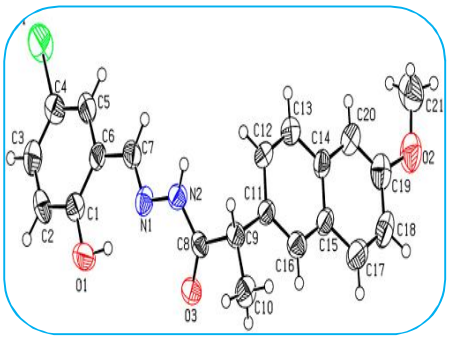
REVIEW OF RESEARCH
ISSN: 2249-894X
IMPACT FACTOR : 5.7631(UIF)
VOLUME - 12 | ISSUE - 11 | AUGUST - 2023

SCHIFF BASE LIGANDS: A VERSATILE SCAFFOLD FOR METAL-BASED THERAPEUTICS

Dr. Rakesh Kumar
Associate Professor, Department of Chemistry
MMM PG College Bhatpar Rani, Deoria, UP, India.

ABSTRACT



Schiff base ligands are formed by the condensation reaction between primary amines and carbonyl compounds. They are widely studied in medicinal chemistry because of their ability to form stable complexes with metal ions. These metal complexes show a wide range of biological activities, including antibacterial, antifungal, antioxidant and anticancer properties. Transition metals such as copper, nickel, cobalt and zinc are commonly used to form these complexes. The enhanced activity of the metal–ligand complexes is due to the combined effect of the metal ion and the ligand. These complexes can interact with biological molecules like DNA and proteins and may generate reactive oxygen species (ROS), leading to cell damage in targeted pathogens or cancer cells. This review discusses the synthesis, coordination chemistry, biological effects and mechanisms of action of Schiff base metal complexes. It also highlights recent developments and their future potential as therapeutic agents.

KEYWORDS: *Schiff base, Metal complexes, Coordination chemistry, Antibacterial activity, Antifungal activity, Antioxidant, Anticancer agents, Transition metals, DNA binding, Reactive oxygen species (ROS) and Therapeutic potential..*

1. INTRODUCTION:

Schiff bases (SBs), also known as imines or azomethines (–C=N–), are a class of organic compounds formed by the condensation of primary amines with carbonyl compounds, typically aldehydes. This reaction, first described by chemist Hugo Schiff in 1864, has become a cornerstone in organic and coordination chemistry due to the simplicity of the synthesis and the structural versatility of the resulting compounds[1-3]. Schiff bases derived from aldehydes are generally more stable and readily formed than those from ketones.

SB ligands exhibit excellent donor properties and readily coordinate with a wide range of metal ions, particularly transition metals such as copper, nickel, cobalt and zinc, forming highly stable complexes. This coordination capability arises from the presence of donor atoms like nitrogen (from the imine group) and sometimes oxygen or sulfur, in their structure[4-9]. These metal complexes often possess enhanced physicochemical and biological properties compared to the free ligands or corresponding metal salts.

Owing to their structural flexibility and thermal stability, Schiff bases and their metal complexes have gained significant attention in medicinal and industrial applications[10-11]. At elevated temperatures and in the presence of moisture, many SBs also show catalytic activity in various organic transformations. Furthermore, SBs act as key intermediates in enzymatic reactions that involve

interactions with amino or carbonyl functional groups of substrates. Their utility extends into industrial chemistry, where they are used in the synthesis of pigments, dyes, polymer stabilizers and catalysts[12-15].

From a medicinal chemistry perspective, Schiff bases are known to exhibit a broad spectrum of biological activities, including anti-inflammatory, antimalarial, antifungal, antibacterial, antiviral, antipyretic and antiproliferative effects. Notably, various SBs have demonstrated antibacterial activity against strains such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas fluorescence*, *Streptococcus pyogenes* and *Mycobacterium tuberculosis*, among others. Similarly, antifungal activity has been reported against *Aspergillus niger*, *Candida albicans*, *Trichophyton rubrum* and *Microsporum gypseum*, highlighting their potential as antimicrobial agents[16-20].

In this review, we explore the synthetic strategies employed for Schiff base ligands and discuss their coordination chemistry with transition metals. A significant focus is placed on the biological activities of Schiff base metal complexes, particularly their application in metal-based therapeutics. The potential of Schiff bases as scaffolds for drug design is also examined in the context of recent advances in medicinal chemistry.

