Synthesis of heteroaryl substituted benzo[c]coumarins

The work incorporated in this chapter is on the synthesis of various 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins, 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins and 7-hydroxy-9-(1-methyl-1H-pyrrol-2-yl)benzo[c]coumarins. The compounds have been synthesized by reacting various 3-coumarinoyl methyl pyridinium bromide salts with 2-acetyl furan or 2-acetyl thiophene or 2-acetyl-1-methyl pyrrole in the presence of sodium acetate in refluxing acetic acid. The structures of all the synthesized compounds have been supported by analytical and spectral data.

4.4 Introduction

The fusion of benzene ring between 3rd and 4th position of coumarin moiety results in a formation of benzo[c]coumarin (I). Many benzo[c]coumarin derivatives are isolated as natural products and are synthesized in laboratories as well. Alternariol\textsuperscript{24} and its related derivatives like Autumnariol\textsuperscript{25}, Autumnarinio\textsuperscript{25} and Altenuisol\textsuperscript{26} are toxic secondary metabolites of various Alternaria fungi. Gilvocarcin\textsuperscript{27}, Ravidomycin\textsuperscript{28} and Chrysomycins\textsuperscript{29} are c-glycoside antibiotics. They are isolated from various strains of streptomyces species. Arnottin\textsuperscript{30} and Defucogilvocarcin\textsuperscript{31} are natural products of the class of Gilvocarcine family and possess an antitumor activity\textsuperscript{32}. 
Various benzo[c]coumarin derivatives have been synthesized by different group of researchers utilizing different methods. Some selected reports on the synthesis of benzo[c]coumarin derivatives are documented below.

*W R H Hurtley*\textsuperscript{33} has synthesized 3-hydroxy benzo[c]coumarin by coupling α-bromo benzoic acid with resorcinol in the presence of CuSO\textsubscript{4} under alkaline condition.

\begin{equation}
\begin{array}{c}
\text{HO} \quad \text{HO} \\
\text{Br} \quad \text{Br} \\
\text{CuSO}_4 \quad \text{NaOH}
\end{array}
\rightarrow
\begin{array}{c}
\text{HO} \quad \text{O} \\
\text{CO} \\
\end{array}
\end{equation}

*Y Yamamoto et al*\textsuperscript{34} have reported the synthesis of 8-(n-butyl) and 9-(n-butyl) benzo[c]coumarins by the reaction of benzene derivative having ester-tether α,ω-diyne functionality and 1-hexyne in the presence of Ru(II)-catalyst.
B I Alo et al\(^{35}\) prepared biphenyl derivatives (II) (II were prepared in four steps from substituted benzamides) which were converted into benzo[c]coumarin derivatives by dealkylation, amide hydrolysis and cyclization.

H Togo et al\(^{36}\) have synthesized benzo[c]coumarin by photocyclization of biphenyl 2-carboxylic acid (III) using [bis(trifluoroacetoxy)-iodo] benzene and free iodine as a radical generators.

P Langer et al\(^{37}\) prepared 2,3-dihydro benzopyran derivatives (IV) (IV were prepared in three steps from benzopyran-4-one) and they were transformed into benzo[c]coumarins by the treatment of triethylamine and ethanol via biphenyl intermediate (IVa).

M S Tremblay and D Sames\(^{38}\) have synthesized benzo[c]coumarins by lactonization of appropriate biphenyl derivatives (V), which were prepared from aromatic boronic acids in three steps.
T H Harris and J V Hay have synthesized 1-methyl-3,7,9-trihydroxy benzo[c]coumarin (alternariol) from 3,5,7,9,11,13-hexaoxotetradecanoic acid by the treatment of NaOAc/AcOH. The acid undergoes 8,13- and 2,7-aldol cyclizations and results a biphenyl intermediate which further cyclizes to alternariol.

The survey of above methods for the synthesis of benzo[c]coumarins reveals that in majority of the methods the benzo[c]coumarin moiety has been built up by lactonization of appropriately substituted biphenyls.

