Chapter – IV

*Mannich bases containing [1,3,4]oxadiazole and pyrazole-3-moiety*
The Mannich reaction has been long of great importance in synthetic organic and pharmaceutical chemistry. Classical Mannich reaction has limited applications, and many attempts have been made to extend this reaction. The essential feature of the reaction is replacement of the active hydrogen atom and an aminomethyl or a substituted aminomethyl group. The Mannich bases have a wide range of applications, for example in drugs, crop protection agents and as general synthetic building blocks.

A review of the recent literature concerning the synthesis and biological activity of various Mannich bases is furnished below.

Mannich bases and their derivatives have many attractive applications, in paint and polymer chemistry as hardeners, cross linkers, reaction accelerations\textsuperscript{1-2} etc. However, the most important applications are in the field of pharmaceutical product\textsuperscript{3-4}. Studies on antineoplastic drugs, analgesic drug, antibiotic drugs etc\textsuperscript{5-9}, including
labeled molecules\textsuperscript{10-12} have received particular attention in the recent past. Mannich bases can either directly be employed or used as intermediates in chemical synthesis.

Kumar \textit{et al.},\textsuperscript{13} reported the synthesis of Mannich bases 1 derived from imidazolone derivatives. The newly synthesized Mannich bases were tested for their anti-inflammatory and ulcerogenic activity. Compounds containing chlorine substituent showed the highest activity.

![Mannich base 1](image1)

Erodgan and yulug\textsuperscript{14} reported Mannich bases of 2-benzoxazolinone 2 [R = H, Cl; R\textsubscript{1} = Ph, anisyl. \textsubscript{o}-Cl-C\textsubscript{6}H\textsubscript{4}; R\textsubscript{2} = Ph, \textsubscript{o}- anisyl, \textsubscript{p}-E-C\textsubscript{6}H\textsubscript{4}, \textsubscript{m}-CF\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}]. These compounds were found to be very effective against yeast like fungi.

![Mannich base 2](image2)

Ebeid \textit{et al.},\textsuperscript{15} synthesized some new quinoline Mannich bases 3 [R = H, Cl, HNC\textsubscript{6}H\textsubscript{4}SO\textsubscript{2}NHR\textsuperscript{1-4} etc] as possible antimicrobial agents.

![Mannich base 3](image3)
Barlin and Ireland\textsuperscript{16} prepared di-Mannich bases 4\textsubscript{a} [\(R_1 = \text{methylpiperidinyl, N(CH}_2\text{-CH}_2\text{OH})_2\text{Me}\)] and 4\textsubscript{b} [\(R_2 = \text{methylpiperidinyl, N(CH}_2\text{-CH}_2\text{OH})_2\text{Me, NMe}_2\)] of 4-[(7-trifluromethylquinolin-4-yl)amino]phenol and 4-[(7-bromo-1,5-naphthyridin-4-yl)amino]phenol respectively. They were found to be active antimalarials especially against chloroquine resistant isolate (K-1) of \textit{Plasmodium falciparum}.

\[
\begin{align*}
4\text{a} &
\begin{array}{c}
\text{NH} \\
\text{F}_2\text{C} \\
\text{N} =
\end{array} \\
\text{R}_1 \\
\text{OH}
\end{align*}
\]

\[
\begin{align*}
4\text{b} &
\begin{array}{c}
\text{NH} \\
\text{Br} \\
\text{N} =
\end{array} \\
\text{R}_1 \\
\text{OH}
\end{align*}
\]

Synthesis of Mannich bases derived from benzimidazoline-2-ones and 2-thiones 5 [\(X = O, S\)] were reported by Bercin \textit{et al.},\textsuperscript{17} These compounds showed significant anthelmintic activity.

\[
\begin{align*}
5 &
\begin{array}{c}
\text{R} \\
\text{N} = \\
\text{X}
\end{array} \\
\text{R}_1 \\
\text{R}
\end{align*}
\]

Mohan\textsuperscript{18} synthesized Mannich bases of the type 6 [\(R = H, Me; R_1 = H, 2\text{-OH, 4-OH, 4-OMe, 4-Me etc}\)]. Several of these compounds showed CNS activity, muscle relaxants and anti-inflammatory activity.
Synthesis and antibacterial activity of a series of Mannich bases of isatin hydrazones 7 were reported by Holla et al from 19. All compounds showed significant antibacterial activity against Gram-positive and Gram-negative bacteria.

