CHAPTER V

SYNTHESIS OF OXYGENATED TRIHETEROCYCLES
INTRODUCTION

One of the earliest reports on the coumarin containing tri heterocycles was the work of A.R. Knight\textsuperscript{1} and C. Silvio\textsuperscript{2} who isolated trimeric coumarin 1 by the reaction of 4-hydroxycoumarin and phosphorous oxychloride.

![Diagram of 1]

In continuation of their work on 4-heteroaryl coumarins, recently Nicolaids et. al.\textsuperscript{3} reported the synthesis and antiinflammatory activity of tri-heterocycles (2, 3, 4, 5) which mainly contain two coumarin rings and a nitrogen heterocyclic system in the form of isoxazole, oxadiazole etc.

![Diagram of 2 and 3]
T. Uday Kumari et al.\textsuperscript{4} have reported the synthesis of 3,4-di(2-thienyl) coumarins 6.

Bilokin et al.\textsuperscript{5} reported a facile stereoselective synthesis of novel heterocycles with hexahydro-2H-indazole, thiazole, and coumarin moieties 7.
Other triheterocycles:

It is thought pertinent to mention about the other triheterocyclic systems, which do not possess the coumarin moiety.

Recently Harrington et. al.\textsuperscript{6} reported enantiospecific total synthesis of natural roseophilin 8 used as antitumor and antibiotic, which was found to contain pyrrole and furan rings.

\begin{center}
\includegraphics[width=0.3\textwidth]{roseophilin.png}
\end{center}

Krayushkin et. al.\textsuperscript{7} reported the synthesis and photochromic properties of bis (dimethyl thienyl) oxazoles 9, bis (dimethyl thienyl) thiazoles 10 and bis (dimethyl thienyl) imidazoles 11 having photochromic properties.

\begin{center}
\includegraphics[width=0.6\textwidth]{oxazole.png}
\end{center}
Asakai et. al.\textsuperscript{8} reported the synthesis of 3,4-di (3-indolyI) pyrrole derivatives 12 as cell death (apoptosis) inhibitors.

A novel three - component one-pot bis thiienyl pyrimidine 13 synthesis based upon a coupling -isomerization sequence was reported by Mueller et. al.\textsuperscript{9}
Sneddon Scott et al.\textsuperscript{10} reported the preparation of pyrazolyl pyrimidines 14 and analogs as TNF-α-signaling modulators.

Macor, John Eugene\textsuperscript{11} reported the synthesis of 3,5-heteroaryl indole 15 as 5HT agonists which is effective at a dose range of 10 - 100 μg/day with an aerosol in the treatment of Migraine, and has been patented.

Oda, Kazuaki et al.\textsuperscript{12} reported the synthesis of 2,3-di(heteroaryl) 2-pyrrolin-5-ones 16, 17, containing furan and thiophene ring systems.
Jiang\textsuperscript{13} reported the synthesis of bis (indolyl) pyrazinones 18, 19, as the core analogues of the cytotoxic marine bisindole alkaloid dragmacidin d.

Quinazolinones 20, 21 were found to be useful as glycoprotein antagonists. Their preparation and use for control of thrombotic disorders was reported by Mederski Wemor et al.\textsuperscript{14,15}
In the light of the above discussion on triheterocyclic systems and in continuation of our work on 4-(2'-benzo (b) furanyl ) coumarins it is contemplated to fix a heterocyclic system at C₃' - position of benzofuran, 

![Diagram of triheterocyclic system]

where R = 6-CH₃, 7-CH₃, 6-Cl, 6-OCH₃, R' = CH₃, Cl, Br, 5', 7'-Cl

which would result in a oxygenated triheterocyclic system possessing coumarin, benzofuran and furan ring systems. The present work reports a novel one pot-synthesis of a three-component triheterocycle I expected to possess interesting medicinal properties and structural features. [In the triheterocyclic system I, the C₂ position of benzofuran is linked to C₄- position of coumarin. Further the C₃ position of benzofuran is linked to C₂- position of benzofuran].

