CHAPTER 3: Alternate Synthetic Approaches to Ziprasidone, Preparation and Characterization of its Related Compounds

3.1: Introduction

Ziprasidone\textsuperscript{55} (24) is a unique dopamine as well as serotonin antagonist resulting in a potent antipsychotic effect particularly in schizophrenia and schizoaffective disorder with a significant impact on negative symptoms including symptoms of depression. Owing to its unique behavior, it has a distinctive advantage over other antipsychotic drugs, while not resulting in increase of the patient weight. Ziprasidone is approved as its hydrochloride salt for the treatment of schizophrenia and for the acute treatment of bipolar disorder.

Ziprasidone is a selective monoaminergic antagonist with high affinity for the serotonin type 2 (5HT\textsubscript{2}), dopamine type 2 (D\textsubscript{2}), 1 & 2 adrenergic and H\textsubscript{1} histaminergic receptors. It also acts with lower potency as an antagonist at other receptors. Ziprasidone is a psychotropic agent belonging to the chemical class of benzisothiazole derivatives and is available as capsules containing the active ingredient
as hydrochloride salt for oral administration and as an injection for intramuscular use having mesylate salt.

**Table-3.1: Product details**

<table>
<thead>
<tr>
<th>Name of the drug</th>
<th>Ziprasidone</th>
</tr>
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<tbody>
<tr>
<td>Active ingredient</td>
<td>Ziprasidone hydrochloride</td>
</tr>
<tr>
<td>Innovator</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Marketed by</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Melting point</td>
<td>Above 300°C</td>
</tr>
<tr>
<td>Dosage details</td>
<td>20, 40, 60 and 80mg</td>
</tr>
<tr>
<td>Approval date</td>
<td>February 05, 2001 (US)</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Geodon</td>
</tr>
<tr>
<td>Therapeutic category</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{21}H_{21}ClN_{4}O_{5}HCl</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>Ziprasidone hydrochloride (448.0)</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in formic acid</td>
</tr>
</tbody>
</table>
3.2: Known Synthetic procedures for the synthesis of Ziprasidone

The group of scientists from Pfizer, Lowe et al., described the synthesis of Ziprasidone (scheme 3.1) for the first time in their basic patent\textsuperscript{56}. The process involves acylation of chloro oxindole 59 with chloroacetyl chloride under Friedel-craft’s reaction conditions to provide the corresponding acylated oxindole 60. The acetyl oxindole was reduced in a combination of trifluoro acetic acid and triethyl silane to yield chloro ethyl oxindole 61, which is one of the principle moieties in their process. The other key moiety piperazinyl benzisothiazole 62 was obtained by reaction of 3-chloro benzisothiazole with piperazine. The two key moieties 61 and 62 were condensed together under basic reaction conditions at elevated temperature in the presence of polar solvents afforded the targeted compound, Ziprasidone (24).

Scheme 3.1

Urban and co-workers\textsuperscript{57} disclosed the process for preparation of Ziprasidone (scheme 3.2) starting from nitration reaction on 2, 5-dichloro toluene (63) with sulfuric acid and nitric acid in glacial acetic
acid to give nitro derivative 64. The nitro derivative was treated with t-butoxy-bis(dimethylamino) methane in tetrahydrofuran to form enamine 65, which was condensed with 4-(1,2-benzisothiazol-3-yl)-piperazine (62) in acetic acid media to result the condensed product 66. The compound 66 was reduced with sodium triacetoxyborohydride in a mixture of 1, 2-dichloroethane and acetic acid to give the unsaturated compound 67. The compound 67 was further reacted with dimethylmalonate in N-methyl-pyrrolidine in the presence of potassium hydroxide to give bis carbonyl derivative 68, which on acidic hydrolysis produced the corresponding acid 69. Finally, the acid group of compound 69 was activated and cyclized to indole ring formation to get the Ziprasidone.
Nagarajan et al., described process for the preparation of 6-chloroxindole (scheme 3.3), which is one of the building blocks for ziprasidone\(^\text{58}\). 2,5-Dichloronitrobenzene (71) was reacted with dimethyl malonate in the presence of potassium carbonate as base and dimethylsulfoxide as solvent to give malonate ester 72. The malonate ester was hydrolyzed with concentrated hydrochloric acid in acetic acid to afford the corresponding phenyl acetic acid derivative 73. The nitro group of 73 was transformed into amine and further cyclized to result
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the oxindole derivative 59. The chloro oxindole was converted to Ziprasidone (24) in known methods.

**Scheme 3.3**

![Chemical structure]

Parthasaradhi Reddy *et al.*, disclosed (scheme 3.4) yet another process for the preparation Ziprasidone involving the use of trimethyl silylchloride\(^59\). The process involves reaction of piperazinyl benzisothiazole (62) with trimethyl silyl chloride to give the silylated compound 74. The compound, 74 was treated with chloroethyl oxindole 61 in the presence of sodium carbonate and catalytic amount of sodium iodide in water media to result Ziprasidone (24).

**Scheme 3.4**

Jacopo Zanon *et al.*, described the process for the preparation of Ziprasidone\(^60\) comprising chemical reduction of chloro acetyl oxindole 60 with sodium borohydride in ethanol to result 1-hydroxy-2-chloroethyl oxindole (75). The hydroxy compound on further reduction with trifluoroacetic acid and triethyl silane resulted into oxindole derivative.
Thus, resulted compound 61 was condensed with 3-piperazinyl-1, 2-benzisothiazole (62) in routine method afforded the targeted compound 24 (scheme 3.5).

**Scheme 3.5**

3.2.1 *Summary of reported synthetic schemes*

As evident from the precedent synthetic schemes, it appears that the organic chemists were mainly utilized the following two synthons 61 and 62 or their derivatives\textsuperscript{61} to build the desired molecule, Ziprasidone in various synthetic pathways. In an alternative methodology, Ziprasidone was prepared by final step heterocyclization of ester derivative of synthon 70. According to the commonly used methodology, synthon 61 was condensed with synthon 62 in polar solvents such as methyl isobutyl ketone in the presence of an acid neutralizing agent such as sodium carbonate and a catalyst such as sodium iodide to afford Ziprasidone.
In general, synthon 61 was obtained by the Friedel crafts acylation of 6-chloro oxindole with a source of acetyl group in presence of a Lewis acid in an appropriate solvent followed by reduction of keto group in the presence of trifluoroacetic acid and triethyl silane. The synthon 62 was prepared by reacting 3-chloro-1,2-benzisothiazole with molar excess of piperazine in a suitable solvent system. The synthon 70 was prepared from the corresponding diester derivative by treatment with an acid followed by esterification with thionyl chloride and an alcohol to afford ester derivative 70.

