*Advanced Pharmaceutical Bulletin,* **2012**, 2(1), 119-122
doi: 10.5681/apb.2012.017
http://apb.tbzmed.ac.ir/

# Modified Synthesis of Erlotinib Hydrochloride

**Leila Barghi[1,2], Ayuob Aghanejad[3,4], Hadi Valizadeh[1,5], Jaleh Barar[1,3], Davoud Asgari[1,3*]**

[1] *Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.*

[2] *Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.*

[3] *Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran.*

[4] *Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.*

[5] *Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

**ARTICLE INFO**

***Article Type:***
Research Article

***Article History:***
Received: 10 April 2012
Accepted: 29 April 2012
ePublished: 5 May 2012

***Keywords:***
Tyrosine kinase
Erlotinib
Palladium/Charcoal (Pd/C)

**ABSTRACT**

***Purpose:*** An improved and economical method has been described for the synthesis of erlotinib hydrochloride, as a useful drug in treatment of non-small-cell lung cancer. ***Methods:*** Erlotinib hydrochloride was synthesized in seven steps starting from 3, 4-dihydroxy benzoic acid. In this study, we were able to modify one of the key steps which involved the reduction of the 6-nitrobenzoic acid derivative to 6-aminobenzoic acid derivative. An inexpensive reagent such as ammonium formate was used as an *in situ* hydrogen donor in the presence of palladium/charcoal (Pd/C) instead of hydrogen gas at high pressure. ***Results:*** This proposed method proceeded with 92% yield at room temperature. Synthesis of erlotinib was completed in 7 steps with overall yield of 44%. ***Conclusion:*** From the results obtained it can be concluded that the modified method eliminated the potential danger associated with the use of hydrogen gas in the presence of flammable catalysts. It should be mentioned that the catalyst was recovered after the reaction and could be used again.

## Introduction

Although there are wide range of cytotoxic drugs with different mechanismsof action, most of them could not distinguish between cancerous and normal cell types. Growth factor signaling pathways have major role in regulating key cellular functions including cellproliferation,differentiation, metastasis and survival. An important mediator of growth factor signaling pathways is the human epidermal receptors (HERs).[1] Tyrosine kinase receptors, which belong to (HER) family, are over expressed in various types of solid tumors, including non-small-cell lung cancer (NSCLC).These receptors are cell membrane bound proteins that consist of three regions: an extracellular ligand binding site; an intracellular domain with tyrosine kinase activity and regulatory functions; and a region that binds the receptor to the cell membrane.[2-4] Phosphorylation of tyrosine residues on HERs is an important stage in signal transduction, leading to cell proliferation for major human carcinomas. Therefore, interruption of this growth signal is a potential target for anticancer treatment.[5] Erlotinib, a 4-anilinoquinazoline, is a potent inhibitor of tyrosine kinase. It reversibly and selectively binds to the adenosine triphosphate (ATP) binding site of the tyrosine kinase domain associated with HERs. Consequently phosphorylation of the tyrosine kinase is inhibited and thereby it can interfere with cell communication, signal transduction and ultimately cellular growth. [6] The common method for preparation of 4-anilinoquinazolines such as erlotinib involves the construction of suitable 4-chloroquinazoline intermediate and then reacting of this intermediate with suitable substituted aniline in acidic media. The 4-chloroquinazolines are key intermediates and their preparation involve a series of reaction and the use of highly flammable gas such as hydrogen at high pressure, and costly reagents such platinum oxide.[7] Erlotinib hydrochloride was synthesized in seven steps starting from 3, 4-dihydroxy benzoic acid. In this study, we were able to modify one of the key steps which involved the reduction of the 6-nitrobenzoic acid derivative to 6-aminobenzoic acid derivative. An inexpensive reagent such as ammonium formate was used as an *in situ* hydrogen donor in the presence of palladium/charcoal (Pd/C) instead of hydrogen gas at high pressure. This modified method eliminated the potential danger associated with the use of hydrogen gas in the presence of flammable catalysts. Furthermore catalyst could be recovered and used again.

