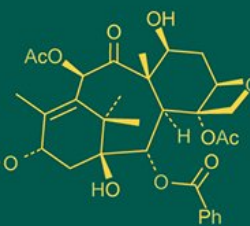
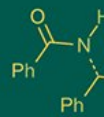


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Structure-guided cheminformatics optimization of NLRP3 inhibitors based on the NP3-253-NLRP3 complex for potential neurodegenerative disease therapeutics

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Abstract

The NLRP3 inflammasome is an important regulator of innate immune signaling and has been strongly implicated in chronic neuroinflammation associated with neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Despite the therapeutic potential of NLRP3 inhibitors such as MCC950, no NLRP3-targeted drug has yet to receive clinical approval, highlighting the need to identify novel candidates with favourable binding and drug-like properties. This study aimed to identify and priorities potential small-molecule inhibitors of NLRP3 using an integrated structure-based computational approach. The three-dimensional structure of (PDB ID: 9GU4), co-crystallized with the inhibitor NP3-253, was retrieved. Sequence conservation, structural validation, and binding-site analysis were performed to identify a biologically relevant target pocket within the NACHT domain. A library of 23 tricyclic compounds obtained from ChEMBL was subsequently screened using molecular docking with AutoDock Vina. The resulting docked compounds were further evaluated using multiple drug-likeness and pharmacokinetic criteria, including Lipinski's Rule of Five, PAINS filtering, synthetic accessibility, blood-brain barrier permeability, and ADMET prediction. The docking analysis produced binding affinities ranging from -6.563 to -4.679 kcal/mol. Sequential filtering based on binding affinity and drug-likeness narrowed the initial library to 10 promising compounds. Among these, ChEMBL422, ChEMBL1688551, and ChEMBL11 emerged as the most favourable candidates based on their overall binding and predicted pharmacokinetic profiles. Chemical space analysis further indicated a strong conservation of the dibenzothiazine scaffold across the screened compounds, suggesting a potential role for hydrophobic interactions in ligand recognition within the target pocket. The shortlisted compounds are promising candidates for further experimental validation and may serve as starting points for future hit-to-lead optimisation and the development of NLRP3-targeted therapeutics for neuroinflammatory and neurodegenerative conditions.

Keywords: NLRP3 inflammasome, structure-based drug design, cheminformatics, molecular docking, NP3-253, NLRP3 inhibitors, neurodegenerative diseases

Introduction

Neurodegenerative diseases are progressive disorders characterised by the deterioration of neuronal structure and function, ultimately leading to cognitive, motor, and behavioural impairments. Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative disorders collectively represent an increasing global health burden, particularly with population ageing. Although these diseases differ in their clinical and pathological manifestations, accumulating evidence indicates that dysregulated interactions between the immune system and the central nervous system (CNS) are common features of disease progression [1]. The principal resident immune cells in the CNS, microglia, play a critical role in maintaining neuronal homeostasis by monitoring the neural environment, removing cellular debris, and responding to injury or infection. However, persistent microglial activation can promote chronic neuroinflammation and contribute to neuronal dysfunction and degeneration. One of the major innate immune pathways implicated in this process is the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome.

NLRP3 functions as an intracellular sensor of cellular stress and danger-associated signals, responding to diverse stimuli, including damaged-cell components, microbial products, and environmental stressors^[2]. NLRP3 assembles with the adaptor protein ASC and pro-caspase-1, resulting in caspase-1 activation. Caspase-1 activation promotes maturation of the pro-inflammatory cytokines interleukin-1 β (IL-1 β) and interleukin-18 (IL-18) and can induce pyroptosis, thereby amplifying inflammatory signalling. While this pathway is essential for host defence, sustained NLRP3 activation in microglia can produce prolonged inflammatory responses and contribute to neuronal injury. Increased NLRP3 activity has been associated with AD and PD, where it may interact with pathological protein aggregation, synaptic dysfunction, and neuronal loss.^[3] Consequently, NLRP3 is likely to be one of the most potential therapeutic targets for neurodegenerative diseases. Small-molecule NLRP3 inhibitors have demonstrated encouraging anti-inflammatory effects in preclinical models, although no NLRP3-targeting compound has yet achieved broad clinical approval^[4]. Structure-guided optimisation and cheminformatics approaches may therefore facilitate the identification of potent, selective, and drug-like NLRP3 inhibitors for future neurodegenerative disease therapeutics.

2. Methodology

2.1 Visualization and Validation of Sample

The crystal structure of human NLRP3 bound to NP3-253 (PDB ID: 9GU4) was visualized using RasMol and PyMOL to examine its overall fold, domain organization, and NACHT-domain-ADP cofactor arrangement. Structural quality was evaluated using SAVES and ERRAT, which assess stereochemical and nonbonded interaction quality.^[5] Structural similarity between 9GU4 and the reference structure 7ALV was assessed using PyMOL alignment and C α RMSD analysis.

2.2 Fetching of NLRP3 Structure

The 9GU4 structure was fetched from the Protein Data Bank in mmCIF format and converted to PDB format using Open Babel. Chain A contained 4,024 atoms and 488 resolved residues (130-895). The similar protein sequence was extracted for subsequent similarity and conservation analyses.

2.3 Similarity and Conservation of Sequence

The chain-A sequence was compared with other NLRP3 sequences using BLAST to identify homologous and conserved regions^[6]. Multiple-sequence alignment and physicochemical colour coding facilitated the identification of conserved residues that are potentially important for structural stability and function.

