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Evaluation of Structure–Activity Relationships in Novel Metal Complexes for Antimicrobial and Anticancer Drug Development

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Abstract: *Metal complexes have emerged as promising candidates in the development of antimicrobial and anticancer therapeutics because coordination with biologically active ligands can substantially modify their physicochemical, biological, and pharmacological properties. The therapeutic behaviour of a metal complex is strongly influenced by its metal centre, oxidation state, coordination geometry, ligand environment, chelation mode, charge, lipophilicity, stability, and ability to interact with cellular targets.*

Structure–activity relationship (SAR) evaluation provides an important framework for understanding how systematic structural modifications affect antimicrobial and anticancer potency and selectivity. In antimicrobial applications, metal complexes can act through multiple mechanisms, including disruption of microbial membranes, interaction with nucleic acids, inhibition of essential enzymes, generation of reactive oxygen species, and interference with cellular metabolism. In cancer research, their activities may involve DNA binding or cleavage, mitochondrial dysfunction, oxidative stress, enzyme inhibition, cell-cycle arrest, and induction of apoptosis. Recent research has demonstrated that complexes containing metals such as platinum, ruthenium, copper, silver, gold, cobalt, nickel, zinc, and manganese can exhibit distinctive biological profiles.

Keywords: Metal complexes; Drug development; Bioinorganic chemistry; DNA interaction; Apoptosis; Drug discovery.

I. INTRODUCTION

Metal-based compounds occupy a distinctive position in medicinal chemistry because metal ions possess coordination, redox, catalytic, and structural properties that cannot be readily reproduced by conventional organic molecules. The incorporation of a metal centre into a ligand framework can alter molecular geometry, electronic distribution, hydrophobicity, solubility, stability, cellular uptake, and interaction with biological macromolecules. These characteristics have encouraged extensive investigation of metal complexes as potential antimicrobial and anticancer agents. The clinical success of platinum-based drugs, particularly cisplatin, carboplatin, and oxaliplatin, established the feasibility of metal-based chemotherapy and stimulated the search for alternative complexes with improved efficacy and reduced toxicity. Similarly, silver and copper complexes have received considerable attention because of their broad antimicrobial properties and diverse mechanisms of action.

Structure–activity relationship evaluation is particularly important for metal complexes because biological activity is rarely determined by the metal ion alone. The ligand system can regulate metal-ion release, coordination stability, lipophilicity, cellular penetration, redox behaviour, and target recognition. Small structural modifications, such as substitution of electron-donating or electron-withdrawing groups, changes in ligand denticity, introduction of heteroatoms, or alteration of aromaticity, can significantly influence biological responses. Consequently, SAR studies provide a systematic approach for correlating molecular structure with biological performance and identifying structural characteristics responsible for desirable pharmacological effects.

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In antimicrobial drug development, metal complexes may interact with bacterial or fungal membranes, proteins, thiol-containing enzymes, DNA, and intracellular redox systems. Their mechanisms can differ according to the metal and ligand combination. Silver complexes, for example, can interact with cellular proteins and membranes, whereas copper complexes may participate in redox reactions and oxidative stress. In anticancer research, metal complexes can exploit differences between malignant and normal cells through DNA interactions, redox imbalance, mitochondrial damage, enzyme inhibition, and apoptosis-related pathways. The diversity of these mechanisms makes metal complexes valuable scaffolds for developing therapeutics against drug-resistant infections and cancers.

II. STRUCTURAL DETERMINANTS GOVERNING BIOLOGICAL ACTIVITY

The metal centre represents one of the principal determinants of the biological properties of a coordination compound. Different metals possess distinct oxidation states, coordination preferences, ligand-exchange kinetics, redox potentials, and biological affinities. Platinum complexes generally demonstrate strong interactions with nucleophilic sites in DNA, while ruthenium complexes have attracted interest because of their variable oxidation states and potentially favourable kinetic and pharmacological characteristics. Copper and silver complexes are particularly relevant to antimicrobial research because of their ability to disturb cellular processes and interact with biomolecules. Gold complexes have also been investigated extensively because of their interactions with thiol-containing proteins and redox-related pathways.

The ligand structure is equally important. Chelating ligands can increase complex stability and alter the electronic characteristics of the metal centre. Aromatic ligands may enhance DNA intercalation and hydrophobic interactions, while ligands containing nitrogen, oxygen, sulfur, or phosphorus donor atoms can influence coordination strength and biological recognition. Substitution patterns on aromatic rings can affect electron density, steric properties, hydrogen bonding, and lipophilicity. Increasing hydrophobicity may improve membrane penetration in some systems, although excessive lipophilicity can reduce aqueous solubility and increase nonspecific toxicity.

