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Scalable and Impurity-Free Process for Dasatinib: Src and BCR-Abl Inhibitor

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An efficient, telescopic, impurity-free and scalable process for Bcr-Abl and Src family tyrosine kinase inhibitor for synthesis of Dasatinib with high yield and purity is described.

Keywords: Impurity-free process, Dasatinib, Src inhibitor, BCR-Abl inhibitor.

INTRODUCTION

Dasatinib, a dual selective Bcr-Abl and Src family tyrosine kinase inhibitor is a novel anticancer drug approved by the US food and drug administration (USFDA) for the treatment of chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia [1-5]. The reported synthetic methods proceeded with complicated work-ups, difficult purification procedures, fairly expensive or unfriendly catalysts, such as *n*-butyl lithium, sodium hydride, *etc*. [6]. While further alterations of the above procedures have also been published in numerous patents. All these methods suffer from several drawbacks, including complicated purification procedures, low overall yields and the employment of some expensive, unstable or environmentally unfriendly catalysts and reagents [7-9]. Consequently, still left overs a high-unmet need for a high yield process valid for the multikilogram production of Dasatinib. Herein, we described the development of a scalable synthesis of Dasatinib in a high overall yield and purity.

EXPERIMENTAL

All reagents were procured from commercial sources and used without any further purification. The melting points of the final products were determined on Stuart melting point apparatus (SMP-30, Stuart, Staffordshire UK) in open capillaries. The progress of the reaction was monitored by thin layer chromatography (TLC) by using commercially available silica coated Merck silica gel 60 F_{254} aluminum sheets and spots were visualized under UV-visible light. The ^{1}H and ^{13}C NMR data were collected on Bruker NMR instrument (Model: AVANCE III 400) operating at 400 and 100MHz respectively, by using DMSO-d_6 as a solvent and tetramethylsilane as internal standard. The electrospray ionization data was collected on waters Quattro micro API triple quadrupole mass spectrometer in positive ionization mode. The IR spectral data of all the compounds were recorded on Bruker FT-IR spectrometer (Model:TENSOR-27). Elemental analyses were performed on Q-Toff-2010 elemental analyzer.

Ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (2): Into a clean and dry 1 L, 4-neck round bottom flask connected to a mechanical stirrer, condenser, thermometer socket is charged with ethyl 2-aminothiazole-5-carboxylate (2-ATC) (50 g), dimethylaminopyridine (DMAP) (3.2 g), di-*tertiary*-butyldicarbonate (DIBOC) (95.2 g), dimethylformamide (DMF) (250 mL) in the presence of N_2 atmosphere and stirred the reaction mass for 24 h at 25-30 °C. After TLC compliance, filter the reaction mass through a Buchner funnel and flask kept under plant vacuum. Washed the wet cake with 100 mL of acetonitrile and dried the wet material in the dryer at 60-65 °C for 4-6 h.

Purification: Into a clean and dry 1 L 4-neck round bottom flask connected to a mechanical stirrer, condenser, thermometer socket and charged above crude (60.0 g) and 300 mL of acetonitrile under stirring at 25-30 °C and stirred the reaction mass for 45-60 min at 75-80 °C. After completion of the maintenance time, cooled the reaction mass temperature to 25-30 °C and transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum. Washed the wet cake with 25 mL of acetonitrile and dried the component in the dryer at 60-65 °C for 4-6 h to furnish 59 g of the title compound with purity above 99 %.

Light brown colour solid; Elemental analysis $C_{11}H_{16}N_2O_4S$ calcd (found) %: C 48.52 (48.22), H 5.92 (5.98), N 10.29 (10.40), O 23.50 (23.20), S 11.77 (11.91). IR (KBr, ν_{max}, cm^{-1}): 3417.47-3388.20, 3162.53-2905.33, 1716.15, 1572.53, 1529.19; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.272-1.308 (t, 3H, -CH_3), 1.508 (s, 9H, -3CH_3), 4.242-4.295 (q, 2H, -CH_2), 8.052 (s, 1H, ArH), 12.040 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.58, 161.77, 152.99, 145.78, 121.21, 82.66, 61.24, 28.06, 14.43; ESI-MS (*m/z*): 273.17 (M+1), 274.18 (M+2).

2-*tert*-Butoxy-carbonylamino-thiazole-5-carboxylic acid (3): Into a clean and dry 2 L 4-neck round bottom flask connected to a mechanical stirrer, condenser, thermometer socket is charged with 600 mL of 6N NaOH solution and slowly add 25 g of ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (**2**) to the 6N NaOH solution at 25-30 °C within 30-60 min period. Maintained the reaction mass at 25-30 °C for 24 h and after TLC compliance added 6N HCl solution (600 mL) to the reaction mass at 25-30 °C within 60-90 min period (pH test limit should be 0.5-1.5). Maintained the reaction mass at 25-30 °C for 60-90 min period and transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum. Washed the wet cake with 100 mL DM water and dried the above wet material in the dryer at 60-65 °C for 6-8 h to furnish 17 g of the title compound with purity above 99 %.

