

A short review on synthetic strategies towards quinazoline based anticancer drugs

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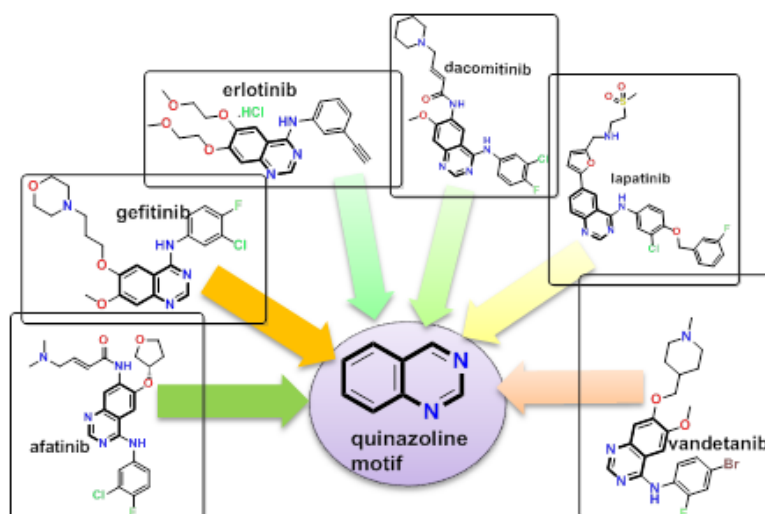
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Abstract

Quinazolines belong to one of the most important classes of heterocyclic compounds owing to their diverse medicinal properties. The synthesis of novel quinazoline derivatives has been a main focus of many researchers during last decades due to the broad scope of this moiety. There are many commercial drugs available with a quinazoline motif and several compounds are in the preliminary development of potential bioactive compounds. This motif is being utilized in drug targets for the treatment of various diseases owing to the anti-cancer, anti-bacterial, anti-inflammatory, anti-malarial and anti-hypertensive activities. This review describes some of synthetic strategies used for manufacturing aminoquinazoline based anticancer drugs on both bench and industrial scales.



Keywords: Quinazoline, epidermal growth factor receptor (EGFR), anti-cancer drugs, Dimroth Rearrangement

Table of Contents

1. Introduction
2. Quinazoline Derivatives as Drug Target
3. Quinazoline Moiety as Anti-cancer Drug Target
4. Synthetic Strategies Towards Quinazoline Based Anticancer Drugs
 - 4.1. Afatinib (Gilotrif®, Giotrif®, Afanix® - Boehringer Ingelheim Pharmaceuticals, Inc.)
 - 4.1.1. Synthesis of Afatinib (A)
 - 4.2. Gefitinib (Iressa® - AstraZeneca Pharmaceuticals)
 - 4.2.1. Synthesis of gefitinib (G)
 - 4.3. Erlotinib (Tarceva® - Roche Pharmaceuticals)
 - 4.3.1. Synthesis of Erlotinib (E)
 - 4.4. Dacomitinib (Vizimpro® - Pfizer Inc.)
 - 4.4.1. Synthesis of dacomitinib (D)
 - 4.5. Lapatinib (Tykerb® and Tyverb® - GlaxoSmithKline (GSK))
 - 4.5.1. Synthesis of Lapatinib (L)
 - 4.6. Vandetanib (Caprelsa® - AstraZeneca)
 - 4.6.1. Synthesis of vandetanib (V)
 - 4.7. Future Perspective of Quinazoline Based Heterocyclic Compounds
5. Conclusions
- Acknowledgements
- References

1. Introduction

Examining practices of medicinal chemistry is enriching as well as challenging. A definitive objective is the advancement of drugs in various therapeutic areas and understanding their mechanism of action. Despite the discovery of many selective and potent drugs that prevent diseases, alleviate pain, and manage the treatment of diseases afflicting humans, challenges to invent safer and efficacious drug molecules still remains.¹ With the development of new tools to expedite drug discovery, the role of organic chemists to synthesize novel drug molecules of biological importance is pivotal to treat various diseases. Organic compounds specifically heterocyclic compounds are of paramount importance as more than half of all known organic compounds are heterocyclic. Synthesis of novel heterocycles in the laboratory has revolutionized the course of medical science. There are many classes of heterocyclic compounds which are being used as drugs for relief from various diseases. It has been observed that compounds containing heterocycles such as pyridine, pyrimidine, indole, thiazolidine-2,4-dione (TZD) and quinazoline etc. are central to the core of many therapeutic drugs.

2. Quinazoline Derivatives as Drug Target

The synthesis of quinazoline itself was first reported by Gabriel in 1903. The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The properties of substituted quinazolines largely depend on the nature of the substituents and whether they are on the pyrimidine ring or on the benzene ring.² Quinazoline derivatives are the central core of many complex natural products, which have been isolated from different plants and microorganisms.^{3,4} The quinazoline motif is pivotal in medicinal chemistry

due to its diverse biological properties such as the anti-cancer, anti-bacterial, anti-inflammatory, anti-malarial, anti-convulsant and anti-hypertensive activities.⁵⁻⁶ Biological activities of quinazoline derivatives are very well established and there are numerous drugs available in the marketplace (Figure 1). This review summarizes the synthetic strategies which have been utilized for aminoquinazoline based commercial anti-cancer drugs on both bench and industrial scales. Though it has been our effort to compile all relevant work, there may be additional references that we have inadvertently missed.

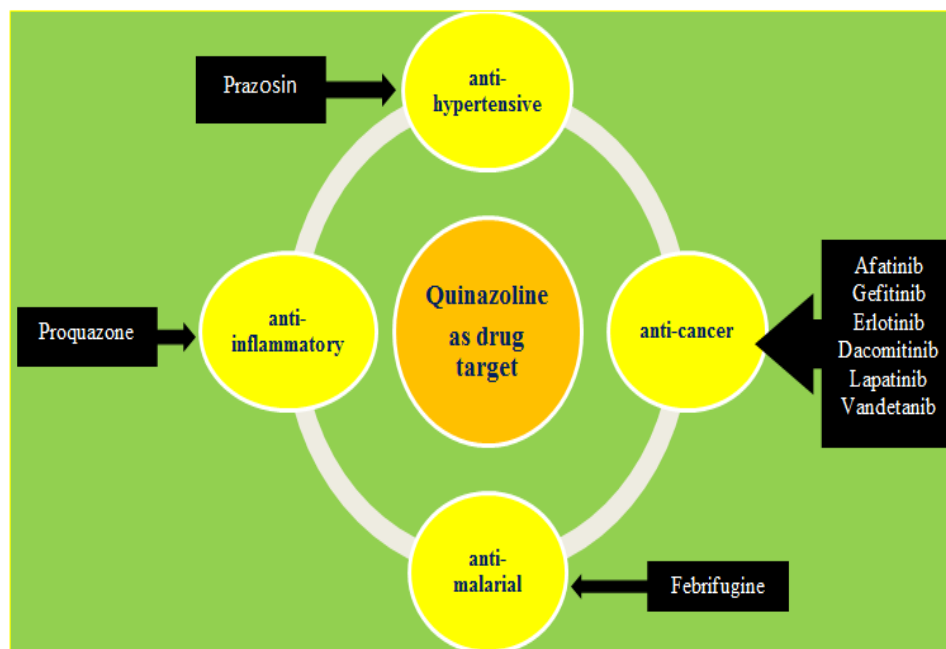


Figure 1. Summary of quinazoline based drugs.

3. Quinazoline Moiety as Anti-cancer Drug Target

There has been a considerable development of promising quinazoline derivatives for cancer treatment during the last few decades. These are well known to inhibit epidermal growth factor receptor (EGFR) protein, albeit that a large panel of other therapeutic protein targets is also there.⁷ EGFR is a member of the tyrosine kinase receptor family. It is a cell membrane receptor which has an extracellular ligand binding domain and an intracellular tyrosine kinase domain. These trans-membrane receptors bind to ligands which lead to the homo- or hetero dimerization of the receptor, which results in trans-phosphorylation of tyrosine residues. These downstream signaling pathways regulate cell division, motility, adhesion and apoptosis. It has been observed that high levels of EGFR expression are present in many tumor cells.^{8,9}

A number of quinazoline derivatives have been approved by the FDA and novel quinazoline derivatives are being investigated as anti-cancer drugs from last two decades. Some of the clinically approved quinazoline derivatives have been depicted in Figure 2. Synthesis of these drug targets from medicinal chemistry scale to efficient, commercially viable and multi-gram scale preparations has been a challenging and thoughtful journey for synthetic chemists. We will describe the synthetic strategies involved for these aminoquinazolines in the following sections of this article.

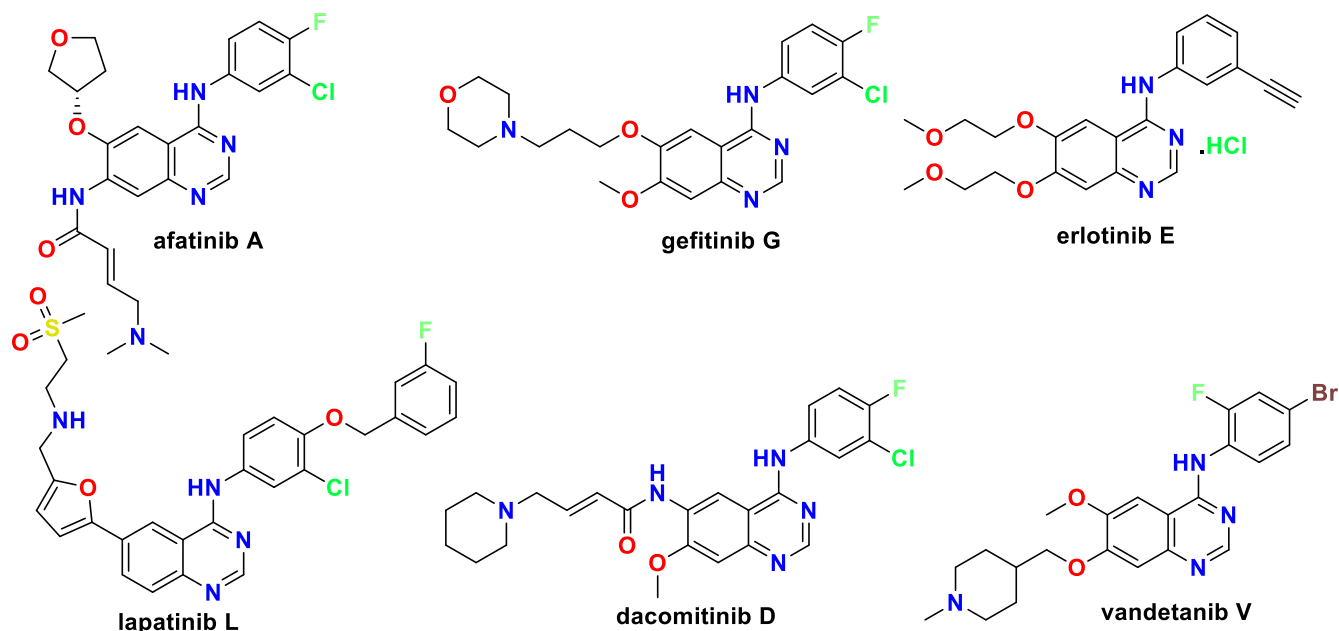


Figure 2. Quinazoline derivatives approved by the FDA as anti-tumor agent.

4. Synthetic Strategies Towards Quinazoline Based Anticancer Drugs

Synthetic strategies utilized for synthesis of quinazoline based anticancer drugs is discussed in subsequent sections:

4.1. Afatinib (Gilotrif®, Giotrif®, Afanix®- Boehringer Ingelheim Pharmaceuticals, Inc.)

Afatinib (**A**) (Figure 3) is a medication which has been used for metastatic non-small cell lung carcinoma (NSCLC).¹⁰ It is an irreversible inhibitor of epidermal growth factor receptor (EGFR) and human epidermal receptor (HER2) tyrosine kinases.¹¹ It is the first lung cancer treatment drug. The drug passed the fast-track approval channel of the US FDA in 2008. It was approved as drug in 2013.¹²

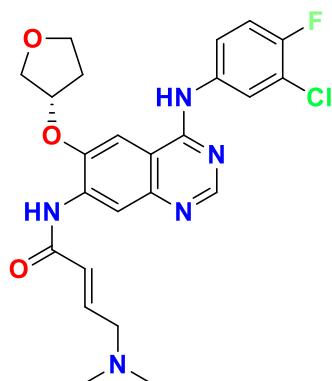
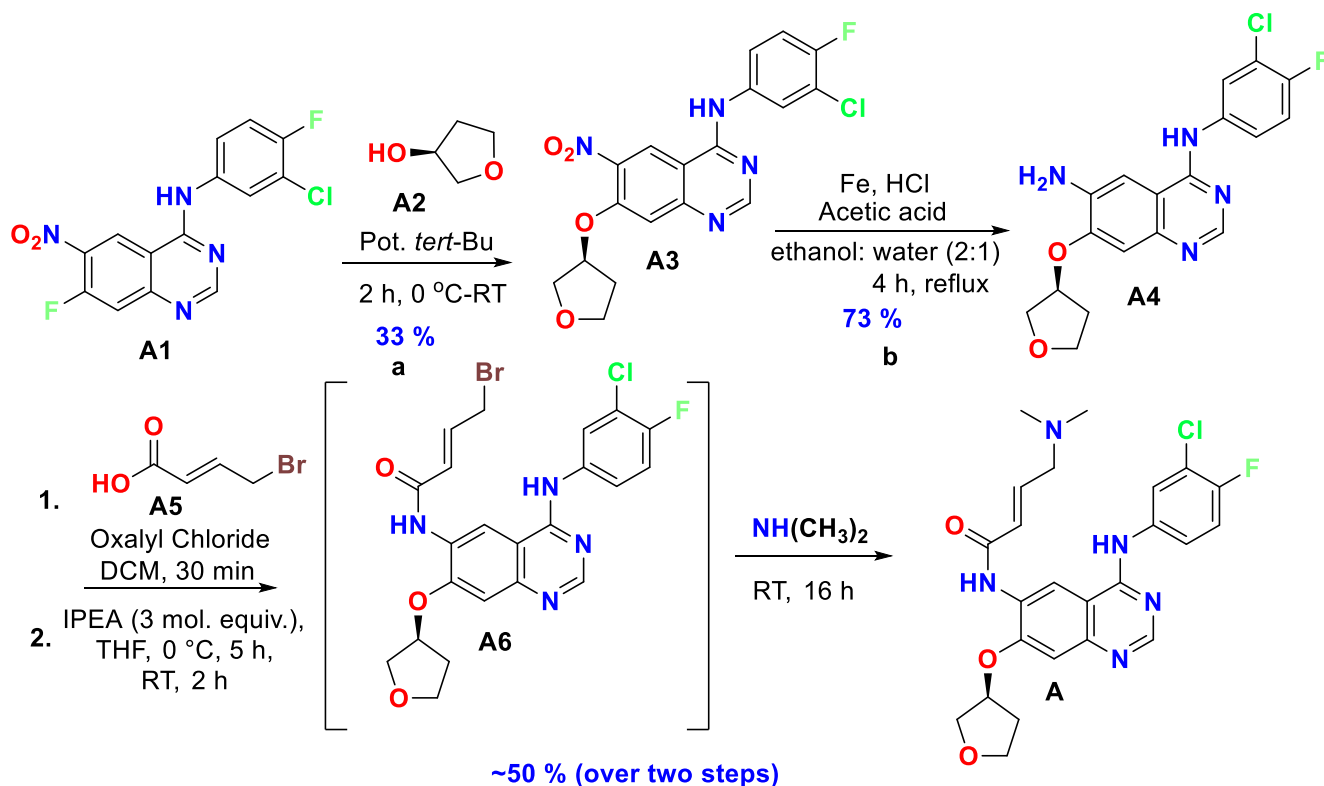


Figure 3. Chemical structure of Afatinib (**A**).

