Synthesis of pyrido/quino fused and pyridyl/quinolinyl carbonyl substituted coumarins

The work incorporated in this section is on the synthesis of various pyrido/quino fused coumarins. The compounds have been synthesized by reacting various 4-hydroxy coumarins with Mannich bases of cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively under Krohnke’s reaction condition. In addition to pyrido/quino fused coumarins, some pyridyl/quinolinyl carbonyl substituted coumarins have also been synthesized by reacting 4-methyl-7-oxa-10-oxo-benzo[h]coumarin-9-carbaldehyde with cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively under Krohnke’s reaction condition. The structures of all the compounds synthesized have been supported by analytical and spectral data.

3.1 Introduction

Large numbers of coumarin derivatives containing heterocyclic moieties are used in drugs and dyes. The varied biological activities of the coumarins fused with other heterocycles have encouraged researchers with regard to the procedures and substrates, improving the feasibility of broad families of these compounds. Several biological activities have been claimed for compounds comprising both coumarins and coumarins fused to pyridine ring. For instance, coumarin nucleus is present in promising drug candidates as nonpeptidic HIV protease inhibitors\(^1\) such as topoisomerase-II\(^2\) and tyrosine kinase\(^3\) inhibitors. Coumarins joined to pyridines have been reported to possess antiallergic\(^4\), anticoagulant\(^5\), antidiabetic\(^6\) activities and even analgesic\(^7\) properties, being characterized by a phenanthrene like structure as found in tetrahydrocannabinol. The pyrido[2,3-\text{c}]coumarin skeleton constitutes the backbone of Santiagonamine\(^8\). This
alkaloid has been isolated from Berberis Darvinii (Berberidacea), has shown interesting wound healing properties\(^9\).

Among four isomeric pyrido fused coumarins i.e. pyrido[3,2-c]coumarins; pyrido[4,3-c]coumarins; pyrido[3,4-c]coumarins and pyrido[2,3-c]coumarins, pyrido[3,2-c]coumarins have been widely studied. Many pyrido[3,2-c]coumarins have been synthesized by variety of methods.

*S G S Farid et al\(^{10}\)* have synthesized 2-amino-4-methyl pyrido[3,2-c]coumarin by condensation of 4-hydroxy coumarin with 1-cyano-2-amino prop-1-ene. *J N Chatterjee et al\(^{11}\)* have synthesized pyrido[3,2-c]coumarin derivatives by reacting 3-arylidene chroman-4-ones with N-arylacyl pyridinium bromide salt in the presence of ammonium acetate in refluxing acetic acid followed by chromium trioxide oxidation. *G Pave et al\(^{12}\)* have synthesized pyrido[3,2-c]coumarins having alkyl substitution in pyridine part by reacting 4-hydroxy coumarin with protected \(\beta\)-aminoketones. *C N O’ Callaghan\(^{13}\)* have synthesized certain pyrido[3,2-c]coumarins by reacting salicylaldehyde with two equivalents of methyl/ethyl acetoacetate.

Considering the importance of pyrido[3,2-c]coumarins and in view of modifying the pyridine moiety, we came across four annulated pyridine nucleus, 6,7-dihydro-5H-cyclopenta[b]pyridine (1); 5,6,7,8-tetrahydroquinoline (2); 5H-indeno[1,2-b]pyridine (3) and 5,6-dihydrobenzo[h]quinoline (4).
Literature survey revealed that certain compounds possessing such type of annulated pyridine moiety have interesting chemical and physiological properties. Certain 6,7-dihydro-5H-cyclopenta[b]pyridine derivatives possess endothelin A receptor antagonist\(^{14,15}\) and anti-inflammatory activity\(^{16}\). The compounds possessing 5,6,7,8-tetrahydroquinoline in their skeleton are reported to have various biological activities such as anti-diabetic activity\(^{17}\), dopaminergic activity\(^{18}\), anti-ulcer properties\(^{19}\) and anti-secretory properties\(^{19}\). The compounds having 5H-indeno[1,2-b]pyridine in their skeleton are reported to be potent dopamine receptors and NK1 antagonists\(^{20}\), inhibitors of bovine liver glutathione S-transferase\(^{21}\) and also possesses cytotoxic activity\(^{22}\), antibacterial and antifungal activity\(^{23}\). Certain compounds containing 5,6-dihydrobenzo[h]quinoline moiety have been reported to possess various biological activities such as anticancer cytotoxicity\(^{24,25}\), antibacterial and antifungal activity\(^{26}\), \textit{in vitro} antioxidant activity\(^{27}\) and also possess topoisomerase I and II inhibitory activity\(^{28}\).

Thus, considering the importance of 6,7-dihydro-5H-cyclopenta[b]pyridine; 5,6,7,8-tetrahydroquinoline; 5H-indeno[1,2-b]pyridine and 5,6-dihydrobenzo[h]quinoline derivatives, it was thought worthwhile to incorporate these moieties in coumarin and therefore in the present work, various 8H-9,10-dihydrocoumarino[4,3-b]cyclopenta[e]pyridines; 8,9,10,11-tetrahydrocoumarino[4,3-b]quinolines; 8H-coumarino[4,3-b]indenox[2,1-e]pyridines and 8,9-dihydrobenzo[h]coumarino[4,3-b]quinolines have been synthesized.

### 3.2 Present work

In the present work, various 8H-9,10-dihydrocoumarino[4,3-b]cyclopenta[e]pyridines (2); 8,9,10,11-tetrahydrocoumarino[4,3-b]quinolines (3); 8H-coumarino[4,3-b]indenox[2,1-e]pyridines (4) and 8,9-dihydrobenzo[h]coumarino[4,3-b]quinolines (5) have been synthesized by reacting various 4-hydroxy coumarins (1) with Mannich bases of cyclopentanone, cyclohexanone, 1-indanone and \(\alpha\)-tetralone respectively in the presence of ammonium acetate in refluxing acetic acid under
Krohnke’s reaction condition. The synthesis of various (2), (3), (4) and (5) is outlined in scheme 1.

![Chemical structure](image)

**Scheme 1**

The detailed mechanism for the formation of (2), (3), (4) and (5) is shown in scheme 2.

The cyclic ketone methide (B) were generated in situ by pyrolysis of the Mannich bases (A) of cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively. This methide provides α,β-unsaturated ketone system and the addition of various 4-hydroxy coumarin anion results in a formation of 1,5-dicarbonyl system which finally gets converted into pyridine moiety.
3.2.1 Synthesis of 8H-9,10-dihydrocoumarino[4,3-b]cyclopenta[e]pyridines (2a-c)

The condensation of various 4-hydroxy coumarins (1a-c) with Mannich base of cyclopentanone in the presence of ammonium
acetate and acetic acid gave $8H$-9,10-dihydrocoumarino[4,3-$b$]cyclopenta[e]pyridines (2a-c) in 72-78% yield (Scheme 3).

\[
\begin{align*}
\text{(1a-c)} & \quad + \quad \text{NH}_4\text{OAc} \\
\Delta & \quad \text{AcOH} \\
\quad & \quad \text{(2a-c)}
\end{align*}
\]

The structures of all the compounds (2a-c) were confirmed by analytical and spectral data.

Thus, the condensation of 4-hydroxy coumarin (1a) with Mannich base of cyclopentanone in the presence of ammonium acetate and acetic acid proceeded smoothly and gave the expected product (2a) as a white colored solid in 72% yield.

The IR spectrum of compound 2a (Fig 1) showed a strong band at 1729 cm$^{-1}$, which is due to carbonyl stretching of δ-lactone ring present in coumarin moiety. The bands observed at 1602 cm$^{-1}$ and 1429 cm$^{-1}$ are due to aromatic C=C and C=N stretching vibrations respectively. A band appeared at 2949 cm$^{-1}$ is due to aliphatic C-H stretching of cyclopentane ring. A band observed at 3054 cm$^{-1}$ is due to aromatic C-H stretching.
The $^1$H NMR spectrum of compound 2a (in CDCl$_3$) (Fig 2) showed a multiplet integrating for two protons and centered at 2.25 δ. This is due to two protons attached at C$_9$. A triplet centered at 3.09 δ (2H) is due to two protons attached at C$_8$. A triplet centered at 3.18 δ (2H) is due to two protons attached at C$_{10}$. A multiplet observed between 7.35-7.39 δ (2H) is due to protons attached at C$_3$ and C$_4$. A multiplet observed between 7.52-7.56 δ (1H) is due to proton attached at C$_2$. A singlet observed at 8.34 δ (1H) is due to proton attached at C$_7$. A multiplet observed between 8.55-8.57 δ integrating for one proton is due to proton attached at C$_1$.

The $^{13}$C NMR spectrum of compound 2a (in CDCl$_3$) (Fig 3) showed signals at 23.06, 30.50, 35.00, 115.32, 116.99, 119.69, 124.44, 124.63, 131.44, 132.85, 138.30, 150.59, 152.18, 161.84 and 173.99 δ corresponding to fifteen different types of carbon atoms present in the compound. The signal appeared at 23.06 δ is due to C$_9$. The signals appeared at 30.50 δ and 35.00 δ are due to C$_8$ and C$_{10}$ respectively. The most downfield signal appeared at 173.99 δ can be assigned to the carbonyl carbon of the δ-lactone ring of coumarin. The DEPT-135 spectrum of compound 2a (in CDCl$_3$) (Fig 4) showed inverted signals at 23.06, 30.50 and 35.00 δ, which are due to C$_9$, C$_8$ and C$_{10}$ respectively. The signals appeared at 116.99, 124.43, 124.63, 131.44 and 132.84 δ are due to five tertiary carbons.

The GC-mass spectrum of compound 2a (Fig 5) showed M$^+$ peak at 237(100%) (m/z %) along with some other fragment peaks at 208(9%), 192(15%), 165(13%), 152(9%), 102(5%), 89(10%), 77(19%), 63(17%), etc.

The IR and NMR data for the other compounds (2b-c) are given below.

**Compound 2b**

**IR (cm$^{-1}$)**

$\nu_{\text{max}}$ 1725 (δ-lactone carbonyl stretching of coumarin), 1602 and 1429 (aromatic C=C and C=N stretching), 2927 (aliphatic C-H stretching), 3065 (aromatic C-H stretching)
In all the compounds (2a-c), the proton attached at C₁ absorbs in the most downfield region. This downfield absorption compared to other aromatic protons is due to the peri effect of nitrogen atom of pyridine ring.
Fig 1  IR spectrum of compound 2a

Fig 2  $^1$H NMR spectrum of compound 2a
Fig 3  $^{13}$C NMR spectrum of compound 2a

Fig 4  DEPT-135 spectrum of compound 2a
Fig 5  GC-Mass spectrum of compound 2a
**Fig 6** $^1$H NMR spectrum of compound 2b

**Fig 7** $^{13}$C NMR spectrum of compound 2b
Fig 8  $^1$H NMR spectrum of compound 2c

Fig 9  $^{13}$C NMR spectrum of compound 2c
3.2.2 Synthesis of 8,9,10,11-tetrahydrocoumarino[4,3-b]quinolines (3a-c)

The condensation of various 4-hydroxy coumarins (1a-c) with Mannich base of cyclohexanone in the presence of ammonium acetate and acetic acid gave 8,9,10,11-tetrahydrocoumarino[4,3-b]quinolines (3a-c) in 77-84% yield (Scheme 4).

![Scheme 4]

The structures of all the compounds (3a-c) were confirmed by analytical and spectral data.

Thus, the condensation of 4-hydroxy coumarin (1a) with Mannich base of cyclohexanone in the presence of ammonium acetate and acetic acid proceeded smoothly and gave the expected product (3a) as a white colored solid in 84% yield.

The IR spectrum of compound 3a (Fig 10) showed a strong band at 1731 cm\(^{-1}\) which is due to carbonyl stretching of \(\delta\)-lactone of coum-
arin moiety. The bands observed at 1609 cm\(^{-1}\) and 1437 cm\(^{-1}\) are due to aromatic C=C and C=N stretching vibrations respectively. The compound showed bands at 2941 cm\(^{-1}\) and 3043 cm\(^{-1}\), which are due to aliphatic C-H stretching of cyclohexane ring and aromatic C-H stretching respectively.

