CHAPTER 4

Synthesis of Piroxicam and Paracetamol based sulphonates and evaluation of their biological activity

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4. Synthesis of Piroxicam and Paracetamol based sulphonates and evaluation of their biological activity

4.1 Introduction

Sulphonates known for important intermediates in organic synthesis are also suitable precursors of sulphonamides and act as alkylating agents also as leaving groups in substitution reactions. In addition to this various sulphonates inhibit interesting pharmacological activities.1 The reaction of sulfonyl chlorides with alcohols in the presence of a base provides a well-established access for alkyl sulfonates.2,3 In general sulfonic esters are prepared under mild conditions from the corresponding sulfonic acids by reaction with diazoalkanes.4,5 In this method the draw back was the lack of general accessibility of suitable diazoalkanes and the parent compound was considered to be highly toxic and explosive6 and diazomethanes are also irritant.7 Other methods include the reaction of sulfonic acids with orthoformates8 and other electrophiles such as epoxides9 or aziridines.10

In this chapter we have synthesized the sulphonate analogues of Piroxicam (1) and Paracetamol (2) and screened for antibacterial activity. The sulphonate analogues of piroxicam has shown moderate to good antibacterial activity compared to the antibacterial activity of paracetamolsulphonate analogues.
The anti-inflammatory, analgesic and anti-pyretic properties of NSAIDs are particularly useful in treating rheumatic and other musculoskeletal disorders. During the last fifty years a plethora of NSAIDs have been introduced on the market indicative of the commercial potential for such compounds and attesting to their utility in the treatment of pain and inflammation of varying origin from the head to the big toe. NSAIDs also show antibacterial activity.\textsuperscript{11} Diclofenac (3), indomethacin (4), and mefenamic acid (5) were also screened for antibacterial activity by using disc diffusion assay and spectrophotometer technique.\textsuperscript{12} Mefenamic acid (5) showed potential ability to prevent growth of dermatophytes.\textsuperscript{13} Piroxicam (1), a non-steroidal anti-inflammatory drug (NSAID) belongs to oxicam class of NSAID, widely used for the treatment of anti-inflammatory conditions in patients suffering from rheumatism and was developed prior to the discovery of cyclooxygenase-2 (COX-2, the second inducible isoform of cyclooxygenase responsible for inflammation). Several piroxicam derivatives\textsuperscript{14-16} were prepared in order to reduce the gastrointestinal side effects, which leaded to many prodrugs.\textsuperscript{17} These derivatives were found to be stable under gastric conditions. Only few studies were reported on acyl derivatives and only one has reported sulfonyl derivatives\textsuperscript{18} which were chemically stable and found to be moderately selective COX-2 inhibitors over COX-1, with lower gastrointestinal side effects than piroxicam. Here in we synthesized the sulfonate molecules related to
piroxicam and paracetamol with simple convenient synthetic route which are stable and studied their biological activity.

Pharmacological activities of piroxicam and paracetamol derivatives

Ampiroxicam (6) is a nonacidic ether carbonate\textsuperscript{19} prodrug of piroxicam, it does not possess detectable prostaglandin synthesis inhibitory activity \textit{in vitro}. Ampiroxicam, however, has similar \textit{in vivo} potency to piroxicam in suppressing paw swelling in rat adjuvant arthritis. In an acute model of paw inflammation in rats, ampiroxicam is less potent than piroxicam itself: the ED\textsubscript{50}'s of ampiroxicam are 9- and 3.5-fold higher than those of piroxicam following a single or multiple daily oral doses, respectively. Using the phenylbenzoquinone stretching test as a method of evaluating acute analgetic activity, the ED\textsubscript{50} for ampiroxicam is about 3-fold higher than that of piroxicam.
Ferrari et al., synthesized\textsuperscript{20} a new benzothiazine derivative 7, after Lombardino, in 1982. It was N-(2-pyridyl)-2-methyl-4-cinnamoyloxy-2H-1,2-benzothiazine-3-carboxamido-1,1-dioxide obtained by the reaction of piroxicam with cinnamic acid or cinnamoyl chloride. Owing to its peculiar ester structure, the new product was endowed with outstanding pharmacological and toxicological activities, particularly with reference to its tolerableness, to make it a therapeutically valuable anti-inflammatory drug.
A series of novel oxyethyl derivatives of certain selected enolic oxicam compounds was disclosed by Charles in 1988, including certain novel oxyethyl derivatives of 4-hydroxy-2-methyl-N-(2-pyridinyl)-1,2-benzothiazine-3-carboxamide1,1-dioxide (piroxicam). These particular compounds 8, 9 are useful in therapy as prodrug forms of the known anti-inflammatory and analgesic oxicams. Typical and preferred member compounds include 4-(2-hydroxyethyloxy)-2-methyl-N-(2-pyridinyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, 4-(2-hydroxyethyloxy)-2-methyl-N-(6-methyl-2-pyridinyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide and N-[1-(2-hydroxyethyl)-2-pyridinium]-2-methyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide 4-enolate.

