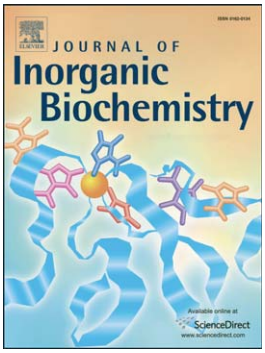

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Tacrine-(hydroxybenzoyl-pyridone) hybrids as potential multifunctional anti-Alzheimer´s agents: AChE inhibition, antioxidant activity and metal chelating capacity

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Abstract

Three novel potentially site-activated multitarget tacrine-(hydroxybenzoyl-pyridone) (TAC-HBP) hybrids were designed, synthesized and evaluated as acetylcholinesterase (AChE) inhibitors, antioxidants and biometal chelators. All of them are dual-binding site AChE inhibitors with activity in sub-micromolar range (IC_{50} = 0.57-0.78 μM), which is comparable to the parent tacrine, and have good 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging capacity (EC_{50} = 204-249 μM) conferred by the hydroxybenzoyl-pyridone (HBP) moiety. Their chelating capacity towards redox-active and/or amyloid-β-binding metal ions (Fe(III), Cu(II)), Zn(II)) was evaluated by using 2′-hydroxy-4′-methoxybenzoyl-2-pyridone derivative as a model compound in 30% w/w DMSO/water medium. It was proved that the HBP moiety acts as a moderate/good chelator of these biometals (pFe = 13.9, pCu = 6.0 and pZn = 6.0 at pH 6.0, C_L/C_M = 10, $C_M = 10^{-6}$ M), being able to form complexes with β-phenol-keto coordination mode, and that this chelating ability is preserved in the TAC-HBP hybrids.