ACS Sustainable Chemistry & Engineering

Research Article

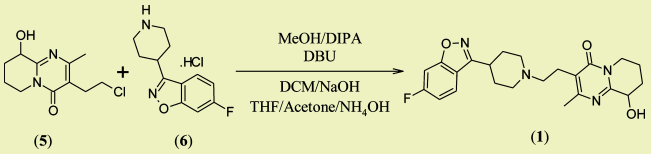
pubs.acs.org/journal/ascecg

An Improved and Efficient Process for the Production of Highly Pure Paliperidone, a Psychotropic Agent, via DBU Catalyzed *N*-Alkylation

Pavankumar V. Solanki, Sekhar Babu Uppelli, Bhushan S. Pandit, and Vijayavitthal T. Mathad*

Department of Process Research and Development, Megafine Pharma (P) Ltd., 201, Lakhmapur, Dindori, Nashik-422 202, Maharashtra, India

ABSTRACT: The present work describes an improved and efficient process for the synthesis of paliperidone (**1**), an antipsychotropic agent. The synthesis comprises the DBU (1,8-diazabicycloundec-7-ene) catalyzed *N*-alkylation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-a]-pyrimidin-4-one (**5**) with 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride (**6**) in methanol as the solvent and diisopropylamine as a base to yield paliperidone (**1**) with 85% yield and over 97% purity by HPLC. The present work also describes an industrially efficient purification process for the removal of critical process related impurities (**8** and **9**) in paliperidone (**1**). The process furnished **1** with an overall yield of about 60% and 99.85% purity.



(5) (6) (1)

KEYWORDS: *DBU Catalyzed Alkylation, Paliperidone, Psychotropic Agent*

INTRODUCTION

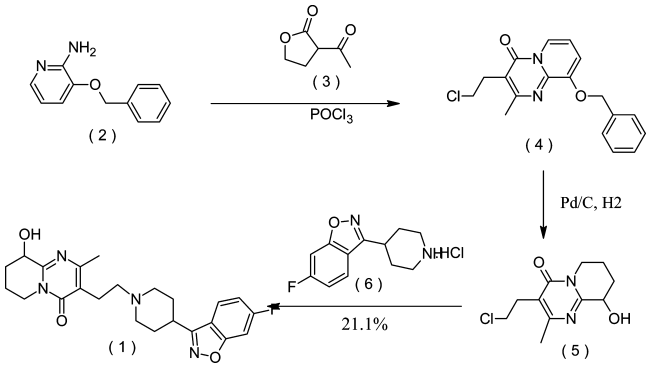
Process research and development of chemical processes for Active Pharmaceutical Ingredients (APIs) in the generic pharmaceutical industry is a highly challenging task due to limitations posed by continuous surfacing of patents and increased competition. Development of chemical processes for chemical intermediates and APIs by striking a balance between sustainability of the processes in terms of greener chemistry, production friendliness, safety, high throughput, reduction in the generation of effluent, minimal use of solvent for reaction or purification, etc., and cost barrier throughout its life cycle is a critical target to the team. Many times, formation of the impurities can be controlled or reduced during the reaction by understanding the thermodynamics and kinetics of the reaction rather than addressing it at later stage by extra purification processes involving huge amount of solvents and solvent mixtures. We report an improved and efficient process for production of highly pure paliperidone (**1**) addressing the above issues. Paliperidone (**1**), chemically designated as (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*pyrido[1,2-*a*]-pyrimidin-4-one (9-hydroxy-risperidone), is a primary active metabolite of risperidone. It is a second generation atypical antipsychotic drug that belongs to benzisoxazole derivatives developed by Janssen Pharmaceutica. Paliperidone (**1**) was approved by the FDA for the treatment of schizophrenia in 2006 and is marketed under the brand name INVEGA.[1−5] Paliperidone (**1**) is a centrally active dopamine D2 and serotinergic 5-HT_{2A} antagonist. It is also active an antagonist at α_1 and α_2 adrenergic receptors and H_1-histaminergic receptors. Paliperidone has one chiral center but as the pharmacological profiles of the racemate and two enantiomers are similar with respect to *in vitro* binding assays, *in vitro* receptor occupancy studies, and *in vivo* functional interaction studies hence, it is marketed in its racemate form.[6−12]

The first synthetic method[13] reported for paliperidone (**1**) involved the reaction of 3-(benzyloxy)pyridine-2-amine (**2**) with 3-acetyldihydrofuran-2-(3*H*)-one (**3**) in the presence of phosphoryl chloride as an activating agent to obtain 9-(benzyloxy)-3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-a]-pyrimidin-4-one (**4**), which was isolated, purified by column chromatography, and subsequently recrystallized from isopropanol. Debenzylation of **4** in methanol using Pd−C followed by condensation of hydroxypyrimidinone (**5**) with benzisoxazole (**6**) in methanol in the presence of diisopropylamine (DIPA) as the base furnished paliperidone (**1**) with an overall yield of 21% after column chromatography and subsequent crystallization from acetone and final crystallization from isopropanol (Scheme 1). The column chromatographic technique employed at various stages in the above-reported process is not feasible at industrial scale and leads to the generation of huge amount of effluents. Further, the overall yield obtained is only 21% thereby making the process expensive.

