Synthesis various thiazolopyrimidine derivative containing coumarins
4.1 Introduction

Coumarin and many of its derivatives occur naturally. The parent heterocycle, coumarin (Fig. 1) was first isolated in 1920 by Vogel from the fruit of *Dipteryx odorata* Wild. The common name, coumarin, comes from another plant *Coumarouna odorata*, in which it is found; the systematic name is 2*H*-1-benzopyran-2-one [1].

![Fig. 1: Structure of coumarin and atom numbering](image1)

Coumarins occupy an important place in the realm of natural products and synthetic organic chemistry [2,3]. Coumarins comprise a group of natural compounds found in a variety of plant sources in the form of benzopyrene derivatives. Coumarins have important effects in plant biochemistry and physiology, as they act as antioxidants, enzyme inhibitors, and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection [4]. Coumarins have long been recognized to possess anti-inflammatory, anti-oxidant, anti-allergic, hepatoprotective, anti-thrombotic, anti-viral and anti-carcinogenic activities [5].

![Fig. 2: Applications of coumarins](image2)

In addition to biological activities they are used as additives to food and cosmetics [6] and optical brightening agents [7]. Synthetic coumarins are widely used as aroma
chemicals because of their odour strength, tenacity, stability to alkali and relatively cheap price; applications include use as a sweetener and fixative (in perfume); fragrance enhancers (for natural essential oils); blenders (in soaps and detergents); aroma enhancers (in tobacco); and for imparting pleasant odours to industrial products.

4.1.1 Naturally Occurring Coumarins

Aflatoxins (b) [8-11] form a group of acutely toxic and extremely carcinogenic, hepatotoxic metabolites produced by some strains of *Aspergillus flavus*. Aflatoxin B$_1$ has been synthesized [12], starting from 5-benzylxy-4-methyl-7-methoxy coumarin (a), via the corresponding 4-formyl derivative.

One of the yellow pigments isolated from the scent glands of beaver has been identified as urolithin-A (c) and urolithin-B (d) [13,14]. Alternariol (e) is the first 3:4-benzocoumarin antibacterial agent of fungal origin isolated from *Alternaria tenus* [15,16]. Benzocoumarins autumnariol (f) and autumnarriniol (g) isolated from bulbs [17] constitute the flavored components of Shilajit. A furocoumarin glapalol (h) [18,19] and a coumastan, namely coumasterol (i), have been isolated.

**Fig. 3:** Naturally occurring coumarins

4.1.2 Methods of coumarin synthesis

Many synthetic routes to the coumarins have been developed. These include use of the Pechmann, Perkin, Knoevenagel, Reformatsky and Wittig reactions.
4.1.2.1 Pechmann reaction

The Pechmann reaction is a widely used method for preparing coumarins in good yield; it involves reacting a phenol with a β-oxo ester in the presence of a catalyst. The Pechmann reaction has been carried out using both homogeneous acid catalysts (such as sulphuric [20a,b], hydrochloric, phosphoric and trifluoroacetic acids [21], and with Lewis acids, such as zinc chloride [22], iron (III) chloride, tin(IV) chloride, titanium chloride and aluminium chloride) and heterogeneous catalysts (such as cationexchange resins, Nafion-H, zeolite-HBEA and other solid acids) [23].

4.1.2.2 Perkin reaction

In 1868, Perkin [24a] reported the synthesis of coumarin by the reaction of sodium salt of salicylaldehyde with Ac₂O. The Perkin reaction [24a-24c] provides a useful method for -unsaturated aromatic acids and involves the condensation of a carboxylic anhydride with an aromatic aldehyde in presence of a weak base such as sodium or potassium acetate or triethylamine.

4.1.2.3 Knoevenagel condensation

In 1988, Armstrong et al. [25] reported a two step method for the synthesis of coumarin-3-carboxylic acids via sulphuric acid catalyzed Knoevenagel condensation of 2-methoxybenzaldehyde with Meldrum’s acid in dimethylformamide followed by cyclization.

4.1.2.4 Reformatsky reaction

Dittmer et al. [26] have achieved the sodium telluride-triggered cyclization of the bromoacetate of salicylaldehyde to coumarin via modified Reformatsky reaction. The
cyclization proceeds by formation of the phenolate ester enolate, elemental tellurium, and bromide ion. The enolate anion either attacks the ortho carbonyl group leading to cyclization or eliminates a phenolate ion to give a ketene

\[
\begin{align*}
\text{R'CH(Br)COBr} & \quad \xrightarrow{\text{base}} \quad \text{R'OBr} \\
& \quad \xrightarrow{\text{M_2Te, THF, M=Na, Li}} \quad \text{R'OBr}
\end{align*}
\]

