Investigating the interactions of a new set of quaternary propargylamine derivatives with monoamine oxidase enzymes.

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INTRODUCTION

MAO inhibitors (monoamine oxidase inhibitors) are crucial in treating neurodegenerative disorders. The aim of this study is the design of novel not terminal propargylamines using Molecular Docking and Dynamics and Toxicity studies.

MATERIALS AND METHODS

We synthesized a diverse group of quaternary propargylamines and assessed their inhibitory effects on both hMAO-A and hMAO-B enzymes, finding them to be notably effective. These compounds adhere to Lipinski's rule of five and show no predicted toxicity. Their binding interactions were explored through molecular docking, all-atom classical molecular dynamics (MD) simulations, and MM/GBSA binding free energy calculations. Overall, the propargylamines described in this study hold significant promise as potential treatments for conditions such as depression, Parkinson's disease, and Alzheimer's disease.

RESULTS

All synthetic propargylamines studied demonstrated sub-micromolar inhibition of both hMAO-A and hMAO-B through molecular docking. Molecular dynamics (MD) simulations revealed that compounds 4j and 4k had Root Mean Square Deviation (RMSD) fluctuations below 4 Å, indicating their stability and consistent binding with the target protein. These compounds also showed significant inhibitory activity, with IC50 values ranging from 765.6 to 861.6 nM for hMAO-A and 152.1 to 164.7 nM for hMAO-B. The Binding Free Energy analysis for compound 4k was calculated at -63.07±5.40 kcal/mol, suggesting a stronger binding affinity for hMAO-B compared to selegiline. MM/GBSA calculations indicated favorable binding for all compounds with both hMAO-A and hMAO-B. Additionally, these propargylamines appear to have good intestinal absorption and comply with Lipinski's rules, showing no predicted toxicity.

CONCLUSIONS

These molecules hold significant promise for treating neurodegenerative diseases. This is the first instance where a propargylamine scaffold with an internal alkyne, as opposed to a terminal one, has demonstrated such biological activity. New compounds are currently under evaluation, and the most effective ones will undergo in vivo testing to further assess their potential benefits.

REFERENCES *1. Behl T et al. Role of Monoamine Oxidase Activity in Alzheimer's Disease: An Insight into the Therapeutic Potential of Inhibitors. Molecules 2021*

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