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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW SCHIFF BASES

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ABSTRACT

In present research work, four novel Schiff bases have been prepared from the combination of three new aldehydes with *p*-toluidine and one aldehyde with *p*-iodoaniline. The structures of these Schiff bases have been characterized by elemental analysis, Mass analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopic methods. All the synthesized Schiff bases possess the significant antimicrobial activities.

Key words: Mannich base, Quinoline aldehyde, Schiff bases, Biological activity.

INTRODUCTION

Schiff base was named after *Hugo Schiff*, who described the condensation between an aldehyde and an amine. Schiff bases are straightforward to prepare and thus, being versatile[1,2]. Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via cyclization ring closure and replacement reactions[3]. Moreover, Schiff bases are also known to have biological activities such as antimicrobial[4-7], antifungal[8,9], antitumor[10,11], and as herbicides[12]. Schiff bases have also been employed as ligands for complex formation of metal ions[13]. On the industrial scale, they have wide range of applications such as dyes and pigments[14]. Schiff bases are an important class of ligands in coordination chemistry and find extensive applications[15,16]. Keeping in view these facts, we decided to synthesize new Schiff bases, which were predicted to have useful biological activity.

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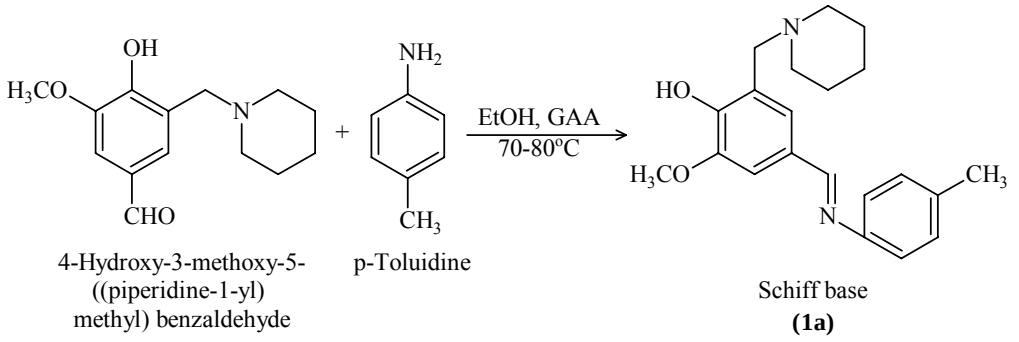
EXPERIMENTAL

Materials and method

All the chemicals used were of AR grade. Aldehyde was prepared in laboratory by well-known M*annich* reaction[17], and purified by usual separation methods. All melting points were uncorrected and taken in normal conditions. Elemental analyses were carried out on EURO EA-3000 RS-232. IR spectra were recorded on 8400 FTIR Simadzu Spectrometer, ^{1}H NMR spectra of the Schiff bases in DMSO were recorded on a Bruker Advance II 400 Spectrometer at room temperature using TMS as internal standard. Mass spectra of Schiff bases were recorded on GC-MS QP-2010 spectrometer.

Preparation of Schiff bases (1a-c)

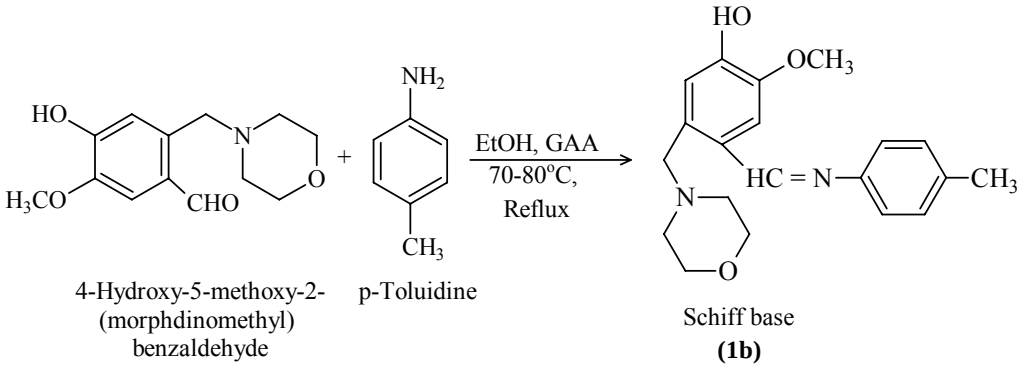
Schiff bases **(1a-c)** were prepared by addition of (0.01 mol, 20 mL ethanol) solution of Mannich aldehyde with (0.01 mol) solution of *p*-toluidine in absolute EtOH. Catalytic amount of glacial acetic acid was added to reaction mixture, followed by heating the mixture overnight on a water bath at 70^0-80^0C. After cooling, solid product was collected and purified by crystallization from hot ethanol.