Off white colour solid; Elemental analysis $C_9H_{12}N_2O_4S$ calcd (found) %: C 44.25 (44.55), H 4.95 (4.72), N 11.47 (11.31), O 26.20 (26.07), S 13.13 (13.16). IR (KBr, ν_{max}, cm^{-1}): 3434.68, 3167.64, 2980.51, 1727.41, 1672.79, 1576.45, 1522.35; ^{1}H NMR (400 MHz, DMSO-d_6): δ1.506 (s, 9H, -3CH_3), 7.970 (s, 1H, ArH), 11.937 (s, 2H, -NH & -OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.34, 163.09, 152.91, 145.39, 122.46, 82.40, 28.04; ESI-MS (*m/z*): 245.12 (M+1), 246.13 (M+2).

2-*tert*-Butoxycarbonylamino-thiazole-5-carboxylic acid chloride (4): Into a clean and dry 1 L 4-neck round bottom flask connected to a mechanical stirrer, condenser, thermometer socket is charged with 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylic acid (3) (25.0 g), THF (1 L) and DMF (1 mL) at 25-30 °C under stirring. Charged thionyl chloride (22.5 mL of thionyl chloride dissolved in 125 mL of dichloromethane) to the mass at 25-30 °C. Maintained the reaction mass at 25-30 °C for 4-6 h and after TLC compliance, distilled-off solvent completely under plant vacuum at the temperature not crossing 50 °C. Charged THF (125 mL) to the reaction mass, stirring the mass for 10-15 min and distilled-off solvent completely under plant vacuum at the temperature not crossing 40 °C. Charged 125 mL of dichloromethane to the reaction mass, stirring the mass for 10-15 min and distilled-off solvent completely under plant vacuum at the temperature not crossing 40 °C to furnish 27-28 g of crude compound.

2-*tert*-Butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide (5): Into a clean and dry 3 L 4-neck round bottom flask connected to a mechanical stirrer, condenser and thermometer socket is charged with 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylic acid chloride (4) crude (27.5 g) and dichloromethane (750 mL) under stirring. Cooled the reaction mass to 0-5 °C and add 2-chloro-6-methyl aniline (22.2 g) to the reaction mass at 0-5 °C within 30-45 min period. Added DiPEA to the reaction mass at 0-5 °C in 30-45 min period, raised the reaction mass temperature to 25-30 °C and stirred the reaction mass at 25-30 °C for 24 h. After TLC compliance distilled-off the solvent completely under plant vacuum at the temperature not crossing 50 °C and Charge 2 N HCl (250 mL) to the reaction mass, Stirred for 15-30 min. Transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum. The wet cake is washed with 500 mL of water and dried the above-wet material in the dryer at temperature 60-65 °C for 10-12 h.

Purification: Into a clean and dry 3.0 L 4-neck round bottom flask connected to a mechanical stirrer, condenser, thermometer socket is charging with 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide crude, methanol and isopropyl ether under stirring at 25- 30 °C. Raised the reaction mass temperature to 60-65 °C and stirred the reaction mass at 60-65 °C for 45-60 min. Cooled the reaction mass temperature to 25-30 °C and transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum. Washed the wet cake with 20.0 mL of methanol and dried the wet material in dryer at 60-65 °C for 4-6 h to furnish 16.0 g of the title compound with purity above 95 %.

Cream colour solid; Elemental analysis $C_{16}H_{18}N_3O_3SCl$ calcd (found) %: C 52.24 (52.12), H 4.93 (5.05), N 11.42 (11.31), O 13.05 (13.25), S 8.72 (8.83). IR (KBr, ν_{max}, cm^{-1}): 3423.42-3276.87, 3162.67, 2928.46, 1724.90, 1632.68-1566, 1522.80, 775.21; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.504 (s, 9H, -3CH_3), 2.225 (s, 3H, -CH_3), 7.262-7.301 (t, 2H, ArH), 7.389-7.412 (m, 1H, ArH), 8.204 (s, 1H, ArH), 10.017 (s, 1H, -NH), 11.847 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.220, 159.74, 152.91, 141.27, 139.02, 133.31, 132.57, 129.34, 128.64, 127.28, 126.62, 82.33, 28.06, 18.45; ESI-MS (*m/z*): 368.21 (M+1), 370.18 (M+3).

2-Aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide (6): Into a clean and dry 2 L 4-neck round bottom flask connected to a mechanical stirrer, condenser, thermometer socket is charged with 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide (50 g) and trifluoroacetic acid (500 mL) under stirring. Maintained the reaction mass at 25-30 °C for 3-5 h under stirring and after TLC compliance distilled-off TFA completely under vacuum at the temperature not crossing 50 °C. Charged 2.0 L of ethyl acetate into reaction mass and washed the reaction mass with 5 % Aq $KHCO_3$ (2 × 2 L) solution. Transferred the reaction mass into a separating funnel, separated aqueous and organic layers. Distilled-off the organic layer completely under plant vacuum at the temperature not crossing 50 °C and cooled the reaction mass temperature to 25-30 °C. Charged acetonitrile (150 mL) and isopropyl ether (400 mL) to the reaction mass and stirred for 60 min at 25-30 °C. Transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum and washed the wet cake with 100 mL of isopropyl ether. Dried the wet material in a dryer at 60-65 °C for 4-6 h to furnish 30 g of the title compound with purity above 99 %.

