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# Pharmacological Potential of Mannich Bases of 1,3,4- Oxadiazole Bearing Benzimidazole and Piperazine Moieties

*Pramilla Sah **Chandra Prakash Gharu

* Organic Synthesis And Medicinal Chemistry Laboratory, Department Of Chemistry, Jai Narain University, Jodhpur, Rajasthan, India-342001

** Organic Synthesis And Medicinal Chemistry Laboratory, Department Of Chemistry, Jai Narain University, Jodhpur, Rajasthan, India-342001

**ABSTRACT**

*Mannich reaction was carried out on 2-mercapto-5-[1'-methyl-2'-phenyl-4''-(N-methyl piperazino)-benzimidazol-1'-yl-]-1,3,4-oxadiazole using formaldehyde and various primary and secondary amines in presence of acetone to obtain compounds (Va-Vi). The chemical structure of the newly synthesized compounds were verified on the basis of elemental and spectral analysis. Investigation of antimicrobial activity of the synthesized compounds was done by diffusion method using bacterial strains S.aureus , E.coli and K.pneumoniae and fungal strains A.flavus and A.niger. Tested compounds showed appreciable antifungal activity.*

**Keywords : 1,3,4-oxadiazole, Benzimidazole, Piperazine, Antimicrobial activity.**

## INTRODUCTION

Toxicity and resistance play an important role in drug development for treating diseases caused by microbes. Thus, there is still need for new classes of antimicrobial agents in the present era. Benzimidazole dithiocabamates (Tangeda & Garlapti, 2011) and other substituted benzimidazole derivatives (Saraf et al., 2011) have been reported to possess antimicrobial activity.

Some new 2-mercapto benzimidazoles (Uma Rani et al. 2011) and thiazolidine subsitituted benzimidazole derivatives have also shown to be bioactive (Sharma & Pathak, 2011)

A wide range of other biological activity like anthelmintic (Sugumaran & Ramanathan, 2011), anti tubercular of triazole incorporated benzimidazoles (Gowda et al. 2010) are also documented.Moreover substituted 1,3,4-oxadiazole derivatives have also been evaluated for antimicrobial activity (Bhardwaj et al. 2009, Fuloria et al. 2009; Yathirajan et al.2010, Chawla et al. 2010). However, anticancer (Kumar et al. 2009), *in vitro* anti proliferative activity (Zamid et al. 2009) and antimycoacterial activity of some oxadiazole subsitituted Mannich bases (Ali & Shaharyar, 2007) are some of the other activities reported by the above authors. Further, piperazine and its derivatives have their own importance in drug discovery and have inhibited the growth of certain microbes (Savaliya et al.2011, Joshi et al. 2012).

## MATERIALS AND METHODS

Melting points were determined in open capillary tubes in a 'Neolab' electrical apparatus and are uncorrected. FTIR was carried out on Schimadzu8101 spectrophotometer in KBr pellets. $^1$HNMR was recorded on a DPX 300 MHz Brucker spectrophotometer in $CDCl_3$.

2-phenyl-4'-(N-methyl piperazino)-benzimidazole (I) was synthesized by the known procedure (Sah &Gharu, 2012).

### Antimicrobial activity:

The antimicrobial activity of all the synthesized Mannich bases (Va-Vi) were examined *in-vitro* against different *S.aureus*, *E.coli, K.pneumonea* bacterial strains and fungal strains *Aspergillus niger* and *Aspergillus flavus* by measuring the zone of inhibition. The antimicrobial activity was performed by Agar well diffusion method at a concentration level of 250µg/ml and 500µg/mlfollowing the procedure reported earlier (Baueer et al., 1966, Barry et al., 1973). Streptomycin and Griseofulvin were used as the standard at a concentration level of 100 µg/ml. Nutrient agar was used as the culture media for antibacterial activity and PDA was used as the culture media for antifungal activity with DMF as control. Zone of inhibition was measured after 24 hrs incubation for antibacterial and 72 hrs for antifungal activityThe result of the antimicrobial activity are shown in Table No.3.

## RESULT AND DISCUSSION:

### IR and 1H NMR spectral interpretation

I.R. spectra of compound II gave a characterstic stretching vibration at 1710 cm$^{-1}$ confirming the presence of a carbonyl group part of an ester linkage. Subsequent reaction with hydrazine hydrate resulted in the formation of compound III which gave a slightly lower frequency signal

at 1645 cm$^{-1}$ and two new frequency modes at 3215 cm$^{-1}$ and 3400 cm$^{-1}$ respectively. The latter signals justified the presence of imino and amino groups. The hydrazide when further treated with carbon disulphide in alkaline ethanol underwent cyclisation yielding compound IV. The IR spectra showed significant frequencies at 1120 cm$^{-1}$, 1225 cm$^{-1}$, 1280 cm$^{-1}$ and 1380 cm$^{-1}$ which were identified as linkages of C-O-C, N-N=C, C=S and N-C=S indicating the formation of an oxadiazole ring and also presence of mercapto group. Compound IV was then subjected to Mannich reaction . Presence of a nitro group in derivatives Vf and Vi at 1525 cm$^{-1}$ and at 1530 cm$^{-1}$ in Vg and imino hydrogen at 3235 cm$^{-1}$ confirmed the formation of a Mannich base.

