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Review

Potential of Organometallic Complex Compounds as Anticancer Drugs: A Review

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Abstract

Cancer is one of the deadliest diseases in the world. Currently, there are various types of anticancer drugs that are used to treat cancer, but they still have various side effects that can interfere with the quality of life of patients. Organometallic complexes (OCOs) are chemical compounds consisting of metal atoms bonded to carbon atoms. OCOs have various potential to be used as anticancer drugs, including their ability to specifically target cancer cells, inhibit cancer cell growth, and reduce the side effects of other anticancer drugs. The mechanism of action of OCOs involves interactions with nucleophilic molecules within the cell, including DNA, RNA, and proteins, as well as the formation of additional platinum products. In this review, we will discuss organometallic compounds that can function as anticancer drugs, such as platinum, ruthenium, iron, carboplatin, and oxaliplatin, which have been shown to be effective in fighting cancer. We will also discuss the mechanism of action of these compounds in cancer cells and the types of cancer cells that can be treated with organometallic compounds.

Keywords: *Anticancer drugs, Organometallic compounds, , Reaction mechanism*

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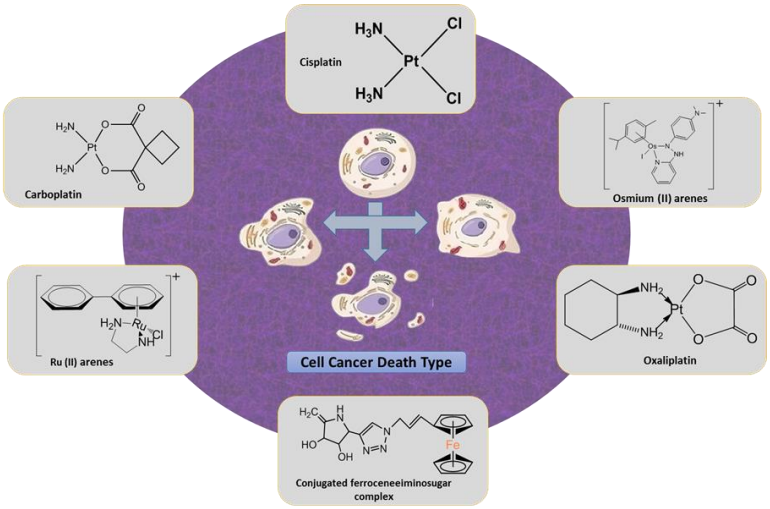
Graphical Abstract



Introduction

Complex compounds, essential for various biological functions, play a critical role in human physiology. Hemoglobin, a well-characterized metallocomplex, exemplifies this concept by facilitating oxygen transport throughout the body. Disruptions in physiological homeostasis, as observed in pathological conditions like cancer, can be attributed to malfunctions in these complex molecules [1].

Malignant neoplasms, commonly referred to as cancers, pose a significant threat to human health. These arise from uncontrolled cellular proliferation – the abnormal and rapid division of cells – that disrupts the delicate balance of tissue homeostasis [2]. Mutations within the DNA sequence, often triggered by environmental factors like radiation, chemicals, or viruses [1]. are a primary driver of this aberrant growth. Furthermore, unlike benign tumors, cancers exhibit the unique ability to invade surrounding tissues and metastasize, establishing secondary tumors at distant sites within the body [11,12].

The fight against cancer currently relies on a well-established arsenal of therapies – surgery, chemotherapy, and radiotherapy [28]. While these approaches offer definitive solutions, their limitations are increasingly recognized. Surgical removal can be ineffective against disseminated cancers, and both chemotherapy and radiotherapy, though potent, often inflict significant side effects [10]. This has spurred the exploration of novel therapeutic avenues, with metal-based compounds emerging as promising candidates. Traditionally, organometallic complexes were dismissed due to concerns about their stability within the body. However, recent advancements have yielded stable organometallic complexes with potent anti-cancer properties, even under physiological conditions [21]. This has opened exciting possibilities for their application not only as targeted anti-tumor agents, but also as radiopharmaceuticals for both cancer diagnosis and therapy.

The past few years have witnessed a surge in the development of transition metal complexes for cancer therapy. Cisplatin, a platinum-based complex, remains a cornerstone treatment for solid tumors [11]. However, the search for even more effective and well-tolerated agents continues. Ruthenium, iron, and osmium complexes are emerging as promising alternatives [27], with carboplatin and oxaliplatin already demonstrating clinical efficacy [3,7]. A key objective in this field is to minimize treatment-associated side effects. Organometallic compounds, with their superior activity and selectivity compared to inorganic counterparts, offer a compelling path forward in this pursuit [22]. The development of next-generation organometallic anticancer agents hinges on the design of novel ligands with enhanced selectivity for specific targets on cancer cells. These ligands can be further optimized to improve the in vivo stability of the drug complex [21]. Targeted

delivery via interaction with overexpressed receptors on cancer cells has the potential to minimize off-target effects associated with current organometallic therapies[4,5].

