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Computational Drug Repurposing to Develop Human EAAT2 Receptor Agonists as Newer Therapeutics for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is an incurable neurodegenerative disorder that requires innovative therapeutic strategies for addressing its underlying causes, rather than simply managing its symptoms. In this study, a computational drug repurposing approach was used to target the human excitatory amino acid transporter 2 (EAAT2), a key regulator of glutamate homeostasis whose dysfunction is implicated in Alzheimer's disease (AD). Molecular docking-based virtual screening of 2,892 FDA-approved drugs revealed metocurine as a promising EAAT2 receptor agonist with strong binding affinity and favorable interactions. Molecular dynamics (MD) simulations for 100 ns confirmed the stability of the metocurine-EAAT2 complex by maintaining hydrogen bonds, hydrophobic, and ionic interactions over time. Analyses of root-mean-square deviation (RMSD) and fluctuation (RMSF) supported the complex's structural thermodynamic stability and its conformational compatibility with itself. These results suggest that metocurine is a promising candidate for EAAT2-targeted therapy in AD, warranting further *in vitro* and *in vivo* studies to evaluate its therapeutic effectiveness and biological safety.

Keywords: drug repurposing; EAAT2; neurodegeneration; Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to significant deterioration of brain function, particularly affecting memory. It occurs worldwide and impacts millions of people, especially older people. The condition is characterized by a gradual decline in cognitive abilities, including memory loss, language difficulties, and poor judgment. Researchers have not found a single definitive cause of Alzheimer's disease. Instead, they believe it develops from a combination of genetic, environmental, and lifestyle factors. A key feature of the condition is the buildup of beta-amyloid protein in the brain, which triggers inflammation and forms sticky plaques. These plaques disrupt nerve signal transmission, contributing to the progression of Alzheimer's [1,2]. Brain cells die due to inflammation and plaques, leading to brain tissue shrinkage. Cognitive issues, such as language problems, decision-making difficulties, and personality changes, often begin with minor memory loss. As the disease progresses, individuals may have difficulty performing ADLs, such as washing and dressing [3,4]. As the disease advances, individuals with Alzheimer's may become entirely

dependent on their caregivers and unable to communicate with others. Alzheimer's disease, the most common form of dementia, accounts for approximately 60-80% of all dementia cases. According to the World Health Organization (WHO), around 50 million people worldwide are living with dementia, with Alzheimer's making up a significant portion of that number. The WHO predicts that by 2030, 82 million people will be affected, and by 2050, this number will reach 152 million. Analysts also project that by 2050, the global cost of dementia care will have tripled from its 2021 estimate of USD 1.3 trillion [5,6].

In terms of country and regional dominance, AD is most commonly found in high-income countries, with rates ranging from 5% to 7% among people aged 60 and older. However, low- and middle-income countries are projected to see an increase in the number by 2030. Alzheimer's disease affects women more than men, making up nearly two-thirds of those with the disease. This may partly be because women tend to live longer than men, but other biological and environmental factors could also play a role [5,7]. Early prevention and intervention are crucial for managing the global impact of Alzheimer's disease. However, currently, there is no cure for AD, although lifestyle changes like regular exercise and a healthy diet have been shown to reduce the risk of developing the disease. Additionally, those affected can benefit from symptom management and an improved quality of life through early detection and treatment.

Currently, no cure exists for this disease, but medications are available to help manage symptoms. Since no specific treatment options are yet available, there is a strong need to develop targeted and effective therapies for the prevention and treatment of this deadly disease. Continuing research to develop new therapies for this debilitating condition is essential.

EAAT2 is a protein that plays a key role in maintaining normal levels of the neurotransmitter glutamate in the brain. It is mainly found in glial cells called astrocytes, which surround neurons. In AD, the progressive loss of neurons results in declining cognitive function. Research indicates that there is a reduction in EAAT2 expression in the brains of Alzheimer's patients, leading to glutamate accumulation and an increased risk of neuronal damage [8–11]. It is believed that activation of inflammatory pathways in the brain, which can damage astrocytes and impair their ability to regulate glutamate levels, causes the loss of EAAT2 expression in Alzheimer's disease. This makes cognitive impairment and neuronal damage caused by Alzheimer's disease worse. Evidence from multiple studies suggests that increasing EAAT2 expression in the brain could be a potential treatment target for Alzheimer's disease [12–14]. This could be achieved by enhancing EAAT2 expression or by developing medications that act as agonists of the EAAT2 protein. To discover new treatments for Alzheimer's disease, this study employed a docking-based computational repurposing strategy to identify agonists for the human EAAT2 receptor.

2. Materials and Methods

2.1. Ligand library.

A library of 2892 FDA-approved drugs with diverse structural compositions was used in the current study [15–19]. The above-mentioned ligand library was procured from the Zinc is Not Commercial (ZINC) database. The downloaded ligand library is intended for computational screening against the human EAAT2 receptor, which is involved in neurodegeneration, to identify potential leads with potent binding affinity for the receptor [20–24].

