RESEARCH PAPER

In Silico Identification of Small Molecule Stabilizers of APOE4 for Alzheimer's Disease Therapy

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Abstract
Background: The apolipoprotein E4 (APOE4) isoform is the strongest genetic risk factor for late-onset Alzheimer's disease (AD) due to its pathological structural conformation that mainly contributes to amyloid aggregation and tau hyperphosphorylation. Indeed, numerous research interests in APOE4, which may lead to a loss of function, have led this study to focus on stabilizing APOE4 using small molecules, using bioinformatics tools to identify the appropriate drug that restores the protein to its normal function. Methods: We used the PyRx program for docking to select the compound with the highest binding affinity to the N-terminal APOE4 protein and the APOE4 protein generated by AlphaFold. Results: While several compounds demonstrated favourable binding to N-terminal or APOE4, one drug selected as a candidate exhibited a superior combination of binding affinity. Conclusion: We observed that 3-(2-phenylphenoxy)-1,2-benzothiazole 1,1-dioxide (CID 892507) was highest binding affinity in two proteins, and its binding with critical residues in the protein that play a role in stabilization. This finding enhances the application of various tests to ensure its efficacy and safety as a corrector drug for APOE4 in the treatment of Alzheimer's disease.

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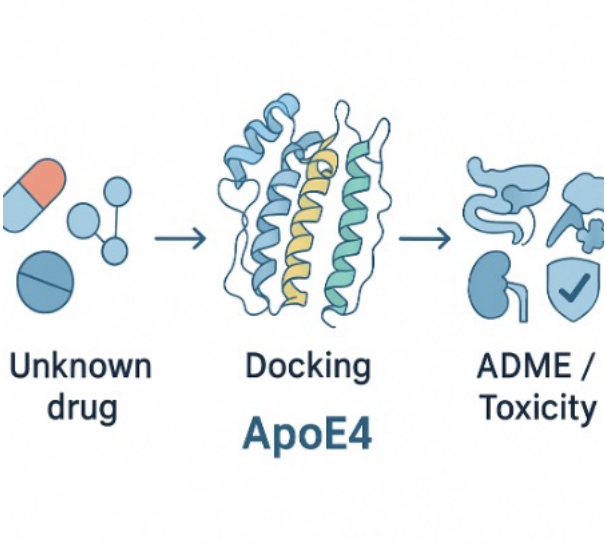

Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting millions. worldwide and accounting for 60-80% of dementia cases(Uddin & Ashraf, 2018). It is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioural changes (Tariot, 1994). Therefore, Alzheimer's disease is a significant factor of disability and dependence in the elderly, with a profound impact on quality of life. It also poses a considerable burden on healthcare systems and society. Alzheimer's disease and other dementias were the fifth most important reason for death and the second leading neurological causes of death globally, with two out of every 10 individuals diagnosed with neurological disorders, having Alzheimer's disease (Feigin et al., 2020; Nichols & Vos, 2021).

AD is a complex neurodegenerative disease resulting from the interactions of various genetic and environmental factors. Molecular and genetic studies have identified three primary genetic mutations related with early-onset Alzheimer's disease (EOAD), especially in genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) (PSEN2)(Andrade-Guerrero et al., 2023) . However, the APOEε4 allele is considered the predominant genetic risk factor for AD, particularly in sporadic AD cases referred to as Late-Onset Alzheimer's Disease (LOAD) (Fortea et al., 2024; Jackson et al., 2024). AD is characterized by two molecular pathological hallmarks: extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) (Braak & Braak, 1991; Glenner & Wong, 1984). The accumulation of Aβ plaques and NFTs is associated with significant neuronal and synaptic loss as well as neuroinflammation (Taddei, 2024). The presence of apoE4 aggravates both pathologies (Therriault et al., 2021).

Apolipoprotein E exists as three major isoforms (E2, E3, and E4) characterized by residue substitutions at positions 112 and 158, with profound effects on Alzheimer's disease pathogenesis(Matsunaga & Saito, 2025). This protein consists of multiple helices: a four- helix bundle that consists of helix 2, helix 3, helix 4, and helix 5, hinge helices, and carboxyl- terminal domains that include lipid-binding residues and helices. The receptor- binding region is located on helix 5 (Yamazaki et al., 2019). Once, a change in substitution 112 and 158 led to a

change in these helices and the appearance of diseases.

