Available online at www.sciencedirect.com
ScienceDirect
Coordination Chemistry Reviews 252 (2008) 1328–1345
COORDINATION CHEMISTRY REVIEWS
www.elsevier.com/locate/ccr

Review

Trans geometry in platinum antitumor complexes

Urszula Kalinowska-Lis [a,*], Justyn Ochocki [a], Ksenia Matlawska-Wasowska [b]

[a] *Department of Bioinorganic Chemistry, Medical University, Muszyńskiego 1, 90-151 Łódź, Poland*
[b] *Laboratory of Cytogenetics, Department of General Genetics, Molecular Biology and Plant Biotechnology, University of Łódź, Banacha 12/16, 90-237 Łódź, Poland*

Received 24 March 2007; accepted 26 July 2007
Available online 2 August 2007

Contents

1. Introduction 1329
2. *trans*-Pt(II)Cl_2 complexes with iminoether ligands 1329
   2.1. *trans*-[$PtCl_2${HN=C(OMe)Me}$_2$] complexes 1330
   2.2. *trans*-[$PtCl_2${HN=C(OEt)Me}$_2$] complexes 1331
   2.3. *trans*-[$PtCl_2${HN=C(OMe)Me}(NH_3)] complexes 1331
   2.4. *trans*-Pt(II) complexes with cyclic ligands mimicking iminoethers 1332
   2.5. *trans*-Pt(II) complexes with acetonimine(s) 1332
3. *trans*-Planar amine (TPA) platinum(II) complexes 1332
4. *trans*-Carboxylato platinum(II) complexes (with $[N_2O_2]$ ligand donor set) 1333
   4.1. *trans*-Pt(II)$(OAc)_2$ complexes with planar amines 1334
   4.2. Asymmetric *trans*-Pt(II)$(OAc)_2$ complexes with azole and isopropylamnie 1335
   4.3. Asymmetric *trans*-Pt(II) carboxylato complexes with azole and ammine ligands 1335
5. *trans*-Pt(II)Cl_2 complexes with nonplanar heterocyclic ligands 1335
   5.1. *trans*-Platinum(II) complexes with piperazine 1335
   5.2. *trans*-Platinum(II) complexes with piperidine (pip) and piperazine (pz) 1336
   5.3. *trans*-Platinum(II) complexes with methylpiperidine (Me-pip) isomeric ligands 1337
6. *trans*-Pt(II)Cl_2 complexes with aliphatic amines and/or heterocyclic ligands 1337
   6.1. *trans*-Platinum(II) complexes with aliphatic amines 1337
   6.2. *trans*-Platinum(II) complexes with (hydroxymethyl)pyridine (py-MeOH) isomers 1338
7. *trans*-Platinum(IV) complexes 1339
   7.1. *trans*-Platinum(IV) (and *trans*-platinum(II)) complex with aliphatic amines 1339
   7.2. *trans*-Platinum(IV) (and *trans*-platinum(II)) complex with (4-hydroxymethyl)-pyridine 1340
8. Polynuclear platinum complexes 1340
9. *trans*-Platinum complexes with various types of ligands 1341
   9.1. *trans*-Platinum complexes containing DMSO 1341
   9.2. *trans*-Platinum complexes containing various phosphoric groups 1341
   9.3. *trans*-Platinum complex with oxime ligand 1342
   9.4. Other *trans*-platinum complexes 1342
10. Methods of synthesis of *trans*-platinum complexes 1342
   10.1. Synthesis of the symmetric *trans*-amine complexes *trans*-[PtL_2X_2] 1342
   10.2. Isomerization 1342
   10.3. Synthesis of the asymmetric *trans*-platinum(II) complexes 1343
   10.4. Synthesis of *trans*-platinum(IV) complexes 1343
11. Conclusion 1344
Acknowledgments 1344
References 1344

* Corresponding author. Tel.: +48 426779216; fax: +48 426788398.
E-mail address: uk@ich.pharm.am.lodz.pl (U. Kalinowska-Lis).

0010-8545/$ – see front matter
doi:10.1016/j.ccr.2007.07.015

Abstract

In this paper we summarize the work on the development of *trans*-platinum complexes as antitumor agents during the last 15 years. We review the structures and chemical properties of many 'transplatin' analogues, symmetric and asymmetric, containing wide range of ligands, e.g.: heterocyclic planar or nonplanar amines, aliphatic amines, iminoethers and phosphoric ligands, as well as polynuclear platinum complexes. We emphasize differences in the cytotoxic activity between the various *trans*-platinum structures in comparison to cisplatin and transplatin in cisplatin-sensitive as well as cisplatin-resistant cell lines. Whenever available, we also report *in vivo* antitumor activity. In addition, for some *trans*-platinum complexes we present interaction with DNA, cell uptake, level of cellular DNA platination and the ability of the complexes to induce apoptosis. Finally, we describe the general methods of synthesis of *trans*-platinum(II) and (IV) complexes.

Keywords: *trans*-Platinum; Cytotoxicity; Antitumor agents; Apoptosis induction; Synthesis

1. Introduction

The discovery of antiproliferative activity of cisplatin (*cis*-DDP) (Fig. 1) by Rosenberg et al. [1] in 1965 contributed to the development of cancer chemotherapy. Today cisplatin is a widely used drug in chemotherapy, but its applicability is limited to a narrow range of tumors. Some tumors have acquired resistance to cisplatin, while others develop resistance after the initial treatment. In addition, this drug causes many severe side effects, including: nephrotoxicity, neurotoxicity, myelotoxicity, hematological toxicity and gastrointestinal reactions [2–4]. In view of these limitations, research has been extended to other platinum complexes. Many hundreds of *cis*-DDP analogues have been tested during the last 20 years. Unfortunately, the vast majority of these compounds were rejected in preclinical or early clinical stages of testing. Only two of the tested platinum compounds, carboplatin and oxaliplatin (Fig. 1), were approved as anticancer drugs worldwide [5–8].

For decades researchers marginalized the platinum complexes of *trans* geometry, because transplatin (*trans*-DDP) (Fig. 1) was recognized to be inactive *in vivo* and significantly less cytotoxic *in vitro* than cisplatin. These properties have been explained by: weaker inhibition of DNA replication and transcription by transplatin than by cisplatin adducts; more rapid repair of transplatin adducts, consistent with the inability of high-mobility group protein HMG1 to recognize transplatin adducts; inability of transplatin to produce 1,2-intrastrand cross-links, which are the most frequent adducts formed by cisplatin. It was shown that transplatin induces monoadducts which may be repaired or undergo further rearrangements forming DNA–DNA cross-links as well as DNA–protein cross-links. Transplatin also forms a lot of interstrand cross-links between cytosine and guanine of double-stranded DNA but it was proven that formation of interstrand cross-links by this compound does not change stability and structure of DNA markedly. Moreover, transplatin is kinetically more reactive than cisplatin, which may contribute to its deactivation [9–15]. Interestingly, the latest results indicate that transplatin can be as cytotoxic as cisplatin after irradiation by UVA light, which activates chloride ligands and in consequence enhances formation of interstrand cross-links and DNA–protein cross-links [16,17].

In the 1990s, the apathy toward *trans*-platinum complexes ended. Many *trans*-platinum complexes were discovered with significant *in vitro* antitumor activity against different tumor cells, including ones resistant to *cis*-DDP. Among these complexes are transplatin analogues with planar amines (e.g. pyridine, quinoline, thiazole, imidazole), iminoethers, aliphatic amines (isopropanamine, *n*-butanamine, dimethylamine), nonplanar heterocyclic ligands (pipreridine, piperazine) and polynuclear complexes, all of which are presented in some detail in this review. Some of these platinum complexes have given positive responses under *in vivo* conditions.

2. *trans*-Pt(II)Cl_2 complexes with iminoether ligands

Replacement of one or two non-leaving ammine ligands in transplatin by iminoether group leads to a significant increase in the cytotoxic activity of the *trans* compounds [18–20].

Iminoether ligands are both aliphatic and aromatic amines. As aliphatic amines they have one hydrogen atom bound with the nitrogen atom suitable for a hydrogen–bond formation. As aromatic amines they have a planar geometry and therefore they introduce steric hindrance to ligand exchange reactions. Another feature of iminoether is the possibility of geometrical isomerism within the ligand moiety, around the C=N double bond, to form *E* or *Z* configurations [18,21].

The cellular accumulation of *trans*-platinum complexes with iminoethers is significantly enhanced with respect to that of cisplatin in A2780 and A278cisR ovarian cancer cells. This peculiarity may be explained by the increased lipophilicity of the

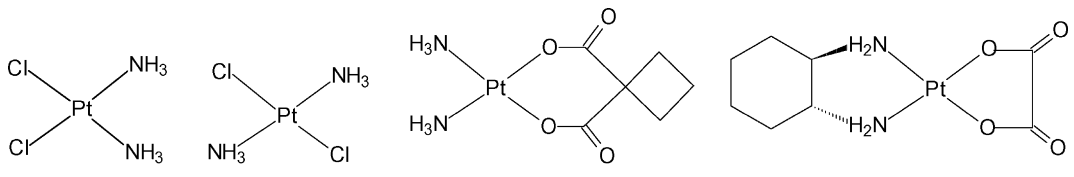


Fig. 1. Structures of: (**1**) cisplatin; (**2**) transplatin; (**3**) carboplatin; (**4**) oxaliplatin.

iminoether compounds [19,22]. The greater intracellular platinum accumulation follows the increased degree of platination of cellular DNA. When compared to cisplatin and transplatin, the *trans* iminoether complexes show much lower interstrand cross-linking DNA efficiency both in cellular and isolated DNA. On the other, hand they produce more monofunctional adducts at guanine residues that are much more resistant to destabilization by sulfur-donor ligands than adducts formed by transplatin [23,24].

cis counterparts of *trans* iminoether complexes are less active both *in vitro* and *in vivo* and lack cross-resistance with cisplatin *in vivo* [18,19].

2.1. *trans*-[$PtCl_2${HN=C(OMe)Me}$_2$] complexes

Three different *trans* isomers (*ZZ*, *EZ* and *EE*) of *trans*-[$PtCl_2${HN=C(OMe)Me}$_2$] were prepared. They were tested for *in vitro* cytotoxicity and *in vivo* antitumor activity against P388 leukemia. The *trans-EE* complex, *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] (Fig. 2: comp. **5**) showed the greatest *in vitro* cytotoxicity (IC_{50} = 2.2 μM, when the activity of cisplatin was 2.05 μM). The results for *trans-EE* compound obtained with P388 and P388cisR leukemia-bearing mice indicated significant antitumor activity (Table 1). Importantly, *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] was better tolerated by tumor-bearing mice than cisplatin. At the end of the treatment a body weight loss was lower than that induced by *cis*-DDP [18].

trans-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] reacts with DNA to form mainly stable monofunctional adducts at guanine residues even after long incubation times. Monoadducts formed by this complex exhibit a reduced reactivity of the second leaving group [25]. The examination of oligodeoxyribonucleotide duplexes containing a single, site-specific and monofunctional adducts proved that major monofunctional adducts of *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] locally distort DNA, bending the

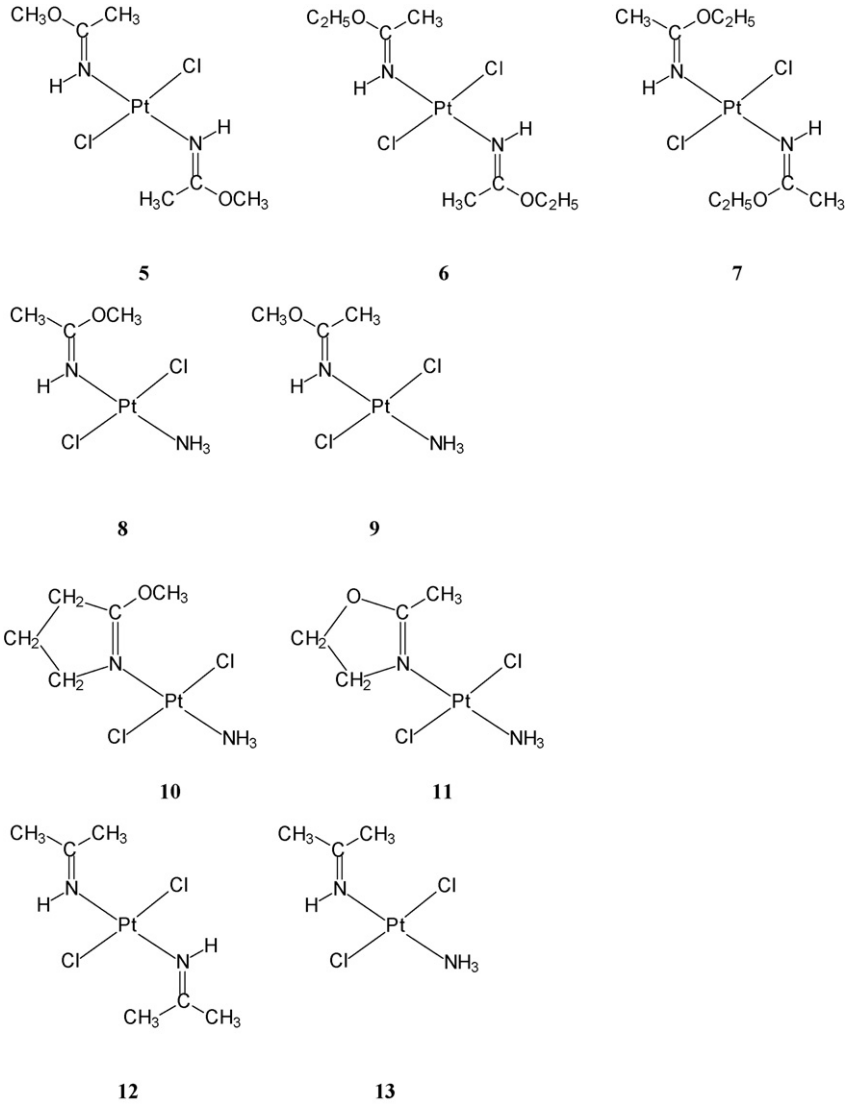


Fig. 2. Structures of *trans*-Pt(II) iminoether complexes: (**5**) *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$]; (**6**) *trans*-[$PtCl_2${*E*–HN=C(OEt)Me}$_2$]; (**7**) *trans*-[$PtCl_2${*Z*–HN=C(OEt)Me}$_2$]; (**8**) *trans*-[$PtCl_2${*Z*–HN=C(OMe)Me}(NH_3)]; (**9**) *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}(NH_3)]; (**10**) 'cyclic ligand comp. **1**'; (**11**) 'cyclic ligand comp. **2**'; (**12**) *trans*-[$PtCl_2${HN=C(Me)$_2$}$_2$]; (**13**) *trans*-[$PtCl_2${HN=C(Me)$_2$}(NH_3)].

