ABSTRACT

This chapter reports synthesis, characterization and antimicrobial activity of thiacalixarene based water soluble sulfonamide derivatives. The sulfonamide derivatives were synthesized by a multi-step route involving ipso sulfonation of parent p-tert-butylthiacalix[4]arene (to render them water soluble), lower rim alkylation (to block them in 1,3-alternate conformation) and amidation (with sulfonamines). Experimental data shows that out of the five derivatives synthesized, three exhibited moderate broad spectrum activity, and two were highly specific and effective in their actions.
1 Introduction

The biological world is rich in ordered assemblies of molecules. The forces holding together these assemblies are van der Waals interactions, hydrogen bonding, π-π and cation-π interactions, metal coordination and hydrophobic effects. Nature has exploited these interactions in bio-recognition and bio-molecular organization for billions of years. These weak, noncovalent interactions are responsible for the protein folding, the selective transport of ions and small molecules across membranes, transduction of signals, enzymatic reactions, and the formation of larger aggregates. They are also the basis of one of the fastest-growing areas of research - supramolecular chemistry. Concepts of supramolecular chemistry closely resemble some biochemical interactions and rely on the phenomena of molecular recognition and self-assembly, that is, molecules (hosts) recognize complementary sites (functionality, geometry, size, etc.) on other molecules (guests) and associate into larger entities, supramolecules, via weak non-covalent interactions.\cite{1,2}

Amongst supramolecules, water soluble (hetera)calixarene have become an increasingly important class of compounds because they allow the study of the interactions involved in host-guest chemistry in aqueous systems as well. The study of the biological properties of the calixarenes is receiving growing interest,\cite{3} with particular emphasis on the p-sulfonato-calixarenes due to their high water solubility. Biological activities including ion channel blocking,\cite{4} enzyme inhibition,\cite{5} anti-viral\cite{6} and antithrombotic properties\cite{7} have been observed. In contrast to the cyclodextrins,\cite{8} the p-sulfonato-calixarenes show no hemolytic toxicity even at concentrations of 50 gL\(^{-1}\).\cite{9} These studies give a deeper understanding of the types of forces involved, as this is important for the design of receptors mimicking biological systems.\cite{10} The chemistry of cyclodextrins and cyclophanes has occupied a central interest in host-guest chemistry, and many derived host molecules have been exploited in mimicking of the in-vivo actions of enzymes.\cite{11}

Although, the biological activities of calixarenes derivatives are well studied, it is only very recently that interest in their biomedical potential has come to the fore again. This considerable interest in water-soluble calixarenes for biological and medical applications has resulted in several publications.\cite{12} p-Sulfonato-calixarenes posses suitable antimicrobial activity against fungal and bacterial microorganisms. Calixarenes were found to exhibit antimicrobial activity against Corynebacterium, Fusarium solani f. sp. Mori (F.s.-26), the fungal strains Resellinia necatrix [R-8], and Collectotrichum dematium [C.d. 8901].\cite{13}
A characteristic feature of conventional calixarene molecules is that they are sparingly soluble in water and they exhibit insufficient inclusion performance in organic solvents. These macrocycles have been functionalized with polar groups, making them water soluble and thus more closely related to cyclodextrins. The host-guest chemistry of cyclodextrins has been studied in aqueous systems and a variety of soluble host-guest type complexes are possible.\textsuperscript{11,13,14} Similarly, in aqueous systems the hydrophobic forces of water soluble calixarenes and thiacalixarenes is expected to encourage the host-guest complexation\textsuperscript{15} and indeed several examples have already been reported.\textsuperscript{16-27} Calixarenes can be made water soluble by introducing sulfonate groups at the upper rim of the calixarene,\textsuperscript{28,29} introducing carboxylates at the bottom rim of the calixarene\textsuperscript{30,31} or forming alkyl ammonium salt derivatives.\textsuperscript{32} Atwood \textit{et al.}\textsuperscript{33-34} reported the direct sulfonation procedure for the preparation of sulfonato-calix[4]arene which was modified for to prepare its analogue tetra sodium-thiacalix[4]arene-tetrasulfonate.

