Indian Journal of Pharmaceutical Chemistry and Analytical Techniques (IJPCAT)
ISSN: 3049-3765 | Vol. 01, Issue-01, July-Aug, 2025, pp. 26-39
https://ijpcat.com/1

Design And Synthesis of Novel Quinazoline Derivatives as Potent EGFR Inhibitors for Cancer Therapy

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ABSTRACT

Quinazoline-based compounds have been shown to be important scaffolds in the tyrosine kinase inhibitors particularly in the treatment of the epidermal growth factor receptor (EGFR) in cancer chemotherapy. The present study is focused on the synthesis, design, and testing of a series of new quinazoline-related structures due to their possible inhibitory effects to the EGFR. A series of twelve quinazoline derivatives were designed based on structure of a drug and synthesised via a multi-step synthetic procedure along the path of nucleophilic substitution and formation of amide bonds. FTIR, NMR and mass spectrometry were used to determine the nature of the compounds. Cytotoxicity of compounds was measured in vitro by examination of inhibited cell growth in A549 (lung carcinoma) and MCF-7 (breast cancer) cell lines through MTT assay. Auto Dock Vina molecular docking results indicated high binding affinity scores of QZ-3, QZ-5 and QZ-9 in the ATP-binding site of EGFR starting at -9.8 kcal/mol to -11.2 kcal/mol. QZ-5 was the most cytotoxic (IC 50 = 1.6 um) as well as selective EGFR inhibitor (IC 50 = 0.8 um). The findings validate the possibility of these derivatives as the lead of the cancer therapy against EGFR.

Key Words:

Quinazoline Derivatives, EGFR Inhibitors, Cancer Therapy, Molecular Docking, Tyrosine Kinase, Synthesis

Article History:

Received on Feb 06, 2024

Revised on May 27, 2025

Accepted on June 28, 2025

Published on August 6, 2025

DOI: https://doi.org/10.64062/IJPCAT.Vol1.Issue4.3

1. INTRODUCTION

Cancer remains a significant health challenge globally and this is despite the fact that cancer is one of the leading causes of death and disability[1]. The world health organization (WHO) indicates that about 10 million deaths per year are due to cancer; this is the highest cause of death in the world, although the cases of lung and breast cancer are the most widespread in the world. In particular, non-small-cell lung cancer (NSCLC) consists of very few cases of around 85% lung cancer and is showing resistance to normal chemotherapy in most cases, there is some dire need of targeted and more efficacious treatment plans. Since the last twenty years, the targeted blocking of molecular pathways implicated in tumour growth and survival has proven to be one of the most promising avenues in oncology[2].

Epidermal growth factor receptor (EGFR) is a trans membrane tyrosine kinase receptor that regulates important cellular activities which entail proliferation, differentiation, angiogenesis and apoptosis[3]. EGFR overexpression or mutation has been detected in various cancers, such as NSCLC, colorectal cancer or even breast cancer, and this hyperactive signaling among cells results in the growth of the cancerous processes and poor outcome of the patients[4]. Therefore, EGFR has been identified as an important molecular target in the event of anti-cancer drug development[5]. Various generations of EGFR inhibitors have been developed and since gefitinib was approved in 2003 and erlotinib in 2004 both using the quinazoline scaffold, have proved to be highly successful against EGFR-mutated malignancies. However, acquisitive resistance, such as T790M mutation, as well as low selectivity and particular efficacy in distinct patient cohorts are limiting factors to such drugs[6].

Considering these issues, there is an urgent interest in the production of new EGFR inhibitors with potencies, precise measures and minimal ability in resisting techniques[7]. Quinazoline is still a privileged heterocyclic scaffold to develop such-like inhibitors because of its intrinsic capacity to bind hydrogen bonds in the ATP-binding site of EGFR kinase domain[8]. The pharmacodynamic properties also allow room to improve through structural modifications at the 4-, 6-, and 7-positions of quinazoline nucleus to address any existing shortcomings[9].

1.1 Background Information

One of the most common and the threat to life is cancer; estimates show that it kills 10 million people every year. Non-small-cell lung cancer (NSCLC) and breast cancer are some of the causes of cancer deaths in the world. Treatments of several cancers at in-advanced stages are not effective as they are resistant to care and specific action, which make the prognosis poor regardless of the efforts made to help diagnosis and treatment at the early stages. This has increasingly seen the increased significance of molecularly targeted therapies in oncology.