![Mannich base of isatin hydrazone 7](image)

Pilli et al.,20 reported the synthesis and analgesic activity of N-Mannich bases of 2-benzoxazolinones 8 [R = 4-phenylpiperazin-1-yl, R-methylpyridin-1-yl, 4-morpholinyl etc; R1 = 2,3-difluro].

![Mannich base of 2-benzoxazolinone 8](image)

Shouhai and Fulin21 synthesized Mannich bases of tetrahydronaphthol derivative 9 [R = CH3, Et, Pr, Me2CH, Bu, iso-Bu, phenyl, isopentyl], which showed strong antimalarial activity comparable to that of chloroquine.

![Mannich base of tetrahydronaphthol 9](image)
Synthesis of morpholine Mannich bases 10 of phenylpropanones were reported by Papadaki-Valiraki et al.,22. These compounds were tested for their effect on DNA synthesis and cell division using cycling Chinese hamster ovary cells. They induced DNA damage and cell proliferation was greatly reduced.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\end{align*}
\]

Choi et al.,23 synthesized Mannich bases 11 of antineoplaston A 10, which showed good cytotoxicity comparable to that of carboplatin.

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{Ph} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

Koteka et al.,24 prepared the quinoline Mannich bases 12 [NR₂ = pyridinyl, 4-methylpiperazinyl, piperidinyl] with greater antimalarial activity than chloroquine, amodiaquine or pyronaridine. These compounds contained 7-chloroquinoline or 7-trifluoromethyl quinoline nucleus.

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4 \\
\end{align*}
\]
Roman et al.,\textsuperscript{25} reported the synthesis of cyclic Mannich bases 13 from the Mannich condensation of 2-(1-hydroxyethyl)benzimidazole with formaldehyde and various substituted arylamines.

![Chemical Structure](image)

Prompted by the above observations, a project was undertaken to synthesize a series of Mannich derivatives carrying pyrazolone moiety containing oxadiazole-2 thione moiety. The results of such studies along with their antoimicrobial activity form the subject matter of chapter.
Present work

Synthesis characterization and antimicrobial studies of substituted aryl hydrazono pyrazoline-3-one containing oxadiazole-2-thione. (Mannich bases)

Prompted by above observations, a project was undertaken to synthesize a series of Mannich derivatives carrying substituted aryl hydrazono pyrazoline-3-one-1,3,4 oxadiazole-2-thiones.

In this chapter we described a synthesis and characterization of

I. 5-methyl-4-(4′-substituted aryl hydrazono)-2-(5-thioxo-4,5- dihydro- [1,3,4] oxadiazole-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17a – f. The reaction sequence leading to the formation of these compound is outlined in the Scheme – I.
[3-methyl-5-oxo-4(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide 16 employed in the present investigation was prepared as per the procedure described in chapter II of this thesis, condensation of [3-methyl-5-oxo-4(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide 16 with a mixture of KOH, ethanol, and carbon disulphide afforded the corresponding 5-methyl-4-(4'-substituted aryl hydrazono)- 2- (5-thioxo- 4,5- dihydro- [1,3,4]-oxadiazol- 2-ylmethyl)-2,4-dihydro-pyrazole-3-one 17 in very good yields.
In a typical example a mixture of 16a KOH, ethanol and carbon disulphide refluxed on a water bath till the evolution of hydrogensulphide ceased in the induction of hydrazone sulfide ceased. After usual work-up the corresponding 17a was obtained in 84 % yield with m.p. 227°C.

The above reaction of 16a with a mixture of KOH, EtOH and carbondisulphide has been extended to 17b – f.

The compounds synthesized 17b – f have been characterized by means of their elemental analysis, IR, ¹HNMR and MS data.