2.2. Macromolecular target selection and preparation.

The excitatory amino-acid transporter-2 (EAAT2) receptor primarily mediates glutamate reuptake from the synaptic cleft, and its overexpression increases glutamate concentration in neurons, leading to a toxic effect and neurodegeneration [8,12]. Specifically, EAAT2 is actively involved in the glutamate reuptake within the neuronal synaptic clefts in the human brain. The upregulation of EAAT2 has been shown to decrease glutamate reuptake rate and reduce the risk of excitatory neurodegeneration [25–28]. Thus, EAAT2 is an important target for controlling glutamate concentration in the neurons. In an ongoing study, we are identifying a potent EAAT2 agonist to develop novel therapeutics for the treatment of neurodegenerative disorders such as Alzheimer's disease [29–31]. A three-dimensional model of the EAAT2 complexed with WAY-213613 (PDB ID: 7xr6) was obtained from the RCSB PDB database [32,33]. To create nascent receptor and ligand molecules for the docking study, the downloaded EAAT2 and the complexed ligand were deleted individually.

2.3. Molecular docking studies.

Autodock software version 4.2 was used for the molecular docking analysis. The nascent EAAT2 receptor was redocked with the isolated reference ligand WAY-213613. The Autodock software uses a Lamarckian Genetic Algorithm (LGA) to perform docking analysis, employing a population size of 150, 2.5 million energy evaluations, and 27,000 generations across 30 independent runs for each ligand. The docking protocol and parameters were validated by comparison of binding scores, structural alignment, and chemical interactions to confirm that the docking simulation accurately reproduced the binding mode observed in the reference bioactive complex [34–37]. The prepared plant-based ligand library was computationally screened against the human EAAT2 receptor by using validated docking parameters.

2.4. Molecular dynamics simulation.

Metacurine was selected for MD simulation based on its pharmacokinetic and safety profile properties, as shown in the docking data. A 100 ns MD simulation was performed using the Desmond module of the Schrodinger software after a macromolecular complex was created by EAAT2 and metocurine [38–40]. To construct an atomic model of these complexes, we first included explicit solvent molecules, neutralised the system, and then added the ions required to attain neutrality. The Desmond uses the OPLS_2005 force field, which is ideal for high-accuracy MD simulations of ligand-protein complexes. Steric conflicts and weak atomic bonds were relaxed using the steepest descent method to reduce the system's energy. The system was brought to equilibrium through the use of brief NPT (low-temperature, constant-pressure) simulations [41–45]. In addition to the limits imposed by the placement position, the temperature is gradually increased. This assists in the preparation process, which, in turn, ensures that the system is stable and equilibrated prior to the simulation [46–51]. To get the desired results, the system's energies, RMSD values, and atomic coordinates are considered during the 100 ns simulation. This sheds light on the complex's structural and functional stability across time, as well as its dynamics and behaviour.

3. Results and Discussion

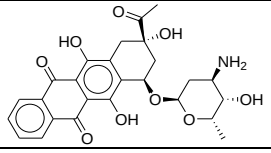
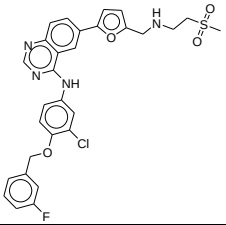
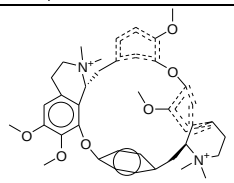
3.1. Macromolecular target selection and preparation.

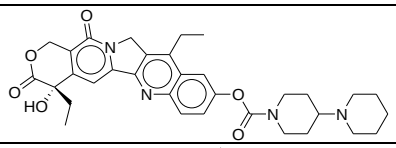
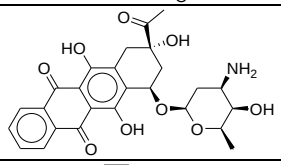
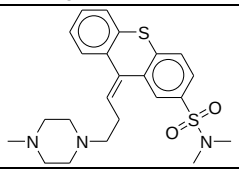
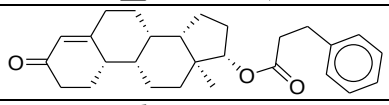
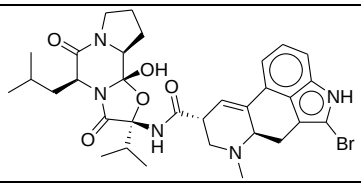
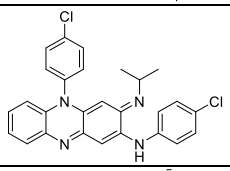
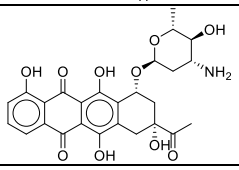
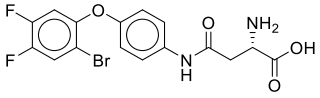
The structural model of the human EAAT2 receptor was revealed by electron microscopy technique at a resolution of 3.40 Å. The EAAT2 receptor has a trimeric chain consisting of 574 amino acids, out of which a single chain was procured by removing the remaining two chains. For the docking research, the bound ligand WAY-213613 is removed from the monomeric chain to obtain the nascent EAAT2 receptor.

