

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
10 June 2010 (10.06.2010)

(10) International Publication Number  
**WO 2010/064134 A2**

PCT

(51) International Patent Classification:  
**C07D 487/02 (2006.01)**

(21) International Application Number:  
PCT/IB2009/007652

(22) International Filing Date:  
4 December 2009 (04.12.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
2544/MUM/2008 5 December 2008 (05.12.2008) IN

(71) Applicant (for all designated States except US): **CADILA PHARMACEUTICALS LTD.** [IN/IN]; "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MODI, Indravadan, Ambalal** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **SODAGAR, Keval, Rameshchandra** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **VINEET, Malik** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **JAIN, Sudhir, Hukamchand** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **PARIKH, Sanjay, Natvarlal** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **SHARMA, Arun, Omprakash** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **BAPAT, Uday, Rajaram** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus",

Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN). **KHAMAR, Bakulesh, Mafatlal** [IN/IN]; Cadila Pharmaceutical Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210 Gujarat (IN).

(74) Agent: **KHAMAR, Bakulesh, Mafatlal**; Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad - 382210 Gujarat (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): **ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW)**, Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- as to the identity of the inventor (Rule 4.17(i))
- of inventorship (Rule 4A.7(iv))

**Published:**

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: PROCESS OF SYNTHESIS OF PALIPERIDONE

(57) Abstract: The invention relates to an improved process for preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, an intermediate used in the synthesis of paliperidone and process for converting the same to Paliperidone.



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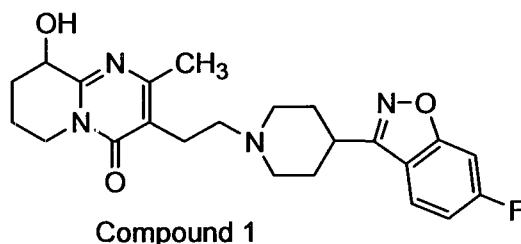
## PROCESS OF SYNTHESIS OF PALIPERIDONE

## FIELD OF THE INVENTION

The invention relates to an improved process for preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, an intermediate used in the synthesis of Paliperidone and process for its conversion in to Paliperidone.

## BACKGROUND OF THE INVENTION

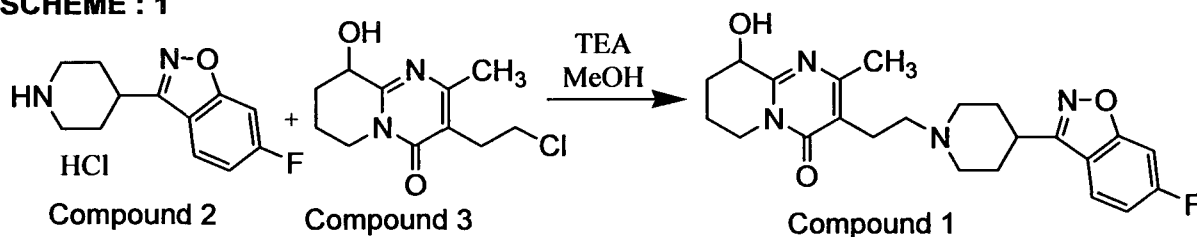
Paliperidone, chemically known as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one is a benzisoxazole derivative having the structural of compound 1.



Paliperidone also known as a 9-hydroxyrisperidone is a metabolite of risperidon. It is marketed in USA under the brand name "Invega®" for the treatment of schizophrenia.

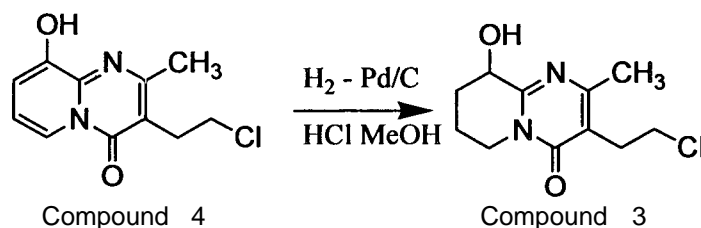
Paliperidone was first disclosed in US patent No. 5,158,952, and 5,254,556 (herein after designated as '952 & '556 patents respectively). '952 patent describes process for synthesis of paliperidone by condensation of 6-fluoro-3-piperidin-4-yl-1,2-benzisoxazole hydrochloride (compound-2) and 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) in presence of organic base (scheme-1). Both these compounds, 6-fluoro-3-piperidin-4-yl-1,2-benzisoxazole hydrochloride (compound-2) and 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) are key intermediates used in the synthesis of paliperidone. While benzisoxazole hydrochloride intermediate (compound-2) is the common intermediate for risperidone and paliperidone, the pyridopyrimidine intermediate (Compound-3) is unique to paliperidone. This intermediate is a subject matter of this instant invention.

