Review Article

Metal Ion Complex -Potential Anticancer Drug- A Review

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ABSTRACT

Many metal-containing compounds have been utilized throughout history to treat a wide variety of disorders. In medicinal chemistry —traditionally dominated by organic chemistry— metal complexes have gained favor as diagnostic tools and anticancer agents. Cancer is the second most frequent cause of death in the world. The discovery of antitumor activity of cisplatin began a search for other metal complexes with cytotoxic properties against cancer cells. Organo-metallic compounds have been used in medicine for centuries. Metal complexes play essential role in pharmaceutical industry and in agriculture. The metallo-elements present in trace quantities play vital roles at the molecular level in living system. The transition metal ions are responsible for proper functioning of different enzymes. Transition metals represent the D block element which includes groups 3 - 12 on the periodic table. Their d shells are in process of filling. The partially filled d orbital in transition metals impart interesting electronic properties that can act as suitable probes in the design of anticancer agents. This property of transition metals resulted in the foundation of coordination complexes. In 1960 the anti-tumor activity of an inorganic complex cis-diammine-dichloroplatinum (II) (cisplatin) was discovered. Cisplatin has developed into one of the most frequently used and most effective drug for treatment of solid carcinomas. This review focuses on recent advances in development of platinum, gold, copper and ruthenium complexes as anticancer agents.

Keywords: Anticancer drugs, metal ion complex, transition metal compound

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INTRODUCTION

Cancer is one of the most widespread and feared diseases in the Western world today feared largely because it is known to be difficult to cure. The main reason for this difficulty is that cancer results from the uncontrolled multiplication of subtly modified normal human cells. One of the main methods of modern cancer treatment is drug therapy. The drugs used to combat cancer belong to one of two broad categories. The first is cytotoxic (cell killing) drugs and the second is cytostatic (cell stabilizing drugs). Both categories lead to a reduction in the size of the tumor because cancer cells have such a high mortality rate that simply preventing them from dividing will lead to a reduction in the population [1]. The global research efforts in this field are focused both on the development of new potent antineoplastic agents and on the discovery of novel biological targets. The platinum metal containing cisplatin is today among the most widely used cytotoxic drug for cancer treatment in the clinics. Medicinal applications of metals can be traced back almost 5000 years [2]. Metal complexes play essential role in pharmaceutical industry and in agriculture. The metallo-elements present in trace quantities play vital roles at the molecular level in living system. The transition metal ions are responsible for proper functioning of different enzymes. The activity of biometals is attained through the formation of complexes with different bio-ligands and the mode of biological action for complexes depends upon the thermodynamic and kinetic properties. The lipophilicity of the drug is increased through the formation of chelates and drug action is significantly increased due to effective

permeability of the drug into the site of action [3].

A characteristic of metal ions is that they easily lose electrons from the familiar elemental or metallic state to form positively charged ions which tend to be soluble in biological fluids. It is in this cationic form that metal plays their role in biology. Metals are electron deficient, most biological molecules such as simple ions and molecules like Cl^-, $(HPO_4)^{2-}$, OH , and H_2O , amino acid, peptides, phosphates like His, Met, Cys, glutathione, metallothionene, and ATP, proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind to and interact with biological molecules [4, 5].

Metal complexes are also known as coordination complex. Metal complex is a structure consisting of a central atom (or) ion (metal) bonded with anions (ligands). Compounds that contain a coordination complex are called coordination compounds [3].

Metal-containing compounds offer many advantages over conventional carbon-based compounds in the development of new medicinal compounds. These advantages are due to their ability to coordinate ligands in a three dimensional configuration, thus allowing functionalization of groups that can be tailored to defined molecular targets. The partially filled *d* orbitals in transition metals impart interesting electronic properties that can act as suitable probes in the design of anticancer agents. The oxidation state of a metal is also an important consideration in the design of coordination compounds, given that it allows the participation in biological redox chemistry and plays an influential role in optimal dose and bioavailability of the agent administered. Furthermore, the ability to undergo ligand exchanged reactions offers a myriad of opportunities for metals to interact and coordinate to biological molecules, as demonstrated by the widely used drug cisplatin Furthermore, when designing metal-based therapeutics, one is not restricted solely by metals selected by nature and can take advantage of the unique properties of nonessential metals, including other 1st and 2nd row transition metals and metals that can impart additional utility not found naturally [6].

