Repurposing the Androgen Receptor Agonist Fluoxymesterone for Alzheimer's Disease via NMDA Receptor Inhibition: A Morgan Fingerprinting and Molecular Docking Approach

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***Abstract*—Glutamate-induced excitotoxicity through overactivation of the NMDA receptor is frequently the cause of Alzheimer's disease (AD), a progressive neurodegenerative illness characterised by cognitive decline and neuronal death. Because memantine, an NMDA receptor antagonist, has limited effectiveness, stronger substitutes are being sought after. In order to find FDA-approved medications with possible NMDA receptor inhibitory activity, this study used a drug repurposing strategy that combined structure-based molecular docking with ligand-based screening using Morgan fingerprinting. The lead compound, memantine, directed the selection of structurally comparable candidates from a database that was carefully curated. Out of the 20 medications that made the short list, the steroidal androgen receptor agonist fluoxymesterone showed the highest binding affinity (–8.0 kcal/mol) to the NMDA receptor at pocket C1, outperforming memantine (–5.1 kcal/mol). The NMDA receptor structure's suitability for docking studies was validated (PDB ID: 5IPQ). Fluoxymesterone has good pharmacokinetic qualities, such as high gastrointestinal absorption, blood-brain barrier permeability, and adherence to Lipinski's and other drug-likeness rules, according to ADME and drug-likeness analysis conducted using SwissADME. According to these results, fluoxymesterone may have off-target neuroprotective effects by inhibiting NMDA receptors and has potential as a repurposed AD treatment candidate. The potential of computational repurposing techniques to speed up drug discovery for complicated neurological disorders is highlighted by this study.**

***Index Terms*—Alzheimer's Disease,Drug Repurposing,NMDA Receptor Inhibition, Fluoxymesterone, Molecular Docking.**

I. INTRODUCTION

Memory, cognition, and behaviour all deteriorate with Alzheimer's disease (AD), a progressive neurodegenerative illness that ultimately results in death and total loss of independence [1-2]. Given rising life expectancy and a rapidly ageing population, it is the most prevalent cause of dementia and presents a significant global health concern. Despite continuous research, there are currently few and mostly symptomatic treatment options for AD that only provide short-term respite without stopping or reversing the course of the disease.

Glutamate-induced excitotoxicity is one of the key processes linked to the pathophysiology of Alzheimer's disease (AD)[3]. When the N-methyl-D-aspartate (NMDA) receptor is overactivated, oxidative stress, mitochondrial dysfunction, prolonged calcium influx, and neuronal apoptosis occur [4-5]. As a result, targeting the NMDA receptor has become a sensible therapeutic strategy to safeguard neurones and maintain cognitive function[6]. One of the few

medications authorised for the treatment of moderate to severe AD is memantine, a non-competitive NMDA receptor antagonist[7-8]. There is a need for stronger substitutes because of its limited clinical effectiveness and low binding affinity to the NMDA receptor[9–10].

One promising approach to meeting this unmet need is drug repurposing[11]. Repurposing can drastically cut down on the time, expense, and risk involved in traditional drug development by finding new therapeutic uses for already-approved FDA medications[12]. Based on structural similarity and predicted binding affinity to known targets, computational methods like structure-based molecular docking and ligand-based virtual screening have emerged as potent tools for finding possible drug candidates[13].

Morgan fingerprinting, a popular algorithm for assessing molecular similarity, was used in this study to screen a database of approved medications using memantine as a lead compound. Using molecular docking simulations against the NMDA receptor, a total of 20 structurally related compounds were found and further assessed. With a greater binding affinity to the NMDA receptor than memantine, fluoxymesterone—a steroidal androgen receptor agonist mainly used in hormone therapy—rose to prominence among these. Fluoxymesterone may more successfully inhibit NMDA receptor activity, according to the docking analysis, which showed stable interactions between the hormone and important residues in the receptor's active site.

These findings indicate that fluoxymesterone holds potential as a repurposed therapeutic agent for AD by targeting the glutamatergic excitotoxic pathway. In addition to its primary use in oncology and endocrinology, this compound may offer neuroprotective effects through NMDA receptor modulation. This study further highlights the value of computational drug repurposing methodologies in identifying novel treatment strategies for complex neurological disorders such as Alzheimer’s disease.

