

Mapping the Ligand Binding Landscape of Nurr1 (NR4A2): Computational Characterization of Small-Molecule Interactions in Alzheimer's Disease Pathway

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AUTHOR BIOGRAPHY

Jiyao Zhou, an upcoming sophomore, currently attends Boston University. His main academic interests are within the discipline of bioinformatics and biotechnology. He first started this project to build experience in bioinfo through completing an independent study, the topic of which, elderly health, is also something he deeply cares about. He has experience in organic chemistry and has dealt with internship projects in a similar way of research on protein processing. Nevertheless, the project has a humbling and fruitful learning arc for him, and he plans to further explore computational structural biology and computer-aided drug design in future undergrad and graduate projects.

ABSTRACT

For a long time, Alzheimer's disease has been among the most commonplace and fearsome neurodegenerative disorders worldwide. It is characterized by progressive cognitive decline caused by a combination of each-interacting molecular pathological processes. Despite decades of effort, therapeutic strategies targeting single mechanisms such as β -amyloid or tau pathologies have failed to achieve durable disease modification. This leads to recently increasingly relevant focus on multi-axis regulatory approaches. Nuclear receptor related 1 protein(Nurr1/NR4A2) has been under the microscope as a promising, key transcriptional regulator of neuroinflammation, neuronal survival, and even mitochondrial function. Stacking evidence shows Nurr1 inactivity to Alzheimer's disease progression, providing grounds and necessity for this project to target it as a potential therapeutic.

In this project, a comprehensive, fully computational framework was developed to map out the ligand-binding features of Nurr1. To start off, Geometric, energetic, and machine-learning-based methods were deployed to identify, through different means, binding pockets. Then, Pharmacophore modeling and mass virtual screenings were subsequently applied to predict various candidate small molecules from trusted public chemical libraries. Next, molecular docking simulations were performed using SwissDock to eventually reveal multiple ligands with the most favorable binding energies and stable clusterings within the previously spotted cavity. Administration of the potential drug is then tested using virtual ADME and toxicity profiling, filtering down to refined candidates of drugs with optimal affinity and no

significant safety concerns. At the end, this project establishes a reproducible computational process for ligand and drug discovery, identifying multiple candidates for Nurr1, which, in the near future, can be put into practical testing grounds for validation and eventually clinical drug design.

INTRODUCTION

Historical Context and Hypotheses:

Before our very discovery and since then the long history of combat against it, Alzheimer's disease has always been and continues to be the most common cause of dementia, marked by progressive cognitive decline, memory loss, and eventual impairment of daily functioning[1]. Since its clinical characterization in the early 20th Centuries, several hypotheses have been put under the microscope to unveil its pathogenesis. The first and earliest cholinergic hypothesis theorizes that memory deficits are to be attributed to lowered acetylcholine level and damaged cholinergic neurons throughout the brain. Subsequent work in the 1990s turned to the amyloid-cascade hypothesis, which posits that β -amyloid plaque/accumulation is the primary driver. [2] Another is the Tau Hypothesis—that abnormal tau protein phosphorylation and neurofibrillary tangle formation were the causes of Alzheimer's disease—grew out of work done by the laboratories of researchers (around 1986—tau & paired-helical filaments discoveries) who clinically documented tau hyperphosphorylation in brain tissues from patients with AD. However, despite extensive investigations over decades, therapeutic approaches aiming to modify single pathological pathways, either β -amyloid or tau, have failed to produce clinically breakthrough success in relation to disease modification.

