Chapter 5

Synthesis of oxadiazoles encompassing 5-bromo benzo-1-furan nucleus
Chapter 5

5.1. Introduction

Oxadiazole is a heterocyclic compound containing one oxygen and two nitrogen atoms in a five membered cyclic ring. Depending upon relative positions of oxygen and nitrogen atoms, there are four possible isomers of oxadiazole, amongst them 1,3,4-oxadiazole play significant role, derivatives of which exhibit wide range of biological activities such as antifungal\(^1\), antimicrobial\(^2\), antiinflammatory\(^3\), analgesic\(^4,5\), antitubercular\(^6,7\), anticonvulsant\(^8,9\), cytotoxic\(^10\) and hypolipidemic\(^11\). These also act as prostaglandin receptor antagonists\(^12\) and antioxidant agent\(^13,14\).

Some interesting observations have been made on applications of 1,3,4-oxadiazoles in agriculture as herbicides, fungicides and insecticides\(^15,16\).

The 1,3,4-oxadiazoles with substitutions by aryl groups at 2\(^{nd}\) and 5\(^{th}\) positions are of significant interest because of their application in polymer and material science because of their electro-chemical luminescence properties\(^17-19\). These 2,5-disubstituted-1,3,4-oxadiazole derivatives possess range of pharmacological activities such as antibacterial\(^20\), antiinflammatory\(^21\), analgesic\(^22\). Some of these compounds display pharmaceutical activities like anticancer\(^23\), antihypertensive\(^24\), anticonvulsant\(^25\), antiproliferative\(^26,27\), hypoglycemic\(^28\), hypnotic and sedative\(^29\) and MAO inhibitor\(^30\). There are also some reports on herbicidal\(^31\), and insecticidal\(^32\) activities.

There are several drugs available in market for the treatment of various diseases, which enclose 1,3,4-oxadiazole ring system in their molecule. The following are the some of the examples:

Furamizole 1 a strong anti-bacterial agent\(^33,34\), it is noteworthy that this drug encloses furan nucleus in its structure.
Chapter 5

Nesapidal $2$ is $\text{Ca}^+$ channel blocker.

Raltegravir$^{36}$ $3$ acts as anti retroviral drug.

Encouraged by the wide range of applications of 1,3,4-oxadiazole, many organic chemists and medicinal chemists all over the world, directed their research work towards the synthesis of various derivatives of 1,3,4-oxadiazole in which this ring system is either condensed or coupled with other homocyclic (aromatic) and heterocyclic nuclei. This type of research work has led to publication of number of research papers, describing methods of synthesis, characterization and biological activities. In view of limitation this thesis, only few recent research findings in this connection are summarized in the following pages.

Different synthetic routes are available for the construction of the oxadiazole nucleus. The synthesis of such compounds by using hydrazines are usually carried out by
Chapter 5

treating with variety of cyclodehydrating agents such as polyphosphoric acid\textsuperscript{37}, phosphorus oxychloride\textsuperscript{38}, thionyl chloride\textsuperscript{39}, boron trifluoride diethyl etherate\textsuperscript{40} and Burgess reagent\textsuperscript{41}.

Shridhar et al., have synthesized Bis alkyl 1,3,4-oxadiazole 4a-f which are incorporated with azo dye derivatives and screened for their antimicrobial and antioxidant activity by using minimum inhibitory concentration method and DPPH radical scavenging method respectively\textsuperscript{42}. It is reported that these derivatives possess potent antibacterial and antioxidant agents.

\begin{align*}
\text{R,} \\
a=-(\text{CH}_2)_6\text{CH}_3 \\
b=-(\text{CH}_2)_8\text{CH}_3 \\
c=-(\text{CH}_2)_{10}\text{CH}_3 \\
d=-(\text{CH}_2)_{12}\text{CH}_3 \\
f=-(\text{CH}_2)_{13}\text{CH}_3
\end{align*}

Bondock et al., carried out synthesis of some 1,3,4-oxadiazole-based heterocycles 5-7 and investigated them for antitumor activity. They found that, the 1,3,4-oxadiazole skeleton incorporating a thiazole ring resulted in better antitumor activities than those displayed by the pyrazole and thiophene ring systems\textsuperscript{43}.
Dodiya et al., carried out synthesis of compounds containing quinoline-oxadiazole-based azetidinone derivatives 8. They studied their antimicrobial activity against different strains of bacteria and fungi by adopting minimum inhibitory concentration (MIC) measurements through broth dilution method\textsuperscript{44}.

