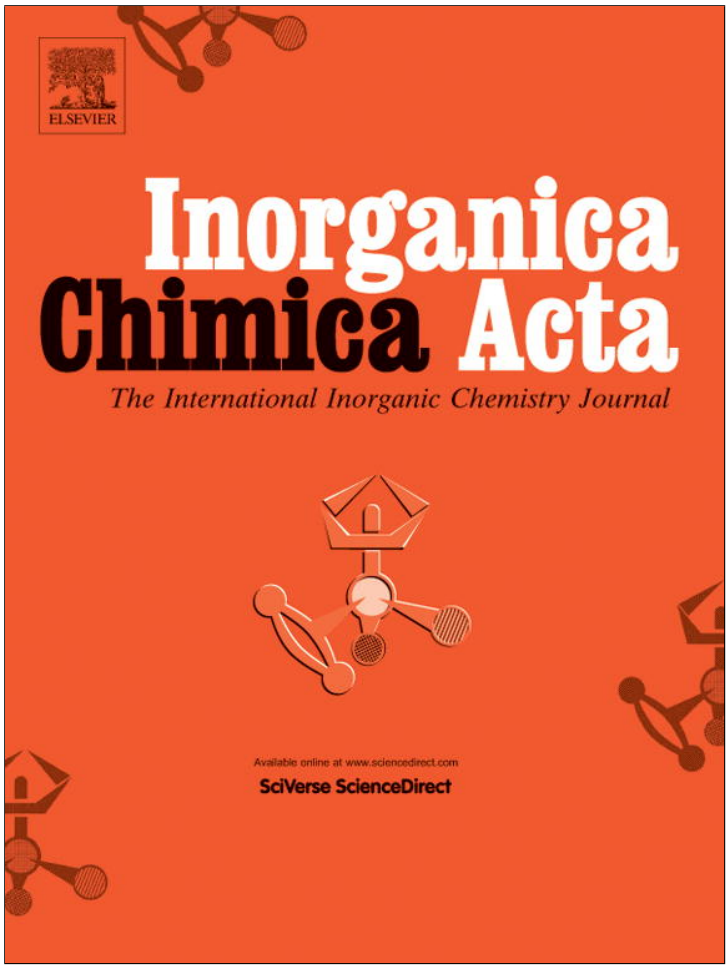

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Stereospecific ligands and their complexes. Part X: Synthesis, characterization and *in vitro* antitumoral activity of platinum(IV) complexes with *O*,*O*′-dialkyl-(*S*,*S*)-ethylenediamine-*N*,*N*′-di-2-(4-methyl)pentanoate ligands

Jelena M. Vujić [a,b], Goran N. Kaluđerović [c,*], Bojana B. Zmejkovski [d], Marija Milovanović [e], Vladislav Volarević [e], Nebojša Arsenijević [e], Tatjana P. Stanojković [f], Srećko R. Trifunović [a,*]

[a] Department of Chemistry, Faculty of Science, University of Kragujevac, R. Domanovića 12, 34000 Kragujevac, Serbia
[b] Faculty of Agronomy, University of Kragujevac, Cara Dušana 34, 32000 Čačak, Serbia
[c] Institut für Chemie, Martin-Luther-Univerität Halle-Wittenberg, Kurt-Mothes-Straβe 2, 06120 Halle, Germany
[d] Department of Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Studentski Trg 14, 11000 Belgrade, Serbia
[e] The Medical Faculty, University of Kragujevac, Svetozara Markovića 69, 34000 Kragujevac, Serbia
[f] Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia

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ABSTRACT

Synthesis of four new platinum(IV) complexes **1**–**4**, with bidentate *N*,*N*′-ligand precursors *O*,*O*′-dialkyl esters (alkyl = ethyl, *n*-propyl, *n*-butyl and *n*-pentyl), of (*S*,*S*)-ethylenediamine-*N*,*N*′-di-2-(4-methyl)pentanoic acid dihydrochloride [(*S*,*S*)-H_4eddl]Cl_2 were reported. The composition of the novel platinum complexes was determined by elemental analysis and characterizations were performed by infrared, ^{1}H and ^{13}C NMR spectroscopy. DFT calculations indicate formation one (*R*,*R*) from three possible diastereoisomers (*S*,*S*; *R*,*S*). Complexes **1**–**4** displayed potent anticancer activity. IC_{50} values range from 0.74 to 70 μM, against tested cell lines, except for CLL cells. The antitumoral activity of **2**–**4** was found to be considerably stronger to Jurkat and K562. Cell cycle analysis of cell lines showed G1 arrest in the presence of analyzed complexes.

1. Introduction

Many platinum complexes have been synthesized not only in order to investigate their chemistry but also to identify novel complexes with improved antitumoral properties in comparison to the drug cisplatin [1,2]. The antitumor activity of cisplatin has been proved over many years in the treatment of various types of cancer [3–8]. Platinum(II) based anticancer drug cisplatin has been considered as one of the most effective chemotherapeutic agents, displaying clinical activity against a wide variety of solid tumors [9–11].

There has been a special interest in platinum(IV) complexes, as their greater inertness in comparison with platinum(II) complexes [12,13] may allow for the oral administration of the drugs, reduce the toxicities associated with platinum-based chemotherapy and decrease the amount of the complex lost or deactivated through reactions on the way to the target site [2,8]. One of the likely candidates for clinical application is the first orally available platinum(IV)-containing anticancer drug satraplatin (JM216) [14].

The selection of satraplatin for clinical studies was based on its potent *in vitro* growth-inhibitory properties against several tumor cell types, and its *in vivo* oral anticancer activity that was largely comparable to that of administered cisplatin or carboplatin in a variety of murine tumor models [8,15]. Satraplatin entered clinical trials in 1992 and is now undergoing phase 3 evaluation [8,15].

Earlier, cytotoxity of platinum(IV) complexes with ethylenediamine-*N*,*N*′-di-3-propanoato (eddp) ligand, *trans*-[Pt(eddp)Cl_2] and *trans*-[Pt(eddp)Br_2] (configuration index *OC*-6-13; Fig. 1A) has been investigated [15,16] against A2780 and A2780cisR cells and found to be low. In order to increase the antitumor action *ONNO*-tetradetnate ligands were substituted with *NN*-bidentates by esterification of the H_2eddp·2HCl. Synthesis and characterization of platinum(IV) complexes with *NN* bidentate esters, R_2eddp (*R* = *n*-Bu, *n*-Pe; Fig. 1B) ligands was reported [17]. Furthermore, the complexes of ethylenediamine-*N*,*N*′-diacetato esters [$PtCl_4$(R_2edda)] (*R* = Me, Et, *n*-Pr; Fig. 1C) were tested on human tumor cell lines 1411HP, H12.1 (both testicular germ cell tumors), DLD-1 (colon carcinoma), 518A2 (melanoma), A549 (lung carcinoma) and liposarcoma [18,19].

Herein the synthesis, characterization and antiproliferative activity against human breast cancer (MDA-MB-361 and MDA-MB-453), T-leukemia (Jurkat), chronic myelogenous leukaemia

* Corresponding authors. Tel.: +49 345 5525678; fax: +49 345 5527028 (G.N. Kaluđerović), tel.: +381 34 300263; fax: +381 34 335040 (S.R. Trifunović).
E-mail addresses: goran.kaluderovic@chemie.uni-halle.de, goran@chem.bg.ac.rs (G.N. Kaluđerović), srecko@kg.ac.rs (S.R. Trifunović).

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