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Computational study of butyrylcholinesterase inhibition by dialkyl phenyl phosphate derivatives. WALTER ALVARADO, SEAN MCCOY, JEANNETTE GONZALEZ, TRINA TRAN, ANALISA GARCIA, KEN NAKAYAMA, JASON SCHWANNS, ERIC SORIN, Cal State Univ- Long Beach — Acetylcholine (ACh) is a neurotransmitter that allows for communication between nerve and muscle cells. While acetylcholinesterase (AChE) is the primary enzyme responsible for the breakdown of ACh to regulate intercellular communication, butyrylcholinesterase (BChE), an AChE-like scavenger enzyme, also breaks down both ACh and larger choline derivatives. In persons suffering from Alzheimer's disease (AD), BChE activity has been found to gradually increase over time and increased BChE activity is believed to significantly decrease synaptic ACh levels, thereby disrupting intercellular communication. It is therefore of interest to explore BChE-specific inhibitors as potential pharmaceutical approaches to the treatment of AD. Dialkyl phenyl phosphate (DAPP) derivatives are organophosphates that mimic the ester moeity of ACh. As such, DAPP derivatives are expected to interact with the BChE binding pocket in a manner similar to that of natural physiological substrates. This study employs massive flexible-inhibitor docking calculations to predict the relative binding affinity between the enzyme and a number of DAPP derivatives, as well as the optimal binding orientation of each DAPP derivative within the BChE active site. Our results reproduce experimental trends in binding affinity and indicate that DAPP derivatives with substitutions at the ortho- and meta- positions of the phenyl ring will show increased inhibitory strength, while para- substitutions will generally be detrimental due to steric clash with active site residues. These findings provide insight into the structural preference of BChE for specific DAPP derivatives and provide a framework for future inhibitor design and testing.

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