Materials and Methods

This journal review goes through several stages, starting with (1) collecting various references in Indonesian and English journal related to organometallic complex compounds as components of anti-cancer drugs, (2) sorting out important literature related to the predetermined topic, (3) examining the content of the selected literature to gain an overview of the recent developments regarding the utilization of organometallic complex compounds as components of anti-cancer drugs, considering their strengths and weaknesses. The literature review in this article is based on 42 scientific articles, comprising 1 national proceeding article, 1 accredited national journal article, and 40 articles from leading international journals such as Nature, Science Direct, ACS, MDPI, SciELO, RSC, AACR, PNAS, Europe PMC, ASCO, Karger, Chemistry Europe, and Spingerlink.

Result and Discussion

Organometallic complexes, characterized by covalent metal-carbon bonds, hold immense promise in the medical field, particularly as anticancer agents. Cisplatin (Cis-diamine-dicholoroplatinum(II)), a clinically established drug since 1980, exemplifies this potential. Its mechanism involves DNA binding within cancer cells, ultimately leading to cell death. Current research is actively exploring a new generation of organometallic complexes to address limitations associated with existing agents, such as severe side effects and the emergence of cancer cell resistance.

The exploration of organometallics as anticancer agents represents a significant advancement in medical chemistry. The discovery timeline began with cisplatin, a pioneering platinum-based drug approved in 1978 for various cancers like testicular, ovarian, bladder, and lung carcinomas. Carboplatin, a derivative of cisplatin with reduced toxicity, followed in 1989, finding application in ovarian and other cancers. The 1980s also witnessed the development of Ru(II) arene complexes, exemplified by RAPTA-C, which capitalized on arene ligands to enhance solubility and stability within biological settings. The 1990s saw the rise of ferrocene-based candidates like ferrocifens, demonstrating activity against diverse cancers including breast cancer. Inspired by the success of ruthenium (II) arenes, osmium (II) arenes emerged as a research focus in the 1990s, targeting anti-proliferative effects against drug-resistant cancer cells. Finally, oxaliplatin received approval in 2002, further expanding the repertoire of clinically relevant organometallic anticancer drugs. Among the aforementioned organometallic complexes, only cisplatin, carboplatin, and oxaliplatin have garnered Food and Drug Administration (FDA) approval for their anticancer properties. Oxaliplatin, specifically, finds application in combination with fluorouracil and leucovorin for the treatment of colorectal cancer. While Ru(II) arenes, ferrocenes, and osmium(II) arenes demonstrated promising preclinical and early clinical trial results, they have yet to receive FDA endorsement for clinical use. Ongoing research continues to meticulously evaluate their efficacy and safety profiles, with the ultimate goal of bringing some of these compounds into the realm of approved anticancer agents.

This selection of six organometallic complexes exemplifies the most prevalent class employed in cancer therapy. These well-studied compounds, including cisplatin, carboplatin, ruthenium complexes, ferrocenes, osmium complexes, and oxaliplatin, find widespread application in clinical settings. Their interaction with biomolecules like DNA, RNA, and proteins contributes significantly to our understanding of complex organometallic mechanisms, a cornerstone for developing more targeted and efficient anticancer agents. Notably, the FDA-approved cisplatin and carboplatin, along with promising new candidates based on ruthenium and osmium, highlight the ongoing research efforts. Similarly, oxaliplatin and ferrocenes demonstrate encouraging preclinical results after thorough investigation. The structural diversity exhibited by these six compounds, encompassing varied geometries

and ligand-metal centers, provides a unique platform for exploring how such differences translate to biological activity. This targeted selection reflects the current research focus, offering a comprehensive overview of established knowledge and propelling future studies in this promising field.

Table 1. Organometallic complexe compounds as anticancer agents

Organometallic compound	Reaction mecanism	Molecular structure	Anticancer agent	Ref
Cisplatin	Induces oxidative stress in cancer cells	Planar tetragonal	Testicles Ovary Vesica urinaria Lungs	[2]
Carboplatin	Efficiently binds to DNA, consequently impeding the processes of replication and transcription, ultimately triggering apoptosis in cancer cells	Planar tetragonal	Testicles Ovary Vesica urinaria Lungs	[3]
Ru (II) arenes	As a cytotoxic agent capable of establishing covalent linkages with DNA molecules	Octahedral	Ovary	[4]
Ferrocenes	The ferrocenium cation reacts with the superoxide anion to regenerate ferrocene and produce dioxygen	Metalosena	Breast	[5]
Osmium (II) arenes	The substance has cytotoxic properties through its ability to bind to DNA	Pseudo-Octahedral	Ovary	[6]
Oxaliplatin	The substance disrupts DNA replication and transcription machinery by forming DNA adducts.	Oktahedral	Pancreas	[7]

Cisplatin. Cisplatin, initially known as Peyrone's chloride following its synthesis in the late 19th century, emerged as a revolutionary cancer treatment after undergoing clinical trials beginning in 1971. This platinum-based organometallic complex received FDA approval for treating testicular and ovarian cancers. Its mechanism of action involves inducing tumor cell death, making it a valuable tool in adjuvant cancer therapy. Cisplatin demonstrates efficacy against a broad spectrum of solid tumors, including ovarian, testicular, bladder, and lung cancers. Notably, its use often leads to favorable early responses, ranging from complete disease remission to partial response or disease stabilization [2]. The synthesis of cisplatin as an anticancer drug involves a reaction between platinum(II) chloride with ammonia and sodium chloride, with an alternative method utilizing platinum(II) acetate and ammonia. However, despite its effectiveness, cisplatin is not without limitations. Platinum-based therapies are known to induce dose-dependent side effects. Common adverse effects encompass damage to healthy cells, manifesting as nausea, vomiting, decreased blood cell counts, and potential harm to the kidneys, nerves, hearing, heart, and liver [8].

