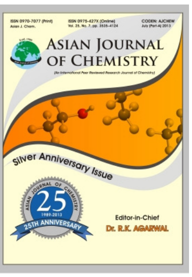
Asian Journal of Chemistry;   Vol. 25, No. 8 (2013), 4599-4602

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14247



Research and Development of a Novel Process for Nilotinib: A Bcr-Abl Inhibitor

K. AMALA[1,*], A.K.S. BHUJANGA RAO[1], R. SREENIVAS[1] and P.K. DUBEY[2]

[1]Natco Research Centre, B-13, Industrial Estate, Sanath Nagar, Hyderabad, India
[2]Department of Chemistry, JNTU College of Engineering, kukatpally, Hyderabad, India

*Corresponding author: Fax: +91 40 23710578; Tel: +91 40 23710575; E-mail: amala@natcopharma.co.in

(*Received*: 30 June 2012;   *Accepted*: 18 February 2013)   AJC-13021

In this study, an efficient, economic and novel process for the production of highly pure nilotinib (**1**), a Bcr-Abl inhibitor in described. The synthesis comprises the chlorination of 4-methyl-3-nitro benzoic acid (**2**) to get 4-methyl-3-nitro benzoyl chloride (**2A**). Condensation of compound (**2**) with 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzeneamine (**11**) to obtain 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-nitro-benzamide hydrochloride (**3**). Reducing compound (**3**) with stannous chloride (or) raney nickel to obtain 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-amino-benzamide (**4**). Reaction of compound (**4**) with cyanamide to obtain 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-guanidino-benzamide (**5**). Condensation of the compound (**5**) with 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (**8**) to obtain nilotinib (**1**).

Key Words: Bcr-Abl inhibitor, Chlorination.

INTRODUCTION

Nilotinib hydrochloride, (4-methyl-N[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-{{4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide hydrochloride), a protein tyrosine inhibitor[1,2] is the orally active drug developed by Novartis, approved in October 2007 by United States Food and Administration as Tasigna (150 mg) for the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib. On June 2010 the US Food and Drug Administration (FDA) granted accelerated approval to nilotinib hydrochloride monohydrate (Tasigna®) Capsules for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP-CML). The recommended nilotinib dose for this indication is 300 mg orally twice daily. The first synthetic approach (Fig. 1) reported[3] for nilotinib (**1**) involved in the condensation of 3-amino-4-methyl benzoic acid ethyl ester (**6**) with cyanamide followed by treatment with ammonium nitrate to provide 3-[(aminoiminomethyl)amino]-4-methylbenzoic acid ethyl ester mononitrate (**7**) (Fig. 1). In our hands it was observed that the yield of compound (**7**) is very low (25-30 %) with low purity (90 %). The condensation of **7** with 3-dimethylamino)-1-(3-pyridinyl)-2-propen-1-one (**8**) in refluxing ethanol for 68 h yielded 4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]-benzoic acid ethyl ester (**9**) after recrystallization with diethyl ether. It was observed that the yield of compound (**9**) is low (35 %) taking long time for completion of reaction (65 h) making the process unviable and the reaction time is very lengthy, which could be problematic for commercial scale operation. Further use of diethyl ether is not adaptable on commercial scale of its high flammable and volatility. Hydrolysis of compound **9** with aqueous ethanol yielded 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinylamino]-benzoic acid (**10**) after treatment with diethyl ether. Compound **10** on condensation with 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzeneamine (**11**) in presence of diethylcyanophosphonate in N,N-dimethylformamide at 60 ºC (12 h) yielded nilotinib base. The whole process is reported for milligram scale and it involves very expensive and toxic reagent diethylcyanophosphate.

