol. Methanol is distilled, under vacuum. On cooling 800 ml ethyl acetate is added to reaction mass. Ethyl acetate is refluxed, insoluble residue thus obtained is filtered at 50 – 60°C. Mass is cooled to room temperature and further chilled to 10°C. This stage of reaction gives 3-(2-chloroethyl)-9-hydroxy-2-methyl-2,3,6,7,8,9-hexahydropyrido[1,2-a]pyrimidin-4-one hydrochloride (PLD-II HCl) (Formula X).

Yield: 65%.

Purity: 95%.

Example 3:

Synthesis of PLD-II HCl (Formula X):

100gm of purified PLD-I HCl of Example 1 and 1000ml of methanol are charged in a 2 lit autoclave. 25gm of Pd/C 10% is charged in reaction vessel and flushed with nitrogen thrice followed by flushing with hydrogen three times. Hydrogen is then passed at a pressure of 1 – 2 kg/cm^2. The reaction is carried out at temperature in range of 25 – 30°C for 4 – 5 hrs till completion as detected by HPLC (HPLC conversion 75%) Release hydrogen gas and catalyst is filtered and washed with methanol. Distill methanol completely. To reaction mass 800 ml of ethyl acetate and 800 ml of water are added and heated to a temperature of 50 – 60°C. pH is adjusted to pH 8 – 9 with ammonia. The layers are separated and organic layer is collected and dried over sodium sulphate The pH of organic layer is then adjusted to pH <2 with purging of HCl gas and refluxed for 30min. The organic layer is then cooled to room temperature and further chilled to 10°C. The solids are filtered. This stage of reaction yields 3-(2-chloroethyl)-9-hydroxy-2-methyl-2,3,6,7,8,9-hexahydropyrido[1,2-a]pyrimidin-4-one hydrochloride (PLD-II HCl) (Formula X).

Yield: 61.55%.

Purity: 94%.

Example 3a:

Purification of PLD-II HCl.

50 gm of PLD-II HCl is refluxed with Ethyl Acetate 500 ml. Mass was cooled to Room Temperature and further chilled to 5°c . Filtered and dry under vacuum dryer. Dry wt is 42 gm.

Purity: 98%.

Example 4

25 gm of PLD-I HCl of example 1, is stirred along with 375 ml methanol and 4gm of $ZnCl_2$ to obtain a clear solution. To the solution thus obtained 10% Pd/C catalyst is added. Hydrogen gas is then bubbled through the reaction mass as 40 -50°C for 8 – 10 hrs. Completion of reaction is checked by HPLC. On completion bubbling is stopped and the catalyst is filtered and washed with methanol. The methanol is distilled and 125ml each of water and ethyl acetate is added. The pH of reaction mass is adjusted to pH 8 – 9 by ammonia. The entire mass separates out in two layers namely, organic layer and aqueous layer. The organic layer thus obtained is taken, HCl gas is purged through this organic layer till pH is below 2 (pH<2). The thus obtained reaction mass is refluxed cooled and filtered to obtain 10gm (dry weight) PLD-II.

Yield: 40%

Purity: 94%

Example 5

Synthesis of Paliperidone (Formula I):

In a reaction vessel 90 gm of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole HCl (Formula XI) in 1000 ml methanol and 100gm PLD-II HCl of example 2 or 3 are charged. To this mass 95 gm diisopropylethyl amine and 1.5 gm of KI are added and mass is refluxed for 19 – 22hrs till completion of reaction, as checked by TLC. The entire mass is cooled and filtered. Solid thus obtained is washed with methanol to get paliperidone.125 gm.80 %.

Yield: 80%.

Purity: 98.3%.

Example 6

Direct synthesis of paliperidone form PLD-I HCl

100gm of purified PLD-1 HCl of example 1 and 1000ml methanol are charged in a 2 lit autoclave. 25gm of Pd/C 10% is charged in reaction vessel and flushed with nitrogen thrice followed by flushing with hydrogen three times. Hydrogen gas is then passed at a pressure of 1 – 2 kg/cm^2 at temperature between 25 – 30°C for 4 – 5 hrs till completion of reaction, as checked by HPLC (HPLC conversion 70%). On completion of reaction hydrogen gas is released and catalyst is filtered and washed with methanol. 90 gm of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole HCl (Formula XI) is added to the alcoholic reaction mass in a round bottom flask. To this mass 180 – 200 ml of diisopropyl ethyl amine is added to maintain pH of >8. 1.0 gm of KI is added and mass is refluxed for 18 – 23 hrs, completion is checked by TLC. The salts are filtered at 40 – 50°C and 70 – 80% methanol is distilled. The mass is then cooled and filtered, the solid thus obtained is washed with methanol to yield paliperidone.

Yield: 62%.

Purity: 98%.

Example 7

Purification of Paliperidone

Paliperidone crude 160 gm Acetone 5000 ml, water 1500 ml is refluxed. Added charcoal 10 gm filtered and washed with Acetone 50 ml. Cooled to RT and further chilled to 0-5 °C. Dry at 50-60°c for 5-6 hrs. Dry wt 125 gm.

Purity: 99.8