



## Metal ions as Antitumor Complexes-Review

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### Abstract

Metal ions are required for many critical functions in humans. Scarcity of some metal ions can lead to disease. Well-known examples include pernicious anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. The ability to recognize, to understand at the molecular level, and to treat diseases caused by inadequate metal-ion function constitutes an important aspect of medicinal bioinorganic chemistry. Understanding the biochemistry and molecular biology of natural detoxification mechanisms of metals can help in designing and applying chelating agents to treat metals to be excellent antitumor agents for several cancer types.

**Keywords:** Anti-tumor; Metal ions; polydentate ligands.

### Introduction

Medicinal inorganic chemistry comprises the introduction of a metal ion into a biological system either by fortuity or by intention. The intentional introduction of metal ions into a biological system will be either for therapeutic or diagnostic purpose.

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. Whereas metals are electron deficient, most biological molecules such as 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.

The first structure-activity relationship, which was developed by Paul Ehrlich in the first decade of the 20<sup>th</sup> century, involved the development of the inorganic compound arsphenamine (otherwise known as Salvarsan or Ehrlich 606) as a successful treatment for syphilis. Ehrlich was the founder of chemotherapy, which he defined as the use of drugs to injure an invading organism without injury to the host [1].

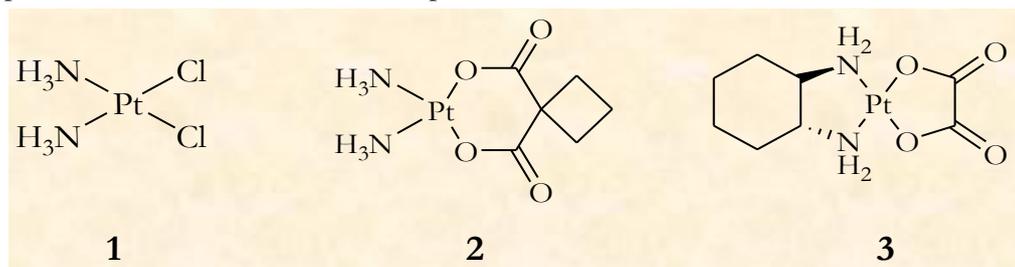
### Platinum Antitumor Complexes

The potential of metal-based anticancer agents has only been fully realized and explored since the landmark discovery of the biological activity of cisplatin (cis-diamminedichloroplatinum(II) or cis-DDP). In the early 1960s, during a study of the effects of electric field on bacterial growth across platinum electrodes immersed in an aerobic solution of Escherichia coli cells growing in the presence of NH<sub>4</sub>Cl, the bacteria did not divide normally but grew into filaments up to 300 times their normal length. An electrolysis product from the platinum electrode, identified as cis-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>4</sub>] responsible for this intriguing behavior. Subsequently, various other platinum group metal complexes were found to induce filamentous growth in bacteria. Interestingly, while the divalent compound cis-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] (Fig. 1.1) and related neutral cis-bis(amine)platinum(II) and platinum(IV) complexes were active, the trans isomers were not. Instead, they suppressed bacterial growth at high concentrations.

To date, this prototypical anticancer drug remains one of the most effective chemotherapeutic agents in clinical use. It is particularly active against testicular cancer and, if tumors are discovered early, an impressive cure rate

of nearly 100% is achieved. The clinical use of cisplatin against this and other malignancies is, however, severely limited by dose-limiting side-effects such as neuro-, hepato- 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. Much effort has been devoted to the development of new platinum drugs and the elucidation of cellular responses to them to alleviate these limitations [2-5].

A second generation analogous of cisplatin, carboplatin (Fig. 1.2) has reduced toxic side effects for the same efficiency thanks to its much lower reactivity. Unfortunately, carboplatin is only active in the same range of tumors as cisplatin and still administrated intravenously. The third generation of drugs includes compounds that contain different types of chiral amines. Oxaliplatin (Fig. 1.3) showed antitumor activity in colorectal cancer, had positive preclinical evaluations for use in cisplatin resistant tumors and can be administrated orally [6-12].

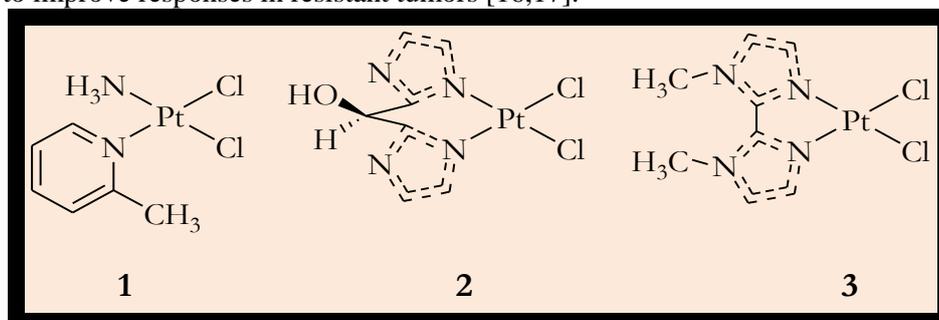


**Figure 1.** Structure of the anticancer drugs, cisplatin (1), carboplatin (2) and oxaliplatin (3)

Recently, some pioneering strategies towards the synthesis of novel platinum anticancer drugs have emerged. Those are based on changing the coordinated nitrogen ligand which is responsible for the structure of the adducts formed upon interacting with DNA or altering the halide leaving groups that influences tissue and intracellular distribution of the platinum complexes and improve the drug's toxicity profile. Other approaches have focused on applying Pt(IV) complexes or changing the type of the metal center (e.g. Pd(II) complexes). Attention also has been shifted to discover "nonclassical" drugs that can act in a manner different from cisplatin. Unconventional structures that violate the empirical structure-activity rules (SAR) of platinum compound lack NH, NH<sub>2</sub> or NH<sub>3</sub> ligands and multinuclear complexes are examples of these compounds. In addition, new treatment techniques have also been applied. For example the photoactivation (photoreduction) of some Pt(IV) complexes to the cytotoxic Pt(II) species by local application of UV or visible light to the tumor or electrochemotherapy with Pt(II) drug followed by local application of electric pulses to the tumor to increase the drug delivery into cells. The advantages of these techniques are their simplicity, short duration of the treatment sessions, low drug doses, and insignificant side effects [7-8, 13-15].

### ***Platinum(II) Complexes Bearing Achiral Nitrogen Ligands***

This new class of sterically hindered or crowded platinum compounds have been designed to circumvent cellular detoxification and cisplatin resistance, as well as to block binding of thiols and DNA-repair proteins [16]. For example, Pt(II) complexes of the general formula cis-[Pt(L)(NH<sub>3</sub>)(Cl)<sub>2</sub>] (L= pyridine, pyrimidine, purine, piperidine) were reported to show promising antitumor activity. ZD0473 [cis-(Pt(2-methylpyridine)(NH<sub>3</sub>)(Cl)<sub>2</sub>] (Fig. 2) was rationally designed in order to reduce the reactivity of glutathione which may be the key to improve responses in resistant tumors [16,17].



**Figure 2.** Platinum(II) complexes bearing aromatic nitrogen ligands

In order to decrease the reactivity of platinum complexes and hinder any possible cis-trans isomerism that may take place in the complexes with monodentate ligands, sterically hindered complexes containing bidentate

nitrogen ligands were prepared [18]. A comparative study about structural, kinetic and biological properties of  $[(\text{BMIC})\text{PtCl}_2]$  and  $[(\text{BMI})\text{PtCl}_2]$  (BIMC: bis(N-methylimidazole-2-yl)carbinol, BMI: N,N'-dimethyl-2,2'-biimidazole) has been reported (Fig. 2.2 & 2.3). The complexes showed significant cytotoxicity even though the tertiary doesn't form hydrogen bonds to DNA constituents, which are considered to be necessary for antitumor activity according to the SAR rules. These findings indicate that the NH group is probably unnecessary due to the absence of steric hindrance directly around the nitrogen, thus allowing a relatively fast reaction with DNA. The BMIC complex (Fig. 2.2) exhibits significant cytotoxic activity against L1210 leukemia.

