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A Convenient new and Efficient Commercial Synthetic Route for Dasatinib (Sprycel®)

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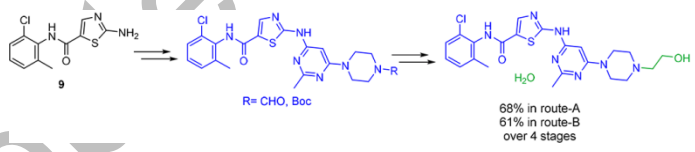
Abstract

A new and efficient synthetic route for dual Src/Abl kinase inhibitor Dasatinib (Sprycel®), an anticancer drug, is described. This commercially viable process yields Dasatinib monohydrate free of potential impurities with consistent yield of 68% in route A and 61% in route B with HPLC purity >99.80% over 4 stages.

GRAPHICAL ABSTRACT



KEYWORDS: chronic myeloid leukemia, Dasatinib monohydrate, des-hydroxy ethyl Dasatinib, 2-bromoethanol, alkylation.

INTRODUCTION

Cancer is a genetic disease characterized by an uncontrolled cell division. As per the World Health Organization (WHO) reports Cancer is a fast growing disease in 21st

century with an estimation of 13.1 million deaths in 2030 [1]. Chronic myeloid leukemia (CML) is a hematopoietic stem cell cancer that affects the blood and bone marrow. CML is a type of myeloproliferative disease resulting in the Philadelphia (Ph) chromosomal translocation, carrying the Bcr-Abl (Breakpoint cluster region-Abelson leukemia) oncogene [2]. In view of the increased demand and seriousness of the deadly cancer disease various tyrosine kinase inhibitors (TKIs), Imatinib, Sunitinib, Nilotinib, Dasatinib and Lapatinib (Figure 2) are developed and are used to treat Chronic myeloid leukemia (CML). Among these clinical agents, Dasatinib is chemically described as N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide.

Crystalline monohydrate form of Dasatinib **1** (Figure 1) is approved by the FDA in 2006 and sold under the brand name SPRYCEL®, had 2015 sales of US$ 1.6 billion with projected sales of US$ 1.917 billion by 2018[3]. SPRYCEL® is the leading kinase inhibitor used for the treatment of chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including Imatinib [4]. In addition, Dasatinib has potent activity against members of the SRC family (Src, Lck, Fyn, Yes, Fgr, Hck, Blk, Frk) and double-digit nanomolar activity against PDGFR, c-Kit, and other members of the Ephrin and Tec kinase families, amongst others [5,6]. It is being evaluated for use in several other cancers, including advanced prostate cancer.

In view of the significance of Dasatinib several routes were developed to make Dasatinib monohydrate. Following are some important synthetic routes which are practiced to make

Dasatinib monohydrate. The Scheme 1 denotes the first and initial synthesis of Dasatinib [5].

The first step of the synthesis in Scheme 1 involves the sulphur directed ortho-lithation of 2- chlorothiazole **10** followed by subsequent nucleophilic reaction with 1-chloro-2-isocyanato-3-methylbenzene **11** to give the compound 2-chloro-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **12**. Protection of amide nitrogen in **12** with 4-methoxybenzyl chloride followed by coupling with 6-chloro-2-methylpyrimidin-4-amine **13a** under basic medium gave an intermediate compound, 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)-N-(4-methoxybenzyl)thiazole-5-carboxamide **14**. Further deprotection of the para methoxy benzyl group (PMB) of **14** afforded the penultimate intermediate, 2-((6-chloro-2-methylpyrimidin-4-yl) amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **5,** which on coupling with 2-(piperazin-1-yl)ethan-1-ol (HEP) **15,** gave Dasatinib free base **1a**. **1a** in 2NHCl, ether/methanol medium converted into hydrochloride salt **1b**. The overall yield of this route is 61% for hydrochloride salt over six stages.

Jagabandhu Das and his co-workers reported the synthesis of Dasatinib monohydrate as shown in Scheme 2 [7]. The initial step of synthesis involves the nucleophilic coupling of amino thiazole carboxamide **9** with 4,6-dichloro-2-methylpyrimidine **8** to give penultimate intermediate **5** in 61% yield which was coupled with 2-(piperazin-1-yl)ethan-1-ol (HEP) **15** and subsequent water addition to give final product Dasatinib monohydrate **1**.

Chen, Bang-Chi et.al reported the synthesis of Dasatinib monohydrate as depicted in Scheme 3 [8]. The first step of the synthesis involves the α-bromination of β-ethoxyacrylamide **16** followed by coupling with thiourea compound **17** to give compound **5** which was condensed with HEP **15** in n-butanol gives a pseudo polymorph crystalline Dasatinib n-butanol solvate **1c**. Further compound **1c** on treatment with 80% aqueous ethanol at 75°C yielded compound **1**. The overall yield of this route is 59% over 3 stages.

Chen, Bang-Chi et.al also reported the another route of synthesis of Dasatinib, as shown in Scheme 4 [8]. The first stage of synthesis involves the coupling of **8** with HEP **15** in DCM, TEA at rt. for 2h to give intermediate, 2-(4-(6-chloro-2-methylpyrimidin-4-yl)piperazin-1-yl)ethan-1-ol **18** which was under taken for Buchwald–Hartwig amination with amino thiazole carboxamide **9** in the presence of K_2CO_3, $Pd(OAc)_2$ and BINAP yielded the crude product which on further column purification yielded **1**.