Priyanka et al., in their research work, carried out the synthesis and antibacterial activity of derivatives of compound 9. They found that some of these compounds exhibited excellent antibacterial activity against the Gram negative bacteria\textsuperscript{45}.

Schiff bases of coumarin incorporated 1,3,4-oxadiazole derivatives 10 were synthesized and evaluated for antimicrobial activity by cup-plate method by Bhat et al.,
and they proved that synthesized compounds showed highly significant \textit{in vitro} growth inhibition against bacteria and fungi\textsuperscript{46}.

Rajesha et al., synthesized various benzocoumarines 11 encompassing 1,3,4-oxadiazoles with long fatty chain and studied their fluorescence spectral properties\textsuperscript{47}.

Bhat et al., studied the anticonvulsant neurotoxic properties of newly synthesized compounds 12 enclosing both 1,3,4-oxadiazole and coumarin moieties\textsuperscript{48}.

Rashid et al., in their search for new methods of synthesizing oxadiazole, involving the benzimidazole 13, adopted the microwave assisted cyclodehydration in presence of phosphorous oxy chloride\textsuperscript{49}. 

\begin{center}
\includegraphics[width=\textwidth]{Figure10.png}
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{Figure11.png}
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{Figure12.png}
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{Figure13.png}
\end{center}
Chapter 5

The synthesis and antioxidant activity of 1,3,4-oxadiazole tagged with thieno[2,3-d]pyrimidine derivatives 14 have been reported by Kotaiah et al. They observed that the following compound exhibited significant radical scavenging activity.

Pawar et al., synthesized some 4,5,6,7-tetrahydrobenzothiophene derivatives encompassing 1,3,4-oxadiazole 15 and evaluated for analgesic and in vitro anti-inflammatory activities. It was observed that some of the synthesized compounds exhibited significant anti-inflammatory activity and analgesic activities compared to standards.

Pimprinine is an indole alkaloid which belongs to the class of naturally occurring 5-(3-indolyl)oxazoles. Zhang et al., synthesized the Pimprinine derivatives 16, 17 and evaluated for antifungal activity. They found that these compounds showed promising antifungal activity against tested organisms.
Giri et al., reported the synthesis of compounds containing 1,3,4-oxadiazole combined with naphtho[2,1-b]furan system. These compounds have been found to possess good to moderate inhibition against some fungi and bacteria.

Jiang et al., have synthesized series of benzofuran and pyrazole linked 1,3,4-oxadiazole derivatives. The structure of the prepared compounds were established by spectral and X-ray crystallographic studies. They also reported the UV absorption and fluorescence spectral characterization of these compounds.

Saitoh et al., studied the glycogen synthase kinase 3β (GSK-3β) inhibition of new 1,3,4-oxadiazole derivatives encompassing benzofuran nucleus which are expected to be a promising therapeutic approach for treating Alzheimer’s disease.
Shinde et al., reported the synthesis of benzofuran based 1,3,4-oxadiazole 22 via cyclocondensation. This synthesis was carried out by using reactant as hydrazide and aryl isothiocyanates by conventional method as well as non-conventional method i.e., by ultrasound irradiation method\textsuperscript{56}.

Balasaheb et al., carried out work on the synthesis and screening of anti-inflammatory activity of benzofuran derivatives bearing oxadiazole 23 and the compound was found to possess good anti-inflammatory activity\textsuperscript{57}.

In discussion summarized in the above paragraphs clearly indicates, importance of 1,3,4-oxadiazoles. Even though, 1,3,4-oxadiazole moiety has been coupled with other
heterocyclic system, there scattered reports in literature, where in this moiety is either
couple or condensed with benzofuran moiety. It has been proved beyond doubt that
combination of two different types of biodynamic heterocyclic systems enhances the
biological profile of the compounds.

