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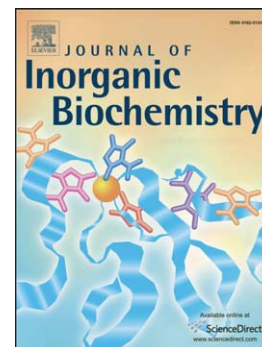
Tacrine-(hydroxybenzoyl-pyridone) hybrids as potential multifunctional anti-Alzheimer agents: AChE inhibition, antioxidant activity and metal chelating capacity

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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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**Keywords:** Hydroxybenzoyl-pyridones; Tacrine; Anti-neurodegeneratives; Anti-AChE activity; Anti-oxidant activity; Metal chelation.

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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 ( $IC_{50} = 0.57-0.78 \mu M$ ), which is comparable to the parent tacrine, and have good 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging capacity ( $EC_{50} = 204-249 \mu M$ ) conferred by the hydroxybenzoyl-pyridone (HBP) moiety. Their chelating capacity towards redox-active and/or amyloid- $\beta$ -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  $\beta$ -phenol-keto coordination mode, and that this chelating ability is preserved in the TAC-HBP hybrids.

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