Summary

Title of the dissertation: Design and synthesis of D-amino acid oxidase inhibitors

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Bibliographic information for the 5 most important publications:

- Szilágyi B, Kovács P, Ferenczy GG, et al. Discovery of isatin and 1H-indazol-3-ol derivatives as D-amino acid oxidase (DAAO) inhibitors. Bioorganic Med. Chem. 2018;26:1579–1587. DOI: 10.1016/j.bmc.2018.02.004; IF: 2.881; I(FI):2(1)
- Orgován Z, Ferenczy GG, Szilágyi B, et al. Validation of tautomeric and protomeric binding modes by free energy calculations. A case study for the structure based optimization of D-amino acid oxidase inhibitors. J. Comput. Aided. Mol. Des. 2018;32:331–345. DOI: 10.1007/s10822-018-0097-y; IF:2.356; I(FI):4(1)
- Szilágyi B, Skok Ž, Rácz A, et al. Discovery of D-amino acid oxidase inhibitors based on virtual screening against the lid-open enzyme conformation. Bioorganic Med. Chem. Lett. 2018;28:1693–1698. DOI: 10.1016/j.bmcl.2018.04.048; IF:2.442; I(FI):1(1)
- Szilágyi B, Hargitai C, Kelemen ÁA, et al. Synthesis and Biochemical Evaluation of Lid-Open D-Amino Acid Oxidase Inhibitors. Molecules. 2019;24:290. DOI: 10.3390/molecules24020290; IF: 3.060 (2018); I(FI):0(0)
- Szilágyi B, Ferenczy GG, Keserű GM. Drug discovery strategies and the preclinical development of D-amino-acid oxidase inhibitors as antipsychotic therapies. Expert Opin. Drug Discov. 2018;13:973–982. DOI: 10.1080/17460441.2018.1524459; IF:4.421; I(FI):1(1)

Due to the structure of the binding pocket of D-amino acid oxidase enzyme, it is possible to bind molecules of fragment size or larger. During my work I investigated fragment size compounds first.

After virtual and *in vitro* screening of compound libraries, a scaffold with potentially DAAO inhibitory properties was identified based on the results. Following the preparation of variously substituted derivatives of the compound family, protonation and tautomeric relationships were mapped, and several molecules with nanomolar activity were identified, which, after metabolic stability and membrane permeability measurements, *in vivo* efficacy of one of the compound was confirmed.

During binding of larger compounds, the flexible loop that surrounds the entrance of the catalytic pocket also plays an important role, because in case of these molecules, the loop is fixed in open state and may interact with the inhibitor.

To investigate interactions with the loop, I prepared (1*H*-pyrrole-2-carbonyl) glycine derivatives substituted with heterocycles. Following *in vitro* assays of the prepared compounds, several inhibitors of nanomolar activity were identified and structure-activity relationship were concluded.

In addition, a compound library has also been prepared to investigate the role of other secondary bonds in the catalytic pocket. These results may assist in the design of new inhibitors with better physico-chemical properties and ADME profile.