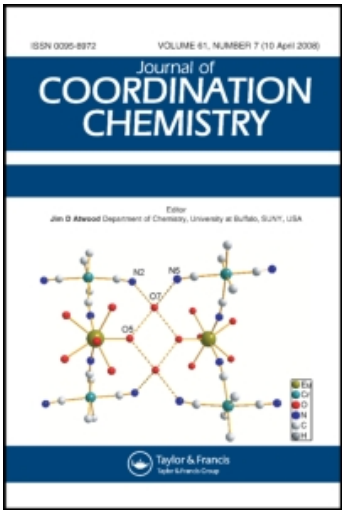

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Activity of some platinum(II/IV) complexes with edda-type ligands against human adenocarcinoma HeLa cells

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Cisplatin analogues, *cis*-dichloro(ethylenediamine-*N*,*N*′-di-3-propanoic acid)platinum(II) (**1**) and *cis*-iodo(ethylenediamine-*N*,*N*′-di-3-propanoic acid)platinum(II) (**2**), as well as *trans*-dichloro-(ethylenediamine-*N*,*N*′-di-3-propanoato)platinum(IV) (**3**), *trans*-dibromo(ethylenediamine-*N*,*N*′-di-3-propanoato)platinum(IV) (**4**), *trans*-dichloro(propylenediamine-*N*,*N*′-diacetato)-platinum(IV) (**5**) and *trans*-dibromo(propylenediamine-*N*,*N*′-diacetato)platinum(IV) (**6**), -([Pt(H_2eddp)Cl_2], [Pt(Heddp)I], *trans*-[Pt(eddp)Cl_2], *trans*-[Pt(eddp)Br_2], *trans*-[Pt(pdda)Cl_2] and *trans*-[Pt(pdda)Br_2], respectively) were used to assess antitumor selectivity against human adenocarcinoma HeLa cells. The results show that different oxidation states of platinum, different halide ligands, chelating aminocarboxylato and diamine backbones have similar effects with edda-type ligands and activity is lower than for cisplatin.

Keywords: Platinum(IV); Platinum(II); Edda; Adenocarcinoma HeLa; Cytotoxicity

1. Introduction

Thousands of platinum complexes have been synthesized not only in order to investigate their chemistry but also to identify novel platinum compounds with improved properties in comparison to the drug cisplatin [1, 2]. Platinum(IV) complexes are generally less liable than those of platinum(II) and their inertness may allow for oral administration [3]. Cytotoxicity of platinum(IV) complexes with ethylenediamine-*N*,*N*′-di-3-propanoato (eddp) and chloro or bromo ligands, *trans*-[Pt(eddp)Cl_2] [4] and *trans*-[Pt(eddp)Br_2], were recently investigated [5]. They showed low activity

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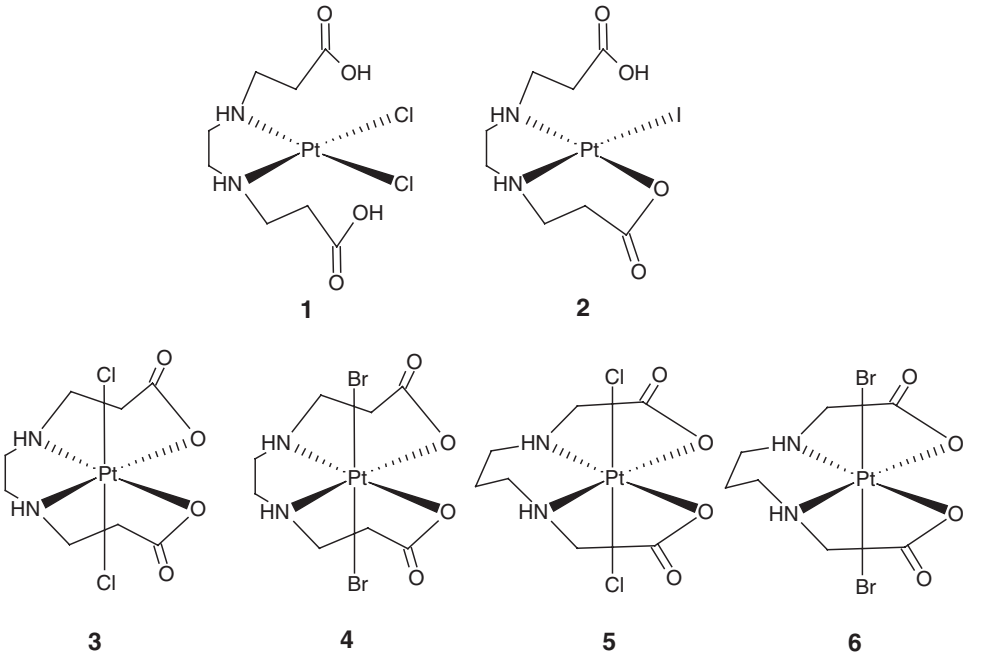

