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MEETING ABSTRACTS

NEW NON-OXIME REACTIVATORS OF ORGANOPHOSPHATE INHIBITED ACETYLCHOLINESTERASE WITH PROMISING REACTIVATION POTENCY

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Organophosphate (OP) compounds inhibit the enzyme acetylcholinesterase (AChE) resulting in severe symptoms and ultimately death. OP intoxications are currently treated by administration of atropine and certain oxime compounds (Obidoxime, HI-6 or 2-PAM). The latter compounds contain nucleophilic oximes that reactivate OP-inhibited AChE by liberating the phosphylated serine. However, these oximes have several drawbacks such as their intrinsic toxicity, their permanent charge which thwarts penetration of brain tissues and their inability to effectively reactivate all types of nerve agent inhibited AChEs. Therefore, the search for new (non-ionic) antidotes of nerve agent poisoning is of great importance. Recently, several papers reported on the discovery of non-oxime compounds as a result of the in vitro or in silico screening of libraries of bioactive compounds and approved drugs. For instance, Katz et al reported[1] a novel class of compounds in which the 4-amino-2-(diethylamino)phenol (ADOC) appeared to be a key motif responsible for reactivation of OP-inhibited AChE.[2] In addition, several structural derivatives of ADOC were synthesized and evaluated for OP-AChE reactivation by Cadieux et al.[3] That study provided valuable information on key structural features of ADOC with respect to reactivation potency and enzyme inhibition, but unfortunately, none of the reported derivatives performed equal or better than the ADOC parent. We here report the design and synthesis of a new series of ADOC derivatives. We report that one of the compounds synthesized so far showed a remarkably improved in vitro performance compared to ADOC towards VX-, sarin-, cyclosarin- and paraoxon-inhibited human AChE.

Keywords: reactivator; non-oxime; acetylcholinesterase

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