Platinum Group Antitumor Chemistry: Design and development of New Anticancer Drugs Complementary to Cisplatin

Adnan Salim Abu-Surrah[*,1] and Mika Kettunen[2]

[1]*Department of Chemistry, Hashemite University, P.O. Box 150459, Zarqa-13115, Jordan*

[2]*Conway Institute of Biomolecular and Biomedical Research, School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4, Ireland*

Abstract: In the next two decades, the world is expected to see around 20 million cases of cancer. Moreover, the types of cancer will vary considerably from country to other. Therefore, all efforts will be needed to face such a vast diversity of problems. With current annual sales of about $500 millions, the platinum(II) complex known as cisplatin [*cis*-$(NH_3)_2PtCl_2$] is still one of the most effective drugs to treat testicular, ovarian, bladder and neck cancers. Since it was launched in 1978 there has been a rapid expansion in research to find new, more effective metal-based anticancer drugs and to study their interactions with biological systems.

This study gives an up to date overview of the anticancer chemistry of the platinum group elements platinum, palladium, and nickel with an emphasis on the new strategies used in the development of new antitumor agents. Methodologies for application of bulky aromatic or aliphatic nitrogen ligands, chiral organic moieties, chelates containing other donor atoms than nitrogen, and biologically active ligands in the design of agents analogous to cisplatin are presented. The review also aims to highlight the class of the unconventional complexes that violate the empirical structure-activity rules (SAR) of platinum compounds and the common features and structural differences between the most successful anticancer complexes that are currently in human clinical trials.

Keywords: Platinum complexes, palladium complexes, nickel complexes, unconventional complexes, anticancer agents, cytotoxicity, chiral ligands.

INTRODUCTION

Since the discovery of the activity of one of the most successful anticancer compound *cis*-diaminedichloroplatinum(II), [*cis*-$(NH_3)_2PtCl_2$] (Fig. **1**, **1A**), clinically called cisplatin [1,2] thousands of platinum complexes have been synthesized and evaluated for their anticancer activity. However, a few of these complexes have entered clinical trials [3,4], of which five are currently approved: cisplatin (1A) and carboplatin (1B) world-wide, oxaliplatin (1C), in a few countries, nedaplatin in Japan, and Lobaplatin in China [3-5].

Most of the platinum compounds that entered clinical trials follow the same empirical structure-activity relationships summarized by Cleare and Hoeschele [6,7]. A necessary prerequisite for an active Pt-drug seems to be *cis* coordination by bidentate amine ligands or two amines (at least one NH group on the amine) and two leaving groups with an intermediate binding strength (e.g. Cl^-, SO_4^{2-}, citrate or oxalate) to platinum.

The limitations of cisplatin have stimulated research in the field of platinum antitumor chemistry by giving specific goals. These include reduction in toxicity of cisplatin (nausea, ear damage, vomiting, loss of sensation in hands, and kidney toxicity), circumvention of the acquired drug resistance observed in certain tumors, increased spectrum of activity since cisplatin is inefficient against some of the commonest tumors (e.g. colon and breast) and oral administration for the new anticancer drugs [3,8]. In addition, enormous efforts have been directed to understand the mechanism of the cytotoxic activity of cisplatin [9-11].

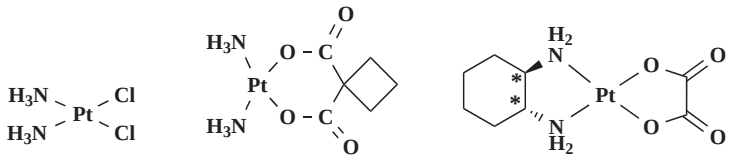
A second generation analogue of cisplatin, carboplatin [*cis*-$(NH_3)_2Pt(CBDC)$] (*cis*-1,1´-cyclobutyldicarboxylatodiamineplatinum(II)), (CBDC, 1,1´-cyclobutyldicarboxylate), (Fig. **1**, **1B**), has reduced toxic side effects for the same efficiency thanks to its much lower reactivity [8,12,13]. Unfortunately, carboplatin is only active in the same range of tumors as cisplatin and still administrated intravenously [14,15].

The third generation of drugs includes compounds that contain different types of chiral amines [15-18]. Oxaliplatin (Fig. **1**, **1C**) (*cis*-oxalato-*trans*-*l*-1,2-diaminocyclohexaneplatinum(II)) showed antitumor activity in colorectal cancer [17,19], had positive preclinical evaluations for use in cisplatin resistant tumors and can be administrated orally [20,21]. Investigations on these types of chiral complexes showed that the *trans* isomer *trans*-*l* (*trans*-(–)-1R,2R) is more efficacious than the corresponding *trans*-*d*- (*trans*-(+)-1S,2S) and the *cis*-isomer (1R,2S) [22]. Thus, the activity might be explained by speculating on the stereochemical structures of the complexes.

Recently, some pioneering strategies towards the synthesis of novel platinum anticancer drugs have emerged [4,5,8,12,23]. Those are based on changing the coordinated

*Address correspondence to this author at the Department of Chemistry, Hashemite University, P. O. Box 150459, Zarqa-13115, Jordan; Tel: +962 5 390 3333 (Ext. 4315); Fax: +962 5 390 3349; E-mail: asurrah@hu.edu.jo

0929-8673/06 $50.00+.00



(1A) (1B) (1C)

Fig. (1). Structures of the anticancer drugs, cisplatin (**1A**), carboplatin (**1B**), and oxaliplatin (**1C**).

nitrogen ligand or altering the leaving groups. Other strategies have focused on changing the type of the metal center (e.g. palladium (II) complexes) or applying platinum(IV) complexes that are relatively more soluble in water. Attention also has been shifted to discover "nonclassical" drugs that can act in a manner different from cisplatin [24]. Unconventional structures that violate the empirical structure-activity rules (SAR) of platinum compounds lacking NH, NH_2, or NH_3 ligands and multinuclear complexes are examples of these compounds that are designed to circumvent cisplatin resistance and enhance its activity.

Several review articles have appeared during recent years dealing with the synthesis, preclinical screening, and mechanism of action of platinum-based anticancer drugs [3,4,8,9,23,25-29]. In this review, the progress in the field of anticancer chemistry of platinum-, palladium-, and nickel-based transition metal complexes during the last 10 years will be highlighted. The complexes that illustrate the prominent strategies utilized in the development of anticancer platinum group-based agents will be presented.

1. CHEMISTRY OF THE PLATINUM GROUP

Oxidation state (II) represents by far the most important state in most of the normal chemistry of palladium and nickel. For platinum it is at least as important as the (IV) state. In the absence of ligands that make special demands on the metal, Ni(II) is usually paramagnetic and octahedrally coordinated, whereas Pd(II) and Pt(II) are diamagnetic and square planar. In the presence of ligands that have special steric and electronic requirements nickel(II) can also adopt a square planar coordination. Ni(II) forms a large number of complexes with a coordination number between three and six. It differs in this respect from its homologues Pd and Pt, which prefer coordination number four. Consequently, ligand exchange processes for Ni(II) tend to be associative, while dissociative pathways are predominate in the case of Pd and Pt [30].

Oxidation of M(II) to M(IV) is usually more difficult for Pd than for Pt, but oxidation to Ni(IV) is much more difficult. Due to the higher electronegativity of nickel (1.75) compared to palladium (1.35) and platinum(1.44), Ni(II) forms more stable aqua complexes than Pd(II) and Pt(II). The $[Pt(H_2O)_4]^{2+}$ ion reacts about 10^6 time less rapidly in water exchange than does its corresponding $[Pd(H_2O)_4]^{2+}$. Of interest in the view of antitumor properties of cisplatin are the cations such as *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, which are known to be the forms that react with DNA.

Comparative studies of the relative rates of substitution of identical complexes of Ni(II), Pd(II), and Pt(II) showed that the relative rates are 5×10^6 (Ni), 1×10^5 (Pd), and 1 (Pt). Generally palladium is intermediate between nickel and platinum, but is perhaps closer to platinum based on the properties presented above [31,32].

2. PLATINUM ANTITUMOR CHEMISTRY: HISTORICAL BACKGROUND

2.1. Cisplatin: The First Generation of Platinum-Based Anticancer Agents

Cisplatin was first synthesized in 1844 by Peyrone, in Turin, but its biological activity was accidentally discovered in 1965 by Rosenberg [33-35]. During the investigation of the influence of weak alternating currents on the growth of *Escherichia coli* bacteria Rosenberg used ostensibly inert platinum electrodes. The result of these experiments was an inhibition of cell reproduction without simultaneous inhibition of bacterial growth, which eventually led to the formation of long, filamentous cells. After extensive research, they realized that small amounts of platinum from the electrodes had reacted with NH_4Cl to produce various platinum amine halide complexes. Two of these, *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin (**1A**)) and its corresponding tetrachloro complex *cis*-$[Pt(NH_3)_2Cl_4]$ were capable of inducing filamentous growth in the absence of an electric field [1]. It has been known that this kind of growth indicates the potential antitumor activity of the corresponding chemicals. Therefore, Rosenberg and coworkers performed experiments with sarcoma 180 and leukemia L1210 bearing mice [36,37]. This led to cisplatin entering phase I clinical trials in 1971. Approval of cisplatin for treatment of testicular and ovarian cancer was given in 1978 [3]. Currently, cisplatin is one of the most widely used antitumor drugs. It is highly effective in treating testicular, ovarian, bladder, cervical, head and neck, and small-cell and non-small cell lung cancers [3,38].

Despite its activity in many cancers, cisplatin is ineffective in others e.g. leukemia, renal and gastrointestinal cancers. The major barrier to cisplatin efficacy is perhaps the drug resistance, which can be either intrinsic or acquired [3,39]. That means for the latter case that many cancers, including ovarian cancer, initially responsive to cisplatin become resistant to it. It also has major toxicity limitations of which nephrotoxicity is the most notable, although nausea and vomiting, peripheral neuropathy, and myelotoxicity can also raise major concerns [40-42].

Cellular resistance to cisplatin is due to several factors and has been reviewed in details [43]. For cisplatin, which is routinely used in dosages at the limit of its systemic toxicity, the level of resistance can completely eliminate clinical effectiveness [44]. The major causes of resistance that have been observed are the prevention of sufficient amount of drug from reaching and binding to DNA and a failure of cell

death which taking place after binding of Pt to DNA [45]. Reduced platinum accumulation and increased cytoplasmic detoxification by glutathione and/or metallothioneins represent the major causes of inadequate drug concentrations reaching DNA. Once DNA binding has occurred, resistance mechanisms include increased DNA repair of adducts, and an ability to tolerate greater levels of DNA damage with concomitant failure to engage programmed cell death (apoptotic) pathways. Elucidation of these mechanisms of resistance has been essential in providing a basis for the development of Pt-based complexes capable of circumventing cisplatin resistance.

2.2. Carboplatin Analogues Complexes: Compounds Containing Chelating Carboxylate Leaving Groups

Since the introduction of cisplatin, thousands of platinum complexes have been synthesized and evaluated for their antitumor activity. The main aim of these intensive investigations was to obtain drugs with at least an equal activity but reduced toxicity compared to cisplatin. The strategy to reduce toxicity involved increasing the solubility in water and stability of the complexes. This has been generally achieved by replacing the chloro ligands either with chelating carboxylate, oxalate, sulfate or glycolate. This kind of leaving group is the main feature of the second generation compounds. The most successful of them is carboplatin [$(NH_3)_2Pt(C_4H_6O_4)$] (Fig. **1**,**1B**). It has improved the therapeutic index of cisplatin by ameliorating some of the toxic side effects [12,13]. Although it has a lower activity than cisplatin, its decreased toxicity allows outpatient administration without need for forced diuresis and very high dosages (up to 2000 mg/dose) can be achieved with possibly more antitumor efficacy [8,12]. Nevertheless, it appears to have the same spectrum of anticancer activity of cisplatin and thus is not active against cisplatin resistant tumors [14,15].

Several carboplatin analogue compounds containing cyclobutane ring were developed in the late 80s, in the hope of improving the carboplatin characteristics. The compounds include zeniplatin (CL 286558), [1,1'-cyclobutanedi-carboxylato{2,2-bis(aminomethyl)-1,3-propandiol}platinum(II)](**2**) [3,16] Enloplatin (CL 287110) [1,1'-cyclobutane-dicarboxylatotetrahydro-4Hpyran-4,4-dimethylamineplatinum(II)] (**3**) [3] Miboplatin (DWA 2114R), [R-(-)-1,1'-cyclobutane dicarboxylato-2-aminomethylpyrrolidine-platinum(II)] (**4**) [3,16,46-48] and CI-973 (NK 121), [1,1'-cyclobutane-dicarboxylato-2-methyl-1,4-butandiamineplatinum(II)] (**5**) [46,49-51] (Fig. **2**).

Other compounds that were developed later but are still linked to the second generation compounds through their structures (Fig. **2**) include Lobaplatin, (D-19466), [lactato-diaminomethylcyclobutaneplatinum(II)] (**6**), SKI 2053 R [malonatomethyl isopropyldimethylaminodioxelane)platinum(II)] (**7**), Cytoplatam [malatoaminecyclo-pentylamine) platinum(II)], (**8**), and Nedaplatin (254-S), [*cis*-glycolato-diamine-platinum(II)] (**9**) [3,4].

From the second generation, only carboplatin fulfilled all the requirements for marketing approval worldwide, while Lobaplatin (**6**) which was introduced into clinical trials in 1992 [52] for cisplatin-resistant ovarian cancer [53], head and neck cancers [54], and small-cell lung cancer [55], has been approved in China for the treatment of breast cancer and Nedaplatin (**9**) received approval for use in Japan in 1998 [4,5]. As a single agent in phase II studies, response rates of about 25% were observed for head and neck, testicular, lung, bladder, ovarian, and cervical cancer [3,46]. The compounds Zeniplatin (**2**), Enloplatin (**3**), Miboplatin

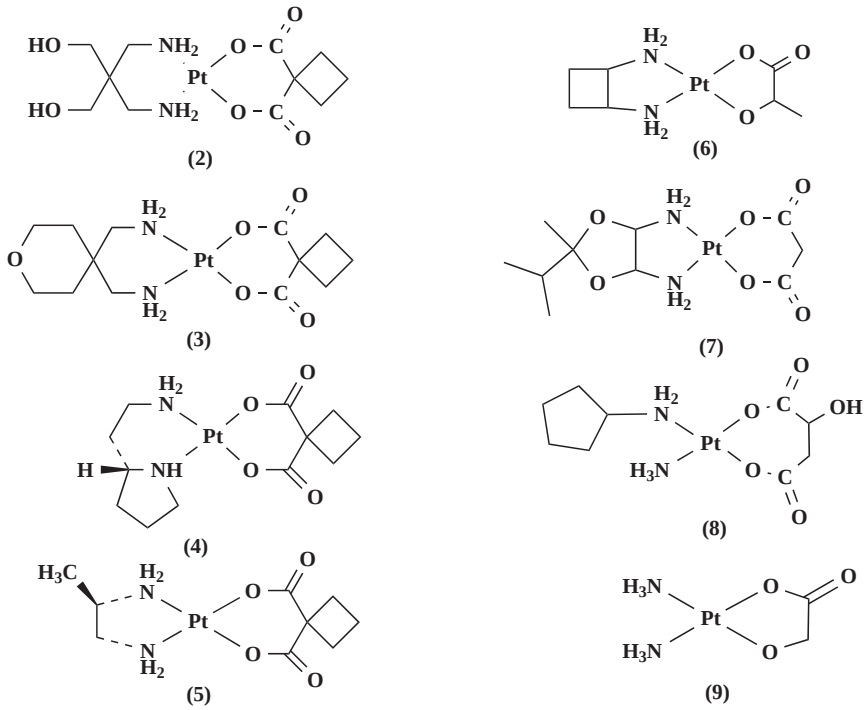


Fig. (2). Carboplatin analogues complexes: Zeniplatin (**2**), Enloplatin (**3**), Miboplatin (**4**), CI-973 (**5**), Lobaplatin (**6**), SKI 2053R (**7**), Cytoplatam (**8**), and Nedaplatin (**9**).

(**4**), and CI-973 (**5**) have all been abandoned due to insufficient activity or unacceptable side effects [3-5].

2.3. Cisplatin Reactivity and the Biological Target

The square planar complex cisplatin is relatively inert kinetically, does not easily expand its coordination number and undergoes ligand substitution reactions by two independent pathways: solvent-assisted and bimolecular pathways [56]. Although the formation of the initial complex is kinetically controlled, it can undergo *cis*-*trans*-isomerism [57]. Thermodynamically, the stability of the complex can be enhanced in the presence of a chelating ligand. It can also be influenced by varying the *trans* ligand which is able to weaken the bond *trans* to itself (*trans* influence) [58]. The *trans*-influence factors are always stronger than the corresponding *cis* ones [59].

The hydrolysis rate is mainly determined by the *trans* effect of the ligand *trans* to Cl [60,61]. Steric hindrance is also well known to slow down the rates of ligand substitution reactions in square-planar metal complexes [62]. Diaqua cisplatin is very reactive but the deprotonated hydroxo forms are usually considered to be relatively inert. Therefore the acidity of the coordinated water molecules in aqua complexes can be directly relevant to their reactivity with target molecules.

