Chapter 3

A New Efficient Method for the Synthesis of 4,5-Disubstituted Thiazole and Antimicrobial Studies
3.1 Introduction to Thiazole

Thiazoles are one of the frequently encountered heterocycles with prominent interest as bioactive compounds. This nucleus is also found in many natural products (Fig. 3.1) and majority of them are isolated from marine sources, which exhibits significant biological activities like antifungal, cytotoxic, antituberculosis, various enzyme inhibitors, analgesics, etc.\(^1\,^2\) A number of drugs bearing thiazole nucleus are currently available in market (Table 1.2) for the treatment of various diseases. Besides, thiazole derivative possesses numerous prominent therapeutic properties such as antibacterial\(^3\), anti-inflammatory (meloxicam),\(^4\) antihypertensive,\(^5\) anti-HIV,\(^6\) antitumor,\(^7\) etc., and also some of these derivatives are used as liquid crystals in cosmetics\(^8\) and ferroelectric display.\(^9\)

![Some natural products bearing thiazole nucleus isolated from marine sources](image)

Fig. 3.1. Some natural products bearing thiazole nucleus isolated from marine sources

Amidst the various methods available for the synthesis of thiazoles, Hantzsch thiazole synthesis\(^10,\,^11\) or its modified methods\(^12-\,^16\) are most commonly used for the
synthesis of trisubstituted thiazoles, which entails the condensation reaction between 
α-haloketones or its analogues and thioamides or thioureas. Other methods include the 
reaction of α-aminonitriles with isothiocyanates, CS₂, COS and dithiocarboxylic 
acids.⁷ Further, synthesis of trisubstituted thiazoles can be achieved by thionation 
followed by cyclization of α-acylaminoketones or its related precursors with various 
thionation reagents like P₂S₅, H₂S, Lawesson’s or Belleu’s reagent.⁸,⁹ Even though 
the advances realized that, very few methods are available for the synthesis of 2-
unsubstituted thiazoles, which involves cyclization of α-metalated methyl isocyanides 
with carbon disulfide,¹⁰,¹¹ thiono esters,¹² isothiocyanates¹³ or carboxymethyl 
dithiatiates.¹⁴ However, these methods have limited applications in synthesis in view of 
both yield and generality of protocols to various isocyanides. The 2-unsubstituted 
thiazoles play a significant role in nature. The thiazolium ring, for instance, present in 
vitamin B₁ serves as an electron sink and its coenzyme form is highly important for 
the decarboxylation of α-keto acids.¹⁵ Therefore, more flexible, generalized, efficient 
novel methods for the synthesis of thiazoles nucleus with more diversity of 
substituents except at the 2⁻nd position are still in demand.

The isocyanide cyclization reaction provides useful methods for the synthesis of 
some nitrogen bearing heterocycles.¹⁶,¹⁷ They often give 2-unsubstituted thiazoles, 
which are not easily accessed by other methods developed by Hantzsch,¹⁰,¹¹ Cook and 
Heilborn¹⁷ and so on.

3.1.1 Literature Survey on Synthesis of Thiazole

Kazmaier et al. described the synthesis of endo-thiopeptides via Ugi reaction. 
But endo-thiopeptides are prepared using isonitriles with an acetal group, which 
directly gives up 2-substituted thiazoles using TMSCl-NaI under microwave 
irradiation with good yield.¹⁸
Ishiwata *et al.* has documented a method for the synthesis of thiazoles through reaction between 1H-1-(1'-alkynyl)-5-methyl-1,2,3-benziodoxathiole-3,3-dioxides and thioamides in the presence of potassium carbonate at RT with high yields.\(^\text{29}\)

Narender *et al.* developed an easy and efficient aqueous method for the synthesis of 2-amino-4-aryl-thiazole-5-carboxylate through the reaction of α-bromo-β-ketoester, which is prepared in situ with NBS and thiourea in the presence of β-cyclodextrin at 50 °C with appreciable yield.\(^\text{18}\)

Sanz-Cervera *et al.* reported a general as well as fluorous technique for 2,5-disubstituted-thiazole 4-carboxylic acid from α-amido-β-ketoesters by treating with Lawesson’s reagent.\(^\text{30}\)

Kaleta *et al.* described the synthesis of 1,3-thiazoles through thionation of *N*-2-oxoalkyl)amides using fluorous Lawesson's reagent with moderate yield.\(^\text{31}\)
Castagnolo et al. synthesized 2-amino thiazoles in very short time through the domino alkylation followed by cyclization of propargyl bromides with thiourea by microwave irradiation at good yield.\(^{19}\)

Wipf et al. reported the convergent single step synthesis of thiazoles by cyclocondensation of alkynyl(phenyl)iodonium mesylate and thioamides in ether with potassium carbonate.\(^{16}\)

Sheldrake et al. described the synthesis of 5-substituted thiazoles on treatment of phosphorus pentasulfide and triethylamine with \(N,N\)-diformylamino methyl aryl ketones with good yield.\(^{32}\)

Sasmal et al. informed the synthesis of substituted thiazoles via one pot \(N\)-desilylation, thioacylation/oxythioacylation/thiothioacylation followed by thia-Michael cycloisomerisation in moderate yield. This method has a general applicability to introduce various substituents at 2\(^{nd}\) position such as alkyl, alkoxy, thioalkoxy, aryl, phenoxy and thiophenoxy groups.\(^{33}\)
Potewar et al. developed an efficient and rapid method for the synthesis of 2,4-disubstituted thiazoles in an excellent yield from α-bromoketone and thiourea or thioamide at RT in ionic liquid.\textsuperscript{34}

\[
\begin{align*}
\text{Ar}^+ \text{CO} \quad \text{H}_2\text{N}^+ \text{R} \quad & \quad [\text{bbim}^+\text{BF}_4^-] \\
\text{Br} & \quad \text{R} & \quad \text{RT} \\
\end{align*}
\]

Thomae et al. described the synthesis of 2,4,5-trisubstituted-1,3-thiazoles in good yield from dimethyl cyanodithioimidocarbonate by reacting with chloroacetonitrile in the presence of potassium carbonate and amine through one-pot four step procedure.\textsuperscript{35}

\[
\begin{align*}
\text{MeS}^+ \text{CN} \quad \text{ClCH}_2\text{CN/K}_2\text{CO}_3 & \quad \text{R}_2^+ \text{N}^- \text{R}_1 \quad \text{DMF} \\
\text{SMe} & \quad \text{CN} & \quad \text{NH}_2 \\
\end{align*}
\]