The \(^1\)H NMR spectrum of compound 3a (in CDCl\(_3\)) (Fig 11) showed multiplet centered at 1.97 \(\delta\) integrating for four protons. This is due to two protons attached at C\(_9\) and two protons attached at C\(_{10}\). A triplet appeared at 2.95 \(\delta\) (2H) is due to protons attached at C\(_8\). A triplet observed at 3.13 \(\delta\) (2H) is due to protons attached at C\(_{11}\). A multiplet observed between 7.37-7.41 \(\delta\) (2H) is due to protons attached at C\(_3\) and C\(_4\). A multiplet observed between 7.53-7.57 \(\delta\) (1H) is due to proton attached at C\(_2\). A singlet observed at 8.29 \(\delta\) (1H) is due to proton attached at C\(_7\). A doublet of a doublet observed at 8.59 \(\delta\) (\(J = 8.2\) and 1.8 Hz) integrating for one proton is due to proton attached at C\(_1\).

The \(^{13}\)C NMR spectrum of compound 3a (in CDCl\(_3\)) (Fig 12) showed signals at 22.38, 22.66, 28.76, 33.60, 115.01, 117.04, 119.52, 124.44, 124.62, 131.38, 133.58, 137.72, 148.91, 152.37, 161.60 and 165.60 \(\delta\) corresponding to sixteen different types of carbon atoms present in the compound. The signals appeared at 22.38, 22.66, 28.76 and 33.60 \(\delta\) are due to C\(_9\), C\(_{10}\), C\(_8\) and C\(_{11}\) respectively. The most downfield signal appeared at 165.60 \(\delta\) can be assigned to the carbonyl carbon of the \(\delta\)-lactone ring of coumarin. The DEPT-135 spectrum of compound 3a (in CDCl\(_3\)) (Fig 13) showed inverted signals at 22.37, 22.66, 28.76 and 33.60 \(\delta\), which are due to C\(_9\), C\(_{10}\), C\(_8\) and C\(_{11}\) respectively. The signals appeared at 117.04, 124.43, 124.62, 131.38 and 137.72 \(\delta\) are due to five tertiary carbons.

The GC-mass spectrum of compound 3a (Fig 14) showed M\(^+\) peak at 251(100%) (m/z %) along with some other fragment peaks at 223(23%), 206(8%), 194(7%), 140(9%), 102(7%), 89(10%), 77(18%), 63(15%), etc.

The IR and NMR data for the other compounds (3b-c) are given below.
**Compound 3b**

**IR (cm$^{-1}$)**

$\nu_{\text{max}}$ 1725 ($\delta$-lactone carbonyl stretching of coumarin), 1606 and 1429 (aromatic C=C and C=N stretching), 2927 (aliphatic C-H stretching), 3043 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (CDCl$_3$) (Fig 15)

1.91 (4H, multiplet, protons at C$_9$ and C$_{10}$), 2.42 (3H, singlet, CH$_3$), 2.87 (2H, singlet, protons at C$_8$), 3.03 (2H, singlet, protons at C$_{11}$), 7.16-7.28 (2H, multiplet, protons at C$_3$ and C$_4$), 8.13-8.19 (2H, multiplet, protons at C$_1$ and C$_7$)

$^{13}$C NMR ($\delta$, ppm) (CDCl$_3$) (Fig 16)

20.95(CH$_3$), 22.35(C$_9$), 22.64(C$_{10}$), 28.71(C$_8$), 33.54(C$_{11}$), 114.90(C), 116.67(CH), 118.95(C), 124.04(CH), 132.23(CH), 133.29(C), 134.23(C), 137.62(CH), 148.83(C), 150.38(C), 161.60(C), 165.33(CO of coumarin)

**Compound 3c**

**IR (cm$^{-1}$)**

$\nu_{\text{max}}$ 1725 ($\delta$-lactone carbonyl stretching of coumarin), 1599 and 1425 (aromatic C=C and C=N stretching), 2934 (aliphatic C-H stretching), 3065 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (CDCl$_3$) (Fig 17)

1.95 (4H, multiplet, protons at C$_9$ and C$_{10}$), 2.93 (2H, triplet, protons at C$_8$), 3.08 (2H, triplet, protons at C$_{11}$), 7.26 (1H, doublet, $J = 8.8$ Hz, proton at C$_4$), 7.45 (1H, doublet of a doublet, $J = 8.8$ and 2.4 Hz, proton at C$_3$), 8.19 (1H, singlet, proton at C$_7$), 8.42 (1H, doublet, $J = 2.4$ Hz, proton at C$_1$)

$^{13}$C NMR ($\delta$, ppm) (CDCl$_3$) (Fig 18)

22.29(C$_9$), 22.57(C$_{10}$), 28.81(C$_8$), 33.53(C$_{11}$), 115.01(C), 118.48(CH), 120.73(C), 123.98(CH), 130.24(C), 131.26(CH), 134.33(C), 137.68(CH), 147.71(C), 150.67(C), 160.93(C), 165.88(CO of coumarin)

In all the compounds (3a-c), C$_1$ proton appears in the downfield region due to the peri effect of nitrogen atom of pyridine ring.
Fig 10  IR spectrum of compound 3a

Fig 11  $^1$H NMR spectrum of compound 3a
Fig 12  $^{13}$C NMR spectrum of compound 3a

Fig 13  DEPT-135 spectrum of compound 3a
Fig 14  GC-Mass spectrum of compound 3a
**Fig 15**  $^1$H NMR spectrum of compound 3b

**Fig 16**  $^{13}$C NMR spectrum of compound 3b
Fig 17  $^1$H NMR spectrum of compound 3c

Fig 18  $^{13}$C NMR spectrum of compound 3c
3.2.3 **Synthesis of 8H-coumarino[4,3-b]indeno[2,1-e]pyridines (4a-c)**

The condensation of various 4-hydroxy coumarins (1a-c) with Mannich base of 1-indanone in the presence of ammonium acetate and acetic acid gave 8H-coumarino[4,3-b]indeno[2,1-e]pyridines (4a-c) in 68-76% yield (Scheme 5).

![Chemical structure of 8H-coumarino[4,3-b]indeno[2,1-e]pyridines (4a-c)](attachment)

The structures of all the compounds (4a-c) were confirmed by analytical and spectral data.

Thus, the condensation of 4-hydroxy coumarin (1a) with Mannich base of 1-indanone in the presence of ammonium acetate and acetic acid proceeded smoothly and gave the expected product (4a) as a white colored solid in 76% yield.
The IR spectrum of compound 4a (Fig 19) showed a strong band at 1729 cm⁻¹, which is due to carbonyl stretching of δ-lactone ring present in coumarin moiety. The bands observed at 1606 cm⁻¹ and 1436 cm⁻¹ are due to aromatic C=C and C=N stretching vibrations respectively. A band appeared at 2920 cm⁻¹ is due to aliphatic C-H stretching. A band observed at 3072 cm⁻¹ is due to aromatic C-H stretching.

The ¹H NMR spectrum of compound 4a (in CDCl₃) (Fig 20) showed a singlet at 4.00 δ (2H) which is due to two protons attached at C₈. A multiplet observed between 7.37-7.63 δ (6H) is due to protons attached at C₂, C₃, C₄, C₉, C₁₀ and C₁₁. A multiplet centered at 8.29 δ (1H) is due to proton attached at C₁₂. A singlet observed at 8.64 δ (1H) is due to proton attached at C₇. A multiplet centered at 8.80 δ (1H) is due to proton attached at C₁.

The ¹³C NMR spectrum of compound 4a (in CDCl₃) (Fig 21) showed signals at 34.44, 114.84, 117.00, 119.86, 122.65, 124.64, 124.83, 125.50, 127.75, 130.96, 131.68, 133.29, 136.86, 139.48, 145.76, 151.40, 152.39, 161.88 and 166.33 δ corresponding to nineteen different types of carbons atoms present in the compound. The signal observed at 34.44 δ is due to C₈. The most downfield signal appeared at 166.33 δ is due to the carbonyl carbon of the δ-lactone ring of coumarin. The DEPT-135 spectrum of compound 4a (in CDCl₃) (Fig 22) showed inverted signal at 34.44 δ, which is due to C₈. The nine signals appeared for nine tertiary carbons at 117.00, 122.65, 124.64, 124.83, 125.50, 127.75, 130.96, 131.68 and 133.29 δ.

The GC-mass spectrum of compound 4a (Fig 23) showed M⁺ peak at 285(93%) (m/z %) along with some other fragment peaks at 256(9%), 241(37%), 227(8%), 200(3%), 143(3%), 121(17%), 114 (13%), 100(7%), 88(4%), 75(3%), 63(2%), 44(100%), etc.

The IR and NMR data for the other compounds (4b-c) are given below.

**Compound 4b**

**IR (cm⁻¹)**

νmax 1732 (δ-lactone carbonyl stretching of coumarin), 1606 and 1396
(aromatic C=C and C=N stretching), 2920 (aliphatic C-H stretching), 3054 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (CDCl$_3$) (Fig 24)

2.55 (3H, singlet, CH$_3$), 4.03 (2H, singlet, protons at C$_8$), 7.30-7.65 (5H, multiplet, protons at C$_3$, C$_4$, C$_9$, C$_{10}$ and C$_{11}$), 8.34 (1H, multiplet, proton at C$_{12}$), 8.59 (1H, poorly resolved doublet, proton at C$_1$), 8.66 (1H, singlet, proton at C$_7$)

$^{13}$C NMR ($\delta$, ppm) (CDCl$_3$) (Fig 25)

21.05(CH$_3$), 34.46(C$_8$), 114.90(C), 116.78(CH), 119.46(C), 122.68(CH), 124.54(CH), 125.53(CH), 127.74 (CH), 130.93(CH), 132.65(CH), 133.38(CH), 134.36(C), 136.73(C), 139.59(C), 145.79(C), 150.54(C), 151.55(C), 162.09(C), 166.33(CO of coumarin)

**Compound 4c**

IR (cm$^{-1}$)

$\nu_{\text{max}}$ 1732 ($\delta$-lactone carbonyl stretching of coumarin), 1609 and 1436 (aromatic C=C and C=N stretching), 2927 aliphatic C-H stretching), 3064 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (CDCl$_3$) (Fig 26)

4.04 (2H, singlet, protons at C$_8$), 7.32-7.66 (5H, multiplet, protons at C$_3$, C$_4$, C$_9$, C$_{10}$ and C$_{11}$), 8.30 (1H, multiplet, proton at C$_{12}$), 8.64 (1H, singlet, proton at C$_7$), 8.74 (1H, poorly resolved doublet, proton at C$_1$)

$^{13}$C NMR ($\delta$, ppm) (CDCl$_3$) (Fig 27)

34.51(C$_8$), 114.94(C), 118.53(CH), 121.18(C), 122.82(CH), 124.45(CH), 125.56(CH), 127.90(CH), 130.32(C), 131.23(CH), 131.59(CH), 133.33(CH), 137.56(C), 139.31(C), 145.80(C), 150.38(C), 150.78(C), 161.36(C), 166.63(CO of coumarin)

In all the compounds (4a-c), C$_1$ and C$_{12}$ protons appear in the downfield region due to the peri effect of nitrogen atom of pyridine ring.
Fig 19  IR spectrum of compound 4a

Fig 20  $^1$H NMR spectrum of compound 4a
Fig 21  $^{13}$C NMR spectrum of compound 4a

Fig 22  DEPT-135 spectrum of compound 4a
Fig 23  GC-Mass spectrum of compound 4a
**Fig 24**  $^1$H NMR spectrum of compound 4b

**Fig 25**  $^{13}$C NMR spectrum of compound 4b
Fig 26 $^1$H NMR spectrum of compound 4c

Fig 27 $^{13}$C NMR spectrum of compound 4c
3.2.4 Synthesis of 8,9-dihydrobenzo[h]coumarino[4,3-b]quinolines (5a-c)

The condensation of various 4-hydroxy coumarins (1a-c) with Mannich base of α-tetralone in the presence of ammonium acetate and acetic acid gave 8,9-dihydrobenzo[h]coumarino[4,3-b]quinolines (5a-c) in 73-81% yield (Scheme 6).

