CHAPTER - II

Microwave assisted facile synthesis of 3-chlorobenzo[b]thiophene-2-substituted-1,3,4-oxadiazo-loyls and comparison with conventional method of synthesis
Introduction

Use of microwave technology in organic and inorganic reactions is reported in a number of publications and reviews\(^1\text{–}^3\). In the last few years, there has been increasing interest in the use of environmentally benign reagents and conditions\(^4\text{–}^6\) particularly, in solvent-free procedures\(^7\). In dry media, reactions occur rapidly and the method avoids hazards associated with solvents especially in sealed vessels. The absence of solvent reduces the reaction time and always improves the yield. Using microwaves with proper control of power and reaction temperature is more efficient than conventional heating. In this context, we planned to prepare oxadiazoles under eco-friendly and environmentally benign solvent-free conditions, wherein several disadvantages like long reaction time and tedious work-up can be overcome.

Microwave radiation provides an alternative to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. The use of microwave irradiation has introduced several new concepts in chemistry, since the absorption and transmission of the energy is completely different from the conventional mode of heating. The microwave technology has been applied to a number of useful research and development processes such as polymer technology, organic synthesis, application to waste treatment; drug release/targeting; ceramic and alkane decomposition\(^8\text{–}^{12}\). We believe that the time saved by using microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high speed combinatorial and medicinal chemistry as well as industrial scale production of chemicals.

In search of synthesis of therapeutically important molecules, Khalid\(^13\) et al. have reported the microwave-assisted synthesis of 2,5-disubstituted-1,3,4-oxadiazole. Conventionally, syntheses of this class of compounds have been achieved in 5-7 hours\(^14\text{–}^{17}\). The substituted oxadiazoles are heterocyclic compounds, which serve both as bio mimetic and reactive pharmacophores and many are key elements with potential biological activities\(^18\text{–}^{20}\) such as
pesticidal\textsuperscript{21}, antiperipheral vasomotility\textsuperscript{22}, CNS stimulant, antiinflammatory, hypotensive\textsuperscript{23}, insecticidal\textsuperscript{24}, bactericidal\textsuperscript{25}, hypoglycemic\textsuperscript{26,27}, analgesic, anticonvulsive, antiemetic, diuretic\textsuperscript{28}, muscle relaxant\textsuperscript{29,30}, herbicidal\textsuperscript{31-32} and fungicidal activity\textsuperscript{33-34}.

N-Substituted 2-amino- and 2-alkylthio-1,3,4-oxadiazoles containing benzothiazole fragments in position 5 possess a wide spectrum of biological activity, including anti-inflammatory\textsuperscript{35,36}, antimicrobial\textsuperscript{37}, antibacterial\textsuperscript{36}, and hypotensive\textsuperscript{38} activity. There is extremely limited information in the literature\textsuperscript{39,40} regarding 2-alkyl(aryl)-5-substituted 1,3,4-oxadiazoles containing benzothiazole fragments. Kelarev\textsuperscript{41} et al., have investigated the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles (I) containing 2-benzothiazolylthiomethyl grouping as potentially biologically active substances and also as stabilizers and additives for polymeric material, hydrocarbon fuel, and lubricating oil\textsuperscript{42}. Hydrochlorides of carboxylic acid imino esters may serve as convenient synthons in the synthesis of 1,3,4-oxadiazoles\textsuperscript{43,44}.

The literature is flooded with reports of a variety of biological activities of substituted-1,3,4-oxadiazoles. These include anti-inflammatory\textsuperscript{45-48}, hypoglycemic\textsuperscript{49,50}, antianxiety and antidepressant\textsuperscript{51}, and antimitotic\textsuperscript{52} activities. In addition to these, a number of researchers have reported antimicrobial activities\textsuperscript{53-57}. Biocidal activities of Schiff bases have also been well established. These have been attributed to the toxophoric C-N linkage in them\textsuperscript{58}. Keeping these above facts Mishra\textsuperscript{59} et al, considered it of interest to synthesize a few Schiff bases of 2,5-disubstituted-1,3,4-oxadiazole for their antimicrobial activities.
In addition to oxadiazole derivatives various quinoline and benzo[\textit{b}]thiophene derivatives also possess high biological profile as discussed in introduction chapter. Many of the drugs which are used for different ailments found to possess important pharmacophores such as, quinoline, oxadiazole, benzo[\textit{b}]thiophenes, etc. It has been reported that presence of two or more pharmacophores in a drug molecule would enhance the biological profile many folds. These heterocycles are of great interest to medicinal chemists for molecular manipulation and to biologists for further pharmacological evaluation.