With a view to developing a new method for the synthesis of benzo[c]coumarin, the present work was carried out. In the present work a new method for the synthesis of benzo[c]coumarin has been developed in which a benzene ring has been built up between 3rd and 4th position of a preformed coumarin moiety.

The compounds having furan, thiophene and N-methyl pyrrole in their skeleton are reported to possess important biological activities such as antitumor, antifungal, microsomal prostaglandin E2 synthase-1 inhibitor, human MAO-B inhibitors etc.
Considering the importance of aforementioned heteroaryl moieties, it was thought worthwhile to synthesize such heteroaryl substituted benzo[c]coumarins and therefore in the present work synthesis of various 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins, 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins and 7-hydroxy-9-(1-methyl-1H-pyrrol-2-yl)benzo[c]coumarins has been carried out.

4.5 Present work

It is reported that the sodium acetate catalyzed reaction of α,β-unsaturated ketones (chalcones) with chloroacetone pyridinium salt gives 1,3,5-trisubstituted benzene derivatives. The detail mechanism is shown in scheme 1.

![Scheme 1](image-url)
The mechanism involves Michael addition of the active methylene functionality of chloroacetone pyridinium salt on \(\alpha,\beta\)-unsaturated ketone system which results a 1,5-dione system with methyl group at one of the ends. This 1,5-dione system upon further internal cyclization involving carbonyl and methyl group followed by aromatization gives 1,3,5-trisubstituted benzene derivative. This methodology has been utilized in our present work for building up a benzene ring between 3\(^{rd}\) and 4\(^{th}\) position of coumarin.

This methodology has been utilized in the present work and various 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins 6a-d, 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins 7a-d and 7-hydroxy-9-(1-methyl-1\(H\)-pyrrol-2-yl)benzo[c]coumarins 8a-d have been synthesized. However in the preparation of compounds 6a-d, 7a-d and 8a-d, AcONa / AcOH was used instead of AcONa / MeOH. It was found that the reaction proceeded smoothly and gave better yield with the use of AcONa/AcOH rather than AcONa/MeOH.

The compounds 6a-d, 7a-d and 8a-d have been synthesized by reacting various 3-coumarinoyl methyl pyridinium bromide salts 2a-d with 2-acetyl furan 3, 2-acetyl thiophene 4 and 2-acetyl-1-methyl pyrrole 5 in the presence of sodium acetate in refluxing acetic acid.
4.5.1 Synthesis of 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins (6a-d), 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins (7a-d) and 7-hydroxy-9-(1-methyl-1H-pyrrol-2-yl)benzo[c]coumarins (8a-d).

The condensation of various 3-coumarinoyl methyl pyridinium bromide salts 2a-d with 2-acetyl furan 3, 2-acetyl thiophene 4 and 2-acetyl-1-methyl pyrrole 5 in the presence of sodium acetate and acetic acid gave 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins 6a-d, 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins 7a-d and 7-hydroxy-9-(1-methyl-1H-pyrrol-2-yl)benzo[c]coumarins 8a-d respectively in 63-76 % yield (Scheme 2).
The detailed mechanism for the formation of 6a-d, 7a-d and 8a-d is shown in scheme 3.

**Scheme 3**

Here, the enolate of acetyl functionality of heteroaryl moiety adds to the 3,4-double bond of coumarin and results in the formation of intermediate \( \text{(A)} \) having 1,5-dione functionality. The active methylene group then gets cyclized with carbonyl group of heteroaryl moiety resulting in the formation of intermediate \( \text{(B)} \) which finally gets converted into the product by loss of water molecule and subsequent aromatization.
The structures of all the compounds 6a-d, 7a-d and 8a-d were confirmed by analytical and spectral data.

Thus, the condensation of 3-coumarinoyl methyl pyridinium bromide salt 1a with 2-acetyl furan 3 in the presence of sodium acetate and acetic acid proceeded smoothly and gave the product 6a as a pale yellow solid in 69% yield.

