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Transition Metal Complexes of Isatin–Tryptamine Schiff Bases: An Emerging Platform for Antibacterial Research

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Abstract

Antimicrobial resistance has increased the need for new antibacterial agents with diverse structures and mechanisms of action. Isatin–tryptamine Schiff bases provide an attractive platform because their indole, carbonyl, and azomethine functionalities can support metal coordination and biological interactions. This review examines the synthesis, coordination chemistry, characterization, antibacterial activity, mechanisms of action, and structure–activity relationships of their transition-metal complexes. The effects of metal identity, coordination geometry, ligand structure, and physicochemical properties on antibacterial performance are considered, together with possible mechanisms involving membrane disruption, biomolecular interactions, enzyme inhibition, oxidative stress, and metal-mediated effects. Computational approaches, toxicity, selectivity, current limitations, and future research directions are also discussed. Overall, isatin–tryptamine metal complexes show promise as antibacterial candidates, but systematic mechanistic, toxicity, and structure–activity studies are required to establish their therapeutic potential.

Keywords: Isatin; tryptamine; Schiff bases; transition-metal complexes; antibacterial activity; antimicrobial resistance; coordination chemistry; structure–activity relationship.

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1.0 Introduction

Bacterial infections remain a major global health concern, particularly due to the increasing emergence of antimicrobial resistance (AMR). Resistant pathogens contribute to treatment failure, prolonged hospitalization, increased healthcare costs, and mortality, creating an urgent need for antibacterial agents with new structures and mechanisms of action. The growing prevalence of resistant Gram-positive and Gram-negative bacteria has encouraged the investigation of heterocyclic compounds,

molecular hybrids, Schiff bases, and metal-based compounds as alternatives to conventional antibiotics (Craig et al., 2024; Sati et al., 2025; World Health Organization, 2024). Transition-metal complexes are particularly promising because metal coordination can modify the physicochemical and biological properties of organic ligands and provide alternative mechanisms of antibacterial action (Jabbi et al., 2020; Jalal et al., 2020; Aminu et al., 2021; Ridal et al., 2026).

Schiff bases contain an azomethine (–C=N–) group, generally formed by condensation of primary amines with aldehydes or ketones. Their structural versatility and donor atoms enable coordination with transition-metal ions, producing complexes with different geometries, electronic properties, stability, and biological activities (Husaini, 2025; Jorge et al., 2024; Thakur et al., 2024). Metal coordination can alter charge, lipophilicity, redox behavior, and interactions with biological targets, potentially enhancing antibacterial activity relative to the free ligand (Arun et al., 2024; Sujatha et al., 2024). These properties have established Schiff-base metal complexes as important candidates in contemporary antimicrobial research.

Isatin (1H-indole-2,3-dione) is a versatile indole scaffold with reported antibacterial, antifungal, antiviral, anticancer, and other biological activities (Shaik et al., 2024; Rathi et al., 2025). Tryptamine contains an indole ring and primary amino group, making it suitable for Schiff-base formation and molecular hybridization. Indole-based compounds continue to attract attention in medicinal chemistry because of their diverse biological properties and antibacterial potential (Zeng et al., 2024; Chen, 2024; Er-rajy et al., 2025). Combining isatin and tryptamine therefore provides a rational platform for generating Schiff bases with an azomethine linkage and potential metal-binding sites, while subsequent metal coordination may further modify their geometry, electronic properties, lipophilicity, stability, and biological activity (Jorge et al., 2024; Shukla et al., 2025).

Despite extensive research on Schiff bases, isatin derivatives, and metal complexes, the relationship between isatin–tryptamine Schiff-base structure, metal coordination, and antibacterial activity remains insufficiently understood. Variations in metal identity, oxidation state, coordination geometry, ligand substitution, and antibacterial testing methods can complicate comparison of reported activities. Computational approaches such as molecular docking and quantum-chemical calculations can provide additional insight into molecular interactions and structure–activity relationships (Mansour et al., 2024; Bonne et al., 2024). Therefore, this review examines the synthesis, coordination chemistry, characterization, antibacterial activity, mechanisms of action, and structure–activity relationships of transition-metal complexes of isatin–tryptamine Schiff bases, with emphasis on identifying research gaps and guiding their rational development as potential antibacterial agents.

2.0 Chemistry of Isatin–Tryptamine Schiff Bases

2.1 Molecular Structure and Nomenclature

Isatin–tryptamine Schiff bases are formed through condensation of isatin (1H-indole-2,3-dione) with tryptamine, producing a characteristic azomethine (C=N) linkage (Bakır et al., 2024). The resulting ligand retains the isatin carbonyl group and contains potential donor sites through the azomethine nitrogen and carbonyl oxygen (Kaur et al., 2024). These donor atoms facilitate coordination with transition-metal ions, while the two indole-containing units contribute to the electronic and biological characteristics of the ligand. Substitution on the isatin or tryptamine moieties can further modify electronic distribution, steric properties, solubility, and biological activity (Kumar et al., 2024).

2.2 Synthesis of Isatin–Tryptamine Schiff Bases

The Schiff bases are generally synthesized by reacting isatin with tryptamine in suitable solvents such as ethanol or methanol (Bakır et al., 2024). Equimolar or near-equimolar quantities are commonly used, while heating or reflux can accelerate condensation and improve conversion. Appropriate reaction conditions can also enhance product formation and facilitate isolation (Kumar et al., 2024). The products may be isolated through precipitation, filtration, washing, or recrystallization, depending on their physical properties. Optimization of solvent, temperature, reaction time, and reactant ratio is important for obtaining satisfactory yield and purity (Meshram et al., 2025).

