

MOLECULAR DOCKING OF QUERCETIN DERIVATIVES AGAINST EGFR IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Abstract

Non-small cell lung cancer (NSCLC) is leading cause of cancer – related mortality. Resistance to existing epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors remains a major therapeutic challenge. This study investigates the potential of thirteen 8 – heteroarylated quercetin derivatives as EGFR inhibitors using a structure – based molecular docking approach integrated with in silico ADMET prediction and drug – likeness assessment. Docking simulations were performed against EGFR (PDB ID: 4WKQ) using MOE 2022, with gefitinib serving as the reference ligand. ADMET evaluation was conducted using the pkCSM web server, while drug – likeness assessment was carried out using SwissADME. The docking results revealed that five compounds (2i, 2b, 2m, 2a, and 2c) exhibited more favorable binding affinity than the control and formed key hydrogen – bond interactions with residue Met793, along with additional interactions within the ATP – binding site. ADMET and drug – likeness analyses predicted that most derivatives complied with Lipinski's criteria, with compounds 2a and 2m demonstrating superior pharmacokinetic profiles, including higher solubility, acceptable intestinal permeability, low blood – brain barrier penetration, and low predicted acute toxicity and mutagenicity. Overall, these in silico findings identify compounds 2a and 2m as the most promising quercetin – based EGFR inhibitor candidates for further development.

Keywords: Docking Molecular, ADMET, EGFR, NSCLC, Quercetin Derivatives

Abstrak

Kanker Paru – paru bukan Sel Kecil (KPBSK) adalah penyebab utama kematian terkait kanker. Resistensi terhadap penghambat tirosin kinase reseptor epidermal growth factor (EGFR) yang ada tetap menjadi tantangan terapi utama. Studi ini menyelidiki potensi tiga belas turunan quercetin termodifikasi 8 – heteroaril sebagai penghambat EGFR menggunakan pendekatan penambatan molekul berbasis struktur yang terintegrasi dengan prediksi ADMET secara in silico dan penilaian kesesuaian obat. Simulasi penambatan dilakukan terhadap EGFR (PDB ID: 4WKQ) menggunakan perangkat lunak MOE 2022 dengan gefitinib berperan sebagai kontrol positif. Evaluasi ADMET dilakukan menggunakan server web pkCSM, sementara penilaian kesesuaian sebagai obat dilakukan menggunakan SwissADME. Hasil penambatan mengungkapkan bahwa lima senyawa (2i, 2b, 2m, 2a, dan 2c) menunjukkan afinitas pengikatan yang lebih menguntungkan daripada kontrol positif dan membentuk interaksi hidrogen kunci dengan residu Met793, bersama dengan interaksi tambahan di dalam situs pengikatan ATP. Analisis ADMET dan kesesuaian sebagai obat memprediksi bahwa sebagian besar turunan memenuhi kriteria Lipinski, dengan senyawa 2a dan 2m menunjukkan profil farmakokinetik yang lebih unggul, termasuk kelarutan yang lebih tinggi, permeabilitas usus yang dapat diterima, penetrasi sawar darah – otak yang rendah, serta prediksi toksisitas akut dan mutagenisitas yang rendah. Secara keseluruhan, temuan in silico ini mengidentifikasi senyawa 2a dan 2m sebagai kandidat penghambat EGFR berbasis quercetin yang paling menjanjikan untuk pengembangan lebih lanjut.

Keywords: Penambatan Molekul, ADMET, EGFR, KPBSK, Turunan Quercetin

1. Introduction

Lung cancer ranks third after breast and cervical cancers, with 34,783 cases (8.8%) out of a total of 396,914 cancer cases in Indonesia. It is also the leading cause of cancer-related mortality, accounting for 25,943 deaths (14.1%) out of 183,368 cancer deaths (Sugiharto et al., 2021).

Lung cancer arises when abnormal cells in the lungs proliferate uncontrollably and disrupt the normal structure and function of lung tissue (Amelia et al., 2025). Lung cancer is histologically divided into two main categories, non-small cell lung cancer (NSCLC), which represents around 85% of all cases and small cell lung cancer (SCLC), accounting for approximately 15% (Giaccone & He, 2023). Since 2004, activating mutations in the epidermal growth factor receptor (EGFR) have been identified as key oncogenic drivers in NSCLC and serve as predictive biomarkers for the effectiveness of EGFR tyrosine kinase inhibitor (TKI) therapy. The prevalence of EGFR mutations varies among different populations, occurring in about 7 – 37% of NSCLC cases in White populations and 40 – 60% in Asian patients. These mutations are reported more frequently in women, individuals who have never smoked, and patients with adenocarcinoma histology (Le et al., 2021).

