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Review: Methods of synthesis of erlotinib and its derivatives as tyrosine kinase inhibitor in 2020-2025

Noor Waleed Ibrahim [a], Rafid M. Hashim [b], Ayad M.R. Raauf [c]

[a] *Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad-Iraq.*
[b] *Department of Pharmaceutical Chemistry, College of Pharmacy, Uruk University, Baghdad, Iraq.*
[c] *Department of Pharmaceutical Chemistry, College of Pharmacy, Al-Farahidi University, Baghdad-Iraq.*

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Keywords:

Erlotinib, EGFR tyrosine kinase inhibitors, Synthesis methods and (SAR).

ABSTRACT

This review focuses on the most important synthetic approaches to produce erlotinib and its derivatives, shows changes in their structure that minimized toxicity, surpassed resistance mechanisms, increased selectivity and improved therapeutic efficacy, the latest applications of green and medicinal chemistry and recent developments are covered. This review seeks to investigate the erlotinib methods of synthesis and recent trends in erlotinib chemistry and new derivatives synthesis, ranging from 2020 to 2025 including modifications on the quinazoline core, side chains, conjugates, and hybrid molecules that incorporate additional pharmacophores and provide some of views and perspectives to the future directions of EGFR targeted drug discovery and development, full texts of potentially relevant articles were reviewed, and data on synthetic routes, structural modifications, biological potency, selectivity, and any ADME/PK findings were extracted and qualitatively synthesized. Erlotinib, a type of targeted cancer drug has been widely studied and modified over the past five years., it has already available in US, EU, Japan and other 100 countries worldwide since approved for medical use in 2004. Erlotinib is a first-generation inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. It is cleared to treat non-small cell lung cancer, pancreatic cancer and a few other cancer. Its brand name is usually Tarceva. The presented review contains the following issue: summary of references concerning the synthesis methods, structure-activity correlation ship (SAR) or biological parameters related to erlotinib family analogues (from 2020 to 2025).

INTRODUCTION

Malignant cancer pose a significant health hazard and are serious cause of morbidity throughout the world (Rahul et al., 2024). Compared with the conventional chemotherapeutic agents, targeted drugs act more selectively with better efficacy and safety by directly acting on the molecular targets that are associated with the proliferation and differentiation of tumor cells rather than nonspecifically affecting normal cells (Huang et al., 2020).

Aberrant expression of PTK by cancer cells An overexpression of the tyrosine kinase activity is seen in many cancers. These enzymes mediate the phosphorylation of a number of protein targets via transfer of the γ-phosphate group from ATP to specific tyrosine residues. Protein tyrosine kinases (PTKs) are crucial regulators of signal transduction (Bhupender et al., 2020). It was later discovered that there are alterations of the kinase protein function in a variety of other cancers so far. Inhibiting these proteins went on to show a dramatic slowing down of the disease process, and in some cases with fewer side effects than traditional chemotherapy (Elena et al., 2023).

E-mail address: noorwaleed@uomustansiriyah.edu.iq [a]
rafid1983@gmail.com [b]
Pharm.dr.ayad@uoalfarahidi.edu.iq [c]
Corresponding* : *Rafid M. Hashim*

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Inhibition of intracellular signalling by drugs has been designed to target key central elements in these cellular pathways. Receptor tyrosine kinase inhibitors (RTKIs) are one of these agents (Charles et al., 2020). Their main mechanism of action is by binding to the active site of kinase, thus blocking intracellular targets phosphorylation that are involved in cell proliferation or angiogenesis(Wang et al., 2025). As the first-generation EGFR TKI, erlotinib has changed treatment paradigm of non-small-cell lung cancer (NSCLC) and pancreatic cancer by enabling patients with EGFR-mutated cancer to achieve much better clinical benefits. The role of erlotinib in clinical was based on the remarkable efficacy against patients with EGFR mutations (Shaban et al., 2024). Reversible or irreversible kinase inhibitors. These irreversible kinase inhibitors, characterized by their ability to covalently modify and block the ATP site, cause an irreversible inhibition. The reversible kinase inhibitors are broken up into four main subtypes, primarily based on the position of the binding crevice and ligand or DFG motif (Thomson et al., 2023). The different modes of TKI binding are listed below. (Thomson et al., 2023; Martin et al., 2020)

• **The type I inhibitors** are ATP-competitive active TK binders, binding to the same pocket. carriers of these inhibitors feature the DFG motif, with its aspartate facing the kinase catalytic pocket.

• **Type II inhibitors** can be designed to inhibit inactive kinases, binding at the ATP site or close to it. FGxGXG motif protrudes away from ATP binding site. The "out" orientation of the DFG motif allows ATP accessibility closer to the ligand-binding cleft in some class II inhibitors.

• **Type III inhibitors** do not bind the ATP site. Type III inhibitors occupy only the allosteric pockets close to ATP binding site.

• **Allosteric Type IV – binding** occurs at a different allosteric site far from the ATP-binding pocket.

• **Type V inhibitors**: multikinase (multi-site) inhibitors (Gvozdeva, 2025).

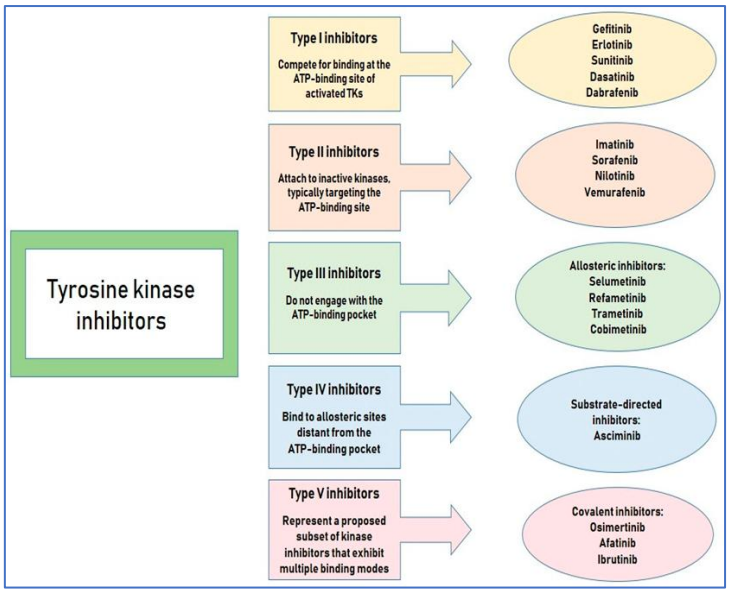

Figure1: *Tyrosine Kinase Inhibitors classification (Gvozdeva, 2025)*

Erlotinib has shown better efficacy over traditional chemotherapy in clinical trial, leading to greatly increased the progress-free survival, objective response rate and quality of life of patients with EGFR-mutated Non-small cell lung cancer (NSCLC) (Runzer-Colmenares et al., 2025).In this light, the synthetic approach allows to medicinal chemists to select EGFR inhibitors into modern synthetic regimens and meticulously tailor molecular interactions on the basis of systematic SAR studies. These studies demonstrate the impact of targeted structural modifications on properties such as binding affinity, kinase selectivity and pharmacokinetic properties indicating patterns that can be used as a roadmap for rational design of more efficacious therapeutic drugs (Al-Karmalawy et al., 2025). Chemical structures can be strategically manipulated to optimize pharmacological properties, including metabolic stability, membrane permeability, and target selectivity; these are key aspects driving clinical success (Azimian & Dastmalchi, 2023). An ideal drug must also be able to be manufactured in bulk using the least number of steps, a major challenge in drug development (An et al., 2025).Modern synthetic strategies rely on different techniques which could include rational drug designing, high- throughput screening (HTS), combinatorial chemistry and fragment-based approaches to maximise the chances for discovering new leads as potential drugs. Pharmaceutical synthesis process can take many forms

depending on what being produced. Integration of computational tools with synthetic chemistry has also played an important role in streamlining the discovery process by facilitating a rationalization of structure-activity relationships (SARs) prediction and leading to design of compounds with the most desirable biological properties (Chetry &Ohto, 2025).

Structure-Activity Relationships (SAR) for erlotinib

Numerous SAR studies have shed light on the key structural demands for optimal EGFR inhibition. The quinazoline scaffold is an essential pharmacophoric feature and the nitrogens at 1- and 3-position act as key hydrogen-bond acceptors to interact with the critical amino acid residues in the EGFR binding site (Șandor et al., 2023).

