CHAPTER - 1

Chemistry of Coumarins
INTRODUCTION

CHEMISTRY OF COUMARINS

Perkin first prepared coumarin in 1868 which is now known as classic synthetic method bearing his name\(^1\). Earlier coumarin was isolated by Vogel in 1820 from Tonka beans\(^2\). Coumarins are naturally occurring lactones which are indexed in the chemical abstracts as 2H[1] benzopyran-2-ones. Coumarin ring is a fusion of pyrone ring with a benzene nucleus. The numbering used with coumarin (1) is illustrated in the following formula.

\[ \text{General Characteristics :} \]

Aromatic nature of heterocyclic ring of coumarin is disputable, because coumarin shows some reactions of aliphatic compounds and other characteristics of aromatic compounds. The complete aromaticity in coumarin can be only be realised if O-CO function contributes two electrons to form 10 \( \pi \) electron system. This means that coumarin should to be a resonance hybrid, to which contribution from canonical form (3) is significant. However no evidence is found in the spectra of coumarin to suggest that contribution from betaine form (3) is considerable.
The infrared absorption spectrum of coumarin shows an absorption band at 1710 cm\(^{-1}\) which is attributed to lactone carbonyl group, but not a betaine form. In the PMR spectrum of coumarin\(^4\), the signals due to protons at C-3 and C-4 appear in the region of \(\delta 6.45\) and 7.80 ppm respectively with a coupling constant of 9.8 Hz. These values are typical of cis alkene rather than an aryl ring\(^4\). Finally, the \(^{13}\)C-NMR spectra of coumarins\(^5\) are consistent with an essentially aliphatic heterocyclic ring. The chemical shifts of C(2), C(3) and C(4) in coumarin are remarkably close to the values for the corresponding carbons in \(\alpha\)-pyrone and are given below.

\(^{13}\)C-NMR data (\(\delta \) ppm)

<table>
<thead>
<tr>
<th>Compound</th>
<th>C(2)</th>
<th>C(3)</th>
<th>C(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-pyrone</td>
<td>162.0</td>
<td>116.7</td>
<td>144.3</td>
</tr>
<tr>
<td>Coumarin</td>
<td>160.4</td>
<td>116.4</td>
<td>143.4</td>
</tr>
</tbody>
</table>

But coumarin does show some aromatic character in its pattern of reactivity.

**Ex. 1**: The carbonyl oxygen can be alkylated by powerful agents to give stable pyrilium salts\(^6\) (4).

\[
\begin{array}{c}
\text{O} & \text{O} \\
\text{EtBF}_4^- \\
\end{array}
\begin{array}{c}
\text{O} & \text{O} \\
\text{EtBF}_4^- \\
\end{array}
\]

(4)

2. Coumarin nucleus is susceptible to electrophilic substitution\(^6\). Sulphonation takes place initially in the carbocyclic ring at C(6), but under more forcing conditions one more -SO\(_2\)H group can be introduced at C(3), to obtain coumarin, 3,6-disulphonic acid (5).

2
As in the case of simple pyrones the properties of the heterocyclic ring of coumarin are greatly influenced by the presence of substituents.

Anantakrishnan\textsuperscript{7} discussed the “Mills Nixon effect” in which the reactivity of coumarin was rationalised based on the comparative studies of bromination, nitration of coumarin, naphthalene and benzene. Considering the possible electron displacements in coumarin molecule, Thakur and Shah\textsuperscript{8} predicted C(6) and C(8) as the most reactive centres. The electron displacements in coumarin can be shown as follows.

Greater electron densities can be seen on C(6) and C(8) from the resonating structures (B) and (C). Out of these two C(6) seems to be more reactive because its proximity to the oxygen atom, similar to the reactivity of para position of phenol. Structure (A) though imparts more electron density to the C(3) position, the electrophilic substitution at C(3) is less probable due to its nearness to the electron withdrawing carbonyl group. In fact the $\pi$ electron
densities calculated by Song and Gordon\textsuperscript{9} are quite close to the resonance picture of the molecule given above. The values of $\pi$-electron densities for the ground state of coumarin are given below (6).

\begin{center}
\begin{tabular}{ccc}
0.982 & 0.940 & 1.107 \\
1.006 & 0.720 & 1.955 \\
0.977 & 1.028 & 1.801
\end{tabular}
\end{center}

(6)

Considering the structures (B), (C) and (D) Bassignana and Cogrossi\textsuperscript{10} have proposed structure (E) which according to them represents the hybrid or resonating state of the molecule.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=1cm]{structure_E.png}
\end{tabular}
\end{center}

(E)

However contributing structures of the type (D) do not have strong spectral evidences, the position of the carbonyl frequency in the IR spectrum (1710 cm\textsuperscript{-1}) is more in favour of an enol lactone\textsuperscript{11}. Hence contribution from such type of structures is negligible and the resonating state (E) appears to be less probable.

