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Full Papers

Convergent Approach for Commercial Synthesis of Gefitinib and Erlotinib

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Abstract:

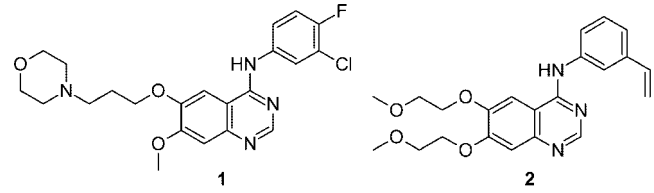
An efficient, economical and large-scale convergent synthesis of epidermal growth factor receptor- tyrosine kinase inhibitors gefitinib (1, Iressa) and erlotinib (2, Tarceva) approved by U.S. FDA for the treatment of non-small-cell lung cancer is described. The formation of 4-anilinoquinazolines are achieved in a simple one-pot reaction of suitable formamidine intermediates and substituted anilines involving Dimroth rearrangement, thereby avoiding the need to make quinazolin-4(3*H*)-one intermediates, which require a large experimental inputs. Using this process, we have produced drug candidates 1 with overall yield of 66% from 4-methoxy-5-[3-(4-morpholinyl) propoxy]-2-nitrobenzonitrile (3) and 2 with 63% from 4,5-bis(2-methoxyethoxy)-2-nitrobenzonitrile (6) on a multigram scale.

Introduction

Epidermal growth factor receptor (EGFR) is a cell membrane receptor consisting of an extracellular ligand binding domain and an intracellular tyrosine kinase domain. Binding of ligand to these transmembrane receptor leads to the homo- or heterodimerization of the receptor, which results in transphosphorylation of tyrosine residues. These events lead to the phosphorylation of several intracellular substrates through the tyrosine kinase activities, and these downstream signaling pathways ultimately regulate cell division, motility, adhesion and cell death or apoptosis.

High levels of EGFR expression is observed in many human solid tumors, in particular, colorectal, pancreatic, bladder, prostate, ovarian, glioma, breast, lung, renal, and head and neck cancer,[1] and this overexpression is connected with poor prognosis of the disease.[2–4]

Of the various EGFR-targeted agents known, the small-molecule 4-anilinoquinazoline class has been widely studied.[5] These small molecules competitively bind to the ATP binding pocket of intracellular kinase domain and block induction of downstream signaling network mediated by tyrosine kinase. The 4-anilinoquinazolines gefitinib (**1**, Iressa) and erlotinib (**2**, Tarceva) have been launched for the treatment of non-small-cell lung cancer and inhibit TK activity and restrict receptor catalytic activity, anti-phosphorylation and its engagement with signal transducers. The traditional synthetic methods for the preparation of these two drugs involve construction of crucial intermediates of suitably substituted quinazolin-4(3*H*)-ones,[6,7] which are prepared from 3, 4-dimethoxybenzaldehyde and 3,4-dihydroxybenzoic acid. However, preparation of these involve a series of reactions and involve the use of corrosive chemicals such as thionyl chloride/phosphoryl chloride, costly reagents such as platinum oxide, and flammable gas such as hydrogen at high temperature reaction conditions. To overcome these difficulties, a one-pot synthesis of quinazolin-4(3*H*)-ones under mild reaction conditions has been reported.[10]



1 **2**

As per the procedure described in the literature,[7–9] synthesis of gefitinib (**1**) involves the preparation of 4-(3′-chloro-4′-fluoroanilino)-6-hydroxy-7-methoxyquinazoline as an intermediate and then the introduction of a 3-morpholino propoxy side chain in the last step of the synthesis. This synthetic procedure comprises the selective demethylation of 6,7-dimethoxyquinazolin-4(3*H*)-one using a large excess of methane sulphonic acid and L-methionine followed by protection of the 6-hydroxy group by acetylation using a large excess of acetic anhydride. Intermediate quinazolones prepared for these drugs were treated with excess thionyl chloride/phosphoryl chloride to get the 4-chloroquinazoline derivative and then coupled with the corresponding aniline. In our earlier experiments,[10] we found that 4-chloroquinazoline intermediates were unstable and decompose on storage. To overcome this instability problem, we have made relatively stable 4-(methylthio)-7-methoxy-6-[3-(4-morpholinyl) propoxy]-quinazoline and 4-(methylthio)-6,7-bis(2-methoxyethoxy)-quinazoline.[11] However, this method involves extra steps.

