European Journal of Medicinal Chemistry 46 (2011) 4559–4565

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Stereospecific ligands and their complexes. Part VII. Synthesis, characterization and *in vitro* antitumoral activity of platinum(II) complexes with *O,O′*-dialkyl esters of (*S,S*)-ethylenediamine-*N,N′*-di-2-(4-methyl)pentanoic acid

Jelena M. Vujić [a,b], Goran N. Kaluđerović [c,d,*], Marija Milovanović [e], Bojana B. Zmejkovski [c], Vladislav Volarević [e], Danijela Živić [e], Predrag Đurđević [e], Nebojša Arsenijević [e], 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] Department of Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Studentski Trg 14, 11000 Belgrade, Serbia
[d] Institut für Chemie, Martin-Luther-Univerität Halle-Wittenberg, Kurt-Mothes-Straβe 2, 06120 Halle, Germany
[e] The Medical Faculty, University of Kragujevac, Svetozara Markovića 69, 34000 Kragujevac, Serbia

ARTICLE INFO

Article history:
Received 4 April 2011
Received in revised form
18 July 2011
Accepted 20 July 2011
Available online 27 July 2011

Keywords:
Platinum(II) complexes
Edda-type ligands
Antitumoral activity
Chronic lymphocytic leukemia cells

ABSTRACT

Platinum(II) complexes (**1**–**4**) with bidentate *N,N′*-ligands, *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 were synthesized and characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis. DFT calculations were performed for the complexes and it was found that only one diastereoisomer could be formed. Cytotoxic activity of complexes **1**–**4** was determined against chronic lymphocytic leukemia cells (CLL) and compared to the activity of ligand precursors **L1**·2HCl–**L4**·2HCl and corresponding palladium(II) complexes, [$PdCl_2$**L**] (**L** = **L1**–**L4**). The complexes were found to exhibit significantly higher antitumor activities than cisplatin on CLL cells. Cytotoxic effect of platinum(II) complexes on CLL cells was higher compared to corresponding palladium(II) complexes. In addition the mode of cell death induced by platinum(II) complexes was determined.

1. Introduction

The starting point of the ever increasing field of bioinorganic chemistry of platinum(II) complexes was Rosenberg's accidental discovery of antitumor activity of cisplatin, *cis*-[$PtCl_2(NH_3)_2$] [1–3]. As a drug, cisplatin was established against diverse tumor types including testicular, ovarian, head and neck, bladder, esophageal, and small lung cancer cells (SCLC) [4]. However, cisplatin exhibits only limited activity against tumors like colon and breast cancer, and in time resistance frequently occurs [5]. Also cisplatin does not differentiate between normal and cancerous tissues, resulting in emphasized side effects including potentially fatal renal failure, bone marrow suppression and compromised immunity, severe nausea and toxicity [6].

The next generation of platinum(II)-based drugs used in the clinical treatmentsincludes carboplatin, with similar cytotoxicity but less side effects than cisplatin, and oxaliplatin, with anti-proliferative effects even in cancers insensitive to cisplatin (for example, advanced colorectal tumors [7]). Because of the proven cytotoxicity of these platinum(II) compounds, a great number of new platinum complexes are continuously being prepared and tested for antitumor activity [8–10].

The synthesis and characterization of platinum(IV) complexes with *NN* bidentate ester ligands, R_2eddp (eddp = ethylenediamine-*N,N′*-di-3-propanoate; R = *n*-Bu, *n*-Pe; Fig. 1A), have recently been reported [11]. The antitumoral investigation was carried out on human adenocarcinoma HeLa cells, human myelogenuos leukemia K562 cells and normal immunocompetent cells (PBMC) and when used [$PtCl_4$(*n*-Bu_2eddp)] cytotoxicity was actually comparable to that of cisplatin. A powerful *in vitro* antitumoral activity of these two compounds was shown on L929 fibrosarcoma and U251 astrocytoma tumor cells [12]. The kinetics of the tumor cell death process induced by using these platinum(IV) complexes was considerably faster in comparison to the classical platinum(II)-based drug cisplatin [13]. Furthermore, the complexes of

* Corresponding author. Department of Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Studentski Trg 14, 11000 Belgrade, Serbia. Tel.: +49 345 5525678, +381 11 3336735; fax: +49 345 5527028, +381 11 636061.
** Corresponding author. Tel.: +381 34 300263; fax: +381 34 335040.
E-mail addresses: goran@chem.bg.ac.rs, goran.kaluderovic@chemie.uni-halle.de (G.N. Kaluđerović), srecko@kg.ac.rs (S. R. Trifunović).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.07.034