Cancer Therapy Vol 6, 1-10, 2008

Palladium-based chemotherapeutic agents: Routes toward complexes with good antitumor activity

Review Article

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Key words: Palladium complexes, Anticancer agents, Cytotoxicity, Chiral ligands

Abbreviations: diethyl-2- quinolmethylphosphonate, (2-dqmp); mercaptopyridines, (MP); monoethyl-2-quinolmethylphosphonate, (2-Hmqmp); structure-activity relationships, (SAR)

Received: 21 November 2007; Revised: 18 December 2007
Accepted: 18 December 2007; electronically published: January 2008

Summary

Chemical-, 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 analogue complexes has been an empirical task. Studies have 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) 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. This study gives an up to date overview of the anticancer chemistry of palladium compounds with an emphasis on the new strategies used in the development of new palladium antitumor agents.

I. Introduction

Cis-diaminedichloroplatinum(II), [cis-$(NH_3)_2PtCl_2$], clinically called cisplatin is one of the most successful anticancer compound (Rosenberg et al, 1969). After the discovery of its activity, thousands of platinum complexes have been synthesized and evaluated for their anticancer activity. Research in the field of platinum-based cancer chemotherapy showed that cisplatin and its analogous compounds 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 metal based anticancer agents should have novel structures unrelated to those agents assigned to platinum complexes. Therefore, several unconventional complexes that violate the SAR rules have been synthesized and evaluated (Abu-Surrah, 2007). 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.

The significant similarity between the coordination chemistry of palladium(II) and platinum(II) compounds has advocated studies of Pd(II) complexes as antitumor drugs (Rau et al, 1996). A key factor that might explain why platinum is most useful comes from the ligand-exchange kinetics. The hydrolysis in palladium complexes is too rapid: 10^5 times faster than for their corresponding platinum analogues. They dissociate readily in solution leading to very reactive species that are unable to reach their pharmacological targets.

Compared to cisplatin, the corresponding cispalladium, *cis*-[$Pd(NH_3)_2Cl_2$] and *cis*-[Pd(DACH)Cl_2]

(DACH: (1R,2R)-(–)-1,2-diaminecyclohexane) do not show antitumoral activity. It is well known that the former undergoes an inactive *trans*-conformation and that the two compounds hydrolyze very fast assuming that they interact *in vivo* with a lot of molecules particularly proteins preventing them to reach the DNA, their pharmalogical target (Butour et al, 1997, Wimmer, et al, 1989, Zhao, et al, 1999). 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.

Several review articles have appeared during recent years dealing with platinum-based anticancer agents (Suzanne et al, 1987; Fuertes et al, 2003; Reedijk, 2003; Wang et al 2005, Kostova, 2006). The biological mechanism of palladium(II) complexes with an emphasis on cyclopalladated complexes has recently been reviewed (Caires, 2007). In this review, the progress in the field of anticancer chemistry of palladium-based transition metal complexes during the last 10 years will be highlighted. Methodologies for application of bulky aromatic or aliphatic nitrogen ligands, chiral organic moieties, chelates containing other donor atoms than nitrogen, and multinuclear palladium complexes will be discussed. The complexes that illustrated the prominent strategies utilized in the development of anticancer palladium-based agents will also be presented.

II. Palladium anticancer chemistry

Numerous palladium complexes with promising activity against tumor cell lines have been synthesized (Graham et al, 1979; Rau et al, 1996). 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. Different types of monodentate ligands were applied in the synthesis of these complexes. In addition, several research groups have focused on the preparation of Pd(II) complexes bearing bidentate ligands as a way to stabilize these compounds and to prevent any possible *cis-trans* isomerism (Mansuri et al, 1992).

A. *Trans*-palladium(II) complexes

Relatively bulky monodentate ligands have been utilized to produce the complexes of this family. Due to the steric effect that results from the bulk on the donor atoms, these ligands could minimize any possible *cis-trans* isomerism and insure the direct separation of the desired *trans*- Pd isomers (Abu-Surrah et al, 2002). In general, research results indicated that most of the *trans*-palladium complexes showed a better activity than the *cis*-platinum isomers and superior activity than that of the *cis*-palladium isomers. More importantly, they showed activities equal to (or superior than) those of cisplatin, carboplatin, and oxaliplatin (the anti-cancer drugs in clinical use) *in vitro*.