These synthetic methods involve huge quantities of HEP **15** to make compound **1,** which accounts costing and generates a potential impurity called Des-hydroxy ethyl Dasatinib **2** (DHED- Impurity) which is a tough task to remove form the final compound. Also synthesis of **1** involves Palladium catalyst and column purification to get the compound **1.** As per the ICH (Q3A, R2) regulatory amendments for a new drug substance (API) having maximum daily dose ≤ 2 g per day, the reporting identification thresholds for a known and an unspecified impurity are 0.15% and 0.10% respectively [9]. Further, as per the International Conference on Harmonization (ICH) guideline (ICH Q3D) for a drug

substance the permitted daily exposure (PDE) limit for Palladium (Pd) is 100 µg/day or 100 ppm or 0.01% for an oral exposure. It is a tough task to achieve the desired yield and purity by avoiding impurities, especially impurity **2 & 5.** Also It is challenging task to achieve the acceptable limits of Palladium (Pd) (limit < 100 ppm) as per the ICH guidelines to meet the pharmaceutical compositions [10], which required a series of purifications, resulting in low yield.

Considering the lacunas of the prior art synthetic routes, we became intrigued by the possibility of streamlining the synthesis of **1** and designed an alternative synthetic route by considering the following points.

a) By avoiding the use of highly reactive premade organometallic species and hazardous chemicals.

b) To make high purity Dasatinib monohydrate.

c) To develop a robust process with consistent yield and quality.

As a part of our research for developing an alternative synthetic route for Dasatinib monohydrate **1,** we designed our synthetic route as depicted in Scheme **6**.

The requisite key starting material for this study, 2-amino-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **9** is made accordingly as shown in Scheme 5 [11]. The first step of the synthesis involves the Boc protection of amine **19** with Boc anhydride to give compound **20** in 68% yield, which was hydrolyzed by NaOH in

THF/MeOH to give **21** in 94% yield. Compound **21** was treated with oxalyl chloride and coupling with amine **22,** yielded compound **23** in 51% yield. Deprotection of Boc functional in compound **23** with Trifluoroacetic acid (TFA) in DCM yields the key intermediate amino thiazole carboxamide **9** in 89% yield as off white solid.

RESULTS AND DISCUSSION

Present synthetic route deals with the synthesis of crystalline Dasatinib monohydrate **1** via two synthetic paths, route **A** and route **B** as shown in Scheme **6.** The developed four stages process yielded compound 1 with an overall yield of 68% in route **A** and 61% in route **B**. The first step of synthesis in route **A** and **B** deals with the nucleophilic displacement of the chlorine in 4,6-dichloro-2-methylpyrimidine **8** with 2-amino-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **9** in presence of base, Sodium *tert*-butoxide (STB-Solid) yielded intermediate **5** about 76% [12]. In view of the costing and safe industrial operations, attempts have made to optimize the reaction conditions to get the optimum yield of compound **5** (94%) with 98.3% HPLC purity. Optimization was done using various reaction media, inorganic bases NaH, $NaNH_2$, Solid KO*t*Bu, KO*t*Bu in THF (25%), NaO*t*Bu in THF (~30%) to obtain the better yield and quality. Finally, obtained 94% yield with 98% HPLC purity by carrying out the reaction in 28-30% NaO*t*Bu in THF solution at 10-20°C for 1h. Experimental results are tabulated in Table-**1**.

In route **A** second step deals with coupling of compound **5** with Boc-piperazine **6** in n-pentanol, yielded the intermediate, tert-butyl 4-(6-((5-((2-chloro-6-

methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazine-1-carboxylate **3** in 84% yield [5]. The structure of the intermediate **3** was established on the basis of its spectral data.

Thus compound **3** was obtained as off white solid. Its positive quasi molecular ion peak at m/z 544.1 $[M + H]^+$ along with Boc eradicated fragment m/z 444.1 $[M + H]^+$ in mass spectrum is compatible with the molecular formulae $C_{25}H_{30}ClN_7O_3S$. Presence of sharp singlet at δ 1.40 along with other thiazole protons in ^1H NMR spectrum confirms the existence of **Boc** functional in compound **3**. In ^{13}C NMR of **3** Boc carbons appeared at δ 29.13 and 80.21. Intermediate **3** on Boc deprotection in dilute hydrochloric acid afforded the penultimate intermediate, N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (DHED) **2** in 93.5% yield [13].

In route **B** second step deals with the coupling of compound **5** with N-formyl piperazine **7,** in DMF gave novel intermediate, N-(2-chloro-6-methylphenyl)-2-((6-(4-formylpiperazin-1-yl)-2-methylpyrimidin-4-yl) amino) thiazole-5-carboxamide **4** in 79% yield [5].

The structure of the novel intermediate **4** was confirmed on the basis of its spectral data. Thus compound **4** was obtained as off white solid. Its negative quasi molecular ion peak at m/z 470.3 $[M - H]^-$ in mass spectrum is compatible with the molecular formulae $C_{21}H_{22}ClN_7O_2S$. Presence of sharp singlet at δ 8.10 along with other thiazole protons in ^1H NMR spectrum confirms the presence of formyl (CHO) functional in compound **4.** In

^{13}C NMR of compound **4** formyl carbon appeared at δ 160.91. Deformylation of compound **4** in presence of H_2SO_4, methanol yielded the penultimate intermediate, DHED **2** in 91% yield.