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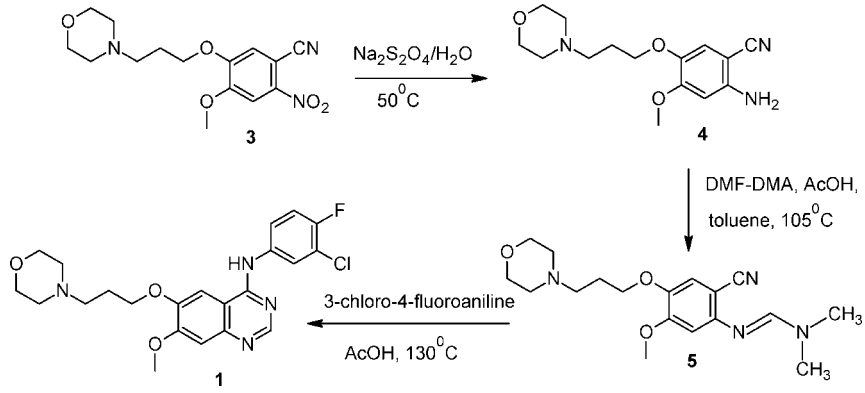
Scheme 1



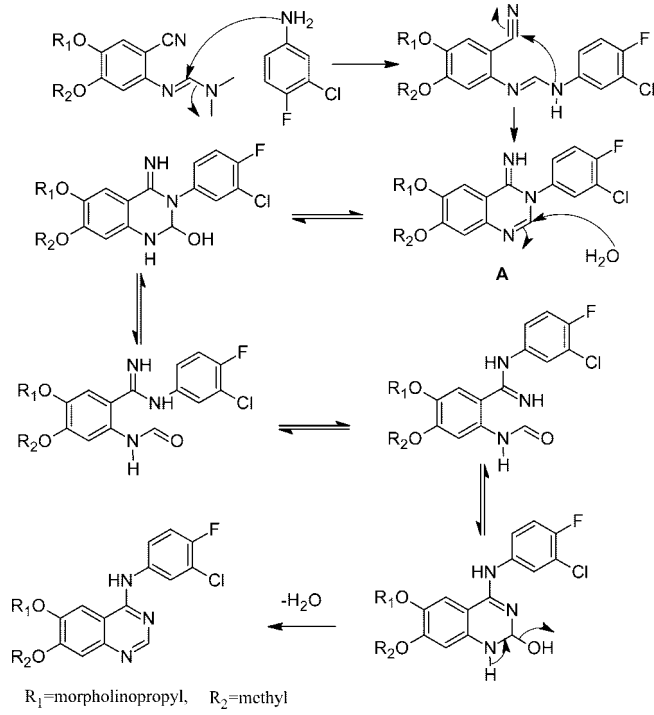
Recently, Giday et al.[12] reported the synthesis of gefitinib by reacting excess of *N*,*N*′-bis(3-chloro-4-fluorophenyl) formamidine with 2-amino-4-methoxy-5-[3-(4-morpholinyl) propoxy]-benzonitrile (**4**). The main disadvantages of this process are the use of excess formamidine compound and poor yields obtained in preparation of *N*-(3-chloropropyl) morpholine. Thus there arises a need to develop a simple, more economical, and commercially viable process. Now we have developed an easily scalable, convergent, and versatile process for the preparation of compounds **1** and **2**. The convergent process developed for the preparation of gefitinib involves reacting *N*′-[2-cyano-5-methoxy-4-{3-(4-morpholinyl) propoxy}phenyl]-*N*,*N*-dimethyl formamidine (**5**) with 3-chloro-4-fluoroaniline and erlotinib by reacting *N*′-[2-cyano-4,5-{bis(2-methoxyethoxy)phenyl}]-*N*,*N*-dimethyl formamidine (**8**) with ethynylaniline. These processes permit reduction in the number of steps with higher yields.