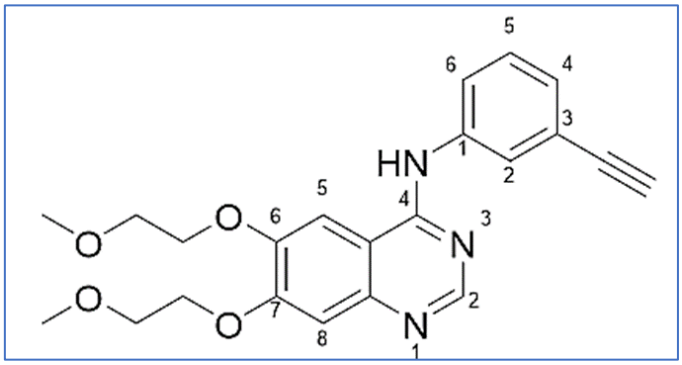

Figure 2: *chemical structure of erlotinib*

Quinazoline Scaffold Requirements

The 4-anilinoquinazoline moiety is a critical structural feature for EGFR tyrosine kinase inhibitory activity. And structure-activity relationship (SAR) studies indicate the fact that quinazoline moiety with C-6 or C-7 side-chains are necessary for maintaining the biological activity because all of the clinically effective EGFR inhibitors are quinazoline-based EGFR TKIs including gefitinib, erlotinib and lapatinib. The quinazoline scaffold is planar and its electron density enabled to form π-π stacking interactions are generated in the hydrophobic ATP-binding pocket (Ban et al., 2010).

Disubstitution Pattern

The bis(2-methoxyethoxy) groups at the 6 and 7 positions are crucial to affinity and specificity. These flexible chains extend into the solvent exposed EGFR binding site and are in contact with important periphery residues that involve hydrogen bonding to Cys773. Structure-activity relationship (SAR) studies have also indicated that the presence of three-carbon linkages is important and could strongly affect activity, as it has been observed that 3-carbon linkers possess higher antiproliferative activities (7.5-fold) in contrast to 2-carbon linkages (Gupta et al., 2012). The methoxyethoxy groups contribute to the lipophilic character and membrane permeability of the compound, yet with adequate solubility in aqueous solutions for oral bioavailability. Displacement of these moieties by other substituents generally leads to reduction in EGFR inhibitory activity, which highlights their contribution to the pharmacophoric model (Klimoszek et al., 2024).

Aniline Substitution at Position 4

In addition, the 3-ethynylphenyl substituent on quinazoline at C4 position is a crucial pharmacophore element. It is greatly preferred to introduce electron-withdrawing group on the aniline ring (especially at meta-position) for improving binding with favoring hydrophobic interaction in the ATP-binding pocket. The terminal ethynyl group is also believed to make an especially distinctive binding profile for the compound, as distinct from other EGFR inhibitors (Zayed, 2023; Mostafa et al., 2024; Azmian & Fatemeh, 2022).

The quantitative SAR results suggested that the aniline part of the structure faces back (to rear) inside ATP binding cleft at 45 degree to quinazoline ring and interacts hydrophobically with its adjacent aa residues. Both the activity and selectivity are sensitive to substitute in this region, in which the ethynyl group plays an important role for good binding conformation. (Felts et al., 2009; Anwar et al., 2024).

Table 1: *SAR features of erlotinib*

Structural element in erlotinib	SAR role and effect
4-anilinoquinazoline core	Acts as the primary EGFR pharmacophore; the planar quinazoline ring fits into the ATP-binding cleft and is essential for EGFR tyrosine kinase inhibition. Removal or replacement of the quinazoline scaffold markedly reduces EGFR affinity and antiproliferative activity.
N-1 and N-3 atoms of quinazoline	Serve as key hydrogen-bond acceptors, forming H-bonds with hinge residues of EGFR (e.g., Met769/Met793, Thr766), anchoring the ligand in the ATP site. Modifying or blocking these nitrogens disrupts hinge binding and sharply decreases inhibitory potency.
4-anilino linkage (–NH–Ar at C-4)	The anilino NH participates in additional H-bonding and positions the phenyl ring deep into the hydrophobic pocket. Removing or rigidifying the anilino linker typically lowers activity and can affect selectivity over other kinases.
3-ethynylphenyl group on aniline (meta-ethynyl substituent)	The meta-ethynyl group extends into a hydrophobic channel, creating unique van der Waals and π-interactions that enhance potency and EGFR selectivity compared with unsubstituted phenyl analogues. Replacement with bulkier or inappropriate substituents (e.g., ortho/para di-halogens) often reduces EGFR inhibition due to steric clash and altered binding orientation.
Electron-withdrawing character on aniline ring	Electron-withdrawing substituents at the meta-position favor stronger hydrophobic and electronic interactions in the ATP-binding pocket and generally correlate with higher inhibitory activity. Strongly electron-donating or sterically demanding groups at inappropriate positions can diminish both activity and selectivity.
6,7-bis(2-methoxyethoxy) substitution on quinazoline	Flexible alkoxy chains at C-6 and C-7 project toward the solvent-exposed region and interact with peripheral residues (e.g., via H-bonding to Cys773), increasing affinity and specificity for EGFR. Removing or shortening these side chains generally decreases potency; three-carbon linkers and ethoxy/methoxyethoxy motifs give better antiproliferative activity than shorter linkers.
Lipophilicity from methoxyethoxy chains	Contributes to membrane permeability and oral bioavailability while maintaining sufficient aqueous solubility, supporting effective pharmacokinetics. Excessive increase in lipophilicity (e.g., more bulky hydrophobic tails) can worsen solubility and ADME; over-polar substitution at 6/7 may reduce permeability and activity.
Overall planarity and π-surface	The extended aromatic system (quinazoline plus aniline) enables π–π stacking with aromatic residues in the ATP pocket, stabilizing binding. Introducing excessive non-planar bulky groups that distort this π-surface typically reduces binding affinity and kinase inhibition.

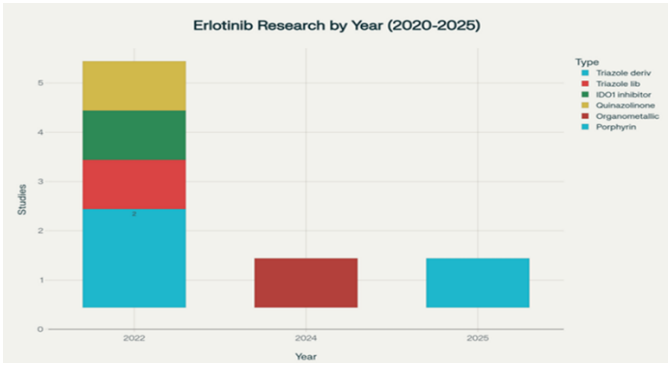

Figure 3: *Timeline of Erlotinib Derivative Research Publications (2020-2025)*

Scope and Goals of This Review

This review seeks to investigate the erlotinib methods of synthesis and recent trends in erlotinib chemistry and new derivatives synthesis, ranging from 2020 to 2025 including modifications on the quinazoline core, side chains, conjugates, and hybrid molecules that incorporate additional pharmacophores. In this-context , here are some of the very important 'specific aims'. Then, a section dedicated to recent creative and alternative synthetic approaches developed in order to synthesize and derivatize erlotinib is presented, including new catalytic systems (metal-based as well as metal free), green chemistry applications and flow methodologies which have offered new perspectives in tradition stablished protocols leading to increase reaction efficiency and sustainability. Finally, the potential of new erlotinib derivatives as drugs will be discussed considering their chemical properties, safety profile and therapeutic advantages over current ones. The review is expected to integrate available information and indicate emerging new trends, presents several viewpoints regarding the future directions of EGFR targeted drug discovery and development. It is our hope that through this broad overview we will illustrate the ongoing evolution of erlotinib chemistry and analog design, as well as serve to exemplify how chemical innovation fuels advancements in precision cancer medicine, while providing much-needed encouragement and optimism for better outcomes for patients in the unrelenting battle against these devastating EGFR-dependent cancers.

Synthetic Strategies of erlotinib

1. Old-fashioned Preparation of erlotinib (Industrial process Description Step by Step)

In 2015, Ta Van Dai et *al*. described a cost-effective and practicable synthesis of erlotinib hydrochloride using easily prepared raw materials from local sources in Vietnam that could be applicable for industrial scale production, and help the pharmaceutical industry in Vietnam. Erlotinib hydrochloride has been synthesized with a simple and efficient method which involves only 6 steps in an overall yield of 51%. The products of each step can be applied in a crude state without silica gel chromatography purification to the next step (Dai et al., 2015).

