

Supporting Information

Development of Green Purification Process for Piperazine-Type Drugs, Taking Quetiapine Process Development as an Example

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1. General information

Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. All reactions were assembled on a Three-necked flask or reactor, were stirred with mixing propeller, and heated by water bath, unless otherwise specified. Hundred-kilogram scale experiments were carried out in the workshop of Zhejiang Huahai Pharmaceutical Co. Ltd. Reactions were monitored using thin-layer chromatography (TLC) and HPLC, and visualization of the developed plates was performed under UV light.

All pH values were measured at 20~30 °C, and all buffer systems were Na₂HPO₄/KH₂PO₄ (3.533 g of Na₂HPO₄ and 3.387 g of KH₂PO₄ were dissolved in 1000 mL of water, pH=6.86).

2. List of impurities

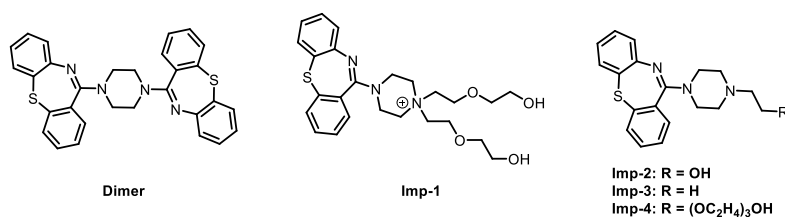


Figure 1 List of impurities

3. The distribution experiment of *Int-2* and dimer in two phases under different pH conditions

Slowly drip HCl (aq.) to the solution of *Int-2* that **SM2** has been removed to adjust to different pH values, test the content of *Int-2* and the dimer in organic phase and aqueous phase.

Table 1 The distribution of *Int-2* and dimer in two phases under different pH conditions

Entry	pH	Phenomenon	Organic phase		Aqueous phase	
			<i>Int-2</i> %	Dimer %	<i>Int-2</i> %	Dimer %
1	7.55	turbid	exist	exist	exist	n.d
2	5.97	turbid	exist	exist	exist	n.d
3	5.94	turbid	exist	exist	exist	n.d
4	5.87	turbid	exist	exist	exist	n.d
5	5.19	turbid	exist	exist	exist	n.d
6	4.55	turbid	exist	exist	exist	n.d
7	3.13	turbid	exist	exist	exist	n.d
8	3.05	turbid	3.98	51.69	99.87	0.03
9	2.45	turbid	0.24	64.38	99.84	0.03
10	2.24	dissolved clear	0.15	68.51	99.86	0.02
11	1.47	dissolved clear	0.10	58.86	99.87	0.02
12	1.15	dissolved clear	0.03	67.73	99.63	0.24
13	0.97	dissolved clear	0.02	48.12	98.85	1.05
14	0.87	dissolved clear	n.d	26.7	98.53	1.36

4. Dissolution experiment of quetiapine fumarate

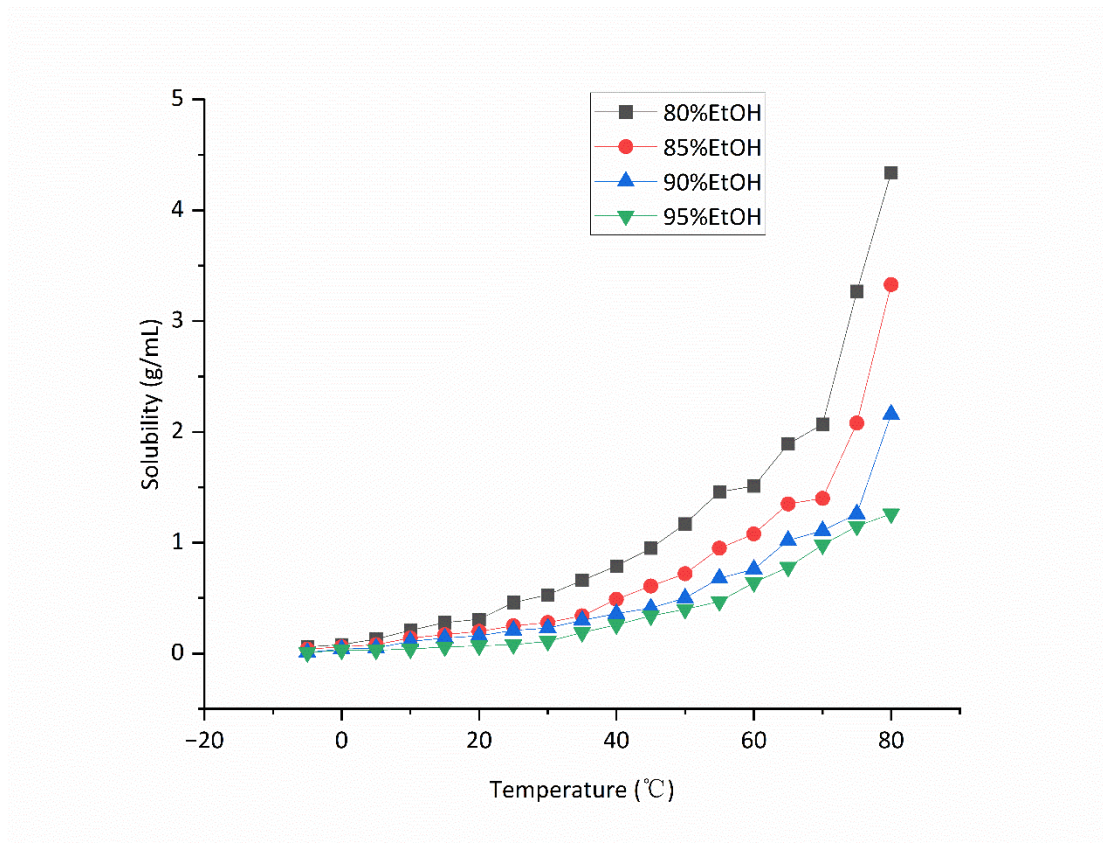
4.1 Dissolution experiment

Add quetiapine fumarate to the ethanol solution at a certain temperature until saturation is reached. Record the weight of quetiapine fumarate at this point, which represents the solubility of quetiapine fumarate in this ethanol solution at this temperature.

Table 2 Dissolution data in different ethanol solution

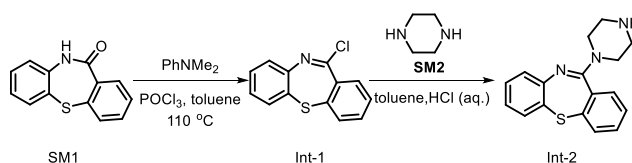
Temp °C	95%EtOH g/mL	90% EtOH g/mL	85% EtOH g/mL	80% EtOH g/mL
-5	0.008	0.01	0.04	0.06
0	0.03	0.04	0.06	0.08
5	0.03	0.05	0.08	0.13
10	0.04	0.11	0.14	0.21
15	0.06	0.14	0.17	0.28
20	0.07	0.16	0.2	0.31
25	0.08	0.21	0.25	0.46
30	0.11	0.23	0.28	0.53
35	0.19	0.3	0.34	0.66
40	0.26	0.36	0.49	0.79
45	0.34	0.41	0.61	0.95
50	0.4	0.5	0.72	1.17
55	0.47	0.68	0.95	1.46
60	0.64	0.76	1.08	1.51
65	0.78	1.02	1.35	1.89
70	0.98	1.11	1.4	2.07
75	1.15	1.26	2.08	3.27
80	1.26	2.16	3.33	4.34

4.2 Solubility curve



5. confirmation experiments of improved process

5.1 The synthesis of *Int-2*



SM1 (150 g), toluene (1500 mL), PhNMe₂ (60 g) and K₂CO₃ (20 g) were added into a three-necked flask. Then, while stirring, POCl₃ (132 g) was added at 25-30 °C. Heat the mixture to 110 ± 5 °C for 8-10 h. After completion, the mixture cooled down to 0-10 °C. Saturated NaHCO₃ was added to wash and separate the layers, collect the organic phase for later use. To the solution of *Int-1*, toluene (500 mL) and **SM2** (225 g) were added, then heat the mixture to 110-115 °C and react for 4 h. Cool the mixture to 20-30 °C and filter to remove the excess **SM2**. Wash the filtrate twice with water. Then add water (1000 mL) and slowly drip in hydrochloric acid until the pH reaches 1.7-2.2. Separate the liquid and collect the aqueous phase to obtain the aqueous solution of *Int-2*.

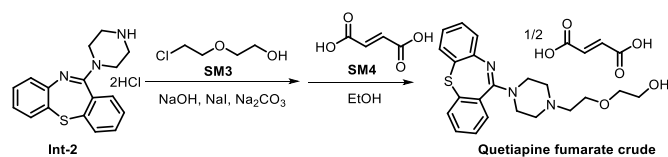
Table 3 The quality of the repeated batches of *Int-2*

Batch	<i>Int-2</i> %	dimer %	SM1 %	unknown impurity %	Total impurity %
1	99.6	0.03	0.02	0.15	0.4
2	99.7	0.04	0.05	0.09	0.3
3	99.6	0.06	0.08	0.07	0.4

Table 4 Mass balance of *Int-2*

Batch	pH	<i>Int-2</i> in Reaction Mixture g	<i>Int-2</i> in Organic Phase g	<i>Int-2</i> in Aqueous Phase g	Product Loss %	Mass Balance %
1	1.9	190.0	0.4	183.1	0.2	96.6
2	2.0	191.3	0.6	188.2	0.3	98.7
3	1.9	190.2	0.5	184.3	0.3	97.2

5.2 The synthesis of quetiapine fumarate crude

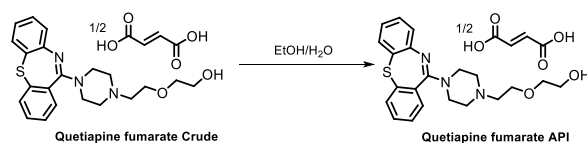


Toluene (800 mL) and NaOH aqueous solution (200 g) were added to the aqueous solution of *Int-2*, start the stirring, and allow separating into layers. Wash the toluene layer with water, and allow separating into layers. Then, **SM3** (85 g), Na₂CO₃ (120 g), and NaI (11 g) were added to the flask while stirring, and heat the mixture to 110±5 °C for 24 hours. After the reaction was complete, cool the mixture to 50~60 °C, add water (800 mL) and stir, allow to separate into layers, then wash the toluene layer with water (500 mL*3), and distill under reduced pressure to obtain an oily substance. Anhydrous ethanol (1350 L) and **SM4** (fumaric acid, 40 g) was added into the reactor, heat to 75~80 °C, reflux for 1 hour, then cool to 0±5 °C, and maintain temperature for 2~3 hours. Filter, the solid was the desired product.

Table 5 The quality of the repeated batches of crude

Batches	pH	quetiapine %	Imp-2 %	Dimer
1	1.9	99.76	n.d	n.d
2	2.0	99.69	n.d	n.d
3	2.1	99.85	n.d	n.d

5.3 The synthesis of quetiapine fumarate API



Crude product (50 g), anhydrous ethanol (180 mL) and water (20 mL) were added into the flask. Start stirring and heat to 75-80 °C until all the solids dissolve. Then, cooled down the solution to -5~0 °C, and stir for 2-3 h, Filter, collect solids and dry.

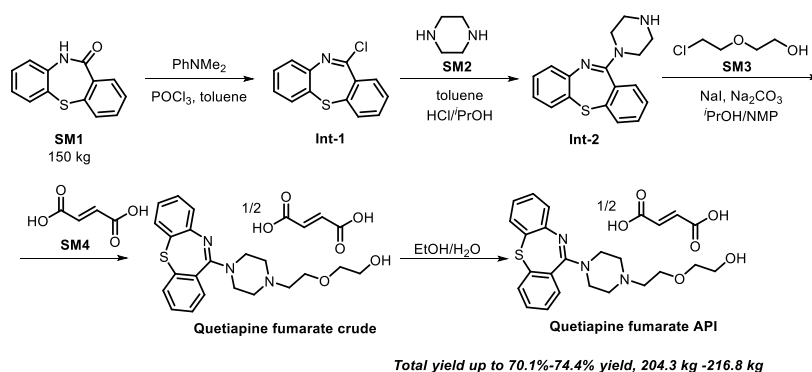
Table 6 The quality of the repeated batches of API

Batch	Quetiapine %	SM1 %	Dimer %	Imp-1 %	Imp-2 %	Imp-3 %	Imp-4 %	Total impurity %	Yield %
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1	99.88	n.d	n.d	n.d	n.d	n.d	n.d	0.12	73.3
2	99.86	n.d	n.d	n.d	n.d	n.d	n.d	0.14	74.6
3	99.89	n.d	n.d	n.d	n.d	n.d	n.d	0.11	73.1

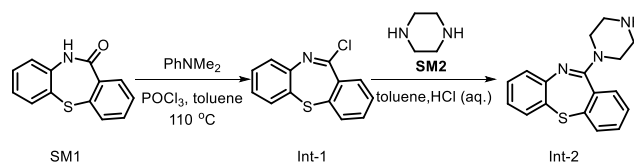
6. Hundred-kilogram scale experiments

Six batches of fumarate quetiapine were produced with total yields ranging from 70.1% to 74.4%, and an average yield of 73.1% (n = 6, SD=1.46, RSD = 2.00%).