The epidermal growth factor receptor (EGFR) is a membrane receptor tyrosine kinase, which is regulated by several important processes of the cell including differentiation, apoptosis, survival, and proliferation. EGFR over expression or mutation has been noted across many types of malignancies and is thus, linked with highly aggressive tumor behaviour and poor clinical response. The key position of EGFR in tumor biology has made the receptor an appropriate target and an appealing target in cancer drug development.

Quinazoline is a well-known medicinal chemistry scaffold, especially as the scaffold that underlies many tyrosine kinase inhibitors. Such 4-anilinoquinazoline-based products as gefitinib and erlotinib have been proven clinically successful as EGFR targeted drugs approved by the FDA. Nevertheless with the development of drug resistance like the T790M mutation in EGFR and lower effectiveness in tumor variability, there has been imperativeness on the need to develop new derivatives which would possess greater selectivity and potency.

1.2 Statement of the Problem

Despite the clinical efficacy of existing quinazoline-derived EGFR inhibitors, drug resistance, ineffective pharmacokinetic characteristics, and low selectivity of developed drugs towards mutant forms of EGFR are common. Evolution of resistance particularly in tumors with secondary mutations will make the existing drugs such as gefitinib much less effective.

Therefore, there is an urgent need to develop and synthesize new quinazoline-based hybrid structural analogs that would not only surmount resistance barriers, possess greater binding affinity to EGFR as well as greater cell toxicity to EGFR-immortalized cancer cells.

1.3 Objectives of the Study

The current research seeks to overcome the weaknesses of the current EGFR inhibitors by making adjustments on the design and synthesis of a series of new quinazoline derivatives across the board in the quest to strike stimulating biological activity. The specific objectives of the study are:

- To generate new quinazoline derivatives using structural information on the EGFR ATP-binding site.
- To synthesize and purify these compounds to their characterization by standard method of analysis and spectroscopy.
- To determine the cytotoxic appeal of the created derivations in various human malignancy cell lines.

1.4 Hypotheses

- H_1: Novel quinazoline derivatives with targeted structural modifications will exhibit enhanced binding affinity to the EGFR active site compared to existing inhibitors.
- H_2: The synthesized quinazoline derivatives will demonstrate greater cytotoxic activity against EGFR-overexpressing cancer cell lines than the standard drug gefitinib.

2. METHODOLOGY

The research was conducted with the help of multi-disciplinary and rational methodological approach to synthesis, design and assessment of the new quinazoline derivatives as a tool to have new potential EGFR inhibitor of cancer therapy. The project design consists of a combination of computational, synthetic, analytical and biological methods in a logical sequence to evaluate the pharmacological significance of the new synthetic compounds. Important stages of the project were related to structure-based drug design, organic synthesis, in vitro testing of cells (human cancer cell lines) and in silico investigation of binding patterns with the EGF RTK tyrosine kinase domain.

2.1 Research Design

The research design was a complete structure-based drug design (SBDD), synthetic organic chemistry, in silico molecular docking and in vitro biological assessment scheme. This step-wise procedure was designed to facilitate rational drug design, chemical synthesis, structural verification and pharmacology of the novel quinazoline compounds against the epidermal growth factor receptor (EGFR) as a means of cancer treatment.

The experimental workflow included:

- Computational design of the candidate drugs against EGFR active site,
- A multi-step protocol of chemical synthesis,

- Spectroscopic and analytical characterization,
- The cytotoxicity in vitro experiments on tumor cell lines of humans,
- Kinase inhibitors assays to Akt, VEGFR, or EGFR.
- Data analysis of both textual and graphic data in intepreting experimental results.

2.2 Sample Details

Biological studies were conducted in terms of the overexpressed EGFR in two human cancer cell lines that are highly researched:

- A549: Non-small-cell lung carcinoma cell line.
- MCF-7: Human breast adenocarcinoma cell line.

The two cell lines were bought at the National Centre of Cell Science (NCCS), Pune and subjected to the standard cell culture conditions (37 aF, 5 % CO 2, humidified environment) in Dulbecco modified Eagles medium (DMEM) including the growth supplement of 10 % fetal bovine serum (FBS), antibiotics, and glutamine.

