Chapter V

Part 1

4-(N-arylsulfonyl-1,2,3,4-tetrahydro-isoquinoline-1-ylmethyl)-coumarins

Part 2

Coumarin analogues of N-methyl-isoquinoline alkaloids
Part 1

4-(N-arylsulfonyl-1,2,3,4-tetrahydro-isoquinoline-1-ylmethyl)-coumarins
5.1.0. INTRODUCTION

The first part of this chapter deals with the synthesis of sulfonamides I obtained from the reaction of aryl sulfonyl chlorides and the coumarin analogue of 1-benzyl-1,2,3,4-tetrahydroisoquinoline II.

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\text{R}_1 = \text{R} = \text{Y} = \text{H} \\
\text{R}_1 = \text{Bn}, \text{R} = \text{Y} = \text{H} \\
\end{align*}
\]

In continuation of the previous chapter, in this part the nitrogen of 1,2,3,4-tetrahydroisoquinoline is being exploited to synthesize the various biologically important \(N\)-arylsulfonyl-1,2,3,4-tetrahydroisoquinoline derivatives. The syntheses, characterization and biological evaluation has been described in subsequent sections.

In view of this it is pertinent to mention the importance of various sulfonamides containing coumarins and isoquinoline rings.

Recently some tetrahydroisoquinoline based sulfonamide hydroxamates 1 have been reported as potent matrix metalloproteinase inhibitors by Ma et al.,\(^1\)

\[
\begin{align*}
1a & \quad \text{R}_1 = \text{R} = \text{Y} = \text{H} \\
1b & \quad \text{R}_1 = \text{R} = \text{H}, \text{Y} = 4' - \text{Me} \\
1c & \quad \text{R}_1 = \text{R} = \text{H}, \text{Y} = 4' - \text{OCH}_3 \\
1d & \quad \text{R}_1 = \text{R} = \text{H}, \text{Y} = 4' - \text{NH}_2 \\
1e & \quad \text{R}_1 = \text{R} = \text{H}, \text{Y} = 4' - \text{NO}_2 \\
1f & \quad \text{R}_1 = \text{R} = \text{H}, \text{Y} = 2' - \text{Cl}, 5' - \text{Cl} \\
1g & \quad \text{R}_1 = \text{Bn}, \text{R} = \text{Y} = \text{H} \\
1h & \quad \text{R}_1 = \text{Bn}, \text{R} = \text{H}, \text{Y} = 4' - \text{Me} \\
1i & \quad \text{R}_1 = \text{Bn}, \text{R} = \text{H}, \text{Y} = 4' - \text{OMe} \\
1j & \quad \text{R}_1 = \text{Bn}, \text{R} = \text{H}, \text{Y} = 2' - \text{Cl}, 5' - \text{Cl} \\
\end{align*}
\]
Inhibition of forskolin-induced neutrite outgrowth and phosphorylation by a newly synthesized selective inhibitor of cyclic AMP-Dependent protein kinase, \( N\-\left[2\-\left(p\-bromocinnamoylamino\right)ethyl\right]-5\-isoquinolinesulfonamide \) (H-89) 2, of PC12D pheochromocytoma cells have been reported by Chijiwa et al. 2

Xu et al. 3 have reported the structural basis for selectivity of the isoquinoline sulfonamide family 3 towards the protein kinase inhibition.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Ring position 5</th>
<th>Ring position 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK17</td>
<td>Cl</td>
<td>-SO_2NH(CH_2)_2NH_2</td>
</tr>
<tr>
<td>CK16</td>
<td>H</td>
<td>-SO_2NH(CH_2)_2NH_2</td>
</tr>
<tr>
<td>H9</td>
<td>-SO_2NH(CH_2)_2NH_2</td>
<td>H</td>
</tr>
<tr>
<td>H89</td>
<td>-SO_2NH(CH_2)_2NHCH_2CH=CH-(p-bromo-ph)</td>
<td>H</td>
</tr>
</tbody>
</table>

Hidaka et al. 4 have reported 5-chloro-6-hexylamino-1-isoquinolinesulfonamide 4 as novel and potent inhibitor of cyclic nucleotide dependent protein kinase and protein kinase C.
Russian workers\(^5\) found that sulphonamides of the type 5 and 6 were found to be ineffective against dysentery \textit{bacilli} and \textit{coccii}.

\[
\begin{align*}
\text{R} & = \text{CH}_3, \text{C}_6\text{H}_5
\end{align*}
\]

Bersch and Dopp\(^6\) have synthesized many 7-sulphanilamido 4-carboethoxymethylcoumarins 4 some of these were tested for their antitubercular activity in sauton medium. They were found to be active against strains of \textit{bacilli} resistant to PAS and Streptomycin.

During their study on \(p\)-hydroxy substituted sulphanilamides Jensen and Christensen\(^7\) found that 6-(\(p\)-hydroxy sulphanilamido)coumarin 7 was inactive against \textit{D. pneumoniae}, \textit{E. typhosa}, \textit{S. aureus} and \textit{E. coli} at 1: 5000 concentration.

Okumura\(^8\) reported the synthesis and MIC of 4-hydroxy-3-sulphanilamido coumarin 8 against various bacterial strains.
Reppel and Schmollack\textsuperscript{9} reported the synthesis of many nitro substituted coumarin sulphonamides \textbf{9}.

During their study on medicinally important coumarins Kitaqawa and Iwaki\textsuperscript{10} found that compounds \textbf{10} had tuberculostatic action.

C-7 hydroxylated sulphonamides \textbf{11} in the carbocyclic ring were synthesized by Chakravarti and Das\textsuperscript{11}.