Light brown colour solid; Elemental analysis $C_{11}H_{10}N_3OSCl$ calcd (found) %: C 49.35 (49.63), H 3.76 (3.54), N 15.69 (15.81), O 5.98 (6.12), S 11.98 (12.04). IR (KBr, ν_{max}, cm^{-1}): 3284.01-3378.81, 3110.16, 1627.01, 1612.25, 1538.42-1481.88, 773.58; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.206 (s, 3H, -CH_3), 7.209-7.272 (m, 2H, ArH), 7.361-7.384 (dd, 1H, ArH), 7.616 (s, 2H,

-NH_2), 7.865 (s, 1H, ArH), 9.642 (s, 2H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.12, 159.54, 143.10, 138.82, 133.68, 132.46, 128.92, 127.98, 126.92, 120.66, 18.27; ESI-MS (*m/z*): 268.12 (M+1), 270.12 (M+3).

2-(6-Chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (7): Into a clean and dry 5 L 4 N round bottom flask connected to a mechanical stirrer and equipped with a condenser and thermometer socket is charged under stirring, 200 g of 2-aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide, 146 g of 4,6-dichloro-2-methyl pyrimidine and 2 L of THF under a nitrogen atmosphere. After clear solution, cooled the mass temperature to 10-20 °C. Added 30 % sodium-*t*-butoxide solution to the reaction mass over a period of 60-75 min at 10-20 °C and brown coloured solution formation is observed. Raised the reaction mass temperature to 25-30 °C and maintained the mass temperature to 25-30 °C for 90-120 min. After HPLC compliance cooled the mass temperature to 0-5 °C and added 2 N HCl solution to the reaction mass over a period of 60-90 min at 0-5 °C. Maintained the mass temperature at 0-5 °C for 105-120 min and transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum. Washed the wet cake with 600.0 mL of water and dried the wet material in a drier at 60-65 °C for 8-10 h gave 210.0 g of the title compound with purity above 99 %.

Off white colour solid; Elemental analysis $C_{16}H_{13}N_5OSCl_2$ calcd (found) %: C 48.74 (48.91), H 3.32 (3.45), N 17.76 (15.97), O 4.06 (4.24), S 8.13 (8.29). IR (KBr, ν_{max}, cm^{-1}): 3424.28, 3241.22, 2876.23-2789.82, 1638.82, 770.36; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.247 (s, 3H, -CH_3), 2.594 (s, 3H, -CH_3), 6.952 (s, 1H, ArH), 7.252-7.314 (m, 2H, ArH), 7.403-7.422 (dd, 1H, ArH), 8.320 (s, 1H, ArH), 10.030 (s, 1H, -NH), 12.251 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.38, 161.23, 159.52, 158.48, 157.51, 140.76, 138.74, 133.28, 132.35, 129.02, 128.24, 127.18-126.99, 103.40, 66.97, 25.12, 18.23; ESI-MS (*m/z*): 394.14 (M+1), 396.15 (M+3).

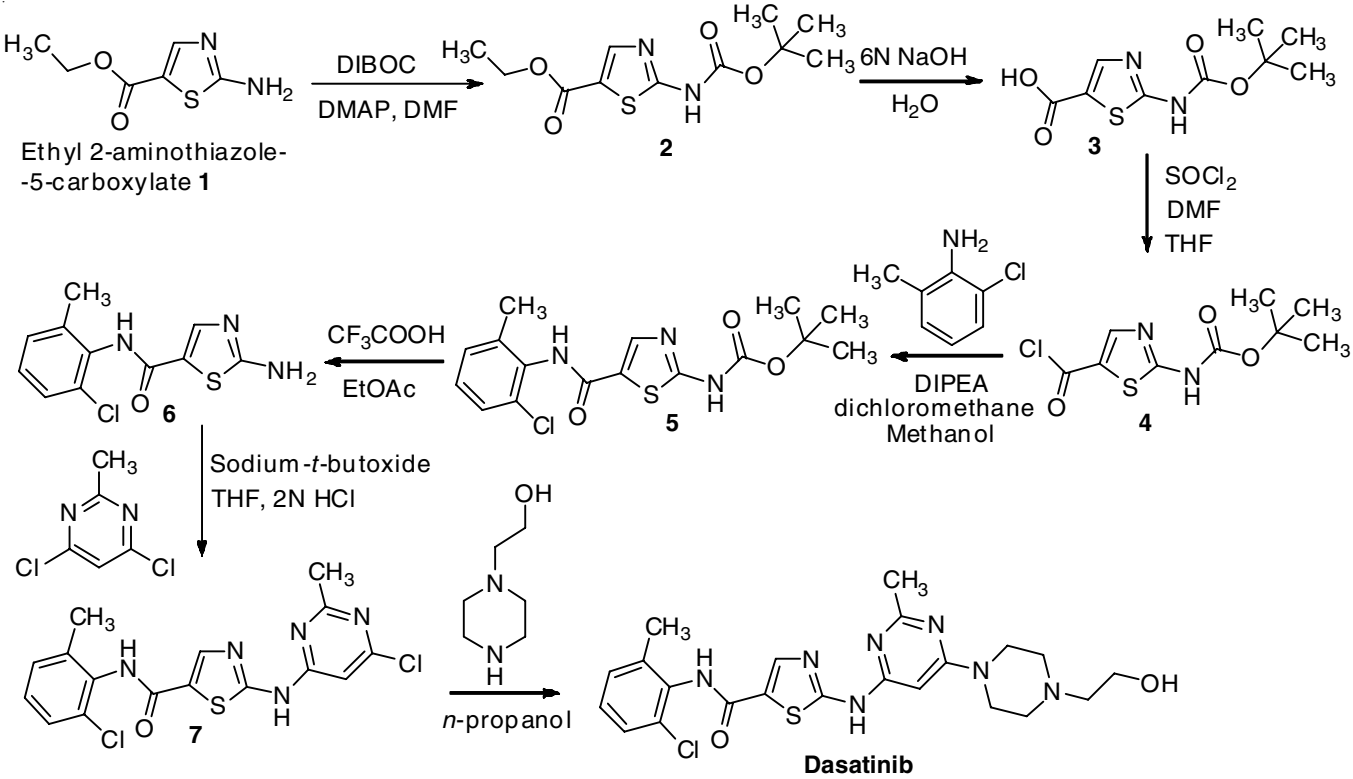
N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)-piperazine-1yl)-2-methylpyrimidin-4-yl-amino)-thiazole-5-carboxamide (Dasatinib): Into clean and dry 1.0 L 4-neck round bottom flask connected to a mechanical stirrer and equipped with a condenser, thermometer socket is charged 2-(6-chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide, N-2-(hydroxyethyl) piperazine and *n*-propanol under stirring. Raised the reaction mass temperature to 115-120 °C and maintained the reaction mass temperature at 115-120 °C for 180-240 min. After HPLC compliance cooled the mass temperature to 25-35 °C. Maintained the reaction mass at 25-35 °C for 30-45 min, transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum and washed the wet cake with 50 mL of 1-propanol. Transferred the wet material into clean 1 L 4 N round bottom flask and charge methanol. Raised the mass temperature to 60-65 °C and maintained for 60-90 min. Cooled the mass temperature to 25-35 °C and maintained for 30-45 min. Transferred the reaction mass into a Buchner funnel, flask kept under plant vacuum and washed the wet cake with 50.0 mL of methanol. Dried the wet material in a drier at 60-65 °C for 8-10 h furnish 50.0 g of the title compound with purity above 99.85 %.