3.2. Molecular docking studies.

The docking approach used in this study was confirmed by redocking the EAAT2 receptor structures with the reference ligand WAY-213613. The reference ligand was found to exhibit reversible binding with sufficient strength within the macromolecular active site, as revealed by the binding score falling within the range of -5 to -15 kcal/mol, which successfully validated the currently used docking parameters, including grid parameters. The grid dimensions used for docking of the EAAT2 receptor include x, y, and z dimensions of 40 x 40 x 40, with a spacing of 0.442 Å and x-center at 123.276, y-center at 162.328, and z-center at 121.519. Furthermore, it has been noted that the docked conformation of the reference ligand exhibits chemical interactions with the target EAAT2 receptor that are identical to those in its bioactive crystallised macromolecular complex. This suggests that the binding occurs in the same way as it does in the human body. At last, the validation results have shown that the docking methodology under consideration is mimicking the natural human body's EAAT2 receptor complexation process with the reference ligand. The validated docking parameters were used to screen a previously collected ligand library of 2892 FDA-approved pharmaceuticals against the constructed EAAT2 receptor. After the virtual screening was run, the lead compounds were narrowed down based on their lowest binding score and maximum binding interactions with the macromolecular target. The results for the leads targeting the EAAT2 receptor considered are shown in Table 1, along with the binding scores and interacting macromolecular residues.

Table 1. Binding score and interacting residues for the shortlisted leads against the EAAT2 receptor.

S. No.	Zinc	Name	Structure	Binding energy
1	ZINC03830925	Idarubicin		-10.73
2	ZINC01550477	Lapatinib		-10.71
3	ZINC04097448	Metocurine		-10.09

S. No.	Zinc	Name	Structure	Binding energy
4	ZINC01612996	Irinotecan		-9.57
5	ZINC03830922			-9.35
6	ZINC30690433	Thiothixine		-9.24
7	ZINC03831193	Nandrolone phenylpropionate		-9.23
8	ZINC53683151	Bromocriptine		-9.21
9	ZINC17953024	Clofazimine		-8.91
10	ZINC11678102	Carminomycin		-8.86
11	Reference			

Based on the best binding energy obtained against the EAAT2 receptor and the observed binding interaction, metocurine was shortlisted to proceed for MD simulation analysis. Figure 1 shows the two- and three-dimensional binding interactions of metocurine with the EAAT2 receptor.

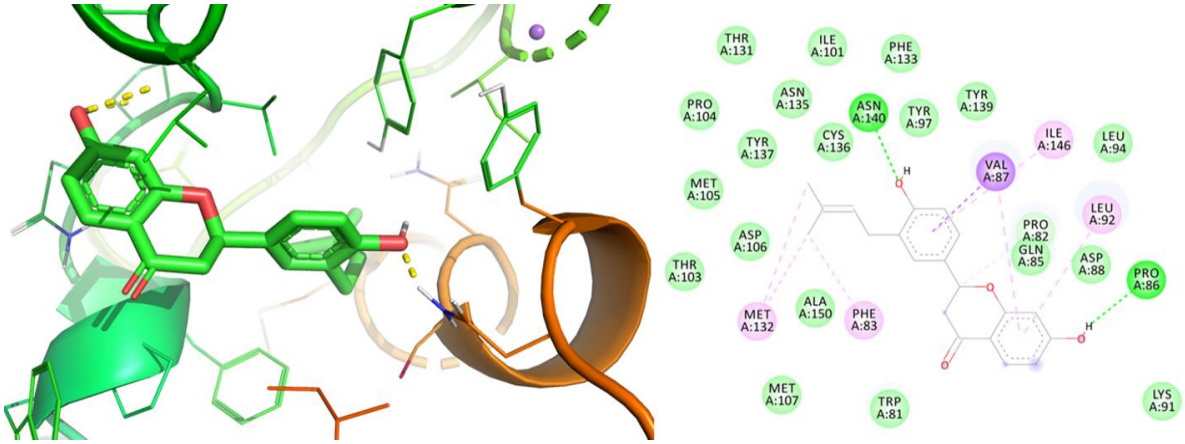


Figure 1. Binding Interactions: Two-dimensional binding interactions and three-dimensional binding conformation of the metocurine with the human EAAT2 receptor.

3.3. MD simulation.

The human EAAT2 receptor complexed with metocurine was selected for MD simulation over 100 ns to evaluate its thermodynamic stability over time. According to reports, the stability of the drug-receptor complex must be sufficient to carry out the therapeutic response within a nanosecond. Consequently, Desmond software was used to conduct a 100 ns MD simulation for every macromolecular complex. The data from molecular dynamics simulations show that the EAAT2 target protein consists of a single long chain of 424 amino acids. Out of a total of 6589 atoms, 3179 of them are heavy and make up the EAAT2 receptor. The structural changes and thermodynamic stability of the macromolecular backbone were revealed by RMSD analysis over a 100 ns time window. Metocurine, a complex ligand, contains 96 atoms in total, 12 of which are rotatable links with 48 heavy atoms. Following the first 20 ns of the simulation, the human EAAT2 receptor complexed with metocurine reached a stable conformation, which was preserved throughout the 100 ns simulation, according to the trajectories. During the first 20 nanoseconds, there was a noticeable fluctuation in both the Cα protein backbone and the complex metocurine. There was a range of RMSD values from 2.4 to 5.0 Å for the macromolecular backbone. Still, the complex metocurine exhibited a couple of conformational changes at the macromolecular site in the first 20 ns before stabilising at a range of 3.5-5.0 Å for the rest of the simulation.

After 100 nanoseconds of simulation, the RMSD of the complex metocurine and the human EAAT2 macromolecular backbone is shown in Figure 2.