The triheterocycle (I) is systematically named as 4-(3'- (2''-furyl) -2'-benzo (b) furanyl) coumarin. Various steps involved in the synthesis of above compounds are discussed under present work.
PRESENT WORK

The work carried out during present investigation in synthesising 4-(3' (-2''-furyl)-2'-benzo (b) furanyl) coumarin is shown schematically as below.

Scheme I

\[
\begin{align*}
\text{PhOH} & \quad \xrightarrow{\text{BrCH}_2\text{-CO-CH}_2\text{-COO C}_2\text{H}_5} \quad \text{PhCON} \quad \xrightarrow{\text{Con H}_2\text{SO}_4 \quad \text{0° C}} \\
\text{R} & \quad \text{Br}
\end{align*}
\]

The required 4-bromomethyl coumarins\textsuperscript{16} II have been prepared by the Pechmann cyclisation of various phenols I with 4-bromoethylacetoacetate.\textsuperscript{17}

Scheme II

\[
\begin{align*}
\text{PhOH} & \quad + \quad \text{PhCl} \quad \xrightarrow{\text{Mg - Benzene reflux}} \quad \text{PhCON} \quad \xrightarrow{\text{1) AlCl}_3 \quad \text{- CS}_2 \quad \text{2) 120° C}} \\
\text{II} & \quad \text{OH} \\
\text{R} & \quad \text{R} \quad \text{Cl} \quad 3,5 - \text{Cl}
\end{align*}
\]

Furoyl esters II have been prepared by the reaction of different phenols and furoyl chloride in benzene in presence of magnesium turnings. These have been subjected to fries migration using AlCl\textsubscript{3} according to literature methods.\textsuperscript{18,19} In these series, steps there in and mechanistic aspects involved in formation of 4- (3' (2''-furyl)-2'-benzo (b) furanyl) coumarins are as shown in scheme III.
Facile conversion of bromomethyl coumarins III into VI occurred when III were refluxed with equimolar quantities of appropriately substituted 2-hydroxyphenyl-2-furyl methanone IV in absolute ethanol in presence of anhydrous potassium carbonate for a period 14-16 hrs.

Formation of VI involves a nucleophilic attack of the phenolate anion on the methylene carbon of III. The resulting ether V contains an active methylene group being flanked by a 2-furoyl moiety and an aryloxy moiety. In presence of a
weak base \( V \) can easily generate carbanion VA, which can undergo an intramolecular aldol condensation to give the dihydrobenzofuranyl alcohol VB. This can easily expel a water molecule by \( \beta \)-elimination, resulting in the formation of carbon-carbon double bond in conjugation with the coumarin ring. This conjugation, resulting in a totally aromatic system appears to be the driving force for such an elimination reaction, which explains the ease of formation of 4-(3'-(2'' furyl)-2'-benzo (b) furanyl) coumarins VI (Scheme III).

The 4- (3'(-2'' furyl)-2'- benzo (b) furanyl) coumarins VI obtained during the present synthesis were all crystalline, coloured solids, crystallisable from polar solvents.
RESULTS AND DISCUSSION

The formation of the oxygenated triheterocycles is confirmed by their IR spectra which exhibit the lactone carbonyl stretching band in the range of 1709-1740 cm\(^{-1}\). The C=C and C-O-C stretching vibrations are observed around 1000 and 1200 cm\(^{-1}\) (Table No.-1) Spectrum No.-1.