### 4.1.2.5 Wittig reaction

Recently, a novel one-pot synthesis of coumarins via intramolecular Wittig cyclization from the reaction of phenolic compounds containing ortho-carbonyl group and triphenyl(α-carboxymethylene)phosphorane imidazolide was reported by Upadhyay and his group [27].

\[
\begin{align*}
\text{Ph}_3\text{P} & \quad \xrightarrow{\text{+}} \quad \text{R'OBr} \\
& \quad \xrightarrow{\text{R'CH(Br)COBr}} \quad \text{R'OBr}
\end{align*}
\]

### 4.1.3 Pharmacological activities

#### 4.1.3.1 Antimicrobial activities

Revankar et al., [28] synthesized two series of 4-aryloxymethyl coumarins derived from the reaction of 4-bromomethyl coumarins with ethyl gallate and ethyl ester of N-benzyol tyrosine. Gallate ethers and tyrosine derivatives were most effective against \textit{E. faecalis}. They were also found to be effective against \textit{A. niger} and \textit{C. albicans}.

\[
\begin{align*}
\text{COOC}_2\text{H}_5 & \quad \xrightarrow{\text{Ethyl gallate}} \quad \text{R'OBr} \\
& \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{Acetone, RT}} \quad \text{R'OBr}
\end{align*}
\]

\[
\begin{align*}
\text{R} & = 6-\text{Me}, 7-\text{Me}, 6-\text{Cl}, 7-\text{Cl}, 6-\text{OMe}, 7-\text{OMe}, 5,7-\text{Me}, 7,8-\text{Me}, 5,6 \text{ Benzo}, 7,8 \text{ Benzo}
\end{align*}
\]

Shivashankar et al., [29] reported the synthesis benzothiazolyl coumarins from the formyl-4-aryloxy methyl coumarins by refluxing with equimolar quantities of o-
aminothiophenol in dimethylsulfoxide. Antimicrobial screening for all compounds was carried out against two bacterial strains *B. subtilis* and *E. coli*. *A. niger* and *C. albicans* were employed as fungal strains with reference to the standard drugs *Ciprofloxacin* and *Gresiofulvin*. Results of the compounds revealed that benzothiazolyl coumarins were more potent than formyl-4-aryloxy methyl coumarins. Among benzothiazolyl coumarins the compound with 6-Br substitution found to be higher antimicrobial activity compared with other substitutions like 6-Br and 6-OMe.

4.1.3.2 Anti-inflammatory activity

Ghate *et al.*, [30] reported the preparation of ethers by treating 4-bromomethyl coumarin with α-hydroxy aromatic aldehydes. Further these ethers have been converted to the corresponding 4-(2′-benzo[b] furanyl) coumarins by an intramolecular aldol condensation. These compounds were evaluated for their anti-inflammatory activity. Out of these the 5,6-benzo-4-2′-benzo[b]furanyl coumarin and aryloxy methyl coumarin with *p*-formyl group were found to be most active.
Shastri et al., [31] reported the synthesis of acetamido-4-phenoxyethyl coumarins and evaluated them for their anti-inflammatory activity by the carrageenan induced edema model in rats using phenylbutazone as standard. Out of tested compounds the one with 6-Cl is highly active.

4.1.3.3 Anticancer activity

Puttaraju et al., [32] developed a simple method for the synthesis of dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones under microwave irradiation. These molecules further reacted with various substituted 4-bromomethylcoumarins to yield a new series of coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones. The coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-one (R= i-Pr, R= 6-Cl) was found to be the most potent cytotoxic compound (88%) against Dalton’s Ascitic Lymphoma cell line at the concentration of 100 mg/mL.
4.1.3.4 DNA cleavage studies

Jadhav et al., [33] reported a series of novel coumarin analogues of 1,2,3,4-tetrahydoisoquinolines and protoberberine alkaloids evaluated for DNA cleavage studies by agarose gel electrophoresis method against Gram positive bacteria S. aureus ATCC 6538, Gram negative bacteria E. coli ATCC 35218 and fungus A. niger. The result showed that coumarin analogues of 1,2,3,4-tetrahydoisoquinolines (R=7,8-benzo, R_1=H, R_2=H and R=7,8-benzo, R_1=OCH_3, R_2=OCH_3) and protoberberine alkaloids (R=7,8-benzo, R_1=H, R_2=H and R=7,8-benzo, R_1=OCH_3, R_2=OCH_3) showed selectivity towards the Gram positive bacteria S. aureus and A. niger. These compounds can act as potent antibacterial agents by genomic cleavage.

