

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

**WEB OF SCIENCE™**Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us? Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com

Interactions of the Platinum(II) Complexes with Nitrogen- and Sulfur-Bonding Bio-Molecules in Chronic Lymphocytic Leukemia

Jovana Bogojeski, Biljana Petrović and Živadin D. Bugarčić*
*University of Kragujevac, Faculty of Science, Department of Chemistry
 Serbia*

1. Introduction

Transition metals and their reactions are in general important in the environment, in technical processes (catalysis, extraction and purification of metal complexes) and in biology and medicine (biological electron transfer, toxicology and use of metal complexes as drugs). Moreover, nonessential metal ions are very often used in biological systems either for therapeutic application or as diagnostic aids. For instance, metal complexes have been used for the treatment of many diseases (cancer, arthritis, diabetes, Alzheimer, *etc.*), but with little understanding of their mechanism of action in biological systems. (Ronconi & Sadler, 2007; Bruijninx & Sadler, 2009) Biochemical studies have not clearly established the molecular basis for the activity and mechanism of action. The growing field of bioinorganic chemistry is presently dealing with the clarification of the mechanisms of action of metal complexes in biological systems. (Ronconi & Sadler, 2007; Bruijninx & Sadler, 2009; Jakupec et al., 2008)

Research in the area of application of metal complex compounds in medicine began with the discovery of antitumor properties of cisplatin. (Rosenberg, 1965, 1967, 1969, 1970) Today cisplatin is in routine use as therapeutics worldwide. Following the success of cisplatin a large number of analogous compounds were synthesized. All these compounds have a several common characteristics:

1. bifunctional complex compounds with *cis*-geometry
2. $PtX_2(amin)_2$ is general formula of this compounds, where X_2 are two labile monodentate or one labile bidentate ligand, and $(amine)_2$ are inert nitrogen-donor ligands
3. nitrogen-donor ligands have to contain at least one NH bond.

Despite the large number of synthesized compounds only a few of them entered the medicinal use and most are still in preclinical investigation. (Jakupec et al., 2003; Reedijk, 2009) At the Fig. 1. are presented some of platinum complexes that are in the medicinal use worldwide.

Chronic lymphocytic leukemia is the most frequent type of leukemia and it accounts for approximately 25% of all leukemias. (Chiorazzi et al., 2005) Although at the present there is no curative treatment, combinations of cytotoxic agents and of immunotherapies that generate high complete remission rates hold promise for altering the natural history of this

disease. (Wierda et al., 2005) Fludarabine (9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate) is the most effective purine nucleoside analogue for the treatment of indolent lymphoproliferative disorders, including Chronic lymphocytic leukemia, low-grade lymphoma, and prolymphocytic leukemia. (Eichhorst et al., 2005)

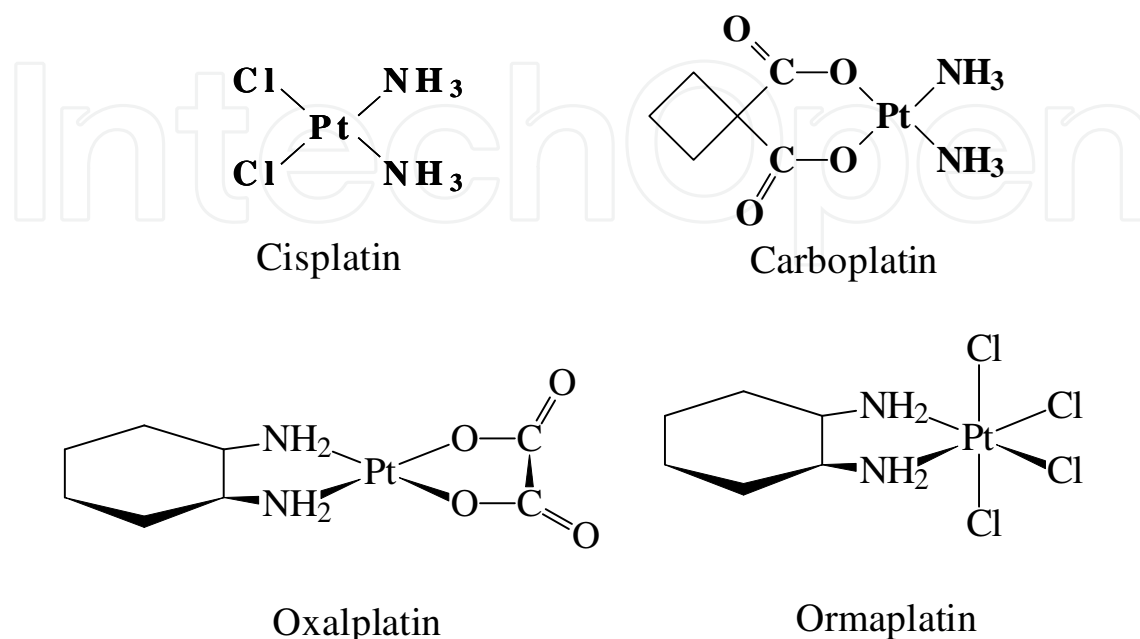


Fig. 1. The structures of some platinum complexes which are in clinical use worldwide.

The studies show that among the best drugs in the treatment of Chronic lymphocytic leukemia are the combination of Pt(II) complexes (cisplatin and oxaliplatin) and alkylating agents and nucleoside analogues such as fludarabine. (Zecevic et al., 2011) The nonoverlapping side effect profiles of oxaliplatin and fludarabine and their different but potentially complementary mechanisms of action provide a basis for investigation of the activity of the drugs in combination. The rationale for combining oxaliplatin with fludarabine is based on preclinical data showing synergistic cytotoxicity between cisplatin in combination with the nucleoside. (Wang et al., 1991; Yamauchi et al., 2001)

Consequently, knowledge of the interaction of the different Pt(II) complexes and nitrogen- and sulfur-bonding bio-molecules, and the results obtained from *in vitro* studies of this type of interactions will help in finding of good antitumor drug for the treatment of many tumors including the Chronic lymphocytic leukemia. The main topic of this chapter will be to show the results obtained in numerous studies of the interactions of the potential antitumor Pt(II) complexes and different biomolecules.

Platinum(II) has a high affinity for sulphur, so after administrating Pt(II) complex in the human body there is a strong possibility for binding with sulphur-donor bio-molecules. Sulphur-donor bio-molecules are present in large amounts in the form of peptides, proteins and enzymes. Binding of platinum complexes with sulphur-donor bio-molecules are responsible for the occurrence of toxic effects. (Lippert, 1999; Reedijk, 1999) However, a certain amount of platinum complexes being bound to nitrogen-donor bio-molecules (amino acids or DNA). Today it is generally accepted that the anti-tumor activity of platinum drugs can be ascribed to interactions between the metal complex and DNA, primarily with the

genetic DNA, which is located in the nucleus. The interactions with mitochondrial DNA are less responsible for the antitumor activity of the platinum complexes. (Fuertes et al., 2003) When the Pt(II) complexes reach the DNA, the possibilities for coordination are different. Binding of Pt(II) complexes to DNA primarily occurs through the N7 atoms of guanine, while a binding to N7 and N1 of adenine and N3 of cytosine occurs in small amount. (Lippert, 1999; Reedijk, 1999) Since the DNA molecule containing a different sequence of purine and pyrimidine bases, it was found that with 60% represented the coordination of the type 1,2-(GPG), i.e., the coordination realizes *via* two molecules of guanosine-5'-monophosphate (5'-GMP), which are located on opposite strands of DNA. About 25% is represented by coordination of the type 1,2-(APG), i.e. coordination with adenosine-5'-monophosphate (5'-AMP) and 5'-GMP placed on opposite DNA strands. Other ways of coordinations (monofunctional binding of the type 1,3-(GPG), coordination *via* guanine located on the same chain of DNA, etc.) are less frequent. On the Fig. 2. is shown the different ways of coordination of cisplatin to DNA. (Jakupec et al., 2003; Kozelka et al., 1999)

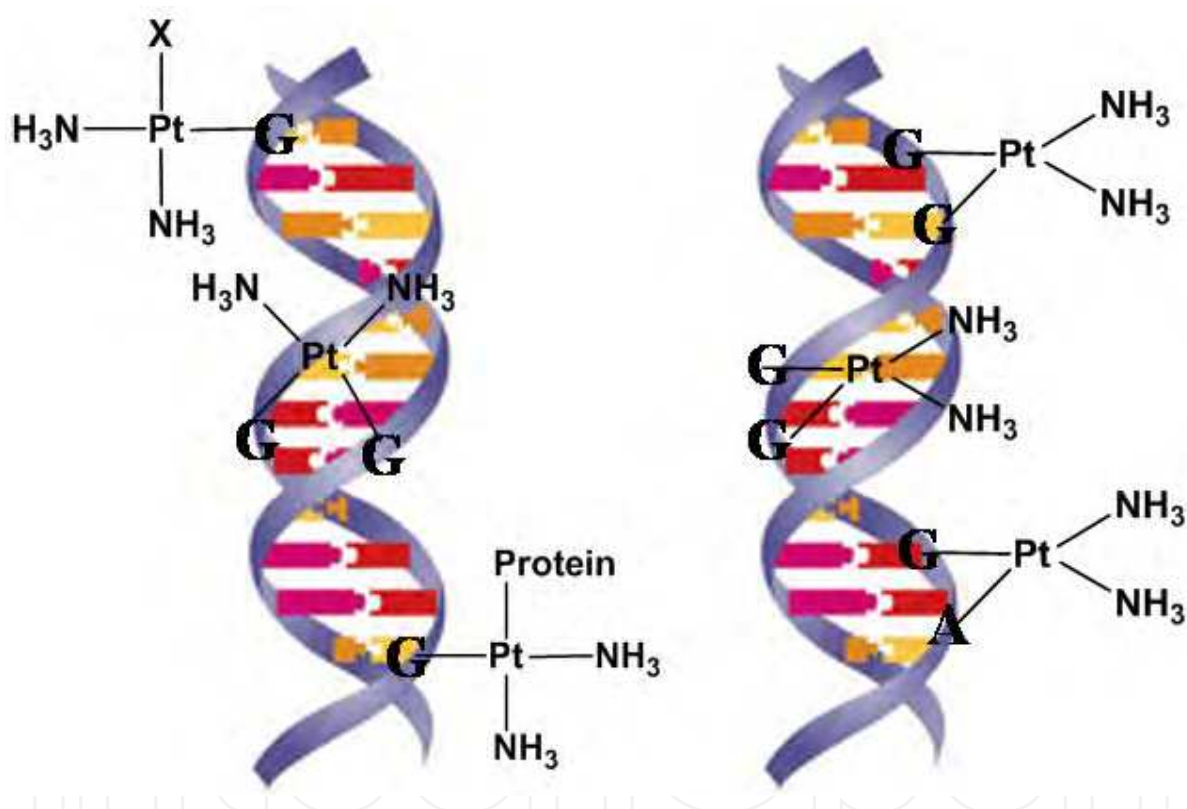
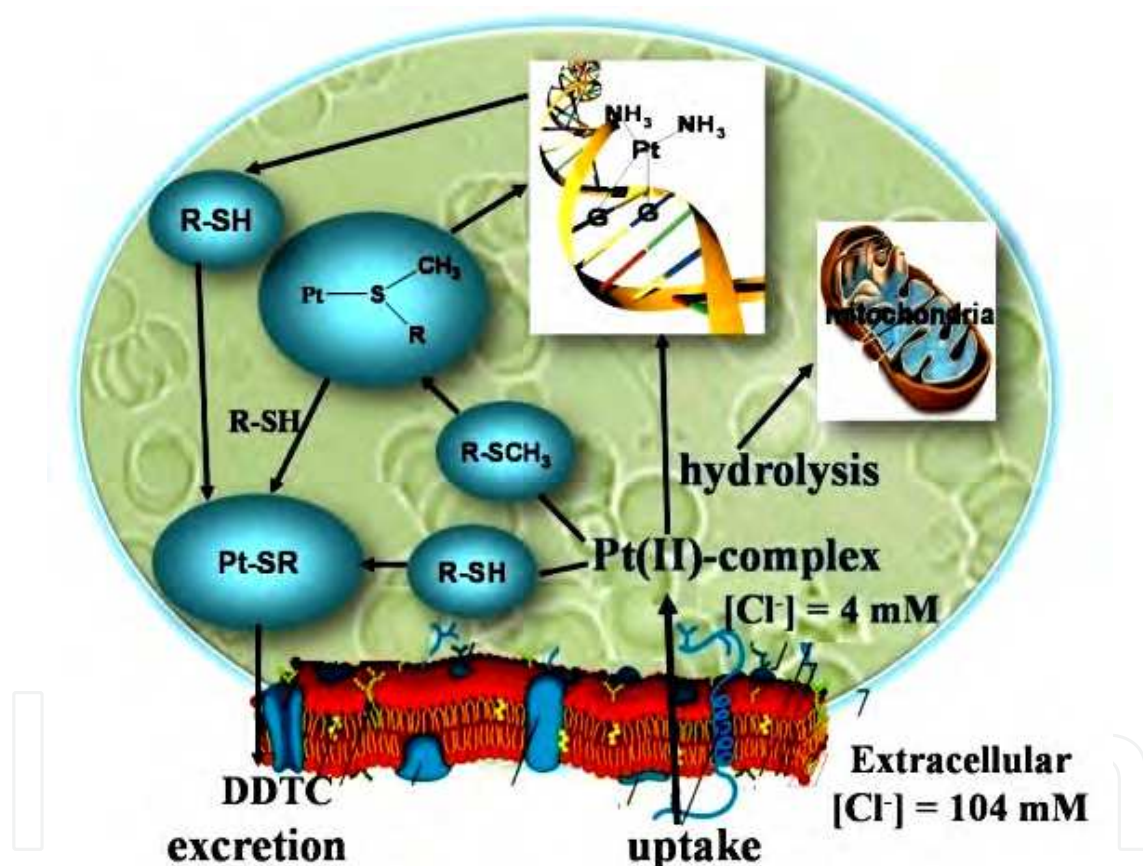


Fig. 2. The different ways of coordinations of cisplatin to DNA.

