Summary

New hybrids of tetrahydroacridine and cyclopentaquinoline derivatives as acetylcholinesterase inhibitors with multifunctional activity

Kamila Anna Czarnecka

Alzheimer's disease is a progressive disease of the central nervous system and the most common cause of dementia. It mainly affects older people after 60. It is characterized by a progressive decrease in cognitive abilities, loss of memory and behavioral changes. These symptoms specify as dementia. The pathogenesis of this disease is complex and despite the fact that this disease is known for over a hundred years, the cause of its development is not fully known. Specialists in this area suggest several theories related to the development of this disease. The most important theories explaining pathomechanism are: cholinergic theory (associated with loss of cholinergic function), amyloid cascade hypothesis, tau protein pathology, as well as inflammation process. The disease leads to the damage to the cholinergic neurotransmission and the decrease of acetylcholine concentration in the synaptic space. Unfortunately, currently available medications can only alleviate the symptoms of the disease, but none of the available drugs can completely reverse its pathogenic progress and restore health. This is undoubtedly related to the multifaceted character of Alzheimer’s disease. Over the last decades, much effort has been put into research of the modifications of existing drugs, as well as the search for new structures. [Gazova at al. 2017; Ulus at al. 2017; Bajda et al. 2015; Kuo et al. 2017]

Taking into account complexity of Alzheimer's disease, one drug that works on a specific target causing the desired clinical effects may not be sufficient. The alternatives for this problem are multidirectional ligands considered an effective therapy. [Sang et al, 2017] Multifunctional drugs have gained popularity in the field of drug design and development over the last decades due to the increasing complexity of diseases that require more advanced pharmacotherapy. The observed fast development gives hope for effective treatment of Alzheimer's disease in the near future. There is an increasing number of elderly people. Age-

related diseases are becoming more and more problematic. For this reason, pharmacological research has become a priority. [Singh et al. 2013]

The research carried out within the scope of the presented thesis concerned the design of new molecules capable of combating the pathomechanisms and symptoms of Alzheimer's disease.

Disertation have focused on the design of new cholinesterase inhibitors as potential drugs in Alzheimer's disease. The goal was to design new multifunctional ligands, synthesize and test their biological properties *in vitro*. The concept of new hybrids was based on combining the properties of cholinesterase inhibition with other important activities in the pathogenesis of Alzheimer's disease. The work included: computer modeling, chemical synthesis and *in vitro* biological assays.

As a result of the presented research, innovative ligands – three teterahydroacidine with 2-fluorobenzoic acid moiety derivatives, three teterahydroacidine with 3-fluorobenzoic acid moiety derivatives, and eight of cyclopentanquinoline with 5,6-dichloronicotinic acid moiety derivatives were obtained. Their ability to inhibit cholinesterases and inhibit β-amyloid aggregation has been obtained. The studies of enzymatic kinetics for the most active derivatives were performed. K_m and V_{max} parameters were determined and the type of inhibition for selected compounds was determined. A mixed type of inhibition was obtained for all tested compounds. Then the viability of selected cell lines was performed. The studies showed that at a concentration close to their IC_{50} values, the cell viability was high, which indicates the safety of the obtained hybrids relative to the tested cell line. In the final stage of the work, molecular modeling studies were performed in order to analyse the docking of the obtained compounds. By combining the all above properties in one molecule, compounds with potential use in Alzheimer's disease were obtained. By combining these activities in one molecule, compounds with potential use in Alzheimer's disease therapy were obtained.