Synthesis and characterization of pharmacopeial impurities of quetiapine hemifumarate: An antipsychotic drug

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ABSTRACT
European Pharmacopeia 7.0 disclosed ten potential impurities in Quetiapine hemifumarate (1). The acceptable range of these impurities in Quetiapine hemifumarate is from 0.05 – 0.15% by reverse-phase HPLC. These impurities were synthesized and analysed by European Pharmacopeial HPLC method and found that these impurities are correlating with the specified retention times. Along with pharmacopeial impurities, Quetiapine S-Oxide impurity is also synthesized. Structural elucidation of all these impurities by spectral data (1H NMR, MS and IR), synthesis and formation of these impurities are discussed in detail.

INTRODUCTION
Quetiapine hemifumarate (1) is a psychoactive organic compound that acts as an antagonist for multiple neurotransmitter receptor sites, including serotonin (5HT1A; 5HT2A), dopamine (D1; D2), histamine (H1) and adrenaline (Alpha 1; Alpha 2), in the brain and acts as an antipsychotic agent reportedly useful for treating, among other things, schizophrenia[1]. Quetiapine has a lower affinity for D2 receptors than dopamine itself, leading to an intermittent D2 blockade, and may contribute to the excellent tolerability profile of this substance. It was hypothesized that Quetiapine may act on depression, through its antagonism of 5-HT2A receptors, and on mania through its antagonism of D2 receptors[2]. Quetiapine was found to be effective in the treatment of acute bipolar mania, both as immunotherapy and in combination with other mood stabilisers[3], as well as immunotherapy in acute bipolar depression[4]. Despite this, to our knowledge, there are very few published experiences with regard to long-term Quetiapine immunotherapy in schizoaffective disorder, bipolar type (SAD) and bipolar disorder (BPD)[5].

Quetiapine hemifumarate is prescribed to control the symptoms of schizophrenia, bipolar depression, and bipolar mania, and for bipolar maintenance. Quetiapine hemifumarate is distinguished from the other
antipsychotics in that it is used to treat both the positive (hallucinations and delusions) and negative symptoms (emotional withdrawal and apathy) of psychosis and is associated with fewer neurological and endocrine-related side effects.

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (i.e. the identity as well as the quantity of impurity in the pharmaceuticals), is now receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the European Pharmacopoeia (EP), British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations.

The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents. There is a good significant demand for the impurity-reference standards for both regulatory authorities and pharmaceutical companies. A number of recent articles have described a designed approach and guidance for isolating and identifying process-related impurities and degradation products using mass spectrometry, Nuclear Magnetic Resonance (NMR), High-performance liquid chromatography (HPLC), Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS), and tandem mass spectrometry for pharmaceutical substances.

The procedure of impurity profiling, begins with the detection of the impurities using the thin-layer chromatography, high-performance liquid chromatography or gas chromatography. Procurement of standard impurity samples from the synthetic organic chemists which include, last intermediate of the synthesis, products of predictable side reaction, degradation products if any, etc.

The possibilities of spectroscopic techniques in drug impurity profiling without chromatographic separation are also worth mentioning. Spectra obtained by using high-resolution, highly sensitive NMR spectrometers and mass spectrometers with APCI/ESI facilities are suitable to provide a fingerprint picture regarding the purity of the sample.

The important step in the impurity profiling is the synthesis of the material (impurity standard) with the proposed structure. The retention and spectral matching of the synthesized material with the impurity in question is useful for analytical method development and validation.

RESULTS OF DISCUSSION

Quetiapine hemifumarate (1) is an antipsychotic drug belonging to the chemical class of dibenzothiazepine derivatives. Its IUPAC name is 2-[(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy ethanol, (E)-2-butenedioate (2 : 1) salt.

A literature survey revealed various methods for the synthesis of Quetiapine (Warawa et al. 2001). We synthesized the Quetiapine hemifumarate (1) according to the process described by Warawa and Migler with modifications to make it simpler and commercially viable. Its molecular formula is \( \text{C}_{21} \text{H}_{25} \text{N}_3 \text{O}_2 \text{S}_2 \cdot \text{C}_4 \text{H}_4 \text{O}_4 \) and molecular weight is 883 as hemifumarate salt and 383 as base.

Quetiapine hemifumarate (1) was synthesized as shown in the Figure 1. Brief description and source of formation of impurities I–XI was discussed in results and discussions section. Impurities synthesis process and their spectral analysis was described in experimental section.

Impurity I

Impurity I is an intermediate (4) during the preparation of Quetiapine (1a). Its chemical name is dibenzo[b,f][1,4]thiazepin-11(10H)-one having the molecular formula \( \text{C}_{13} \text{H}_9 \text{NOS} \) and molecular weight 227.28.

Impurity I was synthesized according the process described in figure 1. 2-Aminodiphenyl sulphide condensation with phenyl chloroformate in toluene followed...
Reagents: (i) Ethanol, aqueous sodium hydroxide, reflux (ii) Phenyl chloroformate, Toluene, RT (iii) Polyphosphoric acid, 100°C (iv) POCl₃, N, N-Dimethyl aniline, reflux (v) Toluene, Piperazine, reflux (vi) 2-(2-Chloroethoxy)ethanol, Na₂CO₃, NaI, N-methyl pyrrolidone, Toluene (vii) Fumaric acid, ethanol

Figure 1: General scheme for the synthesis of quetiapine hemifumarate

Impurity II

Impurity II is an intermediate (6) during the synthesis of Quetiapine (1a) and is a condensed product of compound (4) and piperazine. Its chemical name is 11-(piperazin-1-yl)dibenzo [b,f][1,4]thiazepine. It has the molecular formula of C₁₇H₁₇N₃S and molecular weight of 295.4.