Hwang \textit{et al.}\textsuperscript{16,71} patented a method of treatment of infection by envelope viruses such as HIV, herpes simplex and influenza, with calixarenes having polar substituents: sulfonates, carboxylates or phosphate groups. Atwood and co-workers\textsuperscript{35} demonstrated the activity of different $p$-sulfonato-calixarene derivatives as chloride channel blockers. Droogmans \textit{et al.}\textsuperscript{36} investigated the inhibition of volume-regulated anion channel present on cultured endothelial cells which allows the passage of ions depending on the membrane potential. They used $p$-sulfonato-calixarene and their derivatives, which have shown to posses antithrombotic activity\textsuperscript{37} and in the diagnosis of prion-based disease.\textsuperscript{38} Pinhal \textit{et al.}\textsuperscript{39} found that $p$-sulfonato-calix[8]arene stimulates the synthesis of heparan sulfate proteoglycan secreted by rabbit and human endothelial cells in culture. Coleman \textit{et al.}\textsuperscript{40} investigated $p$-sulfonato-calixarene complexation by bovine serum albumin (BSA), an arginine and lysine rich protein. For anionic $p$-sulfonato-calixarenes one strong and two weak binding sites were found on the protein surface.

The rapid expansion of the chemistry of $p$-sulfonato-thiacalixarenes ($n$=4-8) is due to their good solubility in water ($>$0.1 molL$^{-1}$). In contrast, the host-guest chemistry of carboxylic acids of calixarenes has not been studied extensively because of their limited solubility in water, especially in the presence of salts.\textsuperscript{41,11} Therefore, in order to enhance their water solubility, novel calixarenes have been synthesized bearing double polar hydrophilic functions, which are shown to specifically recognize alkyl and aromatic
ammonium cations. There are also reports of water soluble calixarene having anionic sulfonate groups on the lower rim of the calixarene cavity, which have been shown to have a weak but selective binding process.\textsuperscript{[42]}

Sulfonamides, on the other hand, are a class of antimicrobial agents that have seen extensive use in medicine. They were one of the first synthetic agents to be used for the treatment of bacterial infection.\textsuperscript{[43]} Sulfonamide drugs operate by interfering with enzymes inhibition or pseudo metabolite formation involving \textit{p}-amino benzoic acid (PABA), which is an essential component in the synthesis of dihydrofolate acid (FAH\textsubscript{2}). FAH\textsubscript{2} is required for normal growth of bacterial cells.\textsuperscript{[44]}

Presently, use of sulfonamides is limited to specific disease treatment in human medicine (eg. urinary tract infections), but they are more often encountered in animal medicine. The presence of certain residues in animal products presents a potential health hazard due to their allergenic properties.\textsuperscript{[44]} In addition, a study by the National Center for Toxicological Research indicated that sulfamethazine (SMZ) may be a thyroid carcinogen.\textsuperscript{[45]} Also, some people exhibit hypersensitivity to drug residues. Further, low levels of drug residue may produce genetically altered bacteria that are resistant to existing drug therapy.\textsuperscript{[46]} Bacteria can acquire resistance to sulfonamides by three mechanisms, 1) Genetically altering the cell wall permeability to preformed FAH\textsubscript{2}, 2) Increasing essential enzyme production and 3) Increasing production of an essential metabolite. Thus, sulfonamides can become ineffective in drug therapy.\textsuperscript{[47]} This is where thiacalixarenes may come into play. By appending sulfonamides to the soluble thiacalixarene framework, the sulfonamides can be employed yet again to ‘fool’ the bacterial metabolism, as the thiacalix based sulfonamides are a totally different entity for them. That is, it is anticipated that the bacteria could not differentiate between PABA and sulfonamides, and thus would probably not be able to selectively exclude the thiacalix based derivative. Subsequently, the drug may be 'activated' by hydrolysis of the drug-thiacalix complex through metabolic processes within the cell.

Evidently, water soluble-thiacalixarene based sulfonamide derivatives seem to be worthy of a thorough evaluation for assembling sophisticated systems with tailored biological activity. The present research work attempts to investigate this worth. Herein we report synthesis of water-soluble thiacalixarene-sulfonamide derivatives and preliminary studies of their \textit{in-vitro} antimicrobial activity towards some bacteria.
2 Objectives and Investigations

To synthesize the water-soluble-thiacalix[4]arene-sulfonamide derivatives and in-vitro study of antibacterial activity of this derivatives were the main objectives of this study. Although the calixarene and thiacalixarene derivatives are currently not approved for use in medicines to date, they have shown neither toxicity nor immune responses towards human systems in in-vitro investigations.\textsuperscript{[48-49]}

