Synthesis of some new thiazole derivatives

Chapter-VII

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CHAPTER - VII
Synthesis of some new thiazole derivatives

7.1 Pharmaceutical applications of thiazole derivatives

The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. It is well-known that a number of heterocyclic compounds containing nitrogen and sulfur exhibit a variety of biological activities.\(^1\textsuperscript{−}^4\) Heterocycles bearing isoxazole, thiazole, and thiazolidinones have been found to be associated with diverse pharmacological activities. The chemistry of isoxazole derivatives continues to draw the attention of synthetic organic chemists due to their varied biological activities.\(^5\) Several of these derivatives are potent antitumor\(^6\), CNS-active\(^7\), analgesic\(^8\), antimicrobial\(^9\) and chemotherapeutic agents.\(^10\) Thiazole derivatives have been employed as antipsychotics\(^11\), antimalarials\(^12\), antibacterials\(^13\) and antiparasitics.\(^14\) Thiazolidinones have occupied a unique place, and they have been found to be associated with diverse pharmacological activities, such as antimicrobial, antihistamic, anti-inflammatory, analgesic, and anticonvulsants.\(^15\textsuperscript{−}17\) In addition, thiazolidinones have been proven as calcium antagonists with both calcium overload inhibition and antioxidant activity.\(^18\)

7.2 Present Work

In present chapter we have synthesized some new thiazole containing heterocyclic derivatives.

7.2.1 Synthesis of 4-hydroxythiobenzamide

Reaction of 4-hydroxy benzonitrile with thioacetamide in DMF-HCl yields 4-hydroxythiobenzamide in 80% yield.

![Scheme 7.1](image-url)
7.2.2 Synthesis of 2-(4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate

Reaction of 4-Hydroxy thiobenzamide and 2-chloro ethyl acetoacetate is a simple condensation reaction in appropriate solvent. Among the various solvents tested, ethanol was found to be an excellent solvent.

Scheme 7.2

7.2.3 Synthesis of 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazole carboxylate

2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate is prepared from 2-(4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate. There are many methods reported in the literature for the formylation of phenols to manufacture the corresponding aromatic aldehydes.

(1) The Gattermann methods; make hydrogen cyanide to react with phenols, or to make hydrogen chloride to react with zinc cyanide, using an aluminum chloride and zinc chloride as a catalyst.\(^{[19]}\)

(2) The Gattermann-Koch method; a method in which carbon monoxide is made to act in presence of an aluminum chloride and a copper chloride.\(^{[20]}\)

(3) Formylation with Formyl fluoride.\(^{[21]}\)

(4) Dichloromethyl alkyl ether is made to react under existence of titanium tetrachloride and an aluminum chloride.\(^{[22]}\)

(5) From phosphorus oxychloride, a thionyl chloride, and N-substituted formamides.\(^{[23]}\)

(6) The Reimer-Tiemann method; a method in which chloroform, bromoform, trichloroacetic acid, etc. are made to react under existence of alkali.\(^{[24]}\)

(7) Reaction of paraformaldehyde with Grignard reagent, hexamethylphosphoric triamide, or amines.\(^{[25]}\)
The Duff method; hexamethylenetetramine, boric acid glycerol ester or acetic acid, and trifluoroacetic acid.\textsuperscript{[26]}

However, the method of (1) to (7) uses toxic or corrosive raw materials, or associated with problems, like higher costs and non-suitability for industrial purpose.

Few alternatives to introduce formyl group were tried. Satisfactory yields were obtained using trifluoroacetic acid or polyphosphoric acid in the Duff method.

The Duff reaction is a formylation of phenolic compounds to give benzaldehydes derivatives by the reaction with hexamine. The electrophilic species in this electrophilic aromatic substitution reaction is the iminium ion. The initial reaction product is an iminium which is hydrolyzed to the aldehyde. The reaction requires strongly electron donating substituents on the aromatic ring such as in a phenol.

0.5-6 equivalent of hexamethylenetetramine is used with respect to the phenol derivative. Acids such as acetic acid, trifluoroacetic acid, p-toluene sulfonic acid, methane sulfonic acid, and trifluoromethane sulfonic acid with or without water can be used for the reaction. This reaction is an exothermic and is performed at 60°C - 120°C with slow heating. Reaction time varies from 15 minutes to about 30 hrs.

