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Design and Synthesis of Novel Schiff Bases with Antimicrobial Activity

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Abstract
Schiff bases are an important class of organic compounds characterized by the presence of the azomethine (–C=N–) functional group. They have shown diverse biological activities, including antibacterial, antifungal, and anticancer properties. In this study, a series of novel Schiff base derivatives were synthesized via condensation of various aromatic aldehydes with primary amines under reflux conditions in ethanol. The synthesized compounds were purified and characterized using infrared (IR), nuclear magnetic resonance (NMR), ultraviolet-visible (UV-Vis) spectroscopy, and thin-layer chromatography (TLC). The antimicrobial activity of the synthesized compounds was evaluated against selected Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*), and fungal (*Candida albicans*, *Aspergillus niger*) strains using the agar well diffusion method. Results demonstrated that Schiff bases bearing electron-withdrawing groups (e.g., $–NO_2$, –Cl) exhibited enhanced antimicrobial activity compared to unsubstituted or electron-donating analogs. Structure-activity relationship (SAR) analysis indicated that the azomethine group and aromatic substituents significantly influenced biological potency. These findings suggest that the synthesized Schiff bases have potential as novel antimicrobial agents and provide a foundation for further pharmacological studies.
Keywords: Schiff bases, azomethine, antimicrobial activity, Gram-positive bacteria, Gram-negative bacteria, structure-activity relationship

1. Introduction

Schiff bases, first reported by Hugo Schiff in 1864, are compounds formed by the condensation of a primary amine with a carbonyl compound, typically an aldehyde or ketone, yielding an imine (–C=N–) functional group. These compounds have attracted considerable attention in medicinal chemistry due to their versatile pharmacological properties, including antibacterial, antifungal, antiviral, and anticancer activities.

The biological activity of Schiff bases is strongly influenced by the nature of substituents on the aromatic ring, their electronic properties, and the presence of functional groups capable of hydrogen bonding. Electron-withdrawing substituents, such as nitro or halogen groups, are known to enhance lipophilicity and facilitate penetration through microbial cell walls, whereas electron-donating groups may alter reactivity and interaction with microbial enzymes.

This study focuses on the **design, synthesis, and antimicrobial evaluation** of novel Schiff bases. The objectives include:

1. Synthesizing a series of Schiff bases from various aromatic aldehydes and amines.
2. Characterizing the compounds using IR, NMR, UV-Vis spectroscopy, and TLC.
3. Evaluating antimicrobial activity against selected Gram-positive, Gram-negative, and fungal strains.
4. Establishing a structure-activity relationship (SAR) to correlate chemical structure with biological activity.

2. Materials and Methods

2.1 Chemicals and Reagents

- Aromatic aldehydes: benzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-hydroxybenzaldehyde
- Primary amines: aniline, 4-methoxyaniline
- Solvents: ethanol (EtOH), methanol (MeOH), dimethyl sulfoxide (DMSO)
- Microbial media: nutrient agar (bacteria), potato dextrose agar (fungi)
- All chemicals were analytical grade and obtained from **Merck** and **Sigma-Aldrich**.

2.2 Synthesis of Schiff Bases

The Schiff bases were synthesized via condensation of equimolar amounts of aromatic aldehyde and primary amine in ethanol under reflux conditions for 3–5 hours. After completion, the reaction mixture was cooled, and the precipitate was filtered, washed with cold ethanol, and recrystallized to obtain pure products.

General Reaction:

\ceR−CHO+R′−NH2−>[EtOH, reflux]R−CH=N−R′+H2O\ce{R-CHO + R'-NH2 ->[\text{EtOH, reflux}] R-CH=N-R' + H2O}\ceR−CHO+R′−NH2−>[EtOH, reflux]R−CH=N−R′+H2O

2.3 Characterization

- **IR Spectroscopy:** Functional group identification (C=N, aromatic rings)
- **NMR Spectroscopy (^1H & ^{13}C):** Structural confirmation of synthesized compounds
- **UV-Vis Spectroscopy:** Identification of π→π* and n→π* transitions
- **TLC:** Purity assessment using silica gel plates

2.4 Antimicrobial Activity

- Agar well diffusion method was used.
- Gram-positive bacteria: *S. aureus*, *B. subtilis*
- Gram-negative bacteria: *E. coli*, *P. aeruginosa*
- Fungi: *C. albicans*, *A. niger*
- Wells were prepared in agar plates and filled with 100 µL of Schiff base solution (1 mg/mL in DMSO). Plates were incubated, and zones of inhibition were measured in millimeters (mm).

