การจำลองโมเลกุลเชิงโครงสร้างเพื่อการค้นหายาต้านมะเร็งที่มุ่งเป้าหมายที่ Epidermal Growth Factor Receptor

Structure-Based Molecular Simulation-Assisted Approaches for the Discovery of Anticancer Drugs Targeting the Epidermal Growth Factor Receptor

สิริพร ชูเพชรสมบูรณ์[1*] ศรัณยภัทร แสนนาม[2] รุจิภาส สันนิธิลาวัณย์[3] และ รัตนธร อันจิต[4]

Siriporn Shupetchsomboon[1*] Sarunyapat Sannam[2] Rujipas Sunnithilawan[3] and Rattanathorn Anjit[4]

[1]นักวิจัยอิสระ กรุงเทพมหานคร 10400 ประเทศไทย

[2]โรงเรียนนิวตัน กรุงเทพมหานคร 10330 ประเทศไทย

[3]โรงเรียนสาธิตนานาชาติ มหาวิทยาลัยมหิดล นครปฐม 73170 ประเทศไทย

[4]โรงเรียนราชวินิตบางแก้ว สมุทรปราการ 10540 ประเทศไทย

[1]Independent Researcher, Bangkok 10400, Thailand

[2]The Newton Sixth Form School, Bangkok 10330, Thailand

[3]Mahidol University Demonstration School, Nakhon Pathom 73170, Thailand

[4]Ratwinit BangKaeo School, Samut Prakan 10540, Thailand

*E-mail: siriporn.shu@gmail.com

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บทคัดย่อ

ตัวรับปัจจัยการเจริญเติบโตของผิวหนังชั้นนอก (epidermal growth factor receptor; EGFR) เป็นหนึ่งในตัวขับเคลื่อนสำคัญของการเกิดมะเร็งหลายชนิด โดยเฉพาะมะเร็งปอดชนิดไม่ใช่เซลล์เล็ก (non-small cell lung cancer; NSCLC) ซึ่งการกลายพันธุ์ของ EGFR มีบทบาทสำคัญต่อการตอบสนองต่อการรักษาและการเกิดภาวะดื้อยา แม้ว่ายากลุ่ม EGFR tyrosine kinase inhibitors (EGFR-TKIs) จะช่วยยกระดับผลลัพธ์ทางคลินิกได้อย่างมีนัยสำคัญ แต่การเกิดการกลายพันธุ์ที่เกี่ยวข้องกับภาวะดื้อยา เช่น T790M และ C797S ยังคงเป็นอุปสรรคสำคัญต่อประสิทธิผลของการรักษาในระยะยาว ส่งผลให้การค้นหาและพัฒนายารุ่นใหม่ที่สามารถรับมือกับกลไกการดื้อยาได้อย่างมีประสิทธิภาพเป็นประเด็นสำคัญทางการแพทย์แม่นยำในปัจจุบัน การจำลองเชิงโมเลกุลแบบอาศัยโครงสร้างได้กลายเป็นแนวทางที่มีประสิทธิภาพในการเข้าใจถึงพฤติกรรมของตัวรับที่มีการกลายพันธุ์ และเป็นแนวทางในการค้นพบยาใหม่ บทความปริทัศน์นี้มุ่งวิเคราะห์และสังเคราะห์องค์ความรู้เกี่ยวกับบทบาทของการจำลองเชิงโมเลกุลแบบอาศัยโครงสร้างในการค้นหาและพัฒนายาต้านมะเร็งที่มุ่งเป้า EGFR โดยใช้แนวทางการสืบค้นวรรณกรรมตามหลัก PRISMA-informed literature review และให้ความสำคัญกับการประเมินความเข้มแข็งของระเบียบวิธี การตรวจสอบความถูกต้องทางชีวภาพ และศักยภาพในการประยุกต์ใช้เชิงคลินิก นอกจากนี้ ยังมุ่งเปรียบเทียบจุดแข็ง ข้อจำกัด และคุณค่าเชิงการแปลผลของวิธีการคำนวณที่ใช้ในงานวิจัยด้านการค้นพบยา ผลการสังเคราะห์พบว่า molecular docking ยังคงเป็นเครื่องมือที่ได้รับความนิยมมากที่สุดสำหรับการคัดกรองสารออกฤทธิ์เบื้องต้น อย่างไรก็ตาม ความสามารถในการทำนายประสิทธิภาพทางชีวภาพยังมีข้อจำกัดเมื่อใช้เพียงลำพัง ในทางตรงกันข้าม งานวิจัยที่ผสาน molecular docking เข้ากับ molecular dynamics simulation การคำนวณพลังงานอิสระ และการตรวจสอบเชิงทดลอง ให้ผลลัพธ์ที่มีความน่าเชื่อถือและมีศักยภาพในการนำไปพัฒนาต่อยอดได้มากกว่า แนวโน้มการวิจัยในปัจจุบันมุ่งเน้นการพัฒนาสารยับยั้งที่จำเพาะต่อการกลายพันธุ์ สารออกฤทธิ์หลายเป้าหมาย สารยับยั้งแบบ allosteric ยาที่ได้จากธรรมชาติ และยาที่นำมาใช้ใหม่เพื่อรับมือกับกลไกการดื้อยาที่ซับซ้อน โดยสรุป การจำลองเชิงโมเลกุลแบบอาศัยโครงสร้างได้พัฒนาจากเครื่องมือคัดกรองสารออกฤทธิ์ไปสู่กรอบแนวคิดเชิงกลไกที่ช่วยอธิบายการกระตุ้นของ EGFR การเกิดภาวะดื้อยา และวิวัฒนาการของการดื้อยา องค์ความรู้ที่สังเคราะห์

จากบทความนี้ชี้ให้เห็นว่าการบูรณาการข้อมูลเชิงคำนวณร่วมกับการตรวจสอบเชิงทดลองมีบทบาทสำคัญต่อการพัฒนายาต้านมะเร็งที่มุ่งเป้า EGFR รุ่นถัดไป และสนับสนุนความก้าวหน้าของการแพทย์แม่นยำสำหรับมะเร็งที่เกิดจากการกลายพันธุ์

คำสำคัญ: การจำลองโมเลกุลเชิงโครงสร้าง การกลายพันธุ์ของยีน EGFR มะเร็ง การค้นพบยา

Abstract

Mutations in the epidermal growth factor receptor (EGFR) are major oncogenic drivers in several malignancies, particularly non-small cell lung cancer (NSCLC). The EGFR mutations play a significant role in treatment response and the development of drug resistance. Although successive generations of EGFR tyrosine kinase inhibitors (EGFR-TKIs) have substantially improved clinical outcomes, resistance-associated mutations such as T790M and C797S continue to limit treatment durability and create an urgent need for next-generation therapeutic strategies. Structure-based molecular simulation has emerged as a powerful approach for understanding mutation-dependent receptor behavior and guiding rational drug discovery. This review critically synthesizes current evidence on the application of structure-based computational approaches in EGFR-targeted anticancer drug development. By using a PRISMA-informed literature review, studies were evaluated according to methodological rigor, biological validation, and translational relevance. Furthermore, particular emphasis was placed on comparing strengths, limitations, and interpretive value of computational methods used in drug discovery research. The evidence indicates that molecular docking remains the most frequently applied screening method; however, its predictive value is limited when used alone. Studies integrating molecular docking with molecular dynamics simulation, free-energy calculations, and experimental validation consistently generated more reliable and translationally meaningful findings. Current research trends focus on developing mutant-selective inhibitors, dual-/multi-target compounds, allosteric inhibitors, natural product-derived drugs and repurposed drugs to address complex drug resistance mechanisms. In conclusion, this review highlights that structure-based molecular simulation has evolved beyond virtual screening into a mechanistic framework for understanding EGFR activation, therapeutic vulnerability, and resistance evolution. The findings suggest that integrated computational-experimental workflows are likely to play a central role in the development of next-generation EGFR-targeted therapies and the advancement of precision oncology for mutation-driven cancers.

