## REVOLUTIONIZING BIOMEDICAL RESEARCH: INTEGRATING CUTTING-EDGE AI/ML TO UNLEASH INNOVATION IN DRUG DISCOVERY AND THERAPEUTICS DEVELOPMENT

# Application Of Molecular Docking And Pharmacophore Methods To Identify Potential Reactivators Of Nerve Agent-inhibited Acetylcholinesterase

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Organophosphorus pesticides and nerve agents (OPs) pose risks to warfighters and civilians alike. The current FDA approved treatment for OP-poisoning is 2-pyridine aldoxime methyl chloride (2-PAM), a pyridinium oxime, which reactivates OP-inhibited acetylcholinesterase (AChE) and relieves severe cholinergic crisis, presenting as difficulty breathing and severe seizures. Meanwhile, the chemical space of compounds capable of reactivation remains largely unexplored. The use of computational methods has shown to be a viable tool for designing novel drugs. Utilizing structure-based computational methods of protein-ligand docking and high-throughput screening, numerous potential reactivator scaffolds are theorized to bind within the AChE active site and may have improved properties as therapeutics. Using medicinal chemistry principles, these scaffolds may be modified to obtain desired reactivation characteristics. Currently, the optimized structures of several compound libraries (5-100k compounds) have been screened against multiple OP-inhibited AChE models using Discovery Studio's LibDock program. Poses were scored using LigScore 1 and 2, and down selected to obtain an optimal set of compounds per library, deemed "Top Hits." These "Top Hits" will be evaluated for their structural reactivation potential, appended with groups known to facilitate reactivation (where necessary), and be re-screened/scored. The top results from the second screening will be synthesized and analyzed by an in vitro, multi-agent screening assay to obtain their reactivation parameters. The introduction of computational methods can provide a directed approach to medicinal chemistry and aid in the development of novel AChE reactivators.

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