Coordination geometry also contributes to activity. Square-planar, octahedral, tetrahedral, and other geometries can determine how a complex interacts with biological targets. Charge is another important parameter because cationic complexes may interact favourably with negatively charged cellular membranes, nucleic acids, and mitochondrial components. Conversely, neutral or less charged complexes may exhibit improved passive diffusion through lipid membranes. The balance between stability and reactivity is particularly important. A complex must remain sufficiently stable during transport but should also possess adequate reactivity or controlled ligand exchange to interact with its biological target.

III. STRUCTURE–ACTIVITY RELATIONSHIPS IN ANTIMICROBIAL METAL COMPLEXES

The antimicrobial activity of metal complexes is governed by an interplay between metal identity, ligand structure, charge, lipophilicity, coordination stability, and the ability to reach intracellular targets. A recurring SAR observation is that complex formation can enhance the antimicrobial activity of certain organic ligands by modifying their membrane permeability and biological interactions. Chelation may reduce the polarity of a metal–ligand system and increase its ability to cross microbial membranes. However, this effect depends strongly on the particular ligand and metal combination.

Silver complexes are among the most extensively studied antimicrobial metal systems. Their activity is associated with interactions involving microbial membranes, proteins, thiol groups, and nucleic acids. Structural modification of silver complexes can influence silver-ion availability and cellular uptake. Copper complexes similarly demonstrate broad antimicrobial potential, with activity frequently associated with membrane disruption, protein interactions, and reactive oxygen species generation. The ligand environment can control the redox properties of copper and consequently influence the extent of oxidative stress.

Zinc complexes are attractive because zinc is an essential biological element, although the biological activity of a particular complex depends strongly on its coordination environment and concentration. Cobalt, nickel, manganese, and iron complexes have also been investigated for antimicrobial properties, particularly where their redox characteristics

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can contribute to microbial damage. Ligands containing nitrogen, sulfur, and oxygen donor atoms often produce biologically active complexes because these donor groups facilitate stable coordination while retaining opportunities for interactions with microbial targets.

Table 1. Major structural factors and their influence on antimicrobial activity

Structural factor	Typical modification	Possible effect on antimicrobial activity
Metal centre	Ag, Cu, Zn, Au, Co, Ni, Mn	Changes redox behaviour, stability and biological interactions
Oxidation state	Variation of metal oxidation state	Alters reactivity, ion release and cellular interactions
Ligand donor atoms	N, O, S, P donors	Controls coordination strength and electronic properties
Chelation	Mono- or multidentate ligands	May improve stability and membrane permeability
Lipophilicity	Addition of hydrophobic substituents	Can enhance membrane penetration but may increase nonspecific toxicity
Molecular charge	Neutral, cationic or anionic complexes	Influences membrane interaction and cellular uptake
Aromaticity	Expanded aromatic ligand systems	May enhance nucleic-acid and hydrophobic interactions
Steric bulk	Bulky substituents around metal centre	Can modify target accessibility and stability
Complex stability	Stronger or weaker metal–ligand bonds	Determines persistence and controlled metal release
Redox activity	Redox-active metal/ligand combinations	May promote oxidative stress in microbial cells

IV. STRUCTURE–ACTIVITY RELATIONSHIPS IN ANTICANCER METAL COMPLEXES

The development of anticancer metal complexes has expanded beyond traditional platinum compounds toward ruthenium, copper, gold, iridium, osmium, cobalt, and other metal-based systems. The principal objective of SAR optimization is to retain strong tumour-cell toxicity while reducing resistance and damage to healthy tissues. Structural changes can influence cellular uptake, subcellular localization, DNA interactions, protein binding, redox behaviour, and the ability to trigger programmed cell death.

Platinum complexes provide a classical example of metal-based SAR. Changes in leaving groups, carrier ligands, coordination geometry, and overall molecular architecture can substantially affect DNA binding, pharmacokinetics, and toxicity. The success of cisplatin derivatives demonstrates that geometric arrangement can be more important than simply the presence of platinum. Alternative geometries and ligand systems have therefore been explored to overcome resistance mechanisms associated with conventional platinum therapy.

