Chapter - III B

Synthesis of 2-hetarylamino substituted analogues of the privileged nucleus of pyrrolo-1,5-benzothiazepines of medicinal interest
Chapter - III B

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Abstract

A one pot synthetic approach to the of 2-hetarylamino substituted novel analogues of pyrrolo-[3,4-b][1,5]-benzothiazepin-2',5'-diones (3.034 a-h) has been developed from the corresponding iminothiomylether derivative 3.033. The SMe group of 3.033 underwent smooth nucleophilic displacement reaction with a variety of heteryl amines to afford (3.034 a-h) in acceptable yields. The structure of all compound were established on the basis of IR, $^1$HNMR, and MS spectral data.
3.1 INTRODUCTION

The quest to develop effective therapies for treatment of human immunodeficiency virus (HIV) infection has demonstrated that clinical benefits can be achieved with drugs that target the protease\(^1\) or reverse transcriptase\(^2\) enzymes. The currently available agents however provide only transient benefit, due to the rapid emergence of drug resistant mutants of the virus\(^3\). Combinations of drugs have been tried in an attempt to avoid the problem of resistance with some promising results\(^4\) and combination therapy now represents the standard of care. However, there is a continuing need to identify improved agents with in each class in order to provide the optimum clinical benefits. On account of the wide range of biological properties exhibited by benzothiazepine derived compounds, benzothiazepine class of privileged scaffolds have been considered among the most important molecules for the drug discovery.

It has been observed that the incorporation of the bioactive pharmacophores such as the pyrrolidine, piperidine, morpholine, N-substituted piperazines etc in the existing drug molecules, exert a profound influence on the biological profiles of the parent molecules. Greatly encouraged by such a trend in the literature, it was planned in the present work to incorporate in \(3.033\), the structural features of pyrrolidine, piperidine, morpholine, N-substituted piperazines, (N-methyl, N-ethyl, N-benzyl, N-carboxyethyl and N-acetylpiperazines) to afford the compound \((3.034a-h)\) respectively, following the procedure described for their incorporation on some other related structures in the literature \(^5,6\).

3.2 BIOLOGICAL ASPECTS OF THE HETEROARYL AMINES (PYRROLIDINE, PIPERIDINE, PIPERAZINE)

3.2.1 Pyrrolidine

Bannwart et. al.\(^7\) designed a series of 3, 3-disubstituted pyrrolidine derivatives \((3.001)\). Synthesized compounds were evaluated as monoamine triple reuptake inhibitors. It showed in vivo antidepressant-like effect in the mouse tail suspension assay with a minimum effective dose of 30 mg/kg; i.p. The first compound \(3.001\) revealed potent inhibitor activity [Fig. 3.1].
Lucas et al. synthesized two new series of monoamine triple reuptake inhibitors (TRIS) through scaffold homologation of recently reported series of 3, 3-disubstituted pyrrolidine (3.002). The region isomeric 2 and 3 ketopyrrolidine (3.002a) has a high level of potency against all three monoamine transporters as well as good in human vitro stability [Fig. 3.2].

Zelle et al. synthesized a novel compound ABT-200(+), (1'R*3'R*)-3-phenyl-1[(1', 2', 3', 4'-tetrahydro-5',6'-methylene-dioxy-1'-naphthalanyl) methyl] pyrrolidine (3.003) which was the first example of a new structural class of potent α-antagonists, which possessed the additional property of nor-epinephrine reuptake inhibitor. The compound was evaluated for antidepressant activity and expected to have utility in the treatment of depression [Fig. 3.3].

3.2.2 Piperidine

Piperidine ring is an omnipresent molecular skeleton. A large number of piperidine-containing compounds are biologically and medicinally important.
Biological properties of piperidines are highly dependent on the type and location of substituents on the heterocyclic ring. Various N-heterocyclic piperidine compounds have been mentioned in clinical and preclinical studies. Piperidine nucleus occurs in active pharmacological substances, for example (N-Methyl Daspartic acid (NMDA) antagonist).