Scheme 1 Hundred-kilogram scale experiments

6.1 Preparation of *Int-2*



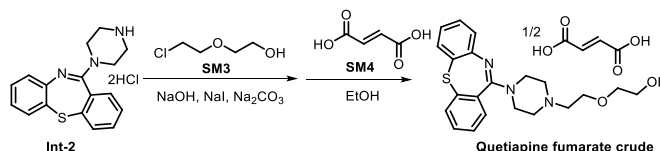
To a stirred solution of **SM1** (150 kg) in toluene (1500 L) and *N, N*-dimethylaniline (60 kg) and potassium carbonate (20 kg) were added phosphorus oxychloride (132 kg) at 25-30 °C. The temperature of the reaction mass was raised to 105-115 °C and maintained for 8-10 h. After completion of the reaction by TLC, cool down to 0-10 °C. Sodium bicarbonate solution (500 L) was added to wash and separate the layers. To the organic layer, supplement with toluene (500 L) and add 225 kg of **SM2** (225 kg), then heat to 110-115 °C and react for 4 hours. Cool the mixture to 20-30 °C and filter to remove the excess **SM2**. Wash the filtrate twice with water. Then add 1000 liters of potable water and slowly drip in hydrochloric acid until the pH reaches 1.7-2.2. Perform a phase separation to obtain the aqueous solution of *Int-2*.

Table 7 Quality statistics for the scaled-up batch of *Int-2*

Batch	<i>Int-2</i> %	Dimer %	SM1 %	Unknown Impurity %	Total Impurities %
001	99.70	N.D	0.01	0.20	0.30

002	99.59	N.D	0.01	0.22	0.41
003	99.56	N.D	0.02	0.23	0.44
004	99.73	0.02	0.02	0.14	0.27
005	99.72	0.03	0.01	0.12	0.28
006	99.60	0.03	0.04	0.16	0.40
SD	0.07	--	--	--	--
RSD	0.07%	--	--	--	--

6.2 Preparation of quetiapine fumarate crude

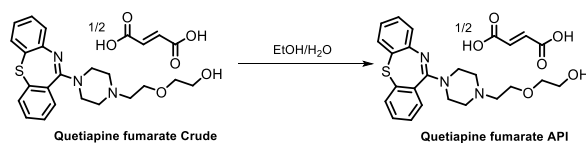


Toluene (800 L) and 200kg of sodium hydroxide aqueous solution were added to the aqueous solution of *Int-2*, start the stirring, and allow separating into layers. Wash the toluene layer with 300L of water, and allow separating into layers. Then, **SM3** (85 kg), Na₂CO₃ (120 kg), and NaI (11 kg) were added to the reactor while stirring, and heat to 110±5 °C, then react for 24 hours. After the reaction was complete, cool the material to 50~60 °C, add water (800 L) and stir, allow to separate into layers, then wash the toluene layer with 500L×3 of water, and distill under reduced pressure to obtain an oily substance. Anhydrous ethanol (1350 L) and **SM4** (fumaric acid, 40 kg) was added into the reactor, heat to 75~80 °C, reflux react for 1 hour, then cool to 0±5 °C, and maintain temperature for 2~3 hours. Centrifuge and filter to obtain the wet product, with the weight recorded as M₁.

Table 8 Quality statistics for the scaled-up batch of quetiapine fumarate crude

Batch	Quetiapine %	Int-2 %	Dimer %	Unknown Impurity %	Total Impurities %
001	99.75	0.03	0.03	0.08	0.25
002	99.68	0.03	0.03	0.07	0.32
003	99.70	0.05	0.03	0.08	0.30
004	99.82	0.05	0.04	0.07	0.18
005	99.84	0.06	0.01	0.05	0.16
006	99.85	0.03	0.02	0.05	0.15
SD	0.09	--	--	--	--
RSD	0.09%	--	--	--	--

6.3 Preparation of quetiapine fumarate API



Crude product (M₁ kg), anhydrous ethanol (2.84M₁ kg) and purified water (0.4M₁ kg) were added into the reactor. Stir and heat to 75-80 °C for 2 h until the solid material was completely dissolved, then cool down to -5~0 °C for crystallization for 2-3 hours, centrifuge and filter, dry to obtain the final finished product.

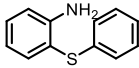
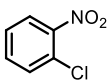
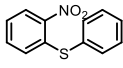


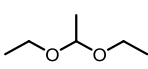


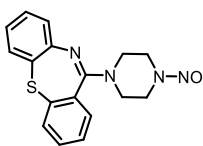
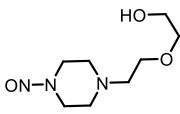
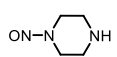
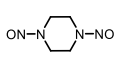
Table 9 Quality statistics for the scaled-up batch of API

Batch	Yield %	Quetiapine %	SM1 %	Int-2 %	Dimer %	Imp-1 %	Imp-2 %	Imp-3 %	Imp-4 %	Unknown Impurity %	Total Impurities %
001	70.1	99.67	N.D	0.01	0.01	0.01	0.05	0.01	0.06	0.03	0.33
002	73.3	99.71	N.D	0.01	0.01	0.01	0.05	0.01	0.05	0.02	0.29
003	73.2	99.68	N.D	0.02	0.01	0.01	0.05	0.01	0.05	0.04	0.32
004	73.0	99.70	N.D	0.02	0.01	0.01	0.05	0.01	0.05	0.02	0.30
005	74.4	99.69	N.D	0.03	0.00	0.01	0.04	0.01	0.04	0.03	0.31
006	74.4	99.80	N.D	0.01	n.d	0.01	0.01	0.01	0.01	0.03	0.20
SD	1.46	0.05	--	--	--	--	--	--	--	--	--
RSD	2.00%	0.05%	--	--	--	--	--	--	--	--	--

6.4 Genotoxic structural alert impurities and N-nitrosamine impurities screening in the API

In order to confirm whether the optimized process meets the control requirements for impurities as stipulated by ICH M7, a total of 12 potential impurities were assessed, including genotoxic structural alert impurities (**Table 9**, entries 1–6) and N-nitrosamine impurities (**Table 9**, entries 7–12). The detailed impurity list, structures, control limits, and investigation results are summarized in the table below.

Table 10 Screening of genotoxic structural alert impurities and N-nitrosamine impurities

Entry	Name	Structure	Limit ppm	Results
1	2-(phenylthio)aniline		1.88	N.D
2	1-chloro-2-nitrobenzene		1.88	N.D
3	(2-nitrophenyl)(phenyl)sulfane		1.88	N.D
4	benzene		1.88	N.D
5	acetaldehyde		10.00	N.D
6	1,1-diethoxyethane		10.00	N.D
7	<i>N,N</i> -diethylnitrous amide (NDEA)		0.03	N.D
8	<i>N,N</i> -dimethylnitrous amide (NDMA)		0.12	N.D
9	11-(4-nitrosopiperazin-1-yl)dibenzo[b,f][1,4]thiazepine		0.43	N.D
10	2-(2-(4-nitrosopiperazin-1-yl)ethoxy)ethan-1-ol		0.43	N.D
11	1-nitrosopiperazine		0.43	N.D
12	1,4-dinitrosopiperazine		0.43	N.D

7. Comparison of the earlier process & new method

7.1 Material balance

Detailed material balance information is shown in the **Table 10**.

Table 11 Material balance

Process	Input			Output			
	No.	Name	kg/batch	No.	Name	kg/batch	
Preparation of Int-2	1	SM1	150	1	Aqueous solution of <i>Int-2</i>	1250	
	2	Toluene	2180	2	Exhaust gas	Toluene	35
	3	K ₂ CO ₃	20	3		Phosphorus oxychloride	3
	4	<i>N, N</i> -dimethylaniline	60	4		hydrogen chloride	5
	5	Phosphorus oxychloride	132	5	Effluent	Brine waste	2250
	6	Water	3000	6	Waste solvent	Toluene (To be recycled)	2243
	7	NaHCO ₃	30				
	8	SM2	225	7	Solid waste	SM2	155
	9	Hydrochloric acid	144				
Preparation of crude	10	Aqueous solution of <i>Int-2</i>	1250	8	Quetiapine fumarate crude		270
	11	Toluene	523.2	9	Exhaust gas	Toluene	8.2
	12	NaOH (aq.)	199.5	10		EtOH	6
	13	SM3	85	11	Effluent	Brine waste	3871.5
	14	Na ₂ CO ₃	120	12	Waste solvent	Toluene (To be recycled)	510
	15	NaI	4				
	16	Water	2600	13			
	17	EtOH	1066				
18	SM4	40					
Preparation of API	19	Quetiapine fumarate crude	270	14	API		213
	20	EtOH	813.3	15	Exhaust gas	EtOH	13.3
	21	Water	110	16	Waste solvent	Mother liquor	967

So, the average output of each batch of API: $M_{API}=213$ kg, total material input: $M_{in}=11502$ kg, and total amount of three wastes: $M_{Wastes}=11289$ kg.

$$PMI' = M_{in} / M_{API} = 11502 \text{ kg} / 213 \text{ kg} = 54.0$$

$$E\text{-factor}' = M_{Wastes} / M_{API} = 11289 \text{ kg} / 213 \text{ kg} = 53.0$$

7.2 Solvent recovery information

Detailed solvent recovery information is shown in the **Table 11**.

Table 12 Solvent recovery information

Entry	Solution	Input kg	Recovery kg	Recovery ratio %	Content in waste kg	Wastage kg
1	toluene	2703	2471	91.42%	189	43
2	EtOH	1879	1314	69.93%	546	19

So, the total amount of solvent recovered from each batch of API: $M_r = 189 \text{ kg} + 546 \text{ kg} = 734 \text{ kg}$; After solvent recovery, total material loss: $M_{in}' = M_{in} - M_r = 11502 \text{ kg} - 734 \text{ kg} = 10768 \text{ kg}$; total amount of the three wastes: $M_{Wastes}' = M_{Wastes} - M_r = 11289 \text{ kg} - 734 \text{ kg} = 10555 \text{ kg}$. Therefore, After solvent recovery:

$$PMI = M_{in}' / M_{API} = 10768 \text{ kg} / 213 \text{ kg} = 50.6$$

$$E\text{-factor} = M_{Wastes}' / M_{API} = 10555 \text{ kg} / 213 \text{ kg} = 49.6$$

7.3 Waste classification

Detailed waste classification is shown in the **Table 12**.

Table 13 Waste classification

Entry	Category of Waste	Weight kg	Proportion %	Main components
1	Exhaust gas	71	0.7	Toluene, phosphorus oxychloride, hydrogen chloride, EtOH
2	Effluent	6122	58.0	Water, inorganic salt
3	Organic waste	4207	39.9	EtOH, Toluene, a small quantity of API
4	Solid residue	155	1.5	Piperazine hydrochloride
5	Total	10555	100.0	-

7.4 Comparison of the earlier process & new method

Based on the above data, a comparison was made between the new method and the earlier process in terms of green chemical indicators. For detailed data, please refer to **Table 13**.

Table 14 Comparison of the earlier process & new method in green chemical indicators

Entry	Green indicator	Earlier process	New method	Improvement
1	Average yield %	60.5	73.1	↑ 20.8%
2	Time/batch h	170	108	↓36.5%
3	E-factor	125.6	49.6	↓60.5%
4	PMI	126.6	50.6	↓60.0%

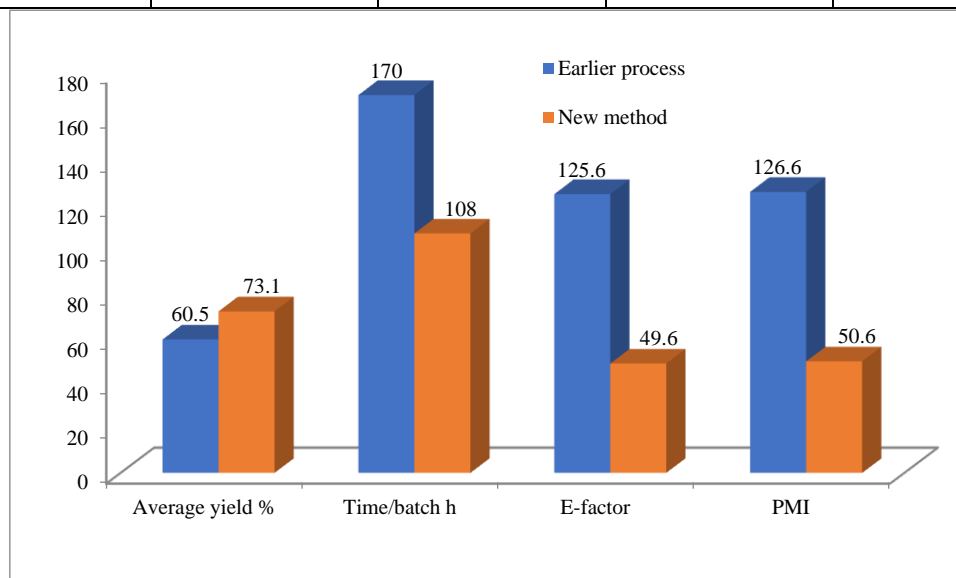
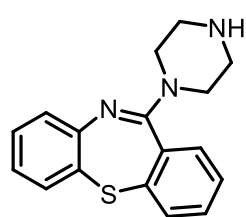


Figure 2 Comparison of the earlier process & new method

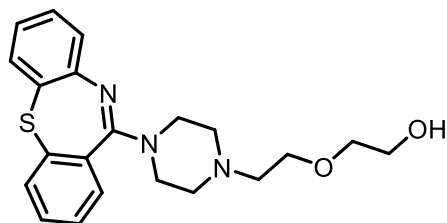
8. Spectra Data of the Compounds

11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepine (*Int-2*)



