

Coordination Compounds as Anticancer Agents: A Review

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ABSTRACT: Anticancer review has focused on coordination chemicals owing to their various coordination geometries, redox characteristics, and capacity to interact with biological macromolecules, and this review discusses platinum and non-platinum coordination complexes, such as gallium, copper, iron, ruthenium, and palladium, as possible anticancer drugs. These chemicals bind DNA, block topoisomerases, induce reactive oxygen species, and disturb cellular redox equilibrium. The structure-activity relationship studies also show how ligand structure, oxidation state, and coordination geometry affect biological activity; Also addressed are metal-based chemotherapy's toxicity, drug resistance, and inadequate cancer cell selectivity. We discuss targeted delivery techniques and ferroptosis-inducing metal complexes as therapeutic efficiency improvements. Overall, coordination chemistry offers intriguing potential for rationally designing next-generation metallodrugs with increased anticancer activity and lower systemic toxicity.



Keywords: Anti-cancer, Chelation, Coordination chemistry, Metals

1. INTRODUCTION

Cancer is among the most lethal illnesses, causing millions of individuals to succumb to excruciating anguish every worldwide. According to global cancer statistics, millions patients of cases are diagnosing annually, highlighting urgent need for more effective therapeutic strategies development [1]. Reports from 2012 indicate around 14 million new cancer diagnoses and 8.2 million deaths attributable to cancer globally. Researchers have examined the many ways that complexes of gallium, copper, iron, ruthenium, and palladium interact with biological targets. Gallium and iron compete for cell metabolism. Copper compounds raise oxidative stress and inhibit topoisomerases. Reactive oxygen species that damage DNA are produced by iron complexes. Ruthenium compounds bind to serum proteins to select cancers. These findings expand on the ideas of metal-based chemotherapy [2].

Few studies provide in vivo validation, whereas the majority concentrate on in vitro potency. Long-term toxicity education, metabolism, and biodistribution are all hampered by this imbalance. Non-platinum complex omics research is rare, although platinum drug resistance pathways have been extensively researched [3, 4].

Discussions of ligand effects that are descriptive rather than quantitative compromise the understanding of causality. It is rare to find comparable studies of platinum and non-platinum compounds in similar experimental settings. You may go from isolated activity reports to logical, mechanism-driven metal-based anticancer drug development by addressing these constraints.

The aims of coordination chemistry on anticancer efficacy are examined in this work, researching the effects of metal, oxidation, and ligand type on cell uptake, enzyme inhibition, and DNA binding. Because toxicity and resistance need alternatives, we investigate platinum and non-platinum systems. By connecting structural characteristics to established IC₅₀ values and mechanisms, safer metal drug design criteria may be discovered. This objective aids in the logical selection of metals and ligands for biological testing and synthesis.

When cisplatin (diamminedichloroplatinum (II)) was discovered to be cytotoxic in 1965, metal complexes may be used to treat cancer [5], as illustrated in Figure 1. In the past 15 years, much work has gone into developing safer, more effective medications. Some novel trans-platinum(II) and platinum(IV) complexes have been created and tested in clinical studies; however, their efficacy and safety differ. Thus, less poisonous metals like ruthenium, gold, and copper were proposed for safe and successful treatment. Reviews on metal complexes as anticancer drugs aim to provide an overview of therapeutic methods for using these systems [6].

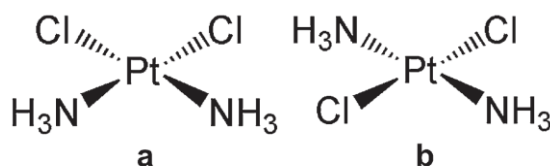


FIGURE 1. - Diamminedichloroplatinum(II), the cisplatin and transplatin structures [5]

The human organic cation transporter (hOCT2) and copper transport protein (Ctr1) facilitate the entry of cisplatin into cells via diffusion or active protein-mediated transport pathways. Within the cytoplasm, cisplatin undergoes hydrolysis, leading to the displacement of one of the two chloride ligands by a water molecule, therefore generating the $[\text{PtCl}(\text{H}_2\text{O})(\text{NH}_3)_2]^+$ species [7]. This species then interacts with DNA bases, mostly at the N7 position of guanine and adenine, as well as the N3 position of cytosine, culminating in the formation of a monofunctional adduct. A water molecule may replace the second chloride ligand to form $[\text{Pt}(\text{H}_2\text{O})_2(\text{DNA})(\text{NH}_3)_2]^+$. These organisms may crosslink DNA to produce a bifunctional adduct, as shown in Figure 2, resulting in cellular apoptosis [8].

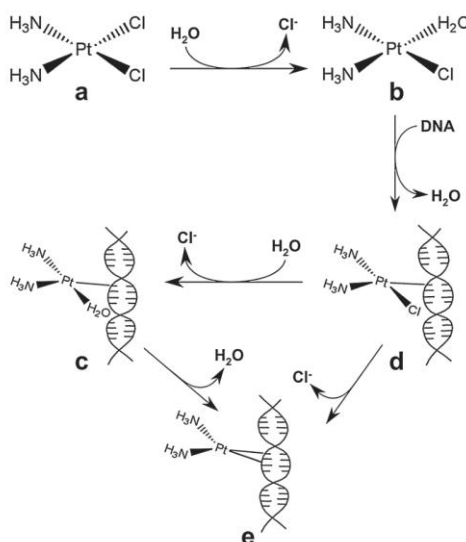


FIGURE 2. - Diagram of the cisplatin, DNA adduct reaction pathway [7]

Metal ions and ligands form coordination complexes, which were essential to inorganic chemistry. Many of these substances have unique physicochemical properties due to structural variation in metal centers, oxidation states, and ligands. These features enable biological, industrial, and environmental applications and give a full understanding of chemical bonding and reactivity. Combining old and modern technologies has improved coordination compound production, stability, and utility. Characterization techniques, including spectroscopic, crystallographic, and electrochemical investigations, are essential for elucidating structural complexities and informing their application [9].

