TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Development Of A Structure-activity Relationship Of Non-oxime Based Reactivators For Nerve Agent-inhibited Acetylcholinesterase

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Organophosphate (OP) nerve agents act through the inhibition of acetylcholinesterase (AChE) at the active site of the enzyme. This leads to acetylcholine buildup and ultimately muscle paralysis throughout the body. Some small molecule medical countermeasures (MCMs), reactivate AChE by displacing the organophosphate nerve agent from the active site. Historically, these molecules are oximes based. 4-amino-2-((diethylamino)methyl)phenol (ADOC) a non-oxime hit compound, was found to possess reactivation potential through a modified mechanism of action. We present here a medicinal chemistry approach to optimize the drug profile of ADOC by systematic synthesis of multiple analogs, followed by initial screening for reactivation ability against an in vitro multi-agent panel. Analogs are also evaluated by their propensity to act as AChE inhibitors themselves. Promising candidates are further evaluated using time and concentration variations, as well as in vitro ADMET profiling. A preliminary structure-activity relationship among the analogs is developed, which informs further investigations.

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