In further details, the isoform APOE4 described by arginine residues at both positions 112 (Arg112) and 158 (Arg158), creates a pathological interdomain interaction distinct from the protective ApoE2 isoform (Cys112/Cys158) and the neutral ApoE3 isoform (Cys112/Arg158); specifically, the Arg112 substitution induces an aberrant salt bridge between Arg61 in the N-terminal domain and Glu255 in the C-terminal domain that "locks" the protein into closed conformation (Dong & Weisgraber, 1996). As a result, the protein becomes less stable than APOE2 and APOE3. These structural and stability issues significantly impair apoE4's lipid transport efficacy and receptor interaction capacity (Belaidi et al., 2025). The structural basis for these functional deficits lies in the long-range conformational effects propagated by the Arg112 substitution, which reorients the critical Trp34 residue from a therapeutically favourable "flip-in" orientation (perpendicular to the protein axis) to a pathological "flip-out" orientation (parallel to the axis), thereby creating an abnormal hydrophobic pocket bordered by Trp26, Leu30, Gly31, Leu148, Leu149, and Ala152 that serves as an allosteric site for structure-correcting drug intervention (Petros et al., 2019; Wang et al., 2018). Treatment approach targeting APOE4 stabilization aims to restore balanced N-terminal/C-terminal domain interactions, as in APOE2 and APOE3, by using small molecules that correct the structure via interactions with the most critical amino acid residues, thereby shifting the structure from unstable to more stable.

However, the attention in converting APOE4 from an unstable protein to a more stable one is a key focus amongst researchers aiming to treat Alzheimer's disease. This study aims to identify small molecules that can stabilize APOE4, thereby reducing the side effects associated with its instability.

Materials and methods

Molecular docking

Molecular docking simulations were performed using PyRx open-source software, taking advantage of the Auto Dock Vina program (Dallakyan & Olson, 2014; Trott & Olson, 2010),Which performed to investigate the binding interactions between the target protein and ligands.

Protein structures and predictions

This study involved two N-terminal protein domains of APOE4 and the full-length APOE4. The N-terminal protein was retrieved from the Protein Data Bank (https://www.rcsb.org/).with PDB ID:6NCN (Petros et al., 2019) The optimization of the target protein was then carried out by separating water residues and ligands using PyMOL software (DeLano, 2002), the full length for APOE4 was created by the AlphaFold web server (Abramson et al., 2024).

Ligand preparation

The ligands selected for evaluation were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in Structure Data Format (SDF) (Patil et al., 2025; Petros et al., 2019; Zhai et al., 2023). All compounds were prepared as ligands and energy minimized using the PyRx program.

Binding site identification and grid generation

We determine the binding site in the N-terminal protein by applying two approaches: previous studies and DoGSiteScorer tools (https://proteins.plus/) (Volkamer et al., 2012). This tool is used to predict the best binding site for a protein. In contrast, the APOE4 full-length was dependent on blind docking to compare the best binding site in protein for stabilization of APOE4. The grid box for the N-terminal was size_x = 38.1104594741, size_y = 25.2968052788, size_z = 49.641860128. center_x = 2.92166076232, center_y = -16.4092532327, center_z = -12.1808676654, and the grid box for APOE4 was size_x = 81.2839911852, size_y = 90.7473101308, size_z=108.805585539, center_x = 7.09188147938, center_y = -15.6384573482, center_z = 1.54698074466. The docking parameters showed an exhaustiveness value of 8. The pose with the lowest binding energy was selected for each ligand. We selected the top seven compounds with the highest binding scores that were shared between two proteins. Subsequently, we discussed and identified one candidate as the best binding affinity, which was visualised using Discovery Studio to determine its interactions with two proteins.

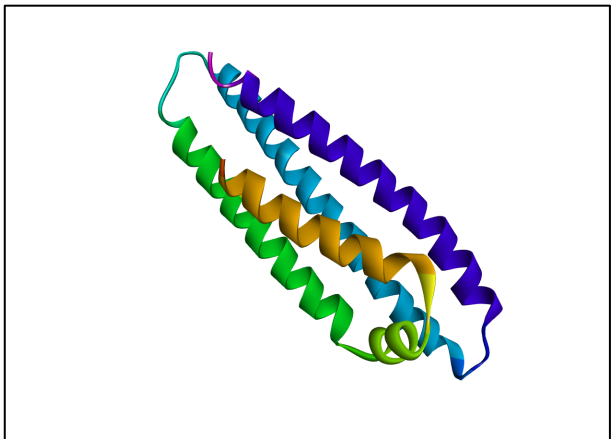

Figure 1: Crystal structure of the 6NCN protein, made using Discovery Studio.

