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MEETING ABSTRACTS

DESIGN, SYNTHESIS AND IN VITRO EVALUATION OF A PROMISING NEW CLASS OF BIFUNCTIONAL UNCHARGED HYBRID REACTIVATORS FOR NERVE AGENT-INHIBITED HUMAN ACETYLCHOLINESTERASE

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Acetylcholinesterase (AChE) is a key enzyme of the Central Nervous System (CNS) hydrolyzing the neurotransmitter acetylcholine. By targeting AChE, OPNA and organophosphorus pesticides irreversibly inhibit the cholinergic transmission leading to a certain death if untreated. The current treatment available in the French army consists of an auto-injector containing a methanesulfonate salt of 2-PAM for AChE reactivation, an anticholinergic drug, atropine and avizafone, a prodrug of diazepam for limiting convulsions. However, this treatment displays major drawbacks in terms of CNS bioavailability, restricted spectrum action and effectiveness.

The aim of this project is to develop a new class of more efficient human nerve agent-inhibited acetylcholinesterase. We designed, synthesized and evaluated a new class of bifunctional uncharged hybrid reactivators composed of a 3-hydroxypyridinaldoxime linked to a tacrine derivative. The *in vitro* efficacy of this reactivators has been assessed. We show that this new class of reactivators outperform HI-6 in restoring the human AChE activity inhibited by VX, sarin, tabun and paraoxon. By X-ray crystallography, we have been able to observe some of these new hybrids inside of the catalytic site of hAChE and TcAChE.

Keywords: Acetylcholinesterase; reactivator; organophosphorus