CHAPTER-5
CHAPTER-V

SECTION-A:

CONVENIENT AND LARGE SCALE SYNTHESIS OF 5-CHLOROINDOLE AND ITS 3-SUBSTITUTED ANALOGUES.

5A.1 Introduction:

Introduction to the pharmacological activity of halogen substituted indole derivatives:

Keeping pharmacological activity of indoles and its derivatives in mind, we have developed the best industrially scalable and commercially feasible production method for the production of 5-chloroindole starting from commercially available and cheap 5-bromoindole. Here we are giving brief introduction to the reported literature for the pharmacological activity of halogen substituted indole derivatives.

McKew et.al.] reported [175] a series of halo Indole derivatives 101, 102 and explored their activity. They found compounds 101, 102 as potent cytosolic phospholipase A2 α inhibitors.

![Chemical structures of 101 and 102](image-url)
Mazzoni et al. [176] synthesized various substituted 1-minoalkyl-5-chloro-2, 3-dioxo indole analogs (103) and tested for their analgesic action by formalin test and compared to WIN 55212-2, AAI acting on the cannabinoid receptors. In receptor binding assay, 103 showed affinity for the CB1 receptor comparable to WIN 55212-2.

![103](image)

Mayers et al. [177] synthesized various 5-chloro-4-fluoro-1H-indole-2-carboxylate derivatives (104). This functionalized scaffold was required during a campaign to evaluate novel phosphoindoles as non-nucleoside reverse transcriptase inhibitor (NNRTI) candidates for the treatment of HIV infection. The 2-carboxy-5-chloro-4-fluoroindole moiety has also been incorporated as an important feature of other NNRTI's, in particular indolylarylsulfones, and of various heterocyclic anticoagulants.

![104](image)

Nirogi et al. [178] prepared 2-arylsulfonylmethyl-3-piperazinylmethyl 5-chloro indole derivatives (105) and explored as 5-HT6 receptor ligands. These compounds showed moderate affinity towards human 5-HT6R, when tested at 100 nm concentration.
Chaudari et. al. reported [179] 5-chloro substituted indole dihydropyrimidines (106) and evaluated their antimicrobial activity. These compounds were proved to be potent antibacterial and antifungal compounds.

Treadway et. al. reported [180] the synthesized [R-(R*,S*)]-5-chloro-\(N\)-[3-(dimethylamino)-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]-1H-indole-2-carboxamide (CP-91149) (107) and this compound was found potent human liver glycogen phosphorylase inhibitor, which lowers the blood glucose in vivo.

Stefano et. al. [181] prepared a novel spiro-indolinone derivatives (108) and it was found to be a potent, selective, and orally
bioavailable CRTH2 (DP2) receptor antagonists for the treatment of allergic inflammatory diseases.

\[
\begin{align*}
\text{R}_1 &= \text{CH}_2\text{COOH}, (\text{CH}_2)_3\text{COOH}, \text{Me} \text{ and } \text{R}_2 = \text{Me, allyl, benzyl, CH}_2\text{CON(Me)}_2 \\
\end{align*}
\]

Ashalatha et.al. [182] synthesized various novel 5-chloro-N1-(4-aryl-1,3-thiazol-2-yl)-1H-indole-2-carbohydrazide derivatives (109) and these compounds were found as potent antifungal and antibacterial agents.

5A.2. Literature survey:

Sugasawa et.al. reported [183] the synthesis of 5-chloro indole (111) derivatives from 2-amino-5-chloroacetophenone (110) using reductive cyclization and dehydrochlorination as key reactions (Scheme – 5A.1).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \quad \text{Cl} \quad \text{NaBH}_4 \quad \text{dioxane, heat} \quad \text{Cl} \\
\text{Cl} & \quad \text{NH}_2 \quad \text{Cl} \\
\end{align*}
\]

...Scheme- 5A.1
Young et al. [184] has utilized classical decarboxylation strategy by heating 5-chloro indole -2-carboxylic acid (112) under thermal conditions for the preparation of 111 (Scheme – 5A.2).

![Scheme-5A.2](image)

Gall et al. [185] has prepared 5-chloro indole (111) by direct chlorination of 1-acetyl-indoline (113) followed by saponification (Scheme – 5A.3).

![Scheme-5A.3](image)

Stille et al. [186] have utilized the palladium-catalyzed cyclization of vinyl anilines (115) for the preparation of 5-chloro indole (111) (Scheme – 5A.4).

![Scheme-5A.4](image)

Cho et al. reported [187] a ruthenium-catalyzed intermolecular cyclization of 4-chloro anilines (117) with ethylene glycol or 1,2-dibromo ethane (118) as C2-fragment for the preparation of 5-chloro indole (111) (Scheme – 5A.5).
5A.3 Present work

Inspired by the pharmacological importance of 111 derivatives as well as in connection with our on-going project for the large-scale industrial production of 111 we were interested in a method that can have high commercial viability and which can utilize very cheap and commercially available starting materials. Although the above methods are good to some extent for the small scale synthesis of 111, but they suffer from one or other disadvantage such as either low yields or use of expensive starting materials and reagents which, limit the applicability for the scale up production at industrial level.

Under analysis of the literature cited methods, it was envisaged to develop a direct one pot method using easily available raw materials that could address this problem and be of high commercial feasibility. However, direct synthesis of 111 by the single step process from 5-bromoindole is not known in the literature so far.

In this regard, we thought of using a halogen - halogen exchange reaction [188-189] as this could be the best method to obtain 111 in a single step starting from commercially available and
cheap raw material 5-bromoindole (119) and the present work paper deals with our efforts in this direction.

**5A.4. RESULTS AND DISCUSSION:**

Initially, we have carried out the reaction of 5-bromoindole (119a) with cuprous chloride in presence of N-methyl pyrrolidone at 200-210 °C, was tried and isolated the halogen exchanged product (111a) in good yields. *(Scheme-5A.6)*

![Scheme-5A.6](image)

The product was confirmed by spectral and analytical data $^1$H, $^{13}$C NMR and Mass data. In $^1$H NMR spectrum broad singlet at 11.26 indicating indole N-H, remaining all aromatic protons were observed at 6.40 (s, 1H, Ar-H), 7.05 (dd, $J$= 8.6, 2.0 Hz, 1H, Ar-H), 7.39 (d, $J$=9.4 Hz, 1H, Ar-H) 7.40 (d, $J$=3.12Hz, 1H, Ar-H), 7.56 (d, $J$=2.0Hz, 1H, indole ring). In addition $^{13}$C NMR peaks at 165.1, 139.3, 135.5, 126.8, 125.2, 123.4, 119.9, 117.5 and 114.1 were showing all aromatic regions. In ESI-Ms spectrum observed molecular ion peak at 152.5 (M+1) confirms formation of 111 from 119.

