



Original article

Palladium(II) complexes with R₂edda 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

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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*)-H₄eddl]Cl₂ and the corresponding palladium(II) complexes **1–4**, were prepared and characterized by IR, ¹H NMR and ¹³C 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**, [PdCl₂{(*S,S*)-*n*Pr₂eddl}], was found to be 13.6 times more active than cisplatin on CLL cells.

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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 ¹⁰³Pd 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

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