CHAPTER 5

5.1 : Syntheses of 4-Benzoyl-N-[5(6)-(2-methoxycarbonylamino)benzimidazolyl]pyrrolidin-2-one

5.2 : Syntheses of β-[(2-Methoxycarbonylamino)-5(6)-benzimidazolyl]-acrylic acid, Methyl 5(6)-[5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-4-yl]benzimidazole-2-carbamate and 2-Methoxycarbonylaminobenzimidazole-5(6)-acetoxime

5.3 : Methyl-5(6)-[2,5-dimethyl-3-methoxycarbonyl-N-substituted pyrrolo]benzimidazole-2-carbamates and Methyl-5(6)-N-[2,5-dimethyl-3-methoxycarbonyl-4-substitutedphenyl]-benzimidazole-2-carbamates

5.4 : Comparative $^{13}$C-NMR study of tetrasubstituted furans and tetra/pentasubstituted pyrroles

5.5 : 2,2'-Dicarboxyamino-5,5'-dibenzimidazol-yl-methanol

5.6 : 5-Ethoxycarbonyl(2-(1-methylpiperazino)-6-phenyl-4(1H)-pyrimidine and 5-Aryl-6-ethoxycarbonyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidine

5.7 : Methyl 5(6)-N-[(2-methylmercapto-6-methyl-4-phenyl pyrimidin-5-yl)methyl]aminobenzimidazole-2-carbamate

5.8 : Methyl-5(6)-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridino)]-N-substituted benzimidazole-2-carbamate and N,N-Dimethoxycarbonyl-N-(substitutedbenzyl)quanidine

5.9 : Methyl-4(5)-methyl-5(4)-[3,4-methylenedioxyphenyl]-4,5-dihydropyridazolo-2-carbamate

5.9a : 1,6-Bis carboxyamino-2-methoxycarbonylaminophenyl-7-methyl-5-[p-methoxyphenyl]-4,5,6,7-tetrahydro-1,3-diazepine
CHAPTER - 5

5.1 The synthesis of prototype IX required appropriately substituted pyrrolidine-2-one derivative as the starting material and for which a model study was considered desirable because substituted butyrolactones after ring opening with primary aromatic amines, in principle, can recyclize to give compounds structurally related to either 99a or 100.

Benzoyl and (p-toluoyl)-γ-butyrolactones (103, 104), required for the model studies, have been prepared by reacting appropriate aroyl propionic acid (101, 102) with formaldehyde and hydrochloric acid. Reactions of 103 and 104 with p-anisidine yielded compounds which were devoid of IR signals for lactone carbonyls. This suggested that the lactone ring had participated in the reaction and the mass spectra of the compounds suggested that the opening of lactone ring must have been followed by a ring closure reaction. In order to eliminate one of the two possible structures (99a and 100), studies on the $^{13}$C-nmr spectra of two compounds (105, 106) were undertaken. The difference in the chemical shifts of methylene carbon attached to the hetero atom in 104 and 105 (Scheme 19) was of a diagnostic value for the structural assignment of the reaction product. The appearance of the methylene carbon attached to the hetero atom in 104 at 69.07 δ ppm and in 105 at 50.58 δ ppm indicated that the methylene carbon in the reaction products was not attached to oxygen. This lent support for structure 105 and further support for the assigned structure was obtained from the $^{15}$N signal. The appearance
SCHEME 19

101. R = H
102. R = Me

103. R = H
104. R = CH₃

105

106

107

108

109

R = H
R = CH₃

R = H
R = CH₃

a. HCHO/HCl, b. p-Anisidine, c. H₂/Pd.C; d. 2-Nitro-p-phenylenediamine, e. H₂/Raney-Ni,
f. HN=C-NH₂/CD₃CO₂Me. ¹³C-NMR data

SCHEME 19
of the $^{15}\text{N}$ signal at 33.689 δ ppm indicated the amide character of the nitrogen $^{218a}$. Catalytic hydrogenation of 105 gave 106 and the methylene carbon of this compound appeared at 51.27 δ ppm providing further evidence for the attachment of the methylene carbon with the nitrogen atom.

These model studies prompted the synthesis of the ninth prototype molecule namely 4-Benzoyl-N-[5(6)-(2-methoxycarbonylamino) benzimidazolyl] pyrrolidin-2-one (109). Reaction of β-benzoyl-γ-butyrolactone (103) with 2-nitro p-phenylene diamine in presence of triethylamine yielded 4-benzoyl-N-(4-amino-3-nitrophenyl)-pyrrolidin-2-one (108; Scheme 19). Catalytic hydrogenation of 108 in presence of Pd/C followed by the ring closure of the resulting diamine with S-methylisothiouroniumsulphate and methylchloroformate furnished the desired prototype molecule (109; Scheme 19).