In this view, we herein report in this chapter, the molecules encompassing benzo[\textit{b}]thiophene, quinoline and oxadiazole moieties. The oxadiazole derivatives synthesized by conventional method were compared with microwave assisted synthesis. Interestingly, the microwave assisted reactions are found to be efficient, fast and high yielding with reduced reaction time.
RESULTS AND DISCUSSION

The reactions carried out in this chapter are depicted in the Scheme-2.

**Scheme-2**

![Scheme-2](image)

<table>
<thead>
<tr>
<th>Comp</th>
<th>M.P. (°C)</th>
<th>Anal. Calcd. (Found) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>2a</td>
<td>153-157</td>
<td>58.09 (57.85)</td>
</tr>
<tr>
<td>2b</td>
<td>144-146</td>
<td>55.03 (56.94)</td>
</tr>
<tr>
<td>2c</td>
<td>166-168</td>
<td>53.41 (53.23)</td>
</tr>
<tr>
<td>2d</td>
<td>160-163</td>
<td>59.21 (59.07)</td>
</tr>
<tr>
<td>2e</td>
<td>148-150</td>
<td>61.05 (59.90)</td>
</tr>
<tr>
<td>3a</td>
<td>141-145</td>
<td>56.93 (56.81)</td>
</tr>
<tr>
<td>3b</td>
<td>146-148</td>
<td>54.43 (54.31)</td>
</tr>
<tr>
<td>3c</td>
<td>160-163</td>
<td>53.09 (52.92)</td>
</tr>
<tr>
<td>3d</td>
<td>155-157</td>
<td>57.90 (57.72)</td>
</tr>
<tr>
<td>3e</td>
<td>148-149</td>
<td>59.30 (59.11)</td>
</tr>
<tr>
<td>4a</td>
<td>280-284</td>
<td>57.01 (56.88)</td>
</tr>
<tr>
<td>4b</td>
<td>276-278</td>
<td>57.98 (57.69)</td>
</tr>
<tr>
<td>4c</td>
<td>271-275</td>
<td>55.82 (55.70)</td>
</tr>
<tr>
<td>4d</td>
<td>256-259</td>
<td>52.49 (52.34)</td>
</tr>
<tr>
<td>4e</td>
<td>270-273</td>
<td>57.98 (57.66)</td>
</tr>
<tr>
<td>5a</td>
<td>210-214</td>
<td>56.18 (56.00)</td>
</tr>
<tr>
<td>5b</td>
<td>222-224</td>
<td>57.03 (56.89)</td>
</tr>
<tr>
<td>5c</td>
<td>235-237</td>
<td>55.21 (55.03)</td>
</tr>
<tr>
<td>5e</td>
<td>228-231</td>
<td>52.35 (52.14)</td>
</tr>
<tr>
<td>5f</td>
<td>219-222</td>
<td>57.03 (56.88)</td>
</tr>
</tbody>
</table>
Table – 2: Comparative data for conventional and microwave assisted synthesis

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Compound</th>
<th>Microwave heating</th>
<th>Conventional heating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (Min)</td>
<td>Power (Watt)</td>
</tr>
<tr>
<td>1</td>
<td>2a</td>
<td>4</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>3.5</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>8</td>
<td>150</td>
</tr>
<tr>
<td>7</td>
<td>3b</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>3c</td>
<td>8</td>
<td>150</td>
</tr>
<tr>
<td>9</td>
<td>3d</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>3e</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>4a</td>
<td>6</td>
<td>150</td>
</tr>
<tr>
<td>12</td>
<td>4b</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>4c</td>
<td>8</td>
<td>150</td>
</tr>
<tr>
<td>14</td>
<td>4d</td>
<td>9</td>
<td>150</td>
</tr>
<tr>
<td>15</td>
<td>4e</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>16</td>
<td>5a</td>
<td>10</td>
<td>150</td>
</tr>
<tr>
<td>17</td>
<td>5b</td>
<td>12</td>
<td>150</td>
</tr>
<tr>
<td>18</td>
<td>5c</td>
<td>13</td>
<td>200</td>
</tr>
<tr>
<td>19</td>
<td>5e</td>
<td>12.5</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>5f</td>
<td>9</td>
<td>150</td>
</tr>
</tbody>
</table>

