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Original article

Studies on antitumor mechanism of two planar platinum(II) complexes with 8-hydroxyquinoline: Synthesis, characterization, cytotoxicity, cell cycle and apoptosis

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ABSTRACT

[Pt(Q)$_2$] (**1**) and [Pt(MQ)$_2$] (**2**) exhibited enhanced cytotoxicity against BEL-7404, Hep-G2, NCI–H460, T-24, A549 tumor cells but low cytotoxicity on normal HL-7702 cells. **1** and **2** could cause the cell cycle arrest in G2 and S phase, respectively. While pifithrin-α, a specific p53 inhibitor, induced cell cycle arrest in G1 phase. Although **1**, **2** and pifithrin-α caused serious inhibition on p53, **1** and **2** significantly cause the loss of mitochondrial membrane potential and increase of the reactive oxygen species level, cytochrome *c*, apaf-1 and caspase-3/9 ratio in BEL-7404 cells. **1** and **2** may trigger the cell apoptosis through a mitochondrial dysfunction pathway whereas pifithrin-α does not. The interactions of **1** and **2** with DNA are most probably via an intercalation.

1. Introduction

The great success in the anticancer chemistry by utilizing the platinum-based agents, such as cisplatin, carboplatin and oxaliplatin, has stimulated the development of new drugs with the metal host [1,2]. Pt-based drugs, however, are subject to severe side effects and drug resistance in the therapeutic process, which has motivated inorganic chemists to find more effective, less toxic, and target-specific metal-based anticancer drugs [3]. As a routine chemotherapeutic agent for a broad range of solid malignancies, cisplatin functions by cross-linking DNA strands via the coordination of nucleic acid bases, which can subsequently induce apoptosis in cancer cells [4,5]. Therefore, designing and developing novel molecules with the capability to interact with nucleic acids so as to trigger apoptosis is currently one of the most promising strategies to discover new DNA-targeted anticancer drugs for chemotherapy [6–9].

The 8-hydroxy-quinoline scaffold's synthesis and their biological properties relative to various pathologies: neurodegenerative diseases [10,11] and cancer [12,13], have been attracted medicinal chemists' great interest. Especially, the copper(II) complexes with 8-hydroxy-quinoline derivatives exhibited the potential treatment of Alzheimer's disease [14–18]. Since the 8-hydroxy-quinoline has good chelating ability to the metal ions, recently, a series of 8-hydroxy-quinoline derivatives transition metal complexes with good anticancer ability have been reported, such as quilamines-iron chelator [19], glycosylated copper(II) ionophores as prodrug for β-glusosidase activation in targeted cancer therapy [20,21], osmium(VI) nitride complexes [22], clioquinol copper(II) and zinc(II) complexes [23], hydroxyquinoline derived vanadium (IV and V), copper(II) and iron(II) complexes [24–26], and ruthenium(II) complexes [27,28]. Meanwhile, recently, our group has reported a series of dihalo-8-hydroxyquinoline-metal complexes with high *in vitro* antitumor activity [29–34]. Our findings also suggested that 8-hydroxyquinoline that can serve as the ligand to the metal centers to form planar or partially planar coordination structure could intercalate between the neighboring bases of DNA resulting in blocking DNA replication and finally inducing tumor cells' death.

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Nonetheless, in spite of a large number of platinum(II) complexes with 8-hydroxyquinoline and derivatives reported [23,35–39], their anticancer activity *in vitro* and mechanism remains unknown, as of yet. In order to develop new platinum(II) antitumor agents [35,36], we synthesized two platinum(II) complexes: [Pt(Q)$_2$] (**1**) (H-Q = 8-hydroxyquinoline) [36,39] and [Pt(MQ)$_2$] (**2**) (H-MQ = 8-hydroxy-2-methylquinoline). By characterizing their cytotoxicity against tumor cells BEL-7404, Hep-G2, NCI–H460, T-24, A549 and human normal liver cell HL-7702, we proposed a possible antitumor mechanism.

2. Results and discussion

2.1. Synthesis

The reactions of 8-hydroxylquinoline ligand (8-hydroxyquinoline and 8-hydroxy-2-methylquinoline) with Pt(DMSO)$_2$Cl$_2$ in presence of methanol/MeCN/acetone (6:1:1) under solvothermal conditions, gave rise to [Pt(Q)$_2$] (**1**) and [Pt(MQ)$_2$] (**2**) (Scheme 1) whose structures were determined by single-crystal X-ray diffraction analysis, elemental analysis, IR, ESI-MS and NMR. Herein, the synthesis method for complex **1** is different from the previous studies [36,39].