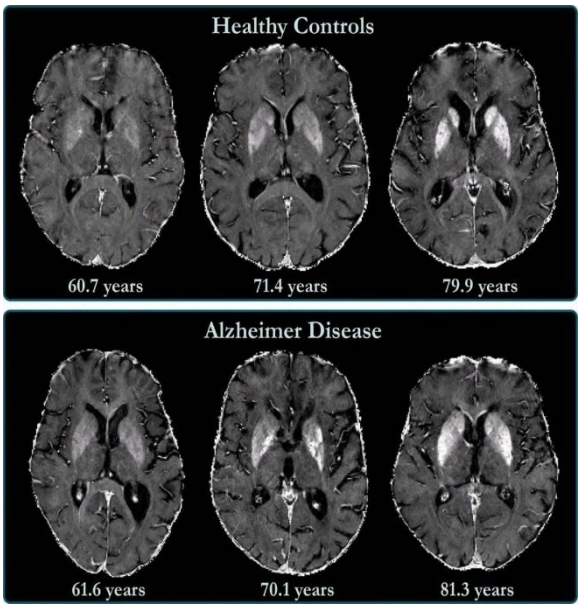

Figure 1: Neuroimaging Comparison of Alzheimer's and Healthy Brains by Age Group

II. MATERIALS AND METHODS

Disease Selection: Alzheimer’s Disease (AD)

Alzheimer's disease (AD), a progressive neurodegenerative illness marked by behavioural abnormalities, memory loss, and cognitive decline, was the subject of this study [14]. Excitotoxicity, which results in calcium overload, oxidative stress, and neuronal death, is a hallmark of AD pathophysiology. It is brought on by excessive glutamatergic signalling through overactivation of the N-Methyl-D-Aspartate (NMDA) receptor[15–16]. Alzheimer's disease is a suitable candidate for structure-based drug repurposing initiatives that target the NMDA receptor because of the receptor's central role in the progression of the disease and the availability of currently available NMDA antagonists[17–18].

Target Preparation:

Because of its high-resolution structure and connection to glutamatergic signalling in Alzheimer's disease, the human NMDA receptor—more especially, its ligand-binding domain—was selected as the study's target protein and was acquired from the Protein Data Bank (PDB ID: 5IPQ)[19–20]. To ensure an accurate simulation of physiological interactions, the receptor structure was prepared using standard procedures prior to docking, such as assigning Gasteiger charges, adding polar hydrogen atoms, and removing

crystallographic water molecules[21–22]. OpenBabel was used for energy minimisation in order to optimise the geometry and alleviate steric clashes. After that, the receptor was transformed into a PDBQT format that AutoDock Vina could use. Using CB-Dock2, which recognised and ranked five possible cavities (C1–C5) according to pocket volume and shape, binding site prediction was performed. These binding sites have been optimised. The docking targets for assessing the interaction of the ligand candidates that made the short list were these optimised binding sites.

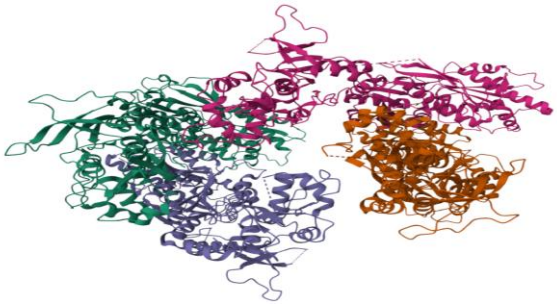

Figure2: Human NMDA receptor (PDB ID: 5IPQ) Validation of Human NMDA receptor (PDB ID: 5IPQ) [via RCSB PDB]

Overall quality at a glance

The following experimental techniques were used to determine the structure:

III. ELECTRON MICROSCOPY

This entry's reported resolution is 13.50 Å. The following graphic displays the percentile scores (which range from 0 to 100) for the entry's global validation metrics. The table shows the number of entries on which the scores are based.

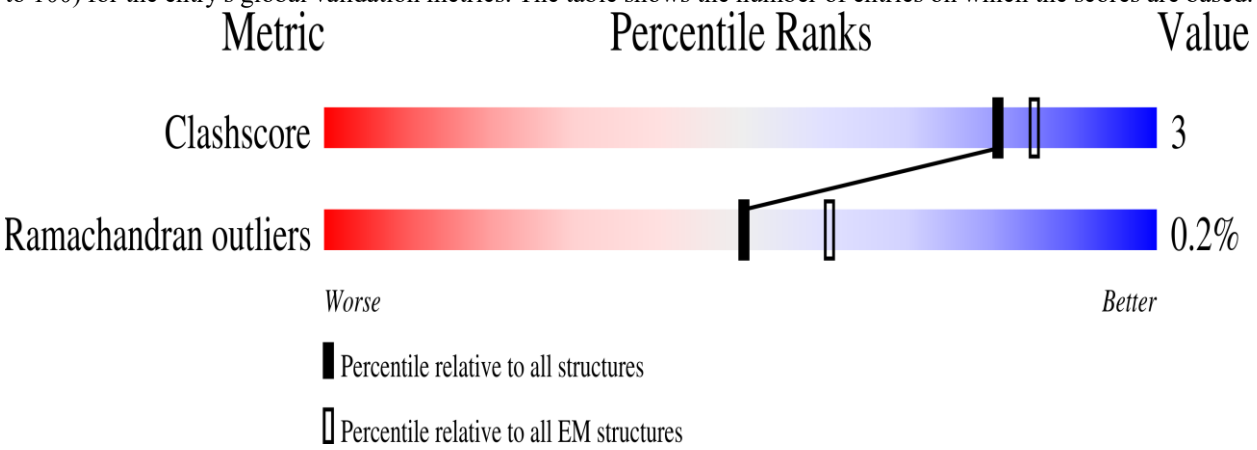

Figure3: Model Validation Metrics Overview

Table 1:Number of Structures Assessed for Each Validation Metric in the Whole Archive and EM Subset

