



Section 4. Pharmaceutical Sciences

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DISCOVERY OF SMALL MOLECULES TARGETING MER-TK AS NOVEL THERAPIES FOR CARDIOVASCULAR DISEASES

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Abstract

Cardiovascular diseases remain the leading cause of death worldwide. Currently, FDA-approved therapies primarily manage cholesterol, blood pressure, and clot formation without correcting the underlying issues in apoptotic cell clearance that drive plaque instability and chronic inflammation. MER proto-oncogene tyrosine kinase (MerTK), a receptor central to efferocytosis, has emerged as a promising target for addressing this gap, yet no MerTK-targeted small molecule therapy currently exists for cardiovascular disease. This study used a structure-based computational pipeline to identify and evaluate candidate small molecules targeting MerTK. First, the MerTK structure was analyzed using ProteinsPlus and PrankWeb to identify its most druggable binding pocket, revealing a single dominant site with a drug score of 0.82–0.83. Second, a pharmacophore model built from this pocket was used to virtually screen compound libraries, yielding fifteen candidates with strong geometric alignment (RMSD $\leq$ 0.127 Å). Third, molecular docking of these fifteen compounds against the binding pocket produced SwissParam scores ranging from –6.85 to –8.83 kcal/mol, narrowing the pool to eight top binders. Fourth, ADME and Lipinski's Rule screening of these eight compounds identified four candidates with favorable absorption, solubility, and drug-likeness profiles. Fifth, toxicity prediction of these four finalists evaluated lethal dose, toxicity class, and toxicological endpoint breadth. Together, these results identified MolPort-047–786–433 as the most promising overall candidate, combining strong predicted binding affinity (–8.2918 kcal/mol), full Lipinski compliance, high gastrointestinal absorption, and the most favorable toxicity profile (LD50 of 1190 mg/kg, toxicity class 4) among all candidates screened.

Keywords *MerTK, efferocytosis, cardiovascular disease, computational drug discovery, molecular docking*

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide and their

impact continues to rise despite major advances in prevention and treatment. They develop through lipid accumulation, chron-

ic inflammation, endothelial dysfunction, and tissue remodeling, ultimately leading to atherosclerosis, myocardial infarction, and heart failure (Jebari-Benslaiman et al., 2022). These processes disrupt vascular homeostasis and impair cardiac function, making CVDs a persistent global health challenge. Understanding the molecular pathways that drive these events is essential for developing more effective therapies.

Current FDA-approved drugs for treating cardiovascular issues primarily target cholesterol, blood pressure, and clot formation. Statins and PCSK9 inhibitors lower LDL cholesterol and reduce cardiovascular risk, but many patients still experience plaque progression and inflammation (Navarese et al., 2015). ACE inhibitors, beta-blockers, and antiplatelet agents improve hemodynamics and reduce the chances of clot formation, but fail to correct defects in immune regulation or apoptotic cell clearance (Vaidya et al., 2023). Anti-inflammatory drugs like canakinumab can reduce cardiovascular events but do not fully resolve plaque cell death and increase infection risk (Ridker et al., 2017). These limitations emphasize the need for therapies that address plaque instability and chronic inflammation directly.

MER proto-oncogene tyrosine kinase (MerTK) is a receptor tyrosine kinase expressed on macrophages, endothelial cells, and other immune cells, where it plays a critical role in clearing apoptotic cells (Lemke, 2013). During efferocytosis, bridging molecules such as Gas6 and Protein S bind to phosphatidylserine on apoptotic cells and activate MerTK, starting anti-inflammatory signaling that promotes engulfment and prevents secondary necrosis, limiting the release of pro-inflammatory cytokines and helping to maintain tissue homeostasis (Lemke, 2013). If MerTK signaling is impaired, apoptotic cells collect together, leading to chronic inflammation, oxidative stress, and plaque instability in the arteries (Cai et al., 2017; Ait-Oufella et al., 2008). Due to its essential role in maintaining normal vascular conditions, MerTK has shown promise as an important drug target for cardiovascular diseases.

The MerTK receptor is especially significant because it combines inflammation resolution, lipid metabolism, and tissue re-

modeling – three processes critical to plaque stability. Elevated MerTK increases efferocytosis efficiency and strengthens the fibrous cap, decreasing plaque vulnerability (Thorp et al., 2008). A lack of MerTK has been linked to mitochondrial dysfunction, increased ROS levels, smooth muscle cell phenotypic switching, and cardiac fibrosis, all of which worsen cardiovascular diseases (Cai et al., 2018). Targeting MerTK therefore appears to be a reliable approach to reduce residual inflammatory risk beyond current therapies.