Keywords: Structure-based molecular simulation-assisted approaches, Epidermal growth factor receptor (EGFR) mutation, Cancer, Drug discovery

1. Introduction

Cancer remains a major global cause of morbidity and mortality, with lung cancer contributing the highest number of cancer-related deaths worldwide [1], [2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and is frequently driven by dysregulated receptor tyrosine kinase signaling [3]. Among these alterations, activating mutations in the epidermal growth factor receptor (EGFR) are clinically important, particularly in Asian populations and never-smokers, and have established EGFR as a central target in precision oncology [4], [5]. Aberrant EGFR activation promotes persistent downstream signaling through PI3K/AKT, RAS/RAF/MEK/ERK, and JAK/STAT pathways, thereby supporting tumor proliferation, survival, invasion, and therapeutic resistance [6].

EGFR-targeted tyrosine kinase inhibitors (EGFR-TKIs) have transformed the treatment of EGFR-

mutant NSCLC. First-generation inhibitors, including gefitinib and erlotinib, improved outcomes in patients with sensitizing mutations such as exon 19 deletions and L858R [7]. However, acquired resistance, especially the T790M mutation, limited long-term efficacy and led to the development of later-generation inhibitors, including afatinib and osimertinib [8], [9]. Despite these advances, resistance remains a persistent clinical challenge due to compound mutations, bypass pathway activation, intratumoral heterogeneity, and adaptive molecular evolution [10]. Emerging resistance variants, particularly C797S, further restrict the durability of current EGFR-directed therapies [11].

Structure-based computational approaches have increasingly been used to support EGFR-targeted drug discovery. Molecular docking, molecular dynamics (MD) simulation, binding free-energy estimation, virtual screening, and in silico ADMET prediction enable atomic-level evaluation of ligand-EGFR interactions, conformational stability, and pharmacokinetic potential [12]-[14]. These approaches can reduce experimental cost, accelerate lead prioritization, and support the rational design of mutation-selective or multi-target inhibitors [15], [16]. However, their predictive value depends strongly on methodological rigor, including protein preparation, docking validation, scoring functions, force fields, simulation duration, and biological confirmation [17]-[19].

Although many studies report promising EGFR inhibitors based on docking and MD simulation, the field remains fragmented and methodologically heterogeneous. Reported compounds vary widely across synthetic molecules, natural products, drug-repurposing candidates, and dual- or multi-target inhibitors. Moreover, many studies rely heavily on docking scores or binding energy estimates without adequate experimental validation or benchmarking against approved EGFR-TKIs [17], [18]. As a result, strong in silico affinity does not necessarily indicate biological efficacy or clinical relevance, particularly in mutation-driven NSCLC where resistance mechanisms are complex and dynamic [20]. A focused synthesis is therefore needed to evaluate not only what computational studies have identified, but also how reliable, reproducible, and translationally meaningful these findings are First, existing EGFR-focused reviews often describe computational methods or therapeutic developments separately, with limited integration between molecular simulation findings, resistance biology, and clinical translation. Second, there is insufficient comparative appraisal of major computational workflows, including molecular docking, MD simulation, MM-PBSA/MM-GBSA analysis, and ADMET prediction, in terms of their strengths, limitations, reproducibility, and translational value. Third, the evidence base has not been clearly stratified according to validation level; many candidate inhibitors supported only by in silico findings are discussed alongside compounds with in vitro, in vivo, or clinical evidence. These gaps limit the ability to judge which computational approaches and reported compounds are most relevant for next-generation EGFR-targeted drug development.

2. Objectives of the study

1. To examine the structural and conformational mechanisms underlying EGFR activation, oncogenic mutations, and therapeutic resistance in cancer

2. To critically evaluate the application of structure-based molecular simulation approaches, including molecular docking, molecular dynamics simulation, free-energy calculations, and related computational methods, in EGFR-targeted drug discovery

3. To assess the translational relevance, methodological limitations, and future opportunities of computationally guided strategies for the development of next-generation EGFR-targeted therapeutics.

3. Study methods

This narrative review was conducted as a structured evidence synthesis incorporating systematic literature search principles to critically evaluate the role of structure-based molecular simulation in epidermal growth factor receptor (EGFR)-targeted anticancer drug discovery. Because the available literature encompasses diverse computational methodologies, ligand classes, EGFR mutation profiles, validation strategies, and outcome measures, a quantitative meta-analysis was not considered appropriate. Instead, a qualitative comparative synthesis was undertaken to identify methodological trends, evaluate translational relevance, and examine the strengths and limitations of contemporary computational approaches. To enhance transparency and reproducibility, the review process was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework.

A comprehensive literature search was performed between October and December 2025 using PubMed, Scopus, Web of Science, and Google Scholar. Eligible studies were published between January 2010 and April 2026, a period selected to capture major developments in EGFR-targeted therapy and the rapid evolution of structure-based drug discovery technologies. The search strategy combined Medical Subject Headings (MeSH), controlled vocabulary terms, and free-text keywords related to EGFR biology, molecular simulation, and anticancer drug development. Representative search terms included (“EGFR” OR “epidermal growth factor receptor”) AND (“molecular docking” OR “molecular dynamics simulation” OR “virtual screening” OR “MM-PBSA” OR “MM-GBSA” OR “structure-based drug design”) AND (“cancer” OR “non-small cell lung cancer” OR “NSCLC”). Reference lists of relevant reviews and primary studies were additionally screened to identify potentially eligible publications.

Studies were included if they (i) investigated EGFR or clinically relevant EGFR mutations associated with cancer, (ii) employed structure-based computational approaches such as molecular docking, molecular dynamics (MD) simulation, virtual screening, pharmacophore modeling, free-energy calculations, quantitative structure-activity relationship (QSAR) modeling, or ADMET prediction, and (iii) focused on anticancer drug discovery, lead optimization, mutation-selective inhibitor design, drug repurposing, or resistance-targeted therapeutic development. Studies were excluded if they did not directly address EGFR-targeted therapeutics, focused solely on clinical outcomes without structural or computational analyses, lacked sufficient methodological detail, or consisted of conference abstracts, editorials, commentaries, letters, or non-peer-reviewed publications.

