# In-silico design towards MAO-B selective covalent inhibitors based on Rasagiline

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Parkinson's disease (PD) is a neurodegenerative disorder that results from oxidative stress in the central nervous system (CNS). It is known that the B isoform of the monoamine oxidase enzyme (MAO-B) contributes to this stress, so inhibiting it is essential for treating PD. While several drugs known as MAO-B inhibitors are currently available on the market, they can cause significant side effects and also engage the other isoform of the MAO enzyme, known as MAO-A. [1]

In this study, we aim to develop novel MAO-B inhibitors using in-silico methods, including molecular docking, virtual screening and molecular generation. In the crystal structure of the covalently bound rasagiline-MAO-B complex (pdb:1s2q) the 4-position of rasagiline overlaps with the entrance cavity[2] of the MAO-B active site and thus, modification at this position offers promising potential for the design of ligands. Using molecular generators as well as manual design based on structural knowledge, we explore diverse substitutions in this position, and evaluate them using covalent and non-covalent molecular docking and molecular dynamics simulations.

This results in a set of de novo designed new potential MAO-B ligands that will be prioritized for synthesis and testing in the future.

[1] del Pozo, J. S. G., et al (2013). Rasagiline meta-analysis: A spotlight on clinical safety and adverse events when treating Parkinson’s disease. In Expert Opinion on Drug Safety (Vol. 12, Issue 4, pp. 479–486). <https://doi.org/10.1517/14740338.2013.790956>

[2]Milczek, E. M., et al (2011). The “gating” residues Ile199 and Tyr326 in human monoamine oxidase B function in substrate and inhibitor recognition. FEBS Journal, 278(24), 4860–4869. <https://doi.org/10.1111/j.1742-4658.2011.08386.x>