Following cellular entry, cisplatin undergoes activation within the cytoplasm. A water molecule replaces a chloride ligand on the platinum center, generating a potent electrophile. This activated species can react with various nucleophiles, including sulfhydryl groups on proteins and nitrogen donors on nucleic acids. Notably, cisplatin preferentially binds to purine residues in cancer cell DNA, leading to DNA damage and ultimately hindering cell division and triggering apoptosis.

While cells maintain a homeostatic balance of reactive oxygen species (ROS) under physiological conditions through scavenger systems, excessive ROS production under oxidative stress can damage cellular proteins, lipids, and DNA, contributing to cell death. Importantly, cisplatin-induced cytotoxicity heavily relies on the generation of oxidative stress within the mitochondria of cancer cells. This oxidative stress can modulate various signaling pathways, including calcium signaling,

protein kinase C activity, Mitogen-Activated Protein Kinase (MAPK) pathways (JNK, p38 MAPK), and the AKT pathway, further amplifying DNA damage in cancer cells[9] as shown in Figure 1. Beyond its direct cytotoxic effects, cisplatin exhibits the ability to induce immunogenic cell death (ICD) at the cellular level. This translates to components within platinum-based chemotherapy triggering the immune system's activation. The mechanism involves a combination of cellular stress and death signals that culminate in a tumor-specific immune response.

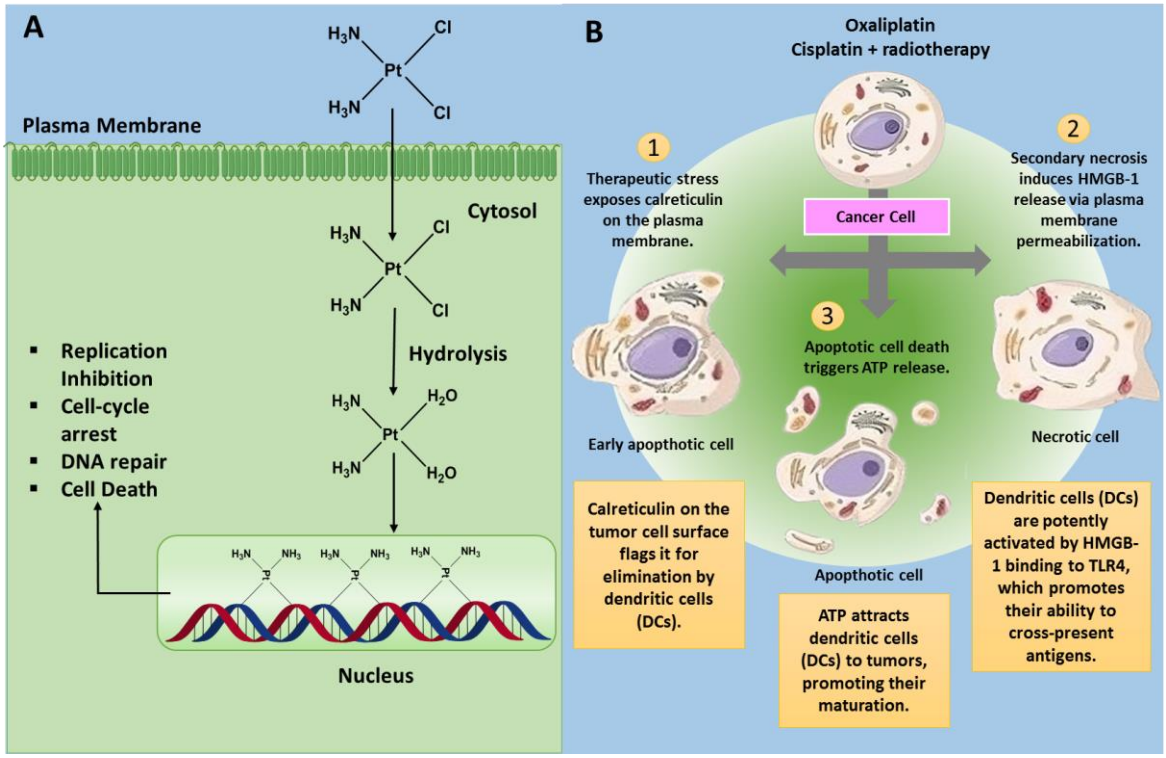


Figure 1. Mechanisms of action of cisplatin on immunogenic molecular pathways

Cisplatin, for instance, cleaves calreticulin, a protein within the endoplasmic reticulum. This cleavage exposes a molecular signal recognized by dendritic cells, prompting them to engulf and process the dead cancer cells. Additionally, ATP release and protein-1 mobility contribute to dendritic cell activation and maturation by stimulating specific receptors – the purinoreceptor P2RX7 and the pattern recognition receptor TLR4. Furthermore, oxaliplatin, another platinum-based drug, upregulates the expression of MHC class I molecules on cancer cells. While this can enhance immune evasion to some extent, it also promotes dendritic cell maturation and subsequent T cell proliferation. Platinum therapy further enhances T cell activation by downregulating the expression of PD-L2, an inhibitory molecule on T cells. This downregulation results from decreased phosphorylation of STAT6, a protein activated by the IL-4/STAT6 signaling pathway. Normally, IL-4 binding to its receptor leads to STAT6 phosphorylation and its translocation to the nucleus, where it promotes the transcription of PD-L2. Disruption of this pathway by platinum therapy leads to decreased PD-L2 expression, ultimately enabling T cell activation against cancer [10].