Several different types of therapeutic molecule types are being explored to control MerTK activity. Small molecules can enhance MerTK signaling or inhibit its cleavage by ADAM17 (Thorp et al., 2011). Large molecules, like Gas6 or Protein S, can activate MerTK directly. Although antibodies are large molecules, they do offer flexibility in how they can be designed to activate, inhibit, or prevent cleavage of the receptor. Peptides can be engineered for both stability and specificity; they enable targeted stimulation of MerTK while limiting unwanted effects on other receptors. Together, these therapeutic approaches aim to restore efferocytosis, reduce inflammation, and improve cardiovascular health.

Recent reviews have highlighted MerTK-mediated efferocytosis as a promising therapeutic target in cardiovascular disease. One review found that boosting MerTK activity reduces necrotic core formation and improves plaque stability (Scott et al., 2001). A second paper, focused on bridging molecules approaches that mimic Gas6 or Protein S to strengthen anti-inflammatory signaling, found that MerTK activation enhances efferocytosis, limits oxidative stress, and supports tissue repair (Rothlin et al., 2007). A third review compared multiple pathways of efferocytosis and found that impaired MerTK signaling leads to persistent inflammation and plaque vulnerability, highlighting the need for therapies that restore efficient apoptotic cell removal (Cohen et al., 2002). Together, these studies show that MerTK-targeted therapies (across small molecules, biologics, and receptor-stabilizing strategies) offer a promising direction for improving plaque stability and reducing cardiovascular disease progression.

SwissDock reports predicted binding strength using the SwissParam score (equiv-

alent to ΔG). Each job was verified to complete within the 1-hour runtime limit, and the search box's size and/or position was adjusted as needed. Each run was submitted using a unique docking name and email address for notification of completion. Swissdock then generated ranked binding modes based on predicted SwissParam score and the most favorable SwissParam score (lowest) was recorded for each. Corresponding interaction figures were screenshotted. All information was recorded into a summary table.

ADME and Drug-Likeness Prediction **SwissADME Submission and Lipinski's Rule Evaluation**

SMILES strings for the eight top-ranked docking candidates were entered individually into the SwissADME web server. For each compound, hydrogen bond donors/acceptors, molecular weight, consensus LogP (averaged LogP value reported across SwissADME's five prediction models), water solubility, and GI absorption were recorded alongside their original SwissParam docking scores (Table 5). Compounds were classified as either agreeing or disagreeing with Lipinski's Rule, and the number of violations were recorded as well.

Toxicity Prediction

Toxicity Prediction and Toxicological Endpoints Recorded

The four lead compounds identified in Section 3.4 (Z25837483, MolPort-047–786–433, Z25837505, and MolPort-052–064–324) were submitted to the ProTox 3.0 and corresponding SMILES string was entered. All toxicological endpoints, pathways, targets, and events were selected before running each prediction. Toxicity classification (active/inactive) was recorded for each endpoint, and radar charts were used to compare each compound's active toxicological aspects against the FDA-approved drug average; any endpoint exceeding the average was noted as a potential limitation. LD50, toxicity class, prediction accuracy, active cluster image, and radar chart were collected for each candidate.

Results Analysis

Identification of Druggable Binding Sites

This research compared predictions from ProteinsPlus and PrankWeb to identify MerTK's most druggable pockets. ProteinsPlus identified P_0, P_1, and P_2 as the highest scoring group (drug score 0.82–0.83) with the largest pocket volumes (Table 1, Figure 2).

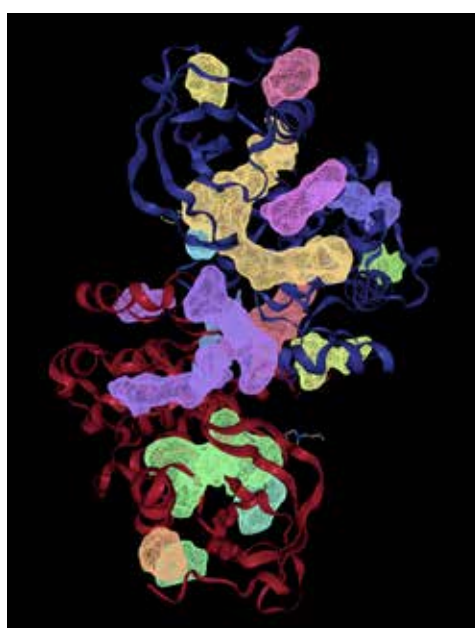
Table 1. This table displays the geometric properties and drug scores of all predicted MerTK binding pockets identified by ProteinsPlus. Higher-ranked pockets (P_0–P_2) show the largest volumes and highest drug scores, while lower-ranked pockets display increasingly smaller cavities and lower drug scores

