PART-I

(Synthesis)
Synthesis of 5-arylidene/chromonylidene-2-thioxo-1,3-thiazolidine-4-ones (rhodanine) via Knoevenagel condensation of aldehydes and 2-thioxo-1,3-thiazolidine-4-one
INTRODUCTION

During the past several years there has been considerable interest in search for developing insulin-sensitizing agents (Sohda et al., 1982). As a result of these efforts few new generation antidiabetic agents (Reginato et al., 1999; Zhang et al., 2000) like Troglitazone (A), Rosiglitazone (B), Epalrestat (C) are now commercially available as antidiabetic agents (Scheme 1).

![Scheme 1](image-url)
From the scaffold of A, B and C it is well clear that all the clinically used antidiabetic drugs do contain crucial intermediate obtainable via Knoevenagel condensation of rhodanine/2,4-thiazolidinedione with various aldehydes. Apart from antidiabetic activity, rhodanine derivatives possess outstanding pharmacological activities (Shukla et al., 1982; Captan et al., 1996) such as antiviral, antimicrobial, and anticonvulsant effect. Additionally, rhodanine based molecules serves as Hepatitis C virus (HCV) protease inhibitor (Sing et al., 2001), Uridine diphospho-N-acetylmuramate/L-alanine ligase (Sim et al., 2002; Bruna et al., 2002) inhibitor.

Because of its commercial importance, the Knoevenagel condensation of rhodanine with aldehydes has been a subject of considerable interest to effect this condensation efficiently, a large number of catalysts have been explored (Libermann et al., 1948; Heerding et al., 2003; Popov-Pergal et al., 1994; Corma et al., 1990; Muzart et al., 1985; Zhou et al., 2006), sodium acetate in glacial acetic acid, piperidinium benzoate in refluxing toluene, morpholine with acetic acid, zeolite, tetrabutyl ammonium bromide (TBAB), refluxing reactants in toluene at 110 °C for 3 days. Certainly these processes can’t be taken as facile and efficient for the synthesis of 5-arylidene rhodanines as these require long reaction times, high temperature and products thus obtained in unsatisfactory yields.

We and others (Baruah et al., 2002; Saini et al., 2006; Ono et al., 2001; Pushin et al., 1988; Seeback et al., 1991; Sortino et al., 2007; Giles et al., 2000; Sawdey et al., 1950) have been developing LiBr as a mild Lewis acid in many
chemical transformations, including Biginelli condensation, Ehrlich-Sachs reaction, Friedel-Crafts reaction, preparation of acylals and xanthenes etc. Most of the synthetic methods to synthesize the clinically used drugs A, B and C employ Knoevenagel condensation involving aldehyde and rhodanine. It prompted us to use LiBr as a mild Lewis acid as catalyst in this step. This methodical intervention was successful as condensation products were obtained in excellent yield (Scheme 2). This seems to be the first ever report employing LiBr as a Lewis acid catalyst in this commercially important step. In the pursuit of this goal, the first ever LiBr catalyzed microwave enhanced Knoevenagel condensation reaction of rhodanine/2,4-thiazolidinedione with a variety of aldehydes to afford the 5-arylidene rhodanine/2,4-thiazolidinedione in excellent yields in few minutes time was accomplished.

Scheme 2
RESULTS AND DISCUSSION

In a typical experimental procedure, rhodanine (2 mmol) and benzaldehyde (2 mmol) and LiBr (0.2 m mol) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 800 W for 5 minutes. After completion of reaction (monitored via TLC), the reaction mixture was cooled to room temperature. About 15 ml of water was added and stirred for 5 minute. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford 5-benzylidene rhodanine 4a in 88 % yield, Mp 204-206 °C Lit. Mp 204- 206 °C. The analytical and spectroscopic data fully support the structural assignment for compound 4a. The ¹H NMR spectra of 5-benzylidene rhodanine shows diagnostic peak at δ = 13.57 (s, 1H NH), 7.68 (s, 1H, =CH) and IR values are \( \nu_{\text{max}}/\text{cm}^{-1} = 3390, 1669, 1600, 1429, 1200 \). The mass spectrum of 4a revealed a strong peak at \( m/z = 220 \) (M⁺).

Similarly, other aromatic aldehydes were condensed with rhodanine/2,4-thiazolidinedione following similar procedure to obtained 5-arylidene rhodanine/2,4-thiazolidinedione 4b-e/5a-c in 84-90 % yields. Under these conditions, reaction time was reduced dramatically and reaction got completed within 4-8 minutes. Aldehydes with electron withdrawing as well as electron donating substituents reacted well with rhodanine, see Table 1. Where LiI was used in place of LiBr, reaction showed incremental increase in results in term of yield and time. This protocol is fairly large
in scope, with very good yields and use of microwave have shorten the reaction time from hours to minutes.

Encouraged by these results, this protocol was extended to other 5-membered heterocycles like 2,4-thiazolidinedione 2 and 3-methyl-1-phenylpyrazol-5-one 6. The condensation of 2,4-thiazolidinedione with aldehydes got completed within 7-8 minutes and the 5-arylidene thiazolidinediones 5a-c were obtained in 80-88 % yield (Table 1, entry 6-8). When 3-methyl-1-phenylpyrazol-5-one was condensed with anisaldehyde, 4-anisylidene-3-methyl-1-phenylpyrazol-5-one was obtained in 83 % yield and reaction got completed in 9 minute (Scheme 3, Table 1, entry 9).