Coumarin has been used as a useful model in elucidating the electronic structures and photoreactivity of psoralenes. The configurational analysis of coumarin by Song et.al.,\textsuperscript{12} in the ground state indicates some charge transfer delocalisation extending to the ethylenic region. The dipole moment of coumarin (4.52\times10\textsuperscript{-18} e.s.u) determined earlier by Rau\textsuperscript{13} also indicates similar delocalisation.
The U.V. spectra of coumarins and its methyl derivatives were reported by Ganguly and Bagchi\textsuperscript{14}. The introduction of methyl group in various positions does not enhance the nature of the spectrum to a great extent. The $\lambda_{\text{max}}$ and $\varepsilon$ values of coumarins are 273 nm (4.0368) 309 nm (3.7449).

In 1938 Murti and Sheshadri\textsuperscript{15} reported the IR spectrum of coumarin. The parent coumarin shows lactone carbonyl at 1705, $v_{\text{C-O}}$ at 1608, 1450 $v_{\text{C-O}}$ at 1254 (\textbar cm$^{-1}$).

Dharmatti et. al\textsuperscript{4}, studied the PMR spectrum of coumarins. The C(3) H of coumarin resonates at $\delta$ 6.45 ppm and C(4) at $\delta$ 7.80 ppm.

Barnes and others studied\textsuperscript{16} the electron impact on coumarin. The molecular ion peak and fragment ion shows transient formation of benzofuran (7).

\begin{align*}
\text{m/z 146} & \quad \text{m/z 118} \\
\text{(7)}
\end{align*}

**Coumarin derivatives of Biological Importance**:

The biological importance of coumarin derivatives as anticoagulants, as aflatoxins, mycotoxins, and antibiotics has led to a considerable amount of synthetic work in the field of coumarins for their pharmacological evaluation. A brief account of some of the important coumarin derivatives are as follows.

Ron and Mayer\textsuperscript{17} observed its toxic action on algae and found that the parent coumarin prevented the growth of *Chlorella vulgaris* in $1.4 \times 10^{-3}$ mol$^{-1}$ concentration. Coumarin inhibits the germination growth of certain roots of the plants. Its effect on wheat, potato are well known and have been reviewed\textsuperscript{18,19}.
Russian workers during their study on the effect of coumarin in higher plants have found that it has growth stimulating action at lower concentration and growth inhibition action at higher concentrations\textsuperscript{20,21}. This indicates at lower concentration coumarin exerts a hormonal action, while in higher concentration it has an antiauxin effect. Coumarin has got a wide range of effects in animals also, the depression of smooth muscles and dilation of peripheral blood vessels in frogs, rabbits and mice were noticed by Rai\textsuperscript{22}.

4-Hydroxy coumarin needs a special mention. Anschute\textsuperscript{23} observed that 4-hydroxy coumarin readily reacts with formaldehyde to give methylene bis hydroxy coumarin derivative which is known as dicoumarol. The parent dicoumarol (8) acts by interfering the function of Vit. K in the liver cells which are the sites of synthesis of clotting factors including prothrombin. This lengthens the clotting time by decreasing the amount of biologically active prothrombin in the blood.

![Diagram of dicoumarol (8)]

Dicoumarol is used alone or as an adjunct to Heparin in prophylaxis and in the treatment of intravascular clotting\textsuperscript{24}. Link and coworkers\textsuperscript{25,26} developed a number of 4-hydroxy coumarins as a consequence of relationship between chemical structure and anticoagulant activity. Warfarin (9) [3-(α-acetonyl benzyl)-4-hydroxycoumarin] is one of the important anticoagulants developed as a result of this study.