3-Chloro-benzo[b]thiophene-2-carbohydrazide 1 was treated various benzaldehydes in dry methanol and acetic acid as catalyst to get respective carbohydrazides 2a-e. The compound 2a was prepared by the stirred solution of 3-chloro-benzo[b]thiophene-2-carbohydrazide 1, salicylaldehyde and a catalytic amount of acetic acid in dried methanol as solvent for about 6 hours at hot condition. The insoluble residue obtained after cooling the reaction mixture to room temperature was filtered, washed with water, then with methanol and recrystallised from ethyl alcohol to get pure hydrazide 2a. The hydrazides 2a-e obtained were of sufficiently pure for next reaction sequence and they needed no column chromatographic purification. The hydrazides 2a-e were also prepared by microwave assisted synthesis. The compound 2a was obtained by the irradiated mixture of 3-chloro-benzo[b]thiophene-2-carbohydrazide 1, salicylaldehyde and a catalytic amount.
of acetic acid in minimum quantity of methanol for about four minutes in an domestic oven
at 150W. Then the reaction mixture was cooled to room temperature, poured onto crushed
ice with stirring, the solid obtained was filtered, washed with water then with methanol and
recrystallised from ethyl alcohol to get pure 2a.

\[
\text{NH-NH, MeOH/H /hot/stirr-6 hours}
\]

The IR spectrum of the compound 2a was exhibited peaks at 3370, 3000, 2940,
1650 and 1500 cm⁻¹ corresponding to OH, NH, Ar-CH, CO and CN respectively. The \(^1\)H
NMR spectrum of the same compound 2a was recorded in CDCl₃ which exhibited a singlet
peak at 10.89 δ ppm due to one proton of OH group, 10.05 δ ppm due to one proton of
CONH group, a peak obtained at 8.54 δ ppm due to one proton of quinoline and the
multiplet in the region 6.92-7.95 δ ppm due to 7 aromatic protons. The formation of the
compound 2a was also confirmed by its mass spectral data which exhibited a molecular ion
peak at 331.8 and fragment peak at 330.8. Similarly, the compounds 2b-e were prepared.

The hydrazides 2a-e were converted into oxadiazoles 3a-e on treating with acetic
anhydride. The compound 2a was refluxed with acetic anhydride was taken in a round
bottomed flask for about 8 hours, the completion of the reaction was monitored through
TLC and after completion the excess of acetic anhydride was removed by distillation under
reduced pressure. Then the reaction mixture was cooled to room temperature, poured onto
crushed ice with stirring and neutralised with saturated solution of sodium bicarbonate.
The solid that obtained was filtered, washed with water, dried and purified through column
chromatography by using ethyl acetate and n-hexane solvent mixture in the ratio of 6:4 as
an eluent to get pure 3a. In microwave method, a mixture of hydrazide 2a and acetic
anhydride was subjected to microwave irradiation for about 7-8 min in a domestic oven.
Chapter - II

operating at 150W. The reaction mixture was cooled to room temperature and poured onto crushed ice with stirring, the solid that separated was filtered, washed with water, dried and purified through column chromatography by using the same solvent mixture as in conventional method. The spectra obtained in both the methods were found to be in concordant with each other.

![Diagram of chemical reaction]

The $^1$H NMR spectrum of the compound 3a was exhibited a singlet at 10.60 ppm due to one proton of OH group, a multiplet in between 7.22 $\delta$ ppm and 8.25 $\delta$ ppm due to 8 aromatic protons and a singlet at 2.45 $\delta$ ppm corresponding to three protons of CH$_3$ group. As an additional proof, the mass spectrum of the compound 3a which exhibited a molecular ion peak at 373.8 confirmed its formation.

In effort to link quinoline moieties to 3-chloro-benzo[b]thiophene through oxadiazole ring, the carbohydrazide 1 was treated with various 2-chloro-3-formyl quinolines to get various hydrazides 4a-e by following the same procedures as above in both conventional and microwave assisted synthesis in presence of dry ethyl alcohol as solvent.

![Diagram of chemical reaction]

In conformation the IR spectrum of 4a was exhibited peaks at 3000, 2940, 1660, and 1540 cm$^{-1}$ corresponding to NH, Ar-CH, CO and CN groups respectively. The $^1$H NMR of the same compound 4a was exhibited a broad singlet at 12.5 $\delta$ ppm due to one
proton of CONH group and multiplet in between 7.62 to 8.20 \( \delta \) ppm due nine aromatic protons. In addition, as an additional proof the mass spectrum which exhibited a molecular ion peak at 404.2 and fragment ion peaks at 403.2 and 400.2 confirmed the formation the compound 4a. Similarly, the compounds 4b-e were prepared.