Cisplatin treatment is associated with a spectrum of adverse effects. Gastrointestinal toxicities, such as nausea and vomiting, are frequently encountered and can lead to complications like dehydration and electrolyte imbalances. Cisplatin also exhibits nephrotoxic properties, potentially causing acute and chronic kidney injury. High-dose regimens may induce neurotoxicity, manifesting as numbness, tingling, and muscle weakness.

Carboplatin. Carboplatin, chemically known as cis-dichloro(1,1-cyclobutanedicarboxylate)

platinum (II), is a derivative of the well-established cancer drug cisplatin. While sharing a similar mechanism of action focused on DNA damage, carboplatin exhibits a distinct chemical structure and toxicity profile compared to its parent compound [II]. Synthesis of carboplatin follows a similar approach to cisplatin. However, a key difference lies in the substitution of ammonia with 1,2-diaminopropane. Multiple synthetic routes exist, utilizing either platinum (II) chloride or acetate as starting materials alongside 1,2-diaminopropane and sodium chloride [II]. As a leading platinum-based chemotherapeutic agent, carboplatin finds application in treating various cancers, including testicular, ovarian, head and neck, and small cell lung cancers [11]. Its primary target is cellular DNA. By efficiently binding to DNA, carboplatin disrupts replication and transcription, ultimately leading to cancer cell death [12]. This DNA damage can further impact numerous cellular signaling pathways, triggering either apoptosis (programmed cell death) or necrosis (cell death) in tumor cells. Notably, carboplatin interactions with DNA can result in the formation of various DNA adducts, both within a single strand (intra-chain) and between different strands (interchain), further contributing to its anti-tumor effects [13] as shown in Figure 2.

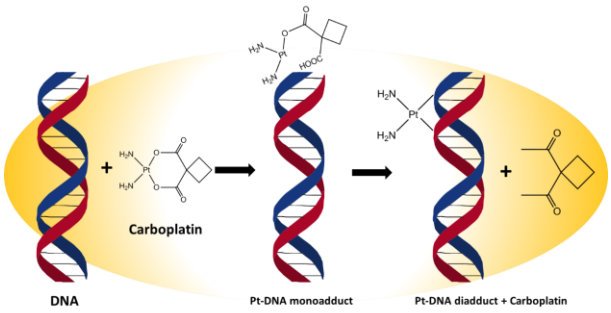


Figure 2. Formation of adducts between DNA and Carboplatin

In vitro investigations have revealed mechanisms by which cells develop resistance to carboplatin. These mechanisms include enhanced drug detoxification mediated by thiol groups within metallothionein and glutathione, improved DNA repair proficiency, and heightened tolerance to DNA damage, ultimately leading to reduced apoptosis and lower intracellular carboplatin accumulation [14,15]. Consequently, strategies that inflict greater DNA damage, impede DNA repair pathways, or activate and potentiate apoptosis hold promise for overcoming resistance and diminishing tumor cell viability [16,17].

Carboplatin's therapeutic activity hinges on its ability to traverse the cell membrane for activation. Within the cellular environment, the molecule undergoes hydrolysis of the 1,1-cyclobutanedicarboxylate moiety, acquiring a positive charge. This electrostatic transformation facilitates interaction with nucleophilic biomolecules, including DNA, RNA, and proteins, as illustrated in figure 3. Notably, carboplatin binding can trigger the formation of additional platinum adducts [18]. The mechanism of membrane permeation involves covalent attachment of carboplatin to the N7 position of purine bases, ultimately leading to the establishment of DNA-protein or DNA-DNA crosslinks [19].

While exhibiting lower cytotoxic potency compared to cisplatin, carboplatin demonstrates a more favorable side effect profile. This disparity might be attributed to variations in the rate of DNA adduct formation. The reduced reactivity of carboplatin with nucleophilic biomolecules, possibly due to the 1,1-cyclobutanedicarboxylate group acting as a less efficient leaving group compared to the chloride ligand in cisplatin, could explain the difference in observed toxicities [13].