The epidermal growth factor receptor (EGFR) is one key members of the growth factor receptor family that has intrinsic tyrosine kinase activity. Significant overexpression of EGFR and large internal deletions are frequently detected in brain tumors, while point mutations and small insertion within the kinase domain are more commonly identified in lung cancer. Consequently, EGFR and its primary heterodimerization partner, HER2/ERBB2, have emerged as important targets in anticancer therapy (Uribe et al., 2021). First-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs), gefitinib and erlotinib, have been approved by the United States Food and Drug Administration (FDA) for the treatment of NSCLC harboring activating EGFR mutations, particularly exon 19 deletions (E746_A750del) and the exon 21 L858R substitution. Patients with the L858R mutation generally exhibit favorable clinical responses to both gefitinib and erlotinib; however, the duration of efficacy is limited by the emergence of acquired resistance, most commonly due to the EGFR T790M mutation, which is found in ~50% of EGFR-mutant NSCLC cases (Ibrahim & Uzairu, 2023). The development of resistance to first-generation agents prompted the introduction of second- and third-generation EGFR inhibitors. Nevertheless, triple mutations such as L858R/T790M/C797S have now been reported in NSCLC, conferring resistance even to osimertinib. Given the biological complexity of adenocarcinoma, patients often require long-term therapy, and drug resistance is frequently unavoidable (Shama Bhat & Shaik Mohammad, 2023). Therefore, it is essential to explore new chemical entities as alternative EGFR inhibitors.

Quercetin is a bioflavonoid abundantly found in plants and exhibits significant antitumor activity by modulating multiple cellular targets, thereby triggering apoptosis, suppressing proliferation, and inhibiting metastasis (Huang et al., 2021). Nevertheless, quercetin has several limitations—namely low bioavailability, hydrophobicity, extremely limited solubility, and poor permeability—leading to suboptimal absorption. Consequently, quercetin has garnered wide attention, with extensive anticancer research and structural modifications undertaken to overcome these shortcomings. In a study by Gao et al. (Gao et al., 2025), 8-heteroarylated quercetin derivatives demonstrated strong anticancer activity at micromolar ($\mu\text{mol/L}$) levels, particularly against HCC287 cells, a human non-small cell lung cancer (NSCLC) line (Gao et al., 2025).

Further development of these active scaffolds into viable drug candidates typically requires extensive experimental work. The development of new drug candidate generally involves multiple laboratory stages, including design, synthesis, characterization, purification, and biological evaluation (Putri & Azra, 2025). This conventional approach is often economically inefficient because it consumes substantial time, energy, and financial resources and generate considerable chemical waste, especially when large series of structurally related derivatives must be synthesized and tested (Toni & Azra, 2022).

Given that 8-heteroarylated quercetin derivatives exhibit strong anticancer activity, the next step is to ensure that these derivatives achieve superior target engagement and possess acceptable drug-like properties. To screen and validate which derivatives interact most effectively with the EGFR kinase domain, molecular docking is employed. Molecular docking has become a standard tool in drug discovery because it can accurately predict ligand–macromolecule conformations and interactions at the binding site. This approach is efficient for estimating the optimal ligand orientation on a drug target, saving cost, time, and resources, and it often aligns well with experimental data (Mahmudah et al., 2021), while *in silico* ADMET prediction and Lipinski's rule of five assessment provide an additional filter for selecting derivatives with more favorable pharmacokinetic profiles.

2. Methodology

2.1. Instrument and Materials

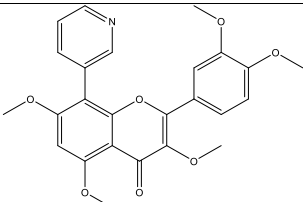
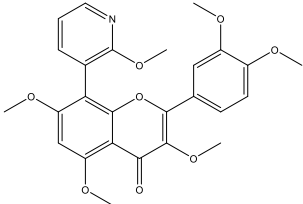
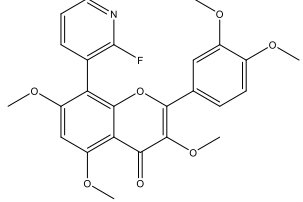
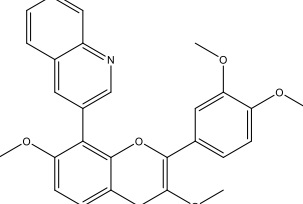
The study materials comprise 13 8-heteroarylated quercetin derivatives with reported IC₅₀ values of a less than 100 against HCC287 cells, as described by Gao et al. (Gao et al., 2025), which can be seen in the Table 1. Gefitinib was used as the positive control; both structures were from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). The target protein was EGFR with PDB ID 4WKQ, downloaded from the RCSB PDB (<https://www.rcsb.org/>).

