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Synthesis and characterization of a novel Pd(II) complex with the condensation product of 2-(diphenylphosphino) benzaldehyde and ethyl hydrazinoacetate. Cytotoxic activity of the synthesized complex and related Pd(II) and Pt(II) complexes

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Abstract

A new palladium(II) complex **1** of the condensation product of 2-(diphenylphosphino)benzaldehyde (dpba) and ethyl hydrazinoacetate (etha) was synthesized and characterized by elemental analyses, IR, and ^{1}H NMR spectroscopy. The bound ligand is a bidentate (PN chromophore), the remaining two coordination places being occupied by chloride ions in overall square planar geometry. The cytotoxic activity of the complex **1** and two related Pd(II) and Pt(II) complexes **2** and **3** was tested against a panel of four tumor cell lines. The activity of the complexes was similar to that of cisplatin, the most widely used metal-based antitumor drug. It is important to notice that complexes **2** and **3** were active to cisplatin-resistant U2-OS/Pt cells. Cell cycle alteration investigation, apoptotic assay and gelatin zymography in relation to invasion and metastasis of tumor cells, were performed with all the investigated complexes on Human cervix carcinoma (HeLa) cells. The results suggest that **1** has a similar effect to cisplatin, inducing apoptosis followed by arrest of cells in S phase of cell cycle, while **2** and **3** induce apoptosis without significant perturbations of cell cycle distribution.

Keywords: Pd(II) complexes; Pt(II) complex; Cytotoxic activity; Antitumor drugs; 2-(Diphenylphosphino)benzaldehyde

1. Introduction

Complexes with condensation products of 2-(diphenylphosphino)benzaldehyde (dpba) as polyfunctional ligand systems have been a subject of extensive recent research. By condensation of the aldehyde with diamines and monoamines, imine ligands were obtained, and used for synthesis of rhodium(I) and ruthenium(II) complexes, in which ligands are bound either as quadridentates via a PNNP donor atom set [1–4], or as bidentates via a PN set [5]. These complexes showed catalytical activity in hydrogenation of acrylic acid [4], and in asymmetric hydrogenation of aromatic ketones [1–3]. Rhodium(I) iminophosphine complexes were studied for application as efficient oxygen transporters [5].

Several complexes of palladium(II) [6–9], platinum(II) [9], nickel(II) [8–11] and copper(I) [12] with condensation derivatives of dpba and hydrazides, thiosemicarbazide or selenosemicarbazide were synthesized. These ligands are

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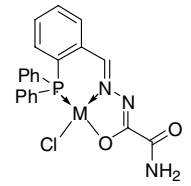
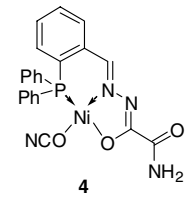


M = Pd(II) (**2**), Pt(II) (**3**)



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Scheme 1.

coordinated as tridentates via PNO, PNS, PNN or PNSe donor atom sets. Some of these complexes are catalytically active in homogeneous hydrogenation of various compounds with double or triple bond [6–8].

Although some platinum complexes are among the most widely used antitumor agents, biological activity of complexes with this ligand system was not studied. Therefore, the subject of this work was the evaluation of cytotoxic activity of platinum(II) (**2**), palladium(II) (**3**) and nickel(II) (**4**) complexes (Scheme 1) with the condensation product of dpba and semioxamazide, 2-{(2*E*)-2-[2-(diphenylphosphino)benzylidene]hydrazino}-2-oxoacetamide (HL1) [9], and synthesis of an analogous palladium(II) complex (**1**) with a modified HL1 ligand and evaluation of its activity.

