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MEETING ABSTRACTS

FLUORINATED AND CHLORINATED PYRIDINIUM OXIMES REACTIVATING CHOLINESTERASES INHIBITED BY NERVE AGENTS

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Nerve agents are organophosphorus compounds (OPs) with very potent toxicity due to their irreversible inhibition of the essential enzymeacetylcholinesterase (AChE; EC 3.1.1.7), which is primarily important in the control of neurotransmission in synapses. The related enzyme butyrylcholinesterase (BChE; EC 3.1.1.8) is inhibited by OPs aswell. Compounds with an oxime group act as reactivatorsof the inhibited AChE by the nucleophilic displacement of OP moiety from the enzyme's catalytic serine and are used as a pharmacological treatment after OP poisoning. However, restoration of the AChE activity is directly related to the oxime structure and standard oximes in medical practice are not equally effective for various OPs (1). It was demonstrated that the chlorine substituent reduce the pKa of the oxime group compared to the non-substituted analogues and result in the higher formation of oximate anion which can be correlated to their increased reactivation ability (2). In this work, the synthesis and thorough evaluation of fluorinated and chlorinated oximes is presented. Firstly, their stability and oximate forming properties (pKa) were determined. Further, the evaluation comprised testing for affinity for human recombinant AChE and human purified plasmatic BChE, the oxime's efficacy in reactivation of sarin-, cyclosarin-, VX-, tabun-inhibited AChE or BChE. Finally, the antidotal potential of the lead halogenated oxime was tested in mice exposed to sarin and cyclosarin (3).

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Keywords: organophosphorus compounds; quaternary oxime; reactivator; cholinesterase; pseudo-catalytic scavenger

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