

DESIGNING NOVEL QUINAZOLINE LIGANDS AS POTENTIAL EGFR-TARGETED ANTICANCER AGENTS: AN INTEGRATED MOLECULAR DOCKING, MOLECULAR DYNAMICS AND ADMET STUDY

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quinazoline derivatives; EGFR; non-small cell lung cancer; molecular docking; molecular dynamics; RMSD; RMSF; ADMET; drug-likeness; computer-aided drug design

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Abstract

Background: Quinazoline is an established scaffold for a number of tyrosine kinase inhibitors that target the epidermal growth factor receptor (EGFR), which is a major therapeutic target in non-small cell lung cancer (NSCLC). The limitations of conventional drug development methods and the continuous push toward acquired resistance continue to the rational computational design of novel chemotypes and analogues. **Objective:** The goal of this study was to design and computationally evaluate twelve novel quinazoline derivatives (QZ-01 – QZ-12) against EGFR by an integrated structure-based workflow. **Methods:** The crystal structure of the EGFR (PDB 7AEI) was prepared for docking. The designed derivatives were screened with AutoDock Vina (PyRx) and were compared with erlotinib, gefitinib and afatinib. The validation of docking was undertaken by re-docking of the co-crystallized ligand and then by carrying out 100-ns molecular dynamics (MD) simulations of six selected derivatives and three reference inhibitors. The behaviour of RMSD, RMSF and hydrogen bond were evaluated and the physicochemical and Lipinski properties and predicted ADMET properties were used for the final prioritisation. The docking scores of the 12 designed derivatives varied from -9.80 to -8.60 kcal/mol. QZ-10 was the leading compound (-9. kcal/mol), followed by QZ-06 (-9.60 kcal/mol) and QZ-12 (-9.50 kcal/mol). All designed compounds had better docking scores than any of the three docked compounds in the reported set. When re-docked, the RMSD was 1.18 Å, which is lower than the 2.0 Å cutoff value. The designed compounds were compared based on the mean protein RMSD (QZ-10: 0.119 nm) and mean hydrogen-bond value (QZ-10: 4.5). The designed compounds were compared by the mean protein RMSD (QZ-10: 0.119 nm) and the mean hydrogen-bond value (QZ-10: 4.5) after the 100-ns MD simulation. None of the 12 derivatives were predicted to have any Lipinski violation, high gastrointestinal absorption, low blood-brain barrier penetration, non-major toxicity alert, and low CYP risk. The following ranks from the prioritization were: integrated 1, 2 and 3 were QZ-10, QZ-06 and QZ-12 respectively. **Conclusion:** It was concluded that QZ-10 is the best computational lead and QZ-06 and QZ-12 are strong contenders for experimental exploration. Since the study is computational, the results are not proof of anticancer activity, but hypotheses of priority.

1. INTRODUCTION

1.1 Background and Clinical Rationale

Cancer continues to be a major global health issue. An estimated 20 million new instances of cancer and 9.7 million cancer-related deaths occurred globally in the past year with the burden determined by the ageing of the population, tobacco use, dietary and lifestyle patterns, the environmental exposure to carcinogens, and the capacity of health systems [1,2]. Lung cancer is important as it is a significant contributor to cancer incidence and mortality worldwide. In the estimates cited the source study reports about 2.5 million new lung cancer cases and about 1.8 million deaths in the world each year from lung cancer. These are encouraging figures which emphasize the importance of therapies that increase the efficacy and minimize nonspecific cytotoxic therapies.

There are histological and molecular different subgroups of lung cancer. NSCLC makes up most of lung cancer cases and includes adenocarcinoma, squamous-cell and large-cell carcinoma. As more and more molecules are characterized, we have learned that NSCLC is not one disease, but rather a collection of molecularly distinct cancers with varying vulnerabilities to treatment [4,5]. This transition has helped in the development of targeted therapeutics targeted to oncogenic drivers such as EGFR.

EGFR is a member of the transmembrane protein family known as ErbB receptor tyrosine kinases. By dimerizing the receptor and starting the phosphorylation of other signaling molecules, a ligand that binds to a receptor activates it. The RAS-RAF-MEK-ERK pathway, which regulates proliferation, differentiation, and survival and is probably involved in tumor progression in the event of dysregulation, can be activated by EGFR signaling. Similarly, the PI3K-AKT-mTOR pathway and the JAK-STAT pathway regulate proliferation, differentiation, and survival and are probably involved in tumor progression in the event of dysregulation [8]. A biological basis for targeted inhibition, EGFR mutations, such as deletions in exon 19 and replacements in exon 21

at L858R, are clinically significant in non-small cell lung cancer [9,11].

Small molecule EGFR tyrosine kinase inhibitors (TKIs) function by attaching themselves to the kinase domain's ATP binding site and preventing phosphotransferase activity. EGFR inhibitors showed the potential of precision oncology in clinical trials, but the development of resistance is still a problem. T790M gatekeeper alteration and subsequent resistance-associated alterations (C797S) are resistance mechanisms [12,19]. Therefore, it is still worth continuing to optimize the structure of the inhibitors targeting EGFR.

1.2 Quinazoline as an EGFR-Targeted Scaffold

The quinazoline skeleton is a bicyclic heteroaromatic compound comprised of a benzene ring fused to a pyrimidine ring. It is planar, has hydrogen bonding ability and a flexible substitution pattern, thus making it valuable in medicinal chemistry. Two clinically relevant EGFR inhibitors, gefitinib, erlotinib and afatinib contain the scaffold [21,22]. Systematic changes in the structure can lead to changes in physicochemical behaviour, binding interactions and the pharmacokinetic properties of the drug at different positions of the rings, enabling systematic exploration of structure-activity relationships [23,24].

