Schiff Base Derivatives: Synthesis, Characterisation, and Antimicrobial Potential – A Comprehensive Review

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Abstract*—The growing emergence of multidrug-resistant pathogens has renewed scientific interest in chemical scaffolds capable of yielding novel antimicrobial leads. Schiff bases, a class of compounds characterised by the azomethine (>C=N–) linkage, have re-emerged as one of the most versatile templates in medicinal and coordination chemistry. The present review consolidates the current understanding of Schiff base derivatives, with particular emphasis on their synthetic strategies, spectroscopic and physicochemical characterisation, and antimicrobial profiles against clinically relevant bacterial and fungal strains. Conventional condensation between primary amines and carbonyl compounds, alongside contemporary green protocols such as microwave-assisted, ultrasound-assisted and solvent-free grinding methods, are critically compared. Structural elucidation strategies employing UV–visible, FT-IR, ^{1}H- and ^{13}C-NMR, and mass spectrometry are summarised. The antimicrobial behaviour of representative Schiff bases and their metal complexes is interpreted through chelation theory, modulation of lipophilicity, and disruption of microbial enzymatic systems. Evidence from recent literature confirms that suitable substitution at the azomethine carbon and on the aromatic rings significantly improves activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, and Aspergillus niger. The review concludes that Schiff bases constitute a privileged scaffold whose rational design may deliver next-generation antimicrobial agents.

***Index Terms*—Schiff base, azomethine, condensation, antimicrobial, chelation, drug resistance, green synthesis.**

I. INTRODUCTION

Antimicrobial resistance has been identified by the World Health Organisation as one of the foremost public-health challenges of the twenty-first century. Continuous misuse of broad-spectrum antibiotics has accelerated the evolution of resistant strains, forcing medicinal chemists

to revisit classical scaffolds in pursuit of new chemical entities. Among such scaffolds, the imine or azomethine functionality occupies a central position, and the compounds containing this moiety are collectively known as Schiff bases.

Schiff bases were first reported by the German chemist Hugo Schiff in 1864, who described the product obtained by condensing a primary amine with a carbonyl compound. The general structure can be represented as $R_1R_2C=N–R_3$, where R_3 is an alkyl or aryl group but not hydrogen. The lone pair of electrons present on the sp^2-hybridised nitrogen confers an exceptional ability to coordinate with transition metals and to interact with biological macromolecules, which explains the broad pharmacological spectrum reported for this family.

In recent decades, Schiff bases and their metal complexes have been investigated for antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, antioxidant and antimalarial activities. The present review aims to provide a critical and updated synthesis of the literature concerning the preparation, characterisation and antimicrobial evaluation of Schiff base derivatives, while highlighting structure–activity relationships and prospects for rational drug design.

II. CHEMISTRY OF SCHIFF BASES

2.1 Definition and General Structure

A Schiff base is a compound bearing the functional group >C=N–R, formed by the condensation of a primary amine with an aldehyde or ketone followed by elimination of one molecule of water. Aromatic aldehydes are preferred because of effective conjugation, which stabilises the azomethine linkage, whereas aliphatic aldehydes tend to undergo tautomeric rearrangement or polymerisation.

2.2 Classification

Schiff bases are classified based on the number of azomethine groups (mono-, di-, tri- and tetradentate), the nature of the substituents (aliphatic, aromatic or heterocyclic) and the presence of additional donor atoms such as oxygen, sulphur or nitrogen. Tridentate and tetradentate Schiff bases bearing ONO, ONN, NNO or N_2O_2 donor sets are particularly valued in coordination chemistry because they form stable chelates with transition metal ions.

2.3 Reaction Mechanism

The formation of a Schiff base proceeds via nucleophilic addition of the amine to the carbonyl carbon, producing a tetrahedral carbinolamine intermediate. Subsequent acid-catalysed dehydration furnishes the imine. The reaction is reversible and is generally favoured at a slightly acidic pH (4–5), where the carbonyl is sufficiently protonated for nucleophilic attack while the amine remains nucleophilic.