Compounds (4) can be converted into imino chloride (5) with phosphorus oxychloride and N,N-dimethyl aniline at reflux temperature. Suitable solvents for the reaction are high boiling inert solvents such as toluene, xylene and chlorobenzene. The temperature limits on the quenching and distillation ensure minimal hydrolysis of imino chloride (5) to compound (4). Imino chloride (5) is highly unstable to moisture and condenses with piperazine in toluene at reflux temperature affords Impurity II.

Impurity III

Impurity III is a dimer impurity of compound (6). Its chemical name is 11,11'-piperazine-1,4-diylbis-
(dibenzo[b,f][1,4]thiazepine. It has the molecular formula of $\text{C}_{30}\text{H}_{24}\text{N}_4\text{S}_2$ and molecular weight of 504.67.

Impurity III is a major byproduct during the synthesis of compound (6) (Impurity II). During the reaction, unreacted imino chloride (5) reacts with the product compound (6) simultaneously and results the impurity III. The formation of this impurity can be minimized with proper reaction conditions like piperazine moles, reaction temperature. Impurity III was synthesized by reacting imino chloride (5) with less moles of piperazine at elevated temperatures. Synthesis of Impurity III was described in figure 2.

Impurity IV

Impurity IV is an ethanol derivative of compound (6). Its chemical name is 2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol. Its molecular formula is $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_3$ and molecular weight is 339.45. The main source for the formation of impurity IV is 2-(2-chloroethoxy) ethanol (used for the formation of Quetiapine side chain). 2-Chloro ethanol is a major impurity during the synthesis of 2-(2-chloroethoxy) ethanol. Commercial 2-(2-chloroethoxy) ethanol contain traces of 2-chloroethanol. During the alkylation step in the preparation of Quetiapine, alkylation of piperazinyl thiazepine with the impurity, 2-chloro ethanol leads to the formation of impurity IV. Synthesis of impurity IV was described in Figure 3.

Impurity V

Impurity V is an acetyl derivative of Quetiapine (1a). Its chemical name is 2-[2-4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethyl acetate. It has molecular formula of $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3\text{S}$ and molecular of 425.54.

Impurity V was synthesis was described in figure 4. Quetiapine (1a) was dissolved in ethyl acetate, tri-
ethyl amine and fed with acetic anhydride slowly at room temperature. Reaction progress was monitored by TLC and Quetiapine (1a) was absent after four hours of maintenance. Evaporation of reaction mass resulted brown oil which was purified by column chromatography.

**Impurity VI**

Impurity VI is a condensed product of Quetiapine (1a) and its degraded impurity product. Its chemical name is 11,11’-[ethane-1,2-diylbis(oxyethane-2,1-diyl)piperazine-4,1-diyl][bis(dibenzo [b,f][1,4]thiazepine. Its molecular formula is $\text{C}_{40}\text{H}_{44}\text{N}_{6}\text{O}_{2}\text{S}_{2}$ and molecular weight is 704.95.

![Impurity VI](image)

Impurity VI was synthesized according to the Figure 5.

Quetiapine (1a) contains aliphatic ether chain, which may break at ether linkage at basic reaction conditions. This degraded impurity reacts with Quetiapine (1a) and results impurity VI. Compound (6) on reaction with 1,2-dichloromethane produces 2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]chloroethane (7), which on condensation with Quetiapine (1a) in the presence of diisopropyl ethyl amine afford Impurity VI.

**Impurity VII**

Impurity VII is N-Oxide impurity of Quetiapine (1a). Its chemical name is 2-[2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)-1-oxidopiperazin-1-yl]ethoxy]ethanol. Its molecular weight is $\text{C}_{21}\text{H}_{25}\text{N}_{3}\text{O}_{3}\text{S}$ and molecular weight is 399.51.

Quetiapine hemifumarate (1) contains two tertiary nitrogen atoms. When exposed to air for long time, it oxidizes slowly and forms N-oxide of Quetiapine. The
When Quetiapine hemifumarate (1) exposed to air for long time, it oxidizes slowly and forms S-oxide impurity of Quetiapine. The synthetic process was described in Figure 7. Impurity VIII was synthesized by the oxidation of Quetiapine with 20% hydrogen peroxide at room temperature in the presence of manganese dioxide. Impurity VIII was observed during long term stability studies of Quetiapine.

Impurity IX

The chemical name of Impurity IX is \([2-\{(2\text{-amino phenyl)thio}\}\text{phenyl}]\{4-\{(2\text{-hydroxyethoxy) ethyl)piperazin-1-yl}\}\text{methanone}\). Its molecular formula is \(C_{21}H_{27}N_3O_3\) and molecular weight is 401.52.