## Materials and methods

Etynyl aniline was purchased from Sigma-Aldrich. Other chemicals were purchased from Merck Chemical

***Corresponding author:** Davoud Asgari (PhD), Research Center for Pharmaceutical Nanotechnology, and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. Tel: +98 (411) 3372252, Fax: +98 (411) 3344798, E-mail: dasgari@tbzmed.ac.ir

Company (Darmstadt, Germany). Melting points were determined by a Gallenkamp capillary apparatus. H NMR spectra were obtained with a Bruken-Spectrospin 400 MHz spectrometer (Varian, Switzerland).

***3,4-bis(2-methoxyethoxy)-benzoic acid (3)***

A suspension of 3,4-dihydroxy benzoic acid (23 g), potassium carbonate (82.5 g) and tetrabutyl ammonium iodide (5.51 g) in DMF (120 ml) was stirred for 1 h at 100 °C. The reaction mixture was cooled to 50 °C, and then 1-chloro-2-methoxyethane (54.18 ml) was added and the reaction mixture was heated to 85 °C and stirred for 20 h at this temperature. The reaction mixture was filtered and the solid material was washed with ethyl acetate (300 ml). The combined filtrates were evaporated under reduced pressure to afford a yellow residue (2). Without any further isolation and purification, the ester residue was dissolved in a solution of ethanol (200 ml), water (70 ml) and potassium hydroxide (33.5g) and stirred for 4 h at room temperature. Ethanol was removed under reduced pressure, and the pH of the solution was adjusted to ~3 by adding a solution HCl (2 N) at 0 °C. A solid was precipitated which was filtered, washed with cold water, and dried ($Na_2SO_4$) to afford carboxylic acid (3: 40 g, 99.27%) as a white solid; $R_f$ (20% n-hexane/ethyl acetate) 0.25; Mp: 101-103 °C, $^1$H-NMR ($CDCl_3$): 0.95-0.99 (t, 3H, $CH_3CH_2$, $^3$J= 7.10 Hz), 3.43 (d, 6H, 2x $OCH_3$), 3.78-3.81 (m, 4H, 2x $CH_2O$), 4.18-4.27 (q, 2H, $CH_2$, 3J=7.10 Hz), 6.90-6.92 (d, 1H, HAr, $^3$J=8.41 Hz), 7.60 (d, 1H, HAr), 7.62-7.71 (dd, 1H, HAr,$^3$J=8.41 Hz, $^4$J=1.96 Hz).

***Ethyl 3,4-bis(2-methoxyethoxy)-benzoate (4)***

To 3,4-bis(2-methoxyethoxy)-benzoic acid (40 g) in ethanol (300 ml) was added sulfuric acid (3 ml). The mixture was stirred under $N_2$ at reflux for 24 hours. The solvent was removed in vacuo and the residue was extracted with ethyl acetate. Then the organic phase was washed with sodium bicarbonate solution and brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford ethyl 3,4-bis(2-methoxyethoxy)-benzoate (31.65 g, 71.63%); Mp: 56.5-57.5°C, $^1$H-NMR ($CDCl_3$): 1.30-1.33 (t, 3H, $CH_3CH_2$, $^3$J= 7.10 Hz), 3.44 (s, 6H, 2x $OCH_3$), 3.76-3.73 (m, 4H, 2x $CH_2O$), 4.16-4.21 (m, 4H, 2 x $CH_2O$), 4.31-4.36 (q, 2H, $CH_2$, 3J=7.10 Hz), 6.89-6.92 (d, 1H, HAr, $^3$J=8.41 Hz), 7.50-7.52 (d, 1H, HAr,$^4$J=1.96 Hz), 7.60-7.62 (dd, 1H, HAr,$^3$J=8.41 Hz, $^4$J=1.96 Hz).