![Scheme 3.](image)

Followed by these results, this protocol was further extended to biologically important heterocyclic aldehydes viz. 3-formylchromones (Gerwick et al., 1979). The substrate 4-oxo-4H-benzopyran-3-carbaldehyde has three active sites; the unsaturated carbonyl group i.e. the pyrone ring, a carbon-carbon double bond and a formyl group. Of these, the formyl group has the highest reactivity towards active methylene compounds (Polyakov et al., 1981; Treibs et al., 1981; Prousek et al., 1993; Prajapati
et al., 1992; Baruah et al., 1988; Baruah et al., 1987; Nohara et al., 1974; Bandyopadhyay et al., 2000; Bandyopadhyay et al., 2002; Ghosh et al., 2008; Lacova et al., 1998; Lacova et al., 1998; Lacova et al., 2000; Lacova et al., 2005; Sabitha et al., 1996; Shingare et al., 1999; Karale et al., 2002; Hangarge et al., 2002). In case of 3-formylchromones, rodanine condensation took place in water, without the involvement of catalysts, at room temperature.

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{R}^1
\end{align*}
\]

Scheme 4.

Knoevenagel condensation of 2,4-thiazolidinedione with 3-formylchromones (Nohara et al., 1974) afforded chromonylidene-rhodanine derivatives in excellent yields see table 2. The structure of the synthesized chromonylidene compounds was elucidated by elementary analysis, \(^1\)H NMR, mass spectral data and IR findings. All spectral data 9a-f were in accordance with assumed structures. IR spectra of compounds showed γ-pyrone C=O stretching bonds at 1634-1660 cm\(^{-1}\). In \(^1\)H NMR spectra, chromone protons were observed between \(\delta_H\) 7.55 and 9.06; methylene protons (\(=\text{CH}\)) for chromonylidene-rhodanines were observed at \(\delta_H\) 7.58-7.77 as a singlet.
To conclude, a quick, clean and simple method for the synthesis of chromonylidene-rhodanines, 5-arylidene rhodanines, 5-arylidene thiazolidinediones and 4-arylidene pyrazol-5-ones was developed – A method employing mild Lewis Acid LiBr as a catalyst, a fairly general method, giving higher yields, got reaction time reduced to few minutes. Overall this new procedure is fairly attractive as being economical as well as a green process.
Table 1. LiBr catalyzed condensation of active methylene compounds with aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar</th>
<th>Products&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (min)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
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<td><img src="image1" alt="Substrate_1" /></td>
<td><img src="image2" alt="Ar_1" /></td>
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<td><img src="image3" alt="Substrate_2" /></td>
<td><img src="image4" alt="Ar_2" /></td>
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<tr>
<td>3</td>
<td><img src="image5" alt="Substrate_3" /></td>
<td><img src="image6" alt="Ar_3" /></td>
<td>4c</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate_4" /></td>
<td><img src="image8" alt="Ar_4" /></td>
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<td>84</td>
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<tr>
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<td>86</td>
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<tr>
<td>6</td>
<td><img src="image11" alt="Substrate_6" /></td>
<td><img src="image12" alt="Ar_6" /></td>
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<tr>
<td>7</td>
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<td><img src="image18" alt="Ar_9" /></td>
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<td>9</td>
<td>83</td>
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</table>

<sup>a</sup> All product were characterized by Mp. and spectral (IR, <sup>1</sup>H NMR) data.

<sup>b</sup> Yields refers to pure isolated products.
Table 2. Condensation of active methylene compounds with 3-formylchromones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>( R )</th>
<th>( R^1 )</th>
<th>Products&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
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<td>H</td>
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<tr>
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<td></td>
<td>H</td>
<td>CH₃</td>
<td>9b</td>
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<tr>
<td>3</td>
<td></td>
<td>H</td>
<td>(CH₃)₂CH</td>
<td>9c</td>
<td>4</td>
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</tr>
<tr>
<td>4</td>
<td></td>
<td>H</td>
<td>Cl</td>
<td>9d</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>H</td>
<td>NO₂</td>
<td>9e</td>
<td>7</td>
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<td></td>
<td>CH₃</td>
<td>CH₃</td>
<td>9f</td>
<td>7</td>
<td>88</td>
</tr>
</tbody>
</table>

<sup>a</sup> All product were characterized by Mp. and spectral (IR, \(^1\)H NMR) data.

<sup>b</sup> Yields refers to pure isolated products.
EXPERIMENTAL

General procedure for arylidene rhodanines/2,4-thiazolidinediones/ pyrazol-5-ones :

Aldehyde (20 mmol) and active methylene compound (20 mmol) and LiBr (10 mol%) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 800 W for time given in Table 1. After completion of reaction (monitored via TLC), the reaction mixture was cooled to room temperature. Added 15 ml of water, stirred for 5 minute. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford product 4a-e, 5a-c and 7.

General procedure for 3-Formylchromones:

To the dry dimethylformamide (121 ml) in a three necked flask, POCl₃ (0.49 mol) was added slowly with intensive stirring at 50 °C. Heating and stirring was continued for 2 hrs at 45 - 55 °C. The solution of 2-hydroxyacetophenone (0.12 mol) in DMF (25 ml) was then slowly added under stirring at 50 °C. The stirring was continued for 2 hrs at 55 - 60 °C. After cooling the mixture was kept over night at room temperature and diluted slowly by adding crushed ice (500 g) and stirred again for 6 hrs. The crystals were filtered off and recrystallized from alcohol.
General procedure for chromonylidene-rhodanines:

3-formylchromones (20 mmol) and rhodanine (20 mmol) were stirred in water in small conical flask at room temperature. The progress of reaction was monitored via TLC. After completion of reaction, the reaction mixture was filtered, dried and recrystallized from DMF or 1,4-dioxane to afford products 9a-f (Table 2, entry 1-6).