### Complexes with Chiral Nitrogen Ligands

Since it has been found that the activity of  $\text{cis-Pt}(\text{N})_2(\text{X})_2$  (N= amine, X= anionic ligand) decreases in the order  $\text{N} = \text{NH}_3 > \text{RNH}_2 > \text{R}_2\text{NH}$  [19], most investigations into the platinum complexes with chiral monodentate ligands were directed at applying chiral primary amine ligands. On the whole, most platinum complexes bearing chiral monodentate ligands showed no significant differences in their biological activity except for one platinum complex that contains a phenylethylamine ligand (Fig. 3.1). This behavior could be due to the steric effect of the ligand [20].

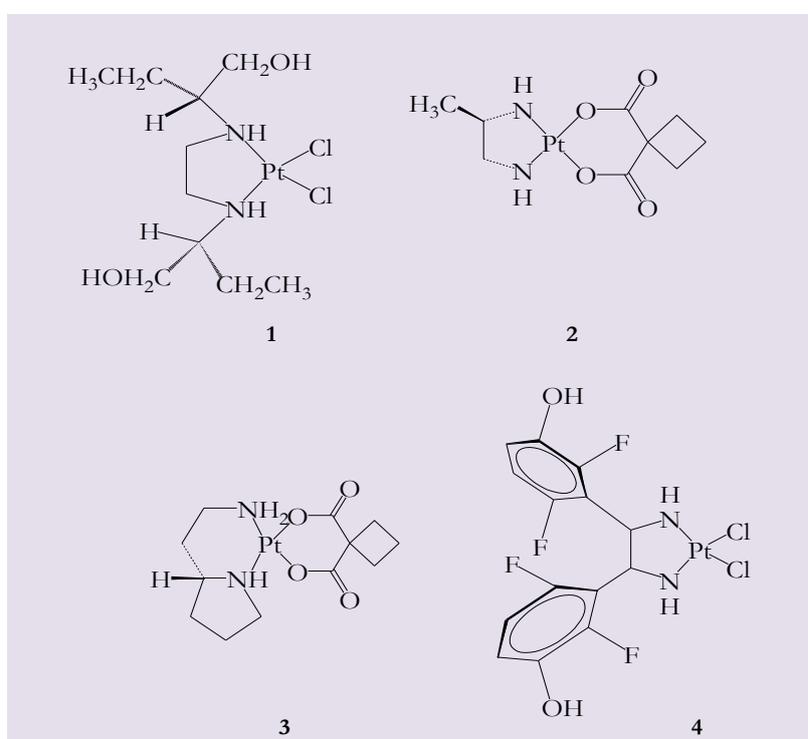


Figure 3. Platinum(II) complexes bearing chiral ligands

The degree of rotation and any possible cis-trans isomerism can be hindered by bridging together the two nitrogens of the amine ligands. Different enantiomerically pure bidentate nitrogen ligands have been complexed to platinum such as in Figures 2.2, 3.2 and 3.3. Interestingly, complex 3 (Fig. 3) bearing the R-enantiomer of the chiral ligand is non toxic, where the S-enantiomer is toxic. Another example in this class are the platinum complexes of the S,S- and R,R-ethanebutanol (Fig. 3.1) [21,22].

Different derivatives of Pt(II) complexes containing ethylene substituted backbone have been prepared (e.g. 1,2-diphenylenediamine). Biological studies of this family of complexes revealed that the introduction of substituents into the phenyl rings, either OH groups in both 3-positions or F atoms in all 2,6-positions led to compounds with marked activity on the hormone-sensitive MXT-M-3,2 breast cancer of the mouse. The most active derivative was the aqua[1,2-bis(2,6-difluoro-3-hydroxyphenyl)ethylene-diamine]sulfonatoplatinum(II) (Fig. 3.4) [23].

### Trans Geometry in Platinum Antitumor Complexes

For decades researchers marginalized the platinum complexes of trans geometry, because transplatin (trans-DDP) (Fig. 4) was recognized to be inactive in vivo and significantly less cytotoxic in vitro than cisplatin.

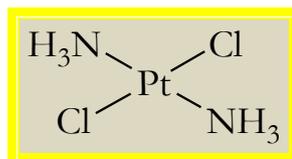


Figure 4. Structure of the transplatin

These properties have been explained by weaker inhibition of DNA replication and transcription by transplatin than by cisplatin adducts; more rapid repair of transplatin adducts, consistent with the inability of high-mobility group protein HMG1 to recognize transplatin adducts; inability of transplatin to produce 1,2-intrastrand crosslinks, which are the most frequent adducts formed by cisplatin [24].

In the 1990s, the apathy toward trans-platinum complexes ended. Many trans-platinum complexes were discovered with significant in vitro antitumor activity against different tumor cells, including ones resistant to cis-DDP. Among these complexes are transplatin analogues with planar amines (e.g. pyridine, quinoline, thiazole, imidazole), iminoethers, aliphatic amines (isopropanamine, n-butanamine, dimethylamine), nonplanar heterocyclic ligands (piperidine, piperazine) and polynuclear complexes. Some of these platinum complexes have given positive responses under in vivo conditions. For example, three different trans isomers (ZZ, EZ and EE) of the iminoether complex trans-[PtCl<sub>2</sub>{HN=C(OMe)Me}<sub>2</sub>] were prepared and tested for in vitro cytotoxicity and in vivo antitumor activity against P388 leukemia. The trans-EE complex, trans-[PtCl<sub>2</sub>{E-HN=C(OMe)Me}<sub>2</sub>] (Fig. 5) showed the greatest in vitro cytotoxicity (IC<sub>50</sub> = 2.2 μM, when the activity of cisplatin was 2.05 μM). Importantly, trans-[PtCl<sub>2</sub>{HN=C(OMe)Me}<sub>2</sub>] was better tolerated by tumor-bearing mice than cisplatin. At the end of the treatment a body weight loss was lower than that induced by cis-DDP [24,25].

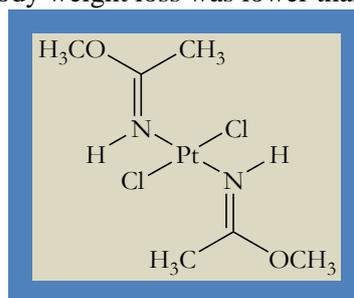


Figure 5. Structure of trans-[PtCl<sub>2</sub>{E-HN=C(OMe)Me}<sub>2</sub>]

Also, trans-planar amine (TPA) platinum(II) complexes such as trans-[PtCl<sub>2</sub>(L)(L')] (L = NH<sub>3</sub>, L' = pyridine, picoline, quinoline, isoquinoline or thiazole ; L=L' = pyridine, thiazole) (Fig. 6), containing a sterically demanding planar amine(s), exhibit increased cytotoxicity in comparison to the parent transplatin. Their cytotoxicity was tested against the panel of human ovarian carcinoma cell lines as well as murine L1210 leukemia cells sensitive to cis-DDP and resistant to cis-DDP. The antitumor activity of these planar amine complexes was likely increased due to the use of sterically hindered ligands that reduce the rate of replacement of the chloride [26].

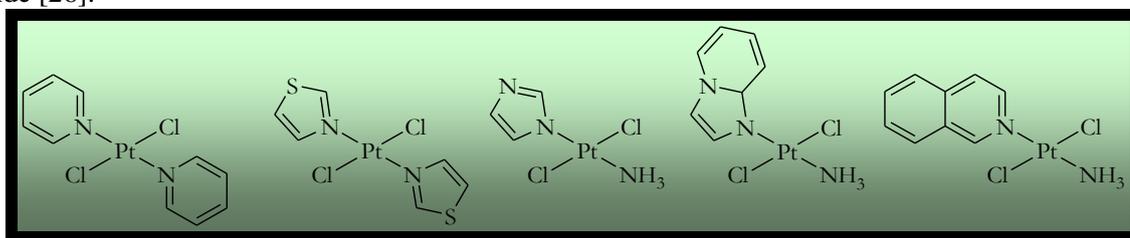


Figure 6. Structures of TPA complexes

Furthermore, trans-[Pt(NH<sub>3</sub>)<sub>2</sub>(OAc)<sub>2</sub>] showed good water-solubility, but its cytotoxicity (IC<sub>50</sub> > 100 μM) shows was enhanced by the presence of planar amine. Thus, the following compounds, with planar amines: trans-[Pt(NH<sub>3</sub>)(OAc)<sub>2</sub>(quin)] (Fig. 7.1), trans-[Pt(iquin)(NH<sub>3</sub>)(OAc)<sub>2</sub>] (Fig. 7.2) and trans-[Pt(OAc)<sub>2</sub>(py)<sub>2</sub>] (Fig. 7.3) (quin = quinoline, iquin = isoquinoline, py = pyridine, OAc=CH<sub>3</sub>COO), were synthesized. These TPA acetato compounds appeared significantly more cytotoxic in many cisplatin-resistant cell lines than in the parent cisplatin-sensitive cell lines (A2780, CH1, 41M) [27].