Results and Discussion

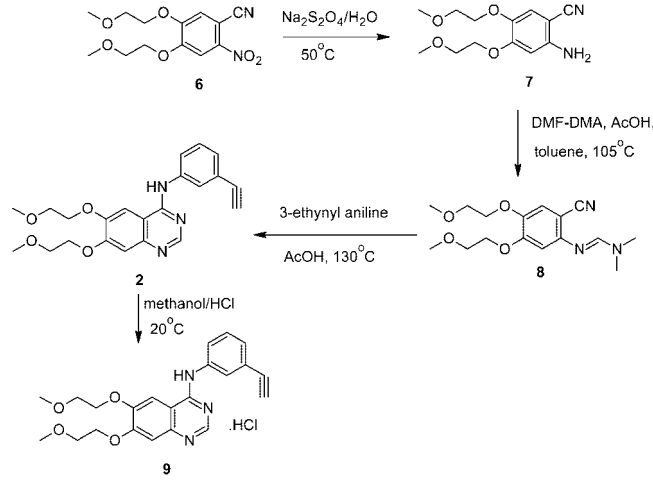
The synthesis of gefitinib (**1**) (Scheme 1) has been accomplished starting from key intermediate **3**, which in turn was prepared from isovanillin in a highly efficient way using our published procedure.[10] Reduction of the nitro group of compound **3** was carried out in aqueous medium using sodium dithionite at 50 °C to obtain compound **4** in 95% yield. Compound **4** was treated with dimethylformamide–dimethylacetal (DMF–DMA) in toluene to produce *N*,*N*-dimethyl formamidine derivative **5**. To the formamidine **5** formed without further purification was added acetic acid and 3-chloro-4-fluoroaniline, and the mixture was heated to 130 °C to produce crude material **1**, which was further purified by recrystallization to give pure material in 70% yield from compound **4** with a purity >99.5% by HPLC.

The preparation of compounds **5** is not reported in the literature, and ours is the first report of multigram preparation in a highly efficient way. The formation of **1** from compound **4** and 3-chloro-4-fluoroaniline is believed to take place via Dimroth rearrangement (Scheme 2).[13,14] Formation of the imine **A** was evidenced by Giday et al.[12] The transformation undergoes through the hydrolysis of the pyrimidine ring at the C–N_3 bond with subsequent rotation of 180° around the C_{10}–C_4 bond and ring closure.

Scheme 2



Scheme 3



The synthesis of erlotinib (**2**) (Scheme 3) has been accomplished starting from compound **6**, which in turn was prepared in an efficient way using our published procedure.[10] Nitro reduction of compound **6** using sodium dithionite in

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aqueous medium gave compound **7** in 95% yield. We treated compound **7** with DMF–DMA in toluene to obtain formamidine derivative **8**, which was reacted with 3-ethynylaniline, involving the same procedure discussed under gefitinib (through Dimroth rearrangement) to give compound **2**. Compound **2** on further recrystallization gave pure compound in 70% yield with purity >99% by HPLC. The free base obtained was converted to erlotinib hydrochloride (**9**) by passing HCl gas.

All of the intermediates employed in the synthesis of erlotinib have been made for the first time and are not reported in the literature. Intermediates obtained from each step were used for further reaction without purification, and yields obtained were good to excellent, thus making the process commercially viable.

Conclusion

Efficient, commercially viable, and multigram-scale preparations of gefitinib and erlotinib with a convergent approach have been described. The convergent processes lead to a reduction of the number of steps, which provides many advantages over the original processes reported in the literature.

Experimental Section

General. Starting materials **3** and **6** were prepared using the procedure described in ref 10. All solvents, sodium hydroxide, hydrochloric acid, and sodium dithionite were procured from Loba chemicals, Bhiwandi, India. DMF–DMA was obtained from spectrochem, Mumbai, India. 3-Chloro-4-fluoro-aniline and 3-ethynyl aniline were available commercially and obtained from D. Maniar and Bros, M/S Madhukar Pharma, Mumbai, India, respectively, and were used without further purification. IR spectra were recorded using a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 at 200 MHz on a Bruker A G Spectrometer. All chemical shift values are reported in δ units downfield from TMS as internal standard. Mass spectra were recorded using GC MS-QP2010S (Direct probe) and on Q-TOF micro AMPS MAX 10/6A system. HPLC analysis was done using a Shimadzu CLASS VP using the following column conditions: ODS-3V 4.6 mm × 250 mm, particle size 5μ, λ = 254 nm, flow rate 1 mL/min, mobile phase (40:60) buffer/acetonitrile (buffer 1% aqueous ammonium acetate). Melting points were recorded using the melting point apparatus Acro Steel Pvt. Ltd.