![Diagram of warfarin (9)]
The other anticoagulants developed as rodenticides are given below:

Table – 1: Coumarin anticoagulants

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tomarin (10)</td>
<td><img src="#" alt="Structure" /></td>
</tr>
<tr>
<td>2.</td>
<td>Acinocoumarol (11)</td>
<td><img src="#" alt="Structure" /></td>
</tr>
<tr>
<td>3.</td>
<td>Tromexon (12)</td>
<td><img src="#" alt="Structure" /></td>
</tr>
<tr>
<td>4.</td>
<td>Mercamour (13)</td>
<td><img src="#" alt="Structure" /></td>
</tr>
</tbody>
</table>
Novobiocin (17), produced from two Streptomyces species like *S. spheroids* and *S. niveu*, is a crystalline antibiotic having basic skeleton of 3-amino-4,7-dihydroxy-8-methyl coumarin. It is primarily active against gram positive microorganisms and has proved to be of considerable use clinically especially in the treatment of penicillin resistant *staphylococci*. Besides being potential antitubercular drug it has also been found to possess fungicidal and amoebicidal activities.\textsuperscript{30,31,32}
Coumaromycin is 50 times more active than Novobiocin against *S. aureus*, *E. coli* and *Klebisell enterobacter*.

The 3-acetyl and 3-n-deconoyl-4-hydroxy coumarins (18) were found to possess potent antibacterial activity against *S. aureus* and *Mycobacterium tuberculosis*. 

![Chemical structure of 18](image)

The synthetic coumarin derivative Chromanar (19) has antialtherosclerotic, and muscle relaxant activity and has been employed in treating anginopectories.

![Chemical structure of 19](image)

Certain 4-hydroxy coumarin derivatives have shown fibrinolytic action. The most active was dibarone (20a). The coumarin 3-carboxylic acid diethylamide (20b) was found to show good hypnotic and sedative action.

![Chemical structure of 20](image)

For 20:
- a: $R = OH$, $R^1 = CONH(CH_2)_2NEt_2$
- b: $R = H$, $R^1 = CON(Et)_2$
The piperidine derivative of 7-hydroxy-4-methyl coumarin (21) was found to stimulate the activity of central nervous system in rats\textsuperscript{38} and glyoxal derivatives (22) have been shown to elicit diuretic action\textsuperscript{39}.

![Chemical structure of piperidine derivative](image)

Several coumarin derivatives (23) have been applied in the treatment of cholera\textsuperscript{40,41}.

![Chemical structure of coumarin derivatives](image)

\[ R^1 = \text{H, CH}_3, \text{C}_6\text{H}_5; R^2 = \text{H, OH, CH}_3 \]

\[ R^3 = \text{H, OH, Cl, Hexyl, R}^4 = \text{H, OH} \]

The coumarin derivatives (24) like 3-phenylcoumarin are potent phytoestrogens\textsuperscript{42}.

![Chemical structure of coumarin derivatives](image)

\[ R^1 = \text{H, CH}_3, \text{COCH}_3; R^2 = \text{H, OH, OCH}_3, \text{COOCH}_3 \]

\[ R^3 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7 \]
Coumarin derivatives (25), (26) and (27) also find their use as pesticides and insecticides. Haloxan (27) is mainly used as an anthelmintic agent^{43}.

\[
\begin{align*}
\text{CH}_3 & \quad \\
\text{H}_2\text{C}_2\text{O} & \quad \text{O} \\
\quad & \quad \text{OC}_2\text{H}_5 \\
\end{align*}
\]

\[
25 = \text{Potasan} = R = H, Y = S \\
26 = \text{Coumaphos} & \quad R = Cl, Y = S \\
27 = \text{Holoxon} & \quad R = Cl, Y = O
\]

B. Sreenivasalu et al.,^{44} synthesised 3-(2'-furanyl)coumarin (28) by cyclising acrylonitriles with pyridine hydrochloride or by o-hydroxy actophenones or salicylaldehyde in the presence of acetic anhydride.

