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Improved preparation of formamidine intermediates used in the synthesis of anticancer agents gefitinib and erlotinib

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ABSTRACT

Formamidine intermediates have been prepared by cost effective reagents and using these formamidines, prepared anticancer agents *Gefitinib* and *Erlotinib*, approved by US FDA for the treatment of non-small-cell-lung cancer and pancreatic cancer. This convergent process reports an improvement in the procedure, yields and reaction times.

KEYWORDS

Formamidines;
Anti-cancer;
Gefitinib;
Erlotinib;
Convergent process.

INTRODUCTION

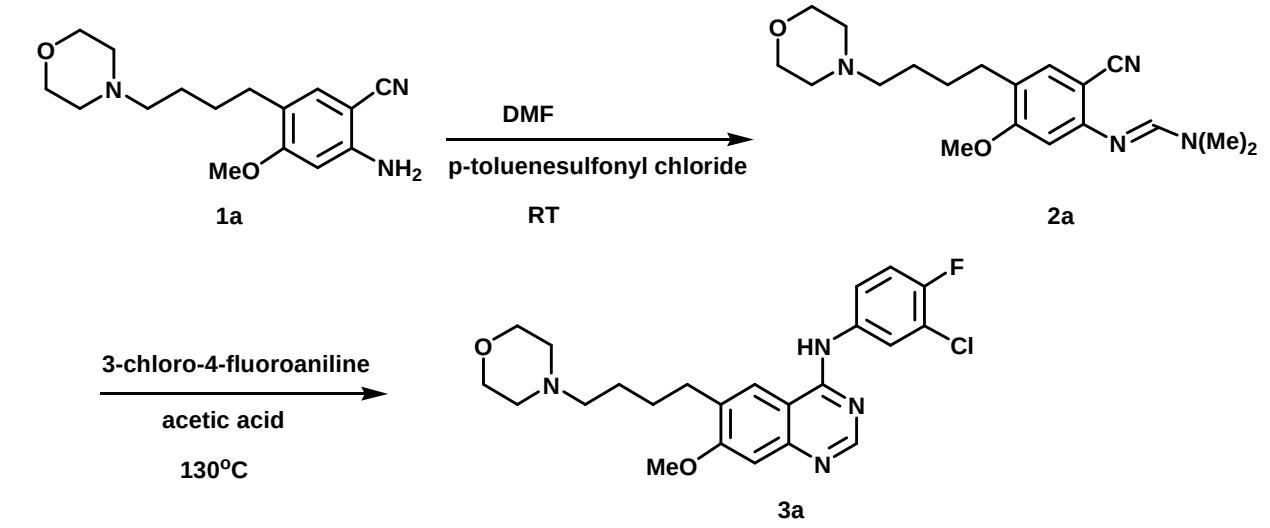
A significant proportion of human tumors overexpress growth factor receptor tyrosine kinase enzymes of the erbB family and this overexpression is associated with poor prognosis of the disease[1-3]. Inhibitors of growth factor signaling through these pathways, especially erbB1 and erbB2 have been identified as potential anti cancer drugs[4]. *Gefitinib* **(3a)** belongs to 4-anilinoquinazoline class[5] and it was the first EGFR-TKI to be approved by US FDA for treating patients with non-small-cell lung cancer (NSCLC). *Erlotinib* **(3b)** which belongs to the same class was approved by US FDA for treating patients with NSCLC and pancreatic cancer[6].

