2.1: Introduction

Quetiapine (23) is dibenzodiazepine derivative and was developed by Astra Zeneca.\textsuperscript{41} It is an atypical antipsychotic agent, indicated for the treatment of schizophrenia, psychiatric conditions such as hallucinations, delusions, hostility and other bipolar disorder.\textsuperscript{42-44} Quetiapine was approved by USFDA in September, 1997 as multi dosage tablets. It is available in the market as hemi fumarate salt. It is a white to off-white crystalline powder, soluble in water, and having melting point of 172–174°C. The Quetiapine hemi fumarate salt is administered orally in a dosage form of 25mg to 400mg. It is chemically described as $2\cdot[2\cdot(4\cdot\text{dibenzo}[b,f][1,4]\text{thiazepin-11-yl-1-piperazinyl}]\text{ethoxy}]\text{ethanol fumarate (2:1) (salt)}$. 

Atypical antipsychotics are specifically prescribed for the treatment of schizophrenia and related disorders. Quetiapine hemi fumarate has been proved to improve positive and potentially negative
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symptoms of schizophrenia without producing extra pyramidal side effects. The effect of Quetiapine hemi fumarate on positive and negative symptoms has been shown to be equivalent to Haloperidol.

The role of antipsychotic drugs is of prominence in day to day life and especially the usefulness of Quetiapine as an effective drug product for the treatment of schizophrenia. Based on its importance, we have taken up the systematic study of Quetiapine to provide a new, simple and commercially viable synthetic route. The industrial importance and large scale requirement of Quetiapine made us to review the literature thoroughly for the development of cheapest possible synthetic route.

2.2: Reported synthetic schemes of Quetiapine

Edward et al., reported the synthetic procedure to prepare Quetiapine which involves the reaction of lactam 24 with phosphorous oxychloride to afford the imino chloride 25. This reaction was also performed with thionyl chloride or phosphorous pentachloride in the presence of $N$, $N'$-dimethyl aniline. The imino chloride derivative was then reacted with excess amount of 1-hydroxyethoxyethyl piperazine (26) in xylene at reflux temperature for excess time delivered the crude desired compound. The resultant crude
compound was subjected to column chromatography to yield Quetiapine (scheme 2.1)\textsuperscript{46}. The lactam 24 was prepared by the reaction of 2-aminothiophenol (27) with chlorobenzene (28) in the presence of sodium hydroxide to give 2-phenylsulfanylphenylamine (29). The resulting intermediate on reaction with phenylchloroformate gave the corresponding amide derivative 30, which was cyclized in the presence of phosphoric acid to yield the desired cyclized lactam derivative 24.

**Scheme 2.1**

\[
\text{\begin{tikzpicture}
  \node (a) at (0,0) {2-phenylsulfanylphenylamine (29)};
  \node (b) at (2,0) {2-phenylsulfanylphenylamine (29)};
  \draw (a) -- (b);
\end{tikzpicture}}
\]

Diller \textit{et al.}, described (scheme 2.2) an improved process for the preparation of Quetiapine by reacting 11-piperazinyl dibenzo[b,f]-[1,4]thiazepine (31) with 2-(2-chloroethoxy)ethanol and sodium carbonate as base, catalytic amount of sodium iodide, TBAB as phase transfer catalyst in polar solvent\textsuperscript{47}. 
Puig Torres and co-workers utilized 2-(4-dibenzo[b,f][1,4]thiazepine-11-yl-piperazine-1-yl) ethanol (32) and protected halo alcohols as key fragments for the preparation of Quetiapine\textsuperscript{48}. The protective groups used for the protection of alcohols should be resistant to alkaline conditions as the coupling involves usage of base. As evident from their synthetic scheme, the piperazine ethanol compound 32 was condensed with protected halo alcohols at an elevated temperatures in the presence of sodium hydroxide and tetra butyl ammonium hydrogen sulphate as phase transfer catalyst to yield the protected Quetiapine as an intermediates 33 (a-c). The protected derivatives were transformed into targeted compound by deprotection with hydrobromic acid in acetic acid media to yield the required product 23 (scheme 2.3). The use of protected hydroxyl group prevents the formation of undesired disubstituted product. The processes for the preparation of protected halo alcohols were described in the literature\textsuperscript{49}.
Grumann et al., described (scheme 2.4) the reaction of (2-chloroethoxymethyl)-benzene (34) with triethanol amine (35) using strong base such as sodium hydride in the presence of potassium iodide as catalyst to yield 2-[[2-benzylxy-ethoxy]-ethyl] bis-(2-hydroxyethyl) amino] ethanol (36)

