

Therapeutic Applications of Heavy Metals: Anticancer Insight Into Ruthenium

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ABSTRACT

Heavy metals have revolutionized the field of oncology, with platinum-based drugs such as cisplatin serving as a foundational treatment. However, their severe side effects and resistance issues have necessitated the exploration of alternative metal-based therapies. Ruthenium has emerged as a promising candidate, offering distinct advantages over platinum due to its unique chemical properties, improved efficacy, and lower toxicity profile. This paper provides a comprehensive review of ruthenium-based anticancer therapies, addressing key aspects that contribute to its potential as a therapeutic agent. The chemical characters of ruthenium, including its versatile oxidation states, coordination chemistry, and ligand exchange dynamics are explored to understand its stability and selectivity. The mechanism of action, such as DNA interaction, reactive oxygen species (ROS) generation, apoptosis induction and tumor microenvironment modulation, are critically analyzed. The efficacy of ruthenium complexes in preclinical and clinical studies is discussed, highlighting their ability to overcome multidrug resistance and reduce off-target effects. Recent advancements in clinical trials of ruthenium complexes are

also reviewed and offering insight into their transitional potential. This review emphasizes the growing importance of ruthenium on anticancer drug development, showcasing its role as a next generation therapeutic agents capable of addressing the limitation of existing treatments. By providing in depth understanding of its therapeutic potential, this paper aims to contribute to advancement of metallopharmateucals in cancer therapy.

Keywords: *ruthenium complexes, anticancer activity, therapeutic targets, clinical research*

INTRODUCTION

The organic ligand associated with the central metal in transition metals is crucial in scientific research, medicine, and pharmacy. Cancer has become a predominant cause of mortality globally. Chemotherapy is a commonly utilized treatment option. Nonetheless, its limited efficacy in certain instances results in a significant failure rate. Heavy metals are being investigated in chemotherapeutic drugs to enhance their efficacy. In 1965, Rosenberg discovered cisplatin, a platinum-based compound that revolutionized cancer chemotherapy and underscored the potential of heavy metals in oncology. Skoczynska A et al. (2023) This compound is utilized for the treatment of head, neck, bladder, and ovarian cancers. Skoczynska A et al. 2023 This drug has emerged as a primary anticancer agent owing to its significant effectiveness in addressing multiple cancer types. Nonetheless, despite its efficacy, it is linked to considerable adverse effects, such as cellular toxicity, peripheral neuropathy, and myelotoxicity [Lin k et al.2018]. These compounds are restricted to certain cancer types, underscoring the necessity for alternatives. The development of non-platinum metallic compounds has emerged as a priority in cancer research. Ruthenium is identified as a more promising option [Seva G et al. 2009]. The mechanisms of action of ruthenium complexes differ from those of platinum and demonstrate greater efficacy. Over the last 30 years, numerous ruthenium complexes have been synthesized and subjected to clinical research to evaluate their effectiveness. This element is a transition metal belonging to the platinum group and shares the same chemical group

as iron, classified as a group 8 element. The complexes are recognized for their stability under physiological conditions. Ruthenium exhibits diverse oxidation states, including Ru(II), Ru(III), and Ru(IV). The elevated oxidation state exhibits reduced stability. The ruthenium ion typically exhibits hexacoordination with an octahedral coordination geometry. Coordination can occur with various types of ligands. The geometry of these complexes can be modified by altering the ligands, facilitating the synthesis of various chiral ruthenium compounds with distinct properties. Ruthenium complexes, particularly Ru[II], are capable of ligand exchange reactions with biomolecules, enhancing their activity against disease targets. Ruthenium complexes demonstrate anticancer effects via a multifaceted mechanism of action, setting them apart from conventional platinum-based drugs. They accumulate selectively in tumor tissues through the enhanced permeability and retention effect and can be activated in the hypoxic and acidic environments of tumors, thereby minimizing damage to normal cells. This selectivity may result from ruthenium's capacity to imitate iron, which is significant for cancer cells due to their higher number of transferrin receptors, reflecting an increased demand for iron. This facilitates the more efficient delivery of ruthenium to cancer cells. The primary mechanism involves binding to DNA via intercalation, groove binding, or covalent attachment, which disrupts replication and transcription, ultimately resulting in apoptosis. Ruthenium complexes also produce reactive oxygen species (ROS), leading to oxidative stress, mitochondrial dysfunction, and subsequent cell death. They inhibit metastasis by targeting matrix metalloproteinases (MMPs), blocking angiogenesis, and interfering with cytoskeletal dynamics. Ruthenium complexes, in contrast to platinum drugs, can modulate essential signaling pathways, disrupt proteins such as heat shock proteins (HSPs), and enhance the immune response through the induction of immunogenic cell death. The diverse mechanisms of ruthenium complexes, along with their reduced toxicity and capacity to overcome drug resistance, position them as a promising alternative in cancer therapy.

