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Cytotoxicity of palladium(II) complexes with some alkyl derivates of thiosalicylic acid. Crystal structure of the *bis*(S-butyl-thiosalicylate)palladium(II) complex, [Pd(S-bu-thiosal)$_2$]

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ABSTRACT

The spectroscopically predicted structure of the obtained *bis*(S-butyl-thiosalicylate)palladium(II) complex, [Pd(S-bu-thiosal)$_2$], was confirmed by an X-ray structural study. The asymmetric unit of [Pd(S-bu-thiosal)$_2$] consists of neutral complex molecules, where the Pd(II) ion is placed in a *cis*-square-planar coordination environment formed by O and S atoms of two deprotonated S-butyl-thiosalicylic acid ligands. The cytotoxic effects of the S-alkyl (R = benzyl (**L1**), methyl (**L2**), ethyl (**L3**), propyl (**L4**) and butyl (**L5**)) derivatives of thiosalicylic acid and the corresponding palladium(II) complexes are reported here. The analysis of cancer cell viability showed that all the tested complexes are cytotoxic to human colon carcinoma cells (HCT-116 and CaCo-2) and human lung carcinoma epithelial cells (A549). The antitumor activities of the above mentioned Pd(II) complexes are higher in comparison to the corresponding ligands.

1. Introduction

Since the seventies when *cisplatin*, with antitumor activity, was discovered by Rosenberg and co-workers [1,2], thousands of platinum complexes have been synthesized in order to obtain new platinum(IV) compounds with improved properties in comparison to the parent drug *cisplatin* [3–5]. It has been shown that platinum(II) complexes with antitumor activity are represented by the general formula [Pt(am)$_2$X$_2$], having a *cis* geometry, where (am) is an inert amine ligand having at least one NH group and X is an easy leaving ligand. The leaving group should be an anion with a moderately strong coordination to the platinum(II) ion, as well as with a weak *trans* effect in order to avoid labilization of the amine ligand bond.

Those discoveries have increased the interest in obtaining efficient ligands and complexes of other metals. The palladium(II) complexes *cis*-diamminedichloridopalladium(II), *cis*-[PdCl$_2$(NH$_3$)$_2$], and *cis*-1,2-diaminocyclohexanedichloridopalladium(II), *cis*-[PdCl$_2$(DACH)], which are analogues to cisplatin, were among the first complexes used in clinical trials as anti-tumor agents [6].

Platinum(II) complexes are known to be thermodynamically and kinetically more stable than their palladium(II) analogues. The reactivity of the palladium(II) complexes for hydrolysis and exchange of the ligands is 10^5 times faster than the corresponding platinum(II) complexes. Therefore the palladium(II) complexes show lower antitumor activity, but higher toxicity [6–8].

Although the initial results showed no significant antitumor activity of the palladium(II) complexes, these complexes have been widely studied. Due to their high reactivity, palladium(II) complexes generally exhibit lower antitumor activity than *cisplatin* [6,7]. It was concluded that the lower activity of the palladium(II) complexes is the result of a very rapid exchange of the ligands and the inability of the complexes, with an unchanged structure, to reach biological targets, increasing the risk of adverse effects on biochemical processes in the cell. In order to overcome these problems some authors [9] suggested that the palladium(II) ion should be coordinated by chelating ligands, reducing the reactivity of the palladium center and increasing the stability of the complex.

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