The synthetic process was described in Figure 8. Impurity IX was prepared by using 2-Iodobenzoic acid as a starting material. 2-Iodobenzoic acid reacts with thionyl chloride and gives 2-Iodobenzoylchloride \((8)\), which on reaction with 2-\{(2-(piperazin-1-yl)ethoxy)ethanol resulted \(4-\{(2-(2\text{-hydroxyethoxy)ethyl)piperazin-1-yl}\}\{(2-iodophenyl)methanone\ (9)\). Compound \((9)\) condenses with 2-Aminothiophenol in the presence of potassium carbonate yields impurity IX.
Impurity X

Impurity X is a acetyl derivative of impurity IX. Its chemical name is N-(2-[[2-(4-[2-(2-hydroxyethoxy)-]ethoxyethoxy)ethyl]piperazin-1-yl]carbonyl)phenyl]thio]phenyl]acetamide. It has the molecular formula of C_{23}H_{29}N_{3}O_{4}S and molecular weight of 443.56.

Impurity X was prepared according to the process described in figure 9. Impurity IX was synthesized from Impurity IX. Alcohol group of impurity IX was protected with 3,4-dihydro-2H-pyan, which on acetylation with acetic anhydride followed by hydrolysis of pyran ring in the presence of Dowex 50-X4 resin (H+ form) results Impurity X.

Impurity XI

Impurity XI is a chloro derivative of Quetiapine (1a). Its chemical name is 2-[4-(9-chlorodibenzo[b,f][1,4]-thiazepin-11-yl)piperazin-1-yl]ethoxy]ethanol. Its mo-
EXPERIMENTAL SECTION

General procedures

FT-IR spectra are recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One). $^1$H NMR spectra are recorded on Varian 400 MHz spectrometer using DMSO-d$_6$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra are recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts are dried over sodium sulfate after work up. Unless otherwise mentioned all the solvents and reagents used are of commercial grade.

Synthesis of 2-(phenylthio)benzenamine (2)

2-Chlorobenzenamine (25 g, 0.2 moles), ethanol (100 mL) and thiophenol (22 g, 0.2 moles) were charged into a RBF and started stirring at 26°C. Aque-
ous NaOH (0.22 moles in 50 mL of water) was added slowly over a period of 10 minutes at the same temperature. Reaction mixture was refluxed for 3 hours and reaction progress was monitored by TLC (mobile phase: ethyl acetate: n-hexane – 5:3). Reaction mass was distilled off under reduced pressure and dissolved the residue in toluene. Washed the toluene layer with water and dried over sodium sulfate followed by vacuum distillation afforded the compound (2) as a colorless residue.

M.F. C$_{12}$H$_{11}$NS; M. Wt. 201.06; IR (KBr) vcm$^{-1}$: 1602 and 1452 (C-C in Ar), 3038 (C-H in Ar), 3480 (N-H); $^1$H-NMR (400 MHz, DMSO-d6) δ ppm: 4.0 (s, 2H, -NH$_2$), 6.2-6.4 (m, 2H, Ar-H), 6.7-7.2 (m, 7H, Ar-H); MS m/z (%) = 202.15 (M+1); Anal. Caled for C$_{12}$H$_{11}$NS: C - 71.60; H - 5.51; N - 6.96%; Found: C - 71.62; H - 5.50; N - 6.98%.

Synthesis of phenyl 2-(phenylthio)phenylcarbamate (3)

Added a mixture of phenyl chloroformate (23.5 g, molar formula is C$_{21}$H$_{24}$ClN$_3$O$_2$S and molecular weight is 417.95.

The main source of impurity XI is the key starting material 2-chloroaniline used for the synthesis of Quetiapine. The presence of 2,5-dichloroaniline traces in 2-chloroaniline culprits the formation of impurity XI. Synthetic process of Impurity XI was described in Figure 10.
0.15 moles) and toluene (100 mL) to an agitating solution of 2-amino diphenyl sulphide (2) (20 g, 0.10 moles) in toluene at 0-5°C over a period of 45-60 minutes. Raised the mass temperature to 25-30°C slowly and continued for 60-90 minutes. Reaction progress was monitored by TLC (mobile phase: ethyl acetate: n-hexane - 1:1). Water was charged and agitated for another 15 minutes at ambient temperature. Separated the organic and aqueous layers and washed the toluene layer with 5% HCl solution. Toluene layer dried over sodium sulfate and distilled off completely under vacuum at below 60°C. n-Heptane (125.0 mL) was added to the residue and agitated for 30 minutes at 25-30°C. Filtered the separated solid and washed with n-heptane. Compound (3) was dried under vacuum at 60-65°C.

\[ C_{19}H_{15}NO_2S; M. Wt. 321.08; IR (KBr) \text{ cm}^{-1}: 1601 \text{ and } 1451 (C-C in Ar), 3033 (C-H in Ar), 3472 (N-H), 1684 (C=O), 1192 (C-O); ]

\[ ^1H-NMR (400MHz, DMSO-d_6) \delta ppm: 6.8 (d, 1H, Ar-H), 7.0 (m, 7H, Ar-H), 7.25 (m, 5H, Ar-H), 7.5 (d, 1H, Ar-H); MS m/z (%) = 322.06 (M+1); \]

\[ \text{Anal. Calcd for } C_{19}H_{15}NO_2S: C - 71.00, H - 4.70, N - 4.36%; \text{ Found: } C - 71.02, H - 4.72, N - 4.35%. \]

