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In Silico Molecular Docking, Molecular Dynamics Simulation, and Pharmacokinetic prediction of Novel N-(2-(4-oxo-2-phenyl quinazoline-3(4H)-yl) Derivatives with Enhanced Anti-proliferative Activity

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Abstract: The design of novel Quinazoline derivatives with integrated molecular modeling techniques, molecular docking, MD simulations, and ADME-T profiling features within medicinal chemistry have a great goal in overcoming drug resistance and reducing toxicity in cancer therapy by developing selective, potent, and nontoxic anti-proliferative agents.

Molecular docking studies of synthesized ligands with EGFR (PDB ID: 4HJO) were analyzed against erlotinib as the reference ligand. From the studies, it was observed that seven assayed ligands showed higher binding affinities compared to erlotinib, which higher PLP fitness scores and crucial interactions with active site essential residues like ASP831 and THR766 can reflect.

The stability of the ligand-receptor complex was reaffirmed by molecular dynamics simulation on the top-performing ligand. The analyses on RMSD and RMSF displayed slight structural deviations along the course of the 25-ns simulation, showing the ligand was strongly stable within the EGFR active site. The other interactions with key residues of EGFR were generally the same, so it is concluded that the ligand can act as a stable anti-proliferating agent.

The ADME-T predictions indicated that all the designed ligands fulfilled Lipinski's Rule of Five, hence suggesting favorable drug-likeness. Human oral absorption for these compounds was high; this enhanced their clinical potential.

The present work underlines the importance of in silico approaches when designing and conducting a study on new anti-proliferative agents. This research combined molecular docking with molecular dynamics and ADME-T profiling to identify potential lead compounds with enhanced binding affinities and also with favorable pharmacokinetic properties. Further experimental studies have to be conducted for confirmation to have therapeutic applications in the treatment of cancer.

Keywords: molecular docking, molecular dynamics, ADME-T, anti-proliferative compounds, epidermal growth factor receptor (EGFR), drug design.

[1] Introduction

While much progress has been achieved in the development of anticancer drugs, more problems remain to be solved regarding the drugs' resistance, low effectiveness, and severe toxicity, which have significantly influenced patients' daily lives. Therefore, one of the biggest challenges in current research into cancer treatment is the search for highly selective, effective, and nontoxic anticancer drugs [1].

Conventional chemotherapy for cancer lacks selectivity at the molecular level in its action, and thereby, its effects on normal and neoplastic tissues result in the development of resistance to drugs in cancer. Some recently promising approaches are targeted drug therapy, which will minimize adverse effects, improve patient tolerability, and modulate

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the host's immune system to restore homeostasis [2].

Targeted anticancer treatment differentiates itself from conventional chemotherapy by explicitly targeting cancer genes, tissue environments, or proteins essential for cancer cells' survival and proliferation. It is excessively expressed in cancerous tissues. Some examples of these are tyrosine kinases, prostate-specific membrane antigen (PSMA), carbonic anhydrase IX, biotin receptor, G-protein-coupled receptor 87 in pancreatic cancer, growth factor receptor in breast cancer, and folate receptor [3].

Tyrosine kinases, which promote signal transduction processes, play the most important and active role in cellular processes, including cell proliferation, differentiation, migration, metabolism, and apoptosis. A group of tyrosine kinase enzymes use ATP molecules to provide a phosphate group for tyrosine residues of target proteins. Covalent bonding-mediated post-translational modification is an essential component of normal cellular signaling and the control of internal stability [4]. The progression of tumors and different phases of carcinogenesis have been linked to tyrosine kinases. Tyrosine kinase signaling pathways usually increase sensitivity to programmed cell death signals or suppress unchecked cell proliferation. Cancer cells commonly alter these signaling pathways at the genetic or epigenetic level to give themselves a competitive edge. The aberrantly elevated signaling that results from tyrosine kinase is not surprising since it provides these enzymes with a prominent oncoprotein status and disrupts the signaling network [5]. In academic literature, receptor tyrosine kinases (RTKs) are widely recognized for their critical role in regulating various cellular processes and their significance in the pathogenesis of numerous diseases. Twenty subgroups have been identified for the human Receptor Tyrosine Kinases (RTKs), and they all have a similar molecular structure that consists of one transmembrane helix and one external ligand-binding segment (Figure 1). The protein tyrosine kinase (TK) domain, additional carboxy-(C-) terminal, and juxtamembrane regulatory regions are located in the cell's cytoplasm. To stabilize interactions between single or multiple receptor units and form activated dimers or oligomers, ligand binding is necessary to activate receptor tyrosine kinases (RTKs). Intracellular kinases then begin to function due to these activated receptor complexes. For receptor tyrosine kinase (RTK) activities to function, signaling molecules must first be phosphorylated for transcription factors to be activated. These transcription factors then control the expression of target genes in response to ligands [6].