After injection (oral administration is not possible due to highly gastric acidity) cisplatin binds to plasma proteins and is renally excreted (30-70%). The remaining fraction is transported by the blood in an unaltered form. After passive transport of neutral cisplatin through cell membranes of different organs or tumor cells, it is rapidly hydrolyzed due to the markedly lower chloride concentration in intracellular regions. The hydrolysis reaction is the rate-determining step for DNA binding. Within cells, about 40% of the platinum is present as $[cis\text{-}Pt(NH_3)_2Cl(H_2O)]^+$ which is assumed to be the active form of the antitumor agent. Furthermore, the cationic species would be likely to approach and coordinate to the negatively charged DNA [35].

DNA offers several nucleophilic centers to which the active $[Pt(N)_2]^{2+}$ species may bind. *In vitro*, binding is possible to N7 of guanine (G), N1 and N7 of adenine (A) and N3 of cytosine (C). But as N1 of adenine (A) and N3 of cytosine (C) are engaged in hydrogen bonding with the DNA framework, and as G-N7 is the most electron-rich site on DNA, this later one is mainly involved in bonding. Thus, *in vivo* aquated cisplatin subsequently binds to G-N7, which displaces the water molecule in a relatively fast reaction step ($t_{1/2}$ about 0.1 h), forming a monofunctional adduct. Then the second chloride undergoes hydrolysis which leads to the formation of a second bond with DNA. Major DNA adducts are cross-links involving adjacent purine: *cis*-$[Pt(NH_3)_2$\{1,2-intrastrand-d(GpG\}] comprising about 65% of the adducts formed followed by *cis*-$[Pt(NH_3)_2$\{1,2-intrastrand-d(ApG\}] comprising 25% (d: deoxy form of ribose, p: phosphate). Minor adducts include 1,3-intrastrand cross-linking to non-adjacent guanines, monofunctional binding to guanine and interstrand bonding [8,9,23i].

Several studies have dealt with the DNA binding of Pt drugs. These studies have covered single nucleosides to oligonucleotides, to plasmids and genomic DNA. This field has been reviewed by others [8, 23i, 63]. Guanine sites have strong affinity for Pt amine compounds and two adjacent guanines are preferred. The two most frequent binding sites, GG and AG, appear to be valid for several sources of DNA [64].

For a better understanding of the toxicity and side effects of the antitumor drugs, the interaction of cisplatin, carboplatin and oxaliplatin with excess Hemoglobin was recently investigated [65]. Only oxaliplatin was found to form three major complexes with Hemoglobin after 1 hr of incubation at room temperature, consuming about 60% of oxaliplatin.

3. RECENT DEVELOPMENT IN PLATINUM ANTICANCER DRUGS: STRATEGIES USED TO DESIGN NEW AGENTS

Cisplatin is not only the first platinum complex which exhibited antitumor activity, but it is also the complex with the simplest structure. Currently, there are still a large number of cisplatin analogous modifications still being pursued world wide. Most of them are based on altering the amine ligand which is responsible for the structure of the adducts formed upon interacting with DNA [66], or the halide leaving group that influences tissue and intracellular distribution of the platinum complexes and improve the drug's toxicity profile [67]. Other approaches have focused on applying platinum(IV) complexes or utilizing ligands bearing other donor atoms than nitrogen (e.g. S, P, O). 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 [68] or electrochemotherapy treatment which consist of chemotherapy with platinum(II) drug followed by local application of electric pulses to the tumor to increase the drug delivery into cells [69]. The advantages of these techniques are their simplicity, short duration of the treatment sessions, low drug doses, and insignificant side effects [70].

Research in the field of platinum-based cancer chemotherapy showed that cisplatin and analogous compounds exhibit very similar patterns of antitumor efficacy and susceptibility to resistance which means that most of them produce identical adducts with DNA. The determining factors of cytotoxicity thus do not always follow the original structure-activity relationships (SAR). Possibly, the new clinically useful platinum based anticancer agents should have novel structures unrelated to those agents assigned to platinum complexes. Therefore, several unconventional complexes such as *trans*-platinum(II) complexes, multinuclear platinum complexes, and palladium(II) complexes have been synthesized and evaluated.

In the following sections we focus on the complexes that illustrate the recent strategies utilized in the development of new platinum-based anticancer agents.

3.1. 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

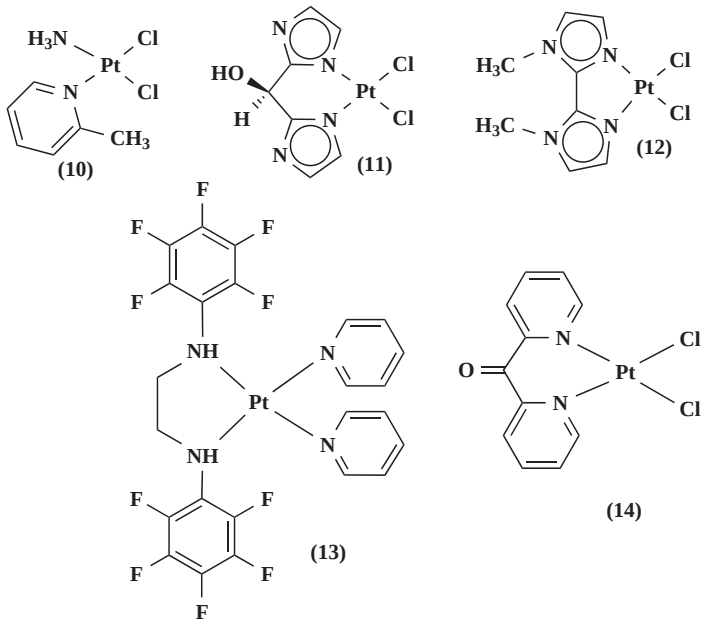


Fig. (3). Platinum(II) complexes bearing bulky aromatic nitrogen ligands (**10**-**14**).

block binding of thiols and DNA-repair proteins [71]. For example, platinum(II) complexes of the general formula *cis*-$[(L)(NH_3)PtCl_2]$ (L= pyridine, pyrimidine, purine, papyridine) were reported to show promising antitumor activity. ZD0473 (also called AMD473) [*cis*-(2-methylpyridine)$(NH_3)PtCl_2$] (**10**) (Fig. **3**) [72] was rationally designed in order to reduce the reactivity of glutathione which may be the key to improve responses in resistant tumors [71,73]. It is active (injection or oral) against acquired cisplatin-resistant cell lines and posses a toxicity profile similar to carboplatin [71,73]. It entered clinical trials in 1997 in the U.K. and was licensed by Zeneca in 1998. In ZD0473 a steric bulk at the platinum center was introduced using a heterocyclic ligand with substituents on the ring atom in order to prohibit the access of sulfur to Pt. Such compounds are expected to favor a dissociative mechanism of substitution. On the contrary, with a relatively unhindered molecule like cisplatin the associative mechanism predominates. It is noticeable that the major requirements in this class of compounds are that they all should contain aromatic ligands with a reasonable amount of steric hindrance, even if the hindrance is not close to the coordinated N atom itself. Although complexes that do have substituents close to the coordinated N atom at the 2 or 6 position on the non leaving pyridine ligand are expected to show less activity than the non-substituted complexes or the 4-substituted compounds. It may be that the structure-activity rule" presence of NH group rule" has as much to do with reducing steric hindrance at platinum as with positive H-bonding interactions.

In order to decrease the reactivity of the 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 [74]. A comparative study about structural, kinetic, and biological properties of $[(BMIC)PtCl_2]$ (**11**) and $[(BMI)PtCl_2]$ (**12**) (BMIC: bis(N-methylimidazol-2-yl)carbinol; BMI: N,N'-dimethyl-2,2'-biimidazole) has been reported (Fig. **3**) [74]. These complexes showed significant cytotoxicity even though the tertiary amine does not 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. Complex **11** exhibits significant cytotoxic activity against L1210 leukemia.

Platinum(II) complexes of the general formula $[(Py)_2Pt\{N(C_6F_{5-n}Y_n)CH_2\}_2]$ (**13**) (Y = H, I, n = 0,1) also showed antitumor activity against various tumor cell lines (some cisplatin resistant ones included) *in vitro* and *in vivo* (Fig. **3**) [75]. These bis(pyridine)platinum(II) organoamide complexes which contain a sterically hindered leaving group, violate the SAR rule not only because they lack the NH group but also because they contain four N-donor ligands. However, it has been discovered that the $[Pt(Py)_2)]^{2+}$ moiety can bind in a way similar to cisplatin [76].

Recently, new cisplatin analogous complexes bearing a bidentate dipyridyl nitrogen ligand have been prepared by Krebs and collaborators (Fig. **3**) [77]. Biological tests of the complex $[Pt(DPK)Cl_2]$ (**14**, Fig. **3**) (DPK = 2,2'-dipyridyl-ketone) showed significant antitumor activity of the complex against the human glioma cell line *U* 87.

Platinum complexes bearing tridentate nitrogen ligands based on amino acid substituted quinolylamide have been syntheisized and evaluated for their cytotoxicity by Guo and collaborators [78]. An example of them is the complex $[(L_3)PtCl]$ (L_3 = N-(tert-butoxycarbonyl)-L-methionine-N'-8-quinolylamide) which is highly cytotoxic against the HCT-116 (IC_{50} = 0.38 μM), SPC-A4 (IC_{50} = 0.43 μM), BEL-7402 (IC_{50} = 0.43 μM), and MOLT-4 (IC_{50} = 0.61 μM) cell lines. The cell line that is most sensitive to this complex is the human liver carcinoma cell line BEL-7402, which has a response rate nearly 6 times higher than that of cisplatin.

3.2. Platinum Complexes Bearing Chiral, Enantiomerically Pure Nitrogen Ligands

Biological systems can recognize the members of a pair of enantiomers as different substances, and two enantiomers will show different responses. Thus, it has been shown by many pharmaceuticals that only one enantiomer contains all the desired activity, while the other is either inactive or toxic. A general method for the synthesis of enantiomerically pure transition metal complexes in a high yield is the direct substitution reaction of the enantiomerically pure chiral ligand with the metal-based starting material [79].

Because double-helical DNA has a chiral structure, interaction with enantiomerically pure platinum complexes should lead to diastereomeric adducts. Results in the field of applications of chiral ligands demonstrated how the stereochemistry of Pt-DNA adduct can influence the cell response and contribute to understanding the processes that are crucial for antitumor activity [80].

3.2.1. Complexes with Chiral Monodentate Nitrogen Ligands

Since it has been found that the activity of *cis*-$Pt(N)_2(X)_2$ (N = amine, X – anionic ligand) decreases in the order N = NH_3 > RNH_2 > R_2NH [81], 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 (**15**) that contains a phenylethylamine ligand (Fig. **4**). This behavior could be due to the steric effect of the ligand [82].

3.2.2. Platinum(II) Complexes with Chiral Ethylene-Bridged Bidentate Nitrogen Ligands

The degree of rotation and any possible *cis-trans* isomerism can be hindered by bridging together the two nitrogens of the amine ligands (i.e. by utilizing bidentate chelates). Different enantiomerically pure bidentate nitrogen ligands have been complexed to platinum such as in the complexes **4**, **5** and **11**. Interestingly, complex **4** bearing the R-enantiomer of the chiral ligand is not toxic, whereas the S-enantiomer is toxic [83]. Another example in this class are the platinum complexes of the S,S- and R,R-ethambutol (**16**, Fig. **4**). Decreasing the rotational freedom of the substituents in these complexes leads to different biological activity for the two enantiomers [84]. Further investigations into the cytotoxicity of this complex were cancelled because it was found that the conformation at the nitrogen atoms was not stable and isomerization took place at high temperature and basic pH.

Recently, the influence of the chelate ring size around the platinum on antitumor activity and interaction with DNA was investigated using platinum complexes of the general formula $[(N\text{-}N)PtCl_2]$ (**17**) (N-N: D,L-2,3-diaminopropionic acid and its ethyl ester, *d*,*l*-diaminobutyric acid and its ethyl ester) (Fig. **4**) [85]. The interaction between Pt complex and DNA takes place at the N7 position of the purine bases, and the platinum complexes of the 2,3-diaminopropionic acid and 2,4-diaminobutyric acid were found to be able to form intrastrand adducts with DNA. The ethyl ester derivatives uncoiled the DNA from the B form to C form. The platinum complexes of the diaminocarboxylic acids exhibit cytotoxic activity in the A431, HeLa, and HL-60 cell lines in a dose and time-dependent manner.

Platinum complexes containing the ligands, 1,2-diaminopropane (1,2-DAP) or 2,3-diaminobutane (2,3-DAB) (**18**, Fig. **4**) have also been evaluated. The *in vitro* biological tests showed a significant difference among stereoisomers, the S,S-isomer being 10 times more mutagenic than its enantiomer [86]. Platinum complexes of N,N'-Me_2DAB (**19**) and bipiperidine (**20**) (Fig. **4**) which do not contain primary nitrogen ligands, were found to be less effective as antitumor drugs [81].

Different derivatives of platinum(II) complexes containing ethylene substituted backbone (e.g. 1,2-diphenylenediamine) have been prepared [87,88]. Biological studies on 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 (MXT-M-3,2-MC). The most active derivative was the aqua[1,2-bis(2,6-

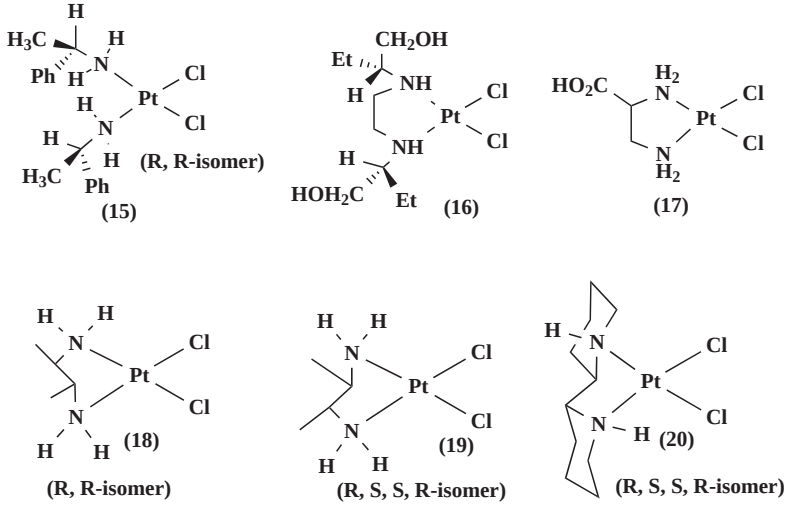
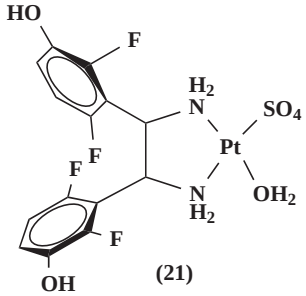


Fig. (4). Platinum(II) complexes containing the chiral ligands: phenylethylamine, ethambutol, 1,2-DAP, 2,3-DAB, N,N'-Me_2DAB and bipiperidine (**15-21**).

difluoro-3-hydroxyphenyl)ethylene-diamine]sulfatoplatinum (II) (**21**, Fig. **5**), and the *meso* iso-mer proved to be more active than the *rac*-one [89].



(21)

Fig. (5). Structure of the 1,2-diphenylenediamine-based complex **21**.

3.2.3. Complexes Containing Chiral DACH-Based Bidentate Nitrogen Ligands

Since Burchenal *et al*. showed that some complexes bearing 1,2-diaminocyclohexane (DACH) were active against cisplatin resistant L1210 leukemia cell lines, [90,91] several complexes containing DACH have received considerable attention. DACH has two asymmetric centers at carbon 1 and 2 in the alicyclic ring and this gives rise to R,R-(*trans*-l), S,S-(*trans*-d), and *cis*-DACH as the possible isomers. The conformation of the platinum complexes bearing DACH ligand may have a relation to their activity. The cyclohexyl ring of *cis*-isomer is nearly perpendicular to the chelate ring, while in both enantiomers of *trans*-DACH complex the ring lies in a common plane. Therefore the *trans* isomers could enter the large groove of the DNA double-helix more easily than the *cis*-isomer (Fig. **6**) [92]. Platinum compounds from another DACH isomer, *cis*-1,4-diaminocyclohexane, have also been prepared [93].

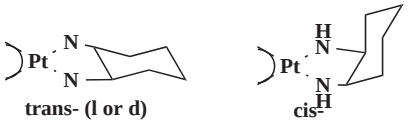
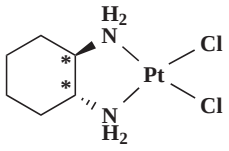


Fig. (6). *Cis* and *trans* isomers of *trans-l*-1,2-diaminocyclohexane (DACH).