The parent thiacalixarenes are completely insoluble in water, which is a major problem for their potential use in pharmaceutical applications. To overcome this caveat, the thiacalixarenes need to be functionalized with ionic or neutral functions with high hydrophilicity on upper or/and lower rims. Functions such as carboxylates, sulfonates, phosphates or ammonium can be used for such modification, however, sulfonation is the only viable option which imparts high enough usable solubility (\textgreater{}0.1 mol\textsuperscript{-1}). It is further known that thiacalixarene moieties are absolutely non-toxic (probably due to their very high stability, it is inaccessible for metabolic processes) and exhibit no hemolytic toxicity even at very high concentration. This forwards their case as much better carrier for drug delivery systems that release active metabolite only when it is in systemic circulation or at intended targets based upon the microenvironment.\textsuperscript{[50,51]}

With this background, we set out to synthesize sulfonamide derivatives of water soluble thiacalix[4]arene and study their in vitro antimicrobial activity against E. coli, K. pneumonae and B. subtilis. Appending bulky substituents on thiacyalixarene results in stabilizing of the calix framework into cone, partial cone and 1,3 alternate (and rarely 1,2-alternate) conformations due to restricted mobility of arene units. Thus, we had to settle upon a specific conformation, which may be most accessible by bacterial consumption. Thus, we decided to go with 1,3-alternate conformation with two sulfonamide units on each side of the molecular plane (arene framework), which intuitively should provide the most exposure/accessibility for metabolic systems. The 1,3-alternate conformer of tert-butyl tetraacetate derivative of sulfonicacid-thiacalix[4]arene was prepared by ipso sulfonation of tert-butylthiacalix[4]arene 2 using conc. sulfuric acid to render it water soluble thiacalixarene derivative 3.\textsuperscript{[43]} Further, alkylation of lower rim –OH group of thiacalix[4]arene 3 with tert-butyl bromoacetate in Cs\textsubscript{2}CO\textsubscript{3} base using acetone as solvent (analogues to chapter 4) gives 4. Finally, the water soluble tetra-acetate was appended with various sulfonamide derivatives 1\textsubscript{a-e} by reaction with respective p-aminobenzene-sulfonamides.
To ascertain their antibacterial activity against Escherichia coli (E. coli), Klebsiella pneumoniae (K. pneumoniae) and Basillus subtilis (B. subtilis), Mullar Hinton Agar was used as media for cultivation. The inhibitory effect of the samples and their corresponding sulfonamides were measured on bacteria after incubation upto 24 h at 37 °C. Here, we have used average zone of inhibition in mm at four different concentrations as antibacterial activity. The experiments were run in four replications and the mean readings were calculated.

The sulfonamide derivatives 1a, 1b and 1c showed high and comparable level of susceptibility with the positive control against all tested bacterial cultures, which was quite an encouraging result. Intermediate susceptibility was observed for compounds 1c and 1d against E. Coli and B. Subtilis, however, they showed a low inhibition activity against K. pneumoniae. When the concentration of sulfonamide derivatives of thiacalixarene was increased from 10 to 80 mg, slight increase in inhibition zones was seen in all the cases. Measured zone diameter increased with introduction of amino substitution, especially, guanidine and pyrazine derivatives. Further increase was also observed when the electron withdrawing substituent (acetyl) was introduced adjacent to the amine.

In summary, the outcome of the study has two noteworthy features. Firstly, sulfonamide derivatives 1a, 1b and 1c have proved to be effective enough for a broad range (all three) of cultures, which is comparable with positive. Secondly, the antimicrobial activity of the sulfonamides were increased by introducing guanidine or electron withdrawing substituents. Parent compound 1 has a little inhibition on the tested cultures however, is
effective against all the cultures, whereas, compounds 1c & 1d are ineffective against K. pneumoniae, but quite effective against the other two cultures.

