‘Metal-Protein Attenuating Compounds’ and Alzheimer’s Disease: Is the 8-Hydroxyquinoline Moiety Really Necessary for Activity?

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Alzheimer’s disease (AD) is the major cause of dementia worldwide. There are different hypotheses about the etiology of AD[1], being the most well-accepted of them based on the excessive Aß peptide aggregation in the brain and its biochemical consequences (amyloid cascade). High amounts of physiological metals such as copper and zinc have been detected in the amyloid plaques. A new class of potential drugs, ‘Metal-Protein Attenuating Compounds’ (MPACs), differs from traditional chelating agents: instead of removing metals, they correct abnormal interactions with Aß, aiding in metal redistribution and Aß removal, as well as preventing redox reactions. In this context, the present study shows the comparison between three different potential MPACs, containing the widely known 8-hydroxyquinoline pharmacophore (H_2QBS)[2], a hydrazonic one (PCIH)[3] or both of them (INHHQ)[4].

Experiments performed in healthy rats, approved by an ethics committee (CEUA/036/2013), show that none of the three compounds is toxic at concentrations up to 200 mg kg^{-1}.

Those compounds do not interact directly with Aß, as proven by ^{1}H NMR, but efficiently compete with it for the biometals Cu^{2+} and Zn^{2+}, as shown by $^{1}Hx^{15}N$ HSQC experiments on an isotopically-labeled version of the peptide. Results show that INHHQ has a behavior much more similar to PCIH than to H_2QBS: whereas there are necessary only 3 eq of the latter to inhibit metal-Aß interactions, 5 eq of the hydrazone-containing compounds are required for getting the same effect. Comparing the three ligands, INHHQ proved to be the most effective, showing less side-effects and interacting in a quite moderate manner with biometals, which is in line with the MPAC concept. This points out to the relevance of the hydrazonic portion for the desired biological effects. In conclusion, more attention should be paid to hydrazone derivatives as potentials MPACs, in contrast with current research trends, which assume that the 8-hydroxyquinoline moiety is central to the performance of an MPAC.

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