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A COMPREHENSIVE REVIEW OF TARGET-BASED DESIGN AND PRECLINICAL EVALUATION OF METAL COMPLEX ANTIMICROBIALS

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ABSTRACT

Antimicrobial resistance presents an urgent global threat, prompting the search for therapeutic agents with mechanisms distinct from conventional antibiotics. Metal complexes have emerged as promising candidates due to their rich structural diversity, tunable redox properties, and ability to interact with bacterial targets through pathways inaccessible to organic molecules. This review highlights the principles guiding the rational design of metal-based antimicrobials, emphasizing target-specific strategies involving DNA gyrase, metalloenzymes, membrane functions, and efflux systems. Key molecular features such as ligand denticity, redox activity, and coordination geometry are explored in relation to antimicrobial potency and selectivity. Pharmacokinetic considerations, including absorption, distribution, metabolism, and excretion, are discussed alongside toxicity challenges and stability requirements. Preclinical evaluation methods encompassing physicochemical characterization, mechanistic assays, cytotoxicity testing, and in vivo infection models are summarized to outline a comprehensive discovery pipeline. Recent advances in computational approaches—including AI-guided stability prediction, molecular dynamics simulations, quantum chemical calculations, and machine learning-based activity forecasting—are shown to accelerate metal complex optimization. Remaining challenges such as host toxicity, resistance potential, and the need for standardized evaluation protocols are addressed, along with future opportunities in personalized metal-based therapy and AI-driven molecular design. Together, these insights underscore the potential of metal complexes to contribute meaningfully to next-generation antimicrobial drug development.

KEYWORDS: Metal complexes**,** Antimicrobial drug discovery**,** Coordination chemistry**,** Computational design**,** Pharmacokinetics

INTRODUCTION

The global rise of antimicrobial resistance has created an urgent need for new therapeutic strategies capable of overcoming multidrug-resistant phenotypes, biofilm-

associated persistence, and declining antibiotic efficacy. Conventional small-molecule antibiotics are increasingly limited by predictable mechanisms of action, enzymatic degradation, membrane impermeability, and efflux-mediated resistance. As discovery pipelines continue to shrink, metal complexes have emerged as structurally versatile and chemically dynamic scaffolds with mechanisms fundamentally distinct from classical organic agents. Their tunable coordination geometry, redox activity, ligand-exchange capacity, and affinity for biological macromolecules offer unique opportunities for designing precision therapeutics that selectively disrupt essential bacterial pathways.

Historically, metals such as silver, copper, and bismuth have demonstrated potent antimicrobial activity, reflecting their intrinsic ability to interfere with microbial homeostasis. Modern coordination chemistry and structural biology have transformed these early observations into a rational drug discovery platform. Metal complexes can be engineered to target specific bacterial proteins through shape complementarity, controlled ligand environments, or redox-triggered activation. Many clinically relevant bacterial enzymes—including DNA gyrase, topoisomerase IV, metallo-β-lactamases, urease, and LpxC—depend on metal cofactors, creating opportunities to design complexes that either mimic native ions, disrupt catalytic centers, or induce competitive inhibition.

Advances in crystallography, cryo-electron microscopy, molecular docking, quantum mechanical modeling, and molecular dynamics simulations now enable high-resolution prediction of metal–protein interactions, guiding the development of selective, stable, and potent antimicrobial agents. However, challenges related to toxicity, metabolic stability, biodistribution, and pharmacokinetics remain significant. Addressing these limitations requires integrating target specificity with ligand engineering, prodrug strategies, and nanoparticle-based delivery.

This review examines major bacterial targets suitable for metal coordination, explores design strategies that enhance selectivity and stability, and highlights computational and pharmacokinetic considerations essential for advancing metal complexes toward clinical relevance. Through a target-driven framework, metal-based therapeutics may offer innovative solutions to overcome resistance and revitalize antimicrobial drug discovery.

Rationale for Using Metal Complexes in Target-Based Drug Discovery

Target-based antimicrobial discovery depends on identifying essential bacterial pathways that can be selectively inhibited without disrupting host functions. Within this framework, metal complexes have emerged as particularly promising candidates because they possess chemical and biological properties distinct from traditional organic antibiotics. Their structural adaptability, diverse redox behavior, customizable coordination geometries, and capacity to form stable interactions with biomacromolecules make them well suited for designing precision antimicrobials. These attributes not only broaden the spectrum of inhibitable bacterial targets but also support the development of compounds capable of bypassing or counteracting common resistance mechanisms. Understanding these intrinsic advantages is therefore fundamental to rational drug development using metal-based scaffolds.

A major driver of renewed interest in metal complexes is their ability to adopt a wide range of geometries that complement bacterial protein surfaces more effectively than many small organic molecules. Whereas conventional antibiotics typically rely on hydrogen bonding or hydrophobic interactions, metal complexes introduce coordination-driven binding that enhances affinity and specificity (11). Octahedral, tetrahedral, square-planar, and trigonal bipyramidal arrangements enable the metal center and its ligands to occupy precise spatial positions within enzyme pockets, facilitating targeted inhibition of catalytic sites. This geometric flexibility allows access to difficult targets such as deeply recessed metalloenzyme centers or nucleic acid structures requiring planar intercalation (12).

Equally important are the unique electronic properties of metal ions. Many can undergo redox transitions under physiological conditions, enabling electron transfer reactions or generating reactive oxygen species that enhance antimicrobial activity (13). These redox processes can damage DNA, disrupt respiratory chains, and compromise membrane integrity. When coupled with appropriately designed ligands, redox-active metal complexes can engage multiple bacterial processes simultaneously, reducing the likelihood of resistance development. Moreover, ligand engineering allows precise control over redox behavior, enabling fine-tuning of reactivity and toxicity (14).

Ligand versatility further strengthens the case for metal-based drug design. Ligands can be modified to improve solubility, permeability, metabolic stability, or target affinity. Aromatic ligands promote DNA interaction, macrocyclic scaffolds enhance enzyme selectivity, and amphiphilic or charged ligands facilitate membrane transport (15). Bioinspired ligands that mimic natural cofactors can increase specificity toward metalloenzymes; for instance, chelators resembling zinc-binding motifs in β-lactamases effectively block NDM-1 and related resistance determinants (16). Thus, both the metal center and its ligand environment collectively shape potency and selectivity.

Another compelling rationale comes from the central role of metalloproteins and metal-dependent pathways in bacterial physiology. Essential enzymes involved in DNA replication, cell wall synthesis, oxidative stress management, and metabolic regulation frequently require metal ions such as zinc, magnesium, manganese, or iron (17). Rationally designed complexes can exploit these dependencies by displacing native cofactors, inhibiting metal-binding sites, or disrupting metal homeostasis. Because these pathways are critical for survival, bacteria have limited evolutionary flexibility, lowering the probability of rapid resistance emergence (18).

Metal complexes also possess inherent advantages in overcoming traditional resistance mechanisms. Many pathogens rely on efflux pumps, enzymatic degradation, or membrane impermeability to neutralize antibiotics. Metal complexes can evade these mechanisms through their structural and physicochemical properties. Their ability to interact with efflux pump components, resist enzymatic cleavage, and modulate membrane potential enables them to maintain effective intracellular concentrations (19). Additionally, their multi-target activity reduces the likelihood that single-gene mutations will eliminate antimicrobial efficacy, in contrast to small molecules that act on narrow biochemical pathways (20).