However, as noted above, the cells contain other bio-molecules which can also react with platinum complexes. High affinities for the platinum complexes show the bio-molecules that contain sulphur, as the thiols and the thioethars. Namely, Pt(II) as "soft" acid forms very stable compounds with sulphur donor ("soft" bases). The resulting compounds are responsible for the occurrence of toxicity (nephrotoxicity, neurotoxicity, resistance, etc.). Since the concentration of thiols, including glutathione (GSH) and L-cysteine, in intracellular liquid is about 10 mM, it is assumed that most of the platinum complex bound to sulphur before it comes to the molecules of DNA. (Jakupec et al., 2003; Reedijk, 2009; Lippert, 1999; Reedijk, 1999) Binding of platinum complexes to sulphur from thioethars are the kinetically favored

process. The resulting Pt-S(thioether) bond may be terminated in the presence of DNA, i.e. N7 atom of 5'-GMP can substitute the molecule of thioether. (Reedijk, 1999; Soldatović & Bugarčić, 2005) For these reasons the compounds of the type Pt-S(thioethers) are believed to be the reservoirs of "platinum complexes" in the body, i.e. they are suitable intermediates in the reaction of Pt(II) complexes and DNA. Pt-S(thioethers) bond can be terminated in the presence of thiol molecules. The product of this substitution is thermodynamically stable. Also, Pt(II) complex can directly bind to sulphur from thiol molecules and the resulting Pt-S(thiol) bond is very stable and can not be easily broken. It is believed that compounds of the type Pt-S(thiol) are responsible for the occurrence of toxic effects during the use of Pt(II) complexes as anticancer reagents. The Pt-S(thiol) bond can be terminated in the presence of compounds known as "rescue agents", which are compounds with sulphur and they are very strong nucleophiles (diethyldithiocarbamate, thiourea, thiosulfate, GSH, cysteine, biotin, etc.). (Jakupec et al., 2003; Fuertes et al., 2003; Soldatović & Bugarčić, 2005)



Scheme 1. Schematic presentation of the levels of action of cisplatin in the cell and possible biological consequences.

In recent years a much attention has given to studies of the antitumor activity of polynuclear Pt(II) complexes structurally similar to cisplatin. (Harris et al., 2005) The bridge ligand can be diamine ligands of the type $\text{NH}_2(\text{CH}_2)_n\text{NH}_2$ ($n = 6$). (Mambanda et al., 2010) In the reaction with DNA primarily is obtained compound in which complex is bound simultaneously to both spirale. (Mambanda et al., 2010; Berners-Price et al., 2003) It was found that the presence of the hydrophobic part of the molecule enhances the absorption of these compounds on the cell membrane, where their activity decrease. Also, the polynuclear Pt(II)

complexes with heterocyclic nitrogen compounds as bridge ligands were synthesized. (Lakomska et al., 2009)

Pt(IV) complexes are also very interesting. They react more slowly than the corresponding Pt(II) complexes. (Ali et al., 2005) It assumed that first Pt(IV) complexes by reduction translate to Pt(II) complexes and then the mechanism of action is the same as in the case of Pt(II) complexes. (Talman et al., 1997) For the reduction of Pt(IV) complexes can serve GSH, L-cysteine, L-methionine, DL-penicilamin (Lemma et al., 2000a) or ascorbic acid. (Lemma et al., 2000b)

Besides the already mentioned complexes of Pt(II), there are other platinum compounds such as *trans*-[PtCl₂(NH₃)₂] which does not show antitumor activity. (Jolley et al., 2001) These complexes were also intensively studied, (Natile & Coluccia, 2001) as well as some dinuclear complexes of *trans*-geometry. (Jansen et al., 2002) Special attention in recent years were given to the investigation of dinuclear complexes of platinum and paladium. (Mock et al., 2001)

2. Interaction of monofunctional Pt(II) complexes with sulphur- and nitrogen-donor bio-molecules

Monofunctional complexes of Pt(II) are a complexes which in structure contains a stable tridentate ligand, while the fourth coordination place is occupied with labile ligand, mostly chloride ligand. Because of this structure these complexes are not able to bind bifunctionally to the DNA molecule. Accordingly to this monofunctional complexes of Pt(II) do not exhibit antitumor properties. However, one place for coordination greatly simplifies testing of substitution reactions of these complexes. For these reasons monofunctional complexes present model molecules for the study of interactions of Pt(II) complexes and bio-molecules which contain sulphur- and nitrogen-donor ligands.

Probably the greatest interest in examining substitution reactions of the monofunctional complexes are for complexes of general formula [Pt(NNN)X], where NNN represents a tridentate ligand coordinated *via* three nitrogen donor atoms, while X is a labile ligand, usually chlorido ion. Most intensively studied compounds from this group are [Pt(dien)Cl]⁺, where *dien* is diethylentriamine or 1,5-diamino-3-azapentane, [Pt(bpma)Cl]⁺, where *bpma* is bis-(2-pyridylmethyl)amine, and [Pt(terpy)Cl]⁺, where *terpy* is (2,2':6',2''-terpyridine).

2.1 Interaction of [Pt(dien)Cl]⁺ complex with sulphur- and nitrogen-donor bio- molecules

There are a large number of studies of substitution reactions of the [Pt(dien)Cl]⁺ complex and his aqua analog, with different ligands and in different experimental conditions. This studies including investigations of the substitution reactions of the [Pt(dien)Cl]⁺ complex with sulphur-donor ligands, especially with thiols and thioethers and nitrogen-donor ligands.

In the substitution reactions of [Pt(dien)Cl]⁺ with GSH it was observed that substitution process depends on the pH value at which the reaction is studied. (Đuran et al. 1991; Bose et al., 1995; Tauben et al. , 2000; Petrović B. & Bugarcic, 2001) At pH > 7 as the only reaction product are obtained mononuclear complexes [Pt(dien)GS]⁺, while at pH < 7 a binuclear

complex $[\text{Pt}(\text{dien})_2\text{GS}]^{3+}$ with GSH as the bridging ligand forms. Also, the process of substitution is followed by deprotonation of GSH, which is observed in the reactions of other Pt(II) complexes with thiols. (Bugarčić & Đorđević, 1998) When the ligand is thioether, S-methyl-glutathione, reactions are much faster, but the product with thiol is thermodynamically more stable. (Tauben et al., 2002) Comparing the values of rate constants of substitution reactions of $[\text{Pt}(\text{dien})\text{Cl}]^+$ complexes with different thiols and thioethers, (Tauben et al., 2000; Petrović B. & Bugarčić, 2001; Bugarčić & Đorđević, 1998; Lampers & Reedijk, 1990) it was noted a discrepancy of GSH compared to other thiols. GSH is a tripeptide that contains an unusual peptide linkage between the amine group of L-cysteine (which is attached by normal peptide linkage to a L-glycine) and the carboxyl group of the glutamate side-chain, with a L-cysteine molecule at the center. It was assumed that the substitution process was much slower compared to L-cysteine. However, the experimentally obtained values showed a much higher reactivity of GSH. This is explained by a suitable geometrical structure of molecules, which cause the formation of intramolecular hydrogen bond involving the proton from the thiol groups, resulting in significantly increased nucleophilicity of the sulphur atoms and therefore higher reactivity. (Bugarčić et al., 2004a; Petrović B. & Bugarčić, 2001; Bugarčić & Đorđević, 1998)

During the substitution reaction of the $[\text{Pt}(\text{dien})\text{Cl}]^+$ complexes with L-methionine (Petrović B. & Bugarčić, 2001; Lampers & Reedijk, 1990; Barnham et al., 1994) as a reaction product primarily has been formed complex $[\text{Pt}(\text{dien})(\text{L-methionine})]^{2+}$. It was noted that only in very acidic solutions ($\text{pH} < 1$) there is a possibility for protonation of the terminal amino groups of *dien* ligand, which leads to the opening of one chelate ring and the creation of *S,N*-chelate. (Chen et al., 1998) Reaction between $[\text{Pt}(\text{dien})\text{Cl}]^+$ complexes and L-methionine was studied in the presence of 5'-GMP, assuming the existence of competition of this two ligands. (Lampers & Reedijk, 1990; Soldatović & Bugarčić, 2005) The $[\text{Pt}(\text{dien})\text{Cl}]^+$ first reacts with L-methionine and form $[\text{Pt}(\text{dien})(\text{L-methionine})]^{2+}$ product. Then 5'-GMP molecule coordinated to Pt(II) by substitution of coordinated L-methionine forming thermodynamically more stable $[\text{Pt}(\text{dien})(\text{N7-GMP})]^{2+}$ complex.

INO, 5'-IMP and 5'-GMP can coordinate to metal ions *via* N1 and N7. (Arpalahti & Lehkoinen, 1990; Arpalahti & Lippert, 1990; Caradonna & Lippard, 1988; Bose et al., 1986; Martin, 1999) Under $\text{pH} = 2.5$ only the N7 position of INO, 5'-IMP and 5'-GMP will be free for coordination to the central metal atom, since at this pH the N1 position is protonated. (Sigel et al., 1994) Binding through the N7 position in a neutral or weakly acidic medium has been verified. (Bugarčić et al., 2004a) 5'-GMP is more reactive toward Pt(II) complexes than either INO or 5'-IMP. Furthermore, the pH at which anti-tumor complexes bind to DNA is significantly higher than this one. It is expected that at neutral pH the phosphate residue on the nucleotide will also bind to the central metal atom as a result of its deprotonation. (Jacobs et al., 1992)

From a comparison of the reactivity of GSH or L-methionine with INO, 5'-IMP and 5'-GMP in the reaction with $[\text{Pt}(\text{dien})(\text{H}_2\text{O})]^{2+}$, $[\text{Pt}(\text{dien})\text{Cl}]^+$ and $[\text{Pt}(\text{dien})\text{Br}]^+$ (Soldatović & Bugarčić, 2005) can be concluded that these N-bonding ligands are good nucleophiles. This small difference in the reactivity of N-bonding (INO, 5'-IMP and 5'-GMP) and S-bonding nucleophiles (GSH and L-methionine) is not usually. The complex formation reactions have been studied at pH 2.5 where GSH and L-methionine are protonated. On the other hand, at pH 2.5, N7 sites of N-bonding ligands are not protonated. However, at

neutral pH, although less than 10% of thiols are deprotonated, the N-bonding ligand cannot compete with the thiols. The second-order rate constant for GSH is 10^2 times higher than for the 5'-GMP. (Bugarčić et al., 2004b) Also, from obtained results, (Soldatović & Bugarčić, 2005) could be concluded that L-methionine is the best nucleophile for the Pt(II) complexes. This could be explaining by positive inductive effect of the methyl group on the sulphur. However, this is in agreement with the previous results. (Petrović B. & Bugarčić, 2001)

Competitive reactions of $[\text{Pt}(\text{dien})\text{Cl}]^+$ with L-methionine and 5'-GMP demonstrated initially rapid formation of $[\text{Pt}(\text{dien})(\text{L-methionine})]^{2+}$ followed by displacement of L-methionine by 5'-GMP. In the later stages the concentration of $[\text{Pt}(\text{dien})(\text{N7-GMP})]^{2+}$ is predominant. (Soldatović & Bugarčić, 2005)

The reactions of $[\text{Pt}(\text{dien})\text{Cl}]^+$ (10 mM) with L-methionine and 5'-GMP in a molar ratio: $[\text{Pt}(\text{dien})\text{Cl}]^+ : \text{L-methionine} : 5'\text{-GMP} = 1:1:3$ were also studied. (Soldatović & Bugarčić, 2005)

In the initial stage of the reactions (< 40 h) ^1H NMR peak for the free L-methionine (d 2.142 ppm) decrease in the intensity and new peak of the $[\text{Pt}(\text{dien})(\text{L-methionine})]^{2+}$ appeared in the spectrum (d 2.544 ppm), whereas a little of the 5'-GMP reacted. In the later stages (72 h), the peaks for the bounded L-methionine and free 5'-GMP (d 8.208 ppm) decreased in intensity, whereas those for free L-methionine increased in intensity, as did those assignable to bound 5'-GMP in $[\text{Pt}(\text{dien})(\text{N7-GMP})]^{2+}$ (d 8.624 ppm) as shown in Fig. 3

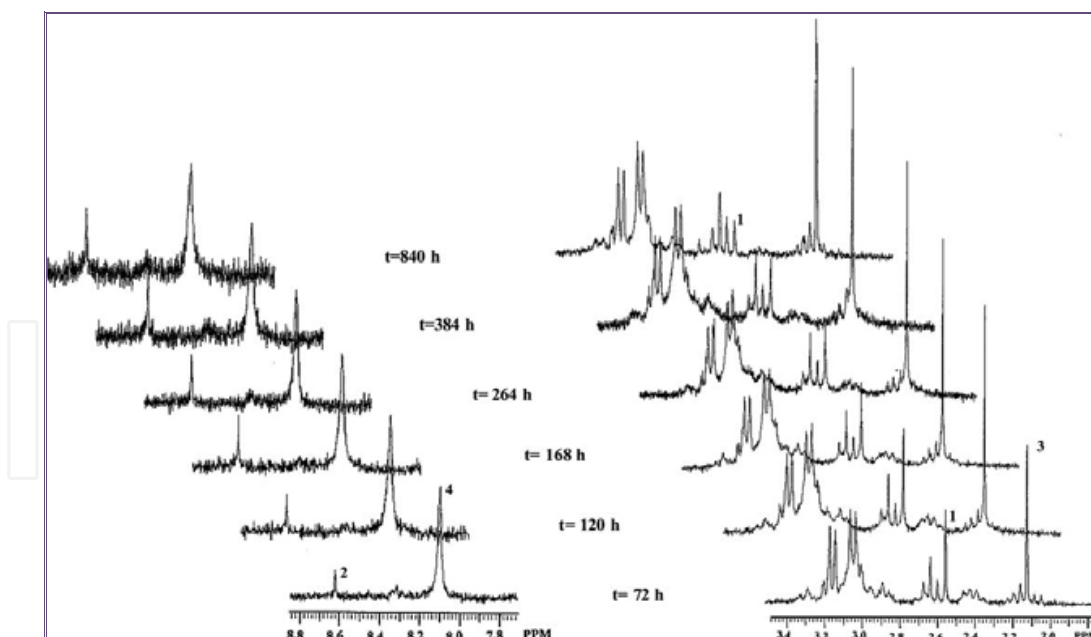


Fig. 3. ^1H NMR spectra of the reactions of $[\text{Pt}(\text{dien})\text{Cl}]^+$ (10 mM) with mixture of L-methionine and 5'-GMP in the ratio 1:1:3 (where 1 is the signal for the $[\text{Pt}(\text{dien})(\text{L-methionine})]^{2+}$, 2 is the signal for the $[\text{Pt}(\text{dien})(\text{N7-GMP})]^{2+}$, 3 is the signal for the free L-methionine and 4 is the signal for the free 5'-GMP. (Soldatović & Bugarčić, 2005)

Moreover, Pt-thioether adducts are more easily converted into Pt-thiolate adduct than Pt-N7-GMP adduct. (Teuben et al., 2000) On the other hand, it has been known that 5'-GMP cannot substitute thiols from Pt-thiolate adduct. (Bugarčić et al., 2004a) These findings could have implications for the mechanism of action of platinum anticancer drugs. Sulphur-bonding ligands have a much higher affinity for Pt(II) complexes than nitrogen-bonding ligands. (Bugarčić et al., 2004a; Bugarčić et al., 2002a) Moreover, nephrotoxicity has been explained by the formation of Pt-S(GSH) adduct.

