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Virtual screening, Molecular Docking, Molecular Dynamic and ADME of new pyrazole derivatives as anticancer

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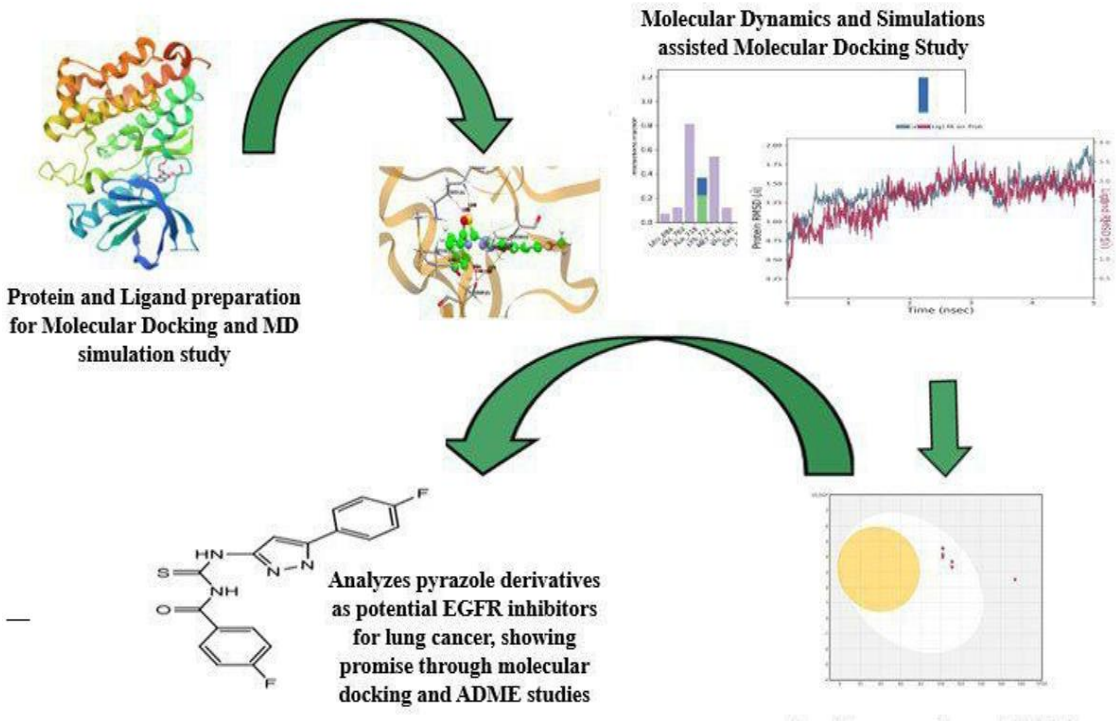
Graphical abstract



Abstract: Cancer poses a significant global health challenge, demanding the continuous development of effective treatments. This paper explores the domains of virtual screening, molecular docking, pharmacokinetic, and anti-cancer estimation of cell-cycle inhibitors as new pyrazole derivatives. Cancer, a complex ailment characterized by uncontrolled cell growth and metastasis, necessitates innovative and safer anticancer drugs. Traditional chemotherapy, while a primary treatment option, faces challenges such as drug resistance. The paper focuses on finding a safer and more effective treatment for lung cancer, the most prevalent and deadly type. NSCLC (non-small cell lung cancer) accounts for about 84% of lung malignancies, with LUAD and LUSC being the predominant subtypes. Despite surgery being a common treatment option for NSCLC, many patients are diagnosed at advanced stages, making radiation and

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chemotherapy the primary treatment modalities. This paper presents emphasizing targeted therapy and the role of epidermal growth factor receptor (EGFR). The study introduces a class of heterocyclic compounds, pyrazole derivatives, that are explored
for their distinctive structures and pharmacological activities against cancer. In silico studies, including molecular docking, molecular dynamics and predictions of ADME of the molecules. The results of the molecular docking studies revealed that all six pyrazole derivatives presented respectable attachment energies with the receptor active pocket compared to erlotinib and were expected to have promising activity with EGFR protein. This paper presents a comprehensive exploration of pyrazole derivatives as potential EGFR inhibitors for lung cancer treatment. The molecular docking and in silico ADME studies collectively suggest the promise of these compounds as anticancer agents.

Keywords: *In silico studies, virtual screening, molecular docking, MDS, pyrazole derivatives, EGFR.*

Highlight

- *New pyrazole derivatives exhibit superior binding affinity compared to the reference drug erlotinib.*
- *These derivatives show potential as effective EGFR inhibitors for lung cancer treatment.*
- *All proposed pyrazole compounds satisfy Lipinski's Rule of Five, indicating favorable drug-like properties.*
- *Molecular dynamics simulations reveal stable binding of compound H5 with an RMSD of approximately 2.5 Å, suggesting robust interaction with the EGFR receptor.*

1. Introduction

Cancer is recognized as one of the world's most basic wellbeing issues and is additionally a critical reason for mortality [1-3]. In the twenty-first century, compelling cancer treatment remains a challenge. More current and more secure anticancer drugs with a wider scale of cytotoxicity to tumor cells are necessary (1). For a long time, chemotherapy has remained the basic choice for cancer treatment in clinical settings, separated from surgical operations and irradiation (2). There are more than a hundred diverse sorts of cancer, all of which are characterized by distorted cell development (3). They vary in the cell growth rate, invasion and spreading to other tissues (4). Lung cancer is the most prevalent sort of cancer, anticipated to result in 1.6 million fatalities each year (5). NSCLC speaks to the critical extent (84%) of lung malignancies, with LUAD and LUSC being the main subtypes (6). The collective influences developing of genotoxicity and/or resistance of the current anticancer specialists are the main contests of present-day medicinal chemistry, leading to an extension of the search for original chemotherapeutic drugs that are secure and productive to anticipate or indeed remedy cancer (7). Quinazoline derivatives are well-known for their anticancer properties. Many derivatives of quinazoline for utilized as anticancer agents and act on the EGFR protein kinase. The Food and Drug Administration (FDA) has authorized many quinazoline derivatives for utilize as anticancer medicines, including Afatinib, Erlotinib, Gefitinib, Lapatinib, and Vandetanib (8).

