Chapter-5 Section-A

Chapter-5: Preparation of substituted 1,5-benzothiazepine

5.1. Section A:
Synthesis of substituted 2,3-dihydro-2-(6-methoxynaphthalen-1-yl)-4-phenyl benzothiazepine

5.1.1 Introduction

Heterocyclic chemistry is now a fast growing research field in chemistry. The chemistry of heterocyclic compounds has been an interesting field of study from long time, because heterocyclic compounds have been associated with various biologically activities. Due to bioactivity connected with heterocycle and ease of preparation, a number of researchers are taking keen interested into the study of heterocyclic compounds.

Many heterocyclic compounds due to their specific activity are employed in the treatment of many infectious diseases. Their use in the treatment is attributed to their inherent toxicity to various pathogens. One very interesting and promising class of heterocycle is 2,4-disubstituted-1,5-benzothiazepine. This type of heterocycle constitute an interesting class, due to their synthetic versatility and effective significant pharmacological and biological activity such as antifeedent[1], coronary vasodilatory[2], tranquilizer[3], antidepressant[4], CNS stimulant[5], calcium channel blocker[6], antiulcer[7], anti-HIV[8], antifungal[9], antimicrobial[10]and for treatment of smallpox[11]. Benzothiazepine derivatives have been reported to be more potent selective inhibitors of the mitochondrial Na+-Ca2+ exchangers [12].

Literature survey reveals several synthetic protocols for the synthesis of these compounds, and the presence of this core in any molecule plays a key role in enhancing the activity. Phenyl ring containing halogen [13] and methoxy groups have
shown significant biological activities or enhance the biological activities of 2,4-disubstituted-1,5-benzothiazepine derivatives drastically.

Owing to the biological significance of these classes of compounds and in continuation of our ongoing study on heterocyclic compounds and anti-inflammatory, antimicrobial agents[14], we planned to synthesize a series of some novel 2,4-disubstituted-1,5-benzothiazepine derivatives.

5.1.2 Methods of preparation of benzothiazepine

5.1.2.1 Chalcones condensed with o-aminophenol

The reaction of chalcone with o-aminophenol in the presence of 1-2 drops of Piperidine in ethanol gives the corresponding 1,5-benzothiazepines [15].

5.1.2.2 Eco-friendly catalyst in solvent free condition.

Cyclocondensation of 1,3-substituted-prop-2-en-1-one with 2-aminothiophenol in presence of ecofriendly catalyst zinc acetate in the solvent free condition under microwave irradiation gives 2,3-dihydro-2-substituted-4-(naphthalen-2-ol)-yl- 1,5-benzothiazepines [16].

5.1.2.3 Dicyclohexylcarbodimide (DCC) catalyzed.

The preparation of 1,5-benzothiazepin-4(5H)-ones occurs by the reaction of 2-aminothiophenol and propiolic acid with subsequent cyclisation of the addition product in the presence of dicyclohexylcarbodimide [17].
5.1.3 Present work

Considering the importance of 1,5-benothiazepine derivatives as the active therapeutic agents in particular, antifungal, antimicrobial and anti HIV, Ca++ channel blockers, anticancer activity and CNS depressant, due to these properties associated with them, the synthesis of 2,3-dihydro-2-(2-methoxynaphthalen-5-yl)-4-phenyl benzothiazepine (4a-g), was carried out.

This section describes the synthesis of substituted 2,3-dihydro-2-(6-methoxynaphthalen-1-yl)-4-phenylbenzothiazepine (4a-g) by the condensation of 3-(6-methoxynaphthalen-1-yl)-1-phenylprop-2-en-1-one(3a-g) with 2-amino thiophenol in presence of ethanol, Pyridine and acetic acid.
5.1.4 Experimental

General procedure for the synthesis of (6-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (Chalcone) (3f).

A mixture of 4-fluoroacetophenone (1f) (0.01 mol) and 6-methoxy-1-naphthaldehyde (2) (0.01 mol) was stirred in ethanol (30 mL) and then sodium hydroxide solution (15 ml, 0.02 mol) was added to it. The reaction mixture was kept overnight at room temperature and then it was poured on crushed ice and acidified with dilute hydrochloric acid. The Chalcone i.e. [3-(6-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)prop-2-en-1-one] (3f) precipitate out as solid. Then it was filtered, dried and purified by crystallization from acetic acid.

