

PREDICTION OF EGFR–QUINAZOLINE DRUG INTERACTIONS
USING MOLECULAR DOCKING AND MOLECULAR DYNAMICSMuhammad Hammad Ali Akbar^{*1}, Dr Rashid Mahmood²^{*1,2}Faculty of Sciences, Superior University of Lahore, Lahore^{*1}hamadalikhan179@gmail.com, ²rashid.mahmood.sgd@superior.edu.pkDOI: <https://doi.org/10.5281/zenodo.22244298>**Keywords**

EGFR, Quinazoline, Molecular docking, Molecular dynamics, Drug design, NSCLC, protein–ligand interaction.

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Abstract

EGFR is a known target molecule in non-small cell lung cancer (NSCLC) and acquired resistance is still a challenge for EGFR-targeted therapy. Structural scaffold of quinazoline containing compounds are useful for structure based inhibition development. A computational approach involving ligand preparation, receptor preparation, binding-site definition, molecular docking, protein–ligand interaction analysis and molecular dynamics (MD) studies of the selected complexes was employed in this study to assess the twelve quinazoline-based compounds against EGFR. All 12 ligands could be successfully optimized, with molecular weights ranging from 284.28 to 418.05 g/mol, minimized energies from -8.84 to -17.77 kcal/mol, and net partial charges from -0.210 to +0.144. The docking scores were found to vary from -7.84 to -9.41 kcal/mol. QZ-12 showed the most favorable docking score (-9.41 kcal/mol), followed by QZ-05 (-9.28), QZ-10 (-9.12), and QZ-11 (-9.01). They were then chosen for dynamic evaluation, these four compounds. Predicted interactions include hydrogen bonding, hydrophobic, electrostatic and π -interactions with important EGFR residues such as Leu718, Val726, Ala743, Lys745, Thr790, Gln791, Leu792, Met793, Gly796, Leu844, Asp855 and Phe856. During the MD analysis, the lowest mean RMSD (1.46 Å) was obtained with QZ-12, while the lowest final RMSD (1.74 Å), lowest mean RMSF (0.98 Å), lowest radius of gyration (21.15 Å) and highest interaction persistence (88.0%) were achieved with QZ-11. In general, the compounds QZ-12, QZ-11, QZ-05 and QZ-10 were determined as the most promising for further investigation. The results are computational predictions which need to be validated by experiments.

1. Introduction

The discovery of new therapeutic agents is expensive, and has significant attrition, so molecular computing technologies are being used to prioritize compounds prior to the extensive experimental testing. A wide variety of structure-based drug discovery methods utilize molecular docking which places possible orientations of a ligand into a binding site of a target protein and estimates the relative binding affinity. The real strength of this is its comparative aspect: compounds can be ranked

and their expected interaction patterns studied prior to synthesis or biological testing [1–4].

EGFR is an important receptor tyrosine kinase in lung cancer. Tumour promoting signalling can be maintained via dysregulated EGFR signalling, such as activating alterations, and mechanisms of acquired resistance. Because the heteroaromatic ring is able to fit into the ATP binding pocket of the EGFR and the substituents can be modified to modify interactions, selectivity and resistance profiles,

quinazoline and related scaffolds have been widely explored as EGFR inhibitors [1,5–7].

An advantage of the conventional docking method is that the flexibility of the receptor, the solvent effect and the binding energetics are simplified. Molecular dynamics could be used alongside docking to study the dynamics of a docked protein–ligand complex and generate

parameters like RMSD, RMSF, compactness, interaction persistence etc. [2,8,9]. For this reason, the present study focused on the docking of 12 quinazoline compounds to prioritize them and then an analysis of the interactions between the compounds and the receptor, with the help of MD-derived stability measures, identified candidates for further study.