Neuroinflammation and the Multi-Pathway Model:

Recent investigation has revealed neuroinflammatory mechanisms to be a prime focus: chronic activation of microglia and astrocytes, chronic expression of inflammatory cytokines and reactive oxygen species, and breakdown of immune homeostasis within the brain, compounded to produce the major characteristics of the AD condition [4, 5]. Evidence exists to suggest that neuroinflammation is by no means an epiphenomenon of Alzheimer's disease but may significantly worsen the pathological development of amyloidosis and neurofibrillary tangles through positive feedback effects [6]. Within this framework, the pathogenesis of Alzheimer's disease is increasingly understood as a multi-adaptation interactive network in which amyloid cascade reactions, tau hyperphosphorylation, neuroinflammatory response, mitochondrial dysfunction, synaptic transmission failure, changes in vascular microenvironment, and immune dysfunction are interrelated, suggesting that coordinated regulation of multiple pathological variables may be the more effective therapeutic strategy.

Nurr1 as a Multi-Axis Therapeutic Regulator:

One promising target buried in this multi-pathway therapeutic potential is the nuclear receptor NR4A2 (also known as Nurr1). Nurr1 is an example of a multi-axis regulator, an orphan nuclear receptor of the NR4A family that is highly expressed in the central nervous system(CNS), including dopaminergic

and glutamatergic neurons, where it regulates gene networks related to neuronal differentiation, mitochondrial fitness, oxidative stress, and inflammatory signalling [7]. Nurr1, under normal physiological conditions, is a transcription factor that has the capacity to inhibit NF- κ B-mediated pro-inflammatory gene activation (for example, through recruitment of the CoREST complex), leading to neuroprotective and anti-inflammatory effects [8].

Notably, downregulation of Nurr1 has been observed in AD mouse models and post-mortem human brains to be correlated with disease progression and A β pathology. Small-molecule agonists such as *amodiaquine* and *vidofludimus* have been used to pharmacologically induce Nurr1 activation, successfully restoring neuronal viability, enhancing dopaminergic signaling, and suppressing inflammatory cascades [9,10]. Structural studies have shown that these small molecules bind to surface pockets formed by helices 1, 5, 7, and 8 of the Nurr1 ligand-binding domain (LBD), which impacts receptor dimerization and coregulator exchange [10].

METHODOLOGY

The protein code used for all experimentation and data collection of human Nurr1 LBD was retrieved from the Protein Data Bank (PDB ID: 5Y41)

This study utilizes a computational, strict-structure-based drug discovery methodology to characterize ligand-binding properties of the Nurr1 protein and identify potential therapeutic candidates relevant to the infamous Alzheimer's disease pathway key.

The design follows a multi-stage procedure:

1. Protein preparation and structural optimization(optional)
2. Binding pocket identification (geometric, energetic, ML-based)
3. Interaction validation and structural interpretation
4. Ligand screening and docking simulations
5. Pharmacokinetic and toxicity filtering

A key design principle is methodological triangulation, where multiple independent computational approaches are used to identify and validate binding pockets. Thus convergent results across these methods increase confidence in biological relevance.

1. Geometric Method: DoGSiteScorer (Proteins.plus)

URL: <https://proteins.plus/>

THEORETICAL FRAMEWORK

A protein is considered a viable therapeutic target only if it contains druggable binding sites, defined as surface cavities capable of accommodating small molecules and modulating protein function upon binding.

DoGSiteScorer identifies such sites using a purely geometric and physicochemical approach, independent of prior ligand knowledge. This is especially critical for Nurr1, which lacks a canonical deep binding pocket typical of classical nuclear receptors.

Geometric pocket detection identifies cavities based purely on protein shape and surface properties. This provides an unbiased, structure-only assessment of whether the protein can physically accommodate small molecules, independent of prior biological knowledge.

The three-dimensional structure of the human Nurr1 is able to be retrieved by the database by recognizing our PDB. Before downstream analysis, the following preprocessing steps were applied.

DoGSiteScorer calculates and marks potential ligand-binding cavities based on geometric and physicochemical analysis of the protein surface. First on parameters such as pocket volume, surface area, depth, and hydrophobicity to quantify binding potential. Subsequently, the method detects regions where molecular docking is most favorable based purely on geometry and atom density.