## SCHEME : 1



The key step in the prior art processes for synthesis of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) is the reduction of pyridine ring of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4W-pyrido[1,2-a]pyrimidin-4-one (compound-4) (Scheme-2).

**SCHEME : 2**



As described in '952 patent reduction of pyridine ring of (compound-4) is carried out using Pd/C catalyst in methanol. International publication WO2008/024415A2 (herein after designated as '415 application) discloses reduction of pyridine ring under highly acidic conditions at pressure of 2 to 2.5 bar in methanol. Journal article in Organic Process Research & Development 2005, 9, pages 344-347 (herein after designated as OPRD paper) , describes reduction of pyridine ring at very low pressure (150 mbar) in methanol using hydrochloride salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound -4).

International publication WO 2008/140646 discloses process for the synthesis of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and intermediates thereof.

International publication WO 2008/087557 describes an improved process for preparation of 9-hydroxy-3-(2-chloroethyl)- 2-methyl-4h-pyrido[1,2-a]pyrimidin-4-one hydrochloride.

International publications WO 2008/140646 and WO 2008/024415 describe process for the synthesis of 3-(2-chloroethyl)- 6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[ 1,2-a]- pyrimidin-4-one (CMHTP) and intermediate thereof.

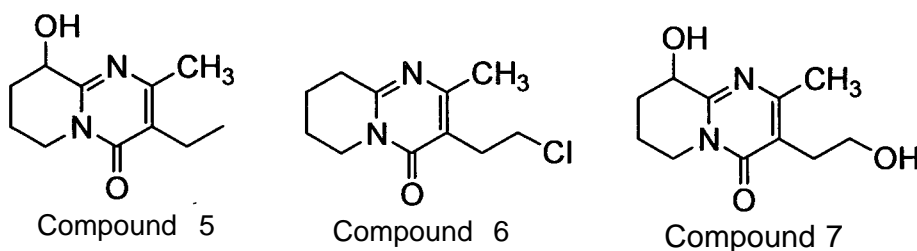
International publication WO 2008/087557 describes an improved process for preparation of 9-hydroxy-3-(2-chloroethyl)- 2-methyl-4h-pyrido[1,2-a]pyrimidin-4-one hydrochloride

International publications WO 2008/140641 and WO2008/021346 provide pure paliperidone and processes for preparing thereof.

International publication WO 2008/021345 describes a process for preparing paliperidone from its intermediate 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one

International publication WO 2008/021342 provides amorphous and crystalline forms of paliperidone, and processes for preparing thereof.

The Organic Process Research & Development (OPRD) paper, 2005, 9, 344-347 and '415 application describe formation of side products (compounds 5, 6 and 7) during hydrogenation process .



Compound 6 can react further in the synthetic path way of Paliperidone and give corresponding Paliperidone analogue as impurity in the final product. The OPRD process mentions hydrogenation at low pressure. Failure to meet stringent requirement of low

pressure leads to formation of impurities. The process of '415 application is fraught with problems like corrosion of plant equipment due to use of hydrochloric acid in the reduction step.

Most of the prior art processes are involving the use of methanol and Hydrogen chloride (HCl) during catalytic hydrogenation. In the absence of HCl the dechloro impurity is formed in higher proportion which results in yield loss. The involvement of HCl leads to corrosion and necessitates use of glass lined autoclave during hydrogenation step.

The other problems associated with these prior art processes are deactivation of catalyst which warrants filtration of deactivated catalyst and charging of fresh catalyst which makes the operation cumbersome.

Thus, there is a need to provide an improved and industrially scalable process for the preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one (compound-3) an intermediate used in the synthesis of Paliperidone and process for converting the same to Paliperidone.

### SUMMARY OF THE INVENTION

The object of present invention is to provide an improved and industrially scalable process for the preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3).

Another object of present invention is to provide a process for the preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) or its benzyl derivatives or their acid addition salts by catalytic hydrogenation using an organic acid as solvent.

