



A Toxidromic Approach for Chemical Medical Countermeasure Development

Development of a Structure-Activity Relationship for Analogs of a Non-oxime Reactivator for Nerve Agent-Inhibited Acetylcholinesterase

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Organophosphate (OP) nerve agents, such as sarin and VX, are chemical warfare agents that present an acute and rapidly lethal threat to both the warfighter and civilians. They act through inhibition of acetylcholinesterase (AChE) at the active site of the enzyme, leading to acetylcholine buildup and ultimately muscle paralysis throughout the body. Current small-molecule medical countermeasures (MCMs), such as 2-PAM and HLo-7, reactivate AChE by displacing the organophosphate nerve agent from the active site using an oxime moiety in the molecule. However, the majority of this class of MCMs also contain a permanent charge crucial to activity, which hinders penetration of the blood-brain barrier (BBB) by the MCM into the nervous system where reactivation is most crucial. Recently, a non-oxime hit compound ADOC has been identified, which possesses promising reactivation potential against several OP nerve agents. The lack of a permanent charge in this compound holds promise for penetration into the nervous system and more efficient reactivation, by ADOC or a suitable analog. 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 a 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 solubility and penetration across the BBB. A preliminary structure-activity relationship among the analogs is developed, which informs further investigations into developing a MCM useful by the warfighter against multiple OP nerve agent threats.