2. Materials and methods

2.1. Preparation of the ligand ethyl 2-{(2*E*)-2-[2-(diphenylphosphino)benzylidene]hydrazino}acetate (HL2)

In a screw-top V-vial with a conical magnet, solutions of 18.7 mg (0.06 mmol) dpba in 1 mL MeOH and 21 mg (0.26 mmol) anhydrous sodium acetate in 1 mL MeOH were mixed, and a solution of 19.5 mg (0.13 mmol) ethyl hydrazinoacetate hydrochloride (etha · HCl) in 1 mL MeOH was then added dropwise. The reaction mixture was stirred for 2 h, concentrated and purified by preparative thin-layer chromatography on silica gel GF_{254} (Merck) using toluene/ethyl acetate (95/5) as the eluent. Yield: 16.18 mg (64.3%). Mp 209 °C. Elemental analysis: Calcd. for HL1 ($C_{23}H_{23}N_2O_2P$): C, 70.8; H, 5.9; N, 7.2. Found: C, 70.6; H, 5.9; N, 7.1%. IR (KBr; cm^{-1}; vs—very strong, s—strong, m—medium, w—weak): 3389 (s), 3359 (s), 3050 (m), 1739 (vs), 1599 (m), 1478 (s), 1435 (s), 1371 (m), 1201 (s), 1155 (s), 1267 (s), 1092 (s), 746 (s), 697 (s), 502 (s). ^{1}H NMR (200 MHz; DMSO-d_6; s—singlet, bs—broad singlet, d—doublet, t—triplet, q—quartet) δ: 1.14 (t, 3H, $J = 7.0$ Hz, C2‴), 3.81 (d, 2H, $J = 5.2$ Hz, C2), 4.01 (q, 2H, $J = 7.0$ Hz, C1‴), 6.71 (complex signal, 1H, C5′), 7.10–7.90 (complex signal, 14H, C1′–C4′, C6′, C1″–C6″, N1), 8.12 (d, 1H, $J = 4.8$ Hz, C7′) ppm.

2.2. Preparation of the palladium(II) complex $[PdCl_2(HL2)] \cdot 1/2H_2O$ (**1**)

A mixture of 180 mg (0.62 mmol) dpba and 90 mg (0.58 mmol) etha · HCl was dissolved in 60 mL EtOH, and then the solution of 200 mg (0.61 mmol) $K_2[PdCl_4]$ in 20 mL H_2O was added to it, whereby the color of the solution changed from yellow to light brown. The mixture was refluxed at 57 °C for 50 min. The solution was left to stand at room temperature for three days. The brown precipitate was filtered off and washed with a small portion of EtOH. Yield: 0.2 g (60.6%). Elemental analysis: Calcd. for **1** ($C_{23}H_{23}Cl_2N_2O_2PPd \cdot 1/2H_2O$): C, 47.9; H, 4.2; N, 4.9. Found: C, 47.9; H, 4.0; N, 4.7%. IR (KBr; cm^{-1}): 3430 (w), 3262 (w), 3059 (w), 1728 (vs), 1581 (w), 1479 (m), 1435 (s), 1224 (s), 1100 (s), 756 (s), 711 (m), 692 (s), 537 (s). ^{1}H NMR (200 MHz; DMSO-d_6) δ: 1.14 (t, 3H, C2‴), 4.06 (q, 2H, C1‴), 4.18 (s, 1H, C2), 7.00 (complex signal, 1H, C5′), 7.40–7.90 (complex signal, 14H, C1′–C4′, C6′, C1″–C6″, N1), 8.82 (bs, 1H, C7′) ppm.

2.3. Preparation of palladium(II) complex [Pd(L1)Cl] (**2**), platinum(II) complex [Pt(L1)Cl] (**3**) and nickel(II) complex $[Ni(L1)(OCN)] \cdot 2H_2O$ (**4**)

Complexes **2**–**4** were prepared as described previously [9]. In short, **2** and **3** were obtained by substitution reactions starting from $K_2[PdCl_4]$ and $K_2[PtCl_4]$, respectively, and the ligand HL1 in EtOH, and **3** was obtained by direct synthesis from $Ni(NO_3)_2 \cdot 6H_2O$, NaOCN and the ligand HL1 in MeOH.

2.4. Physical measurements

Magnetic moment was determined using the magnetic balance MSB-MK1 (Sherwood Scientific Ltd. Cambridge, UK), at room temperature (25 °C) with $Hg[Co(SCN)_4]$ as calibrant; diamagnetic corrections were calculated from Pascal's constants. IR spectra were recorded on Perkin–Elmer FT-IR 1725X spectrophotometer by the KBr technique. ^{1}H NMR spectra (200 MHz) were obtained in DMSO-d_6 using Varian-Gemini 2000 spectrometer. Chemical shifts (δ) are given in parts per million using tetramethylsilane as internal standard. Elemental analysis (C, H, N) was performed by the standard micromethod at the Center for Instrumental Analysis of the Faculty of Chemistry, University of Belgrade, using the ELEMENTAR Vario ELIII C.H.N.S/O analyser. The results of elemental analysis were found to be in good agreement with the calculated values. Molar conductivity of DMF solutions (concentration range 10^{-4}–10^{-3} M) was measured at room temperature (25 °C) on the digital conductometer JENWAY 4009.