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A convenient new and efficient commercial synthetic route for dasatinib (Sprycel®)

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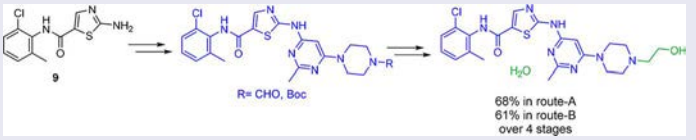
ABSTRACT

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 four stages.

GRAPHICAL ABSTRACT



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Alkylation; 2-bromoethanol; chronic myeloid leukemia; dasatinib monohydrate; Des-hydroxy ethyl dasatinib

Introduction

Cancer is a genetic disease characterized by an uncontrolled cell division. As per the World Health Organization 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 the view of increased demand and seriousness of the deadly cancer disease, various tyrosine kinase inhibitors, imatinib, sunitinib, nilotinib, dasatinib, and lapatinib (Fig. 1) are developed and are used to treat 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** (Fig. 2) 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

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Color versions of one or more of the figures in this article can be found online at www.tandfonline.com/lsyc.
Supplemental data (full experimental detail, elemental analysis, mass, ^{1}H NMR, ^{13}C NMR spectra, and characterization data for all synthesized compounds) can be accessed on the publisher's website.

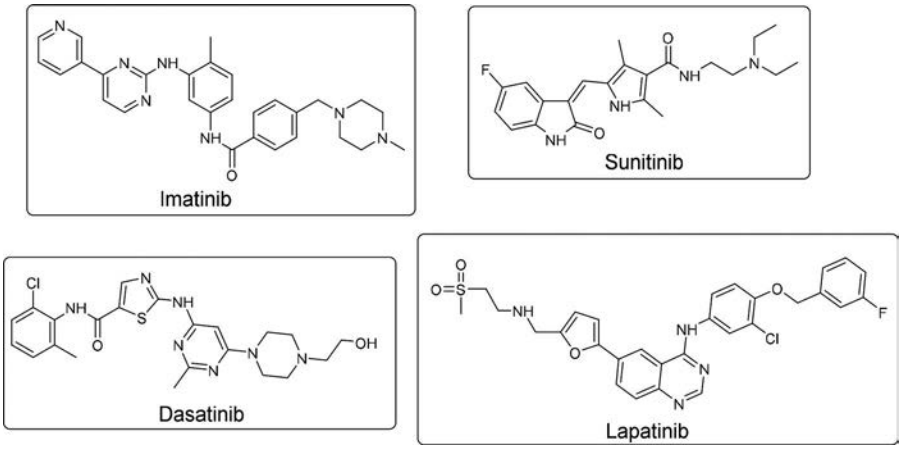
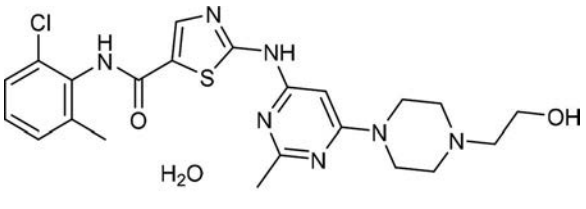


Figure 1. Chemical structures of kinase inhibitors (tinibs).

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, among others.[5,6] It is being evaluated for use in several other cancers, including advanced prostate cancer.

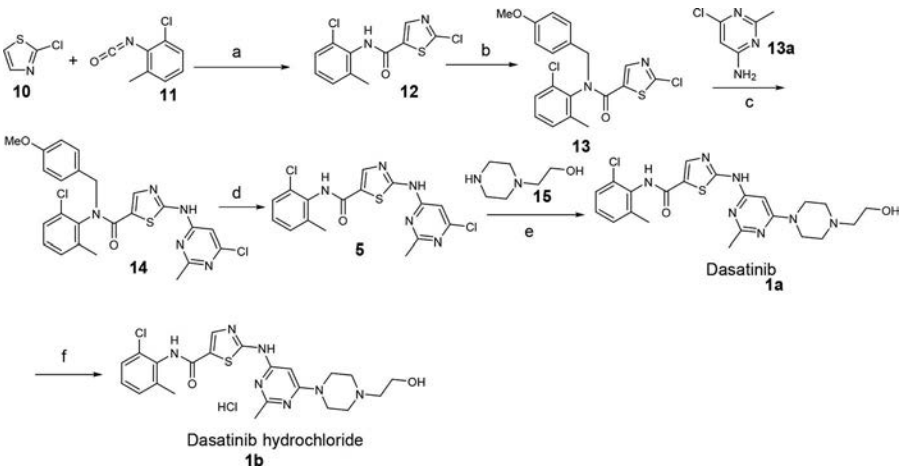
In the view of significance of dasatinib, several routes were developed to make dasatinib monohydrate. Following are some important synthetic routes which are practiced to make dasatinib monohydrate. Scheme 1 denotes the first and initial synthesis of dasatinib.[5]