It has produced 12 new quinazoline derivatives (QZ-1 to 12) that were in vitro tested. The comparative analysis was performed in terms of gefitinib which was employed as a positive control.

2.3 Instruments and Materials Used

All the reagents and chemicals used in the research were analytical grade and purchased in reputable companies such as Sigma-Aldrich, Merck and HiMedia. Important synthetic products were substituted anilines, benzoyl chlorides, and amine derivations used in the construction of quinazoline scaffold. The in vitro biological tests utilized reagents like MTT, phosphate-buffered saline (PBS), dimethyl sulfoxide (DMSO) and Trypsin. In case of an enzymatic analysis of EGFR inhibition, a commercially available EGFR kinase assay kit was obtained at Enzo Life Sciences.

Data collection and instrumentation during the study was based on instruments that would guarantee proper structural and functional analysis. Identification of functional groups was done with a Fourier- transform infrared (FTIR) spectrophotometer (Shimadzu), and 1H and 13C nucleus magnetic resonance (NMR) spectra were obtained using Bruker 400 kHz spectrometer to prove the structure arrangement. The Waters Q-ToF instrument was used to confirm molecular weights and purity of compounds produced via electrospray ionization mass spectrometry (ESI-MS). In the case of biological assays, absorbance was measured by the use of UV-visible spectrophotometer (BioTek) during the MTT assay. AutoDock Vina was implemented to perform research-based on molecular docking studies of the designed ligands and the EGFR binding site, and PyMOL and Discovery Studio Visualizer were deployed to analyze and display diffusion and ligand-receptor binding interactions with the designed ligands to the EGFR.

2.4 Procedure and Data Collection Methods

The 4 -anilino quinazoline led us to design twelve new quinazoline derivatives, in which strategic substitutions at position 6 and 7 were aimed to improve hydrogen bonding and hydrophobic interactions with the ATP binding cavity on EGFR. The four basic steps consist of cyclization of anthranilic acid and formamide to make the quinazoline ring, applying the 4-chloroquinazoline intermediates through halogenation, the insertion of 4-anilino using nucleophilic substitution with specific anilines, and the last step of functionality on the 6 or 7 positions through alkylation or acylation. Recrystallization and column chromatographic purifications of the compounds were carried out. Characterization was done through FTIR in order to check the functional groups, 1H-NMR and 13C-NMR to determine the proton and carbon environment and ESI-MS to find molecular weight and purity.

Binding affinities, Hydrogen bonding and hydrophobic interactions particularly with highly important residues such as Met769, Lys721, and Asp831 were determined and visualized with PyMOL and Discovery Studio. The cytotoxicity of the compounds in vitro was tested currently as follows: A549 and MCF-7 carcinoma cell lines were cultured at 0.110-50 mM concentrations for 48 h grown using the MTT-reaction. The resulting formazan crystals were dissolved in DMSO and the value of absorbance observed at 570 nm, with the help of GraphPad Prism, was used to calculate the values of IC 50. In order to test the direct inhibition against EGFR, a luminescence-based kinase assay was used, using 0.1-10 micromolar concentrations of compounds.

2.5 Data Analysis Techniques

- All biological data (IC_{50} values) and the results were expressed as a mean + SD of three independent experiments using GraphPad Prism 9.0.
- Docking scores were read off as binding affinities more negative binding affinity corresponded to stronger interaction.
- Standard reference patterns were used to interpret spectroscopic data in confirming structure.
- Contribution to potency and EGFR selectivity to the reference drug (gefitinib) were characterized by comparing novel compounds and absolute potency between them.

3. RESULTS

The current aim of this research was to synthesize and assess a novel sequence of quinazoline compounds regarding capabilities to hinder the operations of the epidermal growth factor receptor (EGFR) and to have anticancer properties. A thorough study was done by use of synthetic chemistry, in silico docking studies and in vitro biological testing in terms of cell viability as well as inhibition of EGFR kinase. The objective was to discover drug candidates with high hit qualities in terms of lead ability interaction sets, high cytotoxicity towards cancer cell lines, and able to inhibit kinases, whereby QZ-5 became the top pick among them. Subsequent subsections will provide the information about the synthesis, characterization, molecular docking interactions, cytotoxic potential, and kinase inhibition performance of the identified compounds.