Kumar et al. conveyed an efficient and high yielding greener protocol for the synthesis of substituted thiazoles through the reaction of α-tosyloxy ketones with variety of thioamides in water.\textsuperscript{36}

\[
\begin{align*}
\text{R}_1 \quad \text{R}_2 & \quad [\text{Water/Δ}] \\
\text{OTs} \quad \text{S} \quad \text{NH}_2 \\
\end{align*}
\]

Xie et al. had identified that the reaction of vinyl isothiocyanate with aliphatic secondary amines furnishes 2,4,5-trisubstituted thiazoles in moderate yield. This reaction takes place in two steps; first intramolecular Michael addition followed by dehydrogenating aromatization.\textsuperscript{37}
Alkyl dithiocarboxylates are well known building blocks in heterocyclic chemistry. The dithiocarboxylates react with isocyanides bearing active methylene group in the presence of base undergoes cyclization to afford 4,5-disubstituted thiazoles in moderate to excellent yield. The results of these studies have been described in the subsequent sections.
3.2 Present Work

3.2.1 Chemistry

The reaction of tosylmethyl isocyanide (2a) with phenyl dithioester (1a) (Scheme 3.1) was investigated as a model reaction in the presence of various solvent and base combinations and the results are summarized in Table 3.1.

![Chemical reaction](image)

**Scheme 3.1. Base induced cyclization of TosMIC (2a) with phenyl dithioester (1a)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base (equiv.)</th>
<th>Time</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>DBU (2)</td>
<td>48 h</td>
<td>NRb</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>DBU (2)</td>
<td>48 h</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>NaOH (2)</td>
<td>10 h</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>t-BuOK (2)</td>
<td>9 h</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>NaH (2)</td>
<td>10 min</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>NaH (2)</td>
<td>8 h</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>CH₃CN</td>
<td>NaH (2)</td>
<td>14 h</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>Benzene</td>
<td>NaH (2)</td>
<td>16 h</td>
<td>46</td>
</tr>
</tbody>
</table>

**Note:** a Isolated yield; b No reaction.

The first attempt on cyclization of 2a with 1a in presence of DBU as a base in THF at room temperature was failed to achieve the cyclized product 3a even after a prolonged time with the recovery of 1a (Table 3.1, entry 1). Then, a progress in reaction was observed after replacing THF by DMF, which gives 3a at a yield of 31
% (Table 3.1, entry 2). This might be due to the stabilization of activated 2a by DMF.

Use of sodium hydroxide as a base in DMF proved to be effective in furnishing 3a with 58% yield (Table 3.1, entry 3), probably due to increase in reactivity of the activated 2a with enhanced strength of the base in the reaction. Thereafter, base strength was increased to check the reactivity of 2a in DMF as a solvent of choice. When the reaction was effected using potassium tertiary butoxide, 3a was obtained in 58% yield (Table 3.1, entry 4). Finally, sodium hydride was proved to be the most effective base for cyclization of 2a with 1a to afford 3a in 90% yield within 10 min (Table 3.1, entry 5). Use of sodium hydride in other solvents such as THF, MeCN and benzene (Table 3.1, entries 6-8) gave a low yield of 3a.

\[ \text{Scheme 3.2. Sodium hydride induced cyclization of TosMIC or ethyl isocyanooacetate or aryl methyl isocyanide with dithioesters} \]
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>1</th>
<th>2</th>
<th>3–6&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Time (min)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1a</td>
<td>2a</td>
<td>3a&lt;sup&gt;24&lt;/sup&gt;</td>
<td>10</td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1b</td>
<td>2a</td>
<td>3b&lt;sup&gt;24&lt;/sup&gt;</td>
<td>12</td>
<td>95&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1c</td>
<td>2a</td>
<td>3c&lt;sup&gt;24&lt;/sup&gt;</td>
<td>12</td>
<td>91&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1d</td>
<td>2a</td>
<td>3d&lt;sup&gt;24&lt;/sup&gt;</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1e</td>
<td>2a</td>
<td>3e</td>
<td>15</td>
<td>92&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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<td></td>
<td>1f</td>
<td>2a</td>
<td>3f</td>
<td>20</td>
<td>93&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>1g</td>
<td>2a</td>
<td>3g</td>
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<td></td>
<td>1h</td>
<td>2a</td>
<td>3h</td>
<td>15</td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td></td>
<td>1a</td>
<td>2b</td>
<td>4a&lt;sup&gt;38&lt;/sup&gt;</td>
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<td>1b</td>
<td>2b</td>
<td>4b</td>
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<td>1f</td>
<td>2b</td>
<td>4c</td>
<td>15</td>
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</tr>
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<td>12</td>
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<td>4d</td>
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<td>2c</td>
<td>5a&lt;sup&gt;39&lt;/sup&gt;</td>
<td>25</td>
<td>80</td>
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<tr>
<td>14</td>
<td><img src="image3.png" alt="Image" /></td>
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<td>2c</td>
<td>5b</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>15</td>
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<td>2c</td>
<td>5c</td>
<td>30</td>
<td>83</td>
</tr>
<tr>
<td>16</td>
<td><img src="image5.png" alt="Image" /></td>
<td>1e</td>
<td>2c</td>
<td>5d</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
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<td><img src="image6.png" alt="Image" /></td>
<td>1f</td>
<td>2c</td>
<td>5e</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>18</td>
<td><img src="image7.png" alt="Image" /></td>
<td>1g</td>
<td>2c</td>
<td>5f</td>
<td>25</td>
<td>78</td>
</tr>
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<td>19</td>
<td><img src="image8.png" alt="Image" /></td>
<td>1i</td>
<td>2c</td>
<td>5g</td>
<td>25</td>
<td>83&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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<td>20</td>
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<td>1a</td>
<td>2d</td>
<td>6a</td>
<td>20</td>
<td>88</td>
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<td><img src="image10.png" alt="Image" /></td>
<td>1b</td>
<td>2d</td>
<td>6b</td>
<td>25</td>
<td>90</td>
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<tr>
<td>22</td>
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<td>1f</td>
<td>2d</td>
<td>6c</td>
<td>25</td>
<td>91&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>23</td>
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<td>1i</td>
<td>2d</td>
<td>6d</td>
<td>20</td>
<td>93</td>
</tr>
</tbody>
</table>

Note: aIsolated yields; bPurified by crystallization from ethyl acetate and hexane; cLiterature reference.
Through the optimized reaction conditions, generality and scope of the cyclization reaction of 2a with various dithioesters 1a-h was carried out (Table 3.2, entries 1-8). Results suggested that, cyclization is compatible with various aryl dithioesters 1a-f bearing electron donating and withdrawing substituents and also with heteroaryl dithioesters 1g-h, affording the product 4-[(4-methylphenyl)sulfonyl]-5-aryl/heteroaryl-1,3-thiazoles 3a-h in 84-95% yields (Table 3.2, entry 1-8). Interestingly, all dithioesters 1a-h furnished thiazoles with comparable yields in short reaction time.