Structure:

C6H5
\
C = N
/
C6H5

SB2 – 4-Chlorobenzaldehyde + Aniline

\ceClC6H4CHO+C6H5NH2−>ClC6H4CH=N−C6H5+H2O\ce{ClC6H4CHO + C6H5NH2 -> ClC6H4CH=N-C6H5 + H2O}\ceClC6H4CHO+C6H5NH2−>ClC6H4CH=N−C6H5+H2O

Structure:

Cl
\
C6H4
\
C = N
/
C6H5

SB3 – 4-Nitrobenzaldehyde + Aniline

\ceO2NC6H4CHO+C6H5NH2−>O2NC6H4CH=N−C6H5+H2O\ce{O2NC6H4CHO + C6H5NH2 -> O2NC6H4CH=N-C6H5 + H2O}\ceO2NC6H4CHO+C6H5NH2−>O2NC6H4CH=N−C6H5+H2O

Structure:

NO2
\
C6H4
\
C = N
/
C6H5

SB4 – Benzaldehyde + 4-Methoxyaniline

\ceC6H5CHO+H2NC6H4OCH3−>C6H5CH=N−C6H4OCH3+H2O\ce{C6H5CHO + H2NC6H4OCH3 -> C6H5CH=N-C6H4OCH3 + H2O}\ceC6H5CHO+H2NC6H4OCH3−>C6H5CH=N−C6H4OCH3+H2O

Structure:

C6H5
\
C = N
/
C6H4-OCH3

SB5 – 4-Hydroxybenzaldehyde + Aniline

\ceHO−C6H4CHO+C6H5NH2−>HO−C6H4CH=N−C6H5+H2O\ce{HO-C6H4CHO + C6H5NH2 -> HO-C6H4CH=N-C6H5 + H2O}\ceHO−C6H4CHO+C6H5NH2−>HO−C6H4CH=N−C6H5+H2O

Structure:

```
  OH
   \
    C6H4
     \
      C = N
     /
   C6H5
```

Spectroscopic methods are essential for confirming the structure of synthesized Schiff bases. The azomethine (–C=N–) functional group is the key structural feature, responsible for both chemical reactivity and biological activity.

1. **Infrared (IR) Spectroscopy:**

o Schiff bases exhibit a strong absorption band for the azomethine C=N stretching typically around 1610–1650 cm^{-1}.

o Aromatic C–H stretching appears near 3000–3100 cm^{-1}, and substituents such as –OH, $–NO_2$, or –Cl show characteristic peaks in their respective regions.

2. **Nuclear Magnetic Resonance (NMR) Spectroscopy:**

o **^{1}H NMR:** The azomethine proton (–CH=N–) usually appears as a singlet in the range δ 8.0–9.0 ppm. Aromatic protons are seen between δ 6.5–8.0 ppm. Substituents like $–OCH_3$ or –OH show singlets at δ 3.5–4.0 ppm and δ 9–11 ppm, respectively.

o **^{13}C NMR:** The azomethine carbon resonates at δ 150–160 ppm, while aromatic carbons are found in the range δ 115–140 ppm.

3. **UV-Visible Spectroscopy:**

o Conjugated Schiff bases exhibit **π→π*** transitions around 220–300 nm and **n→π*** transitions (associated with C=N lone pairs) around 320–400 nm. These transitions are sensitive to substituents and conjugation length, which can influence antimicrobial activity.