Pyrazole derivatives are a class of heterocyclic compounds with diverse pharmacological activities, including anticancer properties. The ring demonstrates a pentagonal structure, consisting of a nitrogen (N) atom connected to another nitrogen atom and three carbon (C) atoms. ‘‘Pyrrole-like” is nitrogen atom no. 1 (N1) for the reason that its unshared electrons, which conjugated aromatic system, while N2 atom no.2, exhibits similarities to pyridine and is considered "pyridine-like" as the unshared electrons are not affected by resonance, akin to pyridine systems as shown in figure (2). Owing to the distinctions between the nitrogen atoms, pyrazoles react with both (9). Analyses of the structure-activity relationship have demonstrated that suitable substitution at various positions of the pyrazole ring can notably improve anticancer effectiveness. This type of study often involves in silico approaches such as molecular docking, which assists in predicting ligand-receptor interactions. In drug design, scaffold hopping is a key strategy in molecular discovery and design to improve potency or binding affinity (10).

Molecular docking simulations were studied to understand the molecular core (11). Molecular docking studies are valuable tools for the development of new compounds with the

prediction of their affinity, interaction with receptors, and most significant biological activity. The GOLD genetic algorithm is used to dynamically position ligands within protein binding sites as part of the CCDC GOLD suite (v.5.8.0). It has predictive capabilities for recommending optimal positioning and outcomes during virtual screening (10). The computational physicochemical properties of a compound, such as its level of saturation, lipophilicity, polarity, size, solubility, and flexibility, offer essential data about the likelihood of the compound acting as a pharmaceutical drug in the early stages of its development (11).

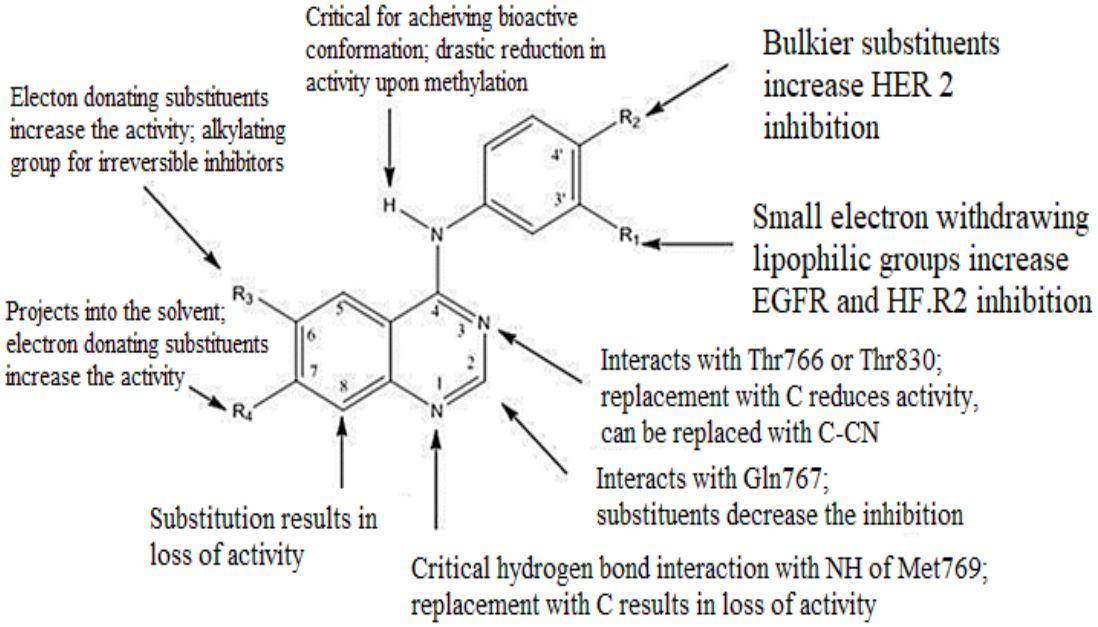


Figure 1. SAR of 4-anilinoquinazoline as EGFR inhibitors.

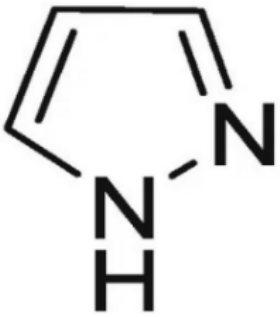


Figure 2. Structure of pyrazole.

