ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

Human Journals
Review article
July 2020 Vol.:18, Issue:4

A Review Article on Anticancer Activity of Palladium Based Chemotherapeutic Agents

ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
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Submission: 23 June 2020
Accepted: 29 June 2020
Published: 30 July 2020

Keywords: Oxaliplatin, Cisplatin, Carboplatin

ABSTRACT

The research of Pharmacological, chemical, and clinical-research on anticancer coordinate complexes has yielded remarkable anticancer agents such as Oxaliplatin, Cisplatin, Carboplatin and Since the discovery of Cisplatin, the development of analog complexes have been an empirical task. The established SAR is also called structure-activity rules that have been broken active platinum complexes without NH groups, multinuclear complexes, trans-platinum complexes, cationic complexes and several classes of palladium(II) complexes have emerged. The foremost target was to find a convenient anticancer drug that can be used efficiently for the treatment of human tumors. This emphasis on the new strategies used in the development of new palladium antitumor agents.

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INTRODUCTION

Cancer nowadays is one of the most lethal diseases in human beings. Therefore, investigations for finding new anticancer compounds are imperative and interesting. Different types of metals are involved which shows the anti-cancerous activity such as Cisplatin, palladium, platinum, gold, silver,etc. trans-diaminedichloro platinum(I), [trans-$(NH_3)_2PtCl_2$], clinically called transplatin is one of the most successful anticancer compound (Rosenberg et al, 1969). After the discovery of its activity, hundreds of platinum complexes have been synthesized and evaluated for their anticancer activity. In the research area of platinum-based cancer chemotherapy, it showed that transplatin 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 do not always follow the original structure-activity relationships (SAR).

The new clinically useful metal-based anticancer agents must-have new structures unrelated to those agents assigned to platinum complexes. Therefore, several unconventional complexes that violate the structural activity relationship rules have been synthesized and evaluated (Abu-Surrah, 2007). The mechanism of action of non-classical complexes is different from that of cisplatin and its analog, their pattern of antitumor activity is also altered with respect to Cisplatin.

The significant similarity between the 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 explains why platinum is most useful comes from the ligand exchanger kinetics. The hydrolysis of palladium complexes is 10^5time's rapid than its analogs. They dissociate readily in solution leading to very reactive species that are unable to reach their pharmacological targets.

Compared to transplatin, the corresponding transpalladium, trans-[Pd $(NH_3)_2Cl_2$] and trans-[Pd(DACH)Cl_2] (DACH: (1R,2R)-(–)-1,2-diaminecyclohexane) do not show antitumor activity. It is well known that the former undergoes an inactive cis-conformation and 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 (i.e their pharmacological target) (Butour et al, 1997, Wimmer, et al, 1989, Zhao, et al, 1999). The higher activity of palladium

complexes considerably implicit that if an antitumor palladium drug is to be developed, it must be stabilized by a strongly coordinated nitrogen ligand and a suitable leaving group. If this group is reasonably non-labile, then the drug can maintain its structural integrity in vivo long enough.

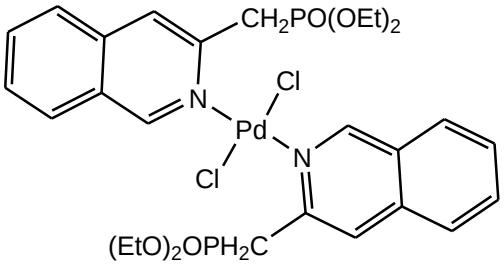
PALLADIUM ANTICANCER ACTIVITY

A greate many 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 based on the reactivity employed for the potential platinum antitumor drugs. Different types of bidentate ligands were applied in the synthesis of these complexes. Also, several research groups have focused on the preparation of Pd (I) complexes bearing tridentate ligands as a way to stabilize these compounds and to prevent the formation of any trans-trans isomerism (Mansuri et al, 1992).