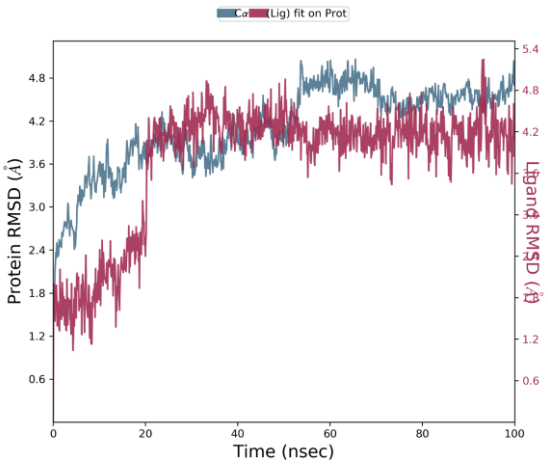


Figure 2. Root mean square deviation: while conducting a 100 ns MD simulation, the observed root mean square deviation (RMSD) for the Cα chain of EAAT2 complexed with methocurin was monitored.

The RMSF of a protein or ligand structure is the dispersion of its atoms around their mean location. When testing the pliability and dynamics of a ligand or protein molecule, it is an invaluable tool. Protein RMSF is important because it indicates the flexibility of different regions, which helps assess stability and predict protein dynamics. MD analysis revealed that the RMSF of the protein backbone varies between 1.0 and 3.5 Å across different residues in the EAAT2 receptor complexed with metocurine. In contrast, the RMSF of metocurine ranges from 1.0 to 2.0 Å. The observed RMSD and RMSF values obtained after MD simulation indicate that the macromolecular complex maintains a high degree of stability throughout the simulation, which is required for the initiation of a therapeutic response. Because of the agonistic activity of metocurine, which is necessary to initiate the intended therapeutic effect, there is a high fluctuation in certain of the critical macromolecular residues, which validates

the target protein's conformational alteration. Figure 3 displays the RMSF detected during MD analysis of the human EAAT2 backbone and the complexed ligand metocurine.

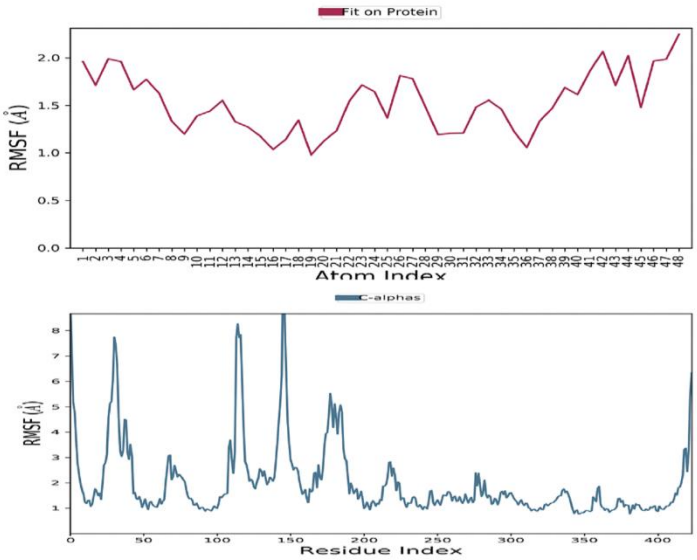


Figure 3. Root mean square fluctuation: the RMSF for the human EAAT2 receptor complexed with Methocurin was found during a 100 ns MD simulation.

In a molecular dynamics (MD) model, the formation of hydrophobic contacts, ionic interactions, and hydrogen bonding explains why a protein-ligand complex is stable. As part of our evaluation of the ligands' longevity in both macromolecular complexes, we consistently monitored the strength of these interactions throughout the simulation. During the simulation procedure, the interaction between the metocurine and the human EAAT2 receptor shows hydrophobic interactions with the amino acids Leu47, Met285, Ala365, Met398, Ala439, and Ala440. Residue Asp471 interacts via an ionic bond; residues Ser288 and Ser436 interact via hydrogen bonds; and Ser444 and Gly446 form a hydrogen bond with the metocurine. The reference inhibitor WAY-213613 interacts with key macromolecular residues Ser441, Ile464, Leu467, and Val468 for an antagonistic effect. In contrast, the identified agonist metocurine does not interact with any of the above-mentioned residues throughout the simulation. Figure 4 illustrates the interacting residues of the human EAAT2 receptor with metocurine.

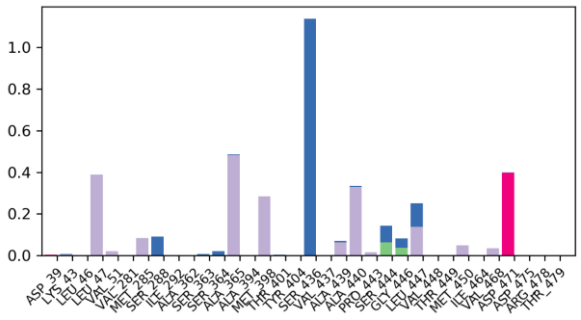


Figure 4. Protein-ligand contacts: the human EAAT2 receptor and metocurine have been studied for their protein-ligand interactions. Various coloured bars were used to depict the interactions; green bars stood for hydrogen bonds, blue for water bridges, and purple for hydrophobic interactions.