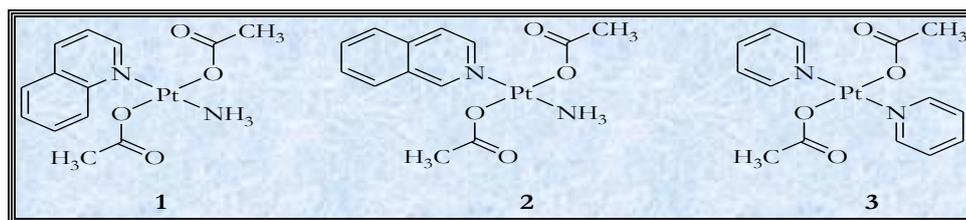


Figure 7. Structures of TPA acetato platinum complexes

### Octahedral Platinum(IV) Complexes

Octahedral Pt(IV) complexes have a tendency towards ligands substitution by a dissociative mechanism versus an associative mechanism for Pt(II), with the net result that Pt(IV) compounds are relatively more substitutionally inert. This is desirable for oral bioavailability and lower toxicity, but it is undesirable for DNA intercalation. Nonetheless, several Pt(IV) complexes are showing considerable activity in initial trials, with functionality thought to depend on the in vivo reduction of Pt(IV) to Pt(II), producing reactive intermediates capable of interacting with DNA. In order to achieve oral bioavailability and overcome cellular resistance, investigators have tried a variety of strategies to improve cisplatin. The reduction of Pt(IV) to Pt(II) compounds by biological agents is necessary to exert their antitumor activity. The reduction potential of Pt(IV) complexes depends on the type of axial and equatorial ligands [28-35].

For instance, Hambley et al. showed reduction occurs most readily when the axial ligands are  $\text{Cl} > \text{OCOR} > \text{OH}$  [26]. In another study, Choi et al. showed that the reduction rates which correlate with the reduction potentials depend on the electron withdrawing influence of the axial ligand [32]. For the studied ethylenediamine-based Pt(IV) complexes the fastest reduction rate ( $\text{OH} < \text{OCOCH}_3 < \text{Cl} < \text{OCOCF}_3$ ) corresponds to the most electron withdrawing ligand and coincides with the highest cytotoxicity.

Kelland et al. have described the synthesis of about 25 trans-Pt(IV) complexes and their trans-Pt(II) counterparts, and then evaluated and compared in vitro as well as in vivo antitumor activity of these complexes. The described compounds centered around the general formula, trans-[(amine)(ammine) $\text{Cl}_2\text{Y}_2$ ]Pt(IV) (Y =OH or Cl). Two chloride atoms together with two amino groups lie in the same plane, in equatorial positions. Opposite them are axial ligands, two hydroxide groups or two chloride atoms (Y ligands). The antitumor activity evaluations gave very promising results. The complexes were in vitro tested against the panel of human ovarian carcinoma cell lines, which contained tumor cells possessing either intrinsic (HX/62 and SKOV-3) or acquired (41McisR, CH1cisR and A2780cisR) resistance to cisplatin. Many of the complexes showed comparable antitumor activity to cisplatin and also overcame acquired cisplatin resistance. Notably, 14 complexes showed significant in vivo antitumor activity in the subcutaneous murine ADJ/PC6 plasmacytoma model. Of these, 13 were complexes with axial hydroxido ligands and one had axial ethylcarbamate ligands, whereas all the platinum(II) and tetrachloroplatinum(IV) complexes were inactive [36].

### Polynuclear Platinum Complexes

Polynuclear platinum complexes are a structurally distinct group. These innovative complexes contain two or more platinum centers linked by various types of ligand (aminoalkane, aromatic, etc.). Thus, polynuclear complexes break many structure-activity rules for platinum drugs. A different set of SARs for polynuclear complexes was created based on their in vitro cytotoxicity results. One of the conditions to achieve satisfactory antitumor activity of the complexes is the locating of the leaving group, preferably chlorido, in trans position to the bridging linker. In the meantime, many cis and trans polynuclear complexes have been synthesized, mainly by Farrell et al. [37-39].

Binuclear platinum(II) complexes with bifunctional thiourea, spermine and modified tetraamine linkers have been prepared and evaluated. The protonated, noncoordinating secondary amines in these molecules may have additional interaction with DNA by hydrogen bonding and electrostatic interaction and thus provide an enhanced activity over the parent dinuclear agents such as BBR3005 [{trans-PtCl(NH<sub>3</sub>)<sub>2</sub>]<sub>2</sub>-μ-[(trans-Pt(NH<sub>3</sub>)<sub>2</sub>(H<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NH<sub>2</sub>)<sub>2</sub>)](NO<sub>3</sub>)<sub>2</sub> (Fig. 8.1) [40,41].

Trinuclear and tetranuclear platinum complexes have also been studied [42,43]. The trinuclear complex BBR3464 (Fig. 8.2) is the first multinuclear complex which entered clinical trials in late 1997. Its preclinical anticancer profile was highlighted by exceptional potency, therapeutic doses approximately 1/10<sup>th</sup> that of cisplatin, and activity in a broad spectrum of solid human tumor [44,45]. Currently, BBR3464 is being entered in phase II clinical trials under the auspices of Novuspharma SpA. The investigations of phase I trials demonstrated that diarrhea and neutropenia were evident as dose-limiting toxicities. The utility of this complex

was not limited by nephrotoxicity, neurotoxicity or pulmonary toxicity [46]. The compound interacts with DNA in novel ways not available to cisplatin or other mononuclear platinum complexes [47]. The tetranuclear platinum complex (Fig. 8.3), showed low cytotoxicity that might be due to transport problems across the cell membranes [43].

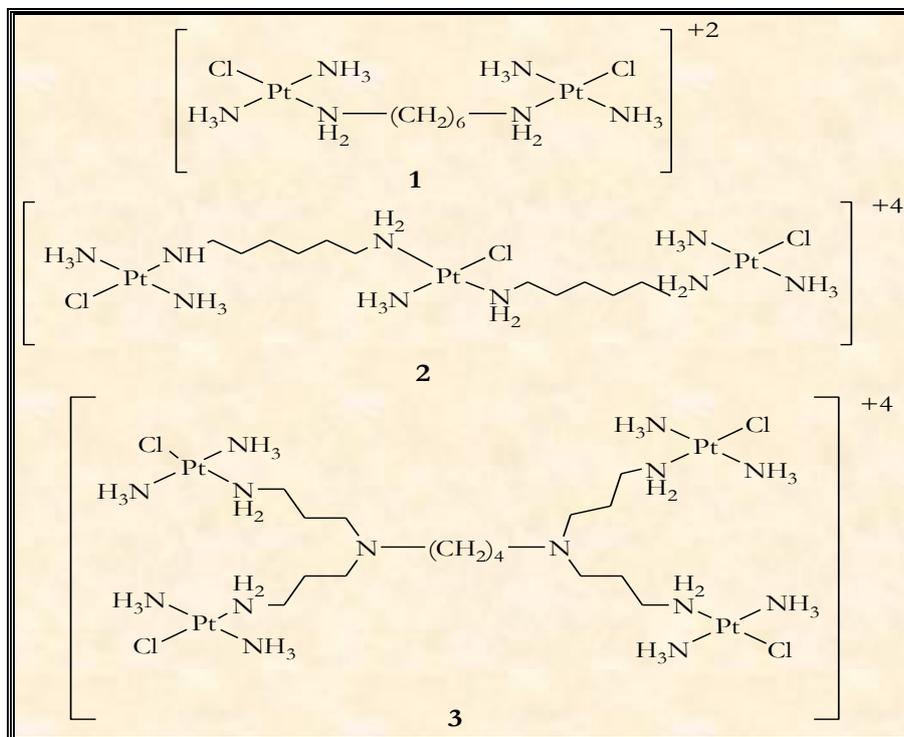


Figure 8. Structures of polynuclear platinum complexes

### Palladium Complexes as Alternative Potential Antitumor Agents

The notable analogy between the coordination chemistry of Pt(II) and Pd(II) compounds has advocated studies of Pd(II) complexes as antitumor drugs [48,49]. A key factor that might explain is most useful come from the ligand-exchange kinetics. The hydrolysis of leaving ligands in palladium complexes is too rapid,  $10^5$  times faster than their corresponding platinum analogues. They dissociate readily in solution leading very reactive species that are unable to reach their pharmacological targets. In addition, some of them undergo an inactive trans-conformation. This considerably higher activity of palladium complexes implies that if an antitumor palladium drug is to be developed, it must somehow be stabilized by a strongly coordinated nitrogen ligand and a suitable leaving group. If this group is reasonably non labile, the drug can maintain its structural integrity in vivo long enough.

