ROLE OF TRANSITION METAL COMPLEXES IN ANTI CANCER BATTLE

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Abstract. *Cancer is a severe health issue that affects people all over the world. The wailing of most cancers affected patients is the primary motivation behind the development of new therapeutic agents and remedies of cancers. Cisplatin, a platinum based anticancer agent, is one of the most potential and commonly used medicines for the treatment of many solid cancers. However, the severe toxic concomitant effects exerted by widely used platinum based complexes have encouraged researchers to apply molecular modeling and engineering to synthesize novel transition metal-based anti-tumor drugs with lowered toxicity. The transition metal complexes that are promising anticancer agents are discussed in depth in this article, with a focus on cisplatin and associated compounds. Detailed metalated DNA structures with mechanisms of action involving intercalation are presented and discussed in light of antitumor activities.*

Keywords: *DNA binding, cancer, chemotherapy, transition metals, platinum, ruthenium*

1.INTRODUCTION

Metals and their salts have been employed for therapeutic purposes since the ancient days. Metals in medicine comprise the administration of metal ions into a living organism either by fortuitously or by intention. Metals, on the other hand, are essential biological elements that nature has chosen to carry out many essential biochemical activities in living organisms [1]. The distinctive features of transition metal ions have been exploited to design new medications in the field of inorganic medicinal chemistry.

Cisplatin with no organic units is one of the most widely used chemotherapeutic agent in clinical applications, began the documented history of transition metal-based anticancer drugs [2]. However, *cisplatin* and its analogs can binds with a large range of biomolecules other than their primary biological target: DNA.

Therefore despite of its clinical success there are various toxic side effects associated with *cisplatin*, such as nausea, nephrotoxicity and neurotoxicity [3]. Since then, an increasing number of platinum based metallo-drugs were synthesized in an endeavor to mitigate those shortcomings, albeit
many complexes have comparable mode of action and resistance indices [4].

Not only platinum, many other transition metal complexes have received considerable interest as a replacement of *cisplatin*, due to their propitious cytotoxic and promising anticancer profiles. In this regard Pd, Ru, Rh, Ir, Au, Cu and Os complexes are the potential members in cancer chemotherapy [5-6].
The activities of transition metals in cancer therapy and recent breakthroughs, as well as innovative strategies for building novel metal complexes as anti-cancer medications, are the topic of this article.

2. TRANSITION METAL BASED CHEMO-THERAPEUTIC ANTICANCER AGENTS

2.1 Platinum

The discovery of *cisplatin* by Barnett Rosenberg and colleagues in late 1960 while exploring the effect of electric fields on bacterial cell division was a watershed moment in the history of inorganic complex drug development in cancer treatments. As a result of *cisplatin's* clinical success, a surge of interest in platinum-based prospective anticancer medicines has emerged, with zillions of analogues being produced and screened for properties that would enhance its therapeutic profile.

Only a few compounds have made it to clinical trials, and more than half of them have been rejected. *Cisplatin*, *carboplatin*, and *oxaliplatin* are the three platinum-based anticancer medicines that have been approved for clinical usage worldwide to date. *Nedaplatin* (Japan), *miriplatin* (Japan), *lobaplatin* (China), and *heptaplatin* (Korea) are four more platinum-containing medicines that have been approved for use in certain countries [7].

Some platinum complexes are still under clinical trials, including those developed for oral administration, like Pt (IV) anticancer agents with the hope that such complexes will be able to meet the demand for novel antitumor drugs.

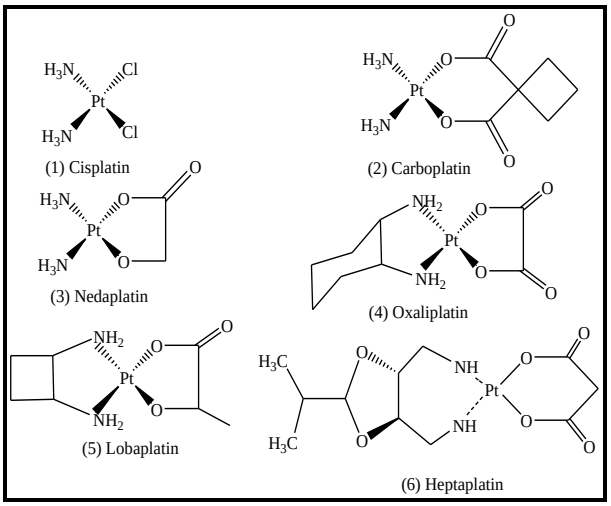

Fig. 1: Chemical structures of some selected platinum drugs

2.2 The proposed mechanism of action

The generalized mechanism of action consists of four discrete chronological processes: (i) cellular uptake, (ii) aquation/activation, (iii) DNA platination, and (iv) cellular processing of drug inducing to apoptosis. *Cisplatin* is given to patients intravenously as a sterile salt solution, and the medicine is carried throughout the body by the bloodstream.

