# Breaking the Loop: Millions to Molecules

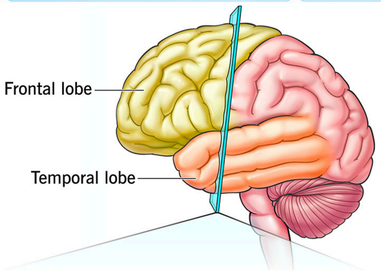
## Dual Mechanism Small-Molecule Discovery via HTVS and Machine Learning Guided Molecular Dynamics for Frontotemporal Dementia

**Can <u>one</u> small molecule both stabilize tau-associated structure AND inhibit tau-relevant kinase**

## The Global Burden of FTD

**~190K**
estimated new cases/year worldwide

**~2.5M**
estimated people living with FTD worldwide




- FTD primarily affects the frontal and temporal lobes.
- Leads to progressive changes in behavior, language, and cognition
- No approved disease-modifying therapy currently exists.

Infographic created by Finalist using Canva, 2026. Image source: Cleveland Clinic. (n.d.). Frontotemporal dementia. https://my.clevelandclinic.org/health/diseases/21075-frontotemporal-dementia

## Tau Pathology in FTD

**Healthy tau**
(stabilizes microtubules)

**Pathological tau**
(hyperphosphorylation, misfolding and aggregation)

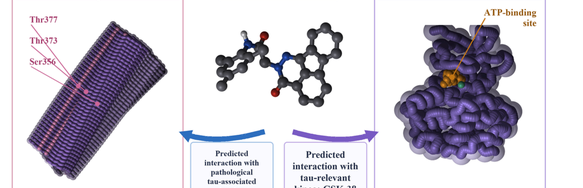
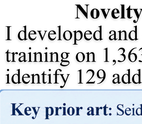



**Figure 1.** Tau pathology contributes to neuronal dysfunction in tau-related FTD
Structures & Infographics created by Finalist using Claude Science Beta and Canva, 2026.

## Current Treatment Gap

### Medications
Manage symptoms, not disease progression.



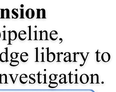

**SSRIs**
Increase serotonin signaling to help manage behavioral symptoms such as disinhibition, compulsions, and irritability.




**Antipsychotics**
May reduce severe agitation or aggression, but side effects can limit use.

### Supportive Therapies
Improve quality of life, not underlying disease.

**Speech & Language Therapy**
Supports communication difficulties.



**Occupational Therapy**
Supports daily living skills and independence.



**Multidisciplinary Care**
Combines medical, behavioral, and social support for patients and caregivers.



**No approved disease-modifying therapy currently exists for FTD.**
Current treatments manage symptoms and support quality of life, but they do not target the underlying tau-driven neurodegeneration.

**Figure 2.** Current symptomatic treatment targets in FTD. Serotonin 5-HT2A and dopamine D2 receptors are targeted to manage behavioral symptoms, not disease progression.
Structures & Infographics created by Finalist using ChimeraX and Canva respectively, 2025-26.

## Aims & Hypothesis

**Aim:** Identify a small-molecule candidate that can engage both tau-related mechanisms in FTD.

**Hypothesis:** CNS-11 will show complementary predicted effects on two targets: restricted dynamics at tau-associated structure and disrupted dynamics at a tau-relevant kinase.

## Novelty & Research Gap

### Novelty I: A New Dual-Mechanism Investigation of CNS-11

**Tau-related FTD**
Pathological tau




Straight filament of pathological tau
PDB 5O3T · 40 rungs propagated

**CNS-11**



Predicted interaction with pathological tau-associated structure

Predicted interaction with tau-relevant kinase GSK-3β

**Dual-mechanism candidate**

**GSK-3β**
Tau-relevant kinase




GSK-3β kinase domain with docked CNS-11
PDB 1J1C chain A · Vina mode 1

**Figure 3.** Proposed dual-mechanism investigation of CNS-11. CNS-11 was computationally evaluated for predicted interactions with straight-filament tau (5O3T) and the GSK-3β ATP-binding pocket (1J1C), supporting its prioritization as a dual-target candidate.Structures & Infographics created by Finalist using Claude Science Beta and Canva, 2026.

### Novelty II: AI-Guided Drug Discovery Expansion

I developed and expanded a custom machine-learning pipeline, training on 1,363 compounds and screening the Maybridge library to identify 129 additional predicted candidates for future investigation.