In continuation of this research work and bearing in mind the importance
of 2,5-disubstitited 1,3,4-oxadiazoles, it is planned, to couple benzofuran nucleus
with 1,3,4-oxadiazoles and evaluate them for antibacterial, antifungal and antioxidant
activities.

5.2. Present work

Forgoing discussion clearly reveals the importance of 1,3,4-oxadiazole ring
system. Thus various biheterocyclic compounds with benzofuran and appropriately
substituted 1,3,4-oxadiazole have been synthesized during the present work. The
resulting new heterocyclic compounds have been evaluated for antibacterial, antifungal
and antioxidant which are discussed in Chapter 8.

Several methods are available in literature for the construction of 1,3,4-oxadiazole
moiety. However, very commonly and familiar method make use of acid hydrazides as
intermediates, which on treatment with carboxylic acid in presence of phosphorous
oxychloride result in the formation of oxadiazole.

Same synthetic methodology has been adopted in present work. The following
three types of biheterocyclic compounds with different substituents at 5th position of
1,3,4-oxadiazole moiety were synthesized.
1. \(N\)-(5-Bromo-2-(5-alkyl-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl)-2-phenylacetamides (4a-f).

2. \(N\)-(5-Bromo-2-(5-heterocyclic-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl)-2-phenylacetamides (5a-c).

3. \(N\)-(5-Bromo-2-(5-aryl-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl)-2-phenylacetamides (6a-f).

Overall sequence of the reactions is depicted in a Scheme 5:
Chapter 5

R,  
Het,  
Ar,  

4a=-(CH2)6CH3,  
5a=  
6a=C6H5-,  

4b=-(CH2)8CH3,  
5b=  
6b= 4-CH3-C6H5-,  

4c=-(CH2)10CH3,  
5b=  
6c=4-NO2-C6H4-,  

4d=-(CH2)12CH3,  
5c=  
6d= 4-Cl-C6H4-,  

4e=-(CH2)14CH3,  
5c=  
6e= 4-OCH3-C6H4-,  

4f=-(CH2)16CH3,  
6f= C6H5- C6H4-

The synthetic strategy devised involved the following steps:

**Step 1:** Synthesis of ethyl 5-bromo-3-[(phenylacetyl)amino]-1-benzofuran-2-carboxylate 2 from ethyl 5-bromo-3-amino-1-benzofuran-2-carboxylate 1.

**Step 2:** Conversion of ethyl 5-bromo-3-[(phenylacetyl)amino]-1-benzofuran-2-carboxylate 2 into N-[5-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]-2-phenylacetamide 3.

**Step 3:** Synthesis of various N-[5-bromo-2-(5-alkyl/hetero/aryl-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl]-2-phenylacetamide 4a-f, 5a-c and 6a-f using N-[5-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]-2-phenylacetamide.

**Step 1: Synthesis of ethyl 5-bromo-3-[(phenylacetyl)amino]-1-benzofuran-2-carboxylate 2 from ethyl 5-bromo-3-amino-1-benzofuran-2-carboxylate 1**

Acylation of ethyl 5-bromo-3-amino-1-benzofuran-2-carboxylate 1 was carried out by using phenyl acetyl chloride. The ester 1 was refluxed with phenyl acetyl chloride in presence of triethylamine and 1,4-dioxane as solvent for about 3 hrs (Scheme 5.1).

