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Coordination Compounds as Anticancer Agents: Mechanisms, Clinical Applications, and Future Perspectives

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Abstract

Cancer remains one of the leading causes of morbidity and mortality worldwide despite significant advances in diagnosis and treatment. Although conventional chemotherapy has improved patient survival, its clinical application is often limited by severe toxicity, poor selectivity, multidrug resistance, and adverse side effects. Coordination compounds, also known as metal complexes, have emerged as an important class of anticancer agents owing to their unique physicochemical properties, versatile coordination geometries, tunable ligand environments, and diverse mechanisms of action. Since the clinical introduction of cisplatin, numerous metal-based complexes incorporating platinum, ruthenium, gold, copper, cobalt, zinc, titanium, iron, and iridium have demonstrated promising anticancer activity against a wide range of malignancies. These compounds exert cytotoxic effects through multiple mechanisms, including DNA binding, oxidative stress induction, apoptosis activation, enzyme inhibition, mitochondrial dysfunction, angiogenesis suppression, and modulation of intracellular signaling pathways. Recent advances in nanotechnology, targeted drug delivery, computational drug design, and ligand engineering have further enhanced the therapeutic potential of coordination compounds while minimizing systemic toxicity. This review summarizes the chemistry, classification, mechanisms of anticancer action, clinically approved metal-based drugs, emerging coordination compounds, current challenges, and future perspectives for the development of next-generation metal-based anticancer therapeutics.

Keywords: *Coordination compounds, Metal complexes, Cisplatin, Ruthenium complexes, Medicinal inorganic chemistry, Metallodrugs, Cancer therapy.*

1. Introduction

Cancer represents a major global health challenge, accounting for millions of new cases and deaths annually. The disease is characterized by uncontrolled cellular proliferation, genetic instability, resistance to apoptosis, angiogenesis, invasion, and metastasis. Although surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, and targeted molecular therapies have substantially improved cancer management, limitations such as drug resistance, non-specific toxicity, tumor recurrence, and treatment failure continue to restrict therapeutic success [1]. Consequently, considerable research has focused on identifying novel classes of anticancer agents with improved efficacy, selectivity, and safety.

Coordination compounds have become one of the most important developments in medicinal inorganic chemistry. These compounds consist of a central metal ion coordinated to one or more organic or inorganic ligands through coordinate covalent bonds. The metal center determines the electronic and redox properties of the complex, whereas the ligands influence stability, solubility, lipophilicity, biological distribution, and target specificity.

The remarkable versatility of coordination chemistry allows precise control over molecular geometry and biological activity, enabling the rational design of compounds with optimized pharmacological properties [2]. The discovery of cisplatin's antitumor activity by Barnett Rosenberg in the 1960s revolutionized cancer chemotherapy and established coordination compounds as clinically valuable anticancer drugs. Cisplatin, carboplatin, and oxaliplatin remain among the most widely prescribed chemotherapeutic agents for treating ovarian, testicular, bladder, lung, colorectal, head and neck, and several other cancers [3]. However, platinum-based drugs are frequently associated with nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal toxicity, and the development of drug resistance. These limitations have stimulated intensive research into alternative metal complexes capable of overcoming the shortcomings of conventional platinum chemotherapy.

Recent advances in coordination chemistry have expanded the range of biologically active metal complexes beyond platinum. Ruthenium, gold, copper, cobalt, iron, titanium, iridium, osmium, gallium, zinc, and palladium complexes have

demonstrated promising anticancer activities through diverse molecular mechanisms. Many of these compounds exhibit selective tumor accumulation, reduced systemic toxicity, and activity against platinum-resistant cancers. Furthermore, advances in nanotechnology, computational chemistry, molecular docking, and targeted drug delivery systems have accelerated the development of multifunctional coordination compounds capable of combining diagnostic and therapeutic functions [4]. This review provides a comprehensive overview of coordination compounds used in cancer therapy, emphasizing their chemistry, mechanisms of action, clinically approved drugs, emerging therapeutic candidates, current challenges, and future research directions.