**Key prior art:** Seidler et al., 2022; Ali et al., 2022; Segura et al., 2024; Pan et al., 2026.

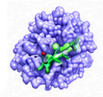
## Methods: A Two Staged AI-Guided Pipeline

### Stage 1: Original study (CNS-11 prioritization)

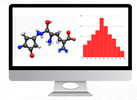
**1 Protein structure libraries & compound library selection**
- Collect CNS-relevant targets
- Prepare protein structures from public databases
- Compile and prepare compound library



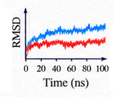
**2 HTVS multi-target docking**
- Dock compounds to selected targets
- Rank by binding affinity and multi-target profile



**3 Curation and ML prioritization**
- Curate top-ranking compounds
- Machine learning prioritization
- Identify CNS-11

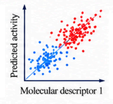


**4 Molecular dynamics simulations**
- 100 ns MD for CNS-11–target complexes
- Analyze stability and binding energetics (RMSD, MM-GBSA)




### Stage 2: Expanded screening (separate from CNS-11)
Note: CNS-11 was identified in the original study, not among the 129 additional hits.

**5 Expanded screening (ML)**
- Screen 129 additional hits (without re-including CNS-11)
- ML-based activity prediction
- Prioritize candidates




**6 Predicted candidates**
- Select top-ranked molecules
- Prioritize for experimental validation



**Figure 4.** Two-stage computational workflow. Infographic and graphics created by Finalist using Canva and Canva AI, 2026

**Key Protein Targets Investigated**

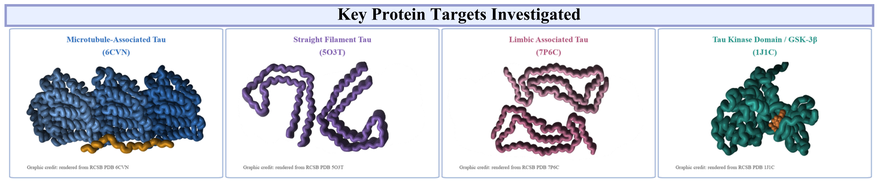
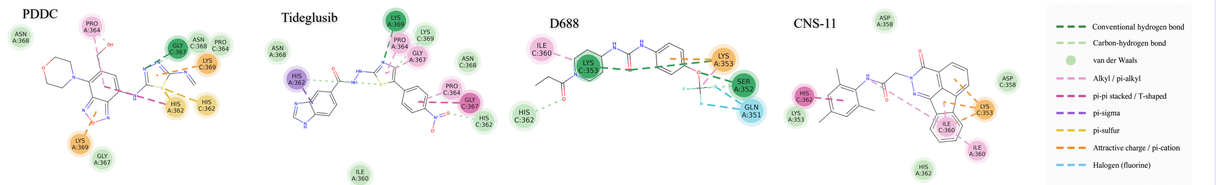



**Figure 5.** Microtubule-associated tau (6CVN), straight-filament tau (5O3T), limbic-associated tau (7P6C), and tau-relevant kinase GSK-3β (1J1C).
Structures generated by Finalist using ChimeraX, 2025

| | |
|---|---|
| **Protein structures & visualization** | RCSB PDB, ChimeraX, Claude Science(Beta) |
| **Compound libraries** | ZINC, ChEMBL, MedChemExpress, Maybridge (Mcule) |
| **Molecular docking** | AutoDock Vina, Schrödinger Glide |
| **AI/ML screening** | Python, RDKit, scikit-learn (Random Forest) |
| **Molecular dynamics** | GROMACS, Schrödinger |
| **Drug-likeness & stability analysis** | SwissADME, CUPSAT |
| **Binding-energy analysis** | MM-GBSA |

## Results

### *Results I: Molecular Docking Interaction Analysis on the Tau Protein of HTVS Leads*




**Figures 6.** 2D interaction Diagram of PDDC, Tideglusib , D688 and CNS-11 on Tau Fibril. *Images created by the Finalist using Discovery Studio,2025*

**<u>KEY DISCOVERY</u>: CNS-11 prioritized for predicted interactions with both tau-associated structure and GSK-3β**

### *Results II: Multi Target Docking Comparison*

| Protein target | PDDC | Tideglusib | D688 | CNS-11 |
|---|---|---|---|---|
| Straight-filament tau (5O3L) | −6.849 ± 0.275 | −6.729 ± 0.015 | −6.766 ± 0.053 | −6.721 ± 0.024 |
| Microtubule-associated tau (6CVN) | −7.051 ± 0.225 | −6.215 ± 0.027 | −6.113 ± 0.018 | −7.468 ± 0.007 |
| Limbic-associated tau (7P6C) | −5.844 ± 0.284 | −5.741 ± 0.023 | −5.807 ± 0.390 | −6.232 ± 0.529 |
| GSK-3β (1J1C) | −8.196 ± 0.022 | −8.881 ± 0.010 | −7.679 ± 0.014 | −9.961 ± 0.019 |