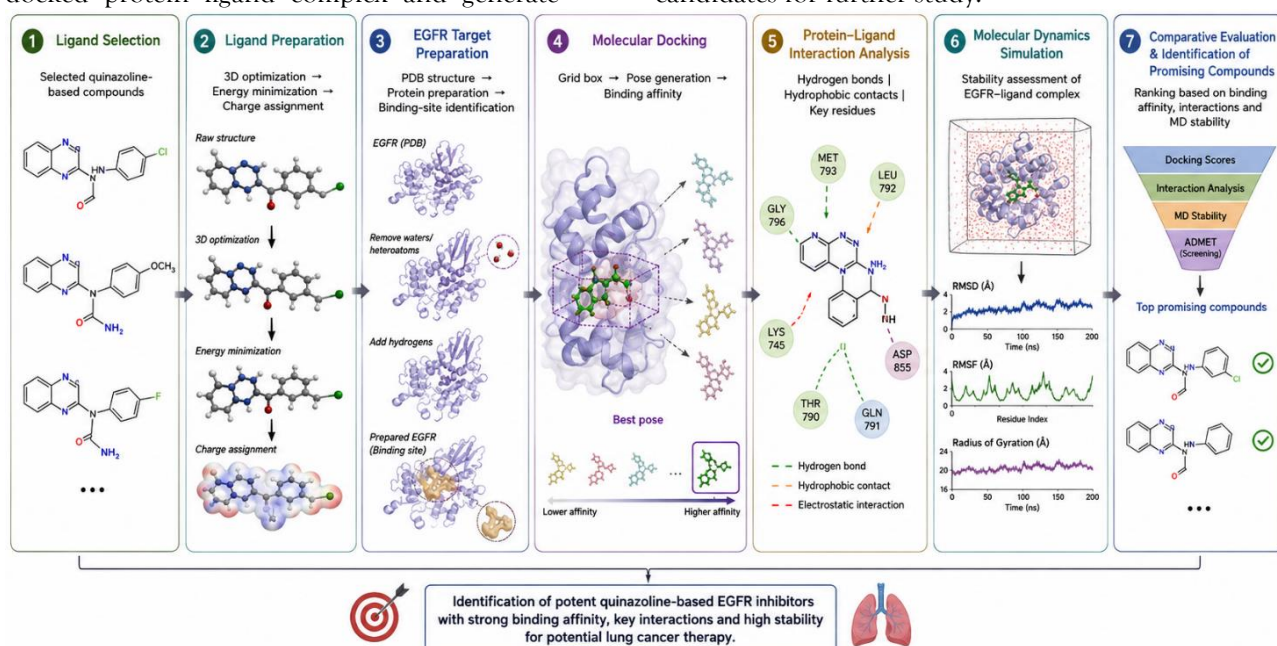


Figure 1. Computational workflow and representative quinazoline structures used in the study

2. Materials and Methods

2.1 Computational design

The study adopted a computational sequential workflow of ligand selection and optimization, retrieval and preparation of the EGFR structure, identification of the binding site, molecular docking, molecular interaction analysis, and comparative assessment. The docking framework included AutoDock/AutoDock Vina and the protein structure used as the receptor was obtained from the Protein Data Bank [4].

2.2 Ligand and receptor preparation

A set of 12 quinazoline ligands have been structurally prepared and energy minimized. Hydrogen atoms and appropriate atomic charges were assigned. A water molecule was removed, non-essential heteroatoms and unwanted co-crystallized ligands were removed, hydrogen atoms were added and charges were assigned to the EGFR receptor. The docked grid was then

placed around the chosen EGFR binding region, and the docking process involved sampling the conformation of ligands.

2.3 Docking and interaction analysis

The docking poses were sorted by the predicted binding score. For the top-ranked poses, hydrogen bonds, hydrophobic contacts, electrostatic interactions, π -interactions, interacting residues and pose RMSD were analyzed. As with the limitations of docking scoring functions [8,9], docking scores were considered relative computational binding free energies rather than actual experimental binding free energies.

2.4 Molecular dynamics analysis

The four compounds that had docking scores less than -9.00 kcal/mol were chosen for further MD studies. The mean and final RMSD, residue-level RMSF, radius of gyration, mean hydrogen-bond counts and interaction

persistence were included in the reported trajectory analysis. These measures were combined with docking and interaction results to rank compounds instead of using a single computational measure.

3. Results

3.1 Ligand preparation and physicochemical range

It was possible to prepare all twelve compounds for docking. The molecular weights were between 284.28 and 418.05 g/mol. QZ-07 had the highest molecular weight (418.05 g/mol), whereas QZ-08 had the lowest (284.28 g/mol). The minimized energies were in the range of

−8.84 to −17.77 kcal/mol, and QZ-12 and QZ-10 had the lowest values of −17.77 and −17.24 kcal/mol, respectively. Net partial charges ranged from −0.210 to +0.144.

3.2 Molecular docking performance

Each of the 12 compounds had their own unique predicted affinity for EGFR. Docking scores were between −7.84 to −9.41 kcal/mol. QZ-12 ranked first, followed by QZ-05, QZ-10, and QZ-11. QZ-04 and QZ-06 were tied at −8.99 kcal/mol, while QZ-08 had the weakest score (−7.84 kcal/mol). The best compound was 1.57 kcal/mol different from the weakest compound.

Table 1. Docking-score ranking of the twelve quinazoline compounds against EGFR.