**IR Spectra**

The IR (KBr) spectra of 5-methyl-4-(4'-substituted aryl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazole-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17a shows NH, C = O, C = S and C = N functional groups around 3126, 1670, 1134 and 1603 cm⁻¹ respectively. The IR spectra of 17a is shown in Fig. IV.1. The data are presented in Table I.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>V&lt;sub&gt;max&lt;/sub&gt; in cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>oxadiazole</td>
<td>NH</td>
</tr>
<tr>
<td>17a</td>
<td>H</td>
<td>3126</td>
</tr>
<tr>
<td>17b</td>
<td>CH₃</td>
<td>3110</td>
</tr>
<tr>
<td>17c</td>
<td>OCH₃</td>
<td>3120</td>
</tr>
<tr>
<td>17d</td>
<td>OC₂H₅</td>
<td>3115</td>
</tr>
<tr>
<td>17e</td>
<td>Cl</td>
<td>3135</td>
</tr>
<tr>
<td>17f</td>
<td>Br</td>
<td>3140</td>
</tr>
</tbody>
</table>
The $^1$HNMR (200MHz) spectra of 5-methyl-4-(4'$\text{-}$substituted aryl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17a – f were recorded in CDCl$_3$ + DMSO – d$_6$ and the data are furnished Table II.

Table II -- $^1$HNMR spectral data of 5-methyl-4-(4'$\text{-}$substituted aryl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>$^1$HNMR (200 MHz, CDCl$_3$ + DMSO-d$_6$) (δppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>H</td>
<td>2.3 (s, 3H CH$_3$), 5.45 (s, 2H N-CH$_2$), 7.9 (s, H, Ar - NH), 14.7 (s, H, thiol – thione tautomeric proton NH), 6.6 – 7.2 (m, 5H, Ar - H).</td>
</tr>
<tr>
<td>17b</td>
<td>CH$_3$</td>
<td>2.0 (s, 3H CH$_3$), 2.26 (s, 3H CH$_3$), 5.40 (s, 2H N –CH$_2$), 7.5 (s, H, Ar - NH), 14.3 (s, H, thiol – thione tautomeric proton NH), 6.5 – 7.1 (m, 5H Ar-H).</td>
</tr>
<tr>
<td>17c</td>
<td>OCH$_3$</td>
<td>2.2 (s, 3H CH$_3$), 3.89 (s, 3H OCH$_3$), 5.42 (s, 2H N – CH$_2$), 7.8 (s, H, Ar - NH), 14.5 (s, H, thiol – thione tautomeric proton NH), 6.6 - 7.2 (m, 5H Ar-H).</td>
</tr>
<tr>
<td>17d</td>
<td>OC$_2$H$_5$</td>
<td>2.1 (s, 3H CH$_3$), 1.8 (t, 3H OCH$_3$), 3.16 (q, 2H O – CH$_2$), 5.41 (s, 2H, NCH$_2$), 7.7 (s, H, Ar –NH), 14.4 (s, H, thiol – thione tautomeric proton NH), 6.5 - 7.1 (m, 5H Ar-H).</td>
</tr>
<tr>
<td>17e</td>
<td>Cl</td>
<td>2.4 (s, 3H CH$_3$), 5.47 (s, 2H N – CH$_2$), 7.9 (s, H, Ar -NH), 14.8 (s, H, thiol – thione tautomeric proton NH), 6.4 (d, 2H, Ar – H), 7.0 (d, 2H, Ar – H).</td>
</tr>
<tr>
<td>17f</td>
<td>Br</td>
<td>2.5 (s, 3H CH$_3$), 5.48 (s, 2H N – CH$_2$), 7.9 (s, H, Ar -NH), 14.9 (s, H, thiol – thione tautomeric proton NH), 6.4 (d, 2H, Ar – H), 7.0 (d, 2H, Ar – H).</td>
</tr>
</tbody>
</table>
Mass spectra

The mass spectra of 5-methyl-4-(4'-phenyl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazole-2-yl methyl)-2,4-dihydro-pyrazol-3-one 17a (R = H) showed molecular ion (M+) peaks at m/z 316.

The mass spectral fragmentation pattern of 5-methyl-4-(4'-phenyl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazole-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17a (R = H) are presented in chart I. The molecular ion (M+ ) peak was observed at m/z 316 (37.3%) and the base peak was at m/z 243 (100%) other prominent peaks appeared at m/z 301 (34.6%), m/z 299 (9.8%), m/z 287 (4.7%), m/z 275 (6.4%), 239 (47.9%).