Table 1
In vivo antitumor activity of *trans*-Pt(II) iminoether complexes against murine P388 leukemia

	Reference	Dose (mg/kg qd 1–7)	%T/C[a]		Body weight variation[b] (%)
			P388	P338R	
trans-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] (**5**)	[24]	8	170	133	–
		12	196		–
trans-[$PtCl_2${*E*–HN=C(OEt)Me}$_2$] (**6**)	[19]	4	151		+5
		8	156		+2
		12	167		0
trans-[$PtCl_2${*Z*–HN=C(OEt)Me}$_2$] (**7**)	[19]	4	154		+5
		8	177		+5
		12	200		0
trans-[$PtCl_2${*E*–HN=C(OMe)Me}(NH_3)] (**9**)	[20]	5	121		0
		10	128		−1.8
		15	152		−3.1
		20	132		−6.2
trans-[$PtCl_2${*Z*–HN=C(OMe)Me}(NH_3)] (**8**)	[20]	5	140		−1.5
		10	165		−2.4
		15	173		−5
		20	190		−5
cis-DDP	[24]	0.6	203	90	−5
trans-DDP	[24]	58	105	107	

[a] %T/C—median survival time (×100) of treated mice versus untreated control mice. (%T/C > 125 is considered active and %T/C > 150 is considered significantly active).
[b] Body weight variation at the end of the treatment with respect to day 0.

DNA's axis by 21° toward the minor groove. These adducts are not recognized by HMGB1 proteins and are not readily removed from DNA by nucleotide excision repair (NER). Monoadducts readily react with different proteins generating DNA–protein cross-links. In consequence, DNA–proteins cross-links are more stable than monoadducts and exhibit the ability to terminate DNA polymerization by DNA polymerases *in vitro*. Moreover, DNA–protein cross-links produced by *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] are not recognized by NER. In summary, activation of the *trans* geometry by platinum(II) complexes containing two iminoether ligands is associated with efficiency to form specific DNA–protein cross-links which are probably responsible for antitumor properties of *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] [26].

Studies performed on P388 murine leukemia and A2780 human ovarian cells revealed that *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}$_2$] effectively induces apoptosis and influences cell-cycle modifications (S-phase accumulation followed by G2M accumulation) [21,26].

2.2. *trans*-[$PtCl_2${HN=C(OEt)Me}$_2$] complexes

Ethoxy analogues of the above described platinum complexes with *trans*-located iminoethers, *trans*-[$PtCl_2${*E*–HN=C(OEt)Me}$_2$] (**6**) and *trans*-[$PtCl_2${Z–HN=C(OEt)Me}$_2$] (**7**) (Fig. 2), were synthesized and characterized. Their in *vitro* tumor cell growth inhibitory activity was evaluated in comparison to that of cisplatin in a panel of human tumor cell lines, e.g.: ovary (A2780), colon (LoVo), lung (Calu-3) or breast (MDA, SKBR3) cancer. Isomer *E* exhibited *in vitro* cytotoxicity similar to that of cisplatin, whereas isomer *Z* showed a lower activity. Both isomers overcame cisplatin resistance of ovary cancer cell lines A2780cisR. Both isomers were also active *in vivo* against the murine P388 leukemia system, but isomer *Z* was slightly more active than isomer *E* (Table 1) [19].

2.3. *trans*-[$PtCl_2${HN=C(OMe)Me}(NH_3)] complexes

The next two active *trans*-Pt complexes containing only one iminoether group and one NH_3 group, *trans*-[$PtCl_2${*Z*–HN=C(OMe)Me}(NH_3)] (**8**) and *trans*-[$PtCl_2${*E*–HN=C(OMe)Me}(NH_3)] (**9**) (Fig. 2), were investigated by Leng and coworkers [20]. *In vitro* cytotoxicity of both isomers with *Z* and *E* configurations of the iminoethers was tested in a panel of ovary (A2780, SK-OV-3, OVCAR-8), lung (A549/ATCC, NCI-116, CALU), colon (KM12, LOVO, COLO 205, HCT-116) and breast (T-47D, MCF7, MDA) human tumor cell lines. The results showed a cytotoxic activity much higher than that of transplatin. The iminoether platinum complexes indicated the highest efficacy against ovarian and colon tumor cells, whereas lung cancer cells appeared to be more resistant. The *in vivo* assays on the complexes showed very promising results (%T/C > 125) (Table 1). It appears that the complex *Z* (Fig. 2: comp. **8**) is more active and less toxic than the complex *E* (Fig. 2: comp. **9**) in the murine P388 leukemia system and retains its efficacy against SK-OV-3 human cancer cell xenograft in nude mice.

The complex *Z* forms monoadducts with DNA which are transformed slowly into interstrand cross-links between complementary cytosine and guanine residues. These interstrand cross-links influence the flexibility of DNA double helix and are not recognized by HMGB1 proteins [20].

2.4. *trans*-Pt(II) complexes with cyclic ligands mimicking iminoethers

The *in vitro* growth inhibitory effect of two *trans*-platinum complexes with cyclic ligands mimicking iminoethers (Fig. 2: comp. **10** and **11**) was compared to the activity of transplatin and the previously mentioned *trans*-platinum complexes with 'classical' iminoethers (Section 2.1). Antitumor activity of the complexes with cyclic ligands was the highest among the tested complexes, in a panel of human tumor cells (ovary, colon, lung and breast) [27].

2.5. *trans*-Pt(II) complexes with acetonimine(s)

Boccarelli et al. synthesized a new group of complexes containing two acetonimines (*trans*-$[PtCl_2\{HN{=}C(Me)_2\}_2]$) (**12**) or one acetonimine and one ammine (*trans*-$[PtCl_2\{HN{=}C(Me)_2\}(NH_3)]$) (**13**) (Fig. 2). Substituting ammine group(s) of transplatin by acetonimine(s) dramatically increases the antitumor properties of platinum complexes. Both bisacetonimines complex and acetonimine/ammine complex show remarkable antitumor activity (with mean IC_{50} [μM] = 10.6 and 26.0, respectively; and 164.0 for transplatin) and circumvent the cisplatin resistance of ovarian cell lines (A2780cisR and 41McisR) [28].

3. *trans*-Planar amine (TPA) platinum(II) complexes

The complexes of the type *trans*-$[PtCl_2(L)(L')]$ (L = NH_3, L′ = pyridine, picoline, quinoline, isoquinoline or thiazole; L = L′ = pyridine, thiazole) (Fig. 3), containing a sterically demanding planar amine(s), exhibit increased cytotoxicity in comparison to the parent transplatin. Their cytotoxicity was tested against the panel of human ovarian carcinoma cell lines [29] as well as murine L1210 leukemia cells sensitive to *cis*-DDP and resistant to *cis*-DDP and the complex [Pt(*R*,*R*-dach)SO_4] (dach-1,2-aminocyclohexane) [30] (Table 2). The antitumor activity of these planar amine complexes was likely increased due to the use of sterically hindered ligands that reduce the rate of replacement of the chlorido

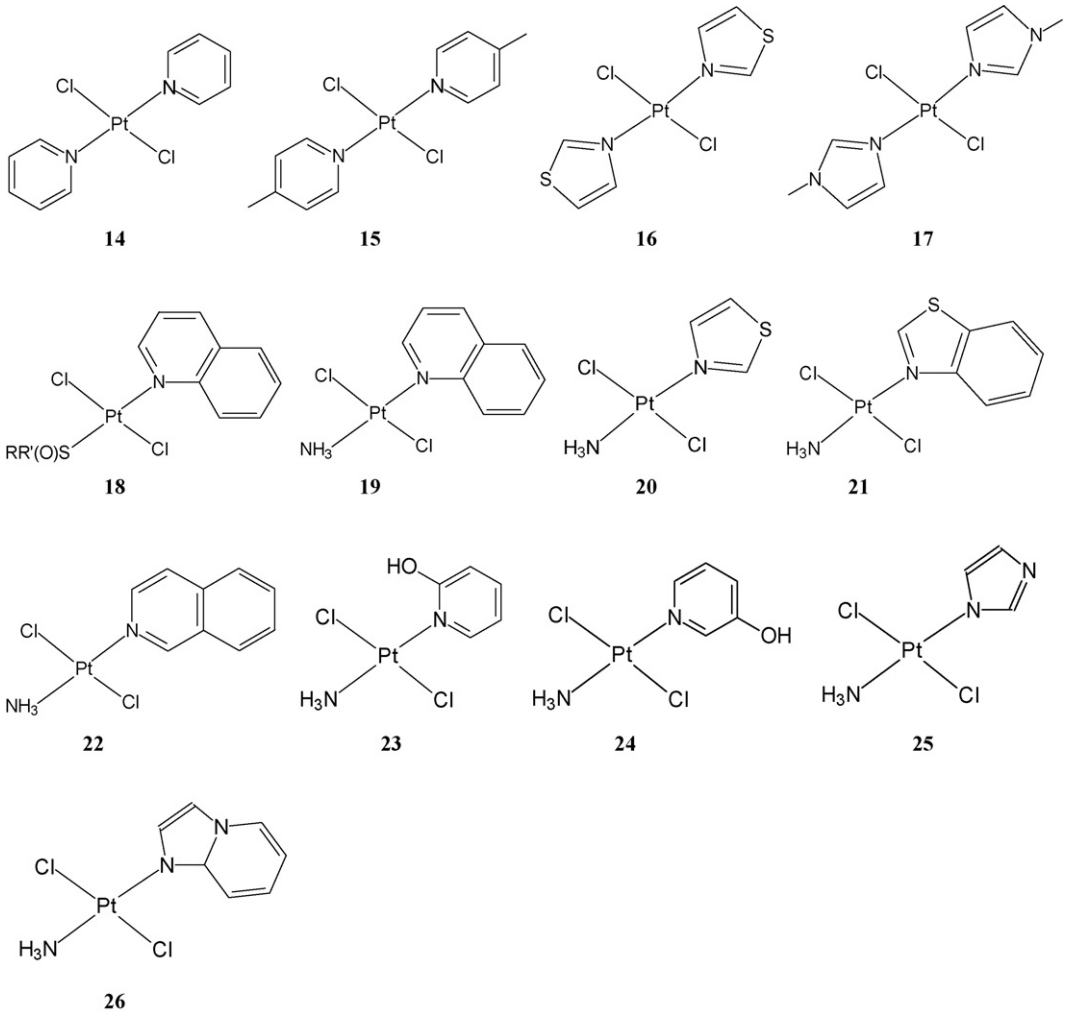


Fig. 3. Structures of TPA complexes: (**14**) *trans*-$[PtCl_2(py)_2]$; (**15**) *trans*-$[PtCl_2(4\text{-pic})_2]$; (**16**) *trans*-$[PtCl_2(Tz)_2]$; (**17**) *trans*-$[PtCl_2(N\text{-Me-im})_2]$; (**18**) *trans*-$[PtCl_2(quin)(RR'(O)S)]$ (R = Me, R′ = Me, Ph, Bz); (**19**) *trans*-$[PtCl_2(NH_3)(quin)]$; (**20**) *trans*-$[PtCl_2(NH_3)(Tz)]$ (ATZ); (**21**) *trans*-$[Pt(BTz)Cl_2(NH_3)]$; (**22**) *trans*-$[PtCl_2(iquin)(NH_3)]$; (**23**) *trans*-$[PtCl_2(NH_3)(2\text{-py-OH})]$; (**24**) *trans*-$[PtCl_2(NH_3)(3\text{-py-OH})]$; (**25**) *trans*-$[PtCl_2(im)(NH_3)]$; (**26**) *trans*-$[PtCl_2(im\text{-py})(NH_3)]$.

Table 2
Selected cytotoxic activity (IC_{50} [μM]) of *trans*-planar amine (TPA) platinum(II) complexes

	References	L1210	L1210cisR	L1210dachR	41M	41McisR	CH1	CH1cisR	HX/62	SKOV-3	PXN94
$[PtCl_2(py)_2]$ (**14**)	[29,30]	1.2	1.1 (0.92)[a]	2.26 (0.66)	2.2	2.0 (0.91)	1.6	1.7 (1.1)	4.5	5.9	7.7
$[PtCl_2(Tz)_2]$ (**16**)	[29,30]	1.6	7.4 (4.63)	5.96 (3.73)	2.2	1.6 (0.73)	1.3	1.4 (1.1)	4.1	6.2	9.6
$[PtCl_2(Me_2SO)(quin)]$ (**18**)	[29,30]	0.36	0.38 (1.06)	0.39 (1.08)	1.32	1.9 (1.4)	0.89	1.0 (1.1)	5.1	4.4	8.2
$[PtCl_2(MePhSO)(quin)]$ (**18′**)	[29,30]	3.5	2.4 (0.69)	1.33 (0.38)	2.1	2.1 (1.0)	2.2	1.6 (1.4)	6.1	4.5	9.5
$[PtCl_2(MeBzSO)(quin)]$ (**18″**)	[29,30]	0.67	0.99 (1.48)	0.90 (1.34)	2.0	1.8 (0.9)	1.3	1.5 (1.1)	4.1	4.1	10.4
$[PtCl_2(NH_3)(quin)]$ (**19**)	[30]	0.51	1.35 (2.65)	0.96 (1.88)							
$[PtCl_2(N\text{-}Me\text{-}imidazole)_2]$ (**17**)	[30]	6.00	5.45 (0.91)	5.34 (0.89)							
cis-DDP	[29,30]	0.33	9.2 (28)	1.81 (5.48)	0.23	1.4 (6.1)	0.1	0.67 (6.7)	12.6	4.4	3.0
trans-DDP	[29,30]	15.7	22.0 (1.40)	19.6 (1.25)	57	69 (1.2)	30	68.5 (2.3)	245	255	222
[Pt(R,R-dach)SO_4]	[30]	0.23	0.75 (3.26)	5.65 (25)							

[a] Resistance factor RF (IC_{50} resistant/IC_{50} sensitive).

ligands. These TPA complexes are usually non-cross-resistant to cisplatin (and [Pt(*R*,*R*-dach)SO_4]) and are characterized by remarkably low resistant factors (RF = IC_{50} resistant/IC_{50} sensitive) in both human and murine tumor cell lines [29,30].

trans-$[PtCl_2L_2]$ complexes, where L consists of planar amine: pyridine (py) (**14**) or 4-methylpyridine (4-pic) (**15**) (Fig. 3), show reasonable *in vitro* antitumor activity in L1210 leukemia cells. This activity is greater than that of their *cis* counterparts. But none of these complexes is active *in vivo* against P388 and L1210 leukemia [31].