Despite clinical success of the quinazoline-based EGFR inhibitors, resistance continues to be a problem for which there is a rationale to investigate other substitution patterns with the core compound. In recent computational explorations, quinazoline derivatives have also been explored by means of virtual screening, docking, molecular dynamics and ADMET prediction prior to experimental synthesis [25,26]. In this way, computational prioritization can narrow down a large theoretical chemical space into a smaller subset of compounds that are good candidates for synthesis and biological testing.

1.3 Computer-Aided Drug Design and Study Rationale

The structure of a protein is utilized in computer-aided drug design (CADD) to direct protein-

ligand research recognition. Molecular docking gives a quick first approximation of the orientation of the ligand with reference to the binding site and its relative strength of binding to the receptor, while molecular dynamics can assess the behaviour of a complex once it has been selected. Information on drug-likeness and potential pharmacokinetic and/or toxicological liabilities are added to the ADMET prediction [27,31,36]. These methods are not interchangeable: docking is relatively static, MD provides a time dependent perspective and ADMET models cover properties that are not defined by binding calculations.

The current study thus adopted a step-wise approach: design and structural optimization of 12 quinazoline derivatives; docking to the EGFR; re-docking the co-crystallized structure to validate the docking results; prioritization of best docked complexes based on 100-ns MD simulation; and final prioritization based on the combination of docking, MD, and ADMET evidence. Rather than being able to claim experimentally proven anticancer activity, the aim was to identify candidates computed to have anticancer activity which could then be synthesized and tested in biological assays.

1.4 Aim and Objectives

The objective was to use an integrated molecular docking, molecular dynamics, and in-silico ADMET approach to create and computationally evaluate new quinazoline derivatives as possible EGFR-targeted anticancer drugs.

- To design a structurally diverse series of quinazoline derivatives while retaining the quinazoline core.
- To assess predicted binding affinity, orientation and protein-ligand interactions in the EGFR active site.
- To validate the docking protocol through re-docking of the co-crystallized ligand.
- To examine the dynamic stability of selected complexes over 100 ns using RMSD, RMSF and hydrogen-bond analyses.
- To evaluate predicted physicochemical, pharmacokinetic, toxicity and drug-likeness properties.
- To prioritize candidates with the most coherent overall computational profiles for future experimental work.

2. Materials and Methods

2.1 Study Design

This is a computational, structure-based drug design study. The process was designed as a funnel with less detailed analyses performed at the lower end and more detailed analyses at the top. A total of 12 quinazoline derivatives were first candidate. The initial screening was done by docking. Six derivatives having relatively good docking score data were further progressed to 100-ns MD simulation: QZ-04, QZ-06, QZ-07, QZ-09, QZ-10 and QZ-12. Erlotinib, gefitinib and afatinib were used as reference inhibitors. Docking and MD results were taken into consideration with ADMET and drug-likeness predictions for final lead selection.

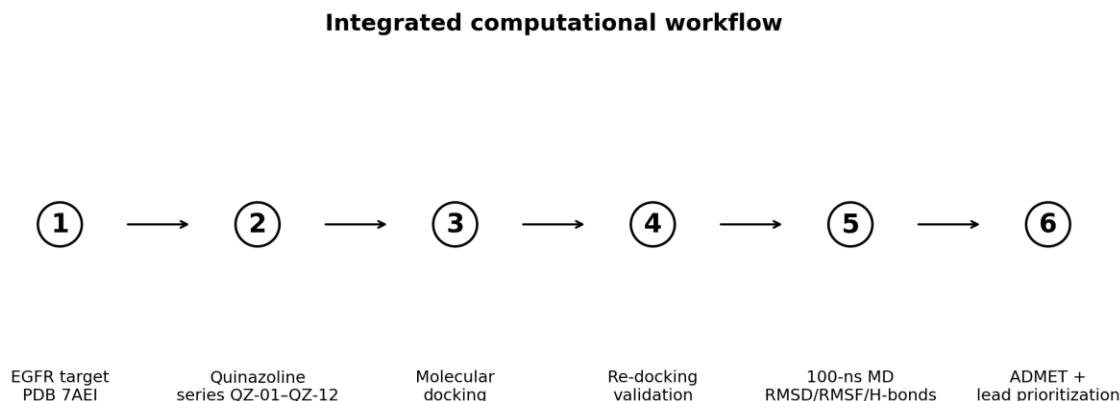


Figure 2. Integrated computational workflow used in the study, from EGFR preparation and quinazoline design through docking, validation, 100-ns molecular dynamics, ADMET assessment and lead prioritization.

2.2 Target Selection and Protein Preparation

The molecular target was selected to be the crystal structure of EGFR (PDB: 7AEI). Energy minimization, the addition of hydrogen atoms, and the removal of crystallographic water molecules were used to create the receptor. The prepared structure was checked for the presence of the dockable by using PyMOL and then docked into the receptor. Residues frequently found in the binding region were among those also found in the analysis of binding residues, in particular, Val702, Ala719, Phe723, Leu764, Leu768 and Met769, which are part of the defined binding region.

2.3 Ligand Design and Preparation

To make a set of twelve derivatives (QZ-01 through QZ-12) with varying substituents, the quinazoline scaffold was retained. The initial 2D structures were turned into 3D structures and then structurally examined. The ligands were protonated at physiological pH, energy-refined and prepared in a docking compatible form. The design approach was based on the known binding affinity of quinazoline to the EGFR and the potential for site-specific modifications to alter the interactions with the ATP-binding site.

