Streszczenie w języku angielskim

Alzheimer's disease is a progressive neurodegenerative disease of the central nervous system characterized by impaired cognitive functions, including memory, orientation, speech, and changes in personality and behavior. This disease mainly affects people over 65 years of age. The pathogenesis of Alzheimer's disease has not been fully elucidated, although more than 100 years have passed since Alois Alzheimer described it. Over the years, scientists have developed several hypotheses as to why this disease develops. Among them, the best-studied and confirmed is the cholinergic hypotheses, the Aβ cascade, and the Tau hypothesis. Unfortunately, pharmacotherapy for Alzheimer's disease is mainly based on relieving symptoms to improve the quality of life of patients. The multifactorial pathomechanism of disease development is a challenge in the design of new drugs. Designing compounds with multidirectional action that affect several pathomechanisms simultaneously is one of the most promising strategies in the fight against Alzheimer's disease.

The aim of the doctoral thesis was to design and synthesize a series of new, innovative cyclopentaquinoline and 9-acridine carboxylic acid hybrids linked by an alkyl chain of various lengths. The structures of the synthesized derivatives have been confirmed by several spectrometric methods, including IR, ^{1}H NMR, ^{13}C NMR, MS, and HR-MS. The new compounds were assessed for the inhibitory activity against AChE and BuChE, the activity of which is a key aspect in the pathogenesis of Alzheimer's disease. From a series of eight compounds, the two most active against each enzyme were selected. The highest inhibitory activity towards AChE was shown by N-[7-({1H,2H,3H-cyclopenta[b]quinolin-9-yl}amino)heptyl]acridine-9-carboxamidehydrochloride (**3f)** (IC_{50} = 113,34 ± 7,14 nM), having seven methylene groups in the alkyl chain. For BuChE, the most active compound is N-[3-({1H,2H,3H-cyclopenta[b]quinolin-9-yl}amino)propyl]acridine-9-carboxamidehydrochloride (**3b)** (IC_{50} = 103,73 ± 7,63 nM) having three methylene groups in the alkyl linker. For both compounds, the type of inhibition was determined to be mixed by examining the kinetics of the enzymatic reaction. The most active compounds **3b** and **3f** were selected for further studies. Oxidative stress and free radicals are an integral part of the pathomechanism of Alzheimer's disease. Taking into account their role in the development of the disease, the antioxidant activity of compounds **3b** and **3f** was determined. Both compounds showed several dozen times higher activity than tacrine, which is a reference compound with significant structural similarity to the synthesized derivatives. Additionally, considering that tacrine was the first Alzheimer's drug to display strong hepatotoxic properties, which led to its withdrawal from treatment, compounds

3b and **3f** were assessed for potential toxic effects on liver cells. The IC_{50} values obtained in the study on the human liver cell line showed that both derivatives caused a 50% reduction in cell survival at concentrations significantly higher than those obtained in the inhibitory activity tests. In order to determine the exact type of interaction of the compound with the enzymes, including the type of interaction between the structure of the compound and the amino acid structure of the interior of the enzyme binding pocket, molecular modeling studies were performed for the entire series of compounds. As a result, the key role of the length of the alkyl linker in the interaction of the compound with the enzyme, including the alignment of acridine and cyclopentaquinoline rings in relation to each other and the involvement of specific amino acid residues in the interaction between ligand and binding site of enzyme, was proved.

Interactions of compounds with AChE and BuChE turned out to be dependent also on the presence of extra- and intramolecular hydrogen bonds, additionally stabilizing the conformation of the compound inside the enzyme. The pharmacokinetic properties and toxicity of compounds **3a**-**3h** were assessed by ADMET computer analysis.

Taking into account the activity, antioxidant potential, and pharmacokinetic properties, derivative **3b** showed the greatest potential as a compound with multidirectional action and potential use in the pharmacotherapy of Alzheimer's disease.