This review focuses on recent advances in developing platinum, ruthenium, copper and gold anticancer agents

ANTICANCER PLATINUM COMPLEX

Platinum (II) complexes has been used as anti cancer drugs since long, among them cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers[1]. This prototypical anticancer drug remains one of the most effective chemotherapeutic agents in clinical use. Cisplatin, (cis-$[PtCl_2(NH_3)_2]$, also known as cis-DDP), (**Fig. 1**) is perhaps the best known example of a small molecule metal-containing drug [2]. Cisplatin enters cells by passive diffusion and also, as recently discovered, by active transport mediated by the copper transporter Ctr1p in yeast and mammals. The cytotoxicity of cisplatin originates from its binding to DNA and the formation of covalent cross-links. Binding of cisplatin to DNA causes significant distortion of helical structure and results in inhibition of DNA replication and transcription. Inside the cell it interacts with a number of other negatively charged biomolecules besides DNA such as proteins, sulphur-containing compounds like metallothioneins and glutathione that sequester heavy metals like Pt and remove it from the cell [7]. DNA damage and subsequent induction of apoptosis may be the primary cytotoxic mechanism of cisplatin and other DNA-binding antitumor drugs [8].

Cisplatin is used for the treatment of testicular cancer, epithelial ovarian cancer, gestational trophoblastic tumors, and small cell lung cancer as well as for cervical, nasopharyngeal, esophageal, and head and neck cancers. Despite this success, the clinical use of cisplatin against this and other malignancies is severely limited by dose-limiting side-effects such as neuro-, hepati- and nephrotoxicity. In addition to the high systemic toxicity, inherent or acquired resistance is a second problem often associated with platinum-based drugs, which further limits their clinical use [4].

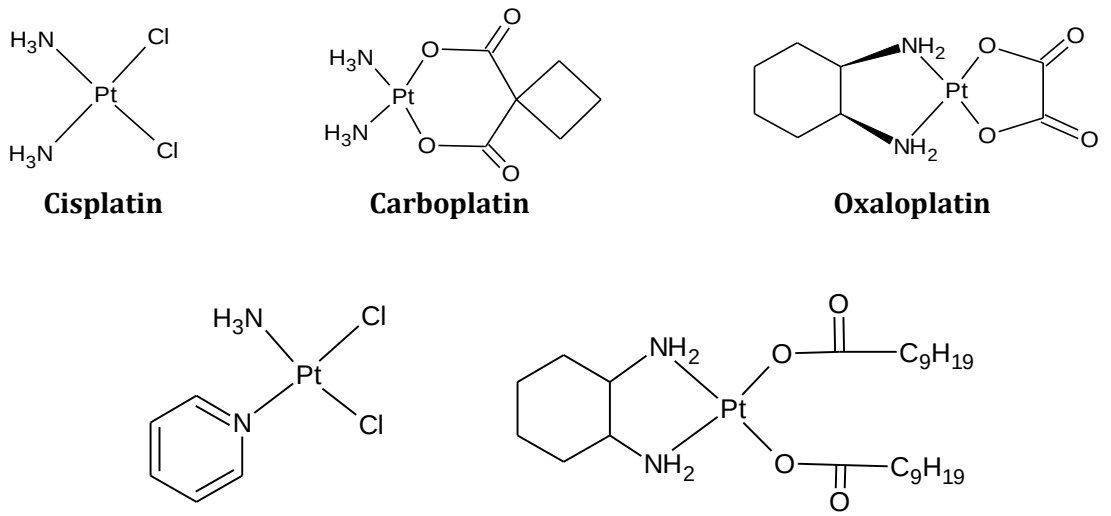
In an effort to address these shortcomings, 2nd and 3rd generation platinum analogs, namely carboplatin and oxaliplatin (**Fig. 1**), have been designed and clinically approved

to maintain a more manageable toxicity profile.

Carboplatin is second generation drug which have lesser side effect. Carboplatin is effective in the treatment of ovarian carcinoma, lung, and head and neck cancers, while oxaliplatin is clinically approved for the treatment of colorectal cancer, which is resistant to cisplatin [9].

Picoplatin (cis-$PtCl_2(NH_3)$(2-pic), previously AMD473; **Figure 1**) is a new generation sterically hindered platinum cytotoxic compound that provides a differentiated spectrum of activity against a wide range of human tumor cell lines and an improved safety profile. It is designed to overcome acquired resistance to cisplatin in vitro and in human tumor xenografts [10].

