

In Silico Identification of DYRK1A-Binding Lead Compounds Relevant to Alzheimer's Disease

James Xu¹

Received May 12, 2026

Accepted October 3, 2026

Electronic access October 31, 2026

Alzheimer's disease is associated with amyloid- β deposition, tau pathology, neuroinflammation, and progressive cognitive decline. This study asked whether a predefined set of MolPort compounds could be prioritized as structural lead candidates for the kinase DYRK1A. A computational workflow combined DoGSiteScorer and PrankWeb pocket prediction, Pharmit pharmacophore screening, SwissDock docking with the Attracting Cavities engine, SwissADME property estimates, and ProTox-3.0 toxicity predictions. All 15 ligands were rerun from the manuscript SMILES against repaired 6EIF chain A using a corrected whole-protein search box. SP-dG ranked MolPort-002-217-232 first (−8.9822), MolPort-002-214-941 second (−8.9139), and MolPort-007-557-644 third (−8.8711). Every top-ranked pose was within 8 Å of the native XMD7-117 centroid. Redocking the co-crystallized XMD7-117 control recovered the native pose at 0.968 Å symmetry-aware heavy-atom RMSD, while the closest generated pose was 0.806 Å. However, all five compounds in the original SwissADME subset were predicted to be blood–brain barrier nonpermeant, and the original Pharmit query metadata and complete ProTox endpoint records were unavailable. The workflow therefore supports pose recovery and computational prioritization only. Biochemical potency, kinase selectivity, cellular target engagement, brain exposure, and empirical safety must be established before any compound can be considered a DYRK1A inhibitor or therapeutic candidate.

Keywords: Alzheimer's disease, DYRK1A, molecular docking, SwissDock, SP-dG, XMD7-117

Introduction

Alzheimer's disease is a progressive neurological disorder. It causes memory loss, cognitive impairment, and loss of independence. It is characterized by extracellular amyloid-beta plaques and intracellular neurofibrillary tangles made of hyperphosphorylated tau protein¹. These features disrupt synaptic signaling and cause neuronal loss. Alzheimer's is still not curable, and it affects more than 40 million people around the world, showing how urgently new treatment methods are needed.

Alzheimer's disease develops through several biological pathways. The first pathway is protein misfolding that results in tau proteins becoming tangled and knotted in brain cells while amyloid-beta forms plaques outside these cells, contributing to neuronal dysfunction and neuroinflammation¹. The second pathway is kinase dysfunction. Enzymes such as DYRK1A regulate protein function through phosphorylation. Dysregulated DYRK1A activity leads to tau hyperphosphorylation, which contributes to tangle formation². DYRK1A also influences amyloid precursor protein processing, resulting in increased amyloid-beta production and plaque formation³. The last pathway is neuroinflammation. Brain immune

cells such as microglia and astrocytes initiate inflammatory responses to plaques and debris, which can contribute to neuronal damage when activated chronically⁴.

Approved symptomatic treatments can temporarily support cognition, while amyloid-targeting antibodies have demonstrated modest slowing of decline in selected patients with early Alzheimer's disease, with treatment-specific risks and monitoring requirements^{5–9}. These results show that disease modification is possible but do not remove the need to investigate additional mechanisms, including tau-associated kinase signaling.

DYRK1A can phosphorylate tau and is linked experimentally to amyloid precursor protein processing^{2,10–13}. DYRK1A-inhibition studies have also reported changes in Alzheimer-like pathology^{14,15}. Because kinase docking does not measure inhibition, the present study asks whether a defined set of MolPort compounds can be prioritized as structural lead candidates for later biochemical testing, not whether they are therapeutically active.

One of the first studies to link DYRK1A to Alzheimer's disease was led by Ryoo et al.². They investigated how DYRK1A affects tau protein, which is the protein that forms the tangles in the cells. The researchers found that DYRK1A phosphorylates tau at sites linked to disease using cell models and tis-

¹West Point Grey Academy, Vancouver, British Columbia, Canada

sues from patients diagnosed with Alzheimer's. This process is called phosphorylation, and it makes tau more likely to be separated from microtubules and form aggregates. The study suggests that DYRK1A plays an important role in tau dysfunction, and it provides a target for drug development and foundational evidence for DYRK1A's involvement in tau pathology.

Nguyen et al.¹⁶ investigated how the inhibition of DYRK1A affects cognitive function in mice with Down syndrome. The researchers treated three Down syndrome mouse models with the inhibitor L41 and evaluated the outcomes using behavioural testing, MRI, and phosphoproteomic analysis. The results showed that treatment improved brain connectivity, memory performance, and synaptic protein levels in all three models. Even though much of the study focused on Down syndrome, the results showed that DYRK1A contributes to the mechanisms of neurodegeneration, which suggests the kinase as a potential therapeutic target for Alzheimer's disease.