Farrell et al. revealed that *trans*-$[PtCl_2(NH)_3$(thiazole)] complex (ATZ) (**20**) (Fig. 3) exhibits significant antiproliferative and cytotoxic effects against MCF-7 breast and A2780 ovarian human cancer cells. Interestingly, ATZ complex poorly induced apoptosis in these cells. The high level of apoptotic cells was visible only after incubation of MCF-7 cells with this complex. ATZ induced DNA strand breakage as well as DNA–protein cross-links more effectively in both A2780 and MCF-7 cells when *cis*-DDP [32].

DNA fragments containing the single, site-specific monofunctional adduct of *trans*-$[PtCl_2(NH)_3$(thiazole)] were analysed. The structural distortion induced in DNA by these monofunctional adduct was similar to that caused in DNA by the major 1,2-GG intrastrand CL of cisplatin. These monofunctional adducts are recognized by high-mobility group (HMG) and removed by nucleotide excision repair (NER) system, the same as in case of cisplatin [33].

Further studies performed by Marini et al. showed that *trans*-$[PtCl_2(NH)_3$(thiazole)] induces monoadducts and bifunctional intrastrand or interstrand cross-links in approximate equal amount. Moreover, 1,3-intrastrand cross-links of the *trans*-$[PtCl_2(NH)_3$(thiazole)] are not recognized by HMG-domain proteins and are not removed by NER [34].

trans-$[PtCl_2(NH_3)$(quinoline)] (**19**) (Fig. 3) forms monoadducts with DNA but a part of it undergoes rearrangement to bifunctional adducts. In addition, this complex generates more interstrand cross-links which are formed more readily in comparison to *trans*-DDP. The adducts of *trans*-$[PtCl_2(NH_3)$(quinoline)] influence termination RNA synthesis *in vitro* preferentially at guanine residues [35].

Evaluation of cytotoxicity of complexes of general formula *trans*-$[PtCl_2L(NH_3)]$, where L = quinoline (**19**), thiazole (**20**), benzothiazole (**21**), isoquinoline (**22**) (Fig. 3) against leukemia L1210 and L1210cisR cells was performed. The tested complexes exhibited a significant enhancement of cytotoxicity in L1210 cells in comparison to *trans*-DDP but not to *cis*-DDP. Importantly, these complexes were very toxic against resistant L1210cisR cell lines. The *trans*-$[PtCl_2(NH_3)$(quin)] (**19**) (Fig. 3) was selected as the most active compound of the tested group in both L1210 as well as L1210cisR cells [36].

trans-Planar amine platinum(II) complexes of the formula *trans*-$[PtCl_2L(NH_3)]$, where L stands for 2-hydroxypyridine (2-py-OH) (**23**), 3-hydroxypyridine (3-py-OH) (**24**), imidazole (im) (**25**) and imidazo(1,2-α)pyridine (im-py) (**26**) (Fig. 3), were synthesized and tested. The cytotoxicity of the complexes against the cell lines: A2780, A2780cisR, $A2780_{ZD0473}R$, NCI-H460 and Me 10538 was determined. It was found to be lower than that of cisplatin against all the tested cell lines except the complex *trans*-$[PtCl_2$(im-py)$(NH_3)]$ which was found to be two-fold more active than cisplatin against cisplatin-resistant ovary cell line A2780cisR [37].

4. *trans*-Carboxylato platinum(II) complexes (with $[N_2O_2]$ ligand donor set)

Complexes containing two halido anions (Cl^- or Br^-) as labile-leaving ligands are characterized by robust activity, but more stable ligands can also yield active compounds. The second generation platinum drugs (carboplatin, oxaliplatin, nedaplatin) consist of kinetically inert chelating dicarboxylato or glycolato ligands. As a result, these drugs cause fewer toxic side effects than platinum drugs possessing chlorido ligands [38]. Thus, the halidos on various *trans*-platinum complexes can be replaced efficiently by carboxylato ligands. Moreover, it was recently proved that *trans*-diaminedicarboxylato complexes have increased aqueous solubility compared to their dichlorido counterparts. The presence of the carboxylato ligands in the complexes makes them not only more water soluble, but also enhances stability toward hydrolysis, which is necessary to achieve more desirable behavior *in vivo*. TPA acetato derivatives maintain cytotoxicity with

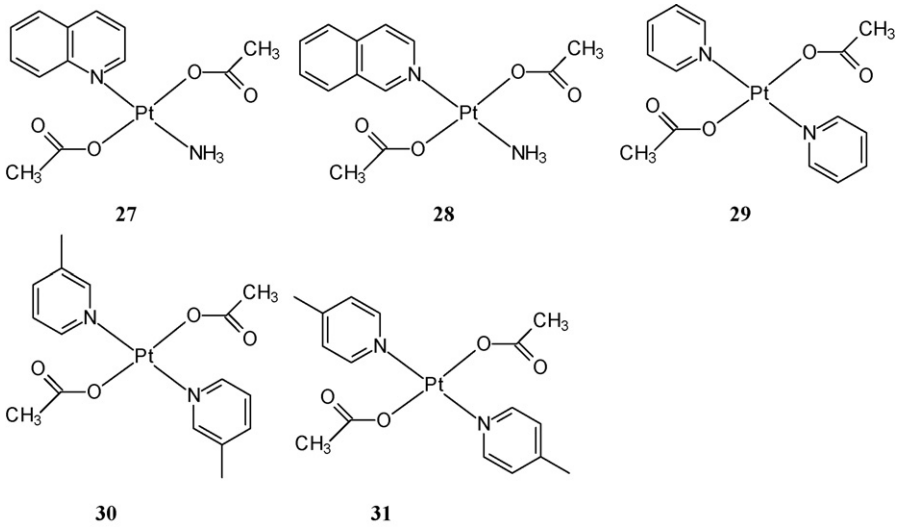


Fig. 4. Structure of *trans*-carboxylato complexes: (**27**) *trans*-[Pt(NH$_3$)(OAc)$_2$(quin)]; (**28**) *trans*-[Pt(iquin)(NH$_3$)(OAc)$_2$]; (**29**) *trans*-[Pt(OAc)$_2$(py)$_2$]; (**30**) *trans*-[Pt(OAc)$_2$(3-pic)$_2$]; (**31**) *trans*-[Pt(OAc)$_2$(4-pic)$_2$].

low resistance factors, lower than for the parent chloridos [39,40].

4.1. *trans*-Pt(II)(OAc)$_2$ complexes with planar amines

The *trans*-[Pt(NH$_3$)$_2$(OAc)$_2$] compound also has good water-solubility, but its cytotoxicity ($IC_{50} > 100\,\mu M$) shows that to enhance cytotoxic effect in the *trans* geometry, the presence of planar amines is required. Thus, the following compounds, with planar amines: *trans*-[Pt(NH$_3$)(OAc)$_2$(quin)] (**27**), *trans*-[Pt(iquin)(NH$_3$)(OAc)$_2$] (**28**) and *trans*-[Pt(OAc)$_2$(py)$_2$] (**29**) (quin = quinoline, iquin = isoqunoline, py = pyridine, OAc = CH$_3$COO) (Fig. 4), were synthesized. These are the first cytotoxic *trans*-platinum complexes containing a [N$_2$O$_2$] donor set, the same as in carboplatin and oxaliplatin. These TPA acetato compounds appeared significantly more cytotoxic in many cisplatin-resistant cell lines than in the parent cisplatin-sensitive cell lines (A2780, CH1, 41M) (Table 3) [40].

The cellular pharmacological properties of eight *trans*-platinum(II) complexes having a formula: *trans*-[PtX$_2$(L)(L′)] (X = Cl or OAc and L = L′ = 3-pic, 4-pic, or L = NH$_3$ and L′ = 3-pic or 4-pic), were investigated in murine keratinocytes Pam 212 and Pam 212-*ras* cells. The difference in cytotoxic activity between chlorido and acetato complexes was proved. However, two of the studied acetato platinum(II) compounds: *trans*-[Pt(OAc)$_2$(3-pic)$_2$] (**30**) and *trans*-[Pt(OAc)$_2$(4-pic)$_2$] (**31**) (Fig. 4) showed the highest cytotoxicity both in Pam 212/Pam 212-*ras* and 41M/41McisR cells (Table 3). Apart from that, all the tested acetato *trans*-platinum(II) complexes induced cell death through the apoptosis pathway in Pam 212-*ras* cells in contrast to *cis*-DDP, which caused cell death by necrosis. Assessment of platinum uptake in Pam 212-*ras* cells revealed that 80% of the input molecules of *trans*-[Pt(OAc)$_2$(3-pic)$_2$] and *trans*-[Pt(OAc)$_2$(4-pic)$_2$] were accumulated in Pam 212-*ras* cells. Moreover, the studies of platinum binding to genomic DNA indicated that these complexes exhibit high levels of DNA platination in Pam 212-*ras* cells at concentrations five times lower than *cis*-DDP. It seems possible that two lipophilic picoline ligands may facilitate through cell and nuclear membranes [41].

Table 3
Selected cytotoxic activity (IC_{50} [μM]) of *trans*-carboxylate platinum(II) complexes

	Reference	L1210	L1210cisR	A2780	Pam 212	Pam 212cisR	41M	CH1
[Pt(NH$_3$)(OAc)$_2$(quin)] (**27**)	[40]			13.0 (1.46)[a]			22.0 (1.00)	17.0 (0.48)
[Pt(iquin)(NH$_3$)(OAc)$_2$] (**28**)				13.0 (1.69)			22.0 (0.26)	20.0 (0.37)
[Pt(OAc)$_2$(py)$_2$] (**29**)				12.8 (0.90)			14.0 (0.32)	19.0 (0.22)
cis-DDP				–			1.4 (6.1)	0.1 (6.7)
[Pt(ipa)(N-Me-im)(OAc)$_2$] (**32**)	[38]	6.43	11.1					
[Pt(ipa)(N-Me-pyrazole)(OAc)$_2$] (**33**)		5.98	7.86					
cis-DDP		1.73	27.5					
carboplatin		10.2	>50					
[Pt(OAc)$_2$(3-pic)$_2$] (**30**)	[41]				19.4	21.0	15	35
[Pt(OAc)$_2$(4-pic)$_2$] (**31**)					16.9	23.3	21	42
cis-DDP					103	106	25	102

[a] Resistance factor RF (IC_{50} resistant/IC_{50} sensitive).

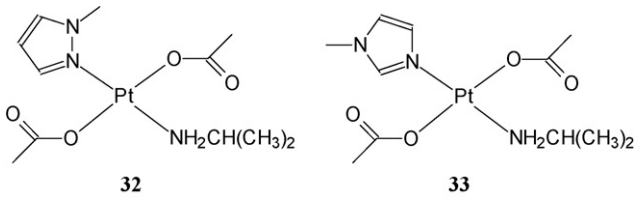


Fig. 5. Structures of *trans*-carboxylato complexes: (**32**) *trans*-[Pt(ipa)(*N*-Me-imidazole)$(OAc)_2$]; (**33**) *trans*-[Pt(ipa)(*N*-Me-pyrazole)$(OAc)_2$].

4.2. Asymmetric trans-Pt(II)$(OAc)_2$ complexes with azole and isopropylamnie

trans-Platinum(II) asymmetric complexes containing azoles, isopropanamine and two carboxylato-leaving ligands: *trans*-[Pt(ipa)(*N*-methylimidazole)$(OAc)_2$] (**32**), *trans*-[Pt(ipa)-(*N*-methylpyrazole)$(OAc)_2$] (**33**) (ipa = isopropanamine; OAc = CH_3COO) (Fig. 5) show high *in vitro* activities in both cisplatin-sensitive and -resistant mouse leukemia L1210cisR cell lines (Table 3). These compounds maintain cytotoxicity with low resistance factors. Reactions with 5′-guanosine monophosphate (5′-GMP) demonstrate low reactivity of the new class *trans*-carboxylato complexes. Their chlorido counterparts show similar cytotoxic activity but a faster reaction with 5′-GMP. This difference is analogous to the difference observed between cisplatin and carboplatin. It may suggest that *trans*-carboxylato complexes could exhibit high anticancer activity in combination with reduced toxic side effects *in vivo*, compared to cisplatin and their chlorido analogues [38].

Pantaoja et al. have tested similar complexes containing the same non-leaving ligands and chlorido ligands instead of carboxylato-leaving groups. They have investigated such complexes *cis* and *trans* orientated. The *trans* complexes showed higher cytotoxic activity than their *cis* analogues in a series of human cell lines (MCF7, EVSA-T, WIDR, IGROV, M19, A498, H226 and A2780). *cis*- and *trans*-[Pt(azole)Cl_2(ipa)] interacted with the model base 5′-GMP at similar rates [42].

The carboxylato complexes *trans*-[Pt(azole)(ipa)$(OAc)_2$] seem to be the better potential antitumor agents from among the three considered complexes, as they have good water solubility, high cytotoxicity and the lowest reactivity with GMP.

4.3. Asymmetric trans-Pt(II) carboxylato complexes with azole and ammine ligands

The structurally similar set of complexes, *trans*-[Pt(L)$(NH_3)(RCOO)_2$] (L = pyridine or substituted pyridine) (Fig. 6), leads us to the next group of complexes with better water solubility when compared to their dichlorido counterparts.