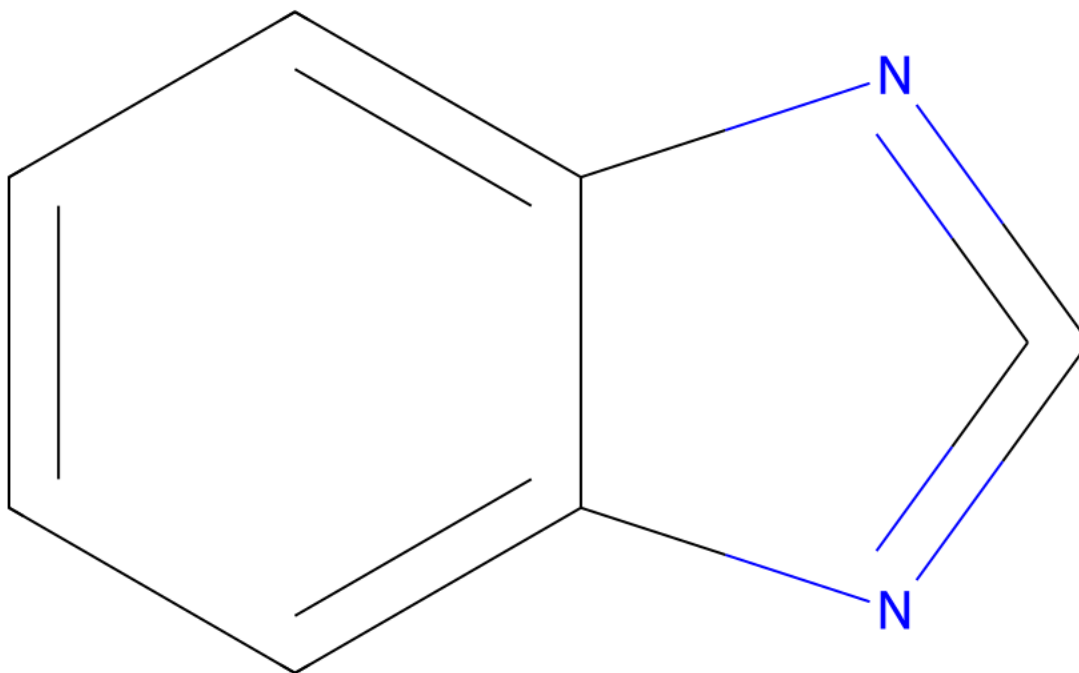


Figure 1. Generic quinazoline scaffold used as the conserved design core. The QZ series was generated by varying substituents around this core; exact QZ-01–QZ-12 structures are not reconstructed here because their full structural drawings were not available in the article dataset.

2.4 Molecular Docking

AutoDock Vina was used to dock using PyRx. The ligands were docked individually into the specified active site of the EGFR and possible alternative. The expected binding affinity was used to rank the binding poses that were produced. The orientation of the compounds and recurring hydrogen-bond, hydrophobic and aromatic interactions were explored by structural visualization. The three reference inhibitors were tested in the same computational framework to provide a comparative benchmark.

2.5 Docking Validation

By re-docking the co-crystallized ligand at the EGFR binding site and comparing the docked structure with the ligand's crystallographic structure, the docking process was evaluated. RMSD, or root mean square deviation, was used as the validation metric. In the source study, a distance of 2.0 Angstrom was used as the

acceptable separation between the X-ray and the reference.

2.6 Molecular Dynamics Simulation

The 100-ns molecular dynamics simulations were performed with GROMACS on the six most important designed complexes that have been identified in the docking stage. The three reference inhibitors were also simulated for 100 ns. Two protein RMSD values, two ligand RMSD values, RMSF and hydrogen-bond behaviour at the residue level were used to assess the trajectories. The Root Mean Square Deviations (RMSD) were used as a measure of overall structural deviation, Root Mean Squares Flexibility (RMSF) as a measure of local flexibility of the residues and hydrogen-bond analysis as a measure of persistence of selected interactions along the trajectory.

2.7 ADMET and Drug-Likeness Assessment

The designed compounds have been screened for the following characteristics: gastrointestinal absorption, blood-brain barrier penetration, hydrogen bond donors and acceptors, Lipinski rule compliance, molecular weight, LogP, Topological Polar Surface Area (TPSA), toxicity alerts and CYP risk. These predictions were not used to replace measures of pharmacokinetics or toxicity, but rather as an initial screen.

2.8 Integrated Lead Prioritization

final prioritization included docking score, dynamic behaviour, characteristics of hydrogen bonding and ADMET/drug-likeness results. The selected candidates were ranked according to the composite scores reported. These composite values have been shown to be used as computational/mock prioritization values in the

source, and are therefore treated here as hypothesis-generating, but not as biologically validated efficacy scores.

3. Results**3.1 EGFR Active-Site Environment**

All the 12 designed derivatives and the three reference inhibitors were described as being in the designated EGFR binding region. Val702 and Leu768 were repeatedly shown as important hydrophobic residues and Met769 was repeatedly identified as a hydrogen bonding residue. Ala719 and Leu764 were found in the reported π -alkyl interaction profile and Phe723 and Val702 had aromatic contacts. The presence of these residues in more than one of the designed derivatives indicated that they were likely to have had a similar binding site, for comparison.

Feature	Reported finding
Target	EGFR, PDB 7AEI
Designed ligands	12 (QZ-01-QZ-12)
Reference inhibitors	Erlotinib, Gefitinib, Afatinib
Recurring hydrophobic residues	Val702, Leu768
Recurring H-bond residue	Met769
Other recurring interaction residues	Ala719, Phe723, Leu764

3.2 Physicochemical Profile

A closely spaced increase in the molecular size and lipophilicity of the designed was observed in the series. Molecular weight increased from 382.00 g/mol for QZ-01 to 428.20 g/mol for QZ-12, while LogP increased from 2.40 to 3.28. TPSA ranged from 72.0 to 81.9 Å². According to source there

are 1 hydrogen-bond donor and 5 hydrogen-bond acceptors in the designed series and no Lipinski-rule violations. The results show that the changes made in the structure are not obvious to affect the essential drug-likeness characteristics used in the study.

