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Synthesis, crystal structures and, antibacterial and antiproliferative activities *in vitro* of palladium(II) complexes of triphenylphosphine and thioamides

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ABSTRACT

Palladium(II) complexes with triphenylphosphine (PPh_3) and thioamides of the general formulae, $[Pd(L)_2(PPh_3)_2]Cl_2$ and $[Pd(L)_2(PPh_3)_2]$ have been prepared and characterized by elemental analysis, IR and NMR (^1H, ^{13}C and ^{31}P) methods, and two of them (*trans*-$[Pd(PPh_3)_2(Dmtu)_2]Cl_2\cdot(H_2O)(CH_3OH)_{0.5}$ (**1**) and *trans*-$[Pd(PPh_3)_2(Mpy)_2]$ (**2**)) by X-ray crystallography; where L = thiourea (Tu), methylthiourea (Metu), *N,N′*-dimethylthiourea (Dmtu), tetramethylthiourea (Tmtu), 2-mercaptopyridine (Mpy), 2-mercaptopyrimidine (Mpm) and thionicotinamide (Tna). The spectral data of the complexes are consistent with the sulfur coordination of thioamides to palladium(II). The crystal structures of the complexes show that (**1**) has ionic character consisting of $[Pd(PPh_3)_2(Dmtu)_2]^{+2}$ cations and uncoordinated Cl^- ions, while (**2**) is a neutral complex with Mpy behaving as anionic thiolate ligand. The coordination environment around palladium in (**2**) is nearly regular square-planar, while in (**1**) the *trans* angles show significant distortions from 180°. The complexes were screened for antibacterial effects, brine shrimps lethality bioassay and antitumor activity. These complexes showed significant activities in most of the cases against the tested bacteria as compared to that of a standard drug. Their antitumor activity against prostate cancer cells (PC3) is comparable with doxorubicin, together with no cytotoxic effects in brine shrimps lethality bioassay study.

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1. Introduction

Platinum compounds are among the most efficacious metal-based anticancer agents [1–7]. However, for the reasons of severe side effects, drug resistance and the limited spectrum of tumors [1–7], there has been a wide spread search for related complexes (*e.g.*, of Pd, Ru and Au) that are able to improve effectiveness and reduce side effects of platinum drugs [8–16]. Special attention in this regard has been given to palladium(II) complexes [17–29], since the coordination geometry and complex forming processes of palladium(II) are very similar to those of platinum(II) [17,21,26]. However, Pt(II) complexes are thermodynamically and kinetically more stable than those of Pd(II). Pd(II) complexes undergo aquation and ligand exchange reactions 10^5 times faster than the corresponding Pt(II) analogues. This kinetic lability leads to the lower antitumor activity of *cis*-$[Pd(en)Cl_2]$ and *cis*-$[Pd(DACH)_2Cl_2]$ when compared to the analogous Pt(II) complexes [15,17,30–33]. The palladium(II) complexes dissociate readily in solution leading to very reactive species that are unable to reach their pharmacological targets such as DNA [15,17,30–33]. This rapid aquation and formation of very reactive species could be overcome if palladium(II) complexes are stabilized by bulky ligands and suitable leaving groups [17]. As a result, some palladium complexes with aromatic N-containing ligands *e.g.*, 1,10-phenanthroline and derivatives of pyridine, quinoline and pyrazole [18–20,34,35], thiosemicarbazones [25,26,36] and

Abbreviations: G (+), gram positive; G (−), gram negative; ATCC, American Type Culture Collection; DSM, Deutsch Sammlung von Mikroorganismen; DMSO, dimethysulfoxide; MTT, 3-(4,5-dimethylthiazole-2-yl) -2,5- diphenyltetrazolium bromide; DMEM, Dulbacco's Modified Eagle Medium; FBS, foetal bovine serum; ELIZA, Enzyme Linked Immuno Sorbent Assay; IC_{50}, inhibitory concentration 50%; LD_{50}, lethal dose 50%; PPh_3, triphenylphosphine; L, ligand; Tu, thiourea; MeTu, methylthiourea; DMTu, dimethylthiourea; TMTu, tetramethylthiourea; Imt, imidazolidine-2-thione; MPy, mercaptopyridine; MPm, mercaptopyrimidine; Tna, thionicotinamide; PC3, prostate cancer -3.

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triphenylphosphine [37] have shown very promising antitumor properties. Antiproliferative activities of some palladacycles have also been reported [24,32].

Although for platinum-based anticancer drugs it is generally accepted that DNA is the primary intracellular target [1–7], the DNA binding studies of palladium complexes showed that their reactivity depends on the ligand environment of Pd(II) [15,17,38–42]. The results of several studies indicated the changes in structure of DNA on Pd binding but the correlations between the structure and the mode of interaction could not be established [31,39,41]. Since Pd(II) can react with many biological molecules of the body, they exhibit high toxicity [30].