Binding Site	Volume (Å ³)	Surface Area (Å ²)	Drug Score
P_0	1109.56	1370.36	0.82
P_1	903.31	1086.28	0.83
P_2	711.46	906.96	0.83
P_3	438.23	464.64	0.73
P_4	295.79	344.77	0.72
P_5	183.58	325.11	0.43
P_6	181.95	287.26	0.25
P_7	175.21	322.93	0.34
P_8	157.14	366.73	0.34
P_9	150.81	235.98	0.49
P_10	147.74	403.25	0.31
P_11	144.48	322.03	0.31

Binding Site	Volume (Å ³)	Surface Area (Å ²)	Drug Score
P_12	132.53	207.04	0.13
P_13	119.87	277.71	0.22
P_14	115.99	373.02	0.23
P_15	111.5	291.89	0.2

Among these, P_0 was the largest cavity, P_1 showed an equally high drug score and well-defined pocket shape, and P_2 matched the same top score range, forming the third major pocket.

Figure 2. All binding pockets identified on the MerTK protein using the ProteinsPlus analysis. Colored mesh regions represent individual predicted pockets, while the red and blue ribbon-like structures depict the protein's backbone.



PrankWeb confirmed this same region by assigning its top two ranks (Rank 1 and Rank 2) the highest Pocket Scores (16.34 and 14.08) and the greatest number of residues (Figure 3). The remaining pockets also aligned well between the two tools (Table 2).

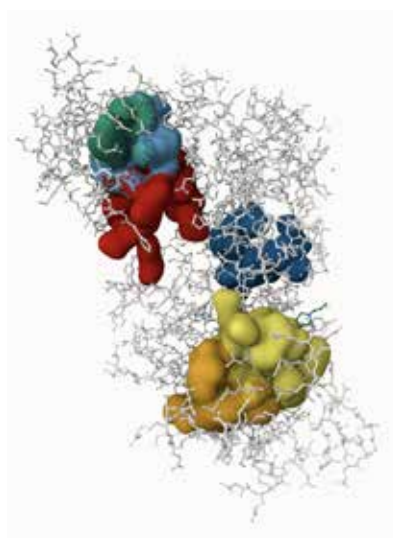
Table 2. This table summarizes the four pocket groups identified across both tools, showing how ProteinsPlus drug scores match with PrankWeb rankings. Higher-ranked pockets (P_0, P_1, P_2) display the strongest druggability, while lower-ranked pockets (P_6–P_15) show low predicted binding potential

Rank	Pockets (ProteinsPlus)	Reason (PrankWeb)
1	P_0, P_1, P_2	Highest drug scores (0.82–0.83), largest pockets (volume/surface area), PrankWeb Rank 1–2 (16.34 and 14.08)
2	P_3, P_4	Intermediate drug scores (0.72–0.73), matches PrankWeb Rank 3
3	P_5, P_9	Medium drug scores (0.43–0.49), matches PrankWeb Rank 4
4	P_6–P_8, P_10–P_15	Low drug scores (0.13–0.34), matches PrankWeb Rank 5–6

The second group, P_3 and P_4, showed intermediate drug scores (from 0.72–0.73) and corresponded to PrankWeb's Rank 3. The third group, P_5 and P_9, displayed medium scores (0.43–0.49) and matched Rank

4. Finally, the lowest group, P_6 through P_15 (except P_9) showed low scores (0.13–0.34) and aligned with PrankWeb's Rank 5 and Rank 6.

Figure 3. Predicted binding sites in MerTK (PDB ID: 7M5Z) using the PrankWeb machine learning model. Colored spheres represent the binding site and the grey residues represent the structure of the protein.



Together, the ranking table and models show strong consistency between the two approaches, confirming both tools independently identified the same primary binding pocket (Figures 2–3). This supports the conclusion that MerTK contains one dominant, highly druggable site, making it a strong candidate for future inhibitor design.