![Chemical structures](image)

The structures of all the compounds (5a-c) were confirmed by analytical and spectral data.

Thus, the condensation of 4-hydroxy coumarin (1a) with Mannich base of α-tetralone in the presence of ammonium acetate and acetic acid proceeded smoothly and gave the expected product (5a) as a white colored solid in 81% yield.
The IR spectrum of compound 5a (Fig 28) showed a strong band at 1732 cm\(^{-1}\), which is due to carbonyl stretching of \(\delta\)-lactone ring present in coumarin moiety. The bands observed at 1599 cm\(^{-1}\) and 1414 cm\(^{-1}\) are due to aromatic C=C and C=N stretching vibrations respectively. A band appeared at 2942 cm\(^{-1}\) is due to aliphatic C-H stretching. A band observed at 3050 cm\(^{-1}\) is due to aromatic C-H stretching.

The \(^1\)H NMR spectrum of compound 5a (in CDCl\(_3\)) (Fig 29) showed multiplet centered at 3.10 \(\delta\) (4H) which is due to two protons attached at C\(_8\) and two protons attached at C\(_9\). A multiplet observed between 7.31-7.61 \(\delta\) (6H) is due to protons attached at C\(_2\), C\(_3\), C\(_4\), C\(_{10}\), C\(_{11}\) and C\(_{12}\). A singlet observed at 8.42 \(\delta\) (1H) is due to proton attached at C\(_7\). A multiplet observed between 8.63-8.65 \(\delta\) (1H) is due to proton attached at C\(_{13}\). A multiplet observed between 8.77-8.79 \(\delta\) (1H) is due to proton attached at C\(_1\).

The \(^{13}\)C NMR spectrum of compound 5a (in CDCl\(_3\)) (Fig 30) showed signals at 27.65, 27.93, 115.57, 117.08, 119.75, 124.66, 126.66, 127.39, 128.11, 131.12, 131.57, 132.57, 133.47, 136.64, 139.65, 150.08, 152.53, 158.16 and 161.45 \(\delta\). Thus total nineteen carbons are seen. The compound is having twenty types of carbon atoms and hence expected number of signals is twenty. Experimentally the numbers of signals observed are nineteen. This may be due to overlapping of two carbon signals, which may have identical chemical shifts. The signals appeared at 27.65 \(\delta\) and 27.93 \(\delta\) are due to C\(_9\) and C\(_8\) respectively. The most downfield signal appeared at 160.45 \(\delta\) is due to the carbonyl carbon of the \(\delta\)-lactone ring of coumarin. The DEPT-135 spectrum of compound 4a (in CDCl\(_3\)) (Fig 31) showed inverted signals at 27.65 \(\delta\) and 27.93 \(\delta\), which are due to C\(_9\) and C\(_8\) respectively. The eight signals appeared for nine tertiary carbons at 117.08, 124.66, 126.66, 127.39, 128.11, 131.12, 131.57 and 136.64 \(\delta\). Thus two tertiary carbons may have identical chemical shifts.

The GC-mass spectrum of compound 5a (Fig 32) showed M\(^+\) peak at 299(100%) (m/z %) along with some other fragment peaks at 270(8%), 254(16%), 241(12%), 215(9%), 127(21%), 121(25%), 108 (17%), 75(5%), 63(5%), etc.
The IR and NMR data for the other compounds (5b-d) are given below.

**Compound 5b**

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

\(\nu_{\text{max}}\) 1732 (\(\delta\)-lactone carbonyl stretching of coumarin), 1602 and 1432 (aromatic C=C and C=N stretching), 2927 (aliphatic C-H stretching), 3043 (aromatic C-H stretching)

\(^1\)H NMR (\(\delta\), ppm) (CDCl\(_3\)) (Fig 33)

2.54 (3H, singlet, CH\(_3\)), 3.09 (4H, multiplet, protons at C\(_8\) and C\(_9\)), 7.28-7.50 (5H, multiplet, protons at C\(_3\), C\(_4\), C\(_10\), C\(_11\) and C\(_12\)), 8.41 (1H, singlet, proton at C\(_7\)), 8.54 (1H, doublet, \(J = 1.6\) Hz, proton at C\(_1\)), 8.64-8.65 (1H, multiplet, proton at C\(_{13}\))

\(^{13}\)C NMR (\(\delta\), ppm) (CDCl\(_3\)) (Fig 34)

21.09(CH\(_3\)), 27.70(C\(_9\)), 27.89(C\(_8\)), 115.60(C), 116.82(CH), 119.29(C), 124.31(CH), 126.60(CH), 127.39(CH), 128.15(CH), 131.03(CH), 132.42(C), 132.52(CH), 133.48(C), 134.33(C), 136.67(CH), 139.59(C), 150.20(C), 150.62(C), 158.09(C), 161.59(CO of coumarin)

**Compound 5c**

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

\(\nu_{\text{max}}\) 1732 (\(\delta\)-lactone carbonyl stretching of coumarin), 1599 and 1432 (aromatic C=C and C=N stretching), 2949 aliphatic C-H stretching), 3032 (aromatic C-H stretching)

\(^1\)H NMR (\(\delta\), ppm) (CDCl\(_3\)) (Fig 35)

3.10 (4H, multiplet, protons at C\(_8\) and C\(_9\)), 7.32-7.54 (5H, multiplet, protons at C\(_3\), C\(_4\), C\(_10\), C\(_11\) and C\(_12\)), 8.41 (1H, singlet, proton at C\(_7\)), 8.62-8.64 (1H, multiplet, proton at C\(_{13}\)), 8.71 (1H, doublet, \(J = 2.4\) Hz, proton at C\(_1\))

\(^{13}\)C NMR (\(\delta\), ppm) (CDCl\(_3\)) (Fig 36)

27.63(C\(_9\)), 27.99(C\(_8\)), 115.64(C), 118.62(CH), 124.18(CH), 126.74(CH), 127.59(CH), 128.26(CH), 130.33(C), 131.25(CH), 131.55(CH), 133.02(C), 133.32(C), 136.62(CH), 136.80(C), 139.55(C), 139.67(C), 150.89(C), 158.51(C), 160.89(CO of coumarin)

In all the compounds (5a-c), C\(_1\) and C\(_{13}\) protons appear in the downfield region due to the peri effect of nitrogen atom of pyridine ring.
Fig 28  IR spectrum of compound 5a

Fig 29  $^1$H NMR spectrum of compound 5a
Fig 30  $^{13}$C NMR spectrum of compound 5a

Fig 31  DEPT-135 spectrum of compound 5a
Fig 32  GC-Mass spectrum of compound 5a
**Fig 33**  $^1$H NMR spectrum of compound 5b

**Fig 34**  $^{13}$C NMR spectrum of compound 5b
Fig 35 \(^{1}H\) NMR spectrum of compound 5c

Fig 36 \(^{13}C\) NMR spectrum of compound 5c
In addition to pyrido/quino fused coumarins (2a-c), (3a-c), (4a-c) and (5a-c); synthesis of some pyridyl/quinolinyl carbonyl substituted coumarins have also been carried out. The compounds have been synthesized by reacting 4-methyl-7-oxa-10-oxo-benzo[h] coumarin-9-carbaldehyde with cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively in the presence of ammonium acetate in refluxing acetic acid. The synthetic methodology is outlined below.

![Chemical Structures](image)

**Scheme 7**

The chromonaldehyde (6) reacts with cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively and gets transformed into (7), (8), (9) and (10). The possible reaction mechanism for this transformation is shown in scheme 8.
3.2.5 Synthesis of 8-(6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonyl)-7-hydroxy-4-methylcoumarin (7), 7-hydroxy-4-methyl-8-(5,6,7,8-tetrahydroquinoline-3-carbonyl)coumarin (8), 7-hydroxy-8-(5H-indeno[1,2-b]pyridine-3-carbonyl)-4-methylcoumarin (9) and 8-(5,6-dihydrobenzo[h]quinoline-3-carbonyl)-7-hydroxy-4-methylcoumarin (10)
The compounds (7-10) have been synthesized by reacting 4-methyl-7-oxa-10-oxo-benzo[\(h\)]coumarin-9-carbaldehyde with cyclopentanone, cyclohexanone, 1-indanone and \(\alpha\)-tetralone respectively in the presence of ammonium acetate in refluxing acetic acid (Scheme 9).
The condensation of 4-methyl-7-oxa-10-oxo-benzo[h]coumarin-9-carbaldehyde with cyclopentanone, cyclohexanone, 1-indanone and \(\alpha\)-tetralone respectively in the presence of ammonium acetate in refluxing glacial acetic acid proceeded smoothly and gave the expected products (7, 8, 9 and 10) in 58-67% yield.

The structures of all the compounds (7-10) were confirmed by analytical and spectral data.

Thus, the reaction of 4-methyl-7-oxa-10-oxo-benzo[h]coumarin-9-carbaldehyde (6) with cyclopentanone in the presence of ammonium acetate in refluxing acetic acid gave compound (7) as a yellow colored solid product in 61% yield.

The IR spectrum of compound 7 (Fig 37) showed a strong band at 1714 cm\(^{-1}\) which is due to carbonyl stretching of \(\delta\)-lactone ring present in coumarin moiety. The ketone carbonyl stretching band was observed at 1680 cm\(^{-1}\). The bands observed at 1593 cm\(^{-1}\) and 1385 cm\(^{-1}\) are due to aromatic C=C and C=N stretching vibrations respectively. A band appeared at 2963 cm\(^{-1}\) is due to aliphatic C-H stretching. The band observed at 3053 cm\(^{-1}\) is due to aromatic C-H stretching vibrations. A broad band observed at 3435 cm\(^{-1}\) is due to phenolic -OH stretchings.

The \(^1\)H NMR spectrum of compound 7 (in DMSO-d\(_6\)) (Fig 38) showed a singlet at 2.42 \(\delta\) and integrating for three protons. This is due to methyl group. A multiplet centered at 2.98 \(\delta\) is for the six protons attached to C5', C6' and C7'. A singlet observed at 6.18 \(\delta\) (1H) is due to proton at C3. The C6-H and C5-H signals appeared as doublets at 6.98 \(\delta\) (\(J = 8.8\) Hz) and 7.76 (\(J = 8.8\) Hz) respectively. The poorly resolved doublets observed at 7.95 \(\delta\) (1H) and 8.61 \(\delta\) (1H) are due to protons at C4' and C2' respectively. A singlet appeared at 10.97 \(\delta\) integrating for one proton is due to –OH proton, which was confirmed by recording D\(_2\)O exchanged spectrum (spectrum not shown).

The \(^{13}\)C NMR spectrum of compound 7 (in DMSO-d\(_6\)) (Fig 39) showed signals at 18.75, 23.19, 30.25, 34.42, 111.16, 112.61, 113.14, 114.75, 128.06, 130.72, 132.08, 138.10, 149.57, 151.95, 154.12, 158.38, 159.89, 171.87 and 192.18 \(\delta\) corresponding to nineteen
different type of carbon atoms present in the compound. The signal appeared at 18.75 \( \delta \) is due to carbon of methyl group. The signal appeared at 23.19 \( \delta \) is due to \( C_{6} \). The signals appeared at 30.25 \( \delta \) and 34.42 \( \delta \) are due to \( C_{5} \) and \( C_{7} \) respectively. The most downfield signal appeared at 192.18 \( \delta \) is due to the carbonyl carbon of ketone function. The DEPT-135 spectrum of compound 7 (in DMSO-\( d_{6} \)) (Fig 40) showed inverted signals at 23.21, 30.24 and 34.42 \( \delta \), which are due to \( C_{6} \), \( C_{5} \) and \( C_{7} \) respectively. The signals appeared at 111.15, 113.20, 128.01, 132.07 and 149.57 \( \delta \) are due to five tertiary carbons.