4.1.1. Synthesis of Afatinib (A). The first reported synthesis of **A** involved the synthesis from the advanced intermediate **A1** which reacts with the hydroxy group of S-tetrahydrofuran-3-ol **A2** in the presence of potassium *tert*-butoxide to form intermediate **A3**. The nitro group at the 6-position in **A3** is reduced with iron

to afford compound **A4**. The compound **A4** undergoes amidation reaction with (E)-4-bromobut-2-enoic acid chloride to obtain intermediate **A6** which after amination reaction with **A6** and dimethylamine, afforded **A** (Scheme 1).^{13,14}

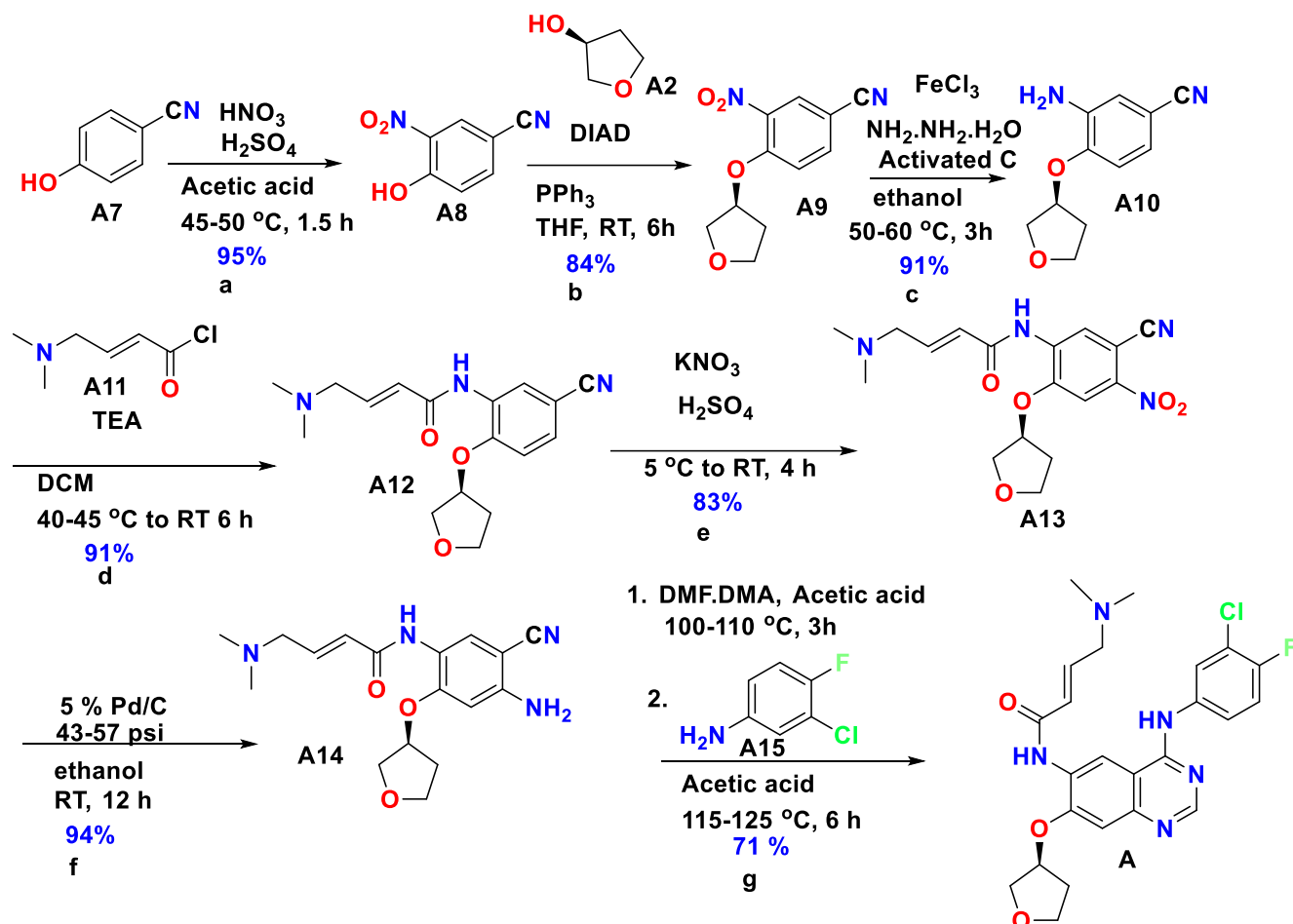


Reagents and conditions: a) (S)-tetrahydrofuran-3-ol **A2** (1 mol. equiv.), potassium *tert*-butoxide (6 mol. equiv.), DMF, 0 °C-RT, 2 h; b) Fe (4 mol. equiv.), acetic acid (9.3 mol. equiv.), ethanol:water (2:1), reflux, 4 h; c) i) (E)-4-bromobut-2-enoic acid (1.5 mol. equiv.), oxalyl chloride (47 mol. equiv.) DMF (1-2 drops), DCM, 30 min.; ii) DIPEA (3 mol. equiv.), THF, 0 °C, 5 h, RT, 2 h; iii) Dimethyl amine, RT, 16 h

Scheme 1. Initial synthesis of Afatinib (**A**).

Since this synthetic strategy first prepares the quinazoline core and then performs the side chain attachments, the overall yield is low and most steps need to be purified by column chromatography. Therefore, this synthetic approach is not suitable for an industrial scale synthesis.

Xu et al. reported a preparation method that has easy-to-obtain raw materials, is a simple process, is economical and ecofriendly. This approach is advantageous for the industrial production of the drug (Scheme 2).¹⁵ The process involves nitration of *p*-hydroxybenzonitrile **A7** in the presence of nitric acid and sulphuric acid to form 4-hydroxy-3-nitrobenzonitrile **A8**. Reaction of S-tetrahydrofuran-3-ol **A2** with **A8** in the presence of DIAD yielded the corresponding ether compound **A9**. Reduction of the nitro group of **A9** using FeCl_3 afforded the corresponding amine **A10** in good yield. **A10** and E-4-(dimethylamino)but-2-enoyl chloride **A11** undergo amidation to produce **A12**. Nitration of **A12** afforded **A13** which was reduced in the presence of Pd/C to form amine **A14**. Cyclization followed by amination of **A14** afforded Afatinib **A**. This process involves classical reactions and easily available starting materials, which are suitable for industrial scale synthesis.



Reagents and conditions: a) HNO_3 (2 mol. equiv.), Conc. H_2SO_4 (2 mol. equiv.), acetic acid, 45-50 °C, 1.5 h; b) DIAD (3 mol. equiv.), triphenylphosphine (3 mol. equiv.), (S)-tetrahydrofuran-3-ol **A2** (1.1 mol. equiv.), THF, RT, 4 h; c) FeCl_3 (4 mol. equiv.), Activated carbon (9.3 mol. equiv.), ethanol, 50-60 °C, 3 h, 80% hydrazine hydrate; d) (E)-4-(dimethylamino)but-2-enoyl chloride **A11** (1.1 mol. equiv.), TEA (1.1 mol. equiv.), 40-45 °C to RT, 6 h; e) KNO_3 (2 mol. equiv.), H_2SO_4 (33 mol. equiv.), 5 °C to RT, 4 h; f) 5% Pd/C (10% w/w), 43-57 psi, hydrogen, ethanol, RT, 12 h; g) i) DMF.DMA (1.5 mol. Equiv.), Acetic acid (1.8 mol. Equiv.), toluene, 100-110 °C, 3 h ii) 3-chloro-4-fluoroaniline (1.4 mol. Equiv.), acetic acid, 115-125 °C, 6 h.

Scheme 2. Industrial scale synthesis of Afatinib (**A**).

4.2. Gefitinib (Iressa® - AstraZeneca Pharmaceuticals)

Gefitinib (**Fig 4**) is a drug used in the treatment of certain types of cancer including breast, lung and other. It selectively targets the mutant proteins in malignant cells. Gefitinib is the first selective inhibitor of EGFR tyrosine kinase (TK) domain. It inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with trans-membrane cell surface receptors, including the EGFR-TK.¹⁶

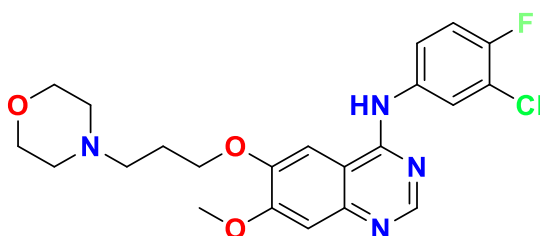
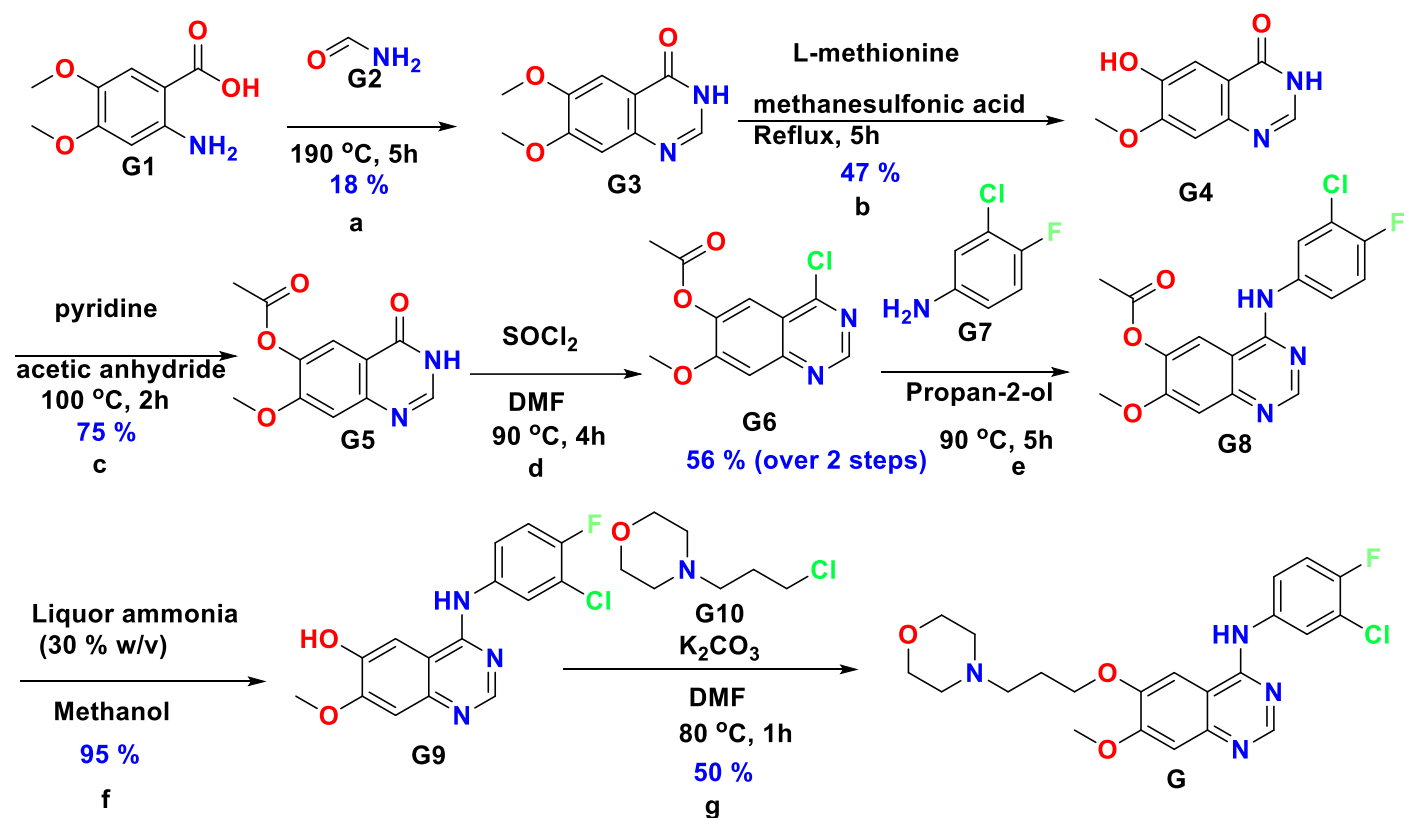


Figure 4. Chemical structure of gefitinib (**G**).

4.2.1. Synthesis of gefitinib (G). The initial synthesis of gefitinib (**G**) as depicted in the literature^{17, 18} involved the synthesis from 2-amino-4,5-dimethoxybenzoic acid **G1** with formamide **G2** to afford 6,7-dimethoxyquinazolin-4(3H)-one **G3**. **G3** undergoes a demethylation reaction in the presence of L-methionine and methanesulfonic acid to form intermediate **G4**. The acetylation of **G4** followed by chlorination afforded **G5** and **G6**; respectively. Amination of **G6** with 4-chloro-3-fluoroaniline **G7** in propan-2-ol under reflux conditions afforded intermediate **G8** which was de-methylated in presence of liquor ammonia to form **G9**. The reaction of **G9** and 4-(3-chloropropyl)morpholine **G10** in the presence of potassium carbonate and *N,N*-dimethyl formamide (DMF) yielded **G**. (Scheme 3)

This synthetic methods for the preparation of gefitinib **G** involves the construction of substituted quinazolin-4(3H)-ones from 2-amino-4,5-dimethoxybenzoic acid **G1**. The yield and methodology improved to 98% by Knesl et al by simply increasing the de-methylation step by 16 h.¹⁹ However, preparation by this method involves the use of corrosive chemicals such as thionyl-chloride, high temperature reaction conditions and poor yields in some of the other steps.