1. Upload the cleaned Nurr1 PDB to <https://proteins.plus/>.
2. Select DoGSiteScorer and run with default parameters.
3. Record pocket volume, surface area, and druggability score.
4. Retain the top-ranked pockets for comparison with later methods.

ALGORITHMIC BASIS

DoGSiteScorer operates on a Difference of Gaussian (DoG) filtering framework applied to a three-dimensional grid representation of the protein surface, in which the protein structure is first embedded into a spatial grid and subsequently analyzed using Gaussian filters at multiple scales to detect variations in atomic density; regions of concavity are then extracted as candidate binding pockets, enabling the identification of surface grooves, buried cavities, and partially enclosed binding regions without reliance on pre-bound ligands. For each detected pocket, the method computes a comprehensive set of descriptors, including geometric parameters such as volume ($\text{\AA}^3$), which reflects ligand accommodation capacity, surface area ($\text{\AA}^2$), which indicates accessibility, and depth or enclosure, which measures the degree of burial; physicochemical properties such as hydrophobicity ratio, amino acid composition, and elemental composition, which together characterize the chemical environment; and structural context features such as residue counts and spatial atom distribution within the pocket. These descriptors are then integrated into two druggability scoring schemes: a simple linear model based on hydrophobicity, size, and shape—where larger, more hydrophobic pockets are generally considered more druggable—and a more advanced machine learning-based model that combines geometric, physicochemical, and structural features to generate a normalized druggability score ranging from 0 to 1, where scores above 0.7 indicate highly druggable pockets, values between 0.4 and 0.7 indicate moderate druggability, and scores below 0.4 suggest low druggability.

2. Energetic Method—FTSite

URL: <https://ftsites.bu.edu/>

Geometric pockets may exist but be energetically unfavorable for ligand binding. FTSite addresses this limitation by identifying **energetically preferred interaction regions**, answering the

question: where would small molecular fragments naturally bind based on interaction energy alone?

FTSite places a library of small chemical probes onto the protein surface and identifies regions where probes repeatedly cluster due to favorable van der Waals, electrostatic, and hydrophobic interactions. These clusters represent binding “hotspots.”

1. Upload the same prepared Nurr1 PDB to <https://ftsites.bu.edu/>.
2. Use default probe and clustering parameters.
3. Download the predicted hotspot coordinates.
4. Compare their spatial location to DoGSiteScorer pockets.

3. Machine Learning Method: PrankWeb

URL: <https://prankweb.cz/>

PROCEDURAL REPLICABILITY:

While geometric and energetic methods are physics-based, they do not incorporate biological patterns learned from known protein–ligand complexes. PrankWeb complements these approaches by using a trained neural network to predict binding probability at the residue level. PrankWeb’s DeepSite model evaluates local atomic environments and evolutionary conservation to assign binding likelihood scores to residues. High-probability residues that cluster spatially indicate likely ligand-binding regions.

1. Submit Nurr1 to <https://prankweb.cz/>.
2. Run prediction with default settings.
3. Record the top-ranked pockets and residues.
4. Identify overlap with geometric and energetic predictions.

4. Virtual Screening: Pharmacophore Map

From pocket prediction to ligand discovery, pharmacophore mapping and a virtual screening process were performed using Pharmit and compatible visualization tools. (See Figures for concept workflow visuals.)

A pharmacophore is a 3D arrangement of features that permit a ligand to bind to its target receptor, specifically, hydrogen bond donors/acceptors, aromatic rings, hydrophobic centers, and charged groups. These features were obtained from the Nurr1 LBD binding pocket, compellingly deduced from previous analyses.

URL: <https://pharmit.cbs.pitt.edu>

Pharmit affords large-scale structure-based screening using pharmacophore maps and millions of compound evaluations from public libraries such as Enamine(Used here) and Molport.

5. Docking Simulations

5.1 SwissDock

Pharmacophore screening identifies candidates that match abstract features, and now we need to predict the candidates' potential binding orientations or affinity to compare levels of performance, evaluating how each ligand fits into the pocket of Nurrl.

