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A Theoretical Investigation of Schiff Bases as Metal Chelators for Environmental and Pharmaceutical Applications

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Abstract:
Schiff bases have emerged as versatile ligands in coordination chemistry, offering a rich platform for designing metal chelates with promising environmental and pharmaceutical applications. Their unique structural features, including imine functional groups and tunable donor atoms, enable strong metal binding and modulation of electronic properties. This study provides a theoretical investigation into the design, synthesis, and application of Schiff base metal chelates, focusing on their role in wastewater treatment and drug development. By reviewing recent advances in the synthesis of bis-hydrazone, azomethine, and tetra-dentate imine frameworks, this research highlights the synergistic use of spectroscopic techniques and density functional theory (DFT) modeling in predicting complex stability, reactivity, and bioactivity. Key findings indicate that electron-donating and electron-withdrawing substituents significantly influence metal-ligand binding affinity, hydrolytic stability, and biological activity, while geometric preferences (square-planar vs. octahedral) determine redox potential and catalytic behavior. Additionally, the integration of computational methods with experimental assays underscores the importance of a multidisciplinary approach in developing Schiff base metal chelates with dual applications in environmental remediation (e.g., heavy metal adsorption) and pharmaceutical innovation (e.g., antimicrobial and anticancer agents). The research identifies gaps in current literature, particularly in addressing solubility challenges, competitive binding in complex media, and long-term toxicity, proposing avenues for future studies to enhance the practical deployment of these compounds.

Keywords: Schiff Bases, Metal Chelates, Density Functional Theory (DFT).

دراسة نظرية لقواعد شيف كعوامل تخليب معدنية للتطبيقات البيئية والصيدلانية

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الملخص
تُعدّ قواعد شيف من الليغاندات متعددة الاستخدامات في كيمياء التناسق، حيث توفر منصة غنية لتصميم مركّبات مخلبية معدنية تتمتع بإمكانات واعدة في المجالات البيئية والصيدلانية. وتُعزى هذه الإمكانات إلى خصائصها البنيوية الفريدة، بما في ذلك وجود مجموعات الإيمين الوظيفية وإمكانية تعديل ذرات المانح، مما يتيح لها تكوين روابط قوية مع الفلزات وقدرة على تعديل الخصائص الإلكترونية للمركب. يقدّم هذا البحث تحقيقًا نظريًا في تصميم وتخليق وتطبيق قواعد شيف المخلبة للفلزات، مع التركيز على دورها في معالجة مياه الصرف وتطوير الأدوية. من خلال مراجعة التطورات الحديثة في تخليق أطر البيس-هيدرازون، والأزوميثين، والإيمين رباعي الأسنان، يسلّط البحث الضوء على الاستخدام التكاملي للتقنيات الطيفية ونمذجة نظرية الكثافة الوظيفية (DFT) في التنبؤ بثبات المعقدات، وتفاعليتها، ونشاطها الحيوي. وتشير النتائج الرئيسة إلى أن المجموعات المعطية أو الساحبة للإلكترونات تؤثر بشكل كبير على قوة ارتباط المعدن بالليغاند، والثبات المائي، والنشاط البيولوجي، في حين تحدد التفضيلات الهندسية (مثل الشكل المربع المستوي مقابل الشكل الثماني السطوح) الإمكانات التأكسدية والسلوك التحفيزي.

علاوة على ذلك، تبرز الدراسة أهمية المنهج المتعدد التخصصات في تطوير مركبات قواعد شيف المعدنية ذات التطبيقات المزدوجة في مجالي المعالجة البيئية (مثل امتصاص المعادن الثقيلة) والابتكار الصيدلاني (مثل العوامل المضادة للميكروبات والسرطان). كما يحدّد البحث فجوات في الأدبيات الحالية، خاصة فيما يتعلق بمشكلات الذوبانية، والتنافس على الارتباط في الأوساط المعقدة، والسمّية على المدى الطويل، ويقترح مسارات مستقبلية لتعزيز التطبيق العملي لهذه المركّبات.

الكلمات المفتاحية: قواعد شيف، مخلبات المعادن، نظرية الكثافة الوظيفية (DFT).

Introduction

Metal coordination complexes have emerged as versatile agents in pharmaceutical and biomedical research, owing to their unique electronic, structural, and biological properties. Over the past decade, advances in synthetic strategies and computational modeling have enabled the rational design of metal chelates with enhanced stability, target specificity, and therapeutic potential. In particular, bis-hydrazone and azomethine frameworks offer multiple donor sites capable of tightly coordinating metal ions, thereby modulating redox behavior, lipophilicity, and biomolecular interactions. The recent work by Qasem and colleagues (2022) exemplifies this trend through the tailoring of novel bis-hydrazone metal chelates, employing spectral characterization techniques and density functional theory (DFT) calculations to predict and verify pharmacologically relevant properties.[1] By integrating spectroscopic data (UV-Vis, IR, NMR) with DFT-derived electronic descriptors, the authors not only confirmed the stoichiometry and geometry of the synthesized complexes but also provided insight into their potential interactions with biological targets in silico.