Finalized process (\textbf{Scheme 7.3}) involves reflux of reaction mixture of hexamethylene tetramine and 2-(4-hydroxyphenyl)-4-methyl-5-thiazole carboxylate in trifluoroacetic acid. Reaction is worked up with addition of water. As acid is soluble in water while product is insoluble. This reaction was also performed with orthophosphoric acid, methane sulfonic acid and acetic acid but non-encouraging results were obtained.

Main issue with the Duff reaction is lower purity of final product which was about 80% by TLC. To improve the purity of the crude FHPTE, purification experiments in various solvents were explored. Best results were obtained in methanol-water at reflux (70°C).
7.3 Results and Discussion

In the context of sustainable chemistry the design and development of sequences allowing highly selective access to elaborated molecular scaffolds while combining structural diversity with eco-compatibility, are great challenges for organic chemists. It is a ability of multicomponent synthesis to build one product in a single operation from three or more reactant molecules with high atom-economy and multiple-bond-forming efficiency. Above prepared 2-(3-formyl-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylate was further utilized in the synthesis of various thiazole compounds through multicomponent cyclocondensations.

7.3.1 Synthesis of thiazolo-bis(indoly)methane derivative

Bis(indoly)alkanes and their derivatives constitute an important group of biologically active metabolites of terrestrial and marine origin. In the recent years bis(indoly)methanes and bis(indoly)ethanes have been found in marine sources. Bis-indole metabolites bearing imidazole or a piperazine nucleus has been isolated from various genera of sponges. Bis(indoly)methanes and their derivatives exhibit diverse biological activities which affect central nervous system and used as tranquilizers. The important indole derivative, 9H-pyrazolo[1,2-a] indole called fluorazine\cite{3} is an important compound because of its anticholinergic activity and the inhibitor of GABA transport and Na+/K+-ATPase.\cite{5} Several synthetic routes to 9H-pyrralo[1,2-a]indoles have been inscripted in literature. However, most of them have been directed towards the synthesis of mitomycin antibiotics.

Another important family of bis(indoly)methanes are cytonortopsentins, which exhibit in-vitro cytotoxicity. Moreover, some other bis(indoly)alkaloids
in which imidazole moiety of nortopsentins was replaced by thiazole, pyrimidine, pyrazine and pyrazinone rings have been reported. 2, 4-
Bis(indolyl) thiazole analogues exhibited cytotoxic activities against a wide range of human tumor cell lines at micromolar concentrations. Similar antitumor properties reported by dragmacidin D. Recently Lee and co-workers found that 1,1,3-tri(3-indolyl)cyclohexane inhibits cancer cell of xenograft model.

We are reporting here a greener and highly efficient route for the synthesis of bis(indolyl)methane using inexpensive and commercially available cyanoacetic acid as a catalyst in water (Scheme 7.4).

Scheme 7.4

7.3.2 Synthesis of thiazolo- acridinedione derivative

Acridinediones, the acridine derivatives having two keto functional groups at the 1st and 8th positions are found to be good anti-malarial agents. Substituted hexahydroacridine-1,8-dione, a novel dihydropyridine molecule, resembles K-channel openers, and relaxes KCl reconstructed urinary-bladder smooth muscle in-vitro. These acridinediones were also found to act as laser dyes. In acridine 1,8-diones, electron delocalization along a stretch of nine non-H atoms facilitate them to exhibit fluorescence and laser activity. The effectiveness of lasing can be controlled by the substituents at C-9 and N-10 of the acridine chromophore. Apart from the above applications, acridinediones also possess other important photo-physical and electrochemical properties.
Acridine dyes reacting with nucleic acids have been received increasing interest as mutagens in microorganisms.

Herein, we report a simple and convenient procedure for the synthesis of thiazolo-1,8-dioxo-decahydroacridine derivatives via one-pot three component reaction of dimedone (2 equivalent), thiazole containing aldehyde (1 equivalent), ammonium acetate (1.2 equivalent) catalyzed by low concentration of anhydrous hydrochloric acid generated in-situ from TMSCl in ethylene glycol (Scheme 7.5).