Parameter	QZ-01	QZ-12	QZ-10
Molecular weight (g/mol)	382.00	428.20	419.80
LogP	2.40	3.28	3.12
TPSA (Å ²)	72.0	81.9	80.1
Lipinski violations	0	0	0
Predicted GI absorption	High	High	High
Predicted BBB penetration	Low	Low	Low
Major toxicity alert	None reported	None reported	None reported
CYP risk	Low	Low	Low

3.3 Molecular Docking Performance

The 12 designed derivatives all had favorable docking scores in the reported data set. QZ-10 ranked first with -9.80 kcal/mol, followed by QZ-06 at -9.60 kcal/mol and QZ-12 at -9.50 kcal/mol. QZ-04, QZ-09 and QZ-07 followed at -9.40 , -9.30 and -9.20 kcal/mol, respectively.

The other designed derivatives, in between, were between -9.10 and -8.60 kcal/mol. The reference inhibitors afatinib and gefitinib and erlotinib showed the highest negative value with -8.50 kcal/mol, -8.20 kcal/mol and -7.90 kcal/mol, respectively.

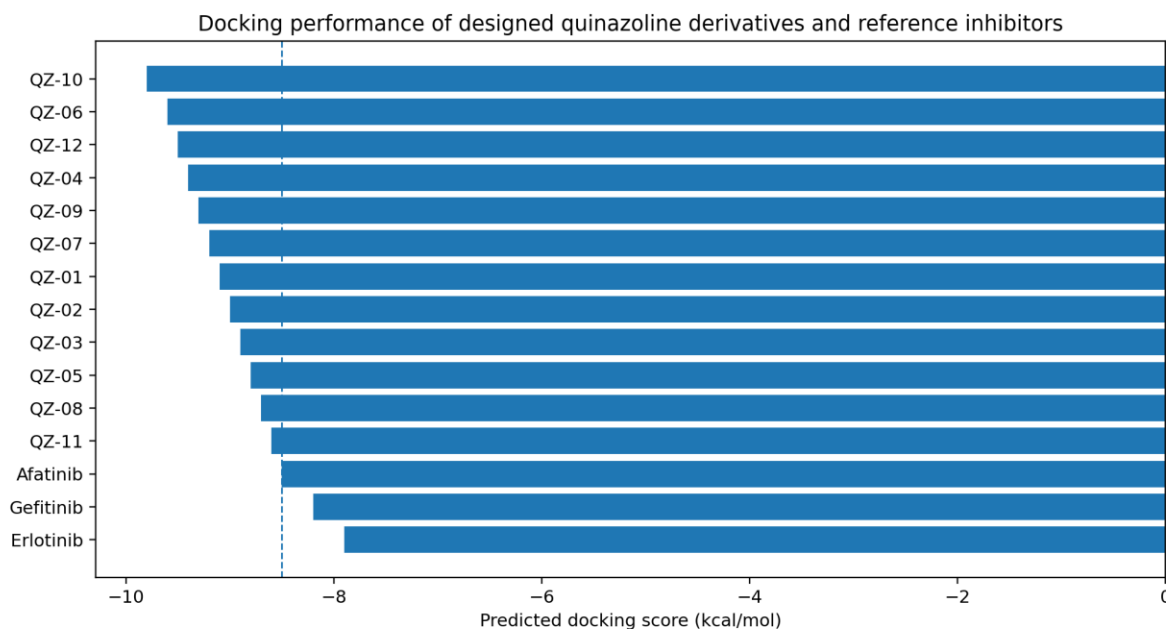


Figure 3. Recreated docking-score comparison for QZ-01–QZ-12 and the three reference inhibitors using the numerical results reported in the supplied study.

Compound	Docking score (kcal/mol)	Reported position
QZ-10	-9.80	1
QZ-06	-9.60	2
QZ-12	-9.50	3
QZ-04	-9.40	4
QZ-09	-9.30	5
QZ-07	-9.20	6
QZ-11	-8.60	12
Afatinib	-8.50	Reference
Gefitinib	-8.20	Reference
Erlotinib	-7.90	Reference

3.4 Docking Validation

The RMSD between the re-docked co-crystallized ligand and the original ligand is $1.18 \text{ \AA}$. This value was significantly lower than the specified criterion of $2.0 \text{ \AA}$ by $0.82 \text{ \AA}$ and considered as a PASS in

the source study. This finding provides internal consistency of the chosen protocol for pose prediction. It does not however, convert docking scores to experimentally determined binding energies, nor set up biological potency.

Validation metric	Observed value	Criterion	Outcome
Re-docking RMSD	1.18 Å	< 2.0 Å	PASS

3.5 Molecular Dynamics Results

A set of 6 designed complexes were chosen for 100-ns MD simulations. QZ-10 showed the lowest mean protein RMSD among the designed compounds at 0.119 nm, followed by QZ-06 (0.128 nm), QZ-12 (0.133 nm), QZ-09 (0.136 nm), QZ-04 (0.142 nm) and QZ-07 (0.151 nm). The

RMSD of protein structures in the reference complexes were 0.121 nm, 0.126 nm and 0.130 nm for erlotinib, gefitinib and afatinib, respectively. So, the mean RMSD for all proteins in QZ-10 is slightly smaller than the three reference complexes in the dataset reported.

