Selective Butyrylcholinesterase Inhibition by α-Acylaminobenzamides: A Quantum Chemical Docking Study

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Alzheimer's disease is a devastating neurodegenerative disorder that progressively impairs individuals' cognitive abilities, ultimately leading to severe memory loss and difficulty performing everyday tasks [1,2]. This incurable illness ranks among the leading causes of death worldwide, highlighting its significant impact on global health. The cholinergic hypothesis posits that an acetylcholine deficiency, a crucial neurotransmitter involved in learning, memory, and attention, contributes significantly to the disease's progression. Acetylcholine exerts its effects by binding to specific receptors in the brain. However, enzymes called cholinesterases, primarily acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), break down acetylcholine, effectively terminating its signaling. In individuals with Alzheimer's disease, acetylcholine levels are significantly reduced due to neuronal degeneration and impaired synthesis, leading to the development of cholinesterase inhibitors as the primary treatment strategy.

This study aims to find the best selective inhibitor of BChE by semi-flexible quantum-chemical molecular docking. A newly developed parallelized Monte Carlo algorithm for sampling the huge configurational spaces was used for structure generation [3]. This algorithm considered all translational, rotational, and torsional degrees of freedom. To ensure physically realistic structures, a *smart structure generator* was used to discard any configurations with atomic overlaps. Binding energies within the active site were estimated using single-point quantum chemical calculations with the PM7 hamiltonian [4]. The top 1000 local minima identified through this process underwent geometry optimization for further refinement. Finally, the optimized structures were clustered and ranked based on binding energy. An automated hydrogen bond search module and visual inspection were used to analyze the resulting docked structures.

References:

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