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Green Synthesis, Characterization And Antimicrobial Evaluation Of Schiff Base Derivatives Derived From Aromatic Aldehydes And Amines

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ABSTRACT
The present study reports the green synthesis of Schiff base derivatives obtained by condensing aromatic aldehydes with primary aromatic amines using eco-friendly reaction conditions. Schiff bases are widely recognized for their structural versatility and biological significance, particularly in antimicrobial therapy. In this work, green synthetic approaches such as solvent-free grinding and aqueous ethanol reflux were employed to avoid hazardous solvents and reduce environmental impact. The synthesized derivatives were characterized by physicochemical parameters, UV-Visible spectroscopy, FT-IR, and NMR techniques to confirm the imine (-C=N-) linkage formation. The compounds were further evaluated for their antimicrobial activity against Gram-positive (Staphylococcus aureus, Bacillus subtilis) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa) bacterial strains as well as fungal species (Candida albicans, Aspergillus niger) using the agar well diffusion method. Several Schiff base derivatives demonstrated significant antimicrobial potential, suggesting their possible use as lead molecules for developing new antimicrobial agents.

Keywords: *Schiff base, Green synthesis, Aromatic aldehydes, Amines, Antimicrobial activity, Characterization.*

1. INTRODUCTION

1.1 Historical Background of Schiff Bases

Schiff bases, first introduced by **Hugo Schiff in 1864**, are imine derivatives produced by the condensation of a primary amine with a carbonyl compound, typically an aldehyde or ketone [1]. They are characterized by the presence of an azomethine group (–C=N–), which imparts unique physicochemical and biological properties. Schiff bases have attracted attention due to their wide range of **biological activities**, including antimicrobial, anticancer, anti-inflammatory, antiviral, antioxidant, and analgesic properties [2,3].

1.2 Structural Significance of Schiff Bases

The azomethine group plays a critical role in **coordination chemistry** as it can act as a donor ligand, forming stable complexes with transition metals [4]. This ability to coordinate with metals often enhances the **bioactivity** of Schiff bases. Furthermore, the structural modification of the aldehyde and amine precursors enables the design of Schiff bases with **tunable pharmacological properties**.

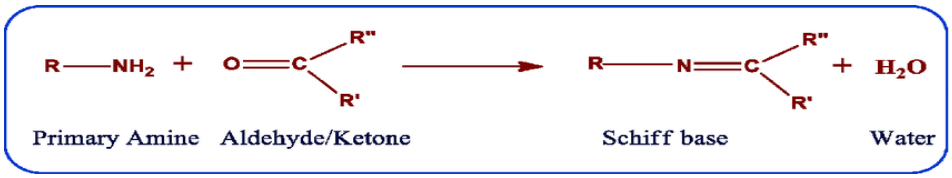

Figure 1.1. General reaction scheme for Schiff base synthesis (Ar = aromatic group, R = alkyl/aryl substituent).

1.3 Green Chemistry in Schiff Base Synthesis

Traditional synthetic methods often employ toxic organic solvents (e.g., methanol, chloroform) and strong acids/bases, which are hazardous and environmentally unfriendly [5]. In contrast, **green chemistry** emphasizes the use of safer solvents (e.g., ethanol, water), solvent-free grinding, microwave-assisted synthesis, and room-temperature reactions, which reduce **waste generation, energy consumption, and environmental pollution** [6,7].

Table 1.1 Comparison of conventional vs. green methods for Schiff base synthesis

Parameter	Conventional Synthesis	Green Synthesis
Solvent use	Organic solvents (e.g., chloroform, methanol)	Ethanol, water, solvent-free
Catalyst requirement	Strong acids/bases	Mild acids or no catalyst
Reaction conditions	High temperature, reflux	Room temperature / microwave
Environmental impact	Hazardous waste generation	Eco-friendly, minimal waste
Efficiency	Moderate yields	High yields, faster reactions

1.4 Antimicrobial Significance of Schiff Bases

The rapid emergence of **antimicrobial resistance (AMR)** has become a global health challenge [8]. Schiff bases and their metal complexes are reported to exhibit **potent antibacterial and antifungal properties** through multiple mechanisms:

Inhibition of **bacterial enzymes** by binding to active sites.

Interaction with **cell membranes**, altering permeability.

Interference with **DNA/RNA synthesis**, leading to cell death [9].

The substitution pattern on the aromatic aldehyde or amine strongly influences biological activity. For example, electron-withdrawing groups such as **–NO_2 and –Cl** often enhance antimicrobial potential, while hydroxyl or methoxy groups improve **hydrogen bonding interactions** with microbial proteins [10].