In order to increase the yields, the reaction was studied in different temperatures and reaction time, results were not encorsaing. Hence we decided to screen a set of aprotic dipolar solvents as well as the refluxing times for the reaction to obtain better yields. The results
are presented in Table-1.1. The screening results indicate that among all the solvents tested for the reaction, NMP was found to be the superior choice for the reaction with good yields.

Table-1  Formation of 111 under a range of solvents and temperatures.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Solvent</th>
<th>Time (h)*</th>
<th>Isolated yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>NMP</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>DMA</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>HMPA</td>
<td>15</td>
<td>59</td>
</tr>
</tbody>
</table>

* Temperatures are the best average with respect to yields obtained.

Having succeeded the synthesis of required 111 starting from 119 in good yields, we have then extended the applicability of the present method to see if we can do this transformation on some other substituted indoles. The reaction was successful for the 5-bromo indoles having substituents such as –CHO, -CN; -COOH at 3\textsuperscript{rd} position (111b, 111c, 111d) and the results has been depicted in Table1.2.
Table-2: Synthesis of 111 and its analogues from 119

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Starting Material</th>
<th>Product</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image" alt="119a" /></td>
<td><img src="image" alt="111a" /></td>
<td>70-72</td>
<td>85</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image" alt="119b" /></td>
<td><img src="image" alt="111b" /></td>
<td>212-215</td>
<td>83</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image" alt="119c" /></td>
<td><img src="image" alt="111c" /></td>
<td>190-194</td>
<td>76</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="119d" /></td>
<td><img src="image" alt="111d" /></td>
<td>240-246</td>
<td>79</td>
</tr>
</tbody>
</table>

In conclusion, we have developed the best industrially scalable and commercially feasible production method for the production of 5-chloroindole starting from commercially available and cheap 5-bromoindole. The protocol has been extended towards the synthesis of other substituted indole analogues in good yields. The advantage of the present method lies in its operational simplicity and yet very productive for producing 111 and analogues, which are very useful and important intermediates in drug industry.
5A.5 Experimental section

Preparation of 111a-d:

5A.5.1. GENERAL PROCEDURE FOR THE PREPARATION 111a-d:

A mixture of 5-Bromoindole (119a-d) (0.51 mmole), cuprous chloride (1.28 mmole) were dissolved in N-methyl-2-pyrrolidone (400 ml). The reaction mixture was slowly heated to 205-210 °C in an oil bath and maintained at the same temperature for 15 h (GC analysis). The reaction mixture was then cooled to room temperature and was added aq. ammonia (2 L, 20-25%), stirred for 30 min and extracted with chloroform (4 x 500 ml). The layers were separated and the organic layer was washed with water (2 x 400 ml) until basic to pH. Evaporation of the solvent under reduced pressure resulted the crude compound as a brown viscous liquid, which upon high vacuum distillation using an oil bath at vapor temperature 110-130 °C / 1 mm/Hg yielded the pure product (111a-d). The pure fraction was further crystallized in n-hexane yielding the pure product as white plates, 65.7 grams with GC purity of 99.8%.

111a: White plates, M.R: 70-72 °C, IR (KBr): 3386, (strong, -NH, stretching); and 1446 cm⁻¹ (strong, -C-Cl, stretching); (400 MHz, DMSO-d6) δ 6.40 (s, 1H, Ar-H); 7.05 (dd, J= 8.6, 2.0 Hz, 1H, indole ring) Ar-H, 7.39 (d, J=9.4 Hz, 1H, Ar-H) 7.40 (d, J=3.12Hz, 1H); 7.56 (d, J=2.0Hz, 1H, Ar-H); 11.26 (s, 1H, -NH, indole ring); 13C-NMR (DMSO d6/TMS) signals showed at δ 134.80, 129.26, 127.53, 123.87, 121.31, 119.61, 113.32, 101.33. MS m/z=152.5 (M+1).
**111b:** white solid, M.R: 212-215 °C, IR (KBr): 3216, (strong –NH, stretching); 2836 (very strong, **formyl**, proton stretching); 1643 cm⁻¹ (strong, **formyl** carbonyl); (400 MHz, DMSO-d₆); 7.26 (dd, 1H, J = 8.6Hz, 2.1Hz, **Ar-H**); 7.52 (d, 1H, J = 8.6 Hz, **Ar-H**); 8.34 (s, 1H, **indole** ring); 8.06 (s, 1H, J=2.0 Hz, **Ar-H** ); 9.92 (s, 1H, **formyl** proton); 12.28 (bs, 1H, -NH, **indole** ring); MS m/z =180.2 (M+1).

**111c:** cream color solid, M.R: 190-194 °C, IR (KBr): 3253 (strong, -NH, stretching); 2226 cm⁻¹ (strong, -CN); 400 MHz, DMSO-d₆);7.28 (dd, J=8.72, 8.68Hz, 1H, **Ar-H**); 7.56 (d, J=8.72Hz, 1H, **Ar-H**); 7.64 (d, J=1.88Hz, 1H, **Ar-H** ); 8.31 (d, J=3.04 Hz, 1H, **indole** ring); 12.38 (s, 1H, strong, -COOH, **indole** ring); MS m/z =175, 177 (M+1);

**111d:** white solid, M.R: 240-246 °C, IR (KBr): **(figure-5A.1)** 3399 (strong, -NH); 3324, (strong, -COOH); 1662 cm⁻¹ (strong, **acid carbonyl**); 400 MHz, DMSO-d₆); **(figure-5A.2)** 6.88 (bs, 1H); 7.14 (dd, J = 8.6, 2.1 Hz, 1H); 7.43 (d, J = 8.6 Hz, 1H); 8.09 (s, 1H); 8.14 (d, J = 2.0 Hz, 1H, -NH, **indole** ring);11.72 (bs, 1H, -COOH, proton); ¹³C-NMR (DMSO d₆/TMS) signals showed **(figure-5A.3)** 165.71, 135.04,133.78, 127.26, 125.89, 122.29, 120.28, 114.07, 107.18, at δ MS m/z =194.9 (M-1) **(figure-5A.4).**
SECTION-B:

HBF₄: SiO₂: AN EFFICIENT HETEROGENEOUS CATALYST FOR

THE ONE STEP SYNTHESIS OF 4(3H)-QUINAZOLINONES UNDER

SOLVENT FREE CONDITIONS

5B.1. INTRODUCTION:

In regards to importance of quinazoline derivatives, especially 4(3H)-quinazolinones have gained more importance in recent years because of their biological activities such as anti-inflammatory, antimalarial, anti-cancer, anti-convulsant, anti-hypertensive, antiparkinsonin, analgesic activities [191-197]. Several bioactive natural products containing quinazolinone skeleton have also been reported from natural sources [198-201]. Some of these compounds were reported as anti-hyperlipidemic active compounds [202].

