Coordination Chemistry Reviews 253 (2009) 1384–1397

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Palladium coordination compounds as anti-viral, anti-fungal, anti-microbial and anti-tumor agents

A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis*

Section of Inorganic and Analytical Chemistry, Department of Chemistry, University of Ioannina, University Campus, 45110 Ioannina, Greece

Contents

ARTICLE INFO

Article history:
Received 27 May 2008
Accepted 15 September 2008
Available online 25 September 2008

Keywords:
Metallotherapeutics
Pd(II) complexes
Anti-tumor, -microbial, -viral and -fungal activities

ABSTRACT

Pd(II) complexes of various donor atom ligands posses anti-tumor and anti-viral, -malarial, -fungal and -microbial activities. This review focuses on such properties of Pd(II) complexes and makes comparisons with similar properties of other metals. In the first part, the anti-viral, anti-fungal and anti-microbial activities of new Pd(II) complexes are described, classified according to the ligands used, namely; sulfur donors, ligands used as drugs, Schiff bases ligands and miscellaneous. The second part describes the anti-tumor properties of new Pd(II) complexes, similarly classified with sulfur and nitrogen and other donor ligands. The results are summarized in 1st and 2nd tables in this article which also contain all Pd(II) complexes described in Ref. [A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis, in: M. Gielen, E.R.T. Tiekink (Eds.), Metals in Medicine, Palladium (Pd), in Metallotherapeutic Drugs and Metal-based Diagnostic Agents: The Use of Metals in Medicine, John Wiley & Sons, Ltd., 2005, p. 399 (Chapter 21)] for comparison and clearly demonstrate the anti-tumor, anti-fungal, -viral, -microbial properties of several of them, as compared to those of other metals and especially to those of cisplatin. These promising results are encouraging further research in this field, for future applications.

1. Introduction

Following the discovery of the anti-tumor properties of cisplatin (*cis*-Pt(NH_3)Cl_2) and related complexes, interest for the discovery of other more efficient complexes of other metals and ligands grew. Among the first to be used for clinical trials against tumors, were the analogues to cisplatin, complexes of Pd(II), *cis*-Pd(en)Cl_2 and

* Corresponding author.
E-mail address: nhadjis@uoi.gr (N. Hadjiliadis).

0010-8545/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ccr.2008.09.011

cis-Pd(DACH)$_2$Cl$_2$ because Pd(II) has a very similar chemistry to Pt(II) forming square planar complexes and more rarely trigonal bipyramidal. Both Pd(II) and Pt(II) are soft Lewis acids and form stronger bonds with nitrogen or sulfur donors (soft bases) than oxygen donors (hard bases). In general, however Pt(II) complexes are thermodynamically and kinetically more stable than those of Pd(II). Pd(II) complexes undergo aquation and ligand exchange reactions 10^5 times faster than the corresponding Pt(II) complexes. This last property explained the lower anti-tumor activity of *cis*-Pd(en)Cl$_2$ and *cis*-Pd(DACH)$_2$Cl$_2$ when compared to the analogous Pt(II) complexes, as well as their high toxicity [1].

In general the use of Pd(II) and its complexes in medicine is limited. The only application is of ^{103}Pd as a radioactive isotope in the treatment of rapidly growing high-grade prostate cancer [2,3]. However, Pd(II) N, S chelates with inert ligands (e.g. sulfur or nitrogen) were suggested by Das and Livingstone [4] to be more effective anti-tumor agents than those of other metals, they possess the proper lability to bring the metal to the target (DNA) and allow it to interact with it. In this respect, Pt(II) chelates are very inert kinetically, while those of other metals like Ni(II), Zn(II), Cu(II), etc. do not have sufficient thermodynamic stability.

The N, S donor ligands used to prepare anti-tumor and anti-microbial Pd(II) complexes were mostly thiosemicarbazones and dithiocarbazates. These ligands possess anti-viral, -malarial, -fungal, -microbial and -tumor activity and their mechanism of action, most probably involves the inhibition of ribonucleotide reductase, converting ribonucleotides to deoxyribonucleotides [5,6].

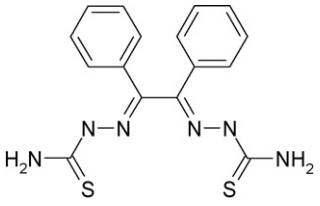
Recently we reviewed [7] the anti-tumor and anti-microbial Pd(II) complexes of these and other similar ligands. The present paper updates these results. The results summarize both the anti-viral, -fungal, -microbial and anti-tumor properties of the previously reported complexes and the updated ones for comparison, in Tables 1 and 2 showing that the use of Pd(II) complexes in medicine may always be promising and encourages further studies in the field. Note that abbreviations used in the text are explained in Table 1 or shown in Schemes.

2. Anti-viral, anti-fungal and anti-microbial activity of Pd(II) complexes

2.1. Sulfur donor ligands

2.1.1. Thiosemicarbazones

Pd(II) complexes with benzyl bis(thiosemicarbazone) (Scheme 1) and 3,5-diacyl-1,2,4-triazole bis(4-methylthiosemicarbazone) were screened against the replication of wild-type herpes simplex virus (HSV-1) and (HSV-2) strains. The data were compared to those under the acyclovir action. The testing of cytotoxic activity suggests that these compounds may be endowed with important anti-viral properties. The complex Pd(BzTSC) (BzTSC is benzyl bis(thiosemicarbazone), with an N_2S_2 coordination sphere, exhibits significant activity against acyclovir-resistant viruses R-100 (HSV-1) and PU (HSV-2) with an *in vitro* selectivity index (SI) of 8.0 vs. 0.01 for acyclovir [8].



Scheme 1. Benzyl bis(thiosemicarbazone), (BzTSC).

A large number (34) of thiosemicarbazones and *S*-alkyl thiosemicarbazones, and some of their Zn(II) and Pd(II) complexes, were investigated for their anti-microbial activity. MIC values of the compounds were determined by the disc diffusion method against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Shigella flexneri*, *Staphylococcus aureus*, *S. epidermidis*, and *Candida albicans*. Both the free ligand thiosemicarbazones and their metal complexes show antibacterial and anti-fungal activities. The ligands picolinaldehyde-*S*-methyl- and -*S*-benzylthiosemicarbazones did not affect the tested microorganisms but their Zn(II) complexes showed selective activity [9].

Pd(II) and Pt(II) complexes with pyridine-2-carbaldehyde thiosemicarbazone (HFoTsc) show anti-viral and cytotoxic activity against HSV (*Human Simplex Virus*) replication. The experiments were performed on continuous M.D.B.K. cells with four HSV-1 and HSV-2 strains (two sensitive to acyclovir and two resistant mutants). The five complexes of formulae [Pt(FoTsc)Cl], [Pt(FoTsc)(H$_2$FoTsc)]Cl$_2$, [Pt(FoTsc)$_2$], [Pd(FoTsc)$_2$] and [Pd(FoTsc)(H$_2$FoTsc)]Cl$_2$, were effective inhibitors of HSV replication. The most active compound was the complex [Pt(FoTsc)(H$_2$FoTsc)]Cl$_2$. which could be useful in the treatment of HSV infections, especially that resistant to acyclovir [10].

A new series of metal complexes with indole-3-carboxaldehyde thiosemicarbazones (TSC), a ligand prepared by condensing indole-3-carboxaldehyde with cycloalkylaminothiocarbonyl hydrazines, were synthesized. In the Pd(II) complexes thiosemicarbazones act as bidentate ligands, with the thione sulfur and azomethine nitrogen atoms coordinated to the metal center. Among all the compounds evaluated for antiamoebic activity using HM1:IMSS strain of *Entamoeba histolytica*, the Pd(II) complexes were more active than their respective ligands [11].

2.1.2. Thiocarbazates-thioamides

Some new Pt(IV) and Pd(II) thiodiamine complexes of type [Pt(L)$_2$Cl$_2$] and [Pd(L)Cl$_2$], where, L = (cyclohexyl-*N*-thio)-1,2-ethylenediamine or (cyclohexyl-*N*-thio)-1,3-propanediamine [12], L = 1,1-diphenyl-2-thiosemicarbazide or (1,1-diphenyl-2-thio)-1,3-propanediamine [13] and 1,1-diphenyl-2-thiosemicarbazide or (1,1-diphenyl-2-thio)-1,3-propanediamine [14], have been have shown *in vitro* moderate anti-fungal and antibacterial activity.

The ligand 1,6-bis(benzimidazol-2-yl)-3,4-dithiahexane (L) and its binuclear complex Pd(II) chloride complex [(μ_2-(L)PdCl]$_2$·C$_2$H$_5$OH with distorted square-planar arrangement around each Pd, were synthesized. The anti-microbial and anti-fungal activities of the free ligand, its hydrochloride salt and its Pd(II)complex were evaluated using the disk diffusion method in dimethyl sulfoxide (DMSO) as well as the minimal inhibitory concentration (MIC) the dilution method, against 10 bacteria and five yeast cultures. In most cases, the compounds showed broad-spectrum (Gram (+) and Gram (−)) activities that were comparatively more active, or as potent pharmaceutical agents [15].

Six Pd(II) dithiocarbamate complexes of general formulae Pd(AmDTC)$_2$, where HAmDTC is piperidinedithiocarbamate (1), 4-methylpiperidinedithiocarbamate (2), *N*-methylbenzyldithiocarbamate (3), dibenzyldithiocarbamate (4), dicyclohexyldithiocarbamate (5) and *N*-cyclohexyl-*N*-methyldithiocarbamate (6), were screened for cytotoxic and antibacterial activities and showed significant antibacterial activity and no substantial *in vitro* cytotoxicity [16]. The X-ray structures of compounds 3 and 4, showed that the ligands are chelated by both sulfur atoms in a distorted square planar geometry around Pd(II).

Table 1
Anti-viral, anti-fungal and anti-microbial activity of Pd(II) complexes.