$^1$H NMR spectra of derivative II gave a triplet at δ 1.98 and a quartet at δ 2.34 integrating for three and two proton each. Such a pattern is indicative of the fact that an ethyl group is present. A downfield signal at δ 3.45 was observed integrating for two protons confirmed the presence of a methylene

group. Derivative III showed a broad upfield signal between δ 5.20-5.56 accounting for three protons, which were characterized as the imino and the amino protons. Cyclisation with $CS_2$ gave compound IV. The NMR spectra showed absence of a signal around this region but a new peak very downfield at δ 9.01 was observed, which was identified as an imino proton confirming that cyclisation had taken place. Further reaction with a secondary amine i.e. N-methyl piperazine gave compound Va. Distinct signal at δ 4.24 and δ 5.05 were visible which integrated for two protons each. These indicated the presence of methylene protons presented as N-$CH_2$-C and N-$CH_2$-N respectively, supporting the formation of the Mannich base. With a change in the nature of the amine as in derivative Ve two signals at δ 2.44 and δ 3.61 were observed again integrating for two protons characterized as the methylene protons. However now the linkages were identified as $CH_2$-N-$CH_2$ and $CH_2$-O-$CH_2$ respectively showing the presence of a morpholino ring. Similarly in other derivatives i.e. Vf, Vg, Vh, and Vi a downfield signal was visible between δ 9.08-9.14 indicating a change in the nature of the amines.

**Interpretation of Antimicrobial activity**

1,3,4- oxadiazoles incorporated with two bioactive nuclei i.e. the benzimidazole and a piperazinyl ring have shown high antibacterial action with all the derivatives inhibiting the

bacterial strains i.e. *E. coli, K. pneumoniae* and *S. aureus* except two derivative Vb and Vc to be inactive. Maximum inhibition was observed against all the three strains in Vg, Vh and Vi. However activity comparable to Streptomycin was visible against *K. pneumonia* by Vi at both the concentration. The other derivatives Va,Vd,Vg and Vh also inhibited *K. pneumonia* (13-19 mm). Against *S. aureus* Va, Vd, Ve and Vf were moderately active. Similar pattern was observed in compounds Va, Vd and Ve against *E. coli*. However derivatives Vf-Vi were active against this strain, with zone of inhibition being between 13-19 mm.

Maximum Antifungal activity was visible in Vb, Vc and Vf against *A. flavus*. Derivatives Va and Vd were also active. Lesser inhibition was observed in Ve, Vg, Vh and Vi. Against *A. niger* Va was the most active at both the concentrations, while Vb and Vc inhibited the growth of *A. niger*., but to a lesser extent. The remaining derivatives showed lesser inhibition.

The above data reveal that Vb and Vc showed similar activity i.e. same zone radii against *A. flavus*, while Va was more active against *A. niger* than *A. flavus*. This was however reversed in compound Vb. All the derivatives however did inhibit the growth of both the fungal strains.

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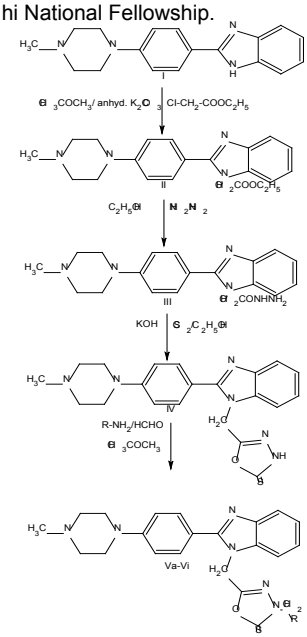

R= N-methyl piperazino, pyrrolino, piperidino, N-ethyl phenyl amino, morpholino, o-nitro aniline, 2,4 dinitro aniline, N-2-piridinyl amino, 2-methyl, 4-nitro aniline

**SCHEME**

**Table 1: Physical data of synthesized compounds**

| Compound code | Molecular Formula (Molecular weight) | Melting Point ( % Yield) | Analytical Data | |
|---|---|---|---|---|
| | | | % C Calcd. ( Found) | % N Calcd. ( Found) |
| II | $C_{22}H_{26}N_4O_2$ (410) | 182 (65) | 64.39 (64.42) | 13.66 (13.61) |
| III | $C_{20}H_{24}N_6O$ (364) | 177 (61) | 65.93 (65.98) | 23.08 (23.10) |
| IV | $C_{20}H_{22}N_6OS$ (406) | 184 (68) | 59.11 (59.15) | 20.69 (20.68) |
| Va | $C_{27}H_{34}N_8OS$ (518) | 200-204 (64) | 62.55 (62.52) | 21.62 (21.64) |
| Vb | $C_{26}H_{27}N_7OS$ (485) | 202-208 (62) | 64.32 (64.38) | 20.21 (20.24) |
| Vc | $C_{27}H_{33}N_7OS$ (503) | 190-142 (69) | 64.41 (64.39) | 19.48 (19.47) |
| Vd | $C_{30}H_{33}N_7OS$ (539) | 185-188 (68) | 66.79 (66.76) | 18.18 (18.20) |
| Ve | $C_{26}H_{31}N_7O_2S$ (505) | 191-193 (72) | 61.78 (61.76) | 19.41 (19.39) |
| Vf | $C_{28}H_{28}N_8O_3S$ (556) | 211-214 (66) | 60.43 (60.48) | 20.14 (20.18) |
| Vg | $C_{28}H_{27}N_9O_5S$ (601) | 185-188 (70) | 55.91 (55.98) | 20.97 (21.10) |
| Vh | $C_{28}H_{28}N_8OS$ (512) | 200-203 (74) | 63.28 (63.32) | 21.88 (21.84) |
| Vi | $C_{29}H_{30}N_8O_3S$ (570) | 172-174 (63) | 61.05 (61.14) | 19.65 (19.69) |

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