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MEETING ABSTRACTS

CHLORINATED PYRIDINIUM OXIMES ARE POTENT REACTIVATORS OF ACETYLCHOLINESTERASE INHIBITED BY NERVE AGENTS

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Chlorinated bispyridinium aldoximes (Cl-oximes) analogous to previously reported efficient reactivators of inhibited AChE (K027, K048, K203) were designed and synthesized with the premise that the addition of a chlorine atom increases their lipophilicity in comparison to the reference oximes and that they could therefore achieve higher brain concentrations than the ones reported for non-chlorinated analogues. The affinity of hAChE for Cl-oximes was moderate, but higher than for analogous non-chlorinated oximes, as well as higher than the affinity of hBChE for Cl-oximes. Their reactivation efficacy for nerve agent-inhibited AChE was in the following order: cyclosarin>VX>sarin>tabun. Predictably, the electron-withdrawing effect of the chlorine atom led to a lower pK_a value of the oxime groups as confirmed by UV/VIS measurements. Finally, using the molecular modelling approach we attempted to attribute the differences in the predicted binding modes of the tested oximes to their observed reactivity. As molecular docking results suggested, the non-bonding interactions between the chlorine atoms and neighbouring amino acid residues play a significant role in the stabilization of Cl-oximes in a productive conformation in the case of cyclosarin-inhibited AChE.

Keywords: organophosphates; antidotes; HI-6; 2-PAM

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