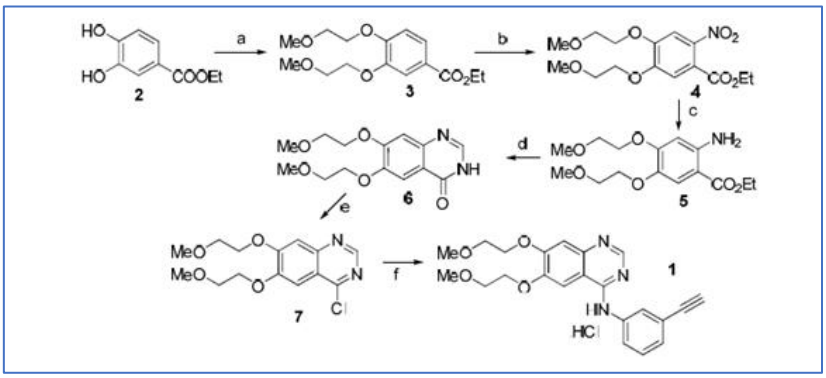

Figure 4: *Synthetic pathway of erlotinib hydrochloride (1): a) $CH_3OCH_2CH_2Br$, K_2CO_3, DMF, 100°C, 2h. b) CH_3COOH, HNO_3, 5°C, ½ hr. c) propanol-2, ammonium formate, Pd/C, 25 ˚C. d)HCO_2NH_4,$HCONH_2$, 160°C, 8hr, e) $POCl_3$, DMAP, 80-90 ^{0}C. f) H_2O, HCl, m-ethynyl aniline, 40 ^{0}C (Dai et al., 2015).*

2. Alternative or Optimized Synthetic Routes:

a) Modified Reduction Methodology

Leila Barghi and co-workers prepared erlotinib hydrochloride in seven steps from 3,4-dihydroxy benzoic acid. A key transformation of the 6-aminobenzoic acid derivative resulted from this study, which allowed to replace a nitro group by an amino group. A cheap reagent such as ammonium formate was in addition employed as a hydrogen-donating group (in situ) with palladium on charcoal (Pd/C), and not just hydrogen gas under high pressure. This approach provided product in 92% yield at rt, leaving a final overall yield of 44% (Barghi et al., 2012).

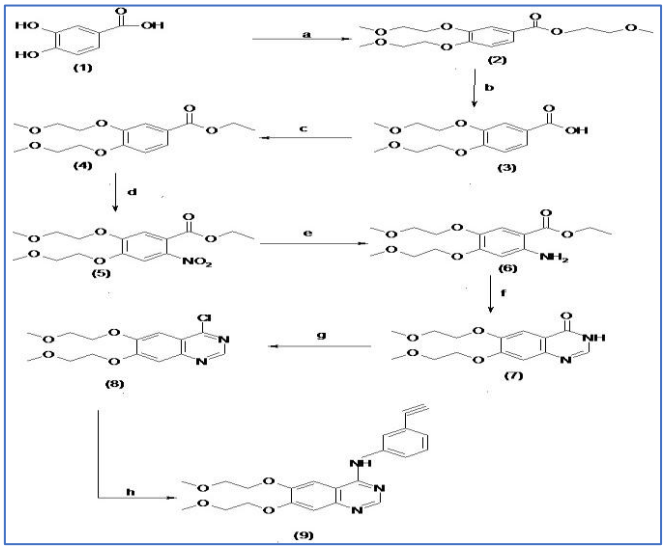

Figure 5: *Modified Synthesis of erlotinib Hydrochloride* ***:*** *a) $ClCH_2CH_2OCH_3$, K_2CO_3, TBAI, DMF, 85 °C, 20hr; b) KOH, CH_3CH_2OH, H_2O, 4hr ; c) CH_3CH_2OH,H_2so_4,90°C; d) HNO_3, glacial acetic acid, 0 °C, 2hr; e)ammonium formate, Pd/C,2-propanol,25°C,20 min; f)ammonium formate, formamide, 160°C, 2hr; g)$CHCl_3$, DMF, oxalylchloride,80°C, 1.5hr; h)H_2O,3-ethynylaniline, HCl, 25°C, 1.5hr. (Barghi et al., 2012)*

a) Flow Chemistry Applications

Hui Jin et *al*. continuous flow preparation of Erlotinib. The new pathway includes 5 steps: etherification, nitration step, reduction reaction, adding reaction as well can cyclization. All steps were optimized and converted to continuous flow process, which drastically reduces the reaction time and considerably improves the process safety as well as the total yield. Continuous flow chemistry, as an emerging technology and a significant trend in the field of pharmaceutical synthesis, has been increasingly employed in both academic laboratories and miniature industrial workshops to produce various compounds and intermediates. Compared to traditional batch production methods, this technology enhances the heat and mass transfer effects during the reaction process, thereby reducing reaction times and yielding purer products with greater consistency in quality. Furthermore, continuous flow technology enables precise control of reaction parameters, minimizes the need for intermediate separation and purification steps, and offers a safer, more efficient and environmentally friendly platform for synthesis and production of chemical drugs. Erlotinib is generated in good space-time yield using 5 continuous flow units (38 E-factor, 83% over-all yield and 25.1 minutes residence time). (Hui et al., 2024).

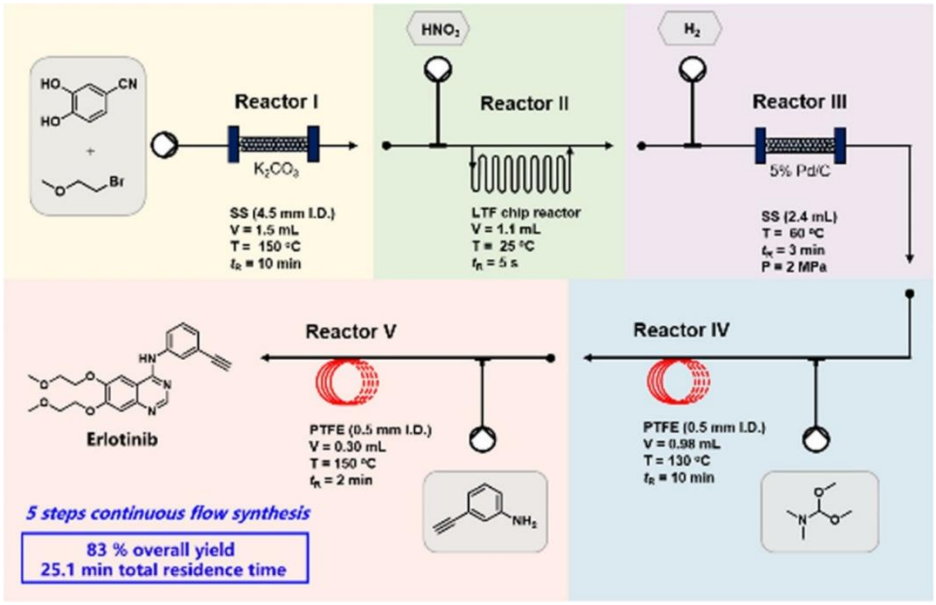

Figure 6: *continuous flow synthesis of Erlotinib (Hui et al., 2024)*

c) Quinazoline-Thione Route

A simple and rapid RP-HPLC method was developed and validated by A. C. Karunakara et *al*. to determine process intermediates and synthetic impurities in erlotinib bulk drug. The proposed method is specific, sensitive and precise for the determination of PRIs in potential trace level as an impurity in erlotinib bulk drug substance. The proposed reverse-phase HPLC method was successfully applied for intermediates and impurities quantification in erlotinib bulk drug, and the recoveries of intermediate were found to be 96.83-100.96% with accuracy below 3 % (Karunakara et al., 2013).