2.4 Preparation of Receptor and Binding-Site Identification

The receptor was converted into PDBQT format using Open Babel for AutoDock Vina docking^[7]. Potential binding pockets were identified using fpocket, which evaluates cavity geometry, volume, solvent accessibility, hydrophobicity, and druggability^[8,9]. Thirty-one candidate pockets were identified, with the biologically relevant NP3-253-binding region selected for docking.

2.5 Ligand Library Preparation

Twenty-three structurally related dibenzothiazepine, dibenzothiazine, and dibenzazepine derivatives were selected from ChEMBL. Canonical SMILES were converted into three-dimensional conformers using RDKit ETKDG and optimized using UFF. Ligands were subsequently converted to PDBQT format using Open Babel^[10,11].

2.6 Hit identification via Virtual screening

Multiple binding poses were generated for each ligand and ranked according to predicted binding affinity with the help of AutoDock Vina. The lowest-energy poses were retained for structural analysis and subsequent candidate prioritization^[12,13].

2.7 Cheminformatics and ADMET Analysis

RDKit was used to calculate molecular descriptors, including molecular weight, LogP, TPSA, hydrogen-bonding properties, and rotatable bonds. Lipinski's Rule of Five, PAINS filtering, and synthetic accessibility were assessed. Morgan fingerprints supported similarity analysis, hierarchical clustering, and chemical-space visualization, while Bemis-Murcko scaffolds identified common structural frameworks. ADMET-AI was used to predict blood-brain barrier permeability, hERG inhibition, hepatotoxicity, and AMES mutagenicity. Finally, docking scores and pharmacokinetic, structural, and toxicity parameters were integrated into a multiparameter ranking framework for prioritizing potential NLRP3 inhibitors^[14,15].

3. Results

3.1 Retrieved Structure Overview

The three-dimensional structure of NLRP3 (PDB ID: 9GU4), retrieved and processed, served as the receptor model for all subsequent analyses in this study. The structural coverage is non-continuous, with several distinct gaps interrupting the sequence. These gaps correspond to regions that were not resolved in the experimental electron density, reflecting flexible loops and linker segments with high conformational mobility. Such discontinuities are common in large multidomain proteins, where highly flexible regions connecting folded domains often remain structurally undefined, even in high-quality crystallographic datasets. The overall distribution of resolved residues indicates that the structured regions of NLRP3 relevant to docking and binding-site analysis are well represented in the 9GU4 model, whereas the unresolved regions are primarily located away from the nucleotide-binding pocket examined in this study^[16,17].

3.2 Structural Quality and Validation

The 9GU4 structure returned an ERRAT score exceeding 90%, a level generally considered indicative of a reliable, well-refined structural model at the 2-3 Å resolution range applicable to this entry. To further assess stereochemical quality, the ϕ (phi) and ψ (psi) backbone dihedral angles were calculated for all residues in chain A and visualized as a Ramachandran plot. The majority of residues cluster within the favoured regions associated with α -helical and β -sheet conformations, consistent with the mixed secondary-structure composition expected of the NLRP3 NACHT domain^[18,19].

3.3 Hydrophobicity Profile

The resulting profile shows alternating hydrophobic and hydrophilic stretches distributed along the sequence, reflecting the heterogeneous physicochemical character typical of a cytosolic, multidomain protein. Notably, no extended hydrophobic stretch characteristic of a transmembrane helix was observed anywhere in the profile,

which is consistent with the known cytosolic localization of NLRP3. Instead, several shorter, localized hydrophobic regions are visible, which likely contribute to the formation of stable hydrophobic cores within the folded domains and may additionally correspond to surfaces relevant to ligand binding, a possibility examined further during binding-site identification^[20, 21].

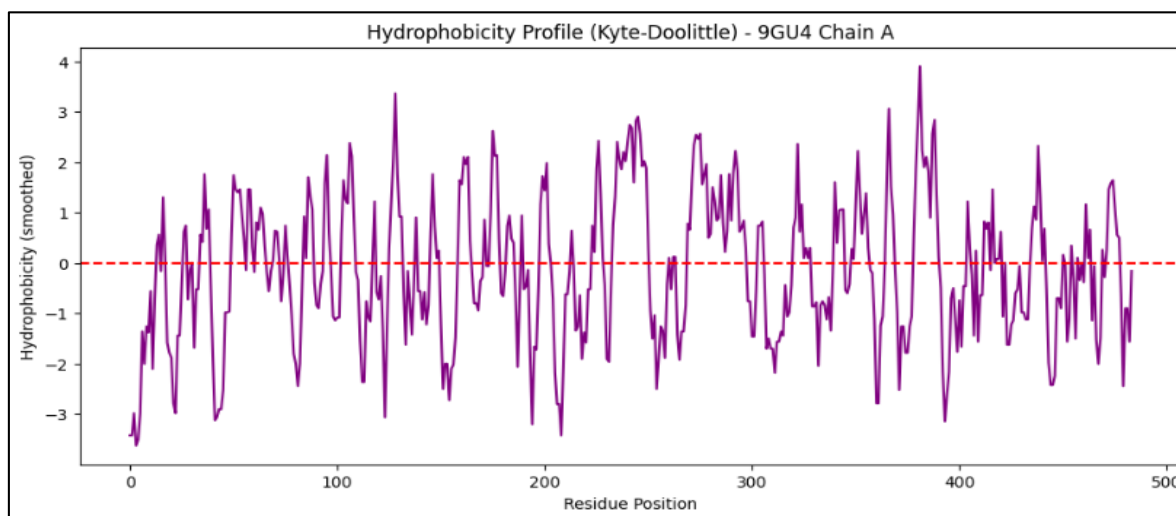


Fig 1: Smoothed Kyte-Doolittle hydrophobicity profile across the NLRP3 sequence (chain A). The profile was generated using a sliding-window averaging approach to reduce local fluctuations in residue-level hydropathy values. Positive scores indicate hydrophobic regions, while negative scores correspond to hydrophilic regions. The dashed red line represents the neutrality threshold (0.0).

