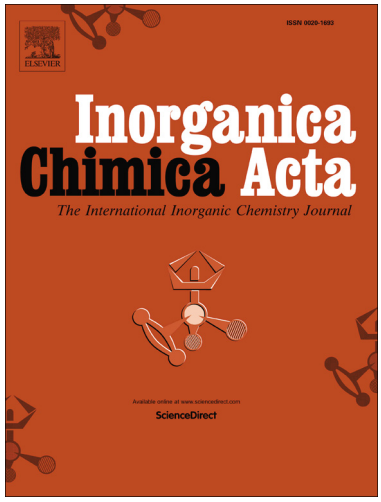

Research paper

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Isomeric Ruthenium(II) Complexes for Cancer Therapy and Cellular Imaging

Pingyu Zhang,[a] Wenxiu Huang,[a] Yi Wang,[a] Haihang Li,[a] Chunmei Liang,[a] Chuanxin He,[a] Haitao Wang*[a] and Qianling Zhang*[a]

Dedication ((optional))

Abstract: Two isomeric ruthenium(II) complexes, [Ru-*m*-OH]$^{2+}$ and [Ru-*o*-OH]$^{2+}$ with two hydroxyl substituents at different positions of ligands, had been designed and synthesized. We found that the cellular uptake efficiency of Ru-*o*-OH]$^{2+}$ was much better than Ru-*m*-OH]$^{2+}$, and it exhibited higher toxicity toward cancer cell (BEL-7402) than its isomeric compound, [Ru-*m*-OH]$^{2+}$. Importantly, [Ru-*o*-OH]$^{2+}$ showed great seletivity between cancer cells and human normal cell (HBMEC). Confocal microscopy and inductively coupled plasma mass spectrometry (ICP-MS) indicated that [Ru-*o*-OH]$^{2+}$ mainly accumulated in mitochondria. It could up-grade the expression of Bax and down-grade the level of Bcl-2, which trigger in mitochondrial apoptotic pathway. This study suggests that isomeric metal complexes might make differences in the field of medicine for anti-cancer.

1. Introduction

Metal complexes contain a variety of structural and electronic features which can be exploited in drug design [1-5]. The metal centre and its oxidation state can be varied, as well as its isomers. These properties allow the fine-tuning of their biological activities [5]. Recently, due to the severe side effect and drug resistance of platinum(II) base anticancer drugs in clinic, ruthenium complexes have been considered as the most promising alternative metallodrugs [6-8]. Four Ru coordination compounds have entered clinical trials: three Ru(III) complexes, [ImH][transRuCl$_4$(DMSO)Im] (NAMI-A, Figure 1), [InH][trans-RuCl$_4$In$_2$] (KP1019), NKP-1339 (the sodium salt of KP1019) [9-16] and a Ru(II) polypyridyl complex will be tested as a PDT agent in the clinics against non-muscle invasive bladder cancer (TLD-1433) [17] (Figure 1). The first Ru-based anticancer drug candidate in clinical trials was NAMI-A, followed by KP1019 in 2003. Both of them successfully completed phase I [9,10], but NAMIA has recently been withdrawn from the clinic after phase I/II because of unconvincing efficacy; the likelihood of further clinical studies of NAMI-A is uncertain [1,3]. Another class of Ru compounds, namely substitutionally inert Ru(II) polypyridyl complexes, is characterized by favourable photophysical properties that make them attractive for applications in photodynamic therapy (PDT) (i.e. TLD-1433) [17]. Some Ru(II) organometallic complexes are also under clinical optimization (i.e. RM175, RAPTA-C) (Figure 1) [18-28]. Dyson group reported that lots of modified RAPTA compounds have been synthesized that have helped to illuminate the mechanism of the anticancer activity and identify mechanisms by which drug activity can be optimized [29,30].

The mechanisms have been proposed to elucidate the anticancer activities of ruthenium complexes, including interaction with DNA [31], inhibition of kinases [32] and topoisomerase [33], blocking of cell cycle [34] and involving in cellular redox chemistry [1]. Apart from DNA targeting drugs, mitochondria is becoming an important cellular target to design novel anticancer drugs. Mitochondria are involved in many cellular functions such as modulation of intracellular calcium concentration and the regulation of apoptotic cell death. Mitochondria are also a major source of free radicals [35]. Moreover, mitochondrial dysfunction contributes to a number of human diseases, ranging from neurodegenerative diseases and ischaemia–reperfusion injury to obesity and diabetes [36].

Two isomeric ruthenium(II) complexes, [Ru(phen)$_2$MDHPIP]$^{2+}$ ([Ru-*m*-OH]$^{2+}$, MDHPIP = (2,4-*m*-dihydroxyphenyl)imidazo[4,5-f][1,10-phenanthroline]) and [Ru(phen)$_2$ODHPIP]$^{2+}$ ([Ru-*o*-OH]$^{2+}$, ODHPIP = (2,3-*o*-dihydroxyphenyl)imidazo[4,5-f][1,10-phenanthroline]), had been synthesized to study their biologocal activities in cells. In our previous work, we found that [Ru-o-OH]$^{2+}$ could bind with DNA, but we did not do any research on the level of living cells [37,38]. In this article, the cytotoxicities of these two complexes towards cancer cells (BEL-7402 cell and NCI-H460 cell) and normal cell (HBMEC) and their mechanism of anti-tumour are firstly reported. The results showed that [Ru-*o*-OH]$^{2+}$ towards to cancer cells was more toxic than its isomeric compound, [Ru-*m*-OH]$^{2+}$. To be noted, [Ru-*o*-OH]$^{2+}$ exhibites

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