![Scheme 5.1](image)
The structure of synthesized compound 2 was established by the recording the IR, $^1$H NMR, and mass spectra. The IR spectrum (Figure 5.1a) of the compound 2 exhibited absorption bands at 3269 cm$^{-1}$, 3092 cm$^{-1}$, 2979 cm$^{-1}$ and 1727 cm$^{-1}$ which were assignable to $\text{-NH}$, $\text{-CH}_2$, $\equiv\text{C-H}$ and $\equiv\text{C}=\text{O}$ stretching frequencies respectively. The $^1$H NMR spectrum (Figure 5.1b) of compound 2 exhibited a singlet at $\delta$ 9.2 assignable to proton of $\text{-NH}$ group at C-3, multiplet at $\delta$ 7.3 to 7.5 was attributed to eight aromatic protons and a singlet at $\delta$ 3.8 was due to $\text{-CH}_2$ connected to carbonyl group, quartet and triplet at $\delta$ 4.3 and $\delta$ 1.4 were due to presence of $\text{-CH}_2$ and $\text{-CH}_3$ of ester group. The mass spectrum (Figure 5.1c) of compound 2 exhibited molecular ion peak corresponding to molecular weight at m/z 402 (M$^+$) and at m/z 404 (M+2)$^+$ of equal intensity as expected for the compounds containing bromine atom.

**Step 2: Conversion of ethyl 5-bromo-3-[(phenylacetyl)amino]-1-benzofuran-2-carboxylate 2 into $\text{N-}[5$-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]-2-phenylacetamide 3**

The conversion of ethyl 5-bromo-3-[(phenylacetyl)amino]-1-benzofuran-2-carboxylate 2 into hydrazide 3 was accomplished by reacting compound 2 with excess of hydrazine hydrate (99 %) in ethanol at reflux temperature for about 1 hr as shown in Scheme 5.2.

![Scheme 5.2](image-url)
The formation of compound 3 was confirmed by recording its IR, \(^1\)H NMR and mass spectra. The IR spectrum (Figure 5.2a) of compound 3 exhibited absorption bands at 3326 cm\(^{-1}\), 3192 cm\(^{-1}\), 3091 cm\(^{-1}\) and 1681 cm\(^{-1}\) due to -NH, -NH\(_2\), -CH\(_2\) and -C=O groups respectively. This was supported by the \(^1\)H NMR spectrum (Figure 5.2b) which showed three singlets at \(\delta\) 10.2, \(\delta\) 10.0 and \(\delta\) 4.6 assigned for two -NH and -NH\(_2\) protons respectively and showed the absence of triplet and quartet of ester group which were observed in starting material. The multiplet from \(\delta\) 7.2 to 8.0 and a singlet at \(\delta\) 3.8 confirmed the presence of eight aromatic protons and -CH\(_2\) groups respectively. The molecular ion peak at m/z 388 (M\(^+\)) and at m/z 390 (M+2)\(^+\) of equal intensity mass spectrum (Figure 5.2c) proved the structure of compound 3.

**Step 3: Synthesis of various N-[5-bromo-2-(5-alkyl/heteroaryl-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl]-2-phenylacetamide 4a-f, 5a-c and 6a-f using N-[5-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]-2-phenylacetamide**

The title compounds were synthesized by reacting carbonyl hydrazide 3 with the different carboxylic acids in the presence of phosphorus oxychloride. Coupling and intramolecular cyclisation took place in a single step to furnish the desired products.

**N-[5-bromo-2-(5-alkyl-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl]-2-phenylacetamide (4a-f)**

Receiving impetus from the observation that substitution at 5\(^{th}\) position of 1,3,4-oxadiazole ring system with long chain hydrocarbon results in the formation of excellent organic fluorescent materials\(^47\), it was envisaged to synthesis similar compounds 4a-f. The title compounds were synthesized by reacting carbonyl hydrazide 3 with the following long chain fatty acids in the presence of phosphorus oxy chloride as shown in Scheme 5.3.
Chapter 5

Octanoic acid
Decanoic acid
Dodecanoic acid
Tetradecanoic acid
Hexadecanoic acid
Heptadecanoic acid

![Scheme 5.3](image)

The structures of 1,3,4-oxadiazoles 4a-f synthesized were established by recording IR, $^1$H NMR, $^{13}$C NMR and mass spectra.

The IR spectrum (Figure 5.4a) of 4c exhibited stretching frequencies at 3308 cm$^{-1}$, 2918 cm$^{-1}$, 2850 cm$^{-1}$ and 1725 cm$^{-1}$ for $-\text{NH}$, $-\text{CH}_2$ and $-\text{C}=\text{O}$ groups respectively.