Sulphonamidocoumarins \textbf{12} and \textbf{13} have been found to be useful as optical brighteners\textsuperscript{12,13}. 
Ichikawa et al.\textsuperscript{14} found that 4-hydroxy-3-sulphonamido coumarins 14 had strong anti-bacterial action.

\[ R = \text{H, Ac} \]

\[ R_1 = \text{H, OCH}_3 \]

Continuing their studies\textsuperscript{15,16} on similar sulphonamides the Japanese workers have found that coumarins 15\textsuperscript{17} were useful in clinical practice as an anti-tuberculosis drug.

\[ R = \text{H, CH}_3, \text{OCH}_3, \text{NHAc} \]

Bis-coumarinyl sulphonamides\textsuperscript{18} 16 were found to be active against Gram-positive bacteria.
Thakar et al.\textsuperscript{19} have found that 4-(6-coumarinyl)-2-sulphanilamido thiazoles 17 inhibited the growth of fungi like \textit{Alternaria solani}, and some of them also inhibited the growth of mustard seed germination.

\begin{center}
\includegraphics[scale=0.5]{image1.png}
\end{center}

R = H, Ac

Some bio-chemically important coumarinsulphonamides 18 have been reported by Chakravarti and Das.\textsuperscript{20}

\begin{center}
\includegraphics[scale=0.5]{image2.png}
\end{center}

R = H, CH\textsubscript{3}, Cl
R = H, OCH\textsubscript{3}

Delaby et al.\textsuperscript{21} have found 4,5,7-trimethyl-8-sulphonamidocoumarins 19 useful as anti-diabetics.

\begin{center}
\includegraphics[scale=0.5]{image3.png}
\end{center}

NRR\textsubscript{1} = Morpholino, NEt\textsubscript{2}

Islam et al.\textsuperscript{22} have found that 6-sulphonamido coumarins 20 possess good anti-bacterial properties, against species like \textit{S. aureus} and \textit{B. subtilis}.
Hanmantgad et al. synthesized various sulphanilamidomethylcoumarins 21. These compounds have been characterized by their spectral data and some of them show better anti-bacterial activity against *S. aureus* and *E. coli* than the standard (sulphanilamide). Structure activity relationship has also been studied.

Synthesis of novel coumarin-3-((N-aryl)-sulfonamides 22 and their ability to activate JNK1 and kill cancer cells *in-vitro* is described by Srinivasreddy et al.
In the light of above said discussion, which shows the diverse biological activities associated with sulfonamides containing isoquinolines and coumarin, the present work is aimed at introducing a pharmacophore in the form isoquinoline, a new class of coumarinsulphonamides of isoquinolines. The synthesis makes use of the nucleophilicity of the nitrogen of isoquinolines. All the newly synthesized compounds have been characterized by spectral methods and screened for their biological activity.

5.1.1. PRESENT WORK

The work carried out during the present investigation is described in scheme 1. This scheme describes the synthesis of 4-(N-arylsulfonyl-1,2,3,4-tetrahydro-isoquinoline-1-ylmethyl)-coumarins.

The required coumarin analogues of 1,2,3,4-tetrahydroisoquinolines 7 were synthesized as described in chapter II. The compounds 13 and 14 were obtained on stirring 7 with various substituted phenyl/naphthylsulfonyl chlorides in dichloromethane.
All the synthesized compounds were purified by crystallization and purity was checked by TLC. All the title compounds are studied for their spectral properties like IR, \(^1\)H, \(^13\)C, 2-D HETCOR NMR and Mass spectra. Some of the synthesized compounds have been screened for their biological activities.

5.1.2. RESULTS AND DISCUSSION

All the synthesized compounds were characterized by their spectral analysis. Absence of \(\nu\text{N-H} \) 3200-3350 cm\(^{-1}\) in the IR spectra of 13 and 14 indicates the formation of the product. Lactone carbonyl of coumarin \(\nu\text{C=O}\) was appeared in the range 1698-1724 cm\(^{-1}\).
In the $^1$H NMR spectra C4-CH$_2$ resonated at $\delta$ 2.8-2.9 as a multiplet and C3-CH$_2$ appeared at $\delta$ 3.65-3.75 as a multiplet. Owing to their diastereotopic nature of $\alpha$-CH$_2$ with respect to asymmetric center C1-H, they appeared as two sets of doublet of doublets in the range $\delta$ 3.1-3.4. C1-H was resonated in the range $\delta$ 5.20 and all the other protons resonated in the expected regions. All the protons and carbons were assigned on the basis of 2D NMR (Figure 1).

**Figure 1**

Assignment of $^1$H NMR of 13a.

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>J Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_X$</td>
<td>2.32</td>
<td>s, 3H</td>
<td></td>
</tr>
<tr>
<td>H$_Y$</td>
<td>2.49</td>
<td>s, 3H</td>
<td></td>
</tr>
<tr>
<td>H$<em>{4a}$ &amp; H$</em>{4e}$</td>
<td>2.82-2.88</td>
<td>m, 2H</td>
<td></td>
</tr>
<tr>
<td>H$<em>{aa}$ &amp; H$</em>{*}$</td>
<td>3.68</td>
<td>t, 3H</td>
<td></td>
</tr>
<tr>
<td>H$_{i}$</td>
<td>5.21</td>
<td>t, 1H</td>
<td></td>
</tr>
<tr>
<td>H$_{3-}$</td>
<td>5.80</td>
<td>s, 1H</td>
<td></td>
</tr>
<tr>
<td>H$_{7-}$</td>
<td>6.77</td>
<td>d, 1H, J = 8.1 Hz</td>
<td></td>
</tr>
<tr>
<td>H$_{5'}$</td>
<td>7.71</td>
<td>s, 1H</td>
<td></td>
</tr>
</tbody>
</table>
Assignment of $^{13}$C NMR of 13a.

