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Role of transition metal complexes of Schiff bases in medicinal field

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Abstract
The medical field of inorganic chemistry relies on Schiff base transition metal complexes because these compounds exhibit unique structural features and show enhanced biological properties. The ligands which exist in this study establish their binding capabilities through the azomethine bond (C=N−) which enables them to create stable chelate complexes with transition metal ions such as copper(II) and zinc(II) and cobalt(II). The coordination process of the compounds results in enhanced lipophilicity and improved membrane permeability, which Tweedy's Chelation Theory explains by showing how ligand binding reduces metal ion polarity.
The metal–Schiff base complexes which were created exhibit various biological effects which include antibacterial and antifungal and antiviral activities. The neoplastic cells experience death through DNA intercalation and other mechanisms which lead to their substantial anticancer effects. Their ability to selectively inhibit vital enzymes such as urease and carbonic anhydrase, which they need for their metabolic functions, demonstrates their wide range of medical applications.
The complexes create a flexible platform for drug development through their ability to combine organic ligand frameworks with unique metal ion reactivity. The compounds control biological activity through their various structural and electronic properties, which make them suitable for developing next-generation Metallo pharmaceuticals that will provide precise treatment methods in modern clinical practice.
Keywords: *Inorganic Chemistry, Tweedy's Chelation Theory, Dna Intercalation, Organic Ligand, Metallo Pharmaceuticals, etc.*

I. Introduction: The Field of Medicinal Inorganic Chemistry

The field of medicinal inorganic chemistry emerged through the combination of inorganic chemistry and pharmacology because transition metal complexes of Schiff bases became essential to this new area of study [1]. The "metal-drug" paradigm has transformed the pharmaceutical industry because it enables drugs to use the unique structural and electrical characteristics of metal ions instead of depending on organic compounds which have traditionally dominated this field. Schiff bases which contain the azomethine or imine group >C=N- function as suitable metal scaffolds. Their synthetic flexibility leads to their widespread use because primary amines and active carbonyl compounds can be combined to produce these compounds. The ligands in biological environments function as chaperones which direct metal ions to specific cellular locations while modifying their reactivity to create therapeutic effects that avoid general toxicity.

Historical Origins of Schiff Bases

The German scientist Hugo Schiff demonstrated the condensation process between an aldehyde and a primary amine in 1864 when he first documented these two compounds. The dye industry and chemical synthesis intermediates have valued Schiff bases for many years because they combine high stability with simple manufacturing processes [2]. Scientists discovered that azomethine nitrogen shows single electron pair behavior which makes it suitable for bonding with metal ions as the twentieth century progressed. This discovery established a connection between organic chemistry and the science of coordination. The initial studies of "imine" ligands showed that they could maintain metal stability across multiple oxidation states which led to the development of "Salen" ligands that function as tetradentate Schiff base which now serves as essential tools in medical research and catalysis [3].

The Coordination Chemistry Framework

Coordination chemistry relies on transition metals because they can create different geometric structures which organic molecules do not naturally produce. The chelate effect results when a Schiff base binds to transition metal ions like copper (II) or zinc (II) or ruthenium (III) The metal and ligand undergo physicochemical property changes because of this chelation process [4]. The Schiff base donor atoms share part of the metal ion positive charge which results in decreased overall complex polarity. The therapeutic applications of this effect increase compound lipophilicity which enables better cell membrane passage than free metal salt or parent ligand. The stability constants of these complexes ensure that the metal is attached until it reaches its designated biological location, avoiding premature side reactions with serum proteins.

The "Metal-Drug" Paradigm in Contemporary Medicine

The "metal-drug" paradigm functions distinctively from the "lock-and-key" approach prevalent in conventional organic drug development. Transition metal complexes can do more than just bind to receptors. They can also conduct redox reactions and make reactive oxygen species that kill cancer cells and act as Lewis acids that stop enzymes from working. Researchers created platinum-based drugs by making Cisplatin, which showed that this type of drug development worked [5]. However, scientists started looking into Schiff base complexes because they needed to find safer ways to treat people. To get the biological effects they want in drugs, scientists use certain transition metals. Iron-based complexes are safe to use in medicine because they are biocompatible. Silver and copper complexes, on the other hand, are good at killing bacteria. Schiff base coordination compounds are still very important for finding new Metallo drugs because they can be used in many ways.

