Exploring Eseroline's Binding Affinity to BACE1 via Computational Docking for Alzheimer's Disease Therapeutic Potential

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Abstract

This poster investigates the binding interaction of Eseroline with BACE1, a key enzyme in Alzheimer's disease pathology. Molecular docking revealed a moderate binding affinity (−4.79 kcal/mol), with eseroline forming hydrogen bonds and hydrophobic interactions with critical active site residues, including ASP259, LYS256, ARG43P, and SER182. The ligand occupied a deep, hydrophobic cleft, indicating stable and specific binding. These findings provide preliminary computational evidence supporting eseroline's potential as a BACE1 inhibitor, warranting further in vitro and in vivo validation for therapeutic application in Alzheimer's disease. **Keywords**: Alzheimer's Disease, BACE1, Ligand Docking, Eseroline, AutoDock 4

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the **accumulation of amyloid-beta (Aβ) plaques in the brain.**

A key contributor to Aβ formation is **β-site amyloid precursor protein cleaving enzyme 1 (BACE1).** This enzyme initiates the amyloidogenic pathway and is therefore a major therapeutic target.

This study explores the potential of **eseroline**, a metabolite of eserine, as a BACE1 inhibitor using **in silico docking techniques**. Identifying novel ligands that effectively bind and inhibit BACE1 could pave the way for future AD treatments.

Methodology

🧬 **Protein Preparation (BACE1 – PDB ID: 1FKN)**
Removed water molecules
↓
Added polar hydrogens
↓
Assigned Gasteiger partial charges

🧪 **Ligand Preparation (Eseroline):**
Retrieved eseroline structure from Pubchem
↓
Performed energy minimization in Pyrx
↓
Converted to PDBQT format

⚙️ **Docking Procedure (AutoDock 4):**
Defined grid box around the BACE1 active site
↓
Applied Lamarckian Genetic Algorithm
↓
Explored multiple conformations

🧠 **Analysis:**
Calculated binding energy (kcal/mol)
↓
Identified key molecular interactions: hydrogen bonding and hydrophobic contacts
↓
Visualized binding site using BIOVIA Discovery Studio

Objective

To evaluate **eseroline's binding potential to BACE1** using molecular docking approaches and determine its viability as an inhibitor for Alzheimer's therapy.

Results

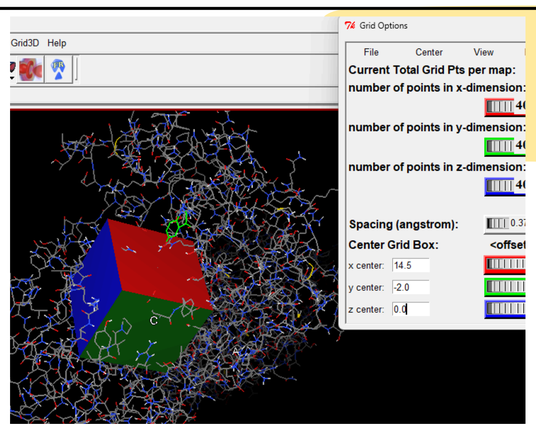


Fig 1: Showing Grid Box Setup

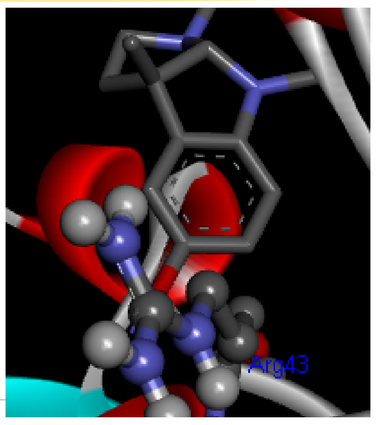


Fig 2: Showing Binding of Eseroline(ligand) to BACE1(receptor) at ARG43P of chain A