The IR spectrum of compound 6a (Fig 1) showed a strong band at 1681 cm\(^{-1}\), which is due to carbonyl stretching of \(\delta\)-lactone ring present in coumarin moiety. The decrease in C=O stretching frequency from the normal value (~1710 cm\(^{-1}\)) is due to hydrogen bonding with C7-OH. The band observed at 1628 cm\(^{-1}\) is due to aromatic C=C stretching vibrations. A band observed at 1110 cm\(^{-1}\) is due asymmetric C-O-C stretching vibrations of furan moiety. The bands appeared at 2921 and 3080 cm\(^{-1}\) are due to aliphatic C-H and aromatic C-H stretching vibrations respectively. A broad band observed around 3428 cm\(^{-1}\) is due to phenolic -OH stretching.

The \(^1\)H-NMR spectrum of compound 6a (in DMSO-d\(_6\)) (Fig 2) showed all the aromatic protons as a multiplet between 6.73-8.48 \(\delta\) (10H). The –OH signal was observed at 11.29 \(\delta\) as a singlet, which was confirmed by recording D\(_2\)O exchange spectrum.

The \(^{13}\)C-APT spectrum of compound 6a (in DMSO-d\(_6\)) (Fig 3) showed signals at 104.96, 108.15, 110.27, 111.28, 113.28, 117.81, 118.30, 124.83, 125.73, 131.67, 136.24, 138.65, 145.56, 150.79, 151.80, 162.25 and 164.58 \(\delta\) corresponding to seventeen types of carbon atoms present in the compound. The most downfield signal appeared at 164.58 \(\delta\) is assigned to the carbonyl carbon of the \(\delta\)-lactone ring of coumarin. The \(^{13}\)C-APT spectrum showed inverted signals at 108.15, 110.27, 111.28, 113.28, 117.81, 124.83, 125.73, 131.67 and 145.56 \(\delta\) which are due to nine tertiary carbons present in the compound.

The mass spectrum of compound 6a (Fig 4) showed M+ peak at 278(100\%) (m/z \%) along with some other fragment peaks at 250 (11\%), 221(13\%), 165(19\%), 139(11\%), 63(6\%), etc. The appearance of molecular ion peak at 278 mass unit supports the structure of compound 6a.
The IR and NMR data for the other compounds 6b-d, 7a-d and 8a-d are given below.

**Compound 6b**

<table>
<thead>
<tr>
<th>IR (cm(^{-1}))</th>
<th>(\nu_{\text{max}}) 1686 (C=O stretching of (\delta)-lactone ring of coumarin), 1621 (aromatic C=C stretching), 3072 (aromatic C-H stretching), 2925 (aliphatic C-H stretching), 1102 (C-O-C stretching of furan moiety), 3423 (O-H stretching).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H-NMR ((\delta), ppm) (Fig 5) (DMSO)</td>
<td>3.91 (3H, singlet, OCH(_3)), 6.72-8.03 (8H, multiplet, aromatic protons), 11.26 (1H, singlet, -OH proton, D(_2)O exchangeable).</td>
</tr>
<tr>
<td>APT ((\delta), ppm) (Fig 6) (DMSO)</td>
<td>56.48(OCH(_3)), 104.75(C), 108.41(CH), 110.19(CH), 111.21(CH), 113.23(CH), 113.57(CH), 115.64(CH), 118.89(CH), 125.40(C), 136.29(C), 138.59(C), 140.22(C), 145.49(CH), 147.77(C), 151.77(C), 162.18(C), 164.23(CO of coumarin).</td>
</tr>
</tbody>
</table>

**Compound 6c**

<table>
<thead>
<tr>
<th>IR (cm(^{-1}))</th>
<th>(\nu_{\text{max}}) 1682 (C=O stretching of (\delta)-lactone ring of coumarin), 1617 (aromatic C=C stretching), 3074 (aromatic C-H stretching), 2922 (aliphatic C-H stretching), 1105 (C-O-C stretching of furan moiety), 3418 (O-H stretching).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H-NMR ((\delta), ppm) (Fig 7) (DMSO)</td>
<td>6.74-8.75 (8H, multiplet, aromatic protons), 11.23 (1H, singlet, -OH proton, D(_2)O exchangeable).</td>
</tr>
<tr>
<td>APT ((\delta), ppm) (Fig 8) (DMSO)</td>
<td>104.62(C), 108.83(CH), 110.75(CH), 111.58(CH), 113.26(CH), 118.04(C), 120.00(CH), 120.50(C), 127.23(CH), 134.11(CH), 135.08(C), 138.71(C), 145.60(CH), 149.97(C), 151.73(C), 162.21(C), 164.01(CO of coumarin).</td>
</tr>
</tbody>
</table>