2.2. Crystal structure

Complexes **1** and **2** are mononuclear structures, however, the single-crystal X-ray diffraction analysis for both compounds revealed that their structures are different from each other. The details of crystallographic data and structural refinement parameters for complexes **1** and **2** were summarized in Table S1. The selected bond lengths are tabulated in Table S2.

Complex **1** crystallinzes in a monoclinic crystal system with space group of P2$_1$/c. Consistent with the reported structure by Kato [36] and Zhao [39], the platinum(II) center in complex **1** adopts an approximately four-coordinated square planar geometry. As shown in Fig. 1, two 8-hydroxyquinolin ligands arrange in the *trans* position. Pt–O and Pt–N bond lengths are in the range of 2.021–2.023 and 2.003–2.004 Å, respectively, which are within the normal range.

As shown in Fig. 2, complex **2** is quite close to complex **1** in structure and the coordination geometry of Pt(II) can also could be described as four-coordinated square planar geometry. The Pt(II) atom is chelated by two H-MQ in which O(1), O(2), N(1), N(2) atoms form the equatorial plane. The N-donor atoms are in a *cis* alignment while the O toms are *trans* to each other. The bite angles (N(1)–Pt(1)–O(1) and N(2)–Pt(1)–O(2)) of the chelate ring are 98.4(2) and 97.8(2)°, respectively, which are smaller than those in complex **1**. The Pt–O distances [2.007(5) and 2.016(5) Å] involving H-MQ are substantially shorter than the Pt–N distances [2.037(6) and 2.051(6) Å]. The remainder bond lengths of the ligand are in normal range.

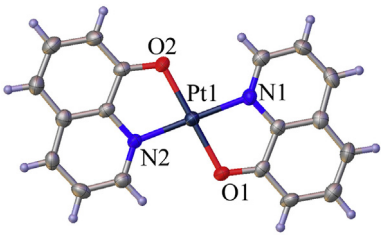


Fig. 1. ORTEP drawing of the complex **1** with atom numbering scheme. Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

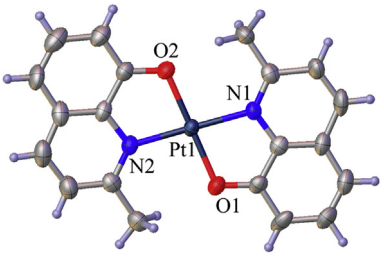
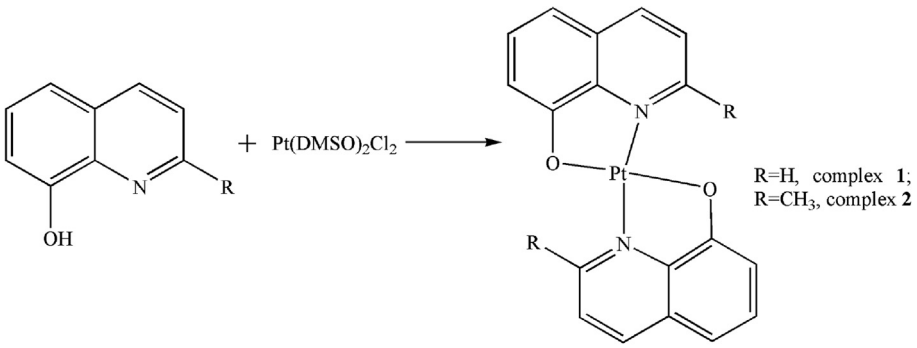


Fig. 2. ORTEP drawing of the complex **2** with atom numbering scheme. Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

2.3. Stability in solution

Stability of complexes **1** and **2** in DMSO and physiological conditions (PBS buffer solution with pH value of 7.35, containing 1% DMSO) was examined by means of UV–Vis spectroscopy, as shown in Figs. S1 and S2. The time-dependent (in the time course of 0, 12, 24 h) UV–Vis spectra of each complex dissolved in PBS solution are indicated in Figs. S1, S2. It can be found that no obvious changes on the spectral character and the peak absorptions for complexes **1**, **2** over the time, suggesting no structural transitions or decompositions on these complexes. In addition, the stability of the complexes was monitored by HPLC in a DMSO solution over 24 h (Fig. S3). These results indicated that complexes **1** and **2** were stable for 24 h in DMSO stock solution and the coordination geometry of the corresponding quinolinol ligand to the metal centre was retained.



Scheme 1. Synthetic routes for the preparation of complexes **1** and **2**.