Synthesis and Biological Evaluation of Some Coumarin Derivatives
N. Prabu¹, Mansur Ahmed¹ and S. Guhanathan²*,
¹ PG and Research Department of Chemistry, Islamiah College (Autonomous), Vaniyambadi - Tamil Nadu, India
² PG and Research Department of Chemistry, Muthurangam Govt. Arts College, (Autonomous), Vellore – 632 002, Tamil Nadu, India.
*Email: sai_gugan@yahoo.com

Abstract: Coumarin belongs to the family of benzopyrone found to have lot of biologically important. The present investigation focused on the synthesis of four derivatives from 4-Hydroxy-chromen-2-one and characterized using spectral (FTIR, ¹H and ¹³C-NMR), Thermal (TGA) and morphological studies (SEM).

Keywords: Ethyl Bromopropionate, Biological activity, SEM and TGA.

I. INTRODUCTION

Coumarins belong to a group compounds known as the benzopyrones, all of which consist of a benzene ring joined to a pyrone. Coumarin and the other members of the coumarin family are benzo-α-pyrones, while the other main members of the benzopyrone group contain the pyrone group (Keating and O’Kennedy, 1997). Coumarins may also be found in nature in combination with sugars, as glycosides.

Coumarins shows a number of diverse biological and pharmaceutical activities, including plant growth regulation,¹ insecticidal action,² antioxidant,³ anticoagulant,⁴ anti-tumor activity,⁵ estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscasidal, antithelmintic, sedative and hypnotic, analgesic and hypothermic activity.⁶-¹⁵

Hence, the scope of the present investigation aimed in developing new coumarin derivatives, thus by, modifying the methyl substitution using ethyl bromopropionate and investigating their antibacterial activity against the micro organisms like staphylococcus aureus, E.coli and Klebsiella.

Many coumarin compounds after some suitable structure modification can be used as drugs.¹⁶ The structures of all compounds were established on the bases of IR and ¹H NMR.

II. MATERIALS AND METHODS
a. Ethyl 2-[(2-oxo-2H-chromen-4-yl)oxy]propanoate (1)

A suspension of 4-hydroxy coumarin (6.10 mmol) in acetone (30 ml) was refluxed with ethylbromo propionate (9.15 mmol) in presence of K₂CO₃ (4.69 g, 33.91 mmol) for 12 hrs. After cooling the mixture was evaporated to dryness and the residue was portioned between CHCl₃ (50 ml) and water (50 ml). The organic phase was dried Na₂SO₄, filtered and evaporated to dryness, recrystallized from acetone. MP: 120°C. FT-IR 1743 (C=O Carbonyl stretching), 1695 (Lactonic-C=O Carbonyl stretching). ¹H NMR spectrum shows ester methyl and methylene of ethyl group respectively ppm 1.282 (d, 3H, CH₃), 4.268 (t, 2H, CH₂). 5.744 ppm shows the proton in coumarin ring. The aromatic regions are 7.260 to 7.928 ppm. (d, 4H). ¹³C NMR spectrum shows ppm 170 (Coumarin carbonyl carbon, 164.53) Ester carbonyl, ppm162.58 Coumarin CH. Ppm 153.69, 124.09, 116.78, 115.48, 123.40, 132.40, & (aromatic region), 62.11 (ester -CH₂), 18.03 (CH₃), 14.17 (ester –CH₃).

b. 2-[(2-oxo-2H-chromen-4-yl)oxy]propane hydrazide (2)

A solution of compound 1 (0.1 mol) and hydrazine hydrate in acetone 0.02 ml, 2 ml in acetone was refluxed for 5–6 hr. Completion of reaction was judged by TLC. After cooling, the reaction mixture was poured into ice cold water. The solid was collected by filtration, dried and recrystallized from acetone. mp: 192-195°C. FT-IR 3398 (-NH-NH₂), 1769 (-C=O Carbonyl stretching), 1707 (Lactonic-C=O Carbonyl stretching). ¹H NMR spectrum shows ppm 1.763 (d, 3H, CH₃), 4.909 (m, 1H, CH), 5.373 (s, 1H, CH), 8.493 (1H, NH), 7.926 (d, 2H, NH₂). ¹³C NMR spectrum shows 169.25, 163.65 & 161.27 (Carbonyl region) 132.9, 124.24 & 122.92 (Aromatic region), 17.38 (CH₃).