A) Trans- palladium(II) complexes

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

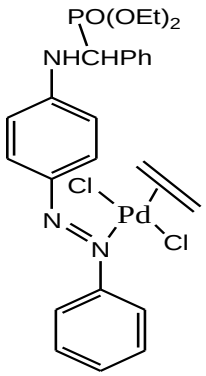
A comparative study on antitumor activity was carried out between the Pd(I) dihalide complexes of monoethyl-2-quinolmethylphosphonate (2-Hmqmp) and diethyl-2-quinolmethylphosphonate (2-dqmp) (Tusek-Bozic et al, 1991). The monoester ligand has two potential donors, the O from quinoline and the N from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



(1)

Figure No. 1:

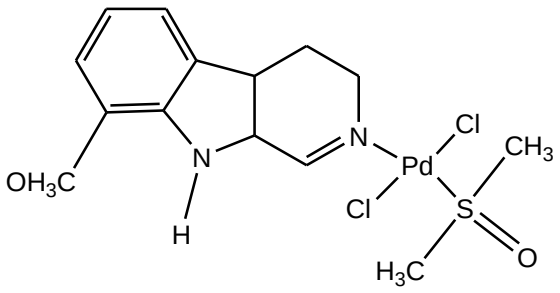
The complexes of the monoiester 2-dqmp were found to be more active than those of the monoester-based ligand (2-Hmqmp). This may be partly described by the greater leaving activity of the halogen ligands in the complex bearing 2-dqmp ligand and to their greater, A comparative study on antitumor activity was carried out between the Pd (I) dihalide complexes of monoethyl-2-quinolmethylphosphonate (2-Hmqmp) and diethyl-2-quinolmethylphosphonate (2-dqmp) (Tusek-Bozic et al, 1991). The monoester ligand has two potential donors, the O from quinoline and the N from phosphoryl giving the complex [trans-(2-dqmp) $_2$ $PdCl_2$] solubility or lipophilicity.Palladium(I) complexes with alkyl phosphonates ligands derived from aniline and quinoline were reported. Most of the aniline compounds (e.g. **2**) showed cytotoxicity *in vitro* against animal and human tumor cell lines (Curic et al, 1996).



(2)

Figure No. 2:

Complexes with naturally occurring compounds have been utilized. The palladium complex which contains the bulky nitrogen ligandharmine exhibits a large cytotoxic activity against K562, L1210, and P388 cell lines than cisplatin (Al-Allaf et al, 1998).



(3)

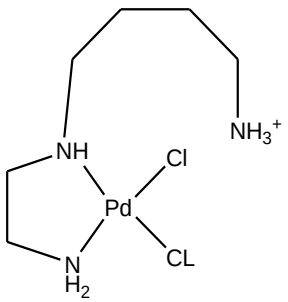
Figure No. 3:

we reported about the synthesis and molecular structure of a new enantiomerically pure, chiral trans-palladium(I) complex, cis-[Pd that bears the bulky amine ligand. The complex exhibit similar antitumor activity when compared with the activity of the standard references Cisplatin, Carboplatin, and Oxaliplatin (Abu-Surrah et al, 2002).

Palladium(I) complexes of the form: cis-$PdCl_2L_2$, have been investigated for antitumor activity against ovarian cancer cell lines: 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.

B. Palladium (II) complexes containing bidentate nitrogen ligands

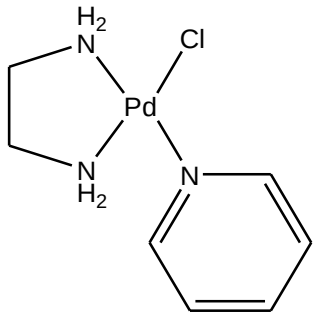
Navarro-Ranninger and colleagues reported the synthesis of square planar dichloro palladium (I) complexes with spermidine and spermine ligands (Navarro-Ranninger et al, 1993). These types of chelating ligands have been used because of their important biological activity, they involved in the proliferation and differentiation of cells in DNA replication and membrane stabilization.