Subsequently, few improved processes reported for **1** follow the reaction sequence similar to that presented in Scheme 1 using compounds **5** and **6** as key starting materials with different bases and solvents.[14−16] The most difficult part of these reported processes is the elimination of keto paliperidone (**8**) formed in the process (Scheme 3). In order to eliminate impurity **8**, many purification processes have been reported, involving an additional reaction step reducing crude paliperidone (**1**) having **8** as an impurity using various reducing agents

Received: September 5, 2012
Revised: November 26, 2012
Published: December 31, 2012

Scheme 1. Reported Synthetic Approach for Paliperidone



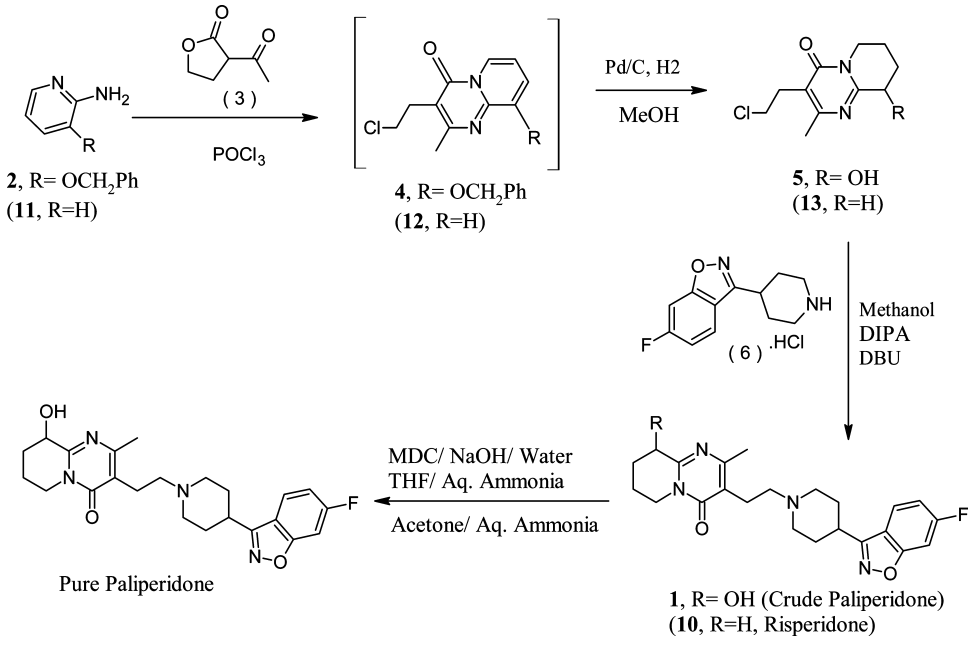
in order to convert **8** into paliperidone (**1**), which leads to an increase in the batch time cycle and thereby reduces the throughput and efficiency.[17−19] Few other processes developed for eliminating **8** involved multiple purifications that employed a huge volume (60−80 volumes per gram of crude **1**) of solvent due to low solubility of **1** in almost all the solvents including water, which in turn restricts the batch size in the commercial production thereby reducing the throughput.[20,21]

In order to overcome these limitations, we explored several experiments to understand process parameters such as mole ratio, solvents, screening of different bases and catalysts, and time and temperature. Herein, we report an improved and efficient process for paliperidone (**1**) via DBU-catalyzed nucleophile substitution (**5** with **6**) in methanol as a solvent and diisopropylamine as a base (Scheme 2). Another advantage of our process lies in a novel and environmentally friendly purification method for the control and removal of impurities (**5**, **6**, **7**, **8**, **9**, and **10**) using a minimum amount of solvent mixture (10−12 volumes per gram of crude **1**).