Off white colour solid; Elemental analysis $C_{22}H_{26}N_7O_2SCl_2$ calcd (found) %: C 54.15 (54.30), H 5.37 (5.47), N 20.09 (20.28), O 6.56 (6.81), S 6.57 (6.41). IR (KBr, ν_{max}, cm^{-1}): 3423.47, 3206.72, 2948.55, 1622.60, 770.53; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.239 (s, 3H, -CH_3), 2.409 (s, 3H, -CH_3), 2.425-2.482 (m, 6H, -3CH_2), 3.511-3.555 (m, 6H, -3CH_2), 4.428-4.455 (t, 1H, -OH), 6.049 (s, 1H, ArH), 7.236-7.300 (m, 2H, ArH), 7.388-7.411 (dd, 1H, ArH), 8.221 (s, 1H, ArH), 9.870 (s, 1H, -NH), 11.640 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.18, 162.62, 162.40, 159.98, 156.93, 140.86, 138.83, 133.54, 132.46, 129.02, 128.15, 127.01, 125.70, 82.63, 60.21, 58.53, 52.73, 43.62, 25.59, 18.32; ESI-MS (*m/z*): 488.1 (M+1), 489.2 (M+2), 490.1(M+3), 491.1(M+4).

RESULTS AND DISCUSSION

The primary stage of the process involves stirring a suspension of ethyl 2-aminothiazole-5-carboxylate (2-ATC) (**1**), dimethylamino pyridine (DMAP), di-*tertiary*-butyldicarbonate (DIBOC), dimethylformamide (DMF) for a time of 24 h at 25-30 °C. The compound was filtered and washed with acetonitrile. The compound purified by recrystallization with acetonitrile. The next stage involves treating ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (**2**) with 6 N NaOH solution at 25-30 °C for 24 h. The aqueous solution was acidified with 6 N HCl solution to obtain a solid, which was filtered, washed with water followed by drying at 60-65 °C to obtain 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylic acid (**3**). The third step involves the adding of thionyl chloride to a stirred solution of 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylic acid (**3**) in tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) and stirring the solution at 25-30 °C for 4-6 h. Distilled-off solvent totally under plant vacuum to get 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylic acid chloride (**4**). The fourth stage involves addition of 2-chloro-6-methyl anilineto a stirred solution of 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylic acid chloride **4** in dichloromethane at 0-5 °C. Diisopropylamine (DiPEA) was added to the reaction mass, raised the reaction mass temperature to 25-30 °C and stirred the reaction mass for 24 h. Distilled-off the solvent completely under plant vacuum, washed with 2 N HCl and filtered the solid to obtain 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide (**5**). The fifth stage involves treating 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamidewith trifluoroacetic acid at 25-30 °C for 3-5 h to obtain 2-aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide (**6**). The sixth step involves reacting 2-aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide with 4,6-dichloro-2-methyl pyrimidine in the presence of sodium-*t*-butoxide in THF to obtain 2-(6-chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (**7**). The seventh step of the process involves reacting 2-(6-chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (**7**) with N-2-(hydroxyethyl)piperazine in *n*-propanol to obtain dasatinib.