Tyrosine kinases represent a significant portion of oncogenic proteins and, as such, are often centrally involved in the neoplastic transformation process in various tumors. Thus, identifying and developing therapeutic agents for diseases involving aberrant tyrosine kinase activation through overexpression, mutation, or autocrine stimulation leading to abnormal downstream oncogenic signaling have emerged as a priority in cancer therapy [7-8]. Since their introduction into clinical practice in 2001, receptor tyrosine kinase inhibitors, or RTKIs, have been profoundly influential as targeted therapeutic agents. Generally, the primary target for such would be the kinase active site, which inhibits the phosphorylation of intracellular targets important in processes such as angiogenesis and cell proliferation [9]. The Food and Drug Administration (FDA) approved 43 RTK inhibitors for cancer treatment by August 2019 [10]. Angiogenesis and cellular proliferation are often mediated by intracellular targets [11]. Reversible inhibitors are typically differentiated from irreversible inhibitors by their ability to bind non-covalently to, or near, an adenosine triphosphate (ATP) binding site. Most non-covalent inhibitors, known as type-I inhibitors, are ATP-competitive inhibitors that bind to active conformations. ATP binding sites typically exhibit a high degree of evolutionary conservation. Thus, selective inhibition can be accomplished by explicitly targeting less conserved amino acid residues, especially those adjacent to the flexible hinge region. Type-II inhibitors interact with a region neighboring the ATP binding site of dormant kinases, thus facilitating the preservation of their dormant structure. This category of inhibitor typically lacks selectivity in its action. Type III allosteric inhibitors function by binding to an allosteric site to inhibit the activity of kinases [12]. ATP binds to the site of inactive kinases to preserve their inactive structure. Typically, this class of

inhibitor does not exhibit selectivity. Type III allosteric inhibitors can inhibit kinases by binding to a site different from the ATP binding site and the hinge region. These are highly selective to a particular kinase substrate [12] as known new inhibitors targeted against a specific substrate or type-IV RTKI [13]. RTKIs play a critical role in precision oncology despite having limited effectiveness due to the emerging resistance mechanisms. Clinical trials demonstrated the efficiency of RTKIs against NSCLC by applying the first generation of reversible EGFR inhibitors targeting ATP binding sites (gefitinib and erlotinib) to cancer patients. Such treatments increased patient survival by 50% compared to chemotherapy due to an overall survival of 30.5 months versus 23.6 months [14]. The second generation of RTKIs includes irreversible inhibitors, such as afatinib and dacomitinib, with more potent binding to the EGFR kinase domain. This class of inhibitors also inhibits other HER family members, including the EGFR. Afatinib has demonstrated increased survival compared to chemotherapy, with a median PFS of 11.1 months versus 6.9 months [15]. According to clinical trials, patients treated with dacomitinib had longer survival rates than those treated with gefitinib. The median progression-free survival (PFS) was 14.7 months versus 9.2 months, and the median overall survival (mOS) was 34.1 months versus 26.8 months, respectively [14,16]. Side effects such as skin irritation or ulcers, as well as gastrointestinal problems like diarrhea, constipation, severe nausea, and vomiting, are more severe and common in patients taking afatinib and dacomitinib. The primary way that these drugs typically encounter resistance is through a secondary mutation in the EGFR kinase domain. Thus, osimertinib, a third-generation EGFR-RTKI, was explicitly developed to bind more strongly to mutated receptors. Osimertinib significantly improved progression-free survival (PFS) compared to first-generation EGFR RTKI, with a favorable safety profile. The PFS was 18.9 months for osimertinib compared to 10.2 months for first-generation EGFR RTKI [14,17,18]. The European Society for Medical Oncology (ESMO) currently advises that patients with EGFR-activating mutations in non-small cell lung cancer (NSCLC) should be treated with erlotinib, gefitinib, afatinib, or osimertinib as their initial therapy [19]. Over 90% of new drugs have heterocyclic rings in their structure, with nitrogen-containing heterocyclic compounds showing more excellent pharmaceutical effects than non-nitrogen compounds [20]. Quinazolines and quinazolinones are fused nitrogen-containing heterocyclic compounds that are very interesting due to their wide variety of biological properties [21]. Quinazoline compounds have also been demonstrated to inhibit the activity of tyrosine kinases, making them helpful in preventing the growth of tumors [22].

Drug design has been revolutionized by in silico research. Molecular docking, for example, can predict ligand-target interactions, binding affinity, and ligand alignment inside the receptor's active site, which ultimately results in the discovery of novel pharmaceuticals [23]. Moreover, molecular dynamics simulation can confirm the ligand-receptor complex's stability determined by molecular docking. This is done by applying Newton's equations of motion. If the root mean square deviation (RMSD) value of the ligand conformation from the molecular dynamics simulation varies significantly from the docking result, it suggests that the complex is unstable [24]. Lastly, to assess the viability of the suggested compounds for further drug development, we employed ADMET and drug-likeness models, including SwissADME [25] and QikProp [26]. These models were used to predict critical physicochemical properties, such as solubility, permeability, and metabolic stability, that are essential for determining the pharmacokinetic profile and overall drug-likeness of the compounds. The objective of this research is to accomplish the following:

- Using swissADME and QikProp to predict the potential target protein of the designed ligands and absorption, distribution, metabolism, and excretion (ADME) properties were obtained.
- Evaluating the PLP fitness score and the binding affinity of the designed compounds compared to the reference medication using molecular docking software.
- Simulation of molecular dynamics to validate the docking result by observing

the ligand-receptor complex behavior at the atomic level over time.

[2] Computational Method

The computational approach adopted in this work is outlined in Fig. 1 [27].

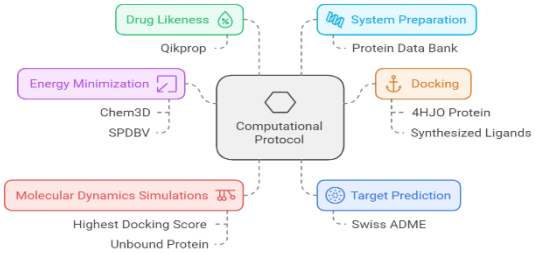


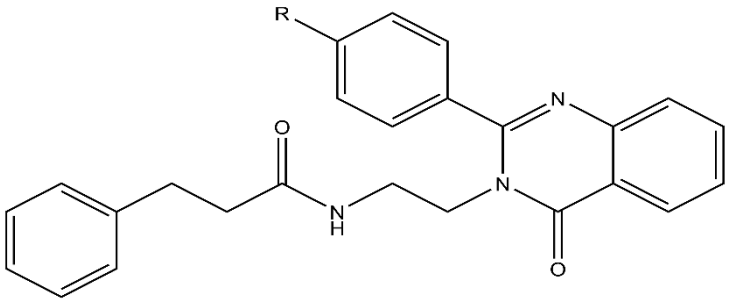
Figure 1. Outline of computational protocol.