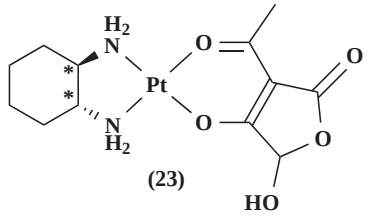
[*cis*-1R,2R-(DACH)$PtCl_2$] (**22**, Fig. **7**) was identified as the most interesting one not only for its activity but also for its remarkable biological properties. It has reduced nephrotoxicity and lack of cross-resistance in a murine system [19,20]. Unfortunately, it is completely insoluble in water and most organic solvents and therefore cannot be administrated intravenously. In order to improve its solubility in water many derivatives of the dichloride complex were synthesized [3,4]. These include oxaliplatin, (**1C**), TRK-710 (**23**), SPH (**24**), PH (**25**), DACCP (**26**), and L-NDDP (**27**) (Fig. **7**).

Due to moderate *in vivo* activity, side effects, difficulties in the synthesis or chemical instability all the prepared compounds were abandoned after some clinical trials except for; Oxaliplatin (**1C**), TRK-710 (**23**), and L-NDDP, (**27**) [3,4,94,95]. The most successful derivative has been Oxaliplatin (**1C**) [*cis*-oxalato-*trans*-*l*-1,2-diaminocyclohexane-platinum(II)], which has been approved for clinical use in France and other European countries as a single agent or in combination with 5-FU(5-flurouracili)/FA (folinic acid) [96]. It showed antitumor activity in cisplatin-resistant murine L1210 leukemia cells [3,18] and various human cancer cell lines [19,20,97].

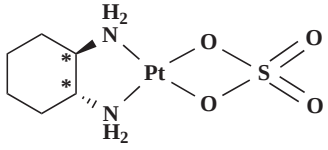
Recently, Veronese and collaborators succeeded in supporting the oxaliplatin on the surface of different molecular weight polyethylene glycol (PEG) by means of peptide spacers and a malonic acid bidentate residue [98]. Tri- and tetrapeptideic substrates of lysosomal enzymes were



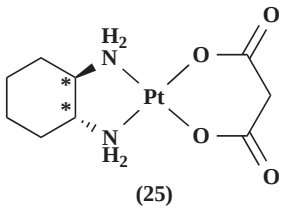
(22)



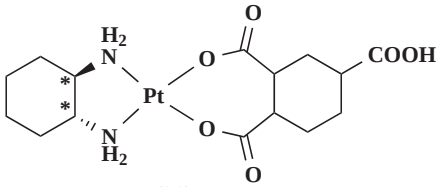
(23)



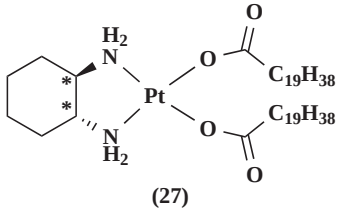
(24)



(25)



(26)



(27)

Fig. (7). Dichloro platinum(II) complex 1R,2R-(DACH)$PtCl_2$ (**22**) and its derivatives: TRK-710 (**23**), SPH (**24**), PH (**25**), DACC (**26**), and L-NDDP (**27**).

used in order to increase the release of Pt-DACH complex inside the cell following endocytosis and enzymatic degradation of the peptide spacer.

In an effort to solve the structure of the active species of the oxaliplatin, Bruck *et al*. were able to carry out X-Ray structural investigations on oxaliplatin [99]. Based on the resultant data, they reported that only the absolute configuration of the trans-*l*-DACH ligand exists in the platinum complex. However, in a recent study, we found that the oxaliplatin that was isolated following the above synthetic procedure or by using K_2PtI_4 as a starting material does not consist only of the desired isomer but a mixture of both the *trans-l* (*trans*-(–)-1R,2R) (**1C1**, Fig. **8**) and *trans-d* (*trans*-(+)-1S,2S) isomers (**1C2**, Fig. **8**) [100]. No retention of optical isomerism was observed even though the enantiomerically pure DACH ligand was utilized.

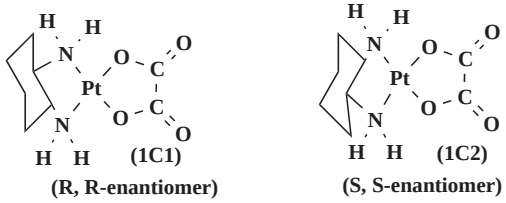


Fig. (8). Drawings for both oxaliplatin enantiomers, R,R- (**1C1**) and S,S- (**1C2**).

Several methodologies have been utilized in order to synthesize the active species, the enantiomerically pure (1R,2R)-oxaliplatin complex in a pure form [100]. One of these was the displacement of the weakly coordinated bidentate ligands (PhNC = benzonitrile) from the complex [*cis*-$Pt(PhNC)_2Cl_2$] with the desired nitrogen ligand [79, 101,102]. However, the nucleophilic substitution reaction of the enantiomerically pure ligand with [*cis*-$Pt(PhCN)_2Cl_2$] did not lead to the formation of the complex [(1R,2R)-(–)-1,2-DACH)$PtCl_2$] (**22**) as expected. Surprisingly, it took a different course, in which nucleophilic addition to the benzonitrile ligand occurred forming the new enantiomerically pure amidine complex [$(PhC{=}NH\text{-}NH(C_6H_{10})NH_2)Pt(N{\equiv}CPh)Cl$] Cl (**28**) (Fig. **9**), where the nitrogen ligand formed a seven-membered chelate around the central atom.

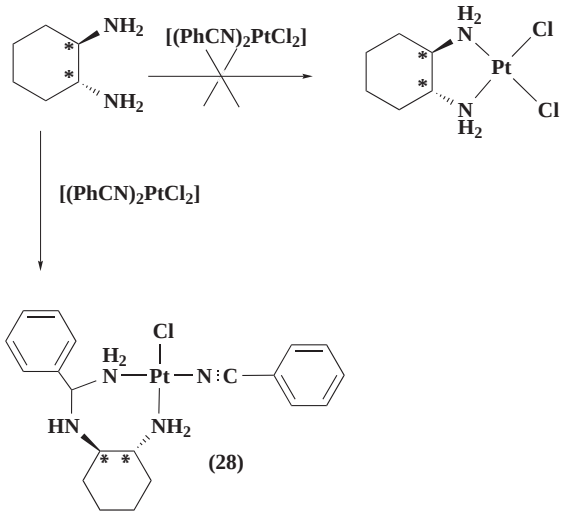


Fig. (9). Synthesis and structure of the complex (**28**).

3.3. *Trans*-Platinum Antitumor Drugs: Reevaluation of SAR Rules

The discovery of several *trans*-Pt complexes with *in vitro* and *in vivo* activity against tumor cells resistant to cisplatin has forced the re-evaluation of the structure-activity relationships (SAR) for platinum antitumor agents [24,103-107]. For the reason that the factors that influence the cytotoxic activity of *trans*-Pt complexes do not follow the same patterns as those found for cisplatin and its analogues, the differences in cellular and molecular pharmacology between *trans*-Pt complexes and cisplatin could be systematically exploited to design novel *trans* platinum complexes with a clinical profile complementary to that of cisplatin and related analogues. While isomerization of the *trans* compounds to an active *cis* isomer could account for some activity of the *trans* isomer, in many cases *cis* isomers are less active than the corresponding *trans* isomers. Transplatin (**29**, Fig. **10**) is kinetically more reactive than cisplatin and more susceptible to deactivation [108]. Careful design applying a sterically hindered ligands may reduce kinetic reactivity of the *trans* isomers of platinum complexes. As the *trans* isomer forms different Pt-DNA adducts than cisplatin analogues [109], it is hoped that *trans* platinum complexes could overcome cisplatin resistance in certain tumors.

Farrell *et al.* reported that the presence of a planar ligand such as pyridine or quinoline (complexes **30** and **31**, Fig. **10**) greatly enhances the cytotoxicity of the *trans* isomer, so that cytotoxicity is equivalent to cisplatin itself [103]. As expected, the cytotoxicity of *trans* complexes containing planar ligands are highlighted by a remarkably low resistance factor in murine and human cisplatin resistance tumor cell lines.

Studies on the DNA interaction of *trans*-[(NH_3)(quinoline)$PtCl_2$] (**31**) reveal that this complex forms considerably more interstrand cross-links than transplatin (**29**) [109]. In addition to this higher cross-linking efficiency, the quinoline ligand can interact with the duplex, which could induce specific conformational alterations around the site of platination and influence in protein recognition.

Natile *et al.* reported that the *trans* platinum-iminoether complexes (**32**) can show higher activity than the corresponding *cis* isomers. They also reported that the E or Z configurations of iminoether ligand affects the activity of the platinum complexes [110]. The greater lipophilicity of the E isomer determines a greater cellular accumulation and *in vitro* cytotoxicity than the Z isomer. On the contrary, in the *in vivo* P388 leukemia system, the Z isomer appears to be more active than the E isomer, and the possible pharmacokinetic reasons for this behavior are at present under investigation [111].

Binding to DNA of these cationic *trans*-Pt complexes might not need as a pre-requisite the formation of platinum aqua species. Hence, there would be an electrostatically drive pre-association process between the positive charge of the *trans*-Pt compound and DNA phosphates prior to coordination of the trans-Pt center to N(7) of guanine or adinine [112].

Also Kelland *et al.* reported that a *trans*-platinum complex exhibited greater *in vitro* cytotoxicity against human

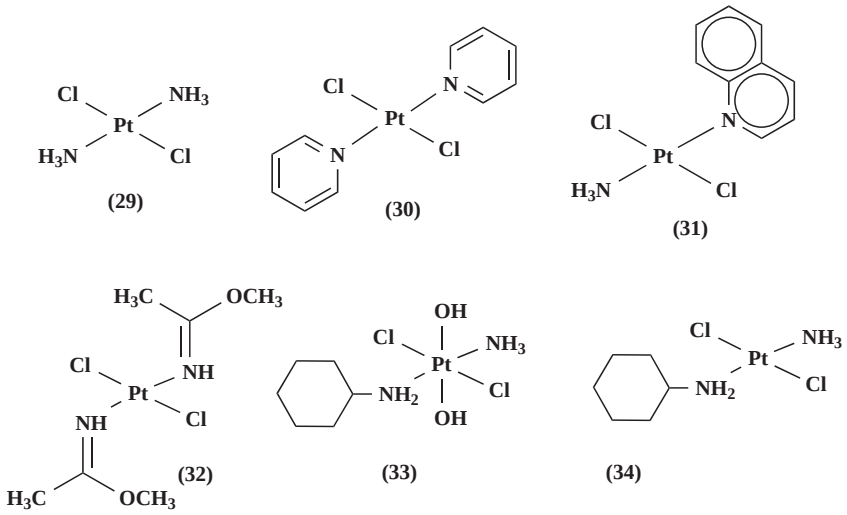


Fig. (10). Structures of some *trans*-platinum(II) complexes (**29**-**34**).

carcinoma cell lines than its corresponding *cis* isomer [106]. The complex is a Pt(IV) species, *trans, trans, trans*-[amin(cyclohexylamine)Pt(IV) dichloride], (JM335) (**33**, Fig. **10**). The platinum(II) counterpart of the complex (JM334) (**34**) did not show *in vivo* antitumor activity.

Positively charged, water soluble *cis*- and *trans*-[$PtCl_2$(piperazine)(amine)] complexes (amine = NH_3, n-butylamine, isopropylamine, 4-picoline, piperidine, and piperazine) were reported to have significant cytotoxic activity against cisplatin resistant ovarian cancer cells [113]. The charged complexes are taken up by cancer cells much more rapidly than cisplatin and bind to cellular DNA and to calf thymus DNA much faster than cisplatin or transplatin. The results reported suggest that combination of positively charged ligands with a *trans*-[Pt(II)Cl_2] species may lead to new family of platinum tumor agents that are able to circumvent cisplatin resistance.

3.4. Octahedral Platinum(IV) Complexes: Water Soluble Antitumor Drugs

Water insolubility and low bioavailability prevent cisplatin from being an orally active drug [23b]. Therefore, a new class of Pt(IV) compounds has been developed to get increased solubility in water. These drugs could represent a clinical advantage in terms of ease administration, particularly in patients who could not be treated systematically and allow the possibility of treatment on an outpatient basis, thus substantially reducing hospitalization costs. These compounds are typically neutral, water soluble, and robust enough to survive the gastric environment.

Platinum(IV) complexes are known to be much more tolerant to ligand substitution reactions than their Pt(II) counterparts [114]. In order to rationally design new Pt(IV) complexes, correlation between structure, reduction and activity were needed, since it is generally admitted that Pt(IV) compounds must be reduced to be activated. Hambley *et al.* showed that the potentials for the reduction of Pt(IV) to Pt(II) depend on the nature of the axial ligand for a series of ethylenediamine-based Pt(IV) complexes. Reduction occurs most readily when the axial ligands are Cl > OCOR > OH [115].

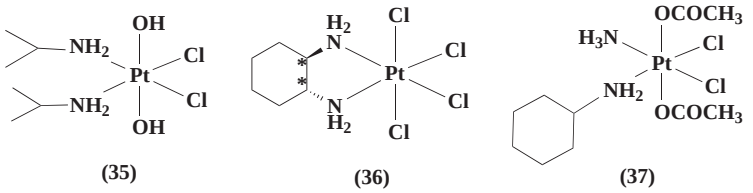
In another study, Choi *et al.* showed that the reduction rates which correlate with the reduction potentials depend on the electron-withdrawing influence of the axial ligands and the steric hindrance of axial and carrier ligand [116]. For the studied ethylenediamine-based Pt(IV) complexes the fastest reduction rate ($OH < OCOCH_3 < Cl < OCOCF_3$) corresponds to the most electron-withdrawing axial ligand and coincides with the highest cytotoxicity.

As Pt(IV) complexes need to be reduced to become active, if illumination could increase in and around the tumor the rate of reduction of Pt(IV) to Pt(II), then a more effective and less toxic therapy could be achieved. The development of Pt(IV) prodrugs that can be photoreduced to cytotoxic Pt(II) species by visible light has been pursued by Sadler and coworkers, who synthesized the *trans, cis*-[$(OCOCH_3)_2$(en)PtI_2] [117]. The toxicity of this complex towards human cancer cells is enhanced by 35% when the treated cells are irradiated with light of $\lambda > 375$ nm.

Other non-toxic, inert photoactive Pt(IV) cisplatin analogues, which after administration might remain inactive until selectively irradiated at target site were designed. Examples include the photoactive diazido complexes, *cis, trans, cis*-[$Pt(N_3)_2(OH)_2(NH_3)_2$] and *cis, trans*-[$Pt(en)(N_3)_2(OH)_2$], which can be activated by UV or visible light to Pt(II) species with the loss of the two azide ligands, and have been shown to bind to guanine on photoactivation [118].

Despite that Kelland and coworkers have found that dicarboxylate Pt(IV) complexes of the general formula *cis, trans, cis*-[$(OCOR_1)(NH_3)(RNH_2)Pt(IV)Cl_2$] (R, R_1: alkyl groups) are up to 840-fold more active than cisplatin in *in vitro* assays, none of the Pt(IV) compounds have revealed significantly greater activity in humans. Reduction of many Pt(IV) complexes, with loss of the axial ligands, occurs rapidly *in vivo* and the consequent loss of lipophilicity probably accounts for the non translation of the *in vitro* activity to animal systems.

Some Pt(IV) complexes have shown sufficient promise to enter clinical trials: Iproplatin (CHIP, JM9, *cis,trans,cis*-[(isopropylamine)$_2Pt(Cl_2)(OH)_2$] (**35**, Fig. **11**) [119-121], Tetraplatin or ormaplatin (**36**) [(*d,l*-cyclohexane-1,2-



(35) **(36)** **(37)**

Fig. (11). Some water soluble octahedral antitumor platinum(IV) complexes (**35-37**).

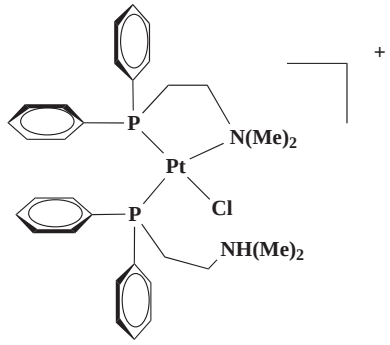
diamine)$PtCl_4$] [3], and Satraplatin (JM216) *cis*,*trans*-[$PtCl_2(OAc)_2(NH_3)$(cyclohexylamine)] (**37**) [122].

Iproplatin (**35**) was sufficiently well tolerated to enter phase II and III clinical trials [120] but found to be less active than cisplatin and so has not entered widespread clinical use [123]. Tetraplatin (**36**) has also been abandoned at the phase I level because it caused severe neurotoxicity in treated patients [4] despite that it exhibits a broad spectrum of antitumor activity and is also active against cisplatin resistant cell lines. Satraplatin (**37**) showed superior activity compared to cisplatin against human cervical, small-cell lung, and ovarian carcinoma cell lines [124]. It entered phase III trials, but the trials were abandoned due to variability in drug uptake [122].

3.5. Platinum Complexes Containing Phosphorous-, Phosphonate-, or Sulfur- Based Donor Ligands

It has been proposed that by changing the ligands on cisplatin to amino-phosphine ligands, it is possible to achieve an attack on the DNA base thymine [23d]. Phosphine complexes such as the cationic complex (**38**, Fig. **12**) are usually soluble in water despite the presence of four phenyl groups attached to the phosphorous donor ligands. Chelate ring-opening in these complexes can be controlled by the substituents on N, by the size of the chelate ring, and by the petting ligand such as Cl^- [125,126]. Complex **38** exhibits activity against cisplatin resistant tumor cells *in vitro*.