II. 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-[alkyl/aryl/heterocyclic amino methyl]-4,5-dihydro-[1,3,4] oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18 (Mannich bases) 18a-k. The reaction sequence leading to the formation of these compound is outlined in the Scheme – II.

\[ \text{Scheme - II} \]

\[ R = H \]
\[ R_1 = H \]
\[ R_2 = p-	ext{tolyl}, p-	ext{anisyl}, p-	ext{fluorophenyl}, p-	ext{chlorophenyl}, p-	ext{bromophenyl}, p-	ext{nitrophenyl}, \text{diethyl}, \text{diphenyl}, \text{morpholinyl}, \text{piperazinyl}, \text{N-methylpiperazinyl}. \]
Compounds 17 were subjected to Mannich reaction with appropriate amines in the presence of formalin in ethanol-dioxan mixture medium to give 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-[alkyl/aryl/heterocyclic amino methyl]-4,5-dihydro-[1,3,4] oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18 (Mannich bases) Scheme II.

For example stirring of 17a (R₁ = H, R₂ = p-tolyl) with aqueous formaldehyde and p-tolylamine in ethanol-dioxan mixture for over night, yielded a single product which was identified as 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-(p-tolylamino-methyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a R₁ = H, R₂ = p-tolyl] on the basis of its spectroscopic data.

Similar treatment of 17a with p-anisylamine/ p-fluorophenylamine/ p-chlorophenylamine/ p-bromophenylamine/ p-nitrophenylamine/ diethyl amine/ diphenyl amine/ piperazine/ morpholino/ N-methyl piperizino in the presence of formaldehyde in ethanol dioxane mixture for over night afforded the respective Mannich bases 18a – k. The characterization data of Mannich bases 18a – k are given in Table VI. The melting points of the newly synthesized compounds were determined in open capillaries and are unconnected. The purity of all the compounds were conformed by TLC.

IR Spectra

The IR (KBr) spectra of 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-(p-anisylamino-methyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a (Mannich base) exhibited characteristic bands Ar-NH, C = N, C = O, C = S, C-H str –NH around 3240, 1620, 1660, 1150, 2925, 3130 cm⁻¹ respectively. The IR spectra of 18b is shown in Fig 4.3. The data are presented in Table III.
Table III – IR Spectral data of 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-(p-tolylamino-methyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a – k

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>Vₘₐₓ in cm⁻¹</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ar – NH</td>
<td>C = N</td>
</tr>
<tr>
<td>18a</td>
<td>H</td>
<td>H</td>
<td>p-tolyl</td>
<td>3250</td>
</tr>
<tr>
<td>18b</td>
<td>H</td>
<td>H</td>
<td>p-anisyl</td>
<td>3240</td>
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<tr>
<td>18c</td>
<td>H</td>
<td>H</td>
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</tr>
<tr>
<td>18d</td>
<td>H</td>
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<td>p-chlorophenyl</td>
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<td>H</td>
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</tr>
<tr>
<td>18i</td>
<td>H</td>
<td>H</td>
<td>Morpholinyl</td>
<td>3265</td>
</tr>
<tr>
<td>18j</td>
<td>H</td>
<td>H</td>
<td>Piperazinyl</td>
<td>3260</td>
</tr>
<tr>
<td>18k</td>
<td>H</td>
<td>H</td>
<td>N-methyl piperazinyl</td>
<td>3255</td>
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</table>