**Compound 6d**

| IR (cm\(^{-1}\)) | \(\nu_{\text{max}}\) 1684 (C=O stretching of \(\delta\)-lactone ring of coumarin), 1619 (aromatic C=C stretching), 3073 (aromatic C-H stretching), 2924 (aliphatic C-H stretching), 1104 (C-O-C stretching of furan moiety), 3416 (O-H stretching). |

\[\text{Compound } 7a\]

**IR (cm}^{-1}\)**  
\(\nu_{\text{max}} \) 1683 (C=O stretching of \(\delta\)-lactone ring of coumarin), 1617 (aromatic C=C stretching), 3075 (aromatic C-H stretching), 2922 (aliphatic C-H stretching), 3430 (O-H stretching).

\[\text{\textsuperscript{1}H-NMR (}\delta, \text{ppm}\) (Fig 11) (DMSO)\]
6.74-8.81 (11H, multiplet, aromatic protons), 11.39 (1H, singlet, -OH proton, D\textsubscript{2}O exchangeable).

\[\text{APT (}\delta, \text{ppm}\) (Fig 12) (DMSO)\]
110.74(C), 114.94(CH), 115.91(CH), 116.76(CH), 117.30(C), 118.07(CH), 122.28(CH), 129.80(CH), 131.01(CH), 133.67(CH), 134.10(C), 134.69(CH), 136.71(C), 137.62(CH), 141.17(C), 143.03(C), 150.50(CH), 154.86(C), 156.46(C), 166.96(C), 169.01(CO of coumarin).

**Compound 7b**

**IR (cm}^{-1}\)**  
\(\nu_{\text{max}} \) 1683 (C=O stretching of \(\delta\)-lactone ring of coumarin), 1624 (aromatic C=C stretching), 3086 (aromatic C-H stretching), 2925 (aliphatic C-H stretching), 3426 (O-H stretching).

\[\text{\textsuperscript{1}H-NMR (}\delta, \text{ppm}\) (Fig 13) (DMSO)\]
3.93 (3H, singlet, OCH\textsubscript{3}), 7.25-8.06 (8H, multiplet, aromatic protons), 11.28 (1H, singlet, -OH proton, D\textsubscript{2}O exchangeable).

\[\text{APT (}\delta, \text{ppm}\) (Fig 14) (DMSO)\]
56.56(OCH\textsubscript{3}), 105.07(C), 110.27(CH), 112.53(CH), 113.74(CH), 115.86(CH), 118.92(C), 125.48(CH), 127.87(CH), 129.23(CH), 129.44(CH), 136.45(C), 141.76(C), 142.73(C), 147.81(C), 157.55(C), 162.20(C), 164.19(CO of coumarin).
**Compound 7c**

IR (cm\(^{-1}\))

\(\nu_{\text{max}}\) 1685 (C=O stretching of \(\delta\)-lactone ring of coumarin), 1619 (aromatic C=C stretching), 3077 (aromatic C-H stretching), 2924 (aliphatic C-H stretching), 3426 (O-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 15) (DMSO)

7.25-8.81 (8H, multiplet, aromatic protons), 11.20 (1H, singlet, -OH proton, D\(_2\)O exchangeable).

APT (\(\delta\), ppm) (Fig 16) (DMSO)

105.15(C), 110.47(CH), 113.16(CH), 118.09(C), 119.99(CH), 120.53(C), 127.42(CH), 128.25(CH), 129.36(CH), 133.44(CH), 134.16(CH), 135.17(C), 141.63(C), 142.84(C), 149.98(C), 162.14(C), 163.99(CO of coumarin).