Complex	Bio-activity	Virus, fungi or bacterial tested	Reference
[Pd(5-N-2-TCA-*o*-TolTSCN)Cl_2], [Pd(5-N-2-TCA-*m*-TolTSCN)Cl_2], [Pd(5-N-2-TCA-*p*-TolTSCN)Cl_2], [Pd(5-N-2-TCA-NMBuTSCN)Cl_2], [Pd(5-N-2-TCA-NMBzTSCN)Cl_2], [Pd(5-N-2-TCA-COTSCN)Cl_2], [Pd(5-N-2-TCA-AdmTSCN)Cl_2], L = 5-nitrothiophene-2-carboxaldehyde-R-thiosemicarbazone. R = *o*-toludine, (5-N-2-TCA-*o*-TolTSCN), R = *m*-toludine, (5-N-2-TCA-*m*-TolTSCN), R = *p*-toludine, (5-N-2-TCA-*p*-TolTSCN), R = *n*-methylbutyl, (5-N-2-TCA-NMBuTSCN), R = *n*-methylbenzyl, (5-N-2-TCA-NMBzTSCN), R = cyclooctyl, (5-N-2-TCA-COTSCN), R = admadamine, (5-N-2-TCA-AdmTSCN)	IC_{50} = 1.95, 2.05 μM IC_{50} = 1.99, 4.06 μM IC_{50} = 1.70, 0.81 μM IC_{50} = 0.73 μM	HK-9 strain of *Entamoeba histolytica*	[29]
[Pd(2-TCA-PYRTSC)Cl_2], [Pd(2-TCA-1,2,3,4-THQTSC)Cl_2], [Pd(2-TCA-2-CBTSC)Cl_2], [Pd(2-TCA-2,4-DFATSC)Cl_2], [Pd(2-TCA-2,6-DFATSC)Cl_2], [Pd(DMSO)$_2Cl_2$], Thiophene-2-carboxaldehyde-pyrrolidine thiosemicarbazone, (2-TCA-PYRTSC); Thiophene-2-carboxaldehyde-1,2,3,4-tetrahydroquinoline thiosemicarbazone, (2-TCA-1,2,3,4 THQTSC); Thiophene-2-carboxaldehyde-R-thiosemicarbazone, R = 2-chlorobenzyl, (2-TCA-CBTSC), R = 2,4-difluoroaniline, (2-TCA-2,4 DFATSC), R = 2,6-difluoroaniline, (2-TCA-2,6 DFATSC)	IC_{50} = 1.65, 1.15 μM IC_{50} = 3.06, 2.65 μM IC_{50} = 2.41, 8.24 μM	(HM-1:1 MSS) strain of *Entamoeba histolytica*	[30]
[Pd(AcTsc)Cl], [Pd(HAcTsc)$_2$]Cl_2 [Pd(AcTsc)], 2-acetylpyridine thiosemicarbazone, (HAcTSC)	IC_{50} = <1 μg/ml	(Gram+) *Staphylococcus aureus*	[31]
[Pd(Ac4Et)], **1**, [Pd(HAc4Et)$_2$]C_2, **2**, [Pd(Ac4Et)$_2$], **3**, [Pd(Fo4PipePiz)Cl], **7**, [Pd(Fo4PipePiz)$_2$], **8**, [Pd(Ac4PipePiz)Cl], **9** and [Pd(Ac4PipePiz)$_2$], **10**, 2-acetylpyridine thiosemicarbazone, (HAcTSC), 2-acetylpyridine-4-ethyl thiosemicarbazone, (HAc4EtTSC), 2-acetylpyridine-4-pyperazinyl thiosemicarbazone, (HAc4PiPizTSC, 2-formyl-4-pyperazinyl thiosemicarbazone, (HFo4PiPizTSC), 4-formyl thiosemicarbazone, (HFo4TSC)	IC_{50} = **1** >100, >100, 6–12, >100 μg/ml IC_{50} = **2** >100, 25–50, 6–12, >100 μg/ml IC_{50} = **3** >100, 50–100, 6–12, >100 μg/ml IC_{50} = **7** >100, 50–100, 6–12, 50–100 μg/ml IC_{50} = **8** >100, >100, >100, 50–100 μg/ml IC_{50} = **9** >100, >100, 50–100, >100 μg/ml IC_{50} = **10** >100, 50–100, 25–50, >100 μg/ml	Gram(+) (*Escherichia coli*, *Bacillus subtilis*), Gram(−) (*Bacillus cereus*, *Staphylococcus aureus*)	[32]
3-Deoxy-D-erythro-hexos-2-ulose bis(thiosemicarbazone) palladium chelate	IC_{50} = 14.4 μg/ml	Poliovirus type 1 on monkey kidney vero cells	[33]
[Pd(HFo4TSC)$_2$]Cl_2, [Pd(Fo4TSC)$_2$], [Pd(Fo4TSC)Cl], 4-formyl thiosemicarbazone, (HFo4TSC)	(MNC) of 1–10 μM	Herpes simplex virus 1 (HSV-1)	[34]
Benzyl bis(thiosemicarbazonate)palladium(II), 1,2,4-triazole bis(4-methylthiosemicarbazonate) palladium(II)	IC_{50} = 0.3, 3, 0.01, 0.01 μM IC_{50} = 0.4, 0.04, 1, 0.1 μM	Herpes simplex virus (HSV-1) and (HSV-2) strains Victoria, BJA, R-100, PU	[8]
[Pd(FoTsc)Cl], [Pd(FoTsc)(H2FoTsc)]Cl2, [Pd(FoTsc)$_2$], pyridine-2-carbaldehyde thiosemicarbazone (HFoTsc)	IC_{50} = NA, ND, ND, ND, μM IC_{50} = 10, 0.01, 0.1, 0.1 μM IC_{50} = 0.06, 1, 1, 1 μM NA: not active and ND: not done	*wt* strains Victoria (HSV-1) and BJA (HSV-2) and ACVR mutants with different *tk* genemutations R-100 (TKA, HSV-1) and PU (TKN, HSV-2)	[10]
[Pd(3-ICA-CPTSC)$_2Cl_2$] (1a), [Pd(3-ICA-COTSC)$_2Cl_2$] (2a), [Pd(3-ICA-4-MPTSC)$_2Cl_2$] (3a), [Pd(3-ICA-PYRTSC)$_2Cl_2$] (4a), [Pd(3-ICA-ADMTSC)$_2Cl_2$] (5a), [Pd(3-ICA-NPPTSC)$_2Cl_2$] (6a), [Pd(3-ICA-4-THQTSC)$_2Cl_2$] (7a), indole-3-carboxaldehyde thiosemicarbazones	IC_{50} = 0.98 μM IC_{50} = 0.62 μM IC_{50} = 1.18 μM IC_{50} = 2.32 μM IC_{50} = 0.47 μM IC_{50} = 1.85 μM IC_{50} = 0.78 μM	HM1:IMSS strain of *Entamoeba histolytica*	[11]
[$PdCl_2$(aadt)], [$PdCl_2$(mntdt)], [$PdCl_2$(bntdt)], *S*-Acetyl-N^{β}-acetyldithiocarbazate (aadt), *S*-methyl-N^{β}-[5-mitrothiophene-2-yl]methylodithiocarbazate, (mmdt) and *S*-benzyl-N^{β}-[5-nitrothophene-2-yl]methylenedithiocarbazate, (bntdt)	IC_{50} = 0.53 μg/ml IC_{50} = 0.32 μg/ml IC_{50} = 0.28 μg/ml	HK-9 strain of *Entamoeba histolytica*	[35]
[Pd(L^2H)$_2$]Cl_2	58 82 71	*R. bataticola*, *Fusarium oxysporum*, *Alternaria alternata*	[36]
[Pd(L^2)$_2$]	59 81 70 Inhibition after 96 h (%) (conc. in p.p.m.)		
[Pd(L^2H)$_2$]Cl_2	7 9 8		
[Pd(L^2)$_2$]	8 10 7		
L = *o*-FC_6H_4C(H)NNC(SH)SCH_2Ph or *o*-FC_6H_4C(Me)NNC(SH)SCH_2Ph	Diameter of inhibition zone (mm) (conc. in p.p.m.)	*E. coli*, *Staphylococcus aureus*, *X. compestris*	
[Pd(RN-XH)$_2$]Cl_2	76–85, 72–76, 90–92	*F. oxysporum*, *S. rolfsi*, *A. alternata*	[37]
[Pd(RN-X)$_2$] benzylidenehydrazinecarboxamide and -carbothiamide	77–86, 73–78, 89–94 Inhibition after 96 h (%) (conc. in p.p.m.)		

Table 1 (*Continued*)

Complex	Bio-activity	Virus, fungi or bacterial tested	Reference
$PdCl(H_2CU)\cdot Py$, H_2Cu is 5-carboxyuracil (isoorotic acid)	<50, 2000, 2000, 2000, <50, 2000, 2000, 1000 (MIC $\mu g\,cm^{-3}$)	a 1, *Pseudomonas* sp.; 2, *E. coli*; 3, *Proteus* sp.; 4, *Salmonella* sp.; 5, *Micrococcus* sp.; 6, *Staphylococcus* sp.; 7, *Bacillus* sp.; 8, *Candida* sp.	[38]
$[Pd(meth)]Cl_2$	1.2, NR, 2.0, 1.8, NR, 2.5, 1.2, 2.0	*V. Parahaemoly ticus*, *Pseudomonas aeruginosa*, *P. vulgaris*, *E. coli*, *Shigella flexneri*, *Salmonella typhi*, *Klebsiella pneumoniae*, *V. cholerae*	[39]
$[Pd(meth)(2merpy)Cl]Cl$	1.9, 3.5, 1.8, 3.6, 3.0, 1.6, 2.1, 3.5		
$[Pd(meth)(2ampy)Cl]Cl$	1.7, 1.5, 2.2, 1.9, 2.3, 1.8, 1.3, 2.9		
$[Pd(ethio)Cl_2]$	2.1, NR, 1.4, 0.9, 1.0, 0.9, 1.1, 1.0		
$[Pd(ethio)(cyt)Cl]\cdot H_2O$	2.0, 0.8, 0.9, 1.4, 0.8, 1.4, 1.3, 1.0		
$[Pd(ethio)(guo)Cl]Cl\cdot H_2O$	1.2, 0.9, 1.5, 1.2, 1.0, 1.3, 1.5, 1.0		
Methionine (meth), 2-mercaptopyrimidine (2-Spym) and 2-aminopyrimidine (2-Spym)	NR = no reaction		
$Pd(L^2)Cl_2$	8, 60.0	*E. coli*, *E. coli*	[12]
L = (cyclohexyl-*N*-thio)-1,2-ethylenediamine or (cyclohexyl-*N*-thio)-1,3-propanediamine	Zone of inhibition (mm) MIC (mg/disc)		
$Pd(L^1)Cl_2$	500 500 1000	*A. fumigatus*, *Aspergillus flavus*, *Aspergillus niger*	[14]
$Pd(L^2)Cl_2$	250 250 500		
1,1-Diphenyl-2-thiosemicarbazide or (1,1-diphenyl-2-thio)-1,3-propanediamine	MIC (mg/ml)		
$[(\mu_2\text{-(L)PdCl}]_2\cdot C_2H_5OH$	14	*E. coli*	[15]
1,6-Bis(benzimidazol-2-yl)-3,4-dithiahexane (L)	16	*Staphylococcus aureus*	
	12	*K. pneumoniae*	
	12	*Pseudomonas aeruginosa*	
	16	*Proteus vulgarise*	
	12	*Bacillus cereus*	
	16	*Mycobacterium smegmatis*	
	12	*Listeria monocytogenes*	
	14	*Micrococcus luteus*	
	17	*Candida albicans*	
	18	*Kluyveromyces fragilis*	
	15	*Rhodotorula rubra*	
	16	*Han. guilliermondii*	
	Inhibition zone (mm)		
$Pd(AmDTC)_2$, where HAmDTC = aminedithiocarbamic acid, [Pd(II) piperidinedithiocarbamate (1), Pd(II) 4-methylpiperidinedithiocarbamate (2), Pd(II) *N*-methylbenzyldithiocarbamate (3), Pd(II) dibenzyldithiocarbamate (4), Pd(II) dicyclohexyldithiocarbamate (5), Pd(II) *N*-cyclohexyl-*N*-methyldithiocarbamate (6)]	28, 18, –, 21, 23 27, 12, –, 25, 18 22, 14, 10, 23, 27 20, 23, 15, 19, 14 18, 20, –, 29, 23 24, 20, 14, 20, 33 % Zone of inhibition of samples (mm)	*E. coli*, *B. subtilis*, *Shigella flexneri*, *Staphylococcus aureus*, *Salmonella typhi*, and *Pseudomonas aeruginosa*	[16]
trans-$[PdCl_2(mnz)_2]$ (1), *trans*-$[PtCl_2(mnz)_2]$ (2), metronidazole	IC_{50} = 0.10 μM IC_{50} = 0.20 μM	*Entamoeba histolytica* (HM1:1MSS)	[40]
cis-$[(pen)_2PdCl_2]$	>400 >400 240 >400	Vesicula stomatitis virus	[41]
cis-$[(nucl)_2Pd(pen)_2]Cl_2$	>400 >400 >400 >400	Coxsaekie virus B4	
Penciclovir (pen), nucl = guanosine, inosine, cytidine, or penciclovir	>400 >400 >400 >400 >400 240 240 >400 MIC (μg/ml)	Respiratory syncytial	
$[Pd(Tc)Cl_2]\cdot 2H_2O$	2.08 2.08 16.6 7.98	*E. coli* HB 101 and *E. coli* ATCC 25922 and in a resistant *E. coli* HB101/pBR322	[17]
$[Pd(Dox)Cl_2]\cdot 2H_2O$	4.16 2.08 33.3 16.01		
$[Pd(Chl)Cl_2]\cdot 2H_2O$, tetracycline family (tetracycline, doxycycline and chlortetracycline)	4.16 4.16 66.5 15.99 MIC (μM)		
$[Pd(L)Br_2]\cdot 2H_2O$, L = 1,10-phenanthroline-2,9-dicarboxaldehyde, 2,3-diamino-1,4-naphthoquinone and 1,2-dibromoethane	13.0 13.4 8.0 8.2 9.5 11.7 7.7 8.0 0 9.0 7.5 8.0 Zone of Inhibition (mm)	G(+) *Staphylococcus aureus* and *Bacillus cereus* and G(−) *Pseudomonas aeruginosa* and *E. coli*	[42]
$Pd_3(L_1')Cl_4$ (4)	45, 59	*Alternaria brasicae* and *Fusarium lycopersici*	[43]
$Pd_3(L_2')Cl_4$ (8)	50, 60		
Azole (thiazolo and triazolo)-2,4-pentanedione (L_1 and L_2)	Inhibition (%) with 250 μg/ml		
$[Pd(2\text{-Acpy-SMDT})Cl_2]$	0.19	*Entamoeba histolytica* (HK-9)	[44]
$[Pd(2\text{-Acpy-SBDT})Cl_2]$	0.16		
$[Pd(2\text{-Acpy-TSCD})Cl_2]$	0.33		
2-Acetylpyridine and *S*-methyldithiocarbazate (SMDT), *S*-benzyldithiocarbazate (SBDT) and thiosemicarbazide (TSCD)	IC_{50} (μg/ml)		
$C_{28}H_{20}N_2O_8Pd$	0, 3	*Aspergillus niger*, *Aspergillus flavus*	[18]
$C_{28}H_{18}N_2Br_2O_8Pd$	3, 5		
$2\text{-}HOC_6H_4C(H){=}NC_6H_3\text{-}2\text{-}(OH)\text{-}5\text{-}CO_2H$	Diameter of clear zone (mm)		
$5\text{-}Br\text{-}2\text{-}HOC_6H_3C(H){=}NC_6H_3\text{-}2\text{-}(OH)\text{-}5\text{-}CO_2H$			
$[Pd(asme)_2]$	6.5, –	B285 *B. subtilis* (mutant defective DNA repair); B295 *B. subtilis* (wild type)	[19]
$[Pd(asbz)_2]$	12, 11		[3]
asme = anionic form of the acetone Schiff base of *S*-methyldithiocarbazate	Inhibition zone (mm)		[8]

Table 1 (*Continued*)

