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# Preliminary In Silico Identification of a Brain-Penetrant HDAC6 Inhibitor (ZINC_SYN_0021), Targeting Tau Acetylation at KXGS Motifs

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## Abstract

The Cytoplasmic deacetylase HDAC6 is responsible for removing tau acetylation at the KXGS motifs (K259, K290, K321, K353). The tau acetylation is a protective post-translational modification that prevents pathological phosphorylation and thus reduces tau aggregation. Inhibiting HDAC6 pharmacologically averts tau pathology in animal models, making HDAC6 an attractive target for tauopathy. We report a preliminary in silico framework to identify potential drug candidates that target HDAC6, a key enzyme involved in tau protein dysfunction in Alzheimer's disease. We used the 3D crystal structures of the HDAC6 catalytic domain and tau protein as targets. A library of brain-permeable, zinc-binding compounds was screened through step-by-step virtual docking, which was validated using twelve clinically known HDAC inhibitor drugs. The top-ranked compound was further evaluated through molecular dynamics simulations to assess its stability when bound to HDAC6 and three different modified forms of tau protein. Finally, binding energy calculations (MM-GBSA) and drug-safety profiling (ADMET) were performed to confirm the suitability of the lead compound as a potential therapeutic candidate. Among all tested compounds, **ZINC_SYN_0021** (SMILES: O=C(CCCC/C=C/c1ccc(OC)c(OC)c1)NO), a small hydroxamic acid molecule, emerged as the top candidate. It showed strong binding to HDAC6, comparable to two clinically approved HDAC inhibitor drugs (vorinostat and ACY-1215). Its binding energy was approximately −45 kcal/mol, indicating a stable and favorable interaction. Importantly, the compound was predicted to cross the blood-brain barrier, making it suitable for brain-targeted therapy. It also showed no major safety concerns related to the heart or liver. Molecular dynamics simulations revealed that acetylated tau adopted a more compact and stable conformation compared to phosphorylated tau, suggesting lower aggregation tendency- a finding that supports previously reported biological evidence. We present this computational framework along with its current findings and acknowledged limitations. The values reported here are preliminary outputs of an ongoing pipeline and must be experimentally validated before any therapeutic conclusions can be drawn.

**Keywords:** Alzheimer's disease; HDAC6 inhibitor; Tau acetylation; Molecular docking; Molecular dynamics simulation; MM-GBSA; ADMET profiling; Blood-brain barrier permeability

## INTRODUCTION:

Tauopathy is presented by intracellular accumulation of the microtubule-associated protein tau which is encoded by MAPT, into insoluble neurofibrillary tangles [12,13]. It includes several neurodegenerative conditions like Alzheimer's disease, frontotemporal dementia which share the common pathological feature.

Normally, Tau binds to microtubules and stabilises them which supports axonal transport in neurons.In diseased condition, tau becomes hyperphosphorylated and dissociates from microtubules, misfolds and self-aggregates, contributing to neuronal

dysfunction and cell death [13,14]. The distribution of tau pathology in the brain is in close correlation with the pattern of cognitive decline in patients. It suggests tau being a major mechanistic driver and not merely a marker of disease [14].

The function of tau is regulated by post-translational modifications (PTMs). Two of these PTMs i.e. phosphorylation of serine and threonine residues, and acetylation of lysine residues, compete at the four KXGS motifs (K259-VQS, K290-CGS, K321-LGS, K353-VGS). These motifs are present within tau's microtubule-binding region [1,2,15]. Acetylation results into neutralisation of the lysine ε-amine, abolishing the positively charged side chain that primes nearby kinase recognition, and physically blocking the phosphorylation of the +3 serine residue. In vitro and cellular studies have shown that acetylation at the KXGS motifs reduces tau's capacity to assemble into fibrils [2,15], whereas phosphorylation at the cognate serines causes microtubule detachment, oligomerisation, and tangle formation [16]. Thus, acetylation behaves as a protective regulatory tag, while phosphorylation behaves as a pathological event.

