

ORIGINAL RESEARCH ARTICLE

In silico identification of pyrazole, pyrimidine, chalcone, and indolinone derivatives as multi-target lung cancer therapeutics

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Abstract

Lung cancer remains a leading cause of cancer-related mortality worldwide, highlighting the need for multi-target therapeutic strategies. In this study, an integrated *in silico* approach combining molecular docking, pharmacokinetic profiling, and interaction analysis was used to identify potential multi-target inhibitors from a curated virtual library of 30 pyrazole, pyrimidine, chalcone, and indolinone derivatives retrieved from the PubChem database. The compounds were screened against seven lung cancer-related targets (epidermal growth factor receptor [EGFR], Kirsten rat sarcoma viral oncogene homolog, B-cell lymphoma 2, anaplastic lymphoma kinase protein, phosphoinositide 3-kinase, protein kinase B [AKT1], and mechanistic target of rapamycin). Docking results showed clear differences between parent scaffolds and optimized derivatives, with eight compounds exhibiting binding affinities below -6.0 kcal/mol across all targets. Among these, CID 317158, CID 637760, and CID 5367146 showed the most consistent and balanced performance. Absorption, distribution, metabolism, excretion, and toxicity analysis indicated favorable drug-like properties, including compliance with Lipinski's Rule of Five, high gastrointestinal absorption, and acceptable toxicity profiles. Interaction analysis revealed stable binding across multiple targets, driven by hydrogen bonding, hydrophobic interactions, and π -mediated contacts among key residues, particularly within the EGFR and AKT1 kinase domains. Overall, CID 317158 and CID 637760 emerged as the most promising multi-target candidates, while CID 5367146 also demonstrated strong potential. These findings support the value of multi-target computational screening in early drug discovery and provide a basis for further experimental validation.

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Citation: Okonji KS, Wellington SB, Anandalakshmanan H, Riyazkhan MS. *In silico* identification of pyrazole, pyrimidine, chalcone, and indolinone derivatives as multi-target lung cancer therapeutics. *Cancer Plus*. doi: 10.36922/CP026200031

Received: May 14, 2026

Revised: July 12, 2026

Accepted: August 6, 2026

Published online: September 4, 2026

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Keywords: Chalcones; Multi-target inhibition; ADMET profiling; Lung cancer; *In silico* drug discovery

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for over 2 million deaths annually.^{1,2} Despite improvements in early diagnosis and targeted therapies, the overall 5-year survival rate remains low due to late-stage presentation, high metastatic potential, and frequent development of resistance to chemotherapy and targeted agents.^{3,4} These challenges necessitate the development of novel therapeutic agents capable of simultaneously targeting multiple oncogenic pathways.

At the molecular level, lung cancer progression is driven by the dysregulation of several critical signaling pathways. Epidermal growth factor receptor (EGFR) mutations are common in non-small cell lung cancer (NSCLC) and drive uncontrolled proliferation.⁵ Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations contribute to aberrant cell signaling and poor prognosis.⁶ B-cell lymphoma 2 (BCL-2) and related anti-apoptotic proteins promote survival and chemoresistance.⁷ Additional pathways, including anaplastic lymphoma kinase protein (ALK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT1)/mechanistic target of rapamycin (mTOR), are implicated in cell proliferation, survival, and metastasis.^{8,9} Collectively, these proteins represent critical nodes for therapeutic intervention.

Traditional single-target therapies often fail due to compensatory activation of alternative pathways. Multi-target small molecules capable of modulating several proteins simultaneously may provide enhanced efficacy while mitigating drug resistance.^{10,11} Computational strategies, including molecular docking, ADMET prediction, and binding interaction analysis, offer cost-effective and rapid means of identifying and prioritizing potential multi-target candidates prior to experimental validation.^{12–14} Molecular docking predicts ligand–protein binding interactions; absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis evaluates pharmacokinetic and toxicity properties; and binding interaction analysis provides detailed insights into the molecular interactions responsible for ligand stability, target recognition, and binding specificity within protein active sites. Among bioactive scaffolds, pyrazole, pyrimidine, chalcone, and indolinone derivatives have demonstrated anticancer potential via apoptosis induction, kinase inhibition, and modulation of cell cycle regulators.^{15–18} Their structural diversity and synthetic accessibility make them well-suited for rational design and computational screening against multiple lung cancer targets.^{19,20}

Although chalcone, pyrazole, pyrimidine, and

indolinone derivatives have been extensively investigated against individual lung cancer targets such as EGFR and PI3K/AKT1/mTOR components, comparative multi-target computational evaluation across several oncogenic proteins using a unified screening framework remains relatively limited. This study aims to fill this gap by performing an *in silico* investigation of 30 pyrazole, pyrimidine, chalcone, and indolinone derivatives as potential multi-target therapeutics for lung cancer. Using molecular docking, ADMET profiling, and detailed binding interaction analysis, this work seeks to identify lead compounds and elucidate their mechanisms of action against EGFR, KRAS, BCL-2, ALK, and PI3K/AKT1/mTOR signaling proteins, thereby advancing the development of effective multi-target therapies for lung cancer.

2. Materials and methods

2.1. Study design

This study employed an integrated *in silico* drug discovery approach combining molecular docking, ADMET evaluation, and binding interaction analysis to identify potential multi-target small molecules against lung cancer. The workflow involved ligand retrieval, protein preparation, docking simulations, pharmacokinetic profiling, and pathway interaction analysis (Figure 1).

2.2. Ligand retrieval and preparation

A curated virtual compound library comprising 30 structurally diverse pyrazole, pyrimidine, chalcone, and indolinone derivatives was assembled from the PubChem database based on scaffold diversity and previously reported anticancer potential in the literature. Three-dimensional (3D) SDF files of all phytochemicals were obtained from the PubChem database. Structures were downloaded in SDF format and converted to PDBQT format using Open Babel (3.1.1, Open Babel Development Team, USA).²¹ Geometry optimization was performed using the MMFF94 force field to obtain energetically minimized conformations prior to docking in AutoDock Tools (1.5.7, The Scripps Research Institute, USA).^{22,23} The selected compounds, structural descriptions, and PubChem CIDs are presented in Table 1.

2.3. Protein selection and preparation

Based on their crucial roles in tumor proliferation, survival, and therapeutic resistance, five key molecular targets associated with lung cancer development were selected: EGFR, KRAS, BCL-2, ALK, and components of the PI3K/AKT1/mTOR signaling pathway. The 3D crystal structures of these proteins were obtained from the Protein Data Bank (PDB). The corresponding PDB accession numbers are provided in Table 2.