Various simple Pd(II) compounds with interesting biological properties have been previously reported such as [cis-(NH<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>] (Fig. 9.1), [trans-(NH<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>] (Fig. 9.2), [(1,5-COD)PdCl<sub>2</sub>] (Fig. 9.3), [( $\eta$ -C<sub>3</sub>H<sub>5</sub>)PdCl<sub>2</sub>]<sub>2</sub> (Fig. 9.4) and [(cyclopentyl)<sub>2</sub>PdCl<sub>2</sub>] (Fig. 9.5). Recent advances in this field have also focused on Pd(II) compounds bearing bidentate ligands as a way to prevent any possible cis-trans isomerism [50-52].

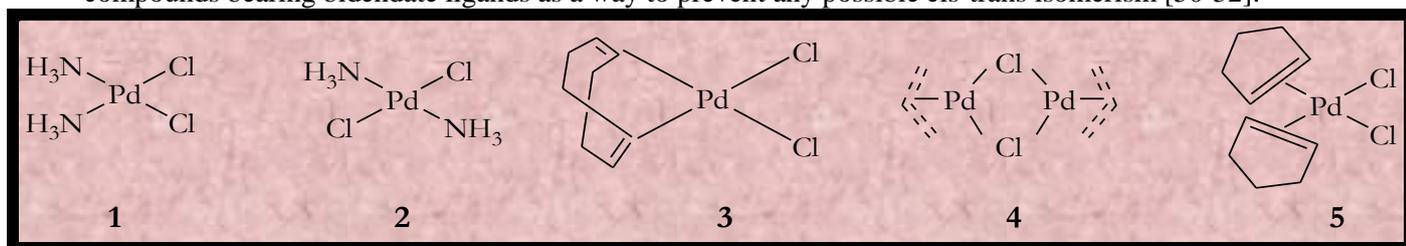
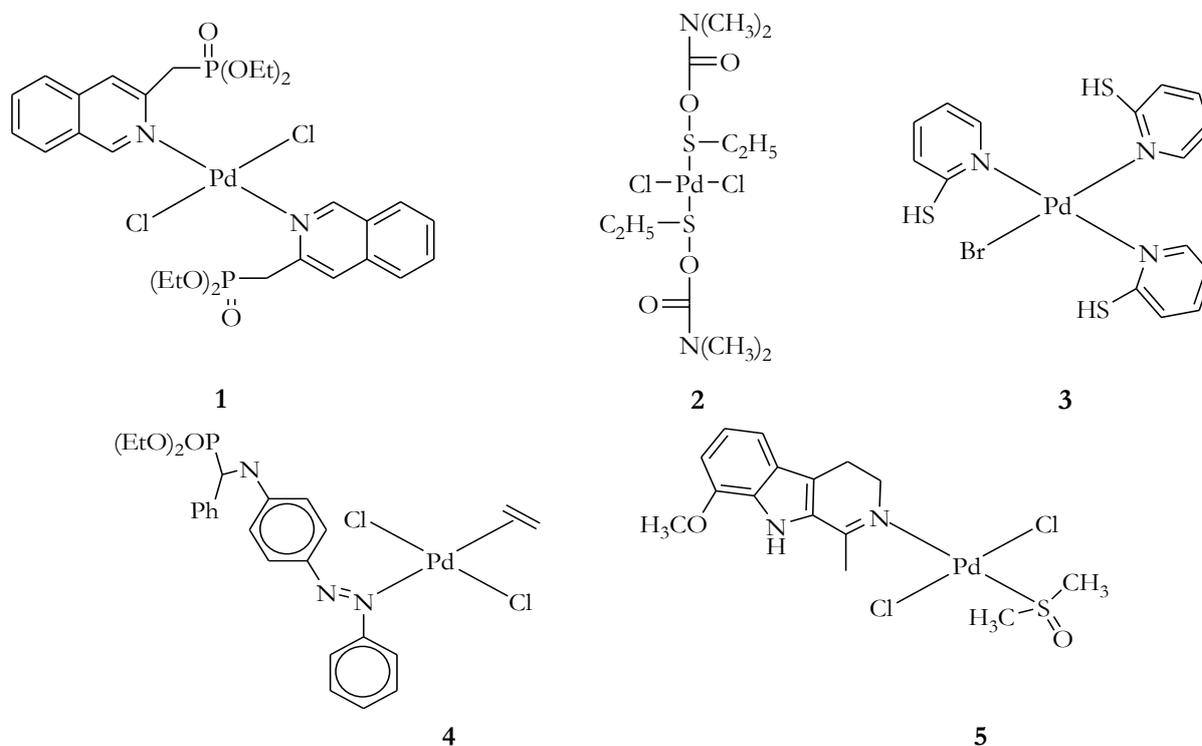


Figure 9. Various simple palladium(II) compounds with biological properties

### Trans-Palladium(II) Complexes Containing Bulky Monodentate Ligands

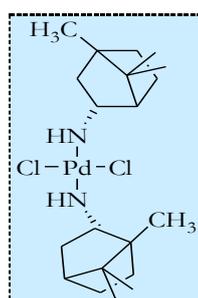
Several trans-Pd complexes with promising activity against tumor cells have been synthesized. In general, the strategies that have been applied to design these agents were on the window of reactivity usually employed for the potential platinum antitumor drugs. A comparative study on antitumor activity was carried out between the

dihalide Pd(II) complexes of monoethyl-2-quinolmethylphosphonate (2-Hmqmp) and diethyl-2-quinolmethylphosphonate (2-dmqmp) [53]. The diester ligand has two potential donors, the N from quinoline and the O from phosphoryl giving the complex  $[\text{trans}-(2\text{-dqmp})_2\text{PdCl}_2]$  (Fig. 10.1). The complexes of the diester 2-dmqmp were found to be more active than those of the monoester-based ligand (2-Hmqmp). This may partly be ascribed to the greater leaving activity of the halogen ligands in the complex bearing the 2-dmqmp ligand and to their greater lipophilicity or solubility.



**Figure 10.** Trans-Palladium(II) complexes containing bulky monodentate ligands

Fulrani et al., reported about the synthesis and cytotoxicity evaluation of some  $\text{trans}-(\text{L})_2\text{Pd}(\text{X})_2$  complexes (Fig. 10.2) (L= N,N-dimethyl-O-ethylthiocarbamate: DMTC or N-methyl-O-ethylthiocarbamate: MTC, X= Cl, Br). Other palladium complexes based on 2-Mercaptopyridines (MP) were also prepared. The  $[(\text{MP})_3\text{Pd}(\text{Br})]\text{Br}$  (Fig. 10.3) is of potential therapeutic use since it has lower  $\text{IC}_{50}$  values on LoVo cell lines than cisplatin and around the same as its Pt(II) analogue [54]. Palladium(II) complexes containing alkyl phosphonates derived from aniline and quinoline were reported. Most of the aniline compounds (e.g. (Fig. 10.4)) showed cytotoxicity in vitro against animal and human tumor cell lines. Complexes with naturally occurring compounds have also been utilized. The palladium complex which contains the bulky nitrogen ligand harmine (7-methoxy-1-methyl-911-pyrido[3,4-b]indole,  $\text{trans}[\text{Pd}(\text{harmine}) (\text{DMSO})\text{Cl}_2]$  (Fig. 10.5) exhibits a greater cytotoxic activity against L1210 and K562 cell lines than cisplatin [55]. More recently, Abu-Surrah et al., reported the synthesis and molecular structure of a new enantiometrically pure, chiral trans-palladium(II) complex,  $\text{trans}[\text{Pd}\{(\text{R})-(+)\text{-bornyl-amine}\}_2\text{Cl}_2]$  (Fig. 11) that bears the bulky amine ligand R-(+)-bornyl-amine [56]. The complex showed similar antitumor activity against HeLa cells when compared with the activity of the standard references, cisplatin, carboplatin and oxaliplatin.