c. 2-[(2-oxo-2H-chromen-4-yl)oxy]-N’-[(E)-phenylmethylidene] propanehydrazide (2a)

An equimolar mixture of 2 and an aromatic aldehyde was refluxed for 5-6 hr. Completion of reaction was judged by TLC. After cooling, the reaction mixture was poured into ice cold water. The solid was collected by filtration, dried and recrystallized from acetone. FT-IR 3396 (NH-NH₂), 1753 (C=O Carbonyl stretching), 1680 (Lactonic-C=O Carbonyl stretching), 1250 (C-O). The ¹H NMR spectrum shows ppm 1.760 (d, 2H, CH-CH₃), 4.907 (m, 1H, CH), 5.537 (s, 1H, CH), 10.013 (s, 1H, NH) (s, 1H, N=CH), around 7 is aromatic proton. ¹³C NMR spectrum shows ppm 169.51, 163.64 & 161.27 (Carbonyl region). 132.9, 124.24 & 122.92 (Aromatic region), 17.38 (CH₃).

d. N’-[(E)-(4-chlorophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy] propanehydrazide (2b)

Pale yellow solid, recrystallized from acetone, mp: 206-208°C, FT-IR 3394 (NH-NH₂), 1739 (C=O, Carbonyl stretching), 1705 (Lactonic-C=O Carbonyl stretching), 1616, (C=N-NH), 761(-C-Cl). The ¹H NMR spectrum shows ppm 1.644 (d, 3H, CH₃), 5.383 (m, 1H, CH), 5.811 (s, 1H, CH), 9.860 (s, 1H, N=CH), 10.013 (s, 1H, NH). ¹³C NMR spectrum shows ppm 169.52, 163.65 & 161.27 (Carbonyl region), 152 (N=C-H), 17.38 (CH-CH₃). ¹³C NMR spectrum shows ppm 169.52, 163.65 & 161.27 (Carbonyl region), 152.73 (CH-CH₃), 132.90, 124.22, 122.91, 116.39 & 114.89 (Aromatic region), 91.40 (N=C-H), 17.37 (CH-CH₃).

e. N’-[(E)-(4-methoxyphenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy] propanehydrazide (2c)

Yellow solid, recrystallized from acetone, mp: 190-193°C. FT-IR 1735 (C=O Carbonyl stretching), 1703 (Lactonic-C=O Carbonyl stretching), 1614 (C=N-NH). The ¹H NMR spectrum shows ppm 1.643 (d, 3H, CH₃), 3.023 (s, 3H, OCH₃), 5.575 (m, 1H, CH), 5.807 (s, 1H, CH), 9.685 (s, 1H, N=CH), 9.987 (s, 1H, NH). ¹³C NMR spectrum shows ppm 169.51, 163.64 & 161.27 (carbonyl region), 132.87, 131.70, 131.25, 124.20, 122.90, 116.38 & 114.89 (aromatic region), 152.73 (N=C-H), 61.31 (O-CH₃), 17.37 (CH-CH₃).
f. N’-[(E)-4-(dimethylamino)phenyl][methylidene]-2-[(2-oxo-2H-chromen-4-yloxy)propanehydrazide (2d)

Pale orange solid, recrystallised from acetone, mp: 197-199°C, FT-IR 1741 (-C=O Carbonyl stretching), 1695 (Lactonic-C=O Carbonyl stretching), 1614 (-C=N-NH), 1327 (-C=N-(CH3)). 1H NMR spectrum shows ppm 1.644 (d, 3H, CH3), 3.030 (s, 3H, N(CH3))2, 5.380 (m, 1H, CH), 5.812 (s, 1H, CH), 9.664 (s, 1H, N=CH), 9.899 (s, 1H, NH). 13C NMR spectrum shows ppm 169.52, 163.65 & 161.28 (carbonyl region), 152.73 (N=C-H), 132.90, 131.72, 131.45, 124.46, 124.23, 116.41 & 114.91 (aromatic region), 17.38 (CH-CH3).

g. N’-[(E)-(4-hydroxyphenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yloxy)propanehydrazide (2e)

Yellow solid, recrystallised from acetone, mp: 216-218°C, FT-IR 3464 (-OH), 1745 (-C=O Carbonyl stretching), 1695 (Lactonic-C=O Carbonyl stretching), 1614 (-C=N-NH) 1327 (-C=N-(CH3)). 1H NMR spectrum shows ppm 1.644 (d, 3H, CH3), 5.381 (m, 1H, CH), 5.810 (s, 1H, CH), 9.653 (s, 1H, N=CH), 9.901 (s, 1H, NH), 10.594 (s, 1H, OH). 13C NMR spectrum shows ppm 169.52, 163.65 & 161.28 (carbonyl region), 152.73 (N=C-H), 132.89, 124.22, 122.91, 116.40 & 114.90 (aromatic region), 17.38 (CH-CH3).