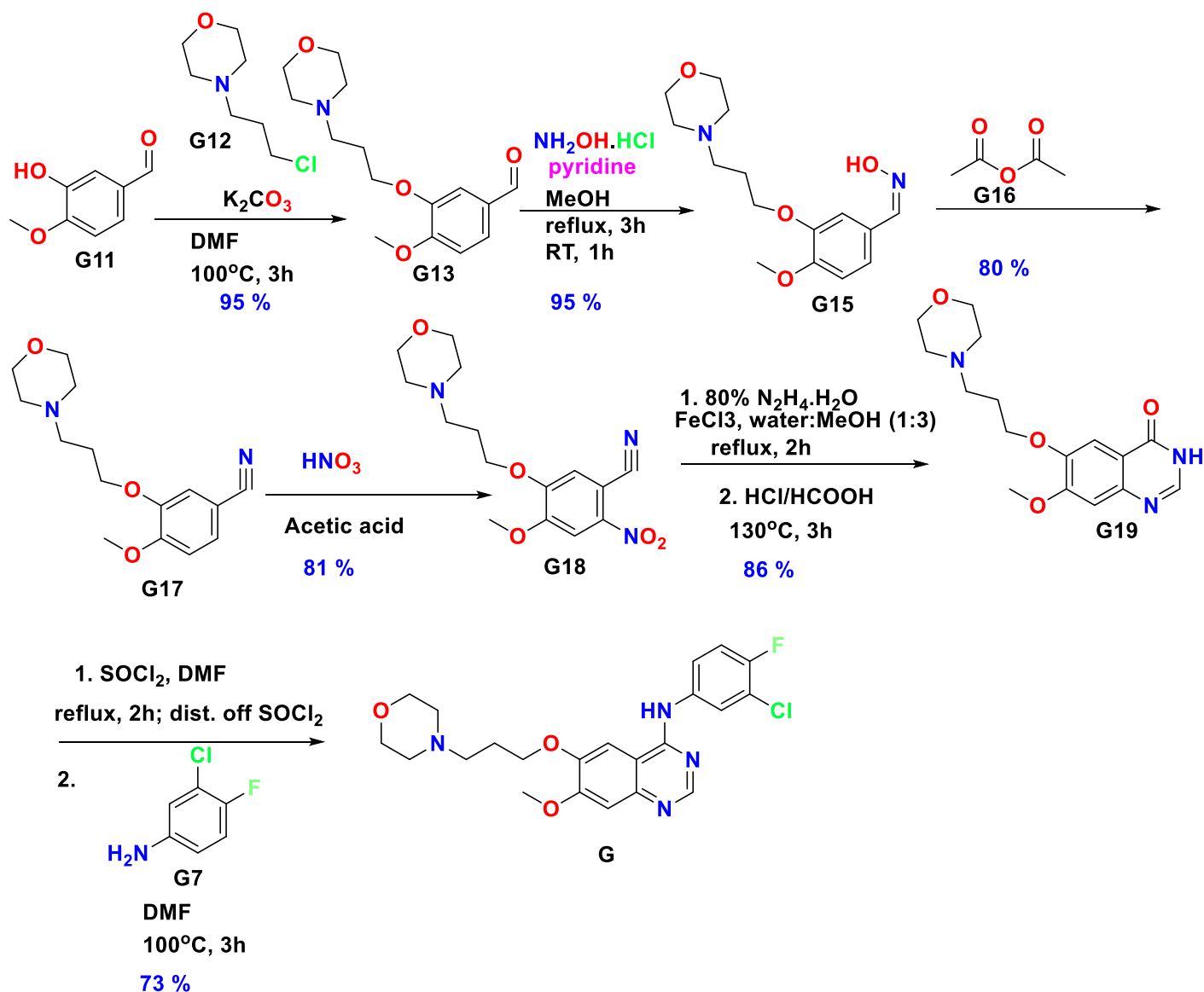


Reagents and conditions: a) formamide (2.5 mol. equiv.), 190 °C, 1.5 h; b) L-methionine (1.2 mol. equiv.), methanesulfonic acid (21 mol. equiv.), Reflux, 5h; c) acetic anhydride (16 mol. equiv.), pyridine (2.4 mol. equiv.), 100 °C, 2 h; d) SOCl₂ (46 mol. equiv.), DMF (0.9 mol. equiv.), 90 °C, 4 h; e) 4-chloro-3-fluoroaniline **G7** (1 mol. equiv.), propan-2-ol, 90 °C, 4 h; f) Liquor ammonia (30% w/v) (1.6 mol. equiv.), methanol, 100 °C, 1.5 h; g) 4-(3-chloropropyl)morpholine (1.1 mol. Equiv.), K₂CO₃ (3.4 mol. equiv.), DMF, 80 °C, 1h .

Scheme 3. Synthesis of gefitinib (**G**).

To overcome these difficulties, a one-pot synthesis of quinazolin-4(3H)-ones under mild reaction conditions has been reported.²⁰ This approach (Scheme 4) uses the isovanillin **G11** which was alkylated with 4-(3-chloropropyl)morpholine **G12** to form 4-methoxy-3-(3-morpholinopropoxy)benzaldehyde **G13** in good yield.

The conversion of **G13** to nitrile **G17** is achieved with a reasonably high yield through the formation of an oxime intermediate **G15**. The synthesis of quinazoline **G19** was performed by reacting *ortho*-nitrobenzonitrile **G18** with a reducing agent such as $\text{FeCl}_3/\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ and in situ cyclisation with HCl -formic acid. Chlorination followed by amination with 4-chloro-3-fluoroaniline **G7** yielded gefitinib (**G**) in good yields.

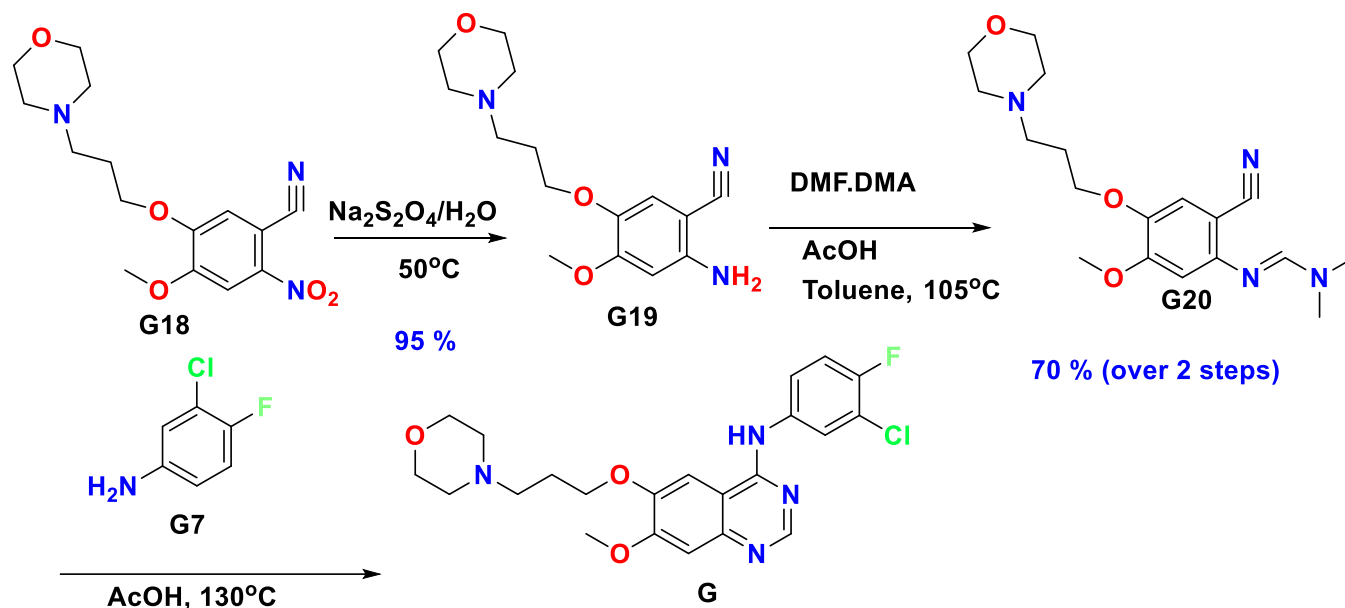


Reagents and conditions: a) 4-(3-chloropropyl)morpholine **G12** (1.1 mol. equiv.), K_2CO_3 (2 mol. equiv.), DMF, 100°C , 3h; b) $\text{NH}_2\text{OH}\cdot\text{HCl}$ (2 mol. equiv.), pyridine (2 mol. equiv.), MeOH, reflux, 1h; c) acetic anhydride **G16** (6.34 mol. equiv.), 110°C , 3 h; d) HNO_3 (70%, 4 mol. equiv.), acetic acid (1.4 vol.), $45\text{--}50^\circ\text{C}$, 8 h; e) i) FeCl_3 (0.006 mol. equiv.), 80% hydrazine hydrate (4.7 mol. equiv.), water:MeOH (1:3), reflux, 3 h; ii) 35% HCl (6 mol. equiv.), formic acid (2.3 mol. equiv.), 130°C , 3 h; f) i) SOCl_2 (27 mol. equiv.), DMF (0.42 mol. equiv.), 100°C , 1 h- distilled off thionyl chloride; ii) 4-chloro-3-fluoroaniline **G7** (27 mol. equiv.), DMF, 100°C , 1 h.

Scheme 4. Industrial scale synthesis of gefitinib (**G**).

Chandregowda et al. later reported an improved convergent approach for commercial synthesis of **G**.²¹ The convergent process (Scheme 5) developed for the preparation of gefitinib involves reducing nitro group of *ortho*-nitrobenzonitrile **G18** with $\text{Na}_2\text{S}_2\text{O}_4\cdot\text{H}_2\text{O}$ to form **G19**. **G19** is reacted with DMF.DMS to synthesize *N'*-2-

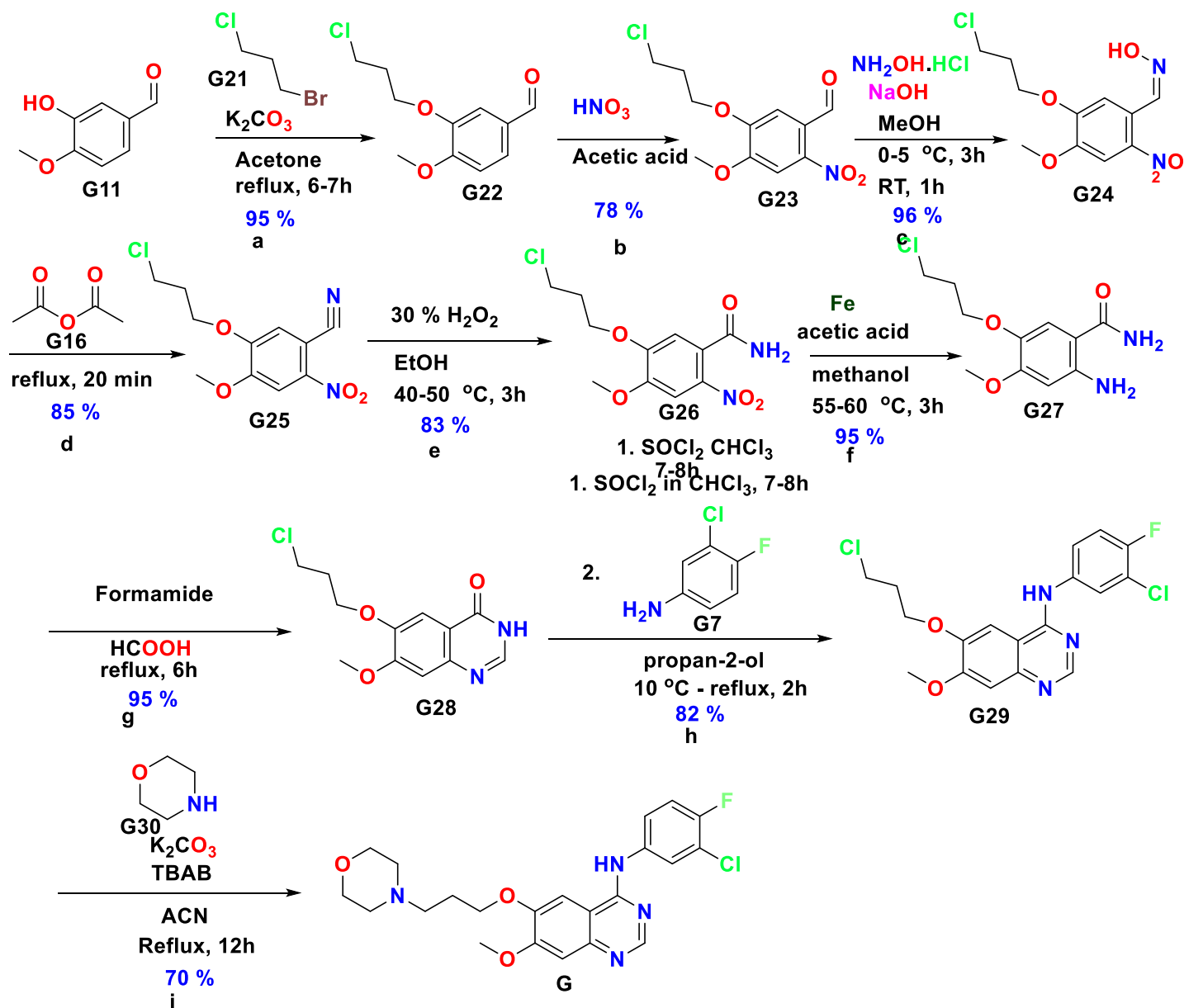
cyano-4,5-[bis(2-methoxyethoxy)phenyl]-*N,N*-dimethylformamidine **G20** which was further reacted by 3-chloro-4-fluoroaniline **G7** to get gefitinib (**G**). This process permits a reduction in the number of steps used and with higher yields.



Reagents and conditions: a) i) sodium dithionite (3.3 mol. Equiv.), water, 50 °C, 2.5 h; ii) 25% HCl (5 vol. w/w), 70 °C, addition over a period 2.5 h b) i) DMF.DMA (2.2 mol. Equiv.), Acetic acid (0.05 mol. equiv.), toluene, 105 °C, dean-stark apparatus, 3 h ii) 3-chloro-4-fluoroaniline **G7** (1.2 mol. Equiv.), acetic acid, 125-130 °C, 3 h.

Scheme 5. Industrial scale synthesis of gefitinib (**G**).