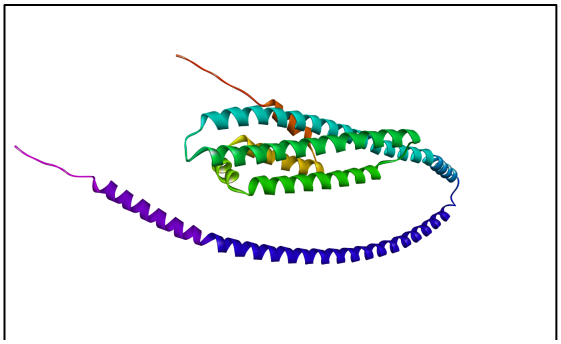

Figure 2:Predicted 3D structure of the APOE4 protein generated using AlphaFold and visualized in Discovery Studio.

Result and discussion

According to Table 4.1 below, we observed that all ligands binding to protein 6NCN exhibit high binding affinity, ranging from -7.5 to -6.4 kcal/mol, indicating that all ligands bind within a similar and comparable affinity range. In contrast, the docking results for APOE4 showed variation in binding affinities, indicating that some ligands bind more strongly than others. Specifically, CID: 892507, 95402243, 121507038, and 794390 exhibited higher binding affinities of -7.0, -6.6, -6.3, and -6.3 kcal/mol, respectively. Other ligands showed moderate binding affinity, such as CID: 155511476, 95716109, and 121507038, with binding values of -5.8, -5.7, and -5.5 kcal/mol, respectively.

Table 0.1: Top Compounds Stabilizing APOE4 (PDB ID: 6NCN & APOE4) Identified through Molecular Docking

protein	Compound no.	IUPAC Name	PubChem CID	chemical formula	Binding Affinity kcal/mol
6NCN	1	3-(2-phenylphenoxy)-1,2-benzothiazole 1,1-dioxide	892507	C19H13NO3S	-7.5
APOE4					-6.8
6NCN	2	[3-(1*H*-imidazol-2-yl)phenyl]-[(2*R*)-2-(3-phenylpropyl)morpholin-4-yl]methanone	95402243	C23H25N3O2	-7.5
APOE4					-6.7
6NCN	3	(5*S*)-9-[2-(1*H*-imidazol-2-yl)benzoyl]-3-methyl-1-oxa-3,9-diazaspiro[4.6]undecan-2-one	95716109	C19H22N4O3_	-6.6
APOE4					-7.4
6NCN	4	2-(3,5-dihydro-2H-1,4-benzoxazepine-4-carbonyl)-1,6-dimethylpyridin-4-one	121507038	C17H18N2O3	-6.8
APOE4					-6.1
6NCN	5	5,5-Dimethyl-3-(naphthalen-1-ylamino)cyclohex-2-en-1-one	794390	C18H19NO	-7.1
APOE4					-6.8
6NCN	6	1-[3-[4-(aminomethyl)phenyl]-5-chlorophenyl]cyclobutane-1-carboximidamide	155511476	C18H20ClN3	-7
APOE4					-6.1
6NCN	7	2-chloro-5-(5-fluoroquinolin-8-yl)benzamide	121495161	C16H10ClFN2O	-7
APOE4					-6

Docking Analysis of Affinity Binding Scoring

Compound1 (3-(2-phenylphenoxy)-1,2-benzothiazole 1,1-dioxide) (CID 892507), as shown in Table 4.1, exhibited the highest overall binding affinity, with the binding energies of −6.9 kcal/mol for 6NCN and −7.1 kcal/mol for APOE4. The interactions between ligand and protein 6NCN and APOE4 are illustrated in Figures 3,4,5, and 6.