Molecular Dynamics (MD) simulations have become a recognized method for understanding macromolecular ligand-receptor interactions. These simulations yield results comparable to biologically relevant ones and offer an advantage over static molecular docking by acknowledging the dynamic nature of proteins (12). Consequently, top-scoring ligands exhibiting promising drug-like properties underwent MD simulations to explore the evolution of receptor binding ability over time. SwissADME is an online tool that offers complimentary entry to a collection of fast and accurate predictive models for physical-chemical properties and drug behavior in the body, drug likeness, and compatibility medicinal chemistry. These models integrate expert methodologies such as the boiled egg, iLog P, and BR (Bioavailability Radar) and ADME (absorption, distribution, metabolism, and excretion) to elucidate the distribution and destiny of pharmaceutical preparations in the body of an organism (13). Inadequate pharmacokinetics (PK) and toxicity are the leading causes of drug discovery setbacks (14). The QSAR/QSPR group has developed methods to predict physicochemical properties in ADME, such as distribution coefficient, solubility, absorption and permeation, ability to pass the blood-brain barrier, elimination, outflow P-glycoprotein (P-gp), and the toxicity of compounds (15). The purpose of this study was to employ the virtual screening to

evaluate of six new pyrazole derivatives through a molecular docking technique with the protein (EGFR) as receptor, and to find a potential lead molecule among proposed compounds with better binding affinities and enhanced molecular-receptor interactions. Additionally, the in-silico ADME and drug similarity properties of the compounds were also assessed

2. Computational Method

The present research investigated the potential efficacy of our suggested compounds through the use of the docking protocol, a technique employed to determine the most favorable arrangement of a ligand when attached to a protein or to create a stable complex. The present study utilized an HP computer system equipped with an Intel® Core i3, 8th generation processor and 12 gigabytes of RAM. The software employed included the licensed GOLD (Genetic Optimization for Ligand Docking) from the CCDC (Cambridge Crystallographic Data Centre) , along with the Hermes visualizer program (version 22.2, Cambridge, England) and ChemDraw version 22.2 (professional edition). Additionally, the ChemOffice suite (version 2022 22.0.0 x64 bit) was utilized for drawing the chemical structures of the ligands. Pharmacokinetic and ADME studies, as well as other physicochemical characteristics of the prepared compounds, were conducted utilizing the online server Swiss ADME (16).

2.1. Molecular docking

Initially, a total of forty-eight pyrazole derivatives were obtained from existing literature, and the chemical structure of our ligands was constructed by professional ChemDraw professional (v.16.0) software (Figure 3-4). Following this, energy minimization for our compounds was performed using Chem3D (v.16.0) and applying the MM2 force field. Subsequently, the recently developed ligands were docked using the 3D structure of the active target: the crystal structure of the protein EGFR (Protein Data bank code: 4HJO) bound to erlotinib (Figure 5).

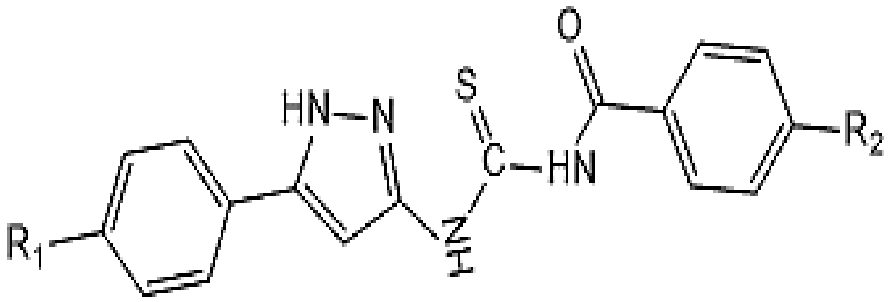
From the protein databank (PDB), the receptors situated on the Hermes module of GOLD are presently operational. Re-docking of the co-crystalized ligands was done to validate the docking process. Further, to ensure the accurate representation of the tautomeric states and ionization of amino acid (AA) residues, polar hydrogen (H) atoms were incorporated. Then, the structure of the EGFR kinase receptor and PDE4A proteins is prepared by removing all crystallographic water molecules except H0H 1104, which is complicated in the active site within the EGFR kinase receptor that mediates the interaction between ligands and proteins. The initial ligand extraction was conducted from the active site of the receptor. In the CCDC GOLD suite, Hermes visualizer software was employed to prepare receptors for docking process Determination of the active site corresponds to primary ligand interaction site. The binding site of protein, measuring 10 A° in size, encompasses all necessary protein residues for the docking process. In the docking method, we set the parameters to default. The team generated 10 poses, setting the highest-ranked solution as the standard, and disabling the initial termination option. The Chem score kinase served as the basis for the researchers' investigation. The ChemPLP scoring function consists of a continuous linear potential. The results were ultimately stored as mol.2 documents, which include knowledge of energy released in the binding process, and the precise locations of binding and poses. We carefully looked at these results to find out how our ligand should best bind and interact with the receptor's amino acid residues (EGFR).

2.2. MD Simulation

The MD (molecular dynamics) was carried out by the Coast program for atomic modeling and drug design with Maestro 11.4 in the Schrodinger software suite (Schrodinger, 2018) on a Windows 7 workstation equipped with an Intel(R) Core (TM) i7 CPU 895 @ 3.4GHz, 32 GB RAM, and a 1TB HD. Classical molecular dynamic (MD) simulations for compound structures were performed using the Desmond program (17). The MD simulations included modeling the structures of compound complexes and enzyme poses, each solvation in an SPC (simple point charge) model within the rectangular container with repeated boundary restrictions. To neutralize the overall charge, sodium or chloride ions were added as needed. The simulations utilized the ensemble NPT in the package of Desmond program for system

reducing and alleviating (17). The simulations ran for 5 nanoseconds, with data being recorded every 100 picoseconds, and maintaining a constant temperature (310 K) and pressure (1.01325 bar) throughout (17).

