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Ruthenium-Based Coordination and Heterocyclic Compounds as Promising Next-Generation Metallotherapeutic Agents for Cancer Treatment

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Abstract

Cancer remains a major global health challenge, and the limitations of conventional chemotherapeutic agents, including systemic toxicity, poor selectivity, drug resistance, and inadequate therapeutic responses, have stimulated the development of alternative therapeutic strategies. Ruthenium-based compounds have emerged as promising candidates in medicinal inorganic chemistry because of their distinctive coordination chemistry, variable oxidation states, tunable ligand exchange kinetics, and ability to interact with diverse biological targets. In particular, coordination compounds containing heterocyclic ligands have attracted considerable attention because heterocycles can modulate lipophilicity, cellular uptake, DNA interactions, redox behavior, and molecular recognition. This review summarizes recent advances in ruthenium-based coordination and heterocyclic compounds as potential anticancer agents. Emphasis is placed on their structural characteristics, ligand design, mechanisms of cellular action, interactions with DNA and proteins, reactive oxygen species generation, mitochondrial dysfunction, apoptosis, cell-cycle regulation, and inhibition of cancer-associated signaling pathways. The influence of ligand architecture and ruthenium oxidation state on biological activity is also discussed. Selected ruthenium complexes investigated in preclinical and clinical research are highlighted to illustrate the progression of this field. Current challenges, including selectivity, stability, pharmacokinetics, resistance, toxicity, and translation from in vitro studies to clinical applications, are considered. Finally, emerging strategies involving targeted ligands, nanocarriers, photoactivated ruthenium complexes, and combination therapy are discussed as potential approaches for developing next-generation ruthenium metallotherapeutics.

Keywords: *Ruthenium complexes; coordination compounds; heterocyclic ligands; metallodrugs; cancer therapy; apoptosis; oxidative stress; DNA interaction.*

1. Introduction

Cancer comprises a diverse group of diseases characterized by uncontrolled cellular proliferation, resistance to programmed cell death, altered metabolism, genomic instability, invasion, and metastatic dissemination. Despite major advances in surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, cancer treatment remains challenging because of tumor heterogeneity, therapeutic resistance, adverse effects, and limited drug selectivity. Conventional platinum-based drugs, particularly cisplatin and its derivatives, have demonstrated substantial clinical value; however, nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal complications, and acquired resistance have encouraged researchers to investigate alternative metal-based therapeutic platforms. Medicinal inorganic chemistry has consequently developed into an important area of anticancer drug discovery. Transition metals offer chemical properties that are fundamentally different from those of conventional organic pharmaceuticals [1]. Their variable oxidation states, coordination geometries, ligand-exchange kinetics, redox properties, and ability to participate in covalent and non-covalent interactions provide opportunities for designing compounds with highly tunable biological properties.

Among transition-metal candidates, ruthenium (Ru) has received considerable attention as a potential alternative to platinum. Ruthenium can exist predominantly in the +2 and +3 oxidation states under biologically relevant conditions, while Ru(II) and Ru(III) complexes can exhibit distinct kinetic and electronic characteristics. Ruthenium compounds can be engineered with a broad range of ligands, including aromatic heterocycles, N-donor ligands, O-donor ligands, phosphines, Schiff bases, polypyridyl ligands, and biologically active heterocyclic scaffolds [2]. The incorporation of heterocyclic ligands is particularly attractive because heterocycles are common structural components of biologically active molecules. Nitrogen-, oxygen-, and sulfur-containing heterocycles can facilitate hydrogen bonding, π–π interactions, metal coordination, membrane permeability, and molecular recognition. Consequently, coordination of these ligands to ruthenium can produce compounds with improved stability, cellular uptake, target affinity, and anticancer activity compared with the free ligands or parent metal complexes.

Ruthenium complexes have been reported to influence several cellular processes, including DNA damage, mitochondrial dysfunction, reactive oxygen species generation, inhibition of protein function, cell-cycle arrest, endoplasmic reticulum stress, and apoptosis. Importantly, their mechanisms are not restricted to direct DNA binding, providing opportunities to overcome some resistance mechanisms associated with platinum drugs. This review discusses the chemical characteristics and biological mechanisms of ruthenium-based coordination and heterocyclic compounds, emphasizing their potential as next-generation metallotherapeutic agents for cancer treatment.