M. Chandrasekhar et al. reported a convenient and easy purification approach to high-yield synthesis of **G** from isovaniline (Scheme 6).²² In this approach, nitrile **G25** was treated with 30% H_2O_2 in ethanol solution to the corresponding amide **G26**. Reduction of intermediate **G26**, was carried out using Fe in AcOH to afford **G27**. Cyclization of the **G27** to the corresponding quinazolin-4(3*H*)-one derivative **G28** was accomplished using formamide and formic acid. Further, 6-(3-chloropropoxy)-7-methoxy quinazoline-4(3*H*)-one **G28** was reacted with SOCl_2 in CHCl_3 to give 4-chloro-7-methoxy-6-(chloropropoxy)quinazoline **G29** which was reacted *in situ* with excess of 3-chloro-4-fluoroaniline to result **G21** in an excellent yield. **G21** was treated with a mixture of anhydrous K_2CO_3 , tetra-*n*-butylammonium bromide (TBAB), and morpholine in acetonitrile to give **G**.



Reagents and conditions: a) 1-bromo-3-chloropropane **G12** (1 mol. equiv.), K_2CO_3 (2 mol. equiv.), acetone, reflux, 6-7 h; b) HNO_3 (70%, 4 mol. equiv.), acetic acid (4 vol.), RT, overnight; c) $NH_2OH.HCl$ (2.2 mol. equiv.), $NaOH$ (4.8 mol. equiv., 50% aqueous solution), $MeOH$, 0-5 °C, 3 h, RT, 1 h; d) acetic anhydride **G16** (305 mol. equiv.), reflux, 20 min.; e) 30% H_2O_2 (2.7 mol. equiv.), $EtOH$, 40-50 °C, 3 h (*caution: the temperature of reaction mixture should not rise above 50 °C, otherwise explosion might occur due to the ignition of an oxygen-ethanol vapor mixture*); f) Fe (1 mol. equiv.), acetic acid (3.6 vol.), methanol (2 vol.), 55-60 °C, 1.5 h; g) Formamide (8.3 mol. equiv.), $HCOOH$ (8.6 mol. equiv.), reflux, 6 h; h) 1) $SOCl_2$ (7 vol.), $CHCl_3$, 7-8 h; 2) 4-chloro-3-fluoroaniline **G7** (27 mol. equiv.), propan-2-ol, 10 °C to reflux, 2 h; i) 4-(3-morpholino)propan-1-ol (**G30**), K_2CO_3 (0.7 mol. equiv.), tetra-n-butylammonium bromide (TBAB) (0.06 mol. equiv.), ACN , reflux, 12 h.

Scheme 6. Multigram scale synthesis of gefitinib (**G**).

4.3. Erlotinib (Tarceva® - Roche Pharmaceuticals)

Erlotinib (**E**) (Figure 5) is an inhibitor of the EGFR-TK that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is typically marketed under the trade name Tarceva.²³

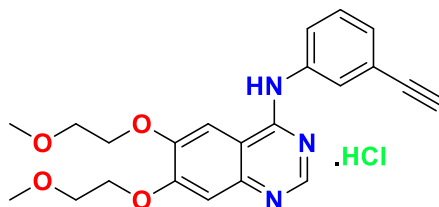
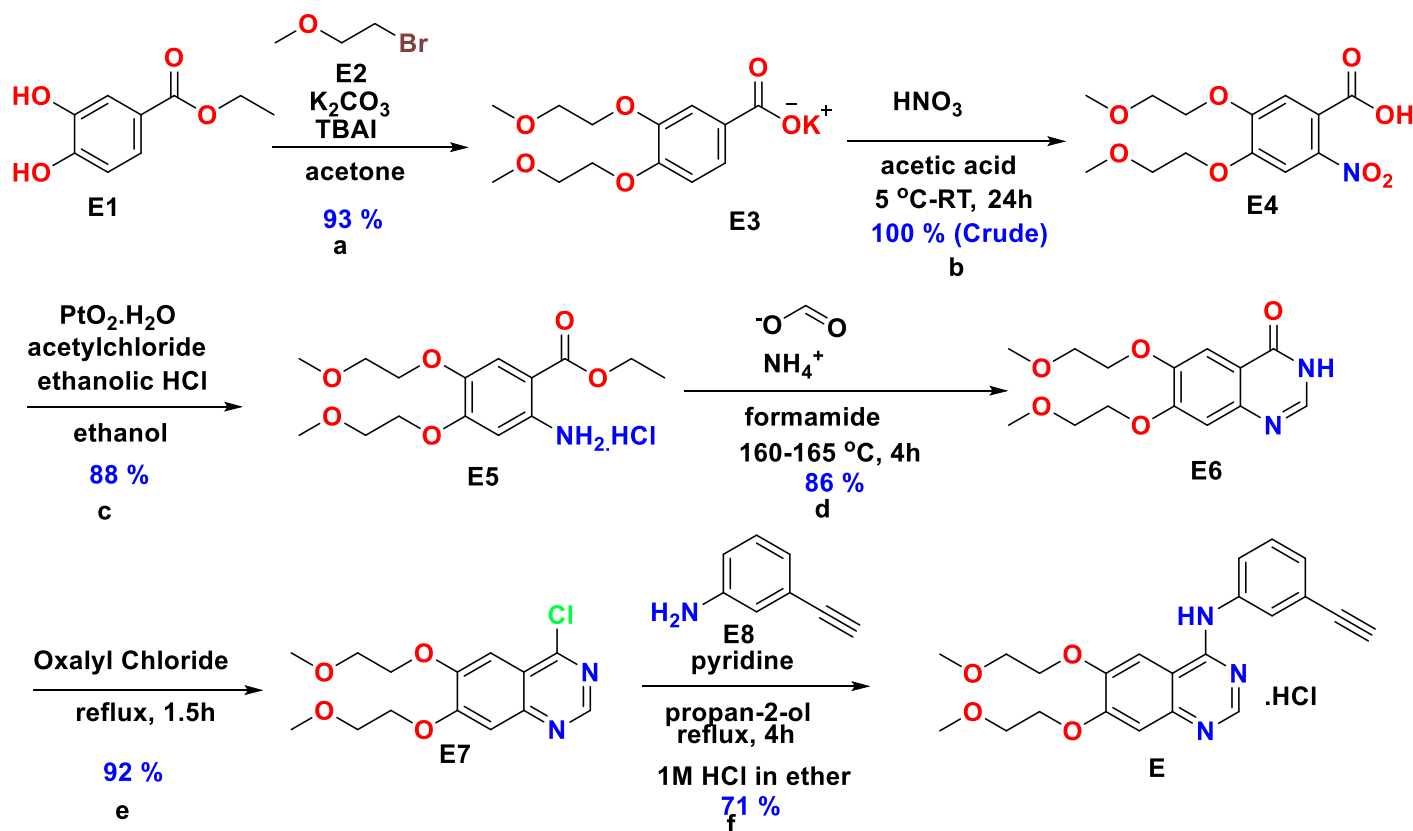


Figure 5. Chemical structure of erlotinib (**E**).

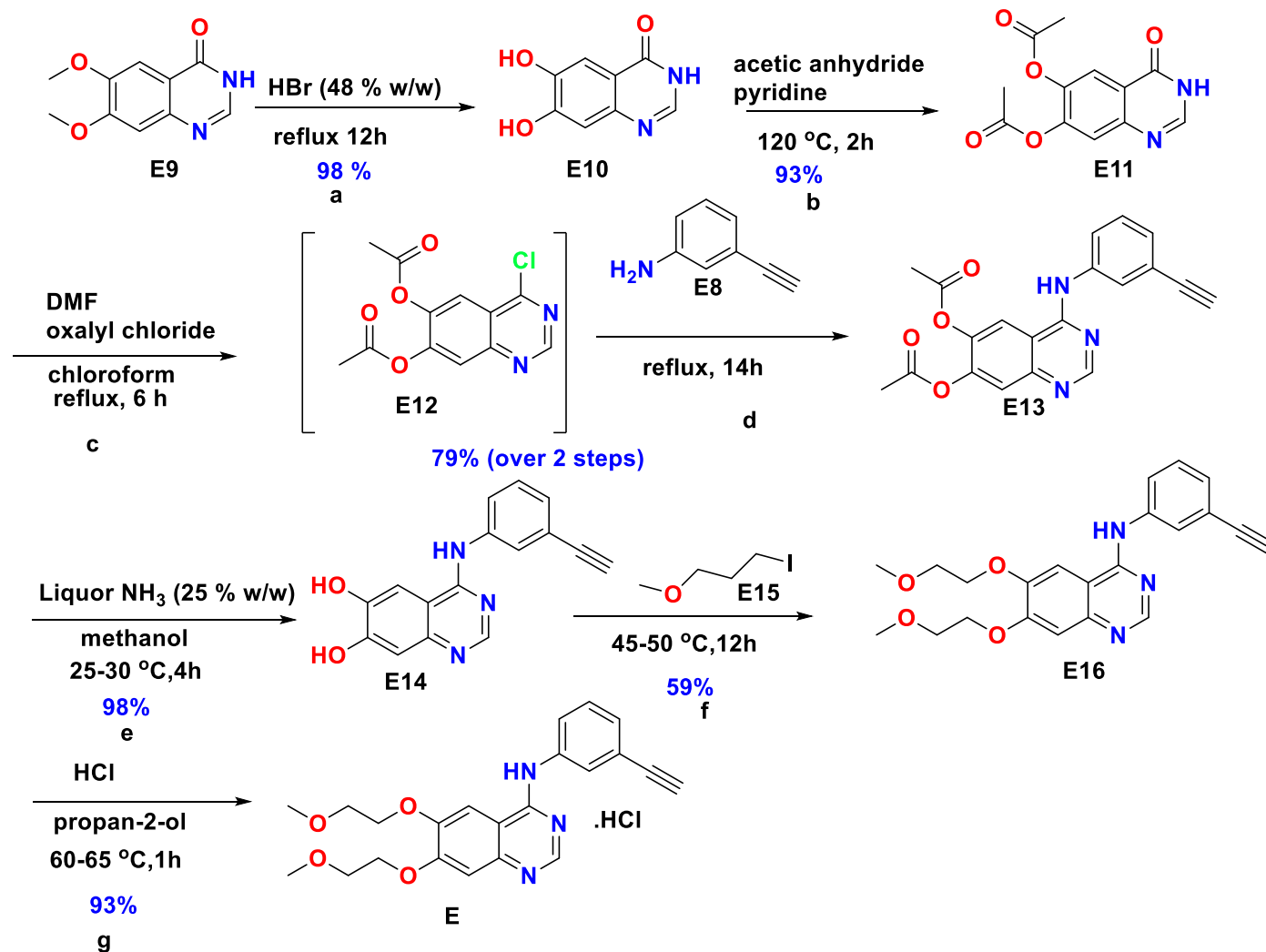
4.3.1. Synthesis of Erlotinib (E). The initial synthesis of **E** was reported by Schnur et al. in 1998. The two hydroxyl groups on ethyl 3,4-dihydroxybenzoate **E1** were alkylated with 1-bromo-2-methoxyethane **E2** to afford potassium salt of 3,4-bis(2-methoxyethoxy)benzoate **E3**. **E3** undergoes a nitration reaction in the presence of nitric acid to afford the corresponding nitro **E4** which was reduced and esterified to afford **E5**. Cyclization of **E5** yielded quinazolin-4(3H)-one **E6**. Chlorination followed by substitution with 3-ethynylaniline **E8** afforded **E** (Scheme 7).²⁴ In this approach, 4-chloro quinazoline **E7** is a key intermediate and its synthesis involves the use of corrosive and toxic reagents such as oxalyl chloride, a highly flammable gas such as hydrogen at high pressure and costly reagents such as platinum oxide.



Reagents and conditions: a) 1-bromo-2-methoxyethane **E2** (2.5 mol. equiv.), K_2CO_3 (2.2 mol. equiv.), tetrabutylammonium iodide **TBAI** (0.01 mol. equiv.), acetone, reflux, 64 h; b) HNO_3 (70%, 2.8 mol. equiv.), acetic acid (17 mol. equiv.), 5 °C -RT, 24 h; c) acetyl chloride (1 mol. equiv.), ethanolic HCl (1 mol. equiv.), $PtO_2 \cdot H_2O$ (0.03 mol. equiv.), EtOH, 45 psi H_2 , 6 h, RT; d) Formamide (13.2 mol. equiv.), ammonium formate (1 mol. equiv.), 160-165 °C, 3 h; e) oxalyl chloride (3.3 mol. equiv.), reflux, 1.5 h; f) 3-ethynylaniline **E8** (1.1 mol. equiv.), pyridine (1.1 mol. equiv.), propan-2-ol, reflux, 4 h, 1M HCl in ether.

Scheme 7. Initial synthesis of erlotinib (**E**).

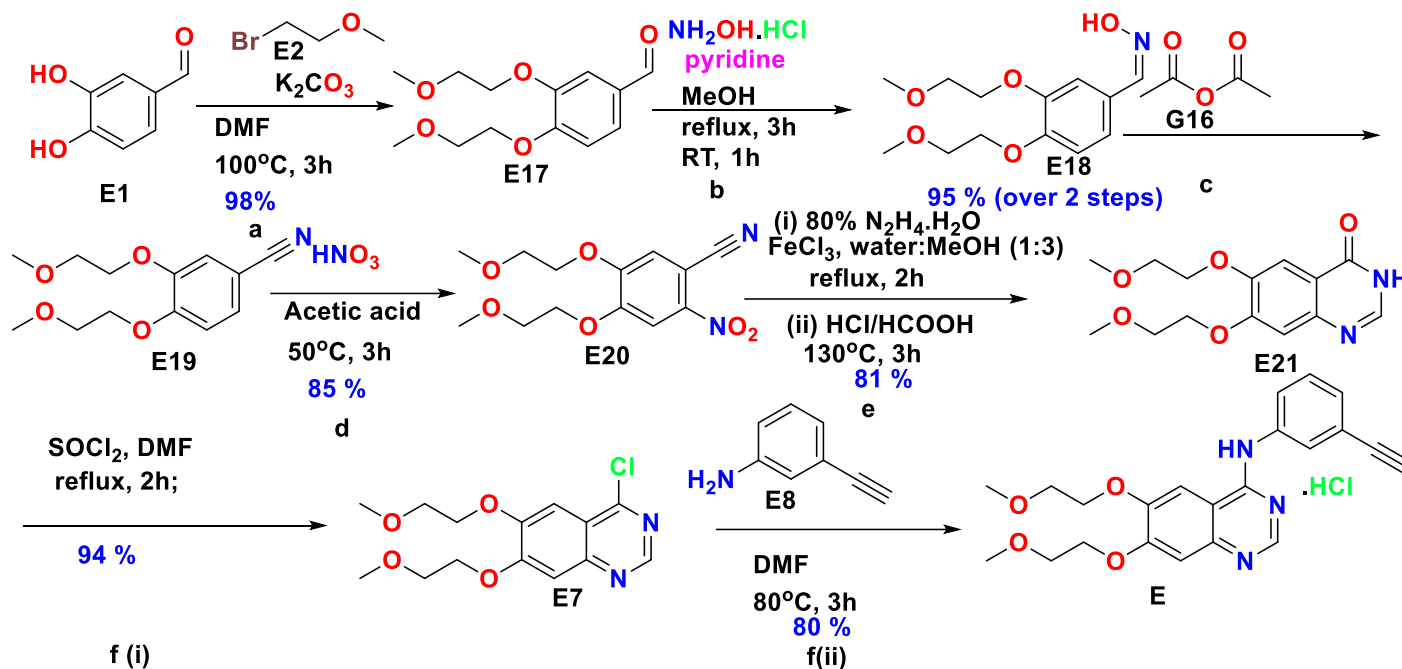
Considering these difficulties Ramanadham et al. developed a simple and economically viable process for the preparation of Erlotinib (**E**) (Scheme 8).²⁵ The basic raw material selected for synthesis is 6,7-dimethoxyquinazolin-4(3H)-one **E9**. **E9** was reacted with aqueous HBr to synthesize dihydroxy **E10**. The acetylation of **E10** with acetic anhydride and pyridine formed the corresponding bis-acetylated derivative **E11**. The carbonyl group of **E11** was converted in to leaving group 'Cl' using oxalylchloride under reflux conditions to afford intermediate **E12** which was condensed in situ after workup with 3-ethynylaniline **E8** under reflux conditions to afford **E13**. **E13** was de-acetylated with aqueous ammonia to form **E14** which was further reacted with 2-iodo-ethylmethylether **E15** in the presence of base to synthesize **E16** which was converted into Erlotinib hydrochloride by treatment with HCl in propan-2-ol.