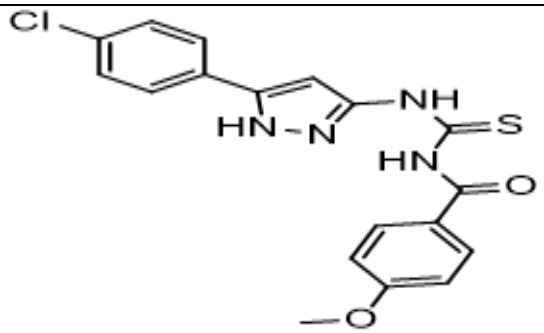
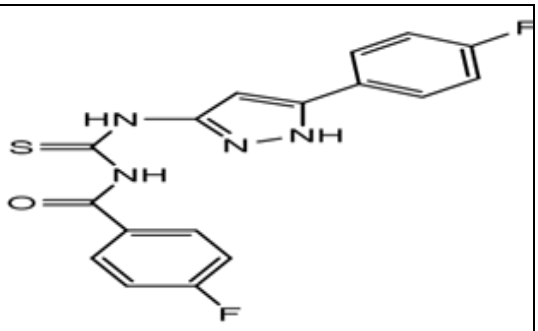
The EGFR protein and ligand's crystal structure was obtained from the PDB with the given designation 4HJO, with a resolution of 2.75 Å. Prior to preparation, the protein underwent optimization and minimization using appropriate software. The structure of ligand is obtained by employing the Lig preprogram for docking, which entailed the hydrogens inclusion to optimize the orientation and ionization position, and the use of low-energy conformations with the Optimized Potentials for Liquid Simulations force field. Established the grid box at 1.20 angstroms with partial atomic charges of (0.27). The most suitable docking orientation was chosen to generate different derivatives using multiple replacement methods. All pyrazole derivatives were preserved and employed for evaluating drug design.

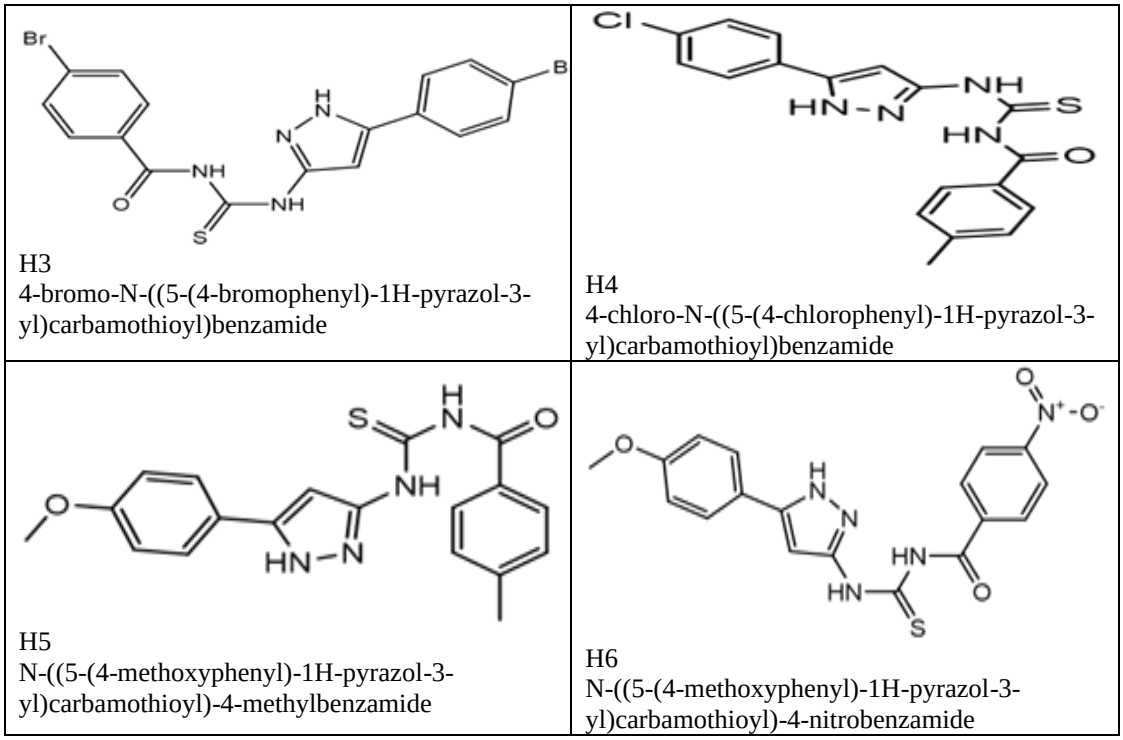


R1= Cl, F, Br, OCH3

R2= F, NO2, CH3, Br, OCH3

Figure 3. General structure of proposed Compounds.

	
H1 4-chloro-N-((5-(4-methoxyphenyl)-1H-pyrazol-3-yl)carbamothioyl)benzamide	H2 4-fluoro-N-((5-(4-fluorophenyl)-1H-pyrazol-3-yl)carbamothioyl)benzamide



H3
4-bromo-N-((5-(4-bromophenyl)-1H-pyrazol-3-yl)carbamothioyl)benzamide

H4
4-chloro-N-((5-(4-chlorophenyl)-1H-pyrazol-3-yl)carbamothioyl)benzamide

H5
N-((5-(4-methoxyphenyl)-1H-pyrazol-3-yl)carbamothioyl)-4-methylbenzamide

H6
N-((5-(4-methoxyphenyl)-1H-pyrazol-3-yl)carbamothioyl)-4-nitrobenzamide

Figure (4), Structures of proposed Molecules.