The hydrazides 4a-e obtained were then converted into oxadiazoles 5a-e by refluxing hydrazides 4a-e with acetic anhydride. Similarly, the microwave assisted synthesis was also performed.

\[ \begin{array}{c}
\text{AcCl} \\
\text{R} \quad \text{Reflux-14 hrs}
\end{array} \]

The IR spectrum of the 5a was exhibited peaks at 2950, 1680 and 1470 cm\(^{-1}\) corresponding to Ar-CH, CO and CN respectively. The \(^1\)HNMR of the same compound 5a was exhibited a peak at 10.10 \( \delta \) ppm due to 1H of quinoline, a multiplet in between 7.58 \( \delta \) ppm and 8.1 \( \delta \) ppm due to 8 aromatic protons and a singlet at 1.90 \( \delta \) ppm corresponding to three protons of one CH\(_3\) group. As an additional proof the mass spectrum of the compound 5a was exhibited a molecular ion peak at 449.3 and fragment peaks at 443.5 and 442.8 also confirmed the formation of the compound 5a. Similarly, the compounds 5b-e were prepared.
IR Spectrum of 2a

Chemical structure:

Cl
\( \text{CH}_3 \text{CH}_2 \text{CH}_2 \text{S} \) \( \text{CH}_3 \text{CH} = \text{CH}_2 \)

\( \text{HO} \)
$^{1}H$ NMR spectrum of 2a

Current Data Parameters

EXPER 1
PROCNO 1

F2 - Acquisition Parameters

Date_ 20050203
Time_ 20.31

INSTRUM spect
PROCNRD 5 = Dl6, R1=1.8
POLRHN opp
TD 132743
SOLVENT CDCl3
MS 9
FS

SNR 7183.90 Hz
FIDRES 0.213235 Hz
AQ 3.1607028 sec
AD 61.00
DM 69.400 usec
DE 4.00 usec
TR 0.0 x
DE 3.0000000 sec
MCRESP 0.0000000 sec
MCIRX 0.01500000 sec

====== CHANNEL f1 ======

KFW 10.0
KLF 0.00
KPOL 300.123712 MHz

F2 - Processing parameters
SI 13768
SF 300.123816 MHz
VDW 9.0
WNN 0
LB 0.30 Hz
GB 0
PC 1.40
<table>
<thead>
<tr>
<th>Peak</th>
<th>RT (min)</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.49</td>
<td>22.82</td>
<td>0.79</td>
</tr>
<tr>
<td>2</td>
<td>3.59</td>
<td>2882.19</td>
<td>99.21</td>
</tr>
</tbody>
</table>

Mass spectrum of 2a

![Mass spectrum of 2a](image-url)
<table>
<thead>
<tr>
<th>Peak</th>
<th>RT (min)</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.657</td>
<td>8.938e+02</td>
<td>6.022</td>
</tr>
<tr>
<td>2</td>
<td>3.539</td>
<td>1.711e+02</td>
<td>1.153</td>
</tr>
<tr>
<td>3</td>
<td>3.968</td>
<td>1.370e+04</td>
<td>92.826</td>
</tr>
</tbody>
</table>

Mass spectrum of 2b
$^1$H NMR Spectrum of 2e

![Chemical structure of 2e](attachment:image.png)
Mass Spectrum of 2e

![Mass Spectrum Diagram]

<table>
<thead>
<tr>
<th>Peak Number</th>
<th>Time</th>
<th>Area Abs</th>
<th>Area %Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>3e+002</td>
<td>1.06</td>
</tr>
<tr>
<td>2</td>
<td>1.12</td>
<td>2e+002</td>
<td>0.87</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>1e+003</td>
<td>3.94</td>
</tr>
<tr>
<td>4</td>
<td>1.18</td>
<td>2e+004</td>
<td>94.12</td>
</tr>
</tbody>
</table>

Peak ID 1: (Time: 1.00) 1:MS ES+ 1.3e+007

Peak ID 2: (Time: 1.12) 1:MS ES+ 1.5e+007

Peak ID 3: (Time: 1.14) 1:MS ES+ 2.9e+007

Peak ID 4: (Time: 1.18) 1:MS ES+ 5.8e+007
Sample Report (continued):

<table>
<thead>
<tr>
<th>Peak ID</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>(Time: 1.00)</td>
<td></td>
</tr>
</tbody>
</table>