The GC-mass spectrum of compound 5a (Fig 41) showed \( M^{+} \) peak at 321(23%) (m/z %) along with some other fragment peaks at 292(1%), 203(1%), 118(6%), 91(3%), 73(5%), 69(18%), 60(4%), 57 (12%), 55(17%), 44(100%), etc.

The IR and NMR data for other compounds (8-10) are given below.

**Compound 8**

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

\( \nu_{\text{max}} \) 1692 (C=O stretching of \( \delta \)-lactone of coumarin), 1684 (carbonyl stretching of ketone group), 1586 and 1382 (aromatic C=C and C=N stretchings), 2934 aliphatic C-H stretching), 3070 (aromatic C-H stretching), 3434 (O-H stretchings).

**\(^{1}\)H NMR (\( \delta \), ppm) (DMSO-\( d_{6} \)) (Fig 42)**

1.80 (4H, multiplet, protons at \( C_{6} \) and \( C_{7} \)), 2.41 (3H, singlet, \( CH_{3} \)), 2.84 (4H, multiplet, protons at \( C_{5} \) and \( C_{8} \)), 6.17 (1H, singlet, proton at \( C_{3} \)), 6.98 (1H, doublet, \( J = 8.8 \) Hz, proton at \( C_{6} \)), 7.75 (1H, doublet, \( J = 8.8 \) Hz, proton at \( C_{5} \)), 7.83 (1H, poorly resolved doublet, proton at \( C_{4} \)), 8.58 (1H, poorly resolved doublet, proton at \( C_{2} \)), 10.95 (1H, singlet, OH proton, \( D_{2}O \) exchangeable)

**\(^{13}\)C NMR (\( \delta \), ppm) (DMSO-\( d_{6} \)) (Fig 43)**

18.70(\( CH_{3} \)), 22.36(\( C_{6} \)), 22.65(\( C_{7} \)), 28.34(\( C_{5} \)), 32.96(\( C_{8} \)), 111.16(\( CH \), 112.64(\( C \)), 113.16(\( CH \)), 114.64(\( C \)), 128.06(\( CH \)), 130.23(\( C \)), 133.01(\( C \)), 136.81(\( CH \)), 147.88(\( CH \)), 151.97(\( C \)), 154.04(\( C \)), 158.41(\( C \)), 159.83(\( C \)), 163.34(\( C \)), 192.04(ketone carbonyl)
**Compound 9**

**IR (cm⁻¹)**

$\nu_{max}$ 1731 (C=O stretching of $\delta$-lactone of coumarin), 1674 (carbonyl stretching of ketone group), 1600 and 1383 (aromatic C=C and C=N stretchings), 2957 aliphatic C-H stretching), 3072 (aromatic C-H stretching), 3380 (O-H stretchings).

$^1$H NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 44)

2.44 (3H, singlet, CH$_3$), 4.05 (2H, singlet, proton at C$_5'$), 6.20 (1H, singlet, proton at C$_3$), 7.02 (1H, doublet, $J = 8.4$ Hz, proton at C$_6$), 7.50-7.73 (3H, multiplet, protons at C$_6'$, C$_7'$ and C$_8'$), 7.80 (1H, doublet, $J = 8.8$ Hz, proton at C$_5$), 8.06 (1H, multiplet, proton at C$_9$), 8.32 (1H, poorly resolved doublet, proton at C$_4'$), 8.91 (1H, poorly resolved doublet, proton at C$_2'$), 11.02 (1H, singlet, OH proton, D$_2$O exchangeable)

$^{13}$C NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 45)

18.75(CH$_3$), 34.68(C$_5'$), 111.20(CH), 112.70(C), 113.22(CH), 114.73(C), 121.89(CH), 126.31(CH), 127.99(CH), 128.16(CH), 130.37(C), 130.68(CH), 133.06(CH), 137.66(C), 139.62(C), 146.38(C), 150.62(CH), 152.03(C), 154.10(C), 158.48(C), 159.88(C), 164.43(C), 192.06 (ketone carbonyl)

**Compound 10**

**IR (cm⁻¹)**

$\nu_{max}$ 1744 (C=O stretching of $\delta$-lactone of coumarin), 1646 (carbonyl stretching of ketone group), 1584 and 1384 (aromatic C=C and C=N stretchings), 2956 aliphatic C-H stretching), 3076 (aromatic C-H stretching), 3249 (O-H stretchings)

$^1$H NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 46)

2.43 (3H, singlet, CH$_3$), 2.98 (4H, multiplet, protons at C$_5'$ and C$_6'$), 6.20 (1H, singlet, proton at C$_3$), 7.01 (1H, doublet, $J = 8.8$ Hz, proton at C$_6$), 7.33-7.44 (3H, multiplet, protons at C$_7'$, C$_8'$ and C$_9'$), 7.79 (1H, doublet, $J = 8.8$ Hz, proton at C$_5$), 8.06 (1H, poorly resolved doublet, proton at C$_4'$), 8.25 (1H, multiplet, proton at C$_10'$), 8.78 (1H, poorly resolved doublet, proton at C$_2'$), 11.02 (1H, singlet, OH proton, D$_2$O exchangeable)
$^{13}$C NMR (δ, ppm) (DMSO-d$_6$) (Fig 47)
18.76(CH$_3$), 27.30(C$_6$'), 27.37(C$_5$'), 111.20(CH), 112.71(C), 113.18(CH), 114.55(C), 125.95(CH), 127.59(CH), 128.18(CH), 128.69(CH), 130.99(CH), 131.05(C), 132.61(C), 133.59(C), 136.13(CH), 139.69(C), 149.38(CH), 152.03(C), 154.09(C), 156.39(C), 158.45(C), 159.88(C), 191.80 (ketone carbonyl)
**Fig 37** IR spectrum of compound 7

**Fig 38** $^1$H NMR spectrum of compound 7
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**Fig 39**  
$^{13}$C NMR spectrum of compound 7

**Fig 40**  
DEPT-135 spectrum of compound 7
Fig 41  GC-Mass spectrum of compound 7
Fig 42 $^1$H NMR spectrum of compound 8

Fig 43 $^{13}$C NMR spectrum of compound 8
Fig 44  $^{1}$H NMR spectrum of compound 9

Fig 45  $^{13}$C NMR spectrum of compound 9
**Fig 46** $^1$H NMR spectrum of compound 10

**Fig 47** $^{13}$C NMR spectrum of compound 10
3.3 Experimental

3.3.1 Preparation of 4-hydroxy coumarin and 6-methyl-4-hydroxy coumarin

\[
\begin{align*}
\text{R} & \quad \text{OH} & \quad \text{COOH} & \quad \text{ZnCl}_2 & \quad \text{POCl}_3 & \quad \text{R} & \quad \text{OH} \\
\text{(1a-b)}
\end{align*}
\]

In a 500 mL round bottom flask attached with a reflux condenser and gas absorption trap, a mixture of appropriate phenol (0.2 mol), malonic acid (0.2 mol), anhydrous zinc chloride (0.6 mol) and phosphorous oxychloride (0.4 mol) was heated with stirring at 60-65°C for 35 hours. The yellow colored mixture was cooled and decomposed with water and left overnight. The resulting crude 4-hydroxy coumarin was filtered out, washed with water and dried. This crude product was purified by dissolving it in 10% sodium bicarbonate solution, filtering and reprecipitating by adding dilute HCl solution. The product was separated out as a yellowish-white colored solid. This was filtered out, washed with water, dried and recrystallized from ethanol.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>%Yield</th>
<th>mp</th>
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<tbody>
<tr>
<td>(1a) R = H,</td>
<td>60%</td>
<td>204°C (lit(^2^9) mp 206°C)</td>
</tr>
<tr>
<td>(1b) R = CH(_3),</td>
<td>43%</td>
<td>238°C (lit(^2^9) mp 240°C)</td>
</tr>
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</table>

3.3.2 Preparation of 6-chloro-4-hydroxy coumarin

In a 250 mL round bottom flask fitted with reflux condenser, a mixture of p-chloro phenol (0.2 mol), malonic acid (0.1 mol) and phosphorous oxychloride (0.2 mol) was placed. The reaction mixture was heated for 30 minutes on boiling water bath. It was cooled and poured into ice-cold water. The white solid obtained was filtered and washed with cold water. It was then washed with saturated sodium bicarbonate solution to remove unreacted malonic acid. Finally, it was washed with water and dried. Thus, diester was obtained which was recrystallized from ether-hexane.

Yield: 68%        mp 115°C
The above diester (20 g) and anhydrous aluminum chloride (20.6 g) were taken in a round bottom flask. The flask was stoppered and shaken vigorously for 2-3 minutes. A reflux condenser provided with gas absorption tube was attached and the flask was heated in an oil bath at 180-185°C for 30 minutes. The reaction mixture was allowed to cool to room temperature and then flask was immersed in an ice bath. The reaction mixture was decomposed by dilute HCl (1:7) over a period of about 2 hours. The content was then heated on steam bath for 30 minutes with vigorous stirring in order to effect the complete decomposition. The solid product obtained was filtered out and washed with water and dried. The product was then dissolved in 5% aqueous sodium hydroxide solution and the solution was filtered. The product was then reprecipitated by adding dilute HCl, until solution was acidic. The precipitates were filtered out, washed with water and dried. It was recrystallized from ethyl acetate-hexane.

Compound: (1c)  Yield:  66%  mp 262°C (lit30 mp 264°C)

3.3.3 Preparation of Mannich bases of cyclopentanone, cyclo-hexanone, 1-indanone and α-tetralone (cyclic ketones)

The following general procedure was used.

In a 100 mL round bottom flask, was placed dimethyl amine hydrochloride (0.033 mol), powdered paraformaldehyde (0.033 mol) and appropriate cyclic ketone (0.025 mol). To this 40 ml ethanol and
0.5 ml HCl were added and the reaction mixture was refluxed on water bath for 3 hours. It was then poured into 200 ml acetone (while still warm), allowed to come to room temperature and left overnight in a refrigerator. The crystalline product separated out was filtered, washed with cold acetone and dried at 40-50°C for 6 hours.

**Mannich base of cyclopentanone (salt form):**

Yield: 76%,

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>%N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found (C₈H₁₆ClNO)</td>
<td>53.86</td>
<td>9.01</td>
<td>7.79</td>
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<td>Calculated</td>
<td>54.08</td>
<td>9.08</td>
<td>7.88</td>
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**IR (cm⁻¹)**

ν max 1720 (C=O stretching of cyclopentanone), 1640 and 1470 (N-H bending of tertiary amine salt), 2850 and 2770 (N-H stretchings of tertiary amine salt), 2970 (aliphatic C-H stretching), 3400 (hydrogen bonded N-H stretching)

^1H NMR (δ, ppm) (CDCl₃)

1.72-2.44 (6H, multiplet, -(CH₂)₃- i.e. protons at C₃, C₄ and C₅ of cyclopentanone ring), 2.70 (1H, multiplet, proton at C₂ of cyclopentanone ring), 2.86 and 2.88 (6H, two singlets, 2 x CH₃), 3.00-3.42 (2H, multiplet, CH₂-N(CH₃)₂)

**Mannich base of cyclohexanone (salt form):**

Yield: 83%,

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<tr>
<td>Found (C₁₂H₁₆ClNO)</td>
<td>63.62</td>
<td>7.08</td>
<td>6.30</td>
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<tr>
<td>Calculated</td>
<td>63.85</td>
<td>7.14</td>
<td>6.21</td>
</tr>
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</table>

**IR (cm⁻¹)**

ν max 1710 (C=O stretching of cyclopentanone), 1610 and 1470 (N-H bending of tertiary amine salt), 2930 and 2770 (N-H stretchings of tertiary amine salt), 2960 (aliphatic C-H stretching), 3400 (hydrogen bonded N-H stretching)

^1H NMR (δ, ppm) (CDCl₃)

2.94 and 2.98 (6H, two singlets, 2 x CH₃), 3.23-3.78 (5H, multiplet, protons at C₂ and C₃ of 1-indanone and CH₂-N(CH₃)₂), 7.37-7.74 (4H,
multiplet, aromatic protons)

**Mannich base of α-tetralone (salt form):**

Yield: 81%, mp 148-149°C (lit\(^{32}\) mp 150°C)

### 3.3.4 Preparation of 8H-9,10-dihydrocoumarino[4,3-b]cyclopepta[e]pyridines (2a-c)

![Chemical Structure of 2a-c](image)

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, an appropriate 4-hydroxy coumarin (1a-c) (0.004 mol) was taken in glacial acetic acid (15 mL). To this, ammonium acetate (0.04 mol) was added with stirring at room temperature. Then a solution of Mannich base of cyclopentanone (0.004 mol) in acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 45 minutes and then refluxed in an oil bath at 140-150°C for 8 hours and cool to room temperature. The reaction mixture was poured into cold water (75 mL) and the gummy mass obtained was extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with 10% sodium bicarbonate solution (3 x 20 mL) and then with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under vacuum gave a solid product. This was purified by column chromatography using silica gel and ethyl acetate-petroleum ether (60-80) (2:8) as an eluent. Thus, 8H-9,10-dihydrocoumarino[4,3-b]cyclopepta[e]pyridines (2a-c) were obtained as white colored solid, which were recrystallized from chloroform-hexane.

