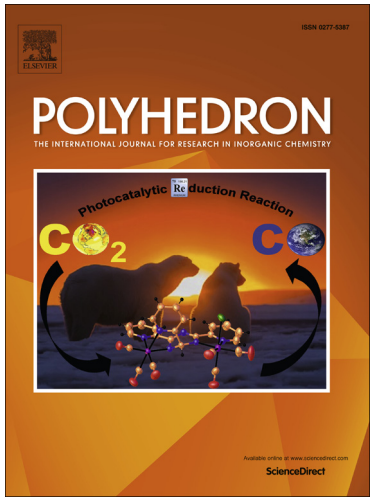

Synthesis, characterization and biological activity of platinum (II) complexes with a tetrapyrazole ligand

Angel R. Higuera-Padilla, Jorlis Capote, Dianela Ortega, William Castro, Mildred Rodriguez-Cordero, David Coll, Fernando Hernández-Medina, Mercedes Fernández-Mestre, Izaskun Urdanibia, Peter Taylor, Barbara Rodriguez, Arquímedes Karam

PII: S0277-5387(15)00575-6
DOI: http://dx.doi.org/10.1016/j.poly.2015.09.065
Reference: POLY 11579

To appear in: *Polyhedron*

Received Date: 26 May 2015
Accepted Date: 30 September 2015

Please cite this article as: A.R. Higuera-Padilla, J. Capote, D. Ortega, W. Castro, M. Rodriguez-Cordero, D. Coll, F. Hernández-Medina, M. Fernández-Mestre, I. Urdanibia, P. Taylor, B. Rodriguez, A. Karam, Synthesis, characterization and biological activity of platinum (II) complexes with a tetrapyrazole ligand, *Polyhedron* (2015), doi: http://dx.doi.org/10.1016/j.poly.2015.09.065

Synthesis, characterization and biological activity of platinum (II) complexes with a tetrapyrazole ligand

Angel R. Higuera-Padilla[a,*], Jorlis Capote[a,b], Dianela Ortega[a], William Castro[a], Mildred Rodriguez-Cordero[c], David Coll[d], Fernando Hernández-Medina[e], Mercedes Fernández-Mestre[e], Izaskun Urdanibia[f], Peter Taylor[f], Barbara Rodriguez[g], Arquímedes Karam[h,*]

[a] Laboratorio de Química Bioinorgánica, Centro de Química, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas 1020-A, Venezuela

[b] Universidad Central de Venezuela, Caracas, Venezuela

[c] Laboratorio de Química Bioinorgánica. Universidad Simón Bolívar, Caracas, 1080, Venezuela

[d] Laboratorio de Química Computacional, Centro de Química, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas 1020-A, Venezuela

[e] Laboratorio de Fisiopatología sección Inmunogenética, Centro de Medicina Experimental, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas 1020-A, Venezuela

[f] Laboratorio de Patología Celular y Molecular, Centro de Medicina Experimental, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas 1020-A, Venezuela

[g] Departamento de Química Inorgánica, Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago-609441, Chile.

[h] Laboratorio de Polímeros, Centro de Química, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas 1020-A, Venezuela

[*] Corresponding authors. Tel.: +58 212 5041775/1832. E-mail addresses: angelruben@hotmail.com (A.R. Higuera-Padilla), akaram@ivic.gob.ve (A. Karam)

In the search of an effective chemotherapy for the treatment of cancer, in this work we describe the synthesis, characterization and biological activity of two new platinum complexes. The general formula is $[Pt_2(L)(X)_4]$, where **L** was 1,2,4,5-tetrakis((1*H*-pyrazol-1-yl)methyl)benzene and X were iodine (**1**) and chlorine (**2**). The most probable structure was established through a combination of spectroscopic analysis and density functional theory (DFT) calculations. Studies of interaction of complexes with DNA were carried out, and the results by spectroscopic titrations, thermal denaturation and viscosity, showed noncovalent interactions of complexes with DNA. The comet assay showed damage to cellular DNA. Inhibition assays of thioredoxin reductase (TrxR) were carried out, and the compounds showed notable inhibitory activity on the enzyme in a concentration dependent manner, with IC_{50} values of 3.9 and 3.5 nM for **1** and **2** respectively. Complex **2** exhibited greater inhibitory effects than complex **1** against all the tumor cell lines, with growth inhibitory effects superior to cisplatin in some cases.

Keywords: Anticancer activity, platinum complexes, DNA, Thioredoxin reductase.

Introduction

According to the World Health Organization, cancer figures among the leading causes of death worldwide, accounting for 8.2 million deaths in 2012 [1]. In the search of an effective