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Original article

Platinum(II) complexes containing aminophosphonate esters: Synthesis, characterization, cytotoxicity and action mechanism

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ABSTRACT

New platinum(II) complexes containing aminophosphonate ester were synthesized and fully characterized, which were found to possess better solubility in both organic solvents and water than cisplatin. These platinum(II) complexes exhibited considerable cytotoxicity against tumor cells MG-63, SK-OV-3, HepG2, BEL-7404 and low cytotoxicity to normal human liver cells HL-7702. Their antitumor activities were achieved through the induction of cell apoptosis and the cell cycle arrest at G1 phase. The electrophoretic mobility studies and CD spectral analysis revealed that the binding mode of complex **6** to DNA might be different from that of cisplatin.

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1. Introduction

Despite cisplatin (cis-diamminedichloroplatinum(II), CDDP)-based chemotherapy is curative for testicular germ cell tumors (TGCT) and constitutes a component of standard treatment regimes for ovarian, cervical, bladder, head and neck, small cell and non-small-cell lung cancers, the development of platinum drugs with improved antitumor activity continues to be a productive field of research [1,2]. Currently, the main focus concentrates on designing cytotoxic agents possessing either oral bioavailability, fewer side effects, or being able to circumvent intrinsic or acquired CDDP resistance, which is a major clinical problem [3,4]. To achieve these goals, chemists employed different strategies for the development of new platinum anticancer agents with different action mechanisms and broader ranges of antitumor activity [5,6]. Especially, in the past two decades, new functional ligands have been used to coordinate platinum and targeted drugs have been designed as an important strategy to overcome the side effects of cisplatin [7,8].

Because alkaline phosphatase is known to be overexpressed in the extracellular space of specific tumor cells such as ovarian and hepatic carcinoma cells [9,10] and the phosphate groups also exhibit high affinity to calcium ions, introduction of a phosphate group has been used to design targeted cisplatin analogs [11,12]. Since phosphonate esters can be hydrolyzed under biological conditions, phosphonate esters were used as a strategy to increase solubility and enhance transport through cellular membrane [11,12]. Platinum complexes incorporating functional phosphoric moieties for targeting cancer cells were first reported by Keppler and co-workers in the early 1990s [13]. More recently, Natile, Bose and Guo also reported platinum phosphonate complexes and found that some of them had a cytotoxic mechanism different from that of cisplatin [7,8,14,15]. However, except for Guo's work, most of published researches attached phosphonate groups to the platinum center as leaving groups. When the functional moieties are attached to platinum as leaving groups, they may detach during the complicated physiological process even before reaching the targeted tissues. As a result, the functional groups of the complexes will be lost. Therefore, one of the key factors for cancer targeting is to use non-leaving functional moieties to guide the platinum to specific tissues.

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Aminophosphonic acids are structural analogs of natural aminocarboxylic acid. The functionalized aminophosphonic acids, especially, α-aminoalkyl-phosphonic derivatives, are a class of important compounds that exhibit intriguing biological activities in the pharmacological and agrochemical fields [16–19]. We have designed and synthesized a series of platinum(II) complexes containing aminophosphonate ester groups recently [20]. As the continuation of this series of researches, herein, we reported six platinum complexes containing new functional ligands of α-aminoalkyl-phosphonate ester derivatives as non-leaving groups. The anticancer structure–property relationship was established for platinum(II) complexes with various alkyl chain lengths $(CH_2)_m$ and three electron-donating and lipophilic methoxy substituents (R1–R3), in which these amides are known to have the potential to induce cell apoptosis [21,22].

2. Results and discussion

2.1. Synthesis

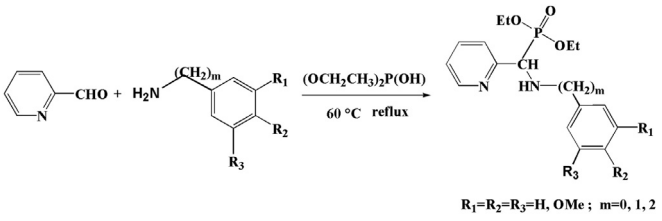
The aminophosphonate ester derivatives (**L^a**–**L^f**) were prepared from pyridinealdehyde, diethylphosphite and various amines via one-step synthetic route (Scheme 1). The products were characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR and ESI-MS spectroscopy.

Corresponding *cis*-dichloroplatinum(II) complexes **1**–**6** were obtained by reacting *cis*-Pt(DMSO)$_2$Cl$_2$ with **L^a**–**L^f** in anhydrous dichloromethane and ethanol (1:1), respectively (Scheme 2).