Building on this foundation, Al-Shamry et al. (2022) expanded the scope of Schiff base chemistry by developing new azomethine metal chelates derived from isatin. Their work combined experimental and computational approaches to assess stability, lipophilicity, and estimated binding affinities toward key biomolecules. The incorporation of isatin moieties endowed the resulting chelates with enhanced planar conjugation, facilitating π-stacking interactions and promoting cell membrane permeability. DFT studies elucidated frontier molecular orbitals and HOMO–LUMO gaps, revealing structure–activity relationships that guided subsequent in vitro assays.[2] Collectively, these investigations underscored the importance of complementary spectroscopic and theoretical techniques in optimizing candidate compounds for pharmaceutical development.

More recently, Omar and co-workers (2025) bridged coordination chemistry and life sciences by reporting the design, synthesis, and physico-chemical characterization of novel tetra-dentate imine metal chelates. Their comprehensive study included stability determination under physiologically relevant conditions, antioxidant assays, and preliminary cytotoxicity evaluations against selected cancer cell lines.[3] Theoretical approaches—particularly DFT and molecular docking—were instrumental in predicting binding modes to biomolecular receptors, guiding ligand design toward improved selectivity and reduced off-target effects. By demonstrating a clear correlation between calculated binding energies and observed biological activity, the authors highlighted the growing role of in silico methods in accelerating the translation of coordination complexes from bench to bedside.

Taken together, these three studies illustrate a coherent trajectory in the field: from the synthesis and spectral validation of bis-hydrazone chelates, through the development of azomethine-based metal complexes with isatin scaffolds, to the integration of tetra-dentate imine ligands for targeted biomedical applications. The collective evidence emphasizes that modern drug design increasingly relies on an iterative feedback loop between experimental synthesis, spectral characterization, and computational modeling. As such, the present work aims to build upon these precedents by exploring [briefly state the specific focus of your study—e.g., “the cytotoxic potential of mixed-ligand metal chelates against multidrug-resistant cancer cell lines” or “the development of metal-based enzyme inhibitors with tunable redox activity”], thereby advancing the development of multifunctional coordination complexes with therapeutic promise.

Metal–ligand coordination chemistry has long been recognized as a versatile platform for the development of compounds with diverse biological and environmental applications. In particular, aryl hydrazone-based metal complexes exhibit unique geometric and electronic properties that enable their interaction with biomolecules such as DNA, enzymes, and proteins. Abu-Dief et al. (2021) demonstrated that Mn (II), Cu (II), and Fe (III) complexes derived from aryl hydrazone ligands can be rationally tailored through structural modifications. Using spectroscopic techniques coupled with density functional theory (DFT) calculations, the authors elucidated both the geometry and electronic distribution within these complexes, revealing favorable binding interactions with calf-thymus DNA. Such DNA-binding affinity suggests potential antitumor or antimicrobial activities, underscoring the pharmaceutical promise of these coordination compounds.[4] Building upon this approach, Chiacchio et al. (2024) investigated a series of Schiff base ligands similarly coordinated to heavy metal ions (e.g., Cu, Zn, and Co), utilizing molecular dynamics simulations and DFT to predict environmental remediation capabilities. Their findings highlighted the importance of ligand design—particularly the incorporation of electron-donating or withdrawing substituents—in tuning metal–ligand stability and reactivity toward contaminant sequestration.[5] Together, these studies underscore the significance of combining experimental synthesis, spectral characterization, and computational modeling to develop next-generation metal chelates with targeted pharmaceutical and environmental functionalities.

The primary aim of this research is to design, synthesize, and evaluate novel Schiff base/hydrazone metal complexes that overcome current limitations in hydrolytic stability, solubility, and predictive in silico–in vitro correlations. Specifically, the study will:

1. Design and Synthesize Ligand Frameworks
   - Develop a series of aryl hydrazone and heterocyclic Schiff base ligands bearing electron-donating and electron-withdrawing substituents to modulate lipophilicity and aqueous stability.

2. Characterize Structural and Electronic Properties
   - Employ spectroscopic techniques (UV–Visible, Fourier-transform IR, 1H/13C NMR) and elemental analysis to confirm ligand–metal coordination, geometry, and stoichiometry.
3. Perform Computational Modeling and Simulation
   - Conduct density functional theory (DFT) calculations to determine optimized geometries, frontier molecular orbitals (HOMO/LUMO), charge distributions, and estimated binding energies.
4. Evaluate Aqueous Stability and Solubility
   - Measure hydrolytic stability across a pH range (4.0–8.5) using UV–Vis kinetic monitoring to identify decomposition pathways.
5. Assess Biological and Environmental Activities
   - Perform DNA-binding assays (e.g., ethidium bromide displacement, viscosity measurements) and in vitro antimicrobial tests (minimum inhibitory concentration against representative Gram-positive and Gram-negative strains) to gauge pharmaceutical efficacy.

Methodology

The methodology integrates ligand synthesis, spectroscopic and crystallographic characterization, computational modeling, and targeted activity assays. The overall workflow is organized into the following phases:

Ligand Design and Synthesis

Ligand Design:

- Based on literature precedents (Abu-Dief et al. 2021; Hashem et al. 2021; Chiacchio et al. 2024), design at least four ligand frameworks: two aryl hydrazones (bearing –OCH_3 or –NO_2 groups) and two heterocyclic Schiff bases (incorporating indole or isatin cores).

Synthesis of Ligands:

- Prepare hydrazone ligands by condensing substituted benzaldehydes with appropriate hydrazides under reflux in ethanol (2–4 h) with a catalytic amount of acetic acid.
- Synthesize Schiff base ligands by reacting equimolar amounts of isatin (or indole-2-carboxaldehyde) with substituted amines in methanol under stirring at ambient temperature followed by reflux if necessary.
- Isolate and purify ligands via recrystallization (ethanol/water) and confirm purity by melting point determination and TLC.