Figure 3. The surface view emphasizes that the binding site addressed by CID 892507 is not a shallow groove but a well-defined internal pocket, which is particularly favourable for conformational stabilization because burial within such cavities often couples ligand binding to compaction and rigidification of the protein core. In the original 6NCN study, the authors reported that fragment-derived stabilizers bound to an analogous buried pocket and that this engagement correlated with functional normalization of apoE4 in cytokine assays (Petros et al., 2019). By occupying an overlapping cavity, CID 892507 is likely to displace structured water molecules and enhance packing

between helices, thereby increasing the thermodynamic stability of the N-terminal domain and potentially shifting apoE4 toward a less pathogenic conformational ensemble.

Figures 4 (A and B) showed the interaction between ligand and 6NCN protein in a two-dimensional and a three-dimensional representation, respectively. These figures depict the primary interaction between the ligand and protein, in which the sulfonyl oxygen atoms form directional conventional hydrogen bonds with the side chain of Gln156. In addition, the heterocyclic nitrogen appears positioned to participate in hydrogen bonding or dipole interactions. The aromatic scaffold engages in π–π stacking with TRP34, while additional π–alkyl interactions are observed with LEU30 and ALA152, reinforcing hydrophobic complementarity. The ligand is deeply embedded within the binding cavity, minimizing solvent exposure and maximizing van der Waals surface contact. Therefore, the binding configuration suggests favorable thermodynamic stabilization driven by hydrogen bonding, and hydrophobic interactions.

Taken together, the three-dimensional binding model and the two-dimensional interaction map give complementary evidence supporting a stable and well-organized 6NCN protein– CID:892507 ligand complexes. Aromatic stacking interactions, especially those involving tryptophan residues, are widely recognized for their role in enhancing binding stabilization and molecular orientation within confined pockets (Patil et al., 2025). Besides, the combination of polar anchoring interactions with hydrophobic packing is a central principle in structure-based drug design. In this study, the structural and interaction analyses support a strong binding interaction for compound 892507 within the 6NCN binding site.

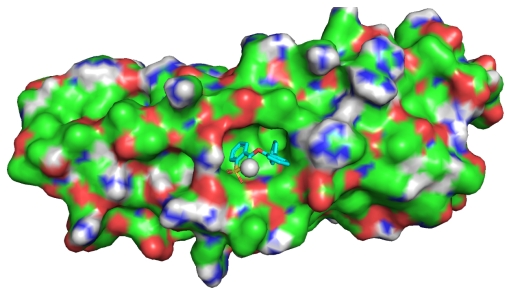

Figure 3: Surface representation of the apoE4 N-terminal domain showing deep burial of CID 892507 in the stabilization cavity.
The molecular surface of the APOE4 N-terminal domain (PDB 6NCN) is colored according to residue physicochemical properties (green, hydrophobic; blue, positively charged; red, negatively charged; white, polar/neutral), with CID 892507 represented as cyan sticks at the center of the structure. The compound is in a buried cavity within a predominantly hydrophobic region of the surface, consistent with the internal binding pocket characterized in the 6NCN APOE4–stabilizer complex.

