Insulin-mimetic oxovanadium-picolinates

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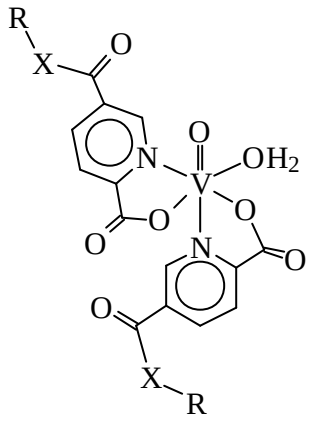
Oxovanadium complexes of the type shown in the Figure have been designed so as to fulfil a couple of indispensable preconditions for a vanadium-based, anti-diabetic drug to be applied orally, *viz.* (*i*) stability in the acidic to slightly alkaline pH range; (*ii*) efficient absorption by the gastro-intestinal tract; (*iii*) stability towards ligand exchange during transport in the blood stream; (*iv*) balanced lipo/hydrophilicity and/or constituents recognizable by membrane receptors in order to facilitate trans-membrane transport; (*v*) low toxicity; and (*vi*) high insulin-mimetic potential, *i.e.* stimulation of cellular uptake and degradation of glucose, and inhibition of lipolysis [1].

Vanadium complexes containing 1,5-dipicolinato ligands modified in the 5-position, *i.e.* in the periphery of the complex, are an excellent basis for the design of the respective properties. The most efficient cellular uptake combined with low cytotoxicity and high insulin-mimetic potential has been noted for R = CH_3 and D-galactose-orthoformiate, in *in vivo* tests with Simian virus modified mice fibroblasts (glucose metabolism) and rat adipocytes (inhibition of lipolysis) [2].



X = O, R = alkyl, galactosyl, inositolyl
X = NH, R = amino acid residue

Results of these tests, syntheses and structure information on several of the vanadium complexes is provided, as well as speciation studies in pH 2-9 range in the presence of low and high molecular mass blood constituents.

[1] D. Rehder, J. Costa Pessoa, C.F.G.C. Geraldes, M.M.C.A. Castro, T. Kabanos, T. Kiss, B. Meier, G. Micera, L. Pettersson, M. Rangel, A. Salifoglou, I. Turel, D. Wang, *J. Biol. Inorg. Chem.* **2002**, *7*, 384-396.

[2] J. Gätjens, B. Meier, T. Kiss, E.M. Nagy, P. Buglyó, H. Sakurai, K. Kawabe, D. Rehder, *Chem. Eur. J.* **2003**, *9*, 2924-2935.