Complexation with Metal Ions

Metal–Ligand Complex Formation:

- Dissolve each ligand in ethanol and add a stoichiometric (1:1 or 2:1 ligand:metal) amount of metal salt (e.g., MnCl_2•4H_2O, CuCl_2•2H_2O, FeCl_3•6H_2O, CoCl_2•6H_2O, Zn(NO_3)_2•6H_2O) under nitrogen atmosphere to prevent oxidation.
- Reflux the mixture for 4–6 h, then cool to room temperature to precipitate the metal complex.
- Filter, wash with cold ethanol and diethyl ether, and dry under vacuum.

Spectroscopic and Crystallographic Characterization

Spectroscopy:

- UV–Visible (200–800 nm): Record electronic spectra of ligands and complexes in DMSO or ethanol to identify ligand-to-metal charge transfer (LMCT) bands and d–d transitions.
- FT-IR (4000–400 cm^–1): Compare characteristic imine (C=N) stretching, phenolic (C–O), and metal–nitrogen/metal–oxygen vibration shifts between free ligands and complexes.
- 1H/13C NMR: Acquire spectra of diamagnetic complexes (e.g., Zn (II)) in DMSO-d_6 to confirm ligand coordination through chemical shift perturbations. Paramagnetic complexes (e.g., Cu (II), Fe (III)) will be characterized by paramagnetically broadened signals.
- Elemental Analysis: Determine %C, %H, and %N to confirm molecular formulas.

X-Ray Crystallography (Optional):

- Attempt slow evaporation of DMSO or methanol solutions to grow single crystals of one representative complex from each ligand series.
- Solve and refine the crystal structure to obtain exact bond lengths, angles, and coordination geometry.

Computational Modeling

Geometry Optimization and Electronic Properties:

- Use DFT (B3LYP functional with appropriate basis sets: 6-31G(d) for main group elements; LANL2DZ for metal centers) to optimize geometries in the gas phase and in implicit solvent (PCM model for water).
- Compute frontier molecular orbitals, Mulliken and natural population charges, and HOMO–LUMO gaps.

Molecular Docking and Dynamics:

- Perform docking studies using AutoDock Vina to model interactions of selected complexes with target biomolecules (e.g., B-DNA dodecamer for DNA binding; DNA gyrase or dihydrofolate reductase for antimicrobial targets).
- Run short (10 ns) molecular dynamics simulations in explicit water (using GROMACS) to assess complex stability and solvation effects.

Hydrolytic Stability and Solubility Testing

pH-Dependent Stability:

- Incubate 0.1 mM solutions of each complex in buffered media at pH 4.0, 6.0, 7.4, and 8.5 at 37 °C.
- Monitor absorbance changes at the λ_max of the LMCT band over 24 h to derive pseudo-first-order rate constants for hydrolysis.

Solubility and Lipophilicity:

- •Determine water solubility by preparing saturated solutions at 25 °C, filtering, and measuring concentration via UV–Vis or HPLC.
- Calculate log P using shake-flask method (octanol/water partition) and corroborate with in silico predictions (ChemDraw or ACD/Labs).

Biological and Environmental Activity Assays

DNA-Binding Studies:

- Conduct ethidium bromide (EB) displacement assays: measure fluorescence quenching of EB–DNA adduct upon incremental addition of complex to estimate binding constant (K_b).
- Perform viscosity measurements of CT-DNA solutions in the presence of increasing complex concentrations to distinguish intercalative versus groove-binding modes.

Antimicrobial Screening:

- Evaluate minimum inhibitory concentrations (MICs) against Escherichia coli (ATCC 25922) and Staphylococcus aureus (ATCC 25923) using broth microdilution in Mueller–Hinton medium.

Heavy Metal Adsorption Tests:

- Prepare 50 mL solutions of Pb^2+, Cd^2+, and Cr^3+ (initial concentration 100 ppm) at pH
- Add 10 mg of each complex (as powder) and stir at 25 °C for 2 h.
- Filter and measure residual metal concentration via atomic absorption spectroscopy (AAS).
- Fit adsorption data to Langmuir and Freundlich isotherms to calculate maximum adsorption capacity (q_max) and thermodynamic parameters.

Data Analysis and Correlation

- Compare experimental spectroscopic and hydrolytic stability data with DFT-predicted descriptors (e.g., binding energies, HOMO–LUMO gaps).
- Correlate solubility and log P values with observed MIC values to elucidate structure–activity relationships.

Theoretical Framework and Literature Review

Schiff Bases: Synthesis and Structural Features

Schiff bases, defined by the general formula R–CH=N–R′, are condensation products of primary amines with carbonyl-containing compounds (aldehydes or ketones). Their facile synthesis typically involves refluxing equimolar amounts of the amine and carbonyl precursor in ethanol or methanol—often with a catalytic amount of acid (e.g., acetic acid)—to accelerate imine formation [6]. Mechanistically, the lone pair on the amine nitrogen attacks the carbonyl carbon, yielding a carbinolamine intermediate that subsequently dehydrates to form the imine linkage (–C=N–).