The high chloride concentration in blood serum (≈100 mM) suppresses the aquation of *cisplatin* i.e. substitution of chloride ions by water molecules, leaving *cisplatin* unchanged and neutral. Therefore, *cisplatin* arrives at the membrane of cancer cells mainly as a neutral molecule. The richest protein in human blood plasma, serum albumin, can bind strongly to *cisplatin*, causing a large amount of the drug to be deactivated. In fact 65 to 95% of *cisplatin* can bind with plasma protein via sulphur from the thiol groups of amino acids like cysteine [8].

The remaining drug, *cisplatin*, enters cells either via passive diffusion through the plasma membrane or active transport arbitrated by membrane proteins.

Lower intracellular chloride ion concentration (2-30 mM) promotes the synthesis of aqua species from *cisplatin* by replacing one or both chloride leaving group(s) with a water molecule(s) inside the cell.

As a result, cationic aquatic products such as *cis*-$[Pt(H_2O)Cl(NH_3)_2]^+$ and *cis*-$[Pt(H_2O)_2(NH_3)_2]^{2+}$ are formed. The first aquation process, which produces *cis*-$[Pt(H_2O)Cl(NH_3)_2]^+$, has a half-life of 2 hrs. Because water is a better leaving group than chloride, these hydrolyzed products are powerful electrophiles that can react with any nucleophilic centre of biomolecules.

Furthermore, the platinum complex's positive charge attracts it to the negatively charged nuclear DNA, where it makes coordinate bonds with the nitrogen groups of the DNA bases.

Nonetheless, *in vitro* investigations have shown that monoaquated complexes are more reactive to DNA binding than diaquated complexes [9].

Due to the chelating leaving groups, opposite to the firmly attached am(m)ine groups, *carboplatin* and *oxaliplatin* are substantially more stable to aquation.

As a result, when compared to *cisplatin*, such chelating ligands imparts a longer half-life in terms of aquation, ranging from weeks to months.

The active drug i.e. aquatic *cisplatin* not only form nuclear DNA (N-donor) adducts, but also can interact with proteins and many other biomolecules. Especially soft S-donor biomolecules are abundant in body as amino acids (L-methionine, L-cysteine), proteins (albumin), and peptides (glutathione), which have very high interest to attached to soft Pt (II) metal center following HSAB theory.

The circulation of Pt (II) drugs in the body, the therapeutic efficacy, the mechanism of metabolism, and the serious toxic side effects are all manifested by its reactivity towards S-containing biomolecules [10]. This affinity of sulphur for Pt (II), has also led to the development of so-called 'rescue-agents' that reduce the negative effects of Pt therapy without lowering its anticancer effectiveness. The protective action of these chemicals is due to the blocking or reversal of Pt-S adducts in proteins, which induce unfavorable toxic consequences.

However, the main target of *cisplatin* is DNA. Only a small percentage of cellular *cisplatin* binds to nuclear DNA, destroying the double helix structure.

Therefore, DNA interaction with *cisplatin* causes biological activities that can result in cell death. It is well established that among the different possible routes of *cisplatin*-DNA interaction, the most important one is the intrastrand cross-linking by two adjacent guanines (G) from single DNA strand.

The N7 atom of purines in DNA is covalently bonded to

Pt (II) an extent about 65%
1,2-intrastrand d(GpG), 25%
1,2-d(ApG), and ~5–10%
d(GpNpG) 1,3- intra-strand

(one DNA strand) crosslinks (p = linking phosphate group, dG = 2'deoxyguanosine and 'N' is any intervening nucleotide) [11].

Mono-functional binding, inter-strand crosslinks (two DNA strands), and DNA-protein crosslinks are examples of other binding patterns.

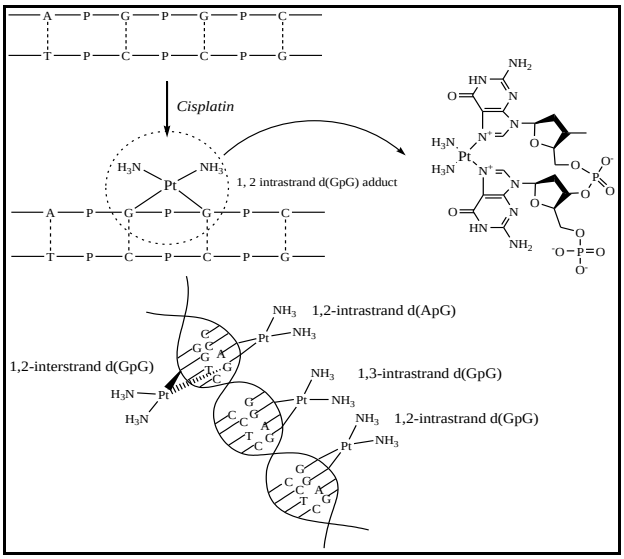

Fig. 2: Schematic representation of DNA-*cisplatin* interactions and types of crosslinks