Metric	Whole archive (#Entries)	EM structures (#Entries)
Clashscore	158937	4297
Ramachandran outliers	154571	4023

The geometric problems found in the polymeric chains and how well they fit the map are summarised in the table below. The percentage of residues with outliers for the >=3, 2, 1, and 0 types of geometric quality criteria is shown by the red, orange, yellow, and green segments of the bar, respectively. The percentage of residues that are not modelled is shown by a grey segment. Each fraction's numerical value is displayed beneath the corresponding segment; fractions less than 5% are represented by a dot. The percentage of residues with poor fit to the EM map (all-atom inclusion 40%) is shown by the upper red bar, if it exists. Above the bar is the numerical value.

Table2:Per-Chain Assessment of Model Quality

Mol	Chain	Length	Quality of chain
1	A	822	8% 78% 20%
1	C	822	9% 75% 24%
2	B	825	18% 74% 23%
2	D	825	13% 73% 24%

Map analysis:

This section contains the results of statistical analysis of the map.

Map-value distribution

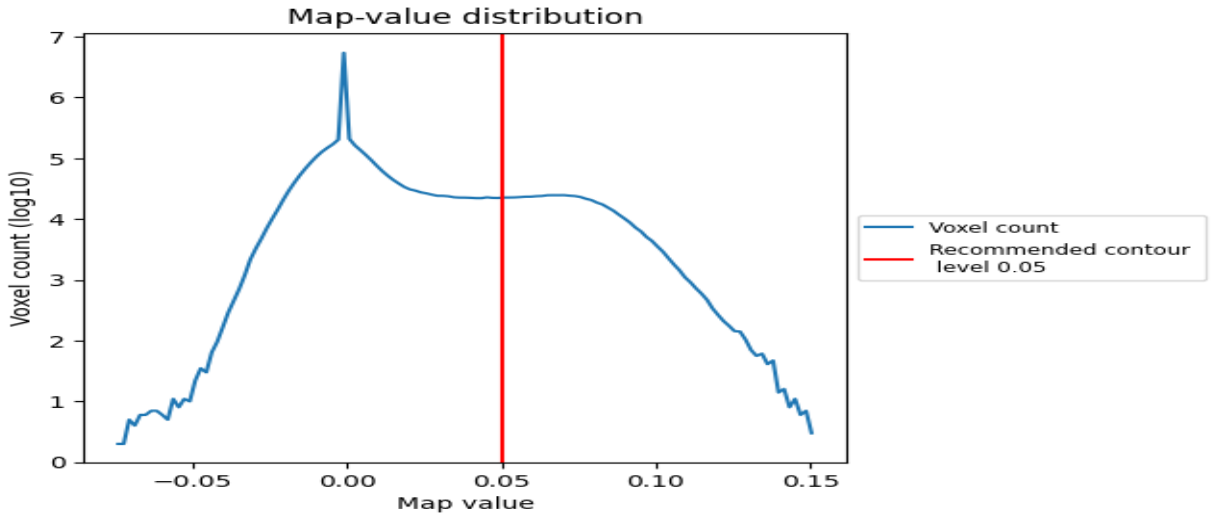

Figure 4:Map-value distribution

Along the x-axis, the map-value distribution is plotted at intervals of 128. The logarithmic y-axis is used. The volume has typically been masked when there is a spike in this graph at zero.