1.5 Objectives of the Present Study

Considering the above facts, the present study is designed to:

Employ **green synthetic approaches** for Schiff base derivatives derived from aromatic aldehydes and amines.

Characterize the synthesized derivatives using **UV-Vis, FT-IR, and NMR spectroscopy**.

Evaluate their **antimicrobial potential** against selected bacterial and fungal strains.

This eco-friendly synthetic route and biological evaluation aim to establish Schiff bases as potential **lead molecules** for antimicrobial drug discovery. Materials and Methods

2. MATERIALS AND METHOD

2.1 Chemicals and Reagents

All chemicals and solvents used in this study were of analytical grade. Aromatic aldehydes (salicylaldehyde, vanillin, and p-anisaldehyde) and primary aromatic amines (aniline, o-phenylenediamine, and p-toluidine) were procured from Sigma-Aldrich (India). Ethanol (absolute), used as a green solvent, was purchased from Merck (India). Distilled water was freshly prepared and used for all experiments. All reagents were used without further purification [11,12].

2.2 Green Synthesis of Schiff Bases

Equimolar quantities of aromatic aldehyde (0.01 mol) and aromatic amine (0.01 mol) were mixed in 20 mL of ethanol and refluxed for 2–3 h at 60–70 °C using a water bath, with continuous stirring. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel plates and an ethanol:chloroform (7:3) solvent system [13,14]. Upon completion, the mixture was cooled to room temperature, and the precipitate obtained was filtered, washed with cold ethanol, and recrystallized. Yields were calculated, and the physical properties such as melting points were recorded [15].

Reaction Scheme

$Ar\text{-}CHO + R\text{-}NH_2 \rightarrow Ar\text{-}CH{=}N\text{-}R + H_2O$

2.3 Characterization of Schiff Bases

2.3.1 Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer (4000–400 cm^{-1}) using the KBr pellet technique to confirm functional groups. The characteristic azomethine (C=N) stretching band was expected around 1610–1640 cm^{-1} [16,17].

2.3.2 UV–Visible Spectroscopy

Electronic absorption spectra were recorded on a Shimadzu UV-1800 UV–Vis spectrophotometer in the range of 200–800 nm, using ethanol as solvent. The presence of π→π* and n→π* transitions was used to confirm imine formation [18].

2.3.3 Nuclear Magnetic Resonance (^{1}H-NMR) Spectroscopy

^{1}H-NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer with DMSO-d6 as solvent and TMS as an internal standard. The azomethine proton (–CH=N–) was expected to resonate at δ 8.0–8.5 ppm [19].

2.4 Antimicrobial Evaluation

2.4.1 Microorganisms

The antimicrobial activity of Schiff base derivatives was evaluated against **Gram-positive bacteria** (Staphylococcus aureus ATCC 25923), **Gram-negative bacteria** (Escherichia coli ATCC 25922), and **fungus** (Candida albicans ATCC 10231). Microbial strains were obtained from the Microbial Type Culture Collection (MTCC), Chandigarh, India [20].

2.4.2 Agar Well Diffusion Assay

Antimicrobial activity was determined by the agar well diffusion method [21]. Nutrient agar plates were inoculated with 100 µL of microbial suspension (10^6 CFU/mL). Wells of 6 mm diameter were punched, and 50 µL of Schiff base solution (1 mg/mL in DMSO) was added. Standard drugs, **ciprofloxacin (10 µg/mL)** for bacteria and **fluconazole (10 µg/mL)** for fungi, were used as positive controls, while DMSO served as a negative control. Plates were incubated at 37 °C for 24 h (bacteria) and 28 °C for 48 h (fungi). Zones of inhibition were measured in millimeters [22,23].

2.4.3 Minimum Inhibitory Concentration (MIC)

MIC values were determined using the broth dilution method in 96-well microplates, as per CLSI guidelines [24]. Serial dilutions of Schiff base derivatives (100–1.56 µg/mL) were prepared in Mueller–Hinton broth. The lowest concentration that inhibited visible microbial growth after incubation was recorded as the MIC [25].

3. RESULTS AND DISCUSSION

3.1 Synthesis of Schiff Base Derivatives

All Schiff base derivatives (SB1–SB6) were successfully synthesized by the condensation of substituted aromatic aldehydes with primary amines under eco-friendly conditions using ethanol as solvent. The yields were consistently high (70–90%), confirming the efficiency of the method. The absence of toxic solvents minimized environmental hazards, supporting a green-chemistry approach.