L-NDDP (Aroplatin; **Figure 1**) is a liposomal formulation of cis-bis-neodecanoato-trans R, R-1,2-diaminocyclohexane platinum (II), a structural analogue of oxaliplatin [10].



Cisplatin **Carboplatin** **Oxaloplatin**

Picoplatin **Aroplatin**

Figure 1: Platinum Containing Drug

ANTI CANCER GOLD COMPLEX

Gold (I) and Gold (III) complexes have long been sought for anti-cancer treatments. Many complexes have displayed interesting anticancer potencies [11]. These complexes act through a different mechanism as compared to cisplatin. Mechanistic studies suggested that, in contrast to cisplatin, DNA was not the primary target for these gold (I) complexes and that their cytotoxicity was mediated by their ability to alter mitochondrial function and inhibit protein synthesis by causing DNA-protein cross-links [11]. Certain gold complexes with aromatic bipyridyl ligands have shown cytotoxicity against cancer cells. The 2-[(dimethylamino) methyl] phenyl gold (III) complex has also proven to be anti tumor agent against human cancers. Gold nanoparticles when used in combination with radio therapy or chemotherapy enhance DNA damage and make the treatment target specific [7].

Auranofin (**Fig 2**) and a number of its analogs showed potent cytotoxic activity against both cell lines *in vitro* and anti-tumor activity against leukemia in vivo, and among them, phosphinecoordinated gold (I) thiosugar complexes appeared to be the most potent. More promising indications were achieved with a series of digold phosphine complexes, such as gold (I) 1,2-bis(diphenylphosphine)ethane (DPPE), which were shown to confer *in vitro* cytotoxic activity especially in some cisplatin-resistant cell lines [11]. In more recent studies gold (I) chloroquin complex has shown good antitumor activity [12].

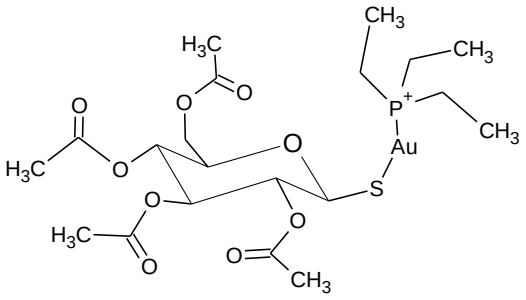


Figure 2: Aurofin

GOLD (III) COMPLEX

Primarily because of the high reactivity of gold (III) complexes, they have not been as thoroughly investigated as gold (I) complexes. Having a high redox potential and relatively poor stability, the use of gold(III) complexes as anticancer drugs was questioned under physiological conditions The first promising result was obtained with a class of gold (III) complexes with 2-[(dimethylamino) methyl]phenyl] (damp) ligand, synthesized in such a way to stabilize gold in its 3^+ oxidation state. These complexes exhibited cytotoxic effects against several human cancer cell lines, comparable to, or greater than cisplatin. Moreover, these complexes retained cytotoxic activity even against cisplatin-resistant cell lines. Recently *in vitro* activity of a series of gold(III) complexes, [Au(en)2]Cl3, [Au(dien)Cl]Cl2, [Au (cyclam)](ClO4)Cl2, [Au(terpy)Cl]Cl2, and [Au(phen) Cl2] Cl, against the A2780 ovarian cancer cell line and a cisplatin-resistant variant were described [11]. A number of other gold (III) complexes have been synthesized and their cytotoxic activities have been evaluated. A group of square planar gold (III) complexes containing at least two gold-chloride bonds in cis-position, trichloro(2- pyridylmetha-nol) gold(III) [AuCl3(Hpm)], dichloro(N-ethylsalicylaldiminato)gold(III) [AuCl2(esal)], trichlorodiethylendiamine-gold(III)[AuCl(dien)]Cl2, and trichlorobis-ethylendiamine gold(III) [Au(en)2]Cl3 showed significant cytotoxic effects against the A2780 human ovarian cancer cell line, comparable to or even greater than cisplatin, and they were able to overcome resistance to cisplatin to a large extent [11]. The gold (III) complexes with general formula [AuCl2L]Cl (L norfloxacin, levofloxacin, sparfloxacin) were tested against A20 (murine lymphoma), B16-F10 (murine melanoma) and K562(human myeloid leukemia) tumor cell lines comparing to the normal cell lines L919 (murine lungfibroblasts) and MCR-5 (human lung fibroblasts). The free ligands did not showed significant activityin the tumor or normal cell lines, whereas the complexes are more active than the parent drugs, and they have with a similar cytotoxic activity [13].