The physical, analytical and spectral data of all the compounds has been given in experimental section of this chapter.

Spectrum No. 1. IR (KBr) of compound 13a.
Spectrum No. 2. $^1$H NMR (CDCl$_3$) of compound 13a.

Spectrum No. 3. $^{13}$C NMR (CDCl$_3$) of compound 13a.
Spectrum No. 4. 2D HETCOR of compound 13a.

Spectrum No. 5. LC MS of compound 13a

<table>
<thead>
<tr>
<th>Peak</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.515</td>
<td>6.121e+000</td>
<td>0.110</td>
</tr>
<tr>
<td>2</td>
<td>2.543</td>
<td>5.071e+000</td>
<td>0.091</td>
</tr>
<tr>
<td>3</td>
<td>3.181</td>
<td>1.107e+001</td>
<td>0.230</td>
</tr>
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<td>4</td>
<td>3.277</td>
<td>5.492e+003</td>
<td>99.336</td>
</tr>
<tr>
<td>5</td>
<td>3.546</td>
<td>3.119e+001</td>
<td>0.562</td>
</tr>
</tbody>
</table>

Spectrum No. 5. LC MS of compound 13a
Spectrum No. 5. LC MS of compound 13a.

Spectrum No. 6. $^1$H NMR (CDCl$_3$) of compound 13b.
Spectrum No. 6. $^1$H NMR (CDCl$_3$) of compound 13b (Expansion)

Spectrum No. 7. $^{13}$C NMR (CDCl$_3$) of compound 13b.
5.1.3. EXPERIMENTAL

5.1.3.0. General procedure for the synthesis of 13 and 14.

To the solution of 4-(1,2,3,4-Tetrahydro-isoquinoline-1-yl-methyl)-coumarins 7 (1 eq.) and pyridine (1.5 eq.), in dichloromethane (DCM)(10 mL) was added slowly substituted sulfonyl chlorides (1.1 eq.) and the resulting mixture was stirred overnight at room temperature. The reaction was then quenched by adding a solution of NH₄Cl and was extracted with DCM. The product was then purified by recrystallization from a suitable solvent.

5.1.3.1. 6-Methyl-4-[2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl]-coumarin 13a.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and p-toluenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 80%; m.p. 162-165 °C, IR (KBr): 3045, 3015, 2926, 1724, 1622, 1570 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.32 (s, 3H, C4''-CH₃), 2.49 (s, 3H, C6'-CH₃), 2.82-2.88 (m, 2H, C4-Ha, He), 3.09 (dd, 1H, J = 7.5, 5.7 Hz, α-H), 3.40 (dd, 1H, J = 6.9, 6.3 Hz, α'-H), 3.68 (t, 2H, C3'-He, Hα), 5.21 (t, 1H, C1-H), 5.80 (s, 1H, C3'-H), 6.77 (d, 1H, J = 8.1 Hz, C7'-H), 7.07-7.52 (m, 9H, Ar-H), 7.71 (s, 1H, C5'-H); ¹³C NMR (75 MHz, CDCl₃): δ 21.4, 21.8, 27.9, 40.9, 41.6, 56.4, 117.3, 117.4, 119.0, 125.1, 126.0, 127.3, 127.3, 127.4, 128.1, 129.4, 129.9, 129.9, 133.1, 133.9, 134.6, 134.7, 136.5, 143.9, 151.6, 152.2, 160.8; Anal. Calcd. for C₂₇H₂₅N₀₄S (%): C, 70.57; H, 5.48; N, 3.05; Found: C, 70.67; H, 5.54; N, 3.18.

5.1.3.2. 4-[6,7-Dimethoxy-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl]-6-methyl-coumarin 13b.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and p-toluenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 85%; m.p. 149-152 °C, IR (KBr): 3058, 3000, 2919, 1714, 1611, 1571
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.34 (s, 3H, C4"-CH$_3$), 2.47 (s, 3H, C6'-CH$_3$), 2.72 (m, 2H, C4-H$_a$, H$_e$), 3.12 (m, 1H, $\alpha$-H), 3.38 (m, 1H, $\alpha'$-H), 3.64 (s, 3H, C6-OCH$_3$), 3.71 (m, 2H, C3-H$_a$, H$_e$), 3.82 (s, 3H, C7-OCH$_3$), 5.14 (m, 1H, C1-H), 5.93 (s, 1H, C5-H), 6.17 (s, 1H, C8-H), 6.52 (s, 1H, C3'-H), 7.10 (d, 2H, 7.9 Hz, C3", C4"-H), 7.24 (d, 1H, J = 6.0 Hz, C7'-H), 7.37 (d, 1H, J = 6.0 Hz, C8'-H), 7.52 (d, 2H, J = 8.0 Hz, C2", C6"-H), 7.64 (s, 1H, C5'-H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 21.4, 21.8, 27.4, 40.6, 41.4, 56.1, 56.2, 56.3, 110.6, 111.9, 117.3, 117.4, 119.0, 125.2, 126.0, 126.5, 127.3, 127.3, 129.9, 129.9, 133.2, 134.6, 136.7, 143.9, 147.5, 148.9, 152.0, 152.2, 160.7; Anal. Calcd. for C$_{29}$H$_{29}$N$_2$O$_6$S (%); C, 67.03; H, 5.63; N, 2.70; Found; C, 67.17; H, 5.74; N, 2.88.

