Novel preparation of gefitinib

Youguang Zheng, Mingdong Li, Shaoning Zhang and Min Ji*

School of Chemistry & Chemical Engineering, Southeast University, Nanjing 210096, P. R. China

A new synthesis of the anticancer drug gefitinib is described starting from methyl 3-hydroxy-4-methoxybenzoate. The sequence involves alkylation of the starting material, followed by nitration, reduction, cyclisation, chlorination and amination reactions. This new method has six steps, uses a much cheaper starting material and has higher yields than other methods. It is suitable for industrial production.

Keywords: epidermal growth factor, protein tyrosine kinase, anticancer, gefitinib, synthesis

The epidermal growth factor receptor (EGFR) protein tyrosine kinase (PTK) is an epithelial cell membrane receptor with an intracellular tyrosine kinase component.[1,2] Many human cancers including breast cancer and lung cancer arise from epithelial tissues and overexpress the epidermal growth factor receptor (EGFR). Blockade of the intracellular domain of the epidermal growth factor receptor (EGFR) is one strategy that has been adopted to limit aberrant signaling. This was recently carried out successfully with low molecular weight tyrosine kinase inhibitors. 4-Anilinoquinazolines, exemplified by the gefitinib, have emerged as a versatile template for inhibition of EGFR. Gefitinib, which was approved by the US FDA has been launched in Japan, Australia and the USA for the treatment of non-small cell lung cancer (NSCLC) patients.[3-5]

Several methods for the synthesis of gefitinib have been reported. The first route started with regioselective demethylation of 6,7-dimethoxy-3H-quinazolin-4-one followed by *O*-protection. The desired chloro compound was prepared using thionyl chloride or phosphoryl chloride, and coupled with 3-chloro-4-fluoroaniline. Further steps added the remaining functionalities of gefitinib. However, this method started with a costly starting material, and gave a low yield because of the regioselective demethylation reaction (Fig. 1).[6,7]

The next method for the synthesis of gefitinib starts from the 3-hydroxy-4-methoxybenzaldehyde. This was converted to the nitrile, alkylated, nitrated, reduced and cyclised, to the substituted quinazolone, which was chlorinated by thionyl chloride to afford the chloro compound. Reaction of the chloride with 3-chloro-4-fluoroaniline afforded gefitinib in eight steps overall. The costly starting material and more steps are the drawbacks of this method (Fig. 2).[8,9]

Another method for the synthesis of gefitinib is described in Fig. 3. It starts with 3,4-dimethoxybenzoic acid. After demethylation, nitration, reduction, cyclisation, chlorination and two amination stages gefitinib was obtained. The weakness of this method is the low yield arising from more steps (Fig. 3).[10]

Our novel synthesis of gefitinib starts from methyl 3-hydroxy-4-methoxybenzoate.[11] This compound is alkylated with 4-(3-chloropropyl)morpholine to afford the intermediate **2** in 86% yield. Nitration of **2** with nitric acid in acetic acid gave compound **3**, which was reduced by sodium dithionite in water to give compound **4** in satisfactory yield (90%). Cyclisation of **4** with formamidine acetate and chlorination with thionyl chloride affords compound **6**. The final product was obtained after reaction with 3-chloro-4-fluoroaniline (Fig. 4).[11]

This new method has six steps and is shorter than all methods that have been reported previously. It is also less costly because of the much cheaper starting material which is used, and it gives higher yields compared to the other methods. It is suitable for industrial production.

Experimental

All reagents were purchased from commercial sources and used without further purification. Melting points were measured in open capillaries and are uncorrected. IR spectra were determined as KBr pellets on a Thermo Nicolet 6700 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO on a Bruker Avance 500 spectrometer; chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), used as an internal standard. Mass spectra (MS) were obtained from Agilent 1100LC/MS Spectrometry Services. All compounds were routinely checked by TLC with silica gel GF-254 glass plates and viewed under UV light at 254 nm.