All records underwent title and abstract screening followed by full-text evaluation according to predefined eligibility criteria. Duplicate records were removed prior to screening, and reasons for exclusion were documented to improve methodological transparency. A total of 1,248 records were identified through database searching, of which 284 duplicates were removed. Following title and abstract screening of 964 records, 122 studies were selected for full-text assessment. After eligibility evaluation, 42 studies were included in the final qualitative synthesis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

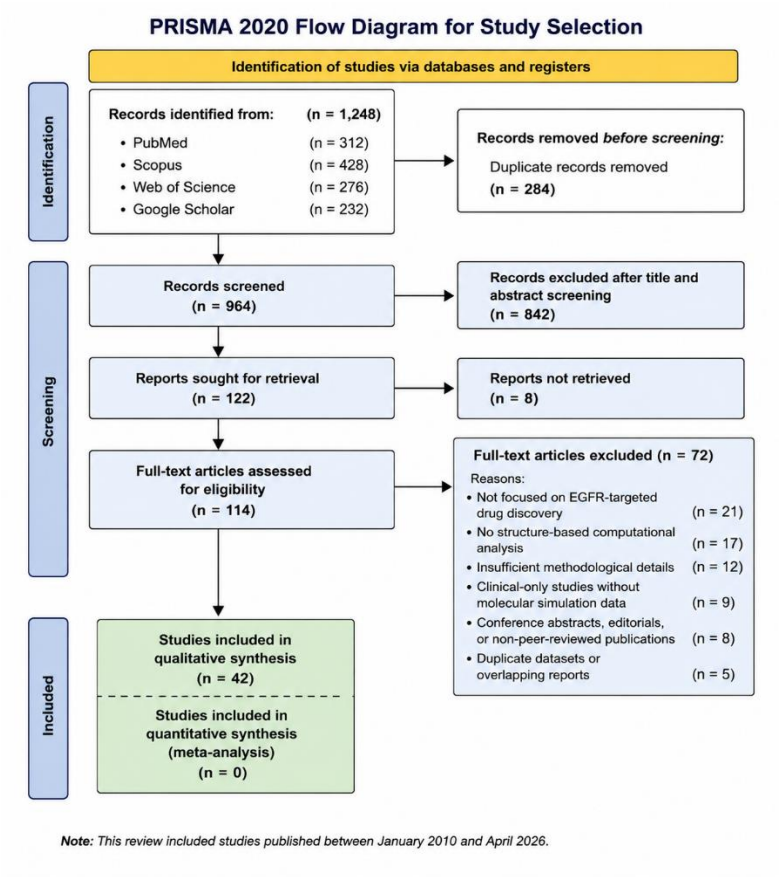


Figure 1 PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion (Created by authors)

Data extraction was performed using a standardized framework. Information collected from each study included publication year, cancer type, EGFR mutation profile, ligand source, computational workflow, docking platform, scoring functions, molecular dynamics simulation parameters, free-energy calculation methods, ADMET prediction tools, biological validation status, and principal findings. Studies were subsequently categorized into major therapeutic domains, including synthetic small-molecule inhibitors, dual-/multi-target strategies, natural product-derived compounds, drug repurposing approaches, and resistance-associated mutant-targeted therapeutics.

To facilitate critical interpretation, studies were additionally evaluated according to methodological rigor and validation level. Assessment criteria included protein and ligand preparation procedures, docking validation, treatment of receptor flexibility, simulation duration, transparency of computational parameters, use of complementary computational techniques, and incorporation of experimental validation. Studies were classified into five validation levels: Level 1 (molecular docking only), Level 2 (docking combined with advanced computational analyses such as MD simulation or ADMET prediction), Level 3 (integrated computational workflow without biological validation), Level 4 (computational studies supported by in vitro experimental validation), and Level 5 (computational studies supported by both in vitro and in vivo validation). This framework was used to compare the translational strength of evidence across therapeutic categories.

Evidence synthesis emphasized comparative analysis rather than descriptive reporting. Particular attention was given to the relationship between

computational predictions and biological outcomes, the ability of different methodologies to capture mutation-dependent conformational dynamics, and the translational relevance of reported compounds. Comparative evaluation focused on the relative contributions, strengths, and limitations of molecular docking, molecular dynamics simulation, free-energy calculations, pharmacophore modeling, QSAR approaches, and ADMET prediction within contemporary EGFR-targeted drug discovery.

Several limitations should be acknowledged. The included studies exhibited substantial methodological heterogeneity with respect to computational workflows, mutation targets, simulation parameters, validation strategies, and outcome measures, limiting direct comparison across investigations. Furthermore, most available evidence originated from computational and preclinical studies, whereas clinically validated data remain limited. Consequently, findings should be interpreted as a critical synthesis of current evidence rather than a quantitative assessment of therapeutic efficacy.

4. Structural biology of EGFR

The epidermal growth factor receptor (EGFR) is a single-pass transmembrane receptor tyrosine kinase whose oncogenic activity is regulated by coordinated conformational transitions linking extracellular ligand recognition to intracellular kinase activation. Structurally, EGFR consists of an extracellular ligand-binding domain, a transmembrane (TM) helix, a juxtamembrane (JM) regulatory segment, an intracellular kinase domain, and a C-terminal signaling tail. Rather than functioning as a static catalytic protein, EGFR operates as a dynamic allosteric system in which conformational plasticity governs receptor activation, signaling output, inhibitor sensitivity, and resistance evolution [1], [8], [9]. This structural complexity is particularly relevant to structure-based drug discovery because many oncogenic and resistance-associated mutations alter the conformational landscape of the receptor rather than simply modifying the ATP-binding site. Consequently, understanding EGFR structural dynamics is essential for interpreting molecular docking results, molecular dynamics (MD) trajectories, and mutation-selective inhibitor design strategies.

4.1. Extracellular ligand-binding domain (ECD I–IV)

The extracellular domain (ECD) regulates ligand recognition, receptor autoinhibition, and dimerization through four subdomains (I–IV). Domains I and III mediate ligand binding, whereas domains II and IV control transitions between inactive tethered and active extended conformations [1], [10]. Ligand engagement induces conformational rearrangements that expose the dimerization arm within domain II, thereby promoting receptor dimerization and activation. Importantly, different ligands can stabilize distinct extracellular conformations, resulting in variations in signaling intensity and downstream pathway activation.

From a therapeutic perspective, extracellular conformational heterogeneity may influence responsiveness to monoclonal antibodies and allosteric inhibitors. Emerging computational studies further suggest that alterations in ECD dynamics can contribute to resistance-associated signaling adaptation, highlighting the importance of considering receptor flexibility when evaluating ligand-binding behavior and therapeutic response.

4.2. Transmembrane helix and juxtamembrane regulatory region

Although EGFR-directed drug discovery has traditionally focused on the kinase domain, increasing evidence indicates that the TM helix and

JM region play critical roles in receptor activation. The TM helix transmits ligand-induced conformational changes from the extracellular domain to the intracellular kinase through rotational and lateral helical movements, whereas the JM segment stabilizes the active receptor configuration [9]. Specifically, the JM-A region promotes receptor association, while the JM-B region functions as a conformational latch that facilitates asymmetric kinase dimerization [1], [8].

These observations underscore a broader view of EGFR regulation in which functionally important structural determinants extend beyond the ATP-binding cleft targeted by conventional tyrosine kinase inhibitors (TKIs). Molecular simulation studies increasingly demonstrate that TM and JM dynamics influence receptor stability, dimerization energetics, and mutation-associated signaling behavior. Consequently, these regions have emerged as potential targets for allosteric modulation and next-generation mutation-selective therapeutic strategies.

Figure 2 Conformational activation, asymmetric dimerization, and resistance-associated structural dynamics of EGFR. The schematic illustrates ligand-induced transition from an inactive tethered conformation to an active dimerization-competent state, stabilization of the asymmetric kinase dimer, and mutation-associated structural alterations affecting inhibitor binding and kinase activation. Key resistance-associated mutations, including T790M and C797S, remodel the ATP-binding region and alter conformational dynamics, thereby contributing to therapeutic resistance. The figure was created by the authors based on structural and molecular simulation studies reported by Bessman et al. [8], Galdadas et al. [9], Hasenahuer et al. [11], and Krishnamurty and Maly [12].