To proceed, upload the protein code and ligand SMILES onto <https://www.swissdock.ch/>. Define the perimeters of the docking box around the selected pocket as precisely as possible to previously discovered pocket space in previous experiment 1-3, avoiding making the box excessively large, as that would induce risks of not passing the predocking checks, as well as increase runtime. Next, run docking, record the AC score and the SwissParam score, repeat the process for as many candidates as desired, which in this project is all 13. With all data recorded, select the lowest energy pose for each ligand and compare to select the top 5 best candidates.

5.2 Drug-likeness and ADME filtering

Strong binding is now filtered and has been confirmed as a shared trait in our top five drug candidates. It is now important to verify their actual therapeutic viability. Sometimes a seemingly perfect candidate might not be a usable drug base at all. Compounds must also possess physicochemical properties compatible with absorption, distribution, metabolism, and excretion.

Use the SwissADME(<http://www.swissadme.ch/>) to all in once input our step-by-step selected five compounds SMILES to gain data on molecular weight, HBD, HBA, and logP for each. Apply Lipinski's Rule of Five to test each candidate, removing compounds that violate multiple criteria.

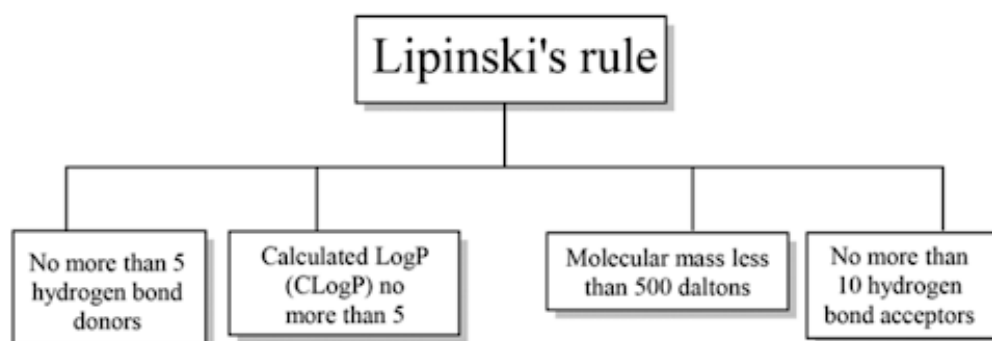
Lipinski's Rule of Five is a set of empirically derived, widely acknowledged guidelines proposed by Christopher A. Lipinski to describe the physicochemical property space possessed by most orally prescribed small-molecule drugs in the market. They are, though, not absolute rules, but heuristics to identify compounds with a very high likelihood of having an actual potential pharmaceutical future.

Molecular weight ≤ 500 daltons: Larger molecules tend to exhibit reduced membrane permeability and poor absorption.

No more than 5 hydrogen bond donors (HBD): Hydrogen bond donors (e.g., $-\text{NH}$, $-\text{OH}$ groups) increase polarity and may hinder passive diffusion across biological membranes.

No more than 10 hydrogen bond acceptors (HBA): Excessive hydrogen bond acceptors similarly increase polarity and reduce permeability.

Calculated logP (cLogP) ≤ 5 : LogP is a measure of lipophilicity; overly lipophilic compounds often suffer from poor solubility and metabolic instability, while overly hydrophilic compounds struggle to cross lipid membranes.



6. Toxicity Prediction

With all drug potentials of top candidates unveiled and ranked, early identification of safety risks are now the priority, preventing costly downstream failures. Mature, in-silico toxicity predictors can do a good job providing preliminary risk assessments prior to in-lab testing.

Submit the final few compounds to the toxicity prediction platform ProTox 3.0 <https://tox.charite.de/protox3/index.php?site=home>. This model is trained on large curated datasets of compounds with experimentally validated toxicological outcomes and supports prediction across organ toxicity, molecular initiating events, nuclear receptor signaling pathways, and clinical toxicity endpoints.