***Ethyl 4,5-bis(2-methoxyethoxy)-2-nitro-benzoate (5)***

The product of previous step (30g) in acetic acid (90 ml)was treated drop wise with conc. $HNO_3$ (25ml) at 5 °C, and the solution was stirred 24 hours before pouring in to the ice. The solvent was removed in vacuo and the residue was extracted with ethyl acetate. Then the organic phase was washed with sodium bicarbonate solution and brine and concentrated in vacuo to afford Ethyl 4,5-bis(2-methoxyethoxy)-2-nitro-benzoate (32 g, 92.75%); $^1$H-NMR ($CDCl_3$): 1.32-1.36 (t,3H, $CH_3CH_2$, $^3$J= 7.20 Hz), 3.44 (s, 6H, 2x $OCH_3$), 3.71-3.81(m, 4H, 2x $CH_2O$), 4.23-4.27 (m, 4H, 2x $CH_2O$), 4.34-4.36 (q, 2H, $CH_2$, $^3$J=7.20 Hz),7.13 (s, 1H, HAr,), 7.50 (s, 1H, HAr).

***2-amino-4,5-bis (2-methoxyethoxy)-benzoate (6)***

2-Propanol (350 ml) was added to a flask containing Pd/C (9.32 g). Ammonium formate (55.14 g) in water (35 mL) was transferred to the same flask. The reaction mixture was stirred for 1 min to activate Pd/C. Next, Ethyl 4,5-bis(2-methoxyethoxy)-2-nitro-benzoate (30 g) were added, and the reaction mixture was stirred at room temperature (20 min). The reaction mixture was filtered and the solid material was washed with ethyl acetate and 2-propanol. The filtrate was evaporated under reduced pressure and the residue was extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated in vacuo to afford 2-amino-4,5-bis (2-methoxyethoxy)-benzoate (25.270 g, 92.33%); $^1$H-NMR ($CDCl_3$):1.34-1.37 (t, 3H, $CH_3CH_2$, $^3$J= 7.10 Hz), 3.43 (s, 6H, 2x $OCH_3$), 3.71-3.77 (m, 4H, 2x $CH_2O$), 4.06-4.10 (m, 4H, 2x $CH_2O$), 4.26-4.31 (q, 2H, $CH_2$, $^3$J=7.10 Hz), 5.65 (br, 2H, $NH_2$), 6.14 (s, 1H, HAr,),7.41 (s, 1H, HAr).

***6,7- bis (2-methoxy-ethoxy) quinazolone (7)***

2-amino-4,5-bis (2-methoxyethoxy)-benzoate(25g) and ammonium formate(5g) were dissolved in formamide(38ml) and the stirred mixture was heated to 160-165 °C under an atmosphere of $N_2$ for 2 hours. Cold $H_2O$ was added and precipitated product was recovered by filtration, washed with cold $H_2O$ and dried in oven. The filtrate was extracted with $CHCl_3$ and the organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue and quinazolone precipitate were combined, treated with ether and filtered to afford 6,7- bis (2-methoxy-ethoxy) quinazolone (20.45, 87.1%); Mp: 190-191°C, $^1$HNMR ($CDCl_3$): 3.48 (s, 6H, $OCH_3$), 3.81-3.87 (m, 4H, 2x $OCH_2$), 4.27-4.29(m, 4H, 2x $OCH_2$), 7.15(s, 1H, HAr), 7.59 (s, 1H, HAr), 8.04 (s, 1H, HAr).

***4-chloro-6,7-bis- (2-methoxy-ethoxy)- quinazoline (8)***

To 6,7- bis (2-methoxy-ethoxy) quinazolone (18.5g) in $CHCl_3$ (470 ml) containing 2.5 ml DMF was added oxalylchloride (19 ml) in four portions over 20 minutes. Once foaming ceased the solution was refluxed 2 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane and washed with brine, sodium bicarbonate and water. The organic phase was dried over sodium sulfate and concentrated in vacuo to give 4-chloro-6,7-bis- (2-methoxy-ethoxy)- quinazoline (19.5g, 99.1%); Mp: 107-108 °C, $^1$H-NMR ($CDCl_3$): 3.49 (s, 3H, $OCH_3$), 3.50 (s, 3H, $OCH_3$), 3.88-3.90 (m, 4H, 2x $OCH_2$), 4.32-4.39 (m, 4H, 2x $OCH_2$), 7.36 (s, 1H, HAr),7.44 (s, 1H, HAr), 8.88 (s, 1H, HAr).