Table 5.1 Antibacterial activity of thiacalix[4]arene-sulfonamides 1a-e

<table>
<thead>
<tr>
<th>Bacterial culture</th>
<th>Compound Name</th>
<th>Zone of inhibition in mm</th>
<th>Average</th>
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<tr>
<td></td>
<td></td>
<td>Concentration in µg.mL⁻¹</td>
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<tr>
<td></td>
<td></td>
<td>10 20 40 80</td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>1a</td>
<td>9.7 17.0 21.2 24.5</td>
<td>18.1</td>
</tr>
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<td></td>
<td>1b</td>
<td>19.3 22.9 23.3 24.3</td>
<td>22.5</td>
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<tr>
<td></td>
<td>1c</td>
<td>15.1 16.3 18.0 18.5</td>
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<td></td>
<td>1d</td>
<td>16.0 17.4 22.5 25.7</td>
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<td></td>
<td>1e</td>
<td>20.3 22.5 28.4 25.1</td>
<td>24.1</td>
</tr>
<tr>
<td>Oxacillin</td>
<td></td>
<td>21.2 21.9 22.6 24.1</td>
<td>22.5</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>1a</td>
<td>27.3 29.2 29.5 25.3</td>
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<tr>
<td></td>
<td>1b</td>
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<td>30.3 29.8 29.6 27.7</td>
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<td>Oxacillin</td>
<td></td>
<td>26.4 27.7 28.5 29.4</td>
<td>28.0</td>
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<tr>
<td>B. subtilis</td>
<td>1a</td>
<td>20.8 27.3 36.5 25.3</td>
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<td>Oxacillin</td>
<td></td>
<td>28.7 29.5 30.0 30.4</td>
<td>29.7</td>
</tr>
</tbody>
</table>

3 Experimental

All the reagents used were of AR grade, procured from Sigma-Aldrich (Banglore, INDIA). The reagents were used without further purification. The solvents were dried appropriately wherever required. Melting points were taken in a single capillary tube using Toshniwal melting point apparatus and are uncorrected. Elemental analysis (EA) was carried out on Heraeus CarloEbra 1108 elemental analyzer. NMR spectra were recorded on Bruker DPX-400. Mass measurements were done on Waters, Quattro Premier XE (Milford, MA, USA), equipped with electrospray ionization and operating in positive ionization mode.

3.1 Synthesis of thiacalix[4]arene-tetrasulfonic acid 3

A mixture of p-tert-butyl-thiacalix[4]arene 2 (15 mmol) and conc. H₂SO₄ (100 mL) was heated at 95°C for 8 h with continuous stirring. After completion of the reaction, the reaction mixture was allowed to cool to ambient temperature and filtered under vacuum. Filtrate was added with sodium chloride (salt) and stirred for 1 h.
The precipitated solid product was filtered and taken into acidic ethanol (1:100, conc. HCl:ethanol, v/v) and stirred for 5 min to recover the free p-sulfonicacid-thiacaIix[4]arene 3. (Yield 70 %)

\(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{D}_2\text{O}): \delta 8.09 (s, 8\text{H}, \text{Ar-H}), \ ^{13}\text{C} \text{NMR} (75 \text{ MHz}, \text{D}_2\text{O}): \delta 158.4, 133.0, 132.6, 119.2, \text{MS: } m/z 1344.7 (M+1), \text{EA: Calc. for } C_{24}H_{12}Cs_4O_{10}S_8 \text{ (C:21.44, H:0.90), Found (C:21.47, H:0.87).}

3.2 Synthesis of tert-butylacetate-thiacalix[4]arene-tetrasulfonic acid 4

A suspension of p-sulfonicacid-thiacaIix[4]arene 3 (10 mmol) and Cs\(_2\)CO\(_3\) (65 mmol) in acetone (150 mL) was stirred under nitrogen atmosphere and tert-butylbromoacetate (50 mmol) was added into reaction mixture under continuous stirring. The reaction mixture was heated to reflux temperature and maintained for 18 h. After completion of the reaction, the reaction mixture was allowed to cool to ambient temperature and acidified using cold 2N HCl dropwise. The reaction mass was stirred for further 30 min and the organic fraction was extracted in CHCl\(_3\) (3x100 mL). The organic layers were combined and dried over Na\(_2\)SO\(_4\). The volatiles were removed completely in vacuo. The residue was triturated with ethanol:water (9:1, v/v) mixture. The product was recovered by filtration and 1,3-alternate conformer 4 was isolated by crystallization from chloroform: acetone vapour diffusion technique in 62 % yield.