Notably, some products were pure enough for analytical characterization after crystallization from ethyl acetate and hexane. It is important to highlight that the compounds 3a-d were obtained by Oldenziel and van Leusen through the reaction of TosMIC with carboxymethyldithioates in the presence of potassium hydroxide in tertiary-butyl alcohol with 48-79% yield.\textsuperscript{24} Whereas, the present method afford the same compounds with 84-95% yield, which indicated that the developed protocol is more effective in comparison with the earlier reported method.

Further, to check the efficiency of the reaction for the synthesis of thiazole ring with ester functionality, the cyclization of ethyl isocyanatoacetate 2b with 1a was examined. Thus, when 2b reacted with 1a under optimized conditions afford the cyclized product ethyl 5-phenylthiazole-4-carboxylate 4a at a yield of 40% (Table 3.2, entry 9). Similarly, the reaction of 1b, 1f and 1i gave ethyl 5-aryl/heteroaryltiazole-4-carboxylate with 42-50% yield (Table 3.2, entries 9-12).

However, the attempts to improve the yield of 4a with various bases (t-BuOK, DBU, NaOH etc.) at different conditions were failed, yielding either an unreacted phenyl dithioester 1a or an intractable reaction mixture even at higher temperature. At
this stage, the moderate yield of ethyl 5-aryl/heteroarylthiazole-4-carboxylates would be attributed to less reactivity of ethyl isocynano acetate enolate ion.

Further, to introduce a point of diversity at fourth position of thiazole ring, cyclization of aryl methyl isocyanides with dithioesters was investigated under the optimized conditions. It is noteworthy to mention that there are no earlier reports on cyclization reactions of aryl methyl isocyanides to construct thiazole ring. The desired aryl methyl isocyanides were prepared by dehydration of corresponding N-benzyl formamides. When 1a reacted with benzyl isocyanide 2c under optimized conditions, 4,5-diphenylthiazole 5a was obtained with 80% yield (Table 3.2, entry 13). Similarly, other dithioesters 1b-g and 1i underwent smooth cyclization with 2c, afford respective 4-phenyl-5-aryl/heteroaryl thiazoles with high yield (Table 2, entries 14-19).

Also, when dithioesters (1a, 1b, 1d, 1f and 1i) reacted with 4-fluorobenzyl isocyanide 2d under optimized conditions furnished 4-(4-fluorophenyl)-5-aryl/heteroaryl thiazoles at high yield (Table 3.2, entries 20-23).

The plausible mechanism for the sodium hydride induced the formation of thiazoles 3-6 from dithioesters 1 and active methylene isocyanides 2 was as shown in Scheme 3.3. Initially, in presence of sodium hydride, the anion 7 formed by the abstraction of an acidic proton from active methylene of 2, attacked dithioester 1 to give unstable intermediate 8. Further, carbanion 9 formed by the abstraction of a proton from 8 by sodium hydride was at equilibrium with enethiolate ion 10. Subsequent intramolecular cyclization of 10 gives the intermediate thiazolyl carbanion 11. Protonation of 11 during workup afford thiazole 3-6.
Scheme 3.3. Plausible mechanism for the formation of thiazoles (3-6).

3.2.2 Antimicrobial Activity

The synthesized thiazoles were screened for antimicrobial activity against a panel of pathogenic bacteria and fungi through agar well diffusion method and the MIC of the active compounds were determined through broth microdilution assay with appropriate positive and negative controls as described in Chapter 2. All the tests were performed in triplicate and the corresponding mean values were presented in Table 3.3 and Table 3.4.

The tested synthesized thiazoles exhibited a broad spectrum antibacterial activity except (3a and 5g). The thiazoles exhibited a maximum zone of inhibition (24 to 33 mm) against B. subtilis and least (11 to 19 mm) against E. coli except for 6c, which exhibited 24 mm of inhibition zone against E. coli. It was also observed that all the compounds were moderately active with a considerable zone of inhibition ranging between 16 mm and 24 mm. Least activity was observed by 6b and 6d against P. aeruginosa and S. aureus with an inhibition zone of 8 mm, whereas compounds 3a and 5g exhibited no zone of inhibition against any of the bacteria tested.

Among tested thiazoles all the compounds exhibited antifungal activity except 3a and 5g, against all the 3 human pathogenic fungi tested. Zone of inhibition was varied with compounds and the fungi. The maximum zone of inhibition was observed
(18 mm to 31 mm) against *C. albicans*, compared with *M. canis* and *M. gypseum*. *M. gypseum* was found to be slightly resistant to tested thiazoles compared with remaining other two fungal species.

The compounds exhibited antimicrobial activity were subjected to determine the MIC against the same panel of microbes selected for antibacterial and antifungal activity.

Compounds recorded MIC against all the bacteria and fungi selected. MIC of the compounds against the bacterial pathogens was in the range of 9.76 μg/mL and 78.12 μg/mL (*Table 3.4*). MIC of 39.06 μg/mL and 19.53 μg/mL were common, exhibited by majority of tested compounds. Least MIC was exhibited by compound 3f (9.76 μg/mL) against *B. subtilis* and compound 6c (9.76 μg/mL) against *B. subtilis* and *S. typhi*. Whereas maximum MIC of 78.12 μg/mL was exhibited by compounds 3d, 5e and 6d against *E. coli*, compound 6b against *P. aeruginosa* and compounds 6b and 6d against *S. aureus*. The standard streptomycin recorded MIC between 7.8 μg/mL and 31.2 μg/mL, which was very much lesser than the MIC exhibited by synthesized compounds except compound 6c. The compound 6c exhibited MIC of 9.76 μg/mL, which is very much lesser than the MIC of streptomycin (15.6 μg/mL) recorded against against *B. subtilis*.