![Molecule 8](image)

![Molecule 9](image)

Analogues of nonsteroidal anti-inflammatory drugs oxicams, in which the active group was linked to a quaternary ammonium function were synthesized. Compounds were labeled with tritium for piroxicam N⁺ and carbon-14 for propoxicam-N⁺ (10). Pharmacokinetic studies conducted on rats showed that these molecules were able to highly concentrate in joint cartilages but their bioavailability by the oral way
was low. Only-N⁺ exhibited a sufficient water solubility to be administered intravenously.

![Structure of piroxicam](image1)

Pankrushina and his team has synthesized a series of novel acyl derivatives²³ of piroxicam in the search for efficient anti-inflammatory agents. All the acyl derivatives (11) synthesized were characterized by spectral data and HPLC.

![Structure of acyl derivatives of piroxicam](image2)

Novel nitrate esters (12) particularly nitric oxide releasing derivatives of paracetamol were derived. These nitrate esters are prepared by reacting the paracetamol with dihaloalkyl compound and followed by reaction with silver nitrate to obtain the corresponding nitrate ester derivatives.²⁴ These has shown better analgesic and anti-
inflammatory activities and decreased liver toxicities as apparent from their biochemical and histopathologic profile.

![Diagram 12](image12)

Dipeptide esters (13) of paracetamol were prepared in high yields. These compounds are quantitatively hydrolyzed to paracetamol and corresponding 2,5-diketopiperazines at pH 7.4 and 37°C. The reactivity is increased in sarcosine and proline peptides and decreased in bulky side chains at both the N- and C-terminal residues of the dipeptide carrier. Moreover dipeptide esters of paracetamol did not affect the levels of hepatic glutathione. Thus, dipeptides seem promising candidates as carrier for cyclisation activated prodrugs.

![Diagram 13](image13)
4.2 Present Work

We report the synthesis of 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^6benzo[e][1,2]thiazin-4-yl esters (14) via simple convenient synthetic route which involves the sulfonation of the OH of piroxicam (1) with an appropriate sulfonyl chloride (13) compounds (Table 4.1).

**Scheme 1**

![Scheme 1 Diagram](image-url)
Table 4.1 Comparison of Time and Yield of products (14a-l)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>ArSO₂Cl (13)</th>
<th>Products (14)</th>
<th>Time/ Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>NHCOCH₃</td>
<td><img src="#" alt="14a" /></td>
<td>4h / 38</td>
</tr>
<tr>
<td>13a</td>
<td>NHCOCH₃</td>
<td><img src="#" alt="14a" /></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NHCOCH₃</td>
<td><img src="#" alt="14b" /></td>
<td>6h / 36</td>
</tr>
<tr>
<td>13b</td>
<td>NHCOCH₃</td>
<td><img src="#" alt="14b" /></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NHCOCH₃</td>
<td><img src="#" alt="14c" /></td>
<td>5h / 37</td>
</tr>
<tr>
<td>13c</td>
<td>NHCOCH₃</td>
<td><img src="#" alt="14c" /></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NHCOCH₂CH₃</td>
<td><img src="#" alt="14d" /></td>
<td>4.5h / 56</td>
</tr>
<tr>
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<td>NHCOCH₂CH₃</td>
<td><img src="#" alt="14d" /></td>
<td></td>
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<tr>
<td>5</td>
<td>NHCOCl</td>
<td><img src="#" alt="14e" /></td>
<td>4h / 66</td>
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<tr>
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<td>Cl SO₂Cl</td>
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<td>6</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image3.png" alt="Chemical Structure 13g" /></td>
<td><img src="image4.png" alt="Chemical Structure 14g" /></td>
<td>6h / 63</td>
</tr>
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<td>8</td>
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<td><img src="image6.png" alt="Chemical Structure 14h" /></td>
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</tr>
<tr>
<td>9</td>
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<td>5h / 66</td>
</tr>
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<td>10</td>
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<td><img src="image12.png" alt="Chemical Structure 14k" /></td>
<td>6h / 63</td>
</tr>
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</table>
Having generated the sulfonate esters (14) of piroxicam (1) we have decided to take a commonly used analgesic drug paracetamol (2) and have derived the sulfonate analogues (15) via simple convenient synthetic route which involves the sulfonation of the paracetamol (2) with an appropriate sulfonyl chloride (13) Scheme 2 compounds to give benzene sulfonic acid phenyl esters (15) (Table 4.2).