The PMR spectra of the compounds are in total agreement with the proposed structure. The methyl protons resonated around 2-ppm as a singlet and the C\(_3\)- proton of coumarin was found to resonate around 6.7 \(\delta\) ppm. The protons of the furan ring were found to resonate upfield with respect to C\(_3\)-H of the coumarin as multiplets. The most downfield proton observed was around 7.7-8.15 \(\delta\) ppm which has been assigned to the C\(_5\)-H of coumarin. The deshielding is likely, because of the ring oxygen of benzofuran which is in agreement with earlier reports\(^{19}\). The other aromatic protons were observed as multiplets in the range of 7.0 to 7.5 \(\delta\) ppm. The aromatic protons in the furan, coumarin and benzofuran rings were found to resonate as a multiplet up to 7.78 ppm. The values are given in Table No-2 (Spectrum No.-2). The PMR spectrum of a methoxy derivative is also presented (Spectrum No.-4).

Mass Spectra:

The molecular weight of VI (2) was confirmed by GC MS spectra. The triheterocycle exhibited base peak at m/z 357 which agreed with (M+H\(^{+}\)) \(^{+}\) ion (Spectrum No.-3).
Spectrum No.-1

IR Spectrum of VI (2)

Medium: KBr  Instrument: FT-IR
Spectrum No.-3
GC MS of VI (2)

GCMS Spectrum
R.Time:8.0(Scan#:960)
MassPeaks:29 BasePeak:357(124930)

[Diagram of molecule with chemical structure]
Table No.-1
IR Spectral data of 4-(3'-((2''- furyl) -2'-benzo (b) furanyl) coumarins

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R</th>
<th>R'</th>
<th>$\nu_{\text{c==O}} \text{cm}^{-1}$</th>
<th>$\nu_{\text{c=c}} \text{cm}^{-1}$</th>
<th>$\nu_{\text{C-O-C}} \text{cm}^{-1}$</th>
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<tbody>
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<td>1</td>
<td>6-CH$_3$</td>
<td>CH$_3$</td>
<td>1721</td>
<td>1604 1567</td>
<td>1258 1196 1023</td>
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<td>CH$_3$</td>
<td>1723</td>
<td>1623</td>
<td>1259 1152 1029</td>
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<tr>
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<td>1597 1554</td>
<td>1256 1178 1017</td>
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<td>1616 1560</td>
<td>1245 1178 1029</td>
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<tr>
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<td>1604 1567</td>
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<tr>
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<td>Cl</td>
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<td>1606 1556</td>
<td>1215 1180 1026</td>
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<td>8</td>
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<td>Cl</td>
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<td>1622 1567</td>
<td>1264 1178 1036</td>
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<td>9</td>
<td>6-CH$_3$</td>
<td>Br</td>
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<td>1616 1573</td>
<td>1258 1184 1036</td>
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<tr>
<td>10</td>
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<td>1616 1567</td>
<td>1258 1196 1029</td>
</tr>
<tr>
<td>11</td>
<td>7-CH$_3$</td>
<td>5',7'-Cl</td>
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<td>1622 1579</td>
<td>1258 1165 1029</td>
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<tr>
<td>12</td>
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<td>5',7'-Cl</td>
<td>1727</td>
<td>1610 1573</td>
<td>1245 1134 1036</td>
</tr>
</tbody>
</table>
Table No.-2
PMR Spectral data of 4-(3'-(2''-furyl)-2'-benzo (b) furanyl) coumarins

