ABSTRACT

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There were about 50 million people living with dementia in 2015. It is expected that number of people living with dementia will reach 130 million by the year of 2050. Alzheimer's disease (AD) is one of the most common causes of dementia and it is estimated to account for about 60 80% of overall cases. Current symptomatic treatment only alleviates symptoms and delays progression of the disease. However, there is no effective treatment, which would address the underlying cause of AD. The extracellular depositions of insoluble amyloid beta peptide (Aβ) were thought to be a causative factor and main target for a long time. Yet, targeted treatment towards the reduction of extracellular Aβ depositions failed to show expected therapeutic merit. Later on, it has been shown that development of AD starts much earlier than any Aβ plaques or symptoms could be observed. With growing evidence of soluble Aβ in intracellular regions, main attention moved to investigations of Aβ within the cells. Aβ interacts with variety of cellular structures and proteins, including those in cellular compartments such as mitochondria.

Presented work is focused on mitochondrial enzymes, which are affected by Aβ and could be potential therapeutic targets for AD treatment. Among those enzymes, Aβ-binding alcohol dehydrogenase (ABAD), also known as 17β-hydroxysteroid dehydrogenase type 10 (17β-HSD10), showed the most favourable potential and it is the enzyme of focus herein. The introductory part covers biological aspects of AD with gradual focus on selected enzymes, while chemistry review is dedicated to aspects around discussed structural scaffolds. Experimental work details the design, synthesis and evaluation of small molecules targeting ABAD. Structural scaffolds were derived from frentizole, fragment database hits or other enzyme scaffolds with partial intent to introduce multi-target-directed ligand strategies.

About 90 final compounds were designed, prepared and evaluated for their ability to inhibit ABAD enzyme. Synthesised diverse pool of compounds provided valuable initial data set to established basic structure and activity relationships and it yielded several potential hits for future development. Moreover, selected compounds are subjects of further in vitro / in vivo studies to assess their desirable pharmacological properties.