2. Fundamentals of Coordination Chemistry in Medicine

Coordination chemistry is a branch of inorganic chemistry that studies compounds consisting of a central metal atom or ion surrounded by molecules or ions known as ligands. These ligands donate electron pairs to the metal center, forming stable coordinate covalent bonds that determine the structural and chemical properties of the complex. The nature of the metal ion, coordination number, oxidation state, ligand type, and molecular geometry collectively influence biological activity, stability, and pharmacological behavior [5]. In medicinal applications, coordination compounds possess several advantages over conventional organic drugs. Metal ions exhibit multiple oxidation states and variable coordination geometries, allowing interactions with diverse biological targets including DNA, proteins, enzymes, membranes, and nucleic acids. Coordination compounds can undergo ligand exchange reactions under physiological conditions, enabling controlled activation within tumor tissues. Their redox activity further contributes to selective cytotoxicity by generating reactive oxygen species that induce oxidative stress in cancer cells.

Ligands play an equally important role by modulating solubility, lipophilicity, stability, cellular uptake, biodistribution, and target selectivity. Chelating ligands, nitrogen-containing heterocycles, phosphines, amino acids, peptides, and naturally derived compounds have been extensively employed to optimize biological performance. The ability to tailor both the metal center and ligand architecture provides medicinal chemists with exceptional flexibility for designing next-generation anticancer agents.

3. Classification of Metal-Based Anticancer Coordination Compounds

Coordination compounds investigated for cancer therapy can be broadly classified according to the central metal ion. Platinum complexes constitute the largest and most clinically successful class, with cisplatin, carboplatin, and oxaliplatin serving as standard chemotherapeutic agents for numerous solid tumors. Their primary mechanism involves covalent binding to DNA, leading to inhibition of DNA replication and activation of apoptosis [6]. Despite their clinical success, platinum drugs are associated with significant toxicity and acquired resistance, motivating the search for alternative metallodrugs.

Ruthenium complexes have emerged as promising second-generation anticancer agents because of their favorable redox properties, lower toxicity, and preferential accumulation within tumor tissues. Several ruthenium compounds have advanced into clinical trials due to their ability to inhibit metastasis, induce apoptosis, and selectively target hypoxic tumor environments [7]. Gold complexes have attracted increasing attention because of their potent inhibition of thioredoxin reductase, a key enzyme involved in maintaining intracellular redox balance. By disrupting antioxidant defense systems, gold compounds induce oxidative stress and programmed cell death in cancer cells. Copper complexes also exhibit significant anticancer activity through redox cycling, reactive oxygen species generation, DNA cleavage, enzyme inhibition, and mitochondrial dysfunction [8]. Other transition metal complexes containing cobalt, iron, titanium, gallium, iridium, osmium, zinc, and palladium continue to demonstrate encouraging preclinical results through diverse molecular mechanisms, broadening the scope of metal-based chemotherapy.

Table 1: Major Metal-Based Coordination Compounds in Cancer Therapy

Metal	Representative Compounds	Primary Mechanism	Clinical Status
Platinum	Cisplatin, Carboplatin, Oxaliplatin	DNA cross-linking	Approved
Ruthenium	NAMI-A, KP1019	Apoptosis, anti-metastatic activity	Clinical evaluation
Gold	Auranofin derivatives	Thioredoxin reductase inhibition	Experimental/Clinical studies
Copper	Copper(II) complexes	ROS generation, DNA damage	Preclinical
Cobalt	Cobalt coordination complexes	Hypoxia targeting	Experimental
Titanium	Titanocene derivatives	DNA interaction	Experimental
Gallium	Gallium nitrate complexes	Iron metabolism disruption	Clinical investigation
Iridium	Cyclometalated iridium complexes	Mitochondrial dysfunction	Experimental

4. Molecular Mechanisms of Anticancer Activity

The remarkable anticancer efficacy of coordination compounds arises from their ability to interact with multiple intracellular targets, distinguishing them from many conventional chemotherapeutic agents that often act through a single mechanism. The versatility of metal ions, combined with rational ligand design, enables coordination compounds to interfere with essential cellular processes involved in cancer progression, proliferation, angiogenesis, metastasis, and apoptosis. Their multifaceted mechanisms reduce the likelihood of therapeutic failure and provide opportunities to overcome multidrug resistance [9]. One of the best-characterized mechanisms is DNA binding and cross-link formation. Platinum-based compounds such as cisplatin enter cancer cells through passive diffusion and transporter-mediated uptake. Following intracellular activation, chloride ligands are replaced by water molecules, producing highly reactive species

that covalently bind to purine bases, particularly the N7 position of guanine residues. The resulting intra- and interstrand DNA cross-links distort the DNA double helix, inhibit DNA replication and transcription, activate DNA damage response pathways, and ultimately trigger programmed cell death. Similar DNA interactions have also been reported for several ruthenium, copper, cobalt, and palladium complexes, although their binding modes may differ depending on ligand architecture.