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R</th>
<th>R'</th>
<th>Chemical shift δH, 300 MHz, CDCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-CH₃</td>
<td>5-CH₃</td>
<td>2.28, (s, 3H, C₆-CH₃ coumarin) 2.55, (s, 3H, C₅'-CH₃, benzo-furan) 6.73, (s, 1H, C₃H coumarin) 6.635, (d, 1H, C₂-H. J 3.6 Hz) 6.50, (m, 1H, C₃H furan) 7.77, (s, 1H, C₅H coumarin) 7.3-7.5, (m, 6H, Ar-H)</td>
</tr>
<tr>
<td>2</td>
<td>7-CH₃</td>
<td>5-CH₃</td>
<td>2.46, (s, 3H, C₆-CH₃ coumarin) 2.54, (s, 3H, C₅'-CH₃ benzo-furan) 6.67, (s, 1H, C₃-H coumarin) 6.63, (m, 1H, C₂-H furan) 6.49-7.77, (m, 1H, C₃-H furan)</td>
</tr>
<tr>
<td>3</td>
<td>6-Cl</td>
<td>5-CH₃</td>
<td>2.55, (s, 3H, C₅'-H- CH₃ benzofuran) 6.78, (s, 1H, C₃-H, C₂-H coumarin) 6.715, (d, 1H, J 3.6 Hz, C₂-H furan) 6.54, (m, 1H, C₃'-H furan) 7.74, (s, 1H, C₅-H coumarin) 7.3-7.57, (m, 6H, Ar-H)</td>
</tr>
<tr>
<td>4</td>
<td>6-OCH₃</td>
<td>5-CH₃</td>
<td>2.55, (s, 3H, C₅'-H-CH₃ benzofuran) 3.61, (s, 3H, C₆-H-OCH₃ ) 6.77, (s, 1H, C₃H coumarin) 6.645, (d, 1H, J 3.3H, C₂'-H furan) 6.50, (m, 1H, C₃'-H furan) 7.76, (s, 1H, C₅'-H coumarin) 6.95-7.5, (m, 6H, Ar-H)</td>
</tr>
<tr>
<td>5</td>
<td>6-CH₃</td>
<td>5-Cl</td>
<td>2.29, (s, 3H, C₆-CH₃ coumarin) 6.73, (s, 1H, C₅H coumarin) 6.60, (d, 1H, C₂-H furan) 6.50, (m, 1H, C₃-H furan) 8.00, (s, 1H, C₂-H coumarin) 7.25-7.57, (m, 6H, Ar-H)</td>
</tr>
<tr>
<td>6</td>
<td>7-CH₃</td>
<td>5-Cl</td>
<td>2.47, (s, 3H, C₇-CH₃ coumarin) 6.69, (s, 1H, C₃-H coumarin) 6.585, (d, 1H, C₂-H furan J 3.3 Hz) 6.495, (m, 1H, C₃-H furan) 8.00, d, 1H, C₅-H coumarin) 7.0-7.55, m, 6H, Ar-H.</td>
</tr>
</tbody>
</table>