RESULTS AND DATA:

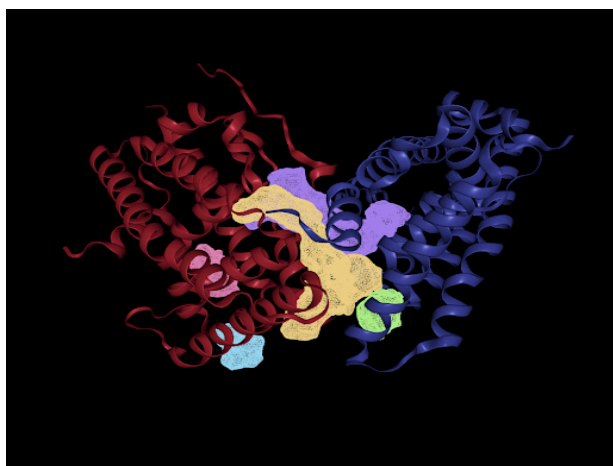


Fig. 2

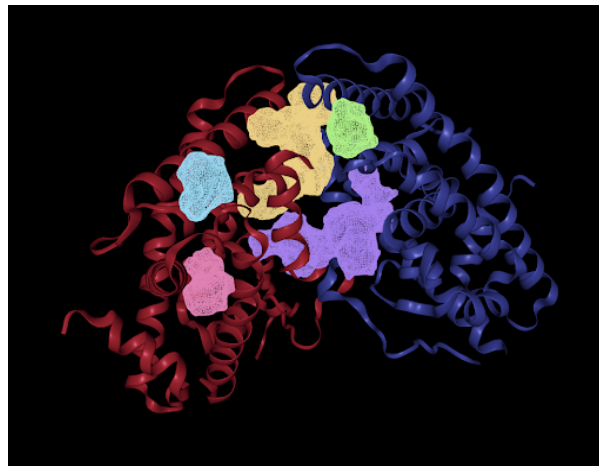


Fig. 3

Predicted binding pockets on the Nurr1 LBD identified using DoGSiteScorer, shown in two Orientations

Keys(2,3):.

- Red/Blue: Protein structure
- Yellow: Top-ranked pocket
- Purple: Secondary pockets
- Green/Cyan: Minor pockets

Pharmacophore Maps:

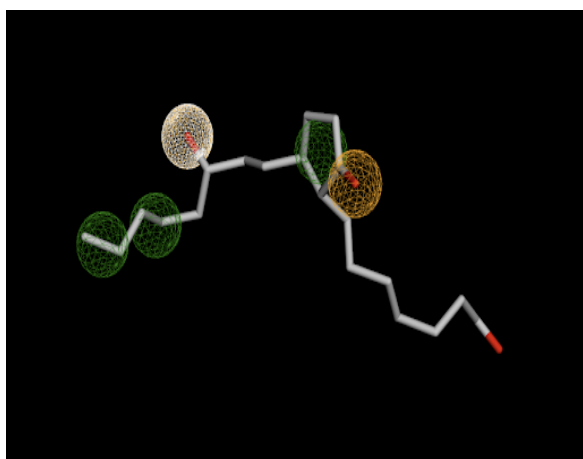


Fig.4

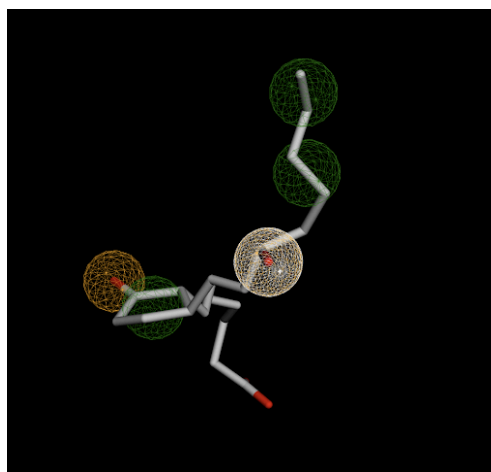


Fig. 5

Pharmacophore features derived from the predicted binding pocket for virtual screening.