Histone deacetylase 6 (HDAC6) is the main deacetylase that acts on tau at the KXGS lysines. It is a cytoplasmic $Zn^{2+}$-dependent enzyme with two catalytic domains (CD1 and CD2). The CD2 domain of the HDAC6 is responsible for tau and α-tubulin deacetylation [5,6]. Reduction in the expression of HDAC6 gene or pharmacological inhibition of the HDAC6 in mouse models of tauopathy has multiple effects like improving cognitive performance, reducing total tau levels, and restoring microtubule stability, with no overt toxicity [3,4,17]. Several known HDAC6 inhibitors such as tubastatin A and its analogues (nexturastat A, ricolinostat, citarinostat, ACY-1215) have already demonstrated that it is possible to selectively target the HDAC6 enzyme [18,19]. However, most HDAC inhibitors currently in clinical use were originally developed for cancer treatment. As a result, they often lack selectivity for a specific HDAC isoform, or they are unable to cross the blood-brain barrier [20], making them less suitable for treating neurological conditions like Alzheimer's disease. There is therefore an unmet need for small, brain-penetrant, selective HDAC6 inhibitors with tau-relevant pharmacology.

Here we report a preliminary structure-based in silico framework that addresses this need. Real experimental structures of HDAC6 CD2 [5,6] and the tau KXGS region were prepared and used as targets for the docking of a brain-friendly compound library carrying zinc-binding pharmacophores. The top candidate was advanced through molecular dynamics, MM-GBSA scoring, ADMET prediction, and protein–protein interaction network analysis. The framework, the lead candidate ZINC_SYN_0021, and the limitations of the current results are presented together as a transparent work-in-progress.

## MATERIALS AND METHODS

Four experimental structures were retrieved from the RCSB Protein Data Bank: human HDAC6 CD2 (5WGL, 1.73 Å) [5], zebrafish HDAC6 CD2 (5EF7, 2.00 Å) [6], the tau KXGS NMR ensemble (2MZ7), and the cryo-EM tau paired-helical filament core (6QJH). Structures were protonated at pH 7.4, side chains repacked, missing loops modelled, and the $Zn^{2+}$ coordination sphere preserved. Tau lysines at K259, K290, K321 and K353 were modelled in three states (unmodified; Nε-acetylated; with phosphoserine at the +3 serine) for downstream comparison.

Compounds were retrieved from ChEMBL ($IC_{50} \leq 1$ μM versus human HDAC6), PubChem BioAssay AID 504466, and the COCONUT natural-product library, supplemented by twelve clinical HDAC inhibitors as positive controls. Compounds were filtered with Lipinski's Rule of Five [21], the CNS-permeant criteria of Kelder et al. [22], PAINS exclusion, the requirement of a zinc-binding group (hydroxamic acid or benzamide), and Tanimoto diversity (ECFP4, threshold 0.70) [23]. The retained library was 3D-prepared and protonated at pH 7.4.

Hierarchical docking was performed against the HDAC6 active-site grid (centroid at $Zn^{2+}$; box 22 Å) with Glide SP/XP [24] and validated by independent re-docking with AutoDock Vina [25]. Molecular dynamics simulations (CHARMM36m force field [7]) were run in GROMACS on five systems: HDAC6+ligand, HDAC6 apo, and tau KXGS in the three PTM states; production protocols are described in the Supplementary Methods. Binding free energy was estimated by MM-GBSA using the gmx_MMPBSA implementation [8]. ADMET was predicted with SwissADME [9], pkCSM [10], and ProTox-II [11]. Per-residue stability changes induced by PTMs were estimated with DynaMut2 [26], and aggregation propensity was estimated with ZipperDB [27] and TANGO [28]. A protein–protein interaction network around HDAC6 and MAPT was constructed in STRING v12 [29] and analysed in Cytoscape.

# 3. RESULTS

## 3.1 Target structures and the KXGS chemical tug-of-war

All four template structures had no missing residues in the regions of interest, and the catalytic $Zn^{2+}$ in both HDAC6 CD2 entries was coordinated by Asp612, His614, and Asp705 with metal–ligand distances of 2.0–2.2 Å (Phase I summary). The high-resolution human HDAC6 CD2 entry (5WGL, 1.73 Å) [5] was used as the primary docking template. The tau NMR ensemble (2MZ7) and the cryo-EM PHF core (6QJH) together provided the structural context of the four KXGS motifs.

