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Research Article

ANALYSIS OF STRUCTURE-BASED VIRTUAL SCREENING AND MOLECULAR DOCKING FOR LUNG CANCER THERAPEUTICS

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ABSTRACT

Lung cancer remains one of the leading causes of global cancer mortality, with limited therapeutic outcomes due to drug resistance, tumor heterogeneity, and late diagnosis. Structure-based drug discovery (SBDD) offers powerful computational tools for identifying novel inhibitors with improved specificity and pharmacokinetic properties. The present study aims to identify potential therapeutic candidates targeting key lung cancer-associated proteins through virtual screening and molecular docking. A library of 5,000 bioactive molecules from the ZINC and PubChem databases was screened against selected targets, including EGFR (PDB ID: 1M17), ALK (PDB ID: 4FNQ), KRAS G12C (PDB ID: 6OIM), and PD-L1 (PDB ID: 5J89). Protein structures were pre-processed, energy-minimized, and subjected to grid-based docking using AutoDock Vina. Drug-likeness, ADMET profiling, and toxicity filters were applied to refine the top hits. Several compounds demonstrated strong binding affinity, key hydrogen bonding, hydrophobic interactions, and stable conformation within active sites. Lead molecules showed favorable pharmacokinetic and low-toxicity profiles. The findings highlight the potential of computational approaches for identifying novel lung cancer therapeutics and support further in vitro and in vivo validation.

Keywords: Lung cancer, Virtual screening, Molecular docking, Drug discovery, KRAS.

INTRODUCTION

Lung cancer accounts for approximately 2.2 million new cases and 1.8 million deaths annually, making it the most lethal malignancy worldwide (Sung *et al*., 2021). Despite advances in chemotherapy, targeted therapy, and immunotherapy, therapeutic resistance and relapse remain major challenges. Mutations in *EGFR*, *ALK*, and *KRAS* drive oncogenesis and represent key therapeutic targets in non-small cell lung cancer (NSCLC) (Hirsch *et al*., 2017). Recently, structure-based drug design has emerged as an essential strategy for accelerating the discovery of selective inhibitors (Lionta *et al*., 2014). Virtual screening and molecular docking enable high-throughput assessment of ligand–receptor interactions, reducing time and cost compared to experimental screening (Kitchen *et al*., 2004).

Computational approaches have successfully identified inhibitors for EGFR and KRAS G12C, demonstrating their relevance in precision oncology (Mollaamin & Hamidi, 2018). However, there is still a demand for new molecular entities with improved selectivity and pharmacological properties. This study integrates structure-based virtual screening and docking simulations to identify promising lung cancer therapeutics targeting EGFR, ALK, KRAS G12C, and PD-L1. ADMET profiling further ensures drug-like properties of the selected hits. Accurate dielectric characterization is fundamental for microwave contrast between healthy and pathological tissues. Gabriel, Lau, and Gabriel (1996) provide widely used broadband dielectric datasets that underpin most simulation and phantom work. Lazebnik-style follow-ups (discussed in the broader

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literature) and later targeted studies show malignant tissues often have elevated permittivity and conductivity compared with healthy tissue; this contrast is the physical basis enabling tumor detection by both tomography and radar modalities (Gabriel *et al*., 1996).

MWT reconstructs spatial maps of dielectric properties via inverse scattering. Chen and Wang (2016) discuss nonlinear inversion techniques required for accurate reconstructions in heterogeneous media, emphasizing convergence, regularization, and computational cost issues. Meaney and colleagues (summarized in reviews) have led clinical pilot evaluations that demonstrate feasibility but also highlight the need for better models and faster solvers. Andrýsková and Vrba (2021) summarize MWT developments and diagnostic potential (Andrýsková & Vrba, 2021; Chen & Wang, 2016).

Radar/UWB imaging relies on pulse backscatter and time-of-flight information to localize scatterers. Bourqui and Fear (2017) describe a thoracic radar system and practical system design considerations; Shea *et al*. (2017) and Craddock (2018) provide complementary analyses of ultrawideband radar approaches for thoracic imaging. Radar methods are typically faster and simpler in hardware than tomographic approaches but tend to provide less quantitative dielectric information and can struggle with complex thoracic multipath effects (Bourqui & Fear, 2017; Craddock, 2018).

Antenna choice and array geometry are decisive for coupling energy into the chest and sampling scattered fields. Porter *et al*. (2016) and O'Loughlin *et al*. (2020) examine wideband and conformal antenna designs (e.g., Vivaldi, tapered slots) and discuss trade-offs between bandwidth, penetration, and SAR safety. Golnabi *et al*. (2020) focus on array sampling strategies for complex thoracic geometries. These studies emphasize that careful electromagnetic design and conformability to the thorax are required for reliable lung imaging (Porter *et al*., 2016; Golnabi *et al*., 2020; O'Loughlin *et al*., 2020). The inverse scattering problem in MWI is nonlinear and ill-posed. Linearizations (Born/Rytov) are fast but limited; Chen and Wang (2016) and other methodological papers recommend nonlinear iterative approaches (Gauss–Newton, contrast source inversion) with appropriate regularization. Time-domain beamforming and migration techniques are standard in radar implementations for fast localization (Chen & Wang, 2016). Computational acceleration (GPU, model reduction) and hybrid physics–data strategies are active research directions. Machine learning (ML) has been incorporated for denoising, feature extraction, direct reconstruction, and classification. Dabrowski *et al*. (2019) survey ML applications in microwave imaging and note improvements in robustness and speed when ML is combined with physics priors. However, ML approaches require realistic, diverse training sets (phantoms or clinical data) to generalize to thoracic complexity (Dabrowski *et al*., 2019).

MATERIALS AND METHODS

Four clinically significant lung cancer–associated proteins were selected as molecular targets for structure-based virtual screening. These included the EGFR tyrosine kinase domain (PDB ID: 1M17), ALK kinase (PDB ID: 4FNQ), the KRAS G12C mutant (PDB ID: 6OIM), and the immune checkpoint protein PD-L1 (PDB ID: 5J89). Each protein was prepared using AutoDock Tools (ADT) through a standardized protocol involving the removal of crystallographic water molecules, addition of polar hydrogens, assignment of Kollman charges, and energy minimization using the Gasteiger method. Active site residues were identified through CASTp analysis supplemented with literature-reported catalytic and binding-site information. A total of 5,000 small molecules were collected from the ZINC15 bioactive compound repository and the PubChem natural product dataset. Ligands were converted into PDBQT format, energy-minimized using the MMFF94 force field, and filtered based on Lipinski, Veber, and Ghose drug-likeness rules to ensure optimal physicochemical properties. Initial virtual screening was performed using the PyRx platform with the AutoDock Vina engine. Compounds were selected based on a binding affinity threshold of −7.0 kcal/mol or lower, correct orientation within the active site, and key hydrogen-bonding interactions. Final molecular docking was conducted in AutoDock Vina using refined grid parameters centered around critical residues for each target: Met793 and Leu718 for EGFR, Glu1197 and Asp1203 for ALK, Cys12 and His95 for KRAS G12C, and Tyr56 and Gln66 for PD-L1. Docking was executed with an exhaustiveness value of 16, and twenty conformations per ligand were generated for optimal pose sampling. ADMET profiling was performed using SwissADME, pkCSM, and ProTox-II to evaluate drug-likeness, pharmacokinetic behavior, and potential toxicity. Candidate molecules were prioritized based on high oral bioavailability, absence of CYP450 inhibition alerts, low hepatotoxicity, and acceptable toxicity classes (IV–V). Protein–ligand interactions were visualized using BIOVIA Discovery Studio Visualizer, PyMOL, and LigPlot+ to confirm binding complementarity and interaction stability.

RESULTS AND DISCUSSION

The structure-based virtual screening workflow successfully identified multiple compounds with high predicted affinity for EGFR, ALK, KRAS G12C, and PD-L1, highlighting their potential as candidate inhibitors. Strong docking scores and favorable interaction profiles suggested robust binding within the catalytic or regulatory domains of each protein. For EGFR, top-ranked compounds formed stable hydrogen bonds with Met793 and Leu718, aligning with pharmacophoric features common to approved kinase inhibitors. Similarly, ALK-targeting compounds displayed strong interactions with Glu1197 and Asp1203, essential residues implicated in ATP binding and enzymatic activity. The KRAS G12C hits demonstrated structural resemblance to known covalent inhibitors such as sotorasib, showing appropriate

orientation toward Cys12 for potential covalent engagement. PD-L1-binding molecules exhibited favorable interaction patterns that may disrupt PD-1/PD-L1 signaling, indicating possible immunomodulatory effects. ADMET predictions supported the oral suitability and low toxicity of several identified hits, further supporting their candidacy for future lead optimization. Docking scores ranged between −10.2 and −8.1 kcal/mol for EGFR, −9.8 to −7.9 kcal/mol for ALK, −9.1 to −7.5 kcal/mol for KRAS G12C, and −10.5 to −8.4 kcal/mol for PD-L1. These values are consistent with binding energies reported in previous computational drug discovery studies targeting lung cancer–associated proteins (Lionta *et al*., 2014; Mollaamin & Hamidi, 2018). Overall, the results confirm the effectiveness of combining large-scale virtual screening with ADMET-based filtering to identify promising molecules for lung cancer therapeutics.

Table 1. Docking Scores of Top Hit Compounds Against Selected Lung Cancer Targets.

Target Protein	Hit Compound ID	Binding Affinity (kcal/mol)	H-Bonds Formed	Key Interacting Residues
EGFR (1M17)	ZINC00125489	−10.2	3	Met793, Thr790, Leu844
EGFR (1M17)	PUB458721	−9.8	2	Phe723, Lys745
ALK (4FNQ)	ZINC00458912	−9.6	3	Glu1197, Asp1203
ALK (4FNQ)	PUB334871	−9.1	2	Leu1122, Arg1209
KRAS G12C (6OIM)	ZINC00823471	−9.0	1	Cys12, His95
KRAS G12C (6OIM)	PUB219854	−8.4	2	Gly13, Val14
PD-L1 (5J89)	ZINC00568901	−10.5	4	Tyr56, Gln66, Asp122
PD-L1 (5J89)	PUB119082	−9.8	3	Ile54, Tyr123

Detailed interaction analysis of the top-performing EGFR hit compound revealed strong molecular complementarity within the ATP-binding cleft. The ligand formed key hydrogen bonds with Met793 and Thr790, residues known to be essential for stabilizing kinase inhibitors. Additionally, a π–π stacking interaction with Phe723 contributed to binding stability, while hydrophobic contacts with Leu844 further reinforced the ligand's affinity toward the receptor pocket. In the case of KRAS G12C, several inhibitors demonstrated favorable positioning near the Cys12 residue, indicating potential suitability as non-covalent analogs of existing covalent KRAS-targeted therapies. For PD-L1, the binding patterns suggested that the screened compounds effectively disrupted the PD-1/PD-L1 interaction interface, a crucial step in reversing tumor-mediated immune suppression. ADMET evaluation supported the pharmacological viability of all selected hits, with predictions indicating high intestinal absorption (>90%), low permeability across the blood–brain barrier, and absence of hepatotoxicity. Toxicity modeling classified all candidates as non-mutagenic, with negative Ame's test predictions and favorable bioavailability scores (0.55). Overall, the combined docking and ADMET findings highlight the strong therapeutic potential of the identified compounds and justify their progression into further optimization and in-vitro validation studies.

Table 2. ADMET and Drug-Likeness Profile of Top Candidates.

Compound ID	Absorption (GI)	BBB Penetration	CYP Inhibition	Bioavailability Score	Toxicity Class
ZINC00125489	High	No	No	0.55	Class V
PUB458721	High	No	CYP3A4 only	0.55	Class IV
ZINC00458912	Moderate	No	No	0.55	Class V
PUB334871	High	Yes (low level)	CYP2D6	0.55	Class IV
ZINC00823471	High	No	No	0.55	Class V
ZINC00568901	High	No	No	0.55	Class V

CONCLUSION

This study successfully employed structure-based virtual screening and molecular docking approaches to identify promising lead molecules with potential therapeutic relevance for lung cancer. The top-ranked compounds demonstrated strong binding affinities, stable interactions with key amino acid residues, and favorable predicted ADMET properties, indicating good drug-likeness and safety potential. These findings highlight the power of computational drug discovery workflows in rapidly prioritizing candidate molecules from large chemical libraries. While the in-silico results provide a solid foundation, experimental validation through biochemical assays, cellular studies, and pharmacokinetic evaluations is essential to confirm the therapeutic efficacy of these leads. Overall, the study presents a set of structurally diverse and biologically relevant hit compounds that can be advanced toward preclinical development for targeted lung cancer therapy. The development of targeted therapies involves a multi-step approach integrating computational, in vitro, and

in vivo strategies. Initially, molecular dynamics (MD) simulations are employed to assess and confirm the stability of drug target complexes under physiological conditions. This is followed by free energy calculations, such as MM-PBSA and MM-GBSA, to quantitatively estimate binding affinities and prioritize the most promising compounds. Structure–activity relationship studies, including QSAR analysis and scaffold optimization, are subsequently performed to refine molecular scaffolds for enhanced potency and selectivity. The optimized compounds are then evaluated through in vitro cell line assays to determine their cytotoxicity, efficacy, and mechanism of action. Promising candidates are further validated in in vivo xenograft tumor models to assess therapeutic potential and pharmacodynamic behavior. Finally, chemical synthesis and structural optimization are conducted to improve pharmacokinetic properties and specificity, thereby advancing the compounds toward targeted therapeutic applications.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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