Int. J. Sci. R. Tech., 2026 3(2)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Biological Evaluation of Novel Schiff Base Metal Complexes: A Review

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ABSTRACT

Schiff base metal complexes have emerged as an important class of compounds in medicinal and coordination chemistry owing to their structural versatility, strong metal-binding ability, and diverse biological activities. The presence of the azomethine (–C=N–) functional group enables effective chelation with a wide range of transition metal ions, thereby enhancing the physicochemical stability, lipophilicity, and pharmacological potential of the parent ligands. Metal complexation often results in improved biological efficacy compared to free Schiff bases, attributed to altered electronic properties and enhanced interaction with biological targets. This review summarizes recent developments in the design, synthesis, and physicochemical characterization of novel Schiff base metal complexes. Emphasis is placed on their biological evaluation, including antimicrobial, anticancer, antioxidant, anti-inflammatory, antiviral, and enzyme inhibitory activities. The underlying mechanisms of action, structure–activity relationships (SAR), and the influence of metal ions and ligand architecture on biological performance are critically discussed. Furthermore, current challenges, toxicity considerations, and future perspectives for the development of Schiff base metal complexes as potential therapeutic agents are highlighted.

Keywords: Schiff base, metal complexes, biological evaluation, antimicrobial activity, anticancer activity, coordination chemistry

INTRODUCTION

Schiff bases are condensation products formed by the reaction of primary amines with aldehydes or ketones, characterized by the presence of an imine or azomethine functional group (–C=N–). These compounds were first reported by Hugo Schiff in 1864 and have since become an important class of ligands in coordination chemistry due to their ease of synthesis, structural diversity, and strong metal-binding ability [1]. The azomethine linkage plays a crucial role in coordination with metal ions through the lone pair of electrons on the nitrogen atom, often accompanied by other donor atoms such as oxygen or sulfur [2]. Schiff bases readily form stable complexes with transition metal ions including copper (II), zinc (II), nickel (II), cobalt (II), iron (III), and manganese (II), among others. The chelation process typically enhances the physicochemical and biological properties of the parent ligand [3]. According to chelation theory, coordination reduces the polarity of the metal ion through partial sharing of its positive charge with donor atoms, thereby increasing lipophilicity and facilitating penetration through biological membranes [4]. As a result, Schiff base metal complexes frequently exhibit superior antimicrobial, anticancer, antioxidant, and enzyme inhibitory activities compared to their free ligands [5].