50. The intermediate 36 was chlorinated with thionyl chloride in dimethyl formamide and toluene solvent mixture to afford [2-(2-benzylxy-ethoxy)-ethyl] bis-(2-chloroethyl) amine (37). The compound 37 was condensed with dibenzo [b, f] [1, 4] thiazepin-11-yl-amine (38) in the presence of sodium hydride and dimethyl formamide to give 11-\{4- [2- (2-benzylxy-ethoxy) ethyl]- piperazin-1-yl\}-dibenzo [b, f] [1, 4]thiazepine 33 (b). Finally, the benzyl group deprotection of 33 (b)

by using boron trichloride in a mixture of xylene and toluene yielded Quetiapine.
Hilden and co-workers reported a different process, which involves the use of 2-phenylsulfanylphenylamine (39), 4-[2-(hydroxyethoxy)-ethyl]piperazine -1-carboxylic acid (40) and a coupling agent such as phosgene to result the condensed product 41. Protection of the hydroxyl group of piperazine alcohol with a suitable protecting group such as benzoyl coupling afforded the protected intermediate 42^51. The resulted unyclized derivative was subjected to ring closure in presence of excess phosphorous oxychloride and phosphorous pentoxide, followed by deprotection of protecting group to afford the targeted compound 23 (scheme 2.5).
Daniel Boszing et al., described the preparation (scheme 2.6) of Quetiapine by reacting urethane derivative 43 with hydroxy ethyl piperazine (44) under neat reaction conditions to yield the condensed product 45. The resultant intermediate was treated with thionyl chloride to produce the corresponding chloro intermediate 46 which was subsequently cyclized in the presence of phosphorous oxy chloride and phosphorous pentoxide to give the dibenzo thiazepine derivative 47. The dibenzo thiazepine intermediate was reacted with ethylene glycol in the presence of sodium metal to afford Quetiapine (23).
2.2.1: Summary of reported synthetic schemes

As evident from the various reported synthetic routes, it appears that the scientists were mainly used the following fragments to build the desired molecule, Quetiapine in various synthetic pathways.

The fragment (A) in general was synthesized by the condensation of ortho amino substituted thiophenol with halo benzene in basic media and the resulting condensed product was treated successively with phenyl chloro formate and phosphoric acid to yield the lactam derivative. The fragment (B) was introduced on to fragment (A) either in the form of without substitution or with full length of alkyl chain or protected alkyl chain at terminal end or mid of the alkyl chain to form the Quetiapine. Some of the literature references were described
a sequential introduction of fragments (B) and (C) on dibenzo moiety for the synthesis of Quetiapine. Very few literature reports were available to build the piperazine fragment (B) for the synthesis of Quetiapine. Generally, the preparation of piperazine involves the usage of diethanolamine as the starting material which increases the scope for the unwanted side reactions. Alternatively, there were reports for the condensation of substituted piperazine or unsubstituted piperazine moiety with dibenzo derivative to form the corresponding amide intermediate. Finally, the resulted amide intermediate was transformed into Quetiapine (23) by a series of chemical transformations.

2.3: Present work

As demonstrated above, though there were good number of references available for the preparation of Quetiapine, these processes suffer with certain disadvantages. These are like usage of hazardous raw materials for example sodium hydride and boron trichloride, complex work up procedures to isolate the intermediates, use of column chromatography, poor yields and excessive time cycles. The above process disadvantages of known synthetic schemes led to inquisitiveness to find the way forward and motivated us to design an alternate process for the preparation of Quetiapine, which has become basis for the present work53.
2.3.1: Results and Discussion - Retro synthetic pathway of Quetiapine

Scheme 2.7

Based on the retro synthetic analysis of Quetiapine (scheme 2.7), the two synthons, 2-mercapto benzoic acid (52) and 1-chloro-2-nitrobenzene (53) are considered as the key starting materials for our proposed synthesis to get the 2-(2-nitrophenylthio)benzoic acid (51). Acid group in 51 was converted in to amide via acid chloride to get 2-(2-nitrophenylthio)benzamide (50). Benzamide derivative was subjected for dehydration with POCl₃ to yield 2-(2-nitrophenylthio) benzonitrile (49). The nitrile compound was reacted with SnCl₂ and HCl to get the tricyclic dibenzo[b,f][1,4]thiazepin-11-amine (38). Amine 38, condensed
with \(N,N\)-bis(2-chloroethyl)-4-methylbenzenesulfonamide (54) to provide the tosylpiperazine derivative of 11-(4-tosylpiperazin-1-yl)dibenzo[\(b,f\)][1,4]thiazepine (48). Tosylpiperazine derivative 48 was further treated with hydrobromic acid in the presence of acetic acid to yield 11-(piperazin-1-yl)dibenzo[\(b,f\)][1,4]thiazepine (31). Finally compound 31, condensed with 2-chloroethoxy ethanol to yield desired compound 23.