Complex	Bio-activity	Virus, fungi or bacterial tested	Reference
asme = anionic form of the acetone Schiff base of *S*-benzyldithiocarbazate			
$[Pd(L^1H)_2]C_{l2}$	48, 47	*F. oxysporum*, *Macrophomina phaseolina*	[20]
$[Pd(L^1)_2]$	47, 45		
$[Pd(L^2H)_2]C_{l2}$	42, 41		
$[Pd(L^2)_2]$	41, 40		
L^1H = 5-chloro-1,3-dihydro-3-[2-(phenyl)-ethylidene]-2*H*-indol-2-one-hydrazinecarbothioamide	Percent inhibition after 96 h (conc. in 50 ppm)		
L^2H = 5-chloro-1,3-dihydro-3-[2-(phenyl)-ethylidene]-2*H*-indol-2-one-hydrazinecarboxamide			
$C_{21}H_{17}ClN_3O_2PPd$ 2-(diphenylphosphino)benzaldehyde	0.7, 0.77, 0.77, 0.77 minimal inhibitory concentration (mM)	*Staphylococcus aureus*, *E. coli*, *S. enteritidis*, *Candida albicans*	[21]
PdL_2 L = Schiff bases of sulfanilamides or aminobenzothiazoles	0–3 clear zone/mm in dose of 100 μg/disk	*Aspergillus niger*, *Aspergillus flavus*	[22]
PdL_2 L = boron-containing *trans*-bis(*N*-arylsalicylaldiminato)	3–6, 0–6 clear zone/mm at dose of 200 (μg/disk)	*Aspergillus niger*, *Aspergillus flavus*	[23]
$PdCl_2$(N–N′A) (N–N′A = pyridinecarboxaldimines derived from pyridin-2-ylcarboxaldehydes and unsaturated amines)	0–45, 0–50, 0–40, 0–74 percent activity: at dose of 200 (μg/disk)	*Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, *S. cerevisiae*	[24]
$[Pd(C_6H_8N_2)_2]Cl_2$	25, 27	*A. alternata*, *F. oxysporum*	[45]
$[Pd(C_6H_6N_2)_2Sn_2(Ph)_4]Cl_2$	38, 41		
$[Pd(C_6H_6N_2)_2Sn_2(Me)_4]Cl_2$	45, 49		
$[Pd(C_6H_6N_2)_2Si_2(Ph)_4]Cl_2$	50, 55		
$[Pd(C_6H_6N_2)_2Ti_2(Cp)_4]Cl_2$	28, 31		
$[Pd(C_6H_6N_2)_2Zr_2(Cp)_4]Cl_2$	32, 38		
	Average inhibition after 96 h (%)		
PdL, H_2L' = *N*,*N*0-bis[2-hydroxy-3-methoxy-*N*-(pyridyl) benzylamine]-2,6-di acetylidenepyridine and H_2L'' = *N*,*N*0-bis[2-hydroxy-3-methoxy-*N*-(pyridyl)benzylamine]-1,2-phthaldialdimine	Both Pd(II) complexes are inactive in towards the bacterial tested	*B. megaterium*, *B. subtilis*, *E. aerogene*	[46]
$Pd(L)Cl_2$, L = 1,3-bis(2-benzimidazyl)-2-thiapropane	8,8, 8, 8, 8, 8, 16, >256, >256, >256 MIC (μg/ml)	*Staphylococcus aureus*, *E. coli*, *E. aerogenes*, *K. pneumoniae*, *A. faecalis*, *C. freundii*, *S. pyogenes*, *P. vulgaris*, *P. mirabilis*, *E. faecalis*	[25]
$Pd[L]Cl_2$, L1 = 7-bromo-1,3-dihydro-3-hydroxymethyl-1-methyl-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one (±), and L2 = 3-acetoxymethyl-7-bromo-1,3-dihydro-1-methyl-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one ((9)-L2)	>40, >40, >40, >40, >40 >40, >40, >40, >40, >40 minimum inhibitory concentration (μg/ml)	Parainfluenza-3 virus Reovirus-1 Sindbis Coxsackie virus B4 Punta toro virus	[27]
$[(3,5\text{-}Hdmpz)_2Pd_2(l\text{-}3,5\text{-}dmpz)_2(2,6\text{-}dipic)]$ (1) (3,5-Hdmpz = 3,5-dimethylpyrazole and 2,6-dipic = 2,6-pyridinedicarboxylate)	100 minimum inhibitory concentration (μg/ml)	*B. subtilis*, *E. coli* and *Aspergillus niger*	[28]

2.2. Metal complexes of drugs used as ligands

Pd(II) complexes with three antibiotics of the tetracycline family (tetracycline, doxycycline and chlortetracycline) as ligands, were synthesized and the interactions between Pd(II) ions and tetracycline investigated in aqueous solution by ^{1}H NMR. All the tetracyclines studied form 1:1 complexes with Pd(II) via the oxygen of the hydroxyl group at ring A and that of the amide group. The effect of the three complexes on the growth of bacterial strains sensitive and resistant to tetracycline was studied. The Pd(II) complex of tetracycline is practically as efficient as tetracycline in inhibiting the growth of two *E. coli* sensitive bacterial strains and 16 times more potent against *E. coli* HB101/pBR322, a bacterial strain resistant to tetracycline. Pd(II) coordination to doxycycline (2-(amino-hydroxy-methylidene)-4-dimethylamino-5,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a,6-tetrahydro-4*H*-tetracene-1,3,12-trione) also increased its activity in the resistant strain by a factor of 2 [17].

2.3. Complexes of Pd(II) with Schiff base ligands

Condensation of salicylaldehyde with 5-aminosalicylic acid afforded the Schiff base 2-$HOC_6H_4C(H)$=NC_6H_3-2-(OH)-5-CO_2H. Similarly 5-bromosalicylaldehyde gives 5-Br-2-$HOC_6H_3C(H)$=NC_6H_3-2-(OH)-5-CO_2H. Reactions of these ligands with Pd(II), gave the corresponding bis(*N*-arylsalicylaldiminato) metal complexes. These compounds were tested in THF at a complex dose of 100 μg/disk for their anti-fungal activity against *Aspergillus niger* and *Aspergillus flavus* with no appreciable activity [18].

Palladium(II) complexes with the general empirical formula, square planar $[Pd(NS)_2]$ (NS = uninegatively charged acetone Schiff bases of *S*-methyl- and *S*-benzyldithiocarbazate) have been prepared. The crystal structure of the $[Pd(asme)_2]$ complex shows that the complex has a distorted *cis*-square planar structure. Antimicrobial tests indicate that the Schiff bases exhibit strong activities against the pathogenic bacteria, *Bacillus subtilis* (mutant defective DNA repair), methicillin-resistant *Staphylococcus aureus*, *B. subtilis* (wild type) and *Pseudomonas aeruginosa* and the fungi, *Candida albicans* (CA), *Candida lypotica* (2075), *Saccharomyces cerevisiae* (20341) and *Aspergillus ochraceous* (398). The activities exhibited by these compounds is greater than that of the standard antibacterial and anti-fungal drugs, streptomycin and nystatin, respectively. However, the corresponding palladium(II) complexes were inactive against most of these organisms. Screening of the compounds for their cytotoxicities against T-lymphoblastic leukemia cancer cells has shown that the acetone Schiff base of *S*-methyldithiocarbazate (Hasme) exhibits a very weak activity, whereas the *S*-benzyl derivative (Hasbz) is inactive, while the Pd(II) complexes exhibit strong cytotoxicities against this cancer; their activities being more than that of the standard anticancer drug, tamoxifen [19].

Table 2
The inhibitory concentrations values of 50% of various cancerous cells lines (IC_{50}) caused by Pd(II) compounds summarized in reference [7] and given also here in comparison of the corresponding IC_{50} values of cisplatin.

Compound	IC_{50} (μM) [a]μg/ml, [b]ID_{50}, [c]nM, [d]mM	Tumor cell line	Reference
Cisplatin	0.44 ± 0.04	A2780	[49]
Cisplatin	4.7 ± 0.3	$A2780^{cisR}$	[49]
Cisplatin	7.0, 1.7, 15.61	HL-60	[50,63,70]
Cisplatin	3.2	Histiocytic lymphoma U-937	[50]
Cisplatin	26–27	Calu-6 (adenocarcinoma, lung)	[58]
Cisplatin	1 ± 3, 2.52 ± 0.6	MCF 7 (mamma carcinoma)	[72,89]
Cisplatin	1.2	HeLa	[63]
Cisplatin	0.9 μM	Leukemia L1210	[71]
Cisplatin	16 ± 3	HCT 116	[72]
Cisplatin	1.84	SW707	[81]
Cisplatin	6.0	T47D	[81]
Cisplatin	2.43	HCV29T	[81]
Cisplatin	1.72	A549	[81]
Cisplatin	3.1 ± 1.2	K-562 CML	[89]
Cisplatin	4.6 ± 1.2	HCT-15	[89]
Cisplatin	10.5 ± 0.05	PC-3	[89]
[Pd(*p*-isoTSCN)$_4$] *p*-isopropylbenzaldehyde thiosemicarbazone (*p*-isoTSCN)	7 ± 0.3	JURKAT	[6]
[Pd(*p*-isoTSCN)$_4$]	4 ± 0.1	HeLa	[6]
[Pd(*p*-isoTSCN)$_4$]	3 ± 0.2	3T3	[6]
[Pd(*p*-isoTSCN)$_4$]	8 ± 0.3	Pam	[6]
[Pd(*p*-isoTSCN)$_4$]	5 ± 0.3	Pam-Ras	[6]
[Pd(*p*-isoTSCN-NHMe)]$_4$	17 ± 1.0	HL-60	[51]
[Pd(*p*-isoTSCN-NHMe)]$_4$	10 ± 0.8	3T3	[51]
[Pd(*p*-isoTSCN-NHMe)]$_4$	82 ± 4.0	JURKAT	[51]
[Pd(*p*-isoTSCN-NHMe)]$_4$	87 ± 3.0	HeLa	[51]
[Pd(*p*-isoTSCN-NHMe)]$_4$	58 ± 2.0	PAM 212	[51]
[Pd(*p*-isoTSCN-NHMe)]$_4$	101 ± 7.0	PAM 2 12-ras	[51]
[Pd(*p*-isoTSCN-NPip)]$_4$	10 ± 0.7	HL-60	[51]
[Pd(*p*-isoTSCN-NPip)]$_4$	9 ± 0.1	3T3	[51]
[Pd(*p*-isoTSCN-NPip)]$_4$	73 ± 3.0	JURKAT	[51]
[Pd(*p*-isoTSCN-NPip)]$_4$	94 ± 1.0	HeLa	[51]
[Pd(*p*-isoTSCN-NPip)]$_4$	68 ± 2.0	PAM 212	[51]
[Pd(*p*-isoTSCN-NPip)]$_4$	90 ± 3.0	PAM 2 12-ras	[51]
Pd(pacTSCN)Cl_2	23 ± 0.2	PAM-RAS	[52]
Pd(pacTSCN)Cl_2	8 ± 0.3	JURKAT	[52]
Pd(pacTSCN)Cl_2	9 ± 0.2	HL-60	[52]
Pd(pacTSCN)Cl_2	47 ± 1	U-937	[52]
Pd(pacTSCN)Cl_2	40 ± 2	HeLa	[52]
Pd(pacTSCN)Cl_2	124 ± 3	PAM	[52]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	21 ± 0.5	PAM-ras	[53]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	59 ± 3	GLIOMA #112	[53]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	30 ± 0.7	HL-60	[53]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	45 ± 1	U-937	[53]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	45 ± 2	HeLa	[53]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	0.1 ± 0.05	3T3	[53]
[Pd(*p*-isoTSCN)(μ-Cl)]$_2$	124 ± 5	PAM	[53]
[Pd(ESDT)Cl]$_n$ ESDT is ethyl ethylaminoacetate dithiocarboxylate	12.5 ± 0.12	Human ovarian carcinoma-2008	[54]
[Pd(ESDT)Cl]$_n$	14.2 ± 0.14	C13	[54]
[Pd(ESDT)Cl]$_n$	7.92 ± 1.15	HL-60	[55]
[Pd(ESDT)Cl]$_n$	11.53 ± 1.70	HeLa	[55]
[Pd(ESDT)($PrNH_2$)Cl]	5.83 ± 0.19	HL-60	[55]
[Pd(ESDT)($PrNH_2$)Cl]	7.50 ± 0.19	HeLa	[55]
[Pd(TSDT)Br]$_n$ TSDT is *tert*-butylsarcosine dithiocarbamate	5.20 ± 0.99	HL-60	[56]
[Pd(TSDT)Br]$_n$	11.01 ± 0.43	HeLa	[56]
[Pd(L^4)] thiosemicarbazone derivatives	16 ± 2	Vero	[57]
[Pd(L^4)]	12 ± 1	Pam 212	[57]
[Pd(L^4)]	20 ± 3	Pam-ras	[57]
[Pd(L^4)]	7 ± 1	HeLa	[57]
[Pd(NQTS)Cl]$_2$·2DMSO *ortho*-naphthaquinone thiosemicarbazone (NQTS)	3.50	MCF7	[48]
[PdL]$_2$ alpha-diphenyl ethanedione bis(thiosemicarbazone), L1, alpha-diphenyl ethanedione bis(4-ethylthiosemicarbazone) L2	17 ± 4	A2780	[49]
[PdL]$_2$	14 ± 4	$A2780^{cisR}$	[49]
[Pd(L1)(PPh_3)] salicylaldehyde thiosemicarbazone (H_2L1)	2.5	HL-60	[50]
[Pd(L1)(PPh_3)]	4.8	U-937	[50]
[Pd(L2)(PPh_3)] 2-hydroxyacetophenone thiosemicarbazone (H_2L2))	0.6	HL-60	[50]
[Pd(L3)(PPh_3)] 2-hydroxynaphthaldehyde thiosemicarbazone (H_2L3)	1.3	U-937	[50]

Table 2 (*Continued*)