\[
\begin{align*}
R & = H, 6-\text{Br}; 6-\text{Cl}, 6, 8-\text{Br}_2, 6, 8-\text{Cl}_2, 7-\text{OH}, 7-\text{OMe}, 6-\text{NO}_2, \\
6-\text{NO}_2, 7-\text{AcNH}, 7-\text{NH}_2; & \quad R^1 = H, \text{Me} \\
2-\text{Aryl-4-coumarinyl-5,6-benzoquinolines} (29) & \quad \text{have been synthesised by N. Z. Kozoly et. al}^{45}, \quad \text{by base catalysed condensation of aromatic schiff bases with 3-acetyl coumarin.}
\end{align*}
\]

\[
\begin{align*}
R^1 & = H, \text{Me, OMe, Cl, Br, NO}_2 \\
R^2 & = \text{NO}_2 \text{or H; } R^3 = \text{OH or H}
\end{align*}
\]
Coumarin derivatives with thiazole moiety have been prepared by A. Gurasay, T. V. Padmanabha Rao et al., and M. Locan et al. R. M. Mohareb et al. reported the synthesis of 4-(coumarin-3'-yl)-thiazoles (30).

\[
\text{PhN} \:
\begin{array}{c}
\text{X} \\
\end{array}
\text{S}
\]

(30)

\[X = \text{CN}, \text{COOMe}, \text{COMe}; \ Y = \text{COOEt}, \text{COMe}, \text{COOEt}\]

K. Rajendra Reddy et al. synthesised 2-(3'-coumarinyl)-4-(1H) anthryridinones (31).

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{O}
\end{array}
\text{N}
\]

(31)

\[R = \text{H, 6-Cl, 6-Br, 6-NO}_2, 8-\text{NO}_2, 7-\text{OH, 8-Ome, 6,8-Cl}\]

S.Z.A. Sowellum et al. and O. Claussen et al. reported the synthesis of fluorine substituted thia Diazolyl coumarins (32).

\[
\begin{array}{c}
\text{Y} \\
\end{array}
\text{CF}_3
\]

(32)

\[R = \text{H, CN}; \ Y = \text{NH}_2\]
Padmanabha Rao et al.\textsuperscript{56} reported one step synthesis of pyrazinyl bisbenzopyranones (33).

\begin{center}
\begin{tikzpicture}
\begin{scope}
\newcommand*\R{0.2cm}
\newcommand*\X{1cm}
\newcommand*\Y{1.5cm}
\coordinate (A) at (0,0);
\coordinate (B) at (\X,0);
\coordinate (C) at (\X,\Y);
\coordinate (D) at (0,\Y);
\coordinate (E) at (-\X,\Y);
\coordinate (F) at (-\X,0);
\coordinate (G) at (0,\Y+\R);
\coordinate (H) at (-\X,\Y+\R);
\coordinate (I) at (\X,\Y+\R);
\coordinate (J) at (0,\Y+2\R);
\coordinate (K) at (-\X,\Y+2\R);
\coordinate (L) at (\X,\Y+2\R);
\coordinate (M) at (0,\Y+3\R);
\coordinate (N) at (-\X,\Y+3\R);
\coordinate (O) at (\X,\Y+3\R);
\draw (A) -- (B) -- (C) -- (D) -- cycle;
\draw (E) -- (F) -- (G) -- (H) -- cycle;
\draw (I) -- (J) -- (K) -- (L) -- cycle;
\draw (M) -- (N) -- (O) -- (A) -- cycle;
\end{scope}
\end{tikzpicture}
\end{center}

(33)

\begin{itemize}
\item $R = H, \text{Br}, \text{Cl}, \text{MeO}, \text{NO}_2$
\item $R' = H, \text{Br}, \text{Cl}$
\end{itemize}

$5-\text{(3'-coumarinyl)oxathioliurn salts (34)}$ have been synthesised by H. Hartmann\textsuperscript{57} by treating 3-bromoacetyl coumarin with thioamides (RCSNR\textsuperscript{3}R where NR\textsuperscript{3}R\textsuperscript{4} = morpholino, NMe\textsubscript{2} morpholino, NMe\textsubscript{2}).