Key:

- White: Ligand structure
- Green: Hydrophobic features
- Orange: H-bond acceptors
- White/Gray spheres: H-bond donors
-

2. Tables:

a. Geometric Method

	Volume ($\text{\AA}^3$)	Surface Area ($\text{\AA}^2$)	Drug Score
Pocket 1 (yellow)	826.92	1077.77	0.8

Pocket 2(purple)	782.21	737.27	0.85
Pocket 3(green)	149.59	233.84	0.27

b. Energetic(FT Site)
c. Machine Learning Method: PrankWeb

Rank ↑	Score	Probability	# of residues	Avg conservation
1	8.21	0.482	19	0.655
2	5.00	0.237	11	0.884
3	4.32	0.192	10	0.986

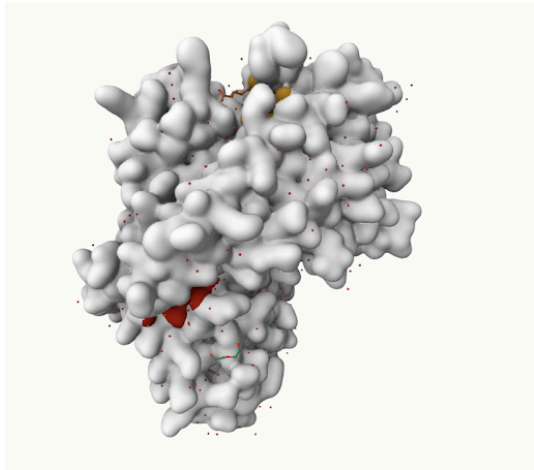


Fig. 6

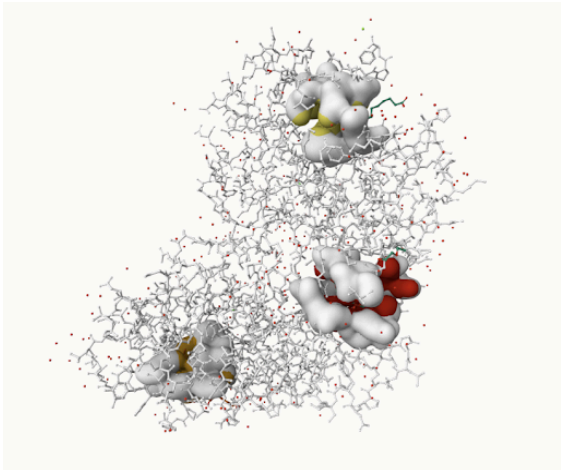


Fig. 7

Binding site prediction using PrankWeb with ranked pocket probabilities.

Key:

- Red: High probability regions
- Yellow: Moderate probability
- White: Protein surfaces

Pocket 1(Red) result aligns with the pocket 1 of highest drug score from the geometric model.

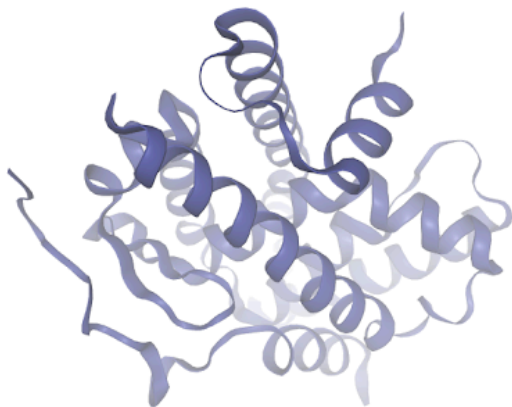
MOLPORT DATABASE: TOP 13 MOST COMPATIBLE LIGANDS