The following is the decreasing order of reactivity of DNA bases: guanine-N7 >> adenine-N7 > cytosine-N3. As a result, the N7 position of guanine, which is exposed in the major groove, is the most nucleophilic site on DNA, and these sites are preferentially bonded with platinum. The intrastrand crosslinks deforms the structure of the DNA duplex and change its interactions with proteins, thus preventing the replication and transcription of DNA, as well as the DNA repair mechanisms. That crosslink creates a significant kink in the DNA helix axis, ranging from 30 to 80º depending on the experimental conditions, and gives DNA a different shape than non-platinated DNA. Such bending sterically prevents the DNA-polymerase enzyme and probably interrupts the polymerase activity. The structure–specific recognition protein 1 (SSRP1) comprises a high mobility group (HMG) DNA-binding motif and binds to particular *cisplatin*-DNA adducts with great affinity. HMG-domain proteins recognise 1,2-intrastrand adducts generated by *cisplatin* on DNA but not those created by *transplatin*, implying that 1,2-intrastrand cross-links are the predominant DNA adducts involved in *cisplatin's* mechanism of action. They can prevent DNA repair enzymes from recognising *cisplatin*-DNA adducts, regulate cell cycle events after DNA damage, and cause cell death (apoptosis).

In response to the formation of a *cisplatin*-DNA adduct, cells activate various repair pathways, the most important of which is the nucleotide excision repair pathway, which detects and repairs *cisplatin* lesions. To remove *cisplatin* damages, two major nucleotide excision repair routes, transcription-coupled repair (TCR) and global repair (GR), have been established [12].

Despite its efficacy against some cancers, *cisplatin's* curative potential is limited due to acquired drug resistance and significant adverse effects. Reduced drug import, increased drug efflux, multiple cellular self-defence adaptations, inactivation by proteins (e.g., metallothionein), cytosolic detoxification (primarily by glutathione), and increased DNA damage repair or tolerance are all factors that contribute to *cisplatin* resistance in tumour cells (reduced accumulation of the compound). *Cisplatin* is also linked to nausea, cardiotoxicity, hepatotoxicity, neurotoxicity, ototoxicity, peripheral neuropathy, myelosuppression, and nephrotoxicity, among other adverse side effects. Furthermore, *cisplatin* can cause damage to non-targeted tissues, suggesting that the drugs' long-term erratic effects are one of the causes of mortality among cancer survivors later in life.

The hunt for new anticancer platinum complexes with improved efficacy has been stimulated by these pharmacological shortcomings. *Carboplatin* was the first derivative (modified leaving group) with a more tolerable toxicological profile, although it also has *cisplatin* cross-resistance. *Carboplatin* alone, on the other hand, has a reduced nephrotoxicity due to its slower rate of conversion to active platinum aquo species. *Oxaliplatin* can overcome *cisplatin* resistance when combined with modified non-leaving spectator ligands.

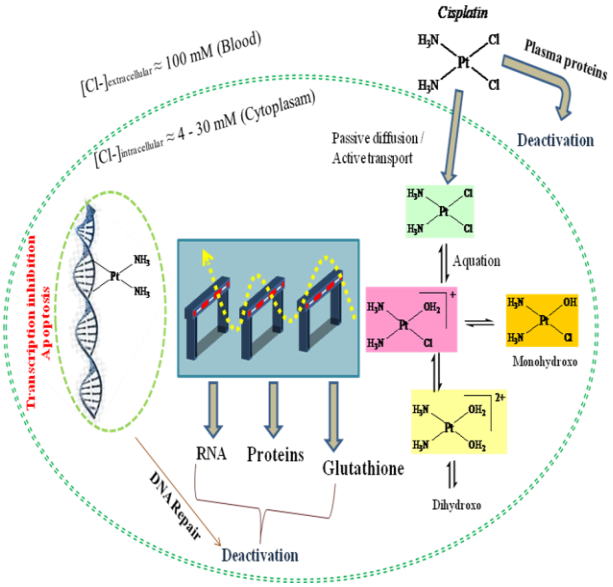

Fig. 3: The plausible *in vivo* reactivity of *cis*-DDP and hurdles faced by drugs before reaching DNA.

2.3 Trans platinum (II) complexes

Platinum(II) complexes with trans geometry were once thought to be ineffective. *Transplatin's* inactivity is hypothesized to be caused by two main causes. Because *trans* chloro species are kinetically more reactive than their analogous *cis* isomers, unwanted reactions could have an impact in the lack of therapeutic activity, at partly. The failure to produce significant cytotoxic DNA lesions is due to the stereochemical inaccessibility of trans isomers to the 1,2-intrastrand cross-link between neighbouring purines. In the 1990s, however, the apathy regarding *trans*-platinum complexes faded. Several trans-platinum complexes having significant anticancer efficacy in vitro against diverse tumour cells, including *cisplatin*-resistant cell lines, were produced. Some transplatin derivatives containing planar amines (e.g. pyridine, quinoline, thiazole, imidazole), iminoethers, aliphatic amines (isopropanamine, n-butanamine, dimethylamine), and nonplanar heterocyclic ligands (pipreridine, piperazine), as well as polynuclear complexes, have demonstrated positive sensitivity in vivo. In certain cases, these compounds are as hazardous as or more toxic than cisplatin, one of the most effective anticancer drugs. Furthermore, several trans-platinum complexes have a high level of cytotoxicity against cisplatin-resistant tumour cells. These complexes could be the key to overcoming cisplatin resistance, whether intrinsic or acquired, in the near future [13].

