

Computational Identification of Small-Molecule Inhibitors Targeting TEAD2 Palmitoylation Pocket in Lung Cancer

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ABSTRACT

Background: Lung carcinoma is one of the most important health problems in the world and there is a need to develop effective and less toxic therapeutic agents. Computational drug discovery is an efficient approach for discovering new small molecule inhibitors that have potential anticancer activity. **Objectives:** In this study, an integrated *in silico* drug discovery approach was used to search for small molecule lead candidates against lung cancer. **Materials and Methods:** The hits identified from the molecular virtual screening were subjected to toxicity and toxicity/cytotoxicity filter, PASS activity filter, drug-likeness, pharmacokinetics, adverse effects, and LD₅₀ filter; then, molecular dynamics analyses (RMSD, RMSF, interactions, and radius of gyration) were performed for stability assessment. **Results:** The computational workflow identified two top-ranked compounds that had good binding affinity, low toxicity, and showed potential for anticancer activity as well as good pharmacokinetic features with minimal side effects. Molecular dynamics simulations showed that the protein-ligand interactions and the structure were stable over the course of the simulation. **Conclusion:** The discovered compounds showed good inhibitory activity against lung carcinoma and could be a potential treatment candidate. There is a need for additional experimental and clinical research to establish their effectiveness and safety.

Keywords: Anti-cancer, Drug designing, Inhibitors, *in silico* analysis, Lung cancer, TEAD, Molecular dynamics.

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INTRODUCTION

Lung cancer is among the most common and life-threatening form of cancer worldwide, with over one million individuals diagnosed each year. It's a significant lethal burden related to the diseases. In spite of many significant advancements in cancer diagnosis and therapeutic interventions, lung cancer remains one of commonly primary causes of cancer-associated deaths globally (Chaitanya *et al.*, 2021). The disease occurs as a consequence of expanding uncontrolled proliferation of abnormal cells within the lung that have developed by capacity to invade adjacent tissues and to metastasize to other sites including the brain liver bones and adrenal glands. They are divided into Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC), with NSCLC comprising around 85% of all diagnosed cancer cases (Smolarz *et al.*, 2025). The molecular heterogeneity and complexity of lung cancer have been of the greatest barriers to effective treatment. Standard treatment options like chemotherapy, surgery, and

radiotherapy are still extensively employed mainly with the disease stage and histological subtype of tumor. Surgery is currently believed to the best form of treatment yet when a localized tumor has been diagnosed at an early stage. Unfortunately, most of the patients present with advanced or metastatic disease, where surgical options are limited. Multidrug resistance and non-selective toxicity limit the efficacy of chemotherapy drugs like platinum chemotherapy. Although, treatment-associated toxicities and tumor recurrence continue to be significant limits, radiotherapy particularly plays a crucial role in management of disease, especially in patients with advanced stages (Debela *et al.*, 2021; Zafar *et al.*, 2025). The main factor of high death rate in lung cancer is mainly due to tumor heterogeneity and resistance of the tumor to current treatments. The evident limitations of current treatment strategies underline the need to discover other molecular targets that are involved in the development of lung cancer and the development of resistance to the therapies that are used. The relevance of dysregulated signaling networks in tumor genesis, proliferation, survival migration and metastasis have place an increased focus in molecular oncology (Choudhary *et al.*, 2023; He *et al.*, 2021).

The Hippo signaling pathway has been identified as a crucial regulator of cellular proliferation, apoptosis, tissue homeostasis, stem cell maintenance and organ size regulation among the



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various molecular signaling pathways linked to the development of lung cancer. By limiting excessive cellular growth and encouraging programmed cell death, the hippo pathway acts as a tumor suppressor mechanism under normal physiological conditions. Dysfunctioning of this pathway treated as common algorithm that has been implicated in tumorigenesis due to the promotion of cell proliferation and resistance to apoptosis caused by the abnormal activation of certain transcriptional regulators (Fu *et al.*, 2022; Yu *et al.*, 2015; Zhong *et al.*, 2024). The Transcriptional co-activators Yes-Associated Protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), which interacts with members of The Transcriptional Enhanced Associate Domain (TEAD) family of transcription factors, are considered as the main downstream effectors of the hippo pathways. Increasing evidence supports the importance of dysregulating the YAP/TAZ-TEAD signaling pathway in the process of tumorigenesis of diverse malignant disease like lung cancer, breast cancer, colorectal cancer, pancreatic tumor and hepatocellular carcinoma (Lo *et al.*, 2018; Yu *et al.*, 2025; Zhao *et al.*, 2020).

Transcriptional Enhanced Associate Domain

The TEAD family contains four highly conserved transcription factors, TEAD1, TEAD2, TEAD3 and TEAD4. This can activate the transcription of growth- and development related genes such as proliferation differentiation, survival and migration and Epithelial-Mesenchymal Transition (EMT). Recently, TEAD2 has become more promising therapeutic target owing to its key role in the oncogenic transcriptional regulating pathway mainly in tumor with hyperactive hippo signaling pathway (Cunningham *et al.*, 2022; Joo *et al.*, 2020; Wang *et al.*, 2024; Zhou *et al.*, 2016). But, due to the particularity of transcription factor that contains few well-defined ligand-binding domains and other prominent active sites attract the traditional design of small molecules inhibitors. The TEAD family was often studied as undruggable target (Tao *et al.*, 2023). Moreover, the current studies have recognized a conserved hydrophobic palmitoylation pocket with the TEAD proteins that particularly played important role for maintaining stability of protein and transcriptional activity. This has welcomed new opportunities for intervention of therapeutic targets. TEAD activity and its interaction with carcinogenic partners are regulated by palmitoylation, a post-translational alteration involving the covalent attachment of palmitic acid (Gridnev *et al.*, 2022; Hu *et al.*, 2022). Therefore, inhibiting the TEAD palmitoylation pocket has emerged as a novel therapeutic approach that can stop the transcriptional activation and slows down the growth of tumor cells and thereby suppressing the progression of the ailment.

The crystal structure of TEAD2 containing a ligand-bound palmitoylation pocket (PDB ID: 6E5G) was selected. This pocket represents a promising druggable site because small molecules capable of binding within this hydrophobic cavity

may destabilize TEAD2 function, inhibit YAP/TAZ interaction, and ultimately suppress downstream oncogenic transcriptional activity, providing a valuable structural basis for structure-based drug discovery. Therefore, the present study aims to identify potential small-molecule inhibitors targeting the TEAD2 palmitoylation pocket involved in lung cancer progression using a structure-based computational approach. The study employs virtual screening of compounds from the MCULE database, molecular docking against the TEAD2 protein structure (PDB ID: 6E5G), and comprehensive evaluation of selected compounds through ADMET profiling, toxicity and side-effect prediction, drug-likeness assessment, and cancer cell-line sensitivity analysis to identify promising therapeutic candidates for lung cancer treatment.

