Synthesis and cytotoxic evaluation of Pd(II) compounds containing thiosemicarbazones derived from natural products

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Keywords:palladium(II); thiosemicarbazones; phosphines; cytotoxic evaluation

Metal complexes containing thiosemicarbazones have attracted considerable interest due to their pharmacological properties[1]. Particularly, their palladium(II) derivatives have emerged as potential candidates of new anti-cancer agents. In this sense, the incorporation of thiosemicarbazones derived from natural sources (such as chalcone and cynmaldeyde) represents an interesting strategy to obtain compounds with reduced toxicity. In this work, we present the synthesis and cytotoxicity evaluation of new mononuclear complexes of the type $[PdCl(L)(PR_3)]$ {L_1=chalcone-4-methyl-3-thiosemicarbazone, L_2=cynmaldeydethiosemicarbazone, PR_3 = triphenylphosphine; tris(4-fluorophenyl)phosphine}. The thiosemicarbazoneswere prepared by the reaction between the suitable thiosemicarbazide and the ketone/aldehyde, in acid media. All the Pd(II) compounds were obtained from the reaction among $[PdCl_2(CH_3CN)_2]$, the appropriate L ligand and PR_3, in the molar ratio 1:1:1, respectively. Elemental analyses for the synthesized ligands and compounds are in agreement with the proposed formulae. Anal. Obt. (calcd.) for (L_1): % C = 69.20 (69.12), % H = 5.48 (5.80), % N = 14.53 (14.22); Anal. Obt. (calcd.) for $[PdCl(L_1)(PPh_3)]$: % C = 60.56(60.18), % H = 4.46(4.47), % N = 6.11(6.02). The formation of the *N,S*-chelated products was strongly supported by IR and NMR data. Coordination of the imine nitrogen from L was inferred by the shift of the νC=N band from ca. 1620 cm^{-1}(free ligand) to *ca*. 1608 cm^{-1}. The downfield shift of the ^{13}C=N from *ca*. 145 ppm (free ligand) to *ca*. 153 ppm (complexes) strongly support the coordination through the iminic nitrogen in all compounds. An up field shift of *ca*.3 ppm of the C=S resonance observed in the $^{13}C\{^1H\}$ NMR spectra of Pd(II) complexes gave a clear evidence of Pd-S bond formation. The cytotoxic activities of the ligands and their Pd(II) derivatives were evaluated against liver hepatocellular carcinoma (HepG2). Cells were exposed to a range of drug concentrations (100–6.25 μg/mL) for 24 h and cell viability was analyzed by resazurine assay.

[1]Matesanz, A. I.; Souza, P. *Mini-Reviews in Medicinal Chemistry***2009**, *9*, 1389.

FAPESP, CAPES and CNPq