Despite these strengths, successful therapeutic development requires addressing pharmacokinetic challenges. Metal ions may dissociate, undergo ligand exchange, or bind host proteins such as albumin or transferrin. Advances in coordination chemistry, however, have enabled the creation of kinetically inert complexes with controlled reactivity, reduced off-target interactions, and enhanced metabolic stability (21). Ligand modifications can extend circulation time, improve selective bacterial uptake, and minimize accumulation in non-target tissues, supporting the translation of metal complexes into clinically compatible agents.

Taken together, the rationale for employing metal complexes in target-based antimicrobial discovery rests on their structural diversity, tunable electronic properties, ability to engage challenging targets, and capacity to evade resistance pathways. When combined with modern computational design tools, structural biology techniques, and pharmacokinetic optimization, metal complexes represent a promising scaffold for developing next-generation antibacterial therapeutics.

Major Bacterial Targets for Metal-Based Antimicrobials

Target-based discovery of metal-based antimicrobials relies on understanding essential bacterial pathways that can be disrupted by metal–ligand coordination, redox reactivity, and structural interference. Metal complexes have demonstrated the ability to modulate a variety of enzymatic, nucleic acid, and membrane-associated targets that are central to bacterial survival. Their flexible coordination geometry and tunable ligand sphere allow them to interact with targets that are often inaccessible to classical antibiotics. The following sections discuss the major bacterial targets where metal complexes have shown substantial mechanistic and therapeutic potential.

DNA gyrase and topoisomerase IV inhibition

DNA gyrase and topoisomerase IV are among the most important antibacterial targets, responsible for regulating DNA supercoiling and chromosome segregation. These enzymes are essential for replication, transcription, and maintenance of DNA topology, and their inhibition results in rapid bacterial death. Fluoroquinolones historically targeted these enzymes, but widespread resistance has necessitated new chemical approaches. Metal complexes offer a structurally distinct strategy for interrupting these pathways.

Many metal complexes interact with DNA gyrase by stabilizing the cleavage complex, intercalating into DNA, or disrupting the Mg^{2+}-dependent catalytic cycle required for strand passage (22). Complexes containing copper, ruthenium, cobalt, and nickel have demonstrated notable affinity for gyrase, particularly when coordinated with planar aromatic ligands that enhance intercalation. Ruthenium polypyridyl complexes, for example, are able to bind to duplex DNA while simultaneously occupying the gyrase active site region, resulting in impaired catalytic turnover (23). The dual interaction with both enzyme and DNA distinguishes metal complexes from traditional inhibitors and can circumvent resistance mutations that reduce quinolone binding.

Topoisomerase IV, essential for chromosome decatenation, is structurally related to gyrase and exhibits similar vulnerabilities. Some metal complexes exert selective inhibition of topoisomerase IV by binding to the ATPase domain or by interacting with DNA–enzyme intermediates (24). Metal-based compounds that target both

gyrase and topoisomerase IV simultaneously have particular therapeutic value because dual inhibition reduces the likelihood of resistance emergence. Structural studies further indicate that ligand variation allows fine control over DNA-binding strength and enzyme selectivity, enabling the design of complexes that achieve optimal inhibitory profiles (25).

Inhibition of bacterial metalloenzymes

Metalloenzymes represent one of the most promising target classes for metal-based antimicrobials. Many bacterial enzymes depend on metal cofactors such as Zn^{2+}, Mg^{2+}, Fe^{2+}, or Mn^{2+} for catalytic function. This dependency creates opportunities to design metal complexes that displace native ions, bind active-site residues, or form inactive metal–protein adducts.

One of the most intensively studied targets is the New Delhi metallo-β-lactamase (NDM-1), which confers resistance to carbapenem antibiotics. NDM-1 contains two Zn^{2+} ions that coordinate water molecules responsible for β-lactam hydrolysis. Metal complexes bearing chelating ligands can compete for these Zn^{2+} sites or alter the conformation of the active site, reducing enzymatic activity (26). Complexes derived from gallium, bismuth, and ruthenium have demonstrated the ability to inhibit NDM-1, restore carbapenem susceptibility, and suppress enzymatic degradation of β-lactams (27).

LpxC, a Zn^{2+}-dependent deacetylase involved in lipid A biosynthesis, is another clinically important metalloenzyme target. Metal complexes with hydroxamate or thiosemicarbazone ligands exhibit strong affinity for the Zn^{2+} center of LpxC, resulting in impaired cell wall formation (28). Similarly, urease, an enzyme implicated in pathogenicity of Helicobacter pylori and Proteus species, can be inhibited by metal complexes that disrupt its Ni^{2+} cofactor environment (29). Carbonic anhydrases, superoxide dismutases, and ribonucleotide reductases are additional examples where metal complexes show significant inhibitory potential.

Metalloenzyme targeting is particularly advantageous because many pathogens cannot easily modify metal-binding residues without compromising enzyme function. This evolutionary constraint decreases the likelihood of resistance development and enhances the long-term efficacy of metal-based inhibitors (30).

Efflux pump inhibition

Efflux pumps are major contributors to multidrug resistance, actively transporting antibiotics out of bacterial cells and reducing intracellular drug concentrations. Metal complexes can inhibit efflux pumps through several mechanisms, including disruption of membrane potential, interference with pump components, or binding to regulatory proteins that govern efflux expression.

Compounds containing copper and silver ions can collapse proton gradients across the membrane, indirectly impairing the activity of RND-type efflux pumps such as AcrAB-TolC and MexAB-OprM (31). Some metal complexes interact directly with efflux proteins, altering their conformational dynamics or blocking substrate channels. Gallium(III) complexes, for example, have demonstrated the capacity to inhibit efflux-mediated resistance by binding to membrane-associated components involved in transport (32).

Efflux pump inhibition is particularly important for combination therapy. Metal complexes can potentiate the effects of existing antibiotics by ensuring increased intracellular retention. This synergistic approach not only enhances antibacterial activity but also revives the potency of antibiotics that have become ineffective due to efflux-driven resistance (33).

Membrane disruption and lipid interference

Bacterial membranes represent a critical structural barrier and functional center for energy production, nutrient transport, and cell signaling. Metal complexes can target membranes through mechanisms that include lipid peroxidation, redox-driven oxidative damage, membrane depolarization, and disruption of ion gradients.

Complexes containing copper and iron often generate reactive oxygen species via Fenton-type chemistry, leading to oxidative degradation of membrane lipids and proteins (34). Ruthenium and silver complexes can interact electrostatically with negatively charged bacterial membranes, increasing permeability and causing structural collapse (35). Some amphiphilic metal complexes incorporate hydrophobic ligands that insert into lipid bilayers, resulting in membrane thinning, pore formation, or ion leakage.

Membrane targeting offers the advantage of rapid bactericidal activity with limited opportunities for resistance development. Because membrane composition is highly conserved and essential, bacteria have limited capacity to evolve structural modifications without compromising viability (36).

Targeting nucleic acids and transcriptional machinery

Beyond gyrase and topoisomerase IV, metal complexes can target other nucleic acid-associated processes, including DNA replication, RNA synthesis, and transcription regulation. Many metal complexes exhibit strong interactions with DNA through groove binding, intercalation, or phosphate backbone coordination. Copper and ruthenium complexes are notable for their ability to cleave DNA via oxidative pathways, disrupting replication and inducing lethal damage (37).

