Chapter - III A

Synthesis of 2-sulphonamido substituted analogues of the privileged nucleus of pyrrolo-[3,4-b][1,5]-benzothiazepine of medicinal interest
Chapter - III A

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Abstract

2-Sulphonamido substituted analogues of the privileged nucleus of 2,3-dihydro pyrrolo-[3,4-b][1,5]-benzothiazepin-(2',5')-diones 3.043 (a-e) were realized by the reaction of its 2-iminothiomethyl ether function with the known sulpha drugs 3.042 (a-e).
3.1 INTRODUCTION

The ubiquity of the sulphonamides in the chemical literature has undoubtedly been a consequence of the multifarious biological responses which these elicit in combating a variety of body ailments\(^1,2\). The positive impact on bio-activity which they inherit in the materials in which they are present, can never be overstated. The \(\text{SO}_2\text{NH}\) group constitutes a key structural motif shared by a large number of bioactive compounds spanning a variety of affects such as the anti-microbial activities\(^3\), specific enzyme inhibition\(^4\) and hormonal regulations\(^5\). Sulphonamides have been recently reported to display a decent binding to HIV protease\(^6\). This discovery provided an impetus for a large number of compounds possessing a sulphonamide group in their molecules to be evaluated for their anti-HIV activity. One compound delavirdine 3.001 (Fig. 3.1) which contained a sulphonamide group in its molecule has found FDA approval for its application as a potent anti-HIV agent\(^7\). After its discovery the interest on the various facets of the chemistry of compounds containing a sulphonamide group has increased exponentially and culminated in the development of several clinically active compounds\(^8\).

![Fig-3.1](image)

The literature\(^9\) is replete with the chemistry and pharmacology of azepine derivatives mainly due to these molecules having been recognized as important scaffolds belonging to the family of ‘privileged medicinal structures’. This term has been coined by Merck researchers\(^10,11\) to those compounds which are capable of forming ligands to a large number of functionally and structurally discrete biological receptors\(^12\). On account of the wide range of biological properties exhibited by 1,4(1,5) benzodiazepine, benzothiazepine and pyridodiazepine class of privileged
scaffolds, these have been considered among the most important molecules for study, with reference to their anti-HIV potential causing global efforts to be directed towards the discovery of potential anti-HIV agents, from these classes of compounds\textsuperscript{13}. In this context, the advent of a FDA approved non-nucleoside reverse transcriptase inhibitor from 1,5-dipyrido diazepine class – the Nevirapine\textsuperscript{14} was hailed as a major step forward in the battle against the HIV infection. Implementation of the highly active anti-retroviral (combination) therapy [HAART]\textsuperscript{15,16} involving the delavirdine and nevirapine as the key components in the cocktail, has though revolutioned the treatment of AIDS but a search of effective antiviral therapy counteracting on to the emergence of viral strains resistant to the approved antiviral drugs has still been a challenging issue. Thus, there is a continuing need to identify the improved agents within each class in order to provide the optimal clinical benefits.

3.2 SULPHONAMIDES

3.2.1 Introduction

Sulfonamide drugs were the first anti microbial drugs, which paved the way for the antibiotic revolution in medicine. The first sulfonamide was Prontosil a red dye (3.002) (Fig-3.2), which is a prodrug\textsuperscript{17}. Experiment with Prontosil (sulfonamidochrysoidine) began in 1932 in the laboratories of Baeyer. It had a strong protective action against infections caused by streptococci, including blood infections, child bed fever, and erysipelas, and a lesser effect caused by other cocci. perplexedly, it had no effect at all in the test tube, exerting its antibacterial effect only in live animals.

