Organic Process Research & Development **2009**, *13*, 792–797

An Improved and Single Pot Process for the Production of Quetiapine Hemifumarate Substantially Free from Potential Impurities

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Abstract:

An improved and single pot process for the preparation of Quetiapine hemifumarate (1), an antipsychotic drug, free from potential impurities is reported with an overall yield of 80%. The reported process for its preparation suffers from the drawback of producing potential impurities identified as 11-piperazin-1-yldibenzo[*b,f*][1,4]thiazepine (6), 2-(4-dibenzo[*b,f*][1,4]thiazepin-11-ylpiperazin-1-yl)ethanol (10), dimer (9), and *N*-methyl-*N*-phenyldibenzo[*b,f*][1,4]thiazapine-11-amine (14). Elimination of these impurities in the process is achieved by chlorination of 3 followed by in situ condensation of obtained 4 with highly pure 8 and subsequently establishing the pH based workup to obtain free base 2, which is further converted to quetiapine hemifumarate salt free from all these impurities. In this report, different aspects of process development such as scheme selection, optimization of different process parameters, identification, synthesis, origin and control of impurities, and development of an accurate analytical method during the development of a scalable process for quetiapine hemifumarate are discussed.

Introduction

Selection of the "synthetic scheme" for a pharmaceutical product prior to process research and development in pharmaceutical companies is a critical activity for chemists not only to meet the economics of the growing competition but also to ensure quality and to be noninfringing under patent restrictions, especially in the generic environment. Impurities in the API are very specific to the scheme selected for its preparation. Their elimination sometimes triggers a change in the scheme or follows techniques, like column chromatography, which are industrially not feasible. In most cases, achieving 99.0% HPLC purity is not difficult by any of the processes known, but bringing the known impurities to below 0.1% and unknowns to below 0.10% or even less proved to be very difficult; thus this activity takes most of the development timeline. Further these limits are made too stringent if the impurity proves to be genotoxic. Understanding of the impurity profile and development of an accurate analytical method during the research and development phase is an important milestone and plays a crucial role in deciding on the scheme and/or reagents. There are mainly three ways to control the impurities during the optimization of a process: first, by addressing them in the raw materials if they are carry-forwarded; second, by addressing them in the process by optimizing the critical parameters responsible for the generation of the same if they are generated as side products; and last, by repeated purification using crystallizations or column chromatography after isolation of the end product. Most of the time chemists adopt a mix of these approaches based on the nature of the impurities to be eliminated from the product. In this report, we would like to discuss our process research and development attempts to achieve efficient and impurity-free production of quetiapine hemifumarate (**1**) in a single pot.

Quetiapine hemifumarate (**1**), a dibenzothiazepine derivative, has international approvals for the treatment of schizophrenia as well as for acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.[1] Edward and co-workers[2] reported two approaches, path A (linear approach) and path B (convergent approach), with an overall yield of 64% and 70%, respectively, for the preparation of **1** as illustrated in Figure 1.

In both of the approaches the chloro compound (**4**) is generated by reacting cyclic amide **3** with ~15 mol of phosphorous oxychloride ($POCl_3$) in the presence of *N*,*N*-dimethylaniline at reflux temperature. Compound **4** was isolated by distilling excess $POCl_3$ under vacuum, dissolving the obtained brown residue in toluene, and concentrating the water washed toluene layer to obtain **4** in 92.6% yield.

Path B comprises condensation of **4** with 2-(2-piperazin-1-ylethoxy)ethanol (**8**) under reflux in xylene followed by workup using diethyl ether provided quetiapine base (**2**) as a viscous oil, which was purified by flash chromatography using a silica gel column and dichloromethane as an eluent with 77.7% yield. Freebase (**2**) was further treated with fumaric acid in ethanol to furnish compound **1** in 99% yield. Though the process is feasible on an industrial scale, it is found to be difficult and uneconomical due to (a) usage of a large amount of phosphorous oxychloride, which is highly toxic and environmentally hazardous; (b) use of diethyl ether, (c) a long reaction time, and (d) use of chromatography for the purification, which is industrially not feasible. Alternatively the linear synthetic route (Path A)

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10.1021/op900097q CCC: $40.75
Published on Web 06/23/2009

