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Biological activities of (*E*)-*N*-(CH_3-substituted-phenyl)-1-phenylmethanimine: Evaluation of ortho-, meta- and para- substitution effects

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ABSTRACT

Schiff bases with ortho-, meta- and para-methyl substituents were synthesized by the condensation of appropriate aromatic amines (o-, m- and p-toluidine) with benzaldehyde. The structures of all the synthesized compounds were confirmed by analytical and spectral data. The sensitivity of the bacteria and fungi was evaluated by measuring the zones of inhibition exhibited by the microorganisms against the tested compounds using disk diffusion method. The results of the antimicrobial activity showed that the methyl group substituted at meta and para positions exhibited more antifungal and antibacterial activities compared to the ortho and unsubstituted derivatives. The results showed that antifungal and antibacterial activities are affected by the position of substituents in the aryl ring of the Schiff bases.

Keywords: Schiff bases, antibacterial activity, antifungal activity, substitution effect, toluidine.

INTRODUCTION

Schiff bases derived from benzaldehyde and derivatives of aniline have attracted attention recently because of their ease of preparation. Schiff bases are easily prepared by the condensation between aldehydes and primary amines. These compounds are also known as imines or azomethines. The lone pair on nitrogen atom of the azomethine group is of considerable chemical and biological importance and the azomethine linkage is responsible for biological activities [1-2]. The presence of hetero atoms such as oxygen and nitrogen are also helpful in the biological activity of the Schiff bases [3].

The biological activity of Schiff bases are vital in the design of antimicrobial agents. Schiff bases are known to exhibit a spectrum of potent activities including antibacterial [4-6], antifungal [7-8], anticancer [9-11], herbicidal [12-13], anti-tumor [14], anti-convulsant [15-16], anti-inflammatory [17-18], anti-hypertensive [19], anti-viral [20], anti-oxidant [21-22], anti-depressant and cytotoxic [23-24] activities.

Microbial activities of Schiff bases are affected by the type of substituent group at the aldehyde or amine fragment. Effects of substituent on antimicrobial activities have been investigated for Schiff bases derived from *O*-carboxymethylchitosan (CMCh) and para-substituted benzaldehydes [25], and salicylaldehyde and 2-aminophenol [26]. Structural activity relationship (SAR) of some Schiff bases derived form 5-chlorosalicyladehyde showed that hydrophilicity and aromaticity are important parameters for antimicrobial activity [3] and the electronic nature of the substituent (electron withdrawing and donating) affects the activity of Schiff bases significantly [27-29]. Schiff bases derived from salicylaldehyde and ortho-, meta- and para-COOH substituted aminobenzoic acids have been

investigated for the presence of antibacterial constituents. The *ortho* and *meta* substituted compounds exhibited better antibacterial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus feacalis* [30].

In this paper, Schiff base, (*E*)-*N*, 1-diphenylmethanimine and its ortho-, meta- and para-CH_3 substituted derivatives are investigated for the presence of antifungal and antibacterial constituents. The biological activities of the ortho, meta and para derivatives are compared.

MATERIALS AND METHODS

All chemicals used were of analytical grade (Sigma-Aldrich) and were used without further purification. The IR spectra were recorded on a Shimadzu FTIR-IR Prestige-21 (200VCE) spectrophotometer as KBr pellets between 4000-400 cm^{-1}. The C, H, N data were determined using a Perkin-Elmer instrument model 240B.

General procedure for preparation of Schiff bases

A solution of benzaldehyde (20 mmol) in 30 mL of ethanol was added to a solution of primary amine (20 mmol) in 30 mL of ethanol. Two drops of glacial acetic acid were added and the mixture was stirred under reflux for 6 hours. The precipitate formed was collected by filtration and recrystallized from ethanol and dried in a desiccator.