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

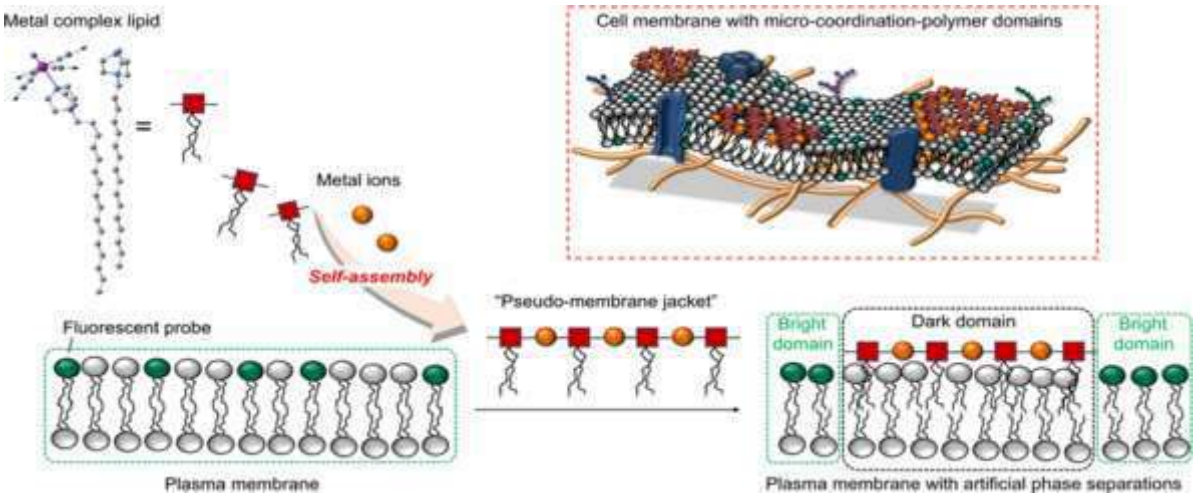

Figure 1: Chelation Theory and Enhanced Biological Activity

Owing to these properties, Schiff base metal complexes have attracted considerable attention in medicinal chemistry and drug design. Their structural flexibility allows for modulation of electronic properties, geometry, and coordination environment, which significantly influence biological performance and therapeutic potential [6].

2. Chemistry of Schiff Base Metal Complexes

2.1 Synthesis of Schiff Bases

Schiff bases are generally synthesized through a condensation reaction between primary amines and aldehydes or ketones, resulting in the formation of an imine (–C=N–) linkage. This reaction typically proceeds via nucleophilic addition of the amine to the carbonyl group followed by dehydration [7]. Conventional synthesis involves refluxing the reactants in alcoholic solvents such as ethanol or methanol to facilitate complete condensation and improve yield [8]. In recent years, alternative approaches including acid-catalyzed synthesis, microwave-assisted reactions, and solvent-free green methodologies have been developed to enhance reaction efficiency, reduce reaction time, and minimize environmental impact [9]. These strategies contribute to improved purity and sustainability in Schiff base preparation.

2.2 Formation of Metal Complexes

Schiff base metal complexes are formed by reacting the synthesized ligands with appropriate metal salts (e.g., chlorides, acetates, nitrates) under controlled pH and temperature conditions. The coordination process generally involves donation of the lone pair electrons from the azomethine nitrogen atom to the metal center [10]. In many cases, additional donor atoms such as phenolic oxygen, thiol sulfur, or extra nitrogen atoms participate in chelation, leading to the formation of stable bidentate, tridentate, or tetradentate complexes [11]. The geometry of the resulting complex (octahedral, square planar, tetrahedral, etc.) depends on the nature of the metal ion, ligand denticity, and reaction conditions [12].

2.3 Characterization Techniques

The structural and physicochemical properties of Schiff base metal complexes are confirmed using various analytical and spectroscopic techniques:

- **UV–Visible Spectroscopy:** Used to study electronic transitions and determine ligand field parameters and geometry of complexes [13].
- **FT-IR Spectroscopy:** Confirms coordination through shifts in the azomethine (C=N) stretching frequency and disappearance or shifting of phenolic –OH bands upon complexation [14].
- **NMR Spectroscopy:** Provides structural information about ligand framework and changes upon metal coordination (mainly for diamagnetic complexes) [15].
- **Mass Spectrometry:** Confirms molecular weight and structural fragments of ligands and complexes [16].

- **X-ray Crystallography:** Provides precise three-dimensional structural information and coordination geometry [17].

- **Elemental Analysis and Magnetic Susceptibility Measurements:** Used to confirm empirical formula, stoichiometry, and magnetic behavior of metal complexes [18].

3. Biological Activities of Schiff Base Metal Complexes

Schiff base metal complexes exhibit a broad spectrum of biological activities due to their enhanced lipophilicity, stability, and ability to interact with biological macromolecules. Metal coordination significantly modifies the electronic distribution of the ligand, thereby influencing pharmacological behavior [19].

3.1 Antimicrobial Activity

Schiff base metal complexes demonstrate potent antibacterial and antifungal activities against both Gram-positive and Gram-negative microorganisms. In many cases, metal complexes show superior activity compared to their parent ligands [20].

Proposed Mechanisms

- **Chelation theory:** Coordination reduces the polarity of the metal ion and increases lipophilicity, enhancing membrane permeability [21].

- **Disruption of microbial cell membrane integrity**, leading to leakage of intracellular components [22].

- **Inhibition of microbial enzymes** by binding to active sites or interacting with thiol groups of proteins [23].

Commonly active metal ions include **Cu (II), Zn (II), Co (II), and Ni (II)**, with copper complexes frequently exhibiting the highest antimicrobial potency due to redox activity [24].