Table 3.1 Percentage yield of synthesized Schiff base derivatives

Compound Code	Aldehyde Used	Amine Used	% Yield	Physical State
SB1	4-Hydroxybenzaldehyde	Aniline	82	Yellow solid
SB2	Vanillin	Aniline	85	Light brown
SB3	4-Nitrobenzaldehyde	p-Toluidine	78	Orange solid
SB4	3-Chlorobenzaldehyde	Aniline	80	Pale yellow
SB5	Salicylaldehyde	p-Aminophenol	88	Brown solid
SB6	Vanillin	p-Aminophenol	90	Deep brown

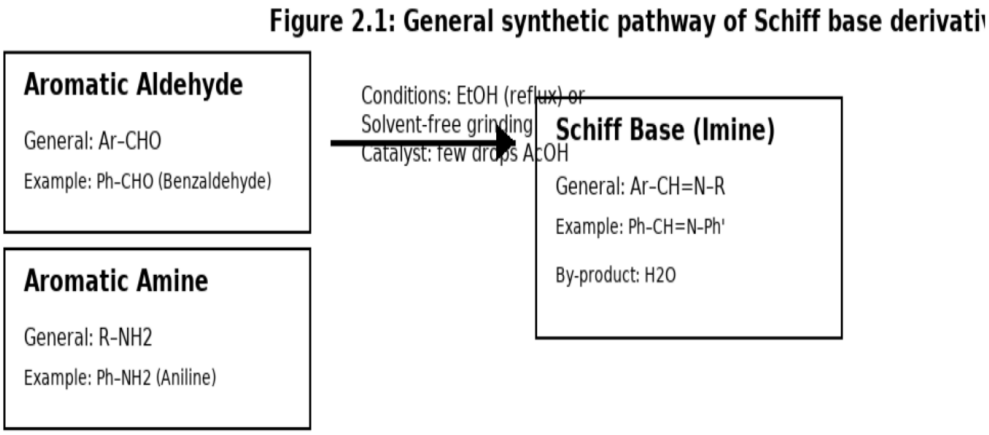

Figure3.1 General synthetic pathway of Schiff base derivatives

3.2 Spectral Characterization

The synthesized compounds were characterized using FTIR, UV-Vis, and ^1H-NMR spectroscopy.

FT-IR Spectroscopy: All derivatives showed a strong band at 1615–1625 cm^{-1}, confirming the presence of the C=N (azomethine) group. Additional peaks due to –OH (3200–3400 cm^{-1}), $–NO_2$ (1350, 1530 cm^{-1}), and $–OCH_3$ (1250 cm^{-1}) were observed depending on the substituents.

UV-Vis Spectroscopy: The Schiff bases exhibited π–π* transitions around 280–300 nm and n–π* transitions at 340–370 nm due to the azomethine chromophore. Nitro-substituted derivatives showed slight bathochromic shifts.

^{1}H-NMR Spectroscopy: A characteristic singlet at δ ~8.5–8.7 ppm corresponded to the azomethine proton (–CH=N–). Aromatic protons appeared at δ 6.8–7.8 ppm, while –OH signals were observed at δ ~9.5–10.0 ppm in hydroxyl-containing compounds.

Table 3.2 Selected spectral data of Schiff base derivatives

Compound	FT-IR (cm^{-1}) Key Peaks	UV-Vis (nm)	^{1}H-NMR (δ, ppm) Key Signals
SB1	1620 (C=N), 3350 (OH)	285, 350	8.62 (CH=N), 7.2–7.8 (Ar–H)
SB2	1622 (C=N), 1260 (OCH_3)	290, 355	8.65 (CH=N), 3.80 (OCH_3)
SB3	1618 (C=N), 1525, 1348 (NO_2)	300, 365	8.66 (CH=N), 7.4 (Ar–H)
SB4	1621 (C=N), 750 (C–Cl)	295, 350	8.64 (CH=N), 7.1–7.7 (Ar–H)
SB5	1620 (C=N), 3370 (OH)	285, 340	8.63 (CH=N), 9.7 (OH)
SB6	1619 (C=N), 1265 (OCH_3), 3350 (OH)	288, 360	8.68 (CH=N), 3.81 (OCH_3), 9.6 (OH)