Requirements for One-pot Reactions:

Two components must combine to generate a substructure that reacts with another component.

The wrong components must not react irreversibly.

An irreversible step is needed to drive the reaction along the desired path.

Advantages of One-pot reactions:

1. Complexity is generated through the combination of multiple functional groups.

2. Diversity is easily incorporated in one step by varying the components.

3. Deprotection steps are often avoided.
4. One-pot reactions are ideal for automation.

5. Efficient solid phase or solution phase synthesis is possible.

**5B.2. Recent literature reports for the synthesis of 4(3H)-quinazolinonones:**

Bogert et.al. reported [203], the synthesized alkyl ketodihydroquinazolines (122) from N-acetyl anthranalic acid (120) and alkyl nitriles (121) under condensed reaction conditions in the presence of a base. *(Scheme-5B.1)*

\[
\begin{align*}
\text{(120)} & \quad \text{NHCOCH}_3 \quad \text{COOH} \\
\text{(121)} & \quad \text{base} \\
\text{base} & \quad \text{(122)}
\end{align*}
\]

*(...Scheme- 5B.1)*

Takeuchi et.al. [204] have established a method from o-azidobenzoyl chloride (123) and lactams (124) to afford the corresponding imides (125). These were treated with tributylphosphine and underwent an intramolecular aza-wittig reaction to give n-membered ring-fused quinazolinones (126) in better yields *(Scheme-5B.2).*

\[
\begin{align*}
\text{(123)} & \quad \text{COCl} \\
\text{(124)} & \quad \text{Et}_3\text{N/benzene} \\
\text{(125)} & \quad \text{PBU}_3\text{/benzene} \\
\text{(126)} & \quad \text{N}
\end{align*}
\]

*(...Scheme-5B.2)*
Xue et al. reported [205] efficient synthesis of N-disubstituted-4 quinazolones (129) in better yields from anilines (128) and N-acylanthranilic acids (127) under lewis acidic conditions. (Scheme-5B.3).

Abdel-Jalil et al. [206] have synthesized 2-substituted quinazolinones (133) by the condensation of anthranilamide (130) with aryl, alkyl or heteroaryl aldehydes (131) in the presence of CuCl₂ under reflux conditions. (Scheme-5B.4).

5.3. Present Work

4(3H)-Quinazolinones have gained more importance in recent years because of their important biological activities such as anti inflammatory, anti malarial, anti cancer, anti convulsant, anti hypertensive, anti parkinsonin, analgesic activities [207]. Several bioactive natural products containing quinazolininone skeleton have also been reported from natural sources [208]. Some of these compounds were
reported as antihyperlipidemic active compounds.[209] The common method for the preparation of quinazolinones involves the amidation of 2-amino benzoic acid or 2-amino benzonitrile followed by oxidative ring closure under basic conditions [210] and aza Wittig reactions of \( \alpha \)-azido substituted aromatic imides[211]. There are different one-pot syntheses of these compounds have been reported [212]. However most of these methods have significant drawbacks such as harsh reaction conditions, long reaction times, low yields, difficult work-up procedures, expensive reagents and difficulty in recovery and reusability of the catalysts.

Heterogeneous catalysts have gained more importance in recent years because of their ease of handling, simple work-up procedures, enhanced reaction rates, recovery of the catalysts and especially economical and environmental considerations. These important utilities keep in mind, we have recently developed silica-supported HBF\(_4\) (HBF\(_4\).SiO\(_2\)) is highly effective to catalyze one pot synthesis of 4(3H)-quinazolines (137) from the reaction of anthranalic acid (134), tri methyl orthoformate (135), and amines (136) (aryl or alkyl) at room temperature under solvent free conditions (Scheme - 5B.5). The catalyst can easily prepare from the readily available ingredients such as HBF\(_4\) and silicagel (finer than 200 mesh) [213].
We prepared various 4(3H)-quinazolinones (137) (Table 1) using anthranalic acid (134) with different substituted aryl and alkyl amines. The reaction procedure is simple and proceeded at room temperature within few minutes (6-25 min) in excellent yields after addition of the catalyst. The anilines containing both electron-withdrawing as well as electron groups underwent reaction smoothly. The reaction with electron withdrawing anilines (entry k, l) required reflux conditions and prolonged reaction times (20, 25 min). The fate of the reaction was tested with aliphatic amines also. Aliphatic amines gave good yields of products in present reaction conditions within short times (entry m). The reusability of the recovered catalyst was tested with the reaction of anthranalic acid (134), trimethyl orthoformate (135) and 4-methyl aniline (136). The first time when the fresh catalyst was used the yield of the product 3-p-tolylquinazolin-4(3H)-one(137) was 97%, while with the recovered catalyst in three subsequent recycles the yields were 90%, 87%, 80%.

In conclusion we have developed a simple and efficient synthesis of 4(3H)-quinazolinones by coupling of 134, 135 and aryl or alkyl amines using HBF₄·SiO₂ as a heterogeneous catalyst under solvent free conditions. The simple experimental procedure, ease of
handling, fast reaction conditions, excellent yields of products and reusability of the catalyst are notable advantages of the present protocol.

5B.4. Experimental section:

Melting points were measured on a Buchi 510 apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer RX 1 FT-IR spectrophotometer, the $^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) spectra on a Brucker-400 MHz spectrometer and the mass spectra on a API-2000, LCMS-MS system. Column chromatography was performed over silica gel (BDH 100-200 mesh) and TLC with silica gel GF 254.