**Figure 11.** Structure of the palladium(II) complexes

### Palladium(II) Complexes with Bidentate N∩N Ligands

Dichloro palladium(II) complexes with spermidine and spermine were reported by Navarro-Ranninger et al. [57]. This kind of chelating ligands have been used because of their relevant biological activity; they are involved in proliferation and differentiation of cells in DNA replication and membrane stabilization. Complexes of spermidine (Fig. 12.1) give values of IC<sub>50</sub> similar to cisplatin, whereas those of spermine (Fig. 12.2) have low antiproliferative activity.

Ethylendiamine palladium(II) complexes with pyridine or its derivatives were also reported (Fig. 12.3) [58]. The increase of the electron donor properties of the substituents firstly led to an increase of the donor strength of the coordinated pyridines, which directly led to the increase of the cytotoxic activity of the palladium complexes.

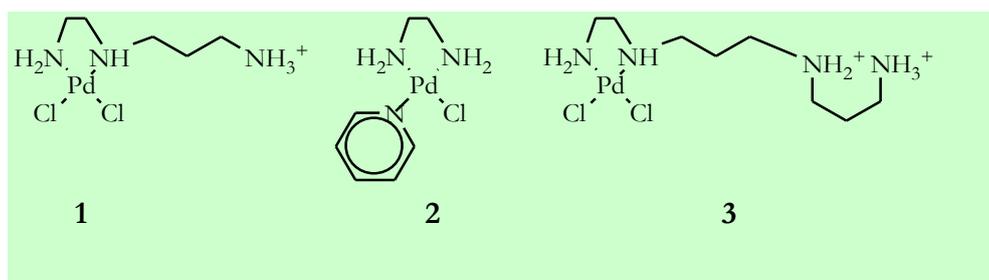


Figure 12. Palladium(II) complexes with bidentate N∩N ligands

Recently, Abu-Surrah et al., applied an alternative method to synthesize the enantiometrically pure DACH-based palladium(II) complexes [59,60]. In this method, the desired organic bidentate ligand was allowed to react with [cis-Pd(PhNC)<sub>2</sub>Cl<sub>2</sub>], a palladium(II) starting material that is soluble in most organic solvents, in CH<sub>2</sub>Cl<sub>2</sub> at 25°C. Following this procedure, the nucleophilic substitution reaction of the complex [cis-Pd(PhNC)<sub>2</sub>Cl<sub>2</sub>] with (1R,2R)-(-)-1,2-diaminecyclohexane afforded the square planar Pd(II) complex [(1R,2R)-(-)-(DACH)PdCl<sub>2</sub>] (Fig. 13.1) in a high yield. The corresponding cationic, aqua complex, [(DACH)Pd(H<sub>2</sub>O)<sub>2</sub>](NO<sub>3</sub>)<sub>2</sub> (Fig. 13.2) and the oxalate complex [(DACH)Pd(C<sub>2</sub>O<sub>4</sub>)] (Fig. 13.3) have also been prepared and characterized [61]. A series of other oxaliplatin like complexes of the type [(DACH)Pd(O-O)] has also been prepared by Khokhar et al. [62] (O-O: malonate, methylmalonate, phenylmalonate, xylate). Unfortunately, the influence of the different dicarboxylate ligands could not be focused since the complexes lack the antitumor activity. This could be due to the low solubility and stability of the above complexes in solution.

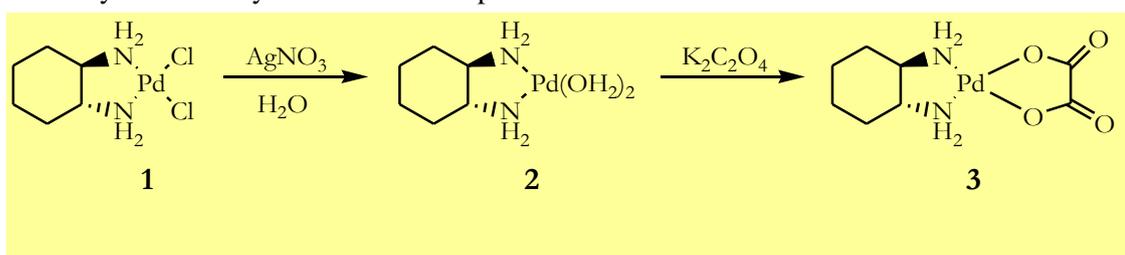


Figure 13. DACH-based palladium(II) complexes

As a way to increase the stability of the palladium(II) complexes, two chelates forming two rings around the central atom were prepared and evaluated. Modified amino acids such as py-CH<sub>2</sub>-accys (Fig. 14.1) (accys: N-acetyl-S-methylene-2-(2-pyridine)-L-cysteine) have been applied [63]. The S,N-chelation mode of these ligands is of importance, since only the side chain of the amino acid is involved in metal metal coordination, whereas the amino acid function remains uncoordinated, leaving this functional group accessible for the attachment of other amino acid or peptides. It has been found that the reactivity of these palladium complexes compete with some platinum(II) complexes.

Another study investigated compounds bearing NO<sub>3</sub> as a chelate in addition to a bidentate nitrogen ligand [64]. A comparison among [(bipy)Pd(NO<sub>3</sub>)<sub>2</sub>], [(AMP)Pd(NO<sub>3</sub>)<sub>2</sub>], [(AEP)Pd(NO<sub>3</sub>)<sub>2</sub>], [(DACH)Pd(Meorot)] (bipy = 2,2'-bipyridyl, AMP = 2-aminomethylpyridine, AEP = 2-aminoethylpyridine, Meorot = 3-methylorotate) showed that only [(DACH)Pd(Meorot)] (Fig. 14.2) was active, giving a high activity for sarcoma 180 but a low one against P388 leukemia. Similarly, [(DACH)Pd(5-fluororot)] (Fig. 14.3) reported later [65], displayed significant antitumor activity. These strong chelating ligands replacing chloro or nitro ligands induce a reduction in the rate of hydrolysis.

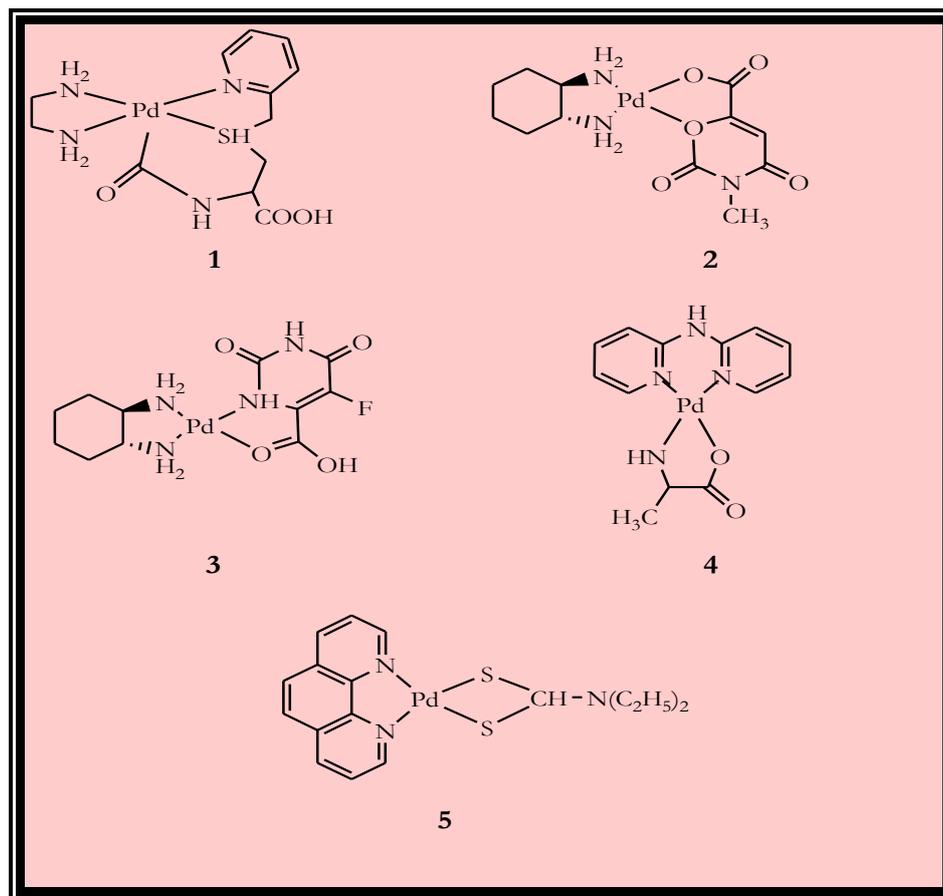


Figure 14. Palladium(II) complexes bearing two bidentate chelates or tetradentate nitrogen ligands