2. Ruthenium Chemistry Relevant to Anticancer Drug Development

The therapeutic potential of ruthenium is closely related to its coordination chemistry. Ruthenium can form complexes with different geometries and ligand environments, allowing considerable structural diversity. Ru(II) complexes commonly exhibit relatively stable octahedral coordination environments, whereas Ru(III) complexes can undergo biological reduction or ligand exchange depending on their chemical environment. The oxidation state can influence solubility, stability, cellular uptake, ligand exchange, redox behavior, and interaction with biomolecules. Ru(II) complexes are frequently investigated for direct biological activity, while some Ru(III) compounds have historically been investigated as potential prodrugs that undergo activation within the tumor microenvironment [3]. Another important characteristic is the ability of ruthenium to coordinate with nitrogen-, sulfur-, and oxygen-containing donor atoms. This enables researchers to introduce pharmacologically relevant ligands into the coordination sphere. By modifying the ligand environment, researchers can alter the hydrophobicity, charge, geometry, stability, and biological distribution of ruthenium complexes. The development of organometallic ruthenium compounds has further expanded this chemical space. Ruthenium–arene complexes, for example, possess a coordinated aromatic ligand that can contribute to molecular recognition and hydrophobic interactions. Such complexes can be combined with biologically active heterocycles to generate multifunctional metallodrugs.

Table 1. Major classes of ruthenium-based anticancer compounds and their characteristic features

Compound class	Representative structural feature	Major proposed mechanism	Therapeutic potential
Ru(II) complexes	Octahedral Ru(II) center	DNA/protein interaction, apoptosis	High
Ru(III) complexes	Ru(III) coordination sphere	Redox activation, protein interaction	High
Ru–arene complexes	Coordinated arene ligand	Protein interaction, DNA interaction	High
Polypyridyl Ru(II) complexes	Bipyridine/phenanthroline ligands	DNA interaction, ROS, photoactivity	High
Ru–heterocyclic complexes	N/S/O heterocyclic ligands	Multifunctional cellular targeting	Very high
Photoactive Ru complexes	Photolabile ligands	Photoinduced ROS/ligand release	Emerging

Table 2. Major biological mechanisms associated with ruthenium-based anticancer compounds

Mechanism	Major cellular consequence
DNA interaction	Replication/transcription disruption
ROS generation	Oxidative stress and macromolecular damage
Mitochondrial dysfunction	Loss of membrane potential and apoptosis
Protein interaction	Enzyme/signaling pathway modulation
Cell-cycle arrest	Suppression of tumor proliferation
Apoptosis induction	Programmed cancer-cell death
Endoplasmic reticulum stress	Proteostasis disruption
Photochemical activation	Controlled cytotoxicity following light exposure

3. Heterocyclic Ligands in Ruthenium Metallotherapeutics

Heterocyclic compounds constitute one of the most important classes of pharmacophores in medicinal chemistry. Their incorporation into ruthenium coordination compounds provides an opportunity to combine the biological properties of organic heterocycles with the distinctive reactivity of a metal center. Nitrogen-containing heterocycles such as pyridine, pyrimidine, imidazole, benzimidazole, quinoline, quinoxaline, triazole, and related systems have been extensively explored as ligands. These structures can coordinate ruthenium through nitrogen donor atoms while simultaneously providing aromatic surfaces capable of interacting with nucleic acids and proteins. Sulfur-containing heterocycles can provide additional coordination behavior and may influence the redox characteristics of ruthenium complexes.

Similarly, oxygen-containing heterocycles can modify hydrogen-bonding capacity and aqueous interactions [4]. The biological activity of a ruthenium–heterocycle complex is therefore determined not only by the ruthenium center but also by the ligand architecture. Substituent modifications can influence cellular permeability, intracellular accumulation, protein binding, and target selectivity. This provides a rational strategy for optimizing activity while reducing nonspecific toxicity.

4. Major Classes of Ruthenium-Based Anticancer Compounds

Ruthenium anticancer compounds can broadly be classified according to their oxidation state, coordination environment, and ligand architecture.

4.1 Ruthenium (II) complexes

Ru(II) compounds represent one of the most extensively studied classes. Their relatively stable coordination chemistry allows researchers to construct well-defined complexes with controlled ligand-exchange properties. Many Ru(II) complexes have demonstrated cytotoxic or cytostatic activity against cancer cell lines. Ruthenium(II)–arene complexes are particularly important because the arene moiety can contribute to hydrophobic interactions and cellular uptake. Depending on the coordinated ligands, these complexes may interact with DNA, proteins, mitochondria, or other intracellular targets.