3.4 B-Factor Analysis: Residue Flexibility and Structural Stability

Residue-level flexibility across the 9GU4 structure was examined by computing average B-factor values per residue and summarizing their distribution in a histogram. The per-residue profile shows substantial variation across the structure, with values ranging from approximately 27 to 105. Several regions exhibit elevated B-factors, indicating

increased atomic displacement and local conformational flexibility, while other segments show comparatively lower values consistent with more rigid, structurally ordered regions. In general, lower B-factor values are concentrated in the protein core, including the nucleotide-binding region, whereas higher values are enriched in surface-exposed loops, in line with the pattern typically expected for a folded, multidomain protein^[22, 23].

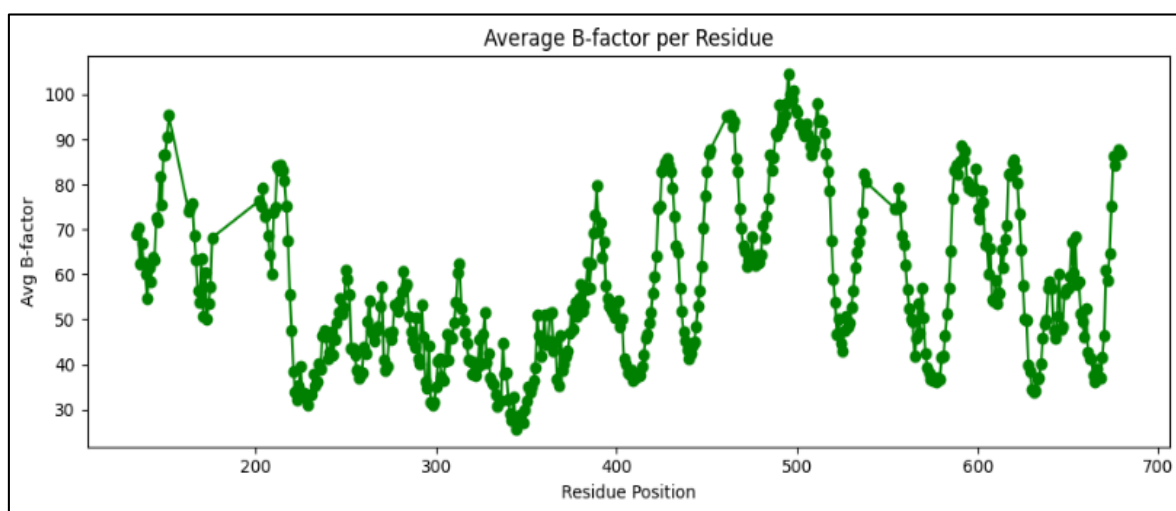


Fig 2: Average B-factor per residue across the NLRP3 chain. Higher values indicate increased conformational flexibility, while lower values correspond to more ordered regions.

3.5 Atomic Composition and Residue Mass Distribution

The elemental composition of the modelled protein was also examined, showing the expected predominance of carbon, followed by oxygen and nitrogen, with a comparatively small proportion of sulphur, consistent with a standard protein composed of the 20 canonical amino acids. The relatively low sulphur content reflects the limited

occurrence of cysteine and methionine residues, which are typical of most protein sequences. No anomalous residue masses were detected, confirming that the modelled structure consists solely of standard proteinogenic residues suitable for the downstream chemoinformatic and docking analyses that follow.

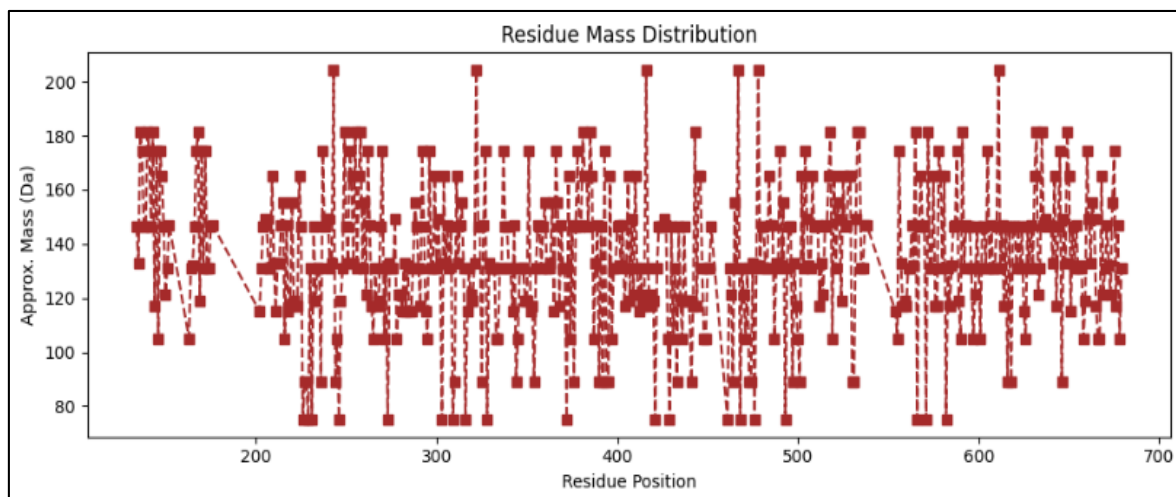


Fig 3: Per-residue molecular mass distribution across the NLRP3 sequence, calculated using standard amino-acid mass values.