Reagents and conditions: a) 48% aqueous HBr (12.2 mol. equiv.), 110 °C 1 h, reflux 12 h; b) pyridine (0.09 mol. equiv.), acetic anhydride (10.5 mol. equiv.); 120 °C, 2 h; c) DMF (0.14 mol. equiv.), oxalyl chloride-*drop wise addition* (2.1 mol. equiv.), reflux, 6 h; d) 3-ethynylaniline **E8** (1 mol. equiv.), reflux, 14 h; e) Liquor ammonia (25% w/w, 2.8 mol. equiv.), methanol, 25-30 °C 1 h, reflux 4 h; f) K₂CO₃ (6 mol. equiv.), 1-iodo-3-methoxypropane **E15** (2 mol. equiv.), DMF, 45-50 °C 12 h; g) propan-2-ol-HCl (1.1 mol. equiv.), propan-2-ol, 60-65 °C 1 h.

Scheme 8. Synthesis of erlotinib (**E**).

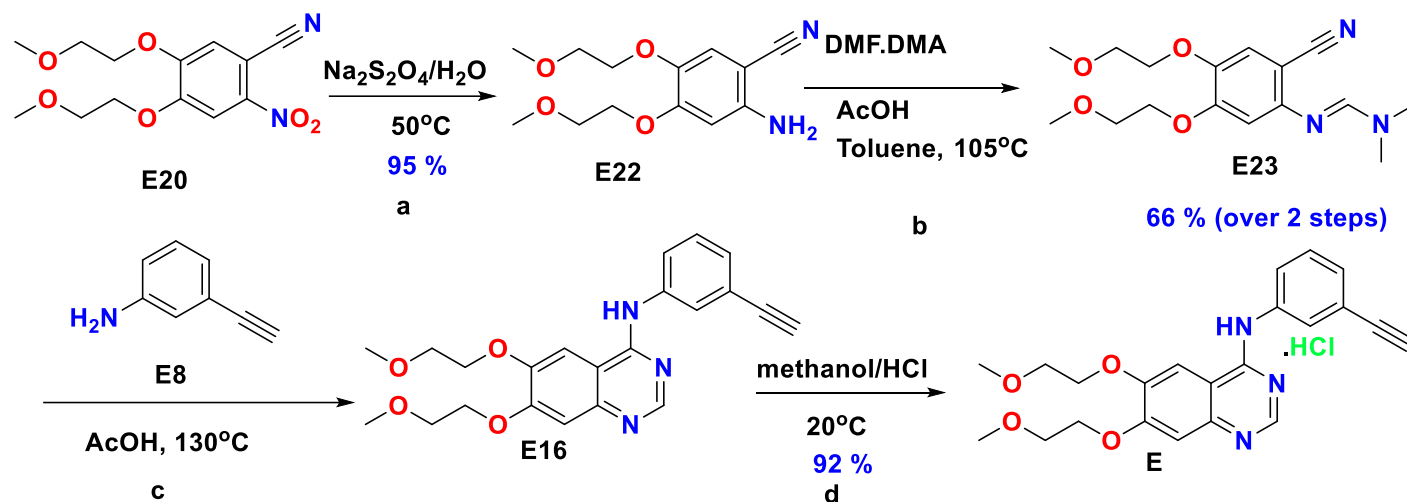
Chandregowda et al. reported simplified conditions for the synthesis of **E** (Scheme 9).²⁶ Their approach involves a similar synthetic process for synthesis of **E7** as depicted in Scheme 8. Treatment of **E7** with 3-ethynylaniline **E8** in DMF without using extra base afforded erlotinib (**E**) as the hydrochloride salt.



Reagents and conditions: a) 1-bromo-2-methoxyethane **E2** (1.1 mol. equiv.), K_2CO_3 (2 mol. equiv.), DMF, 100 °C, 3 h; b) $\text{NH}_2\text{OH} \cdot \text{HCl}$ (2 mol. equiv.), pyridine (2 mol. equiv.), MeOH, reflux, 1h; c) acetic anhydride **G16** (6.34 mol. equiv.), 110 °C, 3 h.; d) HNO_3 (70%, 4 mol. equiv.), acetic acid (1.4 vol.), 45-50 °C, 8 h; e) i) FeCl_3 (0.006 mol. equiv.), 80% hydrazine hydrate (4.7 mol. equiv.), water: MeOH (1:3), reflux, 3 h; ii) 35% HCl (6 mol. equiv.), formic acid (2.3 mol. equiv.), 130 °C, 3 h; f) i) SOCl_2 (24.3 mol. equiv.), DMF (0.42 mol. equiv.), reflux, 2 h; ii) 3-ethynylaniline **E8** (1 mol. equiv.), DMF, 80 °C, 1 h.

Scheme 9. Industrial scale synthesis of erlotinib (**E**).

The synthesis of **E** has also been accomplished by starting from **E20**, which in turn was prepared in an efficient way as described in Scheme 9. Nitro reduction of **E20** using sodium dithionite in aqueous medium gave **E22**. **E22** was treated with DMF–DMA in toluene to obtain formamidine derivative **E23**, which was reacted with 3-ethynylaniline **E8** through Dimroth rearrangement to give erlotinib (**E**) (Scheme 10).²⁷



Reagents and conditions: a) i) sodium dithionite (3.3 mol. Equiv.), water, 50 °C, 2.5 h; ii) 25% HCl (5 vol. w/w), 70 °C, addition over a period 2.5 h; b) i) DMF.DMA (2 mol. Equiv.), Acetic acid (0.06 mol. Equiv.), toluene, 105 °C, dean-stark apparatus, 3 h; ii) acetic acid (0.03 mol. equiv.), 3-ethynylaniline **E8** (1 mol. Equiv.), 125-130 °C, 1 h; c) HCl gas for 0.5 h, methanol, 15-20 °C

Scheme 10. Improved industrial scale synthesis of erlotinib (**E**).

4.4. Dacomitinib (Vizimpro® - Pfizer Inc.)

Dacomitinib (**D**) (Figure 6) is a second-generation tyrosine kinase inhibitor and used for the treatment of non-small-cell lung carcinoma (NSCLC). It is characterized by the irreversible binding at the ATP domain of the epidermal growth factor receptor family kinase domains. Dacomitinib was developed by Pfizer Inc. and approved by the US FDA in 2018.²⁸

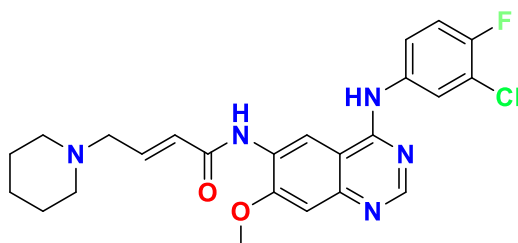
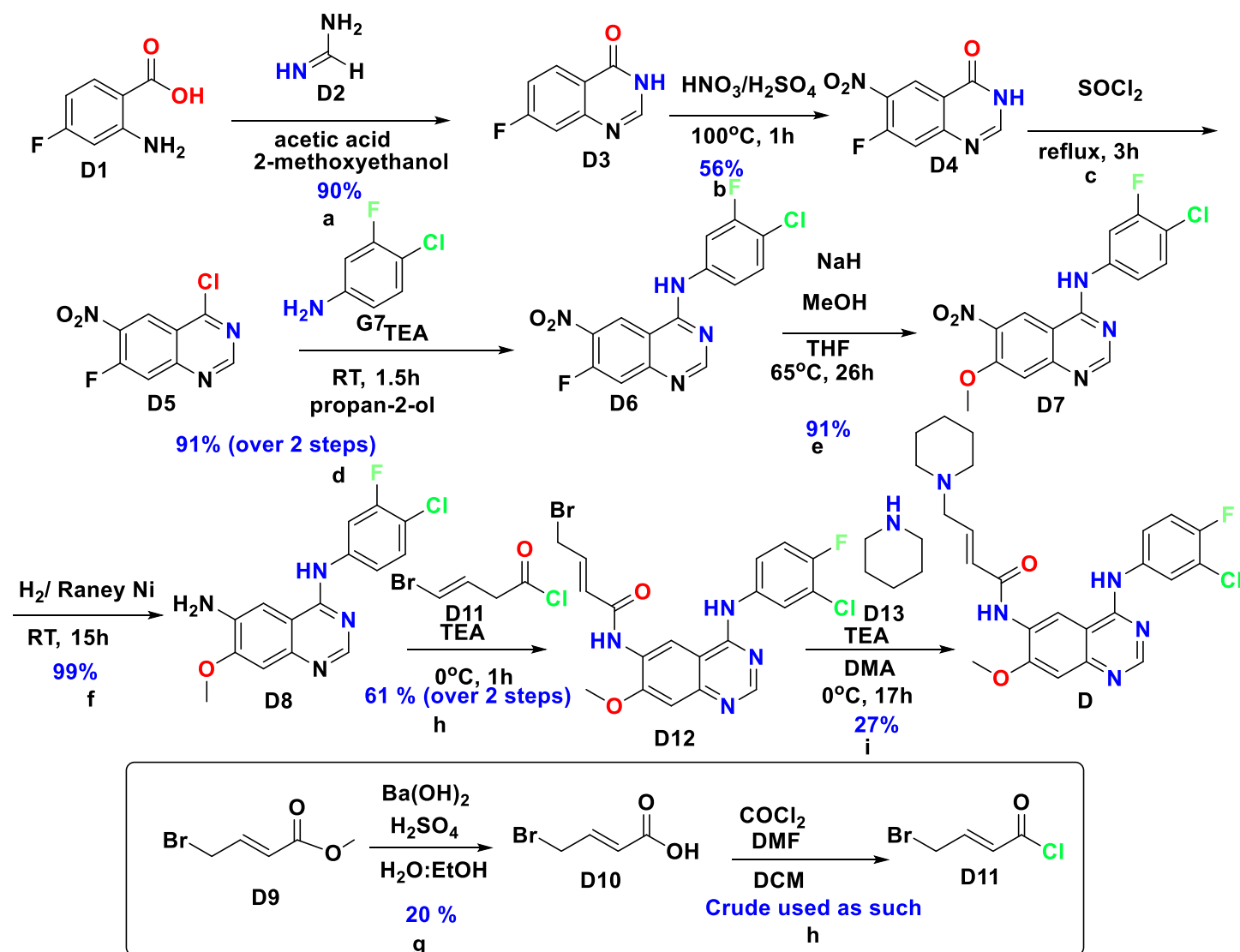


Figure 6. Chemical structure of dacomitinib (**D**).

4.4.1. Synthesis of dacomitinib (D). The synthesis of this is mainly divided into two parts *viz.* *synthesis of the quinazoline* and *synthesis of the crotonate*. In the lab scale synthesis,²⁹⁻³¹ the quinazoline moiety was synthesized from 2-amino-4-fluorobenzoic acid **D1** (Scheme 11). **D1** was cyclized with formamidine **D2** to form 7-fluoroquinazolin-4(3H)-one **D3** which undergoes nitration to get **D4**, Chlorination to form intermediate **D5**, amination with **G7** to afford **D6** followed by *O*-methylation afforded **D7**. Reduction of the nitro group in **D7** to amine in presence of Raney Ni afforded the desired quinazoline **D8**. Synthesis of (E)-4-bromobut-2-enoyl chloride **D11** was done by hydrolysis of methyl (E)-4-bromobut-2-enoate **D9** to form the corresponding acid **D10** which was followed by acyl chloride formation. This intermediate was used to couple with quinazoline **D8** to form the corresponding amide **D12**. **D12** was reacted with piperidine **D13** to afford **D**. The disadvantage of

this approach is that the cost is high, column purification is needed in 2-3 steps and overall yield is low especially for last step in which substitution with pyridine was needed to produce **D**.