The tools included both hardware and software. The hardware consisted of an Acer laptop equipped with an Intel® Core™ i3-8100 CPU @ 3.60 GHz and 4.00 GB RAM (3.8 GB usable). The software comprised ChemDraw Professional v16.0 for modeling 2D structures of quercetin derivatives; MOE 2022 for molecular docking; BIOVIA Discovery Studio Visualizer (DSV) for docking result visualization; the pkCSM web server (<https://biosig.lab.uq.edu.au/pkcsml/>) for ADMET prediction; and SwissADME for Lipinski rule assessment.

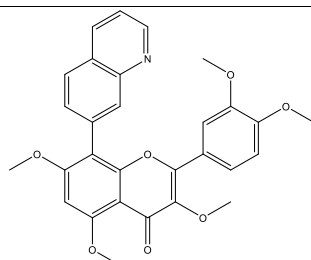
2.2. Protein Preparation

The EGFR target protein was obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/>) with PDB ID 4WKQ. The initial receptor preparation involved removing crystallographic water molecules by checking water under ignore, followed by deleting non-amino-acid residues using the SEQ tool. Next, the energy minimization threshold was set to an RMS gradient of 0.01 kcal·mol⁻¹·Å⁻¹. Then, Compute then Protonate 3D was executed and confirmed. The prepared protein was saved as an .moe file.

Table 1. Structures and IC₅₀ values of 8 - heteroarylated quercetin derivatives reported by Gao et al., (2025)

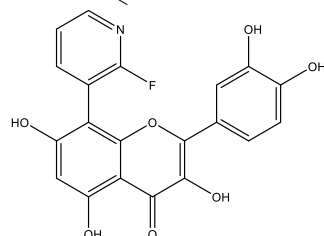
Compound	Structure	IC ₅₀ (μM)
2a		82.46
2b		25.40
2c		63.80
2i		24.47

2m



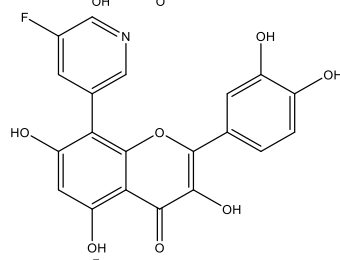
3.20

3c



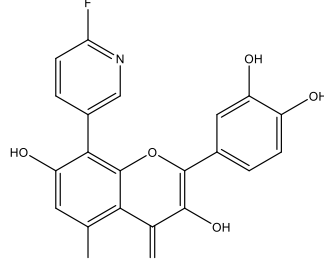
11.07

3d



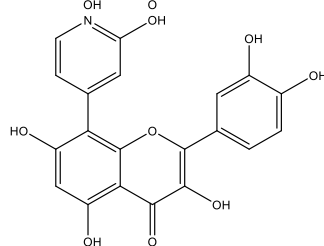
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3e