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**1HNMR Spectra**

The 1HNMR (200MHz) spectra of 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-[alkyl/aryl/heterocyclic amino methyl]-4,5-dihydro-[1,3,4] oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a-k(Mannich bases) were recorded in CDCl₃ + DMSO - d₆ and the data are furnished Table IV.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>¹HNMR (200 MHz, COCl₃) (DMSO-d₆) δppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td>H</td>
<td>H</td>
<td>p- tol</td>
<td>2.36 (s, 3H CH₃), 2.28 (s, 3H, CH₃), 5.64 (s, 2H, N - CH₂ - N), 5.0 (s, 2H, NCH₂), 7.8 (s, H, Ar - NH), 6.95 (d, 2H, Ar - H), 7.45 (d, 2H, Ar - H), 11.2 (s, H, Ar - NH).</td>
</tr>
<tr>
<td>18b</td>
<td>H</td>
<td>H</td>
<td>p- anisyl</td>
<td>2.40 (s, 3H CH₃), 3.82 (s, 3H, CH₃), 5.62 (s, 2H, N - CH₂ - N), 5.06 (s, 2H, NCH₂), 7.9 (s, H, Ar - NH), 6.97 (d, 2H, Ar - H), 7.47 (d, 2H, Ar - H), 11.1 (s, H, Ar - NH).</td>
</tr>
<tr>
<td>18f</td>
<td>H</td>
<td>H</td>
<td>p- nitrophenyl</td>
<td>2.50 (s, 3H CH₃), 5.50 (s, 2H, N - CH₂ - N), 4.96 (s, 2H, N - CH₂), 7.48 (d, 2H, o-protons of p-nitrophenyl), 7.86 (d, 2H, protons of p-nitrophenyl), 7.89 (s, 1H, Ar - NH), 10.23 (s, 1H, NH), 6.8 - 7.2 (m, 5H, Ar - H).</td>
</tr>
<tr>
<td>18h</td>
<td>H</td>
<td>diphenyl</td>
<td>2.67 (s, 3H CH₃), 5.50 (s, 2H, N - CH₂ - N), 5.26 (s, 2H, N - CH₂), 7.26 - 7.56 (m, 10H, aromatic protons of 2 phenyl rings), 7.8 (s, 1H, Ar - NH), 6.6 - 7.2 (m, 5H, Ar - H), 7.6 (s, H, Ar - NH).</td>
<td></td>
</tr>
<tr>
<td>18i</td>
<td>H</td>
<td>morpholino</td>
<td>2.60 (s, 3H CH₃), 5.48 (s, 2H, NCH₂-N), 5.24 (s, 2H, N - CH₂), 2.62 (t, 4H CH₂-NCH₂), 3.70 (t, 4H, CH₂-O-CH₂), 4.50 (s, 2H, NCH₂-N), 10.20 (s, 1H, NH), 6.8 - 7.2 (m, 5H, Ar - H), 7.6 (s, H, Ar - NH).</td>
<td></td>
</tr>
<tr>
<td>18j</td>
<td>H</td>
<td>piperizinyl</td>
<td>2.58 (s, 3H CH₃), 5.45 (s, 2H, NCH₂-N), 5.20 (s, 2H, N - CH₂), 2.56 (t, 4H CH₂-N - CH₂), 4.45 (s, 2H, N-CH₂-n), 7.5 (s, H, Ar - NH), 6.7 - 7.1 (m,5H, Ar-H), 10.19 (s, H, NH).</td>
<td></td>
</tr>
<tr>
<td>18k</td>
<td>H</td>
<td>N-methyl piperizinyl</td>
<td>2.55 (s, 3H CH₃), 5.40 (s, 2H, NCH₂-N), 5.18 (s, 2H, N-CH₂), 2.42 (t, 4H, CH₂-N-CH₂), 4.20 (s, 3H, N-CH₃), 4.52 (s, N-CH₂-N), 7.4 (s, H, Ar - NH), 6.6 - 7.2 (m, 5H, Ar - NH), 10.18 (s, H, NH).</td>
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</table>
Mass spectra

The mass spectra of 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-tolyl-4,5-dihydro-[1,3,4] oxadiazole-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a (R₁=H, R₂=p-CH₃C₆H₄) exploited the molecular ion (M⁺) peaks at m/z 435.

The fragmentation pattern noticed in the mass spectrum of 5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-tolyl-4,5-dihydro-[1,3,4] oxadiazole-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a (R₁=H, R₂=p-CH₃C₆H₄) is presented in Chart II. The spectrum showed the molecular ion (M⁺) peak at m/z 435 with an intensity 12.7% decomposition of molecular ion A at path “a” less of CH₃ radical resulted in the formation of the fragments B at m/z 420 (3.2%), loss of OH radical from molecular ion A yield cation C at m/z 418 (49.2%). Loss of C₆H₅ radical from molecular ion “A” leads to the occurrence of cation “D” at m/z 358 (17.5%). Elimination of C₈H₁₀N molecule from molecular ion “A” leads to the occurrence of cation E at m/z 315 (22.2%), cleavage of molecular ion “A” at path “b” afforded the cation “F” at m/z 201 (9.6%). Successive elimination of C₇H₅N from molecular (M⁺) ion afforded cation G at m/z 329 (100%). Loss from molecular ion (M⁺) afforded the cation H at m/z 234 (66.7%).
Experimental section

Synthesis of certain novel Mannich bases bearing pyrazoline-3-one moiety.