Product in reactions of the $[\text{Pt}(\text{dien})\text{Cl}]^+$ complexes with thioethers or nucleotides in the presence of glutathione is a very stable complexes of the type $[\text{Pt}(\text{dien})\text{SG}]^+$, which confirms the fact that the Pt-S(thiol) bond is the most stable. (Bose et al., 1995) The Pt-S(thiol) bond can be terminated only in the presence of certain nucleophiles with sulphur, such as diethyldithiocarbamate, thiosulphate, thiourea. (Bugarčić et al., 2004a) Interesting is attempt to hydrolysed Pt-S(GSH) bond in the presence of transition metal ions Cu(II) and Zn(II). (Cheng & Pai, 1998)

2.2 Interaction of $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex with sulphur- and nitrogen-donor biomolecules

In addition, $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex was also extensively studied. $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex has some biological activity. (Becker et al., 2001) In square-planar planes it contains tridentate-coordinated terpyridine system (terpy = 2,2':6',2''-terpyridine), while the fourth coordination site occupies chloro ligand.

Tridentate-coordinated terpyridine system, because of the presence of the aromatic pyridine unit and because of their bulkiness, strongly affects on the characteristics of this complex. In fact, $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex is much more reactive than complex with *dien* ligand. (Hofmann et al., 2003) The obtained values for lengths of chemical bonds between the platinum(II) and three nitrogen donor atoms of terpyridine system show that the shortest connection is to the secondary nitrogen atom. This feature is certainly reflected on its reactivity in the processes of substitution. In addition, the presence of electrostatic interactions between the pyridine units and metal ions has been observed in crystal structures of various Pt-terpy complexes. (Bailey et al., 1995)

Although the high reactivity of the complex depend on the electronic interactions between the terpyridine system and Pt(II), (Hofmann et al., 2003) bulkiness of the *terpy* ligand has great influence on the characteristics of this complex. The substitution reactions of the $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complexes with different thioethers has been confirmed that there is no reaction, (Petrović B. et al., 1999; Bugarčić et al., 1997) which can be attributed to the strong steric effect. Although, the reactions of $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complexes with some S-methyl-thioethers and thiones may occur, but in this case as the product of reactions appear dinuclear platinum complexes in which the bridge ligand is S-methyl-group. (Annibale et al., 1999) High reactivity of the $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex in substitution reactions with thiols is explained by formation of intramolecular hydrogen bonds between protons from the thiol-group and outgoing chloro ligand, which further stabilizes the transition state. (Annibale et al., 1998; Petrović B. et al., 1999; Bugarčić et al., 1997)

In the reaction between biologically relevant ligands and Pt(II) complexes, DNA fragments usually coordinated through the N7 atom to Pt(II). (Bugarčić et al., 2004b) Several products

of the reaction between $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex and DNA fragments were synthesized and characterized by X-ray analysis, in which the presence of strong intramolecular hydrogen bonds are observed. The role of these bonds are to further stabilizes the products of the reaction. (Wong & Lippard, 1977)

The kinetics of the complex-formation reactions between $[\text{Pt}(\text{terpy})\text{H}_2\text{O}]^{2+}$, with thiols: L-cysteine, DL-penicillamine, GSH, and with thiourea were studied. (Bugarčić et al., 2002a) Rate constants and activation parameters derived from these experiments are summarized in Table 1.

L	$k_1^{298}/\text{M}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J K}^{-1} \text{mol}^{-1}$	$\Delta V^\ddagger/\text{cm}^3 \text{mol}^{-1}$
L-Cysteine	37.8 ± 0.1	25 ± 0.5	-132 ± 2	-9.3 ± 0.4
L-Glutathione	$(5.8 \pm 0.1) \times 10^2$	23 ± 1	-116 ± 3	-12.4 ± 0.6
DL-Penicillamine	12.8 ± 0.1	38 ± 1	-98 ± 3	-20.6 ± 1.0
Thiourea	$(1.72 \pm 0.02) \times 10^5$	22 ± 1^b	-73 ± 1^b	-6.0 ± 0.3^b

^aAll values refer to 0.10 M HClO₄ (Bugarčić et al., 2002a) ^bData from Jaganyi et al., 2001

Table 1. Rate constants and activation parameters for the reaction of $[\text{Pt}(\text{terpy})\text{H}_2\text{O}]^{2+}$ with thiols and thiourea.

From Table 1. can be seen that although the thiol ligands are good entering groups for the Pt(II) complex, thiourea is the best nucleophile. From a comparison of the thiols used, it can be concluded that the variation in size, bulkiness and salvation of the entering ligands reflect in their properties as nucleophiles. The difference in nucleophilicity of the selected ligands is obvious and their reactivity follows the order; DL-penicillamine < L-cysteine < GSH < thiourea. The sensitivity of the reaction rate towards the σ -donor properties of the entering ligands is in line with that expected for an associative mode of activation. In addition, steric effects are very important as well. For example, DL-penicillamine has the lowest reactivity of the thiols used. This can be attributed to the steric effects involving the two methyl groups on carbon near the sulphur atom. At the same time, GSH is considerably more reactive than expected. This anomaly seems to suggest an appreciable anchimeric effect capable of reducing the activation energy of the substitution reaction, arising from hydrogen bonding interactions between the acidic group located in a suitable position of the nucleophile. The anchimeric effect has been reported for other reactions at Pt(II) complexes and is well known for organic reactions. (Wilkins, 1991) This clearly demonstrates that the versatile kinetic behaviour is controlled by steric hindrance on the tridentate ligand and the nucleophilicity of the entering nucleophiles. Increasing steric hindrance is expected to slow down the ligand substitution reactions, whereas increasing nucleophilicity is expected to speed up this process in terms of an associative mechanism.

A trigonal bipyramidal transition state for reaction of $[\text{Pt}(\text{terpy})\text{H}_2\text{O}]^{2+}$ with thiols, is probably stabilized by hydrogen bonding between the entering thiol and the leaving water ligand as already proposed for the reaction of $[\text{Pd}(\text{H}_2\text{O})_4]^{2+}$ with monodentate acetate, propionate, glycolate, and carboxylic acids (Shi & Elding, 1996, 1997) and for $[\text{Pt}(\text{H}_2\text{O})_4]^{2+}$ with thioglycolic acid. (Bugarčić & Đorđević, 1998) These findings indicate that bond-making with the entering thiol is important in the activation process and that water is still tightly bound to the metal centre in the transition state.

Also, the reactions between $[\text{Pt}(\text{terpy})\text{Cl}]^+$ and thiols, such as GSH, L-cysteine, DL-penicillamine and thioglycolic acid have been studied. (Petrović B. et al., 1999) These thiols are very good entering groups for Pt(II) complex. The reaction of the Pt(II) complex and DL-penicillamine is also the slowest one (Table 2.).

The complex $[\text{Pt}(\text{terpy})\text{Cl}]^+$ appears to be more reactive than $[\text{Pt}(\text{dien})\text{Cl}]^+$ (Table 2.) in accordance with the greater possibility of π -interaction and π -*trans* effect probably operating as well. The Pt-N distance to the middle nitrogen atom of the terpyridine ligand, 1.930(4) Å is slightly shorter than the distances of Pt to the other two nitrogen atoms, N1, 2.018(5) and N3 2.030(5). (Hofmann et al., 2003)

	$k_2/\text{M}^{-1}\text{s}^{-1}$ $[\text{Pt}(\text{dien})\text{Cl}]^+$	$k_2/\text{M}^{-1}\text{s}^{-1}$ $[\text{Pt}(\text{terpy})\text{Cl}]^+$
Thioglycolic acid	7.86×10^{-3}	5.62×10^{-2}
L-Cysteine	1.43×10^{-3}	1.06×10^{-2}
D-penicillamine	8.04×10^{-4}	6.02×10^{-3}
Glutathione	3.85×10^{-3}	7.77×10^{-2}

Table 2. The second-order rate constants for the reactions between thiols and Pt(II) complexes at T = 295 K. (Petrović B. et al., 1999)

As in the case of $[\text{Pt}(\text{dien})\text{H}_2\text{O}]^{2+}$, the kinetic data clearly show that 5'-GMP is more reactive to $[\text{Pt}(\text{terpy})\text{H}_2\text{O}]^{2+}$ than either INO and 5'-IMP in 0.1 M NaClO_4 and at pH = 2.5. (Bugarčić et al., 2004a) On the contrary, in the reactions of $[\text{Pd}(\text{SMC})(\text{H}_2\text{O})_2]^{2+}$ with the same nucleophiles, (Bugarčić et al., 2002b) the most reactive one was INO, which can be attributed to a primary process that involves partial preassociation of the metal complex with the phosphate group in 5'-GMP and 5'-IMP. Furthermore, the pH at which antitumour complexes bind to DNA is significantly higher than used in this study. It is expected that at neutral pH the phosphate residue on the nucleotide will also bind to the central metal atom as a result of its deprotonation. (Jacobs et al., 1992) From a comparison of the reactivity of thiols (L-cysteine, DL-penicillamine and GSH) (Bugarčić et al., 2002a), with INO, 5'-IMP and 5'-GMP in the reaction with $[\text{Pt}(\text{terpy})\text{H}_2\text{O}]^{2+}$, it can be concluded that these N-bonding ligands are even better nucleophiles than the mentioned thiols. The preference of these N-bonding nucleophiles over thiols in acidic solutions needs to be addressed. It must be kept in mind that the reactions with thiols have been investigated at pH 1, where all thiols were protonated. On the other hand, at pH 2.5 the N7 sites of INO, 5'-IMP and 5'-GMP are not protonated. However, at or near neutral pH, although less than 10% of thiols are deprotonated, the N-bonding bases cannot compete with the thiol containing amino acids and peptides. (Bose et al., 1995; Volckova et al., 2002) Therefore, binding primarily takes place through the sulphur donor sites. However, for the GSMc system, rapid coordination to the sulphur atom followed by migration to the N7 site of the purine was observed. (Teuben et al., 1977) Similar competition experiments of the bifunctional platinum complex, *cis*-dichloro-(ethylenediamine)platinum(II) and its hydrolysed forms with a mixture of 5'-GMP or dGpG and thioether containing di- and tri-peptides, also afforded sulphur bound intermediates, followed by the formation of N7 coordinated guanine products. (Barnham et al., 1996)

Several sulphur donor ligands are usually co-administered with platinum drugs to reduce the toxicity. (Chen et al., 1998; Berners-Price et al., 1996) Some of them, such as GSH, DEDTC, thiosulfate and thiourea, were used in the study with $[\text{Pt}(\text{terpy})(\text{cyst-S})]^{2+}$ and $[\text{Pt}(\text{terpy})(\text{gua-N7})]^{2+}$ complexes. (Bugarčić et al., 2004a) The X-ray structure of the $[\text{Pt}(\text{terpy})(\text{cyst-S})]^{2+}$ and $[\text{Pt}(\text{terpy})(\text{gua-N7})]^{2+}$ complexes were determined. (Bugarčić et al., 2004a)

The $[\text{Pt}(\text{terpy})(\text{cyst-S})]^{2+}$ complex is unreactive toward nitrogen binding ligands and cysteine cannot be replaced by N7 from INO, 5'-IMP and 5'-GMP. However, very strong sulphur-donor nucleophiles, such as DEDTC, thiosulfate and thiourea, could reverse the Pt-cysteine bond under pH *ca.* 6. (Bugarčić et al., 2004a) This results clearly show that therapeutic nucleophilic agents for platinum drugs, such as DEDTC, thiosulfate and thiourea, may help to displace Pt from Pt-cysteine adducts and in that way could reduce nephrotoxicity.