These reported processes more often suffer from the formation of impurities such as keto Ziprasidone and bis piperazinyl benzisothiazole up to 1.0%. To make the drug substance with the content of impurities below the ICH limits, it has necessarily required for more number of purifications. Therefore, to overcome these difficulties, it has become essential to develop different alternate processes for the preparation of Ziprasidone. In search of alternative methods, we finally successfully developed three alternative methods for the preparation of Ziprasidone.
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involving new intermediates with an alternate reaction conditions to provide Ziprasidone in an excellent yield with the desired purity.

3.3: Present Work

Schemes 3.6 and 3.10 have been designed to minimize the content of impurities i.e., bis piperazinyl benzisothiazole and keto derivative of Ziprasidone and to increase the overall yield. The removal of these impurities has become difficult and tedious work up procedures were required in earlier known processes, which in turn results in low yield of targeted product Ziprasidone\textsuperscript{62}. Scheme 3.13 is unique from various aspects and also involves new intermediates. This synthetic scheme is derived from the mechanism of Gabriel synthesis of primary alkyl amine.

3.3.1: Results and Discussion

Retro synthetic path way of 1\textsuperscript{st} alternate synthetic approach for Ziprasidone

Accordingly, scheme 3.6 describes an alternate pathway for the preparation of Ziprasidone which involves reaction of \textbf{62} with compound \textbf{60} under basic reaction conditions to yield keto Ziprasidone (\textbf{76}). The resulted keto Ziprasidone was subjected to reduction in the presence of triethyl silane and methane sulfonic acid to afford Ziprasidone (\textbf{24}) with good yield and purity.
The use of methane sulfonic acid is not reported in combination with triethyl silane for the reduction of carbonyl functional group, particularly for the preparation of Ziprasidone. This combination was found to be superior to that of a mixture contains triethyl silane and trifluoro acetic acid. The safety profile of methane sulfonic acid is two folds lesser and less costlier reagent than trifluoro acetic acid. These unique properties of methane sulfonic acid were motivated us to utilize as one of the reagent for instant reaction.

### 3.3.2 Synthesis of 6-chloro-5-(2-chloroacetyl)indolin-2-one (60)

Acylation of compound 59 with chloro acetyl chloride under Friedel-craft’s reaction conditions (scheme 3.7) at reflux temperature provided the corresponding acylated oxindole 60. The resulted compound 60 was compared with the authentic sample by HPLC analysis.
The above resulted acylated derivative 60 was used as a starting material for the preparation of Ziprasidone in one of our proposed alternate methods.

3.3.3 Synthesis of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one (76)

The chloro acylated oxindole 60 was reacted with benzisothiazole 62 involving the use of sodium carbonate as base in cyclohexane at reflux temperature in the presence of catalytic amount of sodium iodide and tetrabutyl ammonium bromide (scheme 3.8) to afford keto Ziprasidone\textsuperscript{63}(76). The resulted compound was fully characterized by its respective spectral data.

Scheme 3.8

The IR spectrum (Fig.3.1) of 76 showed characteristic two CO absorption peaks at 1732 cm\(^{-1}\) and 1716 cm\(^{-1}\), one broad amide NH peak at 3437 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.3.2) displayed six aromatic
protons at $\delta$ 8.05-8.10 (d, 2H, $J=9.2$, Ar-H), $\delta$ 7.65 (s, 1H, Ar-H), $\delta$ 7.55 (m, 1H, Ar-H), $\delta$ 7.45 (m, 1H, Ar-H), 6.92 (s, 1H, Ar-H), amide proton at $\delta$ 10.93 (s, 1H, NH), and 12 methylene protons displayed between $\delta$ 3.30-3.80. The ES mass spectrum (Fig. 3.3) displayed a protonated molecular ion peak at m/z 427.0 (M+1).
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Fig. 3.2: $^1$H NMR spectrum of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one (76)

Fig. 3.3: Mass spectrum of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one (76)
3.3.4 Synthesis of Ziprasidone (24)

The method of present work prominently employed triethyl silane in combination with methane sulfonic acid for the reduction of carbonyl group of keto Ziprasidone (76). The methane sulfonic acid was opted as the solvent for this reaction because of its good solvating properties and less corrosive when compared to trifluoroacetic acid. Two equivalents of triethyl silane were utilized for the reduction of one equivalent of carbonyl compound to afford the required compound 24 (scheme 3.9). The resulted compound was optionally purified from a mixture of methanol and acetone. Ziprasidone obtained in this route is having around 99.8% purity by HPLC along with 76.0% yield.

Scheme 3.9 (Method A)

The UV spectrum (Fig.3.4) of Ziprasidone (24) was recorded on Perkin-Elmer UV – Visible spectrophotometer model Lambda 45 in methanol with concentration of 0.001%. The peak maxima were observed at λ 252 and 315 nm. The IR spectrum (Fig.3.5) of 24 showed characteristic sharp amide CO absorption peak at 1714 cm⁻¹ and one amide NH peak at 3420 cm⁻¹. The ¹H NMR spectrum (Fig.3.6) displayed
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six aromatic protons at \( \delta 8.15 \) (d, 1H, \( J=8.40 \), Ar-H), \( \delta 8.11 \) (d, 1H, \( J=8.0 \), Ar-H), \( \delta 7.68 \) (t, 1H, \( J=8.0 \), Ar-H), \( \delta 7.48 \) (t, 1H, \( J=8.0 \), Ar-H), \( \delta 7.15 \) (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H). The exchangeable proton observed at \( \delta 10.55 \) (s, 1NH) and this was further confirmed by recording the deuterated proton spectra (Fig.3.6a) wherein disappearance of amide NH signal at \( \delta 10.55 \) observed. The 12 methylene protons displayed at \( \delta 4.10 \) (d, 2H, \( J=12.8 \), CH\(_2\)), \( \delta 3.70 \) (m, 2H, CH\(_2\)), \( 3.56 \) (m, 2H, CH\(_2\)), \( 3.54 \) (m, 2H, CH\(_2\)), \( 3.35 \), (d, 2H, CH\(_2\)), \( 3.27 \) (d, 2H, CH\(_2\)) and 3.21 (m, 2H, CH\(_2\)). The mass spectrum (Fig.3.7) displayed a protonated molecular ion peak at m/z 413.0 (M+1) and major fragment obtained as a base peak at m/z 232 was attributed to \( \text{2-(benzo[d]isothiazol-3-yl)-1-methylenepiperazin-1-ium} \ (24a) \). Base peak further fragmented and produced at m/z 177 as a \( \text{2-(benzo[d]isothiazol-3-ylamino)ethan-1-ylium} \) ion (24b)(Scheme 3.9a)