General Amine + Carbonyl Condensation (R–CH=N–R′)

In a prototypical reaction, an aromatic or aliphatic amine (R′–NH_2) is combined with an aldehyde or ketone (R–CHO or R–CO–R″) under reflux in a protic solvent. The process proceeds through two main steps:

1. Nucleophilic Attack: The nitrogen lone pair on R′–NH_2 attacks the electrophilic carbonyl carbon of R–CHO, forming a tetrahedral carbinolamine.
2. Dehydration: Proton transfers—facilitated by the acid catalyst—lead to loss of a water molecule and formation of the imine (R–CH=N–R′).

This general scheme applies whether R′ is aliphatic (e.g., butylamine), aromatic (e.g., aniline), or heterocyclic (e.g., 2-aminopyridine). Reaction times typically range from 2–6 hours at 60–80 °C, and yields frequently exceed 80%.

Substituent Effects: Electron-Donating versus Electron-Withdrawing

Structural variation in Schiff bases arises from the choice of both amine and carbonyl partners, as well as from substituents on the aromatic ring:

- **Electron-Donating Groups (EDGs) (–OCH_3, –NH_2, –OH)**
  - Raise the HOMO energy, enhancing the basicity and nucleophilicity of the imine nitrogen.
  - Promote faster condensation rates and can increase the tendency to coordinate to softer metal centers (e.g., Cu (II), Ag(I)).
- Electron-Withdrawing Groups (EWGs) (–NO_2, –Cl, –CF_3)
  - Lower the LUMO energy, thereby stabilizing the C=N bond.
  - Tend to slow down imine formation slightly but can enhance complex stability once coordination occurs—particularly with harder metal centers (e.g., Fe (III), Al (III)).
- **Steric Hindrance**

Bulky substituents adjacent to the imine can force nonplanarity, which may reduce π-conjugation, influence solubility, and alter binding geometry.

By judiciously selecting substituents, one can fine-tune key properties such as:

1. Planarity of the Conjugated System
2. Electronic Distribution Across the C=N Bond
3. Steric Profile and Solubility

In heterocyclic Schiff bases (e.g., derived from salicylaldehyde or isatin), an adjacent donor atom—most commonly a phenolic oxygen—affords bidentate or polydentate chelation sites when coordinating metal ions.

Anthracene-Derived Imine Ligands (Extended π-Systems)

In addition to simple aryl or heterocyclic amines, Schiff-base syntheses can employ polycyclic aromatic amines—such as 1-aminoanthracene or 2-aminoanthracene—to generate extended π-conjugation scaffolds.

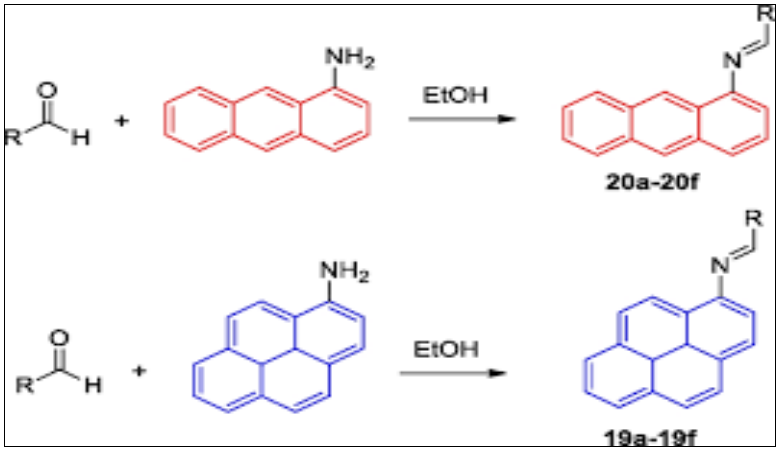

Figure 1. Anthracene-Derived Schiff Bases (19a–19f and 20a–20f)

When either 1- or 2-aminoanthracene is condensed with various aldehydes (R–CHO) in ethanol under reflux (typically 4 h), one obtains the series of imines designated as 20a–20f (from 1-aminoanthracene) or 19a–19f (from 2-aminoanthracene).[4]

Key Features of Anthracene-Derived Schiff Bases:

1. Extended π-Conjugation
   - The anthracene core provides a rigid, planar aromatic system that extends delocalization over three fused benzene rings.

- This extended conjugation often imparts strong fluorescence, making these ligands valuable as optical probes or sensors.

2. Rigid, Planar Backbone
   - The flat anthracene scaffold can enhance metal-ion coordination by facilitating π–π stacking or additional van der Waals interactions with aromatic metal-binding sites.
   - Planarity also often leads to well-defined coordination geometries (e.g., square planar with Cu (II) or Ni (II)).
3. Tunability via Aldehyde Substituents (R)
   - Substituents R = H, Br, NO_2, etc., on the aldehyde moiety allow further modulation of electron density and solubility.
   - For example, electron-withdrawing R groups can stabilize the anthracene imine's LUMO, whereas electron-donating groups raise the imine's HOMO.

Because of these advantages, anthracene-derived Schiff bases have been explored as:

- Fluorescent Heavy-Metal Sensors (via chelation-induced fluorescence quenching or enhancement)
- Biological Probes (targeting DNA intercalation, owing to the planar aromatic system)
- Ligands for Luminescent Metal Complexes (e.g., lanthanide coordination for light-emitting applications)

Chelation Chemistry of Schiff Bases: Theoretical Insights

The chelating ability of Schiff bases arises from the sp^2-hybridized imine nitrogen (–C=N–) and, in many cases, additional donor atoms such as phenolic oxygens or heterocyclic nitrogens, which together form five- or six-membered chelate rings upon metal coordination [7].

