INTRODUCTION

The Mannich reaction has been 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.

Review of literature:

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 accelerations1-3 etc. However, the important applications are in the field of pharmaceutical products1-4. Studies on antineoplastic drugs, analgesic drug, antibiotic drugs etc5-9, including labeled molecules10-12, have received particular attention in the recent past. Mannich bases can either directly be employed or used as intermediates in chemical synthesis.

Kumar et al.,13 reported the synthesis of Mannich bases [I] derived from imidazole derivatives. The newly synthesized Mannich bases were tested for their anti-inflammatory and ulcerogenic activity. Compounds containing chlorine substituent showed the highest activity. Erodag and yulug.,14 reported Mannich bases of 2-benzoazolinone [2][R = H, Cl; R1 = Ph, o-anisyl, p-Et-C6H4, m-CF3-C6H4]. These compounds were found to be very effective against like fungi.
Ebeid et al.\textsuperscript{15} synthesized some new quinoline Mannich bases [3] \([R = \text{H, Cl, HNC}_6\text{H}_4\text{SO}_2\text{NHR}^{1-4}\text{etc}]\) as possible antimicrobial agents.

Barlin and Ireland\textsuperscript{16} prepared di-Mannich bases [4a] \([R_1 = \text{methylpiperidinyl, N(CH}_2\text{-CH}_2\text{OH)Me}]\) and [4b] \([R_2 = \text{methylpiperadinyl, N(CH}_2\text{-CH}_2\text{OH)Me, NMe}_2]\) OF 4-[(7-trifluoromethylquinolin-4-yl)] amino phenol and 4-[(7-bromo-1,5-naphthyridin-4-yl)]aminophenol respectively. They were found to be active antimalarials especially against chloroquine resistant isolate (K-1) of plasmodium flaciperum.

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

Mohan\textsuperscript{18} synthesized Mannich bases of the type [6] \([R = \text{H, Me; R}_1 = \text{H, 2-OH, 4-OH, 4-OMe etc}]\). 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.\textsuperscript{19}. All compounds showed significant antibacterial activity towards Gram-positive and Gram-negative bacteria.

Pilli et al.\textsuperscript{20} reported the synthesis and analgesic activity of N-Mannich bases of 2-benzoxazolinones [8] \([R = \text{4-phenylpiperazin-1-yl, r-methylpyridin-1-yl, 4- morpholinyl etc; R}_1 = 2,3\text{-difluoro}]\).
Shouhai and Fulin synthesized Mannich bases of tritylhydroxyphosphol derivative [9] [R = CH₃, Et, Pr, Me₂CH, Bu, iso-Bu, phenyl, isophenyl], which showed strong antimalarial activity comparable to that of chloroquine.

Synthesis of morpholine Mannich bases [10] of phenylpropanones were reported by Papadaki-Valiraki et al. These compounds were tested for their effect on DNA synthesis and cell proliferation was greatly reduced.

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

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

Roman et al. reported the synthesis of cyclic Mannich bases [13] from the Mannich condensation of 2-(1-hydroxyethyl) benzimidazole with formaldehyde and various substituted arylamines.

Prompted by the above observations, a project was undertaken to synthesize a series of Mannich derivatives carrying pyrazole moiety containing oxadiazole-2-thione moiety. 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 containing oxadiazole-2-thione.

**EXPERIMENTAL METHODS**

I. (4Z)-4-(2-substituted aryl hydrazono)-1-{4-[5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl] methyl - amino[phenyl]-3-methyl-1H-pyrazol-5(4H)-one [Stage-III]a-f.

II. The reaction sequence leading to the formation of these compounds is outlined in the figure-2.

2-[4-{[(4Z)-4-(2-substituted aryl hydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl] phenylamino} aceto-hydrazone [Stage-II] employed in the present investigation was prepared as per the procedure, condensation of 2-{[(4Z)-4-(2-substituted aryl hydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl] phenylamino} acetoxyhydrazone [Stage-II] with a mixture of KOH, ethanol, and carbon disulphide afforded the corresponding (4Z)-4-(2-substituted aryl hydrazono)-1-{4-[5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl] ethylamino} benyl]-3-methyl-1H-pyrazol-5(4H)-one [Stage-III] in very good yields.