### 2.3.2: Synthesis of 2-(2-nitrophenylthio) benzoic acid (51)

Compound 52 was condensed with 1-chloro-2-nitrobenzene (53) in the presence of sodium hydroxide (scheme 2.8) to give benzoic acid derivative 51. The resultant compound was compared with the authentic sample.

**Scheme 2.8**

Accordingly, the above prepared compound was utilized to transform into other derivatives, which are intermediate compounds in our proposed synthetic route to Quetiapine.
2.3.3: Synthesis of 2-(2-nitropheny1thio) benzamide (50)

The compound 51 was reacted with thionyl chloride to get the acid chloride derivative which was further treated with ammonia (scheme 2.9) to afford the corresponding benzamide derivative 50 in excellent yield. The resultant compound was fully characterized by spectral data.

Scheme 2.9

The IR spectrum (Fig.2.1) of 50 showed characteristic sharp amide carbonyl at 1651 cm\(^{-1}\) and two sharp NH absorptions at 3369 cm\(^{-1}\) and 3177 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.2.2) displayed eight aromatic protons in the down field region at \(\delta\) 8.15-8.20 (d, 1H, \(J=7.6\), Ar-H), 7.65 (d, 1H, \(J=7.2\), Ar-H), 7.40-7.60 (m, 3H, Ar-H), 7.37 (m, 2H, Ar-H), 7.00 (d, 1H, \(J=8.4\), Ar-H). The ES mass spectrum (Fig.2.3) displayed a protonated molecular ion peak at m/z 275.
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Fig. 2.1: IR spectrum of 2-(2-nitrophenyl) benzamide (50)

Fig. 2.2: 1H NMR spectrum of 2-(2-nitrophenyl) benzamide (50)
2.3.4: Synthesis of 2-(2-nitrophenylthio) benzonitrile (49)

The required compound 49 was prepared in good yield by refluxing the benzamide compound 50 with phosphorus oxychloride in chloroform for two hours (scheme 2.10). The resultant compound was fully characterized by IR, NMR and Mass spectral data.

**Scheme 2.10**

\[ \text{H}_2 \]

The IR spectrum (Fig.2.4) of 49 was devoid of sharp two NH peaks while it showed a characteristic sharp nitrile peak at 2232 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.2.5) was characterized by the presence of eight aromatic protons appeared at \( \delta \) 8.27 (dd, 1H, J=1.6, 8.4, Ar-H), 7.84 (dd,
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1H, J=1.6, 8.0, Ar-H), 7.75 (dd, 1H, J=7.4, 8.2, Ar-H), 7.70 (m, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.28 (m, 1H, Ar-H) and 6.78 (dd, 1H, J=1.2, 8.4, Ar-H). The ES mass spectrum (Fig. 2.6) displayed the molecular ion peak at m/z 257 (M+1) corresponding to the molecular weight of 256.

![Fig. 2.4: IR spectrum of 2-(2-nitrophenylthio) benzonitrile (49)](image)
Fig. 2.5: $^1$H NMR spectrum of 2-(2-nitrophenylthio) benzonitrile (49)

Fig. 2.6: Mass spectrum of 2-(2-nitrophenylthio) benzonitrile (49)
2.3.5: Synthesis of dibenzo[\textit{b,f}] [1,4]thiazepin-11-amine (38)

A mixture of compound 49 and ethanol was heated to 50°C and to this, a solution of anhydrous stannous chloride in concentrated hydrochloric acid was added and refluxed for one hour to afford tricyclic amine derivative 38 in excellent yield and quality (scheme 2.11). Finally the resultant title compound 38 was fully characterized by using IR, $^1$H NMR and Mass spectral data.