Zhu et al.¹⁷ tested DYRK1A blockers in multiple organisms, including fruit flies and mice. This study evaluated whether DYRK1A inhibition could improve Alzheimer's-related symptoms. They tested in vivo models in which brain damage was caused by amyloid-beta, tau, or DYRK1A over-activity. After using the DYRK1A blockers, the animals showed significant improvements. They had less brain degeneration, cognitive impairment, and better behavior, measured by movement tests and memory tasks. The study demonstrated that DYRK1A contributes to the development of Alzheimer's disease pathology through multiple mechanisms, supporting the kinase as a viable therapeutic target.

An in silico workflow was therefore used to identify candidate DYRK1A-binding poses and to generate experimentally testable priorities. Pocket prediction and pharmacophore filtering were supported by established web-server methods^{18–20}. Docking, physicochemical estimates, and toxicity predictions were treated as complementary computational evidence rather than proof of biological activity^{21–25}.

Methods

A computational workflow was used to identify putative binding pockets in DYRK1A, screen a predefined ligand set, evaluate docking poses, and summarize predicted physicochemical and toxicity properties. Computational outputs were interpreted as hypothesis-generating evidence only.

The human DYRK1A kinase-domain structure (PDB ID: 6EIF) was retrieved from the Protein Data Bank. For the re-run, chain A was retained; XMD7-117 (residue code B5T), crystallographic waters, ions, and other non-protein heterogens were removed. Missing atoms in retained residues were repaired and nonstandard protein residues were regularized. Entire unresolved residues were not modeled. No local energy

minimization was applied before submission; SwissDock performed its server-side target preparation and protonation. The co-crystallized XMD7-117 coordinates were retained separately as the ATP-site reference and positive-control pose.

Geometric-Based Method – DoGSiteScorer

DoGSiteScorer detects cavities using Difference-of-Gaussians geometry and reports pocket descriptors and a druggability estimate^{18,26,27}.

Procedure

PDB 6EIF was analyzed with DoGSiteScorer. Pocket name, volume, surface area, and druggability score were recorded. The archived output did not retain pocket centroids or residue lists; therefore, a quantitative DoGSite-to-ATP-site centroid comparison cannot be reconstructed and is reported as a limitation.

Machine Learning-Based Method – PrankWeb

PrankWeb provides the P2Rank machine-learning method for ligand-binding-site prediction^{19,28,29}.

Procedure

PDB 6EIF was submitted to PrankWeb and pocket rank, score, probability, and centroid were recorded. The first-ranked centroid was (1.6121, 19.8669, -43.5958) Å, 7.67 Å from the native XMD7-117 centroid (7.805, 17.015, -47.098) Å, placing the prediction in the ATP-site neighborhood. This proximity supports site agreement but does not establish ligand affinity.

After identifying potential binding sites on DYRK1A in the first experiment using geometric and machine learning-based methods, a second experiment was conducted to investigate interactions between small molecules and the predicted binding sites. This step focused on pharmacophore modeling and virtual screening to find ligands capable of binding to DYRK1A's druggable pockets.

Virtual Screening - Pharmit

Pharmit enables pharmacophore, shape, and minimization-based searching of chemical libraries²⁰.

Procedure

The original Pharmit session produced the 15 MolPort compounds shown in Table 3. The saved record contains their submitted SMILES, Pharmit RMSD, mass, and rotatable-bond count, but it does not contain the feature coordinates, radii, excluded volumes, MolPort library version or size, total hit count, or a reproducible rule explaining why only 15 compounds advanced. These values were not reconstructed or invented. Accordingly, the 15 compounds are treated here as

a predefined exploratory set rather than a systematic top-15 screen. A future confirmatory screen should export the complete Pharmit query JSON and unfiltered hit table.

Molecular Docking – SwissDock

The 15 predefined MolPort compounds were docked with SwissDock, which supports the Attracting Cavities (AC) engine and reports both AC pose-ranking values and estimated SP-dG²⁴. AC scores were used only to order poses within a SwissDock job. SP-dG was used for the cross-ligand comparison because AC and SP-dG have different meanings. Neither score is equivalent to an AutoDock Vina affinity, and neither establishes inhibition. Molecular docking is commonly used in early-stage drug discovery to simulate ligand poses and identify compounds for further study despite the method not directly measuring biological activity^{21,30}.