In a typical example a mixture of [Stage-II]a KOH, ethanol and carbon disulphide refluxed on a water bath till the evaluation of hydrosulphide ceased. After usual work-up the corresponding [Stage-III]a was obtained in 84% yield with m.p. 227°C.

The above reaction of [Stage-II]a with a mixture of KOH, EtOH and carbon disulphide has been extended to [Stage-III] b-f.
Table 1: IR Spectra of (4Z)-4-(2-substituted aryl hydrazono)-1-4-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methy lamino)phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-III] a-f

| Compd Stage-III | R       | $\nu_{\text{max}}$ in cm$^{-1}$ | Oxadiazole NH | NH | C = N | C = O | C = S |
|-----------------|---------|-------------------------------|---------------|----|-------|-------|-------|
| a               | H       | 3120                          | 3180          | 1603 | 1670  | 1134  |
| b               | CH$_3$  | 3115                          | 3165          | 1600 | 1655  | 1125  |
| c               | OCH$_3$ | 3120                          | 3165          | 1602 | 1660  | 1130  |
| d               | OC$_2$H$_5$ | 3115                | 3165          | 1600 | 1650  | 1125  |
| e               | Cl      | 3135                          | 3195          | 1610 | 1680  | 1140  |
| f               | Br      | 3140                          | 3195          | 1615 | 1685  | 1145  |

Table 2: $^1$HNMR spectral data of (4Z)-4-(2-substituted aryl hydrazono)-1-4-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methy lamino)phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-III]

| Compd Stage-III | R       | $^1$HNMR (200MHz) (DMSO-d$_6$) (δppm) |
|-----------------|---------|-------------------------------------|
| a               | H       | 2.3 (s, 3H, CH$_3$), 4.5(s, 1H, Ar-NH), 5.45 (s, 2H, N-CH$_2$), 6.8 (s, 1H, Ar-NH), 7.1-7.2 (m, 5H, C$_6$H$_5$), 7.4 (d, 2H, C$_6$H$_5$), 7.7 (d, 2H, C$_6$H$_5$), 14.7 (s, H, thiol-thione tautomeric proton NH). |
| b               | CH$_3$  | 2.0 (s, 3H, CH$_3$), 2.3 (s, 3H, CH$_3$), 4.2(s, 1H, Ar-NH), 5.4 (s, 2H, N-CH$_2$), 6.8 (s, 1H, Ar-NH), 7.1-7.3 (m, 4H, C$_6$H$_5$), 7.4 (d, 2H, C$_6$H$_5$), 7.7 (d, 2H, C$_6$H$_5$)14.7(s, H, thiol-thione tautomeric proton NH). |
| c               | OCH$_3$ | 2.2 (s, 3H, CH$_3$), 3.9 (s, 3H, CH$_3$), 4.4(s, 1H, Ar-NH), 5.4 (s, 2H, N-CH$_2$), 6.8 (s, 1H, Ar-NH), 7.1-7.2 (m, 4H, C$_6$H$_5$), 7.4 (d, 2H, C$_6$H$_5$), 7.7 (d, 2H, C$_6$H$_5$), 14.7(s, H, thiol-thione tautomeric proton NH). |
| d               | OC$_2$H$_5$ | 1.8 (s, 3H, CH$_3$), 2.1 (s, 3H, CH$_3$), 3.15 (q, 2H, O-CH$_2$), 4.2(s, 1H, Ar-NH), 5.4 (s, 2H, N-CH$_2$), 6.8 (s, 1H, Ar-NH), 7.1-7.2 (m, 4H, C$_6$H$_5$), 7.4 (d, 2H, C$_6$H$_5$), 7.7 (d, 2H, C$_6$H$_5$), 14.7(s, H, thiol-thione tautomeric proton NH). |
| e               | Cl      | 2.4 (s, 3H, CH$_3$), 4.5(s, 1H, Ar-NH), 5.5 (s, 2H, N-CH$_2$), 6.8 (s, 1H, Ar-NH), 7.1-7.2 (m, 4H, C$_6$H$_5$), 7.4 (d, 2H, C$_6$H$_5$), 7.7 (d, 2H, C$_6$H$_5$), 14.7(s, H, thiol-thione tautomeric proton NH). |
| f               | Br      | 2.5 (s, 3H, CH$_3$), 4.5(s, 1H, Ar-NH), 5.5 (s, 2H, N-CH$_2$), 6.8 (s, 1H, Ar-NH), 7.1-7.2 (m, 4H, C$_6$H$_5$), 7.4 (d, 2H, C$_6$H$_5$), 7.7 (d, 2H, C$_6$H$_5$), 14.7(s, H, thiol-thione tautomeric proton NH). |