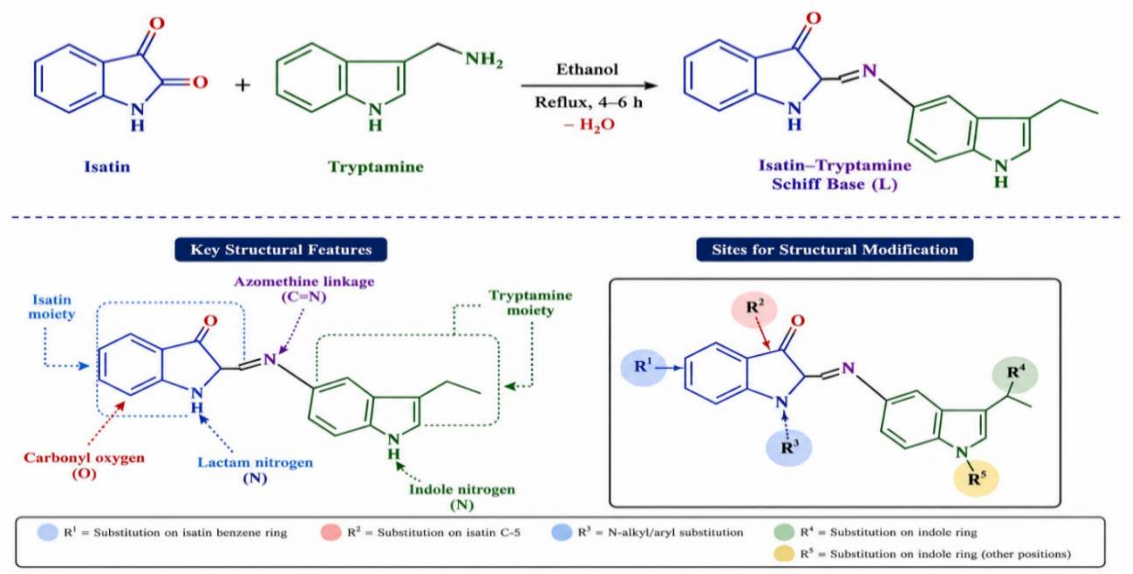

Figure 1: Structural Features and Synthetic Route of Isatin–Tryptamine Schiff Bases

2.3 Reaction Mechanism

Schiff-base formation begins with nucleophilic attack of the primary amino group of tryptamine on the electrophilic carbonyl carbon of isatin, producing a carbinolamine intermediate (Bakır et al., 2024).

Subsequent proton-transfer processes facilitate dehydration, resulting in formation of the C=N linkage and release of water. The equilibrium can be shifted toward Schiff-base formation by conditions that favor water removal (Pillai & Sivan, 2025). The resulting azomethine nitrogen and carbonyl oxygen constitute important donor sites for subsequent coordination with transition-metal ions.

2.4 Structural Modification of the Schiff Base

Structural modification of isatin–tryptamine Schiff bases can be achieved through substitution on the isatin or tryptamine-derived indole rings. Electron-donating and electron-withdrawing groups can alter the electronic characteristics and reactivity of the ligand (Bakır et al., 2024). Polar and hydrophobic substituents may influence solubility, molecular interactions, and biological activity (Kaur et al., 2024). Additional oxygen-, nitrogen-, or sulfur-containing groups can introduce supplementary donor sites and modify metal-binding behavior. Such structural changes provide opportunities to optimize ligand stability, coordination properties, and antibacterial performance (Bahrani-Pour et al., 2024; Meshram et al., 2025).

2.5 Factors Affecting Schiff Base Formation

The formation of isatin–tryptamine Schiff bases is influenced by electronic and steric effects, solvent, pH, temperature, reaction time, and reactant ratio. Electronic effects can influence carbonyl reactivity and amine nucleophilicity, whereas steric effects may hinder condensation. Solvent and temperature affect reactant solubility and reaction efficiency, while excessive acidity may reduce amine nucleophilicity. The stability and reactivity of isatin-derived Schiff bases are strongly influenced by their molecular and electronic characteristics (Al-amiery et al., 2023; Pillai & Sivan, 2025). Appropriate optimization of the reaction conditions is therefore necessary to obtain good yield and purity (Bakır et al., 2024).

3.0 Transition Metal Complexes of Isatin–Tryptamine Schiff Bases

3.1 Principles of Metal–Ligand Coordination

Transition-metal complexes form when metal ions interact with electron-donating atoms of Schiff-base ligands. The azomethine nitrogen and oxygen-containing groups commonly act as coordination sites, producing chelated structures with different geometries and electronic properties (Nandini & Amutha Selvi, 2025). The metal ion and ligand structure determine the coordination number, stability, and electronic configuration of the resulting complex (Poornima et al., 2025). These changes may also influence the physicochemical and biological properties of the ligand (Jorge et al., 2024).

3.2 Common Transition Metals

Transition metals commonly employed in Schiff-base chemistry include Cu(II), Co(II), Ni(II), Zn(II), Mn(II), Fe(II/III), and Cr(III). Their selection depends on oxidation state, electronic configuration, coordination preference, and biological properties (Bhowmik, 2024). Copper, cobalt, nickel, and zinc complexes are particularly important because they can adopt different geometries and exhibit diverse biological activities (Khan et al., 2025). Nevertheless, only metals supported by reliable evidence for the specific isatin–tryptamine system should be considered.

3.3 Coordination Modes

The coordination mode depends on the number and arrangement of donor atoms present in the ligand. Isatin–tryptamine Schiff bases may coordinate through the azomethine nitrogen and isatin carbonyl oxygen, while additional donor groups can provide further binding sites (Alam et al., 2024). These interactions may produce bidentate, tridentate, or bridging coordination depending on the ligand structure and metal ion. Such coordination patterns can significantly influence the geometry and biological properties of the complexes (Kumar et al., 2025).

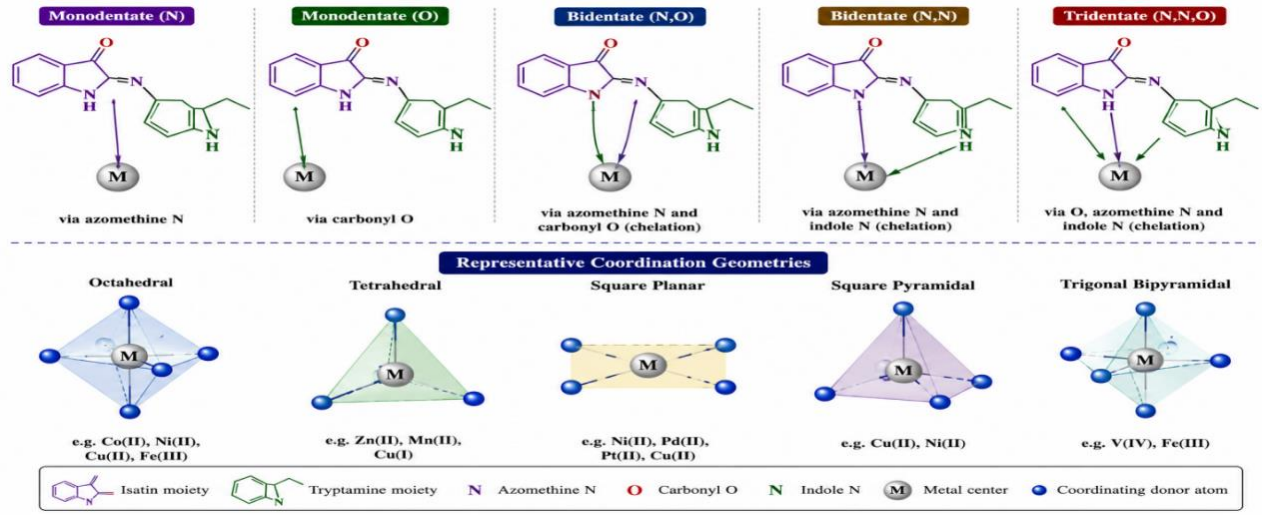

Figure 2: Coordination Modes and Representative Geometries of Transition Metal Complexes