Some complexes interfere with RNA polymerase by binding to transcriptional initiation regions or by forming adducts that hinder polymerase progression along DNA templates. These interactions may be facilitated by ligands that enhance nucleic acid affinity or by redox cycling that damages nucleoprotein complexes (38). Unlike classical antibiotics that target specific protein subunits, metal complexes often act through structural interference, giving them broader applicability across species.

Ribosomal and protein synthesis inhibition

Protein synthesis is another essential bacterial process that can be disrupted by metal complexes. Positively charged complexes may bind to ribosomal RNA, altering ribosome conformation or blocking the binding of tRNA molecules to the A-site (39). Zinc, copper, and gold complexes have been shown to inhibit peptide elongation by interfering with ribosomal subunit assembly or by modifying ribosomal proteins through ligand exchange reactions.

Some organometallic compounds can form covalent interactions with key cysteine or histidine residues in ribosomal proteins, impairing proper tertiary folding and

functional activity (40). Because bacterial ribosomes have structural differences from human ribosomes, selective targeting is achievable through rational design of ligand geometry and charge distribution.

Metal homeostasis disruption

Metal homeostasis is critical for bacterial survival, as cells must carefully regulate intracellular concentrations of essential metals while avoiding toxicity. Metal complexes can disrupt this balance by competing with native ions, blocking uptake pathways, or inducing metal starvation.

Gallium(III) mimics Fe^{3+} in biological systems but cannot perform its redox functions, leading to inhibition of iron-dependent enzymes when taken up by bacteria (41). Similarly, complexes that alter zinc or manganese availability can impair oxidative stress responses, metabolic pathways, and transcriptional regulation.

Metal homeostasis targeting provides a systems-level approach to antimicrobial design, allowing broad interference with metabolic networks rather than single enzymatic pathways.

Rational Design Strategies for Target-Specific Metal Complexes

Rational design of metal-based antimicrobials requires an integrated understanding of coordination chemistry, structural biology, target specificity, and pharmacokinetic behavior. Unlike empirical screening, rational design focuses on creating metal complexes with predictable interactions at defined bacterial targets. These strategies include optimizing ligand architecture, selecting appropriate metal centers, engineering physicochemical properties, and combining computational tools with biological assays. The following sections describe major design principles that guide the development of target-specific metal complexes for antimicrobial drug discovery.

Structure-based drug design

Structure-based drug design has become central to modern medicinal chemistry, enabling researchers to design molecules based on detailed knowledge of target structures. Metal complex design can leverage high-resolution structural information obtained from X-ray crystallography, cryo-electron microscopy, and NMR spectroscopy to position metal centers and ligands precisely within bacterial protein pockets (42).

Metal complexes exhibit geometries such as octahedral, square-planar, tetrahedral, or trigonal bipyramidal arrangements. These configurations allow precise control of spatial orientation, enabling the complex to align its coordination sphere to essential residues in enzyme active sites. For example, metal complexes designed to inhibit DNA gyrase can be engineered to occupy regions adjacent to the Mg^{2+} catalytic center, exploiting structural features that differ from those used by fluoroquinolones (43).

Computational methods complement structural insights. Docking algorithms modified for metal–ligand coordination constraints allow prediction of preferred binding geometries, while molecular dynamics simulations help assess stability and interaction energy with flexible targets (44). Density functional theory provides information on metal reactivity, ligand exchange kinetics, and redox behavior, all of which are critical for predicting interactions with dynamic bacterial proteins.

Structure-based strategies are particularly powerful when targeting metalloenzymes. By analyzing the coordination environment of catalytic metal ions, researchers can design complexes that mimic cofactors, compete for metal binding, or distort the geometry of active sites. This approach has contributed to developing inhibitors of β-lactamases, LpxC, and urease (45).

Ligand engineering for improved specificity

Ligand choice plays a defining role in determining the biological activity, selectivity, solubility, and pharmacokinetic behavior of metal complexes. Ligand engineering involves modifying steric and electronic features to enhance target binding and reduce off-target interactions.

Aromatic ligands, including bipyridines, phenanthrolines, and terpyridines, facilitate intercalation into DNA or interaction with nucleotide-binding proteins. These ligands are frequently used in designing metal complexes that target DNA gyrase or inhibit transcriptional machinery (46). By contrast, macrocyclic ligands such as cyclams and porphyrins offer rigid structures that fit tightly into enzyme pockets, making them useful for metalloenzyme inhibition.

Polydentate ligands capable of chelating essential metal ions provide a rational approach to targeting metalloenzymes. Hydroxamate, thiosemicarbazone, and catechol ligands can replace native cofactors or bind to catalytic metal ions, inhibiting processes such as lipid A biosynthesis or β-lactam degradation (47). Ligands that mimic natural substrates further enhance selectivity by guiding complexes to enzyme active sites through substrate-recognition mechanisms.

The electronic properties of ligands influence redox behavior, stability, and cellular penetration. Electron-donating ligands tend to stabilize higher oxidation states, while electron-withdrawing groups facilitate reduction under physiological conditions. These modifications help control whether the metal complex undergoes redox cycling, generates reactive oxygen species, or remains inert until reaching the target site (48).

Metal selection and coordination tuning

Selecting the appropriate metal ion is a central design step. Each metal possesses unique coordination preferences, redox properties, ligand exchange rates, and biological behavior. Understanding these characteristics allows researchers to match metals with intended targets and mechanisms of action.

Ruthenium complexes are known for their kinetic stability and well-defined octahedral geometry, making them suitable for DNA targeting and enzyme inhibition. Their ability to switch between Ru(II) and Ru(III) oxidation states enables redox-mediated mechanisms when desirable (49). Iridium and rhodium complexes exhibit similar advantages but offer different ligand exchange kinetics that may influence cellular uptake.

Copper, iron, and cobalt complexes are valued for their redox activity. Copper(II) complexes can generate reactive oxygen species that damage nucleic acids and membranes, supplementing target-based inhibition with oxidative killing (50). Cobalt(III) complexes, by contrast, often function as prodrugs that release active species under reducing intracellular conditions.

Silver and gold complexes demonstrate strong interactions with thiol and histidine residues in proteins, making them particularly effective at binding enzymes involved in metabolic regulation or cell wall synthesis (51). Gold(I) complexes, for example, can inhibit thiol-containing enzymes through ligand exchange reactions.

Coordination tuning refers to controlling the number and positioning of ligands around the metal center. By adjusting coordination geometry, designers can influence selectivity toward certain protein residues or structural motifs. This precision is particularly important in designing complexes for metalloenzymes, where active sites often possess highly specific geometries and charge distributions (52).

Prodrug strategies and activatable metal complexes

Prodrug strategies improve selectivity and reduce systemic toxicity by activating the metal complex only in specific environments. Metal complexes can be engineered to undergo ligand release, redox switching, or photochemical activation at the target site.

Reducible complexes, such as Co(III) or Pt(IV), can remain inert during circulation but convert into active species inside bacterial cells where reducing conditions prevail. This approach minimizes premature interactions with host proteins (53). pH-responsive complexes take advantage of acidic microenvironments found in biofilms or infected tissues, where protonation triggers ligand exchange or metal release.