1: ***(E)-N, 1-diphenylmethanimine*** **(dPM)**

Colour: orange; Yield: (2.52 g) 70 %; IR (KBr cm^{-1}): 1604 (C=N, imine), 1495 (C-C, benzene), 3050 (C-H, benzene); Anal.calcd for $C_{13}H_{11}N$: C 86.15, H 6.12, N 7.73; found C 85.93, H 5.91, N 7.58.

2: ***(E)-N-(2-methylphenyl)-1-phenylmethanimine*** **(o-MPM)**

Colour: yellow; Yield: (3.08 g) 79 %; IR (KBr cm^{-1}): 1610 (C=N, imine), 1505 (C-C, benzene) 3058 (C-H, benzene), 3029 (C-H, methyl); Anal.calcd for $C_{14}H_{13}N$: C 86.12, H 6.71, N 7.17; found C 85.90, H 6.51, N 7.04.

3: ***(E)-N-(3-methylphenyl)-1-phenylmethanimine*** **(m-MPM)**

Colour: yellow; Yield: (3.05 g) 78 %; IR (KBr cm^{-1}): 1625 (C=N, imine), 1520 (C-C, benzene), 3076 (C-H, benzene), 3044 (C-H, methyl); Anal.calcd for $C_{14}H_{13}N$: C 86.12, H 6.71, N 7.17; found C 85.82, H 6.53, N 7.02.

4: ***(E)-N-(4-methylphenyl)-1-phenylmethanimine*** **(p-MPM)**

Colour: yellow orange; Yield: (3.12 g) 80 %; IR (KBr cm^{-1}): 1618 (C=N, imine), 1512 (C-C, benzene), 3062 (C-H, benzene), 3038 (C-H, methyl); Anal.calcd for $C_{14}H_{13}N$: C 86.12, H 6.71, N 7.17; found C 85.88, H 6.55, N 7.03.

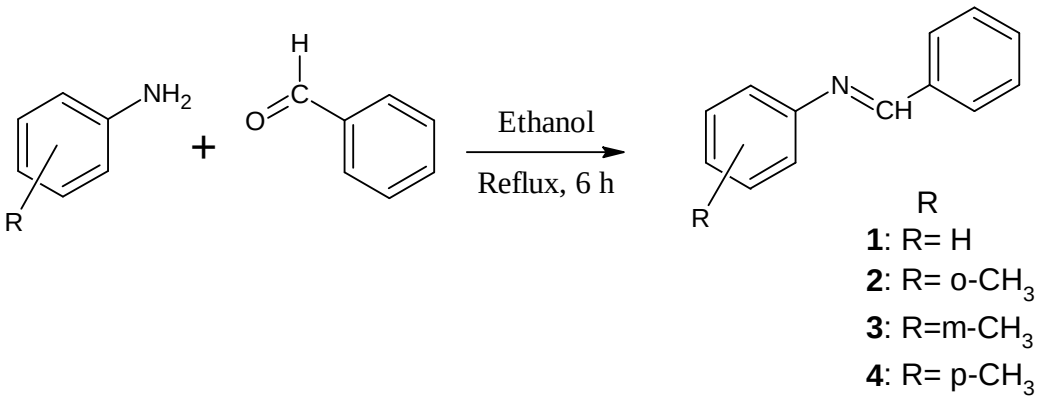
Antimicrobial studies

The *in vitro* antimicrobial activity of Schiff bases **1-4** against fungi, *Aspergillus niger, Aspergillus fumigatus, Candida albican* and *Trichophyton rubrum* and bacteria, *Shigella dysenteriae, Salmonella typhi, Staphylococcus aureus* and *Escherichia coli*, were studied using disk diffusion method [31]. The tested compounds were dissolved in DMSO to give 2 mg/mL solutions. 20 µL solutions of these were applied to sterile disks and placed on Nutrient Agar (NA) plates seeded with *Escherichia coli* and *Staphylococcus aureus*, Salmonella Shigella Agar (SSA) plates with *Salmonella typhi* and *Shigella dysenteriae*, and Sobouraud Dextrose Agar (SDA) plates with *Candida albican, Aspergillus niger, Aspergillus fumigatus* and *Trichophyton rubrum*. The plates were incubated at 37°C for 24 hours except SSA plates with incubation period of 48 hours. The inhibitory activity was measured (in mm) as the diameter of the observed zones of inhibition. Fluconazole and streptomycin were used as reference drugs against fungi and bacteria, respectively. DMSO was used as control and this showed no inhibition in the growth of fungi and bacteria.