The first step of synthesis in Scheme 1 involves the sulfur-directed ortho-lithation of 2-chlorothiazole **10** followed by a 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 couplin 5 g 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*-methoxybenzyl group 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 2N HCl, ether/methanol medium converted into



1

Figure 2. Structure of dasatinib monohydrate.

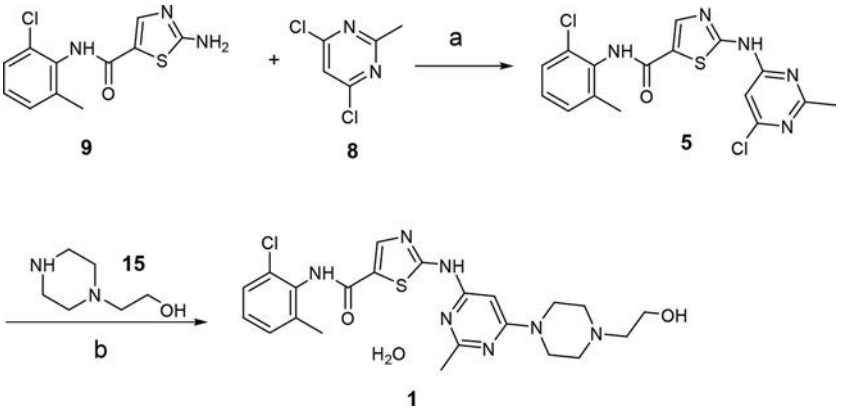


Scheme 1. The first reported synthesis of dasatinib and its hydrochloride salt.[5] *Reagents and conditions:* (a) *n*-BuLi, THF, −78°C, 2 h, 86%; (b) NaH-THF, 4-methoxybenzyl chloride, DMF, TBAB, rt, 16 h, 95%; (c) NaH, THF, rt, 4 h, 83%; (d) triflic acid, TFA, DCM, rt, 3 h, 99%; (e) 1,4-dioxane, DIPEA, reflux, 12 h; (f) 2N HCl, ether–methanol, 30 min, 91% for 2 steps.

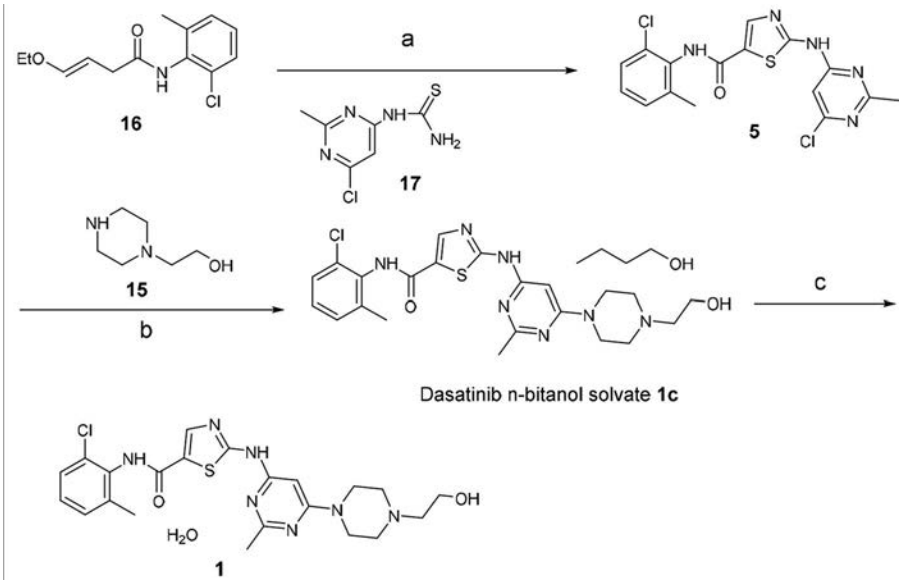
hydrochloride salt **1b**. The overall yield of this route is 61% for hydrochloride salt over six stages.