5.2 Unlike the synthesis of IX, the preparation of compounds relating to prototypes X-XII required the O-nitroaniline derivatives (114, D1 & 123) as the starting materials, which after catalytic hydrogenation and ring closure with N,N-dimethoxycarbonyl-S-methylisothiourea could be expected to furnish the desired compound. Reaction of 4-acetamido-3-nitro benzaldehyde (112) with malonic acid
in the presence of catalytic amount of pyridine gave 4-acetamido-3-nitro cinnamic acid (113; Scheme 20). Alkaline hydrolysis of this compound yielded the desired starting material (114; Scheme 20). Preferential hydrogenation of nitro group in 114 was possible in presence of Raney nickel but it failed for the starting material (D). The reaction of 4-acetamido-3-nitro benzaldehyde (116) with ethyl-acetoacetate and thiourea under acidic condition gave 5-ethoxycarbonyl-6-methyl-2-oxo-4-(4-acetamido-3-nitrophenyl) pyrimidine (117):
Scheme 21) which on alkaline hydrolysis yielded 118. Hydrogenation of this compound in presence of Raney-Ni furnished the desired diamine. The diamines prepared from 114 and 118 were cyclized by reacting them with N,N-dimethoxycarbonyl-S-methylisothiourea to obtain the desired prototype compounds 115 and 119 respectively. Since the preparation of diamine D2 was not possible, 5(6)-acetyl benzimidazole-2-carbamate (124), prepared by the method reported earlier, was reacted with hydroxylamine under controlled conditions to furnish 125 (Scheme 22).

\[ \text{Scheme 22} \]

\[ \text{H}_2\text{N} \]
\[ \text{H}_2\text{N} \]
\[ \text{NOH} \]
\[ \text{Me} \]
\[ \begin{array}{c}
\text{D2} \\
\text{H}_2\text{N} \\
\text{H}_2\text{N} \\
\text{O}_2\text{N} \\
\text{AcHN} \\
\text{Me} \\
\text{AcHN} \\
\text{Me} \\
\text{H}_2\text{N} \\
\text{O}_2\text{N} \\
\text{H}_2\text{N} \\
\text{MeO}_2\text{C} \]
\[ \text{122} \]
\[ \text{123} \]
\[ \text{124} \]
\[ \text{125} \]
\[ \text{H}_2\text{N} \]
\[ \text{MeO}_2\text{C} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{Me}_2\text{C} \]
\[ \text{NOH} \]
\[ \text{Me} \]
\[ \text{AcHN} \]
\[ \text{Me} \]
\[ \text{HN} \]
\[ \text{C} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{MeO}_2\text{C} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{Me}_2\text{C} \]

a, AC\text{O}\text{O}; B, Fuming HNO\text{3}; c, 10% aq. NaOH/MeOH; d, H\text{2}, Raney-Ni/MeOH; e, HN=CH\text{2}/ClCO\text{2}CH\text{3}; f, NH\text{2}OH/MeOH

(Scheme 22)
5.3 In order to study the effect of NH and NR in place of the oxygen atom in the furan ring of a promising anthelmintic compound 83/148 (CDRI Code number), the synthesis of XIII was undertaken and as an extension of this study compounds representing prototype XIV were also synthesised.

![Chemical structures](image)

The synthesis of XIII (X=NH) owes its origin to the observation made during the upscaling studies of the compound 83/148. It was observed that during the preparation of 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl) furan, (the required intermediate for the preparation of 83/148) was invariably associated with a small amount of a red compound formed in the reaction mixture. This was identified as 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl) pyrrole. The formation of this pyrrole derivative along with the corresponding furan in the reaction of 126 in presence of methylacetoacetate and piperidine suggested that a careful study of this reaction may furnish a reaction condition in which the pyrrole could be obtained as the predominant product. This prompted to study the Nef reaction of 126 in presence of primary, secondary and tertiary amines and the results were monitored by HPLC. The reaction of 126 with methylacetoacetate in presence of primary amines gave N-substituted pyrrole derivatives (132-137; Scheme 23) and the corresponding furan derivatives could not be detected in the reaction mixture. This method has a preparative value and gives better yields of the pyrrole derivatives as compared to the method reported in literature which invariably gave poor yields of 2,5-dimethyl-3-methoxycarbonyl-4-substituted phenyl pyroles in our hands. The reaction of 126 and methylacetoacetate in presence of secondary amines gave different percentage ratios of 128 and 130.
\[ R = \text{CI} \]

\[ R = \text{NH}_2 \]

\[ R = \text{O}-\text{Me} \]

\[ R = \text{n-Bu} \]

\[ R = \text{CH}_2\text{Ph} \]

\[ R = 4-\text{anisyl} \]

\[ R = 3,4,5-\text{trimethoxyphenyl} \]

\[ R = 4-\text{amino-3-nitrophenyl} \]

\[ R = \left(\text{CH}_2\right)_3\text{N(C}_2\text{H}_5)_2 \]

\( a, \text{ Piperidine; } b, \text{ Primary amine; } c, \text{ Triethyl amine; } d, \text{ Hydrazine hydrate} \)

(Scheme 23)
MECHANISM OF NEF REACTION IN PRESENCE OF AMINES

107
For example, in the presence of piperidine, the percentage ratio of 128 and 130 was 96:4, in morpholine it was 80:20, in N-methylpiperazine it was 89:11, and in the presence of N-phenylpiperazine it was 87:13. Replacement of piperidine with triethylamine in the reaction of 126 and methylacetoacetate gave only 128 and the presence of 130 in the reaction mixture was not detected.