4.1.3.5 Antitubercular activity

Ambre et al., [34] designed and synthesized a set of 16 compounds, viz. 4-(substituted)phenyl-3,4-dihydro-1H-chromino[4,3-d]pyrimidine-2,5-diones and 4-(substituted)phenyl-
2-thioxo-3,4-dihydro-1Hchromino[4,3-d]pyrimidin-5-ones and evaluated for antitubercular activity by microplate alamar blue assay (MABA) and luminescence-based low oxygen-recovery assay (LORA) with rifampicin as the standard. 4-(substituted)phenyl-2-thioxo-3,4-dihydro-1Hchromino[4,3-d]pyrimidin-5-ones (R=CH₃, R₁=4-OCH₃, X=O; R=CH₃, R₁=3,4-OCH₃, X=O and R=H, R₁=2-OH, X=O) demonstrated maximum antitubercular activity, with % inhibition values of 58, 55, and 45 based on MABA and 62, 35 and 37 based on the LORA tests at 128 μM.

\[
\begin{align*}
R=H, \text{CH}_3; R_1=H, 4-\text{OCH}_3, 3,4-\text{OCH}_3, 3-\text{OCH}_2\text{H}_4\text{OH}, 3-\text{Br}, 2-\text{OH}; X=\text{S, O}
\end{align*}
\]

### 4.1.3.6 Acetyl cholinesterase (AChE) inhibitors

Razavi *et al.* [35] designed and synthesized a series of 4-hydroxycoumarin derivatives as new acetylcholinesterase (AChE) inhibitors which could be considered for Alzheimer’s disease therapeutics. Among the 19 coumarin-derived compounds tested toward Electrophorus electricus acetylcholinesterase (eelAChE) and horse serum butyrylcholinesterase (eqBChE), \(N\)-(1-benzylpiperidin-4-yl)acetamide derivative (NRR’=1-Benzylpiperidin-4-yl-amino, n=1) displayed highest AChE inhibitory activity (IC₅₀ = 1.2 μM) and good selectivity (37 times). The docking study of the most potent \(N\)-(1-benzylpiperidin-4-yl)acetamide derivative (NRR’=1-Benzylpiperidin-4-yl-amino, n=1), indicated that Phe330 is responsible for ligand recognition and trafficking by forming π-cation interaction with benzylpiperidine moiety.

**Synthesis of coumarinyl thiazolopyrimidines**

Chapter 4
4.3.1.7 Diuretic activity

Yaragatti et al. [36] reported the synthesis of coumarinyl thiazolopyrimidines from 3-bromoacetyl coumarins by azole and azine approaches. The results of in vivo diuretic activity showed that substituents on coumarin do not enhance the activity. In vitro antimicrobial activities have shown that the compounds are specifically active against Gram-positive but are inactive against Gram-negative bacterial strains. Moderate fungal activity was observed against *Candida albicans* and *Penicillium chrysogenum* and all the compounds were found to be inactive against *Aspergillus niger*.

\[ \text{R} = \text{H, 6-CH}_3, \text{6-Cl, 6-Br, 6-NO}_2, \text{5,6-benzo} \]
4.2 Present work

The work carried out in the present investigation includes preparation of 3,4-dihydropyrimidine-2-thiones, 4-bromomethylcoumarins, its formyl-4-aryloxyethyl coumarins i.e. 4-(6-methoxy-2-oxo-2H-chromen-4-yl-substituted)-benzaldehyde and construction of various coumarinyl pyrimidines and coumarinyl thiazolopyrimidines using these precursors are described in the following schemes 1-4. Scheme 1 shows the preparation of 4-bromomethylcoumarins. Preparation of 4-aryloxyethylcoumarins is given in Scheme 2. The schemes 3 and 4 show the preparation of coumarinyl pyrimidines and coumarinyl thiazolopyrimidines respectively.

Scheme 1: Synthesis of 4-bromomethyl coumarins

\[
\begin{align*}
\text{Scheme 2: Synthesis of formyl 4-aryloxyethyl coumarins} & \\
\text{Scheme 3: Synthesis of coumarinyl pyrimidines} & \\
\end{align*}
\]

R = Me, OMe

2a, 2b

2a, 2b

2a, 3a R₂=Me 2b, 3b R₂=OMe

3a, 3b

R₁ = Me, Et  Ar = Ph, 3-OCH₃C₆H₄, 4-OCH₃C₆H₄, 3,4-OCH₃C₆H₄, 4-OHC₆H₅, napthyl, thietyl, 4-OH-3-OCH₃C₆H₄  R₂= Me, OMe
**Scheme 4:** Synthesis of arylidene derivatives of coumarinyl thiazolopyrimidines

\[
\begin{align*}
\text{CHO} & \quad \text{O}\text{Ar} \quad \text{NH}\text{S} \\
\text{R}_2 & \quad \text{O}\text{Ar} & \quad \text{R}_1 \quad \text{O} & \quad \text{O} \\
\text{3a, 3b} & \quad \text{ClCH}_2\text{COOH} & \quad \text{AcONa} & \quad \text{AcOH/AC}_2\text{O} \\
\end{align*}
\]