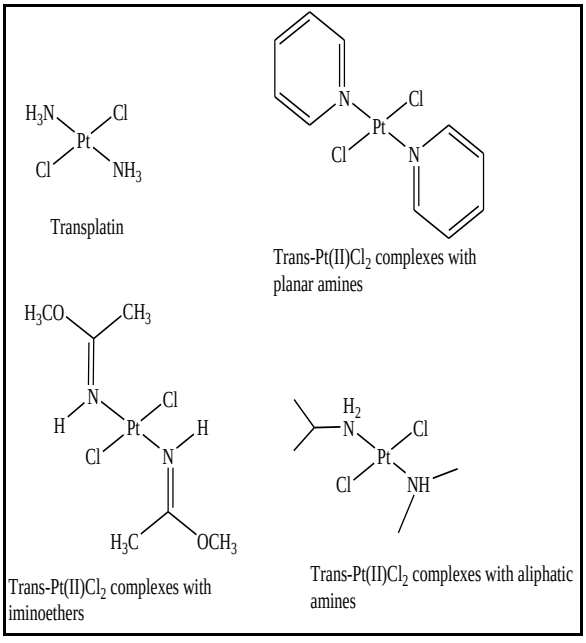

Fig. 4: Chemical structures of some antitumor-active *trans* complexes

2.4 Pt (IV) coordination complexes as prodrug

The improved stability and bioreductive activation of platinum (IV) anticancer drugs contribute to many potential advantages over platinum(II) in the treatments of anticancer. Moreover, Platinum (IV)-based anticancer drugs are octahedral and less susceptible to substitution reactions, thereby arrived at their cellular target with a greater proportion, therefore lowering adverse effects and drug degradation. Some platinum (IV) complexes have a low toxicity profile, do not show cross-resistance with cisplatin, and can be administered orally. Platinum (II)-based anticancer drugs, on the other hand, are associated with high reactivity and, as a result, low biological stability. *In vivo*, reductive elimination to platinum (II), activates the octahedral platinum (IV) complexes, making them kinetically more labile platinum (II) complexes. The platinum (II) complexes can then bind to DNA, generating intrastrand and/or interstrand adducts, which prevent replication and transcription [14].

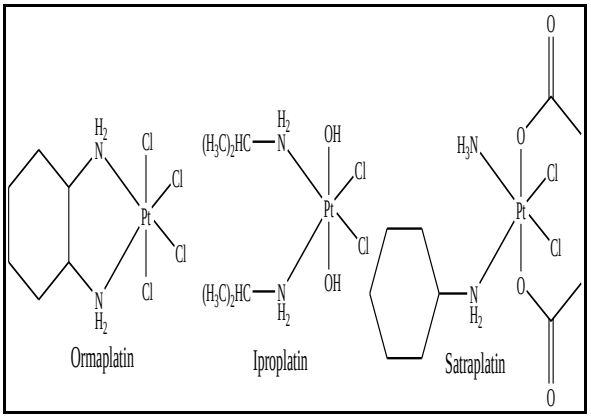

Fig. 5: Chemical structures of some platinum(IV) compounds that have entered clinical trials

2.5 Palladium

Palladium and platinum share a striking resemblance in coordination chemistry due to their most common oxidation state, +II, in which they exhibit a diamagnetic d^8 electronic configuration. Pd (II) and Pt (II) complexes are usually square planar. Studies of Pd (II) complexes as antitumour drugs have been proposed based on the structural and thermodynamic similarities between platinum(II) and palladium (II) complexes. The ligand-exchange kinetics is an essential component that may explain why platinum is suitable. Pd (II) complexes are generally thermodynamically and kinetically less stable than Pt (II) complexes. Pd (II) compounds exchange ligands at a rate of 10^4–10^5 times faster than their platinum

analogues. Palladium complexes easily dissociate *in vivo*, resulting in highly reactive species incapable of reaching their pharmacological targets. Furthermore, some palladium complexes can undergo to form an inactive trans-conformation. The equivalent *cis*-$[Pd(NH_3)_2Cl_2]$ has little antitumoral efficacy when compared to *cisplatin*.

Owing to higher reactivity palladium complexes, if an antitumour palladium drug is to be designed, a strongly coordinated nitrogen ligand and a suitable leaving group must be used to make it inert. If such groups are relatively inert, the drug can maintain its structural integrity *in vivo* for an extended period of time.