An initial convergent synthesis of dasatinib (**Scheme-I**) began with the commercially available 2-amino-thiazole-5-carboxylate (**1**). Synthesis of 2-*tert*-butoxycarbonylamino-



Scheme-I: Synthetic scheme for Dasatinib

thiazole-5-carboxylate (**2**) involves protection of amino group of compound **1**. One method was reported for protection of compound **1** by Das *et al.* [10], involve amine protection using di-*tert*-butyldicarbonate (Boc_2O) in presence of 4-dimethylaminopyridine(DMAP) in tetrahydrofuran (THF) medium without any quality profile. However, this method suffers from i) a large quantity of THF was required ii) a huge amount of solvents required for the purification of crude mass. In connection with attempts to convert ethyl 2-aminothiazole-5-carboxylate (**1**) to ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (**2**) with an excess of di-*tert*-butyl dicarbonate (Boc_2O) in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP) in dimethylformamide at 25-30 °C to obtained in good yields and purity. Initial experiments were tried in different molar equivalents of di-*tert*-butyl dicarbonate (Boc_2O) (1.0, 1.25, 1.5, 1.75, 2.0, 2.25 (Table-1, entries 1-6)). When, 1.0 and 1.25 mol ratio of DIBOC were used, the yields were 51 and 56 %, but the HPLC purities were 99.71 and 99.64 %. However, 1.50, 1.75, 2.0 and 2.25 mol equivalents of DIBOC gave yields were almost similar *i.e.* 75, 74, 74 and 73 % with HPLC purities were 99.75, 99.66, 99.65 and 99.66 %, respectively. Based on the above experimental results, 1.5 mole equivalents of di-*t*-butyl dicarbonate (DIBOC) was taken for further studies. Next, we focused on different solvents like methanol, tetrahydrofuran (THF) (Table-1, entries 7-8) and dimethylformamide (DMF)for the selection of the solvent for the reaction. To minimize the workup, DMF was chosen as medium and proved superior with respect to yield and purity. A variation of the reaction temperature and reaction time study, performed the reaction at different temperatures (20-25, 25-

TABLE-1
EFFECT OF MOLE RATIOS OF REACTANTS, SOLVENTS, TIME AND TEMPERATURE ON SYNTHESIS OF COMPOUND **2**

Entry[a]	Solvent	2-ATC (mol)	DIBOC (mol)	Mole ratios of 2-ATC and DIBOC	Time (h)/ Temp. (°C)	Yield[b] (%)	HPLC purity (%)
1	DMF	0.058	0.081	1.0:1.0	24.0/25-30	51	99.71
2	DMF	0.058	0.084	1.0:1.25	24.0/25-30	56	99.64
3	DMF	0.058	0.087	1.0:1.50	24.0/25-30	75	99.75
4	DMF	0.058	0.090	1.0:1.75	24.0/25-30	74	99.66
5	DMF	0.058	0.093	1.0:2.00	24.0/25-30	74	99.65
6	DMF	0.058	0.095	1.0:2.25	24.0/25-30	73	99.68
7	Methanol	0.058	0.087	1.0:1.50	24.0/25-30	41	91.03
8	THF	0.058	0.087	1.0:1.50	24.0/25-30	63	92.03
9	DMF	0.058	0.087	1.0:1.50	18.0/25-30	51	99.66
10	DMF	0.058	0.087	1.0:1.50	30.0/25-30	70	99.78
11	DMF	0.058	0.087	1.0:1.50	24.0/20-25	73	99.71
12	DMF	0.058	0.087	1.0:1.50	24.0/30-35	70	99.67

[a]Reaction conditions: 2-amino-thiazole-5-carboxylate (**1**), di-*tert*-butyldicarbonate (Boc_2O), 4-dimethylaminopyridine (DMAP) andsolvent. [b]Yields of isolated products.

TABLE-2
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF COMPOUND **3**

Entry[a]	Solvent	Compd. **2** (mol)	NaOH (mol)	Mole ratios of compd. **1** and NaOH	Time (h)/ Temp. (°C)	Yield[b] (%)	HPLC purity (%)
1	Water	0.040	1.8	1.0:45	24.0/25-30	89	99.79
2	Water	0.040	1.5	1.0:37.5	24.0/25-30	78	89.35
3	Water	0.040	2.1	1.0:52.5	24.0/25-30	84	97.75
4	Methanol	0.040	1.8	1.0:45	24.0/25-30	78	97.26
5	Methanol:THF	0.040	1.8	1.0:45	24.0/25-30	88	99.76
6	Water	0.040	1.8	1.0:45	24.0/15-20	67	87.84
7	Water	0.040	1.8	1.0:45	24.0/20-25	71	86.79
8	Water	0.040	1.8	1.0:45	24.0/35-40	87	84.55
9	Water	0.040	1.8	1.0:45	18.0/25-30	72	99.14
10	Water	0.040	1.8	1.0:45	30.0/25-30	89	97.29

[a]Reaction conditions: ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (**2**), NaOH and solvent. [b]Yields of isolated products.

30 and 30-35 °C) and different time periods (18, 24, 30 h) (Table-1, entries 9-12). Based on the results, it is observed that maintenance at temperature 25-30 °C for 18 h period gave 51 % yield of ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (**2**) and the temperature range of 20-25 °C, 25-30 °C and 30-35 °C for times above 24 h and up to 30 h, the yields and purities were almost similar. Therefore, the optimal condition was to maintain the mass temperature at 25-30 °C for 24 h during the protection reaction of ethyl 2-amino thiazole-5-carboxylate with DIBOC for better yields and purities.