### Synthesis of dibenzo[b,f][1,4]thiazepin-11(10H)-one (Impurity I, 4)

Charged phenyl 2-(phenylthio) phenylcarbamate (3) (23g, 0.072 mol) and polyphosphoric acid (115 mL, 5 volumes) into RBF and started the agitation. Maintained the mass at 95-105°C for 6 hours. Reaction progress was monitored by TLC (mobile phase: toluene: methanol - 1:1). Reaction mass was allowed to 80-85°C and feeded with water slowly drop wise. Mass further cooled to 30°C at which solid was precipitated. Filtered the solid and washed with water. Wet material was charged into acetone and stirred for 30 minutes at 28°C. Filtered the solid and washed with acetone. Obtained Impurity I was dried under vacuum at below 60°C to constant weight.

\[ M.F. C_{13}H_9NO_2S; M. Wt. 295.11; IR (KBr) \text{ cm}^{-1}: 3032 (C-H in Ar), 1605 and 1508 (C-C in Ar), 3335 (N-H), 1325 (C-N), 1215 (C=S); ]

\[ ^1H-NMR (400MHz, DMSO-d_6) \delta ppm: 2.0 (bs, 1H, -NH), 2.7 (s, 8H, -CH_2-), 7.0-7.2 (m, 7H, Ar-H), 7.5 (m, 1H, Ar-H); MS m/z (%) = 296.12 (M+1); \]

\[ \text{Anal. Calcd for } C_{13}H_9NO_2S: C - 69.12, H - 5.80, N - 14.22%; \text{ Found: } C - 69.10, H - 5.81, N - 14.23%. \]

### Synthesis of 11,11'-piperazine-1,4-diylbis(dibenzo[b,f][1,4]thiazepine (Impurity III)

Dibenzo[b,f][1,4]thiazepin-11(10H)-one (4) (22g, 0.10 moles), phosphorus oxychloride (122.5 g, 8.0 moles) and N,N-dimethyl aniline (1.2 g, 0.01 moles) were charged and heated to reﬂux. Reaction progress was monitored by TLC (mobile phase: ethyl acetate: n-hexane - 4:1) and was completed after 8 hours maintenance under reﬂux. Mass cooled to 50°C and distilled of unreacted POCl_3 completely under vacuum. Crude was dissolved in toluene and further cooled to 0°C. Chilled water was added at below 5°C slowly. Organic and aqueous layers were separated washed the organic layer with chilled water. Organic layer was dried over sodium sulfate. Slowly added methanolic HCl to the toluene layer at 25-3°C and adjusted pH between 4 to 5. Agitated the mass and ﬁltered the separated material. Impurity II was obtained light brown solid, which was dried under vacuum at below 55°C.
0°C and added chilled water at below 5°C slowly. Organic layer and aqueous layers were separated washed the organic layer with chilled water. Organic layer was dried over sodium sulfate. This toluene layer was added to a stirring solution of piperazine (4.3 g, 0.05 moles) in toluene slowly at 60°C. Maintained the mass under reflux for 10-12 hours and monitored the reaction progress by TLC. Reaction mass cooled to 25°C and filtered the un-dissolved solids, which contains exclusively Impurity III. Filtered solid was purified by refluxing in toluene for 20 minutes. Reaction mass cooled to 25°C and maintained for 30 minutes. Solid was filtered, washed with toluene and dried at below 60°C gives Impurity III.

M.F. C_{30}H_{24}N_{4}S_{2}; M. Wt. 504.14; IR (KBr) vcm⁻¹: 3026 (C-H in Ar), 1325 (C-N), 1228 (C=S); 1H-NMR (400 MHz, DMSO-d6) δppm: 2.8 (s, 8H, -CH₂-), 7.0-7.2 (m, 14H, Ar-H), 7.4 (m, 2H, Ar-H); MS m/z (%): 504.10 (M+1); Anal. Calcd for C_{30}H_{24}N_{4}S_{2}: C - 71.40, H - 4.79, N - 11.10%; Found: C - 71.41, H - 4.80, N - 11.08%.

**Synthesis of 4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)ethanol (Impurity IV)**

Charged 11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepine (Impurity II) (14 g, 0.047 moles), 2-Chloro ethanol (4.1 g, 0.051 moles), sodium iodide (0.70 g, 0.004 moles) and toluene into RBF and started stirring at 25°C. Reaction mass heated to reflux and maintained under reflux till TLC complies. Reaction completed after 11 hours of reaction maintenance. Reaction progress was monitored by TLC (mobile phase: toluene: methanol - 9:1). Reaction mass cooled to 30°C and added water. Separated the toluene layer and washed with water. Toluene was distilled off completely under vacuum to afford the light brown color residue containing about 60% of the compound (7). This residue was purified by column chromatography by eluting with 5% ethyl acetate in n-hexane.