**Compound 7d**

IR (cm\(^{-1}\))

\(\nu_{\text{max}}\) 1682 (C=O stretching of \(\delta\)-lactone ring of coumarin), 1624 (aromatic C=C stretching), 3077 (aromatic C-H stretching), 2923 (aliphatic C-H stretching), 3422 (O-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 17) (DMSO)


APT (\(\delta\), ppm) (Fig 18) (DMSO)

112.15(CH), 114.46(CH), 117.60(CH), 125.09(CH), 126.33(CH), 127.61(CH), 128.98(CH), 129.29(CH), 129.37(C), 129.66(CH), 130.01(CH), 132.00(C), 132.93(CH), 136.43(C), 141.90(C), 142.35(C), 150.23(C), 154.33(C), 162.27(C), 164.21(CO of coumarin).

**Compound 8a**

IR (cm\(^{-1}\))

\(\nu_{\text{max}}\) 1683 (C=O stretching of \(\delta\)-lactone ring of coumarin), 1626 (aromatic C=C stretching), 3075 (aromatic C-H stretching), 2927 (aliphatic C-H stretching), 3424 (O-H stretching).

\(^1\)H-NMR (\(\delta\), ppm) (Fig 19)

4.01 (3H, singlet, >N-CH\(_3\)), 6.73-8.48 (9H, multiplet, aromatic protons), 11.36 (1H, singlet, -OH proton, D\(_2\)O exchangeable).
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(DMSO) exchangeable).

APT  
(δ, ppm)  
(Fig 20)  
(DMSO)  
32.24(>N-CH₃), 105.03(C), 108.31(CH), 110.44(CH), 111.45(CH), 113.47(CH), 118.01(CH), 118.38(C), 125.51(CH), 126.62(CH), 132.13(CH), 136.34(C), 138.79(C), 144.64(CH), 151.02(C), 152.08(C), 161.99(C), 164.10(CO of coumarin).

**Compound 8b**

IR  
(cm⁻¹)  
ν_max 1680 (C=O stretching of δ-lactone ring of coumarin), 1618 (aromatic C=C stretching), 3076 (aromatic C-H stretching), 2923 (aliphatic C-H stretching), 3421 (O-H stretching).

¹H-NMR  
(δ, ppm)  
(Fig 21)  
(DMSO)  
3.93 and 4.01 (6H, two singlets, >N-CH₃ and OCH₃), 6.96-8.09 (8H, multiplet, aromatic protons), 11.25 (1H, singlet, -OH proton, D₂O exchangeable).

APT  
(δ, ppm)  
(Fig 22)  
(DMSO)  
32.41(>N-CH₃), 56.53(OCH₃), 105.05(C), 108.74(CH), 109.99(CH), 111.40(CH), 113.43(CH), 113.78(CH), 115.89(CH), 119.12(C), 126.13(CH), 136.51(C), 138.81(C), 140.445(C), 144.18(CH), 146.11(C), 152.18(C), 161.76(C), 163.83(CO of coumarin).

**Compound 8c**

IR  
(cm⁻¹)  
ν_max 1688 (C=O stretching of δ-lactone ring of coumarin), 1623 (aromatic C=C stretching), 3082 (aromatic C-H stretching), 2924 (aliphatic C-H stretching), 3421 (O-H stretching).

¹H-NMR  
(δ, ppm)  
(Fig 23)  
(DMSO)  
4.02 (3H, singlet, >N-CH₃), 6.79-8.80 (8H, multiplet, aromatic protons), 11.33 (1H, singlet, -OH proton, D₂O exchangeable).