Table 3: IR spectral data of (4Z)-4-(2-substituted aryl hydrazono)-1-4-((5-thioxo-4-((p-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methy lamino)phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV] a-k

| Compd Stage-IV | R       | R$_1$ | R$_2$ | $\nu_{\text{max}}$ in cm$^{-1}$ | Ar-NH | C = N | C = O | C = S | C-HStr | -NH |
|----------------|---------|-------|-------|-------------------------------|-------|-------|-------|-------|--------|-----|
| a              | H       | H     | p-tolyl | 3250                         | 1608  | 1665  | 1156  | 2939  | 3140   |
| b              | H       | H     | p-anisyl | 3240                          | 1620  | 1660  | 1150  | 2925  | 3130   |
| c              | H       | H     | p-fluorophenyl | 3255                  | 1610  | 1670  | 1160  | 2945  | 3145   |
| d              | H       | H     | p-chlorophenyl | 3253                         | 1608  | 1663  | 1158  | 2940  | 3172   |
| e              | H       | H     | p-bromophenyl | 3254                          | 1609  | 1665  | 1155  | 2943  | 3143   |
| f              | H       | H     | p-nitrophenyl | 3245                          | 1605  | 1655  | 1145  | 2930  | 3135   |
| g              | H       | H     | Diethyl | 3230                          | 1590  | 1645  | 1135  | 2925  | 3125   |
| h              | H       | H     | Diphenyl | 3250                          | 1593  | 1667  | 1107  | 2940  | 3150   |
| i              | H       | H     | Morpholinyl | 3265                          | 1610  | 1675  | 1165  | 2955  | 3150   |
| j              | H       | H     | Piperazinyl | 3260                          | 1610  | 1670  | 1160  | 2945  | 3145   |
| k              | H       | H     | N-methyl Piperazinyl | 3255                          | 1605  | 1655  | 1145  | 2935  | 3140   |
IL. (4Z) -4-(2-substituted aryl hydrazono) -1- {[4-(5-thioxo-4-(alkyl / aryl / heterocyclic amino) methyl)-4,5-dihydro -1,3,4-oxadiazol-2 -yl] methylamino] phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV]a.

The reaction sequence leading to the formation of these compounds is outlined in the Figure-2

Comounds [Stage-III] were subjected to Mannich reaction with appropriate amines in the presence of formation of formalin in ethanol-dioxane mixture medium to give (4Z)-4-(2-phenyl hydrazono)-1- {[4-(5-thioxo-4-(alkyl/aryl/heterocyclic amino)methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV] (Mannich bases).

For example stirring of [Stage-III] a (R₁ = H, R₂ = p-tolyl) with formaldehyde and p-tolylamine in ethanol-dioxane mixture overnight, yielded a single product which was identified as (4Z)-4-(2-phenyl hydrazono)-1- {[4-(5-thioxo-4-(p-tolylamino)methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV] a (R₁ = H, R₂ = p-tolyl) on the bases of its spectroscopic data.

Similar treatment of [Stage-III] a with p-anislylamine / p-fluorophenylamine/ p-chlorophenylamine/ p-bromophenylamine/ diethylamine/ diphenylamine/ piperazine/ morpholine/ N-methyl piperiziny in the presence of formaldehyde in ethanol dioxane mixture for overnight afforded the respective Mannich bases [Stage-IV] a-k. The characterization data of Mannich bases [Stage-IV] a-k are given in Table-6. The melting points of the newly synthesized compounds were determined in open capillaries and are unconnected. The purity of all the compounds was confirmed by TLC.