Rank	Compound	Docking score (kcal/mol)
1	QZ-12	-9.41
2	QZ-05	-9.28
3	QZ-10	-9.12
4	QZ-11	-9.01
5	QZ-04	-8.99
5	QZ-06	-8.99
7	QZ-02	-8.73
8	QZ-09	-8.66
9	QZ-01	-8.5
10	QZ-03	-8.29
11	QZ-07	-7.95
12	QZ-08	-7.84

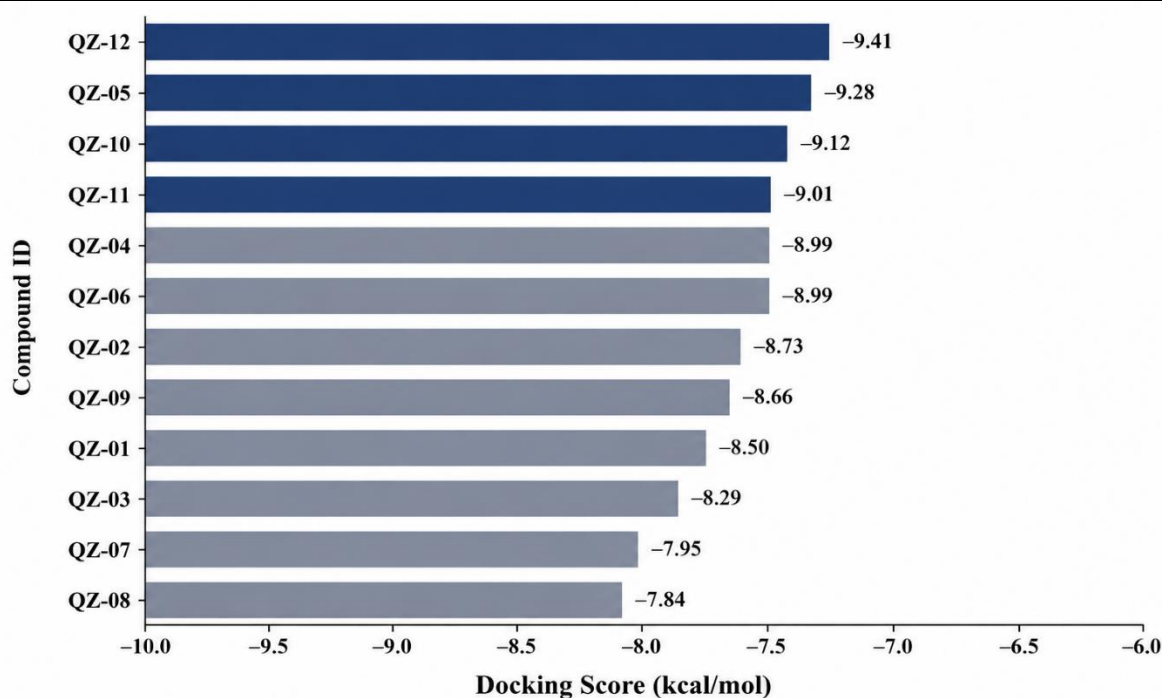


Figure 2. Molecular docking scores of the twelve quinazoline compounds against EGFR.

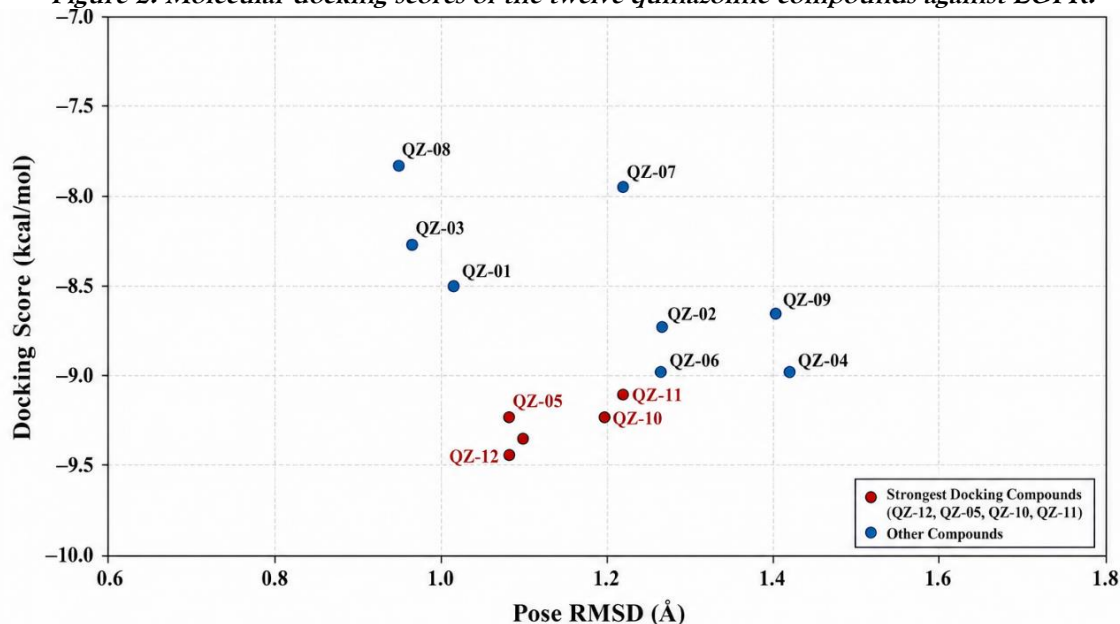


Figure 3. Relationship between docking score and pose RMSD for the selected compounds.