3.2 Anticancer Activity

Numerous Schiff base metal complexes have demonstrated significant cytotoxic effects against various cancer cell lines, including:

- **MCF-7** (breast cancer)

- **HeLa** (cervical cancer)

- **A549** (lung cancer)

These complexes often exhibit selective toxicity toward cancer cells compared to normal cells [25].

Mechanisms of Anticancer Action

- **DNA intercalation and groove binding**, leading to inhibition of replication and transcription [26].

- **Generation of reactive oxygen species (ROS)**, causing oxidative stress and mitochondrial dysfunction [27].

- **Induction of apoptosis** through intrinsic and extrinsic pathways [28].

- **Cell cycle arrest** at G0/G1 or G2/M phases [29].

Copper (II) and ruthenium (II/III) complexes are particularly promising due to their redox properties and ability to mimic biological metal ions [30].

3.3 Antioxidant Activity

Schiff base metal complexes have been widely evaluated for antioxidant potential using:

- **DPPH (2,2-diphenyl-1-picrylhydrazyl) assay**

- **ABTS radical cation decolorization assay**

- **FRAP (Ferric Reducing Antioxidant Power) assay**

Metal coordination often enhances radical scavenging ability compared to free ligands due to improved electron transfer mechanisms and stabilization of radical intermediates [31,32].

3.4 Anti-inflammatory Activity

Several Schiff base metal complexes have shown significant anti-inflammatory activity in experimental models.

Mechanisms include:

- **Inhibition of cyclooxygenase (COX-1 and COX-2) enzymes** [33].
- **Reduction of pro-inflammatory cytokines** such as TNF-α and IL-6 [34].
- **Suppression of oxidative stress-mediated inflammatory pathways** through metal chelation and antioxidant effects [35].

These properties suggest potential therapeutic applications in inflammatory disorders.

3.5 Antiviral Activity

Certain Schiff base metal complexes have demonstrated antiviral properties, particularly:

- **Anti-HIV activity** through inhibition of viral enzymes [36].
- **Anti-HCV activity** via interference with viral replication mechanisms [37].
- Potential inhibitory effects against emerging viral pathogens due to metal-mediated enzyme disruption [38].

Copper and zinc complexes are frequently reported for antiviral activity owing to their ability to interfere with viral proteases and replication enzymes.

3.6 Enzyme Inhibitory Activity

Schiff base metal complexes are known to inhibit various biologically relevant enzymes:

- **Acetylcholinesterase inhibition**, indicating potential in Alzheimer's disease management [39].
- **Urease inhibition**, relevant in gastric ulcer and Helicobacter pylori infection [40].
- **α-Amylase and α-glucosidase inhibition**, suggesting antidiabetic potential [41].

The enzyme inhibitory activity is often attributed to coordination interactions between the metal center and active site residues, leading to altered enzyme conformation and reduced catalytic efficiency [42].

Figure 2: biological application of Schiff base metal complexes

4. Structure–Activity Relationship (SAR)

The biological activity of Schiff base metal complexes is strongly influenced by structural and physicochemical parameters. Variations in ligand framework and metal coordination significantly affect pharmacological behavior, target selectivity, and therapeutic efficacy [43].

Several key factors govern the structure–activity relationship (SAR):

- **Nature of the metal ion:** The type of metal ion determines redox potential, coordination

geometry, and biological reactivity. Transition metals with variable oxidation states often exhibit enhanced biological performance due to redox cycling ability [44].

- **Geometry of the complex:** The spatial arrangement (square planar, tetrahedral, octahedral) influences molecular planarity, steric interactions, and binding affinity toward biological macromolecules such as DNA and proteins [45].

- **Electron-withdrawing or electron-donating substituents:** Substituents on the aromatic ring modulate electron density at the azomethine linkage, thereby affecting metal–ligand stability and biological activity. Electron-withdrawing groups often enhance antimicrobial and anticancer properties by increasing electrophilicity and facilitating target interactions [46].

- **Denticity of the ligand:** Bidentate, tridentate, and tetradentate ligands form complexes with different stability constants and geometries, which directly impact bioavailability and target binding [47].