3.6 RMSD Comparison

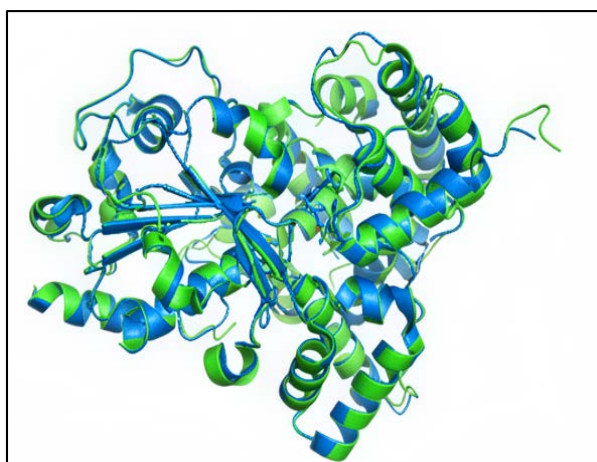


Fig 4: Structural superposition of 9GU4 (green) and 7ALV (blue) generated using PyMOL. The close overlap of the aligned structures and the low RMSD value (0.494 Å) indicate a high degree of structural similarity, consistent with the complete sequence conservation observed

3.7 Molecular Docking Results

All 23 prepared ligands were docked against the prepared NLRP3 receptor using AutoDock Vina. For each ligand, multiple candidate binding poses were generated and ranked by predicted binding free energy; the lowest-energy pose was retained as the representative docked conformation. Predicted binding affinities ranged from -6.563 kcal/mol (CHEMBL1688549) to -4.679 kcal/mol (CHEMBL1764), a

spread of approximately 1.9 kcal/mol across the library. While none of the 23 compounds reached binding energies typically associated with high-affinity lead compounds (generally below -8 kcal/mol), every ligand produced a negative docking score, indicating that the shared tricyclic scaffold is broadly compatible with the geometry of the NLRP3 nucleotide-binding pocket, even where individual substituents produce weaker or stronger predicted binding. The five top-ranked compounds, CHEMBL1688549, CHEMBL422, CHEMBL1688551, CHEMBL11, and CHEMBL570, span both dibenzothiazine and dibenzazepine scaffolds, suggesting that the binding site geometry can accommodate more than one closely related chemotype rather than favouring a single rigid scaffold shape. Notably, no clear correlation was observed between predicted docking score and experimental IC_{50} . For example, CHEMBL1688548 ($IC_{50} = 700$ nM, among the most potent compounds experimentally) ranked only ninth by docking score, while CHEMBL11 ($IC_{50} = 22,000$ nM, comparatively weak experimentally) ranked fourth. This discrepancy is expected rather than concerning: the IC_{50} values were originally measured against a different biological assay target, whereas docking here was performed specifically against the NLRP3 nucleotide-binding pocket. From a structure-activity perspective, several trifluoromethyl-substituted dibenzothiazine derivatives appear among the better-ranked compounds, suggesting this substitution pattern may offer favourable complementarity with the NLRP3 pocket and represents a reasonable starting point for future optimization.

Table 1: Integrated profile of top-ranked ligands including docking scores, experimental IC_{50} values, and molecular descriptors

Molecule ChEMBL ID	Ligand Index	Docking Score (kcal/mol)	IC_{50} (nM)	Molecular Weight (Da)	LogP	TPSA ($\text{\AA}^2$)
CHEMBL1688549	1	-6.563	1300	338.398	5.0470	29.26
CHEMBL422	4	-6.496	1400	407.505	4.9456	9.72
CHEMBL1688551	13	-6.309	6400	324.371	4.6569	29.26
CHEMBL11	20	-6.308	22000	280.415	3.8750	6.48
CHEMBL570	11	-6.257	4900	352.425	5.2598	6.48
CHEMBL418995	22	-5.874	400000	337.463	4.4993	49.33
CHEMBL288110	14	-5.770	7400	256.374	3.6381	29.26
CHEMBL726	5	-5.706	1700	437.531	4.3081	29.95
CHEMBL479	2	-5.470	1300	370.587	5.8856	6.48
CHEMBL643	19	-5.071	17700	284.428	4.2394	6.48

3.8 Structures of the Top-Ranked Candidates

Among the top-ranked ligands, two notable outliers stand apart from the dominant scaffold: CHEMBL11, which carries a dibenzazepine core rather than a dibenzothiazine core, and CHEMBL418995, which carries a carboxylic-acid substituent. Both nonetheless achieved docking scores

competitive with those of the dibenzothiazine-dominated set, demonstrating that, although the phenothiazine-like core clearly dominates the highest-scoring compounds, alternative chemotypes within the same broader chemical space can still be accommodated by the binding pocket.