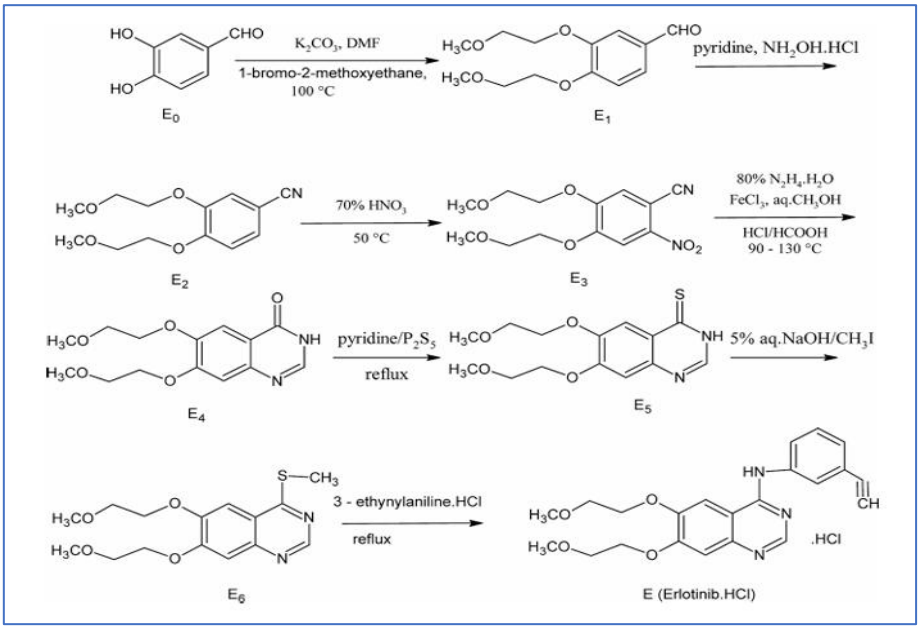

Figure 7: *quinazoline-thione route for synthesis of erlotinib (Karunakara et al., 2013)*

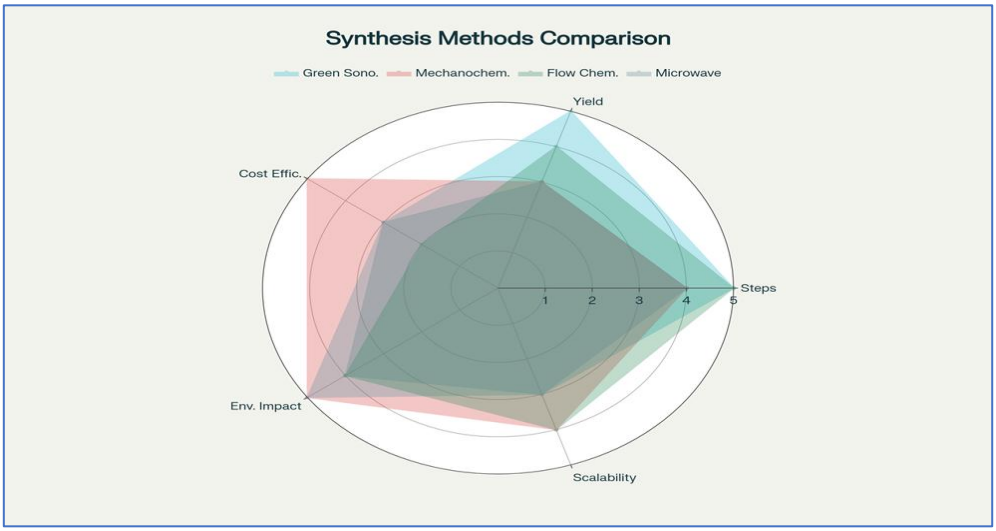

Figure 8: *Radar chart comparison of top erlotinib synthesis methods across key performance parameters*

Synthesis of Erlotinib Derivatives

Synthesis of Erlotinib Derivatives

a) Structural Modifications on the Quinazoline Core
b) Organometallic Conjugates
c) Halogenation and Alkylation Modifications
d) 6,7-Position Modifications

e) Macrocyclic Derivatives
f) Introduction of Polar Groups
g) Semicarbazone Modifications
h) Fused Ring System

Fifteen new erlotinib-1,2,3-triazole derivatives were obtained by Lan W. et *al*. in 2025 using click chemistry as combination reactions (Figure 9). On the basis of anti-proliferative activities against HeLa cells, compound (3h) emerged as the best antitumor active agent with an IC_{50} value of 1.35±0.74 µM (Wang et al., 2025).

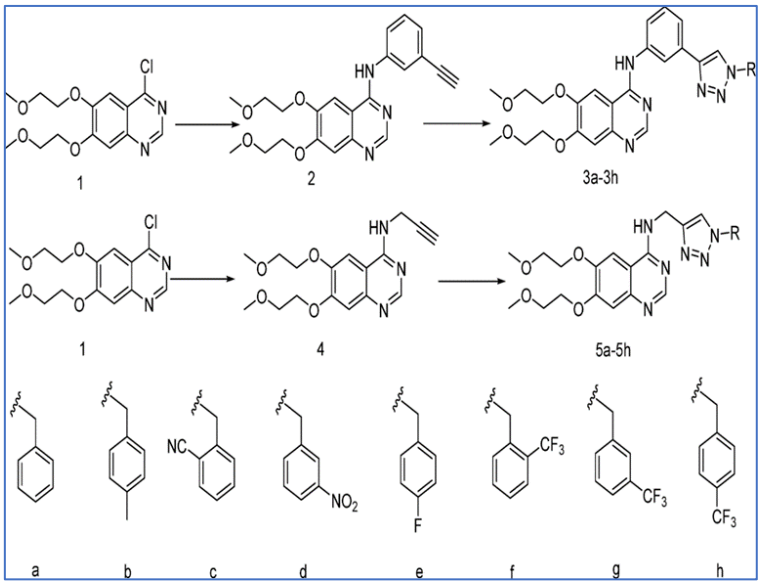

Figure 9: *1,2,3-triazole derivatives of erlotinib (Wang et al., 2025).*

In 2022, Long-fei M et *al*. designed, synthesized, and tested sixteen erlotinib derivatives with structurally diverse 1,2,3 triazole scaffolds for their anticancer activity on different cancer cell lines (Figure 10). Some of these compounds exhibited even greater in vitro antitumor activities than that of erlotinib against one or some cancer cell lines. Compound (3d) was the most potent cytotoxic analog in all ten cancer cell lines compared to other compounds. The roles of (3d)-induced cell death responses include mitochondrial apoptosis and cell cycle arrest. A small amount of analysis has been performed on the binding energies between (3d) and EGFR and found that (3d) can bind both to a wild-type counterpart (H672-E410) as well as mutant (672-1210, L858R) (Mao et al., 2022).

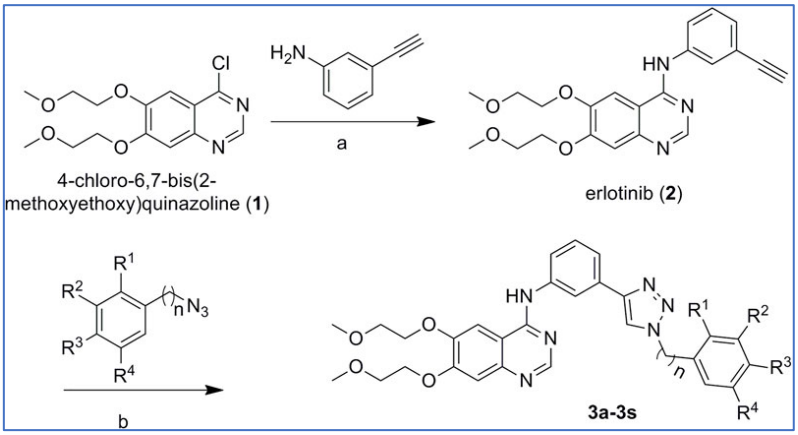

Figure 10: *synthesis of erlotinib–1,2,3-triazole derivatives: (A) isopropanol alcohol, 85°C for 6 hr, and (B) CuI, 80°C (Mao et al., 2022).*

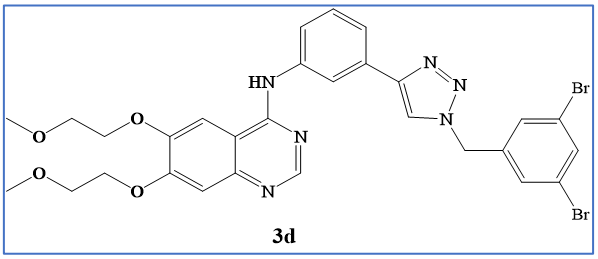

Figure 11: *compound (3d)*

A set of 1,2,3-triazole-containing erlotinib derivatives (Figure 12) was obtained and tested for the antiproliferating effect on HeLa cells by Peng D et *al*. in 2022. Some of the compounds showed better antiproliferative activities than erlotinib itself. Compounds (4d) (IC_{50} = 7.02 μM), (4k) (IC_{50} = 4.16 μM) and (4l) (IC_{50} = 4.51 μM) also induced the apoptosis as well as the cell cycle arrest in HeLa cells. In addition, (4d and 4l) were shown to suppress the survival and growth of HeLa cells (colony formation assay) and they showed potent EGFR inhibition activity. Therefore, these potent antitumor agents (erlotinib-1,2,3-triazole compounds) could act as new antitumor agents against cervical cancer (Deng et al., 2022).