4.2 Ruthenium (III) complexes

Ru(III) complexes have historically attracted attention because of their potential redox activation. The hypothesis that relatively inert Ru(III) compounds could be reduced to more reactive Ru(II) species under tumor-associated conditions stimulated the development of ruthenium prodrug concepts. Although the tumor-selective reduction hypothesis is more complicated than initially proposed, Ru(III) compounds remain valuable platforms for investigating redox-mediated metallotherapy.

4.3 Ruthenium–arene complexes

Ruthenium–arene complexes contain a coordinated aromatic hydrocarbon and additional donor ligands. Their relatively modular architecture allows systematic modification of the ligand sphere. RAPTA-type compounds and related arene-ruthenium complexes have attracted considerable attention because of their potential antimetastatic, anti-inflammatory, and anticancer properties.

4.4 Polypyridyl ruthenium complexes

Polypyridyl Ru(II) compounds have been extensively studied because of their strong photophysical properties. Complexes containing ligands such as bipyridine and phenanthroline can participate in DNA interactions and, under appropriate conditions, photoinduced biological processes. These compounds are particularly relevant to photoactivated chemotherapy and photodynamic therapy, where light exposure can activate the therapeutic properties of the complex.

5. Mechanisms of Anticancer Activity

Ruthenium-based compounds can affect cancer cells through multiple molecular mechanisms. This mechanistic diversity is one of their major advantages over conventional single-target drugs.

5.1 DNA interaction and damage

DNA has traditionally been considered a major target for metal-based anticancer drugs. Ruthenium complexes can interact with DNA through covalent coordination, intercalation, electrostatic interactions, or groove binding, depending on their ligand architecture. Unlike cisplatin, which primarily produces platinum–DNA adducts, many ruthenium complexes demonstrate substantial non-covalent DNA interactions. Aromatic heterocyclic ligands can facilitate intercalation between DNA base pairs, potentially disrupting DNA replication and transcription.

5.2 Reactive oxygen species generation

Reactive oxygen species (ROS) represent another important mechanism. Certain ruthenium complexes can increase intracellular oxidative stress by influencing mitochondrial function or redox processes. Excessive ROS production may damage proteins, lipids, nucleic acids, and mitochondrial membranes, ultimately promoting cancer-cell death. Because many tumor cells already operate under elevated oxidative stress, further disruption of redox homeostasis may provide a therapeutic opportunity.

5.3 Mitochondrial dysfunction

Mitochondria are increasingly recognized as important targets of metal-based anticancer compounds. Ruthenium complexes can alter mitochondrial membrane potential, promote oxidative stress, and induce the release of pro-apoptotic factors. Mitochondrial targeting may be particularly advantageous because cancer cells frequently exhibit altered mitochondrial metabolism and increased dependence on mitochondrial signaling pathways.

5.4 Induction of apoptosis

Apoptosis is one of the most frequently reported outcomes of ruthenium treatment. Depending on the compound, apoptosis may involve mitochondrial membrane depolarization, cytochrome c release, caspase activation, and regulation of Bcl-2 family proteins. Some ruthenium complexes can also activate apoptosis through pathways associated with DNA stress, oxidative damage, or endoplasmic reticulum dysfunction.

5.5 Cell-cycle arrest

Ruthenium complexes may interfere with cell-cycle progression. Arrest at the G0/G1, S, or G2/M phases can prevent proliferation and provide time for cellular damage responses to occur. The precise cell-cycle effect depends strongly on the structure and intracellular target of the complex.

6. Ruthenium–Heterocyclic Complexes and Molecular Targeting

The combination of ruthenium centers with pharmacologically active heterocycles represents a particularly promising strategy for increasing therapeutic selectivity. Benzimidazole, quinoline, imidazole, pyridine, triazole, and related heterocycles can provide additional biological functions beyond simple metal coordination. For example, aromatic heterocycles may enhance DNA binding, while appropriately functionalized ligands can facilitate interactions with enzymes or signaling proteins. This approach can also generate dual-action metallodrugs, in which the metal center and organic ligand contribute independently or synergistically to biological activity. Such compounds may simultaneously promote oxidative stress, inhibit specific proteins, and interfere with nucleic-acid-associated processes. The rational design of these complexes requires careful consideration of ligand dissociation, metal stability, charge, hydrophobicity, cellular uptake, and intracellular speciation.