2.1. Target prediction

swissADME module [25] was used to predict the possible targets for the supposed ligands drawn using ChemDraw 23.1.1.3 [28]. Among many, the epidermal growth factor receptor was chosen as a reference target protein, and erlotinib as the targeted drug.

2.2. Ligands preparation

To obtain the stable conformation of the ligands, the suggested compounds, which are represented in schema 1, were sketched in 2D in ChemDraw 23.1.1.3 and then converted into 3D using Chem3D 23.1.1.3. The MM2 field force was applied for energy minimization [28].



Compound Number	R
1	CH_3
2	Cl
3	NO_2
4	Br
5	H
6	OCH_3
7	OH

Schema 1. Structures of the suggested compounds

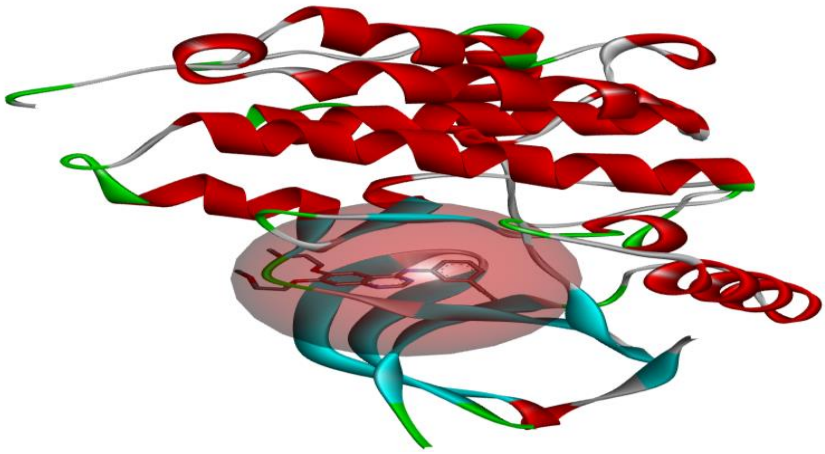


Figure 2. 3D crystal structure of erlotinib bound to inactive EGFR (PDB code: 4HJO) inside the active site of chain A.

2.3. Target preparation

The X-ray crystal structure of the EGFR [PDB ID: 4HJO] was downloaded from the Protein Data Bank (PDB), and missing hydrogen atoms were added to correct the ionization and tautomeric state of the amino acid residues [29]. Structural waters that mediate receptor-ligand interactions at the binding site should be retained and treated as part of the receptor environment. Conversely, deleting unnecessary water molecules allows the active site to accommodate novel ligands that wouldn't otherwise fit [30].

2.4. Molecular Docking procedure

The full license version of Genetic Optimization for Ligand Docking (GOLD) (v. 5.6.2) was used for molecular docking to explore the full range of ligand conformational flexibility with partial flexibility of the protein [31 & 32]. The Hermes visualizer software in the GOLD Suite was used to set up the receptors for the docking process. The binding site used for GOLD docking was defined as all the protein residues within the 10 A^o of the reference ligands in the downloaded protein structure complexes. 4HJO protein was downloaded from the PDB website to perform the docking study for the ligands. The cavity and the active site were determined using a reference ligand of the protein, and the active site radius was set to (10 A^o). Setting the Piecewise Linear Potential (PLP) as the appropriate scoring function. Analyzing the docking result by examining the hydrogen bonds, short contacts, bond length, and other vital interactions to evaluate the binding poses and interactions between the protein and the ligands.

2.5. Molecular dynamics simulation

MD was conducted for the derivative exhibiting the optimal docking score, utilizing the Desmond modules of Schrodinger 2023 [33], and to model the protein interactions, the OPLS4 force field [34] was used, which is highly accurate, modern force fields with comprehensive coverage of chemical space for drug discovery. Defining the simulation box aims to minimize the solvent volume while ensuring sufficient solvent surrounds the solute to prevent the protein from perceiving a periodic image of itself during the simulation. To establish a charge-neutral environment for the protein-ligand complex, sodium ions were introduced, and 0.15 M sodium chloride (NaCl) was incorporated to replicate the natural system. The TIP3P solvent model was employed to generate the system. The simulation duration was 25 ns, with trajectory recording intervals of 25 ps. The NPT ensemble class was engaged, and the system energy was established at 1.2. The simulation was configured to function at 1.01325 bar and 300 K. The simulation interaction diagram was developed after evaluating the relaxed simulated system [35].

2.6. ADMET prediction

ADME-T (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling is crucial in discovering novel pharmaceutical substances, as it assesses their capacity for absorption, distribution, metabolism, excretion, and possible toxicity. This data is essential for evaluating the efficacy and safety of these drugs [36]. A comprehensive ADME-T analysis ensures maximum absorption, precise tissue distribution, and effective metabolism of compounds, transforming them into advantageous active forms while minimizing the generation of harmful by-products [37]. Moreover, it guarantees secure channels for waste disposal, reducing the probability of adverse outcomes. Integrating pharmacokinetic and toxicological insights early in drug development enables scientists to enhance efficacy, foresee potential adverse effects, and streamline the transition from synthesis to clinical use [38].