Selected spectral data:

(E)-5-benzylidene-2-thioxothiazolidin-4-one (4a):

Mp. 204-206 °C
IR, ν_max /KBr/cm⁻¹: 3390, 1669, 1600, 1429, 1200.
¹H NMR (300 MHz, DMSO-d₆) δ_H: 7.48-7.79 (m, 5H, Ar-H), 7.68 (s, 1H, =CH), 13.57 (s, 1H, NH).
MS (ESI) m/z (rel. intensity): 220 (M - H, 100%).
Anal. Calcd. for C₁₀H₇NOS₂: C, 54.27; H, 3.19; N, 6.33; S, 28.98 %; found: C, 54.55; H, 3.81; N, 6.83; S, 29.28 %.

(E)-5-(4-chlorobenzylidene)-2-thioxothiazolidin-4-one (4b):

Mp. 228-230 °C
IR, ν_max /KBr/cm⁻¹: 3390, 1661, 1598, 1431, 1202.
¹H NMR (300 MHz, DMSO-d₆) δ_H: 7.43 (d, 2H, J = 8.5 Hz, Ar-H), 7.67 (d, 2H, J = 8.6 Hz, Ar-H), 7.74 (s, 1H, =CH), 12.97 (s, 1H, NH).
MS (ESI) m/z (rel. intensity): 254 (M - H, 100%).
Anal. Calcd. for C\textsubscript{10}H\textsubscript{6}ClNOS\textsubscript{2}: C, 46.96; H, 2.36; N, 5.48; S, 25.08 %; found: C, 47.76; H, 2.71; N, 5.98; S, 25.17 %.

(E)-5-(3-nitrobenzylidene)-2-thioxothiazolidin-4-one (4c):
Mp. 263-264 °C
IR, \( \nu_{\text{max}} / \text{KBr/cm}^{-1} \): 3396, 1679, 1600, 1423, 1204.
\(^1\)H NMR (300 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \( \delta_H \): 7.31 (d, 2H, \( J = 8.0 \) Hz, Ar-H), 7.53 (d, 2H, \( J = 8.0 \) Hz, Ar-H), 7.65 (s, 1H, =CH), 13.45 (s, 1H, NH).
MS (ESI) \( m/z \) (rel. intensity): 265 (M - H, 100%).

Anal. Calcd. for C\textsubscript{10}H\textsubscript{6}N\textsubscript{2}O\textsubscript{3}S\textsubscript{2}: C, 45.10; H, 2.27; N, 10.52; S, 24.08 %; found: C, 45.54; H, 2.82; N, 11.12; S, 24.31 %.

(E)-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one (4d):
Mp. 249-250 °C
IR, \( \nu_{\text{max}} / \text{KBr/cm}^{-1} \): 3393, 1671, 1605, 1434, 1201.
\(^1\)H NMR (300 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \( \delta_H \): 3.09 (s, 3H, OCH\textsubscript{3}), 7.08 (d, 2H, \( J = 8.2 \) Hz, Ar-H), 7.52 (d, 2H, \( J = 8.2 \) Hz, Ar-H), 7.61 (s, 1H, =CH), 13.71 (s, 1H, NH).
MS (ESI) \( m/z \) (rel. intensity): 250 (M - H, 100%).

Anal. Calcd. for C\textsubscript{11}H\textsubscript{9}NO\textsubscript{2}S\textsubscript{2}: C, 52.57; H, 3.61; N, 5.57; S, 25.52 %; found: C, 52.78; H, 3.95; N, 5.48; S, 25.79 %.

(E)-5-(4-methylbenzylidene)-2-thioxothiazolidin-4-one (4e):
Mp. 221-223 °C
IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 3390, 1671, 1605, 1430, 1203.

$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.22 (s, 3H, CH$_3$), 7.18 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.57 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.64 (s, 1H, =CH), 13.45 (s, 1H, NH).

MS (ESI) $m/z$ (rel. intensity): 234 (M - H, 100%).

Anal. Calcd. for C$_{11}$H$_9$NOS$_2$: C, 56.14; H, 3.85; N, 5.95; S, 27.25%; found: C, 55.97; H, 3.62; N, 6.03; S, 27.57%.

(Z)-5-Phenylmethylene-2,4-thiazolidinedione (5a):

Mp. 247-249 °C

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 3142, 1693, 1609.

$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.49 (3H, m, ArH), 7.57 (2H, m, ArH), 7.77 (1H, s, =CHAr), 12.6 (1H, bs, NH).

$^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$: 123.60, 129.41, 130.08, 130.53, 131.92, 133.08, 167.40, 168.00;

MS (ESI) $m/z$ (rel. intensity): 204 (M - H, 100%).

Anal. Calcd. for C$_{10}$H$_7$NO$_2$S: C, 58.52; H, 3.44; N, 6.82; S, 15.62%; found: C, 59.02; H, 3.91; N, 6.73; S, 16.09%.

(Z)-5-(4-Methoxyphenylmethylene)-2,4-thiazolidinedione (5b):

Mp. 217-218 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 3221, 1730, and 1694.

$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 3.82 (3H, s, OCH$_3$), 7.09 (2H, m, ArH), 7.55 (2H, m, ArH), 7.74 (1H, s, =CHAr), 12.49 (1H, bs, NH).
$^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$C: 55.50, 114.93, 120.25, 129.10, 131.87, 132.11, 160.99, 167.44, 167.98.

MS (ESI) m/z (rel. intensity): 234 (M - H, 100%).