RESULTS AND DISCUSSION

The Schiff bases were prepares as shown in scheme 1.

Scheme 1



The antifungal and antibacterial activities of Schiff bases **1-4** (dPM, o-MPM, m-MPM and p-MPM) were evaluated against fungi, *Aspergillus niger*, *Aspergillus fumigatus*, *Candida albican and Trichophyton rubrum* and bacteria, *Shigella dysenteriae*, *Salmonella typhi*, *Staphylococcus aureus* and *Escherichia coli* using disk diffusion method. All of the Schiff bases studied exhibited *in vitro* antifungal and antibacterial activities against the tested microorganisms. The results of antifungal and antibacterial activities are shown in Fig. 1-2.

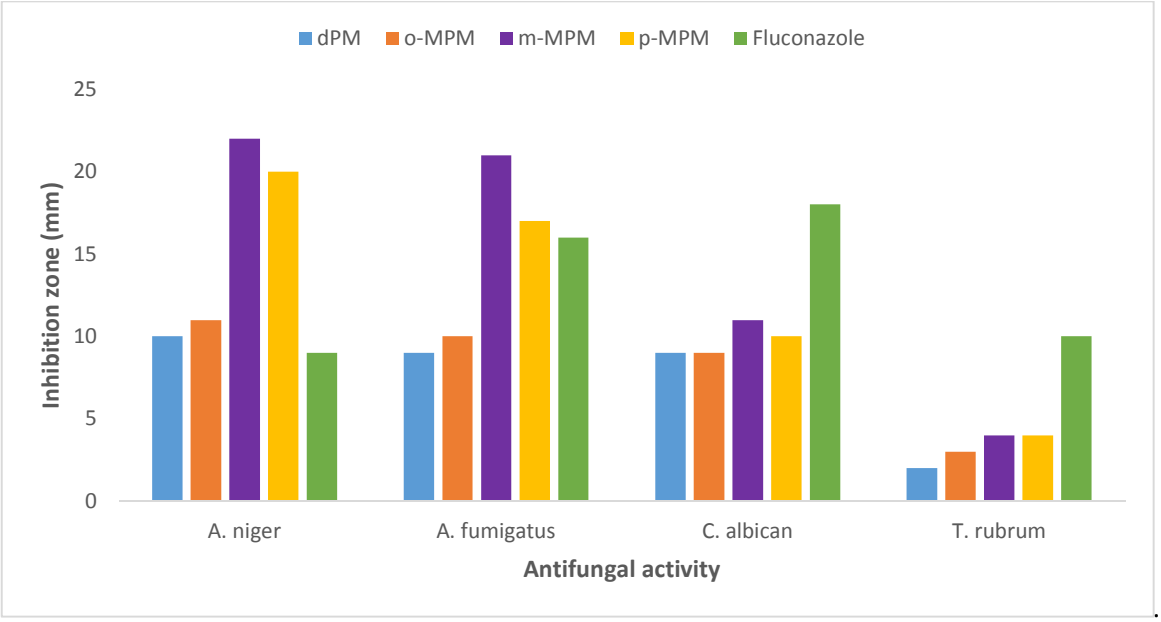


Fig. 1. Antifungal activity of Schiff base, (E)-N, 1-diphenylmethanimine and its *ortho*, *meta* and *para* CH_3-substituted derivatives

The results obtained show that the meta- and para- substituted Schiff bases were highly active against *A. niger* and *A. fumigatus* and all the bacteria with inhibition zones 16-22 mm but moderately active against *C. albican* with inhibition zone of 10-11 mm. The unsubstituted and ortho- substituted Schiff bases show moderate activities against all the microorganisms (inhibition zones 9-11 mm) except *T. rubrum* which was resistant to all the compounds tested (inhibition zones 2-4 mm). The order of potency based on the analysis of results can be given as *meta*>*para*>*ortho*.