5.1.3.3. 6-Bromo-4-[2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl]-coumarin 13c.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and p-bromo-benzenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 80%; m.p. 158-160 °C, IR (KBr), 3337, 3264, 3027, 2922, 1706, 1615, 1569 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.49 (s, 3H, C6'-CH$_3$), 2.86 (m, 2H, C4-H$_a$, H$_e$), 3.12 (dd, 1H, J = 7.2, 6.1 Hz, $\alpha$-H), 3.38 (dd, 1H, J = 7.2, 6.0 Hz, $\alpha'$-H), 3.72 (m, 2H, C3-H$_a$, H$_e$), 5.19 (m, 1H, C1-H), 5.86 (s, 1H, C3'-H), 6.80 (d, 1H, J = 7.2 Hz, C7'-H), 7.08-7.48 (m, 9H, Ar-H), 7.66 (s, 1H, C5'-H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 21.4, 27.4, 40.8, 41.4, 56.5, 117.5, 117.6, 118.8, 124.8, 126.7, 127.4, 128.2, 128.3, 128.7, 129.7, 132.5, 132.5, 133.3, 133.6, 134.4, 134.6, 138.6, 151.3, 152.2, 160.7; Anal. Calcd. for C$_{29}$H$_{29}$BrNO$_6$S (%); C, 59.55; H, 4.23; N, 2.67; Found; C, 59.67; H, 4.34; N, 2.78.

5.1.3.4. 4-[2-(4-Bromo-benzenesulfonyl)-6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl]-6-methyl-coumarin 13d.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and p-bromo-benzenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was
obtained as a colorless powder. Yield: 75%; m.p. 192-194 °C, IR (KBr): 3310, 3118, 3056, 2946, 1698, 1608, 1567 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.46 (s, 3H, C₆'-CH₃), 2.73 (m, 2H, C₄-Hₐ, Hₜ), 3.13 (dd, 1H, J = 7.5, 5.7 Hz, α-H), 3.37 (dd, 1H, J = 6.9, 6.6 Hz, α'-H), 3.67 (s, 3H, C₆-OCH₃), 3.75 (m, 2H, C₃-Hₐ, Hₜ), 3.82 (s, 3H, C₇-OCH₃), 5.14 (m, 1H, C₁-H), 5.99 (s, 1H, C₅-H), 6.21 (s, 1H, C₈-H), 6.52 (s, 1H, C₃'-H), 7.24-7.58 (m, 7H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ 21.4, 27.3, 40.5, 41.2, 56.2, 56.2, 55.3, 110.5, 112.0, 117.5, 117.5, 118.9, 125.0, 125.7, 126.2, 128.1, 128.7, 128.7, 132.5, 132.5, 133.4, 134.6, 138.9, 147.7, 149.1, 151.7, 152.2, 160.6; Anal. Calcd. for C₂₈H₂₆BrN₀₆S (%); C, 57.54; H, 4.48; N, 2.40; Found; C, 57.67; H, 4.54; N, 2.58.

5.1.3.5. 4-[2-(2,4-Dichloro-benzenesulfonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl]-6-methyl-coumarin 13e.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and 2,4-Dichlorobenzenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 70%; m.p. 192-194 °C, IR (KBr): 3076, 2918, 1708, 1624, 1571 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.49 (s, 3H, C₆'-CH₃), 2.84 (m, 2H, C₄-Hₐ, Hₜ), 3.15 (m, 1H, α-H), 3.35 (m, 1H, α'-H), 3.75 (m, 2H, C₃-Hₐ, Hₜ), 5.24 (m, 1H, C₁-H), 5.84 (s, 1H, C₃'-H), 6.48-7.48 (m, 10H, Ar-H); Anal. Calcd. for C₂₈H₂₆Cl₂N₀₆S (%) ; C, 60.70; H, 4.11; N, 2.72; Found; C, 60.77; H, 4.34; N, 2.88.

5.1.3.6. 4-[2-(2,4-Dibromo-benzenesulfonyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl]-6-methyl-coumarin 13f.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and 2,4-Dibromobenzenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 70%; m.p. 196-198 °C, IR (KBr): 3128, 2926, 1710, 1614, 1521 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.49 (s, 3H, C₆'-CH₃), 2.85 (m, 2H, C₄-Hₐ, Hₜ), 3.17 (m, 1H, α-H), 3.36 (m, 1H, α'-H), 3.75 (m, 2H, C₃-
5.1.3.7. 6-Methyl-4-[2-(naphthalene-1-sulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl-methyl]-coumarin 14a.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and 1-Naphthalenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 75%; m.p. 144-146 °C, IR (KBr): 3055, 3005, 2925, 1721, 1620, 1570 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.45 (s, 3H, C6'-CH\(_3\)), 2.80-2.94 (m, 2H, C4-H\(_a\), He), 3.13 (m, 1H, \(\alpha\)-H), 3.37 (m, 1H, \(\alpha'\)-H), 3.73 (m, 1H, C3-H\(_a\)), 3.85 (m, 1H, C3-He), 5.30 (m, 1H, C1-H), 5.87(s, 1H, C3'-H), 6.86-8.2 (m, 14H, Ar-H); 13C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 21.4, 28.0, 40.6, 41.3, 56.2, 117.2, 117.4, 118.7, 122.4, 124.6, 126.7, 127.3, 127.7, 128.1, 128.2, 129.0, 129.2, 129.4, 129.6, 129.7, 132.1, 133.1, 133.8, 134.3, 134.8, 135.0, 136.2, 151.3, 151.9, 160.7; Anal. Calcd. for C\(_{30}\)H\(_{25}\)N\(_2\)O\(_4\)S (%): C, 72.71; H, 5.08; N, 2.83; Found; C, 73.85; H, 5.14; N, 2.88.