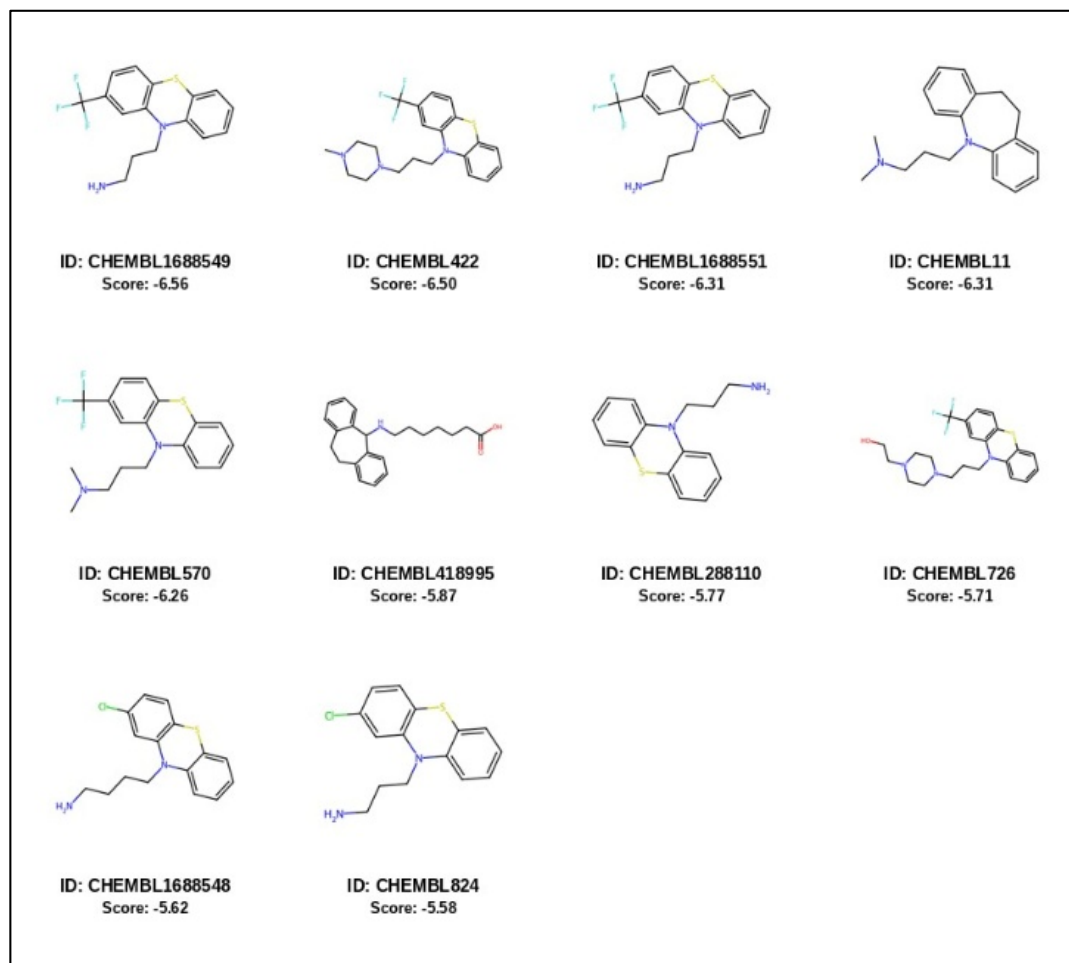


Fig 5: Two-dimensional structures of the ten top-ranked docking candidates, annotated with ChEMBL identifiers and AutoDock Vina binding scores (kcal/mol).

Among the ten top-ranked docking candidates specifically, seven compounds showed no Lipinski violations, while three compounds, CHEMBL1688549, CHEMBL570, and CHEMBL479, each showed a single violation, attributable

to LogP values marginally exceeding the threshold of 5. No compound violated more than one rule, indicating generally good physicochemical suitability for oral bioavailability across the top-ranked set (Table 2).

Table 2: Top candidates with Lipinski's Rule of Five properties and violations

Molecule ChEMBL ID	Docking Score (kcal/mol)	Molecular Weight (Da)	LogP	H Donors	H Acceptors	Lipinski Violations
CHEMBL1688549	-6.563	338.398	5.0470	1	3	1
CHEMBL422	-6.496	407.505	4.9456	0	4	0
CHEMBL1688551	-6.309	324.371	4.6569	1	3	0
CHEMBL11	-6.308	280.415	3.8750	0	2	0
CHEMBL570	-6.257	352.425	5.2598	0	3	1
CHEMBL418995	-5.874	337.463	4.4993	2	2	0
CHEMBL288110	-5.770	256.374	3.6381	1	3	0
CHEMBL726	-5.706	437.531	4.3081	1	5	0
CHEMBL479	-5.470	370.587	5.8856	0	4	1
CHEMBL643	-5.071	284.428	4.2394	0	3	0

These results suggest that the screened chemical space is largely consistent with drug-like property norms, plausibly reflecting the historical optimization of this tricyclic chemotype toward CNS-active small molecules with balanced permeability and lipophilicity.

3.9 Representative Ligand Structure

To illustrate the structural features underlying the screened library, a representative compound, CHEMBL1688548, was visualised in 3D using py3Dmol. The structure displays a tricyclic phenothiazine scaffold composed of two fused

benzene rings connected by a central heterocyclic ring containing sulfur and nitrogen atoms. This aromatic tricyclic system provides a rigid, hydrophobic core capable of favourable interactions within the NLRP3 nucleotide-binding pocket, with structural variation across the library arising primarily from substituent modifications rather than changes to this core framework. ChEMBL1688548 itself achieved a docking score of -5.622 kcal/mol and has an experimentally reported IC_{50} of 700 nM, making it a reasonably representative member of the screened series for the purpose of this structural illustration.

