*Full Paper*

# Synthesis of Gefitinib from Methyl 3-Hydroxy-4-methoxy-benzoate

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**Abstract:** This paper reports a novel synthesis of gefitinib starting from methyl 3-hydroxy-4-methoxybenzoate. The process starts with alkylation of the starting material, followed by nitration, reduction, cyclization, chlorination and two successive amination reactions. The intermediates and target molecule were characterized by $^1$H-NMR, $^{13}$C-NMR, MS and the purities of all these compounds were determined by HPLC. This novel synthetic route produced overall yields as high as 37.4%.

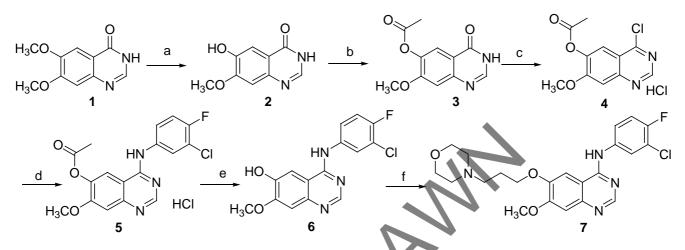**Keywords:** Gefitinib, tyrosine kinase inhibitors, methyl 3-hydroxy-4-methoxybenzoate.

## Introduction

The epidermal growth factor receptor (EGFR) protein tyrosine kinase (PTK) is one of the important kinases that play a fundamental role in signal transduction pathways [1]. Many human cancers overexpress EGFR and the related human epidermal growth factor receptor (HER-2). Compounds, such as gefitinib (**7**, IRESSA®, Scheme 1), that inhibit the kinase activity of EGFR and HER-2 after binding of their cognate ligand, have been used as new therapeutic antitumor agents [2, 3]. Gefitinib, a potent and selective ATP-competitive inhibitor of EGFR and HER-2 kinases, is the first EGFR targeting agent launched as an anticancer drug in Japan, Australia and the United Sates for the

treatment of chemoresistant non-small cell lung cancer (NSCLC) patients [4, 5].

Several methods for the synthesis of gefitinib have been reported. Gibson's route started with regioselective demethylation of a costly starting material, 6,7-dimethoxyquinazolin-4(3H)-one (**1**), which was followed by *O*-protection, preparation of the desired chloro compound using thionyl chloride or phosphoryl chloride, coupling with 3-chloro-4-fluoroaniline and additional steps to add the remaining functionalities of **7** (Scheme 1).

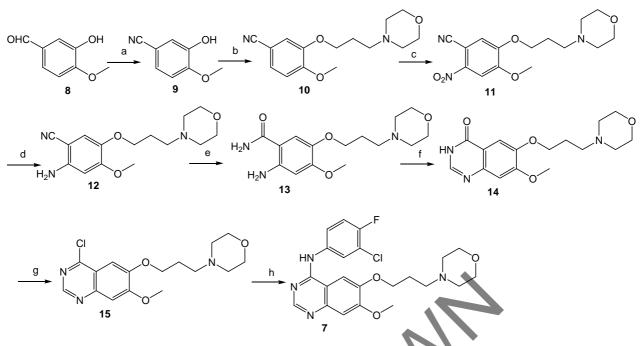**Scheme 1**. Synthesis of gefitinib as reported by Gibson [6].



Methanesulfonic acid, *L*-methionine, reflux; b) Ac$_2$O, pyridine, DMAP; c) POCl$_3$, DEA; d) 3-chloro-4-fluoroaniline, i-PrOH; e) NH$_3$/MeOH, H$_2$O; f) 4-(3-chloropropyl)morpholine, K$_2$CO$_3$, DMF.

Another drawback, aside from the cost, is the fact that the regioselective demethylation reaction with *L*-methionine (step a) only gives a 46% yield of compound **2** [6]. Knesl *et al.*, have modified this route, substantially improving the yield of this step to 98%, thus obtaining a 90% pure (by HPLC) intermediate that could be used for the next step [7].