M.F. C_{23}H_{21}N_{3}O_{3}S; M. Wt. 425.18; IR (KBr) vcm⁻¹: 3029 (C-H in Ar), 1508 and 1452 (C-C in Ar), 2982 (C-H), 1320 (C-N), 1089 (C-O), 1732 (C=O); 1H-NMR (400 MHz, DMSO-d6) δppm: 2.0 (3H, -CH₃), 2.4 (t, 4H, -CH₂-), 2.55 (t, 2H, -CH₂-), 2.7 (t, 4H, -CH₂-), 3.7 (t, 2H, -CH₂-), 7.0-7.1 (m, 5H, Ar-H), 7.25 (m, 2H, Ar-H), 7.45 (d, 1H, Ar-H); MS m/z (%): 426.01 (M+1); Anal. Calcd for C_{23}H_{21}N_{3}O_{3}S: C - 64.92, H - 6.40, N - 9.87%; Found: C - 64.91, H - 6.40, N - 9.88%.

**Synthesis of 2-[2-4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethyl acetate (Impurity V)**

Charged 11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepine (Impurity II) (6.5 g, 0.022 moles), 1,2-dichloroethane (2.2 g, 0.022 moles) and triethyl amine (0.40 g, 0.004 moles) into RBF and started stirring at 25°C. Reaction mass heated to reflux and maintained the progress by TLC (mobile phase: toluene: methanol - 8:2). Reaction was completed after 4 hours of reflux. Mass cooled to 40°C and added water slowly under stirring. Separated the toluene layer and washed with water. Toluene was distilled off completely under vacuum to afford the light brown color residue containing about 60% of the compound (7). This residue was purified by column chromatography by eluting with 6% ethyl acetate in n-hexane.
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M.F. C_{19}H_{20}ClN_{3}S; M. Wt. 357.11; IR (KBr) vcm⁻¹: 3026 (C-H in Ar), 1602 and 1514 (C-C in Ar), 2923 (C-H), 1312 (C-S), 1212 (C-Cl); ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 2.4 (t, 4H, -CH₂-), 2.6 (m, 6H, -CH₂-), 3.5 (t, 2H, -CH₂-), 7.0-7.1 (m, 5H, Ar-H), 7.25 (m, 2H, Ar-H), 7.5 (d, 1H, Ar=H); MS m/z (%): 358.20 (M+1); Anal. Calcd for C_{19}H_{20}ClN_{3}S: C - 63.76, H - 5.63, N - 11.74%; Found: C - 63.77, H - 5.64, N - 11.75%.

Synthesis of 11,11’-[ethane-1,2-diylbis(oxyethane-2,1-diylpiperazine-4,1-diyl)]bis(dibenzo [b,f] [1,4]thiazepine (Impurity VI)

Charged Quetiapine (1a, 4 g, 0.01 moles) and diisopropyl ethyl amine (3.8 g, 0.03 moles) into toluene at 30°C and started agitation. Reaction mass heated to 60-65°C and added 2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethyl chloride (7, 3.6 g, 0.01 moles) in toluene at 30°C under agitation. The reaction mass cooled to 30°C and added water. Separated the layers and washed the toluene layer with saturated sodium bicarbonate solution followed by water. The organic layer was dried over sodium sulfate and distilled off under vacuum. The resulting residue was subjected to column chromatography by eluting with 4% ethyl acetate in n-hexane. M.F. C_{40}H_{44}N_{6}O_{2}S; M. Wt. 704.3; IR (KBr) ν cm⁻¹: 3032 (C-H in Ar), 1608 and 1518 (C-C in Ar), 2998 (C-H), 1320 (C-N), 1220 (C=S), 1086 (C-O); ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 2.44 (m, 8H, -CH₂-), 2.5 (t, 4H, -CH₂-), 2.65 (m, 8H, -CH₂-), 3.4 (t, 2H, -CH₂-), 3.6 (t, 4H, -CH₂-), 7.0-7.1 (m, 10H, Ar-H), 7.25 (m, 4H, Ar-H), 7.5 (d, 2H, Ar-H); MS m/z (%): 705.32 (M+1); Anal. Calcd for C_{40}H_{44}N_{6}O_{2}S: C - 68.15, H - 3.29, N - 11.92%; Found: C - 68.14, H - 3.30, N - 11.95%.

Synthesis of 2-[2-[4-(5-Oxo-5H-1-benzo[b,f][1,4]thiazepin-11-yl)-1-oxidopiperazin-1-yl]ethoxy] ethanol (Impurity VII)

Quetiapine (22 g, 0.057 moles), methanol (100 mL) and manganese dioxide (1 g, 0.011 moles) were charged into a RBF and started agitation. The reaction mass was stirred at the same temperature for 30 hours. The progress of the reaction was monitored by TCL (mobile phase: chloroform: methanol – 9:1). The resulting mass was concentrated under reduced pressure at less than 50°C and the obtained residue was partitioned between chloroform and water. The organic layer was washed with water, dried over sodium sulfate and distilled off under vacuum. The resulting residue was subjected to prep-HPLC to get the impurity VII. M.F. C_{21}H_{25}N_{3}O_{3}S; M. Wt. 399.16; IR (KBr) vcm⁻¹: 3042 (C-H in Ar), 1620 and 1506 (C-C in Ar), 2982 (C-H), 1318 (C-N), 1256 (C=S), 3652 (O-H); ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 2.0 (s, 1H, -OH), 2.35 (t, 4H, -CH₂-), 2.5 (t, 2H, -CH₂-), 2.65 (m, 4H, -CH₂-), 3.4 (t, 2H, -CH₂-), 3.6-3.7 (m, 4H, -CH₂-); MS m/z (%): 400.12 (M+1); Anal. Calcd for C_{21}H_{25}N_{3}O_{3}S: C - 63.13, H - 6.31, N - 10.52%; Found: C - 63.12, H - 6.32, N - 10.53%.