Another synthetic approach (Fig. 2) reported[4] involves the condensation of methyl ester of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinylamino]-benzoic acid (**12**) with 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzeneamine (**11**) in presence of potassium *tert*-butoxide base and THF solvent at -20 ºC to -10 ºC. Work-up involves adding sodium chloride solution to THF, extraction with isopropyl acetate, separation and washing of isopropyl acetate with 15 % aqueous sodium chloride solution and distillation of isopropyl acetate affording nilotinib base after recrystallization with isopropyl acetate, ethanol and water mixture at -15 ºC to -10 ºC. This process involves multiple solvents like THF, isopropyl acetate

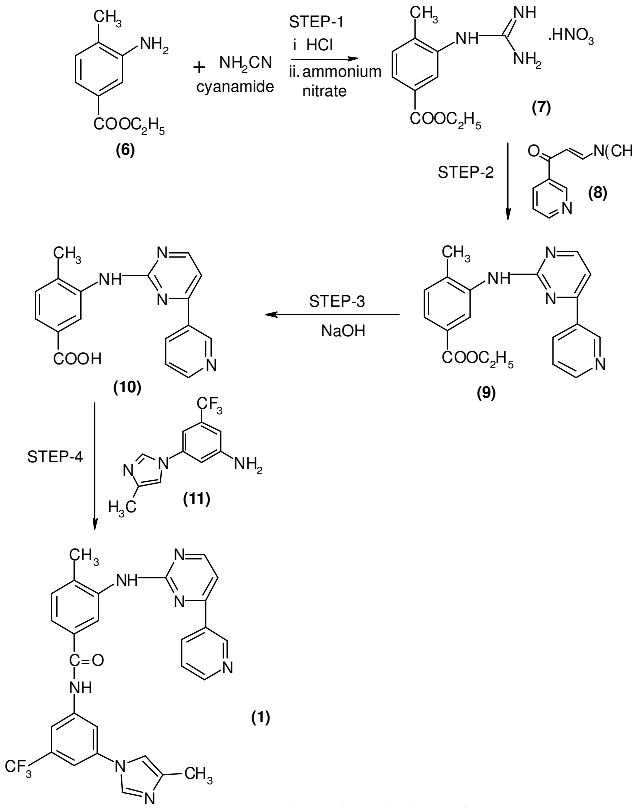


Fig. 1. Preparation of nilotinib (Ref. 3)

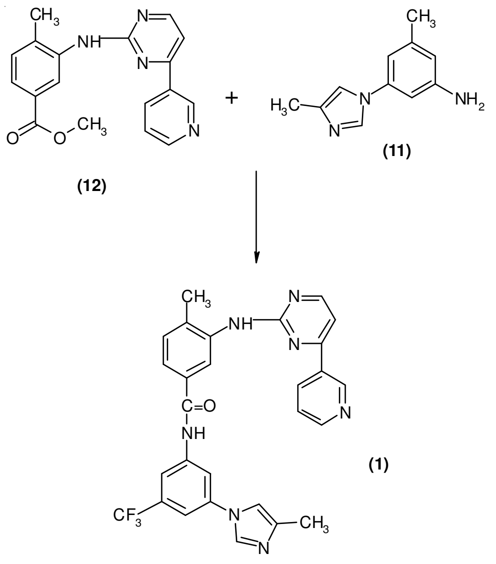


Fig. 2. Synthetic approach of nilotinib (Ref. 4)

and ethanol. Further all these solvents cannot be recovered and recycled as used as mixed solvents with water thus posing environmental problems. Subsequently, another reported process[5] follows a reaction sequence similar to that represented in Fig. 2 involving condensation of the acid chloride of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinylamino]-benzoic acid (**12**) with 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)benzeneamine (**11**). This process results in unaccepted amounts of impurities. Herein, we are reporting an improved, efficient and environment friendly process for nilotinib (**1**), which provides multiple benefits such as safety and increased throughput with economic advantage over the reported processes.