Among the MIC determined against 3 human pathogenic fungi, different pathogens exhibited different range of MIC for different thiazole derivatives. The least MIC recorded was 19.53 μg/mL as maximum MIC observed as high as 156.2 μg/mL. The compound 3f and 6c was observed as potent antifungal agents against *C. albicans* and *M. canis* with a MIC of 19.53 μg/mL. The common MIC observed against *M. canis* and *M. gypseum* was 78.12 μg/mL and 156.2 μg/mL. Analysis of the results of the MIC also showed that *C. albicans* was more susceptible pathogen to the
synthesized thiazoles derivatives (recorded by least MIC) compared with *M. canis* and *M. gypseum*.

In majority of the cases, the potency of the thiazole derivatives was very much comparable to the positive standard Nystatin and recorded the similar MIC values.
Table 3.3. Zone of inhibition (diameter) of synthesized thiazoles by agar well diffusion method (10 mg/mL)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Bacteria</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zone of Inhibition in mm*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC</td>
<td>PA</td>
</tr>
<tr>
<td>3a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3d</td>
<td>11.33±1.53</td>
<td>26.00±1.00</td>
</tr>
<tr>
<td>3e</td>
<td>19.33±1.53</td>
<td>16.67±1.53</td>
</tr>
<tr>
<td>3f</td>
<td>17.67±0.58</td>
<td>18.00±1.00</td>
</tr>
<tr>
<td>5d</td>
<td>17.33±1.15</td>
<td>17.67±0.58</td>
</tr>
<tr>
<td>5e</td>
<td>12.00±1.00</td>
<td>23.33±0.58</td>
</tr>
<tr>
<td>5g</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6b</td>
<td>19.67±1.53</td>
<td>08.67±0.58</td>
</tr>
<tr>
<td>6c</td>
<td>24.33±1.53</td>
<td>24.00±1.00</td>
</tr>
<tr>
<td>6d</td>
<td>13.33±1.15</td>
<td>19.67±0.58</td>
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<tr>
<td>Streptomycin</td>
<td>30.33±0.58</td>
<td>34.00±1.00</td>
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<tr>
<td>Nystatin</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

DMSO-negative control showed no activity. KP: Klebsiella pneumoniae; ST: Salmonella typhi; SA: Staphylococcus aureus; BS: Bacillus subtilis; PA: Pseudomonas aeruginosa; EC: Escherichia coli; CA: Candida albicans; M: Microsporum canis; MG: Microsporum gypseum. 
*Values are average of triplicates ± SD. “-“: Low active or not active at tested concentration.
Table 3.4. Minimum Inhibitory Concentration (MIC) of synthesized thiazoles by microdilution method

<table>
<thead>
<tr>
<th>Compound</th>
<th>Minimum Inhibitory Concentration (MIC) in µg/mL</th>
<th>Fungi</th>
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</thead>
<tbody>
<tr>
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<td>Bacteria</td>
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<tr>
<td></td>
<td>KP</td>
<td>ST</td>
</tr>
<tr>
<td>3a</td>
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<td>Nystatin</td>
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DMSO-negative control showed no activity. KP: Klebsiella pneumoniae; ST: Salmonella typhi; SA: Staphylococcus aureus; BS: Bacillus subtilis; PA: Pseudomonas aeruginosa; EC: Escherichia coli; CA: Candida albicans; MC: Microsporum canis; MG: Microsporum gypseum.

“-”: Low active or not active at tested concentration.
Fig. 3.2. Antimicrobial activity of 4,5-disubstituted thiazoles against pathogenic microbes

KP: *Klebsiella pneumoniae*; ST: *Salmonella typhi*; SA: *Staphylococcus aureus*; BS: *Bacillus subtilis*; PA: *Pseudomonas aeruginosa*; EC: *Escherichia coli*
3.3 Materials and Methods

Chemicals and instruments which have been described in detail in Chapter 2.

3.4 Experimental Section

3.4.1 Chemistry

General procedure of synthesis of dithioesters (1a-i)\textsuperscript{40}

A mixture of aldehyde (1.0 mmol), sulfur (1.0 mmol) and piperidine (1.5 mmol) was heated at 80 °C for 6 h. After completion of reaction mixture (monitored by TLC), workup the mixture to get thioamide. This thioamide upon methylation yielded the salt, which upon subsequent thiolyis by hydrogen sulfide in pyridine at 0 °C afforded the desired dithioester.

General procedure of synthesis of 4,5-disubstituted thiazoles (3-6)

A solution of dithioester (3.0 mmol) and TosMIC (3.0 mmol) (or Ethyl isocyanoacetate/benzylisocyanide/4-flurobenzylisocyanide) in DMF was added dropwise to a stirring suspension of sodium hydride (6 mmol) in DMF at 0 °C. The resulting mixture was stirred for 10-30 min at room temperature (monitored by TLC) and poured into a saturated solution of NH\textsubscript{4}Cl (100 mL). The resultant mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was successively washed with water (2 x 50 mL), brine (1 x 50 mL) and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} followed by concentration under reduced pressure yield crude products, which were purified by column chromatography over silica gel using an eluent mixture of hexane and ethyl acetate in 8:2 ratio. (Except 3a–c, 3e, 3f, 3h, 5g, 6d which were purified by saturation with ethyl acetate and hexane).

3.4.2 Biology

Antimicrobial Activity

The procedure used has been described in detail in Chapter 2.
3.5 Analytical Characterization Data

4-[(4-Methylphenyl)sulfonyl]-5-phenyl-1,3-thiazole (3a)

Yellow solid; Yield = 0.40 g; mp = 149-151 °C. IR (KBr, cm⁻¹):
1): 3035, 2951, 2850, 1886, 1797, 1620, 1396, 1323, 1230,
1145, 1037, 960, 810, 748. ¹H NMR (400 MHz, CDCl₃): δ 8.70
(s, 1H), 7.77 (d, J = 6.8 Hz, 2H), 7.54-7.44 (m, 5H), 7.27 (d, J =
8.0 Hz, 2H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ
151.7, 148.5, 144.5, 144.4, 140.1, 137.7, 130.9, 129.5, 128.9, 128.4, 125.0, 21.4. MS-ESI: m/z = 315.04 (Calcd.) m/z = 316 [M+H]⁺ (found). Anal. Calcd. for
C₁₉H₁₃NO₂S₂: C, 60.93; H, 4.15; N, 4.44. Found: C, 61.09; H, 4.26; N, 4.34.

