New Studies on the Pyrazinamide-derived Antitumor Compound *cis*-$[PtCl_2(PZA)_2]\cdot 2H_2O$: Powder Diffraction Structure and Interactions with DNA and Guanosine-5'-Monophosphate

Juliana M. da Silva Pinheiro[1], Ana Beatriz Pinheiro[1], Rosana Garrido Gomes[1], Ívina P. Souza[2], Alexandre Cuin[3], Elene C. Pereira-Maia[2], Nicolás A. Rey[1]*

[1] *Pontifícia Universidade Católica do Rio de Janeiro, RJ, Brazil,* [2] *Universidade Federal de Minas Gerais, Belo Horizonte, Brazil,* [3] *Universidade Federal de Juiz de Fora, JF, Brazil*

*e-mail: nicoarey@puc-rio.br

Since the serendipitous discovery of cisplatin's antitumor activity, thousands of platinum(II) compounds were systematically synthesized and tested against several tumor cell lines. In this context, we had previously prepared and assayed the complex *cis*-$[PtCl_2(PZA)_2]\cdot 2H_2O$ (**1**),[1] in which PZA refers to the antituberculosis drug pyrazinamide. **1** showed a good activity against K562 cells, with an IC_{50} value of 6.34 μmol L^{-1}. In the present work, the powder diffraction structure of **1**, as well as its interactions with DNA and guanosine-5'-monophosphate (5'-GMP) are reported. In spite of the presence of aromatic and amide nitrogen atoms in PZA, the X-ray diffraction confirms formerly obtained IR/NMR data and fully supports that platinum coordination occurs through the oxygen atom of pyrazinamide (Figure 1, left). Interaction of **1** with calf thymus DNA in pH 7.3 HEPES buffer was followed by UV-Vis spectroscopy and resulted in a binding constant of 5.92 x 10^3 L mol^{-1}. In order to gain further insight concerning the interactions between **1** and DNA, the reaction of **1** with the model nucleotide 5'-GMP was studied by ^1H and ^{31}P NMR spectroscopy, as well as by $^1Hx^1H$ COSY contour plots. Complex **1** originates a chelate involving the guanine N7 and a phosphate O as donors (Figure 1, right).

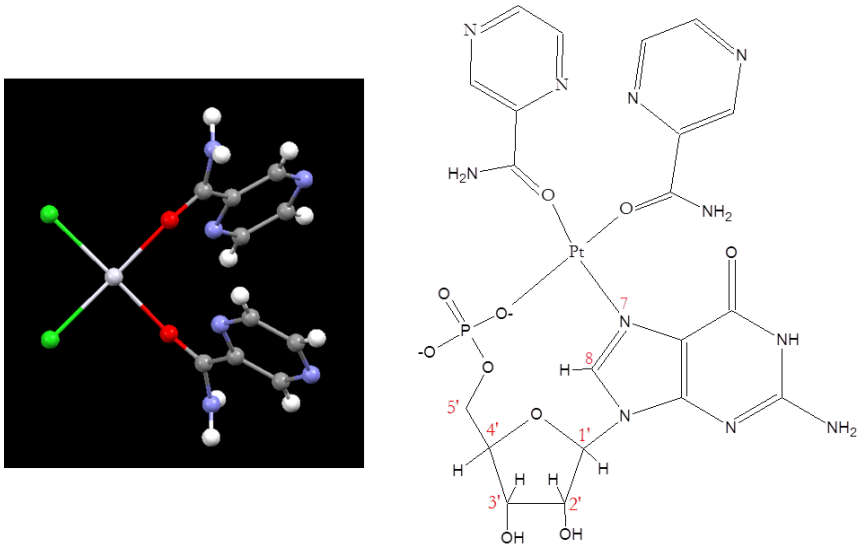

Figure 1. Powder diffraction structure of **1** (left) and proposed structure for the **1**/5'-GMP adduct (right).

1. Oliveira, P. A. S.; Sartori, L. M.; Rey, N. A.; dos Santos, H. F.; de Oliveira, M. A. L.; Costa, L. A. S.; *J. Braz. Chem. Soc.* **2013**, *24*, 1732.

CNPq, FAPERJ, Central Analítica da PUC-Rio