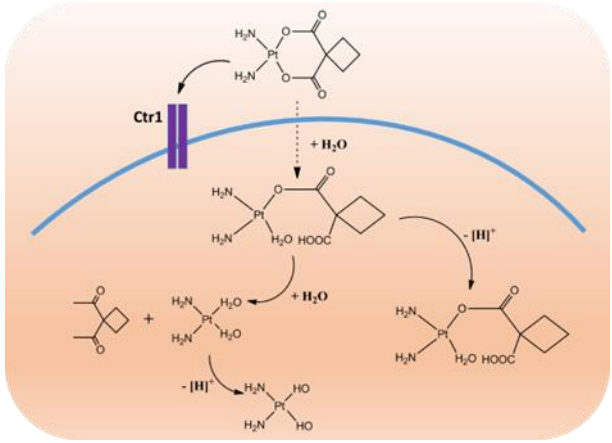


Figure 3. Hydrolysis of carboplatin in the cell. Ctr1 is a high-affinity copper transporter

Carboplatin's interaction with DNA can induce a spectrum of lesions, with interstrand cross-

linking (ISC) exhibiting the most pronounced cytotoxic effect. These ISCs effectively halt DNA replication and introduce errors during the process. This ultimately leads to an accumulation of cells in the G2/M phase of the cell cycle and triggers apoptosis, or programmed cell death. Conversely, single-strand DNA alkylation, another consequence of carboplatin interaction, is readily repaired by the cell's DNA repair machinery. However, interstrand cross-links, a hallmark of bifunctional alkylating agents like carboplatin, necessitate more intricate repair mechanisms due to their complex structure [20].

Cellular recognition of platinum-induced DNA damage relies on the intricate machinery of DNA repair pathways. Within the chromatin structure, the repair system might necessitate the unwinding of the damaged double-stranded DNA from the nucleosome, the fundamental unit of chromatin. Elucidating the interaction between platinum bound to nucleosomal DNA is therefore crucial for understanding the cellular recognition process [20]. The DNA mismatch repair (MMR) system plays a pivotal role in replication fidelity by preventing errors arising from mutations. MMR recognition relies on the distortion of DNA caused by the presence of 6-thioguanine and other carboplatin-derived adducts, generating a damage signal potentially leading to apoptosis initiation. This mechanism suggests a role for MMR proteins in detecting carboplatin-induced DNA lesions. Consequently, loss of functional MMR can contribute to carboplatin resistance, potentially stemming from the inability to recognize the complex formed by DNA adducts with platinum-based drugs[20]. Similar to cisplatin, carboplatin can induce nausea and vomiting, albeit with a less severe incidence. Additionally, carboplatin shares the nephrotoxic potential of cisplatin, leading to kidney damage and potentially progressing to chronic kidney disease.

Ru (II) arenes. Recent research on ruthenium-based anticancer agents has identified Ru(II) half-sandwich arene complexes containing the 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (PTA) ligand (RAPTA) as particularly promising candidates. These complexes adopt a "piano stool" geometry, where n-arene ligands occupy the "seat" and combine with mono- and bidentate ligands to form the "legs." Notably, the chelating nature of the bidentate ligand appears to contribute to their anticancer activity. Ru(II) arene complexes exhibit both hydrophilic and hydrophobic properties, potentially leading to not only additive but also synergistic effects in their interaction with biological targets [4]. Furthermore, the robust Ru(II) arene unit facilitates the incorporation of diverse ancillary ligands, enabling the creation of structurally varied complexes with distinct modes of biomolecular interaction. This versatility holds significant promise for the development of novel and potent anticancer drugs. Synthetically, Ru(II) arenes can be obtained from ruthenium(II) carbonyl precursors through ligand substitution reactions. Alternatively, ruthenium(II) halide compounds can serve as starting materials, utilizing either ligand substitution or transmetalation strategies.

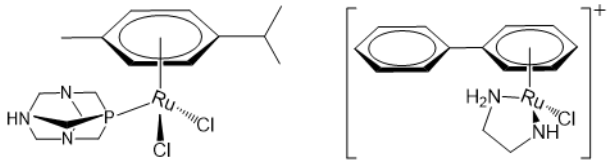


Figure 4. RAPTA-C (a) and RM175 (b) are typical examples of 18-electron Ru arenes complexes with a "piano-bench" geometry, in which the n-arene ring stabilizes the 2+ oxidation state of the central Ru metal.

The Sadler group pioneered the exploration of ruthenium(II) complexes for anticancer applications, with RM175 [Ru(biphenyl)Cl(en)]+ (en = 1,2-ethylenediamine) as one of the first candidates (Figure 4). This complex exhibits a pseudo-octahedral geometry, resembling a "piano stool" with a monodentate chloride ligand, a bidentate ethylenediamine ligand, and a biphenyl arene ligand occupying the three coordination sites. While initially designed to target DNA, RM175's development also capitalized on the advantages of the +2 oxidation state, which bypasses the need for cellular reduction for activation.

The hydrophobic surface conferred by the arene substituents is believed to facilitate cellular diffusion across the lipophilic plasma membrane [21]. Upon entering the cell, the complex likely undergoes activation through ligand exchange at

the monodentate site prior to DNA binding[22,23]. This activation mechanism resembles cisplatin, where the halogen atom acts as a leaving group followed by aquation, creating a vacant coordination site for subsequent covalent bonding with the N7 atom of guanine within the DNA double helix [21]. While ruthenium(II) complexes demonstrably bind to guanine residues in DNA [24], the expanded arene moiety in RM175 is postulated to enable hydrophobic interactions via intercalation between DNA base pairs[25]. The relatively free rotation of the biphenyl ligand around the Ru(II) center imparts flexibility to the complex, potentially minimizing steric hindrance and enhancing its DNA binding affinity. This flexibility allows RM175 to achieve both intercalation and guanine binding simultaneously, which could explain the observed resistance of RM175-DNA adducts to repair mechanisms compared to cisplatin-DNA adducts. These observations contribute to understanding the lack of cross-resistance between RM175 and platinum-based drugs.