RESULTS AND DISCUSSION

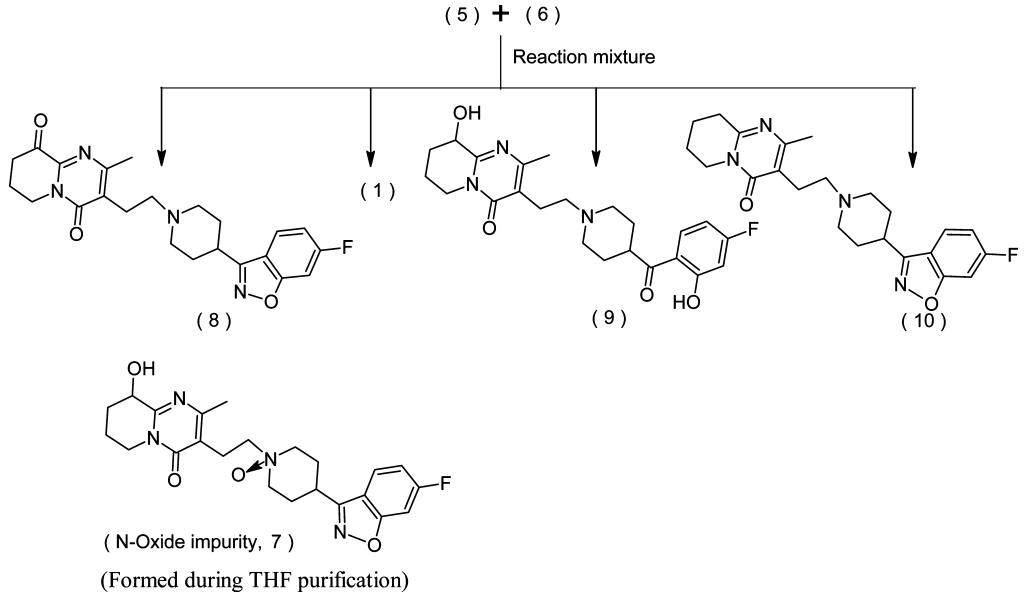
Preparation of Paliperidone (1). Most of the synthetic endeavors reported for the synthesis of paliperidone involve the use of the critical and cost-contributing intermediate **5** as one of the key penultimates. Intermediate **5** was prepared according to a literature process with modifications. Isolation, drying, and column chromatographic purification of **4** were avoided and was used *in situ* for the preparation of **5**.[22] The benzisoxazole intermediate **6** was prepared as per the literature procedure.[23] Condensation of **5** and **6** is a key step in the synthesis of paliperidone (**1**); hence, to establish the reaction parameters and the impurity profile at each stage, the condensation step was explored using various solvents such as DMSO, toluene, DMF, methanol, water, cyclohexane, and acetonitrile along with organic bases, such as pyridine, triethylamine (TEA), diisopropylamine (DIPA), and organic catalysts such as 1,8-diazabicycloundec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), and *N*,*N*-dimethylaminopyridine (DMAP). The reactions using TEA as a base resulted in inconsistent yield and purity along with the formation of **9** up to 20%; whereas the reaction with pyridine as a base did not proceed. The reaction using DIPA as a base in methanol furnished crude **1** with about 50% yield having excess amount of impurities **8** and **9** with a brownish colored tinge to paliperidone (**1**). Further, it was observed that the reaction did not proceed to completion at 45−50 °C even after 58 h, and the level of impurities (especially impurity **8** and some unknown impurities) were observed at higher percentage at reflux temperature. When a catalytic amount of DBU was used for the reaction along with DIPA as a base in methanol (5 volumes of methanol per gram of **5**),[24] the yield drastically improved to 85% with purity of about 97% by HPLC. Hence, the condensation reaction between **5** and **6** was established by employing methanol as a solvent, DIPA as a base, and DBU as a reaction catalyst as depicted in Scheme 2. The reaction temperature was then optimized to 55−60 °C at which the formation of impurities **8** and **9** were controlled below 1.0% during the reaction. After completion of the reaction (by HPLC), the reaction mass was cooled to 10−15 °C and filtered. The wet product was suspended in water, stirred at ambient temperature, filtered, and dried under vacuum at 50−55 °C for 3−5 h to get the

Scheme 2. Improved Process for Paliperidone (1)



dx.doi.org/10.1021/sc3000916 | ACS Sustainable Chem. Eng. 2013, 1, 243−248

Scheme 3. Flowchart for Impurities



crude paliperidone as a yellowish solid with 85% yield and about 97% purity by HPLC. The content of impurities (**5**, **6**, **7**, **8**, **9**, and **10**) has been evaluated thoroughly by HPLC in the crude **1** to establish the purification mechanism, and the data has been provided in Table 2.

Of the six impurities (Scheme 3), **5** and **6** are the key staring materials. Impurity **7** was identified as paliperidone *N*-oxide whose probability to be present in the product was low, and it was found to be a potential degradation product during forced degradation studies using hydrogen peroxide. Impurities **8** and **9** were side products formed in the reaction, whereas impurity **10** is carried over from amino pyridine intermediate (**2**). The formation of **9** was attributed due to benzisoxazole ring scission during the reaction and was eliminated selectively during an alkaline workup that involved the dissolution of crude **1** in dichloromethane and washing the dichloromethane solution with 5% aqueous solution of sodium hydroxide wherein **9** gets converted to its sodium salt and eliminated with water exclusively without any yield loss.