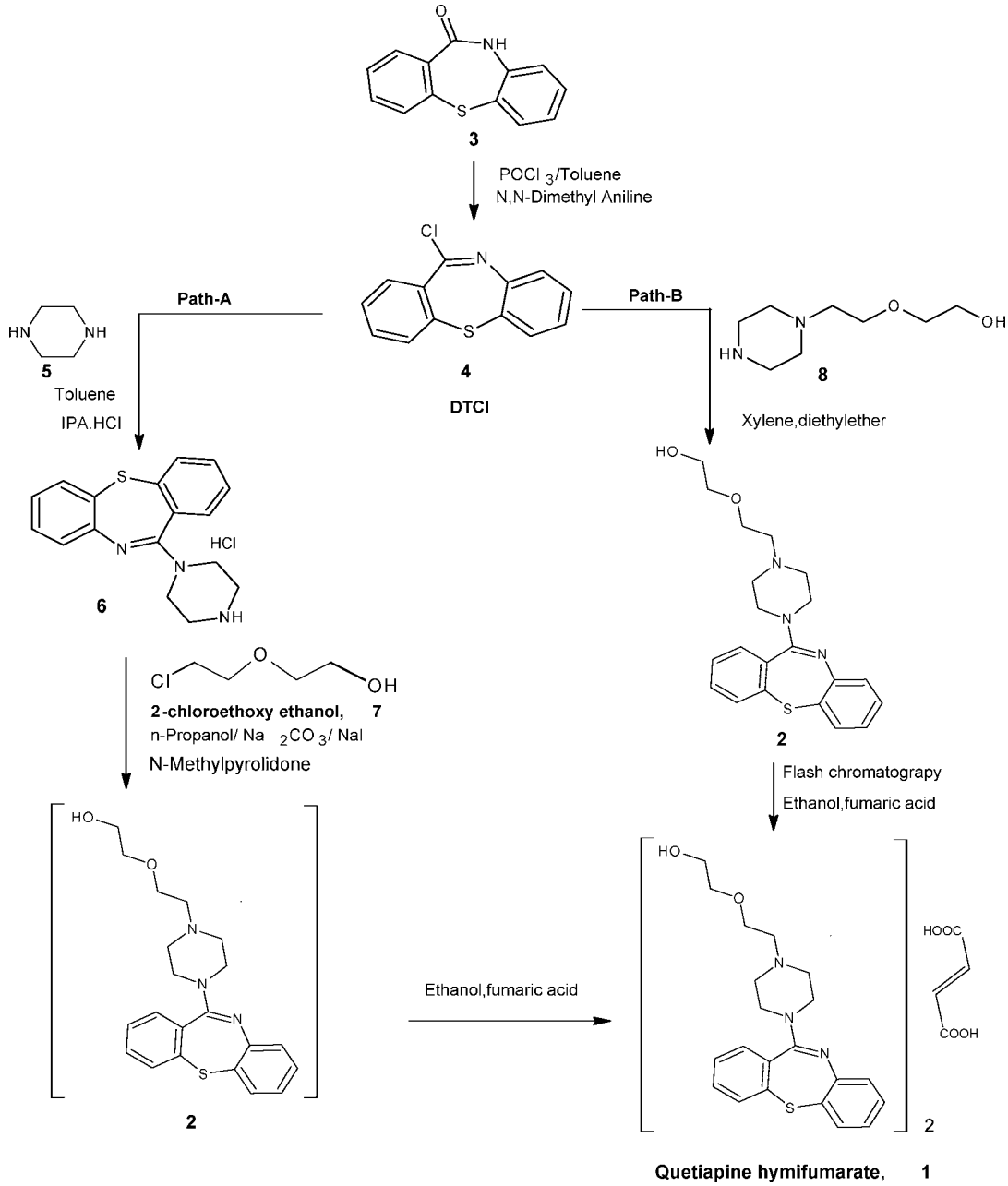

Figure 1. **Reported synthetic approaches for quetiapine hemifumarate.**

disclosed by the same authors involves treating compound **4** with piperazine (**5**) to obtain **6** with 88% yield that was further reacted with 2-chloroethoxyethanol (**7**) to yield compound **2** with a yield of 78%, which was then readily converted to compound **1** (overall yield 64%). Several other reported processes are too long, lead to formation of several process related impurities, use expensive and hazardous reagents, or are uneconomic.[3]

To avoid column chromatography, initially we explored the development of Path A but found it to be uneconomical when the analytical method developed was consistently showing a large amount of dimer impurity (**9**) formed due to the side reaction of **4** with intermediate **6** during the process for making **6** (Figure 2). During process optimization, the isocratic method established was not capable of detecting this impurity, and parallel optimization of analytical method yielded the gradient method[4] wherein the dimer impurity (**9**) peak was eluted in **6**. Our efforts to remove the dimer impurity (**9**) from **6** proved to be very cumbersome and resulted in a heavy loss of the yield.

