DESIGN AND DEVELOPMENT OF NOVEL LOW-MOLECULAR-WEIGHT CARBOXAMIDES AS DUAL MODULATORS OF MAO-B AND α-SYNUCLEIN

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Neurodegenerative disorders such as Parkinson's disease (PD) are characterized by progressive dopaminergic neuronal loss and the pathological aggregation of α-synuclein (α-syn), accompanied by dysregulation of monoaminergic neurotransmission. Monoamine oxidase B (MAO-B) represents a validated enzymatic target involved in dopamine metabolism and oxidative stress[1–4], while α-syn constitutes a central disease-modifying target associated with protein misfolding, aggregation, and neurotoxicity[4]. Simultaneous modulation of both targets represents a rational multitarget strategy for the development of small-molecule therapeutics, as for example, indazole-5-carboxamide derivatives.[2,3]

Inhibition of MAO-B reduces dopamine degradation and limits the formation of reactive oxygen species[1], thereby attenuating oxidative stress–mediated neuronal damage, while modulation of α-Syn–related processes interfere with protein aggregation, toxicity, and pathological spreading. Targeting both mechanisms within a single low-molecular-weight framework is expected to address complementary pathological pathways implicated in neurodegeneration and may contribute to slowing disease progression through combined symptomatic and disease-modifying effects.[4]

This work is focused on the design of novel low-molecular-weight compounds acting as dual MAO-B/α-syn inhibitors, employing an integrated strategy based on molecular docking, molecular dynamics simulations, virtual screening, synthesis, and *in vitro* physicochemical and biological evaluation using the approved drug safinamide (Figure 1). The combined application of these approaches provides a systematic framework for the identification and optimization of small molecules with potential relevance for neurodegenerative disease research.

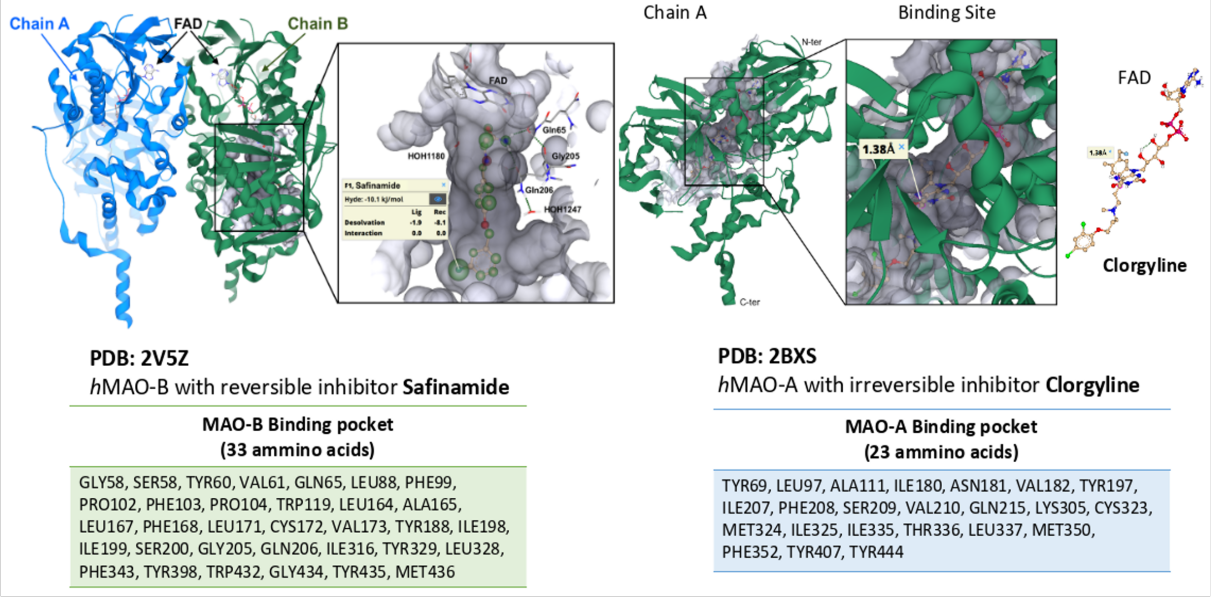


Figure 1. Structural comparison of human MAO-B and MAO-A active sites using safinamide and clorgyline as reference inhibitors.[1,3]

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