***Erlotinib hydrochloride (9)***

4-chloro-6,7-bis- (2-methoxy-ethoxy)- quinazoline (19.5 g ) was suspended in 300 ml water and 3-ethynylaniline (8.4 g )and 37% hydrochloric acid (5.2 ml ) was added at 25-30 °C. The reaction mixture was heated at 40 °C and stirred for 1.5 hours. After cooling, obtained solid material was filtered and washed with water and ethylacetate:n-hexane (50:50) and was dried in oven at 40 °C to afford erlotinib hydrochloride(22.26g, 83%); Mp: 225-227 °C, $^1$H NMR (DMSO-d6) δ 11.13 (s, 1H, NH), 8.70 (s, 1H, H-Ar), 8.14 (s,1H, H-Ar), 7.70-7.81 (m, 2H, H-Ar), 7.28-7.51 (m, 3H, HAr),4.31-4.32 (m, 4H, 2 CH2O), 3.74-3.77 (m, 4H, 2 CH2O), 3.67 (s, 1H, ethynyl), 3.33-3.34 (d, 6H, 2 OCH3).

**Results and Discussions**

The synthesis of erlotinib (Figure 1) was started from 3,4-dihydroxy benzoic acid. O-alkylation of 3,4-dihydroxy benzoic acid with 4.0 equivalent of 1-chloro-2-methoxyethane in hot DMF afforded intermediate methoxyethoxy-3,4-bis(2-methoxyethoxy)-benzoate in quantitative yield. DMF was then removed and basic hydrolysis of the ester was performed in the same batch to afford the 3,4-bis(2-methoxyethoxy)-benzoic acid in 99.27% overall yield. No further purification was performed in this step. Esterification of carboxylic acid in acidic ethanol gave ethyl 3,4-bis (2-methoxy-ethoxy)benzoate. Nitration of ethyl 3,4-bis(2-methoxyethoxy)-benzoate in nitric acid and glacial acetic acid at 0 °C afforded the single nitro product in 92.75% yield. No purification was performed in this step.[8] There have been reports on the reduction of nitro compounds to their corresponding derivatives using ammonium formate as in situ hydrogen donor.[9]So, the reduction of the nitro group of ethyl 3,4-bis(2-methoxyethoxy)-2-nitro-benzoate, by using ammonium formate and Pd/C catalyst in aqueous alcoholic solvent at room temperature gave 2-amino-4,5-bis (2-methoxyethoxy)-benzoate. The cyclization of this product and construction of 6,7- bis (2-methoxy-ethoxy) quinazoloneby using formamide and ammonium formate was the next step. Then chlorination of quinazolone carried out by using oxalylchloride. The reaction mixture was refluxed 1.5 hours and 4-chloro-6,7-bis- (2-methoxy-ethoxy)-quinazoline was formed. Finally erlotinib hydrochloride was prepared in aqueous medium by using 3-ethynylaniline under acidic condition. The proposed method for reduction of 6-nitrobenzoic acid derivative proceeded with 92.33% yield at room temperature. Synthesis of erlotinib was completed in 7 steps with overall yield of 44%.