The $^1$H NMR spectrum (Figure 5.4b) of compound 4c showed a singlet at $\delta$ 8.2 due to $-\text{NH}$ proton, peaks from $\delta$ 7.2 to $\delta$ 7.8 integrating for eight protons confirmed the aromatic system. The double of doublet peak which appeared from $\delta$ 4.0 to $\delta$ 4.2
assignable for deshielded methylene protons which were connected carbonyl and phenyl groups. A triplet at δ 0.8 ppm due to the protons of terminal -CH₃ and another multiplet at δ 2.4 due to protons of -CH₂ group attached to 1,3,4-oxadiazole moiety which special interaction with the amide group were conspicuous in the spectrum. The remaining protons of -CH₂ group appeared as multiplet between δ 1.3 to δ 1.7. The ¹³C NMR spectrum (Figure 5.4c) of compound 4c showed peaks at δ 14.2, 22.8, 25.1, 29.3, 29.42, 29.48, 29.58, 29.75, 32.0, 34.4, 41.2, 114.5, 117, 124.6, 124.7, 128.8, 128.9, 133.0, 138.2, 141.9, 152.2, 156, 159, and 173 which coincides with different carbon atoms of this compound. The structure assigned to the compound 4c was further confirmed by its mass spectrum (Figure 5.4d) showing molecular ion peak at m/z 552 (M)⁺ and bromine isotopic peak of equal intensity at m/z 554 (M⁺2)⁺ which corresponds to its molecular weight. The IR, ¹H NMR and mass spectra of compound 4b are presented in Figure 5.3a, 5.3b and 5.3c respectively. Similarly, IR, ¹H NMR, ¹³C NMR and mass spectra of compound 4d is shown in Figure 5.5a, 5.5b, 5.5c and 5.5d respectively provided another evidence favoring the structures assigned. The ¹H NMR spectrum (Figure 5.6a) and the mass spectrum (Figure 5.6b) of compound 4e substantiated the formation of the compound.

N-[5-bromo-2-(5-heterocylic-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl]-2-phenylacetamide (5a-c)

The 1,3,4-oxadiazoles are reported to possess good pharmacological properties. These properties can be enhanced by substituting the biological active heterocyclic moieties. Hence, the title compounds were synthesized by reacting carbonyl hydrazide 3 with the following heterocyclic acids in the presence of phosphorus oxy chloride.

Department of Chemistry, Kuvempu University
Indole acetic acid,

Nicotinic acid,

6-Bromo nicotinic acid.

\[
\text{POCl}_3, \text{HetCOOH} \rightarrow \Delta, 2 \text{ hrs}
\]

\[
\text{Scheme 5.4}
\]

Where Het,  

\[
\begin{align*}
5a &= \text{Het} \\
5b &= \text{Het} \\
5c &= \text{Het}
\end{align*}
\]

The formation these compounds are established by IR, \(^1\text{H}\) NMR and mass spectra. The IR spectrum (Figure 5.7a) of the compound 5b showed absorption bands at 3282 cm\(^{-1}\), 2995 cm\(^{-1}\), 1714 cm\(^{-1}\) corresponds to -NH, -CH\(_2\) and -C=O groups. The \(^1\text{H}\) NMR spectrum (Figure 5.7b) showed a singlet at \(\delta 9.3\) assignable for -NH group and another singlet at \(\delta 4.7\) integrating for two protons corresponds to methylene protons. The remaining peaks from \(\delta 7.1\) to \(\delta 8.8\) integrate for the twelve aromatic protons. It was further confirmed by its mass spectrum (Figure 5.7c) which showed molecular ion (M\(^+\)) peak at m/z 242 corresponds to molecular weight of compound 5b and isotopic peak at m/z 244 (M+2\(^+\)). Additional proof for the formation of the title compounds was provided by recording IR (Figure 5.8a), \(^1\text{H}\) NMR (Figure 5.8b) and mass spectra (Figure 5.8c) of the compound 5c.