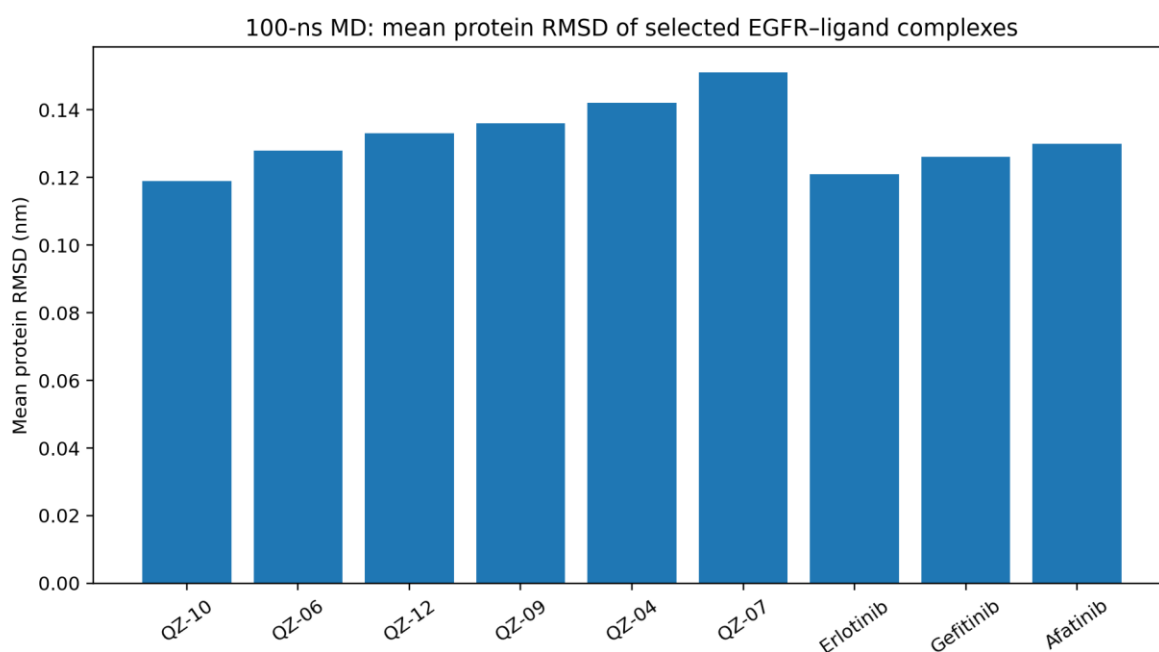


Figure 4. Recreated mean protein RMSD values from the reported 100-ns molecular-dynamics simulations.

Complex	Mean protein RMSD (nm)	Mean ligand RMSD (nm)	Mean H-bond value
QZ-10	0.119	0.460	4.5
QZ-06	0.128	0.480	4.2
QZ-12	0.133	0.490	4.1
QZ-09	0.136	0.500	4.0
QZ-04	0.142	0.520	3.8
QZ-07	0.151	0.550	3.6
Erlotinib	0.121	0.450	4.0
Gefitinib	0.126	0.470	3.9
Afatinib	0.130	0.490	4.1

Ligand RMSD values for the designed series ranged from 0.460 nm for QZ-10 to 0.550 nm for QZ-07. QZ-10 therefore had the lowest mean ligand RMSD among the designed compounds. The corresponding reference values were 0.450 nm for erlotinib, 0.470 nm for gefitinib and 0.490

nm for afatinib. Hydrogen-bond analysis further supported QZ-10, which showed a mean value of 4.5, followed by QZ-06 at 4.2 and QZ-12 at 4.1. The reference values were 4.0, 3.9 and 4.1 for erlotinib, gefitinib and afatinib, respectively.

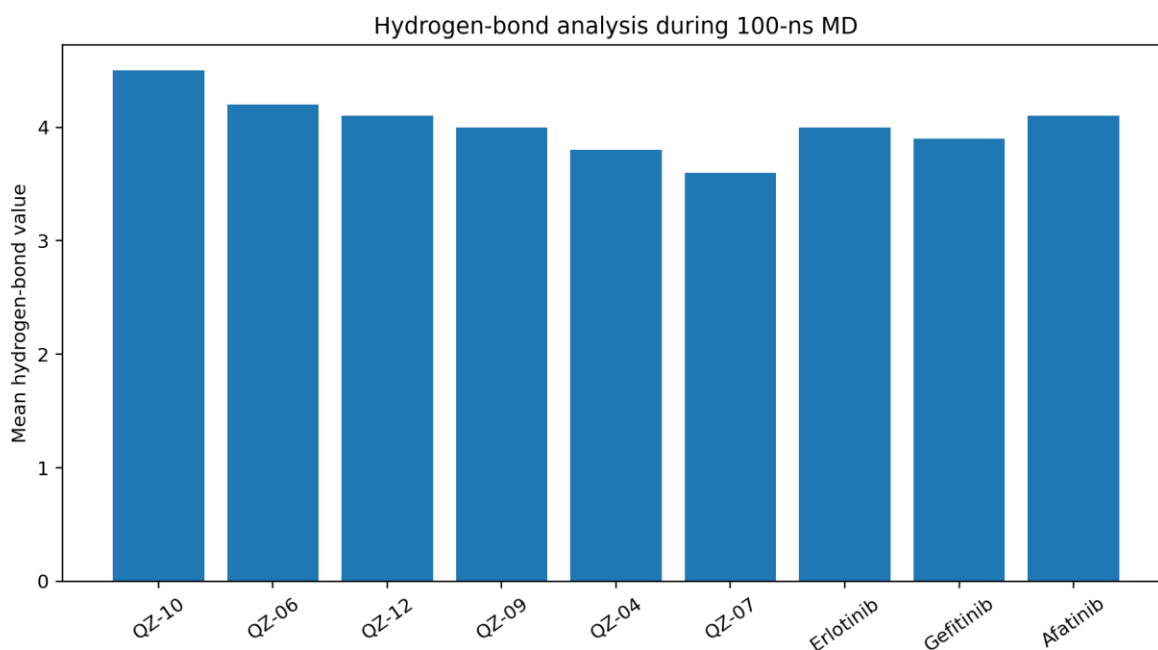


Figure 6. Recreated mean hydrogen-bond values reported during 100-ns molecular-dynamics simulations.