After successful formation of compound **2**, further proceeded to hydrolysis of ethyl 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylate (**2**) with solvent-free conditions, using NaOH in water at 25-30 °C proceeded smoothly and gave the desired carboxylic acid (**3**) with good yield and purity. In order to specify the scope of reaction, we have investigated the progress of the reaction under different molar equivalents (37.5, 45.0 and 52.5 (Table-2, entries 1-3)) of NaOH solution. The above-optimized results indicated that 37.5 and 52.5 mole equivalents of NaOH solutions, the yields were 78 and 84 %, HPLC purities were 89.35 and 97.75 %. However, 45.0 mole equivalent of NaOH solution resulted 89 % yield with 99.79 % HPLC purity. Hydrolysis was studied in different solvents [methanol, methanol: THF mixture (Table-2, entries 4-5) and water]. It was observed that during the hydrolysis reaction of ethyl 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylate (**2**) with NaOH solution, among the solvents tried water gave better yield and highest purity of 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylic acid (**3**), methanol and methanol: THF mixture gave78 % and 88 % yields with 97.26 % and 99.76 % of HPLC purities. In water medium, reaction was going smoothly and after pH adjustment, simply filtered the compound. Although, the temperature varies from 15 to 40 °C. Based on the experimental results, maintenance at temperature 15-20, 20-25 and 35-40 °C (Table-2, entries 6-8) for 24 h time period gave a lesser yield and less than 90 % purity, at 25-30 °C for 24 h time period gave highest yield and purity of 2-*tert*-butoxy-carbonylamino-thiazole-5-carboxylic acid (**3**)**.** To optimize the reaction conditions in terms of time, above reaction was performed using different times [18 h and 30 h (Table-2, entries 9-10)].

Chlorination of 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylic acid (**3**) was performed by reacting with thionyl chloride instead of literature reported oxalyl chloride to get 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylic acid chloride (**4**). Reaction optimization studies were carried out to evaluate the effects of different mole equivalents (1.5, 2.0, 2.5, 3.0, 3.5 and 4.0 (Table-3, entries 1-6)). As the results indicate, 1.5 and 2.0 mole equivalents of thionyl chloride, the yields were on lower, when 2.5, 3.0, 3.5 and 4.0 mol equivalents of thionyl chloride used, the yields were almost similar and on the higher side. 2-*tert*-Butoxycarbonylamino-thiazole-5-carboxylic acid chloride (**4**) was highly unstable. Isolation of the acid chloride material is not feasible and *in situ* proceeded to the next stage.

TABLE-3
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF COMPOUND **4**

Entry[a]	Compd. **3** (mol)	Thionyl chloride (mol)	Mole ratios of compd. **3** and thionyl chloride	Time (h)/ Temp. (°C)
1	0.041	0.0614	1.0:1.5	4-6/25-30
2	0.041	0.082	1.0:2.0	4-6/25-30
3	0.041	0.1024	1.0:2.5	4-6/25-30
4	0.041	0.123	1.0:3.0	4-6/25-30
5	0.041	0.143	1.0:3.5	4-6/25-30
6	0.041	0.164	1.0:4.0	4-6/25-30

[a]Reaction conditions: 2-*tert*-Butoxycarbonylamino-thiazole-5-carboxylic acid (**3**), thionyl chloride.

Above results indicated using 3 mol equivalent of thionyl chloride to obtain optimized yield of the 2-*tert*-butoxycaronyl-amino-thiazole-5-carboxylic acid chloride (**4**).

Conversion of 2-*tert*-butoxycarbonylamino-thiazole-5-carboxylic acid chloride (**4**) to 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide (**5**) in the presence of N,N-diisopropyl ethylamine using 2-chloro-6-methylaniline was achieved. Initially, performed the reaction of compound **4** in the presence of N,N-diisopropyl ethylamine using 2-chloro-6-methylaniline in different mole equivalents (1.4, 1.45, 1.5, 1.55 and 1.6 (Table-4, entries 1-5)). Above results indicated the optimized yield (40 %) and HPLC purity (95.05 %) with 1.5 mole equivalents of 2-chloro-6-methylaniline in dichloromethane. To study the effect of solvents in the course of the reaction was studied indifferent solvents like toluene, 1,4-dioxane (Table-4, entries 6-7) and dichloromethane at 25-30 °C. Among the solvents, tried dichloromethane gave better yield and highest purity of 2-*tert*-butoxy-carbonyl amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide. In toluene and 1,4-dioxane, compound **5** not formed (reaction not procee-