Recent studies on the mechanism of Nef reaction indicate the formation of an intermediate 138 (Scheme 24). It is likely that reaction of 126 and methylacetoacetate in the presence of triethylamine also yielded an intermediate structurally similar to 138, which after elimination of \( \text{H}_2\text{O} \) and \( \text{HNO} \) as suggested by Boberg, yielded the tetrasubstituted furan. In the presence of piperidine, the reaction of 126 and methylacetoacetate possibly proceeds in three directions. The formation of intermediates 138 and enamine possibly contribute towards the formation of tetrasubstituted furan. The third pathway might involve the addition of water in 140 which leads to the ring opening and recycylation of the open product to give tetrasubstituted pyrrole (Scheme 24). This pathway possibly becomes more facile in the presence of primary amines and therefore leads to exclusively N-substituted pyrrole derivatives. Despite a successful synthesis of N-substituted pyrrole derivatives (132-137), the synthesis of 130 by Nef reaction of 126 in the presence of methylacetoacetate and ammonia was not at all promising due to extremely poor yield (\( \sim 10\% \)). An alternate preparation was, therefore, sought and this prompted the reaction of 126 with 144 (Scheme 25) in different solvents. The yield of the compound 130 has been improved up to 90% by using pyridine as a catalyst and methanol as a solvent.
Based on this observation, attempts were made to prepare 2,5-dimethyl-3-acetyl-4-(4-amino-3-nitrophenyl) pyrrole by reacting 126 with enamine 147. However, it failed to give the desired product. It was, therefore, considered of interest to ascertain the reason which led to the failure of this reaction. One of the logical explanations for the failure of 147 to react with 126, would be the lack of adequate nucleophilicity of the carbon α to the acetyl group. In principle, experimental evidence for the same may be obtained from the chemical shift of carbon atoms since substantial difference in nucleophilicity of the carbon atom α to methoxycarbonyl and acetyl groups in enamines 144 and 147 is bound to make a significant difference

![Chemical structures](image)

\[ \begin{array}{c}
\text{H}_3\text{C} & \text{b} & \text{c} & \text{d} & \text{e} \\
\text{O} & \text{CH}_3 & \text{NH}_2 & & \\
\end{array} \]

\[ \begin{array}{c}
\text{H}_3\text{C} & \text{b} & \text{c} & \text{d} & \text{e} \\
\text{CH}_3 & & \text{NH}_2 & & \\
\end{array} \]

\[ \begin{array}{c}
a = 49.48 \\
b = 170.72 \\
c = 81.56 \\
d = 162.59 \\
e = 18.76 \\
\end{array} \]

\[ \begin{array}{c}
a = 28.97 \\
b = 196.17 \\
c = 95.33 \\
d = 162.68 \\
e = 21.93 \\
\end{array} \]

*: \text{\textsuperscript{13}C-NMR data}

(Fig. 4)

in their chemical shifts. This prompted a comparative study of the \text{\textsuperscript{13}C-NMR} spectra of 144 and 147. As would be expected, the carbon α to the acetyl group in 147 was deshielded by almost 14 ppm. This suggested that the enamine carbon in 147 did not possess adequate nucleophilicity to react with 126. The preliminary data of the \text{\textsuperscript{13}C-}

chemical shift of carbon in enamines 144 and 147 tempted to study the chemical shifts of carbon atoms in tetra and pentasubstituted pyrroles (154-158 and 158a-158b). These pyrrole derivatives may be considered as the E-configuration (Fig. 5) of enaminone in a rigid geometry. Since pyrroles exhibit heteroaromatic character while furans failed to do so, the comparative \text{\textsuperscript{13}C-NMR} study of
tetra or pentasubstituted pyrroles (154-158, 158a, 158b) and tetra substituted furans (a-q) was considered interesting. The tetra-substituted pyrroles (154-158) were prepared by reacting enamine 144 with appropriate nitrostyrene derivatives (149-153; Scheme 26). The details of this study are presented in sec. 5.4.

(Scheme 26)

The next phase of the studies on Nef reaction was concerned with the reaction of 126 with methylacetoacetate in presence of hydrazine hydrate. Mechanistic considerations of this reaction suggest the formation of 148a but the excess of hydrazine hydrate possibly gave 148 (Scheme 23; page 106). Preparation of compounds belonging to prototype XIV required N-substituted pyrrole derivatives (171-175) as the starting material. These were obtained by the reaction of 166-170 with methylacetoacetate in presence of 2-nitro-p-phenylene diamine (Scheme 27). Hydrogenation of 130, 132-139 and 171-175 in presence of Raney-Ni followed by their cyclisation with N,N-dimethoxy carbonyl-S-methylisothiourea yielded the compounds structurally related to prototypes XIII and XIV respectively (Scheme 26 & Scheme 27).