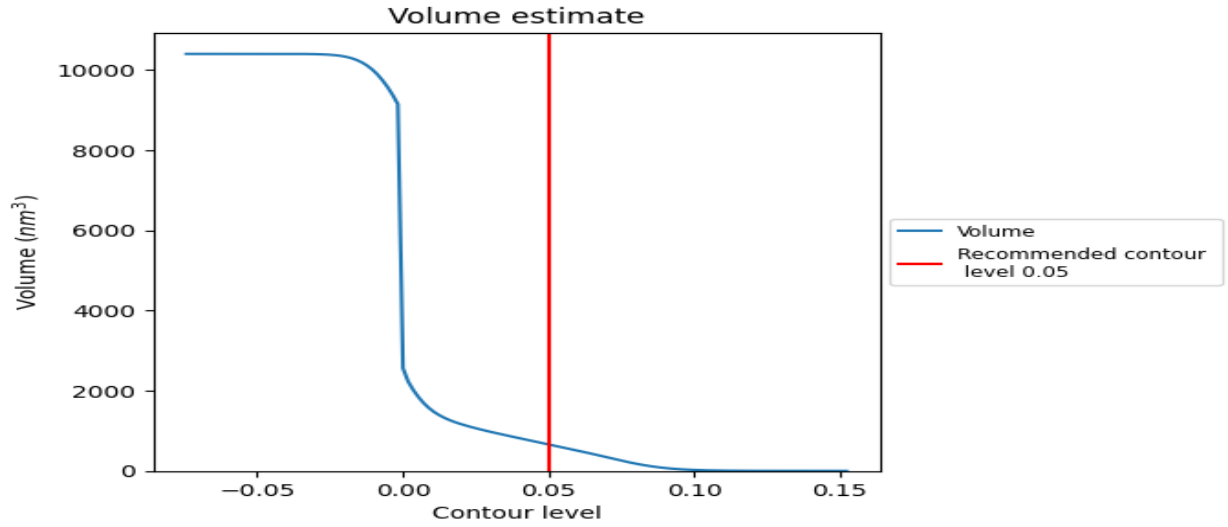

Figure 5: Volume Estimate

At the suggested contour level, the volume is 662 nm3, which is equivalent to a mass of about 598 kDa. The enclosed volume's variation with the contour level is depicted in the volume estimate graph. The volume of the enclosed surface at the recommended contour level is indicated by the intersection of the line and the curve, which is represented by a vertical line.

Map-model fit:

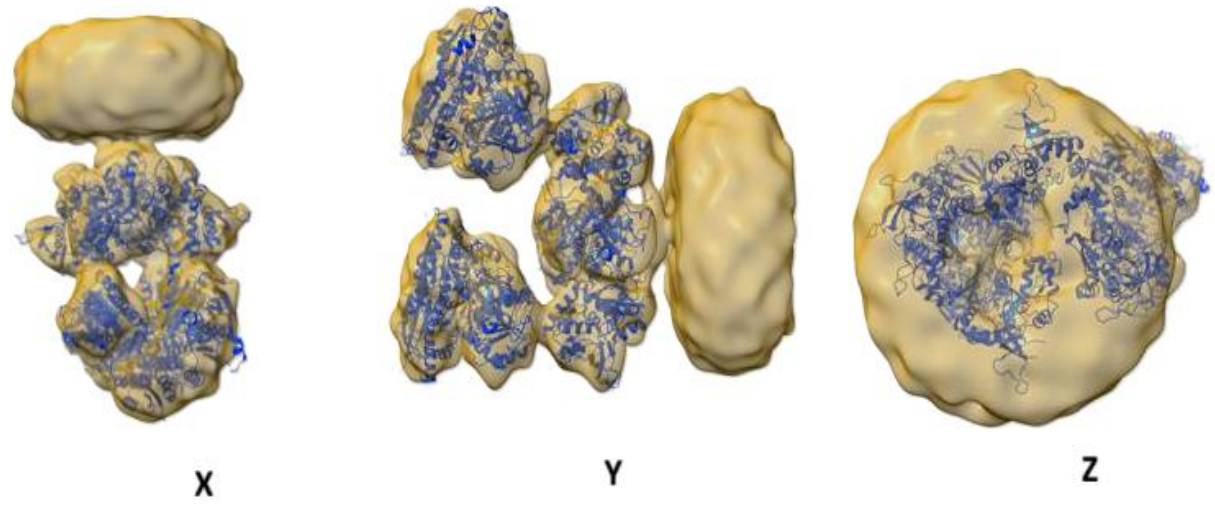

Figure 6: Map-model overlay

The 3D surface view of the map at the suggested contour level of 0.05 at 50% transparency is depicted in the images above in yellow, with a blue ribbon representing the model superimposed. The quality of fit between the map and the atomic model can be visually evaluated thanks to these pictures.

Selection of FDA-Approved Lead Compound: Memantine

Moderate-to-severe Alzheimer's disease can now be treated with memantine, a low-affinity uncompetitive NMDA receptor antagonist. By blocking prolonged calcium influx via the NMDA receptor, it modifies glutamatergic signalling and lowers neuronal excitotoxicity[23–24]. Memantine was chosen as the reference compound for ligand-based virtual screening because of its established safety profile, known structural data, and clinically validated mechanism. During Morgan fingerprinting, similarity comparisons were based on its molecular structure ($C_{12}H_{21}N$).