Methyl 4-methoxy-3-(3-morpholinopropoxy) benzoate (**2**): Potassium carbonate (138.1 g, 1.0 mol) and 4-(3-chloropropyl) morpholine (106.1 g, 0.65 mol) were added to a solution of compound

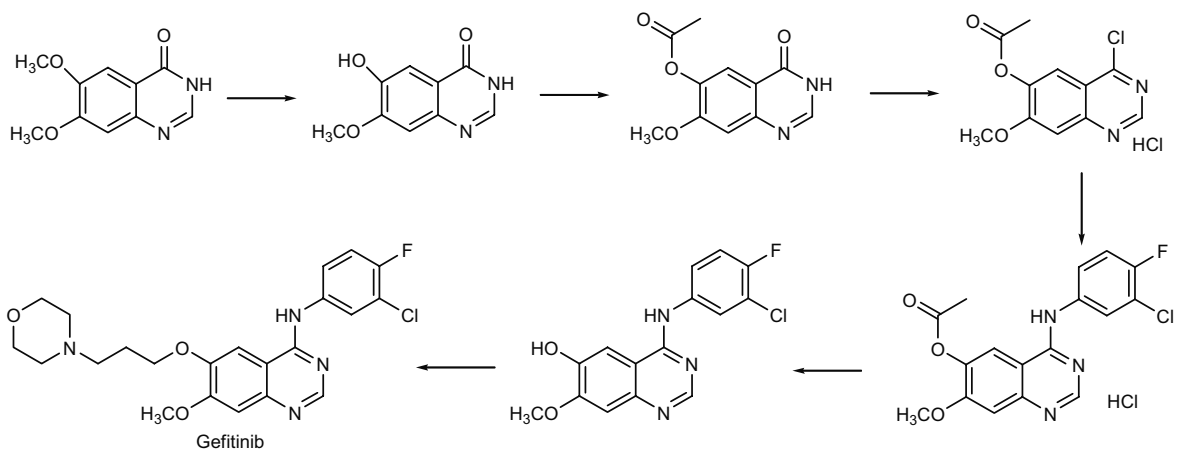

Fig. 1 Synthesis of gefitinib (route 1).

* Correspondent. E-mail: jimin@seu.edu.cn; minji888@hotmail.com

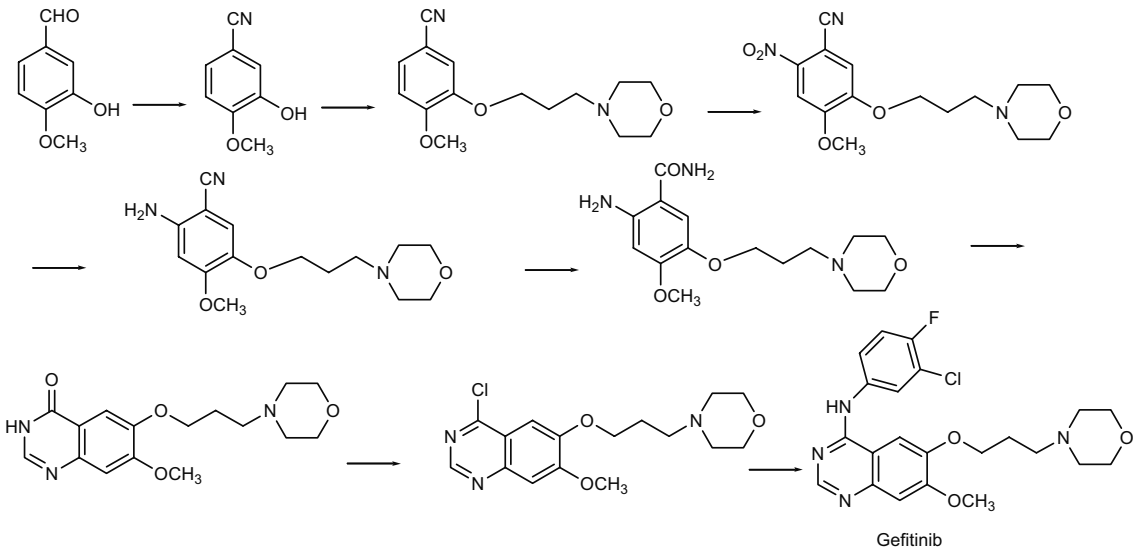

Fig. 2 Synthesis of gefitinib (route 2).