The, Synthesized Des-hydroxy ethyl Dasatinib (DHED) intermediate **2** is fully characterized by UV, IR, ^{1} H NMR, ^{13}C NMR and mass spectral data.

Finally, alkylation of **2** with 2-bromoethanol in the presence of K_2CO_3, NaI, in Acetonitrile followed by the water addition at 70-75°C, yielded the targeted compound **1** [14]. Efforts have been made to optimize the base and solvent to get the optimum yield and quality of the compound **1**. Based on the experimental results, refluxing acetonitrile for 6h in basic Cs_2CO_3 resulted the optimum yield and quality. Experimental results are tabulated in Table-**2.**

Ultimately, we made the target compound **1** with consistent yield of 68% in route A and 61% in route B with 99.91% and 99.89% HPLC purity respectively. Yields, % impurity and purity levels of compound **1** by HPLC are tabulated in Table-**3**. The Desired polymorph, crystalline Dasatinib monohydrate **1** was confirmed by p-XRD, DSC and TGA spectral data. All the intermediates, novel compounds and final drug substance described herein were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass and Elemental analyses as listed in the experimental data.

CONCLUSION

In conclusion, we have successfully developed an alternative synthetic route to make Dasatinib monohydrate with the following merits,

a) Practical and industrially viable process

b) Better yield. 68% in route-A, 61% in route B from compound **9** and an overall yield of 20 % in route A, 18.2% in route B from commercially available thiazole amine **19**.

c) Pure Dasatinib monohydrate with total impurities < 0.10%.

The Desired polymorph, crystalline Dasatinib monohydrate **1** was confirmed by p-XRD, DSC and TGA spectral data.

EXPERIMENTAL

All of the chemicals were obtained from commercial sources and used without further purification. Melting points were determined in open glass capillaries on a Fisher–Johns melting point apparatus and are uncorrected. NMR (^{1}H 400 MHz; ^{13}C 100 MHz) were recorded at room temperature in DMSO as solvent and TMS as an internal standard (δ = 0 ppm), and the values were reported in the following order: chemical shift (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants (J in Hz), and integration. p-XRD was recorded on Bruker D8 Focus Powder X-ray Diffractometer. DSC and TGA were done on PerkinElmer instruments Q2000, Q50 respectively. All the reactions were monitored by thin layer

chromatography (TLC) on precoated silica gel 60 F254 (mesh); spots were visualized under UV light at 254 nm.

Typical Experimental Procedure For The Key Compounds:Tert-Butyl 4-(6-((5-((2-Chloro-6-Methylphenyl)Carbamoyl)Thiazol-2-Yl)Amino)-2-Methylpyrimidin-4-Yl)Piperazine-1-Carboxylate (3)

To the stirred suspension of compound **5** (10.0 g, 0.03 mol), in n-pentanol (120.0 mL) was added N-Boc piperazine (9.5g, 0.05 mol)) and N,N-diisopropylethylamine (DIPEA) (6.6 g, 0.06 mol) and refluxed for 8h, cooled to 25-30°C and charged water (80.0 mL). The precipitated solid was collected by vacuum filtration and washed the wet cake with n-pentanol (15.0 mL) followed by water (30.0 mL), yielded the intermediate **3** (11.6 g, 84%) as off white solid.

MR: 293-295°C; IR (KBr, cm-^{1}): 3397.4 (N-H), 3061.7 (Ar C-H), 1617.0 (amide C=O); 1706.9 (Boc C=O); ^{1}H NMR spectrum (400 MHz, DMSO-*d*6), δ, ppm (*J*, Hz): 11.53 (bs, 1H, thiazole-N<u>H</u>), 9.89 (s, 1H, amide-N<u>H</u>), 8.23 (s, 1H, thiazole-H), 7.40 (d, 1H, *J* =6.9, Ar-H), 7.30-7.23 (m, 2H, Ar-H), 6.06 (s, 1H, pyrimidine-H), 3.53 (bs, 4H, piperazine-CH_2), 3.42 (bs, 4H, piperazine-CH_2), 2.42 (s, 3H, Ar-CH_3), 2.24 (s, 3H, pyrimidine-CH_3), 1.40 (s, 9H, Boc-CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-*d*6), δ, ppm: 165.2 (pyrimidine-C), 162.4 (pyrimidine-C), 161.9 (pyrimidine-C), 160.1 (amide-C), 156.9 (thiazole-C), 151.4 (Boc-C), 140.5 (Ar-C), 139.1 (thiazole-C), 133.7 (thiazole-C), 132.0 (Ar-C), 129.5 (Ar-C), 128.4 (Ar-C), 127.6 (Ar-C), 125.1 (pyrimidine-C), 81.6 (pyrimidine-C), 80.2 (Boc-C), 50.2 (piperazine-2C), 49.9 (piperazine-2C), 29.1 (Boc-

CH_3), 25.6 (Ar-CH_3), 18.2 (pyrimidine-CH_3); HPLC Purity 96.7%; MS (ESI) *m*/*z* 544.1 $[M + H]^+$; *Anal*. Calcd % for $C_{25}H_{30}ClN_7O_3S$: C 55.19; H 5.56; N 18.02. Found: C 55.07; H 5.41; N 18.17.