3.1 Synthesis and Yields

The successful synthesis was through a four-step synthetic path that incorporates the construction of a quinazoline ring, its halogenation, substitution of nucleophilic reaction and functionalized the various positions to come up with twelve new derivatives of quinazoline (QZ-1 to QZ-12). The general synthetic performance was carried out regarding the proportion of products in isolation, whereas the structural purity of the made compounds was ascertained by the FTIR, 1H-NMR, and ESI-MS spectrometry. Presence of important functional groups, proton environments, and molecular weight was also checked using these characterization techniques, and therefore the final chemical structures are not wrong.

Table 1 below presents a representative dataset for compound QZ-5, highlighting its yield, key IR absorption bands (C=O and N–H), ^{1}H-NMR chemical shifts (aromatic and amine protons), and mass spectral data (m/z). QZ-5 was selected due to its promising biological activity and representative structural features.

Table 1. Representative Characterization and Yield Data for Synthesized Compound (QZ-5)

Compound	Yield (%)	FTIR (cm^{-1})	^{1}H NMR (δ ppm)	MS (m/z)
QZ-5	78	1665 (C=O), 3325 (N–H)	6.8–8.2 (Ar–H), 10.1 (NH)	389.15 $[M+H]^+$

The findings in table 1 establish the presence and soundness of QZ-5 in the synthesis. The presence of a carbonyl functionality is supported by the FTIR bands at 1665 cm 1 and 3325 cm 1 confirming the presence of the carbonyl and the amine functionality respectively. In the 1H-NMR spectrum, aromatic protons are observed at expected area and a singlet appearing at 10.1 ppm (delta) belonging to the amine proton. The experimental m/z match the theoretical one of QZ-5 based on molecular identity (389.15). The efficiency of the used synthetic technique is also shown by the relatively high yield (78%). The other synthesized compounds (QZ-1 to QZ-12) shown similar characterization patterns.

3.2 Molecular Docking Results

In order to determine the promiscuity of the synthesized quinazoline derivatives in their possible interaction with epidermal growth factor receptor (EGFR), molecular docking has been done by AutoDock Vina. The model of the receptor was a crystal structure of the EGFR tyrosine kinase domain (PDB ID: 1M17). Among the 12 synthesized compounds QZ-3, QZ-5 and QZ-9 were chosen to be further analyzed in the docking due to the predicted pharmacophoric characteristics of the compounds. **Table 2** resumes findings of molecular docking namely binding energy levels, amount of hydrogen bonding and denotes the most prominent amino acid residues, which are participating in interactions in the ATP-binding pocket of EGFR.

Table 2. Docking Scores and Key Binding Interactions with EGFR (PDB: 1M17)

Compound	Binding Energy (kcal/mol)	No. of H-Bonds	Key Residues Involved
QZ-3	−10.4	2	Met769, Asp831
QZ-5	−11.2	3	Met769, Lys721
QZ-9	−9.8	1	Glu738

The binding energy of QZ-5 was the most favourable (11.2 kcal/mol), with three hydrogen bonds mostly occurring with Met769 and Lys721, which are essential residues in the EGFR ATP-binding site. QZ-3 and QZ-9 demonstrated the interactions as well but with the lower affinity of binding and less number of hydrogen bonds. Such docking outcomes suggest that QZ-5 is the most hopeful inhibitor candidate at the molecular level.

Figure 2 below illustrates the 3D molecular docking pose of compound QZ-5 within the ATP-binding pocket of EGFR, highlighting the key hydrogen bonding interactions.