5-[(4-Methoxyphenyl)-4-[(4-methylphenyl)sulfonyl]-1,3-thiazole (3b)

Yellow solid; Yield = 0.99 g; mp = 181-183 °C. IR (KBr, cm⁻¹):
1): 3035, 2952, 2850, 1967, 1940, 1917, 1890, 1867, 1789,
1604, 1454, 1392, 1296, 1257, 1196, 1083, 1026, 940, 794. ¹H
NMR (400 MHz, CDCl₃): δ 8.65 (s, 1H), 7.78 (d, J = 8.0 Hz,
2H), 7.48 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.96 (d,
J = 8.4 Hz, 2H), 3.87 (s, 3H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.9,
151.4, 148.2, 144.5, 137.7, 131.9, 129.5, 128.4, 120.0, 113.7, 55.3, 21.6. MS-ESI:
m/z = 345.05 (Calcd.) m/z = 346 [M+H]⁺ (found). Anal. Calcd. for C₁₇H₁₅NO₂S₂: C,
59.11; H, 4.38; N, 4.05. Found: C, 59.28; H, 4.25; N, 4.16.
5-(4-Methylphenyl)-4-[(4-methylphenyl)sulfonyl]-1,3-thiazole (3c)

Off-white solid; Yield = 0.90 g; mp = 141-143 °C. IR (KBr, cm\(^{-1}\)): 3033, 2953, 2850, 1951, 1913, 1801, 1597, 1538, 1473, 1384, 1234, 1184, 1083, 1037, 1018, 964, 806, 698. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.66 (s, 1H), 7.79 (d, \(J = 8.4\) Hz, 2H), 7.43 (d, \(J = 8.4\) Hz, 2H), 7.26 (t, \(J = 7.2\) Hz, 4H), 2.42 (s, 3H), 2.40 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 151.6, 148.5, 144.5, 144.4, 140.1, 137.7, 130.3, 129.5, 128.9, 128.4, 125.0, 21.6, 21.3. MS-ESI: m/z = 329.05 (Calcd.) m/z = 330 [M+H]\(^+\) (found). Anal. Calcd. for C\(_{17}\)H\(_{15}\)NO\(_2\)S\(_2\): C, 61.98; H, 4.59; N, 4.25. Found: C, 61.65; H, 4.72; N, 4.43.

5-(4-Chlorophenyl)-4-[(4-methylphenyl)sulfonyl]-1,3-thiazole (3d)

Brownish solid; Yield = 0.70 g; mp = 180-182 °C. IR (KBr, cm\(^{-1}\)): 3033, 2958, 2856, 1990, 1963, 1882, 1789, 1620, 1593, 1415, 1396, 1319, 1296, 1265, 1184, 1145, 1087, 1014, 964, 817, 694. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.71 (s, 1H), 7.75 (d, \(J = 8.4\) Hz, 2H), 7.49-7.42 (m, 4H), 7.25 (d, \(J = 8.4\) Hz, 2H), 2.41 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 152.2, 149.3, 144.8, 142.6, 137.3, 136.2, 131.8, 129.6, 128.5, 128.4, 126.5, 21.6. MS-ESI: m/z = 348.9998 (Calcd.) m/z = 350 [M+H]\(^+\) (found). Anal. Calcd. for C\(_{18}\)H\(_{12}\)ClNO\(_2\)S\(_2\): C, 54.93; H, 3.46; N, 4.00. Found: C, 55.17; H, 3.63; N, 3.77.
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5-(3,4-Dimethoxyphenyl)-4-[(4-methylphenyl)sulfonyl]-1,3-thiazole (3e)

Yellow solid; Yield = 1.03 g; mp = 139-141 °C. IR (KBr, cm⁻¹): 3030, 2955, 2852, 1986, 1913, 1840, 1789, 1728, 1597, 1523, 1473, 1442, 1384, 1265, 1172, 1118, 1026, 960, 829, 763. ¹H NMR (400 MHz, CDCl₃): δ 8.65 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 5.6 Hz, 2H), 7.13 (d, J = 2 Hz, 1H), 7.10 (dd, J = 8.4, 2.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 151.2, 150.5, 148.5, 144.5, 144.2, 137.7, 129.5, 128.3, 127.9, 123.4, 120.2, 113.9, 110.7, 56.5, 55.9, 21.6. MS-ESI: m/z = 375.06 (Calcd.) m/z = 376 [M+H]⁺ (found). Anal. Calcd. for C₁₈H₁₇NO₄S₂: C, 57.48; H, 4.56; N, 3.73. Found: C, 57.26; H, 4.78; N, 3.92.

4-[(4-Methylphenyl)sulfonyl]-5-(3,4,5-trimethoxyphenyl)-1,3-thiazole (3f)

Brownish solid; Yield = 1.09 g; mp = 101-103 °C. IR (KBr, cm⁻¹): 3038, 2956, 2840, 1985, 1913, 1842, 1790, 1718, 1567, 1532, 1478, 1424, 1364, 1269, 1176, 1128, 1026, 960, 829, 763. ¹H NMR (400 MHz, CDCl₃): δ 8.67 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.75 (s, 2H), 3.90 (s, 3H), 3.86 (s, 6H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 153.6, 152.8, 151.3, 149.0, 144.6, 139.4, 138.8, 137.5, 129.5, 128.4, 122.9, 108.2, 60.9, 56.2, 21.6. MS-ESI: m/z = 405.07 (Calcd.) m/z = 406 [M+H]⁺ (found). Anal. Calcd. for C₁₉H₁₉NO₄S₂: C, 56.28; H, 4.72; N, 3.45. Found: C, 56.48; H, 4.96; N, 3.62.
4-((4-Methylphenyl)sulfonyl)-5-(thiophen-2-yl)-1,3-thiazole (3g)

Brownish Sticky liquid; Yield = 0.78 g; IR (KBr, cm⁻¹): 3026, 2968, 2860, 1976, 1903, 1860, 1799, 1748, 1597, 1523, 1473, 1442, 1384, 1265, 1172, 1118, 1026, 960, 829, 763. ¹H NMR (400 MHz, CDCl₃): δ 8.66 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.56 (t, J = 1.2 Hz, 1H), 7.51 (t, J = 1.2 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 151.7, 150.1, 144.7, 137.3, 132.0, 129.7, 129.6, 129.4, 128.3, 127.7, 127.8, 21.6. MS-ESI: m/z = 320.9952 (Calcd.) m/z = 322 [M+H]⁺ (found). Anal. Calcd. for C₁₄H₁₁NO₂S₃: C, 52.31; H, 3.45; N, 4.36. Found: C, 52.09; H, 3.58; N, 4.53.