N-(2-Chloro-6-Methylphenyl)-2-((6-(4-Formylpiperazin-1-Yl)-2-Methylpyrimidin-4-Yl)Amino)Thiazole-5-Carboxamide (4)

To the stirred suspension of compound **5** (10.0 g, 0.03 mol), in N,N-dimethylformamide (DMF) (10.0 ml) was added N-formyl piperazine (5.78, 0.05 mol), N,N-diisopropylethylamine (DIPEA) (6.53 g, 0.05 mol) and heated for 5h at 80-85°C, cooled to 25-30°C. The precipitated solid was collected by vacuum filtration and washed the wet cake with water (30.0 mL) yielded the novel intermediate **4** (9.4 g, 79%) as off white solid.

MR: 291-293°C; IR (KBr, cm^{-1}): 3395.3 (N-H), 2923.7 (Ar C-H), 1660.5(amide C=O); 1773.1 (aldehyde C=O); ^{1}H NMR spectrum (400 MHz, DMSO-*d*6), δ, ppm (*J*, Hz): 11.54 (s, 1H, thiazole-N<u>H</u>, exchangeable with D_2O), 9.89 (s, 1H, amide-N<u>H</u>, exchangeable with D_2O), 8.23 (s, 1H, thiazole-H), 8.10 (s, 1H, aldehyde-H), 7.40 (d, 1H, *J* =7.3, Ar-H), 7.30-7.24 (m, 2H, Ar-H), 6.10 (s, 1H, pyrimidine-H), 3.59-3.55 (bs, 4H, piperazine-CH_2), 3.48 (bs, 4H, piperazine-CH_2), 2.41 (s, 3H, Ar-CH_3), 2.24 (s, 3H, pyrimidine-CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-*d*6), δ, ppm: 166.1 (pyrimidine-C), 163.1 (pyrimidine-C), 162.6 (pyrimidine-C), 160.9 (aldehyde-C), 159.2 (amide-C), 157.5 (thiazole-C), 141.9 (Ar-C), 139.6 (thiazole-C), 132.9 (thiazole-C), 132.1 (Ar-C), 129.2 (Ar-C), 128.4 (Ar-C), 127.0 (Ar-C), 124.6 (pyrimidine-C), 81.6 (pyrimidine-C),

44.1 (piperazine-2C), 44.0 (piperazine-2C), 25.1 (Ar-CH_3), 18.4 (pyrimidine-CH_3); HPLC Purity 97.3%; MS (ESI) *m/z* 470.3 $[M - H]^-$; *Anal*. Calcd % for $C_{21}H_{22}ClN_7O_2S$: C 53.44; H 4.70; N 20.77. Found: C 53.32; H 4.73; N 20.81.

N-(2-Chloro-6-Methylphenyl)-2-((2-Methyl-6-(Piperazin-1-Yl)Pyrimidin-4-Yl)Amino)Thiazole-5-Carboxamide (2)

Con. sulfuric acid (9.36 g, 0.1 mol) was added to the stirred suspension of compound **4** (9.0 g, 0.02 mol) in methanol (108.0 mL) at 5-10°C and heated for 5h at 60-65°C, cooled to 25-30°C. Water (90.0 mL) was added, resulting suspension stirred for 3h at 25-30°C. The precipitated solid was collected by vacuum filtration and washed the wet cake with methanol (27.0 mL), water (36.0 mL) yielded the novel intermediate **2** (7.5 g, 91%, HPLC purity 98.34%) as off white solid.

Similarly, the other Boc-protected compound **3** was deprotected to give compound **2**, by following the same procedure as depicted for compound **4.**

MR: 298-301°C; IR (KBr, cm^{-1}): 3435.8 (N-H), 2950.2 (Ar C-H), 1620.0 (C=O); UV (Methanol): λ_{max} 323.7 nm; ^{1}H NMR spectrum (400 MHz, DMSO-*d*6), δ, ppm (*J*, Hz): 9.88 (s, 1H, amide-NH), 8.23 (s, 1H, thiazole-H), 7.39 (d, 1H, *J* =5.9, Ar-H), 7.29-7.23 (m, 2H, *J* =7.5, Ar-H), 6.04 (s, 1H, pyrimidine-H), 3.48 (t, 4H, piperazine-CH_2), 2.79 (t, 4H, *J* =4.8, piperazine-CH_2), 2.40 (s, 3H, Ar-CH_3), 2.23 (s, 3H, pyrimidine-CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-*d*6), δ, ppm: 165.1 (pyrimidine-C), 162.6 (pyrimidine-C), 162.5 (pyrimidine-C), 160.0 (amide-C), 156.9 (thiazole-C), 140.9 (Ar-

C), 138.8 (thiazole-C), 133.5 (thiazole-C), 132.5 (Ar-C), 129.0 (Ar-C), 128.2 (Ar-C), 127.0 (Ar-C), 125.7 (pyrimidine-C), 82.6 (pyrimidine-C), 45.3 (piperazine-2C), 44.8 (piperazine-2C), 25.6 (Ar-CH_3), 18.3 (pyrimidine-CH_3); MS (ESI) *m*/*z* 444.1 $[M + H]^+$; *Anal*. Calcd % for $C_{20}H_{22}ClN_7OS$: C 54.11; H 4.99; N 22.08. Found: C 54.02; H 5.12; N 22.17; HPLC Purity 98.34%.