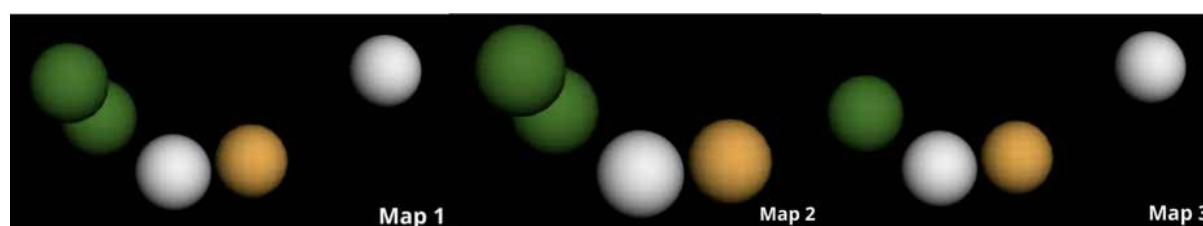
Results of Pharmacophore-based Virtual Screening of MerTK

This experiment aimed to identify small-molecule candidates that align strongly with a pharmacophore model built from the MerTK binding site. Because MerTK is involved in cell-signaling pathways linked to

disease, finding molecules that match its key interaction features is an important early step in drug discovery, testing whether structurally varying compounds could recreate the pharmacophore's donor, acceptor, hydrophobic, and positive-ion features.

The expected outcome was that only a limited number of compounds would achieve low RMSD values (≤ 0.2 Å), a threshold representing a very accurate match. Additionally, with different maps expected to yield different number of hits and small feature-radius adjustments expected to increase accepted compounds without changing the original features.

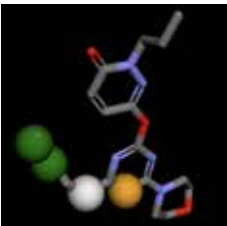
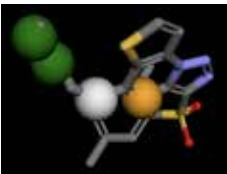
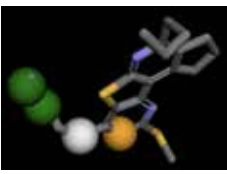
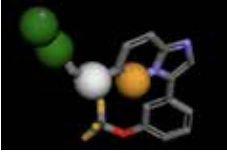
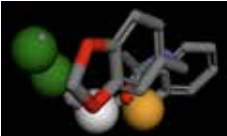
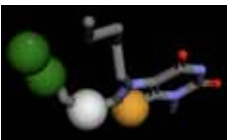
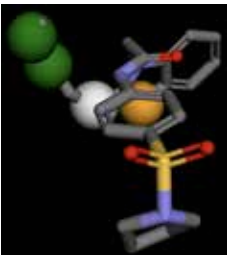
Figure 4. Three pharmacophore maps generated with Pharmit platform, illustrating difference in feature placement and spatial arrangement. Green spheres represent hydrophobic features, white spheres signify hydrogen-donor features, and orange spheres indicate hydrogen-acceptor features. The maps show how feature placement varies across the usable pharmacophore models

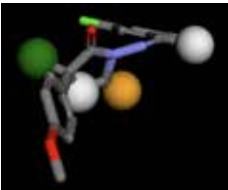
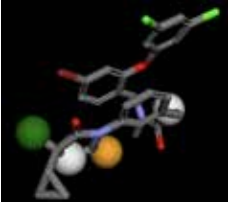
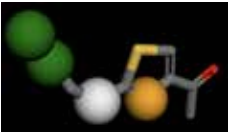
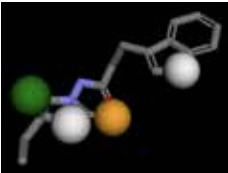
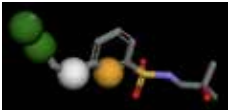
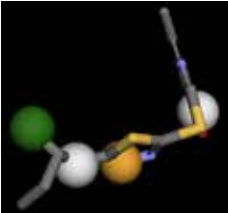
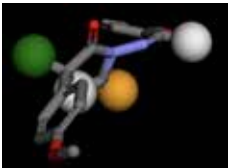
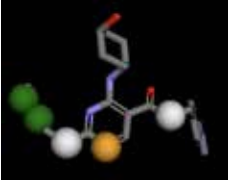


Building on these expectations, screening identified several compounds with strong geometric alignment. Many compounds across usable maps met the RMSD of ≤ 0.2 Å cutoff, and the top fifteen lowest-scoring

molecules were selected for further analysis (Table 3). RMSD values ranged from 0.041 Å (MolPort-004–893–824) to 0.127 Å (MolPort-047–786–433), signifying strong matches.