III. Thermal studies

According to the TGA and DTG data, the thermal degradation occurs in two stage decomposition. The relative thermal stability of different organic compounds and composites was assessed by comparing the weight loss in temperature range ambient to 750°C. TGA of all prepared organic compounds 1, 2, 2a, 2b, 2c, 2d & 2e showed weight loss in two stages.

Table.1 Thermal studies on synthesized coumarin derivatives

<table>
<thead>
<tr>
<th>Compd. Code.</th>
<th>Temperature in percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10% 20% 30% 40% 50% 60% 70% 80% 90% 100%</td>
</tr>
<tr>
<td>1</td>
<td>212 230 241 255 260 266 270 276 285 355</td>
</tr>
<tr>
<td>2</td>
<td>218 226 240 255 263 270 276 280 282 410</td>
</tr>
<tr>
<td>2A</td>
<td>205 223 238 245 252 261 270 275 280 360</td>
</tr>
<tr>
<td>2B</td>
<td>218 228 240 252 260 265 270 276 283 340</td>
</tr>
<tr>
<td>2C</td>
<td>219 236 246 255 260 270 174 289 283 375</td>
</tr>
<tr>
<td>2D</td>
<td>176 202 218 230 240 248 260 270 275 290</td>
</tr>
<tr>
<td>2E</td>
<td>219 232 244 250 268 275 281 290 293 400</td>
</tr>
</tbody>
</table>

Thermogravimetric analysis was employed to get information on thermal stability of the prepared organic compounds. It can be observed that all samples have undergone two stage decomposition with the major weight loss occurring between 280 to 430 °C. The peak temperature and the percentage of residue of all the samples for the both decomposition are listed Table. 1 The 10% weight loss of all compounds was observed at 212, 218, 205, 218, 219, 176 and 219 °C respectively. The 20% weight loss found to have around 230 °C for all compounds. Similarly 50% weight loss was observing around 260 °C. The maximum 70% weight loss have been observe at around 270 °C. Whereas 2D was found to have only at 260 °C. This might be due to the lesser hardness imparted by the compound 2D.
IV. Antimicrobial activity

The newly synthesized compounds were screened for their antimicrobial activities in vitro against two species of Gram-positive bacteria Bacillus subtilis (NCTC- 10400) (BS), Staphylococcus aureus (NCTC 7447) (SA), and three Gram-negative bacteria, Escherichia coli (NCTC 10410) (EC), Candida albicans (IMRU 3669) (CA), and one fungus, Aspergillus niger (ATCC 6275) (AN). The activities of these compounds were tested using the disc diffusion method. The area of zone of inhibition was measured using neomycin (30 g mL⁻¹) as standard antibiotic

<table>
<thead>
<tr>
<th>MICROORGANISM</th>
<th>Control</th>
<th>1</th>
<th>2</th>
<th>2A</th>
<th>2B</th>
<th>2C</th>
<th>2D</th>
<th>2E</th>
<th>CIPROFLOXACIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus cereus (mm)</td>
<td>-</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Staphylococcus aureus (mm)</td>
<td>-</td>
<td>13</td>
<td>14</td>
<td>12</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Escherichia coli (mm)</td>
<td>-</td>
<td>9</td>
<td>12</td>
<td>14</td>
<td>9</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MICROORGANISM</th>
<th>Control</th>
<th>1</th>
<th>2</th>
<th>2A</th>
<th>2B</th>
<th>2C</th>
<th>2D</th>
<th>2E</th>
<th>Amphotericin-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans (mm)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Penicillium sps (mm)</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Aspergillus niger (mm)</td>
<td>-</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>11</td>
<td>10</td>
<td>-</td>
<td>9</td>
</tr>
</tbody>
</table>

V. CONCLUSIONS

A synthesis of coumarin derivatives was prepared. The chemical structures of synthesize compounds were determined according to extensive NMR data. The antimicrobial activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria and fungi. The compound 2 showed moderate bacterial activity.

REFERENCES