5.4 Comparative $^{13}$C-NMR study of 144 and pyrrole derivatives 154-158 revealed two interesting features. Despite the fact that pyrrole has a heteroaromatic character, the C-2 in compounds 154-158, which corresponds to carbon d of 144 (Fig.4; page 112), appears as a shielded carbon while C-3 in 154-158 which corresponds to

---

**Scheme 26**

149 : $R = H$
150 : $R = 3,4$-dimethoxy
151 : $R = 3,4$-methylene dioxy
152 : $R = 4$-benzyloxy-3-methoxy
153 : $R = 4$-acetamido

Substituent $R$ correspondence to 149-153
130, 132-137 $\rightarrow^{a,b}$

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{H}};
\node (b) at (1.5,0) {\text{N}};
\node (c) at (3,0) {\text{C}};
\node (d) at (4.5,0) {\text{N}};
\node (e) at (6,0) {\text{C}};
\node (f) at (7.5,0) {\text{Me}};
\node (g) at (9,0) {\text{Me}};
\node (h) at (10.5,0) {\text{Me}};
\node (i) at (12,0) {\text{Me}};
\node (j) at (13.5,0) {\text{Me}};
\node (k) at (15,0) {\text{Me}};
\node (l) at (16.5,0) {\text{Me}};
\node (m) at (18,0) {\text{Me}};
\node (n) at (19.5,0) {\text{Me}};
\node (o) at (21,0) {\text{Me}};
\node (p) at (22.5,0) {\text{Me}};
\node (q) at (24,0) {\text{Me}};
\node (r) at (25.5,0) {\text{Me}};
\node (s) at (27,0) {\text{Me}};
\node (t) at (28.5,0) {\text{Me}};
\node (u) at (30,0) {\text{Me}};
\node (v) at (31.5,0) {\text{Me}};
\node (w) at (33,0) {\text{Me}};
\node (x) at (34.5,0) {\text{Me}};
\node (y) at (36,0) {\text{Me}};
\node (z) at (37.5,0) {\text{Me}};
\node (aa) at (39,0) {\text{Me}};
\node (bb) at (40.5,0) {\text{Me}};
\node (cc) at (42,0) {\text{Me}};
\node (dd) at (43.5,0) {\text{Me}};
\node (ee) at (45,0) {\text{Me}};
\node (ff) at (46.5,0) {\text{Me}};
\node (gg) at (48,0) {\text{Me}};
\node (hh) at (49.5,0) {\text{Me}};
\node (ii) at (51,0) {\text{Me}};
\node (jj) at (52.5,0) {\text{Me}};
\node (kk) at (54,0) {\text{Me}};
\node (ll) at (55.5,0) {\text{Me}};
\node (mm) at (57,0) {\text{Me}};
\node (nn) at (58.5,0) {\text{Me}};
\node (oo) at (60,0) {\text{Me}};
\node (pp) at (61.5,0) {\text{Me}};
\end{tikzpicture}}
\]

\[
\text{159} \quad R = H
\]
\[
\text{160} \quad R = \text{CH}_3
\]
\[
\text{161} \quad R = n-\text{Bu}
\]
\[
\text{162} \quad R = \text{CH}_2\text{Ph}
\]
\[
\text{163} \quad R = 4-\text{OCH}_3-\text{Phenyl}
\]
\[
\text{164} \quad R = 3,4,5-\text{trimethoxyphenyl}
\]
\[
\text{165} \quad R = \text{N-\text{HCO}_2\text{Me}}
\]
\[
\text{166} \quad R = (\text{CH}_2)_3-\text{N(C}_2\text{H}_5)_2
\]

(Scheme 26)

166a-170

\[
\text{166a} \quad R = H
\]
\[
\text{167} \quad R = 3,4-\text{dimethoxy}
\]
\[
\text{168} \quad R = 4-\text{methyl}
\]
\[
\text{169} \quad R = 4-\text{acetamido}
\]
\[
\text{170} \quad R = 4-\text{benzyloxy-3-methoxy}
\]

a, 2-Nitro-\text{p-phenylene} diamine
b, \text{H}_2, \text{Raney-Ni}/\text{MeOH}
c, \text{MeO}_2\text{CN=C-NHCO}_2\text{Me}_{/2}

Substituent R corresponds to 166a-170

(Scheme 27)

171-175

Substituent R corresponds to 166a-170
carbon C in 144 (Fig.5; page ) appears as deshielded carbon. This may be explained by assuming that 144 in solution possibly exists as 144a. This is why the methyl carbon in 144 appears downfield than the methyl carbon attached to position 2 in compounds 154-158.

The comparative study of the $^{13}$C-NMR spectra of tetrasubstituted furans and tetra or pentasubstituted pyroles (Tables A-R) was concerned with the chemical shift of C-2, C-3, C-4 and C-5 in these class of compounds. As would be expected C-2 and C-5 in furans appeared downfield than the corresponding pyrrole derivatives. However, C-3 and C-4 may be expected to show different chemical shift in these two class of compounds, because furan lacks heteroaromaticity while pyrrole possesses the same. Surprisingly the chemical shift of C-3 and C-4 in furans are marginally different from those of pyroles. This would also explain that effect of substituents on the phenyl ring on C-4 in these class of compounds remains unaltered.