The formation of deshydroxy paliperidone (risperidone, **10**) in the product was investigated, and it was determined that the presence of trace amounts of 2-aminopyridine **11** in **2** undergoes a series of similar reactions along with **2** to generate **10** as an impurity in **1**. Removal of **10** in **1** was very difficult even after multiple crystallizations due to structural similarity to **1**. In order to have better control of **10**, the content of **13** was controlled in **5** with a limit of not more than 0.10% by HPLC (Scheme 2; Table 1). Crystallization of crude **1** was then explored in various solvents (DMF, DMSO, NMP, dimethylacetamide, *n*-propanol, 1-butanol, isopropanol, 1-pentanol, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, ethyl acetate, acetone, dioxane, dichloromethane) and their mixture with water. During the screening of solvents, it was observed that the combination of THF and water, with a volume of around 9−11 times with respect to crude **1**, was found to be effective for purification. During the exploration, it was also observed that crystallization at higher temperature (≥80 °C) imparts a pinkish to orange color to the product indicating sensitivity of the product on heating.

Table 1. Comparative Data of 10 in 1 by Using Varied Content of 13 in 5

exp. no	content of **13** in **5** (%)	content of **10** in **1** (%)
1	0.01	0.02
2	0.29	0.15
3	0.10	0.04

Surprisingly, we observed the formation of *N*-oxide impurity **7** upon THF−water purification that was absent in crude **1**. The formation of *N*-oxide impurity **7** was attributed to the presence of trace amounts of peroxide present in THF. To check the allowable limit of peroxide content in THF, crystallization was performed with THF having different peroxide contents, and it was observed that more than 0.015% of peroxide in THF leads to formation of impurity **7**. Thus THF containing peroxide content of ≤0.015% was used for the purification process. As a precautionary measure, a minimum quantity of ammonia solution along with tetrahydrofuran was used during the crystallization process that surprisingly gave an advantage not only by reducing the impurity **8** but also providing better yield (Table 2). The keto impurity **8** was formed during the course of reaction and identified as an acid degradation impurity.[25,26] An additional purification using a mixture of acetone and aqueous ammonia was established to remove any left over *N*-oxide impurity (**7**) and keto paliperidone (**8**) from the product. Additional purification involves suspending **1** in a mixture of acetone and aqueous ammonia (25−35 volumes with respect to **1**) at 50−54 °C for 2−3 h.

Scaleup Issues. It was observed that though the chemical purity of ≥99.70 was achieved for the scaleup batch in the pilot plant at 1.0 kg scale, the material failed in the organic volatile impurity test (OVI) by GC-HS, and the THF content was observed to be in the range of 2800−3600 ppm, well over its allowed limit of 720 ppm.[27] Removing the THF by different drying processes, i.e., milling and redrying at higher temperature of 80−90 °C, did not work at plant scale. Thus, the wet material obtained after the THF−ammonia purification was suspended in purified water, degassed for 2−3 h under vacuum

dx.doi.org/10.1021/sc3000916 | ACS Sustainable Chem. Eng. 2013, 1, 243−248

Table 2. Content of Impurities in 1 at Crude and Different Stages of Purification Process

batch no.	particulars	contents of impurities by HPLC (%) 5	6	7	8	9	10	1	THF content (ppm)
1	reaction mass	2.42	6.38	ND	1.02	0.30	ND	88.17	–
	crude	1.57	0.98	ND	0.30	0.15	ND	96.97	–
	after alkaline workup	1.52	0.94	ND	0.30	ND	ND	97.20	–
	THF–aq. ammonia purification	0.03	0.06	ND	0.07	ND	ND	99.80	1800
	acetone–aq. ammonia purification	0.01	ND	ND	0.05	ND	ND	99.88	520

at 60–65 °C, filtered hot, washed with purified water, and dried under vacuum to obtain **1** containing THF in the OVI test in the range of 1300–1800 ppm. Further suspension of dried product in a mixture of acetone–ammonia solution (25–35 volumes) furnished highly pure paliperidone (**1**), meeting specification (Table 2).

EXPERIMENTAL SECTION

General. Melting points were determined on Analab melting point apparatus in open capillary tubes and are uncorrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts were reported in parts per million using tetramethylsilane as internal standard and are given in δ units. The solvents for NMR spectra were deuterochloroform and deuterodimethylsulfoxide unless otherwise stated. Infrared spectra were taken on Perkin-Elmer Spectrum 100 in potassium bromide pallets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer, and the results were within ±0.35% of the calculated values. High-resolution mass spectra were obtained with a Shimadzu GC-MS QP mass spectrometer with an ionization potential of 70 eV. All reactions were monitored by high performance liquid chromatography (HPLC) on Agilent Technologies 1200 series. Gas chromatography on Agilent Technologies 7683B with head space was used for analyzing the residual solvents. Common reagent grade chemicals used were either commercially available and were used without further purification or prepared by standard literature procedures.