Procedure

Each ligand was submitted from the exact manuscript SMILES. The repaired 6EIF chain-A receptor was searched using Attracting Cavities 2.0 with a whole-protein box centered at (−6.2, 24.9, −46.8) Å and dimensions 70 × 65 × 73 Å, RIC (random initial conformations) = 1, exhaustiveness = 90, and cavity = 70. Complete clusters and server-prepared ligand structures were archived. The best-ranked pose for each ligand was compared with the native XMD7-117 centroid and screened for protein atoms within 4 Å; N/O/S heavy-atom pairs within 3.5 Å were recorded as distance-based polar proximities, not angle-validated hydrogen bonds. XMD7-117 was redocked in a 24 × 24 × 24 Å box centered on its native centroid using the same AC engine. Symmetry-aware heavy-atom RMSD quantified pose recovery.

Drug Evaluation - SwissADME

SwissADME estimates physicochemical, pharmacokinetic, and medicinal-chemistry properties²³. These outputs are predictions and are not substitutes for permeability or pharmacokinetic experiments. Lipinski's Rule of Five was summarized using molecular weight below 500 g/mol, no more than five hydrogen-bond donors, no more than ten hydrogen-bond acceptors, and log P below five. GI absorption and BBB-permeation predictions were recorded separately because oral drug-likeness does not establish central nervous system exposure^{23,31–33}. In addition, gastrointestinal (GI) absorption was recorded. This metric predicts whether a compound is likely to be absorbed when administered orally. However, even though Lipinski's Rule of Five is a widely used filter in small-molecule drug discovery, it is best interpreted as a guideline rather than an approved predictor of clinical success^{31–33}.

Procedure

SwissADME was applied to the five compounds selected in the original analysis by AC score. Because the corrected cross-ligand ranking uses SP-dG, this subset is retained as an explicitly historical subset and must not be interpreted as the corrected top five. All five were predicted as BBB non-permeant. A follow-up CNS campaign should measure pKa, logD7.4, passive permeability, P-glycoprotein/BCRP efflux, plasma and microsomal stability, and brain-to-plasma exposure, then explore lower-TPSA or prodrug/analog strategies without assuming that reduced polarity will preserve selectivity or safety.

Toxicity Evaluation - ProTox-3.0

ProTox-3.0 was used to summarize predicted oral LD50 and toxicity class for the original five-compound subset²⁵. These predictions are screening-level estimates and do not establish safety.

Procedure

Each retained SMILES was submitted to ProTox-3.0. The archived report contains predicted oral LD50, toxicity class, and radar/network images. The saved record does not preserve the model version date, endpoint probabilities, similarity values, or complete target-pathway output. Therefore, the revision reports only the retained outputs and removes claims of demonstrated safety.

Results

Table 1 Top 10 predicted binding pockets identified by DoGSiteScorer for DYRK1A (PDB ID: 6EIF). The complete pocket table is supplied as Supporting Information.

Name	Volume (Å ³)	Surface (Å ²)	Druggability Score
P_4	795.28	1072.5	0.85
P_6	582.92	645.4	0.84
P_0	1997.63	1985.58	0.81
P_1	1929.33	1968.77	0.81
P_3	832.78	885.63	0.81
P_5	683.26	803.03	0.8
P_2	878.23	1044.31	0.79
P_9	373.3	527.99	0.73
P_8	391.43	589.56	0.72
P_10	350.95	342.8	0.7

Discussion

Pocket prediction and control redocking support the internal structural plausibility of the workflow. PrankWeb's first-

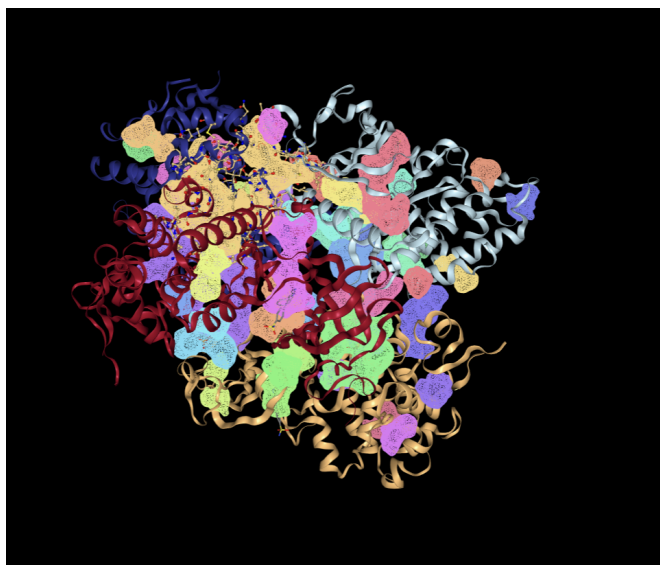


Figure. 1 Predicted binding pockets on the DYRK1A protein using DoGSiteScorer (geometric method). Each colored shape represents a potential ligand-binding site, and it is identified based on its surface and cavity geometry. The protein structure (PDB ID: 6EIF) is shown in ribbon form. This visualization shows the diversity and distribution of cavities suitable for small-molecule targeting.