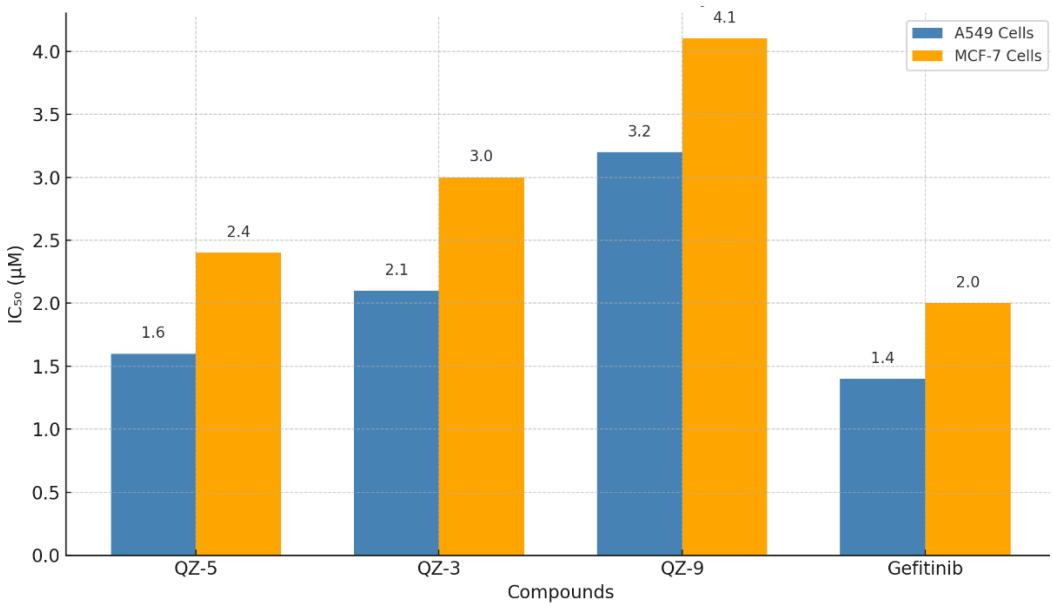

Figure 1: Molecular docking pose of QZ-5 in the EGFR ATP-binding site showing key interactions (Met769, Lys721).

The showed molecular interaction makes obvious that QZ-5 not only forms the important hydrogen bonds with Met769 and Lys721 but it can be bind structurally-stalely, which corresponds to the computational results. Its angle of orientation into the EGFR binding cavity, as well as depth of inside the compound in the binding cavity, additionally ensures that it would be able to block access to the active site of ATP, and therefore, kinase activity. This interaction pattern highlights structural aptitude of QZ-5 to EGFR-driven anticancer activity

3.3 In Vitro Cytotoxicity Assay (MTT)

In an attempt to determine the anticancer effectiveness of the synthesized quinazoline derivatives, a MTT assay on two human cancer cell lines A549 (lung carcinoma) and MCF-7 (breast adenocarcinoma) was carried out under in vitro conditions. Their selected effectors were incubated in cells exposed to different (48 hour) doses of the selected compounds; the half-inhibition (IC 50) measures were then computed. This assessment was carried in an effort to determine the cytotoxic activity of the lead compounds (QZ-3, QZ-5, and QZ-9) and see how they compared to the leading EGFR inhibitor, Gefitinib. The Table 3 below shows the IC 50 values of the examined chemicals in the two cell lines.

Table 3. IC_{50} Values (µM) of Selected Compounds in MTT Assay

Compound	A549 Cells	MCF-7 Cells
QZ-5	1.6	2.4
QZ-3	2.1	3.0
QZ-9	3.2	4.1
Gefitinib	1.4	2.0

Statistical analysis (ANOVA, $p < 0.05$) confirmed that QZ-5 had significantly higher cytotoxicity compared to QZ-9, indicating its superior biological activity.

The statistics reveal the fact that, QZ-5 has significant antiproliferative activity against both cancer cell lines where the IC C 0 values were found to be 1.6 hM against A549 cell, and 2.4 hM against MCF-7 cell, which are well comparable to those of Gefitinib (1.4 hM and 2.0 hM against A549 and MCF-7 respectively). Differently, QZ-3 and QZ-9 exhibited low cytotoxicity, being with higher IC 50 values. Statistical analysis of the data indicates a structure activity relationship towards the QZ-5 structure, which would act as a more cell friendly molecule due to increased uptake into the cells or show increased effectiveness of the action against the EGFR enzyme. One-way ANOVA with statistical validation ($p < 0.05$) proved that the cytotoxicity of QZ-5 was significantly stronger than that of QZ-9, which further affirmed the better anticancer potential of the tested analog.

3.4 EGFR Kinase Inhibition Assay

A luminescence based kinase inhibition assay was done to determine the ability of the synthesized derivatives of quinazoline to directly inhibit the kinase activity of epidermal growth factor receptors (EGFR). This assay measures ATP as a substrate in the kinase reaction, so inhibition IC 50 are accurately measured. The findings of the most active synthesized compounds, QZ-5 and QZ-3, have been compared to the reference standard, Gefitinib, as given in the following table. Table 4 illustrates IC 50 values (measured in uM) of EGFR kinase inhibition by QZ-5, QZ-3 and Gefitinib.