**Scheme 3.9a**
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Fig. 3.4: UV spectrum of 5-(2-(4-benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (24)

Fig. 3.5: IR spectrum of 5-(2-(4-benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (24)
Fig. 3.6: $^1$H NMR spectrum of 5-{$^2$-[4-\{benzo(d)isothiazol-3-yl\}piperazin-1-\{yl\}ethyl]-6-chloroindolin-2-one (24)

Fig. 3.6a: Deuterated $^1$H NMR spectrum of 5-{$^2$-[4-\{benzo(d)isothiazol-3-yl\}piperazin-1-\{yl\}ethyl]-6-chloroindolin-2-one (24)
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Fig. 3.6b: $^{13}$C NMR spectrum of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (24)

Fig. 3.7: Mass spectrum of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (24)
3.4: Retro synthetic pathway of 2nd alternate approach for Ziprasidone

Scheme 3.10 is another alternate process for the preparation of Ziprasidone comprises the reaction of 5 - (2-chloro ethyl)-6-chloro oxindole (61) involving excess molar ratio of piperazine to afford 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (77). The compound 77 is a new intermediate for the preparation of Ziprasidone to the best of our knowledge. The piperazinyl oxindole derivative 77 was condensed with 3-chloro-1,2-benzisothiazole (78) to afford the targeted compound Ziprasidone in a satisfactory yield and purity. The scheme 3.10 has been specifically designed to reduce the formation of bis piperazinyl benzisothiazole impurity by modifying the steps and reactants of condensation to provide Ziprasidone in high purity when compared to previously known processes. The compound 77 is reported as metabolite of Ziprasidone in earlier references\textsuperscript{64, 65} and the synthesis of this compound was not reported in the literature.

Scheme 3.10
**3.4.1 Synthesis of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (77)**

1.0 mole of compound 61 was reacted with 5.0 moles of piperazine in tertiary butanol at refluxing temperature and after systematic workup, it gave piperazinyl oxindole derivative 77 in appreciable yield with required purity (scheme 3.11). The gradual lot wise addition of piperazine to the reaction mixture comprising chloro oxindole derivative 61 in tertiary butanol is preferred to avoid the unwanted side products such as bis chloro oxindole piperazine derivative.

**Scheme 3.11**

The IR spectrum (Fig.3.8) of 77 showed characteristic sharp carbonyl and two NH absorptions at 1716 cm\(^{-1}\), 3317 cm\(^{-1}\) and 3410 cm\(^{-1}\) respectively. The \(^1\)H NMR spectrum (Fig.3.9) displayed amide NH signal at \(\delta\) 10.35-10.45, two aromatic protons appeared as a singlet signals at \(\delta\) 6.80 and 7.20 respectively. The signals corresponding to 14 methylene protons were observed in the up field region at \(\delta\) 3.40-3.45, (s, 2H, CH\(_2\)), \(\delta\) 2.65-2.75 (m, 6H, CH\(_2\)) and 2.30-2.45 (m, 6H, CH\(_2\)). The positive mode mass spectrum (Fig.3.10) displayed a protonated molecular ion peak at m/z 280 (M+1) with chlorine isotopic abundance. This spectral data is in conformity with the structure of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (77).
Fig. 3.8: IR spectrum of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (77)

Fig. 3.9: $^1$H NMR spectrum of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (77)
3.4.2 Synthesis of Ziprasidone (24)

3-Chloro-1, 2-benzothiazole (78) is reacted with 77 in the presence of sodium carbonate and tertiary butanol as solvent medium at reflux temperature provided Ziprasidone in excellent yield with ICH grade purity (Scheme 3.12).

Scheme 3.12 (Method B)
3.5: Retro synthetic pathway of 3rd alternate approach for Ziprasidone

Scheme 3.13 provides yet another alternate process for the preparation of Ziprasidone comprises the reaction of 3-chloro-1, 2-benzisothiazole (78) with slight excess molar ratio of 2-(2-hydroxy-ethylamino)-ethanol (commonly known as bis ethanol amine) at an elevated temperature to yield diol derivative, 2,2'-[benzo[d]isothiazol-3-ylazanediyl]diethanol (81) and isolated in the form of hydrochloride salt. The diol derivative 81, was reacted with thionyl chloride to produce dichloro derivative, \( N, N \)-bis(2-chloroethyl)benzo[d]isothiazol-3-amine (79) as one of the advanced intermediate for this route. 5 - (2-chloro ethyl) – 6 – chloro oxindole (61) was reacted with pthalimide (83) in the presence of potassium carbonate in dimethyl formamide media produced pthalimido protected derivative of 2-(2-(6-chloro-2-oxoindolin-5-yl)ethyl)isoindoline-1,3-dione (82). The resulted protected compound was reacted with aqueous monomethylamine to produce another advanced intermediate 5 - (2-amino ethyl) – 6 – chloro oxindole (80). The condensation of these advanced synthons produced the targeted compound, Ziprasidone (24) with satisfactory yield and purity.
Both these two advanced intermediates 79 and 80 along with their precursors 81 and 82 respectively are new intermediate compounds to the best of our knowledge for the preparation of Ziprasidone. Alternative method of scheme 3.13 has been systematically designed by involving the use of Gabriel synthesis mechanism for the preparation of primary alkyl amine. We have successfully synthesized 5-(2-aminoethyl)-6-chloro oxindole (80) with good purity and was fully characterized by its spectral data. Our few attempts in the isolation of bis dichloro intermediate (79) was unsuccessful. The resulted residual reaction mass from the
chlorination of diol was used as such in the condensation reaction to provide the Ziprasidone with reasonably good yield.