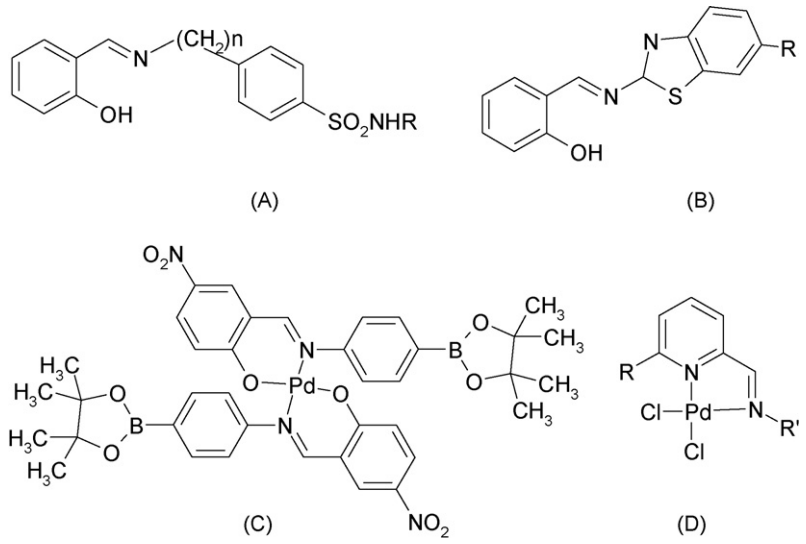
Compound	IC_{50} (μM) [a] μg/ml, [b] ID_{50}, [c] nM, [d] mM	Tumor cell line	Reference
[Pd(asme)$_2$] asme is the acetone Schiff base of *S*-methyldithiocarbazate	2.5 a	T-lymphoplastic leukemia	[19]
[Pd(asbz)$_2$] asbz the acetone Schiff base of *S′*-benzylthiocarbazate	2.9 a	T-lymphoplastic leukemia	[19]
[Pd(ddtc)(phen)] diethyldithiocarbamate (ddtc)	1.60 b	P 388	[67]
[Pd(ddtc)(bpy)]	1.50 b	P 388	[67]
Pd(Morphdtc)$_2$ morpholine dithiocarbamate	19.51	KB	[68]
Pd(MorphdtcCH$_3$)Cl$_2$	6.12	KB	[68]
Pd(TimdtcCH$_3$)Cl$_2$ thiomorpholine dithiocarbamate	8.22	KB	[68]
Pd(S$_2$COiPr)$_2$ bis(*O*-alkyldithiocarbonato)	0.1	Calu-6	[58]
Pd(S$_2$COiPr)$_2$	0.45	MCF-7	[58]
[Pd(DMSO)(PT)] H$_2$PT is pyruvic acid thiosemicarbazone	50 ± 8	F4N leukemia cells	[59]
[Pd(ESDT)(2-pic)Cl]	69.54 ± 0.31	HeLa	[60]
[Pd(ESDT)(2-pic)Cl]	59.62 ± 0.54	HL60	[60]
[Pd(ESDT)(2-pic)Cl]	97.12 ± 1.93	Daudi	[60]
[Pd(ESDT)(2-pic)Cl]	53.24 ± 1.52	LoVo	[60]
[Pd(MSDT)Br]$_n$	3.7	HL60	[63]
[Pd(MSDT)Br]$_n$ methylsarcosinedithiocarbamate (MSDT)	5.0	HeLa	[63]
Pd(6-mp)$_2$·2H$_2$O 6-mercaptopurine (6-Hmp)	4.20 ± 2.7 b	HL-60	[64]
[PdCl$_2$(C$_6$H$_5$CH$_2$C$_3$H$_5$N$_2$)$_2$]	3.1	HL-60	[73]
[PdCl(μ-Cl)(C$_6$H$_5$CH$_2$C$_3$H$_5$N$_2$)]$_2$	1.0	HL-60	[73]
[Pd$_2$(mpba)$_2$](μ-OAc)$_2$ I mpba is 4-methoxy-benzoylbenzylideneimine	29 b	CX-1	[74]
[Pd$_2$(mpba)$_2$](μ-OAc)$_2$ II	24 b	LX-1	[74]
[Pd$_2$(mpba)$_2$](μ-OAc)$_2$ I	22 b	CX-1	[74]
[Pd$_2$(mpba)$_2$](μ-OAc)$_2$ II	24 b	LX-1	[74]
[Pd(C$_2$-dmba)(N3)(dppp)]	1.0	HeLa	[75]
[Pd(C$_2$-dmba)(N3)(dppp)]	1.8	Hep-2	[75]
[Pd(C$_2$-dmba)(N3)(dppp)]	<0.5	C6	[75]
[Pd(C$_2$-*N*-dmba)(*cis*-dppet)](N3)	1.75	HeLa	[75]
[Pd(C$_2$-*N*-dmba)(*cis*-dppet)](N3)	2.20	Hep-2	[75]
[Pd(C$_2$-*N*-dmba)(*cis*-dppet)](N3)	0.75	C6	[75]
[Pd(cpba)(μ-OAc)]$_2$ cpba is *N*-(4-chlorophenyl)-α-benzoylbenzylideneamine	6.75 ± 0.57	MDA-MB 468	[76]
[Pd(cpba)(μ-OAc)]$_2$	6.35 ± 0.70	HL-60	[76]
[Pd(cpba)(μ-Cl)]$_2$	8.95 ± 0.42	MDA-MB 468	[76]
[Pd(cpba)(μ-Cl)]$_2$	8.37 ± 0.63	HL-60	[76]
[Pd(L1)(4-*O*-Acrid)] 9-aminoacridine	3.8 ± 1.9	A2780	[69]
[Pd(L1)(4-*O*-Acrid)] 1-phenylpyrazoles-L1	5.6 ± 1.2	OVCAR 5	[69]
[Pd(L1)(4-*O*-Acrid)]	4.7 ± 1.1	OVCAR 8	[69]
Pd(L2)(3,5-dimethylpyridine)Cl 2-phenylpyridine-L2	1.2	L1210	[71]
Pd(L1)(3,5-dimethylpyridine)Cl	6.4	L1210	[71]
Pd(L2)(POMe$_3$)Cl	1.1	L1210	[71]
(BzBimy)$_2$PdCl$_2$ 1-benzyl-3-*tert*-butylimidazol-2-ylidene (BzBimy)	4	HeLa	[72]
(BzBimy)$_2$PdCl$_2$	0.8	HCT 116	[72]
(BzBimy)$_2$PdCl$_2$	1	MCF-7	[72]
[Pd(sperH)$_2$][PdCl$_4$] spermidine	0.76 a	MDA-MB468	[93]
[(PdCl$_2$)$_3$(sper)$_2$]	0.56 a	MDA-MB468	[93]
trans-PdCl$_2$[(R)(−)bornylamino]$_2$	86.1	HeLa	[94]
trans-PdCl$_2$[(R)(−)bornylamino]$_2$	55.9	K562	[94]
[Pd(bpy)(SeO$_3$)]	3 b	P388	[95]
[Pd(phen)(SeO$_3$)]	3 b	P388	[95]
[Pd(2-dqmp)Br$_2$] 2-quinolylmethylphosphonate (2-dqmp)	12.7	KB	[96]
[Pd(2-dqmp)Br$_2$]	3.30	L1210	[96]
[Pd(L3)]Cl$_2$ *N*,*N′*-dipropyl-1,10-phenanthroline-2,9-dimethanamine (L$_3$)	11.59 b	L1210	[97]
[Pd(L4)]Cl$_2$ *N*,*N′*-di-*tert*-butyl-1,10-phenanthroline-2,9-dimethanamine (L$_4$)	10.26 b	L1210	[97]
[Pd(L5)]Cl$_2$ *N*,*N′*-dicyclohexyl-1,10-phenanthroline-2,9-dimethanamine (L$_5$)	8.20 b	L1210	[97]
[Pd(L3)]Cl$_2$ *N*,*N′*-dipropyl-1,10-phenanthroline-2,9-dimethanamine (L$_3$)	10.62 b	Bel-7402	[97]
[Pd(L4)]Cl$_2$ *N*,*N′*-di-*tert*-butyl-1,10-phenanthroline-2,9-dimethanamine (L$_4$)	9.53 b	Bel-7402	[97]
[Pd(L5)]Cl$_2$ 1,10-phenanthroline-2,9-dimethanamine (L$_5$)	8.20 b	Bel-7402	[97]
[Pd(ethylenediamine)(py)Cl](NO$_3$)	1.17 b	Hl-60	[98]
[Pd(phen)(L-trp)]Cl·5H$_2$O	250	AZGY-38a	[99]
[Pd(5-NO$_2$-phen)(L-trp)]Cl·5H$_2$O	440	AZGY-38a	[99]
trans-[Pd(harmine)(DMSO)Cl$_2$] harmine is an alkaloid	0.385	P388	[100]
trans-[Pd(harmine)(DMSO)Cl$_2$]	0.385	L1210	[100]

Table 2 (*Continued*)

Compound	IC_{50} (μM) [a] μg/ml, [b] ID_{50}, [c] nM, [d] mM	Tumor cell line	Reference
trans-[Pd(harmine)(DMSO)Cl_2]	0.364	K562	[100]
[Pd(Boh-H+)Cl (H_2O)$_2$] bohemine (Boh)	26	G3G1	[101]
[Pd(MMC)Cl_2] MMC is an anti-tumor agent	15.8 ± 5.3	K562	[102]
[Pd-(Altromycine)]	0.5 ± 0.1 c	K562	[103]
[Pd-(Altromycine)]	1.1 ± 0.2 c	GLC4	[104]
[{*trans*-PtCl(NH_3)$_2$}$_2$μ-{*trans*-Pd(NH_3)$_2$-($H_2N(CH_2)_6NH_2$)$_2$}]Cl_4	0.048 ± 0.006	A2780	[80]
[{*trans*-PtCl(NH_3)$_2$}$_2$μ-{*trans*-Pd(NH_3)$_2$-($H_2N(CH_2)_6NH_2$)$_2$}]Cl_4	0.25 ± 0.01	A2780^{cisR}	[80]
[{*trans*-PtCl(NH_3)$_2$}$_2$μ-{*trans*-Pd(NH_3)$_2$-($H_2N(CH_2)_6NH_2$)$_2$}]Cl_4	0.23 ± 0.01	A2780ZD0474	[80]
[Pd(dmnP)$_2Cl_2$] 2,6-dimethyl-4-nitro-pyridine (dmnp)	8.4 a	A549	[81]
[Pd(dmnP)$_2Cl_2$]	0.54 a	SW707	[81]
[Pd(dmnP)$_2Cl_2$]	0.46 a	T47D	[81]
[Pd(dmnP)$_2Cl_2$]	0.54 a	HCV29T	[81]
Pd(2-dqmp)$_2Br_2$	2.76	L1210	[83]
Pd(DAA)Cl_2 3,4-diamine-2,3,4,6-tetradeoxy-(alpha-L-lyxohexopyranoside (DAA)	9	L5178Y-R	[84]
Pd(DAA)Cl_2	23	L5178Y-S	[84]
[{*trans*-PtCl(NH_3)}$_2$μ-{*trans*-Pd(NH_3)(2-hydroxy pyridine)-($H_2N(CH_2)_6NH_2$)$_2$}]Cl_4	0.0103 ± 0.0004	A2780	[85]
[{*trans*-PtCl(NH_3)}$_2$μ-{*trans*-Pd(NH_3)(2-hydroxy pyridine)-($H_2N(CH_2)_6NH_2$)$_2$}]Cl_4	0.064 ± 0.001	A2780^{cisR}	[85]
[Pd(bpy)(bmal)]·2H_2O	55.4	AGZY-83	[86]
trans-[Pd(L1)$_2Cl_2$]·H_2O L1–L2 = cyclin-dependent kinase inhibitors derived from 6-benzylamino-9-isopropylpurine	3	MCF 7	[88]
trans-[Pd(L2)$_2Cl_2$]·H_2O	3	MCF 7	[88]
[Pd(L)Cl_2]$_2$ (*S*)-(−)-(1-phenylethylimino)benzyl phenyl ketone	23.8 ± 2 d	U-251 Glio	[89]
[$PdCl_2$(HL)] HL = 4-(2-hydroxybenzoyl)-2-(pyridin-2-yl)-1*H*-pyrazol-3-ol	7	HL-60	[91]
[$PdCl_2$(HL)]	8.3	NALM-6	[91]
[Pd(CQ)$_2Cl_2$]	49	MDA-MB231	[92]

Palladium(II) complexes of Schiff bases have been prepared by the interactions of palladium(II) chloride with 5-chloro-1,3-dihydro-3-[2-(phenyl)-ethylidene]-2*H*-indol-2-one-hydrazinecarbo-thioamide and 5-chloro-1,3-dihydro-3-[2-(phenyl)-ethylidene]-2*H*-indol-2-one-hydrazine carboxamide. The complexes have square planar geometries around Pd(II) in which the ligands act as neutral bidentate and monobasic bidentate ligands, coordinating through nitrogen and sulfur or oxygen atoms. Free ligands and their metal complexes were screened for their anti-microbial activity on different species of pathogenic fungi and bacteria [20].

The Pd(II) complex with the condensation product of 2-(diphenylphosphino)benzaldehyde and semioxamazide as a ligand was synthesized, and the anti-microbial activities of the complex and the free ligand evaluated. The ligand is coordinated through P, N and O donor atoms, in a square planar geometry. The free ligand showed antibacterial and anti-fungal activity, which was enhanced upon complexation [21].