N-(2-Chloro-6-Methylphenyl)-2-((6-(4-(2-Hydroxyethyl)Piperazin-1-Yl)-2-Methylpyrimidin-4-Yl)Amino)Thiazole-5-Carboxamide Monohydrate (1)

2-bromoethanol (3.9 g, 0.03), Cs_2CO_3 (10.2 g, 0.03 mol), KI (0.17g, 1 mmol) was added to a stirred suspension of compound **2** (7.0 g, 0.02 mol), in acetonitrile (105.0 mL) and refluxed for 6h. Water (280.0 mL) was added slowly at 75-80°C, cooled to 25-30°C and stirred for 2h. The precipitated solid was collected by vacuum filtration, washed the wet cake with Acetonitrile (28.0 mL), water (35.0 mL), yielded the final compound, Dasatinib monohydrate **1** (7.4 g, 93%) as a white solid.

MR: 279-280 °C (free base); IR (KBr, cm-^{1}): 3421.5 (N-H), 3250.58 (O-H), 1618.3 (C=O); UV (Methanol): $\lambda_{max,}$ 322.16 nm; ^{1}H NMR spectrum (400 MHz, DMSO-*d*6), δ, ppm (*J*, Hz): 10.47 (bs, 1H, thiazole-N<u>H</u>), 9.88 (s, 1H, amide-N<u>H</u>), 8.22 (s, 1H, thiazole-H), 7.40 (dd, 1H, *J* =6.1, 1.2, Ar-H), 7.30-7.23 (m, 2H, *J* =7.3, Ar-H), 6.04 (s, 1H, pyrimidine-H), 4.46 (t, *J* = 4.8, -O<u>H</u>), 3.54-3.51 (m, 6H, -CH_2C<u>H_2</u>OH & piperazine-CH_2), 2.48-2.46 (m, 4H, piperazine-CH_2), 2.44-2.42 (m, 2H, -C<u>H_2</u>CH_2OH), 2.40 (s, 3H, Ar-CH_3), 2.24 (s, 3H, pyrimidine-CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-*d*6), δ, ppm: 165.2 (pyrimidine-C), 162.6 (pyrimidine-C), 162.4 (pyrimidine-C), 160.0 (amide-C),

156.9 (thiazole-C), 140.9 (Ar-C), 138.8 (thiazole-C), 133.5 (thiazole-C), 132.5 (Ar-C), 129.0 (Ar-C), 128.2 (Ar-C), 127.0 (Ar-C), 125.7 (pyrimidine-C), 82.6 (pyrimidine-C), 60.2 (piperazine-2C), 58.5 (piperazine-2C), 52.7 (CH_2), 43.6 (CH_2), 25.6 (Ar-CH_3), 18.4 (pyrimidine-CH_3); MS (ESI) *m*/*z* 488.6 $[M + H]^+$; *Anal*. Calcd % for $C_{22}H_{28}ClN_7O_3S$: C 54.15; H 5.37; N 20.09. Found: C 54.13; H 5.36; N 20.13; HPLC Purity: 99.91% (t_R = 27.4 min.); 2-brpmoethanol content by Headspace GC: 3 ppm; *p*-XRD: Observed 2θ values at 18.0, 18.4, 19.2, 19.6, 21.2, 24.5, 25.9; 28.0; DSC (Differential scanning calorimetry): Obtained endotherm at 287.23°C (92.05 J/g); TGA (Thermogravimetric analysis): weight (water) loss (%) = 3.488 [5,9].

SUPPORTING INFORMATION

Full experimental detail, elemental analysis, Mass, ^{1}H NMR, ^{13}C NMR Spectra and characterization data for all synthesized compounds can be found via the "Supplementary Content" section of this article's webpage.

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Table-1. Optimization data of synthesized compound (5).

Entry	***Base*** [a]	***Base Mole Eq.***	***DCMP*** [b] ***Mole Eq.***	***Temp (°C)***	***Yield*** [c] ***(%)***
1	Solid NaO*t*Bu.	2.0	1.1	10-20	45
2	Solid NaO*t*Bu.	3.0	1.1	10-20	62
3	Solid NaO*t*Bu.	4.0	1.1	10-20	76
4	Sodium hydride (NaH)	4.0	1.1	10-20	71
5	Sodamide ($NaNH_2$)	4.0	1.1	10-20	73
6	Solid KO*t*Bu.	4.0	1.1	10-20	68
7	25% KO*t*Bu. in THF	4.0	1.1	10-20	69
8	28-30% NaO*t*Bu. in THF	3.0	1.1	10-20	71
9	28-30% NaO*t*Bu. in THF	4.0	1.1	10-20	84
10	**28-30% NaO*t*Bu. in THF**	**4.0**	**1.2**	**10-20**	**94**
11	28-30% NaO*t*Bu. in THF	4.0	1.2	0-5	88
12	28-30% NaO*t*Bu. in THF	4.0	1.0	10-20	~ 8% unreacted starting material

[a] All the reactions are carried out in THF solvent for 1 h

[b] DCMP, 4,6-dichloro-2-methyl pyrimidine

[c] Isolated yields of compound **(5).**

Table-2. Optimization data of synthesized compound (1).