5.1.3.8. 4-[6,7-Dimethoxy-2-(naphthalene-1-sulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl-methyl]-6-methyl-coumarin 14b.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7a and 1-Naphthalenesulfonyl chloride following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 72%; m.p. 128-131 °C, IR (KBr), 3056, 3000, 2933, 1713, 1617, 1570 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.42 (s, 3H, C6'-CH\(_3\)), 2.72 (m, 2H, C4-H\(_a\), He), 3.15 (m, 1H, \(\alpha\)-H), 3.34 (m, 1H, \(\alpha'\)-H), 3.58 (m, 1H, C3-H\(_a\)), 3.68 (s, 3H, C6-OCH\(_3\)), 3.78 (s, 3H, C7-OCH\(_3\)), 3.88 (m, 1H, C3-He), 5.24 (m, 1H, C1-H), 5.99 (s, 1H, C5-H), 6.24 (s, 1H, C8-H), 6.47 (s, 1H, C3'-H), 6.99-8.2 (m, 10H, Ar-H); 13C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 21.4,
5.1.4. BIOLOGICAL ACTIVITY

Antimicrobial activity

The inhibition of microbial growth under standardized conditions may be utilized for demonstrating the therapeutic efficacy of antimicrobial substances. The antimicrobial activity is based on the comparison of inhibition of growth of bacteria of fungi by measured concentration of antimicrobial substance to be examined with that produced in known concentration with standard antibiotic.

Antibacterial activity

The *in vitro* anti-microbial evaluation of all the synthesized compounds 12a-d and 13a-b was done against two bacterial and two fungal strains viz., *Escherichia coli* (Gram - ve), *Bacillus cirrhosis* (Gram + ve), *Aspergillus niger* and *Pencillium wortmannii*. The tests were carried out by Cup-plate method.  

Materials used

1. Nutrient broth
2. Sterile petridishes
3. 24 hours old growth cultures in nutrient broth
4. Sterile test tubes.
**Preparation of nutrient broth**

Peptone (0.55%), sodium chloride (0.35%), beef extract (1.5 g), yeast extract (0.15%), potassium dihydrogen phosphate (0.13%) and potassium monohydrogen phosphate (0.13%) were weighed and suspended in 1000 ml distilled water. The solution was boiled to dissolve all the ingredients completely. The pH of the solution at 25 °C was adjusted to 7.4 ± 0.2. The resulting solution was sterilized by autoclaving 15 lb pressure (121 °C) for 15 minutes.

**Preparation of subculture**

One day prior to the test inoculation, two cultures of *Escherichia coli* and *Bacillus cirrhosis* were made in the sterile nutrient broth and incubated at 37 °C overnight.

**Preparation of Nutrient Agar**

The media (Mueller Hinton agar) used for culture was procured from Himedia. The concentration taken for the culture preparation was 15 lb/ltr dissolved in distilled water. The solution was boiled to dissolve all the ingredients completely. The pH of the solution at 25 °C was adjusted to 7.4 ± 0.2. The resulting solution was sterilized by at lb pressure (121 °C) for 15 min. in an autoclave. The basal medium (25-30 ml) (with glucose solution to hasten the bacterial growth) with bacterial culture was poured in sterile petri dishes.

**Method of testing**

The sterile nutrient agar was allowed to cool to 40-45 °C. To this, overnight grown liquid culture was added aseptically mixed thoroughly to uniform distribution. Immediately it was poured in to petridishes under aseptic conditions and allowed to attain room temperature. After solidification, the cups were made, by punching the set agar with a sterile cork borer and scooping out the punched part. The diameter of each cup was 8 mm. To these cups 0.02 ml of the sample and the standard solution was added. These plates
were incubated at 37 °C for 24 hours. The extent of inhibition was measured by the width of the inhibition zone in mm.

The total area of inhibition was calculated by the zone of inhibition with the reference drug as follows.

\[
\text{Relative percentage inhibition} = \frac{100 \times \left( X - Y \right)}{Z - Y}
\]

\(X = \text{Total area of inhibition in test plates}\)
\(Y = \text{Total area of inhibition in solvents (DMF) plates}\)
\(Z = \text{Total area of inhibition of reference plates}\).

The zone inhibition was measured in millimeters, and in turn percentage inhibition (%) of test compounds was measured considering the standard as 100%. The results of anti-bacterial activity is given in Table no. 1

**Antifungal activity**

The antifungal activity of the test compounds was carried out against two microorganisms *Aspergillus niger* and *Penicillium wortamannii*.

**Materials used**

1. Sabourds agar media
2. Sterile test tubes
3. 48 hours old grown fungal cultures etc.,

**Preparation of media for fungi**

The media used for culture preparation was procured from Himedia and the concentration has been used in 65g/ltr. The solution was boiled to dissolve the ingredients completely. The pH of the solution at 25 °C was adjusted to 7.3 ± 0.2. The resulting solution was sterilized by autoclaving at 15 lb pressure (121 °C) for 15 minutes.
Preparation of subculture

Pancreatic digest of casein (17 g), sodium chloride (5.0 g), dibasic potassium phosphate (2.5 g), papaic digest of soyabean (3.0 g) and dextrose (2.5 g) were dissolved in water (1000 ml) by warming. The pH of the solution was adjusted to 7.3 ± 0.2. The resulting solution was sterilized by autoclaving at 15 lb pressure (121 °C) for 15 minutes.

Two days prior to the test (48 hours) inoculation, two cultures of *A. niger* and *Pencillium wortamannii* was inoculated in to the broth and incubated for 48 hours at 37 °C.

Method of testing

The method of testing was followed as that adopted for evaluating antibacterial activity. Griseofulvin was used as the standard and DMF was used as the standard control. The results are given in table No. 1.

Conclusion

Among all the tested compounds 12a, 12b, 12c, 12d, 13a have shown good activity against fungal strains at 100 μg ml⁻¹ concentrations. However, almost all the tested compounds are weakly active towards tested bacterial strains. Nevertheless, 12d and 13a have shown promising activity with 90% and 85% fungal inhibition respectively.
Table No.1.