**Scheme 2**

\[
\begin{align*}
12 & \quad \begin{array}{c}
\text{F} \\
\text{SO}_2\text{Cl} \\
\text{13l}
\end{array} & 7h / 62 & \quad \begin{array}{c}
\text{14l}
\end{array}
\end{align*}
\]
Table 4.2 Comparison of Time and Yield of products (15a-g)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>ArSO₂Cl (13)</th>
<th>Products (15)</th>
<th>Time/ Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>13a</td>
<td>15a</td>
<td>5h / 57</td>
</tr>
<tr>
<td>2</td>
<td>13b</td>
<td>15b</td>
<td>7h / 62</td>
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<tr>
<td>3</td>
<td>13c</td>
<td>15c</td>
<td>5h / 56</td>
</tr>
<tr>
<td>4</td>
<td>13d</td>
<td>15d</td>
<td>5h / 56</td>
</tr>
<tr>
<td>5</td>
<td>13e</td>
<td>15e</td>
<td>7h / 62</td>
</tr>
</tbody>
</table>
Compound characterization and structure analysis

All the new compounds prepared were well characterized by IR, Mass and $^1$HNMR. Melting points were all determined by open glass capillary method on a cintex melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer spectrometer in KBr pellets. $^1$HNMR spectra were recorded on a Bruker ACF-300 machine or a Varian 300 or 400MHz spectrometer using either DMSO-d$_6$ or CDCl$_3$ as a solvent with tetramethysilane as internal reference (TMS, $\delta$ =0.00). Mass spectra were recorded on a Jeol JMCD-300 instrument. All solvents used were commercially available and distilled before use. All reactions were monitored by TLC on precoated silica gel plates (60 F 254; Merck). The organic extracts were dried over anhydrous Na$_2$SO$_4$. Piroxicam,
Paracetamol and some aryl sulfonyl chlorides used are commercially available.

4.3 Biological activity evaluation of prepared compounds

Antibacterial activity of selected compounds (14)

Preparation of test compounds: Test compounds were dissolved in DMSO and the concentration was 1 mg per mL.

All the sulfonates derived from piroxicam (1) and paracetamol (2) were tested *in vitro* against the various Gram –ve and Gram +ve bacteria using Amikacin as a standard and concentration used was 1 mg per mL. In general, the compounds 14a-l obtained by reaction between 1 and 13a-l were found to be inactive against gram –ve and gram +ve bacteria and compounds 15a-g were found to be active against gram -ve and gram +ve bacteria. A careful analysis of the data presented in Table 4.3 reveals that the piroxicam based sulfonates show that they are active against various bacteria.
Table 2.5 Antibacterial activity of some compounds of 14a-l against gram +ve and gram -ve bacteria

<table>
<thead>
<tr>
<th>Code</th>
<th>Eschirichia Coli</th>
<th>Klebsiella pneumonia</th>
<th>Bacillus subtilis</th>
<th>Staphylococcus aureus</th>
<th>Staphylococcus epidermis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type of bacteria</td>
<td>Gram +ve, rod shaped</td>
<td>Gram -ve, rod shaped</td>
<td>Gram +ve, rod shaped</td>
<td>Gram +ve, cocci</td>
</tr>
<tr>
<td>14c</td>
<td>1</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>14d</td>
<td>1</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14e</td>
<td>1</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>14f</td>
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<td>+++</td>
<td>+++</td>
<td>+++</td>
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<td>-</td>
<td>++</td>
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<tr>
<td>14j</td>
<td>1</td>
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<td>+++</td>
<td>++</td>
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<td>1</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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</tbody>
</table>

<6 = - , 7-9= +, 10-15 = ++, 16-22 = +++ , 23-30 = ++++
4.4 Conclusions

In summary we have synthesized piroxicam (1) and paracetamol (2) related sulfonatemolecules 14a-l and 15a-g in a convenient synthetic route. The synthesis of these compounds involves the sulfonation of piroxicam and paracetamol with different sulfonyl chlorides 13a-l and was studied under conventional method. The approach showed significant advantages. The piroxicam (1) related sulfonate molecules 14a-l showed moderate to good antibacterial activity against Gram –ve and Gram +ve bacteria than the sulfonate molecules 15a-g of paracetamol (2). These results established the significance of searching of old drugs as a safer template to build new drug candidates. It is concluded that this class of ester derivatives of piroxicam are expected to be safer and holds promise towards search to develop agents with improved pharmacological activity.

4.5 Experimental section

**General procedure for the preparation of 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\mbox{6}benzo[e][1,2]thiazin-4-yl esters (14a-l)**

Piroxicam (1, 1 g, 0.003 mol) in 15 mL chloroform was taken in a 100 mL Round Bottomed flask, sulfonyl chloride (13, 0.003 mol) was added dropwise at 0°C, followed by triethylamine (1.0 mL, 0.007 mol). The
reaction mixture was stirred at room temp for 5 hrs. After the reaction is completed (monitored by TLC), it was poured into ice and extracted with chloroform (2 x 25 mL). The organic layers were collected, washed with 5% NaOH (20 mL) solution followed by 5% HCl (20 mL) solution and then with brine (2 x 30 mL). Combined chloroform extract was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by recrystallization from chloroform and EtOAc.