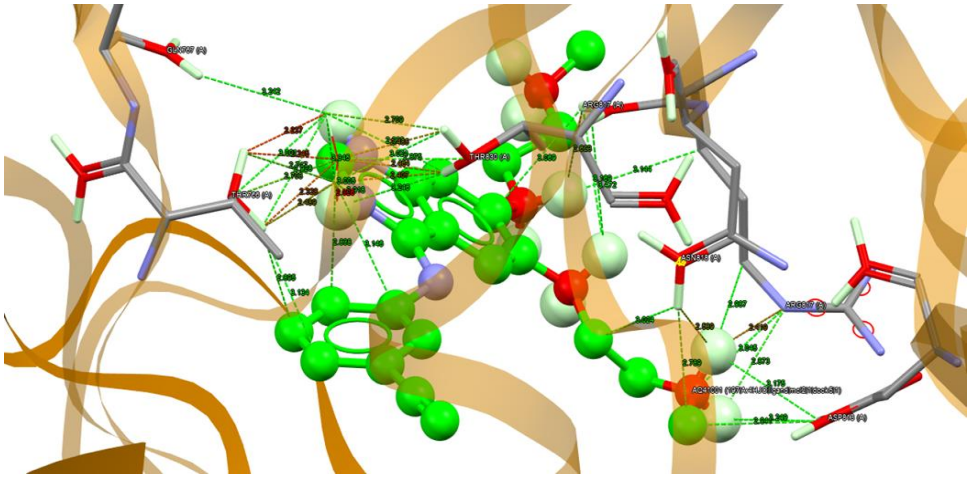


Figure (5), The three-dimensional structure of the hydrogen bond and the short contact interaction of erlotinib bind to the EGFR (Protein Data Dank code: 4HJO).

2.3. ADME prediction

The evaluation of drug pharmacokinetics, which includes ADME processes (absorption, distribution, metabolism, and excretion), is essential, was carried out using the SwissADME tool. Furthermore, factors such as blood-brain barrier penetration, P-gp affinity, and bioavailability were taken into account. All compounds were designed using ChemDraw and then transformed into SMILE names using the SwissADME. Boiled Egg was utilized to assess the lipid solubility and chemical characteristics of small molecules (18). The investigation of ADME prediction facilitated the identification of potential safety issues and the elimination of compounds with unfavorable ADME characteristics, with the aim to reduce the number of experimental drug trials and increase the likelihood of success.

3. Results and discussion

3.1. Molecular Docking

Genetic algorithm GOLD was developed to efficiently dock ligand-protein binding sites (19). Overall, GOLD offers the benefit of accurately

predicting positioning and yielding outstanding results for virtual screening (20). This software is a component of the GOLD suite, which comprises additional software elements such as Hermes, ConQuest, Mercury, CSD Python, Mogul, and others. Using energy optimization methods to alter the structure's shape, we found stable and low-energy conformations. We used molecular interactions to guess the proposed compounds' binding energy and how well they would stick to protein by looking at the compounds' active binding sites. Ranked the results of proposed compounds and erlotinib on how well they could block EGFR by their fitness in forming complexes at the active sites, Table (1) displays the interactions between the docked molecules on the EGFR protein and the PLP fitness score for proposed compounds and erlotinib. The docking results indicate strong binding energies between the designed compounds and the active pocket of the receptor, suggesting potential interactions with the EGFR protein through the formation of hydrogen (H-) bonds and hydrophobic interactions at the active site with amino acid residues.

Table 1. The proficiency of the compounds docked on the EGFR protein was proven using the PLP fitness measurement.

Compoud	PLP fitnesscore	H-bonding interactions	Short contacts interactions
Erlotinib	72.06	ARG817	THR766, THR830, GLN767, ARG817, ARG813, ARG831, ASN818
H1	77.39	THR766 , THR830	THR766, THR830, MET742, LYS721
H2	76.25	NO H-bonding	THR766, THR830, LYS721, ASP831
H3	75.45	LYS721	THR766, THR830, LYS721, MET742, PHE832
H4	76.27	THR766, THR830	THR766, THR830, VAL702, LYS721, LEU694
H5	75.14	THR766, THR830	THR766, THR830, LYS721, VAL702
H6	74.39	THR766, THR830	THR766, THR830, LEU820, LEU834

Docking analysis indicated that THR766, THR830, GLN767, ARG817 ARG813, ARG831, ASN818, MET742, ASP831, MET742, PHE832, VAL702, LYS721, LEU694, LEU820, LEU834 the amino acid components specified in table (1) are located in the active site of EGFR, where they interact with ligands through the formation of hydrogen bonds and show promising anti-cancer activity. All compound gives promise binding affinity to EGFR tyrosine kinase. However, erlotinib give PLP fitness value (72.06) whereas all compounds (H1, H2, H3, H4, H5 and H6) show the highest PLP fitness value (77.09, 76.25, 75.54, 76.27, 75.14 ,74.39) respectively that represent the bonds interaction of high score of final synthesized compounds.

Erlotinib demonstrated a PLP fitness value of 72.06 and formed an H-bond with ARG817, as well as short contacts with THR766, THR830, and GLN767 through an H2O Bridge. Additionally, short contacts were formed through ARG813, ARG817, ARG831, and ASN818. The optimal pose of compound [H1] yielded an average PLP fitness value of 77.09 and formed two H-bonds through an H2O molecule with THR766 and THR830, as well as short contacts with MET742 and LYS7421, as illustrated in Figure (6). The results of molecular docking demonstrated that proposed compounds showed a strong binding affinity to EGFR, exceeding that of erlotinib. This indicates that these compounds can effectively interact with EGFR, an essential focus in the management of cancer.