*In vitro* anti-microbial spectrum of compounds 12a-d and 13a-b

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration</th>
<th>E. coli</th>
<th>B. cirrhosis</th>
<th>A. niger</th>
<th>P. wortamannii</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg ml⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12a</td>
<td>100</td>
<td>39</td>
<td>Nil</td>
<td>66</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Nil</td>
<td>Nil</td>
<td>38</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>12b</td>
<td>100</td>
<td>42</td>
<td>Nil</td>
<td>71</td>
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<td>25</td>
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<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
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<td>Nil</td>
<td>57</td>
<td>Nil</td>
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<td></td>
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<td>25</td>
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<td>Nil</td>
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<tr>
<td>12d</td>
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<td>50</td>
<td>Nil</td>
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<td>13b</td>
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<td>57</td>
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<td>25</td>
<td>65</td>
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<tr>
<td></td>
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<td>..........</td>
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<td>100</td>
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<td>..........</td>
<td>..........</td>
<td>4.45</td>
<td>50.8</td>
</tr>
</tbody>
</table>

\( a \) In the above table Nil refers to inhibitions less than 20%

\( b \) .......... indicates not applicable
REFERENCES


   *Chem. Abstr.*, **1970**, 72, 551604

17. Ichibagase, T.; Ichikawa, M.; Nagasaki, S. *Japan pat.*, 7019, 296;
   *Chem. Abstr.*, **1970**, 73, 66434h


   *Chem. Abstr.*, **1971**, 75, 20112g

21. Delaby, P. A.; Gabriel, J. P.; Pascal, Y. *Fr. Demande.*, 2,184,511;
   *Chem. Abstr.*, **1974**, 80, 146020e


Part 2

Coumarin analogues of $N$-methyl-isoquinoline alkaloids
5.2.0. INTRODUCTION

The work to be described in this chapter is related to the methylation of secondary ring nitrogen of isoquinoline. Since the methylated isoquinolines are naturally occurring and possess diverse biological properties. In view of this it is necessary to survey the biological and structural importance of N-methylated isoquinolines containing benzyl or a different groups at C-1 position of isoquinolines.

Natural Occurrence and Biological Importance of N-Methylated Isoquinolines

Wang et al.; have isolated a new alkaloid 6-O-demethyldeoxothalmicrinone 1 from Thalictrum delavai.

![Chemical structure of 1](image1)

Recently a new alkaloid has been isolated from the plant Sabia parviflora. The structure has been assigned on the basis of spectroscopic studies has a substitution pattern unprecedented in the benzylisoquinoline group and in any other series derived from tyrosine.

![Chemical structure of 2](image2)
A new alkaloid densiberine 3 has been isolated from Berberis densiflora and militanthaline 4 has been isolated from papaver triniflium.

Pictet-Spengler cyclisation of enol methyl ether of 3,4-dimethoxy phenylacetaldehyde 6a with the (-)-8-phenylmenthyl carbamate 5a affords a marked enantiomeric excess of the (IR)-tetrahydroisoquinoline 7a, reduction of which with lithium aluminium hydride affords (R)-(+) laudanosine 7b, which is the enantiomer of the natural alkaloid. Improved stereoselectivity was achieved using 6b in place of 6a. Since the (+)-8-phenylmenthol is not readily available, the corresponding carbamates of (-)-trans-2-(a-cumenyl)cyclohexanol 6b and its (+)-enantiomer have been converted into 2'-bromo-(IR)-laudanosine 7c and its (IS)-isomer.
Oxidation of $O$-methylarmepavine 8a and of laudanosine 8b with iodosylbenzene and tetrabutylammonium iodide has given the lactam 9, together with anisaldehyde 10a and Veratric aldehyde 10b respectively.

\[
\begin{align*}
8a & \quad R = H \\
8b & \quad R = OCH_3
\end{align*}
\]

In the synthesis of dehydroroemerine 11, an aporphine alkaloid, isoquinolinium halides 12a, 12b, 12c afford 11 through electrolytic cyclizations.

\[
\begin{align*}
12a & \quad R = Cl \\
12b & \quad R = Br \\
12c & \quad R = I
\end{align*}
\]

The bis-quaternary salt 13, which is analogue of atracurium has been prepared from tetrahydropapavarine.
The condensation of L-gluconolactone with homoveratrylamine has yielded the amide 14, which was cyclised, N-methylated and reduced to 15a. Oxidation of this to the aldehyde 15b, followed by treatment with 3,4-dimethoxyphenyllithium, afforded hydroxy-(R)-(−)-laudanosine 16a, which was dehydrogenolysed to give (R)-(−)-laudanosine 16b.9

\[ \text{14} \]

\[ \begin{array}{c}
\text{15a } R = [CH(OH)]_4CH_2OH \\
\text{15b } R = \text{CHO}
\end{array} \]

\[ \begin{array}{c}
\text{16a } R = \text{OH} \\
\text{16b } R = \text{H}
\end{array} \]

N-methylhigenamine 17 and dehydroreticuline 18 have been isolated, newly from plants *Gnetum parviflorum*10 and *Stephania cepharantha*11 respectively.

\[ \text{17} \]

\[ \text{18} \]

The new isoquinoline alkaloid Cherianoine 19 has been isolated from *Annona cherimola*12.
A series of isoquinolines, N-methyl-1,2-dihydroisoquinolines 20, N-methyl-1,2,3,4-tetrahydroisoquinolines 21, and N-methyl-isoquinolinium ions 22 were tested as inhibitors of monoamine oxidase (MAO) A and B. These were found to act as reversible and time-independent MAO inhibitors, often with a distinct selectivity towards MAO-A. As a class N-methylisoquinolinium ions were found to be the most active MAO-A inhibitor\textsuperscript{13}.

