CHAPTER-5

SYNTHESIS OF BIOLOGICALLY IMPORTANT COUMARIN DERIVATIVES FROM 3-BROMO-4-HYDROXYCOUMARIN

5.1. REVIEW & LITERATURE

5.1.1. Biological importance.

The synthesis of coumarin derivatives has attracted considerable attention of organic and medicinal chemists as these compounds are widely used as fragrances, pharmaceuticals and agrochemicals.¹ Coumarins possess a variety of bioactivities including estrogenic, dermal, photosensitizing, antimicrobial, vasodilative, molluscacidal, anthelmintic, sedative-hypnotic, analgesic and hypothermic activity.¹² Furthermore, three coumarin antibiotics, novobiocin, chlorobiocin and coumermycin A1 exhibit significant activity on certain tumor cells.³ Various skin diseases are treated using photochemotherapy with linear furanocoumarins (psoralens) followed by irradiation with UVA.⁴ Coumarins constitute an important class of compound due to their presence as an important constituent of natural products⁵ as well as their variety of medicinal applications such as anti-inflammatory,⁶ anticonvulsant,⁷ antiviral,⁸ antioxidant,⁹ antibacterial,¹⁰ antifungal,¹¹ anti-HIV,¹² anticarcinogenic,¹³ antihistamine¹⁴ etc.
5.1.2. Biologically active coumarin derivatives

5.1.2a. Representative biologically active coumarins

- Wedelolactone
  (Venomous snakebite antidote)
- Carbochromen
  (Coronary Vasodilator)
- Novobiocin
  (Antibiotic)
- Seselin
  (Anti-HIV)

5.1.2b. Anticancer active coumarin
5.1.2c. Antioxidant coumarins

\[
\begin{align*}
R^1 &= H, Cl \\
R^2 &= CH_3, CH_2Cl, CH_2OH, CH_2Si(CH_2)_2CH_3, C_6H_5 \\
R^3 &= H, OH \\
R^4 &= H, OCH_3 \\
R^5 &= H, OH, OCOCH_3 \\
R^6 &= H, OH, COOH, COOCH_3, OCOCH_3.
\end{align*}
\]

5.1.2d. Antimicrobial coumarins

\[
\begin{align*}
R^1 &= H \\
R^2 &= CH_2Cl, C_6H_5
\end{align*}
\]
5.1.3. Chemical relevance

Besides the wide spectrum biological applications of coumarin and its derivatives the chemical literature also embodies their some applications from the material viewpoint such as cosmetics, optical brightening agents and laser dyes. A recent literature report has revealed the anion sensing ability of some coumarin derivatives. Coumarin derivatives afford a range of organic materials that are used commercially in a broad range of applications because of their intense fluorescence. They not only operate as enzyme substrates for fluorimetric titrations in biomedical analysis but also provide a fundamental structure for the numerous fluorescent probes and advanced photo physical systems. In addition, coumarin derivatives are intensively used in the coloring or fluorescent whitening of textiles and other materials.

Naturally occurring coumarins are found in several plants, including grasses, orchids, citrus fruits, and legumes, and are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis and defense against infection. Coumarins also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones, and 2-acylresorcinols. It is, therefore, of importance that the synthesis of coumarin derivatives should be achieved by an effective method.

5.2. PRESENT WORK

In continuation of our work on the synthesis of coumarin derivatives and the development of novel synthetic methodologies, herein this chapter we are reporting one pot, efficient and simple methodology for the synthesis of coumarin derivatives by the reaction of 3-bromo-4-hydroxycoumarin with various heteroaldehydes.
5.3. RESULTS AND DISCUSSION

4-Hydroxycoumarin possesses nucleophilic character due to the presence of carbon-carbon double bond at position 3 and reacts with aldehydes and ketones to give dicoumarol derivatives.\textsuperscript{28,29} It was expected, therefore, that 3-bromo-4-hydroxycoumarin would also react with aldehydes to give dicoumarol derivatives. The reaction, as felt, afforded 3a-c in quantitative yields (76-81\%) by refluxing in methanol, 1 and heteroaldehydes 2a-c in the presence of catalytic amount of pyridine (Scheme 1). However, the reaction of 1 with 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde 2d did not stop at dicoumarol product (3e) stage, instead subsequent cyclization took place to give pyrazolopyrone 3d in good yield (80\%) (Table 1). A probable route for the formation of 3d has been shown in Scheme 2. The structural assignment of the compounds isolated was done by elemental and spectral (IR, \textsuperscript{1}H NMR, Mass) analysis.

