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ORIGINAL PAPER

Improved protocol for synthesis of *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine (gefitinib)

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Abstract
An improved three-step process for the synthesis of gefitinib from readily available starting material is discussed in this protocol. The protocol is based on the synthesis, isolation, characterization of novel intermediates and their application in the alkylation step for the synthesis of gefitinib. Excellent results were achieved over the conventional synthetic methodologies. Isolation of these intermediates were effective in replacing high boiling solvent with low boiling solvent(s) but also in eliminating base from the reaction. These conditions led to effective elimination of all the prior art reported impurities. This high-yielding process is cost-effective with isolable and stable intermediates. These intermediates were characterized using NMR, mass spectroscopy, DSC and XRPD analyses.

Keywords Gefitinib · Iressa · Alkali metal salts · *O*-Alkylation · Novel intermediate · Improved protocol

Introduction

In the last decade considerable achievements in cancer chemotherapy have been attained but many of the drugs used in the chemotherapy have a narrow therapeutic index. Importantly, the responses produced with these drugs are often palliative and unpredictable (http://chemoth.com). In contrast, targeted therapy works specifically against the cancer cells and signalling pathways are more specific and have limited non-specific toxicities (Abouzid and Showman 2008; Bridges 2001; Barker and Andrew 1993; Pandey et al. 2002). Thus, tyrosine kinase inhibitors are target-oriented drugs, as they play an important part in the modulation of growth factor signalling (Schnur and Arnold 1998).

Numerous clinically proven tyrosine kinase inhibitors have been studied in the past decades with aminoquinazoline as a core moiety (William et al. 2017; Ciardiello et al. 2005; Wang et al. 2006). The familiar molecules are gefitinib (brand name: Iressa), erlotinib (brand name: Tarceva®), lapatinib (brand name: Tykerb® and Tyverb®), and dacomitinib (PF-00299804, an experimental drug under development by Pfizer) as shown in Fig. 1.

Gefitinib **1** (Gibson 1998), chemically *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine was first reported with the Patent no. US5770599. Gefitinib is the first selective EGFR (epidermal growth factor receptor)-targeting drug to be registered as an anti-cancer drug in Japan, Australia and the USA for the third-line treatment of chemoresistant NSCLC (non-small cell lung carcinoma) patients (Ciardiello et al. 2005) with a dose of 250 mg (Gefitinib-fda label 2003).

As per the prior art methods (Barker and Brown 1996; Schnur and Arnold 1998), the sequential steps for the synthesis of gefitinib involves regioselective demethylation of 6,7-dimethoxy-3,4-dihydroquinazolin-4-one (using reagents methanesulphonic acid and L-methionine), acylation at the sixth position (using excess acetic anhydride), and chlorination (using thionyl chloride/phosphoryl chloride) to obtain chloroquinazoline derivative. The chloroquinazoline

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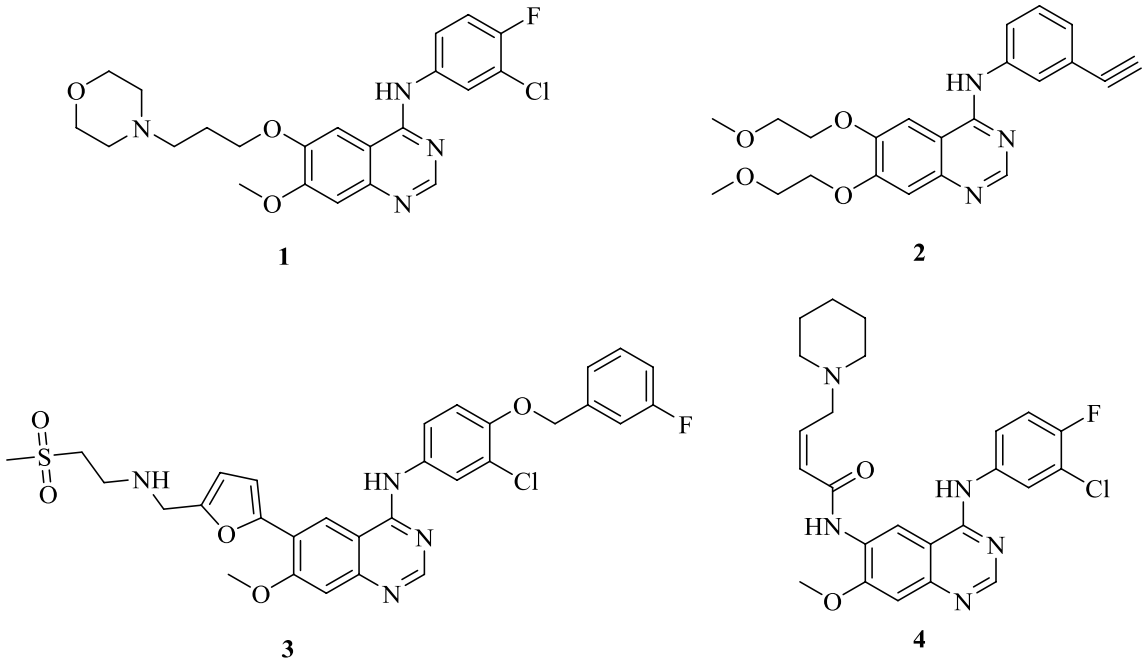