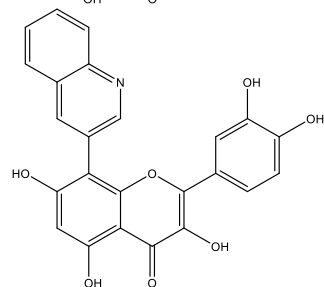
4.87

3g



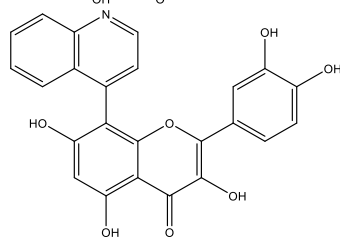
98.42

3i

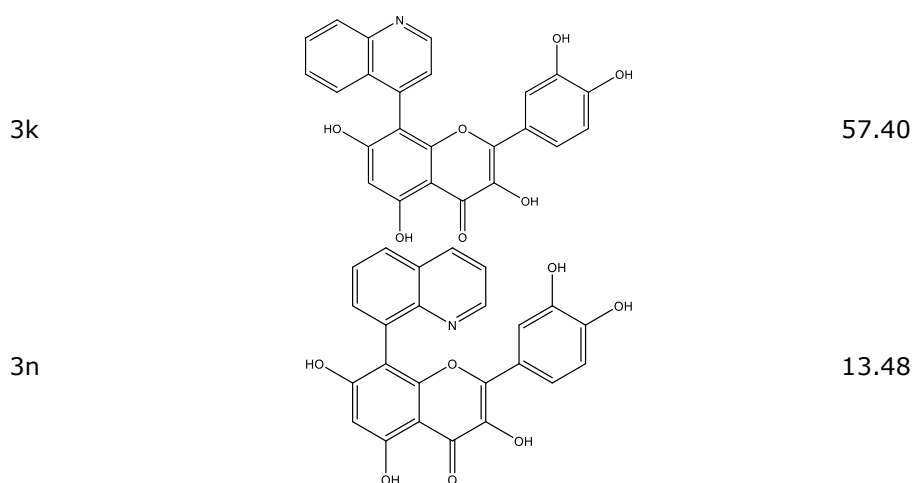


4.97

3j



75.48



2.3. Ligand Preparation

The ligands comprised 13 8-heteroarylated quercetin derivatives with reported IC₅₀ values in HCC287 cells, together with osimertinib and the native ligand, gefitinib. The 13 derivatives were drawn in ChemDraw Professional 16.0 and saved as .sdf files, then transferred into MOE. Gefitinib were obtained from PubChem (pubchem.ncbi.nlm.nih.gov) and downloaded in .sdf format. Ligand preparation for docking was carried out in MOE by parameterizing each structure to reach a minimized energy state: the MMFF94 (modified) force field was assigned, and energy minimization was performed to an RMS gradient of 0.01 kcal·mol⁻¹·Å⁻¹. Upon completion, all ligands were saved into a molecular database (.mdb).

2.4. Molecular Docking and Visualization

The docking procedure was performed in MOE. The prepared protein file was opened and the binding site was identified using the site finder function in the Compute menu and then applied. The selected active site was isolated by atom and backbone, with the options "Select contact atoms" and "Select residues in SE" activated, followed by generation of dummy atoms. Docking was then carried out using the Dock function in the Compute menu by loading the prepared protein and ligand and setting the parameters to use London dG and GBVI/WSA dG as scoring functions, Triangle Matcher as the placement method, and Rigid Receptor for refinement. The protocol generated 100 poses, from which the five best poses were selected. Redocking evaluation was based on the lowest binding energy (score, kcal/mol) and an RMSD value not exceeding 2.0 Å, and the ligand – receptor interactions were visualized using MOE and BIOVIA Discovery Studio Visualizer (DSV).

2.5. In Silico ADMET and Drug – Likeness (Lipinski) Evaluation

ADMET evaluation was conducted using the pkCSM web server (<https://biosig.lab.uq.edu.au/pkcsms/prediction>). The thirteen 8-heteroarylated quercetin derivatives and gefitinib were exported in SMILES format and submitted to pkCSM to obtain ADMET predictions, which were then recorded and analyzed.

Lipinski's rule of five an important role in identifying potential drug candidates by evaluating whether a compound exhibits drug-like characteristic (Aini et al., 2022). Lipinski evaluation was performed using SwissADME (<https://swissadme.ch/>). The thirteen 8-heteroarylated quercetin derivatives and gefitinib were entered as SMILES strings or drawn directly, then submitted to obtain the outputs. The results were recorded and analyzed according to Lipinski's Rule of Five criteria.

3. Results and Discussion

This study investigates the binding propensities of 8 – heteroarylated quercetin derivatives toward the EGFR kinase domain in the context of non – small cell lung cancer (NSCLC), bench marking against gefitinib, using computer using computer – based molecular docking to facilitate new drug design by reducing research costs and accelerating development.

The best ligand complexes were identified by the docking score, a mathematical scoring function that estimates binding affinity, more negative value indicate more favorable binding within the same protocol (Aguiar & Camps, 2024).

As summarized in Table 2, the compounds yielded the following scores: 2i (−9.2084), 2b (−9.1251), 2m (−8.9762), 2a (−8.8522), 2c (−8.6402), Gefitinib (−8.1827) and 3c (−7.1155). Several compounds specifically 2i, 2b, 2m, 2a and 2c display more negative scores than the control positive (Gefitinib), suggesting potentially stronger binding and warranting further investigation.

Beyond the docking score, we next evaluated pose accuracy using RMSD (Root Mean Square Deviation), a parameter used to assess the similarity between two structures. This similarity is quantified as the average distance between corresponding atoms after superposition (Hadisoebroto et al., 2025). As shown in Table 2, all compounds exhibit RMSD values below 2.0 Å, supporting the geometric quality of the poses obtained from docking. In this context, a docked complex with RMSD < 2.0 Å indicates that the system places the ligand effectively (Hussein & Elkhair, 2021).