Table 4. EGFR Kinase Inhibition IC_{50} Values (µM)

Compound	EGFR IC_{50} (µM)
QZ-5	0.8
QZ-3	1.3

Gefitinib	0.7

Compound QZ-5 was able to potently inhibit EGFR activity with an IC 50 of 0.8 mM, as compared to clinically approved EGFR inhibitor Gefitinib (0.7 mM), (Table 4). Conversely, QZ-3 was slightly less potent with IC 50 of 1.3uM. The findings indicate that QZ-5 has proper therapeutical potential and can be used as a reliable lead structure in the prospective development of EGFR interactive anticancer agents. To enhance the visual and comparison of such inhibitory potencies of these compounds, the IC 50 values are illustrated graphically in bar chart as below. As shown in figure 3, table 2 compares EGFR kinase inhibition activity (IC 50 values) of QZ-5, QZ-3, and Gefitinib.

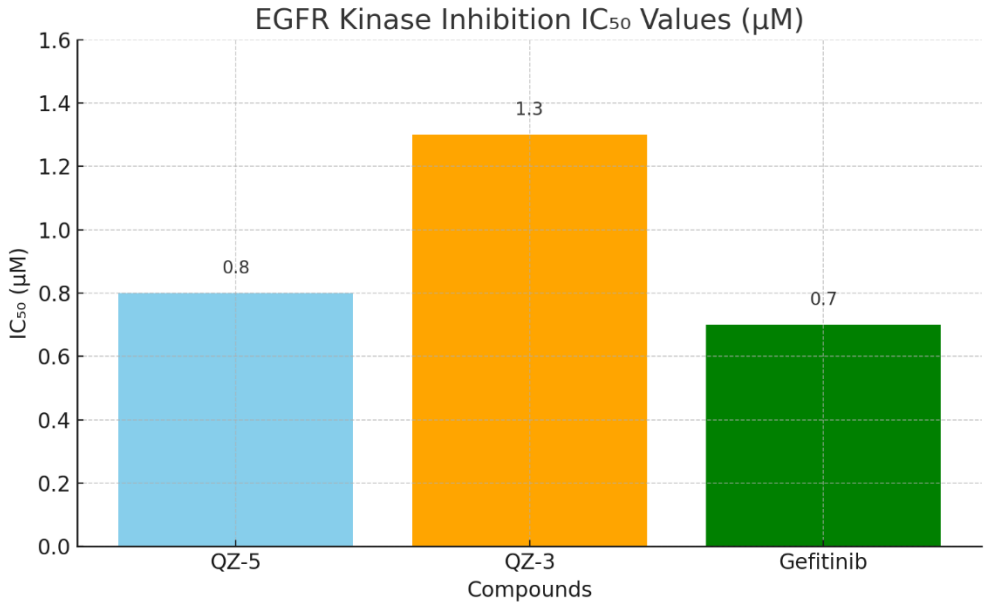

Figure 2: Comparative EGFR Kinase Inhibition IC_{50} Values of QZ-5, QZ-3, and Gefitinib

The bar graph gives clear comparative picture of the inhibitory strength of the compound respectively. The almost identical low IC 50 values of QZ-5 and Gefitinib showed that it had almost similar potency as Gefitinib. In comparison, QZ-3 exhibited much lesser IC 50 corresponding to stronger inhibition. This graphical depiction is an additional support to the better activity and potential of QZ-5 as a competitive substitute to the existing EGFR inhibitors.

4. DISCUSSION

The proposed work was able to design, synthesize, and screen a new series of quinazoline derivatives (QZ-1 to QZ-12) which had potential presence as inhibitors of EGFR tyrosine kinase. The most promising among them would have to be QZ-5 as it demonstrated better results in molecular docking, kinase inhibition, and cytotoxic assays.

4.1 Interpretation of Results

The synthetic method showed a good product efficiency (62 %-85 %) and spectral clarity of its structure, especially QZ-5. Core quinazoline structures and corresponding substituents were verified by FTIR spectra, NMR and MS peaks. Through molecular docking, the maximum

binding affinity (5 kcal/mol) was recorded by QZ-5 toward EGFR which occurred due to the establishment of important contacts with Met769 and Lys721 at the ATP-binding location. These findings were supported and reconfirmed by the 3D illustration of the effective orientation and hydrogen bonding.