The RMSD values for docking pose varied from 0.96 to 1.39 Å. QZ-08 had the lowest pose RMSD (0.96 Å), followed by QZ-03 (0.97 Å) and QZ-01 (1.01 Å). Among the four strongest docking compounds, QZ-05, QZ-12, QZ-10, and QZ-11 showed pose RMSD values of 1.10, 1.12, 1.20, and 1.24 Å, respectively. Therefore the highest docking score was not the lowest pose RMSD value.

3.3 Protein–ligand interaction profiles

The complexes predicted had 1–3 hydrogen bonds, 3–6 hydrophobic contacts, 0–2 electrostatic contacts and 0–2 π -interactions. Both QZ-05 and QZ-11 had the same number of hydrophobic contacts (6), and QZ-11 also exhibited two electrostatic contacts. There were 4 hydrophobic contacts and 2 electrostatic contacts between QZ-12. QZ-03 had the maximum number of hydrogen bonds (three)

while QZ-12 had only one hydrogen bond, even when it had the best docking score.

Using residue level analysis, Leu718, Val726, Ala743, Lys745, Thr790, Gln791, Leu792, Met793, Gly796, Leu844, Asp855 and Phe856 were identified as important predicted

interaction residues. Each EGFR molecule has a different residue-level profile, with QZ-12 interacting with six EGFR residues (Phe856, Lys745, Leu844, Asp855, Leu718, Gln791) and QZ-11 interacting with the widest range of residues, eight.

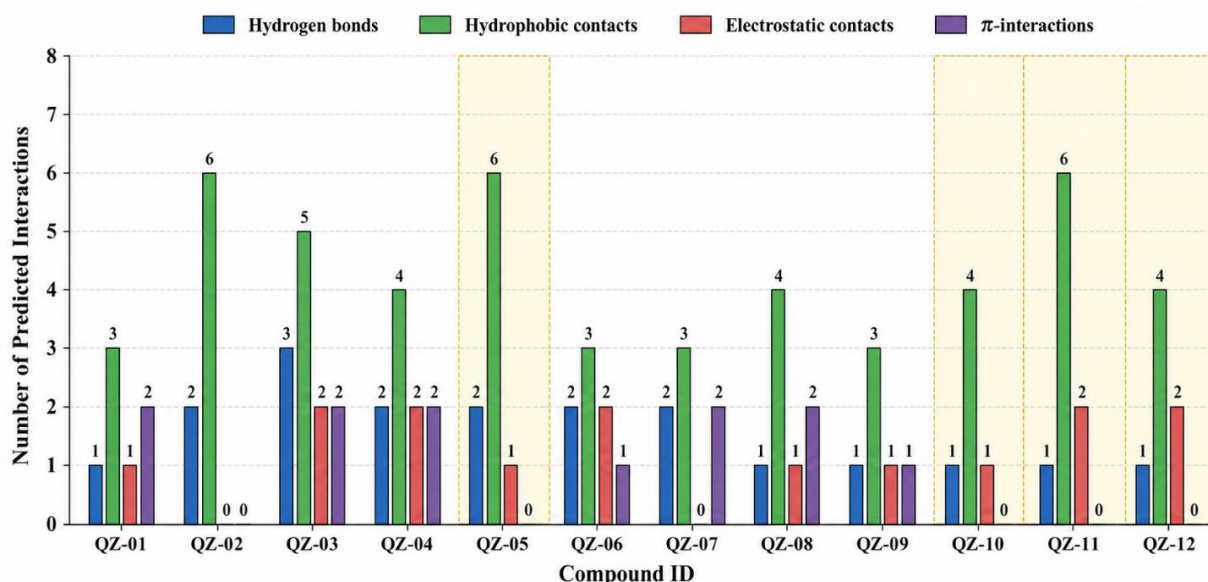


Figure 4. Comparative protein-ligand interaction profiles of the quinazoline compounds.

