Chapter — IX

MANNICH BASES CONTAINING 1,3,4-OXADIAZOLES AND TETRA HYDRO QUINOLINE
Present work

In the chapter we described a synthesis and characterization of
I. Cis-1-{6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yi)
methyl]-2-methylquinolin-4-yl}pyrrolidin-2-one 13.

The reaction sequence leading to the formation of these compound is outlined in the Scheme – I.
Condensation of cis-2-[6-bromo-3,4-dihydro-2-methyl-4-(2-oxopyrrolidin-1-yl)quinolin-1(2H)-yl]acetohydrazide 10 with a mixture of KOH, ethanol and carbon disulphide afforded the corresponding cis-1-[6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-2-methylquinolin-4-yl]pyrrolidin-2-one 13 in very good yields.

In a typical example a mixture of 10, KOH, EtOH and carbon disulphide refluxed on a water bath till evolution of hydrogen sulphide ceased. After usual workup the corresponding 13 was obtained in 50% yield m.p-210°C.

The compound synthesized 13 has been characterized by means of their elemental analysis IR, $^1$HNMR and Mass data.

**IR Spectra**

The IR (KBr) spectra of cis-1-[6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-2-methylquinolin-4-yl]pyrrolidin-2-one 13 shows NH, C = O, C = S, and C = N functional groups around 3126, 1670, 1134 and 1603 cm$^{-1}$ respectively.

**$^1$HNMR Spectra**

The $^1$HNMR (200 MHz) spectra of cis-1-[6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-2-methylquinolin-4-yl]pyrrolidin-2-one 13 was recorded in DMSO-d$_6$.

$^1$HNMR (200MHz, DMSO-d$_6$): $\delta$ = 1.24 (d, 3H, CH3), 1.75 (ddd, 1H, 3-H), 1.91-2.15 (m, 3H, 3-H, 4'-H), 2.5-2.65(m, 2H, 3'-H), 3.1-3.3 (m, 2H, 5'-H), 3.4 (s, 2H, NCH$_2$)3.45-3.6(m, 1H, 2-H), 5.4(dd, 1H, 4-H), 6.6(d, 1H, Ar-H), 7.0 (brs, 1H, NH), 7.1-7.2(m, 2H, Ar-H).

**Mass spectra**

The mass spectra of cis-1-[6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-2-methylquinolin-4-yl]pyrrolidin-2-one 13 showed molecular ion (M$^+$) peaks at m/z 422.
The mass spectral fragmentation pattern of cis-1-{6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-2-methylquinolin-4-yl}pyrrolidin-2-one 13. The molecular ion (M⁺) peak was observed at m/z 422 (20.2%) and the base peak was at m/z 349 (100%) other prominent peaks appeared at m/z 407 (15.4%), m/z 394 (28.2%), m/z 367 (26.3%), m/z 363 (31%), m/z 353 (12.6%), m/z 343 (24.6%), and m/z 322 (13.2%).

II. Cis-1-1-[(4-((p-substituted aryl amino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl) methyl]-6- bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl] pyrrolidin-2-one 14 (Mannich bases) 14a-e.

The reaction sequence leading to the formation of these compounds is outlined in the Scheme – II.
Compound 13 were subjected to Mannich reaction with appropriate amines in the presence of formalin in ethanol-dioxane mixture medium to give cis-1-{1-[((4-((p-substituted aryl amino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl}pyrrolidin-2-one 14 (Mannich bases).

For example, stirring of 13 with aqueous formaldehyde and p-tolylamine in ethanol-dioxane mixture for over night, yielded a single product which was identified as cis-1-{1-[((p-toluidino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl}pyrrolidin-2-one 14a [R1 = H, R2 = p-tolyl] on the basis of its spectroscopic data.