A core metal atom or ion is enveloped by linked particles or ions in coordination complexes. An ion or compound in solution generally retains its identity, albeit partial dissociation may occur. Whether the coordinated item is positive, neutral, or negative depends on the coordinated groups and center atom, these chemicals are ligands [10]. Werner complexes, coordination complexes, chelating agents, complex ions, and simple complexes are additional names for these molecules. Coordination compounds have been studied and empirically identified since the mid-18th century. Metals and metal ions interact with molecules and ions to form connect bonds that are covalent in coordination

chemistry. These reactions show Lewis acid-base interactions. Coordination involves complicated ion or molecule interaction [9].

Synthetic organic chemists benefit from access to an extensive collection of reliable reactions for the construction of smaller molecules, mesoscopic structures, and polymers [11]. The scarcity of high-yield events in transition metal chemistry is a challenge for coordination chemists, and iron-porphyrin complexes of hemoglobin enable the reversible binding of oxygen molecules to the iron atom, hence enhancing its oxygen transport capacity [12].

Many critical proteins include metal centers coordinated with organic ligands, making coordination compounds vital, such as vitamin B12 is a cobalt combination with the macrocyclic corrin ligand, whereas chlorophyll is a magnesium-porphyrin complex that helps plants photosynthesise [13]. These natural coordination molecules show how metal-ligand interactions support biological activities. Metal centers and varying coordination environments provide coordination complexes different structural and electrical characteristics than carbon-carbon covalently bonded organic molecules. Structure diversity allows the construction of complexes with variable reactivity, stability, and biological activity, making it popular in inorganic and medicinal chemistry. Coordination chemistry is a flexible framework for studying metal-ligand interactions and generating useful molecules for catalysis, materials science, and medicinal research [9].

2. COMPLEX STRUCTURES

2.1 METAL ATOM

Electron giving sets up coordinates covalent bonds when the ligand donor atom donates a lone pair of electrons to the central nucleus's empty orbital. The core atom accepts electrons from nearby molecules, which have just a single pair of electrons to fill an empty orbital. Ligands function as electron pair donors. Central atom is Lewis acid, ligand is donor [9].

A coordination substance, coordination complex, or complex is a compound formed by chemical bonding. Figure 3 depicts the metals or metalloids of the core atom. Donor atoms include halide ions and heteroatoms such as nitrogen, oxygen, sulfur, and phosphorus. Ammonia (NH₃), a ligand with a lone pair, is prevalent and efficient. The receiving metal or metalloid forms a covalent connection by coordination. A metalloid consistently forms covalent bonds with additional groups or atoms linked to its central atom, perhaps elucidating multiple-coordinate covalent interactions [9].

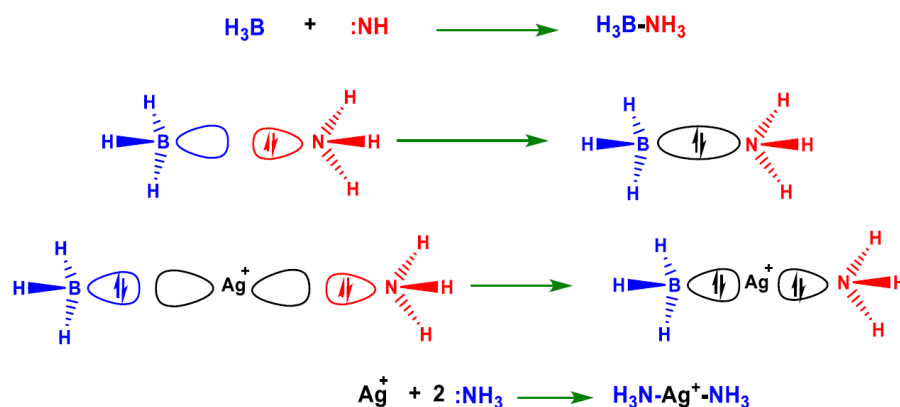


FIGURE 3. - Interaction between metal and ligand

2.2 MOLECULE LIGANDS

The ligands are compounds or electrically charged particles with donor groups that may covalently bond to a central atom; that metalloid atom may serve a comparable role; however, metals often coordinate ligands. The word "ligand" originated in the early 20th century and gained use by the mid-century [14].

These ligands inhabit a singular coordination position ($\text{Mn} \leftarrow \text{L}$). The sign L denotes ligands. Monodentate ligands include NH₃, H₂O, and Cl⁻. Potential polydentate ligands possess many donor groups, each containing a lone pair of electrons that couple with a single metal ion. Many organic heteroatoms, such as oxygen, nitrogen, sulfur, and phosphorus, possess multiple lone electron pairs. Molecular ligands provide metal ions diverse donor sets for binding purposes. The number of donor groups that may coordinate with a metal ion is contingent upon a substance's spatial configuration, outside conditions, and proximity of the donors [15].

