

04j. Therapeutic Targets & Mechanisms for Treatment: neurotransmitter-based targets

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THE ROLE OF CHOLINESTERASES IN ALZHEIMER'S DISEASE: SCREENING OF TARGET COMPOUNDS

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Background: Alzheimer's disease (AD) is the most common form of dementia and causes a progressive and irreversible neurodegeneration. The loss of cholinergic neurons leads to the progressive reduction of acetylcholine (ACh) in the brain and resulting cognitive impairment in AD. ACh is hydrolyzed by both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). It was found that in the course of the disease, levels of AChE in the central nervous system (CNS) decrease, inversely to BuChE levels, so both enzymes represent legitimate therapeutic targets for ameliorating the cholinergic deficit characteristic of AD.

Objective: Screen a library of new isoquinoline, indolinone and benzoazepinone derivatives for their ability to inhibit AChE and BuChE activities, using galantamine and rivastigmine as standards.

Methods: The enzyme activities and inhibition studies were carried out using spectrophotometric techniques, based on the Ellman's method, with acetylthiocholine (ATCI) and butyrylthiocholine (BTCl) as substrates, for AChE and BuChE, respectively. The data were complemented with modeling to analyze the structure-activity relationship.

Results: Our results show that the tested compounds are competitive inhibitors for AChEs and BuChEs, as the benchmarks galantamine and rivastigmine. The isoquinoline and indolinone derivative compounds showed strong anti-cholinesterases activities, with IC₅₀ values ranging from 0.4 to 400 micromolar.

Conclusions: The results presented are promising and provide a pathway for the design of new AChE and BuChE inhibitors.