Many coordination compounds also induce oxidative stress through the generation of reactive oxygen species (ROS). Transition metals such as copper, iron, and ruthenium undergo redox cycling within cells, producing superoxide radicals, hydroxyl radicals, and hydrogen peroxide. Elevated ROS levels damage cellular proteins, lipids, nucleic acids, and mitochondrial membranes, leading to irreversible oxidative injury and apoptosis. Cancer cells are particularly susceptible to oxidative stress because they already maintain relatively high basal ROS levels compared with normal tissues [10]. Mitochondrial dysfunction represents another important mechanism. Several coordination compounds accumulate preferentially within mitochondria, disrupting mitochondrial membrane potential, impairing ATP synthesis, releasing cytochrome c, and activating intrinsic apoptotic pathways. These events initiate caspase activation and ultimately result in controlled cellular death without extensive inflammatory responses [11]. Coordination compounds further exert anticancer effects by inhibiting enzymes essential for tumor survival. Gold complexes, for example, strongly inhibit thioredoxin reductase, a key enzyme responsible for maintaining intracellular redox homeostasis. Inhibition of this enzyme increases oxidative stress and sensitizes cancer cells to apoptosis. Other metal complexes inhibit topoisomerases, proteasomes, kinases, and various DNA repair enzymes, thereby suppressing tumor growth and enhancing chemosensitivity, several coordination compounds interfere with tumor angiogenesis and metastasis. Ruthenium complexes have demonstrated the ability to inhibit vascular endothelial growth factor (VEGF)-mediated angiogenesis, reduce tumor vascularization, and suppress metastatic dissemination. These multiple mechanisms collectively contribute to the broad-spectrum anticancer activity observed for many coordination compounds.

Table 2: Major Anticancer Mechanisms of Coordination Compounds

Mechanism	Biological Effect
DNA cross-linking	Inhibits DNA replication and transcription
Reactive oxygen species generation	Oxidative damage to cellular components
Mitochondrial dysfunction	Activation of intrinsic apoptosis
Enzyme inhibition	Suppression of tumor metabolism and proliferation
Cell-cycle arrest	Prevention of uncontrolled cell division
Anti-angiogenic activity	Reduced tumor blood vessel formation
Anti-metastatic activity	Inhibition of cancer cell migration and invasion
Immune modulation	Enhancement of antitumor immune responses

5. Clinically Approved Coordination Compounds and Emerging Therapeutic Candidates

Platinum-based coordination compounds remain the cornerstone of metal-based chemotherapy. Cisplatin was the first coordination compound approved for clinical use and continues to be widely employed in the treatment of testicular, ovarian, bladder, lung, head and neck, and several other malignancies. Carboplatin was subsequently developed to reduce nephrotoxicity while maintaining comparable therapeutic efficacy. Oxaliplatin introduced improved activity against colorectal cancer and has become an integral component of modern combination chemotherapy regimens [12]. Despite their success, platinum drugs exhibit significant limitations, including nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal toxicity, and the emergence of acquired drug resistance. These challenges have stimulated the development of alternative coordination compounds based on other transition metals.

Ruthenium complexes have attracted considerable attention because they display lower systemic toxicity and preferential accumulation within tumor tissues. Compounds such as NAMI-A and KP1019 demonstrated encouraging anticancer activity in preclinical studies and early clinical trials. Their ability to target metastatic tumors and hypoxic cancer microenvironments distinguishes them from conventional platinum drugs [13]. Gold coordination compounds have emerged as promising anticancer agents owing to their potent inhibition of thioredoxin reductase. Auranofin, originally developed for rheumatoid arthritis, has shown significant anticancer activity against leukemia, ovarian, colorectal, breast, and lung cancers, stimulating renewed interest in gold-based chemotherapy [14]. Copper complexes exhibit broad-spectrum anticancer activity through oxidative stress induction, DNA cleavage, mitochondrial dysfunction, and enzyme inhibition. Likewise, cobalt, iron, gallium, titanium, osmium, iridium, and palladium complexes continue to demonstrate promising preclinical activity and represent important candidates for future clinical development.

