Comparative Analysis of Molecular Docking Programs GOLD, Glide, and MOE on Quinazoline Derivatives as Antiproliferative Agents: Implications for EGFR-Targeted Therapies.

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Abstract:

Background: To aid in the identification of drug candidates and the prediction of protein-ligand interactions, molecular docking predicts how ligands interact with receptors, aiding drug discovery. EGFR's role in NSCLC makes quinazoline derivatives promising anticancer agents. However, accurately predicting their EGFR binding affinities remains a challenge.

Objectives: This research was designed to comparatively analyze three popular molecular docking tools; GOLD, Glide, and MOE by comparing their performance in predicting quinazoline derivative binding poses and affinities against EGFR. This study aimed to identify the most effective docking tool for screening quinazoline-based antiproliferative drugs.

Method: Quinazoline derivatives were docked into the EGFR receptor binding site using GOLD, Glide, and MOE. The ligands were energy-minimized, and the proteins were prepared by removing water molecules and adding hydrogen atoms. Docking simulations ran under default settings, comparing binding affinities via various scoring functions.

Results: GOLD identified N-$(CH_3)_3$ and 3-NO_2 derivatives as strong binders, while Glide favored Erlotinib due to π-π stacking interactions. MOE highlighted Ethyl Vanillin and N-$(CH_3)_3$ derivatives, particularly for their polar interactions. The docking results demonstrated that each program had strengths depending on the ligand's interaction type.

Conclusion: GOLD and MOE showed the most promise in identifying high-affinity binders for quinazoline derivatives targeting EGFR, while Glide excelled in handling hydrophobic interactions. The findings highlight the importance of selecting the appropriate docking tool based on ligand characteristics to optimize the drug discovery process for EGFR inhibitors.

Key Words: Molecular docking, EGFR inhibitors, Quinazoline derivatives, docking software (GOLD, Glide, MOE) evaluation and comparison, Binding affinity prediction, Docking pose accuracy.

التحليل المقارن لبرامج الإرساء الجزيئي GOLD و GlideوMOEعلى مشتقات الكينازولين كعوامل مضادة لتكاثرالخلايا: الآثار المترتبة على العلاجات المستهدفة لمستقبل عامل نمو البشرة(EGFR)

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الخلاصة:

الخلفية: يُعَد الإرساء الجزيئي أداة حاسوبية محورية في اكتشاف الأدوية، حيث يُستخدم للتنبؤ بكيفية ارتباط المركبات بالمستلمات، مما يسهم في تحديد المركبات المرشحة وتوقّع تفاعلات البروتين–المركب. ونظرًا للدور المحوري لمستلم عامل النمو البشري (EGFR)في سرطان الرئة غير صغير الخلايا(NSCLC) ، تُعَد مشتقات الكينازولين من العوامل الواعدة المضادة للسرطان. ومع ذلك، لا يزال التنبؤ الدقيق بألفة ارتباط هذه المشتقات مع EGFR يمثل تحدّيًا كبيرًا.

الأهداف: هدفت هذه الدراسة إلى إجراء مقارنة بين ثلاث من أدوات الإرساء الجزيئي الشائعة :GOLD وGlideوMOE، وذلك لتقييم كفاءتها في التنبؤ بأوضاع الارتباط وألفة مشتقات الكينازولين معEGFR ، بغرض تحديد الأداة الأكثر فعالية لفحص الأدوية المضادة للسرطان المعتمدة على الكينازولين.

الطريقة: تم إرساء مشتقات الكينازولين داخل الموقع الفعّال لمستلم EGFR باستخدام برامج GOLD و GlideوMOE. خضعت المركبات لعملية تقليل للطاقة، بينما تم إعداد البروتينات من خلال إزالة جزيئات الماء وإضافة ذرات الهيدروجين. تم تنفيذ محاكاة الإرساء باستخدام الإعدادات الافتراضية، وتمت مقارنة النتائج بناءً على دوال تسجيل مختلفة.

النتائج: أظهر برنامج GOLD كفاءة في تحديد مشتقات-N (ثلاثي الميثيل) و3 NO_2-كمركبات ذات ارتباط قوي. في المقابل، فضل Glide مركب إرلوتينيب نظرًا لتفاعلات التكدّس–π ، بينما أظهر MOE تميزًا في تحديد مشتقات إيثيل فانيلين و-N (ثلاثي الميثيل)، خصوصًا لما تتمتع به من تفاعلات قطبية. تشير النتائج إلى أن لكل برنامج نقاط قوة تعتمد على نوع التفاعل بين المركب والمستلم.

