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Molecular Modeling Study of Aryl and Arylalkyl Di-n-Butyl Phosphates as Effective Butyrylcholinesterase Inhibitors WALTER ALVARADO, KENSAKU NAKAYAMA, JASON SCHWANS, ERIC SORIN, SEAN MCCOY, Cal State Long Beach — Alzheimer's Disease (AD) is a neurodegenerative disease characterized by plaque buildup in the brain and decreased levels of the neurotransmitter acetylcholine. Decreased levels of acetylcholine lead to decreased cell communication, which is thought to result in the manifestation of dementia. 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. This makes BChE a primary target for treating Alzheimer's symptoms and greatly increases the demand for non-toxic BChE-specific inhibitors. Dialkyl phenyl phosphate (DAPP) derivatives are expected to interact with BChE 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 docking calculations reproduce experimentally observed inhibition trends, with the m-methylphenyl analog binding favored over o-methyl. Structural analysis shows that the o-methylphenyl substituent takes on a rear-facing orientation, located in a vacant region of the pocket relatively void of potential interaction partners. This lack of significant participation during binding results in this species having relatively weak inhibitory power.

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