\(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{D}_2\text{O}): \delta 7.93 (s, 8\text{H}, \text{Ar-H}), 4.71 (s, 8\text{H}, -OCH_2CO_2-), 1.39 (s, 36H, -OBU\(^1\)), \ ^{12}\text{C} \text{NMR} (75 \text{ MHz}, \text{D}_2\text{O}): \delta 168.4, 156.9, 133.7, 132.1, 122.9, 82.3, 73.9, 28.9, \text{MS: } m/z 1274.3 (M+1), \text{EA: Calc. for } C_{48}H_{56}O_{24}S_8 \text{ (C:45.27, H:4.43), Found (C:45.31, H:4.48).}

3.3 General preparation for synthesis of sulfonicacid-thiacaIix[4]arene-tetrasulfonamide derivatives 1\(_{a-e}\)

A solution of sulfonicacid-thiacaIix[4]arene-tetraacetate 4 (10 mmol) in N-methyl pyrrolidine (150 mL) was stirred in a round bottom flask and suspension of p-aminobenzene-sulfonamide a-e (1.2
fold excess) in diisopropylethylamine (55 mmol) were added into the reaction mixture. The reaction mixture was refluxed for 52 h with continuous stirring and then cooled to 15°C. The precipitated solids were filtered and washed with N-methyl pyrrolidine and ethanol successively. The resulting crude product was crystallized in chloroform:acetone (2:8, v/v) mixture to give pure sulfonic acid-thiacalix[4]arene-tetrasulfonamide derivatives 1a-e.

1a: Yield 86 %, $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.80 (s, 8H, -SO$_2$NH$_2$), 10.14 (s, 4H, -SO$_3$H), 9.46 (s, 4H, -CONH), 8.15 (s, 8H, TCA-H), 7.78 (d, 8H, Ar-H), 7.54 (d, 8H, Ar-H), 4.71 (s, 8H, -OCH$_2$CO$_2$-), $^{13}$C NMR (75 MHz, D$_2$O): δ 170.1, 157.1, 146.2, 142.5, 140.4, 132.4, 129.4, 121.9, 118.9, 69.7, MS: m/z 1666.5 (M+1), EA: Calc. for C$_{56}$H$_{48}$N$_8$O$_{28}$S$_{12}$ (C: 40.38, H: 2.90, N: 6.73), Found (C: 40.41, H: 2.94, N: 6.69).

1b: Yield 44 %, $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.14 (s, 12H, -SO$_3$H & -NH), 9.67 (s, 8H, -NH$_2$), 9.47 (s, 4H, -CONH), 8.09 (d, 8H, Ar-H), 7.99 (s, 8H, TCA-H), 7.61 (d, 8H, Ar-H), 4.76 (s, 8H, -OCH$_2$CO$_2$-), $^{13}$C NMR (75 MHz, D$_2$O): δ 171.3, 161.7, 156.2, 145.8, 141.9, 138.6, 132.9, 128.9, 122.2, 119.3, 70.2, MS: m/z 1835.3 (M+1), EA: Calc. for C$_{60}$H$_{56}$N$_{16}$O$_{28}$S$_{12}$ (C: 40.39, H: 2.90, N: 12.22), Found (C: 39.34, H: 3.12, N: 12.18).

1c: Yield 52 %, $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.18 (s, 4H, -SO$_3$H), 9.56 (s, 8H, -SO$_2$NH$_2$ & -CONH), 8.46 (d, 8H, Ar-H pyrazine), 8.23 (s, 8H, TCA-H), 7.97 (d, 8H, Ar-H), 7.78 (d, 8H, Ar-H), 6.98 (t, 4H, Ar-H pyrazine), 4.68 (s, 8H, -OCH$_2$CO$_2$-), $^{13}$C NMR (75 MHz, D$_2$O): δ 169.8, 158.6, 156.6, 152.2, 146.4, 141.4, 140.1, 130.9, 129.2, 122.6, 120.1, 118.5, 69.6, MS: m/z 1979.4 (M+1), EA: Calc. for C$_{72}$H$_{56}$N$_{16}$O$_{28}$S$_{12}$ (C: 43.72, H: 2.85, N: 11.33), Found (C: 43.69, H: 2.90, N: 11.29).