1-Methyl-2-[(4-[(4-methylphenyl)sulfonyl]-1,3-thiazol-5-yl]-1H-indole (3h)

Brownish solid; Yield = 0.97 g; mp = 157-159 °C. IR (KBr, cm⁻¹): 3045, 2978, 2849, 1996, 1913, 1860, 1789, 1728, 1597, 1543, 1493, 1442, 1384, 1265, 1172, 1138, 1026, 980, 829, 763. ¹H NMR (400 MHz, CDCl₃): δ 8.66 (s, 1H), 7.90 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.20 (t, J = 4.8 Hz, 3H), 3.90 (s, 3H), 2.35 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 150.1, 147.1, 144.2, 138.2, 137.8, 136.8, 132.8, 129.4, 128.1, 127.2, 122.6, 120.8, 119.0, 109.9, 101.7, 33.3, 21.5. MS-ESI: m/z = 368.07 (Calcd.) m/z = 369 [M+H]⁺ (found). Anal. Calcd. for C₁₉H₁₆N₂O₂S₂: C, 61.93; H, 4.38; N, 7.60. Found: C, 61.81; H, 4.61; N, 7.43.
5-Phenyl-thiazole-4-carboxylic acid ethyl ester (4a)

Yellow viscous liquid; Yield = 0.38 g; IR (KBr, cm⁻¹): 3036, 2985, 2850, 2823, 1738, 1712, 1586, 1432, 1368, 1203, 876, 762. ¹H NMR (400 MHz, CDCl₃): δ 9.06 (s, 1H), 7.79 (d, J = 6.8 Hz, 2H), 7.51-7.41 (m, 3H), 4.30 (q, J = 6.0 Hz, 2H), 1.29 (t, J = 6.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 152.5, 132.6, 129.9, 129.2, 128.7, 128.2, 119.0, 114.8, 60.9, 55.8, 14.1. MS-ESI: m/z = 233.05 (Calcd.) m/z = 234 [M+H]⁺ (found). Anal. Calcd. for C₁₂H₁₁NO₂S: C, 61.78; H, 4.75; N, 6.00. Found: C, 60.78; H, 4.08; N, 5.80.

5-(4-Methoxy-phenyl)-thiazole-4-carboxylic acid ethyl ester (4b)

Yellow gum; Yield = 0.46 g; IR (KBr, cm⁻¹): 3029, 2951, 2857, 2834, 1741, 1709, 1588, 1402, 1378, 1193, 854, 798. ¹H NMR (400 MHz, CDCl₃): δ 9.05 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 4.28 (q, J = 6.0 Hz, 2H), 3.23 (s, 3H), 1.29 (t, J = 6.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 168.0, 160.6, 152.5, 128.5, 124.9, 119.0, 114.8, 60.9, 55.8, 14.1. MS-ESI: m/z = 263.06 (Calcd.) m/z = 264 [M+H]⁺ (found). Anal. Calcd. for C₁₃H₁₃NO₃S: C, 59.30; H, 4.98; N, 5.32. Found: C, 60.15; H, 4.68; N, 5.20.

Ethyl 5-(3,4,5-trimethoxyphenyl)-1,3-thiazole-4-carboxylate (4c)

Viscous liquid; Yield = 0.41 g; IR (KBr, cm⁻¹): 3035, 2958, 2850, 2835, 2820, 1735, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1066, 881, 778. ¹H NMR (400 MHz, CDCl₃): δ 8.76 (s, 1H), 7.26 (d, J = 7.6 Hz, 2H), 4.29 (q, J = 9.2 Hz, 2H), 3.96 (s, 3H), 3.17 (s, 6H), 1.26 (t, J = 9.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 168.0, 160.6, 152.5, 128.5, 124.9, 119.0, 114.8, 60.9, 55.8, 14.1. MS-ESI: m/z = 263.06 (Calcd.) m/z = 264 [M+H]⁺ (found). Anal. Calcd. for C₁₃H₁₃NO₃S: C, 59.30; H, 4.98; N, 5.32. Found: C, 60.15; H, 4.68; N, 5.20.
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MHz, CDCl₃): δ 167.8, 153.1, 152.5, 139.2, 128.2, 128.0, 118.8, 104.6, 60.9, 55.8,
14.1. MS-ESI: m/z = 323.08 (Calcd.) m/z = 324 [M+H]⁺ (found). Anal. Calcd. for
C₁₅H₁₇NO₃S: C, 55.71; H, 5.30; N, 4.33. Found: C, 55.86; H, 5.72; N, 4.63.

Ethyl 5-(1-methyl-1H-pyrrol-2-yl)-1,3-thiazole-4-carboxylate (4d)

Yellow viscous liquid; Yield = 0.29 g; IR (KBr, cm⁻¹): 3035, 2958,
2850, 1735, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1066, 881,
781. ¹H NMR (400 MHz, CDCl₃): δ 8.87 (s, 1H), 6.71 (d, J = 2.0
Hz, 1H), 6.32 (dd, J = 3.6, 1.6 Hz, 1H), 6.23 (d, J = 3.0 Hz, 1H),
4.34 (q, J = 6.0 Hz, 2H), 3.17 (s, 3H), 1.32 (t, J = 5.8 Hz, 3H). ¹³C NMR (100 MHz,
CDCl₃): δ 189.9, 152.2, 139.9, 137.7, 120.9, 109.9, 105.1, 58.3, 34.1, 22.9. MS-ESI:
m/z = 236.06 (Calcd.) m/z = 237 [M+H]⁺ (found). Anal. Calcd. for C₁₁H₁₂N₂O₂S: C,
55.91; H, 5.12; N, 11.86. Found: C, 56.15; H, 5.40; N, 12.26.