Table 2 Pocket Data for PrankWeb

Rank	Score	Probability	X	Y	Z
1	40.01	0.959	1.6121	19.8669	-43.5958
2	33.29	0.933	-39.8192	1.2708	-29.5460
3	29.02	0.911	-3.6345	24.9499	-15.5135
4	17.17	0.795	-15.4183	-20.8537	-31.3131
5	16.80	0.787	-21.0019	-15.3746	-23.6781
6	4.23	0.186	-27.1407	4.4174	-39.1065
7	2.75	0.084	-13.5199	18.6244	-39.6639
8	2.58	0.075	-4.0979	30.3891	-38.5992
9	2.30	0.058	-20.2482	11.9739	-50.3173
10	2.00	0.042	-44.6589	-0.7229	-40.0261
11	1.79	0.032	2.5733	25.3861	-29.0988
12	1.61	0.025	-33.7413	-4.8970	-39.4198
13	1.41	0.018	-32.1915	-11.7201	-28.6787
14	1.01	0.007	-17.1084	-4.2045	-18.0208
15	1.00	0.007	-47.0172	11.5589	-39.8710
16	0.77	0.003	-3.7776	20.1902	-58.0836
17	0.67	0.001	-7.3320	-25.1923	-17.3221
18	0.65	0.001	-0.6752	19.9573	-0.0990

ranked centroid was 7.67 Å from native XMD7-117, and the redocked XMD7-117 top pose recovered the crystallographic geometry at 0.968 Å RMSD. DoGSite centroid-level agreement could not be quantified because the archived pocket output lacked centroids and residue lists.

SP-dG—not AC—was used for cross-ligand ranking. MolPort-002-217-232 (−8.9822), MolPort-002-214-941 (−8.9139), and MolPort-007-557-644 (−8.8711) were the lead-

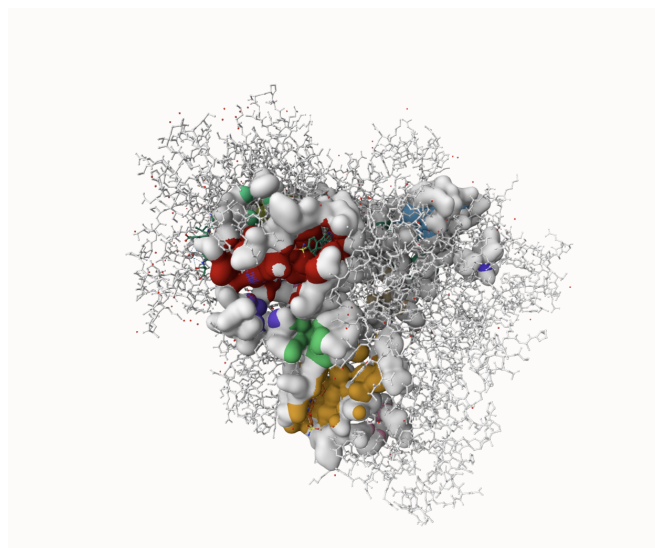


Figure. 2 PrankWeb-predicted DYRK1A binding site. The highest-ranked pocket centroid lies 7.67 Å from the co-crystallized XMD7-117 centroid, placing it in the ATP-site neighborhood.

Table 3 Top 15 Ligands Identified through Pharmit Pharmacophore Screening

Name	RMSD	Mass	RBnds
MolPort-001-574-215	0.083	415	10
MolPort-051-759-771	0.090	527	10
MolPort-002-960-391	0.092	504	8
MolPort-002-960-426	0.096	468	5
MolPort-002-214-941	0.096	424	5
MolPort-002-989-329	0.096	432	9
MolPort-000-301-254	0.096	315	3
MolPort-002-964-537	0.096	334	3
MolPort-007-557-644	0.097	391	4
MolPort-002-217-232	0.097	454	6
MolPort-002-961-764	0.098	464	6
MolPort-002-984-251	0.098	427	10
MolPort-003-831-850	0.100	437	6
MolPort-002-591-074	0.100	329	4
MolPort-002-710-706	0.101	319	4

ing computational hits. MolPort-002-964-537, previously emphasized using AC, fell to thirteenth by SP-dG. All 15 top poses lay within 8 Å of the XMD7-117 centroid and sampled residues in the ATP-site region. This supports prioritization for testing, but not inhibition, potency, or therapeutic activity. Known DYRK1A inhibitor studies provide biological context^{14–17,34}. Mechanistic studies of DYRK1A-related tau and