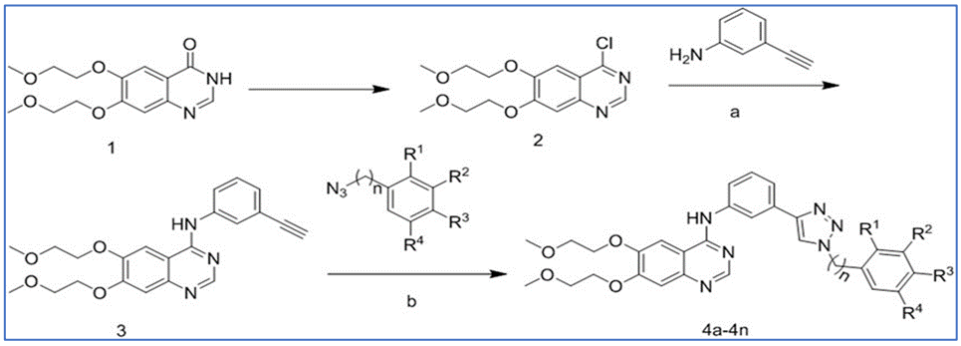

Figure 12: *erlotinib derivatives synthesis: Reagents and conditions. (A) 85°C, isopropanol; (B) 60°C, copper sulfate pentahydrate; sodium ascorbate (Deng et al., 2022).*

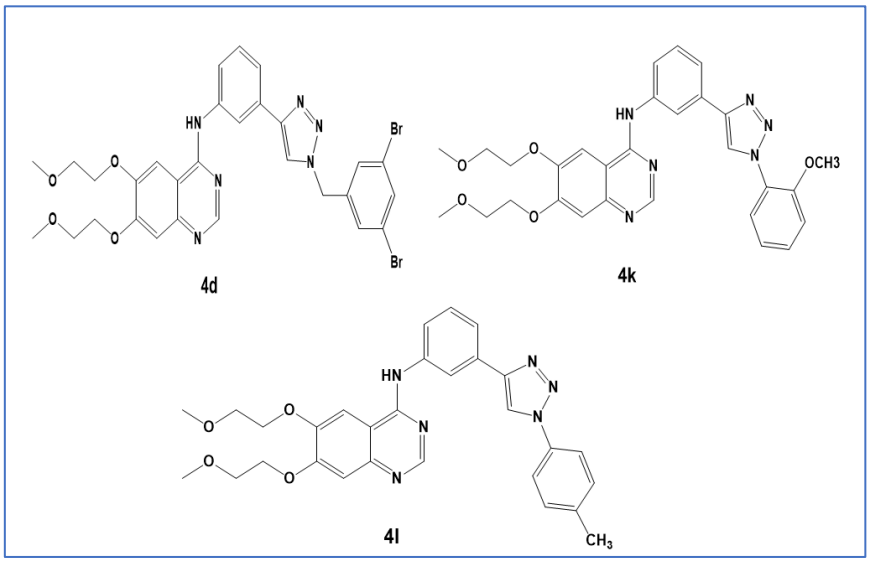

Figure 13: *compound 4d, 4k and 4l*

Cui Q et *al*. (Cui et al., 2022) produced 840 derivatives of Erlotinib using modular click-chemistry (Figure 14), and they screened these compounds using thiazolyl blue (MTT) assay to determine the inhibitory activity on proliferation and metastasis liver adenocarcinoma cells A549. Out of the chemicals tested, P19G1 was most effective as an inhibitor (Figure 15). Furthermore, the in vitro cellular biology and in vivo animal model were used to characterize the anticancer activity and mechanism of P19G1.

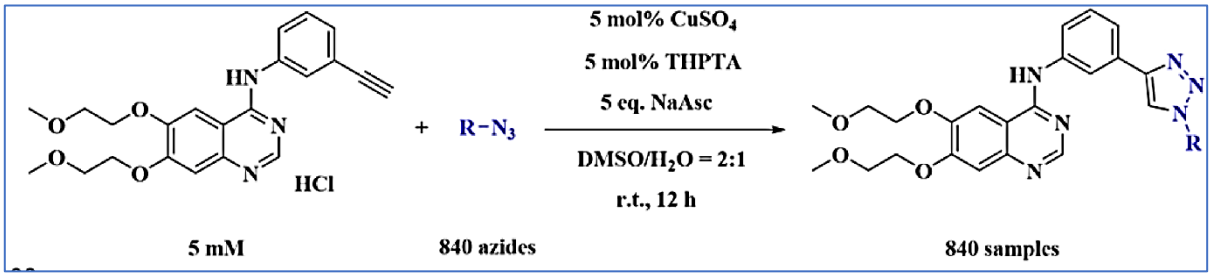

Figure 14: *Synthesis of new 1,2,3-triazole-Erlotinib derivatives by click-chemistry approach(Cui et al., 2022).*

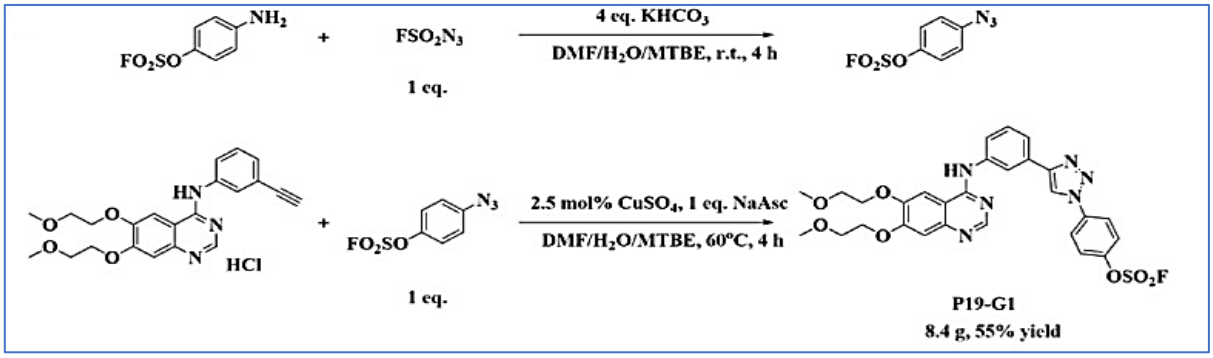

Figure 15*: Synthesis of (P19G1) erlotinib derivative (Cui et al., 2022).*

The report by Gui-Qing Xu et *al*. combined with synthetic effort of novel triazole containing erlotinib derivatives. The design was realized through a structure-informed strategy combined with deep learning predictions of the drug-target interaction affinities. All compounds were prepared and tested for the IDO1 inhibitory activity. The efficacy of some compounds was shown to be better than erlotinib. Compound e with an o-bromobenzyl group on the triazole ring was identified as the most potent IDO1 inhibitor with an IC_{50} value of 0.32 ± 0.07 μM (Xu et al., 2022).