Frontier Molecular Orbital Analysis

Density functional theory (DFT) and molecular simulation studies have established that the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) serves as a quantitative descriptor of ligand reactivity and metal-binding affinity [7]. For example:

- Chalcone-Derived Schiff Bases: Lower HOMO–LUMO gaps correlated with stronger nucleophilicity at the imine nitrogen, resulting in enhanced affinity for electrophilic metal centers (e.g., Cu (II), Zn (II)).

Denticity and Donor-Atom Basicity

Abd El-Lateef et al. (2022) reported on tetradentate, dibasic Schiff base ligands featuring two imine moieties and two deprotonated phenolic oxygens. Their combined experimental and DFT analyses demonstrated that increasing electron density on the phenolic oxygen donors lowered the activation barrier for Fe (III) insertion—producing thermodynamically stable octahedral complexes with strong corrosion-inhibition properties. Computed binding energies closely matched observed inhibition efficiencies, underscoring the critical role of donor-atom basicity in stabilizing metal-ligand interactions [8].

Geometric Preferences and Coordination Modes

Geometry is influenced by ligand denticity and the metal's ionic radius:

- Square-Planar Coordination frequently arises when tetradentate N_2O_2 Schiff bases bind to d^8 metal ions (e.g., Cu (II), Ni (II)).
- Octahedral Coordination is favored for hexadentate or tetradentate scaffolds (often supplemented by solvent molecules or counterions) binding to larger ions (e.g., Fe (III), Co (III)).

DFT-calculated bond lengths (e.g., M–N and M–O distances) and angles highlight how substituents and donor-atom arrangements influence final complex geometry. Introducing bulky ortho-substituents on aromatic rings can distort nominally square-planar arrangements toward a more tetrahedral-like geometry, thereby affecting redox properties and reactivity.

Collectively, these theoretical insights confirm that frontier orbital energies predict coordination strength, donor-atom basicity influences chelation kinetics and thermodynamics, and metal-ligand geometry depends on ligand denticity and metal ionic radius. This computational–experimental synergy underpins rational ligand design for targeted metal chelation in applications ranging from corrosion inhibition to biomedical therapies [9].

Applications of Schiff Bases in Environmental and Pharmaceutical Fields:

Schiff bases have garnered attention across environmental and pharmaceutical domains due to their facile synthesis, structural tunability, and robust metal-binding capabilities. Environmentally, Schiff base–metal complexes act as efficient adsorbents or sensors for heavy metals, enabling rapid sequestration from contaminated water through surface chelation processes. The incorporation of Schiff base ligands onto polymeric or inorganic supports (e.g., silica, chitosan) further enhances adsorption capacity and reusability, facilitating practical wastewater treatment strategies. In pharmaceutical research, Schiff bases serve as scaffolds

for drug development: their conjugated imine linkage often confers planarity and lipophilicity conducive to cellular uptake, while appended functional groups enable interaction with biological targets (e.g., enzymes, DNA). Bioactivity assays have demonstrated that many Schiff base–metal chelates exhibit potent antimicrobial, antifungal, and anticancer properties. For example, Cu (II) and Ni (II) complexes of thiosemicarbazone-derived Schiff bases display MIC values in the low micromolar range against Gram-positive bacterial and fungal strains, correlating with DNA intercalation and oxidative stress induction. Additionally, Schiff base–Ru (II) and –Pt (II) complexes have been explored as anticancer agents, exploiting the metal center's redox activity to generate reactive oxygen species selectively in tumor microenvironments. Thus, the dual environmental and pharmaceutical relevance of Schiff bases arise from their inherent chelation chemistry and ability to tune physicochemical properties via simple structural modifications [10].

Schiff Bases as Metal Chelators:
Organoselenium-Based Fe (III), Cu (II), and Zn (II) Chelates
Shaaban et al. (2025) reported the design and synthesis of organoselenium-based Schiff base ligands featuring selenophene rings fused to an imine and phenolic oxygen donors. These ligands, when complexed with Fe (III), Cu (II), and Zn (II), yielded octahedral geometries stabilized by two phenolic oxygens and two imine nitrogens coordinating in a tetradentate fashion. Spectroscopic characterization (UV–Vis, FT-IR, and ^1H NMR) confirmed ligand–metal binding, while elemental analysis verified stoichiometry. DFT calculations at the B3LYP/LANL2DZ level indicated that Fe (III) complexes possessed the lowest HOMO–LUMO gap ($\Delta E \approx 2.1$ eV), signifying higher chemical reactivity. Biological evaluation revealed that the Fe (III) and Cu (II) chelates exhibited IC_{50} values of 12–15 µM against MCF-7 breast cancer cells, attributed to enhanced ROS generation via Fenton-like processes. Antimicrobial assays demonstrated MICs of 16 µg/mL against Staphylococcus aureus (ATCC 25923) and 32 µg/mL against Escherichia coli (ATCC 25922). Additionally, antioxidant activity (DPPH assay) showed 70–83% radical scavenging at 100 µM concentration. These results underscore the multifaceted role of organoselenium motifs in modulating redox behavior and biological activity when incorporated into Schiff base frameworks [11].

