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In silico design, molecular docking and synthesis of novel [1,1-biphenyl]-4-carbonitril Schiff base derivatives as cholinesterase inhibitors

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Alzheimer's disease (AD) is a neurodegenerative disorder expected to affect over 80 million people by 2040. A decline in acetylcholine (ACh), a key neurotransmitter, is linked to cognitive decline in AD. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes break down ACh, making them targets for AD treatment. This study aimed to synthesize Schiff base derivatives and evaluate their ability to inhibit AChE and BChE. Molecular docking has been used to explore their binding interactions. Three Schiff base derivatives (**N1-N3**) have been synthesized by condensing substituted benzaldehydes with 4-(4'-aminophenyl)benzonitrile. Their cholinesterase inhibitory activity has been tested using a modified Ellman's method, and docking studies have been performed using Glide™. The compounds show strong inhibition of both AChE and BChE. **N1** has the strongest AChE inhibition (IC_{50} = 1.09 µg/mL), while **N3** is most effective against BChE (IC_{50} = 12.32 µg/mL). Molecular docking confirms favorable binding through hydrogen bonding and hydrophobic interactions. *In vitro* and docking results show **N1** and **N3** as potent inhibitors of AChE and BChE. Their interactions with key amino acids supports their inhibitory potential. Novel Schiff base derivatives **N1** and **N3** show promising cholinesterase inhibition. Their dual activity against AChE and BChE positions them as potential candidates for AD treatment. Further studies are recommended.

Keywords: Alzheimer's disease, Molecular docking, AChE, BChE, Schiff base derivatives