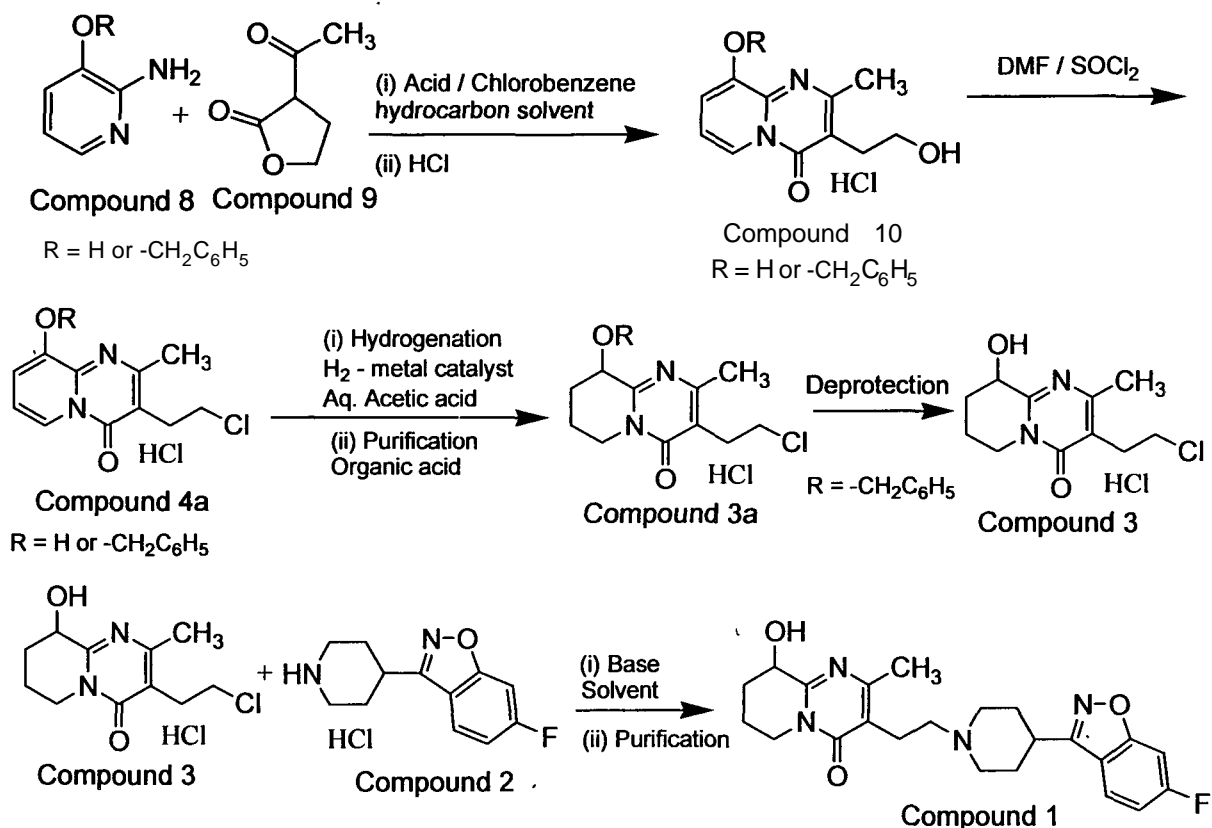
Yet another object of present invention is to provide a process for purification of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) by formation of corresponding acid addition salt.

Yet another object of the invention is to provide a process for conversion of hydrochloride salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) to Paliperidone.

### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) is obtained by catalytic hydrogenation of hydrochloride salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4) using an organic acid as solvent which is further optionally purified by forming an acid addition salt in presence of an organic solvent. The acid addition salt is filtered and base is added to filtrate to form the free base. The free base is further reacted with compound 2 to give Paliperidone. The process of the invention is depicted in scheme-3

## SCHEME: 03



The compound of formula 4a is obtained by the known process in art.

2-Amino-pyridin-3-ol is reacting with 3-Acetyl-dihydro-furan-2-one in presence of strong acid and organic solvent to give 9-Hydroxy-3-(2-hydroxy-ethyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one or its acid addition salts (Compound 10)

Compound 10 is treated with chlorinating agent in presence of organic solvent to give hydrochloride salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4). The strong acid provides a proton source in instant reaction, which is used from sulfuric acid, hydrochloric acid, aryl sulfonic acid, p-toluene sulfonic acid, methane sulfonic acid, strong cation exchange resins, solid acids, super acids and like. The solvent for the reaction is selected from aromatic hydrocarbon solvents such as benzene, toluene, xylene, decalin; alicyclic hydrocarbons such as cyclohexane, methyl cyclohexane; chlorinated solvents such as chlorobenzene, carbon tetrachloride. The reaction is conducted at high temperature ranging from 50 to 160 °C. The reaction is carried out till 2-amino-3-hydroxypyridine is less than 2 %.

