Development and Current Status of Unconventional Platinum Anticancer Complexes

Adnan Salim Abu–Surrah*

Department of Chemistry, Hashemite University, P. O. Box 150459, Zarqa-13115, Jordan

Abstract: Cisplatin is routinely employed for the treatment of testicular, ovarian cancer and head/neck tumors. Typical doses administrated to patients are 100 mg/day for up to five days. It is believed that the mechanism of action appears to be the binding of *cis*-$Pt(NH_3)_2$ unit to DNA at two neighboring guanine bases.

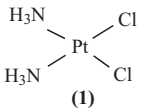
In the years following the introduction of cisplatin, the design of new platinum anticancer drugs concentrated mainly on direct cisplatin analogies, which sticked to the set of structure-activity relationships summarized by Clear and Hoeschele in 1973. Lately, some pioneering strategies towards the synthesis of novel platinum anticancer drugs based on the improved understanding of the mechanism of platinum resistance have emerged. Those are based on either changing the coordinated nitrogen ligand or altering the leaving groups. Other strategies have been shifted to discover "non classical" drugs that can act in a way different from cisplatin. Abnormal structures that violate the empirical structure-activity relationships of platinum compounds and multinuclear complexes are examples of these compounds.

Several review articles appeared during recent years dealing with the synthesis, preclinical screening, and mechanism of action of platinum-based anticancer drugs. In this review, the progress in the field of anticancer chemistry based on unconventional platinum antitumor agents during the last 10 years will be highlighted. Most of the complexes that illustrate the recent and the previous prominent strategies will be presented.

Key Words: Platinum complexes, unconventional complexes, anticancer agents, cytotoxicity.

INTRODUCTION

Since the discovery of the activity of cisplatin (*cis*-dichlorodiamineplatinum(II), [*cis*-$(NH_3)_2PtCl_2$], **1**, Fig. **1**) [1], thousands of platinum complexes have been synthesized and evaluated for their anticancer activity. However, only a few of these complexes have entered clinical trials [2,3], five are currently approved: cisplatin (Platinol, **1**, Fig. **1**) and carboplatin (Paraplatin, *cis*-1,1´-cyclobutyldicarboxylatodiamineplatinum(II), **2**, Fig. **2**) world-wide, oxaliplatin (*cis*-oxalato-*trans*-*l*-1,2-diaminocyclohexaneplatinum(II), **9**, Fig. **3**), in a few countries, nedaplatin (*cis*-glycolatodiamineplatinum(II), **6**, Fig. **2**), and lobaplatin (*cis*-lactatodiaminomethylcyclobutaneplatinum(II), **7**, Fig. **2**) in Japan and China, respectively [2-4].



(1)

Fig. (1). Cisplatin, (**1**, *cis*-dichlorodiamineplatinum(II), [*cis*-$(NH_3)_2PtCl_2$]).

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 [2,5]. In addition, enormous efforts have been directed to understand the mechanism of the cytotoxic activity of cisplatin [6-8].

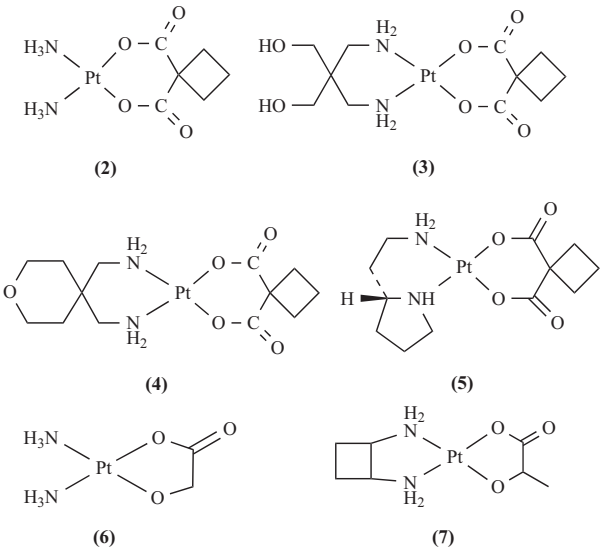
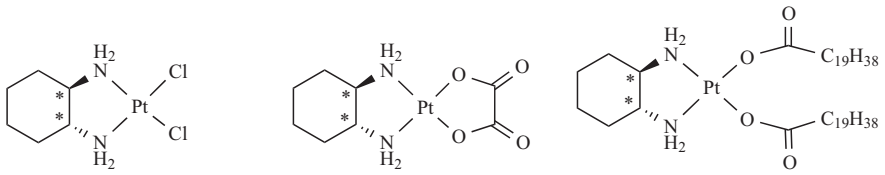


Fig. (2). Carboplatin (**2**) and its analogues complexes: zeniplatin (**3**), enloplatin (**4**), miboplatin (**5**), nedaplatin (**6**), and lobaplatin (**7**).

*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

1389-5575/07 $50.00+.00



(8) **(9)** **(10)**

Fig. (3). Dichloroplatinum(II) complex 1R,2R-(DACH)$PtCl_2$ (**8**) and its derivatives: oxaliplatin (**9**) and L-NDDP (**10**).

A second generation analogue of cisplatin, carboplatin [*cis*-$(NH_3)_2$Pt(CBDC)] (CBDC, 1,1′-cyclobutyldicarboxylate), (**2**, Fig. **2**), has reduced toxic side effects for the same efficiency thanks to its much lower reactivity [9,10]. Unfortunately, carboplatin is only active in the same range of tumors as cisplatin and still administrated intravenously [11].