EXPERIMENTAL

Melting points were determined on mettler melting point apparatus, in open capillary tubes and are uncorrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded on a Bruker avance-III 400MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane as an internal standard and are given in δ units. The solvent used for NMR spectra is deutero dimethyl sulfoxide unless otherwise stated. Infrared spectra were taken on Brucker in potassium bromide pellets unless otherwise stated. High-resolution mass spectra were obtained with a waters mass spectrometer. All reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm). The gas chromatography on Agilent Technologies 6890B with head space was used for analyzing the residual solvents. Common reagent grade commercially available chemicals were used without further purification.

Process for the preparation of nilotinib (1)

Preparation of 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-nitro-benzamide hydrochloride (3): To a suspension of 100 g (0.55 mol) of 4-methyl-3-nitro benzoic acid (**2A**) in chloroform (1 L) thionyl chloride 131.5 g (1.10 mol) and dimethyl formamide (1 mL) were added. The reaction mass was heated to reflux temperature and maintained at the same temperature for 3 h. Solvent chloroform was distilled off completely under vacuum and again 500 mL of chloroform was charged and distilled under vacuum to remove traces of thionyl chloride. The residual 4-methyl-3-nitro benzoyl chloride (**2**) was taken directly to the following condensation step. 5-(4-Methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzeneamine (**11**) 110 g (0.45 mol) was dissolved in 1 L of chloroform. 4-Methyl-3-nitro benzoyl chloride prepared above was added slowly to the reaction mass at 10-15 ºC for 1 h. The temperature of the reaction mass was raised to room temperature and maintained for 4 h. The reaction mass was filtered, washed with chloroform and dried. Yield: 161 g (87 %). Purity: 99 % (by HPLC). ^{1}H NMR DMSO-d_6. Imidazole-CH_3 (3H, 2.18, s) Ar-CH_3(3H, 2.61,s), imidazole -CH (1H, 7.48-S), imidazole-CH-(1H, 7.71, m), Ar-H (6H, 7.71-8.628, m), Ar-amide (1H, 10.8, s). IR was consistent with the proposed structure.

Preparation of 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-amino-benzamide (4): To a chilled solution (10-15 ºC) of stannous chloride 265.6 g (1.18 mol) in 400 mL methanol. 4-Methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-nitro-benzamide hydrochloride (**3**) 130 g (0.29 mol) obtained from step- (a) was added during 0.5 h. The reaction mass was maintained at 10-15 ºC for 1 h and heated to reflux temperature and then brought to room temperature. Purified water (600 mL) was charged to reaction mass at room temperature and maintained under stirring for 6-8 h. Reaction mass was filtered, washed with 1 N HCl. The wet solid was charged into 2 L purified water, cooled to 10-15 ºC and basified with 4 % aqueous sodium hydroxide solution. The reaction mass was brought to room temperature and maintained at the same temperature for

2 h, filtered and dried at 50-60 ºC to yield compound (**4**). Yield: 104 g (80 %). Purity: 99.4 % (by HPLC).

Alternatively compound (**4**) can be prepared by the catalytic hydrogenation of compound (**3**) with raney nickel in methanol medium as follows: In a hydrogenation kettle 50 g (0.123 mol) of 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-nitro-benzamide hydrochloride (**3**) obtained from step- (a) was charged into 250 mL methanol. Raney nickel (20 g) was charged into pressure reactor kettle and hydrogenated at a hydrogen gas pressure of 60 psi for 22 h. After reaction completion reaction mass was filtered and washed with methanol. To the filtrate aqueous ammonia solution (45 mL) was charged and stirred for 0.5 h. Reaction mass was filtered, washed thoroughly with purified water and dried at 50-60 ºC to yield compound (**4**). Yield: 35 g (70 %). Purity: 99.0 % (by HPLC), MR: 210-212 ºC, ^{1}H NMR DMSO-d_6, Ar-CH$_3$(3H , 2.13, s), imidazole-CH$_3$ (3H, 2.18, s), Ar-NH$_2$(2H, 5.14,s), imidazole -CH (1H, 7.104, s), imidazole-CH (1H, 7.11, m), Ar-H (6H, 7.11-8.29, m) Ar-amide-(1H, 10.46, s), IR was consistent with the proposed structure.