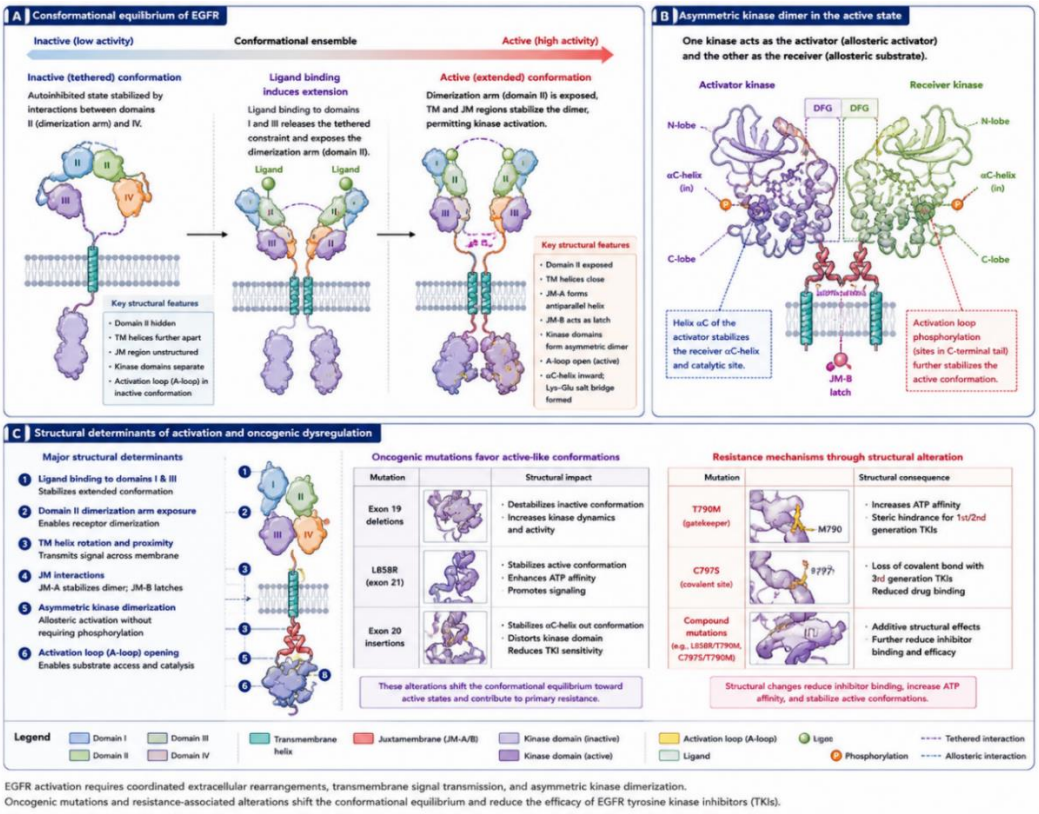


Figure 2 Conformational activation, asymmetric dimerization, and resistance-associated structural dynamics of the epidermal growth factor receptor (EGFR). The figure was created by the authors based on structural and molecular simulation concepts reported in previous studies [8], [9], [11], and [12].

4.3. Kinase domain, activation loop, and conformational activation

The intracellular kinase domain is the principal target of EGFR-directed small-molecule inhibitors and remains the primary focus of structure-based drug discovery efforts. Activation involves inward movement of the αC-helix, formation of the conserved Lys-Glu salt bridge, and reorganization of the activation loop, collectively stabilizing the catalytically competent state [1], [11]. Because different classes of EGFR inhibitors preferentially recognize distinct conformational states, kinase dynamics play a central role in determining inhibitor selectivity, potency, and resistance susceptibility.

A distinctive feature of EGFR activation is asymmetric kinase dimerization, in which one kinase domain acts as an activator and the other as a receiver. This mechanism stabilizes the active conformation independently of activation-loop phosphorylation and partly explains the oncogenic activity of activating mutations such as L858R, exon 19 deletions, and exon 20 insertions [9]. In contrast, resistance-associated mutations frequently act by reshaping conformational equilibria rather than directly preventing inhibitor binding. For example, T790M increases ATP affinity, whereas C797S abolishes the covalent interaction required for third-generation EGFR-TKIs, thereby reducing therapeutic efficacy.

These mutation-dependent structural adaptations highlight the limitations of static receptor models and reinforce the value of molecular docking, MD simulation, and free-energy calculations for characterizing dynamic ligand-protein interactions. Increasingly, successful inhibitor design depends not only on achieving high binding affinity but also on accommodating mutation-induced conformational changes that govern drug sensitivity and resistance.

The intrinsically disordered C-terminal tail further contributes to signaling regulation through multiple autophosphorylation sites that recruit adaptor proteins involved in the RAS/MAPK and PI3K/AKT pathways. Consequently, structural perturbations affecting receptor dimerization, kinase activation, or phosphorylation dynamics can collectively influence both signaling magnitude and persistence, reinforcing the need for integrative computational approaches that consider the full spectrum of EGFR conformational behavior.

Collectively, current structural evidence indicates that EGFR-directed drug discovery is increasingly shifting from a static ATP-binding-site paradigm toward a dynamic conformational framework. This transition has important implications for computational modeling because successful prediction of inhibitor activity requires accurate representation of receptor flexibility, mutation-dependent structural rearrangements, and allosteric communication between functional domains

5. Structural insights into EGFR mutations and oncogenic activation

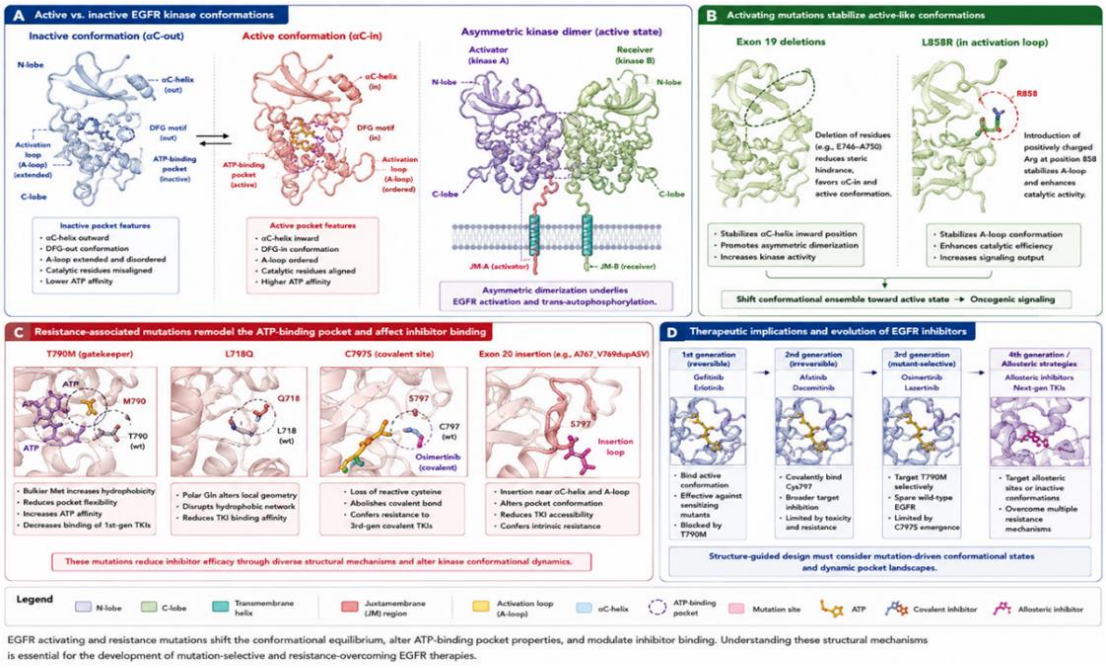
EGFR-driven oncogenesis is frequently mediated by somatic mutations that alter kinase conformation, ATP affinity, and inhibitor recognition. Most clinically relevant mutations occur within the kinase domain, where they shift the equilibrium between inactive and active conformational states, thereby enhancing signaling activity and modifying therapeutic responsiveness [1], [9]. Consequently, the biological effects of EGFR mutations are determined not only by changes in amino acid sequence but also by their impact on receptor structure and conformational dynamics.