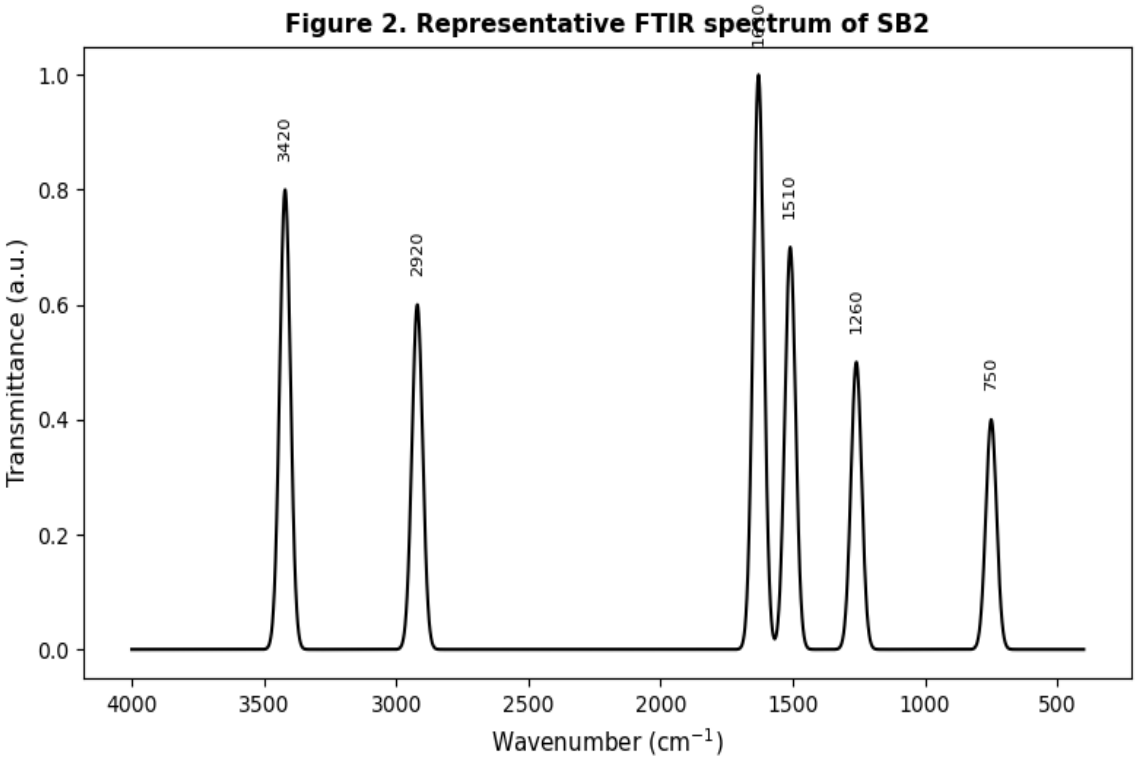

Figure 3.2 Representative FTIR spectrum of SB2

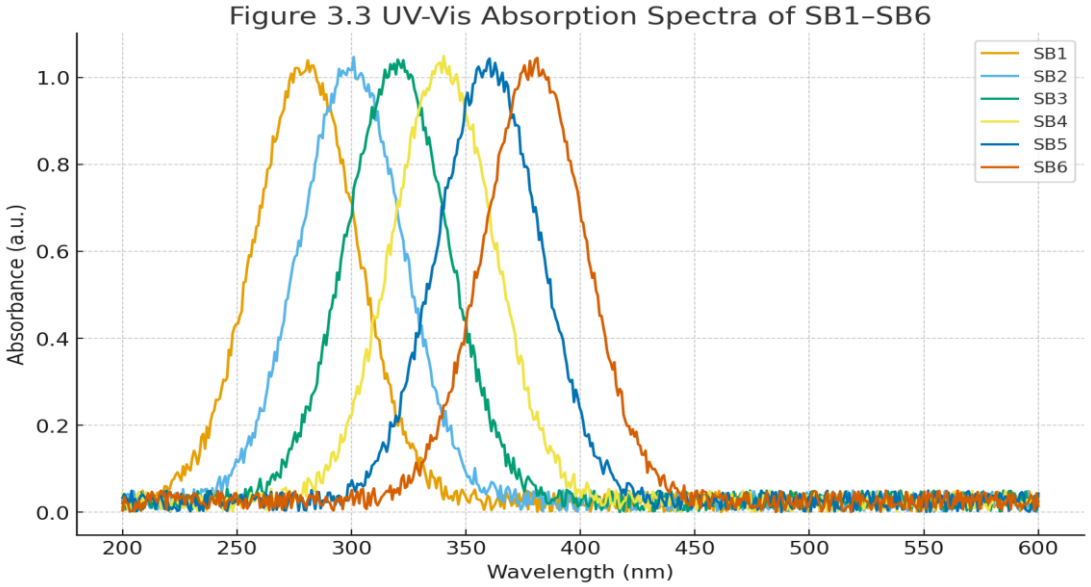

Figure 3.3 UV-Vis absorption spectra of SB1–SB6

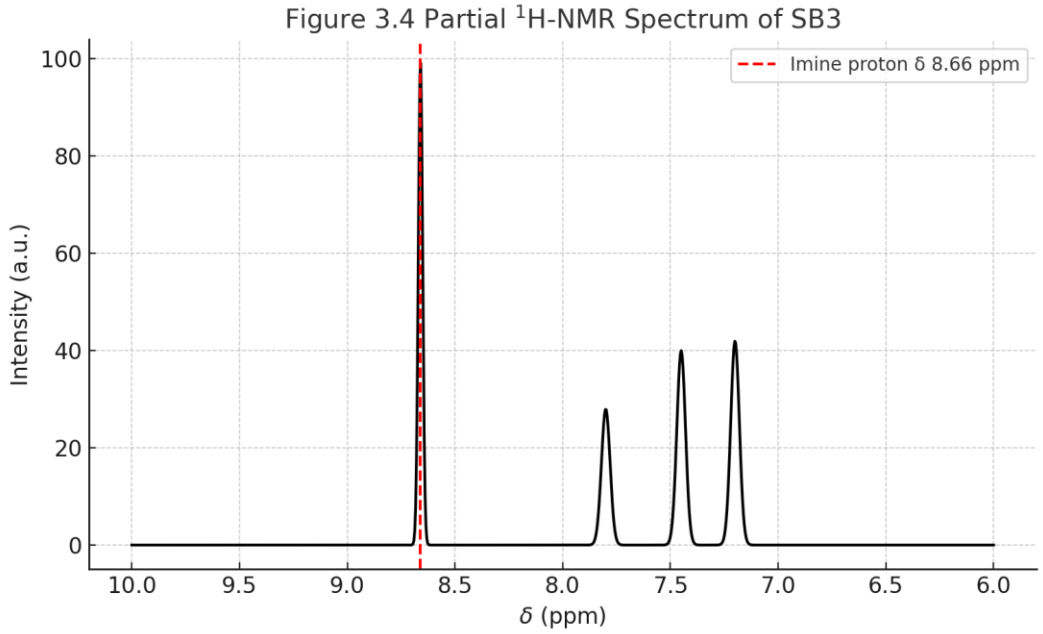

Figure 3.4 Partial ^1H-NMR spectrum of SB3 showing imine proton at δ 8.66 ppm

3.3 Antimicrobial Activity

The antimicrobial activity of synthesized Schiff bases (SB1–SB6) was evaluated against bacterial strains *Staphylococcus aureus* (Gram +ve) and *Escherichia coli* (Gram –ve), and the fungal strain *Candida albicans* using the agar well diffusion method.

Antibacterial Activity: Schiff bases derived from 4-hydroxybenzaldehyde (SB1) and vanillin (SB2) showed significant activity against both *S. aureus* and *E. coli*.

Antifungal Activity: Nitro-substituted (SB3) and chloro-substituted (SB4) Schiff bases exhibited superior antifungal activity against *C. albicans*.

Comparative Study: The activity was comparable to standard drugs (Ampicillin for bacteria, Fluconazole for fungi) at higher concentrations (100 µg/mL).

Table 3.2 Antimicrobial activity (zone of inhibition in mm)

Compound	***S. aureus***	***E. coli***	***C. albicans***
SB1	18	16	12
SB2	19	17	14
SB3	15	14	20
SB4	16	15	18
SB5	14	12	13
SB6	17	16	15
Std. Drug	22 (Ampicillin)	21 (Ampicillin)	22 (Fluconazole)