Scaleup Batch. *Synthesis of Crude Paliperidone (1).* Methanol (50.0L), 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-4H-pyrido-[1,2-a]pyrimidin-4-one (10.0 kg 41.2 mols), diisopropyl amine (9.2 kg 91.08 mols), DBU (100.0 g), and 6-fluoro-3(4-piperidinyl)-1,2-benzisoxazole hydrochloride were charged (11.1 kg 43.24 mols) to the reactor. Reaction mass was then heated to 55–60 °C and was maintained at this temperature for 36–38 h for completion of reaction. Completion of reaction was monitored by HPLC. The reaction mass was cooled to 10–15 °C, stirred for 60 min, and centrifuged. The cake obtained was washed with methanol (5.0 L). Weight of wet product was 17.45 kg; HPLC purity of paliperidone, 96.97%; impurity **8**, 0.30%; impurity **9**, 0.15%. The wet product obtained was suspended in purified water (50.0 L), stirred for 60 min, and centrifuged. The obtained wet cake was washed with purified water (5.0 L). Weight of wet product was 16.45 kg. The obtained wet material was dried under vacuum in a vacuum tray dryer at temperature (50–55 °C) for 3 h to obtain dry product (15.26 kg).

Purification process. *Semi-Pure Paliperidone (1).* Crude **1** (15.26 kg) and dichloromethane (320.5L) were charged to the reactor and stirred at temperature (28–30 °C) until clear solution was obtained. To the obtained clear solution was added 5% aqueous solution of sodium hydroxide (prepared by dissolving sodium hydroxide, 3.81 kg, in purified water, 76.30 L). The mixture was stirred for 30 min, and layers were allowed to settle for 30 min. The dichloromethane layer was separated from the aqueous phase. The dichloromethane layer was further washed with 5% aqueous solution of sodium hydroxide (76.3 L × 2) followed by purified water (76.3 L × 2), and finally the dichloromethane layer was treated with activated carbon (700 g) and stirred for 30 min. The dichloromethane layer was then filtered over a Celite bed, and the bed was washed with dichloromethane (15.0 L). The combined filtrate and washing was subjected for distillation under vacuum to obtain the crude paliperidone.[28]

The crude paliperidone obtained was treated with tetrahydrofuran (15.0 L) and stirred for 10 min. Tetrahydrofuran was distilled under vacuum to obtain the residue.[29] To the obtained residue was added tetrahydrofuran (112.6 L) and aqueous ammonia (48.0 L, prepared by mixing 7.20 L of liquor ammonia and 40.8 L of purified water), and the mixture was heated to reflux temperature (59–61 °C) until clear solution was obtained. The obtained clear solution was gradually cooled to 0–5 °C and stirred for 60 min. The precipitate obtained was filtered and washed with purified water (15.0 L). Weight of wet product was 17.46 kg.

Obtained wet cake (17.46 kg) was charged to purified water (256.0 L), and the obtained slurry was heated to 60–65 °C and degassed for 2–3 h under vacuum. To the obtained slurry after degassing was added purified water (46.0 L), and the slurry was maintained at 60–65 °C for 30 min. Slurry was then hot centrifuged. The wet cake obtained was washed with purified water (46.0 L). Obtained wet cake was dried in a vacuum tray dryer at 70–75 °C for 12–14 h. Dry weight of **1** was 12.0 kg; HPLC purity of paliperidone, 99.80%; impurity **8**, 0.07%; impurity **9**, not detected.

