AMC JOURNAL (DHANGADHI)
Year 9; July, 2026; Vol. 8; Issue 2; PP. (77-92) DOI: https://doi.org/10.3126/amcjd.v8i2.98405

Computational Design of Novel Anticancer Agents for Lung Cancer: A Molecular Docking and ADMET Analysis

Janga Bahadur Kathayat
Aishwarya Multiple Campus, Dhangadhi, Kailali
* Email: jangakathayat@amcdhangadhi.edu.np
ORCID ID https://orcid.org/0009-0002-4407-8742

Article History:
Received: March 20, 2026
Revised: June 28, 2026
Accepted: July 10, 2026

Abstract

NSCLC is still one of the leading causes of cancer mortality around the world, and there is a need for new therapeutic agents to overcome the limitations of existing targeted therapies, including the development of resistance to the drugs and significant side effects. In this study, several 1,2,3-triazole hybrids based on cabotegravir were assessed in an integrated computational methodology for their potential as anticancer agents by targeting a lung cancer-associated protein (PDB ID: 2ITY). Molecular docking was performed using PyRx 0.8 to assess binding affinities. The pharmaceutical properties of the compounds were evaluated for pharmacokinetic properties and the likelihood of toxicity, using SwissADME and pkCSM, respectively, and Gefitinib was used as the reference drug. Many of the compounds had statistically superior binding energies than Gefitinib (−7.5 kcal/mol); among the compounds studied, compounds 5e, 5h, and 6d showed the best binding energies [−10.2 kcal/mol].

Keywords: ADMET; Cabotegravir derivatives; Drug-likeness.; Lung cancer; Molecular docking; Non-small cell lung cancer; 1,2,3-Triazole hybrids.

Introduction

Lung cancer is one of the most serious public health issues around the world. It is also the number one cause of cancer-related death among both men and women (Thandra et al., 2021). Because of the aggressive nature of lung cancer, including late-stage diagnosis and high metastatic potential, it continues to account for a large proportion of cancer deaths in the world despite many advances in diagnosing and treating the disease. Non-small Cell Lung Cancer (NSCLC) is about 85 percent of all lung cancers. Patients with this type of lung cancer typically have a poor prognosis with limited long-term survival (Khalvati et al., 2026). While targeted and immunotherapies have improved clinical outcomes for some patients, there are multiple barriers preventing a successful outcome, including the development of resistance to the drug or treatment, side effects from the drug or treatment and recurrence of the disease (Aldea et al. 2021).Thus, new and more efficient drugs for lung cancer treatment continue to be an important research focus (Bao & Chan, 2011) .

The identification, development, and screening of new and improved anti-cancer drugs is a lengthy, costly, and complicated process (Cui et al., 2020). The conventional method of drug discovery involves extensive experimental screening and huge investment of money, where many of the drug candidate molecules fail during preclinical/clinical development, mainly because of poor efficacy and undesirable pharmacokinetic properties (Sinha & Vohora, 2018). Computational drug discovery methods have gained tremendous significance in the last couple of years to aid the process of discovery and optimization of possible lead compounds. The molecular docking, virtual screening and in silico drug-likeness prediction methods allow the assessment of the biological activity and binding affinity of the compounds in the virtual screening before experimental testing, which helps to save time and cost in the drug

development process (Naithani & Guleria, 2024). Molecular docking is among the computational methods with the widest acceptance to predict the interaction between small molecules and biological targets (Rao et al., 2019). Docking studies can estimate binding affinities and identify important interactions between the ligand and protein which can give insights into the molecular mechanism of therapeutic activity. Additionally, the inclusion of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction and drug-likeness evaluation are indispensable parts of contemporary drug discovery, thus enabling the identification of compounds at an early stage to have desirable ADMET properties and safety attributes (Zhou & Wang, 2012),(Mohapatra et al., 2023), (Bultum et al., 2022). Comparable to the other classes of heterocyclic compounds investigated for their anticancer properties, 1,2,3-triazole derivatives have received much interest because of their wide range of biological activities, such as anticancer, antimicrobial, antiviral, anti-inflammatory and enzyme inhibitory activity (Alam, 2022). The triazole ring has distinct structural and electronic properties that enable it to form highly favorable hydrogen bond, π–π stacking and hydrophobic interactions with biological targets. Furthermore, triazoles are usually more metabolically stable and have more desirable pharmacokinetic properties, which makes them attractive scaffolds for medicinal chemistry applications (Guan et al., 2024). The main application of cabotegravir is to treat and prevent human immunodeficiency virus (HIV) infection (Cattaneo & Gervasoni, 2019). In recent years, some medicinal chemistry work has shown that structural modifications of the cabotegravir scaffold can result in derivatives with a wide range of biological activities other than those of anti-viral action (Starosotnikov & Bastrakov, 2023). Moreover, the use of 1,2,3-triazole moiety in cabotegravir-based structures has been described to increase the biological activity and increase the interactions between the molecules and the therapeutic targets (Dembo et al., 2024). A few 1,2,3-triazole hybrids of cabotegravir have exhibited favorable cytotoxic activity against lung cancer cell lines and are promising new cancer drugs (Guo et al., 2023). The main objective of the present study was to gain insight into the molecular interactions and pharmacokinetic properties of selected 1,2,3-triazole hybrids of cabotegravir derivatives against a protein target, associated with lung cancer (PDB ID: 2ITY) via computational methods. The binding ability and interaction patterns of the compounds within the active site of the target protein were assessed using molecular docking analysis. Furthermore, ADMET prediction, drug-likeness based on Lipinski's Rule of Five and toxicity assessment were performed to select compounds with desirable pharmacological properties. The results of this study can be used to find potential lead molecules for the development of new anti-lung cancer drugs and act as a basis for further experiments.