Quetiapine (22 g, 0.057 moles), methanol (100 mL) and manganese dioxide (1 g, 0.011 moles) were charged into a RBF and started stirring. After 5 minutes, added 5% hydrogen peroxide solution (150 mL, 6.8 volumes) slowly drop wise and maintained the reaction under agitation for 24 hours. The progress of the reaction was monitored by TCL (mobile phase: chloroform: methanol – 9:1). The reaction mass was concentrated under reduced pressure at less than 50°C and the obtained residue was partitioned between chloroform and water. The organic layer was washed with water, dried over sodium sulfate and distilled off under vacuum. The resulting residue was subjected to prep-HPLC to get the impurity VIII. M.F. C_{21}H_{25}N_{3}O_{3}S; M. Wt. 399.16; IR (KBr) vcm⁻¹: 3032 (C-H in Ar), 1622 and 1504 (C-C in Ar), 2945 (C-H), 1314 (C-N), 1252 (C=S), 3643 (O-H); ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 2.05 (s, 1H, -OH), 2.35 (t, 4H, -CH₂-), 2.5 (t, 2H, -CH₂-), 2.65 (m, 4H, -CH₂-), 3.45 (t, 2H, -CH₂-), 3.6-3.7 (m, 4H, -CH₂-); MS m/z (%): 400.12 (M+1); Anal. Calcd for C_{21}H_{25}N_{3}O_{3}S: C - 63.13, H - 6.31, N - 10.53%.
10.52%; Found: C - 63.10, H - 6.34, N - 10.51%.

**Synthesis of 2-iodobenzoyl chloride (8)**

2-Iodobenzoic acid (33 g, 0.13 moles), toluene (200 mL) and thionyl chloride (30.9 g, 0.26 moles) were charged into a RBF and started stirring at 26°C. Reaction mass was heated to reflux and maintained for 10 hours. Progress of the reaction was monitored by TLC (mobile phase: ethyl acetate: n-hexane – 1:1). Added toluene and excess of thionyl chloride was distilled off under reduced pressure. The process was repeated with toluene to get the compound (8) as a residue.

M.F. C₇H₄ClIO; M. Wt. 265.9; IR (KBr) vcm⁻¹: 1623.26 and 1452.95 (C-H), 561.25 (C-I), 1786.21 (C=O).

**Synthesis of {4-[2-(2-hydroxy-ethoxy)ethyl piperazin-1-yl}-(2-iodophenyl)-methanone (9)**

1-[2-(hydroxyethoxy)-ethyl] piperazine (20 g, 0.114 moles), THF (100 mL), water (50 mL) and triethyl amine (2.3 g, 0.023 moles) were charged into a RBF and added slowly to the reaction mixture. The temperature was kept below 20°C during the addition. The reaction mass was allowed to warm to room temperature and stirred 2 hours at ambient temperature. 50.0 mL of water was added and THF was removed by distillation. The pH of the solution was adjusted to 9-10 with saturated sodium bicarbonate solution. The water was extracted with dichloromethane and distillation of organic layer yielded the compound (9) as yellowish oil.

M.F. C₁₅H₂₁N₂O₃; M. Wt. 404.06; IR (KBr) vcm⁻¹: 3029 (C-H in Ar), 1608 and 1503 (C-C in Ar), 2952 (C-H), 1314 (C-N), 3644 (O-H), 1648 (C=O), 3385 (N-H); ¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 2.0 (s, 1H, -OH), 2.5 (2H, -CH₂), 2.66 (m, 4H, -CH₂), 3.30 (m, 4H, -CH₂), 3.45-3.55 (m, 4H, -CH₂), 3.70 (t, 2H, -CH₂), 4.0 (s, 2H, -NH₂), 6.2-6.4 (m, 2H, Ar-H), 6.7 (m, 1H, Ar-H), 7.0-7.2 (m, 2H, Ar-H), 7.3 (m, 2H, Ar-H), 7.8 (d, 1H, Ar-H); MS m/z (%) = 405.20 (M+1); Anal. Calcd for C₁₅H₂₁N₂O₃: C - 44.57, H - 5.24, N - 6.93%; Found: C - 44.57, H - 5.26, N - 6.91%.

**Synthesis of (4-(2-(2-(tetrahydro-2H-pyran-3-yl)oxy)ethoxy)ethyl)piperazin-1-yl)(2-(2-aminophenylthio)phenyl)methanone (10)**

Dihydropyran (2.5 g, 1.2 moles) and p-toluene sulfonic acid monohydrate (2.1 g, 0.012 moles) were charged into a RBF and started stirring at 25°C. Heated the reaction mass to 60°C and [2-[2-(aminophenyl)thio]phenyl][4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl] methanone (impurity IX) (10 g, 0.025 moles) was added slowly drop wise over a period of 30 minutes. Reaction mas was maintained at 60-65°C for another 30 minutes. Reaction progress was monitored by TLC (mobile phase: toluene: methanol – 8:2). Reaction was allowed to ambient temperature and added NaHCO₃.
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(2.0 g) and maintained for another 15 minutes. Filtered the mass distilled off the mass under vacuum afforded compound (10) as light red oil.