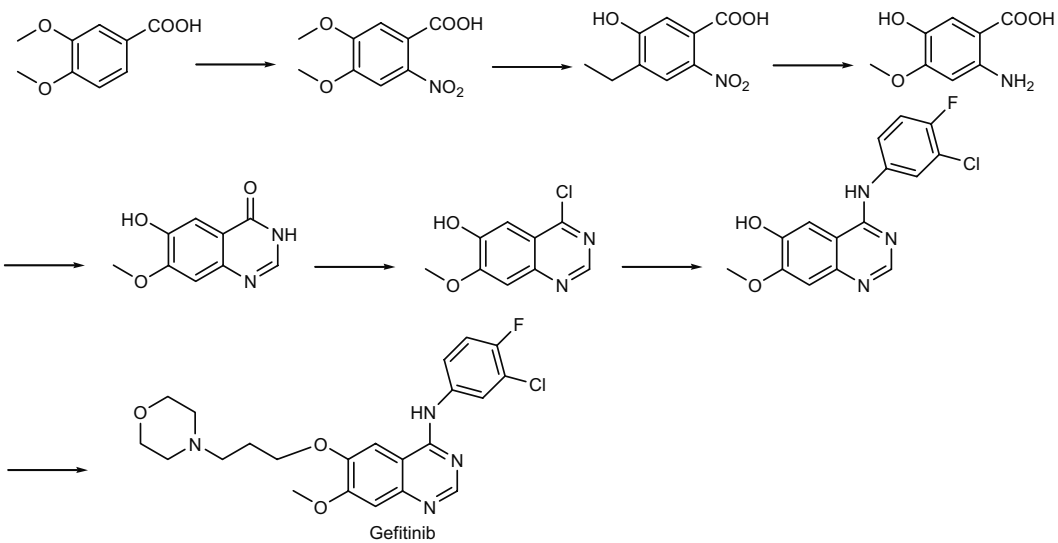

Fig. 3 Synthesis of gefitinib (route 3).