Palladium complexes comprising aromatic N- and N,N-containing ligands, such as derivatives of pyridine, quinoline, pyrazole, and 1,10-phenanthroline, as well as N,S-chelating ligands, such as derivatives of thiosemicarbazones and dithiocarbamates, have shown promising anticancer activities [15].

The cytostatic and cytotoxic actions of Pd (II) complexes have been compared to those of cisplatin in several investigations. Furthermore, Pd (II) complexes appear to have higher solubility and less nephrotoxicity (attributed by the inability of proteins in renal tubules to replace strongly bonded chelating ligands of Pd (II) with sulphydryl group), making them more viable antitumour agents.

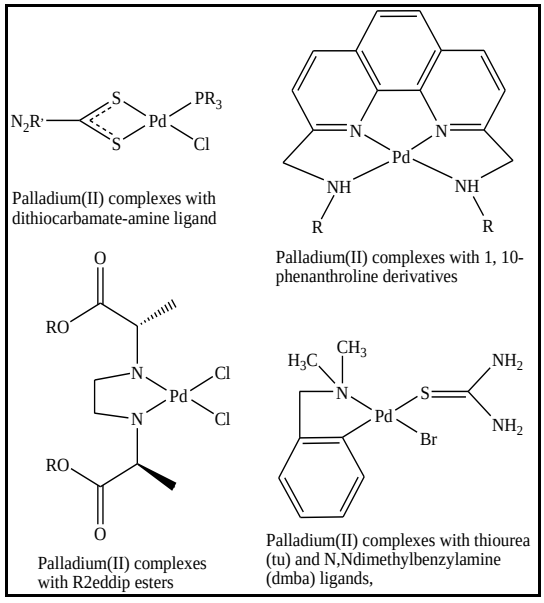

Fig. 6: Chemical structures of various antitumor-active palladium complexes

2.6 Ruthenium

In the recent decade, ruthenium anticancer medicines have received a lot of attention, and a few of them have even advanced into clinical trials. Unlike platinum-based therapeutics, ruthenium complexes are usually found to be less toxic and capable of overcoming platinum-induced resistance in tumour cells. Ru (III) and Ru (II) have interchangeable oxidation states, allowing for a wide range of ligand combinations, and ruthenium compounds' intrinsic fluorescent characteristics and kinetic inertness are extremely valuable in biological research. The ability of Ru (III) to mimic iron binding serum protein, decreasing free plasma ruthenium and increasing the concentration that reaches cancer cells when compared to healthy cells, is largely responsible for probable anticancer activity of ruthenium compounds.

Moreover the biological activities of ruthenium compounds are attributed by the transportation to tumour cells by transferrin and following reduction to more labile and reactive Ru (II) analogues, a process more pronounced in the hypoxic environment of solid tumour cells, thus offering selectivity and subsequent lower toxicity.

NAMI-A and KP1019 are two leading ruthenium based drug candidates possessing antitumor activities. The anticancer activities of the ruthenium (III)-containing NAMI-A complex (imH)[*trans*-$RuCl_4$(DMSO-S)(im)], where im = imidazole and DMSO = dimethylsulfoxide, have been intensively investigated. Clarke and coworkers developed NAMI-A (New Anti-tumour Metastasis Inhibitor, and A stands for the first of a series) in the 1980s, which inhibits cell proliferation and metastasis [16].

KP1019, on the other hand, is a *trans*-$[RuCl_4(Ind)_2]$IndH that causes apoptosis via the mitochondrial pathway.

Organoruthenium compounds have recently been exploited to imitate the structure of staurosporine (a natural protein kinase inhibitor) in an attempt to target the BRAF serine/threonine kinase, which is prevalent in many human malignancies.

Despite being substitutionally very inert, organometallic half-sandwiched (η^6-arene)Ru(II) compounds containing imidazole, sulphoxide, chelating amino acidato, and diamine or diimine ligands are very cytotoxic against various human tumor cell lines [17].