The third generation of drugs, including compounds that contain different types of chiral amines, has launched [12-15]. Oxaliplatin (**9**, Fig. **3**) showed a colorectal antitumor activity [16], and positive preclinical evaluations for use in cisplatin resistant tumors that can be administrated orally [17,18].

Most of the platinum compounds that entered clinical trials belong to the above mentioned three generations, which means that their structure follow the same empirical structure-activity relationships (SAR) [19,20]. The common features of the most active complexes are: (1) the general formulae should be cis-$Pt^{(II)}X_2(N)_2$ and cis-$Pt^{(IV)}Y_2X_2(N)_2$ (where N : amine ligand, X: leaving group, Y: axial group). For the Pt(IV) compounds, the two Y ligands are in trans orientation. (2) The leaving ligands, usually anions, should consist of groups that have intermediate binding strength to $Pt^{(II)}$. Examples of good leaving groups are Cl^-, SO_4^{2-}, citrate, oxalate and other carboxylic acid residues. (3) The amine ligands, either monodentate or bidentate, should have at least one NH group.

Recently, some revolutionary strategies towards the synthesis of novel platinum anticancer drugs that can act in a manner different from cisplatin have emerged [21,22]. The major purpose of this review is to give an overview of the unconventional platinum anticancer complexes that illustrate the recent and the previous prominent strategies employed in the development of "non classical" platinum-based anticancer agents.

1. PLATINUM ANTITUMOR CHEMISTRY: PRECEDING BACKGROUND

1.1. Cisplatin

Cisplatin (**1**, Fig. **1**) was first synthesized in 1844 by Peyrone, in Turin, but its biological activity was only accidentally discovered in 1965 by Rosenberg [23-25]. Approval of cisplatin for treatment of testicular and ovarian cancer was given in 1978 [2]. Currently, cisplatin is one of the most widely used antitumor drugs [2,26].

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 [2,27]. 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 [28-30].

Cellular resistance to cisplatin is due to several factors and has been reviewed in details [31]. 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 takes place after binding of Pt to DNA [32]. 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.

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

Since the introduction of cisplatin, numerous number of platinum complexes has 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. 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 [$(NH_3)_2Pt(C_4H_6O_4)$] (**2**, Fig. **2**). It has improved the therapeutic index of cisplatin by ameliorating some of the toxic side effects [9]. Although it has a lower activity than cisplatin, its decreased toxicity allows outpatient administration without the need for forced diuresis and very high dosages (up to 2000 mg/dose) [9]. Nevertheless, it appears to have the same spectrum of anticancer activity of cisplatin and thus is not active against cisplatin resistant tumor [11].

Several carboplatin analogues compounds containing cyclobutane ring were developed in the hope of improving the carboplatin characteristics. The compounds include zeniplatin (1,1'-cyclobutanedicarboxylato{2,2-bis(aminomethyl)-1,3-propandiol}platinum(II), **3,** Fig. **2**) [2,12], enloplatin (1,1'-cyclobutanedicarboxylato-tetrahydro-4Hpyran-4,4-dimethylamineplatinum(II), **4**, Fig. **2**) [2], miboplatin (DWA,

R-(-)-1,1'-cyclobutane dicarboxylato-2-aminomethylpyrrolidineplatinum(II), **5**, Fig. **2**) [2,12,33-35], nedaplatin (**6**, Fig. **2**) [2,3,33] and lobaplatin, (D-19466, **7**, Fig. **2**). From the second generation, only carboplatin fulfilled all the requirements for marketing approval worldwide.

1.3. Complexes Containing Chiral DACH-Based Bidentate Nitrogen Ligands

Complexes containing 1,2-diaminocyclohexane (DACH) have received considerable attention over the years [36]. [*cis*-1R,2R-(DACH)$PtCl_2$] (**8**, Fig. **3**) was identified as the most interesting complex not only for its activity but also for its remarkable biological properties. This complex has reduced nephrotoxicity and lack of cross-resistance in murine system [16,17]. 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 prepared [2,3]. These include oxaliplatin, (**9**) and L-NDDP (**10**) (Fig. **3**).

Because of moderate *in vivo* activity, side effects, difficulties in the synthesis or chemical instability, all the prepared compounds were abandoned after some clinical trials except of oxaliplatin (**9**) and L-NDDP, (**10**) [2,3,37-39]. The most successful derivative has been Oxaliplatin (**9**) [40]. It showed antitumor activity in cisplatin-resistant murine L1210 leukemia cells [2,14] and various human cancer cell lines [16,17,41].

Investigations on this type of chiral complexes showed that the *trans-l* (*trans*-(–)-1R,2R) is more efficacious than the corresponding *trans-d*- (*trans*-(+)-1S,2S) and *cis*-isomer (1R,2S) [42]. Thus, the activity might be explained by speculating on the stereochemical structures of the complexes.

1.4. Cisplatin Reactivity and Mechanism of Action

Ligand-exchange behavior of platinum compounds is relatively slow, which gives them a high kinetic stability and results in ligand-exchange reactions of minutes to days, rather than microseconds to seconds for many other coordination compounds.

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 [43]. Although the formation of the initial complex is kinetically controlled, it can undergo *cis-trans*-isomerism [44]. 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). [45] The *trans*-influence factors are always stronger than the corresponding *cis* ones [46].

