

Repurposing Of Dual-target Ligands For Acetylcholinesterase And $\alpha 7$ Nicotinic Receptors In Alzheimer's Disease

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Metixene and Piperidolate are promising dual-target leads for AD, with Mettixene showing superior dual-target balance and BBB penetration compared to Donepezil.

INTRODUCTION

- **Alzheimer's disease (AD)** is a multifactorial neurodegenerative disorder driven by cholinergic dysfunction.
- Current FDA-approved acetylcholinesterase (AChE) inhibitors provide only symptomatic benefit and suffer from dose-dependent adverse effects.
- **The Solution:** Dual targeting of AChE and the pro-cognitive $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) enables broader, more balanced cholinergic engagement.

METHODS

Step 1

Step 1: Target Preparation

- Retrieved high-resolution crystal structures for AChE (PDB ID: 4EY7) and $\alpha 7$ nAChR (PDB ID: 4F9W). Binding sites predicted via CB-Dock2.

Step 2

Step 2: Ligand Repurposing

- Identified 15 donepezil analogues via SwissSimilarity using E3FP-based searches of ChEMBL approved drugs.

Step 3

Step 3: Docking & Profiling Pipeline

- Prepared proteins (water removal, Kollman charges, PDBQT format via AutoDockTools-1.5.7). Energy-minimized via Avogadro and docked using AutoDock Vina. Binding interactions visualized in Discovery Studio; ADME properties assessed via ADMETlab 2.0.

RESULTS

Dual-Target & Toxicity Comparison Matrix

Compound	AChE ΔG	$\alpha 7$ nAChR ΔG	Key Notes
Donepezil (Reference)	-12.1	-7.7	Heavily skewed toward AChE.
Metixene (Top Candidate)	-10.5	-10.5	Perfect dual-target balance. Highest BBB penetration (0.995).
Piperidolate (Top Candidate)	-10.0	-9.7	Minimal hepatotoxicity (0.052) and acute toxicity (0.023).

Molecular Interaction Mapping

AChE

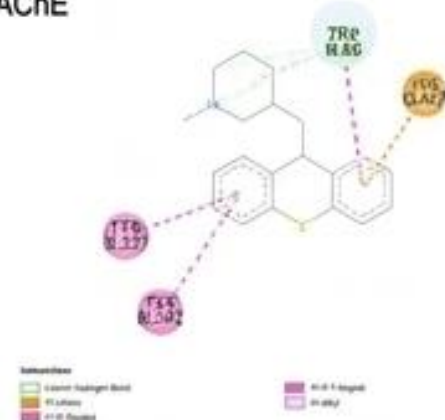


Figure 1. Metixene in AChE pocket. Stabilized by aromatic and hydrogen-bond interactions.

$\alpha 7$ nAChR

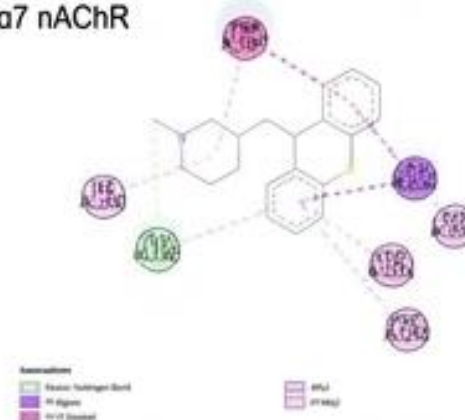


Figure 2. Metixene in $\alpha 7$ nAChR pocket. Demonstrates superior structural balance compared to Donepezil.

Insight: Piperidolate also showed strong engagement, binding via aromatic, Pi-Cation, Pi-Sigma, and hydrophobic contacts, offering a safer toxicity profile alternative. Both compounds outperform Donepezil in achieving dual-target activity with favorable pharmacokinetic profiles.

CONCLUSIONS

- **Metixene and Piperidolate** emerge as highly promising dual-target leads for AD through balanced engagement of AChE and $\alpha 7$ nAChR.
- **Metixene** offers the most balanced engagement and BBB penetration, whereas Piperidolate provides a safer toxicity profile.
- This in-silico roadmap successfully demonstrates how structure-based repurposing prioritizes multi-target ligands.
- **Next Steps:** Future in vitro and in vivo validation is required for broader application and clinical translation.