Other platinum complexes containing phosphonates of naturally occurring phosphate metabolite have demonstrated anticancer, antiviral, and antibacterial activity [127]. Pharmacological studies performed on platinum complexes with aminobis(phosphonates) have confirmed the activity towards bone tumors and other forms of tumors involving an anomalous balance of Ca^{2+} ions and which are resistant to cisplatin [128].

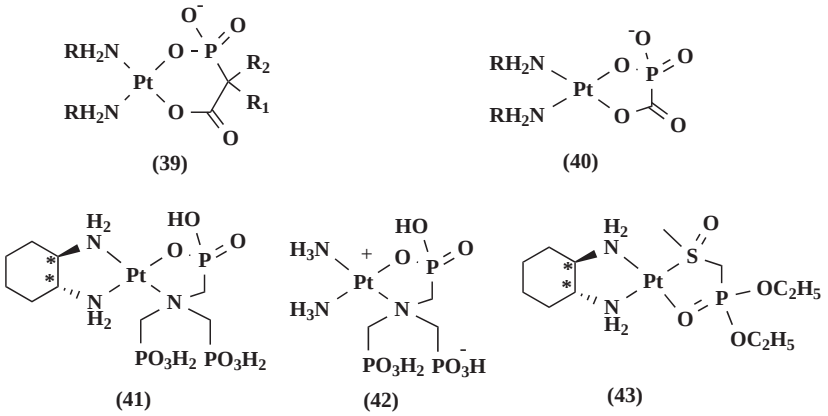


(38)

Fig. (12). Structure of platinum(II) complex with mixed amino-phosphine ligand (**38**).

Phosphono carboxylate complexes such as **39** and **40** (Fig. **13**) were also prepared. The complexes are anionic at physiological pH and possess desirable physical properties such as high solubility and stability in aqueous solutions. Good *in vitro* activity has been found for this class of compounds that showed less renal toxicity than cisplatin [129]. Other phosphonate ligands have been used to prepare platinum complexes linked to amino phosphonic acids (**41** and **42**). These complexes linked to iminophosphonates possess an N-donor ligand that can act as a leaving group. Thus they lose the phosphonate and tertiary amine ligand upon binding to nucleic acids [130].

Chemically more stable platinum-phosphonate complexes were prepared by introducing the group sulfoxide that has as a higher coordination affinity to platinum [131,132]. These complexes showed interesting biological activity [133]. Other S-O ligands have been used for the synthesis of cisplatin analogues. In particular, [2-(methylsulfanyl)-phenyl]phosphonate has been used by Kozelka *et al.* [134]. Very recently, Natile and coworkers reported on new platinum complexes containing the S-O



(39) **(40)** **(41)** **(42)** **(43)**

Fig. (13). Structures of the complexes (**39**-**43**).

ligand (diethyl{(methylsulfinyl)methyl}phosphonate) (**43**). Unlike the vast majority of metal phosphonate complexes reported earlier, this ligand is in the form of dialkyl ester, coordinating to the metal center by the oxygen atom formally double bonded to the phosphorous atom [135].

DACH-platinum complexes containing the ligand (methylsulfinyl)acetate or benzoate have also been tested [136]. The isolated complexes showed moderate cytotoxicity towards L1210 leukemia cells.

Recently, different derivatives of the complex, bis(O-ethyldithiocarbonate)platinum(II), named thioplatin were synthesized and tested for cytotoxic activity in a panel of six human tumor lines [137]. Based on this study, a structure-activity relationship for the family of the sulfur containing antitumoral platinum(II) complexes has been established. Complexes with up to 7-fold increased activity compared to thioplatin and up to 25-fold more activity than cisplatin were identified. Complexes with short n-alkyl chains such as ethyl were found to be superior to compounds with long n-alkyl chain such as octyl. Complexes derived from secondary xanthates displayed significantly higher activity than those derived from primary xanthates. All tested complexes were more active at pH 6.8 than at 7.4.

3.6. Platinum Complexes Bearing Biologically Active Ligands

Another way of providing Pt-DNA adducts of high cytotoxicity is to target the platinum moiety to DNA by attachment to a suitable biologically active ligand. Pasini and coworkers studied a platinum complexes bearing doxorubicin (bioactive carrier ligand), (**44**, Fig. **14**) as a multifunctional drug, combining two antitumor agents which are often administrated together in combination chemotherapy [138]. The resulted complex was active against doxorubicin-resistant P388 and cisplatin-resistant L1210 leukemia while maintaining antitumor activity against sensitive parents lines.

As a part of a study of the cooperative interaction of different DNA-binding ligands, Lippard *et al.* linked acridine orange to the NH of the $PtCl_2$ moiety by a polyethylene chain (**45**) [139]. Also two classes of dichloro complexes bearing either (1,2-ethylenediamine) or (1,3-propylenediamine) have been investigated [140]. These complexes were linked to 9-anilinoacridine (**46**, Fig. **14**). Unfortunately, these ligand-linked platinum complexes appeared very insoluble, and to overcome this they applied acridine carboxamide ligand (**47**) [141]. The resulting complexes exhibited a greater activity in cisplatin resistant cell lines compared to their dichloro analogues and to cisplatin.

Ligands such as estrogen analogues [142], amino acids [143], tryptamine [143], berenil [144], sugars [145], and ferrocene [146] have also been utilized for specific targeting. Recently, novel platinum complexes containing Cantharidin-based bioactive ligands [147] such as dimethylcantharidin (1-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid anhydride) and its alkyl derivatives have been prepared and

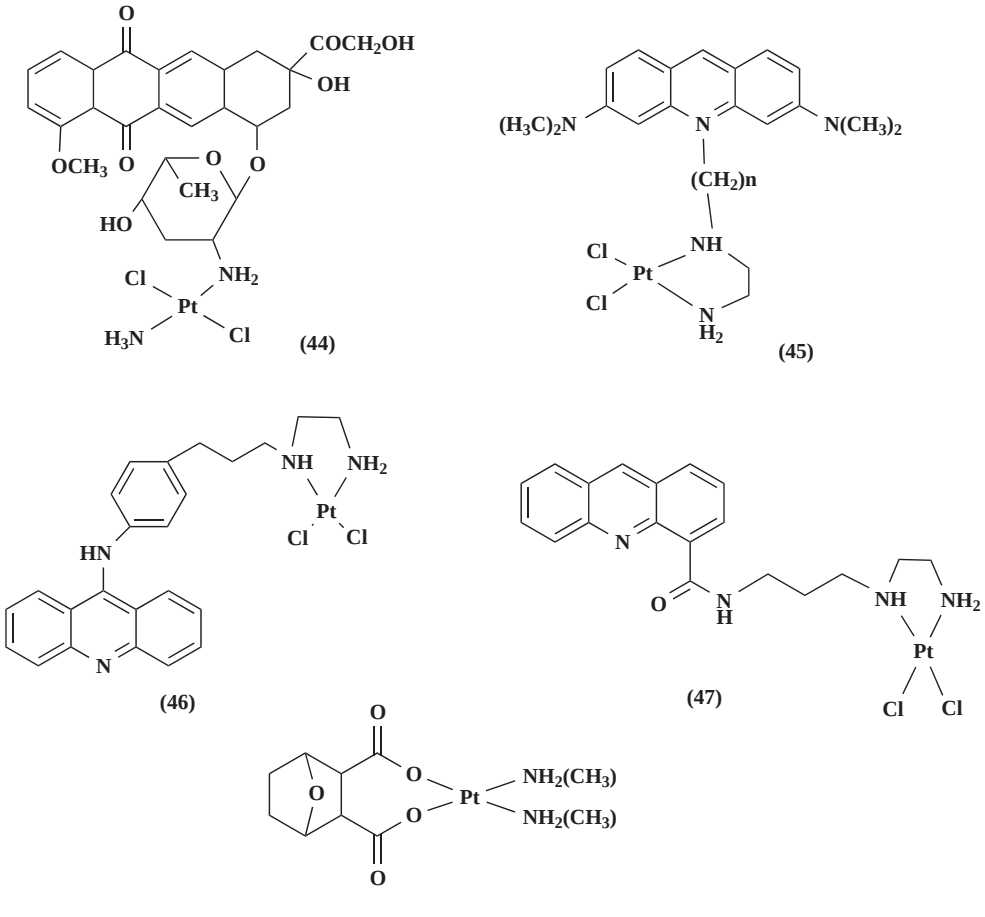


Fig. (14). Selected biologically active carrier ligands-based complexes (**44**-**48**).

evaluated (**48**, Fig. **14**) [148]. The corresponding platinum complexes were found to exhibit potent *in vitro* antitumor activity against L1210 mouse leukemia and a range of human cancer cell lines. The observed activity was comparable to cisplatin in some cell lines and superior to carboplatin in most cases.

Generally, studies of platinum compounds with biologically active carriers have yielded promising results and there is potential for varying the biological activity of these complexes by changing the structure of the carrier. Significant advances have emerged from this methodology of design.

3.7. Cationic Multinuclear Platinum Complexes

Multinuclear platinum complexes represent a distinct structural class of antitumor agents. This group of charged complexes, consisting of di-, tri- or tetra-nuclear compounds, is able to overcome cisplatin and carboplatin resistance in many important human cancer cell lines. The adducts of these complexes with DNA are flexible, non directional and mainly interstrand cross-links. DNA binding of a multinuclear complex is expected to enhance conformational changes, subsequently the difficulties of the cell to repair the drug-DNA lesion and finally the antitumor activity of the compound [149,150]. There is considerable scope for design of highly selective agents from the family of multinuclear complexes. In addition to the possible permutations on each platinum coordination spheres, variation of diamine backbone chain length is also possible. This variation can affect solubility, reactivity with entering nucleophiles, DNA-binding affinity, and like steric effects, H-bonding or possible sequence specificity.

A class of dinuclear platinum complexes that consist of two monofunctional $[Pt(NH)_2Cl]$ moieties connected by a flexible diamine link have been reported by Farrell and coworkers [24,151]. Such complexes represent a unique class of potential anticancer agents with *in vivo* activity in a cisplatin-resistant model system. The most general formula of such complexes is $[\{PtCl_m(NH_3)_{3-m}\}\text{-}\mu\text{-}H_2N\text{-}R\text{-}NH_2\text{-}[\{PtCl_n(NH_3)_{3n}\}]^{\{(2-m)+(2-n)\}+}$, where m or n = 0-3 and R = linear or substituted aliphatic linker.

Binuclear platinum(II) complexes with bifunctional thiourea [152], spermine [153], and modified tetraamine linkers have been prepared and evaluated. The protonated, noncoordinating secondary amines in these molecules may have an additional interaction with DNA by hydrogen bonding and electrostatic interaction and thus provide an enhanced activity over the parent dinuclear agents such as BBR3005 $[trans\text{-}PtCl(NH_3)_2]_2\text{-}\mu\text{-}\{trans\text{-}Pt(NH_3)_2(H_2N(CH_2)_6NH_2)_2\}](NO_3)_2$ (**49**, Fig. **15**) [153].

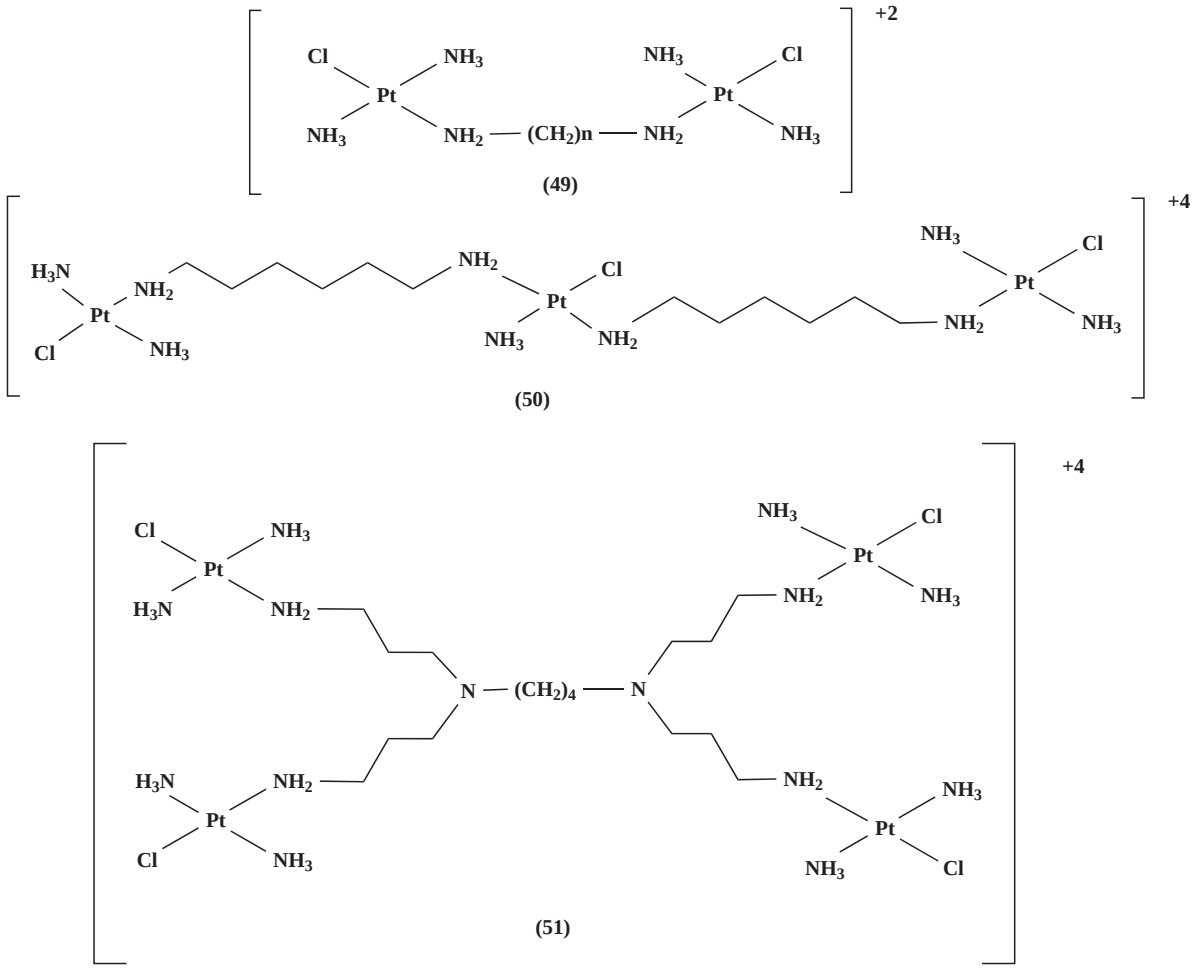


Fig. (15). Structures of the multinuclear platinum complexes (**49**-**51**).

Trinuclear [154] and tetranuclear platinum complexes have also been studied [155,156]. The trinuclear complex BBR3464 (**50**, Fig. **15**) is the first multinuclear complex which entered clinical trials in late 1997. Its preclinical anticancer profile was highlighted by exceptional potency, therapeutic doses approximately 1/10th that of cisplatin, and activity in a broad spectrum of solid human tumor [157-159]. The compound interacts with DNA in novel ways not available to cisplatin or other mononuclear platinum complexes [160].

The tetranuclear platinum complex, DAB(PA-tPt-Cl)$_4$ (**51**), the first of a generation of poly(propyleneimine) dendrimer DAB(PA)$_4$ substituted with four *trans*-diamine-chloroplatinum, showed low cytotoxicity that might be due to transport problems across the cell membranes [156].

More recently, Reedijk *et al*. reported a new class of dinuclear platinum complexes containing an azine-bridge, such as [{*cis*-Pt(NH$_3$)$_2$Cl}$_2$(μ-phthalazine)](NO$_3$)$_2$ (**52**, Fig. **16**) [161]. The isolated complexes have been evaluated for their cytotoxicity against several human tumor cell lines and L1210 murine leukemia cell lines, sensitive and resistant to cisplatin. The cytotoxicity of complex **52** in the L1210 cell lines is similar to that of cisplatin. Analysis of nuclear DNA fragmentation in L1210 cells treated with the azine-bridged complexes indicate induction of apoptosis by the complexes, implying considerable anticancer potential. Due to this behavior these multinuclear platinum complexes may represent a new class of Pt antitumor drugs and help to expand the realm of Pt chemotherapy treatment.

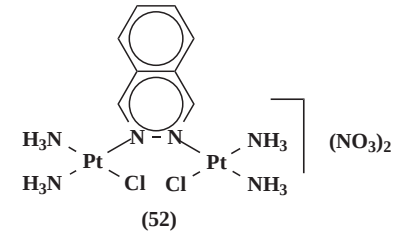
DNA-binding properties of binuclear platinum complexes with two *trans*-[Pt(NH$_3$)$_2$Cl]$^+$ units bridging by 4,4`-dipyridyl sulfide or selenide (*trans*-[Pt(NH$_3$)$_2$Cl]$_2$(DPSU)](NO$_3$)$_2$ and *trans*-[Pt(NH$_3$)$_2$Cl]$_2$(DPSE)](NO$_3$)$_2$ (DPSU = 4,4`-dipyridyl sulfide, DPSE = 4,4`-dipyridyl selenide) have been investigated and compared with the known monofunctional complex *cis*-[Pt(NH$_3$)$_2$Cl(4-methyl-pyridine](NO$_3$) [162]. The result suggested that this complex may bind bifunctionally to DNA.

