INNOVATIVE HYBRID REACTIVATORS OF HACHE INHIBITED WITH NEUROTOXIC ORGANOPHOSPHORUS COMPOUNDS

Camille Voros[1], Franck Razafindrainibe[1], Julien de Sousa[1,2], Alex Maryan-Instone[2], Mallikarjuna Reddy Nimmakayala[1], Yerri Jagadeesh, Keven Mardy[1], Christopher Timperley[3], José Dias[4], Florian Nachon[4], Richard CD Brown[2], Rachid Baati[1]*

[1] *ICPEES UMR CNRS 7515, Ecole de Chimie Polymères et Matériaux, Université de Strasbourg, FR*

[2] *School of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK*

[3] *Dstl Porton Down, Room A117 Building 7, Salisbury, Wiltshire SP4 0PQ, UK.*

[4] *Département de Toxicologie et Risques Chimiques, Institut de Recherche Biomédicale des Armées*

IRBA, BP73, 91223, Brétigny-sur-Orge, France.

Over 200,000 deaths per year are reported to be associated with organophosphorus nerve agent (OPNA) poisoning.[1] Since their development as pesticides during the 1930s, OPNAs have been weaponized and have been declared weapons of mass destruction. Their production and stockpiling has been forbidden since 1992, however their presence persists and OPNAs have been employed in many acts of terror. OPNA poisoning proceeds by the irreversible inhibition of the human acetylcholinesterase enzyme (*h*AChE). *h*AChE is responsible for the regulation of acetylcholine (ACh) at neuromuscular junctions. ACh enables nerve impulse propagation across these junctions and therefore muscular movement. Once muscle movement is complete, AChE down-regulates the ACh within the junction to arrest movement. Upon inhibition of *h*AChE, no ACh regulation exists and hence continuous nerve impulse firing proceeds. This results in muscle paralysis and in severe cases, death by asphyxiation.[2]

Currently, no broad-spectrum antidote is available for the treatment of OPNA poisoning. Our compounds follow an exciting, novel formula, which appears to be working towards combating common problems associated with currently available treatment.[3] This work follows a multi-component approach to the drug design and development of universal OPNA reactivators. Our strategy, backed by *in vitro* and *in vivo* experiments, is based on a 3-hydroxy-2-pyridinaldoxime *h*AChE reactivator linked to a heterocyclic ligand of the peripheral site of the enzyme.

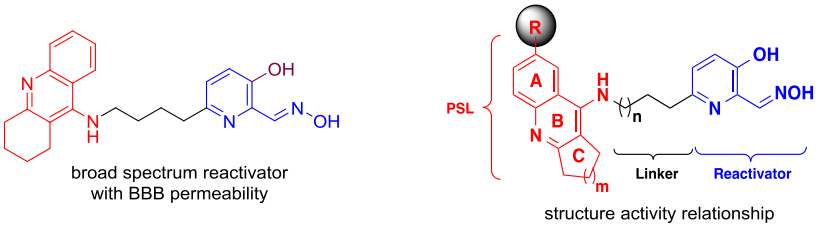

Figure 1: General structure of hybrid reactivators

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