2,2'-bipyridylamine-based palladium(II) complexes containing glycine or L-alanine have been reported and evaluated [66]. The alanine based complex (Fig. 14.4) showed better cytotoxicity against P388 lymphocytic leukemia cells than the glycine based one. Other aromatic ligands such as 1,10-phenanthroline, which is one of the most used ligands in coordination chemistry, has been utilized in the field of antitumor-transition metal chemistry. Its planar nature enables its participation as a DNA intercalator.

Several derivatives of it were prepared and used as tetradentate ligands. The activities of [N,N-dialkyl-1,10-phenanthroline-2,9-dimethamine]Pd(II)] (Fig. 14.5) (alkyl: Me, Ethyl, propyl, cyclohexyl) are significantly dependent on the nature of the alkyl substituents. The complexes bearing the bulkiest groups showed lower IC<sub>50</sub> values than cisplatin [67].

#### **Palladium complexes with Biphosphine P∩P Ligands**

Many of the prepared palladium(II) complexes showed a discrete antitumor activity in vitro compared to the platinum based drugs because of their extremely high lability in biological fluids [68]. Therefore, it has been suggested that the organometallic biphosphine-based cyclopalladated complexes that are more stable and less toxic could have a more specific antitumor activity in vivo [69]. Some cyclopalladate complexes based on biphosphine ligands (Fig. 15) have been prepared and investigated for their antitumor activity in a syngeneic B16F10 murine melanoma model. The ionic complex caused 100% tumor cell death at very low concentration (<1.25 μM). Other Pd(II) complexes containing bidentate phosphine ligands of the general formula [L<sub>2</sub>PdX<sub>m</sub>]<sup>n+</sup>nX (L= Ph<sub>2</sub>P-A-PPh<sub>2</sub>, A= (CH<sub>2</sub>)<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>, X= Cl, Br, NO<sub>3</sub>) were prepared and evaluated for in vitro cytotoxicity, antitumor activity in murine tumor model and mechanism of action. The mechanism of these complexes appears different from that of cisplatin based on effects on DNA.

#### **Palladium(II) complexes with N∩S Mixed Donor Ligand**

Khan et al. reported about palladium(II) complexes with mixed nitrogen-sulfur ligands such as methionine and substituted pyrimidines (mercapto or amino) [70]. Methionine coordinates to Pd(II) through amino nitrogen and sulfur, thus leaving a carboxylic group free. It has been found that the complex [(methionine)Pd(2-merpy)Cl]Cl (Fig. 16) has in vitro IC<sub>50</sub> value lower than 10 μg/ml, so it could act as a potential antitumor agent.

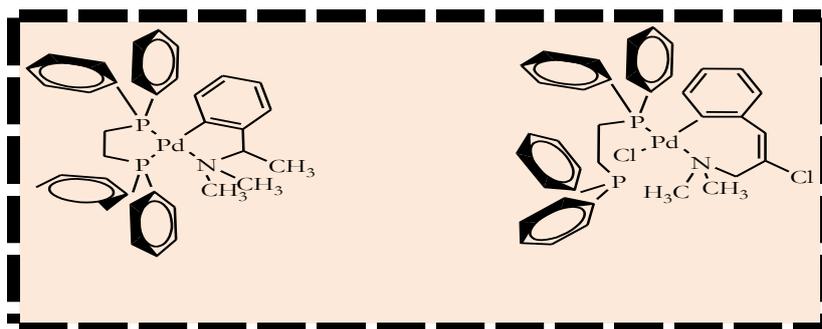


Figure 15. Palladium(II) complexes with biphosphine (P(Ph)<sub>2</sub>) ligands

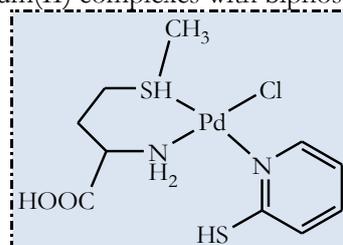


Figure 16. Palladium(II) complex with N(=O)S mixed donor ligand

### ***Dinuclear Palladium(II) Complexes***

In the chemistry of dinuclear palladium complexes, the use of strongly coordinated dinitrogen ligands is conserved. Navarro-Raninger et al. reported the synthesis of putrescine and spermine-based dinuclear complexes: [PdCl<sub>4</sub>(Put)<sub>2</sub>] and [PdCl<sub>4</sub>(Sperm)<sub>2</sub>]. The complex (Fig. 17.1) is a coordination complex of a dimer nature. In (Fig. 17.2) the 4 amino groups of the spermine coordinate to two cis-Pd-centers. The cytotoxicity results showed that the putrescine complex is much more reactive than the spermidine one [57]. Zhao et al. studied dinuclear palladium complexes containing two functional [Pd(en)(pyridine)Cl]<sup>+</sup> units bridged by Se or S were investigated [71]. The complexes are water soluble. The Se-Bridged Pd(II) dimer (Fig. 17.3) has a lower IC<sub>50</sub> than the S analogue or cisplatin against the HCT8 cancer cells line. Dinuclear cyclopalladated organometallic complexes containing biphosphine ligands were also reported by Rodrigues et al. [72]. The dimer Pd(II) complex (Fig. 17.4) showed to be the most active *in vivo* compared to the corresponding mononuclear complexes. It delays tumor growth and prolongs animal survival.

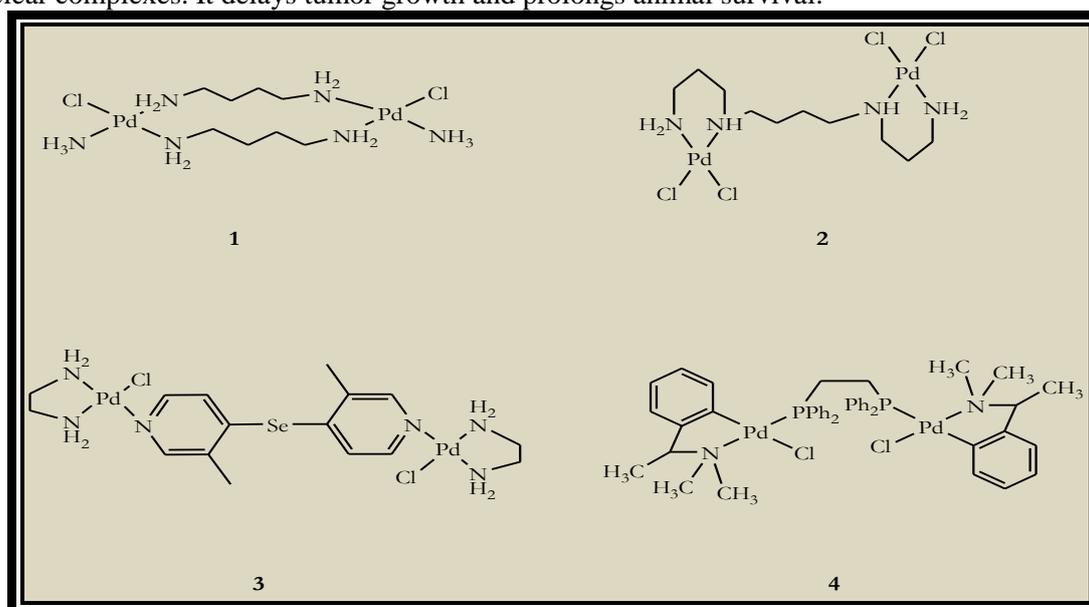


Figure 17. Structures of multinuclear palladium complexes

### ***Ruthenium (II & III) Complexes as Antitumor Agents***

Recently it was shown that ruthenium possesses several favorable chemical properties, suggesting that it may be a strong candidate to replace platinum and to form a basis for rational anticancer drug design. Ruthenium is less

toxic than platinum and it is believed that the remarkable anticancer activity of ruthenium resides in its ability to mimic iron in binding to several biomolecules, including serum transferrin and albumin. Two Ru(III) complexes, namely *trans*-[RuCl<sub>4</sub>(Im)(DMSO)]ImH (NAMI-A) and *trans*-[RuCl<sub>4</sub>(Ind)<sub>2</sub>]IndH (KP1019) (Fig. 18) are undergoing clinical trials. Whilst KP1019 is cytotoxic to cancer cells, NAMI-A is relatively non-toxic but has anti metastatic activity [73-78].