The chlorinating agents are selected from thionyl chloride, sulfonyl chloride, oxalyl chloride, phosphorus trichloride, phosphorus oxychloride and cyanuric chloride. The solvent used for the chlorination reaction is selected from halogenated solvents such as chloroform, dichloromethane, ethylene dichloride, aromatic hydrocarbon solvents such as benzene, toluene, xylene; aprotic polar solvents such as, N,N dimethyl formamide, N,N dimethyl acetamide, N-methyl 2-pyrrolidone, 1,3-dimethyl imidazolidin-2-one, 1,3 dimethyl propylene urea, tetramethyl urea; sulfolane; alicyclic hydrocarbons such as cyclohexane, methyl cyclohexane.

3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) is obtained by catalytic hydrogenation of hydrochloride salt of 3-(2-

chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4) using an organic acid as solvent. The catalytic hydrogenation of hydrochloride salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4) is carried out in presence of raney nickel or other precious metal catalysts such as palladium, rhodium, ruthenium, platinum, iridium, palladium on charcoal and the like in an organic acid as a solvent. The organic acid is selected from formic acid, acetic acid, propanoic acid and the like. The organic acid is optionally being used in aqueous condition wherein the amount of water is ranging from 0% to 99%. The reaction is carried out at temperature ranging from 40 to 140°C under hydrogen pressure after completion of reaction, pH of the reaction mixture is adjusted. In case of compound-3a both the steps hydrogenation of ring double bonds and debenzoylation take place simultaneously to give Compound 3. The crude is purified by the formation of organic acid addition salt in organic solvent. The acid addition salt is filtered and further converted in to free base by treatment with base. The organic acid used for the purification of Compound 3 is oxalic acid, tartaric acid and like. The organic acid addition salt is converted to free base using the base which is selected from potassium acetate, sodium acetate and like. The aqueous acetic acid is preferred as solvent for catalytic hydrogenation of hydrochloride salt of 9-benzyloxy-3-(2-hydroxyethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4a) or 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4) using metal catalyst to give 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3).

N-alkylation reaction of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) with (6-fluoro-3-piperidine-4-yl)-1,2-benzisoxazole is carried out using a base in organic solvent to give Paliperidone. The organic solvent is selected from ethers such as tetrahydro furan (THF), dioxane, methyl tert. butyl ether, di-n-propyl ether; nitriles such as acetonitrile, propionitrile; aliphatic and alicyclic solvents such as hexane, heptane, cyclohexane, methyl cyclohexane; ketonic solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone, alcohols such as C<sub>1</sub> to C<sub>5</sub>; benzotrifluoride, sulfolane, DMSO, N,N-dimethyl formamide [DMF], N,N-dimethyl acetamide [DMA], N-methyl 2-pyrrolidone, 1,3-dimethyl imidazolidin-2-one, 1,3 dimethyl propylene urea, tetramethyl urea; sulfolane. The base used in this reaction is selected from carbonates such as sodium carbonate, potassium carbonate, cesium carbonate; alkoxides of C<sub>1</sub> to C<sub>4</sub> alcohols; or organic tertiary amine bases such as C<sub>1</sub> to C<sub>4</sub> trialkyl amines, N-methyl morpholine, N-methyl pyrrolidine, N-methyl piperidine, Diaza(1,3)bicyclo[5.4.0]undecane [DBU], 1,5-Diazabicyclo[4.3.0]non-5-ene [DBN] and 1,4-diazabicyclo[2.2.2]octane [DABCO]. The reaction is carried out at 0 to 150°C, preferably at 10 to 100°C. N-alkylation can also be carried out using a phase transfer catalyst.

3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one (compound-3) is further purified by forming an acid addition salt in presence of an organic solvent. The acid addition salt is filtered and base is added to filtrate to form the free base. The free base is further reacting with compound 2 to give Paliperidone. The organic

acid used for the purification of compound 3 is oxalic acid, tartaric acid and like. The organic acid addition salt is converted to free base using the base which is selected from potassium acetate, sodium acetate and like.