Activating mutations, particularly exon 19 deletions and L858R, promote stabilization of the active kinase conformation through inward positioning of the αC-helix, activation-loop reorganization, and enhanced asymmetric kinase dimerization [11].

These structural alterations increase downstream signaling and partly explain the remarkable sensitivity of these tumors to first-generation EGFR tyrosine kinase inhibitors (TKIs). In contrast, resistance-associated mutations preserve oncogenic signaling while reducing inhibitor susceptibility. The T790M gatekeeper mutation increases ATP affinity and alters the physicochemical properties of the ATP-binding pocket, thereby diminishing the effectiveness of early-generation TKIs [9], [12]. Similarly, mutations such as C797S and L718Q impair inhibitor engagement through disruption of covalent binding or local conformational remodeling.

These observations highlight that therapeutic resistance is not solely a consequence of steric interference within the ATP-binding site. Increasing structural and computational evidence indicates that resistance-associated mutations also alter kinase flexibility, allosteric communication, and conformational stability, thereby influencing inhibitor recognition through mechanisms that extend beyond direct binding-site modification. Such mutation-dependent structural remodeling has become a major focus of molecular docking, molecular dynamics (MD) simulation, and free-energy analyses aimed at developing mutation-selective inhibitors capable of overcoming resistance-associated adaptations (Figure 3).

The figure illustrates how activating mutations, including exon 19 deletions and L858R, stabilize active kinase conformations, whereas resistance-associated alterations such as T790M, L718Q, C797S, and exon 20 insertions modify ATP-binding-site architecture, kinase dynamics, and inhibitor accessibility. These mutation-specific structural adaptations have guided the development of successive generations of EGFR-targeted therapeutics and remain central targets of structure-based drug design. Adapted from structural and molecular simulation studies reported by Galdadas et al. [9], Hasenahuer et al. [11], and Krishnamurty and Maly [12].



EGFR activating and resistance mutations shift the conformational equilibrium, alter ATP-binding pocket properties, and modulate inhibitor binding. Understanding these structural mechanisms is essential for the development of mutation-selective and resistance-overcoming EGFR therapies.

Figure 3 Structural determinants of EGFR oncogenic activation and resistance-associated conformational remodeling [9], [11], and [12]

5.1. Structural mechanisms of resistance

Resistance to EGFR-targeted therapy is a multifactorial structural phenomenon involving alterations in ATP affinity, hydrophobic interactions, hydrogen-bonding networks, and conformational flexibility. Among resistance-associated mutations, T790M remains the most extensively characterized, primarily because it enhances ATP binding while maintaining catalytic competence, thereby reducing the competitive advantage of reversible TKIs [12]. In contrast, C797S abolishes the covalent interaction required for irreversible third-generation inhibitors such as osimertinib, creating a distinct resistance mechanism that cannot be overcome solely through increased binding affinity.

Compound mutations, including L858R/T790M and T790M/C797S, present an even greater therapeutic challenge because they simultaneously enhance oncogenic activation and reduce inhibitor compatibility. These complex mutational landscapes underscore the limitations of static structure-based design approaches and support the increasing use of ensemble docking, long-timescale MD simulation, and free-energy calculations to characterize mutation-dependent conformational heterogeneity. Consequently, contemporary EGFR drug discovery has shifted toward allosteric inhibition, mutation-selective binding modes, and combination-based therapeutic strategies designed to address dynamic resistance mechanisms rather than individual mutations alone.

5.2. Post-translational modifications (PTMs) and structural regulation

In addition to genetic alterations, EGFR activity is regulated by post-translational modifications (PTMs), including phosphorylation, glycosylation, and ubiquitination, which collectively influence receptor activation, signaling duration, intracellular trafficking, and degradation [1]. Autophosphorylation of tyrosine residues within the C-terminal tail promotes recruitment of signaling adaptors involved in the PI3K/AKT and RAS/MAPK pathways, whereas glycosylation contributes to extracellular-domain stability and ligand responsiveness. Ubiquitination, primarily mediated by c-Cbl, facilitates receptor internalization and signal termination.

Although PTMs remain less extensively studied than kinase-domain mutations in computational drug discovery, emerging molecular simulation studies suggest that they may influence ligand-binding energetics, receptor flexibility, and long-range allosteric communication. These findings indicate that future structure-based investigations should increasingly consider PTM-dependent structural states when evaluating inhibitor binding and resistance mechanisms.

5.3. Structure-guided drug design targeting EGFR

Advances in structural biology have transformed the development of EGFR-targeted therapeutics from empirical screening toward mechanism-based drug design. Most EGFR inhibitors bind within the ATP-binding cleft through a combination of hinge-region hydrogen bonds, hydrophobic interactions, and, in the case of irreversible inhibitors, covalent interaction with Cys797 [1], [11]. Consequently, inhibitor efficacy depends not only on binding affinity but also on compatibility with mutation-specific conformational states.

This structural framework explains the progressive evolution of EGFR-targeted therapies. First-generation TKIs, including gefitinib and erlotinib, demonstrated substantial activity against sensitizing mutations but remained vulnerable to T790M-mediated resistance. Third-generation inhibitors, such as osimertinib and lazertinib, were subsequently developed to selectively target T790M-positive tumors while minimizing wild-type EGFR inhibition [12].

However, the emergence of C797S-mediated resistance has exposed the limitations of ATP-site covalent inhibition and accelerated the development of fourth-generation inhibitors, allosteric modulators, and rational combination therapies.

Importantly, high-resolution crystal structures and molecular simulation studies have demonstrated that resistance-associated mutations remodel pocket topology, alter hydrogen-bonding architecture, and modify kinase dynamics governing inhibitor selectivity. These findings reinforce a central principle of modern EGFR-targeted drug discovery: successful therapeutic design increasingly depends on integrating structural biology, conformational dynamics, and computational modeling to predict and overcome mutation-driven resistance.

The clinical success and subsequent resistance of EGFR-targeted therapies underscore the importance of understanding how individual mutations reshape receptor structure and drug-binding behavior. While activating mutations such as exon 19 deletions and L858R generally enhance sensitivity to tyrosine kinase inhibitors by stabilizing active kinase conformations, resistance-associated alterations employ diverse structural mechanisms, including increased ATP competitiveness, disruption of covalent binding interactions, and modification of kinase conformational dynamics. These differences have important implications for computational drug discovery because the predictive performance of molecular docking, molecular dynamics simulation, and free-energy analyses depends on accurate representation of mutation-specific structural states. Therefore, a comparative evaluation of major EGFR mutations provides a useful framework for understanding therapeutic response, resistance evolution, and emerging opportunities for structure-guided inhibitor design (Table 1).

6. Structure-based molecular docking approaches

Structure-based molecular docking is one of the most widely used computational tools in EGFR-targeted drug discovery because it enables rapid prediction of ligand-binding modes, key protein–ligand interactions, and mutation-specific binding preferences within structurally characterized receptor conformations [1], [13]. The approach has been extensively applied to both wild-type EGFR and clinically relevant mutant forms, including L858R, T790M, and C797S, where structural alterations substantially influence inhibitor recognition and therapeutic response. Consequently, molecular docking serves as an effective first-line strategy for hit identification and lead prioritization.