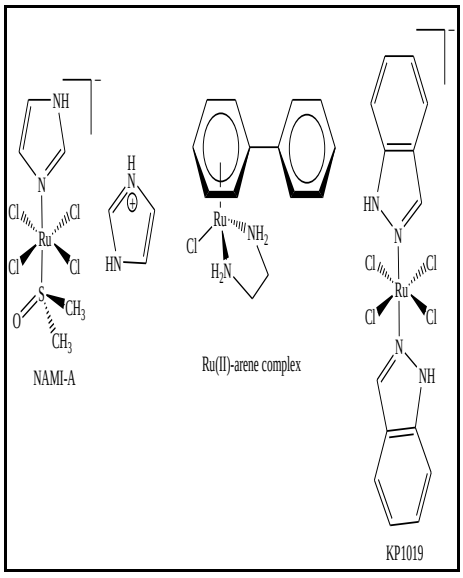

Fig. 7: Structures of some ruthenium complexes

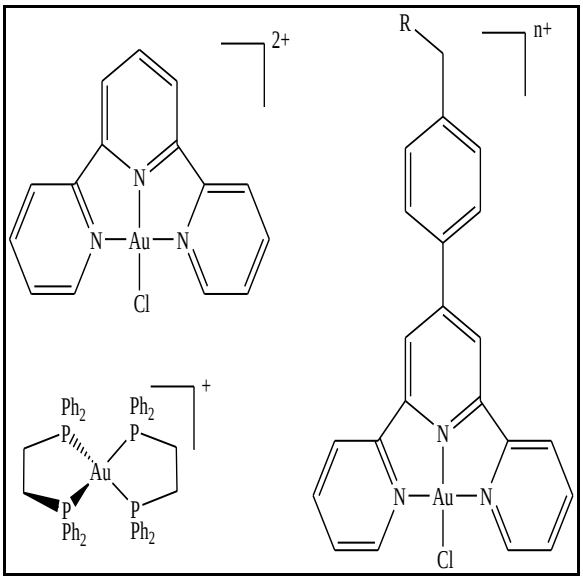

Fig. 8: The structure of some gold complexes

2.7 Gold

Clinical applications of gold complexes (e.g., Auranofin) were mainly confined to the treatment of rheumatoid arthritis, due to their immunosuppressive and anti-inflammatory properties. Gold (I) and gold (III) complexes have gained a lot of interest among non-platinum anticancer drugs due to their significant activity, which is usually achieved by establishing non-cisplatin-like mechanisms of action as the target location of such complexes is mitochondria, not DNA. Recent research has shown that macrocyclic gold (III) complexes with a quinoxaline moiety increase DNA intercalation and subsequent cytotoxicity [18].

Moreover, gold (III) and platinum (II) have the similar d^8 electronic configuration, thus reflects comparable physicochemical and geometrical properties. The correlation between cancer and inflammation, along with the aforesaid chemical features made gold complexes suitable applicants for choosing as anticancer compounds. Many gold complexes in different oxidation states have displayed antiproliferative effects including phosphine complexes.

In A2780/S cell lines, the 2,2':6',2''-terpyridine gold (III) complex $[Au(terpy)Cl]Cl_2$ has exhibited significant activity [19]. Concomitant use of gold nanoparticles with radiotherapy or chemotherapy enhances DNA damage and makes the treatment more targets specific.

2.8 Copper

The essential trace element-copper plays central role in various physiological cellular processes. However, its high redox activity and affinity for binding sites that could otherwise be occupied by other metals makes copper cytoxic. Moreover, the process of angiogenesis, proliferation, and migration of endothelial cells requires copper. Increased copper levels, on the other hand, promote tumour growth and metastasis.

Copper is known to form a wide range of coordination complexes with the oxidation states Cu (I) and Cu (II), as well as few copper (III) compounds. Copper's coordination chemistry is mostly confined to Cu (II) derivatives and a few Cu (I) compounds. Copper (I/II) complexes are reactive, labile, and prone to form deformed coordination geometries. Copper complexes can interact with DNA *via* surface association or intercalation, particularly bind to the N7 reactive center on purine residues of DNA, significantly increase reactive oxygen species (ROS) production, and trigger DNA damage with proliferative arrest. Several copper-based anticancer agents have been reported to have distinct mechanism from current platinum drugs, and might overcome drug resistance.

The development of copper complexes as anticancer drugs is based on differences in tumour cell metabolism and variations in normal and tumour cell responses to copper. Various Cu complexes produced with different sets of N, S, or O ligands have shown substantial cytotoxicity and anticancer activity [20].

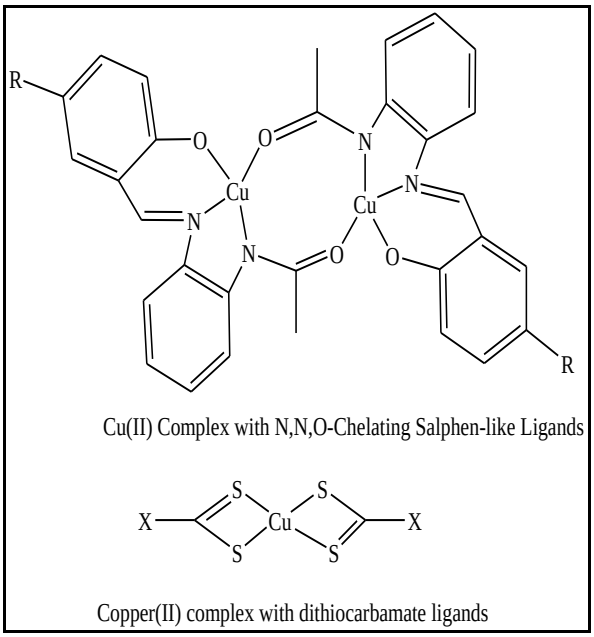

Fig. 9: The structure of some copper complexes with anticancer activity

2.9 Iridium

Immediately after the accidental discovery of *cisplatin*, the iridium complexes were first screened for antitumor activity. $5d^8$ Ir (I) compounds with square-planar geometry comparable to cisplatin, such as [Ir(acac)(cod)] and dinuclear $[IrCl(cod)]_2$, were explored for their anticancer effects in the 1970s.