**Compound 2a**: (R = H)

Yield = 72%  mp 164-166°C  Molecular Formula: C\(_{15}\)H\(_{11}\)NO\(_2\)

Analysis  % C  % H  % N
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Department of Chemistry, Sardar Patel University 150

Found 75.62 4.60 5.98
Calculated 75.94 4.67 5.90

**Compound 2b**: (R = CH₃)
Yield = 75% mp 204-206°C Molecular Formula: C₁₆H₁₃NO₂
Analysis % C % H % N
Found 76.73 5.26 5.49
Calculated 76.48 5.21 5.57

**Compound 2c**: (R = Cl)
Yield = 78% mp 218-219°C Molecular Formula: C₁₅H₁₀ClNO₂
Analysis % C % H % N
Found 66.02 3.65 5.09
Calculated 66.31 3.71 5.16

3.3.5 Preparation of 8,9,10,11-tetrahydrocoumarino[4,3-b]quino- lines (3a-c)

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, an appropriate 4-hydroxy coumarin (1a-c) (0.004 mol) was taken in glacial acetic acid (15 mL). To this, ammonium acetate (0.04 mol) was added with stirring at room temperature. Then a solution of Mannich base of cyclohexanone (0.004 mol) in acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 45 minutes and then refluxed in an oil bath at 140-150°C for 8 hours and cool to room temperature. The reaction mixture was poured into ice cold water (75 mL) and the gummy mass obtained was extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with 10% sodium bicarbonate solution (3 x 20 mL) and then with water (3 x 20 mL). It
was dried over anhydrous sodium sulfate. The removal of chloroform under vacuum gave a solid product. This was purified by column chromatography using silica gel and ethyl acetate-petroleum ether (60-80) (2:8) as an eluent. Thus, 8,9,10,11-tetrahydrocoumarino[4,3-b]quinolines (3a-c) were obtained as white colored solid, which were recrystallized from chloroform-hexane.

**Compound 3a**: (R = H)

Yield = 84%  
mp 159-161°C  
Molecular Formula: C₁₆H₁₃NO₂

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<th>% H</th>
<th>% N</th>
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<td>5.48</td>
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<td>Calculated</td>
<td>76.48</td>
<td>5.21</td>
<td>5.57</td>
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**Compound 3b**: (R = CH₃)

Yield = 80%  
mp 150-152°C  
Molecular Formula: C₁₇H₁₅NO₂

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<tr>
<td>Found</td>
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<tr>
<td>Calculated</td>
<td>76.96</td>
<td>5.70</td>
<td>5.28</td>
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**Compound 3c**: (R = Cl)

Yield = 77%  
mp 208-210°C  
Molecular Formula: C₁₆H₁₂ClNO₂

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<tr>
<td>Found</td>
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<tr>
<td>Calculated</td>
<td>67.26</td>
<td>4.23</td>
<td>4.90</td>
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### 3.3.6 Preparation of 8H-coumarino[4,3-b]inden[2,1-e]pyridines (4a-c)

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, an appropriate 4-hydroxy coumarin (1a-c) (0.004 mol) was taken in
glacial acetic acid (15 mL). To this, ammonium acetate (0.04 mol) was added with stirring at room temperature. Then a solution of Mannich base of 1-indanone (0.004 mol) in acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 45 minutes and then refluxed in an oil bath at 140-150°C for 8 hours and cool to room temperature. The reaction mixture was poured into ice cold water (75 mL) and the gummy mass obtained was extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with 10% sodium bicarbonate solution (3 x 20 mL) and then with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under vacuum gave a solid product. This was purified by column chromatography using silica gel and ethyl acetate-petroleum ether (60-80) (2:8) as an eluent. Thus, 8H-coumarino[4,3-b]indeno[2,1-e]pyridines (4a-c) were obtained as white colored solid, which were recrystallized from chloroform-hexane.

**Compound 4a**: (R = H)

Yield = 76%  
mp 256-258°C  
Molecular Formula: C\textsubscript{19}H\textsubscript{11}NO\textsubscript{2}

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
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<tbody>
<tr>
<td>Found</td>
<td>80.25</td>
<td>3.82</td>
<td>4.83</td>
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<tr>
<td>Calculated</td>
<td>79.99</td>
<td>3.89</td>
<td>4.91</td>
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**Compound 4b**: (R = CH\textsubscript{3})

Yield = 71%  
mp 248-250°C  
Molecular Formula: C\textsubscript{20}H\textsubscript{13}NO\textsubscript{2}

<table>
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<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
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**Compound 4c**: (R = Cl)

Yield = 68%  
mp 294-295°C  
Molecular Formula: C\textsubscript{19}H\textsubscript{10}ClNO\textsubscript{2}

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<th>Analysis</th>
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<td>71.37</td>
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3.3.7 Preparation of 8,9-dihydrobenzo[h]coumarino[4,3-b]quinolines (5a-c)

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, an appropriate 4-hydroxy coumarin (1a-c) (0.004 mol) was taken in glacial acetic acid (15 mL). To this, ammonium acetate (0.04 mol) was added with stirring at room temperature. Then a solution of Mannich base of α-tetralone (0.004 mol) in acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 45 minutes and then refluxed in an oil bath at 140-150˚C for 8 hours and cool to room temperature. The reaction mixture was poured into ice cold water (75 mL) and the gummy mass obtained was extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with 10% sodium bicarbonate solution (3 x 20 mL) and then with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under vacuum gave a solid product. This was purified by column chromatography using silica gel and ethyl acetate-petroleum ether (60-80) (2:8) as an eluent. Thus, 8,9-dihydrobenzo[h]coumarino[4,3-b]quinolines (5a-c) were obtained as white colored solid, which were recrystallized from chloroform-hexane.

**Compound 5a**: (R = H)

Yield = 81%  
mp 212-214˚C  
Molecular Formula: C_{20}H_{13}NO_{2}

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<td>4.68</td>
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**Compound 5b**: (R = CH₃)

Yield = 76%  mp 224-226°C  Molecular Formula: C₂₁H₁₅NO₂

Analysis  % C  % H  % N

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**Compound 5c**: (R = Cl)

Yield = 73%  mp 229-231°C  Molecular Formula: C₂₀H₁₂ClNO₂

Analysis  % C  % H  % N

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<td>71.97</td>
<td>3.62</td>
<td>4.20</td>
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### 3.3.8 Preparation of 4-methyl-7-acetoxy coumarin

![Chemical structure of 4-methyl-7-acetoxy coumarin](image)

A mixture of 4-methyl-7-hydroxy coumarin (0.16 mol) and acetic anhydride (0.56 mol) was placed in a 250 mL round bottom flask fitted with a reflux condenser. The reaction mixture was refluxed for 1.5 hours in an oil bath. It was then cooled to about 50°C and poured with vigorous stirring in to ice cold water. The solid obtained was filtered, washed with cold water and dried. It was recrystallized from ethanol.

Yield: 90%  m.p.148°C (lit.³³ m.p.150-151°C)

### 3.3.9 Preparation of 4-methyl-7-hydroxy-8-acetyl coumarin

![Chemical structure of 4-methyl-7-hydroxy-8-acetyl coumarin](image)

A powdered 4-methyl-7-acetoxy coumarin (0.34 mol) and finely powdered anhydrous aluminum chloride were placed in a 500 mL round bottom flask. The flask was stoppered and shaken vigorously for 3 to 5 minutes in order to mix the ingredients thoroughly. The stopper was removed and the flask was attached with reflux condenser, provided with a gas-absorption tube. The flask was placed
in an oil bath and the temperature was quickly raised to 125°C and then slowly to 170°C over a period of 2 hours. At the end of this, the flask was removed from the oil bath, allowed to cool and immersed in an ice bath. About 100g of crushed ice was added slowly and then 240 mL of dilute hydrochloric acid (1:7) was added over a period of about 2 hours. The reaction mixture was then heated on a steam bath for 30 minutes with vigorous stirring in order to effect complete decomposition. It was cooled and the solid was filtered out, washed with three 50 mL portions of cold water and dried. It was recrystallized from R-spirit.

Yield: 70% m.p.161°C (lit. 162-163°C)

3.3.10 Preparation of 4-methyl-7-oxa-10-oxo-benzo[h]coumarin-9-carbaldehyde (6)

In a 250 mL three necked round bottom flask fitted with addition funnel and guard tube, 4-methyl-7-hydroxy-8-acetyl coumarin (0.06 mol) was taken in anhydrous dimethyl formamide (DMF) (0.6 mol) and the reaction mixture was cooled to 0°C with stirring. In this well stirred reaction mixture, phosphorous oxychloride (POCl₃) (0.18 mol) was added dropwise during one hour. After addition was completed, the reaction mixture was further stirred at 0°C for one hour. The reaction mixture was then heated at 65-70°C for two hours. It was then poured into crushed ice (200 g) and left overnight in refrigerator, during which a solid product was separated out which was filtered off, washed with sodium carbonate (5%, 3 x 30 mL) and water. It was then dried and recrystallized from chloroform.

**Compound 6:** Yield: 87% m.p.309°C (lit. 310-312°C)
3.3.11 Preparation of 8-(6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonyl)-7-hydroxy-4-methylcoumarin (7), 7-hydroxy-4-methyl-8-(5,6,7,8-tetrahydroquinoline-3-carbonyl)coumarin (8), 7-hydroxy-8-(5H-indeno[1,2-b]pyridine-3-carbonyl)-4-methylcoumarin (9) and 8-(5,6-dihydrobenzo[h]quinoline-3-carbonyl)-7-hydroxy-4-methylcoumarin (10)

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 4-methyl-7-oxa-10-oxo-benzo[h]coumarin-9-carbaldehyde (6) (0.004 mol) was taken in glacial acetic acid (15 mL). To this, ammonium acetate (0.04 mol) was added with stirring at room temperature. Then a solution of appropriate cyclic ketone (0.004 mol) in acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 45 minutes and then refluxed in an oil bath at 140°C for 12 hours. It was then cooled to room temperature and was poured into ice cold water (75 mL). The gummy mass obtained was extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with 10% sodium bicarbonate solution (3 x 20 mL) and then with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under vacuum gave a solid product. This was purified by column chromatography using silica gel and ethyl acetate-petroleum ether (60-80) (3:7) as an eluent. Thus, 8-(6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonyl)-7-hydroxy-4-methylcoumarin (7), 7-hydroxy-4-methyl-8-(5,6,7,8-tetrahydroquinoline-3-carbonyl)coumarin (8), 7-hyd-
roxy-8-\{(5H\text{-}indeno[1,2-\text{b}]pyridine-3-carbonyl)\}-4-methylcoumarin (9) and 8-\{(5,6-dihydrobenzo[h]quinoline-3-carbonyl)\}-7-hydroxy-4-methyl coumarin (10) were obtained as yellow colored solid, which were recrystallized from chloroform-hexane.