Despite its widespread use, the predictive performance of docking remains highly dependent on receptor representation, scoring-function accuracy, and treatment of protein flexibility. This limitation is particularly important for EGFR because kinase activation and resistance are governed by dynamic conformational transitions that cannot be fully represented by a single crystal structure. Accordingly, favorable docking scores should be interpreted cautiously, as binding affinity estimates alone rarely predict cellular activity, selectivity, pharmacokinetic behavior, or resistance-overcoming capability. Across the reviewed literature, studies integrating docking with molecular dynamics (MD) simulation, free-energy calculations, ADMET prediction, and biological validation consistently demonstrated greater translational relevance than docking-only investigations.

Table 1 Comparative structural and therapeutic implications of major EGFR mutations in cancer

EGFR mutation	Structural consequence	Effect on kinase activity	Therapeutic impact	Implications for structure-based drug design
Exon 19 deletion	Stabilizes active kinase conformation through activation-loop reorganization and αC-helix positioning	Increased kinase activation	High sensitivity to first-generation EGFR-TKIs	Active-state inhibitors remain effective; serves as benchmark mutation in computational screening
L858R	Enhances asymmetric dimerization and favors active-state equilibrium	Increased kinase activation	High sensitivity to first- and second-generation TKIs	Frequently used as a model system for docking and MD studies evaluating mutation-selective inhibitors
T790M	Increases ATP affinity and alters ATP-binding pocket hydrophobicity	Preserves catalytic activity while reducing inhibitor competitiveness	Major mechanism of acquired resistance to first-generation TKIs	Requires covalent, mutant-selective, or allosteric inhibitor strategies; highlights limitations of affinity-based screening
C797S	Eliminates covalent interaction with Cys797 required for irreversible inhibition	Retains kinase activity	Resistance to third-generation inhibitors such as osimertinib	Promotes development of non-covalent, allosteric, and fourth-generation inhibitors
L718Q	Alters local binding-pocket architecture and inhibitor orientation	Minimal effect on catalytic activity	Reduces efficacy of third-generation inhibitors	Requires evaluation of mutation-specific binding modes through MD simulation and free-energy analysis
Exon 20 insertion	Modifies kinase-domain geometry and restricts inhibitor accessibility	Constitutive signaling activation	Intrinsic resistance to many approved TKIs	Demands structure-guided design of highly selective inhibitors adapted to altered pocket topology
T790M/C797S (compound mutation)	Combines increased ATP affinity with loss of covalent-binding capability	Sustained oncogenic signaling	Resistance to multiple generations of EGFR-TKIs	Represents a major target for allosteric inhibition and combination-based therapeutic strategies

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; MD, molecular dynamics.

6.1. Synthetic small-molecule EGFR inhibitors

Synthetic heterocyclic scaffolds, including quinazolines, pyrimidines, pyrrolopyrimidines, furopyridines, and benzimidazoles, remain the dominant class of EGFR inhibitors because they permit systematic optimization of potency, selectivity, and mutation coverage [5], [14], [16], [17]. Across multiple studies, favorable docking poses were consistently associated with interactions involving hinge-region residue Met793 and catalytic residue Cys797, which are critical determinants of ATP-site inhibitor binding.

However, substantial variability was observed in the strength of supporting evidence. Several quinazoline- and pyrrolopyrimidine-based inhibitors demonstrated concordance between docking predictions, MD-derived stability, and experimental antiproliferative activity, supporting their potential as lead compounds. In contrast, studies relying solely on docking scores frequently lacked sufficient evidence to establish therapeutic relevance. These findings suggest that docking is most effective for prioritizing candidate scaffolds, whereas assessment of mutation selectivity and resistance-overcoming potential requires complementary dynamic and biological validation.

6.2. Dual-targeting strategies

The increasing interest in dual-target EGFR inhibitors reflects the recognition that resistance often arises through compensatory signaling pathways involving HER2, VEGFR2, AKT, HDAC, and other oncogenic regulators [19]. Consequently, docking has evolved from a single-target screening tool into a platform for evaluating network-oriented therapeutic strategies.

Among the reviewed studies, EGFR/HER2 and EGFR/VEGFR2 combinations were the most extensively investigated. Pyrrolopyrimidine, aminoquinoline, benzimidazole-oxadiazole, and quinazoline derivatives demonstrated favorable interaction profiles across multiple kinase targets and, in several cases, were supported by antiproliferative, apoptosis-inducing, or kinase inhibition data. Nevertheless, most dual-target approaches remain at the preclinical stage, and their long-term therapeutic advantage over mutation-selective EGFR inhibitors remains to be established experimentally.

6.3. Natural product-based EGFR inhibitors

Natural products represent an important source of structural diversity for EGFR-targeted drug discovery because their stereochemical complexity may facilitate interaction modes that differ from conventional ATP-competitive inhibitors. Alkaloids, flavonoids, marine metabolites, and plant-derived compounds have therefore been extensively explored using molecular docking and related computational approaches.

However, the quality of evidence supporting natural-product inhibitors remains highly heterogeneous. Most studies relied primarily on docking-derived affinity predictions, with limited incorporation of MD simulation, free-energy calculations, or mechanistic biological validation. As a result, many reported candidates remain exploratory rather than translationally validated leads. Notable exceptions include studies integrating docking with MM-PBSA/MM-GBSA analyses and cellular assays, which provided stronger evidence for biological relevance. Overall, natural products continue to represent a valuable source of novel scaffolds, although their therapeutic potential requires substantially greater experimental validation.

6.4. Targeting drug-resistant EGFR mutants

Resistance-associated EGFR mutants, particularly L858R/T790M and L858R/T790M/C797S, have become major targets of contemporary docking-based drug discovery efforts because they represent critical mechanisms of treatment failure in

NSCLC. Compared with studies focused on wild-type EGFR, investigations targeting resistant mutants increasingly employ integrated computational workflows incorporating pharmacophore modeling, long-timescale MD simulation, and free-energy calculations.

A notable trend is the growing interest in allosteric-site targeting, particularly for overcoming C797S-mediated resistance. By avoiding dependence on covalent ATP-site interactions, allosteric inhibitors may retain activity against mutants that are refractory to third-generation EGFR-TKIs. Nevertheless, most reported candidates remain supported primarily by computational evidence, emphasizing the need for experimental validation to determine whether predicted binding stability translates into clinically meaningful inhibition.

6.5. Drug repurposing and FDA-approved compounds

Drug repurposing offers a pragmatic extension of docking-based discovery because approved compounds possess established pharmacokinetic and safety profiles, thereby reducing developmental uncertainty. Several studies screened FDA-approved drugs and commercial compound libraries against wild-type and resistant EGFR mutants, identifying candidates with favorable predicted binding modes and stable MD trajectories.

Despite these advantages, the translational significance of repurposed candidates should not be overstated. In many cases, favorable docking performance has not been accompanied by direct evidence of EGFR inhibition, target engagement, or antitumor activity. Consequently, repurposing studies should be viewed primarily as hypothesis-generating investigations until supported by mechanistic and biological validation.

6.6. Computational methodologies in EGFR drug discovery

The reviewed literature reveals substantial methodological heterogeneity in docking platforms, receptor preparation procedures, scoring functions, simulation durations, and validation strategies. AutoDock Vina remains the most frequently used docking engine, whereas GROMACS and Desmond dominate MD simulation workflows. Increasingly, studies combine docking with RMSD, RMSF, MM-PBSA/MM-GBSA, and ADMET analyses to improve lead prioritization and reduce false-positive predictions.

Importantly, a consistent pattern emerges across therapeutic categories: studies integrating multiple computational techniques and experimental validation provide substantially greater translational confidence than those relying on docking alone. This observation highlights a broader shift in EGFR-targeted drug discovery from static ligand-ranking approaches toward integrated structure-based workflows that account for receptor flexibility, mutation-dependent conformational dynamics, and biological relevance. Although molecular docking remains indispensable for early-stage screening, its greatest value lies within a multidisciplinary framework that combines structural prediction with dynamic simulation and experimental validation.

