How halogen substitutions steer pharmacological properties of a molecule – development of antidotes for organophosphorus poisoning

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Organophosphorus compounds (OPs) are used as pesticides or misused as chemical warfare nerve agents because they irreversibly inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) that leads to the accumulation of acetylcholine in the synapses of central and peripheral nervous system and to a life-threatening cholinergic crisis. The reactivation of inhibited cholinesterases by oximes in combination with antimuscarinic and anticonvulsive drugs is crucial in the treatment of OP poisoning. Oximes used in medical practice have a permanently charged pyridinium ring and cross the blood-brain barrier (BBB) poorly. However, their BBB penetration rate could be improved by the addition of a halogen substituent that increases lipophilicity. Structures of efficient bispyridinium oxime reactivators that differ in the linker between the rings (propane, butane, butene)[1] were the basis for the synthesis of analogues with chlorine[2,3] or fluorine atoms. Using biochemical techniques, we tested the analogues and observed specific patterns in their interaction with AChE and BChE (pharmacological targets) and in antioxidative potential of oximes (possible supplementary pharmacological mechanism) based on the linker and substituents. Moreover, the structural differences of oximes were reflected in their cytotoxicity on neuroblastoma cell line. Our results highlighted di-chlorinated bispyridinium oxime with propane linker as the best candidate for antidotal treatment after OP poisoning due to its high reactivation potential and no cytotoxic effects at pharmacologically relevant concentrations.

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[1]Kuca et al. JEIMC, 2003, 18 (6), 529−35.
[2]Zorbaz et al., JMC 2018, 61(23), 10753–66.
[3]Zorbaz et al., CBI, 2019, 307, 16-20.