[3] Results and discussion

In-silico studies are essential to the drug discovery process as a potent tool for predicting the therapeutic potential of new pharmaceuticals. They also assist in minimizing the time and resources required to conduct the process, and when utilized alongside other methods, they enhance the probability of developing effective drugs. To verify the findings, we employed a variety of robust and well-established computational modules.

3.1. Molecular Docking Results

This research involved testing seven potential ligands, both erlotinib and EGFR being utilized as

the reference ligand and protein. The binding's pocket was determined based on its PDB ID: 4HJO. The outcome of the docking was exceptional, revealing a highly promising docking score that surpassed that of the reference ligand. Compared to erlotinib's predicted mean PLP fitness (74.8), all the ligands in Table 1 possessed higher values. This suggests that these ligands have favorable interactions and a greater binding affinity for the receptor, as they exhibit the same binding pattern at the erlotinib active site, involving both hydrogen bonding and short contacts interaction.

Amino acids THR766, THR830, ASP831, GLY695, VAL702, LEU764, LEU768, and MET769 were the ones with the best mean docking PLP fitness in Compound 1, which also exhibited the most robust hydrogen bonding interactions with amino acids ASP831. The interaction pattern of the other compounds was identical except for the lack of an H-bond with ASP831 in compound 7. The EGFR active site contains all of the aforementioned amino acids.

In all compounds, there were more short contacts than H-Bonding. Because hydrophobic connections dominate H-bonding contacts—critical for substrate binding to an active site—the pharmacological activity increases as the number of hydrophobic contacts grows. In contrast, the number of H-bonding contacts decreases [39].

Table 1: The PLP fitness score of our Quinazoline derivatives against the active site of the epidermal growth factor receptor (PDB ID: 4HJO), erlotinib, is the reference ligand.

Ligands	PLP Fitness	H-bond	Short contacts
Erlotinib	**74.8**	**LYS704, MET769, CYS773**	**LEU694, GLY695, VAL702, ALA719, CYS773, ASP776, LEU834**
1	**98.1**	**THR766, THR830 By HOH and ASP831**	**GLY695, VAL702, LEU764, LEU768, MET769 THR830, ASP831**
2	**97.3**	**THR766, THR830 By HOH and ASP831**	**GLY695, VAL702, LEU764, LEU768, MET769 THR830, ASP831**
3	**97.1**	**THR766, THR830 By HOH and ASP831**	**GLY695, VAL702, LEU764, LEU768, MET769 THR830, ASP831**
4	**95.6**	**THR766, THR830 By HOH and ASP831**	**GLY695, VAL702, LEU764, LEU768, MET769 THR830, ASP831**
5	**93.4**	**THR766, THR830 By HOH and ASP831**	**GLY695, VAL702, LEU764, LEU768, MET769 THR830, ASP831**
6	**92.9**	**THR766, THR830 By HOH and ASP831**	**GLY695, VAL702, LEU764, LEU768, MET769 THR830, ASP831**

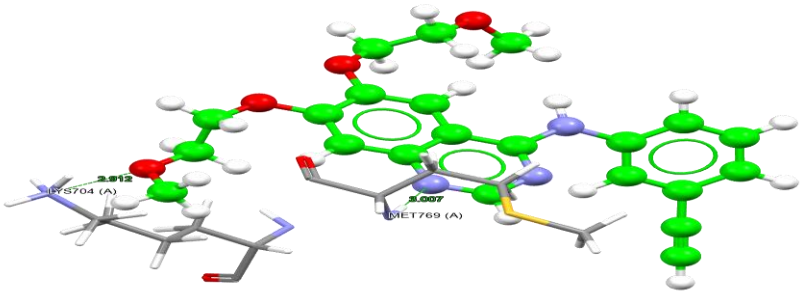


Figure 3. H-bonding of Erlotinib and EGFR (4hjo).

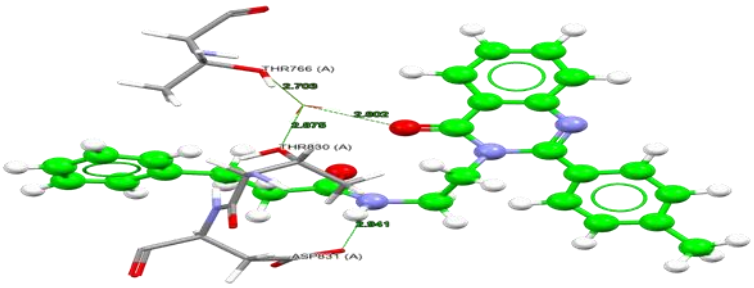


Figure 4. H-bonding of compound 1 and EGFR (4hjo).

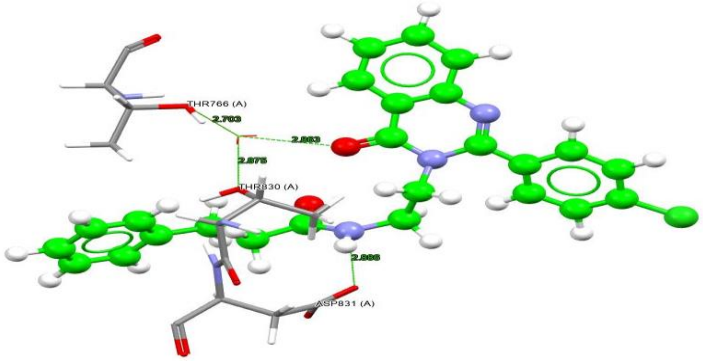


Figure 5. H-bonding of compound 2 and EGFR (4hjo).

