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Multitarget compounds bearing tacrine- and donepezil-like structural and functional motifs for the potential treatment of Alzheimer's disease

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ABSTRACT

Alzheimer's disease is a multifactorial and fatal neurodegenerative disorder characterized by decline of cholinergic function, deregulation of other neurotransmitter systems, β-amyloid fibril deposition, and β-amyloid oligomers formation. Based on the involvement of a relevant number of biological systems in Alzheimer's disease progression, multitarget compounds may enable therapeutic efficacy. Accordingly, compounds possessing, besides anticholinergic activity and β-amyloid aggregation inhibition properties, metal chelating and/or nitric oxide releasing properties with additional antioxidant capacity were developed. Other targets relevant to Alzheimer's disease have also been considered in the last years for producing multitarget compounds such as β-secretase, monoamino oxidases, serotonin receptors and sigma 1 receptors. The purpose of this review will be to highlight recent reports on the development of multitarget compounds for Alzheimer's disease published within the last years focusing on multifunctional ligands characterized by tacrine-like and donepezil-like structures. Q2

Abbreviations: ACh, acetylcholine; ChEs, cholinesterases; AChE, acetylcholinesterase; *Ee*AChE, AChE from *Electrophorus electricus*; *h*AChE, human acetylcholinesterase; BuChE, butyrylcholinesterase; *eq*BuChE, BChE from equine serum; ChEI, ChE inhibitor; AChEI, AChE inhibitor; AD, Alzheimer's disease; DMAAD, disease modifying anti Alzheimer's drug; CNS, central nervous system; Aβ, β-amyloid peptide; CAS, catalytic active site; PAS, peripheral anionic site; MTDL, multi-target-directed ligand; APP, amyloid precursor protein; BACE-1, β-site APP cleaving enzyme 1; MAO-A/B, monoamine oxidase A/B; *h*MAO-A/B, human monoamine oxidase A/B; ROS, reactive oxygen species; BBB, blood brain barrier; NO, nitric oxide; H_3R, histamine H_3 receptor; NMDA, *N*-methyl-D-aspartate.

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Contents

1. Introduction

Q3 Alzheimer disease (AD), the leading cause of dementia among elderly people, is a multifactorial and fatal neurodegenerative disorder characterized by a decline of cholinergic function. AD is hallmarked by the neuropathological accumulation of amyloid beta (Aβ) plaques in the extracellular compartment and by the intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles. Although the molecular mechanisms of AD pathogenesis have not yet been clearly understood, so far the use of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors represents the only therapeutic approach to the disease. Cholinesterase inhibitors (ChEIs), able to improve cognitive functions, only treat disease symptoms and lack disease-modifying effects (Sadowski and Wisniewski, 2007), though, as better explained later, AChE also accelerates the assembly of Aβ into amyloid fibrils (Alvarez et al., 1997). Nevertheless, all the currently registered drugs for the treatment of AD are ChEIs (donepezil, rivastigmine, and galantamine, Fig. 1) with the exception of the *N*-methyl-D-aspartate (NMDA) antagonist memantine (licensed in several countries for treatment of moderate to severe AD) (Cummings, 2004; Standridge, 2004). The ChEI tacrine, the first drug approved for the treatment of AD, was withdrawn (Qizilbash et al., 2007) due to its hepatotoxicity (Lagadic-Gossmann et al., 1998). The narrowness of the therapeutic options makes treatment of AD the current biggest unmet medical need in neurology. Further, as the human population continues to age, AD prevalence is expected to reach epidemic levels unless a disease-modifying anti-Alzheimer's drug (DMAAD) can be found (Mount and Downton, 2006). Although incomplete, the current understanding of the disease process is sufficient to facilitate the development of rational therapeutic strategies. AChE and BuChE are the catabolic enzymes responsible for acetylcholine (ACh) hydrolysis, and it is known that in brains with degenerative changes which suffer a loss of AChE, BuChE has a compensatory role in the hydrolysis of ACh thus making it an additional target for increasing the cholinergic tone in AD patients affected by severe symptoms (Greig et al., 2005). Indeed, in those patients, the levels of AChE decrease while those of BuChE increase, particularly in brain areas associated with learning and memory (Reid et al., 2013). In fact, BuChE influences cognition, awareness, and behavior by modulating ACh levels in the central nervous system (CNS) (Podoly et al., 2009). Thus, dual inhibition of AChE and BuChE could improve the symptomatic treatment of AD.

Dysfunction of the cholinergic system has been established as the most prominent neurotransmitter abnormality of AD patients (cholinergic hypothesis of AD); however cognitive, behavioral and neuropsychiatric symptoms have been linked to deregulation of other neurotransmitter systems such as glutamatergic, serotonergic, adrenergic and peptidergic (Thathiah and De Strooper, 2011). Increasing evidence supports the role of the serotonergic system in learning and memory processes and serotonergic system signaling

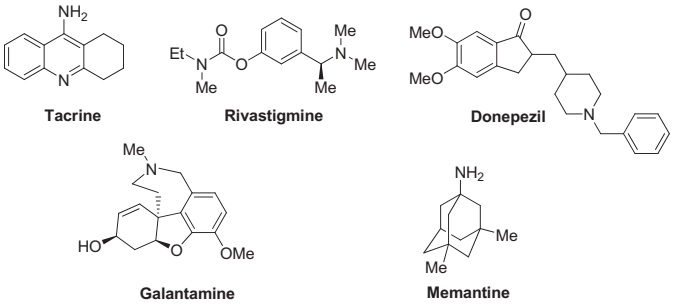

Fig. 1. Drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD (note that tacrine, approved in 1993, was discontinued in the U.S. in May 2012 as better specified in the text in Section 1).

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