3.4 Stoichiometry and Nuclearity

The metal-to-ligand ratio is influenced by ligand denticity, metal oxidation state, coordination number, and auxiliary ligands. Both 1:1 and 1:2 metal-to-ligand ratios are frequently encountered in Schiff-base complexes, while suitably designed ligands can also produce multinuclear structures (Kumar et al., 2025). Differences in stoichiometry and nuclearity can affect molecular geometry, stability, magnetic properties, and biological activity (Iacopetta et al., 2025). Therefore, the proposed composition should be confirmed using appropriate analytical and spectroscopic techniques.

3.5 Effect of Metal Ions on Ligand Properties

Metal coordination can modify the charge distribution, geometry, electronic structure, lipophilicity, solubility, and stability of Schiff bases. These changes may influence interactions with bacterial membranes and intracellular targets (Jorge et al., 2024). The identity and oxidation state of the metal can further affect redox behavior and biological activity (Rana et al., 2024). Consequently, metal selection and ligand structure are important factors in designing Schiff-base complexes with improved antibacterial properties (Barreras-Contreras et al., 2025).

4.0 Synthesis of the Metal Complexes

4.1 Conventional Complexation Methods

Metal complexes of Schiff bases are commonly prepared by reacting the ligand with an appropriate metal salt in a suitable solvent. Ethanol, methanol, water, and mixed solvents may be employed according to the solubility of the reactants. Conventional heating or refluxing promotes metal–ligand interaction and may require several hours for satisfactory complex formation. Reaction temperature, time, concentration, and metal-to-ligand ratio can influence the yield and purity of the products (Thakur & Bhalla, 2024).

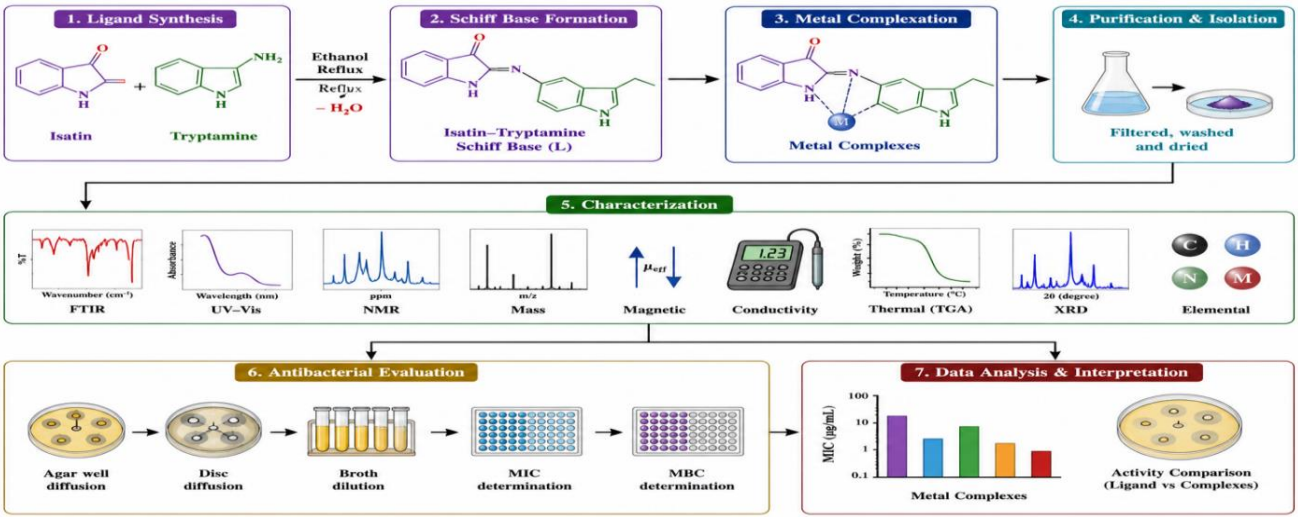

Figure 3: General Workflow for Synthesis, Characterization, and Antibacterial Evaluation

4.2 Effect of Metal Precursors

The metal precursor can influence the composition and coordination environment of the resulting complex. Chlorides, nitrates, acetates, and sulfates are commonly used because of their availability and suitable solubility. Depending on the system, the counter-ion may remain outside the coordination sphere or participate in coordination. Consequently, the choice of metal salt can affect stoichiometry, geometry, crystallization, and other physicochemical properties (Gogoi et al., 2024).

4.3 Optimization of Complex Formation

Efficient complex formation requires appropriate control of the metal-to-ligand ratio, solvent, temperature, concentration, reaction time, and pH. Optimization of these parameters can improve yield and minimize unwanted products. Reaction monitoring and spectroscopic analysis can help establish suitable conditions for complete coordination. Such optimization is particularly important when the complexes are subsequently evaluated for biological activity (Bargujar et al., 2024).

4.4 Stability and Solubility

The stability of a metal complex depends on the strength of metal–ligand interactions, ligand denticity, oxidation state, coordination geometry, and reaction medium. Solubility is influenced by molecular charge, polarity, hydrogen bonding, and the nature of coordinated or counter-ions. These properties are important because poor aqueous solubility may restrict biological applications, whereas insufficient stability can lead to complex dissociation during testing (Thakur & Bhalla, 2024).

4.5 Green Synthesis Approaches

Green approaches aim to reduce solvent use, reaction time, energy consumption, and chemical waste during complex preparation. Microwave irradiation can considerably shorten reaction times and may improve yields compared with conventional heating (Bargujar et al., 2024). Solvent-free, aqueous, ultrasound-assisted, and green-solvent methods provide additional alternatives to conventional synthesis (Thakur & Bhalla, 2024). These approaches are increasingly important for developing more efficient and environmentally sustainable Schiff-base metal complexes (Gogoi et al., 2024).

