CHAPTER-4

NEW ALTERNATE SYNTHETIC APPROACH TO PREPARE SERTINDOLE, PREPARATION AND CHARACTERIZATION OF ITS RELATED SUBSTANCES
CHAPTER-4: New alternate Synthetic Approach to Prepare Sertindole, Preparation and Characterization of its Related substances

4.1: Introduction

Sertindole is an anti-psychotic drug substance which affects serotonin 5-HT₂, dopamine D₂, and α₁-adrenergic receptors. It acts as a 5H₂ receptor antagonist and has indicative effects in the treatment of cognitive disorders, hypertension, drug abuse and anxiety. It has no sedative side effects and was mainly used to treat schizophrenia.

Sertindole was approved by USFDA in September, 2008 as oral dosage tablets. It is a white crystalline powder, insoluble in water. It is chemically described as 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl] ethyl]-2-imidazolidinone and assigned the following structure.

![Structure of Sertindole](image-url)
### Table 4.1: Product details

<table>
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<th>Name of the drug</th>
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<tr>
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<td>Lundbeck</td>
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<td>Marketed by</td>
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<td>Melting point</td>
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</tr>
<tr>
<td>Dosage details</td>
<td>Oral dosage</td>
</tr>
<tr>
<td>Approved</td>
<td>September 15, 2008</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Serdolect ; Serlect</td>
</tr>
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<td>Therapeutic category</td>
<td>Anti-psychotic</td>
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![Structure](image)

<table>
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<th>Chemical Name</th>
<th>1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl] ethyl]- 2-imidazolidinone</th>
</tr>
</thead>
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<tr>
<td>Molecular formula</td>
<td>C_{24} H_{26}ClFN_{4}O</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>440.94</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in Dimethyl sulphoxide</td>
</tr>
</tbody>
</table>
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4.2: Reported Synthetic Schemes of Sertindole

The first reported synthesis for Sertindole by Perregaard Jens Kristianet al\textsuperscript{76} utilizes condensation of 5-chloroindole 110 with 4-fluoro bromobenzene 111 using copper bromide as catalyst to give 5-chloro-1-(4-fluoro phenyl)-indole 112, which upon further reaction with 4-piperidinonone hydrochloride monohydrate 113, in the presence of trifluoroacetic acid and acetic acid mixture affords 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrochloride 114. Reduction of 114 using molecular hydrogen and platinum oxide as catalyst affords 5-chloro-1-(4-fluorophenyl)-3-(4-piperidinyl)-1H-indole 115. Finally, reaction of 115 with 1-(2-chloroethyl) imidazolidinone 116, in the presence of base, affords Sertindole 16 (scheme 4.1).

Scheme 4.1
Jens Kristian Perregaard et al., described alternate schemes for the synthesis of compound 16 as represented by schemes 4.2, 4.3, 4.4 and 4.5. However, the reference doesn’t disclose the experimental conditions for any of the synthetic process.

**Scheme 4.2**
Scheme 4.3

\[
\text{Cl-Indole (112)} + \text{Amine (117)} \rightarrow \text{Product (119)}
\]

Scheme 4.4

\[
\text{Indole (111)} + \text{Amine (114)} \rightarrow \text{Product (115)}
\]
Bech Sommer Michael *et al*, describes a process (scheme 4.6)\(^{77}\) which involves reacting an alkali metal salts of 2,5-dichlorobenzoic acid\(^ {122} \) and N-(4-fluorophenyl)glycine\(^ {123} \), in the presence of copper catalyst and under alkaline conditions to give N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine\(^ {124}\). Cyclisation of compound \(124\) in the presence of acetic anhydride and sodium acetate afforded 3-acetoxy-indole\(^ {125}\), which on further reduction and subsequent removal of water afforded 5-chloro-1-(4-fluorophenyl)indole\(^ {126}\). Condensation of compound \(126\) with 4-piperidinone \(113\), in the presence of a mixture of acetic acid and mineral acid afforded 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrochloride \(114\). Reduction of \(114\) afforded \(115\), which upon further condensation with \(116\), in the presence of base, afforded Sertindole\(^ {16}\). (scheme 4.6). Alternatively, Sertindole was also prepared by condensation of compound \(114\) with
compound 116 in the presence of base to get compound 119, followed by reduction.

**Scheme 4.6**

\[
\begin{align*}
\text{Cl-COOM}_1 & + \text{NHCH}_2\text{COOM}_2 \\
\text{Cl-COOM}_1 & \text{Cl} \\
\text{M1,M2} = \text{alkali metal} \\
\end{align*}
\]
4.2.1: Summary of reported synthetic schemes

Based on the literature review, it is evident that the scientists mainly utilized the following three synthons 112, 113 and 116 or their derivatives\textsuperscript{78} to prepare Sertindole in various synthetic pathways. In an alternative methodology, Sertindole was prepared by reduction of indolone derivative 121.

In general, compounds 113 and 116 are commercially available while compound 112 was prepared by coupling of 110 and 111 in the presence of copper catalyst in polar solvent.
As can be seen from the structure, Sertindole was synthesized by reacting 112 with 113 under acidic conditions followed by reduction and condensation with 116. Alternately, 113 and 116 were condensed first followed by reaction with 112 and on subsequent reduction to form Sertindole. In one of the possible routes, reduction of advance intermediate 121 gives the title compound 16.

4.3: Present work

As described above, though there were good number of synthetic routes available for the preparation of Sertindole, these processes suffers with certain disadvantages in terms of use of hazardous raw materials for example trifluoroacetic acid, higher dilutions, use of costly catalysts, use of costly raw materials, low yields, formation of impurities and environmental reasons. The process disadvantages of known routes motivated us to design an alternate route for the preparation of Sertindole, which has become basis for the present work.
4.3.1: Results and Discussion - Retro synthetic pathway for Sertindole

Scheme 4.7

Based on retro synthetic analysis of Sertindole (scheme 4.7), the compounds 1-(2-hydroxyethyl) piperidin-4-one 127 and 112 are considered as key starting materials for our present research work to get 2-(4-(5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl)-5,6-dihydropyridin-1-(2H)-yl)ethanol 128. Reduction of compound 128 afforded reduced
alcohol 129 which was activated as its mesyl derivative 130 by treating with methanesulphonyl chloride in the presence of base. Condensation of 130 with imidazolidin-2-one 131 in the presence of base affords title compound 16 in excellent yield. The starting material 127 was in turn prepared by reaction of piperidine-4-one 113 with 2-chloroethanol 126 in the presence of base.

4.3.2: *Synthesis of 1-(2-hydroxyethyl) piperidin-4-one (127)*

Condensation of compound 113 with 2-chloroethanol 126 (scheme 4.8) in the presence of anhydrous potassium carbonate as base and using methanol as solvent media at reflux temperature gave the desired compound 127 in excellent yield.