Ligand-Based Drug Repurposing via Morgan Fingerprinting

Morgan fingerprinting, a cheminformatics technique that encodes molecular structures by analysing circular atom environments within a specified radius, was used for ligand-based virtual screening[25]. To find structurally similar FDA-approved compounds, memantine was employed as the query ligand. Compounds were ranked according to their structural overlap with Memantine using Tanimoto similarity scoring based on fingerprints. This method was used to screen a custom database of FDA-approved medications. Higher similarity score compounds were taken into account for further examination. A final list of 19 structurally similar candidate molecules, including fluoxymesterone, saxagliptin, vildagliptin, and others, was produced by applying a threshold Tanimoto coefficient of 0.15. In order to assess these hits' capacity to bind to the NMDA receptor, they were selected for docking simulations.

Molecular Docking Studies

To forecast how identified compounds would interact with the NMDA receptor, structure-based docking simulations were used. The Protein Data Bank provided the human NMDA receptor structure (PDB ID: 5IPQ), which was chosen due to its high-resolution structure and connection to glutamate binding. To get the receptor ready for docking, polar hydrogens were added and water molecules were eliminated. CB-Dock2, a cavity-detection-guided docking tool based on AutoDock Vina, was used to carry out molecular docking. Five high-probability binding pockets are automatically identified by CB-Dock2, which then ranks them according to pocket volume and binding free energy. Every ligand was docked into the NMDA receptor's five anticipated cavities.

Receptor-ligand interactions were simulated using Vina's default scoring functions, and docking grid boxes were dynamically created using pocket centre coordinates.

Memantine, which acted as the benchmark reference and had a Vina binding score of -5.4 kcal/mol, was compared to each compound's docking scores (in kcal/mol). Significantly higher binding affinities of –8.0 kcal/mol were demonstrated by fluoxymesterone, indicating possible therapeutic relevance.

Data Analysis

Two primary criteria were used to rank the shortlisted compounds: (1) their docking scores with the NMDA receptor and (2) their Morgan fingerprint Tanimoto similarity score to memantine. The hits with the strongest predicted binding affinity and the highest structural similarity were the most promising. Hydrogen bonds, hydrophobic interactions, and important binding residues were identified by visualising protein-ligand interactions with Pymol and Discovery Studio.

The cavity that produced the most advantageous binding energy for each ligand was identified by analysing pocket-specific interaction maps. CB-Dock output was used to extract additional information about atomic contact residues, cavity volume, and docking grid dimensions.

Statistical Methods and Visualization

All compounds' docking affinities and similarity scores were compiled using descriptive statistics. To evaluate binding improvements, a comparison between Memantine and the best-performing candidates was done. Matplotlib and Seaborn were utilised to visualise data trends and interaction plots, while Python-based libraries like RDKit were utilised to generate molecular fingerprints.

Tanimoto similarity scores and docking scores were correlated using scatterplots, and hit compounds were indicated for additional verification. High-affinity interactions that required experimental follow-up were defined as having binding scores less than -7.0 kcal/mol.

IV. RESULTS AND DISCUSSION

Results of Ligand-Based Drug Repurposing

In the context of Alzheimer's disease (AD), memantine and fluoxymesterone were chosen as potential ligands for NMDA receptor modulation. With a well-established pharmacological benchmark and a well-documented safety and efficacy profile, memantine is an FDA-approved drug used to treat moderate-to-severe AD. Despite being mainly approved for hormonal disorders, fluoxymesterone's surprisingly high docking affinity for the NMDA receptor active site made it a viable candidate for repurposing. Memantine reduces excitotoxic calcium influx, a significant pathological hallmark in the development of AD, by acting as a non-competitive antagonist of the NMDA receptor. Interestingly, fluoxymesterone, which is typically thought of as an androgen receptor agonist, also showed strong binding interactions within the NMDA receptor, according to molecular docking studies. This suggests that fluoxymesterone may have off-target neuroprotective effects.

Both substances have a wealth of toxicological and pharmacological evidence, which supports their quick translational potential. Amantadine and memantine are structurally similar, which confirms the scaffold's adaptability for optimisation. Because of its steroidal structure, fluoxymesterone makes it possible to create neuroactive steroid derivatives that may selectively alter NMDA receptor activity while minimising hormonal side effects. Regarding the disease's relevance, memantine directly disrupts NMDA receptor-mediated excitotoxicity, which is a key mechanism of AD neuronal damage. Because of its predicted NMDA interaction, fluoxymesterone may indirectly modulate similar pathways, providing a new avenue for intervention.Their safety profiles further support their therapeutic viability; while the side effects of fluoxymesterone, despite being androgenic, are controllable and can be lessened by changing the chemical composition or dosage, memantine is well tolerated in older populations. In the end, this dual-ligand strategy offers chances for the creation of innovative treatments. While fluoxymesterone provides an unusual but promising scaffold for drug discovery in neurodegenerative contexts, derivatives based on memantine may increase efficacy and lessen cognitive decline. These results collectively lend credence to additional research on both molecules as part of a larger approach to Alzheimer's disease medication repurposing.