3.5.1 Synthesis of 2-(2-(6-chloro-2-oxoindolin-5-yl)ethyl)isoindoline-1,3-dione (82)

A solution containing 61 in dimethylformamide was added to the reaction mass containing potassium salt of phthalimide in dimethyl formamide. After systematic workup of the reaction, it was afforded N-alkylated pthalimide 82 (scheme 3.14) with around 98.0% purity. The resulted compound was characterized by IR, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and Mass spectral data.

Scheme 3.14

The IR spectrum (Fig.3.11) of 82 showed characteristic two carbonyl absorptions and broad NH absorption at 1715 cm\(^{-1}\), 1773 cm\(^{-1}\) and 3444 cm\(^{-1}\) respectively. The \textsuperscript{1}H NMR spectrum (Fig.3.12) displayed four pthalimido aromatic protons as multiplet at \(\delta\) 7.65-7.95 and two oxoindoline aromatic protons appeared as singlets at \(\delta\) 6.85 and \(\delta\) 7.05 respectively. Two triplet signals appeared with two proton integration at \(\delta\) 3.95 and \(\delta\) 3.10 are attributed to 2 methylene groups, and oxoindoline methylene group protons appeared as singlet signal at \(\delta\) 3.40. The ES
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mass spectrum (Fig.3.13) displayed a protonated molecular ion peak at m/z 341.10 (M+1).

Fig.3.11: IR spectrum of 2-[2-(6-chloro-2-oxoindolin-5-yl)ethyl]isoindoline-1,3-dione (82)
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Fig. 3.12: $^1$H NMR spectrum of 2-(2-(6-chloro-2-oxoindolin-5-yl)ethyl)isoindoline-1,3-dione \([82]\)

Fig. 3.12a: $^{13}$C NMR spectrum of 2-(2-(6-chloro-2-oxoindolin-5-yl)ethyl)isoindoline-1,3-dione \([82]\)
3.5.2 Synthesis of 5-(2-amino ethyl)–6-chloro oxindole (80)

*N*-alkylated phthalimide 82 was conveniently hydrolyzed with aqueous monomethylamine at 45-50°C to give the new intermediate, primary alkyl amine 80. The resulted crude product was purified by recrystallization from acetone (scheme 3.15) and the compound was obtained as yellowish crystalline solid.

**Scheme 3.15**
The IR spectrum (Fig. 3.14) of 80 showed characteristic carbonyl and three NH absorptions at 1693 cm\(^{-1}\), 3168 cm\(^{-1}\), 3271 cm\(^{-1}\), and 3331 cm\(^{-1}\) respectively. The \(^1\)H NMR spectrum (Fig. 3.15) displayed two aromatic protons at \(\delta 7.18\) and \(\delta 6.82\) as a sharp singlet signals. Six methylene protons collectively appeared at \(\delta 2.65-2.80\) (br, 6H, CH\(_2\)). The mass spectrum (Fig. 3.16) displayed a protonated molecular ion peak at \(m/z 211\) (M+1) with positive segment polarity.

![Fig. 3.14: IR spectrum of 5-(2-amino ethyl)-6-chloro oxindole (80)]
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Fig. 3.15: $^1$H NMR spectrum of 5-(2-amino ethyl)-6-chloro oxindole [80]

Fig. 3.15a: $^{13}$C NMR spectrum of 5-(2-amino ethyl)-6-chloro oxindole [80]
3.5.3 Synthesis of 2,2'-(benzo[d]isothiazol-3-ylazanediyl)diethanol hydrochloride (81)

3-Chloro-1, 2-benzisothiazole (78) was reacted with diethanol amine in \textit{n}-butanol at reflux temperature for about 24 hours. The resulting freebase was converted to its hydrochloride salt by treating with isopropyl alcohol containing hydrochloric acid. The targeted intermediate compound was resulted in light yellow colored crystalline solid (scheme 3.16).

\textbf{Scheme 3.16}
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The IR spectrum (Fig.3.17) of 81 showed characteristic broad OH absorption at 3422 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.3.18) displayed four aromatic protons at \(\delta\) 7.75-7.80 (dd, 2H Ar-H), 7.55-7.70 (t, 1H, Ar-H), 7.40-7.50 (t, 1H, Ar-H), and 8 methylene group protons appeared at \(\delta\) 3.70-3.80 (t, 2H, CH\(_2\)), 3.20-3.30 (br, 4H, CH\(_2\)) and 3.05-3.15 (t, 2H, CH\(_2\)). The ES mass spectrum (Fig.3.19) displayed a protonated molecular ion peak at m/z 239 (M+1).
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Fig. 3.18: $^1\text{H}$ NMR spectrum of 2,2'-(benzo[d]isothiazol-3-ylazanediyl)diethanol hydrochloride [S1]

Fig. 3.19: Mass spectrum of 2,2'-(benzo[d]isothiazol-3-ylazanediyl)diethanol hydrochloride [S1]
3.5.4 Synthesis of Ziprasidone (24)

The hydrochloride salt of 81 was converted into its freebase and then treated with thionyl chloride in chloroform at 50-60°C to afford the corresponding bis chloro derivative 79 (scheme 3.17). The residual crude mass of dichloro derivative as such reacted with oxindole derivative (80) in the presence of sodium hydride in DMF at 10-15°C and after systematic workup resulted crude Ziprasidone (24). The crude compound was purified in a mixture of methanol and chloroform to get ICH grade purity of 24. The resulted compound was fully characterized by its spectral data and also compared with an authentic sample.

Scheme 3.17 (Method C)

3.6: Related compounds or impurities of Ziprasidone

As we have already discussed in our previous chapters about the importance of related compounds for drug substances and also as a part of regulatory requirement, one should satisfy with the specified content
of related compounds listed in pharmacopoeia in the targeted drug substances. Accordingly we have systematically designed to provide processes for the preparation of three listed related compounds involving simple reaction conditions. Apart from this, the HPLC analysis of Ziprasidone \((24)\) showed an impurity peak around 0.10% level. To identify the molecular weight of the respective impurity, Liquid Chromatographic-Mass Spectrometry (LC-MS) was performed. From the molecular weight information, extensive study was undertaken to synthesize the identified process impurity. Finally, three of pharmacopieal listed impurities, a process related impurity were synthesized and characterized by their respective spectral analysis (Mass, \(^1\)H NMR, and IR). Based on the spectral data, these impurities were assigned as 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindoline-2,3-dione \((84)\), 2-(2-amino-5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-4-chlorophenyl)acetic acid \((85)\), 3-(benzo[d]isothiazol-3-yl)-5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one \((86)\) and 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloro-3-(propan-2-ylidene)indolin-2-one\(^{66}\) \((87)\).

