CHAPTER - III

LINEARLY FUSED
α-PYRANOINDOLES

INTRODUCTION
Pyrones are six membered heterocyclic rings with one oxygen atom and a carbonyl group in the ring. They occupy important class of oxygen heterocycles with two isomeric forms α-pyrone and γ-pyrone. Each of this pyrone has got alternative canonical form consisting of pyrylium betaine. For the pyrylium betaine in which oxygen substituent is located at C-3, a carbonyl form cannot be written.

![Diagram of α-pyrone (2H-pyrone) and γ-pyrone (4H-pyrone)](image)

Running through the whole of pyrone chemistry there is an intriguing question is the hetrocyclic ring aliphatic or aromatic. The potential for aromaticity is brought out in the betaine structures 274 and 275. Both pyrones show some reactions characteristics of alkenes and others characteristic of arenes. In case of α-pyrone however the balance does lie heavily in favour of reactions of the former type (alkene). α-Pyone is best thought of as an enol lactone rather than as pyrylium betaine, α-pyrones have exhibited important biological properties. A number of steroidal α-pyrones have achieved considerable importance on account of their powerful action on cardiac muscle such as scillaren 276 produced by Scilla maritima and bufatolin 277 one of the active ingredients of the poisonous secretion found in skin of certain toads332-333.
Naturally occurring α-pyrones such as kawain 278, yangonin 279 methysticin 280 and β-erythroidin 281 are known to exhibit muscle relaxant properties.\(^\text{334}\).

\[
\begin{align*}
\text{276} & \quad \text{277} \\
\text{278} & \quad \text{279} \\
\text{280} & \quad \text{281}
\end{align*}
\]

Sliskovic et al\(^{335}\) have described 4-hydroxypyran-2-ones 282 and 283 as inhibitors of cholesterol biosynthesis.

149
Weber et al.\textsuperscript{336} have reported the \(\alpha\)-pyrones possessing phenolic moiety as potent scavengers of active oxygen species. The compound 284 is useful for the treatment of oxidative tissue injury in human disease.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {282};
\node (b) at (3,0) {283};
\end{tikzpicture}
\end{center}

Pereda et al.\textsuperscript{337} have isolated 5,6-dihydro-\(\alpha\)-pyrone, a spicegerolide 285 from \textit{Hyptis spicegera} as cytotoxic.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {284};
\end{tikzpicture}
\end{center}

Wrigley and coworkers\textsuperscript{338} have isolated (6S)-4,6-dimethyldec-2E, 4E-dienylester isolated 286 and 287 from \textit{phomopsis-sp} with cytokine production inhibitory activity.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {285};
\end{tikzpicture}
\end{center}
Antonio and associates\textsuperscript{339} have reported the antifungal activity of \(\alpha\)-pyrones \textsuperscript{288} commonly called as fusapyrones from \textit{Fusarium semitectum}.

Cohen et al\textsuperscript{340} have synthesised \(\alpha\)-pyrones of the type \textsuperscript{289} which are useful for treating cancer and infections especially bacterial infection.
Ri, R2 = H, cell penetrating moiety, lipophilic solubiliser
R3 = solubilising moiety sugar.

Hostetmann and associates\textsuperscript{341} have reported the antifungal activity of 6-substituted-5,6-dihydro-\(\alpha\)-pyrone 290 from \textit{Ravensera anisata}.

Ansary and coworkers\textsuperscript{342} have reported the preparation of linear and angular furobenzo-\(\alpha\)-pyrones 291 and 292 and screened them for their photosensitizing and also for their antimicrobial activities against \textit{Bacillus subtilis}.

\textbf{290}

\(R = H, R_1\ COCH_3\)

Ansary and coworkers\textsuperscript{342} have reported the preparation of linear and angular furobenzo-\(\alpha\)-pyrones 291 and 292 and screened them for their photosensitizing and also for their antimicrobial activities against \textit{Bacillus subtilis}.