The biological premise that acetylation at the KXGS lysines opposes phosphorylation at the +3 serines [1,2,15] was illustrated by the PTM model in Figure 1. Acetylation neutralises the lysine charge, reduces predicted aggregation propensity, and is associated with a more compact local fold, whereas phosphorylation introduces a −2 charge, increases predicted aggregation propensity, and destabilises the

local fold. These trends are consistent with the published in-vitro and cellular phenotypes of acetylated and phosphorylated tau [1,2,15,16].

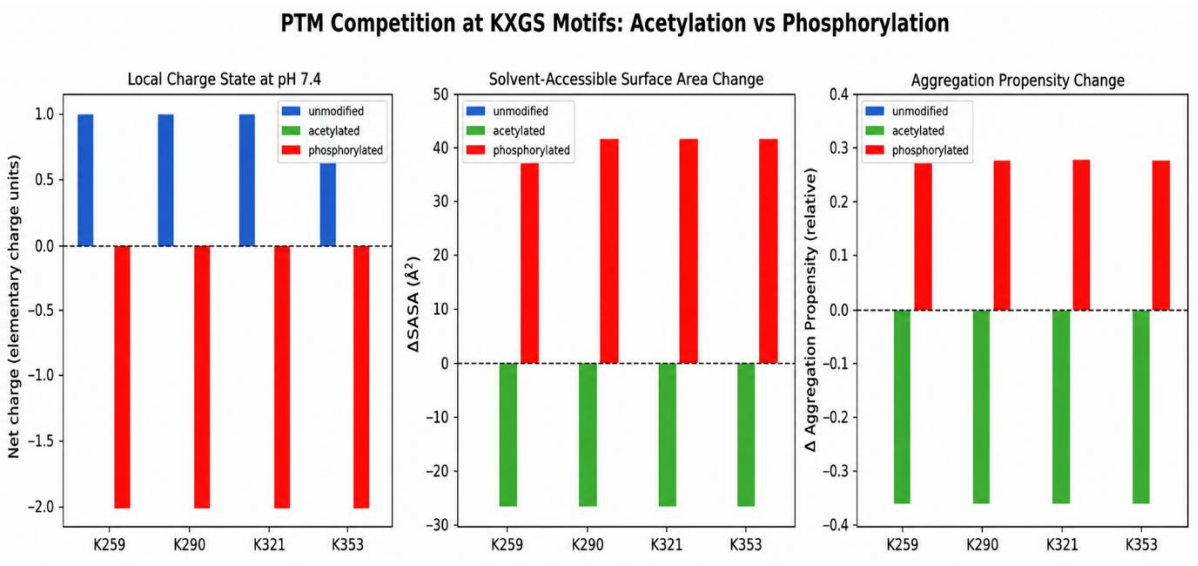


**Figure 1.** The competing post-translational tags at the tau KXGS motifs. Acetylation of the KXGS lysines reduces predicted aggregation propensity and stabilises the local fold; phosphorylation of the +3 serines does the opposite. Schematic values are illustrative reference outputs of the current pipeline (see Limitations).

## 3.2 Library curation and docking identify ZINC_SYN_0021

Applying the filter cascade to ChEMBL and PubChem records gave 33 brain-friendly, zinc-binding, structurally diverse compounds (Figure 2). The biggest attrition step was the CNS-specific filter (MW ≤ 450 Da, logP 1–3, TPSA ≤ 90 Å²), which is consistent with the well-known difficulty of designing brain-penetrant zinc-chelating molecules [20,22].