3. STABILITY AND SENSITIVITY OF COMPLEXES

The most stable complex is often the least reactive or inert. Cobalt (III), chromium (III), and platinum metal complexes exhibit delayed reactivity. The electrical configuration, coordination number, and chelation of the central metal ion influence a compound's reaction rate. First-row transition metals predominantly exhibit +II and +III oxidation

states, as shown by experimental findings. Variations in formal oxidation states: Metals exhibit distinct chemical behaviors at each oxidation state, which is the fundamental principle. Cobalt (III) substitutes ligands gradually, whereas cobalt (II) does so rapidly. All has unique stereochemistry as well as tastes for ligand classes. When mixed with water as a ligand, most first-row transition metals in the two most prevalent oxidation states produce stable complex ions with the formula $[M(OH_2)_6]^{n+}$ ($n = 2$ or 3). The potential of ions in the $M(III)/(II)$ and $M(II)/(0)$ redox pairs varies greatly and is often colored [16].

4. PLATINUM-BASED PHARMACEUTICALS FROM HISTORICAL TO CONTEMPORARY TIMES

Platinum was the first effective cancer treatment metal. Platinum's medicinal properties were unknown until the researchers Rosenberg and coworkers discovered platinum amine halide complexes (cisplatin) in 1965 and studied its impact on human biology. Platinum was given to mice with sarcoma 180 and leukemia L1210 in 1969 to test its anti-cancer effects [17]. Clinical research began in 1971. Exactly nine years after discovering its anticancer properties, the FDA approved this medication for genitourinary cancers in 1978. It is widely employed to treat testicular, ovarian, bladder, cervical, skull base, laryngeal, and tiny-cell and other types of lung tumors. Platinum-containing drugs have been shown to damage the kidneys, brain, neural tissues, and bone marrow, causing renal failure, neurotoxicity, vomiting, ototoxicity, and anemia. To overcome these difficulties, platinum drug structures were continually updated, resulting in numerous generations of platinum drugs [18].

Cisplatin, a first-generation platinum molecule, is used in platinum-based chemotherapies (Figure 4). Italian scientist Michele Peyrone developed cisplatin in 1844 as Peyrone's chloride. Barnett Rosenberg explained its biological activity in 1965, almost a century after its discovery. Beginning with critical biochemical evaluations on yeast cells, cisplatin has changed tumor treatment. In 1978, the FDA authorized cisplatin as a cancer therapy after its 1971 clinical study [19].

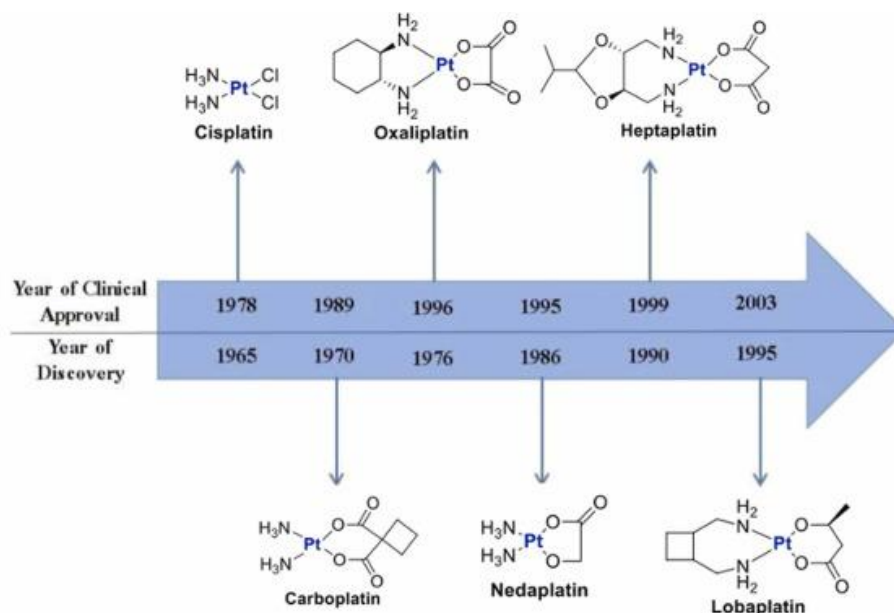


FIGURE 4. - Proven platinum anti-cancer medicines [20]

Platinum compounds provide several potential advantages; nevertheless, their use is limited by significant side effects, including renal, cardiac, auditory, and hepatic toxicity, immune system suppression, and gastrointestinal hemorrhage. Moreover, the emergence of drug resistance, either from inherent or acquired epigenetic and genetic alterations, has constrained the therapeutic use of platinum-based pharmaceuticals. Cross-resistance and diverse alterations are obstacles to the effectiveness of platinum-based therapies. The specified adjustments include decreased drug accumulation, reduced DNA-drug adducts, changed expression of genes related to cell survival, modified DNA damage repair pathways, changes to transporters and protein trafficking, and altered cellular metabolism [20].

5. PLATINUM METAL COMPLEXES

Certain platinum complexes, particularly those containing chloride ligands, may need just a single coordination site to interact with DNA. Numerous compounds have been synthesized, although only a limited number have undergone testing against various cancer cell types and shown lethality [21]. The monofunctional platinum compound phenanthriplatin (1) (Figure 5) exhibits more cytotoxicity than cisplatin. The complexes' action inside the biological

system was associated with a monofunctional adduct. This results from DNA antibodies with a bifunctional platinum adduct being unable to recognize the lesion produced by $\text{cis-}[\text{Pt}(\text{NH}_3)_2(\text{Am})\text{Cl}]^+$. This indicates that the complexes bind to DNA and have a positive biological effect by creating a monofunctional adduct. This signifies that the complexes generate a mono-functional adduct upon binding to DNA, resulting in a favorable biological effect [22].