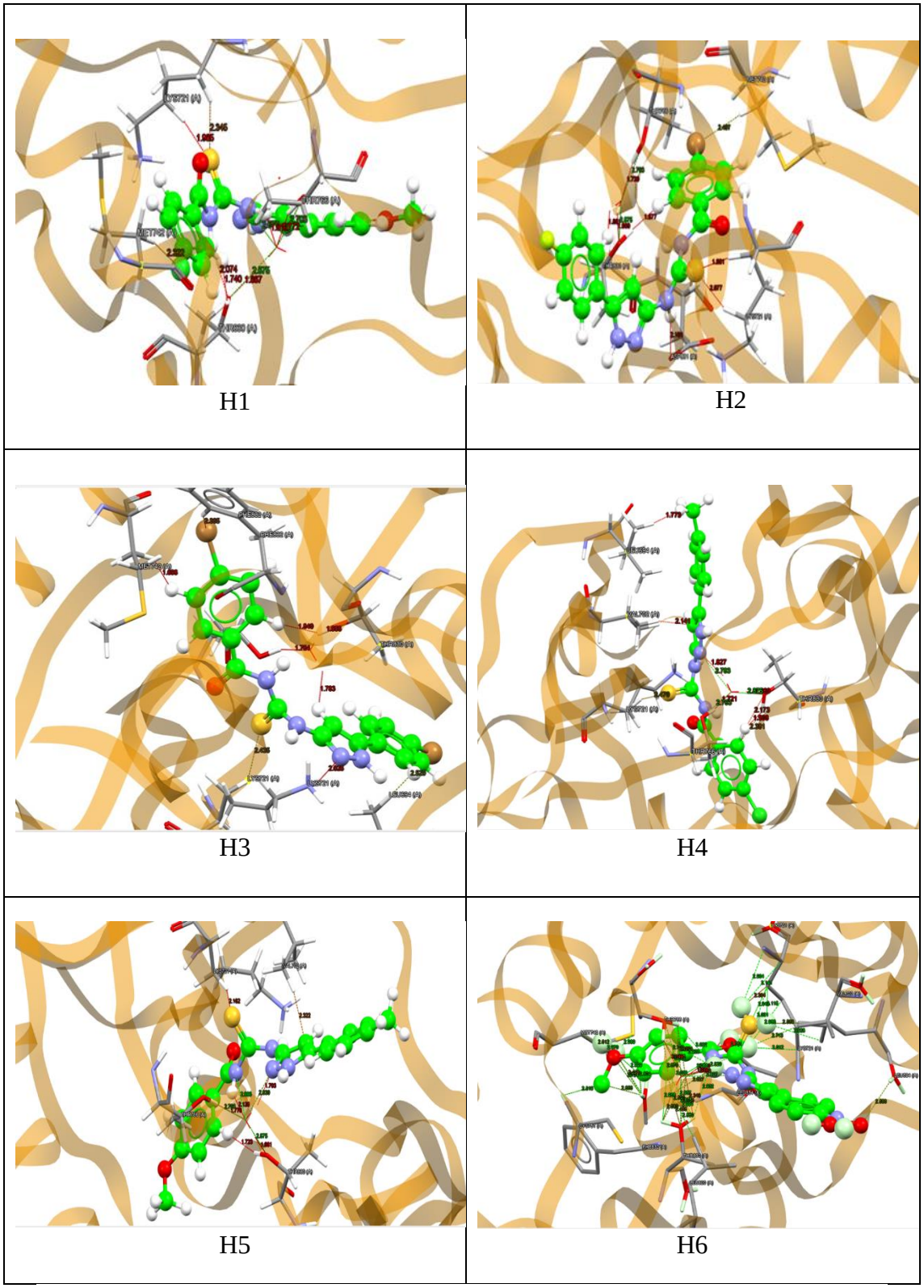


Figure 6. Three-dimensional structural representation chemical interactions of the docking suggested compounds.

3.2. In-silico ADME/Pharmacokinetic Predictions

The effectiveness of an inhibitor as a potential medication cannot be guaranteed by its ability to block a chemical or protein receptor. Therefore,

evaluating ADME and drug-likeness is crucial in the drug discovery process to make well-informed decisions concerning the appropriateness of inhibitors for use in a biological system. (21). The new SwissADME web tool has been used to expedite an ADME study and provides access to several rapid and accurate pred models for the characteristics of the medication including its physical and chemical properties, how it moves through the body, and its chemistry related to medicinal use, as well as how similar it is to other drugs. This includes advanced techniques such as ilog P, BR, and BOILED-Egg analysis (22). The BOILED-Egg analysis for all six proposed compounds in figure (7) indicates that yellow ovals represent molecules likely to pass through the blood brain barrier (BBB) without active effort, white oval-shaped molecules are projected to be absorbed passively through the gastrointestinal tract. Blue dots (P-gp+) represent molecules that are expected to be transported out of the central nervous system (CNS) by the permeability glycoprotein (P-gp), whereas red dots (P-gp-) indicate molecules that are expected not to be transported out of the CNS by P-gp.