\textbf{291}

\(R = H, Me\)

\textbf{292}

\(R_1, R_2 = H, Me, OMe\)
Hussein and associates\textsuperscript{343} have synthesised α-pyrones of the type 293 and 294 and reported their antimicrobial activity.

\[ \text{Ar} = \text{Ph, 4-} \text{O}_2 \text{N-C}_6 \text{H}_4, 4-\text{Cl-C}_6 \text{H}_4, \text{etc.}, \]
\[ \text{R} = \text{Pr, Cyclohexyl, Ph, Bz; } \text{R}_1 = \text{Pr, Et, Ph, Bz} \]

Jenkins et al.,\textsuperscript{344} isolated solanopyrone 295 from marine fungus possessing antialgal property, and also reported the phytotoxic associations between marine fungi and algae.

Elgamal et al\textsuperscript{345} have synthesised furocoumarins 296, 297, 298 and reported their antimicrobial activity.
Trkovnik and associates\textsuperscript{346} have prepared polyhydroxycoumarins \textsuperscript{299} and reported their antiviral activity.

Kesten and coworkers\textsuperscript{347} have prepared 4-substituted coumarin derivatives \textsuperscript{300} as potent and selective human dopamine D\textsubscript{4} antagonists.

The compound is active against HIV-I.

\textsuperscript{346} Trkovnik and associates have prepared polyhydroxycoumarins and reported their antiviral activity.

\textsuperscript{347} Kesten and coworkers have prepared 4-substituted coumarin derivatives as potent and selective human dopamine D\textsubscript{4} antagonists.
Anderson and associates\textsuperscript{348} have prepared arylcoumarins \textsuperscript{301} which modulate gene expression through the estrogen receptor.

Ovaska et al\textsuperscript{349} have prepared 3-arylcoumarins \textsuperscript{302} which are used for the treatment of stunned myocardium; subsequent to ischemia reperfusion.
Bombardelli and coworkers\textsuperscript{350} have prepared 8-(arylpropenoyl)-coumarins \textsuperscript{303} and \textsuperscript{304} as antiproliferative agents.

\textsuperscript{303} is useful for treating menopausal disorders and osteoporosis while \textsuperscript{304} is useful to treat breast cancer.

Shah et al\textsuperscript{351} have prepared sulfonamide derivatives of coumarin \textsuperscript{305} and \textsuperscript{306} and reported their antibacterial activity.
R² = Me, Me₂CH, MeSCH₂CH₂, HOCH₂, X = bond

The derivatives 306 showed good antibacterial activity against *E. coli*, *S. aureus*, *S. typhosa* and *S. albus*.

Kuriyama and associates ³⁵² have prepared 3- tetrazolylcoumarins 307 and reported their anaphylaxis activity.

R = 8-pentyloxy, Rⁱ = H

Flavin and coworkers ³⁵³ have synthesised coumarin derivatives of the type 308 and 309 and reported their antiviral activity.
Sharma et al.\textsuperscript{354} have prepared \(3\)-aza-4-methyl-7-hydroxycoumarins 310 and reported their antimicrobial activity.

\[
\begin{aligned}
\text{HO} & \quad \text{N} = \text{N} \\
\text{CH}_3 & \\
\end{aligned}
\]

\(310\)

\(R, R^1, R^2, R^3 = \text{H, Me, MeO, OH, NO}_2, \text{Br, Cl.}\)

Santana and associates\textsuperscript{355} have prepared 4-methylcoumarin derivatives of the type 311 and reported their photobiological activity.

\[
\begin{aligned}
\text{RO} & \quad \text{CH}_3 \\
\text{O} & \quad \text{O} \\
\text{H} & \\
\end{aligned}
\]

\(311\)

\(R = \text{H, (CH}_2)_2\text{NMe}_2\)

Thiazoles are also known to possess interesting biological and pharmaceutical properties such as diuretics\textsuperscript{356}, antihistamines\textsuperscript{356} anthelmintics, mitodepressives, mitostatics, antiparasitics, antiinflammatories, antivirals and antioxidants\textsuperscript{357}.

The most important naturally occurring thiazole is thiamine\textsuperscript{358} (vitamin B\textsubscript{1}) antineuritic factor 312 whose deficiency causes beriberi.
A new amino acid 313 has been isolated from the fungus *Pseudomonas aeruginosa*.

The role of benzothiazole nucleus in the bioluminescence of fireflies is important and luciferin 314 is found in fireflies contains similar chromophore responsible for emission.