RESULTS AND DISCUSSION

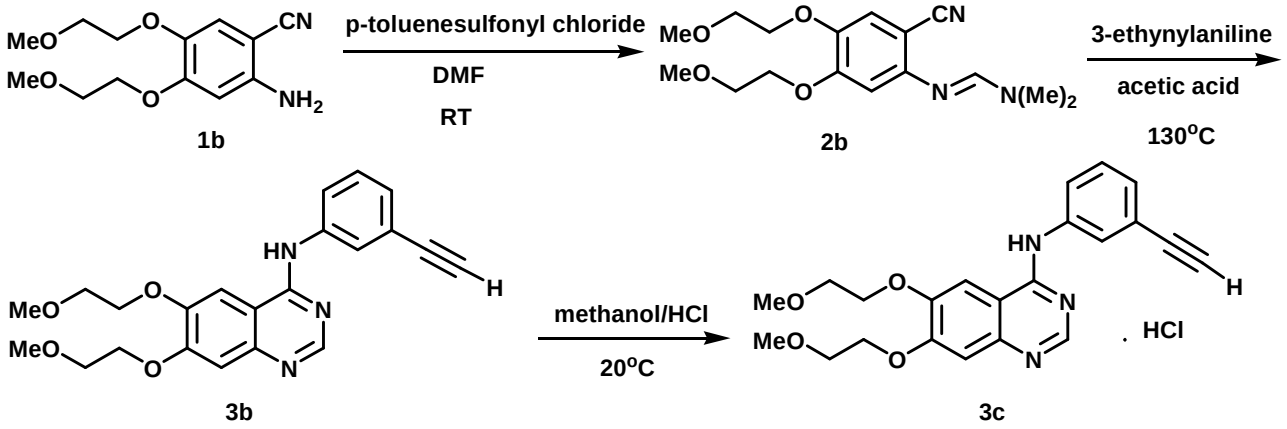
As a continuation of our interest in developing new synthetic methods for the preparation of *gefitinib* and *erlotinib*[7,8], we recently reported[9] a convergent approach to their preparation using formamidine intermediates **(2a)** and **(2b)** starting from **(1a)** and **(1b)** respectively (Scheme 1 & 2). The formamidines **(2a)** and **(2b)** used in this convergent method were prepared from **(1a)** & **(1b)** and using dimethylformamide-dimethyl acetal (DMF-DMA) which is costly and not readily available in large quantity. Thus, the industrial production of these drugs may cost more and therefore there is a need to replace DMF-DMA and make the process more efficient and cost effective.

There are several reagents used to prepare formamidines from primary amines. The use of *N*,*N*-dimethylformamide (DMF) and *p*-toluenesulfonyl chloride (TosCl) provided best results[10] However, when **(1a)** and **(1b)** were added to the pre-mixed DMF and TosCl, disappointing results were obtained and the reaction did not proceed to completion even after stirring for 5h. This procedure was modified by adding DMF-TosCl in two portions and that led to 100% conversion in 20 min. G*efitinib* **(3a)** and *erlotinib* **(3b)** were ob-

tained by treatment of **(2a)** and **(2b)** with 3-chloro-4-fluoroaniline and 3-ethynylaniline respectively.



Scheme 1



Scheme 2

In conclusion, the use of *N,N*-dimethylformamide and *p*-toluenesulfonyl chloride to prepare formamidine derivatives **(2a)** and **(2b)** provides many advantages such as easy availability of reagents, mild reaction conditions and shorter reaction times. Further, we have described the preparation of two anticancer drug molecules gefitinib and erlotinib from readily available and cheap raw materials, thus making the process highly efficient and economical.

EXPERIMENTAL

All the reagents were obtained from commercial sources and were used without further purification. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Bruker A G Spectrometer. Chemical shifts are reported in δ units downfield from TMS as internal standard. Mass spectra were acquired using GC-MS-QP2010S (direct probe) and on a Q-TOF micro™ AMPS MAX 10/6A system. HPLC analysis was performed using a Shimadzu CLASS VP using the column conditions: ODS-3V 4.6×250mm, particle size 5μ, λ=254nm, flow rate 1 mL/min, mobile phase: (40:60) buffer: acetonitrile (buffer-1% ammonium acetate). Melting points were recorded on Acro Steel Pvt. Ltd. melting point apparatus and are uncorrected.