Mass Spectrum of 2e

- Cl
- NHN

Peak ID | Time |
--------|------|
2       | 1.12 |
| MS ES- |
| 1.5e+006 |

Peak ID | Time |
--------|------|
3       | 1.14 |
| (Time: 1.14) |

Peak ID | Time |
--------|------|
4       | 1.18 |
| MS ES- |
| 1.3e+005 |

Peak ID | Time |
--------|------|
5       | 1.22 |
| MS ES- |
| 1.1e+006 |

- Cl
- NHN

Mass Spectrum of 2e

- Cl
- NHN

500.0 1000.0 500.0 1000.0
$\text{H NMR spectrum of } 3a$

![Chemical Structure of 3a]
LC/MS REPORT

Data file : Injection Date : Sample Name : Vial No. :
Injection vol : 2.0μL Acq Method : AT_3070FA.M

Method :A: 0.1% HCOOH, B:ACN; Flow Rate:1.0 ml/min
Column:ATLANTIS C18 (50x4.6mm, 5μ)T3

TIME(MIN): 0--2.5 2.5--4.0 4.0--4.5 4.5--6.0
% B 30 95 95 30

<table>
<thead>
<tr>
<th>Peak</th>
<th>RT(min)</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.33</td>
<td>5.74e+001</td>
<td>12.31</td>
</tr>
<tr>
<td>2</td>
<td>13.83</td>
<td>2.18e+003</td>
<td>187.64</td>
</tr>
<tr>
<td>3</td>
<td>14.39</td>
<td>8.71e+001</td>
<td>13.50</td>
</tr>
<tr>
<td>4</td>
<td>5.07</td>
<td>1.63e+002</td>
<td>16.56</td>
</tr>
</tbody>
</table>

Mass spectrum of 3a

![Mass spectrum of 3a](image)
Mass spectrum of 4a

UV Detector: 264

peak Number | Time | Area/Unit | Area %Total |
--- | --- | --- | --- |
1 | 1.28 | 3e+002 | 0.74 |
2 | 1.35 | 6e+004 | 93.04 |
3 | 1.45 | 3e+002 | 0.62 |

Peak ID | Time | Peak ID | Time |
--- | --- | --- | --- |
1 | 1.28 | 1:MS Br+ | 2.75e+007 |
2 | 1.35 | 1:MS Br+ | 7.9e+007 |
3 | 1.45 | 1:MS Br+ | 2.9e+007 |

Peak ID | Time |
--- | --- |
1 | 1.28 |
2 | 1.35 |
3 | 1.45 |
$^{1}$H NMR spectrum of 5a
**Sample Report:**

**Mass spectrum of 5a**

![Mass spectrum](image)

<table>
<thead>
<tr>
<th>Peak Number</th>
<th>Time</th>
<th>Area Abs</th>
<th>Area % Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>3e+002</td>
<td>1.08</td>
</tr>
<tr>
<td>2</td>
<td>1.12</td>
<td>2e+002</td>
<td>0.87</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>1e+003</td>
<td>2.94</td>
</tr>
<tr>
<td>4</td>
<td>1.18</td>
<td>2e+004</td>
<td>94.12</td>
</tr>
</tbody>
</table>

**Peak ID**

1: (Time: 1.00)  
Peak: 114.1  
MS: 114.1  
Mass: 1.3e+007

2: (Time: 1.12)  
Peak: 114.1  
MS: 114.1  
Mass: 1.5e+007

3: (Time: 1.14)  
Peak: 114.1  
MS: 114.1  
Mass: 1.5e+007

4: (Time: 1.18)  
Peak: 114.1  
MS: 114.1  
Mass: 1.5e+007
$^1$H NMR spectrum of 5b
Sample Name: P
Data File: PTC_NONPOLAR.olp
Instrument Code: UPLC Report

Sample Report:

Mass spectrum of 5b

<table>
<thead>
<tr>
<th>Peak Number</th>
<th>Time</th>
<th>AreaAbs</th>
<th>Area % Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.44</td>
<td>8e+004</td>
<td>98.93</td>
</tr>
<tr>
<td>2</td>
<td>1.58</td>
<td>9e+002</td>
<td>1.07</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peak ID</th>
<th>Time</th>
<th>Mass spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.44</td>
<td>454.3</td>
</tr>
<tr>
<td>2</td>
<td>1.58</td>
<td>7.4e+007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peak ID</th>
<th>Time</th>
<th>Mass spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.44</td>
<td>456.4</td>
</tr>
<tr>
<td>2</td>
<td>1.58</td>
<td>819.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peak ID</th>
<th>Time</th>
<th>Mass spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.44</td>
<td>452.3</td>
</tr>
<tr>
<td>2</td>
<td>1.58</td>
<td>2.0e+006</td>
</tr>
</tbody>
</table>