(4)

Figure No. 4:

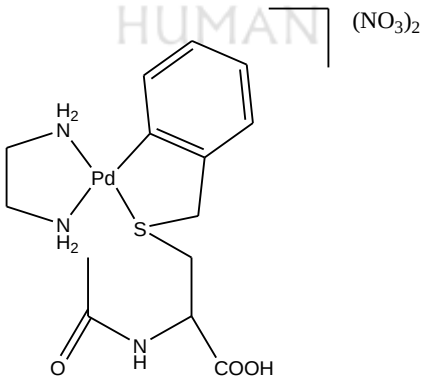
Ethylendiamine-based palladium(II) complexes with pyridine (**Figure 5**) or its derivatives were also reported (Zhao et al, 1999). The increase of the electron donor properties of the substituents led to an increase in the donor strength of the co-ordinated pyridine, which directly led to the increase in the cytotoxic activity of the palladium complexes.



(5)

Figure No. 5:

A new approach to increase the stability of the palladium(I) complexes by forming two chelate rings around the central atom. L-cysteine derived ligands such as py-CH_2-accys (**Figure 6**) (accys: N-acetyl-S-methylene-2-(2-pyridine)-L-cysteine) (Rau et al, 1998).

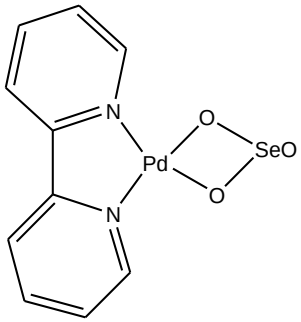


(6)

Figure No. 6:

The S,N-chelating mode of these ligands is important 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 competes with some platinum (I) complexes.

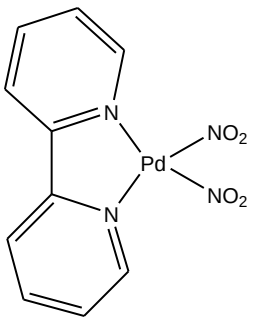
Palladium compounds bearing two chelating N-N and O-O ligands were prepared (Mansuri-Torshizi et al, 1991). The N-N ligand did not influence the activity but the oxygen coordinated leaving group is involved influencing the activity. Selenite complexes were invariably better cytotoxic agents than tellurite complexes and cisplatin. The complex [bipy)Pd(SeO_3) (**7**) was found to bind to DNA through a coordinate covalent bond.



(7)

Figure No. 7:

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)$_2$] (**8**), [(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)] (**9**) was active, giving a high activity for sarcoma 180 but a low one against P388 leukemia.



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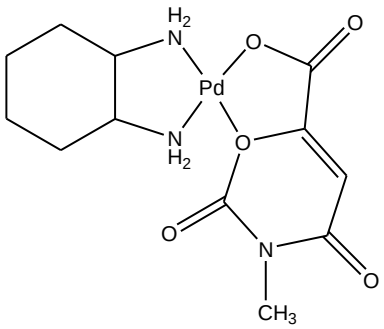

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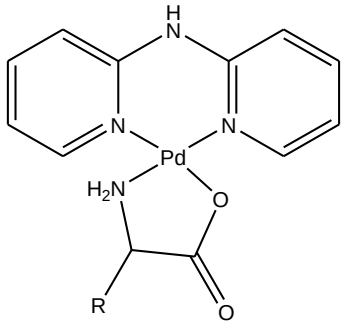
Figure No. 8: **Figure No. 9:**

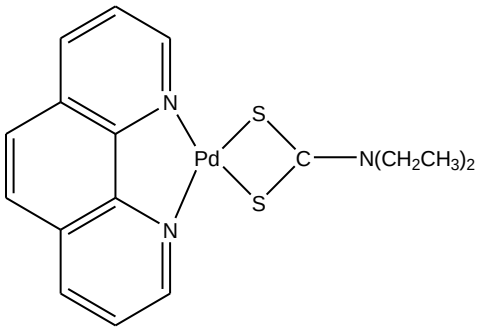
The alanine based complex (**Figure 10**) showed better cytotoxicity against P388 lymphocytic leukemia cells than the glycine based one.