IR Spectra

The IR (KBr) spectra of (4Z)-4-(2-substituted aryl hydrazono)-1- {[4-(5-thioxo-4-(p-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV]a (Mannich base) exhibited characteristic bands Ar-NH, C = N, C = O, C = S, C-Hstr, – NH around 3240, 1620, 1660, 1150, 2925, 3130 cm⁻¹ respectively. The IR spectrum of [Stage-IV]a is shown in Figure-2.

Table-4: 1H NMR spectral data of (4Z)-4-(2-substituted aryl hydrazono)-1- {[4-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl] methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV].

| Compd | R₁ | R₂ | 1H NMR (200MHz) (DMSO-d₆) (δppm) |
|-------|----|----|----------------------------------|
| a     | H  | H  | p-tolyl                          |
| b     | H  | H  | p-anisyl                         |
| c     | H  | H  | p-nitrophenyl                    |
| d     | H  | H  | morpholino                       |
| e     | H  | H  | piperiziny                       |

The mass spectra of (4Z)-4-(2-substituted aryl hydrazono)-1- {[4-(5-thioxo-4-(p-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV]a is presented in chart II.

The fragmentation pattern noticed in the mass spectrum of (4Z)-4-(2-phenyl hydrazono)-1- {[4-(5-thioxo-4-(p-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV]a (R₁=H, R₂=CH₃CH₂H) is presented in chart II.
Table 5: Characterization data of (4Z)-4-(2-substituted aryl hydrazono)-1-{4-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-12-yl)methylaminoo]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-III]

| Compd | R     | M.P   | Yield (%) | Mol. Formula          | Found (%) – Calcd (%) |
|-------|-------|-------|-----------|-----------------------|------------------------|
|       | Stage-III       | °C    | (% )     |                      | C    | H    | N    | O    | S    | Cl   | Br   |
| a     | H     | 150   | 65       | C_{10}H_{11}N_{3}O_{3}S | 56.15 | 4.37 | 24.18 | 8.03 | 8.05 |
| b     | CH_{3} | 152   | 67       | C_{20}H_{19}N_{3}O_{3}S | 57.18 | 4.69 | 23.42 | 7.74 | 7.78 |
| c     | OCH_{3} | 155   | 62       | C_{20}H_{19}N_{3}O_{3}S | 55.06 | 4.56 | 22.58 | 11.04 | 7.47 |
| d     | OC_{2}H_{5} | 160   | 63       | C_{20}H_{19}N_{3}O_{3}S | 55.05 | 4.52 | 22.49 | 11.04 | 7.48 |
| e     | Cl    | 157   | 65       | C_{10}H_{10}ClN_{3}O_{3}S | 51.80 | 3.83 | 22.35 | 7.42 | 7.43 | 8.18 |
| f     | Br    | 162   | 68       | C_{10}H_{10}BrN_{3}O_{3}S | 47.06 | 3.49 | 20.31 | 6.75 | 6.74 | 16.60 |

Table 6: Characterization data of (4Z)-4-(2-substituted aryl hydrazono)-1-{4-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylamino]phenyl}-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV] (Mannich bases)