MATERIALS AND METHODS

Macromolecule Retrieval and Preparation

The three-dimensional structure of the target protein (PDB-6E5G) was retrieved from the Protein Data Bank (<https://www.rcsb.org/>) in PDB format. The downloaded macromolecule structure was prepared with the BIOVIA Discovery Studio Visualizer (version 2021) (Berman, 2000). The preparation steps involved the removal of unwanted molecules, including water and heteroatoms, followed by hydrogen bond optimization and structural refinement to obtain an error-free structure for docking studies.

Structure-Based Virtual Screening of Small Molecules

Structure-based virtual screening was employed using the online Mcule platform considered as a comprehensive platform for computer aided drug discovery that combines multiple approaches including target identification, ligand-based screening, one-click docking, and access to commercially available compounds (Kiss *et al.*, 2012). The hit-identification workflow was chosen within the structure-based virtual screening module of Mcule to screen out the potential molecules. Lipinski rule of five violation criteria was set between zero to one ensuring robust drug-likeness (Muteeb *et al.*, 2022). The sampler option from the diversity section was opted. Rest remaining parameters were kept under pre-set values. For conducting the docking studies, the pre-prepared structure was uploaded and studies were conducted using the Autodock Vina enabled screening workflow. For grid box values, coordinates of the protein-ligand binding region were set (Trott *et al.*, 2010; Roskoski *et al.*, 2023).

Docking Evaluation of Inhibitor

Additionally, to validate the docking efficiency, the reference inhibitor compound was subjected to docked using one-click docking module under the category of lead optimization of Mcule platform. for that, processed macromolecule and inhibitor

compound were uploaded and the binding dimensions were defined as per their complex coordinates. Top 4 poses were generated. The pose exhibiting the best energy and binding site was selected for further evaluations.

Structural Toxicity Screening

The shortlisted compounds were additionally evaluated using the Toxicity checker integrated within the Mcule platform (Kiss *et al.*, 2012). Each molecule was screened by selecting the Mcule compound IDs. The result was categorized as pass or fail, indicating toxicity and safer compounds.

Study of Cancerous Cell Line Activity

The anticancer potential of filtered compounds was analyzed by the online CLC-Pred server, an online tool used for predicting the cytotoxicity effects against various human cell lines based on structure similarity. SMILES notations were submitted individually for each compound to generate the output depicted in the probability of activity and inactivity. Furthermore, inferred antitumor activity values were also generated, indicating greater therapeutic potential (Bishwakarma *et al.*, 2026; Cheng *et al.*, 2024; Lagunin *et al.*, 2023).

Biological Activity Spectra Profiles

A biological activity spectrum was performed using the online server PASS (prediction of activity spectra for substances), which can predict 300+ pharmacological functions based on molecular using SMILES notation (SP, 2011). The SMILES were obtained from the Mcule platform and submitted to the server. The predicted result contained the probability of active and inactive compounds symbolized by Pa and Pi. The selection criteria include compounds having higher Pa values than Pi and are treated as biologically promising compounds.

Drug-likeness Profiling

The pkCSM server was used to examine the drug's pharmacokinetic characteristics. The ADMET parameters- absorption, distribution, metabolism, excretion, and toxicity are widely predicted and are an essential step of drug discovery. Drug-like qualities, mainly including intestinal absorption, blood-brain barrier permeability, cytochrome P450 interactions, and total clearances, can also be evaluated to determine physiological behavior. Compounds' SMILES were respectively used to comprehensively understand systemic exposure and stability of compounds in biological systems (Bultum *et al.*, 2022; Pires *et al.*, 2015).

Side Effects Profiling Assessment

The possible adverse side effects were generated using the online server ADVER-PRED (<http://www.way2drug.com/adverpred/>). The server predicts the probable side effects based on structure similarity trained on known drug safety datasets, thereby

facilitating early safety evaluation during drug discovery (Ivanov *et al.*, 2018).

Prediction of Compounds Lethality

The online server GUSAR (I), the way2drug platform, was used to assess the acute rat toxicity. The server predicts values in terms of median Lethal Dose of 50% (LD₅₀) for various administering routes, including oral, intravenous, intraperitoneal, and subcutaneous. The compounds were also classified according to the toxicity classification system (Zakharov *et al.*, 2012; Zhu *et al.*, 2009).

Simulation Studies for Stability Analysis

Based on integrated analysis of multiple computational approaches, the top-performing compounds were selected for stability investigation. Therefore, the simulation studies were conducted to evaluate dynamic behavior and structural ability in a defined system. The platform GROMACS with the version of 5.1.2 was selected at a temperature of 300k. The topologies and protein-ligand complexes files were generated using gmx grep utility (Khan *et al.*, 2022; Saxena *et al.*, 2019). The CGenFF (CHARMm general force field) was then applied for ligand parameterization, while the system was solvated using the TIP3 cubic box model. Subsequently, charge neutralization was performed by adding salt after the boundary conditions (Liu *et al.*, 2025; Vanommeslaeghe *et al.*, 2010). Steepest descent algorithm with 25,000,000 steps was utilized for minimizing the energy. With constant volume of temperature and pressure conditions (NVT and NPT), the temperature was set. As the last step, interactions were computed using the mesh Ewald method, and the production simulation was conducted at 100ns to gain deeper insights. Trajectories such as root mean square deviation and fluctuation, radius of gyration, solvent-accessible surface area, and hydrogen bonds were analyzed later on to obtain and evaluate the refined complexes (Noumi *et al.*, 2025; Petersen, 1995; Rahmati *et al.*, 2025).