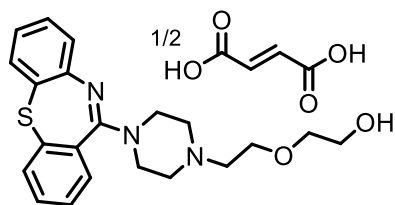
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.51 (t, $J = 7.5$ Hz, 1H), 7.44 – 7.24 (m, 4H), 7.18 (q, $J = 9.3$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.91 (dt, $J = 25.6, 7.9$ Hz, 1H), 4.22 – 3.14 (m, 6H), 2.89 – 2.43 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.9, 160.0, 148.9, 148.1, 140.1, 139.9, 134.2, 133.3, 132.4, 132.3, 132.2, 132.2, 131.5, 130.8, 129.3, 129.1, 129.0, 128.7, 128.7, 128.3, 128.0, 127.9, 125.3, 125.2, 123.8, 122.8, 80.7, 53.5, 51.3, 42.9. **HRMS (ESI):** calcd for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{S}^+$ [$\text{M} + \text{H}$] $^+$: 296.1216, found: 296.1220

2-(2-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy)ethan-1-ol (*quetiapine*)



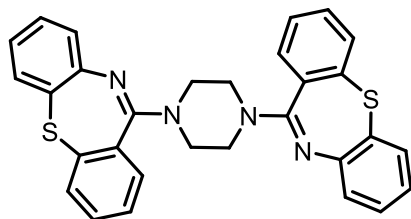
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.50 (d, $J = 7.4$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 11.6$ Hz, 3H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 6.87 (t, $J = 7.8$ Hz, 1H), 4.18 (s, 1H), 3.93 – 3.18 (m, 10H), 2.77 – 2.47 (m, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.6, 148.9, 139.9, 134.1, 132.2, 132.2, 130.8, 129.1, 129.0, 128.3, 128.0, 125.3, 122.8, 72.4, 67.7, 62.0, 58.0, 53.5, 53.1. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_2\text{S}^+$ [$\text{M} + \text{H}$] $^+$: 384.1740, found: 384.1745.

quetiapine fumarate API



$^1\text{H NMR}$ (400 MHz, DMSO) δ 7.57 – 7.51 (m, 1H), 7.47 – 7.35 (m, 4H), 7.18 (td, $J = 8.0, 1.5$ Hz, 1H), 6.99 (dd, $J = 8.0, 1.3$ Hz, 1H), 6.89 (td, $J = 7.5, 1.4$ Hz, 1H), 6.61 (s, 1H), 5.64 (s, 2H), 3.75 – 3.15 (m, 10H), 2.59 (t, $J = 5.8$ Hz, 3H), 2.57 – 2.50 (m, 3H). $^{13}\text{C NMR}$ (100 MHz, DMSO) δ 166.5, 160.1, 148.6, 138.71 (s), 134.3, 133.5, 132.1, 132.0, 131.3, 129.3, 129.1, 129.0, 127.2, 125.1, 122.6, 72.3, 67.9, 60.3, 57.1, 52.6, 46.0.

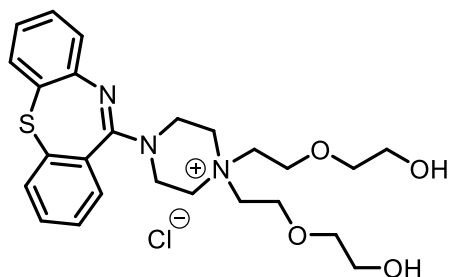
1,4-bis(dibenzo[b,f][1,4]thiazepin-11-yl)piperazine (*Dimer*)



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 – 7.74 (m, 2H), 7.65 (m, 4H), 7.60 – 7.49 (m, 4H), 7.47 – 7.31 (m, 6H), 4.73 – 4.53 (m, 2H), 4.49 (m, 1H), 4.40 – 4.26 (m, 2H), 4.24 – 3.98 (m, 2H), 3.78 – 3.52 (m, 1H). **HRMS (ESI):**

calcd for $\text{C}_{30}\text{H}_{25}\text{N}_4\text{S}_2^+$ $[\text{M} + \text{H}]^+$: 505.1515, found: 505.1511.

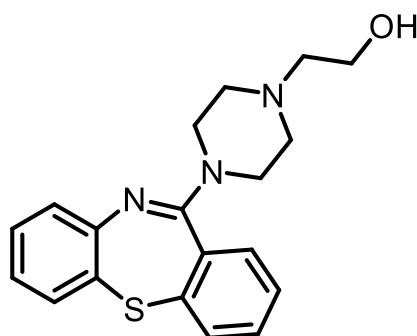
4-(dibenzo[b,f][1,4]thiazepin-11-yl)-1,1-bis(2-(2-hydroxyethoxy)ethyl)piperazin-1-ium chloride (*Imp-1*)



$^1\text{H NMR}$ (400 MHz, EtOD) δ 7.64 (m, 1H), 7.55 (m, 1H), 7.50 – 7.37 (m, 3H), 7.22 (m, 1H), 7.09 (m, 1H), 6.97 (m, 1H), 4.53 (s, 2H), 4.04 – 3.79 (m, 11H), 3.72 – 3.57 (m, 10H), 3.35 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, EtOD) δ 160.4, 148.0, 139.8, 132.9, 132.0, 131.9, 131.6, 129.4, 129.0,

128.1, 125.2, 123.7, 72.5, 64.3, 60.4, 59.6, 48.4, 40.7.

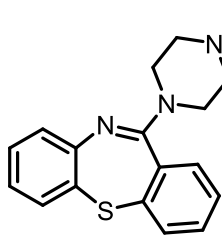
2-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)ethan-1-ol (*Imp-2*)



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.51 (d, $J = 7.2$ Hz, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.35 – 7.26 (m, 3H), 7.17 (t, $J = 7.1$ Hz, 1H), 7.08 (d, $J = 7.8$ Hz, 1H), 6.88 (t, $J = 7.3$ Hz, 1H), 3.75 – 3.33 (m, 6H), 2.75 (s, 1H), 2.58 (m, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.9, 148.9, 140.0, 134.2, 132.3, 130.9, 129.2, 129.1, 129.1, 128.4,

128.1, 125.4, 123.0, 59.6, 57.9, 52.8, 46.9. **HRMS (ESI):** calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{OS}^+$ $[\text{M} + \text{H}]^+$: 340.1478, found: 340.1472.

11-(4-ethylpiperazin-1-yl)dibenzo[b,f][1,4]thiazepine (**Imp-3**)

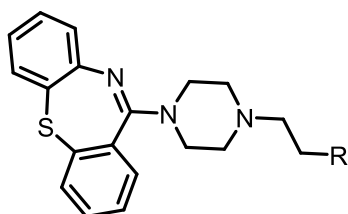


$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.50 (d, $J = 6.0$ Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.29 (m, 3H), 7.16 (t, $J = 7.3$ Hz, 1H), 7.07 (d, $J = 7.7$ Hz, 1H), 6.87 (t, $J = 7.2$ Hz, 1H), 3.56 (s, 4H), 2.50 (m, 6H), 1.11 (t, $J = 6.5$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.9, 149.1, 140.1,

134.3, 132.3, 132.3, 130.8, 129.2, 129.1, 128.3, 128.1, 125.5, 122.9, 52.8, 52.5, 46.7, 12.1.

HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{S}^+$ [$\text{M} + \text{H}$] $^+$: 324.1529, found: 324.1533.

2-(2-(2-(2-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)ethan-1-ol (**Imp-4**)



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.46 (d, $J = 5.9$ Hz, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.26 (m, 3H), 7.12 (t, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 7.7$ Hz, 1H), 6.83 (t, $J = 7.1$ Hz, 1H), 3.66 (m, 6H), 3.60 (m, 10H), 3.54 (m, 3H), 2.57 (m, 6H). $^{13}\text{C NMR}$

Imp-4: R = $(\text{OC}_2\text{H}_4)_3\text{OH}$

(100 MHz, CDCl_3) δ 160.7, 148.7, 139.7, 133.8, 132.0, 132.0,

130.7, 129.0, 128.9, 128.2, 128.0, 125.1, 122.7, 72.6, 70.4, 70.3, 70.0, 70.0, 68.4, 61.3, 57.6,

53.1, 50.0, 46.3. **HRMS (ESI):** calcd for $\text{C}_{25}\text{H}_{34}\text{N}_3\text{O}_4\text{S}^+$ [$\text{M} + \text{H}$] $^+$: 472.2265, found:

472.2266.

9. Analysis methods for intermediates and finished products of quetiapine fumarate

9.1 Analysis methods for *Int-2*

Chromatographic condition:

Instrument: HPLC with a UV detector

Liquid chromatography column: Waters Symmetry C18, 4.6*75 mm, 3.5 µm

Buffer solution preparation: Dissolve KH_2PO_4 (0.68 g) in water (1000 mL), add Et_3N (2.5 mL), and adjust the pH to 3.0 with H_3PO_4

Mobile phase A: The buffer solution

Mobile phase B: Acetonitrile

Flow rate: 1.0 mL/min

Column temperature: 30 °C

Wavelength: 240 nm

Sample load: 40 µL

Gradient table:

Time (min)	Mobile phase A (% V/V)	Mobile phase B (% V/V)
0	90	10
15	73	27
19	15	85
24	15	85
26	90	10
28	90	10

9.2 Analysis methods for quetiapine fumarate crude

Chromatographic condition:

Instrument: HPLC with a UV detector

Liquid chromatography column: Waters XBridge C8, 150*4.6 mm, 3.5 μ m

Buffer solution preparation: Adjust the pH of the 3.1g/L ammonium acetate aqueous solution to 9.5 with ammonia water

Mobile phase A: Buffer solution: acetonitrile = 75: 25 (V/V)

Mobile phase B: Acetonitrile

Flow rate: 1.5 mL/min

Column temperature: 45 °C

Wavelength: 250 nm

Sample load: 20 μ L

Gradient table:

Time (min)	Mobile phase A (% V/V)	Mobile phase B (% V/V)
0	100	0
25	100	0
60	29.3	70.7
60.1	100	0
68	100	0

9.3 Analysis methods for quetiapine fumarate

Chromatographic condition:

Instrument: HPLC with a UV detector

Liquid chromatography column: Waters XTerra RP8, 150*4.6 mm, 3.5 μ m

Buffer solution preparation: Adjust the pH of the 3.1g/L ammonium acetate aqueous solution to 9.5 with ammonia water

Mobile phase A: Buffer solution: acetonitrile = 75: 25 (V/V)

Mobile phase B: Acetonitrile

Flow rate: 1.5 mL/min

Column temperature: 45 °C

Wavelength: 250 nm

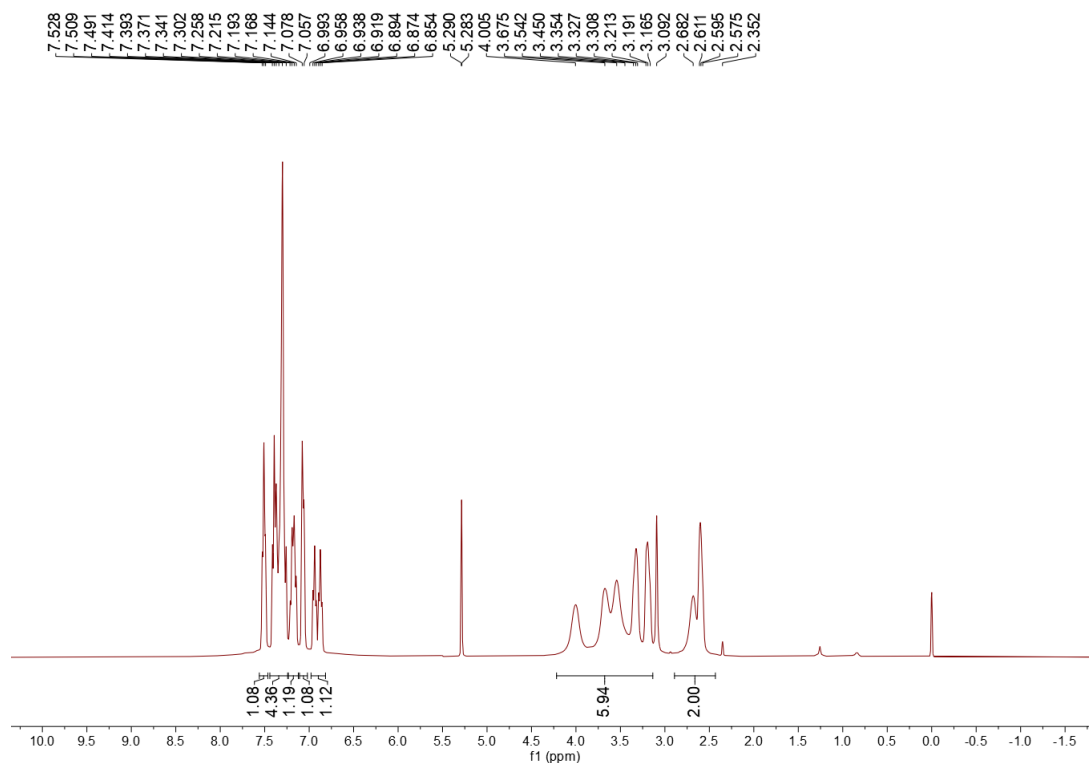
Sample load: 20 µL

Gradient table:

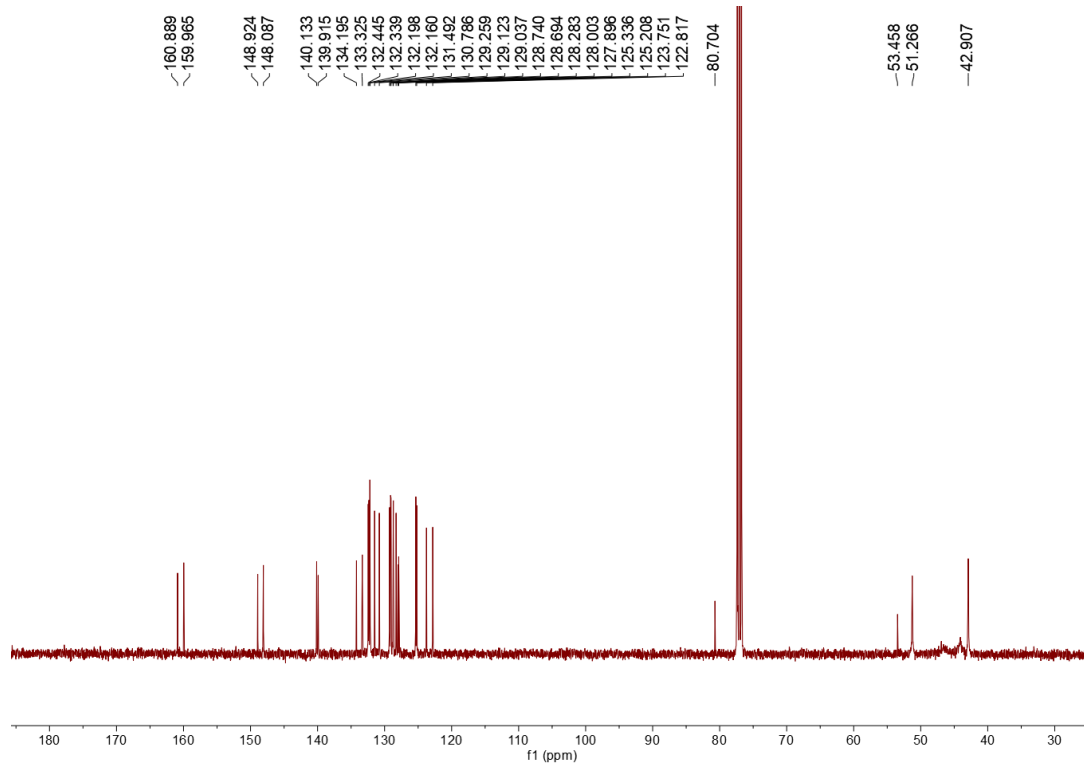
Time (min)	Mobile phase A (% V/V)	Mobile phase B (% V/V)
0	100	0
25	100	0
60	29.3	70.7
60.1	100	0
68	100	0