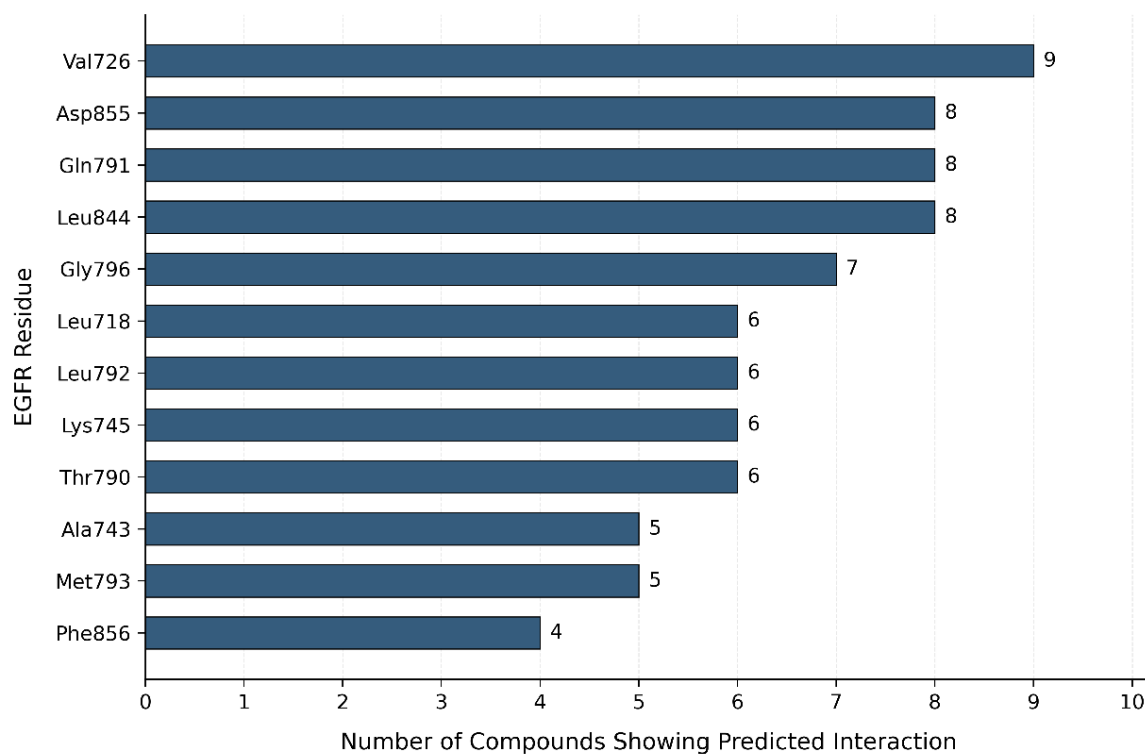


Figure 5. Frequency of EGFR residues involved in predicted ligand interactions.

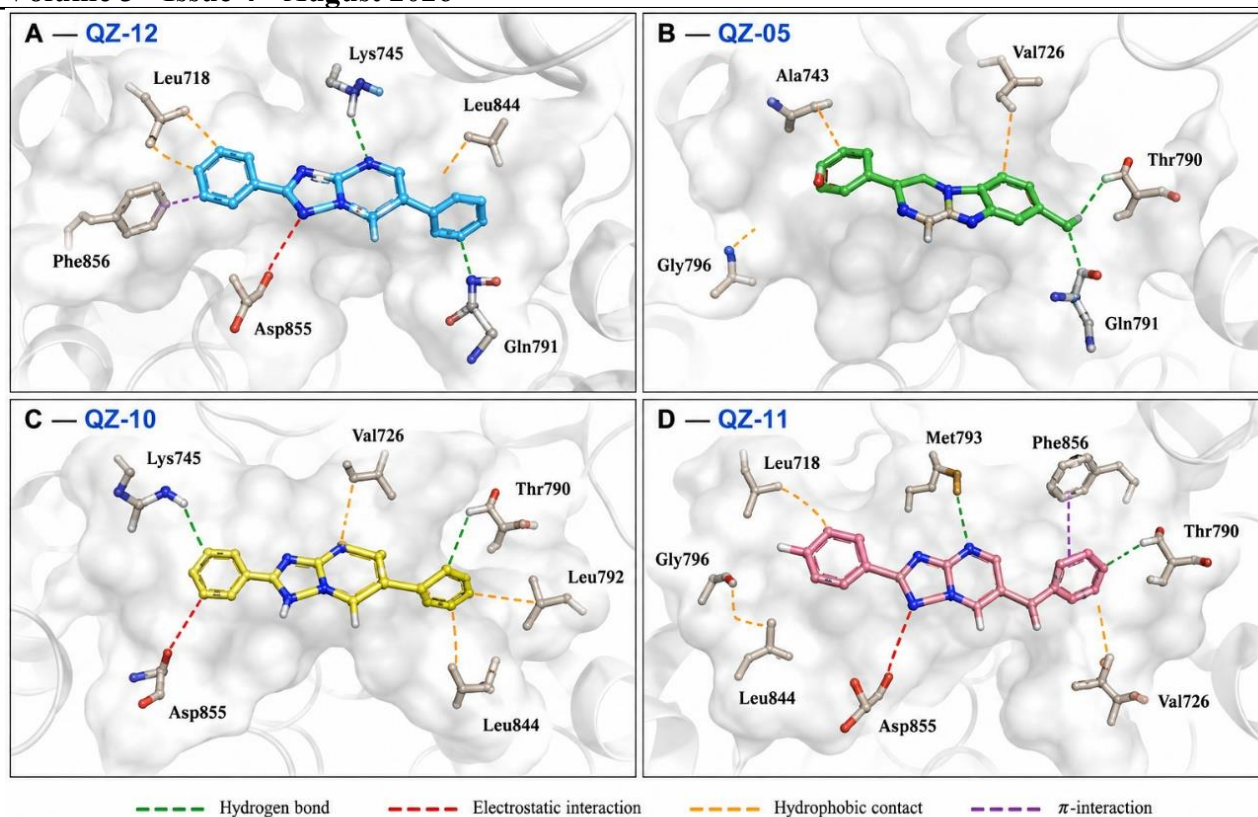


Figure 6. Three-dimensional binding modes of QZ-12, QZ-05, QZ-10, and QZ-11 in the EGFR binding pocket