2. CHEMISTRY OF SCHIFF BASES:

Schiff bases are formed through a condensation reaction between primary amines and carbonyl compounds (aldehydes or ketones), resulting in the formation of a characteristic imine (-C=N-) linkage. This reaction typically proceeds under mild conditions, often aided by heat or acid catalysis. The chemistry of Schiff bases is largely influenced by the nature of the functional groups attached to the amine or carbonyl precursors. Electron-donating or withdrawing substituents can significantly affect the reactivity, stability and metal-binding behavior of the resulting ligands. Structurally, Schiff bases exhibit great diversity and can act as mono-, bi- or polydentate ligands depending on the number and arrangement of donor atoms (such as nitrogen, oxygen or sulfur) within the molecule. This versatility makes them highly effective in forming stable coordination complexes with a wide range of metal ions, which is central to their application in catalysis, sensing and therapeutic drug development.

3. SYNTHESIS OF SCHIFF BASES:

Schiff bases (SBs), also known as imines, were first synthesized by Hugo Schiff in 1864 through the condensation reaction of primary amines with aldehydes or ketones under azeotropic conditions[21]. This reaction results in the formation of a C=N (azomethine) bond with water as a byproduct. The removal of water is crucial to drive the reaction to completion and thus dehydrating agents such as molecular sieves, magnesium sulfate or azeotropic distillation with solvents like toluene are often used[22-23]. The general reaction is as follows:

$$\mathbf{R{-}NH_2 + R'{-}CHO \rightarrow R{-}CH{=}N{-}R' + H_2O}$$

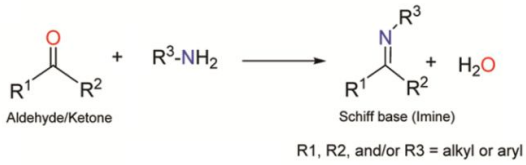
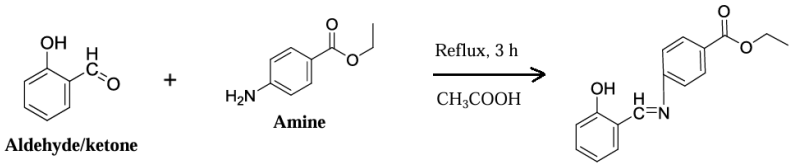


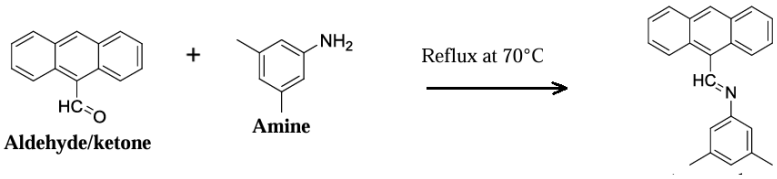
Figure 1 — General pathway for synthesis of a Schiff base

The efficiency of Schiff base formation largely depends on the electrophilicity of the carbonyl compound and the nucleophilicity of the amine involved. Aromatic aldehydes, due to their conjugated π-electron systems, tend to form more stable imines than aliphatic aldehydes, while electron-donating or withdrawing groups on the aromatic ring further modulate reactivity and stability[24-25]. Schiff bases can be synthesized under a variety of **reaction conditions**, including:

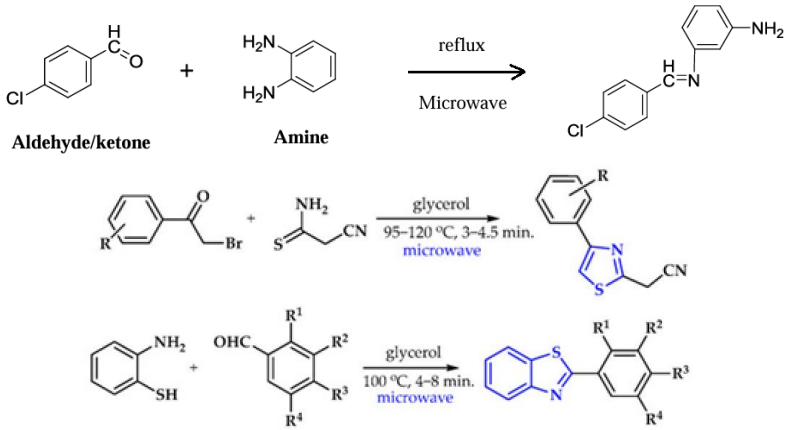
3.1 Acid/Base Catalysis: Acidic conditions often promote protonation of the carbonyl oxygen, enhancing electrophilicity, whereas mild bases can activate amines[26].