RMSF analysis indicated relatively low residue-level fluctuations in the selected complexes. For QZ-10, reported RMSF values ranged from 0.063 nm at Met769 to 0.097 nm at Gly772. Other residues associated with the binding environment included Val702 (0.073 nm), Ala719 (0.084 nm),

Phe723 (0.067 nm), Leu764 (0.080 nm), Leu768 (0.075 nm) and Lys745 (0.089 nm). These values were interpreted as evidence of comparatively controlled local fluctuations within the simulated system.

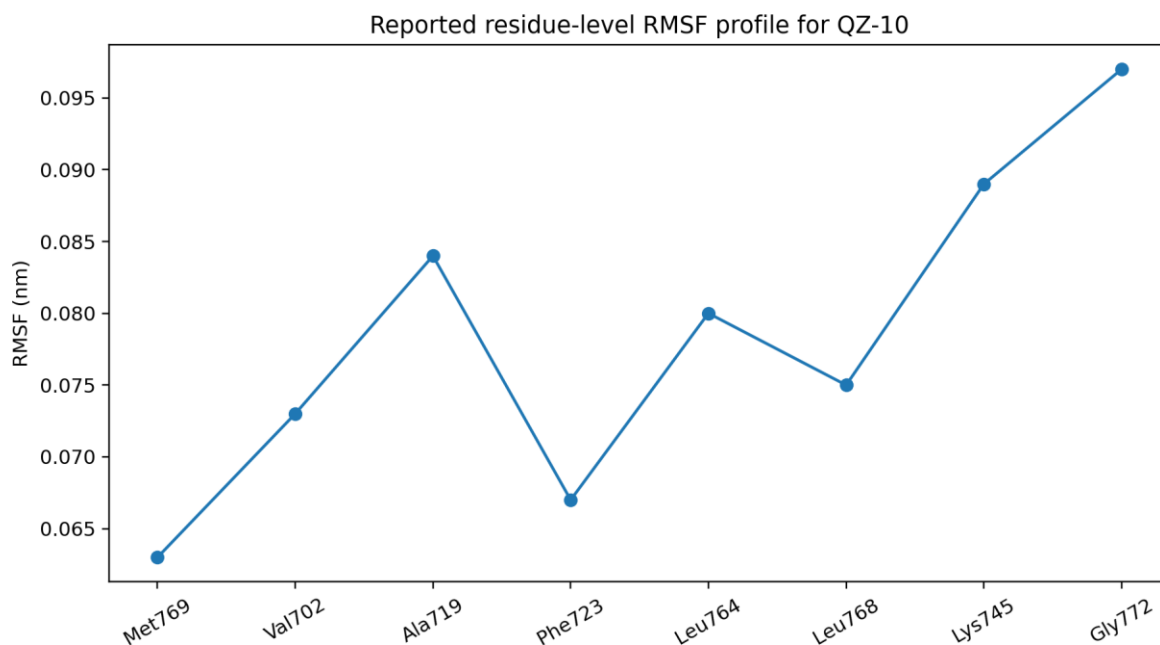


Figure 5. Recreated RMSF profile for the reported QZ-10 EGFR complex at the specified residues.

Derivative	Protein RMSD (nm)	Protein RMSD (nm)	SD	Mean H-bonds
QZ-10	0.119	0.165		4.5
QZ-06	0.128	0.172		4.2
QZ-12	0.133	0.176		4.1
QZ-09	0.136	0.181		4.0
QZ-04	0.142	0.186		3.8
QZ-07	0.151	0.194		3.6

3.6 ADMET and Drug-Likeness

The twelve designed derivatives were all reported as having a good predicted ADMET profile. There were no reported violations of the Lipinski criteria. The gastrointestinal absorption was predicted to be high, and the blood-brain barrier (BBB) penetration was predicted to be low throughout the series; no major toxicity alerts and low risk of CYP. The uniformity of these predictions is significant because it suggests that the predicted liability of the structural change from QZ-01 to QZ-12 was not a significant one in the prediction framework employed.

The molecular weight, LogP and TPSA values of the leading candidate QZ-10 were respectively 419.80 g/mol, 3.12 and 80.1 Å². For comparison, erlotinib had a reported molecular weight of

393.44 g/mol, LogP 2.70 and TPSA 72.7 Å²; gefitinib had 446.90 g/mol, LogP 3.00 and TPSA 68.6 Å²; and afatinib had 485.94 g/mol, LogP 4.10 and TPSA 84.7 Å². The Lipinski violations, gastrointestinal absorption, BBB penetration, toxicity alert and CYP risk were also reported as being low for the reference inhibitors.

3.7 Integrated Lead Prioritization

The integrated analysis lead to a clear ranking. The highest reported composite score was for QZ-10 (95), followed by QZ-06 (90) and QZ-12 (85). QZ-04, QZ-09 and QZ-07 received 80, 75 and 70, respectively. Lower composite scores were achieved for the reference inhibitors afatinib (65), gefitinib (60) and erlotinib (55). Importantly, the final ranking did not use only the docking, it also

used the dynamic stability, hydrogen-bond characteristics and predicted ADMET properties.