Takeuchi et. al. synthesized a series of l-(1H-indol-4-yloxy)-3-(4-benzo[b]thiophen-2-ylpiperidinyl) propan-2-ols and evaluated them for antidepressant activity. They identified some fused bicyclic aryl-substituted piperidines as an essential pharmacophore for 5-HT reuptake inhibition and also having potent dual 5-HT<sub>1A</sub> receptor antagonism and serotonin reuptake inhibition.

On the basis of potency and activity, compound (3.004) showed combined 5-HT<sub>1A</sub>/SSRI activity in a single molecule with no negative feedback effect [Fig. 3.4].

Bollinger et. al. synthesized 1, 4-disubstituted piperidines and piperazines (1, 4-DAPs) and showed the effect of some synthesized compounds on endogenous neurotransmitters including dopamine, serotonin, and (nor) epinephrine. Compound (3.005) reported to be a potent agonist for 5HT<sub>1A</sub> receptor and showed promising antidepressant effect having K<sub>i</sub> value of 2.7 nM and a maximal efficacy of 124%. [Fig. 3.5]
Boot et. al.\textsuperscript{15} reported a set of N-alkyl-N-arylmethylpiperidin-4-amines (3.006a) and derivatives which were demonstrated to be inhibitors of both serotonin and norepinephrin reuptake. 4-Fluro-2-trifluoromethyl substitution 3.006 b pattern was evaluated for optimization towards dual SERT and NET inhibition [Fig. 3.6].

![Fig. 3.6](image)

(a) $R_1 = \text{Me}$, $R_2, R_3 = \text{H}$
(b) $R_1 = \text{Me}$, $R_2 = -\text{CF}_3$, $R_3 = -\text{F}$

Rocco et. al.\textsuperscript{16} designed a series of 1-(IH indole-4-yloxy)-3-(4-aryl pipridinyl) propan-2-ols (3.007 a). Compound (3.007 b) was found to be a potent dual 5-HT\textsubscript{1A} receptor antagonist and serotonin reuptake inhibitor [Fig. 3.7].

![Fig. 3.7](image)

Steckler et. al.\textsuperscript{17} designed a set of derivatives of 4-phenyl-4-[IH-imidazole-2-yl]-piperidine (3.008). It shows antidepressant and anxiolytic activity [Fig. 3.8].

![Fig. 3.8](image)
Trabanco et. al.\textsuperscript{18} synthesized 4-phenyl-4-(1H-imidazol-2-yl)-piperidine derivatives (3.009) and evaluated their antidepressant-like effect by mouse tail suspension test and reported this to be the most potent compounds prepared within this series [Fig. 3.9].

Ahmed et. al.\textsuperscript{19} synthesized several benzhydroxyl alkylpiperidine derivatives 3.010 [Fig. 3.10] and evaluated them by pharmacological tests for antagonism of reserpine and apomorphine-induced hypothermia. Compounds were evaluated by tail suspension test in mice. Preferred compounds were also studied pharmacologically by binding study to serotonin (5HT), norepinephrine (NE) and dopamine (DA) reuptake site and showed antidepressant activity.

3.2.3 Piperazine

Piperazine is a six-membered heterocyclic ring having two opposing nitrogen atoms. The piperazine nucleus has potent antidepressant activity. Nefazodone and Aripiprazole are the typical examples\textsuperscript{20}. WAY-100635 is a 5-HT\textsubscript{1A} receptor antagonist\textsuperscript{21}. 1-(2-Pyrimidinyl)piperazine is a major active metabolite of tandospirone, gepirone, ipsapirone, and buspirone which also have antidepressant/anxiolytic 5-HT\textsubscript{1A} agonists activity\textsuperscript{22}. The pharmaceutical importance of this nucleus is due to extensive occurrence in current marketed drugs\textsuperscript{23}. Various antidepressant drugs have
a piperazine nucleus such as Amoxapine, Befuraline, Binospirone, Alnespirone, Buspirone, Flesinoxan, Gepirone, Ipsapirone, Nefazodone, Piberaline, and Tandospirone. Arylpiperazine moiety is used as a template for designing CNS-active agents. It constitutes the main pharmacophoric fragment, for serotonergic, dopaminergic, and adrenergic receptors.\textsuperscript{24}