It has been proposed that the activity of Ru(III) complexes, which are usually relatively inert towards ligand substitution, is dependent on in vivo reduction to more labile Ru(II) analogues. Thus, the activity of Ru(II) complexes is currently being explored. In particular, since arenes are known to stabilize ruthenium in its 2+ oxidation state, the potential of Ru(II)-(η<sup>6</sup>-arene) complexes as anticancer agents is under investigation [78-80]. Half-sandwich (η<sup>6</sup>-arene)Ru(II) complexes with imidazole, sulfoxide, phosphane, chelating amino acidato, and diamine or diimine ligands have also been evaluated for cytotoxic activity. Both the size of the arene and the lability of the Ru-Cl bond have found to play a crucial role in determining the cytotoxicity of ruthenium(II) complexes of the type [(η<sup>6</sup>-arene)RuCl(LL')](PF<sub>6</sub>) with bidentate ligands LL'. Compounds with extended polycyclic arenes (e.g. tetrahydroanthracene) and LL' = ethylenediamine (en) are most active towards A2780 human ovarian cancer cells, whereas those with polar substituents on the arene such as COOCH<sub>3</sub> (an electronwithdrawing group) or with aromatic diimine ligands such as 2,20-bipyridine (bpy) or 1,10-phenanthroline (phen), exhibit either poor or no activity.

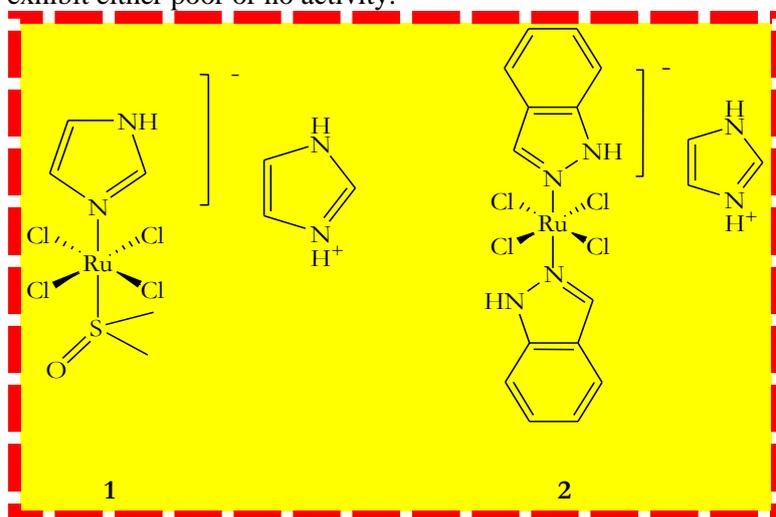
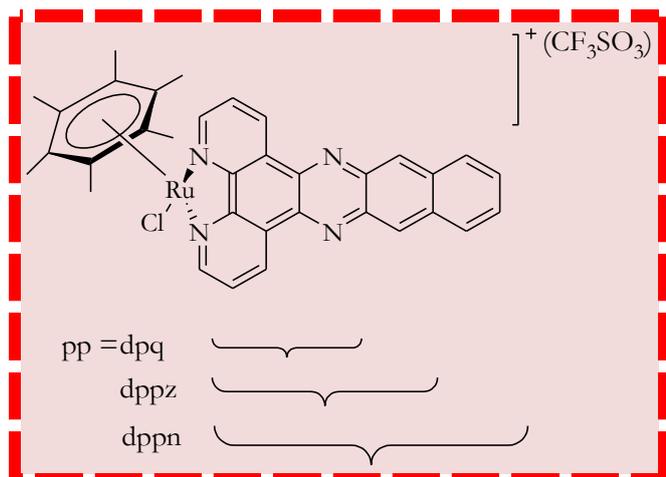


Figure 18. Structure of the anticancer drugs, NAMI-A (1) and KP1019 (2)

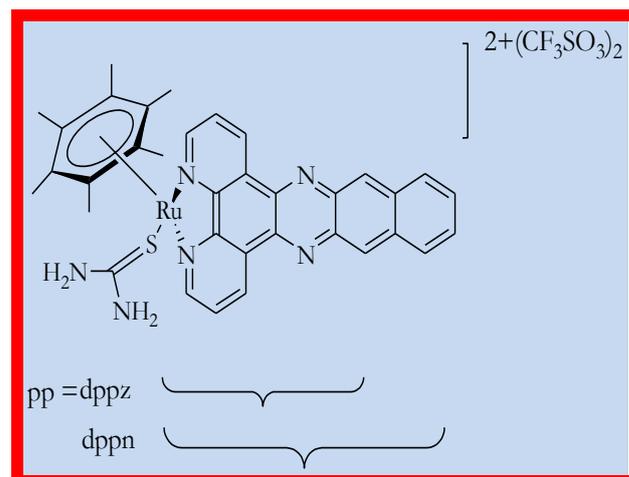
Further increases in the size of the polypyridyl ligand (pp) lead, however, to a dramatic reversal of the latter trend and the in vitro cytotoxicities of the complexes [(η<sup>6</sup>-C<sub>6</sub>Me<sub>6</sub>)RuCl(pp)](CF<sub>3</sub>SO<sub>3</sub>) (Fig. 19) towards the human cell lines HT-29 (colon cancer) and MCF-7 (breast cancer) are strongly dependent on the surface area of the aromatic system. For instance, the IC<sub>50</sub> values decreases from 11.1 over 2.12 to 0.13 μM for MCF-7 cells as the size of the polypyridyl ligand increases in the order dpq < dppz < dppn (dpq = dipyrido- [3,2-f:2',3'-h]quinoxaline; dppz = dipyrido[3,2-a:2',3'-c]phenazine; dppn = benzo[i]dipyrido[3,2-a:2',3'-c]phenazine). These value correlate well with the cellular uptake efficiency, which increases from 1.1 over 146.6 to 906.7 ng(Ru)/mg(protein) within the series.

The kinetically inert complexes [(η<sup>6</sup>-C<sub>6</sub>Me<sub>6</sub>)Ru{(NH<sub>2</sub>)<sub>2</sub>CS}- (pp)](CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> (pp = dppz, dppn) (Fig. 20) are also cytotoxic and this suggests that specific properties of the large polypyridyl ligands (e.g. DNA intercalation and/or cleavage) may be responsible for their biological activity. DNA binding studies indicate that (η<sup>6</sup>-C<sub>6</sub>Me<sub>6</sub>)Ru(II) compounds containing dpq or particularly dppz ligands are good metallointercalators but that the dppn ligand is too large to support stable intercalation between the base pairs of the double helix [81-89].

