One pot conventional synthesis and biological activity of some novel double schiff bases

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ABSTRACT
In this work, we report the synthesis and biological activity of some new double Schiff bases derived from ethylene diamine with 2-acetylnaphthalene and 2-acetylpyridine and were characterised by using UV-Visible, FTIR, 1H NMR and 13C NMR spectroscopy studies. All of the synthesized compounds gave satisfactory analytical and spectroscopic data. We explored the antibacterial activity of the synthesized compounds against *Esherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and the results showed that the compounds exhibits appreciable activity against the selected bacterial strains. The investigation of antifungal screening of the compounds against *Aspergillus niger*, *Candida albicans* and *Cryptococcus* explored that the Schiff bases showed a significant activity against the selected fungal strains.

Keywords: Schiff bases; ethylene diamine; 2-acetylnaphthalene; 2-acetylpyridine; biological activity.

INTRODUCTION
A Schiff base (or azomethine) is a functional group that contains a carbon nitrogen double bond (C=N) with the nitrogen atom connected to an aryl or alkyl group but not to hydrogen [1]. Schiff bases are of the general formula R1R2C=NR3, where R3 is an aryl or alkyl group that makes the Schiff base a stable imine [2]. The importance of Schiff bases in organic synthesis has increased over the past few decades because they are among the most versatile organic synthetic intermediates. The wide use of antibiotics in man and animals and their extensive use in areas other than the treatment made many bacterial strains to become resistant to the available drugs. Various strategies have been worked out and tried upon to cope with the resistance problem and enhance the activity, or broaden the spectrum of drugs [3]. The Schiff base structure provides for a greater choice and flexibility and complexation with a metal element adds to stability and versatility of the molecule [4]. It has been suggested that the azomethine linkage might be responsible for the biological activities displayed by Schiff bases [5].

Schiff bases have been reported to posses the pharmacological activities such as anti-fungal [6], anti-microbial [7], anti-tumor [8], anti-malaria [9], anti-cancer [10], anti-tubercular [11], anti-viral [12], herbicidal [13], anti-bacterial [14], anti-convulsant [15], anti-inflammatory activities [16]. In addition some Schiff bases have been reported to exhibit anti-hypertensive [17], anti-HIV [18] and hypnotic activities [19]. They are also known to be neoplasms inhibitors [20] and as plant growth regulators [21]. They serve as models for biologically important species and find applications in biomimetic catalytic reactions [22]. Furthermore, Schiff bases are reported to show a variety of some other interesting biological actions, including anti-mouse hepatitis virus (MHV) [23], inhibition of simplex virus type I (HSV-1) [24], adenovirus type 5 (Ad 5) [25] and anti-mosquito larvae [26].

EXPERIMENTAL

Materials and Methods
All the chemicals and solvents used for the syntheses were of reagent grade and were obtained commercially from Merck Company. The UV spectra (λmax nm) of the synthesized Schiff bases were recorded on a Techcomp 8500 UV spectrometer. The infrared spectra (υ cm⁻¹) of the Schiff bases were recorded on a Shimadzu FT-IR spectrometer as KBr disks. 1H NMR and 13C NMR spectral measurements were carried out on a Jeol Spectroscopy Advance 500 MHz ultra shield spectrometer using DMSO – d6 as solvent and TMS as an internal reference.

General procedure for the synthesis of Compound A and B
Ethylene diamine (20 mmol) was added to a solution of 2-acetylnaphthalene (40 mmol) in absolute ethanol (60 mL)
or 2-acetylpyridine (40 mmol) in absolute ethanol (60 mL) in 1:2 ratio. The reaction mixture was refluxed at 140-150°C for 4-5 hours. The clear solution was left to overnight and the resulting yellow solid product was extracted with absolute ethanol. The solution was concentrated to dryness to afford the desired Schiff base. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel-G coated aluminium plates (Merks) and spots were visualized by exposing the dry plates in iodine vapours and exposing to UV light.