The hydrolysis rate is mainly determined by the *trans* effect of the ligand *trans* to Cl [47,48]. Steric hindrance is also known to slow down the rates of ligand substitution reactions in square-planar metal complexes [49]. 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, 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 membrane 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*-$Pt(NH_3)_2Cl(H_2O)]^+$ which is assumed to be the active form of the antitumor agent. It has a pKa value of 6.5. Above pH 6 it starts to ionize to form $[PtCl(OH)(NH_3)_2]$ [50], and the cationic species is known to be much more reactive than cisplatin, so the monoaqua species is most likely to react with DNA and other molecules in the cell.

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 and N3 of cytosine. 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 displace 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 formed adducts 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 [22i].

2. NONCLASSICAL PLATINUM-BASED ANTICANCER AGENTS: DEVELOPMENT AND CURRENT STATUS

Research in the field of platinum-based cancer chemotherapy showed that cisplatin and its analogous exhibit very similar patterns of antitumor sensitivity 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 platinum com-plexes that violate the SAR rules for platinum antitumor agents have been synthesized and evaluated. The mechanism of action of nonclassical complexes is different from that of cisplatin and its analogues. Their pattern of antitumor activity is also altered with respect to cisplatin. Comparison of common features and differences between different classes may point to some rules for the rational design of complexes with a different spectrum of clinical activity to cisplatin and activity to cisplatin-resistant tumors.

2.1. *Trans*-Platinum Antitumor Drugs

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 [21,51-54]. 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 biological 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 the 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 (**11**, Fig. **4**) is kinetically more reactive than cisplatin and more susceptible to deactivation [55]. Careful design applying 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 [56,57], 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 **12** and **13**, Fig. **4**) greatly enhances the cytotoxicity of the *trans* isomer, so that cytotoxicity is equivalent to cisplatin itself [51]. As expected, cytotoxicity of *trans* complexes containing planar ligands is highlighted by a remarkable low resistance factor in murine and human cisplatin resistance tumor cell lines.

Studies on the DNA interaction of *trans*-[(NH_3)(quinoline)$PtCl_2$] (**13** Fig. **4**) reveal that this complex forms considerably more interstrand cross-links than transplatin (**11**) [56]. 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. Recently it has been found that the complex *trans*-[(NH_3)(imidazol(1,2-α)pyridine)$PtCl_2$] is more active than cisplatin against cisplatin-resistant ovary cell line $A2780^{cisR}$ [58] .

Natile *et al.* reported that the *trans* platinum-iminoether complexes (**14,** Fig. **4**) can show higher activity than the corresponding *cis* isomers [59,60]. They also reported that the *E* or *Z* configuration of iminoether ligand affects the activity of the platinum complexes. The greater lipophilicity of the *E* isomer determines a greater cellular accumulation and *in vitro* cytotoxicity than the *Z* isomer. Novakova *et al.* have found that the iminoether complex exhibits significant antitumor activity, including activity in cisplatin-resistant tumor cells [61]. In addition, they have also shown that the complex [*trans*-(*E*-iminoether)$_2PtCl_2$] forms mainly monofunctional adducts at guanine residues on DNA.

Moreover, Kelland *et al.* reported that a *trans*-platinum (cyclohexylamine)Pt(IV) dichloride, (JM335) (**15**, Fig. **4**) exhibited greater *in vitro* cytotoxicity against human carcinoma cell lines than its corresponding *cis* isomer [53]. The complex is a Pt(IV) species, *trans*-dihydroxy(amine). The platinum(II) counterpart of the complex (JM334) (**16**) 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 [62]. The results reported suggest that combination of positively charged ligands with a *trans*-[$Pt(II)Cl_2$] species may lead to a new family of platinum tumor agents that are able to circumvent cisplatin resistance.

Nguewa *et al.* have evaluated the cytotoxic properties against the *protozoan Leishmania infantum* of some water soluble cationic *trans*-platinum complexes of the general formula [*trans*-(piperazine)(N)$PtCl_2$] (N = NH_3, 4-picoline, butylamine) [63]. Binding of these complexes to calf thymus DNA induces conformational changes more similar to those of *trans*-diaminedichloroplatinum(II) and this may be attributed to denaturation of the double helix.

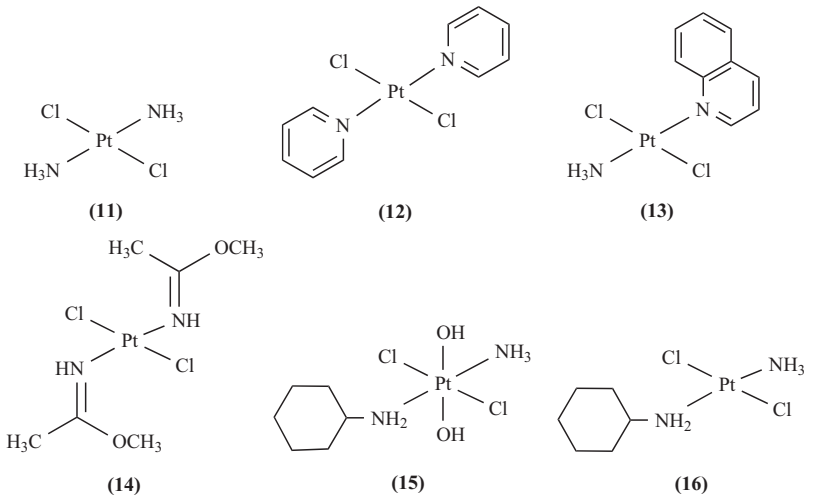


Fig. (4). Structures of some *trans*-platinum(II) complexes (**11-16**).

2.2. Sterically Hindered *cis*-Platinum(II) Complexes Containing *tert*-Amine Ligands

These sterically hindered or crowded platinum compounds have been designed to circumvent cellular detoxification and cisplatin resistance, as well as to block binding of thiols and repair proteins [64].