- **Lipophilicity:** Increased lipophilicity enhances membrane permeability, promoting better cellular uptake and improved biological activity. Chelation generally increases lipophilic character compared to free ligands [48].

General Observations in SAR Studies

- **Cu (II) complexes** frequently demonstrate strong antimicrobial and anticancer activities due to their redox properties and ability to generate reactive oxygen species (ROS) [49].

- **Zn (II) complexes** often show notable enzyme inhibitory activity because zinc plays a structural and catalytic role in many biological enzymes, enhancing binding interactions [50].

- **Planar complexes**, particularly square planar geometries, tend to exhibit superior DNA binding affinity through intercalation mechanisms, thereby enhancing cytotoxic potential [51].

Understanding these SAR parameters enables rational design of Schiff base metal complexes with optimized biological profiles and reduced toxicity.

5. Mechanism of Action

The biological effects of Schiff base metal complexes are mediated through multiple molecular mechanisms, largely influenced by the nature of the metal ion and ligand framework. These mechanisms include enhanced membrane permeability via chelation, interaction with nucleic acids, and redox-mediated oxidative stress pathways [52].

5.1 Chelation Theory

Chelation theory explains the enhanced biological activity of metal complexes compared to free ligands. Upon coordination, the positive charge of the metal ion is partially shared with donor atoms (such as azomethine nitrogen and phenolic oxygen), leading to reduced polarity of the metal center [53]. This reduction in polarity increases the **lipophilic character** of the complex, facilitating its penetration through the lipid bilayer of microbial or cancer cell membranes. Enhanced membrane permeability improves intracellular accumulation, thereby increasing biological efficacy [54]. Additionally, chelation may interfere with normal cellular metal homeostasis, contributing to cytotoxic effects [55].

5.2 DNA Interaction

DNA is one of the primary intracellular targets for many Schiff base metal complexes, particularly those with planar geometries. These complexes may bind DNA through several modes:

- **Intercalation:** Planar aromatic systems insert between DNA base pairs, disrupting replication and transcription processes [56].

- **Groove binding:** Complexes bind along the major or minor grooves of DNA through hydrogen bonding and van der Waals interactions [57].

- **Oxidative cleavage:** Metal-mediated generation of reactive oxygen species can induce strand scission and DNA damage [58].

Such DNA interactions can result in inhibition of cell proliferation, activation of DNA damage response pathways, and eventual induction of apoptosis in cancer cells [59].

5.3 Reactive Oxygen Species (ROS) Generation

Transition metal ions such as Cu (II), Fe(III), and Ru(III) can participate in redox cycling reactions, producing reactive oxygen species (ROS) including superoxide anions, hydroxyl radicals, and hydrogen peroxide [60]. Excessive ROS generation leads to oxidative stress, mitochondrial dysfunction, lipid peroxidation, protein oxidation, and DNA damage. In cancer cells, elevated oxidative stress triggers intrinsic apoptotic pathways through activation of caspases and release of cytochrome c [61]. Therefore, ROS-mediated cytotoxicity is considered one of the major anticancer mechanisms of Schiff base metal complexes [62].

6. Toxicity and Safety Considerations

Although Schiff base metal complexes demonstrate significant therapeutic potential, comprehensive toxicity and safety evaluation is essential prior to clinical application. The biological activity of these complexes is often closely associated with the intrinsic properties of the coordinated metal ion, which may also contribute to adverse effects if not properly controlled [63]. One major concern is **metal-associated toxicity**, particularly for redox-active metals such as copper, iron, and cobalt. Excess accumulation of metal ions may disrupt physiological metal homeostasis, induce oxidative stress, and cause damage to vital organs including the liver and kidneys [64]. Therefore, careful dose optimization and controlled delivery strategies are necessary to minimize systemic toxicity. **In vitro cytotoxicity studies** are crucial during early-stage evaluation to determine selective toxicity toward pathogenic or cancer cells while sparing normal cells. Assays such as MTT, SRB, LDH release, and flow cytometry-based apoptosis analysis are commonly employed to assess cell viability, membrane integrity, and mechanism of cell death [65]. Selectivity index determination provides insight into therapeutic safety margins [66]. Furthermore, **in vivo safety profiling** in appropriate animal models is required to evaluate pharmacokinetics, biodistribution, acute and chronic toxicity, hematological effects, and organ-specific toxicity [67]. Histopathological examination and biochemical parameter analysis help in assessing potential adverse reactions [68]. Such studies are indispensable before advancing Schiff base metal complexes toward preclinical and clinical investigations. Overall, rational ligand design, controlled metal selection, and thorough toxicological assessment are essential to ensure safe therapeutic development of Schiff base metal complexes [69]. Here is your section written in **journal-ready format with reference numbers continuing after 69 (starting from 70 onward)**:

7. Applications in Drug Development

Schiff base metal complexes have emerged as promising candidates in modern drug discovery due to their structural flexibility, tunable coordination environments, and diverse pharmacological properties. Their ability to modulate biological targets through metal-mediated mechanisms has positioned them as potential therapeutic agents in various disease conditions [70].

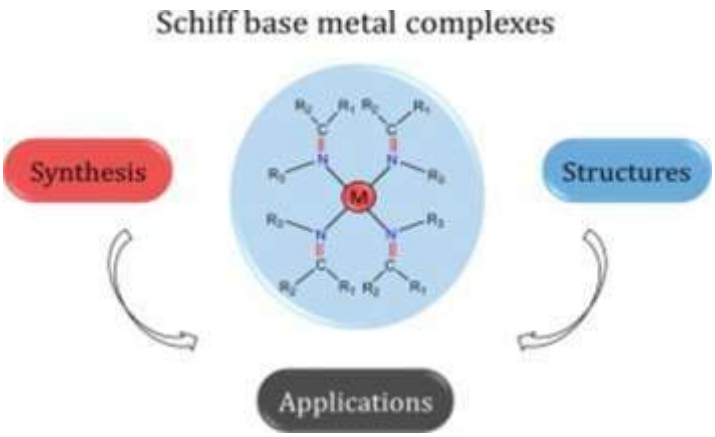

Figure 3: Applications of Schiff Base Metal Complexes in Drug Development

Potential Anticancer Agents

Several Schiff base metal complexes, particularly those containing copper, ruthenium, platinum, and gold, have demonstrated significant cytotoxicity against a range of cancer cell lines. Their mechanisms often involve DNA interaction, ROS generation, and apoptosis induction, making them attractive alternatives to conventional chemotherapeutics [71]. Ruthenium and copper complexes, in particular, are being investigated for their lower systemic toxicity and selective tumor targeting capabilities [72].

Antimicrobial Drug Candidates

The increasing prevalence of antimicrobial resistance has intensified research into metal-based antimicrobial agents. Schiff base metal complexes have shown potent antibacterial and antifungal activities, often surpassing standard antibiotics in resistant strains. Their multimodal mechanisms—membrane disruption, enzyme inhibition, and oxidative stress induction—reduce the likelihood of resistance development [73].

Enzyme Inhibitors

Due to their structural adaptability and metal coordination ability, Schiff base complexes are effective inhibitors of several clinically relevant enzymes, including acetylcholinesterase, urease, carbonic anhydrase, and α-glucosidase. These properties suggest potential therapeutic applications in neurodegenerative diseases, gastric disorders, and diabetes management [74].

Metal-Based Therapeutic Alternatives

Metal-based drugs represent an important class of therapeutics beyond platinum compounds. Schiff base ligands provide a versatile scaffold for designing next-generation metal therapeutics with improved selectivity and controlled reactivity [75]. By fine-tuning ligand substitution patterns and metal choice, pharmacokinetic and pharmacodynamic properties can be optimized.