TABLE-4
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF COMPOUND **5**

Entry[a]	Solvent	Compd. **4** (mol)	2-Chloro-6-methyl aniline (mol)	Mole ratios of compd. **4** and 2-chloro-6-methyl aniline	Time (h)/ Temp. (°C)	Yield[b] (%)	HPLC purity (%)
1	Dichloromethane	0.0380	0.0530	1.0:1.4	24.0/25-30	43	71.47
2	Dichloromethane	0.0380	0.0550	1.0:1.45	24.0/25-30	41	84.24
3	Dichloromethane	0.0380	0.0565	1.0:1.5	24.0/25-30	40	95.05
4	Dichloromethane	0.0380	0.0588	1.0:1.55	24.0/25-30	39	92.98
5	Dichloromethane	0.0380	0.0600	1.0:1.6	24.0/25-30	45	81.39
6	Toluene	0.0380	0.0565	1.0:1.5	24.0/25-30	–	–
7	1,4-Dioxane	0.0380	0.0565	1.0:1.5	24.0/25-30	–	–
8	Dichloromethane	0.0380	0.0565	1.0:1.5	30.0/20-25	39	92.98
9	Dichloromethane	0.0380	0.0565	1.0:1.5	24.0/30-35	39	94.05
10	Dichloromethane	0.0380	0.0565	1.0:1.5	24.0/35-40	38	93.12

[a]Reaction conditions: 2-*tert*-Butoxycarbonylamino-thiazole-5-carboxylic acid chloride (**4**), N,N-diisopropyl ethylamine, 2-chloro-6-methylaniline andsolvent. [b]Yields of isolated products.

ded). Further, it was planned to study the effect of temperature on the course of the reaction, for example, 20-25, 30-35 and 35-40 °C (Table-4, entries 8-10) in dichloromethane, the study disclosed that the optimum temperature for maximum formation of compound **5** was 25-30 °C.

Deprotection of Boc group of 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide (**5**) was achieved by trifluoro acetic acid at 25-30 °C, affording 2-aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide (**6**) in quantitative yield. Initially, 38, 48 and 58 (Table-5, entries 1-3) mole equivalents of TFA were studied. It was observed that with 38 mole equivalent of the reaction gave 47 % of the yield with 99.54 % HPLC purity. When 48 and 58 mole equivalents of trifluoroacetic acid (TFA) were used, obtained yields were on the higher side (78 and 78 %) and HPLC purities (99.56 and 99.5 %). In addition, different types of acids were applied for the deprotection of compound **5**, for example, HCl and acetic acid (Table-5, entries 4-5). The deprotection of Boc group of compound **5** with these acids gave 66 and 39 % yields with 99.25 and 93.14 % purities, it was observed that, the results were lower side on compared with TFA. Then the effect of temperature was studied (20-25 °C, 30-35 °C and 35-40 °C (Table-5, entries 6-8)) on the course of deprotection of Boc group of compound **5**, for instance, deprotection of Boc group at 25-30 °C provided high yield and high purity.

It is planned to develop a one-pot method which consists of preparation of compound 2-(6-chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (**7**) exclusively by coupling of 2-aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide (**6**) and 4,6-dichloro-2-methylpyrimidine in the presence of sodium-*t*-butoxide. With an aim of the study, the mole equivalents, experiments conducted in 1.10, 1.15, 1.20, 1.25 and 1.30 (Table-6, entries 1-5) of 4,6-dichloro-2-methylpyrimidine at 25-30 °C. The study establishes 1.20 mole equivalent of 4,6-dichloro-2-methyl-pyrimidine as the best option at 25-30 °C for the maximum formation of compound **7** with 69 % yield and 99.35 % HPLC purity. Based on these promising results, reaction optimization studies were carried out to evaluate the effect of mole equivalents [2.5, 3.0, 4.0 and 4.5 (Table-6, entries 6-9)] of sodium-*t*-butoxide. As the results indicate that, 3.5 mole equivalents of sodium-*t*-butoxide was found to be most effective, whereas other mole equivalents gave lower yield and lower purity. The effect of the solvents [DMF, chloroform (Table-6, entries 10-11 and THF)] on yields and purity of desired product at 25-30 °C was examined. This study showed that the use of THF as a solvent provided more efficient and clean reaction, while other solvents gave unsatisfactory results. Further, the effect of reaction temperature (15-20 °C, 20-25 °C, 30-35 °C and 35-40 °C (Table-6, entries 12-15)) on product yield was evaluated and found that 25-30 °C temperature led to better yield and purity. Further, the effect time [0.5, 1.0 and 2.0 h (Table-6, entries 16-18)] on the course of the reaction, 1.5 h time gave highest yield and purity.

A novel eco-friendly process was developed for the coupling of 2-(6-chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (**7**) and N-2-hydroxyethyl piperazine as self-base and reagent, without using

TABLE-5
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF COMPOUND **6**

Entry[a]	Acid	Compd. **5** (mol)	Acid (mol)	Mole ratios of compd. **5** and Acid	Time (h)/ Temp. (°C)	Yield[b] (%)	HPLC purity (%)
1	TFA	0.0136	0.522	1:38	3-5/25-30	47	99.54
2	TFA	0.0136	0.653	1:48	3-5/25-30	78	99.56
3	TFA	0.0136	0.783	1:58	3-5/25-30	78	99.50
4	Conc. HCl	0.0136	0.952	1:70	3-5/25-30	66	99.25
5	Acetic acid	0.0136	2.622	1:193	3-5/25-30	39	93.14
6	TFA	0.0136	0.653	1:48	3-5/20-25	38	92.63
7	TFA	0.0136	0.653	1:48	3-5/30-35	67	99.20
8	TFA	0.0136	0.653	1:48	3-5/35-40	48	97.36

[a]Reaction conditions: 2-*tert*-butoxy-carbonyl-amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide (**5**) and acid. [b]Yields of isolated products.