Similar treatment of 13 with p-anisylamine/ p-flurophenylamine/ p-chloro phenylamine/ p-bromo phenylamine/ p-nitro phenyl in the presence of formaldehyde in ethanol dioxane mixture for overnight afforded the respective Mannich bases 14a-e. The characterization data of Mannich bases 14a-e are given in Table 9.3. 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 cis-1-{1-[((p-toluidino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl}pyrrolidin-2-one 14a (Mannich base) exhibited characteristic bands C = N, C = O, C = S, C - H Str around 1608, 1665, 1156, 2939 cm⁻¹ respectively. The IR spectra of 14a-e data are presented in Table 9.1.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R1</th>
<th>R2</th>
<th>( \nu_{\text{max}} ) in cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C=N</td>
</tr>
<tr>
<td>14a</td>
<td>H</td>
<td>p-tolyl</td>
<td>1608</td>
</tr>
<tr>
<td>14b</td>
<td>H</td>
<td>p-anisyl</td>
<td>1620</td>
</tr>
<tr>
<td>14c</td>
<td>H</td>
<td>p-chlorophenyl</td>
<td>1608</td>
</tr>
<tr>
<td>14d</td>
<td>H</td>
<td>p-bromophenyl</td>
<td>1609</td>
</tr>
<tr>
<td>14e</td>
<td>H</td>
<td>p-nitrophenyl</td>
<td>1605</td>
</tr>
</tbody>
</table>
\[ 1^\text{HNMR Spectra} \]

The \( 1^\text{HNMR} \) (200MHz) spectra of cis-1-{1-[((p-substituted aryl amino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methyl quinolin-4-yl} pyrrolidin-2-one 14a-e (Mannich bases) were recorded in DMSO-\( d_6 \) and the data are furnished Table 9.2.

**Table 9.2 – \( 1^\text{HNMR} \) spectral data of cis-1-{1-[((p-substituted aryl amino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methyl quinolin-4-yl} pyrrolidin-2-one 14a-e**

<table>
<thead>
<tr>
<th>Compd</th>
<th>R1</th>
<th>R2</th>
<th>( 1^\text{HNMR} ) (200MHz) (DMSO-( d_6 )) (( \delta )ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td>H</td>
<td>( p )-tolyl</td>
<td>1.23 (s, 3H, CH(_3)), 1.75 (dd, 1H, 3-H), 1.92-2.15 (m, 1H, 3-H, 4'-H) 2.4 (s, 3H, CH(_3)) 2.5-2.65 (m, 2H, 3'-H), 3.1-3.3 (m, 2H, 5'-H), 3.4 (s, 2H, NCH(_2)), 3.45-3.6 (m, 1H, 2-H), 4.45 (brs, 1H, NH), 4.5 (s, 2H, NCH(_2)N), 5.4 (dd, 1H, 4-H), 6.4 (m, 2H, Ar-H), 6.66 (d, 1H, Ar-H), 6.95-7.15 (m, 4H, Ar-H)</td>
</tr>
<tr>
<td>14b</td>
<td>H</td>
<td>( p )-anisyl</td>
<td>1.22 (s, 3H, CH(_3)), 1.74 (dd, 1H, 3-H), 1.92-2.15 (m, 1H, 3-H, 4'-H) 2.5-2.65 (m, 2H, 3'-H), 3.1-3.3 (m, 2H, 5'-H), 3.5 (s, 2H, NCH(_2)), 3.45-3.6 (m, 1H, 2-H), 3.78 (s, 3H, OCH(_3)) 4.45 (brs, 1H, NH), 4.5 (s, 2H, NCH(_2)N) 5.4 (dd, 1H, 4-H), 6.4 (m, 2H, Ar-H), 6.66 (d, 1H, Ar-H), 6.95-7.15 (m, 4H, Ar-H)</td>
</tr>
<tr>
<td>14c</td>
<td>H</td>
<td>( p )-chlorophenyl</td>
<td>1.24 (s, 3H, CH(_3)), 1.74 (dd, 1H, 3-H), 1.92-2.16 (m, 1H, 3-H, 4'-H) 2.5-2.65 (m, 2H, 3'-H), 3.01-3.3 (m, 2H, 5'-H), 3.42-3.6 (m, 1H, 2-H), 4.45 (brs, 1H, NH) 4.5 (s, 2H, NCH(_2)N) 5.4 (dd, 1H, 4-H), 6.4-6.5 (m, 4H, Ar-H), 7.05-7.15 (m, 4H, Ar-H)</td>
</tr>
<tr>
<td>14d</td>
<td>H</td>
<td>( p )-bromophenyl</td>
<td>1.23 (s, 3H, CH(_3)), 1.75 (dd, 1H, 3-H), 1.91-2.15 (m, 1H, 3-H, 4'-H) 2.5-2.65 (m, 2H, 3'-H), 3.0-3.28 (m, 2H, 5'-H), 3.42-3.6 (m, 1H, 2-H), 4.45 (brs, 1H, NH) 4.5 (s, 2H, NCH(_2)N) 5.4 (dd, 1H, 4-H), 6.35-6.45 (m, 4H, Ar-H), 7.1-7.22 (m, 4H, Ar-H)</td>
</tr>
<tr>
<td>14e</td>
<td>H</td>
<td>( p )-nitrophenyl</td>
<td>1.24 (s, 3H, CH(_3)), 1.74 (dd, 1H, 3-H), 1.92-2.16 (m, 1H, 3-H, 4'-H) 2.5-2.65 (m, 2H, 3'-H), 3.01-3.3 (m, 2H, 5'-H), 3.42-3.6 (m, 1H, 2-H), 4.45 (brs, 1H, NH) 4.5 (s, 2H, NCH(_2)N) 5.4 (dd, 1H, 4-H), 7.0-7.15 (m, 4H, Ar-H), 7.95-8.0 (m, 2H, Ar-H)</td>
</tr>
</tbody>
</table>
Mass spectra