Fray et. al\textsuperscript{25} synthesized a new class of dual serotonin noradrenalin reuptake inhibitor N-(1, 2-diphenylethyl) piperazine (3.011) Fig. 3.11. Two compounds possessed comparable in vitro profile to the dual reuptake inhibitor duloxetine. N-Substituted piperazine potently inhibited both [3H]-5HT and [3H]-NA reuptake in HEK 293 cell transfected with human amine transporter with 100-fold selectivity over the DA transporter.

Kang et. al\textsuperscript{26} synthesized aryl piperazine containing pyrrole-3-carboxamide derivatives (3.012), Fig. 3.12 These derivatives were evaluated for binding to 5-HT\textsubscript{2A}, 5-HT\textsubscript{2C} receptor and 5-HT transporter. It showed good efficacy. Antidepressant activity of interesting compounds was evaluated by FST on mice using fluoxetine as reference drug.
Kling et. al.\textsuperscript{27} synthesized 2- methoxy aryl piperazine (3.013) Fig 3.13 series based on the N-4-aryl-piperazinyl-N-ethyl-5, 6, 7, 8-tetrahydropyrido [4,3,4,5] thieno (2,3-d) pyrimidine-4(3H)-one core. Isoquinoline analogue of this compound displayed high affinity and an antagonistic mode of action for the 5-HT\textsubscript{1A} and the 5-HT\textsubscript{1B} receptors.

![3.013]

Torrado et. al.\textsuperscript{28} synthesized a series of compounds combining the naphthylpiperazine (3.014) and thienopyran scaffolds and evaluated for 5-HT reuptake inhibitor with 5-HT\textsubscript{1D} antagonist activity. The designed compound (3.015) has been based on the overlapping type strategy where two pharmacophores (3.014) and thinopyran are linked in a single molecule; the resultant compound (3.015) has a dual pharmacological profile and has the potential to deliver a more efficient treatment for depression [Fig. 3.14].

![3.014]  ![3.015]

Zajdel et. al.\textsuperscript{29} synthesized compound bearing (3-arylamino) pyrrolidine-2,5-dione (3.016) and N-arylprolinamide (3.017) moieties showing high affinity for 5-HT\textsubscript{1A}, high to low for 5-HT\textsubscript{2A} and low for D2 receptor [Fig. 3.15]

![3.016]  ![3.017]
Wu et al. synthesized and reported a novel series of arylpiperazine derivatives of diphenylsulfide and evaluated them for dual 5-HT<sub>1A</sub>/SSRI activities. They concluded that 2-methoxyphenyl-piperazine moiety is essential for 5-HT<sub>1A</sub> affinity. Compound (3.018) of this series showed best antidepressant activity [Fig. 3.16]

![Fig. 3.16](image)

Yoon et al. synthesized a series of 4-methoxy-N-[3-(4-substituted phenyl-piperazin-1-yl) propyl] benzene sulfonamides and N-[3-(4-substituted phenyl-piperazin-1-yl) propyl] naphthyl sulphonamides and evaluated them for 5-HT<sub>7</sub> receptor antagonistic activity. The synthesized compound (3.019) showed a noble activity on 5-HT<sub>7</sub> receptors and good selectivity on 5-HT<sub>1a</sub>, 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, and 5-HT<sub>6</sub> receptors [Fig. 3.17].

![Fig. 3.17](image)

### 3.3 SYNTHETIC ASPECTS OF HETRYL AMINE DERIVATIVES

A new efficient method for the N-heterocyclization of primary amines 3.020 with diols 3.021 catalyzed by a Cp*Ir complex was developed. A variety of five-, six-, and seven-membered cyclic amines 3.022 were synthesized in good to excellent yields [Scheme-3.1].