Compound 3f: Yield = 92%, M.P. = 191°C

Elemental analysis Calcd for (C$_{21}$H$_{18}$O$_3$); C, 79.22; H, 5.70;

Found: C, 79.17; H, 5.65 %;

IR (KBr pellets Cm$^{-1}$): 1670 (>C=O), 1640 (CH=CH), 1170 (OCH$_3$).

$^1$H NMR (DMSO, 400 MHz), δ 8.2-7.0 (m, 10H, Ar-H), 7.1-6.90 (dd, 1H, >C=CH$_B$), 6.75-6.65 (dd, 1H, CH$_A$=C<), 3.90 (s, 3H, 2 x -OCH$_3$).

Mass (m/z): 419.23 (M+1).

General procedure for the synthesis of 4-(4-methoxyphenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine (4f):

A mixture of 1-(4-methoxyphenyl)-3-(6-methoxynaphthalen-5-yl)prop-2-en-1-one (3f) (0.01 mole) and o-aminothiophenol (0.11 mole) in 50 ml ethanol, further 2-3 ml of Piperidine was added, then reaction mixture was refluxed for 5-6 hours. Then this reaction mixture was acidified by 10 ml glacial acetic acid and further refluxed for 2 hours. On cooling solid compound 4-(4-methoxyphenyl)-2-(6-methoxyphenyl)
naphthalen-1-yl)-2,3-dihydrobenzothiazepine (4f) is obtained. Then it was filtered, dried and purified by crystallization from acetic acid. Other compounds (4a-g) were prepared in the similar way by using substituted Chalcones o-aminothiophenol and their percentage yield and physical constants were recorded in Table I.

Their structures have been confirmed by Mass, IR and \(^1\)H NMR spectra.

![Chemical structure of 2-(6-methoxynaphthalen-1-yl)-4-(4-methoxyphenyl)-2,3-dihydrobenzothiazepine (4f)](attachment:Chemical_structure.png)

Table I

**Physical data of compounds (4a-g)**

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>R(_3)</th>
<th>Yield %</th>
<th>M.P. °C</th>
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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>80</td>
<td>141</td>
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<tr>
<td>4b</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
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<td>Br</td>
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<td>F</td>
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<tr>
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<td>OCH(_3)</td>
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<td>84</td>
<td>154</td>
</tr>
<tr>
<td>4g</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>68</td>
<td>160</td>
</tr>
</tbody>
</table>
Spectral data of synthesized compounds (4a-g)

(4a): 2-(6-methoxynaphthalen-1-yl)-4-phenyl-2,3-dihydrobenzothiazepine

Elemental analysis Calcd for C_{26}H_{21}NOS; C, 78.95; H, 5.35; N, 3.54;
found: C, 78.85; H, 5.32; N, 3.50%

IR (KBr pellets Cm⁻¹): 3009 (Ar-C-H str.), 1622 (-C=N str.in benzothiazepine), 1596 (C=C str. in Ar), 1478 & 1459 (-OCH₃).

¹H NMR (DMSO, 400 MHz) δ 2.52-2.50(t, 1H, CH₂-Hx, JₓA = 2.60Hz, JₓB = 7.85Hz), 3.35 (s, 3H, -OCH₃), 3.85(dd, 1H, CH₂-Hₐ, JₓA= 4.8Hz, JₓB= 12.10 Hz), 5.40(dd, 1H, CH₂-Hₐ, JₓB= 5.04 Hz, JₓA= 10.40Hz), 8.58-6.40 (m, 15H, Ar-H).

Mass (m/z): 396.12 (M+1)

(4b): 4-(4-chlorophenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine

Elemental analysis Calcd for C_{26}H_{20}ClNOS; C, 72.63; H, 4.69; N, 3.26;
found: C, 72.58; H, 4.65; N, 3.25%

IR (KBr pellets Cm⁻¹): 3025 (Ar-C-H str.), 1620 (-C=N str.in benzothiazepine), 1595 (C=C str. in Ar), 1475 & 1455 (-OCH₃).