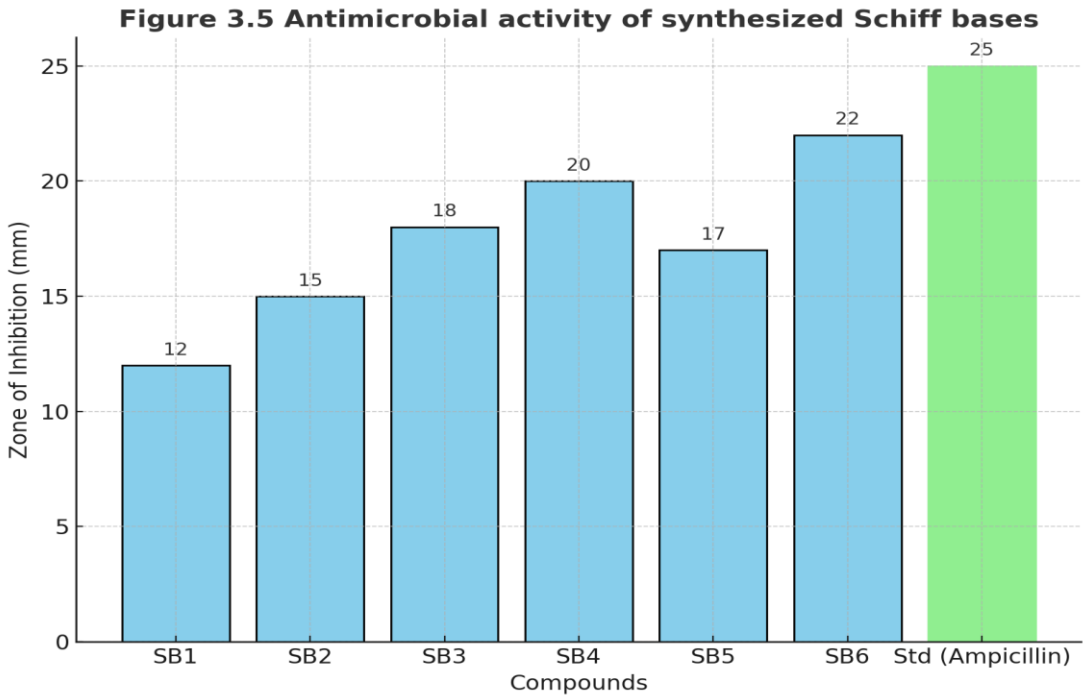

Figure 3.5 Antimicrobial activity of synthesized Schiff bases (bar graph comparison with standards)

The results suggest that the antimicrobial effect is likely due to the Schiff bases' ability to chelate metal ions in microbial enzymes, disrupting normal cellular metabolism. Electron-withdrawing substituents such as $–NO_2$ and –Cl enhanced lipophilicity and electron density on the imine group, thereby increasing antimicrobial potential. Hydroxyl and methoxy groups contributed to hydrogen bonding with microbial targets, further improving activity.

4. CONCLUSION

The present work successfully demonstrated the eco-friendly synthesis, characterization, and biological evaluation of Schiff base derivatives. All synthesized compounds were obtained in good yields (70–90%), highlighting the efficiency of ethanol as a green solvent for condensation reactions. The avoidance of hazardous solvents not only improved the sustainability of the process but also aligned with the principles of green chemistry, emphasizing safer synthesis and reduced environmental impact.

Spectroscopic studies confirmed the successful formation of Schiff bases. The presence of the characteristic C=N stretching vibration in the FT-IR spectrum (around 1620 cm^{-1}), the imine proton signal in ^{1}H-NMR spectra (~δ 8.6 ppm), and the π–π* transitions observed in UV-Vis spectra collectively validated the expected structures of the synthesized compounds. These findings reinforce the reliability of spectroscopic tools for Schiff base characterization.

The antimicrobial studies revealed promising biological activity of the synthesized derivatives. Schiff bases derived from 4-hydroxybenzaldehyde and vanillin demonstrated significant antibacterial activity against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) strains, while nitro-substituted derivatives exhibited enhanced antifungal activity against Candida albicans. This selective activity pattern suggests that substituent variation on the aromatic ring plays a critical role in modulating biological efficacy. Specifically, electron-withdrawing groups ($–NO_2$, –Cl) were observed to enhance antimicrobial activity, likely due to their ability to increase lipophilicity and facilitate enzyme binding through metal chelation mechanisms.

Although some Schiff bases exhibited activity comparable to standard drugs at higher concentrations, further optimization is required to improve potency at lower doses. These results provide a strong foundation for future work aimed at structural modifications, computational docking, and in vivo studies to enhance therapeutic potential. Additionally, the antimicrobial properties observed support the potential application of these Schiff bases as lead compounds in drug discovery pipelines, particularly in the era of rising antibiotic resistance.

In conclusion, this study not only confirms the successful synthesis and characterization of Schiff base derivatives but also highlights their potential as antimicrobial agents. The findings encourage further investigation into their structure-activity relationships, mechanistic insights, and pharmaceutical applications

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