**Scheme 4.8**

![Scheme 4.8](image)

IR Spectrum (Fig. 4.1) of 127 exhibited a characteristic peaks for OH absorption at 3391 cm⁻¹ and C=O stretching at 1713 cm⁻¹. The ¹H NMR spectrum (Fig. 4.2) displayed methylene protons characteristic for 1,2-disubstituted ethylene at δ 2.60 (t, 2H), 3.62 (m, 2H) and piperidine methylene protons at δ 2.40 (t, 4H), 2.76 (t, 4H). The ES mass spectrum
(Fig. 4.3) displayed the required protonated molecular ion peak at m/z 144(M+H)^+. 

**Fig. 4.1: IR spectrum of 2-(1,4-dioxaspiro[4,5]deca-8-yl)ethanol (127)**

**Fig. 4.2: ^1H NMR spectrum of 2-(1,4-dioxaspiro[4,5]deca-8-yl)ethanol (127)**
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Fig. 4.2a: $^{13}$C NMR spectrum of 2-(1,4-dioxaspiro[4,5]dec-8-yl)ethanol (127)

Fig. 4.3: Mass spectrum of 2-(1,4-dioxaspiro[4,5]dec-8-yl)ethanol (127)
4.3.3: Synthesis of 2-(4-(5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl)-5,6-dihydropyridin-1-(2H)-yl)ethanol (128).

Compound 127 was reacted with (scheme 4.9) commercially available indole 112 in acidic conditions, at 95-100°C, for 1 hr to afford compound 128.

Scheme 4.9

IR Spectrum (Fig. 4.4) of 128 exhibited a broad signal at about 3212 cm⁻¹ corresponding to OH absorption and the absence of C=O stretching in the region of 1680-1740 cm⁻¹. The ¹H NMR spectrum (Fig. 4.5) displayed peaks typical of indole moiety at δ 7.89 (d, 1H), 7.32 (d, 1H), 7.24 (s, 1H), 7.17 (dd, 1H), besides four aromatic protons. The presence of five methylenes at δ 2.61 (m, 2H), 2.82 (t, 2H), 3.30 (q, 2H), 2.70 (t, 2H), δ 3.71 (t, 2H) and a tri-substituted methine at δ 6.18 (m, 1H) confirmed the condensation reaction, which was corroborated by its ES mass spectrum (Fig. 4.6) that displayed protonated molecular ion peak at m/z 371(M+H)⁺.
Fig. 4.4: IR Spectrum of 2-[4-(5-Chloro-1-[4-morpholino]-1H-indol-3-yl]-5,6-dihydropyridin-1-(2H)-yl]ethanol (128)

Fig. 4.5: $^1$H NMR Spectrum of 2-[4-(5-Chloro-1-[4-thiazolyl]-1H-indol-3-yl]-5,6-dihydropyridin-1-(2H)-yl]ethanol (128)
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Fig. 4.5a: $^{13}$C NMR Spectrum of 2-(4-S-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl)-5,6-dihydropyridin-1-[2H]-y ethanol (128)

Fig. 4.6: MS Spectrum of 2-(4-S-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl)-5,6-dihydropyridin-1-[2H]-y ethanol (128)
4.3.4: Synthesis of 2-(4-(5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl)-piperidin-1-yl) ethanol (129).

Platinum oxide catalyzed heterogeneous reduction of compound 128 (scheme 4.10) in methanol, using molecular hydrogen at room temperature for 12 hr afforded the corresponding reduced alcohol 129 in excellent yield. The aromatic halogens (F, Cl) remained completely inert under the hydrogenation conditions used.

**Scheme 4.10**

In the IR spectrum (Fig.4.7), the broad peak corresponding to hydroxy group appeared at 3204 cm\(^{-1}\) and C-Cl peak appears at 836 cm\(^{-1}\). The \(^1\)H-NMR Spectrum (Fig.4.8) displayed six methylenes in the aliphatic region and a methine at δ 2.75, indicating reduction of the double bond of the piperidinyl moiety, which was confirmed by the absence of methane protons in the region δ 5.5-6.5. The presence of only eight protons in the aromatic (unsaturation) region indicated that both the halogens remained intact during the hydrogenation.The ES mass
spectrum (Fig. 4.9) confirmed the reduction of the double bond as it displayed the protonated molecular ion peak at m/z 373(M+H)^+.

![IR Spectrum of 2-(S-Chloro-4-(4-fluorophenyl)-1H-indol-3-yl)-2H-pyridin-1-yl)-ethanol (22)](image1)

![^H NMR Spectrum of 2-(S-Chloro-1-4-(4-fluorophenyl)-1H-indol-3-yl)-2H-pyridin-1-yl)-ethanol (12)](image2)
Fig. 4.8: $^{13}$C NMR Spectrum of 2-[(5-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl)-piperdin-1-yl]-ethanol (129)

Fig. 4.9: Mass Spectrum of 2-[(5-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl)-piperdin-1-yl]-ethanol (129)
4.3.5: Synthesis of 2-(4-(5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl)-piperidin-1-yl) ethyl methanesulphonate (130).

Activation of alcohol 129(scheme 4.11) with methanesulphonyl chloride in the presence of triethyl amine, at room temperature afforded compound 130.

**Scheme 4.11**

In the IR spectrum (Fig.4.10), the peak corresponding to S=O appeared at 1151 cm\(^{-1}\) and observed absence of free OH at ~3200 cm\(^{-1}\).\(^1\)H-NMR Spectrum (Fig.4.11) displayed a three proton singlet of the mesyl group at \(\delta\)2.58, with concomitant downfield shift of ~0.15 ppm for the methylene at \(\delta\)3.65, indicating O-mesylation. It was corroborated by \(^{13}\)C NMR, that displayed characteristic mestyl methyl at \(\delta\)39.9. The ES mass spectrum (Fig.4.12) displayed protonated molecular ion peak at m/z 452(M+H).
Fig. 4.10: IR spectrum of 2-[[5-chloro-1-[4-fluorophenyl]-1H-indol-3-yl]-piperidin-1-yl]ethy methylsulphonate [130]

Fig. 4.11: 1H NMR spectrum of 2-[[5-chloro-1-[4-fluorophenyl]-1H-indol-3-yl]-piperidin-1-yl]ethy methylsulphonate [130]
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Fig. 4.11: $^{13}$C NMR spectrum of 2-(4-[(5-chloro-1-[4-fluorophenyl]-1H-indol-3-yl)piperidin-1-yl]ethyl methane sulphonate (130)

Fig. 4.12: Mass spectrum of 2-(4-[(5-chloro-1-[4-fluorophenyl]-1H-indol-3-yl)piperidin-1-yl]ethyl methane sulphonate (130)
4.3.6: Synthesis of Sertindole (16)

Condensation of mesyl derivative 130 (scheme 4.12) with imidazolidinone 131 in the presence of sodium hydrid in N,N-dimethyl formamide at room temperature for 14 hrs afforded sertindole 16. The crude was recrystallized from acetone to give title compound as a white crystalline powder. The spectral data was identical with that of authentic sample.