DISCUSSION

Chemical Properties of Ruthenium:

Ligand exchange:

Ruthenium primarily engages in ligand exchange via substitution reactions, which are influenced by its coordination chemistry and the surrounding environment. The exchange is governed by the thermodynamic stability of the incoming ligand and the kinetics of the substitution reaction, facilitating selective interaction with cells. Ligands coordinated to a ruthenium center are substituted by other molecules from the surrounding environment [Bloemik K J et al. 1996]. The initiation of this ligand exchange is influenced by environmental factors such as pH, redox conditions, and the presence of biomolecules. This property is essential for cancer therapy, as ruthenium complexes can maintain stability in healthy tissues while undergoing selective activation in the tumor microenvironment, where lower pH and higher concentrations of reducing agents facilitate ligand exchange. Yamada H et al. (2001) This selective activation enhances the therapeutic targeting of cancer cells, minimizes side effects on healthy tissues, and facilitates the interaction of ruthenium complexes with molecules such as DNA, proteins, and enzymes [Reejdk J, 2003] [Yamada H et al. (2001)].

Oxidation state:

Ruthenium can exist in multiple oxidation states, typically Ru(II), Ru(III), Ru(IV).the reducing oxidation state is more stable. And under physiological conditions it form stable structures with six ligands in an octahedral shape. Unlike platinum drugs, which tightly bind DNA, ruthenium's geometry often prevents such binding, making it act differently in cells [Seva G et al.1995]

The cancer cell creates a different environment than normal cells. Due to have a reductive environment and reductive agent like glutathione and a lower pH, this initiate the reduction from Ru(III) to Ru(II). Scientist can take advantage of this by designing ruthenium drug as Ru(III) complexes (inactive prodrugs). Once inside the tumor, the reducing environment

activates them by converting Ru(III) to the active Ru(II) form. This allows the drugs to target cancer cells specifically. If the active Ru(II) complex moves to areas with more oxygen, (like in normal cells), it can revert to its inert Ru(III) form, reducing damage to healthy cells. That make ruthenium -based drugs highly selective and less toxic. [Antonarakis E.S. et al. 2010]

Iron mimicking:

Iron is essential for nearly all living cells due to its significant role in crucial biological processes, including oxygen transport and DNA synthesis. Specialized proteins in the human body, such as transferrin and albumin, bind to iron to maintain its solubility in blood and facilitate transport and DNA synthesis. Specialized proteins in the human body, such as transferrin and albumin, bind to iron, maintaining its solubility in blood and facilitating its transport to necessary sites. These proteins facilitate the efficient delivery of iron, particularly to rapidly proliferating cells that require substantial iron to support their accelerated growth. Ruthenium, a transition metal, exhibits a distinctive capacity to bind to proteins similar to iron, especially transferrin. This occurs due to the similarity in chemical properties between ruthenium and iron, specifically in terms of charge and size. Consequently, ruthenium can associate with transferrin and gain entry into cells via receptors. Cancer cells exhibit an increased expression of transferrin receptors, facilitating enhanced iron uptake. Administration of ruthenium results in the uptake of the metal by these receptors, causing a significantly greater accumulation in cancer cells relative to normal cells. Research indicates that the concentration of ruthenium in cancer cells may be 2 to 12 times greater than in healthy cells [Seva G. et al. 2000]. Furthermore, ruthenium can penetrate cells via alternative mechanisms independent of transferrin, enhancing its versatility. The selective targeting of cancer cells by ruthenium minimizes its impact on healthy cells, potentially reducing the systemic toxicity commonly associated with other treatments, such as platinum-based drugs. Antonarakis, E.S., et al. (2010)