Scheme 7.5

7.3.3 Synthesis of thiazolo-4H-benzo[b]pyran derivative

In recent years 4H-benzo[b]pyran and their derivatives have attracted strong interest in scientific communities due to their wide range of biological and pharmaceutical properties such as antibacterial, anticoagulant, spasmolytic and diuretic. Efforts have been directed on the synthesis of an anticancer, antianaphylactic, antibacterial agents. In addition, they have been used as cognitive enhancer for the treatment of neurogenerative disease, including Alzheimer disease, Parkinson’s disease, AIDS associated dementia, Down’s syndrome as well as for the treatment of schizophrenia and myoclonus. Pyrans and benzocondensed derivatives constitute a structural unit of series of natural products and are oftenly used in cosmetics, pigments and as potential biodegradable agrochemicals.

At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials using non-toxic reagents, solvents and catalysts. Recently "ideal synthesis" was defined as one in which the target compound is generated in one
step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally acceptable process. Recently organic reactions in water without use of harmful organic solvents have attracted much attention, because water is a cheap, safe, and environmentally benign solvent.

Consequences of increasing environmental concern, it is necessary to minimize the amount of toxic waste and product from chemical process to develop a new environment friendly synthetic method. During the development of new process, use of cheap catalysts is an important synthetic aspect as they perform a vital role for effective greener organic transformations.

In this scheme, we are reporting the greener method for the synthesis of thiazolo-tetrahydrobenzo[b]pyran by condensation of dimedone, thiazole containing aldehyde and malononitrile in water using Hydroxypropyl- β – cyclodextrin (HP-β-CD) as a catalyst (Scheme 7.6).

![Scheme 7.6](image)

**Scheme 7.6**

**7.3.4 Synthesis of thiazolo-1,8-dioxo-octahydroxanthene derivative**

Xanthene derivatives are parent compounds of a large number of naturally occurring as well as synthetic derivatives, and occupy a prominent position in medicinal chemistry. Xanthenes and benzoanthenes find use as
dyes, fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties. Xanthene based compounds are also explored for their agricultural bactericidal activity, photodynamic therapy, anti-inflammatory effect and anti-viral activity. Particularly of interest are the xanthenediones, which constitute a structural unit in many natural products. They have been also used as versatile synthons because of their inherent reactivity of the inbuilt pyran ring.

In this scheme, we are reporting the condensation between 1.0mole of thiazole containing aldehyde and 2.0mole of dimedone by using TMSCl as a Lewis acid catalyst in ethylene glycol to prepare thiazolo-1,8-dioxooctahydroxanthenes (Scheme 7.7).

![Scheme 7.7](image_url)

### 7.3.5 Synthesis of thiazolo-triazolopyrimidine derivative

The widespread interest in triazole containing systems has promoted extensive studies of their syntheses. Substituted triazoles are useful intermediates for the syntheses of fused heterocyclic ring systems.

In this scheme, we are reporting the multi-component condensation of 3-amino-1, 2, 4-triazole, malononitrile and thiazole containing aldehyde in
ethanol to form thiazolo-triazolopyrimidine by using DBU as a catalyst (Scheme 7.8).

![Scheme 7.8](image)

7.4 Experimental procedure

7.4.1 Preparation of 4-Hydroxythiobenzamide (7a):

To a solution of HCl in DMF (6N, 60ml) was added 4-Hydroxybenzonitrile (20 mmol) and thioacetamide at room temperature and then mixture was heated at 50°C for 72hrs. Reaction was monitored by TLC. After completion of reaction, the product was extracted between ethyl acetate and water. The organic layer was washed with three portions of water to remove thioacetamide, dried over Na₂SO₄, and then evaporated. Crude product was recrystallized from chloroform. Yield: 82%
7.4.2 Preparation of Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (7b):

Charged 4-hydroxybenzothioamide (15 mmol) and 2-chloroethyl acetoacetate (15mmol) in ethanol (100ml). The reaction mixture was stirred at reflux for 5hrs. Upon completion of the reaction, monitored by thin-layer chromatography (TLC), the mixture was cooled to room temperature. The precipitated product was separated by filtration, and recrystallized from acetone. Yield: 86%