Scheme 2. (A) HL_a: *n* = 0, R = 1, HL_b: *n* = 1, R = H, HL_c: *n* = 2, R = H, HL_d: *n* = 0, R = CONHBu, HL_e: *n* = 0, R = 2-pyrimidinyl, HL_f: *n* = 0, R = 2,6-dimethyl-4-pyrimidinyl, HL_g: *n* = 0, R = thiazolyl; (B) HL_h: R = H, HL_i: R = OEt, HL_j: R = NO_2; (C) The *trans*-geometry of the Pd(II) complex with the ligand nitrosalicylaldehyde-4-Bpin; (D) R = H and R′ = oleyl, R = CH_3 and R′ = oleyl.

Schiff bases (HL_{a-j}) (Scheme 2A and B) derived from sulfanilamides or aminobenzothiazoles added to $Pd(OAc)_2$ afforded complexes of the type PdL_2 in moderate to excellent yields. Reactions of Schiff bases containing pyrimidine groups, however, gave several products arising from competing coordination of the pyrimidine nitrogen. Palladium complexes and Schiff bases have been investigated as anti-fungal agents against *Aspergillus niger* and *Aspergillus flavus*. However, only the compound $Pd(L_h)_2$ (Scheme 2B) showed appreciable activity against both fungi [22].

Reactions of salicylaldehydes with boronate ester derivatives of aniline have been examined. Addition of these Schiff base ligands to $Pd(OAc)_2$ or Na_2PdCl_4 afforded novel boron-containing *trans*-bis(*N*-arylsalicylaldiminato) palladium complexes of the type PdL_2 where L = deprotonated Schiff base. The molecular structure of the nitro-salicylaldehyde 4-Bpin (Scheme 2C) Pd(II) complex was characterized by X-ray diffraction studies. These palladium compounds were tested for their anti-fungal activity against *Aspergillus niger* and *Aspergillus flavus* but showed only negligible anti-fungal activity against both fungi *Aspergillus niger* and *Aspergillus flavus* [23].

Pyridinecarboxaldimines (N–N′A) derived from pyridin-2-ylcarboxaldehydes and unsaturated amines were added to $[PdCl_2(coe)]_2$ (coe = *cis*-cyclooctene) to give complexes of the type $PdCl_2$(N–N′A) in moderate yield. The palladium complexes have been investigated as substrates for hydroboration reactions and as anti-fungal agents against *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, and *Saccharomyces cerevisiae*. Only the palladium oleyl starting materials (Scheme 2D) showed promising activity against all fungi tested in this study [24].

2.4. Miscellaneous

$PdCl_2$ reacts with 1,3-bis(2-benzimidazyl)-2-thiapropane (L) to form a 5-coordinate square pyramidal monometallic complex where the ligand acts as a tridentate chelating agent, through two of the nitrogen atoms in the imidazole ring and the sulfur atom of the bridging group together with two chloride ions forming a rare five coordinate complex. Anti-microbial activities were evaluated by the minimal inhibitory concentration (MIC) against 10 bacteria and the results compared with those of ampicillin, ciprofloxacin, cefazolin, ofloxacin, and piperacillin antibacterial agents. In most cases the free ligand and the Pd(II) complex, show broad-spectrum (Gram (+) and Gram (−)) activities that are either, more active, or equipotent to, the antibiotic and anti-fungal agents in the comparison tests [25].

Anti-viral cyclam macrocycles block viral entry into cells by binding to the CXCR4 co-receptor. Cyclams bind transition metal ions strongly and can potentially form a range of *trans*- and *cis*-configurations, which may be recognized directly by co-receptor proteins. The X-ray structures for the square-planar complexes *trans*-[Pd(cyclam)]Cl_2·2MeOH and the C–C linked dimer $[Pd_2$(2,2′-bi-(1,4,8,11-tetraazacyclotetradecane))$](ClO_4)_4$, in which the planes of the two cyclam rings are close to perpendicular (100.1°) are reported. The Pd(II)-cyclam complexes are inactive as anti-HIV agents, which can be attributed to the inability of Pd(II) to bind to axial ligands and possibly due to its inability to adopt configurations other than *trans*- [26].

Pd(II) complexes of 7-bromo-1,3-dihydro-3-hydroxymethyl-1-methyl-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one ((+)-L1), and 3-acetoxymethyl-7-bromo-1,3-dihydro-1-methyl-5-(2′-pyridyl)-2*H*-1,4-benzodiazepin-2-one ((±)-L2) with square-planar coordination were prepared and the free ligands and their complexes evaluated for their *in vitro* cytostatic activity against the murine L1210/0 and human T-lymphoblast Molt/C8 and CEM/0 cell lines, as well as for their *in vitro* anti-viral activity in different assay systems. The anti-viral assays of free benzodiazepine ligands and their complexes were based on an inhibition of virus-induced cytopathogenicity in Vero, HEL or HeLa cell cultures against a variety of DNA and RNA viruses. The compounds showed none or only marginal anti-viral activity. No anti-viral effects were noted for any of the compounds against any of the viruses evaluated at concentrations that were at least five-fold below the cytotoxic concentrations. The latter ranged from 40 to 200 mg/ml [27].

The syntheses of two new Pd(II) complexes $[(3,5\ Hdmpz)_2Pd_2$(l-3,5-dmpz)$_2$(2,6-dipic)] and $[Na_2(H_2O)_4Pd$(2,6-dipic)$_2]$ were reported [49]. The X-ray crystal structure determination showed that $[(3,5\ Hdmpz)_2Pd_2$(l-3,5-dmpz)$_2$(2,6-dipic)] is a binuclear complex bridged by two 3,5-dmpz units and is completely unsymmetric since one palladium atom contains two protonated 3,5-Hdmpz ligands and the other one contains the $[2,6\text{-dipic}]^{2-}$ unit that coordinates in a bidentate fashion. This complex shows anti-microbial activity against *B. subtilis*, *E. coli* and *Aspergillus niger* where the MIC was 100 μg/ml. [28]

Table 1 summarize the anti-viral, anti-fungal and anti-microbial activity of Pd(II) complexes reported in Ref. [7] and in this work.

3. Anti-tumor Pd(II) complexes

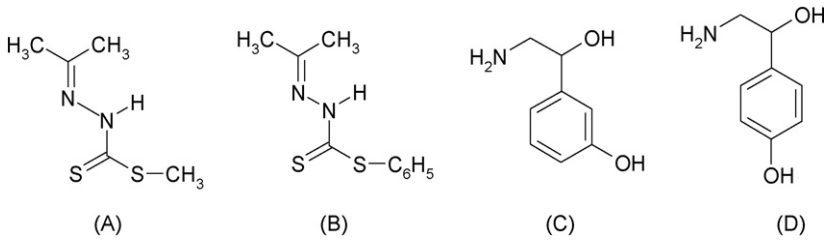
3.1. Sulfur donor ligands

3.1.1. Thiosemicarbazones

Pd(II) complexes of 2-benzoylpyridine thiosemicarbazone (H2Bz4DH) and its N(4)-methyl (H2Bz4M) and N(4)-phenyl (H2Bz4Ph) derivatives were synthesized. The structure of the complexes [Pd(2Bz4DH)Cl], [Pd(2Bz4M)Cl] and [Pd(2Bz4Ph)Cl] were obtained by crystallographic techniques. All complexes show a quite similar planar environment around Pd(II). The ligand is tridental and binds to the metal through the pyridine nitrogen, the imine nitrogen and the sulfur atom. A chloride ion occupies the fourth coordination site. The cytotoxic activity of the ligands and their Pd(II) complexes were tested against the MCF-7, TK-10 and UACC-62 human tumor cell lines. The ligands exhibit lower values of GI_{50} and LD_{50} than the complexes, with the ligand H2Bz4Ph being the most active (growth inhibition, GI, (cytostatic effect) and lethal dose, LD, (cytocidal effect) for 50% of the cells. ($GI_{50} < 0.003$ μM; $LC_{50} = 13.4$ μM; $GI_{50} = 9.3$ μM, $LC_{50} = 12.9$ μM; $GI_{50} < 0.003$, $LC_{50} = 13.8$ μM for the MCF-7, TK-10 and UACC-62 cell lines, respectively). Among the complexes, [Pd(2Bz4Ph)Cl] exhibited the lowest values of $GI_{50} = 6.4$ μM, $GI_{50} = 24.3$ μM, $GI_{50} = 22.2$ μM in the MCF-7, TK-10 and UACC-62 cell lines, respectively [47].

Cu(II), Ni(II), Pd(II) and Pt(II) complexes of *ortho*-naphthaquinone thiosemicarbazone (NQTS) were synthesized. The Pd(II) complex crystallizes as an H-bonded dimer, $[Pd(NQTS)Cl]_2$·2DMSO, where Pd(II) coordinates in a square planar configuration to the monodeprotonated, tridentate thiosemicarbazone ligand. *In vitro* anticancer studies on MCF7 human breast cancer cells reveal that adding a thiosemicarbazone pharmacophore to the parent quinone carbonyl considerably enhances its antiproliferative activity. However, a moderate IC_{50} value (9.75 μM) was observed for the Pd(II) compound which is higher than that of the free ligand (3.50 μM) [48].

The synthesis of new Pd(II) and Pt(II) complexes derived from alpha-diphenyl ethanedione bis(thiosemicarbazone), L1, and alpha-diphenyl ethanedione bis(4-ethylthiosemicarbazone) L2, was reported [49]. The crystal and molecular structures of the dimeric cyclopalladated compound with the ligand L2 and the mononuclear platinum complex with the same ligand were determined by single crystal X-ray diffraction [49]. The cytotoxic activity of the free ligands and palladium and platinum complexes against human A2780 and $A2780^{cisR}$ (acquired resistance to cisplatin)



Scheme 3. (A) The acetone Schiff base (asme); (B) the acetone Schiff base (asbz); (C) norphenylephrine (Nor); (D) synephrine (Syn).

epithelia ovarian carcinoma cells lines showed IC_{50} values for L1, and Pt(II) complexes, higher than that of cisplatin but a similar maximum antiproliferative activity [49].

Reaction of salicylaldehyde thiosemicarbazone (H_2L1), 2-hydroxyacetophenone thiosemicarbazone (H_2L2) and 2-hydroxynaphthaldehyde thiosemicarbazone (H_2L3) with $Na_2[PdCl_4]$ affords a family of polymeric complexes of type [{Pd(L)}(n)]. Reaction of the polymeric species with two monodentate ligands (D), such as triphenylphosphine (PPh_3) and 4-picoline (pic), has yielded complexes of the general formulae [Pd(L)(D)]. *In vitro* cytotoxicity screenings of the complexes along with four anticancer drugs (cisplatin, BCNU, 5-fluorouracil (5-FU) and hydroxyurea) have been carried out in the human tumor cell lines, promyelocytic leukemia HL-60 and histiocytic lymphoma U-937. The complex [Pd(L2)(PPh_3)] shows the lowest IC_{50} value and is much more cytotoxic than the reference anticancer drugs in both the cell lines [50].

Table 2 summarizes the inhibitory concentrations values of 50% of various cancerous cells lines (IC_{50}) caused by Pd(II) compounds reported in Ref. [7] and in this work.

3.1.2. Other sulfur containing ligands

The palladium(II) complexes of formulae [Pd(asme)$_2$] and [Pd(asbz)$_2$], (Scheme 3A and B), were active against T-lymphoplastic leukemia cells and 9KB a human epidermaid carcinoma of nasopharynx [19]. The Pt(II) analogs of the same ligand were inactive [19].

Eighteen bis(*O*-alkyldithiocarbonato) metal complexes of palladium, gold, nickel, copper, rhodium, and bismuth were synthesized, and their cytotoxic activity on two human cancer cell lines was compared with the corresponding platinum bis(*O*-alkyldithiocarbonato) complexes and cisplatin. Palladium complexes were most active with up to 10-fold lower IC_{50} values as compared with the corresponding platinum complexes [58].

The complex [Pd(DMSO)(PT)], exhibits a moderate growth inhibitory factor ($IC_{50} = 50 \pm 8\ \mu M$) and cytotoxic activity ($EC_{50} = 143 \pm 5\ \mu M$) against F4N leukemia cells. In contrast the ligand H_2PT was inactive (IC_{50} and $EC_{50} > 400\ \mu M$) under the same conditions [59].

The complexes [Pd(ESDT)(L)Cl], were synthesized. In both complexes the dithiocarbamate moiety acts as a chelating agent, while chlorine atom and the amino ligand occupy the two remaining sites. The complex [Pd(ESDT)(2-pic)Cl] shows moderate activity against the cancer cell lines HeLa ($IC_{50} = 69.54 \pm 0.31$) HL60 ($IC_{50} = 59.62 \pm 0.54$) Daudi cells line ($IC_{50} = 97.12 \pm 1.93$) LoVo ($IC_{50} = 53.24 \pm 1.52$) in comparison with cisplatin or the corresponding platinum complexes, while the complex [Pd(ESDT)(3-pic)Cl] was inactive [60].

Complexes of the type [M(ESDT)(Am)Cl] (Am = synephryne (Syn) and norphenylephrine (Nor) and M = Pd(II) or Pt(II)) were formed through a reaction between $[M(ESDT)Cl]_n$ and the two chiral amino-alcohols (Syn) and (Nor) (Scheme 3C and D). In all cases coordination of the dithiocarbamate ligand (ESDT) takes place through the two sulfur atoms, in a square-planar geometry around the M(II) ion, while the other two coordination sites are occupied by the chlorine atom and the nitrogen atom of amino-alcohol. The biological activity of the new complexes has been studied by MTT (tetrazolio salt reduction) test and by detecting the inhibition of DNA synthesis and of clonal growth in various cancer cell lines. All Pd(II) derivatives showed a noticeable activity very close to that of cisplatin, used as a reference drug [61,62].