Fig. 1 Formula of gefitinib **1**, erlotinib **2**, lapatinib **3**, and dacomitinib **4**

intermediate is coupled with 3-chloro-4-fluoroaniline to get the so-called "acetoxy hydrochloride intermediate" (**5**), which is then deacylated with ammonium hydroxide to get the penultimate intermediate 4-(3′-chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin and finally alkylated with 4-(3-chloropropyl)morpholine in high boiling solvent DMF and potassium carbonate as base to afford gefitinib, as represented in Scheme 1.

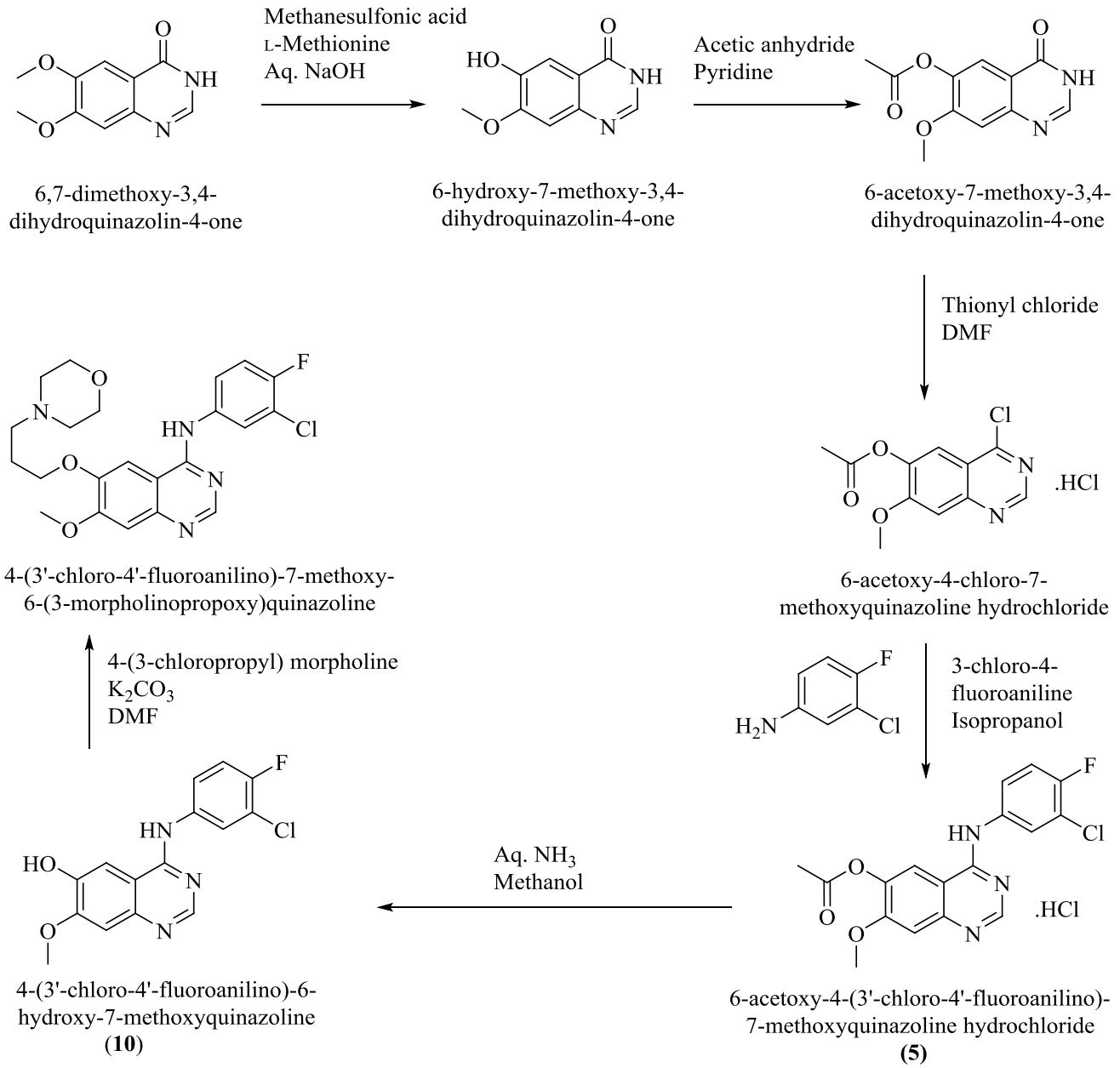
Impurities like 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-hydroxyquinazoline **7** (regioselective impurity), *N*-(3-chloro-4-fluorophenylamino)-6,7-dimethoxyquinazoline **6**, 4-(3,4-dichlorophenylamino)-6,7-dimethoxyquinazoline **8**, *N*-alkylated gefitinib **9** and 4-(3′-chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin **10**, as per Scheme 2, are reported in the prior art. Removal of these impurities is either very difficult or requires extensive purification techniques such as column chromatography (Gibson 1998). In addition to these impurities, use of corrosive reagents, such as methane sulphonic acid, acetic anhydride and thionyl chloride, and use of high boiling solvent, such as DMF in the alkylation step, are other disadvantages which limit the process for commercial manufacture.