الاستنتاج: أظهرت أدوات GOLD وMOE فعالية واعدة في التنبؤ بالمركبات عالية الألفة لمشتقات الكينازولين المستهدفة لـ EGFR، بينما تميز Glide في التعامل مع التفاعلات الكارهة للماء. تؤكد هذه النتائج أهمية اختيار أداة الإرساء المناسبة بناءً على خصائص المركب لضمان فعالية عملية اكتشاف الأدوية المثبطة لـEGFR .

الكلمات المفتاحية: الارساء الجزيئي، مثبطات عامل النمو البشري، مشتقات الكينازولين، تقييم ومقارنة برامج الالتحام الجزيئي (GOLD، Glide، MOE).

Introduction

Molecular docking is a powerful computational tool that helps predict how ligands bind to targets like EGFR, a key player in drug discovery. It plays a crucial role in screening chemical libraries to identify drug candidates for non-small cell lung cancer (NSCLC), where EGFR mutations drive tumor growth and therapy resistance [1]. Over the years, numerous docking programs have been developed, differing in search algorithms and scoring functions [2]. A robust docking tool must accurately predict ligand binding poses, rank them effectively, and minimize false positives [3].

The study is a comparative analysis of three docking programs, i.e., GOLD, Glide, and MOE, based on their accuracy and computational speed in binding pose predictions and computing time. On the basis of a ligand identified previously with EGFR,

ligands were designed, converted into 3D structures, and energy minimized using ChemOffice 23.1.1 [4]. Selected EGFR protein models (PDB ID: 4hjo) was retrieved from the Protein Data Bank (PDB) with the assurance of having co-crystallized ligand [5]. The performance of docking programs was assessed in terms of binding pose predictions and ligand-protein interaction, as in other studies, but were not used in virtual screening comparisons [6].

Background and Significance

NSCLC stands among the top mortality-causing cancers throughout the world despite being a significant health threat at present. Quinazoline-based inhibitors block EGFR function in NSCLC [7,8]. Molecular docking plays a crucial role in drug discovery by predicting ligand-receptor interactions, optimizing drug efficacy, and guiding structure-based drug design [9].

This research has examined the binding strength along with binding manner and interaction types of recently generated quinazoline derivatives through GOLD, Glide, and MOE analysis.

Computational Drug Design and Molecular Docking

Computational approaches have accelerated drug discovery by predicting molecular interactions, reducing experimental costs, and refining candidate selection [10]. Computer-aided drug design (CADD) integrates structure-based and ligand-based approaches to optimize drug discovery pipelines; virtual screening techniques allow for the rapid evaluation of millions of compounds based on docking accuracy and scoring functions [11].

Molecular docking involves two key tasks: search algorithms that explore ligand-protein conformational space and scoring functions that evaluate binding stability [1]. Successful docking programs require robust algorithms and precise scoring functions to optimize ligand ranking and lead selection [12].

Comparative Analysis of GOLD, Glide, and MOE

To better understand the differences among these docking tools, **Table (1)** summarizes their key features, including scoring functions and algorithms. GOLD, Glide, and MOE were compared [13][14][15]. The scoring functions within Glide enable ligand ranking through its three screening modes including high-throughput screening (HTS) and standard precision (SP) and extra precision (XP) docking [14]. MOE incorporates rigid and flexible docking methods with molecular mechanics-based energy calculations [15]. Evaluating these docking programs is essential, as each employs distinct docking approaches.

Table 1: Selected docking tools [13][14][15].

No.	*Tools*	*Year*	*Scoring functions*	*Search algorithms*	*License*
1	Gold [13-14]	1997	Gold Score, Chem Score, Astex Statistical Potential, ChemPiecewise Linear Potential	Genetic Algorithm	Commercial
2	Glide [13-14]	2004	Glide score	Hybrid of Systematic Search and Heuristic Optimization	Commercial
3	MOE [15]	2012	Systematic and Stochastic sampling	Atom-sphere exclusion score, Affinity ΔG score, Alpha Hydrogen Bond score, London ΔG score and Generalized Born-Volume Integral/Weighted Surface Area ΔG score	Academic free