Gilday *et al.* have designed a novel method (Scheme 2) for synthesizing gefitinib starting from the conversion of 3-hydroxy-4-methoxybenzaldehyde (**8**) into the corresponding nitrile, followed by alkylation, nitration, reduction, nitrile hydrolysis, cyclization, chlorination and then the reaction of the chloride with 3-chloro-4-fluoroaniline to afford gefitinib in eight steps overall [8]. Wang *et al.* have used this route to produce the target compound in radiolabeled form in 11% overall yield [9]. In this report, we present a novel approach to synthesizing gefitinib that is not only less expensive but also affords higher yields.

**Results and Discussion**

Our novel synthesis of gefitinib (Scheme 3) starts from methyl 3-hydroxy-4-methoxybenzoate (**16**). This compound is alkylated with 1-bromo-3-chloropropane to afford the intermediate **17** in 94.7% yield. Nitration of **17** with nitric acid in acetic acid gave compound **18**, which was reduced by powdered iron in acetic acid to give compound **19** in satisfactory yield (77%). Catalytic hydrogenation using Raney/Ni or 5% Pd/C gave incomplete conversions even after long reaction times.
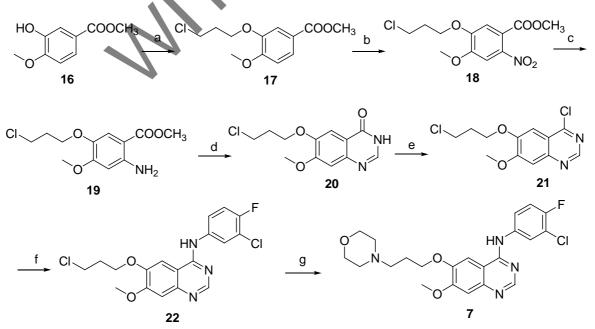
**Scheme 2**. Synthesis of gefitinib reported by Gilday [8].



a) HCOOH, HCOONa; (OHNH$_3$)$_2$SO$_4$; b) 4-(3-chloropropyl)morpholine, base; c) 70%HNO$_3$, 70%H$_2$SO$_4$, CH$_3$COOH; d) Na$_2$S$_2$O$_4$; e) KOH, *t*-amyl alcohol; f) HCOOH, HCOONH$_4$; g) POCl$_3$; h) 3-chloro-4-fluoroaniline, isopropanol.

Cyclization of **19** with formamidine acetate and chlorination with thionyl chloride affords compound **21**. The final product was obtained after two reactions with different amines. This new method is a step shorter than Gilday's eight step one, is less costly because of the much cheaper starting material used, and gives higher yields, compared to the other methods.

**Scheme 3**. Novel synthesis of gefitinib.



a) 1-bromo-3-chloropropane, K$_2$CO$_3$, 60°C; b) Ac$_2$O, AcOH, HNO$_3$, 0-5 °C; c)Fe, AcOH, MeOH; d) formamidine acetate, ethanol, reflux; e) SOCl$_2$, DMF reflux; f) 3-chloro-4-fluoroaniline i-PrOH reflux; g) morpholine, KI, 60°C.

**Experimental**

*General*

All reagents were purchased from commercial sources and used without further purification. Melting points were measured in open capillaries and are uncorrected. $^1$H-NMR and $^{13}$C-NMR spectra were recorded in CDCl$_3$ on a Bruker Avance 500 spectrometer; chemical shifts ($\delta$) 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. The reported HPLC purity is the peak area calculated using Class-VP software on a Shimadzu 2010 instrument.

*Methyl 3-(3-chloropropoxy)-4-methoxybenzoate* (**17**)

A mixture of methyl 3-hydroxy-4-methoxybenzoate (**16**, 84.6 g, 0.47 mol), 1-bromo-3-chloro-propane (101.6 g, 0.65 mol), and potassium carbonate (138.1 g, 1.0 mol) in DMF (500 mL) was heated at 70°C for 4 h. The reaction mixture was cooled to room temperature, then poured slowly into ice-water (3 L) while stirring constantly. The solid formed was filtered off and washed with cold water. The off-white product was recrystallized from ethyl acetate (200 mL) to afford 113.9 g of **17** (95% yield, 99.3% HPLC purity); mp: 111-113 °C; $^1$H-NMR: 2.02-2.22 (tt, 2H, -CH$_2$**CH$_2$**CH$_2$-), 3.65 (t, 2H, -CH$_2$Cl), 3.79 (s, 3H, -OCH$_3$), 3.88 (s, 3H, -OCH$_3$), 4.10 (t, 2H, -CH$_2$O), 6.84 (d, 1H, HAr), 7.49 (s, 1H, HAr), 7.71 (d, 1H, HAr).

