Thiosemicarbazone Pd(II) complexes acting as inhibitors of topoisomerase II

Fillipe V. Rocha[1*] (PQ), Adriano B. de Oliveira[2] (PQ), Francine A. Manente[3] (PG), Iracilda Z. Carlos[3] (PQ), Saulo S. Garrido[4] (PQ), Adelino V. G. Netto[1] (PQ)

[1]*Depto de Química Geral e Inorgânica, IQ Araraquara, UNESP , Araraquara, SP, Brazil.*
[2]*Universidade Federal de Sergipe, UFS, São Cristovão, SE, Brazil*
[3]*Depto. de Análises Clínicas, Faculdade de Ciências Farmacêuticas - Unesp, Araraquara, SP, Brazil.*
[4]*Depto de Bioquímica e Tecnologia Química, IQ Araraquara, UNESP , Araraquara, SP, Brazil*
*e-mail: filliperocha@iq.unesp.br

Palavras Chave: *Topoisomerase II, Palladium, Thiosemicarbazone, Cytotoxicity.*

Introduction

Thiosemicarbazones are compounds that have been studied for their medical applications[1]. Antitumor activity is one of the most promising areas of these compounds, since they can interact with several biomolecules generating their activity.

Furthermore, the presence of a metal ion, in general, increases the activity or contributes to decrease the side effects.

Topoisomerase II is one of the targets of thiosemicarbaones, this enzyme is involved in DNA replication, transcription, chromosome condensation and chromosome segregation. Topoisomerases are very interesting as target due your presence in greater quantities in tumor cells than normal cells of some types of cancer [2].

Therefore, in this work we presents the synthesis, characterization, cytotoxicity and topoisomerase II inhibition of two palladium complexes bearing a thiosemicarbazone derived of cinnamaldehyde and triphenylphosphine as ligand.

Results and discussion

The synthesis of the [PdCl(TSC)(PPh_3)] was achieved starting from [$PdCl_2(MeCN)_2$]. First, PPh_3 and (2E)-N-Methyl-2-[(2E)-3-phenyl-2-propen-1-ylidene]hydrazinecarbothioamide (TSC) displace the labile ligands acetonitrile and one of the two chloro atoms to obtain **1**. In a second step, the Cl atoms are replaced by the SCN^- ion by the addition of one equivalent of the potassium salt to afford **2**.

The complexes was characterized by elemental analysis, IR, ^1H NMR spectroscopy and mass spectrometry ESI / MS.

The characterization techniques demonstrated the complexation of the thiosemicarbazone by anionic bidentate mode. IR spectra showed an important variation of 30 cm^{-1} (lower wavenumbers) for the vC=S after coordination. In the ^1H NMR spectra, variation in the signals of all hydrogens was observed after complexation. Moreover, in the region 7-8 ppm appeared signs corresponding to the aromatic hydrogens of triphenylphosphine. The molecular mass of compounds **1** (m/z 623) and **2** (m/z 646) could be observed in the mass spectra. The results of elementary analysis [exp. (calc.)] agree with the proposed [PdCl(TSC)(PPh_3)].1/2$CHCl_3$, %C= 52.33 (51.94); %H= 4.27 (4.06); %N= 6.42 (6.16) and [Pd(NCS)(TSC)(PPh_3)], %C= 55.73 (55.86); %H= 4.17 (4.22); %N= 8.74 (8.69).

TSC ligand and two new complexes were assayed against the cell line, MCF-7 (human breast cancer) and their cytotocicity were compared with cisplatin. Compounds **1** (IC_{50} = 9.62 ± 2.0 µM) and **2** (IC_{50} = 7.28 ± 1.9 µM) revealed to be significantly more cytotoxic than cisplatin (IC_{50} = 19,6 ± 4,3 µM)[3].

Agarose gel electrophoresis experiments were performed to verify the DNA-topoisomerese inhibition activity of **1** and **2**.

Depending on the ligand (chloride or isothiocyanate) bound to the metal, distinct potential to inhibit topo II was observed. Compounds **1** and **2** avoid the relaxation of DNA performed by the enzyme in the concentrations 25 µM and 3,125 µM, respectively. These results are promising since the compounds inhibits the relaxation of DNA in a lower concentration than some drugs that has topoisomerase II as target (etoposide 35 µM and novobiocin 35 µM)[4].

Conclusion

Two new palladium complexes showed good cytotoxicity surpassing the action of cisplatin. Further, they are capable of inhibit the relaxation of DNA caused by topo II in a low range of concentration.

Acknowledgements

This work was sponsored by grants from FAPESP 2013/20156-5, CNPq, CAPES.

[1] Beraldo, H.; Gambino, D. *Mini. Rev. Med. Chem.* **2004**, *4*, 31.
[2] Tan, K. W.; Seng, H. L.; Lim, F. S.; Cheah, S.-C.; Ng, C. H.; Koo, K. S.; Mustafa, M. R.; Ng, S. W.; Maah, M. J. *Polyhedron* **2012**, *38*, 215.
[3] Štarha, P.; Trávníček, Z.; Popa, I. *J. Inorg. Biochem.* **2010**, *104*, *639*.
[4] Gao, F.; Chao, H.; Ji, L.-N. *Chem. Biodivers.***2008**, *5*, *1962*.