![Scheme-3.1](image)
A convenient two-step preparation\textsuperscript{31} of alkylidenepryrolidines (3.024) is reported from 3.023 (Scheme-3.2)

\begin{equation}
\text{R(O)}\text{C} = \text{C} - \text{R} \quad \xrightarrow{2 \text{ eq. TFA}} \quad \text{CH}_2\text{Cl}_2, \text{r.t., } 3\text{h} \quad \text{CO(O)R} \\
\text{3.023} \quad \text{3.024}
\end{equation}

Scheme-3.2

Ammonium acetate, benzaldehyde, 3.025 4-substituted benzaldehyde 3.027 and 2-butanone 3.026 in ethanol were condensed to form the piperidine derivative\textsuperscript{34} (3.028) [Scheme-3.3].

\begin{equation}
\text{CHO} + \text{H}_3\text{C} = \text{C} - \text{R} \quad \xrightarrow{\text{EtOH;NH}_4\text{OAc}} \quad \text{rt} \quad \text{CHO} \quad \xrightarrow{\text{EtOH;NH}_4\text{OAc}} \quad \text{rt} \\
\text{3.025} \quad \text{3.026} \quad \text{3.027} \quad \text{3.028}
\end{equation}

Scheme-3.3

A novel approach to 2, 4-disubstituted piperidines 3.030 involves the radical cyclization of 7-substituted-6-aza-8-bromoocct-2-enotes (3.029)\textsuperscript{35}[Scheme-3.4].

\begin{equation}
\text{Ts-N} \quad \text{CO}_2\text{R} \quad \xrightarrow{2.8 \text{ eq. (MeSi)}_3\text{SiH}} \quad \text{toluene, } 90^\circ\text{C, } 39\text{h} \quad \text{CO}_2\text{R'} \\
\text{3.029} \quad \text{3.030}
\end{equation}

Scheme-3.4

Reaction of alkyl and N-aryl piperazine\textsuperscript{36} 3.031 with 2-bromo-1-(4-bromophenyl) ethanone in K\textsubscript{2}CO\textsubscript{3} and dry acetonitrile afforded the corresponding analogue of piperazine (3.032) [Scheme-3.5].

\begin{equation}
\text{H}_3\text{C}-\text{N} \quad \xrightarrow{\text{Br}} \quad \text{H}_3\text{C}-\text{N} \quad \xrightarrow{\text{Br}} \quad \text{3.031} \quad \text{3.032}
\end{equation}

Scheme-3.5
3.4 PRESENT WORK

It was shown earlier in chapter III-A, that the iminothiomethylether have been exploited in a wide variety of synthetic applications. It has recently received considerable attention due to their synthetic importance for the construction of a variety of novel fused heterocyclic systems therefore, their synthesis and reactions have recently gained much importance.

The present investigation was undertaken with a view to streamline the synthetic strategies which have been devised in the literature for the preparation of 2-amino substituted derivatives of benzothiazepines. The chemical literature is replete with great variety of synthetic methods which have been employed for the preparation of these potent molecules. This aroused our interest in these; and prompted us to incorporate some such bio-active pharmacophores which had the previous history of being biologically active on the 2-position of pyrrolo-1,5-benzothiazepines to generate their novel heterocyclic analogues shown in Fig. 3.18.