4-Hydroxy-3-methoxy-5-((piperidine-1-yl) methyl) benzaldehyde

p-Toluidine

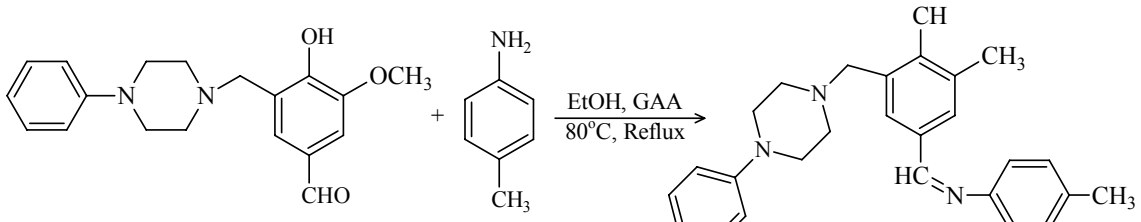
Schiff base **(1a)**



4-Hydroxy-5-methoxy-2-(morphdinomethyl) benzaldehyde

p-Toluidine

Schiff base **(1b)**



4-Hydroxy-3-methoxy-5-((4-phenylpip-erazin-1-yl) methyl) benzaldehyde

p-Toluidine

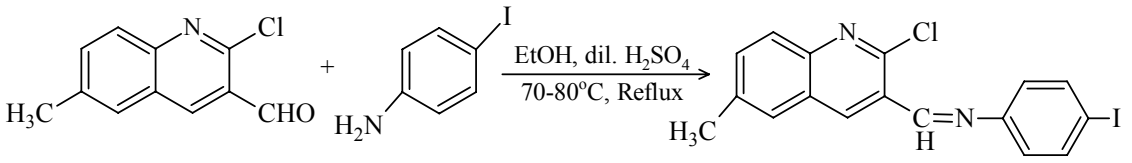
Schiff base

(1c)

GAA = Glacial acetic acid

Preparation of Schiff base (2a)

Schiff base was synthesized by using a simple synthetic approach. An ethanolic solution of *p*-iodoaniline (0.01 M) was added to the solution of 2-chloro-6-methylquinoline-3-carbaldehyde (0.01 M, 30 mL ethanol). Catalytic amount of dil. H_2SO_4 was added to reaction mixture. The resulting reaction mixture was refluxed for 8 hours. The progress of reaction was monitored by TLC (solvent system, benzene: acetone- 8 : 2). After completion of the reaction, the reaction mixture was poured over crushed ice. The separated solid product was filtered, washed with cold saturated sodium bisulphate solution and recrystallized with ethanol.



2-Chloro-6-methylquino-line-3-carbaldehyde

4-Iodoaniline

N-((2-chloro-6-methylquinolin-3-yl)methylene) -4-iodobenzenamine

(2a)

RESULTS AND DISCUSSION

4-((E)-(p-tolylimino) methyl)-2-methoxy-6-(piperidin-1-yl) methyl)phenol (1a)

The yield was 85% and m.p. 181°C; GCMS: m/z 338 (M^+) in agreement with the molecular formula $C_{21}H_{26}N_2O_2$; IR; (KBr, cm^{-1}); 3336 (Ar-OH, str.), 1606 (-HC=N, str.), 3057 (Ar-C-H, str.), 1172 (-OCH_3, str.), 2924 (-CH_3 str.); ^{1}H NMR (DMSO-d_6): δ (ppm) 2.9 (4H, piperidin ring proton), 3.23-3.33 (3H, dd, OCH_3), 9.21 (1 H, s, Ar-OH), 8.68 (1 H, d, -CH=N), 7.47 (2 H, d, Ar-H), 7.32 (2 H, d, Ar-H), 7.30 (1 H, s, Ar-H), 7.15 (3 H, m, Ar-H), 7.02 (1 H, d, Ar-H), 6.1 (1 H, d, Ar-H), 6.9 (1 H, m, Ar-H); 6.8 (1 H, s, Ar-H); ^{13}C NMR

(DMSO-d_6): δ171.2, 144.6, 134.9, 133.1, 131.7, 130.0, 128.8, 123.4, 107.7, 58.1, 54.4, 57.2, 27.8, 25.7; Anal. Calculation for: $C_{21}H_{26}N_2O_2$: C, 74.52%; H, 7.74%; N, 8.28%; O, 9.45%; Found: C, 74.49%; H, 7.72%; N, 8.25%; O, 9.42%.