A comparative study on antitumor activity was carried out between the Pd(II) dihalide complexes of monoethyl-2-quinolmethylphosphonate (2-Hmqmp) and diethyl-2-quinolmethylphosphonate (2-dqmp) (Tusek-Bozic et al, 1991). The diester ligand has two potential donors, the N from quinoline and the O from phosphoryl giving the complex [*trans*-(2-dqmp)$_2$PdCl$_2$] (**1, Figure 1**). 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.

The synthesis and cytotoxicity evaluation of some *trans*-[(L)$_2$Pd(X)$_2$] complexes (**2**) (L = N,N-dimethyl-O-ethylthiocarbamate: DMTC or N-methyl-O-ethylthiocarbamate: MTC, X = Cl, Br) were reported (Furlani et al, 1996). Other palladium complexes based on 2-mercaptopyridines (MP) were also prepared. The [(MP)$_3$Pd(Br)]$^+$. Br$^-$ (**3**) 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 (Carrara et al, 1996).

Palladium(II) complexes with alkyl phosphonates ligands derived from aniline and quinoline were reported. Most of the aniline compounds (e.g. **4**) showed cytotoxicity *in vitro* against animal and human tumor cell lines (Curic et al, 1996).

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$_2$] (**5**, **Figure 1**) exhibits a greater cytotoxic activity against P388, L1210 and K562 cell lines than cisplatin (Al-Allaf et al, 1998).

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$_2$] (**6**) (**Figure 1**) that bears the bulky amine ligand R-(+)-bornylamine (*endo*-(1R)- 1,7,7-trimethyl-bicyclo[2-2-1]-heptan-2-amine). The complex showed similar antitumor activity against HeLa cells when compared with the activity of the standard references, cisplatin, carboplatin and oxaliplatin (Abu-Surrah et al, 2002).

A *trans*-palladium complex of the general formula, *trans*-[Pd(L)$_2$Cl$_2$] (L = 2-chloro-6-[(2-methoxybenzyl)-amino]-9-isopropylpurine) has been reported (Trávníček et al, 2007). The complex has been tested *in vitro* for its cytotoxicity against malignant melanoma (G361) cell lines. Promising *in vitro* cytotoxic effect has been found (IC$_{50}$ = 15 μM).

Palladium(II) complexes of the form: *trans*-PdCl$_2$L$_2$, where L=3-hydroxypyridine, 2-hydroxypyridine and 4-hydroxypyridine respectively have been investigated for antitumour activity against ovarian cancer cell lines: A2780, A2780^{cisR} and A2780^{ZD0473R} (Huq et al, 2007). The compounds were found to be less active than cisplatin but they are often found to be more active against the resistant cell lines than the parent cell line. The 2-hydroxypyridine-based complex was found to be most active against the three cell lines.

B. Palladium(II) complexes containing bidentate nitrogen ligands

Navarro-Ranninger and colleagues reported the synthesis of square planar dichloro palladium(II) complexes with spermidine and spermine ligands

(Navarro-Ranninger et al, 1993). These types 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 (**7**, **Figure 2**) give values of IC_{50} similar to cisplatin, whereas those of spermine have low antiproliferative activity.

Ethylendiamine-based palladium(II) complexes with pyridine (**8**, **Figure 2**) or its derivatives were also reported (Zhao et al, 1999). 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.

An alternative method to the synthesis of the enantiomerically pure DACH-based palladium(II) complexes (DACH: (1R,2R)-(–)-1,2-diaminecyclohexane) was utilized (Abu-Surrah et al, 2002). 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)$PdCl_2$] (**9**) in a high yield (**Figure 3**).The corresponding cationic, aqua complex, $[(DACH)Pd(H_2O)_2]^{2+}$. $2NO_3^-$ (**10**) and the oxalate complex (oxalipalladium) [(DACH)$Pd(C_2O_4)$] (**11**) have also been isolated and characterized (Abu-Surrah et al, 2003).