\(N\)-[5-bromo-2-(5-aryl-1,3,4-oxadiazol-2-yl)-1-benzofuran-3-yl]-2-phenylacetamide (6a-f)
The derivatives of 2,5-di aryl-1,3,4-oxadiazole act as efficient energy and electron transport materials. Hence, it was contemplated to introduce aromatic ring with electron donating and electron withdrawing substituents, at position 5 of 1,3,4-oxadiazoles\textsuperscript{18}. This was accomplished by reacting carbonyl hydrazide 3 with the following aromatic carboxylic acids in presence of phosphorus oxy chloride.

- Benzoic acid
- 4-Methyl benzoic acid
- 4-Chloro benzoic acid
- 4-Methoxy benzoic acid
- 4-Biphenylic acid
- 4-Nitro benzoic acid

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{C} & \quad \text{CONHNH}_2 \\
\text{CONHNH}_2 & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{NH} \\
\text{CONHNH}_2 & \quad \text{POCl}_3, \text{ ArCOOH} \\
\Delta, 2 \text{ hrs} & \quad \text{Br}
\end{align*}
\]

\textbf{Scheme 5.5}

\[
\begin{align*}
6a & = \text{benzene} \\
6b & = 4-\text{CH}_3\text{-C}_6\text{H}_4 \\
6c & = \text{C}_6\text{H}_5\text{-C}_6\text{H}_4 \\
6d & = 4-\text{Cl-C}_6\text{H}_4 \\
6e & = 4-\text{OCH}_3\text{-C}_6\text{H}_4 \\
6f & = 4-\text{NO}_2\text{-C}_6\text{H}_4
\end{align*}
\]

The structures of these synthesized compounds are established by IR, \textsuperscript{1}H NMR and mass spectra. As expected, the IR spectrum (Figure 5.9a) of compound 6b exhibited an absorption band at 3246 cm\textsuperscript{-1}, 3063 cm\textsuperscript{-1}, 3029 cm\textsuperscript{-1} and 1701 cm\textsuperscript{-1} assignable for \(-\text{NH}\), \(-\text{CH}_2\), \(-\text{CH}_3\) and \(-\text{CO}\) groups. The singlets at \(\delta 8.8, \delta 2.3\) and double doublet at \(\delta 4.2\) of \textsuperscript{1}H NMR spectrum (Figure 5.9b) are assignable for the \(-\text{NH}, \text{Ar-CH}_3\) and \(-\text{CH}_2\) groups.
of compound 6b. The remaining peaks between δ 7.1 to δ 8.2 corresponding to twelve aromatic protons. The mass spectrum (Figure 5.9c) of compound 6b showed m/z 488 (M)^+ and 490 (M+2)^+ of its molecular weight and isotopic peak. The IR, ^1H NMR and mass spectra of compound 6e are appended in Figure 5.10a, 5.10b and 5.10c respectively.

Similarly, additional proof for the formation of the oxadiazole moiety has been provided by recording IR (Figure 5.11a), ^1H NMR (Figure 5.11b), ^13C NMR (Figure 5.11c) and mass (Figure 5.11d) spectra of the compound 6f.

The general mechanism of the formation of 1,3,4-oxadiazoles 4a-f, 5a-c and 6a-f has been depicted in Scheme 5.6.

![Scheme 5.6](image-url)
Figure 5.1a: IR spectrum of compound 2

Figure 5.1b: $^1$H NMR spectrum of compound 2
Chapter 5

User Spectra

<table>
<thead>
<tr>
<th>Fragmentor Voltage</th>
<th>Collision Energy</th>
<th>Ionization Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>0</td>
<td>ESI</td>
</tr>
</tbody>
</table>

+ESI Scan (0.447 min) Frag=175.0V GP-NTA.d

Figure 5.1c: Mass spectrum of compound 2

![Mass spectrum of compound 2]