The high molecular weight of the compound 3b in the electron spray mass spectrum (M\textsuperscript{+} = 494.16) (Fig. 3), indicated the incorporation of more than one coumarin moiety in the product. The infra red (IR) spectrum (Fig. 1) exhibited a strong absorption bands at 1636 and 1710 cm\textsuperscript{-1} for the carbonyl groups of chromone and coumarin moieties respectively. Absorption band at 1572 cm\textsuperscript{-1} was due to C=C of coumarin units. Another absorption band at 3437 cm\textsuperscript{-1} was assigned to OH group of coumarin unit. The proton nuclear magnetic resonance (\textsuperscript{1}H NMR) spectrum (Fig. 2) showed a sharp singlet at \(\delta\) 2.42 for the methyl protons of chromone moiety. The upfield singlet of methine proton appeared at \(\delta\) 6.25. The 11 aromatic protons (three protons of chromone moiety and 8 protons of coumarin units) were discernible in the form of multiplet at \(\delta\) 7.33-8.01. Diagnostic singlet of C-2 proton of chromone moiety was present as sharp singlet at \(\delta\) 7.66. Another
singlet (D$_2$O exchangeable) at $\delta$ 11.20 integrating for more than one proton was assigned to OH protons of coumarin units. Further confirmation for the structure 3b, was provided by mass spectrum (Fig. 3) which has given subsequent fragmentation pattern. The spectral studies of the other compounds followed similar pattern.

5.4. CONCLUSION

In summary we have developed a clean and convenient method to synthesize new coumarin derivatives in good yields. The method is advantageous in terms of reduced reaction time, high yield of products, simple experimental work-up procedure etc. thus, adding a useful procedure to existing methodologies.

Scheme 1. Synthetic pathway of products (3a-d)
Scheme 2. Mechanism of formation of product 3d.
Table 1. Synthesis of compounds 3a-d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>Molecular Structure</th>
<th>Time (h)</th>
<th>Yield (°C)</th>
<th>M.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td><img src="image1" alt="Molecular Structure" /></td>
<td>3</td>
<td>76</td>
<td>&gt;300</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td><img src="image2" alt="Molecular Structure" /></td>
<td>3.5</td>
<td>78</td>
<td>&gt;300</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td><img src="image3" alt="Molecular Structure" /></td>
<td>2.5</td>
<td>81</td>
<td>242-245</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td><img src="image4" alt="Molecular Structure" /></td>
<td>3</td>
<td>80</td>
<td>270-272</td>
</tr>
</tbody>
</table>

*All yields refer to isolated products.*
5.5. EXPERIMENTAL
Melting points of all synthesized compounds were taken in Riechert Thermover instrument and are uncorrected. The IR spectra (KBr) were recorded on Perkin Elmer RXI spectrometer. $^1$H NMR spectra were recorded on Bruker DRX-300 and Bruker Avance II-400 spectrometer using tetramethyl silane (TMS) as the internal standard and DMSO-$d_6$ as solvent. Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC DART-MS spectrometer, Micromass Quattro II triple quadrupol mass spectrometer and Jeol-SX-102 (FAB) spectrometer. Elemental analyses (C, H, and N) were conducted using Carlo Erba analyzer model 1108. 3-Bromo-4-hydroxycoumarin$^{40}$ 3-formylchromone, 6-methyl-3-formylchromone$^{31}$ indole-3-carboxaldehyde$^{32}$ and 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde$^{33}$ were prepared by reported procedures. Other chemicals were purchased from Merck (Mumbai, India), Sigma-Aldrich (Switzerland) and used without further purification. The purity of all compounds was checked by TLC on glass plates (20 x 5 cm) coated with silica gel (E-Merck G$_{254}$ 0.5 mm thickness). The plates were run in chloroform-methanol (3:1) mixture and were visualized by iodine vapours.

5.5.1. General procedure for the preparation of coumarin derivatives (3a-d)
To a solution of 3-bromo-4-hydroxycoumarin 1 (4.14 mmol) in methanol (12 mL), containing 0.4 mL of pyridine, heteroaldehyde 2a-d (2.07 mmol) was added. The reaction mixture was refluxed on a heating mantle for 2.5-3.5 hours. After completion of the reaction (checked by TLC), the reaction mixture was cooled at room temperature. The solid part separated out was collected by filtration, dried and recrystallized either from chloroform or from benzene to afford 3a-d in pure form.
Spectral data

1,1-Bis(4-hydroxy-1-benzopyran-2-one-3-yl)-1-(4-oxo-4H-1-benzopyran-3-yl)methane (3a)

Purified by recrystallization from chloroform.

White powder.

Yield : 76 %

M.p : >300 °C.

IR (KBr) \( \nu_{\text{max}} / \text{cm}^{-1} \) : 1570 (C=C), 1633 (C=O), 1708 (C=O), 3428 (OH).