Table 4 Corrected SwissDock results for all 15 MolPort compounds, ranked by SP-dG. AC member scores are shown separately and are not compared with AutoDock Vina scores.

Compound	SP-dG rank	SwissDock job	AC member score	SP-dG	Distance to XMD7-117 centroid (Å)
MolPort-002-217-232	1	302973	-24.664	-8.9822	0.37
MolPort-002-214-941	2	99739622	-31.422	-8.9139	1.24
MolPort-007-557-644	3	36328640	13.176	-8.8711	0.48
MolPort-002-960-391	4	44504267	1.506	-8.7412	2.26
MolPort-002-961-764	5	94102524	-8.910	-8.6765	2.19
MolPort-051-759-771	6	34825370	-7.621	-8.6764	1.71
MolPort-003-831-850	7	24932752	-27.609	-8.6570	0.77
MolPort-002-989-329	8	34340885	-7.223	-8.6320	2.57
MolPort-002-960-426	9	75644603	-32.467	-8.5492	0.50
MolPort-002-984-251	10	81066807	-14.763	-8.5306	2.57
MolPort-000-301-254	11	47232499	-27.490	-8.4733	2.93
MolPort-002-591-074	12	42798857	-32.763	-8.3754	1.74
MolPort-002-964-537	13	12464732	-38.216	-8.3043	1.79
MolPort-001-574-215	14	84198843	-40.412	-8.2805	1.63
MolPort-002-710-706	15	53230559	32.199	-7.8800	1.48

Table 5 SwissADME predictions for the original AC-selected five-compound subset; this is not the corrected SP-dG top five.

Name	# of H-bond acceptors	# of H-bond donors	Consensus Log P Value	BBB Permeant	GI absorption
MolPort-001-574-215	6	1	1.46	No	Low
MolPort-002-964-537	5	2	1.56	No	High
MolPort-002-214-941	5	1	3.10	No	High
MolPort-002-960-426	5	1	3.19	No	High
MolPort-002-591-074	6	2	0.15	No	High

Table 6 Retained ProTox-3.0 oral LD50 and toxicity-class predictions for the original five-compound subset. Classes are model outputs, not experimental safety classifications.

Name	Predicted LD50 (mg/kg)	Predicted Toxicity Class
MolPort-001-574-215	1000	4
MolPort-002-964-537	2000	4
MolPort-002-214-941	2900	5
MolPort-002-960-426	2000	4
MolPort-002-591-074	2900	5

amyloid pathways also inform interpretation^{11–13}. Biochemical IC50/Ki measurements and selectivity panels remain necessary³⁵.

Brain exposure is a central limitation. Every compound in

the original SwissADME subset was predicted BBB nonpermeant, so none can presently be advanced as a CNS therapeutic candidate. The results instead nominate chemotypes for medicinal-chemistry review. Advancement should require measured pKa and logD7.4, parallel artificial membrane or MDCK permeability, P-glycoprotein/BCRP efflux, metabolic stability, and in vivo brain-to-plasma ratios before efficacy testing.

Kinase selectivity is also unresolved because ATP-binding sites are conserved. A useful next step is biochemical DYRK1A potency testing followed by counterscreens against related DYRK family members and a broader kinome panel. Cellular target-engagement and tau-phosphorylation assays should follow only for compounds with confirmed potency and acceptable selectivity.

Limitations include a static receptor, scoring-function uncertainty, incomplete retention of the original Pharmit query

Table 7 SwissDock XMD7-117 pose-recovery control and comparison with the leading MolPort hits. AC is an intrajob pose-ranking score; SP-dG is reported separately for cross-ligand comparison.