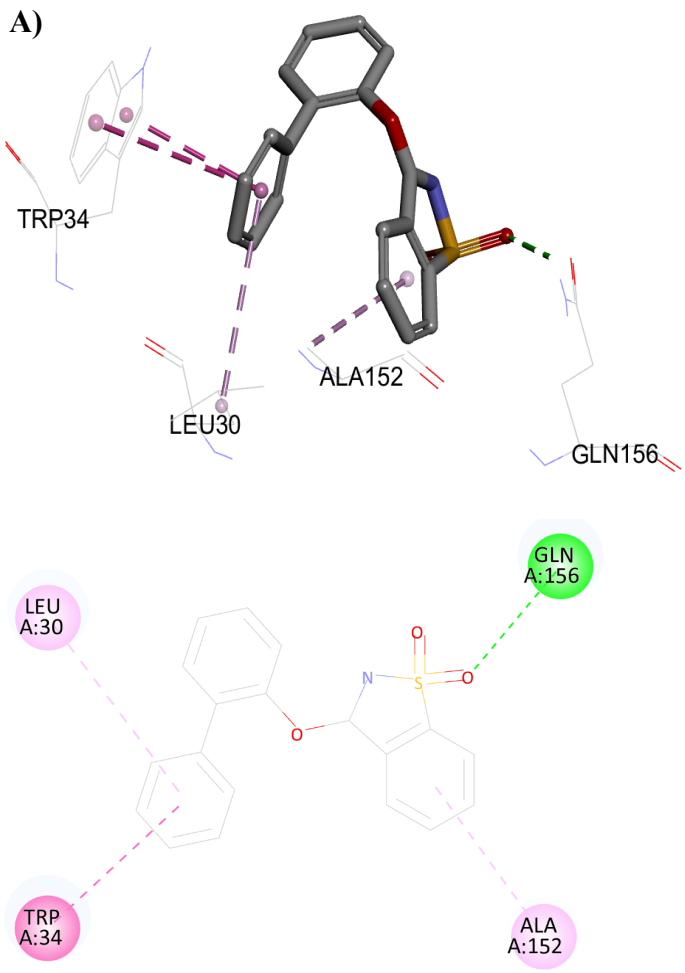

Figure 4: Display interaction between CID 892507 with the APOE4 N-terminal domain

The three-and two-dimensional binding conformation of compound CID: 892507 within the active pocket of 6NCN. The ligand adopts a compact conformation stabilized by a network of hydrogen bonds, hydrophobic contacts, and aromatic interactions. Key residues involved in ligand recognition include GLN156, ALA152, LEU30, and TRP34. The sulfonyl-containing heterocyclic core of 892507 is oriented toward polar residues, while the aromatic rings extend into a hydrophobic subpacket lined by aliphatic and aromatic side chains. Dashed green lines denote conventional hydrogen bond interactions, whereas magenta dashed lines indicate π–π and π–alkyl contacts. Figure A) displays integration in a three-dimensional structure. Figure B) displays interaction in a two-dimensional structure.

In Figure 5, the molecular surface illustration of the AlphaFold-predicted APOE4 structure shows that PubChem CID 892507 is deeply embedded within a defined hydrophobic cavity of the protein. The compound occupies a compact pocket characterized by mixed hydrophobic and polar surface regions, demonstrating strong steric complementarity. The aromatic rings of the ligand are positioned within predominantly hydrophobic surface patches, reducing solvent exposure and increasing van der Waals interactions. However, the polar sulfonyl group is directed toward surface-exposed charged and polar residues, facilitating electrostatic stabilization. This interaction may contribute to local conformational stabilization of the APOE4 structure, which can be used to treat Alzheimer's disease (Zhai et al., 2023).

Figure 6 (A & B) illustrates the interaction of the protein with the drug in the Two-dimensional and the three-dimensional docking models, which establishes a network of stabilizing interactions within the APOE4 binding region. The ligand is accommodated in the protein by both hydrogen bonding and hydrophobic contacts. We observed conventional hydrogen bonds between the ligand's sulfonyl oxygen atoms and the side chains of GLN41 and ARG142, which likely contribute significantly to binding affinity and positional stability. These hydrogen bonds orient the ligand appropriately within the cavity and may reduce local conformational flexibility.

In addition to polar interactions, multiple hydrophobic contacts are noted. π–alkyl interactions occur between the aromatic rings of the ligand and residues LEU43, ARG134, and ALA138, where a π–sigma interaction is detected with VAL135. These interactions together stabilize the aromatic core of the ligand within a hydrophobic microenvironment. The interaction pattern observed is consistent with known structural stabilization strategies targeting ApoE4. ApoE4 exhibits increased conformational instability compared to ApoE3 due to domain interaction between its N-terminal and C-terminal regions (Anthony et al., 2025). Small molecules that form stabilizing hydrogen bonds while reinforcing hydrophobic packing can reduce structural rearrangement and potentially mitigate pathogenic conformational transitions. The binding orientation of CID 892507 suggests that it may contribute to local structural rigidity by anchoring flexible regions through polar contacts and simultaneously enhancing hydrophobic core packing (Zhai et al., 2023).

Moreover, ligand binding in helix five, which is in the N-terminal of the protein, is considered the receptor binding region, and it carries a positive charge, and the drug contains a sulfonyl group, a negative charge, which increases binding within the cavity and may stabilise this region, thereby stabilising the full-length protein. Once the protein ApoE4 is stabilised to resemble APOE2 or APOE3, it leads to a reduced accumulation of amyloid beta, which impacts the treatment of Alzheimer's disease (Yamazaki et al., 2019).