In order to decrease the reactivity of the platinum complexes and hindering any possible *cis-trans* isomerism that may take place in these complexes with monodentate ligands, sterically hindered complexes containing bidenatate nitrogen ligands were prepared [65]. A comparative study about structural, kinetic, and biological properties of [(BMIC) $PtCl_2$] (**17**, Fig. **5**) and [(BMI)$PtCl_2$] (**18**, Fig. **5**) (BMIC: bis(N-methylimidazol-2-yl)carbinol; BMI: N,N'-dimethyl-2,2'-biimidazole) has been reported [65]. The 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 **17** exhibits significant cytotoxic activity against L1210 leukemia.

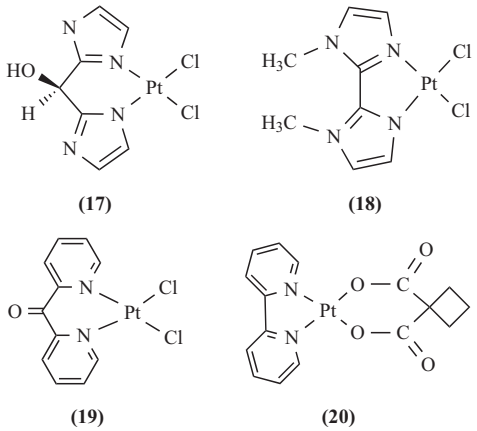


Fig. (5). Structures of the platinum(II) complexes (**17**-**20**).

Platinum(II) complexes of the general formula [$(Py)_2Pt\{N(C_6F_{5-n}Y_n)CH_2\}_2$] (Y = H, I, n = 0,1) can also showed antitumor activity against various tumor cell lines (some cisplatin resistant ones included) both *in vitro* and *in vivo* [66]. 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 [67].

Okada, *et al.* reported the synthesis of an organometallic, cycloplatinate 2-phenylpyridine-based complex that exhibited high antitumor efficacy against cisplatin-resistant mouse sarcoma 180 cell lines [68]. In addition, more efficient cellular uptake of the isolated complexes compared with cisplatin was demonstrated.

Recently, new cisplatin analogous complexes bearing a bidentate dipyridyl nitrogen ligand have been prepared by Krebs and collaborators [69]. Biological tests of the complex [Pt(DPK)Cl_2] (**19**, Fig. **5**) (DPK = 2,2'-dipyridylketone) showed significant antitumor activity of this complex against the human glioma cell line *U* 87.

Another dipyridyl-based platinum complex of the formula [(2,2′-bipyridine)Pt(CBDCA)] (CBDCA: 1,1-cyclobutanedicarboxylate) has been synthesized (**20**, Fig. **5**) [70] and showed inhibition of the growth of P388 lymphocytic leukemia cells and its target is DNA.

Platinum complexes bearing tridentate nitrogen ligands based on amino acid substituted quinolylamide have been synthesized and evaluated for their cytotoxicity by Guo and collaborators [71]. An example of these complexes is [(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 lines that most sensitive to the complex is human liver carcinoma cell line BEL-7402, which has a response rate nearly 6 times higher than that of cisplatin.

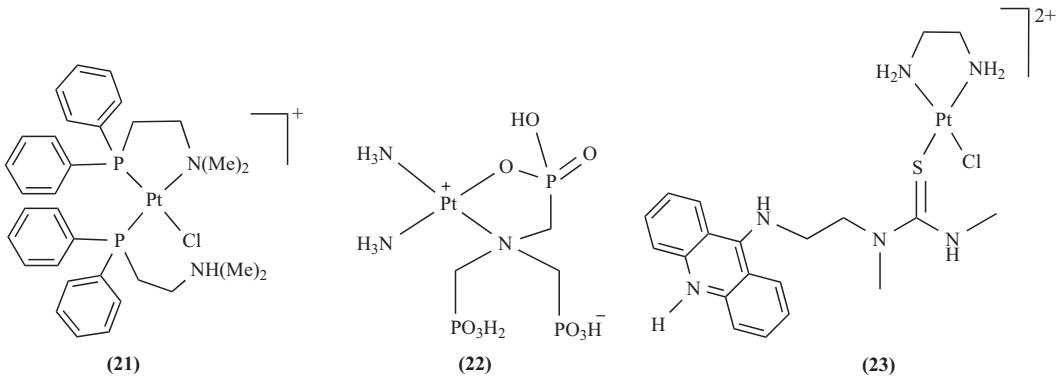
Platinum(II) complexes with moieties such as mepirizol [72], pyrimidine, carboxamide [73], and crown ester-linked bipyridine [74] have also been synthesized and evaluated for their cytotoxic activity. The cytotoxicity and solubility of some complexes could be modified and improved.

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.

2.3. 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 [22d]. Phosphine complexes such as the cationic complex (**21**, Fig. **6**), 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 and by the size of the chelate ring [75,76]. Complex **21** 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 [77]. 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 are resistant to cisplatin [78].



(21) **(22)** **(23)**

Fig. (6). Structures of the complexes (**21**-**23**).

Some platinum complexes linked to amino phosphonic acids (**22**, Fig. **6**) have been prepared. These complexes linked 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 [79].

A dicationic platinum(II) complex bearing a acridinyl-thiourea ligand was also reported (**23**, Fig. **6**) to bind to DNA in a dual manner involving platinum and acridine intercalation. The complex showed slightly less activity against two ovarian cancer cell lines than that of the free ligand [80,81].

The effect of a *cis*-platinum(II) phosphonate complex *cis*-$[(4\text{-PMPE})_2PtCl_2]$ (4-PMPE = diethyl-4-pyridylmethylphosphonate) on murine mast cells was investigated [82]. The complex was able to evoke histamine release from murine mast cells. The histamine secretion was dependent on the concentration of compound and on the time and temperature of the reaction.

Very 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 [83]. 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.

Carrara *et al.* investigated the cytotoxic influence of mercaptopyridine-based platinum complexes on several tumoral cell lines (e.g. HeLa) [84]. The result showed that the presence of sulfur containing ligands may be of particular importance in confirming the antitumor properties of platinum complexes.

2.4. Ionic Multinuclear Platinum Complexes

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 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 [85,86]. 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 back- bone 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 $[Pt(NH_3)_2Cl]$ moieties connected by a flexible diamine link has been reported by Farrell and coworkers [87]. 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 $[\{PtCl_m(NH_3)_{3-m}\}\text{-}\mu\text{-}H_2N\text{-}R\text{-}NH_2\text{-}[\{PtCl_n(NH_3)_{3-n}\}]^{[(2-m)+(2-n)]+}$, where m or n = 0─3 and R = a linear or substituted aliphatic linker.

Binuclear platinum(II) complexes with bifunctional thiourea [88] 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*-PtCl$(NH_3)_2\}_2$-μ-{*trans*-$Pt(NH_3)_2(H_2N(CH_2)_6\text{-}NH_2)_2\}](NO_3)_2$ (**24**, Fig. **7**).

Cesar *et al.* described the synthesis and characterization of new dinuclear platinum complexes containing N,N′-di(2-aminoethyl)-1,3-diamino-2-propanol, aryl substituted N-benzyl-1,4-butanediamines and N-benzyl-1,6-hexanediamines ligands [89]. They reported that the cytotoxic activity of these compounds in human small-cell lung carcinoma cell line and its resistant subline. Resistant cells exhibited a lesser degree of cross-resistance to these complexes when compared to cisplatin.

Recently, Reedijk *et al.*, reported a new class of dinuclear platinum complexes containing an azine-bridge, such as [{*cis*-$Pt(NH_3)_2Cl\}_2$(μ-phthalazine)]$(NO_3)_2$ (**25**, Fig. **7**) [90]. 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 **25** in the L1210 cell lines is similar to that of cisplatin. Analysis of nuclear DNA

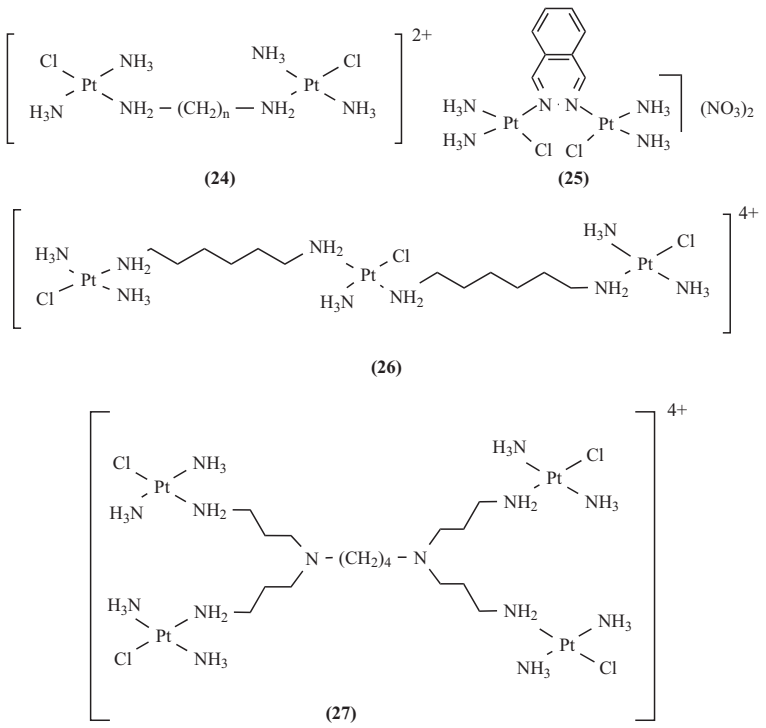


Fig. (7). Structures of the multinuclear platinum complexes (**24**-**27**).

fragmentation in L1210 cells treated with the azine-bridged complexes indicates 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 that can help to expand the realm of Pt chemotherapy treatment.

Trinuclear and tetranuclear platinum complexes have also been studied [91-93]. The trinuclear complex BBR3464 (**26**, Fig. **7**) 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 [94, 95]. The compound interacts with DNA in novel ways not available to cisplatin or other mononuclear platinum complexes [96].

The tetranuclear platinum complex, $DAB(PA\text{-}tPt\text{-}Cl)_4$ (**27**, Fig. **7**), 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 [93].

DNA-binding properties of binuclear platinum complexes with two *trans*-$[Pt(NH_3)_2Cl]^+$ units bridging by 4,4`-dipyridyl sulfide or selenide (*trans*-$[Pt(NH_3)_2Cl]_2(DPSU)](NO_3)_2$ and *trans*-$[Pt(NH_3)_2Cl]_2(DPSE)](NO_3)_2$ (DPSU = 4,4`-dipyridyl sulfide, DPSE = 4,4`-dipyridyl selenide) have been investigated and compared with the known monofunctional complex *cis*-$[Pt(NH_3)_2Cl(4\text{-methylpyridine}](NO_3)$ [97]. The result suggested that this complex may bind bifunctionally to DNA.

Several polynuclear platinum complexes with biogenic polyamines were synthesized and evaluated for their cytotoxic activity in different human cancer cell lines (e.g. HeLa, THP-1, and CCRF-CEM leukemia cell lines) [98]. Distinct effects were found with different structural characteristics of the complexes.

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 synthesized and evaluated, but only few were approved. Studies have also shown that the range of platinum complexes with antitumor activity is not restricted to the structural analogues of cisplatin. 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. 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. The most profitable one could be that of good solubility in water and the ability to transport (through the membranes), fortitude in the cell, binding to the DNA, and eventually excretion from the body with minimum side effects. More understanding of the physiological processing of metal complexes and Combinatorial chemistry, extensively applied in organic drug discovery and formulation,

could assist in the development of new methodologies for the design of new inorganic compounds as therapeutics.

REFERENCES

[1] Rosenberg, B.; Van Camp, L.; Trosko, J. E.; Mansour, V. H. *Nature*, **1969**, *222*, 385.
[2] Weiss R. B.; Christian M. C, *Drugs*, **1993**, *46*, 360.
[3] Lebwohl, D.; Canetta, R. *Eur. J. Cancer*, **1998**, *34*, 1522.
[4] Wong, E.; Giandomenico, C. M. *Chem. Rev*., **1999**, *99*, 2451.
[5] Reedjik, *J. Chem. Commun*., **1996**, 801.
[6] Reedijk, J. *J. Pure Appl. Chem*., **1987**, *59*, 181.
[7] Farrell, N. *Transition Metal Complexes as Drugs and Chemotherapeutic Agents*, Kluwer Academic Publisher: Boston, **1989**.
[8] *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*, Howell, S. B., Ed.; Plenum Press: New York, **1991**.
[9] Evans, B. D.; Raju, K. S.; Calvert, A. H.; Harland, S. J.; Wiltshaw, E. *Cancer Treat. Rep*., **1983**, *67*, 997.
[10] Kelland, L. R. *Crit. Rev. Oncol. Hematol*., **1993**, *15*, 191.
[11] Rixe, O.; Ortuzar, W.; Alvarez, M. *Biochem. Pharmacol*., **1996**, *52*, 1855.
[12] 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.
[13] Connors, T. A.; Jones, M.; Ross, W. C.; Braddock, P. D.; Khokhar, A. R.; Lobe, M. L. *Chem. Biol. Interact.*, **1972**, *5*, 415.
[14] Tashiro, T.; Kawada, Y.; Sakurai, Y. *Biomed. Pharmacoth*., **1989**, *43*, 251.
[15] Kidani,Y.; Inagaki, K.; Iigo, M.; Hoshi, A.; Kuretani, K. *J. Med. Chem*., **1978**, *21*, 1315.
[16] Khokhar, A. R.; Al-Baker, S.; Krakoff, I. H.; Perez-Solar, R. *Cancer Chemother. Pharamcol*., **1989**, *23*, 219.
[17] Burchenal, J. H.; Kalaher, K.; O'Toole, T.; Chisholm, J. *Cancer Res*., **1977**, *37*, 2455.
[18] Perez, R. P.; Perez, K. M.; Handel, L. M.; Hamilton, T. C. *Cancer Chemother. Pharmacol.*, **1992**, *29*, 430.
[19] Cleare, M. J.; Hoeschele, J. D. *Bioinorg. Chem*., **1973**, *2*, 187.
[20] Connors, T. A.; Cleare, M. J.; Harrap, K. R. *Cancer Treat. Rep*., **1979**, *63*, 1499.
[21] Farrell, N. *Cancer Invest.*, **1993**, *11*, 578.
[22] For recent review articles: (a) Wang, D.; Lippard, S. J. *Nat. Rev. Drug. Discov*., **2005**, *4*, 307; (b) Barnes, K.R., Lippard, S. J. *Metal Ions in Biological Systems*, **2004**, *42*, 143; (c) Fuertes, M. A.; Alonso, C.; Perez, J. M. *Chem. Rev*., **2003**, *103*, 645; (d) Ho, Y.-P.; Au-Yeung, S. C. F.; To, K. K. W. *Med. Res. Rev*., **2003**, *23*, 633; (e) Hall, M. D.; Hambley, T. W. *Coord. Chem. Rev.*, **2002**, *232*, 49; (f) 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; (g) Reedijk, J. *Chem. Rev*., **1999**, *99*, 2499; (h) Trimmer, E. E.; Essigmann, J. M. *Essays Biochem*., **1999**, *34*, 191; (i) Kozelka, J.; Legendre, F.; Reeder, F.; Chottard, J.-C. *Coord. Chem. Rev*., **1999**, *190-192*, 61; (j) Arpalahti, J. *Persp. Bioinorg. Chem*., **1999**, *4*, 165; (k) Jamieson, E. R.; Lippard, S. J. *Chem. Rev*., **1999**, *99*, 2467.
[23] Rosenberg, B.; Van Camp, L.; Krigas, T. *Nature*, **1965**, *205*, 698.
[24] Bertini, I, Gray, H.B., Lippard, S.J, Valentine J.S. *Bioinorganic Chemistry*, California, **1994**; pp. 523-590.