Table 3: Representative Coordination Compounds in Cancer Therapy

Compound	Metal Center	Major Clinical Application/Status
Cisplatin	Platinum	Approved; multiple solid tumors
Carboplatin	Platinum	Approved; ovarian and lung cancers
Oxaliplatin	Platinum	Approved; colorectal cancer
NAMI-A	Ruthenium	Clinical investigation
KP1019	Ruthenium	Clinical investigation
Auranofin	Gold	Repurposed for cancer therapy
Copper(II) complexes	Copper	Preclinical evaluation
Titanocene derivatives	Titanium	Experimental anticancer agents

6. Nanotechnology and Targeted Delivery of Coordination Compounds

Nanotechnology has significantly advanced the therapeutic potential of coordination compounds by improving drug delivery, enhancing tumor selectivity, and reducing systemic toxicity. Conventional chemotherapy often suffers from poor biodistribution and non-specific accumulation in healthy tissues. Nanocarrier systems overcome these limitations by protecting coordination compounds from premature degradation, prolonging circulation time, and promoting preferential accumulation within tumors through the enhanced permeability and retention (EPR) effect [15]. Various nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, mesoporous silica nanoparticles, lipid nanoparticles, micelles, and metal-organic

frameworks (MOFs), have been investigated for delivering metal-based anticancer drugs. These systems enable controlled drug release, improved pharmacokinetics, and enhanced intracellular uptake. Surface functionalization with antibodies, peptides, folic acid, or other targeting ligands further increases specificity toward cancer cells while minimizing toxicity to normal tissues [16]. Recent developments have also focused on multifunctional nanoplatforms capable of combining chemotherapy with photodynamic therapy, photothermal therapy, immunotherapy, and diagnostic imaging. Such theranostic systems integrate treatment and diagnosis within a single platform, offering new opportunities for precision oncology.

7. Current Challenges and Future Perspectives

Although coordination compounds have transformed cancer chemotherapy, several scientific and clinical challenges remain. Drug resistance continues to be a major obstacle, arising from reduced cellular uptake, increased drug efflux, enhanced DNA repair, detoxification mechanisms, and altered apoptotic signaling. Additionally, systemic toxicity affecting the kidneys, nervous system, liver, and gastrointestinal tract limits the therapeutic dose of many metal-based drugs [17]. Another challenge involves improving tumor selectivity while minimizing off-target effects. Rational ligand design, computational drug discovery, artificial intelligence-assisted molecular modeling, and structure-based drug design are accelerating the development of highly selective coordination compounds. Advances in bioinorganic chemistry, supramolecular chemistry, and nanomedicine are expected to produce multifunctional metallodrugs with enhanced efficacy and lower toxicity [18]. Future research should focus on developing personalized metal-based therapeutics, biodegradable coordination compounds, combination therapies with immunotherapy and targeted agents, and stimuli-responsive drug delivery systems. Clinical translation will require comprehensive toxicological evaluation, optimization of pharmacokinetics, and large-scale clinical trials to establish long-term safety and efficacy.

8. Conclusion

Coordination compounds have revolutionized medicinal inorganic chemistry and remain among the most important classes of anticancer therapeutics. Since the introduction of cisplatin, metal-based drugs have demonstrated outstanding clinical success in the treatment of numerous malignancies by targeting multiple cellular pathways, including DNA damage, oxidative stress, mitochondrial dysfunction, enzyme inhibition, and apoptosis. The diversity of coordination chemistry enables the rational design of compounds with tailored biological properties, making metal complexes highly versatile candidates for next-generation cancer therapy. Recent advances in ligand engineering, nanotechnology, computational chemistry, and targeted drug delivery have significantly expanded the therapeutic potential of coordination compounds beyond conventional platinum-based chemotherapy. Ruthenium, gold, copper, cobalt, titanium, gallium, iridium, and other transition metal complexes have shown promising anticancer activities, particularly against drug-resistant tumors, while exhibiting improved selectivity and reduced systemic toxicity. Nanocarrier-based delivery systems and multifunctional theranostic platforms further enhance treatment efficacy by improving pharmacokinetics, tumor targeting, and controlled drug release. Despite substantial progress, challenges such as acquired drug resistance, adverse effects, limited tumor specificity, and complex pharmacokinetics continue to hinder the widespread clinical application of many emerging coordination compounds. Addressing these limitations will require interdisciplinary collaboration among inorganic chemists, medicinal chemists, pharmacologists, oncologists, and materials scientists, coordination compounds represent a dynamic and rapidly evolving field with immense potential for improving cancer treatment.

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