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## MEETING ABSTRACTS

# UTILIZING STRUCTURE-ACTIVITY RELATIONSHIPS AND MECHANISTIC INSIGHTS TO DESIGN NON-OXIME REACTIVATORS

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Organophosphorus nerve agents are highly toxic compounds which pose a threat worldwide. These compounds induce toxicity by covalently binding to the active site serine of acetylcholinesterase, which results in inhibition of the enzyme. Without functional acetylcholinesterase, the levels of the neurotransmitter acetylcholine in neuromuscular junctions rise quickly, causing overstimulation of the nervous system, which will culminate in death if not treated. Current treatments rely on small molecules to interact with inhibited enzyme to disrupt the covalently bound phosphorus moiety at the active site. The most effective molecules incorporate a pyridinium oxime which acts via direct nucleophilic attack on the phosphorus to achieve reactivation of the enzyme. These compounds have limited effectiveness because the charged portion of the molecule does not allow them to cross into the central nervous system where acetylcholinesterase inhibition is most harmful. The results of studies that characterized a small molecule reactivator (4-amino-2-((diethylamino)methyl)phenol [ADOC]) that does not incorporate an oxime but is capable of reactivating nerve agent-inhibited enzyme as well as or better than current treatments have been used to inform the design of additional novel compounds. This study describes the *in vitro* characterization of these novel compounds as reactivators of phosphonylated human acetylcholinesterase.

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