Very recently, Noji *et al*. reported a new methodology for the synthesis of dinuclear platinum complexes. They react the well known complexes oxaliplatin and cisplatin with each other [163]. The isolated docking Pt(II) complex, [oxalato(*cis*-diamine)(DACH)(μ-dichloro)-diplatinum(II)] (**53**, Fig. **16**) showed higher cytotoxicity against L1210 than the parent complexes.

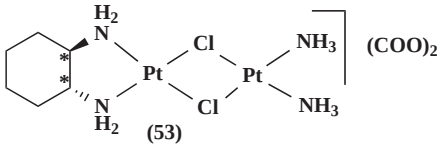
It also showed much higher activity than the mixture (1:1 molar ratio) of oxaliplatin and cisplatin. The antitumor effect against L1210/cisplatin was very high, showing collateral sensitivity and being similar to that of oxaliplatin.

4. PALLADIUM(II) COMPLEXES AS ALTERNATIVE POTENTIAL ANTITUMOR AGENTS

The notable analogy between the coordination chemistry of platinum(II) and palladium(II) compounds has advocated studies of Pd(II) complexes as antitumor drugs [31,164]. A key factor that might explain why platinum is most useful comes from the ligand-exchange kinetics. The hydrolysis of the leaving ligands in palladium complexes is too rapid: 10^5 times faster than their corresponding platinum analogues.



(52)



(53)

Fig. (16). Structures of the dinuclear platinum complexes (**52** and **53**).

They dissociate readily in solution leading to 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 palladium(II) compounds with interesting biological properties have been previously reported [165] such as [*cis*-(NH$_3$)$_2$PdCl$_2$] (**54**) [166], [*trans*-(NH$_3$)$_2$PdCl$_2$] (**55**), [(1,5-COD)PdCl$_2$] (**56**), [(π-C$_3$H$_5$)PdCl$_2$]$_2$ (**57**), and [(cyclopentyl)$_2$PdCl$_2$] (**58**) (Fig. **17**). Recent advances in this field have also focused on Pd(II) compounds bearing bidentate ligands as away to prevent any possible *cis-trans* isomerism [57,167]. In the sections below the numerous outstanding strategies applied for the development of new alternative potential antitumor agents based on palladium metal are illustrated.

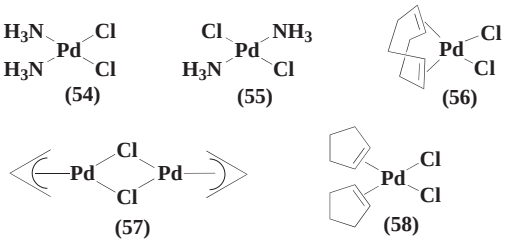


Fig. (17). Various simple palladium(II) compounds with biological properties (**54**-**58**).

4.1. *Trans*-Palladium(II) Complexes Containing Bulky Monodentate Ligands

Several *trans*-Pd complexes with promising activity against tumor cell lines 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- quinolmethyl-phosphonate (2-dqmp) [168]. The diester ligand has two potential donors, the

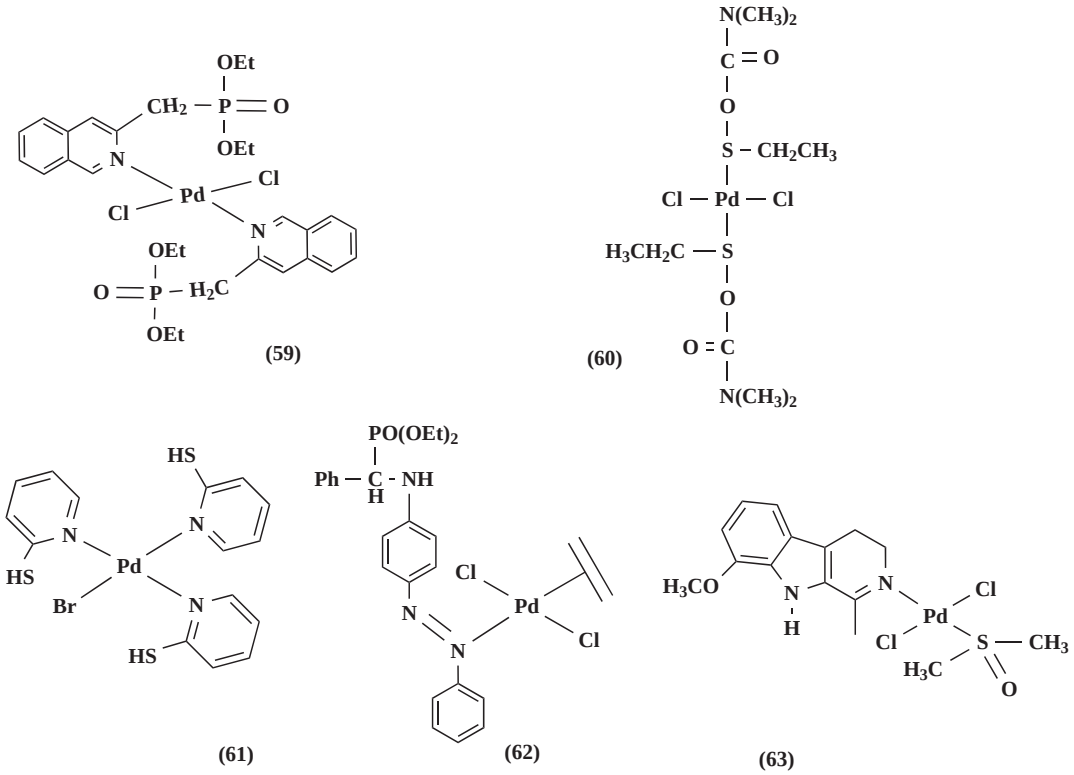


Fig. (18). *Trans*-Palladium(II) complexes containing bulky monodentate ligands (**59**-**63**).

N from quinoline and the O from phosphoryl giving the complex [*trans*-(2-dqmp)$_2$PdCl$_2$] (**59**).

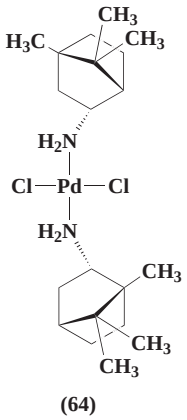
The complexes of the diester 2-dqmp were found to be more active than those of the monoester-based ligand (2-Hmqmp). This may partly be ascribed to the greater leaving activity of the halogen ligands in the complex bearing the 2-dqmp ligand and to their greater lipophilicity or solubility.

Furlani *et al*. reported about the synthesis and cytotoxicity evaluation of some *trans*-[(L)$_2$Pd(X)$_2$] complexes (**60**) (L = N,N-dimethyl-O-ethylthiocarbamate: DMTC or N-methyl-O-ethylthiocarbamate:MTC, X = Cl, Br) [169]. Other palladium complexes based on 2-Merca-ptopyridines (MP) were also prepared. The [(MP)$_3$Pd(Br)]Br (**61**) is of potential therapeutic use since it has lower IC$_{50}$ values on LoVo cell lines than cisplatin and around the same as its Pt(II) analogue [170].

Palladium(II) complexes containing alkyl phosphonates derived from aniline and quinoline were reported. Most of the aniline compounds (e.g. **62**) showed cytotoxicity *in vitro* against animal and human tumor cell lines [171].

Complexes with naturally occurring compounds have also been utilized. The palladium complex which contains the bulky nitrogen ligand harmine (7-methoxy-1-methyl-9H-pyrido[3,4-b]indole, *trans*-[Pd(harmine)(DMSO)Cl$_2$] (**63**, Fig. **18**) exhibits a greater cytotoxic activity against P388, L1210 and K562 cell lines than cisplatin [172].

More recently, we reported about the synthesis and molecular structure of a new enantiometrically pure, chiral *trans*-palladium(II) complex, *trans*-[Pd{(R)-(+)-bornyl-amine}$_2$ Cl$_2$] (**64**) (Fig. **19**) that bears the bulky amine ligand R-(+)-bornylamine (*endo*-(1R)- 1,7,7-trimethyl-bicyclo[2-2-1]-heptan-2-amine) [173]. The complex showed similar antitumor activity against HeLa cells when compared with the activity of the standard references, cisplatin, carboplatin and oxaliplatin [102].



(64)

Fig. (19). Structure of the palladium(II) complex **64**.

4.2. Palladium(II) Complexes with Bidentate N∩N Ligands

Dichloro palladium(II) complexes with spermidine and spermine were reported by Navarro-Ranninger *et al*. [174]. 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 (**65**) give values of IC$_{50}$ similar to cisplatin, whereas those of spermine (**66**) have low antiproliferative activity (Fig. **20**).

Ethylendiamine palladium(II) complexes with pyridine or its derivatives were also reported (**67**, Fig. **20**) [175]. 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.

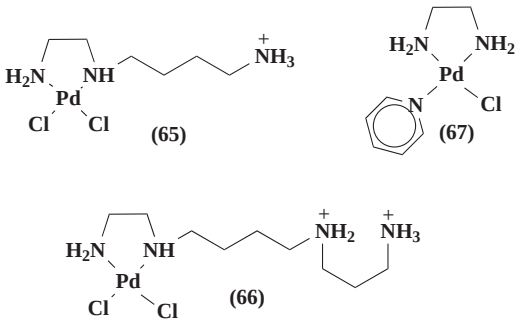


Fig. (20). Palladium(II) complexes with bidentate N∩N ligands (**65**, **66**, and **67**).

Recently, we applied an alternative method to synthesise the enantiomerically pure DACH-based palladium(II) complexes [79]. In this method the desired organic bidentate ligand was allowed to react with [*cis*-$Pd(PhNC)_2Cl_2$], a palladium(II) starting material that is soluble in most organic solvents, in CH_2Cl_2 at 25°C. Following this procedure, the nucleophilic substitution reaction of the complex [*cis*-$Pd(PhNC)_2Cl_2$] with (1R,2R)-(–)-1,2-diaminecyclohexane afforded the square planar Pd(II) complex [(1R,2R)-(–)-(DACH)$PdCl_2$] (**68**) in a high yield (Fig. **21**). The corresponding cationic, aqua complex, [(DACH)$Pd(H_2O)_2$]$(NO_3)_2$ (**69**) and the oxalate complex (oxalipalladium) [(DACH)$Pd(C_2O_4)$] (**70**) have also been prepared and characterized [100]. A series of other oxaliplatin like complexes of the type [(DACH)Pd(O-O)] has also been prepared by Khokhar *et al.* [176] (O-O: malonate, methylmalonate, phenylmalonate, tartronate, maleate, citraconate, 1,1-cyclobutandicarboxylate). 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.

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_2-accys (**71**, Fig. **22**) (accys: N-acetyl-S-methylene-2-(2-pyridine)-L-cysteine) have been applied [177]. 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.

A different series of compounds bearing two chelating ligands the N-N and O-O ligand (XO_3: selenite or tellurite) were prepared [178]. The N-N ligand did not influence the activity but the oxygen coordinated leaving group did. Selenite complexes were invariably better cytotoxic agents than tellurite complexes and cisplatin. The complex [bipy)Pd(SeO_3) (**72**) was found to bind to DNA through a coordinate covalent bond.

Another study investigated compounds bearing NO_3 as chelate in addition to a bidentate nitrogen ligand [179]. A comparison among [(bipy)Pd$(NO_3)_2$], [(AMP)Pd$(NO_3)_2$], [(AEP)Pd$(NO_3)_2$], [(DACH)Pd(Meorot)] (bipy = 2,2'-bipyridyl, AMP = 2-aminometylpyridine, AEP = 2-aminoethylpyridine, Meorot = 3-methylorotate) showed that only [(DACH)Pd(Meorot)] (**73**) was active, giving a high activity for sarcoma 180 but a low one against P388 leukemia. Similarly, [(DACH)Pd(5-fluroorot)] (**74**) reported later [180], displayed significant antitumor activity. These strong chelating ligands replacing chloro or nitro ligands induce a reduction in the rate of hydrolysis.

2,2'-dipyridylamine-based palladium(II) complexes containing glycine or L-alanine have been prepared and evaluated [181]. The alanine based complex (**75**) 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-dimathamine)Pd(II)] (**76**) (alkyl: Me, Ethyl, propyl, cyclohexyl) are significantly dependent on the nature of the alkyl substituents (Fig. **22**). The complexes bearing the bulkiest groups showed lower IC50 values than cisplatin [182]. Palladium(II) complexes containing S-donors (diethyldithiocarbamate: ddtc) in addition to the N-N ligands (bipyridine, phenanthroline, and DACH) have also been investigated [183]. The most active were the bipyridine and phenanthroline-based complexes (**77**, Fig. **22**).

This was related to the flat structure of the aromatic N-N

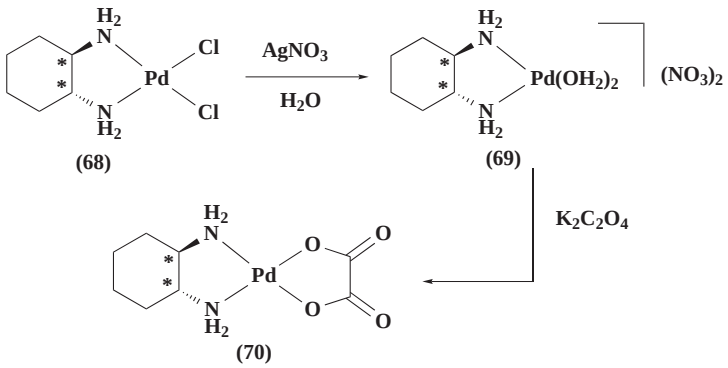


Fig. (21). DACH-based palladium(II) complexes (**68**, **69**, and **70**).

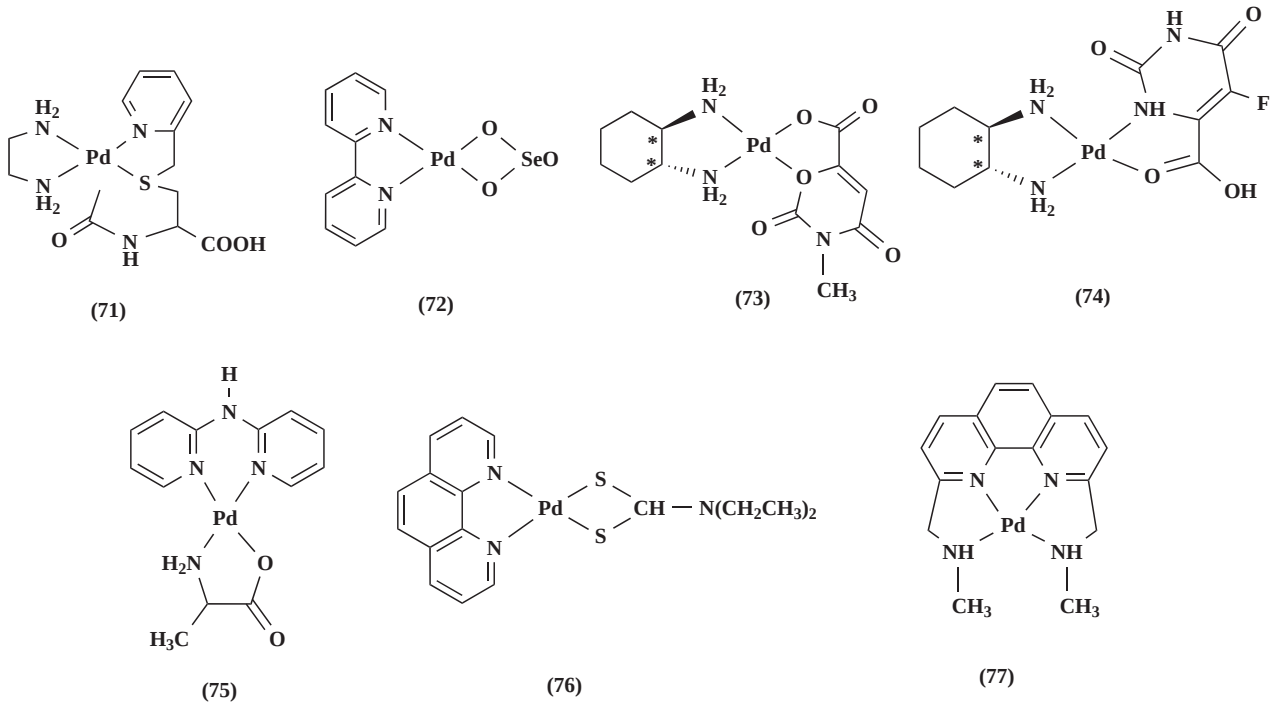


Fig. (22). Palladium(II) complexes bearing two bidentate chelates or tetradentate nitrogen ligands (**71-77**).

ligands and the more hydrophobic nature of the complex. Bipy and phen complexes showed IC_{50} values lower than cisplatin against P388 lymphocytic leukemia cells [183].