M.F. \( \text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_4\); M. Wt. 485.23; IR (KBr) vcm\(^{-1}\): 3031 (C-H in Ar), 1602 and 1581 (C-C in Ar), 2944 (C-H), 1652 (C=O), 3380 (N-H), 1082 (C-O);

\(^1\)H-NMR (400 MHz, DMSO-d6) \( \delta \) ppm: 1.6-1.9 (m, 4H, -CH\(_2\)-), 2.5 (t, 2H, -CH\(_2\)-), 2.66 (m, 4H, -CH\(_2\)-), 2.95 (m, 1H, -CH-), 3.3 (m, 4H, -CH\(_2\)-), 3.4 (m, 2H, -CH\(_2\)-), 3.5-3.8 (m, 8H, -CH\(_2\)-), 4.0 (s, 2H, -NH\(_2\)), 6.2-6.4 (m, 2H, Ar-H), 6.7 (m, 1H, Ar-H), 7.0-7.2 (m, 2H, Ar-H), 7.3 (m, 2H, Ar-H), 7.8 (d, 1H, Ar-H); MS m/z (%) = 486.15 (M+1); Anal. Calcd for \( \text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_4\): C - 64.30, H - 7.26, N - 8.65%; Found: C - 64.31, H - 7.25, N - 8.66%.

Synthesis of (4-(2-(2-(tetrahydro-2H-pyran-3-yloxy)ethoxy)ethyl)piperazin-1-yl)(2-(2-(acetylamino)-phenylthio)phenyl)methanone (11)

Charged (4-(2-(2-(tetrahydro-2H-pyran-3-yloxy)ethoxy)ethyl)piperazin-1-yl)(2-(2-amino phenylthio)phenyl)methanone (10) ... re-action progress by TLC. Reaction was completed after 6 hours of maintenance under reflux. Mass temperature was to 60\(^{\circ}\)C and distilled off solvent completely under reduced pressure to get dark brown residue. Residue was dissolved in toluene and washed with saturated sodium bicarbonate solution. Distillation of toluene under reduced pressure afforded compound (11) as a brown oil.

M.F. \( \text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_5\); M. Wt. 527.25; IR (KBr) vcm\(^{-1}\): 3026 (C-H in Ar), 1598 and 1579 (C-C in Ar), 2965 (C-H), 1686 (C=O), 3372 (N-H), 1086 (C-O),

\(^1\)H-NMR (400 MHz, DMSO-d6) \( \delta \) ppm: 1.6-1.9 (m, 4H, -CH\(_2\)-), 2.1 (s, 3H, -CH\(_3\)), 2.5 (t, 2H, -CH\(_2\)-), 2.66 (m, 4H, -CH\(_2\)-), 2.95 (m, 1H, -CH-), 3.3 (m, 4H, -CH\(_2\)-), 3.4 (m, 2H, -CH\(_2\)-), 3.5-3.8 (m, 8H, -CH\(_2\)-), 4.0 (s, 1H, -NH), 6.8-7.0 (m, 2H, Ar-H), 7.2 (m, 2H, Ar-H), 7.3-7.4 (m, 2H, Ar-H), 7.45 (m, 1H, Ar-H), 7.8 (d, 1H, Ar-H); MS m/z (%) = 528.15 (M+1); Anal. Calcd for \( \text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_5\): C - 63.73, H - 7.07, N - 7.96%; Found: C - 63.72, H - 7.08, N - 7.97%.


Dissolved (4-(2-(2-(tetrahydro-2H-pyran-3-yloxy)ethoxy)ethyl)piperazin-1-yl)(2-(2-acetamino) -phenylthio) phenyl)methanone (11) (5.6 g, 0.01 moles) in anhydrous methanol and started agitation at ambient temperature. 25 mL of Dowex 50-X4 cation resin (H\(^{+}\) form, prewashed with anhydrous methanol) was added and the mixture stirred for 90 minutes at 25\(^{\circ}\)C. The ion exchange resin was removed by filtration through a sintered-glass filter and then washed with anhydrous methanol. Distilled off methanol under reduced pressure afforded a oily brown residue. Pure impurity X was obtained by prep HPLC technique.

M.F. \( \text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\); M. Wt. 443.19; IR (KBr) vcm\(^{-1}\): 3028 (C-H in Ar), 1608 and 1582 (C-C in Ar), 2989 (C-H), 1702 (C=O),

\(^1\)H-NMR (400 MHz, DMSO-d6) \( \delta \) ppm: 2.0 (s, 1H, -OH), 2.1 (s, 3H, -CH\(_3\)), 2.5 (t, 2H, -CH\(_2\)-), 2.66 (m, 4H, -CH\(_2\)-), 3.3 (m, 4H, -CH\(_2\)-), 3.4 (m, 2H, -CH\(_2\)-), 3.5-3.8 (m, 8H, -CH\(_2\)-), 8.0 (s, 1H, -NH), 6.8-7.0 (m, 2H, Ar-H), 7.2 (m, 2H, Ar-H), 7.3-7.4 (m, 2H, Ar-H), 7.45 (m, 1H, Ar-H), 7.8 (d, 1H, Ar-H); MS m/z (%) = 444.20 (M+1); Anal. Calcd for \( \text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\): C - 62.28, H - 6.59, N - 9.47%; Found: C - 62.29, H - 6.60, N - 9.45%.