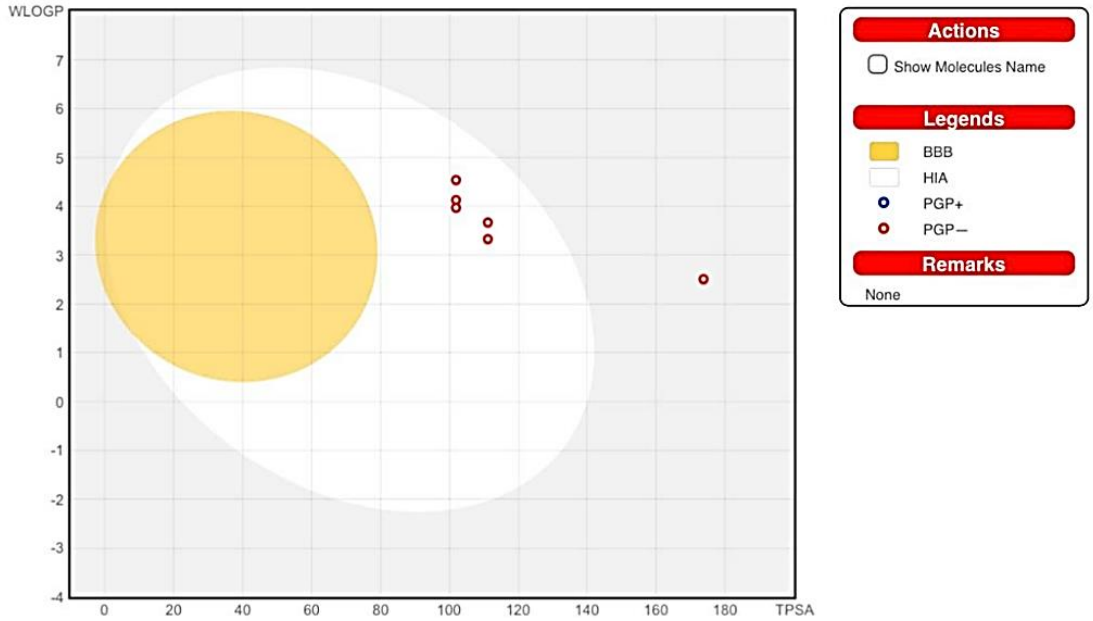


Figure 7. BOILED-Egg analysis for all six compounds.

Lipinski rule states that for a medicine to be suitable for oral administration, it should have no more than 5 hydrogen (H-) bond donors, a log P value of 5 or less, no more than 10 H-bonds acceptors, and a molecular weight of 500 or less (23). The topological polar surface area (TPSA) was computed due to its significant correlation with medication bioavailability. Molecules with a TPSA greater than 140 A^{o} and that are passively absorbed are generally believed to the oral bioavailability is low.

Table (2), Lipinski properties of all proposed compounds analyzed with Swiss-ADME.

Compound	M.W	HBA	HBDs	LogP	Rotatable bonds
Erlotinib	393.44	6	1	3.67	10
H1	386.86	3	3	2.60	7
H2	358.37	4	3	2.49	6

Table (2), Lipinski properties of all proposed compounds analyzed with Swiss-ADME.

Compound	M.W	HBA	HBDs	LogP	Rotatable bonds
H3	480.18	2	3	2.82	6
H4	370.86	2	3	2.89	6
H5	366.44	3	3	2.64	7
H6	382.40	4	4	1.39	7

Table (3), The pharmacokinetic characteristics of all the proposed compounds analyzed with Swiss-ADME.

Name	TPS(Å)	GI absorption	BBB permeability	BS	P-gp substrate
Erlotinib	74.73	High	Yes	0.55	No
H1	111.13	High	No	0.55	No
H2	101.90	High	No	0.55	No
H3	101.90	High	No	0.55	No
H4	101.90	High	No	0.55	No
H5	111.13	High	No	0.55	No
H6	173.74	Low	No	0.55	No

Our research revealed that compounds H1, H2, H3, H4, and H5 all have a TPSA below 140, except for compound H6 which has a TPSA of 173.74 A^{o}. The bioavailability for all compounds was 0.55, suggesting that they can circulate effectively in the body as illustrated in table (3). The proposed compounds also met Lipinski rule, table (2). Additionally, they satisfied the topologic parameters and molecular drug similarity structure keys such as Log P and Log S. findings indicated that the gastrointestinal absorption of the proposed compound suggested that they could be well absorbed from the digestive tract.

3.3. MD simulations

Molecular Dynamics, analyzed how ligand interacts dynamically with crucial residues that affect its effectiveness and presence in the protein's binding pocket. By examining the RMSD plots of compound H5, its binding capability throughout the simulation period on the 4HJO protein. This process helps determine the stability of fragment fluctuations by the simulation's end, based on the chosen ligand structure. The results indicate consistent fluctuations within an acceptable range of 1-3 Å during the simulation. Additionally, The RMSD values remain steady at approximately 2.5 nanoseconds, preserving a consistent alignment of the fluctuations in the receptor-ligand complex until the simulation comes to an end illustrated in the figure (8).

The diverse percentage ratio of amino acid interactions within the active pocket, as observed during the simulation, closely mirrors the docking results, with certain amino acids consistently maintaining their binding to the pocket throughout the entirety of the simulation (24).

Notably, ASP831, MET796, and THR766 demonstrate significant binding through hydrogen

bond interactions, while PHE832, LEU820, MET742, and ALA719 display notable hydrophobic interactions within the active pocket of 4HJO figure (9). Overall, within the active pocket of the 4HJO protein, the primary interactions observed were hydrogen bonding and hydrophobic interactions.