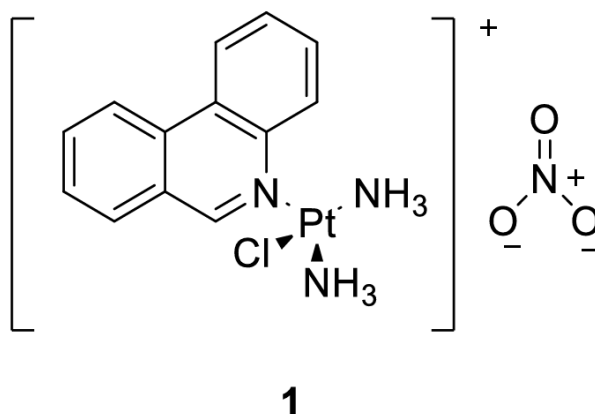


FIGURE 5. - Phenanthriplatin structure [22]

6. NON-PLATINUM METAL COMPLEXES

6.1 GALLIUM (III) COMPLEXES

Because Ga and Fe ions have an ionic radius, electron affinity, electro-negativity, coordination geometry, and Lewis base affinity, gallium (III) complexes are highly anticancer. Trivalent Ga (III) is chemically similar to Fe (III) except for redox activity [23]. Ga's antineoplastic action is enhanced by its competitive Fe (III) inhibition in vitro and in vivo. Ga (III) may be taken up by transferrin and stored in ferritin in cells as Fe (III). It also inhibits Fe-dependent processes such as the respiratory chain Fe-containing proteins and ribonucleotide reductase. Figure 5 shows the anticancer metal chelating chemical 8-hydroxyquinoline in metallodrug KP46 (tris(8-hydroxyquinoline) gallium (III)). KP46 (2) allows larger and more bearable tissue gallium concentrations than gallium salts because to its toxicological and pharmacokinetic advantages. KP46 also suppresses cell growth better in vitro and in vivo with low micromolar IC₅₀ values. KP46 (IT-235) showed unique cytotoxicity and synergism with multiple endoplasmic reticulum-targeted anticancer drugs in various cancers. Niikipharma and Intezyme provide this oral formulation [24], as shown in Figure 6.

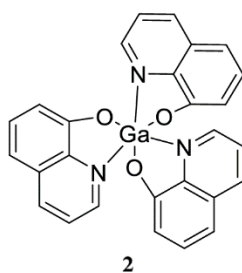


FIGURE 6. - Structure of KP46-Gallium (III) complex [24]

6.2 COPPER AND RUTHENIUM COMPLEX

Copper is an essential micronutrient and cofactor for numerous metalloenzymes that defend cells against ROS or mitochondrial metabolism (cytochrome c oxidase, superoxide dismutase). Copper is needed for angiogenesis, cell proliferation, and endothelial cell migration. Too much copper promotes tumor growth. Some brain, breast, stomach, prostate, and lung cancers have it. It tracks illness progression. Different copper interactions between tumor and normal cells lead to copper complex anticancer medicines. Several copper complexes are cytotoxic and antitumor. They contain N, S, or O ligands. Copper medications fight cancer via numerous mechanisms. By sequestering endogenous copper, their chelatory activities limit copper availability for tumor formation and angiogenesis [25].

Copper complexes (3-8), the target of chemotherapy, inhibit topoisomerases Top1 and Top2, causing DNA damage, cell cycle arrest, and death [26, 27]. The bispyrazolyl carboxylate ligand in heteroleptic Cu (I) complexes with auxiliary phosphine (9) may inhibit Top1 by preventing the lowering step and Top2 α by preventing ATP hydrolysis, according to molecular docking studies [28], as shown in Figure 7. They initiate apoptosis, create ROS, and hinder DNA replication.

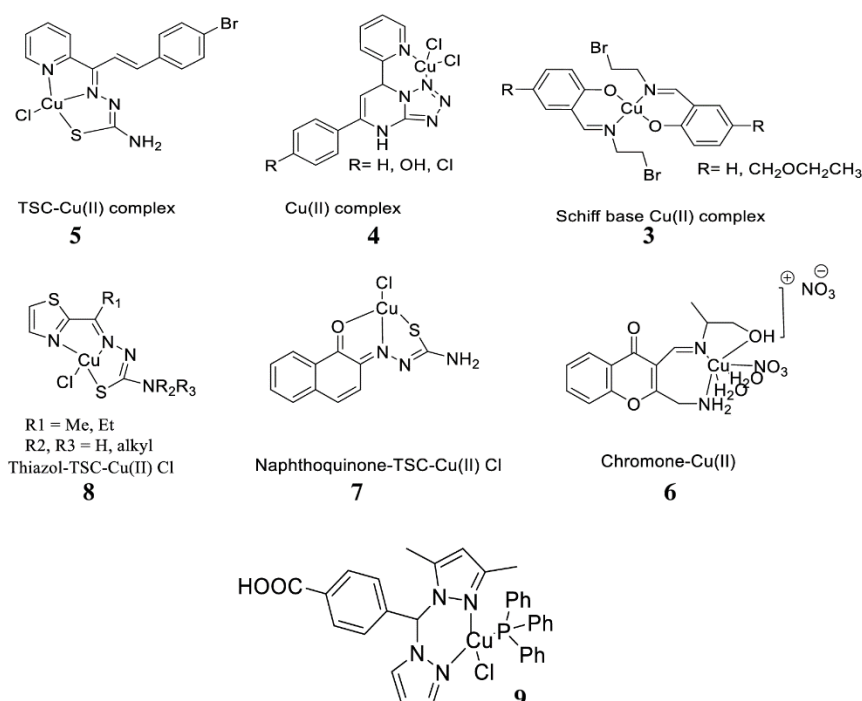


FIGURE 7. - Complexes of Cu ions having different inhibitors [26-28]