7.4.3 Preparation of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (7c):

Charged Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (10 mmol), hexamethylenetetramine (15 mmol) and trifluoroacetic acid (30ml). The reaction mixture was stirred at reflux for 72hrs. Upon completion of the reaction, which is monitored by thin-layer chromatography (TLC), the mixture was cooled to room temperature. 1.0lit water was added slowly to the reaction mass. Stirred the reaction mass for 2hrs. The precipitated products were separated by filtration, and recrystallized from methanol-water. Yield : 78%
7.4.4 Preparation of 3,3’–Bis(indolyl)–Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate methane (7d):

To the mixture of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (1 mmol), indole (2mmol), 15mole% of cyanoacetic acid in water (5 mL) were added and the mixture stirred at room temperature for 2.5hr. The product was isolated by simple filtration and further purified by column chromatography using solvent system [ethyl acetate / petroleum ether (1:9)] to get desired bis (indolyl) methanes in high yields. Yield: 83%

7.4.5 Preparation of Ethyl 2-[3-(3,3,6,6-Tetra-methyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate (7e):

To a solution of an Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (2 mmole) and 5,5-dimethyl-1,3-cyclohexanedione (4 mmole) in 20 ml ethylene glycol, trimethylsilyl chloride (8mmole) was added and stirred at 80°C. The progress of the reaction was monitored by TLC (Silica gel, 7:3, Pet ether: EtOAc). After completion of the reaction it was cooled to room temperature and water (20 mL) was added, separated solid was filtered, washed with water (20 mL) and dried under vacuum to get the desired Ethyl 2-
[3-(3,3,6,6-Tetra-methyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate. Yield: 83%

7.4.6 Preparation of Ethyl 2-[3-(2-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate (7f):

To a solution of HP-β-cyclodextrin (25mole%) dissolved in tap water (15 ml) added a mixture of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (1 mmol), dimedone (1 mmol), and malononitrile (1 mmol). Obtained reaction mixture was refluxed for about 1.5hr (Progress of the reaction was monitored by TLC), the mixture was cooled in ice and filtered to give crude product which was then recrystallized in DMF-acetone. Yield: 86%

7.4.7 Preparation of Ethyl 2-[3-(3,3,6,6-Tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate (7g):

To a solution of an Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (2 mmole) and 5,5-dimethyl-1,3-cyclohexanedione (4 mmole) in 20 ml ethylene glycol, trimethylsilyl chloride (8mmole) was added
and stirred at 80°C. The progress of the reaction was monitored by TLC (silica gel, 7:3, Pet ether: EtOAc). After completion of the reaction it was cooled to room temperature and water (20 mL) was added, solid separated was filtered washed with water (20 mL). Crude product is recrystallized from DMF-ethanol solvent system. Yield: 87%

7.4.8 Preparation of Ethyl 2-[3-(5-amino-6-cyano-3,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate (7h):

A mixture of the 3-Amino-1,2,4-triazole (2 mmol), Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate (2 mmol), and malononitrile (2 mmol) in ethanol (25 mL) was refluxed with stirring in the presence of DBU (0.4 ml). The reactions were continued until completion, as monitored by TLC. Precipitated product was filtered and washed with ethanol-water. Crude product is recrystallized from DMF-acetone. Yield: 84%
7.5 Spectral Analysis

The structures of synthesized compounds were confirmed on the basis of melting points and IR, $^1$H NMR, $^{13}$C NMR and mass spectroscopic data.