| Compd | R     | R_{1} | R_{2} | M.P   | Yield (%) | Mol. Formula          | Found (%) – Calcd (%) |
|-------|-------|-------|-------|-------|-----------|-----------------------|------------------------|
|       | Stage-IV       | °C    | (%)     |       |           |                      | C    | H    | N    | O    | S    | Cl   | Br   | F |
| a     | H     | H     | p-tolyl | 240   | 75       | C_{2}H_{2}N_{3}O_{3}S | 61.48 | 4.94 | 21.22 | 6.03 | 6.04 |
| b     | H     | H     | p-anisyl | 245   | 77       | C_{2}H_{2}N_{3}O_{3}S | 59.65 | 4.74 | 20.58 | 8.82 | 5.81 |
| c     | H     | H     | P\textsuperscript{4} fluorenphyl | 235   | 72       | C_{2}H_{2}F_{3}N_{3}O_{3}S | 58.81 | 4.28 | 21.11 | 6.01 | 5.94 |
| d     | H     | H     | P\textsuperscript{4} chlorophenyl | 250   | 73       | C_{2}H_{2}ClN_{3}O_{3}S | 57.23 | 4.38 | 20.56 | 6.07 | 6.01 | 6.64 |
| e     | H     | H     | P\textsuperscript{4} bromophenyl | 230   | 75       | C_{2}H_{2}BrN_{3}O_{3}S | 52.96 | 4.00 | 19.10 | 5.49 | 5.59 |
| f     | H     | H     | P\textsuperscript{4} nitrophenyl | 255   | 78       | C_{2}H_{2}N_{3}O_{3}S | 56.15 | 4.23 | 22.76 | 11.65 | 5.90 |
| g     | H     | H     | diethyl | 260   | 72       | C_{2}H_{2}N_{3}O_{3}S | 59.32 | 5.92 | 22.08 | 6.22 | 6.38 |
| h     | H     | H     | diphenyl | 265   | 76       | C_{2}H_{2}N_{3}O_{3}S | 65.70 | 4.96 | 18.53 | 5.24 | 5.26 |
| i     | H     | H     | Morpholinyl | 270   | 70       | C_{2}H_{2}N_{3}O_{3}S | 55.21 | 5.12 | 24.09 | 9.12 | 6.08 |
| j     | H     | H     | Piperazinyl | 272   | 72       | C_{2}H_{2}N_{3}O_{3}S | 55.29 | 5.49 | 26.83 | 6.10 | 6.09 |
| k     | H     | H     | N-methyl piperezinyl | 267   | 68       | C_{2}H_{2}N_{3}O_{3}S | 56.30 | 5.83 | 26.35 | 6.16 | 6.15 |

(a) 2-{4-[(4Z)-4-(2-substituted aryl hydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl]phenylamino} acetohydrazide [Stage-II].
(i) Ethyl 2-{4-[(4Z)-4-(2-phenylhydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl]phenyl amino} acetate [Stage-I].
A mixture of (4Z) -4- (2-phenylhydrazono) -1- (4-aminophenyl)- 3- methyl- 1H-pyrazol-5(4H)-one [Starting material], 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 [Stage-I]. This was collected by filtration and recrystallized from ethanol m.p.204°C, yield 78%.

International Journal of Organic and Bioorganic Chemistry 2015; 5(1): 1-8
Table 7 Antibacterial activity by disc diffusion method for Mannich bases Stage-IV (a-k)

| S.No | Compd Stage-IV | R1            | R2            | Staphylococcus aureus NCCS 2079 | Bacillus Cereus NCCS 2106 | Escherichia Coli NCCS 2065 | Pseudomonas Aeruginosus NCCS 2200 |
|------|----------------|---------------|---------------|-------------------------------|----------------------------|----------------------------|-----------------------------------|
| 1    | a H            | p-tolyl       | 6             | 7                            | 5                          | 6                          |                                   |
| 2    | b H            | p-anisyl      | 7             | 6                            | 6                          | 5                          |                                   |
| 3    | c H            | p-fluoro phenyl | 10           | 11                           | 9                          | 10                         |                                   |
| 4    | d H            | p-chloro phenyl | 12           | 10                           | 9                          | 11                         |                                   |
| 5    | e H            | p-bromo phenyl | 10           | 11                           | 9                          | 9                          |                                   |
| 6    | f H            | p-nitro phenyl | 11           | 10                           | 10                         | 10                         |                                   |
| 7    | g H            | diethyl       | 7             | 8                            | 6                          | 5                          |                                   |
| 8    | h H            | di phenyl     | 7             | 7                            | 5                          | 6                          |                                   |
| 9    | i H            | morphonil     | 10            | 12                           | 10                         | 11                         |                                   |
| 10   | j H            | piperizylin   | 11            | 10                           | 9                          | 10                         |                                   |
| 11   | k H            | N-methyl piperizine | 10        | 11                           | 9                          | 11                         |                                   |
| 12   | Amoxicillin    | 21            | 27            | 24                           | 22                         |                            |                                   |
| 13   | Cefaclor       | 19            | 22            | 19                           | 20                         |                            |                                   |

(ii) 2-(4-[(4Z)-4-(2-substituted aryl hydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl] phenylamino) acetohydrazide [Stage-II],

A solution of [Stage-I] and hydrazide hydrate in ethanol was refluxed for 5 hours. The reaction mixture cooled and poured onto ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford [Stage-II] a (R = H).