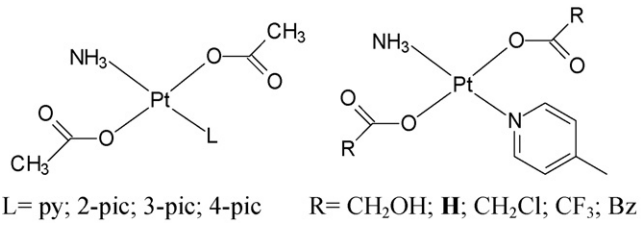


Fig. 6. Structures of *trans*-carboxylato complexes.

The aqueous solubility of these carboxylato series depends on the steric hindrance of the heterocycle. There is a slight difference between the various substitution patterns around the pyridine ring. In contrast, significant differences are observed when the carboxylato group is changed. For the series of 4-pic complexes, the solubility decreases in the order: formato, hydroxyacetato, chloroacetato, trifluoroacetato and benzoato derivatives, according to a decrease in hydrogen bonding capability.

The complexes considered show high cytotoxicity, as well as the parent chlorido compounds. All the tested TPA carboxylatos exhibit cytotoxic behavior in the human ovarian cancer cell lines A2780 in the micromolar range. *trans*-[Pt$(NH_3)(OFm)_2$(4-pic)] appears to be the most cytotoxic compound. It was also the most soluble and displayed the fastest hydrolysis. The cytotoxicity of the carboxylato complexes increases in the order (OAc < OAcOH < OFm), suggesting that the nature of the carboxylato-leaving group is related to cytotoxicity. The steric hindrance of the methyl group also influences cytotoxicity as follows: 2-pic < 3-pic < 4-pic [39].

5. *trans*-Pt(II)Cl_2 complexes with nonplanar heterocyclic ligands

5.1. trans-Platinum(II) complexes with piperazine

A series of water soluble, positively charged complexes *trans*-[Pt(Am)Cl_2(piperazine)]·HCl (Am consists of NH_3 (**34**), 4-picoline (4-pic) (**35**), *n*-butanamine (nba) (**36**), isopropanamine (ipa) (**37**)) were prepared (Fig. 7) [43]. The piperazine (pz) acts here as a monodentate ligand; it was achieved by using pz in which one of the amines was protected with the acid labile *tert*-butyloxycarbonyl (BOC). The complexes have significant cytotoxic activity especially against cisplatin-resistant ovarian cancer cell lines (Table 4). The cytotoxic activity of complexes was tested in three pairs of cisplatin-sensitive and -resistant cancer cell lines (A2780/A2780cisR, 41M/41McisR and CH1/CH1cisR). The cell lines were selected on the basis of all the major mechanisms of resistance to cisplatin: 41McisR being resistant through reduced drug transport, CH1cisR through increased DNA repair/tolerance and A2780cisR through a combination of decreased uptake, enhanced DNA repair/tolerance, and elevated reduced glutathione (GSH) levels.

These cationic complexes bind more rapidly to DNA than cisplatin and transplatin, whereas their interactions with cellular proteins (ubiquitin and myoglobin) are much slower than those of cisplatin and their neutral piperidine analogues [43].

Cationic *trans*-Pt(II)Cl_2 compounds containing NH_3 and piperazine (**34**), 4-picoline and piperazine (**35**), *n*-butanamine and piperazine (**36**), NH_3 and piperidino-piperazine (pip-pz) (**38**) (Fig. 7) as inert groups were tested for their cytotoxic activity against the protozoan *Leishmania infantum* (Table 4). The cytotoxicity of compounds (**36**) and (**38**) against *L. infantum* was higher in comparison to *cis*- and *trans*-DDP.

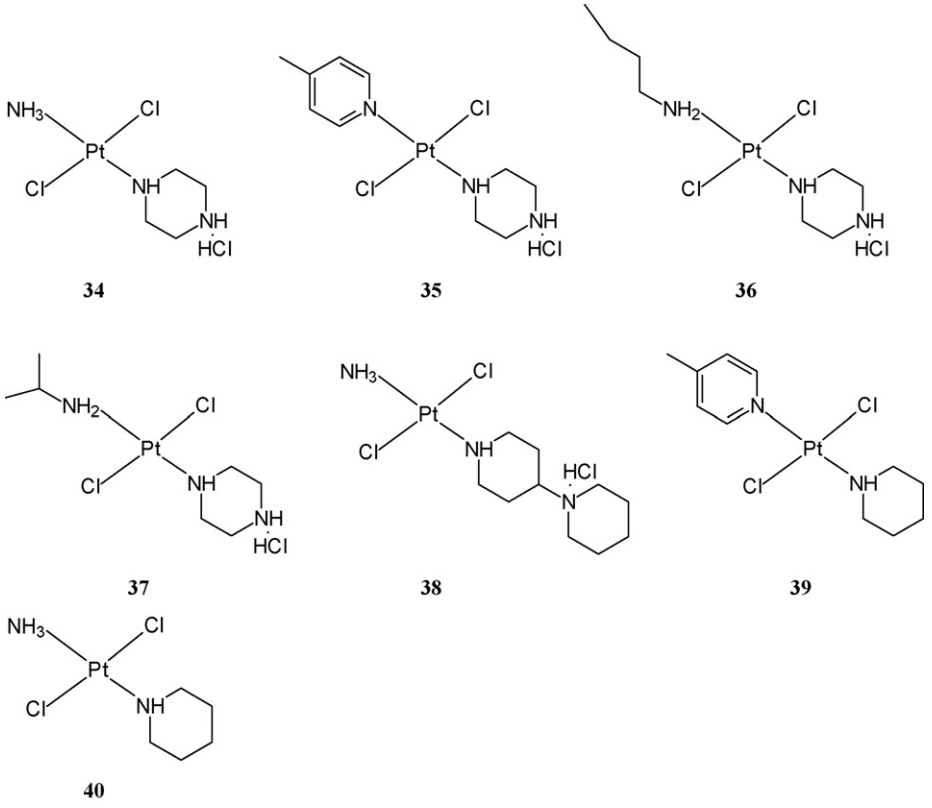


Fig. 7. Piperazine (pz) and piperidine (pip) complexes: (**34**) *trans*-[$PtCl_2(NH_3)$(pz)]·HCl; (**35**) *trans*-[$PtCl_2$(4-pic)(pz)]·HCl; (**36**) *trans*-[$PtCl_2$(nba)(pz)]·HCl; (**37**) *trans*-[$PtCl_2$(ipa)(pz)]·HCl; (**38**) *trans*-[$PtCl_2(NH_3)$(pip-pz)]·HCl; (**39**) *trans*-[$PtCl_2$(4-pic)(pip)]; (**40**) *trans*-[$PtCl_2(NH_3)$(pip)].

The compounds (**36**) and (**38**) induce effectively cell-cycle arrest in G2/M and in consequence caused cell death through apoptosis. DNA interaction studies revealed that complexes (**36**) and (**38**) induce conformational changes of double helix DNA similar to those generated by *trans*-DDP. Moreover, these complexes cause conformational changes in ubiquitin via stabilization of the α-helical content of this protein. These complexes are the first *trans*-platinum(II) agents with antiparasitic activity [44].

5.2. *trans*-Platinum(II) complexes with piperidine (pip) and piperazine (pz)

trans-Platinum(II) compounds with monofunctional piperidine (pip) or piperazine (pz) (Fig. 7: comp. **35**, **39** and **40**) were *in vitro* evaluated in OV-1063 (human ovarian carcinoma) and C-26 (human colon carcinoma) cells. The *trans*-[$PtCl_2$(4-pic)(pz)]·HCl (**35**) and *trans*-[$PtCl_2$(4-pic)(pip)] (**39**) (Fig. 7) measured the most cytotoxic among the tested group (Table 4).

Table 4
Selected cytotoxic activity (IC_{50} [μM]) of *trans*-Pt(II) complexes with nonplanar heterocyclic ligands

	References	A2780	A2780cisR	41M	41McisR	CH1	CH1cisR	Protozoan parasite *L. infantum*	C-26	OV-1063
[$PtCl_2(NH_3)$(pz)]·HCl (**34**)	[43,44]	5	44 (8.8)[a]	52	155 (3.0)	12	34 (2.8)	263		
[$PtCl_2$(4-pic)(pz)]·HCl (**35**)	[43–45]	10	24 (2.4)	45	147 (3.3)	16	42 (2.6)	188	4.5	6.0
[$PtCl_2$(nba)(pz)]·HCl (**36**)	[43,44]	16	28 (1.8)	32	48 (1.5)	17	19 (1.1)	60		
[$PtCl_2$(ipa)(pz)]·HCl (**37**)	[43]	14	30 (2.1)	38	122 (3.2)	10	50 (5.0)			
[$PtCl_2(NH_3)$(pip-pz)]·HCl (**38**)	[44]							95		
cis-DDP	[43,44]	2.2	38 (17.3)	26	107 (4.1)	6	23 (3.8)	150		
trans-DDP	[43,44]	>200	>200	>200	>200	>200	>200	>300		
[$PtCl_2(NH_3)$(2-Me-pip)] (**41**)	[49]	8	33	33	144	19	118			
[$PtCl_2(NH_3)$(3-Me-pip)] (**42**)		10	30	35	156	22	124			
[$PtCl_2(NH_3)$(4-Me-pip)] (**43**)		7	30	30	152	20	115			
cis-DDP		2.2	38	26	107	6	23			
[$PtCl_2$(4-pic)(pip)] (**39**)	[45]								2.5	6.0
cis-DDP									0.6	0.7
trans-DDP									46.0	73.0

[a] Resistance factor RF (IC_{50} resistant/IC_{50} sensitive).

Cell penetration and Pt–DNA adducts formation for these two complexes were also evaluated and it was shown that both compounds penetrate efficiently the cellular membrane of the tumor cells and platinate the cellular DNA. Positively charged *trans*-[$PtCl_2$(4-pic)(pz)]·HCl (**35**) is not only more soluble in water but also much more efficient (seven-fold higher) in platinating DNA than its neutral *trans*-[$PtCl_2$(4-pic)(pip)] (**39**) analogue [45].

Interestingly, *trans*-[$PtCl_2$(4-pic)(pz)]·HCl (**35**) and *trans*-[$PtCl_2$(4-pic)(pip)] (**39**) effectively induced apoptosis in OV-1063 ovarian but not in C-26 colon cancer cells. After treatment of the cells with these complexes many symptoms of apoptosis such as chromatin condensation and fragmentation, activation of caspase-3, externalization of phosphatidylserine were observed [45].

Kasparkova et al. tested the DNA interaction properties of *trans*-[Pt(Am)$Cl_2(NH_3)$] complexes, where Am = piperidine, piperazine or 4-picoline (Fig. 7: comp. **35**, **39** and **40**). These complexes induce more interstrand cross-links with DNA in comparison to *cis*- and *trans*-DDP. Apart from that, all complexes form more stable 1,3-GNG intrastrand cross-links than the corresponding lesions of transplatin in double helical DNA. These factors are likely to be responsible for their markedly high activity in tumor cells (A2780, A2780cisR, CH1, CH1cisR, 41M, 41cisR) [46,47].

The 1,3-GNG intrastrand cross-links formed by *trans*-[$PtCl_2(NH_3)$(pip)] (Fig. 7: comp. **40**) are removed from DNA by nucleotide excision repair (NER) system with lower efficiency than the 1,2-intrastrand CLs of cisplatin. *trans*-[$PtCl_2(NH_3)$(pip)] also forms in DNA minor interstrand CLs, properties of which are very similar to properties of CLs produced by clinically ineffective transplatin. Supposedly, the cytotoxic effect of comp. **40** is connected with the presence of 1,3-intrastrand cross-links [48].

5.3. *trans*-Platinum(II) complexes with methylpiperidine (Me-pip) isomeric ligands

The cytotoxicity and interactions with biological nucleophiles of three isomeric platinum(II) complexes with methylpiperidine (Me-pip) ligands: *trans*-[$PtCl_2$(2-Me-pip)(NH_3)] (**41**), *trans*-[$PtCl_2$(3-Me-pip)(NH_3)] (**42**) and

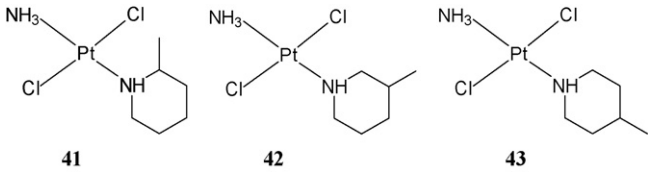


Fig. 8. Structures of *trans*-Pt(II)Cl_2 complexes with nonplanar heterocyclic ligands: (**41**) *trans*-[$PtCl_2$(2-Me-pip)(NH_3)]; (**42**) *trans*-[$PtCl_2$(3-Me-pip)(NH_3)] (**43**) *trans*-[$PtCl_2$(4-Me-pip)(NH_3)].

trans-[$PtCl_2$(4-Me-pip)(NH_3)] (**43**) (Fig. 8) were investigated. The cytotoxic activity of the complexes was tested against three pairs of cisplatin-sensitive and -resistant cancer cell lines (A2780/A2780cisR, 41M/41McisR and CH1/CH1cisR). There were no significant differences in the cytotoxicities of the three isomers against these cell lines and they were only slightly less effective than cisplatin (Table 4). The interactions of the three complexes with glutathione (GSH) and ubiquitin (Ub), as a model protein, indicated that *trans*-[$PtCl_2$(2-Me-pip)(NH_3)] reacts more slowly than the other two isomers yet this is not reflected in the cytotoxicity values. These differences are probably due to the steric hindrance of the 2-methyl group [49].