Ruthenium, the rarest platinum component and particularly newly identified in the earth's crust, is steady and resistant to rust. Ruthenium complexes' various oxidation states, little toxicity, selectivity for tumor cells, antimetastatic impacts, and capacity to imitate iron in binding to biological molecules attract pharmacists and chemical technologists. Ruthenium is seldom utilized metallicity [29].

In *in vitro* studies, several ruthenium complexes bind DNA or proteins and are harmful. Serum proteins deliver mature ruthenium-related compounds KP1019 and KP1339 to tumor cells, damaging DNA and killing them. Consequently, complexes made of ruthenium and blood proteins have to communicate well [29].

Due to ruthenium's propensity to imitate iron, different Ru(II) complexes containing ligands were created for cancer prevention. Ru(II) polypyridyl complexes may bind DNA electrostatically and intercalatively. Thus, their binding reagent potential has been thoroughly studied [30].

Mangiapia and colleagues produced many novel Ru-based antineoplastic drugs, including the organometallic complex AziRu and three amphiphilic nucleolipid derivatives (ToThyRu, HoThyRu, and DoHuRu) [31] (Figure 8). The three products combined with AziRu inside a framework based on pyrimidine deoxyribonucleoside (Thymidine, represented by ToThyRu and HoThyRu) or ribonucleoside (Uridine, for DoThyRu) [31].

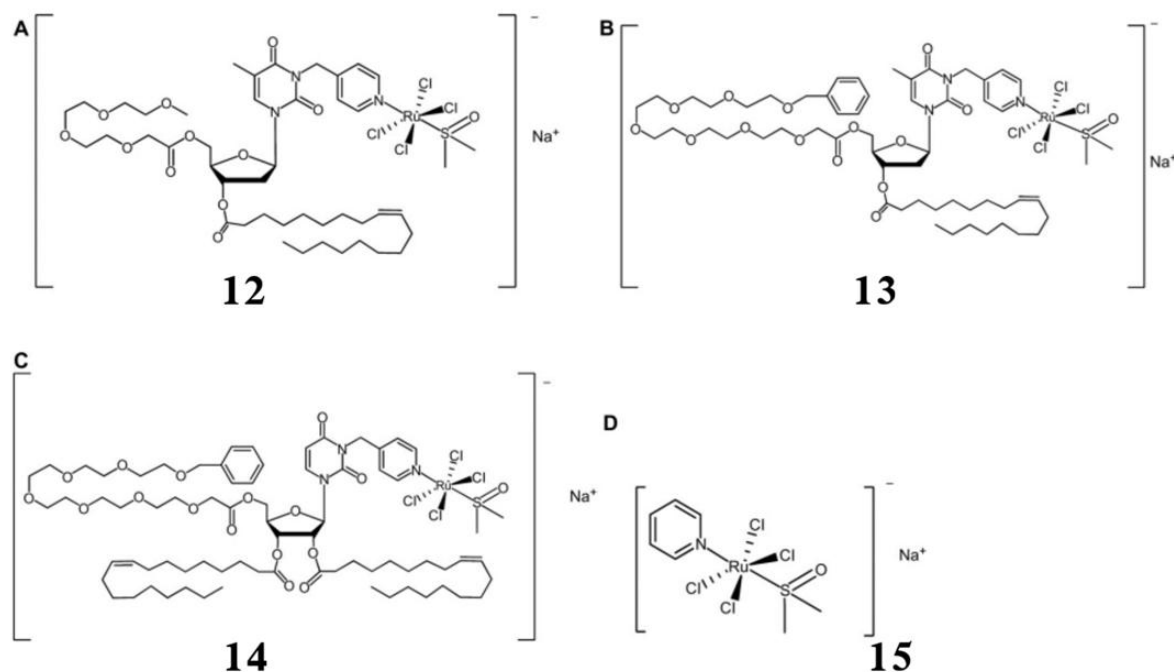


FIGURE 8. - Useful nucleolipids such as ToThyRu (A), HoThyRu (B), DoHuRu (C), and AziRu (D) [31]

6.3 IRON COMPLEXES

Iron, a prevalent metal, facilitates functions in biology such as cellular development, DNA synthesis, and proliferation. Mammalian heme complexes include iron. Heme is essential to cytochrome proteins, which allow oxygen-based redox processes, and it is found in proteins such as hemoglobin, leghemoglobin, and myoglobin [32].

Some biological functions need the intake or release of electrons to alter valence states, and iron complexes have been investigated in anticancer research owing to their association with cellular metabolic processes. Ferrocenium picrate and ferrocenium trichloroacetate salts, the first iron-based anticancer agents, generate reactive oxygen species that inflict DNA damage [6], as seen in Figure 9 [33].