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(4) Related substances of quetiapine hemifumarate were estimated by gradient HPLC analysis developed at Megafine using an Eclipse XDB C18, 250 mm × 4.6 mm ID column; mobile phase A comprising 0.025 M KH_2PO_4 and 0.01 M 1-pentane sulphonic acid sodium salt in water; mobile phase B comprising acetonitrile/methanol/water in the ratio 45: 45:10 v/v/v; gradient elution: T/% B: 0/45, 5/45, 40/90, 55/90, 58/45, and 65/45; flow rate 1.0 mL/min; column temperature 40 °C; wavelength 250 nm. Sanjay A. J.; Shashikant B. L.; Sonali J.; Anil, C. M.; Navanath, C. N.; Saroj R. B.; Vijayavitthal, T. M. Stability-Indicating Specific and Accurate HPLC Method for Determination of Related Substances in quetiapine hemifumarate, 2009 (A manuscript is recently communicated).

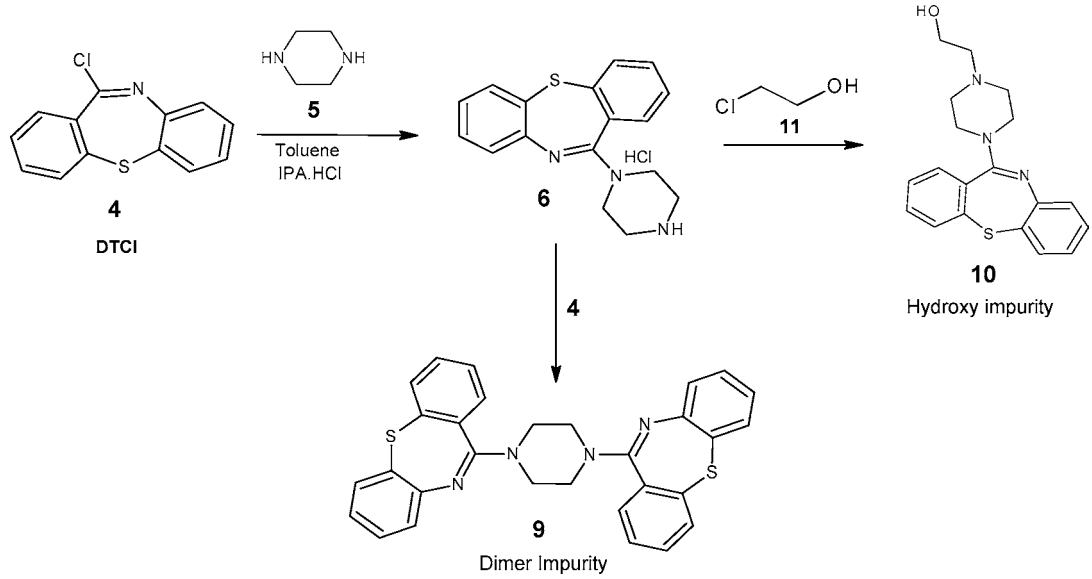

Figure 2. **Formation and synthetic approaches for the impurities from Path A.**

Table 1. **Content of dimer impurity (9) in quetiapine hemifumarate prepared by Path A**

sr. no.	batch no.	imp **6**	imp **10**	imp **3**	imp **9**	purity
1	QF0705003	ND	0.14	ND	0.38	97.12
2	QTH/A010/II/74	ND	0.08	ND	0.32	98.01
3	QTH/A010/II/89	0.14	0.08	ND	0.57	98.37
4	QTH0PP07001	0.05	0.15	ND	0.56	98.26

Any traces of **9** left in **6** were found to be retained in **1** without any reduction in its quantity, though many process operations are involved due to their structural similarities (Table 1).

Apart from the quality at the API stage, handling of **6** as a key starting material was also found to be an issue because of difficulties in controlling the moisture content to the desired limit during drying of **6** in the production. With varying moisture and hydrochloric acid content in **6**, fixing the mole ratio of the other reagents and raw materials during the next stage at manufacturing would be another issue wherein batch processing records are to be strictly followed. Yet another drawback of this route was the formation of a hydroxyl impurity (**10**) which is formed due to the reaction of **6** with traces of chloroethanol (**11**) present in another key starting material **7** (Figure 2, Table 1).