![Scheme 1: Synthetic route to Symmetrical Schiff bases](image1)

**Scheme 1: Synthetic route to Symmetrical Schiff bases**

**General procedure for the synthesis of Compound C**
Ethylenediamine (20 mmol) was added to a solution of 2-acetylnaphthalene (20 mmol) in absolute ethanol (30 mL) and 2-acetylpyridine (20 mmol) in absolute ethanol (30 mL) in 1:1:1 ratio. The reaction mixture was refluxed at 140-150°C for 4-5 hours and process as above.

![Scheme 2: Synthetic route to Unsymmetrical Schiff base](image2)

**Scheme 2: Synthetic route to Unsymmetrical Schiff base**

**Antibacterial and Antifungal studies**
The main characteristics of the medium were to support the growth of the organisms normally tested and not contain antagonist of antimicrobial activity. The medium must allow free diffusion of plant extract from the well. The sterilized medium was poured into a Petri dish in a uniform thickness and kept aside for solidification. Using sterilized swabs, even distribution of lawn culture was prepared using bacteria and fungi chosen in Muller Hinton Agar (MHA) plates and Sabouraud’s dextrose (SDA) agar, respectively [30].

**Compound A:** Yield: 75%; UV ($\lambda_{max}$ nm): 200, 285; IR (υ cm$^{-1}$): 725, 1450, 1620, 3059; $^1$H NMR (δ ppm): 1.13, 2.67, 3.89, 7.59-8.09, 8.28; $^{13}$C NMR (δ ppm): 14.04, 28.99, 58.59, 120.60, 122.47, 124.34, 136.90, 137.04, 158.05, 166.32.

**Compound B:** Yield: 73%; UV ($\lambda_{max}$ nm): 200, 285; IR (υ cm$^{-1}$): 771, 1450, 1637, 3059; $^1$H NMR (δ ppm): 1.25, 1.36, 2.31, 3.55, 3.83, 7.59-8.25, 8.56; $^{13}$C NMR (δ ppm): 14.31, 26.14, 28.98, 58.41, 120.06, 122.06, 124.55, 124.98, 136.90, 137.04, 148.74, 149.74, 158.13, 166.32.

**Compound C:** Yield: 70%; UV ($\lambda_{max}$ nm): 195, 275; IR (υ cm$^{-1}$): 748, 1448, 1620, 3059; $^1$H NMR (δ ppm): 1.25, 1.34, 1.77, 2.46, 2.67, 3.87, 7.50-8.09, 8.64; $^{13}$C NMR (δ ppm): 14.31, 28.70, 58.02, 120.77, 122.92, 124.55, 128.18, 137.07, 148.47, 148.78, 149.74, 157.30, 166.32, 167.01.
RESULTS AND DISCUSSION

A peak at 195-200 nm is observed which is due to \( \pi-\pi^* \) transition of C=N and benzene. A broad band at 275-285 nm is observed which is due to \( n-\pi^* \) transition.

A peak at 1606-1637 cm\(^{-1}\) corresponds to C=N stretching absorption \([27, 28, 29]\). A sharp peak at 3047-3059 cm\(^{-1}\) is characteristic of C-H stretching absorption of aromatic hydrocarbon. A band at 2895-2999 cm\(^{-1}\) is due to C-H stretching absorption in CH\(_2\) and CH\(_3\).

In the nuclear magnetic resonance spectra the signals of the respective protons of the compound A is verified on the basis of its chemical shifts, multiplicities and coupling constants. The spectra showed the aromatic proton at 7.5-8.0 ppm, the imine proton (N=C-H) at 8.2-8.6 ppm, methyl proton at 2.3-2.6 ppm and methylene proton at 3.8 ppm \([29]\).

The \(^{13}\)C NMR spectrum showed a signal at 137.05 ppm which indicates the presence of C=N group in the structure.