4-((E)-(p-tolylimino)methyl)-2-methoxy-5-(morpholinomethyl)phenol (1b)

The yield was 78% and m.p.172 °C; GCMS: m/z 340 (M^+), in agreement with the molecular formula $C_{20}H_{24}N_2O_3$; IR; (KBr, cm^{-1}): 3336 (Ar-OH, str.); 1678 (-HC = N, str.), 3057 (Ar-C-H str),1290 (-O-CH_3, str.), 2924 (aliphatic, CH_3, str.); ^{1}H NMR (DMSO-d_6): δ (ppm) 2.89 (3 H, d, methyl), 9.27 (1 H, s, Ar-OH), 8.87 (1 H, m, HC = N), 3.69 (3 H, m, methoxy group proton), 2.8 (2 H, morpholine ring proton), 6.53 (1 H, m, Ar-H), 6.4 (2 H, d, Ar-H), 7.36-7.56 (3 H, m, Ar-H), 7.86 (2 H, m, Ar-H), 8.21 (1H, s, Ar-H); ^{13}C NMR (DMSO-d_6): δ162.2, 144.6, 134.9, 133.1, 131.7, 130.0, 128.8, 118.4, 117.7, 69.5, 56.8, 56.2, 29.7; Anal. Cal. For $C_{20}H_{24}N_2O_3$: C, 70.56%; H, 7.11%; N, 8.23%; O, 14.10%; Found: C, 74.49%; H, 7.72%; N, 8.25%; O, 9.42%.

4-((E)-(p-tolylimino) methyl)-2-methoxy-6-((4-phenylpiperazin-1-yl) methyl) phenol (1c)

The yield was 81% and m.p. 159.7°C; GCMS: m/z 415 (M^+), in agreement with the molecular formula $C_{26}H_{29}N_3O_2$; IR, (KBr, cm^{-1}): 3369 (Ar-OH), 1600 (-HC=N), 2929 (Ar-CH, str), 1271 (-O-CH_3), 2852 (CH_3, str.); ^{1}H NMR (DMSO-d_6): δ 3.31 (3H, m, -O-CH_3), 3.82 (4H, piperazine ring proton), 9.27 (1 H, s, Ar-OH), 8.75 (1 H, d, -CH=N), 6.58 (1 H, d, Ar-H), 6.77 (2 H, m, Ar-H), 6.81 (1 H, d, Ar-H), 7.55 (1 H, d, Ar-H), 7.78 (1 H, d, Ar-H), 7.88 (3 H, m, Ar-H); 8.1-8.12 (2 H, d, Ar-H); 8.61 (2 H-d-Ar-H); ^{13}C NMR (DMSO-d_6): δ171.2, 160.6, 150.2, 134.9, 133.1, 131.7, 130.0, 128.8, 123.4,122.5 113.7,51.8, 52.4, 57.9, 26.4; Anal. Calcd. for: $C_{26}H_{29}N_3O_2$: C, 75.15%; H, 7.03%; N, 10.11%; O, 7.70%; Found: C, 74.49%; H, 7.72%; N, 10.05%; O, 7.42%.

(E)-N-((2-chloro-6-methylquinolin-3-yl)methylene)-4-iodobenzenamine (2a)

The yield was 75% and m.p. 159.3 °C; GCMS: m/z 405.65 (M^+) in agreement with the molecular formula $C_{17}H_{12}ClIN_2$; IR; (KBr, cm^{-1}): 1683 (-HC = N), 3076 (Ar-C-H, str), 2825 (CH_3-Str.), 1487 (CH_3-bending); ^{1}H NMR (DMSO-d_6): δ3.45 (3H, s,-CH_3), 6.59 (2H, d, Ar-H), 7.01 (1 H, t, Ar-H), 7.19 (1 H, s, Ar-H), 7.4-7.51 (4 H, m, Ar-H), 7.78-7.9 (2 H, d, Ar-H), 8.67 (1H, s, -CH=N): ^{13}C-NMR (DMSO-d_6): δ28.2(-CH_3), 160.2(-CH=N), 123.8, 138.9, 134.9, 147.1, 124.7, 127.0, 128.8, 133.4, 142.7, 144.6,152; Anal. Cal. For $C_{17}H_{12}ClIN_2$: C, 50.21%; H, 2.97%; Cl, 8.72%; I, 31.21%; N, 6.89%; Found: C, 50.11%; H, 2.93%; Cl, 8.70%; I, 31.24%; N, 6.84%.