4.3. 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 [184]. 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* [185]. Some cyclopalladate complex based on biphosphine ligands (**78**, **79**, Fig. **23**) have been prepared and investigated for their antitumor activity in a syngeneic B16F10 murine melanoma model [186]. The ionic complex (**78**) caused 100% tumor cell death at very low concentration (< 1.25 μM). Other palladium(II) complexes containing bidentate phosphine ligands of the general formula $[L_2PdX_m]^{n+}nX$ (L = Ph_2P-A-PPh_2, A = $(CH_2)_2$, $(CH_2)_3$, X = Cl, Br, NO_3) were prepared and evaluated for *in vitro* cytotoxicity, *in vivo* 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 and lack of cross resistance with L1210/DDP, a line of L1210 murine leukemia resistant to cisplatin [187].

4.4. Palladium(II) Complexes with N∩S or N∩O Mixed Donor Ligands

Khan *et al.* reported about palladium(II) complexes with mixed nitrogen-sulfur ligands such as methionine and substituted pyrimdines (mercapto or amino) [188]. Methionene 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 (**80**, Fig. **24**) has *in vitro* IC_{50} value lower than 10 μg/ml, so it could act as a potential antitumor agent.

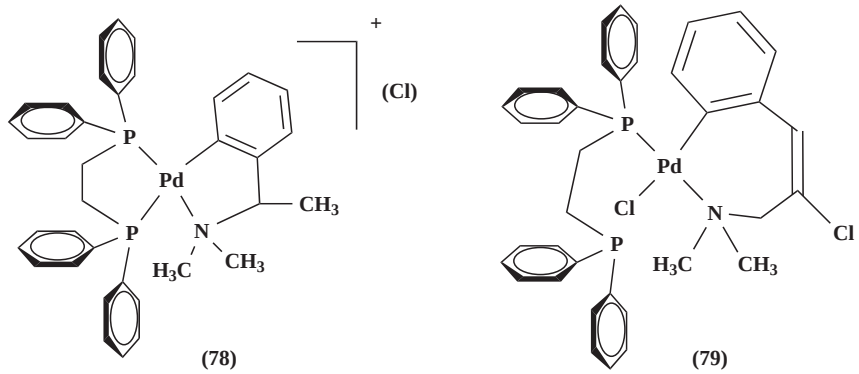


Fig. (23). Palladium(II) complexes with biphosphine (P∩P) ligands (**78** and **79**).

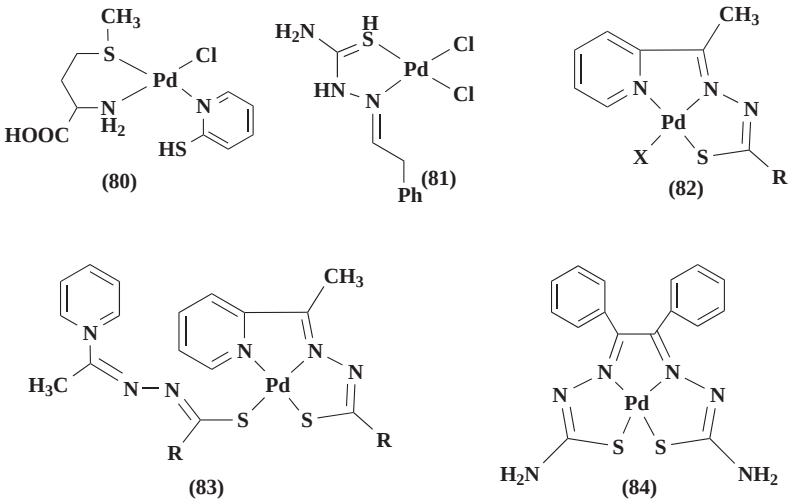


Fig. (24). Palladium(II) complexes with N∩S mixed donor ligands (**80**-**84**).

Heterocyclic thiosemicarbazones are of considerable interest due to their potential beneficial antineoplastic, activity. It is assumed that the presence of some metallic ions may enhance their antitumor activity due to their ability to form chelates. The phenyl acetaldehyde thiosemicarbazone-based palladium complex (**81**, Fig. **24**) has been found to display an enhanced *in vitro* activity compared to its platinum analogue [189]. In addition, this complex is active in cisplatin resistant cell lines. The exchange of the bulky 4N-substituent in the 2-acetylpyridinethiosemicarabazone from propyl (**82**) to hexamethyleneiminyl (**83**) leads to an increase of antineoplastic activity, which is inversely related to the ease of their reduction [190]. It was assumed that the biological activity of their platinum complexes could be due to their hemilabile behavior [191].

Other thiosemicarbazide derivatives have also been studied. [(Benzyl)Pd-{bis(thiosemicarbazonate)}] (**84**, Fig. **24**) showed IC_{50} values in a concentration range similar to that of cisplatin and a notable activity in cisplatin-resistant cell lines [192].

Recently, the antitumor functions and mechanisms of a 1,2-naphthoquinone-2-thiosemi-carbazone-based palladium (II) complex were investigated against MCF-7 human breast cancer cells [193]. The results revealed that the complex is an effective antitumor agent. The mechanistic study of action showed that the metal complex can only stabilize the single-strand nicked DNA, but not double-strand breakage intermediates.

4.5. 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: $[PdCl_4(Put)_2)]$ (**85**) and $[PdCl_4(Sperm)_2]$ (**86**), (Fig. **25**). The complex (**85**) is a coordination complex of a dimmer nature. In **86**, the 4 amino groups of the spermine coordinate to two *cis*-Pd-centers. The cytotoxicity results showed that the putrescine complex is much more active than the spermidine one [194].

Zhao, *et al.* studied dinuclear palladium complexes containing two functional $[Pd(en)(pyridine)Cl]^+$ units bridged by Se or S were investigated [195]. The complexes are water soluble. The Se-bridged Pd(II) dimmer (**87**) has a lower IC_{50} 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*. [186]. The dimer Pd(II) complex $[Pd_2(S(-)C^2, N\text{-}dmpa)_2(\mu\text{-}dppe)Cl_2]$ (**88**) (dmpa = enantiomer S(-) of N,N-dimethyl-1-phenylethylamine; dppe = 1,2-bis(diphenylphosphino)ethane) showed to be the most active *in vivo* compared to the corresponding mononuclear complexes. It delays tumor growth and prolongs animal survival.

Recently, new palladium(II) complexes of the general formula $[Pd(MSDT)X]_n$ (MSDT = methylsarcosinedithiocarbamate; X = Cl, Br) were reported [196]. The complexes show a strong dose-dependent growth inhibition of both HL60 and HeLa cells, with IC_{50} values slightly higher than those recorded for cisplatin.

5. NICKEL(II) COMPLEXES AS ANTITUMOR AGENTS

Nickel is an essential component in different types of enzymes such as urease, carbon monoxide dehydrogenase, and hydrogenase [197]. Recently, some results showing also apparent potential of this platinum group element in antitumor studies have been reported. For example the cytotoxicity of the nickel (II) complexes containing 1,2-naphtoquinone-based thiosemicarbazone ligands (NQTS) was tested on MCF7 human breast cancer cell line and compared to free ligand and another naphthoquinone, commercial antitumor drug etoposide [198]. According to the reported data, Ni-NQTS complex has the highest antitumor activity with an IC_{50} of 2.2 μM. The mechanistic study of action showed inhibition of topoisomerase II [198]. Recent studies showed that the corresponding nickel complexes of semicarbazones (**89**, Fig. **26**) have even greater inhibitory effect on MCF7 cell growth. They display IC_{50} values in 2-5 μM range and also in general they produce lower side effect than thiosemicarbazones [199].

Water soluble Ni(II) complexes based on salen Schiff bases such as 3,3'-[1,2-propylenediylbis(nitrilomethyl-

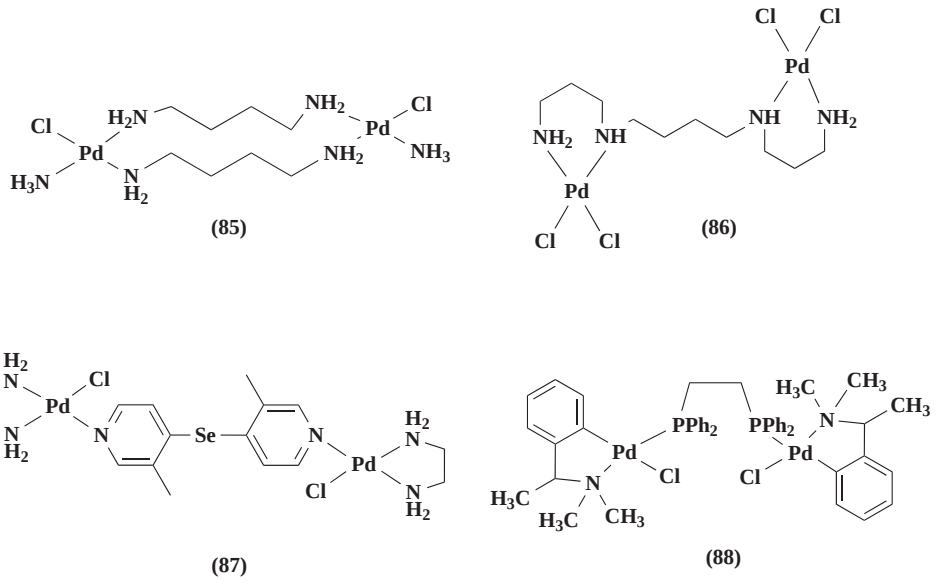


Fig. (25). Structures of multinuclear palladium complexes (**85-88**).

idyne)]bis[2-hydroxy] have also been investigated and found to exhibit anticancer activity [200].

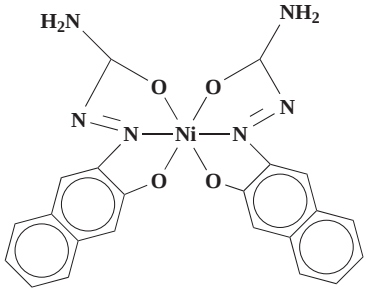


Fig. (26). Structure of Ni(II)-based antitumor complex (**89**).

Pharmaceutical tests showed that a nickel(II) complex containing tetraazamacrocyclic ligand with four neutral 2-cyanoethyl pendent groups $[Ni(L)(NO_3)]NO_3$ (L = 1,4,7,10-tetrakis(2-cyanoethyl)-1,4,7,10-tetraazacyclododecane) exhibit antitumor activity against HL-60 and BEL-7404 tumor cell lines *in vitro*, even at a concentration of 10^{-8} mol/L [201]. In a recent study, the ligands, N-salicyloyl-N'-O-hydroxythiobenzohydrazide [202] and N-nicotinoyl-N'-O-hydroxy-thiobenzohydrazide [203] were also reported to form aqua complexes with Ni(II) and observed to inhibit tumor growth *in vitro*. *In vivo* administration resulted in prolongation of survival of tumor bearing mice and reversal of tumor growth associated induction of apoptosis in lymphocytes was observed [204].

CONCLUSIONS

More than 30 years of chemical-, biochemical-, pharmacological-, and clinical-research on anticancer coordination complexes has yielded remarkable anticancer agents such as cisplatin, carboplatin, and oxaliplatin. Since the discovery of cisplatin, the development of analogues complexes has been an empirical task. Thousands of platinum complexes were evaluated, but only five were approved. Consequently, it is estimated that more than 10000 compounds need to be screened in order to obtain a new, effective anticancer drug. The foremost target of most research groups was to find a convenient anticancer drug that can be used efficiently for the treatment of human tumors. For this purpose, sterically hindered complexes, enantiomerically pure chiral complexes, and complexes containing biologically active ligands have been investigated. Furthermore, the established structure-activity rules have been broken: active platinum complexes without NH groups, *trans*-platinum complexes, multinuclear complexes, cationic complexes, and several classes of palladium(II) and nickel(II) complexes have emerged.

With the aid of inorganic- or coordination- chemistry, it is possible to design novel therapeutic and diagnostic agents. Solubility, reactivity, electronic and steric properties, and the geometry of metal complexes can be controlled by simply varying or modifying the ligand around the metal center. It is apparent from the data presented in this review that both the metal and the ligand determine the biological activity. Platinum(II) attacks DNA, but other metal ions may have different target sites, and it will be interesting to follow the progress of the further metals in the clinincal trials.

AKNOWLEDGEMENTS

The authors would like to thank Professor Yousef Al-Abed, North Shore University Hospital, 300 Community Dr, Manhasset, NY 11030-3801, USA and Dr. John Baugh, UCD Conway Institute, Dublin, Ireland, for reading the manuscript. Thanks are also to MSc Abdussalam K. Qaroush for assistance with the preparation of the figures.

REFERENCES

[1] Rosenberg, B.; Van Camp, L.; Trosko, J. E.; Mansour, V. H. *Nature*, **1969**, *222*, 385.
[2] Gordon, M.; Hollander, S. *J. Med*., **1993**, 209.
[3] Weiss, R. B.; Christian, M. C. *Drugs*, **1993**, *46*, 360.
[4] Lebwohl, D.; Canetta, R. *Eur. J.Cancer*, **1998**, *34*, 1522.
[5] Wong, E.; Giandomenico, C. M. *Chem. Rev*., **1999**, *99*, 2451.
[6] Cleare, M. J.; Hoeschele, J. D. *Bioinorg. Chem*., **1973**, *2*, 187.
[7] Connors, T. A.; Cleare, M. J.; Harrap, K. R. *Cancer Treat. Rep*., **1979**, *63*, 1499.
[8] Reedijk, J. *J. Chem. Commun*., **1996**, *7*, 801.