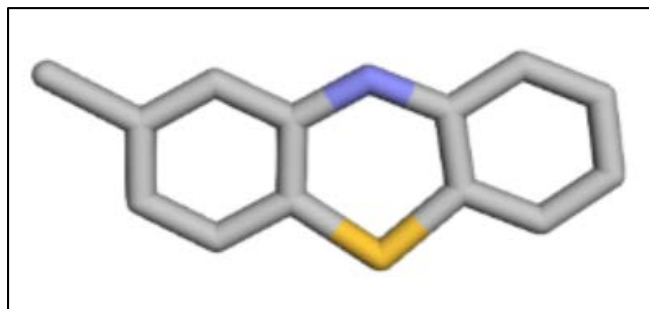


Fig 6: Three-dimensional representation of ChEMBL1688548 generated from the energy-minimized ligand structure using py3Dmol. Carbon atoms are in grey, nitrogen in blue, and sulfur in yellow. The characteristic tricyclic phenothiazine scaffold is visible as the central structural framework.

On the basis of its predicted binding affinity of -5.622 kcal/mol, ChEMBL1688548 was retained, alongside the remaining 22 screened compounds, for the chemoinformatic and ADMET analyses presented in the sections that follow.

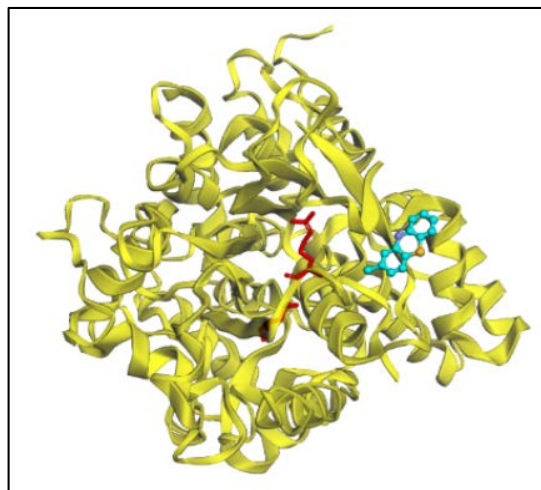


Fig 7: Predicted docking pose of ChEMBL1688548 within the nucleotide-binding pocket of the NLRP3 receptor (PDB ID: 9GU4), visualized using py3Dmol. The protein is shown as a semi-transparent cartoon representation, while the ligand is displayed as a stick model. Highlighted residues indicate selected amino acids located in the vicinity of the docked ligand.

3.10 Synthetic Accessibility (SA) Score

Synthetic accessibility for each compound was estimated using the RDKit implementation of the SA score (Ertl & Schuffenhauer, 2009), which ranges from approximately 1 (very easy to synthesize) to 10 (highly complex). As shown in Figure 14, the distribution of SA scores across the full 23-compound library is tightly clustered between approximately 1.9 and 2.95, with most compounds concentrated in the 2.0-2.4 range.

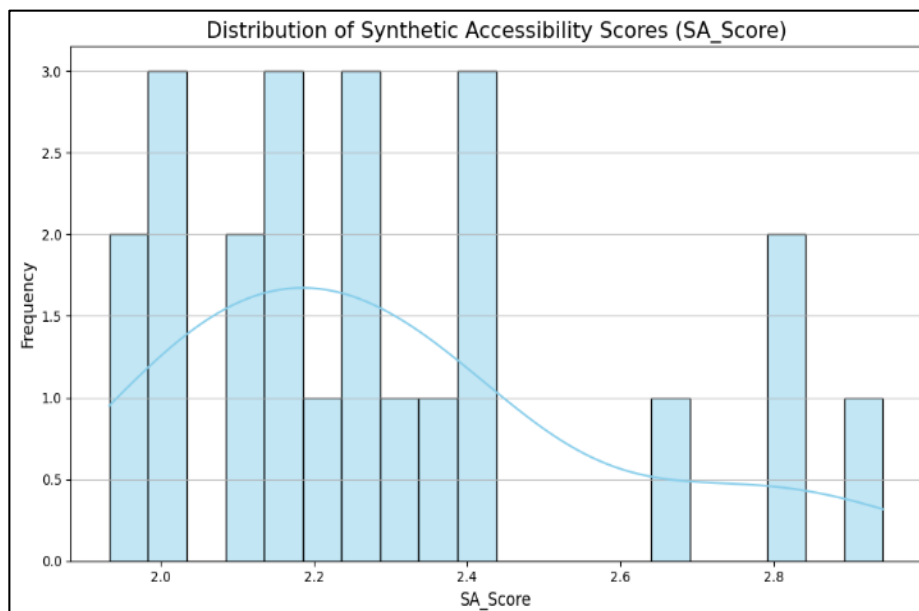


Fig 8: Distribution of RDKit Synthetic Accessibility (SA) scores across the 23-compound library, showing a narrow and favourable range of approximately 1.9-2.95.

3.11 Bemis-Murcko Scaffold Analysis

Bemis-Murcko scaffolds (Bemis & Murcko, 1996), representing the core ring systems of each compound after removal of peripheral side chains, were extracted for all 23 compounds. This analysis confirmed that the library is dominated by two related scaffold families: a tricyclic dibenzo[b, f][1, 4]thiazepine/phenothiazine-type scaffold, present in the majority of compounds, and a dibenzazepine

(iminodibenzyl) scaffold, represented by ChEMBL11 and ChEMBL418995 (Table 3). This confirms that the dataset represents a focused, scaffold-conserved chemical series rather than a structurally diverse screening library, an observation consistent with the shared-core structure-activity trends and one that makes the library well suited to SAR-driven optimization in future work.