RESULTS

Screening of small molecules

From the Mcule platform, docked compounds were generated. Along with the RO5 violations from 0-1, a hundred Mcule molecules were produced. Out of which 17 compounds showed 0 violations, while 44 compounds turned up having 1 violation. The binding energies range from -11.3 kcal/mol to -8.8 kcal/mol and were recorded by the docking investigations, which were greater from the reference compound. The inhibitor compound was taken from the protein itself. The structural toxicity of every single compound was assessed through the Mcule platform's toxicity checker. A total of 39 compounds were found to be structurally toxic. The safer compounds were stored for further evaluation. A

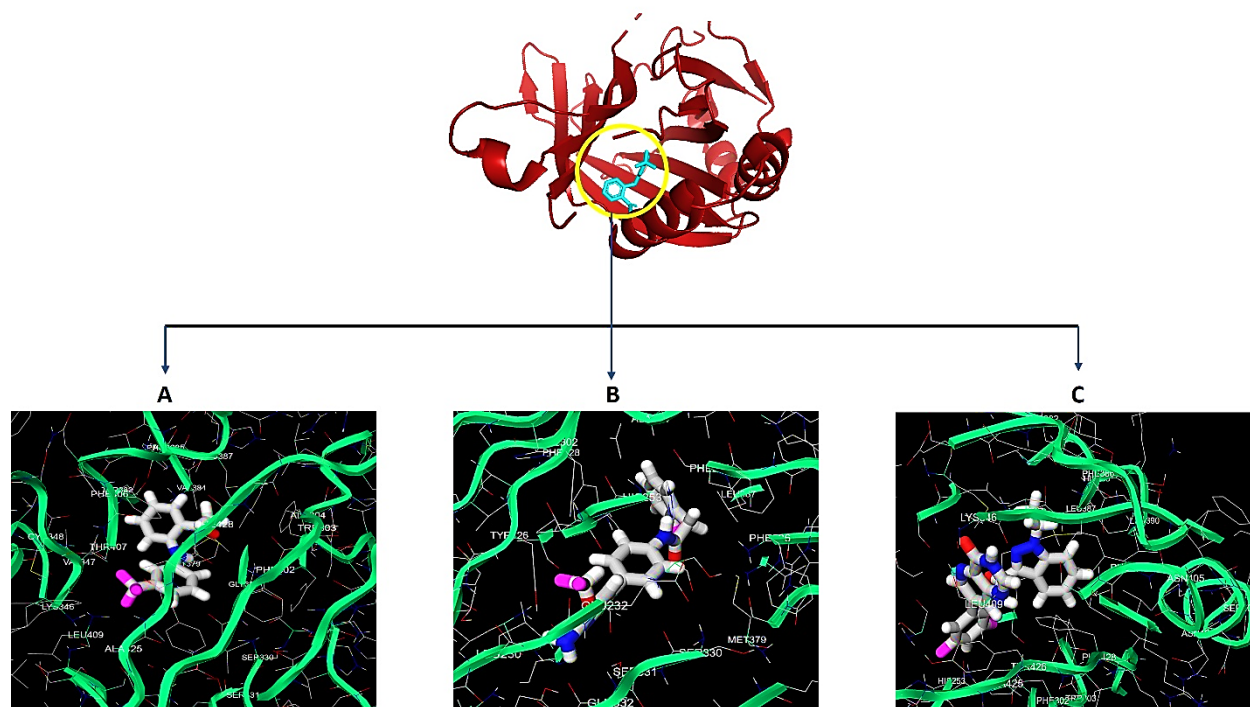


Figure 1: 3-D Interacting Illustration of Compounds. A) Reference, B) Compound 6, and C) Compound 2.

compound with 0 violations, along with the binding energies has been shown (Table 1).

Cytotoxicity Screening

The potential of selected compounds against lung cancer cell lines was evaluated with the CLC-Pred server. Out of all the 17 compounds having 0 violations, all the compounds exhibited potential cell lines. Compound 7 exhibited the highest predicted activity with a greater Pa value against the NCI-H460 NSCLC cell line. Additionally, it also demonstrated broad-spectrum activity across various cell lines, indicating strong anti-cancer potential. On observation, all the compounds predicted various cell lines in lung cancer. Interestingly, the reference compound showed moderate activity across cell lines, with the highest Pa value (0.511) observed only for SK-LU-1 adenocarcinoma cell lines, while the rest of the compounds exhibited broader activities suggesting superior cytotoxicity potential against lung cancer (Table 2).

Assessing Biological Activity Prediction

The biological activity prediction analysis was performed using the online software PASS prediction. The results in Table 3 revealed the compounds showing different probability scores against parameters. Different activities related to lung cancer were targeted. The results were analyzed based on the probability of being active and inactive. All compounds gave favorable results.

Among all, compound 2 demonstrated the highest predicted antineoplastic activity with an active probability score of 0.602, indicating strong anticancer potential. It also exhibited strong

angiogenesis inhibition, indicating tumor associated blood vessel inhibition. Interestingly, compound 6 also displayed broad-spectrum activities such as anti-inflammatory, anti-allergic, and anti-asthmatic, indicating its potential major supportive role in lung-related conditions/symptom.

Drug-likeness Evaluation

The lead-like molecule depends on various factors; one of the main factors is its favorable pharmacokinetic properties. The drug kinetic profile of all compounds was assessed using the ADME and pKCSM prediction tool containing several parameters such as water solubility, Caco-2 permeability, human intestinal absorption, skin permeability, AMES etc. the predicted properties of all screened compounds with the reference compounds are given in Table 4.

The analysis revealed compounds demonstrated acceptable properties with high intestinal absorption and membrane permeability. HIA ranges from 96% - 85%. The highest CaCo₂ permeability recorded was 1.283 for compound 2. Except compound 1, all compounds were AMES negative (non-mutagenic) having a good clearance range. The max dose calculated was 0.5 to 0.06. Overall, the compounds represent a safety window.

Prediction of Safety Concerns

Adver-Pred server was used to assess possible side effects of filtered compounds. The prediction was based on calculating the probability of activity and inactivity of various drug reactions. The lower Pa values compare to Pi indicates a minimal likelihood

of adverse effects and improved safer profile. Effects such as arrhythmia, cardiac failure, myocardial infarction, hepatotoxicity and nephrotoxicity. The predicted values of all compounds with the control is mentioned in Table 5.

The data revealed the minimum side effects recorded for compound 6 and compound 7 having only 1 side effect. Notably, compound 2 demonstrated moderate effect probabilities with two side effects, with no evidence of severe organ-specific outcomes. Compound 1 exhibited the lowest probability of adverse effect. Comparatively with control, it delivered higher probabilities of cardiotoxic effects. The results indicate that the compounds represent better safety profiles relative to control.

Lethal Dose Evaluation

Acute rat Lethal Dose (LD_{50}) profile was predicted by GUSAR online platform through multiple routes to determine if the compounds fall within the Applicable Domain (AD) to ensure reliability (Gadaleta *et al.*, 2019; Zwickl *et al.*, 2022). Every route was determined in mmol/kg, mg/kg, and with the safety class shown in Table 6.