Representative docking studies included in this review are summarized in Table 2, with emphasis on EGFR mutation specificity, computational workflow integration, validation level, and translational relevance.

Table 2 Comparative analysis of representative structure-based molecular docking studies targeting wild-type and mutant EGFR in cancer drug discovery, highlighting computational workflows, validation levels, and translational relevance

Therapeutic category	EGFR Target / mutation	Ligand class	Computational workflow	Biological validation	Validation level	Comparator / reference	Key translational insight	Major limitation
Synthetic inhibitors	WT EGFR	Quinazoline derivatives	AutoDock Vina + ADMET	Limited in vitro validation	Level 3	Afatinib	Several derivatives demonstrated lower predicted binding energies than reference scaffolds and favorable pharmacokinetic profiles	Primarily docking-based interpretation
	WT and L858R/T790M	Furopyridines	GOLD + MD simulation	Cytotoxicity in A549 and H1975 cells	Level 4	Erlotinib	Stable MD trajectories supported mutant-selective inhibitory activity	Limited in vivo evidence
	WT, L858R, T790M	Quinazolinone derivatives	Docking + cytotoxicity assays	Apoptosis and kinase inhibition	Level 4	Erlotinib	Structural optimization improved activity against resistant mutants while reducing toxicity toward normal cells	Mechanistic resistance analyses incomplete
	WT EGFR	Pyrrolopyrimidine derivatives	Docking + oral drug-likeness prediction	Cytotoxicity assays	Level 4	Standard EGFR-TKIs	Combined computational and experimental data supported scaffold optimization	Limited mutation-specific analysis
Dual-/multi-target strategies	EGFR/HER2	Panaxadiol	Docking + MD simulation	Limited biological validation	Level 2	Lapatinib	Dual-binding compatibility suggested potential network-level inhibition	Predominantly computational evidence
	EGFR/VEGFR2	Trimethoxy quinazolines	AutoDock Vina + GROMACS	Kinase inhibition assays	Level 4	VEGFR2 inhibitors	Demonstrated feasibility of simultaneous EGFR/VEGFR2 targeting	Limited translational validation

Therapeutic category	EGFR Target / mutation	Ligand class	Computational workflow	Biological validation	Validation level	Comparator / reference	Key translational insight	Major limitation
	EGFR/HER2	Benzimidazole–oxadiazoles	Docking + 3D-QSAR	Apoptosis and cell-cycle assays	Level 4	Erlotinib	Multi-target inhibition supported anti-proliferative activity	Lack of in vivo confirmation
	EGFR/HDAC	Pyrimidine derivatives	Docking studies	Enzymatic inhibition	Level 4	HDAC inhibitors	Supported rationale for epigenetic–kinase co-targeting	Limited resistance-focused evaluation
Natural product-based compounds	WT EGFR	Marine alkaloids	AutoDock Vina	No biological validation	Level 1	Erlotinib	Several compounds demonstrated favorable predicted binding energies	Docking-only evidence
	WT EGFR	Glycyrrhizin analogs	AutoDock 4.2	In vitro and in vivo activity	Level 5	Standard inhibitors	Combined computational and experimental findings supported anticancer activity	Limited mechanistic simulation
	WT and mutant EGFR	Flavonoids	DFT descriptors + docking	Limited validation	Level 2	Osimertinib	Certain flavonoids demonstrated favorable predicted binding relative to osimertinib	Lack of kinase-specific assays
	EGFR/HER2	Phytochemicals	AutoDock Vina + MD simulation	Minimal experimental support	Level 2	HER2 inhibitors	Suggested potential dual-target interactions	Translational relevance uncertain
	EGFR T790M	Morusin	SwissDock	Cell-based validation in resistant H1975 cells	Level 4	Erlotinib	Suppressed EGFR/STAT3 signaling in resistant NSCLC models	Limited pharmacokinetic evaluation

Therapeutic category	EGFR Target / mutation	Ligand class	Computational workflow	Biological validation	Validation level	Comparator / reference	Key translational insight	Major limitation
Resistance-associated mutant targeting	L858R/T790M/C797S	PubChem hits	AutoDock Vina + 100-ns MD	No biological validation	Level 2	Osimertinib	Stable MD trajectories suggested potential activity against triple-mutant EGFR	Computational-only evidence
	T790M/C797S	Tetrahydropyrazolo derivatives	Molegro Virtual Docker	Limited experimental validation	Level 2	WZ4002	Several derivatives demonstrated improved predicted binding against resistant EGFR	Lack of cellular validation
	L858R/T790M/C797S	QSAR-designed purine derivatives	Docking + GROMACS	No experimental validation	Level 2	Reference inhibitors	Suggested mutation-selective binding stability	Preclinical computational stage only
Drug repurposing and screening	WT and resistant EGFR mutants	FDA-approved compounds	Docking + MD simulation	Limited validation	Level 2	Osimertinib	Repurposed compounds demonstrated stable binding trajectories in resistant EGFR models	Functional EGFR inhibition not confirmed
	EGFR kinase domain	Pharmacophore-screened commercial compounds	Glide SP + 200-ns MD + ADMET	No biological validation	Level 3	Gefitinib	Integrated workflow improved prioritization of stable candidate inhibitors	Translation beyond computational evidence remains uncertain

Note: Validation level reflects the strength of supporting evidence reported in each study. Level 1 = docking only; Level 2 = docking plus additional computational validation; Level 3 = integrated computational workflow without biological validation; Level 4 = computational analyses with in vitro validation; Level 5 = computational analyses with both in vitro and in vivo validation.

7. Discussion

This review aimed to critically synthesize current evidence regarding structure-based molecular simulation-assisted approaches for EGFR-targeted anticancer drug discovery, examine the structural biology underlying EGFR oncogenic activation, evaluate computational strategies used in inhibitor discovery, and assess emerging approaches for overcoming resistance-associated mutations. Collectively, the evidence indicates that structural and computational methodologies have become indispensable components of contemporary EGFR drug discovery. However, their value extends beyond ligand screening alone. Rather, the reviewed literature suggests that the greatest contribution of molecular simulation lies in elucidating the dynamic structural mechanisms governing receptor activation, mutation-dependent drug sensitivity, and resistance evolution.

A central finding of this review is that EGFR-directed drug discovery has progressively shifted from a static ATP-binding-site paradigm toward a dynamic conformational framework. Structural, biochemical, and computational evidence consistently indicates that clinically important EGFR mutations do not merely alter ligand-binding affinity but fundamentally reshape kinase conformational equilibria, dimerization behavior, ATP accessibility, and allosteric communication [1], [9]. Activating mutations such as exon 19 deletions and L858R preferentially stabilize active kinase conformations, whereas resistance-associated alterations including T790M, C797S, and exon 20 insertions remodel the energetic landscape governing inhibitor recognition. This conceptual shift has important implications because it suggests that therapeutic response is determined not solely by target occupancy but also by mutation-dependent conformational adaptability. Consequently, successful inhibitor design increasingly requires accurate representation of receptor dynamics rather than reliance on static crystallographic structures alone.