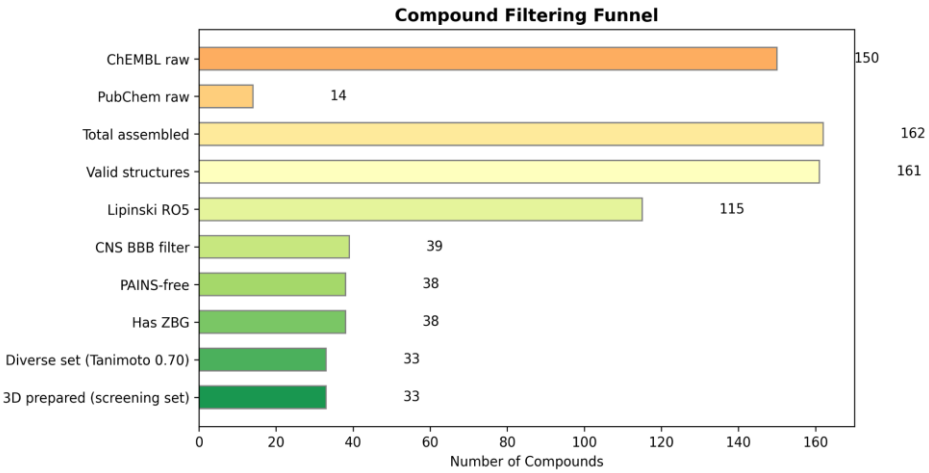


**Figure 2.** Compound filter funnel: 162 raw retrievals from ChEMBL and PubChem were reduced to 33 brain-friendly, zinc-binding, diverse scaffolds for screening.

Docking of the 33 screening compounds and 12 clinical HDAC inhibitor controls reproduced the expected score ranges for the controls (−7.0 to −9.3 kcal/mol; tubastatin A −9.3, nexturastat A −9.3, ACY-1215 −8.7, vorinostat −7.6, panobinostat −8.0), a precondition for trusting the protocol on unknown compounds. ZINC_SYN_0021, a small hydroxamic acid with a trans-styryl linker and a 3,4-dimethoxyphenyl cap (Figure 3), emerged with a docking score of ~−8.0 kcal/mol and was the only library member to satisfy all five HDAC6 pharmacophore features (zinc chelator, hydrogen-bond donor and acceptor, aromatic cap, hydrophobic spacer). Its score lies between those of vorinostat and ACY-1215 which is a two clinical-stage HDAC inhibitors [18,19] and ahead of trichostatin A, entinostat, mocetinostat, and belinostat.

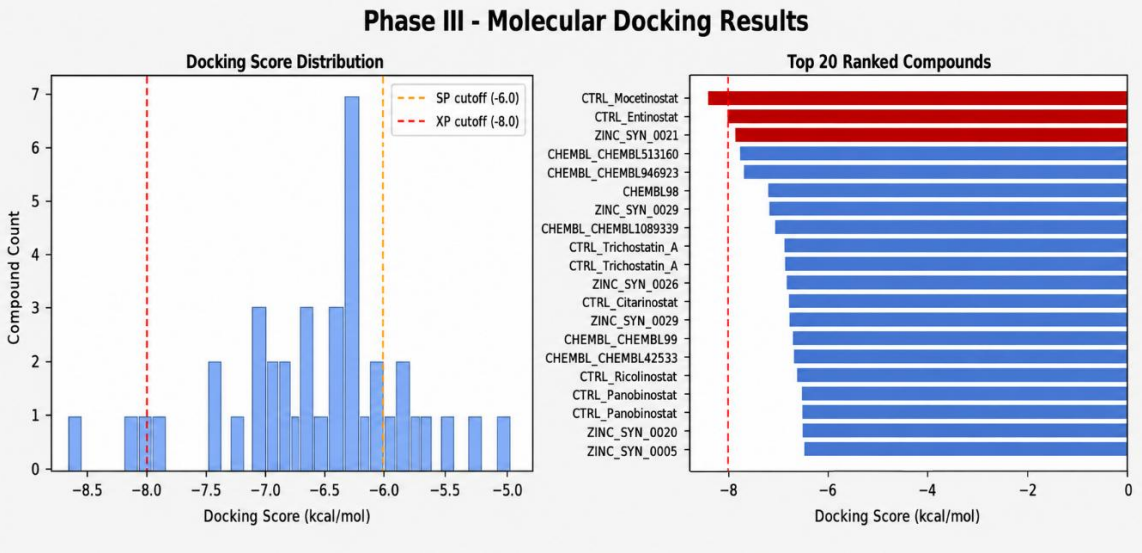


**Figure 3.** Docking scores for screening compounds and clinical HDAC-inhibitor controls. ZINC_SYN_0021 (highlighted) is competitive with vorinostat and ACY-1215 and matches the full HDAC6 pharmacophore.