N'-[2-Cyano-5-methoxy-4-{3-(4-morpholinyl) propoxy}phenyl]-N,N-dimethyl formamidine (2a): To a stirred solution of DMF (500 mL) and *p*-toluenesulfonyl chloride (32.5g, 0.16 mol) at RT was added **(1a)** (50g, 0.17 mol) and stirring was continued for another 10 min. Then a second portion of pre-mixed *p*-toluenesulfonyl chloride (32.5g) and DMF (500 mL)

was added and stirring continued for another 10 min. DMF was distilled off and to the liquid residue was added ice water and pH of the reaction mixture was adjusted to 9 using 4M aqueous potassium carbonate solution. The material was extracted into ethyl acetate. The organic layer was separated and washed with water. After drying, the organic layer was concentrated to afford **(2a)** as a light yellow liquid (52.5g, 90%) which was homogenous on thin layer chromatography[9] and identified to an authentic sample. IR (neat): 864, 1010, 1118, 1384, 2214, 2812, 2950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.0 (2H, m), 2.47 (6H, m), 3.06 (6H, s), 3.72 (4H, t, J = 4.5 Hz), 3.87 (3H, s), 4.03 (2H, t, J = 6.5 Hz), 6.45 (1H, s), 6.98 (1H, s), 7.57 (1H, s); HRMS: Calcd for $C_{18}H_{26}N_4O_3$ (M+H): 347.2083, Found: 347.2081.

4-[(3-chloro-4-flourophenyl)amino]-7-methoxy-6-[3-(4-morpholinyl)propoxy] quinazoline (3a): To the residue **(2a)** (52.5g, 0.151 mol) was added acetic acid (420 mL) and 3-chloro-4-fluoroaniline (26.5g, 0.175 mol). Then the reaction mixture was heated to 125-130°C and stirred for about 3h. The reaction mixture was cooled to 25°C and quenched in ice-water (700 mL). It was then neutralized to pH 8-9 with conc. ammonia. Ethyl acetate (150mL) was added and stirred for about 1h. The solid obtained was collected and then suspended in MeOH (700 mL). The reaction mixture was cooled to 20°C and conc. HCl (30 mL) was added slowly with efficient stirring. The solid was collected and washed with chilled methanol (30 mL). The solid gefitinib hydrochloride **(3a)** collected was further suspended in H_2O (850 mL), stirred for 1h at RT and then cooled to 5°C and it was washed with chilled water (30 mL) and free base was liberated using aq. ammonia to afford **(3a)** as off-white solid (52.5g, 69% yield), mp 193-195 ºC (lit. mp 194-198 ºC)[11]; HPLC purity>99%; ^1H NMR ($CDCl_3$)[7]: δ 2.11 (2H, m), 2.46-2.59 (6H, m), 3.74 (4H, dd, J = 4.5 Hz & 4.4 Hz), 3.98 (3H, s), 4.17 (2H, t, J = 6.5 Hz), 7.09 (1H, s), 7.16 (1H, t, J = 8.8 Hz), 7.26 (1H, s), 7.34 (1H, brs, exchangeable with D_2O), 7.50-7.58 (1H, m), 7.84-7.88 (1H, m), 8.66 (1H, s); GC-MS (DI, m/z): 446 (M+); *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.

N'-[2-Cyano-4,5-{bis(2-methoxyethoxy) phenyl}]-N,N-dimethyl formamidine (2b): To a stirred solution of DMF (500 mL) and *p*-toluenesulfonyl chloride (36g, 0.19 mol) at RT was added **(1b)** (50g, 0.188 mol) and stirred for about 10 min. Then a second portion of pre-mixed p-toluenesulfonyl chloride (36g) and DMF (500 mL) was added. The procedure described for **(2a)** was followed to afford **(2b)** as a light yellow liquid (60g) in quantitative yield which was homogenous on thin layer chromatography and identified to an authentic sample[9]. IR (neat): 860, 1033, 1122, 1211, 1225, 1388, 1500, 1600, 1670, 2214, 2950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.06 (6H, s), 3.44 (6H, s), 3.75 (4H, m), 4.13 (4H, m), 6.48 (1H, s), 7.02 (1H, s), 7.55 (1H, s); HRMS: Calcd for $C_{16}H_{23}N_3O_4$ (M+H): 322.1767, Found: 322.1762.