4. Conclusions

Finally, our research centred on identifying potential Alzheimer's disease treatments targeting the human EAAT2 receptor using a computational drug repurposing strategy. We selected the EAAT2 (Excitatory Amino Acid Transporter 2) receptor for docking analysis

because of its crucial role in maintaining glutamate balance in the central nervous system. Mainly found in astrocytes, EAAT2 handles about 90% of extracellular glutamate removal. In Alzheimer's disease (AD), reduced or impaired EAAT2 function leads to excess glutamate buildup in the synaptic cleft, causing excitotoxicity, an overload of neuronal stimulation that damages neurons and impairs cognition. Consequently, EAAT2 has become a key target for neuroprotection efforts. Thus, enhancing or mimicking its activity could help reduce glutamate toxicity and slow neurodegeneration in AD.

Metacurine was found to be a promising candidate with drug-like characteristics and a favourable binding affinity through molecular docking-based virtual screening and subsequent dynamic simulation investigations. These results provide fresh evidence that targeting the EAAT2 receptor with already-existing pharmaceuticals might provide a more efficient and less expensive way to treat Alzheimer's disease. Our research sheds light on how computational drug repurposing could help find new uses for metocurine, which could pave the way for more effective treatments for neurodegenerative disorders like Alzheimer's. To confirm the effectiveness and safety of these drugs for clinical usage, additional in vitro and in vivo investigations are necessary.

Author Contributions

Conceptualization, S.M. and T.G.S.; methodology, S.M., M.S., and S.C.; validation, S.M., S.D., and K.K.M.; formal analysis, S.C. and S.D.; investigation, M.S., R.S., and S.C.; resources, T.G.S. and K.K.M.; data curation, S.C. and S.D.; writing original draft preparation, S.M. and S.D.; writing review and editing, T.G.S., K.K.M., and R.S.; visualization, S.C. and S.D.; supervision, T.G.S. and K.K.M.; project administration.

All authors have read and agreed to this version of the manuscript..

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that there are no financial or non-financial interests that are directly or indirectly related to the work.

References

1. DeTure, M.A.; Dickson, D.W. The neuropathological diagnosis of Alzheimer's disease. *Mol. Neurodegener.* **2019**, *14*, 32, https://doi.org/10.1186/S13024-019-0333-5.
2. Serrano-Pozo, A.; Frosch, M.P.; Masliah, E.; Hyman, B.T. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* **2011**, *1*, a006189, https://doi.org/10.1101/CSHPERSPECT.A006189.
3. Shivani, B.; Manish, K. Current Status of Alzheimer's Disease and Pathological Mechanisms Investigating the Therapeutic Molecular Targets. *Curr. Mol. Med.* **2023**, *23*, 492-508, https://doi.org/10.2174/1566524022666220404112843.
4. Han, Z.; Yang, X.; Huang, S. Sleep deprivation: A risk factor for the pathogenesis and progression of Alzheimer's disease. *Heliyon* **2024**, *10*, e28819, https://doi.org/10.1016/j.heliyon.2024.e28819.
5. Gustavsson, A.; Norton, N.; Fast, T.; Frölich, L.; Georges, J.; Holzapfel, D.; Kirabali, T.; Krolak-Salmon, P.; Rossini, P.M.; Ferretti, M.T.; Lanman, L.; Chadha, A.S.; van der Flier, W.M. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement.* **2023**, *19*, 658-670, https://doi.org/10.1002/alz.12694.
6. Dintica, C.S.; Bahorik, A.; Xia, F.; Kind, A.; Yaffe, K. Dementia Risk and Disadvantaged Neighborhoods. *JAMA Neurol.* **2023**, *80*, 903-909, https://doi.org/10.1001/jamaneurol.2023.2120.
7. Lim, A.C.; Barnes, L.L.; Weissberger, G.H.; Lamar, M.; Nguyen, A.L.; Fenton, L.; Herrera, J.; Han, S.D. Quantification of race/ethnicity representation in Alzheimer's disease neuroimaging research in the USA: a systematic review. *Commun. Med.* **2023**, *3*, 101, https://doi.org/10.1038/s43856-023-00333-6.
8. Wood, O.W.G.; Yeung, J.H.Y.; Faull, R.L.M.; Kwakowsky, A. EAAT2 as a therapeutic research target in Alzheimer's disease: A systematic review. *Front. Neurosci.* **2022**, *16*, 952096, https://doi.org/10.3389/FNINS.2022.952096.
9. Bhatnagar, A.; Parmar, V.; Barbieri, N.; Bearoff, F.; Elefant, F.; Kortagere, S. Novel EAAT2 activators improve motor and cognitive impairment in a transgenic model of Huntington's disease. *Front. Behav. Neurosci.* **2023**, *17*, 1176777, https://doi.org/10.3389/FNBEH.2023.1176777.
10. Pajer, K.; Bellák, T.; Grósz, T.; Nógrádi, B.; Patai, R.; Sinkó, J.; Vinay, L.; Liabeuf, S.; Erdélyi, M.; Nógrádi, A. Riluzole treatment modulates KCC2 and EAAT-2 receptor expression and Ca^{2+} accumulation following ventral root avulsion injury. *Eur. J. Cell Biol.* **2023**, *102*, 151317, https://doi.org/10.1016/J.EJCB.2023.151317.
11. Takahashi, K.; Sato, K. The Conventional and Breakthrough Tool for the Study of L-Glutamate Transporters. *Membranes* **2024**, *14*, 77, https://doi.org/10.3390/MEMBRANES14040077.
12. Fontana, I.C.; Souza, D.G.; Souza, D.O.; Gee, A.; Zimmer, E.R.; Bongarzone, S. A Medicinal Chemistry Perspective on Excitatory Amino Acid Transporter 2 Dysfunction in Neurodegenerative Diseases. *J. Med. Chem.* **2023**, *66*, 2330-2346, https://doi.org/10.1021/acs.jmedchem.2c01572.
13. Xu, X.; Wang, J.; Du, S.; Shen, X.; Lian, J.; Zhou, J.; Wang, M.; Feng, W.; Lv, Z.; Zhu, J.; Jin, L.; Sun, H.; Wu, L.; Wang, X.; Qiu, H.; Wang, W.; Teng, H.; Wang, Y.; Huang, Z. Yes-associated protein regulates glutamate homeostasis through promoting the expression of excitatory amino acid transporter-2 in astrocytes via β-catenin signaling. *Glia* **2023**, *71*, 1197-1216, https://doi.org/10.1002/glia.24332.
14. Liang, T.; Hu, X.; Zeng, L.; Zhou, Z.; Zhang, J.; Xu, Z.; Zeng, J.; Xu, P. HSP90β regulates EAAT2 expression and participates in ischemia-reperfusion injury in rats. *Mol. Med. Rep.* **2024**, *29*, 5, https://doi.org/10.3892/mmr.2023.13128.
15. Somdutt, M. Computational Bioprospecting of Andrographolide Derivatives as Potent Cyclooxygenase-2 Inhibitors. *Biomed. Biotechnol. Res. J.* **2021**, *5*, 446–450, https://doi.org/10.4103/bbrj.bbrj_56_21.
16. Mujwar, S.; Shah, K.; Gupta, J.K.; Gour, A. Docking based screening of curcumin derivatives: a novel approach in the inhibition of tubercular DHFR. *Int. J. Comput. Biol. Drug Des.* **2021**, *14*, 297-314, https://doi.org/10.1504/IJCBDD.2021.118830.