In conclusion

We noted that the drug can stabilize the protein in two cases: the N-terminal region and full-length protein; therefore, this drug candidate requires further evaluation to ensure its safety and appropriate use for the treatment of Alzheimer's disease.

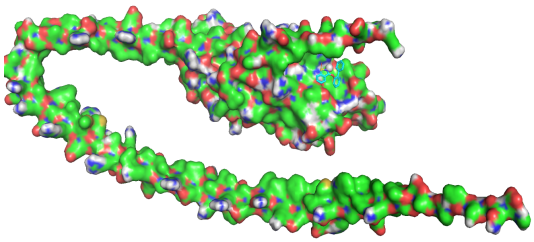

Figure 5: Display interaction between APOE4 and PubChem CID 892507

The molecular surface representation illustrates: The ligand buried within a defined binding cavity, Good steric complementarity between the ligand and ApoE4 surface, Hydrophobic patches (green) surrounding aromatic portions of the ligand, and polar regions (red/blue) accommodating the sulfonyl and heterocyclic moieties. This suggests: Proper pocket occupation, reduced solvent exposure of hydrophobic rings, and potential entropic stabilization. The ligand appears deeply embedded rather than superficially bound, indicating possible stable complex formation.

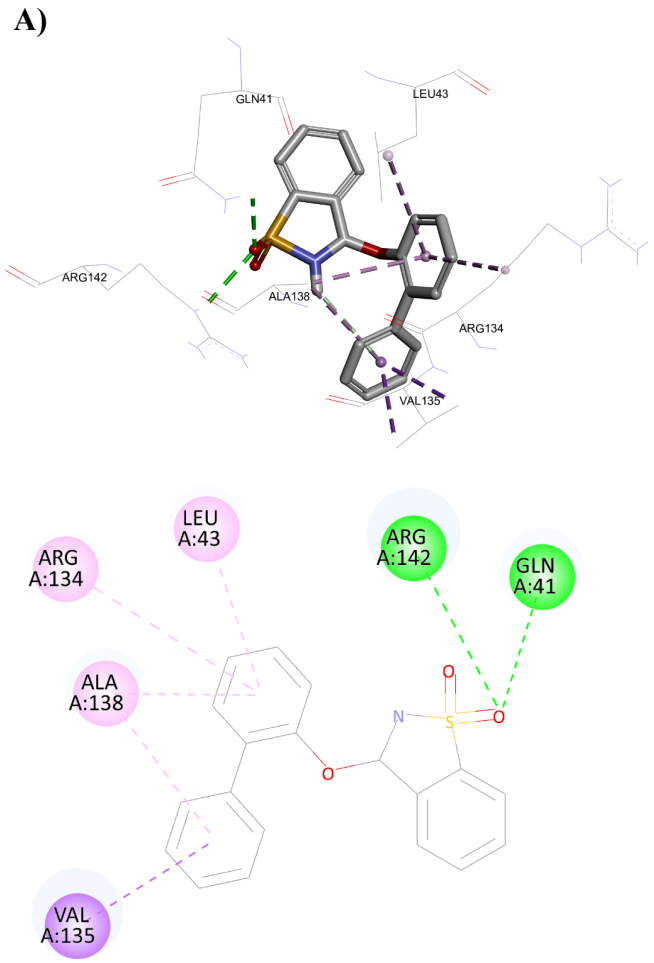

Figure 6: Three-dimensional and Two-dimensional for the APOE4 interaction with PubChem CID 892507.
The 3D and 2D interaction diagrams show PubChem CID 892507 docked within a binding pocket of the ApoE4 structure predicted by AlphaFold. The ligand is positioned in a hydrophobic cavity and forms multiple stabilizing interactions with s ing amino acid residues. Key interacting residues include: GLN41, LEU43, , VAL135, ALA138, and ARG142. In Figure A. It's demonstrated interactions in (conventional hydrogen bonds (green dashed lines): Between the sulfonyl oxygen atoms of the ligand and GLN41 and ARG142, π–alkyl interactions (pink dashed lines): With ALA138, ARG134, LEU43, and π–sigma interactions: With VAL135.The ligand's aromatic rings are buried in the hydrophobic region, while polar sulfonyl groups are oriented toward charged residues, suggesting favourable electrostatic complementary.

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