Anal. Calcd. for C$_{11}$H$_9$NO$_3$S: C, 56.16; H, 3.86; N, 5.95; S, 13.63 %; found: C, 55.89; H, 3.96; N, 5.90; S, 13.21 %.

(Z)-5-(4-Hydroxyphenylmethylene)-2,4-thiazolidinedione (5c):

Mp. >300 ºC.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 3426, 3403, 3123, 1725, 1719, 1704, 1680.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$H: 6.90 (2H, m, ArH), 7.43 (2H, m, ArH), 7.68 (1H, s, =CHAr), 10.28 (1H, s, ArOH), 12.42 (1H, bs, NH).

$^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$C: 116.32, 118.95, 123.92, 132.33, 132.38, 159.89, 167.46, 168.03.

MS (ESI) m/z (rel. intensity): 220 (M - H, 100%).

Anal. Calcd. for C$_{10}$H$_7$NO$_3$S: C, 54.29; H, 3.19; N, 6.33; S, 14.49 %; found: C, 54.65; H, 3.32; N, 6.02; S, 14.11 %.

(Z)-4-(4-methoxybenzylidene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (7):

M.p. 124–125 ºC.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.36 (s, 3H, CH$_3$), 3.45 (s, 3H, OCH$_3$), 7.21 (t, 1H), 7.32 (s, 1H), 7.43 (t, 2H), 7.65 (d, 2H), 7.95 (d, 2H), 8.39 (d, 2H).

MS (ESI) m/z (rel. intensity): 291 (M - H, 100%).
Anal. Calcd. for C_{18}H_{16}N_{2}O_{2}: C, 73.95; H, 5.52; N, 9.58 %; found: C, 74.15; H, 5.87; N, 10.03 %.

5-[(4-Oxo-4H-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidine-4-one (9a)

Mp.: 259-260 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 1647 (γ pyrone CO);

$^1$H NMR: δ 7.54 (ddd, 1H, 6-H), 7.62 (s, 1H, C=C-H), 7.71 (d, 1H, J_{8,7} = 8.41 Hz, 8-H), 7.98 (ddd, 1H, 7-H), 8.17 (dd, 1H, J_{5,6} = 8.41 Hz, J_{5,7} = 1.68 Hz, 5-H), 8.83 (s, 1H, 2-H), 12.41 (s, 1H, NH);

MS (ESI) m/z (rel. intensity): 288 (M - H, 100%).

Anal. Calcd. for C_{13}H_{7}NO_{3}S: C, 53.98; H, 2.42; N, 4.84; S, 22.15 %; found: C, 53.84; H, 2.74; N, 4.95; S, 21.96 %.

5-[(6-Methyl-4-oxo-4H-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidine-4-one (9b)

Mp.: 196-197 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 1649 (γ pyrone CO);

$^1$H NMR: δ 2.52 (s, 3H, CH$_3$), 7.52 (s, 1H, C=C-H), 7.66 (d, 1H, J_{8,7} = 8.80 Hz, 8-H), 7.77 (dd, 1H, J_{7,8} = 8.48 Hz, J_{7,5} = 2.44 Hz, 7-H), 7.95 (d, 1H, J_{5,7} = 1.62 Hz, 5-H), 8.78 (s, 1H, 2-H), 12.42 (s, 1H, NH);

MS (ESI) m/z (rel. intensity): 302 (M - H, 100%).

Anal. Calcd. for C_{14}H_{9}NO_{3}S_{2}: C, 55.45; H, 2.97; N, 4.62; S, 21.12 %; found: C, 55.66; H, 2.80; N, 5.00; S, 20.85 %.
5-[(6-Isopropyl-4-oxo-4H-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidine-4-one (9c)

Mp.: 182-183 °C.

IR, \( \nu_{\text{max}} / \text{KBr/cm}^{-1} \): 1651 (\( \gamma \) pyrone CO);

\(^1\)H NMR : \( \delta \) 1.34 (d, 6H, CH\( \_3 \)), 3.17-3.23 (m, 1H, CH), 7.60 (s, 1H, C=CH), 7.59 (d, 1H, J\( _{8,7} \) = 8.83 Hz, 8-H), 7.84 (dd, 1H, J\( _{7,8} \) = 8.83 Hz, J\( _{7,5} \) = 2.44 Hz, 7-H), 7.97 (d, 1H, J\( _{5,7} \) = 2.45 Hz, 5-H), 8.81 (s, 1H, 2-H), 12.45 (s, 1H, NH);

MS (ESI) \( m/z \) (rel. intensity): 330 (M - H, 100%).

Anal. Calcd. for C\(_{16}\)H\(_{13}\)NO\(_3\)S\(_2\).0.1H\(_2\)O: C, 58.01; H, 3.93; N, 4.23; S, 19.34 %; found: C, 58.11; H, 4.23; N, 4.44; S, 19.71%.

5-[(6-Chloro-4-oxo-4H-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidine-4-one (9d)

Mp.: 201-203 °C.

IR, \( \nu_{\text{max}} / \text{KBr/cm}^{-1} \): 1650 (\( \gamma \) pyrone CO);

\(^1\)H NMR : \( \delta \) 7.50 (s, 1H, C=CH), 7.85 (d, 1H, J\( _{8,7} \) = 9.45 Hz, 8-H), 7.93 (dd, 1H, J\( _{7,8} \) = 9.38 Hz, J\( _{7,5} \) = 2.85 Hz, 7-H), 8.48 (d, 1H, J\( _{5,7} \) = 2.85 Hz, 5-H), 8.86 (s, 1H, 2-H), 12.58 (s, 1H, NH);

MS (ESI) \( m/z \) (rel. intensity): 324 (M - H, 100%).