ANTICANCER COPPER COMPLEX

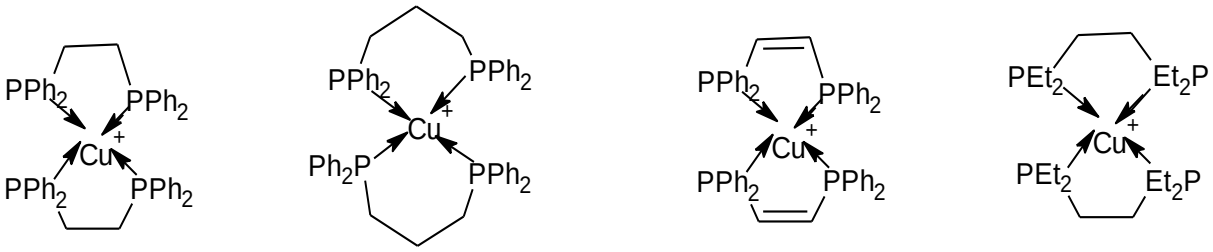
Anticancer activity of copper (I) compounds may be a result of different mechanisms, that is their ability to produce reactive oxygen species (ROS). Copper (I) ions can reduce hydrogen peroxide to hydroxyl radical. Copper (II) ions may in turn be reduced to Cu (I) by superoxide anion ($O^{2\bullet-}$) or glutathione. Therefore, it can be concluded that the production of reactive oxygen species such as $OH^\bullet$ are driven by the copper, regardless of the form in which it is initially introduced into the body– Cu^+, or Cu^{2+}

$Cu^{2+} + O_2 \bullet- \rightarrow Cu^+ + O_2$

$Cu^+ + H_2O_2 \rightarrow Cu^{2+} + OH^\bullet + OH^-$

Superoxide anion ($O^{2\bullet-}$) is the product of reduction of the molecular oxygen that occurs in many biological processes. It is converted into hydrogen peroxide through dismutation. Both of these forms of ROS lead to the formation of another type of reactive oxygen species – the hydroxyl radical ($OH^\bullet$). It occurs in a reaction catalysed by copper (or iron) ions. This radical is believed to be the main factor causing DNA damage in cells under oxidative stress.

The compound in (**Fig. 4**) $[Cu(thp)_4][PF_6]$ exhibits even 40-fold higher cytotoxicity than cisplatin (in survey performed on cancer cells of a colon reacts selectively with cancer cells, but at the same time it is not harmful for healthy cells. The selectivity is higher than the one observed at cisplatin or oxaliplatin – the drug applied in colorectal cancer treatment. Anticancer activity is exhibited by copper (I) complexes possessing pyridine-type ligands (pyridine, bipyridine, phenanthroline etc.) or such where copper(I) ion is coordinated to phosphine ligands (**Fig. 3**) Presumably, introduction of both types of ligands mentioned to one molecule would make it possible to create a compound with an increased activity against cancer cells [14].



[Cu(dppe)$_2$]Cl **[Cu(dppp)$_2$]Cl** **[Cu(dppey)$_2$]Cl** **[Cu(eppe)$_2$]Cl**

Figure 3: The structures of copper (I) complexes with bidentate phosphine

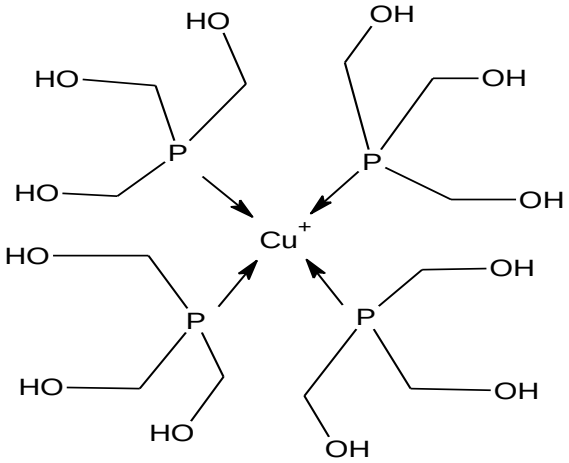


Figure 4: Complex ion of the compound [Cu(thp)$_4$][PF$_6$]