\textit{Scheme 2.11}

The IR spectrum (Fig.2.7) of 38 showed two characteristic sharp NH absorptions at 3341 cm$^{-1}$ and 3225 cm$^{-1}$ respectively and devoid of starting material CN signal at 2232 cm$^{-1}$. The $^1$H NMR spectrum (Fig.2.8) recorded in DMSO-d$_6$ was characterized by the presence of eight aromatic protons in the region of $\delta$ 6.60-7.90. The Electro spray mass spectrum (Fig.2.9) displayed the protonated molecular ion peak at m/z 227.
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Fig. 2.7: IR spectrum of dibenzo[b,f][1,4]thiazepin-11-amine (38)

Fig. 2.8: $^1$H NMR spectrum of dibenzo[b,f][1,4]thiazepin-11-amine (38)
2.3.6: Synthesis of 11-(4-tosylpiperazin-1-yl)dibenzo[b,f][1,4]thiazepine (48)

Amine derivative 38 was reacted (scheme 2.12) with compound 54 in methylene chloride in the presence of triethylamine at ambient temperature followed by systematic workup afforded the title compound 48. The resultant compound was fully characterized by IR, $^1$H NMR and Mass spectral data.

Scheme 2.12
The IR spectrum (Fig. 2.10) of 48 showed a characteristic sharp sulfonyl and C-N aromatic absorptions at 1168 cm\(^{-1}\) and 1396 cm\(^{-1}\) respectively. The \(^1\)H NMR spectrum (Fig. 2.11) recorded in CDCl\(_3\) was characterized by the presence of twelve aromatic protons in the region of δ 6.80-7.80, presence of aromatic methyl sharp signal at δ 2.40 along with eight piperazine protons at δ 3.60-3.80 (br, 2H, CH\(_2\)), 3.50-3.60 (br, 2H, CH\(_2\)), 3.15-3.20 (br, 2H, CH\(_2\)), 3.07 (m, 2H, CH\(_2\)). The ES mass spectrum (Fig. 2.12) displayed the molecular ion peak at m/z 450 (M+1). The major fragment (scheme 2.12a) obtained at m/z 296 is attributed to 11-(piperazin-1-yl)dibenzo[\(b,f\)][1,4]thiazepine (48a) ion.
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Fig. 2.11: $^1$H NMR spectrum of 11-({4-tosylpiperazin-1-yl)dibenzo[b,cf][1,4]thiazepine (48)

Fig. 2.12: Mass spectrum of 11-({4-tosylpiperazin-1-yl)dibenzo[b,cf][1,4]thiazepine (48)
2.3.7: Synthesis of 11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepine (31)

The desired compound 31 was obtained in 80.0% yield by deprotection of tosyl group of compound 48 with 30% HBr in acetic acid at 75°C for 4 hours (scheme 2.13). The resultant compound was confirmed by spectral data and it is also further confirmed by authentic sample.

The IR spectrum (Fig.2.13) of 31 was showed a characteristic NH absorption at 3409 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.2.14) was characterized by the presence of twelve aromatic protons in the region of \(\delta 6.80-7.45\). Piperazine eight protons appeared at \(\delta 3.60 \text{ (br, } 2\text{H, CH}_2)\), 3.55 (m, 2H, CH\(_2\)), 3.00 (br, 2H, CH\(_2\)), 2.85-2.95 (m, 2H, CH\(_2\)). The ES
mass spectrum (Fig.2.15) displayed the protonated molecular ion peak at m/z 296 (M+1).

Fig.2.13: IR spectrum of 11-[piperazin-1-yl]dibenzo[b,f][1,4]thiazepine [31]
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Fig. 2.14: $^1$H NMR spectrum of 11-(piperazin-1-yl)dibenzo[9,10][1,4]thiazepine (31)

Fig. 2.15: Mass spectrum of 11-(piperazin-1-yl)dibenzo[9,10][1,4]thiazepine (31)
2.3.8: Synthesis of 2-(2-(4-(dibenzo\[b,f\][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy)ethanol (23)

According to our proposed synthetic pathway, the penultimate compound 31 was condensed with 2-chloroethoxy ethanol in N-methyl pyrrolidine, sodium carbonate as a base in the presence sodium iodide at 110°C for 15 hours to yield the desired compound 23 (scheme 2.14) in 85.0% yield. The target compound was fully characterized by their spectral data and also compared with authentic sample by HPLC analysis.