It is widely accepted that, once formed, the Pt-nucleobase complexes are inert under mild conditions and in the absence of strong *trans*-labilising ligands. (Lippert, 1999) In contrast, the presence of strong nucleophiles, for instance sulphur-containing bio-molecules, could facilitate the dissociation of N-coordinated nucleobases from the Pt(II) complex. In particular, various sulphur-containing molecules have aroused considerable interest owing to their important roles in the biological processing of anticancer platinum drugs. (Reedijk, 1999) The substitution reactions of monofunctional $[\text{Pt}(\text{dien})(\text{L-N7})]^{2+}$ (L = adenosine or guanosine) with thiourea have been studied in acidic aqueous solution. (Mikola et al., 1999) The substitution of guanosine from $[\text{Pt}(\text{terpy})(\text{guo-N7})]^{2+}$ by some sulphur-donor nucleophiles which have been used as protecting agents were studied. (Bugarčić et al., 2004a) This result strongly indicate that all studied sulphur-donor nucleophiles could substitute guanosine from the Pt(II) complex. Also it is noticed that DEDTC and thiosulfate are the strongest nucleophiles and that these nucleophiles can very easily substitute guanosine from $[\text{Pt}(\text{terpy})(\text{guo-N7})]^{2+}$. However, the tripeptide GSH is a very efficient nucleophile as well. This observation could be very important since it is already known that GSH has numerous cellular functions, including the detoxification of chemotherapeutic agents. However, GSH has been used as protecting agent and administered before or after cisplatin. (Reedijk, 1999) Cisplatin readily reacts with GSH and as much as 67% of the administered platinum has been found to coordinate to GSH. However, the role of GSH appears to be dual: GSH deactivates and activates cisplatin. (Volckova et al., 2002) The higher effectiveness of cisplatin has also been demonstrated by co-administering cisplatin and GSH in patients. However, it is not clear whether this increase in effectiveness is due to the reduced toxicity or due to the modification of the platinum drug by binding to the metal. Currently there is much interest in the mechanisms responsible for the development of resistance. Such resistance is often associated with increased cellular GSH, consistent with the view that GSH protects cells against foreign compounds and the effects of radiation. (Jaganyi & Tiba, 2003) From our results we can conclude that the employed rescue or protecting agents such as thiourea, thiosulfate and DEDTC can much easier substitute guanosine than L-cysteine form the $[\text{Pt}(\text{terpy})\text{X}]^{2+}$ complex (X is guo-N7 or cyst-S). This is in excellent agreement with previous investigations, where has been shown that the Pt-S (cysteine) bond is very stable. (van Boom et al., 1999; Teuben et al., 2000; Pitteri et al., 2001) The thiolate ion is capable of providing a stronger binding affinity owing to its better σ -donating ability. Such a Pt-S bond is considered relatively inert may cause the inhibition of the anticancer activity of platinum drugs.

The kinetics for the complex formation of the $[\text{Pt}(\text{terpy})\text{Cl}]^+$ with 5'-GMP in the presence and absence of GSH at pH *ca.* 6, with a concentration ratio $[\text{Pt}(\text{terpy})\text{Cl}]^+ : \text{GSH} : 5'\text{-GMP} = 1 : 2 : 10$ were studied. (Bugarčić et al., 2004b) The second order rate constants, obtained from linear least-squares analysis of the kinetic data (Bugarčić et al., 2004b) clearly point to a kinetic preference of $[\text{Pt}(\text{terpy})\text{Cl}]^+$ toward the GSH at pH *ca.* 6. 5'-GMP is also a very good nucleophile for Pt(II) complexes, but at neutral pH cannot compete with GSH. The second-order rate constant for GSH is 10^2 times higher than for 5'-GMP. This is also reflected in the competition reactions utilizing mixtures of GSH and GMP. Also, proton and ^{195}Pt NMR data did not show any N7 coordination of GMP, in spite of its excess, in the presence of thiols. (Teuben et al., 2000) However, at or near neutral pH, although less than 10% of thiols are deprotonated, the N-bonding bases cannot compete with the thiol containing amino acids and peptides. (Bugarčić et al., 2004a; Teuben et al., 2000) Therefore, binding primarily takes place through the sulphur donor sites. However, for the GSMe system, rapid coordination to the sulphur atom followed by migration to the N7 site of the purine was observed. (van Boom et al., 1999; Barnham et al., 1994)

The progress of the reaction of $[\text{Pt}(\text{terpy})\text{Cl}]^+$ with other compounds over extended periods of time can be monitored with techniques such as HPLC which allows aliquots separated from the reaction mixture at programmed times to be analyzed. The studied reactions were carried out in water, without any buffer, since buffer ions (*e.g.* phosphate) are potential ligands for Pt(II). The pH of each solution was regularly checked over the reaction time, and was shown to be kept between 4.5 and 5.5. The products formed were isolated by reversed-phase HPLC and characterized by MALDI-TOF mass spectrometry. As expected, the products obtained corresponded to the adducts $[\text{Pt}(\text{terpy})(\text{GS})]^+$ and $[\text{Pt}(\text{terpy})(5'\text{-GMP})]^+$ (m/z 734,2 and 789,8, respectively). The reaction between $[\text{Pt}(\text{terpy})\text{Cl}]^+$, GSH and 5'-GMP was then followed by HPLC. The ratio of the three compounds in the repeated assays was 1:1:12, respectively. It was observed that $[\text{Pt}(\text{terpy})\text{Cl}]^+$ reacted much faster with GSH than with 5'-GMP, but this did not prevent a small amount (< 16%) of $[\text{Pt}(\text{terpy})(5'\text{-GMP})]^+$ from being formed at the very beginning of the process. The relative proportion of this adduct remained virtually constant throughout the reaction process, which indicates that once formed it remains unaltered. The possibility that $[\text{Pt}(\text{terpy})(\text{GS})]^+$ reacts with the excess of 5'-GMP present in the reaction mixture to give $[\text{Pt}(\text{terpy})(5'\text{-GMP})]^+$ can be ruled out, unless GSH can replace 5'-GMP from $[\text{Pt}(\text{terpy})(5'\text{-GMP})]^+$ at the same reaction rate. The identity of the formed adducts was confirmed by mass spectrometric analysis of the products isolated from the reaction mixture by HPLC (Fig. 4.). (Bugarčić et al., 2004b)

2.3 Interaction of $[\text{Pt}(\text{bpma})\text{Cl}]^+$ complex with sulphur- and nitrogen-donor bio-molecules

In recent years, an intensive investigation of the substitution reactions of Pt(II) complexes which containing an inert tridentate nitrogen donor ligand with two or three pyridine units was performed. The role of these studies is to explain the effect of present pyridine on the reactivity of these compounds. For example, the complex $[\text{Pt}(\text{bpma})\text{Cl}]^+$, contains tridentate nitrogen donor ligand consisting of two pyridines connected *via* amide.

This complex in substitution reactions react faster than the $[\text{Pt}(\text{dien})\text{Cl}]^+$ complex, but slower compared to $[\text{Pt}(\text{terpy})\text{Cl}]^+$ complex. The substitution reactions of this complex with thiols. (Jaganyi & Tiba, 2003) pyridine, derivatives of pyridine (Pitteri et al., 2001), 5'-GMP, azoles

and diazines (Bogojeski and Bugarčić, 2011) were studied. It is interesting that the aqua complex, $[\text{Pt}(\text{bpma})(\text{H}_2\text{O})]^{2+}$, which crystallizes with perchlorate as external ions, acts as a double base acid, because in the process of deprotonation the second stage involved coordinated amido group. (Pitteri et al., 2002)

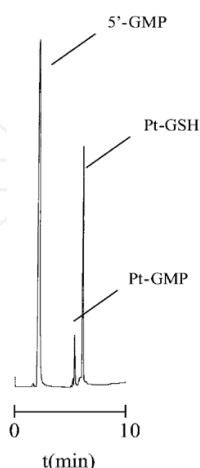
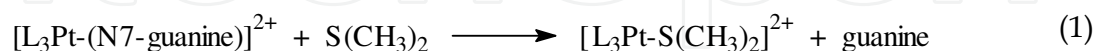


Fig. 4. HPLC profile of an aliquot of the reaction mixture $[\text{Pt}(\text{terpy})\text{Cl}]^+/\text{glutathione}/5'\text{-GMP} = 1:1:12$ after 1 week reaction time.

The substitution reactions of $[\text{Pt}(\text{bpma})\text{Cl}]^+$ and $[\text{Pt}(\text{bpma})(\text{H}_2\text{O})]^{2+}$ with L-methionine, GSH and 5'-GMP were studied. (Bugarčić et al., 2007) The reactions of the chloro complexes were followed in the presence of 10 mM NaCl and at $\text{pH} \approx 5$, whereas the reactions of the aqua complexes were studied at $\text{pH} 2.5$. The nucleophilic attack of these ligands occurs *via* the sulphur donor of the thioether group in the case of L-methionine and of the thiol group in the case of GSH. L-methionine appears to be a better nucleophile than GSH under these experimental conditions. This could be explained by the positive inductive effect of the methyl group on the sulphur donor. (Bugarčić et al., 2007)

Transformation from Pt-S(thioether) to Pt-N7(GMP) coordination seems to be common. (Reedijk, 1999; Soldatović & Bugarčić, 2005) To obtain more quantitative data for the stability differences between Pt-DNA and Pt-S(thioether) adducts, it was performed DFT calculations applying the model reaction (Eq. 1.) (L_3 is terpy, bpma, dien, gly-met-S,N,N), where guanine approximates the guanosine-based interactions and SR_2 represents a generic thioether:



In all cases guanine coordination to the L_3Pt fragment is much more favored than thioether coordination. As shown in Table 3.

The $[\text{Pt}(\text{bpma})\text{Cl}]^+$ and $[\text{Pt}(\text{bpma})(\text{H}_2\text{O})]^{2+}$ complexes are more reactive than $[\text{PtCl}(\text{gly-met-S,N,N})]$ and $[\text{Pt}(\text{glymet-S,N,N})(\text{H}_2\text{O})]^+$. This can be explained by the steric effect of the coordinated S- CH_3 group in the *cis* position in $[\text{Pt}(\text{gly-met-S,N,N})(\text{H}_2\text{O})]^+$ and $[\text{PtCl}(\text{gly-met-S,N,N})]$. Moreover, another reason for the higher reactivity of the $[\text{Pt}(\text{bpma})(\text{H}_2\text{O})]^{2+}$ and $[\text{Pt}(\text{bpma})\text{Cl}]^+$ complexes is the presence of two pyridine rings in the coordination sphere. This has been studied in detail for a set of monofunctional Pt(II) complexes with

tridentate ligands in which the number and position of the amine and pyridine groups were systematically varied. (Hofmann et al., 2003) The presence of π -acceptor ligands promotes the electrophilicity of the metal center and thereby the nucleophilic attack. (Hofmann et al., 2003; Jaganyi et al., 2001) This behavior distinguishes these complexes from classic platinum drugs where such effects are not present.

L ₃	B3LYP/LANL2DZp	B3LYP(CPCM)/LANL2DZp// B3LYP/LANL2DZp
terpy	running (ca. 27 kcal/mol)	Still running kcal/mol
bpma	+28.7 kcal/mol	+12.8 kcal/mol
dien	+34.1 kcal/mol	+11.0 kcal/mol
Gly-Met-N,N,S	+21.5 kcal/mol	+9.5 kcal/mol
Gly-Met-N,N,S (without H-bond)	+17.5 kcal/mol	+8.5 kcal/mol

Table 3. DFT results for model eq. (1)

¹H NMR spectroscopy was used to investigate the substitution reactions of the chloro complexes [Pt(bpma)Cl]⁺ and [PtCl(gly-met-S,N,N)] with 5'-GMP. The substitution reactions were studied in D₂O at 298 K. (Bugarčić et al., 2007)

The reaction of [PtCl(gly-met-S,N,N)] with 5'-GMP is approximately 50 times slower than the reactions of this complex with L-methionine or GSH. This could be accounted for in terms of steric effects of the incoming 5'-GMP and the complex as well. On the other hand, for the reactions with [Pt(bpma)Cl]⁺ the rate constants are of the same order of magnitude, but L-methionine is the best nucleophile and 5'-GMP is the poorest one. However, the [Pt(bpma)Cl]⁺ complex is much more reactive towards 5'-GMP than [PtCl(gly-met-S,N,N)]. (Bugarčić et al., 2007) This is in agreement with earlier published findings. (Volckova et al., 2002; Tauben et al., 2000)

Substitution reactions of the complex [Pt(bpma)(H₂O)]²⁺ with TU, DMTU and TMTU Cl⁻, Br⁻, I⁻ and SCN⁻, were studied in aqueous 0.10 M NaClO₄ at pH 2.5. (Jaganyi et al., 2006) Based on the second order rate constants, *k*₂, it can be concluded that the reactivity of the nucleophiles towards the complex follows the order: TMTU < TU < DMTU. The observed trend for the platinum complex was also reported earlier in the literature for the substitution reactions of the coordinated water molecule from [Pt(dien)(H₂O)]²⁺, [Pt(terpy)(H₂O)]²⁺ and [Pt(bpma)(H₂O)]²⁺ complexes. (Shoukry et al., 1998; Bugarčić et al., 2004c)

The observed trends can be attributed to the different structures (in terms of steric and inductive effects) of these three nucleophiles. The order of increasing steric hindrance for these nucleophiles is: TMTU < DMTU < TU. Theoretically, it would be expected that TU would react much faster than the other two nucleophiles. Instead, it turns out that DMTU is a much better nucleophile than TMTU and TU. This enhanced reactivity is due to the inductive effect introduced by the two methyl groups in the case of the DMTU, which over compensate the steric effect. (Jaganyi et al., 2006)

3. Interaction of bifunctional Pt(II) complexes with sulphur- and nitrogen-donor bio-molecules

In order to achieve the best possible strategy in the designing of antitumor platinum complexes, it is necessary to know how mentioned compounds react with various sulfur- and nitrogen-donor bio-molecules. Significant information about these interactions were obtained from a number of studies implemented *in vitro*, among which are investigation of the substitution reactions of bifunctional platinum complexes with various bio-molecules at different conditions.