Light-activated complexes offer spatial precision by allowing controlled activation through photochemical reactions. Ru(II) polypyridyl complexes, for example, undergo ligand dissociation when exposed to visible light, generating reactive species that can bind DNA or proteins (54). Although not yet widely applied in antimicrobial therapy, photodynamic metal complexes represent a promising frontier for localized infection control.

Hybrid antibiotic–metal conjugates

Hybrid molecules combine metal complexes with existing antibiotics to enhance potency, overcome resistance, and broaden the spectrum of activity. By linking metal complexes to fluoroquinolones, β-lactams, or antimicrobial peptides, researchers can create dual-action compounds that inhibit multiple targets simultaneously.

Hybridization may increase cellular uptake, stabilize antibiotic structures, or allow metal-mediated mechanisms such as ROS generation or efflux pump inhibition to complement antibiotic activity (55). These conjugates can restore susceptibility to resistant strains or reduce required antibiotic doses, mitigating toxicity and resistance pressure.

Physicochemical optimization and drug-like properties

For metal complexes to function as viable drug candidates, their physicochemical profile must support adequate solubility, membrane permeability, metabolic stability, and distribution. Many metal complexes face challenges related to serum protein binding, rapid clearance, or poor penetration across bacterial membranes.

Ligand modifications such as introducing hydrophilic groups, reducing overall charge, or adjusting lipophilicity can significantly improve pharmacokinetics (56). Encapsulation in nanoparticles, liposomes, or polymer matrices offers additional approaches to enhance delivery, prolong circulation, and stabilize reactive complexes.

A delicate balance is required: overly stable complexes may not release active species inside cells, while unstable complexes may decompose prematurely. Rational design must therefore consider kinetic parameters and ligand exchange rates to ensure controlled activation aligned with biological needs (57).

Computational tools for guiding rational design

Computational chemistry has become indispensable in predicting interactions between metal complexes and bacterial targets. Docking algorithms tailored to metal coordination help identify favorable binding orientations and rank candidate complexes. Molecular dynamics simulations enable exploration of protein flexibility, solvation effects, and conformational transitions during binding (58).

Quantum mechanical calculations provide insight into electronic structure, oxidation state preferences, and reaction pathways, guiding the selection of metals and ligands with optimal reactivity. Machine learning models, trained on datasets of metal complex activity, can predict antimicrobial potency or toxicity, accelerating the design process (59).

Integrating computational predictions with experimental validation enables iterative optimization of complexes before costly synthesis and biological testing.

ADME and Pharmacokinetic Considerations of Metal Complexes

Pharmacokinetic behavior determines whether a metal complex can reach its bacterial target at therapeutically effective concentrations without imposing unacceptable toxicity on the host. Although many metal complexes demonstrate strong in vitro antibacterial activity, their effectiveness in vivo depends heavily on absorption, distribution, metabolism, and excretion processes. Rational drug development requires careful optimization of these parameters to ensure adequate systemic stability, selective accumulation within infected tissues, and minimal off-target interactions. The following subsections outline major pharmacokinetic considerations relevant to metal-based antimicrobial agents.

Absorption and membrane permeability

Absorption represents the first barrier to the bioavailability of metal complexes. Many complexes possess high molecular weight, charged coordination spheres, and limited lipophilicity, which restricts gastrointestinal absorption and membrane penetration. These properties can limit oral delivery and necessitate parenteral administration unless ligand engineering is used to improve permeability. Hydrophobic ligands, neutral charge, and amphiphilic architectures can enhance passive diffusion across epithelial and bacterial membranes, but must be balanced to prevent excessive non-specific uptake into host tissues (60).

Transporter interactions may also influence absorption. Some metal complexes exploit metal ion transport systems or peptide transporters to gain entry into bacterial cells, improving intracellular accumulation. However, host transporters may also capture these complexes, altering distribution or promoting accumulation in unintended tissues. Understanding the role of specific membrane transport pathways is important for achieving selective uptake into bacterial cells while minimizing uptake by host cells (61).

Distribution and tissue targeting

Distribution determines how a metal complex is partitioned among organs, plasma, and infected tissues. Many metal complexes exhibit strong binding to serum proteins such as albumin, transferrin, and ceruloplasmin. While moderate protein binding can prolong circulation time and reduce renal clearance, excessive binding may sequester the complex in plasma and limit its availability at the infection site (62). The challenge lies in engineering complexes with an optimal balance of protein affinity and free fraction.

Metal complexes often accumulate in organs involved in detoxification, including the liver, spleen, and kidneys. This distribution pattern reflects scavenging mechanisms that remove foreign metal species from circulation. Designing kinetically inert complexes with strong ligand stability reduces premature dissociation and prevents redistribution of free metal ions into sensitive tissues (63). Ligand modifications such as PEGylation or incorporation of zwitterionic groups can increase systemic half-life and reduce recognition by clearance mechanisms.

Targeting infected tissues can be enhanced through mechanisms such as passive accumulation in inflamed regions with compromised vasculature, selective uptake by bacteria via nutrient transporters, or conjugation of targeting moieties such as peptides or carbohydrates. Some metal complexes preferentially accumulate in bacterial cells because of differences in membrane potential, metal ion gradients, or intracellular reducing environments (64).

Metabolic stability and biotransformation

Metabolic transformation poses a significant challenge to metal complex pharmacokinetics. Biotransformation processes may include ligand hydrolysis, oxidation–reduction cycling, demetallation, or enzymatic degradation of ligands. Excessive metabolic breakdown can generate inactive species or release free metal ions that may contribute to toxicity (65).

Redox-active metals such as copper or iron may undergo spontaneous redox cycling in biological environments, especially in tissues with high oxidative potential. While some redox activity contributes to antimicrobial action, uncontrolled cycling can lead to off-target damage to host tissues. Stabilizing ligands that control redox potential, limit ligand exchange, and reduce unintended reactivity are critical for achieving metabolic safety (66).

Biotransformation can also be exploited deliberately. Prodrug metal complexes such as Co(III) or Pt(IV) compounds rely on intracellular reduction to release active species. In such cases, metabolic activation enhances selectivity by confining reactivity to bacterial cells or infected environments. Understanding how specific physiological conditions affect complex activation allows designers to fine-tune prodrug behavior (67).

Excretion and clearance pathways

Excretion determines the duration of action and systemic exposure of metal complexes. Renal and hepatic clearance are the major pathways for elimination. Complexes with low molecular weight or insufficient protein binding are rapidly filtered by the kidneys, limiting their therapeutic window. Conversely, complexes that

bind strongly to serum proteins or accumulate in the liver may undergo biliary excretion (68).

Ligand stability plays a central role in excretion. Unstable complexes may release metal ions that follow ionic clearance pathways rather than the excretion route of the parent compound. This can lead to unpredictable pharmacokinetics and potential accumulation of free metal ions in organs such as the liver or kidneys. Designing kinetically inert complexes reduces ligand dissociation and provides greater control over clearance patterns (69).

Toxicokinetics and host safety considerations

Safety is a central concern in developing metal-based therapeutics. Pharmacokinetic profiles influence the extent of metal exposure to host tissues, and toxicity may arise from off-target interactions, metal ion release, or cellular accumulation. Key toxicokinetic considerations include the rate of ligand dissociation, redox reactivity, and the capacity of the complex to interact with host proteins, enzymes, or nucleic acids (70).