RMSD TABLE

Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD	Reference RMSD	Grep Pattern
1	1	6	-4.79	0.00	37.49	RANKING
1	2	8	-4.79	0.02	37.49	RANKING
1	3	10	-4.79	0.03	37.48	RANKING
1	1	5	-4.79	0.02	37.48	RANKING
1	5	1	-4.79	0.01	37.49	RANKING
1	6	2	-4.79	0.05	37.46	RANKING
1	7	4	-4.78	0.02	37.48	RANKING
1	8	3	-4.78	0.04	37.46	RANKING
1	9	7	-4.78	0.02	37.48	RANKING
1	10	9	-4.78	0.05	37.45	RANKING

Fig 4: RMSD chart for showing parameters of various docked poses

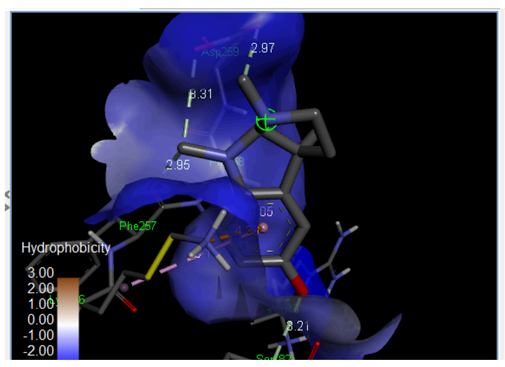


Fig 5: Showing Hydrophobic Interactions

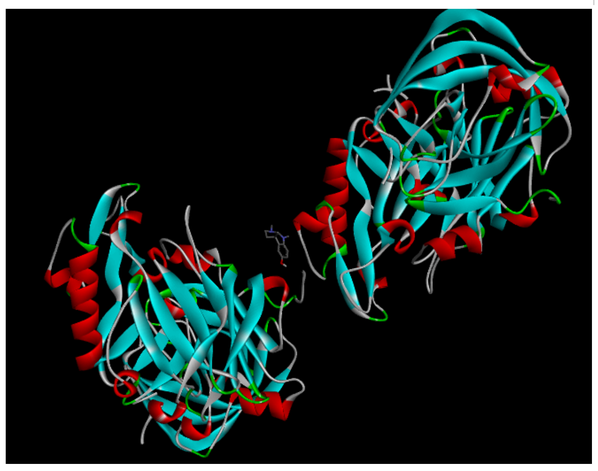
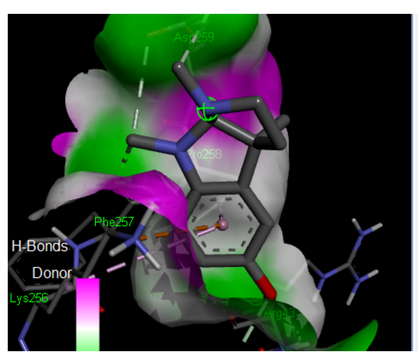


Fig 3: Showing BACE1 - Eseroline Complex



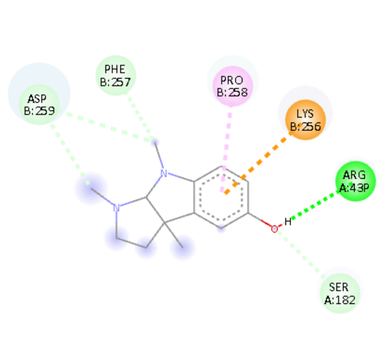


Fig 6: Showing H- bond Interactions

Discussion

- Eseroline showed **moderate binding affinity** to BACE1 (**−4.79 kcal/mol**).
- Formed key **hydrogen bonds** with **ASP259, LYS256, ARG43P, and SER182**.
- Engaged in **hydrophobic contacts** with **LYS256, ARG43P, SER182, and PHE257.**
- Occupied a hydrophobic binding cleft with low solvent accessibility, indicating deep and stable binding.
- Binding pose suggests **potential to inhibit BACE1 activity** by **blocking the active site.**
- Provides **preliminary computational evidence** for eseroline as a BACE1 inhibitor.
- Further in vitro and in vivo studies are needed to validate its therapeutic role in Alzheimer's disease.

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