The obtained Paliperidone is purified from solvent selected from acetonitrile, C1 to C5 alcohols, amides such as DMF, DMA, ethers such as 2-methyl THF, THF, dioxanes, esters such as alkyl acetates, water, benzotrifluoride, methyl cellosolve, or mixtures thereof. The invention is further illustrated with following non-limiting examples.

**Example-1 Preparation of 9-hydroxy-3-(2-hydroxyethyl)-2-methyl-4W-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Compound-10)**

100 g of 2-Amino-3-hydroxypyridine, 6 g of p-toluene sulfonic acid, 140 g of  $\alpha$ -acetyl- $\gamma$ -butyrolactone, and 800 mL of chlorobenzene were charged into RBF outfitted with Dean-Stark distillation apparatus. The reaction mixture was heated up to 130 °C and maintained for 18-20 h in 200 mL of IPA was added to the reaction mass. The reaction mass was stirred at 95 °C. Charcoal was added followed by stirring for 20 - 30 min. and then mass was filtered through Hy-flow. The hyflow bed was washed with of hot IPA. Filtrate was transferred in another 4-necked RBF and 15% IPA-HCl was added followed by cooling to about 25°C and then stirred. The precipitated solid was filtered and washed with of IPA. The solid was suck dried under vacuum to yield 175 g of product (compound-10) in 75% yield and >97% purity.

**Example -2 Preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one HCl salt (Compound-4a)**

A mixture of 9-hydroxy-3-(2-hydroxyethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (100 g) and N.N-dimethyl formamide (400 mL) were charged into RBF at ambient temperature. Thionyl chloride (42.4 mL) was added in portion to reaction mixture at 30-40°C. The reaction mass was heated up to 65-70 °C and maintained for 3 h. Then reaction mass was cooled to 50 - 55°C. 25 mL Methanol was added to the reaction mass and the resultant mixture was allowed to stir for 30 min.. Ethyl acetate was added and the reaction mass and was allowed to cool down to 30 - 35 °C. This reaction mass was stirred for 1 hr. The solid compound was filtered and the wet cake washed with Acetone. The solid was dried under vacuum to afford 92-95 g of product (Compound-4a) with HPLC purity >99%.

**Example-3 Preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one HCl salt (Compound-3) using an Acetic acid as solvent**

Hydrochloride salt of Compound-4 (100 g) was dissolved in 1:1 aqueous acetic acid (800 mL) and heated up to 50 - 55 °C followed by the addition of charcoal (10 g) at 50 - 55 °C. The content was stirred for 30 min at 50 - 55 °C. The mass was filtered through hyflow and washed with 1:1 aqueous acetic acid (100 mL). This filtered mass was charged into a 2 L hydrogenator at 25 - 35 °C followed by the addition of Pd-C (10%, 10 g) and the pressure of hydrogen gas was maintained in the range of 4.0 -4.5 kg/cm<sup>2</sup> at 40-45 °C. The reaction progress was monitored by HPLC. If reaction rate

comes down, then again slurry of Pd/C (10 %, 5 g) in 1:1 aqueous acetic acid (50 mL) was charged and the reaction continued. After completion of the reaction, catalyst is filtered and filtrate distilled off completely to afford 100-105 g crude product in the form of oily mass which is used in the next step.

**Example-4 Preparation of 9-benzyloxy-3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one HCl salt (Compound-3a) using an Acetic acid as solvent**

Hydrochloride salt of Compound-3a (125 g) was dissolved in aqueous acetic acid (800 mL) and heated up to 50 - 55 °C followed by the addition of charcoal to reaction mixture. The content was stirred for 30 min. The mass was filtered through hyflow and washed with aqueous acetic acid (100 mL). This filtered mass was charged into a 2 L hydrogenator at 25 - 35 °C followed by the addition of 10% Pd-C and the pressure of hydrogen gas was maintained in the range of 4.0 -4.5 kg/cm<sup>2</sup> at 40-45°C. On completion of the reaction, catalyst is filtered and filtrate was distilled off to afford 100-105 g crude product in the form of oily mass which is used in the next step.