5B.4.1. General procedure for the preparation of 4(3H)-Quinazolinones 137(a-l)

To a mixture of substituted anthranillic acid (134) (1 mmol), triethyorthoformate (135) (1.2 mmol) and substituted amine (136a-l) (1.2 mmol), silicagel supported HBF$_4$ (100 mg) was added. The mixture was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, 10 ml of chloroform was added to the reaction mixture and the catalyst was recovered by filtration. The filtrate was concentrated under vacuum and the obtained residue was chromatographed through silica gel using chloroform: Methanol as eluent to obtain 4(3H)-quinazolinones 137(a-l) in pure form.

137a: ($R_1 = \text{Ph}$); White color solid, Yield: 94%; Reaction time: 6 min; Reaction temperature: RT; M.R: 136-138 °C; I.R (KBr) cm$^{-1}$
5B.1): 3055 (very strong, \(-\text{CH}=\text{N},\) stretching); 1671 (\(-\text{C}=\text{O},\) hetro aryl, ring); \(^1\)H-NMR (400 MHz, DMSO-d\(_6\)) (figure-5B.2) \(\delta\): 7.59-7.49 (6H, m, 5 protons in Ar-H ring, 1H, hetro aryl ring); 7.72 (1H, dd, \(J=8.0, 1.9\) Hz, hetro aryl ring), 7.85 (1H, td, \(J=8.0\) Hz, hetro aryl ring), 8.19 (1H, dd, \(J=8.0\) Hz, hetro aryl ring), 8.33 (1H, s, \(-\text{CH}=\text{N}\)), \(^{13}\)C-NMR (100 MHz, DMSO-d\(_6\)) (figure-5B.3) \(\delta\): 160.3, 148.0, 147.4, 137.9, 134.9, 129.6, 127.8, 126.8, 122.2; MS \(m/z\): 223 [M+1] (figure-5B.4).

137b: (\(R_1=2-\text{F-Ph}\)); off white solid, Yield: 91%; Reaction time; 10 min; Reaction temperature: RT; M.R: 119-121 \(^0\)C; I.R (KBr) cm\(^{-1}\): 3054 (strong, \(-\text{CH}=\text{N}\)); 1674 (strong, \(-\text{C}=\text{O},\) hetro aryl, ring); \(^1\)H-NMR (400 MHz, DMSO-d\(_6\)) \(\delta\): 7.40-7.42 (td, 1H, Ar-H ring); 7.50 (td, 1H, Ar-H ring); 7.59-7.62 (m, 2H, Ar-H ring); 7.66-7.68 (td, 1H, hetro aryl ring); 7.75-7.77 (dd, 1H, J=8.0 Hz, hetro aryl ring); 8.19-8.21 (1H, dd, \(J=7.9, 1.9\) Hz, hetro aryl ring); 8.38 (1H, s, \(-\text{CH}=\text{N}\)); \(^{13}\)C-NMR (100 MHz, DMSO-d\(_6\)) \(\delta\): 159.7, 158.7, 156.2, 148.0, 147.4, 135.3, 131.8, 130.3, 128.0, 126.7, 125.3, 121.9, 116.8, 116.6; MS \(m/z\): 241.4 [M+1]\(^+\).

137c: (\(R_1=2-\text{Cl-Ph}\)); off white solid, Yield: 89%; Reaction time; 15 min; Reaction temperature: RT; M.R: 160-163 \(^0\)C; I.R (KBr) cm\(^{-1}\): 3062 (very strong,\(-\text{CH}=\text{N},\) hetroaryl); 1676.7 (strong, \(-\text{C}=\text{O},\) hetro aryl); \(^1\)H-NMR (400 MHz, DMSO-d\(_6\)) \(\delta\): 7.56-7.62 (3H, m, Ar-H ring); 7.70-7.78 (3H, m, two protons hetro aryl ring, one Ar-H ring); 7.85 (1H, t, \(J=8.0\) Hz); hetro aryl ring); 8.20 (1H, dd, \(J=8.0, 2.0\) Hz, hetro aryl ring); 8.31 (1H, s,\(-\text{CH}=\text{N}\)); \(^{13}\)C-NMR (100 MHz, DMSO-d\(_6\)) \(\delta\): 159.8,
143.1, 147.3, 135.3, 131.8, 131.0, 130.4, 128.8, 128.0, 127.8, 126.8, 122.1, MS m/z: 257.3 [M+H]+.

**137d**: (R$_1= 3$-Cl-Ph); Light orange solid, Yield: 93%; Reaction time; 15 min; Reaction temperature: RT; M.R: 164-166 °C; I.R (KBr) cm$^{-1}$: 3072 (very strong, -CH=N-, hetero aryl); 1678 (strong,-C=O hetero aryl); $^1$H-NMR (400 MHz, DMSO-d$_6$) δ: 7.56-7.62 (3H, m, Ar-H ring); 7.70-7.91 (3H, m, 2H protons hetero aryl ring, 1H, Ar-H ring); 8.19 (1H, t, $J$=8.0 Hz, hetero aryl ring); 8.21 (1H, dd, $J$ = 8.0, 2.0 Hz, hetero aryl ring); 8.31 (1H, s, -CH=N); $^{13}$C-NMR (100 MHz, DMSO-d$_6$) δ: 159.8, 148.1, 147.3, 135.3, 131.8, 130.9, 128.8, 128.0, 127.8, 126.8, 122.09; MS m/z: 157.3[M+H]+.

**137e**: (R$_1= 3,4$-Cl-Ph); Off white solid, Yield: 91%; Reaction time; 10 min; Reaction temperature: RT; M.R: 213-215 °C; I.R (KBr) cm$^{-1}$: 3067 (very strong, -CH=N-, hetero aryl); 1677 (strong,-C=O); $^1$H-NMR (400 MHz, DMSO-d$_6$) δ: 7.59-7.62 (3H, m, Ar-H ring); 7.74 (1H, dd, $J$=8.0, 2.0 Hz, Ar-H ring); 7.84-7.89 (2H, m, hetero aryl ring); 7.97 (1H, d, hetero aryl ring); 8.20 (1H, dd, $J$=8.0, 2.0 Hz, hetero aryl ring); 8.36 (1H, s,-CH=N); $^{13}$C-NMR (100 MHz, DMSO-d$_6$) δ: 160.2, 147.9, 146.9, 137.6, 135.2, 132.0, 131.3, 130.2, 128.5, 127.7, 126.8, 122.1; MS m/z: 291[M+H]+.