Compound	Role	SP-dG	AC score	RMSD (Å)	Interpretation
MolPort-002-217-232	MolPort computational hit	-8.9822	-24.664140	not applicable	screening hit; score does not establish inhibition
MolPort-002-214-941	MolPort computational hit	-8.9139	-31.422287	not applicable	screening hit; score does not establish inhibition
MolPort-007-557-644	MolPort computational hit	-8.8711	13.176183	not applicable	screening hit; score does not establish inhibition
MolPort-002-960-391	MolPort computational hit	-8.7412	1.506102	not applicable	screening hit; score does not establish inhibition
XMD7-117 (B5T)	co-crystallized positive control	-8.5421	-56.629909	0.968	positive control; top pose recovered the native binding mode

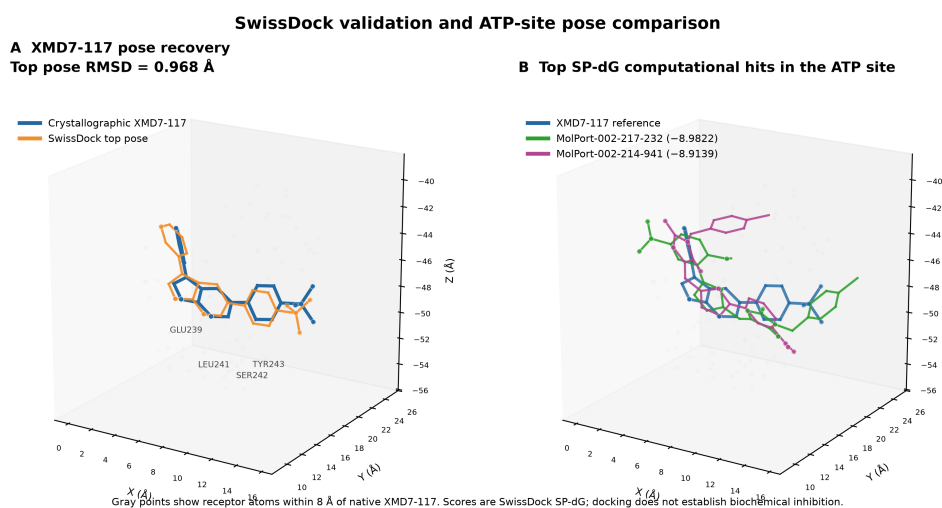


Figure. 3 XMD7-117 positive-control pose recovery and corrected SP-dG ranking. The top control pose reproduced the crystallographic binding mode with a symmetry-aware heavy-atom RMSD of 0.968 Å; the closest generated pose was 0.806 Å. Scores are computational and do not establish inhibition.

and ProTox detail, an ADME subset selected using AC rather than SP-dG, absent biochemical activity data, absent kinase-selectivity data, and absent CNS exposure measurements. The polar-contact screen is distance-based and not an angle-validated interaction analysis. These limitations prevent claims of inhibition, efficacy, or safety. Within these limits, the corrected workflow provides a reproducible pose-recovery control, preserves all ligand identities and docking records, and generates a transparent experimental priority list. It should be viewed as hypothesis generation for biochemical and CNS-development studies.

Conclusions and future work

This study combined pocket prediction, a predefined Pharmit-derived ligand set, SwissDock docking, SwissADME, and

ProTox-3.0 to prioritize computational DYRK1A-binding hits. The XMD7-117 control recovered the crystallographic pose, supporting the docking protocol's ability to reproduce this known geometry. The corrected SP-dG ranking placed MolPort-002-217-232 first, MolPort-002-214-941 second, and MolPort-007-557-644 third. These rankings differ from the original AC-based interpretation. All 15 top poses localized to the native ATP-site region, but docking scores alone do not identify inhibitors. The compounds should therefore be described as computational hits or lead candidates. Required next experiments are biochemical DYRK1A binding and inhibition assays, counterscreens for kinase selectivity, cellular target-engagement and tau-phosphorylation assays, measured permeability and efflux, pharmacokinetics and brain exposure, and empirical toxicity studies. Complete compound identities, submitted SMILES, SwissDock-prepared structures, job

records, and pose results are provided in the Supporting Information.