\(^1\text{H} \text{NMR} (300 \text{ MHz, DMSO-d}_{6}) \) : \( \delta \) (ppm) 6.02 (s, 1H, CH), 7.18-7.79 (m, 11H, Ar-H), 7.88 (d, 1H, \( J=7.8 \) Hz, C-5, chromone), 7.98 (s, 1H, C-2, chromone), 11.31 (s, 2H, OH).

MS-ESI : \( m/z \) 480.13 (M\(^+\)), 453.12, 451.11, 320.08, 319.08, 317.06, 99.11.

Elemental analysis for C\(_{28}\)H\(_{16}\)O\(_8\) : Calculated C, 70.01; H, 3.35. Found C, 70.18; H, 3.42 %.

1,1-Bis(4-hydroxy-1-benzopyran-2-one-3-yl)-1-(6-methyl-4-oxo-4H-1-benzopyran-3-yl)methane (3b)

Purified by recrystallization from chloroform.

White powder.

Yield : 78 %
M.p : >300 °C.

IR (KBr) ν_{max}/cm^{-1} : 1572 (C=C), 1636 (C=O), 1710 (C=O), 3437 (OH).

^1^H NMR (400 MHz, DMSO-d$_6$) : δ (ppm) 2.42 (s, 3H, CH$_3$), 6.25 (s, 1H, CH). 7.33-8.01 (m, 11H, Ar-H), 7.66 (s, 1H, C-2, chromone), 11.20 (s, 2H, OH).

MS-ESI : m/z 494.16 (M'), 493.16, 318.07, 317.06, 277.15, 99.11, 74.09.

Elemental analysis for C$_{29}$H$_{18}$O$_8$ : Calculated C, 70.44; H, 3.66. Found C, 70.56; H, 3.69%.

1,1-Bis(4-hydroxy-1-benzopyran-2-one-3-yl)-1-(indol-3-yl)methane (3c)

Purified by recrystallization from chloroform.

Yellow solid.

Yield : 81%

M.p : 242-245 °C.

IR (KBr) ν_{max}/cm^{-1} : 1290 (C-N), 1572 (C=C), 1719 (C=O), 3065 (NH), 3398 (OH).

^1^H NMR (400 MHz, DMSO-d$_6$) : δ (ppm) 5.04 (s, 1H, CH), 6.46 (s, 1H, -C=C- H, indole), 6.81-7.97 (m, 11H, Ar-H), 10.43 (s, 1H, NH), 11.63 (s, 2H, OH).

MS-ESI : m/z 451.3 (M'), 446.3, 413.5, 377.4, 375.4, 360.6, 358.6, 332.6, 274.6, 238.5, 225.5, 134.5, 116.5.
Elemental analysis for

C$_{27}$H$_{17}$NO$_6$ : Calculated C, 71.83; H, 3.79; N, 3.10.

Found C, 71.91; H, 3.64, N, 3.06 %.

4-(4-Hydroxy-2-oxo-2H-1-benzopyran-2-one-3-yl)-3-methyl-1-phenylpyrazolo[3,4-
2,3]-4H-pyran[3,2-b]-1-benzopyran-5-one (3d)

Purified by recrystallization from benzene.

White crystals.

Yield : 80 %

M.p : 270-272 °C.

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1368 (C=N), 1608 (C=N), 1633 (C=C), 1719 (C=O), 3480 (OH).

$^1$H NMR (300 MHz, DMSO-d$_6$) : $\delta$ (ppm) 2.50 (s, 3H, CH$_3$), 4.67 (s, 1H, CH), 7.09-8.40 (m, 13H, Ar-H), 11.38 (s, 1H, OH).

MS- FAB (% rel. int) : $m/z$ 490 (M$^+$, 25), 329 (50), 331 (60), 346 (5), 302 (15), 318 (25), 317 (100), 269 (90), 267 (85), 185 (5), 150 (20), 149 (70), 142 (5), 115 (50).

Elemental analysis for

C$_{29}$H$_{18}$N$_3$O$_6$ : Calculated C, 71.02; H, 3.69; N, 5.71.

Found C, 71.09; H, 3.81; N, 5.63 %.
Fig. 1. IR spectrum of 3b.
Fig. 2. $^1$H NMR spectrum of 3b.

Solvent- DMSO, Frequency- 400.129 MHz
Fig. 3. Mass spectrum of 3b.

Data Name: 9AUG093E
Sample Id: CB Mode: MUSTHAFA AKU [411]
Mode: F5H
Calibration Name: YOKOKERUK [FS2_2000]
Acquired m/z Range: 10.0, 1050.0
Present DateTime: 6/17/2009 13:14 PM
Sample Comments, DART
Spec. Record Interval: 0.400
Ring Lens Volt: 120V
Time of Maximum: 0.120[ms]
Operator Name: admin

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5.6. REFERENCES


25. (a) Riordan, D. J.; Daly, I. *J. Med. Sci.* 1954, 6, 157.