Table 7.1 Spectral analysis of synthesized heterocyclic thiazole derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Spectrum</th>
<th>Spectrum No.</th>
<th>Structure Elucidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>IR (KBr)</td>
<td>7.1</td>
<td>$\nu_{max}= 3342, 3165, 1604, 1583, 1448 \text{ cm}^{-1}$</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (DMSO-d$_6$)</td>
<td>7.2</td>
<td>$\delta = 6.746-6.768 \text{ (d, 2H, Ar-H)}, 7.859-7.881 \text{ (d, 2H, Ar-H)}, 9.210 \text{ (s, 1H, 1-NH$_2$)}, 9.521 \text{ (s, 1H, 1-NH$_2$)}, 10.094 \text{ (s, 1H, 1-OH) \ ppm}$</td>
</tr>
<tr>
<td></td>
<td>$^{13}$C NMR (DMSO-d$_6$)</td>
<td>7.3</td>
<td>$\delta = 199.22, 161.13, 130.33, 130.17, 114.87 \text{ ppm}$</td>
</tr>
<tr>
<td></td>
<td>$^{13}$C APT (DMSO-d$_6$)</td>
<td>7.4</td>
<td>$\delta = 199.22, 161.13, 130.33, 130.17 \text{ ppm}$</td>
</tr>
<tr>
<td></td>
<td>Mass</td>
<td>7.5</td>
<td>$m/z = 154.0 \text{ (M+1)}, 136.8, 109.1, 95.0, 77.2, 60.0$</td>
</tr>
<tr>
<td>7b</td>
<td>IR (KBr)</td>
<td>7.6</td>
<td>$\nu_{max}= 3200, 2983, 1723, 1603 \text{ cm}^{-1}$</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (DMSO-d$_6$)</td>
<td>7.7</td>
<td>$\delta = 1.273-1.309 \text{ (t, 3H, 1-CH$_3$)}, 2.642 \text{ (s, 3H, 1-CH$_3$)}, 4.242-4.295 \text{ (q, 2H, 1-CH$_2$)}, 6.854-6.890 \text{ (dd, 2H, Ar-H)}, 7.804-7.840 \text{ (dd, 2H, Ar-H)}, 10.220 \text{ (s, 1H, 1-OH) \ ppm}$</td>
</tr>
<tr>
<td></td>
<td>$^{13}$C NMR (DMSO-d$_6$)</td>
<td>7.8</td>
<td>$\delta = 169.82, 161.91, 160.99, 160.58, 128.80, 123.92, 120.01, 116.38, 61.31, 17.60, 14.50 \text{ ppm}$</td>
</tr>
<tr>
<td></td>
<td>$^{13}$C APT (DMSO-d$_6$)</td>
<td>7.9</td>
<td>$\delta = 169.82, 161.91, 160.99, 160.58, 123.92, 120.01, 61.31 \text{ ppm}$</td>
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<tr>
<td>Mass</td>
<td>m/z</td>
<td>7.10</td>
<td><strong>m/z = 264.0 (M+1), 235.9, 192.1, 164.2, 136.9</strong></td>
</tr>
<tr>
<td>--------</td>
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<td>-------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>7c</td>
<td>IR (KBr)</td>
<td>7.11</td>
<td>$\nu_{\text{max}}$ = 3400-3065, 2990, 1704, 1664, 1588 cm$^{-1}$</td>
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<tr>
<td>$^1$H NMR (DMSO-d$_6$)</td>
<td>7.12</td>
<td>$\delta = 1.272$-$1.307$ (t, 3H, 1-CH$_3$), 2.618 (s, 3H, 1-CH$_3$), 4.227-4.280 (q, 2H, 1-CH$_2$), 7.063-7.085 (d, 1H, 1-Aromatic CH), 8.004-8.032 (dd, 1H, 1-Aromatic CH), 8.143-8.149 (d, 1H, 1-Aromatic CH), 10.282 (s, 1H, 1-CHO), 11.379 (s, 1H, 1-OH) ppm</td>
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<tr>
<td>13C NMR (DMSO-d$_6$)</td>
<td>7.13</td>
<td>$\delta$ = 190.76 (1-CHO carbon), 168.22 (1-CO carbon), 163.26 (1-C-quatervnary carbon), 161.62 (1-C-quatervnary carbon), 160.46 (1-C-quatervnary carbon), 134.10 (1-CH-aromatic carbon), 127.23 (1-CH-aromatic carbon), 124.06 (1-C-quatervnary carbon), 122.76 (1-C-quatervnary carbon), 120.67 (1-C-quatervnary carbon), 118.48 (1-CH-aromatic carbon), 61.38 (1-CH$_2$-aliphatic carbon), 17.46 (1-CH$_3$-aliphatic carbon), 14.42 (1-CH$_3$-aliphatic carbon) ppm</td>
<td></td>
</tr>
<tr>
<td>13C APT (DMSO-d$_6$)</td>
<td>7.14</td>
<td>$\delta$ = 168.22, 163.26, 161.62, 160.46, 124.06, 122.76, 120.67, 11.38 ppm</td>
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<tr>
<td>Mass</td>
<td>m/z</td>
<td>7.15</td>
<td><strong>m/z = 293.0 (M+1), 275.4, 265.0, 263.2, 237.1, 236.0, 193.2</strong></td>
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<tr>
<td>7d</td>
<td>IR (KBr)</td>
<td>7.16</td>
<td>$\nu_{\text{max}}$ = 3407, 3165, 2930, 1698, 1669, 1602 cm$^{-1}$</td>
</tr>
<tr>
<td>7e</td>
<td>IR (KBr)</td>
<td>7.17</td>
<td>$\nu_{\text{max}}$ = 3136, 3016, 2808, 2003, 1708, 1401 cm$^{-1}$</td>
</tr>
<tr>
<td>Mass</td>
<td>m/z</td>
<td>7.18</td>
<td><strong>m/z = 538.2 (M+3), 536.6 (M+1), 453.4, 444.5</strong></td>
</tr>
<tr>
<td>7f</td>
<td>IR (KBr)</td>
<td>7.19</td>
<td>3175, 2956, 2192, 1704, 1645, 1592</td>
</tr>
<tr>
<td>Mass</td>
<td>m/z</td>
<td>7.20</td>
<td><strong>m/z = 480.15 (M+1), 399.4, 395.8, 380.0, 367.9, 314.5, 312.1, 285.2, 236.3</strong></td>
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<tr>
<td></td>
<td>IR (KBr)</td>
<td>Mass</td>
<td></td>
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<tr>
<td>----</td>
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<td></td>
</tr>
<tr>
<td>7g</td>
<td>7.21</td>
<td>3314, 3165, 2954, 1703, 1622, 1580</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.22</td>
<td>m/z = 536.22 (M+1), 396.1, 368.2, 340.1, 325.9, 273.1, 217.2, 161.2</td>
</tr>
<tr>
<td>7h</td>
<td>7.23</td>
<td>3390, 3294, 3047, 2992, 2230, 1703, 1658, 1614, 1599</td>
<td></td>
</tr>
</tbody>
</table>