Scheme 2.14

The UV spectrum (Fig.2.16) of Quetiapine (23) recorded in methanol (Conc=0.001% w/v) using shimadzu model 2100S double beam UV – Visible spectrophotometer. It exhibited two peaks with maxima at λ 210 and 295 nm. A hydroxy absorption peak at 3318 cm⁻¹ was observed in the solid phase KBr dispersion IR spectrum (Fig 2.17). The ¹H NMR spectrum (Fig.2.18) showed characteristic eight aromatic protons at δ 6.85-7.80. Eight piperazine ring protons and 4 methylene group protons appeared at δ 2.40-3.80. Hydroxyl proton was evidenced
by exchange with deuterium in D$_2$O $^{1}$H NMR spectrum. The CI mass spectrum (Fig. 2.19) displayed a strong protonated molecular ion of Quetiapine at m/z 384. However, ESI mass spectrum displayed a week protonated molecular ion of Quetiapine at m/z 384 corresponding to the molecular weight of 383. The major fragment ions (scheme 2.14a) obtained at m/z 322, 239, 227, and 210 are attributed to $23_b$, $23_c$, $23_d$ and $23_e$ ions, respectively.

Scheme 2.14a
Fig. 2.16: UV spectrum of 2-(2-[4-((dibenzo[b,d][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy]ethanol [23]

Fig. 2.17: IR spectrum of 2-(2-[4-((dibenzo[b,d][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy]ethanol [23]
Fig. 2.18: $^1$H NMR spectrum of 2-[(4-{dibenzo[h,j]1,4-thiazepin-11-yl}piperazin-1-yl)ethoxy]ethanol (23)

Fig. 2.18a: $^{13}$C NMR spectrum of 2-[(4-{dibenzo[h,j]1,4-thiazepin-11-yl}piperazin-1-yl)ethoxy]ethanol (23)
2.4 Total new synthetic route of Quetiapine

The scheme 2.15 depicted as follows describes the total synthetic route to Quetiapine according to our proposed work.
2.5: Related substances of Quetiapine (23)

The purity of drug substance produced in the manufacturing process is important for the large scale production and followed by its commercialization. Impurities generated during the synthesis must be limited to very lower level as per ICH guidelines\textsuperscript{54}. According to the ICH guidelines, in general an identified impurity should be restricted to not more than 0.15\% level and an unidentified (unknown) impurity should not be more than 0.10\% level by HPLC analysis. In the later case, where the identification is not possible, the drug substance required for extra purification and this may result in yield loss and indirectly affects the overall manufacturing cost. In this context, we have taken up
comprehensive studies to identify the impurities generated during the synthesis of Quetiapine.

The HPLC analysis of Quetiapine (23), showed impurity peaks ranging around 0.01-0.15% level. To identify the molecular weight of the respective impurities, our samples were submitted for Liquid Chromatographic-Mass Spectrometry (LC-MS) analysis. From the molecular weight information, extensive study was undertaken to identify and synthesize the two impurities of Quetiapine. Finally these two impurities were synthesized and subsequently subjected for spectral analysis (Mass, $^1$H NMR and IR). Based on the spectral data, these impurities were characterized as $N$-(dibenzo[b,f][1,4]thiazepin-11-yl)-4-methylbenzenesulfonamide (55) and dibenzo[b,f][1,4]thiazepin-11(10$H$)-one (56).

2.5.1. Preparation of Related Substance (55) of Quetiapine

4-Methyl benzene sulfonic acid (57) is a potential impurity present in $N$, $N$-bis-(2-chloroethyl)-4-methyl benzene sulfonamide (54). The sulfonamide 54 was condensed with 38 in the synthesis of compound 48 (scheme 2.12). During this condensation, a side reaction occurs between the trace amount of 57 and 38 to yield the related compound 55. However, the compound 55 was prepared conveniently by treating compound 38 with 4-methyl benzene sulfonyl chloride (58) in dichloromethane in the presence of triethylamine at ambient temperature followed by usual workup (scheme 2.16).
The IR spectrum (Fig.2.20) of 55 displayed one sharp NH signal at 3221 cm\(^{-1}\) along with the S=O stretching signals at 1149 cm\(^{-1}\) and 1217 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.2.21) also contained a singlet at \(\delta 2.15\) ppm corresponding to a three-proton aromatic methyl group along with the presence of multiplet signals between \(\delta \ 6.70\) to 8.0 ppm with 12 proton integration. The electron impact mass spectrum of 55 (Fig.2.22) displayed a protonated molecular ion at \(m/z \ 381\). This spectral data is consistent with the structure of 55.
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Fig. 2.20: IR spectrum of \(N\)-dibenzo[\(b,j\)][1,4]thiazepin-11-yl)-4-methylbenzenesulfonamide (55)

Fig. 2.21: \(^1\)H NMR spectrum of \(N\)-dibenzo[\(b,j\)][1,4]thiazepin-11-yl)-4-methylbenzenesulfonamide (55)
2.5.2. Preparation of Related Substance (56) of Quetiapine

The tricyclic amine derivative 38 is one of the key intermediate for the preparation of Quetiapine in our proposed synthetic route. During the synthesis, if traces of compound 38 present in advanced intermediates, it would be converted to compound 56 in any one of the further sequential reactions. Hence, the required related compound 56 was prepared synthetically (scheme 2.17) by treating the compound 38 with aqueous sodium hydroxide at reflux temperature.