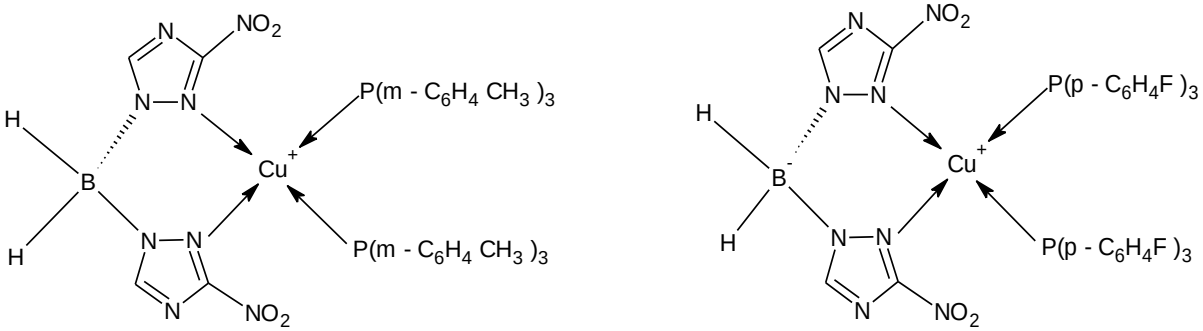


Figure 5: Complexes of Cu$^+$ with triazolylborate ligands

Compound in (**Fig. 5**) exhibits activity from 2 to 19 times higher than cisplatin for investigated cell lines (*e.g.* for breast cancer cell line).

In (**Fig. 6**) examples of polinuclear copper (I) complexes, are depicted which possessed in their coordination sphere both pyridine-type and phospine-type ligands.

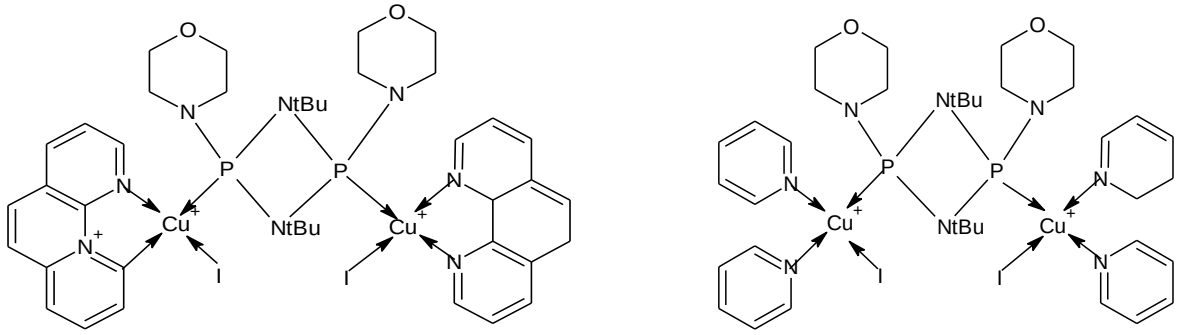


Figure 6: Binuclear copper (I) complexes

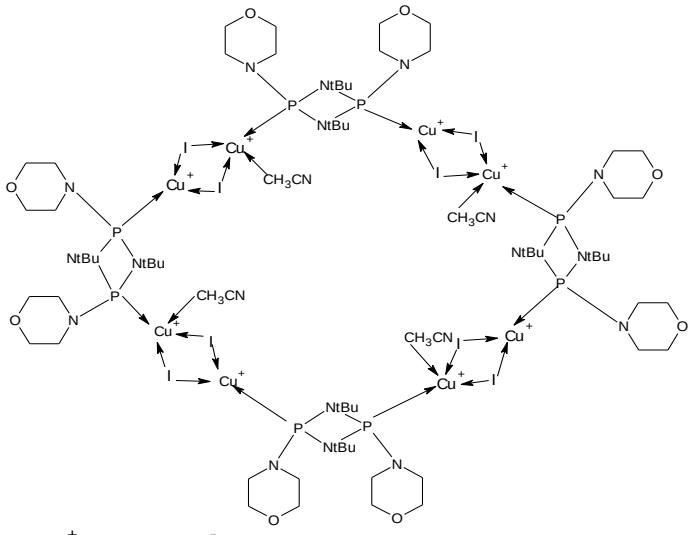


Figure 7: Octanuclear Cu^{+} compound

Antiproliferative activity for cervical cancer cells was proved for all three copper complexes presented in (**Figures 6 and 7**). Moreover, it was observed that inhibition of proliferation was more effective for the complexes discussed, than for cisplatin [14, 15].