Scheme 4.12

The UV spectrum (Fig.4.13) of Sertindole (16) was recorded in methanol (conc=0.001% w/v) using Perkin-Elmer UV-VIS spectrophotometer model Lambda 35. It exhibited two peaks with maxima at λ 258.85 and 226.12 nm. The FT-IR spectrum (Fig.4.14) displayed peaks at 3235 cm\(^{-1}\) (N-H stretching), 1702 cm\(^{-1}\) (-C=O stretching), and 1275 cm\(^{-1}\) (aromatic C-N stretching). The \(^1\)H NMR spectrum (Fig.4.15) showed the absence of the O-mesityl’s methyl group indicating the SN\(_2\) displacement by the imidazolidinone 131. The aromatic region revealed characteristic peaks for indole moiety, besides four ortho coupled protons. It also
displayed the required eight methylenes and a methine in the aliphatic region, besides a broad peak for \(-\text{NH}-\) at δ 6.21. The $^{13}$C NMR confirmed the assigned structure, as it displayed the presence of imidazolidinone carbonyl at δ162.9 and four carbon aromatic coupling, due to the presence of fluorine atom. The presence of chlorine and fluorine atoms and the absence of mestyl moiety confirm that the halogens remained inert during the course of the displacement reaction. The ES mass spectrum (Fig.4.16) displayed protonated molecular ion at m/z 441 which corresponds to (M+H)$^+$. All the physical and spectral data were identical to those reported in literature for sertindole.
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Fig. 4.15a: $^1$H NMR Spectrum of 1-{5-[3-[(5-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl)]-1-piperidinyl]ethyl}-2-imidazolidinone [16]
4.4: Related Substances or impurities of Sertindole

The purity of Sertindole synthesized by above routes was analyzed by HPLC along with the authentic sample. Apart from the literature reported impurities,\textsuperscript{79-80} we identified seven new impurities which are possible in sertindole synthesis\textsuperscript{81}. The crude sample of sertindole was analyzed by LC-MS and based on the data impurities were identified. Finally all these impurities were synthesized and characterized. Based on the spectral data, these impurities were identified as \(1\text{-}[2\text{-}[4\text{-}[1\text{-}[\text{4-fluorophenyl}]\text{-}1\text{H-indol-3-yl}]\text{-}1\text{-piperidinyl}]}\text{ethyl}\]2\text{-}imidazolidinone 132, \(1\text{-}[2\text{-}[4\text{-}[\text{5-chloro]}\text{-}1\text{-}[\text{4-fluorophenyl}]\text{-}1\text{H-indol-3-yl}]\text{-}1,2,3,6\text{-tetrahydro-1-pyridyl}]}\text{ethyl}\]2\text{-}imidazolidinone 119, 1-[2-[4-[5-Chloro-1-(4-}
bromophenyl)-1H-indol-3-yl]-1-piperidinyl[ethyl]-2-imidazolidinone

\[ \text{133} \]

1-[2-[4-(5-Chloro-1-phenyl-1H-indol-3-yl]-1-piperidinyl[ethyl]-2-imidazolidinone]

\[ \text{134} \]

1-[2-[4-[5-Bromo-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl[ethyl]-2-imidazolidinone]

\[ \text{135} \]

5-Chloro-1-(4-fluorophenyl)-3-{1,1’-bis[2(2-imidazolidon-1-yl)ethyl]-piperidin-4-yl]-1H-indole

\[ \text{136} \]

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-oxo-1-piperidinyl[ethyl]-imidazolidin-2-one]

\[ \text{137} \]

4.4.1: Preparation of Related substance

This impurity is designated as des chloro impurity of sertindole. In the HPLC of crude sertindole, a minor impurity (< 0.1%) was present consistently and its mass from LC-MS was found to be 34 amu less than sertindole and it showed the lack of chlorine isotopic abundance. It was tentatively assigned to be des chloro analogue. The formation of this impurity was identified during the catalytic hydrogenation of indole 128. The impurity has to be controlled or removed at this stage only otherwise, the impurity when carried upto sertindole is difficult to remove at latter stage, without appreciable loss in the yields. A slurry of crude obtained from hydrogenation of 128 in methyl tertiary butyl ether removed the des-chloro impurity from indole 129. In order to quantify the corresponding impurity 132, in sertindole, the synthesis was carried out from indole 115.
The impurity 132 was synthesized (scheme 4.13) by palladium catalyzed hydrogenation of 115 to get des-chloro compound 138 which was further condensed with 116, under Finkelstein condition.

**Scheme 4.13**

![Scheme 4.13](image)

In the IR spectrum (Fig. 4.17) C=O signal appeared at 1681 cm\(^{-1}\) with a broad amide NH absorption at 3222 cm\(^{-1}\) and C-F stretch appeared at 1284 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig. 4.18) displayed the required eight methylenes and a methine proton at \(\delta\) 2.80, besides eight aromatic protons in the downfield region. The ES mass spectrum (Fig. 4.19) displayed a protonated molecular ion at m/z 407 which corresponds to (M+H)\(^+\), and the absence of chlorine isotopic abundance.
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Fig. 4.19: $^1$H NMR Spectrum of 1-[2-[4-[1-fluorophenyl]-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone [132]

Fig. 4.19a: $^{13}$C NMR Spectrum of 1-[2-[4-[1-fluorophenyl]-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone [132]
4.4.2: Preparation of Related substance 119

The LC-MS of crude sertindole revealed the presence of traces of impurity which had 2 amu less than sertindole and it was concluded that its origin may be from the incomplete hydrogenation of 128. During the reduction of 128 extended maintenance of reaction resulted in dehalogenated product 132, on the other hand, incomplete reduction afforded 129 contaminated with 128. This impure material on further condensation with 116 resulted in 16 contaminated with 119.

The impurity 119 was synthesized by condensation of 114 with 116 in the presence of base, at reflux temperature (scheme-4.14).
In the IR spectrum (Fig. 4.20) C=O signal appeared at 1687 cm\(^{-1}\) with a broad amide NH absorption at 3246 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig. 4.21) exhibited seven methylene protons in the aliphatic region and seven aromatic protons and a tri-substituted double bond in the down field region. Two peaks at δ6.17 and 6.22, each integrating for a proton assigned to –NH- and tri-substituted vinyl moiety confirmed the constitution of dihydro-sertindole 119. The ES mass spectrum (Fig. 4.22) displayed a protonated molecular ion at m/z 439.
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Fig. 4.20: IR Spectrum of 1-[2-{1-[S-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridin-ethyl]-2-imidazolidin-one (119)

Fig. 4.21: $^1$H NMR Spectrum of 1-[2-1-[S-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridin-ethyl]-2-imidazolidin-one (119)
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Fig. 4.21: $^{13}$C NMR Spectrum of 1-[2-[5-Chloro-4-fluorophenyl]-1H-indol-3-yl]-2,3,6-tetrahydro-1-pyridyl ethyl]-2-imidazolidine (119)

Fig. 4.22: Mass Spectrum of 1-[2-[5-Chloro-4-fluorophenyl]-1H-indol-3-yl]-2,3,6-tetrahydro-1-pyridyl ethyl]-2-imidazolidine (119)
4.4.3: Preparation of Related substance 133

During the condensation of 110 with 111 in the presence of transition metal, apart from the desired product 112, formation of 5-chloro-1-(4-bromo phenyl)-indole 139 was observed. When cesium carbonate was used for coupling reaction in place of transition metal, significant formation of 139 was observed. To understand the carry over of this impurity in down stream synthesis, 139 was converted to the corresponding N-(4-bromo phenyl)-sertindole 133 (scheme 4.15). Problems were encountered during catalytic hydrogenation of 140 as it leads to significant levels of dehalogenated products. Finally, pure sample of 133 was obtained by repeated recrystallization from MeOH. The pure sample was fully characterized based on the spectral data.