### 3.6.1: Preparation of Related compound \((84)\)

The impurity compound dione \((84)\) was observed in very trace level in the crude product of Ziprasidone and its formation could be tentatively attributed to possible aerial oxidation of indolinone moiety.
Selenium dioxide is known to be a good oxidizing agent for the preparation of cyclohexane dione compounds, by following the characteristic feature of this reagent, compound 84 was synthesized by oxidizing the indolin-2-one ring of Ziprasidone in the presence of toluene (scheme 3.18).

Scheme 3.18

In the IR spectrum (Fig.3.20) two sharp CO signals appeared at 1729 cm$^{-1}$ and 1743 cm$^{-1}$ along with the broad amide NH absorption at 3426 cm$^{-1}$. The $^1$H NMR spectrum (Fig.3.21) displayed sharp amide proton signal at $\delta$ 11.25. Six aromatic protons appeared at $\delta$ 8.10-8.20 (m, 2H, Ar-H), $\delta$ 7.50-7.70 (m, 2H, Ar-H), $\delta$ 7.40-7.50 (m, 1H, Ar-H) and $\delta$ 7.00 (s, 1H, Ar-H). Methylene protons appeared at $\delta$ 3.60-4.00 (m, 4H, CH$_2$) and 3.00-3.50 (m, 8H, CH$_2$). The ESI-MS spectrum of 84 (Fig.3.22) displayed a molecular ion at $m/z$ 425 with negative segment polarity. This spectral data is consistent with the structure of 84.
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Fig. 3.20: IR spectrum of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethy1)-6-chloroindoline-2,3-dione [84]

Fig. 3.21: 'H NMR spectrum of 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethy1)-6-chloroindoline-2,3-dione [84]
3.6.2: Preparation of Related Compound (85)

In scheme 3.12 the condensation of compounds 77 and 78 in presence of base also results the generation of acid impurity 85 due to cleavage of indolin-2-one ring in small quantity. The compound 85 was easily synthesized by hydrolysis of Ziprasidone with caustic lye at the reflux temperature (scheme 3.19).

Scheme 3.19
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The IR spectrum (Fig.3.23) displayed broad hydroxyl signal of carboxylic acid in the range of 3400 - 2600 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.3.24) displayed six aromatic protons at \(\delta\) 8.05-8.15 (dd, 2H, \(J=4.4, 7.6\) Ar-H), 7.50-7.60 (t, 1H, Ar-H), 7.40-7.50 (t, 1H, Ar-H), 6.85 (s, 1H, Ar-H) and 6.65 (s, 1H, Ar-H). Aliphatic methylene protons appeared at \(\delta\) 3.35-3.60 (br, 6H, CH\(_2\)), 3.05 (s, 2H, CH\(_2\)), 2.60-2.80 (m, 2H, CH\(_2\)), 2.45-2.55 (br, 4H, CH\(_2\)). The ESI-MS spectrum of \(\textbf{85}\) (Fig.3.25) displayed a protonated molecular ion at 431 \(m/z\) with positive segment polarity. This spectral data confirms the assigned structure.

![Fig.3.23: IR spectrum of 2-(2-amino-5-|2|4-[benzo[d]isothiazol-3-yl]piperazin-1-yl)ethyl]-4-chlorophenyl|acetic acid (85)](image-url)
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Fig. 3.24: $^1$H NMR spectrum of 2-(2-amino-5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-4-chlorophenyl)acetic acid (85)

Fig. 3.26: Mass spectrum of 2-(2-amino-5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-4-chlorophenyl)acetic acid (85)
3.6.3: Preparation of Related Compound (86)

In scheme 3.12, during the synthesis of 24, the presence of excessive moles of compound 78 resulted in dimer impurity 86 due to condensation with the final product of Ziprasidone in the presence of basic conditions. Compound 86 was conveniently synthesized by condensing the compound of formula 78 with Ziprasidone in dimethyl formamide and in the presence of potassium carbonate (Scheme 3.20).

Scheme 3.20

In the IR spectrum of 86 (Fig.3.26), one sharp NH signal appeared at 3249 cm\(^{-1}\) along with the C=O stretching signal at 1691 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.3.27) displayed ten aromatic protons at \(\delta\) 8.05-8.10 (m, 3H, Ar-H), \(\delta\) 7.90 - 8.00 (d, 1H, Ar-H), \(\delta\) 7.55-7.60 (t, 1H, Ar-H), \(\delta\) 7.35-7.45 (m, 4H, Ar-H), \(\delta\) 7.20 (s, 1H, Ar-H) and amide NH at \(\delta\) 9.45 (s, 1H). Aliphatic methylene protons appeared at \(\delta\) 3.45-3.60 (br, 4H, CH\(_2\)), 2.95 (t, 2H, CH\(_2\)), 2.70-2.75 (s, 1H, CH\(_2\)), 2.60-2.65 (t, 2H, \(J=8.0\), CH\(_2\)), 2.45-2.55 (br, 4H, CH\(_2\)). The electro spray mass spectrum (Fig.3.28) displayed a protonated molecular ion at \(m/z\) 546.
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Fig. 3.26: IR spectrum of 3-(benzo[d]isothiazol-3-yl)-5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (86)

Fig. 3.27: 'H NMR spectrum of 3-(benzo[d]isothiazol-3-yl)-5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (86)
3.6.4: Preparation of Related Compound (87)

The related compound 87 formation could be attributed due to possible side reaction between Ziprasidone and acetone in the presence of acidic medium. Compound 87 was synthesized by treating Ziprasidone 24 with acetone in presence of acetic acid (Scheme 3.21).

Scheme 3.21

The IR spectrum (Fig.3.29) displayed NH signal at 3431 cm\(^{-1}\), strong carbonyl absorption at 1694 cm\(^{-1}\), whilst \(^1\)H NMR spectrum
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(Fig.3.30) displayed six aromatic protons at δ 8.10-8.20 (m, 2H, Ar-H), δ 7.60-7.65 (m, 2H, Ar-H), δ 7.45-7.50 (t, 1H, Ar-H) and 6.95 (s, 1H, Ar-H). The exchangeable proton observed at δ 10.60 (s, 1NH). Piperazine protons displayed between δ 3.15-3.45 (br, 8H, CH2). Gem methyl groups substituted at olefinic carbon appeared as a sharp signal at δ 2.55 and two methylene protons appeared at δ 2.35. The ESI-Mass spectrum (Fig.3.31) displayed M+1 ion at m/z 453. This spectral data is matching with the structure of 87.