Ruthenium complexes have attracted attention because their ligand environments can be extensively modified to regulate hydrolytic stability, cellular uptake, redox properties, and target interactions. Copper complexes can exploit the altered redox environment of cancer cells and may induce oxidative stress, mitochondrial dysfunction, and apoptosis. Gold complexes have been studied for their ability to interact with thiol-containing proteins and inhibit cellular redox systems. In each case, ligand modification is essential for controlling biological behaviour.

Table 2. Representative metal systems and important SAR characteristics in anticancer research

Metal system	Important structural features	Major biological interactions	Potential anticancer outcome
Platinum	Square-planar geometry, leaving groups, amine ligands	DNA coordination and cross-linking	DNA damage and apoptosis
Ruthenium	Variable oxidation states and	DNA/protein interactions, redox	Cell-cycle disruption and

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	tunable ligands	processes	apoptosis
Copper	Redox-active coordination environment	ROS generation, protein and mitochondrial interactions	Oxidative stress and apoptosis
Gold	Soft metal centre with sulfur-affine ligands	Thiol-containing proteins and redox enzymes	Redox imbalance and cell death
Iridium	Organometallic and polypyridyl frameworks	Mitochondrial and redox-related pathways	Apoptosis and metabolic disruption
Osmium	Tunable coordination and redox properties	Protein and cellular pathway interactions	Cytotoxic and antiproliferative effects
Cobalt	Variable coordination and oxidation state	ROS and biomolecular interactions	Oxidative stress and apoptosis
Zinc	Biocompatible metal with ligand-dependent behaviour	Enzyme/protein interactions	Growth inhibition and cellular dysfunction

V. BIOLOGICAL MECHANISMS, SELECTIVITY AND PHARMACOLOGICAL CHALLENGES

Metal complexes can exert biological effects through several simultaneous mechanisms, which represents both an advantage and a challenge for drug development. DNA is a major target for many metal-based anticancer compounds, but proteins, enzymes, membranes, mitochondria, and intracellular redox systems can also participate in their pharmacological activity. DNA binding may produce replication stress and genomic damage, whereas mitochondrial interactions can cause membrane depolarization and activation of apoptosis. Reactive oxygen species can further amplify cellular damage, particularly in cancer cells that already experience elevated oxidative stress.

For antimicrobial agents, membrane disruption, enzyme inhibition, nucleic-acid interaction, metal-ion homeostasis disturbance, and oxidative stress are among the principal mechanisms. Multiple mechanisms may reduce the probability of resistance developing through a single mutation, although resistance to metal-based agents can still emerge through altered uptake, efflux, sequestration, detoxification, or modification of cellular targets.

Despite promising activity, several pharmacological limitations must be addressed. Poor water solubility can restrict formulation and bioavailability, while excessive stability may prevent the complex from reaching its intended biological target. Conversely, excessive lability may result in premature decomposition or nonspecific interactions. Toxicity toward healthy cells remains a major concern, particularly for highly reactive metal complexes. Therefore, future SAR studies should evaluate not only potency but also selectivity indices, metabolic stability, cellular uptake, protein binding, pharmacokinetics, and long-term toxicity.

VI. FUTURE PERSPECTIVES AND CONCLUSION

The SAR-driven development of metal complexes represents a promising strategy for generating next-generation antimicrobial and anticancer therapeutics. Rational modification of metal centres, oxidation states, ligand architecture, coordination geometry, molecular charge, hydrophobicity, and steric characteristics can provide substantial control over biological activity. The most effective approach is unlikely to depend on maximizing cytotoxic or antimicrobial potency alone; rather, successful drug candidates should demonstrate an appropriate balance between target engagement, cellular uptake, stability, selectivity, pharmacokinetics, and safety.

Future research should increasingly combine coordination chemistry with computational drug design, molecular docking, quantitative structure–activity relationship modelling, bioinformatics, metabolomics, and advanced cellular assays. Such integrated approaches can help identify structural descriptors associated with potency and selectivity and reduce dependence on empirical trial-and-error synthesis. Particular attention should be given to complexes capable of overcoming antimicrobial resistance and cancer-drug resistance while maintaining acceptable toxicity toward normal cells. Controlled metal release, tumour- or pathogen-specific targeting, stimulus-responsive activation, and combination therapies also represent important directions. Overall, systematic SAR evaluation provides a powerful foundation for

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transforming novel metal complexes from experimental bioactive compounds into rationally designed therapeutic candidates.

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