The table revealed that all the compounds showed higher values, indicating a higher dosage threshold before toxicity occurs. The highest dose record as 1972 mg/kg in the oral route by compound 2, suggesting excellent safety upon oral consumption. Similarly, compound 6 also records the highest value for 1469 mg/kg for oral administration, indicating lower toxicity. Compound 1 represents

the highest dose as 1594 mg/kg for SC routes. Interestingly, most of the predictions, including control, fall into classes IV and V, which are characterized as low-toxicity categories, indicating a favorable toxic profile. The findings suggest compounds possess an acceptable window for further investigations.

Based on the integrated analysis of all the parameters analysis top two compounds were selected and identified for stability analysis enrichment, namely, compound 2 and compound 6, due to their balanced profiles for anticancer activities, favorable pharmacokinetics characteristics, and acceptable safety profile. Therefore, the protein-ligand interaction diagram of these two compounds with the reference compound has been illustrated (Figures 1, 2A-2C). Optimizing these compounds enables evaluation of different trajectories, thereby validating the docking results and detecting the most promising therapeutic lead candidate.

The diagram represents such as van der Waals interaction, conventional hydrogen bonds, Pi alkyl, alkyl, Pi sigma, carbon hydrogen bonds, and halogen interactions. while the reference compounds lack hydrogen bonds. But, on the other hand, the selected compounds shared common residues with the control. Table 7 represents interacting residues.

The commonly residues are observed as PHE428, PHE302, MET379, LEU387, PHE386 and PHE406. However, some additional residues, TYR382 and VAL384 are also observed in

Table 1: Docking scores with RO5 violations of filtered compounds.

Sl. No.	Molecule ID	Docking score	violations
1.	MCULE-8771183622-0-1	-11.1	0
2.	MCULE-4863298419-0-1	-10.1	0
3.	MCULE-4496122324-0-1	-9.7	0
4.	MCULE-5254694469-0-1	-9.6	0
5.	MCULE-5561418673-0-1	-9.6	0
6.	MCULE-5625593640-0-1	-9.5	0
7.	MCULE-3754730312-0-1	-9.4	0
8.	MCULE-1649235890-0-1	-9.3	0
9.	MCULE-9299360684-0-1	-9.2	0
10.	MCULE-2778445894-0-1	-9.2	0
11.	MCULE-2594749586-0-1	-9.2	0
12.	MCULE-9166446723-0-1	-9.2	0
13.	MCULE-1892307880-0-1	-9.1	0
14.	MCULE-1368703310-0-1	-9.1	0
15.	MCULE-2504052738-0-1	-8.9	0
16.	MCULE-5370961987-0-1	-8.9	0
17.	MCULE-2406472115-0-2	-8.8	0
	Inhibitor	-7.5	

Scores are presented in kcal/mol.

Table 2: Probability Score of Activity and Inactivity Among Various Cancerous Cell Lines.

Compounds	Pa	Pi	Cell-line	Description	Tissue/Organ	Type	IAP*
1	0.084	0.034	NCI-H2286	Small cell lung cancer	Lung	Adenocarcinoma	0.968
	0.353	0.216	SK-LU-1	Adenocarcinoma	Lung	Carcinoma	0.81
	0.349	0.067	NCI-H292	Mucoepidermoid Pulmonary Carcinoma	Lung	Carcinoma	0.845
2	0.377	0.1	NCI-H358	Bronchioalveolar carcinoma	Lung	Carcinoma	0.805
	0.161	0.065	NCI-H1993	Non-small cell lung cancer	Lung	Adenocarcinoma	0.913
	0.074	0.053	NCL-H2286	small cell lung cancer	Lung	Adenocarcinoma	0.968
3	0.29	0.066	HEL299	Fibroblasts	Lung	Normal	0.899
	0.268	0.146	NCI-H1703	Non-small cell lung cancer	Lung	Carcinoma	0.851
	0.157	0.075	NCI-H1993	Non-small cell lung cancer	Lung	Carcinoma	0.913
4	0.439	0.024	CL97	lung Adenocarcinoma	Lung	Adenocarcinoma	0.872
	0.391	0.086	NCI-H358	Bronchioalveolar carcinoma	Lung	Carcinoma	0.805
	0.381	0.063	DMS-114	Lung carcinoma	Lung	Carcinoma	0.834
	0.381	0.113	NCI-H441	Papillary Adenocarcinoma	Lung	Adenocarcinoma	0.813
	0.341	0.226	SK-LU-1	Adenocarcinoma	Lung	Carcinoma	0.81
	0.275	0.23	SK-MES-1	Squamous cell lung carcinoma	Lung	Carcinoma	0.834
	0.271	0.097	NCI-H226	Non-small cell lung carcinoma	Lung	Carcinoma	0.88
	0.339	0.076	CL97	lung Adenocarcinoma	Lung	Adenocarcinoma	0.872
5	0.281	0.109	NCI-H1703	Non-small cell lung carcinoma	Lung	Carcinoma	0.851
	0.284	0.117	NCI-H1650	Bronchioalveolar carcinoma	Lung	Carcinoma	0.839
	0.237	0.143	NCI-H1581	Non-small cell lung carcinoma	Lung	Carcinoma	0.871
	0.194	0.037	NCI-H1975	Bronchioalveolar carcinoma	Lung	Carcinoma	0.95
	0.291	0.208	COR-L23	Lung large cell carcinoma	Lung	Carcinoma	0.834
6	0.209	0.03	NCI-H1975	Bronchioalveolar carcinoma	Lung	Carcinoma	0.95
	0.177	0.032	NCI-H1993	Non-small cell lung cancer	Lung	Carcinoma	0.913
	0.177	0.032	NCI-H1993	Non-small cell lung cancer	Lung	Carcinoma	0.913
7	0.46	0.026	NCI-H460	Non-small cell lung carcinoma	Lung	Carcinoma	0.906
	0.326	0.14	SK-MES-1	Squamous cell lung carcinoma	Lung	Carcinoma	0.834
	0.323	0.243	SK-LU-1	Adenocarcinoma	Lung	Carcinoma	0.81
	0.316	0.22	NCI-H441	Papillary Adenocarcinoma	Lung	Adenocarcinoma	0.813
	0.315	0.103	CL97	lung Adenocarcinoma	Lung	Adenocarcinoma	0.872
	0.265	0.218	NCI-H661	Lung carcinoma	Lung	Carcinoma	0.831
	0.162	0.061	NCI-H1993	Non-small cell lung cancer	Lung	Adenocarcinoma	0.913
	0.162	0.061	NCI-H1993	Non-small cell lung cancer	Lung	Adenocarcinoma	0.913
Control	0.511	0.047	SK-LU-1	Adenocarcinoma	Lung	Carcinoma	0.81
	0.279	0.087	NCI-H522	Squamous cell lung carcinoma	Lung	Carcinoma	0.834
	0.355	0.05	HOP-92	Non-small cell lung carcinoma	Lung	Carcinoma	0.862
	0.318	0.099	CL97	Lung adenocarcinoma	Lung	Adenocarcinoma	0.872
	0.753	0.005	MOLT-4	Acute T-lymphoblastic leukemia	Blood	Leukemia	0.885
	0.228	0.147	NCI-H661	Lung carcinoma	Lung	Carcinoma	0.831
	0.288	0.147	NCI-H23	Non-small cell lung carcinoma	Lung	Carcinoma	0.883
	0.287	0.11	NCI-H1650	Bronchioalveolar carcinoma	Lung	Adenocarcinoma	0.839
	0.264	0.098	NCI-H322M	Non-small cell lung carcinoma	Lung	Carcinoma	0.881
	0.246	0.135	CL1-0	Lung adenocarcinoma	Lung	Adenocarcinoma	0.83
	0.23	0.132	NCI-H522	Non-small cell lung carcinoma	Lung	Carcinoma	0.877
	0.23	0.165	NCI-H226	Non-small cell lung carcinoma	Lung	Carcinoma	0.88
	0.181	0.163	HOP-18	Non-small cell lung carcinoma	Lung	Carcinoma	0.933

