REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

New Synthetic Analogs Of 2-pralidoxime With A Broader Spectrum Against Organophosphorus Nerve Agents

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Organophosphorus nerve agents react with the serine residue of acetylcholinesterase (AChE) to inhibit its enzyme activity. When AChE is inhibited, acetylcholine is accumulated, causing acute symptoms, including death. 2-Pralidoxime (2-PAM) can remove the phosphyl group on the serine of AChE, restoring the balance between acetylcholine and choline in the central nervous system, but the efficacy is mostly limited to sarin. Because there are five or more other organophosphorus agents, there is a need to develop antidotes with a broader spectrum.

Our laboratory performed a methyl scan study on 2-PAM to determine that the 4- and 6-positions of 2-PAM can tolerate alkylation without losing potency. Due to the synthetic accessibility, we chose to focus on modifying the 4-position. The 4-position was modified by functionalized alkyl groups, sulfides, ethers, and amines. These analogs were tested against paraoxon with either eel or human AChE to identify promising 2-PAM analogs. These analogs were then tested at U.S. Army Medical Research Institute of Chemical Defense to find that some of the promising analogs were more potent against various organophosphorus agents than 2-PAM. Two of the analogs were also tested in mice exposed to paraoxon to demonstrate better potency than 2-PAM.

This work was financially supported by the US Defense Threat Reduction Agency (HDTRA1-16-1-0041).