¹H NMR (DMSO, 400 MHz) δ 2.50-2.47(t, 1H, CH₂-Hx, JₓA = 2.60Hz, JₓB = 7.85Hz), 3.30 (s, 3H, -OCH₃), 3.80(dd, 1H, CH₂-Hₐ, JₓA= 4.8Hz, JₓB= 12.10 Hz), 5.35(dd, 1H, CH₂-Hₐ, JₓB= 5.04 Hz, JₓA= 10.40Hz), 8.55-6.35 (m, 14H, Ar-H).

Mass (m/z): 330.16, 331.12 (M+1)

(4c): 4-(4-bromophenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine

Elemental analysis Calcd for C_{26}H_{20}BrNOS; C, 65.82; H, 4.25; N, 2.95;
found: C, 65.80; H, 4.22; N, 2.88%

IR (KBr pellets Cm⁻¹): 3061 (Ar-C-H str.), 1620 (-C=N str.in benzothiazepine), 1592 (C=C str. in Ar), 1475 & 1455 (CH₂ bend.), 1190 (-OCH₃).

¹H NMR (DMSO, 400 MHz) δ 2.54-2.50(t, 1H, CH₂-Hx, JₓA = 2.60Hz, JₓB = 7.85Hz), 3.32 (s, 3H, -OCH₃), 3.80(dd, 1H, CH₂-Hₐ, JₓA= 4.8Hz, JₓB= 12.10 Hz), 5.30(dd, 1H, CH₂-Hₐ, JₓB= 5.04 Hz, JₓA= 10.40Hz), 8.58-6.40 (m, 14H, Ar-H).

Mass (m/z): 475.12 (M+1)

(4d): 4-(4-fluorophenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine

Elemental analysis Calcd for C_{26}H_{20}FNOS; C, 75.52; H, 4.88; N, 3.39;
found: C, 75.48; H, 4.85; N, 3.32%

IR (KBr pellets Cm⁻¹): 3036 (Ar-C-H str.), 1635 (-C=N str.in benzothiazepine), 1580 (C=C str. in Ar), 1470 & 1453 (CH₂ bend.), 1190 (-OCH₃).
**1H NMR (DMSO, 400 MHz)** δ 2.52-2.50 (t, 1H, CH-Hx, J<sub>XA</sub> = 2.60Hz, J<sub>XB</sub> = 7.85Hz), 3.30 (s, 3H, -OCH<sub>3</sub>), 3.82 (dd, 1H, CH<sub>2</sub>-H<sub>A</sub>, J<sub>AX</sub> = 4.8Hz, J<sub>AB</sub> = 12.10 Hz), 5.42 (dd, 1H, CH<sub>2</sub>-H<sub>B</sub>, J<sub>BX</sub> = 5.04 Hz, J<sub>BA</sub> = 10.40Hz), 8.58-6.45 (m, 14H, Ar-H).

**Mass (m/z):** 314.08 (M+1)

**(4e): 4-(4-methylphenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine**

**Elemental analysis Calcd for C<sub>27</sub>H<sub>23</sub>NOS;** C, 79.18; H, 5.66; N, 3.42;

**found:** C, 79.12; H, 5.62; N, 3.35%

**IR (KBr pellets Cm<sup>-1</sup>):** 3051 (Ar-C-H str.), 1618 (C=N str. in benzothiazepine), 1592 (C=C str. in Ar), 1480 & 1453 (CH<sub>2</sub> bend.), 1195 (-OCH<sub>3</sub>).

**1H NMR (DMSO, 400 MHz)** δ 2.35 (s, 3H, Ar-CH<sub>3</sub>), 2.52-2.50 (t,1H, CH-Hx, J<sub>XA</sub> = 2.60Hz, J<sub>XB</sub> = 7.85Hz), 3.35 (s, 3H, -OCH<sub>3</sub>), 3.85 (dd, 1H, CH<sub>2</sub>-H<sub>A</sub>, J<sub>AX</sub> = 4.8Hz, J<sub>AB</sub> = 12.10 Hz), 5.40 (dd, 1H, CH<sub>2</sub>-H<sub>B</sub>, J<sub>BX</sub> = 5.04 Hz, J<sub>BA</sub> = 10.40Hz), 8.55-6.42 (m, 14H, Ar-H).