Das et al.[7] reported the synthesis of dasatinib monohydrate as shown in Scheme 2. 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**.

Bang-Chi et al.[8] reported the synthesis of dasatinib monohydrate as depicted in Scheme 3. The first step of 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



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, 2 h, H_2O, 94%.

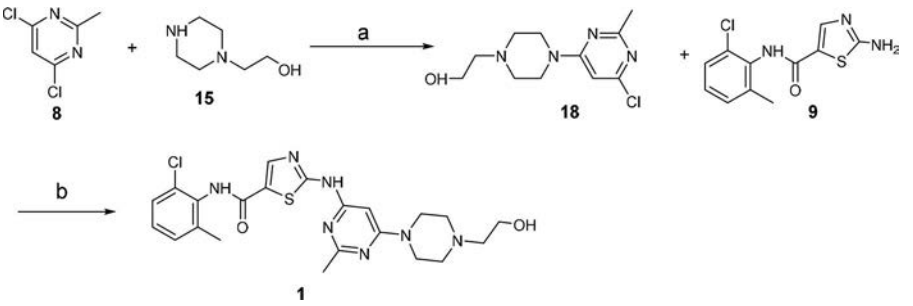


Scheme 3. Synthesis of dasatinib monohydrate.[8] *Reagents and conditions:* (a) NBS, THF, H_2O, 20–22°C, 3 h then reflux, 2 h, 71%; (b) n-butanol, DIPEA, 118°C, 4.5 h, 83%; (c) 80% EtOH/H_2O, 93%.

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 three stages.

Bang-Chi et al.[8] also reported the another route of synthesis of dasatinib, as shown in Scheme 4. The first stage of synthesis involves the coupling of **8** with HEP **15** in DCM, TEA at rt. for 2 h 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 from the final compound. Also, the synthesis of **1** involves palladium catalyst and column purification to get compound **1**. As per the International Conference on Harmonization (ICH) (Q3A, R2) regulatory amendments