Table 2. Molecular docking results of quercetin and osimertinib derivative compounds

Compound	Score	RMSD	Hydrogen Bond	Other Amino Acid residues
2a	-8.8522	1.5983	Met793, Pro794, Leu718, Gln791, Thr854, Glu762.	Leu718, Val726, Lys745, Ala743, Leu788, Met766, Leu844.
2b	-9.1251	1.4983	Met793, Lys745, Leu718, Pro794, Gln791, Thr854, Glu762, Arg841.	Val726, Ala743, Leu788, Gly796, Leu844, Asp855, Met766, Lys745, Leu718
2c	-8.6402	1.3357	Met793, Lys745, Pro794, Glu762, Gln791, Pro794	Leu718, Val726, Leu788, Leu792, Leu844, Met766, Ala743, Lys745
2i	-9.2084	1.7967	Met793, Leu718, Pro794, Gln791, Glu762, Thr854.	Leu718, Val726, Leu844, Leu788, Ala743, Asp855.
2m	-8.9762	1.5708	Met793, Lys745, Gly719, Pro794, Gln791, Glu762.	Leu718, Leu844, Leu792, Leu788, Val726, Phe856, Met766, Lys745
3c	-7.1155	1.7764	Glu762, Met793	Leu718, Val726, Lys745, Ala743, Leu844.
3d	-7.0952	1.3721	Glu762, Met793	Leu718, Val726, Gly719, Lys745, Ala743, Leu844.
3e	-7.1424	1.8318	Glu762, Met793	Leu718, Val726, Lys745, Ala743, Leu844.
3g	-7.1473	0.7072	Glu762, Met793, Gly719	Leu718, Leu844, Ala743, Lys745, Val726.
3i	-8.0427	1.2976	Met793, Lys745, Asn842, Csy797	Leu718, Leu844, Val726, Ala743, Met766, Lys745.
3j	-7.9404	1.6755	Ala743, Lys745, Glu762, Asn842, Thr790, Asp855.	Leu718, Val726, Leu844, Met766, Ala743, Lys745.
3k	-7.8809	1.4792	Ala743, Lys745, Glu762, Asn842, Thr790, Asp855.	Leu718, Val726, Leu844, Met766, Ala743, Lys745.
3n	-8.0982	1.6347	Ala743, Arg841, Asn842, Lys745, Leu788, Asp855, Thr790,	Leu718, Val726, Leu844, Met766, Lys745.
Gefitinib	-8.1827	1.5128	Met793, Arg841, Gln791	Lys745, Met766, Glu762, Ala743, Leu844, Leu718, Val726.

Hydrogen bonding is a primary determinant of ligand – receptor affinity, the stronger and more persistent this interaction, the greater the binding capability between ligand and protein (Hussein & Elkhair, 2021). Viewed from Table 2, nearly all compounds form a hydrogen bond with Met793, notably 2a, 2b, 2c, 2i, and 2m which exhibit more negative docking scores than gefitinib, consistent with ATP – competitive inhibition and strengthened binding. Beyond Met793, these four ligand also engage additional polar residues (Figure 1) 2a (Met793, Pro794, Leu718, Gln791,

Thr854, Glu762); 2b (Met793, Lys745, Leu718, Pro794, Gln791, Thr854, Glu762, Arg841); 2c (Met793, Lys745, Pro794, Glu762, Gln791, Pro794); 2i (Met793, Leu718, Pro794, Gln791, Glu762, Thr854); and 2m (Met793, Lys745, Gly719, Pro794, Gln791, Glu762). In the positive control, gefitinib binds to Met793, Arg841, and Gln791. In addition to hydrogen bonding, the four ligands also establish hydrophobic contacts with other residues, specifically, 2a interact with Leu718, Val726, Lys745, Ala743, Leu788, Met766, Leu844; 2b with Val726, Ala743, Leu788, Gly796, Leu844, Asp855, Met766, Lys745, Leu718; 2c with Val726, Leu788, Leu792, Leu844, Met766, Ala743, Lys745; 2i with Leu718, Val726, Leu844, Leu788, Ala743, Asp855; and 2m with Leu718, Leu844, Leu792, Leu788, Val726, Phe856, Met766, Lys745. These contacts create a strong nonpolar “enclosure” around the hydrophobic cores of the ligands, reducing solvent exposure of nonpolar surface area and thereby lowering the binding free energy. In summary, the combination of hydrogen – bond anchoring and a supporting hydrophobic network acts synergistically to maintain a tight, stable ligand orientation within the EGFR binding (Ndaghiya Adawara et al., 2025)