Fig.3.29: IR spectrum of 5-{2-[4-([benzo[d]isothiazol-3-yl]piperazin-1-yl)ethyl]-6-chloro-3-{propan-2-ylidene}indolin-2-enc (87)
Fig. 3.30: $^1$H NMR spectrum of 5-{2-[4-(benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloro-3-(propan-2-ylidene)indolin-2-one (87)

Fig. 3.31: Mass spectrum of 5-{2-[4-(benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloro-3-(propan-2-ylidene)indolin-2-one (87)
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3.7. Conclusions

In conclusion, we have provided useful and new scalable alternate processes for the preparation of 5-(2-(4-(1, 2-benzisothiozole-3-yl) 1-piperazinyl) ethyl) - 6- chloro-1, 3-dihydro-2H-indole-2-one, commonly known as Ziprasidone (24). Perhaps, it may also be emphasized that compounds 77, 80, 81 and 82 are reported herewithin by this alternate process for the first time in the literature. Apart from this, we have also provided method for synthesis for four process related compounds of Ziprasidone.

3.8: Experimental section

Preparation of 60 from 59: To a mixture of aluminum chloride (30.0 g, 0.225 moles), methylene chloride (50.0 mL) was added 59 (10.0 g, 0.059 moles) at 0-5°C. Subsequently, chloroacetyl chloride (11.0 g, 0.097 moles) was added at 25-35°C, followed by heating to reflux and stirred till the reaction completion. The reaction mass was decomposed into a mixture of ice and HCl. The precipitated solid was filtered, washed appropriately with water and dried. The resultant compound was recrystallised from acetic acid to afford compound 60 (12.0 g, 83.3%, HPLC purity: 99.2%).

Preparation of 76 by condensation of 62 with 60: To a stirred solution of 62 (8.9 g, 0.04 mol) in cyclohexane (100.0 mL), sodium carbonate (8.5 g, 0.08 mol), sodium iodide (0.6 g, 0.004 mol), tetrabutyl
ammonium bromide (2.6 g, 0.008 mol), compound 60 (10.0 g, 0.041 mol) was added sequentially at ambient temperature. The resulting mixture was slowly heated to reflux and stirred for reaction completion. Water (100.0 mL) was added to the reaction mixture at ambient temperature and stirred to isolate the title compound. The separated solid was filtered, washed with water, methanol and dried at 60-65°C to give title compound 76 (15.0 g, 88.0%, HPLC Purity: 98.4%). IR (cm⁻¹): 1732 (C=O), 1716 (C=O) and 3437 (amide NH); ¹H NMR (DMSO-d₆, δ ppm): 3.31 (br, 8H, CH₂), 3.57, (s, 2H, CH₂), 3.83 (s, 2H, CH₂), 6.92 (s, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 8.05-8.10 (d, 2H, J=9.2, Ar-H), 10.93 (s, 1H, N-H); Mass: 427 (M+1); C H N Analysis calcd. for C₂₁H₁₉ClN₄O₂S: C, 59.08; H, 4.49; N, 13.12; Found: C, 59.11; H, 4.45; N, 13.09.

**Preparation of compound 77:** To a stirred mixture of 61 (5.0 g, 0.022 moles) in tertiary butanol (50.0 mL), piperazine (9.0 g, 0.105 moles) was added in three different portions at reflux temperature. The reaction mass was stirred at reflux temperature for about 6 hours to complete the reaction. Distilled off tertiary butanol completely, water (100.0 mL) was added to the residual mass to dissolve and extracted with dichloromethane (50x2 mL). The dichloromethane layer was washed with water and distilled off completely. The residual mass was triturated with hexane (30 mL) to separate the solid. The separated solid was filtered off, washed with hexane (10 mL) and dried at room temperature to give the
desired compound **77** (Yield: 4.0 g, 65.2%, Purity: 95.0%). IR (cm\(^{-1}\)): 1716 (C=O), 3317 (NH) 3410 (NH); \(^1\)H NMR (DMSO-d\(_6\), \(\delta\) ppm): 2.30-2.45, (m, 6H, CH\(_2\)), 2.65-2.75, (m, 6H, CH\(_2\)), 3.40-3.45 (s, 2H, CH\(_2\)), 6.80 (s, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 10.35-10.45 (s, 1H, N-H); Mass: 280 (M+1); C H N Analysis calcd. for C\(_{14}\)H\(_{18}\)ClN\(_3\)O: C, 60.10; H, 6.49; N, 15.02; Found: C, 60.05; H, 6.44; N, 15.08.

**Preparation of compound 82:** To a mixture of phthalimide (6.8 g, 0.046 moles) and dimethyl formamide (20.0 mL) was added anhydrous potassium carbonate (6.8 g, 0.049 mol) and stirred at 60-70°C for about 1-2 hours. The solution of **61** (10.0 g, 0.043 moles) prepared in dimethyl formamide (20.0 mL) was added to the reaction mass and heated to 100-120°C to complete the reaction. The mass was cooled to room temperature and decomposed into chilled water. The reaction mixture was extracted with ethyl acetate (100x3 mL) and the combined organic layer was washed with water (50.0 mL). The solvent was distilled off, residual mass was triturated with hexane, filtered off the solid and dried at 70-80°C to give title compound. The crude compound is recrystallized from methanol (8.0 g, 53.5%, HPLC Purity: 97.4%). IR (cm\(^{-1}\)): 1715 (amide C=O), 1773 (amide C=O) and NH signal at 3444 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), \(\delta\) ppm): 3.10 (t, 2H, CH\(_2\)), 3.40 (s, 2H, CH\(_2\)) 3.95 (t, 2H, CH\(_2\)), 6.85 (s, Ar-H), 7.05 (s, Ar-H), 7.65-7.95 (m, 4H, Ar-H); \(^{13}\)C NMR (200 MHz, DMSO-d\(_6\), \(\delta\) ppm): 31.4, 35.4, 37.8, 123.1, 125.3, 126.9, 128.2, 131.5, 134.5, 143.5, 167.7, 176.3 MS: m/z 341 (M+1); C H N Analysis
calcd. for $\text{C}_{18}\text{H}_{13}\text{ClN}_2\text{O}_3$: C, 63.44; H, 3.85; N, 8.22; Found: C, 63.48; H, 3.82; N, 8.26.