*Methyl 5-(3-chloropropoxy)-4-methoxy-2-nitrobenzoate* (**18**)

Nitric acid (84.5 ml, 66%) was added dropwise at 0-5 °C to a solution of methyl 3-(3-chloropropoxy)-4- methoxybenzoate (**17**, 93.0 g, 0.36 mol) in a mixture of acetic acid (300 mL) and acetic anhydride (100 mL). This mixture was stirred at room temperature for 6 h, then slowly poured into ice-water (2 L) and extracted with ethyl acetate (4 × 200 mL). The combined organic layer was washed with saturated sodium bicarbonate (2 × 200 mL) and brine (2 × 100 mL) and dried (Na$_2$SO$_4$). 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 and was then recrystallized from ethyl acetate/ petroleum ether to afford the product as light yellow crystals (97.1 g, 89% yield, 98.7% HPLC purity); mp: 54-56 °C; $^1$H-NMR: 2.03-2.24 (tt, 2H, -CH$_2$**CH$_2$**CH$_2$-), 3.66 (t, 2H, -CH$_2$Cl), 3.78 (s, 3H, -OCH$_3$), 3.89 (s, 3H, -OCH$_3$), 4.12 (t, 2H, -CH$_2$O), 7.82 (s, 1H, HAr), 8.01 (d, 1H, HAr).

*Methyl 5-(3-chloropropoxy)-2-amino-4-methoxybenzoate* (**19**)

Powdered iron (50 g, 0.89 mol) was added to acetic acid (500 mL). The resulting suspension was stirred for 15 min at 50°C under an atmosphere of N$_2$, then a solution of methyl 5-(3-chloropropoxy)-4-methoxy-2-nitrobenzoate (**18**, 90.0 g, 0.30 mol) in methanol (300 mL) was added dropwise. The mixture was stirred for 30 min at 50~60°C. The catalyst was filtered, washed

with methanol and the volatiles evaporated from the combined filtrate and washes. The residue was poured into water (4 L), extracted with ethyl acetate (4 × 200 mL). The organic phase was washed with a saturated solution of sodium carbonate (2 × 100 mL) and brine (2 × 100 mL) and then dried (Na$_2$SO$_4$). The solvent was removed under vacuum and the brown solid residue was recrystallized from ethyl acetate/petroleum ether to afford the product as light brown crystals (63.1 g, 77% yield, 98.2% HPLC purity); mp: 96-98 °C; $^1$H-NMR: 1.98-2.20 (tt, 2H, -CH$_2$**CH$_2$**CH$_2$-), 3.62 (t, 2H, -CH$_2$Cl), 3.76 (s, 3H, -OCH$_3$), 3.85 (s, 3H, -OCH$_3$), 4.07 (t, 2H, -CH$_2$O), 5.10-5.35 (b, 2H,-NH$_2$), 6.09 (d, 1H, HAr), 7.21 (s, 1H, HAr).

### *6-(3-Chloropropoxy)-7-methoxyquinazolin-4(3H)-one* (**20**)

A solution of methyl 5-(3-chloropropoxy)-2-amino-4-methoxybenzoate (**19**, 98.2 g, 0.36 mol) and formamidine acetate (52.6 g, 0.51 mol) in ethanol (800 mL) was heated at reflux for 6 h with overhead stirring. The mixture was allow to stand in the refrigerator overnight, then the precipitate was collected by filtration, washed with ethanol and air dried to give **20** as a white power (88.7 g, 92% yield, 99.3% HPLC purity); mp: 218-219 °C; $^1$H-NMR: 2.10-2.31 (tt, 2H, -CH$_2$**CH$_2$**CH$_2$-), 3.72 (t, 2H, -CH$_2$Cl), 3.83 (s, 3H, -OCH$_3$), 4.02 (t, 2H, -CH$_2$O), 6.98 (d, 1H, HAr), 7.89 (s, 1H, HAr), 8.02 (d, 1H, HAr), 9.03-9.42 (b, 1H, -NH-).