Molecular Architecture: Synthesis and Coordination of Schiff Bases

The process for developing Schiff base transition metal complexes requires expertise in both organic condensation methods and inorganic coordination chemistry techniques. The process begins when a primary amine attacks the carbonyl carbon atom of an aldehyde or ketone through nucleophilic reaction which takes place in boiling ethanol or methanol solutions. The reaction starts with the production of a hemiaminal intermediate which undergoes dehydration to form a stable azomethine bond (C=N−) structure [6]. The reaction requires a small amount of acid catalyst which scientists use glacial acetic acid to drive the reaction toward product formation. After scientists isolate and purify the Schiff base ligand base they combine it with transition metal salts which include Copper(II) Nickel(II) and Zinc(II) chlorides nitrates and acetates. The resultant complexes demonstrate increased stability relative to the free ligand owing to the chelate effect which enables the polydentate ligand to form stable cyclic structures through metal core binding.

General Reaction for Synthesis of Schiff Base Metal Complexes

Formation of Schiff Base (Ligand)

$$\text{R–CHO} + \text{R'–NH}_2 \xrightarrow[\text{heat}]{\text{EtOH, CH}_3\text{COOH}} \text{R–CH=N–R'} + \text{H}_2\text{O}$$

Where:
R–CHO = Aldehyde
R'–NH_2 = Primary amine
Product = Schiff base (azomethine, C=N)

Complexation with Transition Metal

$$\text{M}^{n+} + 2(\text{R–CH=N–R'}) \rightarrow [\text{M(Schiff Base)}_2]^{n+}$$

Where:
M^{n+} = Metal ion (Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, etc.)
Product = Metal–Schiff base complex

Combined Representation

$$\text{Aldehyde} + \text{Amine} \rightarrow \text{Schiff Base} \xrightarrow{\text{+ Metal Salt}} \text{Metal Complex}$$

Spectroscopic Characterization and Structural Verification

The process of validating coordination geometry requires complete spectroscopic analysis including multiple different analysis methods. The main diagnostic tool of Fourier-Transform Infrared (FT-IR) spectroscopy allows researchers to identify key changes through measuring azomethine stretching frequency $\nu(C{=}N)$ variations. Uncoordinated Schiff bases display their band between 1610 and 1660 cm^{-1} while metal ion coordination causes a band shift to lower wavenumbers 1580 to 1620 cm^{-1} because azomethine nitrogen participates in bonding through lone pair donation [7]. The presence of extra bands between 400 and 600 cm^{-1} proves metal–ligand interaction because these bands correspond to M–N and M–O vibrations. Nuclear Magnetic Resonance (NMR) spectroscopy enables effective analysis of both 1H and 13C in ZnII and CdII diamagnetic complexes because the azomethine proton (H–C=N) signal undergoes downward shift as a result of metal ion coordination which withdraws electrons. Electronic (UV–Vis) spectroscopy enables researchers to study electronic transitions in the complex which helps them identify the three geometries of tetrahedral square planar and octahedral through specific d–d transitions and ligand-to-metal charge transfer (LMCT) bands [8]. The combined results of these spectroscopic methods create a trustworthy structural fingerprint which guarantees that Schiff base metal complexes can be accurately identified before their upcoming uses.

Pharmacological Heterogeneity: Efficacy Against Antimicrobial, Antifungal, and Antiviral Agents

The biological profile of transition metal complexes formed from Schiff bases displays a significant increase in their medicinal properties when compared to their original organic ligands because the metal center and the azomethine structure create a combination effect which produces superior results. The complexes show strong antibacterial activity against Staphylococcus aureus which is a Gram-positive bacterium and against Escherichia coli which is a Gram-negative bacterium. The increased activity is typically explained through Tweedy's Chelation Theory and Overtone's Concept which state that chelation causes the metal ion to lose its polarity because the Schiff base ligand donor atoms share its positive charge [9]. The complex gains lipophilicity through electron density redistribution which allows it to cross microbial cell lipid membranes. The complex enters cells and disrupts critical biological processes which include protein synthesis and enzymatic respiration and this leads to cell death.

The antifungal properties of Cobalt(II), Nickel(II), and Copper(II) transition metal complexes have received recognition because these metals demonstrate effectiveness against eukaryotic pathogens which present treatment difficulties. The Schiff base complexes disrupt fungal cell wall formation through their two mechanisms which are cell wall disruption and inhibition of ergosterol synthesis which maintains membrane structure. Zinc(II) complexes derived from sulfonamide-based Schiff bases show better antifungal effects against Candida albicans and Aspergillus niger than standard antifungal medications [10].