5.0 Characterization of Isatin–Tryptamine Schiff Base Complexes

Characterization is essential for establishing the molecular composition, coordination mode, geometry, and physicochemical properties of isatin–tryptamine Schiff-base metal complexes. Because no single analytical technique provides complete structural information, complementary spectroscopic, thermal, magnetic, diffraction, and elemental methods are generally required. These techniques collectively help confirm ligand formation, metal binding, complex stoichiometry, and structural features that may influence biological activity (Moustafa et al., 2024; Waziri et al., 2025).

5.1 FTIR Spectroscopy

FTIR spectroscopy is widely used to identify functional groups and investigate metal–ligand interactions. Schiff-base formation is associated with the azomethine ν(C=N) vibration, while coordination may cause a shift in this band. Changes in the isatin ν(C=O) band can indicate involvement of the carbonyl oxygen in coordination. Lower-frequency bands may also provide evidence for metal–N and metal–O bonds (Moustafa et al., 2024; Saad et al., 2024).

5.2 UV–Visible Spectroscopy

UV–Visible spectroscopy provides information on electronic transitions in Schiff bases and their metal complexes. The ligands commonly exhibit π→π* and n→π* transitions associated with conjugated and azomethine groups. Metal complexation may introduce d–d or charge-transfer transitions depending on the metal ion and its electronic configuration. Changes in absorption maxima can therefore support complex formation and provide information about the electronic environment of the metal centre (Waziri et al., 2025; Moustafa et al., 2024).

5.3 NMR Spectroscopy

NMR spectroscopy is particularly useful for studying diamagnetic Schiff bases and metal complexes. Changes in the ^{1}H NMR signals of the azomethine proton and other ligand protons can indicate structural changes following coordination. Similarly, ^{13}C NMR can reveal changes around the azomethine and carbonyl carbon atoms. Chemical-shift variations therefore provide useful supporting evidence for ligand structure and metal–ligand interactions (Abbass et al., 2025).

5.4 Mass Spectrometry

Mass spectrometry provides molecular-mass information that can support the proposed molecular formula of Schiff bases and their complexes. Molecular or characteristic fragment ions can be compared with calculated masses, while isotope patterns may provide additional information about metal-containing species. The technique therefore complements spectroscopic and elemental methods in establishing molecular composition (Moustafa et al., 2024; Waziri et al., 2025).

5.5 Magnetic Susceptibility

Magnetic susceptibility is particularly useful for transition-metal complexes containing unpaired electrons. The measured magnetic moment can provide information about the number of unpaired electrons, electronic configuration, and possible spin state of the metal centre. When combined with electronic spectra and other characterization results, magnetic measurements can also help distinguish between possible coordination geometries (Vijayalakshmi & Arockiasamy, 2025).

5.6 Molar Conductivity

Molar conductivity measurements provide information about the ionic character of metal complexes in solution. Conductivity values can help distinguish electrolytic complexes from predominantly non-electrolytic species and provide evidence concerning the position of counter-ions. This technique is therefore useful for supporting proposed formulations and coordination structures (Moustafa et al., 2024).

5.7 Thermal Analysis

Thermogravimetric analysis (TGA) and differential thermogravimetry (DTG) are useful for evaluating the thermal stability and decomposition behaviour of metal complexes. Initial mass losses may correspond to physically held or coordinated solvent molecules, whereas later stages may involve decomposition of the ligand framework. The temperature ranges and mass changes can consequently provide information about complex composition and thermal stability (Moustafa et al., 2024; Abbass et al., 2025).

5.8 Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) provides information about the crystalline nature and phase composition of synthesized complexes. Diffraction patterns can be used to assess crystallinity and identify differences between solid phases. Changes in peak positions and intensities following complex formation may reflect alterations in crystal structure. PXRD is especially useful when suitable single crystals cannot be obtained (Saad et al., 2024; Abbass et al., 2025).

5.9 Single-Crystal X-ray Diffraction

Single-crystal X-ray diffraction provides detailed structural information when suitable crystals are available. It can establish coordination geometry, metal–donor bond lengths, bond angles, ligand conformation, and the precise coordination mode. The technique can also reveal intermolecular interactions and crystal-packing arrangements, making it particularly valuable for confirming proposed molecular structures (Vijayalakshmi & Arockiasamy, 2025).

5.10 Elemental Analysis

Elemental analysis determines the percentages of carbon, hydrogen, nitrogen, and, where applicable, the metal present in a complex. Experimental values are compared with theoretical values calculated from the proposed molecular formula. Close agreement supports the assigned stoichiometry and provides complementary evidence for the proposed structure. Elemental analysis is therefore most informative when interpreted together with spectroscopic and other characterization techniques (Waziri et al., 2025; Moustafa et al., 2024).

6.0 Coordination Geometry and Electronic Structure

6.1 Octahedral Complexes

Octahedral geometry occurs when a metal centre is surrounded by six donor atoms, producing a structure commonly encountered in transition-metal Schiff-base complexes. The arrangement and ligand-field environment influence electronic transitions, magnetic properties, and stability. Isatin-

derived Schiff-base complexes have been reported with structural features that can be interpreted through spectroscopic, XRD, and DFT investigations (Moustafa et al., 2024). The electronic configuration of the metal ion and the nature of the coordinated donor atoms are important determinants of the resulting geometry and properties (Sindhu et al., 2025).

6.2 Tetrahedral Complexes

Tetrahedral complexes contain four donor atoms arranged around the central metal ion and are commonly associated with metal centres that favor four-coordinate environments. The geometry can influence orbital splitting, molecular polarity, and the accessibility of the metal centre. Schiff-base ligands may stabilize tetrahedral structures depending on their denticity, steric characteristics, and the electronic configuration of the metal ion (Nayab et al., 2025). Differences in tetrahedral coordination can consequently produce changes in electronic and biological properties among related complexes (Waziri et al., 2025).

6.3 Square-Planar Complexes

Square-planar coordination involves four donor atoms positioned approximately within a single plane around the metal centre. This geometry is particularly characteristic of several d8 metal ions and is strongly influenced by ligand-field effects and the electronic configuration of the metal. Schiff-base ligands with suitable donor atoms can stabilize square-planar arrangements and produce complexes with distinctive spectroscopic and electronic properties (Nayab et al., 2025). Structural investigations using spectroscopy and computational methods can help establish the relationship between molecular geometry and electronic characteristics (Abbass et al., 2025).