Num	SMILES	RMSD	Mass	RBnds	Figure
1	<chem>N1C2=CC=C(C=C2C=C(CC(C(NCCCN2CCCC2)=O)C=1O)C</chem>	0.192	355	8	
2	<chem>CCCCC[C@@H](/C=C/[C@H]1C=CC(=O)[C@@H]1C/C=C/CCCC(=O)O)O</chem>	0.202	334	12	
3	<chem>CCCCC[C@@H](/C=C/[C@H]1C=CC(=O)[C@@H]1C/C=C/CCCC(=O)O)O</chem>	0.213	350	12	
4	<chem>[C@]1(CO)(C2=CC=C(C=C2)F)[C@@H](O)CCN(CCC(COC2C=CC=CC=2)C1</chem>	0.225	387	9	
5	<chem>CCCCCC(/C=C/[C@@H]1C(C(CC1=O)O)C/C=C/CCCC(=O)O)O</chem>	0.254	352	12	
6	<chem>N1(CC2(CCN(CC2)CC2=CC=NN2C)CC(O)C1(C)C)C(C)=</chem>	0.256	334	3	

	O				
7	<chem>N1(C(C2=CC=C(C=C2)Br)C(C=N1)C1C(O)=NC2C(=CC(=CC=2)Br)C=1C1C=CC=CC=1)C(=O)C1C=C(OC)C=C(O)C=1</chem>	0.268	687	7	
8	<chem>C12C(NCCC=1C1=C(C=CC=C1)N2)C1=C=C(C(CSC2S C3=C(C=CC=C3)N=2)=C1)OC.Cl</chem>	0.287	458	5	
9	<chem>C12C(C3C=C(C=CC=3)C(C)(C)C)N(C(=O)C1=NNC=2C1C(O)=CC(=C(Cl)C=1)C)CCCO</chem>	0.290	454	6	
10	<chem>N1(C(CCSC)C(=O)NC2=CC=C3C(OCC(=O)N3)=C2)C(=O)C2=CC=CC=C2N=C1O</chem>	0.290	440	7	
11	<chem>C1(C(C2C=CC(=CC=2)OC)N(C(=O)C=1O)CCCN(CC)CC)C(=O)C1=C(O)C=C(C(C)=C1)C</chem>	0.295	467	10	
12	<chem>CN(CCCN1C(</chem>	0.296	285	4	

	<chem>=O)C(O)=C(C(C2=C(O)C=C(C)C(C)=C2)=O)C1C1=CC(N(=O)=O)=CC=C1)C</chem>				
13	<chem>C1(C2=NCCSC(C3C=CC=C(O)C=3)C2)=C(O)C=C(OC1=O)C</chem>	0.297	453kk	8	

SWISSDOCKING:



Parameters:
Box center: 15 - -37 - -3
Sampling exhaustivity: medium
Number of RIC: 1

Box size: 20 - 23 - 22
Cavity prioritization: buried

RESULTS CHART:

Molecule	Best SwissParam Score
#1: <chem>N1C2=CC=C(C=C2C=C(CCC(NCCCN2CCCCC2)=O)C=1O)C</chem>	-7.2008
#5 <chem>CCCCC(/C=C/[C@@H]1C(C(CC1=O)O)C/C=C/C/CCCC(=O)O)O</chem>	-7.3857
#3 <chem>CCCC[C@@H](/C=C/[C@H]1C=CC(=O)[C@H]1C/C=C/C/CCCC(=O)O)O</chem>	-7.3097
#2 <chem>CCCC[C@@H](/C=C/[C@H]1C=CC(=O)[C@H]1C/C=C/C/CCCC(=O)O)O</chem>	-7.2628
#10 <chem>N1(C(CCSC)C(=O)NC2=CC=C3C(OCC(=O)N3)=C2)C(=O)C2=CC=CC=C2N=C1O</chem>	-7.5231

Docking Rank:

1. Sample 1
2. Sample 5
3. Sample 3
4. Sample 2
5. Sample 10

Docking simulations were conducted using SwissDock (Attracting Cavities 2.0) with the Nurr1. The ligand exhibited a best-pose AC Score of around -71.9 kcal/mol and a SwissParam binding energy of around -7.64 kcal/mol, suggesting strong affinity for the pocket between Chain A and B. Consistent clustering and buried cavity prioritization confirmed stable binding conformations, which align with known Nurr1 agonists aforementioned in literature in the introduction section.