Redox activity:

As ruthenium exhibit many oxidation states, its redox reactivity is crucial for anticancer therapy. In the reducing environment of cancer cells, ruthenium complex is reduced to ruthenium (III) to ruthenium (II) by intracellular reducing agents like glutathione and ascorbic acid, abundant in cancer cells. The redox flexibility allows ruthenium to generate ROS such as superoxide ions this superoxide ions undergoes further reaction, such as dismutation to form hydrogen peroxide (H_2O_2), then it generate hydroxyl radicals, within cancer cells causing oxidative stress that damage DNA, protein and induce apoptosis .

Stability and reactivity:

Ruthenium complexes are generally stable under physiological conditions, releasing hydrolysis and degradation. Their stability can be enhanced by selecting ancillary ligands, ensuring controlled reactivity in biological environment.

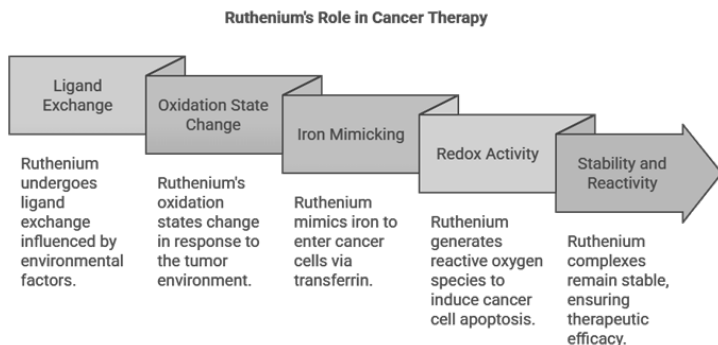


Fig 1: Chemical properties of ruthenium

Mechanism Of Action:

The ruthenium complexes have a diverse effect on human body. due to its coordination chemistry, stability and reactivity, it can target multiple sites and shows a diverse

mechanism for its antitumor properties. The Ru complexes some time bind directly with DNA and may cause DNA damage, and sometime it inhibits the enzyme responsible for DNA replication. it can also be effective deep down to the organelles and can cause cell death.

Binding with the DNA:

Ruthenium complexes demonstrate a variety of mechanisms of action against cancer, targeting DNA via different binding models, including electrostatic attraction, intercalative binding, and groove binding. This interaction interferes with replication and transcription, resulting in DNA damage and the inhibition of associated enzymes. Ru(II) complexes exhibit a preference for binding at the N7 site of guanine and the N3 site of thymidine. In contrast, Ru(III) complexes demonstrate a greater affinity for the phosphate backbone, attributed to electrostatic interactions, while also engaging with the N7 site of guanine.[Zeng W. et al., 2019] This interaction resulted in the unwinding and lengthening of the DNA helix, as confirmed by UV-Vis spectroscopy, viscosity studies, and fluorescence spectrometry.[Huang et al., 2016] Some Ru complexes, such as dinuclear and polynuclear Ru(II) polypyridyl compounds, exhibit stable binding to the G-quadruplex structure of telomere DNA, thereby inhibiting telomerase activity and obstructing tumor cell immortality.[Hiyama H. et al., 1995] Ruthenium complexes, including Ru(III)-PTA and Ru(II)-arene compounds, induce DNA damage through the formation of adducts with guanine residues, leading to apoptosis in cancer cells. Some compounds exhibit synergistic effects with ionizing radiation, demonstrating greater potency than traditional drugs such as oxaliplatin.