Table 3. Top 15 compounds identified across all usable pharmacophore maps, each demonstrating strong alignment with the MerTK pharmacophore model (RMSD ≤ 0.2 Å). For each compound the table reports the compound ID, RMSD value, the pharmacophore map it was selected from, and the overlay figure showing its alignment with the features

Compound Name	RMSD Value / Map Number	Overlay Figure between Compound and Pharmacophore Map
1. Mol-Port-004–893–824	0.041 / 2	
2. Mol-Port-007–741–957	0.05 / 2	
3. Mol-Port-002–612–851	0.052 / 2	
4. Mol-Port-052–064–324	0.059 / 2	
5. Z25837505	0.064 / 2	
6. Z223825236	0.065 / 2	
7. Z25837483	0.065 / 2	

Compound Name	RMSD Value / Map Number	Overlay Figure between Compound and Pharmacophore Map
8. Z49975822	0.07 / 3	
9. Z5198624731	0.075 / 3	
10. Z4081324527	0.081 / 3	
11. Z30056937	0.083 / 3	
12. Z3074709999	0.085 / 2	
13. Z154287422	0.089 / 3	
14. Z49975836	0.091 / 3	
15. Mol-Port-047–786–433	0.127 / 1	

These results also supported the expectation that different maps would yield different sets of hits – some producing multiple strong matches, others only one or none. Small adjustments to feature radii and location in-

creased the number of matches by lowering the RMSD values without removing the originals can improve screening performance integrity.

Overall, the MerTK pharmacophore model identified a consistent set of well-aligned compounds across multiple maps (Table 3). The strong RMSD values and clear feature alignment confirm these fifteen molecules are reliable candidates for further analysis.

Results of Molecular Docking

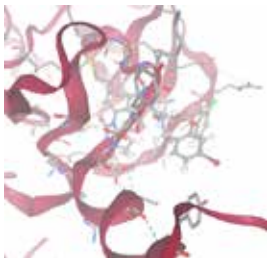
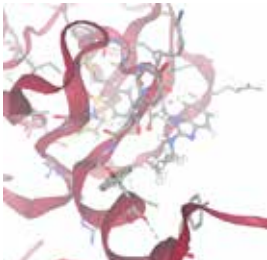
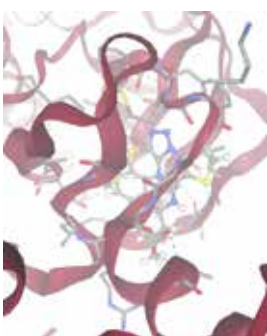
This experiment evaluated whether the fifteen pharmacophore-matched compounds could form stable predicted interactions with the primary MerTK binding pocket, using SwissParam score (equivalent to ΔG) to quantify predicted binding strength and identify the most promising candidates for future MerTK-targeted drug development.

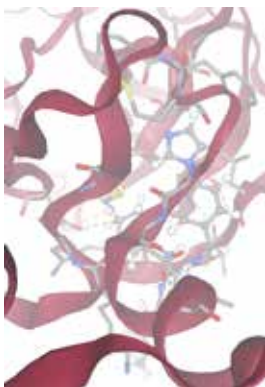
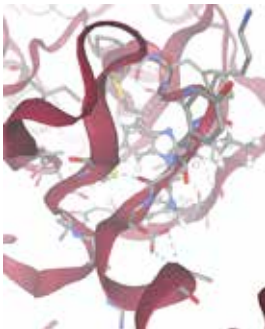
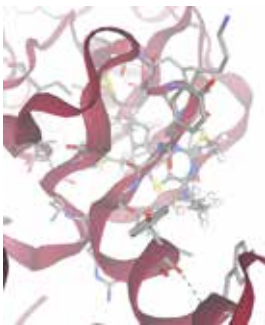
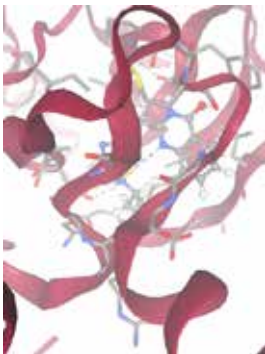
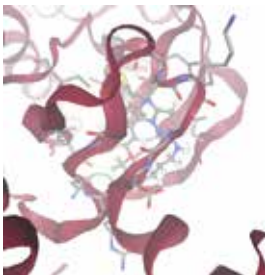
The expected outcome was that only a small group would produce a highly favor-