Sulfonamides have a powerful $\text{SO}_2\text{NH}_2$ structural motif, basically derived from sulfanilamide and inhibit folic acid synthesis in bacteria and microorganism. It is bacteriostatic in nature and is effective in treating infections caused by many gram-negative and gram-positive micro-organisms depending on the speed with which they are excreted. Sulfonamides are of three types short -acting, intermediate-acting and long acting.
The three sulpha pyrimidines namely sulfadiazine (3.003), sulphamerazine (3.004), and sulphamethazine (3.005) are superior to many other sulfonamides used in some uterine infections, cerebrospinal meningitis and for patients allergic to Penicillins. They are homologs in which the N-substituents in sulphanilamide is 2-pyrimidinyl in sulfadiazine, 4-methyl-2-pyrimidinyl in sulphamerazine, and 4,6-dimethyl-2-pyrimidinyl in sulphamethazine. Sulphadiazine introduced in 1941 is a drug of choice for the treatment of CNS infections. It is superior to other soluble sulfa drugs in treating urinary tract infections. Sulfadoxine, an intermediate acting as sulfonamide with a half-life of 7-9 days is used as a combination sulfa therapy in veterinary medicine. Another pyrimidine derivative, 2-p-aminosulfonylamino-5-methylpyrimidine have also been used as an antibacterial drug. Sulfadiazine (3.003), sulfamerazine (3.004) and sulfamethazine (3.005) (Fig- 3.3) possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe in patients with impaired renal functions.
3.2.2 Biological aspects of sulphonamides

In view of the impressive biological activities shown by the molecules containing the sulphonamide group, it seems appropriate in the account to follow, to highlight those features of these compounds which has inspired us to undertake this study. Some important sulphonamides which deserved to be mentioned here are as follows:

**Antibiotic sulphonamides**

Sulpha drugs are a group of compounds used for eliminating a wide range of infections in human and animal systems. Many chemotherapeutically important sulpha drugs, like sulphadiazine, sulphathiazole, sulphamerazine, sulphamethazine, sulphaguanidine and sulphacetamide all possess $\text{SO}_2\text{NH}$ moiety which is an important toxophoric function\textsuperscript{20-22} Prontosil (3.006) Fig-3.4, the first commercially available antibacterial, antibiotic\textsuperscript{23} with a relatively broad effect against gram positive Cocci (but not against enterobacteria), was developed by a research team at the Laboratories in Germany in 1932.

Diversification of the sulphonamide structure led to the development of improved antibiotics\textsuperscript{24}, insulin-releasing hypoglycemic drugs\textsuperscript{25}, carbonic anhydrase inhibitory diuretics\textsuperscript{26}, and anti- hypertensive drugs\textsuperscript{27}.

**Anticancer sulphonamides**

Badawi et. al.\textsuperscript{28} synthesized some substituted sulphonamides (3.007, 3.008, 3.009, and 3.010), (Fig- 3.5, 3.6, 3.7 and 3.8). These compounds were tested for potential anti tumor activity against three of human tumor cell lines, liver carcinoma cell line [HEPG2], brain tumor cell line [U251] and colon carcinoma cell line [HEPG2], colon carcinoma cell line [U251] and colon carcinoma cell line [HCT116].
Out of compounds shown below for example: N-(7-bromo-2-cyano-9-oxo-9H-xanthene-3-yl) amino] sulfonyl] acetamide 3.007, [Fig-3.5]

(i) N-(4-{[7-bromo-2-cyano-9-oxo-9H-xanthen-3yl)-l -cyanobenzene-4-sulphonamide 3.008, [Fig-3.6].

(ii) N-{ 4-[ (laurylamino )sulfonyl]phenyl} acetamide 3.009,(Fig-3.7).

(iii) N-4-(cyanobenzene) sulfonamide 3.009 (Fig-3.7), 3.010 (Fig-3.8) were more cytotoxic against HEPG2 and also effective against colon carcinoma cell lines. This compound was only slightly effective against brain tumor cell line.
Mohan and Banerjee, et. al.\textsuperscript{29} elucidated the anti proliferative mechanism of action of five indole sulphonamides \textbf{3.011}, (Fig-3.9). The indole sulphonamides inhibited the polymerization of microtubule protein in vitro.

\begin{center}
\includegraphics[width=0.3\textwidth]{3.011.png}
\end{center}

\textbf{Fig. 3.9}

CPT-11 (\textbf{3.012}) antitumor prodrug is hydrolysed by carboxylesterase (CE) to give the drug which is topoisomerase-1 inhibitor\textsuperscript{30}. But this drug is associated with several side effects like delayed diarrhea, nausea etc. due to activation of human intestinal CE (HICE). Therefore selective inhibitor of HICE was developed having sulphonamide moiety (Fig-3.10).

\begin{center}
\includegraphics[width=0.3\textwidth]{3.012.png}
\end{center}

\textbf{Fig. 3.10}

Pyridinyl and pyrimidinyl carbazole (\textbf{3.013}) sulphonamides have been reported as antiproliferative agents by Boykin, et. al.\textsuperscript{31} (Fig-3.11).

