Frontotemporal Dementia: Discovery of Novel TTK Kinase Inhibitors

Hasini Gajendran[1] and Divya Ramamoorthy[1]*

[1] Moxie Scientist, Georgetown, Texas, USA.

KEYWORDS: Frontotemporal Dementia (FTD), TTK Kinase (Threonine Tyrosine Kinase), Tau Protein, Neurofibrillary Tangles, Blood-Brain Barrier (BBB) Permeability

ABSTRACT

Frontotemporal dementia (FTD) is a devastating neurodegenerative disorder for which there are currently no disease-modifying treatments. In this project, we explored threonine tyrosine kinase (TTK) as a potential therapeutic target because of its role in phosphorylating Tau, a key protein implicated in FTD. Using the Schrödinger Suite 2024-3, we performed detailed docking studies, cross-structure comparisons, and substructure-based ligand design. Several candidate compounds demonstrated stronger predicted binding (docking scores down to –15 kcal/mol) than previously known inhibitors and also showed favorable absorption and blood–brain permeability profiles when assessed with QikProp. These findings provide a computational foundation for future experimental validation and point toward new avenues for the treatment of FTD.

INTRODUCTION

Frontotemporal dementia (FTD) is a progressive disorder that gradually affects personality, behavior, and language. Unlike Alzheimer's disease, which primarily impacts memory, FTD attacks the frontal and temporal lobes of the brain, leading to dramatic changes in social behavior and communication. Current therapies mainly aim to manage symptoms, and there are no approved drugs that slow or stop the underlying neurodegenerative process.

One major driver of FTD pathology is the abnormal accumulation and phosphorylation of the Tau protein. Phosphorylated Tau forms neurofibrillary tangles that interfere with neuronal function. Among the many enzymes that can modify Tau, threonine tyrosine kinase (TTK) emerged from our literature review as a particularly interesting candidate. TTK can phosphorylate Tau and thereby promote the formation of these tangles.

Despite this link, selective inhibitors for TTK in the context of FTD have not yet been developed. We therefore set out to identify novel compounds capable of binding to and

First published on the web on Dec 29, 2025

inhibiting TTK. Our hypothesis was that designing or discovering such inhibitors could help reduce Tau phosphorylation and ultimately slow the progression of FTD.Tau is a microtubule-associated protein that helps stabilize neuron structure, but when abnormally phosphorylated, it detaches and forms neurofibrillary tangles that impair cell function. TTK kinase has been shown to phosphorylate Tau at specific sites, linking it to pathways that promote tangle formation and neuronal degeneration in FTD.

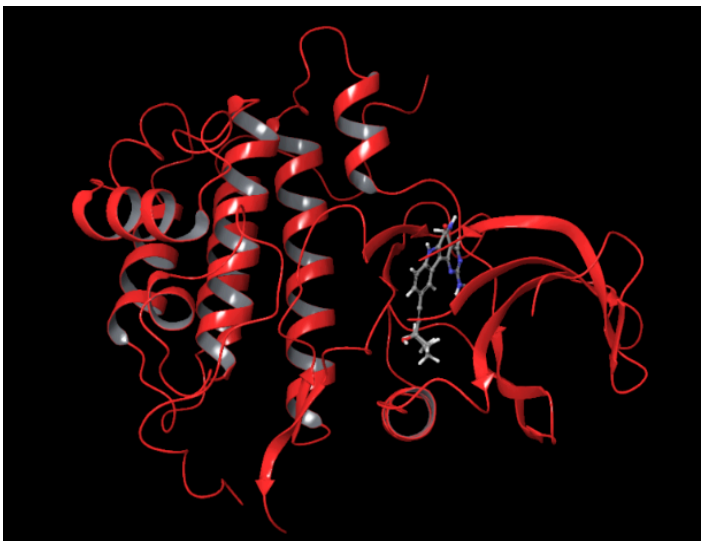


Figure 1: Crystal structure of TTK Kinase (PDB 7AJX)