Synthesis of 2-chloro-6-(phenylthio)benzenamine (12)

2,6-dichlorobenzenamine (32 g, 0.2 moles), ethanol (150 mL) and thiophenol (22 g, 0.02 moles) were charged into a RBF and started stirring at 26\(^{\circ}\)C. Aqueous NaOH (0.5 mol in 100 mL of water) was added slowly over a period of 10 minutes at the same temperature. Reaction mixture was refluxed for 3 hours and reaction progress was monitored by TLC (mobile phase: ethyl acetate: n-hexane = 5:3). Reaction mass was distilled off under reduced pressure and dissolved the residue in toluene. Washed the toluene layer with water and dried over sodium sulfate followed by vacuum distillation afforded the compound (12) as a colorless residue.

M.F. \( \text{C}_{12}\text{H}_{10}\text{ClN}\text{S}\); M. Wt. 235.02; IR (KBr) vcm\(^{-1}\): 3042 (C-H in Ar), 1604 and 1582 (C-C in Ar),

\(^1\)H-NMR (400 MHz, DMSO-d6) \( \delta \) ppm: 4.0 (s, 2H, -NH\(_2\)), 6.3 (m, 1H, Ar-
H), 6.8 (m, 2H, Ar-H), 7.0 (m, 3H, Ar-H), 7.2 (m, 2H, Ar-H); MS m/z (%) = 236.12 (M+1); Anal. Calcd for C_{12}H_{10}ClN: C - 61.14, H - 4.28, N - 5.94%; Found: C - 61.12, H - 4.30, N - 5.94%.

**Synthesis of phenyl 2-chloro-6-(phenylthio)phenyl-carbamate (13)**

2-chloro-6-(phenylthio)benzenamine (12) (26 g, 0.11 moles) was dissolved in toluene (100 mL) and started agitation at 28°C. A solution of phenyl chloroformate (20.6 g, 0.132 moles) in toluene (100 mL) was dropped into the reaction mass at 5-10°C over a period of 3 hours. Reaction mass maintained understirring at 5-10°C for 30 minutes. 10 g of NaHCO₃ in 300 mL of water was added slowly to the mass. Allowed the mass to 25-30°C and stirred for 60 minutes at the same temperature. Separated both the layers and washed the organic layer with 10% HCl solution followed by water. Distillation of toluene completely under vacuum afforded compound (13) as a light brown oil. M.F. C_{19}H_{14}ClNO_2S; M. Wt. 355.04; IR (KBr) cm⁻¹: 3036 (C-H in Ar), 1606 and 1580 (C-C in Ar), 3392 (N-H), 764 (C-Cl); 1H-NMR (400 MHz, DMSO-d₆) δ ppm: 6.7 (m, 1H, Ar-H), 7.0-7.1 (m, 8H, Ar-H), 7.2 (m, 3H, Ar-H), 8.0 (s, 2H, -NH_2); MS m/z (%) = 356.08 (M+1); Anal. Calcd for C_{19}H_{14}ClNO_2S: C - 64.13, H - 3.97, N - 3.94%; Found: C - 64.12, H - 3.98, N - 3.96%.

**Synthesis of 4-(2-(2-hydroxyethoxy)ethyl)-N-(2-chloro-6-(phenylthio)phenyl)piperazine-1-carboxamide (14)**

Charged phenyl 2-chloro-6-(phenylthio)phenylcarbamate (13) (22 g, 0.062 moles), toluene (120 mL) and 2-(2-(piperazin-1-yl)ethoxy)ethanol (12 g, 0.07 moles) were charged into a RBF and started agitation. The mixture was refluxed for 12 hours and reaction progress was monitored by TLC. Reaction mass was cooled to 50°C and distilled off the mass completely under reduced pressure. Dissolved the residue in dichloromethane and stirred at ambient temperature for 30 minutes. The precipitate formed was filtered and the filtrate was washed with 10% NaOH solution followed by water. Dichloromethane dried over sodium sulfate and evaporation under reduced pressure afforded impurity XI as a light brown colored residue. Residue was purified by column chromatography by eluting with 3% ethyl acetate in n-hexane to afforded pure impurity XI. M.F. C_{21}H_{24}ClN_3O_2S; M. Wt. 417.13; IR (KBr) cm⁻¹: 3041 (C-H in Ar), 1611 (C-C in Ar), 765 (C-Cl), 2998 (C-H), 1089 (C-O), 3568 (O-H); 1H-NMR (400 MHz, DMSO-d₆) δ ppm: 2.0 (s, 1H, -OH), 2.4 (t, 4H, -CH₂), 2.5 (t, 2H, -CH₂), 2.65 (m, 4H, -CH₂), 3.4 (t, 2H, -CH₂), 3.6-3.7 (m, 4H, -CH₂), 7.0-7.1 (m, 4H, Ar-H), 7.25 (m, 2H, Ar-H), 7.5 (d, 1H, Ar-H); MS m/z (%) = 418.25 (M+1); Anal. Calcd for C_{21}H_{24}ClN_3O_2S: C - 60.35, H - 5.79, N - 10.05; Found: C - 60.33, H - 5.78, N - 10.04%.

**REFERENCES**