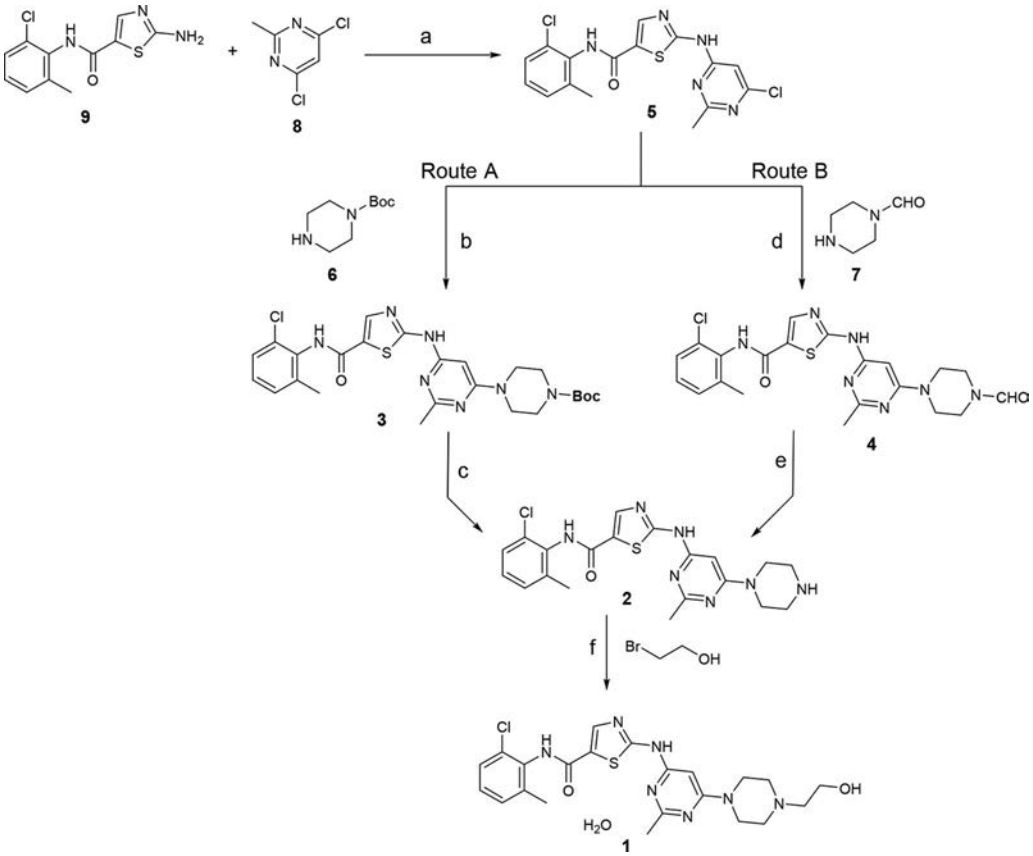


Scheme 4. Synthesis of dasatinib.[8] *Reagents and conditions:* (a) DCM, TEA, rt, 2 h, 99%; (b) K_2CO_3, Pd (OAc)2, BINAP, toluene, 100–110°C, 20 h, 62%.

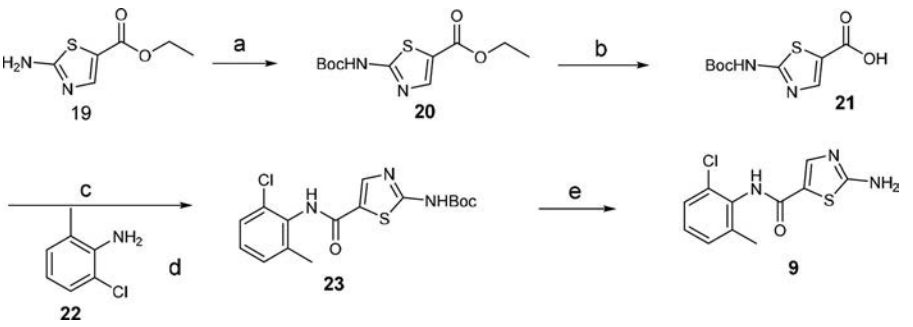
for a new drug substance (API) having maximum daily dose ≤2 g per day, the reporting identification thresholds for a known and an unspecified impurity are 0.15 and 0.10%, respectively.[9] Further, as per the ICH guideline (ICH Q3D) for a drug substance, the permitted daily exposure limit for palladium (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 impurities **2** and **5**. Also, it is a 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.



Scheme 5. Present synthetic route for dasatinib monohydrate. *Reagents and conditions:* (a) NaO*t*Bu-in THF, 20–25°C, 1 h, 94%; (b) DIPEA, pentan-1-ol, reflux, 8 h, 84%; (c) 6N HCl, 55–60°C, 3 h, 93.5%; (d) DIPEA, DMF, 80–85°C, 2 h, 79%; (e) H_2SO_4, methanol, reflux, 5 h, 91%; (f) Cs_2CO_3, NaI, acetonitrile, reflux, 6 h, H_2O, 93%.



Scheme 6. Synthetic route for key starting material **9**.[11] *Reagents and conditions:* (a) Boc_2O, DMAP, THF, rt, 2 h, 68%; (b) 6N NaOH, THF–MeOH, rt, 24 h, 94%; (c) (COCl)2, cat. DMF, DCM, rt, 4 h; (d) DCM, DIPEA, rt, 2 h, 51% over two steps; (e) trifluoroacetic acid, rt, 3 h, 89%.

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 5.

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 6.[11] The first step of 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 in DCM yields the key intermediate amino thiazole carboxamide **9** in 89% yield as off-white solid.

Results and discussion

The present synthetic route deals with the synthesis of crystalline dasatinib monohydrate **1** through two synthetic paths, route **A** and route **B** as shown in Scheme 5. The developed four-stage 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 chlorine in 4,6-dichloro-2-methylpyrimidine **8** with 2-amino-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **9** in the presence of base, sodium *tert*-butoxide (solid) yielded intermediate **5** about 76%.[12] In the view of 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 performed 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 performing the reaction in 28–30% NaO*t*Bu in THF solution at 10–20 °C for 1 h. 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** (Fig. 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

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% NaOtBu 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% NaOtBu in THF	4.0	1.0	10–20	~8% Unreacted starting material

Bold values represents the optimized conditions where yield is maximum.
[a]All the reactions are performed in THF solvent for 1 h.
[b]DCMP, 4,6-dichloro-2-methyl pyrimidine.
[c]Isolated yields of compound (**5**).