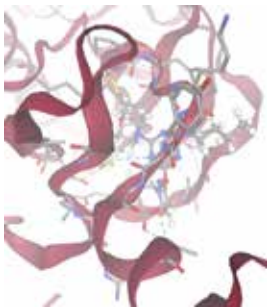
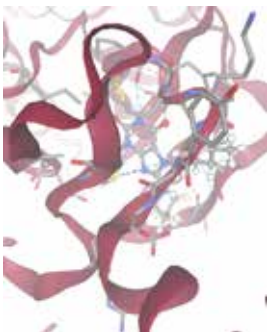
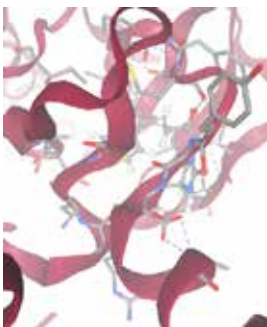
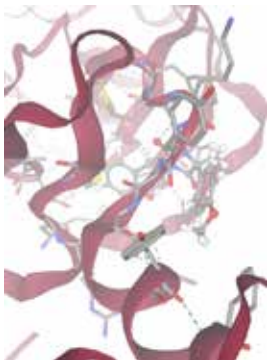
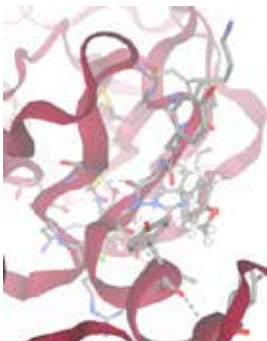
able SwissParam score, with predicted binding strengths varying in compound structure, and those that aligned well with the pharmacophore expected to also show lower (better) SwissParam scores, since the geometric fit and interaction stability are closely related.

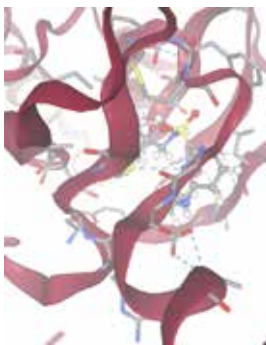
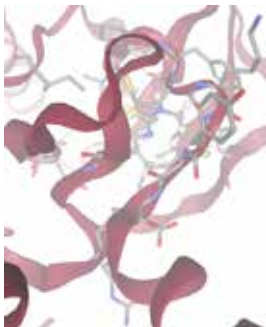
The docking results supported these expectations. All fifteen compounds produced measurable scores, ranging from -6.8518 to -8.8348 kcal/mol (Table 4). Z5198624731 showed the strongest score (-8.8348) followed by Z25837483 (-8.3922), MolPort-047-786-433 (-8.2918), MolPort-007-741-957 (-8.3820), and Z154287422 (-8.2285). Weaker compounds, such as Z4081324527 (-6.8518), still docked successfully but fewer stabilizing interactions.

Table 4. Predicted SwissParam scores for all fifteen docked compounds, along with corresponding interaction figures generated using the Swissdock platform. Lower SwissParam score indicates stronger predicted binding strength between each ligand and the MerTK binding pocket. Color-coded dashed lines in the figures represent the types of non-covalent interactions formed within the pocket

Compound Name	Docking Pose of the Compound Into MerTK
Z5198624731 SwissParam: -8.83448 kcal/mol	
Z25837483 SwissParam: -8.3922 kcal/mol	
MolPort-007-741-957 SwissParam: -8.3820 kcal/mol	

Compound Name	Docking Pose of the Compound Into MerTK
<i>MolPort-047-786-433</i> <i>SwissParam: -8.2918 kcal/mol</i>	
<i>Z25837505</i> <i>SwissParam: -8.2394 kcal/mol</i>	
<i>MolPort-002-612-851</i> <i>SwissParam: -8.2387 kcal/mol</i>	
<i>Z154287422</i> <i>SwissParam: -8.2285 kcal/mol</i>	
<i>MolPort-052-064-324</i> <i>SwissParam: -8.0968 kcal/mol</i>	