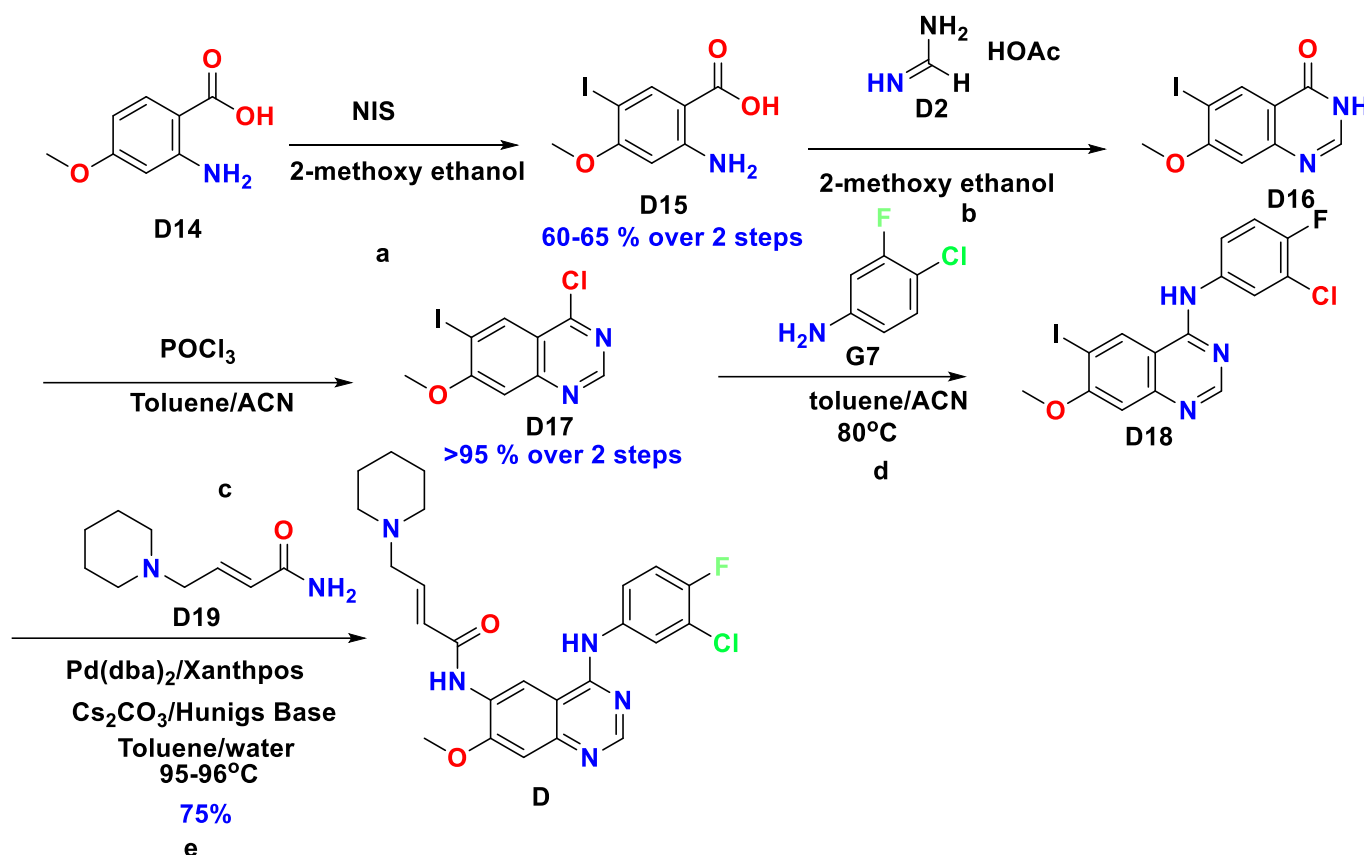


Reagents and conditions: a) formamidine **D2** (2 mol. equiv.), 2-methoxy ethanol, reflux, 18 h; b) fuming HNO_3 (8.2 mol. equiv.), 100 °C, 1 h; c) SOCl_2 (55.2 mol. equiv.), reflux, 3 h; d) 4-chloro-3-fluoroaniline **G7** (1 mol. equiv.), TEA (1 mol. equiv.), propan-2-ol, RT, 1.5 h; e) NaH (60% in mineral oil, 1.5 mol. equiv.), methanol (1.5 mol. equiv.), THF, 26 h, 65 °C; f) Raney Ni (0.6 w/w), hydrogen balloon, 15 h, RT; g) $\text{Ba}(\text{OH})_2$ (0.5 mol. equiv.), H_2SO_4 (0.5 mol. equiv.), water:EtOH (1:0.34), -11 °C to RT, 16 h; h) i) oxalyl chloride (0.45 mol. equiv.), DMF (3-4 drops), DCM, RT, 1.5 h; ii) (E)-4-bromobut-2-enoyl chloride **D11**(crude), N4-(4-chloro-3-fluorophenyl)-7-methoxyquinazoline-4,6-diamine **D8** (1.6 mol. equiv.), TEA (1.5 mol. equiv.), 0 °C, 1 h; j) piperidine **D13** (1 mol. equiv.), TEA (3 mol. equiv.), DMA, 0 °C, 17 h.

Scheme 11. Lab scale synthesis of dacomitinib (**D**).

This last approach was further improved by slight modification in some of the reaction conditions and alterations in reaction sequences.³² Yu et al. developed *N*-arylation route (Scheme 12) in which easily available 2-amino-4-methoxybenzoic acid **D14** was used as starting material. Iodination of **D14** using *N*-Iodosuccinimide

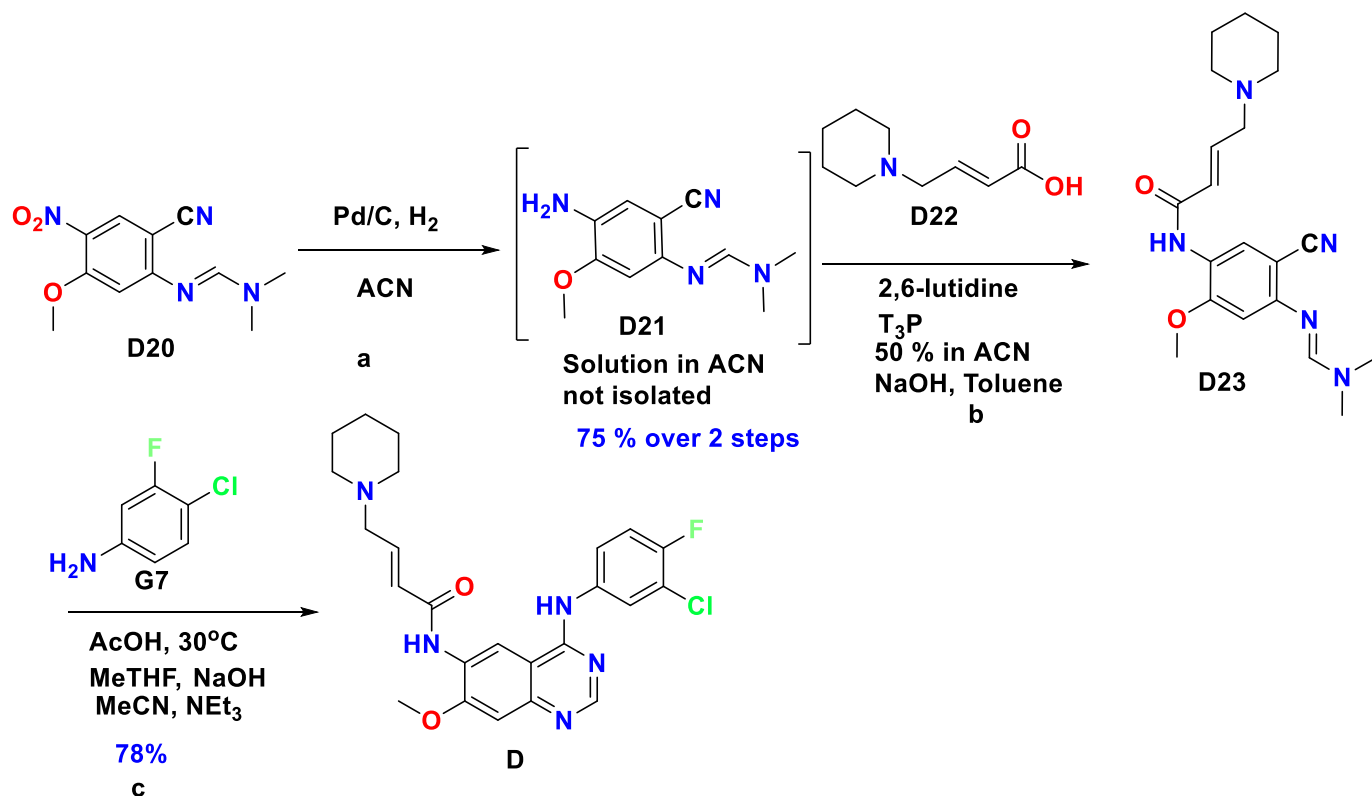
afforded **D15** in excellent yield and regioselectivity.³³ Condensation of **D15** with amidine acetate **D2** yielded intermediate **D16**, which was crystallized from the reaction mixture to afford a pure compound.



Reagents and conditions: a) 2-amino-4-methoxybenzoic acid **D14**, NIS, 2-methoxy ethanol; b) formimidamide acetate, 2-methoxy ethanol, reflux, overnight; c) POCl_3 , toluene/acetonitrile, reflux; d) 4-chloro-3-fluoroaniline **G7** (1 mol. equiv.), toluene/acetonitrile, 80 °C, 3 h; e) (E)-4-(piperidin-1-yl)but-2-enamide **D16**, $\text{Pd}(\text{dba})_2/\text{Xanthpos}$, $\text{Cs}_2\text{CO}_3/\text{Hunigs Base}$, Toluene/water, 95-96 °C.

Scheme 12. N-arylation route to dacomitinib (**D**).

The chlorination of **D16** was conducted in a mixture of toluene and acetonitrile. This mixture of solvents also served well during the nucleophilic aromatic substitution to afford **D18**. Therefore, **D18** was produced through telescoped process from **D16** via **D17** over two steps. Palladium catalyzed *N*-arylation with **D19** was done at this stage to form **D**. The initial synthesis route was significantly improved to enable the delivery of kilo scale synthesis by changing reagents, solvents and conditions in due course. The medicinal chemistry route was changed in order to meet the API demand for pre-clinical and clinical studies. An efficient three-step process was developed to manufacture dacomitinib (**D**) on a commercial scale by utilizing the Dimroth Rearrangement for cyclization.³⁴ The nitro group reduction of **D20** was performed with Pd/C carbon catalysts using acetonitrile as solvent to enable telescoping with the next step to afford **D21**. Propanephosphonic acid anhydride (T3P®) solution in acetonitrile in the presence of 2, 6-lutidine was used for the coupling reaction to afford **D23** without isolation of intermediate **D21**. A Dimroth reaction in acetic acid in acetonitrile at 30 °C afforded **D** (Scheme 13).



Reagents and conditions: a) Pd/C, hydrogen gas, ACN, 3 h; b) 2,6-lutidine, propanephosphonic acid anhydride T₃P, 50% in acetonitrile:toluene, RT; c) 4-chloro-3-fluoroaniline **G7**, AcOH, Me-THF, acetonitrile, 30 °C, 16 h.

Scheme 13. Commercial process to dacomitinib (**D**).

4.5. Lapatinib (Tykerb® and Tyverb® - GlaxoSmithKline (GSK))

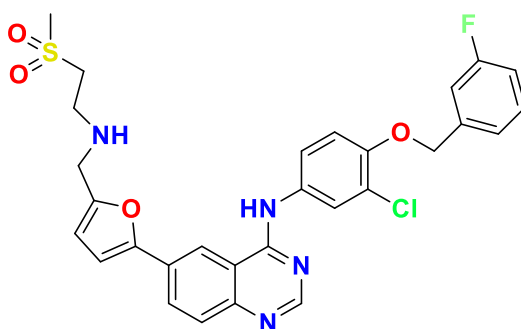
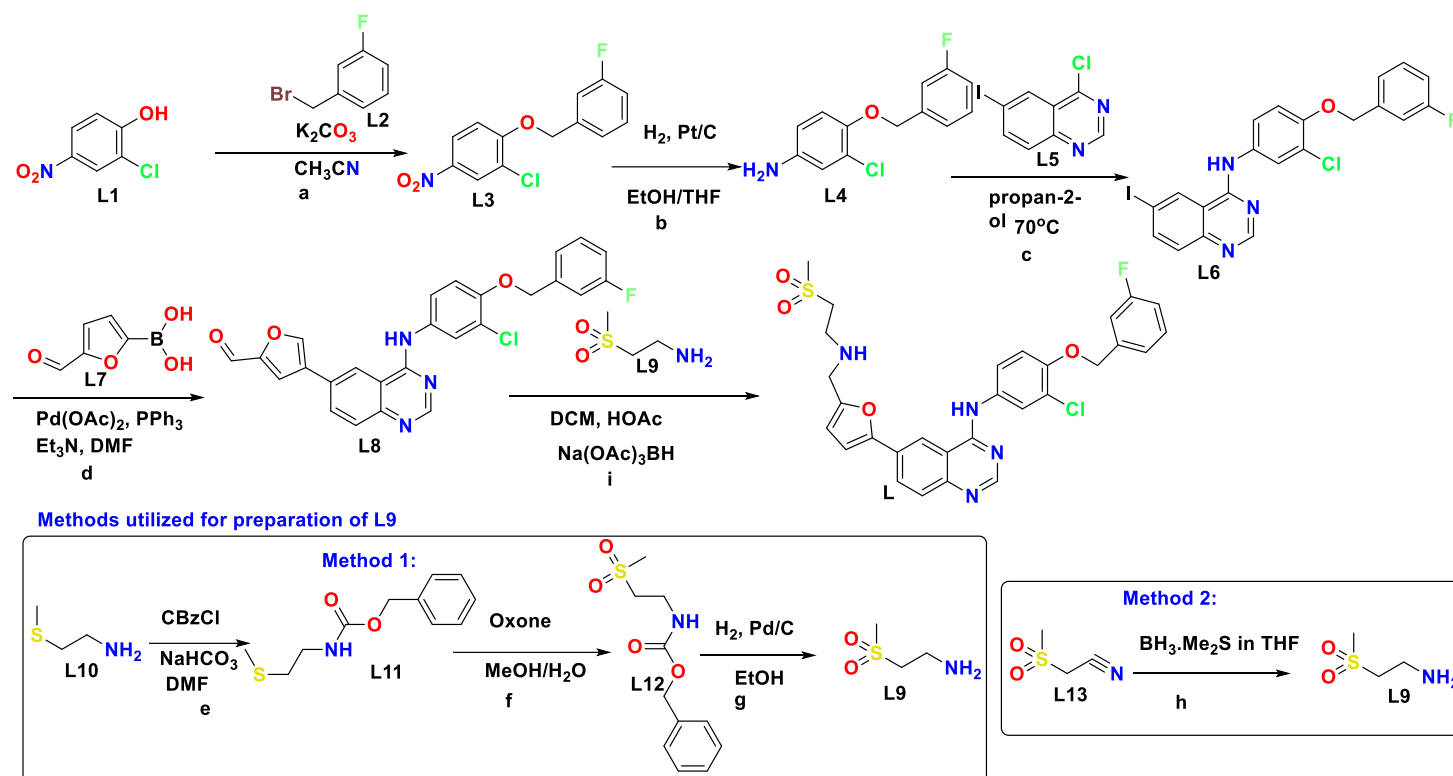


Figure 7. Chemical structure of lapatinib (**L**).

