Search For New Insulin Mimetic Drugs: Chemical And Biochemical Studies Of A Pyrimidinone V(V) Complex

M. M. Castro[1,2], F. Avecilla[3], I. Tomaz[4], G. Gonçalves[4],
H. Faneca[1,2], L. Palacio[3], M. Maestro[3], M.C.P. Lima[1,2], C.F.G.C. Geraldes[1,2] and J. C. Pessoa[4]

[1] Dept. of Biochemistry , [2] Center of Neuroscience and Cell Biology; University of Coimbra, 3001-401 Coimbra, Portugal;
[3] Dept. of Fundamental Chemistry, University of A Coruña, A Coruña, Spain;
[4] Center of Structural Chemistry, Instituto Superior Técnico, TU Lisbon, 1049-001, Lisbon, Portugal

The importance of Vanadium Compounds (VCs) has increased in the last years due to their pharmacological properties, in diabetes and cancer therapy. VCs exhibit anti-cancer activity[1] and their potential use as oral insulin mimetics[2] has been demonstrated by *in vivo* and *ex vivo* studies, as well as in clinical trials.

Up to the present, the use of VCs as therapeutic agents is limited by the narrow range between beneficial and toxic effects. The synthesis of many V(IV) and V(V) complexes containing adequate ligands has been improved searching for desired properties such as hydrolytic stability, water solubility, neutral charge and/or lipophilicity, low toxicity and anti-diabetic or antitumoural activity.[3]

This work reports a study of the interaction, in aqueous solution, of vanadate with the ligand, the 2-methyl-3H-5-hydroxy-6-carboxy-4-pyrimidinone ethyl ester (MHCPE) by Potentiometry and ^{51}V NMR spectroscopy. The species formed in solution at different M/L ratios and pH values were identified and structurally characterized and the respective formation constants were determined. The results obtained indicated the presence in solution of two main species with stoichiometries 1:1, $(V^{V}O_2)L$, and 1:2 $(V^{V}O_2)L_2$ and their most probable binding modes were established according to spectroscopic data.

The solution behaviour of these main V(V) species at physiological pH and in different cell culture media was also studied, showing some favorable properties concerning solubility and stability. Their cytotoxic effects were tested in the HeLa tumor cell line and the 3T3-L1 cell line and were demonstrated to be concentration- and time- dependent, being correlated with VC cellular uptake.

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This work has been carried out in the frame of a COST D21 Project. The authors thank the financial support from FEDER and Fundação para a Ciência e Tecnologia (FCT), Portugal, POCI 2010, Project PPCDT/QUI/56949/2004, the Spanish-Portuguese Bilateral Programme (Acção Integrada E-56/05) and University of A Coruña.