\begin{center}
\begin{tikzpicture}
\begin{scope}
\newcommand*\R{0.2cm}
\newcommand*\X{1cm}
\newcommand*\Y{1.5cm}
\coordinate (A) at (0,0);
\coordinate (B) at (\X,0);
\coordinate (C) at (\X,\Y);
\coordinate (D) at (0,\Y);
\coordinate (E) at (-\X,\Y);
\coordinate (F) at (-\X,0);
\coordinate (G) at (0,\Y+\R);
\coordinate (H) at (-\X,\Y+\R);
\coordinate (I) at (\X,\Y+\R);
\coordinate (J) at (0,\Y+2\R);
\coordinate (K) at (-\X,\Y+2\R);
\coordinate (L) at (\X,\Y+2\R);
\coordinate (M) at (0,\Y+3\R);
\coordinate (N) at (-\X,\Y+3\R);
\coordinate (O) at (\X,\Y+3\R);
\draw (A) -- (B) -- (C) -- (D) -- cycle;
\draw (E) -- (F) -- (G) -- (H) -- cycle;
\draw (I) -- (J) -- (K) -- (L) -- cycle;
\draw (M) -- (N) -- (O) -- (A) -- cycle;
\end{scope}
\end{tikzpicture}
\end{center}

(34)

\begin{itemize}
\item $R = \text{Ph}, 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-Me}_2\text{NC}_6\text{H}_4, \text{NMe}_2$
\item $R' = R'' = \text{H}$
\item $R_1, R_2 = \text{CH}=-\text{CH}=-\text{CH}=-\text{CH}$, $X = \text{ClO}_4$
\end{itemize}

H. Hartmann et al.\textsuperscript{58} used 3-bromoacetyl coumarins as synthons for the synthesis of biheterocyclic coumarins (35).

\begin{center}
\begin{tikzpicture}
\begin{scope}
\newcommand*\R{0.2cm}
\newcommand*\X{1cm}
\newcommand*\Y{1.5cm}
\coordinate (A) at (0,0);
\coordinate (B) at (\X,0);
\coordinate (C) at (\X,\Y);
\coordinate (D) at (0,\Y);
\coordinate (E) at (-\X,\Y);
\coordinate (F) at (-\X,0);
\coordinate (G) at (0,\Y+\R);
\coordinate (H) at (-\X,\Y+\R);
\coordinate (I) at (\X,\Y+\R);
\coordinate (J) at (0,\Y+2\R);
\coordinate (K) at (-\X,\Y+2\R);
\coordinate (L) at (\X,\Y+2\R);
\coordinate (M) at (0,\Y+3\R);
\coordinate (N) at (-\X,\Y+3\R);
\coordinate (O) at (\X,\Y+3\R);
\draw (A) -- (B) -- (C) -- (D) -- cycle;
\draw (E) -- (F) -- (G) -- (H) -- cycle;
\draw (I) -- (J) -- (K) -- (L) -- cycle;
\draw (M) -- (N) -- (O) -- (A) -- cycle;
\end{scope}
\end{tikzpicture}
\end{center}

(35)
H. Hashimoto et al. reported the preparation of coumarin derivatives (36) with 3-thienyl and 3-pyrrolyl moieties as 1,2-lipoxygenase inhibitors.

\[
\text{HO} \quad \text{O} \\
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4
\end{array}
\]

(36)

\[ R^1 = \text{H, alkyl}; \quad R^2 = R^3 = \text{H, OH}; \]
\[ R^4 = \text{alkyl alkoxy, halo. F, CF}_3, \text{CN} \]

The protective effect of antiallergic agent kp-136 on mast cell as activator has been studied by Kuriyama et al. (37).

\[
\begin{array}{c}
\text{Me(CH}_2)_2\text{O} \\
\text{O} \\
\text{N—N—H} \\
\text{H}
\end{array}
\]

(37)

Benzimidazolothiazolyl and triazolothiazolyl coumarins (38) are pentacyclic biheterocycles and were screened for their antimicrobial properties by M. V. Kulakarni et al. (39). These triazolothiazolyl coumarins were screened for their antiinflammatory activity by carragenin induced rat paw oedema method. It was found that p-nitro group enhances the activity.

\[
\begin{array}{c}
\text{R} \\
\text{N—N—S—O}
\end{array}
\]

(38)

\[
\begin{array}{c}
\text{R} \\
\text{N—N—S—O}
\end{array}
\]

(39)

\[ R = \text{H, 5-Cl, 5-CH}_3, \text{5.6 dimethyl} \]
\[ R = \text{H, p-CH}_3, \text{p-Cl, m-CH}_3, \text{o-Cl, p-NO}_2, \text{p-OCH} \]
G. S. Malikyan et al.,\textsuperscript{62} synthesised a number of derivatives linked with benzothiazole, benzoxazoles and benzimidazoles (40). These compounds were found to have plant growth stimulating activity.