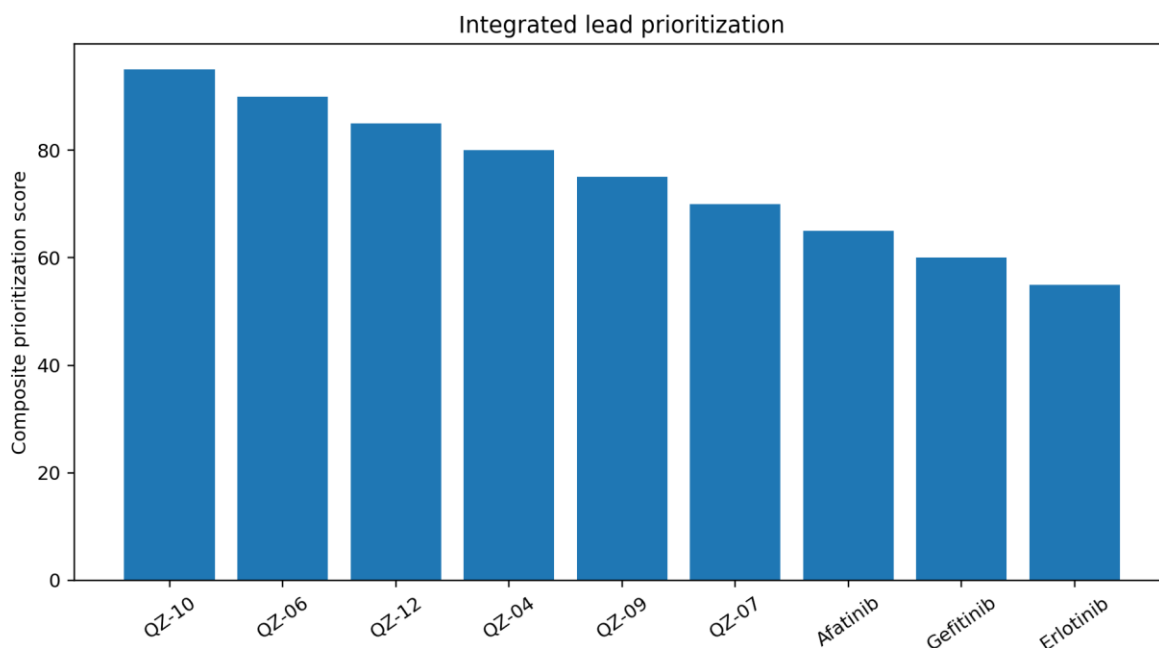


Figure 7. Recreated integrated lead-prioritization scores from the reported computational dataset.

Rank	Compound	Docking (kcal/mol)	Protein RMSD (nm)	Mean H-bonds	Composite score
1	QZ-10	-9.80	0.119	4.5	95
2	QZ-06	-9.60	0.128	4.2	90
3	QZ-12	-9.50	0.133	4.1	85
4	QZ-04	-9.40	0.142	3.8	80
5	QZ-09	-9.30	0.136	4.0	75
6	QZ-07	-9.20	0.151	3.6	70
7	Afatinib	-8.50	0.130	4.1	65
8	Gefitinib	-8.20	0.126	3.9	60
9	Erlotinib	-7.90	0.121	4.0	55

4. Discussion

The results validate the utility of a computational tool for drug prioritization in the early discovery phase of EGFR ligands that contain quinazolines. The main point taken was the uniformity of QZ-10 on several computational dimensions. It possessed the highest docking score, the lowest mean protein RMSD among the designed compounds, the lowest mean ligand RMSD within the designed set, the highest mean hydrogen-bond value and it had a favorable predicted ADMET profile. The two workflows QZ-

06 and QZ-12 showed coherent profiles, meaning that the workflow did not just pick out a single compound to investigate, but identified a small number of compounds to investigate.

4.1 Interpretation of Docking Results

The docking results show that there is a significant difference in the computational separation of the designed derivatives from the reference inhibitors. QZ-10 bound to the PDB target with a reported binding affinity of -1.30 kcal/mol more favorable than erlotinib, -1.60 kcal/mol more favorable than

gefitinib and -1.30 kcal/mol more favorable than afatinib in the reported docking dataset. All of the 12 designed derivatives were found to have better scores than the 3 references. This approach is in line with the idea that rational modification of a known scaffold can lead to the discovery of novel theoretical binding arrangements in the ATP binding region of the EGFR.

It is also remarkable that the reoccurring interaction situation is present. Val702, Leu768 were consistently found as hydrophobic contributors and Met769 as a hydrogen-bond interaction. The presence of these residues in the designed series implies that the derivatives did not bind to proteins at random locations on the protein surface, but instead have a common recognition pattern. Consistent with the current medicinal-chemistry rationale for the inhibition of EGFR by quinazoline derivatives [21–26].

However, the docking scores are only computational estimates of the binding free energy, and should not be used as a direct measure of the experimental binding free energy. Docking makes binding easier to handle the receptor flexibility, effects of solvents and other factors. Thus, it is not the superiority of QZ-10 in docking that should be interpreted as a sign of its greater ability to inhibit EGFR in biochemical or cellular assays, but rather as a sign of prioritization.

4.2 Value of Docking Validation

The use of the re-docking RMSD of 1.18 Å as an internal validation is useful since the selected protocol was able to reproduce the crystallographic ligand orientation within the pre-defined RMSD value of 2.0 Å. This helps to boost the confidence in the work flow applied to comparative pose screening. But validation of the reproduction of pose is not a validation of the quantitative affinity. A docking protocol can be used to recreate a reference pose without being able to predict absolute binding energies. Validation result, therefore, should encourage use of docking as a screening tool, and not as an alternative to experimental measurements of affinity.

4.3 Dynamic Stability of the Leading Candidates

The MD results support the prioritization of QZ-10 due to its lowest protein RMSD of 0.119 nm, which is slightly lower than the ones of the reference complexes reported in the study, among all the designed derivatives. It also had the lowest RMSD value of 0.460 nm in the set of designed series. Moreover, the mean hydrogen-bond value of QZ-10 was the highest (4.5). These indicators convey more information than any single indicator alone, as they indicate that the predominant docking pose was not one that had an obvious unfavorable trajectory behaviour in the simulated conditions.