17. Gupta, N.; Qayum, A.; Singh, S.; Mujwar, S.; Sangwan, P.L. Isolation, Anticancer Evaluation, Molecular Docking, Drug likeness and ADMET Studies of Secondary Metabolites from *Psoralea corylifolia* seeds. *ChemistrySelect* **2022**, *7*, e202202115, https://doi.org/10.1002/SLCT.202202115.
18. Gupta, N.; Qayum, A.; Singh, S.; Mujwar, S.; Sangwan, P.L. Isolation, Cytotoxicity Evaluation, Docking, ADMET and Drug Likeness Studies of Secondary Metabolites from the Stem Bark of *Anthocephalus cadamba* (Roxb.). *ChemistrySelect* **2022**, *7*, e202202950, https://doi.org/10.1002/SLCT.202202950.
19. Gupta, S.M.; Behera, A.; Jain, N.K.; Kumar, D.; Tripathi, A.; Tripathi, S.M.; Mujwar, S.; Patra, J.; Negi, A. Indene-Derived Hydrazides Targeting Acetylcholinesterase Enzyme in Alzheimer's: Design, Synthesis, and Biological Evaluation. *Pharmaceutics* **2023**, *15*, 94, https://doi.org/10.3390/PHARMACEUTICS15010094.
20. Agrawal, N.; Upadhyay, P.K.; Mujwar, S.; Mishra, P. Analgesic, anti-inflammatory activity and docking study of 2-(substituted phenyl)-3-(naphthalen1-yl) thiazolidin-4-ones. *J. Indian Chem. Soc.* **2020**, *97*, 39-46.
21. Neetu, A.; Somdutt, M.; Ahsas, G.; Jeetendra Kumar, G. Phytoestrogens as Potential Antiandrogenic Agents Against Prostate Cancer: An *In Silico* Analysis. *Lett. Drug Des. Discov.* **2022**, *19*, 69-78, https://doi.org/10.2174/1570180818666210813121431.
22. Shah, K.; Mujwar, S.; Krishna, G.; Gupta, J.K. Computational Design and Biological Depiction of Novel Naproxen Derivative. *Assay Drug Dev. Technol.* **2020**, *18*, 308-317, https://doi.org/10.1089/ADT.2020.977.
23. Kaur, A.; Mujwar, S.; Adlakha, N. In-silico analysis of riboswitch of Nocardia farcinica for design of its inhibitors and pharmacophores. *Int. J. Comput. Biol. Drug Des.* **2016**, *9*, 261-276, https://doi.org/10.1504/IJCBDD.2016.078278.
24. Fidan, O.; Mujwar, S.; Kciuk, M. Discovery of adapalene and dihydrotachysterol as antiviral agents for the Omicron variant of SARS-CoV-2 through computational drug repurposing. *Mol. Divers.* **2023**, *27*, 463-475, https://doi.org/10.1007/s11030-022-10440-6.
25. Bukke, V.N.; Archana, M.; Villani, R.; Romano, A.D.; Wawrzyniak, A.; Balawender, K.; Orkisz, S.; Beggiato, S.; Serviddio, G.; Cassano, T. The Dual Role of Glutamatergic Neurotransmission in Alzheimer's Disease: From Pathophysiology to Pharmacotherapy. *Int. J. Mol. Sci.* **2020**, *21*, 7452, https://doi.org/10.3390/IJMS21207452.
26. Su, Z.-z.; Leszczyniecka, M.; Kang, D.-c.; Sarkar, D.; Chao, W.; Volsky, D.J.; Fisher, P.B. Insights into glutamate transport regulation in human astrocytes: Cloning of the promoter for excitatory amino acid transporter 2 (EAAT2). *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 1955-1960, https://doi.org/10.1073/pnas.0136555100.
27. Rao, G.N.; Jupudi, S.; Justin, A. A Review on Neuroinflammatory Pathway Mediating Through Ang-II/AT1 Receptors and a Novel Approach for the Treatment of Cerebral Ischemia in Combination with ARB's and Ceftriaxone. *Ann. Neurosci.* **2024**, *31*, 53-62, https://doi.org/10.1177/09727531231182554.
28. Manisha, C.; Palathoti, N.; Chand, J.; Krishna Swaroop, A.; Selvaraj, J.; Kumar, B.R.P.; Naveentha X, P.; Durairaj, B.; Justin, A. Hybrid virtual screening and molecular dynamics approach for identification of allosteric modulator of EAAT2. *Results Chem.* **2024**, *11*, 101766, https://doi.org/10.1016/j.rechem.2024.101766.
29. Takahashi, K.; Kong, Q.; Lin, Y.; Stouffer, N.; Schulte, D.A.; Lai, L.; Liu, Q.; Chang, L.-C.; Dominguez, S.; Xing, X.; Cuny, G.D.; Hodgetts, K.J.; Glicksman, M.A.; Lin, C.-L.G. Restored glial glutamate transporter EAAT2 function as a potential therapeutic approach for Alzheimer's disease. *J. Exp. Med.* **2015**, *212*, 319-332, https://doi.org/10.1084/JEM.20140413.
30. Yeung, J.H.Y.; Palpagama, T.H.; Wood, O.W.G.; Turner, C.; Waldvogel, H.J.; Faull, R.L.M.; Kwakowsky, A. EAAT2 Expression in the Hippocampus, Subiculum, Entorhinal Cortex and Superior Temporal Gyrus in Alzheimer's Disease. *Front. Cell. Neurosci.* **2021**, *15*, 702824, https://doi.org/10.3389/FNCEL.2021.702824.
31. Fontana, A.C.K. Current approaches to enhance glutamate transporter function and expression. *J. Neurochem.* **2015**, *134*, 982-1007, https://doi.org/10.1111/JNC.13200.
32. Berman, H.M.; Battistuz, T.; Bhat, T.N.; Bluhm, W.F.; Bourne, P.E.; Burkhardt, K.; Feng, Z.; Gilliland, G.L.; Iype, L.; Jain, S.; Fagan, P.; Marvin, J.; Padilla, D.; Ravichandran, V.; Schneider, B.; Thanki, N.; Weissig, H.; Westbrook, J.D.; Zardecki, C. The Protein Data Bank. *Acta Cryst.* **2002**, *58*, 899-907, https://doi.org/10.1107/S0907444902003451.