\[
\begin{array}{c}
\text{R} \\
\text{X} = \text{S, O, NH}
\end{array}
\]

(40)

**Naturally occurring coumarins:**

Coumarin nucleus is found in variety of natural products which exhibit different pharmacological effects. Coumarin itself is found in as many as eighty different species of plants including woodruff, tonka beans, lavender oil, white sweet clover oil etc. Coumarin has the pleasant odour of asperula and therefore till recently it was used as flavouring agent. But now it is not in use because of its toxic effect on liver.

In contrast there are a number of naturally occurring coumarins that are components of important drugs having varied properties. Umbelliferone (41) is most widely spread coumarin derivative in nature. The derivatives of umbelliferone\textsuperscript{63} have attracted the attention as sun burn preventives, as they absorb a wide range of ultraviolet light, dissipate the energy as fluorescence and modify erythermal response to ultraviolet light. Umbelliferone itself is active against infection by \textit{Brucella malitensis} and \textit{B. abrotus}\textsuperscript{31}.

\[
\begin{array}{c}
\text{HO} \\
\text{O}
\end{array}
\]

(41)
Coumarin is present in many plants\textsuperscript{64} and has been found to occur in roots, barks, leaves and fruits. It has been also isolated from microorganisms\textsuperscript{65} and animals\textsuperscript{66}. The list of some naturally occurring coumarins is given below.

Table – 2: Some naturally occurring coumarins

<table>
<thead>
<tr>
<th>No.</th>
<th>Common Name</th>
<th>Structure</th>
<th>Occurrence/ Source</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Scopoletin (42)</td>
<td><img src="image" alt="Structure" /></td>
<td>Extracted from fraximus species. Barks of wild cherry, atropa belladona, Jalap.</td>
<td>67</td>
</tr>
<tr>
<td>2.</td>
<td>Esculetin (43)</td>
<td><img src="image" alt="Structure" /></td>
<td>Bark of horse chestnut</td>
<td>63</td>
</tr>
<tr>
<td>3.</td>
<td>Lehmferdin (44)</td>
<td><img src="image" alt="Structure" /></td>
<td>Ferula lehmanni</td>
<td>68</td>
</tr>
<tr>
<td>4.</td>
<td>Angustifolin (45)</td>
<td><img src="image" alt="Structure" /></td>
<td>Ruta Angustifolia</td>
<td>69</td>
</tr>
<tr>
<td>5.</td>
<td>Dihydrosuberenol (46)</td>
<td><img src="image" alt="Structure" /></td>
<td>Defatted roots of limonia acidissima</td>
<td>70</td>
</tr>
<tr>
<td>6.</td>
<td>Ethyl suberenol (47)</td>
<td><img src="image" alt="Structure" /></td>
<td>Roots and barks of citrus sinensis</td>
<td>71</td>
</tr>
<tr>
<td>7.</td>
<td>Dihydroxanthyletin (48)</td>
<td><img src="image" alt="Structure" /></td>
<td>Aerial parts of seseli tortuosum</td>
<td>72</td>
</tr>
<tr>
<td>No.</td>
<td>Common Name</td>
<td>Structure</td>
<td>Occurrence/Source</td>
<td>Ref</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>8.</td>
<td>Paniculal (49)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Leaves of M. Exotica and M. Paniculata</td>
<td>73</td>
</tr>
<tr>
<td>9.</td>
<td>Osthodon (50)</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>M. exotica</td>
<td>74</td>
</tr>
<tr>
<td>10.</td>
<td>7-ethoxy-3,4-dimethyl coumarin (51)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Edgeworthia gerdanari</td>
<td>75</td>
</tr>
<tr>
<td>11.</td>
<td>Seretin (52)</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>roots of Haplophyllum dauricum</td>
<td>76</td>
</tr>
<tr>
<td>12.</td>
<td>Nivegin (53)</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>Echinops niveus</td>
<td>77</td>
</tr>
<tr>
<td>13.</td>
<td>Glycocoumarin (54)</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>Licorice roots of Glycyrrhiza uralensis</td>
<td>78</td>
</tr>
<tr>
<td>No.</td>
<td>Common Name</td>
<td>Structure</td>
<td>Occurrence/Source</td>
<td>Ref</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------</td>
<td>-----------</td>
<td>---------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>14</td>
<td>Daphxetin (55)</td>
<td><img src="image" alt="Daphxetin Structure" /></td>
<td>Melampodium divaricatum</td>
<td>79</td>
</tr>
<tr>
<td>15</td>
<td>Foetidin (56)</td>
<td><img src="image" alt="Foetidin Structure" /></td>
<td>Ferula assafoetida roots</td>
<td>80</td>
</tr>
<tr>
<td>16</td>
<td>Apaensin (57)</td>
<td><img src="image" alt="Apaensin Structure" /></td>
<td>Angelica apaensis</td>
<td>81</td>
</tr>
<tr>
<td>17</td>
<td>Fraxetin (7-β-D-glucopyranoside) (58)</td>
<td><img src="image" alt="Fraxetin Structure" /></td>
<td>Halphophyllum obtusifolium</td>
<td>82</td>
</tr>
<tr>
<td>18</td>
<td>Piloselloidain (59)</td>
<td><img src="image" alt="Piloselloidain Structure" /></td>
<td>Roots of mutisia spinosa</td>
<td>83</td>
</tr>
</tbody>
</table>