Metal ions such as silver, copper, and gold exhibit strong affinity for thiol groups in proteins, which may lead to enzyme inhibition or oxidative stress in host cells. Ligand frameworks must therefore minimize indiscriminate reactivity while preserving antimicrobial action. Pharmacokinetic modeling can help predict tissue accumulation and guide dose adjustments to ensure therapeutic activity without toxicity (71).

Another important aspect of toxicokinetics is the potential for chronic exposure. Some metal complexes may persist in tissues or deposit in organs, raising concerns about long-term effects. Clearance studies, repeated-dose experiments, and bioaccumulation assessments are essential for evaluating chronic safety. Designing complexes with predictable degradation pathways and minimal organ retention helps reduce long-term toxicological risks (72).

Strategies to optimize pharmacokinetics

Several strategies have been employed to improve the pharmacokinetic behavior of metal complexes. Ligand engineering is the most widely used approach. Introducing hydrophilic or hydrophobic substituents can improve solubility or membrane permeability. Chelating ligands enhance kinetic stability and reduce dissociation. Macrocyclic ligands decrease interaction with serum proteins and enzymes, while flexible ligands may improve cell penetration (73).

Nanotechnology-based approaches, including encapsulation in liposomes, polymeric nanoparticles, or metal–organic frameworks, have shown promise in improving biodistribution and reducing systemic toxicity. Such carriers protect complexes from premature degradation and allow controlled release at the infection site. Moreover, nanoparticle formulations can bypass efflux pumps and enhance intracellular delivery (74).

Another approach involves conjugating metal complexes to targeting molecules such as antimicrobial peptides, antibodies, or receptor-binding ligands. These conjugates enhance selectivity and reduce exposure to non-infected tissues. Improved targeting increases local concentration at the site of infection and reduces systemic doses required for efficacy (75).

Computational tools also contribute significantly to pharmacokinetic optimization. In silico prediction of absorption, solubility, metabolic stability, and clearance can guide ligand adjustments before synthesis. Machine learning models trained on pharmacokinetic datasets can predict clearance pathways, serum protein binding, or tissue distribution patterns for newly designed complexes (76).

Integration of PK parameters with antimicrobial activity

Effective antimicrobial therapy requires alignment between pharmacokinetic behavior and pharmacodynamic mechanisms. Metal complexes with strong in vitro antibacterial activity may fail clinically if PK parameters prevent adequate exposure at target sites. Conversely, highly stable complexes that accumulate excessively may pose safety risks despite potent target inhibition (77).

Understanding the relationship between concentration–time profiles and bacterial killing dynamics is essential. Some metal complexes act rapidly through oxidative burst mechanisms, requiring short but high intracellular concentrations. Others, such as enzyme inhibitors, rely on sustained exposure to outperform bacterial repair mechanisms. PK–PD modeling helps define optimal dosing regimens, minimizes toxicity, and informs the transition from preclinical testing to clinical evaluation (78).

Preclinical Evaluation Pipeline for Metal Complex Antimicrobials

Developing metal complexes as antimicrobial agents requires a systematic preclinical evaluation strategy that integrates chemical characterization, biological screening, mechanistic validation, toxicity assessment, and in vivo efficacy testing. Metal complexes differ from traditional organic antibiotics in their coordination behavior, redox activity, and ligand exchange properties; therefore, tailored evaluation methods are needed to determine their suitability as therapeutic candidates. A structured preclinical pipeline ensures that metal complexes with desirable antimicrobial properties are advanced appropriately while eliminating those with unfavorable pharmacological or toxicity profiles. The subsections below outline the key components of such a pipeline.

Initial physicochemical characterization

Preclinical evaluation begins with detailed physicochemical characterization. This includes establishing molecular identity through NMR spectroscopy, mass spectrometry, elemental analysis, and single-crystal X-ray diffraction when feasible. These analyses confirm the coordination geometry, ligand arrangement, and oxidation state of the metal center. Additional assessments such as aqueous solubility, stability under physiological pH, and susceptibility to ligand exchange are critical for predicting biological performance (79).

Metal complexes often undergo redox transformations in biological systems, making electrochemical profiling necessary. Cyclic voltammetry provides insight into redox potentials and helps determine whether the complex is likely to generate reactive oxygen species or undergo activation under intracellular conditions. Spectrophotometric studies can further assess ligand exchange kinetics, hydrolysis rates, and protein-binding tendencies (80).

In vitro antibacterial screening

Following physicochemical analysis, metal complexes undergo antibacterial screening to determine their activity spectrum. Minimum inhibitory concentration assays remain the core method, allowing comparison against standard antibiotics and assessing potency across Gram-positive and Gram-negative species (81). Metal complexes sometimes display modest activity in standard assays but strong activity under specific conditions such as low pH or biofilm-forming environments, making supplementary testing essential.

Time–kill studies provide insight into bactericidal versus bacteriostatic behavior. Some metal complexes act rapidly by inducing oxidative stress or membrane disruption, whereas others show slower, target-specific activity. Determining the killing kinetics helps define the mechanisms that will be later evaluated in mechanistic studies (82). Combination assays with existing antibiotics can reveal synergistic interactions arising from efflux pump inhibition, enzyme targeting, or membrane permeabilization.

Mechanistic assays and target validation

Mechanistic evaluation is a central component of metal complex development, as these compounds may interact with bacterial targets through multiple pathways. Target validation requires integration of biochemical, genetic, and spectroscopic approaches.

For DNA-targeting complexes, assays such as gel electrophoresis, DNA cleavage studies, and topoisomerase inhibition assays help determine whether the complex stabilizes cleavage intermediates or disrupts enzyme function (83). Metalloenzyme inhibition studies often involve recombinant enzymes such as NDM-1 or LpxC, where metal complexes are screened for competitive or non-competitive inhibitory behavior. Inhibition constants and structural modeling provide additional insight into binding modes (84).

Fluorescence microscopy, membrane potential assays, and lipid peroxidation measurements are used to evaluate membrane-targeting mechanisms. Redox-active complexes may generate reactive oxygen species, which can be quantified using cell-permeant probes. Genetic approaches, such as evaluating susceptibility in knockout strains lacking efflux pumps or metal transport systems, further support mechanistic conclusions (85).

Cytotoxicity and safety screening

Assessing host toxicity is essential for differentiating therapeutic metal complexes from compounds with unacceptable off-target effects. Cytotoxicity assays using human cell lines such as HEK293, HepG2, or macrophage-derived lines evaluate whether the complex selectively inhibits bacterial growth without damaging mammalian cells (86). Additional assays measure hemolysis, mitochondrial function, and oxidative stress responses in host cells.

Serum stability assays determine whether metal complexes maintain structural integrity in the presence of proteins such as albumin or transferrin. High serum reactivity may lead to premature dissociation or formation of inactive adducts, limiting therapeutic potential. Toxicity evaluations also include assessment of

proinflammatory responses and evaluation of genotoxic potential using micronucleus and comet assays (87).

In vivo efficacy models

Metal complexes that demonstrate strong in vitro activity and acceptable cytotoxicity profiles are progressed to animal models. Galleria mellonella larvae serve as ethical and cost-effective preliminary models for evaluating toxicity and efficacy. They allow rapid determination of therapeutic index and offer a simple platform for comparing structurally related complexes (88).