RUTHENIUM COMPLEX

To overcome the limitations of platinum complex some compounds based on ruthenium have been developed and tested against cancer cell lines. These compounds tend to cause fewer (and less severe) side effects compared to platinum drugs. Many ruthenium complexes with oxidation state 2^{+} or 3^{+} display antitumor activity, especially against metastatic cancers. Ruthenium's properties are well suited towards pharmacological applications. Also, the energy barriers to interconversion between these oxidation states is relatively low, allowing for ready oxidation state changes when inside the cell. Furthermore, ruthenium tends to form octahedral complexes, which gives the chemist two more ligands to exploit compared with platinum (II) complexes, which adopt a square planar geometry. Ruthenium can also form strong chemical bonds with a range of different elements of varying chemical 'hardness' and electronegativities, meaning that ruthenium can bind to a range of biomolecules, not just DNA. One hypothesis as to why ruthenium compounds are less toxic in general than platinum drugs is 'Activation by Reduction'. This theory is based on the observation that ruthenium (III) complexes are more inert than ruthenium (II), which can partially be attributed to its higher effective nuclear charge. Also, cancerous cells tend to have a more chemically reducing environment than healthy cells, owing to their lower concentration of molecular oxygen (due to their higher metabolic rate and remoteness from the blood supply). These two factors taken in parallel mean that compounds of ruthenium can be administered in the (relatively inert) III oxidation state, causing minimal damage to healthy cells, but being reduced to the (active) II oxidation state in cancer cells Two ruthenium compounds are currently undergoing clinical evaluation as anticancer drugs - NAMI-A and KP1019 (**Fig. 8**). KP1019 and NAMI-A appear to be quite similar structurally (both are Ru(III)+ complexes with chloride and heterocyclic ligands and a heterocyclic counter ion) yet they display remarkably different types of anticancer activity. KP1019 is active against primary cancers (i.e. the main tumor mass which forms first in a patient), whereas NAMI-A is active against secondary tumor cells (i.e. the metastasis which form after cells from the primary tumor have moved to a different organ, e.g. via the bloodstream). Currently there are very few treatment options for secondary (metastatic) cancers, and the prognosis for patients who develop this form of the disease is much worse [16,17].

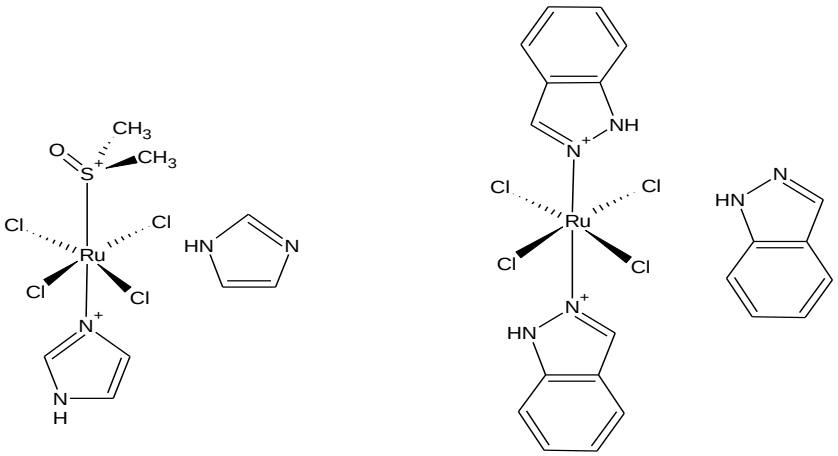


Figure 8: NAMI-A and KP1019

CONCLUSION

Recent advances in medicinal inorganic chemistry gives significant prospects for the utilization of metal complexes in the development anticancer drugs. Platinum complexes cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers. Besides the established use to treat arthritis, gold complexes exhibit anticancer property. Since higher concentrations of copper is a common trademark of many human tumors, targeting tumor cellular copper with copper chelating agents emerged as an exciting new approach in cancer therapy Antiproli-ferative activity for cervical cancer cells was proved for copper complexes. Ruthenium complexes with antitumor activity are also emerging rapidly. Since metals are endowed with unique properties that are absent in conventional carbon-based drugs, the positive trend in anticancer drug discovery can be continued for the design of new metal based drugs.

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