6.4 Square-Pyramidal and Other Geometries

Five-coordinate Schiff-base complexes may adopt square-pyramidal or trigonal-bipyramidal arrangements, while higher coordination numbers can produce distorted octahedral structures. The geometry adopted by a complex depends on metal-ion characteristics, ligand denticity, steric effects, auxiliary ligands, and crystal-packing forces (Marinova & Tamahkyarova, 2025). Such structural variations can be identified through single-crystal or powder X-ray diffraction supported by spectroscopic and computational analyses. DFT calculations are particularly useful for examining optimized geometries and comparing the relative stability of different structural arrangements (Waziri et al., 2025).

6.5 Relationship Between Geometry and Biological Activity

Coordination geometry can influence the biological behavior of metal complexes by modifying molecular shape, charge distribution, lipophilicity, stability, and the accessibility of the metal centre. These characteristics may affect membrane interactions and binding to biological macromolecules (Hamad et al., 2025). Computational and experimental investigations have further demonstrated that structural parameters, electronic properties, and metal–ligand interactions can contribute to differences in antimicrobial activity (Dhanya et al., 2025). However, antibacterial activity should not be attributed to geometry alone because metal identity, oxidation state, ligand structure, stability, and cellular interactions also contribute to the overall biological response (Arun et al., 2024).

7.0 Antibacterial Activity

7.1 Principles of Antibacterial Evaluation

Antibacterial evaluation determines the ability of a compound to inhibit or kill bacterial cells under controlled experimental conditions. The activity of Schiff bases and their metal complexes is commonly assessed by measuring growth inhibition and determining parameters such as inhibition zones, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) (Jorge et al., 2024). Results are influenced by bacterial species, inoculum density, compound concentration, incubation conditions, and assay medium. Standardized procedures are therefore essential for obtaining reliable and comparable antibacterial data (Fallah-Mehrjardi et al., 2025).

7.2 Commonly Tested Bacterial Strains

Antibacterial studies of Schiff bases and metal complexes commonly include both Gram-positive and Gram-negative organisms to provide a broader assessment of activity. Frequently investigated Gram-positive bacteria include *Staphylococcus aureus*, *Bacillus subtilis*, and *Streptococcus* spp., whereas common Gram-negative organisms include *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Salmonella* spp. (Kaur et al., 2024). Differences in cell-wall structure, membrane composition, efflux systems, and resistance mechanisms can produce different responses to the same compound (Shakir et al., 2025). Testing multiple bacterial groups therefore provides a more meaningful assessment of antibacterial potential.

7.3 Antibacterial Testing Methods

Several laboratory methods are available for evaluating antibacterial activity. Agar well and disc diffusion assays provide a preliminary assessment based on the diameter of growth-inhibition zones, whereas broth dilution methods allow quantitative determination of MIC values (Jorge et al., 2024). The MBC is subsequently used to estimate the lowest concentration capable of producing bactericidal activity under the specified test conditions. Because diffusion-based methods can be affected by compound solubility and diffusion through agar, MIC and MBC measurements are generally more informative for quantitative comparison (Meshram et al., 2025).

7.4 Antibacterial Activity of Free Schiff Bases

Free Schiff bases may exhibit antibacterial activity because of their functional groups, molecular planarity, lipophilicity, and ability to interact with cellular components. Their activity can vary substantially with substituent type, electronic properties, molecular size, and bacterial species (Kaur et al., 2024). Isatin-containing Schiff bases have attracted particular interest because modification of the isatin scaffold can alter both physicochemical properties and biological activity (Meshram et al., 2025; Shakir et al., 2025). Consequently, evaluation of the uncomplexed ligand provides an essential reference for determining the effect of subsequent metal coordination.

7.5 Antibacterial Activity of Metal Complexes

Metal complexation can modify the antibacterial performance of Schiff bases by changing their charge, geometry, lipophilicity, stability, and redox properties. In some cases, the resulting complex demonstrates greater antibacterial activity than the corresponding free ligand, although enhancement is not universal and depends on both the metal and ligand structures (Jorge et al., 2024). Recent investigations of isatin-based metal complexes have demonstrated the importance of metal identity and coordination chemistry in determining antimicrobial performance (Saad et al., 2024). Direct comparison of free ligands and their corresponding metal complexes using standardized MIC and MBC measurements is therefore important for establishing meaningful structure–activity relationships (Uddin et al., 2025).

8.0 Mechanisms of Antibacterial Action

Transition-metal complexes of Schiff bases can exert antibacterial effects through several interconnected mechanisms. Their activity may involve membrane damage, interactions with proteins and DNA, enzyme inhibition, metal-mediated oxidative processes, and disruption of essential cellular functions. The relative contribution of each pathway depends on the metal ion, ligand structure, coordination geometry, and stability of the complex (Arun et al., 2024; Wu et al., 2025).

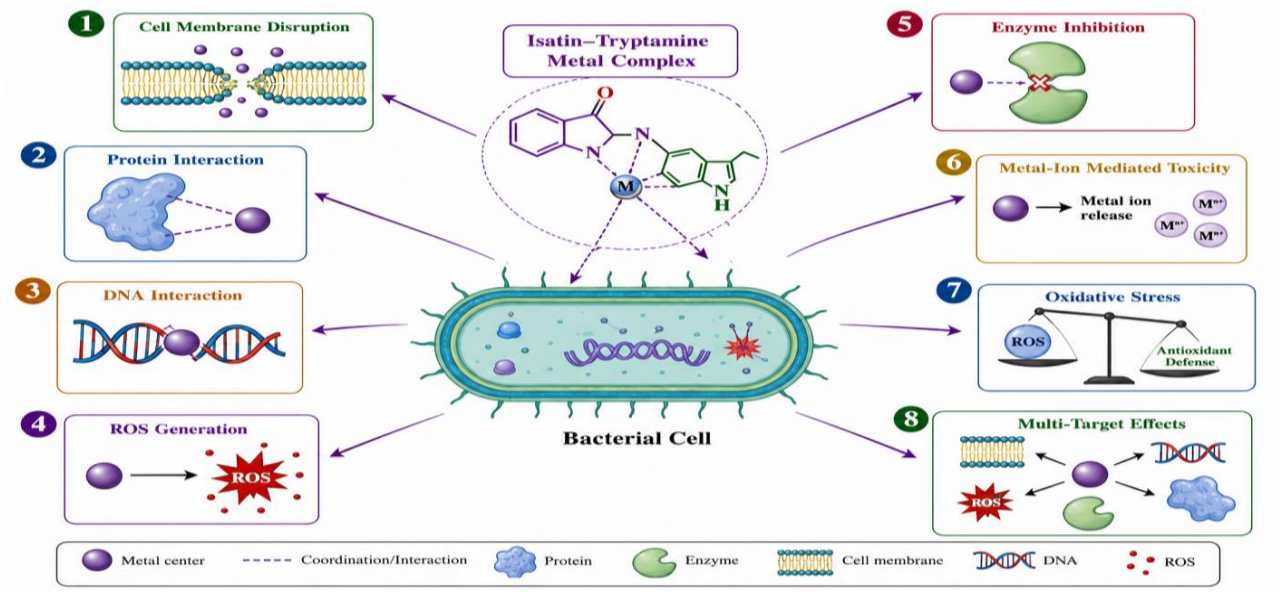

Figure 4: Proposed Mechanisms of Antibacterial Action of Isatin–Tryptamine Metal Complexes

