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A Facile Total Synthesis for Large-Scale Production of Imatinib Base

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ABSTRACT: An efficient, economic process has been developed for the production of imatinib with 99.99% purity and 50% overall yield from four steps. Formation and control of all possible impurities is described. The synthesis comprises the condensation of *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine with 4-(4-methylpiperazinomethyl)benzoyl chloride in isopropyl alcohol solvent in the presence of potassium carbonate to yield imatinib base.

1. INTRODUCTION

Imatinib mesylate (Gleevec, (4-(4-methylpiperazin-1-ylmethyl)-*N*-4-[methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)-phenyl]benzamide methane sulfonate, (Figure 1) is known as an inhibitor of tyrosine kinases and is indicated for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs).[1] It was approved by the FDA on 7 November 2001.In recent years research concerning imatinib has increased over the years in particular due to its positive effects on those patients with chronic myeloid leukemia. But, the method for synthesis of imatinib has been rarely reported.

The first synthetic pathway for imatinib was described by Zimmermann in 1993 (Scheme 1).[2] This synthetic approach involved the reaction of 2-amino-4-nitrotoluene (**2**) with 65% nitric acid to form its nitrate salt which was condensed with an aqueous solution of cyanamide to give guanidine nitrate intermediate (**3**). Intermediate **3** was condensed with the 3-dimethylamino-l-(3-pyridyl)-2-propen-l-one (**4**) in the presence of sodium hydroxide solution in isopropyl alcohol to form a nitro pyrimidine intermediate (**5**). Nitro pyrimidine (**5**) was then reduced using an amount 50 times by volume of ethyl acetate as solvent and palladium on carbon as the catalyst to yield *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**). The amine intermediate (**6**) was condensed with 4-(4-methylpiperazinomethyl)benzoyl chloride (**7**) in pyridine to give crude imatinib, which was then purified by column chromatography. The yields were not mentioned for the steps in the synthesis shown in Zimmermann's paper and patent document. We have found the process described in the above patent to be unsatisfactory, where the yield of the nitro intermediate was found to be only 50%. The nitro intermediate is also found to be contaminated with inorganic impurities, and use of the impure material leads to a very low yield of the final compound, i.e., imatinib. Usage of pyridine as a solvent and purification of the final product by column chromatography are added disadvantages of the process described in the patent.

Loiseleur et al.[3] described the second synthetic pathway for the preparation of imatinib base (Scheme 2). This method comprises condensation of 4-(3-pyridinyl)-2-pyrimidineamine (**8**), or a precursor thereof, with *N*-[3-bromo-4-methylphenyl)-4-(4-methylpiperazin-1-ylmethyl)benzamide (**9**). This scheme involved $Pd_2(dba)_3CHCl_3$-catalyzed C−N coupling reaction with the use of an organic phosphorous reagent *rac*-BINAP as ligand.

However, the shortcoming of this approach is special sonication equipment, as well as tedious purification of the product by flash chromatography and separating the desired from the undesired isomers using reverse-phase preparative chromatography and usage of expensive palladium as catalyst. Amala et al.,[4] Szakacs et al.,[5] and Szczepek et al.[6] also respectively provided the third synthetic path way, an improved process based on Loiseleur's approach (Scheme 3). It comprises the condensation of 4-methyl-*N*-3-(4-pyridin-3-yl-pyrimidin-2-yl)benzene-1,3-diamine (**6**) with 4-chloromethyl benzoyl chloride (**10**) to yield 4-chloromethyl-*N*-{4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl}benzamide (**11**), followed by its reaction with *N*-methyl piperazine.

However, a shortcoming of these approaches is the use of excess moles of tin(II) chloride/Raney nickel and hydrazine hydrate reagents for the reduction of the nitropyrimidine intermediate to prepare the corresponding amino compound, *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**6**). Tin(II) chloride and hydrazine hydrate are not ecofriendly but are reagents posing adverse affects on the environment. It should also be noted that several previous studies have reported the synthesis of imatinib base: (i) by employing sodium dithionate for nitropyrimidine (**5**) reduction followed by condensation with 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride in the presence of *N*,*N*-carbonyldiimidazole [7] and (ii) by employing iron chloride/hydrazine hydrate for nitropyrimidine (**5**) reduction followed by condensation with 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride in the presence of *N*,*N*-carbonyldiimidazole.[8] However, in these processes there was no mention of imatinib base purity.