The mass spectra of cis-\{1-[(4-((p-toluidino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl}\} pyrrolidin-2-one 14a (R₁ = H, R₂ = p-CH₃C₆H₄) exploited the molecular ion (M⁺) peaks at m/z 527.

The fragmentation pattern noticed in the mass spectrum of cis-\{1-[(4-((p-toluidino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl]-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl\} pyrrolidin-2-one 14a (R₁ = H, R₂ = p-CH₃C₆H₄) is presented in Chart II. The molecular ion (M⁺) peak was observed at m/z 527 (14.2%) and the base peak was at m/z 512 (100%) other prominent peaks appeared at m/z 512(25%), m/z 499 (24.3%), m/z 484 (12.1%), m/z 482 (16.5%), m/z 472(23%),m/z 450 (22.6%),and m/z 444 (31.5%).

Experimental section

I. (a) Synthesis of cis-\{6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl) methyl]-2-methylquinolin-4-yl\}pyrrolidin-2-one 13.

i) Synthesis of cis-ethyl2-[6-bromo-3,4-dihydro-2-methyl-4-(2-oxopyrrolidin-1-yl)quinolin-1(2H)-yl]acetate 9.

A mixture of cis-\{6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl\} pyrrolidin-2-one 8, anhydrous K₂CO₃, chloroethyl acetate and DMF was stirred at room temperature for 8 hours. The reaction mixture was diluted with ice cold water. The separated solid was identified as cis-ethyl2-[6-bromo-3,4-dihydro-2-methyl-4-(2-oxopyrrolidin-1-yl)quinolin-1(2H)-yl]acetate 9. It was collected by filtration and recrystalized from ethanol m.p. 1950C, yield 72%.


A solution of 9 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 recrystalized from ethanol to afford cis-2-[6-bromo-3,4-dihydro-2-methyl-4-(2-oxopyrrolidin-1-yl)quinolin-1(2H)-yl]acetohydrazide 10.
(a) Synthesis of cis-1-{6-bromo-1,2,3,4-tetrahydro-1-[(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl) methyl]-2-methylquinolin-4-yl}pyrrolidin-2-one 13.

A mixture of 10 (10.0g, 0.1mol), KOH (2.75g, 0.1mol) ethanol (50mL) and carbon disulphide (3.01ml, 0.1mol) taken in a round bottomed flask fitted with a water cooled condenser was refluxed on a water bath till the evaluation 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 to give 13 yield 50%, m.p. 209-210°C.