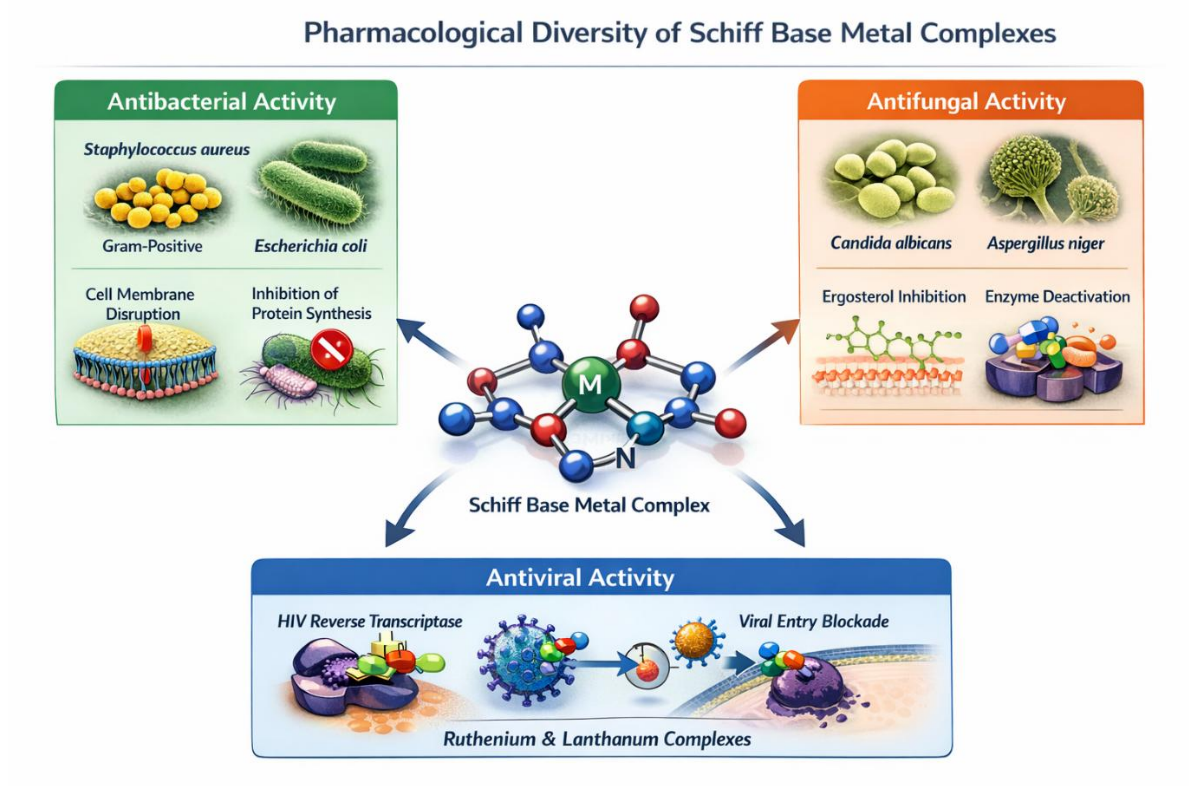

Figure 1: Pharmacological activities of Schiff base complexes

The Schiff base transition metal complexes show antibacterial and antifungal effects but they also have strong antiviral activity which addresses the current global increase in viral outbreaks. The chemicals function as viral replication blockers because they interfere with particular viral proteins and enzymes or they stop viruses from entering host cells. Certain complexes especially those which contain Ruthenium II or Lanthanum III show the ability to bind with viral envelopes and prevent host virus interactions. Researchers conduct extensive studies on Schiff base complexes which show the ability to inhibit two essential Human Immunodeficiency Virus enzymes reverse transcriptase and protease. The metal-Schiff base framework exhibits structural and geometric flexibility which enables it to bind accurately with hydrophobic active sites of viral enzymes to compete effectively with native substrates. The increasing problem of resistance against traditional organic antiviral drugs creates an opportunity for metal-based complexes which use multiple targeting methods to become the foundation of upcoming broad-spectrum antiviral drug development.