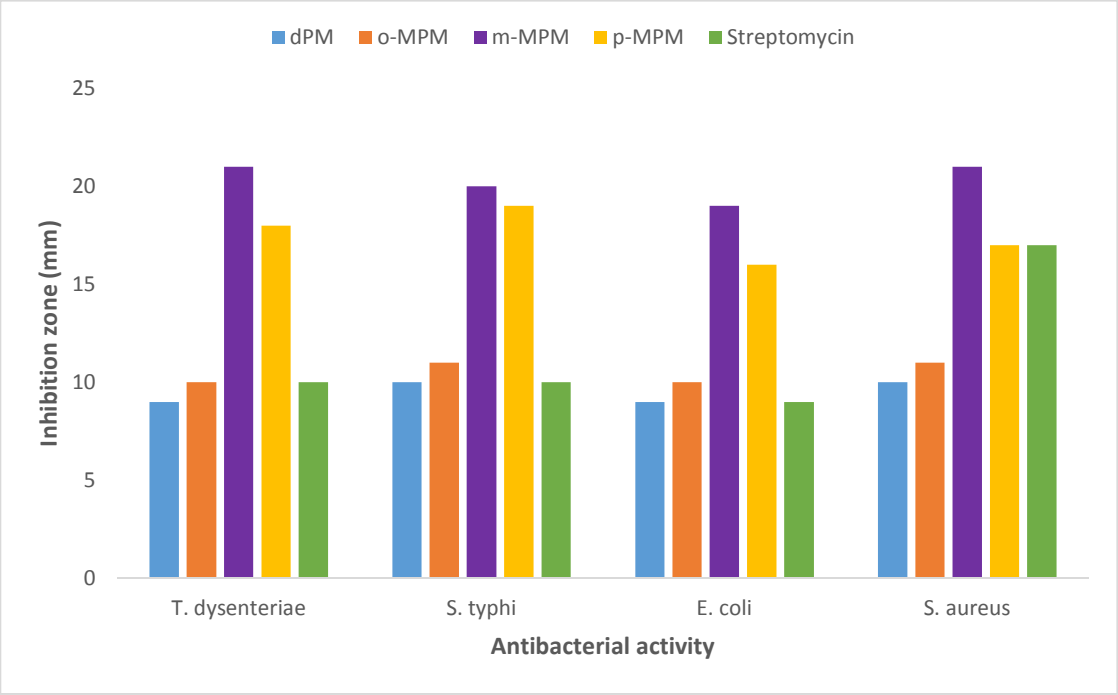


Fig. 1. Antibacterial activity of Schiff base, (E)-N, 1-diphenylmethanimine and its *ortho*, *meta* and *para* CH_3-substituted derivatives

Fluconazole, a well-known antifungal substance showed inhibition zones 9-10 mm for moderate activities and 11-12 mm for high activities whereas streptomycin exhibited moderate activities against all the tested bacteria with inhibition zones 9-10 mm.

CONCLUSION

Schiff base, (E)-N, 1-diphenylmethanimine and its ortho-, meta- and para- CH_3-substituted derivatives were screened for the presence of antifungal and antibacterial contituents against four fungi, *Aspergillus niger*, *Aspergillus fumigatus*, *Candida albican* and *Trichophyton rubrum* and four bacteria, *Shigella dysenteriae*, *Salmonella typhi*, *Staphylococcus aureus* and *Escherichia coli*. The compounds exhibited significant antimicrobial activities against all the microorganism except *T. rubrum* which was resistant. The *meta* and *para* derivatives showed higher activities compared to the *ortho* and unsubstituted compounds. The compounds constitute potent antibacterial and antifungal agents.

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