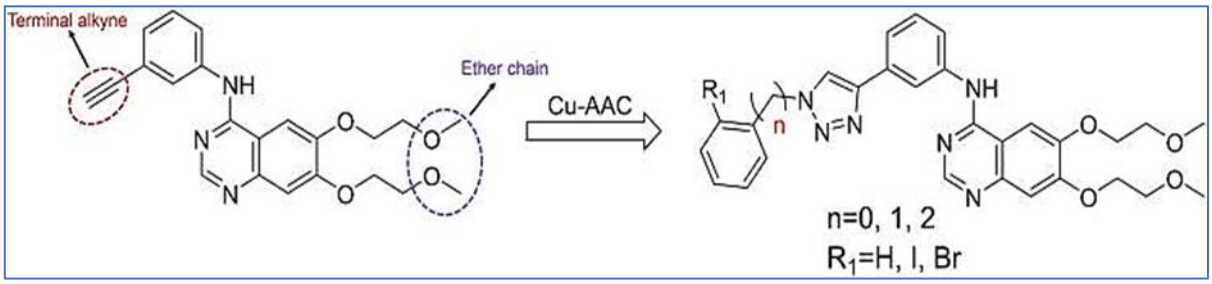

Figure 16: *Design of erlotinib-1,2,3-triazole derivatives (Xu et al., 2022)*

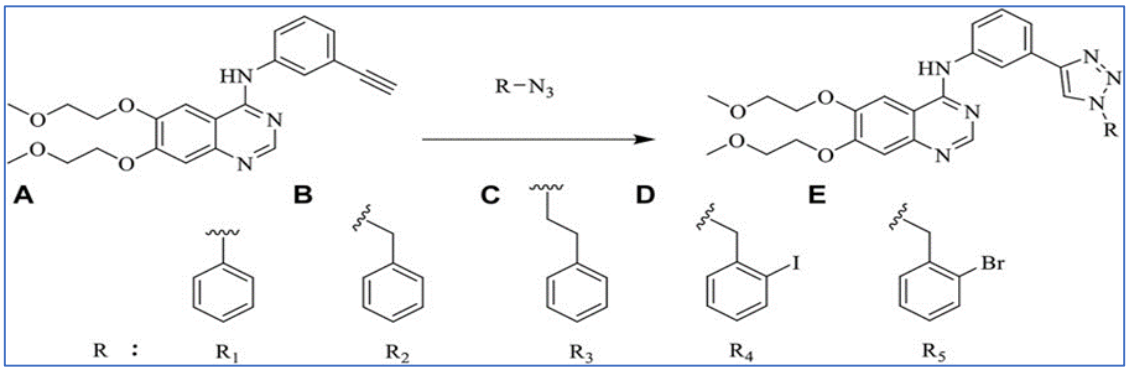

Figure 17: *The reaction routes to erlotinib-1,2,3-triazole derivatives (Xu et al., 2022).*

Hou et al. prepared and evaluated a group of erlotinib-derived 1,2,3-triazole compounds (Figure 18) targeting (IDO1) enzyme. The synthesized compounds were tested for their (IDO1) inhibitory activities in HeLa and SHEE cell lines. Potency test of other

new compounds Compound (14b) revealed a strong activity (IC50 = 0.59 ± 0.05 μM) and low toxicity against IDO1 was exhibited in these novel inhibitors. 14b was shown to be a better inhibitor of IDO1 relative to that of compound 13, which is a reported inhibitor against IDO1 (Hou et al., 2022).

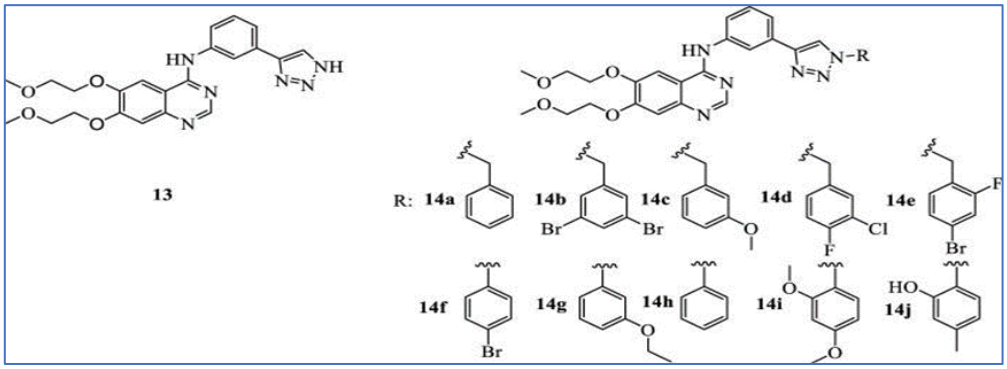

Figure 18: *compound (13, 14a-14j) (Hou et al., 2022)*

A total of 58 derivatives of erlotinib were efficiently generated through a late-stage functionalization (LSF) method by Lian Sun et *al*., inserting aryl, heteroaryl, vinyl groups into the alkynyl motif in anti-cancer drug erlotinib. Five compounds (3d, 3l, 5i, 5p and 7c) were found to possess high cytotoxic activity for A549 cancer cell lines. 3l was the most active with IC_{50} = 11.4 μM comparing to erlotinib IC_{50} of 35.5 μM (Sun et al., 2023).

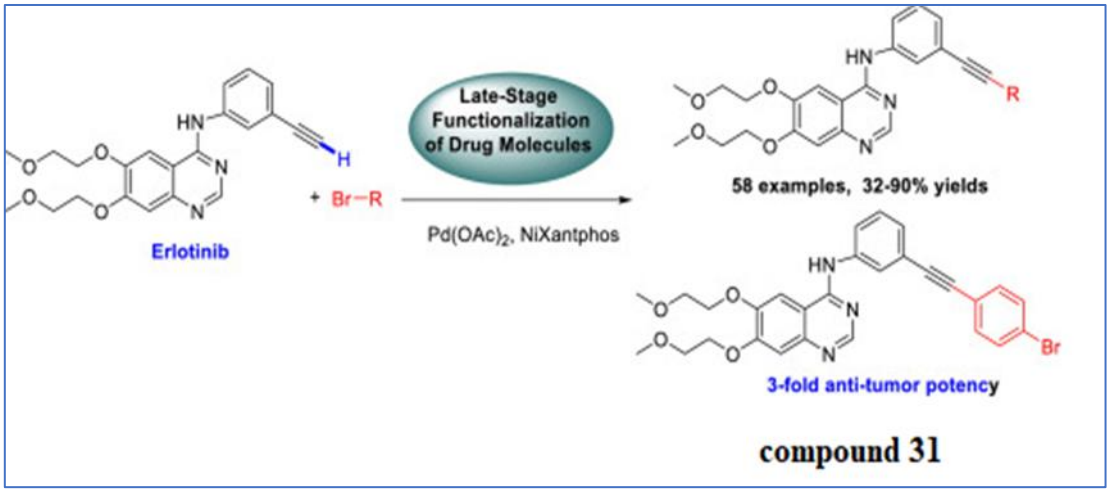

Figure 19: *late-stage Sonogashira reaction for Synthesis of erlotinib derivatives (Sun et al., 2023)*

Wenqiang Wu and his colleagues have prepared the successful synthesis of a BODIPY-Erlotinib dyad, 1 named conjugate 6, by imaginatively incorporating the small molecule-targeted agent erlotinib within a BODIPY dye with a triethylene glycol spacer. This interesting MNW (Multifunctional Nano Worms) is rationally designed for promoting targeted PTT (photothermal therapy) of cancer. Optical in vitro studies demonstrated that the addition of erlotinib preserves the photophysical and photochemical properties of the conjugate (i.e., its electronic absorption, fluorescence emission, singlet oxygen generation) with little or no perturbation. Competitive uptake studies showed that erlotinib-conjugated 6 can selectively accumulate in HepG2 cancer cells that overexpress EGFR and exhibit no cellular sequestration in HELF normal cells. on the other hand, compound 7 that without erlotinib component failed to show this specificity (Figure 20) (Wu et al., 2024).