Using different starting materials (such as isovanillin), various other schemes have been reported in the prior art (Feng et al. 2007). Hence, the reported processes are not appropriate for the effective elimination of these impurities.

To overcome these impurities and yield problem, there is a need to develop a simple, convenient, economic and commercially viable process. Thus, we have developed an improved protocol for the synthesis of *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine, gefitinib, by isolating the alkali metal salts **11**–**13** of the phenolate anion of structure **10**. Use of optimal phenolate salts (from among Li^+, Na^+ and K^+: Scheme 3) overcame all of these problems, giving a highly robust process for gefitinib **1** synthesis with high overall yield.

Results and discussion

The initial studies were based on the isolation and stability of all the alkali metal salts of compounds **5** and **10** and their impact on the *O*-alkylation reaction. The formation of the compounds **11**, **12** and **13** not only helped in eliminating the high boiling solvent (DMF) and potassium carbonate from the process, but also the by-product could be easily removed by water washing. The synthesis of these salts was screened based on various parameters, starting from the quantity of alkali metal hydroxide, reaction solvent and reaction time to reaction temperature. Except for the normality, no other parameters were effective in the selection of alkali metal hydroxide. Normality ranging from 1 N to 4 N was studied, but 2 N was finalized based on the content of alkali metal, colour, yield and impurity profile of the final compound. In the prior art process,