**137f**: (R$_1= 4$-bromo pyridine); Pale yellow color solid, Yield: 92%; Reaction time; 20 min; Reaction temperature: RT; M.R: 212-214 °C; I.R (KBr) cm$^{-1}$:3060 (very strong, -CH=N-, hetero aryl); 1681 (strong, -C=O); $^1$H-NMR (400 MHz, DMSO-d$_6$) δ: 7.63 (1H, t, $J$= 8.0 Hz, hetero aryl ring); 7.75-7.77 (d,1H, Ar-H ring); 7.82-7.84 (d, 1H, Ar-H ring);
7.91 (t, 1H, hetro aryl ring); 8.22-8.24 (1H, dd, J=8.0 Hz, hetro aryl ring); 8.33 (1H, dd, J=8.0, 2.0 Hz, hetro aryl ring); 8.56 (1H, s, Ar-H ring); 8.81 (1H, s, J=1.9 Hz, -CH=N, hetro aryl ring); 13C-NMR (100 MHz, DMSO-d$_6$) δ: 159.9, 150.2, 148.8, 147.6, 145.7, 141.4, 135.5, 128.1, 127.8, 126.9, 124.3, 121.9, 120.4; MS m/z: 302 [M+1]$^+$. 

137g: (R$_1$ = 2-Br-Ph); off white solid, Yield: 96%; Reaction time; 10 min; Reaction temperature: RT; M.R: 186-188 0°C; I.R (KBr) cm$^{-1}$: 3061 (very strong, -CH=N, hetro aryl); 1677 (strong,-C=O); 1H-NMR (400 MHz, DMSO-d$_6$) δ: 7.50-7.52 (td, 1H, Ar-H ring); 7.58-7.63 (m, 2H, Ar-H ring); 7.69-7.71 (1H,dd, Ar-H ring); 7.76-7.78 (1H, dd, J=8.0 Hz, hetro aryl ring), 7.87-7.93 (2H, m, hetro aryl ring); 8.20 (1H, dd, J=8.0, 2.0 Hz, hetro aryl ring), 8.28 (1H, s, -CH=N); 13C-NMR (100 MHz, DMSO-d$_6$) δ: 159.8, 148.1, 147.3, 137.0, 135.3, 133.5, 131.7, 129.3, 128.0, 127.8, 126.8, 122.2; MS m/z: 301 [M+1]$^+$. 

137h: (R$_1$ = 4-CH$_3$-Ph); White solid, Yield: 97%; Reaction time; 15 min; Reaction temperature: RT; M.R: 140-143 0°C; IR (KBr) cm$^{-1}$: 1690 (strong,-C=O); 1515 (strong,-CH$_3$); 1H-NMR (400 MHz, DMSO-d$_6$) δ: 2.38 (3H, s, -CH$_3$); 7.34-7.41 (4H, m, Ar-H ring); 7.59-7.61 (1H, t, J=8.0 Hz, hetro aryl); 7.73 (1H, dd, J=8.0 Hz hetro aryl ring); 7.85-7.87 (1H, t, J=8.0 Hz hetro aryl, ring); 8.20 (1H, dd, J=8.0 Hz, hetro aryl ring); 8.30 (1H, s, -CH-N); 13C-NMR (100 MHz, DMSO-d$_6$) δ: 160.4, 148.1, 147.6, 138.6, 1354.4, 134.9, 130.0, 127.6, 126.7, 122.2, 21.0; MS m/z: 237 [M+1]$^+$. 

137i: (R$_1$ = 3-CH$_3$-Ph); White solid, Yield: 94%; Reaction time; 20 min; Reaction temperature: RT; M.R: 125-128 0°C; I.R (KBr) cm$^{-1}$: 3051 (very
strong, -CH=N-, hetero aryl); 1671 (strong, -C=O); 1470 (strong, -CH₃); ¹H-NMR (400 MHz, DMSO-d₆) δ: 2.37 (3H, s, -CH₃); 7.30-7.33 (3H, m, Ar-H ring); 7.41-7.45 (t, 1H, Ar-H ring); 7.56-7.60 (1H, td, J=8.0 Hz, hetero aryl ring); 7.72 (1H, dd, J=8.0 Hz, hetero aryl ring); 7.84-7.88 (1H, td, J=8.0 Hz, hetero aryl ring); 8.17-8.19 (1H, dd, J=8.0 Hz, hetero aryl ring); 8.30 (1H, s,-CH=N, hetero aryl); ¹³C-NMR (100 MHz, DMSO-d₆) δ: 160.3, 148.0, 147.4, 139.2, 137.8, 135.0, 129.7, 128.2, 127.6, 124.8, 122.2, 21.1; MS m/z: 237[M+1]+.

137j: (R₁ = 3-OCH₃-Ph); Light cream color solid, Yield: 90%; Reaction time; 15 min; Reaction temperature: RT; M.R: 155-157 °C; I.R (KBr) cm⁻¹: 3050 (very strong, -CH=N-, hetero aryl); 1686 (strong, -C=O); 1260 (strong, O-CH₃, stretching); ¹H-NMR (400 MHz, DMSO-d₆) δ: 3.79-3.81 (3H, s,-CH₃); 7.06-7.16 (3H, m, Ar-H ring); 7.44-7.48 (1H, t, J=8.0 Hz, Ar-H ring); 7.59 (1H, t, J=8.0 Hz, hetero aryl ring); 7.72-7.74 (1H, dd, J=8.0 Hz, hetero aryl ring); 7.87 (1H, td, J=8.0 Hz, hetero aryl ring); 8.18-8.20 (1H, dd, J=8.0 Hz, hetero aryl ring) 8.32 (1H, s,-CH=N); ¹³C-NMR (100 MHz, DMSO-d₆) δ: 160.2, 160.1, 148.0, 147.4, 139.0, 135.0, 130.3, 127.6, 122.2, 115.0, 113.7, 55.8; MS m/z: 253.2[M+1]+.