A new approach to increase the stability of the palladium(II) complexes by forming two chelate rings around the central atom was applied. L-cysteine derived ligands such as py-CH_2-accys (**12**, **Figure 4**) (accys: N-acetyl-S-methylene-2-(2-pyridine)-L-cysteine) have been applied (Rau et al, 1998).

The S,N-chelating mode of these ligands is of importance, since only the side chain of the amino acid is involved in 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.

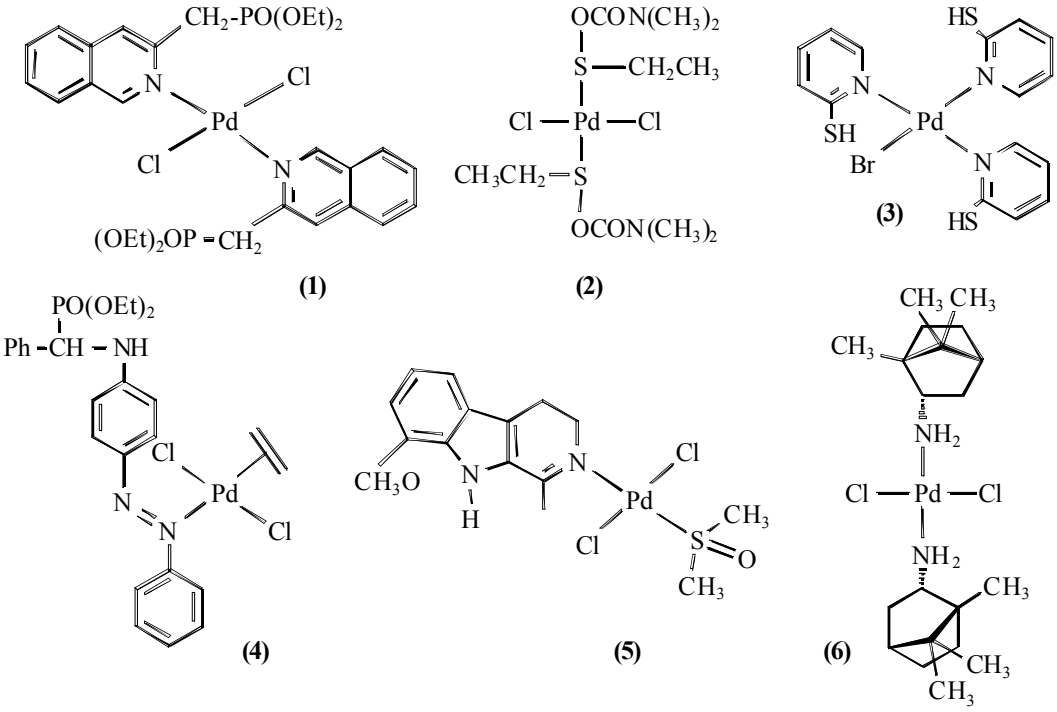


Figure 1. Structures of some *trans*-palladium(II) complexes (**1**-**6**).

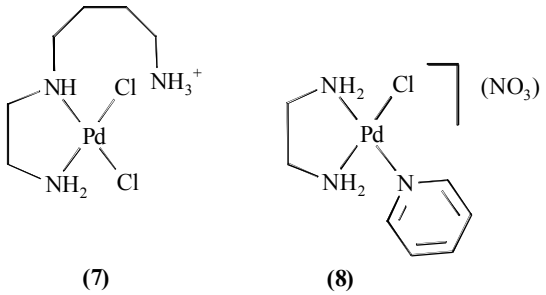


Figure 2. Palladium(II) complexes with ethylenediamine nitrogen ligand (**7** and **8**).

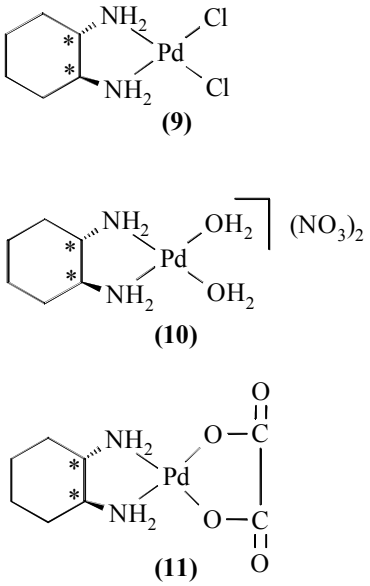


Figure 3. Palladium(II) complexes with (1R,2R)-(–)-1,2-diaminecyclohexane (DACH) (**9-11**).