The Oncological Frontier: DNA Interaction and Cytotoxicity

Schiff base transition metal complex development for anticancer drug research functions as a highly active research field which scientists study within medicinal inorganic chemistry. The clinical efficacy of Cisplatin has demonstrated the therapeutic value of metal-based drugs; however, its nephrotoxicity and the development of drug resistance have prompted researchers to seek non-platinum treatment options. Scientists have developed Copper(II) and Ruthenium(III) and Zinc(II) Schiff base complexes which work to specifically destroy cancer cells through multiple different pathways [11]. The basic mechanism which produces their anticancer effects operates through their binding with Deoxyribonucleic Acid (DNA). Most transition metal Schiff bases display either planar structures or planar aromatic ring systems which enable their function as intercalators. The complex intercalates between the hydrophobic base pairs of the DNA double helix, resulting in structural abnormalities that impede replication and transcription. The complexes use intercalation to bind with DNA through either minor groove or major groove binding, which allows the complexes to effectively "lock" the genetic machinery of the cancerous cell.

The MTT assay is a common method for assessing how toxic these complexes are to cells. This is done by measuring how active the cells are metabolically, which helps determine if they are alive. The study's results show that when a Schiff base is attached to a metal, it becomes more effective at killing cells compared to when it is not attached.

The "pro-drug" properties of various coordination compounds lead to this phenomenon because the complex stays intact during blood circulation but releases its ligands through redox processes in tumor acid or reductive environments. Transition metals such as copper and iron display high efficiency because they participate in Fenton-like reactions which generate highly reactive hydroxyl radicals (OH). The Reactive Oxygen Species (ROS) create extensive oxidative damage that affects cellular membranes and proteins and organelles which exceeds the cancer cell's ability to protect itself resulting in cell destruction.

The main goal of Metallo pharmaceuticals is to trigger programmed cell death through apoptosis which should replace necrosis because necrosis creates harmful inflammation that damages nearby healthy tissues. The intrinsic mitochondrial cell death process gets activated by Schiff base complexes through their ability to initiate apoptosis. The complexes create mitochondrial membrane changes which allow Cytochrome c to exit into the cytosol where it starts the caspase cascade that includes Caspase-3 and Caspase-9 activation. The metabolic pathway produces DNA fragmentation together with chromatin condensation which leads to the process of cellular shrinkage. The new ruthenium-based Schiff base complexes can bypass standard resistance mechanisms because they attack endoplasmic reticulum (ER) stress which creates a twofold method to treat aggressive carcinomas. The Schiff base ligand's modular design allows researchers to enhance these complexes for better tumor cytotoxic effects while minimizing harm to normal body cells.

