Summary

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

Author: Bence Szilágyi

Bibliographic information for the 5 most important publications:

- 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)

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 (1H-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.