33. Berman, H.M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T.N.; Weissig, H.; Shindyalov, I.N.; Bourne, P.E. The Protein Data Bank. *Nucleic Acids Res.* **2000**, *28*, 235-242, https://doi.org/10.1093/NAR/28.1.235.
34. Soni, N.; Pardasani, K.R.; Mujwar, S. *Insilico* analysis of dietary agents as anticancer inhibitors of insulin like growth factor 1 receptor (IGF1R). *J. Pharm. Pharm. Sci.* **2015**, *7*, 191-196.
35. Mujwar, S.; Harwansh, R.K. In silico bioprospecting of taraxerol as a main protease inhibitor of SARS-CoV-2 to develop therapy against COVID-19. *Struct. Chem.* **2022**, *33*, 1517-1528, https://doi.org/10.1007/s11224-022-01943-x.
36. Mujwar, S.; Tripathi, A. Repurposing benzbromarone as antifolate to develop novel antifungal therapy for *Candida albicans*. *J. Mol. Model.* **2022**, *28*, 193, https://doi.org/10.1007/s00894-022-05185-w.
37. Pradhan, P.; Soni, N.K.; Chaudhary, L.; Mujwar, S.; Pardasani, K.R. In-silico prediction of riboswitches and design of their potent inhibitors for H1N1, H2N2 and H3N2 strains of influenza virus. *Biosci. Biotechnol. Res. Asia* **2015**, *12*, 2173-2186, https://doi.org/10.13005/bbra/1889.
38. Bowers, K.J.; Chow, D.E.; Xu, H.; Dror, R.O.; Eastwood, M.P.; Gregersen, B.A.; Klepeis, J.L.; Kolossvary, I.; Moraes, M.A.; Sacerdoti, F.D.; Salmon, J.K.; Shan, Y.; Shaw, D.E. Scalable Algorithms for Molecular Dynamics Simulations on Commodity Clusters. Proceedings of the SC '06: Proceedings of the 2006 ACM/IEEE Conference on Supercomputing, Tampa, FL, USA, 11-17 Nov. 2006; IEEE: **2006**; pp. 43-43, https://doi.org/10.1109/SC.2006.54.
39. Jiang, W.; Phillips, J.C.; Huang, L.; Fajer, M.; Meng, Y.; Gumbart, J.C.; Luo, Y.; Schulten, K.; Roux, B. Generalized scalable multiple copy algorithms for molecular dynamics simulations in NAMD. *Comput. Phys. Commun.* **2014**, *185*, 908-916, https://doi.org/10.1016/j.cpc.2013.12.014.
40. Li, Q.; Zhang, H.; Guan, S.; Du, J.; Zhang, Y.; Wang, S. Molecular dynamics simulation of the inhibition mechanism of factor XIa by Milvexian-like macrocyclic inhibitors. *Comput. Theor. Chem.* **2023**, *1225*, 114131, https://doi.org/10.1016/J.COMPTC.2023.114131.
41. Shinu, P.; Sharma, M.; Gupta, G.L.; Mujwar, S.; Kandeel, M.; Kumar, M.; Nair, A.B.; Goyal, M.; Singh, P.; Attimarad, M.; Venugopala, K.N.; Nagaraja, S.; Telsang, M.; Aldhubiab, B.E.; Morsy, M.A. Computational Design, Synthesis, and Pharmacological Evaluation of Naproxen-Guaiacol Chimera for Gastro-Sparing Anti-Inflammatory Response by Selective COX2 Inhibition. *Molecules* **2022**, *27*, 6905, https://doi.org/10.3390/MOLECULES27206905.
42. Kciuk, M.; Mujwar, S.; Rani, I.; Munjal, K.; Gielecińska, A.; Kontek, R.; Shah, K. Computational Bioprospecting Guggulsterone against ADP Ribose Phosphatase of SARS-CoV-2. *Molecules* **2022**, *27*, 8287, https://doi.org/10.3390/molecules27238287.