APT  
(δ, ppm)  
(Fig 24)  
(DMSO)  
32.26(>N-CH₃), 105.61(C), 109.08(CH), 111.02(CH), 111.85(CH), 113.64(CH), 117.93(C), 119.97(CH), 120.62(C), 127.51(CH), 133.95(CH), 135.27(C), 139.17(C), 144.92(CH), 150.14(C), 152.15(C), 162.51(C), 164.33(CO of coumarin).
**Compound 8d**

**IR (cm⁻¹)**

$\nu_{\text{max}}$ 1681 (C=O stretching of $\delta$-lactone ring of coumarin), 1624 (aromatic C=C stretching), 3079 (aromatic C-H stretching), 2920 (aliphatic C-H stretching), 3426 (O-H stretching).

**$^1$H-NMR (δ, ppm) (Fig 25) (DMSO)**

4.02 (3H, singlet, $>\text{N-CH}_3$), 6.74-8.82 (11H, multiplet, aromatic protons), 11.30 (1H, singlet, $-\text{OH}$ proton, D$_2$O exchangeable).

**APT (δ, ppm) (Fig 26) (DMSO)**

32.54($>\text{N-CH}_3$), 110.94(C), 115.17(CH), 116.03(CH), 116.79(CH), 117.41(C), 118.26(CH), 121.98(CH), 130.00(CH), 131.22(CH), 133.86(CH), 134.31(C), 134.79(CH), 137.03(C), 137.84(CH), 140.96(C), 142.89(C), 150.75(CH), 155.01(C), 156.49(C), 166.66(C), 168.87(CO of coumarin).
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**Fig 1**  IR spectrum of compound 6a

**Fig 2**  $^1$H-NMR spectrum of compound 6a
**Fig 3**  APT spectrum of compound 6a

**Fig 4**  Mass spectrum of compound 6a
**Fig 5**  $^1$H-NMR spectrum of compound 6b

**Fig 6**  APT spectrum of compound 6b
**Fig 7** $^1$H-NMR spectrum of compound 6c

**Fig 8** APT spectrum of compound 6c
Fig 9    $^1$H-NMR spectrum of compound 6d

Fig 10    APT spectrum of compound 6d
Fig 11  $^1$H-NMR spectrum of compound 7a

Fig 12  APT spectrum of compound 7a
**Fig 13**  $^1$H-NMR spectrum of compound 7b

**Fig 14**  APT spectrum of compound 7b
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Fig 15  $^1$H-NMR spectrum of compound 7c

Fig 16  APT spectrum of compound 7c
Fig 17  $^1$H-NMR spectrum of compound 7d

Fig 18  APT spectrum of compound 7d
Fig 19  $^1$H-NMR spectrum of compound 8a

Fig 20  APT spectrum of compound 8a
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Fig 21  $^1$H-NMR spectrum of compound 8b

Fig 22  APT spectrum of compound 8b
Fig 23  
$^1$H-NMR spectrum of compound 8c

Fig 24  
APT spectrum of compound 8c
**Fig 25** $^1$H-NMR spectrum of compound 8d

**Fig 26** APT spectrum of compound 8d
4.6 Experimental

The following starting materials were used.

- Substituted 3bromoacetylcoumarins used:
  
  **1a** 3-bromoacetyl coumarin
  
  **1b** 8-methoxy-3-bromoacetyl coumarin
  
  **1c** 6-bromo-3-bromoacetyl coumarin
  
  **1d** 5,6-benzo-3-bromoacetyl coumarin

The preparation of 1a, 1b and 1d is described in chapter 3. The preparation of 1c is presented in this experimental part.

4.6.1 Preparation of 6-bromo-3-acetyl coumarin.

In a 100 mL round bottom flask, a mixture of 5-bromo salicylaldehyde (0.01 mol), ethyl acetoacetate (0.01 mol) and 3-4 drops of piperidine was stirred for 10 minutes at room temperature. It was then heated for 30 minutes in boiling water bath. On cooling, a yellow solid product was obtained, which was filtered out and washed with cold ether. It was recrystallized from chloroform-hexane.