Flow Rate: 0.8 ml/min
Inj Date: 27-Feb-2008
EXPERIMENTAL

3-Chloro-N’-[(1E)-(2-hydroxyphenyl)methylene]-1-benzo[b]thiophene-2-carbohydrazide: 2a

**Conventional method:** A mixture of salicylaldehyde (0.01 mol, 1.2 g, 1.1 ml), a catalytic amount of acetic acid in 20ml methanol was taken in 100 ml of round bottomed flask and it was kept for stirring at room temperature for about 10 minute. Then a powdered 3-chloro-1-benzo[b]thiophene-2-carbohydrazide (0.01 mol, 2.26 g) was added slowly with constant stirring and kept for refluxion with stirring for about 5 hours. The completion of the reaction was monitored through TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, a light yellow solid that separated was filtered, washed with methanol and dried to get analytically pure sample of 2a. Similarly, the compounds 2b-e were prepared.

**Microwave method:** A mixture of salicylaldehyde (0.01 mol, 1.2 g, 1.1 ml), a catalytic amount of acetic acid and 3-chloro-1-benzo[b]thiophene-2-carbohydrazide (0.01 mol, 2.26 g) in 10ml methanol was subjected to microwave irradiation for about 4 minutes in a domestic oven (Whirlpool) at 150 W as required to complete the reaction, the completion of the reaction was monitored through TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured onto 200 ml ice-cooled water with stirring, the solid separated was filtered, washed with water and then with methanol, dried and recrystallized from ethyl alcohol to get pure 2a. Similarly, the compounds 2b-e were prepared.
3-Chloro-N'-(1E)-(4-chlorophenyl)methylene]-1-benzothiophene-2-carboxyhydrazide: 2b

Solid (Crystalline); C_{16}H_{10}Cl_{2}N_{2}O_{2}S; IR (KBr) \nu (\text{cm}^{-1}): 3230 (N-H), 1708 (C=O), 1565 (C=N); \ ^1\text{H} NMR (300 MHz, CDCl\textsubscript{3}) \delta (ppm): 10.20 (1H, s, CONH), 8.64 (1H, s, CH), 7.30-8.20 (8H, m, ArH), MS m/z = (M\textsuperscript{+}) 360, 315, 281.

3-Chloro-N'-(1E)-(4-methoxyphenyl)methylene]-1-benzothiophene-2-carboxyhydrazide: 2d

Solid (Crystalline); C_{17}H_{13}ClN_{2}O_{2}S; IR (KBr) \nu (\text{cm}^{-1}): 3310 (N-H), 1700 (C=O); \ ^1\text{H} NMR (300 MHz, CDCl\textsubscript{3}) \delta (ppm): 9.40 (1H, s, CONH), 8.45 (1H, s, CH), 6.8-7.86 (8H, m, ArH), 3.8 (3H, OCH\textsubscript{3}); MS: m/z = (M\textsuperscript{+}) 349, 334.
3-Chloro-N'-(1E)-phenylmethylene]-1-benzo[b]thiophene-2-carbohydrazide: 2e

Solid (Crystalline); C_{16}H_{11}ClN_{2}OS; IR (KBr) ν (cm⁻¹):

3310 (N-H), 1690 (C=O);

¹H NMR (300 MHz, CDCl₃)

δ (ppm): 8.92 (1H, s, CONH), 8.39 (1H, s, CH), 7.30-7.92 (9H, m, ArH), MS m/z = (M⁺) 313.3, 317.7, 315.2.

2-[3-Acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl]-2,3-dihydro-1,3,4-oxadiazol-2-yl]phenol: 3a

**Conventional method:** A mixture of 3-Chloro-N'-(1E)-(2-hydroxyphenyl)methylene]-1-benzo[b]thiophene-2-carbohydrazide (0.005 mol, 1.66 g) 2a and acetic anhydride (0.019 mol, 2 g, 1.9 ml) in 100 ml round bottomed flask was refluxed for about 8 hours, the completion of the reaction was monitored through TLC. After completion the reaction, excess of the acetic anhydride was removed through distillation, then the reaction mixture was poured onto ice cooled water with stirring and then it was neutralized by saturated sodium bicarbonate solution, a solid obtained was filtered, washed with water and dried. Then it was purified through column chromatography by using ethyl acetate and n-hexane (6:4) solvent used as eluent to get the pure 5a. Similarly, the compounds 5b-e were prepared.