Yuen et al.,\textsuperscript{14} have reported N-methyl-isooquinoline 23 as a potent Voltage Activated Calcium Channel (VACC) blockers.

Perez et al.,\textsuperscript{15} have recently isolated a psychoactive Glaziovine 24 alkaloid from the leaves of Duguetia vallicola.
The reaction of 6'-hydroxymethylaudanosine 25a and its 6-hydroxymethyl analogue 25b with various thio derivatives of alkyl chloroformates has been used to prepare the cyclic ethers 26a and 26b.\textsuperscript{16}

\[\begin{align*}
25a & \quad R = H \\
25b & \quad R = Me \\
26a & \quad R = H \\
26b & \quad R = Me
\end{align*}\]

A detailed conformational study of \(N\)-alkyl-1-benzyltetrahydroisoquinoline alkaloids has been made as an aid for the design of suitable agents for better dopamine-D\(_1\) receptor inhibition\textsuperscript{17}.

The hitherto surveyed literature offers greater possibilities of introducing a different alkyl groups at the isoquinoline nitrogen. The present work of the coumarin analogues of \(N\)-methylated isoquinoline alkaloids will be described in the subsequent sections.

\section*{5.2.1. PRESENT WORK}

The work carried out during the present investigation is described in scheme 1. This scheme describes the synthesis of coumarin analogues of \(N\)-methyl-isoquinoline alkaloids.

The synthesis of 4-(3,4-dihydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin 5 (Chapter II, Scheme 1) has been described in chapter II. When 5 was refluxed with iodomethane in dry acetone for 6 hours, a bright yellow colored solids 2-Methyl-1-(2-oxo-2\(H\)-coumarin-4-ylmethyl)-3,4-dihydro-isoquinolininium iodides 15 (Scheme 1) were obtained.
When 15 was subjected to sodium borohydride reduction at -10 °C 6-Methyl-4-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarins 16 in good yield. When the same reaction was carried out at room temperature the compound 8 (chapter II) were isolated.

Attempted reaction of methylation to 1,2,3,4-tetrahydroisoquinoline 7 using varied conditions did not afford the desired product rather a cleavage product 8 was isolated.

The mechanism of the formation of this unusual fragmentation product 8 has been described in chapter II (p. 64)
All the synthesized compounds have been characterized using spectral techniques like IR, $^1$H, $^{13}$C NMR and Mass spectra.

5.2.2. RESULTS AND DISCUSSION

The intermediate 15 were obtained in a good yield by the treatment of 5 with iodomethane. These quaternary iodide salts 15 were of high melting solids. These were further reduced to their corresponding 2-methyl-1,2,3,4-tetrahydro derivatives 16.
The sodium borohydride reduction of 15 at -10 °C yielded 16 in better yields. In $^1$H NMR spectra a signal at $\delta$ 3.97-4.0 due to C1- H indicates the formation of the product. Further, signals at the range of $\delta$ 2.95-3.28 as two multiplets due to $\alpha$ and $\alpha'$-H substantiates the formation of the product. These multiplets were observed owing to their diastereotopicity with respect to C1-H, asymmetric center. Methyl group attached to nitrogen was observed in the range of $\delta$ 2.5 as a singlet. The C3-CH$_2$ and C4-CH$_2$ protons were also resonated as multiplets at $\delta$ 2.65-3.25.

The $^{13}$C NMR agreed with the structure and all the carbons resonated at the expected regions. The LC MS showed a M+1 peak at m/z 320 (16a) confirms the products 16.

When reaction mixture was warmed to room temperature in methanol, surprisingly, by the unusual cleavage of C-C bond, substituted 4-methyl coumarins 8 were isolated and were characterized by spectral methods and they were found to be in agreement with the literature. The plausible mechanism for this cleavage is given in figure 2 in chapter II (p. 64).

Attempted reaction of methylation/alkylation directly to 1,2,3,4-tetrahydroisoquinolines 7 using iodomethane and dibromoethane did not afford the desired product rather it led to the formation of the cleavage product 8 in room temperature. The compounds 7 were very prone to cleavage with various bases.

It is likely that the C-C bond cleavage is thermodynamically favoured process occurring at relatively higher temperatures. Therefore, this methylation was achieved via 3,4-dihydroisoquinoline derivatives at - 10 °C.

The assignment of $^1$H and $^{13}$C NMR of 15a is given in figure 1.
Assignment of $^1$H NMR of 16a.

$H_x = 2.41$ (s, 3H)
$H_y = 2.51$ (s, 3H)
$H_{3a} = 2.69$ (m, 1H)
$H_{4a} = 2.93$ (m, 1H)
$H_{4e}$ & $H_{\alpha} = 2.98-3.05$ (m, 2H)
$H_{3e}$ & $H_{\alpha'} = 3.24-3.28$ (m, 2H)
$H_1 = 3.97$ (t, 1H)
$H_{3y} = 6.31$ (s, 1H)
$H^* = 6.91-7.43$ (m, 7H)

Assignment of $^{13}$C NMR of 16a.
The physical, analytical and spectral data of all the synthesized compounds is given in experimental part of this chapter.

Some of the representative spectra are given herein.

Spectrum No. 1. IR (KBr) of compound 16a.

Spectrum No. 2. $^1$H NMR (CDCl$_3$) of compound 16a.
Spectrum No. 2. $^1$H NMR (CDCl$_3$) of compound 16a (Expansion)

Spectrum No. 3. $^{13}$C NMR (CDCl$_3$) of compound 16a.
5.2.3. EXPERIMENTAL

5.2.3.1. 2-Methyl-1-(2-oxo-2H-coumarin-4-ylmethyl)-3,4-dihydroisoquinolinium; iodide 15: General procedure.