**6-Bromo-3-acetyl coumarin**: Yield: 69% mp 223-225°C (lit. mp 223°C)

4.6.2 Preparation of 6-bromo-3-bromoacetyl coumarin (1c).

In a 100 mL three necked flask, a solution of 6-bromo-3-acetyl coumarin (0.01 mol) in glacial acetic acid (20 mL) was taken. To this, bromine (0.01 mol) in glacial acetic acid (10 mL) was added with stirring during 30 minutes at room temperature. The reaction mixture was stirred at room temperature for 3 hours. It was then poured into
ice cold water and the solid obtained was filtered out. It was washed with water and dried. The product was recrystallized from chloroform.

**6-Bromo-3-bromoacetyl coumarin (1c):** Yield: 65%, mp 178°C (lit.\(^46\) mp 178-180°C)

### 4.6.3 Preparation of 3-coumarinoyl methyl pyridinium bromide salts (2a-d).

![Reaction Scheme](reaction_scheme.png)

In a 100 mL round bottom flask fitted with a reflux condenser, a solution of appropriate 3-bromoacetyl coumarin (0.01 mol) in dry toluene (30 mL) was taken and pyridine (0.01 mol) was added. The reaction mixture was refluxed in an oil bath for 2 hours. It was then allowed to come to room temperature and was left for 4 to 5 hours. The pyridinium salt was separated out which was filtered out and washed with hot toluene and dried. It was recrystallized from acetic acid.

**3-Coumarinoyl methyl pyridinium bromide salt (2a):** \(R = R_1 = R_2 = \text{H}\), Yield: 93%, mp 218°C(dec.) (lit.\(^47\) mp 220°C(dec.))

**8-Methoxy-3-coumarinoyl methyl pyridinium bromide salt (2b):** \(R = \text{OCH}_3\), \(R_1 = R_2 = \text{H}\), Yield: 91%, mp 250°C(dec.) (lit.\(^48\) mp 250°C(dec.))

**6-Bromo-3-coumarinoyl methyl pyridinium bromide salt (2c):** \(R=R_2=\text{H}; R_1=\text{Br}\), Yield: 70%, mp 260°C (lit.\(^46\) mp 260-262°C)

**5,6-Benzoyl-3-coumarinoyl methyl pyridinium bromide salt (2d):** \(R = \text{H}, R_1 + R_2 = \text{benzo}\), Yield: 84%, mp 179-180°C (dec.) [lit.\(^49\) mp 180°C (dec.)]
4.6.4 Synthesis of 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins (6a-d), 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins (7a-d) and 7-hydroxy-9-(1-methyl-1H-pyrrol-2-yl)benzo[c]coumarins (8a-d).

![Chemical Structures]

The following general procedure was used.

In a 100 mL three-necked round bottom flask equipped with a dropping funnel, condenser, guard tube and magnetic needle, a solution of an appropriate 3-coumarinoyl methyl pyridinium bromide salt 2a-d (0.004 mol) was taken in glacial acetic acid (15 mL). To this, sodium acetate (0.012 mol) was added with stirring. Then, 2-acetyl furan 3 or 2-acetyl thiophene 4 or 2-acetyl-1-methyl pyrrole 5 in glacial acetic acid (10 mL) was added with stirring at room temperature during 10 minutes. The reaction mixture was further stirred for 20 minutes at room temperature and then refluxed for 8 hours. It was then allowed to cool to room temperature and poured into cold water (75 mL). The crude solid was then extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under reduced pressure gave a solid product. This was purified by column chromatography using silica gel and chloroform-petroleum ether (60-80) (6:4) as an eluent. Thus, 7-hydroxy-9-(furan-2-yl)benzo[c]coumarins 6a-d, 7-hydroxy-9-(thiophen-2-yl)benzo[c]coumarins 7a-d and 7-hydroxy-9-(1-methyl-1H-pyrrol-2-yl)benzo[c]coumarins 8a-d were obtained as pale yellow colored solid, which were recrystallized from chloroform-hexane.