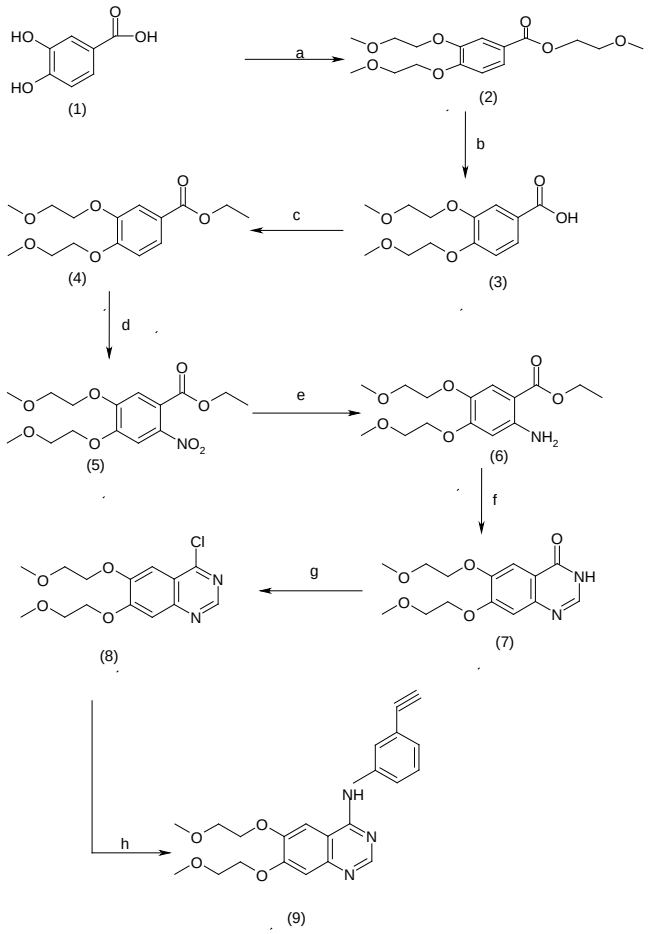


**Figure 1.** a) $K_2CO_3$, $ClCH_2CH_2OCH_3$, TBAI, DMF, 85 °C, 20h; b) KOH, $CH_3CH_2OH$, $H_2O$, 4h; C) $CH_3CH_2OH$,$H_2so_4$,90°C; d) $HNO_3$, glacial acetic acid, 0 °C, 2h; e)ammonium formate, Pd/C,2-propanol,25°C,20 min; f)ammonium formate, formamide, 160°C, 2h; g)$CHCl_3$, DMF, oxalylchloride,80°C, 1.5h; h)$H_2O$,3-ethynylaniline, HCl, 25°C, 1.5h.

**Conclusion**

An improved and economical method has been described for the synthesis of erlotinib hydrochloride, which is used as a second- and third-line treatment of advanced or metastatic NSCLC. One of the key steps of erlotinib formation which involved the reduction of the 6-nitrobenzoic acid derivative to 6-aminobenzoic acid derivative was modified. An inexpensive reagent such as ammonium formate was used as an in situ hydrogen donor in the presence of Pd/C instead of hydrogen gas at high pressure. This modified method eliminated the potential danger associated with the use of hydrogen gas in the presence of flammable catalysts. Furthermore catalyst could be recovered and used again.

**Acknowledgement**

The authors would like to thank research center for pharmaceutical nanotechnology. This article was a part of a thesis submitted for PhD degree (No.51) in Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

**Conflict of interest**

The authors report no conflicts of interest.

**References**

1. Chandregowda V, Kush AK, Chandrasekara Reddy G. Synthesis and in vitro antitumor activities of novel 4-anilinoquinazoline derivatives. *European Journal of Medicinal Chemistry* 2009;44(7):3046-3055.
2. Danielle M G. Molecular targets in cancer therapy. *Seminars in Oncology Nursing* 2003;19(3):193-205.
3. Janine S. Erlotinib: Small-molecule targeted therapy in the treatment of non-small-cell lung cancer. *Clinical Therapeutics* 2005;27(10):1513-1534.
4. Ullrich A, Schlessinger J. Signal transduction by receptors with tyrosine kinase activity. *Cell* 1990;61(2):203-212.
5. Lepper ER, Swain SM, Tan AR, Figg WD, Sparreboom A. Liquid-chromatographic determination of erlotinib (OSI-774), an epidermal growth factor receptor tyrosine kinase inhibitor. *Journal of Chromatography* 2003;796(1):181-188.
6. Clay D, Lipman YM, Bonk ME. Erlotinib (Tarceva): A brief overview.*P and T* 2005;30(10):561-562, 571-572, 602.
7. Rodney CaughrenSchunr, Arnold LD. Inventors; Pfizer Inc. New york,N.Y, assignee. Alkynyl and Azido substituted 4-Anilinoquinazolines. US patent 5747498, 1998.
8. Asgari D, Aghanejad A, Mojarrad JS. An Improved Convergent Approach for Synthesis of Erlotinib, a Tyrosine Kinase Inhibitor, via a Ring Closure Reaction of Phenyl Benzamidine Intermediate. Bull Korean Chem Soc. 2011;32(3):909
9. Byun E, Hong B, De Castro KA, Lim M, Rhee H. One-pot reductive mono-N-alkylation of aniline and nitroarene derivatives using aldehydes. *J Org Chem* 2007;72(25):9815-9817.

 