[25] Kaim, W., Schwederski, B., *Bioinorganic Chemistry: Inorganic Element in the Chemistry of Life*, Wiley: Stuttgart, **1993**; pp. 363-384.
[26] 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.
[27] Perez, R. P.; Hamilton, T. C.; Ozols, R. F.; Young, R. C. *Cancer*, **1993**, *71*, 1571.
[28] Goren, M. P.; Wright, R. K.; Horowitz, M. E. *Cancer Chemother. Pharmacol*., **1986**, *18*, 69.
[29] Alberts, D. S.; Noel, J. K. *Anticancer Drugs*, **1995**, *6*, 369.
[30] Hamers, F. P. T.; Gispen, Y. H.; Neijt, J. P. *Eur. J. Cancer*, **1991**, *27*, 72.
[31] Kelland, L. R. *Drugs*, **2000**, *59*, 1.
[32] (a) Mistry, P.; Lelland, L. R. *Brit. J. Cancer*, **1991**, *64*, 215; (b) Chaney, S. G.; Vaisman, A. *J. Inorg. Biochem*., **1999**, *77*, 71.
[33] Majima, H.; *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Howell, S. B., Ed.; Plenum Press: New York, **1991**; pp. 345-355.
[34] Kobayashi, H.; Takemura, Y.; Miyachi, H.; Ogawa, T. *Invest. New Drugs*, **1991**, *9*, 313.
[35] Yang, L. Y.; Liu, Y. Z.; Li, L., Kantajian, H. H.; Keating, M. J. *Int. J. Oncol*., **1994**, *5*, 597.
[36] Burchenal, K.; Kalaher, K.; Dew, K.; Lokys, L., *Cancer Treat. Rep*., **1979**, *63*, 1493.
[37] Perez-Soler, R.; Khokhar, A. R. *Proc. Am. Assoc. Cancer Res*., **1998**, *29*, 509.
[38] 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.
[39] Abu-Surrah, A. S.; Al-Allaf, T. A. K.; Klinga, M.; Leskelä, M. *Polyhedron*, **2003**, *22*, 1529.
[40] Misset, J. L. *Brit. J. Cancer*, **1998**, *77*, 4.
[41] Rixe, O.; Ortuzar, W.; Alvarez, M. *Biochem. Pharmacol.*, **1996**, *52*, 1855.
[42] Kidani,Y.; Inagaki, K.; Iigo, M.; Hoshi, A.; Kuretani, K. *J. Med. Chem*., **1978**, *21*, 1315.
[43] Bertini, I.; Gray, H.B.; Lippard, S.J.; Valentine, J.S. *Bioinorganic Chemistry*, University Science Books: California, **1994**; pp. 53-590.
[44] 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.
[45] Abu-Surrah, A. S.; Hodali, H. A. *Inorg. Chim. Acta*, **1990**, *174*, 223.
[46] Abu-Surrah, A. S.; Lappalainen, K.; Klinga, M.; Leskelä, M., Hodali, H. A. *Acta Cryst.*, **1999**, *C55*, 188.
[47] Oe, T.; Tian, Y.; O'Dwyer, Roberts, D. W.; Malone, M. D.; Bailey, C. J.; Blair, I. A. *Anal. Chem.*, **2002**, *74*, 591.
[48] Barton, S. J.; Barnham, K. J.; Habtemariam, A.; Sue, R. E.; Frey, U.; Sadler, P. J. *Aust. J. Chem*., **1999**, *52*, 173.
[49] Chen, Y.; Guo, Z.; Parsons, S.; Sadler, P. J. *Chem.Eur. J.*, **1998**, *4*, 672.
[50] Berners-Price, S. J.; Frenkiel, T. A.; Frey, U.; Ranford, J. D.; Sadler, P. J. *J. Chem. Soc. Chem. Commun.*, **1992**, 789.
[51] Farrell, N.; Ha, T. T. B.; Souchard, J. P.; Wimmer, F. L.; Cross, S.; Johnson, N. P. *J. Med. Chem.*, **1989**, *32*, 2241.
[52] Perez, J. M; Fuertes, M. A.; Alonso, C.; Navarro-Ranninger, C. *Crit. Rev. Oncol. Hematol.*, **2000**, *35*, 109.
[53] Kelland, L. R.; Barnard, C. F. J.; Evans, I. G.; Murrer, B. A.; Theobald, B. R.; Wyer, S. B.; Goddard, P. M.; Jones, M.; Valenti, M.; Bryant, A. *J. Med. Chem*., **1995**, *38*, 3016.
[54] 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.
[55] Hartley, F. R. *The Chemistry of Platinum and Palladium*, John Wiley: NY, **1973**.
[56] Zakovka, A.; Novakova, O.; Balcarova, Z.; Bierbach, U.; Farrell, N.; Brabec, V. *Eur. J. Biochem.*, **1998**, *254*, 547.
[57] Gibson, D.; Lippard, S. J. *Inorg. Chem*., **1987**, *26*, 2275.
[58] Huq, F.; Daghriri, H.; Yu, J. Q.; Beale, P.; Fisher, K. *Eur. J. Med. Chem*., **2004**, *39*, 691.
[59] 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.
[60] 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.
[61] Novakova, O.; Kasparkova, J.; Malina, J.; Natile, G.; Brabec, V. *Nucleic Acids Res.*, **2003**, *31*, 6450.
[62] Najajreh, Y.; Perez, J. M.; Navarro-Ranninger, C.; Gibson, D. *J. Med. Chem*., **2002**, *45*, 5189.
[63] Nguewa, P. A.; Fuertes, M. A.; Iborra, S. Najajreh, Y.; Gibson, D.; Martínez, E.; Alonso, C.; Pérez, J. M. *J. Inorg. Biochem*., **2005**, *99*, 727.
[64] Holford, J.; Sharp, S. Y.; Murrer, B. A.; Abrams, M.; Kelland, L. R. *Br. J. Cancer*, **1998**, *77*, 366.
[65] Bloemink, M. J.; Engelking, H.; Karentzopoulos, S.; Krebs, B.; Reedijk, *J. Inorg. Chem*., **1996**, *35*, 619.
[66] 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.

