Chapter - 4

Synthesis of some Mannich bases and novel benzofuran derivatives containing imidazo[2,1-6][1,3,4]thiadiazoles
4.1. Introduction

A wide variety of pharmacological properties have been associated with benzofuran derivatives[1-4]. These are an important class of organic compounds, which were known to be present in many natural products[5]. They found their applications in agrochemicals[6,7], pharmaceuticals[8-13] and cosmetics[14,15]. Benzo[\(b\)] furans are building blocks of optical brighteners[16]. Many of the natural Benzo[\(b\)]furans have physiological, pharmacological and toxic properties and as a result, there is continuing interest in their chemical synthesis. Cyclization reactions of various types have been used, to produce substituted benzo[\(b\)]furans[17-20]. 1,3,4-Thiadiazole derivatives are well known for their wide spectrum of biological, pharmacological and antileukemic activities[21-23]. Imidazo[2,1-b]thiadiazole skeleton is an important pharmacophore of synthetic origin. A number of heterocycles possessing this bicyclic system have been found to exhibit antitubercular[24], analgesic[25] and antibacterial[26] activities. Biheterocyclic benzofuranylimidazo[2,1-b]thiadiazoles have been patented[27] for their biological importance. It has been observed that methylene bridged benzofuranyl imidazo[2,1-b]thiadiazoles and the Mannich bases derived from them exhibit promising anti-inflammatory activity[28].

Nitrogen and sulphur containing heterocyclic compounds are of biological interest and the development of new synthetic approaches for their synthesis is a challenge for organic chemists. The presence of imidazo[2,1-b][1,3,4]thiadiazole ring reflects interesting biological properties[29-31]. Thus, encouraged by their potential clinical application and as part of our research to synthesize new bioactive compounds, in the present investigation, we made an efficient attempt in synthesizing a new series of
benzofuran derivatives containing an imidazo[2,1-b][1,3,4] thiadiazole moiety at the 2-
postion.

The Mannich reaction is known to be one of the most important synthetic
methods in organic chemistry[32-36]. At present, the great potentialities of this reaction
are far from being exhausted and are still of interest for chemists. For instance, a number
of recent studies are devoted to the "nonclassical" Mannich synthesis using new
substrates under modified aminomethylation conditions[37]. The intermolecular Mannich
reactions[38] are of particular attention since they are very promising for designing of
novel carbocyclic and heterocyclic systems. With the present work, we open up a series
of publications concerned with the study of the structures, methods for the synthesis, and
chemical transformations of nitrogen and sulfur containing heterocyclic compounds
obtained by the Mannich reaction.

Frolov and coworkers have synthesized some imidazo[2,1-b][1,3,5]thiadiazine 1
derivatives by the reaction of (Z)-5-benzylidene-2-thiohydantoin with formaldehyde and
primary aromatic amines[39].

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{NH} & \quad \text{S} \\
\text{NH} & \quad \text{H} \\
\text{NH} & \quad \text{HCHO, DMF, } \Delta \\
\text{Ph} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{NH} & \quad \text{H} \\
\text{HCHO} & \quad \text{Ph} \\
\end{align*}
\]
Andreani et al. reported the synthesis and antitumor activity of some new 3-[(2-
substituted-6-methyl-7H-pyrrolo[1,2-a]imidazol-3-yl)methylidene]-5-substituted-1-
substituted-1,3-dihydro-2H-indol-2-one derivatives 2 [40].

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{N} \\
\text{O} \\
\text{R}
\end{array}
\]

Ramakrishna et al. synthesized and studied the crystal structure of 2-[6-methyl
benzofuran-3-ylmethyl]-5-morpholino-4-ylmethyl]-6-(4-chlorophenyl)-imidazo[2,1-b]
[1,3,4]thiadiazoles 3 [41].

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{Cl} \\
\text{O} \\
\text{N}
\end{array}
\]

Jadhav and coworkers reported variety of methylene bridged benzofuran-3-yl
imidazothiadiazole derivatives 4. They adapted a novel route starting from 6-methyl
benzofuran-3-acetic acid and thiosemicarbazide. The intermediate, aminothiadiazole
obtained was reacted with phenacyl bromides to obtain the title skeleton. The reactivity
of this system has been exploited to introduce various groups at C-5. Newly synthesized compounds were screened for their anti-inflammatory and analgesic activities [28].