Antimicrobial activity

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by agar dilution method with four bacterial strains namely *Bacillus subtilis*, *Staphylococcus aureus* (Gram positive), *Escherichia coli* and *Salmonella paratyphi* (Gram negative) and two fungal strains namely *Candida albicans* and *Aspergillus niger* by agar dilution method.

The agar dilution method for determining antimicrobial susceptibility is a well established technique[18,19]. The antimicrobial agent is incorporated into the agar medium in each plate containing different concentrations of the synthesized organic compound. Standard antibacterial drug (ciprofloxacin) and antifungal drug (fluconazole) were used for comparison. Synthesized organic compounds were stored in air tight container or under desiccation at 40°C, if in powder form. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. Antimicrobial activity of Schiff bases are presented graphically in Figs. 1 and 2.

Antibectarial activity

The results of the antibacterial screening of the Schiff bases at diffrent concentration against all bacteria have been found. The results of antimicrobial screening indicate that compound **(1b)** show significant activity against *Escherichia coli*, *Bacillus subtilis* and *Salmona paratybhi* while compound **(2a)** were found to be more active against *Bacillus Subt*ilis, *E. coli* and *Salmona paratybhi* bacterial strains because of the presence of chloro group, which itself is active against microbes.

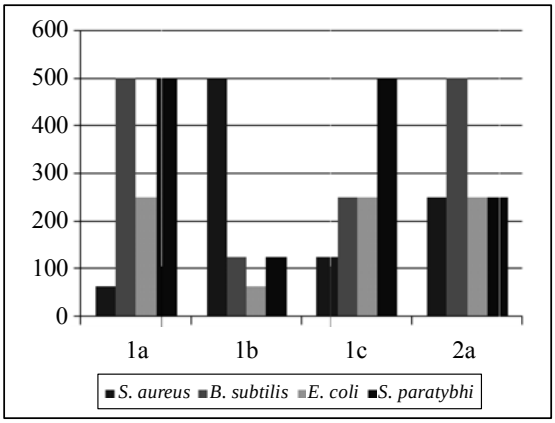


Fig. 1 : Comparison of MIC of synthesized Schiff bases against *S. aureus, B. subtilis, E. coli* and *Salmonella paratybhi B* with standard drugs

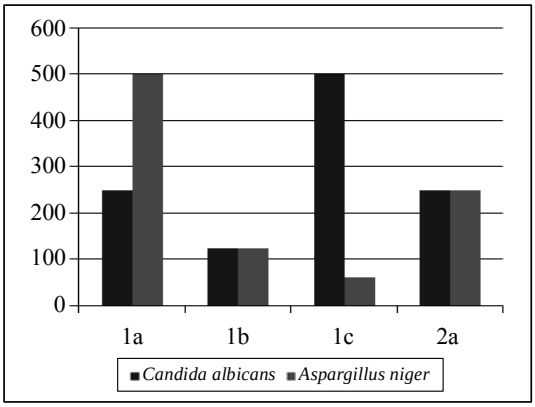


Fig. 2 : Comparison of MIC of synthesized Schiff bases against *Candida albicans and Aspargillus niger with standard drugs*

Antibacterial activity of these compounds show ascending order. When concentration was increased area of inhibited growth also increased. Antibacterial activity result are shown in Table 1.

Table 1: MIC against different bacteria (µg/mL)

Code	*S. aureus*	*B. subtilis*	*E. coli*	*S. paratybhi*
1a	500	500	250	500
1b	500	125	62.5	125
1c	125	250	250	500
2a	250	500	500	250

Antifungal activity

From the results obtained by the antifungal activity, it was found that the compound **(1b)** and **(2a)** are more active against all tested fungi. Compound **(1a)** is more active against *Candida albicans* and compound **(1c)** is more active against *Aspargillus Niger*. Antifungal activity results are shown in Table 2.

Table 2: MIC against different Fungi (µg/mL)

Code	*C. albicans*	*A. Niger*
1a	250	500
1b	125	125
1c	500	62.5
2a	250	250

CONCLUSION

The newly synthesized Schiff bases were characterized by several spectral techniques like Mass, IR, ^{1}H NMR, ^{13}C NMR, etc. All the structures of these compounds were in good agreement with spectral and analytical data. Newly suynthesized Schiff bases have shown the significant biological activity.

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