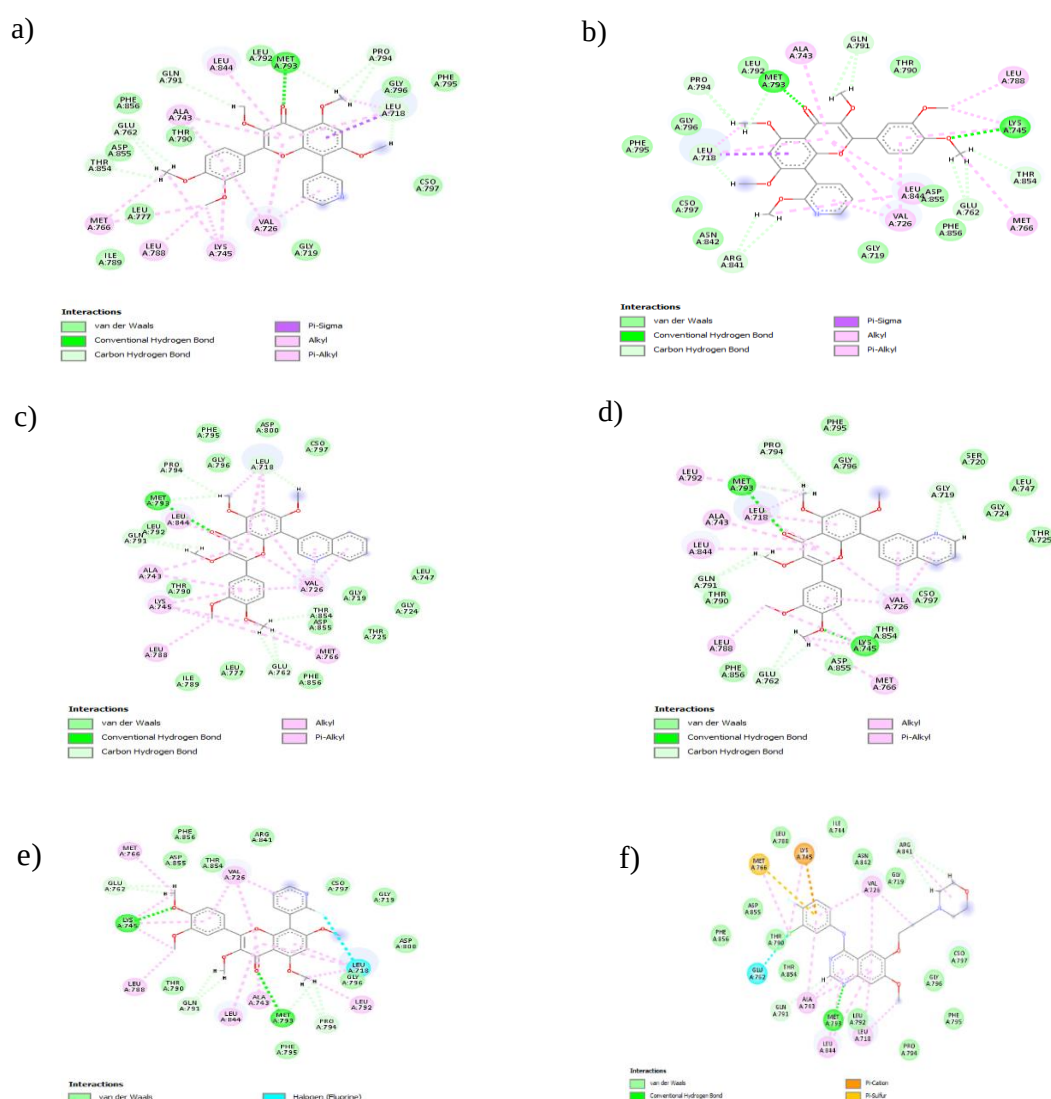


Figure 1. Visualization 2D 2a (a), 2b (b), 2i (c), 2m (d), 2c (e), Gefitinib

In parallel with the safety screening, drug – likeness was evaluated using Lipinski’s Rule of Five. The rule posits that good oral absorption/penetration is more likely when molecular weight (MW) < 500 Da, LogP < 5, Hydrogen – bond donors (HBD) ≤ 5, and hydrogen – bond acceptors ≤ 10 (Al-Jumaili et al., 2023). As shown in Table 3, only 3g failed to comply because its HBD count exceeded 5.

Extending the structure – based findings, the ADMET evaluation provides a robust pharmacokinetic and safety basis for compound selection. Within the absorption domain, three parameters are considered in sequence, water solubility, Caco2 permeability, and P – glycoprotein substrate. Aqueous solubility is a key determinant of whether dissolution will limit oral bioavailability. In this study, predictions from multiple platforms are mutually consistent, falling in the range logS -5.254 to - 2.116 (Didigwu & Nnadi, 2024). According to the Table 4, all compounds including gefitinib meet the working criteria for water solubility.