Andanappa and coworkers reported a series of 2-trifluoromethyl/sulfonamido-5,6-diaryl substituted imidazo[2,1-b]-1,3,4-thiadiazole derivatives 5. The selected compounds were evaluated for their preliminary \textit{in vitro} cyclooxygenase inhibitory activity against COX-2 and COX-1 enzymes using colorimetric method. The compounds tested showed selective inhibitory activity towards COX-2 (80.6–49.4%) and COX-1 (30.6–8.6). Same compounds were tested for anti-inflammatory activity (70.09–42.32%), which shown good activity with comparable to that of celecoxib[42].

Thus, encouraged by their potential clinical applications and as part of our research programme to synthesize new bioactive compounds, in the present investigation, we have synthesized a new series of benzofuran derivatives containing a imidazo[2,1-b]...
[1,3,4] thia diazole moiety at 2-position and Mannich bases and the bioactivity of the newly synthesized compounds were carried out and came up with good results.

4.2. Present work

The various biological activities associated with naturally occurring and the synthetic compounds containing fused benzofuran moiety prompted us to synthesize a series of 6-(1-benzofuran-2-yl)-2-(4-chlorophenyl)imidazo[2,1-b][1,3,4]thiadiazoles and its Mannich bases.

The synthetic strategy involved the following steps:

1. Synthesis of 1-(1-benzofuran-2-yl)-2-bromoethanone as a starting material (2).
2. Synthesis of 5-aryl-1,3,4-thiadiazol-2-amine (3a–e) via condensation reaction of thiosemicarbazide with aromatic carboxylic acids.
3. The reaction of 1-(1-benzofuran-2-yl)-2-bromoethanone with compounds (3a–e) to furnish 6-(1-benzofuran-2-yl)-2-(4-substitutedphenyl)imidazo[2,1-b][1,3,4]thiadiazoles (4a–e).
4. The synthesis of Mannich bases (5–7) by the reaction of formaldehyde, secondary amines and compound 4d in acid media.
Schematic representation of the synthesized title compounds is given in the following scheme-4.

4.2.1. Synthesis of 1-(1-benzofuran-2-yl)-2-bromoethanone 2

1-(1-Benzofuran-2-yl)-2-bromoethanone 2 which is a key intermediate for the synthesis of title compounds. The key intermediate compound 2 can be synthesized by two alternative methods. In first method, 2-acetylbenzofuran upon bromination by bromine in acetic acid furnished compound 2. In another method, bromination was carried out by using N-bromosuccinamide (NBS) in CCl₄. In the present investigation we adopted first method because of high yield and minimum reaction time.
The structure of \(1-(1\text{-benzofuran-2-yl})\text{-2-bromoethanone} \) (2) was evidenced by its spectral data. The IR spectrum of compound 2 displayed an absorption band at 1685 cm\(^{-1}\) due to C=O group. \(^1\text{H-NMR}\) spectrum of compound 2 exhibited a multiplet between \(\delta 7.36 - 8.09\) ppm due to five aromatic protons and a singlet at \(\delta 4.31\) ppm due to two \(-\text{CH}_2\) protons. In mass spectrum it showed a molecular ion peak M\(^+\) at m/z 239 which correspond to the molecular weight of compound 2, along with the isotopic peak [M+2] at 241.

4.2.2. Synthesis of 5-aryl-1,3,4-thiadiazol-2-amine (3a-e)

The synthesis of 5-aryl-1,3,4-thiadiazol-2-amine (3a-e) is carried out by using the known procedure available in the literature. The synthesized compounds were confirmed by compared melting point[43].
4.2.3. Synthesis of 6-(1-benzofuran-2-yl)-2-phénylimidazo[2,1-b][1,3,4]thiadiazoles (4a-e)

When a mixture of equimolar quantities of 1-(1-benzofuran-2-yl)-2-bromoethanone (2) and 5-aryl-1,3,4-thiadiazole-2-amine (3a–e) was refluxed in ethanol, it furnished 6-(1-benzofuran-2-yl)-2-(4-substitutedphenyl)imidazo[2,1-b][1,3,4]thiadiazoles (4a–e), the structure of which were confirmed by with their spectral data.