References

- 1 D. J. Selkoe, J. Hardy, The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*. Vol. 8, pg. 595–608, 2016, <https://doi.org/10.15252/emmm.201606210>.
- 2 S. R. Ryoo, H. J. Cho, H. W. Lee, H. K. Jeong, C. Radnaabazar, Y. S. Kim, M. J. Kim, M. Y. Son, H. Seo, S. H. Chung, W. J. Song, Dual-specificity tyrosine(y)-phosphorylation regulated kinase 1A-mediated phosphorylation of amyloid precursor protein: evidence for a functional link between Down syndrome and Alzheimer's disease. *Journal of Neurochemistry*. Vol. 104, pg. 1333–1344, 2008, <https://doi.org/10.1111/j.1471-4159.2007.05075.x>.
- 3 J. Wegiel, C. X. Gong, Y. W. Hwang, The role of DYRK1A in neurodegenerative diseases. *The FEBS Journal*. Vol. 278, pg. 236–245, 2011, <https://doi.org/10.1111/j.1742-4658.2010.07955.x>.
- 4 M. T. Heneka, D. T. Golenbock, E. Latz, Innate immunity in Alzheimer's disease. *Nature Immunology*. Vol. 16, pg. 229–236, 2015, <https://doi.org/10.1038/ni.3102>.
- 5 C. H. van Dyck et al., Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*. Vol. 388, pg. 9–21, 2023, <https://doi.org/10.1056/NEJMoa2212948>.
- 6 J. R. Sims et al., Donanemab in early symptomatic Alzheimer disease. *JAMA*. Vol. 330, pg. 512–527, 2023, <https://doi.org/10.1001/jama.2023.13239>.
- 7 M. A. Mintun et al., Donanemab in early Alzheimer's disease. *New England Journal of Medicine*. Vol. 384, pg. 1691–1704, 2021, <https://doi.org/10.1056/NEJMoa2100708>.
- 8 J. Sevigny et al., The antibody aducanumab reduces $\alpha\beta$ plaques in Alzheimer's disease. *Nature*. Vol. 537, pg. 50–56, 2016, <https://doi.org/10.1038/nature19323>.
- 9 C. J. Swanson et al., A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti- $\alpha\beta$ protofibril antibody. *Alzheimer's Research & Therapy*. Vol. 13, pg. 80, 2021, <https://doi.org/10.1186/s13195-021-00813-8>.
- 10 Y. L. Woods, P. Cohen, W. Becker, R. Jakes, M. Goedert, X. Wang, C. G. Proud, The kinase DYRK phosphorylates protein-synthesis initiation factor eIF2B ϵ at Ser539 and the microtubule-associated protein tau at Thr212: potential role for DYRK as a glycogen synthase kinase 3-priming kinase. *Biochemical Journal*. Vol. 355, pg. 609–615, 2001, <https://doi.org/10.1042/bj3550609>.
- 11 F. Liu et al., Overexpression of DYRK1A contributes to neurofibrillary degeneration in Down syndrome. *The FASEB Journal*. Vol. 22, pg. 3224–3233, 2008, <https://doi.org/10.1096/fj.07-104539>.
- 12 R. Kimura et al., The DYRK1A gene, encoded in chromosome 21 Down syndrome critical region, bridges between beta-amyloid production and tau phosphorylation in Alzheimer disease. *Human Molecular Genetics*. Vol. 16, pg. 15–23, 2007, <https://doi.org/10.1093/hmg/dd1437>.
- 13 N. Jin et al., Truncation and activation of dual specificity tyrosine phosphorylation-regulated kinase 1A by calpain I: a molecular mechanism linked to tau pathology in Alzheimer disease. *Journal of Biological Chemistry*. Vol. 290, pg. 15219–15237, 2015, <https://doi.org/10.1074/jbc.M115.645507>.
- 14 C. Branca et al., Dyrk1 inhibition improves Alzheimer's disease-like pathology. *Aging Cell*. Vol. 16, pg. 1146–1154, 2017, <https://doi.org/10.1111/acer.12648>.
- 15 R. Velazquez et al., Chronic Dyrk1 inhibition delays the onset of AD-Like pathology in 3xTg-AD mice. *Molecular Neurobiology*. Vol. 56, pg. 8364–8375, 2019, <https://doi.org/10.1007/s12035-019-01684-9>.
- 16 T. L. Nguyen et al., Correction of cognitive deficits in mouse models of Down syndrome by a pharmacological inhibitor of DYRK1A. *Disease Models & Mechanisms*. Vol. 11, pg. dmm035634, 2018, <https://doi.org/10.1242/dmm.035634>.
- 17 B. Zhu et al., DYRK1A antagonists rescue degeneration and behavioural deficits of in vivo models based on amyloid-beta, tau and DYRK1A neurotoxicity. *Scientific Reports*. Vol. 12, pg. 15847, 2022, <https://doi.org/10.1038/s41598-022-19967-y>.