Cisplatin is most investigated bifunctional Pt(II) complex. (Redijk, 1999, 2009; Lippert, 1999) In details has been described how cisplatin coordinate to a molecule of DNA. (Redijk, 1999, Lippert, 1999) In addition to investigate the interaction with the classical nucleoside (Barry et al., 2005; Anzellotti et al., 2005) The interactions with AMP, ADP and ATP were investigated, and the best reactivity toward Pt(II) complexes showed to be ATP. (Arpalahti & Lehtikoinen, 1990; Arpalahti & Lippert, 1990; Caradonna & Lippard, 1988; Bose et al., 1986; Martin, 1999) Also, the interactions of cisplatin with sulfur-donor bio-molecules, L-cysteine, GSH, L-methionine were studied. GSH is more reactive than L-cysteine. (Bugarčić et al., 2004a) In reactions with L-methionine, amino acid coordinates bidentate to platinum building *S,N*-chelate. If the amino acids is presented in excess the reaction may lead to the bidentate coordination of two molecules of amino acid for Pt(II)-ion. (Norman et al., 1992) The competitive reaction between cisplatin, L-methionine and 5'-GMP in the mixture were also examined. A predominant product is complex $[\text{Pt}(\text{NH}_3)_2(\text{N}7\text{-GMP})_2]$, while compounds $[\text{Pt}(\text{N},\text{L-methionine})(\text{N}7\text{-GMP})(\text{NH}_3)]$ and $[\text{Pt}(\text{N},\text{L-methionine})_2]$ are formed in a very small concentrations. (Kung et al., 2001) The competitive reactions between 5'-GMP and thiols were also studied, but only found product where is platinum coordinated to sulphur from thiols. (Volckova et al., 2002) The reactions of cisplatin with 5'-GMP and GSH were studied spectrophotometrically at 37 °C. NMR technique was also applied to study the reactions of cisplatin with guanosine-5'-monophosphate. (Petrović D. et al., 2007) The rate constants for the reactions of cisplatin with 5'-GMP, obtained by ^1H NMR experiments and obtained by Uv-Vis experiments, are in a good agreement. However, these results are in a good agreement with the published results. (Barnham et al., 1994)

Fig. 5. show ^1H NMR spectra of the reaction between cisplatin and 5'-GMP. The peak for the free 5'-GMP is at δ 8.22 ppm, and for the product the peaks are at δ 8.69 and at 8.71 ppm. The peak at 8.69 ppm is smaller than the peak at 8.71 ppm at the later stage of the reaction. (Petrović D. et al., 2007)

During the reaction the peak at 8.71 ppm, which corresponds to the product, $[\text{Pt}(\text{NH}_3)_2\text{Cl}(\text{N}7\text{-GMP})]^+$, increased in intensity, while the peak for the free 5'-GMP (δ 8.22 ppm) decreased in intensity. At the end of the reaction all 5'-GMP is coordinated to Pt(II), and the peak for the free 5'-GMP disappears as shown in Fig. 5.

The reactions of cisplatin with GSH were studied spectrophotometrically, and it has been found that GSH is better nucleophile for cisplatin than 5'-GMP, (Petrović D. et al., 2007) what is also in agreement with previously published results. (Soldatović & Bugarčić, 2005; Hagrman et al., 2004)

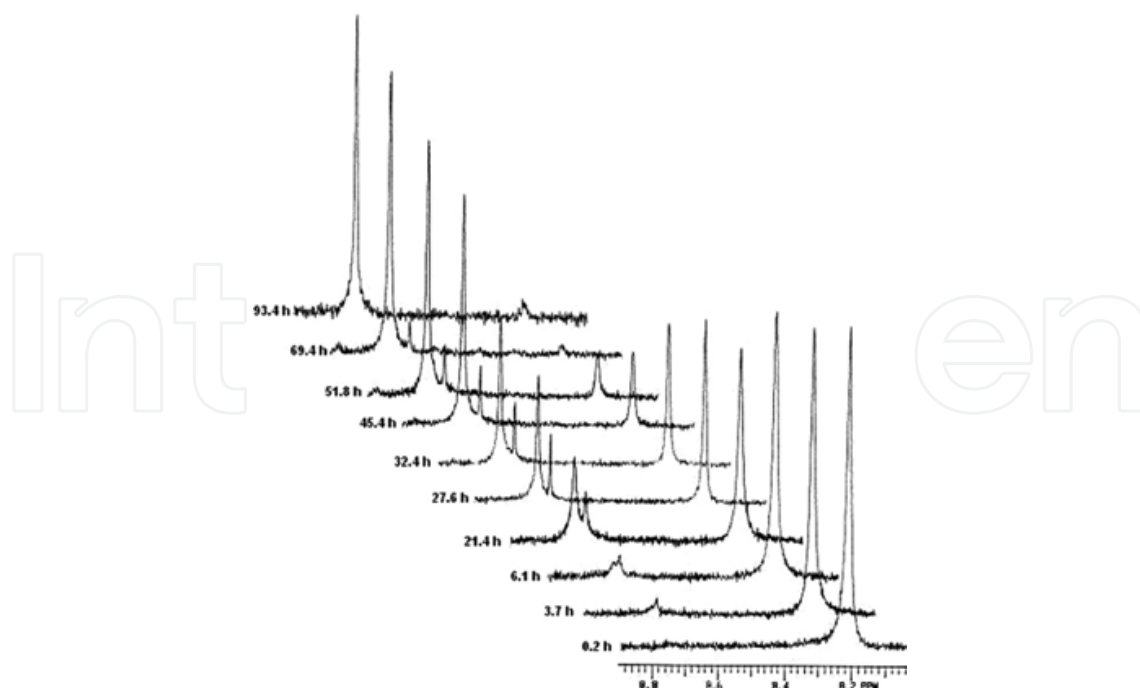


Fig. 5. ^1H HMR spectra of a solution of cisplatin (7.5 mM) and 5'-GMP (7.5 mM) in D_2O at pH 7.4 and 298 K recorded as a function of time.

Substitution reactions of the complexes $\text{cis-}[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$, $[\text{Pt}(\text{SMC})\text{Cl}_2]^-$, $[\text{Pt}(\text{en})\text{Cl}_2]$, and $[\text{Pt}(\text{dach})\text{Cl}_2]$, with selected biologically important ligands, *viz.* 5'-GMP, L-histidine and 1,2,4-triazole, were studied. (Bogojeski et al., 2010) All reactions were studied in aqueous 25 mM Hepes buffer in the presence of 5 mM NaCl at pH = 7.2 under *pseudo*-first-order conditions as a function of concentration at 310 K by using UV/Vis spectrophotometry. The substitution reactions were studied in the presence of 5 mM chloride to be close to the conditions in the cell where the concentration is ca. 4 mM. Two consecutive reaction steps, which both depend on the nucleophile concentration, were observed in all cases.

The most reactive N-donor nucleophile is 1,2,4 triazole. L-Histidine has the same order of reactivity as 5'-GMP and it is only slightly faster than 5'-GMP. The difference in the reactivity of these nucleophiles can be accounted in terms of electronic and steric effects. 5'-GMP is sterically more crowded than L-histidine and that can be the reason why the reactions with 5'-GMP are a bit slower. From a comparison of the values of the second-order rate constants for the first reaction step, k_2 , it can be concluded that the order of reactivity of the complexes is: $[\text{Pt}(\text{SMC})\text{Cl}_2]^- > \text{cis-}[\text{Pt}(\text{NH}_3)_2\text{Cl}_2] > [\text{Pt}(\text{en})\text{Cl}_2] > [\text{Pt}(\text{dach})\text{Cl}_2]$. The high reactivity of $[\text{Pt}(\text{SMC})\text{Cl}_2]^-$ can be attributed to the strong *trans*-labilization effect of the coordinated sulfur atom from the S-methyl-L-cysteine chelate. Such labilization has clearly been illustrated by an earlier study. (Bugarčić et al., 2004b) The reactivity of the complexes $\text{cis-}[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$, $[\text{Pt}(\text{en})\text{Cl}_2]$ and $[\text{Pt}(\text{dach})\text{Cl}_2]$ depends on steric effects. The $[\text{Pt}(\text{dach})\text{Cl}_2]$ complex is the sterically most crowded one and the reactions are found to be slower than those with $[\text{Pt}(\text{en})\text{Cl}_2]$ and $\text{cis-}[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$. The reactions with $[\text{Pt}(\text{dach})\text{Cl}_2]$ were expected to be slower than those with $[\text{Pt}(\text{en})\text{Cl}_2]$, because the Pt(II) center should be less electrophilic due to the positive inductive effect of the cyclohexane ring. (Summa et al., 2006) The second step of the reaction are significantly slower than the reactions of the first step in all cases.

Transformation from Pt-S(thioether) to Pt-N7(GMP) coordination seems to be common in biological processes. (Reedijk, 1999; Soldatović & Bugarčić, 2005; Jansen et al., 2002; van Boom et al., 1999; Tauben et al., 2000; Barnham et al., 1996) We performed quantum chemical calculations to gain more insight into this process. To obtain more quantitative data for the difference in stability between Pt-DNA and Pt-S(thioether) adducts, DFT calculations were performed.

In all cases guanine coordination to the fragments Pt(NH₃)₂, Pt(en) and Pt(dach) is much more favored than thioether coordination. For the first step in the gas phase Pt-N7(Gua) is more stable than Pt-S(thioether) by *ca.* 31–33 kcal/mol, and for the second step by 32–34 kcal/mol.

Finally, this result could be the first to clearly show how much the Pt-N7(Gua) adduct is more stable than the Pt-S(thioether) adduct. This is important since Pt-S(thioether) adducts have been postulated to be a drug reservoir for the binding of platinum to DNA, which may act as intermediates and then be transformed into Pt-N7(Gua) adduct. (Lippert, 1999; Reedijk, 1999; Jansen et al., 2002; van Boom et al., 1999; Jung & Lippard, 2007)

The kinetics and mechanism of ligand substitution reactions of [Pt(SMC)Cl₂] with biologically relevant ligands were studied as a function of chloride and nucleophile concentrations at pH 2.5 and 7.2. (Soldatović et al., 2009) It was observed that the slope and intercept obtained from the linear dependence of the observed rate constant on the nucleophile concentration strongly depend on the [Cl⁻] for all the studied substitution reactions. At high [Cl⁻], the rate constant for the forward reaction is almost zero and that for the back reaction follows the order: L-methionine > GSH ~ INO > 5'-GMP. Ion-pair formation between the positively charged Pt(II) complex and the chloride ion is suggested to account for the saturation kinetics observed for the back reaction.

At the highest [Cl⁻] of 0.1 M the binding of the nucleophiles is drastically slowed down and almost completely suppressed. This will be the case during the transport of such anti-tumour complexes in blood. At low chloride concentrations as found in cells, effective binding of the studied nucleophiles will occur. The order of reactivity L-met > GSH ~ INO > 5'-GMP clearly shows the high affinity of the Pt(II) complex for thioether. These interactions are more favourable because the transformation from Pt-S(thioether) to Pt-N7 coordination was observed. (Soldatović & Bugarčić, 2005) In our earlier work we did not observe any measurable transformation from Pt-S(thiol) to Pt-N7 coordination. (Bugarčić et al., 2004b) The lower reactivity of 5'-GMP compared to INO can be explained by the fact that at pH 2.5 the N7 position of inosine is almost fully deprotonated whereas in 5'-GMP it is still partially protonated (N7 pK_a = 2.33). (Bugarčić et al., 2004b) At pH = 7.2, it is possible that the 5'-monophosphate residue of the nucleotide (pK_a a 6) binds to the metal center, which can lead to additional complications in the complex-formation at higher pH and slower second-order rate constants are obtained.

A set of three oxaliplatin derivatives containing 1,2-*trans*-R,R-diaminocyclohexane (dach) as a spectator ligand and different chelating leaving groups X-Y, *viz.*, [Pt(dach)(O,O-cyclobutane-1,1-dicarboxylate)], or Pt(dach)(CBDCA), [Pt(dach)(N,O-glycine)]⁺, or Pt(dach)(gly), and [Pt(dach)(N,L-methioninehionine)]⁺, or Pt(dach)(L-Met), where L-Met is L-methionine, were synthesized and the crystal structure of Pt(dach)(gly) was determined by X-ray diffraction. (Summa et al., 2007) The effect of the leaving group on the reactivity of

the resulting Pt(II) complexes was studied for the nucleophiles thiourea, GSH and L-Met under *pseudo*-first-order conditions as a function of nucleophile concentration and temperature, using Uv-Vis spectrophotometric techniques. ^1H NMR spectroscopy was used to follow the substitution of the leaving group by guanosine 5'-monophosphate ($5'\text{-GMP}^{2-}$). The rate constants for all reactions of direct substitution of the X-Y chelate by the selected nucleophiles, showing that the nature of the chelate, viz., O-O (CBDCA $^{2-}$), N-O (glycine) or S-N(L-Met), respectively, plays an important role in the kinetic and mechanistic behavior of the Pt(II) complex.

The nature of the chelate, being O-O(CBDCA $^{2-}$), N-O(glycine) or S-N(L-Met) was shown to play an important role in the kinetic and mechanistic behavior of the Pt(II) complexes. Pt(dach)(CBDCA) exhibits a higher reactivity towards the sulfur donor L-Met than Pt(dach)(gly), whereas the order is the opposite for the nitrogen donor $5'\text{-GMP}^{2-}$ and the sulfur donors thiourea and GSH in the first reaction step. The Pt-N bond was always found to be very strong, especially for the reaction with $5'\text{-GMP}^{2-}$, in which the 1:1 reaction product [Pt(N-gly)(N7-GMP)] is very stable and hardly (7%) reacts with another molecule of $5'\text{-GMP}^{2-}$ to form the 1:2 product. By contrast, the liberation of H_2CBDCA in Pt(dach)(CBDCA) in the second reaction step was faster than the rate-determining first reaction step and could not be analyzed under the selected experimental conditions. The mechanism of the substitution reactions is associative as supported by the large and negative values of ΔS^\ddagger .

