High-throughput Screening and Molecular Dynamics Simulation of Natural Product-like Compounds Against Alzheimer's Disease through Multitarget Approach

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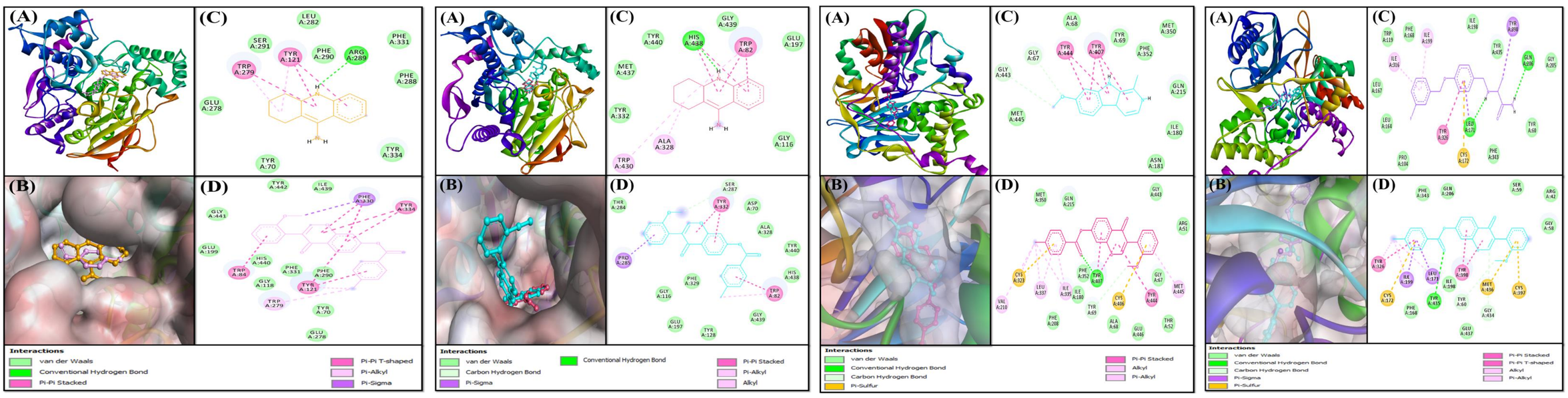
INTRODUCTION: Neurological disorders including Alzheimer's disease (AD) have a significant negative impact on the mental, psychological, physical, and economic health of patients and their caregivers. several reports have hypothesized that the four major pathophysiological pathways (oxidative stress, amyloid-beta pathway, tau pathway, and cholinergic pathway) are responsible for the progression of AD. At present, there is a lack of disease-modifying medications or a complete cure for AD. In the present study, we explored a library of natural product-like compounds for their multi-targeting (AChE, BChE, MAO-A, MOA-B) potential against AD through in silico high-throughput screening and ADME-T analysis. Furthermore, the validation of the best hit via molecular dynamics simulation was also conducted. To the best of our knowledge, this study is the first to explore this library of natural product-like compounds for multi-targeting against AD.

RESULTS: Based on the binding energy of these target enzymes, approximately 189 compounds exhibited a score of less than -10 kcal/mol against all targets. However, none of the control inhibitors exhibited a binding affinity of less than -10 kcal/mol. Among these, the top 10 hits of compounds against all four targets were selected for ADME-T analysis. As a result, only F0850-4777 exhibited an acceptable range of physicochemical properties, drug-likeness, pharmacokinetics, and suitability for BBB permeation with high GI-A and non-toxic effects. The molecular dynamics study confirmed that F0850-4777 remained inside the binding cavity of targets in a stable conformation throughout the simulation and Prime-MM/GBSA study revealed that van der Waals' energy (ΔGvdW) and non-polar solvation or lipophilic energy (ΔGSol_Lipo) contribute favorably towards the formation of a stable protein–ligand complex.

Table **1.** Molecular docking scores of best hit natural product-like compounds against AChE, BChE, MAO-A and MAO-B.

S. No.	ID number	Targets/ Formula	Docking energy (kcal/mol)			
			AChE (1acj)	BChE (4bds)	MAO-A (225x)	MAO-B (2v5z)
1	F0870-0001	$C_{24}H_{15}NO_6$	-12.9	-12.6	-11.5	-13.6
2	F1094-0205	$C_{26}H_{23}NO_4$	-12.9	-11	-10.8	-12.6
3	F3293-0320	$C_{22}H_{13}NO_7$	-12.4	-11.1	-12.3	-13.4
4	F1094-0201	$C_{26}H_{19}NO_4$	-12.3	-11.2	-12.3	-11.5
5	F0850-4777	$C_{24}H_{18}O_5$	-12.2	-10.7	-13.6	-12.5
6	F3385-6048	$C_{27}H_{21}NO_8$	-12.2	-11.1	-13.2	-12.6
7	F1094-0200	$C_{25}H_{17}NO_4$	-12.1	-11.2	-11	-13.2
8	F1865-0198	$C_{23}H_{15}NO_6$	-12	-10.9	-12.6	-13.3
9	F3139-1101	$C_{24}H_{16}O_4$	-12	-10.3	-12.4	-13.6
10	F3139-1218	$C_{26}H_{18}O_6$	-11.8	-10.4	-12.9	-13.3
11	Tacrine	$C_{13}H_{14}N_2$	-8.5	-8.4	ND	ND
12	Harmine	$C_{13}H_{12}N_2O$	ND	ND	-8.7	ND
13	Safinamide	$C_{17}H_{19}FN_2O_2$	ND	ND	ND	-9.5



Figures 1. Interactions of F0850-4777 with target protein, AChE (1), BChE (2), MAO-A (3), and MAO-B (4)

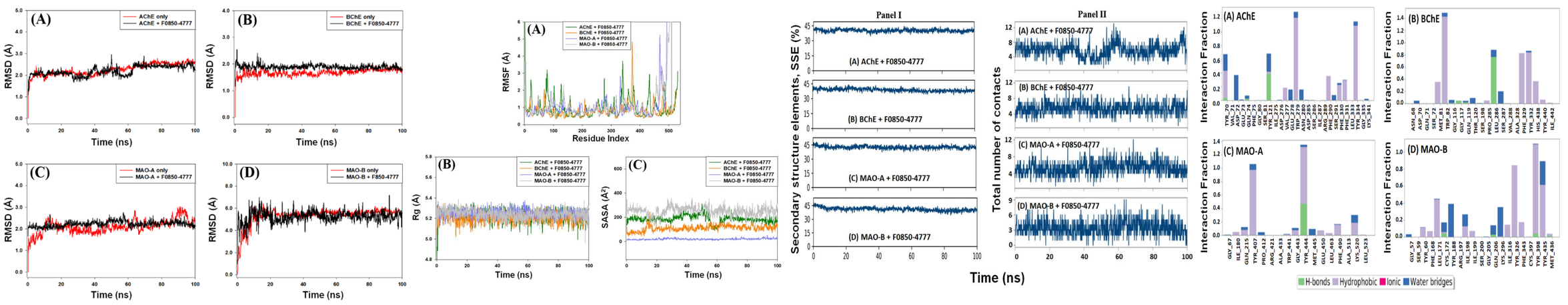


Figure 2: Molecular Dynamics study, RMSD (1), RMSF (2A), Rg (2B), SASA (2C), SSE (3), Interactions (4)

CONCLUSSION: F0850-4777 could be a potential candidate against multiple targets of two pathophysiological pathways of AD and opens the doors for further confirmation through in vitro and in vivo systems.

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