Results of Ligand-Based Screening using the DrugRep platform:

Table 3: Compounds and their structure similarity scores

Sr.No	Compound ID	Name	Score	Sr.No	Compound ID	Name	Score
1	DB01043	Memantine	1.000	11	DB06335	Saxagliptin	0.174
2	DB00915	Amantadine	0.308	12	DB00657	Mecamylamine	0.172
3	DB00478	Rimantadine	0.237	13	DB06710	Methyltestosterone	0.169
4	DB14156	Synthetic camphor	0.182	14	DB00621	Oxandrolone	0.169
5	DB01744	Camphor	0.182	15	DB01000	Cyclacillin	0.167
6	DB13288	Tromantadine	0.177	16	DB04876	Vildagliptin	0.165
7	DB01185	Fluoxymesterone	0.174	17	DB09091	Tixocortol	0.163
8	DB00741	Hydrocortisone	0.163	18	DB13146	Fluciclovine (18F)	0.160
9	DB00687	Fludrocortisone	0.160	19	DB06412	Oxymetholone	0.159
10	DB01708	Prasterone	0.159	20	DB00624	Testosterone	0.159

Docking results:

Table 4: Binding Affinity Analysis of DrugBank Compounds to Target Pockets: Identification of Potential Drug Candidate

Sr.no	Compound Name	CurPocket (Best)	Best Vina Score	Sr no.	Compound Name	CurPocket (Best)	Best Vina Score
1	Memantine	C5	-5.1	11	Oxandrolone	C1	-7.4
2	Amantadine	C5	-4.3	12	Cyclacillin	C1	-7.0
3	Rimantadine	C5	-5.0	13	Vildagliptin	C1	-7.7
4	Synthetic camphor	C3 / C5	-4.4	14	Tixocortol	C1 / C2	-7.4
5	Camphor	C3 / C5	-4.4	15	Hydrocortisone	C1	-7.7
6	Tromantadine	C2 / C5	-5.8	16	Fluciclovine (18F)	C1	-4.3
7	Fluoxymesterone	C1	-8.0	17	Fludrocortisone	C1	-7.7
8	Saxagliptin	C5	-7.7	18	Oxymetholone	C1	-7.7
9	Mecamylamine	C5	-4.4	19	Prasterone	C1	-7.1
10	Methyltestosterone	C1 / C2 / C3	-7.2	20	Testosterone	C1	-7.4

The docking study identified Fluoxymesterone, Saxagliptin, and Hydrocortisone as top candidates with strong binding affinities to pocket C1 and C5, each exhibiting Vina scores of -7.7 or lower, indicating high binding potential and hence repurposing potential. Tromantadine's dual-site interaction ability was further demonstrated by its favourable binding in pockets C2 and C5, which had a moderate score of -5.8.

In pocket C1, compounds like methyltestosterone, vildagliptin, and fludrocortisone also showed encouraging binding profiles. Vina scores for these compounds ranged from -7.2 to -7.7, indicating moderate to strong interactions. Smaller molecules such as memantine, rimantadine, and camphor, on the other hand, exhibited comparatively weaker binding in pocket C5, indicating limited potential for repurposing unless altered or used in combination.