43. Shah, K.; Mujwar, S. Delineation of a Novel Non-Steroidal Anti-Inflammatory Drugs Derivative Using Molecular Docking and Pharmacological Assessment. *Indian J. Pharm. Sci.* **2022**, *84*, 642-653, https://doi.org/10.36468/pharmaceutical-sciences.959.
44. Er-rajy, M.; Fadili, M.E.; Mujwar, S.; Lenda, F.Z.; Zarougui, S.; Elhallaoui, M. QSAR, molecular docking, and molecular dynamics simulation–based design of novel anti-cancer drugs targeting thioredoxin reductase enzyme. *Struct. Chem.* **2023**, *34*, 1527-1543, https://doi.org/10.1007/S11224-022-02111-X.
45. Er-rajy, M.; El fadili, M.; Mujwar, S.; Zarougui, S.; Elhallaoui, M. Design of novel anti-cancer drugs targeting TRKs inhibitors based 3D QSAR, molecular docking and molecular dynamics simulation. *J. Biomol. Struct. Dyn.* **2023**, *41*, 11657-11670, https://doi.org/10.1080/07391102.2023.2170471.
46. Rani, I.; Goyal, A. ROLE OF GSK3 (GLYCOGEN SYNTHASE KINASE 3) AS TUMOR PROMOTER AND TUMOR SUPPRESSOR–A REVIEW. *Plant Arch.* **2019**, *19*, 1360–1365.
47. Rani, I.; Goyal, A.; Sharma, M. Computational Design of Phosphatidylinositol 3-Kinase Inhibitors. *Assay Drug Dev. Technol.* **2022**, *20*, 317-337, https://doi.org/10.1089/adt.2022.057.
48. Song, P.N.; Lynch, S.E.; DeMellier, C.T.; Mansur, A.; Gallegos, C.A.; Wright, B.D.; Hartman, Y.E.; Minton, L.E.; Lapi, S.E.; Warram, J.M.; Sorace, A.G. Dual anti-HER2/EGFR inhibition synergistically increases therapeutic effects and alters tumor oxygenation in HNSCC. *Sci. Rep.* **2024**, *14*, 3771, https://doi.org/10.1038/s41598-024-52897-5.
49. Duklan, S.; Saha, S.; Jakhmola, V.; Gairola, N.; Pandey, P.; Singh, M.; Kawsar, S.M.A. Molecular docking, synthesis, in-vitro alpha amylase and antibacterial activities of newer generation pyrimidine derivatives. *Adv. J. Chem., Sect. A* **2024**, *7*, 459-476, https://doi.org/10.48309/ajca.2024.448978.1499.
50. Akter, N.; Bourougaa, L.; Ouassaf, M.; Bhowmic, R.C.; Uddin, K.M.; Bhat, A.R.; Ahmed, S.; Kawsar, S.M.A. Molecular docking, ADME-Tox, DFT and molecular dynamics simulation of butyroyl glucopyranoside derivatives against DNA gyrase inhibitors as antimicrobial agents. *J. Mol. Struct.* **2024**, *1307*, 137930, https://doi.org/10.1016/j.molstruc.2024.137930.

51. Ahmmed, F.; Al-Mijalli, S.H.; Abdallah, E.M.; Eissa, I.H.; Ali, F.; Bhat, A.R.; Jamalis, J.; Ben Hadda, T.; Kawsar, S.M.A. Galactoside-Based Molecule Enhanced Antimicrobial Activity through Acyl Moiety Incorporation: Synthesis and In Silico Exploration for Therapeutic Target. *Pharmaceuticals* **2023**, *16*, 998, https://doi.org/10.3390/ph16070998.

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