**Preparation of 80 from 82:** Compound **82** (5.0 g, 0.0147), 40% aqueous monomethylamine solution (20.0 mL) and water (20.0 mL) were stirred at 45-50°C for about 60-90 minutes. Water (25.0 mL) was added and extracted into dichloromethane (50x3 mL). The dichloromethane was distilled completely and the residual mass was triturated with hexane. The resulting crude compound was purified from acetone to get **80** (1.9 g, 61.5%, HPLC Purity: 98.25%). IR (cm$^{-1}$): 1693 (amide C=O), 3168 (NH), 3271 (NH) and 3331 (NH); $^1$H NMR (DMSO-$d_6$, δ ppm): 2.65-2.80 (br, 6H, CH$_2$), 6.82 (s, Ar-H), 7.18 (s, Ar-H); $^{13}$C NMR (200 MHz, DMSO-$d_6$, δ ppm): 25.0, 40.7, 41.9, 126.0, 126.8, 129.7, 131.9, 143.1, 176.3 MS: m/z 211 (M+1); C H N Analysis calcd. for $\text{C}_{10}\text{H}_{11}\text{ClN}_2\text{O}$: C, 57.01; H, 5.26; N, 13.30; Found: C, 57.08; H, 5.31; N, 13.28.

**Preparation of 81:** The compound **78** (5.0 g, 0.0294 moles), diethanol amine (5.0 g, 0.035 moles) and n-butanol (50.0 mL) were heated to reflux overnight to complete the reaction. n-Butanol was distilled off completely under vacuum and the residual mass was dissolved in isopropyl alcohol (10.0 mL). The reaction mass was cooled to 0-5°C, isopropyl alcohol containing HCl was added till pH of the mass attains to 2.0 and stirred the mass for 15 minutes. The light yellow colored solid was filtered, washed with chilled isopropyl alcohol and dried at 25-35°C to afford compound **81** (6.5 g, 81.2%, HPLC Purity: 98.5%). IR (cm$^{-1}$):
3422 (OH); $^1$H NMR (DMSO-d$_6$, $\delta$ ppm): 3.05-3.15 (t, 2H, CH$_2$), 3.20-3.30 (br, 4H, CH$_2$), 3.70-3.80 (t, 2H, CH$_2$), 7.40-7.50 (t, 1H, Ar-H), 7.55-7.70 (t, 1H, Ar-H), 7.75-7.80 (dd, 2H Ar-H), MS: $m/z$ 239 (M+1); C H N Analysis calcd. for C$_{11}$H$_{14}$N$_2$O$_2$S: C, 55.44; H, 5.92; N, 11.76; Found: C, 55.49; H, 5.87; N, 11.78.

**Preparation of compound 24-Method A:** Triethyl silane (10.0 g, 0.086 moles) was added slowly to the reaction mixture containing 76 (10.0 g, 0.024 moles) and methane sulfinic acid (20.0 g, 0.20 moles) at below 25°C. Heated the reaction mass to 50-55°C and stirred for reaction completion. The reaction mass cooled to 0-5°C and stirred for 1 hour to isolate the compound. The isolated compound was filtered, washed with water (50.0 mL). The wet compound further slurry washed with water (100.0 mL), filtered, and dried at 60-65°C. The resultant crude product was purified from a mixture of methanol and acetone (Yield: 7.5 g, 76%, Purity: 99.8%).

**Method-B:** To stirred mixture of 77 (3.0 g, 0.010 moles), sodium carbonate (1.2 g, 0.011 moles) and tertiary butanol (10 mL) was added a solution containing 78 (1.7 g, 0.010 moles) in tertiary butanol (10 mL). The reaction mass slowly heated to reflux and maintained for 20-22 hours for reaction completion. Tertiary butanol was concentrated under vacuum and water (50.0 mL) was added and stirred for 30 minutes. The solid was filtered, washed with water and dried at 60-65°C. The resultant
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crude compound was further recrystallized from a mixture of methanol and acetone (Yield: 3.3 g, 80.0%, HPLC Purity: 99.2%).

**Method-C:** The compound \( \textbf{81} \) (2.0 g, 0.007 mol) was taken in water (20.0 mL) and pH adjusted to 10.0 with 10% aqueous sodium hydroxide solution, and the liberated free base extracted into chloroform (50 mL). The chloroform layer was dried over sodium sulfate, thionyl chloride (3.0 g, 0.025 mol) was added and stirred at 50-60°C till the reaction completion to get chloro derivative. The organic layer concentrated under vacuum and the residual mass dissolved in dimethyl formamide (10.0 ml). In another flask, compound \( \textbf{80} \) (4.0 g, 0.0190 moles), dimethyl formamide (10 ml) was taken, cooled to 0-5°C and 60% NaH (2.3 g, 0.057 moles) was added in three different portions and stirred for 30 minutes. The above dimethyl formamide solution containing chloro derivative was added slowly at 0-5°C. The temperature of the reaction mass was raised to 10-15°C and stirred for reaction completion. Methanol (10.0 mL) was added to decompose excess sodium hydride and stirred at room temperature for 10-15 minutes. Water (100.0 mL) was added and stirred for solid separation. The separated solid was filtered, washed with water, further slurry washed with water and dried. The crude compound was recrystallized from a mixture of methanol and chloroform (Yield: 2.0 g, 72.0%, HPLC Purity: 99.12%). IR (cm\(^{-1}\)): 1714 (C=O), and 3420 (amide NH); \(^1\)H NMR (DMSO-d\(_6\), \(\delta\) ppm): 3.21, (m, 2H, \(\text{CH}_2\)), 3.27 (d, 2H, \(\text{CH}_2\)), 3.35, (d, 2H, \(\text{CH}_2\)), 3.54 (m, 2H, \(\text{CH}_2\)), 3.56 (m,
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2H, CH₂), 3.70 (m, 2H, CH₂), 4.10 (d, 2H, J=12.8, CH₂), 6.95 (s, 1H, Ar-H), 7.15 s, 1H, Ar-H), 7.48 (t, 1H, J=8.0, Ar-H), 7.68 (t, 1H, J=8.0, Ar-H), 8.11 (d, 1H, J=8.0, Ar-H), 8.15 (d, 1H, J=8.4, Ar-H), 10.55 (s, 1H, N-H);

¹³C NMR (200 MHz, CDCl₃, δ ppm): 26.9, 35.3, 46.5, 50.6, 54.9, 109.7, 121.2, 124.0, 124.6, 126.4, 126.7, 126.9, 128.1, 131.4, 144.0, 152.0, 162.2, 176.1 Mass: 413(M+1); C H N Analysis calcd. for C₂₁H₂₁ClN₄O₂S: C, 61.08; H, 5.13; N, 13.57; Found: C, 61.11; H, 5.18; N, 13.52.