II. Synthesis cis-1-{1-[(4-((p-substituted aryl amino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl) methyl]-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl} pyrrolidin-2-one 14 (Mannich bases) 14a.

A solution of 13 (0.01 mol) in absolute ethanol and dioxane mixture (20mL) was treated with formaldehyde (40%, 1.5ml). Later, 4-methyl aniline (0.01 mol) in ethanol (10 mL) was added with stirring and the reaction mixture was stirred over night. The precipitated Mannich base was collected by filtration and dried. Recrystallization was done from ethanol-DMF mixture to give compound 14a.
Table - 9.3: Characterization data of (Cis-1-{1-[(4-((p-substituted aryl amino) methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl) methyl]-6-bromo-1,2,3,4-tetrahydro-2- methylquinolin-4-yl} pyrrolidin-2-one 14

<table>
<thead>
<tr>
<th>Compd</th>
<th>R₁</th>
<th>R₂</th>
<th>M.P °C</th>
<th>Yield (%)</th>
<th>Mol. Formula</th>
<th>Found (%)</th>
<th>Calcd (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>14a</td>
<td>CH₄</td>
<td>CH₃C₆H₅</td>
<td>218</td>
<td>68</td>
<td>C₂₂H₂₃N₃O₂</td>
<td>66.87</td>
<td>5.42</td>
</tr>
<tr>
<td>14b</td>
<td>CH₄</td>
<td>OCH₃C₆H₄</td>
<td>240</td>
<td>60</td>
<td>C₂₃H₂₇N₃O₂</td>
<td>67.43</td>
<td>5.73</td>
</tr>
<tr>
<td>14c</td>
<td>CH₃</td>
<td>ClC₆H₄</td>
<td>225</td>
<td>55</td>
<td>C₂₃H₂₇N₃O₃</td>
<td>65.28</td>
<td>5.53</td>
</tr>
<tr>
<td>14d</td>
<td>CH₄</td>
<td>BrC₆H₄</td>
<td>200</td>
<td>58</td>
<td>C₂₃H₂₉N₃O₃</td>
<td>65.82</td>
<td>5.78</td>
</tr>
<tr>
<td>14e</td>
<td>CH₄</td>
<td>NO₂C₆H₄</td>
<td>195</td>
<td>63</td>
<td>C₂₈H₂₄ClN₃O₃</td>
<td>62.29</td>
<td>4.89</td>
</tr>
</tbody>
</table>
Fig 9.1: IR Spectrum of 1-((2R,4S)-6-bromo-1,2,3,4-tetrahydro-1-((4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-2-methylquinolin-4-yl)pyrrolidin-2-one 13

Fig. 9.2: 'HNMR Spectrum of 1-((2R,4S)-6-bromo-1,2,3,4-tetrahydro-1-((4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-2-methylquinolin-4-yl)pyrrolidin-2-one (Solvent DMSO-d6) 13
Fig. 9.3: IR Spectrum of 1-((2R,4S)-1-((4-((p-toluidino)methyl)-4,5-dihydro-5-thiolo-1,3,4-oxadiazol-2-yl)methyl)-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl)pyrrolidin-2-one (Solvent DMSO-d6) 14a

Fig. 9.4: $^1$HNMR Spectrum of 1-((2R,4S)-1-((4-((p-toluidino)methyl)-4,5-dihydro-5-thiolo-1,3,4-oxadiazol-2-yl)methyl)-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl)pyrrolidin-2-one (Solvent DMSO-d$_6$) 14a
Fig. 9.5: IR Spectrum of 1-((2R,4S)-1-((4-((4-chlorophenylamino)methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl)pyrrolidin-2-one 14c

Fig. 9.6: $^1$HNMR Spectrum of 1-((2R,4S)-1-((4-((4-chlorophenylamino)methyl)-4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)methyl)-6-bromo-1,2,3,4-tetrahydro-2-methylquinolin-4-yl)pyrrolidin-2-one (Solvent DMSO-d$_6$) 14c
Chart - 1
References