\begin{center}
\includegraphics[width=0.3\textwidth]{3.013.png}
\end{center}

\textbf{Fig. 3.11}

Analogues of above structure N-(2,6-dimethoxypyridine-3-yl)-9-methylcarbazole-3-sulphonamide (\textbf{3.014}) (Fig-3.12) have been reported as tubulin ligand against human cancer\textsuperscript{32}.
A series of carbazole sulphonamides (3.015) have been synthesized by Hu.et.al.\textsuperscript{33} as a novel class of antimitotic agent against tumors (Fig-3.13).

\begin{equation*}
\text{R}_1=\text{Me, H} \\
\text{X}=\text{SO}_2\text{NH} \\
\text{R}=3, 4, 5-\text{OMe}
\end{equation*}

**Fig. 3.13**

**Anti-viral sulphonamides**

4-\{1,2-Dihydro-2-oxo-3H-indol-ylidene)amino\}-N-(4,6-dimethyl-2-pyrimidinyl) benzene sulphonamide (3.016), Fig-3.14 and its derivatives were evaluated by Selvam, et. al.\textsuperscript{34} for antiviral activity against pathogenic viruses such as Hepatitis C virus and SARS-CoV in vitro and Huh 5-2 cells, respectively. The 5-fluoro derivative was found to be the most active.
Jhon C. Me Kew. et. al.\textsuperscript{35} reported a clinically active candidate 3.017, (Fig. 3.15) against both the genotype-I and genotype-2 NS3/4a protease enzymes which has good plasma exposure and excellent liver exposure in multiple species.

![3.017](image)

**Fig. 3.15**

Tung and Gatell et. al.\textsuperscript{36} reported Amprenavir 3.018, (Fig. 3.16) and Tipranavir 3.019, (Fig. 3.17) as potential PIs.

![3.018](image) ![3.019](image)

**Fig. 3.16** **Fig. 3.17**

**Carbonic anhydrase inhibitor (CAIs) sulphonamides**

Gitto. et. al.\textsuperscript{37} reported active anhydrase inhibitors 3.020, 3.021, 3.022 as shown in **Fig. 3.18**.

![3.020](image) ![3.021](image) ![3.022](image)

**Fig. 3.18**
Most of the CAIS contain a sulphonamide moiety able to co-ordinate the zinc ion at the catalytic binding site inhibiting the enzyme activity\textsuperscript{38}.

**Other important sulphonamides**

In 1942 Janbon\textsuperscript{39,40} and his colleagues in the course of treating typhoid fever in patients with p-aminobenzenesulphonamido-isopropyl-thiadiazole (3.023), observed that hypoglycemia sometimes developed. (Fig-3.19)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{S} & \quad \text{N}
\end{align*}
\]

p-aminobenzenesulphonamido-isopropyl-thiadiazole

3.023

Fig. 3.19

Jonathan et. al.\textsuperscript{41} synthesized and evaluated novel biphenyl sulphonamide derivatives (3.024) with potent histamin H3 receptor inverse agonist activity (Fig-3.20).

\[
\begin{align*}
\text{O}_2\text{S} & \quad \text{N} \\
\text{R}_1 & \quad \text{R}_2
\end{align*}
\]

3.024

Fig. 3.20

Compounds bearing sulphonamides group have been known to have MMP-12 (Macro phage metalloelastase) inhibitory activity\textsuperscript{42}. MMP-129 (3.025, 3.026) has been demonstrated to play a significant role in allergic airway inflammation and remodeling. Increased expression and production of MMP-12 have been observed with in the lungs of asthmatic patients\textsuperscript{43} (Fig-3.21 and 3.22).
4-Chloro-N-(2-[[5-trifluoromethyl)-2-pyridyl] sulfonyl] ethyl) benzamide (3.027) was identified as a potent and selective ligand for PPAR with good pharmacokinetic properties\(^{44}\) (Fig-3.23).