I. 5-methyl-4- (4'-substituted aryl hydrazono)-2- 5-thioxo- 4,5-dihydro-[1,3,4] oxadiazol- 2-yl-methyl)-2,4-dihydro-pyrazol-3-one 17.

(a) [3-methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide 16.

(i) [3-methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid ethyl ester 15.

A mixture of [3-methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-pyrazoline-5-one 14, anhydrous K$_2$CO$_3$ chloro ethyl acetate and DMF was stirred at room temperature for 8 hours. The reaction mixture was distilled with ice cold water. The separated solid was identified as 15. Which was collected by filtration and recrystallized form ethanol m.p. 204°C, yield 78 %.

(ii) [3-methyl-5-oxo-4-(4'-substituted aryl hydrazono)-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide 16.

A solution of 15 and hydrazine hydrate in ethanol was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 16a (R - H).

(b) 5-methyl-4- (phenyl hydrazono)-2- 5-thioxo-4,5-dihydro-[1,3,4] oxadiazol- 2-yl-methyl)-2,4-dihydro-pyrazol-3-one 17a.

A mixture of 16 (19.9g, 0.1 mole), KOH (5.5g, 0.1mol) ethanol (100 mL) and carbon disulphide (6.02 ml, 0.1 mol) taken in a round bottomed flask fitted with a water cooled condenser was refluxed on a water bath till the evolution of hydrogen sulphide ceased. The excess of alcohol was removed by distillation. The reaction mixture was cooled to room temperature and the contents were poured to ice cold water and neutralized with dilute hydrochloric acid. The solid precipitated was filtered, washed thoroughly with water and dried. The product was further purified by recrystallization from ethanol-dioxane mixture to give 17a yield 59 %, m.p. 229 – 30°C.
Other members of the series 17 b-f were similarly prepared and their characterization data are given in Table V.

II. 5-methyl-4- (phenyl hydrazone)-2-[5-thioxo-4-(p-tolylamino -methyl)-4,5-dihydro-[1,3,4] oxadiazol- 2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a.

A solution of 17a (0.01 mole) in absolute ethanol and dioxan mixture (20 mL) was treated with formaldehyde (40%, 1.5ml). Later, the appropriate amine (0.01 mol) in ethanol (10 mL) was added with stirring and the reaction mixture was stirred overnight. The precipitated Mannich base was collected by filtration and dried. Recrystallization was done from ethanol-DMF mixture to give compounds 18b – k. Characterization data of these compounds are given in Table VI.
Fig. 4.1 IR Spectrum of 1,3,4-oxadiazole-2-thione 17a
Fig. 4.2 $^1$HNMR Spectrum of 1,3,4-oxadiazole-2-thione 17a [Solvent: DMSO $-d_6$]
Fig. 4.2b $^1$HNMR Spectrum of 1,3,4-oxadiazole 2-thione 17a [solvent: DMSO – d$_6$]
Fig. 4.4 IR Spectrum of Mannich base 18g
Fig. 4.5a 1HNMR Spectrum of Mannich base 18b

Fig. 4.5b 1HNMR Spectrum of Mannich base 18b [Solvent: CDCl3 + DMSO – d6]
Fig. 4.6 $^1$HNMR Spectrum of Mannich base 18h [Solvent: CDCl$_3$]
Mass spectral fragmentation of 5-methyl-4-(phenyl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazole-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17a

Chart -

[A] M+ 316 (37.3%)

[B] m/z 311 (34.6%)

[C] m/z 299 m/z (9.8%)

[D] 287 m/z (9.8%)

[E] 275 m/z (6.4%)

[F] m/z 243 (100%)

-CHO

-C,H,N

-HN=N

-CH4
Mass spectral fragmentation of
5-methyl-4-(phenyl hydrazono)-2-[5-thioxo-4-(p-tolylamino-methyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl-methyl]-2,4-dihydro-pyrazol-3-one 18a