Rodent infection models provide more detailed pharmacokinetic and efficacy information. Depending on the target pathogen, studies may involve pneumonia, urinary tract infection, systemic sepsis, or biofilm-associated infections. These models allow determination of dose–response relationships, tissue distribution, bacterial burden reduction, and survival outcomes. Monitoring metal accumulation in organs such as the liver or kidneys helps assess safety and informs dose optimization (89).

Pharmacokinetic and biodistribution studies

Pharmacokinetic studies determine absorption, distribution, metabolism, and elimination in vivo. Inductively coupled plasma mass spectrometry enables quantification of metal concentrations in plasma and tissues, providing insight into biodistribution and clearance pathways (90). Ligand integrity is evaluated by comparing parent compound levels with breakdown products.

Understanding biodistribution is critical for establishing whether the metal complex reaches the infection site at therapeutic concentrations. Infections localized in biofilms or intracellular environments require complexes with adequate penetration properties. Time–concentration curves support decisions on dosing frequency and help define therapeutic windows (91).

Summary of preclinical evaluation parameters for metal-based antimicrobials

Table 1. Key preclinical evaluation stages for metal complex antimicrobials and associated methods.

Evaluation stage	Key parameters assessed	Representative methods	Citation
Physicochemical characterization	Coordination structure, redox potential, ligand stability	NMR, XRD, cyclic voltammetry, UV–Vis spectroscopy	(79), (80)
In vitro antibacterial testing	MIC, time–kill dynamics, synergy	Broth microdilution, checkerboard assay, kill-curves	(81), (82)
Target mechanism studies	Enzyme inhibition, DNA interaction, ROS production	Topoisomerase assays, enzyme kinetics, fluorescence assays	(83), (84), (85)
Cytotoxicity evaluation	Host cell toxicity, genotoxicity, serum stability	MTT assays, hemolysis, comet assay	(86), (87)
In vivo efficacy	Therapeutic index, organ accumulation, survival	Galleria mellonella model, murine infection models	(88), (89)

Pharmacokinetics	Plasma levels, biodistribution, metabolism	ICP-MS, LC–MS, organ concentration studies	(90), (91)

6.8 Integration of preclinical data into drug development decisions

Successful translation of metal complexes from laboratory studies to clinical candidates depends on integrating chemical, biological, and pharmacokinetic findings. A metal complex demonstrating potent antibacterial activity but poor stability or high host toxicity is unlikely to succeed clinically. Likewise, complexes with moderate in vitro activity may excel in vivo if they exhibit favorable distribution or mechanisms that require host-dependent activation.

Developers must therefore prioritize compounds that combine target specificity, selective toxicity, pharmacokinetic suitability, and chemical stability. Iterative optimization informed by preclinical results allows refinement of ligand structures, metal selection, and delivery strategies. Only complexes meeting stringent thresholds across multiple evaluation domains progress to advanced development stages, including formulation studies and eventual regulatory assessment.

Challenges and Future Directions

Despite significant progress in the development of metal complexes as antimicrobial agents, numerous challenges must be addressed before these compounds can be fully integrated into the clinical antibacterial pipeline. Many of these challenges arise from the unique chemical and biological properties of metal complexes, which differ substantially from those of conventional small-molecule antibiotics. At the same time, these limitations present opportunities for innovation, driving research toward more selective, stable, and clinically relevant agents. This chapter examines key challenges related to toxicity, selectivity, stability, pharmacokinetics, resistance risk, and regulatory considerations, followed by an assessment of future directions that can advance the field.

Toxicity and off-target reactivity

One of the most significant barriers to clinical translation is the potential for toxicity associated with metal ions. Many metal complexes interact strongly with thiol-containing proteins, nucleic acids, or redox-sensitive cellular components in host tissues. While such interactions contribute to antimicrobial activity, they may also lead to adverse effects, including mitochondrial dysfunction, oxidative stress, and disruption of essential host enzymes (92).

Balancing reactivity and selectivity remains a central challenge. Complexes that are too reactive may induce systemic toxicity, whereas overly inert complexes may fail to activate within bacterial cells. Achieving this balance requires precise control of ligand exchange kinetics, redox behavior, and metal–protein interactions. Developing ligands that stabilize the metal center in circulation but permit activation only after reaching bacterial environments may help reduce systemic side effects (93).

Selectivity toward bacterial targets

Selectivity is critical for ensuring that metal complexes disrupt bacterial pathways without affecting host cells. However, many essential bacterial targets—such as metalloenzymes or nucleic acids—have structural analogs in human cells. Designing complexes that exploit subtle differences in metal coordination environments or target residues requires deep structural knowledge.

Improving selectivity involves engineering ligands that recognize specific bacterial motifs or metabolic cues. For example, incorporating fragments resembling bacterial substrates or targeting periplasmic pathways specific to Gram-negative bacteria can enhance selectivity. Nevertheless, achieving reliable selectivity across diverse pathogens remains a substantial challenge (94).

Stability and metabolic degradation

Metal complexes must maintain structural integrity long enough to reach their targets. Instability in biological fluids can lead to premature ligand dissociation, alteration of oxidation states, or formation of inactive adducts. These processes may not only reduce efficacy but also release free metal ions that contribute to toxicity (95).

Biological environments contain competing ligands such as albumin, transferrin, and glutathione that may interact with metal complexes. Designing kinetically inert complexes or using macrocyclic ligands with strong chelating ability can reduce degradation. Another strategy involves formulating complexes in nanocarriers to protect them from premature interaction with host biomolecules (96).

Pharmacokinetic limitations

Even when metal complexes are stable and selective, their pharmacokinetic profiles may limit therapeutic potential. Many complexes have poor membrane permeability, limited oral bioavailability, or rapid clearance from circulation. Highly charged or hydrophilic complexes struggle to penetrate bacterial envelopes, whereas highly lipophilic complexes may distribute excessively into fatty tissues or cause membrane disruption in host cells (97).

Controlling pharmacokinetics requires a balance of charge, hydrophobicity, size, and ligand stability. Delivery systems such as nanoparticles, liposomes, and polymer conjugates offer promising ways to improve distribution and prolong circulation. However, these approaches introduce additional challenges such as formulation complexity, cost, and regulatory hurdles (98).

Resistance potential and bacterial adaptation

A frequent misconception is that metal complexes are inherently resistant-proof. Although metal-based antimicrobials can disrupt multiple pathways, bacteria may still develop resistance through efflux pump upregulation, metal sequestration, enzymatic detoxification, or changes in cell envelope composition. Some pathogens possess transporters that specifically export metal ions or express metallothioneins that bind and neutralize metal complexes (99).

Understanding the likelihood and mechanisms of resistance development is crucial for designing durable metal-based therapies. Combining metal complexes with antibiotics or efflux pump inhibitors may reduce resistance risk. Designing complexes that target

multiple pathways simultaneously can further enhance robustness against resistance (100).

Limited structural and mechanistic understanding

Although many metal complexes demonstrate antimicrobial activity, the precise mechanisms often remain poorly characterized. Metal complexes may act through multiple simultaneous pathways, making it difficult to identify primary mechanisms of action. This complexity complicates rational optimization and prediction of structure–activity relationships (101).