8.1 Chelation Theory

Chelation can modify the electronic and physicochemical properties of a Schiff-base ligand following metal coordination. In some complexes, this may increase lipophilicity and facilitate interaction with bacterial membranes, thereby improving cellular penetration. The resulting biological activity also depends on the nature of the metal centre and stability of the complex (Arun et al., 2024).

8.2 Cell Membrane Disruption

Metal complexes may interact with bacterial membranes through electrostatic and hydrophobic interactions, leading to changes in membrane organization and permeability. Such damage can cause leakage of intracellular components and interfere with essential membrane functions. Copper-containing complexes, in particular, have been associated with membrane damage as one of several possible antibacterial pathways (Ngece et al., 2025; Wu et al., 2025).

8.3 Interaction with Bacterial Proteins

Schiff-base metal complexes can interact with bacterial proteins through hydrogen bonding, electrostatic forces, hydrophobic interactions, and coordination with functional groups present in proteins. These interactions may alter protein structure or interfere with essential cellular processes. Such protein-level effects can contribute to the biological activity reported for transition-metal complexes (Arun et al., 2024; Rana et al., 2024).

8.4 DNA Interaction

Some transition-metal complexes can associate with bacterial DNA through electrostatic interactions, intercalation, or groove binding. Such interactions may interfere with DNA replication and transcription and consequently inhibit bacterial proliferation. The extent of DNA interaction is influenced by the geometry, charge, planarity, and electronic properties of the complex (Sujatha et al., 2024).

8.5 Reactive Oxygen Species (ROS) Generation

Redox-active metal centres can promote the formation of reactive oxygen species, including superoxide and other reactive intermediates. Excessive ROS can damage bacterial DNA, proteins, lipids, and membranes, ultimately impairing cellular viability. Copper complexes are particularly relevant because copper can undergo redox cycling under appropriate biological conditions (Ngece et al., 2025; Wu et al., 2025).

8.6 Enzyme Inhibition

Metal complexes may inhibit bacterial enzymes by interacting with catalytic residues or modifying the structural environment of active sites. Coordination with nitrogen-, oxygen-, or sulfur-containing groups can interfere with enzyme function and disrupt essential metabolic pathways. Enzyme inhibition may therefore complement membrane, DNA, and oxidative mechanisms in producing antibacterial effects (Arun et al., 2024; Sujatha et al., 2024).

8.7 Metal-Ion-Mediated Toxicity

The metal centre can contribute directly to antibacterial activity through disruption of metal homeostasis and interaction with essential cellular components. Depending on the metal and oxidation state, released metal ions may interfere with proteins, enzymes, membrane functions, and intracellular redox balance. The extent of these effects is influenced by the stability and chemical environment of the complex (Wu et al., 2025).

8.8 Oxidative Stress and Cellular Damage

When ROS generation exceeds the bacterial antioxidant capacity, oxidative stress can develop and produce widespread cellular damage. Oxidation of membrane lipids, proteins, and nucleic acids may occur simultaneously, eventually compromising bacterial survival. Oxidative stress may therefore represent a downstream consequence of several metal-dependent antibacterial processes (Ngece et al., 2025).

8.9 Possible Multi-Target Antibacterial Mechanisms

The antibacterial action of isatin–tryptamine Schiff-base metal complexes is unlikely to be explained by a single pathway. A complex may simultaneously affect membrane integrity, bacterial proteins, DNA, enzymes, and intracellular redox balance. Such multi-target activity may be advantageous against resistant bacteria, although specific mechanistic claims should be supported by experimental evidence (Sujatha et al., 2024; Wu et al., 2025).

9.0 Structure–Activity Relationships

Structure–activity relationship (SAR) analysis is essential for understanding how structural modifications influence the antibacterial performance of isatin–tryptamine Schiff-base metal complexes. Factors such as metal identity, oxidation state, coordination geometry, electronic properties, lipophilicity, and metal–ligand stability can influence cellular uptake and interactions with bacterial targets. A systematic SAR approach can therefore support the rational design of more effective antibacterial complexes (Narita et al., 2025; Paswan et al., 2026).

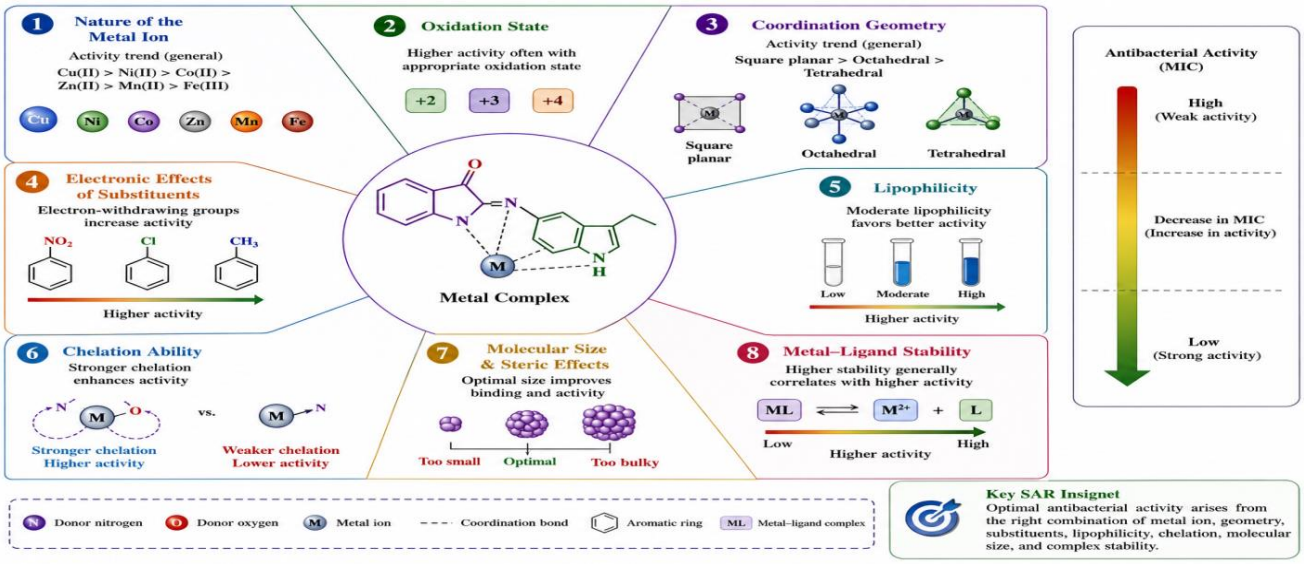

Figure 5: Structure–Activity Relationships of Isatin–Tryptamine Schiff Base Metal Complexes