**Synthesis of 4-Acetylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\(\lambda^6\)benzo[e][1,2]thiazin-4-yl ester (14a):**

![Chemical Structure](image)

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-acetylamino-benzenesulfonylchloride (13a, 0.696 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 38% of the product as off white solid; mp: 172-174°C; R$_f$: 0.57 (Chloroform/Ethylacetate 9:1); IR (KBr cm$^{-1}$): 3386, 1692, 1590, 1090; MS (ES): m/z 528 (M$^+$, 100%); $^1$HNMR (400MHz, DMSO-d$_6$): δ 10.88 (s, 1H, NH, D$_2$O exchangeable), 10.35 (s, 1H, NH, D$_2$O exchangeable), 8.35 (s, ArH, 1H), 7.89-7.50 (m,
10H, ArH), 7.20 (t, ArH, 1H, J=4.9Hz), 3.03 (s, >NCH₃, 1H), 2.10 (s, 3H, NHCOCH₃); Molecular formula: C₂₃H₂₀N₄O₇S₂.

**Synthesis of 4-Acetylamino-2-chloro-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridine-2-ylcarbamoyl)-1,2-dihydro-1λ₆benzo[e][1,2]thiazin-4-yl ester (14b):**

![Chemical Structure](image)

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-acetylamino-2-chloro-benzenesulfonylchloride (13b, 0.80 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 36% of the product white solid: mp:182-184°C; Rₓ: 0.57 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3402, 2852, 1697, 1452, 1030, 751; MS (ES): m/z 563 (M⁺, 100%); ¹H NMR (300MHz, DMSO-d₆): δ 11.12(s, 1H, NH,D₂O exchangeable), 10.53 (s, 1H, NH, D₂O exchangeable), 8.34 (s, ArH, 1H), 7.91-7.79 (m, ArH, 7H), 7.65 (d, ArH, 1H, J=8.7Hz), 7.41 (d, ArH, 1H, J=8.3Hz), 7.19 (s, 1H), 3.17 (s, >NCH₃, 1H), 2.13 (s, 3H, NHCOCH₃); Molecular formula: C₂₃H₁₉ClN₄O₇S₂.
Synthesis of 4-Acetylamino-2-methyl-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14c):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-acetylamino-2-methyl-benzenesulfonylchloride (13c, 0.74g,0.003mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described general procedure to give 37% of the product as white solid; Yield: 37%; mp: 188-190°C; Rf: 0.61 (Chloroform/Ethylacetate 9:1); MS (ES): m/z 543 (M+, 100%); 1HNMR (300MHz, DMSO-d6): δ 11.04 (s, 1H, NH, D2O exchangeable), 10.93 (s, 1H, NH, D2O exchangeable), 8.35 (d, ArH, 1H, J=3.9Hz), 7.92-7.75 (m, ArH, 6H), 7.52 (d, ArH, 1H, J=8.4Hz), 7.40 (d, ArH, 2H, J=11.7Hz), 7.20 (s, ArH, 1H), 2.99 (s, >NCH3, 3H), 2.25 (ArCH3, 3H), 2.11 (s, -NHOCH3, 3H); Molecular formula: C24H22N4O7S2.
Synthesis of 4-Propionylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\(^{6}\)benzo[e][1,2]thiazin-4-yl ester(14d):

![Chemical Structure](image)