Advances in structural biology, such as cryo-electron microscopy and metal-specific spectroscopic techniques, have improved mechanistic understanding, but further development is needed. Comprehensive mechanistic profiling—including omics approaches, target engagement studies, and metalloproteomics—will be essential for identifying high-value targets for future metal-based drug design (102).

Challenges in regulatory approval and standardization

Metal-based therapeutics face additional regulatory scrutiny due to concerns about long-term safety, environmental impact, and systemic accumulation. Many existing toxicology frameworks were developed for organic compounds and may not fully address the complexity of metal pharmacokinetics or biodistribution. Standardization of testing protocols, including metal-specific toxicity assessments, remains incomplete (103).

Furthermore, manufacturing metal complexes at pharmaceutical grade presents challenges related to purity, reproducibility, and batch-to-batch consistency. Developing clear regulatory guidelines and validated analytical methods is necessary to support clinical translation of metal-based antimicrobials (104).

Future directions in metal-based antimicrobial discovery

The future of metal-based antimicrobial research lies in integrating chemistry, computational approaches, materials science, and systems biology. Several promising directions may accelerate the advancement of metal complexes toward clinical application.

One emerging strategy is the development of activatable complexes that remain inert during circulation and activate only in specific environments, such as acidic infection sites or biofilms. These smart complexes can reduce systemic toxicity while delivering high local potency (105).

Computational chemistry and machine learning will play increasingly important roles in predicting target interactions, ligand stability, redox properties, and antimicrobial activity. AI-driven models can significantly reduce experimental burden and guide the design of selective and stable complexes (106).

Nanotechnology-based delivery systems offer opportunities to overcome pharmacokinetic barriers by enabling targeted release and improved biofilm penetration. Metal–organic frameworks, polymer carriers, and hybrid nanoparticles can enhance distribution and minimize toxicity by controlling release kinetics (107).

Another key direction is the exploration of unique bacterial pathways that are especially suited for metal complex targeting. These include metal-dependent

metabolic enzymes, redox-active pathways, membrane transporters, and metal homeostasis regulators. Targeting such systems may provide opportunities for pathogen-specific therapies with reduced impact on host cells (108).
Collaboration between chemists, microbiologists, pharmacologists, and regulatory scientists will be essential for translating promising candidates into clinical trials. Establishing shared databases, standardized evaluation criteria, and open-access mechanistic tools can accelerate progress in the field.

Emerging Computational Tools in Metal Complex Antimicrobial Design

Advances in computational chemistry have significantly accelerated the discovery of metal-based antimicrobial agents. Metal complexes pose unique challenges because of their variable coordination geometries, diverse oxidation states, and complex electronic structures. Traditional drug discovery tools developed for purely organic molecules often fail to capture the stereoelectronic behavior of metal-containing systems. As a result, specialized computational frameworks have emerged to support rational design, mechanistic prediction, and activity optimization. This section discusses the most important computational methodologies currently applied to metal-based antimicrobial development.

AI-based prediction of metal–ligand stability

Metal–ligand stability is a major determinant of biological behavior, influencing cellular uptake, target interaction, serum stability, and toxicity. Predicting stability experimentally is labor-intensive, particularly for complexes with dynamic coordination spheres. Artificial intelligence models trained on large datasets of metal–ligand complexes provide an efficient alternative for evaluating thermodynamic and kinetic stability.
AI models integrate descriptors such as metal ionic radius, ligand donor atom types, ligand field strength, frontier orbital energies, and complex geometry. Machine learning approaches such as random forests, support vector machines, and neural networks have been applied successfully to estimate formation constants and dissociation energies of transition-metal complexes (105). These predictions help identify ligand scaffolds that minimize premature dissociation in vivo while maintaining target reactivity.
Recent developments include graph neural networks that encode metal coordination environments and use message-passing algorithms to learn metal–ligand interaction patterns. These tools can rapidly screen thousands of hypothetical ligand–metal combinations before synthesis, significantly reducing experimental workload (106). Furthermore, AI-based prediction aids in designing complexes that remain inert in circulation but activate upon encountering bacterial microenvironments.

Machine learning models for MIC prediction

Minimum inhibitory concentration (MIC) is the most widely used measure of antimicrobial potency. Predicting MIC values computationally for metal complexes is challenging because activity depends on multiple factors, including ligand denticity, charge distribution, redox state, lipophilicity, and the target pathogen.

Machine learning models trained on curated datasets of metal complexes and their MIC values have begun to exhibit meaningful predictive power. Algorithms such as gradient boosting, kernel regression, and deep neural networks incorporate structural descriptors, electronic parameters, lipophilicity indices, and steric features (107). This enables prediction of MIC across different bacterial species, including Gram-positive and Gram-negative pathogens.

These models help identify patterns linking structural motifs with antimicrobial activity. For example, studies show that complexes with planar aromatic ligands frequently demonstrate enhanced DNA-binding affinity and lower MIC values. Similarly, complexes exhibiting moderate lipophilicity tend to show improved membrane penetration. ML-driven MIC prediction supports lead prioritization and guides ligand optimization (108).

Quantitative structure–activity relationships for metal complexes

Quantitative structure–activity relationship (QSAR) modeling has long been used for organic drug optimization; however, its application to metal complexes remained limited due to the unique structural complexity of coordination compounds. Recent advances have introduced metal-specific descriptors that capture coordination geometry, ligand donor properties, electronic distribution, and bond strength.

QSAR models for metal complexes typically incorporate:

- Metal–ligand bond order
- Coordination number
- Ligand denticity
- HOMO–LUMO energy gap
- Oxidation state
- Steric and topological indices

These descriptors allow regression or classification models to predict antimicrobial activity, selectivity, and cytotoxicity. QSAR-guided optimization has been particularly effective for designing metal complexes targeting metalloenzymes or DNA, where electron distribution strongly influences binding behavior (109).

Modern QSAR approaches often integrate quantum mechanical descriptors to capture the subtleties of metal-centered reactivity. Machine learning-enhanced QSAR models further refine predictive accuracy and allow high-throughput virtual screening of hypothetical metal–ligand frameworks (110).

Molecular dynamics for metal–protein interactions

Molecular dynamics (MD) simulations provide time-resolved insights into the behavior of metal complexes interacting with protein targets. Because bacterial proteins undergo constant conformational fluctuations, static structures from crystallography may not fully capture binding dynamics. MD simulations help determine whether a metal complex remains stably bound within the active site over physiologically relevant timescales.

Specialized force fields have been developed to simulate transition-metal systems, enabling accurate modeling of coordination geometries and ligand dynamics (111). MD simulations are widely applied to:

• assess stability of metal complexes in enzyme active sites
• predict displacement of catalytic metal ions in metalloenzymes
• study interactions with DNA gyrase, LpxC, or efflux pumps
• evaluate how ligand modifications affect protein binding
• investigate solvent-mediated effects on geometry or redox behavior
For complexes that rely on ligand exchange or redox activation, MD simulations help identify pathways for activation and reveal interactions that contribute to antibacterial activity. These insights inform ligand engineering strategies and metal selection (112).