**Compound 7:** \( n = 1, \)

- **Yield** = 61%
- **mp** 241-243°C
- **Molecular Formula:** \( \text{C}_{19}\text{H}_{15}\text{NO}_4 \)
- **Analysis**
  - % C: Found 71.31, Calculated 71.02
  - % H: 4.77, 4.71
  - % N: 4.28, 4.36

**Compound 8:** \( n = 2, \)

- **Yield** = 65%
- **mp** 254-256°C
- **Molecular Formula:** \( \text{C}_{20}\text{H}_{17}\text{NO}_4 \)
- **Analysis**
  - % C: Found 71.32, Calculated 71.63
  - % H: 5.06, 5.11
  - % N: 4.11, 4.18

**Compound 9:** \( n = 1, \)

- **Yield** = 58%
- **mp** 136-138°C
- **Molecular Formula:** \( \text{C}_{23}\text{H}_{15}\text{NO}_4 \)
- **Analysis**
  - % C: Found 74.48, Calculated 74.79
  - % H: 4.03, 4.09
  - % N: 3.70, 3.79

**Compound 10:** \( n = 2, \)

- **Yield** = 67%
- **mp** 239-241°C
- **Molecular Formula:** \( \text{C}_{24}\text{H}_{17}\text{NO}_4 \)
- **Analysis**
  - % C: Found 74.86, Calculated 75.19
  - % H: 4.42, 4.47
  - % N: 3.57, 3.65
Synthesis of coumarinyl substituted coumarino[4,3-b]pyridines

The work incorporated in this section is on the synthesis of various coumarinyl substituted coumarino[4,3-b]pyridines. The compounds have been synthesized by reacting various 4-chloro-3-formyl coumarins with 3-coumarinoyl methyl pyridinium salts in the presence of ammonium acetate in refluxing acetic acid. The structures of all the synthesized compounds have been supported by analytical and spectral data.

3.4 Introduction

Pyrido fused coumarins form an important group of coumarin derivatives among the nitrogen containing heterocyclic fused coumarin derivatives and thus, are widely studied by number of chemists as discussed in section 1 of this chapter. Similarly, pyridyl substituted coumarins are also widely studied as discussed in chapter 2. Thus both, pyrido fused and pyridyl substituted coumarins, are important derivatives from biological activity point of view. This prompted us to synthesize coumarin derivatives of type (A) which incorporate both of these structural features as shown below.
The above structure (A) possesses both the structural features i.e. pyrido fused and pyridyl substituted pattern and therefore, one can expect a better biological efficiency from such coumarin derivatives.

Considering this objective in mind, synthesis of various coumarinyl substituted pyrido[3,2-c]coumarins i.e. 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines have been carried out.

3.5 Present work

In the present work, various 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines (3) have been synthesized by reacting various 4-chloro-3-formyl coumarins (1) with 3-coumarinoyl methyl pyridinium salts (2) in the presence of ammonium acetate in refluxing acetic acid (Scheme 1).

![Scheme 1](image.png)

The present synthetic methodology provides a new method for the synthesis of pyrido[3,2-c]coumarins and utilizes a simple and easily available starting materials.

3.5.1 Synthesis of 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines (3a-l)

The synthesis of 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines (3a-l) have been carried out by reacting various 4-chloro-3-formyl coumarins (1a-d) with 3-(ω-bromoacetyl) coumarin pyridinium salt (2a-c) in the presence of ammonium acetate in refluxing acetic acid (Scheme 2).
**Scheme 2**

The condensation of various 4-chloro-3-formyl coumarins (1a-d) with 3-(ω-bromoacetyl)coumarin pyridinium salt (2a-c) in the presence of ammonium acetate in refluxing acetic acid proceeded smoothly and gave the expected products (3a-l) in 54-79% yield. In the reaction, the salt acts as an enolate of 3-acetyl coumarin. The detailed mechanism for the formation of compounds (3a-l) is shown in scheme 3.
The structures of all the compounds (3a-l) were confirmed by analytical and spectral data.

Thus, the reaction of 4-chloro-3-formyl coumarin (1a) with 3-(ω-bromoacetyl)coumarin pyridinium salt (2a) in the presence of ammonium acetate in refluxing acetic acid gave a compound (3a) as a light brown colored solid product in 62% yield.
The IR spectrum of 3a (Fig 1) showed a strong band at 1689 cm\(^{-1}\) which is due to carbonyl stretching of δ-lactone ring present in coumarin nucleus. The bands observed at 1624 and 1501 cm\(^{-1}\) are due to aromatic C=C and C=N stretching vibrations respectively. The band observed at 3123 cm\(^{-1}\) is due to aromatic C-H stretching vibrations.

In the \(^1^H\) NMR spectrum of compound 3a (in CDCl\(_3\)+TFA-d\(_1\)) (Fig 2), all the ten aromatic protons were observed in the region 7.35-8.74 δ. The most downfield signal appearing as a singlet at 9.03 δ is due to a proton attached at C\(_4\)′. A broad singlet appeared at 8.74 δ integrating for one proton, is due to proton attached at C\(_{10}\). The remaining nine aromatic protons were observed between 7.35-8.12 δ as a multiplet. The protons at C\(_4\)′ and C\(_{10}\) appear in the downfield region compared to other aromatic protons due to peri effect of nitrogen atom.

The \(^1^3^C\) spectrum of compound 3a (in CDCl\(_3\)+TFA-d\(_1\)) (Fig 3) showed signals at 110.00, 112.82, 115.63, 117.62, 117.77, 118.48, 119.46, 125.58, 125.75, 126.64, 131.44, 133.15, 136.24, 136.51, 139.18, 142.86, 147.78, 154.52, 163.22 and 163.96 δ corresponding to twenty different types of carbon atoms present in the compound. The most downfield signals appearing at 163.22 and 163.96 δ can be assigned to the carbonyl carbons of the δ-lactone ring of coumarin. The DEPT-135 spectrum of compound 3a (in CDCl\(_3\)+TFA-d\(_1\)) (Fig 4) showed signals at 117.63, 117.79, 118.49, 119.48, 125.60, 125.77, 126.63, 136.25, 136.49, 142.96 and 147.81 δ are for eleven tertiary carbons.

The mass spectrum of compound 3a (Fig 5) did not show M\(^+\) peak. The peak at highest m/z value observed is at 285(5%) (m/z %) which corresponds to (M\(^+\)-56). This can be due to the loss of two neutral carbon monoxide molecules from molecular ion. Some other fragments peaks were observed at 189 (100%), 172(17%), 162(21%), 144(15%), 133(36%), 121(93%), 105(11%), 92(68%), 77(10%), 63(31%), etc.

It is important to note over here that in the IR spectra, the δ-lactone carbonyl stretching frequency of all the compounds was
observed somewhat lower than the expected frequency (~1710 cm\(^{-1}\)). This may possibly due to the reduction of carbonyl character of \(\delta\)-lactone ring by the nitrogen of pyridine ring. In the \(^1\)H NMR spectra, which were recorded in CDCl\(_3\), the aromatic protons signals were observed in the region 6.5-8.0 \(\delta\). However, in the spectra which were recorded in CDCl\(_3\)+TFA-d\(_1\), the aromatic protons signals were observed in somewhat downfield range (7.3-9.0 \(\delta\)). Similarly, those spectra which were recorded in DMSO-d\(_6\), the aromatic protons signals were observed even in more downfield region (7.3-10.8 \(\delta\)). The shifting of the aromatic signals in the downfield region in DMSO-d\(_6\) compared to CDCl\(_3\) is expected. However, in the present case the shifting of the signals is somewhat more than expected which may be due to the electric field and magnetic anisotropy of the DMSO solvent\(^{35}\). Such type of shift in downfield region was also observed in \(^{13}\)C NMR spectra when they were recorded in DMSO-d\(_6\).

In \(^1\)H NMR (the spectra recorded in CDCl\(_3\)), the C\(_4\)' proton and C\(_{10}\) proton were observed in most downfield region and were separated out from other aromatic protons. Similarly, in the spectra which were recorded in DMSO-d\(_6\), C\(_4\)' proton, C\(_{10}\) proton and C\(_4\) proton were observed in downfield region compared to other aromatic protons. The appearance of C\(_4\)' proton, C\(_{10}\) proton and C\(_4\) proton in downfield region is due to the peri effect.

The IR and NMR data for other compounds (3b-l) are given below.

**Compound 3b**

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

\(\nu_{\text{max}}\) 1696 (C=O stretching of \(\delta\)-lactone of coumarin), 1631 and 1502 (aromatic C=C and C=N stretchings), 3137 (aromatic C-H stretching)

\(\text{\(^1\)H NMR (}\delta, \text{ ppm) (CDCl}_3\text{+TFA-d}_1\) (Fig 6)\)

3.97 (3H, singlet, OCH\(_3\)), 6.98-8.11 (8H, multiplet, aromatic protons), 8.73 (1H, broad singlet, proton at C\(_{10}\)), 9.01 (1H, singlet, proton at C\(_4\)')

\(\text{\(^{13}\)C NMR (}\delta, \text{ ppm) (DMSO-d}_6\) (Fig 7)\)

56.45(OCH\(_3\)), 96.69(C), 96.81(C), 115.65(C), 117.40(CH), 117.52(CH),
Chapter 3, Section 2  

Coumarinyl substituted pyrido[3,2-c]coumarins

Department of Chemistry, Sardar Patel University

120.32(C), 120.88(C), 120.94(C), 124.38(CH), 124.48(CH), 125.82(CH), 126.23(CH), 134.83(CH), 134.92(CH), 154.77(C), 160.80(CH), 162.50(CH), 163.37(C), 163.56(C), 178.03(CO of coumarin at C2′), 180.28(CO of coumarin at C5)

**Compound 3c**

*IR (cm⁻¹)*

\[ \nu_{\text{max}} 1692 \ (C=O \text{ stretching of } \delta\text{-lactone of coumarin}), \ 1627 \text{ and } 1505 \ (\text{aromatic } C=C \text{ and } C=N \text{ stretchings}), \ 3137 \ (\text{aromatic } C-H \text{ stretching}) \]

\[ ^1H \text{ NMR (δ, ppm) (DMSO-d₆) (Fig 8)} \]

7.26-8.48 (9H, multiplet, aromatic protons), 9.71-9.92 (3H, multiplet, protons at C₄, C₁₀ and C₅′), 10.83 (1H, singlet, proton at C₄′)

\[ ^{13}C \text{ NMR (δ, ppm) (DMSO-d₆) (Fig 9)} \]

96.69(C), 96.82(C), 117.39(CH), 117.49(CH), 120.88(C), 120.93(CH), 124.40(CH), 124.48(CH), 125.82(CH), 126.20(CH), 134.83(CH), 134.94(CH), 152.04(CH), 154.78(C), 160.78(CH), 162.49(CH), 163.41(C), 163.53(C), 163.81(C), 178.05(CO of coumarin at C2′), 180.29(CO of coumarin at C5)

**Compound 3d**

*IR (cm⁻¹)*

\[ \nu_{\text{max}} 1701 \ (C=O \text{ stretching of } \delta\text{-lactone of coumarin}), \ 1620 \text{ and } 1497 \ (\text{aromatic } C=C \text{ and } C=N \text{ stretchings}), \ 3141 \ (\text{aromatic } C-H \text{ stretching}) \]

\[ ^1H \text{ NMR (δ, ppm) (DMSO-d₆) (Fig 10)} \]

2.34 (3H, singlet, CH₃), 7.14-8.47 (7H, multiplet, aromatic protons), 9.69-9.87 (2H, multiplet, protons at C₄ and C₁₀), 10.82 (1H, singlet, proton at C₄′)

\[ ^{13}C \text{ NMR (δ, ppm) (DMSO-d₆) (Fig 11)} \]