Scheme 2.17
In the IR spectrum (Fig.2.23), a band at 1649 cm\(^{-1}\) corresponding to C=O stretching was observed along with the amide NH signal at 3171 cm\(^{-1}\). In the \(^1\)H NMR spectrum (Fig.2.24), four multiplet signals and four doublet signals were appeared between \(\delta\) 7.10-7.80 along with sharp amide proton signal at \(\delta\) 10.70. The ESI-MS spectrum (Fig.2.25) of 56 displayed an M + 1 ion at \(m/z\) 228, and this spectral data is consistent with the structure of dibenzo[b,f][1,4]thiazepin-11(10H)-one (56).
Fig. 2.24: $^1$H NMR spectrum of dibenzo[bf][1,4]thiazepin-11(10H)-one (56)

Fig. 2.25: Mass spectrum of dibenzo[bf][1,4]thiazepin-11(10H)-one (56)
2.6: Conclusion

Thus, we have developed a simple, new and cost-effective synthetic route for the synthesis of Quetiapine. Further to this, two related compounds formed during the synthesis of Quetiapine were also identified, synthesized and characterized by their individual spectral data.

2.7: Experimental section

The mass spectrum was recorded on 4000-Q-trap LC-Mass spectrometer. The FT-IR spectrum was recorded on Perkin-Elmer model spectrum GX series FT-IR as KBr pellet. The $^1$H NMR data were recorded at 400 MHz on Varian mercury plus 400 MHz spectrometer and $^{13}$C NMR data were recorded at 200 MHz. The chemical shift values were reported on $\delta$ scale in ppm with respect to TMS ($\delta$ 0.00 ppm) as internal standard.

**Preparation of 51 by condensation of 52 and 53:** To a mixture of 52 (50 g, 0.325 mol) and sodium hydroxide (26.1 g, 0.653 mol) in water (170 mL) was added 53 (54 g, 0.343 mol) and refluxed at 100-105°C for 5 hours. The reaction mixture was cooled to room temperature and washed with ethyl acetate (200 mL) to remove the un-reacted 1-chloro-2-nitrobenzene. The aqueous reaction layer was neutralized with aqueous hydrochloric acid (125 mL) and the product was extracted into ethyl
acetate (400 mL). The ethyl acetate solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 51 (80.7 g, Yield: 90.1%)

**Preparation of compound 50**: To a mixture of 51 (50 g, 0.182 mol), DMF (2 mL) and chloroform (500 mL) was added thionyl chloride (26 g, 0.22 mol) and refluxed for two hours. The reaction mixture was concentrated under reduced pressure, poured into a mixture of 25% aqueous ammonia solution (500 mL) and ice (100 g), and then stirred for 2 hours. The separated solid product was filtered, washed with water (100 mL) and dried at 60°C to afford the title compound 50 (40 g, yield: 80%). IR (cm\(^{-1}\)): 1651 (C=O), 3369 (NH), 3177 (NH); \(^1\)H NMR (CDCl\(_3\), \(\delta\) ppm): 7.00 (d, 1H, J=8.4, Ar-H), 7.37 (m, 2H, Ar-H), 7.40-7.60 (m, 3H, Ar-H), 7.65 (d, 1H, J=7.2, Ar-H), 8.15-8.20 (d, 1H, J=7.6, Ar-H); MS: \(m/z\) 275 (M+1); Analysis Calcd. for C\(_{13}\)H\(_{10}\)N\(_2\)O\(_3\)S: C, 56.92; H, 3.67; N, 10.21. Found: C, 56.89; H, 3.69; N, 10.25.