3.5 RESULTS AND DISCUSSION

It has been reported that iminothiomethylether derivative of 1, 5-benzothiazepines are useful synthons in view of their activation for nucleophilic attack. Benzothiazepines embellished with pharmacophores such as pyrrolidine, piperidine, piperazine, etc have been the subject of several reports in the journals and patented literature on account of the positive impact which they showed by their presence in these molecules. In view of the impressive biological activities shown by the hetrylamine substituted derivatives of the 1,5-benzothiazepines, it was thought of interest in the present work to synthesize molecules which carried the indicated hetrylamine bearing substituents at C-2 of the pyrrolo-1,5-benzothiazepine nucleus based on the strategy shown in Scheme 3.6, which consisted of the treatment of 3.033 in acetone in presence of the base triethylamine with the hetrylamines (such as pyrrolidine, piperidine, morpholine, N-d-(methyl, ethyl, benzyl, ethoxycarbonyl and acetyl)) substituted piperazines to produce 2-hetrylamino substituted analogues 3.034 (a-h) of pyrrolo-[3,4-b][1,5]-benzothiazepin-2',5'-diones respectively.
3.6 STRUCTURE OF COMPOUNDS 3.034 (a-h) WHOSE SYNTHESIS IS DESCRIBED IN THE EXPERIMENTAL SECTION IN THIS CHAPTER

(Fig. 3.18)

Scheme-3.6
### Table-3.1: Physical and analytical data of the compounds 3.034a-3.034h

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound No.</th>
<th>Molecular Formula</th>
<th>M.W.</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis (Cald/ found)</th>
<th>Elemental Analysis (Cald/ found)</th>
<th>Elemental Analysis (Cald/ found)</th>
<th>Elemental Analysis (Cald/ found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>3.034a</td>
<td>C_{15}H_{15}N_{3}S</td>
<td>301.36</td>
<td>140-142</td>
<td>71</td>
<td>59.78/59.49 5.02/4.99 13.94/13.87 10.64/10.69</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>2.</td>
<td>3.034b</td>
<td>C_{16}H_{17}N_{3}S</td>
<td>315.39</td>
<td>222-225</td>
<td>68</td>
<td>60.93/60.63 5.43/5.45 13.32/13.38 10.17/10.22</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>3.</td>
<td>3.034c</td>
<td>C_{15}H_{15}N_{3}S</td>
<td>317.36</td>
<td>152-154</td>
<td>78</td>
<td>56.77/57.05 4.76/4.73 13.24/13.31 10.10/10.05</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>4.</td>
<td>3.034d</td>
<td>C_{16}H_{19}N_{3}S</td>
<td>330.40</td>
<td>135-137</td>
<td>73</td>
<td>58.16/57.87 5.49/5.47 16.96/16.88 9.70/9.74</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>5.</td>
<td>3.034e</td>
<td>C_{17}H_{20}N_{3}S</td>
<td>344.43</td>
<td>201-203</td>
<td>62</td>
<td>59.28/58.99 5.85/5.87 16.27/16.19 9.31/9.36</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>6.</td>
<td>3.034f</td>
<td>C_{18}H_{20}N_{3}S</td>
<td>406.50</td>
<td>120-122</td>
<td>75</td>
<td>65.00/65.32 5.46/5.48 13.78/13.71 7.89/7.85</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>7.</td>
<td>3.034g</td>
<td>C_{18}H_{20}N_{3}S</td>
<td>388.44</td>
<td>97-99</td>
<td>77</td>
<td>55.66/55.93 5.19/5.17 14.42/14.49 8.25/8.21</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>8.</td>
<td>3.034h</td>
<td>C_{17}H_{19}N_{3}S</td>
<td>358.41</td>
<td>105-106</td>
<td>75</td>
<td>56.97/56.69 5.06/5.08 15.63/15.70 8.95/8.91</td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
</tr>
</tbody>
</table>

### Table-3.2: Spectral data of compound 3.034a-3.034h

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound No.</th>
<th>IR(KBr)cm⁻¹</th>
<th>¹HNMR (in CDCl₃ + DMSO d₆) (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>3.034a</td>
<td>3400[NH str.], 1660 [C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 690[C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 1.7-2.4[8H,m, pyrrolidine ring], 10.0[1H,s,NH] MS(m/z%) 301.36 (85%), 231.09(100.0%), 302.09(18.4%), 303.08(4.5%)</td>
</tr>
<tr>
<td>2.</td>
<td>3.034b</td>
<td>3390[NH str.], 1660[C=O str.], 1625[C=N str.], 3010[C-H str. ArH], 1560 [C=C str. ArH], 690[C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 1.5-2.7[10H,m, piperidine ring], 10.0[1H,s,NH]</td>
</tr>
<tr>
<td>3.</td>
<td>3.034c</td>
<td>3410[NH str.], 1660 [C=O str.], 1630[C=N str.], 3025[C-H str. ArH], 1565 [C=C str. ArH], 700 [C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.9[4H,t, morpholine ring], 3.65[4H,t, morpholine ring], 10.0[1H,s,NH]</td>
</tr>
</tbody>
</table>
### Synthesis of 2-hetarylamino substituted analogues