These multiple issues discouraged us from selecting Path A, and hence, we have diverted our attention to path B wherein formation of dimer impurity **9**, which is critical to the process, can be avoided completely.

Following Path B, we have developed an improved, impurity-free, and economic process for the large-scale synthesis of quetiapine wherein synthesis begun with chlorination of dibenzo[*b*,*f*][1,4]thiazepine-11(10*H*)-one (**3**) to furnish **4** which was condensed in the same pot with **8** to furnish quetiapine (**2**) with 99.5% HPLC purity, and subsequently freebase (**2**) was converted to quetiapine hemifumarate (**1**) in the same pot with ~99.85% HPLC purity with an overall yield of 80%; the details are furnished here (Figure 3).

Results and Discussion

(a) Chlorination of 3. Chlorination of **3** was performed by modifying the reported procedure using 1.5 mol of $POCl_3$ in

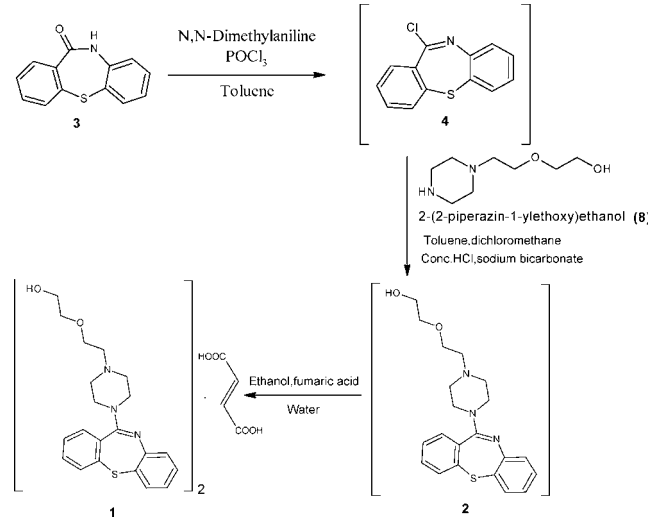

Figure 3. **Improved and single pot process for 1.**

the presence of *N*,*N*-dimethylaniline as a base and toluene as a solvent, thereby decreasing the $POCl_3$ quantity by ~13 times. After completion of the reaction by TLC, toluene was distilled to remove the traces of phosphorous oxychloride under vacuum to yield a brown residue, which was then dissolved in toluene and washed with prechilled water. The toluene layer is separated, washed twice with water, dried over anhydrous sodium sulphate, and used directly in the next step without isolation of **4**. As per our observation, chloro compound **4** is moisture sensitive and converted back to **3** if it is isolated and stored. Hence its isolation was avoided by directly using the dried toluene layer in the next step. HPLC data of the toluene layer containing **4** are shown in Table 2.

A critical reaction parameter in the next reaction is to control the moisture content in the toluene layer for a smooth reaction conversion that was difficult to achieve if it is isolated as a solid, dried, and stored. The critical impurities present in the toluene layer were unreacted **3** and *N*-methyl-*N*-phenyldibenzo[*b*,*f*]-[1,4]thiazapine-11-amine **14**, which is formed due to a side reaction of chloro compound **4** with traces of *N*-methylaniline (**13**) present in *N*,*N*-dimethylaniline used as a base in the