1d: Yield 67 %, $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.15 (s, 4H, -SO$_3$H), 9.68 (s, 8H, -SO$_2$NH$_2$ & -CONH), 8.02 (d, 8H, Ar-H), 7.95 (s, 8H, TCA-H), 7.72 (d, 8H, Ar-H), 6.68 (t, 4H, Ar-H pyrazine), 4.63 (s, 8H, -OCH$_2$CO$_2$-), 2.34 (s, 24H, Ar-CH$_3$), $^{13}$C NMR (75 MHz, D$_2$O): δ 164.9, 158.9, 156.2, 145.8, 141.6, 139.8, 131.5, 129.0, 122.9, 118.8, 117.9, 68.7, 24.2, MS: m/z 2091.7 (M+1), EA: Calc. for C$_{80}$H$_{72}$N$_{16}$O$_{28}$S$_{12}$ (C: 45.97, H: 3.47, N: 10.72), Found (C: 46.01, H: 3.51, N: 10.69).

1e: Yield 49 %, $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.08 (s, 8H, -SO$_2$NH$_2$ & -SO$_3$H), 9.48 (s, 4H, -CONH), 7.97 (s, 8H, TCA-H), 7.89 (d, 8H, Ar-H), 7.56 (d, 8H, Ar-H), 4.78 (s, 8H, -OCH$_2$CO$_2$-), 2.13 (s, 12H, -COCH$_3$), $^{13}$C NMR (75 MHz, D$_2$O): δ 171.8, 169.2, 158.2, 143.1, 141.1, 140.4, 133.1, 129.2, 122.3, 119.1, 118.4, 67.9, 23.9, MS: m/z 1835.1 (M+1), EA: Calc. for C$_{64}$H$_{56}$N$_{8}$O$_{32}$S$_{12}$ (C: 41.91, H: 3.08, N: 6.11), Found (C: 41.97, H: 3.13, N: 6.07).
**SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF p-SULFONICACID-THIAZOLE-4-ARENESULFONAMIDE DERIVATIVES: CHAPTER 5**

\[ ^1H \text{NMR spectrum of } 1_a \]

\[ ^{13}C \text{NMR spectrum of } 1_a \]
$^1$H NMR spectrum of $1_b$

$^{13}$C NMR spectrum of $1_b$

$^1$H NMR spectrum of $1_c$

$^{13}$C NMR spectrum of $1_c$
\(^1\)H NMR spectrum of 1\(_d\)

\[^{13}\text{C}\] NMR spectrum of 1\(_d\)

$^1$H NMR spectrum of 1e

$^{13}$C NMR spectrum of 1e
3.4 Antimicrobial activity screening

Antimicrobial studies were performed according to agar disc diffusion method. To obtain more significant information as to the antibacterial potency of sulfonamide derivatives against bacteria, subcultures were carried out and minimal bactericidal concentration was determined. The following test conditions were applied; all the compounds were dissolved in DMSO and agar plates were prepared and dried at 35-36°C for about 30 min in an incubator. Test stains were spread on solid agar surface by using sterile swap. Spread inoculums were 3.5×10⁵ colony forming unit/mL⁻¹ (0.5 McFarland standards, Biomeriux Colorimeter). At the same time, absorbent paper disc were placed on agar surface (5 mm for compounds and 6 mm for antibiotics) and impregnated with known concentrations which were determined previously by MIC tests (500 µg for each disc). Oxacillin 1 µg was also used for all test microorganisms as positive control. Blank test showed that DMSO in the preparations of the test solutions does not show a zone of confluent growth which usually corresponds to the sharpest edge of the zone and to be measured in diameter (mm). All tests were repeated four times and average data taken as final results.

4 Conclusion

In conclusion, water soluble thiacalixarene based sulfonamides were synthesized and the rate of antimicrobial activities of substituted sulfonamides on three bacterial cultures was studied. Although sulfonamide-based therapy is generally effective, optimal treatment could be guided by antimicrobial susceptibility testing of candidate compounds. Moreover, experimental data shows that compounds 1, 2 and 5 may also be considered as a broad spectral effective sulfonamide against tested infections, whereas compounds 3 & 4 may be employed for specific infections with high efficacy. It may also be emphasized here that in vitro antimicrobial susceptibility testing results for tested cultures need standardization with extensive samples, and it should also have a correlation with in vivo therapeutic response experiments.

References


Appendix for chapter 5

$^1$H & $^{13}$C NMR spectra of intermediates

$^1$H NMR spectrum of 3

$^{13}$C NMR spectrum of 3

$^1$H NMR spectrum of 4

$^{13}$C NMR spectrum of 4