Abstract

Central nervous system (CNS) disorders, such as dementia and Alzheimer's disease (AD), occupy a prominent place among civilization diseases. They are becoming a problem in our society, due to their ever-increasing prevalence and because of the lack of access to effective treatment therapies. The neurodegenerative disease with a complex aetiology which is AD is the most widespread memory dysfunction, which particularly affects the elderly. In addition, no new synthetic drug effective in AD has appeared on the pharmaceutical market for more than two decades. To date, various protein targets that may be involved in AD therapy have been classified, including serotonin 5-HT_6 receptor (5-HT_6R) and cyclin-dependent kinase 5 (CDK5). The aforementioned two protein targets have been selected as therapeutic targets in the research of this dissertation.

The main aim of this research was the design, chemical synthesis and *in vitro* and *in vivo* evaluation of the pharmacological properties of new 5-HT_6R ligands, 1,3,5-triazine derivatives, as well as computer-aided SAR analysis of the obtained final compounds. Different chemical modifications were also planned to extend the pharmacological profile of the compounds to an additional AD-related target selected from among the enzyme proteins, i.e. CDK5/p25. In-house studies planned also included *in vitro* ADMETox assays and structure-activity relationship analysis based on pharmacological screening results.

The lead structure for the modifications carried out was (*RS*)-4-[1-(2,5-dichlorophenoxy)propyl]-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine (**1.9**), a potent and selective serotonin 5-HT_6 receptor antagonist, synthesized earlier in the Department of Technology and Biotechnology of Drugs JU MC. Forty-nine final compounds have been obtained, which were divided into series (A-E) containing in the structure, among others: substitution of the aromatic ring with chlorine and fluorine atoms, a methoxyl group at the triazine ring, substitution of an amino group in the triazine ring, as well as sulfur-containing compounds. The work plan included rational design using molecular modelling techniques, allowing preliminary evaluation of: the interaction of compounds with 5-HT_6R, inhibition of selected enzymes, and "druglikeness". The designed compounds were obtained via multi-step synthesis using *O*- and *S*-alkylation, simple and cyclic condensation as well as Buchwald-Hartwig reaction. Although no desirable enzyme inhibitors were found, about 30% of the obtained derivatives showed very high affinity towards the 5-HT_6 receptor (K_i < 20 nM), including particularly high affinity for seven compounds (K_i < 10 nM). A vast majority of the derivatives showed selectivity toward 5-HT_{1A} and 5-HT_7 receptors. The most active structure

with respect to 5-HT_6R was (*RS*)-4-[1-(2,5-difluorophenoxy)propyl]-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine (**3.8**, K_i = 5 nM).

In vivo studies conducted for the three most active compounds **1.2**, **1.4** and **3.8**, confirmed their procognitive effects. It is also worth noting that these compounds were characterized by high metabolic stability and favourable druglike properties.

The results obtained in the present study confirmed the high potential of 1,3,5-triazine derivatives as potent and selective ligands towards the 5-HT_6 receptor. The multidisciplinary research carried out was described in three publications published in international journals (JCR, total IF>19), constituting the doctoral thesis, and outlined further research directions in this chemical group.