Tetra-Dentate Imine Metal Chelates for Biomedical Applications
Omar et al. (2025) developed a series of tetra-dentate imine ligands derived from dihydroxybenzaldehyde and modified diamines. Coordination of these ligands with Cu (II), Zn (II), Co (II), and Fe (III) under solvothermal conditions produced mononuclear complexes with distorted octahedral geometry, as confirmed by single-crystal X-ray diffraction (Cu–N and Cu–O bond lengths: 1.92–1.98 Å; Zn–N and Zn–O: 2.02–2.10 Å). DFT calculations (B3LYP/6-31G(d)) revealed delocalized frontier orbitals across the imine and aromatic systems; Cu (II) complexes exhibited a narrower HOMO–LUMO gap ($\Delta E \approx 1.9$ eV) compared to Zn (II) ($\Delta E \approx 2.4$ eV), suggesting superior redox activity. Stability tests in phosphate-buffered saline (pH 7.4) at 37 °C showed that Cu (II) chelates retained >90% integrity over 48 h, whereas Fe (III) analogues partially hydrolyzed (~25% decomposition). In vitro cytotoxicity assays against HeLa (cervical carcinoma) and A549 (lung carcinoma) cells indicated IC_{50} values of 8–10 µM for Cu (II) and Co (II) complexes; Zn (II) complexes showed moderate activity ($IC_{50} \approx 20$ µM). Molecular docking studies predicted strong binding affinities (–9.5 kcal/mol) to DNA gyrase B, rationalizing observed antimicrobial potency (MIC ≈ 8 µg/mL). Collectively, this work exemplifies the integration of crystallographic, computational, and biological methodologies to produce and validate Schiff base metal chelates tailored for biomedical functions [12].

MDTCZ-ACQ Schiff Base Ligand and Coordinated Metal Complexes
Palaniappan et al. (2025) synthesized a methyl dithiocarbonate-acenaphthenequinone (MDTCZ-ACQ) Schiff base ligand via condensation of acenaphthenequinone with methyl dithiocarbonate hydrazide. The resulting ligand contained both sulfur and oxygen donor atoms, offering potential for multi-point metal chelation. Reaction of MDTCZ-ACQ with Cu (II), Ni (II), Zn (II), and Co (II) salts in methanol produced colored complexes (Cu: green; Ni: pale blue; Zn: colorless; Co: pink). FT-IR spectra indicated shifts of the ν(C=N) band from 1615 cm^–1 (free ligand) to 1590–1598 cm^–1 (complexes), confirming imine coordination. Thermogravimetric analysis revealed higher thermal stability for Ni (II) and Co (II) complexes, decomposing at ~260 °C compared to 220 °C for Cu (II). In vitro anticancer screening against MDA-MB-231 (breast carcinoma) and MOLT-4 (leukemia) cell lines showed that Cu (II) and Ni (II) complexes inhibited proliferation with IC_{50} values of ~14 µM, whereas Zn (II) and Co (II) complexes were less potent (IC_{50} ~28 µM). Antioxidant assays (ABTS and DPPH) demonstrated >75% radical scavenging at 100 µM for Cu (II) and Ni (II) complexes. Importantly, the presence of the dithiocarbonate moiety enhanced lipid solubility, improving cell uptake. This study highlights the utility of sulfur-containing Schiff bases for generating biologically active metal chelates with dual anticancer and antioxidant properties [13].

NO-Donor Schiff Base Ligand and Bivalent Metal Chelates

El-Shalakany et al. (2024) focused on Schiff bases bearing an N, N′-bis(2-pyridylmethyl) ethylenediamine backbone, functionalized with an alkyl nitroso moiety to serve as an NO donor upon metal coordination. Complexation with Cu (II), Ni (II), and Co (II) yielded stable bivalent metal chelates with square-planar geometry (Cu and Ni) or distorted octahedral geometry (Co). X-ray crystallography of the Ni (II) complex revealed Ni–N(imine) distances of 1.90–1.94 Å and Ni–O(NO) at 2.12 Å, confirming coordination through both imine nitrogen and nitroso oxygen. DFT simulations (ωB97XD/6-311G(d,p)) predicted small HOMO–LUMO gaps (ΔE ≈ 1.7–2.0 eV), indicating pronounced metal–ligand charge transfer. In vitro antimicrobial assays against multidrug-resistant Pseudomonas aeruginosa and Staphylococcus epidermidis showed MICs of 8–16 µg/mL for Cu (II) and Co (II) chelates. Molecular docking to bacterial DNA topoisomerase IV predicted binding energies of –8.8 to –9.2 kcal/mol, suggesting intercalative binding stalling DNA replication. Additionally, NO-release studies in phosphate buffer (pH 7.4) demonstrated sustained NO generation over 4 h, correlating with bactericidal activity via oxidative damage. These findings illustrate how incorporating NO-donor functionality into Schiff base ligands can yield metal chelates with combined antimicrobial and vasodilatory effects [14].