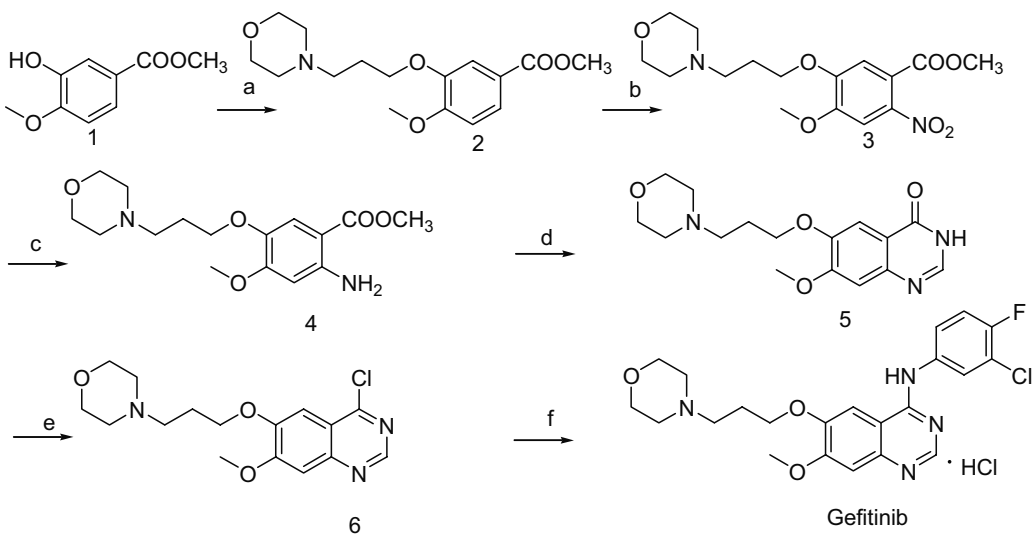

Fig. 4 Novel synthesis of gefitinib. Reagents and conditions: (a) 4-(3-chloropropyl) morpholine, potassium carbonate, DMF, 70 °C; (b) nitric acid, acetic acid, acetic anhydride, 0-5 °C; (c) sodium dithionite, concentrated hydrochloric acid, 70 °C; (d) formamidine acetate, alcohol, reflux; (e) thionyl chloride, DMF, reflux; and (f) 3-chloro-4-fluoroaniline, isopropanol, reflux.

1 (90.2 g, 0.50 mol) in DMF (300 mL), The reaction mixture was heated at 70 °C for 6 h. The mixture was cooled to room temperature, and then poured slowly into ice-water (3 L) while stirring constantly. The solid which formed was filtered off and washed with cold water. The off-white product was recrystallised from ethyl acetate (200 mL) to afford 132.2 g (86% yield) of white compound **2**; m.p. 96–98 °C. IR (cm^{-1}): 1712 (CO). ^1H NMR (DMSO-d_6) δ: 1.84–1.93 (m, 2H, $–CH_2–$), 2.35 (t, 4H, $–CH_2–CH_2–$), 2.41 (t, 2H, $–CH_2–$), 3.57 (t, 4H, $–CH_2–CH_2–$), 3.81 (s, 3H, $–CH_3$), 3.83 (s, 3H, $–CH_3$), 4.03 (t, 2H, $–CH_2–$), 7.08 (d, 1H, HAr, J = 8.52 Hz), 7.44 (d, 1H, HAr, J = 2.04 Hz), 7.59 (dd, 1H, HAr, J_1 = 2.04 Hz, J_2 = 1.92 Hz). ^{13}C NMR δ: 25.77, 51.81, 53.31, 54.69, 55.68, 66.15, 66.66, 111.31, 112.88, 121.71, 123.13, 147.70, 153.14, 165.91. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.21; H, 7.47; N, 4.52%.

Methyl 4-methoxy-5-(3-morpholinopropoxy)-2-nitrobenzoate (**3**): Nitric acid (80 ml, 65–68%) was added dropwise to a solution of compound **2** (102.9 g, 0.33 mol) in a mixture of acetic acid (360 mL) and acetic anhydride (100 mL) at 0–5 °C. The mixture was stirred at room temperature for 6 h, and then slowly poured into ice-water (5 L) and extracted with ethyl acetate (4 × 300 mL). The combined organic layer was washed with saturated sodium bicarbonate (2 × 200 mL) and brine (2 × 100 mL) and dried (Na_2SO_4). The ethyl acetate was then removed by letting it stand under vacuum to give a yellow oil that solidified after standing in a refrigerator for 12 h. It was then recrystallised from ethyl acetate/petroleum ether to afford the product as light yellow crystals (87.5 g, 75% yield); m.p. 119–120 °C. IR (cm^{-1}): 1720 (CO), 1529 (NO_2). ^1H NMR (DMSO-d_6) δ: 2.06 (t, 2H, $–CH_2$), 2.48–2.56 (m, 6H, $–CH_2–CH_2–CH_2–$), 3.73 (t, 4H, $–CH_2–CH_2–$), 3.91 (s, 3H, $–OCH_3$), 3.95 (s, 3H, $–OCH_3$), 4.19 (t, 2H, $–CH_2$), 7.11 (s, 1H, HAr), 7.46 (s, 1H, HAr). ^{13}C NMR δ: 25.48, 52.93, 53.23, 54.45, 56.43, 66.06, 67.53, 107.47, 111.87, 120.36, 140.63, 150.38, 151.62, 165.33. Anal. Calcd for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.26; N, 7.91. Found: C, 54.12; H, 7.45; N, 7.94%.