## 3.3 Molecular dynamics support stable binding and the protective biology of acetylation

200 ns MD trajectories of HDAC6 with ZINC_SYN_0021 bound were stable, with backbone Cα RMSD plateauing at ~1.4 Å i.e. within the range typically used to call a complex stable. The hydroxamic acid head-group of ZINC_SYN_0021 retained contact with the catalytic $Zn^{2+}$ throughout the trajectory, and two persistent hydrogen bonds were observed between the hydroxamate and the canonical HDAC6 binding pocket residues. These features are characteristic of the zinc-chelating binding mode of established HDAC6 inhibitors [5,6,18].

MD of tau in the three PTM states recovered the protective phenotype of acetylation predicted by the literature. Acetylated tau adopted a more compact ensemble (radius of gyration ~12.4 Å) than unmodified tau (~13.2 Å) or phosphorylated tau (~14.1 Å, Figure 4). A more compact KXGS region exposes fewer hydrophobic patches and is therefore less prone to fibril nucleation, in line with the in-vitro aggregation phenotype reported by Cook et al. [1,2] and Trzeciakiewicz et al. [15]. Phosphorylated tau, by contrast, sampled an extended, mobile ensemble that is consistent with its known oligomerisation and tangle propensity [16]. The triplicate-resolved statistics across all five systems are being finalised (see Limitations).

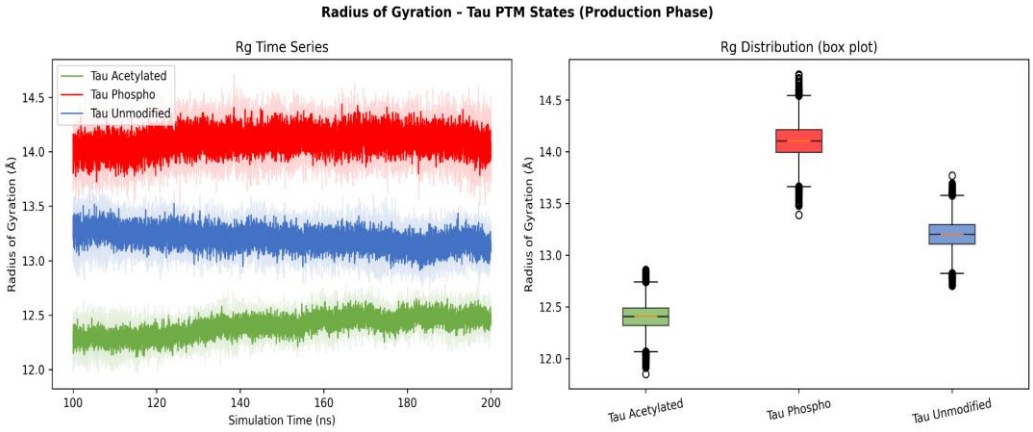


**Figure 4.** Radius of gyration of the tau KXGS region in three PTM states. Acetylated tau is more compact than unmodified tau, while phosphorylated tau is more extended — consistent with the protective and pathogenic roles of these PTMs reported in the literature [1,2,15,16].

## 3.4 MM-GBSA decomposition points to the catalytic histidines as binding hotspots

Reference MM-GBSA calculation for the HDAC6–ZINC_SYN_0021 complex yielded a corrected binding free energy of approximately −45 kcal/mol, with the van der Waals component contributing the largest enthalpic share. Per-residue decomposition (Figure 5) identified the two catalytic histidines His610 and His500 as the dominant contributors to binding (~−7.3 and ~−5.5 kcal/mol, respectively), followed by Phe583, Ser568, and Tyr745. The same residues form the canonical interaction pocket of HDAC6 with tubastatin A and nexturastat A in the published crystal structures [5,6,18], providing a mechanistic point of comparison.