The *in vitro* cytotoxic activity of Pd(II), Pt(II), and Au(III) complexes with the ligand methylsarcosinedithiocarbamate (MSDT) and its *S*-methyl ester (MSDTM) have been reported. The spectroscopic results suggest that coordination takes place in a near square-planar geometry through the sulfur atoms, with the –NCSS moiety coordinating the metal ion in a bidentate mode. However, both Pd(II) complexes $[Pd(MSDT)X]_n$ and $[Pd(MSDTM)X]_n$ are probably constituted of a mixture of trimeric, tetrameric, and pentameric structures, as suggested by ESI-MS results. The biological activity of these compounds, as determined by growth inhibition and apoptosis induction, has been investigated in both HL60 and HeLa cell lines. On the basis of these experimental results, $[Pd(MSDT)Br]_n$ shows a strong dose-dependent growth inhibition of both HL60 and HeLa cells, with IC_{50} values being slightly higher than those recorded for cisplatin ($[Pd(MSDT)Br]_n$: IC_{50} in μM, HL60 = 3.7, HeLa = 5.0; cisplatin: IC_{50} in μM, HL60 = 1.7, HeLa = 1.2) [63].

A series of Pd(II) and Pt(II) complexes with 6-mercaptopurine (6-Hmp) was synthesized. From multinuclear NMR studies it is likely that S and N(7) are the coordination sites of the ligand in Pd(II) complexes. The ID_{50} value for the *in vitro* antiproliferative activity of the complex $[Pd(6\text{-}mp)_2]\cdot 2H_2O$ against human leukemia HL-60 cells was six times higher than cisplatin ($Pd(6\text{-}mp)_2\cdot 2H_2O$: $ID_{50} = 4.20 \pm 2.7$, cisplatin: $ID_{50} = 0.71 \pm 0.16$) [64].

Pd(II) complexes with organophosphines and dithiocarbamates, derivatives of α-amino acids were synthesized by reacting *N*,*N*-dicyclohexyldithiocarbamate (DCHDTC) and *N*-methylcyclohexyldithiocarbamate (MCHDTC) with $(R_3P)_2PdCl_2$ (R = Ph, o-tolyl, Ph_2Cl) in a 1:1 molar ratio. The dithiocarbamate acts as a bidentate ligand coordinating to Pd(II) through the two sulfur atoms in a square planar geometry. The cytotoxicity of the compounds determined *in vitro* against various human tumour cell lines, showed a moderate to low cytotoxicity [65].

Square planar metallic and homonuclear bimetallic complexes of Pd(II) with 2-thiouracil (HTU) and organophosphines have been synthesized where the thiouracil TU acts as bidentate ligand and coordinates through the thioxo group and the *endo* amino group forming a bridge between a $PdCl(R_3P)$ and a $PdCl(R_3P)_2$ moiety [$R_3P = Ph_3P$ (o-tolyl)$_3$P, $ClPh_2P$] in the homonuclear bimetallic complexes. $[Pd_2(TU)(PPh_3)_3Cl_2]$ the Pd(II) cation is square planar (X-ray). The compounds were screened against various human tumor cell lines and showed promising *in vitro* cytotoxicity [66].

The IC_{50} values against cancerous cells lines caused by Pd(II) compounds with other sulfur containing ligands apart thiosemicarbazones, reported in Ref. [7] and in this work are given in Table 2.

3.2. Nitrogen and other donor atoms

3.2.1. Organopalladates

Four new square planar metal complexes of Pd(II) and Pt(II), containing the bidentate ligand 9-aminoacridine (9AA) were synthesized. The complex [Pd(L^1)(4-*O*-Acrid)] shows high cytotoxic activity against three human ovarian cancer cell lines A2780 ($IC_{50} = 3.8 \pm 1.9$ μM), OVCAR 5 ($IC_{50} = 5.6 \pm 1.2$ μM) and OVCAR 8 ($IC_{50} = 4.7 \pm 1.1$ μM). In all cell lines the complex inhibits cell proliferation in a dose dependent manner and was more effective than both cisplatin and the free ligand (4-OH-Acrid) [69].

New palladium organometallic complexes derived from the 2-(dimethylaminomethyl)phenyl (dmba), bis(3,5-dimethylpyrazol-1-yl)methane (dbpzm), bis(pyrazol-1-yl)methane (bpzm) and pentafluorphenyl groups with 1-methylcytosine have been synthesized. The crystal structures of [Pd(dbpzm)(C_6F_5)(1-Mecyt)]ClO_4 and *cis*-[Pd(t-BuNC)(C_6F_5)(1-Mecyt)$_2$]ClO_4 have been determined by crystallographic techniques. In all cases the complexes seem to modify the morphology of the *p*BR322 DNA in a similar mode to that of cisplatin. The IC_{50}values for the new complexes against the HL-60 cell line at short incubation time (24 h) were lower to that of cisplatin (except complex [Pd-(bpzm)(C_6F_5)(1-Mecyt)]ClO_4). In addition, the majority of the cell death observed in cytotoxic assays is by apoptosis [70].

Cyclometallated μ-halogeno dimers derived from nitrogen donor ligands (1-phenylpyrazoles-L1, 2-phenylpyridine-L2, and 1-(2′-pyridyl)indole-L3) were treated with unidentate nitrogen and phosphorus donor ligands to give a series of neutral monomeric Pd(II) and Pt(II) complexes. An initial prescreen of the complexes against the mouse lymphoid leukemia cell line L1210 indicated that almost all the complexes exhibited growth inhibitory activity over a relatively wide concentration range. The factors that gave rise to increased activity were (i) the steric hindrance about the metal center resulting from hindered ligands and (ii) the presence of a phosphorus donor ligand. Three of the synthesized Pd(II) complexes, Pd(L2)(3,5-dimethylpyridine)Cl, Pd(L1)(3,5-dimethylpyridine)Cl and Pd(L2)($POMe_3$)Cl, were selected for further *in vivo* studies showing interesting IC_{50} values *in vitro* against Leukemia L1210 cell line (1.2, 6.4 and 1.1 μM, respectively). For comparison, cisplatin IC_{50} is 0.9 μM under similar conditions [71].

Pd(II) complexes, as well as Au and Ag with 1-benzyl-3-*tert*-butylimidazol-2-ylidene (BzBimy) were studied for their anticancer and antiproliferative activities. The palladium complexes displayed potent anticancer activity and strong antiproliferative activity against three types of human tumor cells (cervical cancer (HeLa), breast cancer (MCF-7), and colon adenocarcinoma (HCT 116) with the compound $(BzBimy)_2PdCl_2$ to be the most active (IC_{50} in μM; 4 (HeLa); 0.8 HCT 116; 1 MCF-7). Also, the antiproliferative activity of $(BzBimy)_2PdCl_2$ was considerably stronger than that of cisplatin [72].

The IC_{50} values against cancerous cells lines caused by organopalladates, reported in Ref. [7] and in this work are included in Table 2.

3.2.2. Amine complexes

The cytotoxic activity of the complex $[PdCl_2]_2$(sperm) against a human cancer cell line (HSC-3) was also evaluated and show an activity higher than that of the analogous Pt(II) compound, identical to that of cisplatin [77].

Two polynuclear palladium complexes of formulae, [{*trans*-$PdCl(NH_3)_2$}$_2$-μ-{*trans*-$Pd(NH_3)_2(H_2N(CH_2)_6NH_2)_2$}]$Cl_4$ (MH1) and [{*trans*-$PdCl(NH_3)_2$]μ-{*trans*-$Pd(NH_3)_2(H_2N(CH_2)_5NH_2)_2$}]$Cl_4$ (MH2) have been evaluated for their activity against A2780 and $A2780^{cisR}$ ovary cell lines using MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) reduction assay. Both MH1 and MH2 display a lower activity than cisplatin, MH1 being marginally more active than MH2. The low anticancer activity of the compounds is caused by aquated species, which are deactivated by binding with other biomolecules, before they have a chance to bind with DNA [78].

Platinum and palladium complexes containing the novel, sterically hindered ligand 6-(methylpyridin-2-yl)acetate (PICAC) have been synthesized. The structure of the complex [Pd(en)(PICAC-N,O)]NO_3 (en = ethane-1,2-diamine) was determined by crystallographic techniques. The complex exhibits a mixed [N_3O] coordination, whereas the ligand PICAC forms a sterically crowded six-membered chelate. In a human leukemia cell line (HL-60) the complex [Pd(en)(PICAC-N,O)]NO_3 showed a cytotoxic effect at concentrations in the high micromolar range with IC_{50} values in the magnitude of some hundred. For comparison, in the same study, cisplatin caused cell kill with an IC_{50} of 0.69 μM. In this respect, the palladium complex proved to be most labile and can be expected to undergo random reactions in biological media [79].

Four multinuclear complexes of the general formula [{*trans*-$PtCl(NH_3)_2$}$_2$μ-{*trans*-$Pd(NH_3)_2$-$(H_2N(CH_2)_nNH_2)_2$}]Cl_4 where $n = 4–7$ were tested against ovarian (A2780, $A2780^{cisR}$ and $A2780^{ZD0473}$), melanoma (Me-10538) and lung cancer (NCI-H460) human cancer cell lines. The compounds exhibit significant anticancer activity against ovarian cancer cell lines, especially the compound [{*trans*-$PtCl(NH_3)_2$}$_2$μ-{*trans*-$Pd(NH_3)_2$-$(H_2N(CH_2)_6NH_2)_2$}]Cl_4 which is the most active (IC_{50} (μM): 0.048 ± 0.006, 0.25 ± 0.01 and 0.23 ± 0.01 for A2780, $A2780^{cisR}$ and $A2780^{ZD0474}$, respectively). As the number of carbon atoms in the linking diamine is decreased below six and increased above six, the activity decreases, illustrating a structure–activity relationship. All the multinuclear compounds form a plethora of long-range interstrand GG adducts with DNA, dictated by the sequence of bases in the DNA strands [80].

Mononuclear [Pd(dmnP)$_2$Cl$_2$] and dinuclear [Pd_2(dmnP)$_2$Cl$_4$] palladium(II) complexes with 2,6-dimethyl-4-nitro-pyridine (dmnp) were synthesized. The crystal structures of the ligand and the mononuclear complex were determined by three-dimensional X-ray methods. The preliminary assessments of anti-tumor properties of both complexes and ligand were evaluated as *in vitro* anti-proliferative activity in four human cancer cell lines; SW707 (adenocarcinoma of the rectum), T47D (breast cancer), HCV29T (bladder cancer) and A549 (non-small cell lung carcinoma). The mononuclear compound exhibits strong cytotoxic activity against almost all cell lines in comparison with cisplatin, whereas the free ligand and the dinuclear complex were only moderately active [81].

Six Pd(II) complexes with ligands involved a sugar unit (D-glucose, D-galactose, D-mannose, D-xylose, and maltose) were tested *in vivo* against P388 leukemia cells implanted in mice. Most of palladium complexes did not show any significant activity, except the compound with maltose unit: T/C value of 120% was obtained at the dose of 400 mg/kg. This T/C value is indicative of anti-tumor activity. No other relationship between activity and type of sugar was observed [82].

Spectroscopic and biological studies of Pd(II) complexes of monoethyl-2-quinolymethylphosphonate (2-Hmqmp) and diethyl 2-quinolymethylphosphonate (2-Hdqmp), dihalide adducts, chelates and ion-pair salt complexes, have been carried out, to determine their biological properties. The complexes were evaluated *in vitro* for their cytostatic activity against several cancer cell lines. The L1210 cell line was the most responsive line and in general the ligand's (2-dqmp) complexes were more active than those of (2-mqmp). The complex Pd(2-dqmp)$_2$Br$_2$ was the most active with IC_{50} value of 2.76 μM. A good relationship was

observed between the cytostatic activity of the complexes and their lypophilicity or solubility. Some complexes exhibited cell growth inhibitory effects, but none of them was more cytostatic than cisplatin [83].

A comparative study of the cytotoxicity of *cis*-Pd(II) and Pt(II) complexes with methyl 3,4-diamine-2,3,4,6-tetradeoxy-(alpha-L-lyxohexopyranoside (DAA), against two mouse lymphoma cell lines (L5178Y) differing in their double strand breaks and nucleotide excision repair ability, has been reported. Cisplatin was used as a reference compound. The toxicity of $Pt(DAA)Cl_2$ appeared to be similar for both cell lines with IC_{50} value of 8 μM for L5178Y-R and 12 μM for L5178Y-S, respectively. The palladium complex was more toxic for the L5178Y-R (IC_{50} = 9 μM) than for the L5178Y-S cells (IC_{50} = 23 μM). The results indicate that these two compounds may cause a different type of DNA damage and/or that the DNA damage caused by the Pd(II) compound was dealt with, in a different manner from that induced by the Pt(II) complex [84].