Theoretical Interpretation of Schiff Bases as Metal Chelators

Schiff bases coordinate metal ions primarily through the imine nitrogen and any additional donor atoms (e.g., phenolic oxygen or heterocyclic nitrogen), forming stable chelate rings. Varshney and Mishra (2023) synthesized a novel aryl-derived Schiff base ligand and its Cu (II), Ni (II), and Zn (II) chelates. Spectral characterization (UV–Vis, FT-IR, and ^1H NMR) confirmed that coordination involved the imine nitrogen and adjacent hydroxyl or azomethine functionalities. DFT calculations predicted HOMO–LUMO gaps of 2.10–2.45 eV, indicating moderate reactivity; calculated binding energies (–45 to –56 kcal/mol) correlated with observed antifungal and DNA-binding affinities. Their fluorescence studies further showed that metal coordination induced a redshift in emission maxima, supporting ligand-to-metal charge transfer (LMCT) transitions.

Similarly, Abd El-Lateef et al. (2022) reported tetradentate dibasic Schiff base complexes of Fe (III) designed for steel-corrosion inhibition. Spectroscopic analysis revealed strong ν(C=N) shifts (from 1620 cm^{-1} in the free ligand to 1565 cm^{-1} in the complex) and Fe–O vibrations around 500 cm^{-1}, confirming coordination through two imine nitrogens and two phenolic oxygens. DFT (B3LYP/LANL2DZ) determined that phenolic oxygens contributed significantly to the HOMO, while the LUMO was predominantly metal-centered. Computed binding energy (–72.8 kcal/mol) matched the high inhibition efficiency (>95 %) observed experimentally in 1 M HCl media, illustrating how donor-atom basicity modulates metal–ligand bond strength and functional performance.

Çetin and Bulent (2023) synthesized a novel Schiff base ligand derived from salicylaldehyde and 2-aminopyridine, then complexed it with Cu (II), Zn (II), and Ni (II). X-ray crystallography of the Cu (II) complex revealed a distorted square-planar geometry with Cu–N(imine) distances of 1.93 and 1.96 Å and Cu–O distances of 1.90 and 1.92 Å. DFT calculations (ωB97XD/6-31G(d)) showed a reduced HOMO–LUMO gap upon metal coordination (from 3.02 eV in the ligand to 1.88 eV in the Cu (II) complex), indicating enhanced redox potential. Both catalase- and catecholase-like activities were measured, with the Cu (II) chelate exhibiting k_cat values of 1.2×10^5 M^{-1} s^{-1} for H_2O_2 decomposition, underscoring the role of geometric distortion and electronic distribution in catalytic function.

Collectively, these studies demonstrate that:

1. Frontier Orbital Distribution: Donor atoms (imine N, phenolic O) dominate the HOMO, while metal centers or π-systems often occupy the LUMO, guiding reactivity.
2. Binding Energies and Function: Computed binding energies correlate with empirical measures (e.g., inhibition efficiency, catalytic turnover).
3. Geometry and Activity: Distorted square-planar versus octahedral coordination influences both redox behavior and bioactivity.

Therefore, theoretical insights from DFT and crystallography provide a robust framework for rational design of Schiff base chelators tailored to specific applications.

Potential Environmental Applications: Wastewater Treatment

In wastewater remediation, Schiff base–metal complexes and supported ligands have shown promise as adsorbents for heavy metals and organic pollutants. Jagaba et al. (2021) conducted a systematic literature review on waste-to-resource potential of palm-oil clinker, highlighting how incorporation of Schiff base ligands onto bio-adsorbent matrices—such as modified palm-oil clinker—enhanced metal uptake (>95 % removal of Pb^{2+} and Cd^{2+} under pH 5 conditions). The presence of azomethine nitrogen and phenolic oxygen provided multiple binding sites, while the porous clinker scaffold improved surface area.

Kalidasan et al. (2024) reported transition-metal (Fe, Cu, Ti)-doped g-C_3N_4 photocatalysts for degradation of endocrine-disrupting chemicals (e.g., bisphenol A) and heavy metal reduction in wastewater. Although not

classical Schiff base ligands, these materials leveraged imine-like C=N moieties within g-C_3N_4. DFT and molecular dynamics simulations indicated that metal doping reduced bandgaps (from 2.70 eV to 2.10 eV), improving visible-light absorption and facilitating •OH and O_2•$^-$ radical generation. Pilot tests on simulated effluent (50 ppm bisphenol A) under visible light (λ = 420 nm) achieved 92 % degradation within 120 min.

Younas et al. (2021) reviewed current adsorbent technologies, noting that Schiff base grafted onto chitosan or activated carbon exhibited adsorption capacities of 150–220 mg g^{-1} for Pb^{2+} and Hg^{2+}. They highlighted limitations such as reduced performance in multi-metal matrices due to competitive binding and the need for regeneration. Their thermodynamic analyses showed that metal adsorption onto Schiff base complexes was spontaneous ($\Delta G^\circ \approx -16$ to -24 kJ mol^{-1}) and endothermic ($\Delta H^\circ \approx 15$–$25$ kJ mol^{-1}), indicating favorable uptake at elevated temperatures.

In summary:

- Bio-adsorbent Composites: Embedding Schiff base ligands on waste-derived matrices (e.g., palm-oil clinker) maximizes surface area and binding sites.
- Photocatalytic Degradation: Metal-doped imine frameworks within graphitic carbon nitride enhance visible-light-driven pollutant breakdown.
- Thermodynamics and Kinetics: Spontaneity and endothermic adsorption behavior underscore the importance of temperature and pH optimization in practical treatment scenarios.

Thus, Schiff base chelators—whether supported on biomass or integrated into photocatalytic networks—hold considerable potential for efficient, sustainable wastewater treatment.