\(\text{R}_1 = \text{Me, Et} \quad \text{Ar} = \text{Ph, 3-OCH}_3\text{C}_6\text{H}_5, 4\text{-OCH}_3\text{C}_6\text{H}_5, 3,4\text{-OCH}_3\text{C}_6\text{H}_4, 4\text{-OHC}_6\text{H}_5, \text{napthyl, thienyl, 4-OH-3-OCH}_3\text{C}_6\text{H}_4 \quad \text{R}_2 = \text{Me, OMe}\)

**4.3 Result and discussion**

The required 3,4-dihydropyrimidine-2-thiones 1 was obtained by a well known Biginelli multi-component one pot reaction on refluxing the substituted aryl aldehydes, thiourea and ethyl/methyl acetoacetate in ethanol for 7-9 h in the presence of catalytic amount of concentrated hydrochloric acid. The reaction mixture was kept overnight and the precipitate obtained was filtered and the compound was recrystallized with ethanol in good yield (reported in Chapter 2).

4-bromomethylcoumarins were prepared by the Pechmann cyclization of substituted phenols with 4-bromoethylacetoacetate using sulphuric acid as the condensing agent (Scheme 1). Further treatment of 4-bromomethylcoumarins with para hydroxy benzaldehyde gave 3a and 3b (Scheme 2).

Coumarinyl pyrimidines were obtained under standard acetone-potassium carbonate conditions at room temperature (Scheme 3). The formation of products 4(a-f) were evidenced by the presence of band around 1717 cm\(^{-1}\) due to ester or lactone ring and presence of one N-H stretching band in the region around 3300 cm\(^{-1}\) in its IR spectrum. Further it was supported by the presence of one singlet around \(\delta 10.00\) ppm corresponds to NH, presence of a singlet at around \(\delta 6.35\) ppm correspond to C3-H of coumarin and a doublet around \(\delta 3.7\) ppm corresponds to S-CH\(_2\) in the \(^1\)HNMR spectrum, while remaining protons resonated in the expected region. Formation of products was also confirmed by \(^{13}\)CNMR and mass spectra.

Coumarinyl thiazolopyrimidines 5(a-f) were prepared by the reaction of 3,4-dihydropyrimidine2-thiones with compounds 2a/2b in 1:1 mixture of acetic acid and acetic anhydride in presence of sodium acetate (Scheme 4). Formation of coumarinyl
thiazolopyrimidines was established by the presence of carbonyl stretch at 1717 cm\(^{-1}\), that corresponds to ester or lactone ring in IR spectra. The \(^1\)HNMR spectra showed the presence of singlet around \(\delta\) 6.6 ppm corresponds to C3-H of coumarin, doublet around \(\delta\) 5.25 ppm corresponds to OCH\(_2\) and the down field shift of C5-H singlet from \(\delta\) 5 to 6 ppm with all the other protons in the expected region. The \(^{13}\)CNMR spectrum of the products further confirmed the assigned structure.