(b) (4Z)-4-(2-phenyl hydrazono)-1-(4-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylamino] phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-III]a.

A mixture of [Stage-II] (19.9 g, 0.1 mol), KOH (5.5 g, 0.1 mol) 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 evaluation of hydrogen sulphide ceased. The excess of ethanol 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 [Stage-III] a yield 59%, m.p. 229-230°C.

Other members of the series [Stage-III] b-f were similarly prepared and their characterization data are given in Table-5.

II. (4Z)-4-(2-phenyl hydrazono)-1-(4-[(5-thioxo-4-(p-tolylamino) methyl]-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylamino]phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-IV] a.

A solution of [Stage-III] a (0.01 mol) in ethanol and dioxane (20 mL) was treated with formaldehyde (40%, 1.5 mL). Later, the appropriate amine (0.01 mol) in ethanol (10 mL) was added with stirring and the reaction mixture was stirred over night. The precipitated Mannich bases was collected by filtration and dried. Recrystallization was done from ethanol-DMF to give compounds [Stage-IV] a-k. Characterization data of these compounds are given in Table-6.

MICROBIAL ACTIVITY:

Mannich bases step-2 product (a,e,f) have good antifungal activity against Aspergillus Niger NCCS 1196 and Candida albicans NCCS 2106. In this series chloro, bromo and nitro, p-phenyl syndronyl, p-tolyl syndronyl and N-phenyl syndronyl showed good antifungal activity against Aspergillus Niger and Candida albicans at the concentration of 250 μg/mL.

SUMMARY AND CONCLUSION

The synthesis of Mannich bases bearing [1,3,4]-oxadiazole and pyrazol-3-one moiety. In the preceding section of this research a brief review of literature concerning the synthesis and biological activity of Mannich bases are incorporated. The synthesis and characterization has completed for the following.

I. (4Z)-4-(2-substituted aryl hydrazono)-1-(4-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylamino]phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-III].

II. (4Z)-4-(2-substituted aryl hydrazono)-1-(4-[(5-thioxo-4-(alkyl/amyl/heterocyclic amino) methyl]-4,5-dihydro -1,3,4-oxadiazol -2-yl) methylamino]phenyl)-3-methyl-1H-pyrazol-5(4H)-one (Mannich bases) [Stage-IV].

A mixture (4Z) -2- (4- (15Z) -4- (2-phenylhydrazono) -4,5- dihydro -3- methyl -5- oxopyrazol-1-yl) phenylamino)-N’-(2-oxindolin-3-ylidene) acetohydrazide [Stage-II], KOH, ethanol and carbon disulfide was refluxed on a water bath afforded (4Z)-4-(2-substituted arylhydrazono)-1-(4- [(5-thioxo-4,5-dihydro -1,3,4-oxadiazol -2-yl) methylamino] phenyl)-3-methyl-1H-pyrazol-5(4H)-one [Stage-III]. A solution of [Stage-III] in absolute ethanol and dioxin mixture was reacted with formaldehyde and secondary amine furnished the (4Z)-4-(2-substituted aryl hydrazono)-1-(4-[(5-thioxo-4-(alkyl/amyl/heterocyclic amino)methyl]-4,5-dihydro-1,3,4-oxadiazol-2-yl] methyl amino]phenyl)-3-methyl-1H-pyrazol-5(4H)-one (Mannich bases) [Stage-IV].
The structural assignments to compounds [stage-III] and [Stage-IV] were based on their elemental analysis and spectral (IR, 1H NMR and MS) data. The reaction sequence is laid out in figure-2.