4-(3,4-Dihydro-isoquinoline-1-ylmethyl)-coumarin (1g) and methyl iodide (1 ml) were refluxed for 6 h. in acetone. Separated bright yellow solids were filtered and washed with acetone. 15a: mp. 238-241°C, yield, 69%; 15b: 203-205°C, yield, 72%; 15c: 209-212°C, yield, 79%; 15d: 188-190°C, yield, 68%. Thus obtained salts were pure (monitored by TLC) and carried to the next step.
5.2.3.2. **4-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin 16**: General Procedure.

To the solution of 2-Methyl-1-(2-oxo-2H-coumarin-4-ylmethyl)-3,4-dihydro-isoquinolinium; iodide 15 (0.0022 mol) in methanol (20 mL) added slowly sodium borohydride (0.01 mol) at -5°C and continued stirring for one hour to complete the reaction (TLC monitored). Reaction mixture was poured over ice-cold water (50 mL). Solid separated was extracted with dichloromethane and washed with water. Dried over sodium sulfate and solvent evaporated off. Separated solid was recrystallized from alcohol.

5.2.3.3. **6-Methyl-4-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin 16a.**

![Chemical Structure](image)

Starting from 2-Methyl-1-(6-methyl-2-oxo-2H-coumarin-4-ylmethyl)-3,4-dihydro-isoquinolinium iodide 15a following the general procedure and recrystallizing from alcohol a colorless compound was obtained. M.p. 110-112°C. Yield, 72%; IR (KBr), 3057, 3032, 2927, 2840, 2763, 1711, 1636, 1577 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.41 (s, 3H, C₆'-CH₃), 2.51 (s, 3H, N-CH₃), 2.66-2.72 (m, 1H, C₄-H₆), 2.90-2.95 (m, 1H, C₄-H₅), 2.98-3.05 (m, 2H, α-H, α'-H ), 3.24-3.28 (m, 2H, C₃-H₂, C₃-H₆), 3.97 (t, 1H, Cl-H), 6.31 (s, 1H, C₃'-H), 6.91-7.43 (m, 7H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ 21.4, 24.7, 38.0, 42.7, 46.3, 62.5, 116.2, 117.4, 119.7, 124.7, 126.2, 127.1, 128.0, 129.5, 132.8, 134.0, 134.5, 136.9, 152.2, 153.8, 161.8; LC MS 320 [M+1]; Anal. Calcd. for C₂₁H₂₁NO₂ (%); C, 78.97; H, 6.63; N, 4.39; Found; C, 79.03; H, 6.74; N, 4.28.

5.2.3.4. **4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin 16b.**

Starting from 6,7-Dimethoxy-2-methyl-1-(6-methyl-2-oxo-2H-coumarin-4-ylmethyl)-3,4-dihydro-isoquinolinium iodide 15b following the general procedure and recrystallizing from alcohol a colorless compound was obtained. M.p. 128-131°C. Yield, 68%; IR (KBr), 3056, 3030, 2927, 2830, 2763, 1713, 1636, 1567; ¹H NMR (300 MHz,
5.1.3.5. 7-Methyl-4-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-
coumarin 16c.

Starting from 2-Methyl-1-(7-methyl-2-oxo-2H-coumarin-4-
ylmethyl)-3,4-dihydro-isoquinolinium iodide 15c following the
general procedure and recrystallizing from alcohol a colorless
compound was obtained. M.p. 131-133°C. Yield, 70%; IR (KBr), 3058, 3027,
2917, 2820, 2753, 1708, 1639, 1576 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.40 (s, 3H, C₆'-CH₃), 2.52 (s, 3H, N-CH₃), 2.66-2.74 (m, 1H, C₄-H₄), 2.89-
2.95 (m, 1H, C₄-H₄ 2.95-3.05 (m, 2H, C₃-H₃, C₃-H₃' ), 3.23-3.28 (m, 2H, C₃-H₃, 
C₃-H₃'), 3.98 (t, 1H, C₃-H₃), 6.27 (s, 1H, C₃'-H), 6.88-7.45 (m, 7H, Ar-H); 
Anal. Calcd. for C₂₃H₂₅N₂O₄ (%); C, 72.80; H, 6.64; N, 3.69; Found; C, 72.93; H, 
6.74; N, 3.78.

5.2.3.6. 4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-
ylmethyl)-7-methyl-coumarin 16d.

Starting from 6,7-Dimethoxy-2-methyl-1-(6-methyl-2-oxo-2H-
coumarin-4-ylmethyl)-3,4-dihydro-isoquinolinium iodide 15d following the
general procedure and recrystallizing from 
alcohol a colorless compound was obtained. M.p. 119-121°C. Yield, 65%; IR 
(KBr), 3056, 3022, 2925, 2830, 2773, 1714, 1632, 1577 cm⁻¹; ¹H NMR (300 
MHz, CDCl₃): δ 2.42 (s, 3H, C₆'-CH₃), 2.50 (s, 3H, N-CH₃), 2.73 (m, 2H, C₃-
H₃, C₄-H₄), 2.86 (m, 1H, C₄-H₄), 3.17 (m, 1H, C₃-H₃), 3.55 (m, 2H, C₃-
H₃, C₃-H₃'), 3.84 (s, 3H, C₆-OCH₃), 3.92 (s, 3H, C₇-OCH₃), 3.92 (m, 1H, C₁-H), 5.99 
(s, 1H, C₅-H), 6.17 (s, 1H, C₈-H), 6.27 (s, C₃'-H), 6.90-7.44 (m, 3H, Ar-H); 
Anal. Calcd. for C₂₃H₂₅N₂O₄ (%); C, 72.80; H, 6.64; N, 3.69; Found; C, 72.90; 
H, 6.54; N, 3.75.
REFERENCES


4. San, A.; Sariyar, G. *Plant Med.*, 1997, 63, 575


