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MEETING ABSTRACTS

DESIGN AND SYNTHESIS OF BIFUNCTIONAL FLUOROPYRIDINALDOXIME REACTIVATORS FOR NERVE AGENT-INHIBITED *HUMAN* ACETYLCHOLINESTERASE

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Acetylcholinesterase (AChE) is a key enzyme of the Central Nervous System (CNS), which hydrolyzes the neurotransmitter acetylcholine.[1] By targeting AChE, organophosphorus nerve agents (OPNA) and organophosphorus pesticides irreversibly inhibit the cholinergic transmission, which is leading to death if untreated.[2] 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.[3] By analogy, recently, we designed bifunctional reactivators that comprise a peripheral site ligand (PSL) connected to a fluorinated reactivator function using a covalent linker. On the basis of our previous work on the synthesis of central hybrid reactivators bearing 6-alkanyl-3-hydroxy-2-pyridinadoxime moiety, and with the goal to develop reactivator with greater lipophilicity and enhanced blood brain barrier (BBB) permeability, 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-pyridinadoxime scaffold, appeared valuable for both practical and fundamental reasons, eventually providing reactivators with increased reactivation potency and better pharmacological profiles.

Keywords: Acetylcholinesterase (AChE); Central Nervous System (CNS); Organophosph-orus nerve agents (OPNA); 2-Pyridine Aldoxime Methyl Chloride (2-PAM) and Bifunctional reactivators

References

1. Bajar, J., *Adv. Clin. Chem*., **2004**, 38, 151-216.
2. G. Mercey, T. Verdelet, J. Renou, M. Kliachyna, R. Baati, F. Nachon, L. Jean, P.-Y. Renard, *Account of Chem. Res*. **2012**, 756–766.
3. (a). M. Kliachyna, V. Nussbaum, J. Renou, G. Santoni, B. Sanson, J.-P. Colletier, M. Arboléas, M. Loiodice, M. Weik, L. Jean, P.-Y. Renard, F. Nachon, R. Baati., *Eur. J. Med. Chem*. **2014**, 78, 455-467 and (b). T. Zorbaz, A. Braïki, N. Maraković, J. Renou, E. de la Mora,N. M. Hrvat, M. Katalinić, I. Silma, J. L. Sussman, G. Mercey, C. Gomez, R. Mougeot, B. Pérez, R. Baati, F. Nachon, M. Weik, L. Jean, Z. Kovarik, P.-Y. Renard, *Chem. Eur. J*. **2018**, 10.1002/chem.201801394.