Compound Name	Docking Pose of the Compound Into MerTK
<i>MolPort-004-893-824</i> <i>SwissParam: -8.0798 kcal/mol</i>	
<i>Z223825236</i> <i>SwissParam: -7.7731 kcal/mol</i>	
<i>Z30056937</i> <i>SwissParam: -7.6032 kcal/mol</i>	
<i>Z49975836</i> <i>SwissParam: -7.5680 kcal/mol</i>	
<i>Z49975822</i> <i>SwissParam: -7.5112 kcal/mol</i>	

Compound Name	Docking Pose of the Compound Into MerTK
<i>Z3074709999</i> <i>SwissParam: –7.4394 kcal/mol</i>	
<i>Z4081324527</i> <i>SwissParam: –6.8518 kcal/mol</i>	

The docking figures displayed color-coded dashed interaction lines: blue for hydrogen bonds, yellow for ionic interactions, orange for cation- π interactions, dark gray for hydrophobic contacts, and green for π -stacking interactions. The strongest binders typically showed two to three blue hydrogen bonds, helping explain why they also produced the lowest SwissParam scores.

Overall, several pharmacophore-matched compounds showed strong predicted binding, with multiple scores falling below -8.2 kcal/mol (Table 4). These results confirm the docking experiment identified ligands capable of stable predicted binding, with Z5198624731 and other top-scorers representing promising candidates for further analysis.

Results of ADME and Drug-Likeness Prediction

This experiment determined which top docking candidates also had favorable drug-like properties, since a compound's ability to bind to MerTK (its pharmacodynamic profile, how the drug affects the body) is only useful if it can also survive the body's

own processing (its pharmacokinetic profile, how the body affects the drug). This evaluation mirrors the role of an ADME department, which advances or discontinues based on its absorption, distribution, metabolism, and excretion profile; failing any step is enough to disqualify a compound regardless of target binding. Lipinski's Rule of Five was used as the primary screen, based on LogP, the coefficient describing lipid versus aqueous phase distribution, with an ideal balanced range of roughly 0–5. Because binding affinity and drug-likeness are governed differently, not every strong docking candidate was expected to satisfy Lipinski's Rule.

Of the eight compounds sourced from MolPort and Enamine, six fully agreed with Lipinski's Rule. The exception was Z5198624731, the strongest docking candidate, which failed with two violations (MW 646.36 g/mol; CLogP 5.46) and poorly water-soluble despite showing high GI absorption (Table 5)—showing the single best docking candidate isn't necessarily the best overall drug candidate once absorption and distribution are considered.

Table 5. ADME and drug-likeness profiles for the eight top-ranked docking candidates (in order of SwissParam score), generated using the SwissADME platform, alongside each compound's SwissParam docking score. Compounds were evaluated against Lipinski's Rule of Five using hydrogen bond donor/acceptor counts, molecular weight, and Consensus LogP (CLogP). Water solubility classification and predicted gastrointestinal (GI) absorption are also reported. Compounds with zero Lipinski violations and high predicted GI absorption were prioritized as lead candidates

Compound	H-Bond Donors	H-Bond Acceptors	MW (g/mol)	Consensus LogP (CLogP)	Lipinski (Y/N, # violations)	Water Solubility Class	GI Absorption
1. Z5198624731	2	4	646.36	5.46	No, 2	Poorly Soluble	High
2. Z25837483	2	5	455.57	2.66	Yes, 0	Moderately Soluble	High
3. Mol-Port-007–741–957	1	5	415.53	3.88	Yes, 0	Moderately Soluble	Low
4. Mol-Port-047–786–433	4	5	463.58	2.39	Yes, 0	Moderately Soluble	High
5. Z25837505	2	4	380.44	2.72	Yes, 0	Moderately Soluble	High
6. Mol-Port-002–612–851	1	3	400.60	5.97	No, 1	Poorly Soluble	Low
7. Z154287422	2	4	361.48	3.66	Yes, 0	Moderately Soluble	Low
8. Mol-Port-052–064–324	1	6	350.34	3.90	Yes, 0	Moderately Soluble	High

Among the six Lipinski-compliant, GI absorption further separated the candidates. Z25837483, MolPort-047–786–433, Z25837505, and MolPort-052–064–324, showed both full Lipinski agreement and high GI absorption, while MolPort-007–741–957 and Z154287422 showed low absorption. These four compounds – all moderately water-soluble Lipinski-compliant, and high absorption – were carried forward as the final candidate pool. This stage primarily addressed the absorption and distribution aspects of ADME; metabolism and excretion were not assessed.