Organo-Ir (III) anticancer drugs have shown significant antiproliferative efficacy against a variety of cancer cells in recent years [21]. Iridium (III) is third row low spin d^6 metal ion and it is often considered as one of the most inert ion in the biological system. The aquated iridium (III) ion, $[Ir(H_2O)_6^{3+}]$ has an extremely low water exchange rate constant k_{ex} 10^{-10} s^{-1}, which does not make it promising. However, when three of the facial water molecules of $[Ir(H_2O)_6^{3+}$ were substituted with a cyclopentadienyl ligand (Cp), the residual bonded water molecules had a 14 times higher exchange rate than those of $Ir(H_2O)_6^{3+}$. Because of the increased water exchange rates for bonded Cp ligands, many Ir(III) 'half-sandwich' molecules containing a Cp ligand have recently been prepared and screened for anticancer activities [22].

As a result, inertness and stability are the guiding criteria for rational drug modelling, allowing the complex to reach its target site without being altered. Furthermore, the associated ligands could play a function in target-site recognition.

Cancer cells are preferentially damaged over nontumorigenic cells by dual-targeting organometallic half-sandwich iridium(III) anticancer complexes, which have no cross-resistance with *cisplatin* [23]. Furthermore, by triggering nuclear DNA damage and mitochondrial malfunction via synchronous ROS production, these complexes promote cell apoptosis. In summary, iridium complexes have a low toxicity profile and are water resistant.

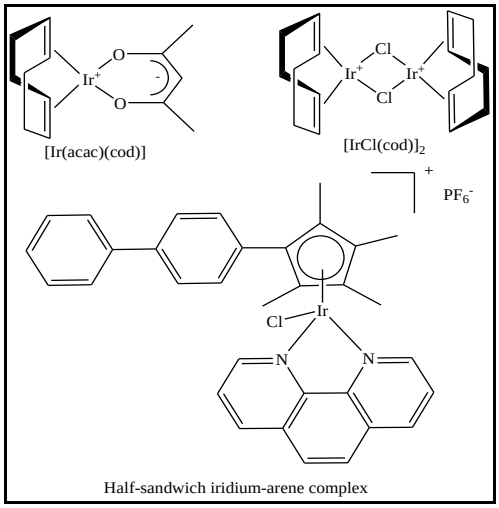

Fig. 10: The structure of some iridium complexes with anticancer activity

2.10 Rhodium

Like iridium (III), rhodium (III) metal centers are also kinetically inert for drug development and to show biological activity. In fact, rhodium (III) complexes with ammonia or imidazole ligands that are isostructural to antitumour-active ruthenium (III) compounds, such as KP-1019, undergo exchange reactions more slowly and are biologically inactive than their ruthenium (III) analogues. A series of rational approaches have been designed to enhance the biological activity of rhodium complexes. The first is to introduce one or more ligands with a strong *trans* effect to increase the kinetic lability of the opposite ligand, such as chloride. For example, the "half-sandwich" (three-legged piano–stool complexes have a pseudo-octahedral geometry at the metal centre, with three monodentate ligands or one bidentate and one monodentate ligand occupying the three legs) rhodium complexes with monodentate halide ligand can contribute a kinetically labile site for substitution reactions for target molecules, which is responsible for their observed anti-cancer activity [24].

A second strategy is to introduce cytotoxic ligands that can potentially participate in specific interactions with different biomolecules. This could explain the excellent cytotoxic activities of several rhodium complexes containing polypyridyl ligands through formation of stable intercalative binding with DNA or groove binding. The use of metal complexes as structurally inert scaffolding for enzyme inhibitors is a third approach. The spatial distribution of the substituents around the metal core is more flexible in this regard, increasing the possibility of constructing complex three-dimensional enzyme inhibitor complexes [25]. Metal does not play a direct part in the inhibition here; it just allows the substituents to be distributed spatially around the metal centre. Protein kinases, which are known to regulate many aspects of cellular physiology, are the preferred targets of such complexes. Furthermore, inhibitors are very selective because organic ligands are arranged in such a way that they occupy the open space at the active site while simultaneously interacting with hydrogen bonds.