III. METHODS OF SYNTHESIS

3.1 Conventional Condensation

The classical preparation involves refluxing equimolar quantities of a primary amine and an aromatic aldehyde in ethanol or methanol, often with a catalytic amount of glacial acetic acid. After completion, monitored by thin-layer chromatography, the crystalline product is filtered, washed with cold solvent and recrystallised from ethanol.

3.2 Green and Energy-Efficient Protocols

- Microwave-assisted synthesis reduces reaction time from hours to minutes and improves yields through uniform dielectric heating.
- Ultrasound-assisted synthesis: cavitation enhances mass transfer, enabling reactions at ambient temperature.
- Solvent-free grinding (mechanochemistry): the reactants are ground in a mortar with a few drops of acid catalyst, eliminating organic solvents.
- Ionic liquid and deep eutectic solvent-mediated synthesis: provide recyclable green media.
- Water-mediated synthesis exploits the hydrophobic effect to drive imine formation while permitting easy product isolation.

These methods adhere to the principles of green chemistry and have been shown to deliver higher-purity products with shorter reaction times relative to conventional reflux methods.

IV. CHARACTERISATION TECHNIQUES

Reliable structural confirmation of Schiff bases is essential before any biological evaluation. The following techniques are routinely employed:

- Physical characterisation: melting point, colour, solubility profile and recrystallisation yield.
- UV–visible spectroscopy: characteristic $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the C=N chromophore is observed between 270 and 380 nm.
- FT-IR spectroscopy: a strong absorption band in the region 1600–1640 cm^{-1} confirms the azomethine stretch, while the disappearance of the carbonyl stretch (~1700 cm^{-1}) and the amine band (~3400 cm^{-1}) corroborates condensation.
- ^{1}H-NMR spectroscopy: the azomethine proton (HC=N) typically resonates as a singlet between 8.3 and 9.0 ppm.
- ^{13}C-NMR spectroscopy: the imine carbon appears between 155 and 165 ppm.
- Mass spectrometry provides a molecular ion peak consistent with the proposed structure and supports purity assessment.
- Elemental analysis (CHN): validates the empirical formula within acceptable deviation (±0.4 %).
- Powder X-ray diffraction and thermal analysis (TGA/DSC) are additionally employed for metal complexes.

V. ANTIMICROBIAL AGENTS: BRIEF BACKGROUND

Antimicrobial agents are substances that inhibit growth or destroy microorganisms, including bacteria, fungi, viruses and protozoa. On the basis of mode of action, they are classified as cell-wall inhibitors, protein-synthesis inhibitors, nucleic-acid synthesis inhibitors, membrane disruptors and metabolic-pathway inhibitors. The continual emergence of resistance mechanisms such as enzymatic inactivation (β-lactamases), efflux pumps, target modification and biofilm formation has narrowed therapeutic options and reinforced the need for new molecular templates.

VI. ANTIMICROBIAL ACTIVITY OF SCHIFF BASE DERIVATIVES

6.1 Rationale

The biological activity of Schiff bases is attributed primarily to the azomethine nitrogen, which can form hydrogen bonds with active sites of enzymes and can coordinate to essential metal centres in microbial metalloenzymes. According to Tweedy's chelation theory, complexation reduces the polarity of the metal ion through partial sharing of its positive charge with donor groups, thereby increasing lipophilicity. Enhanced lipophilicity facilitates penetration through the lipid bilayer of microbial membranes and disrupts vital cellular processes.

6.2 Activity Against Bacteria

Numerous Schiff bases derived from salicylaldehyde, 4-hydroxybenzaldehyde, isatin, vanillin and pyridine-2-carbaldehyde have shown inhibitory activity against Gram-positive organisms (Staphylococcus aureus, Bacillus subtilis) and Gram-negative organisms (Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae). Electron-withdrawing substituents such as –NO_2, –Cl and –Br on the aromatic ring generally enhance activity, whereas bulky alkyl groups tend to reduce it owing to steric hindrance during target binding.