Multinuclear complexes of platinum(II) represent a third generation of antitumor drugs as and platinum(IV) complexes. (Esposito & Najjar, 2002) The reason for the increasing interest in multinuclear complexes is their ability to form DNA adducts that differ significantly from those formed cisplatin and related complexes, (McGregor et al., 1999) which results in a completely different anti tumor behaviour. The biological activity of polynuclear platinum complexes maybe modulated by the geometry and number of leaving groups in the coordination sphere of platinum atoms as well as by the nature of linkers connecting the platinum centers. In contrast with the mononuclear complexes, such as antitumor cisplatin and clinically ineffective transplatin, in the dinuclear case both geometries are antitumor active. (Farrell, 2004)

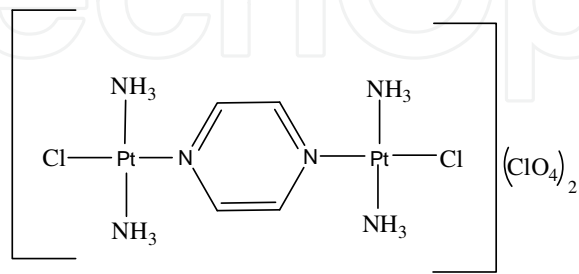
We compared the cytotoxic capacity of platinum complexes (Fig. 6.) towards TOV21G, HCT 116 tumour human cell lines and human MSC, normal rapidly dividing cells (Fig. 7.). (Jovanović et al., 2011)

All complexes displayed a dose-dependent and time-dependent cytotoxicity towards the tested cell lines but the most cytotoxic effect showed towards TOV21G cells (Fig. 7). The complex [PtCl $_4$ (dach)] at the lower concentrations induced significantly higher cytotoxic effect towards TOV21G cells than other four complexes.

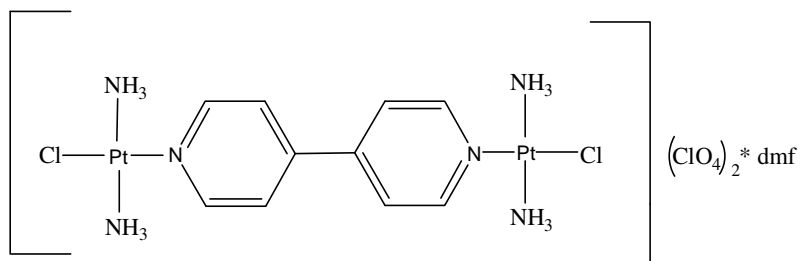
HCT116 cells were more resistant to the cytotoxic effects of selected complexes (Fig. 7). Again, [PtCl $_4$ (dach)] was the most efficient and exerted very similar activity towards HCT116 cells as cisplatin.

The complexes **Pt2** and **Pt3** displayed cytotoxicity towards MSC similar as cisplatin, but the other three complexes **Pt1**, [PtCl $_4$ (dach)] and [PtCl $_4$ (bipy)] were more toxic. (Jovanović et al., 2011)

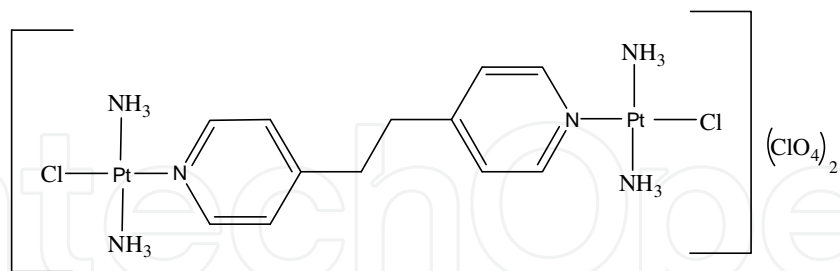
IntechOpen



$[\{trans\text{-Pt}(\text{NH}_3)_2\text{Cl}\}_2(\mu\text{-pyrazine})](\text{ClO}_4)_2$, **Pt1**



$[\{trans\text{-Pt}(\text{NH}_3)_2\text{Cl}\}_2(\mu\text{-4,4'}\text{-bipyridyl})](\text{ClO}_4)_2\text{DMF}$, **Pt2**



$[\{trans\text{-Pt}(\text{NH}_3)_2\text{Cl}\}_2(\mu\text{-1,2-bis(4-pyridyl)ethane})](\text{ClO}_4)_2$, **Pt3**

Fig. 6. Structures of investigated dinuclear platinum(II) complexes.

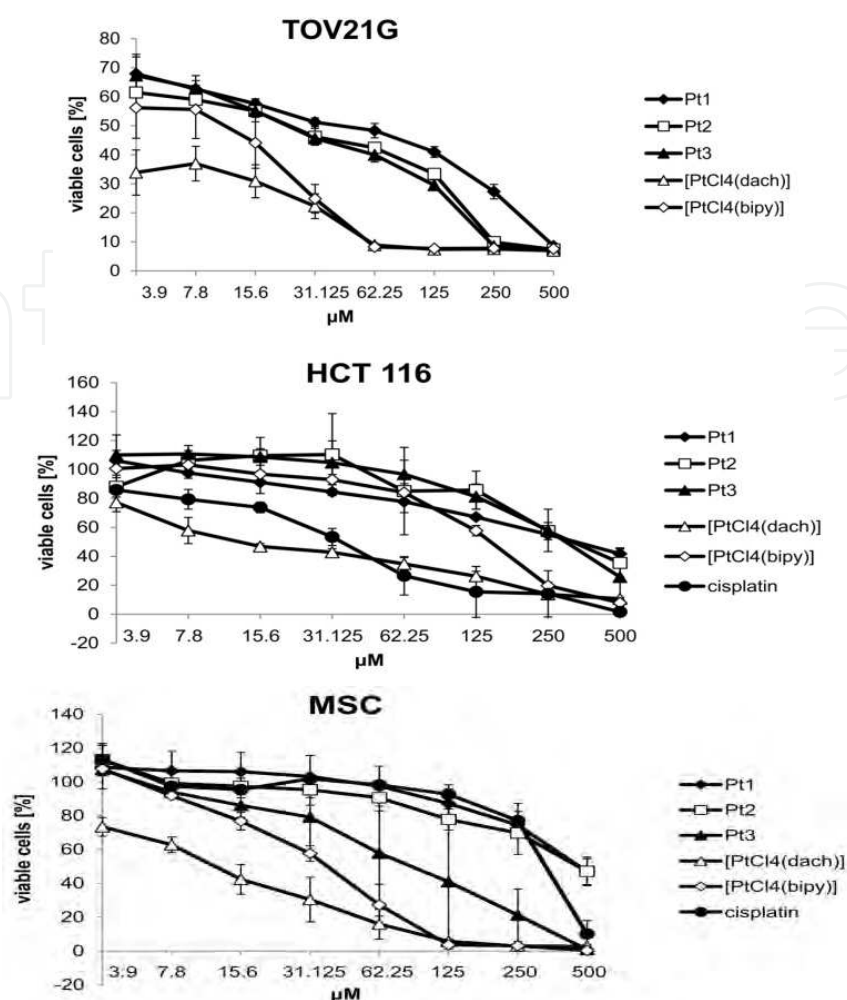


Fig. 7. Cytotoxic activity of tested complexes measured by MTT test (Mean+/-SE).

4. Conclusion

Results presented here, could contribute to a better understanding of the precise biochemical mechanism of some Pt(II) complexes. Moreover, the results of the substitution reactions with biologically relevant ligands could help to get more information on the possible interaction modes of Pt(II) complexes with *in vivo* targets and their representative application in the study of their anti-tumour properties. Detailed knowledge of the interactions between transition metal ions complexes with biomolecules and stability of final products under varying experimental conditions is fundamental for future investigations of new pharmacological agents and discovery of the alternative tumor treatment. Connecting theoretical calculations, chemistry, biochemistry and cellular biology and establishment of the structure-activity relationship Pt(II) complexes will help to solve some of the questions and will finally result in more tailored drug design. Numerous data imply that interactions of Pt(II) complexes and investigation of the mechanism of their reaction with DNA fragments (purine and pyrimidine bases, as well as oligonucleotides) are important for antitumor activity of Pt(II) complexes and the results of studies presented above contribute to that. Investigations of the interaction of Pt(II) complexes with other S-donor biomolecules can help us to get better insights in the destiny of anti-tumor drugs in

the cells after their uptake, as well as to obtain more information about the inner cellular processes, which are affected by therapy.

Further research in this area will be based on the synthesis and investigation of the substitution reactions of the transition metals complexes especially Pt(II), Pt(IV), Au(III) and Ru(II/III) complexes. These complexes are investigated in order to find compounds that would demonstrate greater anti-tumour activity and less toxicity and resistance compared to cisplatin. It turned out that some complexes of Pt(IV) are toxic to cancers where cisplatin developed resistance. A good feature of the complexes of Pt(IV) is that some of them can be taken orally. When the complex of Pt(IV) enters the cell, it leads to the reduction of Pt(IV) to Pt(II) and binding to DNA. Au(III) is isoelectronic with Pt(II) and forms square planar complexes, and is therefore a good candidate for the synthesis of new complexes that could show better properties than the complexes of Pt(II). Also, complexes of Ru(II/III) are potential anti-cancer agents and consequently the study of these complexes is of great importance.

5. Acknowledgements

The authors gratefully acknowledge financial support from the Ministry of Education and Science of the Republic of Serbia, project No. 172011.

6. References

- Ali M. S.; Khan S. R. A.; Ojima H.; Guzman I. Y.; Whitmire K. H.; Siddik Z. H. & Khokhar A. R. (2005). Model platinum nucleobase and nucleoside complexes and antitumor activity: X-ray crystal structure of $[\text{PtIV}(\text{trans-1R,2R-diaminocyclohexane})\text{trans}(\text{acetate})_2(9\text{-ethylguanine})\text{Cl}]\text{NO}_3\text{H}_2\text{O}$. *Journal of Inorganic Biochemistry*, Vol. 99, pp. 795-804, ISSN:0162-0134.
- Annibale G.; Bergamini P.; Bertolasi V.; Cattabriga M.; Lazzaro A.; Marchi A. & Vertuani G. (1999). Platinum assisted cyclization of S-methyl 3-acyl-2-methyldithiocarbazates under mild conditions. Crystal structure of $[\text{Pt}_2(\mu\text{-SMe})(\text{terpy})_2][\text{ClO}_4]_3$. *Journal of the Chemical Society, Dalton Transactions: Inorganic Chemistry*, No. 21, pp. 3877-3882, ISSN:0300-9246.
- Annibale G.; Brandolisio M.; Bugarčić Ž. D. & Cattalini L. (1998). Nucleophilicity of thiols towards planar tetracoordinated platinum(II) complexes. *Transition Metal Chemistry*, Vol. 23, pp. 715-719, ISSN:0340-4285.
- Anzellotti A. I.; Ma E. S. & Farrell N. (2005). Platination of Nucleobases To Enhance Noncovalent Recognition in Protein-DNA/RNA Complexes. *Inorganic Chemistry*, Vol. 44, pp. 483-485, ISSN:0020-1669.
- Arpalahti J. & Lehtikoinen P. (1990). Kinetics of complexation of aquated (diethylenetriamine)platinum(II) with inosine and 1-methylinosine as a function of pH. *Inorganic Chemistry*, Vol. 29, pp. 2564-2567, ISSN:0020-1669.
- Arpalahti J. & Lippert B. (1990) Coordination of aquated cis-platinum(II) diamines to purine nucleosides. Kinetics of complex formation. *Inorganic Chemistry*, Vol. 29, pp. 104-110, ISSN:0020-1669.

- Bailey J. A.; Hill M. G.; Marsh R. E.; Miskowski V. M.; Schaefer W. P. & Gray H. B. (1995). Electronic Spectroscopy of Chloro(terpyridine)platinum(II). *Inorganic Chemistry*, Vol. 34, pp. 4591-4599, ISSN:0020-1669.
- Barnham K. J.; Djuran M.I.; del Socorro P. & Sadler P.J. (1994). Intermolecular displacement of S-bound L-methionine on platinum(II) by guanosine 5'-monophosphate: implications for the mechanism of action of anticancer drugs. *Journal of the Chemical Society, Chemical Communications*, No. 6, pp. 721-722, ISSN:0022-4936.
- Barnham K. J.; Guo Z. J. & Sadler P. J. (1996). Stabilization of monofunctional platinum-nucleotide adducts: reactions of N-acetyl-L-methionine complexes with guanosine 5'-monophosphate and guanylyl(3'-5')guanosine. *Journal of the Chemical Society, Dalton Transactions*, No. 13, pp. 2867-2876, ISSN:0300-9246.
- Barnham K. J.; Djuran M. I.; Murdoch P. d. S.; Ranford J. D. & Sadler P. J. (1996). Ring-Opened Adducts of the Anticancer Drug Carboplatin with Sulfur Amino Acids. *Inorganic Chemistry*, Vol. 35, pp. 1065-1072, ISSN:0020-1669.
- Barry C. G.; Day C. S. & Bierbach U. (2005). Duplex-Promoted Platination of Adenine-N3 in the Minor Groove of DNA: Challenging a Longstanding Bioinorganic Paradigm. *Journal of the American Chemical Society*, Vol. 127, pp. 1160-1169, ISSN:0002-7863.
- Becker K.; Herold-Mende C.; Park J. J.; Lowe G. & Shirmer R. H. (2001). Human thioredoxin reductase is efficiently inhibited by (2,2':6',2''-terpyridine)platinum(II) complexes. Possible implications for a novel antitumor strategy. *Journal of medicinal chemistry*, Vol. 44, pp. 2784-2792, ISSN:0022-2623.
- Berners-Price S. J.; Barnham K. J.; Frey U. & Sadler P. J. (1996). Kinetic analysis of the stepwise platination of single- and double-stranded GG oligonucleotides with cisplatin and cis-[PtCl(H₂O)(NH₃)₂]⁺. *Chemistry--A European Journal*, Vol. 2, pp. 1283-1291, ISSN:0947-6539.
- Berners-Price S. J.; Davies M. S.; Cox J. W.; Thomas D. S. & Farrell N. (2003) Competitive reactions of interstrand and intrastrand DNA-Pt adducts: A dinuclear-platinum complex preferentially forms a 1,4-interstrand cross-link rather than a 1,2 intrastrand cross-link on binding to a GG 14-mer duplex. *Chemistry--A European Journal*, Vol. 9, pp. 713-725, ISSN:0947-6539.
- Bogojeski J.; Bugarčić Ž. D.; Puchta R. & van Eldik R. (2010). Kinetic studies on the reactions of different bifunctional platinum(II) complexes with selected nucleophiles. *European Journal of Inorganic Chemistry*, No. 34, 5439-5445, ISSN:1434-1948.
- Bogojeski J. & Bugarčić Ž. D. (2011). Kinetic and thermodynamic studies on reactions of [Pt(bpma)Cl]⁺ and [Pt(bpma)H₂O]²⁺ (bpma = bis-(2-pyridylmethyl)amine) with some azoles and diazines. *Transaction Metal Chemistry*, Vol. 36, pp. 73-78, ISSN:0340-4285.
- Bose N.; Cornelius R. D. & Viola R. E. (1986). Multinuclear NMR studies and the kinetics of formation of platinum(II)-adenine nucleotide complexes. *Journal of the American Chemical Society*, Vol. 108, pp. 4403-4408, ISSN:0002-7863.
- Bose N.; Moghaddas S.; Weaver E. L. & Cox E. H. (1995). Reactivity of Glutathione and Cysteine toward Platinum(II) in the Presence and Absence of Guanosine 5'-Monophosphate. *Inorganic Chemistry*, Vol. 34, pp. 5878-5883, ISSN:0020-1669.
- Brujinincx P. C. A. & Sadler P. J. (2009). Controlling platinum, ruthenium, and osmium reactivity for anticancer drug design. *Advances in Inorganic Chemistry*, Vol. 61, pp. 1-62, ISSN:0898-8838.