\[
\begin{align*}
\text{2} & \quad \text{H}_2\text{N} \quad \text{S} \quad \text{NN} \\
\text{CH}_2\text{Br} & \quad \text{R} \\
\text{Ethanol/NaHCO}_3 & \quad \text{Reflux for 6-10hrs} \\
\text{3a-e} & \quad \text{4a-e}
\end{align*}
\]

Where

\[
\begin{align*}
\text{R} & = \text{Cl, H, OCH}_3, \text{CH}_3, \text{F} \\
\text{a, b, c, d, e} & 
\end{align*}
\]

The IR spectrum of compound 4a displayed a absorption band at 1597 cm\(^{-1}\) due to C=\(N\) and 1543 is due to C=C group. \(^1\)H NMR spectrum of Compound 4a exhibited a multiplet between \(\delta 7.20 - 8.35\) ppm due to nine aromatic protons and a singlet at \(\delta 8.56\) ppm due to one –CH proton of imidazole moiety. In the mass spectrum, it showed a molecular ion peak \(\text{M}^+\) at \(m/z\) 352 which corresponding to the molecular weight of compound 4a.
Chapter-4

imidazo[2,1-b][1,3,4]thiadiazoles and Mannich Base derivatives

The possible mechanism for the formation of compounds (4a-e) is given below.

**Mechanism:**
Chapter 4

imidazo[2,1-b][1,3,4]thiadiazoles and Mannich Base derivatives

[Diagram of molecular structure with IR spectrum]
Table 4.1. Spectral data of 6-(1-benzofuran-2-yl)-2-phenylimidazo[2,1-b][1,3,4] thiadiazoles (4a-e)

<table>
<thead>
<tr>
<th>comp</th>
<th>R</th>
<th>IR in cm(^{-1})</th>
<th>(^1)HNMR in (\delta) ppm</th>
<th>Molecular ion(m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cl</td>
<td>3053, 2920-2853, 1597(C=N), 1543(C=C),</td>
<td>8.56(s,1H,CH, imidazole), 7.20-8.35 (Ar-H, 9H)</td>
<td>352</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>3080, 2938-2853, 1576(C=N), 1532(C=C).</td>
<td>8.4 (s,1H,imidazole), 7.19-8.03(m, Ar-H, 10H)</td>
<td>317</td>
</tr>
<tr>
<td>c</td>
<td>OCH(_3)</td>
<td>3078, 2921-2856, 1548(C=N), 1438 (C=C)</td>
<td>4.36(s,3H, OCH(_3)), 8.1 (s,1H, imidazole) , 7.12-7.72( m, Ar-H, 9H )</td>
<td>347</td>
</tr>
<tr>
<td>d</td>
<td>CH(_3)</td>
<td>3093, 2924-2851, 1527(C=N), 1598 (C=C)</td>
<td>2.34(s,3H, CH(_3)), 8.4 (s,1H,imidazole), 7.18-7.80(m, Ar-H, 9H )</td>
<td>331</td>
</tr>
<tr>
<td>e</td>
<td>F</td>
<td>3123, 2924-2855, 1556(C=N), 1478 (C=C)</td>
<td>8.35(s,1H,imidazole), 7.20-7.87( m, Ar-H, 9H )</td>
<td>335</td>
</tr>
</tbody>
</table>
4.2.4. Synthesis of 6-(1-benzofuran-2-yl)-2-(4-chlorophenyl)-5-(amino-1-yl methyl) imidazo[2,1-b][1,3,4]thiadiazole (5d, 6d, 7d)

When a mixture of 6-(1-benzofuran-2-yl)-2-(4-chlorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (4d), secondary amine and formaldehyde was refluxed in ethanol using catalytic amount of acetic acid, it furnished the Mannich bases (5d-7d).