Entry	***Base***	***Solvent***	***Temp. (°C)***	***Yield [a] (%)***
1	K_2CO_3	Acetonitrile / H_2O	Reflux	84
2	**Cs_2CO_3**	**Acetonitrile / H_2O**	**Reflux**	**93**
3	Na_2CO_3	Acetonitrile / H_2O	Reflux	78
4	DIPEA	Acetonitrile / H_2O	Reflux	45
5	DMAP	Acetonitrile / H_2O	Reflux	51
6	NaOH	Acetonitrile / H_2O	Reflux	--
7	Cs_2CO_3	1,4-dioxane / H_2O	Reflux	69
8	Cs_2CO_3	n-butanol / H_2O	Reflux	71
9	Cs_2CO_3	DMF / H_2O	125	84

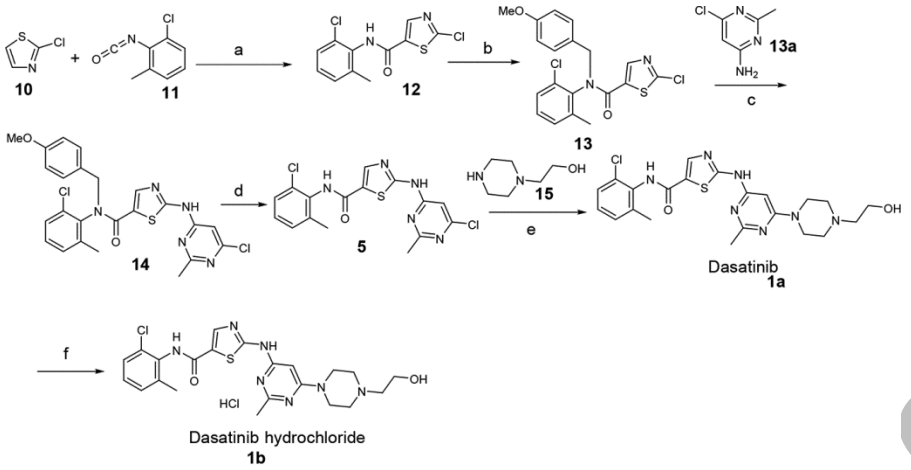
[a] Isolated yields of compound **(1).**

Table-3. Yields and Quality of compound (1).

Entry	***Scheme***	***No of Stages***	***Yield (%)***	***% Impurity and purity levels of compound (1) by HPLC***						
				Imp A ***(9)***	*Imp B* ***(5)***	*Imp C* ***(2)***	*Imp D* ***(3)***	*Imp E* ***(4)***	***1***	*TI*
1	1	6 from compound **10**	61	NA						
2	2	2 from compound **9**	57	0.31	0.42	0.21	NA	NA	98.91	1.09
3	3	3 from compound **16**	59	0.21	0.29	0.16	NA	NA	99.23	0.44
4	4	2 from compound **8**	61	NA						
5	6	4 from compound **9**	68 **(Route A)**	0.02	0.01	0.02	ND	NA	99.91	0.04
			61 (**Route B**)	0.01	0.02	0.03	NA	ND	99.89	0.06

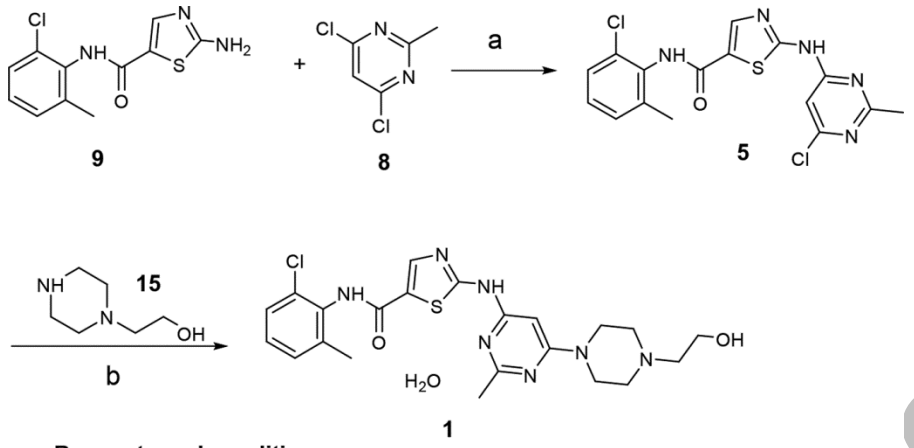
NA = Not applicable, ND = Not detected, Imp = Impurity. TI = Total impurities

Scheme 1. The first reported synthesis of Dasatinib and its hydrochloride salt [5].