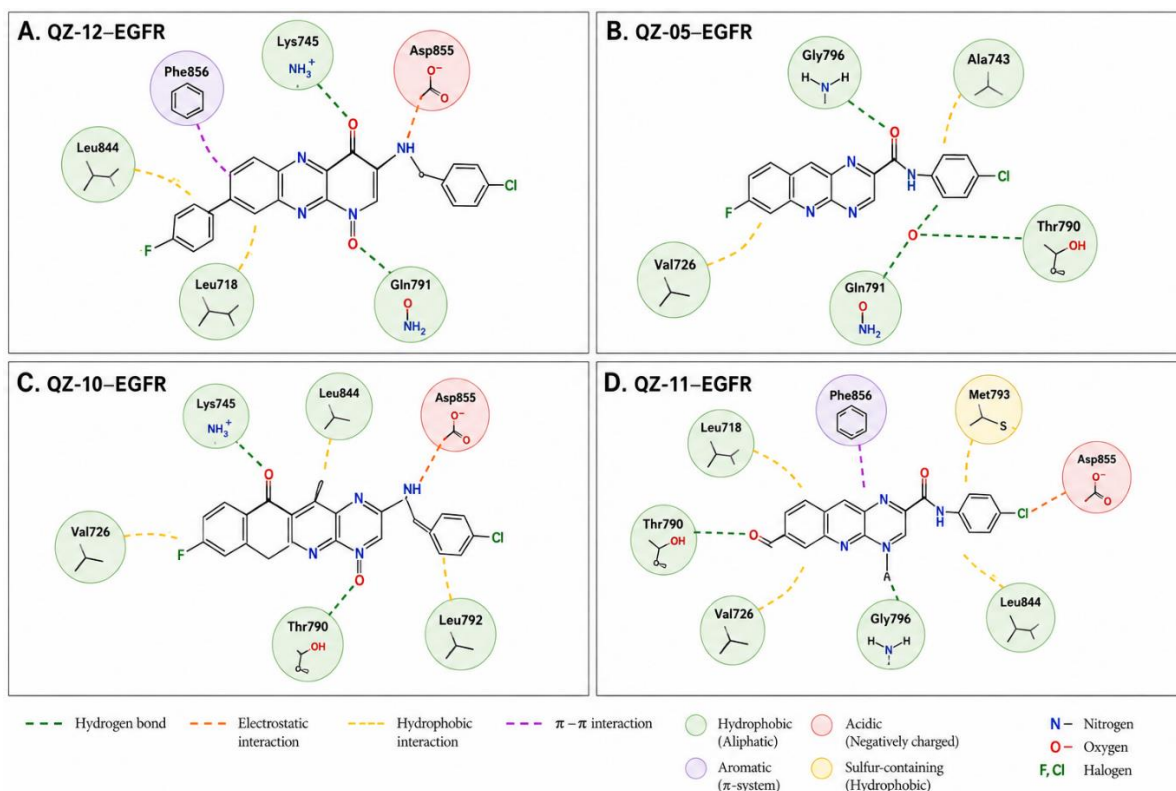


Figure 7. Two-dimensional interaction maps of the four prioritized EGFR-quinazoline complexes

Table 2. Comparative docking and interaction characteristics of the four compounds selected for MD analysis.

Compound	Docking score	Pose RMSD	H-bonds	Hydrophobic	Electrostatic
QZ-12	−9.41	1.12 Å	1	4	2
QZ-05	−9.28	1.10 Å	2	6	1
QZ-10	−9.12	1.20 Å	1	4	1
QZ-11	−9.01	1.24 Å	1	6	2

3.4 Molecular dynamics stability

The RMSD values of the four prioritized complexes were found to be 1.46–1.62 Å when analyzed by MD. QZ-12 had the lowest mean RMSD (1.46 Å), followed by QZ-11 (1.49 Å), QZ-10 (1.60 Å), and QZ-05 (1.62 Å). Final

RMSD values were 1.74 Å for QZ-11, 1.81 Å for QZ-12, 1.95 Å for QZ-05, and 2.07 Å for QZ-10. The mean RMSF for all compounds was between 0.98 and 1.46 Å with the lowest value for QZ-11.