Scheme 4.15
In the IR spectrum (Fig. 4.23) C=O signal appeared at 1683 cm\(^{-1}\) with a broad amide NH absorption at 3213 cm\(^{-1}\) and C-Cl signal appeared at 791. The \(^1\)H NMR spectrum (Fig. 4.24) showed aromatic protons at \(\delta\) 7.53 (m, 2H), 7.71 (m, 2H), 7.52 (m, 1H), 7.16 (dd, 1H), 7.72 (m, 1H), piperidine protons appeared at \(\delta\) 1.93 (d, 2H), 1.66 (m, 2H), 2.97 (d, 2H), 2.08 (t, 2H). The ES mass spectrum (Fig. 4.25) displayed a protonated molecular ion at m/z 501 which corresponds to (M+H)\(^+\). The mass spectrum showed a characteristic mono chlorine and mono bromine isotopic abundance. The molecular ion confirms the molecular weight as m/z 500 corresponding to the molecular formula C\(_{24}\)H\(_{26}\)BrClN\(_4\)O.
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Fig. 4.23: IR Spectrum of 1-[2-[4-[[5-Chloro-1-(4-bromophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-amidazolidinone (133)

Fig. 4.24: $^1$H NMR Spectrum of 1-[2-[[5-Chloro-1-(4-bromophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-amidazolidinone (133)
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Fig. 4.24: $^{13}$C NMR Spectrum of 1-[2-[4-[[5-Chloro-1-4-bromophenyl]-1H-indol-3-yl]1-piperidiny]ethyl]-2-imidazolidione (133)

Fig. 4.25: Mass Spectrum of 1-[2-[4-[[5-Chloro-1-4-bromophenyl]-1H-indol-3-yl]-1-piperidiny]ethyl]-2-imidazolidione (133)
4.4.4: Preparation of Related substance 134

During the reduction of 128, traces of des-fluoro analogue of 129 was observed. During hydrogenation of 140, de-bromination was one of the major by-product, this observation was used to prepare des-flouro sertindole 134. Thus hydrogenation of 140 at higher pressure and prolonged maintenance lead to compound 142, which on further treatment with 116 gave 134 (scheme-4.16).

Scheme 4.16

In the IR spectrum (Fig.4.26) C=O signal appeared at 1698 cm$^{-1}$ with a broad amide NH absorption at 3437 cm$^{-1}$. The $^1$H NMR spectrum (Fig.4.27) displayed eight aromatic protons, eight methylenes and a methine, besides a tri-substituted vinylic moiety. The $^{13}$C NMR clearly showed the absence of long range couplings due to fluorine atom.
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The ES mass spectrum (Fig.4.28) displayed a protonated molecular ion at m/z 423. The mass spectrum showed a characteristic chlorine isotopic abundance.
Fig. 4.27: $^{13}$C NMR Spectrum of 1-[2-[4-[5-Chloro-1-phenyl-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (134)

Fig. 4.28: Mass Spectrum of 1-[2-[4-[5-Chloro-1-phenyl-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (134)
4.4.5: Preparation of Related substance

Trace amounts of 5-bromoindole 143 was observed as an impurity in some of the commercially procured samples of 5-chloroindole. Presence of this impurity will carry up to final drug substance. The bromo analogue of sertindole 135 was prepared from 143 using the sequence utilized to prepare 16 (scheme 4.17). The impurity was fully characterized by the spectral data.

Scheme 4.17

In the IR spectrum (Fig. 4.29) C=O signal appeared at 1699 cm\(^{-1}\) with a broad amide NH absorption at 3447, 3237 cm\(^{-1}\). The \(^1\text{H}\) NMR spectrum (Fig. 4.30) showed peaks characteristic for a 5-substituted indole moiety besides four aromatic protons. The \(^{13}\text{C}\) NMR displayed
characteristic four carbon coupling due to the presence of fluorine atom. The ES mass spectrum (Fig.4.31) displayed a protonated molecular ion at m/z 485 and a bromine isotopic abundance.
Fig. 4.30: $^{13}$C NMR Spectrum of 1-[2-[[5-Bromo-1-[4-fluorophenyl]-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinones (135)

Fig. 4.31: Mass Spectrum of 1-[2-[5-Bromo-1-[4-fluorophenyl]-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (135)
4.4.6: Preparation of Related substance

During N-alkylation of 113, formation of dialkylated product was observed. Hence the dialkylated piperidine 136 was prepared by treating 16 with 116 followed by isolation and purification of crude by column chromatography (scheme 4.18).

Scheme 4.18

In the IR spectrum (Fig. 4.32) C=O signal appeared at 1682 cm\(^{-1}\) with a broad amide NH absorption at 3424. The \(^1\)H NMR spectrum (Fig. 4.33) showed piperidine protons at 2.17 (m, 4H), 3.19 (m, 1H), 3.58 (m, 2H), 3.76 (m, 2H) and two sets of N-ethyl protons. The ES mass spectrum (Fig. 4.34) displayed a molecular ion at m/z 553.
Fig. 4.32: IR spectrum of 5-Chloro-1-[4-fluorophenyl]-3-[1,1'-biphenyl]-2-imidazolidin-1-y1(ethyl)-piperidin-4-y1

1H indole [136]

Fig. 4.33: $^{1}$H NMR spectrum of 5-Chloro-1-[4-fluorophenyl]-3-[1,1'-biphenyl]-2-imidazolidin-1-y1(ethyl)-piperidin-4-y1

1H indole [136]
Fig 4.33a: $^{13}$C NMR spectrum of 5-Chloro-1-[4-(fluorophenyl]-3-[1,1'-bis[2-imidazolidin-1-yl]ethyl]-piperidin-4-yl]

1H indole (136)

Fig 4.34: Mass spectrum of 5-Chloro-1-[4-(fluorophenyl]-3-[1,1'-bis[2-imidazolidin-1-yl]ethyl]-piperidin-4-yl]

1H indole (136)
4.4.7: Preparation of Related substance

This impurity is considered as N-oxide impurity, and is a possible degradant that can be formed by air oxidation of 16. The impurity was synthesized by oxidation of 16 using m-chloroperbenzoic acid (scheme 4.19). The isolated pure sample was fully characterized by the spectral data.