**Microwave method:** A mixture of 3-Chloro-N'-(1E)-(2-hydroxyphenyl)methylene]-1-benzo[b]thiophene-2-carbohydrazide (0.005 mol, 1.66 g) 2a and acetic anhydride (0.019 mol, 2 g, 1.9 ml) was subjected to microwave for about 7-8 minutes in a domestic oven (Whirlpool) at 150 W as required to complete the reaction (TLC). Then the reaction mixture was cooled to room temperature and poured onto ice-cooled water with vigorous stirring. The solid thus obtained was filtered, dried and purified through column chromatography by using ethyl acetate and n-hexane (2:8) as an eluent to get pure 3a. Similarly, the compounds 3b-e were prepared.
Chapter - II

Solid (Amorphous); C_{18}H_{13}ClN_{2}O_{3}S; IR (KBr) \nu (cm^{-1}):
1690 (C=O); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta (ppm): 10.60 (1H, s, OH), 7.25-8.25 (8H, m, ArH), 2.45 (3H, s, CH\textsubscript{3}); MS m/z = (M\textsuperscript{+}) 373.8.

3-Acetyl-5-(3-chloro-1-benzothien-2-yl)-2-(4-chlorophenyl)-2,3-dihydro-1,3,4-oxadiazole: 3b

Solid (Amorphous); C_{18}H_{12}Cl_{2}N_{2}O_{2}S; IR (KBr) \nu (cm^{-1}):
1698 (C=O), 1610 (C=N); \textsuperscript{1}HNMR (300 MHz, CDCl\textsubscript{3}) \delta (ppm): 7.20-7.78 (8H, m, ArH), 2.25 (3H, s, CH\textsubscript{3}); MS: m/z = (M\textsuperscript{+}) 392, 323.

3-Acetyl-5-(3-chloro-1-benzothien-2-yl)-2-(4-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole: 3c

Solid (Amorphous); C_{18}H_{12}Cl_{2}N_{3}O_{4}S; IR (KBr) \nu (cm^{-1}):
1690 (C=O), 1605 (C=N), 1540 (NO\textsubscript{2}); \textsuperscript{1}HNMR (300 MHz, CDCl\textsubscript{3}) \delta (ppm): 7.30-8.69 (8H, m, ArH), 2.23 (3H, CH\textsubscript{3}); MS (M\textsuperscript{+}) 402, 368.

3-Acetyl-5-(1-benzothien-2-yl)-2-phenyl-2,3-dihydro-1,3,4-oxadiazole: 3e

Solid (Amorphous); C_{19}H_{15}ClN_{2}O_{3}S; IR (KBr) \nu (cm^{-1}):
1700 (C=O), 1600 (C=N); \textsuperscript{1}HNMR (300 MHz, CDCl\textsubscript{3}) \delta (ppm): 7.10-7.82 (9H, m, ArH), 2.22 (3H, CH\textsubscript{3}); MS (M\textsuperscript{+}) 357, 353.
3-Chloro-N'-{[(1E)-(2-chloroquinolin-3-yl)methylene]-1-benzo[b]thiophene-2-carbohydrazide: 4a

**Conventional method:** A mixture of 2-chloroquinoline-3-carbaldehyde (0.01 mol, 1.91 g) and a catalytic amount of acetic acid was dissolved in 20 ml of absolute ethyl alcohol was taken in 100 ml of round bottomed flask and it was kept for stirring at room temperature for about 10 minutes. Then powdered 3-chloro-1-benzo[b]thiophene-2-carbohydrazide (0.01 mol, 2.26 g) was added slowly with constant stirring. Then the reaction mixture was refluxed with stirring for about 8 hours. Mean while a fine yellow precipitate of 3a was obtained and the completion of the reaction was monitored through TLC. After completion of the reaction, it was cooled to room temperature and filtered, washed with ethyl alcohol and recrystallized from ethyl alcohol to get pure sample of 4a. Similarly, the compounds 4b-e were prepared.

**Microwave method:** A mixture of 2-chloroquinoline-3-carbaldehyde (0.01 mol, 1.91 g), powdered 3-chloro-1-benzo[b]thiophene-2-carbohydrazide (0.01 mol, 2.26 g) and a catalytic amount of acetic acid was dissolved in 20 ml of absolute ethyl alcohol was subjected to microwave irradiation for about 6 minutes in a domestic oven (Whirlpool) at 150 W as required to complete the reaction (TLC). Then the reaction mixture was cooled to room temperature and poured onto ice-cooled water with stirring. The solid obtained was filtered and recrystallized from dilute N,N-dimethyl formamide to get pure 4a. Similarly, the compounds 4b-e were prepared.