6. *trans*-Pt(II)Cl_2 complexes with aliphatic amines and/or heterocyclic ligands

6.1. trans-Platinum(II) complexes with aliphatic amines

Montero et al. have described the synthesis of a new group of *trans*-$PtCl_2$ complexes with asymmetric aliphatic amines of structural formula *trans*-[Pt(amine)Cl_2(isopropanamine)] (amine is *N*,*N*-dimethylamine = dma (**44**), propanamine = npa (**45**) and butanamine = nba (**46**) [Fig. 9]). They exhibit similar to cisplatin or higher than cisplatin cytotoxic activity against cell lines sensitive (Jurat, Hela, Vero) and resistant (HL-60, Pam 212-*ras*) to this drug (Table 5) [50]. Additionally, the cytotoxic activity of these three complexes was compared with that of their corresponding *cis* analogues in tumor cell lines sensitive to *cis*-DDP (CH1 and Pam 212) and resistant to *cis*-DDP (CH1cisR and Pam 212-*ras*). The results indicated that *trans*-[Pt(amine)Cl_2(ipa)] isomers have better antitumor properties than the *cis*-[Pt(amine)Cl_2(ipa)] [51].

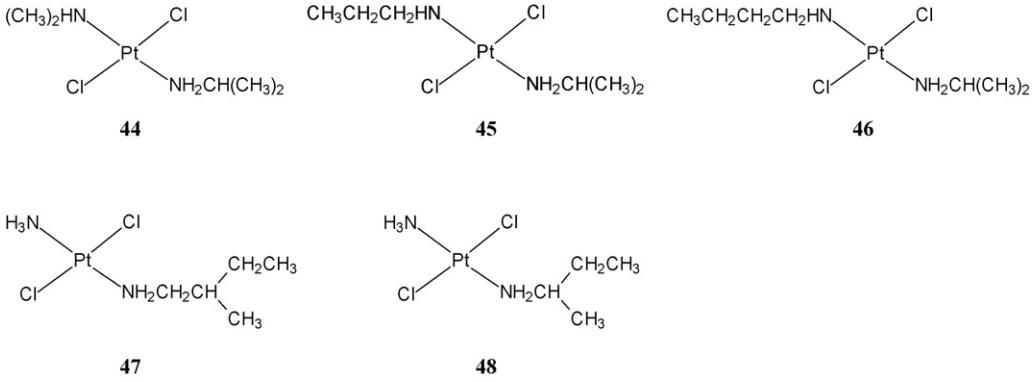


Fig. 9. Structures of *trans*-Pt(II)Cl_2 complexes with aliphatic amines: (**44**) *trans*-[$PtCl_2$(dma)(ipa)]; (**45**) *trans*-[$PtCl_2$(ipa)(npa)]; (**46**) *trans*-[$PtCl_2$(ipa)(nba)]; (**47**) *trans*-[$PtCl_2$(mba)(NH_3)]; (**48**) *trans*-[$PtCl_2(NH_3)$(sba)].

Table 5
Selected cytotoxic activity (IC_{50} [μM]) of *trans*-$PtCl_2$ complexes with aliphatic amines and/or heterocyclic ligands

	Reference	A2780/A2780cisR		Pam 212/Pam 212-*ras*		41M	41McisR	CH1	CH1cisR	HL-60 (72 h)	Jurat	HeLa	Vero
[$PtCl_2$(ipa)(npa)] (**45**)	[51]			50	32			43	39	20	5	43	52
[$PtCl_2$(ipa)(nba)] (**46**)	[51]			71	21			16	>100	18	7	35	46
[$PtCl_2$(dma)(ipa)] (**44**)	[51,61]	9.0	57.0 (6.3)[a]	56	6	13.0	54.0 (4.1)	19.0	15.0 (0.8)	17	5	32	47
[$PtCl_2$(dma)(ipa) (OH_2)] (**54**)	[61]	5.7	8.4 (1.5)			23.5	1.3 (0.05)	7.0	5.7 (0.8)				
cis-DDP	[51,61]	4.0	58.0 (14.5)	114	156	56.0	128.0 (2.3)	13.0	50.0 (3.8)	25	7	38	50
trans-DDP	[51,61]	>200	>200	123	164	>200	>200	>200	>200	50	22	89	148
cis-[$PtCl_2$(ipa)$_2$]	[51]			112	158					30	9	65	93
[$PtCl_2$(NH_3)(2-py-MeOH)] (**51**)	[56]									18			
[$PtCl_2$(NH_3)(3-py-MeOH)] (**50**)	[54,56]	>100	>100					>100	>100	18			
[$PtCl_2$(NH_3)(4-py-MeOH)] (**49**)	[54,56]	>100	>100					>100	84	3			
[$PtCl_4$(NH_3)(4-py-MeOH)] (**55**)	[52]									11.69			
cis-DDP	[54,56]	3.6	58					6	23	2			
[$PtCl_2$(ipa)(3-py-MeOH)] (**52**)	[57]	0.7	3.5					1.3	7.4				
[$PtCl_2$(ipa)(4-py-MeOH)] (**53**)		1.0	4.4					1.7	8.0				
cis-DDP		1.3	28					2.1	17				
trans-DDP		>300	>300					>300	>300				
[$PtCl_2$(mba)(NH_3)] (**47**)	[53]	1.7	9.3					4.2	15.1				
[$PtCl_2$(NH_3)(sba)] (**48**)		2.1	15.5					5.5	18.0				
cis-DDP		2.2	38					6.0	23.0				
trans-DDP		>200	>200					>200	>200				

[a] Resistance factor RF (IC_{50} resistant/IC_{50} sensitive).

Two of these complexes, *trans*-[$PtCl_2$(dma)(ipa)] (**44**) and *trans*-[$PtCl_2$(ipa)(nba)] (**46**), kill Pam 212-*ras* cisplatin resistant cells through apoptosis induction [50]. The complex (**44**) was also tested in A2780cisR cell lines and induced of apoptosis two-fold higher than cisplatin [52].

The additional data for *trans*-[$PtCl_2$(dma)(ipa)] (**44**) in A2780cisR cell lines show that this compound is higher cytotoxic than *cis*- and *trans*-DDP, moreover is able to circumvent resistance to cisplatin in A2780cisRcells. The level of DNA interstrand cross-links (between complementary guanidine and cytosine residue) induced by this complex is two and three times higher, respectively, than those induced by cisplatin and transplatin [52].

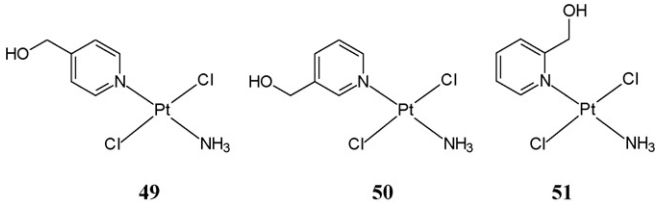
The *trans*-[$PtCl_2$(dma)(ipa)] (**44**) complex is also mentioned in Section 7.1, when some of its properties were described in comparison to its *trans*-Pt(IV) counterpart.

The analogues of transplatin with asymmetric aliphatic amine ligands, such as *trans*-[Pt(amine)Cl_2(NH_3)] where amine is 2-methylbutanamine = mba (**47**) and *sec*-butanamine = sba (**48**) (Fig. 9), show increased activity in sensitive and resistant to cisplatin tumor cell lines in comparison to this drug (Table 5). The DNA adducts formed by these complexes are not recognized by the HMGB1 protein. The formation of interstrand CLs (40–50%) and monofunctional lesions (*ca*. 36%) is four- and eight-fold higher than in the cases of transplatin and cisplatin, respectively [53].

6.2. *trans*-Platinum(II) complexes with (hydroxymethyl)pyridine (py-MeOH) isomers

The next example displayed that the replacement of the ammine ligand in transplatin by 4-(hydroxymethyl)pyridine (**49**) or 3-(hydroxymethyl)pyridine (**50**) (Fig. 10) does not increase the cytotoxic activity probably because of the lack of a stability of the intrastrand cross-links in DNA. Cytotoxic studies in platinum-resistant cells (A2780cisR and CH1cisR) confirmed that this chemical modification of the *trans*-DDP structure was unsuccessful (with IC_{50} values >100 μM) [54].

On the other hand, *trans*-[$PtCl_2$(NH_3)(4-py-MeOH)] (**49**) induce stable intrastrand (64%) and interstrand (26%) cross-links with DNA in the cell-free media. In consequence, these adducts cause conformational DNA alterations such as unwinding (28°) of double helix of DNA. Adducts of *trans*-[$PtCl_2$(NH_3)(4-py-MeOH)] reduce the affinity of the p53 protein to its DNA consensus sequence [55].



49 **50** **51**

Fig. 10. Structures of *trans*-Pt(II)Cl_2 complexes with (hydroxymethyl)pyridine isomers: (**49**) *trans*-[$PtCl_2$(NH_3)(4-py-MeOH)]; (**50**) *trans*-[$PtCl_2$(NH_3)(3-py-MeOH)]; (**51**) *trans*-[$PtCl_2$(NH_3)(2-py-MeOH).

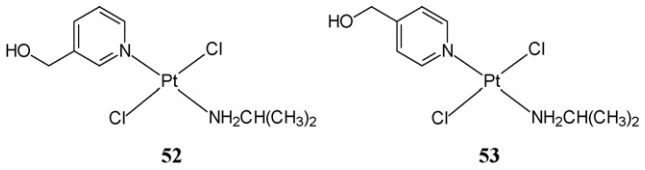


Fig. 11. Structures of *trans*-Pt(II)Cl_2 complexes with isopropanamine and (hydroxymethyl)-pyridine isomers: (**52**) *trans*-[$PtCl_2$(ipa)(3-py-MeOH)]; (**53**) *trans*-[$PtCl_2$(ipa)(4-py-MeOH)].

Despite the fact that the above cytotoxic studies [54] were not encouraging, Martinez et al. have recently synthesized the third missing isomer *trans*-[$PtCl_2(NH_3)$(2-py-MeOH)] (**51**) (Fig. 10) and tested antiproliferative activity of the three isomers (comp. **49**, **50** and **51**) against cell tumor lines HL-60. The results were surprising and showed that complexes (**50**) and (**51**) are far less active than complex (**49**), which has activity very similar to cisplatin (Table 5). Among the considered complexes, the compound (**49**) can reach the highest Pt uptake and interacts with DNA most effectively. As far as the apoptosis induction is concerned, the complex (**49**) is able to induce more than 80% of apoptotic death, in comparison to the 50% of cisplatin or the 20% of the other two complexes [56].

For further information on compound (**49**) see also Section 7.2.

Ramos-Lima et al. modified the 'classical' transplatin by the replacement of both ammine groups, one by the planar heterocyclic ((hydroxymethyl)-pyridine) and the other by an aliphatic (isopropanamine) ligand. The modification led to the complexes of the type: *trans*-[$PtCl_2$(ipa)(3-py-MeOH)] (**52**) and *trans*-[$PtCl_2$(ipa)(4-py-MeOH)] (**53**) (Fig. 11). The presence of the hydroxido subsistent in the ligand molecule probably increases the aqueous solubility of the complexes and introduces the group, which may have important hydrogen-bond donor properties in the approach to the biological target.

The cytotoxicity of these complexes, determined against A2780/A2780cisR and CH1/CH1cisR, was found to be higher than that of cisplatin (Table 5). These two compounds exhibited markedly better cytotoxic effects than antitumor cisplatin in cisplatin-resistant cells [57].

The majority of newly generated DNA adducts of these complexes were stable intrastrand cross-links; however, interstrand cross-links and monoadducts were also observed. These complexes exhibit preference for guanine and some preference for adenine residue in helix of DNA. The DNA binding demonstrated a higher rate of reaction with DNA than *cis*- and *trans*-DDP [57].

7. *trans*-Platinum(IV) complexes

The knowledge of the *trans*-platinum(IV) complexes is too broad to encompass in this short review frame. We have chosen to concentrate on platinum(IV) complexes possessing both equatorial (i.e., in the plane of the am(m)ine ligands) and axial (i.e., laying above and below the plane of the am(m)ine ligands) ligands in *trans* configuration.

It is commonly known that the reduction to platinum(II) is required to activate platinum(IV) complexes. The kinetic inertness of platinum(IV) complexes increases the probability that the complexes efficiently reach the tumor site. Modifying the axial ligands can alter the complexes' ability to enter tumor cells before being reduced to the active platinum(II) complexes. Some physicochemical properties of the *trans*-platinum(IV) complexes, i.e., lipophilicity (or hydrophobicity) and reduction potential, depend on the nature of the axial ligands. The value of the reduction potential (the ease of reduction) of platinum(IV) complexes, when the axial ligands are considered, increases as follows: Cl > OAc > OH. It means that the complexes with OH axial ligands are the most active ones. Moreover, it was observed that the higher lipophilicity the complex shows, the more its cellular uptake increases [58,59].

Kelland et al. have described the synthesis of about 25 *trans*-platinum(IV) complexes and their *trans*-platinum(II) counterparts, and then evaluated and compared *in vitro* as well as *in vivo* antitumor activity of these complexes. The described compounds centred around the general formula, *trans*-[(amine)(ammine)Cl_2Y_2]platinum(IV) (Y = OH or Cl). Two chlorido atoms together with ammine and amine groups lie in the same plane, in equatorial positions. Opposite them are axial ligands, two hydroxido or chlorido groups (Y ligands). The antitumor activity evaluations gave very promising results. The complexes were *in vitro* tested against the panel of human ovarian carcinoma cell lines, which contained tumor cells possessing either intrinsic (HX/62 and SKOV-3) or acquired (41McisR, CH1cisR and A2780cisR) resistance to cisplatin. Many of the complexes showed comparable antitumor activity to cisplatin and also overcame acquired cisplatin resistance. Notably, 14 complexes showed significant *in vivo* antitumor activity in the subcutaneous murine ADJ/PC6 plasmacytoma model. Of these, 13 were complexes with axial hydroxido ligands and one had axial ethylcarbamate ligands, whereas all the platinum(II) and tetrachloridoplatinum(IV) complexes were inactive [60].

7.1. *trans*-Platinum(IV) (and *trans*-platinum(II)) complex with aliphatic amines

The antitumor and cellular pharmacological properties of the *trans*-Pt(IV) complex, *trans*-[$PtCl_2$(dma)(ipa)$(OH)_2$] (**54**), were evaluated in comparison to its corresponding *trans*-Pt(II) counterpart, *trans*-[$PtCl_2$(dma)(ipa)] (**44**) (dma = dimethylamine, ipa = isopropanamine) (Fig. 12) (Table 5). The results showed that *trans*-Pt(IV) complex exhibits significant cytotoxicity

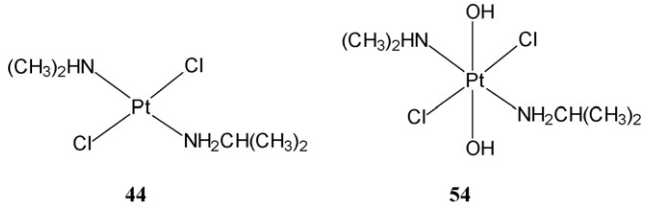


Fig. 12. Structures of *trans*-Pt complexes with aliphatic amines: (**44**) *trans*-[$PtCl_2$(dma)(ipa)]; (**54**) *trans*-[$PtCl_2$(dma)(ipa)$(OH)_2$].