... contd...
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R</th>
<th>R'</th>
<th>Chemical shift $\delta$H, 300 MHz, CDCl$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>6-Cl</td>
<td>5-Cl</td>
<td>6.80, s, 1H, C$_3$-H coumarin) 6.68, s, 1H, C$_2$-H furans) 6.54, m, 1H, C$_3$-H furans) 7.97, s, 1H, C$_3$-H coumarin) 7.27-7.58, m, 6H, Ar-H)</td>
</tr>
<tr>
<td>8</td>
<td>6-OCH$_3$</td>
<td>5-Cl</td>
<td>3.62, s, 3H, C$_6$-OCH$_3$; coumarin) 6.78, s, 1H, C$_3$-H; coumarin) 6.605, d, 1H, C$_3$-H; furan) 6.51, m, 1H, C$_3$-H; furan) 7.98, d, 1H, C$<em>8$-H; coumarin J$</em>{meta}$ 1.8 Hz) 6.9-7.5, m, 6H, Ar-H)</td>
</tr>
<tr>
<td>9</td>
<td>6-CH$_3$</td>
<td>5-Br</td>
<td>2.29, s, 3H, C$_6$-CH$_3$; coumarin) 6.74, s, 1H, C$_3$-H; coumarin) 6.605, d, 1H, C$_2$'-H furan) J 3Hz) 6.50, (m, 1H, C$_3$'-H; furan) 8.16, s, 1H, C$_5$-H; coumarin) 7.24-7.61, m, 6H, Ar-H)</td>
</tr>
<tr>
<td>10</td>
<td>6-CH$_3$</td>
<td>5,7-Cl</td>
<td>2.29, s, 3H, C$_6$-CH$_3$ coumarin) 6.77, s, 1H, C$_3$-H coumarin) 6.585, d, 1H, C$_2$'-H furan J 2.7Hz) 6.50, (m, 1H, C$_3$-H furan) 7.92, (s, 1H, C$_3$-H coumarin) 7.50, s, 2H, C$_9$ C$_8$-H; AB quartet 7.385, (C$_9$H, 1H J 8.1Hz) 7.325, (C$_7$H, 1H, J 8.4 Hz) 7.25, m, C$_4$'-H furan)</td>
</tr>
<tr>
<td>11</td>
<td>7-CH$_3$</td>
<td>5,7-Cl</td>
<td>2.47, (s, 3H, C$_7$-CH$_3$ coumarin) 6.72, (s, 1H, C$_3$-H coumarin) 6.575, (d, 1H, C$_2$-H furan J 3.3 Hz; 6.50, (m, 1H, C$_3$-H furan) 7.925, (d, 1H, C$_2$-H coumarin) 7.50, (s, 2H, C$_9$ C$_8$H benzofuran) 7.25, (s, 1H, C$_8$H coumarin) 7.04, (d, 1H, C$_4$H furan J 9 Hz) 7.43, (d, 1H, C$_6$H coumarin)</td>
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<tr>
<td>12</td>
<td>6-OCH$_3$</td>
<td>5,7-Cl</td>
<td>3.66, (s, 3H, C$_6$-OCH$_3$ coumarin) 6.82, (s, 1H, C$_3$-H coumarin) 6.625, (d, 1H, C$_3$-H furan J 3Hz) 6.52, (m, 1H, C$_3$-H furan) 7.91, (s, 1H, C$_5$-H coumarin) 7.50, (s, 2H, C$_6$-H - C$_4$-H benzofuran) 7.365, (d, 1H, C$_8$-H coumarin J 9Hz) 7.16, (d, 1H, C$_7$-H coumarin J 9Hz) 6.96, (m, 1H, C$_4$-H furan)</td>
</tr>
</tbody>
</table>
Experimental

The synthesis of substituted 4-(3'(2''-furyl)-2''-benzo (b) furanyl) coumarins, involved the following steps. Commercial samples of different substituted phenols were used after purification.
1. Preparation of 4-bromoethyl acetoacetate
2. Preparation of substituted 4-bromomethyl coumarins
3. Preparation of -Furoyl chloride
4. Preparation of furoyl benzoates
5. Preparation of 2-hydroxyphenyl-2-furyl methanones
6. Synthesis of 4-(3'(2''-furyl)-2''-benzo (b) furanyl coumarins

1. Preparation of 4-bromoethylacetoacetate
   Prepared by the procedure given in experimental part of Chapter No.-1.

2. Preparation of substituted 4-bromomethyl coumarins
   Various substituted 4-bromomethyl coumarins were prepared by the procedure given in experimental part of Chapter No.-1.

3. Preparation of -Furoyl chloride

   ![Reaction Diagram]

   A mixture of thionyl chloride (5.0 parts) and furoic acid (1.0 parts) was refluxed on a water-bath under anhydrous condition for 6 hours, excess thionyl chloride was then distilled off and α furoyl chloride is obtained, B.P 173°c yield 80%.
4. Preparation of furoyl benzoates

R' \cdot \text{Cl} \quad \text{OH} \quad \text{II} \quad \text{O} \quad \text{Mg-Benzene} \\
R' = \text{CH}_3, \text{Cl}, \text{Br}, 2, 4-\text{Cl}

Furoyl benzoates

A mixture of p-cresol 0.1 mole (10.814 gm) anhydrous benzene 25 ml, magnesium 1.2 gm and furoyl chloride 14 gm, was refluxed on a waterbath for 1 hr. magnesium was filtered off, the benzene was removed under reduced pressure and the residue was taken in ether and it was washed with 1% sodium hydroxide solution, then with water. The ethereal layer was dried over anhydrous sodium sulphate. Ether was distilled off and the residue was recrystallised from aqueous ethanol in yellow coloured flakes (12 gms yield 80% M.P. 88\textdegree c).