10. NMR Spectra

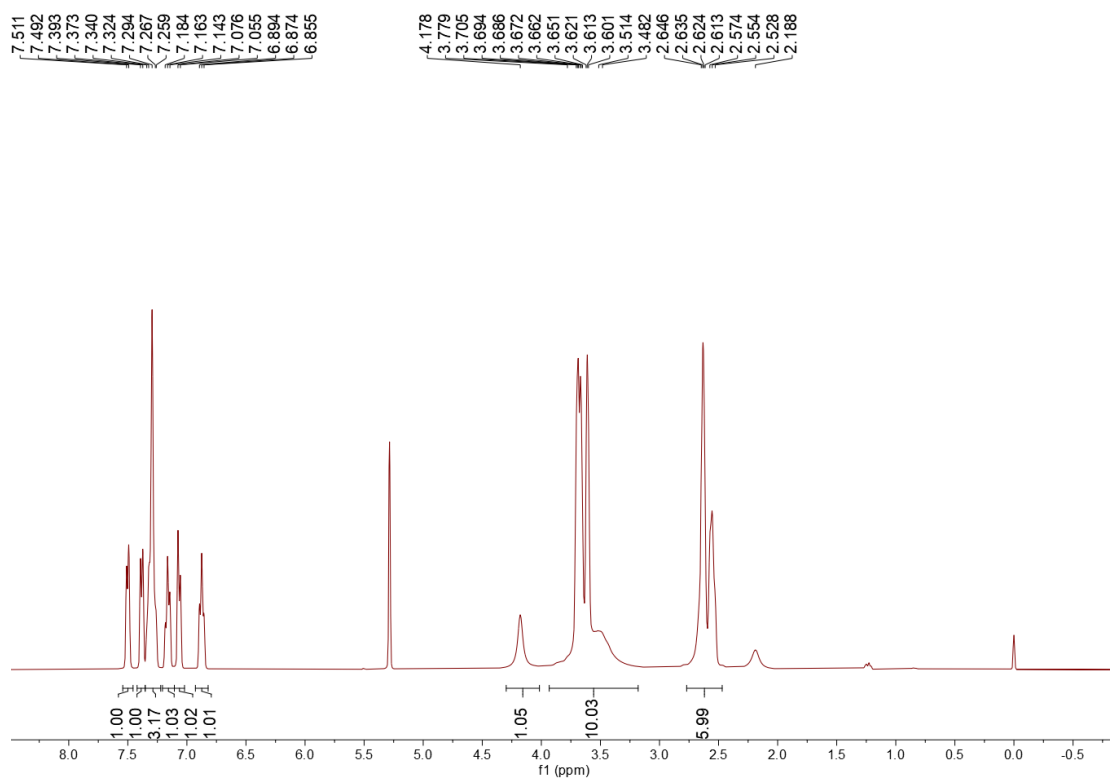
¹H NMR Spectra of *Int-2*



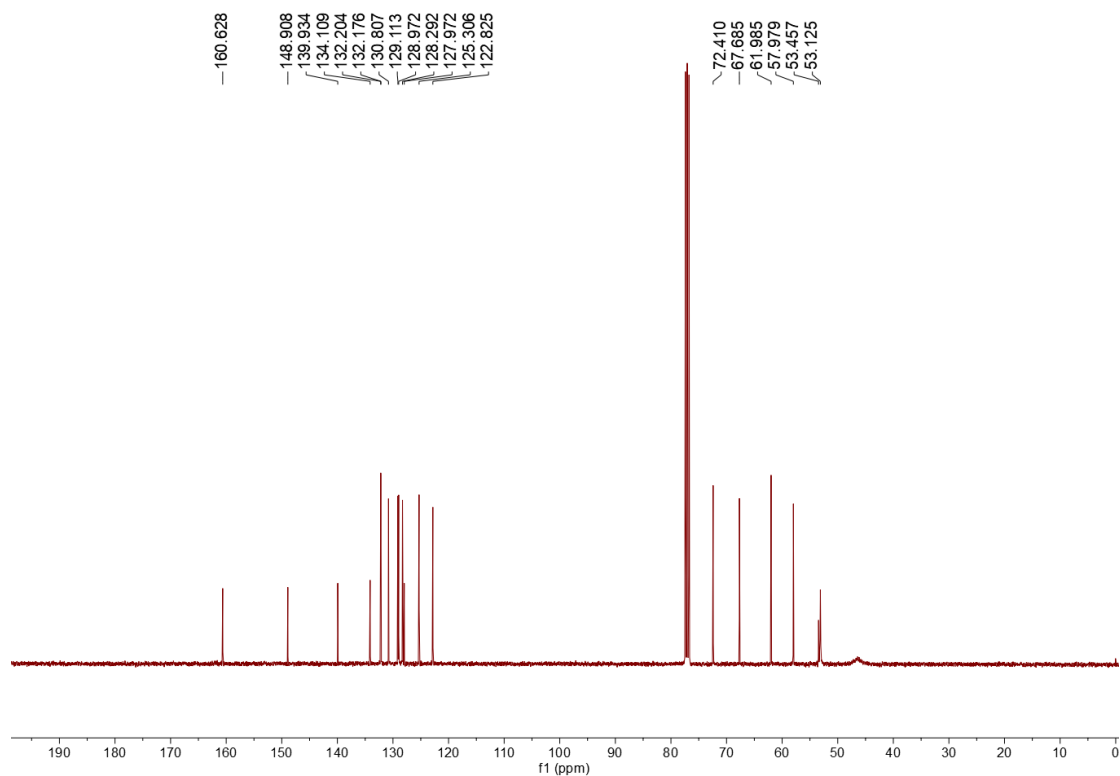
¹³C NMR Spectra of *Int-2*



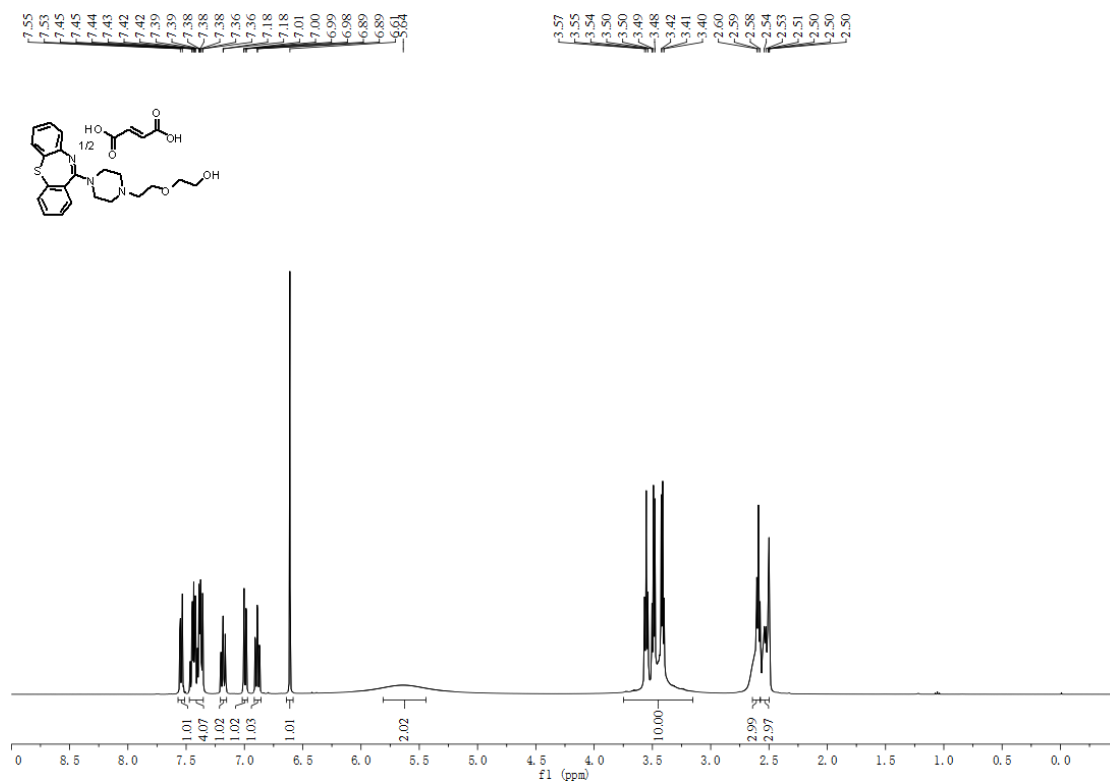
¹H NMR Spectra of quetiapine



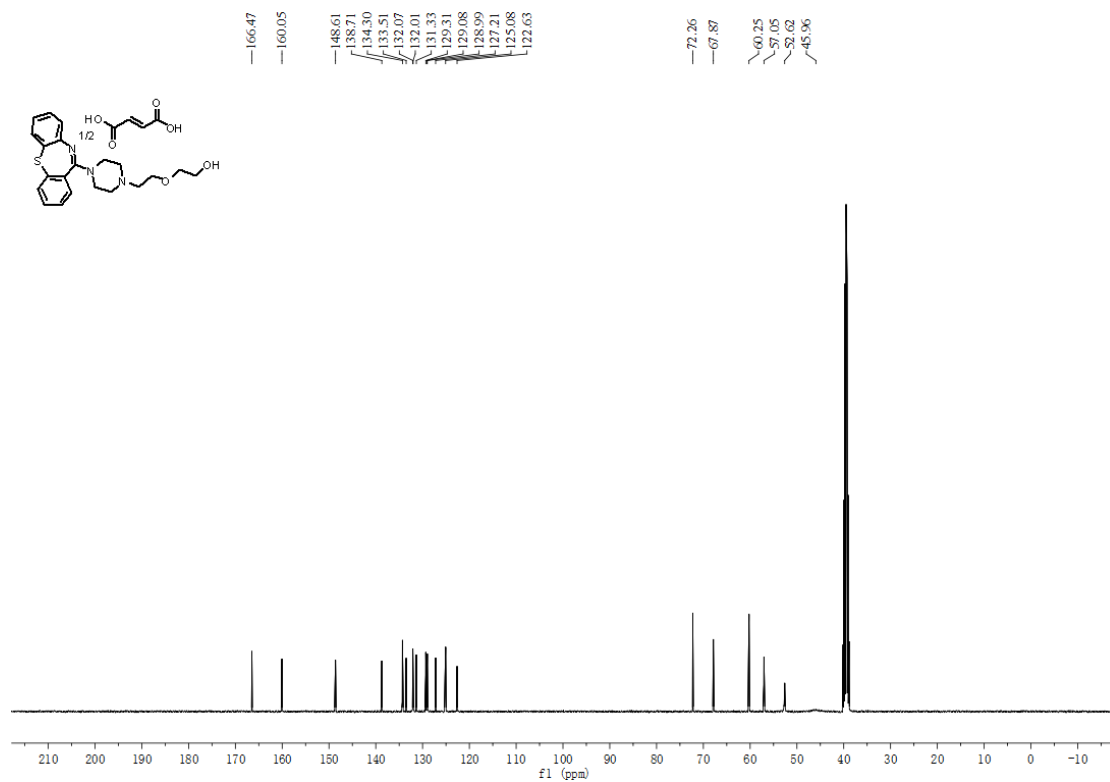
¹³C NMR Spectra of quetiapine



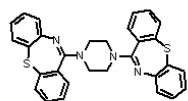
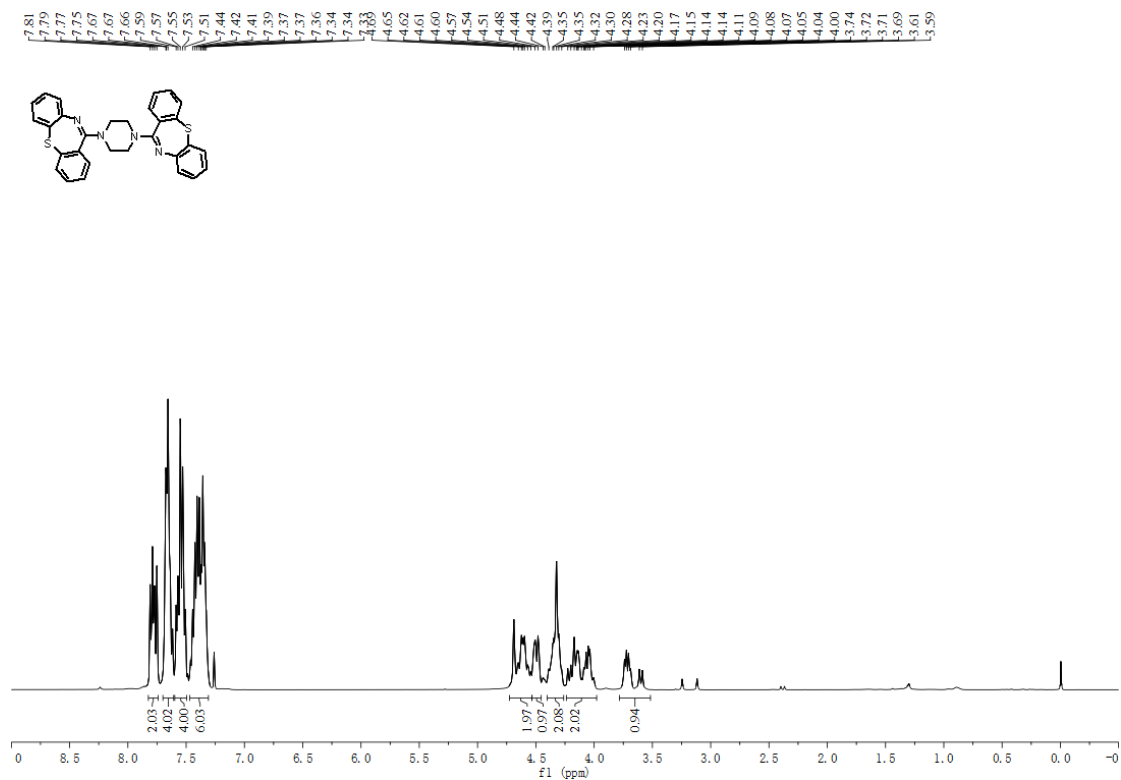
¹H NMR Spectra of API



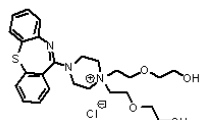
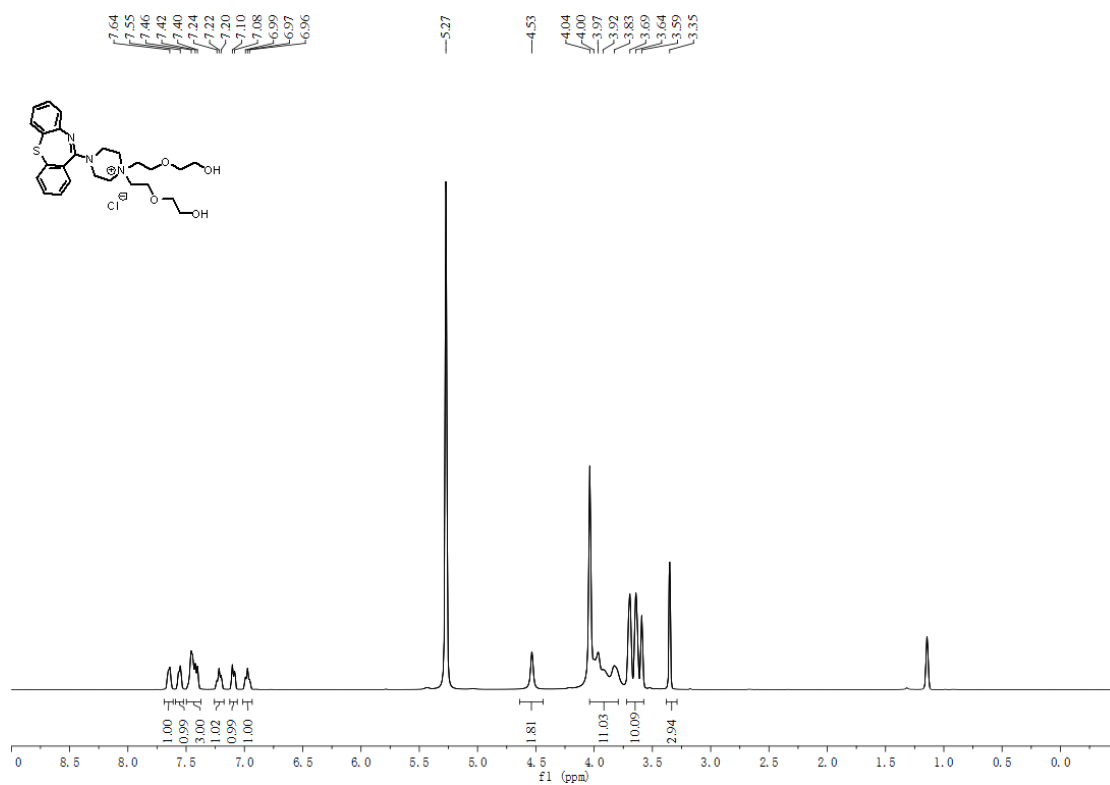
¹³C NMR Spectra of API