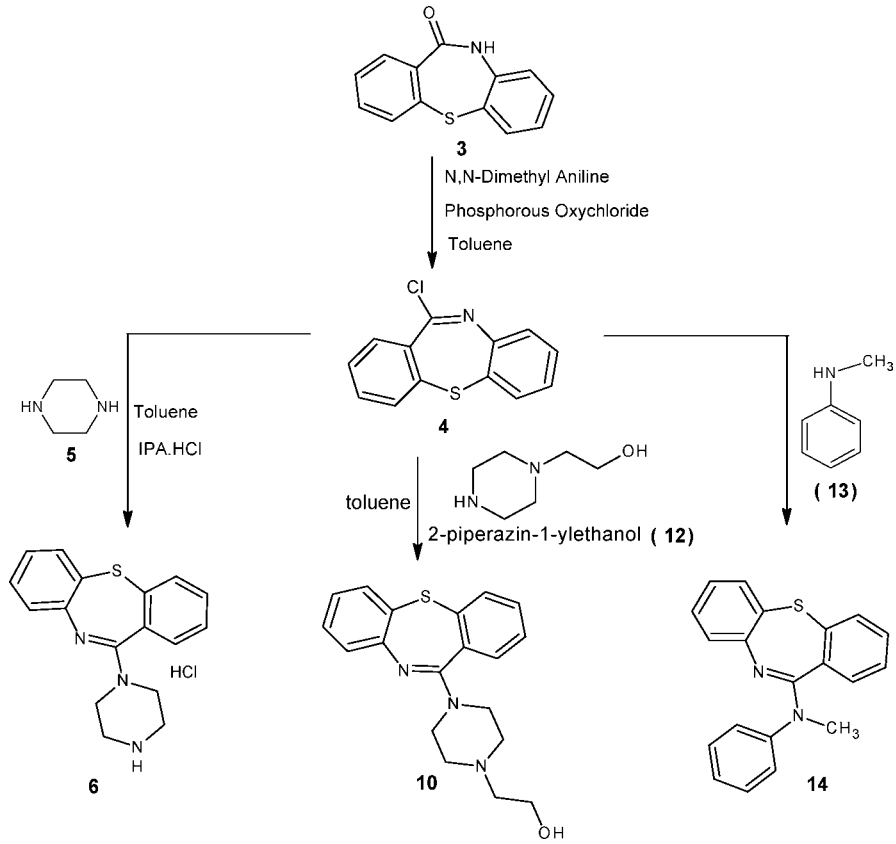

Figure 4. **Formation and synthetic approaches for the impurities from Path B.**

Table 2. **Trend HPLC data and moisture content of dried toluene solution of 4**

		content of impurities **3** and **14** in toluene solution of **4** by HPLC			moisture content of toluene solution
s. no.	batch no.	**4** (%)	**3** (%)	**14** (%)	**4** (%)
1	QTF-01	98.93	0.42	0.27	0.07
2	QTF-02	99.01	0.10	0.14	0.10
3	QTF-03	98.66	0.02	0.11	0.07

reaction (Figure 4). The commercial lots of *N*,*N*-dimethylaniline procured were shown to contain ~0.2% of *N*-methylaniline which was sufficient to produce the impurity **14** at ~0.2% by HPLC (Table 2). The novel impurity **14** was identified by LC-MS followed by its synthesis, coinjection with sample in HPLC, and detailed characterization by spectroscopic techniques.[5] As *N*,*N*-dimethylaniline is the basic raw material and control of impurity **13** in the raw material is beyond our control, we have established a downstream workup process to eliminate these impurities.

(b) Condensation of 4 with 8 to furnish 1. To the toluene solution containing **4** was added 2-(2-piperazin-1-yl-ethoxy)-ethanol (**8**), and the contents were refluxed at 110 °C until reaction completion by HPLC. The reaction mass was then cooled, a 1 N sodium hydroxide solution was added, the mixture was stirred for 30 min, and both of the layers were separated. The toluene layer was then treated with a 1 N hydrochloric acid solution to extract the quetiapine (**2**) selectively in acidic water in the form of its hydrochloride salt by leaving behind the impurities (**3**, **4,** and **14**) into the toluene layer.

The acidic aqueous layer having 99.1% to 99.6% pure (by HPLC) quetiapine was once again washed with toluene and basified to pH 9 to 10 using sodium carbonate, and the quetiapine freebase was extracted into dichloromethane. The dichloromethane layer was washed with water and concentrated to furnish quetiapine freebase (**2**) as syrup, which was further converted to its hemifumarate salt in ethanol in a single pot as shown in Figure 3.

The possible impurities, such as byproducts, carryover impurities from starting materials, reaction of carryover impurities with the reagents or key starting materials, etc., are identified, characterized, and synthesized to establish an analyti-

(5) The new impurity **14** observed in the scheme was synthesized by treating compound **4** with *N*-methylanline in toluene at reflux temperature. After completion of the reaction the mass was cooled and washed with water and the toluene layer was concentrated to obtain the thick residue which was triturated in *n*-heptane to obtain **14** as a solid as shown in Figure 4. Compound **14** was characterized by IR, mass, and NMR studies; IR (KBR absorption bands in cm^{-1}). 3029 aromatic C—H stretch, 2933 aliphatic C—H stretch, 1600 aryl C═C stretch, 1552 C═N stretch, 1122 C—N stretch, 761 C—S stretch; MS; *m*/*z* 317.9 ($M^+ + 1$); ^1H NMR (DMSO): δ 7.42−7.45 (m, 3H), 7.13−7.27 (m, 6H), 6.97−7.08 (m, 4H), 3.52 (s, 3H), further confirmed to be present in the sample by HPLC coinjection and spiking method (0.10%).