### *6-(3-Chloropropoxy)-4-chloro-7-methoxyquinazoline* (**21**)

6-(3-Chloropropoxy)-7-methoxyquinazolin-4(3*H*)-one (**20**, 102 g, 0.38 mol) was added to thionyl chloride (500 mL) with magnetic stirring, then DMF (20 mL) was slowly added dropwise and the reaction flask was heated to reflux for 4 h. Most of the excess of thionyl chloride was then removed under reduced pressure and the yellow residue was dissolved in chloroform (500 mL), then washed with a saturated solution of sodium carbonate (2 × 100 mL) and water (2 × 100 mL) and dried (Na$_2$SO$_4$). The chloroform was then removed under reduced pressure to give an off-white power, which was recrystalized from ethyl acetate to afford the product (93.5 g, 86% yield, 98.7% HPLC purity); mp: 150-152°C; $^1$H-NMR: 2.43 (tt, 2H, -CH$_2$C**H$_2$**CH$_2$-), 3.85 (t, 2H,-CH$_2$Cl), 4.09 (s, 3H, -OCH$_3$), 4.39 (t, 2H, -OCH$_2$), 7.43 (s, 1H, HAr), 7.47 (s, 1H, HAr), 8.91 (s, 1H, HAr).

### *6-(3-Chloropropoxy)-N-(3-chloro-4-fluorophenyl)-7-methoxyquinazolin-4-amine* (**22**)

3-Chloro-4-fluoroaniline (75.2 g, 0.52 mol) was added to a solution of 6-(3-chloropropoxy)-4-chloro-7-methoxyquinazoline (**21**, 80.0 g, 0.28 mol) in isopropanol (1000 mL). The mixture was heated to reflux for 3 h, and then left standing in the refrigerator overnight; the precipitate was collected by filtration, washed with chilled isopropanol (2 × 150 mL) and dried to afford the product as a yellow powder (103.1 g, 93% yield, 99.5% HPLC purity); mp: 234-236°C; $^1$H-NMR: 2.42 (tt, 2H, -CH$_2$C**H$_2$**CH$_2$-), 3.81 (t, 2H,-CH$_2$Cl), 4.07 (s,3H, -OCH$_3$), 4.36 (t, 2H, -OCH$_2$), 6.93 (s, 1H, HAr), 7.06 (s, 1H, HAr), 7.30 (s, 1H, HAr), 7.44 (d, 1H, HAr), 7.87 (d, 1H, HAr), 8.54 (s, 1H, HAr), 10.53-10.89 (b, 1H, -NH-).

*N-(3-Chloro-4-fluorophenyl)-7[methoxy-6-[(3-morpholin-4-yl) propoxy]-quinazolin-4-yl] amine* (**7**)

6-(3-Chloropropoxy)-N-(3-chloro-4-fluorophenyl)-7-methoxyquinazolin-4-amine (**22**, 87.5 g, 0.22 mol) and potassium iodide (2.0 g) were added to the solution of morpholine (43 g, 0.5 mol) in DMF (200 mL). The solution was stirred at 60 °C for 30 min, then poured into ice-water (2 L) and extracted with chloroform (3 × 300 mL). The organic layers were combined, washed with a saturated solution of sodium carbonate (2 × 200 mL) and brine (1 × 100 mL) and then dried (Na$_2$SO$_4$). The solvent was removed under vacuum. The crude product was crystallized from ethyl acetate to afford compound **7** (76.5 g, 78% yield, 99.6% HPLC purity); mp: 119-120°C; $^1$H-NMR: 2.43 (tt, 2H, -CH$_2$C**H$_2$**CH$_2$-), 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: 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%).

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*Sample availability:* Samples of compounds **16**-**21** are available from the authors.