*IAP: Invariant accuracy of prediction.

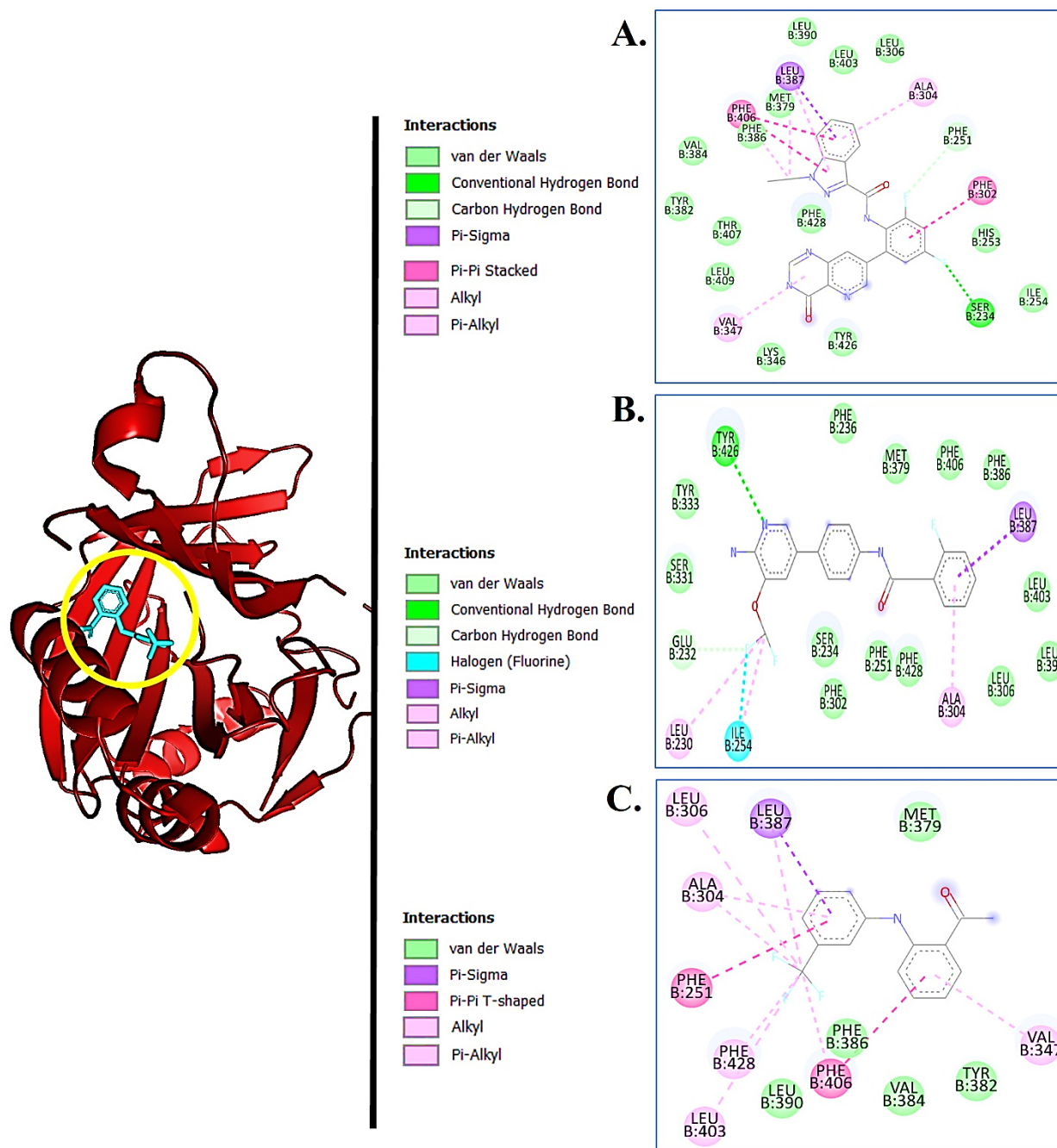


Figure 2: (A) 2d Illustration of top two compounds showing multiple interactions (B) Compound 6. (C) 2d Interacting Illustration reference compound (Control) showing multiple interactions like van der waals, Pi-Sigma, Pi-Pi T-shaped, alkyl and Pi-alkyl bonds.

compound 02 from the reference inhibitor indicating a strong interacting profile of the compounds which supports the findings.

Molecular Dynamics Analysis

Deviation and Residual Fluctuation Analysis

The deviation profile (RMSD) was analyzed to find out the stability of the structure of protein-ligand complex throughout 100 ns simulation. The analysis indicated that compound 2 and reference compound showed an increment during the initial phase of simulation and stabilized around 1.2-1.5 nm, indicating

moderate deviations. In contrast, compound 6 was observed to exhibit lower RMSD values within the range of 0.5-0.8 nm with some minute fluctuations observed after 60ns, suggesting enhanced stability (Figure 3A).

Similarly, RMSF analysis was also performed to assess the flexibility of residues and the dynamic behavior of the protein. the noting point observed is that the majority of the residues exhibited fluctuations below the range of 0.5 nm, indicating overall stability. However, the fluctuations observed around 320-400 range might represent a loop of binding-associated regions. The

reference inhibitor displayed higher fluctuations approximately at 1.5 nm, whereas compound 2 showed moderate fluctuations, and minimal fluctuations were observed for compound 6 throughout the range (Figure 3B).

