Abstract

Schizophrenia is a mental illness whose causes are not fully understood and the symptoms of which are only partially treated with the use of available neuroleptics. The prevalence of schizophrenia in the population is estimated at about 1%. The disease causes positive symptoms (e.g. hallucinations), negative symptoms (e.g. social withdrawal) and cognitive symptoms. At the molecular level, the pathomechanism of schizophrenia results from the over stimulation of dopamine D_2 receptors in the striatum and lack of stimulation of dopamine D_1 receptors in the prefrontal cortex, as well as changes in the functioning of the glutamatergic system in the prefrontal cortex. Currently, the most important concept of schizophrenia is the dopaminergic hypothesis, supplemented with the glutamatergic hypothesis. Developmental and environmental factors are also important in the development of this disease. Modern drugs used in schizophrenia are divided into first, second and third generation neuroleptics.

Designing new substances modulating the signaling complexity of the dopamine D_2 receptor (belonging to the G-protein coupled receptors, GPCRs, which are the targets of approximately 30% of drugs available on the market) is still an up-to-date approach to the development of new neuroleptics. Careful characterization of GPCR receptor ligands has shown that many substances can interact with more than one receptor (promiscuous ligands). This was initially thought to be a hindrance to the discovery of drugs that act through these receptors. Today, however, it is known that in diseases with a complex pathomechanism, such as disorders of the central nervous system or cancer, drugs acting through several molecular targets are more effective than selective drugs. Multi-target ligands have become one of the "hot" topics in medical chemistry in recent years.

This dissertation is essentially divided into two parts. The first part contains one review and two original publications presenting published research. The second part, in turn, describes further research results on derivatives of the virtual hit D2AAK1.

The aim of the study was to develop new multi-target monoamine receptor ligands with antipsychotic, anxiolytic and procognitive activity with potential application in the treatment of schizophrenia. The above goal was achieved by optimizing the D2AAK1 virtual hit which was identified in structure based virtual screening. The new substances were subjected to structural, *in vitro* and *in vivo* tests and thermal analysis. Molecular modeling was also

performed for them to investigate their interactions with relevant GPCRs at the molecular level.

The presented research results constitute the basis for further research on multi-target compounds, and thus finding the optimal treatment for schizophrenia. Additionally, the presented data will contribute to a better understanding of the still not fully understood pathophysiology of schizophrenia.

Key words: schizophrenia, dopamine, multi-target ligands, indole, GPCR.