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The Total Synthesis of a Conformationally Constrained Organophosphorus Analog of Acetylcholine

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Poster Presentation 33

THE TOTAL SYNTHESIS OF A CONFORMATIONALLY CONSTRAINED ORGANOPHOSPHORUS ANALOG OF ACETYLCHOLINE

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Acetylcholinesterase (AChE) is an important enzyme in the human nervous system. AChE helps nerves function by catalyzing the hydrolysis of acetylcholine (ACh) into choline and acetate. AChE has been targeted as having a potential role in the pathology of neurodegenerative diseases such as Alzheimer's disease. It is known that AChE is inhibited by organophosphorus compounds such as soman and sarin. Past research has focused on the use of different organophosphorus inhibitors to study the structure of AChE, the mechanism by which it catalyzes the hydrolysis of ACh, and the stereoselectivity of AChE phosphorylation. This research has yielded conflicting results about the stereoselectivity of the phosphorylation of AChE. We propose that a conformationally constrained analog of ACh may provide more definitive answers about the stereoselectivity of the mechanism of AChE phosphorylation. These answers could lead to a better understanding of how AChE catalysis works. We intend to synthesize a novel organophosphorus analog of ACh. Long term goals of the project include the synthesis of all four stereoisomers of this inhibitor followed by biological assays to determine the inhibitory potency of these compounds.