DESIGN, SYNTHESIS AND EVALUATION OF NOVEL INHIBITORS OF KYNURENINE AMINOTRANSFERASE II

Michal Maryška[a,b], Wim Dehaen[c], Lukáš Mikulů[a,b], Michaela Rumlová[d] and Martin Kuchař[a,b,e]

[a]Department of Chemistry of Natural Compounds, University of Chemistry and Technology, 16628 Prague, Czech Republic
[b]Forensic Laboratory of Biologically Active Substances, University of Chemistry and Technology, 16628 Prague, Czech Republic
[c]Department of Informatics and Chemistry, University of Chemistry and Technology, 16628 Prague, Czech Republic
[d]Department of Biotechnology, University of Chemistry and Technology, 16628 Prague, Czech Republic
[e]National Institute of Mental Health, 25067 Klecany, Czech Republic

The kynurenine metabolic pathway is believed to play an important role in the pathogenesis of psychiatric disorders and neurodegenerative diseases. One of the enzymes of this pathway, kynurenin aminotransferase (KAT), appears to be a promising target for schizophrenia treatment, especially its isoform KAT II. Although several generations of inhibitors have been discovered, only a few chemotypes represent their structures. Therefore, using computer-aided drug design, we synthesized potential inhibitors of KAT II and evaluated their activity.

We used Molecular Operating Environment software to construct a pharmacophore model based on a structural analysis of known inhibitors. Several ligands were designed and validated using the model and molecular docking. Representative heterocyclic aminoketones achieved the best docking score.

To examine the potency of the designed compounds, we synthesized a series of aminoketone derivatives with different heterocycles and tested them for inhibition activity using *in vitro* fluorescence assay. Some of them showed good inhibition activity with IC_{50} values in the micromolar range.

Observed activities of the prepared inhibitors indicate their potential as leading structures for further optimization and possibly for the development of a clinical candidate.

This work was supported by Ministry of Interior of the Czech Republic (MV0/VI20172020056) and by ERDF/ESF PharmaBrain (No. CZ.02.1.01/0.0/0.0/16_025/0007444).