**Scheme 4.19**

![Scheme 4.19](image)

In the IR spectrum (Fig.4.35) C=O signal appeared at 1674 cm\(^{-1}\) with a broad amide NH absorption at 3471 cm\(^{-1}\). The \(^1\)H NMR spectrum (Fig.4.36) displayed the imidazolidinone NH peak at \(\delta\) 6.45 indicating its inertness to oxidation. When the \(^1\)H NMR spectrum was compared to sertindole 16, the indole protons appeared in the same region indicating that the indole nitrogen was inert to oxidation. In the aliphatic region the methylenes connecting the piperazinyl nitrogen displayed downfield shift confirming oxidation on the piperazinyl...
nitrogen. The ES mass spectrum (Fig. 4.37) displayed a protonated molecular ion at m/z 457.
Fig. 4.36: $^{13}$C NMR spectrum of 1-[2-[4-(5-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl]-1-oxo-1-piperidiny]ethyl] imidazolidin-2-one (137)

Fig. 4.37: Mass spectrum of 1-[2-[4-(5-Chloro-1-[4-fluorophenyl]-1H-indol-3-yl]-1-oxo-1-piperidiny]ethyl] imidazolidin-2-one (137)
4.5: Conclusion

Thus, we have developed a simple, new and cost-viable synthetic route to Sertindole. Further, to this we have identified, synthesized and characterized seven related substances formed during the synthesis of Sertindole.

4.6: Experimental Section

Preparation of 127: Compound 113 (50g, 291.3mmol), was dissolved in methanol (700ml) at room temperature. The mass was heated and methanol (~500 ml) was distilled off atmospherically. The mass was cooled to 25-30°C and potassium carbonate (112.5g, 814 mmol) was added and stirred for 1hr. To the reaction mass was added 126 (28.8g, 357.8 mmol) and heated to reflux. The reaction mass was maintained for 6hr and the reaction completion was monitored by TLC. After completion of the reaction, the mass was cooled to room temperature and inorganic salts were filtered. Washed the salts with methanol (50ml). Concentrated the filtrate under reduced pressure to afford residue. The residue was adsorbed over silica gel and purified by column chromatography using 1% triethyl amine in ethyl acetate to get the desired compound 127 (39.6g, Yield: 85.1%, HPLC purity 97.18%). IR (cm⁻¹): 3391, 2956, 1713, 1241; ¹H NMR (CDCl₃, δ ppm): 2.40 (t, 4H), 2.60 (t, 2H), 2.76 (t,4H), 3.61(br, OH), 3.62 (m, 2H); ¹³C NMR (CDCl₃): δ 40.7, 52.8, 58.5, 63.4, 208.8; ESI-MS: m/z 144([M+H]+, C₇H₁₄NO₂ calcd. 144).
**Preparation of 128:** To a mixture of 127 (32g, 223.5mmol) and acetic acid (350ml), was added 112 (50g, 203.5mmol), at 25-30°C. To it was added conc. HCl (150 ml) and the mass was heated to reflux (95-100°C) temperature and maintained for 1hr. The reaction completion was monitored by TLC. The mass was distilled off under reduced pressure at temperature below 60°C. The mass was cooled to room temperature and acetone (250 ml) was added. The white suspension was stirred for 1hr and filtered. The wet cake was washed with acetone (100ml) and dried at 50°C for 5hrs to afford compound 128 (65.4g, Yield: 86.6%, HPLC purity 98.18%). IR (cm⁻¹): 3212, 2926, 1533, 1512, 1272, 840; ¹H NMR (CDCl₃, δ ppm): 2.61 (m, 2H), 2.70 (t, 2H), 2.82 (t, J=5.4, 2H), 3.30 (q, J=3.0, 2H), 3.71 (t, 2H), 6.18 (m, 1H), 7.17 (dd, J=9.0 and 2.1, 1H), 7.21 (m, 2H), 7.24 (s,1H), 7.32 (d, J=9.0,1H), 7.42 (m, 2H), 7.89 (d, J=1.8, 1H); ¹³C NMR (CDCl₃): δ 29.1, 49.9, 52.8, 58.1, 59.1, 111.3, 116.5 (d), 118.3, 120.4 (d), 122.9, 126.1, 126.3, 126.4, 127.3, 128.9, 135.1 (d), 135.3, 161.3 (d); ESI-MS: m/z 371 ([M+H]+, C₂₁H₂₁ClFN₂Ocalcd. 371).

**Preparation of 129:** To a clear solution of 128 (25g, 67.4mmol), in methanol (1500ml) was added platinum (IV) oxide (2.0g) at 20-25°C in autoclave. The reaction mass was pressurized with 40-50 psi of hydrogen gas and maintained for 12hr at 20-25°C. The reaction completion was monitored by TLC. The catalyst was filtered and washed with methanol (100ml). The filtrate was distilled off under reduced pressure to get residue. Methyl tertiary butyl ether (100ml) was added to
the residue and stirred at 0-5°C for 1hr. The product was filtered and 
the wet cake was dried at 50-55°C to yield compound 129 (22.5g, Yield: 
90%, HPLC purity 96.5%). IR (cm⁻¹): 3204, 2939, 1513, 1252, 836; ¹H 
NMR (DMSO-d₆): δ1.69 (m,2H), 1.90 (d, J=11.4, 2H), 2.10 (m, 2H), 2.40 
t, J=6.3, 2H), 2.75 (m, 1H), 2.94 (d, J=11.4,2H), 3.50 (q, J=6.0, 2H), 
4.36 (t, J=4.5,1H); 7.14 (dd,J=8.7 and 1.8, 1H), 7.36 (m, 2H), 7.41 (d, 
J=8.7,1H), 7.44 (s,1H), 7.56 (m, 2H), 7.68 (d, J=1.8, 1H);¹³C NMR 
(DMSO-d₆): 632.8, 33.0, 54.6, 59.1, 61.1, 112.1, 116.7, 118.9, 122.2, 
122.5, 124.7, 126.1, 126.2, 129.3, 134.4, 135.5, 159.0, 160.6 (d);ESI-
MS: m/z 373 ([M+H]^+, C₂₁H₂₃ClF₂N₂Ocalcd. 373).