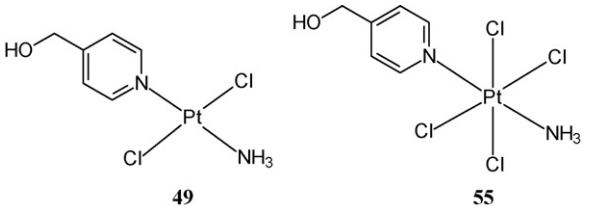


Fig. 13. Structures of *trans*-Pt complexes with (hydroxymethyl)pyridine isomers: (**49**) *trans*-[$PtCl_2(NH_3)$(4-py-MeOH)]; (**55**) *trans*-[$PtCl_4(NH_3)$(4-py-MeOH)].

against cisplatin resistance 41McisR and CH1cisR ovarian tumor cell lines. These cell lines are endowed with different mechanisms of resistance (41McisR: decreased platinum accumulation; CH1cisR: enhanced DNA repair/tolerance). The *trans*-Pt(II) compound circumvents cisplatin resistance only in CH1cisR cells. This complex does not possess *in vivo* antitumor activity in human ovarian carcinoma xenografts in mice, in contrast to its corresponding *trans*-Pt(IV) counterpart.

Moreover, the results indicated that the reactivity of *trans*-Pt(IV) is lower than that of *trans*-Pt(II), because it is much more inert to ligand substitution. The authors support the hypothesis, based on decreased reactivity of Pt(IV) compounds, that Pt(IV) complexes may act as prodrugs that efficiently reach the tumor site to be transformed into active Pt(II) species within the cell.

Compound *trans*-Pt(II) possesses a much higher reactivity against albumin than compound *trans*-Pt(IV). In addition, the level of binding of *trans*-Pt(II) to plasma proteins is 2.5-fold higher than that indicated by *trans*-Pt(IV). This might be connected with the lack of *in vivo* antitumor activity of *trans*-Pt(II) compound, because of its high rate of binding to plasma proteins.

Both considered compounds induce a higher amount of apoptotic cells than cisplatin in CH1cisR cells. The number of apoptotic cells induced by these compounds correlates with their ability to form DNA interstrand cross-links in CH1cisR cells [61].

These complexes also killed Pam 212-*ras* cells through the apoptosis pathway. Interestingly, the results indicate that the induction of apoptosis in Pam 212-*ras* cells by the considered complexes was highly associated with the inhibition of the overexpression of the H-*ras* protein [62].

7.2. trans-Platinum(IV) (and trans-platinum(II)) complex with (4-hydroxymethyl)-pyridine

Two similar platinum compounds with different oxidation states were synthesized: *trans*-[$PtCl_2(NH_3)$(4-py-MeOH)] (**49**) and *trans*-[$PtCl_4(NH_3)$(4-py-MeOH)] (**55**) (Fig. 13). The *trans*-Pt(II) compound (**49**) is highly soluble in water and other common organic and inorganic solvents, while the *trans*-Pt(IV) compound is poorly soluble.

The interaction between the Pt atom of complex *trans*-Pt(II) (**49**) and DNA is stronger than that of complex *trans*-Pt(IV) (**55**) as shown on the basis of circular dichroism, electrophoretic mobility in agarose gel and atomic force microscopy studies. Cytotoxicity tests against HL-60 tumor cells (after 24 h of incubation) showed that complex *trans*-Pt(IV) has similar activity to cisplatin and that the activity of *trans*-Pt(II) is about four-fold higher than for *trans*-Pt(IV) complex (Table 5 (72 h)). Despite the fact that Pt(IV) complex is less active, it can be easily activated by reduction with some common reducing agents in cells, such as ascorbate, glutathione or methionine. These species reduce the Pt(IV) compound to the corresponding analogue Pt(II). It is well known that Pt(II) compound can be deactivated by coordination of the thiol groups to the metal ion when the concentration of glutathione is higher than this stoichiometrically required to reduce Pt(IV) compound [63].

Both the tested complexes induce apoptosis in HL-60 cells however, the complex (**49**) was more potent [63].

8. Polynuclear platinum complexes

Polynuclear platinum complexes are a structurally distinct group. These innovative complexes contain two or more platinum centers linked by various types of ligand (aminoalkane, aromatic, etc.). Thus, polynuclear complexes break many structure–activity rules for platinum drugs. A different set of SARs for polynuclear complexes was created based on their *in vitro* cytotoxicity results. One of the conditions to achieve satisfactory antitumor activity of the complexes is the locating of the leaving group, preferably chlorido, in *trans* position to the bridging linker. In the meantime many *cis* and *trans* polynuclear complexes have been synthesized, mainly by Farrell et al. [64–66].

When *trans* complexes are considered, dinuclear complexes linked by the 4,4′-dipyrazolylmethane (dpzm) and containing either two chlorido or two DMSO ligands on each platinum center were synthesized. These complexes exhibited high cytotoxicity but were insoluble in water and did not show any significant advantages in comparison to cisplatin [67]. On the basis of the structure of BBR3464 (**56**) (Fig. 14), a compound with excellent *in vitro* and *in vivo* cytotoxicity, many new polynuclear complexes were prepared. In these complexes the linking aminoalkane ligand of BBR3464 has been replaced by either 4,4′-dipyridyl selenides, 4,4′-dipyridyl sulfides or thiol containing ligands [68,69]. Another example shows tetranuclear complex with a branched aminoalkane linking chain [70].

While these complexes showed good cytotoxic activity, they were much less active than the aminoalkane linked complexes, BBR-series of complexes [BBR3464 (**56**), BBR3571 (**57**), BBR3610 (**58**), BBR3611 (**59**)] (Fig. 14), which have entered clinical trials during the last few years. They were selected from more than 50 polynuclear complexes which have been tested for cytotoxicity against a variety of cancer cell lines [71]. The complexes of BBR-series fulfill the structure–activity conditions for polynuclear complexes. For maximum cytotoxicity the complex should contain the flexible linker, not aromatic rings, of the ideal length at least 8–10 atoms. The bridging linker should possess functional groups capable of forming hydrogen bonds with DNA [68,72].

From BBR-series of complexes the BBR3464 complex is the most significant, it has entered II phase of clinical trials. A wide range of *in vitro* studies confirmed its significant cytotoxicity against different cancer cell lines. The mean IC_{50} of BBR3464

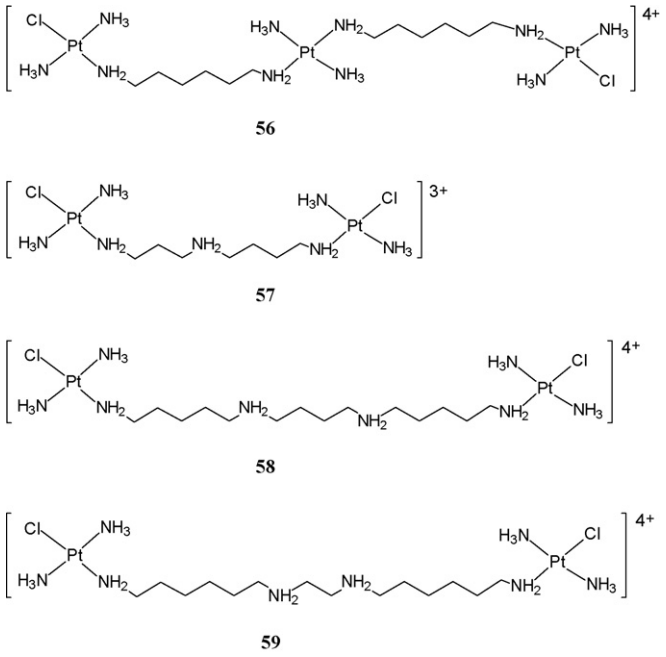


Fig. 14. Structures of polynuclear complexes: (**56**) BBR3464; (**57**) BBR3571; (**58**) BBR3610; (**59**) BBR3611.

is 0.6 μM, when seven human cancer cell lines assayed in comparison to cisplatin is 27.8 μM on average. BBR3464 showed a complete lack of cross-resistance in *cis*-DDP resistant cells [68,73]. BBR3464 also indicated very promising *in vivo* antitumor activity, independent of p53 level, in a range of human tumor xenografts [71,74].

This complex exhibits the ability to rapid formation of intrastrand as well as a typical 1,4-interstrand cross-links with DNA. The 1,4-interstrand cross-links are formed mainly between guanine residues. Interestingly, these type of adducts and intrastrand cross-links is not recognized by HMG1 proteins. However, only the 1,4-interstrand cross-links are not efficiently removed by nucleotide excision repair system (NER) in contrary to intrastrand cross-links. BBR3464 adducts cause rather small local distortions of DNA double helix and this is probably the reason why they are not substrates for HMG-proteins [75–78].

Currently, BBR3464 is being entered in phase II clinical trials under the auspices of Novuspharma SpA. The investigations of phase I trials demonstrated that diarrhea and neuropenia were evident as dose-limiting toxicities. The utility of this complex was not limited by nephrotoxicity, neurotoxicity or pulmonary toxicity [71]. Hitherto the clinical trials results revealed that this tri-nuclear complex will be the most useful in the treatment of small and non-small cell lung cancer, gastric cancer, ovarian cancer and possibly other solid tumors.

Recently Woodhouse and Rendina have synthesized completely innovative polynuclear complexes that incorporate cisplatin-like DNA binding with carborane used in radiation therapy. Carborane, *N*-dicarba-*closo*-dodecaborane, is a caged sphere consisting of boron, carbon and hydrogen atoms ($C_2B_{10}H_{12}$). It is believed that by combining two or more anticancer components the synergistic benefits may be achieved. Basic DNA studies have shown that these complexes are able to bind calf thymus DNA and inhibit transcription at concentrations similar to cisplatin [72].

To sum up, the polynuclear complexes are able to overcome cisplatin and carboplatin resistance in many human cancer cell lines. As the 'non-classical' platinum complexes, they form a different range of interstrand and intrastrand DNA adducts and therefore display a different spectrum of antitumor activity compared to cisplatin and their analogues. The adducts they form with DNA are flexible and non-directional. Possibly because of their flexibility, the intrastrand adducts are not recognized by HMG1 domain proteins but are effectively removed, while the interstrand adducts are not. As a result, the interstrand adducts are mainly responsible for cytotoxic effect of polynuclear complexes.

9. *trans*-Platinum complexes with various types of ligands

9.1. *trans*-Platinum complexes containing DMSO

The complex *trans*-Pt(II)Cl_2 with DMSO and tetrahydro-1,4-oxazine (Fig. 15), was tested for its cytotoxicity against the ovarian cancer cell line A2780, the cisplatin-resistant cell line A2780cisR and the AMD 473 resistant cell line A2780473R. This complex appeared to be about 30-fold less active than cisplatin against the tested cell lines but was not cross-resistant against the A2780473R cell line [79].

9.2. *trans*-Platinum complexes containing various phosphoric groups

The complexes of type *trans*-[$PtCl_2$(L)(PPh_3)] (where L is $NH_2CH(CH_3)CH_2CH_3$, (*R*)-$NH_2CH(CH_3)CH_2CH_3$, (*S*)-$NH_2CH(CH_3)CH_2CH_3$ and $NH_2CH(CH_3)_2$) are the first platinum complexes with phosphane groups and chiral amines in *trans* configurations (Fig. 16). The cytotoxic activity of the complexes was determined against the Pam 212-*ras* lines, which are cisplatin-resistant cells through overexpression of H-*ras* onco-

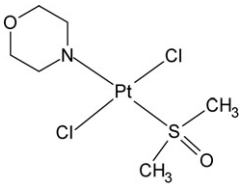


Fig. 15. Structure of *trans*-[$PtCl_2$(DMSO)(tetrahydro-1,4-oxazine)] complex.

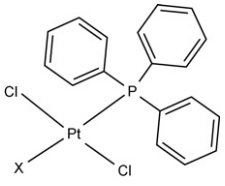


Fig. 16. X = $NH_2CH(CH_3)CH_2CH_3$ (racemic); (*R*)-$NH_2CH(CH_3)CH_2CH_3$; (*S*)-$NH_2CH(CH_3)CH_2CH_3$; $NH_2CH(CH_3)_2$.

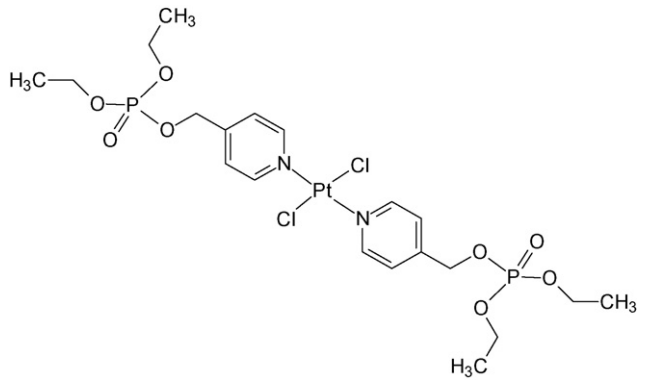


Fig. 17. Structure of *trans*-[$PtCl_2$(4-pmOpe)$_2$] complex.

gene. All the new *trans* configuration compounds displayed IC_{50} values significantly lower than cisplatin.

The hydrophobic PPh_3 ligand in the complexes considered, similar to the 1,2-diamniecyclohexane ligand in oxaliplatin, probably directs drug reactivity toward cellular proteins with sulfhydryl groups in hydrophobic areas that may be poorly reactive with cisplatin.