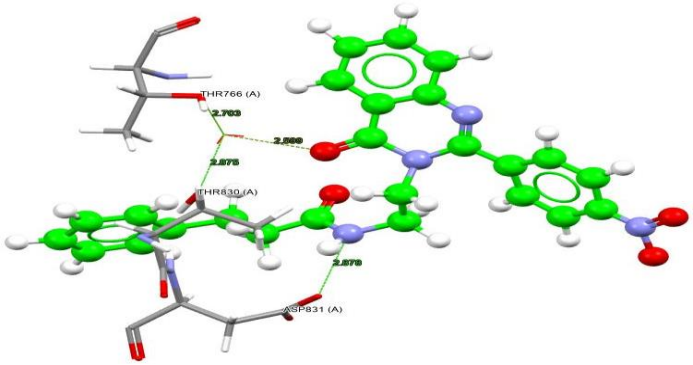


Figure 6. H-bonding of compound 3 and EGFR (4hjo).

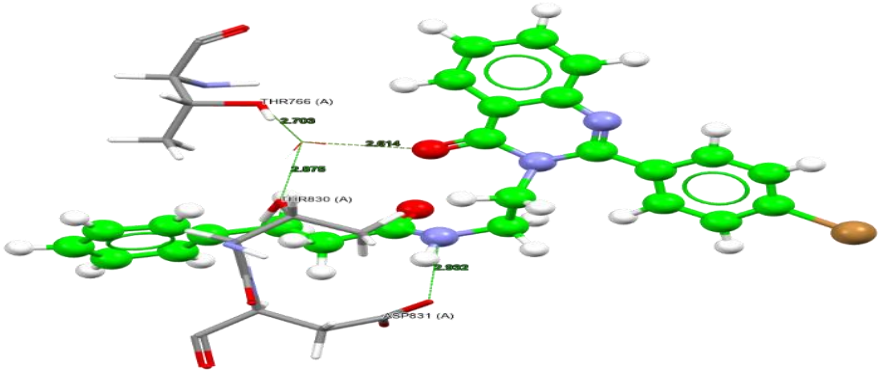


Figure 7. H-bonding of compound 4 and EGFR (4hjo).

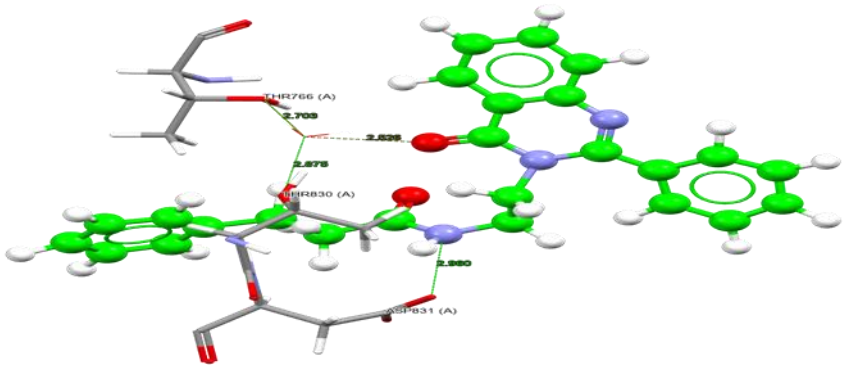


Figure 8. H-bonding of compound 5 and EGFR (4hjo).

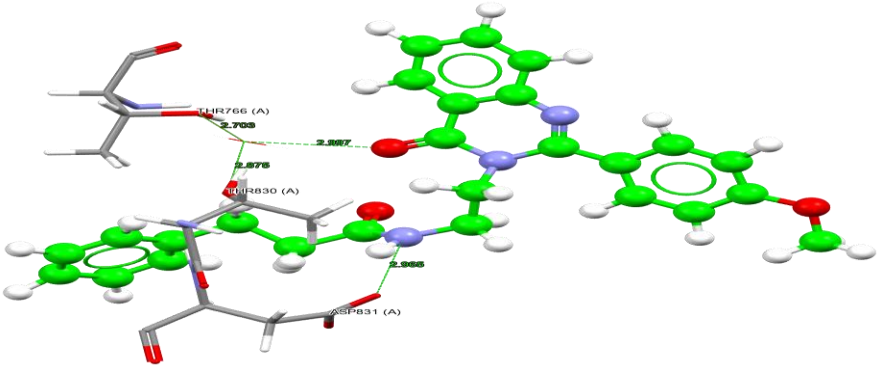


Figure 9. H-bonding of compound 6 and EGFR (4hjo).

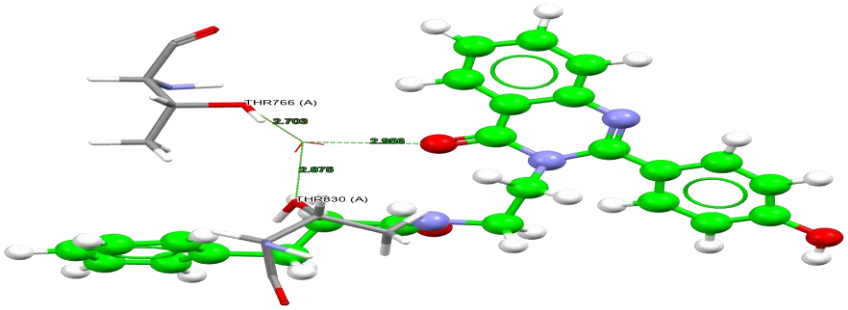


Figure 10. H-bonding of compound 7 and EGFR (4hjo).