DRUG PROPERTIES TESTING:

Molecule	MW(g/mol)	HBD	HBA	Consensus Log P	LiPinski Result
#1	355.47	2	4	3.18	Pass
5	352.47	3	5	2.97	Pass
3	334.45	2	4	3.63	Pass
2	334.45	2	4	3.63	Pass
10	440.47	3	6	1.81	Pass

TOXICITY PREDICTION:

Molecular #1:

Predicted LD50: 200mg/kg

Predicted class: 3

Category	Target	Prediction	Probability
Organ toxicity	Neurotoxicity	Active	0.83
Organ toxicity	Respiratory toxicity	active	0.77
Toxicity endpoints	Immunotoxicity	active	0.65
Toxicity endpoints	BBB-barrier	active	0.65
Toxicity endpoints	Clinical toxicity	active	0.78
Molecular initiating event	Acetylcholinesterase	active	0.80

Molecule #5:

Predicted LD50: 500mg/kg

Predicted class: 4

Category	Target	Prediction	Probability
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Organ toxicity	Respiratory toxicity	active	0.98
Toxicity endpoints	BBB barrier	active	0.53
Toxicity endpoints	Clinical toxicity	active	0.61
Molecular initiating event	NADH-quinone oxidoreductase	active	0.71

Molecular #3:

Predicted LD50: 400mg/kg

Class: 4

Organ toxicity	Respiratory toxicity	active	0.92
Toxicity endpoints	immunotoxicity	active	0.91
Toxicity endpoints	BBB-barrier	active	0.54
Toxicity endpoints	Clinical toxicity	active	0.55
Molecular initiating event	NADH-quinone oxidoreductase	active	0.70

Molecule #10:

Predicted LD50: 1000mg/kg

Predicted Class: 4

Organ toxicity	Neurotoxicity	active	0.81
Organ toxicity	Respiratory toxicity	active	0.86
Organ toxicity	Clinical toxicity	active	0.77

CONCLUSION

In the project, we describe a computational treatment of small-molecule binding to the Nurr1 ligand-binding domain that begins systematically from first principles, and arises from an unmet clinical need for therapeutics targeting AD's multi-faceted pathology. By combining geometric cavity detection with energetic fragment mapping and machine learning residue-level prediction, a converged binding

pocket was consistently determined among different methodologies: convergent-predicted across isolated groups, which made us more confident of the biological relevance.

Pharmacophore modeling turned these structural mappings into screenable constraints to rapidly examine tens of thousands of compounds. Pharmacophore-based virtual screening and SwissDocking result in the identification of a number of top-ranked (mainly molecules #1, #3, #5, #2, and #10, see table 3) with a consistent clustering profile with favorable binding energies and best SwissParam scores as low as -7.64 kcal/mol. These docking outcomes indicate stable, buried binding conformations that are in agreement with agonist-type binding as opposed to nonspecific surface binding.

These 5 leading candidates all met Lipinski's Rule of Five, according to drug-likeness and ADME analysis, and toxicity predictions showed tolerable but not insignificant safety signals, such as respiratory toxicity, BBB penetration, and specific molecular initiating events like NADH-quinone oxidoreductase interaction. Crucially, different chemicals had different toxicity profiles, which made it possible to rationally prioritize options rather than reject them outright (Though all of them are theoretically viable therapeutic candidates). This distinction is crucial from a commercial and translational standpoint since early-stage computational triage lowers the expense and failure risk of subsequent experiments.

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