137k: (R₁ = 4-COOH-Ph); Cream color solid, Yield: 81%; Reaction time; 20 min; Reaction temperature: reflux; M.R: > 260 °C; I.R (KBr) cm⁻¹: 3072 (very strong, -CH=N-, hetero aryl); 3368 (strong, acid –OH); 1694 (strong, acid carbonyl); 1619 (strong,-C=O, hetero aryl ring); ¹H-NMR (400 MHz, DMSO-d₆) δ: 7.58-7.66 (3H, m, phenyl ring); 7.73-7.79 (2H, m, one proton Ar-H ring + 1H hetero aryl ring);
7.88 (1H, t, J= 8.0 Hz, hetero aryl ring), 8.06-8.08 (1H, dd, J=7.8, 1.8 Hz, hetero aryl ring); 8.14-8.16 (1H, dd, J=8.0, 1.8 Hz, hetero aryl ring); 8.31 (1H, s,-CH=N); 13.1 (1H, s, acid proton), $^{13}$C-NMR (100 MHz, DMSO-d$_6$) δ: 166.2, 160.6, 148.3, 147.5, 137.5, 133.8, 131.4, 130.1, 129.5, 127.6, 126.7, 122.2; MS m/z: 267[M+1]$^+$. 

137l: (R$_1$= 4-COOCH$_2$CH$_3$-Ph); off white solid, Yield: 79%; Reaction time; 25 min; Reaction temperature: Reflux; M.R: 199-201 °C; I.R (KBr) (figure-5B.5). 3054 (very strong, -CH=N-, hetero aryl); cm$^{-1}$: 1716(-C=O, ester carbonyl); 1692 (-C=O, hetero aryl ring); 1596, $^1$H-NMR (400 MHz, DMSO-d$_6$) (figure-5B.6). δ: 1.32-1.36 (3H, t, J=7.0 Hz,-CH$_3$); 4.33-4.38 (2H, q, J= 7.0 Hz,-OCH$_2$), 7.61-7.63 (1H, t, hetero aryl ring); 7.71-7.77 (3H, m, Ar-H ring); 7.87-7.89 (1H, t, J = 8.0 Hz, hetero aryl ring); 8.11-8.13 (2H, d, J= 8.0 Hz, Ar-H ring + hetero aryl ring); 8.20-8.22(1H, dd, J=8.0, 2.0 Hz, hetero aryl ring); 8.38 (1H, s, -CH=N); $^{13}$C-NMR (100 MHz, DMSO-d$_6$) (figure-5B.7) δ: 165.4, 160.1, 147.9, 146.9, 141.8, 135.2, 130.3, 128.2, 127.7, 126.8, 122.1, 61.4, 14.4; MS m/z: 295 [M+1]$^+$. (figure-5B.8).
SECTION-C:

CONVENIENT AND LARGE SCALE SYNTHESIS OF FUNCTIONALISED ARYLPIPERAZINE DERIVATIVES

5C.1. PRESENT WORK:

The present chapter deals with the synthesis of different arylpiperazine products. The condensation between the aniline and bis(2-chloroethyl) amine mono chloride groups containing compounds. After that condensation gave a different piperazine derivatives obtain.

5C.2. Introduction:

N-arylpiperazines are an interesting family of compounds in the field of neuropharmaceuticals where these piperazines are common structure unit for many neurological ligands. Arylpiperazines are the most notable among the agents that bind the various 5-HT1 sites[214,215]. N-arylpiperazine are the key moieties in the modified analogues of KN-62, a potent antagonist of the purinergic P2X7 receptor KN-62 antagonist that are potent inducers of human primary osteoclasts[217]. A novel series of N-arylpiperazine-1-carboxamide derivatives was synthesized and their androgen receptor (AR) antagonist activities and in vivo antiandrogenic properties [218]. Arylpiperazines were also found to be nonsteroidal androgen receptor antagonists [219]. A new series of arylpiperazines coupled with benzimidazoles were shown to possess nonnucleoside reverse transcriptase inhibitor activities[220] Similarly other arylpiperazine
derivatives were found to possess anti-bacterial [221] and anti-
microbial activities [222, 223].

5C.3. LITERATURE SURVEY:

Masakazu et.al. reported [224] reaction of halo benzene (138) with piperazine using outstanding activities and selectivity’s of a Pd/P (t-Bu), in o-xylene containing sodium tert.butoxide. Excellent selectivity for the formation of piperazine derivative (139) over the bis compound (140) was observed (Scheme-5C-1).

\[
\begin{align*}
\text{R} & \quad \text{X} = \text{Cl, Br, I} \\
\text{(138)} & \\
\text{H} & \quad \text{N} & \quad \text{H} \\
\text{Pd} & \quad (\text{dba})_2 & \quad \text{P} (\text{t-Bu})_3 \\
\text{NaO} & \quad \text{Bu} & \quad \text{O-xylene} \\
\text{R} & \quad \text{N} & \quad \text{N} & \quad \text{R} \\
\text{(139)} & \\
\text{R} & \quad \text{N} & \quad \text{N} & \quad \text{R} \\
\text{(140)} & \\
\end{align*}
\]

…Scheme-5C-1

John et.al. reported [225] the reaction of 4-tert.butylphenyl triflate (141) with N-methylpiperazine (142), employing a mixture of Pd(OAc)\textsubscript{2} / BINAP(2%Pd) and NaOEtBu(1.4eq) in toluene at 80 °C for 3hrs gave N-aryl piperazine (143) in 73% yield. (Scheme-5C-2).

\[
\begin{align*}
\text{O} & \quad \text{Tf} \\
\text{(141)} & \\
\text{H} & \quad \text{N} & \quad \text{CH}_3 \\
\text{Pd(OAc)} & \quad (2\%\text{Pd}) \\
\text{NaO} & \quad \text{EtBu} & \quad \text{Toluene} / 80^\circ\text{C} \\
\text{But} & \quad \text{N} & \quad \text{N} & \quad \text{CH}_3 \\
\text{(143)} & \\
\end{align*}
\]

…Scheme-5C-2

Eyal et.al. reported [226] the synthesis of aryl piperazine, on reaction of aniline derivatives (144) with bis(2-bromoethyl)-N-
(substituted)amine(145) under solvent free condition to give the phenyl piperazine derivatives(146) (Scheme-5C-3).

![Chemical Reaction](image_url)

Shu-Hai et.al. reported [227] a convenient procedure for synthesizing aryl piperazine (149) using with or without substitution on the piperazine (147) ring is react with aryl halogen derivatives (148) via palladium-catalyzed coupling reactions. (Scheme-5C-4).