3.2. Molecular Dynamics Results

An MDS analysis had been performed on the compound 1-EGFR complex to verify the interaction. A method proven effective in studying macromolecular ligand-receptor interactions is the simulation of molecular dynamics (MD). Further, MD modeling is adept at accommodating proteins' mobility and adaptability. To comprehend the evolution of receptor binding capacity over time, MD simulations were conducted on the ligand that achieved the greatest score. The dynamic behavior of ligand 1-EGFR was tracked and recorded for 25 ns. The protein-ligand complex's stability was assessed by analyzing the RMSD and RMSF values.

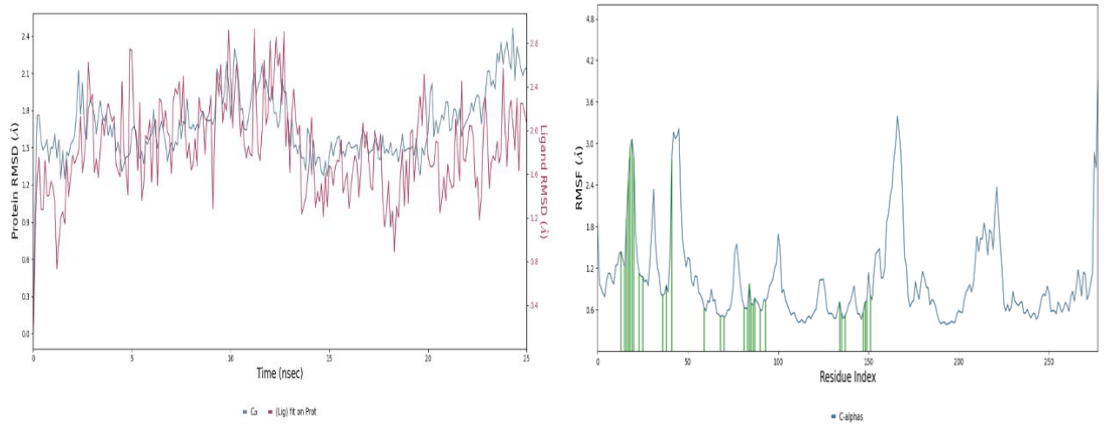
The graph in Figure 11 (A) showed that the protein RMSD fluctuated in the initial few nanoseconds. This fluctuation was observed as the system attained its equilibrium state. During the first five ns, the value of RMSD increased to around 1.8 Å. Eventually, convergence is achieved with deviation within a range of 1.5 to 2.4 Å, which indicates minor conformational changes but the overall stability of the structural protein during the simulation. The RMSD of the ligand equilibrated along the course of simulation after five ns, just like the protein, whereas in that time frame, the RMSD

increased rapidly. Then, the RMSD range of 1.2 to 2.0 Å clearly shows very slight movements and flexibility of the ligand within the active site of the receptor due to good stability, and importantly, such fluctuations are concordant with the ligand's adoption into the binding pocket; hence no substantial dissociation occurs. These results showed that the slight deviation within the RMSD values was because the ligand explored the binding site, which is quite normal during MD simulations since the ligand is forced to fit within the active site of a protein. In addition, the overall RMSD values of both the ligand and the protein displayed relatively stable interactions and synchronized behavior along the simulation.

Besides, RMSF data was used to study flexibility during simulation for individual protein residues, as shown in Figure 11 (B), and lower values indicated less movement, hence higher stability for the particular residues. Most of the residues obtain RMSF below 2.0 Å, showing that flexibility within the protein is restricted during the simulation period. This will be one of the contributors to the overall stability of the protein, especially toward the residues in the secondary structural elements. Several peaks are observed to cross 2.0 Å with fluctuations as high as 4.8 Å at points, indicating highly flexible residues in either the loop regions or at the terminal ends. A sharp peak in the C-terminal part revealed higher mobility of the protein. The terminal ends of both N- and C-terminals will have fewer structural restraints and more solvent accessibility during the MD simulation, which results in large fluctuations without compromising overall stability. Below 1.5 Å, RMSF values were observed in a region between residues 50-150 and represent minimal fluctuations with a well-defined secondary structure, Alpha-Helix, and Beta-Pleated sheets within the protein further stabilized through intra-molecular hydrogen bonds. Finally, areas around the binding site essentially indicate the optimal level of flexibility required during an induced-fit mechanism of the ligand-protein binding complex. The small molecule RMSF in Figure 11 (C) illustrates atomic flexibility throughout the simulation.

Indeed, the ligand molecular structure ranges from aromatic compounds to aliphatic chains to polar functional groups. Such variety gives rise to oscillations in the ligand. The core region of the molecule had a small RMSF, which is a signature of stability in their interaction as part of the active site. Therefore, a higher RMSF belonging to atoms either in the solvent-exposed areas or explicit participation in binding resulted in possible mobility.

A. **B.**



C.