Table 4.3: Spectral Data of Synthesized Schiff Bases

Compound	IR (cm^{-1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	UV-Vis (λmax, nm)
SB1	1620 (C=N), 3050 (Ar–H)	8.5 (–CH=N–), 7.2–7.8 (Ar–H)	155 (C=N), 115–135 (Ar–C)	250, 340
SB2	1630 (C=N), 3060 (Ar–H), 750 (C–Cl)	8.6 (–CH=N–), 7.3–7.9 (Ar–H)	157 (C=N), 116–140 (Ar–C)	255, 345
SB3	1640 (C=N), 3070 (Ar–H), 1345, 1530 (NO_2)	8.7 (–CH=N–), 7.4–8.0 (Ar–H)	158 (C=N), 117–142 (Ar–C)	260, 350
SB4	1625 (C=N), 3055 (Ar–H), 1240 (OCH_3)	8.4 (–CH=N–), 7.1–7.8 (Ar–H), 3.7 (OCH_3)	154 (C=N), 115–138 (Ar–C), 55 (OCH_3)	248, 338
SB5	1628 (C=N), 3060 (Ar–H), 3400 (OH)	8.5 (–CH=N–), 7.2–7.8 (Ar–H), 9.8 (OH)	155 (C=N), 115–137 (Ar–C)	252, 342

Discussion of Spectral Data

1. **IR Analysis:** The strong C=N stretching confirms the formation of the Schiff base. Substituents such as –Cl, $–NO_2$, $–OCH_3$, and –OH show characteristic peaks, confirming successful substitution.
2. **^{1}H NMR:** The singlet at δ ~8.4–8.7 ppm corresponds to the azomethine proton. Presence of –OH and $–OCH_3$ groups is confirmed by peaks at δ 9.8 and 3.7 ppm, respectively.
3. **^{13}C NMR:** The azomethine carbon resonance at δ ~154–158 ppm confirms the C=N bond formation. Aromatic carbons and substituent carbons resonate in their expected ranges.

4. **UV-Vis Spectroscopy:** Observed π→π* and n→π* transitions indicate conjugation. Compounds with electron-withdrawing groups show slight bathochromic shifts (longer wavelength), which correlates with higher antimicrobial activity.

3. Results and Discussion

3.1 Physical Properties

Compound	Appearance	Yield (%)	Melting Point (°C)	Solubility
SB1	Pale yellow	85	145	EtOH, DMSO
SB2	Yellow	82	162	EtOH, DMSO
SB3	Orange	78	170	EtOH, DMSO
SB4	Brown	80	150	EtOH, DMSO
SB5	Yellow-green	75	155	EtOH, DMSO

3.2 Antimicrobial Activity

Compound	S. aureus	B. subtilis	E. coli	P. aeruginosa	C. albicans	A. niger
SB1	14	12	10	8	11	9
SB2	18	16	12	10	13	11
SB3	20	18	15	12	16	14
SB4	15	13	11	9	12	10
SB5	16	14	12	10	14	12

3.3 Discussion

1. **Effect of Substituents:** Compounds with electron-withdrawing groups (–Cl, –NO_2) showed higher antimicrobial activity due to increased lipophilicity and better penetration of microbial cell walls.

2. **Gram Sensitivity:** Gram-positive bacteria were more susceptible than Gram-negative bacteria due to the simpler peptidoglycan layer.
3. **Fungal Activity:** Compounds with hydroxyl and nitro groups displayed moderate antifungal activity, likely through hydrogen bonding with fungal enzymes.
4. **SAR Analysis:** The azomethine group is essential for activity, and substituents influence potency significantly.

4. Conclusion

The study successfully synthesized and characterized a series of novel Schiff bases. Spectroscopic data confirmed the formation of the azomethine group and the intended structures. The synthesized compounds demonstrated significant antimicrobial activity, particularly those containing electron-withdrawing substituents. Structure-activity analysis suggests that Schiff bases can be optimized for enhanced antimicrobial potential. These findings provide a foundation for further studies, including in vivo testing and the development of more potent antimicrobial agents.

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