**Figure 7.** More negative values indicate more favourable predicted docking. CNS-11 showed the most favorable mean scores at 6CVN, 7P6Cand 1J1C

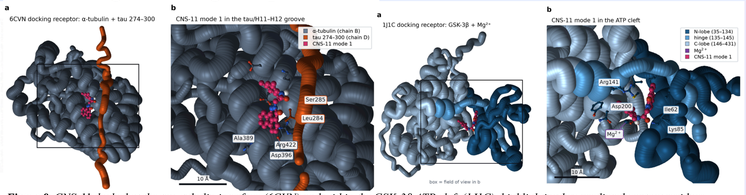
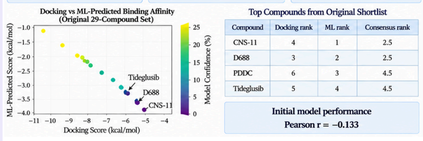



***Figure 8.*** *CNS-11 docked at the tau–tubulin interface (6CVN) and within the GSK-3β ATP cleft (1J1C), highlighting key predicted contact residues.*
*Docking data generated using AutoDock Vina; visualizations created in ChimeraX; table formatted in Canva, 2026*

### *Results III: Custom AI-ML Assisted Prioritization and Expanded Virtual Screening*

**29** Starting compounds
**15** Exploratory ML shortlist
**4** Advanced to follow-up




Top Compounds from Original Shortlist

| Compound | Docking rank | ML rank | Consensus rank |
|---|---|---|---|
| CNS-11 | 4 | 1 | 2.5 |
| D688 | 3 | 2 | 2.5 |
| PDDC | 6 | 3 | 4.5 |
| Tideglusib | 5 | 4 | 4.5 |

**Initial model performance**
**Pearson r = −0.133**

**Figure 9**. Initial ML-assisted compound prioritization. Comparison of docking scores and ML-predicted binding affinities for the original 29-compound set, followed by exploratory ranking to 15 compounds and selection of four candidates for advanced follow-up. CNS-11 and D688 achieved the highest consensus rank (2.5). Limited initial agreement between ML predictions and docking scores (Pearson r = −0.133) motivated subsequent expansion of the training dataset.

**1,363** Training compounds
**51,775** Maybridge library (initial)
**46,320** After CNS drug-likeness filters (scored)
**129** Predicted hits (≤ −9.0 kcal/mol)

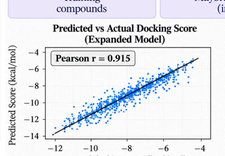



**Figure 10**. Expanded model performance. Predicted vs. actual docking scores for the expanded model. Reported Pearson r = 0.915.

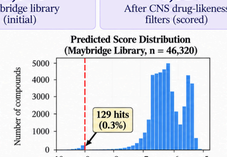



**Figure 11.** Predicted docking score distribution. Distribution of predicted scores for 46,320 filtered Maybridge compounds. The dashed line indicates the −9.0 kcal/mol threshold; 129 compounds (0.3%) met this criterion.

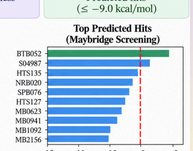



**Figure 12.** Top predicted hits from Maybridge screening.
Top 10 compounds with the most negative predicted docking scores. The red dashed line indicates the −9.0 kcal/mol cutoff.

**EFFICIENCY IMPACT**

The trained AI/ML pipeline screened 46,320 CNS-filtered Maybridge compounds in **<1 minute**, rapidly narrowing the library to **129 predicted hits (0.3%)** for follow-up evaluation.

*Infographic created by Finalist using Canva. Data & Plots generated by Finalist using Finalist's ML Code, 2025.*

### *Results IV- A: Quantitative Dual-Target Validation (ADMET, ΔΔG, MM-GBSA)*

| Property | Predicted value |
|---|---|
| Molecular weight | 395.45 g/mol |
| Consensus Log P | 4.41 |
| TPSA | 63.99 Å² |
| BBB permeation | Yes |
| GI absorption | High |
| P-gp substrate | Yes |
| CYP inhibition | 3 of 5 enzymes |
| Bioavailability score | 0.55 |

**Figure 13.** Swiss ADMET parameters for CNS-11

**Takeaway: CNS-11 shows predicted blood–brain barrier permeability and high gastrointestinal absorption, supporting further investigation as a potential CNS drug candidate. Predicted CYP inhibition and P-gp efflux remain important limitations.**

| Target | 0 ns (kcal/mol) | 100 ns (kcal/mol) |
|---|---|---|
| MAP-tau (6CVN) | −35.552 | −77.309 |
| GSK-3β (1J1C) | −66.973 | −88.663 |

