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Development of a new thiazole-containing hydrazone as a potential metallophore for the management of Alzheimer's disease

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Alzheimer's disease is characterized by the extracellular deposition of fibrillar plaques of amyloid-β peptide (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein.[1,2] Metal ions, such as copper(II), are capable of binding to the Aβ peptide with high affinity, forming Aβ-copper complexes capable of accentuating oligomerization and fibrillation, increasing membrane permeability and causing oxidative stress.[1,3] Based on this, our group has been working with a class of polydentate ligands called *N*-acylhydrazones, capable of competing with the peptide for the binding of copper.[4] Thus, this work describes the synthesis and characterization of a new *N*-acylhydrazone called **X1-TCB**, whose structure is derived from thiazole-4-carbohydrazide. **X1-TCB** was characterized by mid-IR, ^{1}H NMR and UV-Vis. NMR demonstrates only the presence of the (*E*)-isomer along the C=N bond. A Job's complexation study revealed that **X1-TCB** reacts with copper(II) under pseudo-physiological conditions (buffered aqueous solution, pH=7.4), in an M_2L stoichiometry, indicating two potential coordination sites. Crystals of copper(II)-**X1-TCB** (**Figure 1**) show that the ligand underwent an isomerization during the coordination process, binding copper in its fully deprotonated (*Z*)-iminolate form. Two different copper centers are present: a square-planar one in which **X1-TCB** binds the metal through the imidazole, iminolate and thiazole nitrogen atoms and a distorted octahedral one in which copper interacts with the azomethine nitrogen and the carbonyl oxygen of the ligand. The last center acts as a bridge for dimerization. Other studies are underway in order to evaluate the interaction of **X1-TCB** with the copper(II)-Aβ peptide system.

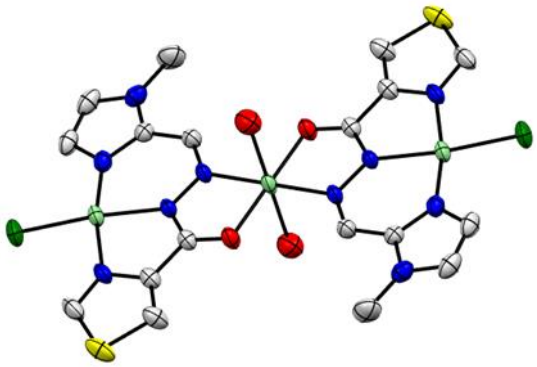

Figure 1. *ORTEP representation of the copper(II)-**X1-TCB** complex.*

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