All of the tested complexes with phosphane ligands killed Pam 212 and Pam 212-*ras* cells more effectively than *cis*-DDP. Further studies showed that these complexes induce cell death through necrosis and/or unfinished apoptosis [80].

Novel complex with diethyl (pyridin-4-ylmethyl)phosphate (4-pmOpe), *trans*-[$PtCl_2$(4-pmOpe)$_2$] (Fig. 17), was assayed for its potential cytotoxic effect against human colorectal carcinoma (HT 29), human non-small lung cancer cell lines (A 549) and normal human peripheral blood lymphocytes.

The results demonstrate that the new cisplatin analogue showed substantial antiproliferative activity (equal to or better than cisplatin) against the tested cells and exerted approximately two-fold stronger cytotoxic influence on tumor cells than on normal human blood lymphocytes. It seems to be very important, since new chemotherapeutic agents should be characterized by a limited spectrum of side-effects [81].

9.3. trans-Platinum complex with oxime ligand

The water-soluble oxime *trans*-platinum complex *trans*-[$Pt((CH_3)_2C{=}NOH)(CH_3)_2CHNH_2)Cl_2$] (*t-Pt*(*oxm*)), and its *cis* counterpart (*c-Pt*(*oxm*)) were examined in NRK-52E (rat renal tubular) and HepG2 (human hepatoma) cells. Interestingly, cytotoxicity values were higher in the case of *cis* complex than in *trans* complex in both cell lines. This difference is probably due to the fact that *c-Pt*(*oxm*) rapidly caused necrosis, whereas *t-Pt*(*oxm*) cased death by apoptosis [82].

9.4. Other trans-platinum complexes

A number of chlorido or carboxylato platinum(II) complexes possessing *trans* geometry with various inert ligands, e.g. β-carboline alkaloids, DMSO, pyrazoles, ferrocenylphosphines, were tested for their antitumor activity. Initial *in vitro* experiments against a number of fluid suspension (P388, L 1210, K 562, Raji) and solid (KB, T 47D, SW 948, HeLa, A 549, L 929, Hep-2, RD) tumor cell lines revealed that some of these compounds are more (or equally) active than cisplatin (or carboplatin and oxaliplatin) [83].

10. Methods of synthesis of *trans*-platinum complexes

10.1. Synthesis of the symmetric trans-amine complexes *trans*-[PtL_2X_2]

The general method of synthesis of the symmetric *trans*-amine complexes, accomplished by the method of Kauffman and Cowan [84], is the conversion of an appropriate *cis* isomer into *trans* isomer as summarized in Scheme 1. The synthesis was conducted in a two-step reaction. Initially, the reaction of *cis*-[$PtCl_2L_2$] complex with the excess of the ligand L (where L = amine or heterocyclic compound) gave the tetraamineplatinate(II) [PtL_4]Cl_2 complex. Afterwards the preparation of the desired *trans*-[$PtCl_2L_2$] was carried out either by the thermal decomposition of tetrakis platinum complex (sometimes under reduced pressure) or by its treating with concentrated HCl.

The mechanism of the above-mentioned reaction explains the so-called kinetic *trans* effect, which is responsible for ligand-exchange reactions on metals ions. This effect is simply formulated as follows: ligands located *trans* to another ligand with a strong *trans* effect are more rapidly substituted than ligands in *cis* positions [85].

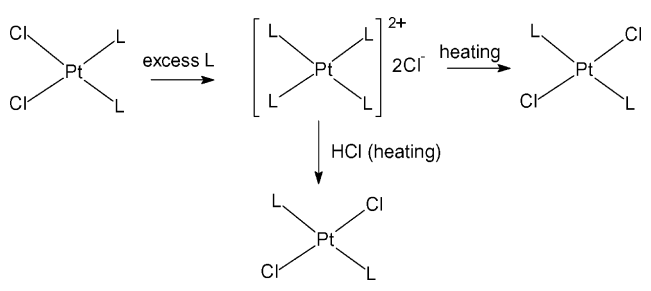
As examples of the use of this synthetic method, we present the thermal degradation of the solid complexes [PtL_4]X_2 (L = 2-, 3- and 4-picoline, pyridine, 3,5-lutidine; X = Cl, Br, NCS) [86] and the synthesis of *trans*-[$PtCl_2$(py)$_2$] obtained by using concentrated hydrochloric acid [87].

10.2. Isomerization

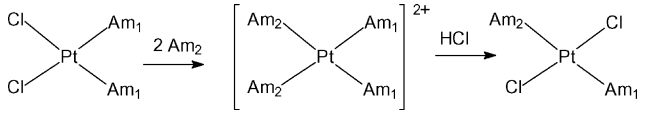
The isomeric instability of the platinum complexes in suitable solvent may be utilized as the next method for the *trans* complexes preparation.

To exemplify, the isomerization of *cis*-[$PtCl_2L_2$] (L is cyclobutylamine) to the *trans* isomer was observed in acetone solution [88].

Partial isomerization of *cis* complex with diethyl (pyridin-4-ylmethyl)phosphate to its *trans* counterpart under the reaction conditions (water–methanol, 45 °C) was observed. The isomers were isolated from each other by utilizing their solubility difference [81].



Scheme 1. General method of synthesis of *trans* complexes.



Scheme 2. Synthesis pathway for asymmetric complexes.

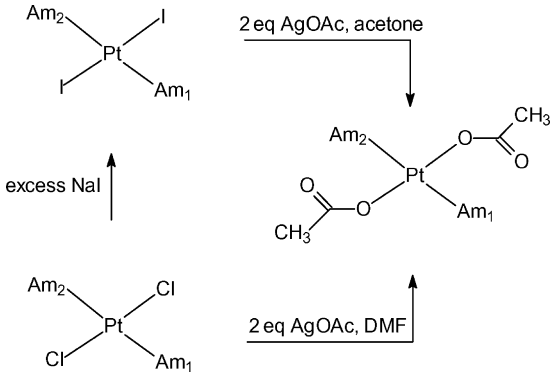
10.3. Synthesis of the asymmetric trans-platinum(II) complexes

The asymmetric *trans*-platinum(II) complexes of the type *trans*-[Pt(Am$_1$)(Am$_2$)Cl$_2$] (Scheme 2) were synthesized according to the general method accomplished by Kauffman and Cowan [84] shown in Scheme 2. The reaction involves direct substitution of both chlorido ligands by am(m)ine (Am$_2$) to give intermediate *cis*-oriented tetraam(m)ine complex *cis*-[Pt(Am$_2$)$_2$(Am$_1$)$_2$]$^{2+}$. Afterwards this tetraam(m)ine complex is treated with hydrochloric acid to yield the desired *trans*-dichlorido complex. Using strongly acidic conditions the first amine ligand is labilized at low pH and subsequently substituted by chlorido. This chlorido ligand directs the second chlorido into the *trans* position, due to the relative order of *trans* effects, i.e., $Cl^- >$ am(m)ine [85].

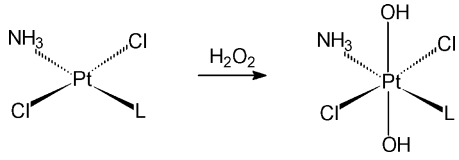
This way four *trans*-planar amine platinum(II) complexes of the type *trans*-[Pt(Am$_2$)Cl$_2$(NH$_3$)] where Am$_2$ stands for 2-hydroxypyridine, 3-hydroxypyridine, imidazole and imidazo(1,2-α)pyridine were obtained [30]. The syntheses of *trans*-[PtCl$_2$(NH$_3$)(quin)], *trans*-[PtCl$_2$(iquin)(NH$_3$)], *trans*-[PtCl$_2$(NH$_3$)(Tz)] or *trans*-[Pt(BTz)Cl$_2$(NH$_3$)] are another examples of the use of the above preparation method [36].

The mixed complexes of *trans* configuration are also prepared in a three-step reaction. Firstly K_2PtCl_4 reacts with ligands L′ to produce the *cis* isomers [PtCl$_2$(L′)$_2$]. In the second step, the reaction of the *cis* isomers and PtCl$_2$ give the binuclear chlorido-bridged complexes [(μ-Cl)PtCl(L′)]$_2$. Finally, the addition of the desired amines L split the chlorido bridged complexes to afford the *trans*-[PtCl$_2$(L′)(L)]complexes [89]. The reaction course is depicted in Scheme 3. The L′ ligands are a wide variety of uncharged molecules, e.g. PPh_3 [80], C_2H_4, $P(OR)_3$, AsR_3, PR_3, SbR_3, R_2S, R_2Se and R_2Te, and the halogen is usually chlorine [89].

In order to obtain asymmetric *trans*-carboxylato platinum complexes *trans*-[Pt(Am$_1$)(Am$_2$)(OAc)$_2$], e.g. *trans*-[Pt(NH$_3$)(OAc)$_2$(quin)] [40], *trans*-[Pt(ipa)(N-Me-imidazole)(OAc)$_2$] [38] or *trans*-[Pt(NH$_3$)(OAc)$_2$(4-pic)] [39], the dichlorido compounds *trans*-[Pt(Am$_1$)(Am$_2$)Cl$_2$] were used as starting materials. The general procedure consists of treating the dichlorido complexes with two equivalents of silver acetate AgOAc [38]. The addition of silver acetate in acetone suspension to a suitable solvent (DMF or acetone) solution of *trans*-[Pt(Am$_1$)(Am$_2$)X$_2$] results in the metathesis reaction and formation of the corresponding acetatos. In order to dissolve the sparingly soluble chloridos it is necessary to use high-boiling solvent such as DMF. Alternatively, acetone can be used as a reaction solvent, but on the condition that the acetatos formation starts from diiodido complexes instead of dichlorido compounds (Scheme 4) [40,41].



Scheme 4. Synthesis of *trans*-carboxylato platinum complexes.



Scheme 5. Synthesis of *trans*-platinum(IV) complexes.

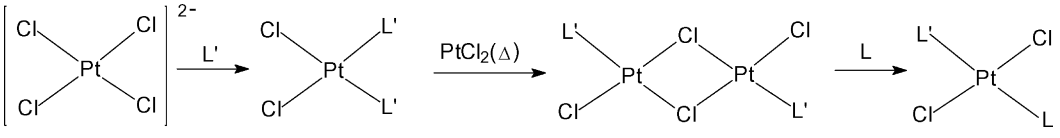
10.4. Synthesis of trans-platinum(IV) complexes

The *trans*-platinum(IV) complexes are obtained from the *trans*-platinum(II) complexes. After the reaction, the stereochemistry of the *trans*-platinum(IV) complexes is the same as the stereochemistry of the starting platinum(II) complexes. Moreover, the suitable ligands are added in axial positions to yield the *trans*-platinum(IV) complex [21].

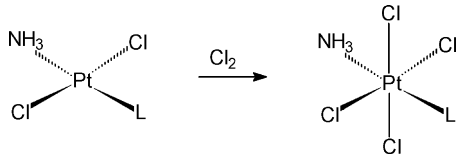
The oxidation of the Pt(II) complexes by using hydrogen peroxide leads to the Pt(IV) complexes containing hydroxido ligands in axial positions as shown in Scheme 5. Generally, the most suitable solvent for this type of reaction is *N*,*N*-dimethylacetamide taking into consideration the hydrophobic properties of the platinum complexes containing the higher amines [60].

Analogous reaction is given below (Scheme 6), where *trans*-platinum(IV) complex was obtained by treating *trans*-platinum(II) complex with a stream of gaseous Cl_2 [63].

Dicarboxylato, dicarbonato and dicarbamato *trans*-platinum(IV) complexes can be obtained from the dihydroxido



Scheme 3. Synthesis pathway for asymmetric complexes.



Scheme 6. Synthesis of *trans*-platinum(IV) complexes.

species by carboxylation reaction with carboxylic anhydride, pyrocarbonate and alkylisocyanate, respectively [90].

11. Conclusion

Many studies revealed that replacement of ammine group(s) in classical molecule of *trans*-DDP enhances cytotoxicity of the resulting complexes in comparison to parent *trans*-DDP. These complexes are very often similarly or more toxic than the one of the most successful antineoplastic drug *cis*-DDP. Notably, many *trans*-platinum complexes exhibit strong cytotoxic activity against *cis*-DDP resistant tumor cells. These complexes may be the key to overcoming intrinsic or acquired resistance to *cis*-DDP in the future. Moreover, some of *trans*-platinum complexes are able to kill cancer cells through apoptosis induction, a desirable feature of novel potential anticancer drugs. The most promising data have been obtained for *trans*-platinum complexes containing heterocyclic, aliphatic, phosphoric or iminoether ligands. The mechanism of action of *trans*-platinum complexes seems to depend on *trans* configuration as well as on the nature of the ligands. Different reactivity of these complexes with DNA and other cellular components such as glutathione, HMG proteins, DNA repair proteins and the ability of these complexes to form structurally different DNA adducts in different proportions make them behave differently from *cis*- and *trans*-DDP. However, some similarities persist. Future studies of some novel platinum are appear to be promising, however the mechanism of their activity need to be elucidated. The results obtained so far can also be a source of information for design of novel *trans*-platinum complexes. Furthermore, the beneficial antitumor properties of *trans*-platinum complexes prompted the studies of their interactions/synergism with other anticancer agent 5-fluorouracil, one of the most cytotoxic agents in the treatment of various solid tumors/carcinomas of the gastro-intestinal tract, breast, head and neck [91]. In summary, in the article we briefly described the novel concept in searching for the effective drugs in the field of *trans*-platinum-based chemotherapy.

Acknowledgments

We thank Prof. Dr. Dr.h.c. A. Bartke and Steve Sandstrom (School of Medicine Department of Medicine Springfield, USA) for the carefully reading of the manuscript and helpful discussion. The financial support from Medical University of Lodz (grant no. 503-3016-2) is acknowledged.