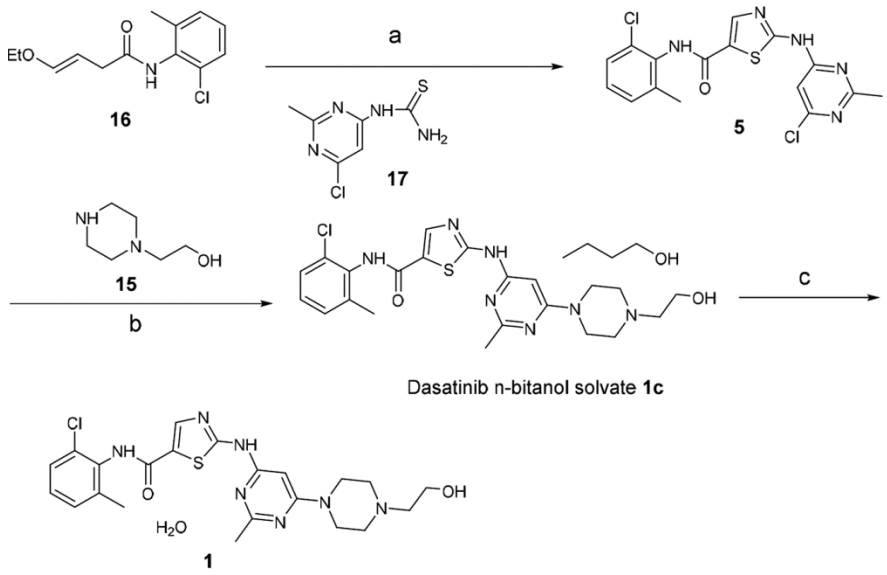
Reagents and conditions: (a) n-BuLi, THF, -78°C, 2hrs, 86%; (b) NaH-THF, 4-methoxybenzyl chloride, DMF, TBAB, rt,16hrs,95%; (c) NaH, THF, rt, 4hrs, 83%; (d) Triflic acid, TFA, DCM, rt, 3hrs, 99%; (e) 1,4-dioxane, DIPEA, reflux, 12hrs; (f) 2N HCl, ether-methanol, 30 min, 91% for 2 steps.

Scheme 2. Synthesis of Dasatinib monohydrate [7].



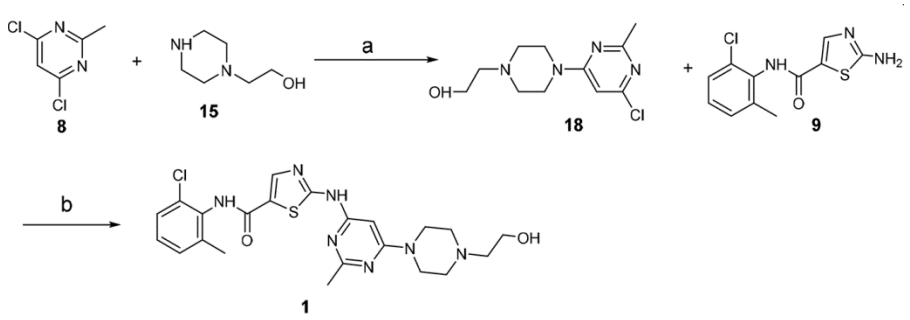
Reagents and conditions:
(a) NaH, THF, rt, overnight, AcOH, $NaHCO_3$, DCM, column purification, 61%;
(b) 80°C, 2h, H_2O, 94%.

Scheme 3. Synthesis of Dasatinib monohydrate [8].



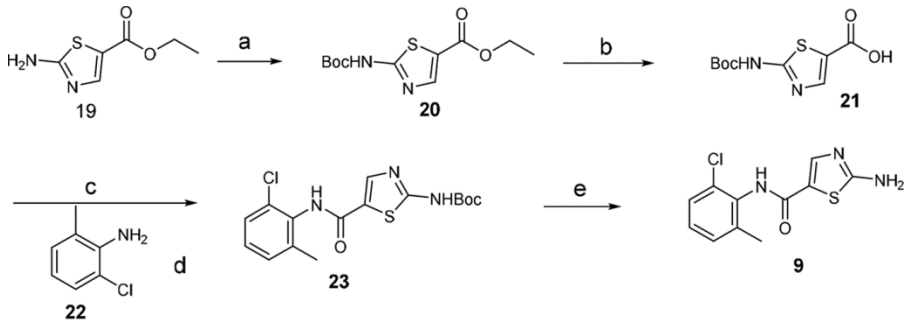
Reagents and conditions: (a) NBS, THF, H_2O, 20-22°C, 3hrs then Reflux, 2hrs, 71%; (b) n-Butanol, DIPEA,118°C, 4.5h, H_2O, 83%; (c) 80% EtOH/H_2O, 93%.

Scheme 4. Synthesis of Dasatinib [8].



Reagents and conditions:
(a) DCM, TEA, RT, 2hrs, 99%; (b) K_2CO_3, $Pd(OAc)_2$, BINAP, Toluene, 100-110°C, 20hrs, 62%

Scheme 5. Synthetic route for key starting material 9 [11].



Reagents and conditions: (a) Boc_2O, DMAP, THF, RT, 24hrs, 68%;
(b) 6N NaOH,THF-MeOH, RT, 24hrs, 94%; (c) $(COCl)_2$, cat.DMF, DCM, RT, 4hrs;
(d) DCM, DIPEA, RT, 2hrs, 51% over 2 steps; (e) Trifluoroacetic acid, RT,3hrs, 89%.