Results of Toxicity Prediction

Beyond binding affinity and drug-likeness, a candidate must also be evaluated for toxic effects – not simply whether it is toxic, but to what degree, and whether that degree falls within an approved limit. Toxicity was considered as both acute (short-term, with-

in hours), and organ (long-term, accumulating over repeated dosing), with the liver and kidney checked first as primary metabolism/excretion sites, though all organs were considered relevant.

All four compounds met the 300 mg/kg minimum LD50 threshold. MolPort-047–786–433 scored highest (1190 mg/kg), followed by MolPort-052–064–324 (807 mg/kg); Z25837483 and Z25837505 sat exactly at the minimum. All four compounds reached an acceptable toxicity class (≥ 3), with MolPort-047–786–433 and MolPort-052–064–324 in class 4, indicating lower toxicity (Table 6).

Prediction accuracy remained above the 50% minimum for all four. Z25837483, MolPort-047–786–433, and Z25837505 were each predicted with 67.38% accuracy, while MolPort-052–064–324 was significantly lower at 54.26%, narrowly clearing the threshold (Table 6). Although its LD50 is

BBB interaction – indicating a shared mechanism profile despite differing severity (Table 6). Radar charts showed Z25837483 and MolPort-047–786–433 stayed close to the FDA-approved baseline, while Z25837505 and MolPort-052–064–324 varied on certain endpoints, indicating a somewhat more toxic profile.

Table 6. Predicted toxicity profiles for the four lead compounds, generated using ProTox 3.0. LD50 reflects the predicted dose lethal to 50% of a population; toxicity class follows the GHS-based classification used by ProTox, where higher classes indicate lower toxicity. Prediction accuracy reflects the model’s confidence in the overall toxicity classification. Active cluster images and radar charts illustrate each compound’s predicted toxicological targets and pathways relative to the average profile of FDA-approved drugs

Altogether, Z25837483 carries the most favorable toxicological profile in terms of endpoints, though its LD50 is at the minimum. MolPort-047-786-433, with a strong LD50, acceptable toxicity class, and a moderate active cluster, is the strongest candidate overall. Z25837505 shows a pronounced CYP2E1 deviation, a clear limitation. MolPort-052-064-324, despite an acceptable LD50 and toxicity class, has the lowest prediction accuracy and the most flagged toxicological endpoints, making it the weakest candidate.

Conclusion (Discussion)

This study identified MolPort-047–786–433 as the strongest overall candidate for MerTK-targeted small molecule therapy in cardiovascular disease, emerging from an initial pool of fifteen pharmacophore-matched compounds. It combined favorable predicted binding (–8.2918 kcal/mol), full Lipinski compliance (MW 463.58 g/mol, CLogP 2.39, zero violations), high GI absorption, and the most favorable toxicity profile of the four finalists, (LD50 1190 mg/kg, toxicity class 4). Z25837483 and Z25837505 also performed well but were limited by having minimum-threshold LD50 values and, for Z25837505, a pronounced deviation in CYP2E1 activity compared to the average FDA-approved drug.

This pipeline's success stemmed from its layered screening, filtering candidates at each stage using different pharmacological criteria instead of relying on only one metric. Identifying one dominant binding pocket through two independent computational tools provided a reliable foundation for pharmacophore modeling, which generated

a diverse but consistent set of candidates for docking. ADME and toxicity screening then ensured binding affinity was not mistaken for overall drug viability, most clearly illustrated by Z5198624731, the top docking candidate, ultimately disqualified for poor drug-likeness and solubility. This progression narrowed the short four-compound list to one lead candidate grounded in multiple independent lines of evidence.

This study has two key limitations. First, several strong early-stage compounds, including the top docking candidate, were excluded due to unfavorable toxicity or drug-likeness, indicating that binding affinity alone is an unreliable predictor of overall candidate viability. Second, all findings were computational; no laboratory testing was performed, so the binding, ADME, and toxicity profiles are purely theoretical until experimentally validated. Future work should prioritize laboratory validation of MolPort-047–786–433, including in vitro binding affinity and efferyocytosis functional testing, to confirm its potential as a MerTK-targeted therapeutic for cardiovascular disease.

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