DFT-guided redox potential tuning
Redox activity plays a central role in the biological function of many metal complexes. Some complexes generate reactive oxygen species, while others undergo reduction inside bacterial cells to release active species. Density functional theory (DFT) is the preferred method for calculating redox potentials, charge distribution, orbital energies, and electron-transfer pathways.
DFT enables prediction of oxidation state preferences, ligand field effects, and the relative stability of metal-centered redox states. These calculations help identify whether a metal complex will remain inert in circulation or undergo redox activation in bacterial environments (113).
For example:
• Ru(II)/Ru(III) and Co(III)/Co(II) redox couples influence activation behavior
• Cu(II)/Cu(I) cycling affects ROS generation
• Metal–ligand charge transfer transitions correlate with DNA-binding affinity

DFT-guided tuning ensures that complexes possess the desired redox potential to maximize antimicrobial action while minimizing off-target oxidative stress. Integration of DFT with experimental electrochemistry allows iterative optimization of ligand frameworks (114).

Challenges and Future Directions
The field of metal-based antimicrobial drug discovery continues to advance, yet significant challenges remain before these compounds can transition into clinically accepted therapies. Their chemical complexity, multi-target behavior, and potential for host interaction require careful evaluation and thoughtful design. At the same time, rapid progress in computational chemistry, high-throughput screening, and systems biology offers new opportunities to overcome current hurdles. This section addresses key challenges and highlights emerging directions that may shape the future of metal-complex antimicrobial development.

Selectivity versus host toxicity
Achieving selective toxicity toward bacterial cells while minimizing harm to the host is one of the greatest challenges in metal-based drug development. Many metal complexes interact with biological molecules through mechanisms such as thiol binding, redox cycling, or coordination to nucleophilic residues. These interactions can be beneficial for antibacterial activity but may also disrupt essential host processes (115).

Selective targeting is hindered by the fact that several bacterial pathways, particularly metalloenzymes and nucleic acid structures, share similarities with mammalian counterparts. Without structural differences that can be exploited, metal complexes may engage host proteins, leading to oxidative damage, mitochondrial dysfunction, or altered signaling pathways. Future strategies to improve selectivity may include designing activatable complexes that respond to bacterial-specific conditions such as low pH, distinctive metal ion gradients, or unique redox states. Delivery systems that target infected tissues or microbial biofilms may further enhance selectivity and reduce systemic toxicity (116).

Need for better models for metal–protein docking

Metal–protein interactions are difficult to model because of the diverse coordination geometries, variable oxidation states, and complex electronic structures associated with transition metals. Most docking algorithms were developed for organic ligands and fail to capture metal coordination preferences, ligand denticity, and metal-centered reactivity. As a result, predicted binding poses may not reflect true biological interactions (117).

Advancement in metal-aware docking tools is essential for accurate prediction of binding modes and affinities. Improved scoring functions, quantum mechanics–based corrections, and algorithms capable of modeling ligand exchange pathways will enhance modeling accuracy. Integration of hybrid QM/MM approaches with molecular dynamics simulations may allow realistic representation of protein flexibility and metal coordination. Developing comprehensive experimental datasets of metal–protein interactions will further guide refinement of these computational models (118).

Need for standardized evaluation protocols

The field lacks standardized protocols for evaluating the antimicrobial activity, toxicity, and pharmacokinetics of metal complexes. Unlike organic antibiotics, metal complexes undergo redox transformations, ligand exchange, and binding to serum proteins in ways that complicate interpretation of standard microbiological assays. Variability in testing conditions—including pH, media composition, and assay duration—can significantly affect observed activity (119).

Standardization is necessary to ensure reproducibility across laboratories and to establish benchmarks for advancing complexes into preclinical testing. Recommended improvements include defining specific media for testing redox-active complexes, evaluating ligand stability during assays, and incorporating metal homeostasis mutants of bacteria for mechanistic assessment. Additionally, standardized cell-line panels for toxicity assessment and harmonized protocols for serum stability testing would help in comparing complexes across research groups (120).

AI-guided libraries of metal complexes

Artificial intelligence is transforming drug discovery, and its application to metal-based antimicrobials offers substantial promise. AI can analyze large datasets to uncover patterns linking ligand structures, metal identities, and biological activities.

However, public databases containing well-annotated metal complex data remain limited, hindering the development of robust predictive models (121).
Future progress will depend on establishing shared repositories of metal complex structures, antimicrobial activities, physicochemical parameters, and toxicity profiles. Once such datasets exist, AI can enable automated generation of virtual libraries that explore chemical space beyond traditional metal–ligand combinations. Generative neural networks and reinforcement learning frameworks may design complexes optimized for target affinity, metabolic stability, and safety. AI-driven prediction of metal–ligand stability, MIC values, and redox behavior could drastically reduce development time (122).

Regulatory challenges

Regulatory frameworks for metal-based therapeutics are less mature than those for organic small molecules. Metal complexes raise unique concerns regarding long-term tissue accumulation, environmental persistence, potential metallotoxicity, and unclear metabolic pathways. Existing guidelines may not adequately address ligand dissociation, metal ion release, or interactions with metalloproteins (123).
Manufacturing challenges also complicate regulatory approval. Metal complexes require stringent control of oxidation state, purity, ligand-to-metal stoichiometry, and kinetic stability. Batch-to-batch variability must be minimized to meet regulatory expectations. Developing specific guidelines for metallodrugs—including standardized toxicity metrics, bioaccumulation studies, and environmental risk assessments—would facilitate smoother regulatory evaluation (124).

Opportunities for personalised metal-based antimicrobial therapy

Personalised medicine offers promising opportunities for advancing metal-based antimicrobial therapy. Differences in host metal metabolism, immune status, and microbiome composition influence how metal complexes behave in vivo. Additionally, bacterial strains vary in metal homeostasis pathways, efflux mechanisms, and enzyme profiles, making certain metal complexes more effective against specific pathogens or infection types (125).
Personalisation may involve selecting metal complexes based on host metabolic profiles or bacterial metal utilization pathways. For example, infections caused by pathogens with impaired iron acquisition may be particularly susceptible to gallium complexes. Similarly, bacteria overexpressing certain metalloenzymes could be targeted selectively with metal-based inhibitors. Integration of microbiome analysis, host-genomic data, and bacterial metallomics could guide individualized therapeutic approaches (126).
Advances in computational profiling, biosensors, and predictive diagnostics may soon allow rapid identification of effective metal complexes tailored to specific infections. Such strategies could optimize outcomes and reduce toxicity by avoiding one-size-fits-all treatments.

CONCLUSION

Metal complexes represent a rapidly emerging class of antimicrobial agents with the potential to address the escalating global crisis of antibiotic resistance. Their unique

ability to engage bacterial targets through redox activity, ligand exchange, coordination chemistry, and multi-pathway disruption distinguishes them from traditional organic molecules. Advances in ligand engineering, computational modeling, and mechanistic profiling have expanded the range of metal complexes capable of selective, potent antibacterial action. Nevertheless, challenges remain, particularly in achieving host–pathogen selectivity, optimizing pharmacokinetic behavior, ensuring structural stability, and developing appropriate evaluation frameworks tailored to metallodrugs. Progress in these areas will rely on integrating chemical innovation with modern computational tools, standardized biological testing, and interdisciplinary collaboration. The future of metal-based antimicrobial discovery lies in combining precise molecular design with systems-level understanding of bacterial metal homeostasis, host biology, and environmental interactions. As computational tools improve and regulatory guidance evolves, metal complexes are poised to become valuable contributors to the next generation of antimicrobial therapies, offering new strategies to combat resistant pathogens while enabling more personalized approaches to treatment.

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