Figure 5.2a: IR spectrum of compound 3

![IR spectrum of compound 3]
Figure 5.2b: $^1$H NMR spectrum of compound 3

Figure 5.2c: Mass spectrum of compound 3
Chapter 5

Figure 5.3a: IR spectrum of compound 4b

Figure 5.3b: IR spectrum of compound 4b
**Chapter 5**

**User Spectra**

<table>
<thead>
<tr>
<th>Fragmentor Voltage</th>
<th>Collision Energy</th>
<th>Ionization Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>0</td>
<td>ESI</td>
</tr>
</tbody>
</table>

+ESI Scan (0.183 min) Frag=175.0V GP-Y05.d

![Mass Spectrum of Compound 4b](image)

Figure 5.3c: Mass spectrum of compound 4b

![IR Spectrum of Compound 4c](image)

Figure 5.4a: IR spectrum of compound 4c

*Department of Chemistry, Kuvempu University* 177
Figure 5.4b: $^1$H NMR spectrum of compound 4c

Figure 5.4c: $^{13}$C NMR spectrum of compound 4c
Chapter 5

Figure 5.4d: Mass spectrum of compound 4c

Figure 5.5a: IR spectrum of compound 4d
Chapter 5

Figure 5.5b: $^1$HNMR spectrum of compound 4d

Figure 5.5c: $^{13}$CNMR spectrum of compound 4d
Chapter 5

User Spectra

<table>
<thead>
<tr>
<th>Fragmentor Voltage</th>
<th>Collision Energy</th>
<th>Ionization Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>0</td>
<td>ESI</td>
</tr>
</tbody>
</table>

+ESI Scan (0.230 min) Frag=175.0V GP-Y04.d

![Mass spectrum of compound 4d](image)

Figure 5.5d: Mass spectrum of compound 4d

![IR spectrum of compound 4e](image)

Figure 5.6a: IR spectrum of compound 4e
Chapter 5

User Spectra

<table>
<thead>
<tr>
<th>Fragmentor Voltage</th>
<th>Collision Energy</th>
<th>Ionization Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>175</td>
<td>0</td>
<td>ESI</td>
</tr>
</tbody>
</table>

Figure 5.6b: Mass spectrum of compound 4e

Figure 5.7a: IR spectrum of compound 5b
Figure 5.7b: $^1$H NMR spectrum of compound 5b

Figure 5.7c: Mass spectrum of compound 5b
Chapter 5

Figure 5.8a: IR spectrum of compound 5c

Figure 5.8b: ^H NMR spectrum of compound 5c

Department of Chemistry, Kuvempu University
Figure 5.8c: Mass spectrum of compound 5c

Figure 5.9a: IR spectrum of compound 6b
Figure 5.9b: $^1$H NMR spectrum of compound 6b

Figure 5.9c: Mass spectrum of compound 6b
Figure 5.10a: IR spectrum of compound 6e

Figure 5.10b: $^1$H NMR spectrum of compound 6e
Figure 5.10c: Mass spectrum of compound 6e

Figure 5.11a: IR spectrum of compound 6f
Figure 5.11b: $^1$H NMR spectrum of compound 6f

Figure 5.11c: $^{13}$C NMR spectrum of compound 6f
Figure 5.11d: $^1$H NMR spectrum of compound 6f
5.3. Experimental

Synthesis of ethyl 5-bromo-3-[(phenylacetyl)amino]-1-benzofuran-2-carboxylate 2:

A mixture of ethyl 3-amino-5-bromobenzofuran-2-carboxylate (2.84 g, 0.01 mole), phenyl acetyl chloride (1.168 ml, 0.01 mole) and triethylamine (1.35 ml, 0.01 mole) in 1,4-dioxane (20 ml) was refluxed for 3 hrs. The reaction was monitored by TLC. The reaction mixture was cooled, added to crushed ice with constant stirring. The solid separated was filtered, dried and recrystallized from alcohol. Yield (3.61 g), 90%, m.p.138-140 °C.

Synthesis of N-[5-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]-2-phenylacetamide 3:

A mixture of compound 6 (4.02 g, 0.01 mole) and hydrazine hydrate (2.5 ml, 0.05 mole) with few drops of acetic acid in ethanol (20 ml) was refluxed for 2 hrs. The solid separated was filtered, dried and recrystallized from alcohol. Yield (1.85g, 50%) m.p.212-214 °C.