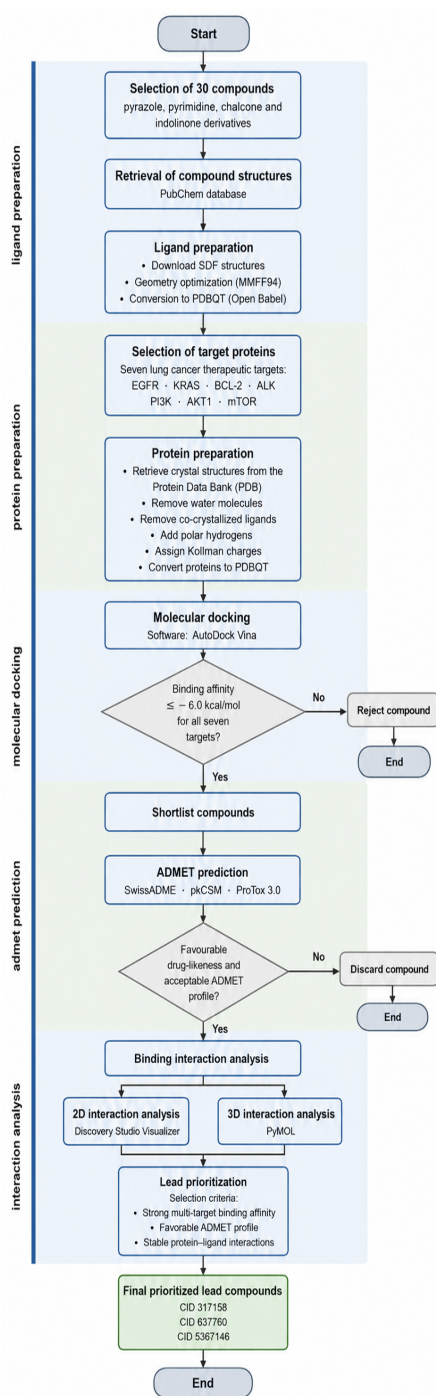


Figure 1. Schematic workflow of the integrated *in silico* pipeline used for the identification of multi-target lung cancer lead compounds

Abbreviations: 2D: Two-dimensional; 3D: Three-dimensional; ADMET: Absorption, distribution, metabolism, excretion, and toxicity; AKT1: Protein kinase B; ALK: Anaplastic lymphoma kinase protein; BCL-2: B-cell lymphoma kinase; EGFR: Epidermal growth factor receptor protein; KRAS: Kirsten rat sarcoma viral oncogene homolog; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

To ensure compatibility with docking simulations, AutoDock Tools was used to generate protein models. To appropriately reflect the hydrogen-bonding potential, polar hydrogens were added after co-crystallized ligands and water molecules were removed to reduce structural noise. The generated protein structures were then converted to PDBQT format for subsequent docking analyses, with Kollman charges applied to account for electrostatic interactions.

2.4. Molecular docking analysis

Molecular docking was performed using AutoDock Vina.^{22,23} The grid box was defined to encompass the active site of each protein, with active-site regions identified using co-crystallized ligand coordinates and functionally relevant residues associated with substrate recognition or catalytic activity, obtained from PDBsum obtained from PDBsum (University College London, UK).²⁴ Default docking parameters were used with sufficient exhaustiveness to ensure conformational sampling.

Binding affinities were recorded in kcal/mol, and best docking poses were selected based on the lowest binding energy and favorable ligand–protein interaction profiles. Interactions, including hydrogen bonding, hydrophobic contacts, and π – π stacking, were visualized using Discovery Studio Visualizer (2025, Dassault Systèmes, France).²⁵

2.5. Absorption, distribution, metabolism, excretion, and toxicity prediction

SwissADME (Swiss Institute of Bioinformatics, Switzerland), ProTox (3.0, Charité–Universitätsmedizin Berlin, Germany), and pkCSM (University of Melbourne, Australia) were used to assess and predict the pharmacokinetic and toxicological characteristics of the nominated drugs.^{26–28} Important factors related to drug-likeness, absorption, distribution, metabolism, and toxicity were methodically evaluated. To assess potential oral bioavailability, drug-likeness was evaluated using Lipinski's Rule of Five. Predicted gastrointestinal absorption was used to analyze absorption features, while blood–brain barrier (BBB) permeability was used to analyze distribution qualities. To identify potential risks of drug–drug interactions, metabolic profiling focused on interactions involving cytochrome P450 (CYP) enzymes. To evaluate the safety profile of the candidate drugs, toxicological endpoints such as hepatotoxicity, mutagenicity, and cardiotoxicity were also predicted.

2.6. Statistical analysis

This study employed a computational screening workflow based on molecular docking and *in silico* ADMET prediction. Docking scores generated by AutoDock

Table 1. Selected pyrazole, pyrimidine, chalcone, and indolinone derivatives for the lung cancer study

No.	Compound name	Scaffold/modification	PubChem CID
1	Pyrazole	Parent scaffold	1048
2	3,5-dimethylpyrazole	Methyl substitution	6210
3	4-amino-1H-pyrazole	Amino substitution	78035
4	1-phenylpyrazole	Aromatic substitution	70769
5	Pyrimidine	Parent scaffold	9260
6	2-aminopyrimidine	Amino substitution	7978
7	4,6-dichloropyrimidine	Halogenation	70943
8	5-phenylpyrimidine	Aromatic substitution	817373
9	Chalcone	Parent scaffold	637760
10	4-methoxychalcone	Methoxy substitution	641819
11	4-hydroxychalcone	Hydroxyl substitution	5282361
12	2'-bromochalcone	Bromination	71334668
13	Oxindole/indolin-2-one	Parent scaffold	321710
14	5-methoxyoxindole	Methoxy substitution	1514286
15	5-hydroxyindolinone	Hydroxyl substitution	76955
16	3-phenyloxindole	Aromatic substitution	317527
17	1-methylpyrazole	N-methyl substitution	70255
18	2-methylpyrimidine	C-2 methyl substitution	78748
19	4-chloropyrimidine	Halogen substitution	642834
20	2-hydroxychalcone	Hydroxyl substitution	5367146
21	3,4-dimethoxychalcone	Methoxy substitution	5354494
22	5-nitro-2-oxindole	Nitro substitution	230366
23	6-methoxyoxindole	Methoxy substitution	2793749
24	4,5-dimethylpyrimidine	Methyl substitution	572516
25	4-chloropyrazole	Halogenated derivative	27524
26	3-bromo-1H-pyrazole	Halogen substitution	1201443
27	4-phenylpyrimidine	Aromatic substitution	18923
28	4-methylchalcone	Methyl substitution	5375849
29	3-hydroxychalcone	Hydroxyl substitution	317158
30	5-methylindolinone	Methyl substitution	14023679

Table 2. Molecular targets selected for the multi-target docking study, including UniProt accession numbers, Protein Data Bank (PDB) identifiers, and crystal structure resolution

No.	Target protein	UniProt accession	PDB ID	Resolution (Å)
1	Epidermal growth factor receptor (EGFR)	P00533	3W2S	1.90
2	KRAS	P01116	6OIM	1.65
3	B-cell lymphoma 2 (BCL-2)	P10415	6O0K	1.62
4	Anaplastic lymphoma kinase (ALK)	Q9UM73	2YFX	1.70
5	Phosphoinositide 3-kinase α (PI3K α)	P42336	4JPS	2.20
6	Protein kinase B (AKT1)	P31749	7NH5	1.90
7	Mammalian target of rapamycin (mTOR)	P42345	4JSV	3.50

Vina were interpreted descriptively, and compounds were prioritized using predefined binding affinity (≤ -6.0 kcal/mol) and ADMET selection criteria. Therefore, no inferential statistical analyses were performed.

3. Results

3.1. Molecular docking analysis

The ligand library was clearly stratified into high-affinity multi-target candidates and weak binders by molecular docking across seven important oncogenic targets: EGFR, KRAS, BCL-2, ALK, PI3K, AKT1, and mTOR (Table S1). Only compounds that consistently exhibited binding affinity more than -6.0 kcal/mol across all proteins were retained after a strict selection (Table 3). The initial library of 30 compounds was drastically reduced to eight candidates after the filtering step. This displays a significant difference between scaffold molecules and structurally optimized derivatives.

