DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF BIFUNCTIONAL FLUOROPYRIDINALDOXIME AND FLUOROPYRIDINAMIDOXIME REACTIVATORS FOR NERVE AGENT-INHIBITED HUMAN ACETYLCHOLINESTERASE

Franck Razafindrainibe[1] Camille Voros,[1] Mallikarjuna Reddy Nimmakayala,[1] Jagadeesh Yerri,[1] Keven Mardy,[1] José Dias,[2] Florian Nachon,[2] Rachid Baati [1]*

[1] ICPEES UMR CNRS 7515, Ecole de Chimie Polymères et Matériaux, Université de Strasbourg 25 rue Becquerel, 67087 Strasbourg, France.
[2] Département de Toxicologie et Risques Chimiques, IRBA, BP73, 91223, Brétigny-sur-Orge, France.

Acetylcholinesterase (AChE) is a key enzyme of the Central Nervous System (CNS), which hydrolyzes the neurotransmitter acetylcholine. By targeting AChE, organophosphorus nerve agents (OPNA) and organophosphorus pesticides irreversibly inhibit the cholinergic transmission, which is leading to death if untreated. Over several years, our group and colleagues have been concentrating on the development a new class of non-permanently charged bifunctional reactivators, that display higher affinity for AChE and high *in vitro* and *in vivo* efficiencies compared to 2-PAM and HI6.[1] By analogy, recently, we designed bifunctional reactivators that comprise a peripheral site ligand (PSL) connected to a fluorinated reactivator function using a covalent linker.[2] On the basis of our previous work on the synthesis of central hybrid reactivators bearing 6-alkanyl-3-hydroxy-2-pyridinaldoxime moiety, and with the goal to develop reactivator with greater lipophilicity and enhanced blood brain barrier (BBB) permeability,[2] we decided to substitute the 3-hydroxy group, initially designed to decrease the oxime pka, with a more electronegative and electron-withdrawing group such as fluorine. Fluorine is known to modulate the pKa of the proximal oxime, the conformational bias and the binding properties *via* molecular interactions. This structural change, compared to the known 6-substituted 3-hydroxy-2-pyridinaldoxime scaffold, appeared valuable for both practical and fundamental reasons, eventually providing reactivators with increased reactivation potency and better pharmacological profiles. The synthesis of original 3-fluoro-2-pyridinaldoximes[3] as well as 3-fluoro-2-pyridinamidoximes[4] will be presented, followed by the results of their ability to reactivated OP-inhibited cholinesterases (AChE and BuChE). The most promising candidates exhibited impressive ability to cross efficiently the blood-brain-barrier *in vitro*, for the development of new generation antidotes for OP-poisoning.

References

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