

Simultaneous Modulation of Amyloidogenesis, Tau Signaling, and Apoptosis: An In-Silico Multi-Target Strategy for Alzheimer's Disease

aaic2026.559098c

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Alzheimer's disease requires therapies targeting multiple pathological pathways rather than a single mechanism.

- HTVS of ~500,000 ASINEX compounds identified LAS512463592 as a common inhibitor of BACE1, GSK-3 β , PKA, and Caspase-3.
- LAS512463592 demonstrated strong binding affinity, BBB permeability, and stable protein-ligand interactions during molecular dynamics simulations.
- The compound represents a promising multi-target disease-modifying candidate for Alzheimer's disease requiring further biological validation.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																																																																											
Alzheimer's disease is characterized by amyloid-β accumulation, tau hyperphosphorylation, synaptic dysfunction, and neuronal apoptosis. Current FDA-approved therapies mainly target individual pathological mechanisms and provide only symptomatic benefit. Multi-target directed ligands (MTDLs) capable of simultaneously modulating multiple disease pathways may provide superior therapeutic efficacy. This study aimed to identify a brain-penetrant multi-target small molecule against four major Alzheimer's disease targets: BACE1 (3VF3), GSK-3β (7B6F), PKA (4UJI), and Caspase-3 (AF-P42574-F1).	ASINEX LIBRARY ~500,000 Compounds High Throughput Virtual Screening (HTVS) Schrödinger Maestro Screening Against 4 AD Targets BACE1 (3VF3) Amyloid Pathway GSK-3β (7B6F) Tau Pathway Caspase-3 (AF-P42574-F1) Apoptosis Pathway PKA (4UJI) Tau Pathway Top Scoring Compounds (~478) Top Scoring Compounds (~478) Top Scoring Compounds (~478) Top Scoring Compounds (~478) BBB Permeability Screening (Brain Penetrant Compounds) 45 Compounds (~10–12 Hits from Each Target) Cross-Docking Against All 4 Targets 16 Common Hits Identified (Per Target) Selection of Lead Compound LAS512463592 Molecular Dynamics Simulation (GROMACS) RMSD Analysis (Stability) RMSF Analysis (Flexibility) Radius of Gyration (Rg) (Compactness)	Identification of Lead Compound: Approximately 500,000 compounds were screened against four Alzheimer's disease therapeutic targets, BBB filtering reduced the library to 45 promising candidates, Cross-target screening identified 16 common ligands, LAS512463592 demonstrated the highest overall affinity across all four proteins. <table><tr><th>Target</th><th>Docking Score (kcal/mol)</th><th>MMGBSA (kcal/mol)</th></tr><tr><td>BACE1</td><td>~9.33</td><td>~40.60</td></tr><tr><td>GSK-3β</td><td>~8.14</td><td>~50.80</td></tr><tr><td>Caspase-3</td><td>~7.92</td><td>~46.69</td></tr><tr><td>PKA</td><td>~9.67</td><td>~49.14</td></tr></table> Molecular Dynamics Simulation RMSD: <table><tr><th>RMSD (nm)</th><th>APO</th><th>LAS</th><th>Control</th></tr><tr><td>BACE1</td><td>0.133$\pm$0.017</td><td>0.141$\pm$0.021</td><td>0.132$\pm$0.021</td></tr><tr><td>GSK</td><td>0.416$\pm$0.059</td><td>0.303$\pm$0.056</td><td>0.275$\pm$0.036</td></tr><tr><td>CASP</td><td>0.822$\pm$0.101</td><td>1.068$\pm$0.198</td><td>0.782$\pm$0.107</td></tr><tr><td>PKA</td><td>0.218$\pm$0.033</td><td>0.175$\pm$0.024</td><td>0.173$\pm$0.026</td></tr></table> RMSF: Low residue fluctuations, Stable binding pocket interactions. <table><tr><th>RMSF (nm)</th><th>APO</th><th>LAS</th><th>Control</th></tr><tr><td>BACE1</td><td>0.075$\pm$0.036</td><td>0.079$\pm$0.044</td><td>0.079$\pm$0.039</td></tr><tr><td>GSK</td><td>0.114$\pm$0.081</td><td>0.136$\pm$0.079</td><td>0.0126$\pm$0.089</td></tr><tr><td>CASP</td><td>0.171$\pm$0.194</td><td>0.312$\pm$0.331</td><td>0.234$\pm$0.221</td></tr><tr><td>PKA</td><td>0.090$\pm$0.043</td><td>0.084$\pm$0.042</td><td>0.098$\pm$0.036</td></tr></table> Radius of Gyration: <table><tr><th>Rg (nm)</th><th>APO</th><th>LAS</th><th>Control</th></tr><tr><td>BACE1</td><td>2.122$\pm$0.008</td><td>2.119$\pm$0.010</td><td>2.138$\pm$0.010</td></tr><tr><td>GSK</td><td>2.148$\pm$0.011</td><td>2.159$\pm$0.013</td><td>2.185$\pm$0.014</td></tr><tr><td>CASP</td><td>1.920$\pm$0.04</td><td>1.965$\pm$0.10</td><td>2.018$\pm$0.04</td></tr><tr><td>PKA</td><td>2.070$\pm$0.010</td><td>2.050$\pm$0.008</td><td>2.055$\pm$0.010</td></tr></table>	Target	Docking Score (kcal/mol)	MMGBSA (kcal/mol)	BACE1	~9.33	~40.60	GSK-3 β	~8.14	~50.80	Caspase-3	~7.92	~46.69	PKA	~9.67	~49.14	RMSD (nm)	APO	LAS	Control	BACE1	0.133 $\pm$ 0.017	0.141 $\pm$ 0.021	0.132 $\pm$ 0.021	GSK	0.416 $\pm$ 0.059	0.303 $\pm$ 0.056	0.275 $\pm$ 0.036	CASP	0.822 $\pm$ 0.101	1.068 $\pm$ 0.198	0.782 $\pm$ 0.107	PKA	0.218 $\pm$ 0.033	0.175 $\pm$ 0.024	0.173 $\pm$ 0.026	RMSF (nm)	APO	LAS	Control	BACE1	0.075 $\pm$ 0.036	0.079 $\pm$ 0.044	0.079 $\pm$ 0.039	GSK	0.114 $\pm$ 0.081	0.136 $\pm$ 0.079	0.0126 $\pm$ 0.089	CASP	0.171 $\pm$ 0.194	0.312 $\pm$ 0.331	0.234 $\pm$ 0.221	PKA	0.090 $\pm$ 0.043	0.084 $\pm$ 0.042	0.098 $\pm$ 0.036	Rg (nm)	APO	LAS	Control	BACE1	2.122 $\pm$ 0.008	2.119 $\pm$ 0.010	2.138 $\pm$ 0.010	GSK	2.148 $\pm$ 0.011	2.159 $\pm$ 0.013	2.185 $\pm$ 0.014	CASP	1.920 $\pm$ 0.04	1.965 $\pm$ 0.10	2.018 $\pm$ 0.04	PKA	2.070 $\pm$ 0.010	2.050 $\pm$ 0.008	2.055 $\pm$ 0.010	LAS512463592 was identified as a promising multi-target directed ligand against four key Alzheimer's disease proteins. Docking and MMGBSA analyses demonstrated favorable binding affinity across BACE1, GSK-3β, PKA, and Caspase-3. Molecular dynamics simulations confirmed stable protein-ligand complexes with minimal conformational fluctuations. These findings support LAS512463592 as a potential disease-modifying candidate for Alzheimer's disease. Experimental <i>in-vitro</i> and <i>in-vivo</i> validation is warranted.	Alzheimer's Association. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid-β pathway in Alzheimer's disease. Nat Rev Drug Discov. 2021;20(8):630–656. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J Med Chem. 2004;47(7):1739–1749. Abraham MJ, Murtola T, Schulz R, Páll S, Smith JC, Hess B, Lindahl E. GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX. 2015;1–2:19–25.
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