As the biological activity of a complex strongly depends on the nature of the ligands and on the metal coordination pattern, the recent research has been directed to synthesis and evaluation of complexes with biologically interesting ligands with the aim of widening spectrum of complex activity [17,30,43]. These findings have stimulated investigation of palladium(II) complexes with thiones and thiolate ligands because of their relevance to the biological systems [24–29,43,44]. Most of the palladium(II) complexes with thioamide ligands show a square-planar geometry in which these ligands act as terminal S bonded [29,45–50], bidentate chelating [24–26,28,29,49–54] or bidentate bridging [55–57]. It appears from these studies that thiourea derivatives and thioamides with saturated rings bind to Pd(II) in neutral thione form [45–48], while the unsaturated heterocyclic thiones (being electron-rich) such as mercaptopyridine and mercaptopyrimidine prefer to coordinate to Pd(II) as anionic thiolate ligands [28,29,49–54]. Furthermore, in the thione form, thioamides usually bind through sulfur atom only behaving as a monodentate ligand [45–48]. We are interested in investigating the structural chemistry and biological properties of Pd–thione complexes and in this regard we have already reported the spectroscopic and structural characterization of a number of palladium(II) complexes with thiones [45,46,58]. In this paper we present the synthesis and characterization of new palladium(II) complexes containing triphenylphosphine and a number of thioamides as ligands including the crystal structures of two of them. It is interesting to note that in one of them, *trans*-$[Pd(PPh_3)_2(Dmtu)_2]$-$Cl_2{\cdot}(H_2O)(CH_3OH)_{0.5}$ (**1**), the thioamide ligand coordinates in neutral thione form while in the other, *trans*-$[Pd(PPh_3)_2(Mpy)_2]$ (**2**), it behaves as an anionic thiolate ligand. The synthesized complexes have been screened for antibacterial and antitumor activities including brine shrimps lethality bioassay study. The results showed significant antibacterial activity as compared to the standard drugs indicating their potential for future antibacterial agents. Data obtained on human prostate cancer cells (PC3) indicated that there is a considerable potential for further testing of some of the complexes as antitumor agents, while data of brine shrimps lethality bioassay showed no toxicity to normal cells *in vitro*. The structures of the ligands used in this study are shown in Scheme 1.

2. Experimental

2.1. Chemicals

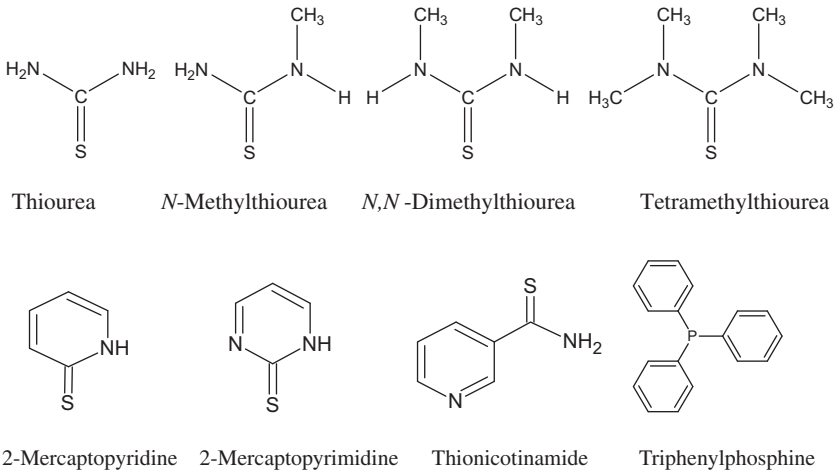
Palladium(II) chloride was purchased from Degussa AG 40474, Dusseldorf, Germany. Thiourea (Tu), methylthiourea (Metu), *N*,*N*′-dimethylthiourea (Dmtu), tetramethylthiourea (Tmtu), 2-mercaptopyridine (Mpy), 2-mercaptopyrimidine (Mpm) and thionicotinamide (Tna) were purchased from ACROS Organics, Belgium. Triphenylphosphine (PPh_3) was obtained from Alfa Aesar, USA.

2.2. Synthesis of the complexes

Potassium tetrachloropalladate(II) was prepared as described in the literature; by the reaction of palladium chloride with an excess of potassium chloride [45]. The complexes were prepared by adding 2 equiv. of triphenylphosphine in 15 mL acetonitrile to a solution of $K_2[PdCl_4]$ (0.326 g) in 15 mL of water followed by addition of 2 equiv. of thioamides in 15 mL methanol. The mixture was stirred for 15 min before addition of thioamides and for further half an hour after their addition. For the complexes of Tu, Metu, Dmtu and Tmtu, yellow colored; for Tna light brown and, for Mpy and Mpm, light orange colored solutions were obtained. The resulting solutions were filtrated and filtrates were kept at room temperature for crystallization for 3–5 days. As a result yellow powders were obtained. Crystals of **1** and **2** were grown by slow evaporation of acetonitrile/methanol solutions at room temperature. The experimental yield of the products was around 50–60%. The elemental analyses and melting points (m.p.) of the complexes are given in Table 1.

2.3. Measurements

Elemental analysis was carried out on a Leco CHNS-932 Leco Corporation USA. Melting point was recorded on an Electrothermal IA 9000 Series, Essex SS2 5PH UK. FT-IR spectra were recorded on a Thermo Nicolet Nexus 6700 USA. The ^1H and ^{13}C NMR spectra of the ligands and their complexes in DMSO-d_6 (Tmtu complex in $CDCl_3$) were obtained on Bruker Avance 300 MHz NMR spectrometer operating at frequencies of 300.00 MHz and 75.47 MHz,



Scheme 1. Structures of the ligands used in the study.

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