Palladium compounds bearing two chelating N-N and O-O ligands were prepared (Mansuri-Torshizi et al, 1991). 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) (**13**) was found to bind to DNA through a coordinate covalent bond.

The cytotoxic activity of palladium complexes bearing nitrate (NO_3) in addition to a bidentate nitrogen ligand (Wimmer et al, 1989) was investigated. A comparison among [(bipy)Pd(NO_3)$_2$] (**14**), [(AMP)Pd(NO_3)$_2$], [(AEP)Pd(NO_3)$_2$], [(DACH)Pd-(Meorot)] (bipy = 2,2'-bipyridyl, AMP = 2-aminometyl-pyridine, AEP = 2-aminoethylpyridine, Meorot = 3-methylorotate) showed that only [(DACH)Pd(Meorot)] (**15**) was active, giving a high activity for sarcoma 180 but a low one against P388 leukemia. Similarly, [(DACH)Pd(5-fluroorot)] reported later (Butour et al, 1997), 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 (Paul et al, 1993). The alanine based complex (**16**, **Figure 4**) showed better cytotoxicity against P388 lymphocytic leukemia cells than the glycine based one.

The 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-dimathanamine)Pd(II)] (**17**) (alkyl: Me, Ethyl, propyl, cyclohexyl) are significantly dependent on the nature of the alkyl substituents. The complexes bearing the bulkiest groups showed lower IC_{50} values than cisplatin (Zhao et al, 1998). Palladium(II) complexes containing S-donors (diethyldithiocarbamate: ddtc) in addition to the N-N ligands (bipyridine, phenanthroline, and DACH) have also been investigated (Mital et al, 1989). The most active were the bipyridine and phenanthroline-based complexes (**18**, **Figure 4**).

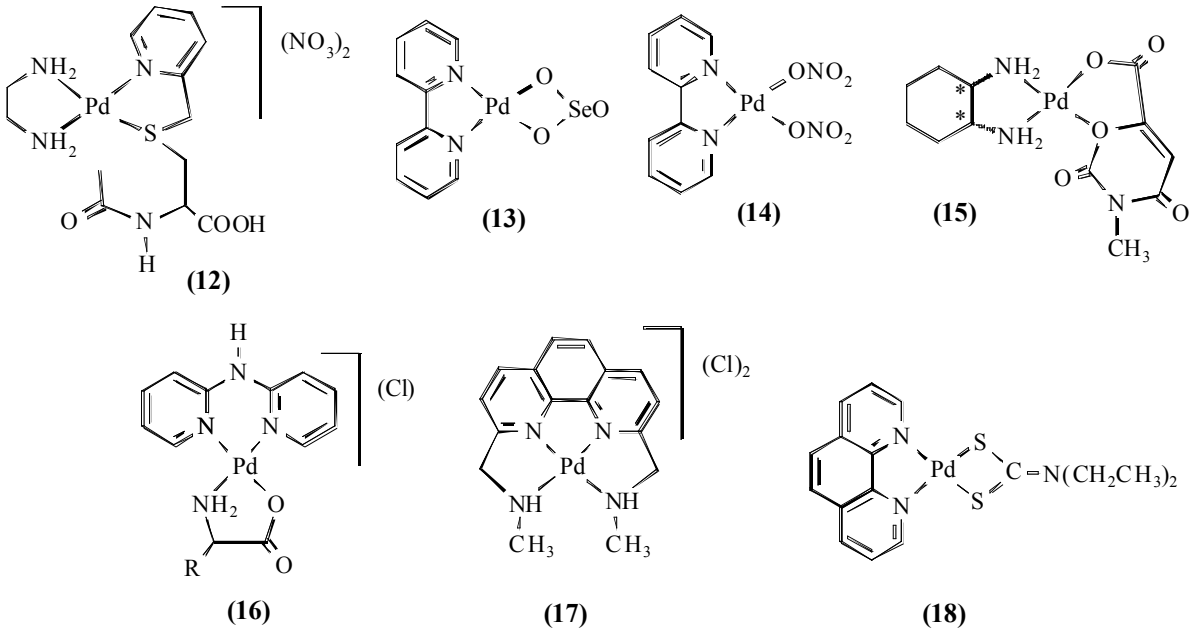


Figure 4. Palladium(II) complexes containing different types of nitrogen ligands (**12-18**).