![Chemical Reaction](image_url)

Kevin et.al. reported[228] the preparation of general and convenient synthesis of aryl piperazine (152) from bis (2-chloroethyl) amine hydrochloride (151) and a broad range of anilines (150) in diethyl glycol monomethyl ether is described. (Scheme-5C-5).
5C.4. RESULTS AND DISCUSSIONS:

Reaction of substituted anilines (150a-n) with bis (2-chloroethyl) amine mono hydro chloride (151) in o-xylene as a solvent reflux at 140-145 °C for 24 hrs, gave a respected piperazine derivatives (153a-n) which have been characterized on the basis of its spectral data. (Scheme-5C.6).

**GENERAL:** The reagents which are used in the synthesis i.e. bis (2-chloro ethyl) amine mono hydrochloride, substituted anilines, o-xylene, ect., were purchased from commercial suppliers and used as supplied.

**Preparation of 153a-n from 153a-n:**

A mixture of substituted aniline (150a-n) (0.05moles) was treated with bis (2-chloroethyl) amine mono chloride (151) (1.5eq.) in o-xylene (100ml) as a solvent reflux for 24 hrs. After completion of reaction cool to RT and stir for one hour at RT, then filter the mass and wash with Acetone collect the materiel and recrystalisation from
suitable solvent and obtained the pure compounds (153a-n). Then all compounds are identified by IR (KBr), ^1^H-NMR (DMSO d$_6$/TMS) and ^1^C-NMR (DMSO-d6).

**153a: (i.e., R=4-bromo phenyl)** Yield 10.5 gm (92.5%); off white solid. M.R: 262-268 °C. IR (KBr): (figure-5C.1) 3412 (strong, –NH, stretching); ^1^H-NMR (DMSO d$_6$/TMS) (figure-5C.2) δ 3.14 (m, 4H, hetro aryl ring); 3.3 (m, 4H, hetro aryl ring); 6.9-6.92 (d, 2H, benzene ring); 7.34-7.36 (d, 2H, benzene ring); 9.29 (s, 2H, -NH.HCl); ^1^C-NMR (DMSO,d6): (figure-5C.3) 149.5,132.0,118.3,111.5,45.4,42.7 MS m/z = 242 .7(M+2) (figure-5C.4).

**153b: (i.e., R=2-chloro phenyl)** Yield 10.5 gm (91.5 %); off white solid. M.R: 120-125°C. IR (KBr): 3359 (strong, –NH, stretching); ^1^H-NMR (DMSO d$_6$/TMS) δ 3.13-3.53 (m, 8H, hetro aryl ring); 7.02-7.06 (t, 1H, Ar-H ring); 7.11-7.13 (d, 1H, Ar-H ring); 7.24-7.28 (t,1H, Ar-H ring); 7.36-7.38 (d,1H, Ar-H ring); 9.64 (s, 2H, -NH.HCl); ^1^C-NMR (DMSO-d6): 148.2, 130.7, 128.5, 127.9, 125.0, 121.3, 48.0, 43.3, MS m/z= 199 (M+2).

**153c: (i.e., R=3-chloro phenyl)** Yield 10.5 gm (92.0 %); off white solid. M.R: 210-213 °C. IR (KBr): 3416 (broad, –NH, stretching); ^1^H-NMR (DMSO d$_6$/TMS) δ 3.12-3.2 (m, 4H, hetro aryl ring ); 3.38-3.51 ( m, 4H, hetro aryl); 6.81-6.83 (d, 1H, Ar-H ring); 6.86-6.91 (d, 1H, Ar-H ring); 6.98 (s,1H, Ar-H ring); 7.19-7.23 (t, 1H, Ar-H ring), 9.61 (s, 2H, -NH.HCl); ^1^C-NMR (DMSO-d6): 151.5, 134.2, 130.9, 119.5, 115.6, 114.5, 45.1, 42.6; MS m/z = 197 (M).
153d: (i.e., R=4-chloro phenyl) Yield 10.5 gm (90.5 %); off white solid. M.R: 76-79 °C. IR (KBr): 3333 (strong, –NH, stretching), $^1$H-NMR (DMSO d$_6$/TMS) δ 2.77-2.79 (m, 4H, hetero aryl ring); 2.92-3.10 (m, 5H, 4H in hetero aryl +1H in -NH ) 6.81-6.93 (d, 2H, Ar-H ring) 7.12-7.22 (d, 2H, Ar-H); $^{13}$C-NMR (DMSO-d$_6$): 150.8, 128.8, 122.4, 116.9, 49.5, 45.8; MS m/z = 197 (M).

153e: (i.e., R= 2, 3-dichloro phenyl) Yield 10.5 gm (92.5 %); off white solid. M.R: 240-243 °C. IR (KBr): 3422 (broad, –NH, stretching), $^1$H-NMR (DMSO d$_6$/TMS) δ 3.17 (m, 8H, hetero aryl ring); 7.14-7.17 (dd, 1H, Ar-H); 7.28-7.33 (m, 2H, Ar-H ring); 9.43 (s, 2H, -NH.HCl); $^{13}$C-NMR (DMSO-d$_6$): 150.3, 133.0, 128.9, 126.5, 125.5, 120.1, 48.0, 43.2; MS m/z = 232.9 (M+2).

153f: (i.e., R=3, 4-dichloro phenyl) Yield 10.0 gm (91.5 %); off white solid. M.R: 212-214 °C. IR (KBr): 3436 (strong, –NH, stretching), $^1$H-NMR (DMSO d$_6$/TMS) δ 3.14-3.24 (m, 4H, hetero aryl ring); 3.42-3.45 (m, 4H, hetero aryl) 6.93-6.95 (d, 1H, Ar-H ring); 7.12-7.16 (s, 1H, Ar-H ring); 7.37-7.39 (d, 1H, Ar-H ring); 9.60 (s, 2H, -NH.HCl); MS m/z = 231.2 (M+1).