All the above shortcomings of these processes make them unattractive and economically inefficient at the industrial level. Further in all these processes there is no mention of genotoxic impurities and their control. The classification of a compound (impurity) as genotoxic in general means that there are positive findings in established in vitro and in vivo genotoxicity tests

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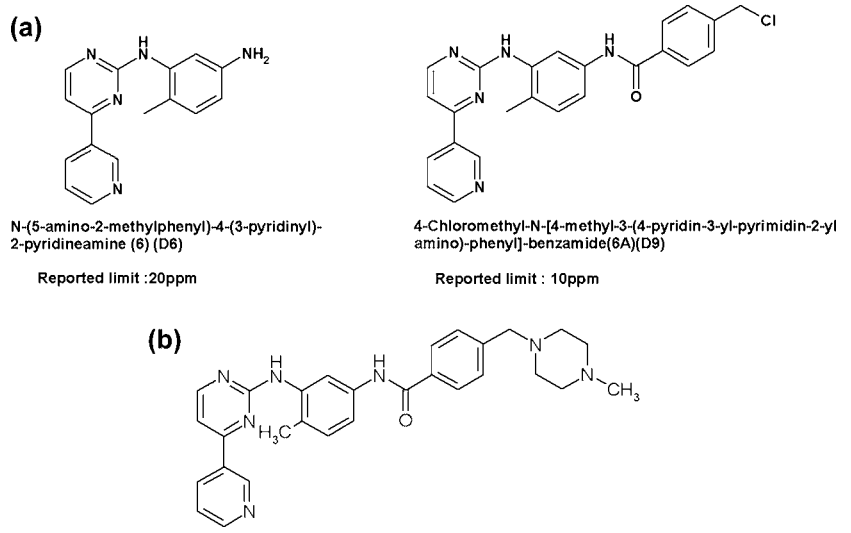
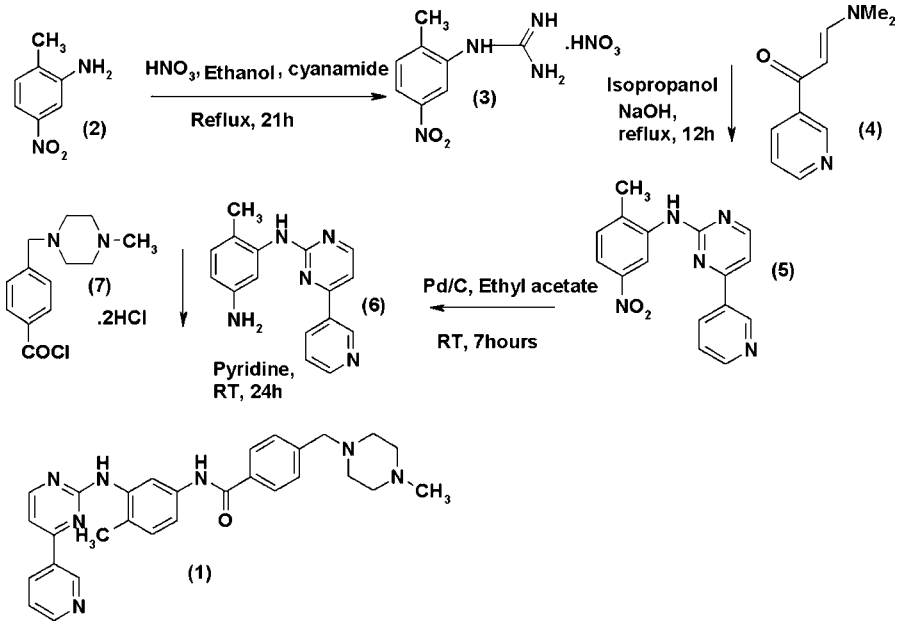


Figure 1. (A) Reported genotoxic impurities of imatinib mesylate. (B) Chemical structure of imatinib base.

Scheme 1. Zimmermann's route for the preparation of imatinib base



with the main focus on DNA-reactive substances that have a potential for direct DNA damage. For imatinib mesylate two genotoxic impurities, *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**6**, **D6**) and 4-chloromethyl-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-yl-amino)-phenyl]-benzamide (**6A**, **D9**), are reported as per FDA drug review.[9] Further daily dosage of imatinib mesylate is 800 mg; therefore, for the starting material, *o*-toluidine, the genotoxic impurity limit must be below 1.87 ppm.[10]

In view of the stringent quality requirement, we planned to study Scheme 1 in detail and aimed for control of all the impurities at the imatinib base stage.

In Scheme 1 *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**6**) is reacted with 4-(4-methylpiperazinemethyl)benzoyl chloride (**7**) in the form of a dihydrochloride. This acid chloride (**7**) is prepared by the reaction of 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride (**14**) with thionyl chloride.

4-(4-Methylpiperazinomethyl)benzoic acid dihydrochloride was synthesized by Lambardino in 1996 (Scheme 4).[11] This method employs the condensation of *α*-chloro-*p*-toluic acid with 4 mol of *N*-methyl piperazine in ethanol under reflux conditions to give 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride in only 35% yield.

The low yield may be explained by the simultaneous formation of product along with the following quaternary salt as a major impurity (**14A**, Figure 2)

Batchelor et al.[12] described the second pathway for the preparation of 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride (Scheme 5). This method employs the substitution of *N*-methyl piperazine with the primary halide moiety of *α*-bromotoluic acid methyl ester by heating for 6 h in DMF, yielding the methyl ester of 4-(4-methylpiperazinomethyl)-benzoic acid dihydrochloride in only 47% yield. Thus, the reactions of both the acid and its ester analogues are documented.