Solid(Crystalline); C_{19}H_{11}Cl_{2}N_{3}O_{5}; IR (KBr) v (cm\(^{-1}\)) : 3320 (NH), 2950 (Ar-CH), 1660 (C=O), 1590 (C=N); \(^1\)H NMR (300 MHz, DMSO) (δ ppm): 12.5 (1H, CONH), 7.62-8.20 (9H, m, ArH); MS m/z = (M\(^{+}\)) 404.2, 403.2, 400.2.
3-Chloro-N'-[(1E)-(2-chloro-6-methylquinolin-3-yl)methylene]-1-benzothiophene-2-carbohydrazide: 4b

Solid (Crystalline); C_{20}H_{13}Cl_{2}N_{3}O_{5}S; IR (KBr) v (cm^{-1}): 1712 (C=O), 1580 (C=N); $^1$H NMR (300 MHz, DMSO) δ (ppm): 12.25 (1H, CONH), 7.5-8.9 (8H, m, ArH), 2.35 (3H, CH_{3}); MS m/z = (M^+) 415, 346.

3-Chloro-N'-[(1E)-(2-chloro-6-methoxyquinolin-3-yl)methylene]-1-benzothiophene-2-carbohydrazide: 4c

Solid (Crystalline); C_{20}H_{13}Cl_{2}N_{3}O_{5}S; IR (KBr) v (cm^{-1}): 1708 (C=O), 1586 (C=N); $^1$H NMR (300 MHz, DMSO) δ (ppm): 12.30 (1H, CONH), 7.50-8.90 (8H, m, ArH), 3.8 (3H, OCH_{3}); MS m/z = (M^+) 431, 362.

3-Chloro-N'-[(1E)-(2,6-dichloroquinolin-3-yl)methylene]-1-benzothiophene-2-carbohydrazide: 4d

Solid (Crystalline); C_{19}H_{10}Cl_{3}N_{3}O_{5}S; IR (KBr) v (cm^{-1}): 1710 (C=O), 1586 (C=N); $^1$H NMR (300 MHz, DMSO) δ (ppm): 12.55 (1H, CONH), 7.6-9 (8H, m, ArH); MS m/z: (M^+) 435, 332.

3-Chloro-N'-[(1E)-(2-chloro-7-methylquinolin-3-yl)methylene]-1-benzothiophene-2-carbohydrazide: 4e

Solid (Crystalline); C_{20}H_{13}Cl_{2}N_{3}O_{5}S; IR (KBr) v (cm^{-1}): 1705 (C=O), 1580 (C=N); $^1$H NMR (300 MHz, DMSO) δ (ppm): 12.33 (1H, CONH), 7.50-8.90 (8H, m, ArH), 2.34 (3H, CH_{3}); MS (M^+) 415, 346.
Acetyl-5-(3-chloro-1-benzo[b]thien-2-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl]-2-chloro quinoline: 5a

**Conventional method:** A mixture of 3-chloro-N'-(1E)-(2-chloroquinolin-3-yl)methylene]-1-benzo[b]thiophene-2-carbohydrazide (0.005 mol, 2 g) 4a and acetic anhydride (0.02 mol, 2 g, 2 ml) in 20ml DMF was taken in 100ml round bottomed flask and it was refluxed for about 14 hours. The completion of the reaction was monitored through TLC, after completion the reaction excess of the acetic anhydride was removed through distillation and then the reaction mixture was poured onto ice cooled water with stirring. Then the obtained solid was filtered, washed with water and dried. Then it was purified through column chromatography by using a combination of ethyl acetate and n-hexane (3:7) as an eluent to get the pure sample of 5a. Similarly, the compounds 5b-e were prepared.

**Microwave method:** A mixture of 3-chloro-N'-(1E)-(2-chloroquinolin-3-yl)methylene]-1-benzo[b]thiophene-2-carbohydrazide (0.005 mol, 2g) 4a, acetic anhydride (0.02 mol, 2 g, 2 ml) in 20ml DMF was subjected to microwave irradiation for about 10 minutes in a domestic oven (Whirlpool) at 150 W as required to complete the reaction, the completion of the reaction was monitored through TLC. After completion of the reaction, excess of acetic anhydride was distilled off and the reaction mixture was cooled to room temperature and poured onto 200 ml ice-cooled water with vigorous stirring. The solid thus obtained was filtered, dried and purified through column chromatography by using ethyl acetate and n-hexane (4:6) as an eluent to get pure 5a. Similarly, the compounds 5b-e were prepared.
Some of the selected compounds have been tested for antibacterial and antifungal activities and the results have been discussed in Chapter-VII.
REFERENCES