Anal. Calcd. for C\(_{13}\)H\(_6\)ClNO\(_3\)S\(_2\).0.1H\(_2\)O: C, 48.00; H, 1.85; N, 4.31; S, 19.69 %; found: C, 47.96; H, 2.01; N, 4.55; S, 19.43 %.
5-[(6-Nitro-4-oxo-4H-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidine-4-one (9e)

Mp.: 219-221 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 1652 (γ pyrone CO);

$^1$H NMR : $\delta$ 7.63 (s, 1H, C=C-H), 8.21 (d, 1H, J$_{8,7} = 9.62$ Hz, 8-H), 8.67 (dd, 1H, J$_{7,8} = 9.60$ Hz, J$_{7,5} = 2.84$ Hz, 7-H), 8.79 (d, 1H, J$_{5,7} = 2.84$ Hz, 5-H), 8.95 (s, 1H, 2-H), 12.57 (s, 1H, NH);

MS (ESI) $m/z$ (rel. intensity): 333 (M - H, 100%).

Anal. Calcd. for C$_{13}$H$_6$N$_2$O$_5$S$_2$·0.1H$_2$O: C, 46.71; H, 1.80; N, 8.38; S, 19.16 %; found: C, 46.96; H, 1.49; N, 8.51; S, 19.47 %.

5-[(6,8-Dimethyl-4-oxo-4H-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidine-4-one (9f)

Mp.: 247-248 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 1655 (γ pyrone CO);

$^1$H NMR : $\delta$ 2.44 (s, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$), 7.61 (s, 1H, 7-H), 7.69 (s, 1H, C=C-H), 7.71 (s, 1H, 5-H), 8.87 (s, 1H, 2-H), 12.54 (s, 1H, NH);

MS (ESI) $m/z$ (rel. intensity): 316 (M - H, 100%).

Anal. Calcd. for C$_{15}$H$_{11}$NO$_3$S$_2$·0.1H$_2$O: C, 56.78; H, 3.47; N, 4.42; S, 20.19 %; found: C, 56.67; H, 3.63; N, 4.79; S, 20.34 %.
CHAPTER – I : SECTION – 2

Synthesis of 5-arylidene/chromonylidene -2,4-Thiazolidinediones via. Knoevenagel condensation of aldehydes and 2,4-thiazolidinedione
INTRODUCTION

Thiazolidinedione and its derivatives represents a group of chemical compounds with significant pharmacological activities like anti-bacterial (DeLima et al., 1992), antidiabetic (Strumvoll et al., 2002), cardiotonic (Andreani et al., 1993), anticonvulsant (El-Feky et al., 1993), antiproliferative (Peuler et al., 1996), antifungal (Goes et al., 1991; Lesyk et al., 2004). In addition, thiazolidinedione based molecules have become popular as small molecule inhibitors such as aldose reductase (Seno et al., 2000). Therefore, the synthesis of thiazolidinedione derivatives is an area, currently of great interest for synthetic chemists. The methylene group at fifth position of 2,4-thiazolidinedione being relatively more reactive (Baranov et al., 1961; Katritzky et al., 2000), most of the alterations on this particular position to synthesize new biologically important molecules (Lesyk et al., 2002; Lesyk et al., 2004). The significant synthetic method to the synthesize 5-arylidene-2,4-thiazolidinediones is Knoevenagel condensation of aromatic aldehydes with 2,4-thiazolidinedione using different catalyst systems and varying the reaction conditions like piperidine in EtOH, AlPO₄-Zeolite in EtOH:H₂O, polyethylene glycol etc. (Sachan et al., 2007; Gadekar et al., 2008; Mahalle et al., 2008). A careful scrutiny of above reported synthetic protocols, it was concluded that a scope of further improvement in these synthetic procedures for 5-arylidene-2,4-thiazolidinediones was still there as some of limitations of these procedures were longer reaction times and some affording not very good yields.
Recently, bismuth (III) compounds have attracted much attention of synthetic Chemists due to their low toxicity, low cost, mild, relatively insensitive to air and small amounts of moisture. Bismuth has an electron configuration of [Xe]4f^{14}5d^{10}6s^{2}6p^{3}. Due to the weak shielding of the 4f electrons (lanthanide contraction), bismuth (III) compounds exhibit Lewis acidity and they have been used in many chemical transformations (Suzuki et al., 2002; Postel et al., 1996; Bhatti et al., 2010; Suresh et al., 2010). Bismuth trichloride is particularly attractive because it is not only commercially available and inexpensive, but also of high stability. Herein, we wish to report that in an effort to optimizes various limitations of procedure, an efficient BiCl₃-catalyzed knoevenagel reaction of aromatic aldehydes and 2,4-thiazolidinediones, to afford the corresponding products in high yields under mild reaction conditions was developed.

\[
\text{CHO} \quad \rightarrow \quad \text{NH} \quad \text{O} \quad \text{O} \quad \text{R} \quad \text{R} \quad \text{S} \quad \text{R} \quad \text{R} \quad \text{1} \quad \text{2} \quad \text{3}
\]

Scheme 1.
RESULTS AND DISCUSSION

In a typical experimental procedure, 2,4-thiazolidinediones (2 mmol) and benzaldehyde (2 mmol) and BiCl₃ (0.2 m mol) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations for 3 minutes. After completion of reaction (monitored via TLC), the reaction mixture was cooled to room temperature. Added 15 ml of water, stirred for 5 minute. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford 5-benzylidene 2,4-thiazolidinediones 3a in 98 % yield, Mp 240 °C Lit. Mp 240-242 °C. The analytical and spectroscopic data fully support the structural assignment for compound 3a. The ¹H NMR spectra of 5-benzylidene 2,4-thiazolidinediones shows diagnostic peak at δ = 12.27 (s, 1H NH), 7.86 (s, 1H, =CH), 7.26 (5H, m, aromatic protons) and IR values are νmax/cm⁻¹ = 3155 (NH), 3049, 879 (CH; aromatic), 2868 (CH; aliphatic), 1739, 1691 (C=O). The mass spectrum of 3a revealed a strong peak at m/z – 204 (M - H, 100%).