9.1 Nature of the Metal Ion

The nature of the coordinated metal can substantially influence antibacterial activity because metal ions differ in electronic configuration, coordination preference, redox behaviour, and biological reactivity. Schiff-base complexes containing different metal centres may consequently exhibit markedly different antibacterial potencies despite having similar ligand frameworks. Such differences emphasize the importance of metal selection in complex design (Al Riyami et al., 2025).

9.2 Oxidation State

The oxidation state of a metal influences its electronic configuration, charge, coordination behaviour, and redox properties. Changes in oxidation state may therefore modify complex stability and biological reactivity. Redox-active metal centres can also contribute to oxidative processes that affect bacterial cells, making oxidation state an important parameter in SAR investigations (Rani et al., 2026).

9.3 Coordination Geometry

Coordination geometry determines the three-dimensional arrangement of the ligand around the metal centre and can affect molecular polarity, steric accessibility, and interactions with biological targets. Octahedral, tetrahedral, square-planar, and related geometries may consequently produce different antibacterial responses. Geometry should therefore be considered alongside metal identity when evaluating biological activity (Al Riyami et al., 2025; Rani et al., 2026).

9.4 Electronic Effects of Substituents

Substituents introduced into the ligand framework can alter electron density, donor strength, molecular polarity, and metal-binding characteristics. Electron-donating and electron-withdrawing groups may consequently influence the electronic properties of the resulting complexes and their interactions with bacterial targets. Computational electronic descriptors can provide useful evidence for relating these structural changes to antibacterial activity (Narita et al., 2025).

9.5 Lipophilicity

Lipophilicity can influence the interaction of metal complexes with bacterial membranes and their subsequent cellular uptake. Moderate lipophilicity may favour membrane penetration, whereas excessive hydrophobicity can reduce aqueous solubility and biological availability. Therefore, an appropriate balance between hydrophobic and hydrophilic properties is important when optimizing antibacterial Schiff-base complexes (Paswan et al., 2026).

9.6 Chelation Ability

The donor atoms and denticity of a Schiff base determine its ability to chelate a metal centre. Chelation can modify charge distribution, electronic structure, stability, and physicochemical properties of the complex. These changes may enhance biological activity by altering membrane interactions and the reactivity of the metal centre, although excessively strong coordination may reduce the availability of biologically active species (Rani et al., 2026).

9.7 Molecular Size and Steric Effects

Molecular size and steric configuration can influence solubility, membrane penetration, and accessibility of biologically relevant sites. Bulky substituents may improve certain physicochemical properties but can also hinder coordination or interactions with bacterial targets. Consequently, structural optimization should maintain a balance between molecular complexity, steric demand, and biological accessibility (Paswan et al., 2026).

9.8 Metal–Ligand Stability

Metal–ligand stability is an important determinant of the behaviour of Schiff-base complexes in biological environments. A sufficiently stable complex can retain its structural characteristics during biological testing, whereas excessive instability may lead to premature ligand or metal dissociation. The optimal complex should therefore possess adequate stability while retaining sufficient reactivity for interaction with bacterial components (Al Riyami et al., 2025).

9.9 Relationship Between Structural Features and MIC Values

Minimum inhibitory concentration (MIC) provides a quantitative measure for comparing antibacterial potency, but differences in MIC should be interpreted together with structural and experimental parameters. Variations in metal centre, electronic properties, ligand substitution, geometry, and molecular interactions can contribute to differences in antibacterial activity. Consequently, reliable SAR conclusions require standardized antibacterial assays and systematic comparison of structurally related complexes (Narita et al., 2025; Paswan et al., 2026).

10.0 Toxicity, Selectivity and Biological Safety

The development of metal-based antibacterial agents requires careful assessment of toxicity, selectivity, and biological safety. Although metal complexes may exhibit strong antimicrobial effects, their therapeutic usefulness depends on achieving effective bacterial inhibition while minimizing undesirable effects on host cells. The biological response can be influenced by the metal ion, ligand structure, coordination geometry, stability, and concentration. Recent studies have therefore combined antimicrobial testing with cytotoxicity and molecular investigations to obtain a broader assessment of Schiff-base metal complexes (Tawfiq et al., 2025; Helal et al., 2026).

10.1 Cytotoxicity

Cytotoxicity assessment determines whether an antibacterial complex produces harmful effects on mammalian cells at concentrations required for bacterial inhibition. In vitro cell-viability assays can provide preliminary information on concentration-dependent toxicity and help identify compounds

with a potentially favourable safety profile. Recent investigations of Schiff-base metal complexes have demonstrated that cytotoxic responses can vary considerably with the coordinated metal and ligand structure (Tawfiq et al., 2025).

10.2 Selectivity Toward Bacteria

Selective antibacterial activity refers to the ability of a compound to inhibit bacterial cells while producing comparatively limited effects on mammalian cells. Differences in bacterial membrane composition, cellular targets, metal uptake, and susceptibility to oxidative stress may contribute to such selectivity. Therefore, antibacterial potency should be evaluated together with cytotoxicity rather than considered independently when assessing the biological potential of metal complexes (Helal et al., 2026).

10.3 Toxicity Toward Mammalian Cells

Potential toxicity toward mammalian cells should be investigated to establish whether a complex can produce antibacterial effects within a biologically acceptable concentration range. Cell-viability studies, together with appropriate concentration–response measurements, can provide useful preliminary evidence of cellular tolerance. Comparative studies have shown that different metal centres within related Schiff-base systems may produce substantially different cytotoxic responses (Tawfiq et al., 2025; Helal et al., 2026).