**Table 1.** Physical and analytical data of the compounds 4(a–f) and 5(a–f).

<table>
<thead>
<tr>
<th>Products</th>
<th>Ar</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Mol. formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C(_6)H(_5)</td>
<td>Me</td>
<td>Me</td>
<td>85</td>
<td>137-138</td>
<td>C(<em>{24})H(</em>{22})N(_2)O(_4)S</td>
</tr>
<tr>
<td>4b</td>
<td>3-OCH(_3)C(_6)H(_4)</td>
<td>Et</td>
<td>Me</td>
<td>80</td>
<td>149-150</td>
<td>C(<em>{26})H(</em>{26})N(_2)O(_5)S</td>
</tr>
<tr>
<td>4c</td>
<td>4-OCH(_3)C(_6)H(_4)</td>
<td>Et</td>
<td>OMe</td>
<td>81</td>
<td>144-145</td>
<td>C(<em>{26})H(</em>{26})N(_2)O(_6)S</td>
</tr>
<tr>
<td>4d</td>
<td>(\alpha)-napthyl</td>
<td>Et</td>
<td>OMe</td>
<td>83</td>
<td>140-141</td>
<td>C(<em>{29})H(</em>{26})N(_2)O(_5)S</td>
</tr>
<tr>
<td>4e</td>
<td>C(_4)H(_5)S (Thienyl)</td>
<td>Me</td>
<td>OMe</td>
<td>78</td>
<td>138-139</td>
<td>C(<em>{22})H(</em>{20})N(_2)O(_5)S(_2)</td>
</tr>
<tr>
<td>4f</td>
<td>C(_6)H(_5)</td>
<td>Et</td>
<td>OMe</td>
<td>80</td>
<td>145-146</td>
<td>C(<em>{25})H(</em>{24})N(_2)O(_5)S</td>
</tr>
<tr>
<td>5a</td>
<td>C(_6)H(_5)</td>
<td>Et</td>
<td>Me</td>
<td>74</td>
<td>172-173</td>
<td>C(<em>{34})H(</em>{28})N(_2)O(_6)S</td>
</tr>
<tr>
<td>5b</td>
<td>4-OCH(_3) 3-OCH(_3)C(_6)H(_3)</td>
<td>Et</td>
<td>Me</td>
<td>72</td>
<td>169-170</td>
<td>C(<em>{36})H(</em>{32})N(_2)O(_6)S</td>
</tr>
<tr>
<td>5c</td>
<td>4-OH 3-OCH(_3)C(_6)H(_3)</td>
<td>Et</td>
<td>Me</td>
<td>72</td>
<td>165-166</td>
<td>C(<em>{35})H(</em>{30})N(_2)O(_6)S</td>
</tr>
<tr>
<td>5d</td>
<td>3-OCH(_3)C(_6)H(_4)</td>
<td>Me</td>
<td>OMe</td>
<td>76</td>
<td>174-175</td>
<td>C(<em>{34})H(</em>{28})N(_2)O(_6)S</td>
</tr>
<tr>
<td>5e</td>
<td>C(_6)H(_5)</td>
<td>Me</td>
<td>Me</td>
<td>79</td>
<td>169-170</td>
<td>C(<em>{33})H(</em>{26})N(_2)O(_6)S</td>
</tr>
<tr>
<td>5f</td>
<td>C(_6)H(_5)</td>
<td>Me</td>
<td>OMe</td>
<td>75</td>
<td>170-171</td>
<td>C(<em>{33})H(</em>{26})N(_2)O(_7)S</td>
</tr>
</tbody>
</table>
4.4 Experimental

4.4.1 Analytical methods

Guna melting point apparatus was used to determine the melting point in open capillaries and are uncorrected. The IR spectra were recorded on Nicolet Impact 400D FT IR spectrophotometer using KBr pellets. Bruker 400-MHz FT NMR spectrometer was used to record $^1$H and $^{13}$CNMR in CDCl$_3$ and DMSO-d$_6$ with TMS as internal standard. The reactions and purity of the products were monitored by TLC silica gel plates. Mass spectra were recorded on LC-MSD-Trap-SL spectrometer. Elemental analyses were carried out using CHNS Elimentar (Vario-micro cube).

4.4.2 Procedure for the preparation of 3,4-dihydropyrimidine2-thiones 1(a-h)

Analytical data and procedure for the synthesis of 3,4-dihydropyrimidine2-thiones 1(a-h) is already given in the Chapter 2.

4.4.3 Procedure for the preparation of 4-bromoethylacetoacetate

To an ice cold solution of ethylacetoacetate (10 mmol) in dry ether 25 mL was added bromine drop wise at 0-5 °C during the course of 30 min with vigorous stirring. The mixture was allowed to stand at room temperature for 24 h and added to crushed ice (100 mL). Aqueous layer was decanted off and the oily product was washed with aqueous sodium bicarbonate solution and then by aqueous NaCl solution. It was dissolved in ether and the ethereal solution was dried over sodium sulphate. The solvent was removed and it was used directly in the next reaction.

4.4.4 Procedure for the preparation of substituted 4-bromomethylcoumarins (2a, 2b)

The required substituted 4-bromomethylcoumarins [37] 2a and 2b have been synthesized by the Pechmann cyclization of various phenols with 4-bromoethylacetoacetate [38]. Accordingly, a mixture of 4-bromoethylacetoacetate (10 mmol) and substituted phenol (10 mmol) was cooled to 0 °C. To this mixture, concentrated sulphuric acid (3.2 mL) was added, drop wise with stirring. After the addition of sulphuric acid, the reaction mixture was allowed to stand at room temperature for 24 h. The reaction mixture was then poured onto crushed ice; the separated solid was filtered and washed with ethanol to give the products 2a and 2b.
4.4.5 Procedure for the preparation of compounds 3a and 3b

4-hydroxybenzaldehyde (10 mmol) and anhydrous K$_2$CO$_3$ (1.38 g, 10 mmol) were stirred in dry acetone (30 mL) for 30 min. 4-bromomethyl coumarins 2a/2b (10 mmol) were added, and stirring was continued for 24 h. The reaction mixture was concentrated and poured into ice cold water. The solid separated was filtered and washed with 5% HCl (10 mL) to neutralize the excess of potassium carbonate. Then it was washed with 100 mL of cold water and with ethanol. The crude product was dried and recrystallised from DMF.