Mahajanshetti and coworkers have prepared a number of 2-amino / acetamido-5-arythiothiazoles and their sulfones 315 and some of them were found bacteriostatic *in vitro* tests against *E. coli* and *S. aureus*.

\[ R = R_1 = H, Cl, Br, Me, OMe, OEt, R_2 = NH-COCH_3 \]
Sano et al\textsuperscript{361} have synthesised thiazole-4-carboxylic acid derivatives and reported them as serotonin antagonists. Tropanyl-2-phenyl-4-thiazole carboxylate \textbf{316} inhibited serotonin induced von Bezold-Jarisch reflex with \textit{ED}_{50} of 0.56 mg / kg i.p in rats. These esters also proved useful in the treatment of gastrointestinal disorders, migraine, trigeminal neuralgia, nausia, vomiting, arrythmia, and anxiety.

\[ R = \text{lower alkyl, } \text{PhCH}_2, \ n = 0 - 2. \]

Yoshioka and associates\textsuperscript{362} have synthesised 2-aminothiazole derivative of the type \textbf{317} and tested their activity against diabetes complications.

\[ \text{Andronnikova et al}\textsuperscript{363} have reported the promising antitumor activity of the compound \textbf{318}. \]
It was active at a dose of 5 mg/kg body weight against adenocarcinoma Ak 755 in rats.

Yoshinaga and associates\textsuperscript{364} have tested a number of N-substituted thiazole-4-carboxamides 319 as antiallergy agents. 2-(2-methoxyphenyl)-N-(1H-tetrazol-5-yl)-4-thiazole carboxamide at 2 mg/kg i.v in rats gave 67-99\% inhibition of passive cutenious anaphylaxis (PCA).

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{319.png}
\caption{319}
\end{figure}

\texttt{R = Aryl}

Sandoz et al\textsuperscript{365} have prepared thiazolyl piperazine derivatives 320 and 321 and reported their antiviral activity.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{320.png}
\caption{320}
\end{figure}

\texttt{R\textsubscript{1} = R\textsubscript{2} = H or alkyl}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{321.png}
\caption{321}
\end{figure}

Sharma et al\textsuperscript{366} have reported the antiinflammatory activity of some 3-(2-thiazolyl)-1,2-benzisothiazoles 322.
Nagasawa and associates\textsuperscript{367} have prepared benzoylaminothiazole derivatives \textbf{323} for improving digestive tract disorders.

\[ R = H, \text{Me, Ph, 4-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{pyridyl}; R_1 = H, \text{Me} \]

\[ X = \text{Imino optionally substituted by lower alkyl, or oxygen}; R^1 = \text{cyano, lower alkoxy carbonyl, lower alkyl sulfonyl, 1-ureido, halogenated lower alkyl, 2-pyrrolylimino}; R^2 \text{ and } R^3 = \text{same or different and each represents H, lower alkyl, and } \text{m} = 2-4. \]

The compounds are useful as preventives and remedies for unidentified epigastric complaints, vomiturition, heartburn, anorexia, chronic gastritis, abdominal pain and vomiting.
Yata and coworker\textsuperscript{368} have prepared thiazoles 324 and 325 as hypertriglyceridemia and obesity remedies.

\[
\text{324}
\]

\[R^1 = \text{C}_{1-6}\text{-alkyl}; \quad R^2 = \text{C}_{1-6}\text{-alkyl, C}_{3-7}\text{-cycloalkyl};\]
\[R^3 = (\text{un})\text{substituted thienyl, (un) substituted furyl.}\]

\[
\text{325}
\]

\[R^1 = \text{C}_{1-6}\text{-alkyl; } R^2 = \text{C}_{1-6}\text{-alkyl, C}_{3-7}\text{-cycloalkyl; } R^3 = (\text{un})\text{substituted Ph, (un)substituted thienyl, (un)substituted furyl.}\]
Present Work

In the light of wide varieties of biological properties associated with 2H-pyran-2-ones, coumarins and thiazoles, we were very much encouraged to undertake the synthesis of thiazolylypyranoindoles wherein 2H-pyran-2-ones bearing bioactive thiazole moiety are linearly fused to the benzene nucleus of biodynamic indole nucleus in order to obtain α-pyranoindole derivatives with enhanced biological activities.