Lapatinib (**L**) (Figure 7) is an anti-cancer drug developed by GlaxoSmithKline (GSK) as a treatment for solid tumours such as breast and lung cancer. It was approved by the US FDA, in 2007, for use in patients with advanced metastatic breast cancer in conjunction with the chemotherapy drug Capecitabine.³⁵

4.5.1. Synthesis of Lapatinib (L). The first reported synthesis of lapatinib (**L**) was conducted using three convergent steps (Scheme 14).³⁶ The hydroxyl group of commercially available 2-chloro-4-nitrophenol **L1** was reacted with 1-(bromomethyl)-3-fluorobenzene **L2** to afford 2-chloro-1-((3-fluorobenzyl)oxy)-4-nitrobenzene **L3** which was reduced to corresponding amine **L4**. **L4** was reacted with 4-chloro-6-iodoquinazoline **L5** to afford **L6**. Suzuki-Miyaura (S-M) coupling of **L6** with (5-formylfuran-2-yl)boronic acid **L7** afforded intermediate

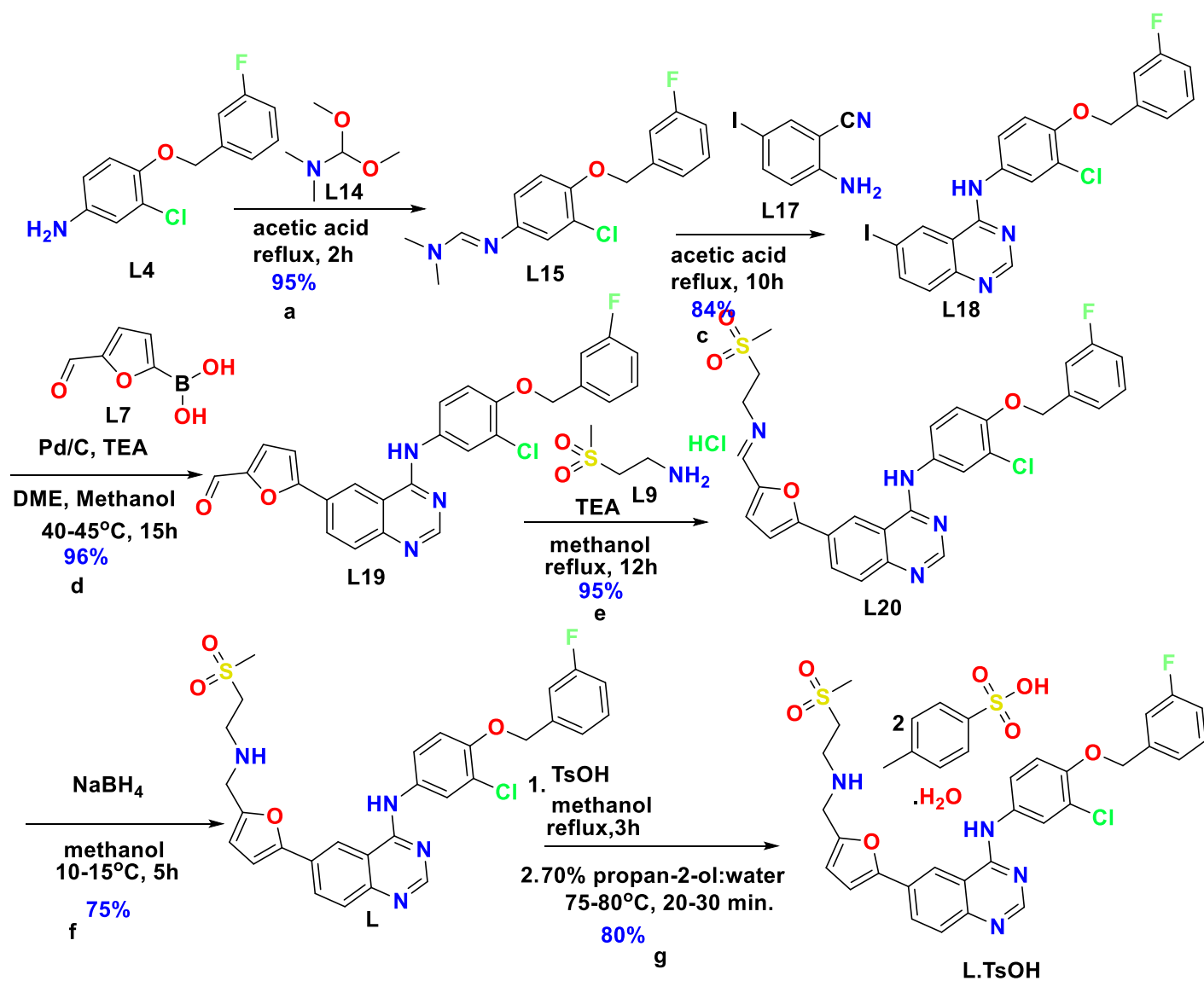
L8. Reductive amination of **L8** with 2-(methylsulfonyl)ethan-1-amine **L9** (synthesized by method 1 or method 2 as shown in scheme 13) afforded lapatinib **L**. This approach was good for synthesis on a milligram scale but optimization work was necessary to improve the yield and reproducibility of the reactions specifically for the S-M coupling reaction to afford **L8** in sufficient scale.



Reagents and conditions: a) 1-(bromomethyl)-3-fluorobenzene **L2**, K₂CO₃, acetonitrile; b) Pd/C, hydrogen gas, EtOH/THF; c) 4-chloro-6-iodoquinazoline **L5**, propan-2-ol, 70 °C; d) (5-formylfuran-2-yl)boronic acid **L7**, Pd(OAc)₂, PPh₃, triethylamine, DMF; e) 2-(methylthio)ethan-1-amine **L10**, benzyl carbonochloridate CBzCl, NaHCO₃, DMF; f) Oxone, MeOH/H₂O; g) Pd/C, hydrogen gas, EtOH; h) 2-(methylsulfonyl)acetonitrile **L13**, BH₃.Me₂S in THF, THF; i) 2-(methylsulfonyl)ethan-1-amine **L9**, sodium triacetoxyborohydride Na(OAc)₃BH, acetic acid, DCM.

Scheme 14. Synthesis of lapatinib (**L**).

A new pathway for the synthesis of this was reported in which the hydroxyl group of 6-iodoquinazoline-4-ol is protected by the tetrahydropyranyl group hence entailing greater solubility of the intermediates in common organic solvents the lack of which was a major disadvantage of the process discussed above.³⁷ Keeping in mind the difficulties for the preparation of Lapatinib **L** on a commercial scale, Prasad et al. developed a simple, economically viable and commercially applicable process for the preparation of lapatinib **L**.³² This process involved the reaction of 3-chloro-4-(3-fluorobenzyloxy)aniline **L4** with *N,N*-dimethylformamide dimethylacetal **L14** carried out in the presence of acetic acid to afford **L15**. Reaction of 2-aminobenzonitrile **L16** with iodine monochloride **ICI** in acetic acid yielded **L17** which underwent Dimorth Rearrangement with **L15** in acetic acid to afford **L18**. S-M coupling of **L18** with (5-formylfuran-2-yl)boronic acid **L7** afforded the corresponding aldehyde **L19**. Imination followed by reduction of **L19** yielded lapatinib **L** which was converted to its pharmaceutically acceptable ditosylate monohydrate salt **L.TSOH** (Scheme 15).



Reagents and conditions: a) 3,4-dihydro-2H-pyran **L14** (8.6 mol. equiv.), TFA (0.1 mol. equiv.), toluene, 110-115 °C, 2-3 h; b) (5-formylfuran-2-yl)boronic acid **L7** (1.3 mol. equiv.), Pd₂(dba)₃ (0.013 mol. equiv.), triphenylarsine (0.025 mol. equiv.), K₂CO₃ (2 mol. equiv.), DMF, 60-65 °C, 2 h; c) 2-(methylsulfonyl)ethan-1-amine.HCl **L9** (1.5 mol. equiv.), DIPEA (1.5 mol. equiv.), sodium triacetoxyborohydride (2 mol. equiv.), DCM, 20-25 °C, 2 h; d) *p*-toluenesulfonic acid TsOH (1.3 mol. equiv.), MeOH, 25 °C, 1 h; e) POCl₃ (1.2 mol. equiv.), TEA (1.2 mol. equiv.), toluene, 75 °C, 3 h; f) 3-chloro-4-((3-fluorobenzyl)oxy)aniline **L4** (1 mol. equiv.), propan-2-ol, 70 °C, 4 h; g) NaOH (30% aqueous solution, 5.1 mol. equiv.) TsOH (2.25 mol. equiv.), 40 °C, 3-4 h; water (10 vol.), RT, 36 h.

Scheme 15. Commercial process to lapatinib (**L**).

4.6. Vandetanib (Caprelsa® - AstraZeneca)

Vandetanib (**V**) (Figure 8) is a kinase inhibitor of tumor angiogenesis and cell proliferation with the potential for use in a broad range of tumor types. Vandetanib was approved in 2011 by the US FDA to treat unresectable, locally advanced, or metastatic medullary thyroid cancer in adult patients.³⁸

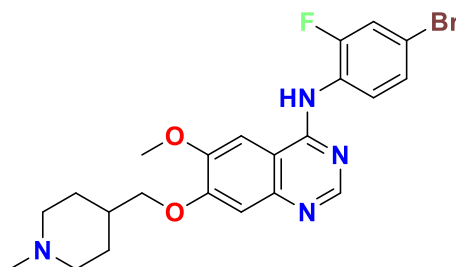
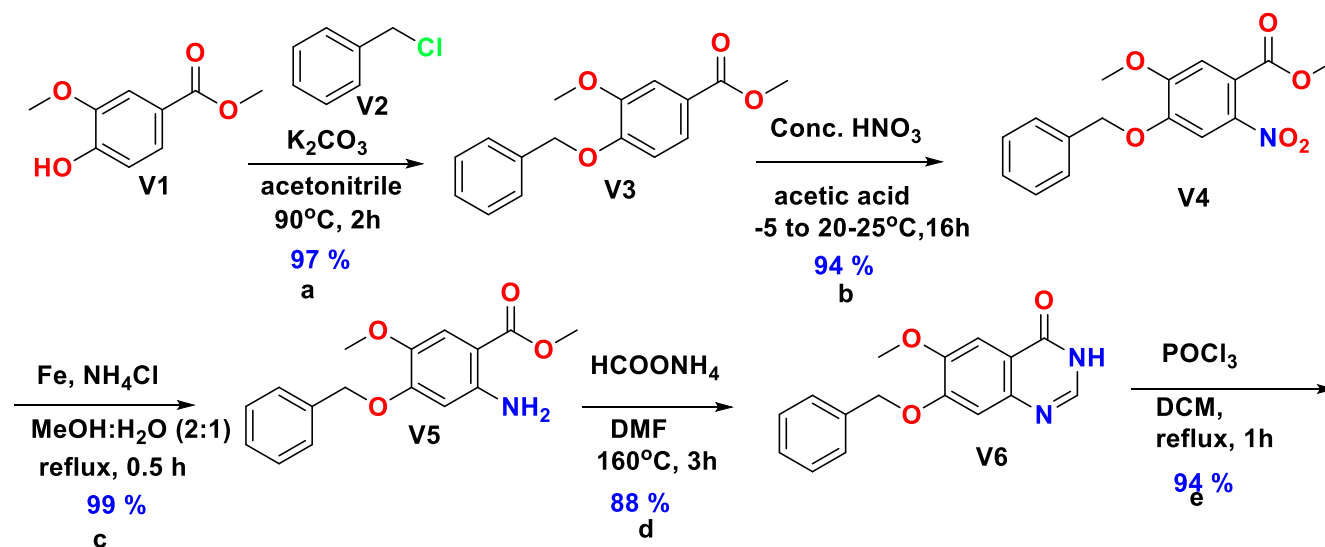
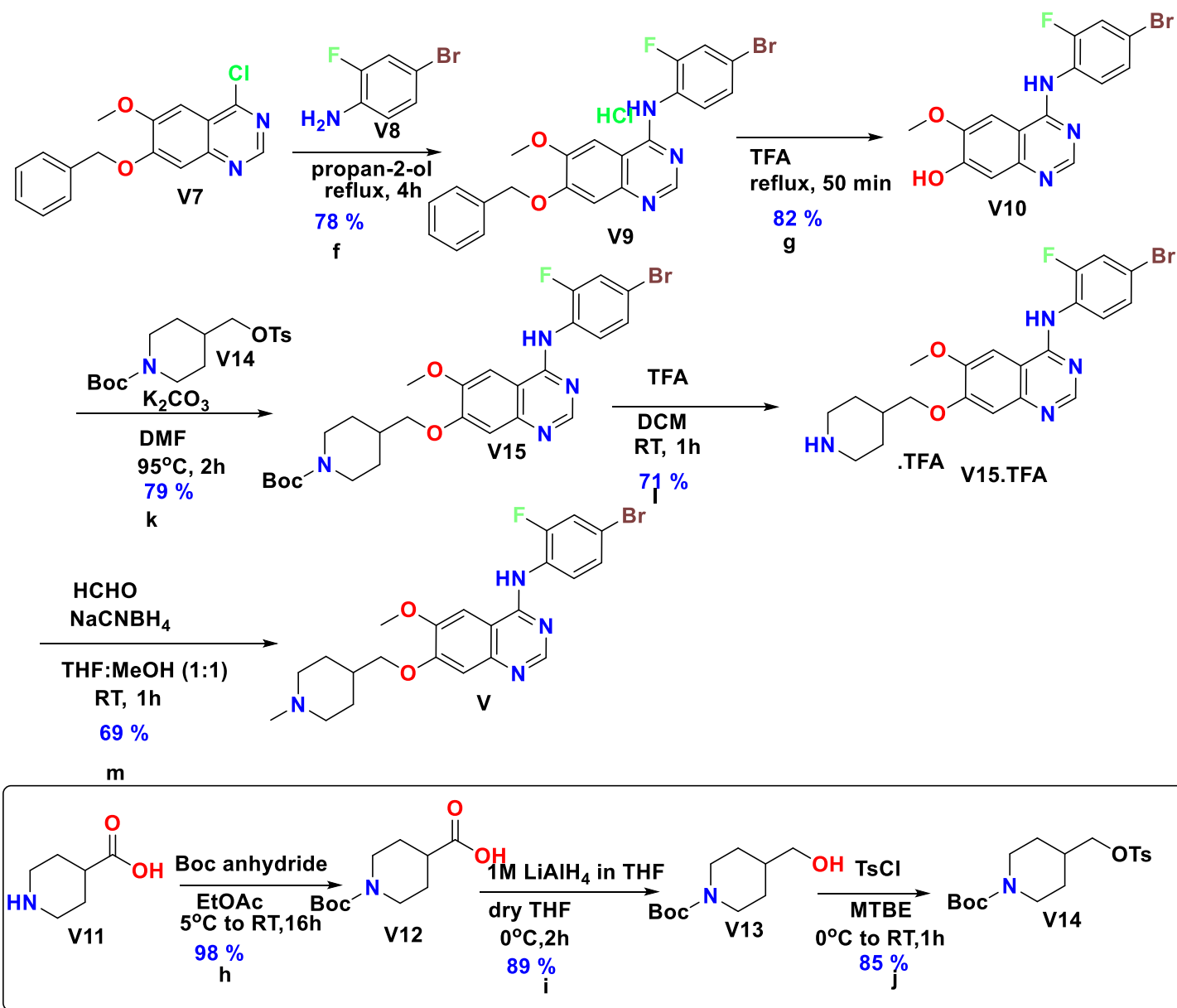


Figure 8. Chemical structure of vandetanib (**V**).