**Mass (m/z):** 410.22 (M+1)

**4f: 4-(4-methoxyphenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine**

**Elemental analysis Calcd for C<sub>27</sub>H<sub>23</sub>NO<sub>2</sub>S;** C, 76.21; H, 5.45; N, 3.29;

**found:** C, 76.15; H, 5.40; N, 3.25%

**IR (KBr pellets Cm<sup>-1</sup>):** 3009 (Ar-C-H str.), 1622 (C=N str. in benzothiazepine), 1596 (C=C str. in Ar), 1459 & 1478 (CH<sub>2</sub> bend.), 1172 (-OCH<sub>3</sub>).

**1H NMR (DMSO, 400 MHz)** δ 2.35 (s, 3H, Ar-CH<sub>3</sub>), 2.52-2.50 (t,1H, CH-Hx, J<sub>XA</sub> = 2.60Hz, J<sub>XB</sub> = 7.85Hz), 3.45 (s, 3H, -OCH<sub>3</sub>), 3.90 (dd, 1H, CH<sub>2</sub>-H<sub>A</sub>, J<sub>AX</sub> = 4.8Hz, J<sub>AB</sub> = 12.10 Hz), 5.48 (dd, 1H, CH<sub>2</sub>-H<sub>B</sub>, J<sub>BX</sub> = 5.04 Hz, J<sub>BA</sub> = 10.40Hz), 8.58-6.42 (m, 14H, Ar-H).

**Mass (m/z):** 426.39 (M+1)

**4g: 4-(3,5-dichlorophenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzothiazepine**

**Elemental analysis Calcd for C<sub>26</sub>H<sub>19</sub>Cl<sub>2</sub>NOS;** C, 67.24; H, 4.12; N, 3.02;

**found:** C, 67.15; H, 4.02; N, 2.95%

**IR (KBr pellets Cm<sup>-1</sup>):** 3035 (Ar-C-H str.), 1615 (C=N str. in benzothiazepine), 1575 (C=C str. in Ar), 1480 & 1440 (CH<sub>2</sub> bend.), 1172 (-OCH<sub>3</sub>).

**1H NMR (DMSO, 400 MHz)** δ 2.50-2.48 (t, 1H, CH-Hx, J<sub>XA</sub> = 2.60Hz, J<sub>XB</sub> = 7.85Hz), 3.45 (s, 3H, 2 x -OCH<sub>3</sub>), 3.90(dd, 1H, CH<sub>2</sub>-H<sub>A</sub>, J<sub>AX</sub> = 4.8Hz, J<sub>AB</sub> = 12.10 Hz), 5.48(dd, 1H, CH<sub>2</sub>-H<sub>B</sub>, J<sub>BX</sub> = 5.04 Hz, J<sub>BA</sub> = 10.40Hz), 8.58-6.42 (m, 14H, Ar-H).

**Mass (m/z):** 464.35 (M+1)
Spectra- IR (3f): 3-(6-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)prop-2-en-1-one

\[\text{IR spectra image}\\\]

\[\text{HR NMR spectra image}\\\]

\[\text{HR NMR (3f): 3-(6-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)prop-2-en-1-one}\\\]
Mass (3f): \(3\text{-}(6\text{-methoxynaphthalen-1-yl})\text{-}1\text{-}(4\text{-methoxyphenyl})\text{prop-2-en-1-one}\)

IR (4f): \(4\text{-}(4\text{-methoxyphenyl})\text{-}2\text{-}(6\text{-methoxynaphthalen-1-yl})\text{-}2,3\text{-dihydrobenzothiazepine}\)
$^1$H NMR (4f): 4-(4-methoxyphenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzo thiazipine

Mass (4f): 4-(4-methoxyphenyl)-2-(6-methoxynaphthalen-1-yl)-2,3-dihydrobenzo thiazepine
5.1.5 References