Methyl 2-amino-4-methoxy-5-(3-morpholinopropoxy) benzoate (**4**): Sodium dithionite (80.0 g, 0.45 mol) was added to a solution of compound **3** in water (400 mL), and the mixture was heated to 50 °C for 2 h. When the reaction was complete after 0.5 h, concentrated hydrochloric acid (200 g) was added at 70 °C. Then the mixture was cooled to room temperature, and aqueous NaOH solution (47%) was added to adjust the pH of the mixture to 8.0–9.0. After the pH was adjusted, the mixture was stirred for 30 min and the product filtered under vacuum. The filter cake was recrystallised from ethyl acetate to afford white crystals (67.2 g, 90% yield); m.p. 89–90 °C. IR (cm^{-1}): 3472 (NH_2), 1684 (CO). ^1H NMR (DMSO-d_6) δ: 1.75–1.84 (m, 2H, $–CH_2–$), 2.34–2.41 (m, 6H, $–CH_2–CH_2–CH_2–$), 3.56 (t, 4H, $–CH_2–CH_2–$), 3.73 (d, 6H, $–CH_3$, J = 0.99 Hz), 3.83 (t, 2H, $–CH_2–$), 6.35 (s, 1H, HAr), 6.43 (s, 2H, $–NH_2$), 7.14 (s, 1H, HAr). ^{13}C NMR δ: 25.99, 50.97, 53.31, 54.84, 55.20, 66.14, 67.60, 99.10, 99.74, 114.67, 148.41, 155.34, 167.26. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 54.15; H, 7.44; N, 8.66%.

7-methoxy-6-(3-morpholinopropoxy) quinazolin-4(3H)-one (**5**): Formamidine acetate (120.0 g, 1.15 mol) and compound **4** were added to dry alcohol (600 mL). The mixture was refluxed for 4 h, and then cooled to 0 °C. The precipitate was collected by filtration and washed with cold ethanol to afford white powder (70.2 g, 88% yield); m.p. 248–250 °C. IR (cm^{-1}): 1675 (CO), 1615 (NH). ^1H NMR (DMSO-d_6) δ: 1.89–1.96 (m, 2H, $–CH_2–$), 2.36–2.45 (m, 6H, $–CH_2–CH_2–CH_2–$), 3.57 (t, 4H, $–CH_2–CH_2–$), 4.10 (t, 2H, $–CH_2–$), 7.12 (s, 1H, H_8), 7.43 (s, 1H, H_5), 7.97 (s, 1H, H_2), 12.01 (s, 1H, –NH–). ^{13}C NMR δ: 25.66, 53.31, 54.70, 55.90, 66.15, 66.75, 105.81, 108, 06, 115.55, 143.77, 144.73, 147.82, 154.56, 160.02. Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.05; H, 6.62; N, 13.20%.

4-chloro-7-methoxy-6-(3-morpholinopropoxy)-3, 4-dihydroquinazoline (**6**): Thionyl chloride (400 mL) and N,N-dimethylformamide (40 mL) was added to compound **5** (70.0 g, 0.22 mol), The mixture was refluxed for 24 h, and the excess thionyl chloride distilled. The yellow residue was dissolved in chloroform (500 mL), then washed with a saturated solution of sodium carbonate (3 × 100 mL) and water (2 × 100 mL) and dried (Na_2SO_4). The chloroform was then removed under reduced pressure to give an off-white powder, which was recrystallised from ethyl acetate to afford the product (60.4 g, 81% yield); m.p. 117 °C. IR (cm^{-1}): 1115 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.93–2.03 (m, 2H, $–CH_2–$), 2.38 (s, 4H, $–CH_2–CH_2–$), 2.44 (t, 2H, $–CH_2–$), 3.57 (t, 4H, $–CH_2–CH_2–$), 4.01 (s, 3H, $–CH_3$), 4.23 (t, 2H, $–CH_2–$), 7.37 (s, 1H, H_8), 7.44 (s, 1H, H_5), 8.87 (s, 1H, H_2). ^{13}C NMR δ: 25.49, 53.31, 54.67, 56.52, 66.15, 67.16, 102.82, 106.91, 118.54, 148.45, 150.68, 152.11, 156.82, 157.78. Anal. Calcd for $C_{16}H_{20}ClN_3O_3$: C, 56.89; H, 5.97; N, 12.44. Found: C, 56.76; H, 6.60; N, 12.42%.