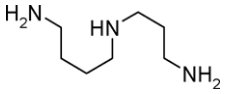
The trinuclear mixed metal complex, $[\{trans\text{-}PtCl(NH_3)\}_2\mu\text{-}\{trans\text{-}Pd(NH_3)(2\text{-hydroxypyridine})\text{-}(H_2N(CH_2)_6NH_2)_2]Cl_4$, has been synthesized. The activity of the compound against human ovarian cancer cell lines: A2780, $A2780^{cisR}$ and $A2780^{ZD0473R}$, cell up take, level of binding with DNA and nature of its interaction with pBR322 plasmid DNA have been determined. The compound exhibits much higher anticancer activity against the cell lines, than cisplatin [85] (IC_{50} (μM): 0.0103 ± 0.0004, 0.064 ± 0.001 for A2780 and $A2780^{cisR}$, respectively) (see Table 2).

The novel Pd(II) complex of formula $[Pd(bpy)(bmal)]\cdot 2H_2O$ (bpy = 2,2′-bipyridyl, bmal = benzylmalonate) has been synthesized. Electronic spectra confirm that the main reaction mode of the compound with DNA is non-covalent. Electrophoresis experiments show the cleavage of both supercoiled and circular DNA. The complex was screened against lung cancer cell line AGZY-83 and shows significant activity with IC_{50} value of 55.4 μg/ml [86].

The homologous trinuclear Pt(II) or Pd(II) polyamine chelate complexes with spermidine (Scheme 4), were screened for their anticancer properties. Their growth-inhibition activity towards a human tongue epithelioma (HSC-3) was assessed *in vitro*. All complexes showed similar activity, with the Pd(II) compound being somewhat more active (IC_{50} = 32 μM) than the Pt(II) one (IC_{50} = 66 μM) [87].

Trans-Pd(II) and *cis*-Pt(II) complexes of formulae, *trans*-$[Pd(L1)_2Cl_2]\cdot H_2O$, *trans*-$[Pd(L2)_2Cl_2]\cdot H_2O$, *trans*-$[Pd(L3)_2Cl_2]\cdot 2DMF$ *trans*-$[Pd(L4)_2Cl_2]\cdot 2DMF$ and *cis*-$[Pt(L1)_2Cl_2]\cdot H_2O$, *cis*-$[Pt(L2)_2Cl_2]\cdot 3H_2O$ (L1–L4 = cyclin-dependent kinase inhibitors derived from 6-benzylamino-9-isopropylpurine) have been synthesized. The molecular structures of L1, *trans*-$[Pd(L3)_2Cl_2]\cdot 2DMF$ and *trans*-$[Pd(L4)_2Cl_2]\cdot 2DMF$ were determined by single crystal X-ray analysis and the complexes tested *in vitro* due to their presumable anticancer activity against the human cancer cell lines: MCF7 (breast adenocarcinoma), K-562 (chronic myelogenous leukemia), G-361 (malignant melanoma), HOS (osteogenic sarcoma). The lowest values of IC_{50} were achieved for the complexes *trans*-$[Pd(L1)_2Cl_2]\cdot H_2O$ and *trans*-$[Pd(L2)_2Cl_2]\cdot H_2O$ against MCF 7 cell line with IC_{50} = 3 μM for both compounds [88].

New chiral mono- and dinuclear Pd(II) complexes with the ligand (*S*)-(−)-(1-phenylethylimino)benzyl phenyl ketone have been synthesized. In the case of mononuclear complex, *trans*-$Pd(L)Cl_2$, the ligand acts through the nitrogen donor atoms in a *trans*-geometry and in the dinuclear $[Pd(L)Cl_2]_2$, through the nitrogen and carbon atoms (X-ray). *In vitro* investigations have displayed growth inhibition against the cancer cell lines K-562 CML (leukemia), HCT-15 (colon cancer), MCF-7 (cancer breast), U-251 Glio (central nervous system) and PC-3 (prostate cancer). In all cases the IC_{50} values were higher than those of cisplatin, except in the case of U-251 Glio cell line, where only the dinuclear complex exhibits a good activity ($IC_{50} = 23.8 \pm 2 \times 10^{-3}$ M) [89].



Scheme 4. The ligand spermidine (sper).

Four new square planar metal complexes of Pd(II) and Pt(II) containing the ligand 9-aminoacridine (9AA) were synthesized. By reacting with phosphine or pyridine, the Cl bridges broke and compounds with general formulae [Pd(9AA)(L)Cl] (where $L = PPh_3$ or py) were formed. Both Pd(II) and Pt(II) compounds were active in the modification of both the secondary and tertiary DNA structures. AFM images showed noticeable modifications of the morphology of the plasmid pBR322 DNA by the compounds probably due to the intercalation of the complexes between base pairs of the DNA molecule. Moreover, the complex $[Pd(9AA)(\mu\text{-}Cl)]_2$ showed significant antiproliferative activity against three different human tumor cell lines [90].

Novel Pt(II) and Pd(II) complexes of formulae $[PtCl_2(HL)]$, $[NH_2(CH_3)_2][PtCl_2(L)]$, $[PdCl_2(HL)]$, $[NH_2(CH_3)_2][PdCl_2(L)]$, and $[PdCl(CH_3CN)(L)]$, where HL = 4-(2-hydroxybenzoyl)-2-(pyridin-2-yl)-1*H*-pyrazol-3-ol, have been synthesized. The solid-state structures of complexes $[NH_2(CH_3)_2][PtCl_2(L1)]$ and $[PdCl(CH_3CN)(L1)]$ showing square-planar coordination geometry around Pt(II) and Pd(II) ions (X-ray). Preliminary results on the *in vitro* cytotoxic activity against HL-60 and NALM-6 leukemia cell lines of the complex $[PdCl_2(HL)]$, revealed that the complex was active with IC_{50} values in the micromolar concentration range (HL-60 IC_{50} = 7.0 μM and NALM-6 IC_{50} = 8.3 μM) [91].

New Pd(II) complexes of chloroquine, *N*′-(7-chloroquinolin-4-yl)-*N*,*N*-diethyl-pentane-1,4-diamine (CQ), and clotrimazole, 1-[(2-chlorophenyl)-diphenyl-methyl] imidazole (CTZ), have been evaluated against four tumor cell lines (PANC-1, human pancreatic carcinoma; SKBR-3, human breast carcinoma; MDA-MB231, human breast adenocarcinoma and HT-29, human colon adenocarcinoma) *in vitro*. Their cytotoxicity was compared with that of the original ligands. Coordination of Pd(II) to CTZ led to an increase in the IC_{50} from 39 to 159 μM, however a three-fold reduction in the IC_{50} of CQ was observed on coordination to the metal (from 158 to 49 μM) when tested against the MDA-MB231 cell line [92]. The IC_{50} values against cancerous cells lines caused by Pd(II) compounds with amine as ligands, reported in Ref. [7] and in this work are included in Table 2.

4. Concluding remarks

Das and Livingstone [4] had suggested that S,N-chelate complexes of Pd(II) were expected to exhibit anti-tumor and anti-microbial activities, despite the non-activity and high toxicity of its complexes with mono-dentate ligands. These properties were explained by the faster aquation and ligand exchange reaction that the Pd(II) complexes undergo, compared to those with Pt(II) (10^5 time faster). This prevent the Pd(II) complexes to reach their pharmacological targets (DNA) like the corresponding Pt(II) complexes do and thereby to exhibit anti-tumor activity, since they can react with many other biological molecules of the body, thus exhibiting high toxicity. The S,N chelates however cannot hydrolyse or aquate early and constitute a class of new potent anti-tumor and anti-microbial agents. Their anti-tumor and anti-microbial activities are enhanced whenever the ligands used possess such properties in their own right or their lipophilicity allows an earlier transfer through cell membranes of the complexes. Many of the

inert Pd(II) chelates reported here, showed very promising results both as anti-viral, -fungal-microbial and anti-tumor agents. All relevant results are summarized in Tables 1 and 2 and comparisons, especially with cisplatin, can thus be made. This review aims to encourage further research in the field, in order to discover and establish new Pd(II) complexes, to be used as anti-tumor and anti-microbial agents.

