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Stereospecific ligands and their complexes. Part XV. Synthesis, characterization and cytotoxicity of novel platinum(IV) complexes with some esters of ethylenediamine-*N*,*N*′-di-*S*,*S*-(2,2′-dibenzyl)acetic acid. Crystal structure of *O*,*O*′-dipropyl-ethylenediamine-*N*,*N*′-di-*S*,*S*-(2,2′-dibenzyl)acetate dihydrochloride ☆

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ABSTRACT

The synthesis of ethylenediamine-*N*,*N*′-di-*S*,*S*-(2,2′-dibenzyl)acetic acid (H_2-*S*,*S*-eddba) and its ethyl-, propyl-, butyl-esters (R_2-*S*,*S*-eddba) are reported here. The esters were used for synthesis of the corresponding platinum(IV) complexes, [$PtCl_4$(R_2-*S*,*S*-eddba)]. The compounds were characterized by elemental analysis, infrared, ^{1}H and ^{13}C NMR spectroscopy. The structure of propyl ester of H_2-*S*,*S*-eddba was confirmed by single-crystal X-ray analysis. All [$PtCl_4$(R_2-*S*,*S*-eddba)] complexes displayed significantly higher *in vitro* cytotoxicity in comparison to cisplatin.

1. Introduction

Platinum(II/IV) and other metal complexes have attracted a great attention as chemotherapeutic drugs mostly against cancer [1,2]. Investigations in this field have stimulated successful application of cisplatin in treatment of various types of human cancer [3]. The high nephrotoxicity and neuorotoxicity seriously limit the cisplatin usage. Faced with these problems in clinical usage, numerous novel platinum complexes have been synthesized and tested with respect to their anticancer activity [1–7].

Although a lot of platinum complexes have been prepared and tested as antitumor reagents, just a few of them have been included in clinical use, such as carboplatin. Compared with cisplatin, carboplatin should be used in much higher doses [1,8,9]. Taking in consideration the mentioned problems, considerable progress in platinum chemistry concerning the synthesis of kinetically inert platinum(IV) compounds was made, like JM216 (*cis*,*trans*,*cis*-[$PtCl_2(CH_3COO)_2(NH_3)\{NH_2(C_6H_{11})\}$], configuration index *OC*-6-32) with an octahedral coordination sphere [10]. These complexes are much more inert than similar platinum(II) complexes and can therefore be administered orally [9–12]. The kinetical inertness of the platinum(IV) complexes also offers the advantage of reduced side-reactions *in vivo* and a significant decrease in drug loss through reactions with plasma proteins or other low molecular weight biomolecules should expected.

Recently, some Pt(II/IV) complexes with linear O–N–N–O edda-type (edda = ethylenediamine-*N*,*N*′-diacetate ion) ligands: ethylenediamine-*N*,*N*′-di-(*S*,*S*)-2-propanoato (*S*,*S*-eddp) [7,12], ethylenediamine-*N*,*N*′-di-3-propanoato (eddp) and 1,3-propylenediamine-*N*,*N*′-diacetato (1,3-pdda) [13] have been prepared and their *in vitro* antitumor activity has been tested. Also, the *in vitro* antitumor activity of platinum(II/IV) complexes with methylene modified cyclohexyl ethylenediamine-*N*,*N*′-diacetate [14], *O*,*O*′-dialkyl esters of (*S*,*S*)-ethylenediamine-*N*,*N*′-di-2-(4-methyl)

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