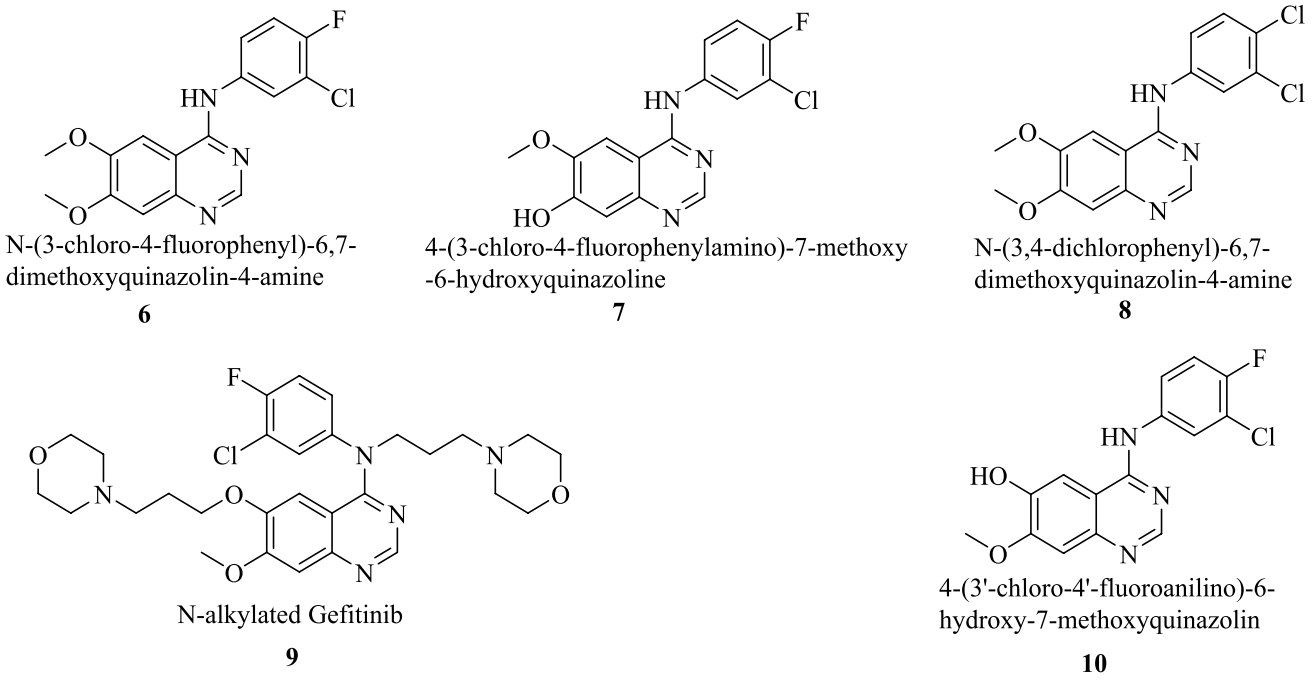


Scheme 1 Prior art scheme

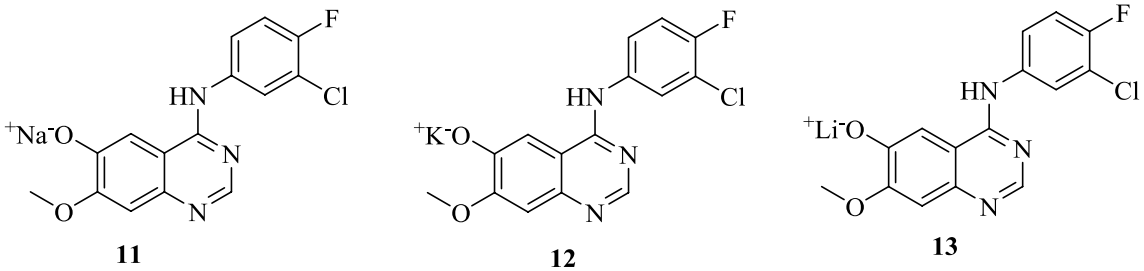
excess quantity of potassium carbonate was used which led to the formation of various impurities, including the *N*-alkylated gefitinib **9**. In the developed protocol, since the alkali metal content was the limiting factor to prevent impurity formation (absence of *N*-alkylated impurity), a 2 N solution was finalized to give the best results. Sodium content less than the required value (i.e. 6.70%) resulted in incomplete reaction.

Next, to select the alkali metal hydroxide was a big challenge, since each compound (**11**, **12** and **13**) was equally effective in the *O*-alkylation reaction. Surprisingly, compound **11** showed better crystalline nature and colour of the isolated product; thus, sodium hydroxide was preferred over others.

To replace the high boiling solvent (DMF), almost all solvents were screened starting from low boiling solvents such as dichloromethane, methanol, acetone, *n*-hexane, ethyl acetate, water and toluene to high boiling solvents such as DMSO, DMF, *N*-methyl pyrrolidine, dimethyl acetamide and so on, but the best result (shorter reaction time, yield and quality) was achieved with isopropanol and acetonitrile. Since acetonitrile has limited applicability in commercial production due to toxic by-products, isopropanol was selected as the solvent of choice.



Scheme 2 Process-related impurities of gefitinib



Scheme 3 Sodium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate (**11**), potassium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate (**12**) and lithium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate (**13**)

As per the above process, the synthesis of gefitinib was completed in three steps, starting from 4-(3′-chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin **10** or 6-acetoxy-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline hydrochloride, **5.** These materials are converted into the corresponding alkali metal salts of formula **11**, **12** and **13**, which are isolated as stable intermediates with HPLC purity more than 99.70%. Alkali metal salts of formula **11, 12** and **13** are alkylated with 4-(3-chloropropyl) morpholine in isopropanol without using any reagent to get *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine (gefitinib, **1**) of high purity. The yield in every step is quantitative. The entire protocol is depicted in Scheme 4.

Purification of several phenolic compounds by preparing their corresponding alkali metal salts is a common technique (Armarego and Chai 2012), though these intermediates are neither reported nor isolated in their pure form. Our study is first to report a multigram synthesis in a highly efficient way. The yield of the intermediates obtained from each step was nearly equivalent to the theoretical yield and used for further reaction without purification. Even the yields obtained after the *O*-alkylation reaction were excellent as compared to the prior art process, which in turn makes the process commercially viable.

The reported process of Kang et al. to overcome the formation of the *N*-alkylated impurity has a number of disadvantages: on the commercial scale, the working temperature for the formation of the transient intermediate is around − 10 °C which adds to the cost; also for the transient intermediate, expensive reagents such as iodotrimethylsilane and 4-dimethylaminopyridine are

used, and these reagents are moisture sensitive, making it difficult to handle at the commercial scale; again a large volume of high boiling solvent DMF is used in the process with excess amount of base (potassium carbonate, 3.5 mol equivalent with respect to compound **10**), which is difficult to handle in plants at such a high temperature (80 °C). The reported base is hygroscopic and at such an elevated temperature a number of degradation impurities are formed. Elimination of these impurities is very difficult and column purification is required, resulting in yield loss. Regardless of these impurities, this paper has not indicated any process for the removal of unreacted compound **10**. The HPLC purity disclosed is 99.21% and it is not disclosed on the related substances. This also does not relate to the fact that whether the compound complies as per ICH or not, whereas in our process we do not use potassium carbonate and DMF; thus, all these disadvantages are taken care of and an overall purity of 99.91% is attained (by HPLC, *N*-alkylated impurity not detected). The material synthesized by our protocol complies with the ICH guidelines and is well accepted by regulatory bodies.