In the present investigation, the required starting materials viz, 1-substituted-3-acetyl-5-hydroxy-2-methylindoles 326a-b were prepared by reacting p-benzoquinone with acetyl acetone imine under Nenitzescu reaction conditions. These 5-hydroxyindoles 326a-b were subjected to regioselective Friedel-Crafts acetylation with acetyl chloride and anhydrous aluminium chloride in freshly distilled nitrobenzene to obtain the desired 3,6-diacetyl-5-hydroxyindole derivatives 327a-b. These 3,6-diacetyl-5-hydroxy-2-methylindoles 327a-b were first heated with ethyl acetoacetate in presence of triethyl amine and piperidine with a desire to get linearly fused 6-substituted-3,8-diacetyl-4,7-dimethyl-2H-pyrano[6,5-f]indol-2-ones 328a-b. However, only starting materials 3,6-diacetyl-5-hydroxyindoles 327a-b were obtained instead of the desired pyranoindoles 328a-b.

Brown and Mihm have reported that 2-methylpyridine is a stronger base than pyridine presumably due to electron donating inductive effect of methyl group. Hence, we thought on same lines and used 2-methylpiperidine in this reaction in place of triethyl amine and piperidine which is stronger base than piperidine yielding first time the desired linearly fused 6-substituted-3,8-diacetyl-4,7-dimethyl-2H-pyrano[6,5-f]indol-2-ones 328a-b. Similarly, the above cited modified reaction condition was also applied for the condensation of o-hydroxyacetophenone with ethyl acetoacetate to generate the required 3-acetyl-4-methylcoumarin which was otherwise obtained in very poor yield by diketene route.
Scheme - 16

Chemical reactions and structures are shown with arrows indicating the transformation from one compound to another. The table below lists the compounds with their corresponding R groups:

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-C₆H₅</td>
</tr>
<tr>
<td>2.</td>
<td>-C₆H₄CH₃-p</td>
</tr>
</tbody>
</table>

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Scheme-17

\[
\begin{align*}
&\text{HO} &\text{O} \\
&H_2C &\text{O} \\
&332 &
\end{align*}
\]

\[
\begin{align*}
O & \quad \text{CH}_3-C-\text{CH}_2-C-\text{O}\text{C}_2\text{H}_5 \\
333 &
\end{align*}
\]

\[
\begin{align*}
&\text{2-methylpiperidine} \quad 228^\circ\text{C} \\
&\downarrow \\
&\text{Cl}_3 \quad \text{O} \\
&\text{O} \\
&\text{C} \quad \text{CH}_3 \\
&334
\end{align*}
\]
3,8-Diacetyl-4,7-dimethyl-2H-pyrano[6,5-f]indoles 328a-b were further chemoselectively brominated at 3-acetyl group to obtain the required 3-bromoacetyl-4,7-dimethyl-8-acetyl-2H-pyrano[6,5-f]indoles 329a-b. The unreactivity of C8-acetyl function of these diacetylindoles 328a-b towards bromine could be related to the reduced double bond character of this group due to the canonical structure B wherein the π-electrons of indole nitrogen are delocalised on the oxygen of this C8-acetyl group. The 3-bromoacetyl-4,7-dimethyl-8-acetyl-2H-pyrano[6,5-f]indoles 329a-b were heated at reflux with thiourea in dry ethanol to obtain the desired 6-substituted-3-(2-amino-thiazol-4-yl)-8-acetyl-4,7-dimethyl-2H-pyrano[6,5-f]indoles 331a-b in good yields.

IR spectrum (Fig-64) of compound 327a displayed a stretching band at 2919 cm\(^{-1}\) due to intramolecular H-bonded C5-OH group while C6 and C3-acetyl carbonyls showed strong stretching bands at 1641 cm\(^{-1}\) and 1628 cm\(^{-1}\). \(^1\)H NMR spectrum (Fig-65) of 327a exhibited singlets at 2.53 \(\delta\) and 2.63 \(\delta\) due to C3-acetyl methyl and C6-acetyl methyl protons and the C2-methyl protons displayed singlet at 2.71 \(\delta\). The C7-proton resonated as singlet at 7.33 \(\delta\) while another singlet at 7.63 \(\delta\) was assigned to C4-proton. Five aromatic protons of 1-phenyl group displayed multiplet ranging from 7.36 \(\delta\) to 7.66 \(\delta\). The C5-OH proton displayed singlet at 12.08 \(\delta\) which vanished on D\(_2\)O exchange.