Inhibiting Topoisomerase Activity:

Topoisomerase II is essential for addressing topological challenges encountered during DNA replication, transcription, chromatin remodeling, and recombination by creating single- or double-strand breaks in DNA [Kurzweinhart A. et al. 2012]. Ruthenium-based complexes exhibit significant topoisomerase inhibitory activity, particularly against Topo II, disrupting its catalytic cycle and inducing apoptosis in cancer

cells by inhibiting DNA replication. Intense half-sandwich Ru-arene complexes with thiosemicarbazones function as Topo II inhibitors. Certain compounds demonstrate moderate anti-proliferative activity, and some have the higher potency than etoposide (ETP). To overcome limitations in single target inhibition, researchers have developed ruthenium complexes exhibiting dual inhibitory properties against Topo I and Topo II, resulting in significant suppression of tumor cell proliferation. Multi-target ruthenium complexes exhibiting dual effects on G4-DNA and Topo have been synthesized, as reported by Liao et al. (2015), demonstrating synergistic apoptotic effects on tumor cells and efficacy against drug-resistant strains.

Targeting cell organelles:

In mitochondria:

Mitochondria serve as essential energy hubs within the cell, modulating apoptosis via pathways that involve mitochondrial membrane potential and related signaling proteins. Ruthenium complexes exhibit a strong affinity for mitochondria, leading to disruption of mitochondrial function upon accumulation [Wang X. et al. 2013]. Ruthenium complexes rapidly diminish the mitochondrial membrane potential through the generation of reactive oxygen species (ROS). It can occasionally disrupt the electron transport chain, particularly at complexes I, II, and III. Ruthenium disrupts electron flow, leading to a buildup of protons and electrons, which destabilizes the gradient necessary for membrane potential. This interference can result in electron leakage and mitochondrial dysfunction. This disruption impairs mitochondrial ATP production, resulting in an energy crisis within tumor cells. Dysfunctional mitochondria release cytochrome C into the cytosol, activating pro-apoptotic proteins such as Bcl2. This initiates a cascade reaction of caspase enzymes, which dismantle the cell in a regulated process of apoptosis (Sano R. et al., 2013). An efficient Ru-based compound $[\text{Ru}(\text{dppz})_2(\text{CppH})]^{2+}$ accumulates in mitochondria and demonstrates cytotoxic effects against cisplatin-resistant cancer cells, indicating ruthenium's ability to circumvent traditional resistance mechanisms.

In Endoplasmic Reticulum:

The ER plays a vital role in protein folding, lipid synthesis, and calcium storage. In cancer, it is often involved in promoting cell survival under stress. Ruthenium complexes can target the ER, leading to oxidative stress. Ruthenium complexes can cause the accumulation of reactive oxygen species within the ER, leading to the oxidative stress. The accumulation of misfolded proteins and other disruption in the ER activates stress response that led to apoptosis. Ruthenium -induced ERS involves activation of caspases, which triggers programmed cell death. By targeting the ER, ruthenium complexes can reduce autophagy and inhibit mechanism that typically allow tumor cells to evade drugs. [Gill M R.et al.2009] [Sano R.et al.2013]

In lysosomes:

Ru complexes can localize in lysosomes disrupting their structure and function. They increase lysosomal membrane permeability by the generation of ROS by fenton reaction leading to the production of hydroxyl radicals. This can cause lipid peroxidation of the lysosomal membrane, disrupting its integrity. These complexes also can directly interact with lysosomal membrane components, such as phospholipids and lysome-associated membrane proteins (LAMPs). Some ruthenium complexes down regulate LAMPs expression, which is crucial for maintaining lysosomal activity. Reduced LAMP level destabilizes the membrane and leading to increased permeability. This increase membrane permeability can cause the release of digestive enzyme like (cathepsin B) into the cytoplasm. The release of his enzyme damages cellular components, leading to lysosomal mediated cell death. [Sano R.et al.2012] [Lin K.et al.2018]