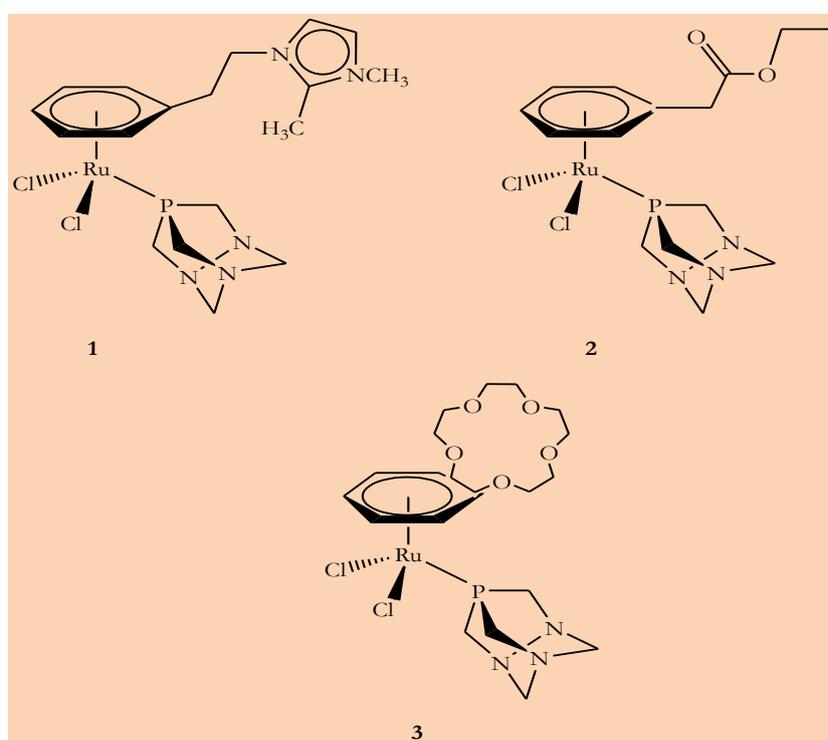
The in vitro and in vivo assessment of a series of η<sup>6</sup>-arene ruthenium complexes containing a pta ligand (pta = 1,3,5-triaza-7- phosphadamantane) were evaluated as anticancer agents [90]. In addition to the benzene, toluene, para-cymene and hexamethylbenzene derivatives, three systems with functionalised arene ligands were tested, complexes 1, 2 and 3 (Fig. 21).



**Figure 19.** Chemical Structure of  $[(\eta^6\text{-C}_6\text{Me}_6)\text{RuCl}(\text{pp})](\text{CF}_3\text{SO}_3)$



**Figure 20.** Chemical Structure of  $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}\{(\text{NH}_2)_2\text{CS}\}-(\text{pp})](\text{CF}_3\text{SO}_3)_2$



**Figure 21.** Chemical Structure of a series of  $\eta^6$ -arene ruthenium complexes containing a pta ligand

All pta complexes were found to cause pH-dependent DNA damage, in such a way that DNA was damaged at the typical pH of hypoxic tumor cells, whereas little or no damage was observed at characteristic pH values of healthy cells. This behavior was attributed to the pta ligand, which can be protonated at low pH, and the protonated form was considered to be the active agent. Therefore, the introduction of functionalised pendant arms on the arene ligand, such as in the below complexes (Fig. 19), did not show any significant improvement in the cytotoxicity of the compounds ( $\text{IC}_{50}$  (TS/A cells) = 66  $\mu\text{M}$ ; 103  $\mu\text{M}$ ; 159  $\mu\text{M}$ .) as compared to the  $\eta^6$ -aromatic hydrocarbon systems.

### ***Copper Complexes as Antitumor Agents***

The anticancer activities of range of simple copper complexes incorporating different types of nitrogen donor ligands such as purine, thiosemicarbazone, imidazole, benzohydroxamic acid and amino acid ligands have been studied [91–95]. Some mixed chelate copper-based drugs have exhibited greater antineoplastic potency than cisplatin in vitro and in vivo studies [96,97].

Copper complexes appear to have a mechanism of action significantly different to that of the clinically used drug cisplatin. For example, the complex  $[\text{Cu}(\text{malonate})(\text{phen})_2]$  was shown to induce apoptosis in cultured mammalian cells and is known to mediate significant cellular oxidative stress, promote membrane lipid peroxidation and interfere with mitochondria respiratory activity in fungal cells [98,99]. Similar copper chelates of phen were studied and also showed high antineoplastic activity by inhibiting respiration and ATP synthesis [100]. Furthermore,  $[\text{Cu}(\text{phen})]^{2+}$  type complexes are known to bind to DNA both intercalatively and non-intercalatively and are known as potent oxidative nucleases but the exact structure of  $[\text{Cu}(\text{phen})]^{2+}$  when bound to DNA has not been fully characterized [101]. Recently Devereux et al. have been examining alternative chelating ligands such as TBZH and 2-PyBZIMH (Fig. 22). The anti-cancer activity of TBZH is enhanced greatly when it is bound to a copper centre [102,103] but none of the complexes reported so far have exhibited activity close to that of cisplatin.

Reports of the biological activity of 2-PyBZIMH are scarce with no papers published describing the anti-cancer activity of its copper complexes. Its use as a ligand in the preparation of novel Pt(II) and Pd(II) anti-cancer agents has been reported [94]. These workers did not test the free 2-PyBZIMH ligand but found that  $[\text{Pt}(2\text{-PyBZIMH})\text{Cl}_2]$  was the most efficient anti-cancer agent against eight brain tumour cell lines, but the activity was significantly less than that of cisplatin.

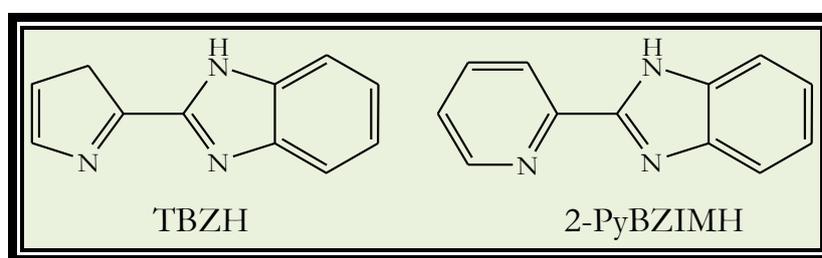


Figure 22. The structure of the TBZH and 2-PyBZIMH ligands

Recently, Sathisha et al. synthesized a complex of Cu(II) with bis(3 acetyl coumarin) thiocarbohydrazone (Fig. 23). This distorted octahedral complex has shown promising cytotoxic activity when screened using the in vitro method for certain types of cell lines [103].

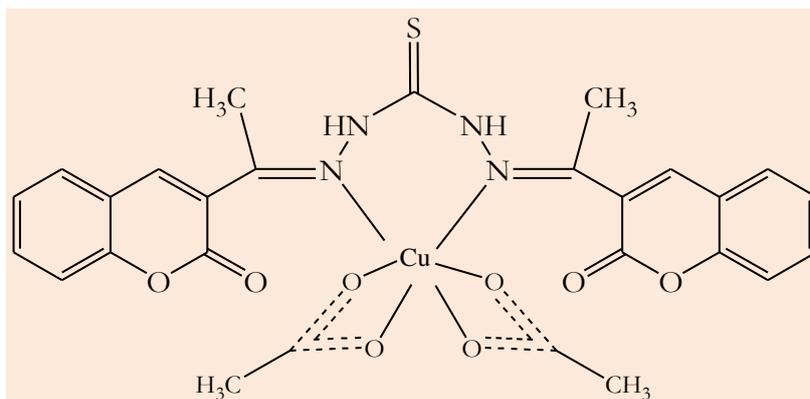


Figure 23. Proposed structure of the copper complex synthesized by Sathisha et al.

Bravo-Gómez et al. selected a mixed chelate copper(II) complexes of  $[\text{Cu}(\text{N-N})(\text{acac})]\text{NO}_3$  and  $[\text{Cu}(\text{N-N})(\text{gly})]\text{NO}_3$  with several substituents on the diimine ligand to perform a quantitative structure-activity relationship (QSAR) study [103].

Moreover, Chen et al. have synthesized copper(II) complexes of ethyl 2-[bis(2-pyridylmethyl)amino]propionate ligand (ETDPA). These complexes are stable in air with the formula of  $[(\text{ETDPA})\text{CuCl}_2]$  and  $[(\text{ETDPA})\text{Cu}(\text{phen})](\text{ClO}_4)_2$ . The DNA-binding properties of the two Cu complexes with DNA was different. The binding mode of  $[(\text{ETDPA})\text{CuCl}_2]$  is not the classical intercalation binding, and the binding mode of  $[(\text{ETDPA})\text{Cu}(\text{phen})](\text{ClO}_4)_2$  with DNA is intercalation. The cytotoxic assay shows that the  $[(\text{ETDPA})\text{Cu}(\text{phen})](\text{ClO}_4)_2$  is more active on the proliferation of cancer cells than the  $[(\text{ETDPA})\text{CuCl}_2]$  [106].

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