TABLE-6
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF COMPOUND **7**

Entry[a]	Solvent	Compd. **6** (mol)	4,6-Dichloro-2-methyl pyrimidine (mol)	Sodium-*t*-butoxide (mol)	Mole ratios of compd. **6**; 4,6-dichloro-2-methyl pyrimidine and sodium-*t*-butoxide	Time (h)/ Temp. (°C)	Yield[b] (%)	HPLC purity (%)
1	THF	0.0186	0.0205	0.0658	1.0:1.10:3.5	1.5/25-30	57	96.62
2	THF	0.0186	0.0214	0.0658	1.0:1.15:3.5	1.5/25-30	60	97.18
3	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/25-30	69	99.35
4	THF	0.0186	0.0233	0.0658	1.0:1.25:3.5	1.5/25-30	68	99.69
5	THF	0.0186	0.0241	0.0658	1.0:1.30:3.5	1.5/25-30	62	92.54
6	THF	0.0186	0.0220	0.0464	1.0:1.20:2.5	1.5/25-30	60	97.04
7	THF	0.0186	0.0220	0.0557	1.0:1.20:3.0	1.5/25-30	61	99.35
8	THF	0.0186	0.0220	0.0743	1.0:1.20:4.0	1.5/25-30	65	98.52
9	THF	0.0186	0.0220	0.0836	1.0:1.20:4.5	1.5/25-30	65	98.51
10	DMF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/25-30	5	4.82
11	$CHCl_3$	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/25-30	–	–
12	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/15-20	63	99.49
13	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/20-25	65	99.35
14	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/30-35	66	99.26
15	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.5/35-40	63	99.05
16	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	0.5/25-30	64	95.87
17	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	1.0/25-30	66	97.47
18	THF	0.0186	0.0220	0.0658	1.0:1.20:3.5	2.0/25-30	67	98.97

[a]Reaction conditions: 2-aminothiazole-N-(2-chloro-6-methylphenyl)-5-carboxamide (**6**), 4,6-dichloro-2-methylpyrimidine, 2 sodium-*t*-butoxide andsolvent. [b]Yields of isolated products.

TABLE-7
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF DASATINIB

Entry[a]	Solvent	Compd. **7** (mol)	N-2-Hydroxyethyl piperazine (mol)	Mole ratios of compd. **7**; N-2-hydroxyethyl piperazine and DIPEA	Time (h)/ Temp. (°C)	Yield[b] (%)	HPLC purity (%)
1	*n*-Propanol	0.01267	0.0507	1.0:4.0	4-5/115-120	73	96.88
2	*n*-Propanol	0.01267	0.0567	1.0:4.5	4-5/115-120	74	98.66
3	*n*-Propanol	0.01267	0.0633	1.0:5.0	4-5/115-120	93	99.87
4	*n*-Propanol	0.01267	0.0697	1.0:5.5	4-5/115-120	83	98.65
5	*n*-Propanol	0.01267	0.0760	1.0:6.0	4-5/115-120	79	99.00
6	Methanol	0.01267	0.0633	1.0:5.0	4-5/115-120	–	–
7	Toluene	0.01267	0.0633	1.0:5.0	4-5/115-120	–	–
8	*n*-Propanol	0.01267	0.0633	1.0:5.0	6-10/100-110	78	99.14
9	*n*-Propanol	0.01267	0.0633	1.0:5.0	10-12/90-100	65	99.14

[a]Reaction conditions: 2-(6-chloro-2-methylpyrimidine-4-yl-amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (**7**), N-2-hydroxyethyl piperazine andsolvent. [b]Yields of isolated products.

organic or inorganic base in *n*-propanol medium at elevated temperatures affords the key precursor N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)-piperazine-1yl)-2-methylpyrimidin-4-yl-amino)-thiazole-5-carboxamide (dasatinib). After optimization studies of this stage, it was observed that the most suitable method to carry out, the reaction was by performing the coupling of compound **7** and N-2-hydroxyethyl piperazine in *n*-propanol solvent at 115-120 °C. These experiments indicated that mole ratios, solvent, temperature and time play a major role in the formation of dasatinib. During the study, it was found that the moles (4.0, 4.5, 5.0, 5.5, 6.0 (Table-7, entries 1-5)) of N-2-hydroxyethyl piperazine have a significant impact on the reaction. The formation of dasatinib was proceeding smoothly when 5.0 mol equivalent of N-2-hydroxyethyl piperazine. Thus, 1.0:5.0 mol equivalent of compound **7** and N-2-hydroxyethyl piperazine were ideal for preparation of dasatinib (93 % yield and 99.87 % HPLC purity). Consequently, various solvents were examined in the preparation of dasatinib including methanol, toluene (Table-7, entries 6-7) and *n*-propanol. Apart from *n*-propanol, all other solvents furnished (in methanol and toluene reaction not pro-ceeded). After fixing the mole ratios and solvent, another key parameter, the reaction temperature was studied. The reaction was carried out at different temperatures [90-100 ºC for 10-12 h and 100-110 ºC for 6-10 h (Table-7, entries 8-9)] and the results clearly indicated that the rate of reaction and chemical purities were significantly influenced by temperature. The optimum reaction temperature for the reaction was found to be 115-120 ºC.

Conclusion

In conclusion, we have developed an efficient and commercially viable process for the synthesis of dasatinib substantially free from impurities and meets the regulatory norms in terms of yield and purity.

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