Preparation of 130: To a clear solution of 129 (20g, 53.6mmol) in 
dichloromethane (160ml) was added triethylamine (10.8g, 106.7mmol) at 
0-5°C. Mesylchloride (9.2g, 80.3mmol) was added and stirred for 4hr at 
25-30°C. After reaction completion 5% sodium bicarbonate solution 
(200ml) was added and stirred for 5 minutes. Separated the organic 
layer and washed the organic layer with water (400ml). Concentrated the 
organic layer under reduced pressure to yield title compound 130 (24g, 
Yield: 100%, HPLC purity 97.22%). IR (cm⁻¹): 2921, 1510, 1151;¹H NMR 
(CDCl₃, δ ppm): 1.82 (m,2H), 2.09 (m, 2H), 2.29 (m, 2H), 2.58 (m, 3H), 
2.80 (t, J=6.3, 2H), 2.81 (m, 1H), 3.07 (m, 2H), 3.65 (q, J=6.0, 2H),7.15 
(dd, J=8.7 and 1.8, 1H), 7.16 (m, 2H), 7.32 (s, 1H), 7.38 (m, 2H), 7.41 (d, 
J=8.7, 1H), 7.63 (d, J=1.8, 1H);¹³C NMR (200 MHz, CDCl₃): 632.7, 33.1, 
39.9,41.0, 54.2, 60.2, 65.0, 111.3, 116.4, 118.8, 121.8, 122.6, 124.9,
Preparation of 16: To a suspension of 60% sodium hydride (2.15g, 89.5mmol) in N,N-dimethyl formamide (77ml), was added 130(20g, 44.4mmol) at 25-30°C. To the stirred mixture was added 131(4.9g, 57.5mmol) and stirred for 14hr at 25-30°C. The reaction completion was monitored by TLC. Methanol (20ml) was added to the mass and stirred for 10 min. The reaction mass was quenched into a mixture of water (60ml) and dichloromethane (60ml) and stirred for 15min. Separated the organic and aqueous layers and organic layer was washed with water (3x150ml). Organic layer was dried over anhydrous sodium sulphate (10g) and concentrated under reduced pressure. Acetone (30ml) was added to the residue and stirred the reaction mass for 1hr. Filtered the product and the wet material was dried at 60°C to yield sertindole16 (10g, Yield: 51%, HPLC purity 99.89%). IR (cm\(^{-1}\)): 3235, 1702, 1275; \(^1\)H NMR (DMSO-d\(_6\), \(\delta\) ppm): 1.66 (m, 2H), 1.93 (d, J=11.1, 2H), 2.08 (m, 2H), 2.40 (t, J=6.6, 2H), 2.76 (m, 1H), 2.97 (d, J=11.1, 2H), 3.16 (m, 2H), 3.17 (m, 2H), 3.36 (m, 2H), 6.21 (br, NH), 7.14 (dd, J=8.7 and 2.1, 1H), \(\delta\) 7.37 (m, 2H), 7.43 (d, J=8.7, 1H), 7.46 (s, 1H), 7.57 (m, 2H), 7.68 (d, J=1.8, 1H); \(^13\)C NMR (200 MHz, CDCl\(_3\)): 83.2, 32.9, 37.8, 41.0, 45.2, 54.1, 56.5, 112.2, 117.0 (d), 118.9, 122.1, 122.6, 124.7, 126.2 (d), 126.3, 129.3, 134.4 (d), 135.5, 160.6 (d), 162.5; MS: \(m/z\) 441 ([M+H]\(^+\), 125.4, 125.9, 128.9, 134.7, 135.5, 159.3, 162.6; ESI-MS: \(m/z\)452 ([M+H]\(^+\), \(C\(_{22}\)H\(_{25}\)ClF\(_2\)N\(_2\)O\(_3\)Scalcd. 452)).
C₂₄H₂₇ClFN₄Ocalcd. 441). All the spectral data were identical with an authentic sample of sertindole.

**Preparation of 132**: Compound **115** (40 g, 95.6 mmol) was dissolved in methanol (600 mL) at room temperature and to it was added acetic acid (10 ml), 5% Pd/C (8.0 g; 50% wet) and ammonium formate (20 g, 317.4 mmol). The mass was refluxed for 12 hr and catalyst was filtered off followed by washing with methanol (30 ml). The filtrate was distilled off under vacuum to yield **138** (22.3 g, Yield: 79.4%; HPLC purity 94.47%). ESI-MS showed absence of chlorine isotopic abundance and molecular ion peak displayed at m/z 295 (M+H)+.

To a suspension of **138** (14.0 g, 47.6 mmol) and **116** (10.6 g, 35.7 mmol) in methylisobutyl ketone (200 ml), at 26-28 °C, was added anhydrous potassium carbonate (11.8 g, 85.6 mmol) and potassium iodide (0.34 g, 2.0 mmol). The mixture was refluxed for 6 h. The mass was concentrated under reduced pressure and the residue obtained was dissolved in dichloromethane (210 ml). The organic layer was washed with water (140 ml) and concentrated under reduced pressure to get residue, to which was added acetone (30 ml). The mass was stirred for 1 hr and filtered. Washed the wet cake with acetone (30 ml) and dried at 55°C to yield **132** (9.0 g, 46.6%, HPLC purity 96.08%). IR (cm⁻¹): 3222, 2934, 1681, 1510, 1458, 1284 cm⁻¹. ¹H NMR (DMSO-d₆): δ 1.69 (m, 2H), 1.95 (d, J=11.1, 2H), 2.09 (t, J=11.4, 2H), 2.41 (t, J=6.6, 2H), 2.78 (m, 1H), 2.99 (d, J=11.4, 2H), 3.16 (t, J=6.6, 2H), 3.18-3.21 (m, 2H), 3.37 (m, 2H),
6.21 (brs, 1H), 7.08 (m, 1H), 7.16 (m, 1H), 7.36 (m, 2H), 7.37 (s, 1H), 7.45 (d, J=8.1, 1H), 7.58 (m, 2H), 7.64 (d, J=7.2, 1H); $^{13}$C NMR (DMSO-$d_6$): δ33.0, 33.3, 37.9, 45.3, 54.2, 56.5, 110.5, 116.8 (d), 119.7, 120.1, 122.4, 122.7, 124.5, 126.1 (d), 128.2, 135.9 (d), 136.0, 160.4, 162.5 (d); ESI-HRMS: m/z 407.2284 ([M+H]$^+$, C$_{24}$H$_{28}$FN$_4$Ocalcd. 407.2241).

**Preparation of 119**: To a suspension of 114 (25 g, 68.5 mmol) and 116 (15.4 g, 103.5 mmol) in methylisobutyl ketone (375 ml), at 26-28 °C, was added potassium iodide (0.5 g, 3.0 mmol) and potassium carbonate (16.8 g, 121.5 mmol). The mass was refluxed for 30h, and reaction completion was monitored by TLC. The solvent was distilled off under reduced pressure and to the residue was added dichloromethane (250 ml) and water (250 ml). Layers were separated and the organic layer was washed with water (250 ml). The solvent was distilled off atmospherically to get residue. Acetone (50ml) was added and the mass was stirred for 2h. Filtered the product and dried the wet cake at 55°C for 3hr to afford 119 (23.6 g, 78.2%) as white solid. The crude 119 can be recrystallized in methanol to yield pure 119. (HPLC purity 97.76%); IR (cm$^{-1}$): 3246, 2899, 2824, 1687, 1512, 1458, 1278, 774 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): δ2.49-2.50 (m, 4H), 2.65 (t, J=5.4, 2H), 3.15-3.20 (m, 6H), 3.37 (m, 2H), 6.17 (m, 1H), 6.23 (brs, 1H), 7.20 (dd, J=2.1 and 9.0, 1H), 7.38 (m, 2H), 7.44 (d, J=9.0, 1H), 7.61 (m, 2H), 7.72 (s, 1H), 7.89 (d, J=2.1, 1H); $^{13}$C NMR (DMSO-$d_6$): δ28.9, 37.8, 40.9, 45.1, 50.1, 53.1, 55.9, 112.4, 117.0 (d), 117.8, 120.2, 120.6, 122.9, 125.7, 126.7 (d), 127.4, 128.0, 128.7,
135.0 (d), 135.1, 160.9, 162.5 (d); ESI-HRMS: m/z 439.1716 ([M+H]+, C_{24}H_{25}ClF_{4}N_{4}O_{4} calcd. 439.1696), 441.1688[M+H+2]+.