Pure Paliperidone (1). Semi-pure paliperidone (**1**) (12.0 kg) obtained above was charged to a mixture of acetone (225.0 L) and aqueous ammonia (75 L prepared by mixing 11.25 L of liquor ammonia and 63.75 L of purified water), and the obtained slurry was heated to reflux temperature (50–54 °C) for 2–3 h. The reaction mass was then gradually cooled to 0–5 °C and stirred for 60 min. The slurry was then filtered and washed with purified water (36.0 L). Weight of wet product was 15.30 kg. Obtained wet product was dried under vacuum at 70–75 °C for 12–14 h. Dry weight of **1** was 10.5 kg (60% over all). HPLC purity of paliperidon, 99.88%; impurity **8**, 0.05%; mp, 185–188 °C. IR (KBr) cm^{-1}: 3291, 2935, 2785, 2755, 2726, 2660, 1628, 1535, 1270, 1184, 1131. MS *m*/*z* (%): 245.26 [M-H]$^{+}$. ^{1}H NMR (400 MHz, DMSO): δ = 1.80–1.95 (m, 8H), 2.00–2.04(t, 2H), 2.26 (s, 3H), 2.36–2.41(t, 2H), 2.60–2.64(t, 2H), 3.01–3.09(t, 2H), 3.13–3.16(m, 1H), 3.64–3.68(t, 1H), 3.87–3.92(d, 1H), 4.43–4.44(bs, 1H), 5.70–5.72(bs, 1H), 7.24–7.30(t, 1H), 7.66–7.30(d,1H), 7.98–8.03(q,1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 16.86 (CH2), 20.87(CH2), 23.35(CH3), 27.08(CH2), 30.11 (2 CH), 33.42(CH); 41.73(CH2), 52.78 (2 CH), 56.24(CH2), 66.27(CH), 97.40, 112.54, 117.18, 119.48, 123.80, 157.08, 157.72, 161.30, 162.32, 162.99,164.77 ppm. Anal. Calcd for $C_{23}H_{27}FN_4O_3$: C, 64.76; H, 6.33; N, 13.13. Found C, 65.11; H, 5.94; N, 13.07.

Preparation of Compound 5. To a stirred solution of toluene (500 mL) and 2-amino-3-benzyloxy pyridine (50 g,0.25 mol) was added phosphoryl chloride (150.0 g) in a period of 2–3 h, followed by stirring at 25 to 30 °C for 1 h. 3-Acetyldihydrofuran-2-(3H)-1 (75 g, 0.59 mol) was added to the reaction mass at 50–55 °C in a period of 3–4 h followed by stirring for 1 h. The reaction mass was heated to 68–70 °C and maintained for about 30–35 h. Phosphoryl chloride and toluene was distilled out under reduced pressure below 75 °C. Toluene (100 mL) was added to this reaction mass, and it was further quenched over crushed ice (350gm) and stirred for 30 min at 30–35 °C. The reaction mass was heated to 45–50 °C. Layers were allowed to settle, and the toluene layer was separated from the aqueous layer. The aqueous layer was washed with toluene (100 mL), and toluene layer was separated at 45–50 °C. The aqueous layer was stirred for 12 h at 25–30 °C, and the Pd/C catalyst (50% wet; 15 g of 10%) was charged to the aqueous layer. The reaction mass was heated to 50–55

dx.doi.org/10.1021/sc3000916 | ACS Sustainable Chem. Eng. 2013, 1, 243–248

°C and was further hydrogenated at atmospheric pressure for 20 to 25 h. The reaction mass was filtered to recover the Pd/C catalyst. To the obtained filtrate was added chloroform (400 mL), and pH of the filtrate was adjusted to 6.0−7.0 using ammonia solution. The reaction mass was stirred for 30 min. Layers were allowed to settle for 30 min. The chloroform layer was separated from the aqueous phase and decolorized using activated carbon (3 g). The chloroform layer was filtered over a Celite bed, and the bed was washed with chloroform (100 mL). Combined filtrate was subjected for distillation under vacuum to obtain the crude **5** as a solid. To the obtained crude **5** was charged methanol (150 mL) and heated to 60−65 °C to obtain a clear solution. The reaction mass was gradually cooled to 0−5 °C and stirred for 60 min to obtain precipitate. The obtained precipitate was filtered and washed with methanol (30 mL) and dried at 70−80 °C to obtain 30 g of desired product. HPLC purity: 99.5%. IR (KBr): 3145.80, 2965.68, 1664.21, 1531.82, 1486.08, 1326.72, 1183.89 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ = 3.64−3.72 (t, 3H), 1.792−2.07 (m, 4H), 4.43−4.45 (bs, 1H), 5.73 (s, 1H), 2.28 (s, 3H), 2.87−2.91(t, 2H), 3.88−3.92 (t, 1H). MS *m*/*z* (%): 242.95 $[M+1]^+$ (100).

Preparation of Keto Paliperidone 8. Paliperidone (50 g) was charged to methanol (500 mL), and to the obtained slurry was added concentrated hydrochloric acid (20 mL). The obtained clear solution was heated to 45−50 °C for over 160 h. Formation of keto paliperidone was monitored by HPLC. Once the desire conversion of product was achieved (40%, content of paliperidone 5%), methanol was then distilled under vacuum to obtain syrup. Acetonitrile (500 mL) was added and heated to reflux for 30 min and hot filtered over a Celite bed. Obtained filtrate was concentrated under vacuum to obtain the syrup. To the obtained syrup was added isopropyl alcohol (100 mL) and heated to reflux for 15 min and filtered hot over a Celite bed. The filtrate was cooled to 25−30 °C, and the obtained precipitate was filtered and dried under vacuum. Yield: 4.3 g. HPLC purity: 87%. IR (KBr): 1721.52, 1655.23, 1608.81, 1519.39, 1276.03, 959.64 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ = 2.20−2.27 (m, 2H), 2.32−2.38 (m, 4H), 2.41 (s, 3H), 2.74−2.76 (t, 2H), 3.02−3.07 (dd, 2H), 3.14−3.23 (m, 4H), 3.48 (s, 1H), 3.73−3.76 (t, 2H), 4.02−4.06 (t, 2H), 7.31−7.38 (td, 1H), 7.72−7.75 (dd,1H), 8.18−8.23 (dd, 1H). MS *m*/*z* (%): 425.2 $[M+1]^+$ (100).