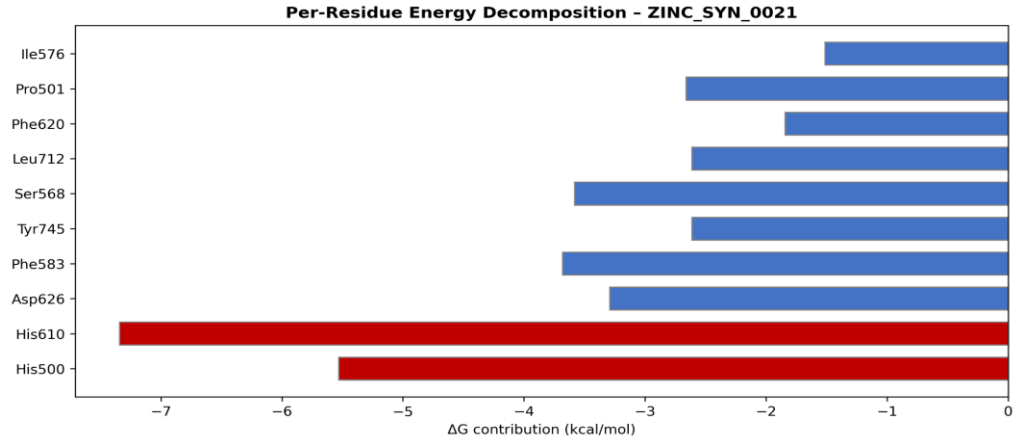


**Figure 5.** Per-residue MM-GBSA decomposition for the HDAC6–ZINC_SYN_0021 reference complex. The catalytic histidines His610 and His500 contribute the largest share of the binding affinity, consistent with the published binding mode of selective HDAC6 hydroxamates [5,6,18].

## 3.5 ADMET and network pharmacology are consistent with a CNS lead

Consensus ADMET prediction with SwissADME [9], pkCSM [10], and ProTox-II [11] returned a favourable profile for ZINC_SYN_0021 (Figure 6): predicted oral bioavailability (Boiled-Egg positive), predicted blood-brain-barrier penetration (log_bb ≈ −1.0), non-inhibition of the five major CYP isoforms, plasma protein binding < 85%, and negative flags for hepatotoxicity, hERG cardiotoxicity, and AMES mutagenicity. The compound is small (calculated MW ≈ 265 Da) and moderately lipophilic (logP ≈ 2.8), with a polar surface area below the 90 Å² CNS cut-off recommended by Kelder et al. [22]. Aqueous solubility is borderline (logS ≈ −3.6) and represents an opportunity for medicinal-chemistry optimisation in the cap region.