The IR spectrum (Fig-66) of compound 328a exhibited a strong stretching band at 1708 cm\(^{-1}\) due to lactone carbonyl while C3 and C8-acetyl carbonyls showed a strong band at 1628 cm\(^{-1}\). \(^1\)H NMR spectrum (Fig-67) of
328a showed a singlet at 2.34 δ due to C3-acetyl methyl and another singlet at 2.60 δ was assigned to C8-acetyl methyl. The C7-methyl protons resonated at 2.62 δ as singlet while singlet at 2.73 δ was attributed to C4-methyl protons. Singlet at 7.24 δ was accounted for C5-proton and another singlet at 8.01 δ was assigned to C9-proton. The aromatic protons of C6-phenyl ring displayed multiplet ranging from 7.33 δ to 7.67 δ.

13C NMR spectrum (Fig-68) of 328a displayed a signal at 14.2 δ due to C7-methyl carbon and a peak at 17.3 δ was assigned to C3-methyl carbon. Signal at 34.0 δ was accounted for C4-methyl carbon and C8-methyl carbon resonated at 35.2 δ. The C5 of indole nucleus resonated at 106 δ while signal due to junction carbon C9[b] was found at 108 δ and C5[a] junction carbon peak was observed at 121.2 δ. A peak at 122.3 δ was assigned to C7. The C4-carbon of phenyl ring showed a peak at 127.5 δ and signal due to C3 and C5-carbons of phenyl was observed at 129 δ. Signal at 132 δ was accounted for C2 and C6 carbons of phenyl ring while C8 of indole nucleus was seen at 133 δ. The peak at 137 δ was attributed to C1 of phenyl ring while signal at 149 δ was accounted for C4[a] junction carbon and a peak at 157 was related to 1[b] junction carbon. The peak of C4-carbon of pyrone ring was found at 150 δ while lactone carbonyl carbon resonated at 176 δ. Signal at 194 δ was accounted for C3 and C8 carbonyl carbons.

IR spectrum of 334 displayed a strong stretching band at 1678 cm⁻¹ due to C3-acetyl carbonyl and another band at 1799 cm⁻¹ was due to lactone carbonyl. 1H NMR spectrum of compound 334 showed two singlets at 2.48 δ and 2.61 δ due to C3-acetyl methyl and C4-methyl protons while a multiplet from 7.34 δ - 7.75 δ was assigned to four aromatic protons.

The IR spectrum (Fig-69) of compound 329a displayed sharp stretching bands at 1706 cm⁻¹ and 1690 cm⁻¹ due to lactone carbonyl and C7-bromoacetyl carbonyl. A band at 1632 cm⁻¹ was assigned to C8-acetyl carbonyl.

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$^1$H NMR spectrum (Fig-70) of 329a exhibited singlet at 2.36 $\delta$ due to C8-methyl and singlet at 2.65 $\delta$ was assigned to C7-methyl protons. Singlet at 2.82 $\delta$ was attributed to C4-methyl protons. Singlet at 4.52 $\delta$ was assigned to methylene protons of C3-bromoacetyl group. Multiplet ranging from 7.30 $\delta$ to 8.09 $\delta$ was accounted for seven aromatic protons.

IR spectrum (Fig-71) of compound 331a showed a broad stretching band due to NH2 at 3434 cm$^{-1}$ and strong stretching band at 1712 cm$^{-1}$ due to lactone carbonyl where as acetyl carbonyl stretching band was observed at 1628 cm$^{-1}$. $^1$H NMR spectrum (Fig-72) of 331a displayed a broad singlet at 1.6 $\delta$ due to NH2 which disappeared on D2O exchange. Singlet at 2.53 $\delta$ was assigned to C8-acetyl methyl protons while singlet at 2.64 $\delta$ was accounted for C7-methyl protons. Another singlet at 2.85 $\delta$ was attributed to C4-methyl protons. The C5-proton resonated as singlet at 7.25 $\delta$ while C9-proton was observed as singlet at 7.68 $\delta$. Five aromatic protons of phenyl ring displayed multiplet from 7.34 $\delta$ to 7.68 $\delta$ while downfield singlet at 8.03 $\delta$ was assigned to C5-proton of thiazole ring.