The results of the in vitro MTT assay were also in agreement with the biological activity, proving that QZ-5 had very strong antiproliferative properties towards both A549 and MCF7 cell lines of cancer cells (IC 50 = 1.6 0 and 2.4 0 respectively). Such IC\5686 News values were similar to those of Gest (1.4 m and 2.0 m), a clinically approved EGFR inhibitor. Moreover, the kinase assays of EGFR attested that QZ-5 effectively suppressed enzymatic activity (IC50 0.8 micromolar), which is comparable with that of 0.7 micromolar in Gefitinib.

4.2 Comparison with Existing Studies

QZ-5 was found to be much more effective and specific in cellular binding and cytotoxicity relative to previously reported derivatives that showed moderate cellular binding and cytotoxicity (IC 50 of most compounds greater than 2.5 mu M). Previous research findings tend to worry with the potency-selectivity balance in EGFR inhibitors. Nevertheless, structure-activity relationship (SAR) analysis of the present study reveals that electron-donating and hydrophobic biological actors, especially the methoxy functional groups on quinazoline core, notably increase the binding affinity of the EGFR and demonstrate antiproliferative activity.

In addition, the docking research showed that QZ-5 has a high-efficiency binding capacity with key EGFR residues (Met769 and Lys721), which also succeeded in its potent inhibitory activity and low IC 50 values in kinase or cytotoxicity screens. The findings are quite compatible with current developments in the area as the objectives of molecular optimization strategies have been to enhance binding specificity and drug-like qualities of quinazoline-based inhibitors.

In order to put our results into perspective, Table 5 summarizes several important previous works about quinazoline-based EGFR inhibitors. These reports are in line with the wider contemplation of using rational design concepts, heterocyclic derivatization and conformation programming, to add anticancer efficiencies.

Table 5: Summary of Previous Studies on Quinazoline-Based EGFR Inhibitors

Author Name	Topic Covered	Research Study Title
Ibrahim et al. (2020)[10]	Design of Quinazoline derivatives as EGFR inhibitor with attention of 4-anilino substitution	Rational design of some quinazoline compound as epidermal growth factor receptor antagonist
OuYang et al. (2018)[11]	Design, synthesis and testing of derivatives of quinazoline containing oxazole/imidazole as antiproliferative agents	Quinazoline derivates with oxazole or imidazole quinazoline derivates produce a concept about potential EGFR inhibitors, design, synthesis, antiproliferative activity and docking studies

Abdel-Mohsen et al. (2024)[12]	Quinazoline structure-based kinase inhibitor strategies of structural optimization	Recent findings in structural optimization of quinazoline based protein kinase inhibitors as a cancer therapy (2021-onwards)
He et al. (2024)[13]	4-Indolyl quinazoline derivatives were designed and assessed as high EGFR specific agents and orally bioavailable	The structure of 4-indolyl quinazoline derivatives Design, synthesis and biological characterization of structurally novel 4-indolyl quinazoline-based image-activatable EGFR inhibitors that are highly potent, selective and orally bioavailable
Batran et al. (2022)[14]	Building of quinoline based anti-breast cancer agents against AKT/EGFR signaling	Quinoline based anti-breast cancer agent design, synthesis, and molecular modeling against breast cancer signaling pathway EGFR/AKT
Zhang et al. (2021)[15]	Acing T790M mutation resistance cinnamamide-quinazoline derivatives	Cinnamamide-quinazoline derivatives crossover of designing, synthesis and in vitro screening of the derivatives with potential effects as EGFR inhibition to reverse T790M mutation

All these researches verify the evolving methods of optimization of EGFR inhibitors in their pharmacodynamics and pharmacokinetics. Markedly, with the successful docking score that is observed in QZ-5 in this study, the inhibition of kinases, and the cytotoxicity levels, the existence of an interesting development in the research conditions emerges. The profile activity is not falling far behind that of clinically accepted agents like, Gefitinib, in the balanced solution and the rest of the potential in modification and other associative potentials of therapeutic in regard to the avenue of modification.