2-Amino-4-methoxy-5-(3-morpholinopropoxy)benzonitrile (4). To a suspension of **3** (329 g, 1.02 mol) in water (5 L) was added sodium dithionite (585 g, 3.35 mol). The reaction mixture was heated to 50 °C and stirred for 2.5 h, and then the temperature of the reaction mixture was raised to 70 °C and 25% HCl (1.5 L) was added slowly in 3 h. The reaction mixture was cooled to 20 °C and adjusted to pH ~10 with 50% aqueous sodium hydroxide solution (1.5 L). The product was extracted into dichloromethane (1.5 L), the organic phase washed with water (2 × 200 mL) and brine (1 × 200 mL), and the organic solvent was evaporated to give **4** as brown solid (283g, 95% yield). ^{1}H NMR ($CDCl_3$): δ 2.01 (m, 2H), 2.51 (m, 6H), 3.72 (t, J = 4.6 Hz, 4H), 3.84 (s, 3H), 3.97 (t, J = 6.5 Hz, 2H), 4.14 (br s, 2H), 6.23 (s, 1H), 6.85 (s, 1H).

4-(3′-Chloro-4′-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (1). To a reaction flask fitted with a condenser and a Dean–Stark apparatus were added compound **4** (283 g, 0.97 mol), toluene (2.5 L), acetic acid (3 mL), and DMF–DMA (280 mL, 2.10 mol). The reaction mixture was heated to 105 °C and stirred for 3 h. While stirring, methanol was collected using the Dean–Stark apparatus. Toluene was completely stripped off under vacuum to obtain *N*′-[2-cyano-5-methoxy-4-{3-(4-morpholinyl) propoxy}phenyl]-*N*,*N*-dimethyl formamidine (**5**) as a brown liquid. IR (thin film): 864, 1010, 1118, 1384, 2214, 2812, 2950 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.0 (m, 2H), 2.47 (m, 6H), 3.06 (s, 6H), 3.72 (t, J = 4.5 Hz, 4H), 3.87 (s, 3H), 4.03 (t, J = 6.5 Hz, 2H), 6.45 (s, 1H), 6.98 (s, 1H), 7.57 (s, 1H). HRMS: calcd for $C_{18}H_{26}N_4O_3$ (M + H) 347.2083, found 347.2081.

To the residue (**5**) were added acetic acid (2.5 L) and 3-chloro-4-fluoroaniline (175 g, 1.20 mol). The reaction mixture was heated to 125–130 °C and stirred for 3 h. The reaction mixture was then cooled to 25 °C, quenched in ice–water (4 L), and adjusted pH ~9 with ammonia solution. To this reaction mass was added ethyl acetate (1 L), and the mixture was stirred for 1 h. The solid precipitate was filtered to obtain crude product **1**. Crude material was suspended in MeOH (4 L, and cooled to 20 °C. To this reaction mass was added concentrated HCl (190 mL) slowly with efficient stirring. The precipitate was filtered and washed with chilled methanol (200 mL) to give gefitinib hydrochloride. The solid was suspended in H_2O (5 L), stirred for 1 h at room temperature, cooled to 5 °C, filtered, and washed with chilled water (100 mL) to obtain an off-white solid of gefitinib hydrochloride. The solid was then suspended in water (2 L), and the suspension was adjusted to pH ~8 using ammonia solution, filtered, and dried at 50 °C to give **1** as off-white solid (304 g, 70% yield). Mp 193–195 °C. HPLC purity >99%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.11 (m, 2H), 2.46–2.59 (m, 6H), 3.74 (dd, J = 4.5 and 4.4Hz, 4H), 3.98 (s, 3H), 4.17 (t, J = 6.5Hz, 2H), 7.09 (s, 1H), 7.16 (t, J = 8.8Hz, 1H), 7.26 (s, 1H), 7.34 (brs, 1H, exchangeable with D_2O), 7.50–7.58 (m, 1H), 7.84–7.88 (m, 1H), 8.66 (s, 1H). MS (m/z): 446(M^+),128, 100. Elemental Anal. Calcd for $C_{22}H_{24}ClFN_4O_3$: C, 59.19; H, 5.38; N, 12.55. Found: C, 59.17; H, 5.21; N, 12.33.