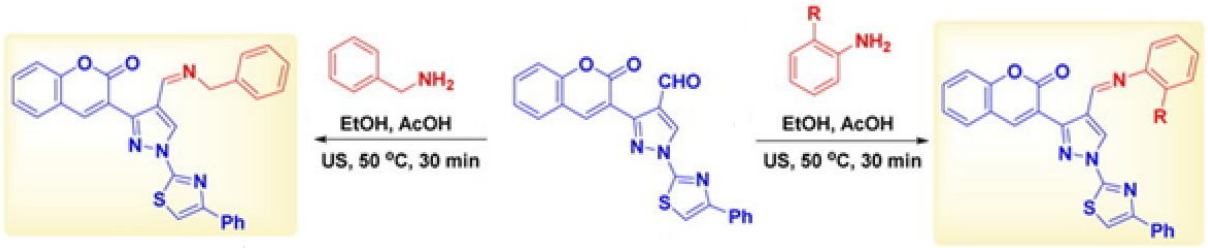
3.2 Thermal Methods: Conventional heating remains one of the simplest approaches.



3.3 Microwave-Assisted Synthesis: Offers faster reaction rates, cleaner products and energy efficiency[27].



3.4 Ultrasound and Solid-State Synthesis: These green chemistry techniques avoid the use of solvents and provide excellent yields in shorter time frames[28-29].



3.5 Ionic Liquid and Water-Based Systems: Environmentally benign methods with good atom economy[30-31].

These techniques have broadened the scope of SB synthesis, especially for structurally diverse ligands including mono-, bi- and polydentate Schiff bases, which can coordinate to metals through nitrogen and other donor atoms like oxygen or sulfur, thereby forming stable complexes with varied geometries.

4. METAL–LIGAND COMPLEXATION:

Schiff bases are renowned for their excellent metal-binding capabilities due to the presence of the azomethine group (–C=N–), often in conjunction with additional donor atoms such as –OH, –SH or –

COOH, which enhance their chelating properties. These ligands readily coordinate with transition metals such as copper (Cu), nickel (Ni), cobalt (Co), zinc (Zn) and iron (Fe), forming stable metal–ligand complexes with diverse geometries and electronic properties.

4.1 Coordination Behavior: The lone pair on the azomethine nitrogen and often an adjacent phenolic oxygen or another donor site, acts as a bidentate or polydentate ligand. This leads to the formation of five- or six-membered chelate rings with the metal centre. Schiff bases derived from salicylaldehyde, o-vanillin or 2-hydroxyacetophenone are especially prominent in this regard.

4.2 Structural Features and Stability: The geometry of Schiff base metal complexes depends on the nature of both the metal ion and the ligand. The stability of these complexes is enhanced by the chelate effect and the delocalization of electrons over the azomethine linkage, which helps in stabilizing various oxidation states of the metal ion.

- Square planar geometry is commonly observed in Ni(II) and Cu(II) complexes.
- Octahedral geometry is typical for Fe(III), Co(II/III) and Mn(II) complexes.
- Tetrahedral coordination is often found in Zn(II) or low-spin d10 systems.

4.3 Spectral Characterization: A range of analytical techniques is used to confirm the formation and geometry of Schiff base metal complexes. These spectral techniques collectively confirm the mode of coordination and structural integrity of the metal–ligand complexes[32-37].

- **UV-Vis Spectroscopy**: Gives information about ligand-to-metal charge transfer (LMCT) and d–d transitions, useful for deducing geometry.
- **Infrared (IR) Spectroscopy**: Shows a shift in the ν(C=N) stretching frequency upon coordination, typically from ~1620 cm^{-1} to lower wavenumbers.
- **NMR Spectroscopy**: For diamagnetic complexes, helps confirm ligand structure and symmetry.
- **Mass Spectrometry**: Provides molecular ion peaks and fragmentation patterns confirming the metal complex.
- **Electron Paramagnetic Resonance (EPR)**: Especially useful for paramagnetic metal centers like Cu(II).
- **X-ray Crystallography**: Gives precise three-dimensional structures and bond metrics, confirming geometry and coordination sites.

5. BIOLOGICAL ACTIVITIES OF SCHIFF BASE METAL COMPLEXES:

Schiff base metal complexes exhibit a wide range of biological activities due to their ability to interact with biomolecular targets and generate reactive species. Their pharmacological effectiveness often surpasses that of the free ligands or the corresponding metal salts, largely due to increased lipophilicity and stability upon chelation.