4.6.1. Synthesis of vandetanib (V). The initial literature precedence for the synthesis of vandetanib (**V**) was reported via quinazolinone intermediate **V6** starting from 3,4-dihydroxybenzoate **V1**.³⁹⁻⁴³ The hydroxyl group of **V1** was protected using benzyl chloride **V2** to afford intermediate **V3** which was nitrated using conc. nitric acid in acetic acid to form **V4**. **V4** was reduced to get methyl 2-amino-4-(benzyloxy)-5-methoxybenzoate **V5** which was cyclized to afford quinazolinone intermediate **V6**. Chlorination of **V6** yielded intermediate **V7** which was substituted with 4-bromo-2-fluoroaniline **V8** to afford **V9**. The benzyl group of **V9** was de-protected and the hydroxyl group of compound **V10** was substituted with boc-protected piperidine methyl group using *tert*-butyl 4-((tosyloxy)methyl) piperidine-1-carboxylate **V14** to afford intermediate **V15**. Boc deprotection followed by methylation of **V15** yielded vandetanib **V** (Scheme 16). In another route, quinazolin-4(3H)-one was protected with pivaloyloxymethyl chloride (POM-Cl) to afford *N*-3-POM-protected quinazoline. Subsequent course of reactions was conducted to afford **V**.⁴⁴ The synthetic strategies described above however are time-consuming and involve harsh reaction conditions. Brocklesby et al reported an alternative synthesis of **V** via a Dimroth rearrangement avoiding quinazolinone.⁴⁵



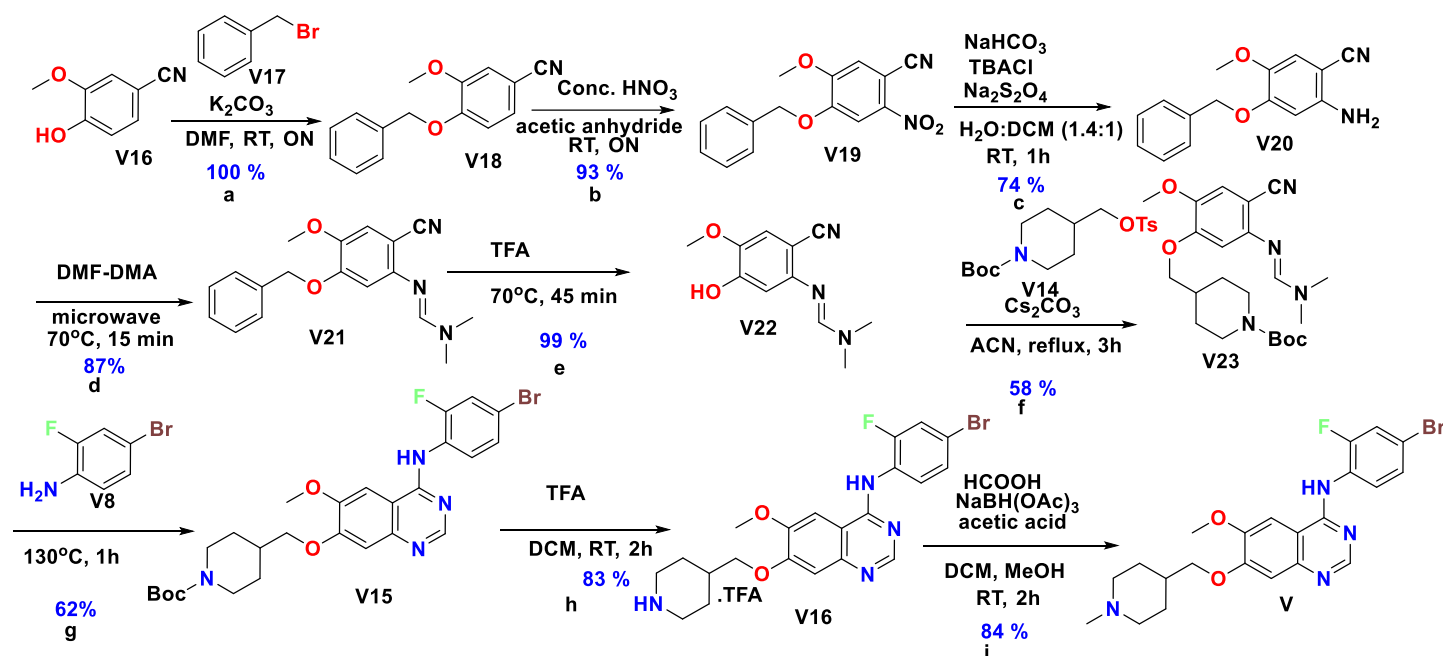


Reagents and conditions: a) (chloromethyl)benzene **V2** (1 mol. equiv.), potassium carbonate (2.5 mol. equiv.), acetonitrile, 90 °C, 2 h; b) Conc. HNO₃ (24.7 mol. equiv.), acetic acid -5 to 20-25 °C, 16 h; c) iron Fe (18.5 mol. equiv.), ammonium chloride (9.2 mol. equiv.), MeOH:H₂O (2:1), reflux, 0.5 h; d) POCl₃ (8 mol. equiv.), DCM, reflux, 1 h; e) 4-bromo-2-fluoroaniline **V8** (1.1 mol. equiv.), propan-2-ol, reflux, 4 h; g) TFA (5.1 mol. equiv.), reflux, 50 min; h) Boc anhydride (1 mol. equiv.), ethyl acetate, 5 °C to RT, 16 h; i) 1M LiAlH₄ in THF (0.7 mol. equiv.), dry THF, 0 °C, 2 h; j) DBU (1.5 mol. equiv.), toluene sulfonyl chloride TsCl (1.4 mol. equiv.), MTBE, 0 °C to RT, 1h; k) tert-butyl 4-((tosyloxy)methyl)piperidine-1-carboxylate **V14** (1.14 mol. equiv.), potassium carbonate (2 mol. equiv.), DMF, 95 °C, 2 h; l) TFA (33.3 mol. equiv.), DCM, RT, 1 h; m) 37% aqueous formaldehyde (2 mol. equiv.), sodium cyanoborohydride (1.2 mol. equiv.), THF:MeOH (1:1), RT, 1 h.

Scheme 16. Initial synthesis of vandetib (**V**).

The synthesis started from the inexpensive building block 4-hydroxy-3-methoxybenzonitrile **V16** (Scheme 17), which was alkylated with benzyl bromide **V17** to form intermediate **V18**. Nitration of **V18** under

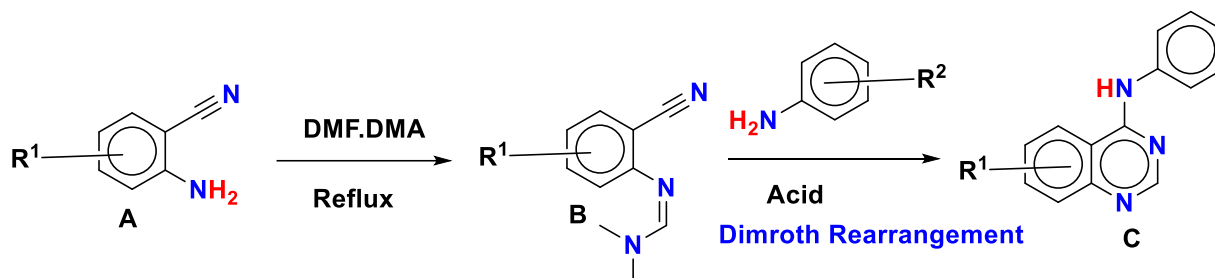
mild conditions afforded **V19** in good yield. Selective reduction was done using sodium dithionite to afford **V20**. Compound **V20** was reacted with large excess of DMF-DMA to aid solubility and formation of the formamidine **V21**. Microwave irradiation for 30 minutes at 90 °C afforded **V21** in 95 % yield while conventional heating at the same temperature provided **V21** in a reduced yield of 58% despite extending the reaction time to 120 minutes. TFA-mediated debenzoylation of **V21** yielded **V22**. Alkylation of **V22** using *tert*-butyl-4(tosyloxy)methyl)piperidine-1-carboxylate **V14**, which was synthesized by the method afforded **V23**. The key Dimroth rearrangement step was conducted in the presence of 4-bromo-3-fluoroaniline **V8** and acetic acid with microwave heating at 130 °C for 45 minutes to afford **V15**. The penultimate step in the synthesis of **V** was the Boc deprotection of piperidine, which was done as per above procedure.



Reagents and conditions: a) (bromomethyl) benzene **V26** (1.1 mol. equiv.), potassium carbonate (2.5 mol. equiv.), DMF, RT, ON; b) Conc. HNO₃ (4.4 mol. equiv.), acetic anhydride RT, ON; c) NaHCO₃ (0.2 mol. equiv.), tetra-butyl ammonium chloride TBACl (0.66 mol. equiv.), Sodium dithionite (2.3 mol. equiv.), DCM, water, rt, 2 h; d) DMF.DMA (1.2 mol. Equiv.), microwave (max. power 400 W), 70 °C, 45 min; e) TFA, 70 °C, 45 min; f) *tert*-butyl 4-((tosyloxy)methyl)piperidine-1-carboxylate **V14** (1.1 mol. equiv.), cesium carbonate (2.5 mol. equiv.), ACN, reflux, 3 h; g) 4-bromo-2-fluoroaniline **V8** (1.1 mol. equiv.), acetic acid 130 °C, 1 h; h) TFA (12.5 mol. equiv.), DCM, RT, 2 h; i) acetic acid (1.2 mol. equiv.), sodium triacetoxyborohydride (1.4 mol. equiv.), formic acid (1.3 mol. equiv.), MeOH:DCM (2:1), RT, 2 h.

Scheme 17. Synthesis of vandetib (**V**).

The quinazoline motif has been further explored for more potent anticancer agents and sapitinib **S** (AZD8931) is being studied as a more potent ATP competitive inhibitor of EGFR and erbB2. Compared to gefitinib or erbB2 inhibitors, AZD8931 was a much more potent inhibitor of EGF-driven cellular proliferation in multiple tumour cell lines⁴⁶ William et al. reported an industrial scale synthesis using Dimroth rearrangement route as has been shown to be utilized to some of commercially available drug of this series.⁴⁷ All in all, Dimroth Rearrangement is the most versatile method to synthesize amino quinazoline derivatives. A general synthetic approach for isolation of such compounds is depicted in Scheme 18.



Scheme 18. General approach for synthesis of amino quinazoline.

Therefore, it is worth to mention general mechanism of Dimroth Rearrangement for such derivatives which is given in Figure 9.

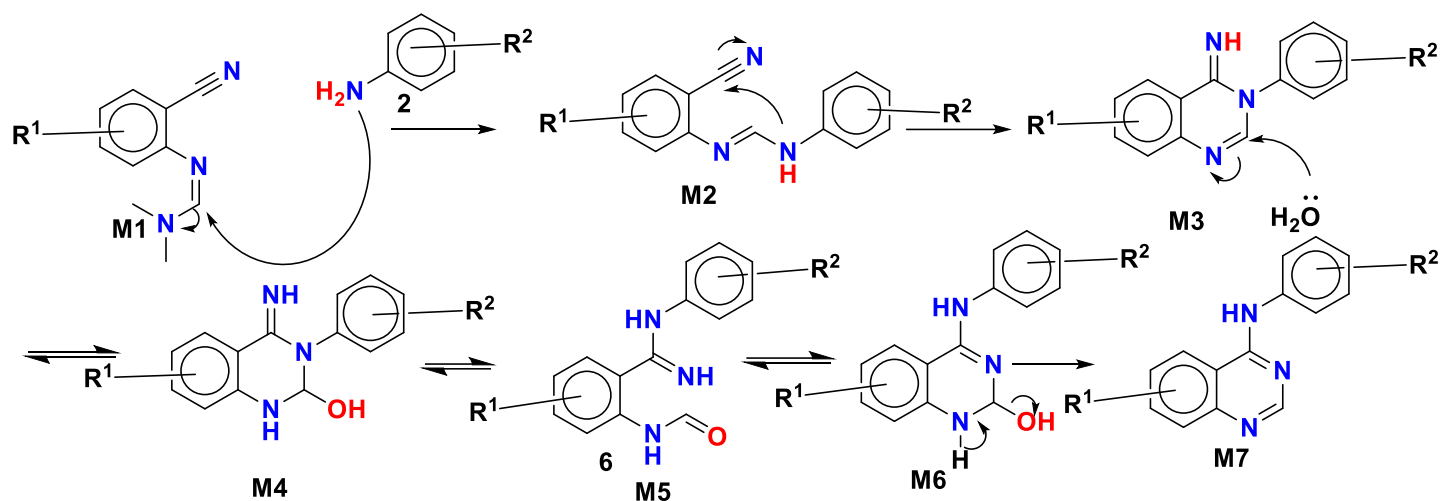


Figure 9. Mechanism of Dimroth Rearrangement.

4.7. Future perspective of quinazoline based heterocyclic compounds

Since quinazoline motif is highly prevalent in pharmaceutical compounds specifically anti-cancer drugs, novel scaffolds are being synthesized and investigated as biologically active compounds. This motif has broad scope for synthesis of novel compounds due to diverse reactive positions for derivatization. Piperazine based quinazoline derivatives have been reported recently, which are being investigated preventing neurodegenerative diseases such as Parkinson's disease (PD).⁴⁸ V. K. Sharma et al recently reported efficient and versatile one-pot sequential synthesis of quinazolin-8-ol derivatives employing heterogeneous catalyst for S-M coupling.⁴⁹

5. Conclusions

This review of literature summarizes several synthetic methods for industrial and small-scale quinazoline based anti-cancer drugs. The use of quinazolines for the treatment of various diseases has motivated researchers to improve synthetic approaches and overcome challenges of industrial-scale synthesis. There is a variety of strategies developed for synthesis of such drugs, but the Dimroth rearrangement dominates the

synthetic chemistry toolbox to produce aminoquinazoline derivatives specifically for industrial scale. The reported syntheses of quinazoline based anti-cancer drugs majorly illustrates the efforts toward efficient and cost-effective approaches which may be utilized for further development or synthesis of novel biologically active derivatives.

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