[6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine (3b): To the residue **(2b)** (60g, 0.186 mol) was added acetic acid (500 mL) and 3-ethynyl-aniline (26g, 0.22 mol) and then the reaction mixture was heated to 125-130°C and stirred for about 3h. The reaction mass was cooled to 25°C and quenched in ice water (800 mL). It was then neutralized to pH 8-9 with conc. ammonia. The material was extracted into ethyl acetate. The organic layer was washed with water and on evaporation of organic solvent obtained **(3b)** as crude material. It was then recrystallized from ethyl acetate and methanol to afford **(3b)** as cream color crystalline compound (50g, 68% yield), mp: 149-153°C. (lit. mp 149-153 ºC)[11]; ^1H NMR ($CDCl_3$): δ 3.08 (1H, s), 3.43 (6H, s), 3.80 (4H, m), 4.22 (4H, m), 7.17 (1H, s), 7.24-7.37 (3H, m), 7.61 (1H, brs), 7.74 (1H, d, J = 7.8 Hz), 7.85 (1H, s), 8.63 (1H, s); GC-MS (DI, m/z): 393 (M+).

[6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-thynylphenyl)amine hydrochloride (3c): A suspension of erlotinib **(3b)** (50g) in methanol (2 L) was cooled to 15-20°C and passed dry HCl gas for about 0.5 h. The solid was collected to afford off-white crystalline material of erlotinib hydrochloride **(3c)** (50g, 92% yield), mp: 228-230°C (lit. mp: 228-230°C)[12]; ^1H NMR (DMSO-d_6, 200 MHz): δ 3.36 (6H, s), 3.77 (4H, m), 4.29 (1H, s), 4.32-4.38 (4H, m), 7.38-7.55 (3H, m), 7.78 (1H, d, J = 8.0 Hz), 7.88 (1H, s), 8.38 (1H, s), 8.86 (1H, s), 11.42 (1H, s); *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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REFERENCES

[1] M.A.Lemmon; Breast Dis., **18**, 33-43 **(2003)**.
[2] K.K.Ang, N.H.Andratschke, L.Milas; Int.J.Radiat.Oncol.Biol.Phy., **58**, 959-965 **(2004)**.
[3] A.P.Meert, B.Martin, M.Paesmans, T.Berghmans, C.Mascaux, J.M.Verdebout, P.Delmotte, J.J.Lafitte, J.P.Sculier; J.Cancer, **89**, 959-965 **(2003)**.
[4] N.E.Hynes, H.A.Lanne; Nat.Rev.Cancer, **5**, 341-354 **(2005)**.
[5] J.F.Vansteenkiste, Expert Rev.Anticancer Ther., **4**, 5-17 **(2004)**.
[6] P.Bonomi, Expert Opin.Invest.Drugs, **12**, 1395-1401 **(2003)**.
[7] V.Chandregowda, G.Venkateswara Rao, G.C.Reddy; Heterocycles, **71**, 39-48 **(2007)**.
[8] V.Chandregowda, G.Venkateswara Rao, G.C.Reddy; Synth.Comm., **37**, 3409-15 **(2007)**.
[9] V.Chandregowda, G.V.Rao, G.C.Reddy; Org.Proc.Res and Dev., **11**, 813-816 **(2007)**.
[10] Y.Han, L.Cai; Tetrahedron Lett., **38**, 5423-5426 **(1997)**.
[11] J.P.Gilday, M.J.Welham; WO 023783 A1 **(2005)**; Chem.Abstr. **142**, 298128.
[12] R.C.Schnur, L.D.Arnold; US Patent 5747498 **(1998)**; Chem.Abstr, **128**, 321653.