Similarly, other aromatic aldehydes were condensed with 2,4-thiazolidinedione following similar procedure to obtaine 5-arylidene 2,4-thiazolidinedione 3b-n in 89-98 % yields. Under these conditions, reaction time reduced dramatically and reaction got completed within 3-8 minutes reaction time (table 2). Electron withdrawing and electron donating substituents on aryl aldehydes does not effect products yields and reaction rate, clearly the catalyst was effective.
over a wide range of aryl aldehydes. This protocol is fairly large in scope, yields are very good and use of microwave has shortened the reaction from hours to minutes.

In order to optimize the amount of catalyst, it was found only 10 mol % was enough for this protocol and more than 10 mol % did not effect any drastic changes in reaction time and yields.

Further, on similar lines, the present protocol was extended to condense heterocyclic aldehydes viz. 3-formylchromones 4a-f, 2,4-thiazolidinedione. This Knoevenagel condensation was carried out by refluxing the reactants in acetic acid/anhydrous sodium acetate for 5h, (Scheme 2). The required starting reactants 4-oxo-4H-benzopyran-3-carbaldehydes or 3-formylchromones was prepared by Vilsmeir-Haack reaction (Nohara et al., 1974).

Scheme 2.

2,4-thiazolidinedione condensed with 3-formylchromones via. Knoevenagel reaction to afford corresponding chromonyl-2,4-TZD derivatives 5a-f in excellent yields (table 2). The structure of the synthesized chromonyl compounds was elucidated by elementary analysis, 1H NMR, mass spectral data and IR findings. All
spectral data were in accordance with assumed structures. IR spectra of compounds showed γ-pyrone C=O stretching bonds at 1634-1660 cm\(^{-1}\). In \(^1\)H NMR spectra, chromone protons were observed between δ\(_\text{H}\) 7.55 and 9.06; methylene protons (=CH) for chromonyl-2,4-TZDs were observed at δ\(_\text{H}\) 7.58-7.77 as a singlet.

To summarize, the present method of employing BiCl\(_3\) as a catalyst in Knoevenagel condensation, is a mild, efficient and environment benign protocol for the synthesis of 5-arylidene-2,4-thiazolidinediones. Products were obtained in excellent yields in short reaction time. The evident factor in favor of present protocol is the use of inexpensive catalyst and a well-known non-toxic inorganic salt. Furthermore, operational simplicity, easy work-up are the other attractive features of this procedure. These features place this protocol at superior position to the existing ones. Needless to say during no hazardous/unsafe corrosive by-products were encountered during the aqueous work up of products thus obtained in this novel method.
Table 1. BiCl₃ catalysed synthesis of 5-arylidene-2,4-thiazolidinediones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>Product ¹</th>
<th>Time (min)</th>
<th>Yield (%) b</th>
<th>m.p. [Lit.] (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>3a</td>
<td>3</td>
<td>98</td>
<td>240[240-242]</td>
</tr>
<tr>
<td>2</td>
<td>MeO</td>
<td>H</td>
<td>H</td>
<td>3b</td>
<td>4</td>
<td>97</td>
<td>235-236[235-238]</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>3c</td>
<td>5</td>
<td>95</td>
<td>268-269[267-268]</td>
</tr>
<tr>
<td>4</td>
<td>CF₃</td>
<td>H</td>
<td>H</td>
<td>3d</td>
<td>3.5</td>
<td>87</td>
<td>234-235[234-236]</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>3e</td>
<td>6</td>
<td>94</td>
<td>214-216[215-216]</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>NO₂</td>
<td>H</td>
<td>3f</td>
<td>7.5</td>
<td>92</td>
<td>196-197[197]</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>3g</td>
<td>6.5</td>
<td>89</td>
<td>277-278[278-280]</td>
</tr>
<tr>
<td>8</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>3i</td>
<td>5</td>
<td>94</td>
<td>282-283[282-285]</td>
</tr>
<tr>
<td>9</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>3k</td>
<td>6.5</td>
<td>89</td>
<td>267-268[266-268]</td>
</tr>
<tr>
<td>10</td>
<td>OH</td>
<td>MeO</td>
<td>H</td>
<td>3l</td>
<td>5</td>
<td>93</td>
<td>195[194-196]</td>
</tr>
<tr>
<td>11</td>
<td>MeO</td>
<td>MeO</td>
<td>H</td>
<td>3m</td>
<td>4</td>
<td>90</td>
<td>181-182[181-183]</td>
</tr>
<tr>
<td>12</td>
<td>Me₂N</td>
<td>H</td>
<td>H</td>
<td>3n</td>
<td>8</td>
<td>91</td>
<td>281-282[282-283]</td>
</tr>
</tbody>
</table>

¹ The products were characterized by comparison of their melting points and spectral (IR, ¹H NMR) data with those of authentic samples. ² Isolated yields after recrystallization.