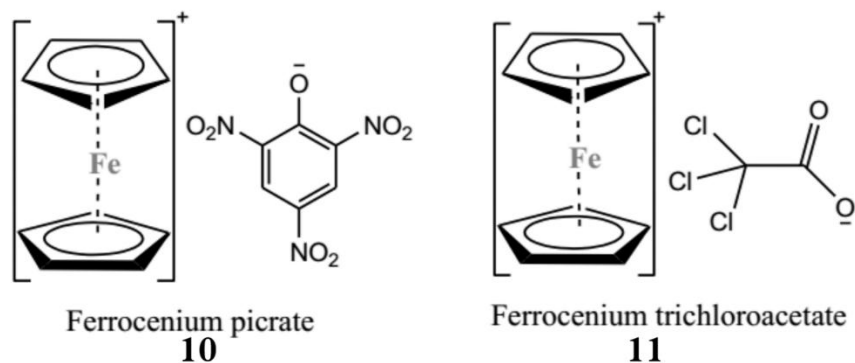


FIGURE 9. - Structures of ferrocenium picrate and ferrocenium trichloroacetate [33]

Iron complexes' amazing cytotoxicity against many cancers has garnered notice. Specific approaches have created a large number of iron complexes with various ligands. The structures of the compounds are changed to circumvent typical restrictions such as inadequate choice, breakdown, restricted dissolution, and bodily harm. However, metal NPs and comparable nanostructures offer great promise in treatments for cancer, involving thermal therapy, imaging with magnetic resonance, and targeted medicine administration. Integration of iron complexes with nanomaterials and multipurpose nanoparticles may be a novel cancer therapy method [32].

6.4 RUTHENIUM COMPLEXES

6.5 PALLADIUM COMPLEXES

In light of the limitations of platinum complexes used as adjuvant therapies for cancer to promote tumor cell death, researchers have sought to enhance methodologies, adjust techniques, or even develop novel concepts to ensure that

chemotherapeutic antitumor agents align with the requirements of modern society. Different anticancer drugs may be made by changing the core metal of platinum-based drugs, including cisplatin. Palladium(II) molecules have coordination chemistry comparable to Pt(II) complexes. Pd(II) complexes have better solubility and mechanical sensitivity. Palladium complexes may exhibit comparable therapeutic efficacy against malignancies as Pt-based molecules, while perhaps offering reduced side effects or facilitating faster development. In recent years, several research groups have investigated palladium-based anticancer medicines as chemotherapeutic treatments [34, 35].

Due to azoles' strong coordination, chelating reagent benzimidazole is being widely explored in physiological models. Flubendazole (FLU), a benzimidazole carbamate, was utilized to make new Pd(II) complexes for cystic echinococcosis in humans and animals. Complexes 16-19 effectively fight MCF7 cancer at IC₅₀ doses of 4.13, 3.53, 3.68, and 3.68 μM , comparable to cisplatin's 3.57 μM [36], as shown in Figure 10.

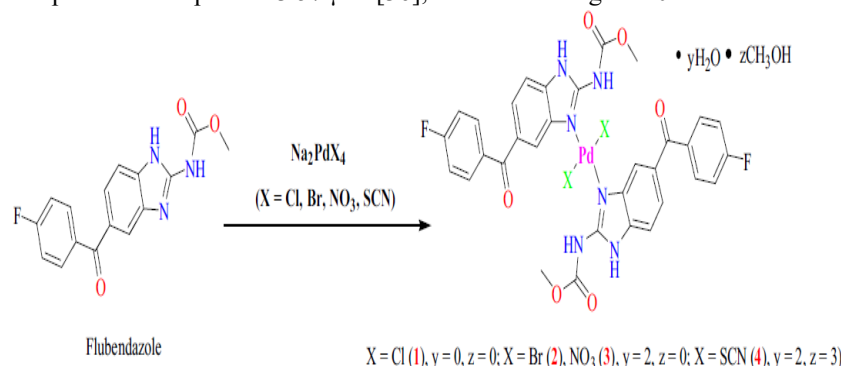


FIGURE 10. - Pd(II)-flubendazole complexes synthesis [36]

6.6 COPPER COMPLEXES

Copper is a biologically vital and important element in biological systems, physiological functions, and cellular components. It contributes to normal human metabolism and the creation of medicinal medicines. Copper serves as a structural and catalytic cofactor, needed for cancerous tumors blood vessels growth and cancer metastasis. Normal cells have a lower uptake of copper compared to numerous cancer cells, especially those associated with hematological malignancies and solid tumors. Copper participates in several essential cellular functions and has shown potential in the creation of novel pharmacological drugs via considerable research on copper complexes as anticancer medicines, exhibiting antitumoral, antimalarial, and antifungal activities [37].

Elesclomol- Cu^{2+} combination inhibits colorectal cancer cells well (SW480). It degrades ATP7A, blocking copper removal. Promotes ferroptosis by increasing ROS and decreasing GSH [38], as shown in Figure 11.