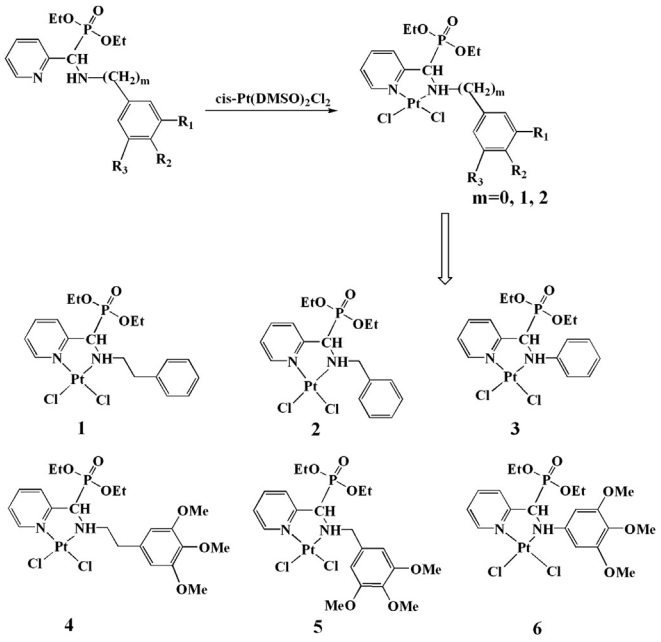
The synthesized platinum(II) complexes were characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR and ESI-MS spectroscopy as well as single crystal X-ray diffraction analysis (for complexes **1**, **3**, **5**, **6**).

2.2. Structures of platinum(II) complexes

The crystal structures of complexes **1**, **3**, **5** and **6** indicated that the platinum centers adopt an approximately square-planar geometry in which the dihedral angle between the pyridyl ring and Pt(II) coordination plane is 13.2° (complex **1**), 9.2° (complex **3**), 14.7° (complex **5**) and 7.1° (complex **6**). Selected bond lengths and angles are given in the captions of Figs. 1 and 2, which are within the normal range expected for Pt(II) complexes. One notable feature is that the carbon atom attached to P forms a half chair conformation with respect to the platinum coordination plane in all complexes, which is consistent with the steric interaction between the phosphonate ester moiety and the platinum coordination plane. The major structural distinctions among the complexes are the presence or absence of the three electron-donating and lipophilic methoxy groups at the C_3, C_4 and C_5 of the benzene ring, and the different spatial separations of the benzene ring from the platinum coordination plane. Additionally, complexes **1**–**6** exhibited higher solubility in both organic solvents and water compared with cisplatin.



Scheme 1. Synthesis route of aminophosphonate esters.



Scheme 2. Synthesis route of the platinum(II) complexes.

2.3. In vitro cytotoxic activity

The *in vitro* cytotoxicities of complexes **1**–**6** against MG-63, SK-OV-3, HepG2, BEL-7404 and HL-7702 cell lines were investigated by MTT method and compared with those of cisplatin. As shown in Table 1, the IC_{50} values of complexes **1**–**6** against tumor cell lines MG-63, SK-OV-3, HepG2 were higher than that of cisplatin. However, they exhibited lower IC_{50} (higher cytotoxicity) toward BEL-7404 than cisplatin. Complex **6** showed the highest cytotoxicity against BEL-7404 cell line. In addition, complexes **1**–**6** displayed lower cytotoxicities to normal human liver cells HL-7702 than to the tested tumor cells, and there was about an order of magnitude of difference. Comparison of the cytotoxicity of complexes **1** and **4**, **2** and **5**, **3** and **6** against the BEL-7404 tumor cells indicated that the presence of three methoxy groups at the C_3, C_4 and C_5 of the benzene ring enhanced cytotoxicity. Similar trends were observed for complexes **1** and **4**, **2** and **5**, **3** and **6** toward the other four tested tumor cell lines. Therefore, structures with the shortest distance of the phenyl ring to the platinum complex and the presence of the methoxy groups at the C_3, C_4 and C_5 of the benzene ring exhibited the highest cytotoxicity.

2.4. Apoptosis study by flow cytometry

Apoptosis is the programmed cell death that controls the development and homeostasis of multicellular organisms by elimination of aged, damaged, or mutated cells, which has been shown to be the key cellular event responsible for the anticancer activity of most of the anticancer drugs [23]. To determine whether the observed cell death induced by the complexes was due to apoptosis, the interaction of BEL-7404 cells with complex **6** was further investigated using an Annexin V-FITC/propidium iodide assay (Fig. 3). As phosphatidylserine (PS) exposure usually precedes loss of plasma membrane integrity in apoptosis, the presence of annexin V+/PI− cells is considered as an indicator of apoptosis. When treated with complex **6**, the population of annexin V+/PI− cells (Q4) was 50.8%, which suggested that apoptotic death was induced in BEL-7404 cells.

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