Preparation of Paliperidone *N*-oxide 7. Paliperione (25 g) was added to 50% hydrogen peroxide (875 mL) and stirred to obtain clear solution. Obtained clear solution was maintained at a temperature of 30−35 °C for 52 h. Formation of paliperidone *N*-oxide was monitored by HPLC. Once the desire conversion of product was achieved (85−90%, content of paliperidone 2%), the reaction mass was cooled to 0−5 °C and basified with ammonia solution until pH 9−10 was achieved. Obtained solid was stirred for 1 h at 0−5 °C and then filtered and dried under vacuum at 50−55 °C. Yield, 9.5 g; HPLC purity, 92.59%. Obtained product was further charged to a mixture of isopropyl alcohol (178 mL) and water (59 mL), and the mixture was refluxed for 30 min, cooled to 25−30 °C, and then filtered and dried under vacuum at 50−55 °C. Yield: 7.3 g. HPLC purity: 97.04%. IR (KBr): 3399.9, 3054.70, 1638.38, 1528.97, 1474.56, 1268.70, 1117.65, 959.45 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ = 7.30−7.36 (td, 1H), 8.01−8.04 (dd, 1H), 7.71−7.74 (dd, 1H), 1.78−2.03 (m, 6H), 3.15−3.23 (m, 4H), 3.33−3.41 (m, 3H), 3.00−3.04 (t, 2H), 3.60−3.71 (m, 1H), 3.89−3.95 (td, 1H), 2.60−2.70 (d, 2H), 4.45 (s,1H), 2.29 (s 3H), 5.98 (s, 1H). MS *m*/*z* (%): 443$[M+1]^+$ (100).

AUTHOR INFORMATION

Corresponding Author

*Telephone: +91 2557 250121, +91 9822581611. Fax: +912557 250586. E-mail: drvtmathad@yahoo.co.in, vt.mathad@megafine.in.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the management of Megafine Pharma (P) Ltd., for supporting this work. We also thank colleagues of the Analytical Research and Development Department, Megafine Pharma (P) Ltd., for their valuable cooperation in developing the chromatographic methods for establishing the process and identifying the impurities. Funding was provided by Megafine, Publication Number MF/013/2012.

REFERENCES

(1) Green, B. Paliperidone: A clinical review. *Curr. Drug Ther.* **2009**, *4*, 7−11.

(2) Schotte, A.; Janssen, P. F. M.; Gommeren, W. Risperidone compared with new and reference antipsychotic drugs: In vitro and in vivo receptor binding. *Psychopharmacology* **1996**, *124*, 57−73.

(3) INVEGA. http://www.invega.com (accesed January 3, 2013).

(4) Medscape. http://www.medscape.com/viewarticle/740676 (accesed January 3, 2013).

(5) Highlights of Prescribing Information, INVEGA, Paliperidone, Extended-Release Tablets. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021999s018lbl.pdf (accesed January 3, 2013).

(6) Megens, A. A. H. P.; Awouters, F. H. L. In vivo pharmacological profile of 9-hydroxyrisperidone, the major metabolite of the novel antipsychotic risperidone. *Drug Dev. Res.* **1994**, *33* (4), 399−412.

(7) Yasui-Furukori, N.; Hidestrand, M.; Spina, E.; Facciola, G.; Scordo, M. G.; Tybring, G. Different enantioselective 9-hydroxylation of risperidone by the two human CYP2D6 and CYP3A4 enzymes. *Am. Soc. Pharmacol. Exp. Ther.* **2001**, *29*, 1263−1268.

(8) Tianmei, S.; Liang, S.; Yi, L.; Yun'Ai, S.; Chunmei, G.; Hongyan, Z. Single-dose pharmacokinetics of paliperidone extended release tablets in healthy Chinese subjects. *Hum. Psychopharmacol.* **2010**, *25* (5), 404−409.

(9) Corena-McLeod, M. P.; Oliveros, A.; Charlesworth, C. Paliperidone as a mood stabilizer: A pre-frontal cortex synaptoneurosomal proteomics comparison with lithium and valproic acid after chronic treatment reveals similarities in protein expression. *Brain Res.* **2008**, *1233*, 8−9.