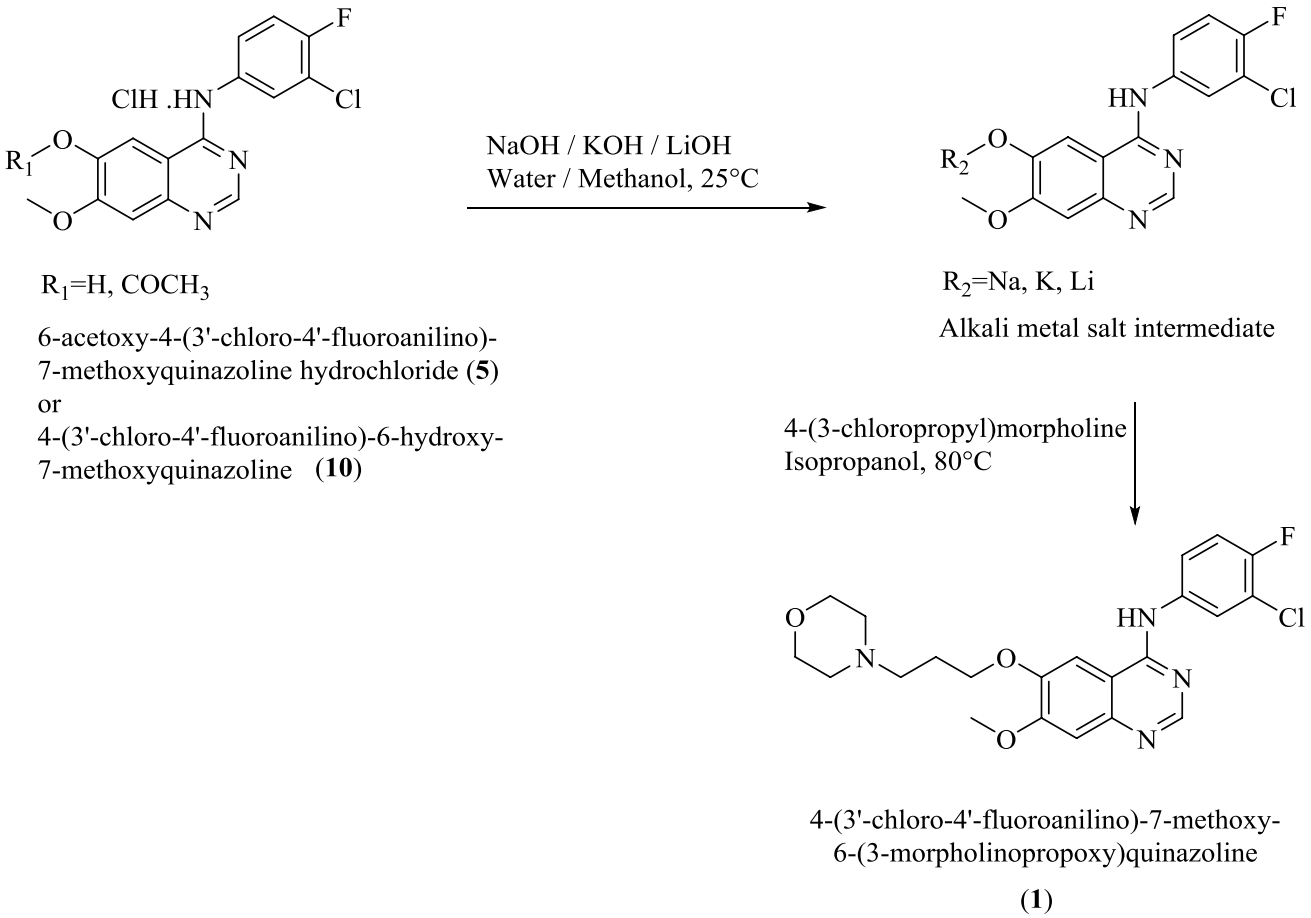
Conclusion

The developed protocol is greatly effective in producing highly pure gefitinib with isolable and stable intermediates. All the intermediates were stable and easy to handle from milligram to multigram scale. *O*-Alkylation reaction of sodium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate with 4-(3-chloropropyl) morpholine was immaculate, efficient and economically viable. Elimination of high boiling solvent (DMF) and base from the process is highly advantageous in terms of scale-up and yield.