**Compound 6a:** (R = R₁ = R₂ = H)

Yield = 69%  
mp 214°C  
Molecular Formula: C₁₇H₁₀O₄

Analysis

<table>
<thead>
<tr>
<th>% C</th>
<th>% H</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Compound 6b**: \((R = \text{OCH}_3, R_1 = R_2 = \text{H})\)

Yield = 72\%  
mp 227-228°C  
Molecular Formula: C_{18}H_{12}O_{5}

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>70.08</td>
<td>3.88</td>
</tr>
<tr>
<td>Calculated</td>
<td>70.13</td>
<td>3.92</td>
</tr>
</tbody>
</table>

**Compound 6c**: \((R_1 = \text{Br}, R = R_2 = \text{H})\)

Yield = 74\%  
mp 249°C  
Molecular Formula: C_{17}H_{9}BrO_{4}

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>57.13</td>
<td>2.57</td>
</tr>
<tr>
<td>Calculated</td>
<td>57.17</td>
<td>2.54</td>
</tr>
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</table>

**Compound 6d**: \((R = \text{H}, R_1 + R_2 = \text{benzo})\)

Yield = 67\%  
mp 221-223°C  
Molecular Formula: C_{21}H_{12}O_{4}

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>76.85</td>
<td>3.63</td>
</tr>
<tr>
<td>Calculated</td>
<td>76.82</td>
<td>3.68</td>
</tr>
</tbody>
</table>

**Compound 7a**: \((R = R_1 = R_2 = \text{H})\)

Yield = 68\%  
mp 203-204°C  
Molecular Formula: C_{17}H_{10}O_{3}S

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>69.32</td>
<td>3.45</td>
<td>10.92</td>
</tr>
<tr>
<td>Calculated</td>
<td>69.37</td>
<td>3.42</td>
<td>10.89</td>
</tr>
</tbody>
</table>

**Compound 7b**: \((R = \text{OCH}_3, R_1 = R_2 = \text{H})\)

Yield = 76\%  
mp 210°C  
Molecular Formula: C_{18}H_{12}O_{4}S

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>66.68</td>
<td>3.70</td>
<td>9.83</td>
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<tr>
<td>Calculated</td>
<td>66.65</td>
<td>3.73</td>
<td>9.89</td>
</tr>
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</table>

**Compound 7c**: \((R_1 = \text{Br}, R = R_2 = \text{H})\)

Yield = 65\%  
mp 253-254°C  
Molecular Formula: C_{17}H_{9}BrO_{3}S

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>54.68</td>
<td>2.38</td>
<td>8.63</td>
</tr>
<tr>
<td>Calculated</td>
<td>54.71</td>
<td>2.43</td>
<td>8.59</td>
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</tbody>
</table>

**Compound 7d**: \((R = \text{H}, R_1 + R_2 = \text{benzo})\)

Yield = 69\%  
mp 222°C  
Molecular Formula: C_{21}H_{12}O_{3}S
Chapter 4, Section 2

Heteroaryl substituted benzo[c]coumarins

Department of Chemistry, Sardar Patel University

Analysis  % C  % H  % S  
Found    73.27  3.56  9.34  
Calculated 73.24  3.51  9.31  

**Compound 8a:** (R = R₁ = R₂ = H)
Yield = 64%  mp 201-203°C  Molecular Formula: C₁₈H₁₃NO₃
Analysis  % C  % H  % N  
Found    74.25  4.54  4.78  
Calculated 74.22  4.50  4.81  

**Compound 8b:** (R = OCH₃, R₁ = R₂ = H)
Yield = 71%  mp 231-233°C  Molecular Formula: C₁₉H₁₅NO₄
Analysis  % C  % H  % N  
Found    71.08  4.74  4.30  
Calculated 71.02  4.71  4.36  

**Compound 8c:** (R₁ = Br, R = R₂ = H)
Yield = 66%  mp 245°C  Molecular Formula: C₁₈H₁₂BrNO₃
Analysis  % C  % H  % N  
Found    58.37  3.31  3.82  
Calculated 58.40  3.27  3.78  

**Compound 8d:** (R = H, R₁ + R₂ = benzo)
Yield = 63%  mp 249°C  Molecular Formula: C₂₂H₁₅NO₃
Analysis  % C  % H  % N  
Found    77.38  4.47  4.07  
Calculated 77.41  4.43  4.10  

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