DONEPEZIL-BASED HETERODIMERS AS INHIBITORS OF BETAMETHYLOID AGGREGATION AND FORMATION


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Introduction: Simultaneous blockade of the catalytic and peripheral sites of the enzyme acetylcholinesterase (AChE) by dual binding site AChE inhibitors results in a potent inhibition of the hydrolysis of the neurotransmitter acetylcholine and, more interestingly, in the inhibition of the AChE-induced aggregation of beta-amyloid peptide (Abeta), the latter effect endowing these compounds with the potential to modify the natural course of Alzheimer’s disease. Moreover, some of these inhibitors have been found to be able to inhibit BACE-1, and therefore the synthesis of Abeta.

Aims: We planned the synthesis of novel dual binding site AChE inhibitors able to interfere both Abeta formation and aggregation as potential disease-modifying anti-Alzheimer agents.

Methods: The novel compounds have been designed by connection of a unit of huprine Y and a large fragment structurally related to donepezil through ethylene or trimethylene linkers that allow the dual site binding to AChE. The anti-cholinesterase and anti-amyloid activities of our compounds have been determined in vitro using reported protocols. The potential of these compounds to cross the blood-brain barrier has been assessed by in vitro and ex vivo studies.

Results: The novel donepezil-huprine heterodimers exhibit a moderate inhibitory activity of AChE-induced and self-induced Abeta aggregation and BACE-1, apart from a potent inhibitory activity of both AChE and butyrylcholinesterase, and seem to be able to enter the central nervous system.

Conclusions: Donepezil-huprine heterodimers hit different targets involved upstream and downstream in the neurotoxic cascade of Alzheimer’s disease, thereby constituting promising drug candidates with potential to positively modify AD progression besides its symptomatology.