Radius of Gyration and SASA Analysis

The Rg was evaluated to determine the compactness and depict the behavior of protein complexes during the simulation period. The reference compound and compound 2 also displayed relatively stable values between 2.8 and 3.2 nm, which suggests maintain structure with slight fluctuations. Conversely, compound 6 demonstrated a lower and highly stable Rg value of approx 1.7-1.8 nm, which indicates compact structural conformation. Moreover, the SASA (solvent accessible surface area) was analyzed to depict the extension of protein surface exposure to the solvent during

simulation. Plots of SASA also depict compounds 2, and the reference compound relies on the same manner to maintain values between 45-55 nm². This reflects higher exposure and moderate solubility. Comparatively, compound 6 exhibits better results, ranging from 7-10 nm², which remain stable throughout the simulation. The plots of both strategies are given in Figures 3C and 3D.

Solvation Free Energy Analysis and Hydrogen Bondings

The solvation profile was evaluated to check which solvent molecules surround and interact with the solute ions. The values are plotted against a 100 ns runtime. Compound 6 stands out alone, depicting higher values of fluctuations around -10 to -20 kJ/mol, reflecting constant energy across the simulation.

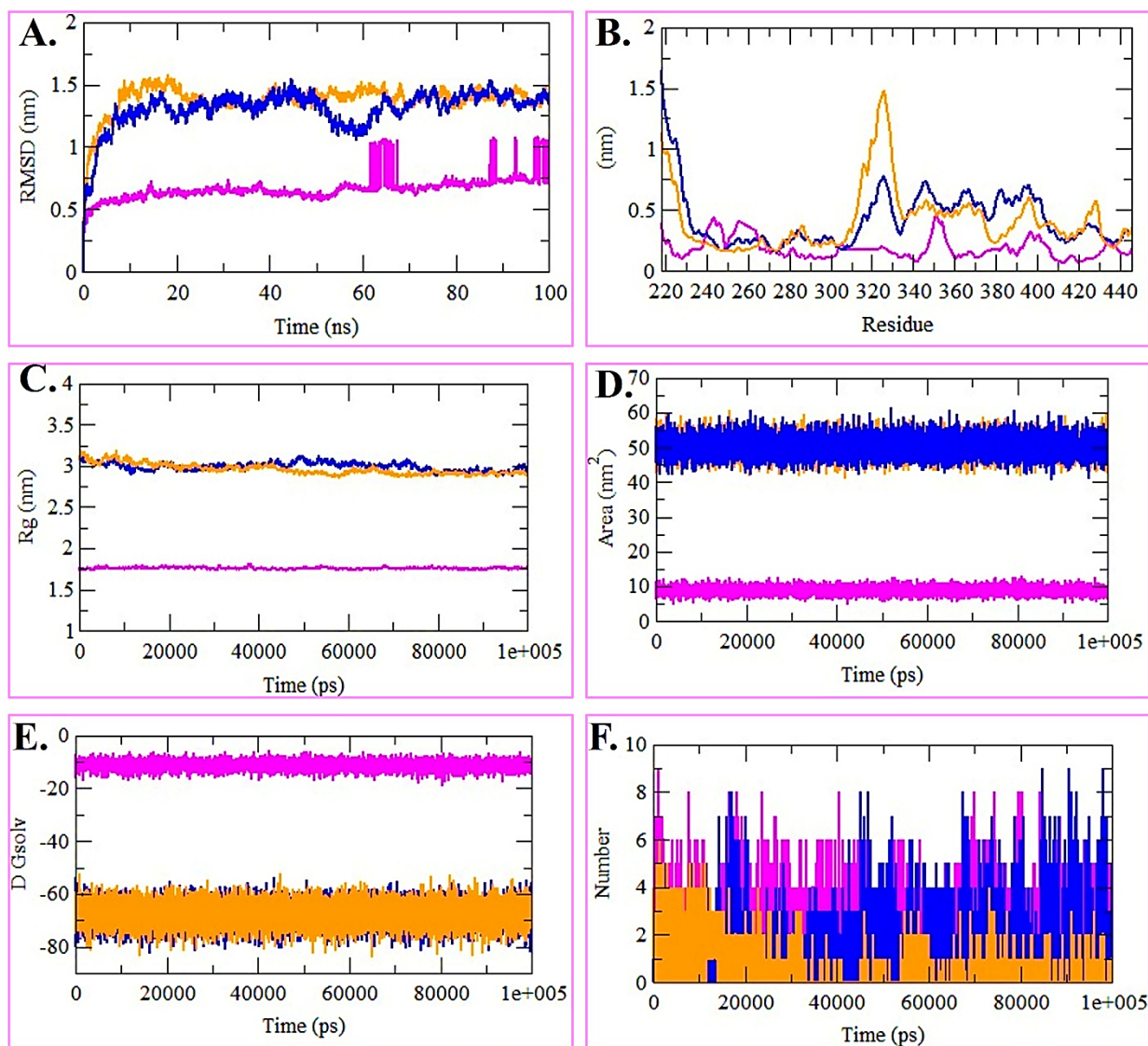


Figure 3: (A) Plots of RMSD and (B) RMSF representing compounds with an inhibitor. Pink-compound 6, Blue-compound 2, and Orange-Reference compound. (C) Plots of radius of gyration and SASA represent compounds with a reference molecule. (D) Pink-compound 6, Blue-compound 2, and Orange-Reference compound. (E) Illustration of compound 6 and compound 2 with reference compounds. (F) Pink-compound 6, Blue-compound 2, and Orange-Reference compound.

Table 3: Biological Activities Parameters.

Sl. No.	Anti-inflammatory		Angiogenesis inhibitor		Antiallergic		Anti-asthmatic		Antineoplastic	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
1.	NA	NA	0,233	0,108	0,305	0,090	0,263	0,113	NA	NA
2.	NA	NA	0,642	0,008	NA	NA	0,388	0,052	0,620	0,041
3.	0,267	0,084	0,232	0,119	0,336	0,149	NA	NA	0,244	0,017
4.	0,296	0,164	0,508	0,019	NA	NA	NA	NA	0,376	0,114
5.	NA	NA	NA	NA	0,250	0,130	0,235	0,134	0,219	0,184
6.	0,458	0,070	0,274	0,084	0,720	0,008	0,751	0,006	0,270	0,116
7.	0,379	0,107	0,372	0,044	NA	NA	NA	NA	0,407	0,035
Control	0,473	0,065	0,428	0,031	0,313	0,087	0,306	0,086	0,287	0,161

NA: Not Applicable, Comma (,) is used as a decimal.