Table 3: Representative Bemis-Murcko scaffolds of selected ligands.

Molecule ChEMBL ID	Scaffold
CHEMBL11	dibenzoazepine core
CHEMBL288110	dibenzothiazine core
CHEMBL1688549	dibenzothiazine core
CHEMBL422	substituted dibenzothiazine scaffold
CHEMBL1688551	dibenzothiazine core

3.12 Tanimoto Similarity Heatmap

The resulting matrix exhibits a clear block-diagonal pattern, indicating the presence of structurally coherent clusters rather than a uniformly diverse library. High-similarity

clusters (Tanimoto > 0.6-0.7) are observed among compounds CHEMBL1688548, CHEMBL1688549, CHEMBL824, and CHEMBL1688551, corresponding to halogenated and non-halogenated dibenzothiazine derivatives bearing primary amine side chains, while a second closely related pair is observed between CHEMBL1323355 and CHEMBL1764, reflecting near-identical two-dimensional structural features. In contrast, CHEMBL418995, a dibenzazepine carboxylic-acid derivative, shows consistently low similarity (Tanimoto < 0.15) to nearly all other compounds, confirming its position as the most structurally distinct member of the library.

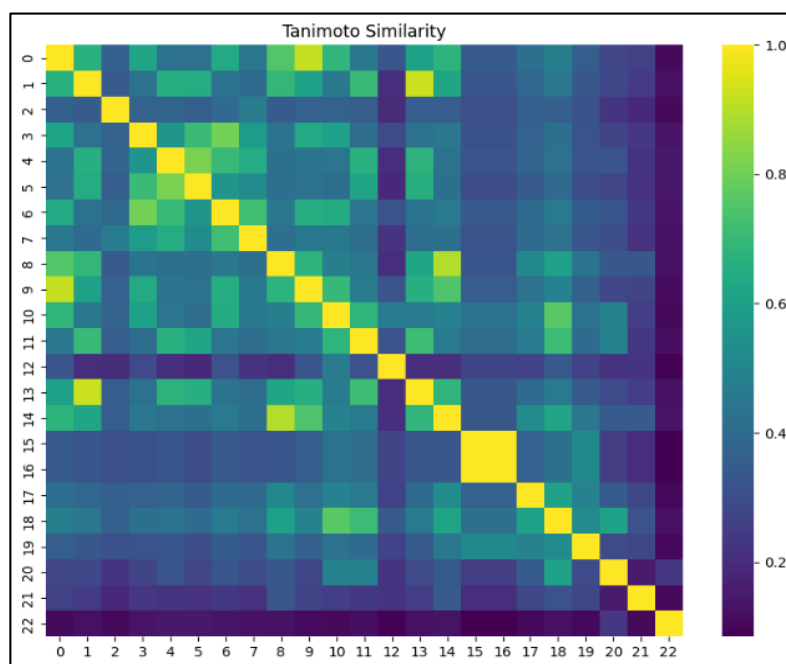


Fig 9: Pairwise Tanimoto similarity heatmap based on Morgan fingerprints (radius = 2) for the 23-compound library. Compound indices correspond to the original dataset order (0-22). Higher similarity is represented by brighter regions, while lower similarity is shown in darker shades. CHEMBL418995 appears as the most structurally distinct compound in the dataset.

3.13 Hierarchical Clustering

Ward-linkage clustering of Morgan fingerprints identified

three major structural clusters, with CHEMBL728 emerging as a distinct outlier.

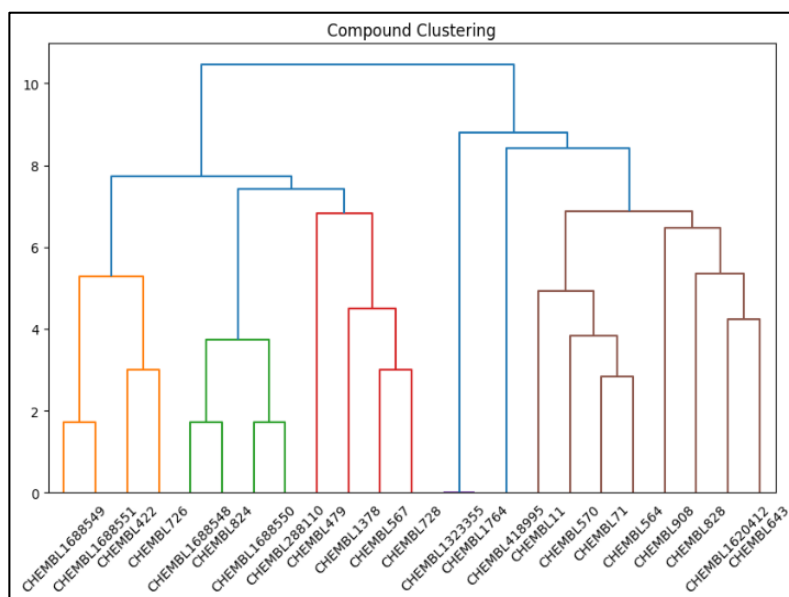


Fig 10: Ward-linkage hierarchical clustering dendrogram of the 23-compound library based on Morgan fingerprint Tanimoto similarity, with ChEMBL IDs as labels.

The best-performing ligand, CHEMBL1688549 (−6.563 kcal/mol), exhibits a moderate molecular weight (338 Da) and a LogP value close to the Lipinski threshold (5.05), positioning it near the upper boundary of favourable lipophilicity rather than at a physicochemical extreme.