4-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-benzaldehyde (3a). Colorless solid, Yield: 77%. M.p: 225-226 °C. IR (KBr) ν cm$^{-1}$: 3043, 2976 (CH), 1715 (lactone C=O), 1694 (aldehyde C=O). $^1$HNMR (400MHz, CDCl$_3$) δ ppm: 2.46 (s, 3H, CH$_3$), 5.34 (s, 2H, OCH$_2$), 6.67 (s, 1H, C3-H), 7.14–7.93 (m, 7H, Ar-H), 9.95 (s, 1H, CHO).

4-(6-Methoxy-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (3b). Colorless solid, Yield: 80%. M.p: 205-206 °C. IR (KBr) ν cm$^{-1}$: 2977 (CH), 1712 (lactone C=O), 1702 (aldehyde C=O). $^1$HNMR (400MHz, CDCl$_3$) δ ppm: 3.88 (s, 3H, OCH$_3$), 5.31 (s, 2H, OCH$_2$), 6.68 (s, 1H, C3-H), 7.00–7.93 (m, 7H, Ar-H), 9.94 (s, 1H, CHO).

4.4.6 Procedure for the preparation of compounds 4(a-f)

A mixture of 3,4-dihydropyrimidine-2-thiones (10 mmol) and anhydrous potassium carbonate (10 mmol) was stirred for 30 min in dry acetone. To this, 1 equivalent of 4-bromomethylcoumarin 1a/1b was added and the stirring was continued for 6 h. Then, the resulting reaction mixture was poured to crushed ice. The separated solid was filtered and washed with ethanol and dried.

Methyl 1,6-dihydro-4-methyl-2-(((6-methyl-2-oxo-2H-chromen-4-yl)methyl)sulfanyl)-6-phenylpyrimidine-5-carboxylate (4a). Light brown solid, IR (KBr) ν cm$^{-1}$: 3328 (NH), 2978 (CH), 1714 (lactone/ester C=O). $^1$HNMR (400MHz, DMSO-d$_6$) δ ppm: 2.23 (s, 3H, CH$_3$), 2.31 (s, 3H, CH$_3$), 3.68 (s, 3H, OCH$_3$), 3.72 (s, 2H, SCH$_2$), 5.51 (s, 1H, C$_3$H of
thiazolopyrimidine), 6.37 (s, 1H, C$_3$H of coumarin), 7.11-7.47 (m, 8H, ArH), 9.70 (s, 1H, NH). %CHNS found (calc): C 66.34 (66.62), H 5.10 (5.12), N 6.45 (6.39), S 7.38 (7.43).

**Ethyl 1,6-dihydro-6-(3-methoxyphenyl)-4-methyl-2-(((6-methyl-2-oxo-2H-chromen-4-yl)methyl)sulfanyl)pyrimidine-5-carboxylate (4b).** Light brown solid, IR (KBr) ν cm$^{-1}$: 3324 (NH), 2974 (CH), 1714 (lactone/ester C=O). $^1$HNMR (400MHz, DMSO-d$_6$) δ ppm: 1.12 (t, J=7.2 Hz, 3H, CH$_2$CH$_3$), 2.21 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 3.65 (s, 3H, OCH$_3$), 3.71 (s, 2H, SCH$_2$), 4.02 (q, J=7.2 Hz, 2H, CH$_2$CH$_3$), 5.50 (s, 1H, C$_3$H of thiazolopyrimidine), 6.35 (s, 1H, C$_3$H of coumarin), 6.67–7.62 (m, 7H, ArH), 9.69 (s, 1H, NH). $^{13}$CNMR (400MHz, DMSO-d$_6$) δ ppm: 14.07, 20.27, 22.70, 29.20, 54.71, 58.87, 59.55, 100.59, 111.65, 112.47, 114.66, 116.41, 118.27, 124.74, 125.00, 129.16, 132.84, 144.88, 145.77, 148.68, 151.27, 154.33, 158.39, 159.47, 166.04, 174.35. Mass (m/z):479 M+1. %CHNS found (calc): C 65.25 (65.23), H 5.48 (5.66), N 5.85 (5.61), S 6.70 (6.49).

**Ethyl 1,6-dihydro-2-(((6-methoxy-2-oxo-2H-chromen-4-yl)methyl)sulfanyl)-6-(4-methoxy phenyl)-4-methylpyrimidine-5-carboxylate (4c).** Light brown solid, IR (KBr) ν cm$^{-1}$: 3325 (NH), 2987 (CH), 1712 (lactone/ester C=O). $^1$HNMR (400MHz, DMSO-d$_6$) δ ppm: 1.07 (t, J=7.2 Hz, 3H, CH$_2$CH$_3$), 2.45 (s, 3H, CH$_3$), 3.76 (s, 3H, OCH$_3$), 3.79 (s, 2H, SCH$_2$), 3.85 (s, 2H, OCH$_3$), 4.07 (q, J=7.2 Hz, 2H, CH$_2$CH$_3$), 5.52 (s, 1H, C$_3$H of thiazolopyrimidine), 6.37 (s, 1H, C$_3$H of coumarin), 7.07–7.48 (m, 7H, ArH), 9.70 (s, 1H, NH). %CHNS found (calc): C 63.14 (63.16), H 5.30 (5.39), N 5.66 (5.41), S 6.48 (6.41).