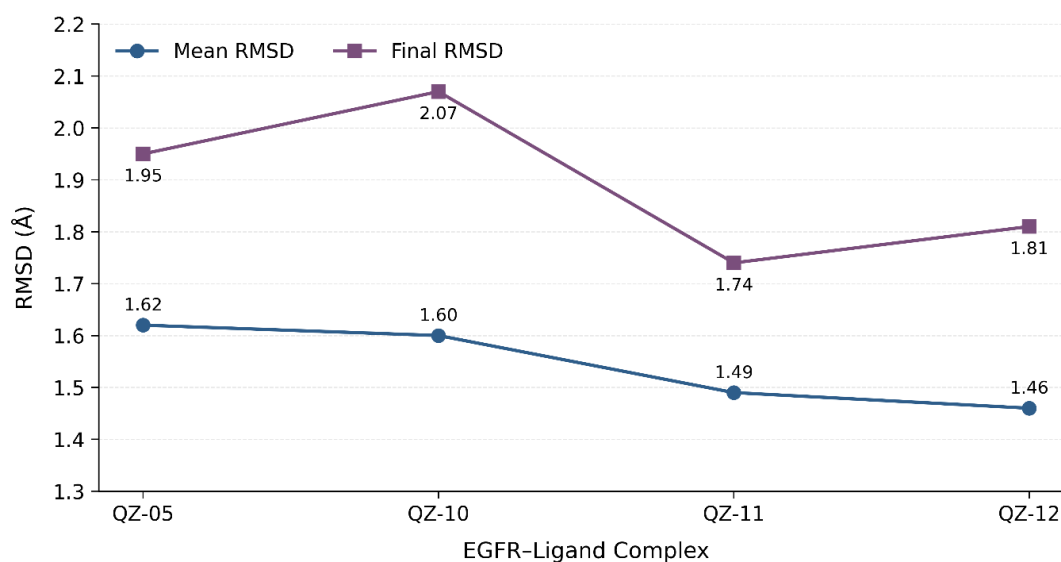


Figure 8. Mean and final RMSD values for the four selected EGFR–ligand complexes

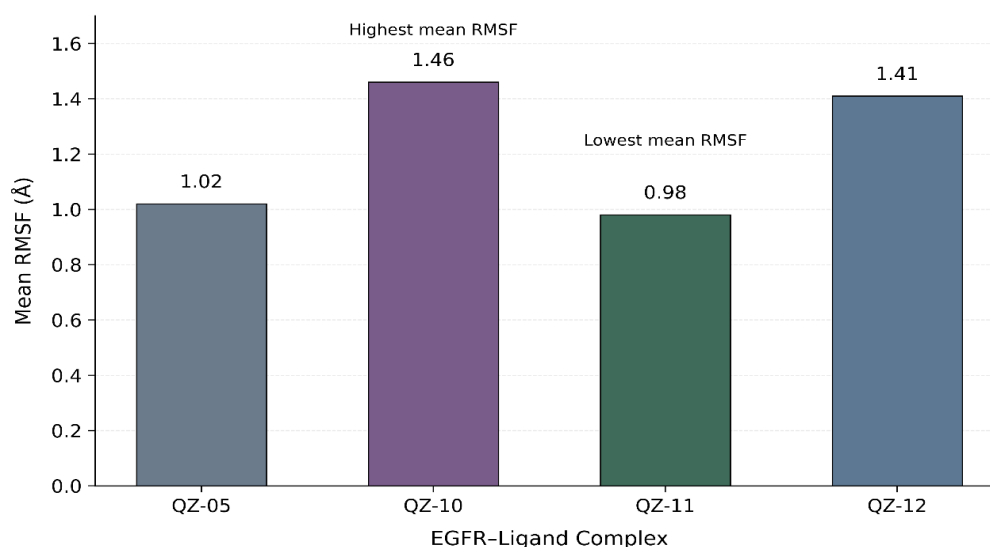


Figure 9. Comparative mean RMSF values for the selected EGFR–ligand complexes.

The radius of gyration ranged from 21.15 to 22.79 Å. QZ-11 had the lowest value (21.15 Å), followed by QZ-05 (21.24 Å) and QZ-12 (21.42 Å), while QZ-10 showed the highest value (22.79 Å).

Mean hydrogen-bond counts ranged from 1.6 to 2.8, with QZ-10 highest at 2.8. Interaction persistence ranged from 81.6% to 88.0%, with QZ-11 showing the highest persistence (88.0%).