With average binding affinities ranging from -7.42 to -7.86 kcal/mol, the retained compounds (PubChem CIDs 317158, 317527, 637760, 641819, 5282361, 5354494, 5367146, and 5375849) showed strong and consistent binding across all targets. The best-performing ligand among them was CID 5375849, which had an average affinity of -7.86 kcal/mol and the strongest overall binding profile. Notably, this drug exhibited particularly high affinities for EGFR (-8.458 kcal/mol) and AKT1

(-9.259 kcal/mol), suggesting substantial interactions with downstream survival pathways and receptor tyrosine kinase signaling. Similarly, CID 317158 showed a highly competitive binding profile (average -7.80 kcal/mol), with the most favorable interaction with AKT1 (-9.341 kcal/mol), indicating strong ligand compatibility with the AKT1 active site.

Protein kinase B consistently displayed the strongest binding interactions, with few compounds achieving binding energies lower than -9.0 kcal/mol, according to a broader trend throughout the retained ligands. EGFR and PI3K came next, both of which showed positive interactions with most of the top candidates. ALK, on the other hand, showed relatively lower binding affinities, with values often between -6.5 and -7.0 kcal/mol, indicating either decreased pocket compatibility or structural limitations that restrict ligand accommodation. All preserved compounds, however, continued to exhibit binding energies below the -6.0 kcal/mol threshold for ALK, supporting their designation as genuine multi-target binders.

On the other hand, most of the excluded compounds, including unsubstituted parent scaffolds such as pyrimidine (CID 9260) and pyrazole (CID 1048), exhibited much lower binding profiles, with average affinities typically between -3.4 and -4.5 kcal/mol. The multi-target criterion was not met by even moderately substituted derivatives,

suggesting that successful binding requires more than the mere presence of a scaffold. Rather, greater structural complexity and functional group diversity were associated with the shift toward higher-affinity ligands, especially in chalcone and oxindole derivatives.

These findings show that only a small number of physically enriched compounds consistently inhibit multiple targets across key lung cancer pathways. The eight compounds found provided a streamlined pool of candidates with broad target engagement and strong binding stability, serving as the foundation for further pharmacokinetic studies and interaction research.

3.2. Absorption, distribution, metabolism, excretion, and toxicity profiling

The pharmacokinetic and toxicity profiles of the eight selected compounds demonstrated a highly stable, advantageous drug-like profile, supporting their eligibility as orally accessible multi-target candidates (Table 4). All substances showed consistent bioavailability scores of 0.55, indicating a significant baseline likelihood for oral absorption, and entirely adhered to Lipinski's Rule of Five, with no infractions noted. All candidates fell within the ideal lipophilicity window for membrane permeability without exhibiting excessive hydrophobicity, with consensus LogP values ranging from 2.48 to 4.01.

Concurrently, low topological polar surface area values (17.07–37.30 Å²) continued to facilitate effective passive diffusion across biological membranes.

A uniformly high-performance profile across the dataset was displayed by the absorption and distribution parameters. All of the substances were found to be non-substrates of P-glycoprotein and were anticipated to show good gastrointestinal absorption, indicating few efflux-related restrictions. Interestingly, every candidate exhibited positive BBB permeability, suggesting the potential to access core compartments, which could be useful for treating brain-related metastases or advanced-stage diseases. Effective intestinal transit was supported by Caco-2 permeability values consistently within a favorable range (0.872–1.628). Predictions of plasma protein binding, however, showed variation among the compounds, with some ligands (such as CID 5282361 and 5354494) exhibiting comparatively greater binding fractions, which may affect pharmacodynamic response and free drug availability.

Cytochrome P450 interactions, identified by metabolic profiling, were a crucial differentiator between the candidates. The degree and variety of enzyme interactions varied greatly, even though all drugs showed some degree of CYP inhibition. Compounds like CID 317158 and 637760, which primarily targeted CYP2C19, exhibited

Table 3. Multi-target docking performance of shortlisted ligands meeting the binding affinity threshold (≤ -6.0 kcal/mol) across selected proteins

Ligand	EGFR (kcal/mol)	KRAS (kcal/mol)	BCL-2 (kcal/mol)	ALK (kcal/mol)	PI3K (kcal/mol)	AKT1 (kcal/mol)	mTOR (kcal/mol)	Average (kcal/mol)
5375849	-8.46	-7.70	-7.90	-7.00	-7.53	-9.26	-7.16	-7.86
317158	-8.41	-7.48	-7.57	-6.79	-8.07	-9.34	-6.96	-7.80
5367146	-8.57	-7.56	-7.76	-6.78	-7.88	-8.95	-6.75	-7.75
5354494	-7.81	-7.45	-7.49	-7.05	-7.77	-8.95	-7.05	-7.65
5282361	-8.20	-7.36	-7.54	-6.79	-7.61	-9.10	-6.92	-7.65
641819	-8.02	-7.33	-7.60	-6.87	-7.50	-9.05	-7.13	-7.64
637760	-8.10	-7.51	-7.68	-6.63	-7.80	-9.04	-6.69	-7.64
71334668	-8.03	-7.76	-7.79	-6.55	-8.06	-8.40	-6.85	-7.63
317527	-8.61	-6.98	-7.46	-6.64	-7.31	-8.16	-6.79	-7.42

Abbreviations: AKT1: Protein kinase B; ALK: Anaplastic lymphoma kinase protein; BCL-2: B-cell lymphoma kinase; EGFR: Epidermal growth factor receptor protein; KRAS: Kirsten rat sarcoma viral oncogene homolog; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

Table 4. Predicted ADMET and drug-likeness profiles of shortlisted multi-target ligands identified after docking-based screening

Parameter	317158	317527	637760	641819	5282361	5354494	5367146	5375849	71334668
Physicochemical properties									
LogP (consensus)	2.87	2.48	3.29	3.27	2.87	3.46	3.09	3.63	4.01
TPSA ($\text{\AA}^2$)	37.30	29.10	17.07	26.30	37.30	35.53	37.30	17.07	17.07
Lipinski violations	None	None	None	None	None	None	None	None	None
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Absorption and distribution									
GI absorption	High	High	High	High	High	High	High	High	High
P-gp substrate	No	No	No	No	No	No	No	No	No
BBB permeability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Plasma protein binding	0.048	0.067	0.000	0.000	0.385	0.381	0.048	0.000	0.000
Caco-2 permeability	1.609	1.628	1.335	1.220	1.076	0.872	1.609	1.333	1.344
Metabolism and excretion									
CYP inhibition profile	CYP2C19	CYP1A2	CYP2C19	CYP1A2, CYP2C19, CYP2D6	CYP2C19	CYP1A2, CYP2C19, CYP2C9, CYP2D6	CYP2C19, CYP2C9	CYP2C19, CYP2D6	CYP1A2, CYP2C19, CYP2C9
Total clearance	0.135	0.022	0.223	0.248	-30.986	-0.001	0.207	0.225	0.052
Toxicity									
Predicted toxicity class	4	4	4	5	4	5	4	4	5
LD ₅₀ (mg/kg)	1048	1000	1048	3600	1048	2100	1048	1048	3000
Respiratory toxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Mutagenicity (Ames)	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Active
Immunotoxicity	Active	Inactive	Inactive	Active	Inactive	Active	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

Abbreviations: BBB: Blood–brain barrier; CYP: Cytochrome P450; GI: Gastrointestinal; LD₅₀: Median lethal dose; P-gp: P-glycoprotein; TPSA: Topological polar surface area.

simpler inhibition profiles, whereas CID 641819 and 5354494, which interacted with several isoforms such as CYP1A2, CYP2C9, CYP2C19, and CYP2D6, showed more complex inhibition patterns. This implies a possible trade-off between the risk of drug-drug interactions and metabolic stability, especially for multi-CYP inhibitors. This variability was further highlighted by total clearance values, which showed that most compounds had moderate clearance rates. However, anomalous predictions (such as extremely negative values for CID 5282361) suggest possible model limitations or compound-specific metabolic complexities that need additional validation.

Toxicological assessment revealed an overall acceptable safety profile, with the majority of compounds classified in toxicity classes 4 and 5, indicating relatively low acute toxicity. Predicted LD50 values indicated a largely safe treatment window, ranging from approximately 1,000 mg/kg to 3,600 mg/kg. Crucially, none of the substances showed signs of cytotoxicity or respiratory toxicity. Nonetheless, certain candidates were shown to have particular liabilities. While CID 71334668 also demonstrated carcinogenic potential, CID 317527 demonstrated anticipated mutagenicity and carcinogenicity. A selection of drugs, such as CID 317158, 641819, and 5354494, showed signs of immunotoxicity, suggesting the need for careful interpretation and possible subsequent confirmation.

When considered collectively, the ADMET analysis confirmed that the compounds on the short list exhibited strong drug-like properties, high potential for oral absorption, and acceptable safety profiles. The overall balance between pharmacokinetic favorability and safety supports their sustained prioritization, despite minor concerns regarding CYP inhibition and specific toxicity endpoints. When combined with the docking results, these insights enable a more precise selection of lead compounds with translational potential and strong target interaction.

3.3. Lead prioritization

The nominated compounds were systematically refined into a smaller set of high-confidence lead candidates by the integration of molecular docking and ADMET profiling. Eight compounds met the multi-target docking threshold at first; when pharmacokinetic behavior and toxicity risks were taken into account in addition to binding performance, not all of them showed an equally balanced profile. Therefore, three main criteria were used to prioritize leads: (i) strong binding consistency across all seven targets; (ii) favorable ADMET characteristics with low safety liabilities; and (iii) structural capacity to support stable and diverse interaction networks within protein active sites.

Three compounds—CID 317158, 637760, and 5367146—emerged as the most promising leads among the shortlisted possibilities (Figure 2). These compounds showed acceptable pharmacokinetic characteristics, including good gastrointestinal absorption, appropriate lipophilicity, and no significant rule-of-five violations, while maintaining strong and consistent binding affinities across all targets. Compounds like CID 317527 and 71334668 were excluded despite having similar docking performance, as they showed fewer critical toxicity flags than other candidates and no concomitant mutagenic or carcinogenic hazards.

The balance between safety and efficacy was a crucial differentiator in the prioritization process. Even though a number of drugs demonstrated significant binding, their translational potential may have been limited by complex CYP inhibition profiles or anticipated toxicological issues, which led to their deprioritization. CID 317158 and 637760, on the other hand, showed consistent safety profiles and somewhat simpler metabolic interaction patterns, making them pharmacologically and structurally sound candidates. Despite being associated with somewhat more complex metabolic interactions, CID 5367146 was retained due to its robust multi-target binding and generally satisfactory ADMET properties.

Taken as a whole, this prioritization approach ensured that the final lead compounds were chosen based on a comprehensive assessment of drug-likeness, safety, and multi-target engagement rather than just binding affinity. To clarify the molecular compatibility of these three drugs with key oncogenic targets, a thorough investigation of binding interactions was conducted.

3.4. Binding interaction analysis

The three main compounds (CID 317158, 637760, and 5367146) showed a highly conserved binding pattern, characterized by hydrophobic stabilization, hydrogen bonding, and π -mediated interactions, when profiled across seven major oncogenic targets. These interaction networks further validate the multi-target inhibitory potential of the chosen ligands and offer a mechanistic justification for the significant docking affinities reported.

All three ligands continuously occupied hydrophobic nooks rich in residues such as leucine, isoleucine, valine, and methionine, and van der Waals interactions were the predominant stabilizing force across all targets. In AKT1, EGFR, and mTOR, where dense clusters of nonpolar residues enabled sustained ligand accommodation, this broad hydrophobic complementarity was especially noticeable. All three drugs showed consistent π - π stacking interactions with tryptophan residues (TRP80/81) and

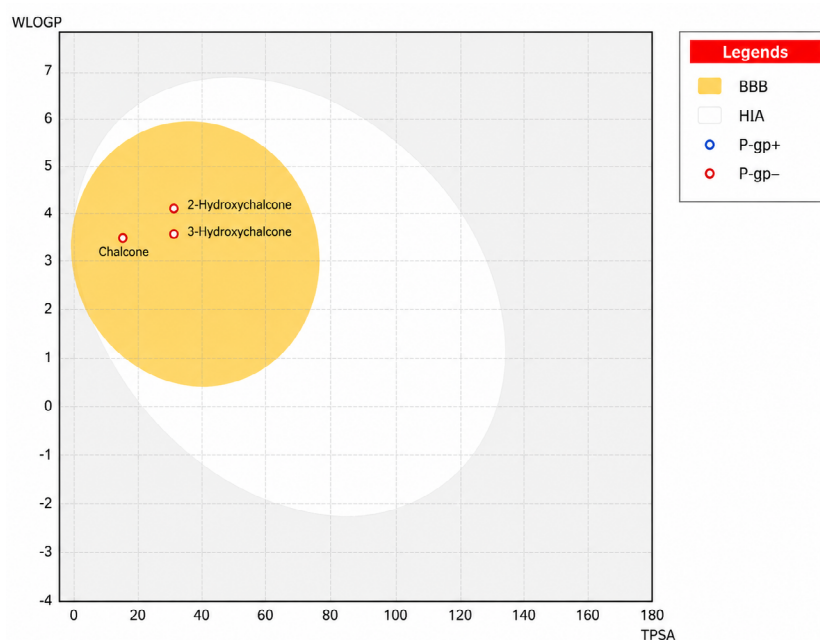


Figure 2. Boiled-egg model predicting HIA and BBB permeability of the prioritized lead compounds (CID 317158, CID 637760, and CID 5367146). All three compounds are predicted to exhibit high gastrointestinal absorption and BBB permeability, and to be non-substrates of PGP, supporting their favorable pharmacokinetic profiles.

Abbreviations: BBB: Blood–brain barrier; HIA: Gastrointestinal absorption; P-gp: P-glycoprotein; TPSA: Topological polar surface area; WLOGP: Wildman–Crippen LogP.

a conserved interaction pattern involving important residues ASN204, LEU210, and TYR272 in AKT1. The remarkably high binding affinities observed for this target may be attributed to a structurally conserved binding mechanism within the kinase domain, as suggested by these interactions and hydrogen bonding at ASN204.

All three ligands in EGFR showed very similar binding orientations, stabilized by π -cation interactions at the same location and anchored by conventional hydrogen bonding with LYS745, a crucial catalytic residue. LYS745 plays a crucial role in ligand recognition, as evidenced by the recurrence of LYS745-mediated interactions across all ligands. This shows that these drugs successfully target the ATP-binding pocket of EGFR. Binding selectivity is further strengthened by stabilization via hydrophobic contacts and π -sigma interactions with residues such as LEU718 and THR790.

Amide- π stacking with ASP111 and π - π T-shaped interactions involving aromatic residues PHE104 and TYR108 dominated the BCL-2 interaction profile. This suggests that the ligands' aromatic ring systems are essential for interacting with BCL-2's hydrophobic groove, which is a characteristic of potent BCL-2 inhibitors. Similarly, π -anion and π -sulfur interactions in PI3K, particularly those involving ASP810 and CYS838, suggest

additional electrostatic and sulfur-mediated stabilization that enhances binding affinity.

Residues such as LYS2187 and TYR2225 were found to bind to mTOR in a conserved manner, with contributions from hydrophobic contacts, π - π stacking, and hydrogen bonding. Interestingly, CID 5367146 showed an unfavorable metal-donor interaction with MG2602 despite maintaining a similar interaction density. This suggests a possible structural constraint that could impact binding stability under physiological settings.

Despite being relatively simpler, ALK interactions showed significant engagement through hydrophobic contacts and hydrogen bonding (MET1199, GLU1197). In contrast to the other ligands, CID 317158 showed a distinct π -anion interaction with GLU1132, indicating improved electrostatic stabilization. CID 637760, on the other hand, exhibited greater variety in interaction types, including π -sulfur bonding, suggesting a more adaptable binding profile.

The most complex interaction pattern was observed for KRAS, particularly for CID 317158, which formed a salt-bridge interaction with LYS16 in addition to a large hydrogen-bonding network. Nevertheless, the presence of several unfavorable interaction points indicates less-

than-ideal binding geometry, reflecting the well-known challenge of using small compounds to target KRAS.

Overall, the interaction analysis shows that the three lead compounds exhibit a conserved multi-target binding approach that includes specific hydrogen bonding and π interactions, in addition to hydrophobic core stabilization. While CID 5367146 showed slight structural irregularities despite strong binding, CID 317158 and CID 637760 demonstrated the most stable and balanced interaction profiles across all targets. These results confirm their potential as broad-spectrum inhibitors targeting key signaling pathways in lung cancer and provide mechanistic support for their selection as lead candidates. To illustrate the molecular basis of ligand binding, representative two-dimensional and 3D interaction profiles of the three prioritized lead compounds with selected target proteins are presented in Figure 3. These representative complexes highlight the key hydrogen-bonding, hydrophobic, and π -mediated interactions that underlie the observed multi-target binding patterns. Detailed interaction residues and interaction types for all target proteins are summarized in Tables 5–7, with the corresponding two-dimensional interaction diagrams presented in Figures 4–6.

4. Discussion

A targeted group of chalcone-based small molecules with coherent multi-target engagement of EGFR, KRAS, BCL-2, ALK, and PI3K/AKT1/mTOR, along with generally favorable *in silico* ADMET properties, is identified in this study, making them promising candidates for next-generation polypharmacological lung cancer treatments. The three prioritized leads (CIDs 317158, 637760, and 5367146) are especially noteworthy because they directly address several failure modes of existing single-target NSCLC therapies by combining strong AKT1- and EGFR-centered binding profiles with oral drug-like features and acceptable predicted safety.

For molecularly defined subgroups of NSCLC, targeted therapy against single oncogenic drivers like EGFR or ALK has improved outcomes; nonetheless, almost all patients eventually relapse due to additional mutations, route rewiring, or activation of bypass tracks.^{29,30} The systems-level durability of lung cancer signaling networks is highlighted by the fact that resistance to EGFR tyrosine kinase inhibitors (TKIs) often arises through EGFR gatekeeper mutations, amplification of *MET* or *HER2*, and compensatory activation of the PI3K/AKT1/mTOR and rat sarcoma viral oncogene homolog/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase (MEK) cascades.^{31,32} Precision oncology analyses focused on polypharmacology increasingly

argue that well-designed multi-target ligands can reduce adaptive resistance, eliminate the need for complex drug combinations, and yield longer-lasting effects than highly selective monotherapies.³³

The current study identified ligands that simultaneously interact with multiple oncogenic proteins, including EGFR, AKT1, PI3K, mTOR, BCL-2, and, to a lesser extent, KRAS. This multi-target binding profile is consistent with current polypharmacology strategies in cancer drug discovery, where simultaneous modulation of interconnected signaling pathways may help reduce compensatory pathway activation and therapeutic resistance. In particular, the recurrent strong binding observed for AKT1, together with favorable interactions with EGFR and PI3K, suggests that the shortlisted chalcone derivatives may influence multiple survival and proliferation pathways relevant to lung cancer progression. Such broad target engagement may offer potential advantages over highly selective single-target inhibitors, especially in complex and adaptive tumor systems. The ability of the prioritized chalcone derivatives to interact with multiple oncogenic proteins is consistent with polypharmacology, in which a single small molecule can modulate several therapeutically relevant targets. Rather than exhibiting absolute target specificity, these compounds possess structural features, including aromatic ring systems, hydrogen-bond donors and acceptors, and hydrophobic substituents, that enable complementary interactions with the conserved physicochemical characteristics of different protein-binding pockets. Consequently, the same ligand can establish stable hydrogen bonding, hydrophobic, and π -mediated interactions with multiple proteins involved in interconnected signaling pathways, including EGFR, PI3K, AKT1, mTOR, ALK, KRAS, and BCL-2. Such multi-target engagement is increasingly recognized as a promising therapeutic strategy for complex diseases such as lung cancer, where simultaneous modulation of multiple signaling pathways may reduce compensatory pathway activation and delay the development of drug resistance compared with conventional single-target therapies.

One of the most commonly dysregulated pathways in lung cancer is the PI3K/AKT1/mTOR axis, which is closely associated with unchecked growth, apoptosis evasion, and resistance to chemotherapy and targeted treatments.^{34,35} Dual-node blockade is a logical therapeutic design principle because preclinical research has shown that simultaneous inhibition of EGFR and PI3K/AKT1/mTOR produces synergistic anti-tumor effects in NSCLC models, including those with concurrent EGFR mutations and downstream pathway alterations.³⁶ Therefore, the ability to blunt a major survival bottleneck in NSCLC cells

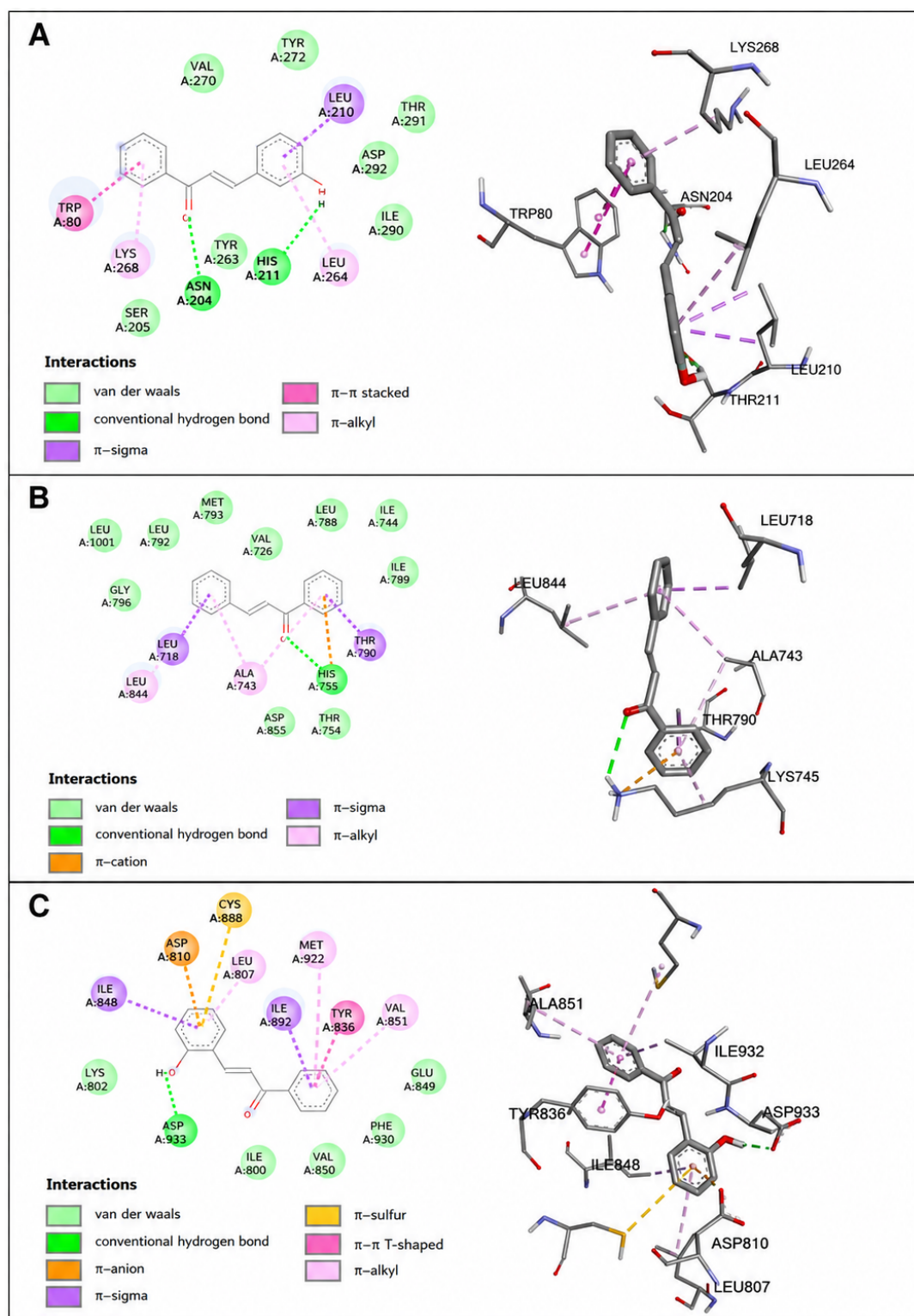


Figure 3. Representative two-dimensional (left) and three-dimensional (right) protein–ligand interaction profiles of the prioritized lead compounds. (A) CID 317158 bound to protein kinase B. (B) CID 637760 bound to epidermal growth factor receptor. (C) CID 5367146 bound to phosphoinositide-3-kinase. The interaction profiles demonstrate hydrogen bonding, hydrophobic interactions, and π -mediated contacts with key active-site residues, supporting stable multi-target binding.

Table 5. Ligand CID 317158 binding interactions with target proteins

Proteins	Interaction residues	Interaction type
AKT1	SER 205, TYR 263, VAL 270, TYR 272, THR 291, ASP 292, ILE 290	van der Waals
	ASN 204, THR 211	Conventional hydrogen bond
	LEU 210	π -sigma
	TRP 80	π - π stacked
	LYS 268, LEU 264	π -alkyl
ALK	GLY 1202, MET 1196	van der Waals
	MET 1199, GLU 1197	Conventional hydrogen bond
	GLU 1132	π -anion
	LEU 1256, ALA 1148, LEU 1198, ALA 1200, LEU 1122, VAL 1130	π -alkyl
BCL-2	PHE 153, GLU 152, PHE 112, LEU 137, ARG 146	van der Waals
	ASP 111,	Amide- π stacked
	PHE 104, TYR 108	π - π T-shaped
	VAL 156, MET 115, ALA 149	π -alkyl
EGFR	ILE 744, ILE 789, LEU 792, MET 793, GLY 796, THR 854, ASP 855, LEU 1001	van der Waals
	LYS 745, LEU 788	Conventional hydrogen bond
	LEU 718, THR 790	π -sigma
	VAL 726, ALA 743, LEU 844, LYS 745	π -alkyl
	LYS 745	π -cation
KRAS	ARG 68	Conventional hydrogen bond
	GLU 62, GLU 63, ASP 69, ARG 73, TYR 96, GLN 99, ILE 100	van der Waals
	MET 72, VAL 103	π -sigma
	MET 72	π -sulfur
	TYR 64	π - π T-shaped
	VAL 9, ARG 102	π -alkyl

(Cont'd...)

Table 5. (Continued)

Proteins	Interaction residues	Interaction type
mTOR	ILE 2163, LEU 2185, ASP 2357, ILE 2237, GLY 2238, VAL 2240, LEU 2354, TRP 2239, MET 2345, GLN 2167	van der Waals
	SER 2165, LYS 2187	Conventional hydrogen bond
	ILE 2356	π -sigma
	PRO 2169	π -alkyl
	TYR 2225	π - π T-shaped
PI3KA	VAL 850, PHE 930, GLU 849, LEU 807, ILE 800, MET 772	van der Waals
	LYS 802, ASP 933	Conventional hydrogen bond
	ILE 848, ILE 932	π -sigma
	VAL 851, MET 922	π -alkyl
	TYR 836	π - π T-shaped
	ASP 810	π -anion
	CYS 838	π -sulfur

Abbreviations: AKT1: Protein kinase B; ALK: Anaplastic lymphoma kinase protein; BCL-2: B-cell lymphoma kinase; EGFR: Epidermal growth factor receptor protein; KRAS: Kirsten rat sarcoma viral oncogene homolog; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

is mechanistically consistent with the three lead chalcones' strong and recurrent interaction patterns with AKT1, which are stabilized by conserved hydrogen bonding and π -stacking within the kinase domain, especially when coupled with robust binding at the EGFR ATP-binding site.

Due to its shallow binding surface and strong affinity for guanosine triphosphate/guanosine diphosphate, KRAS remains a major yet "undruggable" driver in NSCLC.³⁷ Only lately have selective covalent KRAS G12C inhibitors started to enter the clinic.^{38,39} Despite these developments, on-target mutations and the activation of parallel pathways can lead to resistance to KRAS G12C inhibitors, underscoring the necessity of network-level interventions that also affect downstream effectors such as PI3K/AKT1/mTOR and B-Raf proto-oncogene/MEK/extracellular

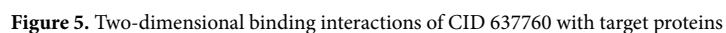
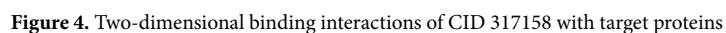


Table 6. Ligand CID 637760 binding interactions with target proteins

Proteins	Interaction residues	Interaction type
AKT1	ASN 53, TYR 272, ILE 290, THR 291, ASP 292, THR 211	van der Waals
	ASN 204	Conventional hydrogen bond
	LEU 210	π -sigma
	TRP 81	π - π stacked
	LYS 268, VAL 270, LEU 264	π -alkyl
ALK	GLU 1197, GLY 1202, LEU 1198, ALA 1200	van der Waals
	MET 1199	Conventional hydrogen bond
	LEU 1256, ALA 1148	π -alkyl
	VAL 1130, LEU 1122	π -sigma
	MET 1196	π -sulfur
BCL-2	GLU 152, PHE 112, LEU 137, PHE 153	van der Waals
	ASP 111	Amide- π stacked
	TYR 108, PHE 104	π - π T-shaped
	MET 115, ALA 149, VAL 156	π -alkyl
EGFR	VAL 726, ILE 744, LEU 788, ILE 789, THR 854, ASP 855, LEU 792, MET 793, GLY 796, LEU 1001	van der Waals
	LYS 745	Conventional hydrogen bond
	LEU 718, THR 790	π -sigma
	ALA 743, LEU 844, LYS 745	π -alkyl
	LYS 745	π -cation

(Cont'd...)

Table 6. (Continued)

Proteins	Interaction residues	Interaction type
KRAS	ARG 68	Conventional hydrogen bond
	GLU 63, ASP 69, TYR 96, GLN 99, ILE 100	van der Waals
	MET 72, VAL 103	π -sigma
	MET 72	π -sulfur
	TYR 64	π - π T-shaped
mTOR	ARG 102	Amide- π stacked
	VAL 9	π -alkyl
	ILE 2163, SER 2165, LEU 2185, MET 2345, LEU 2354, VAL 2240, GLY 2238, ILE 2237, ASP 2357	van der Waals
	LYS 2187	Conventional hydrogen bond
	ILE 2356	π -sigma
PI3KA	PRO 2169	π -alkyl
	TYR 2225	π - π T-shaped
	TRP 2239	π - π stacked
	VAL 850, GLU 849, PHE 930, ILE 800, ASP 933, LYS 802	van der Waals
	ILE 848, ILE 932	π -sigma
	LEU 807, VAL 851, MET 922	π -alkyl
	TYR 836	π - π T-shaped
	ASP 810	π -anion
	CYS 838	π -sulfur

Abbreviations: AKT1: Protein kinase B; ALK: Anaplastic lymphoma kinase protein; BCL-2: B-cell lymphoma kinase; EGFR: Epidermal growth factor receptor protein; KRAS: Kirsten rat sarcoma viral oncogene homolog; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

Table 7. Ligand CID 5367146 binding interactions with target proteins

Proteins	Interaction residues	Interaction type
AKT1	ILE 290, THR 291, TYR 272, SER 206, ASP 292, THR 211, VAL 270	van der Waals
	ASN 204	Conventional hydrogen bond
	LEU 210	π -sigma
	TRP 80	π - π stacked
	LEU 264, LYS 268	π -alkyl
ALK	ALA 1200, MET 1199, LEU 1198, AL 1148, VAL 1130, MET 1196, GLY 1269, ASP 1270, ASN 1254, ARG 1253, ASP 1203, GLY 1202	van der Waals
	LEU 1122, LEU 1256	π -sigma
BCL-2	SER 105, ASP 111, PHE 112, LEU 137, ARG 146, PHE 153, VAL 156	van der Waals
	MET 115, ALA 149	π -alkyl
	PHE 104, TYR 108	π - π T-shaped
	ILE 744, LEU 788, ILE 789, LEU 792, MET 793, GLY 796, THR 854, ASP 855, LEU 1001	van der Waals
EGFR	LYS 745	Conventional hydrogen bond
	LEU 718, THR 790	π -sigma
	VAL 726, ALA 743, LEU 844, LYS 745	π -alkyl
	LYS 745	π -cation
KRAS	ARG 68, GLN 99	Conventional hydrogen bond
	GLU 62, GLU 63, ASP 69, TYR 96, ILE 100	van der Waals
	MET 72, VAL 103	π -sigma
	MET 72	π -sulfur
	TYR 64	π - π T-shaped
	VAL 9, ARG 102	π -alkyl

(Cont'd...)

Table 7. (Continued)

Proteins	Interaction residues	Interaction type
mTOR	VAL 2240, GLY 2238, ILE 2237, SER 2165, GLN 2167, GLU 2190, ASP 2357, ASN 2343, THR 2245, ILE 2356, MET 2345	van der Waals
	LEU 2185, PRO 2169	π -alkyl
	TRP 2239	π - π stacked
	LYS 2187	π -cation
	MG 2602	Unfavorable metal-donor
PI3KA	LYS 802, ILE 800, VAL 850, PHE 930, GLU 849	van der Waals
	ASP 933	Conventional hydrogen bond
	LEU 807, MET 922, VAL 851	π -alkyl
	ILE 848, ILE 932	π -sigma
	TYR 836	π - π T-shaped
	ASP 810	π -anion
	CYS 838	π -sulfur

Abbreviations: AKT1: Protein kinase B; ALK: Anaplastic lymphoma kinase protein; BCL-2: B-cell lymphoma kinase; EGFR: Epidermal growth factor receptor protein; KRAS: Kirsten rat sarcoma viral oncogene homolog; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

signal-regulated kinase.^{40–42} Emerging polypharmacology concepts in KRAS-mutant NSCLC, where multi-target compounds can outperform single-node approaches by simultaneously suppressing driver and effector signaling, are consistent with the observation that the current ligands achieve meaningful, though not dominant, docking to KRAS while strongly engaging AKT1 and PI3K.⁴³

Concurrently, pharmacological BCL-2 inhibition can resensitize tumors to cytotoxic drugs in preclinical models, and overexpression of anti-apoptotic BCL-2 family proteins has been shown to contribute to chemoresistance in both small-cell and non-small-cell lung cancer.⁴⁴ Chalcones and related flavonoids have been shown to cause intrinsic apoptosis in a variety of cancer cell lines, including lung

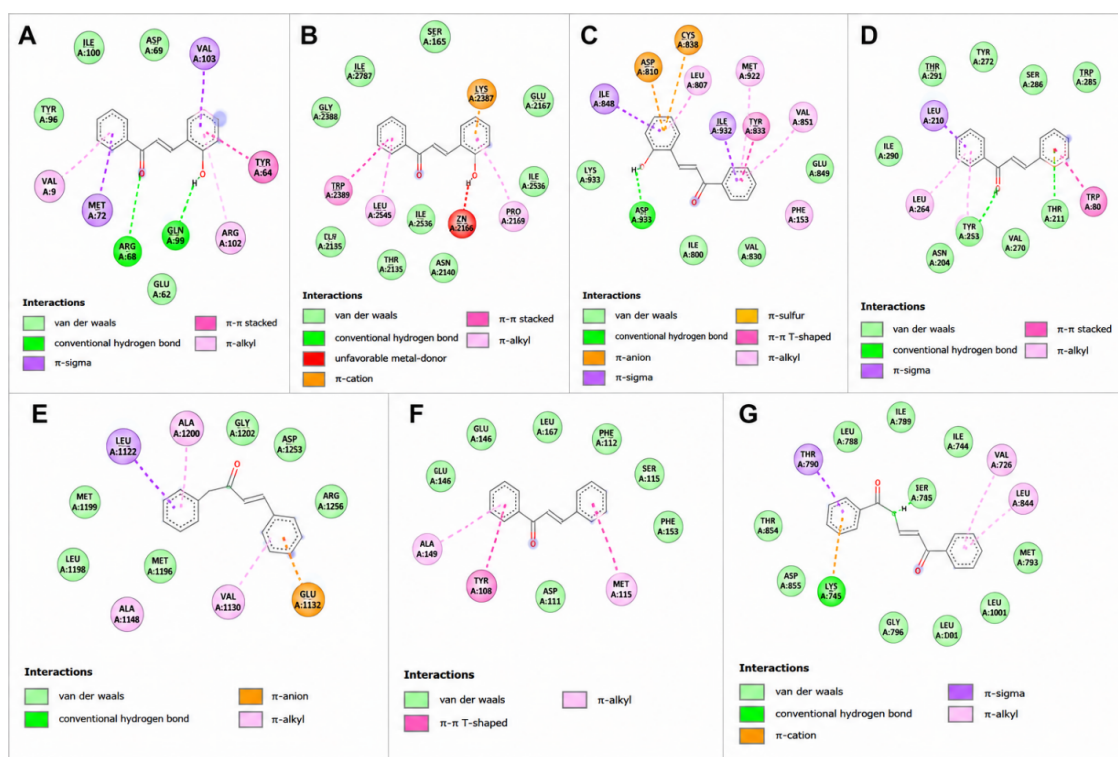


Figure 6. Two-dimensional binding interactions of CID 5367146 with target proteins

cancer, by altering the BCL-2-associated X/BCL-2 balance, triggering caspase-9, and compromising mitochondrial integrity.⁴⁵ These findings independently support the mechanistic plausibility of BCL-2-directed effects in this scaffold class. Because it may combine kinase inhibition with direct pro-apoptotic signaling in a single chemotype, the three prioritized chalcones' capacity to insert their aromatic systems into the hydrophobic BCL-2 groove via π - π and amide- π interactions is highly appealing.

Furthermore, considering the proven effectiveness of ALK inhibitors in ALK-rearranged NSCLC and the increasing recognition that combination EGFR/ALK or ALK/PI3K inhibition can be beneficial in heterogeneous tumors, the inclusion of ALK among the targeted kinases is therapeutically relevant.^{46,47} In line with the idea of "soft" polypharmacology, where secondary targets are modulated at lower potency but still contribute to therapeutic efficacy, the docking energies against ALK were somewhat weaker than those against AKT1 and EGFR, but they are still within a range compatible with auxiliary target engagement. When considered collectively, the multi-target profile presented here fits in nicely with the current paradigm change in lung cancer drug discovery from one-target/one-drug to

rationally planned multi-node inhibition across apoptotic control and oncogenic signaling.

Chalcone derivatives' predominance among the top-ranked ligands supports this scaffold's reputation as a preferred chemotype in the search for anticancer drugs.⁴⁸ In lung cancer models, a variety of chalcone analogs have shown strong antiproliferative effects by inhibiting EGFR phosphorylation, interfering with tubulin polymerization, causing cell-cycle arrest at G2/M, and strongly inducing apoptosis.⁴⁹ Chalcones that occupy the EGFR ATP-binding pocket with docking scores in the -7 to -9 kcal/mol range and exhibit selective activity against both wild-type and mutant EGFR have been specifically reported in *in silico* and experimental studies.⁵⁰ These findings are consistent with the binding energies found here for the best-performing ligands.

In the setting of lung cancer, where brain metastases are common, and efflux across the BBB can significantly limit therapeutic central nervous system (CNS) exposure, the anticipated lack of P-glycoprotein substrate behavior across the lead set is advantageous.⁵¹ P-glycoprotein (P-gp) and associated efflux transporters at the BBB have been frequently linked to the variability and failure of CNS-

active medicines, including TKIs, and are important factors in determining CNS drug penetration. Clinical and imaging studies using third-generation EGFR TKIs, like Osimertinib, show that BBB-penetrant TKIs can cause significant intracranial responses even in the absence of upfront radiotherapy, and that attaining high, homogeneous brain distribution is essential to controlling brain metastases in EGFR-mutant NSCLC.⁵² The combination of moderate lipophilicity, low polar surface area, and non-substrate status for P-gp indicates that at least a subset of these chalcones may be amenable to optimization as agents capable of addressing both pulmonary and CNS disease compartments, even though the current predictions cannot replace direct CNS pharmacokinetic data.

In that regard, a prototype pathway for evaluating chemotypes with multi-target potential prior to resource-intensive experimental validation is provided by the current study's combination of docking, ADMET, and network-based thinking. A targeted starting set for such systems-level follow-up is provided by the discovery of three chalcone leads with convergent engagement of EGFR, PI3K/AKT1/mTOR, BCL-2, and ALK. This includes mapping their predicted targets onto patient-derived signaling networks and investigating possible synergistic combinations with approved EGFR, ALK, or KRAS G12C inhibitors as well as immune checkpoint blockade. Further medicinal chemistry optimization around these scaffolds may have a real translational impact, given the mounting evidence that polypharmacological drugs might, in some situations, lessen the establishment of resistance and simplify treatment regimens compared to multi-drug combinations.

4.1. Study limitations

Despite these advantages, the data's immediate translational interpretation is tempered by a number of caveats. Molecular docking remains an approximate method; entropic contributions, protein flexibility, and solvent effects are not fully captured by scoring functions, and correlations between docking scores and experimental affinities are frequently weak, especially across chemically varied series. Similarly, even while *in silico* ADMET and toxicity models are becoming more accurate, they can still produce false positives and negatives. Therefore, their predictions need to be grounded in experimental pharmacokinetic, metabolic, and safety data from pertinent preclinical models.

It is necessary to refine the binding hypotheses for AKT1, EGFR, BCL-2, and KRAS using molecular dynamics simulations and free-energy calculations. This is followed by biochemical kinase and BCL-2 family binding assays,

as well as cell-based viability and apoptosis experiments in EGFR-mutant, KRAS-mutant, and BCL-2-high lung cancer models. To validate the favorable *in silico* ADMET profile, parallel assessment of metabolic stability, CYP inhibition, and plasma protein binding in microsomal and hepatocyte systems will be necessary, and brain-penetration studies in pertinent animal models will be necessary to validate any suggested utility against CNS metastases. Lastly, a more thorough evaluation of the areas in the lung cancer signaling landscape where these chalcone-based multi-target ligands are most likely to provide clinical benefit will be possible by integrating these experimental data into network pharmacology frameworks that incorporate genomic and transcriptomic profiles from patient-derived samples.

When considered collectively, the current *in silico* results provide compelling evidence for chalcone-centered chemotypes, especially the three highlighted leads, as manageable starting points for the development of orally bioavailable, multi-target lung cancer therapies that concurrently modulate apoptotic regulators, downstream survival kinases, and receptor tyrosine kinases within a network-pharmacology paradigm.

5. Conclusion

This study demonstrates the effectiveness of an integrated computational workflow for identifying multi-target inhibitors against key proteins involved in lung cancer progression. By systematically combining molecular docking, pharmacokinetic evaluation, and interaction analysis, a diverse compound library was refined into a small set of high-confidence lead candidates with consistent performance across multiple oncogenic targets. The docking results highlighted the importance of structural modifications in enhancing binding affinity, with substituted chalcone and oxindole derivatives significantly outperforming parent scaffolds. Subsequent ADMET profiling ensured that lead selection was not driven solely by binding strength but also accounted for drug-likeness, bioavailability, and safety considerations. Among the shortlisted compounds, CID 317158 and CID 637760 emerged as the most promising candidates, exhibiting strong multi-target binding, favorable pharmacokinetic profiles, and minimal toxicity concerns. CID 5367146 also demonstrated robust binding behavior, although minor limitations were observed in its interaction profile.

Mechanistic insights from binding interaction analysis confirmed that these compounds effectively engage key residues within active sites, supporting their potential to disrupt critical signaling pathways such as PI3K/AKT1/mTOR and EGFR-mediated proliferation. Collectively,

these findings underscore the value of multi-target drug discovery strategies in addressing the complexity of cancer signaling networks. While the results provide a strong computational foundation, experimental validation through in vitro and in vivo studies is necessary to confirm the therapeutic potential of the identified compounds. Future work should focus on structural optimization, dynamic simulations, and biological assays to advance these candidates toward clinical relevance.

Acknowledgments

The authors appreciate the collaborative support of the Chemistry Collaborative Research Environment (CHEMCORE) for providing and enabling an academic network for interdisciplinary research discussions and technical guidance during manuscript preparation.

Funding

None.

Conflict of interest

The authors declare that they have no competing financial or non-financial interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data generated or analyzed during this study are included in this manuscript.

Further disclosure

The authors declare that artificial intelligence tools (ChatGPT, OpenAI) were used only for language polishing and readability enhancement. No AI tools were used in the generation, analysis, or interpretation of scientific data. The authors retain full responsibility for the content of this manuscript.

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