**Example-5 Purification of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one using organic acid**

13.6 gm of oxalic acid dihydrate was taken in 250 ml water. 25 gm of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one was added and stirred at about 35-40°C for about 30 minutes. Clear solution was obtained. The solution was treated with charcoal and filtered. The filtered solution of oxalate salt was treated with ~25 gm of potassium acetate up to pH 4.8. The obtained mass was stirred at 0-5°C for about 1 hour. The obtained solid mass was washed with cold water. The wet mass was stirred with water for about 1 hour at 25-30°C. The mass was filtered and dried to give purified 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one. Wt. =15.2 gm

**Example- 6 Preparation of 3-[2-[4-(6-Fluoro-1, 2-benzisoxazol-3-yl) piperidin-1-yl] ethyl]-9-hydroxy -2-methyl-6, 7,8,9-tetrahydro-4H-pyrido [1,2-a] -pyrimidin-4-one (Compound-1)**

6-Fluoro-3-piperidin-4-yl-1, 2-benzisoxazole hydrochloride, (Compound-2) (100 g), potassium carbonate (143.4 g), potassium iodide (6.5 g) in acetonitrile was charged in RBF at 30 °C. The mixture was gradually heated upto 55-60 °C and stirred for 1 hr at 60 °C. Then previously prepared solution of hydrochloride salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (Compound-3) (100 g, compound 2) dissolved into 600 mL acetonitrile was charged drop wise into the reaction mass at 60 ± 2 °C in 1 h. Reaction was maintained under stirring for 46 h at 60 ± 2 °C. Reaction progress monitored continuously by HPLC and after reaction completion, acetonitrile was distilled out completely at 50°C- 55°C under reduced pressure. The obtained distilled crude product was slurried in DM water (1500 mL) and stirred for 1 h at 25°C-30 °C. The solid Product was filtered and washed with DM water. The solid product was dried in vacuum oven at 60 - 65°C for 10-12h to afford 140 - 145 g of crude Paliperidone (purity >95%) was obtained.

**Example- 7 Purification of 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl] ethyl ]-9-hydroxy -2-methyl-6,7,8,9-tetrahydro-4H-pyrido [1,2-a] -pyrimidin-4-one (Compound-1)**



Crude paliperidone (140 g) obtained in previous step was dissolved in of Isopropyl alcohol (4200 mL) at  $80 \pm 2^{\circ}\text{C}$  and charged activated charcoal (8.8 g). The content was stirred at  $80 \pm 2^{\circ}\text{C}$  for 30 min and filtered through hyflow in hot condition. The hyflo bed was washed with hot Isopropyl alcohol (140 mL). The filtered mass was gradually cooled up to  $0^{\circ}\text{C}$  and stirred it for 2 h at  $0-5^{\circ}\text{C}$ . The solid product was filtered and washed twice with chilled IPA (70 mL). The product was dried in vacuum oven at  $65-70^{\circ}\text{C}$  for 24 h. 85-90 g product (purity >99%) was obtained. Repeated purification was also made to afford adequate quality and color of the compound.

We claim,

1. Process for the preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, its benzyl derivative or their acid addition salts comprising:
  - a. catalytic hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido-[1,2-a]-pyrimidin-4-one or its acid addition salt using organic acid as solvent,
  - b. adjusting the pH and isolating the product,
  - c. purifying the product as obtained in step (b) by,
    - i. preparing the solution of a crude in organic solvent,
    - ii. forming the organic acid addition salt,
    - iii. converting the acid addition salt to free base by adding base,
  - d. optionally converting the product obtained in step (c) to 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]-pyrimidin-4-one or their acid addition salts.
2. Process for purification of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one comprising:
  - a. preparing a solution of crude 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in an organic solvent,
  - b. forming the organic acid addition salt,
  - c. converting the acid addition salt to free base by adding base,
  - d. isolating the product.
3. Process according to claim 1 Step (c) or 2 wherein organic acid is oxalic acid or tartaric acid.
4. Process according to claim 1 Step (c) or 2 wherein free base is potassium acetate.
5. Process according to claim 1 Step (c) or 2 wherein organic solvent is alcohol preferably methanol.
6. The process according to claim 1 wherein catalytic hydrogenation is carried out in presence of raney nickel or metal catalyst such as palladium, rhodium, ruthenium, platinum, indium, palladium on charcoal
7. Process for the preparation of pure Paliperidone comprising catalytic hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound-4) or its acid addition salt to 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (compound-3) or its acid addition salts using an organic acid as solvent.
8. Process according to claim 1 Step (a), 2 or 6 wherein organic acid is selected from acetic acid, formic acid, propanoic acid wherein acetic acid is preferred.
9. Process according to claim 1 Step (a), 2, 7 or 8 wherein organic acid is optionally used with water.
10. An oxalic acid or tartaric acid addition salt of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one.

Date: 03 December 2009

For, Cadila Pharmaceuticals Ltd.,

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Dr. Bakulesh M. Khamar  
Executive Director, Research