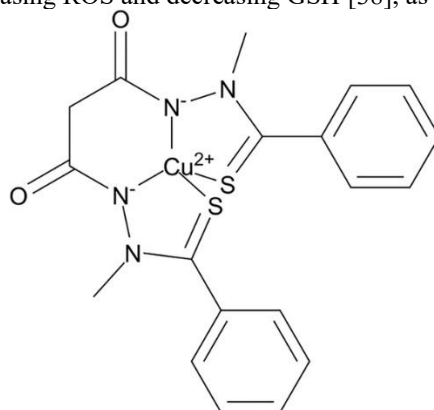
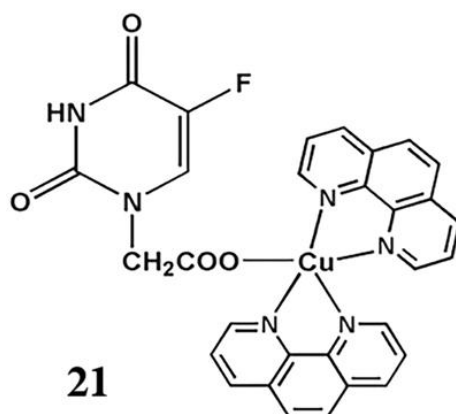


FIGURE 11. - Anticancer of copper metal complex [38]

The intricate compound $[\text{Cu}(\text{phen})_2\text{L1}] \text{BF}_4\text{H}_2\text{O}$ (21). It elicits cytotoxic effects on colon cancer cells (HCT116) and triple-negative breast cancer cells (TNBC). Apoptosis induction in neoplastic cells via DNA interaction and oxidative stress [39], as shown in Figure 12.

**FIGURE 12. - Synthesize Cu-complex 12 [39]**

7. CANCER THERAPY USING METAL COMPLEXES

Because metals have distinctive properties including redox activity, various coordination modes, and reactivity toward organic substrates, metal complexes have garnered attention for cancer treatment. These features are intriguing probes for designing metal complexes that selectively attach to biomolecular targets and influence cellular growth [40]. Table 1 summarizes the in vitro cytotoxic impact of metal-based drugs throughout six years, including their putative mode of action and target. Some metal-based molecules with potential anticancer effects are in research studies, while others are being used for diagnostics and therapy. Recently manufactured metal-based molecules are drug design products that meet certain goals the original chemical could not, and they have a distinct cytotoxicity spectrum. This category includes these compounds.

Table 1. - Cancer prevention properties of metal compounds

Metal complexes	Molecular formula	Proposed mechanism of action	Target enzymes / cell lines / therapeutic indications	IC ₅₀ range (μM)
gold(I) and gold(III) NHC complexes [41]	C ₅₂ H ₄₄ Au ₂ N ₁₂ P ₂ F ₁₂	Induction of apoptosis	TrxR	5.2 ± 1.5 (A549)
	C ₂₆ H ₂₄ AuCl ₂ OF ₆ N ₆ P	Inhibition of TrxR Induction of ROS	A549, HCT-116, HepG2, MCF-7 Chemotherapy of solid tumors	3.6 ± 4.1 (HCT-116) 3.7 ± 2.3 (HepG2) 4.7 ± 0.8 (MCF-7) 5.2 ± 3.0 (A549) 5.9 ± 3.6 (HCT-116) 5.1 ± 3.8 (HepG2) 6.2 ± 1.4 (MCF-7)
Caffeine-based gold(I) NHCs [42]	[Au(Caffeine-2-ylidene) ₂][BF ₄]	Inhibition of protein PARP-1	DNA A2780, A2780R, SKOV3, A549, HEK-293T	0.54–28.4 (A2780) 17.1–49 (A2780R) 0.75–62.7 (SKOV3) 5.9–90.0 (A549) 0.20–84 (HEK-293T)
Ester- and amide-functionalized imidazole NHC complexes [43]	[Im ^a]AgCl	Inhibition of tyrosine by Au(I)-NHC ligands	TrxR	24.65 (A375)
	[Im ^a]AuCl	Targeting TrxR	A375, A549, HCT-15, MCF-7	22.14 (A549)
	[Im ^b]AgCl	Cell cycle arrest	Human colon adenocarcinoma	20.32 (HCT-15)
	[Im ^b]AuCl	G1-phase progression inhibition	Leukemia and breast cancer	21.14 (MCF-7)

	Anticancer activity linked to lipophilic aromatic carbenes	44.64 (A375)
		42.37 (A549)
		41.33 (HCT-15)
		38.53 (MCF-7)
		24.46 (A375)
		16.23 (A549)
		14.11 (HCT-15)
		15.31 (MCF-7)

8. METALS COMPLEX SAFETY ISSUES

The chemotherapeutic and diagnostic properties of metal-based complexes make them significant in cancer therapy. Since the introduction of cisplatin, the primary aim of drug design and research has been to alter the toxicity profile to enhance safety, circumvent resistance, and augment the efficacy of metal complexes. Notwithstanding the advancement in cancer treatment with cisplatin, significant adverse effects such as dose-limiting nephrotoxicity, neurotoxicity, ototoxicity, and emetogenesis continued to occur [44]. This resulted in the production of carboplatin and other platinum-based cytotoxic agents. Regrettably, alternative platinum-based drugs developed to address cisplatin's therapeutic shortcomings exhibited considerable side effects that obstructed regulatory approval. This class comprises Johnson Matthey's JM-11, which has inferior blood and renal clearance compared to cisplatin; NCI/Upjohn's ormaplatin, which exhibits severe and unpredictable cumulative neurotoxicity; and American Cyanamid's zeniplatin, which presents significant nephrotoxicity. Bristol Myers' spiroplatin, associated with unexpected renal failure, has not received marketing approval. Gold(III) complexes have been shown to be detrimental, mostly impacting the skin and mucous membranes in blind clinical experiments. Moreover, elevated tissue ceruloplasmin and copper concentrations have been associated with cancer advancement. Many of these adverse effects are dose-dependent and may be mitigated by structurally altering the metal-based complex to enhance selectivity and reduce effects on healthy cells [45].