- Bugarčić Ž. D.; Đorđević B. V. & Đuran M. I. (1997). Mechanism of the reactions between chloro(2,2':6',2''-terpyridine)platinum(II) and ligands containing a thiol group. *Journal of the Serbian Chemical Society*, Vol. 62, pp. 1031-1036, ISSN:0352-5139.
- Bugarčić Ž. D. & Đorđević B. V. (1998). Kinetics and mechanism of the reaction of platinum(II) complexes with thioglycolic acid. *Monatshefte fuer Chemie*, Vol. 129, pp. 1267-1274, ISSN:0026-9247.
- Bugarčić Ž. D.; Liehr G. & van Eldik R. (2002). Kinetics and mechanism of the reactions of $[Pt(terpy)H_2O]^{2+}$ with thiols in acidic aqueous solution. Synthesis and crystal structure of $[Pt(terpy)(tu)](ClO_4)_2$ (tu = thiourea). *Journal of the Chemical Society, Dalton Transactions*, No. 14, pp. 2825-2830, SSN:1472-7773.
- Bugarčić Ž. D.; Shoukry M. M. & van Eldik R. (2002). Equilibrium and kinetic data for the interaction of diaqua-(S- methyl-L-cysteine)palladium(II) with biologically relevant ligands. *Journal of the Chemical Society, Dalton Transactions*, No. 21, pp. 3945-3951, SSN:1472-7773.
- Bugarčić Ž. D.; Heinemann F. W. & van Eldik R. (2004). Substitution reactions of $[Pt(terpy)X]^{2+}$ with some biologically relevant ligands. Synthesis and crystal structure of $[Pt(terpy)(cyst-S)](ClO_4)_2 \cdot 0.5H_2O$ and $[Pt(terpy)(guo-N7)](ClO_4)_2 \cdot 0.5guo \cdot 1.5H_2O$. *Dalton Transactions*, No. 2, pp. 279-286, ISSN:1477-9226.
- Bugarčić Ž. D.; Soldatović T.; Jelić R.; Alguero B. & Grandas A. (2004). Equilibrium, kinetic and HPLC study of the reactions between platinum(II) complexes and DNA constituents in the presence and absence of glutathione. *Dalton Transactions*, No. 22, pp. 3869-3877, ISSN:1477-9226.
- Bugarčić Ž. D.; Petrović B. & Zangrando E. (2004). Kinetics and mechanism of the complex formation of $[Pd(NNN)Cl]^+$ with pyridines in methanol: synthesis and crystal structure of $[Pd(terpy)(py)](ClO_4)_2$. *Inorganica Chimica Acta*, Vol. 357, pp. 2650-2656, ISSN:0020-1693.
- Bugarčić Ž. D.; Rosić J.; Petrović B. V.; Summa N.; Puchta R. & van Eldik R. (2007). Kinetics and mechanism of the substitution reactions of $[Pt(bpma)Cl]^+$, $[PtCl(gly-met-S,N,N)]$ and their aqua analogs with L-methionine, glutathione and 5'-GMP. *Journal of Biological Inorganic Chemistry*, Vol. 12., pp. 1141-1150, ISSN:0949-8257.
- Caradonna J. P. & Lippard S. J. (1988). Synthesis and characterization of $[d(ApGpGpCpCpT)]_2$ and its adduct with the anticancer drug cis-diamminedichloroplatinum(II). *Inorganic Chemistry*, Vol. 27, pp. 1454-1466.
- Chen Y.; Guo Z.; Murdoch P. S.; Zang E. & Sadler P. J. (1998). Interconversion between S- and N-bound L-methionine adducts of $Pt(dien)^{2+}$ (dien = diethylenetriamine) via dien ring-opened intermediates. *Journal of the Chemical Society, Dalton Transactions: Inorganic Chemistry*, No. 9, pp. 1503-1508.
- Cheng C. C. & Pai C. H. (1998). Specific displacement of glutathione from the Pt(II)-glutathione adduct by Cu(II) in neutral phosphate buffer. *Journal of Inorganic Biochemistry*, Vol. 71, pp. 109-113.
- Chiorazzi N.; Rai K. R. & Ferrarini M. (2005). Chronic lymphocytic leukemia. *New England Journal of Medicine*, Vol. 352, pp. 804-815, ISSN:0028-4793.
- Eichhorst B. F.; Busch R. Hopfinger G. et al. (2005) Fludarabine plus cyclophosphamide versus fludarabine alone in first line therapy of younger patients with chronic lymphocytic leukemia. *Blood*, Vol. 107, pp. 885-891.

- Esposito B.P. & Najjar R. (2002). Interactions of antitumoral platinum- group metallodrugs with albumin, *Coordination Chemistry Reviews*, Vol. 232, pp. 137-149, ISSN 0010-8545.
- Farrell N. (2004). Polynuclear platinum drugs in: A. Sigel, H. Sigel (Eds.), *Metal ions in biological systems*, New York and Basel Marcel Dekker Inc., New York, pp. 251-296.
- Frey U.; Ranford J.D. & Sadler P.J. (1993). Ring-opening reactions of the anticancer drug carboplatin: NMR characterization of cis-[Pt(NH₃)₂(CBDCA-O)(5'-GMP-N7)] in solution. *Inorganic Chemistry*, Vol. 32, pp. 1333-1340, ISSN:0020-1669.
- Fuertes M. A.; Alonso C. & Perez J. M. (2003). Biochemical modulation of cisplatin mechanisms of action: enhancement of antitumor activity and circumvention of drug resistance. *Chemical Reviews*, Vol. 103, pp. 645-662, ISSN:0009-2665.
- Hagrman D.; Goodisman J. & Soud A-K. (2004). Kinetic study on the reactions of platinum drugs with glutathione. *Journal of Pharmacology and Experimental Therapeutics*, Vol. 308, pp. 658-666, ISSN:0022-3565.
- Harris A.; Qu Y. & Farrell N. (2005). Unique Cooperative Binding Interaction Observed between a Minor Groove Binding Pt Antitumor Agent and Hoeschst Dye 33258. *Inorganic Chemistry*, Vol. 44, pp. 1196-1198, ISSN:0020-1669.
- Hofmann A.; Jaganyi D.; Munro O. Q.; Liehr G. & van Eldik R. (2003). Electronic Tuning of the Lability of Pt(II) Complexes through π -Acceptor Effects. Correlations between Thermodynamic, Kinetic, and Theoretical Parameters. *Inorganic Chemistry*, Vol. 42, pp. 1688-1700, ISSN:0020-1669.
- Jacobs R.; Prinsloo F. & Breet E. (1992). Kinetics of binding of DNA nucleotides to antitumor type complexes. *Journal of the Chemical Society, Chemical Communications*, No. 3, pp. 212-213, ISSN:0022-4936.
- Jaganyi D.; Hofmann A. & van Eldik R. (2001). Controlling the lability of square-planar PtII complexes through electronic communication between π -acceptor ligands. *Angewandte Chemie, International Edition*, Vol. 40, pp. 1680-1683, ISSN:1433-7851.
- Jaganyi D. & Tiba F. (2003). Substitution of [Pt(terpy)H₂O]²⁺ and [Pt(bpma)H₂O]²⁺ with thiols in acidic aqueous solution. terpy = 2,2':6'2"-terpyridine; bpma = bis(2-pyridylmethyl)amine. *Transition Metal Chemistry*, Vol. 28, pp. 803-807, SSN:0340-4285.
- Jaganyi D.; Tiba F.; Munro O. Q.; Petrović B. & Bugarčić Ž. D. (2006). Kinetic and mechanistic study on the reactions of [Pt(bpma)(H₂O)]²⁺ and [Pd(bpma)(H₂O)]²⁺ with some nucleophiles. Crystal structure of [Pd(bpma)(py)](ClO₄)₂. *Dalton Transactions*, No. 24, pp. 2943-2949, ISSN:1477-9226.
- Jakupec M. A.; Galanski M. & Keppler B. K. (2003). Tumour-inhibiting platinum complexes-state of the art and future perspectives. *Reviews of Physiology, Biochemistry and Pharmacology*, Vol. 146, pp. 1-53, ISSN:0303-4240.
- Jakupec M. A.; Galanski M.; Arion V. B.; Hartinger C. G. & Keppler B. K. (2008). Antitumor metal compounds: more than theme and variations. *Dalton Transactions*, No. 2, pp. 183-194, ISSN:1477-9226.
- Jansen B. A. J.; Brouwer J. & Reedijk J. (2002). Glutathione induces cellular resistance against cationic dinuclear platinum anticancer drugs. *Journal of Inorganic Biochemistry*, Vol. 89, pp. 197-202, ISSN:0162-0134.

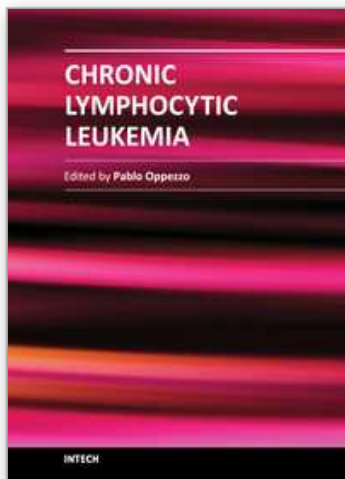
- Jolley J. N.; Yanovsky A. I.; Kelland L. R. & Nolan K. B. (2001). Synthesis and antitumour activity of platinum(II) and platinum(IV) complexes containing ethylenediamine-derived ligands having alcohol, carboxylic acid and acetate substituents. Crystal and molecular structure of $[PtL_4Cl_2] \cdot H_2O$ where L_4 is ethylenediamine- N,N' -diacetate. *Journal of Inorganic Biochemistry*, Vol. 83, pp. 91-100, ISSN:0162-0134.
- Jovanović S.; Soldatović T.; Milovanović M.; Volarević V.; Čanović D.; Arsenijević N. & Bugarčić Ž. D. (2011). Ligand substitution reactions of Pt(IV) and dinuclear Pt(II) complexes with 5'-GMP and their cytotoxic properties. Submitted in European Journal of Medicinal Chemistry
- Jung Y. & S. J. Lippard (2007). Direct Cellular Responses to Platinum-Induced DNA Damage. *Chemical Reviews*, Vol. 107, pp. 1387-1407, ISSN:0009-2665.
- Kozelka J.; Legendre F.; Reeder F. & Chottard J. C. (1999). Kinetic aspects of interactions between DNA and platinum complexes. *Coordination Chemistry Reviews*, Vol. 190-192.
- Kung A.; Strickman D. B.; Galanski M. & Keppler B. K. (2001). Comparison of the binding behavior of oxaliplatin, cisplatin and analogues to 5'-GMP in the presence of sulfur-containing molecules by means of capillary electrophoresis and electrospray mass spectrometry. *Journal of Inorganic Biochemistry*, Vol. 86, pp. 691-698, ISSN:0162-0134.
- Lakomska I.; Kooijman H.; Spek A. L.; Shen W. & Reedijk J. (2009). Mono- and dinuclear platinum(II) compounds with 5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine. Structure, cytotoxic activity and reaction with 5'-GMP. *Dalton Transactions*, Vol. 48, pp. 10736-10741, ISSN:1477-9226.
- Lampers L. M. & Reedijk J. (1990). Reversibility of binding of cisplatin-methionine in proteins by diethyldithiocarbamate or thiourea: a study with model adducts. *Inorganic Chemistry*, Vol. 29, pp. 217-222, ISSN:0020-1669.
- Lemma K.; Shi T. & Elding L. I. (2000). Kinetics and mechanism for reduction of the anticancer prodrug trans,trans,trans- $[PtCl_2(OH)_2(c-C_6H_{11}NH_2)(NH_3)]$ (JM335) by thiols. *Inorganic chemistry*, Vol. 39, pp. 1728-1734, ISSN:0020-1669.
- Lemma K.; Sargeson A. M. & Elding L. I. (2000). Kinetics and mechanism for reduction of oral anticancer platinum(IV) dicarboxylate compounds by L-ascorbate ions. *Dalton Transaction*, No. 7, pp. 1167-1172, ISSN:1470-479X.
- Lippert B. (1999). *Cisplatin, Chemistry and Biochemistry of Leading Antitumor Drugs*, Wiley-VCH, Zurich.
- Lippert B. (1999). Impact of Cisplatin on the recent development of Pt coordination chemistry: a case study. *Coordination Chemistry Reviews*, Vol. 182, pp. 263-295, ISSN:0010-8545.
- Mambanda A.; Jaganyi D.; Hochreuther S. & van Eldik R. (2010). Tuning the reactivity of chelated dinuclear Pt(II) complexes through a flexible diamine linker. A detailed kinetic and mechanistic study. *Dalton Transactions*, Vol. 39, 3595-3608, ISSN:1477-9226.
- Martin R. B. , *Cisplatin, Chemistry and Biochemistry of Leading Antitumor Drugs*, ed. B. Lippert, Wiley-VCH, Zurich, 1999, p. 193-200.
- McGregor T.D.; Balcarova Z.; Qu Y.; Tran M.-C.; Zaludova R.; Brabec V. & Farrell N. (1999). Sequence-dependent conformational changes in DNA induced by polynuclear platinum complexes. *Journal of Inorganic Biochemistry*, Vol. 77, pp. 43-46, ISSN:0162-0134.