- 18 A. Volkamer, D. Kuhn, F. Rippmann, M. Rarey, DoGSiteScorer: a web server for automatic binding site prediction, analysis and druggability assessment. *Bioinformatics*. Vol. 28, pg. 2074–2075, 2012, <https://doi.org/10.1093/bioinformatics/bts310>.
- 19 D. Jakubec, P. Skoda, R. Krivak, M. Novotny, D. Hoksza, PrankWeb 3: accelerated ligand-binding site predictions for experimental and modelled protein structures. *Nucleic Acids Research*. Vol. 50, pg. W593–W597, 2022, <https://doi.org/10.1093/nar/gkac389>.
- 20 J. Sunseri, D. R. Koes, Pharmit: interactive exploration of chemical space. *Nucleic Acids Research*. Vol. 44, pg. W442–W448, 2016, <https://doi.org/10.1093/nar/gkw287>.
- 21 J. M. Paggi, A. Pandit, R. O. Dror, The art and science of molecular docking. *Annual Review of Biochemistry*. Vol. 93, pg. 389–410, 2024, <https://doi.org/10.1146/annurev-biochem-030222-120000>.
- 22 Y. C. Chen, Beware of docking! *Trends in Pharmacological Sciences*. Vol. 36, pg. 78–95, 2015, <https://doi.org/10.1016/j.tips.2014.12.001>.
- 23 A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*. Vol. 7, pg. 42717, 2017, <https://doi.org/10.1038/srep42717>.
- 24 M. Bugnon et al., SwissDock 2024: major enhancements for small-molecule docking with Attracting Cavities and AutoDock Vina. *Nucleic Acids Research*. Vol. 52, pg. W324–W332, 2024, <https://doi.org/10.1093/nar/gkac300>.
- 25 P. Banerjee, E. Kemmler, M. Dunkel, R. Preissner, ProTox 3.0: a web-server for the prediction of toxicity of chemicals. *Nucleic Acids Research*. Vol. 52, pg. W513–W520, 2024, <https://doi.org/10.1093/nar/gkac303>.
- 26 A. Volkamer, A. Griewel, T. Grombacher, M. Rarey, Analyzing the topology of active sites: on the prediction of pockets and subpockets. *Journal of Chemical Information and Modeling*. Vol. 50, pg. 2041–2052, 2010, <https://doi.org/10.1021/ci100241y>.
- 27 A. Volkamer, D. Kuhn, T. Grombacher, F. Rippmann, M. Rarey, Combining global and local measures for structure-based druggability predictions. *Journal of Chemical Information and Modeling*. Vol. 52, pg. 360–372, 2012, <https://doi.org/10.1021/ci200454v>.
- 28 R. Krivák, D. Hoksza, P2Rank: machine learning based tool for rapid and accurate prediction of ligand binding sites from protein structure. *Journal of Cheminformatics*. Vol. 10, pg. 39, 2018, <https://doi.org/10.1186/s13321-018-0285-8>.
- 29 L. Jendele, R. Krivak, P. Skoda, M. Novotny, D. Hoksza, PrankWeb: a web server for ligand binding site prediction and visualization. *Nucleic Acids Research*. Vol. 47, pg. W345–W349, 2019, <https://doi.org/10.1093/nar/gkz424>.
- 30 G. Chen, A. J. Seukep, M. Guo, Recent advances in molecular docking for the research and discovery of potential marine drugs. *Marine Drugs*. Vol. 18, pg. 545, 2020, <https://doi.org/10.3390/md18110545>.
- 31 C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*. Vol. 46, pg. 3–26, 2001, [https://doi.org/10.1016/s0169-409x\(00\)00129-0](https://doi.org/10.1016/s0169-409x(00)00129-0).
- 32 W. P. Walters, Going further than Lipinski's rule in drug design. *Expert Opinion on Drug Discovery*. Vol. 7, pg. 99–107, 2012, <https://doi.org/10.1080/14713099.2012.668888>.

-
- org/10.1517/17460441.2012.648612.
- 33 A. Caminero Gomes Soares et al., Absorption matters: a closer look at popular oral bioavailability rules for drug approvals. *Molecular Informatics*. Vol. 42, pg. e202300115, 2023, <https://doi.org/10.1002/minf.202300115>.
- 34 Y. Ogawa et al., Development of a novel selective inhibitor of the Down syndrome-related kinase DYRK1A. *Nature Communications*. Vol. 1, pg. 86, 2010, <https://doi.org/10.1038/ncomms1090>.
- 35 T. Tahtouh et al., Selectivity, cocrystal structures, and neuroprotective properties of leucettines, a family of protein kinase inhibitors derived from the marine sponge alkaloid leucettamine b. *Journal of Medicinal Chemistry*. Vol. 55, pg. 9312–9330, 2012, <https://doi.org/10.1021/jm301034u>.

Supplementary Information

The online version contains supplementary material available at <https://nhsjs.com/?p=58884>.