5.1 Antibacterial and Antifungal Activity: These complexes have shown potent inhibitory effects against various bacterial and fungal strains[38]. Minimum Inhibitory Concentration (MIC) studies have demonstrated that Schiff base complexes of Cu(II), Co(II) and Zn(II) are effective against pathogens such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Candida albicans* and *Aspergillus niger*. The enhanced bioactivity is attributed to the metal ion's ability to disrupt microbial enzyme systems and cell wall permeability.

5.2 Anticancer Activity: Many Schiff base complexes exhibit cytotoxic effects against cancer cell lines like MCF-7 (breast cancer), HeLa (cervical cancer) and A549 (lung cancer)[39]. These complexes often induce apoptosis through DNA binding, cleavage and reactive oxygen species (ROS) generation. Transition metals like Cu(II) and Ni(II) facilitate redox cycling, enhancing oxidative stress in tumor cells, while the planar nature of some complexes promotes intercalation with DNA.

5.3 Antioxidant Properties: Several Schiff base metal complexes demonstrate free radical scavenging ability, as evidenced by DPPH and ABTS assays[40]. The presence of phenolic groups and redox-active metals enhances their antioxidant potential by stabilizing reactive species and preventing oxidative damage in cells.

5.4 Enzyme Inhibition and Anti-Inflammatory Activity: Schiff base complexes can inhibit key enzymes such as urease, tyrosinase and acetylcholinesterase[41]. This makes them potential candidates for treating diseases like Alzheimer's and ulcers. Anti-inflammatory activity has also been observed, particularly in complexes that modulate the production of inflammatory mediators or inhibit enzymes like cyclooxygenase.

6. MECHANISMS OF THERAPEUTIC ACTION:

The therapeutic efficacy of Schiff base metal complexes is closely linked to their unique mechanisms of action, which integrate both the metal ion's properties and the ligand's molecular architecture[43].

6.1 Metal Ion Delivery and Redox Cycling: One major advantage of Schiff base complexes is their ability to act as delivery systems for bioactive metal ions like Cu^{2+}, $Fe^{2+}/^{3+}$ or Ni^{2+}. These ions play essential roles in disrupting cancer cell metabolism, bacterial respiration and enzymatic processes. Redox-active metals, particularly copper and iron, can undergo redox cycling inside biological environments[44]. This cycling facilitates the generation of reactive oxygen species (ROS), which can induce oxidative stress in cancer or microbial cells, leading to mitochondrial dysfunction and cell death.

6.2 DNA Cleavage and ROS Generation: Many Schiff base complexes exhibit DNA-binding properties through intercalation or groove binding. In the presence of redox-active metals, these complexes can mediate DNA cleavage via the generation of hydroxyl radicals or other ROS. This DNA damage impedes replication and transcription processes in cancer cells or microbes, ultimately triggering apoptosis. Some complexes also act as artificial nucleases, cleaving DNA even in the absence of light (non-photoinduced DNA scission)[45].

6.3 Ligand-Based Targeting and Selectivity: The ligand framework in Schiff base complexes can be fine-tuned for target selectivity by introducing specific functional groups (e.g., hydroxyl, nitro, halogen) or bulky substituents. These modifications influence cellular uptake, localization and interaction with enzymes or receptors[46]. For example, ligands derived from bioactive scaffolds (such as salicylaldehyde or quinoline) enhance selectivity towards cancer cells or microbial pathogens, minimizing toxicity to normal cells. Such molecular design enables dual action: the ligand contributes to biological targeting while the metal exerts cytotoxic or catalytic activity.

7. ADVANTAGES OVER FREE LIGANDS AND DRUGS:

Schiff base metal complexes offer several significant advantages over their corresponding free ligands and conventional drugs, making them valuable candidates in the development of novel therapeutic agents.

7.1 Enhanced Solubility, Stability and Bioavailability: One of the primary benefits of metal complexation is the improvement in physicochemical properties. Coordination with metal ions often enhances the aqueous solubility of Schiff base ligands, which is essential for effective drug delivery. Furthermore, the formation of metal-ligand bonds can stabilize the ligand structure, protecting it from hydrolysis or enzymatic degradation in biological systems[47]. This leads to increased bioavailability and a longer half-life in circulation.

7.2 Reduced Toxicity through Targeting: Schiff base metal complexes can be selectively directed to disease sites by modifying the ligand architecture with targeting moieties or by exploiting the unique microenvironment of diseased tissues (e.g., acidic pH in tumors)[48]. Such targeted delivery minimizes off-target interactions and reduces systemic toxicity commonly associated with conventional chemotherapeutics. For example, copper or zinc complexes show selective cytotoxicity against tumor cells while sparing normal cells.