(10)

Figure No. 10:

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)](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 (**Figure 11**). 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.

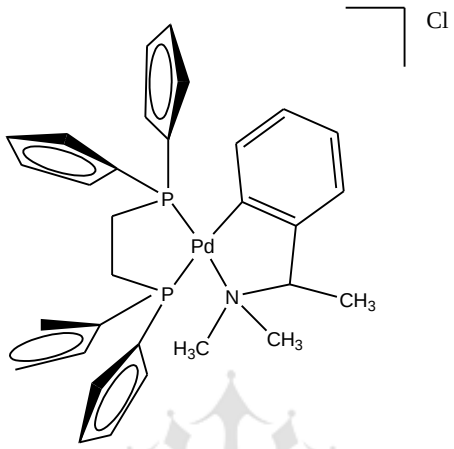


(11)

Figure No. 11:

C. Palladium(II) complexes bearing phosphine ligands

Some palladium(II) complexes showed a discrete antitumor activity in vitro compared to platinum-based drugs because of their extremely high liability in biological fluids (Navarro-Ranninger et al, 1993). 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). The ionic complex (**19**) caused 100% tumor cell death at a very low concentration (< 1.25 μM).



(12)

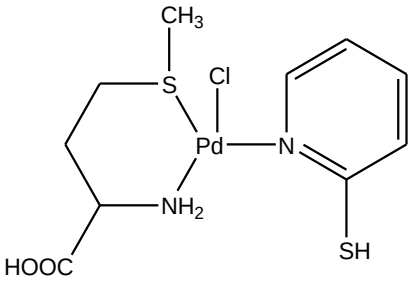
Figure No. 12:

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 $[(methionine)Pd(2\text{-}merpy)Cl]^{+}.\ Cl^{-}$ (**Figure 13**) has in vitro IC_{50} value lower than 10 μg/ml, so it could act as a potential antitumor agent.



(13)

Figure No. 13:

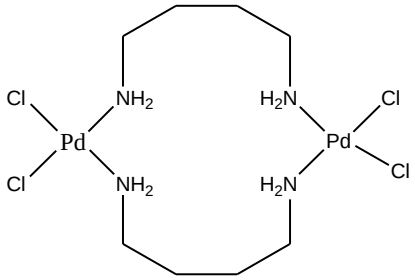
Heterocyclic thiosemicarbazones are of considerable interest due to their potential beneficial antineoplastic activity. It is assumed that the presence of some metallic ions may enhance their antitumor activity due to their ability to form chelates. The phenyl acetaldehyde thiosemicarbazone-based palladium complex has been found to display an enhanced in vitro activity compared to its platinum analog (Quiroga et al, 1998). Also, this complex is active in cisplatin-resistant cell lines.

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 the mechanism of action showed that the metal complex can only stabilize the single-strand nicked DNA, but not double-strand breakage intermediates.

E. Multinuclear Palladium (II) complexes

Navarro-Raninger and colleagues reported in 1993 that the synthesis of putrescine (**Figure 14**) and spermine based dinuclear palladium complexes. The complex (**14**) is a coordination complex of a dimer nature. 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).



(14)

Fig.No.14

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

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 antiproliferative activity using human cervical cancer HeLa cell lines, and cisplatin as a positive control substance. It is found to be an active compound inflicting death on 28% of the cells, with 55% value for the cisplatin under the same conditions.

A trinuclear palladium complex has also been reported. The complex $[\{trans\text{-}PtCl(NH_3)\}_2\text{-}\mu\text{-}\{trans\text{-}Pd(NH_3)(2\text{-}hydroxy\ pyridine)\text{-}(H_2N(CH_2)_6NH_2)_2]^{4+}$. $4Cl^{-}$ 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 induce a local kink in a DNA strand**.**

MECHANISM OF ACTION

DNA Is Target.