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound No.</th>
<th>IR(KBr)cm⁻¹</th>
<th>¹HNMR (in CDCl₃ + DMSO d₆) (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>4</td>
<td>3.034d</td>
<td>3400[NH str.], 1660 [C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2970 [C-H str. CH₃], 690[C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.13-2.65[8H,m, piperazine ring], 2.26[3H,s,CH₃], 10.0[1H,s,NH]</td>
</tr>
<tr>
<td>5</td>
<td>3.034e</td>
<td>3390[NH str.], 1660[C=O str.], 1625[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2975[C-H str. CH₃], 680[C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.3-2.6 [8H,m, piperazine ring], 2.38[2H,q,CH₂], 1.02[3H,t,CH₃], 10.0[1H,s,NH]</td>
</tr>
<tr>
<td>6</td>
<td>3.034f</td>
<td>3400[NH str.], 1680[C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2850 [C-H str. CH₃], 690[C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.37-2.65[8H,m, piperazine ring], 3.66[2H,s,CH₂], 7.22-7.34[5H,m,Ar-H], 10.0[1H,s,NH]</td>
</tr>
<tr>
<td>7</td>
<td>3.034g</td>
<td>3433[NH str.], 1660,1730 [C=O str.], 1630 [C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2957,2851[C-H str. CH₃,CH₂], 694 [C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.7-2.9[8H,m, piperazine ring], 4.13[2H,q,CH₂], 1.29[3H,t,CH₂], 10.0[1H,s,NH] MS(m/z%) 388.40(75%), 231.12(100.0%), 389.12(21.9%), 390.12(5.8%)</td>
</tr>
<tr>
<td>8</td>
<td>3.034h</td>
<td>3400[NH str.], 1660,1700 [C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2970[C-H str. CH₃], 690 [C-S str.]</td>
<td>7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.81-3.46[8H,m, piperazine ring], 2.32[3H,s,CH₃], 10.0[1H,s,NH]</td>
</tr>
</tbody>
</table>
3.7 INTERPRETATION OF SPECTRAL DATA FOR THE ELUCIDATION OF STRUCTURE OF COMPOUNDS 3.034 (a-h)

Structures of all the compounds 3.034 (a-h) were established on the basis of elemental analysis, IR and $^1$HNMR data. Physical data of all the compounds were found to be consistent to the structures assigned to these molecules.

The physical microanalysis, infrared and $^1$HNMR spectral data of all the compounds are given in table: 3.1 and 3.2 and the spectral graphs are presented at the end of this chapter.

Infrared spectra

Infrared spectrum of compound (3.034-a) on KBr exhibited bands near 1660 cm$^{-1}$ for [C=O str.], 1630 cm$^{-1}$ for [C=N str.], 3030 cm$^{-1}$ for [C-H str. ArH], 1560 cm$^{-1}$ for [C=C str.], 3400 cm$^{-1}$ for [N-H str.] and at 690 cm$^{-1}$ for [C-S str.].

In a likewise manner, the formation of other compounds (3.034 b-h) was ascertained on the basis of IR spectrum.

$^1$HNMR Spectra

$^1$HNMR spectrum of a compound (3.034-a) in CDCl$_3$+DMSO-d$_6$ displayed signals for the presence of 15 protons. Appearance of two doublets at $\delta$ 3.0 and $\delta$ 3.8 were assigned to two protons of the thiazepine ring. Appearance of a multiplet at $\delta$ 7.21-7.39 was attributed to four protons of the benzene ring of benzothiazepine, along with this another multiplet which appeared at $\delta$ 1.7-2.8 for eight protons was assigned to the four methylene group of pyrrolidine group, which strongly corroborated the formation of (3.034-a). A singlet for one proton which appeared at $\delta$ 10.0 was attributed to NH of the pyrrole ring.