3.2.3 Synthetic aspects of sulphonamides

A new synthesis of sulphonamide (3.029) by aminolysis of p-nitrophenylsulfonates (3.028) yielding potent and selective adenosine A2B receptor antagonist has been developed\(^{45}\) (Scheme-3.1)

A copper catalyzed amidation of allylic and benzylic C-H is applicable to the coupling of a diverse set of hydrocarbon species (3.030) with aryl, heteroaryl and alkyl sulphonamides (3.031) and is tolerant to a variety of functional groups\(^{46}\). Scheme-3.2
An efficient amidation reaction of saturated C-H bonds (3.033) catalyzed by a unique disilver (I) complex is reported. The reaction is stereospecific and practical for the construction of amine-containing molecules (Scheme-3.3)

A Rh(II)-catalyzed oxidative coupling of sulphonamides (3.035) and aldehydes (3.036) provides n-sulfonylcarboxamides in one step. Various sulphonamides were found to react with aromatic and aliphatic aldehydes to afford the desired products (3.037) in very good yields (Scheme-3.4).

A series of vinyl sulphonamides (3.040) were synthesized using the Horner reaction of aldehydes and diphenylphosphorylmethanesulphonamide (3.038). The sulphonamide reagent is easily prepared and can be stored indefinitely (Scheme-3.5).
3.3 PRESENT WORK

We discussed earlier in the introductory part in this chapter that the quest to develop effective therapies for the treatment of human immunodeficiency virus (HIV) infection from compounds possessing sulphonamide group in their molecules led to the discovery of a highly potent anti-HIV agent 'the delavirdine' which found FDA approval for its application in the treatment of AIDS. This drug, however, provided only a short term benefit due to the rapid emergence of drug resistant mutant of the virus. Its use was therefore recommended in combination with other anti HIV drugs. Though the combination therapy has emerged with promising results in avoiding the problems of viral resistance to the drugs, but there is a continuing need to identify the improved agents with in each class in order to provide the optimum clinical benefits.

Literature is replete with examples showing that the existence of the sulphonamide moiety in molecules imparts a profound influence on the biological activity of the materials, in which they are present. In view of this, it was expected that incorporation of SO$_2$NH group at 2-position (at place of SMe group) in $\text{3.041}$ (Scheme 3.6) could provide a beneficial effect on the overall biological activity of the parent molecule. The present investigation was therefore undertaken with a view to construct novel molecules incorporated with the sulphonamide group in 1,5-benzothiazepine nucleus. Clearly, a refinement in the existing methodology and development of newer strategies for the synthesis of the desired products was required. Consideration of reactivity and simplicity in operation, has led us to favour the use of 2-thiomethylether substituted pyrrolo-1,5-benzothiazepines in the present work for the synthesis of the corresponding sulphonamide derivatives.

3.4 RESULTS AND DISCUSSION

Eversince, Waldman et. al.$^{50}$ have carried out a quantitative analysis of physiologically active natural products and showed that ones with two or three rings were often found in active natural products, the interest on the various facets of chemistry and biology of small bicyclic and tricyclic molecules has expanded exponentially, thereafter$^{51,52}$. Since then the development of molecular libraries of small molecules and exploration of their potential biological activities has been a major focus of research in the area of chemical biology and medicinal chemistry. In
these efforts particular emphasis has been placed upon the preparation of compounds based on the privileged templates\textsuperscript{13}.

Sulpha drugs have emerged as one of the privileged structural templates in medicinal chemistry due to their broad pharmacological spectrum and their affinity to various biotargets. On account of their such features, the combination of sulpha drug motifs, to the other heterocycles has been a well known approach to the ‘drug like molecule build up’ in medicinal chemistry. Encouraged by the bioactive potential of the sulpha drugs and the tricyclic structure of pyrrolo-1,5-benzothiazepine, we considered it of interest to develop a protocol to incorporate these in the same molecular framework on this premise that their presence in tandem in the same molecule could contribute significantly to the biological efficacy in the resulting materials.

We describe here, the preliminary results of our synthetic efforts focused in the direction of developing a one step protocol to the incorporation of the sulpha drug components on to the 2-position of pyrrolo-[3,4-b][1,5]-benzothiazepine nucleus. In view of the ability of the iminothiomethyl ether function to participate actively in the nucleophilic displacement reactions\textsuperscript{53}, we examined the potential of this function when present on 2-position of pyrrolo-[3,4-b][1,5]-benzothiazepine nucleus in the nucleophilic reaction with the amine function of a few known sulpha drugs. Application of this strategy on 3.041 with the sulpha drugs 3.042(a-e) (a, sulphacetamide ; b, sulphapyridine ; c, sulphamerazine ; d, sulphathiazole ; e, sulphabenzothiazole) afforded their 2-sulpha drug incorporated analogues 3.043(a-e) respectively (Scheme-3.6). Compound 3.041 was obtained by the Michael addition\textsuperscript{54} of the thiophenol function of o-aminothiophenol on the maleimide molecule followed by its conversion to corresponding ketenedithioacetal derivative on its reaction\textsuperscript{55} with CS\textsubscript{2} + CH\textsubscript{3}I (in presence of a base). Its concomitant cyclocondensation with the amine function of o-aminothiophenol produced 3.041 bearing an iminothiomethyl ether function on its 2-position.