The effect of substituents on C-3, the chemical shifts of C-2 in furans (a-q) indicated that a methoxycarbonyl or an acetyl residue predominantly deshielded C-2 while an amide function led to a shielding of almost 9-10 ppm. In continuation of this study the observed chemical shifts of C-2, C-3, C-4 & C-5 in furans and pyroles were compared with the theoretical values computed by a computer for representative compounds (Table C).

5.5 The synthesis of next prototype molecule (XV) namely 2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolylmethanol is based on the presumption that the carbinol of 82/437 (CDRI Code number) in biophase may slowly get oxidized to the parent compound which has exhibited significant broad-spectrum anthelmintic activity. In a situation such as this the carbinol may exhibit longer duration of action.
### Table A: Chemical shifts of various carbons of Tetrasubstituted Furans

![Formula](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>2-CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>5-CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Other Carbons</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>157.09</td>
<td>113.01</td>
<td>121.13</td>
<td>146.82</td>
<td>13.54</td>
<td>11.21</td>
<td>132.89, 129.61, 127.25, 126.84, 126.40, 125.97, (Aromatic-C), 164.11, (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 50.27, (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;)</td>
</tr>
<tr>
<td>b</td>
<td>3,4-methylene-dioxy</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>156.80</td>
<td>112.85</td>
<td>120.61</td>
<td>146.65</td>
<td>13.31</td>
<td>10.93</td>
<td>146.12, 145.64, 126.32, 122.71, 110.11, 107.05, (Aromatic-C), 163.80, (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 50.10, (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;)</td>
</tr>
<tr>
<td>c</td>
<td>3,4-dimethoxy</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>156.87</td>
<td>112.91</td>
<td>120.69</td>
<td>146.62</td>
<td>13.48</td>
<td>11.19</td>
<td>147.91, 147.79, 125.38, 121.90, 113.60, 110.43, (Aromatic-C), 164.08 (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 50.21 (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 54.97, 55.36, (2xOCH&lt;sub&gt;3&lt;/sub&gt;)</td>
</tr>
<tr>
<td>d</td>
<td>4-NHCOCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>157.33</td>
<td>112.93</td>
<td>120.69</td>
<td>147.12</td>
<td>13.93</td>
<td>11.41</td>
<td>136.99, 130.04, 129.16, 128.47, 120.12, 119.23</td>
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<tr>
<td>e</td>
<td>4-benzyl</td>
<td>CO₂CH₃</td>
<td>157.24</td>
<td>113.26</td>
<td>120.94</td>
<td>147.00</td>
<td>13.90</td>
<td>11.64</td>
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<tr>
<td>f</td>
<td>4-ethoxy-3-methoxy</td>
<td>CO₂CH₃</td>
<td>157.14</td>
<td>113.20</td>
<td>120.95</td>
<td>146.88</td>
<td>13.77</td>
<td>11.50</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>2,4-dimethoxy</td>
<td>CO₂CH₃</td>
<td>156.26</td>
<td>112.55</td>
<td>123.18</td>
<td>147.07</td>
<td>13.43</td>
<td>11.45</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>4-chloro3-nitro</td>
<td>CO₂CH₃</td>
<td>158.37</td>
<td>126.67</td>
<td>118.58</td>
<td>147.33</td>
<td>13.92</td>
<td>11.56</td>
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<td>50.29</td>
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<td>11.44</td>
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**Table B: Chemical shifts of various carbons of Tetra and Pentasubstituted Pyrroles**

![Chemical structure of a pyrrole](image)

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<th>Compound</th>
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<th>R₁</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>2-CH₃</th>
<th>5-CH₃</th>
<th>Other Carbons</th>
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<td>154</td>
<td>H</td>
<td>NH</td>
<td>134.09</td>
<td>110.01</td>
<td>122.28</td>
<td>123.78</td>
<td>13.44</td>
<td>10.94</td>
<td>136.19, 130.21, 127.27, 127.07, 125.70, 114.66, (Aromatic-C), 166.46, (CO₂CH₃), 50.19 (CO₂CH₃)</td>
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<tr>
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<td>3,4-methylene-dioxy</td>
<td>NH</td>
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<td>110.83</td>
<td>121.84</td>
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<td>10.74</td>
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<td>10.89</td>
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- 130.62, 119.38, 110.02, (Aromatic-C), 166.42, (CO₂CH₃), 50.28 (CO₂CH₃), 168.25, (N=COCH₃), 24.23 (NHCOCH₃).
- 148.82, 146.75, 137.52, 129.89, 129.30, 128.78, 128.34, 127.64, 127.41, 122.70, 115.23, 113.83, (Aromatic-C), 166.24, (CO₂CH₃), 50.14 (CO₂CH₃), 71.42 (OCH₂), 55.99 (OCH₃).
- 159.58, 143.28, 138.93, 135.36, 131.63, 130.15, 128.88, 127.44, 126.62, 124.98, 120.65, 117.70, (Aromatic-C), 165.98 (CO₂CH₃), 50.27 (CO₂CH₃), 11.39 (CH₂Ph).