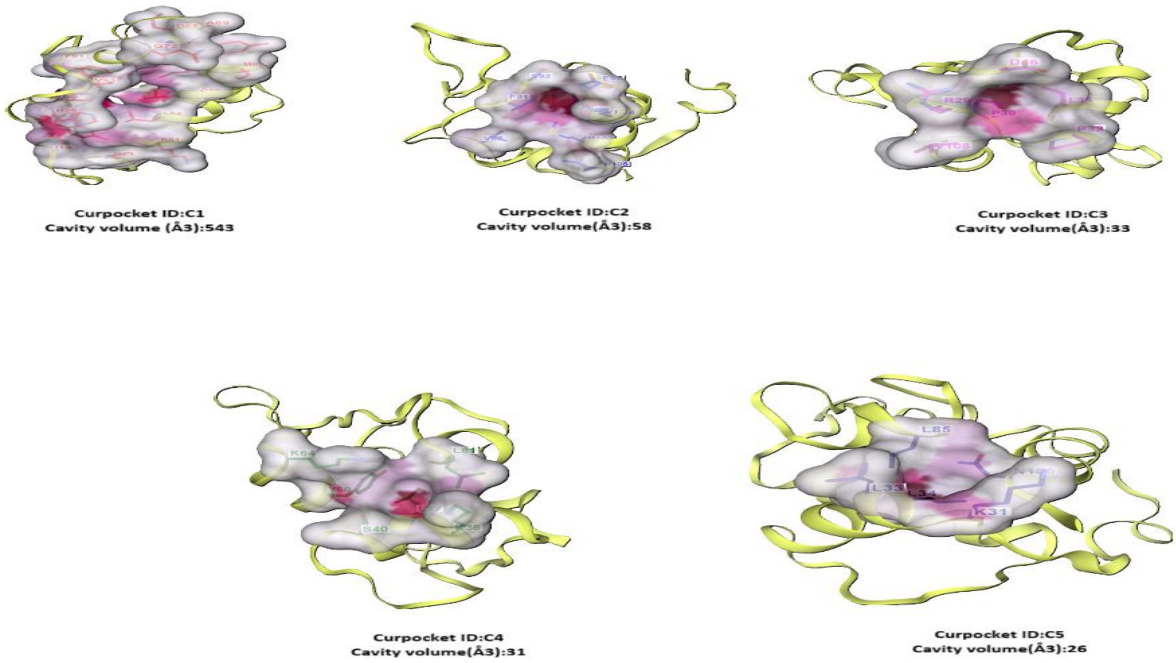

Figure 7: Visualization of five binding pockets (Cur Pocket IDs C1–C5) on the target protein

Memantine and its analogues' binding efficiency can be investigated, and their repurposing for Alzheimer's disease (AD) can be optimised through better drug-target interactions. Figure 3 displays five distinct CurPocket binding sites with different cavity volumes, ranging from 543Å³ to 26 Å³.

Pharmacokinetic Evaluation of Irinotecan

ADME and drug likeness of Fluoxymesteron:

Table 5 : Predicted ADME and Drug – Likeness Properties of Fluoxymesteron (via SwissADME)

Category	Parameter	Value
Physicochemical	Molecular Formula	C20H29FO3
	Molecular Weight	336.44 g/mol
	TPSA	57.53 Å²
	H-bond Acceptors / Donors	4/2
	Rotatable Bonds	0
	Molar Refractivity	91.45
	Fraction Csp³	0.85
Lipophilicity (Log P)	iLOGP / XLOGP3 / Consensus	2.62/2.13/3.02
Water Solubility	Log S (ESOL / SILICOS-IT)	–3.27/3.55
	Solubility Class	Soluble
Pharmacokinetics	GI Absorption	High
	BBB Permeation	Yes
	P-gp Substrate	Yes
	CYP Inhibition (1A2,2C19,2C9,2D6,3A4)	No

	Skin Permeation (Log Kp)	–6.84cm/s
Drug-Likeness	Lipinski / Ghose	Yes;0 violations
	Other Rules (Veber, Egan, etc.)	Passed
	Bioavailability Score	0.55
	PAINS / Brenk Alerts	0 / 0
	Lead-Likeness	Yes
	Synthetic Accessibility	5.09 (moderately difficult)

Fluoxymesterone is a synthetic androgen that is taken orally. Its molecular weight is 336.44 g/mol, and its molecular formula is C20H29FO3. Its structure is primarily rigid and lipophilic, as evidenced by its topological polar surface area (TPSA) of 57.53 Å², four hydrogen bond acceptors, two hydrogen bond donors, lack of rotatable bonds, and fraction of sp^3 carbons of 0.85. With iLOGP, XLOGP3, and consensus Log P values of 2.62, 2.13, and 3.02, respectively, it has a moderate level of lipophilicity, supporting effective membrane permeability. With Log S values of –3.27 (ESOL) and 3.55 (SILICOS-IT), fluoxymesterone is categorised as soluble in water and promotes good gastrointestinal absorption. Pharmacokinetically, it has a skin penetration log Kp of –6.84 cm/s, is a substrate for P-glycoprotein, has a high oral bioavailability, and crosses the blood-brain barrier without blocking the main CYP450 enzymes (1A2, 2C19, 2C9, 2D6, and 3A4). Fluoxymesterone is regarded as lead-like, has a moderate synthetic accessibility (5.09), a bioavailability score of 0.55, no PAINS or Brenk alerts, and zero violations of the Lipinski, Ghose, Veber, and Egan rules from the standpoint of drug-likeness. Overall, the ADME profile of fluoxymesterone shows good distribution, absorption, and drug-like properties appropriate for oral administration.