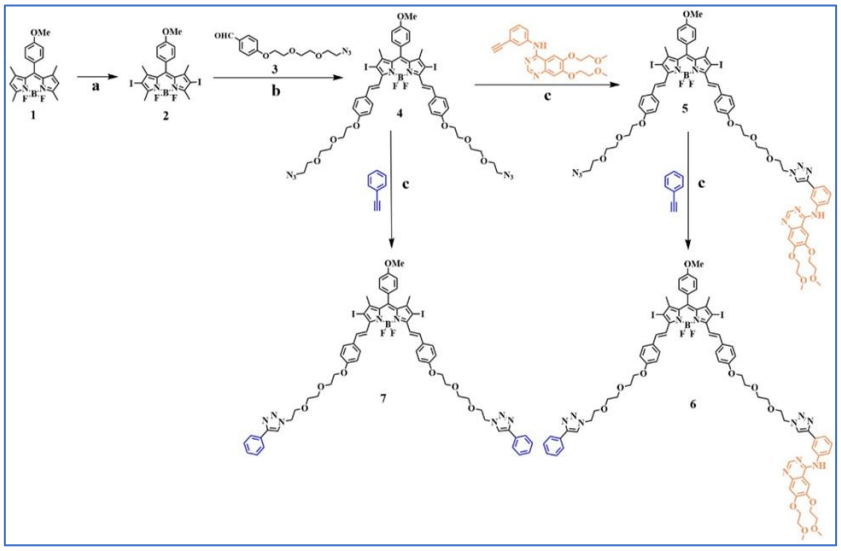

Figure 20: *BODIPY-Erlotinib conjugate (6) and compound (7) Synthesis. Reagents and conditions: (a) I2, HIO3, ethanol, 60 °C; (b) Acetic acid, piperidine, toluene, reflux, 2 hr; (c) Phenylacetylene, CuSO4·5H2O, sodium ascorbate (Wu et al., 2024).*

Current Challenges in Erlotinib Synthesis and Derivative Development

Resistance Evolution and Therapeutic Limitations

The principal limitation of erlotinib and the other first-generation EGFR TKIs is the development of resistance-mediating mutations, primarily T790M gatekeeper mutation which affects 50-60% patients (Zhou et al., 2024). With the emergence of C797S resistance to third generation inhibitors, a remedy to this `arms race' needs better molecular design (Wang et al., 2025; Romaniello et al., 2025; Cooper et al., 2022).

Newer 4th generation inhibitors, though attractive in preclinical activity, may lack adequate therapeutic window to be able to show selectivity for multiple resistance mutations. The challenges encountered with the triple mutant EGFR variants (L858R/T790M/C797S) with a combination of L858R and C797S substitution also need inhibitors to accommodate structural changes and maintain high affinity binding in relation to wild-type kinases (Li et al., 2024; Su & Sun, 2024).

Bioavailability and Central Nervous System Penetration

The limitations of erlotinib's native bioavailability (oral absorption varies from 4.7 to 60% depending on food status have led to challenges in achieving predictable therapeutic effects. In treating brain CNS metastases the difficulty of penetrating the blood-brain barrier to achieve sufficient exposure is particularly problematic (Pahwa et al., 2024).

Although new formulation strategies, such as cyclodextrin complexation and macrocyclic structural modification have shown significant success and progress, the translation of such breakthroughs into clinical use are associated with long safety assessments and strict regulation procedures. Balance is yet to be struck between better penetration and minimal toxicity profiles (Păduraru et al., 2025).

Manufacturing Sustainability and Regulatory Compliance

The shift of the pharmaceutical industry from batch to sustainable manufacturing is significantly hampered by technical and economical hurdles. Conventional synthetic pathways produce 15-20 kg of waste for each kg of product, posing both environmental and cost problems. New capital investment will be required for new equipment, catalyst systems and process analytical technologies to fully deploy green chemistry principles (Islam et al., 2025).

The acceptance of new synthetic approaches by regulatory bodies further complicates matters, due to the fact that many traditional routes take advantage of a long back history and record of approval. Green methodologies must not only show environmental benefits, they should also offer comparable or improved quality of product, safety profile and batch-to-batch reproducibility (Stefanache et al., 2025).

Results

The history of the production of erlotinib from traditional industrial process routes to novel green chemistry methods illustrates the paradigm shift occurring in pharmaceutical manufacture as a whole. The way in which environmental responsibility is being incorporated into therapeutic progress has evolved from a key consideration to one that transcends industry regulations and shifts our collective focus on drug development.

These difficulties of erlotinib and its EGFR TKI siblings-resistance development, bioavailability issues, supply-demand sustainability are not unconnected obstacles but should be dealt with concomitantly for a systemic remedy in a rational design.

The most exciting strategies pair therapeutic innovation with environmental stewardship, and in doing so yield synergistic gains for patient well-being and planetary health.

In the future, the more innovative you are as a pharmaceutical company, the greater emphasis that will need to be placed on getting life-saving medicines to patients by environmentally friendly means. The erlotinib case study shows that this can be done – and should be done if lasting value for patients, society, and the environment is to be generated. As we transition into the era of personalized medicine and precision therapeutics, the knowledge gained from their synthesis of erlotinib will inform new drugs to be developed that are more potent, affordable, and green. This confluence of state-of-the-art medicinal chemistry, advanced manufacturing solutions and environmental stewardship defines contemporary pharmaceutical development for the 21st century. By developing synthetic methodology, design of medicines and manufacturing more sustainable the pharmaceutical industry can serve its mission of enhancing human health in ways that are truly sustainable for a planet which is vital to sustaining all life. P19G1 derivative is the strongest overall candidate because it has both *in vitro* and *in vivo* data showing superior antitumor efficacy at tolerated doses, implying a better integrated PK/PD profile.

The BODIPY–erlotinib conjugate 6 markedly improves tumor targeting and cellular selectivity, representing the clearest enhancement in distribution and effective exposure at the tumor site.

Triazole incorporation in multiple series (Lan Wang, Mao, Deng, Xu, Hou) is repeatedly associated with improved drug-like properties (stability, polarity balance) alongside higher potency, indicating class-wide PK/PD advantages over parent erlotinib

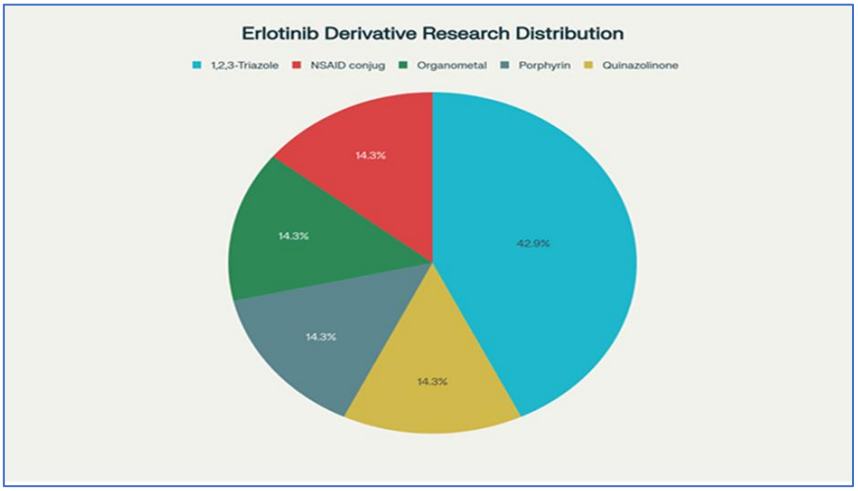

Figure 21: *Distribution of Erlotinib Derivative Research Types (2020-2025)*

Table 2: *Comparison of erlotinib synthetic methods*

Aspect	Old industrial route	Modified batch route	Continuous flow route	Quinazoline-thione "analytical" route
Starting material	Readily available intermediates, locally sourced in Vietnam.	3,4-dihydroxybenzoic acid.	Same basic starting framework as classical route, adapted to flow.	Quinazoline-thione intermediates specifically designed for impurity profiling.
Number of steps	6 synthetic steps overall.	7 steps overall.	5continuous-flow steps (etherification, nitration, reduction, addition, cyclization).	Multi-step, but optimized around analytical detectability of intermediates and impurities.
Overall yield	51% overall; crude intermediates can be telescoped without chromatography.	44% overall; key nitro→amino reduction step gives 92% yield at room temperature using ammonium formate/Pd-C.	83% overall yield with only 25.1 min total residence time.	Not optimized for overall yield of erlotinib; focused on trace-level detection of process-related impurities.