Caco2 permeability together with predicted human intestinal absorption is used to anticipate oral uptake across the intestinal epithelium. Operationally, compounds with higher Caco2 values (practical benchmark > 0.90) are expected to exhibit favorable intestinal absorption (Alvarez et al., 2023), in line with the Tabel 4, 2a, 2c, 2i, 2m and gefitinib meet this criterion. P – glycoprotein or p – gp, an ATP – binding cassette efflux transporter, reduces intracellular drug concentrations by pumping xenobiotics out of cells, it is broadly distributed across tissues, abundant in the adrenal gland and clearly expressed in brain endothelial cells where it contributes to the blood – barrier (Vottero, 2021). ADMET predictions indicate whether a compound is likely to be a substrate or inhibitor of P – gp. In this data set, 2a, 2b, 2c, 2i, 2m, 3j, 3k, and 3n not predicted to be P – gp substrates, whereas gefitinib (the positive control) is predicted to be a P – gp substrate. In the distribution parameter, we evaluated VDss, fraction unbound (Fu), and BBB permeability. Volume of distribution at steady state (VDss) is the theoretical volume in which the administered dose must be uniformly distributes to yield the same concentration as in blood plasma. Higher VDss indicates a greater proportion of drug residing in tissues rather than plasma. Predicted values are considered low when below - 0.15 log L/Kg (VDss < 0.71 L/Kg) and high when above 0.45 log L/Kg (VDss > 2.81 L/Kg) (Vottero, 2021). In our data set, only gefitinib exhibits a high VDss. The Fraction unbound (Fu) estimates the proportion of compound not bound to plasma proteins (Vottero, 2021). In this set, Fu generally falls within 0.15 – 0.45 (Hemalatha Nakka et al., 2025). According to Table 4, 2a, 2b, 2c, 2i, 2m, 3i, 3j, 3k, and 3n meet this criterion, whereas gefitinib shows a value fer below the desired range, indicating stronger protein binding and a smaller free fraction. The blood – brain barrier (BBB) is the microvasculature of the central nervous system that protects the brain from exogenous compounds and regulates the movement of molecules, ions, and cells between blood and neural tissue (Didigwu & Nnadi, 2024). For lug targeted anticancer agents, lower BBB permeability is preferable (logBBB < - 1). BBB permeability predictions estimate whether a drug can cross the barrier into the central nervous system (CNS), operationally, logBBB > 0.3 indicates efficient bain penetration (Alvarez et al., 2023). Based on the table, Gefitinib has a BBB value above -1. Nevertheless, low brain permeability also implies reduced exposure within the CNS and fewer related adverse effects, which is advantageous for a CNS target such as EGFR in the lugs (Alvarez et al., 2023).

Table 3. Results of the lipinski's Rule of Five Evaluation

Compound	Molecular Weight (g/mol)	H - bond acceptors	H - bond donors	Log P
2a	449.45	8	0	0.7
2b	479.48	9	0	0.8
2c	467.44	9	0	1.07
2i	499.51	8	0	1.6
2m	499.51	8	0	1.6
3c	397.31	9	5	0.01
3d	397.31	9	5	0.01
3e	397.31	9	5	-0,48
3g	395.32	9	6	0.59
3i	429.38	8	5	0.59
3j	429.38	8	5	0.59
3k	429.38	8	5	0.59
3n	429.38	8	5	0.59
Gefitinib	446.90	7	1	2.82

Adverse drug reactions are often triggered by drug – drug interaction arising from inhibition of major cytochrome P50 (CYP) isoenzymes. CYPs are membrane – bound hemoproteins located predominantly in the smooth endoplasmic reticulum of hepatocytes. Enzyme inhibition occurs when two co – administered drugs follow the same biotransformation route and thus compete at enzyme’s catalytic site. A more potent inhibitor will dominate and disrupt the biotransformation of the competing drug, decreasing its metabolic clearance and increasing its serum concentration, consequently, toxicological risk rises, particularly for drugs with a narrow therapeutic index, such as chemotherapeutics (Beck et al., 2021). In our prediction panel for CYP1A2, CYP2C9, and CYP3A4, the results indicate: for CYP1A2, compounds 2i, 2m, 3g, 3i, 3j, 3k, and 3n are predicted not to be inhibitors; for CYP2C9, compounds 3c, 3d, 3e, 3g, 3i, 3k and 3n are predicted not to be inhibitors; and for CYP3A4, compounds 3c, 3g, 3i, 3j, 3k, and 3n are likewise predicted not to be inhibitors. As the positive control, gefitinib is predicted not to inhibit CYP2C9 only, while showing potential inhibition of CYP1A2 and CYP3A4.

The consistent non – inhibitor status across all three isoforms for compounds 3g, 3i, 3k and 3n suggests a comparatively cleaner DDI risk profile than the other candidates.