7.6 Conclusion

In light of the synthetic methods reported herein, the synthetic strategies and subsequent chemical transformations of the resulting thiazole containing heterocyclic compounds provides several important classes of functionalized diversified molecules. The simplicity and flexibility of the experimental procedures in the generation of these classes, together with the diversity of thiazole chemistry, make these synthetic methodologies a highly efficient and practical method for preparation of various biologically active derivatives. The investigations in the pharmaceutical field and medicinal applications are developing quite rapidly and we hope it will bring new and useful results.
Spectrum 7.1: IR spectrum of 4-Hydroxythiobenzamide
Spectrum 7.2: $^1$H NMR spectrum of 4-Hydroxythiobenzamide
Spectrum 7.3: $^{13}$C NMR spectrum of 4-Hydroxythiobenzamide
Spectrum 7.4: $^{13}$C APT NMR spectrum of 4-Hydroxythiobenzamide

388
**Spectrum 7.5**: Mass spectrum of 4-Hydroxythiobenzamide
**Spectrum 7.6:** IR spectrum of Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.7: $^1$H NMR spectrum of Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.8: $^{13}$C NMR spectrum of Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
**Spectrum 7.9**: $^{13}$C APT NMR spectrum of Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.10: Mass spectrum of Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.11: IR spectrum of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.12: $^1H$ NMR spectrum of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.13: $^{13}$C NMR spectrum of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.14: $^{13}$C APT NMR spectrum of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.15: Mass spectrum of Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
**Spectrum 7.16:** IR spectrum of 3,3´–Bis(indolyl)–Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate methane
**Spectrum 7.17**: IR spectrum of Ethyl 2-[3-(3,3,6,6-Tetra-methyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
**Spectrum 7.18:** Mass spectrum of Ethyl 2-[3-(3,3,6,6-Tetra-methyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
**Spectrum 7.19:** IR spectrum of Ethyl 2-[3-(2-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.20: Mass spectrum of Ethyl 2-[3-(2-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
Spectrum 7.21: IR spectrum of Ethyl 2-[3-(3,3,6,6-Tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
**Spectrum 7.22:** Mass spectrum of Ethyl 2-[3-(3,3,6-Tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
**Spectrum 7.23:** IR spectrum of Ethyl 2-[3-(5-amino-6-cyano-3,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-4-hydroxyphenyl]-4-methyl-1,3-thiazole-5-carboxylate
7.8 References:


[24] Collective volume *Ber.*, nine volumes, 423 pages, and 1876