Quinazoline Derivatives as Antiproliferative Agents

Cancer therapy now uses quinazoline derivatives as promising antiproliferative compounds because these molecules target essential cancer-related molecular pathways which promote tumor survival and growth. The compounds exhibit effectiveness against several forms of cancer such as lung cancer and breast cancer and colon cancer and ovarian cancer and prostate cancer and accomplish their actions through blocking protein tyrosine kinases (PTKs) together with the vascular endothelial growth factor (VEGF) pathway that supports tumor growth and angiogenesis [16] [17]. The anticancer effectiveness of quinazolines improves when researchers make structural modifications with aniline and aryloxy functional groups because these derivatives show strong activity against MCF-7 and A549 cancer cell lines [16]. The anticancer properties of quinazoline derivatives result from their ability to induce cell death through apoptosis while also disrupting normal cell cycles according to study results published in [17]. These compounds show good pharmacokinetic properties together with low toxicity that makes them desirable prospects for additional medical research [17]. The advantageous characteristics of these compounds need additional preclinical research for clinical application because of a need to optimize both safety and effectiveness [18]. The research focus on structure-activity relationships (SAR) persists as an essential field because it drives development of new quinazoline analogues that demonstrate better therapeutic traits [19]. Quinazoline derivatives demonstrate substantial therapeutic potential as specific chemotherapeutic agents that could serve as a better alternative treatment while causing less harm to patients [20]. Although quinazoline derivatives have shown strong potential as EGFR-targeted anticancer agents, there is still a lack of clear guidance on which molecular docking software provides the most reliable predictions. Different programs use varied algorithms and scoring methods, which can lead to inconsistent results. This study addresses that gap by comparing three widely used docking tools (**GOLD, Glide,** and **MOE**) to assess

their accuracy in predicting binding poses and affinities for quinazoline derivatives. The goal is to help researchers choose the most effective platform for EGFR-focused drug discovery.

Methodology

Selection of Quinazoline Derivatives

A uniform set of quinazoline derivatives was docked into a single receptor site using GOLD, Glide, and MOE. The method of molecular docking predicts which orientation a ligand will adopt while binding with its target protein [21]. The data aids in designing drugs with improved binding properties. High-throughput screening and combinatorial chemistry have increased drug candidate availability. However, experimental testing of large chemical libraries is both time-consuming and expensive [22]. In silico docking helps prioritize promising compounds for further investigation, reducing the cost and effort required for experimental validation [3]. The study focused on quinazoline derivatives due to their known anticancer potential and their ability to interact with tyrosine kinase domains [24, 25].

Preparation of Ligands and Receptors

Molecular docking was conducted using GOLD, Glide, and MOE. The programs followed their established protocols to prepare both ligands and proteins. The PDB-formatted protein structure required cleaning our protein (ID: 4hjo) by removing water molecules followed by hydrogen atom addition before optimizing protonation states to match physiological conditions [26]. Ligands as shown in **Figure (1)** are initially drawn in 2D and converted into 3D structures using ChemDraw, followed by energy minimization using the MM2 force field.

GOLD: Ligands and proteins were protonated at physiological pH, and the protein's binding site was defined by selecting a sphere around the co-crystallized ligand, including all residues within a 10 Å radius [27].

Glide: Ligands were docked into a receptor prepared using the default "Protein preparation workflow" option, which assigned missing hydrogens, protonated at physiological pH, calculated charges, and minimized energy. A receptor grid was generated, centered on the co-crystallized ligand, to define the active site [28].

MOE: Ligands and proteins were prepared using the "quick prep" tool, which optimized protonation states at pH 7.0. A binding site sphere of 10 Å was selected around the co-crystallized ligand for docking studies [29].

Derivative	R1	R2	R3
3-NO_2	H	NO_2	H
4-NO_2	H	H	NO_2
4-Br	H	H	Br
4-CH_3	H	H	CH_3
4-Cl	H	H	Cl
Ethyl vanillin	H	OCH_2CH_3	OH
H (unsubstituted)	H	H	H
Isophthalaldehyde	H	CHO	H
4-$N(CH_3)_2$	H	H	$N(CH_3)_2$
4-OCH_3	H	H	OCH_3
4-OH	H	H	OH
Orthophthalaldehyde	CHO	H	H
Terephthalaldehyde	H	H	CHO
Vanillin	H	OCH_3	OH

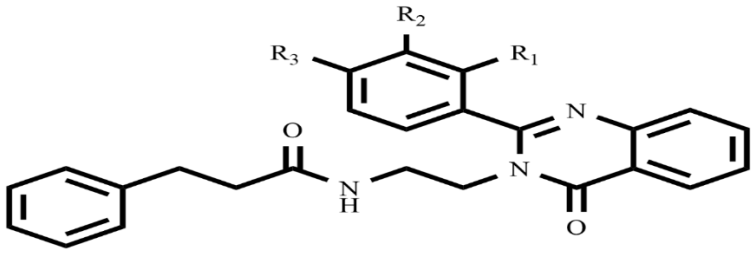


Figure (1): suggested ligands

Molecular Docking Protocols

Molecular docking studies were performed under default settings unless specified otherwise. Hydrogens were added to the protein, and appropriate protonation states were assigned. Each docking software uses a different scoring function to evaluate ligand binding affinities [30].