Figure 1. Complexes of platinum(II) and platinum(IV) with eddp and pdda ligands.

against A2780 and A2780cisR cells. Several new complexes have been synthesized and tested against a tumor system, with the aim of more fully exploring these systems. The present work deals with platinum complexes with variation in the chelating aminocarboxylato and diamine backbone, halide ligands and oxidation states (figure 1). The complexes have been tested *in vitro* against human adenocarcinoma HeLa cells.

2. Experimental

2.1. *Materials*

All reagents were of analytical grade. The complexes *trans*-[Pt(eddp)Cl_2] (**3**), *trans*-[Pt(eddp)Br_2] (**4**), *trans*-[Pt(pdda)Cl_2] (**5**) and *trans*-[Pt(pdda)Br_2] (**6**) were prepared according to published methods [4–7].

2.2. *Dichloro(ethylenediamine-N,N′-di-3-propanoic acid)platinum(II), [Pt(H_2eddp)Cl_2] (1)*

$K_2[PtCl_4]$ (0.200 g, 0.482 mmol) was dissolved in 10 cm^3 of water at 90°C. H_2eddp · 2HCl (0.133 g, 0.482 mmol) was then added. This solution was stirred for 4 h, during which period LiOH (0.964 mmol) was added. The solution was then filtered and evaporated on a steam bath to small volume. After a few days the yellow power that formed was filtered off, washed and air dried. Yield: 0.153 g (67.80%). Anal. Calcd for $PtC_8H_{16}Cl_2N_2O_4$ (%): C, 20.4; H, 3.4; N, 6.0. Found: C, 20.5; H, 3.7; N, 5.8%.

2.3. *Iodo(ethylenediamine-N,N′-di-3-propanoic acid)platinum(II), [Pt(Heddp)I] (2)*

$K_2[PtCl_4]$ (0.200 g, 0.482 mmol) was dissolved in 10 cm^3 of water at room temperature. KI (0.320 g, 1.928 mmol) was then added. This solution was stirred for 10 min and then $H_2eddp \cdot 2HCl$ (0.133 g, 0.482 mmol) was added. The mixture was and stirred for 2 h, during which period LiOH (0.266 mmol) have added in small portions. The solution was then filtered and evaporated on a steam bath to small volume. After few days a dark powder was obtained, filtered off, washed and air dried. Yield: 0.110 g (43.47%). Anal. Calcd for $PtC_8H_{15}IN_2O_4$ (%): C, 18.3; H, 2.9; N, 5.3. Found: C, 18.5; H, 3.2; N, 5.3.

2.4. *Spectroscopy*

Infrared spectra were recorded on a Perkin-Elmer FTIR 31725-X spectrophotometer (KBr pellets). ^1H and ^{13}C NMR spectra (DMSO) were recorded on a Varian Gemini-200 NMR spectrometer.

2.5. In vitro *cytotoxicity studies*

Stock solutions of platinum complexes were made up in DMSO at a concentration of 10 mM, filtered through a 0.22 μm Millipore filter and diluted by nutrient medium to various working concentrations. Each drug solution was prepared freshly before use. Nutrient medium was RPMI 1640 medium, without phenol red, supplemented with *s*-glutamine (3 mM), streptomycin (100 μg cm^{-3}), and penicillin (100 IU cm^{-3}), 10% heat-inactivated (56°C) foetal bovine serum and 25 mM Hepes. The pH was adjusted to 7.2 by bicarbonate solution. MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, was dissolved (5 mg cm^{-3}) in phosphate-buffered saline at pH 7.2 and filtered through a 0.22 μm Millipore filter before use.