- 159.62, 143.34, 138.77, 131.59, 130.19, 129.09, 128.68, 127.52, 126.45, 125.37, 120.14, 117.77, (Aromatic-C), 165.99, (CO₂CH₃), 50.28 (CO₂CH₃), 55.40 (OCH₃).
Table C: Chemical shifts of various carbons of tetrasubstituted furans and tetra/pentasubstituted pyroles computed on the basis of literature data by a computer (Bold letters are observed values)

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<th>Compd. No.</th>
<th>R</th>
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<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
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<td>(±0.0)</td>
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<td>11.58</td>
<td>10.21</td>
<td>165.98</td>
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</table>

Ar-C: 140.2 (±0.5)
It was also considered desirable to evaluate the carbinol as a chemo-prophylactic. The synthesis of 183, reported earlier in this laboratory was slightly modified to obtain a better yield and the main sequence of reactions are described in Scheme 28. The reduction of the carbonyl group in 183 was difficult but large excess of sodium borohydride helped in obtaining 184. Hydrogenation of this compound followed by ring closure with N,N-dimethoxycarbonyl-S-methylisothiourea furnished 185 (Scheme 28).

\[ \text{181} \xrightarrow{\text{a}} \text{182} \]

\[ \text{183} \xrightarrow{\text{b}} \text{184} \xrightarrow{\text{c, d, e}} \text{185} \]

\( \text{a, Conc. HNO}_3; \text{ b, aq. NH}_3; \text{ c, NaBH}_4/\text{MeOH}; \text{ d, H}_2, \text{ Raney-Ni/MeOH}; \text{ e, MeO}_2\text{CN=CNHCO}_2\text{Me} \)

(Scheme 28)
As an extension of our exploratory research activities for identifying new molecular structures associated with broad-spectrum anthelmintic activity, the syntheses of prototype XVI-XVII were considered of interest. The starting compounds 192-197 were obtained by Biginelli reaction.

\[
\begin{align*}
\text{XVI} & \quad \text{XVII}
\end{align*}
\]

Acid catalysed reaction of aromatic aldehyde with ethylacetocacetate in presence of urea to yield 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one (202), commonly known as Biginelli reaction, was reinvestigated by Hinkle and Hey and it was observed that the replacement of urea with thiourea led to the formation of the corresponding 3,4-dihydropyrimidin-2-thione derivatives (192-197; Scheme 29).

Before undertaking the synthesis of dihydropyrimidine prototypes XVI and XVII, model studies on the alkylation of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-thione (192), were considered as essential prerequisites. Reaction of 192 with methyl iodide under various experimental conditions was studied. This reaction in presence of sodium hydroxide in methanol yielded 198 (Scheme 29). Earlier workers have prepared this compound by reacting 5-ethoxycarbonyl-2-methylmercapto-4-methylpyrimidine with phenyl magnesium halide and the spectroscopic data of the reaction product reported by them agreed well with that of 198. Reaction of 192 with methyl iodide in presence of sodium hydroxide in DMSO gave 190 (Scheme 29). Demercaptation of 199 with strong acid gave 201 (Scheme 27). The U.V. absorption maxima at 290 nm supported the assigned structure. Finally the reaction of 198 with N-methylpiperazine yielded the prototype molecule 200 (Scheme 29).
Substituent R corresponds to 186-191

186 : R = H
187 : R = 3,4-dimethoxy
188 : R = 4-methoxy
189 : R = 3-methyl
190 : R = 4-acetamido
191 : R = 4-nitro

(Scheme 29)
In the light of these observations alkylation of (192-195) with monochloroacetic acid in presence of potassium hydroxide in methanol could be expected to yield the prototype (XVII) molecules 202-205 but the reaction of 192, 194, 195 with monochloroacetic acid in presence of potassium hydroxide yielded 205-208 (Scheme 30) while the reaction of 192-195 with monochloroacetic acid in presence

\[
\begin{array}{c}
\text{a} & 192-195 & \text{b} \\
\end{array}
\]

202 : R = H
203 : R = 3,4-dimethoxy
204 : R = 4-OCH₃
205 : R = 3-CH₃

\[
\begin{array}{c}
206 : R = H \\
207 : R = 4-OCH₃ \\
208 : R = 4-NHCOCH₃ \\
\end{array}
\]

a, CICH₂CO₂H, BF₃·Et₂O/MeOH; b, CICH₂CO₂H, NaOH/MeOH

(Scheme 30)

BF₃ etherate yielded 202-205 (Scheme 30). The cyclocondensation of 192-196 with monochloroacetic acid is expected to yield two isomeric bicyclics, 5-Aryl-6-ethoxycarbonyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidines (202-205) and 7-Aryl-6-ethoxycarbonyl 5-methyl-3-oxo-2,3-dihydro-7H-thiazolo [3,2-a] pyrimidines. Of these the former could be isolated from the reaction mixture. The structure of 202-205 was supported by their PMR data (Table 24, page 174 ) which revealed a downfield shift (\(\sim 0.70 \delta \text{ ppm}\)) of the methine proton at position 6. This can only be explained if 3-N is involved in ring closure to form 202-205.