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

C. Palladium(II) complexes bearing phosphine ligands

Some 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 (Navarro-Ranninger et al, 1993). 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* (Caires et al, 1999). Some cyclopalladated complexs based on biphosphine ligands (**19** and **20**, **Figure 5**) have been prepared and investigated for their antitumor activity in a syngeneic B16F10 murine melanoma model (Rodrigues et al, 2003). The ionic complex (**19**) caused 100% tumor cell death at very low concentration (< 1.25 μM).

Palladium and a broad series of group VIII transition metal complexes containing bidentate phosphine ligands of the general formula $[L_2MX_m]^{n+}$ nX^- [L = Ph_2P-A-PPh_2, A = $(CH_2)_2$, $(CH_2)_3$ or cis-CH = CH; M = Fe, Co, Rh, Ir, Ni, Pd; X = Cl, Br, I, NO_3, ClO_4, CF_3SO_3; m = 0-2; n = 0-3] 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 (Shurig et al, 1989).

Recently, it has been reported on a new palladium(II) complex bearing a bidentate P-N ligand which was formed via the condensation of 2-(diphenylphosphino)benzaldehyde and ethyl hydrazinoacetate (Malešević et al, 2006). The cytotoxic activity of the complex was similar to that of cisplatin.

D. Palladium(II) complexes bearing mixed donor atom ligands

Palladium(II) complexes with mixed nitrogen-sulfur ligands such as methionine and substituted pyrimidines (mercapto or amino) have been reported by Khan and colleagues in 1991. 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^- (**21**, **Figure 6**) has *in vitro* IC_{50} value lower than 10 μg/ml, so it could act as a potential antitumor agent.

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 (**22**, **Figure 6**) has been found to display an enhanced *in vitro* activity compared to its platinum analogue (Quiroga et al, 1998). In addition, this complex is active in cisplatin resistant cell lines.

Other thiosemicarbazide derivatives have also been studied. [(Benzyl)Pd{bis(thiosemicarbazonate)}] (**23**, **Figure 6**) showed IC_{50} values in a concentration range similar to that of cisplatin and a notable activity in cisplatin-resistant cell lines (Matesanz, 1999).

Palladium complexes with 2-benzoylpyridine derived thiosemicarbazones with good antitumor activity were also reported (Rebolledo, et al, 2005).

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 (Chen et al, 2004). The results revealed that the complex is an effective antitumor agent. The study of mechanism of action showed that the metal complex can only stabilize the single-strand nicked DNA, but not double-strand breakage intermediates.

The synthesis of a palladium(II) complex of the general formula $[Pd(N\text{-}O)_2]$ (N-O: 3-ethanimidoyl-2-methoxy-2H-1,2-benzoxa-phospinin-4-ol-2-oxide) has also been reported (Budzisz, et al, 2004). The cytotoxic activity of this complex against the human leukemia cell lines, HL-60 and NALM-6 showed that the effects exhibited by this complex was comparable to those reported for cisplatin and carboplatin.