(10) Marchese, G.; Pittau, B.; Casu, G. A comparison of continuous subcutaneous paliperidone infusion and repeated subcutaneous injection of risperidone free-base in rats. *Eur. Psychiatry* **2010**, *25* (2), 92−100.

(11) Arakawa, R.; Ito, H.; Takano, A. Dose-finding study of paliperidone ER based on striatal and extrastriatal dopamine D2 receptor occupancy in patients with schizophrenia. *Psychopharmacology* **2007**, *197* (2), 229−235.

(12) INVEGA Product Monograph. http://www.janssen.ca/product/168 (accessed January 9, 2013).

(13) Janssen, C. G.M.; Knaeps, A. G.; Kennis, L. E. J.; Vandenberk, J. 3-[2-[4-(6-Fluoro-1,2-benzisoxozol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9 Tetrahydro-9-hydroxy-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one, Compositions and Method of Use. U.S. Patent 5,158,952, 1992.

(14) Rameshchandra, S. K.; Vineet, M.; Hukamchand, J. S.; Natvarlal, P. S.; Omprakash, S. A.; Rajaram, B. U.; Ambalal, M. I. An Improved Process for the Preparation of Paliperidone. Patent WO2010/089643A1, 2010.

(15) Narayanrao, K. R.; Ramachandra, R. D.; Laxminarayan, P. S. Processes for the Preparation of Paliperidone and Pharmaceutically Acceptable Salts Thereof and Intermediates for Use in the Processes. WO2009/047499A2, 2009.

(16) Reddy, R. B.; Muthulingam, A.; Saravanakumar, K. G.; Kondalarao, P. An Improved Process for the Preparation of Pure Paliperidone. Patent WO2011/015936A2, 2011.

(17) Bapat, U. R.; Jayamani, M.; Ravisaravanan, S.; Sodha, V. A; Valgeirsson, J. Highly Pure Paliperidone or a Pharmaceutically Acceptable Salt Thereof Substantially Free of Keto Impurity. U.S. Patent 20090247553 A1, 2009.

(18) Manne, S. R.; Sajja, E.; Revu, S. Novel and Improved Processes for the Preparation of Paliperidone. Patent WO2010/004578 A2, 2010.
(19) Girish, D.; Shahaji, K. A.; Laljibhai, P. J.; Sharadchandra, P. N. Paliperidone or a Pharmaceutically Acceptable Salt Thereof Substantially Free of Impurities. Patent WO2011/030224 A2, 2011.
(20) Janakiramarao, R.; Muddasani, P.; Bhujangarao, A. K.; Nannapaneni, V. C. An Improved, Industrially Viable Process for the Preparation of High Purity Paliperidone. Patent WO2009/010988 A1, 2009.
(21) Milos. R.; Darja, P.; Anica, P.; Matej, S. Process for the Preparation of Paliperidone. Patent WO2010/014047 A1, 2010.
(22) Mathad, V. T.; Joshi, D. R.; Lad, H. D.; Patel, P. I.; Solanki, P. V. An improved One-Pot Process for the Preparation of CHP, a Paliperidone Intermediate. Indian Patent Application No. 80/MUM/2012, 2012.
(23) Strupczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Stache, U.; Glamkowski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. Synthesis and neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. *J. Med. Chem.* **1985**, *28*, 761−769.
(24) Volume of methanol required for the reaction has been critically evaluated during optimization [3,5 and 7 times with respect to compound **5** and found that any amount less than 5 times leads to formation of thick mass and creates problems in stirring and mixing, whereas volume greater than 5 results in loss of yield.
(25) Milos, R.; Anica, P.; Darja, P.; Igor, P.; Andrej, K.; Jernej, H.; Miha, P. Process for the Synthesis of Paliperidone. European Patent 2275423A1, 2011.
(26) Jadhav, S. A.; Landge, S. B.; Choudhari, P. B.; Solanki, P. V.; Mathad, V. T.; Bembalkar, S. R. Stress degradation behavior of paliperidone, an antipsychotic drug, and development of suitable stability-indicating RP-LC method. *Chromatogr. Res. Int.*.**2011**, DOI:10.4061/2011/256812.
(27) ICH Harmonized Tripartite Guideline. Impurities: Guideline for Residual Solvents, Q3C (R5). http://www.ich.org/products/guidelines/quality/quality-single/article/impurities-guideline-for-residual-solvents.html (accessed January 3, 2013).
(28) Distillation of the dichloromethane layer was ceased once the collection of solvent is stopped at the solvent receiver unit.
(29) Distillation of tetrahydrofuran was ceased once the collection of solvent is stopped at the solvent receiver unit.