2-Amino-4,5-bis(2-methoxyethoxy)benzonitrile (7). To a suspension of **6** (420 g, 1.41 mol) in water (7 L) was added sodium dithionite (736 g, 4.24 mol). The reaction mixture was heated to 50 °C and stirred for 2.5 h. Temperature was raised to 70 °C, and concentrated HCl (1.8 L) was added slowly in 3 h. The reaction mass was cooled to 20 °C and adjusted to pH ~10 with 50% aqueous sodium hydroxide solution (1.8 L). The product was extracted into dichloromethane (3 × 250 mL), the organic phase was washed with water (2 × 200 mL) and brine (1 × 200 mL), and the organic solvent was evaporated to give **10** as brown solid (358 g, 95% yield). Mp 73–77 °C. IR (KBr): 866, 1048, 1132, 2202, 2889, 3359, 3455 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.43 (s, 6H), 3.73 (m, 4H), 4.08 (m, 4H), 4.20 (br s, 2H), 6.25 (s, 1H), 6.90 (s, 1H). HRMS: calcd for $C_{13}H_{18}N_2O_4$ (M + Na) 289.1164, found 289.1165.

[6,7-Bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl) Amine (2). To a reaction flask fitted with a condenser and a Dean–Stark apparatus were added compound **7** (358

g, 1.34 mol), toluene (3.5 L), acetic acid (5 mL), and DMF–DMA (319 g, 2.68 mol). The reaction mixture was heated to 105 °C and stirred for 3 h. Toluene was completely stripped off under vacuum to obtain *N*′-[2-cyano-4,5-{bis(2-methoxyethoxy)phenyl}]-*N*,*N*-dimethyl formamidine (**8**). ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 6H), 3.44 (s, 6H), 3.75 (m, 4H), 4.13 (m, 4H), 6.48 (s, 1H), 7.02 (s, 1H), 7.55 (s, 1H). HRMS: calcd for $C_{16}H_{23}N_3O_4$ (M + H) 322.1767, found 322.1762.

To the residue (**8**) were added acetic acid (2.5 mL) and 3-ethynyl aniline (141 g, 1.21 mol). The reaction mixture was heated to 125–130 °C and stirred for 3 h. The reaction mixture was then cooled to 25 °C, quenched in ice–water (5 L), and adjusted pH ∼9 with ammonia solution. The product was extracted into ethyl acetate (3 × 500 mL), the organic phase was washed with water (1 × 250 mL) and brine (1 × 250 mL), and the organic solvent was evaporated to obtain **2** as crude material, which was further recrystallized from ethyl acetate (1 L) and then with methanol (500 mL) to give off-white crystalline compound **2** (350 g, 66% yield). HPLC >99%. Mp 149–153 °C. ^{1}H NMR ($CDCl_3$): δ 3.08 (s, 1H), 3.43 (s, 6H), 3.80 (m, 4H), 4.22 (m, 4H), 7.17 (s, 1H), 7.24–7.37 (m, 3H), 7.61 (brs, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.85 (s, 1H), 8.63 (s, 1H). MS (*m*/*z*): 393 (M^+), 334, 276, 230, 59.

[6,7-Bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)-Amine Hydrochloride (Erlotinib Hydrochloride, 9). Through a stirred suspension of erlotinib free base **2** (200 g) in methanol (2 L) was passed dry hydrochloric acid gas for 0.5 h, keeping the temperature of the reaction mass at 15–20 °C. The solid precipitate was filtered and dried at 50 °C to give off-white crystalline material of erlotinib hydrochloride (**9**) (200 g, 92% yield). Mp 228–230 °C. HPLC >99%. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.36 (s, 6H), 3.77 (m, 4H), 4.29 (s, 1H), 4.32–4.38 (m, 4H), 7.38–7.55 (m, 3H), 7.78 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 8.38 (s, 1H), 8.86 (s, 1H), 11.42 (s, 1H). Elemental Anal. Calcd for $C_{22}H_{24}N_3O_4Cl$: C, 61.32; H, 5.85; N, 9.75. Found: C, 61.45; H, 5.62; N, 9.60. Chloride assay by potentiometric method 98.82%.

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Supporting Information Available

^{1}H NMR spectra for compounds **1**, **2**, **4**, **5**, and **7–9**, mass spectra for compounds **1**, **2**, **5**, and **8**, and HPLC spectra for compounds **1** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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