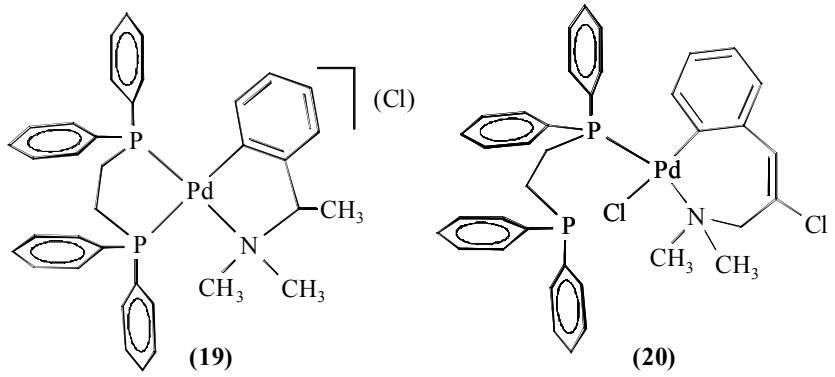
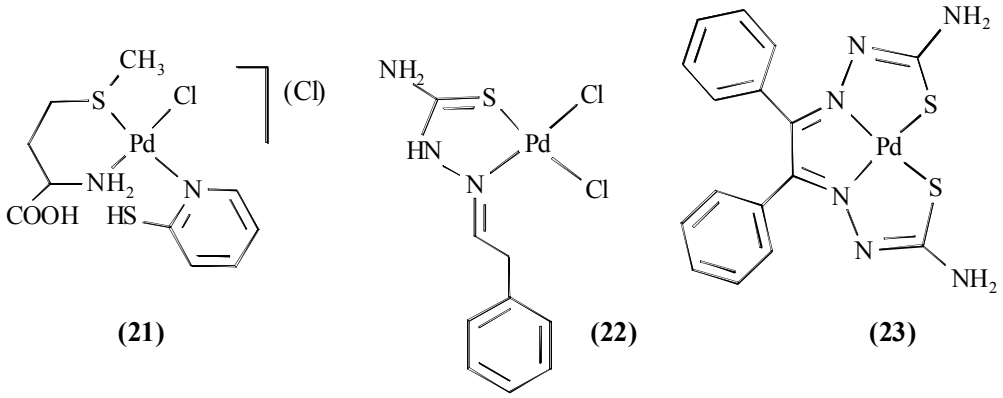


Figure 5. Palladium(II) complexes bearing 1,2-bis(diphenylphosphino)ethane (dppe) (**19** and **20**).



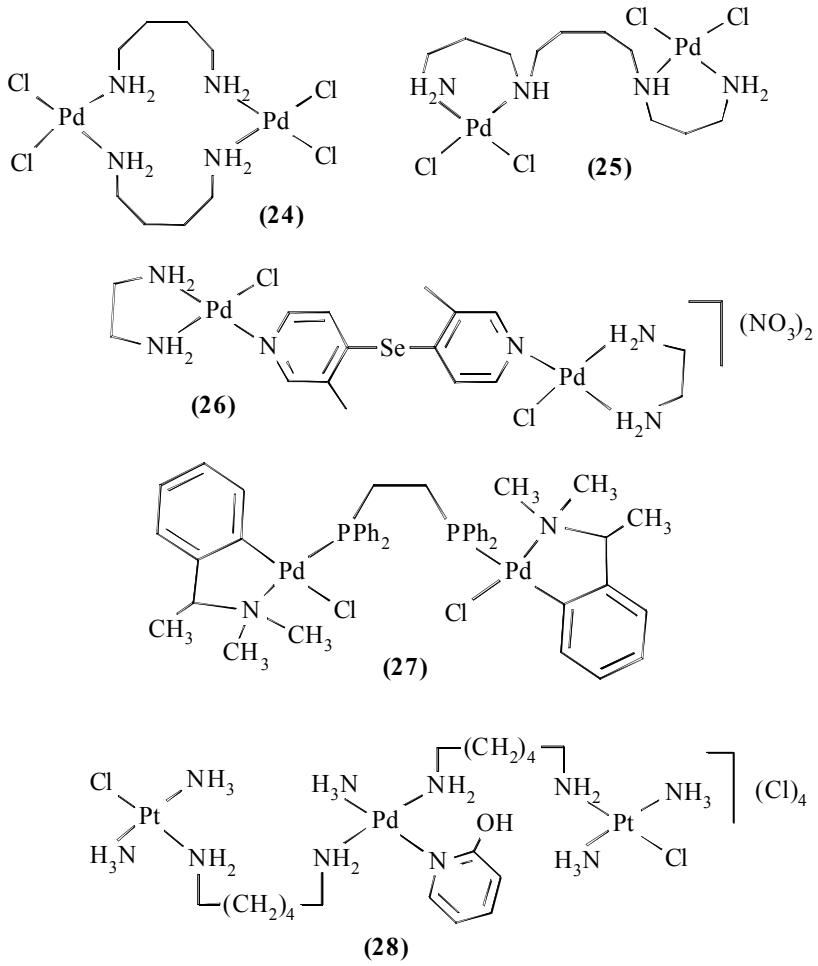
(21) **(22)** **(23)**

Figure 6. Palladium(II) complexes with mixed donor ligands (**21**-**23**).