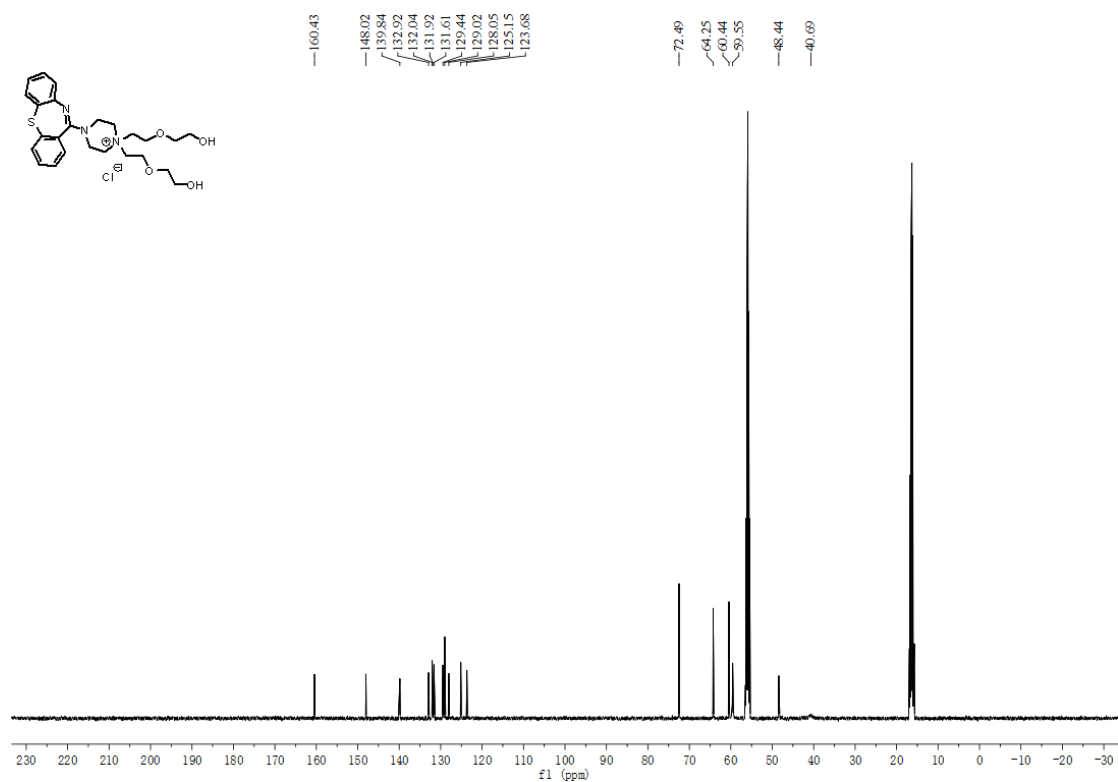
¹H NMR Spectra of dimer impurity



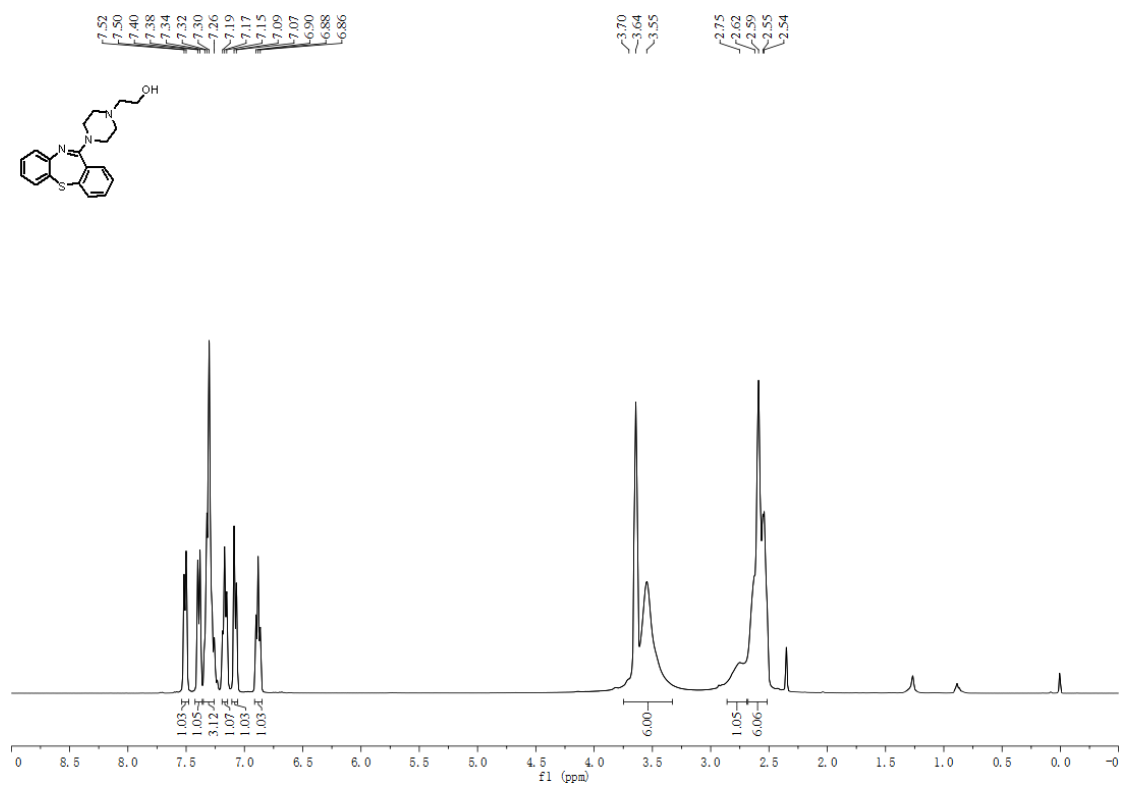
¹H NMR Spectra of *Imp-1*



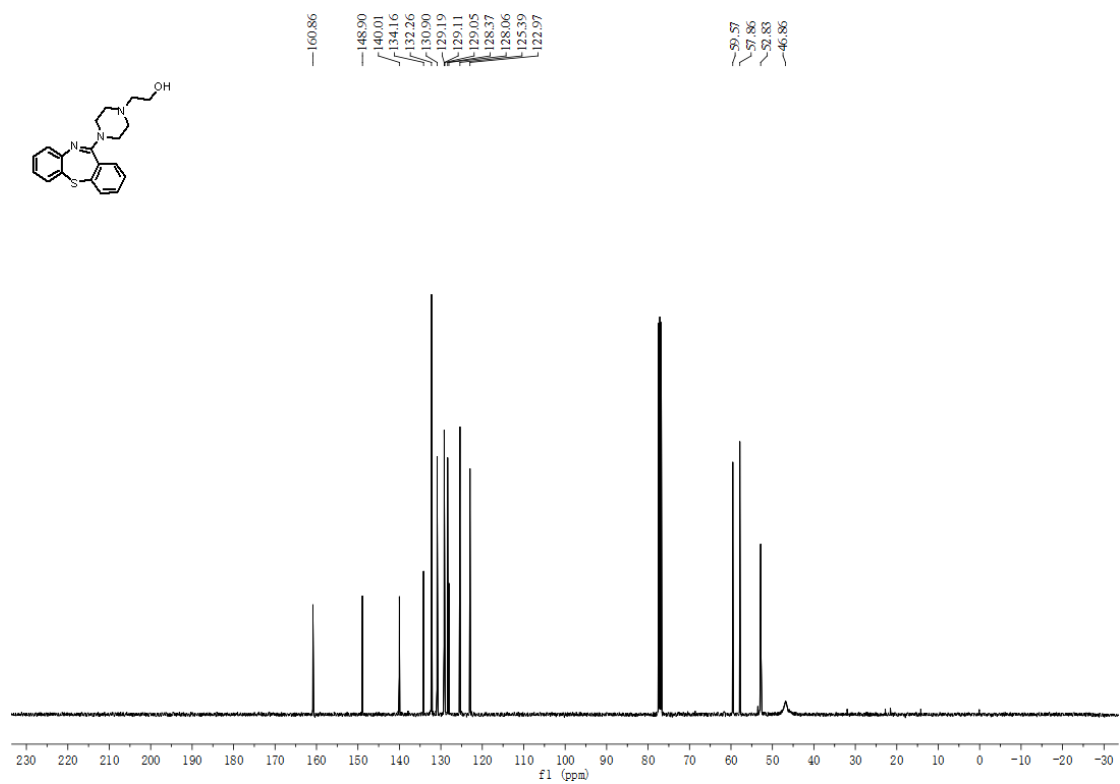
¹³C NMR Spectra of *Imp-1*



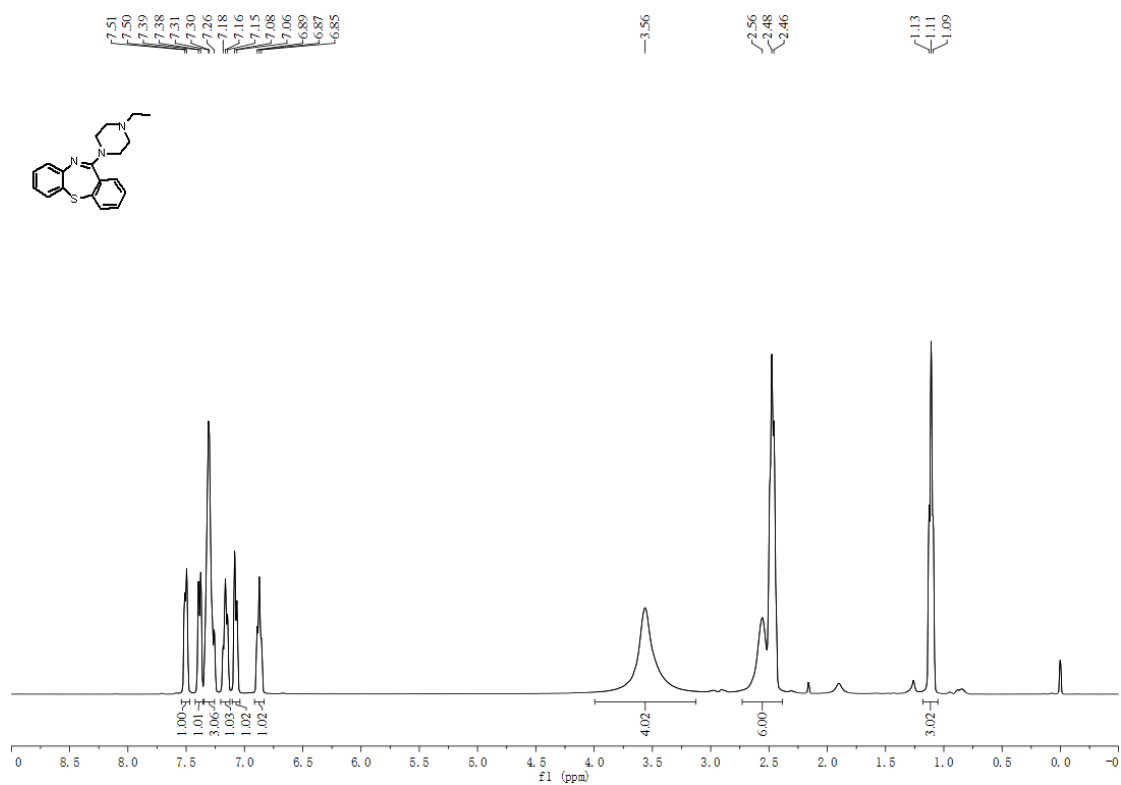
¹H NMR Spectra of *Imp-2*



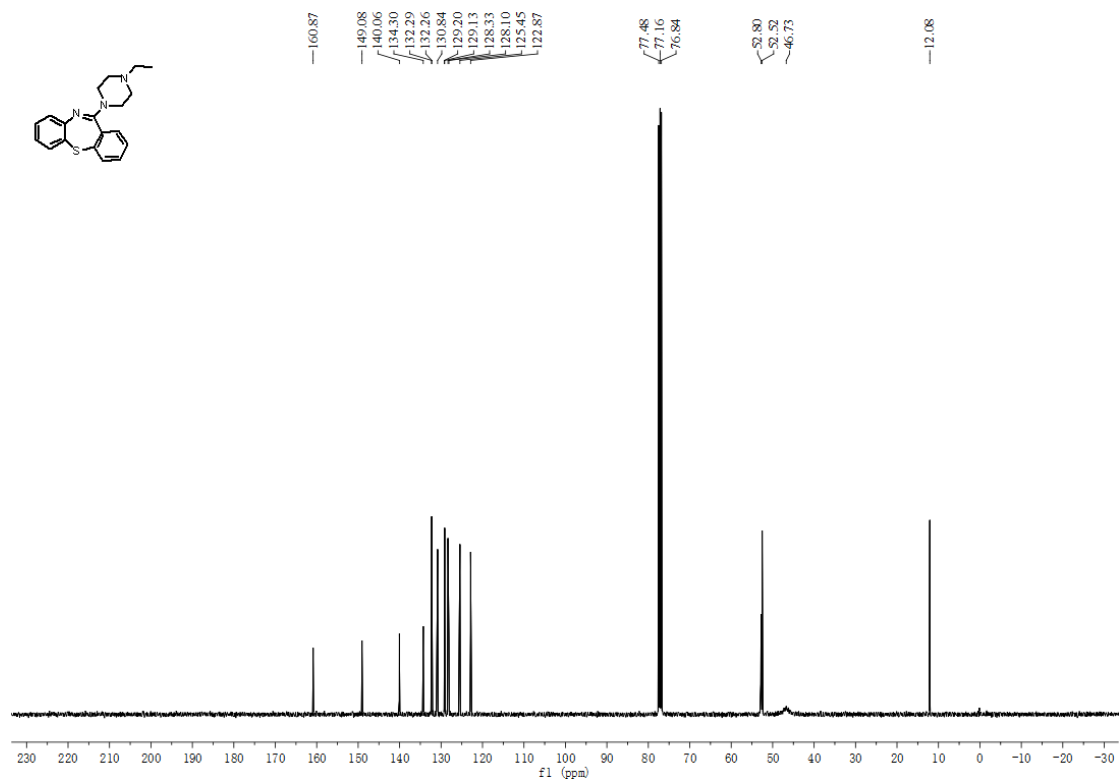
¹³C NMR Spectra of *Imp-2*



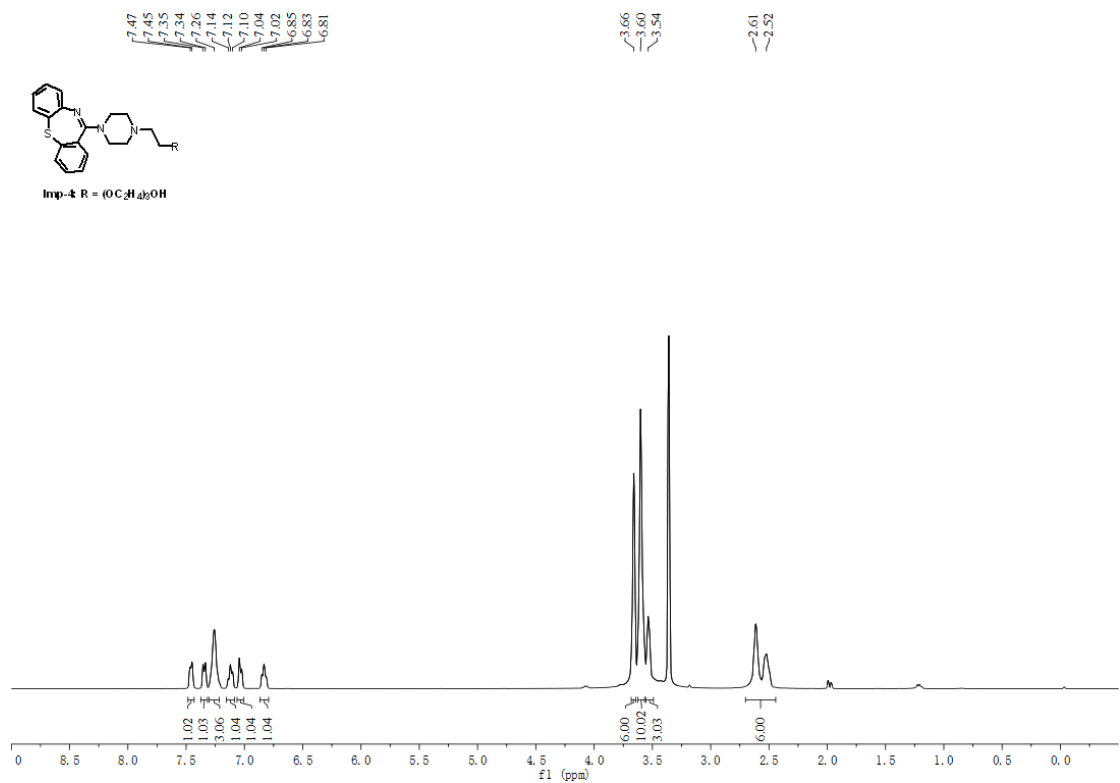
¹H NMR Spectra of *Imp-3*



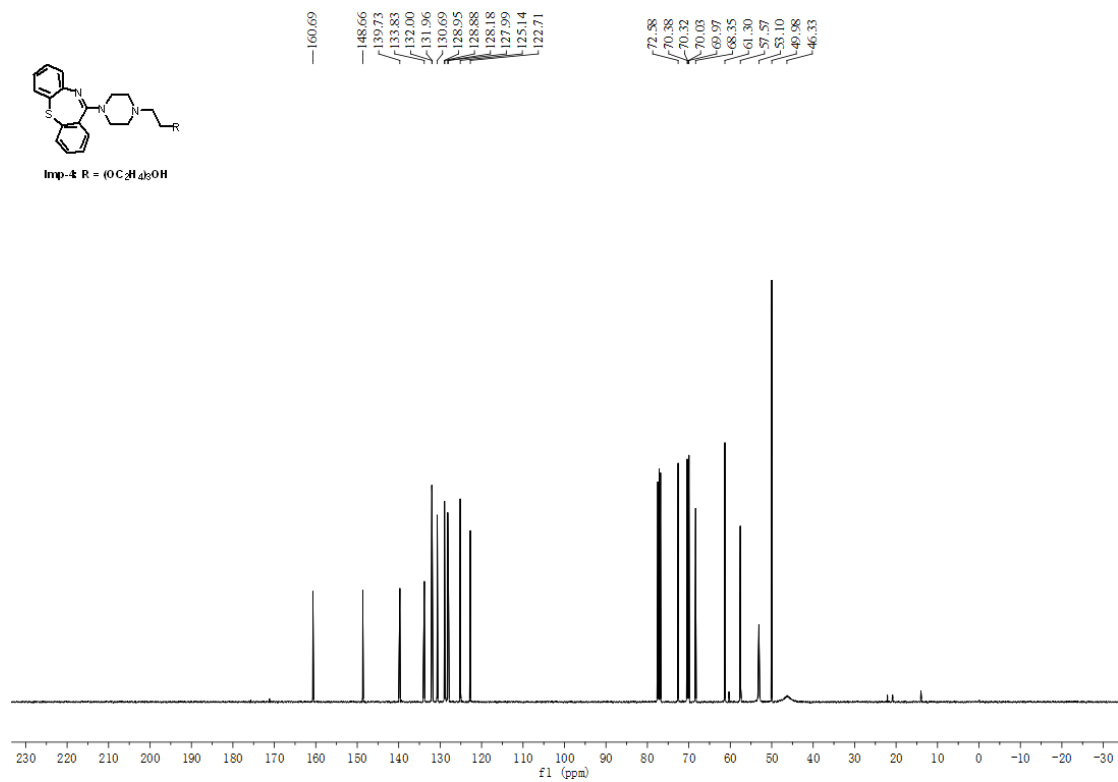
¹³C NMR Spectra of *Imp-3*



¹H NMR Spectra of *Imp-4*



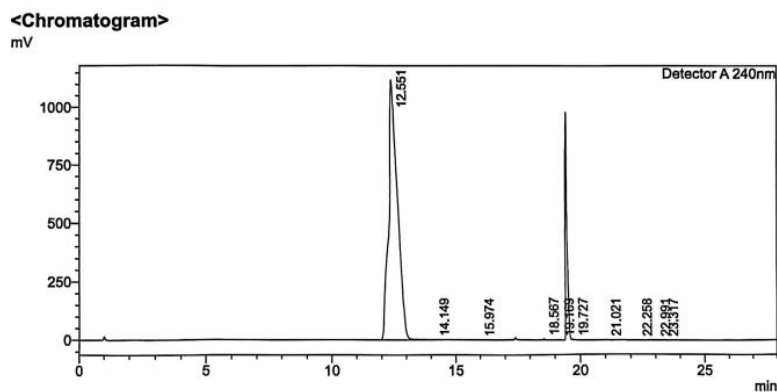
¹³C NMR Spectra of *Imp-4*



11. Representative HPLC chromatograms

11.1 HPLC chromatograms of Int-2 before and after pH optimization

HPLC chromatograms of *Int-2* before pH optimization

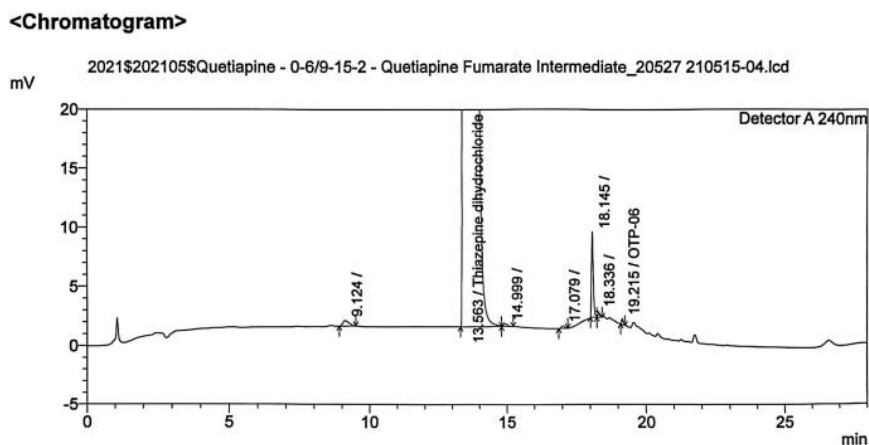


<Peak Table>

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	12.551	28285335	1117819	0.000	mg/L		Quetiapine
2	14.149	19690	951	0.000		V	
3	15.974	5789	394	0.000			
4	18.567	22105	5343	0.000	mg/L		QTP-06
5	19.169	6149	946	0.000			
6	19.727	7472	1918	0.000			
7	21.021	12874	1899	0.000			
8	22.258	5490	929	0.000			
9	22.991	7656	934	0.000		V	
10	23.317	17491	1617	0.000	mg/L	V	QTP-03
Total		28390051	1132748				

HPLC chromatograms of *Int-2* after pH optimization

Int-2 of batch 1

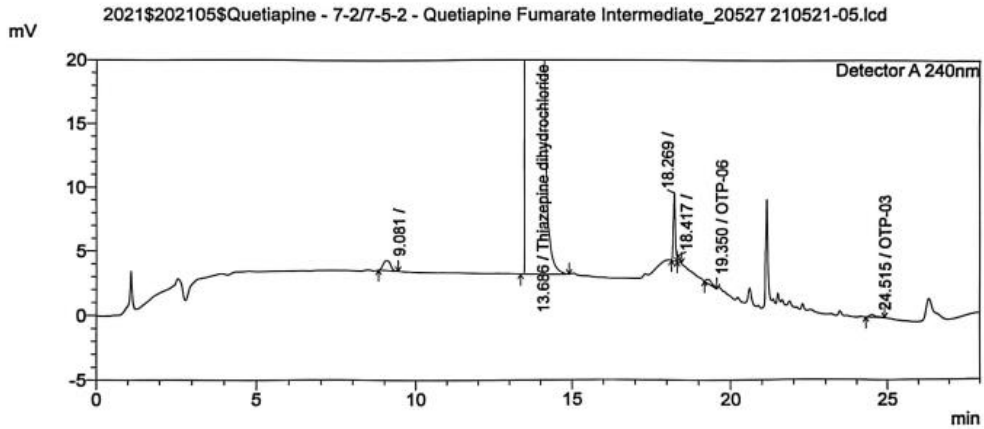


<Results>

Peak#	Ret. Time	Mark	Area	Area%	Name
1	9.124		7594	0.0459	
2	13.563		16494601	99.6981	Thiazepine dihydrochloride
3	14.999	V	2382	0.0144	
4	17.079		1853	0.0112	
5	18.145		33299	0.2013	
6	18.336	V	2731	0.0165	
7	19.215		2091	0.0126	OTP-06
Total			16544551	100.0000	

Int-2 of batch 2

<Chromatogram>



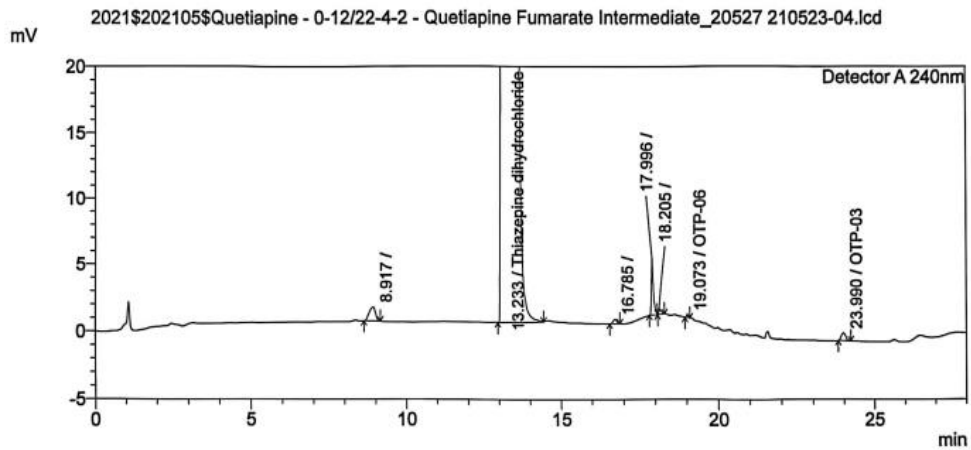
<Results>

Detector A 240nm

Peak#	Ret. Time	Mark	Area	Area%	Name
1	9.081		13050	0.0805	
2	13.686		16165473	99.7275	Thiazepine dihydrochloride
3	18.269		22126	0.1365	
4	18.417	V	2579	0.0159	
5	19.350		3630	0.0224	OTP-06
6	24.515		2788	0.0172	OTP-03
Total			16209646	100.0000	

Int-2 of batch 3

<Chromatogram>



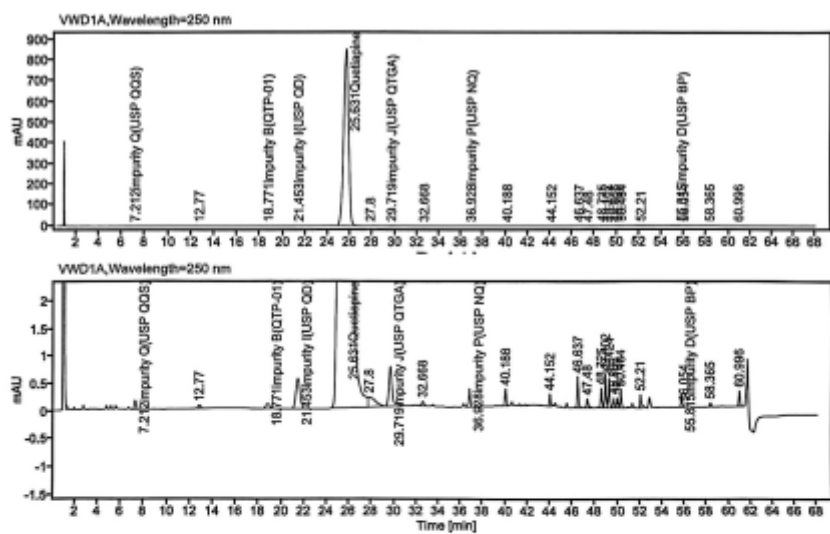
<Results>

Detector A 240nm

Peak#	Ret. Time	Mark	Area	Area%	Name
