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# Novel acetylcholinesterase inhibitors developed by structure-based drug design in DDBL@MUS

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The inhibitors of the enzyme acetylcholinesterase (AChE) improve impaired cognitive functions due to increased levels of the neurotransmitter acetylcholin. They are widely used for symptomatic treatment of neurodegenerative diseases like Alzheimer's disease (AD). Among them, galantamine (GAL) is the most frequently prescribed drug.

Here, we describe the discovery and development of several GAL derivatives as multitarget agents against AD using structure-based methods for drug design. Initially, two libraries of derivatives were designed. The first library included hybrid molecules between GAL and novel AChE inhibitors that we previously discovered by in silico screening of compounds from ZINC database. The second library included hybrid molecules between GAL and curcumin (CU). The compounds were tested in silico for permeability across the intestinal mucosa and the blood-brain barrier (BBB), then docked into the binding site of human AChE. Among the best-scored compounds, one from the first library and 14 from the second library were selected, synthesized and tested in vitro for neurotoxicity and anticholinesterase activity. The compound from the first library was found to be non-toxic and 68 times more active than GAL. From the second library, 5 compounds were more active than GAL and less toxic than CU. The most active compound, named 4b, was 186 times more active than GAL. It was additionally tested for anticholinesterase, antioxidant and antiamyloid activity in vitro, in vivo and ex vivo. In all tests, the new GAL-CU hybrid 4b outperformed its parent compounds GAL and CU and emerged as a promising multitarget agent for the treatment of neurodegenerative diseases.

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