GOLD: The genetic algorithm (GA) search efficiency was set to automatic tautomerism, using three GOLD scoring functions: CHEMPLP, GoldScore, and ChemScore, with the ligand protonation state set to "Auto Tautomer" and the macromolecule at pH 7.0.

Glide: Extra precision (XP) & Standard precision (SP) docking was used to refine ligand conformations, and the ligand protonation state was set to +2 at pH 7.0.

MOE: The ligand protonation state was set to +2 at pH 7.0, and docking was performed using both flexible and rigid-body docking techniques.

Each program evaluates ligand binding differently: **GOLD** ranks docked poses using a fitness function that considers internal energy, hydrogen bonding, van der Waals interactions, and metal-binding interactions. **Glide** calculates binding free energy using a combination of van der Waals and electrostatic interaction terms. **MOE** incorporates a force-field-based scoring function that evaluates the ligand's stability within the binding site.

Multiple ligand poses were generated, with the highest-affinity pose selected for analysis. The interactions between ligands and EGFR were visualized to confirm binding mode accuracy and consistency with experimental structures. With the docking simulations completed, the next step was to evaluate their performance based on binding affinity, pose accuracy, and interactions analysis.

Comparison of Docking Programs

1- The docking results were analyzed based on: Binding **Affinity:** The best binding & lowest binding energy pose among the ligands was compared across all three programs.

2- **Reproduction of Experimental Binding Poses:** The docked poses were aligned with the known co-crystallized ligand to evaluate accuracy.
3- **Interaction Analysis:** Hydrogen bonding, van der Waals interactions, and π-π stacking interactions were examined for each ligand-protein complex.

Results

Proteins were preprocessed with the default settings and results shown in **Table (2)**.

Table 2: Docking Results

Comp.	Gold Docking			Glide Docking		MOE Docking	
	Gold score	Chem score	PLP fitness	Glide score SP ΔG binding (Kcl mol^{-1})	Glide score XP ΔG binding (Kcl mol^{-1})	Rigid ΔG binding (Kcl mol^{-1})	Induced fit ΔG binding (Kcl mol^{-1})
3-NO_2	80.2	40.1	96.8	-7.480	-8.453	-8.656	-8.984
4-NO_2	76.2	38.6	97.1	-7.620	-8.217	-8.573	-8.594
4-Br	78.2	40.9	95.6	-7.965	-8.306	-8.530	-8.677
4-CH_3	74.0	38.0	98.1	-8.364	-8.318	-8.328	-8.583
4-Cl	72.4	39.2	97.3	-8.386	-7.395	-8.176	-8.633
Ethyl vanillin	79.0	36.4	95.1	-7.198	-8.582	-8.306	-9.161
H	71.2	39.1	93.4	-8.187	-8.311	-7.746	-8.646
isophthalaldehyde	70.0	36.7	90.2	-7.739	-8.120	-8.231	-8.606
4-$N(CH_3)_2$	82.8	39.6	94.1	-8.010	-8.544	-8.385	-9.105
4-OCH_3	72.0	37.8	92.9	-8.437	-7.810	-8.070	-8.838
4-OH	73.7	34.6	83.7	-6.924	-8.848	-8.304	-8.401
Ortho-phthalaldehyde	70.9	33.2	84.6	-7.543	-9.070	-8.460	-8.518
terephthalaldehyde	77.0	37.1	93.0	-7.700	-8.137	-8.0754	-8.630
Vanillin	81.0	36.9	92.3	-7.593	-8.969	-8.318	-8.955
Erlotinib	70.2	30.0	74.8	-9.650	-10.038	-7.651	-8.183