References

[1] J.L. Butour, S. Wimmer, F. Wimmer, P. Castan, Chem. Biol. Inter. 104 (1997) 165.
[2] N.N. Stone, P.G. Stock, Eur. Urol. 41 (2002) 427.
[3] L. Potters, Y. Cao, E. Calugaru, T. Torre, P. Fearn, X.H. Wang, Int. J. Radiat. Oncol. Biol. Phys. 50 (2001) 605.
[4] M. Das, S.E. Livingstone, Br. J. Cancer 37 (1978) 466.
[5] E. Bermejo, R. Carballa, A. Castineiras, R. Dominguez, A.E. Liberta, C. Maichelle-Mössmer, M.M. Salberg, D.X. West, Eur. J. Inorg. Chem. (1999) 965.
[6] A.G. Quiroga, J.M. Perez, I. Lopez-Solera, J.R. Masaguer, A. Luque, P. Roman, A. Edwaeds, C. Alonso, C. Navarro-Ranninger, J. Med. Chem. 41 (1998) 1399.
[7] A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis, in: M. Gielen, E.R.T. Tiekink (Eds.), Metals in Medicine, Palladium (Pd), in Metallotherapeutic Drugs and Metal-based Diagnostic Agents: The Use of Metals in Medicine, John Wiley & Sons, Ltd., 2005, p. 399 (Chapter 21).
[8] P. Genova, T. Varadinova, A.I. Matesanz, D. Marinova, P. Souza, Toxicol. Appl. Pharmacol. 197 (2004) 107.
[9] I. Kizilcikli, Y.D. Kurt, B. Akkurt, A.Y. Genel, S. Birteksoz, G. Otuk, B. Ulkuseven, Fol. Microbiol. 52 (2007) 15.
[10] D. Kovala-Demertzi, T. Varadinova, P. Genova, P. Souza, M.A. Demertzis, Bioinorg. Chem. Appl. (2007), ID 56165.
[11] K. Husain, M. Abid, A. Azam, Eur. J. Med. Chem. 42 (2007) 1308.
[12] A.K. Mishra, N.K. Kaushik, Eur. J. Med. Chem. 42 (2007) 1239.
[13] A.K. Mishra, S.B. Mishra, N. Manav, N.K. Kaushik, J. Coord. Chem. 60 (2007) 1923.
[14] A.K. Mishra, S.B. Mishra, N.K. Kaushik, J. Coord. Chem. 60 (2007) 1691.
[15] N.M. Aghatabay, M. Somer, M. Senel, B. Dulger, F. Gucin, Eur. J. Med. Chem. 42 (2007) 1069.
[16] F. Shaheen, A. Badshah, M. Gielen, M. Dusek, K. Fejfarova, D. de Vos, B. Mirza, J. Organanomet. Chem. 692 (2007) 3019.
[17] W. Guerra, E. de Andrade Azevedo, A.R. de Souza Monteiro, M. Bucciarelli-Rodriguez, E. Chartone-Souza, A.M. Amaral Nascimento, A.P. Soares Fontes, L. Le Moyec, E.C. Pereira-Maia, J. Inorg. Biochem. 99 (2005) 2348.
[18] T.A. Bourque, M.E. Nelles, T.J. Gullon, C.N. Garon, M.K. Ringer, L.J. Leger, J.W. Mason, S.L. Wheaton, F.J. Baerlocher, C.M. Vogels, A. Decken, S.A. Westcott, Can. J. Chem. 83 (2005) 1063.
[19] M.A. Ali, A.H. Mirza, R.J. Butcher, M.T.H. Tarafder, T.B. Keat, A.M. Ali, J. Inorg. Biochem. 92 (2002) 141.
[20] R.V. Singh, N. Fahmi, M.K. Biyala, J. Iranian Chem. Soc. 2 (2005) 40.
[21] V. Radulovic, A. Bacchi, G. Pelizzi, D. Sladic, I. Brceski, K. Andjelkovic, Monatsh. Chem. 137 (2006) 681.
[22] R.R. Coombs, M.K. Ringer, J.M. Blacquiere, J.C. Smith, J. Scott Neilsen, Y.-S. Uh, J. Bryson Gilbert, L.J. Leger, H. Zhang, A.M. Irving, S.L. Wheaton, C.M. Vogels, S.A. Westcott, A. Decken, F.J. Baerlocher, Transition Met. Chem. 30 (2005) 411.
[23] H. Zhang, D.W. Norman, T.M. Wentzell, A.M. Irving, J.P. Edwards, S.L. Wheaton, C.M. Vogels, S.A. Westcott, F.J. Baerlocher, A. Decken, Transition Met. Chem. 30 (2005) 63.
[24] H. Zhang, J.E. Enman, M.L. Conrad, M.J. Manning, C.S. Turner, S.L. Wheaton, C.M. Vogels, S.A. Westcott, A. Decken, F.J. Baerlocher, Transition Met. Chem. 31 (2006) 13.
[25] N.M. Agh-Atabay, B. Dulger, F. Gucin, Eur. J. Med. Chem. 40 (2005) 1096.
[26] T.M. Hunter, S.J. Paisey, H. Park, L. Cleghorn, A. Parkin, S. Parsons, P.J. Sadler, J. Inorg. Biochem. 98 (2004) 713.
[27] A. Visnjevac, L. Tusjek-Bozjic, M. Majeric-Elenkov, Z. Hamersjak, H. Kooijman, E. De Clercq, B. Kojic-Prodic, Polyhedron 21 (2002) 2567.
[28] J. Chakraborty, H. Mayer-Figge, W.S. Sheldrick, P. Banerjee, Polyhedron 25 (2006) 3138.
[29] N. Bharti, Shailendra, S. Sharma, F. Naqvi, A. Azam, Bioorg. Med. Chem. 11 (2003) 2923.
[30] Shailendra, N. Bharti, F. Naqvi, A. Azam, Bioorg. Med. Chem. Lett. 13 (2003) 689.
[31] D. Kovala-Demertzi, M.A. Demertzis, J.R. Miller, C. Papadopoulou, C. Dodorou, G. Filousis, J. Inorg. Biochem. 86 (2001) 555.
[32] D. Kovala-Demertzi, M.A. Demertzis, E. Filiou, A.A. Pantazani, P.N. Yadar, J.R. Miller, Y. Zheug, D.A. Kyriakidis, Biometals 16 (2003) 411.
[33] D. Harton, O. Varela, Carbohyd. Res. 328 (2000) 425.
[34] T. Varadinova, D. Kovala-Demertzi, M. Rupelieva, M.A. Demertzis, P. Genova, Acta Virol. 45 (2001) 87.
[35] Shailendra, N. Bharti, F. Naqvi, A. Azam, Helv. Chim. Acta 85 (2002) 2713.
[36] R. Singh, K. Sharma, N. Fahmi, Transition Met. Chem. 24 (1999) 562.
[37] N. Fahmi, C. Saxena, R.V. Singh, Bull. Chem. Soc. Jpn. 69 (1996) 963.
[38] F. Hueso-Urena, M. Moreno-Carretero, J.M. Salas-Peregrin, G.A. de Cienfuegos-Lopez, Transition Met. Chem. 20 (1995) 262.
[39] B. Khan, J. Bhatt, K. Najmuddin, S. Shamsuddin, K. Annapoorna, J. Inorg. Biochem. 44 (1991) 55.
[40] N. Bharti, Shailendra, S.J. Coles, M.B. Hursthouse, T.A. Mayer, M.T. Gonzalez, D.E. Cruz-Vega, B.D. Mata-Cardemas, F. Naqvi, M.R. Maurya, A. Azam, Helv. Chim. Acta 85 (2002) 2704.
[41] A. Garoufis, K. Karidi, N. Hadjiliadis, S. Kasselouri, J. Kobe, J. Balzarini, E. De Clercq, Met.-Based Drugs 8 (2001) 57.
[42] J.R. Anacona, E. Bastardo, Transition Met. Chem. 24 (1999) 478.
[43] L. Mishra, A. Jha, A.K. Yadaw, Transition Met. Chem. 22 (1997) 406.
[44] N. Bharti, M.R. Manrya, F. Naqvi, B. Alox, B. Sudha, A. Amin, Eur. J. Med. Chem. 35 (2000) 481.
[45] K. Sharma, N. Fahmi, R. Singh, Appl. Organomet. Chem. 15 (2001) 221.
[46] H. Koksal, M. Dolaz, M. Tumer, S. Serin, Synth. React. Inorg. Met.-Org. Chem. 31 (2001) 1141.
[47] A.P. Rebolledo, M. Vieites, D. Gambino, O.E. Piro, E.E. Castellano, C.L. Zani, E.M. Souza-Fagundes, L.R. Teixeira, A.A. Batista, H. Beraldo, J. Inorg. Biochem. 99 (2005) 698.
[48] Z. Afrasiabi, E. Sinn, J.N. Chen, Y.F. Ma, A.L. Rheingold, L.N. Zakharov, N. Rath, S. Padhye, Inorg. Chim. Acta 357 (2004) 271.
[49] A.I. Matesanz, P. Souza, J. Inorg. Biochem. 101 (2007) 1354.
[50] S. Halder, S.M. Peng, G.H. Lee, T. Chatterjee, A. Mukherjee, S. Dutta, U. Sanyal, S. Bhattacharya, New J. Chem. 32 (2008) 105.
[51] A.G. Quiroga, J.M. Perez, E.I. Montero, D.X. Westm, C. Alonso, C. Navarro-Ranninger, J. Inorg. Biochem. 75 (1999) 293.
[52] A.G. Quiroga, J.M. Perez, I. Lopez-Solera, E.I. Montero, J.R. Masaguer, C. Alonso, C. Navarro-Ranninger, J. Inorg. Biochem. 70 (1998) 117.
[53] A.G. Quiroga, J.M. Perez, I. Lopez-Solera, E.I. Montero, J.R. Masaguer, C. Alonso, C. Navarro-Ranninger, J. Inorg. Biochem. 69 (1998) 275.
[54] A. Trevisan, C. Marzano, P. Cristofori, M.B. Venturini, L. Giovagnini, D. Fregona, Arch. Toxicol. 76 (2002) 262.
[55] G. Faraglia, D. Fregona, S. Sitran, L. Giovagnini, C. Marzano, F. Baccichetti, U. Casellato, R. Graziani, J. Inorg. Biochem. 83 (2001) 31.
[56] D. Fregona, L. Givagnini, L. Ronconi, C. Marzano, A. Trevisan, S. Sitran, B. Biondi, F. Bordin, J. Inorg. Biochem. 93 (2003) 181.
[57] A.I. Matesanz, J.M. Perez, P. Navarro, J.M. Moreno, E. Colacio, P. Souza, J. Inorg. Biochem. 76 (1999) 29.
[58] W. Friebolin, G. Schilling, M. Zoller, E. Amtmann, J. Med. Chem. 48 (2005) 7925.
[59] N.I. Dodoff, D. Kovala-Demertzi, M. Kubiak, J. Kuduk-Jaworska, A. Kochel, G.A. Gorneva, Z. Naturforsch. B: Chem. Sci. 61 (2006) 1110.
[60] L. Giovagnini, C. Marzano, F. Bettio, D. Fregona, J. Inorg. Biochem. 99 (2005) 2139.
[61] G. Faraglia, D. Fregona, S. Sitran, L. Giovagnini, C. Marzano, F. Baccichetti, U. Cesellato, R. Graziani, J. Inorg. Biochem. 83 (2001) 31.
[62] V. Alverdi, L. Giovagnini, C. Marzano, R. Seraglia, F. Bettio, S. Sitran, R. Graziani, D. Fregona, J. Inorg. Biochem. 98 (2004) 1117.
[63] L. Giovagnini, L. Ronconi, D. Aldinucci, D. Lorenzon, S. Sitran, D. Fregona, J. Med. Chem. 48 (2005) 1588.
[64] W. Lakomska, L. Pazderski, J. Sitkowski, L. Kozerski, M. Pelczynska, A. Nasulewicz, A. Opolski, E. Szlyk, J. Mol. Struct. 707 (2004) 241.
[65] F. Shaheen, A. Badshah, M. Gielen, C. Gieck, D. de Vos, Appl. Organomet. Chem. 21 (2007) 633.
[66] F. Shaheen, A. Badashah, M. Gielen, L. Marchio, D. de Vos, M.K. Khosa, Appl. Organomet. Chem. 21 (2007) 626.
[67] R. Mital, N. Jain, T.S. Srivastava, Inorg. Chim. Acta 166 (1989) 135.
[68] L. Marcheselli, C. Preti, M. Tagliazucchi, V. Cherchi, L. Sindellari, A. Furlani, A. Papaioannou, Eur. J. Med. Chem. 28 (1993) 347.
[69] D. Pucci, V. Albertini, R. Bloise, A. Bellusci, A. Cataldi, C.V. Catapano, M. Ghedini, A. Crispini, J. Inorg. Biochem. 100 (2006) 1575.
[70] J. Ruiz, N. Cutillas, C. Vicente, M.D. Villa, G. Lopez, J. Lorenzo, F.X. Aviles, V. Moreno, D. Bautista, Inorg. Chem. 44 (2005) 7365.
[71] G.L. Edwards, D.S.C. Black, G.B. Deacon, L.P.G. Wakelin, Can. J. Chem. 83 (2005) 980.
[72] S. Ray, R. Mohan, J.K. Singh, M.K. Samantaray, M.M. Shaikh, D. Panda, P. Ghosh, J. Am. Chem. Soc. 129 (2007) 15042.
[73] F. Zamora, V.M. Gonzalez, J.M. Perez, J.R. Masaguer, C. Alonso, C. Navarro-Ranninger, Appl. Organometal. Chem. 11 (1997) 659.
[74] C. Navarro-Ranninger, I. Lopez-Solera, J.M. Perez, J.R. Masaguer, C. Alonso, Appl. Organometal. Chem. 7 (1993) 57.
[75] A.C.F. Caires, E.T. Almeida, A.E. Mauro, J.P. Hemerly, S.R. Valentini, Quim. Nova 22 (1999) 329.
[76] C. Navarro-Ranninger, I. Lopez-Solera, V.M. Gonzalez, J.M. Perez, A. Alvarez-Valdes, A. Martin, P.R. Raithby, J.R. Masaguer, C. Alonso, Inorg. Chem. 35 (1996) 5181.
[77] A.S. Soares, S.M. Fiuza, M.J. Goncalves, L.A.E.B. de Carvalho, M. Paula, M. Marques, A.M. Urbano, Lett. Drug Des. Discov. 4 (2007) 460.
[78] F. Huq, M. Farhad, A. Abdullah, P. Beale, M. Zhang, Asian J. Chem. 18 (2006) 1625.
[79] Y. Ma, C.S. Day, U. Bierbach, J. Inorg. Biochem. 99 (2005) 2013.
[80] H. Daghriri, F. Huq, P. Beale, J. Inorg. Biochem. 98 (2004) 1722.
[81] J. Kuduk-Jaworska, A. Puszko, M. Kubiak, M. Pelczynska, J. Inorg. Biochem. 98 (2004) 1447.
[82] I. Brudzinska, Y. Mikata, M. Obata, C. Ohtsuki, S. Yano, Bioorg. Med. Chem. Lett. 14 (2004) 2533.
[83] L. Tusek-Bozic, A. Furlani, V. Scarcia, E. De Clercq, J. Balzarini, J. Inorg. Biochem. 72 (1998) 201.

[84] M. Kruszewski, E. Bouzyk, T. Oldak, K. Samochocka, L. Fuks, W. Lewandowski, I. Fokt, W. Priebe, Terat. Carc. Mutag. S1 (2003) 1.
[85] H. Cheng, F. Huq, P. Beale, K. Fisher, Eur. J. Med. Chem. 41 (2006) 896.
[86] E.J. Gao, Y.G. Sun, Q.T. Liu, L.Y. Duan, J. Coord. Chem. 59 (2006) 1295.
[87] S.M. Fiuza, A.M. Amado, P.J. Oliveira, V.A. Sardao, L.A.E.B. de Carvalho, M.P.M. Marques, Lett. Drug Des. Discov. 3 (2006) 149.
[88] L. Szucova, Z. Travnicek, M. Zatloukal, I. Popa, Bioorg. Med. Chem. 14 (2006) 479.
[89] M.A. Pelaez, T. Ramiirez, M. Martiinez, P. Sharma, C. Alvarez, R. Gutierrez, Zeit. Anorg. Allgm. Chem. 630 (2004) 1489.
[90] X. Riera, V. Moreno, C.J. Ciudad, V. Noe, M. Font-Bardia, X. Solans, Bioinorg. Chem. Appl. (2007), ID 98732.
[91] E. Budzisz, M. Malecka, B.K. Keppler, V.B. Arion, G. Andrijewski, U. Krajewska, M. Rozalski, Eur. J. Inorg. Chem. (2007) 3728.
[92] M. Navarro, N.P. Pena, I. Colmenares, T. González, M. Arsenak, P. Taylor, J. Inorg. Biochem. 100 (2006) 152.
[93] C. Navarro-Ranninger, F. Zamora, I. López-Solera, J.R. Masaguer, J.M. Pérez, C. Alonso, S. Martínez-Carrara, J. Inorg. Biochem. 46 (1992) 267.
[94] A.S. Abu-Surrah, T.A.K. Al-Allaf, L.J. Rashan, M. Klinga, M. Leskela, Eur. J. Med. Chem. 37 (2002) 919.
[95] H. Mansuri-Torshizi, R. Mital, T.S. Srivastava, H. Parekh, M.P. Chitnis, J. Inorg. Biochem. 44 (1991) 239.
[96] L. Tusek-Bozic, I. Matijasic, G. Bocelli, G. Calestani, A. Furlani, V. Scarcia, A. Papaioannou, J. Chem. Soc. Dalton Trans. (1991) 195.
[97] G.H. Zhao, H.W. Sun, H.K. Lin, S.R. Zhu, X.C. Su, Y.T. Chen, J. Inorg. Biochem. 72 (1998) 173.
[98] G.H. Zhao, H.K. Lin, P. Yu, H.W. Sun, S.R. Zhu, X.C. Su, Y.T. Chen, J. Inorg. Biochem. 73 (1999) 145.
[99] E.J. Gao, Q.T. Liu, Acta Chim. Sin. 60 (2002) 674.
[100] T.A.K. Al-Allaf, L.J. Rashan, Eur. J. Inorg. Chem. 33 (1998) 820.
[101] Z. Travnicek, M. Malon, M. Zatloukal, K. Dolezal, M. Strnad, J. Marek, J. Inorg. Biochem. 94 (2003) 307.
[102] M.M.L. Fiallo, E. Deydier, M. Bracci, A. Garnier-Suillerot, K. Halvorsen, J. Med. Chem. 46 (2003) 1683.
[103] N. Nikolis, C. Methenitis, G. Pneumatikakis, M.M.L. Fiallo, J. Inorg. Biochem. 89 (2002) 131.
[104] H. Mansuritorshizi, T.S. Srivastava, H.K. Parekh, M.P. Chitnis, J. Inorg. Biochem. 45 (1992) 135.