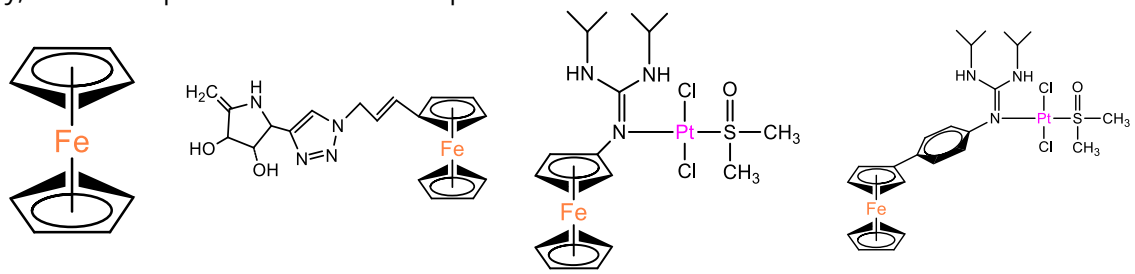
A key feature of this complex is the pre-existing lower oxidation state of the metal center, which may contribute to its cytotoxic activity [26]. The n-donor/acceptor properties of the arene ligands offer stability to the +2 oxidation state. Additionally, the bidentate XY ligand enhances the overall structural integrity and allows for fine-tuning of the electronic properties at the metal center. Notably, the monodentate ligand Z serves a crucial role in molecular activation. If readily displaced, such as in the case of a halide ligand, it can vacate a coordination site for interaction with biomolecules [22,27].

Ru(II) arene complexes exhibit promising cytotoxic activity against human ovarian cancer cell lines, demonstrating potency comparable to cisplatin and carboplatin in some cases [28]. Research efforts have identified several key structure-activity relationships[29,30]. One such relationship involves the chelating ligand and the leaving group. When ethylenediamine is employed as the chelating ligand and chloride serves as the leaving group, cytotoxicity against A2780 human ovarian cancer cells increases with the size of the coordinated arenes[28]. Conversely, substituting the chelating ligand with a more readily displaced monodentate ligand results in a diminished cytotoxic effect [31]. While ruthenium complexes hold promise as therapeutic agents, their administration can be associated with adverse effects on red blood cells, potentially leading to anemia and other blood disorders [32]. Additionally, some ruthenium complexes exhibit nephrotoxic properties similar to cisplatin and carboplatin, potentially causing kidney damage and progression to chronic kidney disease

Ferrocenes. Despite its relatively low toxicity, the organometallic ferrocene complex $Fe(\eta^5\text{-}C_5H_5)_2$ (figure 5a) can be oxidized to the ferrocenium cation $[Fe(\eta^5\text{-}C_5H_5)_2]^+$, which exhibits cytotoxicity against various cancer cell lines. Synthetically, ferrocene derivatives can be obtained from iron(II) precursors via cyclopentadienide reactions. The precise mechanism of the ferrocenium cation's antiproliferative activity remains elusive, although hydroxyl radical generation likely plays a role in DNA and cell membrane damage within cancer cells, ultimately leading to cell death [31]. Conjugating ferrocene with tamoxifen, a known antiestrogen, yields "ferrocifene" derivatives (e.g., $HO(CH_2)_3C(Fe)=C(C_6H_4OH)_2$, in figure 6 that demonstrate enhanced antiproliferative activity against cancer cell lines. Chemical oxidation of these ferrocifene derivatives leads to the formation of unique tetrahydrofuran-substituted methidequinones (QM) through internal cyclization. Notably, the ferrocenyl group acts as both a reversible intramolecular redox antenna and a stabilizing carbocation modulator in this complex[32].

Another promising class of anticancer agents combines ferrocenyl moieties with iminosugars (Figure 5b). These ferrocenyl-iminosugar conjugates exhibit dual functionality, inhibiting fucosidase activity and exerting antiproliferative effects [33]. Studies have shown significant antiproliferative activity against MDA-MB-231 and SK-MEL28 cell lines for these conjugates. Functionalized ferrocene can also serve as a precursor for the synthesis of heterometallic eguanidine Pt(II) complexes with antiproliferative properties. These Fe-Pt complexes containing guanidine ligands (Figures 5c and 6d) exhibit

activity against various human cancer cell lines, with GI_{50} values ranging from 1.4 to 2.6 μM. Notably, these complexes demonstrate superior cytotoxicity compared to cisplatin against resistant T-47D and WiDr cell lines [34].