Targeting Cell Membranes:

The cell membrane acts as a both protective barrier and a direct target for Ru complexes. Ru complexes alter the membrane's permeability, allowing cellular components to leak out, leading cell death. Some Ru complexes emit red phosphorescence and produce singlet oxygen upon activation. This destroys the cell and mitochondrial membrane simultaneously, enhancing

cytotoxicity. [Lin K. et al. 2018]

Ruthenium Based Anti-Cancer Drugs:

NAMI -A

NAMI-A, or [ImH][trans-RuCl₄(DMSO)(Im)], is a Ru(III) complex featuring DMSO and imidazole coordinated to a ruthenium center. Preclinical studies have shown that NAMI-A exhibits significant antitumor effects, particularly in its anti-metastatic properties. The mode of action of NAMI-A includes interaction with cell cycle regulation, resulting in a temporary accumulation of cells in the G₂/M phase. Inhibition of matrix metalloproteinase. Promotion of an extracellular matrix surrounding the tumor vasculature prevents tumor cells from invading adjacent tissues and blood vessels, while also coordinating with nucleic acids, thereby directly impacting tumor cell DNA. Animal studies indicate that more frequent, smaller doses of NAMI-a exhibit a stronger anti-metastatic effect. Importantly, its effect appears to be independent of the type of primary tumor. NAMI A has demonstrated efficacy in both preventing the formation of metastases and inhibiting the growth of established metastases. Preclinical studies using murine models demonstrated the selective efficacy of NAMI A against lung metastases originating from diverse primary tumors. The treatment reduces the weight of lung metastases more significantly than their quantity. The absence of higher concentrations of NAMI A in the lung compared to other tissues suggests that NAMI A selectively interferes with the growth of established lung metastases. Toxicity studies in mice and dogs demonstrated an acceptable safety profile, with a half-life of approximately 18 hours. Toxicity occurs at doses exceeding 50 mg/kg/day; however, any adverse effects were reversible within three weeks following the cessation of treatment. NAMI A was the inaugural ruthenium-based drug to advance to human clinical trials. A phase one pharmacokinetic study commenced in 1999 and was published in 2004. The study involved 24 patients with various metastatic solid tumors. Including collateral, lung, melanoma, ovarian, and pancreatic cancers that exhibited resistance to conventional therapies. Patients received NAMI A through a three-hour intravenous infusion daily for five days, repeated every three weeks, in

accordance with a dose escalation protocol. The dose range was 2.4 mg/m²/day to 500 mg/m²/day. At a dosage of 400 mg/m²/day, the patient developed painful blisters on the hands and feet, which persisted at the 500 mg/m²/day dosage. This condition is well recognized as a dose-limiting toxicity. The Phase II trials indicate that a dosage of 300 mg/m²/day is optimal, as it did not result in blisters, thereby enhancing tolerability. Additional side effects encompass anaemia, lymphopenia, fatigue, anorexia, stomatitis, peripheral oedema, nausea, and phlebitis at the infusion site. Occasionally, patients experienced hypersensitivity reactions that were resolved with dexamethasone. The study indicates that some patients were evaluable for tumor responses. A patient with a history of extensive treatment exhibited stable disease for 21 weeks in the context of progressive metastatic non-small cell lung cancer. The remaining patients exhibit disease progression. A phase II study evaluating NAMI-A has not been performed. [Antonarakis E. S. et al., 2010]