Materials and Methods

Selection and Preparation of Protein

The crystal structure of the protein that is a diagnostic target for lung cancer (PDB ID: 2ITY) was obtained from the RCSB PDB database in complex with the small molecule compound IRE. (https://www.rcsb.org/) in .pdb format with resolution 3.42 Å (Akash et al., 2024) . The co-crystallized small molecule (IRE), along with heteroatoms and water molecules were extracted with BIOVIA Discovery Studio Visualizer (version 2021) (Dassault Systèmes,

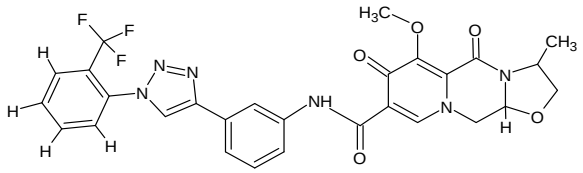
2021). The processed protein structure was then converted to PDBQT format with PyRx version 0.8, with the addition of polar hydrogens and Kollman charges added by Autodock vina. Finally, molecular docking were carried out using PyRx 0.8. The parameters of the docking were all kept at their default values (Kondapuram, Sarvagalla, & Coumar, 2021).

Selection and Preparation of Ligand

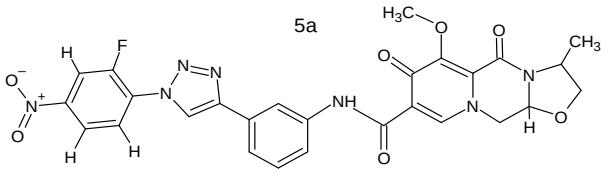
The present study was conducted on the ligands of the 1,2,3-triazole hybrid derivatives of cabotegravir, which have been reported to show promising anticancer activity against lung cancer cells (Guo et al., 2024). Based on the above, compounds 5a–5s and 6a–6i were chosen for molecular modelling and structural analysis among the synthesized derivatives. Substituents including CF3, OCF3, CH3, Br, Cl and F were selected for attachment to the scaffolds due to their ability to impart improved cytotoxic activity, particularly compound 5i which demonstrated the greatest anti-cancer activity against H460 lung cancer cells. The chemical structures of all the selected ligands were taken from the published research article entitled "Synthesis and biological evaluation of novel 1,2,3-triazole hybrids of cabotegravir: identification of potent antitumor activity against lung cancer. The 2D structures of the derivatives were manually drawn in ACD/ChemSketch software. Molecular structures were drawn and geometry optimized using the ChemSketch software and the compounds saved in appropriate formats for further computational studies (Li et al., 2004). To attain a stable 3D structure of the molecules and to remove any structural strain, energy minimization of the 3D structure of the ligand was performed with the UFF force field. After that, the ligands were further prepared by optimizing their geometry and checking their chirality using AutoDock Tools (version 1.5.7) in the PyRx virtual screening platform, running on Ubuntu 20.04.6 LTS (Issahaku et al., 2023), (Forli et al., 2016) .

Selection of reference drug for docking studies

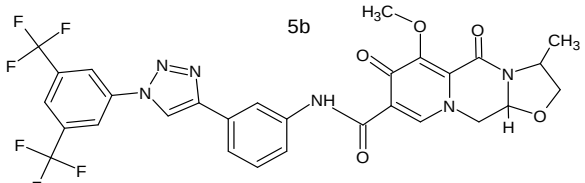
The molecular docking was done with the reference compound Gefitinib in this study. Gefitinib is an FDA approved anti-cancer medicine which was first approved for the treatment of non small cell lung cancer (NSCLC) in 2003 (U.S. Food and Drug Administration, 2003; Verma et al., 2016). The structure 3D (PubChem CID: 123631) was obtained from the PubChem database, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy), 4-quinazolinamine. The same grid parameters as used for the test compounds were used to prepare and dock the reference ligand into the 2ITY active site.



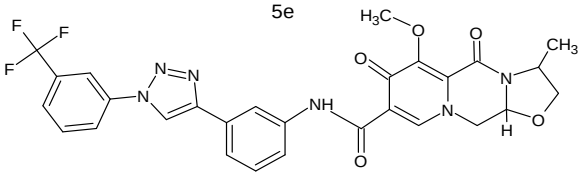
5a



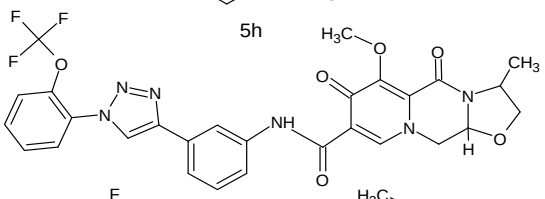
5b



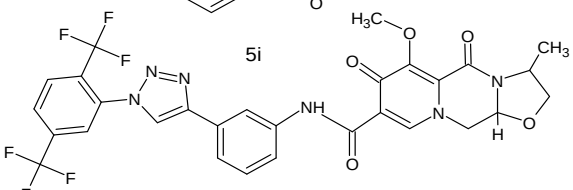
5e



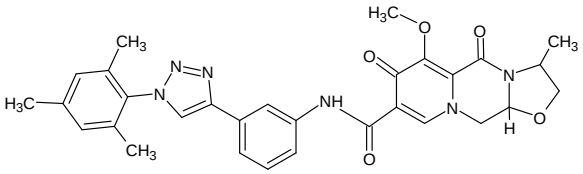
5h



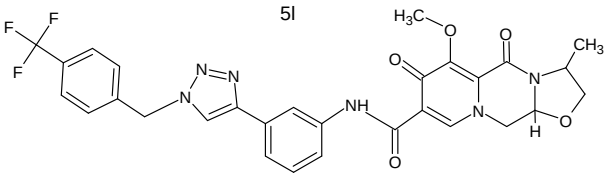
5i



5k



5l



6d

Year 9; July, 2026; Vol. 8; Issue 2; PP. (77-92) DOI: https://doi.org/10.3126/amcjd.v8i2.98405

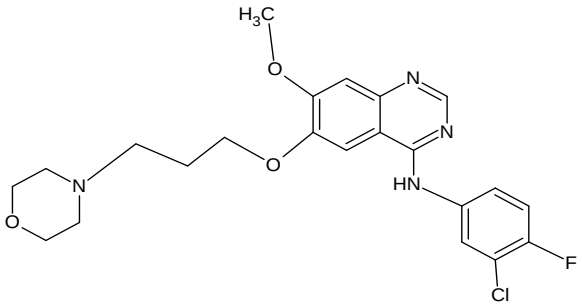


Figure 1: 2D structure of top 8 best 1,2,3-triazole hybrids of cabotegravir derivatives. .

Grid Box Generation

The molecular docking grid box was generated within the PyRx 0.8 environment to define the docking parameters (Azmal et al., 2024)(Siam et al., 2017). The docking grid was centered on the active site of the target protein at coordinates x = 43.9469, y = 8.0021, and z = 24.5547, with a grid size of 25 Å in each dimension. This preparation guaranteed complete coverage of the binding pocket and enabled effective investigation of ligand conformations, leading to dependable ligand–protein interaction predictions.

Docking Protocol

By using PyRx 0.8 platform molecular docking was conducted (Thapa et al., 2023a). While preparing 2ITY protein, water molecules and unrelated heteroatoms were removed but polar hydrogens, Gasteiger charges were included and simultaneously changed into the PDBQT format For making stable conformation energy minimization was performed on the 1,2,3-triazole hybrids of cabotegravir derivatives. Then, partial charges were then assigned, and rotatable bonds defined, before converting the ligands to PDBQT format for import into PyRx along with the prepared 2ITY protein. A number of docking simulations were accepted out for each ligand and the resulting docked poses were ranked according to predicted binding energies (kcal/mol). The lowest energy structure with the best interaction patterns was chosen for complete analysis.

Visualization

The docked complexes of 2ITY with 1,2,3-triazole hybrids of cabotegravir derivatives were analysed and visualised in BIOVIA Discovery Studio Visualizer 2021. The key interactions of the 1,2,3-triazole hybrids of Cabotegravir derivatives with 2ITY were studied using BIOVIA Discovery Studio Visualizer 2021. Four types of interactions, namely, hydrogen bonds, hydrophobic contacts, π–π stacking, and van der Waals interactions were found to give insight into the binding modes and stability of the docked complexes. The use of 2D interaction diagram, together with the visual representation of the structure in 3D, allowed the interpretation of the docking result and a precise visualization of the interaction between ligand and receptor (Syriopoulou, Markopoulos, Tzakos, & Mavromoustakos, 2021).

ADMET Prediction

In silico ADMET analysis of the selected 1,2,3-triazole hybrids of cabotegir derivatives was carried out to assess their pharmacokinetic properties and drug-likeness (Chandrasekaran et al., 2018) (Mathakiya et al., 2026) . Computation prediction of these properties is a crucial and indispensable part of computational drug discovery, because it can identify compounds that have desirable drug-likeness properties before experimental studies are performed. The potential of these selected quinazolinone compounds to possess ADMET properties and drug-likeness were predicted using the SwissADME web server (http://www.swissadme.ch/). SwissADME provides a comprehensive analysis of key pharmacokinetic properties such as lipophilicity, solubility, gastrointestinal absorption, permeability to the blood-brain barrier and compliance with popular ADME criteria. The pharmacokinetics behavior, toxicity and clearance properties of the quinazolinone derivatives were also predicted using the pkCSM web server (https://biosig.lab.uq.edu.au/pkcsm/), to further assess the pharmacokinetic behavior. pkCSM applies a computational approach based on a graph to estimate potential toxicity risks and pharmacokinetic parameters of small molecules. The quinazolinone compounds were evaluated using SwissADME and pkCSM together, to provide a comprehensive and reliable evaluation of the ADMET profile, supporting their possible use as promising drug candidates (Alamri et al., 2024; Alsibaee et al., 2023).

Results

Molecular Docking Analysis

To assess the binding affinity and interaction pattern of selected 1,2,3-triazole hybrid of cabotegravir derivatives, molecular docking studies were done against the target protein (PDB ID: 2ITY) for the lung cancer. The docking results showed that all the compounds selected have good docking score of -7.4 to -10.2 kcal/mol that means strong interaction in the target protein's active binding site. The binding energies of the selected drugs Gefitinib and several synthesized derivatives were found to be −7.5 and −11.7, −12.1, −12.4, and −12.6 kcal/mol respectively, indicating that the synthesized drugs have higher binding affinity and thus are better potential candidate drugs to combat cancer. Derivatives 5e, 5h and 6d showed the best binding affinity with docking score of −10.2 kcal/mol, followed by the compounds 5k and 5l with docking score of −9.8 kcal/mol, compound 5a with docking score of −9.7 kcal/mol and compound 5i with docking score of −9.4 kcal/mol. The compound 5b exhibited the weakest binding affinity among the derivatives studied (−7.4 kcal/mol). The results show that the introduction of halogens and electron withdrawing functional groups could be crucial for receptor binding. On detailed analysis of the interaction, it was found that the compounds in the top ranks had several stabilizing interactions with important amino acid residues residing in the active site of the target protein. The conventional hydrogen bond interactions were found between compound 5e and Leu844 and Lys745, whereas other nonclassical hydrogen bond interactions were found with Val726, Ala743, Met793, Cys797, Arg841, Glu758, and Asn842 (along with alkyl and π-alkyl, π-sulfur, π-sigma, and halogen interactions). The interactions in totality result in the compound's high binding affinity. Likewise, compound 5h formed traditional hydrogen bonds, π-sigma, π-alkyl, alkyl, and halogen interactions with Leu844,

Val726, Ala743, Cys797, Asp855, and Arg841. The compound 6d showed a large number of interactions such as hydrogen bonds, carbon-hydrogen bonds, π-sulfur, π-sigma, and halogen interactions with Leu788, Leu844, Lys745, Ala743, Glu758, Asp837, Asp855, and Arg841, which contributed to its high docking score. Leu844, Lys745, Val726, Ala743, Asp855, Cys797, Glu758 and Arg841 were found to play critical roles in the ligand recognition and stabilization in the top performing compounds within the binding cavity. Remarkably, compounds 5k and 5l showed significant contacts with these critical residues through conventional hydrogen bonding, π-sulfur, π-sigma, alkyl and halogen interactions with binding energies of −9.8 kcal/mol.The reference drug Gefitinib formed predominant π-alkyl, Leu844, Leu718, Lys745, and Val726, and π-sigma interactions with the protein with a binding energy of -7.5 kcal/mol. In most of the synthesized derivatives, the binding energies are stronger than that of the standard drug, indicating that the synthesized derivatives have better binding affinity towards the target protein. Overall, the molecular docking results suggest that compounds 5e, 5h and 6d show the best binding properties and interaction profiles with the active site of the target protein, making them promising candidates for further investigation. The various hydrogen bond, hydrophobic interactions, halogen mediated contacts are involved in stabilizing the ligand–protein complexes and might make the complexes more effective against lung cancer. The results, therefore, offer a solid foundation for continued experimental testing and optimization of these derivatives as therapeutic agents for the treatment of lung cancer.

Table 1: Molecular docking studies, binding energy, types of interaction, interacting amino acids, for the top 8 compounds.

SN	Compound Code	Binding energy (Kcal/mol)	Types of interaction	Interacting amino acids
1	5a	-9.7	C-H bond, pi-alkyl bond, alkyl bond, conventional H- bond	Leu 858, Val 726, Lys 748, Glu 758,Ala 743,Leu 844
2	5b	-7.4	Conventional H bond C-H bond, Pi-alkyl, Pi-sigma	Leu 844,Cys 797, Val 726, Asp 855,Glu 758, Arg 841 ,Cys 797
3	5e	-10.2	Conventional H bond, carbon-H bond, alkyl bond, Pi-alkyl bond, Pi-sulfur, Pi-sigma, Halogen	Leu 844 Lys 745 , Val 726, Ala 743 , Met 793 ,Cys 797,Arg 841,Glu 758,Asn 842.
4	5h	-10.2	Conventional H bond, Alkyl bond, Pi-Sigma, Pi-Alkyl,Halogen (fluorine)	Leu 844, Val 726, Ala 743, Cys 797 , Arg 481 ,Asp 855,
5	5i	-9.4	Conventional H bond, Alkyl; bond, Pi- alkyl, Pi – sigma, Halogen	Leu 858, Glu 762, Asp 855, Lys 745,

SN	Compound Code	Binding energy (Kcal/mol)	Types of interaction	Interacting amino acids
6	5k	-9.8	Conventional H bond Alkyl bond, Pi-alkyl, Pi-sulfur Pi-sigma, Halogen,	Leu (718 ,844) Lys 745, Asp 855, Ala 743 ,Val 745 ,Asp 855 ,Cys 797
7	5l	-9.8	Conventional Hydrogen bond, Alkyl bond, Pi – alkyl, Halogen (fluorine), Pi –sigma	Leu (844,718), Lys 745, Val 726 , Ala 743,Asp 855,Arg 841, Pro 794,Met 793,
8	6d	-10.2	Conventional H bond, Alkyl bond carbon H bond , Pi-sigma, Pi- sulfur ,Halogen	Leu (788,844), Lys 745,Ala 743 ,Glu 758 ,Asp (855, 837) , Arg 841,
9	Gifitinib	-7.5	alkyl ,pi sigma , pi-alkyl	Leu (844 ,718) lys 745, Val 726, Ala 743

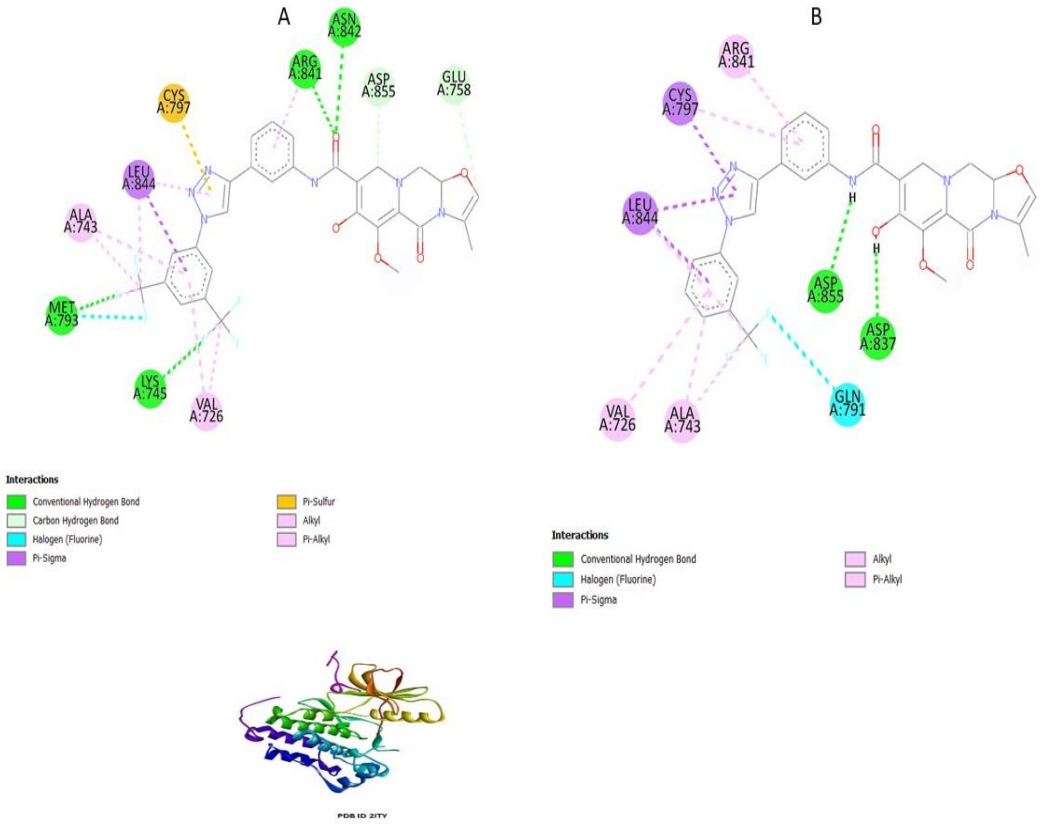


Figure 2: 2D interaction of 5e (A) and 5h (B) with 2ITY

Year 9; July, 2026; Vol. 8; Issue 2; PP. (77-92) DOI: https://doi.org/10.3126/amcjd.v8i2.98405

ADME Profiling and Drug-Likeness Assessment

SwissADME and pkCSM were used to determine the pharmacokinetic profiles of the top eight 1, 2, 3-triazole-cabotegravir hybrids (5a, 5b, 5e, 5h, 5i, 5k, 5l, and 6d) to evaluate their ADMET properties (Vondom et al., 2018). The solubility of all the compounds in water was in the range of −3.769 to −3.330 log mol/L, which is considered moderate; and the gastrointestinal absorption was high, suggesting favorable oral bioavailability. These were also suspected to be substrates and inhibitors of P-glycoprotein, indicating participation in an active transport system. The predicted volume of distribution (VDss) values of the compounds were in the range of −0.375 to 0.442 log L/kg; compounds 5l, 5k, 5h, and 6d had higher tissue distribution potential. All the derivatives were all predicted to pass through the blood–brain barrier. All compounds were found to be substrates of CYP3A4 and CYP1A2, but not inhibitors of CYP3A4, to suggest a low risk of CYP3A4-mediated drug–drug interactions. The predicted total clearance values were between −0.295 and −0.026 log mL/min/kg; compounds 5i, 5a and 5h had relatively high clearance values. All of them, in general, possessed good absorption and distribution, predictable metabolic fate, Lipinski's rule compliance, and low toxicity, with compounds 5e, 5h, 5i, 5k, 5l, and 6d showing the most desirable pharmacokinetic properties. These compounds have shown excellent molecular docking and are potential lead compounds for further development for lung cancer. Other ADME properties such as lipophilicity, solubility, and pharmacokinetic descriptors are listed in Table 2.

Table 2: ADME profiling of 8 compounds.

	Absorption					**Distribution**		**Metabolism**			**Excretion**
CC	WS	SP	P-g Sub.	P-g in.-I	GIA	VDss	BBB	CYP1A2 inhibitor	CYP3A4 inhibitor	CYP3A4 substrate	Total CL
5a	-3.769	-2.735	yes	yes	High	-0.214	Yes	No	Yes	yes	-0.039
5b	-3.579	-2.735	Yes	Yes	High	-0.375	Yes	No	yes	Yes	-0.295
5e	-3.434	-2.735	Yes	Yes	High	-0.287	Yes	No	Yes	Yes	-0.257
5h	-3.421	-2.736	Yes	Yes	High	0.261	Yes	No	Yes	Yes	-0.044
5i	-3.485	-2.735	Yes	Yes	High	0.155	Yes	No	Yes	Yes	-0.026
5k	-3.434	-2.735	Yes	yes	High	0.287	Yes	No	Yes	Yes	-0.244
5l	-3.33	-2.736	Yes	Yes	High	0.442	Yes	No	Yes	Yes	-0.278
6d	-3.629	-2.737	yes	Yes	High	0.197	Yes	N0	Yes	Yes	-0.063

Note: CC= Compound Code, WS = Water Solubility, SP =Skin Permeability, P-g sub =P-glycoprotein substrate, P-g inh-I= P-glycoprotein inhibitor -I, GIA=Gastrointestinal absorption, VDss =Volume Distribution, BBB = Blood Brain Barrier

Drug-Likeness and Lipinski's Rule of Five

Selected 1,2,3-triazole-cabotegravir hybrids (5a, 5b, 5e, 5h, 5i, 5k, 5l and 6d) were assessed for their drug-likeness property by Lipinski's Rule of Five. All the compounds were compliant with the rule, suggesting good properties for oral drug development. The molecular weights of the compounds were in the range 554.61-648.52 Da, and the LogP values were 2.60-4.60, which was considered to be a good balance between lipophilicity and membrane permeability. The number of hydrogen bond donors was 1, and the number of hydrogen bond acceptors was 9–11, which indicated moderate molecular flexibility. The topological polar surface area (TPSA) was between 233.40 Å² and 254.48 Å², suggesting that there are several polar functional groups that can interact with the target. Overall, it is noted that these compounds do not seem to contain any Lipinski rule violations, which indicates that these compounds have good drug-like properties and can be used as orally active anticancer agents. Of these, compounds 5e, 5h, 5i, 5k, 5l, and 6d showed the most favorable compromise between physicochemical properties and molecular docking score, and hence are attractive leads for further development against lung cancer (Daina, Michielin, & Zoete, 2017).

Drug-likeness and Lipinski's Rule of Five

Compound Code	Drug likeness/ Lipinski's rule of five						Violation
	Mol.Wt.	Log P	HBD	HBA	RB	TSA	
5a	580.523	3.5763	1	9	5	235.618	No
5b	575.513	2.6048	1	11	6	235.575	No
5e	648.52	4.5951	1	9	5	254.480	No
5h	580.523	3.576	1	9	5	235.618	No
5i	596.522	3.456	1	10	6	240.732	No
5k	648.52	4.595	1	9	5	254.480	No
5l	554.607	3.482	1	9	6	233.4	No
6d	594.55	3.635	1	9	6	241.98	No

Note: Mol.Wt =Molecular weight, HBD =Hydrogen Bond Donor, HBA =Hydrogen Bond Acceptor, RB =Rotatable Bond, TSA =Total Surface Area

Toxicity Analysis

The pkCSM web server was used to predict the toxicity profiles for the triazole-cabotegravir hybrids selected for this study, as a way to assess their safety as anticancer agents. This is an important step in the process of drug discovery, because compounds that show promise for their biological activity can fail due to unwanted toxic effects (Blomme & Will, 2016). The predicted oral acute toxicity values of these hybrids (LD50) in rats ranged between 2.507 and 2.992 moles per kg; the hybrid with the highest LD50 value was 6d, indicating that this compound has the lowest predicted acute toxicity, while the compound with the lowest LD50 value was 5b, meaning it has a higher prediction of acute toxicity. The predicted chronic toxicity values of these hybrids (LOAEL) ranged from -0.115 to 0.940 log mg/kg/day, with

hybrids 5e and 5k having the lowest predicted LOAEL values, indicating greater potential for chronic toxicity compared with hybrid 5l, which had the highest predicted LOAEL.

Toxicity study of top 8 compounds

Compound Code	Toxicity Score	
	Oral Rat Acute toxicity (LD50)	Oral Rat Chronic toxicity (LOAEL)
5a	2.907	0.376
5b	2.507	0.553
5e	2.928	-0.115
5h	2.895	0.388
5i	2.927	0.283
5k	2.928	-0.115
5l	2.893	0.94
6d	2.992	0.525

Note: LD50 = lethal dose 50, LOAEL = Lowest dose observed adverse effect level.

Discussion

This research used an integrated computational method to investigate the use of cabotegravir 1,2,3-triazole hybrids as anticancer therapies that target lung cancer protein (2ITY). The results of docking analysis showed the majority of compounds exhibited greater binding affinities than the standard chemotherapy agent, gefitinib (compound 5e: -10.2 kcal/mole; 5h: -10.2 kcal/mole; 6d: -10.2 kcal/mole). The compounds strongly interacted with several key active-site residues (Leu844, Lys745, Val726, Ala743, Asp855, Cys797), indicating strong potential to inhibit the target protein. ADMET analysis showed that all compounds have favorable pharmacokinetic properties (high GI absorption, acceptable solubility and lipophilicity) and very low probability for CYP3A4-mediated Drug-Drug Interactions, suggesting an appropriate route of administration (i.e., oral) (Bhandare & Nannor, 2024). Finally, drug-likeness assessments confirmed that all of the selected derivatives meet the criteria for drug likeness.

Molecular Docking Result Analysis

The molecular docking study was performed to check the interaction of 1,2,3-triazole hybrids of cabotegravir with the target protein (PDB ID: 2ITY) of lung cancer. The results indicated higher binding affinity for most derivatives compared to the reference drug Gefitinib (−7.5 kcal/mol) suggesting that they could be used efficiently to inhibit the target. The docking score for compounds 5e, 5h and 6d were found to be highest as −10.2 kcal/mol, followed by 5k (-9.8 kcal/mol), 5l (-9.7 kcal/mol), 5a (-9.7 kcal/mol) and 5i (-9.4 kcal/mol) and 5b had the lowest score as −7.4 kcal/mol. The best compounds were identified to have multiple stabilizing interactions such as conventional hydrogen bond, π-alkyl, π-sigma, π-sulfur, halogen and

hydrophobic interactions with key active site residues through analysis of their interactions. Residues Leu844, Lys745, Val726, Ala743, Asp855, Cys797, Glu758, and Arg841 were found to be consistently involved in the interactions with the ligand, which are important for target inhibition. The synthesized derivatives showed higher and broader interacting networks compared with Gefitinib, which may be responsible for their enhanced binding affinities. In summary, compounds 5e, 5h and 6d were found to be the most promising lead compounds, with excellent receptor binding and favourable interaction patterns and should be further validated using molecular dynamics and experimental studies.

ADME and Pharmacokinetic Analysis

The PK properties of the 1,2,3-triazole hybrids of cabotegravir selected for ADME analysis showed good drug development potential. The gastrointestinal absorption was high and the water solubility was moderate for all compounds, suggesting good oral bioavailability. The acceptable VDss values that were obtained from the distribution studies revealed that compounds 5l, 5k, 5h and 6d had improved tissue penetration. All the derivatives were predicted to have good membrane permeability. Metabolic studies revealed that all of the compounds were CYP3A4 substrates but not inhibitors, suggesting potential for drug–drug interactions and predictable hepatic metabolism with a lower risk of drug–drug interactions, though some inhibition of CYP1A2 was noted (Andrade et al., 2016). Balanced clearance values were evident in excretion profiles, with compound 5i having the highest predicted clearance (Fagerholm, 2007). In general, compounds 5e, 5h, 5i, 5k, 5l and 6d exhibited the most positive ADME properties, hence their potential as orally active anticancer agents, and are promising candidates to be subjected to further experimental testing.

Lipinski's Rule of Five Analysis

All the 1,2,3-triazole hybrids of Cabotegravir selected were found to have favorable physicochemical properties by using drug-likeness evaluation based on Lipinski's Rule of Five and showed no violation of the 5 drug-likeness rules. The compounds exhibited good levels of lipophilicity (LogP 2.60–4.60), hydrogen bonding and molecular flexibility, which is indicative of potential oral bioavailability (Caminero Gomes Soares et al., 2023) . Some of the derivatives had a molecular weight greater than 500 Da, but it was still within the acceptable drug-likeness. The presence of polar functional groups, which could increase the target interaction, was suggested by TPSA values (Luo et al., 2020). In conclusion, these compounds have good drug-likeness, docking, and ADME properties and are potential anticancer agents, with compounds 5e, 5h, 5k, 5l, and 6d being the most promising for further development.

Toxicity Profiling

The designed 1,2,3-triazole hybrids of cabotegravir were shown to be safe using in silico toxicity assessment. From the predicted oral rat acute toxicity (LD50) values, it is clear that the compounds are not toxic in low levels as the values are ranging between 2.507 and 2.992 mol/kg, with compound 6d having the highest of these values which is the least toxic. Chronic toxicity evaluation using LOAEL values was also performed, and most compounds were found to be safe for long-term use, especially 5e and 5k. After molecular docking, ADME and drug-

likeness calculations (El Fadili et al., 2024), compounds 5e, 5h, 5k and 6d were found to be the most promising compounds. On a general level, the toxicity predictions are in favor of the potential of these derivatives as anticancer lead compounds, but additional in vitro and in vivo testing is needed to prove their safety and therapeutic effectiveness.

Reference Compound (Gefitinib) Docking Analysis

In the molecular docking study, gefitinib (NSCLCT approved EGFR inhibitor) was taken as a reference compound against the target protein (PDB ID: 2ITY). Gefitinib had a binding energy of −7.5 kcal/mol, and bound to the important residues of the active site such as Leu844, Leu718, Lys745, Val726, and Ala743. Seven out of the eight derivatives of 1,2,3-triazole (compounds) selected in this comparative analysis exhibited higher binding affinity than that of Gefitinib. Compounds 5e, 5h, and 6d demonstrated the highest binding energies (−10.2 kcal/mol), followed by 5k and 5l (−9.8 kcal/mol), 5a (−9.7 kcal/mol), and 5i (−9.4 kcal/mol). These increased binding affinities were largely attributed to hydrogen, halogen bond, π-sulfur contact, and hydrophobic interaction(s) with key residues, namely Lys745, Asp855, Cys797, Glu758 and Arg841. Based on these results, the synthesized derivatives, especially 5e, 5h and 6d, have better binding potential than Gefitinib and should be further studied using molecular dynamics simulation and biological experiments as therapeutic agents for lung cancer.

Conclusion

In the present study, a series of 1,2,3-triazole cabinets analogues of cabotegravir were explored for their anticancer activity against lung cancer by applying an integrated computational approach including the molecular docking study, ADMET prediction, drug-likeness assessment and toxicity study. Molecular docking study showed that majority of selected derivatives showed higher binding affinity towards the target protein (PDB ID: 2ITY) than Gefitinib (reference drug). The derivatives 5e, 5h, and 6d had the highest binding affinities (−10.2 kcal/mol) and these compounds formed stable interactions with the key active-site residues, suggesting good inhibitory potential. The selected compounds showed good gastrointestinal absorption, acceptable distribution and predicted metabolic disposition, and appropriate clearance properties in the ADMET analysis. Additionally, drug-likeness evaluation was carried out for all the derivatives investigated; none of them showed any violation of Lipinski's Rule of 5, thus indicating their potential as orally active drug candidates. In addition, these compounds showed acceptable toxicity properties according to the toxicity profiling: compounds 5e, 5k and 6d showed particularly favourable toxicity properties.Based on the analysis of all the compounds evaluated, 5e, 5h and 6d were identified as the most promising lead candidates, showing good binding affinity, favourable interaction pattern, desirable pharmacokinetic properties, compliance with drug-likeness criteria and acceptable predicted toxicity. The results suggest that the 1,2,3-triazole structural motif could be a useful strategy for designing new anticancer drugs for lung cancer. The outcome of this study is very promising, but computation is based on predictions, which have to be validated by experimental investigations. Thus, in vitro cytotoxicity, molecular dynamics simulations, enzyme inhibition and in vivo pharmacological tests are suggested in order to validate the biological activity and safety of the selected lead compounds. The findings of the present study

suggest that the compounds 5e, 5h and 6d are prospective candidates for further development in the context of drug discovery for lung cancer and further optimization of the triazole-based anticancer agents is warranted on the basis of their strong structural features.

Acknowledgement

I would like to express my sincere thanks to the Research Management Cell (RMC), Aishwarya Multiple Campus, Dhangadhi, Kailali, Nepal for its continuous encouragement, guidance and support during the process of this research. Their dedication to research and academic excellence has been immensely helpful in completing this study.

Conflict of interest

There is no any conflict of interest.

References

Aldea, M., Andre, F., Marabelle, A., Dogan, S., Barlesi, F., & Soria, J. C. (2021). Overcoming resistance to tumor-targeted and immune-targeted therapies. Cancer Discovery, 11(4), 874–899.

Ahmad, I., Khan, H., & Serdaroğlu, G. (2023). Physicochemical properties, drug likeness, ADMET, DFT studies, and in vitro antioxidant activity of oxindole derivatives. Computational Biology and Chemistry, 104, 107861.

Alam, M. M. (2022). 1,2,3-triazole hybrids as anticancer agents: A review. Archiv der Pharmazie, 355(1), 2100158.

Andrade, E. L., Bento, A. F., Cavalli, J., Oliveira, S. K., Freitas, C. S., Marcon, R., et al. (2016). Non-clinical studies required for new drug development—Part I: Early in silico and in vitro studies, new target discovery and validation, proof of principles and robustness of animal studies. Brazilian Journal of Medical and Biological Research, 49, e5644.

Bao, R., & Chan, P. (2011). Novel compounds in the treatment of lung cancer: Current and developing therapeutic agents. Journal of Experimental Pharmacology, 21–34.

Bhandare, A., & Nannor, K. M. (2024). Bioavailability in drug design and development: A comprehensive review. World Journal of Pharmaceutical Research, 13(17), 145–168.

Blomme, E. A., & Will, Y. (2016). Toxicology strategies for drug discovery: Present and future. Chemical Research in Toxicology, 29(4), 473–504.

Bultum, L. E., Tolossa, G. B., & Lee, D. (2022). Combining empirical knowledge, in silico molecular docking and ADMET profiling to identify therapeutic phytochemicals from Brucea antidysentrica for acute myeloid leukemia. PLoS ONE, 17(7), e0270050.

Caldwell, G. W., Yan, Z., Tang, W., Dasgupta, M., & Hasting, B. (2009). ADME optimization and toxicity assessment in early- and late-phase drug discovery. Current Topics in Medicinal Chemistry, 9(11), 965–980.

Caminero Gomes Soares, A., Marques Sousa, G. H., Calil, R. L., & Goulart Trossini, G. H. (2023). Absorption matters: A closer look at popular oral bioavailability rules for drug approvals. Molecular Informatics, 42(11), e202300115.

Cattaneo, D., & Gervasoni, C. (2019). Pharmacokinetics and pharmacodynamics of cabotegravir, a long-acting HIV integrase strand transfer inhibitor. European Journal of Drug Metabolism and Pharmacokinetics, 44(3), 319–327.

Cui, W., Aouidate, A., Wang, S., Yu, Q., Li, Y., & Yuan, S. (2020). Discovering anti-cancer drugs via computational methods. Frontiers in Pharmacology, 11, 733.

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7(1), 42717.

Dembo, A., Ferenczi, E., Jernei, T., Bor, A., Schelz, Z., Zupko, I., et al. (2024). CuAAC-based synthesis, copper-catalyzed aldehyde-forming hydrolytic fission and antiproliferative evaluation of novel ferrocenoylamino-substituted triazole-tethered quinine–chalcone hybrids. Molecules, 29(2), 375.

El Fadili, M., Er-Rajy, M., Mujwar, S., Ajala, A., Bouzammit, R., Kara, M., et al. (2024). In silico insights into the design of novel NR2B-selective NMDA receptor antagonists: QSAR modeling, ADME-toxicity predictions, molecular docking, and molecular dynamics investigations. BMC Chemistry, 18(1), 142.

Fagerholm, U. (2007). Prediction of human pharmacokinetics—renal metabolic and excretion clearance. Journal of Pharmacy and Pharmacology, 59(11), 1463–1471.

Forli, S., Huey, R., Pique, M. E., Sanner, M., Goodsell, D. S., & Arthur, J. (2016). AutoDock tools for docking analysis. Journal of Computational Chemistry, 37(13), 1097–1106.

Guan, Q., Xing, S., Wang, L., Zhu, J., Guo, C., Xu, C., et al. (2024). Triazoles in medicinal chemistry: Physicochemical properties, bioisosterism, and application. Journal of Medicinal Chemistry, 67(10), 7788–7824.

Khalvati, B., Kavousi, K., Behmard, E., Keyhanipour, A. H., & Arabfard, M. (2025). Discovery of drug candidate to inhibit bronchogenic carcinoma genes biomarkers based on drug repurposing. Discovery Oncology, 17(1), 114. https://doi.org/10.1007/s12672-025-04268-3

Kondapuram, S. K., Sarvagalla, S., & Coumar, M. S. (2021). Docking-based virtual screening using PyRx tool: Autophagy target Vps34 as a case study. In Molecular Docking for Computer-Aided Drug Design (pp. 463–477). Academic Press.

Li, Z., Wan, H., Shi, Y., & Ouyang, P. (2004). Personal experience with four kinds of chemical structure drawing software: Review on ChemDraw, ChemWindow, ISIS/Draw, and ChemSketch. Journal of Chemical Information and Computer Sciences, 44(5), 1886–1890.

Luo, Z., Liu, C., Quan, P., Yang, D., Zhao, H., Wan, X., & Fang, L. (2020). Mechanistic insights of the controlled release capacity of polar functional group in transdermal drug delivery system. Acta Pharmaceutica Sinica B, 10(5), 928–945.

Mathakiya, A., Patel, B., Raval, K., & Dhalani, J. (2026). Synthesis and anticancer assessment of cabotegravir-inspired compounds using Allium cepa model: Molecular docking, ADMET and DFT approaches. Tetrahedron, 135307.

Naithani, U., & Guleria, V. (2024). Integrative computational approaches for discovery and evaluation of lead compound for drug design. Frontiers in Drug Discovery, 4, 1362456.

Rao, M. S., Gupta, R., Liguori, M. J., Hu, M., Huang, X., Mantena, S. R., et al. (2019). Novel computational approach to predict off-target interactions for small molecules. Frontiers in Big Data, 2, 25.

Sinha, S., & Vohora, D. (2018). Drug discovery and development: An overview. Pharmaceutical Medicine and Translational Clinical Research, 19–32.

Systèmes, D. (2021). Discovery Studio Visualizer (Version 16.1). Dassault Systèmes.

Thandra, K. C., Barsouk, A., Saginala, K., Aluru, J. S., & Barsouk, A. (2021). Epidemiology of lung cancer. Contemporary Oncology, 25(1), 45–52.

Thapa, S., Nargund, S. L., Biradar, M. S., Banerjee, J., & Karati, D. (2023). In-silico investigation and drug-likeness studies of benzimidazole congeners: The new face of innovation. Informatics in Medicine Unlocked, 38, 101213.

El Fadili, M., Er-Rajy, M., Mujwar, S., Ajala, A., Bouzammit, R., Kara, M., et al. (2024). In silico insights into the design of novel NR2B-selective NMDA receptor antagonists: QSAR modeling, ADME-toxicity predictions, molecular docking, and molecular dynamics investigations. BMC Chemistry, 18(1), 142.