Table 3. **Analytical data of quetiapine hemifumarate using different qualities of 8**

		input			output		
		content of imp **5** and **12** in **8** by GC (%)			quality of quetiapine hemifumarate by HPLC (%)		
sr. no.	exp. no.	**8**	**5**	**12**	**1**	**6**	**10**
1	QTF/A061/II/03	99.60%	0.01%	0.02%	99.84%	0.03%	0.04%
2	QTF/A061/II/04	99.60%	0.01%	0.02%	99.82%	0.01%	0.04%
3	QTF/A061/II/15	98.98%	0.34%	0.09%	98.63%	0.60%	0.11%

Table 4. **Monitoring the elimination of impurities in downstream process for 1**

		impurities and their content by HPLC (%)						
batch no.	sample station (for HPLC analysis)	**1**	**3**	**4**	**6**	**9**	**10**	**14**
QTF-01	reaction mass as such	94.75	0.16	1.86	0.03	ND	0.02	0.2
	acidic aqueous layer	99.69	0.03	0.01	0.01	ND	0.02	ND
	quetiapine free base	99.74	0.05	0.01	0.01	ND	0.02	ND
	quetiapine hemifumarate	99.87	0.04	ND	0.01	ND	0.02	ND
QTF-02	reaction mass as such	96.03	0.14	2.68	0.03	ND	0.02	0.14
	acidic aqueous layer	99.58	0.04	ND	0.03	ND	0.02	ND
	quetiapine free base	99.74	0.03	ND	0.03	ND	ND	ND
	quetiapine hemifumarate	99.86	0.01	ND	0.03	ND	ND	ND
QTF-03	reaction mass (as such)	96.98	0.36	2.09	0.02	ND	0.01	0.11
	acidic aqueous layer	99.44	0.11	0.03	0.01	ND	0.01	ND
	quetiapine free base	99.71	0.12	0.01	0.01	ND	ND	ND
	quetiapine hemifumarate	99.88	0.01	ND	0.01	ND	ND	ND

Table 5. **Residual solvent analysis data of wet material and after water leaching**

		methanol limit NMT 3000 ppm		ethanol limit NMT 5000 ppm		dichloromethane limit NMT 600 ppm		toluene limit NMT 890 ppm	
sr. no.	batch no.	before water leaching	after water leaching	before water leaching	after water leaching	before water leaching	after water leaching	before water leaching	after water leaching
1	QTF-01	ND	ND	8628	126	ND	ND	448	73
2	QTF-02	ND	ND	5135	462	187	ND	236	124
3	QTF-03	100.0	41.83	6474	128	ND	ND	220	ND

cal method. The structures of the impurities, their formation, and possible routes for their synthesis are shown in Figure 4.

Piperazine (**5**) and 2-piperazin-1-yl ethanol (**12**) are the two potential carryover impurities from the key starting material 2-(2-piperazin-1-yl-ethoxy)ethanol (**8**). A parallel reaction of **5** and **12** present in **8** with chloro compound **4** may lead to the formation of impurities **6** and **10**, respectively. Hence, the control of impurities **5** and **12** in starting material **8** or control of **6** and **10** in quetiapine **2** is essential to achieve the desired quality of the quetiapine hemifumarate (**1**).

As we had learned that the removal of **6** from the quetiapine is difficult, the key starting material **8** was purified by fractional distillation to ensure control of impurities **5** and **12** below 0.10% by GC quantitatively, which subsequently controlled impurities **6** and **10** in **1** as evidenced in Table 3 (entries 1 and 2). The higher content of **5** and **12** in **8** lead to the substantial amounts of **6** and **10** in **1** (entry 3, Table 3), and thus highly pure **8** is essential.

Other major impurities found in the reaction mass are starting material **3**, chloro compound **4**, and *N*-methyl-*N*-phenyldibenzo[*b*,*f*][1,4]thiazapine-11-amine (**14**). Elimination of these impurities in the downstream process was systematically monitored and captured in Table 4. The most critical impurities such as the 11-piperazin-1-yldibenzo[*b*,*f*][1,4]-thiazepine impurity (**6**) and dimer impurity (**9**) formed in higher quantity in path A were found negligible in path B as given in Table 4.