References

[1] B. Rosenberg, L. Van Camp, T. Crigas, Nature 205 (1965) 698.
[2] S. Garattini, C. La Vecchia, Eur. J. Cancer 37 (2001) 128.
[3] L.R. Ferguson, A.E. Pearson, Mutat. Res. 355 (1996) 1.
[4] D. Lebwohl, R. Canetta, Eur. J. Cancer 34 (1998) 1522.
[5] E. Wong, C.M. Giandomenico, Chem. Rev. 99 (1999) 2451.
[6] B. Lippert, Cisplatin Chemistry and Biochemistry of a Leading Anticancer Drug, Wiley-VCH, New York, 1999.
[7] M. Galanski, B.K. Keppler, Anti-Cancer Agents Med. Chem. 7 (2007) 55.
[8] I. Kostova, Recent Patents Anti-Cancer Drug Discov. 1 (2006) 1.
[9] V. Brabec, M. Leng, Proc. Natl. Acad. Sci. U.S.A. 90 (1993) 5345.
[10] M. Kartalou, J.M. Essigmann, Mutat. Res. 478 (2001) 1.
[11] M.A. Jakupec, M. Galanski, B.K. Keppler, Rev. Physiol. Biochem. Pharmacol. 146 (2003) 1.
[12] A. Erxleben, S. Metzger, J.F. Britten, C.J.L. Lock, A. Albinati, B. Lippert, Inorg. Chim. Acta 339 (2002) 461.
[13] C. Hofr, V. Brabec, Biopolymers 77 (2005) 222.
[14] T. Peleg-Shulman, Y. Najajreh, D. Gibson, J. Inorg. Biochem. 91 (2002) 306.
[15] V. Marchan, E. Pedroso, A. Grandas, Chem.-Eur. J. 10 (2004) 5369.
[16] P. Heringova, J. Woods, F.S. Mackay, J. Kasparkova, P.J. Sadler, V. Brabec, J. Med. Chem. 49 (2006) 7792.
[17] F.S. Mackay, J.A. Woods, H. Moseley, J. Ferguson, A. Dawson, S. Parsons, P.J. Sadler, Chem.-Eur. J. 12 (2006) 3155.
[18] M. Coluccia, A. Nassi, F. Loseto, A. Boccarelli, M.A. Mariggio, D. Giordano, F.P. Intini, P. Caputo, G.J. Natile, J. Med. Chem. 36 (1993) 510.
[19] M. Coluccia, A. Nassi, A. Boccarelli, D. Giordano, N. Cardellicchio, D. Locker, M. Leng, M. Sivo, F.P. Intini, G. Natile, J. Inorg. Biochem. 77 (1999) 31.
[20] M. Leng, D. Locker, M.-J. Giraud-Panis, A. Schwartz, F.P. Intini, G. Natile, C. Pisano, A. Boccarelli, D. Giordano, M. Coluccia, Mol. Pharmacol. 58 (2000) 1525.
[21] G. Natile, M. Coluccia, Coord. Chem. Rev. 216/217 (2001) 383.
[22] S. Radulovic, Z. Tesic, S. Manic, Curr. Med. Chem. 9 (2002) 1611.
[23] R. Zaludova, A. Zakovska, J. Kasparkova, Z. Balcarova, O. Vrana, M. Coluccia, G. Natile, V. Brabec, Mol. Pharmacol. 52 (1997) 354.
[24] J.M. Perez, M.A. Fuertes, C. Alonso, C. Navarro-Ranninger, Crit. Rev. Oncol. Hematol. 35 (2000) 109.
[25] V. Brabec, O. Vrana, O. Novakova, V. Kleinwachter, F.P. Intrini, M. Coluccia, G. Natile, Nucleic Acids Res. 24 (2) (1996) 336.
[26] O. Novakova, J. Kasparkova, J. Malina, G. Natile, V. Brabec, Nucleic Acids Res. 31 (2003) 6450.
[27] F.P. Intini, A. Boccarelli, V.C. Francia, C. Pacifico, M.F. Sivo, G. Natile, D. Gordano, P. De Rinaldis, M. Coluccia, J. Biol. Inorg. Chem. 9 (2004) 768.
[28] A. Boccarelli, F.P. Intini, R. Sasanelli, M.F. Sivo, M. Coluccia, G. Natile, J. Med. Chem. 9 (2006) 829.
[29] N. Farrell, L.R. Kelland, J.D. Roberts, M. Van Beusichem, Cancer Res. 52 (1992) 5065.
[30] M. van Beusichem, N. Farrell, Inorg. Chem. 31 (1992) 634.
[31] N. Farrell, T.T.B. Ha, J.-P. Souchard, F.L. Wimmer, S. Cros, N.P. Johnson, J. Med. Chem. 32 (1989) 2240.
[32] N. Farrell, L.F. Povirk, Y. Dange, G. DeMasters, M.S. Gupta, G. Kohlhagen, Q.A. Khan, Y. Pommier, D.A. Gewirtz, Biochem. Pharmacol. 68 (2004) 857.
[33] J. Kasparkova, O. Novakova, N. Farrell, V. Brabec, Biochemistry 42 (2003) 792.
[34] V. Marini, P. Christofis, O. Novakova, J. Kasparkova, N. Farrell, V. Brabec, Nucleic Acids Res. 33 (2005) 5819.
[35] A. Zakovska, O. Novakova, Z. Balcarova, U. Bierbach, N. Farrell, V. Brabec, Eur. J. Biochem. 254 (1998) 547.
[36] U. Bierbach, Y. Qu, T.W. Hambley, J. Peroutka, H.L. Nguyen, M. Doedee, N. Farrell, Inorg. Chem. 38 (1999) 3535.
[37] F. Huq, H. Daghriri, J.Q. Yu, P. Beale, K. Fisher, Eur. J. Med. Chem. 39 (2004) 691.
[38] S. van Zutphen, E. Pantoja, R. Soriano, C. Soro, D.M. Tooke, A.L. Spek, J. den Dulk, J. Reedijk, Dalton Trans. (2006) 1020.
[39] G.H. Bulluss, K.M. Knott, E.S.F. Ma, S.M. Aris, E. Alvarado, N. Farrell, Inorg. Chem. 45 (2006) 5733.
[40] E.S.F. Ma, W.D. Bates, A. Edmunds, L.R. Kelland, T. Fojo, N. Farrell, J. Med. Chem. 48 (2005) 5651.

[41] A.G. Quiroga, J.M. Perez, C. Alonso, C. Navarro-Ranninger, N. Farrell, J. Med. Chem. 49 (2006) 224.
[42] E. Pantoja, A. Gallipoli, S. van Zutphen, D.M. Tooke, A.L. Spek, C. Navarro-Ranninger, J. Reedijk, Inorg. Chim. Acta 359 (2006) 4335.
[43] Y. Najajreh, J.M. Perez, C. Navarro-Ranninger, D. Gibson, J. Med. Chem. 42 (2002) 5189.
[44] P.A. Nguewa, M.A. Fuertes, S. Iborra, Y. Najajreh, D. Gibson, E. Martinez, C. Alonso, J.M. Perez, J. Inorg. Biochem. 99 (2005) 727.
[45] E. Khazanov, Y. Barenholz, D. Gibson, Y. Najajreh, J. Med. Chem. 45 (2002) 5196.
[46] J. Kasparkova, V. Marini, Y. Najajreh, D. Gibson, V. Brabec, Biochemistry 42 (2003) 6321.
[47] Y. Najajreh, J. Kasparkova, V. Marini, D. Gibson, V. Brabec, J. Biol. Inorg. Chem. 10 (2005) 722.
[48] J. Kasparkova, o. Novakova, V. Marini, Y. Najajreh, D. Gibson, J.-M. Perez, V. Brabec, J. Biol. Chem. 278 (2003) 47516.
[49] S. Jawbry, I. Freikman, Y. Najajreh, J.M. Perez, D. Gibson, J. Inorg. Biochem. 99 (2005) 1983.
[50] E.I. Montero, S. Diaz, A.M. Gonzalez-Vadillo, J.M. Perez, C. Alonso, C. Navarro-Ranninger, J. Med. Chem. 42 (1999) 4264.
[51] E. Pantoja, A. Álvarez-Valdés, J.M. Pérez, C. Navarro-Ranninger, J. Reedijk, Inorg. Chim. Acta 339 (2002) 525.
[52] E.I. Montero, J.M. Perez, A. Schwartz, M.A. Fuertes, J.M. Malinge, C. Alonso, M. Leng, C. Navarro-Ranninger, ChemBioChem 3 (2002) 61.
[53] R. Prokop, J. Kasparkova, O. Novakova, V. Marini, A.M. Pizarro, C. Navarro_Ranninger, V. Brabec, Biochem. Pharmacol. 67 (2004) 1097.
[54] F. Ramos-Lima, A.G. Quiroga, K.M. Perez, C. Navarro-Ranninger, Polyhedron 22 (2003) 3379.
[55] K. Stehlikova, J. Kasparkova, O. Novakova, A. Martiney, V. Moreno, FEBS J. 273 (2006) 301.
[56] A. Martinez, J. Lorenzo, M.J. Prieto, M. Font-Bardia, X. Solans, F.X. Aviles, V. Moreno, Bioorg. Med. Chem. 15 (2007) 969.
[57] F. Ramos-Lima, O. Vrána, A.G. Quiroga, C. Navarro-Ranninger, A. Halámiková, H. Rybničková, L. Hejmalová, V. Brabec, J. Med. Chem. 49 (2006) 2640.
[58] M.D. Hall, T.W. Hambley, Coord. Chem. Rev. 232 (2002) 49.
[59] M.D. Hall, C.T. Dillon, M. Zhang, P. Beale, Z. Cai, B. Lai, A.P.J. Stampfl, T.W. Hambley, J. Biol. Inorg. Chem. 8 (2003) 726.
[60] L.R. Kelland, C.F.J. Barnard, I.G. Evans, B.A. Murrer, B.R.C. Theobald, S.B. Wyer, P.M. Goddard, M. Jones, M. Valenti, A. Bryant, P.M. Rogers, K.R. Harrap, J. Med. Chem. 38 (1995) 3016.
[61] J.M. Perez, L.R. Kelland, E.I. Montero, F.E. Boxall, C.A. Fuertes, C. Navarro-Ranninger, Mol. Pharmacol. 63 (2003) 933.
[62] J.M. Perez, E.I. Montero, A.M. Gonzalez, A. Alvarez-Valdes, C. Alonso, C. Navarro-Ranninger, J. Inorg. Biochem. 77 (1999) 37.
[63] A. Martinez, J. Lorenzo, M.J. Prieto, R. de Llorens, M. Font-Bardia, X. Solans, F.X. Aviles, V. Moreno, ChemBioChem 6 (2005) 2068.
[64] N. Farrell, S.G. del Ameida, K.A. Skov, J. Am. Chem. Soc. 110 (1988) 5018.
[65] N. Farrell, Y. Qu, Inorg. Chem. 28 (1989) 3416.
[66] N. Farrell, Y. Qu, M.P. Hacker, J. Med. Chem. 33 (1990) 2179.
[67] J.A. Broomhead, M.J. Lynch, Inorg. Chim. Acta 240 (1995) 13.
[68] N.J. Wheate, J.G. Collins, Coord. Chem. Rev. 241 (2003) 133.
[69] G. Zhao, H. Lin, S. Zhu, H. Sun, Y. Chen, Anti-Cancer Drug Des. 13 (1998) 769.
[70] B.A.J. Jansen, J. van der Zwan, J. Reedijk, H. den Dulk, J. Brouwer, Eur. J. Inorg. Chem. (1999) 1429.
[71] I. Judson, L.R. Kelland, Drugs 59 (Suppl. 4) (2000) 29.
[72] N.J. Wheate, J.G. Collins, Curr. Med. Chem. -Anti-Cancer Agents 5 (2005) 267.
[73] J.D. Roberts, N. Peroutka, N. Farrell, J. Inorg. Biochem. 77 (1999) 51.
[74] P. Perego, C. Caserini, L. Gatti, N. Carenini, S. Romanelli, R. Supino, D. Colangelo, L. Viano, R. Leone, S. Spinelli, G. Pezzoni, C. Manzotti, N. Farrell, F. Zunino, Mol. Pharmacol. 55 (3) (1999) 528.
[75] T. Boulikas, M. Vougiouka, Oncol. Rep. 10 (2003) 1663.
[76] J. Zehnulova, J. Kasparkova, N. Farell, V. Brabec, J. Biol. Chem. 276 (25) (2001) 22191.
[77] J. Kasparkova, J. Zehnulova, N. Farell, V. Brabec, J. Biol. Chem. 277 (50) (2002) 48076.
[78] S.M. Cohen, S.J. Lippard, Prog. Nucleic Acids Res. Mol. Biol. 67 (2001) 93.
[79] G. Giannikopoulos, C.-L. Teo, M.D. Hall, R.R. Fenton, T.W. Hambley, Aust. J. Chem. 56 (2003) 685.
[80] F. Ramos-Lima, A.G. Quiroga, K.M. Perez, M. Font-Bardia, X. Solans, C. Navarro-Ranninger, Eur. J. Inorg. Chem. (2003) 1591.
[81] U. Kalinowska, K. Matławska, L. Chęcińska, M. Domagała, R. Kontek, R. Osiecka, J. Ochocki, J. Inorg. Biochem. 99 (2005) 2024.
[82] A.G. Quiroga, L. Cubo, E. de Blas, P. Aller, C. Navarro-Ranninger, J. Inorg. Biochem. 101 (2007) 104.
[83] T.A. Al.-Allaf, L.J. Rashan, Boll. Chim. Farm. 140 (2001) 205.
[84] G.B. Kauffman, D.O. Cowan, Inorg. Synth. 7 (1963) 239.
[85] G. Wulfsberg, Inorganic Chemistry, University Science Books, Sausalito, CA, 2000, p. 855.
[86] L.K. Thompson, Inorg. Chim. Acta 38 (1980) 117.
[87] G.B. Kauffman, Inorg. Synth. 7 (1963) 249.
[88] J.-P. Souchard, F.L. Wimmer, T.T.B. Ha, N.P. Johnson, J. Chem. Soc. Dalton Trans. (1980) 307.
[89] J. Chatt, L.M. Venanzi, J. Chem. Soc. (1955) 3858.
[90] C.M. Giandomenico, M.J. Abrams, B.A. Murrer, J.F. Vollano, M.I. Rheinheimer, S.B. Wyer, G.E. Bossard, J.D. Higgins, Inorg. Chem. 35 (1995) 2372.
[91] B. Nakata, S. Yamagata, I. Kanehara, T. Shirasaka, K. Hirakawa, J. Exp. Clin. Cancer Res. 25 (2006) 195.