The structures of these molecules were found to be consistent to their microanalytical and spectral (IR, \textsuperscript{1}HNMR and MS data).
3.5 STRUCTURE OF COMPOUNDS 3.043(a) - 3.043(e) WHOSE SYNTHESIS IS DESCRIBED IN THIS CHAPTER

Fig. 3.24

Scheme-3.6
Table-3.1: Physical and analytical data of the compounds 3.043 a-e

<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>3.043a</td>
<td>C₁₉H₁₆N₄O₅S₂</td>
<td>444.48</td>
<td>214-216</td>
<td>75</td>
<td>51.34/51.09</td>
<td>3.63/3.65</td>
<td>12.60/12.66</td>
<td>14.43/14.36</td>
</tr>
<tr>
<td>2.</td>
<td>3.043b</td>
<td>C₂₂H₁₇N₅O₅S₂</td>
<td>479.53</td>
<td>198-199</td>
<td>81</td>
<td>55.10/54.83</td>
<td>3.57/3.59</td>
<td>14.60/14.53</td>
<td>13.37/13.30</td>
</tr>
<tr>
<td>3.</td>
<td>3.043c</td>
<td>C₂₂H₁₈N₆O₅S₂</td>
<td>494.55</td>
<td>220-222</td>
<td>69</td>
<td>53.43/3.69</td>
<td>3.67/3.69</td>
<td>16.99/16.91</td>
<td>12.97/13.03</td>
</tr>
<tr>
<td>4.</td>
<td>3.043d</td>
<td>C₂₀H₁₅N₅O₅S₃</td>
<td>485.56</td>
<td>186-188</td>
<td>72</td>
<td>49.47/49.22</td>
<td>3.11/3.09</td>
<td>14.42/14.49</td>
<td>19.81/19.90</td>
</tr>
<tr>
<td>5.</td>
<td>3.043e</td>
<td>C₂₂H₁₇N₅O₅S₃</td>
<td>535.62</td>
<td>203-205</td>
<td>67</td>
<td>53.82/54.09</td>
<td>3.20/3.22</td>
<td>13.08/13.14</td>
<td>17.96/17.87</td>
</tr>
</tbody>
</table>