**Figure 14.** MMGBSA Energy Components of CNS-11 bound to MAP-Tau and Tau Kinase over 0-100ns

**MM-GBSA estimates became more negative at 100 ns for both modeled complexes, providing computational support for further investigation of CNS-11's proposed dual-target interactions.**

| Target | Residue | Mean ΔΔG (kcal/mol) | Interpretation |
|---|---|---|---|
| MAP-tau (6CVN) | Glu279 | −3.123 | Mutation-sensitive region |
| MAP-tau (6CVN) | Gly310 | −2.890 | Mutations generally destabilizing |
| MAP-tau (6CVN) | Lys352 | +1.497 | Mixed mutational responses |
| GSK-3β (1J1C) | Lys85 | −2.972 | ATP-pocket residue; bound-structure calculation |
| GSK-3β (1J1C) | Arg141 | +0.244 | ATP-pocket residue; bound-structure calculation |

**Figure 15.** CUPSAT Mutation-Stability Analysis

**CUPSAT identified differences in predicted mutation sensitivity at selected tau and GSK-3β residues, including regions relevant to microtubule interactions and kinase function. These results help characterize the structural targets but do not demonstrate CNS-11–induced stabilization.**

*Data generated by Finalist using SwissADME (ADMET), CUPSAT (ΔΔG stability), MM-GBSA on GROMACS MD trajectories and tables formatted in Excel, 2025*

## Results IV- B: MD Simulation and MMGBSA

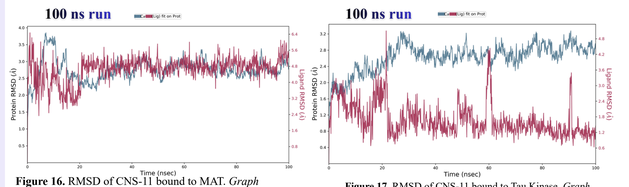



**Figure 16.** RMSD of CNS-11 bound to MAT. *Graph generated by Finalist using Schrodinger, 2025.*

**Figure 17.** RMSD of CNS-11 bound to Tau Kinase *Graph generated by Finalist using Schrodinger, 2025.*

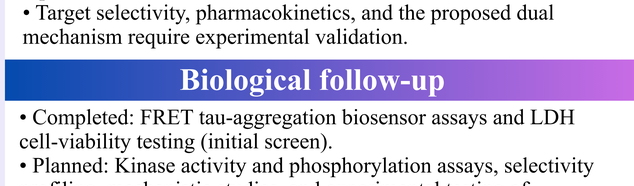



**Figure 18.** CNS-11 exhibited recurring contacts at the tau–tubulin interface during a 100-ns simulation, including interactions with tau Leu284, Ser285 and Val287 and tubulin Arg422.*Graph generated by Finalist using Schrodinger, 2025.*

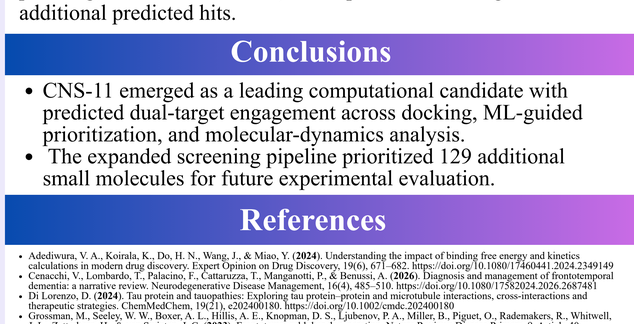



**Figure 19.** PCA of CNS-11 bound to MAT and Tau Kinase. *Graph created by Finalist using Schrodinger, 2025.*

## Molecular-Dynamics Evidence

- CNS-11 maintained stable protein–ligand interactions over 100 ns in both complexes, with recurring contacts near Leu284, Ser285 and Val287 (MAP-tau) and within the ATP-pocket region (GSK-3β).
- RMSD, contact and PCA analyses support the predicted dual-target engagement, while endpoint MM-GBSA estimates became more negative for both modeled complexes.

## Limitations

- Computational predictions, including docking, ML, and MD, do not establish biological activity or therapeutic efficacy.
- Single 100-ns simulations limit reproducibility; independent replication is needed.
- Target selectivity, pharmacokinetics, and the proposed dual mechanism require experimental validation.

## Biological follow-up

- Completed: FRET tau-aggregation biosensor assays and LDH cell-viability testing (initial screen).
- Planned: Kinase activity and phosphorylation assays, selectivity profiling, mechanistic studies, and experimental testing of additional predicted hits.

## Conclusions

- CNS-11 emerged as a leading computational candidate with predicted dual-target engagement across docking, ML-guided prioritization, and molecular-dynamics analysis.
- The expanded screening pipeline prioritized 129 additional small molecules for future experimental evaluation.

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