**Industrial Importance of Coumarins**

Several coumarin derivatives have been patented for a variety of industrial applications. Usually 3-biheterocyclic coumarins with substituents at position (7) has shown fluorescent property. 7-diethylamino substituted 3-benzazoyl coumarins (60) and 3-(2'-thienyl)coumarins (61) have been useful as
photographic sensitizers and optical brighteners. Several of these derivatives sensitize the silver chloride emulsion which very well falls in the visible region. Some 3-(2'-benzofuranyl) coumarins (62) have been found to be useful as fluorescent dyes and Whiteners. B. Hirsch et. al., reported that 3-(3'-methylpyrazol-5'-yl) coumarins (63) can be used as dye intermediates. P. Moeckli reported the synthesis of water insoluble coumarin dyes of general structure (64) and (65). The photopolymerizable composition of 3-benzothiazoyl coumarins (66) has been studied by S. Ishikawa. I. Yoshihana et al., reported the visible radiation sensitive composition of (67) and the composition can be used in printed circuit manufacture. Some of the industrially important coumarins are presented in the following table.

**Table – 3 : Coumarins of industrial importance**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Structure</th>
<th>Properties</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>60</td>
<td><img src="image1" alt="Image" /></td>
<td>Photographic sensitizers and optical brighteners</td>
<td>84</td>
</tr>
<tr>
<td>2.</td>
<td>61</td>
<td><img src="image2" alt="Image" /></td>
<td>Photographic sensitizers and optical brighteners</td>
<td>85</td>
</tr>
<tr>
<td>3.</td>
<td>62</td>
<td><img src="image3" alt="Image" /></td>
<td>Fluorescent dyes and optical brighteners</td>
<td>86</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Structure</td>
<td>Properties</td>
<td>Ref</td>
</tr>
<tr>
<td>-----</td>
<td>----------</td>
<td>-----------</td>
<td>------------</td>
<td>-----</td>
</tr>
<tr>
<td>4.</td>
<td>63</td>
<td><img src="image" alt="Structure 63" /></td>
<td>Dye intermediates</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R\textsuperscript{1} = R\textsuperscript{2} = H, alkoxy, arylazo, nitro, halo R\textsuperscript{3} = H, -CONH\textsubscript{2}, 4- C\textsubscript{6}H\textsubscript{4}N\textsubscript{0}\textsubscript{2} 2,4-(NO\textsubscript{2})C\textsubscript{6}H\textsubscript{3}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>64</td>
<td><img src="image" alt="Structure 64" /></td>
<td>Dye</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R = Me, R\textsuperscript{1} = H RR\textsuperscript{1} = CMe\textsubscript{2}CH=CH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>65</td>
<td><img src="image" alt="Structure 65" /></td>
<td>Dye</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R = Me R\textsuperscript{1} = H RR\textsuperscript{1} = -CHMe\textsubscript{2}, -CH=CH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>66</td>
<td><img src="image" alt="Structure 66" /></td>
<td>Dyes</td>
<td>89</td>
</tr>
<tr>
<td>8.</td>
<td>67</td>
<td><img src="image" alt="Structure 67" /></td>
<td>Used in the manufacture of printed circuit</td>
<td>90</td>
</tr>
</tbody>
</table>

The synthesis of 4-hydroxy-3(2-pyridyl)coumarin (68) has been reported by Alonosa et al.\textsuperscript{91}.