Table 4. Absorption, Distribution Prediction

compound	Parameters					
	Absorption			Distribution		
	Water solubility (Log mol/L)	Caco2 permeability (Log Papp in 10 ⁻⁶ cm/s)	P-gp (Log L/kg)	VDss (human)	Fraction unbound (human) (Fu)	BBB permeability (Log BB)
2a	-3.524	1.3	No	0.342	0.238	-1.274
2b	-3.55	0.515	No	0.115	0.208	-1.489
2c	-3.415	1.351	No	0.071	0.214	-1.484
2i	-3.412	1.325	No	-0.238	0.338	-1.303
2m	-3.258	1.301	No	-0.243	0.348	-1.319
3c	-3.003	0.482	Yes	-0.605	0.121	-2.061
3d	-3.002	0.439	Yes	-0.539	0.143	-2.061
3e	-2.999	0.507	Yes	-0.545	0.139	-2.083
3g	-2.923	0.4	Yes	-0.564	0.121	-2.037
3i	-2.963	0.456	Yes	-1.293	0.233	-1.83
3j	-2.949	0.324	No	-1.398	0.253	-1.837
3k	-2.933	0.322	No	-1.265	0.247	-1.894
3n	-2.922	0.478	No	-1.122	0.272	-1.88
Gefitinib	-4.124	1.246	Yes	1.08	0.111	-0.738

Table 5. Metabolism, Excretion and Toxicity Prediction

compound	Parameters						
	metabolism			Excretion	Toxicity		
	CYP1A2 inhibitor	CYP2C9 inhibitor	CYP3A4 inhibitor	Total clearance (Log ml/min/kg)	AMES toxicity	Oral rat acute toxicity (LD50) (mol/kg)	Hepatotoxicity
2a	Yes	Yes	Yes	0.659	No	2,483	No
2b	Yes	Yes	Yes	0.998	No	2,552	Yes
2c	Yes	Yes	Yes	0.872	No	2,467	Yes
2i	No	Yes	Yes	0.634	No	2,613	Yes

2m	No	Yes	Yes	0.581	No	2,573	No
3c	Yes	No	No	0.513	No	2,567	Yes
3d	Yes	No	Yes	0.508	No	2,597	Yes
3e	Yes	No	Yes	0.51	No	2,594	No
3g	No	No	No	0.584	No	2,63	No
3i	No	No	No	0.27	No	2,601	Yes
3j	No	Yes	No	0.249	No	2,858	Yes
3k	No	No	No	0.179	No	2,589	Yes
3n	No	No	No	0.31	No	2,554	Yes
Gefitinib	Yes	No	Yes	0.937	No	2.859	Yes

Clearance (CL) is a key pharmacokinetic parameter that describes drug elimination. Total clearance (CL_{tot}) reflects the efficiency with which a drug is removed from the body and is crucial for determining dosing intervals (Fijałkowska & Jurowski, 2025). In general, the faster a molecule is eliminated, the higher its CL_{tot}, which can reduce the tendency for accumulation. As shown in Table 5, 2b exhibits the highest CL_{tot} at 0.998, followed by 2c (0.872), 2a (0.659), and 2i (0.634). For comparison, gefitinib as the positive control has CL_{tot} of 0.937.

The Ames test is a standard assay used to evaluate the mutagenic potential of a compound using specific bacterial strains. A positive result indicates mutagenicity and therefore, potential carcinogenicity, whereas a negative result suggests no mutagenic activity under the test conditions (Al-Jumaili et al., 2023). In this study, all compounds produced negative Ames results, indicating they are non – mutagenic based on this assay. A common approach to estimate acute toxicity and compare the relative toxicity of compounds is the median lethal dose (LD₅₀). LD₅₀ is defined as the single administered dose of a chemical that causes death in 50% of the test animals in a group. In the present work, LD₅₀ was predicted (mol/kg) using a model developed from > 1000 chemicals evaluated in rats (Alifiansyah et al., 2024). For acute oral toxicity, values in the range 2,000 < LD₅₀ ≤ 5,000 indicate low toxicity (Rogério et al., 2022). In the Table 5, all candidate compounds exhibited predicted LD₅₀ values > 2,000 mol/kg, consistent with acute oral toxicity. Based on the modeling results, compounds 2a, 2m, 3e, and 3g are predicted to be non – hepatotoxic. Overall, the hepatotoxicity predictions indicate that none of the selected ligands pose a significant risk to liver function under the applied modeling conditions, thereby supporting their suitability for further drug development (Srinivasan et al., 2025).

4. Conclusion

Molecular docking of thirteen 8-heteroarylated quercetin derivatives identified several potential EGFR inhibitors for NSCLC. Compounds 2i, 2b, 2m, 2a, and 2c showed stronger predicted binding affinity than gefitinib and formed key hydrogen bonds with MET793 within the ATP-binding pocket, indicating stable interactions.

In silico ADMET analysis suggested favorable drug-likeness, particularly for compounds 2a and 2m, which exhibited good solubility, accepted intestinal permeability, low BBB penetration, and low predicted toxicity.

Overall, compounds 2a and 2m emerged as the most promising quercetin based EGFR inhibitor candidates for NSCLC, although further validation through in vitro and in vivo studies is required.

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