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-propionylamino-benzenesulfonyl chloride (13d, 0.74 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 56% of the product as white solid; mp: 192-194\(^{0}\)C; R\(_f\): 0.57 (Chloroform/Ethylacetate 9:1); IR (KBr, cm\(^{-1}\)): 3381, 3300, 1670, 1390, 1050; MS (ES): m/z 543 (M\(^+\), 99%); \(^1\)HNMR (300MHz, CDCl\(_3\)): \(\delta\) 8.29 (bs, ArH, 2H), 7.98 (t, ArH, 2H, J=7.7Hz), 7.86 (d, 1H, J=7.3Hz), 7.77-7.67 (m, ArH, 5H), 7.47 (d, ArH, 2H, J=8.8Hz), 7.12 (t, ArH, 2H, J=4.0Hz), 3.02 (s, >NCH\(_3\), 3H), 2.33 (q, CH\(_2\), 2H, J=7.4Hz), 1.22 (t, -NHCOCH\(_3\), 3H, J=7.4Hz); Molecular formula: C\(_{24}\)H\(_{22}\)N\(_4\)O\(_7\)S\(_2\).
Synthesis of 4-Chloro-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\textalpha\textbeta benzoz[1,2]thiazin-4-yl ester(14e):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-chloro-benzenesulfonyl chloride (13e, 0.62 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 62% of the product as light yellow solid; mp: 184-186\degree C ; Rf: 0.59 (Chloroform/Ethylacetate 9:1); IR (KBr cm\textsuperscript{-1}): 3341, 2899, 1569, 1089; MS (ES): m/z 508.1 (M\textsuperscript{+}, M\textsuperscript{+}+2, 3:1 ratio); \textsuperscript{1}HNMR (400MHz, DMSO-d\textsubscript{6}): δ11.02 (s, 1H, NH, D\textsubscript{2}O exchangeable), 8.38 (s, ArH, 1H), 7.96-7.76 (m, ArH, 6H), 7.66 (d, 2H, J=6.4Hz), 7.47 (d, 2H, J=4Hz), 7.24 (t, 1H, J=8Hz),3.15 (m, >NCH\textsubscript{3}, 3H); Molecular formula: C\textsubscript{21}H\textsubscript{16}ClN\textsubscript{3}O\textsubscript{6}S\textsubscript{2}. 
Synthesis of 4-Bromo-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\(\lambda^6\)benzo[e][1,2]thiazin-4-yl ester(14f):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-bromo-benzenesulfonylchloride (13f, 0.75 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in method A to give 67% of the product as white solid; mp: 184-186\(^\circ\)C; R\(_f\): 0.62 (Chloroform/Ethylacetate 9:1); IR (KBr cm\(^{-1}\)): 3372, 3102, 1681, 1031; MS (ES): m/z 552 (\(M^+\): \(M+2\), 1:1 ratio); \(^1\)HNMR (300MHz, DMSO-d\(_6\)): \(\delta\) 11.00 (s, 1H, NH, D\(_2\)O exchangeable), 8.37 (d, ArH, 1H, \(J=3.9\)Hz), 7.92-7.78 (m, ArH, 6H), 7.76-7.75 (m, ArH, 4H), 7.22 (t, ArH, 1H, \(J=5.6\)Hz), 3.04 (s, >NCH\(_3\), 3H); Molecular formula: C\(_{21}\)H\(_{16}\)BrN\(_3\)O\(_6\)S\(_2\).
Synthesis of Benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\( \lambda^6 \)benzo[e][1,2]thiazin-4-yl ester(14g):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), Benzenesulfonylchloride (13g, 0.52 g, 0.004 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 68% of the product as yellow solid; mp: 256-258\(^\circ\)C; R\( _f \): 0.58 (Chloroform/Ethylacetate 9:1); IR (KBr cm\(^{-1}\)): 3086, 2850, 1705, 1016.52; MS (ES): m/z 417 (M\(^+\), 100%); \(^1\)HNMR (300MHz, DMSO-d\(_6\)): \( \delta \) 11.00 (s, NH, 1H, D\(_2\)O exchangeable), 9.12 (t, 1H, J=8Hz), 8.32-7.95 (m, ArH, 5H), 7.72-7.46 (m, ArH, 4H), 7.30 (m, ArH, 3H), 3.16 (s,>NCH\(_3\), 3H); Molecular formula: C\(_{21}\)H\(_{17}\)N\(_3\)O\(_6\)S\(_2\).
Synthesis of 5-Acetylamino-napthalene-1-sulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester(14h):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 5-Acetylamino-napthalene-1-sulfonylchloride (13h, 0.84 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 38% of the product as off white solid; mp: 194-196°C; Rf: 0.63 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3332, 2892, 1651, 1152; MS (ES): m/z 579.2 (M⁺, 100%); ¹HNMR (400MHz, DMSO-d₆): δ 11.02 (s, 1H, NH, D₂O exchangeable), 10.05 (s, 1H, NH, D₂O exchangeable), 8.47 (d, ArH, 1H, J=12Hz), 8.26-7.05 (m, ArH, 13H), 3.00 (s, NCH₃, 3H), 2.20 (s, -NHOCH₃, 3H); Molecular formula: C₂₇H₂₂N₄O₇S₂.
Synthesis of Toulene-4-sulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benz[e][1,2]thiazin-4-yl ester(14i):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-methylsulfonylchloride (13i, 0.56 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 65% of the product as off white solid; mp: 146-148ºC ; Rf: 0.57 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3352, 1738, 1688; MS (ES): m/z 486 (M⁺, 99%); ¹HNMR (300MHz, CDCl₃): δ 8.33 (d, ArH, 1H, J=3.83Hz), 8.25 (s, 1H, NH, D₂O exchangeable), 8.01-7.67 (m, ArH, 8H), 7.13-7.11 (m, ArH, 1H), 7.04 (d, ArH, 2H, J=9.0Hz), 3.01 (s, >NCH₃, 3H), 2.10 (s, CH₃, 3H); Molecular formula: C₂₂H₁₉N₃O₆S₂.
Synthesis of 3,4-Dichloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1\(\lambda^6\)benzo[e][1,2]thiazin-4-yl ester(14j):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 3,4-dichloro-benzenesulfonylchloride (13j, 0.73 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 62% of the product as off white solid; mp: 170-172\(^\circ\)C; R\(_f\): 0.58 (chloroform/Ethylacetate 9:1); IR (KBr cm\(^{-1}\)): 3384, 2993, 1555, 1052; MS (ES): m/z 542 (M\(^+\), M+2, 3:1 ratio, 100\%); \(^1\)HNMR (400MHz, DMSO-d\(_6\)): \(\delta\) 11.10 (s, 1H, NH D\(_2\)O exchangeable), 8.41 (s, ArH, 1H), 7.90-7.22 (m, ArH, 10H), 3.02 (s, >NCH\(_3\), 1H); Molecular formula: C\(_{21}\)H\(_{15}\)Cl\(_2\)N\(_3\)O\(_6\)S\(_2\).
Synthesis of 4-Ethyl-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester(14k):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-Ethyl-benzenesulfonylchloride (13k, 0.61 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in method A to give 61% of the product as off white solid; mp: 160-162°C; Rf: 0.62 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3317, 2930, 1687, 1149; MS (ES): m/z 500 (M⁺, 100%);¹HNMR (300MHz, CDCl₃): δ 10.58 (s, 1H, NH, D₂O exchangeable), 8.38 (s, ArH, 1H), 7.90-7.73 (m, ArH, 6H), 7.59 (d, 2H, J=8.8Hz), 7.24 (d, 2H, J=7.8Hz), 3.20 (m, >NCH₃, 3H), 2.57 (m, 2H), 1.15 (m, 6H); Molecular formula: C₂₃H₂₁N₃O₆S₂.
Synthesis of 4-Fluoro-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6-benzo[e][1,2]thiazin-4-yl ester (14I):