153g: (i.e., R= 4-fluoro phenyl) Yield 10.5 gm (92.5 %); off white solid. M.R: >230°C. IR (KBr): 3376 (strong, –NH stretching); $^1$H-NMR (DMSO d$_6$/TMS) δ 3.25 (m, 4H, hetero aryl ring); 3.42-3.43 (m, 4H, hetero aryl ring); 6.3 (d, 2H, Ar-H ring); 7.07-7.18 (d, 2H, Ar-H ring); 9.75 (s, 1H, -NH ); $^{13}$C-NMR (DMSO-d$_6$): 159.3, 156.9,145.1, 119.6, 116.3, 47.5, 42.3.; MS m/z = 180.9 (M+2).
153h: (i.e., R= 2-Hydroxy phenyl) Yield 10.0 gm (90.5 %); off white solid. M.R: 259-265 °C (decompose). IR (KBr): 3066 (strong, -NH, stretching); 3006 (strong, -OH, stretching); $^1$H-NMR (DMSO d$_6$/TMS) δ 3.41 (m, 4H, hetero aryl ring); 3.58 (m, 4H, hetero aryl); 6.27 (s, 1H, -OH); 6.59-6.63 (t, 1H, Ar-H ring); 6.75-7.11 (m, 2H, Ar-H ring); 7.40-7.42 (d, 1H, Ar-H ring); 9.77 (s, 2H, -NH.HCl); $^{13}$C-NMR (DMSO-d$_6$): 150.9, 133.1, 127.9, 121.3, 119.8, 117.4, 48.2, 41.8, MS m/z= 179.3 (M+1).

153i: (i.e., R=4-Methoxy phenyl): Yield 10.0 gm (85.5 %). Tan color powder, M.R: 244-248 °C; IR (KBr): 3426 (broad, -NH, stretching); 1107 (strong, -OCH$_3$); $^1$H-NMR (DMSO-d$_6$): 2.75-2.81 (m, 4H, hetero aryl ring); 2.86-2.91 (m, 4H, hetero aryl ring); 3.62-3.7 (s, 3H, -OCH$_3$); 6.77-6.87 (m, J=7.2Hz, 4H, Ar-H ring); 9.52 (s, 2H, NH.HCl); $^{13}$C-NMR (DMSO-d$_6$): 153.1, 146.5, 117.6, 114.5, 55.4, 51.2, 46.1; m/z = 193.1 (M+1).

153j: (i.e., R=4-Methyl phenyl): Yield 10.0 gm (85.5 %). Tan color powder, MR: >248 °C; IR (KBr): 3413.7 (broad, -NH, stretching); 1515 (strong, -CH$_3$); $^1$H-NMR (DMSO-d$_6$): 2.13-2.23 (s, 3H, -CH$_3$), 3.14-3.30 (m, 4H, hetero aryl); 3.38-3.43 (m, 4H, hetero aryl ring); 6.81-6.86 (d, J=8.0 Hz, 2H, Ar-H ring); 6.99-7.04 (d, 2H, Ar-H ring); 9.52 (s, 2H, NH.HCl); $^{13}$C-NMR (DMSO-d$_6$): 148.2, 129.8, 129.2, 116.6, 46.2, 42.8, 20.4, m/z = 177 (M+1).

153k: (i.e., R = 3-Nitro phenyl): Yield 10.0 gm (90.5 %). Pale yellow solid. M.R: 266.5-268.4 °C (decompose).IR (KBr): 3409 (broad -NH, stretching); 1334 (strong, -NO$_2$); $^1$H-NMR (DMSO-d$_6$): 3.08-3.1 (m, 4H,
hetero aryl); 3.63-3.76 (m, 4H, hetero aryl ring); 6.98-7.11 (d, J=8.0Hz, 2H, Ar-H ring); 7.94-8.06 (m, J=8.0Hz, 2H, Ar-H ring); 9.7 (s, 2H, -NH.HCl); $^{13}$C-NMR (DMSO-d6): 150.9, 149.1, 130.7, 122.1, 114.0, 109.5, 45.0, 42.5; m/z = 208 (M+1).

153l: R = 4-Nitro phenyl: Yield 10.0 gm (90.5%). Pale yellow solid.
M.R: 247-252 0 C.; IR (KBr): 3366 (br, -NH, stretching); 1354 (strong, -NO$_2$); $^1$H-NMR (DMSO-d6): 3.13-3.18 (m, 4H, hetero aryl ring); 3.5-3.53 (m, 4H, hetero aryl ring); 7.37-7.49 (d, J=8.0Hz, 2H, Ar-H ring); 7.52-7.66 (d, J=8.0Hz, 2H, Ar-H ring); 9.66 (s, 2H, -NH.HCl); $^{13}$C-NMR (DMSO-d6): 154.3, 138.1, 125.9, 103.7, 43.8, 42.4.; m/z=208.1(M+1).

153m: (R=3-Carboxy phenyl), Yield 10.0g (85.5 %). Tan color powder,
M.R: >2600 C; IR (KBr): 3388 (braod, -NH); 3119 (braod, -COOH, stretching); 1702 (strong, acid carbonyl, stretching); $^1$H-NMR (DMSO-d6): 3.13-3.17 (m, 4H, hetero aryl ring); 3.29-3.35(m, 4H, hetero aryl ring); 7.20-7.22 (d, J=8.0Hz, 1H, Ar-H ring); 7.27-7.29(t, 1H, Ar-H ring); 7.32-7.39 (d, 1H, Ar-H ring); 7.41-7.52(s, 1H, Ar-H ring); 9.55 (s, 2H, -NH.HCl); 12.9 (s, 1H, -COOH); $^{13}$C-NMR (DMSO-d6): 167.7, 150.4, 132.0, 129.7, 121.1, 120.7, 116.5, 45.5, 42.7.; m/z=207 (M+1).

153n: (R= Ethyl benzoate): Yield 10.0 gm (85.5 %). Tan color powder,
M.R:100-102 0 C; IR(KBr): (figure-5C.5) 3337 (strong, -NH, stretching); 1688 (strong, ester carbonyl); 1192 (strong, -OCH$_2$CH$_3$); $^1$H-NMR (DMSO-d6): (figure-5C.6) 1.21-1.31 (t, 3H, -CH$_2$CH$_3$); 2.48 (s, 1H, -NH); 2.76-2.79 (m, 4H, hetero aryl); 3.15-3.22 (m, 4H, hetero aryl ring); 4.17-4.25 (q, 2H, OCH$_2$); 6.86-6.94 (d, 2H, Ar-H ring); 7.71-7.76
(d, J=8.0Hz, 2H, **Ar-H ring**); $\text{^{13}C-NMR (DMSO-d6): (figure-5C.7)}. \text{166.0, 154.7, 130.9, 118.5, 113.4, 60.1, 48.1, 45.7, 14.6. m/z = 235 (M+1). (figure-5C.8).}$