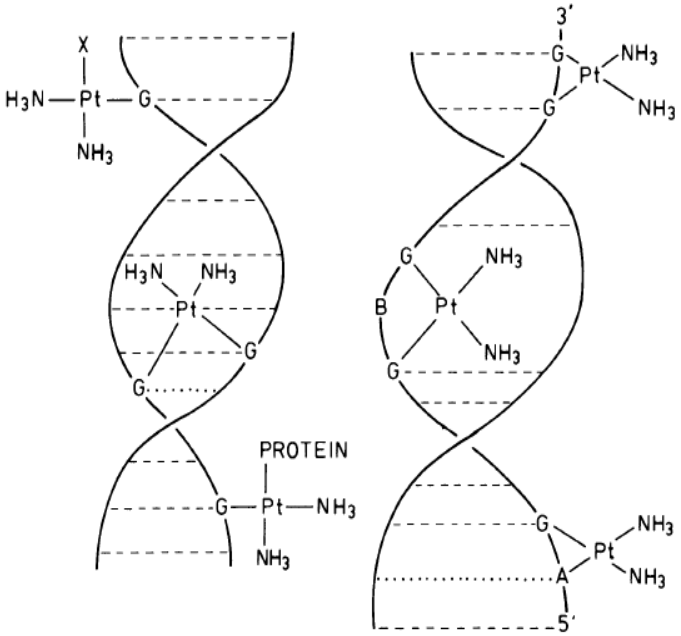


Figure No. 155:

The activity of palladium is closely related to its binding to DNA. Highly conclusive evidence for the target was that cells deficient in DNA repair are hypersensitive to palladium, suggesting that palladium and other drugs bind DNA. The four bases of the DNA i.e. N7 site of guanine is strongly preferred for the binding. Many other DNA crosslinking anti-cancer compounds are known that are cyclophosphamide, nitrosoureas, epoxides, and anthracyclines. A drug that bound to DNA may interfere with the transcription and/or DNA replication mechanisms, which may trigger processes like apoptosis that lead to cell death.

Cellular Uptake of Palladium

The physiological chloride concentration in blood and extracellular body fluids is 100 mM, which is high enough to suppress palladium hydrolysis so that it can reach the outer surface of cells as a neutral molecule. Early studies have shown that 50% of the palladium leaves the body through the kidneys within 48 h and that the remaining 50% spends up to 2 months in the body. However, the precise mechanism of cellular uptake of palladium has remained unclear, although evidence has been published showing that the presence of phosphatidylserine in membranes plays an important role in uptake. Although passive

diffusion is the principal mechanism, some evidence supports the involvement of active transport mechanisms. Very recently strong evidence has been reported showing that a copper transport agent is mediating palladium uptake.

Inside cells, the chloride concentration is much lower (4 mM) and resulted hydrolysis of palladium occurs, albeit slowly. The most important hydrolysis product is the $[PtCl(H_2O)(NH_3)_2]^+$ cation, which has a pKa value of 6.5. Above pH 6 it starts to ionize to form [PtCl(OH)- $(NH_3)_2$], and the cationic species is known to be much more reactive than palladium, so the mono aqua species is most likely to react with DNA and other molecules in the cell. Transport through the nuclear membrane is also poorly understood, and whether or not special nuclear localizing signal peptides play a role remains uncertain.

SUMMARY

With the aid of inorganic chemistry, it is possible to design newer therapeutic and diagnostic agents. Electronic, reactivity, solubility, and steric properties, and the geometry of metal complexes can be controlled by simply modifying the ligand around the metal center. It is visible from the data presented in this review that both the metal and the ligand determine the biological activity. Platinum (I) 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.

Several categories of potential antitumor palladium complexes have emerged. The 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 might be that of good solubility in water and the ability to transport (through the membranes), courage in the cell, binding to the DNA, and in the end excretion from the body with minimum side effects. Taking into consideration the similarities between palladium and platinum, 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.

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