1	8.917		14723	0.0861	
2	13.233		17050009	99.7242	Thiazepine dihydrochloride
3	16.785		2742	0.0160	
4	17.996		20284	0.1186	
5	18.205	V	2828	0.0165	
6	19.073		847	0.0050	OTP-06
7	23.990		5725	0.0335	OTP-03
Total			17097158	100.0000	

11.2 For Hundred-kilogram scale experiments

API of Batch 001

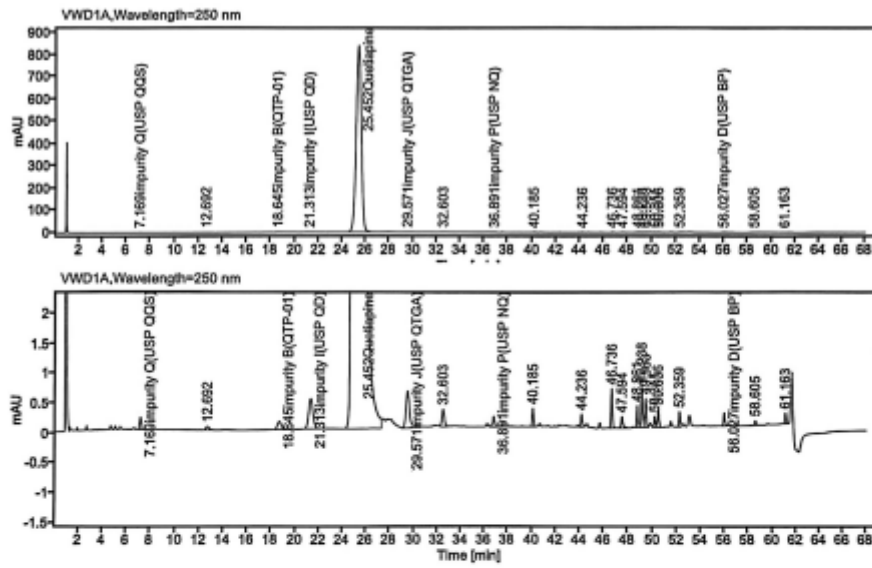


Signal: WVD1A,Wavelength=250 nm

RT [min]	Type	Height	Area	Area%	Concentration	Name
7.212	BB	0.159	1.721	0.0067	0.0107	impurity Q(USP QQS)
12.770	BB	0.059	1.084	0.0042	0.0042	
14.350						impurity G(USP ImpG)
18.771	VV	0.091	2.070	0.0080	0.0088	impurity B(QTP-01)
21.453	BV	0.557	14.179	0.0549	0.0548	impurity I(USP QD)
25.631	BV	848.918	25740.466	99.6700	99.5709	Quetiapine
25.960						impurity N
27.800	VV	0.188	8.755	0.0339	0.0339	
29.719	VB	0.735	15.935	0.0617	0.0616	impurity J(USP QTGA)

32.668	VB	0.083	1.192	0.0046	0.0046	
36.928	VB	0.331	3.354	0.0130	0.0118	impurity P(USP NQ)
40.188	BV	0.303	2.786	0.0108	0.0108	
44.152	BV	0.221	1.795	0.0069	0.0069	
46.637	VB	0.574	4.718	0.0183	0.0183	
47.480	BB	0.164	1.891	0.0073	0.0073	
48.725	BV	0.352	2.812	0.0109	0.0109	
49.102	VV	0.617	4.955	0.0192	0.0192	
49.424	VB	0.550	4.677	0.0181	0.0181	
49.866	BB	0.181	1.773	0.0069	0.0069	
50.168	BV	0.182	1.500	0.0058	0.0058	
50.464	VB	0.330	2.767	0.0107	0.0107	
52.210	BV	0.245	2.004	0.0078	0.0078	
55.815	BV	0.242	1.910	0.0074	0.0074	impurity D(USP BP)
56.054	VB	0.031	0.326	0.0013	0.0013	
58.365	BB	0.074	0.716	0.0028	0.0028	
60.996	BB	0.284	2.299	0.0089	0.0089	

API of Batch 002

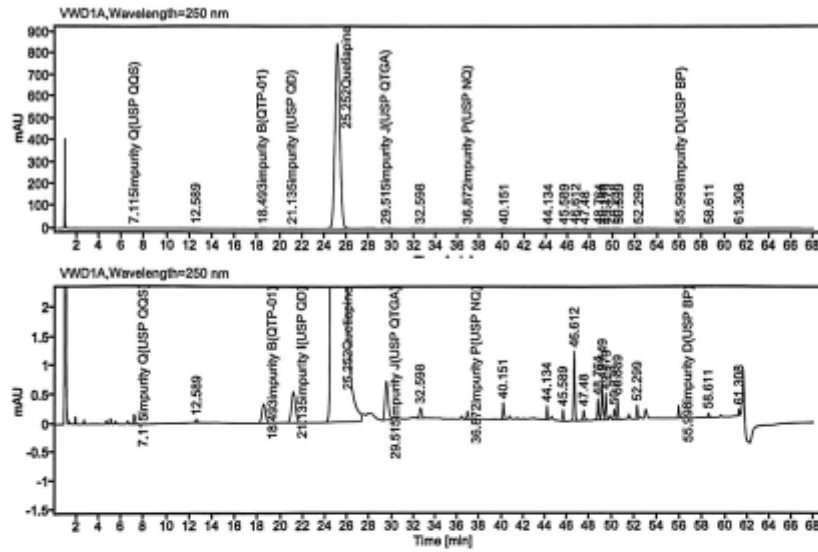


Signal: VWD1A, Wavelength=250 nm

RT [min]	Type	Height	Area	Area%	Concentration	Name
7.169	BB	0.199	2.133	0.0084	0.0134	Impurity Q(USP QQS)
12.692	BB	0.058	1.060	0.0042	0.0041	
14.350						Impurity G(USP ImpG)
18.645	VV	0.137	3.119	0.0123	0.0101	Impurity B(QTP-01)
21.313	VV	0.511	12.928	0.0509	0.0504	Impurity I(USP QD)
25.452	BH	840.464	25324.437	99.7089	98.6708	Quetiapine
25.960						Impurity N
29.571	BV	0.628	13.722	0.0540	0.0535	Impurity J(USP QTGA)
32.603	VV	0.291	4.316	0.0170	0.0168	
36.891	VB	0.174	2.015	0.0079	0.0071	Impurity P(USP NQ)