There are currently no FDA-approved drugs that can slow or stop frontotemporal dementia; existing treatments such as antidepressants and antipsychotics only help alleviate behavioral and emotional symptoms. These medications are only moderately effective in managing symptoms and do not address the underlying Tau pathology or halt disease progression. Our research aims to identify novel TTK kinase inhibitors that could reduce Tau phosphorylation and potentially slow or prevent the neurodegenerative process in FTD. We analyzed multiple Tau-related and kinase protein structures from the Protein Data Bank, including 7AJX and others with varying conformations. The different PDB structures vary in resolution, ligand binding states, and the regions of the protein that are crystallized, which can influence docking precision. We selected PDB 7AJX (Figure 1) because it had high structural resolution and a well-defined active site suitable for accurate docking of potential TTK inhibitors.

MATERIALS AND METHODS

To begin, we studied how FTD develops at the molecular level and to identify kinases connected to Tau phosphorylation. We then retrieved crystal structures of TTK kinase from the Protein Data Bank (PDB). Six different structures were selected to give a broad

picture of possible binding conformations, including one structure that already contained a known inhibitor for reference.

Using Schrödinger Maestro within the 2024-3 software suite, we prepared the protein structures and ligands for docking. Molecular docking was performed using Glide (Schrödinger Suite 2024-3) to predict the most favorable binding poses and affinities of ligands within the TTK active site. Receptor grids were generated around the native ligand or key binding residues identified through SiteMap analysis. Both Standard Precision (SP) and Extra Precision (XP) docking modes were used, SP for broad virtual screening and XP for refined evaluation of top candidates with higher accuracy in ligand-protein interaction scoring.To search for new inhibitors, we screened the CNS-active database from SelleckChem and used MolView for substructure searches. Potential compounds were processed with LigPrep and scored using Glide docking. We further evaluated their predicted properties with QikProp, focusing on blood–brain barrier permeability and overall drug-likeness.

RESULTS AND DISCUSSION

Docking studies revealed that several candidate compounds bound more strongly to TTK than known inhibitors. Our top scoring compounds exhibited docking scores around –15 kcal/mol, indicating very favorable predicted binding. We screened the CNS-active compound library from SelleckChem, which contains molecules known or predicted to penetrate the blood–brain barrier.This library was chosen because compounds with central nervous system activity are more likely to reach neurons and be effective against neurodegenerative targets such as TTK in FTD. In MolView, we conducted substructure searches using fragments of known kinase inhibitors to design and identify new candidate molecules. We selected these compounds because their ring systems and substituents could enhance hydrogen bonding and hydrophobic interactions within the TTK binding pocket.The most promising compounds achieved docking scores between –13 and –15 kcal/mol, which indicates strong predicted binding affinity compared to the reference inhibitors.

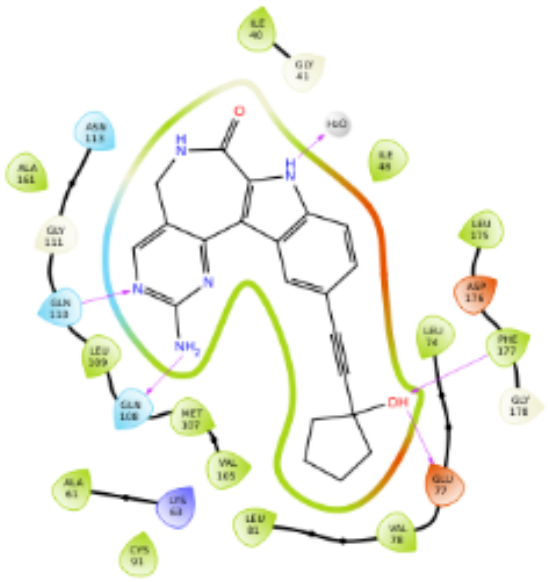
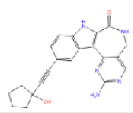
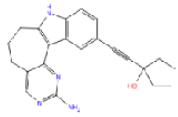
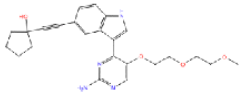
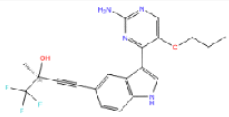
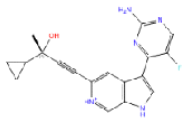
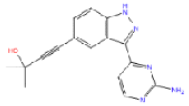
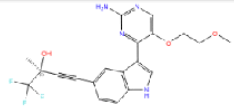
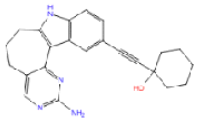