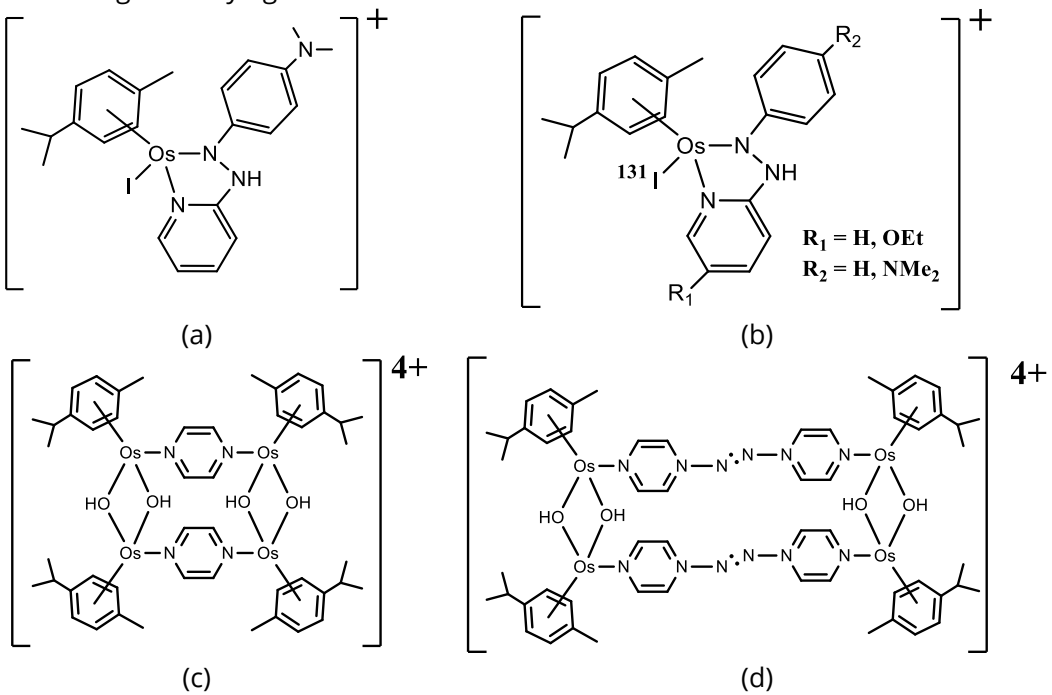


(a) (b) (c) (d)

Figure 5. Molecular structures of ferrocene complex (a), conjugated ferroceneeiminosugar complex (b) and Pt(II) eguanidine complex functionalized with ferrocenee (c)

Ferrocene-based compounds has been associated with hematological toxicities, such as anemia and thrombocytopenia. Additionally, gastrointestinal side effects, including nausea and vomiting, may also occur.

Osmium (II). Os(II)-arene complexes containing specific phenylazopyridine ligands and iodide (Figure 7a) demonstrate enhanced potency and reduced reactivity compared to complexes with monodentate ligands[35]. These complexes exhibit not only superior cytotoxicity to cisplatin in NCI-60 cell line studies but also a remarkable 49-fold higher average activity against a broader panel of 809 cancer cell lines (Sanger panel). Furthermore, in vivo testing suggests their efficacy. The proposed mechanism of cell death involves a redox process, triggering the rapid generation of intracellular reactive oxygen species (ROS), particularly superoxide. A recent study employing focused nano-X-ray fluorescence revealed osmium localization within specific cellular regions resembling mitochondria following treatment with physiologically relevant conjugate doses. These findings highlight the promise of this complex as a candidate for preclinical development [36].



(a) (b) (c) (d)

Figure 7. Molecular structures of Os(II)-arenes complex (a), iodide-Os(II)-azopyridine conjugate (b), $[Os_4(\eta^6\text{-p-cym})_4(\mu^2\text{-OH})_4(pap)_2][PF_6]_4$(1-$[PF_6]_4$) complex (c), and $[Os_4(\eta^6\text{-p-cym})_4(\mu^2\text{-OH})_4(prz)_2][PF_6]_4$(2-$[PF_6]_4$) complex (d).

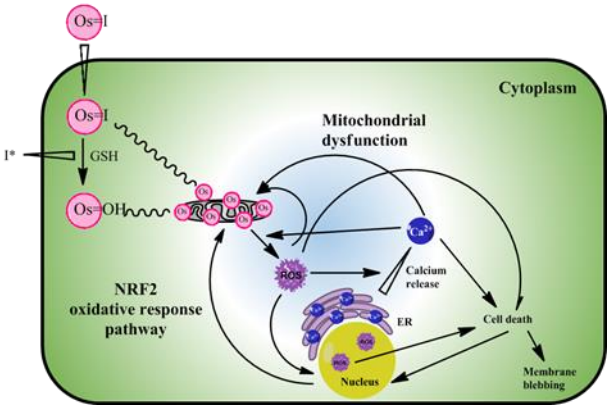


Figure 8. The possible pathways connecting the intracellular activation of azopyridinium iodide Os(II) arena anticancer complex with Ca mobilization, mitochondrial dysfunction, ROS generation, and cell death.

Similar to cisplatin and carboplatin, osmium complexes can induce nephrotoxicity, potentially leading to kidney damage and progression to chronic kidney disease. Additionally, administration of high-dose osmium complexes has been associated with neurotoxic effects, manifesting as numbness, tingling, and muscle weakness.