4,5-Diphenyl-1,3-thiazole (5a)

Yellow gum; Yield = 0.56 g; IR (KBr, cm⁻¹): 3032, 2955, 2851,
1722, 1597, 1433, 1372, 1288, 1203, 1124, 1066, 956, 881, 787. ¹H
NMR (400 MHz, CDCl₃): δ 8.79 (s, 1H), 7.53-7.48 (m, 2H) 7.34 (s,
5H), 7.00-6.95 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.7,
161.2, 151.0, 149.6, 131.6, 130.8, 129.6, 128.6, 128.8, 128.4, 115.4, 115.1. MS-ESI: m/z =
237.06 (Calcd.) m/z = 238 [M+H]⁺ (found). Anal. Calcd. for C₁₅H₁₅NS: C, 75.91; H,
4.67; N, 5.90. Found: C, 76.02; H, 4.76; N, 6.12.
5-(4-Methoxyphenyl)-4-phenyl-1,3-thiazole (5b)

Yellow gum; Yield = 0.68 g; IR (KBr, cm⁻¹): 3040, 2957, 2850, 2830, 1722, 1623 1597, 1433, 1372, 1288, 1203, 1134, 1066, 861, 755. ¹H NMR (400 MHz, CDCl₃): δ 8.77 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.32-7.25 (m, 5H), 6.86 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 159.6, 150.4, 150.1, 134.8, 132.8, 130.9, 128.9, 128.2, 127.6, 123.9, 114.2, 55.2. MS-ESI: m/z = 267.07 (Calcd.) m/z = 268 [M+H]+ (found). Anal. Calcd. for C₁₆H₁₂NOS: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.64; H, 5.15; N, 5.41.

5-(4-Methylphenyl)-4-phenyl-1,3-thiazole (5c)

Brownish gum; Yield = 0.63 g; IR (KBr, cm⁻¹): 3025, 2957, 2840, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1059, 967, 891, 735. ¹H NMR (400 MHz, CDCl₃): δ 8.79 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.30-7.23 (m, 5H), 7.13 (d, J = 8.8 Hz, 2H), 2.36 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 150.7, 149.7, 138.2, 134.7, 133.1, 129.5, 129.4, 128.9, 128.3, 127.9, 126.8, 21.2. MS-ESI: m/z = 251.08 (Calcd.) m/z = 252 [M+H]+ (found). Anal. Calcd. for C₁₆H₁₃NS: C, 76.46; H, 5.21; N, 5.57. Found: C, 76.64; H, 5.82; N, 5.23.

5-(3,4-Dimethoxyphenyl)-4-phenyl-1,3-thiazole (5d)

Yellow gum; Yield = 0.75 g; IR (KBr, cm⁻¹): 3023, 2965, 2863, 2830, 2816, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1066, 894, 756. ¹H NMR (400 MHz, CDCl₃): δ 8.77 (s, 1H), 7.55 (dd, J = 8.4, 1.6 Hz, 2H), 7.32-7.25 (m, 3H), 6.96 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (t, J = 8.4 Hz, 2H), 3.89 (s, 3H), 3.66 (s, 3H). ¹³C NMR (100
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**4-Phenyl-5-(3,4,5-trimethoxyphenyl)-1,3-thiazole (5e)**

Greenish gum; Yield = 0.85 g; IR (KBr, cm\(^{-1}\)): 3036, 2960, 2836, 2836, 2820, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1066, 896, 732. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.79 (s, 1H), 7.56 (d, \(J = 7.6\) Hz, 2H), 7.34-7.25 (m, 3H), 6.55 (s, 2H), 3.87 (s, 3H), 3.70 (s, 6H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 153.3, 150.6, 138.2, 134.7, 132.9, 129.0, 128.2, 127.9, 126.9, 106.9, 104.0, 60.9, 56.0. MS-ESI: m/z = 327.09 (Calcd.) m/z = 328 [M+H]\(^+\) (found). Anal. Calcd. for C\(_{17}\)H\(_{13}\)NO\(_2\): C, 66.66; H, 5.08; N, 4.71. Found: C, 68.83; H, 5.29; N, 4.98.

**1-Methyl-2-(4-phenyl-1,3-thiazol-5-yl)-1H-indole (5f)**

Yellowish-brown gum; Yield = 0.66 g; IR (KBr, cm\(^{-1}\)): 3036, 2959, 2852, 1722, 1670, 1597, 1433, 1372, 1295, 1288, 1203, 1124, 1066, 861, 756. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.89 (s, 1H), 7.65 (dd, \(J = 8.0, 3.8\) Hz, 2H), 7.39 (d, \(J = 8.4\) Hz, 1H), 7.35 (d, \(J = 8.4\) Hz, 2H), 7.28 (s, 1H), 7.27-7.24 (m, 3H), 7.08 (t, \(J = 7.6\) Hz, 2H), 3.78 (s, 3H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 150.5, 150.2, 136.9, 135.3, 135.1, 134.0, 128.7, 128.5, 128.2, 127.5, 126.8, 122.3, 120.1, 109.4, 32.9. MS-ESI: m/z = 290.09 (Calcd.) m/z = 291 [M+H]\(^+\) (found). Anal. Calcd. for C\(_{18}\)H\(_{14}\)N\(_2\): C, 74.45; H, 4.86; N, 9.65. Found: C, 74.86; H, 5.10; N, 9.85.
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5-(1-Methyl-1H-pyrrol-2-yl)-4-phenyl-1,3-thiazole (5g)

Off-white solid; Yield = 0.59 g; mp = 99-101 °C. IR (KBr, cm⁻¹): 3035, 2958, 2850, 1886, 1612, 1415, 1338, 1269, 1222, 1157, 1130, 1103, 1083, 964, 829, 740. ¹H NMR (400 MHz, CDCl₃): δ 8.87 (s, 1H), 7.51 (d, J = 6.8 Hz, 2H), 7.33-7.30 (m, 3H), 6.71 (d, J = 2Hz, 1H), 6.32 (dd, J = 3.6, 1.6 Hz, 1H), 6.23 (t, J = 3.2 Hz, 1H), 3.17 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 152.2, 152.0, 134.7, 128.5, 127.8, 127.6, 123.8, 123.8, 121.7, 112.1, 108.4, 34.1. MS-ESI: m/z = 240.07 (Calcd.) m/z = 241 [M+H]⁺ (found). Anal. Calcd. for C₁₄H₁₂N₂S: C, 69.97; H, 5.03; N, 11.66. Found: C, 70.12; H, 5.26; N, 11.83.