Experimental segment

General

Starting materials 6-acetoxy-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline hydrochloride **5**, 4-(3′-chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin and

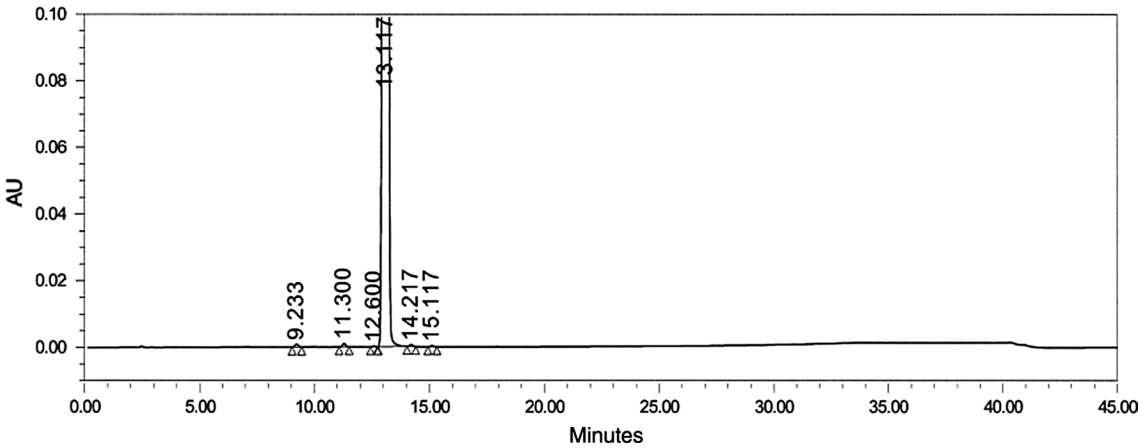


Scheme 4 Synthesis of Gefitinib using alkali metals salt(s) of compound **5** or compound **10**

4-(3-chloropropyl) morpholine were procured from intermediate manufacturing companies in China (Beijing Lunarsun Pharmaceutical Co. Ltd., Hefei Home Sunshine Pharmaceutical Technology Co., Ltd.) and used as such without purification. All the general chemicals were brought from Merck Sdn Bhd., Malaysia. Solvents were from Polyscientific Enterprise Sdn. Bhd. Malaysia. IR spectra were recorded with KBr pellets using Shimadzu FTIR Tracer-100 spectrophotometer, ^{1}H NMR and ^{13}C NMR were recorded in solvents like $CDCl_3$ and DMSO-d_6 at 300 and 75 MHz, respectively, using Bruker instrument. All the chemical shift values are reported in δ units downfield from TMS as internal standard. Differential scanning calorimetry (DSC) was performed using TA Instrument model DSCQ20. X-Ray diffraction pattern (XRD) analysis was performed using PANalytical instrument model Empyrean. Melting points were recorded using BUCHI melting point apparatus, model M-565.

HPLC details

The HPLC details are: X-Bridge phenyl column 250 × 4.6 (5 µ), wavelength = 250 nm, column temperature = 60 °C, flow rate 1.0 ml/min [mobile phase (70:30) mobile phase A: 0.02 M potassium dihydrogen phosphate to 1% triethylamine, pH 6.5 with OPA, mobile phase B: acetonitrile]. The typical chromatographic pattern is shown below:



The result was analysed weight/weight (w/w) with respect to reference standard and all the total impurities were 0.09%, complying with the ICH guidelines.

The HPLC method reported in Kang et al. (2017) has certain limitations in terms of resolution. Since the method is isocratic, there is interference from the blank for polar impurities. Also, the peak symmetry is not appropriate, thus separation of starting material, intermediates, impurities and by-products is difficult, as well as non-elution of non-polar impurities. The developed analytical method is simple, selective, specific, precise, accurate and robust. Also, the method is gradient, so there is no interference from blank for polar impurities. The method is linear from LOQ (limit of quantification) to 200% of specification [correlation coefficient is greater than 0.999]. The LOQ (i.e. sensitivity of detection) for the developed method is 0.01%. The developed method was validated as per ICH guidelines with respect to precision, accuracy, linearity, robustness, specificity and system suitability.

Preparation of sodium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate (11)

6-Acetoxy-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline hydrochloride, **5** (25.0 g, 0.0627 mol), was added to a solution of sodium hydroxide (10.04 g, 0.251 mol) in methanol (500 ml) at 25–30 °C and stirred at the same temperature for 60 min. After reaction completion (by TLC as well as HPLC), the reaction mass was evaporated to dryness, and water (125 ml) was added to the residue and stirred for 60 min. The solid was filtered and washed with water (12.5 ml), followed by toluene wash (50 ml). The wet solid was dried under vacuum, not less than 660 mmHg, for 4 h at 60–65 °C to get the title compound **11** (21.4 g, 85.6% with respect to compound **5**).