Preparation of 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-guanidino-benzamide (5): To a suspension of 80 g (0.213 mol) of 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-amino-benzamide (**4**) obtained from step-(b) in 480 mL *n*-butanol 20.2 mL of concentrated hydrochloric acid was added. A solution of 18 g (0.427 mol) of cyanamide in 18 mL water was added and reaction mass was heated to 90-95 ºC for 20 h while maintaining pH at 2-3 with concentrated hydrochloric acid (22 mL). The reaction mass was cooled to 10-15 ºC, filtered and washed with chilled *n*-butanol. Wet solid was charged into 1.5 L purified water and, basified with 40 % aqueous sodium hydroxide solution. The reaction mass was maintained at room temperature for 2 h, filtered, washed with water and dried at 60-65 ºC to yield compound (**5**). Yield: 86.3 g (97 %), purity: 99.1 %, ^{1}H NMR DMSO-d_6, imidazole-CH$_3$ (3H, 2.14, s), Ar-CH$_3$(3H, 2.18, s), Ar-NH-(4H, 3.789, s) imidazole-CH(1H, 7.24, s), imidazole-CH-(1H, 7.26, m), Ar-H-(6H, 7.26-8.13, m) Ar-amide-(1H, 10.46, s). IR was consistent with the proposed structure.

Preparation of nilotinib (1): A mixture of 65 g (0.156 mol) of 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-guanidino-benzamide from step-(c), 30.0 g (0.171 mol) of 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (8) in 650 mL *n*-butanol was heated at 110-115 ºC for 9 h. The reaction mass was brought to room temperature and the separated solid (70 g) was filtered off. Wet solid was leached with hot water (700 mL) and hot methanol (700 mL) successively. The wet product was dried at 60-65 ºC under vacuum to yield Nilotinib (**1**). Yield: 52.1 g (63 %), MR: 235-236 ºC, Purity: 99.2 % (by HPLC), ^{1}H NMR DMSO-d_6, Ar-CH$_3$(3H , 2.18, s) imidazole-CH$_3$ (3H, 2.36, s) Ar-NH (1H, 9.17, s) Ar-H (14, 7.44-9.28, m) Ar-amide (1H, 10.61, s). IR was consistent with the proposed structure.

RESULTS AND DISCUSSION

Preparation of nilotinib (1) (Fig. 3): Critical and cost contributing intermediate 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzeneamine (**11**) is prepared as per the literature procedure[6].

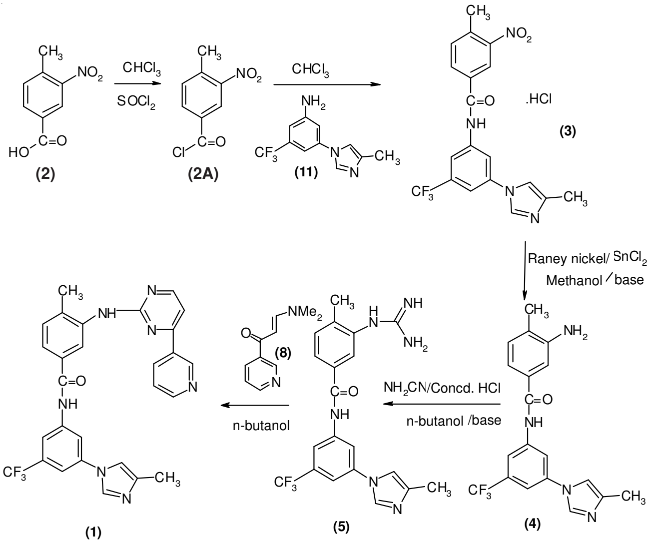


Fig. 3. Synthetic route of nilotinib

Step-1 consists of chlorination of 4-methyl-3-nitro benzoic acid (**2**) to get 4-methyl-3-nitro benzoyl chloride (**2A**). Condensation of compound (**2A**) with 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzeneamine (**11**) to obtain 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-nitro-benzamide hydrochloride (**3**). **Step-1** condensation has been attempted with solvents such as DMF, chloroform and isopropanol using different inorganic bases such as sodium hydroxide, potassium hydroxide and sodium carbonate. Among these combination, it was found that chloroform using potassium hydroxide base at 30-40 ºC provided the intermediate **3** with quantitative yield and high purity (99 %).