Molecular Docking Outcomes

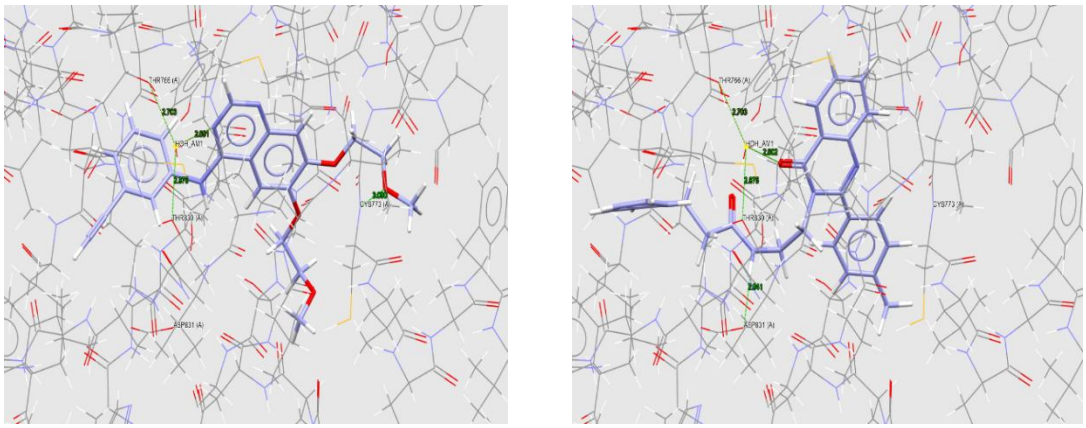
The docking outcomes from GOLD revealed that ligands with electronegative (NO_2) or bulky, hydrophobic groups (4-$N(CH_3)_2$) exhibited strong binding interactions. 4-$N(CH_3)_2$ (Gold Score: 82.8, ChemScore: 39.6, PLP Fitness: 94.1) and 3-NO_2 (Gold Score: 80.2, ChemScore: 40.1, PLP Fitness: 96.8) showed optimal hydrogen bonding and hydrophobic interactions. Erlotinib (Gold Score: 70.2, ChemScore: 30.0, PLP Fitness: 74.8) had lower scores, suggesting weaker interactions. 4-Br had the highest ChemScore (40.9), while 4-CH_3 had the highest PLP Fitness (98.1), indicating excellent binding.

Glide's SP/XP scoring prioritized hydrophobic and aromatic interactions, favoring Erlotinib (-9.650 & -10.038) as the best-scoring compound. Its quinazoline scaffold enhanced π-π stacking interactions,

making it outperform other ligands. Less hydrophobic ligands scored lower due to fewer favorable nonpolar contacts.

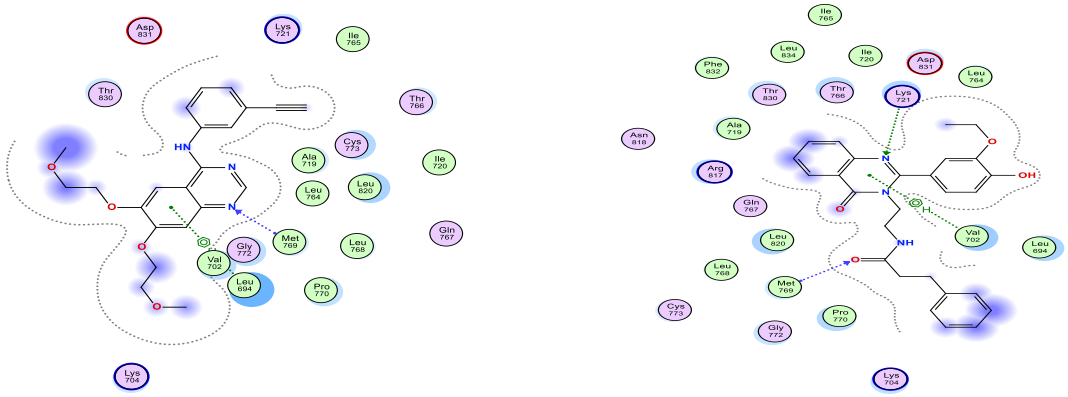
MOE predicted Ethyl Vanillin (-9.161) and 4-N(CH_3)$_2$ (-9.105) as top binders due to strong polar interactions. Erlotinib (-8.183) scored lower than Glide, likely due to MOE's different weighting of desolvation effects. Bulky, aromatic ligands performed better due to π-π stacking, while smaller polar ligands, like 4-OH (-8.401), showed weaker hydrophobic interactions.

The protein-ligands interactions shown in **Figures (2-4)**.



