Cytotoxic properties of platinum(IV) and dinuclear platinum(II) complexes and their ligand substitution reactions with guanosine-5#-monophosphate

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Cytotoxic properties of platinum(IV) and dinuclear platinum(II) complexes and their ligand substitution reactions with guanosine-5′-monophosphate

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Abstract The substitution reaction of the Pt(IV) complex [$PtCl_4$(bipy)] with guanosine-5′-monophosphate (5′-GMP) was studied by UV–Vis spectrophotometry. This reaction was investigated under *pseudo*-first-order conditions at 37 °C in 25 mM Hepes buffer (pH = 7.2) in the presence of 10 mM NaCl to prevent the hydrolysis of the complex. The substitution of chlorides in [{*trans*-$Pt(NH_3)_2Cl\}_2$(μ-1,2-bis(4-pyridyl)ethane)]$(ClO_4)_2$ (**Pt3**) complex by 5′-GMP was followed by ^{1}H NMR spectroscopy under second-order conditions. Very similar values for the rate constants of both substitution steps were obtained. The Pt(IV) complexes, [$PtCl_4$(bipy)] and [$PtCl_4$(dach)], as well as dinuclaer Pt(II) [{*trans*-$Pt(NH_3)_2Cl\}_2$(μ-pyrazine)]$(ClO_4)_2$ (**Pt1**), [{*trans*-$Pt(NH_3)_2Cl\}_2$(μ-4,4′-bipyridyl)]$(ClO_4)_2 \cdot$ DMF (**Pt2**) and [{*trans*-$Pt(NH_3)_2Cl\}_2$(μ-1,2-bis(4-pyridyl)ethane)]$(ClO_4)_2$ (**Pt3**) complexes, displayed potent cytotoxic activity against human ovarium carcinoma cell line TOV21G and lower activity toward human colon carcinoma HCT116 cell line at the same concentrations. Our data indicate that these platinum complexes could be explored further, as potential therapeutic agents for ovarian cancer.

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Introduction

The use of platinum coordination compounds in cancer chemotherapy has been extensively studied following the discovery of the therapeutic properties of *cis*-diamminedichloroplatinum(II) (*cis*-$[Pt(NH_3)_2Cl_2]$, cisplatin) by Rosenberg et al. [1, 2]. Cisplatin is one of the most widely utilized antitumor drugs, exhibiting high efficacy against solid tumors, particularly testicular and ovarian cancer [3–5]. The anticancer activity of cisplatin is based on its ability to form intrastrand covalent adducts with DNA by binding of Pt to the N7 atoms of two adjacent guanine bases [6, 7]. However, the clinical efficiency of cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, is limited by toxic side effects, in particular a dose-limiting nephrotoxicity, by drug resistance in tumor cells, and by a narrow range of activity [8, 9].

Platinum(IV) complexes have greater inertness than the corresponding Pt(II) complexes. Hence, these complexes may have some advantages, such as: allowing oral administration, reduced toxicity, and decrease in the amount of the complex that is lost or deactivated on the path to the target cell [10]. Platinum(IV) complexes have enormous potential as anticancer agents in terms of both high activity and low toxicity. About 3000 Pt(IV) complexes have been synthesized and investigated in an attempt to improve the antitumor activity, lower toxicity and to design a drug that would be able to overcome resistance. Only about 30 platinum complexes have entered into clinical trials [11, 12]. However, it is generally believed that since Pt(IV) complexes are less reactive in