Table 4: Pharmacokinetics Profiling.

Sl. No.	water solubility	Caco2	HIA	Skin	BBB	CYP2D6	Clearance	Renal	AMES	Max Dose	hERG I	hERG II
1.	-5.096	0.725	90.572	-2.778	0.725	No	0.439	No	Yes	0.065	No	Yes
2.	-3.744	1.283	93.195	-2.735	1.283	No	0.171	No	No	0.511	No	Yes
3.	-2.855	1.276	85.820	-2.737	1.276	No	0.194	No	No	0.126	No	Yes
4.	-5.218	1.373	92.07	-2.982	1.373	No	-0.124	No	No	0.092	No	Yes
5.	-4.724	1.219	92.07	-2.941	1.219	No	0.406	No	No	0.36	No	No
6.	-4.907	0.511	89.829	-2.848	0.511	No	-0.127	No	No	0.095	No	Yes
7.	-3.433	1.064	96.24	-2.704	1.064	No	0.398	Yes	No	-0.116	No	Yes
Ref	-4.648	1.183	90.16	-2.753	1.183	No	0.008	No	No	0.423	No	No

Table 5: Predicted Adverse Reactions of Compounds.

Compounds	Pa/Pi	Hepatotoxicity	Arrhythmia	Myocardial infarction	Cardiac failure	Nephrotoxicity
1	Pa	NA	0.319	0.335	NA	NA
	Pi	NA	0.274	0.137	NA	NA
2	Pa	0.627	0.456	NA	NA	0.627
	Pi	0.13	0.144	NA	NA	0.13
3	Pa	0.775	NA	0.42	0.612	NA
	Pi	0.069	NA	0.063	0.017	NA
4	Pa	0.915	0.609	0.672	0.768	NA
	Pi	0.021	0.044	0.016	0.005	NA
5	Pa	0.853	0.443	NA	0.254	0.287
	Pi	0.046	0.153	NA	0.216	0.172
6	Pa	0.69	NA	NA	NA	NA
	Pi	0.104	NA	NA	NA	NA
7	Pa	0.835	NA	NA	NA	NA
	Pi	0.051	NA	NA	NA	NA
Control	Pa	0.708	0.563	0.368	0.761	NA
	Pi	0.097	0.064	0.092	0.005	NA

NA- Not Applicable; Pa-Probability of activity; Pi-Probability of Inactivity.

Meanwhile, both the compounds, reference and compound 2, showed similar stability, fluctuating around -60 and -80 kJ/mol, indicating favorable solvation conditions during simulation. Despite the differences, all compounds showed stability over the run time. From the hydrogen bonds interpretation, maximum hydrogen bonds 4-5 were seen from the reference compound at initial stage and gradually decreased further. Whereas, compound 2 bonding around 15-2 ns showing bonds from 0-8 and reach up to 9 bonds at last stage showing fluctuations. Compound 6 maintains the hydrogen bonding at initial level showing 9 bonds. Afterwards, it also shows bouncing fluctuations between 6-8. Both the compounds showed much better results from the reference compound. The graphical plots of SASA and hydrogen bonds have shown in diagram (Figures 3E and 3F).

DISCUSSION

The present study investigated the therapeutic screen of the TEAD2 palmitoylation pocket targeting lung carcinoma by utilizing a computational drug discovery approach. In the current scenario, TEAD2 emerged as a prominent regulator of the Hippo signaling pathway, which heavily drives tumor growth when activated, leading to therapeutic resistance in lung cancer. Since palmitoylation plays a primary role and is vital for maintaining TEAD2 conformational stability and interaction with co-activator proteins such as YAP/TAZ (Kumar *et al.*, 2024). In view of that, inhibition of the binding pocket of TEAD2 is considered a promising path for intervention as palmitoylation is essential for the stability of TEAD2. Therefore, the current research study

focused on structural based virtual screening through the Mcule platform, an online server (Ott *et al.*, 2025; Sun *et al.*, 2022).

The platform enables the screening of small molecule inhibitors with strong binding energies comparatively to control. The control HUY itself attached to the reference protein PDB:6E5G was selected. The identification of promising therapeutic drug candidates required evaluation of multiple approaches to ensure effectiveness and safety. Therefore, integrated *in silico* approach involving cytotoxic prediction, biological activities, ADMET profiling and acute rat toxicity with boost of MD was employed. Initially, Mcule platform revealed 7 compounds having 0 violations having the best energy were proceed with cell lines prediction. Various cell lines had been predicted for all compounds. Compound 2 (MCULE-4863298419-0-1) demonstrated moderate cytotoxicity against NSCLC cells suggesting distinct lung cancer subtypes. Similarly, compound 6 (MCULE2504052738-0-1) exhibited cell lines such as COR-L23, a large lung cell carcinoma, NCI-H1985, a bronchio carcinoma, and NCI-H1993 NSCLC, representing a wide spectrum of cell lines. Moreover, validation through the PASS parameter provides insights of compound 2, demonstrating the strongest antineoplastic activity, higher than control, depicting support to suppress tumor-associated blood vessel formation, which is a mechanism involved in invasion and metastasis, along with growth of cells. Angiogenesis is highly considered as proliferating tumors found in Compound 2 (C2). Whereas, Compound 6 (C6) also demonstrated multiple activities, such as anti-asthmatic (Pa=0.751), antiallergic (Pa=0.720), and anti-inflammatory (Pa=0.458). These activities are particularly present in lung cancer as pulmonary malignancies are usually

Table 6: Acute Rat Toxicity Determination.