Oxaliplatin. Oxaliplatin (cis-diammine-(1,2-cyclohexanediamine)platinum(II) oxalate), a DNA intercalating agent, presents as a newer platinum-based chemotherapeutic with superior antitumor activity compared to cisplatin and carboplatin. This complex is often used in combination regimens for treating various cancers. Its synthesis involves the reaction of platinum(II) precursors with 1,2-cyclohexanediamine and oxalic acid. In vitro studies utilizing the NCI-60 drug screening panel demonstrate oxaliplatin's generally superior efficacy compared to cisplatin, as measured by IG50 values. The mechanism of action involves disruption of DNA replication and transcription through the formation of intrastrand DNA adducts, particularly Pt-guanosine-guanosine (Pt-GG) adducts. These Pt-DNA complexes at the nucleotide level ultimately trigger activation of DNA repair mechanisms or apoptosis pathways[7].

Tabel 2. Advantage and Shortage of each organometallic complex compound as an anticancer agent

Types of Organometallic	Advantage	Shortage	Ref
Cisplatin	As an initial therapeutic response associated with complete disease remission, partial response, or disease stabilization.	Has side effects such as: nausea and vomiting, decreased blood cells, damage to the kidneys, nerves, decreased hearing, heart, and liver.	[8]
Carboplatin	Pharmacodynamics of carboplatin, has fewer side effects than its precursor cisplatin.	Has side effects such as: Anemia, nausea, vomiting, abdominal pain, diarrhea, contipation, mucous membrane disorders, and spinal cord suppression.	[13]
Ru (II)*arenes*	Shows promising cytotoxic activity against cancer cell lines.	Lack of cross-resistance with platinum	[28]
Ferrocenes	Generates hydroxyl radicals in cancer cells that can cause damage to DNA and cell membranes	The mechanism by which [Fe(h5-C5H5)2]+ exerts its antiproliferative effect is not fully understood.	[31]
Osmium (II) *arenes*	Common toxicities that may reduce the side effects of chemotherapy	Lower reactivity of transition metal bonds	[37]
Oxaliplatin	Considered the standard first-line treatment for colorectal cancer	Most oxiplatin studies have not been able to significantly improve survival	[40]

Currently, resistance to platinum-based chemotherapeutics, including oxaliplatin, remains a significant challenge in cancer treatment. Recent research suggests that overexpression of DNA repair proteins, such as DNA polymerase beta (Pol β), may play a role in this resistance. A study by Yang et al. (2010) demonstrated that tumors with elevated Pol β expression exhibited increased sensitivity to oxaliplatin-induced DNA damage. This finding highlights the potential importance of protein expression profiles in predicting patient

response to oxaliplatin therapy. Beyond the formation of Pt-DNA adducts, oxaliplatin's mechanism of action likely involves additional cellular targets. Therefore, a comprehensive understanding of both oxaliplatin's interaction with DNA repair pathways and its effect on protein expression profiles is essential for optimizing platinum-based cancer therapies [39].

Oxaliplatin demonstrates limited clinical efficacy as a single agent and is typically used in combination regimens. The FOLFOX regimen, combining oxaliplatin with 5-fluorouracil (5-FU) and leucovorin (LV), is the current standard first-line treatment for colorectal cancer. Clinical trials are also investigating the efficacy of FOLFOX for other malignancies, such as pancreatic cancer. The order of administration, duration, and cytotoxicity within these combination regimens are complex and require careful optimization for individual patients due to variability in efficacy. Unfortunately, existing studies on combination therapies with oxaliplatin haven't shown significant improvement in overall survival rates, highlighting the need for novel systemic therapies for complex cancers [40].

Adjuvant therapy using oxaliplatin following surgical resection for colorectal cancer has shown modest improvements in survival. However, a comprehensive understanding of oxaliplatin's efficacy compared to other treatment options in this context remains elusive[41]. Emerging evidence suggests that oxaliplatin may target protein networks beyond DNA, potentially forming platinum-protein adducts. Further investigation into these interactions is crucial, as they may play a role beyond simple drug inactivation [42]. Oxaliplatin can be associated with neurotoxic side effects, such as numbness, tingling, and muscle weakness, predominantly affecting the hands and feet. Additionally, gastrointestinal toxicities, including nausea and vomiting, may also occur.

Conclusion

Organometallic complexes, also known as coordination compounds, play an important role in life. Organometallic complexes, such as cisplatin, carboplatin, ruthenium, ferrocenes, osmium, and oxaliplatin, have been the focus of research for the development of effective and efficient anti-cancer drugs. The mechanism of action of organometallic complexes involves interaction with nucleophilic molecules inside the cell, including DNA, RNA, and proteins. This interaction can cause damage to DNA, RNA, or proteins, which can lead to cancer cell death. Although organometallic complexes show potential as anti-cancer drugs, their use still has some advantages and disadvantages. The advantages of organometallic complexes are their effectiveness in killing cancer cells. The disadvantages are that organometallic complexes can cause side effects, such as nausea, vomiting, and kidney damage. Therefore, further research is needed to optimize the use of organometallic complexes as anti-cancer drugs with minimal side effects.

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Author Contribution

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Conflic of Interest

The authors declare no conflict of interest

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