(Lit.: Sachan et al., 2007, Gadekar et al., 2008)
Table 2. Condensation of active methylene compounds with 3-formylchromones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Products&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>H</td>
<td>H</td>
<td>5a</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5b</td>
<td>5</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>H</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CH</td>
<td>5c</td>
<td>7</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>H</td>
<td>Cl</td>
<td>5d</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>H</td>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5e</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5f</td>
<td>6</td>
<td>88</td>
</tr>
</tbody>
</table>

<sup>a</sup> All product were characterized by Mp. and spectral (IR, <sup>1</sup>H NMR) data.

<sup>b</sup> Yields refers to pure isolated products.
EXPERIMENTAL

General procedure for preparation of trans-Cinnamic Acids

Aryl aldehydes (10 mmol), 2,4-thiazolidinediones (10 mmol) and BiCl$_3$ (0.1 mmol) were mixed for 3-4 min in Erlenmeyer flask. Irradiated this reaction mixture under MWI for time given in Table-1 using solvent free condition. After completion of reaction (Monitored via TLC), crude product was cooled and washed with water and filtered. Which was then recrystallized from ethanol.

General procedure for chromonyl-2,4-TZDs:

A mixture of 2,4-TZD 1 (20 mmol) and 3-formylchromones (20 mmol) was heated at 100 °C in the presence of 10 mL glacial acetic acid and sodium acetate (20 mmol) for 5 h. After reaction completion (as followed by TLC), excess solvent was evaporated under reduced pressure. The obtained crude product was crystallized from DMF/ethanol to afford chromonyl-2,4-TZDs 5a-f in good to excellent yields (Table 2, entry 1-6).
Selected spectral data:

(Z)-5-Phenylmethylene-2,4-thiazolidinedione (3a):

Mp. 240 °C

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 3142, 1693, 1609.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta_H$: 7.49 (3H, m, ArH), 7.57 (2H, m, ArH), 7.77 (1H, s, =CHAr), 12.6 (1H, bs, NH).

$^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta_C$: 123.60, 129.41, 130.08, 130.53, 131.92, 133.08, 167.40, 168.00;

MS (ESI) m/z (rel. intensity): 204 (M - H, 100%).

Anal. Calcd. for C$_{10}$H$_7$NO$_2$S: C, 58.52; H, 3.44; N, 6.82; S, 15.62 %; found: C, 59.02; H, 3.91; N, 6.73; S, 16.09 %.

(Z)-5-(4-Methoxyphenylmethylene)-2,4-thiazolidinedione (3b):

Mp. 217-218 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 3221, 1730, 1694.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta_H$: 3.82 (3H, s, OCH$_3$), 7.09 (2H, m, ArH), 7.55 (2H, m, ArH), 7.74 (1H, s, =CHAr), 12.49 (1H, bs, NH).

$^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta_C$: 55.50, 114.93, 120.25, 131.87, 132.11, 160.99, 167.44, 167.98.

MS (ESI) m/z (rel. intensity): 234 (M - H, 100%).

Anal. Calcd. for C$_{11}$H$_9$NO$_3$S: C, 56.16; H, 3.86; N, 5.95; S, 13.63 %; found: C, 55.89; H, 3.96; N, 5.90; S, 13.21 %.
(Z)-5-(4-chlorophenylmethylene)-2,4-thiazolidinedione (3c):

Mp. 268-269 °C.

IR, $\nu_{\text{max}}$ /KBr/cm$^{-1}$: 3148, 1719, 1610.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$H: 7.53 (2H, m, ArH), 7.72 (2H, m, ArH), 7.76 (1H, s, =CHAr), 12.65 (1H, bs, NH).

$^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$C: 123.88, 124.35, 130.54, 131.76, 132.24, 132.29, 167.05, 167.48.

MS (ESI) m/z (rel. intensity): 238 (M - H, 100%).

Anal. Calcd. for C$_{10}$H$_6$ClNO$_2$S: C, 50.11; H, 2.52; N, 5.84; S, 13.38 %; found: C, 49.87; H, 2.63; N, 5.92; S, 13.78 %.

(Z)-5-(4-Hydroxyphenylmethylene)-2,4-thiazolidinedione (3i):

Mp. >300 °C.

IR, $\nu_{\text{max}}$ /KBr/cm$^{-1}$: 3426, 3403, 3123, 1725, 1719, 1704, 1680.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$H: 6.90 (2H, m, ArH), 7.43 (2H, m, ArH), 7.68 (1H, s, =CHAr), 10.28 (1H, s, ArOH), 12.42 (1H, bs, NH).

$^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$C: 116.32, 118.95, 123.92, 132.33, 132.38, 159.89, 167.46, 168.03.

MS (ESI) m/z (rel. intensity): 220 (M - H, 100%).

Anal. Calcd. for C$_{10}$H$_7$NO$_3$S: C, 54.29; H, 3.19; N, 6.33; S, 14.49 %; found: C, 54.65; H, 3.32; N, 6.02; S, 14.11 %.
5-[(4-Oxo-4H-chromen-3-yl)methylene]thiazolidine-2,4-dione (10a)

Mp.: 290 °C.

IR, $\nu_{max}$/KBr/cm$^{-1}$: 1637 ($\gamma$ pyrone CO).

$^1$H NMR: $\delta$ 7.58 (ddd, 1H, 6-H), 7.61 (s, 1H, C=C-H), 7.74 (d, 1H, $J_{8,7} = 8.40$ Hz, 8-H), 7.88 (ddd, 1H, 7-H), 8.13 (dd, 1H, $J_{5,6} = 8.40$ Hz, $J_{5,7} = 1.60$ Hz, 5-H), 8.85 (s, 1H, 2-H), 12.48 (s, 1H, NH).