7.3 Synergistic Effects of Ligand and Metal: The therapeutic potential of Schiff base metal complexes often exceeds the activity of either the metal ion or ligand alone. This synergistic effect results from the combined action of the metal's redox behavior, catalytic activity and the ligand's biological affinity. The metal center may induce ROS-mediated cytotoxicity or DNA cleavage, while the ligand may facilitate cellular uptake or inhibit key biomolecular targets such as enzymes[49]. This dual-action mechanism not only enhances therapeutic potency but also helps in overcoming drug resistance in microbes and cancer cells.

8. RECENT ADVANCES AND CASE STUDIES:

Over the past decade, Schiff base metal complexes have witnessed significant innovation, particularly in their design, biological evaluation and delivery methods. These recent advances have propelled them to the forefront of medicinal chemistry research.

8.1 Recent Examples and Therapeutic Trends (2014–2024): New Schiff base complexes, especially those containing Cu(II), Ni(II), Co(II) and Zn(II), have shown promising **anticancer**, **antimicrobial** and **antioxidant** properties[50]. For instance, Cu(II)–Schiff base complexes derived from salicylaldehyde derivatives have demonstrated selective cytotoxicity against breast and colon cancer cell lines via ROS generation and DNA interaction. Ni(II) and Zn(II) complexes, meanwhile, have exhibited significant MIC values against resistant strains of *Staphylococcus aureus* and *Candida albicans*.

8.2 Structure-Activity Relationship (SAR): Recent SAR studies suggest that electron-donating substituents on the aromatic ring of Schiff bases enhance antimicrobial activity, whereas electron-withdrawing groups improve anticancer potency[50]. Planarity and extended conjugation within the ligand system also influence DNA binding affinity. Ligand denticity (mono-, bi- or tridentate) and the geometry around the metal center (square planar or octahedral) significantly affect biological outcomes.

8.3 Nanoformulations and Smart Delivery: Modern research is exploring nanoencapsulation of Schiff base complexes using polymeric nanoparticles, liposomes and cyclodextrin systems to improve solubility, protect the drug from degradation and enable targeted delivery[51]. Recent studies report increased tumor selectivity and reduced systemic toxicity of nanoformulated Cu(II)–Schiff base complexes. Hybrid systems combining Schiff base complexes with magnetic nanoparticles or gold nanoparticles are also under investigation for theranostic applications—combining therapy and diagnostics.

9. CHALLENGES AND FUTURE PERSPECTIVES:

Despite the promising therapeutic potential of Schiff base metal complexes, several challenges must be addressed before their widespread clinical application. One major limitation is their poor solubility in aqueous media, which affects bioavailability and hampers effective drug delivery. Additionally, concerns related to in vivo stability, toxicity and off-target effects remain critical obstacles, particularly for transition metal complexes that can undergo redox cycling and generate reactive intermediates. Moreover, comprehensive toxicological profiling and pharmacokinetic studies are often lacking and most research remains at the in vitro level. The transition from laboratory to clinical

practice requires well-structured animal studies and clinical trials to assess therapeutic efficacy, safety, dosage and side effects.

Future research is increasingly focused on molecular docking and computational modeling to predict target interactions, theranostics that integrate diagnosis and therapy (e.g., imaging with treatment) and green synthesis approaches that employ eco-friendly solvents and reaction conditions. These strategies aim to enhance the therapeutic index, minimize environmental impact and accelerate clinical translation of Schiff base metal complexes.

10. CONCLUSION

Schiff base ligands have emerged as a highly versatile and promising class of compounds in the design of metal-based therapeutic agents. Their ease of synthesis, structural tunability and strong coordination with biologically active metals such as Cu, Ni, Co and Zn contribute significantly to their broad spectrum of biological applications, including antimicrobial, anticancer, antioxidant and enzyme inhibition activities. The enhanced bioactivity of Schiff base metal complexes often results from synergistic effects between the ligand and metal, improved solubility, redox behavior and site-specific interactions like DNA or protein binding.

Recent developments in structural modification, nanoformulation and mechanistic understanding—along with computational tools such as molecular docking—have opened new avenues for drug design and delivery. However, despite substantial in vitro success, clinical translation remains limited, underscoring the need for detailed toxicological, pharmacokinetic and in vivo studies. In summary, Schiff base metal complexes represent a powerful scaffold for future therapeutic innovation, holding immense potential for the development of more selective, potent and less toxic drugs across a range of diseases. Their integration into modern drug discovery pipelines, particularly in combination with green synthesis and nanotechnology, is expected to further accelerate progress in medicinal chemistry.

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