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine (Gefitinib): Compound **6** (50.0 g, 0.15 mol) was dissolved in isopropanol (300 mL), and 3-chloro-4-fluoroaniline (36.2 g, 0.25 mol) was added. The reaction mixture was heated under reflux for 3 h and concentrated under reduced pressure. The mixture was cooled to room temperature, and the precipitate was collected by filtration and washed with cold isopropanol (2 × 50 mL) to afford a white powder, which was recrystallised from ethyl acetate to afford the white product (59.5 g, 89% yield); m.p. 195–198 °C, (lit.[12] M.p. 197 °C). IR (cm^{-1}): 1502 (NH), 1209 (C–F), 1075 (C–Cl). ^1H NMR(DMSO-d_6) δ: 2.43 (tt, 2H, $–CH_2CH_2CH_2–$), 2.64 (m, 4H,), 2.73 (t, 2H, $–CH_2$), 3.82 (m, 4H), 4.02 (s, 3H, $–OCH_3$), 4.26 (t, 2H, $–OCH_2$), 7.13 (s, 1H, HAr), 7.29 (s, 1H, HAr), 7.49 (s, 1H, HAr), 7.61 (d, 1H, HAr), 7.98 (d, 1H, HAr), 8.66 (s, 1H, HAr), 10.44–10.80 (b, 1H, –NH–); ^{13}C NMR δ: 26.23, 53.79, 55.40, 56.22, 60.39, 61.67, 66.95, 67.76, 100.79, 108.19, 109.04, 118.07, 122.71, 123.13, 135.18, 136.18, 147.67, 149.15, 153.63, 155.30, 156.47, 162.74.; MS *m/z*: 447.1 ($[M + H]^+$, 100%). Anal. Calcd for $C_{22}H_{25}Cl_2FN_4O_3$: C, 54.67; H, 5.21; N, 11.59. Found: C, 54.69; H, 5.22; N, 11.56%.

Received 17 February 2009; accepted 14 April 2009
Paper 09/0463 doi: 10.3184/030823409X460740
Published online: 30 June 2009

References

1 Y. Yarden and M.X. Sliwkowski, *Nat Rev. Mol. Cell Biol.*, 2001, **2**, 127.
2 T. Holbro and N.E. Hynes, *Annu. Rev. Pharmacol. Toxicol.*, 2004, **44**, 195.
3 D.S. Salomon, R. Brandt, F. Ciardiello and N. Normanno, *Crit. Rev. Oncol. Hematol.*, 1995, **19**, 183.
4 K. Grosios and P. Traxler, *Drugs Fut.*, 2003, **28**, 679.
5 A.J. Barker, K.H. Gibson and W. Grundy, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1911.
6 H.K. Gibson, *US*5770599, 1998.
7 P. Knesl, D. Röseling and U. Jordis, *Molecules*, 2006, **11**, 286.
8 J.P. Gilday and M. David, *WO2004024703*, 2006.
9 J.Q. Wang, M.Z. Gao and K.D. Miller, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4102.
10 C.Q. Zhu, Y.S. Chi and Y.L. Deng, *CN1733738*, 2006.
11 M. Ji, Y.G. Zheng and M.D. Li, *CN101148439*, 2008.
12 J.P. Ramanadham, P.R. Muddasani, N.R. Bollepalli and V.C. Nannapaneni, WO2005020909, 2005.