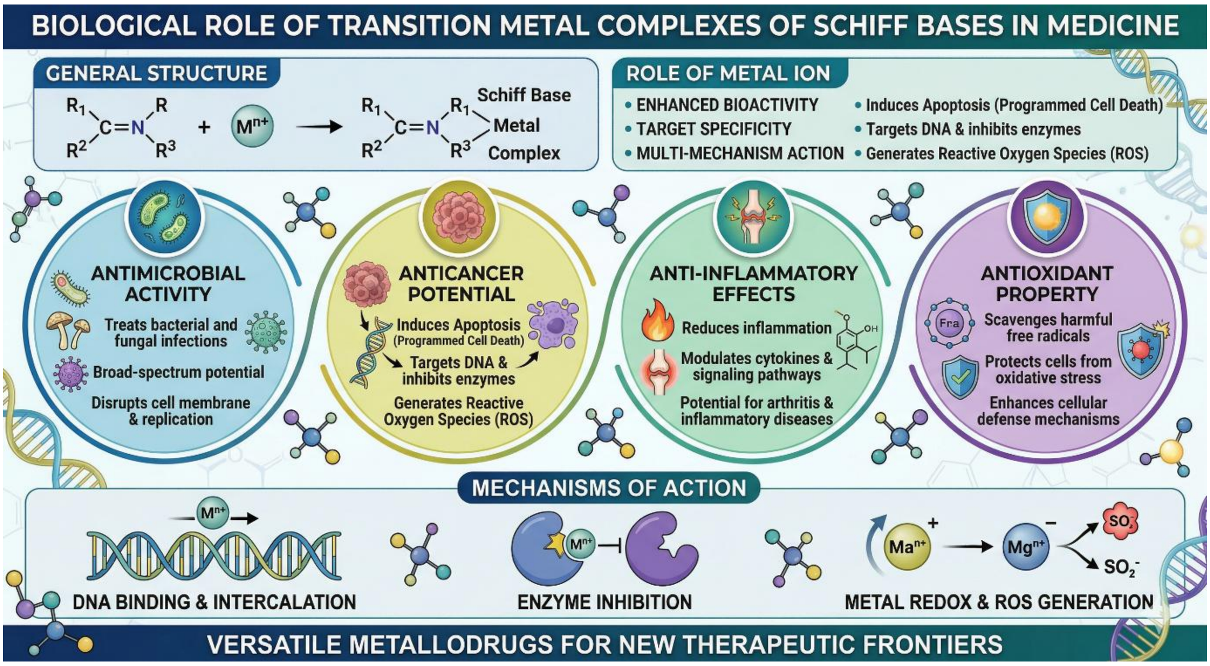

Figure 2: General Structure & Synthesis

Precision Targeting: Schiff Bases as Efficacious Enzyme Inhibitors

Transition metal Schiff base complexes have been found by scientists to act as targeted enzyme inhibitors, and their potential for medical use is significant.Enzyme inhibitors present a more precise treatment method than broad-spectrum cytotoxins because they block particular metabolic routes which pathogens need to survive and which diseases need to progress. The function requires transition metal complexes because their metal center can eitheract as a Lewis acid which binds with active site amino acids of the enzyme oract as a structural framework which presents the Schiff base ligand for specific hydrophobic or hydrogen-bonding connections. Scientists have conducted extensive research to discover how Urease exists in Helicobacter pylori because this enzyme helps the bacteria survive in stomach acid conditions [12]. The Copper(II) and Nickel(II) Schiff base complexes perform better at inhibiting urease enzyme activity than standard inhibitors which include acetohydroxamic acid. The compounds show effectiveness against Carbonic Anhydrase which functions in glaucoma and some cancer types. The metal complex effectively blocks the active site because it disrupts the zinc-catalyzed process which hydrates carbon dioxide [13]. The primary target for research involves protease suppression because these enzymes play essential roles in both viral replication and tumor invasion. Scientists have discovered that Cobalt(III) and Ruthenium(II) Schiff base complexes can permanently bind to protease active sites which enables researchers to create new antiviral and antimetastatic drugs [14].

Molecular Governance: Mechanisms of Action

The biological efficiency of transition metal Schiff base complexes depends on specific physicochemical factors which determine their interaction with cellular targets. The coordination of a metal ion to a multidentate Schiff base results in a reduction of the metal center's polarity according to Tweedy's Chelation Theory [15]. The metal center demonstrates partial positive charge distribution to the nitrogen and oxygen donor atoms which constitute the azomethine framework. The complex demonstrates increased lipophilicity which enables it to pass through lipid-rich pathogen and tumor cell membranes through passive diffusion according to Overtone's Concept.

The complexes initiate their functions through various operational methods after they enter the body. The agents act as Lewis acids when they bond with vital enzymes through thiol or hydroxyl group interactions which disrupt the enzymes' ability to catalyze reactions. The redox cycling process involves various transition metal complexes, especially copper and iron, which participate in this process [16]. The Fenton-type processes generate Reactive Oxygen Species (ROS) which cause permanent oxidative harm to mitochondrial membranes and genomic DNA. The multi-modal mechanism of action combines structural mimicry with membrane penetration and oxidative stress to ensure that Schiff base complexes maintain their effectiveness against resistant biological strains.

II. Conclusion and Future Prospects

The current medical field relies on transition metal Schiff base complexes because their structural flexibility and their chemical properties enable multiple practical applications. The review demonstrates that the combined properties of azomethine and Copper Zinc and Ruthenium transition metals create a design system that can solve multiple medical challenges which involve treating multidrug-resistant bacteria and fungi and aggressive malignant carcinomas. Researchers have developed molecules that achieve better biological barrier movement than their organic counterparts according to the principles of Tweedy's Chelation Theory and Overtone's Concept while displaying multiple action mechanisms which include DNA intercalation and location-specific enzyme inhibition.

The scientific community still faces major difficulties because researchers need to translate their laboratory discoveries into practical medical applications. Researchers need to address three main problems which involve the coordination compounds showing permanent toxic effects throughout their existence and their inability to maintain metabolic processes and their need for water-soluble coordination compounds. Researchers need to study how nanotechnology and personalized delivery systems work together. The therapeutic value of Schiff base complexes increases when researchers combine them with biocompatible nanocarriers which include gold nanoparticles and liposomes because these combinations enable targeted drug delivery to both tumor sites and infected body areas. The research of smart complexes which activate through specific triggers that include pH changes and enzymatic activities will help researchers create methods to eliminate unwanted side effects from their work.

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