RT [min]	Type	Height	Area	Area%	Concentration	Name
40.185	BV	0.309	2.726	0.0107	0.0106	
44.236	BV	0.218	1.723	0.0068	0.0067	
46.736	VV	0.674	5.369	0.0211	0.0209	
47.594	BB	0.189	2.157	0.0085	0.0084	
48.861	BV	0.365	2.924	0.0115	0.0114	
49.236	VV	0.683	5.482	0.0216	0.0214	
49.563	VB	0.493	4.281	0.0169	0.0167	
50.311	BV	0.179	1.474	0.0058	0.0057	
50.606	VB	0.303	2.518	0.0099	0.0098	
52.359	BV	0.254	2.064	0.0081	0.0080	
56.027	BV	0.219	1.715	0.0068	0.0067	Impurity D(USP BP)
58.605	VV	0.061	0.772	0.0030	0.0030	
61.163	VB	0.178	1.443	0.0057	0.0056	

API of Batch 003

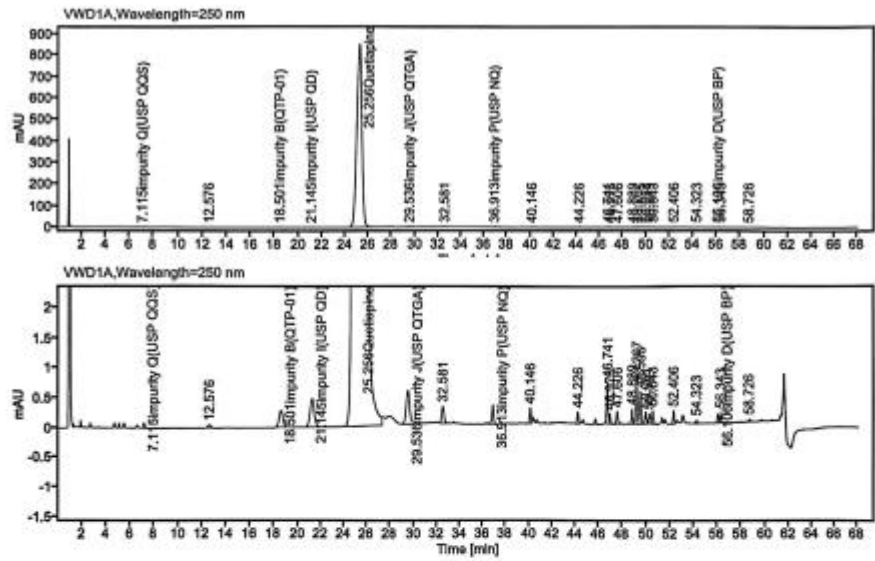


Signal: VWD1A, Wavelength=250 nm

RT [min]	Type	Height	Area	Area%	Concentration	Name
7.115	BB	0.161	1.729	0.0068	0.0108	Impurity Q(USP QQS)
12.589	BB	0.055	0.837	0.0037	0.0036	
14.350						Impurity G(USP ImpG)
18.493	BV	0.324	7.291	0.0288	0.0234	Impurity B(QTP-01)
21.135	BB	0.535	13.288	0.0524	0.0514	Impurity I(USP QD)
25.252	BH	844.290	25263.671	99.6804	97.6493	Quetlapline
25.960						Impurity N
29.515	BV	0.668	13.722	0.0541	0.0530	Impurity J(USP QTGA)
32.598	VV	0.176	2.837	0.0112	0.0110	
36.872	VB	0.141	1.677	0.0066	0.0059	Impurity P(USP NQ)

RT [min]	Type	Height	Area	Area%	Concentration	Name
40.151	BV	0.288	2.734	0.0108	0.0106	
44.134	BV	0.235	1.833	0.0072	0.0071	
45.589	VB	0.189	1.493	0.0059	0.0066	
46.612	VB	1.205	9.647	0.0381	0.0373	
47.480	BV	0.175	2.018	0.0080	0.0078	
48.764	BV	0.356	2.839	0.0112	0.0110	
49.149	VV	0.643	5.195	0.0205	0.0201	
49.479	VB	0.450	3.969	0.0157	0.0154	
50.238	BV	0.180	1.511	0.0060	0.0066	
50.539	VB	0.364	3.086	0.0122	0.0119	
52.299	BV	0.235	1.927	0.0076	0.0074	
55.998	BV	0.218	1.738	0.0069	0.0067	Impurity D(USP BP)
58.611	BV	0.074	0.731	0.0029	0.0028	
61.308	BBA	0.104	0.776	0.0031	0.0030	

API of Batch 004

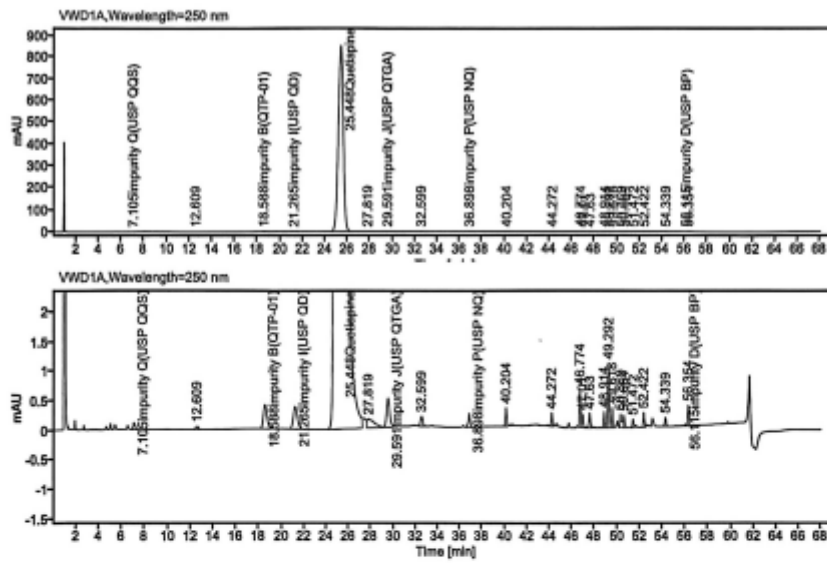


Signal: VWD1A, Wavelength=250 nm

RT [min]	Type	Height	Area	Area%	Concentration	Name
7.115	BB	0.085	0.957	0.0038	0.0059	Impurity Q(USP QQS)
12.576	BB	0.052	0.824	0.0032	0.0032	
14.350						Impurity G(USP ImpG)
18.501	VV	0.285	6.336	0.0249	0.0202	Impurity B(QTP-01)
21.145	VV	0.483	12.189	0.0478	0.0469	Impurity I(USP QD)
25.256	VH	849.854	25421.894	98.7036	97.8306	Quetiapine
25.980						Impurity N
29.536	BV	0.570	12.518	0.0491	0.0482	Impurity J(USP QTGA)
32.581	VB	0.281	4.091	0.0160	0.0157	
36.913	VV	0.324	3.469	0.0136	0.0121	impurity P(USP NQ)

RT [min]	Type	Height	Area	Area%	Concentration	Name
40.146	BV	0.262	2.303	0.0080	0.0089	
44.226	BV	0.202	1.635	0.0064	0.0063	
46.741	BV	0.715	5.643	0.0217	0.0213	
46.976	VB	0.171	1.247	0.0049	0.0048	
47.606	VV	0.210	2.027	0.0080	0.0078	
48.889	BV	0.261	2.028	0.0080	0.0078	
49.267	VV	0.651	5.323	0.0209	0.0205	
49.596	VB	0.555	4.656	0.0179	0.0175	
50.051	BB	0.198	1.741	0.0068	0.0067	
50.349	BV	0.169	1.359	0.0053	0.0052	
50.643	VB	0.221	1.969	0.0078	0.0077	
52.406	BV	0.219	1.768	0.0069	0.0068	
54.323	VB	0.059	0.574	0.0023	0.0022	
56.106	BV	0.150	1.210	0.0047	0.0047	Impurity D(USP BP)
56.343	VB	0.169	1.393	0.0055	0.0054	
58.726	BV	0.046	0.461	0.0019	0.0019	

API of Batch 005

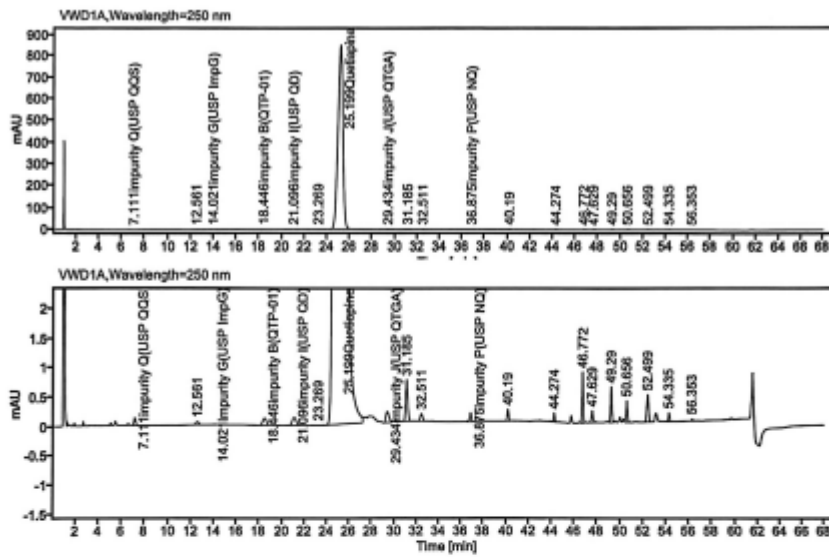


Signal: WVD1A, Wavelength=250 nm

RT [min]	Type	Height	Area	Area%	Concentration	Name
7.105	BB	0.109	1.219	0.0047	0.0075	Impurity Q(USP QQS)
12.609	BB	0.048	0.823	0.0032	0.0032	
14.350						Impurity G(USP ImpG)
18.588	VV	0.401	9.057	0.0349	0.0289	Impurity B(QTP-01)
21.285	VV	0.377	9.825	0.0371	0.0370	Impurity I(USP QD)
25.448	BH	851.947	25875.507	99.6865	99.4577	Quetiapine
25.980						Impurity N
27.819	VB	0.151	6.964	0.0268	0.0268	
29.591	BV	0.487	10.282	0.0396	0.0395	Impurity J(USP QTGA)
32.599	VB	0.165	2.435	0.0094	0.0094	

RT [min]	Type	Height	Area	Area%	Concentration	Name
36.898	VB	0.233	2.613	0.0101	0.0091	Impurity P(USP NQ)
40.204	BV	0.312	2.783	0.0107	0.0107	
44.272	BV	0.219	1.720	0.0066	0.0066	
46.774	BV	0.643	4.895	0.0189	0.0188	
47.010	VB	0.221	1.651	0.0064	0.0063	
47.630	BV	0.238	2.283	0.0088	0.0088	
48.914	BV	0.266	2.114	0.0081	0.0081	
49.292	VV	1.086	8.630	0.0332	0.0332	
49.618	VB	0.337	2.604	0.0100	0.0100	
50.399	BV	0.216	2.247	0.0087	0.0086	
50.864	VB	0.204	1.914	0.0074	0.0074	
51.472	VV	0.136	1.167	0.0046	0.0046	
52.422	BV	0.242	1.930	0.0074	0.0074	
54.339	VB	0.149	1.303	0.0050	0.0050	
56.115	BV	0.032	0.297	0.0011	0.0011	Impurity D(USP BP)
56.354	VV	0.344	2.809	0.0108	0.0108	

API of Batch 006



Signal: WVD1A, Wavelength=250 nm

RT [min]	Type	Height	Area	Area%	Concentration	Name
7.111	BB	0.127	1.418	0.0056	0.0088	impurity Q(USP QQS)
12.561	BB	0.050	0.881	0.0034	0.0033	
14.021	BV	0.007	0.091	0.0004	0.0003	impurity G(USP ImpG)
18.446	VV	0.117	2.808	0.0102	0.0083	impurity B(QTP-01)
21.096	VV	0.136	3.480	0.0136	0.0133	impurity I(USP QD)
23.269	VB	0.004	0.096	0.0004	0.0004	
25.199	BH	850.766	25465.621	99.7958	97.6884	Quetiapine
25.960						impurity N
29.434	BV	0.187	3.749	0.0147	0.0144	impurity J(USP QTGA)
31.185	BB	0.710	9.446	0.0370	0.0362	

RT [min]	Type	Height	Area	Area%	Concentration	Name
32.511	BV	0.126	1.807	0.0071	0.0069	
36.875	VB	0.153	1.699	0.0067	0.0059	impurity P(USP NQ)
40.190	BV	0.195	1.681	0.0066	0.0064	
44.274	BB	0.150	1.209	0.0047	0.0046	
46.772	VV	0.878	6.864	0.0269	0.0263	
47.829	BV	0.200	2.241	0.0088	0.0086	
49.290	VV	0.611	4.776	0.0187	0.0183	
50.656	VB	0.363	3.050	0.0120	0.0117	
52.499	BB	0.467	5.329	0.0209	0.0204	
54.335	BV	0.146	1.266	0.0050	0.0049	
55.700						impurity D(USP BP)
56.353	VV	0.036	0.429	0.0017	0.0016	