Table-3.2: Spectral data of compound 3.043 a-e

<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>1.</td>
<td>3.043a</td>
<td>3320, 3260 [NH str.], 1660,1695 [C=O str.], 1602 [C=N str.], 3030 [C-H str. ArH], 1560 [C=C str. ArH], 2970[C-H str. CH₃], 690 [C-S str.], 1360,1160 [S=O str.]</td>
<td>6.4-7.2 [8H,m,Ar-], 9.8 [1H,s,NH of benzothiazepine ring], 12.60 [1H,s,NH of SO₂NH], 3.0 [1H,d, pyrrole ring], 3.8 [1H,d, pyrrole ring], 2.04 [3H,s,CH₃], 10.0 [1H,s,NH] MS(m/z%) 444.48(80%), 231.06(100%), 445.06(22.5%), 446.05(9.1%)</td>
</tr>
<tr>
<td>2.</td>
<td>3.043b</td>
<td>3310, 3260 [NH str.], 1660, 1680 [C=O str.], 1600 [C=N str.], 3030 [C-H str. ArH], 1560 [C=C str. ArH], 2970[C-H str. CH₃], 680 [C-S str.], 1360,1165 [S=O str.]</td>
<td>6.46-8.07 [12H,m,Ar-H], 9.8 [1H,s,NH of benzothiazepine ring], 11.27 [1H,s,NH of SO₂NH], 3.0 [1H,d, pyrrole ring], 3.8 [1H,d, pyrrole ring], 10.0 [1H,s,NH]</td>
</tr>
<tr>
<td>3.</td>
<td>3.043c</td>
<td>3320, 3260 [NH str.], 1660, 1695 [C=O str.], 1602 [C=N str.], 3015 [C-H str. ArH], 1560 [C=C str. ArH], 2960[C-H str. CH₃], 690 [C-S str.], 1360,1160 [S=O str.]</td>
<td>6.50-7.61 [8H,m,Ar-H], 9.89 [1H,s,NH of benzothiazepine ring], 11.34 [1H,s,NH of SO₂NH], 3.0 [1H,d, pyrrole ring], 3.8 [1H,d, pyrrole ring], 2.33 [3H,s,CH₃], 6.9 [1H,d, pyrimidine ring], 8.35 [1H,d, pyrimidine ring], 10.0 [1H,s,NH]</td>
</tr>
<tr>
<td>S. No.</td>
<td>Compound No.</td>
<td>IR(KBr)cm⁻¹</td>
<td>¹H NMR (in CDCl₃ + DMSO d₆) (δ ppm)</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>-------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>4</td>
<td>3.043d</td>
<td>3320, 3265 [NH str.], 1660, 1695 [C=O str.], 1610 [C=N str.], 3030 [C-H str. ArH], 1560[C=C str. ArH], 2970 [C-H str. CH₃], 700 [C=S str], 1365,1160 [S=O str.]</td>
<td>6.46-7.61 [8H,m,Ar-], 9.89 [1H,s,NH of benzothiazepine ring], 12.64 [1H,s,NH of SO₂NH], 3.0 [1H,d, pyrrole ring], 3.8 [1H,d, pyrrole ring], 6.75 [1H,d, thiazole ring], 7.22 [1H,d, thiazole ring], 10.0 [1H,s,NH]</td>
</tr>
<tr>
<td>5</td>
<td>3.043e</td>
<td>3320, 3260 [NH str.], 1660, 1695 [C=O str.],1602 [C=N str.], 3030 [C-H str. ArH], 1560[C=C str. ArH], 2970 [C-H str. CH₃], 690 [C=S str.], 1360,1160 [S=O str.]</td>
<td>6.46-7.61 [8H,m, Ar-H], 7.53-8.01 [4H,m, Ar-H of benzothiazole ring], 9.89 [1H,s,NH of benzothiazepine ring], 12.64 [1H,s,NH of SO₂NH], 3.0 [1H,d, pyrrole ring], 3.8 [1H,d, pyrrole ring], 10.0 [1H,s,NH]</td>
</tr>
</tbody>
</table>

3.6 INTERPRETATION OF SPECTRAL DATA FOR THE ELUCIDATION OF STRUCTURE OF COMPOUNDS 3.043 (a-e)

Structures of all the compounds 3.043 (a-e) were established on the basis of elemental analysis, IR and ¹H NMR data. Physical data of all the compounds were found to be consistent to the structures assigned to these molecules.

The physical microanalysis, infrared and ¹H NMR 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 (3.043-a) on KBr exhibited peaks at 3320 cm⁻¹ for [NH str.], 3260 cm⁻¹ for [NH str. of SO₂NH], 1602 cm⁻¹ for [C=N str.], 1660 cm⁻¹ and 1695 cm⁻¹ for [C=O str.], 1560 cm⁻¹ for [C=C str. ArH], 1360, 1160 cm⁻¹ for [S=O str. of SO₂NH] which indicated clearly the formation of 3.043-a from 3.041.
In a likewise manner, the IR spectrum of 3.043-b exhibited the peaks 3260 cm\(^{-1}\) for [NH str. of \(\text{SO}_2\text{NH}\)], 3030 cm\(^{-1}\) for [C-H str. ArH], 1600 cm\(^{-1}\) for [C=N str.], 1560 cm\(^{-1}\) for [C=C str. ArH], 1660 cm\(^{-1}\) and 1680 cm\(^{-1}\) for [C=O str.], 1360, 1165 cm\(^{-1}\) for [S=O str. of \(\text{SO}_2\text{NH}\)], 680 cm\(^{-1}\) for [C=S str.], 3310 cm\(^{-1}\) for [NH str.] which indicated the formation of 3.043-b from 3.041.

Similar, IR interpretations were applied on (3.043-c,d,e) to ascertain their formation from 3.041.