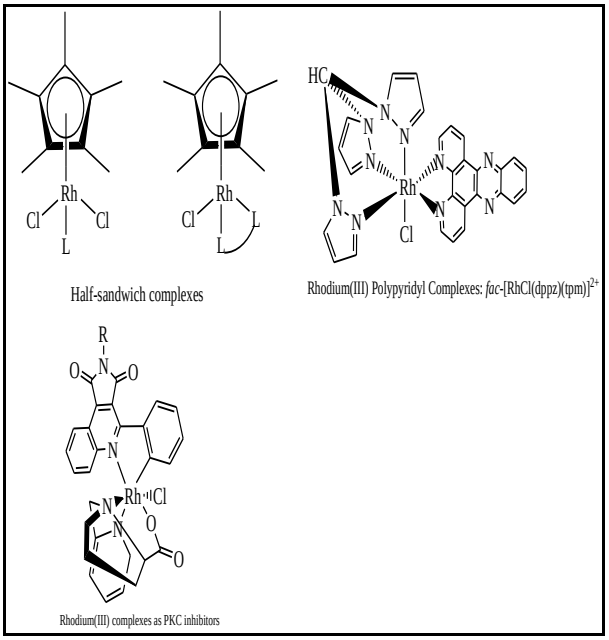

Fig. 11: The structure of some rhodium complexes with anticancer activity

2.11 Osmium

Osmium is the heavier congener of ruthenium, therefore it is logical to assume that osmium-containing complexes will have anti-cancer characteristics similar to ruthenium-containing complexes. Osmium, on the other hand, has various advantages over ruthenium, including a preference for higher oxidation states, slower ligand exchange kinetics, and stronger -back-donation from lower oxidation states. In addition, the three-dimensional spatial arrangement of osmium compounds (usually CN 6) complements molecular targets like proteins and DNA sites in a sequence-specific manner. Osmium compounds in various oxidation states are said to have a key role in biological redox regulation in cancer cells. Os (II/III)-based anticancer complexes, such as Os-NAMI-A, were developed as congeners of the well-studied Ru (II/III) complexes. The selective anti-proliferative actions of analogue osmium compounds are comparable to or greater than that of parent ruthenium structures [26]. FY26, an organometallic arene-Os (II)-azopyridine molecule with anticancer activity comparable to cisplatin and carboplatin and a novel anticancer mechanism of action, has been discovered. FY26 is a powerful prodrug that can be catalytically activated by cellular glutathione (GSH) and significantly raises intracellular reactive oxygen species (ROS) levels in cancer cells. Excess ROS can cause cell death by activating pathways that lead to apoptosis, necrosis, and autophagy, causing more toxicity towards cancer cells than normal cells.

Other Os (II) polypyridyl complexes have shown biological activity, however due to lack of labile ligands, they bind to intracellular targets via non-covalent interactions.

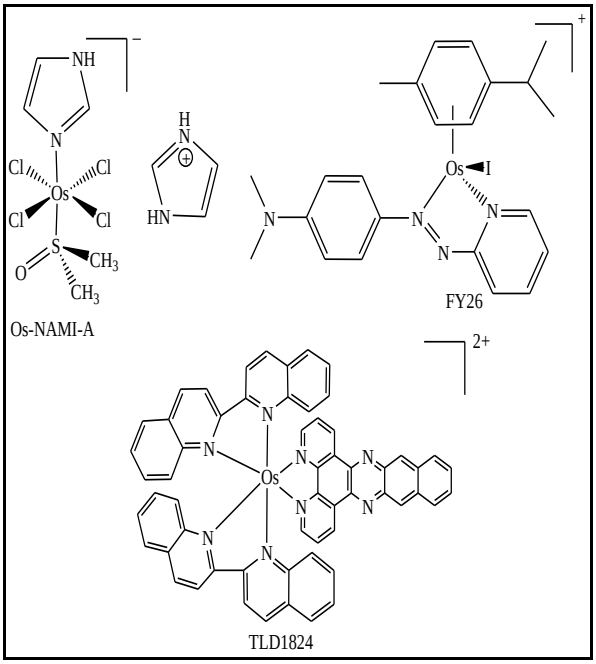

Fig. 12: The structure of some osmium-based anticancer agents

3. CONCLUSION

The success of cisplatin has prompted scientists to synthesize a huge number of metal complexes and examine them as antitumor drugs, with the primary goal of overcoming the limitations of currently used metallodrugs. This paper discusses a number of transition metal-based promising therapeutic agents, all of which are cytotoxic and exhibit DNA intercalation. Moreover, the prior structural and charge requirements for an active anticancer complex have been questioned, resulting in the appearance of a large variety of potential metal complex candidates. Metal complexes can also provide a wide range of structural variety and the possibility of ligand exchange, allowing for host-guest interaction, coordinated bonding with cellular biological targets, and redox activity focused on the metal or the ligands.

Transition metal complexes other than Pt with different modes of action and/or cellular targets can be used in combination with existing therapies like *cisplatin* to alleviate some of the clinical drawbacks. The unique features of metal complexes with various biological targets and modes of action can be utilized to develop novel drugs.

The numerous combinations of transition metal and ligand have resulted in a diverse range of anticancer complexes, each with its own mechanism of action.

The ongoing growth of this library holds considerable promise for the discovery of novel transition metal-based compounds that can outperform current metallodrugs and deliver more effective chemotherapeutic agents.

4. ACKNOWLEDGEMENTS

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Graphical Abstract