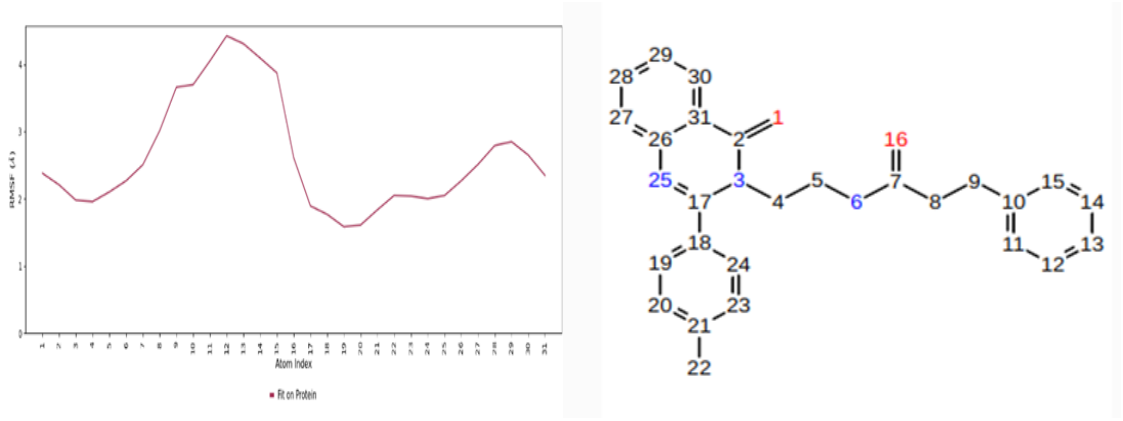


Figure 11. Root-mean-square deviation (A) and root mean square fluctuations (B), and (C) particular residue fluctuations during molecular dynamics simulation analysis of compound 1–EGF Receptor complex.

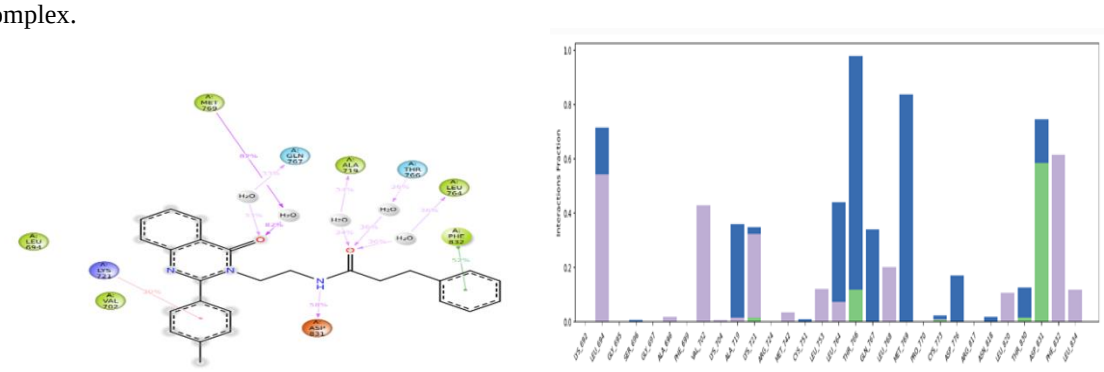


Figure 12. Interacting fraction (A) and interacting residues (B) in the EGFR-compound 1 complex during MDS analysis.

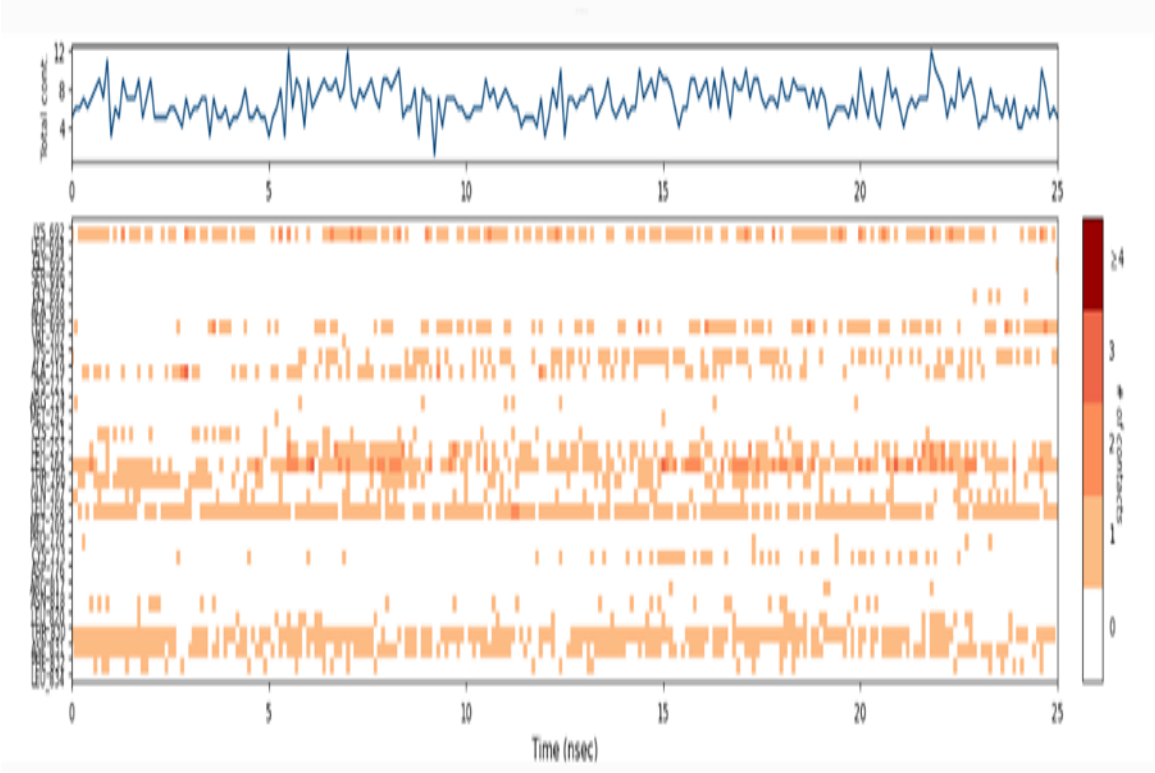


Figure 13. Depiction of the interactions and contacts (hydrogen bonds, hydrophobic interactions, ionic interactions, water bridges) between ligand 1 and the EGF Receptor.