Step-2 consists of reducing compound (**3**) with stannous chloride (or) raney nickel to obtain 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-amino-benzamide (**4**). The reduction has been attempted using different reducing agent such as stannous chloride/cond. HCl, stannous chloride/methanol, Pd-C and raney nickel. Among these reducing agents stannous chloride/methanol and raney nickel in methanol medium gave the intermediate **4** with quantitative yield and high purity (99 %).

Step-3 consists of reaction of compound (**4**) with cyanamide to obtain 4-methyl-N-[3-(4-methyl-1*H*-imidazol-1-yl-5-(trifluoromethyl)phenyl]-3-guanidino-benzamide (**5**). This condensation has been attempted in presence of molar quantities of acids such as concentrated sulfuric acid, concentrated hydrochloric acid and concentrated nitric acid employing ethanol, isopropyl alcohol and *n*-butanol as solvents. Among these combinations it was found that using concentrated hydrochloric acid lot wise in *n*-butanol solvent at 90-95 ºC yielded intermediate **5** with quantitative yield and high purity (99 %).

Step-4 consists of condensation of the compound (**5**) with 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (**8**) to obtain Nilotinib (**1**). The condensation has been attempted in solvents such as ethanol, isopropanol and *n*-butanol. Among these solvents *n*-butanol solvent at 110-115 ºC for 9 h gave nilotinib (**1**) with quantitative yield and 99.2 % HPLC purity.

Conclusion

Yields realized are fairly high in all the steps (60-97 %) as compared to 20-50 % realized by the process disclosed in the prior art(WO2004/005281). Reaction times are fairly low (9-20 h) at all the steps as compared to the time 12-65 h for most of the stages in the processes disclosed in the above mentioned patent. Obnoxious and foul smelling, difficult to handle reagents are avoided making the process environmentally safe for commercial application. Consequently the process is simple, economical and viable for plant scale operations.

ACKNOWLEDGEMENTS

The authors thank the Management of Natco Pharma Limited for encouragement and support. The technical help from the Analytical department is gratefully acknowledged.

REFERENCES

1. T. O'Hare, D.K. Walters, M.W.N. Deininger and B.J. Druker, *Cancer Cell*, **7**, 117 (2005).
2. E. Weisberg, P.W. Manley, W. Breitenstein, J. Bruggen, S.W. Cowan-Jacob, A. Ray, B. Huntly, D. Fabbro, G. Fendrich, E. Hall-Meyers, A.L. Kung, J. Mestan, G.Q. Daley, L. Callahan, L. Catley, C. Cavazza, M. Azam, D. Neuberg, R.D. Wright, D.G. Gilliland and J.D. Griffin, *Cancer Cell*, **7**, 129 (2005).
3. B. Werner, F. Pascal, J. Sandra and M.P. William, CAS No. 140: P77161v, WO 2004/005281 (2004).
4. M. Joseph and S. Wen-Chung, CAS No. 146:81883, WO2006/135641 (2006).
5. Y. Wang, V.K. Kansal, J. Zhu, R. Lifshitz-Liron, D.K.N. Mistry, S.I. Vasoya, S. Ariyamuthu and G. Pilarski, CAS No. 152:192145, US 2010/0016590 (2010).
6. A. Stephen, A. Murat, E.R.B. Bernard, K. Chrostoph, S. Joseph, M. Mark, P. Mahavir, S. Wen-chung and X. Song, WO2006/135640 (2006).