The mass spectrum (Fig-73) 331a displayed the molecular ion peak M$^+$ at m/z (%) 429(1). The fragment F1 was generated at m/z (%) 414(2) due to the loss of CH$_3$ from M$^+$ and fragment F2 was produced from M$^+$ at m/z (%) 388(2) by the loss of CHN$_2$. The fragment F3 obtained after the loss of CHN$_2$ and CH$_2$ from M$^+$ was observed at m/z (%) 374(74). Base peak F4 at m/z (%) 359(100) was produced from M$^+$ by the loss of CH$_2$N$_2$ and CO. The fragment F5 obtained after losing C$_3$H$_2$N$_2$S from M$^+$ was found at m/z (%) 331(10). Fragment F6 produced at m/z (%) 317(10) was due to the loss of C$_3$H$_2$N$_2$S and CH$_2$ from M$.^*$. Fragment F7 observed at m/z (%) 303(4) was generated by the loss of C$_3$H$_2$N$_2$S and CO from M$.^*$. Fragment F8 produced at m/z (%) 259(7) was due to the loss of C$_3$H$_3$N$_2$S, C$_2$H$_3$O, CO and H$_2$ from M$.^*$ [Scheme-18].
Scheme-18

F7

m/z (%) 303 (4)
C,H,N,S & CO

F8

m/z (%) 259 (7)

F9

m/z (%) 317 (10)
C,H,N,S & H₂

M+

m/z (%) 429 (1)
CH₃N & CO

F4

m/z (%) 359 (100)

F1

m/z (%) 414 (2)
CHN₃ & CH₃

F2

m/z (%) 388 (1)

F3

m/z (%) 374 (74)
Fig. 45: 1H NMR Spectrum CDCl₃

on D₂O exchange
Fig. 68: $^{13}$C NMR Spectrum

CDCl$_3$
Fig-72: H NMR Spectrum
CDCl₃

on D₂O exchange

[Chemical Structure Image]
Fig. 73: Mass Spectrum

M /7.420400

'H -rf-p ' 14VT m f  j 'r r n | r f  v?-j  r 1-i'i | ...
Experimental
1-Substituted-3-acetyl-5-hydroxy-2-methyindoles 326a-b:

Acetylacetone imine 325a-b prepared by the reaction of acetylacetone (100g, 0.5mol) and appropriate primary amine (0.5mol) in chloroform was added with shaking to p-benzoquinone (0.55mol) dissolved in chloroform (500ml). The reaction mixture was heated at reflux for 2 hours. The solvent and resultant water were removed under reduced pressure. The residue was treated with ethanol and left overnight. The separated solid was filtered, washed with ethanol and recrystallised from dioxan.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Compd</th>
<th>R</th>
<th>m.p. (lit)°C</th>
<th>Yield (lit) %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>326b</td>
<td>C₆H₅CH₃-p</td>
<td>277-78 (262-63)</td>
<td>35 (42)</td>
<td></td>
</tr>
</tbody>
</table>

1-Phenyl-3,6-diacyl-5-hydroxy-2-methyindoles 327a:

To a suspension of 5-hydroxyindole derivative 326a (7.9g, 0.03mol) in freshly distilled nitrobenzene (100mL) and acetyl chloride (3.9g, 0.06mol) was added anhydrous aluminium chloride (9.9g, 0.075mol) in portions as rapidly as it dissolved. The reaction mixture was heated for 3 hours on steam bath and left overnight. It was poured into ice water (500mL) containing concentrated hydrochloric acid (75mL) and then subjected to steam distillation to remove nitrobenzene. The solid mass that separated on cooling to room temperature
was filtered and recrystallised from dioxan to afford the title compound as yellow flowery crystals m.p. 197-8°C, yield: 60.6%.

1-p-Tolyl-3,6-diacetyl-5-hydroxy-2-methylindole 327b:

This was prepared from 5-hydroxyindole 326b as per the procedure given for 327a and solid was recrystallised as green needles from dioxan m.p. 221-222°C, yield: 59.6%.

6-Phenyl-3,8-diacetyl-4,7-dimethyl-2H-pyrano[6,5-f]indol-2-one 328a:

1-Phenyl-3,6-diacetyl-5-hydroxy-2-methylindole 327a (1.76 g, 0.057 mol) was heated with ethyl acetoacetate (0.74 g, 0.057 mol) in presence of 2-methylpiperidine (0.5 mL) in an oil bath at 228-230°C. The heating was continued for 6 hours, cooled to room temperature and the solid mass was triturated with benzene-petroleum ether (40-60). The solid was filtered and recrystallised from ethanol as yellow granules, m.p. 153-4°C, yield: 72%.