**Ethyl 1,6-dihydro-2-(((6-methoxy-2-oxo-2H-chromen-4-yl)methyl)sulfanyl)-4-methyl-6-(naphthalen-1-yl)pyrimidine-5-carboxylate (4d).** Light brown solid, IR (KBr) ν cm$^{-1}$: 3330 (NH), 2996 (CH), 1715 (lactone/ester C=O). $^1$HNMR (400MHz, DMSO-d$_6$) δ ppm: 1.05 (t, J=7.2 Hz, 3H, CH$_2$CH$_3$), 2.47 (s, 3H, CH$_3$), 3.77 (s, 2H, SCH$_2$), 3.83 (s, 3H, OCH$_3$), 4.00 (q, J=7.2 Hz, 2H, CH$_2$CH$_3$), 5.92 (s, 1H, C$_3$H of thiazolopyrimidine), 6.37 (s, 1H, C$_3$H of coumarin), 7.29-8.32 (m, 10H, ArH), 9.72 (s, 1H, NH). %CHNS
found (calc): C 67.69 (67.91), H 5.09 (5.03), N 5.44 (4.61), S 6.23 (5.99).

2-(6-Methoxy-2-oxo-2H-chromen-4-ylmethylsulfanyl)-4-methyl-6-thiophen-2-yl-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (4e). Light brown solid, IR (KBr) ν cm⁻¹: 3329 (NH), 2979 (CH), 1711 (lactone/ester C=O). ¹H NMR (400MHz, DMSO-d₆) δ ppm: 2.46 (s, 3H, CH₃), 3.74 (s, 3H, OCH₃), 3.79 (s, 2H, SCH₂), 3.86 (s, 3H, OCH₃), 5.64 (s, 1H, CₛH of thiazolopyrimidine), 6.38 (s, 1H, CₛH of coumarin), 6.97–7.67 (m, 6H, ArH), 9.75 (s, 1H, NH).

%CHNS found (calc): C 57.88 (57.91), H 4.42 (4.72), N 6.14 (5.88), S 14.05 (13.87).

Ethyl 1,6-dihydro-2-((6-methoxy-2-oxo-2H-chromen-4-yl)methylsulfanyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (4f). Light brown solid, IR (KBr) ν cm⁻¹: 3326 (NH), 2972 (CH), 1711 (lactone/ester C=O). ¹H NMR (400MHz, DMSO-d₆) δ ppm: 1.09 (t, J=7.2 Hz, 3H, CH₂CH₃), 2.44 (s, 3H, CH₃), 3.80 (s, 2H, SCH₂), 3.87 (s, 3H, OCH₃), 4.04 (q, J=7.2 Hz, 2H, CH₂CH₃), 5.52 (s, 1H, CₛH of thiazolopyrimidine), 6.34 (s, 1H, CₛH of coumarin), 7.11–7.47 (m, 8H, ArH), 9.73 (s, 1H, NH). %CHNS found (calc): C 64.64 (64.43), H 5.21 (5.60), N 6.03 (5.97), S 6.90 (7.05).

4.4.7 Procedure for the preparation of compounds 5(a-f)

A mixture of 3,4dihydropyrimidine2-thiones (10 mmol), chloroacetic acid (10 mmol), compound 3a/3b (10 mmol) and sodium acetate (1.5 g) in a mixture of glacial acetic acid and acetic anhydride (25 mL; 1:1) was refluxed for 8-10 h. The reaction mixture was concentrated and the solid thus obtained was filtered, washed with water and dried.

7-Methyl-2-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzylidene]-3-oxo-5-phenyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester (5a). Yellow solid, IR (KBr) ν cm⁻¹: 2976 (CH), 1707 (ester/lactone C=O). ¹H NMR (400MHz, CDCl₃) δ ppm: 1.16 (t, J=7.2 Hz, 3H, CH₂CH₃), 2.46 (s, 3H, CH₃), 2.55 (s, 3H, CH₃), 4.11 (q, J=7.2 Hz, 2H, CH₂CH₃), 5.26 (s, 2H, OCH₂), 6.21 (s, 1H, CₛH of thiazolopyrimidine), 6.62 (s, 1H, CₛH of coumarin), 7.07–7.73 (m, 13H, ArH
and arylidene-H). \(^{13}\)CNMR (400MHz, DMSO-d\(_6\)) \(\delta\) ppm: 14.04, 22.18, 29.68, 55.61, 60.61, 65.65, 109.05, 112.71, 113.60, 114.60, 115.65, 117.67, 123.03, 125.68, 126.91, 128.03, 128.68, 128.79, 132.30, 133.75, 139.73, 143.53, 149.01, 151.24, 153.85, 157.16, 159.51, 160.61, 165.02, 165.20. Mass (m/z): 593 M+1. %CHNS found (calc): C 68.90 (68.78), H 4.76 (4.79), N 4.73 (4.63), S 5.41 (5.59).