KP1019

KP1019 is a ruthenium-based compound demonstrating potential efficacy in cancer therapy. It induces apoptosis in cancer cells, specifically targeting collateral cancer cells. This occurs via mechanisms such as disrupting cellular energy production, damaging mitochondria, and activating specific proteins that induce apoptosis. The mechanism of action does not appear to depend on DNA damage as other cancer drugs do; however, it may induce some DNA damage indirectly via the generation of reactive oxygen species. Research involving mice demonstrated that KP1019 exhibited significant efficacy against colon cancer, including tumors that were resistant to conventional therapies such as 5-fluorouracil and cisplatin. The treatment resulted in significant tumor reduction, accompanied by mild side effects such as increased red blood cell production. In clinical trials involving humans, KP1019 was administered intravenously to patients with advanced solid tumors, including colorectal, endometrial, melanoma, and bladder cancers. The maximum dose evaluated was 600 mg

administered biweekly, which demonstrated good tolerance with only mild adverse effects. The drug exhibited slow absorption into the bloodstream, with a significant portion binding to proteins such as albumin. A minimal quantity was eliminated via the kidneys. In a trial, five out of six patients exhibited disease stabilization, with no progression of cells observed for a duration of 8 to 10 weeks. This suggests that KP1019 may have potential as a cancer treatment, and a phase II study is being planned to evaluate its efficacy in patients with advanced collateral cancer. Antonarakis, E. S., et al. (2010)

Other Ruthenium Complexes:

Polypyridyl-Ru complexes:

Researchers are investigating ruthenium-based complexes with polypyridyl ligands as potential anticancer agents due to their ability to bind to DNA and disrupt its function. Early studies indicate that certain ruthenium complexes, such as mer-[Ru(terpy)Cl₃], exhibit greater cytotoxicity towards cancer cells compared to other drugs, primarily through the formation of DNA crosslinks. Modifications to these complexes, including the addition of various ligands and the combination of ruthenium with platinum, have been evaluated to improve DNA binding and enhance anticancer efficacy. Certain ruthenium complexes release nitric oxide upon light exposure, presenting potential applications in phototherapy. Despite their potential, these complexes have not yet commenced clinical trials. Ang, W. H., et al. (2006).

Arene PTA Ruthenium (II)(RAPTA) complexes:

The synthesis of RAPTA compounds occurs in two steps. Initially, a Birch reduction is employed to synthesize the desired arene, which subsequently reacts with hydrated Ru(III)Cl₃ to yield a dimeric complex. In the second step, two equivalents of 1, 3, 5-triaza-7-phosphatricyclo [3.3.1.1] decane (PTA) are introduced to this complex to yield the final RAPTA compound. Alternatively, ligand exchange may be employed for arene ligands that are challenging to reduce via the Birch reaction, although this approach typically results in lower yields. The products exhibit stability in air,

thermodynamic stability, and solubility in both organic solvents and water. The RAPTA-C prototype has been pivotal in biological research, focusing on two primary approaches: the development of RAPTA as a selective anticancer agent and the exploration of its non-classical therapeutic potential via protein binding studies. More than 20 RAPTA complexes have been synthesized, encompassing derivatives with various ligands and metal fragments. Enhancing their applicability in pharmaceutical development. Ang, W. H., et al. (2006).

Ru complexes with nanoparticles:

Ruthenium based anticancer therapies faces many challenges due to its ideal balance of steric hindrance and lipophilicity is difficult. To address this, Nano drug delivery system offer significant advantages, including enhanced targeting through the EPR effect and active targeting via receptors receptor or enzyme modifications, reduced systemic toxicity, improved lipophilicity without structural changes, and the ability to deliver multiple therapeutic agents simultaneously. Encapsulation of Ru complexes such as selenium nanoparticles, gold nanomaterial and carbon nanotubes, improves targeting and delivery to tumor cells. Additionally, excipient free Nano drugs, composed primarily of active pharmaceutical ingredients with minimal additives, offers a unique approach where the matrix itself contributes to the therapeutic effect, distinguish them from traditional drug carriers. This integration of Ru complexes with advanced NDDS demonstrate great potential for enhancing antitumor activity. [Lu Y.et al.2022]

Using gold as a carrier for ruthenium complex:

The application of gold nanoparticles as carriers for ruthenium complexes in biomedical contexts, especially in cancer treatment, is highly effective. Gold nanoparticles exhibit various morphologies, including nanospheres, nanorods, nanocages, and nanoshells, and possess unique plasmon resonance properties that enable the absorption of near-infrared light and its conversion into heat for photothermal therapy. Initial research employed Ru polypyridine

complexes as stabilizers and coatings for AuNPs, investigating their photophysical and luminescent characteristics. Combining Ru complexes with gold nanoparticles resulted in enhanced luminescence, whereas their interaction with gold nanorods led to quenching of emissions. Further research has advanced the application of these conjugates in imaging, as they emit strong luminescence detectable through confocal laser microscopy and two-photon microscopy. Advanced design should enhance photothermal efficiency and stability, providing effective treatment in cellular and animal models. Recent studies have concentrated on the modification of gold nanoparticles (AuNPs) using ruthenium polypyridine complexes through sulfur-gold interactions. This complex demonstrated improved solubility, prolonged blood circulation, and enhanced memory permeability. This modification has enhanced therapeutic efficacy, particularly in collateral adenocarcinoma cells, and promoted apoptosis through improved cellular uptake facilitated by hydrophobic ligands and polymers [Lu Y.et al.2022]

Use of cationic liposome as a Nano carrier:

Cationic liposomes serve as effective organic carriers for the delivery of ruthenium complexes in cancer treatment. These liposomes effectively transport Ru complexes to tumor sites. In 2013, researchers developed an anti-tumor nanocarrier utilizing cationic DOTAP for the delivery of amphiphilic Ru complexes. The aggregates formed by mixing Ru complexes with phospholipid carriers at a 50/50 molar ratio exhibited 10 to 20 times greater activity compared to other compounds. In 2015, it was discovered that cholesterol complexes with DOTAP liposomes effectively prevented the degradation of Ru-based anti-tumor drugs. Recent developments involve the formulation of cationic Ru metal complexes with DOPE for the delivery of genetic material in gene therapy, thereby broadening the application of Ru complexes in biomedical fields [Lu Y.et al.2022]

Conclusion

Ruthenium-based compounds have emerged as a promising alternative to traditional platinum-based anticancer drugs

due to their low toxicity, organelle-specific targeting, and effectiveness against platinum-resistant tumors. The complexes demonstrate various mechanisms of action, including the disruption of mitochondrial function, induction of oxidative stress, and interference with lysosomal stability, all contributing to apoptosis in cancer cells. Their capacity to modulate lysosomal membrane permeability, decrease mitochondrial membrane potential, and induce endoplasmic reticulum stress highlights their multi-targeted therapeutic potential. Innovations in ligand design have led to Ruthenium complexes exhibiting dual inhibitory effects on topoisomerase, enhancing G4-DNA stabilization and photosensitizing capabilities, thereby broadening their application in targeted cancer therapy. Recent advancements in ruthenium-based photodynamic therapy agents, utilizing their photophysical properties for selective tumor targeting, have enhanced the therapeutic application. Research on Ruthenium-based nanocarriers and drug delivery systems has shown enhanced cellular uptake and tumor specificity, thereby reducing off-target effects. Ruthenium complexes exhibiting dual targeting capabilities, which facilitate organelle-specific accumulation and address drug resistance pathways, present significant potential for overcoming challenges associated with chemotherapy. The exploration of Ruthenium complexes as multi-targeted agents has the potential to significantly advance cancer therapy. By integrating their inherent anti-cancer properties with advanced technologies like nanoparticle conjugation, gene delivery systems, and theragnostic, these compounds may attain enhanced therapeutic efficacy and precision. The integration of artificial intelligence in drug design and predictive modeling may accelerate the identification of novel ruthenium compounds with optimal activity profiles. Ongoing research and clinical trials indicate that ruthenium-based therapies are positioned to overcome limitations in current treatments, offering more effective, targeted, and patient-friendly solutions. Their versatility, along with advancements in nanotechnology and bioengineering, positions them at the forefront of next-generation anti-cancer strategies.

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