Figure 2: Ligand interaction diagram of Compound 44602928 from the CNS-active SelleckChem library docked into the active site of TTK kinase.

Visualization of ligand–protein interactions highlighted key amino acid residues forming hydrogen bonds and other stabilizing contacts with our top compounds. Figure 2 shows the ligand interaction diagram of Compound 44602928 from the CNS-active library, showing hydrogen-bond interactions with key active-site residues including Glu77, along with additional stabilizing hydrophobic contacts. QikProp analysis predicted good blood–brain barrier permeability and acceptable toxicity profiles for the leading candidates, supporting their potential as central nervous system (CNS) drugs.

Table 1: ADME analysis of the top-scoring compounds in this study

Structure	docking score	mol MW	QPlogS	QPlogBB	PercentHumanOralAbsorption
	-14.794	373.413	-5.07	-2.06	71.458
	-14.61	360.458	-5.811	-1.27	100
	-14.303	436.51	-5.678	-1.785	94.366
	-14.175	404.391	-5.888	-1.122	100
	-13.341	337.356	-4.708	-1.412	84.2
	-12.966	293.327	-4.283	-1.58	78.221
	-12.768	420.39	-5.455	-1.229	94.146
	-11.402	372.469	-5.979	-1.233	95.348

The new compounds showed better performance than the original inhibitors, with more negative docking scores indicating stronger predicted binding.

The newly identified compounds (Table 1) performed better than the original inhibitors, as shown by their more negative docking scores, indicating stronger predicted binding to the target. This improved binding was achieved while maintaining acceptable ADME properties, including moderate lipophilicity, reasonable solubility, and good oral absorption. Overall, the compounds represent improved lead candidates compared to the original inhibitors.

Our computational approach strongly supports the idea that TTK kinase is a promising target in FTD. By inhibiting TTK, we may be able to reduce Tau phosphorylation and slow or prevent the formation of neurofibrillary tangles. The new compounds we discovered not only achieved stronger docking scores than existing TTK inhibitors but

also showed promising pharmacokinetic features. Although these results come from computational modeling and still need to be confirmed in the lab, they mark an important early step. In the future, we plan to refine these compounds with Ligand Designer and evaluate them in biochemical assays to verify their activity.

CONCLUSION

By combining careful literature review, structural analysis, and computer-aided drug design, we identified novel chemical families of potential TTK kinase inhibitors. Our findings provide a solid foundation for future experimental work that could one day lead to effective treatments for frontotemporal dementia. Our top compound from the CNS-active library showed the strongest predicted binding to TTK1, with a docking score of –15 kcal/mol, indicating high affinity and stable interaction within the active site. It also displayed a favorable QikProp profile, suggesting good blood–brain barrier permeability and overall drug-like characteristics. Moving forward, we plan to conduct hit-to-lead optimization to further enhance the compound's potency, selectivity, and stability, advancing it as a promising TTK1 inhibitor candidate for frontotemporal dementia therapy.

AUTHOR INFORMATION

Corresponding Author
*Email: divya@moxiescientist.com

Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Moxie Scientist for computational resources.

ABBREVIATIONS

FTD: Frontotemporal Dementia; ADME: Absorption, Distribution, Metabolism, and Excretion; CNS: Central Nervous System; TTK: Threonine Tyrosine Kinase

REFERENCES

(1) Clark DG. Frontotemporal Dementia. Continuum (Minneap Minn). 2024 Dec 1;30(6):1642-1672.