\(^1\)HNMR Spectra

\(^1\)HNMR spectrum of a compound 3.043-a in CDCl\(_3\)+DMSO-d\(_6\) displayed signals for the presence of 16 protons. Out of this 13 protons were bound to carbon atom, and three others were bound to N atoms (protons bound to nitrogen exchanged with D\(_2\)O). Out of the four singlets which the \(^1\)HNMR displayed, the downfield singlet for one proton at \(\delta 12.60\) was attributed to the \(\text{SO}_2\text{NH}\), second singlet at \(\delta 9.8\) was due to the para NH of the sulpha drug, another singlet at \(\delta 2.04\) was attributed to the CH\(_3\) of the acetyl group and the singlet at \(\delta 10.0\) was attributed to the NH of pyrrole ring. Appearance of two doublets at \(\delta 3.0\) and \(\delta 3.8\) were assigned to the two protons of the pyrrole ring. Eight protons of benzene ring of the sulpha drug and the benzene ring of benzothiazepine appeared as multiplets around \(\delta 6.4\text{-}7.5\).

Similar spectral interpretations established the structure of 3.043-b.

\(^1\)HNMR spectrum of the compound 3.043-c in CDCl\(_3\)+DMSO-d\(_6\) displayed signals for the presence of 18 protons. Out of which 15 protons were bound to carbon atom, and three others were bound to N atoms (protons bound to nitrogen exchanged with D\(_2\)O). Out of the four singlets which the \(^1\)HNMR displayed, a singlet at \(\delta 9.89\), \(\delta 11.34\) and at \(\delta 10.0\) was assigned to three NH protons, one for amino group of sulphonamide, second for NH of \(\text{SO}_2\text{NH}\) and the third for NH of pyrrole ring, another singlet at \(\delta 2.33\) for three protons indicated the presence of CH\(_3\) group in pyrimidine ring. Appearance of two doublets at \(\delta 3.0\) and \(\delta 3.8\) accounted for two protons of pyrrole ring, two doublets at \(\delta 6.9\) and \(\delta 8.35\) was assigned to the two protons of pyrimidine ring. Four protons of benzene ring of the sulpha drug and four protons of the benzene ring of the benzothiazepine ring appeared as multiplets around \(\delta 6.50\text{-}7.61\) which confirmed their presence.
Similar spectral interpretations established the structure of the compounds 3.043 d-e.

**Mass spectra**

Mass spectrum of 3.043-a gave peaks at m/z 444.48(M⁺ 80%), 231.06(100.0%), 445.06(22.5%), 446.05(9.1%). The M⁺ peak which appeared at m/z 444.48 (M⁺ 80%) was consistent to its molecular weight.

In a likewise manner, the molecular weights of the compounds 3.043 (b-e) were ascertained on the basis of their mass spectrum.

### 3.7 MECHANISM OF FORMATION OF THE COMPOUND

![Mechanism Diagram]

### 3.8 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-sulphacetamido-2,3-dihydro-pyrrolo-[3,4-b][1,5]-benzothiazepin-2',5'-dione 3.043-a*

Compound 3.041 (0.27 gm, .001 mol) was taken in dry THF and to this K$_2$CO$_3$ (0.138 gm, .001 mol), sulphaacetamide 3.042a (0.21 g, .001 mol) were added. The mixture was stirred at 30-35°C for 2h. It was then poured on crushed ice and neutralized with dil. HCl. The resulting solid mass was filtered and washed with water and recrystallized from ethanol water (1:9) mixture to give 3.043a, 0.33g, yield (75%), m.p: 214-216°C. In a similar manner other compounds 3.043 (b-e) were prepared by changing the reaction time and reagents. Completion of reaction was checked by tlc.

![Chart 3.1: IR spectrum of 2-sulphacetamido-2,3-dihydro-pyrrolo-[3,4-b][1,5]-benzothiazepin-2', 5'-dione 3.043-a](image)
Synthesis of 2-sulphonamide substituted analogues......

Chart 3.2: $^1$HNMR spectrum of 2-sulphacetamido-2,3-dihydro-pyrrolo-[3,4-b] [1,5]-benzothiazepin-2', 5'-dione 3.043-a

Chart 3.3: Mass spectrum of 2-sulphacetamido-2,3-dihydro-pyrrolo-[3,4-b] [1,5]-benzothiazepin-2', 5'-dione 3.043-a