20.70(CH₃), 96.73(C), 96.87(C), 117.17(CH), 117.31(CH), 120.49(CH), 120.61(CH), 125.40(CH), 125.83(CH), 133.58(C), 133.66(C), 135.54(CH), 135.65(CH), 152.85(C), 158.60(C), 160.77(CH), 162.41(CH), 162.65(C), 163.55(C), 163.65(C), 178.10(CO of coumarin at C2′), 180.39(CO of coumarin at C5)

**Compound 3e**

*IR (cm⁻¹)*

\[ \nu_{\text{max}} 1703 \ (C=O \text{ stretching of } \delta\text{-lactone of coumarin}), \ 1620 \text{ and } 1490 \]
(aromatic C=C and C=N stretchings), 3144 (aromatic C-H stretching)

\(^1\)H NMR (\(\delta\), ppm) (DMSO-d\(\delta\)) (Fig 12)

2.35 (3H, singlet, CH\(\text{3}\)), 3.92 (3H, singlet, OCH\(\text{3}\)), 7.10-8.47 (6H, multiplet, aromatic protons), 9.69-9.87 (2H, multiplet, protons at C\(\text{4}\) and C\(\text{10}\)), 10.81 (1H, singlet, proton at C\(\text{4}'\))

\(^{13}\)C NMR (\(\delta\), ppm) (DMSO-d\(\delta\)) (Fig 13)

20.71(CH\(\text{3}\)), 56.76(OCH\(\text{3}\)), 96.68(C), 96.84(C), 117.20(CH), 117.29(CH), 120.50(C), 120.58(C), 125.40(CH), 125.82(CH), 133.57(C), 133.67(C), 135.6(C), 135.65(CH), 152.86(CH), 160.75(CH), 162.41(CH), 163.56(C), 163.64(C), 178.08(CO of coumarin at C\(\text{2}'\)), 180.36(CO of coumarin at C\(\text{5}'\))

**Compound 3f**

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

\(\nu_{\text{max}}\) 1696 (C=O stretching of \(\delta\)-lactone of coumarin), 1620 and 1490 (aromatic C=C and C=N stretchings), 3144 (aromatic C-H stretching)

\(^1\)H NMR (\(\delta\), ppm) (DMSO-d\(\delta\)) (Fig 14)

2.35 (3H, singlet, CH\(\text{3}\)), 7.14-8.47 (8H, multiplet, aromatic protons), 9.69-9.87 (3H, multiplet, protons at C\(\text{4}\), C\(\text{10}\) and C\(\text{5}'\)), 10.82 (1H, singlet, proton at C\(\text{4}'\))

\(^{13}\)C NMR (\(\delta\), ppm) (DMSO-d\(\delta\)) (Fig 15)

20.71(CH\(\text{3}\)), 96.70(C), 96.84(C), 117.20(CH), 117.29(CH), 120.50(C), 120.58(C), 125.40(CH), 125.82(CH), 133.56(C), 133.66(C), 135.55(CH), 135.64(CH), 152.86(CH), 160.74(CH), 162.41(CH), 163.57(C), 163.64(C), 178.08(CO of coumarin at C\(\text{2}'\)), 180.36(CO of coumarin at C\(\text{5}'\))

**Compound 3g**

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

\(\nu_{\text{max}}\) 1704 (C=O stretching of \(\delta\)-lactone of coumarin), 1621 and 1494 (aromatic C=C and C=N stretchings), 3123 (aromatic C-H stretching)

\(^1\)H NMR (\(\delta\), ppm) (DMSO-d\(\delta\)) (Fig 16)

2.32 (3H, singlet, CH\(\text{3}\)), 7.17-8.48 (7H, multiplet, aromatic protons), 9.70-9.92 (2H, multiplet, protons at C\(\text{4}\) and C\(\text{10}\)), 10.83 (1H, singlet, proton at C\(\text{4}'\))
\[^{13}\text{C} \text{NMR} \ (\delta, \text{ppm}) \ (\text{DMSO-d}_6) \ (\text{Fig 17})\]

15.77(\text{CH}_3), 96.52(\text{C}), 96.71(\text{C}), 117.87(\text{CH}), 120.69(\text{C}), 120.75(\text{C}), 121.05(\text{C}), 123.45(\text{CH}), 123.77(\text{CH}), 123.87(\text{CH}), 126.12(\text{C}), 126.26(\text{CH}), 135.69(\text{CH}), 135.81(\text{CH}), 153.05(\text{CH}), 160.82(\text{CH}), 161.64(\text{C}), 162.46(\text{CH}), 163.29(\text{C}), 163.41(\text{C}), 178.29(\text{CO of coumarin at C}_2'), 180.58(\text{CO of coumarin at C}_5)

**Compound 3h**

\(\nu_{\text{max}}\) 1708 (C=O stretching of \(\delta\)-lactone of coumarin), 1606 and 1479 (aromatic C=C and C=N stretchings), 3093 (aromatic C-H stretching)

\[^{1}H \text{ NMR} \ (\delta, \text{ppm}) \ (\text{CDCl}_3) \ (\text{Fig 18})\]

2.50 (3H, singlet, \text{CH}_3), 3.99 (3H, singlet, O\text{CH}_3), 6.45-7.36 (7H, multiplet, aromatic protons), 7.63 (1H, poorly resolved doublet of a doublet, proton at C\_10), 7.94 (1H, singlet, proton at C\_4')

\[^{13}\text{C} \text{NMR} \ (\delta, \text{ppm}) \ (\text{CDCl}_3) \ (\text{Fig 19})\]

16.07(\text{CH}_3), 56.33(O\text{CH}_3), 105.71(\text{CH}), 111.18(\text{C}), 112.21(\text{C}), 114.31(\text{CH}), 118.55(\text{CH}), 119.28(\text{C}), 119.72(\text{CH}), 124.06(\text{CH}), 124.46(\text{C}), 124.95(\text{CH}), 126.90(\text{CH}), 132.19(\text{CH}), 142.44(\text{CH}), 143.33(\text{C}), 147.26(\text{C}), 151.02(\text{C}), 154.88(\text{C}), 157.80(\text{C}), 157.97(\text{C}), 160.03(\text{CO of coumarin at C}_2'), 169.59(\text{CO of coumarin at C}_5)

**Compound 3i**

\(\nu_{\text{max}}\) 1704 (C=O stretching of \(\delta\)-lactone of coumarin), 1621 and 1495 (aromatic C=C and C=N stretchings), 3132 (aromatic C-H stretching)

\[^{1}H \text{ NMR} \ (\delta, \text{ppm}) \ (\text{DMSO-d}_6) \ (\text{Fig 20})\]

2.32 (3H, singlet, \text{CH}_3), 7.17-8.36 (8H, multiplet, aromatic protons), 9.70-9.92 (3H, multiplet, protons at C\_4, C\_10 and C\_5'), 10.83 (1H, singlet, proton at C\_4')

\[^{13}\text{C} \text{NMR} \ (\delta, \text{ppm}) \ (\text{DMSO-d}_6) \ (\text{Fig 21})\]

15.73(\text{CH}_3), 96.50(\text{C}), 96.64(\text{C}), 116.94(\text{CH}), 120.39(\text{C}), 120.68(\text{C}), 120.79(\text{C}), 121.90(\text{C}), 123.48(\text{CH}), 123.80(\text{CH}), 123.86(\text{CH}), 126.15(\text{C}), 126.29(\text{C}), 129.14(\text{C}), 135.73(\text{CH}), 135.84(\text{CH}), 153.04(\text{C}), 160.82(\text{CH}), 161.21(\text{CH}), 161.98(\text{C}), 162.45(\text{CH}), 162.83(\text{C}), 163.30(\text{C}), 163.44(\text{C}), 178.32(\text{CO of coumarin at C}_2'), 180.61(\text{CO of coumarin at C}_5)
Compound 3j

IR (cm$^{-1}$)

$\nu_{\text{max}}$ 1696 (C=O stretching of $\delta$-lactone of coumarin), 1632 and 1502 (aromatic C=C and C=N stretchings), 3115 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 22)

7.32-8.48 (7H, multiplet, aromatic protons), 9.77-10.03 (2H, multiplet, protons at C$_4$ and C$_{10}$), 10.81 (1H, singlet, proton at C$_{4}'$)

$^{13}$C NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 23)

96.43(C), 96.64(C), 119.74(CH), 119.86(CH), 122.27(C), 124.84(CH), 125.23(CH), 128.57(C), 128.69(CH), 134.39(CH), 134.49(CH), 153.39(C), 155.41(C), 161.03(CH), 161.72(CH), 162.70(CH), 162.92(C), 163.08(C), 175.62(C), 176.84(CO of coumarin at C$_2'$), 178.82(CO of coumarin at C$_5$)

Compound 3k

IR (cm$^{-1}$)

$\nu_{\text{max}}$ 1695 (C=O stretching of $\delta$-lactone of coumarin), 1627 and 1501 (aromatic C=C and C=N stretchings), 3123 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 24)

3.93 (3H, singlet, OCH$_3$), 7.31-8.48 (6H, multiplet, aromatic protons), 9.77-10.06 (2H, multiplet, protons at C$_4$ and C$_{10}$), 10.81 (1H, singlet, proton at C$_{4}'$)

$^{13}$C NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 25)

56.15(OCH$_3$), 96.42(C), 96.65(C), 119.73(CH), 119.84(CH), 122.28(C), 124.83(CH), 125.22(CH), 128.60(C), 128.69(C), 134.37(CH), 134.48(CH), 153.38(C), 156.92(C), 160.99(CH), 162.70(CH), 162.92(C), 163.09(C), 176.83(CO of coumarin at C$_2'$), 178.84(CO of coumarin at C$_5$)

Compound 3l

IR (cm$^{-1}$)

$\nu_{\text{max}}$ 1695 (C=O stretching of $\delta$-lactone of coumarin), 1631 and 1501 (aromatic C=C and C=N stretchings), 3123 (aromatic C-H stretching)

$^1$H NMR ($\delta$, ppm) (DMSO-d$_6$) (Fig 26)

7.31-8.47 (8H, multiplet, aromatic protons), 9.80-10.05 (3H,
multiplet, protons at C₄, C₁₀ and C₅'), 10.81 (1H, singlet, proton at C₄')

\(^{13}\text{C} \text{ NMR} (δ, \text{ ppm}) (\text{DMSO-d}_6) \text{ (Fig 27)}

96.45(C), 96.64(C), 119.75(CH), 119.86(CH), 122.26(C), 122.53(C), 124.84(CH), 125.21(CH), 128.58(C), 128.68(C), 133.77(CH), 134.37(CH), 134.46(CH), 152.45(C), 153.37(C), 158.64(CH), 161.02(CH), 162.68(CH), 162.92(C), 163.07(C), 176.83(CO of coumarin at C₂'), 178.80(CO of coumarin at C₅)

In case of the compounds 3a, 3c, 3e, 3f, 3k and 3l, the number of carbon signals in \(^{13}\text{C} \text{ NMR} \text{ spectra} \text{ is less than expected} \text{ (in case of compound 3a - one signal, in case of compound 3c - four signals, in case of compound 3e and 3k - two signals, in case of compound 3f - six signals and in case of compound 3l - three signals were less). This may be due to identical chemical shifts of certain carbon atoms which may appear at same position.
**Fig 1**  IR spectrum of compound 3a

**Fig 2**  $^1$H NMR spectrum of compound 3a
Chapter 3, Section 2  
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Fig 3  $^{13}$C NMR spectrum of compound 3a

Fig 4  DEPT-135 spectrum of compound 3a
Fig 5  Mass spectrum of compound 3a
Figure 6  $^1$H NMR spectrum of compound 3b

Figure 7  $^{13}$C NMR spectrum of compound 3b
**Fig 8**  $^1$H NMR spectrum of compound 3c

**Fig 9**  $^{13}$C NMR spectrum of compound 3c
Fig 10  $^1$H NMR spectrum of compound 3d

Fig 11  $^{13}$C NMR spectrum of compound 3d
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Fig 12  $^1$H NMR spectrum of compound 3e

Fig 13  $^{13}$C NMR spectrum of compound 3e
Fig 14  $^1$H NMR spectrum of compound 3f

Fig 15  $^{13}$C NMR spectrum of compound 3f
Fig 16  $^1$H NMR spectrum of compound 3g

Fig 17  $^{13}$C NMR spectrum of compound 3g
Fig 18  $^1$H NMR spectrum of compound 3h

Fig 19  $^{13}$C NMR spectrum of compound 3h
Fig 20 \( ^1\text{H} \) NMR spectrum of compound 3i

Fig 21 \( ^{13}\text{C} \) NMR spectrum of compound 3i
Fig 22 $^1$H NMR spectrum of compound 3j

Fig 23 $^{13}$C NMR spectrum of compound 3j
**Fig 24** $^1$H NMR spectrum of compound 3k

**Fig 25** $^{13}$C NMR spectrum of compound 3k
Fig 26  $^1$H NMR spectrum of compound 3l

Fig 27  $^{13}$C NMR spectrum of compound 3l
3.6 Experimental

The following starting materials were used.