2.6. *Cell culture and treatment of cell lines*

Human cervix adenocarcinoma HeLa cells were cultured as monolayers in the nutrient medium. The cells were grown at 37°C in 5% CO_2 and humidified air atmosphere. HeLa cells were seeded (2000 cells per well) into 96-well microtitre plates and 20 h later, after cell adherence, five different concentrations of complex compounds were added. For all compounds final concentrations were in the range 12.5–200 μM; for **2** and **5**, from 6.25–100 μM; **3** and **6** final concentrations were in the range 12.5–200 μM. In control wells only nutrient medium was added to the cells. Most experiments were done in triplicate. Nutrient medium with corresponding concentrations of compounds, but void of cells was used as blank.

3. Results and discussion

3.1. *Infrared and NMR spectra*

IR spectra of $[Pt(H_2eddp)Cl_2]$ show characteristic asymmetric COOH bands at 1702 and 1721 cm^{-1}. This is in a good agreement with values for the free ligand [8]. In [Pt(Heddp)I] one band is found at 1722, like the free ligand, and another at 1644 cm^{-1}, characteristic of a coordinated COO group [9]. Symmetric stretching

Table 1. IC50 (μM) values for 72 h of action of investigated compounds against HeLa cells determined by the MTT test.

	IC50 (μM) ± SD
cis-[Pt(H_2eddp)Cl_2] (**1**)	165 ± 6
cis-[Pt(Heddp)I] (**2**)	194 ± 3
trans-[Pt(eddp)Cl_2] (**3**)	179 ± 7
trans-[Pt(eddp)Br_2] (**4**)	143 ± 3
trans-[Pt(pdda)Cl_2] (**5**)	175*
trans-[Pt(pdda)Br_2] (**6**)	149*

*$n = 1$.

bands appear at 1377 and 1375 cm^{-1} for [Pt(H_2eddp)Cl_2] and [Pt(Heddp)I], respectively. ^{1}H NMR has been used extensively for characterization of metal chelates containing aminocarboxylate ligands [8]. Protons on carbons between nitrogen donor atoms are found between 2.3 and 2.7 for [Pt(H_2eddp)Cl_2] and between 2.5 and 2.8 for [Pt(Heddp)I]. Protons associated with the β-alaninato fragments of the eddp showed characteristic patterns between 2.8 and 3.3 and 3.0 and 3.3 for [Pt(H_2eddp)Cl_2] and [Pt(Heddp)I], respectively. Because of the highly collapsed nature and overlap of the patterns, a complete analysis is difficult. In ^{13}C NMR spectra complexes exhibit a quartet at around 172 ppm. All methylene carbons resonances occur within the range 53.3–39.1 and 51.9–32.2 ppm for [Pt(H_2eddp)Cl_2] and [Pt(Heddp)I], respectively.

3.2. In vitro *cytotoxicities*

Values for IC50 (μM) for the 72 h of action of investigated compounds against HeLa cells determined by the MTT test are presented in table 1. Complexes **3** and **4** were previously used in a cytotoxicity evaluation against A2780/A2780cisR human ovarian cancer cell lines [5]. Reduction released tetracoordinated platinum(II) species. These consists of platinum(II) ion with eddp occupying all four coordination sites, preventing their interaction with biological substrates such as DNA bases. The greater activity of **4** with respect to **3** is noteworthy. In the present case the situation is similar. Complexes with bromide showed greater activity against human adenocarcinoma HeLa cells than those with chloride ligands. Because of this it is supposed that the mechanism is similar to that previously reported [5]. Comparing activity of **1**, **3** and **5**, complexes with chloride ligands, **1** is the most active and **3** is the least. This order is expected, because complexes **3** and **5** can be reduced to square planar platinum(II) species with tetracoordinated eddp and pdda ligands, respectively. Complex **5** is more active than **3** because the glycinato fragment, forming five-membered rings, is more strained than with the β-alaninato fragment (six-membered rings), causing the Pt–O bond in **5** to be weaker [4, 6]. In addition, complex **1** contain bicoordinated eddp and two leaving chlorides which could be easily displaced by DNA bases, making this complex potentially more active than **3** and **5**.

Complex **1** showed greater activity than **2**. Complex **2** contains an iodide ligand and tricoordinated eddp. This unusual coordination mode of eddp gives a complex that could react with DNA bases via loss of one halide. Substitution of chloride in complex **3** by bromide, complex **4**, increased cytotoxic activity. The same trend was noticed for compounds **5** and **6**, with substitutions of chloro ligands, in complex **5**, with bromo ligands in complex **6**. All complexes have lower activity than cisplatin.

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