[67] Bloemink, M.J.; Heetebrij, R. G.; Ireland, J.; Deacon, G.B.; Reedijk. J. *J. Biol. Inorg. Chem.,* **1996**, *1*, 278.
[68] Okada, T.; El-Mehasseb, I. M.; Kodaka, M.; Tomohiro, T.; Okamato, K., Okuno, H. *J. Med. Chem.*, **2001**, *44*, 4661.
[69] 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.
[70] Mansuri-Torshizi, H.; Ghadimy, S.; Akbarzadeh, N. *Chem. Pharm. Bull*., **2001**, *49*, 1517.
[71] 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.
[72] Onoa, G. B.; Moreno, V.; Font-Bardia, M.; Solans, X.; Perez, J. M.; Alonso, C. *J. Inorg. Biochem*., **1999**, *75*, 205.
[73] Drewa, T.; Woźniak, A.; Olszewska, D.; Szłyk, E.; Łukomska, I.; Mila-Kierzenkowska, C.; Czajkowski, R. *Acta Pol. Pharm*., **2001**, *58*, 169.
[74] Yoo, J.; Sohn, Y. S.; Do, Y. *J. Inorg. Biochem*., **1999**, *73*, 187.
[75] Habtemariam, A.; Sadler, P. *J. Chem. Commun*., **1996,** 1785.
[76] Habtemariam, A.; Nevplechova, K.; Brabec, V.; Margiotta, N.; Sadler, P.J. *J. Inorg. Biochem*., **1997**, *67*, 161.
[77] 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.
[78] Keppler, B. K.; Berger, M. R.; Klenner, T.; Heim, M. E. *Adv. Drug Res*., **1990**, *19*, 243.
[79] Bloemink, M. J.; Dorenbos, J. P.; Heetebrij, R. J.; Keppler, B. K.; Reedijk, J.; Zahn, H. *Inorg. Chem*., **1994**, *33*, 1127.
[80] Martins, E. T.; Baruah, H.; Kramarczyk, J. Saluta, G.; Day, C. S.; Kucera, G. L.; Bierbach, U. *J. Med. Chem*., **2001**, *44*, 4492.
[81] Brow, J. M.; Pleatman, C. R., Bierbach, U. *Bioorg. Med. Chem. Lett*., **2002**, *12*, 2953.
[82] Brzezinska-Blaszczyk, E.; Mincikiewicz, M.; Ochocki, J. *Eur. J. Pharmacol*., **1996**, *298*, 155.
[83] Friebolin, W.; Schilling, G.; Zöller, M.; Amtmann, E. *J. Med. Chem*., **2004**, *47*, 2256.
[84] Carrara, M.; Berti, T.; D'Ancona, S.; Cherchi, V.; Sindellari, L. *Anticancer Res*., **1997**, *17*, 975.
[85] Wheat, N. J.; Collins, J. G. *Coord. Chem. Rev*., **2003**, *241*, 133.
[86] Roberts, J. D.; Peroutka, J.; Farell, N. *J. Inorg. Biochem*., **1999,** *77*, 51.
[87] Wu, P. K.; Qu, Y.; Van Houten, M. P.; Farrell, N. *J. Inorg. Chem.*, **1994**, *77*, 3.
[88] Bierbach, U.; Hambley, T. W.; Farrell, N. *Inorg. Chem.*, **1998**, *37*, 708.
[89] Cesar, E. T.; Almeida, M. V.; Fontes, A. P.; Pereira Maia, E. C.; Garnier-Suillerot, A.; Couri, M. R. C.; Felício, E. D. A. *J. Inorg. Biochem*., **2003**, *95*, 297.
[90] Kalayda, G. V.; Komeda, S.; Ikeda, K.; Sato, T.; Chikuma, M.; Reedijk, J. *Eur. J. Inorg. Chem.*, **2003**, *24*, 4347.
[91] Qu. Y.; Farrell, N.; Kasparkova, J.; Brabec, V. *J. Inorg. Biochem*., **1997**, *67*, 174.
[92] 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.
[93] Jansen, B. A. J.; Van der Zwan, J.; Reedijk, J.; den Dulk, H.; Brouwer, J. *Eur. J. Inorg. Chem*., **1999**, 1429.
[94] Di Blasi, P.; Bernareggi, A.; Beggiolin, G.; Piazzoni, L.; Mernta, E.; Formento, M. L. *Anticancer Res.*, **1998**, *18*, 3113.
[95] Pratesi, G.; Giuliani, F. C.; Polzzi, D.; Righetti, S.; Pezzoni, C.; Farrell, N.; Zunino, F.; *Proc. Am. Assoc. Cancer Res*., **1997**, *38*, 3310.
[96] Perego, P.; Gatti, L.; Caserini, C.; Supino, R.; Colangelo, D.; Leone, R.; Spinelli, S.; Farrell, N.; Zunino, F. *J. Inorg. Biochem*., **1999**, *77*, 59.
[97] Zhao, G.; Hu, X.; Yu, P.; Lin, H. *Trans. Metal Chem*., **2004**, *29*, 607.
[98] Teixeira, L. J; Seabra, M.; Reis, E. *J. Med. Chem*., **2004**, *47*, 2917.

Received: 14 June, 2006 Revised: 18 September, 2006 Accepted: 19 September, 2006