Different furoyl benzoates prepared by above method are listed below.

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>M.P\textdegree c</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CH\textsubscript{3}</td>
<td>88\textdegree c</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>79\textdegree c</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>4-Br</td>
<td>85\textdegree c</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Cl</td>
<td>82\textdegree c</td>
<td>22</td>
</tr>
</tbody>
</table>

5. Preparation of 2-hydroxy phenyl-2-furoyl methanone

Furoyl benzoate (1.0 m) was dissolved in CS\textsubscript{2} and the solution was cooled to 5\textdegree c to which 1.5 m anhydrous aluminium chloride was added. The mixture was first heated on a water bath for 2 hrs and subsequently CS\textsubscript{2} was distilled off.
and then during a period of half an hour the reaction temperature was raised to 110°c and maintained for 1½ hrs more. It was then decomposed by dilute hydrochloric acid. The solid was taken up in ether and the ether layer was washed with water and then extracted with 5 % sodium hydroxide. The sodium hydroxide extract on acidification with hydrochloric acid gave a precipitate of the hydroxy ketone, which was filtered, washed with water and recrystallised from ethanol.

Different 2-hydroxyphenyl-2-furyl methanones prepared by above method are listed below.

![Chemical structure](image)

2-hydroxy phenyl-2-furyl methanone

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>MP°C</th>
<th>Ref</th>
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<td>1</td>
<td>CH₃</td>
<td>92°C</td>
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</tr>
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<td>2</td>
<td>Cl</td>
<td>81°C</td>
<td>18</td>
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<tr>
<td>3</td>
<td>Br</td>
<td>90°C</td>
<td>18</td>
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<tr>
<td>4</td>
<td>2,4-Cl</td>
<td>111°C</td>
<td>18</td>
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6. Synthesis of 4-(3'-furyl)-2'-benzo (b) furanyl coumarins

To a solution of 4- bromomethylcoumarin (0.005 m) and 2- hydroxy phenyl-2-furyl methane (0.005 m) in absolute ethanol (50 ml) taken in a 100 ml round bottom flask anhydrous potassium carbonate 1.38 gm (0.01 mole) was added. The mixture was refluxed on water bath for 14 to 16 hours and filtered hot. The filtrate was concentrated, cooled to room temperature and poured into crushed ice (100 gm). The separated solid was washed with water and crystallised from a suitable solvent.
<table>
<thead>
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<th>Sl. No.</th>
<th>R</th>
<th>R¹</th>
<th>Yield %</th>
<th>*MP °C</th>
<th>Mol. Formula</th>
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<td>7-CH₃</td>
<td>Cl</td>
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<td>C₂₂H₁₃ClO₄</td>
<td>70.14</td>
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<tr>
<td>7</td>
<td>6-Cl</td>
<td>Cl</td>
<td>74</td>
<td>218°</td>
<td>C₂₁H₁₀Cl₂O₄</td>
<td>63.50</td>
</tr>
<tr>
<td>8</td>
<td>6-OCH₃</td>
<td>Cl</td>
<td>73</td>
<td>192°</td>
<td>C₂₂H₁₃ClO₅</td>
<td>67.26</td>
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<td>9</td>
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<td>Br</td>
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<td>174°</td>
<td>C₂₂H₁₃BrO₄</td>
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<td>10</td>
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<td>5, 7-Cl</td>
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<td>172°</td>
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<td>11</td>
<td>7-CH₃</td>
<td>5', 7'-Cl</td>
<td>82</td>
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<td>C₂₂H₁₂Cl₂O₄</td>
<td>64.24</td>
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<td>12</td>
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<td>5, 7-Cl</td>
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<td>205°</td>
<td>C₂₂H₁₃Cl₂O₅</td>
<td>64.26</td>
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