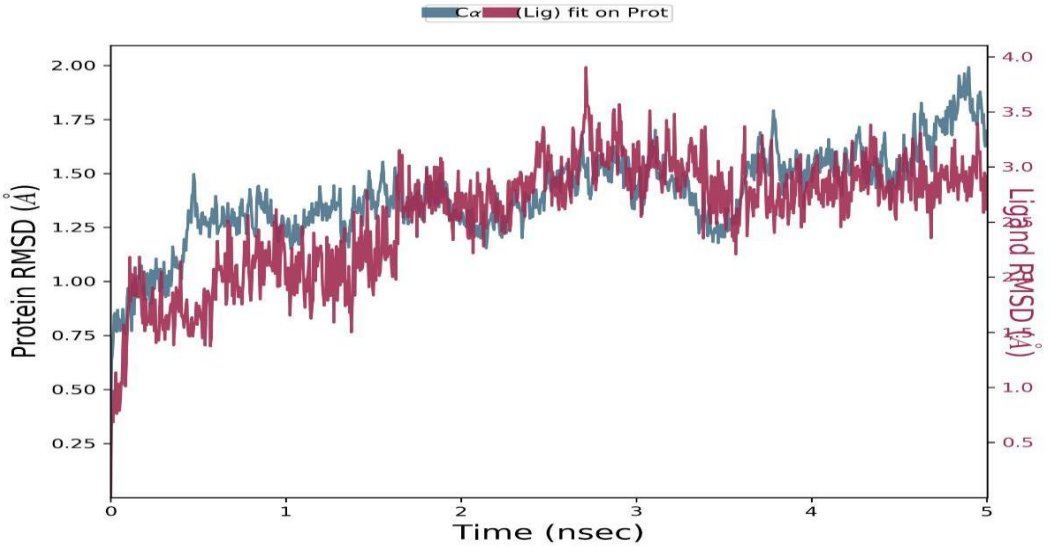


Figure (8), The RMSD of 4HJO protein with compound H5.

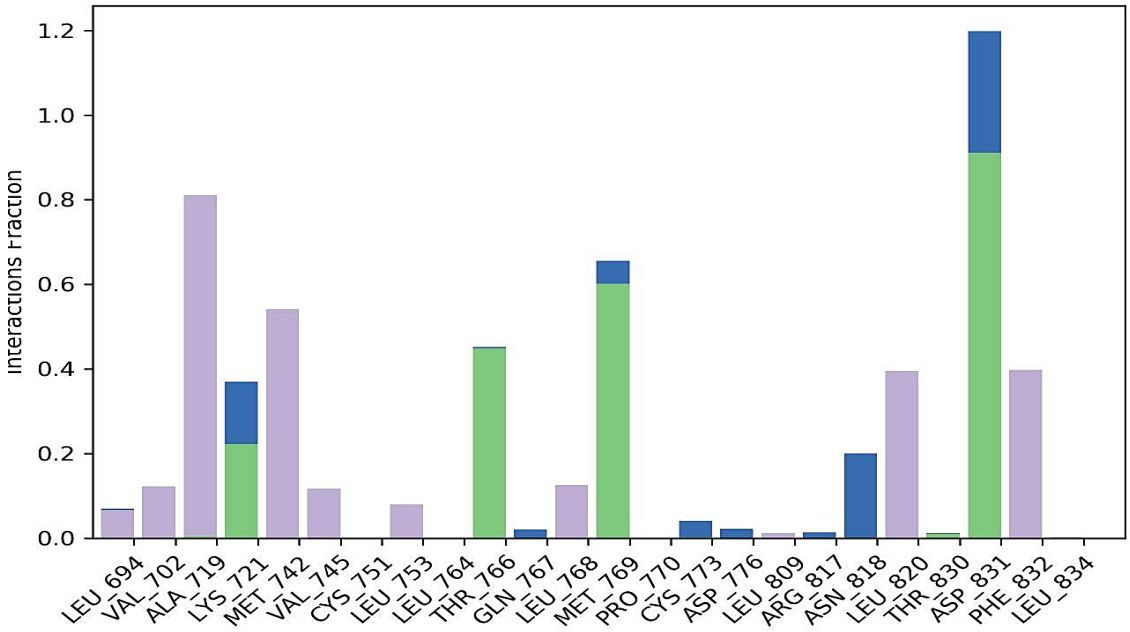


Figure (9), Amino acids interactions of 4HJO with compound H5 during simulation time.

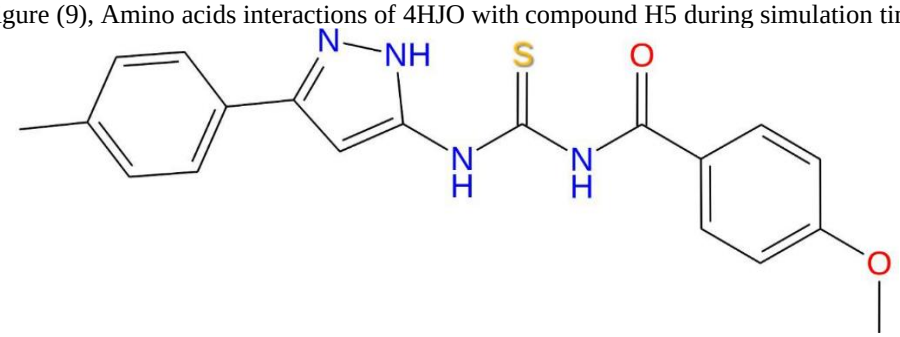


Figure (10), Compound H5.

4. Conclusions

This paper presents a comprehensive exploration of pyrazole derivatives as potential EGFR inhibitors for lung cancer treatment. The molecular docking and in silico ADME studies collectively suggest the promise of these compounds as anticancer agents. Further experimental validation is warranted to confirm their efficacy and safety profiles. The study contributes to the ongoing pursuit of innovative and targeted therapies for cancer treatment.

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