[9] Reedijk, J. *J. Pure and Appl. Chem*., **1987**, *59*, 181.
[10] Farrell, N. Transition Metal Complexes as Drugs and Chemotherapeutic Agents, Kluwer Academic Publisher: Boston, **1989**.
[11] Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, Howell, S. B., Ed.; Plenum Press: New York, **1991**.
[12] Kelland, L. R. *Crit. Rev. Oncol./Hematol*., **1993**, *15*, 191.
[13] Evans, B. D.; Raju, K. S.; Calvert, A. H.; Harland, S. J.; Wiltshaw, E. *Cancer Treat. Rep*., **1983**, *67*, 997.
[14] Harrap, K. R. *Cancer Treat. Rev*., **1985**, *12*, 21.
[15] Rixe, O.; Ortuzar, W.; Alvarez, M. *Biochem. Pharmacol*., **1996**, *52*, 1855.
[16] Bitha, P.; Carvajal, S.G.; Citarella, R.V.; Child, R. G.; Delos Santos, E. F.; Dunne, T. S.; Durr, F. E.; Hlavka, J. J.; Lang, S. A.; Jr. Lindsay, H. L. *J. Med. Chem*., **1989**, *32*, 2015.
[17] Connors, T. A.; Jones, M.; Ross, W. C.; Braddock, P. D.; Khokhar, A. R.; Lobe, M. L. *Chem. Biol. Interact.*, **1972**, *5*, 415.
[18] Tashiro, T.; Kawada, Y.; Sakurai, Y. *Biomed. Pharmacoth*., **1989**, *43*, 251.
[19] Khokhar, A. R.; Al-Baker, S.; Krakoff, I. H.; Perez-Solar, R. *Cancer Chemother. Pharamcol*., **1989**, *23*, 219.
[20] Burchenal, J. H.; Kalaher, K.; O'Toole, T.; Chisholm, J. *Cancer Res*., **1977**, *37*, 2455.
[21] Perez, R. P.; Perez, K. M.; Handel, L. M.; Hamilton, T. C. *Cancer Chemother. Pharmacol*., **1992**, *29*, 430.
[22] Kidani,Y.; Inagaki, K.; Iigo, M.; Hoshi, A.; Kuretani, K. *J. Med. Chem*., **1978**, *21*, 1315.
[23] For recent review articles: (a) Barnes, K.R.; Lippard, S.J. *Metal Ions Biological Systems*, **2004**, *42*, 143; (b) Ho, Y.-P.; Au-Yeung, S. C. F.; To, K. K. W. *Med. Res. Rev*., **2003**, *23*, 633; (c) Hall, M. D.; Hambley, T. W. *Coord. Chem. Rev*., **2002**, *232*, 49; (d) Guo, Z.; Sadler, P. *Medicinal inorganic chemistry* in "*Advances in inorganic chemistry*" Sykes, A. G. Ed.; Academic Press: N Y, **2000**, Vol. 49, pp. 187-223; (e) Reedijk, J. *Chem. Rev*., **1999**, *99*, 2499; (f) Trimmer, E.E.; Essigmann, J. M. *Essays Biochem*., **1999**, *34*, 191; (g) Kozelka, J.; Legendre, F.; Reeder, F.; Chottard, J.-C. *Coord. Chem. Rev*., **1999**, *190-192*, 61; (h) Arpalahti, J. *Persp. Bioinorg. Chem*., **1999**, *4*, 165; (i) Jamieson, E. R.; Lippard, S. J. *Chem. Rev*., **1999**, *99*, 2467.
[24] Farrell, N. *Cancer Invest*., **1993**, *11*, 578.
[25] Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy 2; Pinedo, H. M.; Schornagel, J. H., Eds.; Plenum Press: New York, **1996**.
[26] Sherman, S. E.; Lippard, S. J. *Chem. Rev*., **1987**, *87*, 1153.
[27] Fuertes, M. A.; Alonso, C.; Perez, J. M. *Chem. Rev*., **2003**, *103*, 645.
[28] Reedijk, J. *Proc. Natl. Acad. Sci. USA*, **2003**, *100*, 3611.
[29] Wang, D.; Lippard, S. J. *Nat. Rev. Drug. Discover*., **2005**, *4*, 307.
[30] Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advance Inorganic Chemistry*, 6th Ed.; John Wiley & Sons. INC: New York, **1999**, pp. 837-852, 1063-1081.
[31] Maitlis, P.M. *The organic chemistry of palladium in Organometallic Chemistry, A series of monographs*; Maitlis, P. M.; Stone, F. G. A.; West, R. Eds.; Academic Press Inc.: New York, **1971**, Vol. 1.
[32] Rau, T.; van Eldik, R. *Metal Ions In Biological Systems*, Sigel, H.; Sigel, A.; Eds.; Marcel Dekker: New York, **1996**, Vol. 31, pp 339-378.
[33] Rosenberg, B.; Van Camp, L.; Krigas, T. *Nature*, **1965**, *205*, 698.
[34] Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S. *Bioinorganic Chemistry*, California, **1994**, pp. 523-590.
[35] Kaim, W.; Schwederski, B. Bioinorganic chemistry: Inorganic element in the chemistry of life, Wiley: Stuttgart, **1993**, p. 363-384.
[36] Rosenberg, B.; Van Camp, L. *Cancer Res*., **1970**, *30*, 1799.
[37] Kociba, R.; Sleiht, S. D.; Rosenberg, B. *Cancer Chemother. Rep. Part I*, **1970**, *54*, 325.
[38] Rosenberg, B.; Platinum complexes for the treatment of cancer: Why the search goes on, in Chemistry and biochemistry of a leading anticancer drug, Lippert, B. Ed.; Wiley-VCH: New York, **1999**, pp. 1-27.
[39] Perez, R. P.; Hamilton, T. C.; Ozols, R. F.; Young, R. C. *Cancer*, **1993**, *71*, 1571.
[40] Goren, M. P.; Wright, R. K.; Horowitz, M. E. *Cancer Chemother. Pharmacol*., **1986**, *18*, 69.
[41] Alberts, D. S.; Noel, J. K. *Anticancer Drugs*, **1995**, *6*, 369.
[42] Hamers, F. P. T.; Gispen, Y. H.; Neijt, J. P. *Eur. J. Cancer*, **1991**, *27*, 72.
[43] Kelland, L. R. *Drugs*, **2000**, *59*, 1.
[44] Wolf, C. R.; Hayward, I. P.; Lawrie, S. S.; Buckton, K.; Mclntyre, M. A.; Adams, D. L.; Lewis, A. D.; Scott, A. R. R.; Smyth, J. F. *Int. J. Cancer*, **1987**, *39*, 696.
[45] (a) Mistry, P.; Lelland, L. R. *Br. J. Cancer*, **1991**, *64*, 215. (b) Chaney, S. G.; Vaisman, A. *J. Inorg. Biochem*., **1999**, *77*, 71.
[46] Majima, H. *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Howell, S. B., Ed.; Plenum Press: New York, **1991**, pp. 345-355.
[47] Kobayashi, H.; Takemura, Y.; Miyachi, H.; Ogawa, T. *Invest. New Drugs*, **1991**, *9*, 313.
[48] Yang, L.Y.; Liu, Y. Z.; Li, L.; Kantajian, H. H.; Keating, M. J. *Int. J. Oncol*., **1994**, *5*, 597.
[49] Kraker, A. J.; Moore, C. W.; Roberts, B. J.; Leopold, W. R.; Elliott, W. L. *Invest. New Drugs*, **1991**, *9*, 1.
[50] Perez, R. P.; O'Dwyer, P. J.; Handel, L. M.; Ozols, R. F.; Hamilton, T. C. *Inter. J. Cancer*, **1991**, *48*, 265.
[51] Takahashi, K.; Okamoto, K.; Minamide, S.; Yamashita, T. *Proc, Am. Assoc. Cancer Res*., **1988**, *29*, 339.
[52] Mross, K.; Meyberg, F.; Fiebig, H.H.; Hamm, K.; Hieberr, U.; Aulenbacher, P.; Hossfeld, D.K. *Onkologie*, **1992**, *15*, 139.
[53] Gietema, J. A.; Veldhuis, G. J.; Guchelaar, H. J.; Willemse, P. H. B.; Uges, D. R. A.; Cats, A.; Boonstra, H.; van der Graaf, W. T. A.; Sleijfer, D. T.; Devries, E. G. E.; Mulder, N. H. *Br. J. Cancer*, **1995**, *71*, 1302.
[54] De Garddin, M.; Armand, J. P.; Chevallier, B.; Cappelaere, P.; Lentz, M.A.; David, M.; Roche, H. *Invest. New Drugs*, **1995**, *13*, 253.
[55] Fiebig, H. H.; Henss, H.; Vonpawel, L.; Gatzemeier, U.; Manegold, C; Edler, L.; Berdel, W. *Onkologie*, **1996**, *19*, 328.
[56] Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S. *Bioinorganic Chemistry*; University Science Books: California, **1994**, p 53-590.
[57] González, M. L.; Tercero, J. M.; Matilla, A.; Niclós-Gutiérrez, J.; Fernández, M. T.; López, M. C.; Alonso, C.; Gonzálz, S. *Inorg. Chem*., **1997**, *36*, 1806.
[58] Abu-Surrah, A. S.; Hodali, H. A. *Inorg. Chim. Acta*, **1990**, *174*, 223.
[59] Abu-Surrah, A. S.; Lappalainen, K.; Klinga, M.; Leskelä, M.; Hodali. H. A. *Acta Cryst*., 1999, *C55*, 188.
[60] Oe, T.; Tian. Y.; O'Dwyer, P. J.; Roberts, D.W.; Malone, M. D.; Bailey, C. J.; Blair, I. A. *Anal. Chem*., **2002**, *74*, 591.
[61] Barton, S.J.; Barnham, K.J.; Habtemariam, A.; Sue, R.E.; Frey, U.; Sadler, P.J.; *Aust. J. Chem*., **1999**, *52*, 173.
[62] Chen, Y.; Guo, Z.; Parsons, S.; sadler, P.J. *Chem.Eur. J*., **1998**, *4*, 672.
[63] (a) Wong, E.; Giandomenico, C. M. *Chem. Rev*., **1999**, *99*, 2451. (b) Lippert B. *Coord. Chem. Rev*., **1999**, *182*, 263. (c) Hall, M. D.; Hambley, T. W. *Coord. Chem. Rev*., **2002**, *232*, 49. (d) Reeder, F.; Guo, Z. J.; Murdoch, P. D.; Corazza, A.; Hambley, T. W.; Berners-Price, S. J.; Chottard, J. C.; Sadler, P. J. *Eur. J. Biochem*., **1997**, *249*, 370.
[64] Eastman, A.; Schulte, N. *Biochemistry*, **1988**, *27*, 4730.
[65] Mandal, R.; Kalke, R.; Li, X-F. *Chem. Res. Toxicol*., **2004**, *17*, 1391.
[66] Reedijk, J.; Fichtiger-Schepmann, A. M. J.; van Oosterom, A. T.; van de Putte, P. *Struct. Bonding*, **1987**, *67*, 53.
[67] Knox, R.J.; Friedlos, F.; Lydall, D.A.; Roberts, J. *J. Cancer Res*., **1986**, *46*, 1972.
[68] Kartochwill, N. A.; Zabel, M.; Range, K-J.; Bednardski, P. J. *J. Med. Chem*., **1996**, *39*, 2499.
[69] Mir, L. M.; Orlowski, S.; Belehradek, J. Jr.; Teissie, J.; Rols, M. P.; Serša, G.; Miklavčič, D.; Gilbert, R.; Heller, R. *Bioelectrochem. Bioenerg*., **1995**, *38*, 203.
[70] Serša, G.; Stabuc, B.; Cemažar, M.; Miklavčič, D.; Rudolf, Z. *Clin. Cancer Res*., **2000**, *6*, 863.
[71] Holford, J.; Sharp, S. Y.; Murrer, B. A.; Abrams, M.; Kelland, L. R. *Br. J. Cancer*, **1998**, *77*, 366.
[72] Chen, Y.; Guo, Z.; Parsons, S.; Sadler, P. J. *Chem. Eur. J*., **1998**, *4*, 672.
[73] Raynaud, F. I.; Boxall, F. E.; Goddard, P. M. *Clin. Cancer Res*., **1997**, *3*, 2063.
[74] Bloemink, M. J.; Engelking, H.; Karentopoulos, S.; Krebs, B.; Reedijk. J. *J. Inorg. Chem*., **1996**, *35*, 619.
[75] Webster, L. K.; Deacon, G. B.; Buxton, D. P.; Hillcoat, B. L.; James, A.M.; Roos, I. A. G.; Thomson, R. G.; Wakelin, L. P. G.; Williams, T. L. *J. Med. Chem*., **1992**, *35*, 3349.

[76] Bloemink, M. J.; Heetebrij, R. G.; Ireland, J.; Deacon, G.B.; Reedijk. J. *J.B.I.C.*, **1996**, *1*, 278.

[77] Puscasu, I.; Mock, C.; Rauterkus, M.; Rondigs, A.; Tallen, G.; Gangopadhyay, S.; Wolff. J. E. A.; Krebs, B. *Z. Anorg. Allg. Chem*., **2001**, *627*, 1292.

[78] Zhang, J.; Wang, X.; Tu, C.; Lin, J.; Ding, J.; Lin, L.; Wang, Z.; He, C.; Yan, C.; You, X.; Guo, Z. *J. Med. Chem*., **2003**, *46*, 3502.

[79] (a) Abu–Surrah, A. S.; Kettunen, M.; Lappalainen, K.; Piironen, U.; Klinga, M.; Leskelä, M. *Polyhedron*, **2002**, *21*, 27; (b) Abu-Surrah, A. S.; Lappalainen, K.; Piironen, U.; Lehmus, P.; Repo, T.; Leskelä, M. *J. Organomet. Chem*., **2002**, *648*, 55.

[80] Noji, M.; Okamoto, K.; Kidani, Y. *J. Med. Chem.*, **1981**, *24*, 508.

[81] Orbell, J. D.; Taylor, M. R.; Birch, S. L.; Lawton, S. E.; Vilkins, L. M.; Keefe, L. J. *Inorg. Chim. Acta*, **1988**, *152*, 125.

[82] Coluccia, M.; Correala, M.; Giordano, D.; Mariggió, M. A.; Moscelli, S.; Fanizzi, F. P.; Natile, G.; Maresca, L. *Inorg. Chim. Acta*, **1986**, *123*, 225.

[83] Matsumoto, T.; Endoh, K.; Akamatsu, K.; Kamisango, K.; Mitsui, H.; Koizumi, K.; Morikawa, K.; Koizumi, M.; Matsuno, T. *Br. J. Cancer*, **1991**, *64*, 41.

[84] Coluccia, M.; Fanizzi, F. P.; Giannini, G.; Giordano, D.; Intini, F. P.; Lacidogona, G.; Loseto, F.; Mariggió, M. A.; Nassi, A.; Natile, G. *Anticancer Res*., **1991**, *11*, 281.

[85] Moradell, S.; Lorenzo, J.; Rovira, A.; Robillard, M. S.; Avilés, E. X.; Moreno, V.; de Llorens, R.; Martinez, M. A.; Reedijk, J.; Llobet, A. *J. Inorg. Biochem*., **2003**, *96*, 493.

[86] Fanizzi, F.P.; Intini, F.P.; Maresca, L.; Natile, G.; Quaranata, R.; Coluccia, M.; DiBari, L.; Giordano, D.; Mariggió, M.A. *Inorg. Chim. Acta*, **1987**, *137*, 45.

[87] Spruβ, T.; Bernhardt, G.; Schickaneder, E.; Schönenberger, H. *J. Cancer Res. Clin. Oncol*., **1991**, *117*, 435.

[88] Gust, R.; Schönenberger, H. *Eur. J. Med. Chem*., **1993**, *28*, 103.

[89] Schertl, S.; Hartmann, R. W.; Batzl-Hartmann, C.; Bernhardt, G.; Spruβ, T.; Beckenlehner, K.; Koch, M.; Krauser, R.; Schlemmer, R.; Gust, R.; Schönenberger, H. *Arch. Pharm. Pharm. Med. Chem*., **2004**, *337*, 335.

[90] Burchenal, K.; Kalaher, K.; Dew, K.; Lokys, L.; Gale, G. *Biochimie*, **1978**, *60*, 961.

[91] Burchenal, K.; Kalaher, K.; Dew, K.; Lokys, L. *Cancer Treat. Rep*., **1979**, *63*, 1493.

[92] Bruck, M. A.; Bau, R.; Noji, M.; Inagaki, K.; Kidani, Y. *Inorg. Chim. Acta*, **1984**, *92*, 279.

[93] Hoeschele, J. D.; Showalter, H. D. H.; Kraker, A. J.; Elliot, W. L.; Roberts, B. J.; Kampf, J. W. *J. Med. Chem*., **1994**, *37*, 2630.

[94] Perez-Soler, R.; Khokhar, A. R. *Proc. Am. Assoc. Cancer Res*., **1998**, *29*, 509.

[95] Soulie, P.; Raymond, E.; Misset, J. L.; Cvitkovic, E. *in Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy 2*, Pinedo, H. M., Schornagel, J. H., Eds.; Plenum Press: New York, **1996**, pp. 165.

[96] Misset, J. L. *Brit. J. Cancer*, **1998**, *77*, 4.

[97] Rixe, O.; Ortuzar, W.; Alvarez, M. *Biochem. Pharmacol*., **1996**, *52*, 1855.

[98] Furin, A.; Guiotto, A.; Baccichetti, F.; Pasut, G.; Deuschel, C.; Bertani, R.; Veronese, F. M. *Eur. J. Med. Chem*., **2003**, *38*, 739.

[99] Bruck, M. A.; Bau, R.; Noji, M.; Inagaki, K.; Kidani, Y. *Inorg. Chim. Acta*, **1984**, *92*, 279.

[100] Abu-Surrah, A. S.; Al-Allaf, T. A. K.; Klinga, M.; Leskelä, M. *Polyhedron*, **2003**, *22*, 1529.

[101] Abu-Surrah, A. S.; Lappalainen, K.; Repo, T.; Klinga, M.; Leskelä, M.; Hodali,. H. A. *Polyhedron*, **2000**, *13*, 1601.

[102] Abu-Surrah, A. S.; Al-Allaf, T. A. K.; Rashan, L. J.; Klinga, M.; Leskelä, M. *Eur. J. Med. Chem*., **2002**, *37*, 919.

[103] Farrell, N.; Ha, T. T. B.; Souchard, J. P.; Wimmer, F. L.; Cros, S.; Johnson, N. P. *J. Med. Chem.*, **1989**, *32*, 2241.

[104] Van Beusichem, M.; Farrell, N. *Inorg. Chem*., **1992**, *31*, 634.

[105] Perez, J. M.; Fuertes, M. A.; Alonso, C.; Navarro-Ranninger, C. *Crit. Rev. Oncolog/hematolog*., **2000**, *35*, 109.

[106] Kelland, L. R.; Barnard, C. F. J.; Mellish, K. J.; Jones, M.; Goddard, P. M.; Valenti, M.; Bryant, A.; Murrer, B. A.; Harrap, K. R. *Cancer Res*., **1994**, *54*, 5618.

[107] Natile, G.; Coluccia, M. *Coord. Chem. Rev*., **2001**, *216-217*, 383.

[108] Hartley, F. R. *The Chemistry of Platinum and Palladium*; John Wiley: NY, **1973**.

[109] Zakovka, A.; Novakova, O.; Balcarova, Z.; Bierbach, U.; Farrell, N.; Brabec, V. *Eur. J. Biochem*., **1998**, *254*, 547.

[110] Collucia, M.; Nassi, A.; Loseto, F.; Boccarelli, A.; Mariggio, M. A.; Giordano, D.; Intini, F. P.; Caputo, P.; Natile, G. *J. Med. Chem*., **1993**, *36*, 510.

[111] Collucia, M.; Nassi, A.; Boccarelli, A.; Giordano, D.; Cardellicchio, N.; Locker, D.; Leng, M.; Sivo, M.; Intini, F. P.; Natile, G. *J. Inorg. Biochem*., **1999**, *77*, 31.

[112] Najajreh, Y.; Khazanov, E.; Priltuski, D.; Perez, J.M.; Barenholz, Y.; Aredeli, Y.; Kasparkova, J.; Brabec, V.; Gibson, D. *Angew. Chem. Int. Ed*., **2005**, *44*, 2885.

[113] Najajreh, Y.; Perez, J. M.; Navarro-Ranninger, C.; Gibson, D. *J. Med. Chem*., **2002**, *45*, 5189.

[114] Drougge, L. I.; Elding, L. *Inorg. Chim. Acta*, **1986**, *121*, 175.

