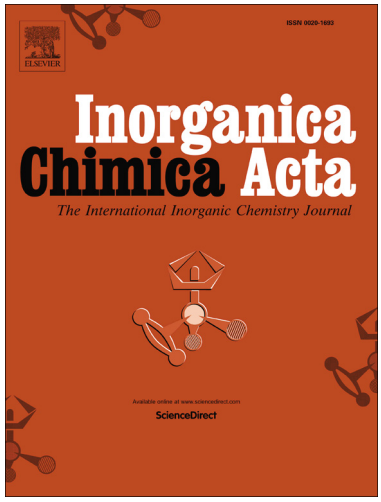

Research paper

Synthesis and cytotoxicity of N,N'-dibisphosphonate ethylenediamine derivatives and platinum(II) complexes with high binding property to hydroxyapatite

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Synthesis and cytotoxicity of N,N'-dibisphosphonate ethylenediamine derivatives and platinum(II) complexes with high binding property to hydroxyapatite

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Abstract A series of N,N'-dibisphosphonate ethylenediamine derivatives (**L1-L6**) and their corresponding dichloroplatinum(II) complexes (**1-6**) have been prepared and characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and HRMS spectra. The *in vitro* antitumor of compounds **L1-L6** and **1-6** was tested by WST-8 assay with Cell Counting Kit-8, indicating that platinum-based complexes **1-6** showed higher cytotoxic efficacy than platinum-free compounds **L1-L6** against SKOV3 and MG-63, especially complex **2** (R = CH_3, n = 2) with comparable cytotoxicity to cisplatin after 72 h incubation. And complexes **1-6** were highly selective in cytotoxicity against MG-63 tumor cells than hFOB 1.19 normal cells. The *in vitro* hydroxyapatite binding test revealed that complexes **1** and **2** showed higher affinity (K' = 4.2 and 3.5, respectively) for bone hydroxyapatite than cisplatin (K' < 0.1) and zoledronate (K' = 2.8). On basis of flow cytometry results, complex **2** induced cell death by apoptosis effect similar to cisplatin, different from zoledronate. Representative complex **2** has been proved to be a promising bone-targeting antitumor agent for subsequent *in vivo* study.

Keywords bisphosphonates; platinum(II) complexes; cytotoxicity; hydroxyapatite affinity; apoptosis

1. Introduction

Osteosarcoma is considered as one of the most untreatable and painful malignant tumors in the world [1]. Among the chemotherapeutic agents for the treatment of osteosarcoma, cisplatin is one of the most active drugs and the primary choices, which was approved by FDA in 1978 [2-4]. However, the clinical applications of cisplatin are confined by several drawbacks including side effects and drug resistance due to its poor tumor-selectivity [5-7]. Therefore, based on these disadvantages, it is necessary to develop novel platinum-based drugs with bone-targeting ability in order to reduce the side effects and improve the tumor-selectivity towards osteosarcoma. Much effort has been made in an attempt to overcome these limitations [8-12]. And it is a useful strategy that the bone-targeting groups can be introduced in the non-leaving or leaving moieties of platinum-based complexes to develop novel bone-targeting agents towards osteosarcoma.

Geminal bisphosphonates (BPs) are known to be metabolically stable analogs of inorganic pyrophosphate (Figure 1), which show high affinity for bone mineral hydroxyapatite (HAP) and other calcified tissues [13]. A number of BPs have been approved for clinical use in several bone-related diseases including myeloma, hypercalcemia of malignancy, osteoporosis, and Paget's disease due to bone-targeting property [14-17]. Besides, BPs have also been reported to exhibit significant inhibition of osteoclastic bone resorption and antitumor effect such as zoledronate, an established bisphosphonate drug in clinic [18].

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