European Journal of Medicinal Chemistry 45 (2010) 3601–3606

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Palladium(II) complexes with R_2edda derived ligands. Part IV. *O,O′*-dialkyl esters of (*S,S*)-ethylenediamine-*N,N′*-di-2-(4-methyl)-pentanoic acid dihydrochloride and their palladium(II) complexes: Synthesis, characterization and *in vitro* antitumoral activity against chronic lymphocytic leukemia (CLL) cells

Jelena M. Vujić [a,b], Milica Cvijović [b], Goran N. Kaluđerović [c,d,*], Marija Milovanović [e], Bojana B. Zmejkovski [c], Vladislav Volarević [e], Nebojša Arsenijević [e], Tibor J. Sabo [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] 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 Helle-Wittenberg, Kurt-Mothes-Straβe 2, 06120 Halle, Germany
[e] The Medical Faculty, University of Kragujevac, Svetozara Markovića 69, 34000 Kragujevac, Serbia
[f] Faculty of Chemistry, University of Belgrade, P.O. Box 158, 11001 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 7 November 2009
Received in revised form
9 April 2010
Accepted 5 May 2010
Available online 12 May 2010

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

ABSTRACT

Four novel bidentate *N,N′*-ligand precursors, including *O,O′*-dialkyl esters (alkyl = ethyl, *n*-propyl, *n*-butyl and *n*-pentyl), L1·2HCl–L4·2HCl, of (*S,S*)-ethylenediamine-*N,N′*-di-2-(4-methyl)-pentanoic acid dihydrochloride [(*S,S*)-H_4eddl]Cl_2 and the corresponding palladium(II) complexes **1**–**4**, were prepared and characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis. *In vitro* cytotoxicity of all compounds was determined against chronic lymphocytic leukemia cells (CLL). The compounds were found to exhibit higher antitumoral activity than cisplatin. The most active compound **2**, [$PdCl_2${(*S,S*)-nPr$_2$eddl}], was found to be 13.6 times more active than cisplatin on CLL cells.

1. Introduction

The simple and well known platinum(II) complex cisplatin has been the most commonly used antitumor platinum-based drug for several decades. The antitumor activity of platinum based drugs still captures the attention of scientists worldwide, and new potential drugs are being synthesized and investigated [1–5]. To date, apart from cisplatin, metal-based anticancer agents that are in worldwide clinical use include carboplatin and oxaliplatin [6].

Complexes with other central metal ions such as palladium [7–9], ruthenium [10,11], gold [12,13], titanium [14,15] and tin [16,17] have been investigated as potential antitumor agents. In principle, the aim of developing non-platinum anticancer complexes is that of overcoming the main limits of platinum drugs: narrow range of activity, acquired resistance after treatment, and severe toxicity on healthy tissue [1–5]. Non-platinum complexes may exhibit anticancer activity and toxic side-effects markedly different from that of platinum based drugs for a number of obvious reasons, as they are expected to have different chemical behaviour, hydrolytic rates, and mechanism(s) of action.

Research on palladium(II) complexes should be pointed out due to their structural analogy with platinum(II) complexes. The use of Pd(II) and its complexes in medicine is limited. The only application is of ^{103}Pd as a radioactive isotope in the treatment of rapidly growing high-grade prostate cancer [18,19].

Initially, palladium complexes showed lower *in vitro* antitumoral activity when compared with platinum(II) complexes. This could be correlated to the more labile nature of palladium(II) relative to platinum(II) complexes [20,21]. As a consequence of rapid ligand exchange, the probability of palladium(II) complexes to reach the biological target in organisms unchanged is low. Several reports have indicated that using chelating ligands may

* Corresponding author. Institut für Chemie, Martin-Luther-Univerität Helle-Wittenberg, Kurt-Mothes-Straβe 2, 06120 Halle, Germany. Tel.: +49 345 5525678/+381 11 3336736; fax: +49 345 5527028/+381 11 2636061.
E-mail addresses: goran.kaluderovic@chemie.uni-halle.de, goran@chem.bg.ac.rs (G.N. Kaluđerović).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.05.005