- Substituted 4-hydroxy coumarins used:
  - a) 4-hydroxy coumarin
  - b) 6-methyl-4-hydroxy coumarin
  - c) 8-methyl-4-hydroxy coumarin
  - d) 6-chloro-4-hydroxy coumarin

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

- Substituted 3-coumarinoyl methyl pyridinium salts used:
  - a) 3-coumarinoyl methyl pyridinium salt
  - b) 8-methoxy-3-coumarinoyl methyl pyridinium salt
  - c) 5,6-benzo-3-coumarinoyl methyl pyridinium salt

The preparation of (a), (b) and (c) is described in chapter 2.

3.6.1 Preparation of 8-methyl-4-hydroxy coumarin

In a 500 mL round bottom flask attached with a reflux condenser and gas absorption trap, a mixture of o-cresol (0.2 mole), malonic acid (0.1 mole), anhydrous zinc chloride (0.6 mole) and phosphorous oxychloride (0.4 mole) were heated with stirring at 60-65 °C for 35 hours. The yellow coloured mixture was cooled and decomposed with water and left overnight. The resulting crude 4-hydroxy coumarin was filtered out, washed with water and dried. This crude product was purified by dissolving it in 10% sodium bicarbonate solution, filtering and reprecipitating by adding dilute HCl solution. The 8-methyl-4-hydroxy coumarin was separated out as a
yellowish-white solid. This was filtered out, washed with water, dried and recrystallized from ethanol.

**8-methyl-4-hydroxy coumarin**: Yield: 53%, mp 222°C (lit.29 mp 223°C)

### 3.6.2 Preparation of 4-chloro-3-formyl coumarins (1a-d)

![Chemical Reaction Diagram]

In a 250 mL three necked round bottom flask fitted with addition funnel and guard tube, an appropriate 4-hydroxy coumarin (0.06 mole) was taken in anhydrous dimethyl formamide (DMF) (0.6 mole) and the reaction mixture was cooled to 0°C with stirring. In this well stirred reaction mixture, phosphorous oxychloride (POCl₃) (0.18 mole) was added dropwise during one hour. After addition was completed, the reaction mixture was further stirred at 0°C for one hour. The reaction mixture was then heated at 65-70°C for two hours. It was then poured into crushed ice (200 g) and left overnight in refrigerator, during which a solid product was separated out which was filtered off, washed with 5% sodium carbonate (3 x 30 mL) and water. It was then dried and recrystallized from acetone-water.

**Compound 1a**: \( R = R_1 = H \), Yield: 58%, mp 155°C (lit.36 mp 156°C)

**Compound 1b**: \( R = CH_3, R_1 = H \), Yield: 56%, mp 188°C (lit.36 mp 190°C)

**Compound 1c**: \( R = H, R_1 = CH_3 \), Yield: 58%, mp 155°C (lit.36 mp 156°C)

**Compound 1d**: \( R = Cl, R_1 = H \), Yield: 50%, mp 240°C (lit.36 mp 242°C)
3.6.3 Preparation of 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines (3a-l)

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, an appropriate 3-coumarinoyl methyl pyridinium salts (2a-c) (0.005 mole) was taken in glacial acetic acid (15 mL). To this, ammonium acetate (0.05 mole) was added with stirring at room temperature. Then a solution of appropriate 4-chloro-3-formyl coumarin (1a-d) (0.005 mole) in acetic acid (15 mL) was added with stirring at room temperature during 15 minutes. The reaction mixture was further stirred for 45 minutes at room temperature and then refluxed in an oil bath at 140°C for 8 hours. It was then allowed to come to room temperature and poured into ice cold water (75 mL). The gummy mass obtained was extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with 10% sodium bicarbonate solution (3 x 20 mL) and then with water (3 x 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under vacuum gave a solid product. This was purified by column chromatography using silica gel and ethyl acetate-petroleum ether (60:80) (3:7) as an eluent. Thus, 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines (3a-l) were obtained as brownish colored solid, which were recrystallized from chloroform-hexane.
**Compound 3a:** \( R = R_1 = R_2 = R_3 = R_4 = H; \)
Yield = 62% \( \text{mp 218-220°C} \) Molecular Formula: C\(_{21}\)H\(_{11}\)NO\(_4\)
Analysis
% C  % H  % N  
Found 74.17 3.19 4.18
Calculated 73.90 3.25 4.10

**Compound 3b:** \( R = R_1 = R_3 = R_4 = H, R_2 = OCH_3; \)
Yield = 54% \( \text{mp 211-213°C} \) Molecular Formula: C\(_{22}\)H\(_{13}\)NO\(_5\)
Analysis
% C  % H  % N  
Found 70.88 3.48 3.70
Calculated 71.16 3.53 3.77

**Compound 3c:** \( R = R_1 = R_2 = H, R_3 + R_4 = \text{Benzo}; \)
Yield = 64% \( \text{mp 222-224°C} \) Molecular Formula: C\(_{25}\)H\(_{13}\)NO\(_4\)
Analysis
% C  % H  % N  
Found 76.46 3.28 3.51
Calculated 76.72 3.35 3.58

**Compound 3d:** \( R = R_2 = R_3 = R_4 = H, R_1 = \text{CH}_3; \)
Yield = 59% \( \text{mp 225-227°C} \) Molecular Formula: C\(_{22}\)H\(_{13}\)NO\(_4\)
Analysis
% C  % H  % N  
Found 74.62 3.65 3.87
Calculated 74.36 3.69 3.94

**Compound 3e:** \( R = R_3 = R_4 = H, R_1 = \text{CH}_3, R_2 = \text{OCH}_3; \)
Yield = 61% \( \text{mp 219-221°C} \) Molecular Formula: C\(_{23}\)H\(_{15}\)NO\(_5\)
Analysis
% C  % H  % N  
Found 71.45 3.98 3.71
Calculated 71.68 3.92 3.63

**Compound 3f:** \( R = R_2 = H, R_1 = \text{CH}_3, R_3 + R_4 = \text{Benzo}; \)
Yield = 58% \( \text{mp 214-216°C} \) Molecular Formula: C\(_{26}\)H\(_{15}\)NO\(_4\)
Analysis
% C  % H  % N  
Found 77.28 3.67 3.39
Calculated 77.03 3.73 3.46

**Compound 3g:** \( R = \text{CH}_3, R_1 = R_2 = R_3 = R_4 = H; \)
Yield = 69% \( \text{mp 253-255°C} \) Molecular Formula: C\(_{22}\)H\(_{13}\)NO\(_4\)
Analysis
% C  % H  % N  
Found 74.09 3.63 3.84
Calculated  74.36  3.69  3.94

**Compound 3h:**  \( \text{R} = \text{CH}_3, \  \text{R}_1 = \text{R}_3 = \text{R}_4 = \text{H}, \  \text{R}_2 = \text{OCH}_3; \)
Yield = 56%  \( \text{mp} \ 240-242^\circ \text{C} \)  Molecular Formula: \(\text{C}_{23}\text{H}_{15}\text{NO}_5\)  
Analysis  % C  % H  % N  
Found  71.44  3.99  3.70  
Calculated  71.68  3.92  3.63

**Compound 3i:**  \( \text{R} = \text{CH}_3, \  \text{R}_1 = \text{R}_2 = \text{H}, \  \text{R}_3 + \text{R}_4 = \text{Benzo}; \)
Yield = 73%  \( \text{mp} \ 256-258^\circ \text{C} \)  Molecular Formula: \(\text{C}_{26}\text{H}_{15}\text{NO}_4\)  
Analysis  % C  % H  % N  
Found  76.79  3.67  3.38  
Calculated  77.03  3.73  3.46

**Compound 3j:**  \( \text{R} = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}, \  \text{R}_1 = \text{Cl}; \)
Yield = 78%  \( \text{mp} \ 264-265^\circ \text{C} \)  Molecular Formula: \(\text{C}_{21}\text{H}_{10}\text{ClNO}_4\)  
Analysis  % C  % H  % N  
Found  67.41  2.63  3.66  
Calculated  67.12  2.68  3.73

**Compound 3k:**  \( \text{R} = \text{R}_3 = \text{R}_4 = \text{H}, \  \text{R}_1 = \text{Cl}, \  \text{R}_2 = \text{OCH}_3; \)
Yield = 79%  \( \text{mp} \ 260-261^\circ \text{C} \)  Molecular Formula: \(\text{C}_{22}\text{H}_{12}\text{ClNO}_5\)  
Analysis  % C  % H  % N  
Found  65.38  2.92  3.36  
Calculated  65.12  2.98  3.45

**Compound 3l:**  \( \text{R} = \text{R}_2 = \text{H}, \  \text{R}_1 = \text{Cl}, \  \text{R}_3 + \text{R}_4 = \text{Benzo}; \)
Yield = 76%  \( \text{mp} \ 258-260^\circ \text{C} \)  Molecular Formula: \(\text{C}_{25}\text{H}_{12}\text{ClNO}_5\)  
Analysis  % C  % H  % N  
Found  70.32  2.80  3.22  
Calculated  70.52  2.84  3.29
References

1. S Thaisrivongs, M N Janakiraman, K T Chong, P K Tomich, L A Dolack S R Turner, J W Strohbach, J C Lynn, M M Horng, R R Hinshaw

2. G Rappa, K Shyam, A Lorico, O Fodstad, A C Sartorelli

3. E B Yang, Y N Zhao, K Zhang, P Mack

4. K Ukawa, T Ishiguro, Y Wada, A Nohara

5. H Brauninger, R Plagemann, H D Schalicke, K Peseke,

6. D Heber

7. D Heber, Berghaus


10. S G S Farid, K Thomas
    *CA*, **85**, 46458p (1976)


12. G Pave

13. C N O’Callaghan


Department of Chemistry, Sardar Patel University
16. R Crossley, A Opalko, R G Shepherd


18. S A Glase, A E Corbin, T A Pugaley, T G Heffner

19. R Crossley, D E Beattie, A C W Curran, D G Hill, A E Lawrence

20. K V Emelen, T D Wit, G J Hoornaert, F Compernolle

21. D Tirzite, G Tirzitisa, B Vigantea, G Dubursa

22. Y Song, Z Shao, T S Dexheimer, E S Scher, Y Pommier, M Cushman

23. Y A El-Ossaily

24. M Andaloussi, E Moreau, N Masurier, J Lacroix, R C Gaudreault, J M Chezal, A E Laghdach, D Canitrot, E Debiton, J C Teulade, O Chavignon

25. S Chackal, R Houssin, N Pommery, J P Henischart


28. B S Jeong, H Choi, P Thapa, R Karki, E Lee, J M Nam, Y Na, E M Ha, Y Kwon, E S Lee

29. V R Shah, J L Bose, R C Shah
30. J R Geigy A – G  
   Brit, 755, 162 (1956)
31. C Alvarado, A Guzmán, E Diaz, R Patiño  
32. P Horstmann, B Unterhalt  
33. E. Horning  
34. M Lacova, D Loos, M Furdik, M Matulova H M El-Shaar  
   Molecules, 3, 149 (1998)
35. R J Abraham, M Mobli  
36. S R Moorty, V Sundaramurthy, N V Subba Rao  
   Ind. J. Chem., 11, 854 (1973)