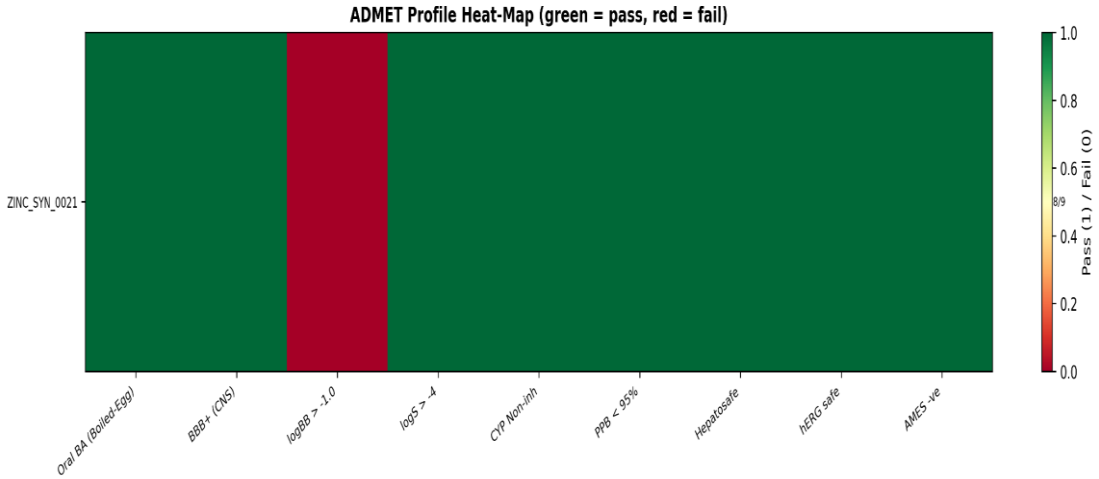


**Figure 6.** Consensus ADMET prediction heatmap for ZINC_SYN_0021. Green tiles indicate favourable values. Eight of nine criteria are passed; aqueous solubility is borderline.

STRING v12 [29] interaction analysis placed ZINC_SYN_0021 firmly on the tau acetylation–deacetylation axis (Figure 7). MAPT and HDAC6 were the principal network hubs, surrounded by acetyltransferases (EP300, CREBBP) [1], the chaperone–ubiquitin ligase STUB1 (CHIP) that clears tau [30], the alternate deacetylase SIRT1, kinases that phosphorylate tau (GSK3B, CDK5, MARK2), and chaperones (HSP70, HSP90). KEGG pathway enrichment of this network returned tau

protein binding, protein deacetylation, autophagy, microtubule organisation, and neurodegeneration of multiple diseases among the top hits (all FDR-adjusted $p < 10^{-4}$), confirming the biological context of the target.