5-(3,4-Dimethoxy-phenyl)-7-methyl-2-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzyldiene]-3-oxo-2,3-dihydro-5H-thiazolopyrimidine-6-carboxylic acid ethyl ester (5b). Yellow solid, IR (KBr) \(\nu \text{ cm}^{-1}\): 2996 (CH), 1709 (ester/lactone C=O). \(^1\)HNMR (400MHz, CDCl\(_3\)) \(\delta\) ppm: 1.18 (t, \(J=7.2\) Hz, 3H, CH\(_2\)CH\(_3\)), 2.39 (s, 3H, CH\(_3\)), 2.53 (s, 3H, CH\(_3\)), 3.81 (s, 3H, OCH\(_3\)), 3.87 (s, 3H, OCH\(_3\)), 4.11 (q, \(J=7.2\) Hz, 2H, CH\(_2\)CH\(_3\)), 5.23 (s, 2H, OCH\(_2\)), 6.16 (s, 1H, C\(_5\)H of thiazolopyrimidine), 6.60 (s, 1H, C\(_3\)H of coumarin), 6.73–7.71 (m, 11H, ArH and arylidene-H). %CHNS found (calc): C 66.24 (66.32), H 4.94 (4.64), N 4.29 (4.18), S 4.91 (4.65).

5-(4-Hydroxy-3-methoxy-phenyl)-7-methyl-2-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzyldiene]-3-oxo-2,3-dihydro-5H-thiazolopyrimidine-6-carboxylic acid ethyl ester (5c). Yellow solid, IR (KBr) \(\nu \text{ cm}^{-1}\): 2986 (CH), 1706 (ester/lactone C=O). \(^1\)HNMR (400MHz, CDCl\(_3\)) \(\delta\) ppm: 1.16 (t, \(J=7.2\) Hz, 3H, CH\(_2\)CH\(_3\)), 2.43 (s, 3H, CH\(_3\)), 2.53 (s, 3H, CH\(_3\)), 3.81 (s, 3H, OCH\(_3\)), 4.06 (q, \(J=7.2\) Hz, 2H, CH\(_2\)CH\(_3\)), 5.24 (s, 2H, OCH\(_2\)), 6.19 (s, 1H, C\(_5\)H of thiazolopyrimidine), 6.61 (s, 1H, C\(_3\)H of coumarin), 6.89–7.74 (m, 12H, ArH, OH and benzylidene-H). %CHNS found (calc): C 65.82 (65.71), H 4.73 (4.76), N 4.39 (4.63), S 5.02 (5.17).

2-[4-(6-Methoxy-2-oxo-2H-chromen-4-ylmethoxy)-benzyldiene]-5-(3-methoxy-phenyl)7-methyl-3-oxo-2,3-dihydro-5H-thiazolopyrimidine-6-carboxylic acid methyl ester (5d). Yellow solid, IR (KBr) \(\nu \text{ cm}^{-1}\): 2992 (CH), 1707 (ester/lactone C=O). \(^1\)HNMR (400MHz, CDCl\(_3\)) \(\delta\) ppm: 2.51 (s, 3H, CH\(_3\)), 3.79 (s, 3H,
4.5 Conclusion

The structures of all the synthesized compounds were thiazolopyrimidines respectively. These were further reacted with various 3,4 dihydropyrimidine-2-thione to yield a new series of Coumarinyl pyrimidines and Coumarinyl thiazolopyrimidines respectively. The product was obtained with good yield. The structures of all the synthesized compounds were confirmed by spectral studies.
Spectrum 1: IR spectrum of compound 4b.

Spectrum 2: $^1$HNMR (400 MHz) spectrum of compound 4b in DMSO-d$_6$. 
Spectrum 3: $^{13}$CNMR (400 MHz) spectrum of compound 4b in DMSO-d$_6$.

Spectrum 4: Mass spectrum of compound 4b.
Spectrum 5: IR spectrum of compound 5a.

Spectrum 6: $^1$HNMR (400 MHz) spectrum of compound 5a in CDCl$_3$. 
Spectrum 7: $^{13}$CNMR (400 MHz) spectrum of compound 5a in CDCl$_3$.

Spectrum 8: Mass spectrum of compound 5a.
References