6.3 Activity Against Fungi

Antifungal screening of Schiff bases against Candida albicans, Aspergillus niger and Aspergillus flavus has revealed appreciable inhibition zones comparable to standard drugs such as fluconazole and ketoconazole. Heterocyclic Schiff bases incorporating thiazole, triazole and benzimidazole moieties exhibit pronounced antifungal action through interference with ergosterol biosynthesis.

6.4 Role of Metal Complexation

Coordination of Schiff bases with Cu, Co, Ni, Zn and Mn ions frequently yields complexes whose antimicrobial potency exceeds that of the free ligand. Copper and zinc complexes are the most extensively studied because of their favourable redox behaviour and relatively low mammalian toxicity.

VII. EVALUATION METHODS

The in vitro antimicrobial efficacy of Schiff base derivatives is routinely assessed by the following techniques:

- Agar well diffusion method – measurement of zone of inhibition (mm).
- Disc diffusion method (Kirby–Bauer) – standardised for clinical isolates.
- Broth dilution methods – determination of Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal/Fungicidal Concentration (MBC/MFC).
- Time-kill kinetic studies – evaluation of bactericidal versus bacteriostatic behaviour.
- Biofilm inhibition assays – using crystal violet staining.

Statistical validation of results is generally performed by one-way analysis of variance (ANOVA) followed by post-hoc tests, with data expressed as mean ± standard deviation of triplicate experiments.

VIII. STRUCTURE–ACTIVITY RELATIONSHIP

- Presence of an intact azomethine (–HC=N–) linkage is essential for activity.
- Hydroxyl groups ortho to the imine carbon enable additional intramolecular hydrogen bonding and metal chelation, enhancing activity.
- Electron-withdrawing groups (–NO_2, –Cl, –Br, –CF_3) increase antimicrobial potency by reducing electron density at the imine and improving membrane penetration.
- Heterocyclic substituents (thiazole, triazole, benzimidazole, pyridine) provide additional pharmacophoric features and improve selectivity.
- Suitable lipophilicity (logP between 2 and 5) ensures optimum penetration without compromising solubility.

IX. DISCUSSION

The cumulative evidence collected from the studies surveyed demonstrates that Schiff bases constitute a privileged structural class for the design of new antimicrobial agents. Their synthetic accessibility, structural diversity and the ease with which substituents can be modulated allow medicinal chemists to fine-tune lipophilicity, electronic distribution and steric bulk in order to optimise potency and selectivity. The marked enhancement of activity observed upon coordination with transition metals supports the chelation theory and underlines the role of metal-based pharmacophores. However, several limitations remain: most studies are confined to in vitro assays, toxicity profiles in mammalian cell lines and in vivo efficacy data are scarce, and the absence of standardised protocols hampers cross-study comparison. Future research should therefore integrate computational tools such as molecular docking, ADMET prediction and QSAR modelling with rigorous in vivo and clinical evaluation.

X. CONCLUSION

Schiff base derivatives continue to occupy a prominent position in medicinal chemistry owing to their straightforward synthesis, remarkable structural versatility and broad-spectrum biological activity. The azomethine linkage, in combination with appropriate aromatic or heterocyclic substituents, generates molecules capable of inhibiting clinically important Gram-positive and Gram-negative bacteria as well as pathogenic fungi. Coordination with transition metal ions frequently potentiates this activity through improved lipophilicity and target interaction. With the alarming progression of antimicrobial resistance, rational design and systematic exploration of new Schiff base scaffolds, supported by modern green synthetic methods and computational drug-design tools, offer a promising avenue for the discovery of next-generation antimicrobial therapeutics.

XI. FUTURE PERSPECTIVES

- Development of green, scalable and economically viable synthetic routes.
- Systematic in vivo pharmacological and toxicological evaluation of promising leads.
- Integration of molecular docking, dynamics and machine-learning-based QSAR for predictive design.
- Exploration of Schiff base–nanoparticle conjugates and polymer-supported derivatives for targeted delivery.
- Investigation of Schiff bases as potential inhibitors of biofilm formation and resistance enzymes such as β-lactamases.

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