The structure of 6-(1-benzofuran-2-yl)-2-(4-chlorophenyl)-5-(pyrrolidin-1-ylmethyl) imidazo[2,1-b][1,3,4]thiadiazole 5d was confirmed by its spectral data. The IR spectrum of compound 5d displayed absorption bands at 1626 cm⁻¹ and 1597 cm⁻¹ due to C=N and C=C groups respectively. ¹H NMR spectrum of Compound 5d exhibited a multiplet between δ 6.58 - 7.85 ppm due to nine aromatic protons, a singlet at δ 3.08 ppm due to a –CH₂ protons and at δ 2.36 and δ 2.88 it displayed two triplets due to eight protons of pyrrolidine moiety. In mass spectrum it showed a molecular ion peak M⁺ at m/z 434 which corresponds to molecular weight of compound 5d.
Chapter-4

imidazo[2,1-b][1,3,4]thiadiazoles and Mannich Base derivatives
LC - MS Report

Method: NEUTRALM.M
Data File: 90228007.D
Sample Name: RM-9002592
Instrument: Agilent 6330 Ion Trap
Analysis Info: V2

Print Date: 2/28/2009 11:33:31 AM
Acq. Date: 2/28/2009 11:13:54 AM
Instrument Code: BIL/LAB/RND/801
Analyst

--- 90228007.D: TIC +All MS

+MS, 1.6min #59

--- 90228007.D: TIC +All MS

+MS, 4.5min #171

--- 90228007.D: TIC +All MS

+MS, 11.8min #79

--- 90228007.D: TIC +All MS

+MS, 11.8min #79
Chapter-4

imidazo[2,1-b][1,3,4]thiadiazoles and Mannich Base derivatives
Table: 4.2. Spectral data of Mannich bases

<table>
<thead>
<tr>
<th>comp</th>
<th>Structure</th>
<th>IR in cm⁻¹</th>
<th>¹HNMR in δ ppm</th>
<th>Molecular ion (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5d</td>
<td><img src="image" alt="Structure" /></td>
<td>3057, 2972, 1626 (C=N), 1597 (C=C)</td>
<td>δ83.08 (S, 2H, -CH₂), δ6.58–7.85 (m, Ar-H, 9H), δ 2.36 (t, 4H, 2-CH₂) and δ 2.88 (t, 4H, 2-CH₂)</td>
<td>434</td>
</tr>
<tr>
<td>6d</td>
<td><img src="image" alt="Structure" /></td>
<td>3034, 2923–2852, 1607 (C=N), 1570 (C=C)</td>
<td>1.48–152 (m, 6H, CH₂), 2.45 (t, 4H, -CH₂), 3.57 (s, 2H, -CH₂), 7.18–8.16 (m, Ar-H, 9H)</td>
<td>448</td>
</tr>
<tr>
<td>7d</td>
<td><img src="image" alt="Structure" /></td>
<td>3105, 2922–2854, 1607 (C=N), 1552 (C=C)</td>
<td>4.22 (S, 2H, -CH₂), δ6.71–8.40 (m, Ar-H, 9H), δ 3.19 (t, 4H, 2-CH₂) and δ 3.85 (t, 4H, 2-CH₂)</td>
<td>450</td>
</tr>
</tbody>
</table>

4.3. Experimental

4.3.1. Synthesis of 1-(1-benzofuran-2-yl)-2-bromoethanone(2)

**Method-I:** 2-Acetylbenzofuran (0.005M, 0.8g) was dissolved in 10 ml of (minimum amount) CH₃COOH taken in a round flask. The reaction mixture was kept for stirring at 20 °C. A solution of brominating mixture (0.9 ml Br₂ in 15 ml acetic acid) was taken in a dropping funnel and was added slowly to the reaction mixture with constant stirring. After the complete addition, the reaction mixture was removed from the ice bath and it was kept at room temperature with continuous stirring then for about 1 hrs. The completion of the reaction was checked by TLC. The solution was poured into ice cold water and neutralized with NaHCO₃. The solid separated was filtrated, dried and recrystallized in ethanol. As light brown colored crystals; m.p. 78–81°C; yield 92%.
Method-II: An equimolar ratio of 1-(1-benzofuran-2-yl)-2-bromoethanone (2) (0.001 mol, 0.16 g) and N-Bromosuccinamide (NBS) (0.001 mol, 0.17 g) was taken in carbon tetrachloride (5 ml) and stirred at room temperature for about 5 hrs. The resulting compound was filtered, dried and recrystallized using ethanol.