Subsequently, the hemifumarate salt was formed by dissolving the syrup containing the quetiapine freebase (**2**) in ethanol in the same pot and adding fumaric acid. The salt was isolated by filtration and dried under vacuum to yield **1** with more than 99.8% HPLC purity. Residual solvent results of the material after drying were found to contain solvent beyond the acceptable limits, and hence the wet material of **1** was leached with water at elevated temperature to obtain the residual solvents below the limit as shown in Table 5.

Conclusion

An efficient, cost-effective, and single pot process for the production of quetiapine hemifumarate (**1**) via chlorination of **3** with $POCl_3$ and condensation of obtained chloro compound **4** with **8** followed by fumarate salt formation of resulting quetiapine (**2**) is provided.

Experimental Section

General. All reagents, solvents, and processing aids are commercial products and were used as received. For reactions run of pilot scale, glass line reactors having variable rate

agitation, a −10 to 150 °C jacket temperature range were used for the reaction. ^{1}H NMR spectra was recorded in $CDCl_3$ and DMSO using Varian Gemini 400 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS.

Quetiapine Hemifumarate. To a stirred solution of DTO (**3**, 10.0 kg) in toluene (60 L) and phosphorus oxychloride (10.1 kg) was added *N*,*N*-dimethylaniline (6.12 kg) at 25−30 °C followed by stirring for 15−20 min. The temperature of the reaction mass was raised to 108−112 °C and maintained for 5−6 h. After completion of the reaction (by TLC, Mobile phase: DCM/methanol/ammonia = 9:1:0.1 mL), the mixture was distilled under vacuum to remove the solvent and excess phosphorus oxychloride. The residue was diluted with toluene (80 L) and cooled to 10 °C, and to water (40 L) was added the resulting solution below 20 °C. The mass was stirred for 15−20 min, and the organic layer was separated, washed with water, and dried over sodium sulphate. 2-(2-Piperazin-1-ylethoxy-)ethanol (**8**, 14.54 kg) was added to the dried toluene layer containing **4** at 25−30 °C and stirred for 15−20 min. The temperature of the resulting mass was raised to 108−112 °C and maintained for 16−20 h. After completion of the reaction (by HPLC), the mass was cooled to 25−30 °C, and a solution of 1 N sodium hydroxide (40 L) was added; the contents were then stirred, and both the layers were separated. The toluene layer was treated with 1 N hydrochloric acid (40.0 L), and the acidic aqueous layer was separated and further washed with toluene (20 L). The acidic aqueous layer was diluted with dichloromethane (40 L), and the pH of the aqueous layer was adjusted to 9−10 using sodium carbonate. The contents were stirred, and the dichloromethane layer was separated. The aqueous layer was re-extracted with dichloromethane (20 L × 2). The combined dichloromethane layers were washed with water (40 L × 2), and the solvent was distilled off completely to obtain the residue. The residue was dissolved in ethanol (104 L), decolorized with activated charcoal, and treated with fumaric acid (3.04 kg). The contents were heated at 55−60 °C for 30 min, cooled to 25−30 °C, maintained for 60 min, and filtered to obtain compound **1** as a crystalline solid. The wet solid was mixed with water (140 L), heated to 85−90 °C, maintained for the 30 min, cooled to 25−30 °C, and then chilled to 5−10 °C, again maintained for 2−3 h. The crystalline solid was filtered and dried under vacuum (650−700 mm/Hg) to afford pure **1** as a white crystalline solid. Yield: 15.4 kg (79.38%). MS; *m*/*z* 384 ($M^+ + 1$): ^{1}H NMR (DMSO-d_6): δ 7.56−7.53 (m, 1H), 7.35−7.48 (m, 4H), 7.15−7.20 (d, 1H), 6.91−7.00 (d, 1 H), 6.86−7.00 (t, 1H), 6.6 (s, 1H), 3.39−4.00 (m, 10H), 2.45−2.62 (m, 6H). HPLC Purity 99.88%.

Acknowledgment

Authors thank the management of Megafine Pharma (P) Ltd. for the permission to publish this work. Authors also thank colleagues of the Analytical Research and Development team for their continuous and valuable contribution to this work.

Supporting Information Available

Further experimental details and additional information on the work. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review April 20, 2009.

OP900097Q