MS (ESI) $m/z$ (rel. intensity): 272 (M - H, 100%).

Anal. Calcd. for C$_{13}$H$_7$NO$_4$S: C 57.14, H 2.58, N 5.13, S 11.73%; found: C 56.84, H 2.74, N 5.25, S 11.46%.

5-[(6-Methyl-4-oxo-4H-chromen-3-yl)methylene]thiazolidine-2,4-dione (10b)

Mp.: 257 °C.

IR, $\nu_{max}$/KBr/cm$^{-1}$: 1646 ($\gamma$ pyrone CO);

$^1$H NMR: $\delta$ 2.42 (s, 3H, CH$_3$), 7.58 (s, 1H, C=C-H), 7.61 (d, 1H, $J_{8,7} = 8.80$ Hz, 8-H), 7.67 (dd, 1H, $J_{7,8} = 8.40$ Hz, $J_{7,5} = 2.40$ Hz, 7-H), 7.90 (d, 1H, $J_{5,7} = 1.60$ Hz, 5-H), 8.79 (s, 1H, 2-H), 12.42 (s, 1H, NH);

MS (ESI) $m/z$ (rel. intensity): 286 (M - H, 100%).

Anal. Calcd. for C$_{14}$H$_9$NO$_4$S: C 58.53, H 3.16, N 4.88, S 11.16%; found: C 58.26, H 3.30, N 5.00, S 10.85%.

5-[(6-Isopropyl-4-oxo-4H-chromen-3-yl)methylene]thiazolidine-2,4-dione (10c)

Mp.: 242 °C.

IR, $\nu_{max}$/KBr/cm$^{-1}$: 1650 ($\gamma$ pyrone CO);
$^1$H NMR: δ 7.61 (s, 1H, C=C-H), 8.01 (d, 1H, J$_{8,7}$ = 9.60 Hz, 8-H), 8.51 (dd, 1H, J$_{7,8}$ = 2.80 Hz, 7-H), 8.68 (d, 1H, J$_{5,7}$ = 2.80 Hz, 5-H), 8.86 (s, 1H, 2-H), 12.54 (s, 1H, NH);

MS (ESI$^+$) $m/z$ (rel. intensity): 308 (M - H, 100%).

Anal. Calcd. for C$_{13}$H$_6$ClNO$_4$S0.1H$_2$O: C 50.49, H 1.94, N 4.53, S 10.36%; found: C 50.56, H 2.21, N 4.39, S 10.57%.

5-[(6-Chloro-4-oxo-4H-chromen-3-yl)methylene]thiazolidine-2,4-dione (10d)

Mp.: 268 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 1654 (γ pyrone CO);

$^1$H NMR: δ 7.61 (s, 1H, C=C-H), 8.01 (d, 1H, J$_{8,7}$ = 9.60 Hz, 8-H), 8.51 (dd, 1H, J$_{7,8}$ = 9.20 Hz, J$_{7,5}$ = 2.80 Hz, 7-H), 8.68 (d, 1H, J$_{5,7}$ = 2.80 Hz, 5-H), 8.86 (s, 1H, 2-H), 12.54 (s, 1H, NH);

MS (ESI$^+$) $m/z$ (rel. intensity): 308 (M - H, 100%).

Anal. Calcd. for C$_{13}$H$_6$ClNO$_4$S0.1H$_2$O: C 50.49, H 1.94, N 4.53, S 10.36%; found: C 50.56, H 2.21, N 4.39, S 10.57%.

5-[(6-Nitro-4-oxo-4H-chromen-3-yl)methylene]thiazolidine-2,4-dione (10e)

Mp.: 277 °C.

IR, $\nu_{\text{max}}$/KBr/cm$^{-1}$: 1654 (γ pyrone CO);

$^1$H NMR: δ 7.61 (s, 1H, C=C-H), 8.01 (d, 1H, J$_{8,7}$ = 9.60 Hz, 8-H), 8.63 (dd, 1H, J$_{7,8}$ = 9.20 Hz, J$_{7,5}$ = 2.80 Hz, 7-H), 8.78 (d, 1H, J$_{5,7}$ = 2.80 Hz, 5-H), 8.93 (s, 1H, 2-H), 12.54 (s, 1H, NH);
MS (ESI) m/z (rel. intensity): 317 (M - H, 100%).

Anal. Calcd. for C_{13}H_{6}N_{2}O_{6}S0.1H_{2}O: C 47.71, H 2.14, N 8.56, S 9.78%; found: C 47.96, H 2.41, N 8.50, S 9.47%.

5-[(6,8-Dimethyl-4-oxo-4H-chromen-3-yl)methylene]thiazolidine-2,4-dione (10f)

Mp.: 298 °C.

IR, \( \nu_{\text{max}} / \text{KBr/cm}^{-1} \): 1654 (\( \gamma \) pyrone CO);

\(^1\)H NMR : \( \delta \) 2.40 (s, 3H, CH\(_3\)), 2.44 (s, 3H, CH\(_3\)), 7.57 (s, 1H, 7-H), 7.60 (s, 1H, C=C-H), 7.75 (s, 1H, 5-H), 8.83 (s, 1H, 2-H), 12.44 (s, 1H, NH);

MS (ESI) m/z (rel. intensity): 300 (M - H, 100%).

Anal. Calcd. for C_{15}H_{11}NO_{4}S0.1H_{2}O: C 59.43, H 3.69, N 4.62, S 10.56%; found: C 59.30, H 3.60, N 4.79, S 10.34%.