4-(3′-Chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin, **10** (25.0 g, 0.0781 mol), was added to 2 N aqueous sodium hydroxide solution (625 ml) at 25–30 °C and stirred at the same temperature for 60 min. The obtained solid was filtered and washed with water (12.5 ml), followed by toluene wash (50 ml). The wet solid was dried under vacuum, not less than 660 mmHg, for 4 h at 60–65 °C to get the title compound **11** (27.4 g, 109% with respect to compound **10**). *m/z* 320.05 ES + mode. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 6.87 (s, 1H), 7.14 (s, 1H), 7.32 (t, 1H), 7.98(m, 1H), 8.17(s, 1H), 8.37(m, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.12, 101.67, 105.28, 112.71, 116.41, 118.70, 120.84, 121.76, 138.81, 141.11, 146.83, 150.59, 153.28, 158.99 and 161.05 ppm. The X-ray powder diffractogram peaks were at 8.17, 15.42, 16.87, 18.68, 21.10,

22.67, 24.66, 25.57, 27.32 and 28.16 ± 0.2 [°theta] and DSC endotherms at 164.8 and 167.5 °C. A sharp melting point was not observed, but solid discoloration with decomposition of the compound was observed within the range of 196–223 °C. Sodium content by the titration method was 6.70% (theoretical 6.73%, with respect to compound **11**).

Preparation of potassium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate (12)

4-(3′-Chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin, **10** (10.0 g, 0.0312 mol), was added to 2 N aqueous potassium hydroxide solution (250 ml) at 25–30 °C and stirred at the same temperature for 60 min. The obtained solid was filtered and washed with water (12.5 ml), followed by toluene wash (20 ml). The wet solid was dried under vacuum, not less than 660 mmHg for 4 h at 60–65 °C, to get the title compound **12** (13.5 g, 135% with respect to compound **10**). X-Ray powder diffractogram peaks were at 11.13, 12.34, 12.88, 16.08, 17.23, 20.86, 21.70, 22.67, 23.27, 24.30, 24.54, 25.51, 27.14, 28.34, 29.61, 31.36, 32.39, 34.32, 35.83 and 36.92 ± 0.2 [°theta]. A sharp melting point was not observed, but solid discoloration with decomposition of compound was observed within the range of 147.7–171.1 °C.

Preparation of lithium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate (13)

4-(3′-Chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin **10** (10.0 g, 0.0312 mol) was added to 3 N aqueous lithium hydroxide solution (250 ml) at 25–30 °C and stirred at the same temperature for 60 min. The obtained solid was filtered and washed with water (12.5 ml), followed by toluene wash (20 ml). The wet solid was dried under vacuum, not less than 660 mmHg at 60–65 °C for 4 h, to get the title compound **13** (10.25 g, 102.5% with respect to compound **10**). X-Ray powder diffractogram peaks were at 10.71, 11.80, 14.88, 17.41, 18.38, 18.74, 23.57, 24.36, 25.02, 25.45, 26.41, 27.32, 28.41, 29.55, 30.22, 32.39, 35.96 and 36.98 ± 0.2 [°theta] and DSC endotherms at 224.2 °C. A sharp melting point was not observed, but solid discoloration with decomposition of the compound was observed within the range of 222.4–239.8 °C.

Preparation of *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine (gefitinib, 1)