As a next step towards the synthesis of yet another 1,4-dihydropyrimidine derivative, benzaldehyde was reacted with ethyl
trifluoromethylacetoacetate in presence of thiourea. It was interesting to note that instead of 1,4-dihydropyrimidine derivative, the intermediate \textbf{209, 210} (Scheme 31) was obtained as a mixture of diastereomers. Isolation of these compounds has a significance because no intermediate appears to have been isolated from the Biginelli reaction\textsuperscript{223}. Ring closure of \textbf{209} with polyphosphoric acid gave \textbf{211} (Scheme 31).

\begin{equation}
\text{R} = \text{H, 4-NHCOCH}_3
\end{equation}

\textbf{211} : R = H  
\textbf{209} : R = H  
\textbf{210} : R = 4-NHCOCH\textsubscript{3}

\textbf{(Scheme 31)}

5.7 In order to evaluate the contribution of pyrimidine moiety appended with benzimidazole-2-carbamate nucleus, the synthesis of prototype XVIII namely methyl 5(6)-N-[(2-methylmercapto-6-methyl-4-phenyl pyrimidin-5-yl)methyl] amino benzimidazole-2-carbamate was undertaken. The synthetic strategy of prototype XVIII involves oxidation of \textbf{198} with manganic acetate to obtain \textbf{212} (Scheme 32) which on reduction with sodium borohydride yielded a mixture of \textbf{213} and \textbf{214} (Scheme 32) which were separated through column chromatography. However, LAH reduction of \textbf{212} did not lead to the
Scheme 32

I. Mangnic acetate/Benzene, II NaBH₄/MeOH, III LAH/Ether, IV Pyridinium chlorochromate, V. PBr₃, Et₃N/Benzene, VI. H₂N·H₂N, Et₃N / Benzene
VII. H₂/Raney Ni, VIII. MeS·C=NO₂Me

NHCO₂Me
reduction of pyrimidine ring but gave a mixture of 215 and 216 (Scheme 32) which were also separated through column chromatography. The spectroscopic data of these compounds supported the assigned structures and as an additional evidence 216 was oxidized with pyridinium chlorochromate to yield 217 (Scheme 32). Reaction of 216 with PBr₃ gave 218 which in turn was reacted with 2-nitro-p-phenylene diamine to get 219. Finally hydrogenation of 219 in presence of Raney-Ni as a Catalyst and cyclisation of the resulting diamine with N,N-dimethoxycarbonyl-S-methylisothiourea furnished the prototype molecule 220 (Scheme 32).

5.8 Synthesis of molecules belonging to prototype XIX required 87, 88 and 90 as the starting materials and their synthesis have already been reported in section 2.5. Hydrogenation of 87 or 88 gave the desired diamines which were cyclized with N,N-dimethoxycarbonyl-S-methylisothiourea to obtain the desired benzimidazole carbamate derivatives (Scheme 33). The compounds representing prototype XX (227-229) were prepared by reacting appropriate benzylamines with N,N-dimethoxycarbonyl-S-methylisothiourea (Scheme 33).

5.9 The synthetic strategy employed for the prototype XXI involved the reaction of 2-nitro-1-(3,4-methylenedioxyphenyl)-propene with hydroxylamine hydrochloride and as would be expected, a mixture of theo isomers of 1-hydroxylamino-1-(3,4-methylenedioxyphenyl)-2-nitro propane was obtained (230; Scheme 34). Separation of these two isomers by fractional crystallisation or preparative TLC was unsuccessful but the column chromatography of the isomeric mixture over silica gel revealed an interesting feature. It was observed that only one of
Scheme 33
a, NH$_2$OH/MeOH; b, H$_2$/Raney-Ni; c, MeS-C=NO$_2$Me

(Scheme 34)
the two possible diastereomers was obtained in pure state while the second isomer was possibly involved in a retroreaction leading to the formation of starting nitropropene. Two possible conclusions can be drawn from this observation. Firstly, the orientation of the NHOH and H in one of the diastereomers must be anti to each other otherwise the elimination of NH$_2$OH would not have occurred. Secondly, the isomer which was obtained in a pure state must possess NHOH and H groups in orientation which would not allow the elimination of NH$_2$OH. In a situation such as this, two possible diastereomers (230a and 230b) can be envisaged. The diastereomer 230b ($R^S$; erythro) would be expected to be energetically favoured since the bulky groups (Ph & NO$_2$) are trans to each other thereby minimising the gauche interactions. The stereochemistry would also permit hydrogen-bonding between NHOH and NO$_2$ and thus becomes the favoured diastereomer. Hydrogenation of 230 with Raney-Ni led to the formation of 231 which was cyclized with N,N-dimethoxycarbonyl-S-methylisothiourea to obtain the required prototype molecule 232. The intermediate diamine 231 was not very stable and was therefore characterized as its dihydrochloride. The relative stereochemistry in 232 was ascertained from the decoupled PMR spectrum. A doublet (J = 7Hz) at 3.63 - 3.71 $\delta$ ppm for the methine proton adjacent to methyl group and a doublet (J = 7 Hz) at 4.23 - 4.31 $\delta$ ppm for $CH$ adjacent to aryl group supported trans stereochemistry$^{226}$ for two protons. A retrospective analysis of the stereochemistry of 230b, on the basis of observed relative stereochemistry in 232 also supports the assigned stereochemistry of 230b.