Sl. No.	IP LD ₅₀ Log 10			IV LD ₅₀ Log 10			Oral LD ₅₀ Log 10			SC LD ₅₀ Log 10		
	mmol/kg	mg/kg	Class	mmol/kg	mg/kg	Class	mmol/kg	mg/kg	Class	mmol/kg	Mg/kg	Class
1.	0,204 in AD	719,800 in AD	V in AD	-0,397 in AD	180,000 in AD	IV in AD	0,298 in AD	893,200 in AD	IV in AD	0,550 in AD	1594,000 in AD	V in AD
2.	-0,139 out of AD	324,400 out of AD	IV out of AD	-0,282 in AD	233,100 in AD	IV in AD	0,645 out of AD	1972,000 out of AD	IV out of AD	0,395 out of AD	1109,000 out of AD	V out of AD
3.	0,372 out of AD	960,700 out of AD	V out of AD	-0,320 in AD	195,600 in AD	IV in AD	-0,100 out of AD	324,200 out of AD	IV out of AD	0,068 out of AD	477,700 out of AD	IV out of AD
4.	0,471 out of AD	1082,000 out of AD	V out of AD	-0,273 in AD	195,100 in AD	IV in AD	0,205 in AD	586,500 in AD	IV in AD	0,378 in AD	873,300 out of AD	IV out of AD
5.	0,244 in AD	702,000 in AD	V in AD	-0,751 in AD	70,900 in AD	IV in AD	0,361 in AD	920,500 in AD	IV in AD	0,080 in AD	481,500 out of AD	IV out of AD
6.	0,387 in AD	944,800 in AD	V in AD	-0,447 in AD	138,500 in AD	IV in AD	0,579 in AD	1469,000 in AD	IV in AD	0,292 out of AD	758,900 in AD	IV out of AD
7.	0,365 in AD	769,500 in AD	V in AD	-0,441 in AD	120,500 in AD	IV in AD	0,225 out of AD	557,500 in AD	IV out of AD	0,206 out of AD	534,300 in AD	IV out of AD
Control	0,459 in AD	802,900 in AD	V in AD	-0,501 in AD	88,020 in AD	IV in AD	0,336 in AD	604,800 in AD	IV in AD	0,502 in AD	886,900 in AD	IV in AD

IP-Intraperitoneal route of administration, IV-Intravenous route of administration, Oral-Oral route of administration, SC-Subcutaneous route of administration, NT-Non-Toxic; Comma (,) is used as a decimal separator (e.g., 719,800=719.800).

Table 7: Interacting Residues.

Compounds	Interacting Residues	Carbon Bonds
C2	PHE428, LEU409, VAL347, LYS346, TYR426, SER234, ILE254, HIS253, PHE302, PHE251, ALA304, LEU403, LEU306, LEU390, LEU387, MET379, PHE386, PHE406, VAL384, TYR382, THR407	1ConH, 1CH
C6	TYR426, TYR333, SER331, GLU232, LEU230, ILE254, SER234, PHE302, PHE251, PHE428, ALA304, LEU306, LEU390, LEU403, LEU387, PHE386, 406, MET379, PHE236	1ConH, 1CH
Reference	LEU403, LEU390, VAL347, PHE428, PHE251, ALA304, LEU306, MET379, LEU387, PHE386, VAL384, PHE406, TYR382	NA

ConH-Conventional hydrogen; CH-Carbon Hydrogen; NA-Not applicable.

associated with inflammation, respiratory distress, and altered immune response. On the other hand, drug-likeness also revealed favorable results. C2 was predicted to be non-mutagenic and showed no hERG-I inhibition, suggesting a lower risk, possessing superior characteristics desirable for oral administration with safety. While C6 also exhibited supporting results and maintained the overall pharmacokinetic profile. Compared to the control, both compounds stand out. AdverPred analysis and side effect profiling further pointed out the importance of efficacy with toxicity. Although C1 demonstrated fewer side effects but lacked other parameters, thereby reducing its potential. In contrast, C2 and C6 demonstrated manageable toxic profiles while standing out among other parameters as well. Interestingly, both compounds also strengthen the LD₅₀ analysis, exhibiting the highest value 1972 mg/kg by C2, enhancing safety upon oral administration, and 1469 mg/kg by C6, suggesting low toxicity. Both compounds exhibited higher doses than the control. The dynamics studies performed for these top two compounds further revealed as a support. Different trajectories, such as RMSD, RMSF, SASA, Rg, and hydrogen bonds, were conducted, indicating stability, compactness, and interactions of the complexes. From the dynamics analysis, the results demonstrated MCULE2504052738-0-1 (C6) exhibited the highest structural stability among the tested compounds, showing lower RMSD values, minimal fluctuation of residues, stability, and compactness throughout the simulation. However, other compounds show a similar range, with the reference compounds also exhibiting good results. Furthermore, maximum hydrogen bonds were recorded for both compounds 8-9 bonds, compared to the control, which only showed 4 bonds at the starting phase. Overall, the findings support the selection of both compounds, indicating therapeutic evidence.

CONCLUSION

In the present study, an integrated *in silico* multi-approach was conducted to identify the promising lead candidate against lung carcinoma. The findings revealed the screened compounds exhibiting varying degrees of anti-cancer potential, drug-likeness profile, safety profiling, and acute toxicity profile, emphasizing the vital role of multiple strategies for rational candidate

selection. Additionally, the molecular dynamics studies were also conducted to support the evidence. After investigations, among the investigated compounds, MCULE2504052738-0-1 and MCULE-4863298419-0-1 were proven best for all the parameters. Overall findings indicate that MCULE2504052738-0-1 emerged as the most promising lead candidate, demonstrating a superior balance profile of therapeutic efficacy, pharmacological relevance, and safety with higher stability and robustness. However, to confirm its advanced therapeutic potentials, experimental validation is required.

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ABBREVIATIONS

TEAD: Transcriptional Enhanced Associate Domain; **NSCLC:** Non-Small Cell Lung Cancer; **SCLC:** Small Cell Lung Cancer; **YAP:** Yes-Associated Protein; **TAZ:** Transcriptional Co-Activator with PDZ-Binding Motif; **PDB:** Protein Data Bank; **LD₅₀:** Lethal Dose of 50%; **RMSD:** Root Mean Square Deviation; **RMSF:** Root Mean Square Fluctuation; **PASS:** Prediction of Activity Spectra for Substances; **MCULE:** Molecular Computational Utility for Lead Exploration Database; **ADMET:** Absorption, Distribution, Metabolism, Excretion, and Toxicity; **CLC-Pred server:** Cell Line Cytotoxicity Predictor Server; **SMILES:** Simplified Molecular Input Line Entry System; **pkCSM server:** Pharmacokinetics of Small Molecules server; **ADVER-PRED:** Adverse Effect Prediction Server; **GUSAR:** General Unrestricted Structure Activity Relationships; **GROMACS:** GRONingen MACHine for Chemical Simulations; **CGenFF:** CHARMM General Force Field; **CHARMM:** Chemistry at HARvard Macromolecular Mechanics; **TIP3:** Transferable Intermolecular Potential with 3 Points; **Rg:** Radius of Gyration; **SASA:** Solvent Accessible Surface Area Analysis.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Amani Alharthi: Conceptualization, experimental design, data curation and analysis, literature review, manuscript drafting and final manuscript approval.

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