REFERENCES
1. M. Tramontini and L. Angioloni, Mannich-Bases, Chemistry and Uses, CRC, Boca Raton, F.L. (1994).
2. M. Arend, B. Westermann and N. Risch, Angew. Chem Int Ed., 37, 1044 (1998).
3. S. K. Sridhar, S. N. Pandeya, J. P. Stables and A. Ramesh, Eur. J. Pharm. Scien., 16 (3), 129 (2002).
4. J. R. Dimmock and P. Kumar, Curr. Med. Chem., 4(1), 1-22 (1977).
5. I. A. Poplevskaya, G. N. Kondaurou, K. A. Abdullin, L. K. Shipunova, G. B. Chermanova and O. K. Kabiev, Tr. Inst. Khim. Naul. Akad. Nauk. Kaz., SSR. 52, 52 (1980); Chem. Abstr., 94, 120781 (1981).
6. P. Caganiant, G. Krisch, M. Wierzbicki, F. Lepage, D. Caganiant, D. Loebenberg, R. Parmergianian and Scherlock, Eur. J. Med. Chem., 15, 439 (1980).
7. Korea Inst. Of Science and Technology: Jpn. Kokai Tokkyo Koho, JP, 5, 867, 693 (1983). Chem. Abstr., 99, 7047A (1983).
8. J. R. Dimmock, S. K. Raghavan, B. M. Logan and G. E. Bigam, Eur. J. Med. Chem., 18, 249 (1983).
9. H. Bundgaard, Methods in Enzymology., 112, 347 (1985).
10. K. Masuda, T. Toga and N. Hayashi, J. Labelled Compd., 11, 301 (1975); Chem. Abstr., 84, 121730f (1976).
11. J. S. Fowler, J. Org. Chem., 42, 2637 (1977).
12. E. Scheier, Helv. Chim. Acta., 59, 585 (1977).
13. A. Kumar, M. Verma, A. K. Saxena and Shanker, Indian J. Chem., 27B (3), 301 (1988).
14. H. Ergodan and N. Yulug. Hacettepe Univ. Eezacilik Fak. Derg., 9, 35-40 (1989); Chem. Abstr., 112, 198187p (1990).
15. M. Y. Ebeid, M. K. El-said, M. M. Kamel, K. Z. Gadalla and L. M. Fadda, Egypt. J. Pharm. Sci., 32, 653 (1991).
16. G. B. Barlin, S. J. Ireland, Aust. J. Chem., 41(11), 1727 (1998); Chem. Abstr., 114, 247197u (1991).
17. E. Bercin, S. Ersan, O. Atay and Ucucu, J. Fac. Pharm. Gaz. Univ., 7(1), 5 (1990); Chem. Abstr., 114, 247197u (1991).
18. R. R. Mohan, Indian Drugs., 29(3), 120 (1991); Chem. Abstr., 116, 106155h (1992).
19. B. S. Holla, S. Sreenivasa and B. Kaluraya, Boll. Chem. Farm., 133(8), 527 (1994).
20. G. Filli, H. Erdogan, C. Safak, U. Clays and R. Sunal, Arch. Pharm. (Weinheim.), 325(8), 537 (1992).
21. G. Shouhai and L. Fulin, Zhongguo Yaowce Huaxue Zazhi., 3(3), 175 (1993).
22. A. Papadaki-Valiraki, G. T. Ppaioannu, T. Siatra-Papastaikoudi, C. Sambani and H. Thoumou, Eut. J. Med. Chem., 24(4), 455 (1989).
23. Bo-Gil Choi, S. Hee-Kyoung, C. Byung-Ho, C. Sang-Vs and L. Cong-Ock, Arch. Pharmacol. Res., 17(6), 455 (1989).
24. B. M. Kotecka, G. B. Barlin, M. D. Estein and K. H. Rieckmann, Antimicrob. Agents. Chemother., 41(6), 1369 (1997); Chem. Abstr., 127, 90155x (1997).
25. G. Roman, E. Comanita and B. Comanita, Indian J. Heterocyclic Chem., 11, 89 (2001).
E. J. Stokes and Rdgw, Clinical Bacteriology, Edward Arnold.

Source of support: Nil; Conflict of interest: None declared