[115] Ellis, L. A.; Er, H. M.; Hambley, T. W. *Aust. J. Chem*., **1995**, *48*, 793.

[116] Choi, S.; Filotto, C.; Bisanzo, M.; Delaney, S.; Lagasee, D.; Whitworth, J. L.; Jusko, A.; Li, C.; Wood, N. A.; Willingham, J., Schwenker, A.; Spaulding, K. *Inorg. Chem*., **1998**, *37*, 2500.

[117] Kratochwil, N. A.; Parkinson, J. A.; Bednardski, P. J.; Sadler, P. J. *Angew. Chem. Int. Ed*., **1999**, *38*, 1460.

[118] Müller, P.; Schröder, B.; Parkinson, J. A.; Kratochwil, N. A.; Coxall, A.; Parkin, A.; Parsons, S.; Sadler, P. J. *Angew. Chem. Int. Ed*., **2003**, *42*, 335.

[119] Braddock, P. D.; Connors, T. A.; Jones, M.; Khokhar, A. R.; Melzack, D. H.; Tobe, M. L. *Chem.-Biol. Interact*., **1975**, *11*, 145.

[120] Bramwell, V. H. C.; Crowther, D.; O'Malley, S.; Swindell, R.; Johnson, R.; Cooper, E. H.; Thatcher, N.; Howell, A. *Cancer Treat. Rep*., **1985**, *69*, 409.

[121] Gordon, M.; Hollander, S. *J. Med*., **1993**, *24*, 209.

[122] McKeage, M. J.; Raynaud, F.; Ward, J.; Berry, C.; O'Dell, D.; Kelland, L.R., Murrer, B.; Santabarabara, P.; Harrap, K.R.; Judson, I. R. *J. Clin. Oncol*., **1997**, *15*, 2691.

[123] Pendyala, L.; Arakali, A.V.; Sansone, P.; Cowens, J. W.; Creaven, P. J. *Cancer Chemother. Pharmacol*., **1990**, *27*, 248.

[124] Kelland, L.R.; Abel, G.; Mckeage, M. J.; Jones, M.; Goddard, P.M.; Valenti, M.; Murrer, B.A.; Harrap, K.R. *Cancer Res*., **1993**, *53*, 2581.

[125] Habtemariam, A.; Sadler, P. *J. Chem. Commun*., **1996,** *15*, 1785.

[126] Habtemariam, A.; Nevplechova, K.; Brabec, V.; Margiotta, N.; Sadler, P. *J. Inorg. Biochem*., **1997**, *67*, 161.

[127] Klenner, T.; Valenzuela-Paz, P.; Amelung, F.; Munch, H.; Zahn, H.; Keppler, K.; Blum, H. *In Metal Complexes in Cancer Chemotherapy*; Keppler, B. K. Ed.; VCH: Weinheim, **1993**, pp. 85-127.

[128] Keppler, B. K.; Berger, M. R.; Klenner, T.; Heim, M. E. *Adv. Drug Res*., **1990**, *19*, 243.

[129] Sachinvala, N. D.; Chen, H.; Niemczura, W. P.; Furusawa, E.; Cramer, R. E.; Rupp, J. J.; Ganjian, I. *J. Med. Chem*., **1993**, *36*, 1791.

[130] Bloemink, M. J.; Dorenbos, J. P.; Heetebrij, R. J.; Keppler, B. K.; Reedijk, J.; Zahn, H. *Inorg. Chem*., **1994**, *33*, 1127.

[131] Landi, J.; Hacker, M. P.; Farrell, N. *Inorg. Chim. Acta*, **1992**, *202*, 79.

[132] Farrell, N. *J. Chem. Soc., Chem. Commun*., **1982**, *6*, 331.

[133] Landi, J.; Hacker, P.; Farrell, N. *Inorg. Chim. Acta*, **1992**, *202*, 79.

[134] Mauger, C.; Vazeux, M.; Albinati, A.; Kozelka, J. *Inorg. Chem. Commun*., **2000**, *3*, 704.

[135] Laforgia, M.; Cerasino, L.; Margiotta, N., Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Natile, G. *Eur. J. Inorg. Chem*., **2004**, 3445.

[136] Pasini, A.; D'Alfonso, G.; Manzotti, C.; Moret, M.; Spinelli, S.; Valsecchi, M. *Inorg. Chem*., **1994**, *33*, 4140.

[137] Friebolin, W.; Schilling, G.; Zöller, M.; Amtmann, E. *J. Med. Chem*., **2004**, *47*, 2256.

[138] Zunino, F.; Savi, G.; Pasini, A. *Cancer Chemother. Pharmacol*., **1986**, *18*, 180.

[139] Bowler, B. E.; Ahmed, K. J.; Sundquist, W. I.; Hdlis, L. S.; Whang, E. E.; Lippard, S. J., *J. Am. Chem. Soc*., **1989**, *11*, 1299.

[140] Palmer, B. D.; Lee, H. H.; Johnson, P.; Baguley, B. C.; Wickham, G.; Wakelin, L. P. G.; McFayden, W. D.; Denny, W. A. *J. Med. Chem*., **1990**, *33*, 3008.

[141] Lee, H. H.; Palmer, B.D.; Baguley, B.C.; Chin, M.; McFadyen, W. D.; Wickham, G.; Thorsbourne-Palmer, D.; Wakelin, L.P.G.; Denny, W.A. *J. Med. Chem*., **1992**, *35*, 2983.

[142] Gust, R.; Niebler, K.; Schönenberger, H. *J. Med. Chem*., **1995**, *38*, 2070.

[143] Apfelbaum, H. C.; Blum, J.; Mandelbaumshavit, E. *Inorg. Chim. Acta*, **1991**, *186*, 243.
[144] Gonzalez, V. M.; Fuertes, M. A.; Jimenez-Ruiz, A.; Alonso, C.; Perez, J.M.; *Mol. Pharmacol*., **1999**, *85*, 770.
[145] Sachinvala, N. D.; Chen, H.; Niemezura, W.P.; Furusawa, E.; Cramer, R. E.; Rupp, J. J.; Ganjan, I. *J. Med. Chem.*, **1993**, *36*, 1791.
[146] Rosenfeld, A.; Blum, J.; Gibson, D.; Ramu, A., *Inorg. Chim. Acta*, **1992**, *201*, 219.
[147] Wang, G. S. *J. Ethnopharm*, **1989**, *26*, 147.
[148] Ho, Y-P.; To, K. K. W.; Au-Yeung, S. C. F.; Wang, X.; Lin, G.; Han, X. *J. Med. Chem*., **2001**, *44*, 2065.
[149] Wheat, N. J.; Collins, J. G. *Coord. Chem. Rev*., **2003**, *241*, 133.
[150] Roberts, J. D.; Peroutka, J.; Farell, N. *J. Inorg. Biochem*. **1999**, *77*, 51.
[151] Wu, P. K.; Qu, Y.; Van Houten, M. P.; Farrell, N. *J. Inorg. Chem.*, **1994**, *77*, 3.
[152] Bierbach, U.; Hambley, T. W.; Farrell, N. *Inorg. Chem.*, **1998**, *37*, 708.
[153] Rauter, H.; Di Domenico, R.; Menta, E.; Oliva, A.; Qu, Y.; Farrell, N. *Inorg. Chem.*, **1997**, *36*, 3919.
[154] Qu, Y.; Farrell, N.; Kasparkova, J.; Brabec, V. *J. Inorg. Biochem.*, **1997**, *67*, 174.
[155] Quiroga, A. G.; Perez, J. M.; Lopwz-Solera, J.; Masaguer, J. R.; Luque, A.; Roman, P.; Edwards, A., Alonso, C., Navarro-Ranninger, C. *J. Med. Chem*., **1998**, *41*, 1399.
[156] Jansen, B. A. J.; Van der Zwan, J.; Reedijk, J.; den Dulk, H.; Brouwer, J. *Eur. J. Inorg. Chem*., **1999**, 1429.
[157] Di Blasi, P.; Bernareggi, A.; Beggiolin, G.; Piazzoni, L.; Mernta, E.; Formento, M. L. *Anticancer Res*., **1998**, *18*, 3113.
[158] Pratesi, G.; Giuliani, F. C.; Polzzi, D.; Righetti, S.; Pezzoni, C.; Farrell, N.; Zunino, F. *Proc. Am. Assoc. Cancer Res*., **1997**, *38*, 3310.
[159] Perego, P.; Caserini, C.; Gatti, L.; Garenini, N.; Romanelli, S.; Supino, R.; Colangelo, D.; Viano, L.; Leone, R.; Spinelli, S.; Pezzoni, G.; Mazotti, C.; Farrell, N.; Znino, F. *Mol. Pharm.*, **1999**, *55*, 528.
[160] Perego, P.; Gatti, L.; Caserini, C.; Supino, R.; Colangelo, D.; Leone, R.; Spinelli, S.; Farrell, N.; Zunino, F. *J. Inorg. Biochem.*, **1999**, *77*, 59.
[161] Kalayda, G. V.; Komeda, S.; Ikeda, K.; Sato, T.; Chikuma, M.; Reedijk, J. *Eur. J. Inorg. Chem*., **2003**, *24*, 4347.
[162] Zhao, G.; Hu, X.; Yu, P.; Lin, H. *Trans. Metal Chem*., **2004**, *29*, 607.
[163] Noji, M.; Kizu, R.; Takeda, Y.; Akiyama, N.; Yoshizaki, I.; Eriguchi, M.; Kidani, Y. *Biomed. Pharmacother*., **2005**, *59*, 224.
[164] Rau, T.; van Eldik, R.; *In Metal Ions In Biological Systems*; Sigel, H.; Sigel, A., Eds.; Marcel Dekker: New York, **1996**, Vol. 31, pp. 339-378.
[165] Graham, R. D.; Williams, D. R. *J. Inorg. Nucl. Chem.*, **1979**, 1245.
[166] Butour, J. L.; Wimmer, S.; Wimmer, F.; Castan, P. *Chem. Biol. Interact*., **1997**, *11*,165.
[167] Mansuri-Torshizi, H.; Srivastava, T. S.; Parekh, H. K.; Chitnis, M. P. *J. Inorg. Biochem*., **1992**, *45*, 135.
[168] Tusek-Bozic, L. J.; Matijasic, I.; Bocelli, G.; Calestani, G.; Furlani, A.; Scarcia, V.; Papaioannou, A. *J. Chem. Soc. Dalton Trans.*, **1991**, *2*, 195.
[169] Furlani, A.; Scarcia, V. *Inorg. Chim. Acta*, **1982**, *67*, L41.
[170] Carrara, M.; Berti, T.; D'Ancona, S.; Cherchi, V.; Sindellari, L. *Anticancer Res*., **1996**, *17*, 975.
[171] Curic, M.; Tusek-Bozic, L.; Vikic-Topic, D.; Scarcia, V.; Furlani, A.; Balzarni, J.; Declercq, E. *J. Inorg. Biochem*., **1996**, *63*, 125.
[172] Al-Allaf T. A. K.; Rashan L. J. *Eur. J. Med. Chem*., **1998**, *33*, 817.
[173] Abu-Surrah, A. S.; Klinga, M.; Leskelä, M. *Z. Kristallogr. NCS*, **2002**, *217*, 257.
[174] Navarro-Ranninger, C.; Perez, J. M.; Zamora, F.; Gonzalez, V. M.; Masaguer, J. R.; Alono, C. *J. Inorg. Biochem*., **1993**, *52*, 37.
[175] Zhao, G.; Lin, H.; Yu, P.; Sun, H.; Su, X.; Chen, Y. *J. Inorg. Biochem*., **1999**, *73*, 145.
[176] Khokhar, A. R.; Lumetta, G. J. *Inorg. Chem. Acta*, **1988**, 255.
[177] Rau, T.; Alsfasser, R.; Zahl, A.; Van Eldik, R. *Inorg. Chem*., **1998**, *37*, 4223.
[178] Mansuri-Torshizi, H.; Mital, R.; Srivastava, T. S.; Parekh, H.; Chitnis, M. P. *J. Inorg. Biochem*., **1991**, *44*, 239.
[179] Wimmer, F.Z.; Wimmer, S.; Castan, P., Cros, S.; Johnson, N.; Colacio-Rodrigez, E. *Anticancer Res*., **1989**, *9*, 791.
[180] Butour, J. L.; Wimmer, S.; Wimmer, F.; Catan, P. *Chem. Biol. Interact*., **1997**, *11*, 165.
[181] Paul, A. K.; Mansuri-Torshizi, H.; Srivastava, T. S.; Chavan, J.; Chitnis, M. P. *J. Inorg. Biochem*., **1993**, *50*, 9.
[182] Zhao, G.; Sun, H.; Lin, H.; Zhu, S.; Su, X.; Chen, Y. *J. Inorg. Biochem*., **1998**, *72*, 173.
[183] Mital, R.; Jain, N.; Srivastava, T. S. *Inorg. Chim. Acta*, **1989**, *166*, 135.
[184] Navarro-Ranninger, C.; López-Solera, I.; Pérez, J. M.; Masaguer, J. R.; Alonso C.; *Appl. Organomet. Chem.*, **1993**, *7*, 57.
[185] Caires, A. C. F.; Almeide, E. T.; Mauro, A. E.; Hemerly, J. P.; Valentini, S. R. *Quimica Nova*, **1999**, *22*, 329.
[186] Rodrigues, E. G.; Silva, L. S.; Fausto, D. M.; Hayashi, M. S.; Dreher, S.; Santos, E. L.; Pesquero, J. B.; Travassos, L. R.; Caires, A. C. F. *Int. J. Cancer*, **2003**, *107*, 498.
[187] Shurig, J. E.; Harry, H. A.; Timmer, K.; Long, B. H.; Casazza, A. M. *Prog. Clin. Biochem. Med*., **1989**, *10*, 205.
[188] Khan, B. T.; Bhatt, J.; Najmuddin, K.; Shamsuddin, S.; Annapoorna, K. *J. Inorg. Biochem*., **1991**, *44*, 55.
[189] Quiroga, A. G.; Perez, J. M.; Montero, E. I.; Masaguer, J. R.; Alonso, C.; Navarro-Ranninger, C. *J. Inorg. Biochem*., **1998**, *70*, 117.
[190] Kovola-Demertzi, D.; Domopoulou, A.; Demertzis, M. A.; Papageorgiou, A.; West, D. X. *Polyhedron*, **1997**, *16*, 3625.
[191] Papageorgiou, A.; Iakovidou, Z.; Mourelatos, D.; Mioglou, E.; Boutis, L.; Kotsis, A.; Kovala-Demertzi, D.; Domopoulou, A.; West, D. X.; Dermetzis, M. A. *Anticancer Res*., **1997**, *17*, 247.
[192] Matesanz, A. I.; Perez, J. M.; Navarro, P.; Moreno, J. M.; Colacio, E.; Souza, P. *J. Inorg. Biochem*., **1999**, *76*, 29.
[193] Chen, J.; Huang, Y.-W.; Liu, G.; Afrasiabi, Z.; Sinn, E.; Padhye, S.; Ma, Y. *Toxic. Appl. Pharmacol*., **2004**, *197*, 40.
[194] Navarro-Ranninger, C.; Perez, J. M.; Zamora, F.; Gonzalez, V. M.; Masaguer, J. R.; Alonso, C. *J. Inorg. Biochem*., **1993**, *52*, 37.
[195] Zhao, G.; Lin, H.; Zhu, S.; Sun, H.; Chen, Y. *J. Inorg. Biochem*., **1998**, *70*, 219.
[196] Giovagnini, L.; Ronconi, L.; Aldinucci, D.; Lorenzon, D.; Sitran, S.; Fregona, D. *J. Med. Chem*., **2005**, *48*, 1588.
[197] Rau, T.; van Eldik, R. *In Metal Ions In Biological Systems*; Sigel, H., Sigel, A., Eds.; Marcel Dekker: New York, vol. 31, **1996**, pp. 339-378.
[198] Chen, J.; Huang, Y.-W.; Liu, G.; Afrasiabi, Z.; Sinn, E.; Padhye, S.; Ma, Y. *Toxicol. App. Pharmacol*., **2004**, *197*, 40.
[199] Afrasiabi, Z.; Sinn, E.; Lin, W.; Ma, Y.; Campana, C.; Padhye, S. *J. Inorg. Biochem*., **2005**, *99*, 1526.
[200] Liu, G.; Liao, J.; Huang, S.; Shen, G.; Yu, R. *Anal. Sci*., **2001**, *17*, 1031.
[201] Kong, D.-Y.; Meng, L.-H.; Ding, J.; Xie, Y.-Y.; Huang, X. *Polyhedron*, **2000**, *19*, 217.
[202] Shrivastav, A.; Singh, N.K.; Singh, S. M. *Bioorg. Med. Chem*., **2002**, *10*, 887.
[203] Liang, F.; Wang, P.; Zhou, X.; Li, T.; Li, Z.; Lin, H.; Gao, D.; Zheng, C.; Wu, C. *Bioorg. Med. Chem. Lett*., **2004**, 14, 1901.
[204] Shrivastav, A.; Singh, N. K.; Singh, S. M. *Biometals*, **2003**, *16*, 311.

Received: September 14, 2005 **Revised: January 24, 2006** **Accepted: January 25, 2006**