Chart - II
<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p.</th>
<th>Yield</th>
<th>Mol.formula</th>
<th>Found % (Cacld)</th>
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<tr>
<td></td>
<td></td>
<td>°C</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>17a</td>
<td>H</td>
<td>150</td>
<td>65</td>
<td>C_{13}H_{12}N_{6}O_{2}S</td>
<td>49.50</td>
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<td></td>
<td></td>
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<td>(49.36)</td>
</tr>
<tr>
<td>17b</td>
<td>CH₃</td>
<td>152</td>
<td>67</td>
<td>C_{14}H_{14}N_{6}O_{2}S</td>
<td>51.09</td>
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<td></td>
<td>(50.90)</td>
</tr>
<tr>
<td>17c</td>
<td>OCH₃</td>
<td>155</td>
<td>62</td>
<td>C_{14}H_{14}N_{6}O_{3}S</td>
<td>48.70</td>
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<tr>
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<td>(48.55)</td>
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<tr>
<td>17d</td>
<td>OC₂H₅</td>
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<td>63</td>
<td>C_{15}H_{16}N_{6}O_{3}S</td>
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<td>(49.99)</td>
</tr>
<tr>
<td>17e</td>
<td>Cl</td>
<td>157</td>
<td>65</td>
<td>C_{15}H_{11}ClN_{6}O_{2}S</td>
<td>44.67</td>
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<td>(44.51)</td>
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<tr>
<td>17f</td>
<td>Br</td>
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<td>C_{13}H_{11}BrN_{6}O_{2}S</td>
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<td>(39.51)</td>
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Table V – Characterization data of 5-methyl-4-(4'-substituted aryl hydrazono)-2-(5-thioxo-4,5-dihydro-
[1,3,4]oxadiazol-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 17
Table VI – Characterization data of 5-methyl-4-(4'-substituted aryl hydrazono)-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-2,4-dihydro-pyrazol-3-one 18

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>m.p. ¹°C</th>
<th>Yield</th>
<th>Mol. formula</th>
<th>Found % (Cacld)</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
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<tr>
<td>18a</td>
<td>H</td>
<td>H</td>
<td>p-tolyl</td>
<td>240</td>
<td>75</td>
<td>C₂₁H₂₁N₇O₂S</td>
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<td>H</td>
<td>H</td>
<td>p-anisyl</td>
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<td>77</td>
<td>C₂₁H₂₁N₇O₂S</td>
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<tr>
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<td>H</td>
<td>p-fluorophenyl</td>
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<td>72</td>
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<td>51.45 (51.50)</td>
</tr>
<tr>
<td>18d</td>
<td>H</td>
<td>H</td>
<td>p-chlorophenyl</td>
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<td>73</td>
<td>C₂₆H₂₃N₇O₂S</td>
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</tr>
<tr>
<td>18e</td>
<td>H</td>
<td>H</td>
<td>p-bromophenyl</td>
<td>230</td>
<td>75</td>
<td>C₁₉H₂₃N₇O₂S</td>
<td>44.67 (44.51)</td>
</tr>
<tr>
<td>18f</td>
<td>H</td>
<td>H</td>
<td>p-nitrophenyl</td>
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<td>78</td>
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<td>39.65 (39.51)</td>
</tr>
<tr>
<td>18g</td>
<td>H</td>
<td>H</td>
<td>diethyl</td>
<td>260</td>
<td>72</td>
<td>C₂₀H₂₃N₇O₂S</td>
<td>52.70 (52.65)</td>
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<tr>
<td>18h</td>
<td>H</td>
<td>H</td>
<td>Diphenyl</td>
<td>265</td>
<td>76</td>
<td>C₂₆H₃₂N₇O₂S</td>
<td>62.70 (62.76)</td>
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<tr>
<td>18i</td>
<td>H</td>
<td>H</td>
<td>Morpholinyl</td>
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<td>70</td>
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<td>18j</td>
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<td>H</td>
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<td>N-methyl piperazinyl</td>
<td>267</td>
<td>68</td>
<td>C₂₀H₂₆N₈O₂S</td>
<td>39.65 (39.51)</td>
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