9. PLATINUM RESISTANCE LESSONS FROM THE OMICS

Several biological systems withstand cisplatin and other metal-based cytotoxic medicines, and membrane transporter-mediated drug uptake or efflux limits intracellular drug accumulation. Platinum link DNA adducts are eliminated by cancer cells' enhanced DNA repair systems, reducing cytotoxicity, and glutathione and metallothioneins may bind and inactivate platinum complexes before they interact with DNA, increasing resistance during detoxification. Mutations in apoptotic signaling pathways protect tumor cells from DNA damage [46].

Recently developed omics methods have revealed these pathways, and proteomic analysis revealed that cisplatin-resistant cancer cells vary in transcription regulation, cytoskeleton architecture, metabolic pathways, and cell-cycle regulatory proteins. The NGS technologies including mRNA sequencing, miRNA profiling, and SNP analysis have uncovered chemoresistance's molecular basis. Transcriptomics of ovarian cancer cell models revealed approximately 2,500 gene expression variations between cisplatin-sensitive and resistant cells [47]. Integrative studies have linked cisplatin sensitivity to SNP rs11138019, miRNA expression (miR-30a), and membrane efflux transporters, such as ABCD2. Platinum resistance's complex molecular network may improve metal-based anticancer therapies [48], as shown in Figure 13.

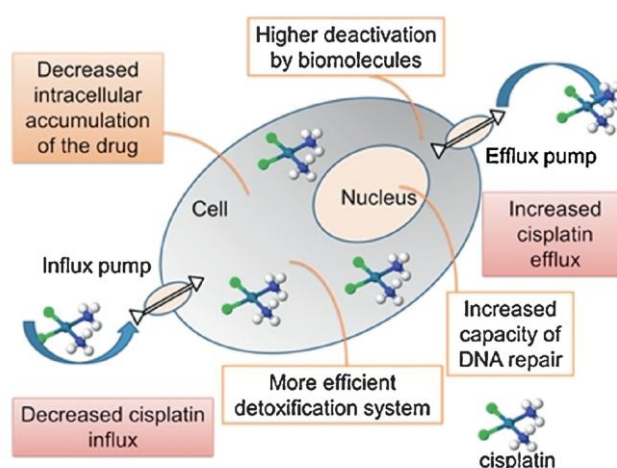


FIGURE 13. - Cancer cells become resistant to cisplatin due to lower inflow and intracellular storage, enhanced enzymatic deactivation, improved DNA repair, and improved outflow [46]

10. COORDINATION COMPOUND STRUCTURE-ACTIVITY RELATIONSHIP (SAR)

SAR studies are needed to understand coordination compounds' anticancer characteristics since structural variables affect cellular uptake, selectivity, and cytotoxicity. The core metal ion's chemistry, oxidation state, and coordination geometry profoundly affect DNA and regulatory protein interactions. Octahedral complexes like Ru(III) and Ga(III) prefer proteins and serum transport systems, whereas square-planar complexes like Pt(II) and Pd(II) generate nucleobase covalent adducts. Nitrogen or sulfur donor atoms boost binding affinity, whereas lipophilicity promotes membrane permeability but risk systemic toxicity. Complex stability and intracellular persistence rely on denticity and ligand rigidity. Systematic SAR modification of coordination environments may build metal complexes with increased anticancer activity, cancer cell selectivity, and tissue damage [49].

11. TARGETED DELIVERY AND TUMOR SELECTIVITY

Tumor selectivity is a critical issue in metal-based anticancer medication development due to systemic toxicity from nonspecific accumulation. Personalized delivery approaches boost malignant cell uptake in current tactics. Many malignancies overexpress ruthenium and gallium complexes, which bind to serum proteins including transferrin and albumin, using endogenous transport pathways. Charge and lipophilicity may be tailored to selectively localize in mitochondria and nuclei. Through acidic pH, redox imbalance, or increased reactive oxygen species, prodrugs activate tumor microenvironment metal complexes. These strategies improve therapeutic effectiveness and lessen side effects. Current anticancer coordination chemistry emphasizes targeted delivery [50, 51].

12. METAL COMPLEXES WITH FERROPTOSIS MECHANISM

Cancer drug resistance may be treated by ferroptosis, a non-apoptotic, iron-dependent cell death. Iron and copper complexes promote lipid peroxidation and reactive oxygen species generation, causing ferroptosis. Cell membrane oxidation is irreversible due to glutathione depletion and antioxidant defense system inhibition. Apoptosis requires caspase activation, while ferroptosis does not, allowing metal complexes to avoid platinum-based chemotherapy resistance. Copper complexes like elesclomol–Cu systems change cellular redox balance, causing ferroptotic effects. Thus, creating coordination compounds that trigger ferroptosis is a novel and effective treatment for aggressive and resistant malignancies [52].

13. CONCLUSION

Coordination compounds are essential for anticancer drug development because metal ions regulate geometry, redox activity, and biomolecular interaction. Platinum drugs are toxic and resistant yet set clinical standards. Iron creates reactive oxygen species, copper targets topoisomerases, gallium inhibits iron metabolism, and ruthenium uses protein transport routes. These differences explain cytotoxicity and justify metal substitution approaches. This work indicates that the coordination environment links cellular targets, metal oxidation state, and ligand donor atoms to biological effects. We will research combination treatment, combine coordination complexes with nanocarriers, and broaden in vivo assessment to suit new needs. A detailed comparison with biological models is suggested. Positively, assay variability hinders study comparisons. Standardized testing and structural activity mapping could accelerate metal-based anticancer medication development and improve results.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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