Scheme 6. Present synthetic route for Dasatinib monohydrate.

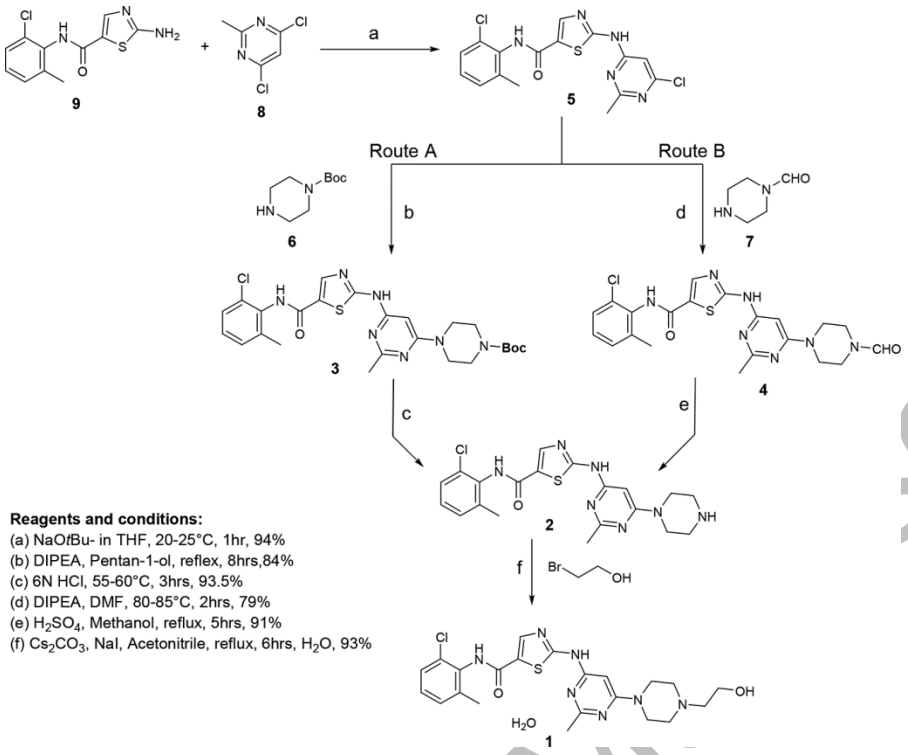


Figure 1. Structure of Dasatinib monohydrate

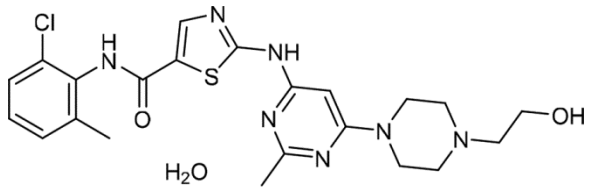


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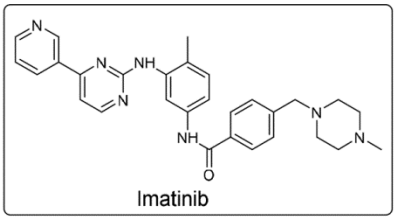
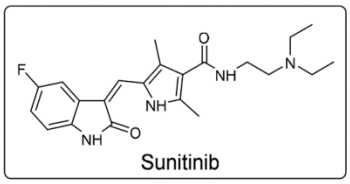
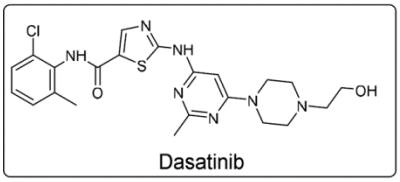
Figure 2. Chemical structures of Kinase inhibitors (tinibs)







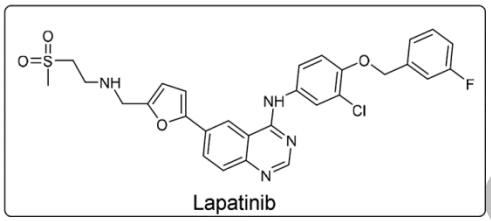
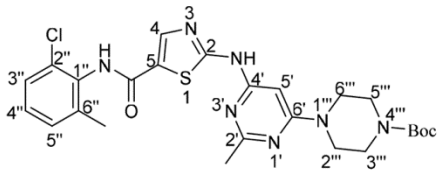


Figure 3 Structures of novel intermediate **(4)** and **(3).**



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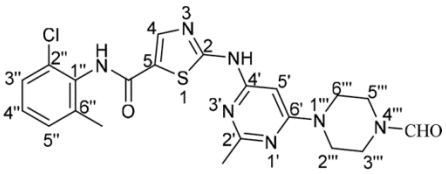

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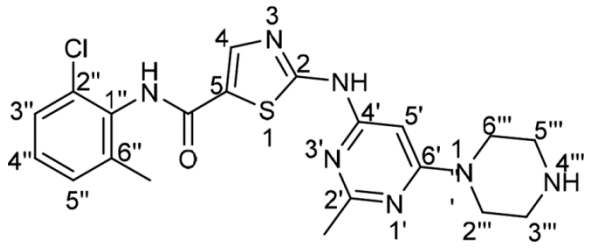
Figure 4. Des-hydroxy ethyl Dasatinib (DHED)-Impurity.



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