- Mikola M.; Klika K. D.; Hakala A. & Arpalahti J. (1999). Substitution Reactions of Platinum(II)-Nucleobase Complexes by Associative Mechanism Involving Pseudorotation of the Five-Coordinate Intermediate. *Inorganic Chemistry*, Vol. 38, pp. 571-578, ISSN:0020-1669.
- Mock C.; Puscasu I.; Rauterkus M. J.; Tallen G.; Wolff J. E. A. & Krebs B. (2001). Novel Pt(II) anticancer agents and their Pd(II) analogues: syntheses, crystal structures, reactions with nucleobases and cytotoxicities. *Inorganica Chimica Acta*, Vol. 319, pp. 109-116, ISSN:0020-1693.
- Natile G. & Coluccia M. (2001). Current status of trans-platinum compounds in cancer therapy. *Coordination Chemistry Reviews*, Vol. 216-217, pp. 383-410, ISSN:0010-8545.
- Norman R. E.; Ranford J. D. & Sadler P. J. (1992). Studies of platinum(II) methionine complexes: metabolites of cisplatin. *Inorganic Chemistry*, Vol. 31, pp. 877-888, ISSN:0020-1669.
- Petrović B. & Bugarčić Ž. D. (2001). Kinetics and mechanism of complex formation between [Pt(dien)Cl]⁺ and thiols and thioethers. *Journal of Coordination Chemistry*, Vol. 53, pp. 35-45, ISSN:0095-8972.
- Petrović B. V.; Đuran M. I. & Bugarčić Ž. D. (1999). Binding of platinum(II) to some biologically important thiols. *Metal-Based Drugs*, Vol. 6, pp. 355-360, ISSN:0793-0291.
- Petrović D.; Stojimirović B.; Petrović B.; Bugarčić Z. M. & Bugarčić Ž. D. (2007). Studies of interactions between platinum(II) complexes and some biologically relevant molecules. *Bioorganic & Medicinal Chemistry*, Vol. 15, pp. 4203-4211, ISSN:0968-0896.
- Pitteri B.; Marangoni G.; Cattalini L.; Visentin F.; Bertolasi V. & Gilli P. (2001). The role of the non-participating groups in substitution reactions at cationic Pt(II) complexes containing tridentate chelating nitrogen donors. Crystal structure of {Pt[bis(2-pyridylmethyl)amine](py)}(CF₃SO₃)₂. *Polyhedron*, Vol. 20, pp. 869-880, ISSN:0277-5387.
- Pitteri B.; Annibale G.; Marangoni G.; Bertolasi V. & Ferretti V. (2002). Base hydrolysis kinetics and equilibria of [bis(2-pyridylmethyl)amine]chloroplatinum(II) and crystal and molecular structures of [Pt(bpma)Cl]Cl · H₂O and [Pt(bpma)(OH₂)](ClO₄)₂ · 2H₂O. *Polyhedron*, 2002, Vol. 21, pp. 2283-2291, ISSN:0277-5387.
- Reedijk J. (1999). Why does cisplatin reach guanine-N7 with competing S-donor ligands available in the cell? *Chemical Reviews*, Vol. 99, pp. 2499-2510, ISSN:0009-2665.
- Reedijk J. (2009). Platinum anticancer coordination compounds: study of DNA binding inspires new drug design. *European Journal of Inorganic Chemistry*, No. 10, pp. 1303-1312, ISSN:1434-1948.
- Ronconi L. & Sadler P. J. (2007). Using coordination chemistry to design new medicines. *Coordination Chemistry Reviews*, Vol. 251, pp. 1633-1648, ISSN:0010-8545.
- Rosenberg B. & Camp L. V. (1965). INHIBITION OF CELL DIVISION IN ESCHERICHIA COLI BY ELECTROLYSIS PRODUCTS FROM A PLATINUM ELECTRODE, *Nature*, Vol. 205, pp. 698-699, ISSN:0028-0836.
- Rosenberg B.; Camp L. V.; Trosko J. E. & Mansour V. H. (1969). Platinum compounds: a new class of potent antitumor agents. *Nature*, Vol. 222, pp. 385-386, ISSN:0028-0836.

- Rosenberg B. & Camp L. V. (1970). Successful regression of large solid sarcoma 180 tumors by platinum compounds. *Cancer Research*, Vol. 30, pp. 1799-1802, ISSN:0008-5472.
- Rosenberg B.; Camp L. V.; Grimley E. B. & Thomson A. J. (1967). Inhibition of growth or cell division in *Escherichia coli* by different ionic species of platinum(IV) complexes. *Journal of Biological Chemistry*, Vol. 242, pp. 1347-1352, ISSN:0021-9258.
- Shi T. & Elding L. I. (1996). Equilibrium and High-Pressure Kinetic Study of Formation and Proton-Assisted Aquation of Monodentate Acetate, Propionate, and Glycolate Complexes of Palladium(II) in Aqueous Solution. *Inorganic Chemistry*, Vol. 35, pp. 735-740, ISSN:0020-1669.
- Shi T. & Elding L. I. (1997). Linear Free Energy Relationships for Complex Formation Reactions between Carboxylic Acids and Palladium(II). Equilibrium and High-Pressure Kinetics Study. *Inorganic Chemistry*, Vol. 34, pp. 528-536, ISSN:0020-1669.
- Shoukry A.; Rau T.; Shoukry M. & van Eldik R. (1998). Kinetics and mechanisms of the ligand substitution reactions of bis(amine)(cyclobutane-1,1-dicarboxylato)palladium(II). *Journal of the Chemical Society, Dalton Transactions*, No. 18, pp. 3105-3112.
- Sigel H.; Massoud S. S.; Corfu N. A. (1994). Comparison of the Extent of Macrochelate Formation in Complexes of Divalent Metal Ions with Guanosine (GMP²⁻), Inosine (IMP²⁻), and Adenosine 5'-Monophosphate (AMP²⁻). The Crucial Role of N-7 Basicity in Metal Ion-Nucleic Base Recognition. *Journal of the American Chemical Society*, Vol. 116, pp. 2958-2971, ISSN:0002-7863.
- Soldatović T. & Bugarčić Ž. D. (2005). Study of the reactions between platinum(II) complexes and L-methionine in the presence and absence of 5'-GMP. *Journal of Inorganic Biochemistry*, Vol. 99, pp. 1472-1479, ISSN:0162-0134.
- Soldatović T.; Bugarčić Ž. D. & van Eldik R. (2009). Influence of the chloride concentration on ligand substitution reactions of [Pt(SMC)Cl₂] with biologically relevant nucleophiles. *Dalton Transactions*, No. 23, pp. 4526-4531, ISSN:1477-9226.
- Summa N.; Schiessl W.; Puchta R.; van Eikema Hommes N. & van Eldik R. (2006). Thermodynamic and Kinetic Studies on Reactions of Pt(II) Complexes with Biologically Relevant Nucleophiles. *Inorganic Chemistry*, Vol. 45, pp. 2948-2959, ISSN:0020-1669.
- Summa N.; Soldatović T.; Dahlenburg L.; Bugarčić Ž. D. & van Eldik R. (2007). Kinetics and mechanism of the substitution reactions of [Pt(bpma)Cl]⁺, [PtCl(gly-met-S,N,N)] and their aqua analogs with L-methionine, glutathione and 5'-GMP. *Journal of Biological Inorganic Chemistry*, Vol. 12, pp. 1141-1150, ISSN:0949-8257.
- Talman E. G.; Bruning W.; Reedijk J.; Spek A. L. & Veldman N. (1997). Crystal and Molecular Structures of Asymmetric cis- and trans-Platinum(II/IV) Compounds and Their Reactions with DNA Fragments. *Inorganic Chemistry*, Vol. 36, pp. 854-861, ISSN:0020-1669.
- Tauben J. M.; Rodrugez M.; Zubiri & Reedijk J. (2000). Glutathione readily replaces the thioether on platinum in the reaction with [Pt(dien)(GSMe)]²⁺ (GSMe = S-methylated glutathione); a model study for cisplatin-protein interactions. *Dalton*, No. 3, pp. 369-372, ISSN:1470-479X.
- Teuben J. M.; van Boom S. S. G. E. & Reedijk J. (1997). Intramolecular migration of coordinated platinum from a sulfur to N7 in the nucleopeptide Met-d(TpG) (5'-O-

- methioninate-N-ylcarbonylthymidine 2'-deoxyguanosine monophosphate). *Journal of the Chemical Society, Dalton Transactions*, No. 21, pp. 3979-3980, ISSN:0300-9246.
- van Boom S.S.G.E.; Chen B.W; Tauben J.M. & Reedijk J. (1999). Platinum-Thioether Bonds Can Be Reverted by Guanine-N7 Bonds in Pt(dien)₂⁺ Model Adducts. *Inorganic Chemistry*, Vol. 38, pp. 1450-1455.
- Volckova E.; Dudones L. P. & Bose R. N. (2002). HPLC determination of binding of cisplatin to DNA in the presence of biological thiols: implications of dominant platinum-thiol binding to its anticancer action. *Pharmaceutical research*, Vol. 19, pp. 124-131, ISSN:0724-8741.
- Wierda W.; O'Brien S.; Wen S.; Faderl S.; Garcia-Manero G.; Thomas D.; Do K-A.; Cortes J.; Koller C.; Beran M.; Ferrajoli A.; Giles F.; Lerner S.; Albitar M.; Kantarijan H. & Keating M. (2005) Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology*, Vol. 23, pp. 4070-4078 ISSN:0732-183X.
- Wang Y. F.; Curtis J. E.; Lipton J.; Minkin S. & McCulloch E. A. (1991) Cytosine arabinoside (ara-C) and cis-dichlorodiammineplatinum(II) (cisplatin) alone and in combination: effects on acute myeloblastic leukemia blast cells in culture and in vivo. *Leukemia*, Vol. 5, pp. 522-527.
- Wilkins R. G. (1991) *Kinetics and Mechanism of Reactions of Transition metal Complexes*, 2nd edn., Verlag, Berlin, p. 300.
- Wong Y. S. & Lippard S. J. (1977). X-ray crystal structure of a 2:2 chloroterpyridineplatinum(II)-adenosine-5'-monophosphate intercalation complex. *Journal of the Chemical Society, Chemical Communications*, No. 22, pp. 824-825, ISSN:0022-4936.
- Yamauchi T.; Nowak B. J.; Keating M. J. & Plunkett W. (2001). DNA repair initiated in chronic lymphocytic leukemia lymphocytes by 4-hydroperoxycyclophosphamide is inhibited by fludarabine and clofarabine. *Clinical Cancer Research*, Vol. 7, pp. 3580-3589.
- Zecevic A.; Sampath D.; Ewald B.; Chen R.; Wierda W. & Plunkett W.. (2011) Killing of Chronic Lymphocytic Leukemia by the Combination of Fludarabine and Oxaliplatin Is Dependent on the Activity of XPF Endonuclease. *Clinical Cancer Research*, Vol. 17, pp. 4731-4741, ISSN:1078-0432.

IntechOpen



Chronic Lymphocytic Leukemia

Edited by Dr. Pablo Oppezzo

ISBN 978-953-307-881-6

Hard cover, 448 pages

Publisher InTech

Published online 10, February, 2012

Published in print edition February, 2012

B-cell chronic lymphocytic leukemia (CLL) is considered a single disease with extremely variable course, and survival rates ranging from months to decades. It is clear that clinical heterogeneity reflects biologic diversity with at least two major subtypes in terms of cellular proliferation, clinical aggressiveness and prognosis. As CLL progresses, abnormal hematopoiesis results in pancytopenia and decreased immunoglobulin production, followed by nonspecific symptoms such as fatigue or malaise. A cure is usually not possible, and delayed treatment (until symptoms develop) is aimed at lengthening life and decreasing symptoms. Researchers are playing a lead role in investigating CLL's cause and the role of genetics in the pathogenesis of this disorder. Research programs are dedicated towards understanding the basic mechanisms underlying CLL with the hope of improving treatment options.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jovana Bogojeski, Biljana Petrović and Živadin D. Bugarčić (2012). Interactions of the Platinum(II) Complexes with Nitrogen- and Sulfur-Bonding Bio-Molecules in Chronic Lymphocytic Leukemia, Chronic Lymphocytic Leukemia, Dr. Pablo Oppezzo (Ed.), ISBN: 978-953-307-881-6, InTech, Available from:

<http://www.intechopen.com/books/chronic-lymphocytic-leukemia/interactions-of-the-platinum-ii-complexes-with-nitrogen-and-sulfur-bonding-bio-molecules-in-chronic->

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen