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In-silico study of potential antiviral drug compounds against EGFR kinase domain to target non-small cell lung cancer (NSCLC)

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Abstract

Purpose of Research: Worldwide, lung cancer is the biggest cause of cancer-related deaths. Cancer of non-small lung cells (NSCLC) is the most prevalent kind of lung cancer. Targeting NSCLC, we investigate the anticancer effect of antiviral drug compounds against the EGFR kinase domain.

Scope of The Experiments: The 3D protein structure of the EGFR kinase domain (1XKK) was derived from the RCSB PDB library. First, an ADME study was conducted, followed by Lipinski's rule of five-based toxicity analysis of the compounds. After screening for ADME and toxicity, the remaining drugs were docked to the EGFR kinase domain (PDB ID: 1XKK). For docking, the Autodock Vina application was deployed. Using the application Discovery Studio 2019, the docking discovery was investigated.

Results: The binding affinity of the standard drug compounds Afatinib Dimaleate, and Gemcitabine to the active site of the EGFR kinase domain was -8.9, and -8.4, respectively. In contrast, the binding affinity of our lead drug compound (Diphyllin) to the active region of the EGFR kinase domain was -10 kcal/mol, which is superior to the both selected standard drug compounds. In addition, the found chemical generates a greater number of hydrogen bonds than our chosen benchmark compounds, indicating that it is more stable. An examination of root means square fluctuation was done to appreciate the dynamic motions of the ligand-protein complex.

Findings and Conclusions: Due to its capacity to suppress the activity of the target protein EGFR kinase domain, which plays a vital role in the progression of NSCLC, Diphyllin shows great potential as an anti-NSCLC medication. To validate

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further our promising findings based on preliminary and in-silico analysis, in-vitro and in-vivo investigations are necessary.

Keywords: Antiviral compounds; EGFR kinase domain; NSCLC; ADMET; Molecular Docking

1. Introduction

Lung cancer is one of the worst cancers for both men and women (1). It has a greater fatality rate than combined in the three most common cancers (colon, breast, and pancreatic) (2). Over fifty percent of lung cancer patients die within one year of diagnosis, and the five-year survival rate is only 17.8 percent (3). Small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) are the two primary subtypes of lung cancer, representing 15% and 85%, respectively, of all lung cancer (4). The subtypes of NSCLC include squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. Squamous cell carcinoma comprises 25–30 percent of all lung cancer cases. It begins in the bronchial tubes in the center of the lungs, in the airway epithelial cells. This subtype of NSCLC is strongly related to cigarette smoking (5). Adenocarcinoma is the most prevalent form of lung cancer, accounting for around 40% of all cases. It is produced by small airway epithelial type II alveolar cells that secrete mucus and other chemicals (6). Adenocarcinoma is the most prevalent form of lung cancer in both smokers and nonsmokers, regardless of gender or age (7). It tends to develop in the lung's periphery (8) because cigarette filters prevent large particles from entering the lungs. This results in a deeper inhalation of cigarette smoke, leading to peripheral lesions (9). Compared to other types of lung cancer, adenocarcinoma grows more slowly and is more likely to be diagnosed before it spreads outside of the lungs. 5–10% of lung tumors are undifferentiated (big cell) carcinoma. Lacking signs of squamous or glandular growth, this type of cancer is typically discovered by default after eliminating other possibilities. Large cell carcinoma often begins in the middle of the lungs and can spread to nearby lymph nodes, the chest wall, and distant organs (10). Large cell carcinoma cancers are closely linked to smoking (11).

EGFR is a cell-surface tyrosine kinase receptor that can activate pathways associated with cell growth and proliferation when it is activated. Mutations of EGFR in malignancies result in uncontrolled cell division via constant activation. EGFR gene mutations are present in 10–15 percent of lung cancer adenocarcinoma patients of European and Asian descent who have never smoked and are female (12-14). Mutation testing is critical for identifying patients who would benefit from targeted tyrosine kinase inhibitor therapy despite the prevalence of these features. These exons code for a kinase domain component of the EGFR gene. The most prevalent site for EGFR mutations that provide susceptibility to EGFR tyrosine kinase inhibitors is exons 18–21. Ninety percent of these mutations include exon 19 deletions and exon 21 L858R point mutations, which are associated with a 70% response rate in erlotinib/gefitinib-treated patients (15).

Drug repositioning, also known as drug repurposing, is the investigation of existing drugs for new therapeutic applications (16). Numerous strategies are utilized to discover new drugs and predict the pharmacokinetic properties of substances. This investigation discovered 185 antiviral pharmacological compounds having antiviral activity. We explore the anticancer effect of antiviral pharmacological agents against the EGFR kinase domain in non-small cell lung cancer. The EGFR kinase domain (1XKK) 3D protein structure was obtained from the RCSB PDB collection. First, a toxicity investigation of the identified antiviral medication molecules was conducted. After toxicity screening, an ADME study and Lipinski's rule of five were made, and the remaining drugs were docked to the EGFR kinase domain (PDB ID: 1XKK). The Autodock Vina application was deployed for docking. The discovery of docking was examined using the application Discovery Studio 2019. Both Afatinib Dimaleate and Gemcitabine are the most popular medication choices for treating NSCLC, so we chose them as the standard. The binding affinity of Afatinib Dimaleate and Gemcitabine for the active site of the EGFR kinase domain was 8.9 and 8.4, respectively. Diphyllin, in contrast, has a binding affinity of -10 kcal/mol for the active area of the EGFR kinase domain. In addition, the discovered hit compound (Diphyllin) has more hydrogen bonds than our chosen benchmark molecules, indicating increased stability. To assess the dynamic motions of the ligand-protein complex, root means square fluctuation was analyzed. Diphyllin has significant potential as an anti-NSCLC drug due to its ability to inhibit the activity of the EGFR kinase domain of the target protein, which plays a crucial role in the progression of NSCLC. To further validate our promising preliminary and in-silico findings, in-vitro and in-vivo investigations are required

2. Material and methods

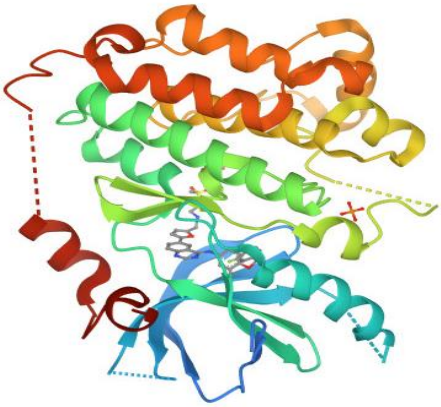
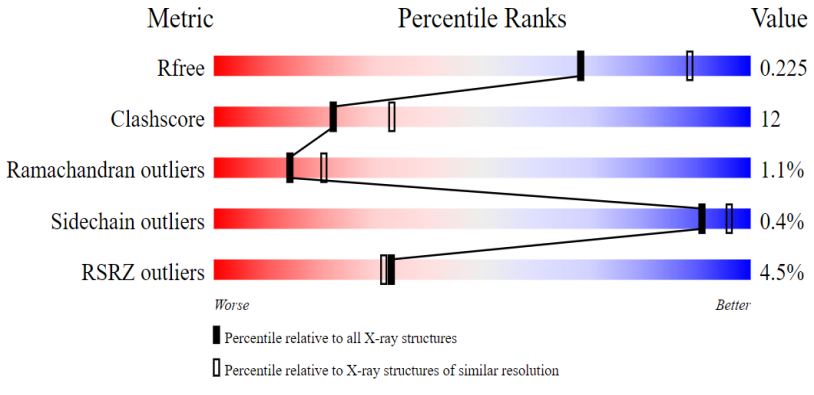
2.1. Selection of compounds

We selected 185 antiviral drug compounds by a comprehensive literature search of recent years across many databases in an effort to discover a possible therapeutic antiviral drug compound and repurpose it against non-small-cell lung cancer.

2.2. Protein preparation

The EGFR kinase domain's (3D) structure (1XKK) was retrieved from the PDBJ database (https://pdbj.org/) (17). The contaminating compounds were eliminated using the Biovia Discovery Studio 2019 program (18) (Table 1).

Table 1 Information about the target protein (EGFR kinase domain)

Title	EGFR Kinase Domain
Structure	
Classification	Transferase
PDB ID	1XKK
MMDB ID	31111
PUBMED ID	15374980
Experimental Method	X-Ray diffraction
Resolution	2.4 Å
Source Organism	Homo sapiens
Structure validation	

2.3. Organ toxicity and toxicity endpoints analysis

Toxicity is a drug's capacity to poison the body. A drug's toxicity can impact an entire organism (animal, plant, bacteria). To examine the toxicity of a pharmacological molecule, the PKCSM web server (http://biosig.unimelb.edu.au/pkcsm/prediction) is an online database that can simply analyze the drug molecule by entering its canonical smiles (19). PKCSM includes all toxicity parameters, such as molecular weight, AMES toxicity, oral rat acute toxicity (LD50), hepatotoxicity, minnow toxicity HERG-I inhibitor, maximum tolerated dose (human), etc.

2.4. ADME screening

An in-silico integrative model of absorption, distribution, metabolism, and excretion (ADME) was utilized to explore potential orally bioactive antiviral medication molecules. Using SWISSADME prediction (http://www.swissadme.ch), drug-like characteristics were computed using Lipinski's rule of five (20).

2.5. Molecular docking and visualization

After ADMET screening, specific protein-ligand docking was performed using Autodock Vina (21) and PyRx 8.0 to identify a hit drug that could potentially limit the activity of a protein to target non-small cell lung cancer (NSCLC) with low binding affinity values. A specific docking approach is achieved by configuring the grid box to cover only the protein binding pocket (Table 2). The software Biovia Discovery Studio 2019 was used to assess the binding site and chemical interactions created between proteins and ligands.

Table 2 Binding pocket position and grid setting for specific docking

Target Protein	**Binding pocket**	**Grid**	
Center			Dimension
EGFR kinase domain (1XKK)	Leu718, Val726, Gly745, Leu788, Gly796, Cys797, Leu844, Asp855	X: 16.3451 Y: 32.3674 Z: 35.9235	X: 31.3579 Y: 30.0286 Z: 34.7935

2.6. Target prediction

Swiss Target Prediction (http://www.swisstargetprediction.ch) is a web-based tool for predicting the macromolecular target of a tiny bioactive chemical (22). Identifying the phenotypical side effects and potential cross-reactivity of tiny biomolecules is essential. It is founded on the similarity principle, which posits that two molecules with similar structures are likely to have comparable properties. In order to forecast the target of our hit compound, the canonical smile is entered and processed in the search field.

2.7. Molecular Dynamics simulations

Using the CABS-flex 2.0 server, molecular dynamics simulations were performed to analyze the structural flexibility and stability of the ligand-protein complex (23). Using the default settings, the root-mean-square fluctuations (RMSF) were calculated based on the MD trajectory or NMR ensemble.

3. Results and discussion

3.1. Organ toxicity and toxicity endpoints analysis

Using the PKCSM online server, the toxicity study was conducted in order to anticipate the safety features of the selected antiviral medication compounds. As demonstrated in Table 3, the key toxicity endpoints considered included molecular weight, AMES toxicity, oral rat acute toxicity (LD50), hepatotoxicity, HERG-I inhibitor, maximum tolerated dose (human), etc.

Table 3 Toxicity analysis of the selected antiviral drug compounds

S. N.	Compounds	AMES toxicity	Max. tolerated dose for human (log mg/kg/ day)	hERG-I inhibitor	hERG-II inhibitor	Oral Rat Acute Toxicity (LD50)(mol/ kg)	Hepatotoxicity	Skin Sensitization
1.	Ritonavir	No	0.472	No	Yes	2.083	Yes	No
2.	Mericitabine	No	0.902	No	No	1.849	Yes	No
3.	Deleobuvir	No	0.305	No	No	2.522	No	No
4.	ABT- 333	No	0.149	No	Yes	3.081	Yes	No
5.	Ledipasvir	No	0.438	No	Yes	2.482	No	No
6.	Daclatasvir	No	0.437	No	Yes	2.485	No	No
7.	ABT	No	0.073	No	Yes	2.557	Yes	No
8.	Telaprevir	No	-0.94	No	No	4.624	Yes	No
9.	Boceprevir	No	-1.248	No	No	3.692	Yes	No
10.	Simeprevir	No	0.083	No	Yes	3.212	Yes	No
11.	Faldaprevir	No	0.752	No	No	2.496	Yes	No
12.	Vaniprevir	No	-1.583	No	Yes	4.704	Yes	No
13.	Samatasvir	No	0.438	No	Yes	2.482	Yes	No
14.	MK- 5172	No	-0.781	No	No	3.477	Yes	No
15.	MK- 8742	No	0.438	No	Yes	2.483	Yes	No
16.	AZT	No	0.656	No	No	2.298	Yes	No
17.	Ganciclovir	No	0.417	No	No	2.277	Yes	No
18.	Zanamivir	No	0.454	No	No	2.483	No	No
19.	Peramivir	No	0.462	No	No	2.468	No	No
20.	Oseltamivir	No	0.475	No	No	2.677	No	No
21.	Maraviroc	No	-0.962	No	Yes	2.808	Yes	No
22.	Zidovudine	No	0.656	No	No	2.298	Yes	No
23.	Zalcitabine	No	1.022	No	No	1.809	Yes	No
24.	Didanosine	Yes	0.914	No	No	1.742	Yes	No
25.	Stavudine	No	0.822	No	No	2.048	Yes	No
26.	Lamivudine	No	1.006	No	No	1.834	Yes	No
27.	Emtricitabine	No	1.054	No	No	1.761	Yes	No
28.	Carbovir	No	0.727	No	No	2.457	Yes	No
29.	Nevirapine	No	-0.167	No	No	2.715	Yes	No
30.	Efavirenz	No	0.111	No	No	2.768	No	No
31.	Delavirdine	No	0.041	No	Yes	2.49	Yes	No
32.	Etravirine	No	0.417	No	Yes	2.873	Yes	No

33.	Raltegravir	No	0.603	No	No	1.707	Yes	No
34.	Amprenavir	No	-0.633	No	No	2.177	Yes	No
35.	Nelfinavir	No	-0.576	No	Yes	2.54	Yes	No
36.	Zidovudine	No	0.656	No	No	2.298	Yes	No
37.	Interferon α-2B	Yes	0.988	No	No	2.368	Yes	No
38.	Interferon α-N3	No	0.437	No	Yes	2.485	No	No
39.	Ganciclovir Sodium	No	0.417	No	No	2.277	Yes	No
40.	Famciclovir	Yes	0.942	No	No	2.215	Yes	No
41.	Foscarnet sodium	Yes	0.678	No	No	0.96	No	No
42.	Didanosine	Yes	0.914	No	No	1.742	Yes	No
43.	Valacyclovir hydrochloride	No	0.537	No	No	2.284	Yes	No
44.	Lamivudine	No	1.006	No	No	1.834	Yes	No
45.	Rimantadine	No	0.41	No	No	2.771	No	Yes
46.	Saquinavir Mesylate	No	0.157	No	Yes	2.621	Yes	No
47.	Indinavir sulfate	No	0.347	No	Yes	2.673	Yes	No
48.	Nevirapine	No	- 0.167	No	No	2.715	Yes	No
49.	Cidofovir	No	0.187	No	No	1.74	Yes	No
50.	Penciclovir	Yes	0.481	No	No	2.294	Yes	No
51.	Imiquimod	Yes	0.675	No	No	2.665	Yes	No
52.	Nelfinavir Mesylate	No	-0.227	No	Yes	2.436	Yes	No
53.	Delavirdine Mesylate	No	0.475	No	No	2.464	Yes	No
54.	Interferon Alfacon-1	No	0.437	No	Yes	2.485	No	No
55.	Palivizumab	Yes	0.914	No	No	1.742	Yes	No
56.	Ribavirin	No	1.011	No	No	1.988	No	No
57.	Fomivirsen Sodium	Yes	0.438	No	Yes	2.482	No	No
58.	Lamivudine	No	1.006	No	No	1.834	Yes	No
59.	Abacavir sulfate	No	0.443	No	No	2.474	No	No
60.	Didanosine	Yes	0.914	No	No	1.742	Yes	No
61.	Lopinavir	No	-0.297	No	Yes	2.382	Yes	No
62.	Pegi interferon α-2B	No	0.437	No	Yes	2.485	No	No
63.	Valganciclovir Hydrochloride	No	0.537	No	No	2.284	Yes	No
64.	Tenofovir Disoproxil Fumarate	No	0.421	No	No	2.476	Yes	No
65.	Adefovir Dipivoxil	No	0.543	No	No	2.38	Yes	No
66.	Enfuvirtide	No	0.438	No	No	2.482	No	No
67.	Fosamprenavir Calcium	No	-0.487	No	No	2.078	Yes	No
68.	Pegi interferon α-2A	Yes	0.914	No	No	1.742	Yes	No
69.	Atazanavir Sulfate	No	0.296	No	No	2.629	Yes	No
70.	Emtricitabine	No	1.054	No	No	1.761	Yes	No
71.	Entecavir	No	0.282	No	No	2.315	Yes	No

72.	Tipranavir	No	-0.354	No	Yes	2.367	Yes	No
73.	Darunavir	No	-0.763	No	No	2.107	Yes	No
74.	Telbivudine	No	1.079	No	No	2.054	Yes	No
75.	Sinecatchins	Yes	0.914	No	No	1.742	Yes	No
76.	Raltegravir Potassium	No	0.584	No	No	1.688	Yes	No
77.	Etravirine	No	0.417	No	Yes	2.873	Yes	No
78.	Hydrocortisone	No	-0.183	No	No	2.088	No	No
79.	Boceprevir	No	-1.248	No	No	3.692	Yes	No
80.	Rilpivirine Hydrochloride	No	0.112	No	No	2.629	Yes	No
81.	Telaprevir	No	-0.94	No	No	4.624	Yes	No
82.	Cobicistat	No	-0.263	No	Yes	2.794	Yes	No
83.	Elvitegravir	No	0.87	No	No	2.377	Yes	No
84.	Dolutegravir Sodium	No	-0.097	No	No	1.739	Yes	No
85.	Simeprevir Sodium	No	0.087	No	Yes	3.043	Yes	No
86.	EIPA	Yes	1.315	No	No	2.022	No	No
87.	Sofosbuvir	No	1.049	No	No	2.31	Yes	No
88.	Abacavi	No	0.443	No	No	2.474	No	No
89.	Ledipasvir	No	0.438	No	Yes	2.482	No	No
90	Peramivir	No	0.462	No	No	2.486	No	No
91.	Pimodivir	No	0.731	No	No	2.561	Yes	No
92.	Fludase	No	0.752	No	Yes	2.68	No	No
93.	Laninamivir Octanoate	No	0.452	No	No	2.485	Yes	No
94.	Radavirsen	Yes	0.438	No	Yes	2.482	No	No
95.	Presatovir	No	-0.592	No	Yes	2.677	Yes	No
96.	Lumicitabine	No	0.633	No	No	2.183	Yes	No
97.	ALX-0171	Yes	0.438	No	Yes	2.482	No	No
98.	Tecovirimat	No	-0.63	No	No	2.743	No	No
99.	Modipafant	No	0.126	No	Yes	2.484	Yes	No
100.	Gelgosivir	Yes	0.914	No	No	1.742	Yes	No
101.	NT-300	No	0.584	No	No	1.688	Yes	No
102.	Pritelivir	No	-0.231	No	No	2.373	Yes	No
103.	Ranpirn	No	0.545	Yes	Yes	2.599	No	No
104.	Maribovir	No	0.752	No	Yes	2.68	No	No
105.	Cyclopropavir	Yes	0.704	No	No	2.464	Yes	No
106.	Brincidofovir	No	0.767	No	No	2.531	Yes	No
107.	Virolym M	No	0.112	No	No	2.629	Yes	No
108.	Lonafamib	No	1.054	No	No	1.761	Yes	No
109.	Virolym C	No	-0.94	No	No	4.624	Yes	No
110.	Pegylated IFN-λ	Yes	0.438	No	Yes	2.482	No	No

111.	Z Mapp	No	1.066	No	No	1.867	No	No
112.	SB206	No	0.437	No	Yes	2.485	No	No
113.	Tenofovir Alafenamide	Yes	0.639	No	Yes	2.347	Yes	No
114.	Atazanavir	No	-0.16	No	No	2.665	Yes	No
115.	Bictegravir	No	-0.016	No	No	2.097	Yes	No
116.	Ibalizumab	No	0.112	No	No	2.629	Yes	No
117.	Dasabu	No	0.086	No	Yes	3.485	Yes	No
118.	Ombitasvir	No	0.073	No	Yes	2.557	Yes	No
119.	Daclatasvir Dihydro chloride	No	0.437	No	Yes	2.485	No	No
120.	Grazoprevir	No	-0.913	No	No	3.662	Yes	No
121.	Velpatasvir	No	0.438	No	Yes	2.482	No	No
122.	Tenofovir Alafenamide fumarate	No	0.438	No	No	2.482	No	No
123.	Voxilaprevir	No	-0.58	No	Yes	3.902	Yes	No
124.	Glecaprevir	No	-0.738	No	Yes	3.812	Yes	No
125.	Pibrentasvir	No	0.436	No	Yes	2.483	Yes	No
126.	Letermovir	No	0.752	No	Yes	2.68	No	No
127.	ABT- 263	No	-0.039	No	Yes	2.305	Yes	No
128.	Niclosamide	Yes	0.333	No	No	2.918	No	No
129.	Glycyrrhizin	No	0.389	No	No	2.48	No	No
130.	Monensin	No	-0.375	No	No	3.277	No	No
131.	Tilorone	Yes	0.27	Yes	Yes	2.91	Yes	No
132.	Aprotinin	No	0.438	No	No	2.428	Yes	No
133.	Eflornithine	No	0.814	No	No	2.306	No	No
134.	Oritavancin	No	0.438	No	No	2.482	No	No
135.	Topotecan	No	-0.031	No	Yes	3.061	Yes	No
136.	Bartezomib	No	-0.94	No	No	4.624	Yes	No
137.	Ivermectin	No	-1.454	No	No	3.013	Yes	No
138.	Raloxifene	Yes	0.164	No	Yes	2.495	Yes	No
139.	Silvestrol	No	0.312	No	Yes	3.073	No	No
140.	Sunitinib	No	-0.291	No	Yes	2.327	Yes	No
141.	Suramin	No	0.438	No	Yes	2.482	No	No
142.	Obatoclax	No	0.406	No	No	2.672	Yes	No
143.	Nelfinavir	No	-0.576	No	Yes	2.54	Yes	No
144.	Simvastatin	No	-0.452	No	No	2.057	No	No
145.	Itraconazole	No	0.91	No	Yes	2.966	Yes	No
146.	Emetine	No	-0.019	No	Yes	2.793	No	No
147.	Sorafenib	No	0.253	No	yes	2.14	Yes	No
148.	Mitoxantrone	No	0.689	No	Yes	2.499	Yes	No
149.	Novobiocin	No	0.475	No	Yes	2.714	Yes	No

150.	Labyrinthopeptin A1	Yes	0.438	No	Yes	2.482	No	No
151.	Camptothecin	No	-0.354	No	No	2.565	Yes	No
152.	Minocycline	No	0.127	No	No	2.025	No	No
153.	Nitazoxaniole	No	0.752	No	Yes	2.68	No	No
154.	Amodiaquine	No	0.095	No	Yes	2.686	Yes	No
155.	Brequinar	No	0.576	No	No	2.553	Yes	No
156.	Luteolin	No	0.499	No	No	2.455	No	No
157.	Azacytidine	No	1.245	No	No	2.33	No	No
158.	Emodine	Yes	-0.089	No	No	2.329	No	No
159.	Dasatinib	No	0.107	No	No	2.676	Yes	No
160.	Gefitinib	No	0.011	No	Yes	2.859	Yes	No
161.	Genistin	No	0.421	No	No	2.643	No	No
162.	Flavopiridol	No	0.169	No	Yes	2.803	Yes	No
163.	Metformin	Yes	0.902	No	No	2.453	No	Yes
164.	Fluvastatin	No	0.299	No	No	2.615	Yes	No
165.	Artesunate	No	0.256	No	No	3.112	No	No
166.	BCX-4430	No	0.485	No	No	2.77	Yes	No
167.	Barnidipine	Yes	-0.472	No	Yes	2.972	No	No
168.	Azinomycin	No	0.095	No	Yes	2.803	Yes	No
169.	Chloroquine	Yes	-0.167	No	Yes	2.85	Yes	No
170.	Posaconazole	No	0.875	No	Yes	2.938	Yes	No
171.	Pentosan polysulfate	No	0.438	No	No	2.482	No	No
172.	Itraconazole	No	0.91	No	Yes	2.966	Yes	No
173.	4-HPR	No	-0.213	No	Yes	2.315	Yes	No
174.	N-MCT	No	0.853	No	No	2.068	Yes	No
175.	Hexachlorophene	No	0.752	No	Yes	2.68	No	No
176.	Kasugamycin	No	1.086	No	No	2.117	No	No
177.	EIPA	Yes	1.315	No	No	2.022	No	No
178.	Esomeprazole	Yes	0.5	No	No	2.201	Yes	No
179.	Diphyllin	Yes	-0.336	No	Yes	2.308	No	No
180.	Doxycycline	No	0.294	No	No	2.23	No	No
181.	Amiodarone	No	0.545	Yes	Yes	2.599	No	No
182.	Berberine	Yes	0.144	No	No	2.571	Yes	No
183.	Fluoxetine	No	0.535	No	Yes	2.877	Yes	No
184.	Ritonavir	No	0.472	No	Yes	2.083	Yes	No
185.	Sunitinib	No	-0.291	No	Yes	2.327	Yes	No

138 antiviral medication compounds cause hepatotoxicity, whereas 48 antiviral drug compounds do not cause hepatotoxicity. Only those chemicals were examined further for ADME and the docking investigation that meets the toxicity endpoint safety requirements.

3.2. ADME analysis

After toxicity analysis, we performed ADME (absorption, distribution, metabolism, and excretion) screening, which aids in identifying compounds with drug-like properties. The selected ligands that did not violate Lipinski's criteria might be utilized for future molecular docking research with the target protein. The results of the ADME analysis (Table 4) are as follows:

Table 4 ADME analysis of selected antiviral drug compounds

S. No.	Compounds name	Mol. Wt. (g/mol)	Consensus Log Po/w	H-bond acceptors	H-bond donors	Lipinski violation	Bio-availability score	Solubility (mg/ml)
1	Deleobuvir	653.57	5.10	6	2	Yes	0.56	3.94e-10
2	Ledipasvir	86.13	1.14	1	0	Yes	0.55	1.12e-01
3	Daclatasvir	738.87	4.06	8	4	No	0.17	3.56e-10
4	Zanamivir	44.05	0.07	1	0	Yes	0.55	1.04e+00
5	Peramivir	170.29	2.94	1	1	Yes	0.55	5.46e-03
6	Oseltamivir	312.40	1.43	5	2	Yes	0.55	3.37e-03
7	Efavirenz	315.67	3.80	5	1	Yes	0.55	1.64e-05
8	Foscarnet sodium	191.95	-1.33	5	0	Yes	0.55	2.11e+01
9	Rimantadine	179.30	2.62	1	1	Yes	0.55	9.53e-03
10	Ribavirin	244.20	-2.18	7	4	Yes	0.55	5.73e+01
11	Fomivirsen Sodium	499.41	1.33	9	1	Yes	0.11	1.13e-01
12	Abacavir sulfate	670.74	1.02	12	8	No	0.17	1.21e-02
13	Enfuvirtide	3562.8	-8.79	54	50	No	0.11	3.33e-20
14	Hydrocortisone	286.41	3.46	2	0	Yes	0.55	3.96e-04
15	EIPA	185.61	0.97	3	1	Yes	0.55	8.67e-04
16	Abacavir sulfate	672.76	0.17	11	9	No	0.17	3.94e-01
17	Ledipasvir	889	6.38	10	4	No	0.17	4.71e-13
18	Peramivir	328.41	0.07	5	5	Yes	0.55	2.73e-01
19	Radavirsen	7076.0	-27.34	158	29	No	0.17	2.29e-06
20	Tecovirimat	376.33	2.77	6	1	Yes	0.55	2.96e-04
21	Z Mapp	80.13	1.63	0	0	Yes	0.55	8.00e-01
22	Daclatasvir Dihydrochloride	44.10	1.54	0	0	Yes	0.55	1.50e-0
23	Velpatasvir	883.00	5.02	10	4	No	0.17	6.12e-13
24	Tenofovir Alafenamide fumarate	116.16	1.42	2	0	Yes	0.55	7.41e-02
25	Niclosamide	327.12	2.95	4	2	Yes	0.55	1.18e-05
26	Glycyrrhizin	822.93	1.55	16	8	No	0.11	4.10e-02
27	Monensin	670.87	3.74	11	4	No	0.11	3.27e-04
28	Eflornithine	182.17	-0.87	6	3	Yes	0.55	3.93e-01
29	Oritavancin	1793.10	0.99	29	20	No	0.17	1.84e-16

30	Silvestrol	449.38	2.23	8	2	Yes	0.55	2.22e-05
31	Suramin	1297.28	2.59	23	12	No	0.11	1.77e-14
32	Simvastatin	418.57	4.12	5	1	Yes	0.55	2.74e-04
33	Emetine	480.64	4.19	6	1	Yes	0.55	2.00e-08
34	Minocycline	457.48	0.22	8	5	Yes	0.11	7.60e-03
35	Luteolin	286.24	1.73	6	4	Yes	0.55	1.50e-04
36	Azacytidine	244.20	-2.15	7	4	Yes	0.55	2.42e+01
37	Emodine	270.24	1.50	5	3	Yes	0.55	1.19e-04
38	Genistin	432.38	0.35	10	6	Yes	0.55	2.03e-03
39	Metformin	129.16	-0.89	2	3	Yes	0.55	3.79e+00
40	Artesunate	384.42	2.13	8	1	Yes	0.56	1.88e-02
41	Barnidipine	95.14	1.27	0	1	Yes	0.55	1.25e-01
42	Pentosan polysulfate	86.13	1.35	1	0	Yes	0.55	1.25e-01
43	Hexachlorophene	407.91	5.07	2	2	Yes	0.55	1.64e-08
44	Kasugamycin	379.36	-4.24	11	8	No	0.17	4.86e+03
45	Diphyllin	380.35	3.23	7	1	Yes	0.55	7.21e-07
46	Doxycycline	444.43	-0.22	9	6	Yes	0.11	4.24e-02
47	Amiodarone	645.31	6.49	4	0	No	0.17	4.37e-11
48	Barnidipine	95.14	1.27	0	1	Yes	0.55	1.25e-01

In the screening criteria for chosen antiviral medication compounds, we only considered for further molecular docking those compounds that did not cause hepatotoxicity and met the drug-likeness property according to Lipinski's Rule of five. We discovered that 34 antiviral medication compounds out of 185 do not cause hepatotoxicity and also adhere to Lipinski's Rule of five.

3.3. Molecular Docking

The conformations of docked molecules were ordered by their energies and then selected via superposition based on their similarity to the co-crystallized ligand. The docking of ligands was visualized using UCSF Chimera. The results of molecular docking are reported in Table 5. Discovery Studio Visualizer was used to visualize hydrogen bonds around hydrophobic amino acids that interact (Figure 1).

Table 5 Molecular docking results of antiviral drug compounds against EGFR kinase domain (1XKK)

S. No.	Compounds name	Binding affinity (kcal/mol)
Standard compounds		
	Afatinib dimaleate	-8.9
	Gemcitabine	-8.4
Screened antiviral drug compounds		
	Deleobuvir	-5.9
	Ledipasvir	-8
	Zanamivir	-7.2
	Peramivir	-6.2

	Oseltamivir	-7.6
	Efavirenz	-6.4
	Foscarnet sodium	-8.1
	Rimantadine	-6.3
	Ribavirin	-7.6
	Fomivirsen sodium	-6.9
	Hydrocortisone	-6.8
	EIPA	-8.1
	Peramivir	-7.8
	Tecovirimat	-7.3
	Z Mapp	-7
	Daclatasvir dihydrochloride	-6.1
	Tenofovir alafenamide fumarate	-7.4
	Niclosamide	-6.2
	Eflornithine	-7.1
	Simvastatin	-5.9
	Emetine	-8.2
	Minocycline	-6.2
	Luteolin	-5.4
	Azacytidine	-5.6
	Emodine	-6.4
	Genistin	-7.1
	Metformin	-6.3
	Artesunate	-6.6
	Barnidipine	-6.9
	Pentosan polysulfate	-6.8
	Hexachlorophene	-5.9
	Diphyllin	-10.0
	Doxycycline	-5.8
	Barnidipine	-7.8

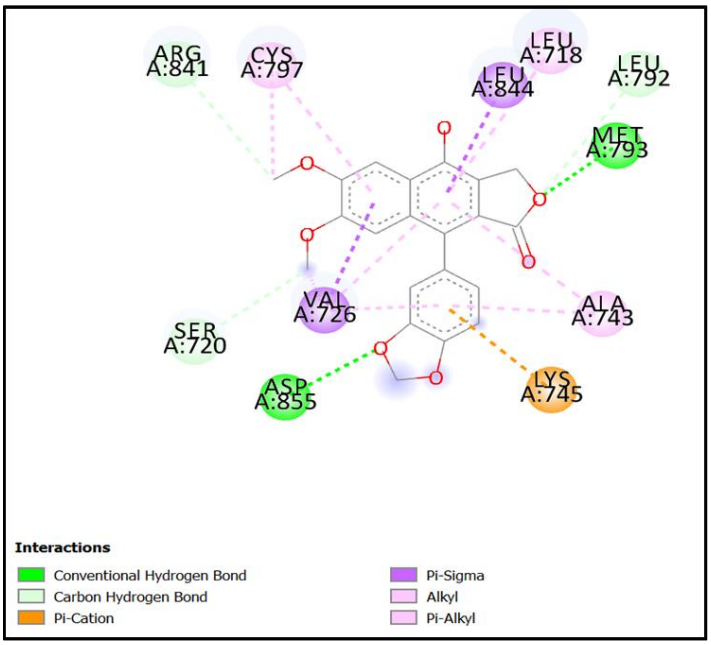


Figure 1 Protein-ligand interactions between Diphyllin in complex with EGFR kinase domain (1XKK)

3.4. Molecular Target Analysis

After the screening and molecular docking study, the molecular targets of our hit chemical, Diphyllin (Figure 2), are investigated further. 40 percent of enzymes, 20 percent of kinase, 13.3 percent of Cytochrome P450, 6.7% of Oxidoreductase, 6.7% of Phosphodiesterase, 6.7% of Phosphatase, and 6.7% of Ligand-gated ion channel were predicted for Diphyllin.

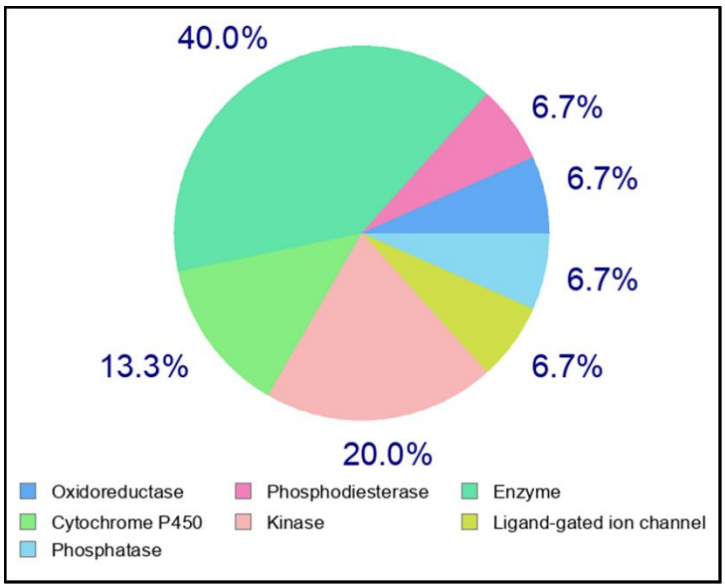


Figure 2 Molecular targets of Diphyllin

3.5. Molecular Dynamics simulations

Figure 3 depicts the molecular dynamics investigations of Diphyllin in contact with the EGFR kinase domain of the target protein (1XKK). The RMSF graph illustrated the stability and adaptability of the amino acids in the structure of the hit compound with bound amino acids.

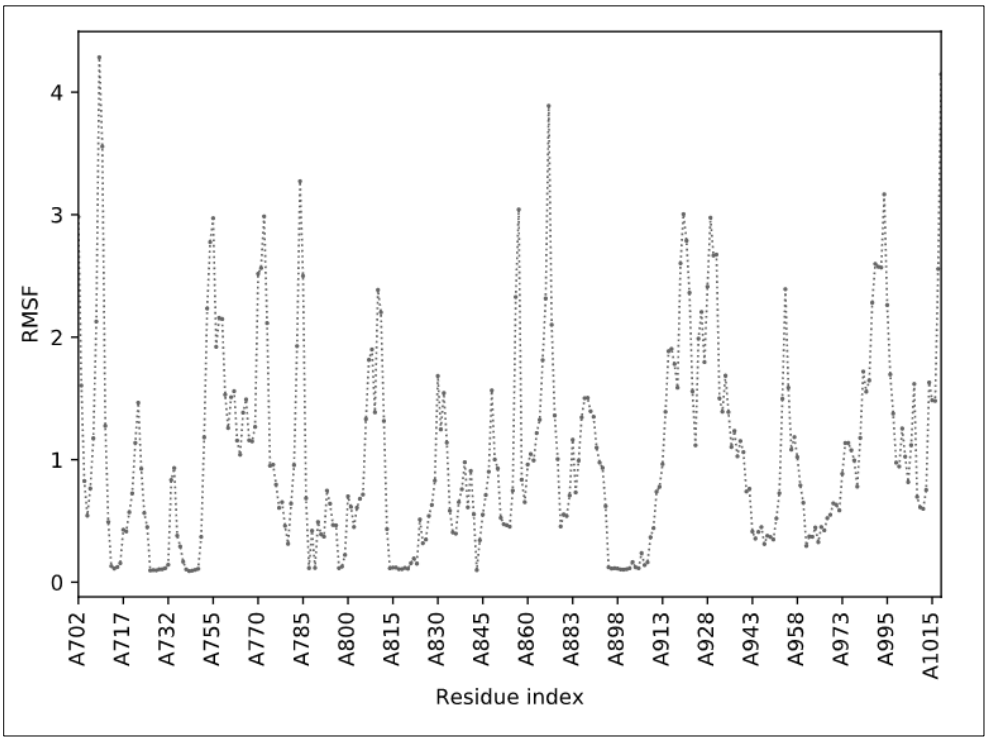


Figure 3 RMSF graph of Diphyllin in complex with EGFR kinase domain (1XKK)

4. Conclusion

Significant progress has been made in reducing occupational health risks associated with lung cancer, especially smoking, and preventing several disorders. In recent decades, targeted therapy and immunotherapy have significantly contributed to the development of lung cancer treatment. EGFR mutations are significant drivers of non-small cell lung cancer, especially in never-smoking Asian females with adenocarcinoma histology. Ten percent of EGFR mutant non-small cell lung cancer patients have a smoking history, and twelve percent are male. In this work, the EGFR kinase domain crystal structure was utilized (PDB ID: 1XKK). This study aimed to develop a potential treatment for non-small cell lung cancer. Initially, an ADME analysis was conducted on the 185 compounds selected. In the screening criteria for these antiviral medication compounds, we only examined those that did not cause hepatotoxicity and met Lipinski's Rule of five for the drug-likeness property. We discovered that 34 antiviral medication compounds out of 185 do not cause hepatotoxicity and also adhere to Lipinski's Rule of five (Table 7). We only consider these chemicals for future molecular docking research. Diphyllin was deemed the optimal molecule by a molecular docking analysis since it had the lowest binding energy and satisfied all of our study conditions. In addition, we investigate the root mean square fluctuation to assess the ligand-protein complex's dynamic movements. Diphyllin has potential as an anti-NSCLC treatment since it inhibits the activity of the EGFR kinase domain among the 185 antiviral medication molecules chosen. In-vitro and in-vivo research is required to validate the promising outcomes of our preliminary and in-silico analyses.

Compliance with ethical standards

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Disclosure of conflict of interest

All the authors disclose no conflicts of interest/competing interests.

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