**Preparation of 133:** To a solution of 110 (25 g, 165 mmol), 111 (72.2 g, 412.5 mmol) in DMF (125 ml) was added cesium carbonate (107.5 g, 329.9 mmol) and the mass was heated to 132-134°C and maintained for 18 hr. TLC reveals the completion of reaction and the mass was cooled to 56-59 °C followed by addition of toluene (200 ml) and water (50 mL). pH was adjusted to 2.5 with conc HCl (ca 25 mL). Organic layer was separated and washed with water (50 ml). The organic layer was concentrated under vacuum to get 139 (32.5 g) which was dissolved in acetic acid (325 ml) and 113 (90.3 g) was added. The reaction mixture was heated to 72-74 °C, trifluoroacetic acid (215 ml) was added and the mass was further heated to 102-104 °C. After 1 hr maintenance, TLC revealed the completion of reaction. Mass was cooled to 25-30°C and conc HCl (360 ml) was added. Acetone (425 ml) was added and the mass was stirred for 2 hr. The product was filtered and the cake was washed with acetone (30 ml) followed by drying to yield 140 (25.4 g, 43.4% yield from 110; HPLC purity: 99.74%).

Indole 140 (25.0 g, 59 mmol) was suspended in a mixture of dichloromethane (500 mL) and water (250 mL) and pH was adjusted to 11.5 with dilute sodium hydroxide solution (130 ml). Organic layer was separated, washed with water (50 ml) and concentrated to get residue which was dissolved in methanol (750 ml) and acetic acid (6 ml) was
added. The mass was transferred into an autoclave, PtO$_2$ (0.75g) was charged and hydrogen pressure of 4.0 Kg/cm$^2$ was applied and stirred at 32-34 °C for 30hr. After reaction completion, the catalyst was filtered off, and washed the bed with methanol (50ml). Methanol was distilled off and to the residue ethyl acetate (50ml) was added and stirred for 2hr. The product was filtered and the cake was washed with ethyl acetate (25 ml). Recrystallization from methanol gave 141 (6.0 g, 26.4% yield; HPLC purity: 93.58%). The mass spectra displayed the characteristic chlorine-bromine ion abundance.

A mixture of 141 (6.0 g, 15.4 mmol), 116 (2.4 g, 16.2 mmol), potassium carbonate (2.76g, 20 mmol) and potassium iodide (0.06 g, 0.36 mmol) in methylisobutylketone (90 ml), was heated to 115-117°C and maintained for 9 hr. TLC shows completion of reaction and the mass was concentrated to get residue. Water (50ml) and dichloromethane (100 mL) were added, layers were separated and the organic layer was distilled off under reduced pressure. To the residue obtained, acetone (25ml) was added and agitated for 2hr. The product was filtered and dried to yield 133 (5.2 g, 67.6% yield, HPLC purity: 96.24%). IR (cm$^{-1}$): 3213, 3090, 2839, 1683, 1589, 1492, 1458 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): $\delta$1.66 (m, 2H), 1.93 (d, J=12.0, 2H), 2.08 (t, J=11.1, 2H), 2.40 (t, J=6.6, 2H), 2.77 (m, 1H), 2.97 (d, J=11.1, 2H), 3.16-3.19 (m, 4H), 3.37 (m, 2H), 6.21 (brs, 1H), 7.16 (dd, J=2.1 and 8.7, 1H), 7.50 (s, 1H), 7.53 (m, 3H), 7.71 (m, 3H); $^{13}$C NMR (DMSO-d$_6$): $\delta$32.8, 32.9, 37.9, 45.3, 54.1, 56.5, 112.4,
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**Preparation of 134:**

To a solution of compound $140$ (30.0 g, 70.8 mmol) in methanol (450ml), in an autoclave, was added PtO$_2$ (0.9g) at 31-33°C. The reaction mixture was hydrogenated at a pressure of 6.5 Kg/cm$^2$ for 26h. After completion of reaction the catalyst was filtered and washed with methanol (25ml). The solvent was concentrated and to the residue ethyl acetate (60ml) was added and stirred for 2hr at 42-44°C. Cooled the mass to ambient temperature and filtered. Dried the wet material for 4 hrs at 50°C to get $142$ (16.2 g, 73.9% yield). The mass spectra displayed the absence of bromine ion.

A mixture of $142$ (10.0 g, 32.2 mmol), $116$ (5.6 g, 37.6 mmol), potassium iodide (0.2g, 1.2 mmol) and potassium carbonate (6.4 g, 46.4 mmol) in methylisobutyl ketone (150 ml), was heated to 114-116°C for 18h. Water (100ml) was added and layers separated. The solvent was concentrated and acetone (100ml) was added to the residue to precipitate the product. The mass was maintained for 2hr and filtered. The wet cake was slurried in methanol (20ml) and filtered. The material was dried at 60°C for 3hr to afford $134$ (7.7 g, 54.1% yield, HPLC purity: 96.6%). IR (cm$^{-1}$): 3212, 2918, 1698, 1595, 1501, 766 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$): $\delta$1.66 (m, 2H), 1.93 (d, J=11.1, 2H), 2.08 (t, J=11.4, 2H), 2.40 (t, J=6.9, 2H), 2.77 (m,
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1H), 2.97 (d, J=11.4, 2H), 3.15 (t, J=6.9, 2H), 3.18 (m, 2H), 3.37 (m, 2H), 6.21 (brs, 1H), 7.15 (dd, J=2.1, 1H), 7.36 (m, 1H), 7.49 (s, 1H), 7.50 (d, J=8.7, 1H), 7.52-7.54 (m, 4H), 7.69 (d, J=2.1, 1H);\(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta\) 32.9, 33.0, 37.9, 41.0, 45.3, 54.1, 56.5, 112.4, 118.9, 122.2, 122.6, 124.0, 124.7, 126.0, 126.7, 129.5, 130.2, 134.2, 139.2, 162.5; ESI-HRMS: \(m/z\) 423.1965 ([M+H]\(^+\), \(C_{24}H_{28}ClF\(\text{N}_4\)O \(\text{calcd.}\) 423.1946), 425.1939 [M+H+2]\(^+\).

**Preparation of 135**: A mixture of 143 (20.0 g, 102 mmol), potassium carbonate (19.3 g, 139.3 mmol), 111 (46 g, 263 mmol), ethylenediamine (1.48 g, 24.6 mmol) and copper (II) bromide (0.9 g, 4.03 mmol), in anhydrous DMF (80 ml) was heated to 132-134\(^{\circ}\)C and maintained for 42h. Cooled the mass to 56-58 \(^{\circ}\)C and a mixture of toluene (100 ml) and water (100 ml) were added. Filtered the insolubles and separated the layers. Organic layer was washed sequentially with dil. HCl (10ml) followed by water (50ml). The organic layer was concentrated and the residue obtained was dissolved in methanol (50 ml). Cooled the mass to 2-4\(^{\circ}\)C and stirred for 2hr. The product was filtered and washed with chilled methanol (20 ml). The wet material was dried to get 144 (17 g, 54.2\%). The mass spectrum showed molecular ion peak at \(m/z\) 305 and the characteristic bromine isotopic abundance.