The synthesis and preliminary pharmacological evaluation of coumestans has been reported by Brito F. V. et al.\textsuperscript{92}. The compound (69) was prepared from the reaction of resorcinol with aromatic aldehydes. These compounds were screened for their antimycotoxic activity.

Ismail Imam et al.\textsuperscript{93} reported the synthesis of coumarin 6-sulphonamides (70) from the reaction of coumarinyl 6-sulphonyl chloride with different amino compounds.
D. I. Brahmbhatt et. al.,\textsuperscript{94} reported synthesis of 3-(3'-aryl pyridin 2'-yl) (71) and 8-(6'-arylpyridin 2'-yl) coumarins (72) by the reaction of coumarinyl methyl pyridine salts with mannich bases in the presence of ammonium acetate and acetic acid.

Further Brahmbhatt et. al.,\textsuperscript{95} synthesised some 3-arylfuro [3,2-c] coumarins (73) by the base catalysed reaction of 4-hydroxy coumarins with \( \beta \)-nitrostyrenes.

\begin{align*}
\text{R}^1 &= \text{H, CH}_3, \text{Cl} \\
\text{R}^2 &= \text{H, CH}_3
\end{align*}

\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6 = \text{H} \\
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5 = \text{OCH}_3, \text{R}^6 = \text{H}

\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6 = \text{H} \\
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5 = \text{OCH}_3, \text{R}^6 = \text{H}
The synthesis and fluorescent property of substituted 7-aminocoumarin 3-carboxylic acid derivatives (74) were reported by John and Ranjith\textsuperscript{96}.

![Chemical Structure](image)

(74)

\[ R = \text{H, CF}_3 \quad R^1 = \text{H, Br} \]

The pesticidal bioassay and synthesis of o-dialkyl o-coumarin phosphorothoniates (75) were reported by P. Vishal et. al.,\textsuperscript{97} these compounds were tested for pesticidal bioassay against \textit{Halicoverpa armigera}.

![Chemical Structure](image)

(75)

\[ R^1 = \text{H, CH}_3, \quad R^2 = \text{H, CH}_3, \quad R^3 = \text{H, CH}_3, \quad R^4 = -\text{C}_2\text{H}_5, \quad R^5 = \text{H, CH}_3; \quad R = \text{C}_2\text{H}_5 \]

The synthesis and pharmacological evaluation of 3,5-disubstituted indole-2-[(substituted benzopyran 2-one)3-carboxy] carboxy hydrazides (76) were reported by Mruthyunjayaswamy and Shanthaverappa\textsuperscript{98}.

![Chemical Structure](image)

(76)

\[ R = \text{Ph}; \quad R^1 = \text{H, CH}_3, \text{OCH}_3, \text{Cl, Br}; \quad R^2 = \text{H, OCH}_3; \quad R^3 = \text{H, CH}_3\text{Cl, OCH}_3\]
The preparation of 8-substituted 4',5'-dihydropsoralens (77) for the treatment of proliferative skin diseases and microbial infections has been patented.\(^9\)

\[
\text{R = H, F, Cl, Br, I, CN; } T = \text{Br, I, CN, carboxy}
\]

Deshrath et al.,\(^{100}\) reported the synthesis and antibacterial activity of some 8-iodocoumarins (78).

\[
\text{R = H, C}_6\text{H}_5, \text{acetamido benzamido; } R^1 = \text{CH}_3
\]

The antitumour activity of 6 or 7 styril coumarins (79) were described by chinese workers.\(^{101}\)

In view of the vital role played by coumarins in nature and the utility of its innumerable derivatives in the fields of medicine, industry and agriculture, synthesis of number of coumarins derivatives have been undertaken during the present work and many of these have been studied for their effect on bacterial, fungal species and also animals. The structure of all the compounds have been confirmed by analytical and spectral data and is presented in the forthcoming parts of the thesis.
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