The \( \textit{in-vitro} \) antibacterial activities was evaluated against a series of bacterial strains namely (Gram positive: \textit{Staphylococcus aureus}; Gram negative: \textit{Escherichia coli}, \textit{Pseudomonas aeruginosa}) with the \textit{Ciprofloxacin} as standard reference broad antibiotic. The data of antibacterial activity of the reported compounds are given in Table (1 & 3) \([27, 28]\). The results showed that the tested double Schiff bases containing pyridine moiety are in general capable of inhibiting the growth of bacteria to an appreciable extent.

The \( \textit{in-vitro} \) antifungal screening effect of the synthesized double Schiff bases were evaluated against \textit{Aspergillus niger}, \textit{Candida albicans} and \textit{Cryptococcus} using \textit{Ketoconazole} as standard antifungal reference by well diffusion technique. The data of antifungal activity of the reported compounds are given in Table (2 & 4). The results showed that the tested double Schiff bases exhibited potent inhibitory activity against all the three fungal strains.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Organism (Bacteria)</th>
<th>Zone of Inhibition (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A (AN)</td>
</tr>
<tr>
<td>1.</td>
<td>\textit{E. coli}</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>\textit{Pseudomonas}</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>\textit{Aeruginosa}</td>
<td>5</td>
</tr>
<tr>
<td>4.</td>
<td>\textit{Staphylococcus}</td>
<td>14</td>
</tr>
<tr>
<td>5.</td>
<td>\textit{Aureus}</td>
<td>16</td>
</tr>
</tbody>
</table>

Table – 1: Antibacterial activity of compounds A, B & C
Key to symbols:
Highly active = + + + (inhibition zone > 14 mm).
Moderately active = + + (inhibition zone 10-14 mm)
Slightly active = + (inhibition zone 5-9 mm)
Inactive = - (inhibition zone < 5 mm)

Table – 2: Antibacterial activity of compounds A, B & C

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Organism (Fungus)</th>
<th>Zone of Inhibition (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A (AN)</td>
</tr>
<tr>
<td>1.</td>
<td><em>Aspergillus niger</em></td>
<td>12</td>
</tr>
<tr>
<td>2.</td>
<td><em>Candida albicans</em></td>
<td>8</td>
</tr>
<tr>
<td>3.</td>
<td><em>Cryptococcus</em></td>
<td>9</td>
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Table – 3: Effect of Schiff Bases on the Growth of Tested Bacteria

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Gram Negative</th>
<th>Gram Positive</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td><em>Esherichia</em></td>
<td><em>Pseudomonas</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Coli</em></td>
<td><em>aeruginosa</em></td>
</tr>
<tr>
<td>1.</td>
<td>Ciprofloxacin</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>2.</td>
<td>A (AN)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>B (AP)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>4.</td>
<td>C (ANAP)</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Table – 4: Effect of Schiff Bases on the Growth of Tested Fungus

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Fungus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>Aspergillus niger</em></td>
</tr>
<tr>
<td>1.</td>
<td>Ketoconazole</td>
<td>+++</td>
</tr>
<tr>
<td>2.</td>
<td>A (AN)</td>
<td>++</td>
</tr>
<tr>
<td>3.</td>
<td>B (AP)</td>
<td>+++</td>
</tr>
<tr>
<td>4.</td>
<td>C (ANAP)</td>
<td>+++</td>
</tr>
</tbody>
</table>

CONCLUSION
In summary, some novel double Schiff bases have been designed and prepared from ethylenediamine, 2-acetylnaphthalene and 2-acetylpyridine. The synthesized compounds were characterized by using UV-Visible, FT-IR, $^1$H NMR and $^{13}$C NMR spectra.
We explored the antibacterial activity of the synthesized compounds against *Esherichia coli*, *Staphylococcus aureus*
and *Pseudomonas aeruginosa* and the results showed that the compounds (B) and (C) exhibits appreciable activity against the selected bacterial strains. The investigation of antifungal screening of the compounds against *Aspergillus niger*, *Candida albicans* and *Cryptococcus* explored that the Schiff bases (A), (B) and (C) showed a significant activity against the selected fungal strains.

**REFERENCES**