This compound was prepared according to the general procedure using Piroxicam (1, 1 g, 0.003 mol), 4-fluorobenzenesulfonylchloride (13I, 0.58 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in method A to give 63% of the product as off white solid; mp: 190-192°C; Rf: 0.58 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3329, 3080, 2917, 1693; MS (ES): m/z 490 (M⁺, 100%); ¹HNMR (400MHz, DMSO-d₆): δ 11.05 (s, 1H, NH, D₂O exchangeable), 8.38 (s, ArH, 1H), 7.90-7.68 (m, ArH, 8H), 7.25 (m, ArH, 3H), 3.05 (s, >NCH₃,3H); Molecular formula: C₂₁H₁₆FN₃O₆S₂.

Synthesis of Benzenesulfonic acid 4-acetylamino-phenyl ester (15a):
This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 4-Methylsulfonylchloride (13a, 0.56 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in the procedure to give 58% of the product as an off-white solid; mp: 130-132°C; Rf: 0.48 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3335, 3216, 3139, 3064, 2922, 1677, 1604, 1546, 1502, 366, 1310, 1174; MS (ES): m/z 306 (M⁺, 99.9%); ¹HNMR (400MHz, DMSO-d₆): δ 10.03 (s, 1H), 7.65 (d, 2H, J=4Hz), 7.43 (d, 2H, J=4Hz), 6.86 (d, 2H, J=4Hz), 2.45 (s, 3H), 2.02 (s, 3H); Molecular formula: C₁₅H₁₅NO₄S.

**Synthesis of 4-Chloro-benzenesulfonic acid 4-acetylamino-phenyl ester (15b):**

This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 4-chloro-benzenesulfonylchloride (13b, 0.62 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in the procedure to give 62% of the product as a white solid; mp: 148-150°C; Rf: 0.53 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3371, 3275, 3211, 3139, 3083, 1676, 1608, 1546, 1501,
1365, 1313, 1270, 1175; MS (ES): m/z 326 (M+, 99.9%); $^1$HNMR (400MHz, DMSO-d$_6$): 67.74 (d, 2H, $J$=4Hz), 7.47 (m, 4H), 7.21 (s, 1H, NH, D$_2$O exchangeable), 6.94 (d, 2H, $J$=8Hz), 2.20 (s, 3H); Molecular formula: C$_{14}$H$_{12}$ClNO$_4$S.

**Synthesis of 4-Bromo-benzenesulfonic acid 4-acetylamino-phenyl ester (15c):**

![Chemical Structure]

This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 4-bromo-benzenesulfonylchloride (13c, 0.75g,0.003mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in the procedure to give 66% of the product as off white solid; mp: 150-152°C; R$_f$: 0.52 (Chloroform/Ethylacetate 9:1); IR (KBr cm$^{-1}$): 3316, 1666, 1605, 1574, 1520, 1504; MS (ES): m/z 372 (M$^{+2}$, 99.9%); $^1$HNMR (400MHz, DMSO-d$_6$): δ 7.66 (s, 4H), 7.42 (s, 2H, $J$=16Hz), 7.14 (s, 1H, NH, D$_2$O exchangeable), 6.94 (d, 2H, $J$=16Hz), 2.18 (s, 3H); Molecular formula: C$_{14}$H$_{12}$BrNO$_4$S.
Synthesis of 4-Ethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15d):