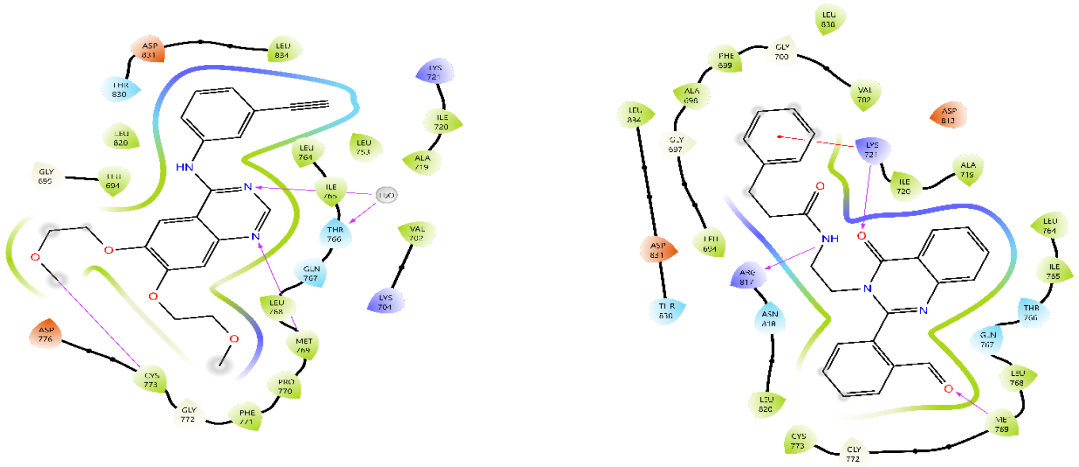
(A) (B)

Figure (2): Gold interactions between receptor (4HJO) and A: Erlotinib, B: comp. CH_3.



(C) **(D)**

Figure (3): MOE 2D interactions between receptor (4HJO) and C: Erlotinib, D: ethyl vanillin.



(E) **(F)**

Figure (4): Glide 2D interactions between receptor (4HJO) and E: Erlotinib, F: Ortho-phthalaldehyde.

Discussion

Different binding affinities emerged from molecular docking studies according to the docking software selection. The GOLD analysis demonstrated that 4-N$(CH_3)_2$, 3-NO_2 and 4-CH3 demonstrated the most potent binding capacity because they participate in both hydrogen bonds and hydrophobic contacts yet Erlotinib displayed weaker binding. Receptor binding patterns obtained from MOE indicated Ethyl Vanillin together with 4-N$(CH_3)_2$ provided optimal binding through polar forces because Ethyl Vanillin exhibited stronger binding than Erlotinib. Glide selected Erlotinib (-10.038) against Ortho-Phthalaldehyde because it uses hydrophobic and aromatic π-π interactions. The study shows that scoring algorithms combine with processing functions affect docking predictions because hydrophobic groups and electron-withdrawing functions together with flexible ligands improve binding efficiency. Seven scoring functions and processing functions produced varying results during docking prediction tests where 4-CH3 and Ethyl Vanillin demonstrated stronger binding abilities in GOLD and MOE but Erlotinib displayed the best outcomes in Glide suggesting new potential candidates. Multiple docking techniques should be combined to enhance the accuracy of predicting quinazoline-based anticancer agents. Additional MD simulation runs combined with ADME examinations must validate the discovered findings regarding drug-likeness assessment of potential candidates.

Conclusion

This study compared GOLD, Glide, and MOE docking programs in evaluating quinazoline derivatives as potential EGFR inhibitors for NSCLC. To ensure fair comparison, all docking simulations were conducted under consistent preparation protocols, with default settings standardized across platforms wherever applicable (e.g., solvation, protonation states). Additionally, only the respective docking platforms were used for structure optimization to avoid external influences. The results revealed distinct differences in how each software

predicted binding affinities and interaction modes. GOLD identified 4-N-$(CH_3)_3$, 3-NO_2, and 4-CH3 as strong binders, emphasizing the importance of hydrogen bonding and hydrophobic interactions. MOE favored Ethyl Vanillin and 4-N-$(CH_3)_3$ derivatives due to their polar interactions, while Glide ranked Erlotinib highest, likely due to its strong hydrophobic and π-π interactions with key residues.

Given these differences, GOLD and MOE appear most effective for predicting high-affinity binders with strong hydrogen bonding and hydrophobic properties, while Glide excels in handling ligands with hydrophobic and aromatic interactions. Overall, GOLD and MOE may be the docking programs of choice for quinazoline derivatives. Further MD simulations and ADME studies are needed to validate these findings and assess the drug-likeness of top candidates.

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