Other noteworthy ones were QZ-06 and QZ-12. The mean protein RMSD values for them were 0.128 and 0.133 nm, respectively, and the mean hydrogen-bond values were 4.2 and 4.1. The values put them near QZ-10 and suggest that both require advancement to experimental testing. The results are in accord with the general idea of docking and MD, which is that a static docking pose cannot be used to make a time-dependent estimation as can be done with MD [31–35].

4.4 ADMET and Drug-Likeness as a Second Filter

The ADMET results are also important second layer evidence. Even though a molecule has strong predicted binding, it does not automatically mean that the molecule has properties that are favorable for drug development. All 12 compounds in the current series were predicted to meet the reported Lipinski criteria, have high gastrointestinal absorption and low BBB penetration and no major toxicity alert and low CYP risk. This consistency is especially helpful in prioritizing leads to chemical optimization as it does not require sacrificing clear predicted pharmacokinetic liability (PKLiability) in selecting QZ-10, QZ-06 and QZ-12.

The physicochemical trends also indicate that the series was modified relatively in a controlled manner. The molecular weight of the compounds shifted from 382.00 to 428.20 g/mol between QZ-01 and QZ-12, whereas TPSA values were within a relatively small range. This was a medium-high

molecular weight (419.80 g/mol), LogP (3.12), and TPSA (80.1 Å²) in this series. These properties were predicted to meet the criteria for drug-likeness used in the study.

4.5 Integrated Prioritization Rather Than Single-Metric Ranking

The great methodological advantage of the study is that the selection of the final molecules was not solely done on the basis of the docking score. Even if only docking was utilized, the rank would remain the same, but the extra MD and ADMET analyses offer additional computational dimensions for supporting the ranking of QZ-10. It did the same for QZ-06 and QZ-12, making them secondary leads. This multi-parameter logic is consistent with modern CADD use, in which a variety of methods will deal with different sources of uncertainty [27,32,36].

However, reported composite scores should be used with caution. These values are assigned from the source material as computational priority scores that are not genuine. They are a good way to arrange the candidate set but not to be interpreted as "actively calibrated" or "clinically successful" probabilities. The scientific results of the study are thus three computational hypotheses: QZ-10, QZ-06 and QZ-12, which are the most promising ones.

4.6 Relationship to Existing EGFR-Quinazoline Research

The results are part of a long line of work which has established that quinazoline derivatives are good substrates for rational design of EGFR inhibitors. To optimize the quinazoline-based compounds, previous studies applied docking, QSAR, molecular dynamics, ADMET prediction, and other computational methods [25-30]. The main contribution of the present study is that the one set of designed 12-member series, from the structural design to the docking, validation, dynamic analysis and prioritization of the series by ADMET, is treated in one workflow.

This integrated approach is especially important in light of the ongoing resistance problem. The presence of resistance mechanisms implies that none of the currently successful inhibitors will be

a complete solution and there is still room for further chemical space. Computational exploration can then be regarded as a discovery strategy that can be used at the front end to help identify structures that should be synthesized and tested. The present work does not give rise to resistance breaking activity, but offers candidates that can be explored in further experiments.

4.7 Limitations

Several limitations must be emphasized. First, the study is entirely computational: no chemical synthesis, biochemical EGFR inhibition assay, cellular cytotoxicity experiment or in-vivo study was performed. Second, docking scores are comparative predictions and are not experimentally measured binding free energies. Third, MD trajectories provide computational stability information under the selected simulation conditions, not proof of kinetic or thermodynamic stability in biological systems. Fourth, ADMET predictions are model-based estimates and cannot establish human pharmacokinetics or toxicity. Finally, the interaction and composite-prioritization values in the source dataset are identified as mock computational values in places; consequently, the results should be treated as hypotheses requiring experimental confirmation.

5. Conclusion

In this work, 12 novel quinazoline derivatives were designed and screened for their activity against EGFR, through an integrated computational drug design workflow. The 3D structure of EGFR (PDB 7AEI) was generated for docking and then all the 12 derivatives were compared with erlotinib, gefitinib and afatinib. The designed series yielded docking scores of between -9.80 and -8.60 kcal/mol, with QZ-10 yielding the most favourable docking score (-9.80 kcal/mol). The RMSD obtained during docking validation was 1.18 Å, which is within the acceptable limit of < 2.0 Å. Six of these compounds were taken forward to 100-ns MD simulations. The lowest mean protein RMSD value (0.119 nm) was observed for QZ-10, while the lowest mean ligand RMSD value within

the designed series was 0.460 nm for QZ-10 and the highest value was 4.5 for hydrogen-bond for the same molecule. Dynamic profiles of QZ-06 and QZ-12 were also good. All 12 compounds designed were predicted to be non-violating the drug-likeness and ADMET criteria, with a high gastrointestinal absorption, low BBB penetration, no major toxicity alert and low CYP risk.

The integrated prioritization resulted in QZ-10 being the first, QZ-06 second and QZ-12 third. These compounds are thus the most promising ones from the above-reported computational data set for experimental investigations. They should not be said to be "confirmed anticancer agents", however. The activity and/or pharmacokinetic properties they predict should be evaluated experimentally in real biological systems via chemical synthesis, biochemical EGFR inhibition assays, and cellular assays. The novelty of the present study is therefore that it allows for the reduction of the large theoretical chemical space to a small number of testable quinazoline leads.

6. Future Directions

Synthesis and structural confirmation of QZ-10, QZ-06 and QZ-12 are the next steps to be started. They then should be evaluated for possible biochemical activities against EGFR to be followed by cellular tests in appropriate EGFR dependent NSCLC models. In the event of confirmed activity, other optimizing parameters should be considered such as selectivity, resistance associated EGFR variants and pharmacokinetic behaviour. The experimental results can then be utilized to improve the computational models and develop structure-activity relationships for the quinazoline series. In this manner, the computational predictions can serve as a rational starting point and not an end of the drug discovery process.

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