4-(3-Chloropropyl) morpholine (15.44 g, 0.0943 mol) was added to a suspension of sodium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate **11** (21.5 g, 0.0629 mol) in isopropanol (430 ml), the resulting mass was stirred at 80–85 °C and progress of the reaction was monitored by HPLC. The reaction was completed in 2–3 h, isopropanol was distilled, water (110.0 ml) was added to the resulting residue, stirred for 30 min, the solid filtered, washed with water (50.0 ml) and dried under vacuum for 30 min. The wet solid was dissolved in dilute aq. HCl solution (1 N, 215 ml) at 80–85 °C, to get a clear solution which was treated with activated charcoal and filtered through a celite bed. The bed was washed with dilute aq HCl solution (1 N, 50 ml) and the pH of the clear filtrate adjusted to 8–9 using 2 N sodium hydroxide solution (145–160 ml) at 80–85 °C. The resulting heterogenous mass was cooled to 25–30 °C and stirred for 30 min. The solid was filtered, washed with water (50 ml) and dried under vacuum at 60–65 °C. The obtained crude *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine (gefitinib **1**) was crystallized from isopropanol by the following procedure: the crude compound was dissolved in 800 ml isopropanol, the suspension was heated to reflux to get a clear solution, the clear solution was filtered through a micron filter, the clear filtrate was cooled to 0–10 °C and stirred for 3 h, and the crystallized solid was filtered and washed with chilled isopropanol, 25 ml, and dried under a vacuum not less than 660 mmHg at 70–75 °C for 6 h to get 23.4 g pure *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine (gefitinib **1**) as pale yellow-coloured crystals. The compound was anhydrous and crystalline in nature. HPLC purity was 99.90%. Melting point: 193.3–194.0 °C. DSC endotherm: at 195.4 °C. Moisture content, 0.10%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.966-2.007 (t, 2H), 2.289–2.498 (m, 6H), 3.579 (s, 4H), 3.931 (s, 3H), 4.143 (s, 2H), 7.178 (s, 1H), 7.394–7.455 (t, 1H), 7.773 (s, 2H), 8.099–8.129 (m, 1H), 8.489 (s, 1H), 9.531 (s, 1H) ppm. ^{13}C NMR (300 MHz, DMSO-d_6): δ 26.06, 53.62, 55.16, 56.04, 66.37, 67.33, 102.69, 107.44, 108.98, 116.51, 116.79, 118.84, 119.04, 122.44, 123.65, 137.00, 147.14, 148.53, 151.72, 152.77, 154.69 and 156.19 ppm. The principal IR peaks were at 3398, 2958, 2808, 1624, 1577, 1531, 1500, 1469, 1427, 1388, 1265, 1246, 1219, 1107, 1026, 1010, 952, 929, 910, 844, 775 and 682 cm^{-1}. X-Ray powder diffractogram peaks were at 7.149, 9.384, 11.317, 12.283, 13.914, 14.276, 14.518, 15.363, 15.967, 16.390, 17.659, 18.746, 19.350, 20.739, 21.403, 22.370, 22.672, 23.336, 24.001, 24.363, 25.148, 26.417, 26.779, 27.383, 28.651, 29.255, 29.739, 30.705, 32.094, 33.000, 33.906, 34.269, 34.933, 35.960, 37.711, 38.074, 38.738 and 39.523 [°theta]. Elemental analysis: C, 59.13%; H, 5.41%; N, 12.54% (calculated), C, 59.44%; H, 5.09%; N, 12.21% (found).

The above process was repeated at the scale of 100.0 g (input quantity) and the details obtained are given below.

4-(3′-Chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazolin **10** (100.0 g, 0.312 mol) was added

to 2 N aqueous sodium hydroxide solution (2500 ml) at 25–30 °C and stirred at the same temperature for 60 min. The obtained solid was filtered and washed with water (50 ml), followed by toluene wash (200 ml). The wet solid was dried under vacuum not less than 660 mmHg for 6 h at 60–65 °C to get the title compound of formula **11** (116.0 g, 116% with respect to compound **10**).

4-(3-Chloropropyl)morpholine (71.83 g, 0.438 mol) was added to a suspension of sodium-4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-olate **11** (100 g, 0.292 mol) in isopropanol (2000 ml), the resulting mass was stirred at 80–85 °C and the progress of the reaction was monitored by HPLC. The reaction was terminated in 3 h after completion, isopropanol was distilled and water (510 ml) was added to the residue and stirred for 30 min. The solid was filtered, washed with water (230 ml) and dried under a vacuum for 30 min. The wet solid was dissolved in dilute aq. HCl solution (1 N, 1000 ml) at 80–85 °C, treated the clear solution with activated charcoal and filtered through a celite bed. The bed was washed with dilute aq. HCl solution (1 N, 200 ml) and the pH of the clear filtrate adjusted to 8–9 using 2 N sodium hydroxide solution (725–80.0 ml) at 80–85 °C. The resulting heterogenous mass was cooled to 25–30 °C, stirred for 30 min, filtered, washed with water (230 ml) and dried under vacuum, not less than 660 mmHg for 6 h at 60–65 °C. The crude compound *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine was crystallized using isopropanol by the following procedure: the crude compound was dissolved in 3900 ml isopropanol, the suspension heated up to reflux to achieve a clear solution, the clear solution was filtered through a micron filter, the clear filtrate was cooled to 0–10 °C and stirred for 3 h, and the solid was filtered and washed with chilled isopropanol, 115 ml, and dried under vacuum not less than 660 mmHg at 70–75 °C for 6 h, to get the 108.8 g pure *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine (gefitinib **1**) as pale yellow-coloured crystals. The compound was anhydrous and crystalline in nature. HPLC purity was 99.92%. The overall yield of the *O*-alkylation step is 83.72% on theoretical basis.

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