E. Multinuclear Palladium(II) complexes

Navarro-Raninger and colleagues reported in 1993 that the synthesis of putrescine (**24, Figure 7**) and spermine (**25**)-based dinuclear palladium complexes. The complex (**24**) is a coordination complex of a dimer nature. In **25**, 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 (Navarro-Ranninger et al, 1993).

Zhao and colleagues studied dinuclear palladium complexes containing two functional [Pd(en)(pyridine)-Cl]$^{+}$ units bridged by Se or S (Zhao et al, 1999). The complexes are water soluble. The Se-bridged Pd(II) dimer (**26**) has a lower IC_{50} than the S analogue or cisplatin against the HCT8 cancer cells line.



(24) **(25)** **(26)** **(27)** **(28)**

Figure 7. Multinuclear palladium-based complexes (**24**-**28**).

Dinuclear cyclopalladated organometallic complexes containing biphosphine ligands were also reported by Rodrigues *et al*. (Rodrigues et al, 2003). The dimer Pd(II) complex $[Pd_2(S(-)C^2, N\text{-dmpa})_2(\mu\text{-dppe})Cl_2]$ (**27**) (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.

Eddings and colleagues reported the first 2-cyano-2-isonitroso-*N*-morpholinylacetamide (HMCO) based dimeric palladium (II) complex, $[Pd(MCO)]_2$. (Eddings et al, 2004) The complex was tested *in vitro* on antiproliferating activity using human cervical cancer HeLa cell lines, and cisplatin as a positive control substance. It is found to be active compound inflicting death on 28% of the cells, with 55% value for the cisplatin under the same conditions.

Giovagnini and colleagues have reported the synthesis and *in vitro* cytotoxic activity of new palladium(II) derivatives of methylsarcosinedithiocarbamate and its *S*-methyl ester (Giovagnini et al, 2005). The biological activity of these compounds, as determined by growth inhibition and apoptosis induction, has been investigated in both human leukemic promyelocites HL60 and human squamous cervical adenocarcinoma HeLa cell lines, and their activity has been compared to the well-known platinum-based anticancer agent cisplatin. On the basis of these experimental results, $[Pd(MSDT)X]_n$ (MSDT = methylsarcosinedithiocarbamate; X = Cl, Br) 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.

A trinuclear palladium complex has also been reported. The complex $[\{trans\text{-}PtCl(NH_3)\}_2\text{-}\mu\text{-}\{trans\text{-}Pd(NH_3)(2\text{-hydroxypyridine})\text{-}(H_2N(CH_2)_6NH_2)_2]^{4+}$. $4Cl^-$ (**28**, **Figure 7**) was found to exhibit significant anticancer activity against the cell lines A2780 $A2780^{cisR}$ and A2780 (Cheng et al, 2006).

The compound is believed to form a range of interstrand GG adducts with duplex DNA that induces global changes in the DNA conformation, unlike cisplatin and ZD0473 ([*cis*-(2-methylpyridine)(ammine)dichloro-platinum(II)]) that form mainly intrastrand adducts that induces a local kink in a DNA strand.

III. Conclusions

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 clinical trials.

Our review provides a perfect example of how small changes in molecular structure could lead to profound differences in biological activity. Several classes of potential antitumour palladium complexes have been 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.

Taking into consideration the similarities between platinum and palladium, the role of thiol compounds in drug resistance should thoroughly be studied. It has been shown that cellular thiols can sequester cisplatin, leading to a reduction in the levels of cisplatin–DNA damage.

Acknowledgment

Financial support by the Hashemite University is gratefully acknowledged.

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From left to right: Maher Abdalla, Adnan Abu-Surrah, Haitham Al-Sa'doni