**Preparation of compound 49**: To a mixture of 50 (30 g, 0.109 mol) in chloroform (250 mL) was added phosphorus oxychloride (51.2 mL 0.55 mol) and refluxed for two hours. The reaction mixture was cooled to 20 °C, poured into water (100 ml), and then stirred for one hour. The organic layer was separated, dried over sodium sulfate and the solvent was removed under reduced pressure to yield 49 (19 g, yield: 67.8%). IR (cm\(^{-1}\)): 2232 (CN); \(^1\)H NMR (CDCl\(_3\), \(\delta\) ppm): 6.78 (dd, 1H, J=1.2, 8.4, Ar-H), 7.28 (m, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.70 (m,
1H, Ar-H), 7.75 (dd, 1H, J=7.4, 8.2, Ar-H), 7.84 (dd, 1H, J=1.6, 8.0, Ar-H) 8.27 (d, 1H, Ar-H); MS: m/z 255 (M-1); Analysis Calcd. for C_{13}H_{8}N_{2}O_{2}S: C, 60.93; H, 3.15; N, 10.93. Found: C, 60.90; H, 3.18; N, 10.95.

**Preparation of 38 from 49:** A mixture of 49 (16 g, 0.063 mol) and ethanol (200 mL) was heated to 50°C and to this, a solution of anhydrous stannous chloride (39 g, 0.20 mol) in concentrated hydrochloric acid (60 mL) was added and stirred for 1 hour at reflux. The reaction mixture was concentrated under reduced pressure to yield the title compound 38 (12.8 g, yield: 90.0%); IR (cm⁻¹): 3341 (NH), 3235 (NH); ¹H NMR (DMSO-d₆, δ ppm): 6.60-6.86 (m, 1H, Ar-H), 6.70-6.80 (d, 1H, J=8.4, Ar-H), 6.95-7.00 (d, 1H, J=7.6, Ar-H), 7.20-7.40 (m, 3H, Ar-H), 7.50-7.60 (m, 1H, Ar-H), 7.90 (d, 1H, J=6.4, Ar-H); MS: m/z 227 (M+1); Analysis Calcd. for C_{13}H_{10}N_{2}S: C, 69.00; H, 4.45; N, 12.38. Found: C, 69.03; H, 4.46; N, 12.36.

**Preparation of 48 by condensation of 38 and 54:** To a mixture of 38 (12 g, 0.053 mol) in methylene chloride (80 mL) was added 54 (20.3 g, 0.068 mol), triethyl amine (19 g, 0.19 mol) and stirred for 3 hours at room temperature. The reaction mixture was washed with water, dried over sodium sulfate and the solvent was removed under reduced pressure to afford the title compound 48 (19 g, yield 80.0%). IR (cm⁻¹): 1396, 1168 (S=O); ¹H NMR (CDCl₃, δ ppm): 2.40 (s, 3H, CH₃), 3.07 (m, 2H, CH₂), 3.15-3.20 (b, 2H, CH₂), 3.50-3.60 (br, 2H, CH₂), 3.60-3.80 (br,
2H, CH₂), 6.85-6.90 (m, 1H, Ar-H), 7.00-7.05 (dd, 1H, J=1.6, 8.4, Ar-H), 7.15-7.30 (m, 7H, Ar-H), 7.50 (dd, 1H, J=1.2, 7.6, Ar-H), 7.60-7.70 (d, 2H, J=8.4, Ar-H); MS: m/z 450(M+1); Analysis Calcd. for C_{24}H_{23}N_{3}O_{2}S_{2}: C, 64.12; H, 5.16; N, 9.35. Found: C, 64.17; H, 5.15; N, 9.38

**Preparation of compound 31**: A mixture of 48 (20 g, 0.045 mol) and 30% HBr in acetic acid (80 mL) was heated to 75°C and maintained for 4 hours. The reaction mixture was cooled to room temperature and water (100 mL), toluene (100 mL) was added and layers were separated. The aqueous layer pH was adjusted to 10-11 with 20% aqueous sodium hydroxide solution and the product was extracted into methylene chloride (100 mL). Organic layer was concentrated under vacuum to yield the desired compound 31 (10.5 g, yield: 80.0%). IR (cm⁻¹): 3409 (NH); ¹H NMR (DMSO-d₆, δ ppm): 2.85-2.95 (m, 2H, CH₂), 3.00 (br, 2H, CH₂), 3.55 (m, 2H, CH₂), 3.60 (br, 2H, CH₂), 6.80-6.90 (m, 1H, Ar-H), 7.00-7.10 (dd, 1H, J=1.6, 8.0, Ar-H), 7.15-7.20 (m, 1H, Ar-H), 7.25-7.35 (m, 3H, Ar-H), 7.40 (dd, 1H, J=2.0, 8.0, Ar-H), 7.45 (d, 1H, Ar-H); MS: m/z 296 (M+1); Analysis Calcd. for C_{17}H_{17}N_{3}S: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.14; H, 5.82; N, 14.27.