This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 4-ethyl-benzenesulfonylchloride (13d, 0.61 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in the procedure to give 63% of the product as off white solid; mp: 105-107°C; Rf: 0.51 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3599, 3255, 3200, 3144, 3082, 2966, 2932, 1665, 1615, 1596, 1557, 1500, 1407, 1370, 1200, 1174, 1157; MS (ES): m/z 320 (M⁺, 99.9%); ¹H NMR (300MHz, DMSO-d₆): δ 10.03 (s, 1H, NH), 7.74 (d, 2H, J=8Hz), 7.51 (t, 4H, J=8Hz), 6.92 (d, 2H, J=8Hz), 2.71 (q, 2H, J=8Hz), 2.01 (s, 3H), 1.20 (t, 3H, J=8Hz); Molecular formula: C₁₆H₁₇NO₄S.
Synthesis of 2,4-Dimethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15e):

This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 3,4-Dimethylbenzene sulfonylchloride (13e, 0.60 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in the procedure to give 58% of the product as white solid; mp: 116-118°C; Rf: 0.63 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3382, 2920, 1694, 1670, 1605, 536, 1504, 1406, 1361, 1310, 1200, 1153; MS (ES): m/z 320 (M⁺, 99.9%); ¹HNMR (300MHz, DMSO-d₆): δ 7.51 (m, 4H), 7.26 (d, 2H, J=8.6Hz), 6.94 (d, 2H, J=8.8Hz), 6.92, 2.34 (d, 4H, J=10.8Hz), 2.16 (s, 3H), 1.29 (d, 2H, J=12Hz); Molecular formula: C₁₆H₁₇NO₄S.
Synthesis of 3,4-Dichloro-benenesulfonic acid 4-acetylamino-phenyl ester (15f):

This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 3,4-Dichlorobenzene sulfonylchloride (13f, 0.73 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in the procedure to give 63% of the product as white solid; mp: 82-840°C; Rf: 0.59 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3368, 3251, 3211, 3129, 3076, 1662, 1618, 1537, 1506, 1362, 1323, 1276, 1171; MS (ES): m/z 362 (M⁺², 99.9%); ¹HNMR (400MHz, DMSO-d₆): δ 10.10 (s, 1H), 8.09 (s, 1H), 7.94 (d, 1H, J=4Hz), 7.78 (d, 1H, J=4Hz), 7.58 (d, 1H, J=4Hz), 7.21 (d, 2H, J=4Hz), 2.10 (s, 3H); Molecular formula: C₁₄H₁₁Cl₂NO₄S.
Synthesis of 4-Fuoro-benzenesulfonic acid 4-acetylamino-phenyl ester (15g):

![Chemical Structure](image)

This compound was prepared according to the general procedure using Paracetamol (2, 1 g, 0.003 mol), 4-fluorobenzenesulfonylchloride (13g, 0.58 g, 0.003 mol), triethylamine (1.0 mL, 0.007 mol) and solvent (15 mL) as described in general procedure to give 62% of the product as off white solid; mp: 150-152°C; Rf: 0.59 (Chloroform/Ethylacetate 9:1); IR (KBr cm⁻¹): 3434, 3188, 3090, 2959, 1671, 1615, 1509, 1458, 1387, 1233; MS (ES): m/z 310 (M⁺, 99.9%); ¹H NMR (400MHz, DMSO-d₆): δ 10.10 (s, 1H), 8.09 (s, 1H), 7.94 (d, 1H, J=4Hz), 7.78 (d, 1H, J=4Hz), 7.58 (d, 1H, J=4Hz), 6.98 (m, 2H), 2.10 (s, 3H); Molecular formula: C₁₄H₁₂FNO₄S.
4.6 References


7. Technical Bulletin AL-180 (Aldrich)


4.7 Some important spectra of the compounds

**Figure 4.1** $^1$HNMR spectrum of 4-Acetylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1$\lambda^6$benzo[e] [1,2]thiazin-4-yl ester (14a)

**Figure 4.2** Mass spectrum of 4-Acetylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1$\lambda^6$benzo[e][1,2]thiazin-4-yl ester (14a)
**Figure 4.3** IR spectrum of 4-Acetylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14a)

**Figure 4.4** $^{13}$C NMR spectrum of 4-Acetylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14a)
**Figure 4.5** $^1$HNMR spectrum of 4-Acetylamino-2-chloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridine-2-ylcarbamoyl)-1,2-dihydro-\(\lambda^6\)benzo[e][1,2]thiazin-4-yl ester (14b)

**Figure 4.6** Mass spectrum of 4-Acetylamino-2-chloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridine-2-ylcarbamoyl)-1,2-dihydro-\(\lambda^6\)benzo[e][1,2]thiazin-4-yl ester (14b)
Figure 4.7 IR spectrum of 4-Acetylamino-2-chloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridine-2-ylcarbamoyl)-1,2-dihydro-λ6benzo[e][1,2]thiazin-4-yl ester (14b)