5.9a A retro-synthetic approach for obtaining prototype XXII revealed methyl-2-substituted-3-amino crotonates (233-236) as starting materials. These were prepared by reacting 1-aryl-2-nitro ethylene with methyl-3-amino crotonate$^{227}$. Nucleophilic displacement of NH$_2$ with NHOH group in 233-235 gave 237-239 (Scheme 35). The structural and stereochemical assignments of these compounds were concerned with three problems. Firstly, it was essential to ascertain whether the compounds existed as oximes or as the tautomeric hydroxylamines. In case the compounds were oximes, the stereochemistry across the -C=N, the second problem
\[
\begin{align*}
R - \text{Ph} \text{CH} = \text{NO}_2 + \text{MeCO}_2\text{Me} & \xrightarrow{a} \quad \text{c} & \quad \text{d} \\
& \quad \text{R} = \text{H} & \quad \text{R} = \text{H} \\
& \quad \text{R} = \text{3,4-Dimethoxy} & \quad \text{R} = \text{3,4-Dimethoxy} \\
& \quad \text{R} = \text{4-Methoxy} & \quad \text{R} = \text{4-Methoxy} \\
& \quad \text{R} = \text{4-Nitro} & \quad \text{R} = \text{4-Nitro} \\
\end{align*}
\]

233: R = H  
234: R = 3,4-Dimethoxy  
235: R = 4-Methoxy  
236: R = 4-Nitro  

240-242  
237-239  
243-246  

\[
\begin{align*}
249 & \xrightarrow{e, f}  \\
247: R = H & \quad \text{248: R = 4-Methoxy}
\end{align*}
\]

a, MeOH; b, NH\textsubscript{2}OH/MeOH;  
c, dill H\textsubscript{2}SO\textsubscript{4}/MeOH;  
d, Mono perphthallic acid or m-CPBA; e, H\textsubscript{2}, Raney-Ni/MeOH;  
f, Me\textsubscript{3}S=C=\text{NCO}_2\text{CH}_3  
\text{NHCO}_2\text{CH}_3  
(Scheme 35)
in the present context, had to be ascertained. Thirdly, the relative stereochemistry across the two asymmetric carbon centres (in case the compounds were oximes) had to be worked out. Indirect evidence for the structure of compounds 237-239 was obtained from the following chemical reactions. Acid hydrolysis of 233-235 furnished the ketones 240-242 which could then be converted into 237-239 by reacting them with hydroxylamine hydrochloride. The direct evidence for the assigned structures of the compounds was obtained from the $^{13}\text{C}$-NMR spectrum of one of the representative compound (239). The $^{13}\text{C}$ signal for $\text{-C=N}$ at 158.51 $\delta$ ppm in the NMR spectrum of 239 and the appearance of the carbon of methyl group at 12.05 $\delta$ ppm indicated it to be anti oxime 228. In order to ascertain the stereochemical purity of compounds 237-239, the multiplicity of the methine proton (CH-CO$_2$Me) was studied. However, this methine proton in these compounds appeared along with the signals of other methine and methylene protons in a 90 MHz PMR spectrum. This prompted to record a 400 MHz PMR spectrum of one of the representative compound (239). The appearance of a neat doublet at 3.72 $\delta$ ppm in the PMR spectrum suggested stereochemical homogenity and indicated stereoselective formation of only one diastereomer. The other minor diastereomer could not be isolated from the reaction mixture and in the absence of this minor diastereomer, the relative stereochemistry of 239 could not be ascertained. Reaction of 233-236 with either monoperphthalic acid or m-chloro perbenzoic acid yielded 243-246. It was interesting to note that the tertiary hydroxyl group in these compounds was not prone to easy elimination reaction and the reaction of 243-244 with hydroxylamine hydrochloride yielded oximes 247-248 without eliminating a molecule of water. The presence of a tertiary hydroxyl group in these compounds was evident from the PMR signal (D$_2$O exchangeable) at 4.0 $\delta$ ppm. The stability of the tertiary hydroxyl groups in compounds 247-248 suggested that the hydroxyl group was not placed anti to vicinal CH. In the light of this observation the Dreiding models of various rotamers of the two possible diastereomers were studied to ascertain the steric crowding in the molecule. On the basis of Dreiding model the stereochemically most favoured diastereomer (I : R R , threo) is described below:
In order to obtain a representative compound of the desired prototype XXII, compound 239 was hydrogenated over Raney-Ni and the resulting solution was reacted with N,N-dimethoxycarbonyl-S-methyl-isothiourea to yield 249. The appearance of one broad singlet and a sharp doublet for the methyl protons in the PMR spectrum (400 MHz) indicated it to be a mixture of stereomers. This was further supported by the appearance of two extremely close peaks in the HPLC spectrum. Preparative HPLC to separate the isomers was not attempted. The possible mechanism of formation of compound 249 is described in scheme 36.
Scheme 36