**Preparation of 23 from 31**: A mixture of 31 (6 g, 0.020 mol), toluene (20 mL) and soda ash (3.3 g) were stirred together for 3 hours at 40 °C. To this mixture, N-methyl pyrrolidine (11 mL), Sodium iodide (0.5 g) and 2-chloroethoxy ethanol (2.7g) were added and stirred for 15 hours at 110 °C for completion of the reaction. The reaction mixture was cooled to
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room temperature and washed with water for three times (3x 40 mL). The organic layer was concentrated under reduced pressure to afford the title compound 23 (6.6 g, yield: 85.0%). IR (cm$^{-1}$): 3318 (-OH); $^1$H NMR (CDCl$_3$, $\delta$ ppm): 2.45-2.55 (m, 2H, CH$_2$), 2.45-2.70 (m, 2H, CH$_2$), 3.60-3.70 (m, 6H, CH$_2$), 3.70-3.80 (m, 6H, CH$_2$), 6.85 (d, 1H, $J$=8.0, Ar-H), 7.10 (m, 1H, Ar-H), 7.20 (d, 1H, $J$=7.6, Ar-H), 7.25-7.40 (m, 4H, Ar-H), 7.55 (m, 1H, Ar-H); $^{13}$C NMR (200 MHz, CDCl$_3$): $\delta$ 52.43, 56.9, 60.3, 67.2, 72.3, 122.6, 125.1, 127.2, 128.9, 129.2, 131.9, 132.0, 133.5, 134.4, 138.7, 148.6, 153.4 MS: $m/z$ 384 (M + 1); Analysis Calcd. for C$_{21}$H$_{25}$N$_3$O$_2$S: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.72; H, 6.53; N, 11.01.

**Preparation of Related compound 55**: To a mixture of 38 (20.0 g, 0.09 mol), dichloromethane (200 mL) and triethyl amine (10 mL) was added p-toluene sulphonyl chloride (25 g, 0.14 mol) and maintained at room temperature. The reaction progress was monitored by thin layer chromatography and after completion of the reaction, 5% aqueous sodium bicarbonate solution (400 mL) was added stirred for 30 minutes and layers were separated. The organic layer was washed with water (2X 50 mL) and concentrated under reduced pressure to yield the required compound 55 (12.5 g, Yield: 74.3%). IR (cm$^{-1}$): 3221 (NH), 1149 and 1217 (S=O); $^1$H NMR (DMSO-d$_6$, $\delta$ ppm): 2.90-3.00 (s, 3H, CH$_3$), 6.70-6.80 (m, 2H, CH$_2$), 6.80-6.95 (m, 2H, Ar-H), 7.05-7.15 (d, 1H, Ar-H), 7.15-7.30 (m, 4H, Ar-H), 7.70-7.75 (m, 1H, Ar-H), 7.80-7.90 (m, 2H, Ar-
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H). MS: \( m/z \) 380 (M); Analysis Calcd. for \( \text{C}_{20}\text{H}_{16}\text{N}_{2}\text{O}_{2}\text{S}_{2}: \) C, 63.13; H, 4.24; N, 7.36. Found: C, 63.17; H, 4.26; N, 7.32.

**Preparation of Related compound 56:** A mixture of 38 (25.0 g, 0.11 mol) and 30% aqueous sodium hydroxide (150.0 mL) were heated to reflux for reaction completion. The reaction mass was cooled to room temperature and the solid was filtered and washed with water (100.0 mL). The resultant wet cake was dissolved in methanol (300.0 mL) at reflux temperature, treated with carbon (5.0 g), filtered and finally water (500.0 mL) was added to it for isolation of the solid. The isolated solid was filtered, washed with water (50.0 mL) and dried at 70°C to yield the compound 56 (17 g, Yield: 69.7%). IR (cm\(^{-1}\)): 3171 (NH), 1649 (CO); \(^1\text{H}\) NMR (DMSO-\(\text{d}_6, \delta \) ppm): 7.10-7.20 (m, 1H, Ar-H), 7.20-7.25(d,1H, Ar-H), 7.30-7.40 (t, 1H, Ar-H), 7.40-7.60 (4m, 4H, Ar-H), 7.60-7.70 (d, 1H, Ar-H), 10.70 (d, 1H, NH); Mass: 228 (M+1); C H N Analysis Calcd. for \( \text{C}_{13}\text{H}_{9}\text{NOS}: \) C, 68.70; H, 3.99; N, 6.16; Found: C, 68.96; H, 3.94; N, 6.20.