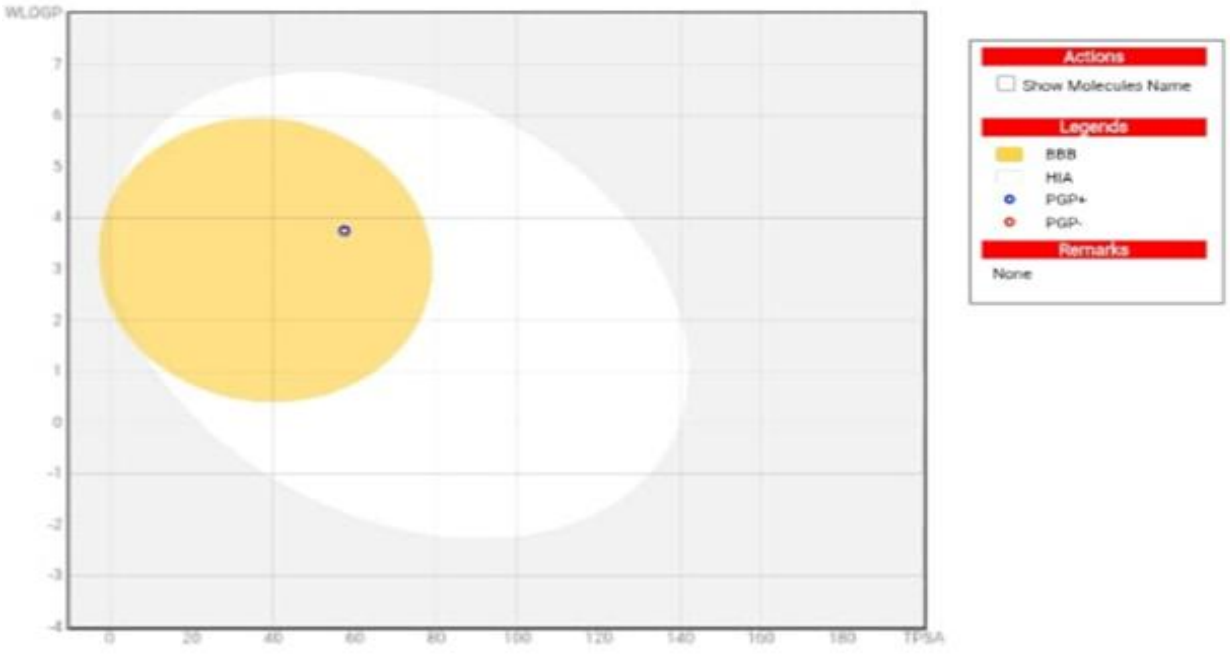

Figure 8: BOILED-Egg plot showing HIA and BBB permeability prediction for Fluoxymesterone

Fluoxymesterone's BOILED-Egg diagram shows that the molecule is located inside the yellow region (yolk), which indicates high gastrointestinal absorption, and inside the white region, which confirms that it can cross the blood–brain barrier (BBB). Fluoxymesterone exhibits good physicochemical characteristics for CNS penetration, with a molecular weight of 336.44 g/mol, a TPSA of 57.53 Å², and a consensus Log P of 2.62. Although its status as a P-glycoprotein substrate may affect the degree of brain exposure, these predictions imply that the drug is pharmacokinetically appropriate for disorders of the central nervous system, such as Alzheimer's disease, because it is oral bioavailable and BBB permeant.

V. CONCLUSION

This study investigated the possibility of using FDA-approved medications to treat Alzheimer's disease (AD) by focussing on the N-Methyl-D-Aspartate (NMDA) receptor, a key player in the neurodegenerative cascade linked to AD and a crucial mediator of glutamate-induced excitotoxicity. A ligand-based virtual screening method using Morgan fingerprinting was used to find structurally similar medications from a carefully curated database of FDA-approved compounds, with memantine—a well-known NMDA receptor antagonist—serving as the reference compound. Molecular docking simulations were then used to assess the binding affinities and interaction profiles within the active sites of the NMDA receptor. With a substantially higher binding affinity (–8.0 kcal/mol) than memantine (–5.1 kcal/mol), especially within the C1 binding pocket, fluoxymesterone—a steroidal androgen receptor agonist typically used in hormone therapy—rose to the top of the list of the 19 candidates that were found. Fluoxymesterone's stable and advantageous interactions with important NMDA receptor residues were validated by visualisation and interaction analysis, indicating that the substance may successfully block excessive glutamatergic activity and lessen neuronal damage.

Fluoxymesterone has positive drug-like characteristics, such as high gastrointestinal absorption, blood–brain barrier permeability, no significant CYP450 inhibition, and no infractions of significant drug-likeness rules, according to pharmacokinetic profiling using SwissADME (Lipinski, Ghose, Veber, Egan). Its suitability for neurological applications was further supported by its BOILED-Egg plot, which further demonstrated its capacity to penetrate the central nervous system. Despite being mainly prescribed for androgen-related disorders, fluoxymesterone's potent interaction with the NMDA receptor points to a potential off-target neuroprotective mechanism that may be used to treat AD. This repurposing opportunity not only increases a drug's therapeutic potential but also demonstrates the usefulness of integrated computational techniques, like structure-based docking and molecular fingerprinting, in speeding up the development of new uses for approved medications.

In conclusion, this study offers strong in silico support for the idea that fluoxymesterone could be a good option for AD treatment through NMDA receptor inhibition. To evaluate its effectiveness, safety, and mode of action in the context of neurodegeneration, these results call for additional experimental validation through in vitro and in vivo investigations. Finally, this work creates new opportunities for creative treatment approaches and reaffirms the strategic significance of drug repurposing in treating complex, multifactorial diseases like Alzheimer's.

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