3.15 ADMET Prediction and Final Candidate Selection

ADMET properties were predicted for the full ligand library using the ADMET-AI platform, which provides DrugBank-referenced percentile rankings for pharmacokinetic and toxicity-related endpoints, including solubility, lipophilicity, plasma-protein binding, volume of distribution (VDs), half-life, and multiple toxicity predictors. Predicted VDs values were moderate to high, suggesting effective tissue distribution. The top candidates showed moderate-to-high predicted lipophilicity and relatively low aqueous solubility,

a pattern typical of tricyclic aromatic scaffolds that may favor membrane permeability and intracellular target engagement, though formulation optimization may be required for the least soluble compounds. This composite ranking identified CHEMBL11, CHEMBL288110, CHEMBL1688549, CHEMBL422, and CHEMBL1688551 among the highest-priority compounds. Notably, CHEMBL11 achieved the best overall composite score despite not being the single strongest docking hit, reflecting a favourable balance of binding affinity, molecular size, lipophilicity, and synthetic accessibility rather than dominance in any one criterion. Overall, the convergence of docking performance, drug-likeness, synthetic accessibility, BBB permeability, and PAINS filtering supports the prioritization of this final candidate set for future experimental validation.

Table 4: Final prioritized NLRP3 inhibitor candidates after sequential filtering (PAINS, BBB permeability, Lipinski compliance, synthetic accessibility), ranked by docking score.

Rank	Molecule ChEMBL ID	Docking Score (kcal/mol)	PAINS/BBB/Lipinski
1	CHEMBL422	−6.496	Clean/BBB + /0
2	CHEMBL1688551	−6.309	Clean/BBB + /0
3	CHEMBL11	−6.308	Clean/BBB + /0
4	CHEMBL418995	−5.874	Clean/BBB + /0
5	CHEMBL726	−5.706	Clean/BBB + /0
6	CHEMBL1688548	−5.622	Clean/BBB + /0
7	CHEMBL824	−5.585	Clean/BBB + /0
8	CHEMBL567	−5.454	Clean/BBB + /0
9	CHEMBL728	−5.404	Clean/BBB + /0
10	CHEMBL71	−5.282	Clean/BBB + /0

Overall, this docked complex supports the structural plausibility of CHEMBL1688549 as a binder of the NLRP3 NACHT-domain nucleotide pocket. The observed binding mode is consistent with the cavity definition used throughout docking and corroborates the earlier fpocket and docking results, reinforcing that the selected pocket represents a chemically and geometrically reasonable binding site for this compound class, and providing a structurally grounded conclusion to the results presented in this chapter.

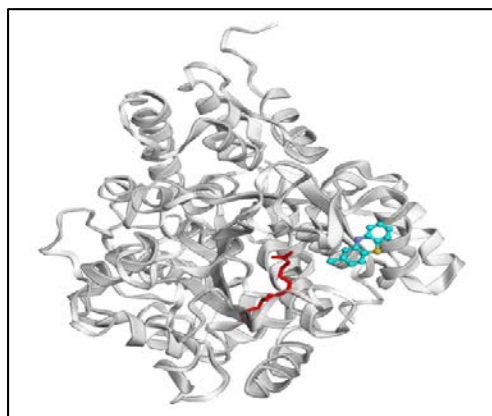


Fig 13: Three-dimensional visualization of the highest-ranked docking pose of CHEMBL1688549 (cyan) bound within the NLRP3 NACHT-domain nucleotide-binding pocket.

4. Conclusion

This study set out to characterize the NLRP3 inflammasome structurally and to identify potential small-molecule inhibitors relevant to neurodegenerative disease therapeutics, using an integrated computational workflow

spanning structural bioinformatics, molecular docking, and chemoinformatic profiling. The retrieved NLRP3 structure (PDB: 9GU4) was validated through multiple independent measures, including a high ERRAT score^[24, 25], a favorable Ramachandran distribution, and near-complete structural identity with a closely related homolog (7ALV, RMSD = 0.494 Å), confirming its reliability as a target for downstream analysis. Binding-site identification using fpocket correctly recovered the biologically relevant nucleotide-binding cleft of the NACHT domain, the native site of the co-crystallised ADP cofactor, providing a structurally grounded docking target rather than an arbitrarily selected cavity. Molecular docking^[26] of twenty-three tricyclic candidate compounds against this pocket identified a consistent structure-activity pattern centred on a dibenzothiazine/phenothiazine core, with docking scores ranging from −6.563 to −4.679 kcal/mol. Subsequent chemoinformatic and ADMET profiling narrowed this library to ten candidates that simultaneously met Lipinski, PAINS, blood-brain barrier permeability, and synthetic accessibility criteria, with CHEMBL422, CHEMBL1688551, and CHEMBL11 emerging as the most promising overall candidates when binding affinity and drug-likeness were considered together. Taken as a whole, this study demonstrates that a structure-guided computational pipeline, combining validated structural data, biologically informed binding-site selection, docking, and multi-parameter chemoinformatic filtering, can meaningfully prioritize a small, experimentally tractable set of NLRP3 inhibitor candidates from a larger starting library. While the absence of experimental validation and the inherent limitations of rigid-receptor docking mean these findings represent a starting point rather than a conclusive result, the convergence of favourable binding, drug-likeness, and predicted pharmacokinetic properties across the final

candidate set offers a reasonable, defensible basis for future experimental follow-up. In doing so, this work contributes to a reproducible computational framework that may support future efforts toward NLRP3-targeted therapeutics for Alzheimer's disease, Parkinson's disease, and related neurodegenerative conditions.

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