Abstract

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Title of Thesis: Preparation of phenyl derived benzothiazoles as potential ABAD modulators

Alzheimer's disease (AD) is neurodegenerative disease, which is characterized by progressive cognitive decline. Characteristic symptoms are memory loss, change of behaviour and personality. The pathological hallmarks of AD are senile plaques and neurofibrillary tangles of hyperphosphorylated τ protein. Currently there is no causal treatment, because the aetiology stays unexplained, despite of intensive research.

Nowadays, the hypothesis assumes that soluble form of amyloid-β (Aβ) is associated with toxic effects inside the cells, among others in mitochondria. There are many intracellular proteins, which interact with Aβ, such as amyloid binding alcohol dehydrogenase (ABAD). Interaction Aβ-ABAD with consequent alteration of ABAD function has been shown to cause mitochondrial dysfunction, consequently leading to the cell death. Therefore, inhibition of Aβ-ABAD along with ABAD inhibition seems as a potential pharmacological target.

The aim of this thesis was to synthesize substituted benzothiazole ureas as potential modulators of ABAD and subsequently to test their inhibition ability. New compounds are comprised of structure of frentizole, an immunosuppressive drug which displayed some minor inhibition (IC_{50} = 200 μM). This benzothiazole urea is relatively facile to modify, therefore there were synthesized several series of its analogues.

In the diploma thesis, 21 potential modulators of ABAD were synthesized. The structure activity relationship was determined from obtained results. The inhibition ability was determined *in vitro* against ABAD enzyme. The results were presented as percentage of remaining activity of ABAD enzyme.

13 compounds exert inhibition ability, 8 substances increase effects of ABAD enzyme. Slightly better inhibiting ability was observed in compounds with methoxy group at position C6 of benzo[*d*]thiazole scaffold in contrast with chlorine and fluorine at the same position. The inhibition activity of compounds with modifications of benzene scaffold at position C3 by fluorine and C4 by hydroxy group has been observed as the most satisfying, therefore, these compounds are suitable candidates for further evaluation. One compound was able to inhibit ABAD more than 85 % in comparison to the control.

On the other hand, compounds with modification of benzene scaffold at position C2 methoxy group and at position C4 fluorine exert activating ability of ABAD. The most potent activator of ABAD was able to activate the enzyme by more then 15 %.

Keywords

Alzheimer's disease, Amyloid-β, Mitochondria, Amyloid binding alcohol dehydrogenase, Frentizole