7. Selected Ruthenium Anticancer Candidates and Clinical Development

Several ruthenium compounds have progressed beyond basic chemical characterization into advanced preclinical or clinical investigation. Among the most recognized examples are NAMI-A, KP1019, and NKP-1339. NAMI-A was investigated primarily for its potential antimetastatic activity, particularly in combination with other therapeutic approaches. KP1019 and its sodium analogue KP1339 attracted attention because of their cytotoxic and pro-apoptotic properties. NKP-1339, also known as IT-139, represents a more recent development in the ruthenium field and has been investigated in clinical studies. Its proposed mechanisms include stress responses, altered protein homeostasis, and effects on tumor-cell survival. Although these compounds have demonstrated the clinical potential of ruthenium chemistry, their development also illustrates the challenges involved in translating promising laboratory findings into effective medicines. Pharmacokinetic behavior, toxicity, tumor selectivity, formulation, and reproducibility of therapeutic exposure remain critical considerations.

8. Challenges and Limitations

Despite promising findings, ruthenium metallotherapy remains associated with significant challenges. A major issue is the discrepancy between strong *in vitro* activity and limited clinical translation.

Many ruthenium compounds show substantial cytotoxicity in cultured cancer cells but fail to demonstrate equivalent efficacy in complex biological systems. Achieving preferential accumulation in tumor tissue while minimizing exposure to healthy organs remains a central challenge. Ruthenium complexes may undergo ligand exchange, hydrolysis, redox reactions, and interactions with serum proteins. Consequently, the compound administered to an organism may not necessarily be identical to the species responsible for biological activity. Absorption, distribution, metabolism, and excretion can substantially influence therapeutic performance. Poor solubility or rapid clearance can limit the effectiveness of otherwise potent compounds. Cancer cells can develop resistance through altered drug uptake, efflux mechanisms, detoxification, enhanced DNA repair, antioxidant defenses, and changes in apoptosis signaling. Although some ruthenium compounds show favorable toxicity profiles compared with traditional chemotherapy, comprehensive toxicological characterization is necessary before clinical application.

9. Future Perspectives

The future of ruthenium-based cancer therapy will depend on moving beyond the simple development of highly cytotoxic complexes toward mechanistically defined, selective, and clinically translatable metallotherapeutics. Understanding intracellular speciation and identifying molecular targets should become central components of future studies. Greater emphasis should also be placed on pharmacokinetic and pharmacodynamic investigations rather than relying predominantly on cell-line cytotoxicity. Three-dimensional tumor models, organoids, patient-derived models, and appropriate animal models can provide more informative assessments of therapeutic performance. The integration of ruthenium coordination chemistry with targeted delivery, nanomedicine, phototherapy, immunotherapy, and precision oncology offers particularly promising opportunities. Heterocyclic ligands may serve as multifunctional components capable of simultaneously controlling metal coordination, biological recognition, and intracellular localization. Future studies should also investigate whether ruthenium compounds can selectively exploit characteristics of the tumor microenvironment, including hypoxia, altered redox status, acidic pH, and increased metabolic activity. Such approaches could facilitate tumor-selective activation and reduce systemic toxicity.

10. Conclusion

Ruthenium-based coordination compounds have emerged as an important class of potential metallotherapeutics for cancer treatment. Their variable oxidation states, versatile coordination chemistry, tunable ligand environments, and diverse biological mechanisms provide opportunities to overcome some limitations associated with conventional metal-based chemotherapy.

In particular, the incorporation of biologically active heterocyclic ligands can enhance molecular recognition, cellular uptake, DNA and protein interactions, and overall pharmacological activity. Ruthenium complexes can act through multiple mechanisms, including DNA interaction, oxidative stress, mitochondrial dysfunction, cell-cycle arrest, and apoptosis. The clinical investigation of compounds such as NAMI-A, KP1019, and NKP-1339 demonstrates the translational potential of this field, although significant challenges involving selectivity, pharmacokinetics, toxicity, stability, and resistance remain. Future progress will likely depend on rational ligand design, tumor-targeted delivery, nanotechnology, photoactivation, computational drug design, and combination treatment strategies, ruthenium–heterocyclic compounds represent a versatile and promising platform for developing next-generation metallotherapeutic agents, but rigorous mechanistic, pharmacological, and clinical studies are required to establish their true therapeutic potential.

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