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MEETING ABSTRACTS

FROM SELECTIVE BUTYRYLCHOLINESTERASE INHIBITORS TO MULTI-TARGET-DIRECTED LIGANDS AS LEAD COMPOUNDS FOR ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is characterized by severe basal forebrain cholinergic deficit, which results in progressive and chronic deterioration of memory and cognitive functions. Similar to acetylcholinesterase, butyrylcholinesterase (BChE) contributes to the termination of cholinergic neurotransmission. Its enzymatic activity increases with the disease progression, thus classifying BChE as a viable therapeutic target in advanced AD. Potent, selective and reversible human BChE inhibitors were developed. First, a hierarchical virtual screening was performed followed by biochemical evaluation of highest scoring hit compounds. Three compounds showed significant inhibitory activities against BChE and the best inhibitor was selected for further SAR studies. More than 100 different analogues were synthesized and among them, two compounds were found to be promising lead compounds as they were not cytotoxic, they crossed the blood-brain barrier and improved memory, cognitive functions and learning abilities of mice in a model of the cholinergic deficit that characterizes AD, without producing acute cholinergic adverse effects. The solved crystal structures of human BChE in complex with the most potent inhibitors revealed their binding modes and provided the structural basis for their further development into multi-target-directed ligands, which in addition to good inhibition of BChE possess good antioxidant, metal chelating, neuroprotective and other properties beneficial for AD.

Keywords: Alzheimer's disease; butyrylcholinesterase; multi-target-directed ligands

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