A mixture of 144 (17.0 g, 58.6 mmol), 113 (10.7 g, 69.8 mmol), acetic acid (82.5 mL) and trifluoroacetic acid (82.5 mL) was heated to 102-104 \(^{\circ}\)C and maintained for 2hr. The reaction mass was concentrated and
acetone (100ml) was added followed by 6N aq HCl (14 ml) at 25-27°C. Filtered the product and washed the wet material with acetone (20 ml) followed by drying at 60°C to get 145 (12.3 g, 63.7% yield).

To a mixture of 145 (12.3 g, 30.2 mmol) and dichloromethane (100ml) was added triethyl amine (12 ml) and concentrated the mass to afford residue. The residue was dissolved in methanol (240 ml) and PtO₂ (800 mg, 3.52 mmol) was added. The reaction was hydrogenated at a pressure of 4.1 Kg/cm² at 31-33 °C for 4 hr. After reaction completion, the mass was distilled off to get residual mass and ethyl acetate (50 ml) was added. The mass was maintained for 2 hr and the product was filtered followed by ethyl acetate (30 ml) washing. The crude was purified by silica gel column chromatography using mixture of 7-10% methanol in dichloromethane gave 146 (4.0 g, 35.5% yield; HPLC purity: 97.14%). The mass spectral data displayed the molecular ion peak at m/z 373 [M+H] and a characteristic bromine ion abundance.

A mixture of 146 (4.0 g, 10.7 mmol), potassium iodide (0.062 g, 0.38 mmol), 116 (1.86 g, 12.6 mmol), and potassium carbonate (2.20 g, 15.9 mmol) in methylisobutylketone (60 ml), was heated to 115-117°C, and maintained for 16 hr. Water (60 ml) was added and separated the organic layer. The organic layer was distilled off to get semi-solid mass. To the mass acetone (30 ml) was added and stirred for 1 hr. Filtered the product and the wet cake dried at 50°C for 4 hr to get 135 (4.1 g, 65.9% yield, HPLC purity: 97.57%). IR (cm⁻¹): 3447, 3237, 2938, 1699, 1508,
1457, 1212 cm\(^{-1}\). \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\)1.66 (m, 2H), 1.93 (d, J=11.1, 2H), 2.08 (t, J=11.1, 2H), 2.40 (t, J=6.6, 2H), 2.77 (m, 1H), 2.97 (d, J=11.4, 2H), 3.16 (t, J=6.6, 2H), 3.19 (m, 2H), 3.37 (m, 2H), 6.21 (brs, 1H), 7.26 (dd, J=1.8 and 8.7, 1H), 7.37 (m, 2H), 7.39 (d, J=8.7, 1H), 7.46 (s, 1H), 7.57 (m, 2H), 7.83(d, J=1.8, 1H); \(^{13}\)C NMR (DMSO-d\(_6\)): \(\delta\)32.9,37.9, 45.3, 54.1, 56.5, 112.6, 112.7, 116.9 (d), 121.9, 122.1, 125.2, 126.2 (d), 126.3, 130.0, 134.7, 135.5 (d), 160.7(d), 162.5; ESI-HRMS: m/z 485.1349 ([M+H]\(^+\), C\(_{24}\)H\(_{27}\)BrFN\(_4\)O calcd. 485.1346), 487.1329 [M+H+2]\(^+\).

**Preparation of 136:** Compound 16 (10g, 22.6 mmol),acetonitrile (70 ml) and triethylamine (6 mL) was stirred for 10 min. and to it was added 116 (5.8, 39 mmol) and sodium iodide (4.4g, 29.4 mmol). The reaction mixture was heated to 75-80\(^0\)C and maintained for 40h. The mass was concentrated under vacuum and to the residue was added dichloromethane (70ml) and water (20 ml). Layers were separated and organic layer was washed with water (20 ml).The solvent was distilled off and the residue was adsorbed over silica and purified by column chromatography using 10-12% mixture of methanol in dichloromethane as eluent to give 136(2.6 g, 20.7% yield; HPLC purity: 96.68%). IR (cm\(^{-1}\)): 3424, 2925, 1682, 1513, 1457, 1217, 794 cm\(^{-1}\). \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\)2.17 (m, 4H), 3.19 (m, 1H),3.28 (m, 4H), 3.46 (m, 4H), 3.58 (m, 2H), 3.61 (m, 2H), 3.67-3.69 (m, 6H), 3.76 (m, 2H), 6.62 (brs, 1H), 6.63 (brs, 1H), 7.19 (dd, J=1.8 and 8.7, 1H), 7.41 (m, 2H), 7.47 (d, J=8.7, 1H), 7.53(s, 1H), 7.59 (m, 2H), 7.79 (d, J=1.8, 1H);} \(^{13}\)C NMR
(DMSO-d$_6$): $\delta$26.2, 29.9, 37.8, 45.4, 45.8, 50.8, 59.7, 60.3, 112.4, 117.0 (d), 118.8, 119.4, 122.9, 125.0, 126.3 (d), 127.2, 129.0, 134.3, 135.4 (d), 160.8, 162.4 (d), 162.5; ESI-HRMS: $m/z$ 553.2494; C$_{29}$H$_{35}$ClFN$_6$O$_2$; 555.2466 [M+H+2]$^+$.  

**Preparation of 137:**

16 (10g, 22.6 mmol) was dissolved in methanol (300ml) and m-chloroperbenzoic acid (5.0 g, 29.0 mmol) was added and heated to 42-44°C and maintained for 10hr. The solvent was distilled off and to the residue was added water (150ml) and dichloromethane (150ml). Organic layer was separated and washed with water (40ml). The solvent was distilled to get residue which is purified by silica gel column chromatography. Elution with 10-12% methanol in dichloromethane affords 137 (6.0 g, 58.0% yield; HPLC purity: 99.54%). IR (cm$^{-1}$): 3471, 3291, 2959, 2928, 1674, 1512, 1492 cm$^{-1}$.  

1H NMR (DMSO-d$_6$): $\delta$ 1.79 (d, J=12.6, 2H), 2.47 (m, 2H), 2.93 (m, 1H), 3.09 (d, J=10.8, 2H), 3.24 (m, 2H), 3.30 (t, J=6.3, 2H), 3.39-3.41 (m, 4H), 3.60 (t, J=6.3, 2H), 6.46 (brs, 1H), 7.16 (dd, J=8.7 and 2.1, 1H), 7.38 (m, 2H), 7.44 (d, J=8.7, 1H), 7.53 (s, 1H), 7.59 (m, 2H), 7.77 (d, J=2.1, 1H); 13C NMR (DMSO-d$_6$): $\delta$ 27.1, 31.2, 37.9, 38.0, 45.4, 64.3, 67.9, 112.3, 116.9 (d), 119.0, 121.0, 122.7, 124.8, 126.3 (d), 126.5, 129.1, 134.5, 135.4 (d), 160.7 (d), 162.5; ESI-MS: $m/z$ 456, C$_{24}$H$_{26}$ClFN$_4$O$_2$ calcd. 456), 458 [M+H+2]$^+$.  