Recent Research Trends

Current research in Schiff base metal complexes is focused on improving efficacy, selectivity, and safety profiles through advanced strategies:

- **Targeted drug delivery systems:** Conjugation with biomolecules (e.g., peptides, antibodies) or incorporation into delivery carriers enhances site-specific action and reduces systemic toxicity [76].
- **Nanoparticle-loaded metal complexes:** Encapsulation in polymeric nanoparticles, liposomes, or metallic nanocarriers improves solubility, bioavailability, and controlled release characteristics [77].
- **Green synthesis approaches:** Environmentally friendly methods such as microwave-assisted synthesis, solvent-free reactions, and plant-mediated synthesis are being developed to reduce environmental impact and improve sustainability [78].

These innovative strategies are expanding the therapeutic horizon of Schiff base metal complexes and supporting their progression toward clinical applications.

8. Future Perspectives

The expanding field of Schiff base metal complexes continues to offer promising opportunities for the development of next-generation therapeutic agents. Despite significant progress in synthesis and biological evaluation, further research is required to enhance selectivity, minimize toxicity, and facilitate clinical translation [79].

Development of Selective and Less Toxic Metal Complexes

Future studies should prioritize the rational design of metal complexes with improved target specificity and reduced systemic toxicity. Fine-tuning ligand architecture, denticity, and electronic properties can modulate metal reactivity and optimize therapeutic indices. The incorporation of biologically compatible metals such as zinc and iron, along with controlled redox-active metals, may improve safety profiles [80].

Use of Computational Docking and Molecular Modeling

Computational approaches, including molecular docking, density functional theory (DFT), and molecular dynamics simulations, are increasingly employed to predict binding interactions with biological targets such as DNA, enzymes, and receptors. These in silico tools assist in understanding structure–activity relationships (SAR), optimizing ligand design, and reducing experimental workload [81]. Integration of computational modeling with experimental validation is expected to accelerate drug discovery processes [82].

Exploration of Hybrid Drug–Metal Systems

The design of hybrid systems combining organic pharmacophores with metal centers represents a promising strategy for enhancing therapeutic efficacy. Such systems may exhibit synergistic effects by integrating conventional drug mechanisms with metal-mediated cytotoxic or catalytic properties [83]. Conjugation with peptides, natural products, or approved drugs can further enhance selectivity and pharmacokinetic performance [84].

Clinical Translation Studies

Although numerous Schiff base metal complexes have demonstrated potent in vitro and in vivo activity, clinical translation remains limited. Comprehensive pharmacokinetic profiling, toxicity assessment, and long-term safety studies are essential before human trials. Collaborative efforts between chemists, pharmacologists, and clinicians are necessary to bridge the gap between laboratory research and clinical application [85]. Overall, continued interdisciplinary research combining synthetic chemistry, computational modeling, nanotechnology, and biomedical sciences will be crucial for advancing Schiff base metal complexes toward practical therapeutic use.

CONCLUSION

Schiff base metal complexes constitute a versatile and promising class of bioactive compounds with significant potential in medicinal chemistry. The presence of the azomethine (–C=N–) group, combined with the ability to coordinate various transition metal ions, provides structural diversity and tunable physicochemical properties. The synergistic interaction between ligand architecture and metal coordination enhances biological performance, including antimicrobial, anticancer, antioxidant, anti-inflammatory, antiviral, and enzyme inhibitory activities. Extensive studies have demonstrated that metal complexation improves lipophilicity, cellular uptake, and target interaction, often resulting in superior efficacy compared to free Schiff bases. Mechanistic investigations involving DNA interaction, reactive oxygen species generation, and enzyme inhibition further support their therapeutic relevance. However, despite promising in vitro and in vivo findings, challenges related to toxicity, selectivity, pharmacokinetics, and clinical translation remain. Continued interdisciplinary research focusing on rational design, computational modeling, targeted delivery systems, and comprehensive safety profiling is essential. With systematic optimization and rigorous evaluation, Schiff base metal complexes hold substantial promise for the development of novel metal-based therapeutic agents with improved efficacy, reduced toxicity, and potential clinical applicability.

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HOW TO CITE: Suchita Bondre*, Deepika Gupta, Biological Evaluation of Novel Schiff Base Metal Complexes: A Review, Int. J. Sci. R. Tech., 2026, 3 (2), 197-207. https://doi.org/10.5281/zenodo.18661728