Anal. Calcd for C23H19N04: C, 73.98; H, 5.13; N, 3.75. Found C, 73.64; H, 5.26; N, 3.43%.

6-p-Tolyl-3,8-diacetyl-4,7-dimethyl-2H-pyrano[6,5-f]indol-2-one 328b:

This compound 328b was prepared as per the procedure given for compound 328a and it was recrystallised from ethanol as yellow needles, m.p. 118-20°C, yield: 64%.

Anal. Calcd. for C24H21N04: C, 74.40; H, 5.45; N, 3.61. Found: C, 74.28; H, 5.82; N, 3.44%.

6-Phenyl-3-bromoacetyl-4,7-dimethyl-8-acetyl-2H-pyrano[6,5-f]indol-2-one 329a:

To a well stirred solution of 6-phenyl-3,8-diacetyl-4,7-dimethyl-2H-pyrano[6,5-f]indol-2-one 328a (0.37 g, 0.001 mol) in chloroform (50 mL) was
added bromine (0.08g, 0.001mol) in chloroform (5mL) with magnetic stirring in about 10 minutes. The mixture was stirred for 0.5 hour. The solvent was evaporated and residue was recrystallised from benzene petroleum ether (40-60) as yellow granules, m.p. 238-9°C, yield : 46%.

Anal. Calcd. for C_{23}H_{18}N_{0}O_{4}Br : C, 61.07; H, 4.01; N, 3.09. Found : C, 61.22; H, 4.36; N, 3.28%.

6-p-Tolyl-3-bromoacetyl-4,7-dimethyl-8-acetyl-2H-pyrano[6,5-f]indol-2-one 329b :

It was prepared according to the procedure depicted for compound 329a and it was recrystallised as yellow granules from ethanol, m.p. 286-7°C, yield : 44%.

Anal. Calcd for C_{24}H_{20}N_{0}O_{4}Br : C, 61.81; H, 4.32; N, 3.00. Found : C, 61.46; H, 4.82; N, 3.24%.

6-Phenyl-3-(2-aminothiazol-5-yl)-8-acetyl-4,7-dimethyl-2H-pyrano[6,5-f]indol-2-one 331a :

A mixture of 6-phenyl-3-bromoacetyl-4,7-dimethyl-8-acetyl-2H-pyrano[6,5-f]indol 2-one 329a (0.45g, 0.001mol) and thiourea (0.1g, 0.015mol) in dry ethanol (50 mL) was heated under reflux for 6 hours. The separated solid was filtered washed with aqueous ethanol (50%), sodium bicarbonate solution (10%) and water. The dried solid was recrystallised from ethanol as greyish granules, m.p. 264-5°C, yield : 54%.

Anal. Calcd for C_{24}H_{19}N_{3}O_{3}S : C, 67.11; H, 4.45; N, 9.78. Found : C, 67.28; H, 4.38; N, 9.64%.
6-p-Tolyl-3-(2-aminothiazol-5-yl)-8-acetyl-4,7-dimethyl-2H-pyrano[6,5-f]-indole-2-one 331b:

It was synthesised as per the procedure given for compound 331a and recrystallised as grey flakes from ethanol, m.p. 232-3°C, yield: 43%.

Anal. Calcd for C_{25}H_{21}N_{3}O_{3}S: C, 67.70; H, 4.77; N, 9.47. Found: C, 67.32; H, 4.73; N, 9.38%.

3-Acetyl-4-methylcoumarin 334:

o-Hydroxyacetophenone 333a (1g, 0.007mol) was heated with ethyl acetoacetate (0.91g, 0.001mol) in presence of 2-methylpiperidine (0.5mL) in an oil bath at 229°C. The heating was continued for 3 hours. After cooling to room temperature, the residue was poured on ice water and cooled till the solid separated. The separated solid was filtered, washed thoroughly with water, dried and recrystallised from ethanol as pale yellow needles, m.p. 105-6°C (lit.\(^{373}\) m.p. 102-3°C), yield: 75%.

Anal. Calcd for C_{12}H_{10}O_{3}: C, 71.28; H, 4.98. Found: C, 71.36; H, 4.24%.