Work-up / purification	No silica-gel chromatography; intermediates carried forward in crude form, making it practical for large-scale manufacture.	Classical batch work-up; chromatography not emphasized as avoided, but route is more lab-scale oriented.	Fully continuous; inherently amenable to in-line work-up and process control.	Requires RP-HPLC; intended for analytical quality control, not production.
Reducing agent / safety	Uses conventional conditions including hydrogenation step with Pd/C and i-propanol under standard conditions.	Replaces high-pressure hydrogen with ammonium formate in situ as hydrogen donor plus Pd/C, improving safety and practicality (no high-pressure H_2).	Flow design intrinsically improves safety of exothermic steps (nitration, reduction) by small volume and precise control.	Not primarily a synthetic safety optimization; main goal is detection of intermediates and impurities.
Green / sustainability profile	Reduces solvent- and chromatography-related waste vs many lab routes but remains a conventional batch process.	Some improvement (safer reduction reagent), but still traditional batch chemistry with multiple heating/reflux steps.	Best green metrics: 38 E-factor reported, high space-time yield, efficient use of reagents and energy via continuous flow.	Focuses on analytical specificity and trace impurity quantification, not green metrics.
Scale-up potential	Demonstrated as cost-effective, practicable, and applicable to industrial-scale production in Vietnam.	Potentially scalable, but originally reported as a modified lab synthesis rather than an established industrial process.	Explicitly designed as a multistep continuous-flow industrial strategy with high throughput and robustness.	Not intended as a manufacturing route; supports QC of other synthetic processes.
Main advantage	Simple 6-step, chromatography-free batch route with decent yield and local raw materials.	Safer, efficient nitro reduction (92% yield) using cheap, mild hydrogen donor; conceptually attractive where H_2 handling is limited.	Highest overall yield (83%), shortest effective residence time (≈25 min), best mass efficiency and safety, directly aligned with green and modern manufacturing paradigms.	Highly specific, sensitive RP-HPLC method for monitoring intermediates and impurities in any erlotinib process.
Main limitation	Classical batch process with higher waste and lower process intensification vs flow; less aligned with current sustainability goals.	Lower overall yield than old route; more steps; not explicitly demonstrated as industrial-scale or optimized for waste minimization.	Requires specialized flow equipment, process engineering expertise, and upfront capital investment for industrial implementation.	Not competitive as a synthetic route in terms of yield, cost or step economy.

Best overall synthetic option

From a contemporary medicinal and process chemistry perspective, the multistep continuous-flow synthesis of erlotinib (Hui Jin et *al*.) is the best route overall. It combines superior overall yield (≈83%), short residence time, lower E-factor, and improved safety and process control, making it most consistent with the review's emphasis on green chemistry, efficiency, and sustainable industrial manufacture. For settings where flow infrastructure is not available, the Dai et *al*. industrial 6-step batch route remains the most practical alternative, with the Barghi modified reduction protocol offering a useful safer variation for the nitro-to-amino step.

Table 3: *Erlotinib derivative classes with improved properties*

Derivative / series	Main structural change vs erlotinib	Improved pharmacodynamic properties	Improved pharmacokinetic / delivery aspects	Evidence type in review
Lan Wang et *al*. 1,2,3-triazole hybrids (compound 3h, 2025)	Erlotinib–1,2,3-triazole hybrids attached to the alkyne side chain.	3h showed strongest antiproliferative activity on HeLa cells (IC50 ≈ 1.35 μM), markedly more potent than erlotinib; acts via MAPK-pathway modulation and induces apoptosis.	Triazole ring expected to enhance metabolic stability and H-bonding capacity; review notes better overall "drug-like" profile, though detailed in vivo PK not reported.	In vitro cytotoxicity, mechanistic signaling data.
Mao et *al*. 1,2,3-triazole-erlotinib (compound 3d, 2022)	Diverse triazole scaffolds on erlotinib; 3d is a lead.	3d more potent than erlotinib across 10 cancer cell lines; triggers mitochondrial apoptosis and cell-cycle arrest; binds both wild-type and mutant EGFR (H672-E410, L858R).	Docking/MD suggest improved binding to mutant EGFR and potentially better selectivity, which may translate into improved therapeutic index.	In vitro cytotoxicity; docking and binding-mode analysis.
Deng et *al*. triazole conjugates (4d, 4k, 4l, 2022)	Erlotinib linked to 1,2,3-triazole with varied substituents.	4d, 4k, 4l more potent than erlotinib on HeLa (IC50 7.02, 4.16, 4.51 μM), with confirmed EGFR inhibition and apoptosis plus cell-cycle arrest.	Triazole moiety improves polarity/lipophilicity balance; review indicates better EGFR inhibition with maintained or improved cell selectivity vs normal cells, hinting at a better safety window.	In vitro potency, functional assays.
Cui et *al*. P19G1 (click-library hit, 2022)	Large library (840) of triazole-erlotinib derivatives; P19G1 identified as best lead.	P19G1 showed strongest inhibition of proliferation and metastasis in A549 cells, with robust in vitro and in vivo antitumor activity, outperforming erlotinib.	In vivo studies in the cited work showed improved antitumor efficacy at tolerated doses, implying a superior exposure–toxicity balance (PK/PD integration better than erlotinib).	MTT, in-depth in vitro biology, and in vivo animal models.
Xu et *al*. IDO1-targeting triazole derivatives (compound e, 2022)	Erlotinib–triazole hybrids optimized as dual EGFR/IDO1 modulators; compound e has o-bromobenzyl on triazole.	Compound e is a potent IDO1 inhibitor (IC50 ≈ 0.32 μM), stronger than erlotinib; design introduces dual-target activity (EGFR and IDO1), potentially improving antitumor immune modulation.	ADME prediction and docking indicate acceptable oral drug-likeness and improved multi-target engagement, which may allow lower required exposure for clinical effect.	Enzyme assays, docking, in silico ADME.
Hou et *al*. IDO1 inhibitors (compound 14b, 2022)	Erlotinib-based triazoles optimized for IDO1; 14b is lead.	14b shows strong IDO1 inhibition (IC50 ≈ 0.59 μM) with low toxicity and better potency than a known reference inhibitor.	Selective IDO1 inhibition with low cytotoxicity suggests an improved safety and PD profile relative to non-optimized erlotinib in this setting.	Cell-based IDO1 inhibition assays.

Sun et *al*. late-stage Sonogashira LSF series (3l and others, 2023)	Pd-catalyzed late-stage aryl/heteroaryl/vinyl substitution on the alkyne of erlotinib.	Several analogues (3d, 3l, 5i, 5p, 7c) highly cytotoxic vs A549; 3l IC50 11.4 µM vs 35.5 µM for erlotinib (≈3-fold potency gain).	Modification of the alkyne tail tunes lipophilicity and may enhance metabolic stability and membrane permeability, thus potentially improving PK; the review notes these as promising leads for further ADME optimization.	In vitro cytotoxicity; medicinal-chemistry rationale for ADME improvement.
Wu et *al*. BODIPY–erlotinib conjugate 6 (2024)	Erlotinib covalently linked to BODIPY dye via triethylene glycol spacer (multifunctional nanoworm system).	Maintains EGFR-targeting capability and enables photodynamic/photothermal therapy; selectively accumulates in EGFR-overexpressing HepG2 cells with minimal uptake in normal HELF cells.	Conjugate 6 shows preserved photophysical properties plus targeted cellular uptake, effectively improving distribution (tumor selectivity) and potentially reducing systemic exposure versus erlotinib alone.	In vitro photophysics, uptake, and selectivity experiments.

Methodology

This narrative review was conducted by searching electronic databases including PubMed, Scopus, Web of Science, and Google Scholar for articles published between January 2020 and November 2025 using combinations of the terms “erlotinib”, “EGFR tyrosine kinase inhibitor”, “synthesis”, “derivative”, “triazole”, “click chemistry”, “flow chemistry”, and “green chemistry”. Titles and abstracts were screened to identify studies reporting synthetic methods for erlotinib or its derivatives together with at least basic biological, SAR, or pharmacokinetic data; non-EGFR TKIs, purely clinical or epidemiological reports without chemical synthesis information, conference abstracts without full experimental details, non-English articles, and duplicate publications were excluded. Full texts of potentially relevant articles were then reviewed, and data on synthetic routes, structural modifications, biological potency, selectivity, and any ADME/PK findings were extracted and qualitatively synthesized without formal meta-analysis.

Conclusion

In the last five years, tremendous achievements in derivatives of erlotinib have been achieved, 1,2,3-triazole-modification-based cancers are thus still one of most widely used approaches. Click chemistry has opened the door for synthetic accessibility, allowing the generation of vast libraries and discovery of very potent compounds. The successful creation of multi-functional conjugates that target not only EGFR but also other mechanisms of therapeutic intervention was a major step toward overcoming resistance and achieving therapeutic benefits. Notable advances included potent second-generation compounds against drug-resistant cell lines, dual-targeted agents, and improved selectivity. The combination of high throughput synthetic techniques guided with systematic SAR studies has expedited the development of potential lead molecules for further optimization. Subsequent studies should concentrate on developing the most promising derivatives towards preclinical development, improving its pharmacokinetic properties, as well exploring new combination schemas. The promising ground work laid in the last few years has paved way for the next level erlotinib-based therapeutics.

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Conflicts of interest

The authors report no conflicts of interest.

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