$^1$HNMR spectrum of a compound (3.034-b) in CDCl$_3$+DMSO-d$_6$ displayed signals for the presence of 17 protons. Appearance of two doublets at $\delta$ 3.0 and $\delta$ 3.8 was assigned to the two protons of thiazepine ring. Appearance of a multiplet for ten protons at $\delta$ 1.5-2.7 was due to the methylene protons of piperidine ring which strongly corroborated the formation of 3.034-b. A singlet for one protons which
appeared at δ 10.0 was attributed to NH of the pyrrole ring. Multiplet at δ 7.21-7.39 was attributed to the protons of benzene ring of benzothiazepine nucleus.

In a likewise manner, the formation of (3.034 c-h) was established on the basis of their ¹H NMR spectra.

**Mass spectra**

Mass spectrum of 3.034-a gave peaks at m/z 301.36 (M⁺ 85%), 231.09 (100.0%), 302.09 (18.4%), 303.08 (4.5%). The molecular ion peak of this compound appeared at 301.36 (M⁺ 85%) which provided a strong evidence to the molecular weight of this compound. The base peak which appeared at m/z 231.09 substantiated further the structure assigned to this molecule.

In a likewise manner the molecular weights of the compounds 3.034 (b-h) were ascertained on the basis of their mass spectrum.

### 3.8 MECHANISM OF FORMATION OF 3.034a FROM 3.033

![Mechanism diagram]

### 3.9 EXPERIMENTAL SECTION

1. Melting points were determined in open glass capillaries and are uncorrected.
2. The purity of the compounds were checked by TLC on silica gel (G) plates in the solvent system (9:1, benzene: methanol).
3. IR spectra were recorded on CE (SHIMADZU FTIR-8400S) on KBr.
4. Before analysis all samples were dried for one hour under reduced pressure.
5. Physical and spectral data for all the compounds are given in table 3.1 and 3.2.
6. ¹H NMR spectra were recorded on model AC-300F (Bruker) using CDCl₃/DMSO-d₆ as solvent and TMS as an internal reference. Chemical shift are
expressed in δ ppm. MS spectra were recorded on a Joel SX-102 (EI) mass spectrometer at 70 eV.

**Experimental procedures**

*Preparation of 2-[N'-pyrrolidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (3.034-a)*

To the solution of 3.033 (2.4 g, 0.0085 mol) in dry acetone (10 mL), an equimolar amount of triethylamine (0.78 mL, 0.0055 mol) was added. The solution was cooled to 0°C, and the pyrrolidine (5.0 ml) was added drop wise. The reaction mixture was stirred at room temperature for 2 h. The precipitated triethylamine hydrochloride was filtered off, the solvent was removed by distillation and the crude product was recrystallized from acetonitrile to give 3.034-a, 1.81g, yield (71%), m.pt.-140-142°C. Other compounds (3.034 b-h) were prepared using the same procedure.

![IR spectrum of 2-[N'-pyrrolidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-a](image)

**Chart 3.1:** IR spectrum of 2-[N'-pyrrolidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-a
Chart 3.2: IR spectrum of 2-[N\textsuperscript{4}-ethoxycarbonylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-g

Chart 3.3: \textsuperscript{1}HNMR spectrum of 2-[N\textsuperscript{'}-pyrrolidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-a
Synthesis of 2-hetarylamine substituted analogues......

Chart 3.4 ¹HNMR spectrum of 2-[N¹-ethoxycarbonylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-g

Chart 3.5: Mass spectrum of 2-[N'-pyrrolidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-a
Chart 3.6: Mass spectrum of 2-[N\(^4\)-ethoxycarbonylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione 3.034-g