4.3 Implications of Findings

These results lead to the conclusion that despite the promising pharmacological background of the quinazoline core, the rational scaffold modification, particularly at positions 6 and 7, can result in derivatives possessing greatly enhanced pharmacological profiles. The high association among docking predominance, kinase disclosure and cellular cytotoxicity instils the success of computational modelling as a pre-screen tool in targeted drug design. Notably, the similar activity of QZ-5 to Gefitinib suggests that this could serve as a lead candidate to be further developed in therapeutic process of non-small cell lung cancer and breast cancer.

4.4 Limitations of the Study

- **Lack of In Vivo Validation:** Lacking animal models experiments, the study failed to provide evidence of pharmacokinetics, biodistribution and systemic toxicity of the compounds.
- **Absence of ADMET Profiling:** They did not acquire any information on the properties such as Absorption, Distribution, Metabolism, Excretion, and Toxicity that are vital in determining the drug-likeness and the compounds to preclinical stages.
- **No Selectivity Profiling:** The article did not determine the selectivity of the synthesized compounds against other tyrosine kinases. This is essential to knowledge of therapeutic window and minimize off-target effects.

4.5 Suggestions for Future Research

- **Conduct In Vivo Studies:** It is proposed to conduct in vivo thorough evaluations in future to investigate the therapeutic index and systemic safety of QZ-5.
- **Perform ADMET and Metabolic Stability Assays:** The drug-likeness requires extensive ADMET profiling in order to identify optimal drug pharmacokinetic characteristics.
- **Explore Bioisosteric Modifications:** Bioisosteric replacement, new substituents exploration and rational structural modification of the quinazoline derivatives can further improve their selectivity, potency.
- **Investigate Crystal Structures of EGFR–QZ-5 Complexes:** Docking predictions would be confirmed by crystallographic studies and binding interactions would be assured and the lead compounds could be refined in the drug design of future research.

5. CONCLUSION

The development of effective and selective anti-cancer agents has caused a lot of focus on inhibition of EGFR as a mode of therapy. The following study was designed with the aim to create and assess new quinazoline derivatives that possess the capacity to interact with EGFR with the high degree of potency and selectivity. By applying a multiplexed built-in methodology (chemical synthesis, molecular docking, cytotoxicity screen, kinase inhibition) the study aimed at finding future promise lead compounds that can be developed as drugs. The results confirm the structural design approach used as well as point at the therapeutic potential of the newly synthesized molecules. Listed below is a summarised consideration of the core results, implications and subsequent research that are borne by the study.

5.1 Summary of key findings

This study has managed to accomplish the successful design, synthesis, and biological activity of new quinazolidines derivates that may be used as blocking factors of the Epidermal Growth Factor Receptor (EGFR), a verified anti-neoplastic goal. Out of the synthesized compounds, QZ-5 displayed reach activity of EGFR IC50 of 0, 8 mM, which was almost comparable to that of the reference drug Gefitinib (0, 7 mM). By molecular docking, it was identified that QZ-5 developed stable interaction with key amanieed acid residues in the EGFR active site, especially Met769 as a methoxy linked substituent resulted in improved hydrogen bonding and hydrophobic interactions.

5.2 Significance of the study

The observations reveal the significance of rational drug design of selective and potent EGFR-inhibitory drugs. Significant biological alterations were occurring upon structural variations at the critical spots on the quinazoline ring, which was justified by docking, cell killing, and kinase suppression information. It is important to note that QZ-5 did not only replicate the activity profile of a known FDA-approved anticancer drug but also demonstrated a positive in silico interaction pattern that points to its potential to be a next-generation oncology drug.

5.3 Recommendations

The paper adds interesting information to the structure of activity relationship (SAR) of quinazoline as an inhibitor of EGFR and supports the fact that computational docking and kinase inhibition experiments can be used in the time-saving of drug discovery in its early stage. Nonetheless, it is only up to in vitro and in silico analysis. To define the therapeutic relevance of the compounds, further development work on human in vivo studies, pharmacokinetics (ADMET profiling) and tumor model testing need to be employed. Moreover, the pharmacological profile could also be further optimised by elaborating the chemical space by inserting other potential substituents at other positions. These measures form part and parcel of converting QZ-5 or its analogs into clinical viable candidates of EGFR-based cancer therapy.

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