Synthesis of compounds 4a-f, 5a-c and 6a-f:

Compound 3 (3.88 g, 0.01 mole), stearic acid (2.84 g, 0.01 mole) and phosphorous oxy chloride taken in round bottomed flask and refluxed at 70-80 °C for about 2 hrs in dry condition. Then reaction mixture was cooled and slowly added to crushed ice with constant stirring. The solution was neutralized by using sodium bicarbonate. Solid separated was filtered, dried and recrystallized from alcohol.

Similarly, the compounds 4b-f, 5a-c and 6a-f were synthesized by using appropriate carboxylic acids.
The physical characteristics of the compounds 4a-f, 5a-c and 6a-f are depicted in Table 5.

Table 5: Analytical and physical characterization data of synthesized compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular formula</th>
<th>Yield %</th>
<th>Melting Point °C</th>
<th>Analytical data % Found (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>4a</td>
<td>C_{35}H_{46}BrN_{3}O_{3}</td>
<td>94</td>
<td>96-98</td>
<td>66.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(66.03)</td>
</tr>
<tr>
<td>4b</td>
<td>C_{29}H_{34}BrN_{3}O_{3}</td>
<td>95</td>
<td>130-132</td>
<td>63.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(63.03)</td>
</tr>
<tr>
<td>4c</td>
<td>C_{33}H_{42}BrN_{3}O_{3}</td>
<td>89</td>
<td>84-86</td>
<td>65.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(65.12)</td>
</tr>
<tr>
<td>4d</td>
<td>C_{31}H_{38}BrN_{3}O_{3}</td>
<td>95</td>
<td>110-112</td>
<td>64.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(64.13)</td>
</tr>
<tr>
<td>4e</td>
<td>C_{27}H_{30}BrN_{3}O_{3}</td>
<td>74</td>
<td>140-142</td>
<td>61.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(61.83)</td>
</tr>
<tr>
<td>4f</td>
<td>C_{26}H_{26}BrN_{3}O_{3}</td>
<td>87</td>
<td>114-116</td>
<td>60.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(60.49)</td>
</tr>
<tr>
<td>5a</td>
<td>C_{27}H_{18}BrN_{3}O_{4}</td>
<td>90</td>
<td>150-152</td>
<td>61.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(60.38)</td>
</tr>
<tr>
<td>5b</td>
<td>C_{23}H_{15}BrN_{4}O_{3}</td>
<td>65</td>
<td>246-248</td>
<td>58.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(58.12)</td>
</tr>
<tr>
<td>5c</td>
<td>C_{23}H_{14}Br_{2}N_{4}O_{3}</td>
<td>73</td>
<td>256-258</td>
<td>49.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(49.85)</td>
</tr>
<tr>
<td>6a</td>
<td>C_{24}H_{16}BrN_{3}O_{3}</td>
<td>68</td>
<td>126-128</td>
<td>60.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(60.77)</td>
</tr>
<tr>
<td>6b</td>
<td>C_{23}H_{18}BrN_{3}O_{3}</td>
<td>73</td>
<td>250-252</td>
<td>61.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(61.49)</td>
</tr>
<tr>
<td>6c</td>
<td>C_{24}H_{15}BrN_{4}O_{3}</td>
<td>67</td>
<td>220-222</td>
<td>55.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(55.51)</td>
</tr>
<tr>
<td>6d</td>
<td>C_{24}H_{13}BrClN_{3}O_{3}</td>
<td>84</td>
<td>142-144</td>
<td>56.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(56.66)</td>
</tr>
<tr>
<td>6e</td>
<td>C_{25}H_{18}BrN_{3}O_{4}</td>
<td>85</td>
<td>220-222</td>
<td>59.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(59.54)</td>
</tr>
<tr>
<td>6f</td>
<td>C_{30}H_{20}BrN_{3}O_{3}</td>
<td>91</td>
<td>210-212</td>
<td>65.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(65.47)</td>
</tr>
</tbody>
</table>

*Isolated yield
Chapter 5

References


Chapter 5