Figure 4.8 1HNMR spectrum of 4-Propionylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14d)
Figure 4.9 Mass spectrum of 4-Propionylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2] thiazin-4-yl ester (14d)

Figure 4.10 IR spectrum of 4-Propionylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2] thiazin-4-yl ester (14d)
Figure 4.11 $^1$HNMR spectrum of 4-Bromo-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2] thiazin-4-yl ester (14f)

Figure 4.12 Mass spectrum of 4-Bromo-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2] thiazin-4-yl ester (14f)
**Figure 4.13** IR spectrum of 4-Bromo-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ⁶benzo[e][1,2]thiazin-4-yl ester (14f)

**Figure 4.14** ¹H NMR spectrum of Benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ⁶benzo[e][1,2]thiazin-4-yl ester (14g)
**Figure 4.15** Mass spectrum of Benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14g)

![Mass spectrum of Benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14g)](image)

**Figure 4.16** IR spectrum of Benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14g)

![IR spectrum of Benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ6benzo[e][1,2]thiazin-4-yl ester (14g)](image)
Figure 4.17 $^1$HNMR spectrum of Toulene-4-sulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-$\lambda^6$benz[e][1,2]thiazin-4-yl ester (14i)

Figure 4.18 Mass spectrum of Toulene-4-sulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-$\lambda^6$benz[e][1,2]thiazin-4-yl ester (14i)
Figure 4.19 $^1$HNMR spectrum of 3,4-Dichloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1$\lambda^6$benzo[e][1,2] thiazin-4-yl ester (14j)

Figure 4.20 Mass spectrum of 3,4-Dichloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1$\lambda^6$benzo[e][1,2] thiazin-4-yl ester (14j)
**Figure 4.21** $^1$HNMR spectrum of 4-Fluoro-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1$\lambda^6$-benzo[e][1,2]thiazin-4-yl ester (14l)

**Figure 4.22** Mass spectrum of 4-Fluoro-benzenesulfonic acid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1$\lambda^6$-benzo[e][1,2]thiazin-4-yl ester (14l)
Figure 4.23 $^1$HNMR spectrum of Toluene-4-sulfonic acid 4-acetylamino-phenyl ester (15a)

Figure 4.24 Mass spectrum of Toluene-4-sulfonic acid 4-acetylamino-phenyl ester (15a)
Figure 4.25 IR spectrum of Toluene-4-sulfonic acid 4-acetylamino-phenyl ester (15a)

Figure 4.26 $^1$HNMR spectrum of 4-Chloro-benzenesulfonic acid 4-acetylamino-phenyl ester (15b)
Figure 4.27 Mass spectrum of 4-Chloro-benzenesulfonic acid 4-acetylamino-phenyl ester (15b)

Figure 4.28 IR spectrum of 4-Chloro-benzenesulfonic acid 4-acetylamino-phenyl ester (15b)
Figure 4.30 \(^1\)HNMR spectrum of 4-Bromo-benzenesulfonic acid 4-acetylamino-phenyl ester (15c)

Figure 4.31 Mass spectrum of 4-Bromo-benzenesulfonic acid 4-acetylamino-phenyl ester (15c)
**Figure 4.32** IR spectrum of 4-Bromo-benzenesulfonic acid 4-acetylamino-phenyl ester (15c)

**Figure 4.33** $^1$HNMR spectrum of 4-Ethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15d)
Figure 4.34 Mass spectrum of 4-Ethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15d)

Figure 4.35 IR spectrum of 4-Ethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15d)
Figure 4.36 $^1$HNMR spectrum of 2,4-Dimethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15e)

Figure 4.37 Mass spectrum of 2,4-Dimethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15e)
Figure 4.38 IR spectrum of 2,4-Dimethyl-benzenesulfonic acid 4-acetylamino-phenyl ester (15e)

Figure 4.39 $^1$HNMR spectrum of 3,4-Dichloro-benzenesulfonic acid 4-acetylamino-phenyl ester (15f)
**Figure 4.40** D$_2$O exchange $^1$HNMR spectrum of 3,4-Dichloro-benenesulfonic acid 4-acetylamino-phenyl ester (15f)

![D$_2$O exchange $^1$HNMR spectrum of 3,4-Dichloro-benenesulfonic acid 4-acetylamino-phenyl ester (15f)](image)

**Figure 4.41** Mass spectrum of 3,4-Dichloro-benenesulfonic acid 4-acetylamino-phenyl ester (15f)

![Mass spectrum of 3,4-Dichloro-benenesulfonic acid 4-acetylamino-phenyl ester (15f)](image)
Figure 4.42 $^1$HNMR spectrum of 4-Fuoro-benenesulfonic acid 4-acetylamino-phenyl ester (15g)

Figure 4.43 Mass spectrum of 4-Fuoro-benenesulfonic acid 4-acetylamino-phenyl ester (15g)