Preparation of Related Compound 84: Compound 24 (4.0 g, 0.009 moles) was taken in toluene (50.0 mL) and selenium dioxide (2.8 g, 0.025 moles) was added under stirring. The resulting reaction mixture was heated to 60-65°C and stirred for reaction completion. The reaction mass was cooled to 20-25°C and decanted toluene layer. The residual gummy mass was taken in methanol (80.0 mL), heated to reflux and stirred for 30 minutes. The reaction mixture was cooled to 20-25°C, filtered the material, washed with methanol (20 mL) and dried at 50°C (Yield: 2.5 g, 65.7%, HPLC Purity: 96.5%). IR (cm⁻¹): 1729 (amide C=O), 1743 (amide C=O) and 3426 (amide NH); ¹H NMR (DMSO-d₆, δ ppm): 3.00-3.50 (m, 8H, CH₂), 3.60-4.00 (m, 4H, CH₂), 7.00 (s, 1H, Ar-H), 7.40-7.50 (s, 1H, Ar-H), 7.50-7.70 (m, 2H, Ar-H), 8.10-8.20 (m, 2H, Ar-H), 11.25 (s, 1H, NH); MS: m/z 425 (M-1); C H N Analysis calcd. for C₂₁H₁₉ClN₄O₂S: C, 59.08; H, 4.49; N, 13.12; Found: C, 59.12; H, 4.53; N, 13.16.
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**Preparation of Related Compound 85**: The reaction mixture containing 24 (4.0 g, 0.009 moles) and 50% aqueous sodium hydroxide solution (15.0 mL, 0.187 moles) was heated to reflux and stirred for reaction completion. The resultant reaction mixture was cooled to 25-35°C and stirred for 30 minutes. Water (100.0 mL) was added and stirred to isolate the solid. The separated solid was filtered, washed with water (30.0 mL) and dried at 80°C (Yield: 2.5 g, 65.0%, HPLC Purity: 98.5%). IR (cm⁻¹): 1652 (acid C=O) and 2600-3400 (acid OH); ¹H NMR (DMSO-d₆, δ ppm): 2.45-2.55 (br, 4H, CH₂), 2.60-2.80 (m, 2H, CH₂), 3.05 (s, 2H, CH₂), 3.35-3.60 (br, 6H, CH₂), 6.65 (s, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 7.40-7.50 (m, 1H, Ar-H), 7.50-7.60 (m, 1H, Ar-H), 8.05-8.15 (dd, 2H, J=4.4, 7.6, Ar-H), 11; MS: m/z 431 (M+1); C H N Analysis calcd. for C₂₁H₂₃ClN₄O₂S: C, 58.53; H, 5.38; N, 13.00; Found: C, 58.69; H, 5.42; N, 13.20.

**Preparation of Related Compound 86**: Compound 24 (10.0 g, 0.024 moles) and compound 78 (4.1 g, 0.024 mol) was taken into dimethyl formamide (80 mL) and potassium carbonate (13.0 g, 0.094 moles) was added slowly in portions. The reaction mixture was stirred at 25-35°C till completion of the reaction. The separated solid was filtered off, washed twice with water and dried 60°C (Yield: 8.0 g, 67.0%). IR (cm⁻¹): 1691 (C=O) and 3249 (amide NH); ¹H NMR (DMSO-d₆, δ ppm): 2.45-2.55 (br, 4H, CH₂), 2.60-2.65 (t, 2H, J=8.0, CH₂), 2.70-2.75 (s, 1H, CH₂), 2.95 (t, 2H, CH₂), 3.45-3.60 (br, 4H, CH₂), 7.20 (s, 1H, Ar-H), 7.35-7.45 (m,
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4H, Ar-H), 7.55-7.60 (m, 1H, Ar-H), 7.90-8.00 (m, 1H, Ar-H), 8.05-8.10 (m, 3H, Ar-H) and amide NH at 9.45 (s, 1H); MS: m/z 546 (M+1); C H N Analysis calcd. for C_{28}H_{24}ClN_{5}O_{2}: C, 61.58; H, 4.43; N, 12.82; Found: C, 61.63; H, 4.42; N, 12.86.

Preparation of Related Compound 87: The mixture containing compound 24 (5.0 g, 0.012 mol) and acetic acid (15.0 mL) was stirred at ambient temperature to get the clear solution. To this solution, acetone (50.0 mL) was added and stirred for 10-12 hours. The resulting solution was filtered and to the filtrate dry HCl gas was purged at below 10°C. The reaction mass was stirred to separate the solid. The separated solid was filtered, washed with water 3 times (10x3 mL) and acetone (10.0 mL). The product was dried at 70°C and purified by recrystallization from formic acid to get the hydrochloride salt of compound 87 (Yield: 2.8 g, 52.0%, HPLC Purity: 98.2%) IR (cm\(^{-1}\)): 1694 (C=O) and 3431 (amide NH); \(^1\)H NMR (DMSO-d\(_6\), δ ppm): 2.35 (s, 4H, CH\(_2\)), 2.55 (s, 6H, CH\(_3\)), 3.15-3.45 (br, 8H,CH\(_2\)), 6.95 (s, 1H, Ar-H), 7.45-7.50 (m, 1H, Ar-H), 7.60-7.65 (m, 2H, Ar-H), 8.10-8.20 (m, 2H, Ar-H), and amide NH at 10.60 (s, 1H); MS: m/z 453 (M+1); C H N Analysis calcd. for C_{24}H_{25}ClN_{4}O: C, 63.63; H, 5.56; N, 12.37; Found: C, 63.69; H, 5.48; N, 12.44.