High-Throughput Quantum-Chemical Docking for Novel Compounds as Potential Alzheimer's Therapeutics

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Alzheimer's disease, a devastating neurodegenerative disorder, progressively impairs cognitive function and memory [1]. The cholinergic hypothesis links disease progression to acetylcholine (ACh) deficiency, a compound vital for the transmission of nerve signals. ACh is degraded by the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which are the targets of current Alzheimer's disease symptom treatments focused on cholinesterase inhibition [2]. This study investigates novel, selective and joint AChE and BChE inhibitors *via* semi-flexible quantum-chemical molecular docking.

Building upon previous research [3] and employing a rational drug design approach, a diverse set of 27 novel peptidomimetic compounds was methodically synthesized. These were specifically designed to enhance interactions with cholinesterases. A parallelized high-throughput *Monte Carlo* algorithm generated diverse configurational landscapes that accounted for all degrees of freedom and eliminated overlapping structures (Fig. 1). Binding energies within the AChE and BChE active sites were estimated using the PM7 Hamiltonian, followed by geometry optimization and calculation of standard Gibbs energies of binding for the top 1000 local minima. Structures were clustered and ranked by binding energies. Automated interaction analysis, assisted with visual inspection, identified promising candidates. The goal is to identify compounds with high affinity and selectivity for inhibiting both AChE and BChE. Targeting both enzymes may offer a more comprehensive approach to treating Alzheimer's disease and lead to improved therapeutics.

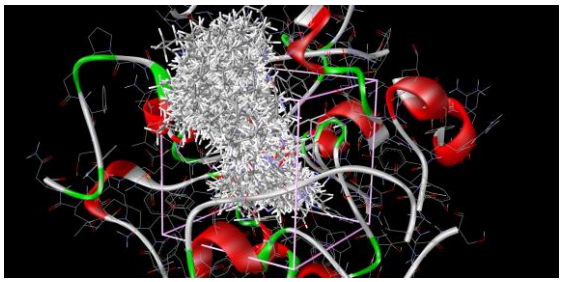

Figure 1. Configurational landscape in AChE for one of the investigated compounds

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References:

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