O,O-Dialkyl-O-(1-carbometoxy-2,2,2-trifluoroethyl) phosphates. Structure - Antiesterase Activity - Toxicity Relationships.

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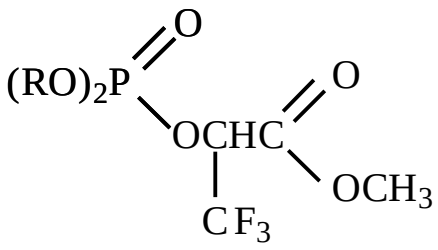
Inhibitors of acetylcholinesterase (AChE) are used as pesticides, anti-Alzheimer drugs and as ophthalmic agents. A binding of these compounds to nonspecific esterases may effect essentially to their acute toxicity to mammalians. The interaction of a series of O,O-dialkyl-O(1-carbometoxy-2,2,2-trifluoroethyl) phosphates



(DCFP, where R= Me, Et, Pr, iPr, Bu, iBu, Pent, Hex) with mammalian AChE, butyrylcholinesterase (BuChE) and carboxylesterase (CE) has been studied. An acute toxicity of compounds to mice was determined. It was found that DCFP were not hydrolyzed by CE, slowly and irreversibly inhibited AChE (k_i = 10^2-10^4 $M^{-1}min^{-1}$), and more efficiently inhibited BuChE and CE (k_i = 10^3-10^7 $M^{-1}min^{-1}$). α-Branching in alkoxy groups leads to sharp reducing of anti-AChE and anti-BuChE activity, the CE inhibition becoming reversible. With multiple regression analysis (Hansh's and Kubinyi models) structure-antienzymatic activity relationships were investigated. The contribution of hydrophobic interactions to BuChE and CE inhibition was shown to be more significant than that to AChE inhibition, the influence of steric hindrances is revealed at the phosphorylation stage. The linear dependencies of $logk_i$ on hydrophobicity of alkyl radicals ($logk_i$ = a + bΣπ) were shown for DCFP with R ≤ Pent containing no α-branched substituents, a slope was about one for inhibition of nonspecific esterases, BuChE and CE, and 0.5 for inhibition of target enzyme AChE. DCFP was found to possess low acute toxicity to mice (LD_{50} 900-2000 mg/ kg), the toxicity appears to be independent of hydrophobicity. The results suggest that the binding to nonspecific esterases which increases greatly, and much more than AChE inhibition, with hydrophobicity increasing is responsible for the absence of correlation between anti-AChE activity and toxicity for compounds studied.

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