The findings further demonstrate substantial evolution in computational methodologies. Molecular docking remains the most widely used approach because of its computational efficiency and utility in early-stage compound prioritization. However, the evidence reviewed here consistently suggests that docking alone provides limited predictive value for a conformationally flexible target such as EGFR. Across multiple therapeutic categories, studies integrating docking with molecular dynamics (MD) simulation, MM-PBSA/MM-GBSA free-energy calculations, ADMET prediction, and experimental validation generally produced more biologically meaningful and translationally relevant findings than docking-only investigations. This pattern was observed regardless of ligand class, indicating that methodological integration may be a stronger determinant of translational value than the specific chemical scaffold under investigation. The growing adoption of ensemble-based simulations and long-timescale MD approaches further reflects recognition that mutation-induced flexibility and transient conformational states are critical determinants of inhibitor performance.

Notably, the quality of evidence differed substantially across therapeutic categories. Synthetic small-molecule inhibitors generally demonstrated the strongest evidence base because computational predictions were frequently complemented by kinase inhibition assays, cytotoxicity studies, apoptosis analyses, and, in some cases, in vivo validation. In contrast, natural product-derived compounds and drug-repurposing candidates were often supported primarily by docking scores and limited biological confirmation. Although several natural products exhibited favorable predicted binding interactions, these findings should be interpreted cautiously because docking-derived affinity estimates do not

necessarily translate into target engagement, cellular efficacy, or therapeutic benefit. Therefore, the apparent promise of many natural-product and repurposed compounds remains largely exploratory rather than clinically actionable.

The increasing emphasis on dual-target and multi-target inhibitors represents another important trend emerging from this review. Resistance to EGFR-targeted therapy frequently involves activation of compensatory pathways, including HER2, VEGFR2, MET, AKT, and other signaling networks. Consequently, several studies explored compounds designed to simultaneously engage multiple oncogenic targets. While these approaches may theoretically reduce pathway redundancy and delay resistance emergence, current evidence remains predominantly preclinical. Furthermore, simultaneous pathway inhibition may introduce additional pharmacological complexity, including off-target toxicity and adaptive network rewiring. Thus, although multi-target strategies appear mechanistically attractive, their superiority over highly selective mutation-targeted inhibitors remains uncertain.

Resistance-associated EGFR mutations remain the dominant challenge driving innovation in structure-based drug discovery. The reviewed evidence suggests that resistance cannot be fully explained by alterations in ATP-pocket geometry alone. Instead, resistance-associated mutations appear to influence a broader spectrum of structural and energetic properties, including kinase flexibility, conformational stability, and long-range allosteric communication. This interpretation is supported by both molecular simulation studies and structural analyses demonstrating that mutations such as T790M and C797S modify receptor behavior beyond direct inhibitor-contact residues [9]. The emergence of fourth-generation inhibitors and allosteric targeting strategies therefore reflects a broader shift toward exploiting alternative structural vulnerabilities rather than simply increasing ATP-site binding affinity.

An important knowledge gap identified by this review concerns post-translational modifications (PTMs). Although phosphorylation, glycosylation, and ubiquitination are recognized regulators of EGFR signaling, relatively few computational studies have systematically incorporated PTM-dependent structural states into inhibitor discovery workflows. This omission may limit biological relevance because PTMs can influence receptor conformation, signaling persistence, intracellular trafficking, and ligand-binding energetics. Given increasing recognition of tumor heterogeneity and signaling plasticity, future simulation studies incorporating PTM-associated structural variation may provide a more realistic representation of receptor behavior in vivo.

Several limitations within the current evidence base warrant consideration. First, substantial methodological heterogeneity exists across studies, including differences in receptor preparation, docking protocols, scoring functions, simulation duration, solvent models, and free-energy methodologies. Such variability limits reproducibility and complicates direct comparison across investigations. Second, many studies employed relatively short MD simulations that may not adequately capture biologically relevant conformational transitions occurring on longer timescales. Third, the majority of available evidence originates from computational and preclinical experimental studies. Human clinical evidence directly validating computationally identified EGFR inhibitors remains limited. Consequently, causal inferences regarding clinical efficacy cannot be drawn from computational affinity predictions alone.

This review itself also has limitations. Although systematic search principles and PRISMA-informed procedures were incorporated, the study represents a structured narrative synthesis rather than a formal quantitative systematic review or meta-analysis. The

included studies were highly heterogeneous with respect to computational workflows, mutation targets, validation strategies, and outcome measures, limiting quantitative comparison. In addition, publication bias may favor studies reporting positive docking or simulation results, potentially overestimating the apparent success of computational approaches.

Despite these limitations, several important implications emerge. Scientifically, the findings reinforce the concept that EGFR functions as a dynamic allosteric signaling system whose therapeutic vulnerabilities are governed by conformational regulation rather than solely by ATP-site architecture. Clinically, the evidence supports continued development of mutation-selective and allosteric inhibitors capable of addressing resistance-associated structural adaptation. From a drug-discovery perspective, the findings suggest that integrated computational-experimental pipelines are likely to provide more reliable lead prioritization than isolated computational screening approaches.

Future research should focus on improving methodological standardization, particularly regarding docking validation procedures, MD simulation reporting, free-energy calculations, and benchmarking against clinically validated inhibitors. Greater emphasis should also be placed on compound-mutation systems, PTM-dependent structural states, allosteric targeting strategies, and network-level therapeutic approaches that more accurately reflect the biological complexity of resistant tumors. Importantly, future investigations should prioritize integration of molecular simulation with biochemical, pharmacological, and translational validation to improve confidence in computational predictions and facilitate clinical translation.

Overall, the evidence synthesized in this review suggests that structure-based molecular simulation has evolved from a ligand-ranking methodology into a mechanistic framework for understanding EGFR activation, resistance evolution, and therapeutic vulnerability. Although computational approaches alone cannot establish clinical efficacy, their integration with structural biology, medicinal chemistry, and experimental oncology appears increasingly capable of guiding rational development of next-generation EGFR-targeted therapeutics. The future success of EGFR drug discovery will likely depend not on identifying compounds with the strongest predicted binding affinity, but on understanding how dynamic structural states shape therapeutic response across the heterogeneous landscape of EGFR-driven cancers.

8. Conclusion

Structure-based molecular simulation has become a cornerstone of contemporary EGFR-targeted anticancer drug discovery, providing critical insights into receptor conformational dynamics, mutation-dependent drug sensitivity, and resistance mechanisms. The evidence reviewed indicates that computational approaches are most informative when integrated with molecular dynamics simulation, free-energy analyses, and experimental validation, rather than being used as standalone screening tools. Increasingly, EGFR drug discovery is shifting from static ATP-site targeting toward strategies that account for conformational plasticity, resistant mutations, and allosteric regulation. Collectively, the literature suggests that the future of EGFR-targeted therapy will depend on integrated structure-guided approaches capable of addressing the biological complexity of mutation-driven cancers. Although significant challenges remain in translating computational predictions into clinical benefit, advances in molecular simulation, structural biology, and rational inhibitor design are creating new opportunities for the development of next-generation therapeutics against resistant EGFR variants.

9. Recommendation

Future research should prioritize integrated computational-experimental workflows combining molecular docking, longer-timescale molecular dynamics simulation, free-energy analysis, ADMET prediction, and biological validation. Greater emphasis should also be placed on resistance-oriented drug design targeting clinically relevant EGFR mutations such as T790M, C797S, exon 20 insertions, and compound-mutant systems. In addition, allosteric inhibitors, dual-/multi-target strategies, and mutation-selective scaffolds may provide advantages over conventional ATP-competitive inhibitors in overcoming adaptive resistance. Future studies should further explore the influence of post-translational modifications on EGFR conformational dynamics and inhibitor binding. Although natural products and repurposed FDA-approved drugs remain promising sources of novel scaffolds, stronger mechanistic evaluation and experimental confirmation are necessary to determine their translational and therapeutic relevance.

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