4-(4-Fluorophenyl)-5-phenyl-1,3-thiazole (6a)

Yellow gum; Yield = 0.67 g; IR (KBr, cm⁻¹): 3055, 2968, 2859, 1958, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1100, 1066, 831, 735. ¹H NMR (400 MHz, CDCl₃): δ 8.79 (s, 1H), 7.53-7.48 (m, 2H), 7.54 (s, 5H), 7.00-6.95 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 163.6, 151.0, 149.6, 131.6, 130.7, 129.6, 128.8, 128.4, 115.3, 115.1. MS-ESI: m/z = 255.05 (Calcd.) m/z = 256 [M+H]⁺ (found). Anal. Calcd. for C₁₅H₁₀FNS: C, 70.57; H, 3.95; N, 5.49. Found: C, 70.78; H, 4.26; N, 5.68.

4-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1,3-thiazole (6b)

Yellow gum; Yield = 0.77 g; IR (KBr, cm⁻¹): 3035, 2958, 2850, 2830, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1100, 1066, 841, 725. ¹H NMR (400 MHz, CDCl₃): δ 8.76 (s, 1H), 7.53-7.49 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.98 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.5, 161.1,
159.7, 150.5, 149.1, 132.7, 130.9, 130.7, 130.6, 123.7, 115.3, 115.1, 114.3, 55.2. **MS-ESI:** $m/z = 285.06$ (Calcd.) $m/z = 286 [M+H]^+$ (found). Anal. Calcd. for C$_{18}$H$_{12}$FNOS: C, 67.35; H, 4.24; N, 4.91. Found: C, 67.84; H, 4.46; N, 5.19.

4-(4-Fluorophenyl)-5-(3,4,5-trimethoxyphenyl)-1,3-thiazole (6c)

Brownish solid; Yield = 0.91 g; mp = 95-98 °C. **IR (KBr, cm$^{-1}$):** 3033, 2955, 2856, 2830, 2820, 1722, 1597, 1433, 1372, 1288, 1203, 1124, 1100, 1066, 821, 736. **$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 8.79 (s, 1H), 7.57-7.53 (m, 2H), 7.01 (m, 2H), 6.53 (s, 2H), 3.88 (s, 3H), 3.72 (s, 6H). **$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 163.6, 161.2, 153.4, 150.7, 149.4, 138.3, 132.6, 130.8, 130.7, 126.7, 115.3, 115.1, 106.9, 60.9, 56.2. **MS-ESI:** $m/z = 345.08$ (Calcd.) $m/z = 346 [M+H]^+$ (found). Anal. Calcd. for C$_{18}$H$_{16}$FNO$_3$S: C, 62.59; H, 4.67; N, 4.06. Found: C, 62.42; H, 4.96; N, 4.36.

4-(4-Fluorophenyl)-5-(1-methyl-1H-pyrr-2-yl)-1,3-thiazole (6d)

Off-white solid; Yield = 0.71 g; mp = 90-92 °C. **IR (KBr, cm$^{-1}$):** 3031, 2952, 2850, 1994, 1924, 1894, 1643, 1589, 1450, 1354, 1307, 1226, 1130, 1002, 902, 833, 767, 671. **$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 8.83 (s, 1H), 7.50-7.47 (m, 2H), 6.98 (t, $J = 8.8$ Hz, 2H), 6.72 (d, $J = 1.6$ Hz, 1H), 6.30 (d, $J = 1.6$ Hz, 1H), 6.23 (t, $J = 3.2$ Hz, 1H), 3.17 (s, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 163.6, 161.1, 152.3, 151.2, 130.9, 129.5, 129.4, 124.0, 121.5, 115.5, 115.3, 112.2, 108.6, 34.0. **MS-ESI:** $m/z = 258.06$ (Calcd.) $m/z = 259 [M+H]^+$ (found). Anal. Calcd. for C$_{14}$H$_{11}$FN$_2$S: C, 65.10; H, 4.29; N, 10.84. Found: C, 65.30; H, 4.56; N, 11.05.
3.6 Conclusions

A general and efficient protocol for the synthesis of 4,5-disubstituted thiazoles from easily accessible dithioesters and activated methylene isocyanides has been developed. The methodology allowed different functionalities like tosyl, carbalkoxy, aryl at the 4th position of thiazole ring. The protocol developed was very simple and rapid. Some of the products synthesized through this protocol were pure enough for analytical characterization, thus avoiding the need of purification by column chromatography or other methods. Hence the method represents a new click reaction. The present attempt is the first report on the synthesis of thiazoles from aryl methyl isocyanides through cyclization.

Antimicrobial studies of the synthesized thiazoles against a panel of human pathogen bacteria and fungi revealed that some of the tested synthesized thiazoles were effective in inhibiting the growth/killing the pathogens tested except 3a and 5g. The MIC of the tested compounds were in a range of 19.53 μg/mL and 156.2 μg/mL.

An interesting result was recorded by compound 6c, which recorded the least MIC against B. subtilis (9.76 μg/mL) and C. albicans and M. canis (19.53 μg/mL) which was very much lesser than the positive controls streptomycin and Nystatin.
3.7 Bibliography

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APPENDICES
$^1$H NMR spectrum of compound 3a

$^{13}$C NMR spectrum of compound 3a
$^1$H NMR spectrum of compound 3b

$^{13}$C NMR spectrum of compound 3b
Mass spectrum of compound 3b

$^1$H NMR spectrum of compound 3c

$^{13}$C NMR spectrum of compound 3c
Chapter 3

Mass spectrum of compound 3c

\[ \text{\textsuperscript{1}H NMR spectrum of compound 3d} \]

\[ \text{\textsuperscript{13}C NMR spectrum of compound 3d} \]

Mass spectrum of compound 3d
Chapter 3

^1H NMR spectrum of compound 3e

^13C NMR spectrum of compound 3e

Mass spectrum of compound 3e
Chapter 3

$^1$H NMR spectrum of compound 3h

$^{13}$C NMR spectrum of compound 3h

Mass spectrum of compound 3h
$^1$H NMR spectrum of compound 4d

$^{13}$C NMR spectrum of compound 4d
Chapter 3

\(^1\)H NMR spectrum of compound 5c

\(^{13}\)C NMR spectrum of compound 5c

Mass spectrum of compound 5c
$^1$H NMR spectrum of compound 5g

$^{13}$C NMR spectrum of compound 5g

Mass spectrum of compound 5g
$^1$H NMR spectrum of compound 6b

$^{13}$C NMR spectrum of compound 6b

Mass spectrum of compound 6b
$^1$H NMR spectrum of compound 6d

$^{13}$C NMR spectrum of compound 6d

Mass spectrum of compound 6d