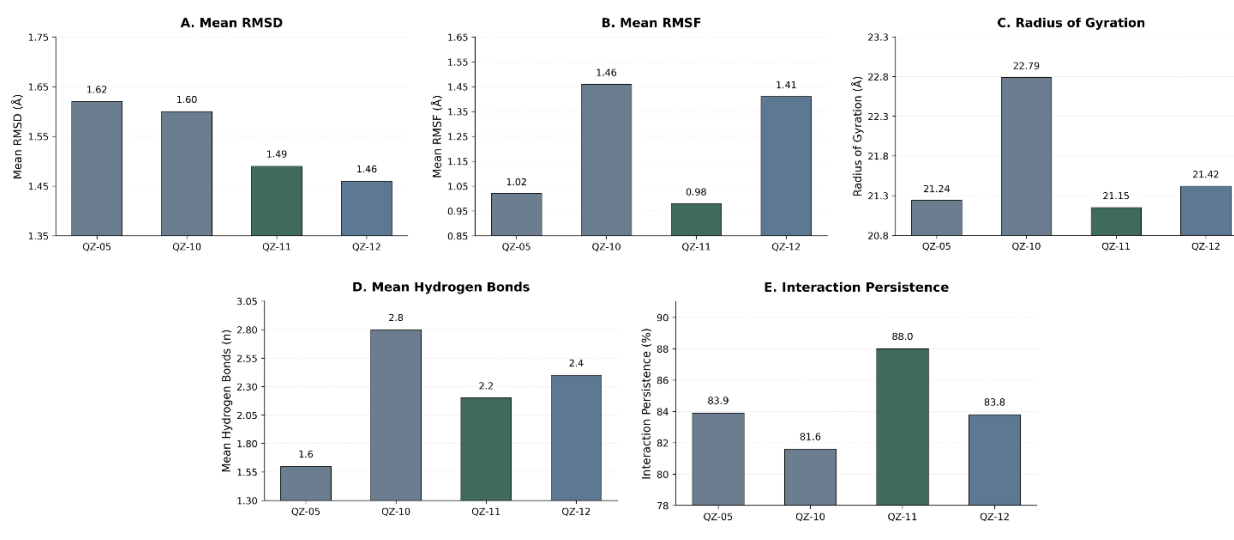


Figure 10. Comparative molecular-dynamics metrics for the selected complexes, including radius of gyration, hydrogen bonding, and interaction persistence.

Table 3. Molecular-dynamics stability and interaction-persistence metrics reported for the four prioritized complexes.

Compound	Mean RMSD (Å)	Final RMSD (Å)	Mean RMSF (Å)	Rg (Å)	Interaction persistence
QZ-05	1.62	1.95	1.02	21.24	83.9%
QZ-10	1.60	2.07	1.46	22.79	81.6%
QZ-11	1.49	1.74	0.98	21.15	88.0%
QZ-12	1.46	1.81	1.41	21.42	83.8%

4. Discussion

This computational analysis shows that structures within the quinazoline series that vary gave measurable differences in predicted EGFR binding. The highest docking score and the best dynamic profile (lowest mean RMSD) was obtained for QZ-12. QZ-05 had a strong docking result in addition to having 6 hydrophobic contacts and low mean RMSF result. Among the MD selected compounds, QZ-10 had the highest mean H-bond count while QZ-11 had the widest interaction profile at the residue level and the highest persistence of interactions. The observations confirm the thesis statement that several descriptors are needed to evaluate computational performance, and not just the docking score. The interaction data agree with

the significance of the EGFR kinase binding environment. The residues that are found in more than one copy in the structure, Leu718, Lys745, Thr790, Met793, Leu844, Asp855, and Phe856 all recur and offer a structural framework for understanding the comparison of the ligands and possible differences in the way the quinazoline core is accommodated. Previous structure-activity and computational studies also highlight that the substitutions of quinazoline may influence affinity, selectivity, and resistance-related properties [5,7,10]. One important result is that there is no direct correlation between the docking score and pose RMSD. The pose RMSD for QZ-08 was the lowest, while the docking score was the lowest for the same compound. The pose RMSD for

QZ-12 was moderate, while the docking score was the highest for the same compound. This underscores the importance of using docking scores and pose similarity in combination with interaction chemistry and, if possible, dynamic stability. The molecular dynamics distinguished among the four best docking candidates, especially for QZ-11 which had a relatively poor docking score when compared to QZ-12, but the interaction network was the longest lived.

5. Conclusion

A computational study comparing the interactions of 12 quinazoline-based compounds with EGFR revealed significant differences in their predicted binding with EGFR. QZ-12 produced the best docking score (−9.41 kcal/mol), followed by QZ-05, QZ-10, and QZ-11. The analysis of interactions revealed that the combinations of hydrogen bonding, hydrophobic contacts, electrostatic and residue complementarity was associated with favorable docking, and not the individual interactions. The favorable stability properties were also identified by the MD analysis, with the lowest mean RMSD being observed for QZ-12, and the lowest final RMSD, lowest mean RMSF, lowest radius of gyration, and highest interaction persistence observed for QZ-11. The main candidates for further investigation are QZ-12, QZ-11, QZ-05, and QZ-10, based upon the integrated computational profile. This data should be considered to be prioritization data and not evidence of anticancer activity. Independent molecular-dynamics replication and/or more comprehensive free-energy calculations, ADMET assessment, biochemical EGFR inhibition assay, cellular studies and ultimately appropriate in vivo validation should proceed. The computational ranking can then be used as a rational basis for picking compounds for these more costly stages.

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