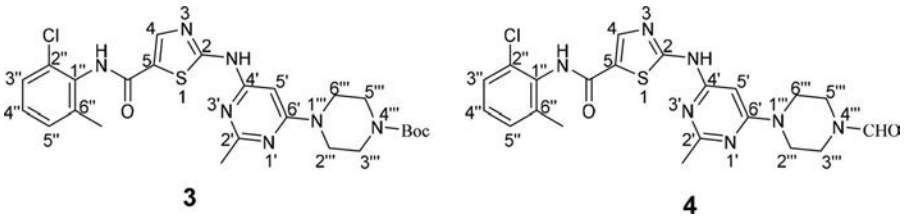
spectrum is compatible with the molecular formula $C_{25}H_{30}ClN_7O_3S$. The presence of sharp singlet at δ 1.40 along with other thiazole protons in ^{1}H NMR spectrum confirms the existence of Boc functional in compound **3**. In ^{13}C NMR of **3**, Boc carbons appeared at δ 29.13 and 80.21. Intermediate **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 *N*,*N*-dimethylformamide (DMF) gave novel intermediate, *N*-(2-chloro-6-methylphenyl)-2-((6-(4-formylpiperazin-1-yl)-2-methylpyrimidin-4-yl) amino) thiazole-5-carboxamide **4** (Fig. 3) in 79% yield.[5]

The structure of 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 formula $C_{21}H_{22}ClN_7O_2S$. The presence of sharp singlet at δ 8.10 along with other thiazole protons in ^{1}H 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 the presence of H_2SO_4, methanol yielded the penultimate intermediate, DHED **2** in 91% yield.

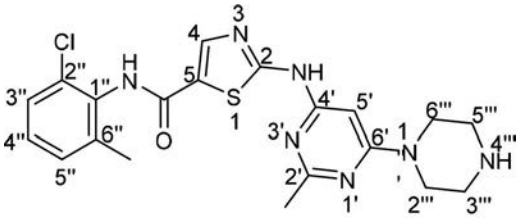
The, synthesized Des-hydroxy ethyl dasatinib intermediate **2** is fully characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data (Fig. 4).

Finally, alkylation of **2** with 2-bromoethanol in the presence of K_2CO_3, NaI, in acetonitrile followed by water addition at 70–75 °C, yielded the targeted compound **1**.[14] Efforts have



3 **4**

Figure 3. Structure of novel intermediates (**4**) and (**3**).



2

Figure 4. Des-hydroxy ethyl dasatinib-impurity.

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 6 h 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, percentage 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, differential scanning calorimetry (DSC), and thermogravimetric analysis (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.

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**).

				Percentage impurity and purity levels of compound (1) by HPLC						
Entry	Scheme	No of stages	Yield (%)	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.

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 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 a solvent and TMS as an internal standard ($\delta = 0$ 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 performed on PerkinElmer instruments Q2000, Q50 respectively. All the reactions were monitored by thin-layer chromatography on precoated silica gel 60 F_{254} (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) were added N-Boc piperazine (9.5 g, 0.05 mol) and *N,N*-diisopropylethylamine (DIPEA) (6.6 g, 0.06 mol) and refluxed for 8 h, 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-NH), 9.89 (s, 1H, amide-NH), 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 DMF (10.0 mL) were added N-formyl piperazine (5.78, 0.05 mol), DIPEA (6.53 g, 0.05 mol) and heated for 5 h 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-NH, exchangeable with D_2O), 9.89 (s, 1H, amide-NH, 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 5 h at 60–65 °C, cooled to 25–30 °C. Water (90.0 mL) was added, resulting suspension stirred for 3 h 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): $\lambda_{max,}$ 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), and KI (0.17 g, 1 mmol) were added to a stirred suspension of compound **2** (7.0 g, 0.02 mol), in acetonitrile (105.0 mL) and refluxed for 6 h. Water (280.0 mL) was added slowly at 75–80 °C, cooled to 25–30 °C, and stirred for 2 h. 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-NH), 9.88 (s, 1H, amide-NH), 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, $J = 4.8$, –OH), 3.54–3.51 (m, 6H, $-CH_2CH_2OH$ and piperazine-CH_2), 2.48–2.46 (m, 4H, piperazine-CH_2), 2.44–2.42 (m, 2H, $-CH_2CH_2OH$), 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: obtained endotherm at 287.23 °C (92.05 J/g); TGA: weight (water) loss (%) = 3.488.[5,9]

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