4.3.2. Synthesis of 5-aryl-1,3,4-thiadiazol-2-amine (3a-e)

General procedure:

A mixture of 5-arylbenzoic acids (0.02 mol) and thiosemicarbazide (0.02 mol, 1.8 g) in 10 ml of POCl₃ were taken in round bottom flask, fixed with the guard tube and refluxed for about 14-16 hrs. The completion of the reaction was judged by TLC. The reaction mixture was cooled to room temperature, then poured into ice cold water and neutralized with NaHCO₃. The solid separated was collected by filtration, dried and recrystallized using ethanol.

4.3.3. Synthesis of 6-(1-benzofuran-2-yl)-2-phenylimidazo[2,1-b][1,3,4]thiadiazole (4a-e)

General procedure:

An equimolar quantities of 1-(1-benzofuran-2-yl)-2-bromoethanone 2 (0.01 mol) and 2-amino-5-aryl-1, 3, 4-thiadiazole (3a-e) (0.01 mol) was refluxed in dry ethanol (5 ml) for about 8-10 hrs. Excess of solvent was distilled off under reduced pressure and hydrobromide salt separated was collected by filtration, suspended in water, which was further neutralized using aqueous sodium carbonate solution to get free base. It was filtered, washed with water, dried and recrystallized using ethanol. The analytical data of compounds (4a-e) given in the table 4.3.
### Table: 4.3. Analytical data of 6-(1-benzofuran-2-yl)-2-phenylimidazo[2,1-b][1,3,4]thiadiazoles derivatives (4a-e)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>M.P.(°C)</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cl</td>
<td>211-213</td>
<td>82</td>
<td>C$<em>{18}$H$</em>{10}$ClN$_{3}$OS</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>183-185</td>
<td>68</td>
<td>C$<em>{18}$H$</em>{11}$N$_{3}$OS</td>
</tr>
<tr>
<td>c</td>
<td>OCH$_{3}$</td>
<td>228-230</td>
<td>65</td>
<td>C$<em>{19}$H$</em>{13}$N$<em>{3}$O$</em>{2}$S</td>
</tr>
<tr>
<td>d</td>
<td>CH$_{3}$</td>
<td>169-172</td>
<td>71</td>
<td>C$<em>{19}$H$</em>{13}$N$_{3}$OS</td>
</tr>
<tr>
<td>e</td>
<td>F</td>
<td>194-197</td>
<td>63</td>
<td>C$<em>{18}$H$</em>{10}$FN$_{3}$OS</td>
</tr>
</tbody>
</table>

### 4.3.4. Preparation of 6-(1-benzofuran-2-yl)-2-(4-chlorophenyl)-5-(amine-1-ylmethyl)imidazo[2,1-b][1,3,4]thiadiazole (5d, 6d, 7d)

**General procedure:**

A mixture of 6-(1-benzofuran-2-yl)-2-(4-chlorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (4d) (0.351g, 0.001mol), a secondary amine (0.071g, 0.001mol) and formaldehyde (0.5ml) with catalytic amount of glacial acetic acid (0.5ml) in ethanol (10 ml) was refluxed for about 6-8 hrs on water bath. The completion of reaction was
checked by TLC. Whole reaction mixture was transferred into a separating funnel, diluted with water and extracted using diethyl ether. The ether layer was collected and dried over anhydrous CaCl₂. The solvent was removed and the obtained residue was recrystallized using benzene and pet-ether in a 2:8 ratio to give final compounds. The characterization data of compounds 5d-7d is given in the following table 4.4.

Table: 4.4. Characterization data of Mannich bases

<table>
<thead>
<tr>
<th>comp</th>
<th>Structure</th>
<th>M.P.(°C)</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>5d</td>
<td><img src="image" alt="Structure 5d" /></td>
<td>208-211</td>
<td>73</td>
<td>C₂₃H₁₉ClN₄OS</td>
</tr>
<tr>
<td>6d</td>
<td><img src="image" alt="Structure 6d" /></td>
<td>238-241</td>
<td>61</td>
<td>C₂₄H₂₁ClN₄OS</td>
</tr>
<tr>
<td>7d</td>
<td><img src="image" alt="Structure 7d" /></td>
<td>244-246</td>
<td>60</td>
<td>C₂₅H₁₉ClN₄O₂S</td>
</tr>
</tbody>
</table>
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