The binding mode of Ligand 1 and its several important contacts in the interaction map to EGFR are shown in Figure 12 (A). MET769 initially forms Hydrogen bonds with the ligand through water molecules and additional water bridges, which are essential for keeping the ligand in its binding pocket. The ongoing and strong interactions were reflected by the interaction rate being significantly high in 82% of simulations. Two, the compound is directly interacting with ASP831 for about 58% of end-to-end simulation time. It is important to have these interactions, as ASP forms ionic bonds most of the time, which are really helpful in stabilizing the ligand-binding complex. Direct contact was made for about 58% of the length of the simulation with PHE382, which is highly important for stability through Van der Waals interactions or pi-pi stacking. The remaining residual contact contributed about 33-36% of the length of the simulation, showing that it is moderately but quite significantly involved in the strengthening of the binding complex.

Specific residues involved in this interaction are shown in Figure 12 (B), including the following: LEU694, VAL702, ALA719, LEU764, THR766, GLN767, MET769, ASP831, and PHE832.

The line graph at the top of Figure (13) shows the total number of ligand-protein contacts throughout the simulation, where the number of contacts ranges from 4-essentially few contacts with some variability to 12, a greater number of contacts and implying stability. These differences reflect the conformational changes of both the ligand-protein complexes through the simulation as they adapt to one another while maintaining an average contact count. The following heat map describes the interaction frequency and points toward ASP 831 as the key residue for binding and stabilization.

3.3. ADMET Results

Using the QikProp [26] module of Maestro-Schrodinger, the research employed a highly accurate method to anticipate a range of pharmacokinetic and physicochemical properties. This renowned software is recognized for its user-friendly interface, precise calculations, and rapid prediction of essential descriptors that aid in comprehending the absorption, distribution, metabolism, excretion, and potential toxicity (ADME-T) of drugs [40].

Based on the data presented in Table (2), all compounds adhere to Lipinski's Rule of Five, which asserts that all permissible limitations for molecular weight, hydrogen bond donor and acceptor count, and TPSA values are within the acceptable ranges.

One tool that predicts a drug's probability of reaching its target by estimating the number of metabolic processes it may undergo (#metab). Each suggested compound exhibits a #metab within the acceptable range of 1 to 8, indicating a suitable metabolic profile.

Moreover, all these substances exhibit a human oral absorption rate exceeding 80%, indicating that, despite non-compliance with Lipinski's Rule of Five, their bioavailability is unlikely to be substantially affected.

Table 2. Insilco ADMET screening for suggested compounds (1-7).

molecule	MW.	TPSA	nHBA	nHBD	QPlog Po/w	#metab	Rule Of Five	Percent Human Oral Absorption
Erlotinib	**393.441**	**74.73**	**1.5**	**7.4**	**4.259**	**6**	**0**	**100**
1	**411.502**	**63.99**	**1**	**6.5**	**4.13**	**3**	**0**	**100**
2	**431.921**	**63.99**	**1**	**6.5**	**4.387**	**2**	**0**	**100**
3	**442.473**	**109.81**	**1**	**7.5**	**3.097**	**3**	**0**	**80.062**
4	**476.372**	**63.99**	**1**	**6.5**	**4.401**	**2**	**0**	**100**
5	**397.476**	**63.99**	**1**	**6.5**	**3.59**	**2**	**0**	**100**
6	**427.502**	**73.22**	**1**	**7.25**	**3.383**	**3**	**0**	**100**
7	**413.475**	**84.22**	**2**	**7.25**	**3.016**	**3**	**0**	**88.135**
recommended values	**< 500**	**20-140 Å²**	**<5**	**<10**	**2 – 6.5**	**1 – 8**	**Max. is 4**	**>80% is high**

MW: Molecular Weight; TPSA: Topological Polar Surface Area; nHBA: Number hydrogen bond acceptor; nHBD: Number hydrogen bond donors; QPlogPo/w: Predicted octanol/water partition coefficient; #metab: Number of likely metabolic reactions.

[4] Conclusions

In this study, novel Quinazoline compounds with prospective anti-proliferative properties are developed by computational methods. The significance of computational approaches in contemporary drug design, including molecular docking, molecular dynamics simulations, and ADME-T prediction, cannot be overstated. The in-silico tools used in this study have greatly aided our understanding of binding affinities and stabilities of ligand-protein interactions and predicting the molecular pharmacokinetic features of the developed compounds.

The molecular docking studies demonstrated that the synthesized ligand molecules interacted with EGFR to differing degrees, yielding superior predictive PLP fitness ratings compared to the reference drug erlotinib. The MD further validated these findings by confirming the stability of the ligand-receptor complexes, particularly Compound I, whose dynamic behavior remained consistent throughout the 25-nanosecond duration of the simulation. The conclusions of the RMSD and RMSF analyses demonstrated low variations, suggesting that the ligand was firmly anchored inside the active site of EGFR.

The subsequent ADME-T predictions indicated that all these compounds adhered to Lipinski's Rule of Five and exhibited drug-like properties. Thus, elevated human oral absorption rates highlighted the therapeutic potential of the evaluated drugs based on pharmacokinetic profile. This work emphasizes the significance of computational tools in expediting drug creation through the swift discovery and optimization of lead compounds. Implementing these technologies will facilitate the creation of novel anti-proliferative drugs, enhancing binding affinity and pharmacokinetic features and advancing cancer therapy while minimizing toxicity. Additional in vitro and in vivo testing will be necessary to validate these findings and advance the most promising molecules to clinical applications.

Conflict of interest

The authors declare no conflict of interest.

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