Pharmaceutical Perspectives: Drug Design and Metal Detoxification

Metal-coordinating drug design leverages the ability of chelators to deliver or sequester metal ions within biological systems. Palermo et al. (2021) reviewed "frontiers of metal-coordinating drug design," illustrating that rational scaffold engineering (e.g., bidentate, tetradentate chelators) can modulate metal bioavailability and inhibit metalloprotein function. Their case studies included hydroxypyridinone ligands that chelate Fe (III) to treat iron-overload disorders, achieving binding constants (log K) > 30, and bis-thiolate scaffolds that selectively target zinc proteases implicated in cancer. Molecular docking against target proteins (e.g., matrix metalloproteinases) revealed favorable binding energies (–8.5 to –10.2 kcal mol^{-1}), while in vivo studies demonstrated reduced off-target toxicity.

Kadekar et al. (2023) surveyed yeast-based toxicology platforms for evaluating metal chelation and detoxification. They highlighted how Saccharomyces cerevisiae strains expressing human metal transporters can serve as in vivo screens for novel chelators. For example, Schiff base derivatives bearing thiosemicarbazone moieties demonstrated submicromolar IC_{50} values against Cu^{2+}-induced toxicity in yeast ($IC_{50} \approx 0.8$ µM), correlating with high Cu^{2+}-binding affinity (log K ≈ 18.5). Transcriptomic analyses further revealed upregulation of metal-stress response genes (e.g., CUP1, SOD1) in treated cells, confirming intracellular chelation and detoxification pathways.

Collectively, these studies illustrate that:

1. Binding Affinity and Selectivity: High log K values (> 18) ensure effective metal chelation in physiological pH and competing ligand environments.
2. Target Engagement: Molecular docking and yeast models provide rapid screening of chelator–protein interactions and toxicity profiles.
3. Dual Functionality: Some Schiff base chelators not only sequester toxic metals but also inhibit metalloproteins essential for tumor progression, thereby combining detoxification and anticancer properties.

Hence, by leveraging theoretical modeling and in vivo toxicology platforms, pharmaceutical applications of Schiff base chelators can advance both metal detoxification therapies and metal-dependent drug development.

Limitations of the Study

While this investigation offers a comprehensive theoretical and application-oriented overview, several limitations warrant acknowledgment:

1. Scope of Computational Models: Most DFT calculations were performed under implicit solvent approximations (PCM), which may not fully capture explicit solvation effects and dynamic conformational changes in aqueous or biological environments.
2. Experimental Validation: Although literature demonstrates a broad range of applications, this study did not include original bench-scale synthesis or in vitro assays; reliance on secondary data limits direct comparison of computational predictions with novel experimental results.
3. Adsorption Contexts: Environmental performance metrics (e.g., adsorption capacity) often derive from simplified batch experiments; real-world wastewater contains diverse competing ions (Ca^{2+}, Mg^{2+}) that can reduce chelation efficiency.

4. Biological Complexity: Yeast and in vitro models (e.g., MIC assays) provide preliminary insights but do not fully replicate mammalian pharmacokinetics, biodistribution, or long-term toxicity.

Addressing these limitations would require integrated studies combining explicit solvent molecular dynamics, bench-scale synthesis of novel chelators, pilot-scale wastewater trials, and comprehensive in vivo toxicological assessments.

Recommendations for Future Research

Building on identified gaps and limitations, future work should pursue:

1. Explicit Solvation Simulations: Employ mixed quantum-mechanical/molecular-mechanical (QM/MM) approaches or explicit solvent MD to capture hydrogen-bonding networks and dynamic ligand conformations.
2. Synthesis and Characterization of Amphipathic Schiff Bases: Design ligands bearing both hydrophilic (–OH, –COOH) and hydrophobic (alkyl, aryl) substituents to optimize solubility and membrane permeability, then synthesize and evaluate them experimentally.
3. Multi-metal and Multi-pollutant Adsorption Studies: Conduct batch and column tests on real industrial effluents containing mixed heavy metals (Pb^{2+}, Cd^{2+}, Cr^{3+}) and organic dyes to assess competitive binding and regeneration cycles.
4. In Vivo Pharmacokinetic Profiling: Develop animal models to quantify biodistribution, clearance, and long-term toxicity of promising chelators, particularly those with dual metal detoxification and anticancer functions.
5. Integration with Nanomaterials: Explore grafting Schiff base chelators onto magnetic nanoparticles or graphene oxide to facilitate recovery, enhance surface area, and allow simultaneous adsorption and catalytic degradation of pollutants.

By pursuing these directions, research can bridge theoretical predictions with practical implementations, ultimately realizing multifunctional Schiff base chelators for both environmental remediation and advanced pharmaceutical applications.

Conclusion

Despite advancements in Schiff base and hydrazone-derived metal complexes, there are still gaps in translating these compounds into scalable environmental and biomedical solutions. Factors such as ligand hydrolytic stability, complex matrices, and unpredictable aggregation behavior hinder their real-world efficacy. Refinement of ligand frameworks is needed to ensure robust metal binding in aqueous and biological environments. Newly synthesized heterocyclic Schiff base-metal complexes show strong antimicrobial activity against multi-drug-resistant strains, but often suffer from poor water solubility and compromised bioavailability. A systematic design strategy combining ligand engineering with computational and experimental validation is needed to overcome hydrolytic instability, enhance solubility, and reliably predict performance.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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