Computational and Experimental Design of a Novel Acetylcholinesterase Inhibitor: Silanediols for Alzheimer's Disease Treatment

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Alzheimer’s Disease (AD) is currently the sixth leading cause of death. The Food and Drug Administration (FDA) has only approved six AD drugs, all of which are associated with severe side effects as drug dosage increases, including vomiting, syncope, and bradycardia. Therefore, there remains a critical need to develop more effective AD drugs. One hypothesis for the development of AD is the dysfunction of cholinergic neurons and decline in acetylcholine concentrations, which can be regulated with acetylcholinesterase (AChE) inhibitors. Silanediols have been researched as alternative AChE inhibitors because they can serve as transition state analogues of amide hydrolysis and have a high lipophilicity, allowing increased AChE binding and reducing adverse reactions. This project assesses the AChE inhibition, drug-likeness, and synthetic accessibility of silanediols, specifically with the parent structures of amantadine and memantine. Ligand binding affinities to AChE were determined using the Lamarckian Genetic Algorithm in the docking software Autodock, which was parameterized for silicon atoms. The SWISS ADME software was utilized to predict drug lipophilicity, blood-brain barrier permanence, and more. Two methods, a Grignard reagent and reduced adamantane, were used to form the carbon-silicon bonds necessary for silanediol synthesis. Results showed that three of our eleven ligands outperformed Rivastigmine, an FDA-approved AD drug, in terms of binding energy and lipophilicity. Evidence of the successful formation of our silanediols was shown through the reduced adamantane method of synthesis. This project demonstrates for the first time that adamantylsilanediols have high AChE inhibition and are viable as oral drugs, making immense progress toward better AD treatments.

Awards Won:
Fourth Award of $500