10.4 Metal-Related Toxicity

The toxicity of a metal complex is strongly influenced by the identity, oxidation state, dose, and chemical stability of its metal centre. Some transition metals may participate in redox reactions, interact with proteins and nucleic acids, or release biologically active metal ions. Consequently, metal selection should consider both antimicrobial effectiveness and potential toxicity. Recent studies involving different transition-metal Schiff-base complexes demonstrate the importance of comparing biological responses across metal centres (Helal et al., 2026).

10.5 Environmental Considerations

Environmental safety is an additional consideration in the development of metal-containing antibacterial compounds because released metal ions or persistent complexes may enter aquatic and terrestrial environments. Their environmental behaviour may depend on chemical stability, solubility, degradation, and metal release. Green preparation methods and appropriate evaluation of degradation products may help minimize potential environmental risks. Such considerations should accompany biological safety assessments during the development of new metal-based antibacterial agents (El-Hakeem et al., 2026).

10.6 Therapeutic Index

The therapeutic index provides an important conceptual measure of the separation between desirable antibacterial activity and undesirable toxicity. A promising complex should ideally inhibit bacterial growth at concentrations substantially below those producing significant mammalian-cell toxicity. Therefore, MIC values should be interpreted together with cytotoxicity data to obtain a more meaningful estimate of selectivity and therapeutic potential. Integrating antimicrobial, cytotoxicity, DNA-binding, and computational data can provide a more comprehensive basis for evaluating candidate metal complexes (Helal et al., 2026; El-Hakeem et al., 2026).

11.0 Comparison with Other Schiff Base Metal Complexes

Isatin–tryptamine Schiff-base complexes can be compared with other Schiff-base metal systems to understand how ligand architecture and metal coordination influence antibacterial activity. Important comparison groups include isatin–hydrazone, salicylaldehyde Schiff-base, thiosemicarbazone, and other indole-based complexes. Differences in donor atoms, molecular structure, coordination behaviour, and electronic properties can substantially affect biological performance. Recent studies emphasize that metal coordination may modify the physicochemical properties of Schiff bases and consequently alter their interactions with biological targets (Zahra et al., 2025; Jyothi, 2026).

11.1 Isatin–Hydrazone Complexes

Isatin–hydrazone complexes contain additional nitrogen atoms that can participate in metal coordination and provide flexible chelating arrangements. Their biological activity may vary according to the metal centre, ligand substitution, coordination geometry, and molecular stability. Compared with isatin–tryptamine Schiff bases, hydrazone systems may provide different donor environments and electronic characteristics, which can influence antibacterial potency and cellular interactions. Such structural differences highlight the importance of comparing closely related ligands under similar biological testing conditions.

11.2 Salicylaldehyde Schiff-Base Complexes

Salicylaldehyde-derived Schiff bases commonly contain phenolic oxygen and azomethine nitrogen donor atoms, enabling stable chelation with many transition metals. Their metal complexes have demonstrated considerable structural diversity and a broad range of biological properties. In comparison, isatin–tryptamine Schiff bases incorporate an indole-containing framework together with the isatin carbonyl and azomethine functionalities, potentially providing a different combination of metal-binding and biological interaction sites. These differences can influence complex stability, lipophilicity, and biological activity.

11.3 Thiosemicarbazone Complexes

Thiosemicarbazones are particularly versatile ligands because their nitrogen and sulfur donor atoms can support diverse coordination modes with transition metals. Metal complexation can modify their electronic structure, stability, redox behaviour, and biological properties. Recent reviews indicate that thiosemicarbazone metal complexes exhibit broad biological activities, including antibacterial and anticancer effects (Zahra et al., 2025). Compared with these sulfur-containing systems, isatin–tryptamine Schiff bases provide an oxygen/nitrogen donor environment and a distinctive indole-rich molecular framework.

11.4 Other Indole-Based Schiff Bases

Indole-based Schiff bases provide an important comparison because the indole nucleus occurs in numerous biologically active molecules. Incorporating an indole-containing tryptamine unit into an isatin Schiff base creates a molecular hybrid with potentially complementary electronic and biological characteristics. Structural modification of the indole or isatin components can further influence metal binding and biological activity. Such molecular diversification provides opportunities for developing complexes with tailored physicochemical and pharmacological properties.

11.5 Antibacterial Activity

The antibacterial activity of Schiff-base metal complexes is influenced by both the ligand framework and the coordinated metal ion. Experimental studies of thiosemicarbazone metal complexes, for example, have demonstrated that metal coordination can produce complexes with significant effects against bacterial growth and biofilm formation (El-Sayed et al., 2025). Therefore, comparison with isatin–tryptamine complexes should consider MIC and MBC values, bacterial species, experimental conditions, and the activity of the corresponding free ligand rather than relying solely on inhibition-zone measurements.

11.6 Structural Diversity and Metal Effects

The structural diversity of Schiff-base complexes arises from variations in ligand denticity, donor atoms, substituents, metal identity, oxidation state, and coordination geometry. Thiosemicarbazone systems illustrate how changes in ligand structure and metal coordination can produce substantial differences in biological behaviour (Jyothi, 2026). Similar principles can be applied to isatin–tryptamine complexes, where systematic variation of the metal centre and ligand substituents could provide useful information about structure–activity relationships.

11.7 Mechanistic Advantages

Different Schiff-base metal complexes may exert antibacterial effects through multiple mechanisms, including interaction with bacterial biomolecules, disruption of cellular processes, oxidative stress, and interference with biofilm formation. Recent experimental and computational investigations of metal complexes have demonstrated the value of combining structural analysis with biological assays to clarify these mechanisms (El-Sayed et al., 2025). Thus, isatin–tryptamine complexes may offer a useful platform for exploring multi-target antibacterial activity, although proposed mechanisms should be supported by appropriate experimental evidence rather than inferred solely from antibacterial potency.

Conclusion

Isatin–tryptamine Schiff bases represent a versatile platform for developing transition-metal complexes with promising antibacterial properties. Combining the isatin and tryptamine frameworks provides opportunities to modify ligand structure, electronic properties, and metal-binding behaviour, while metal coordination can influence molecular geometry, stability, lipophilicity, and biological activity. However, antibacterial performance depends on factors such as metal identity, oxidation state, coordination geometry, ligand substitution, and bacterial species, making comparison of reported results challenging. Future studies should emphasize standardized antibacterial assays, systematic structure–activity investigations, mechanistic studies, and comprehensive cytotoxicity and selectivity assessment. Integrating experimental characterization with computational approaches and evaluating promising complexes against resistant bacteria and in vivo models will be important for establishing their therapeutic potential and advancing them toward practical antibacterial applications.

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