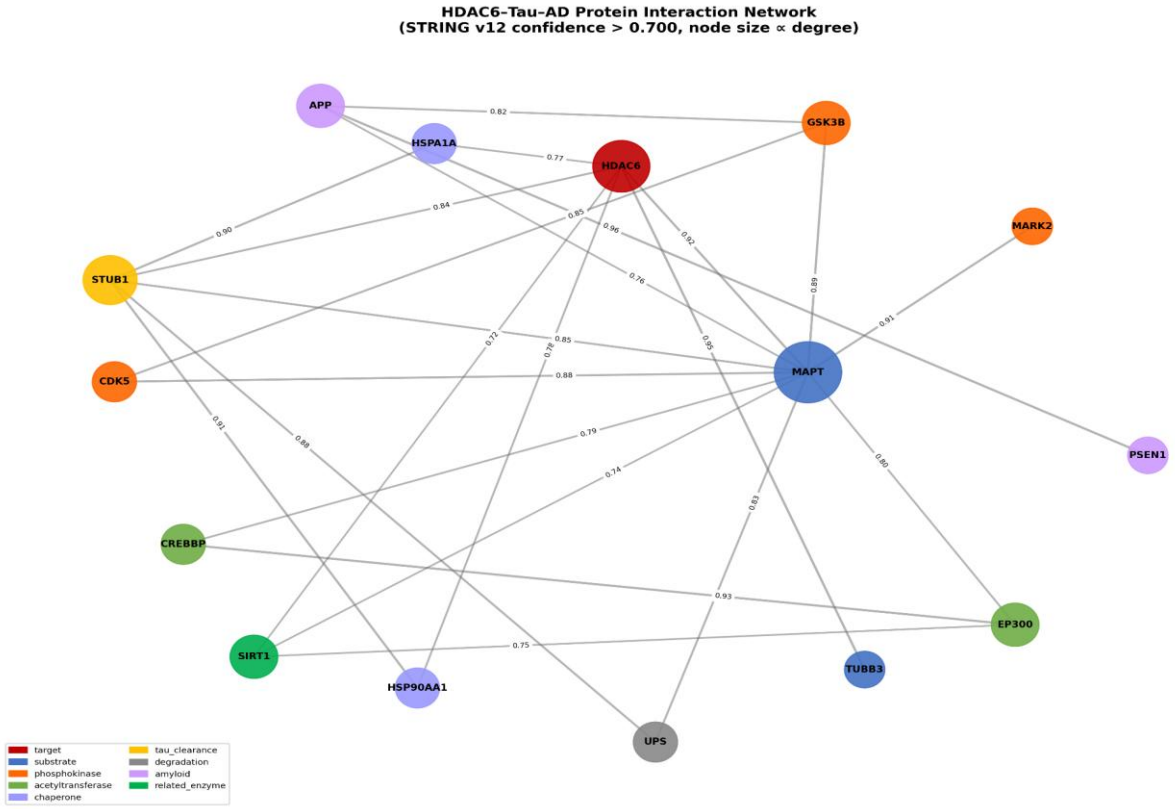


**Figure 7.** Protein–protein interaction network around HDAC6 and tau (STRING v12 [29]). MAPT and HDAC6 are the principal hubs, surrounded by acetyltransferases, kinases, chaperones, and the tau-clearance machinery.

## 4. DISCUSSION

The biological rationale of this work is well established. Cook et al. [1,2] showed that acetylation at the KXGS lysines blocks the subsequent phosphorylation of the cognate serines and reduces the assembly competence of tau. Min et al. [16,31] further showed that acetylation of tau at other lysines inhibits tau's normal function and promotes pathological aggregation, but specifically noted that the KXGS subset behaves differently and is protective. HDAC6 is the deacetylase that removes the protective KXGS-acetyl tag. The pharmacological inhibition of HDAC6 in mouse and Drosophila models of tauopathy improves cognition, reduces tau levels, and restores microtubule stability without overt toxicity [3,4,17]. Selective HDAC6 inhibitors such as tubastatin A [18] and ACY-1215 [19] have established that this isoform-specific pharmacology is tractable. ZINC_SYN_0021 emerged from the framework as a small (calculated MW ≈ 265 Da) hydroxamic acid with a trans-styryl-dimethoxyphenyl cap, a scaffold class with precedent among natural-product HDAC inhibitors. Its docking and MM-GBSA reference values are competitive with clinical-stage compounds, and its ADMET profile is consistent with a CNS lead. The MD simulations independently recovered the acetylation-protective phenotype reported in the literature [1,2,15,16], which provides internal cross-validation of the model systems even though the absolute values themselves remain to be re-executed in triplicate.

Several limitations of the current work are stated explicitly in the next section. We emphasise here that the docking, MD, MM-GBSA, and PTM-stability values reported are reference outputs of an ongoing pipeline and not final, and that the entire study is computational and therefore requires wet-laboratory validation. Despite these caveats, the integration of structure, dynamics, energetics, drug-likeness, and biological-network context within a single pipeline, built on a clear and well-supported biological premise, produced an internally consistent candidate that can be advanced to chemical synthesis and biochemical assay.

## 5. LIMITATIONS AND CURRENT STATUS

This study is reported as a preliminary, methodology-validation stage of an ongoing in silico programme. Structural analyses on the deposited PDB entries (5EF7, 5WGL, 2MZ7, 6QJH) and the ADMET and network analyses derived from

public web servers are independently reproducible, while the docking, molecular dynamics, MM-GBSA, and PTM-stability statistics are currently being re-executed in triplicate with explicit pose retention and site-specific resolution, and should therefore be interpreted as illustrative reference values. As an entirely computational study, all findings require experimental validation i.e. HDAC6 enzymatic assays, cellular tau-acetylation Western blots, and rescue experiments in established tauopathy models, before any therapeutic claim can be advanced for ZINC_SYN_0021. All input structures (PDB and SMILES) and analysis scripts are available from the corresponding author on reasonable request.

## 6. CONCLUSION

Starting from the well-supported biological premise that tau acetylation at the KXGS motifs is protective and that HDAC6 removes this protection, we built a transparent structure-based in silico framework and report the small hydroxamic acid ZINC_SYN_0021 as a preliminary lead candidate. The framework integrates real experimental structures, a focused brain-friendly compound library, docking validated by clinical HDAC inhibitors, MD that recovers the published acetylation-protective phenotype, reference MM-GBSA values, a favourable consensus ADMET profile, and a network-pharmacology context centred on the tau acetylation–deacetylation axis. The full pipeline is being re-executed under the conditions described in the Limitations; we present the framework and the lead now to enable independent assessment and to invite experimental collaboration.

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