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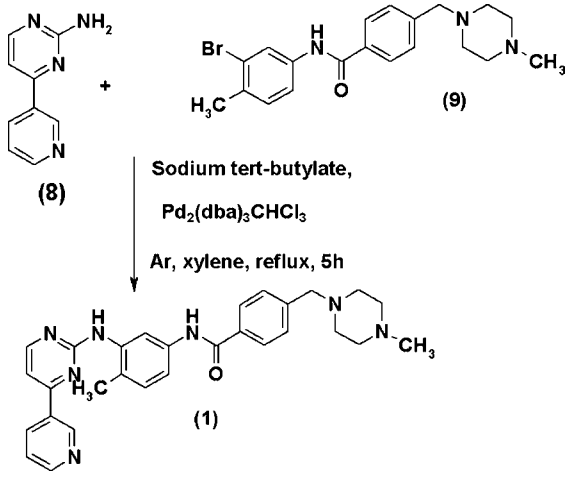
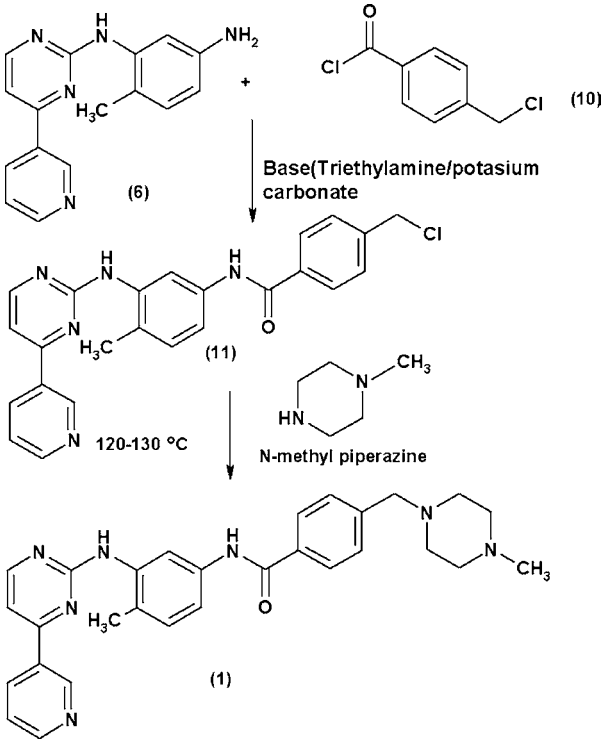
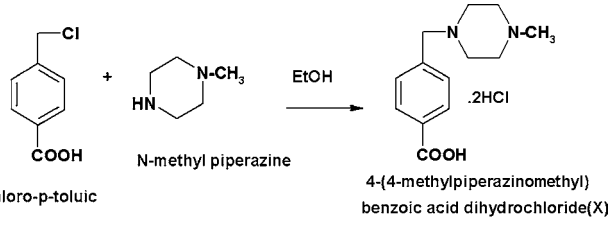
Scheme 2. Loiseleur's route for the preparation of imatinib base



Scheme 3. Amala's/Szczepek's route for the preparation of imatinib base



Scheme 4. Lambardino's route for the preparation of 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride



Subsequently, a few more reported processes[13,14] follow a reaction sequence similar to that represented in Scheme 4.

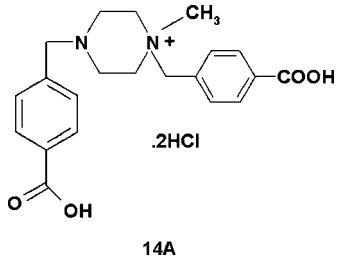
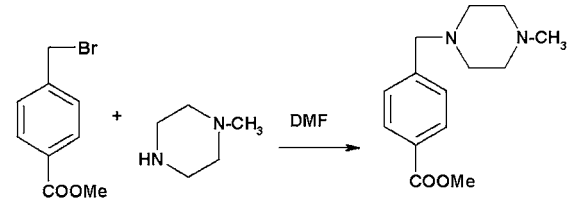


Figure 2. Structure of impurity **14A**.

Scheme 5. Batchelor's route for the preparation of 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride



Kazuto[15] discloses a two-step process for the preparation of 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride by the reaction of 1-methylpiperazine with 4-chloromethylbenzonitrile in xylene in the presence of potassium carbonate. Hydrolysis of the intermediate product affords 4-[(4-methyl-1-piperazinyl)methyl]benzoic acid dihydrochloride. In this process all intermediates are isolated for commercial-scale operations and dried before using in the next step. Isolation and drying operations are time consuming and expose the production personnel to solvent vapors, affecting the productivity. Ivanov et al.[7] disclosed a three-step process for the synthesis of 4-(4-methylpiperazino)methyl benzoic acid dihydrochloride employing methyl *p*-toluate as the starting material with an overall yield of 58%. In this process highly toxic carbon tetrachloride solvent was used for the *N*-bromination step. Sairam et al.[16] reported the preparation of 4-(4-methylpiperazino)methyl benzoic acid dihydrochloride by the reaction of *p*-bromo methyl benzonitrile with *N*-methyl piperazine followed by basic hydrolysis of the nitrile group and acidification with hydrochloric acid to provided product in 63% yield in two steps. Liu et al.[8] reported the preparation of 4-(4-methylpiperazino)methyl benzoic acid dihydrochloride by the reaction of *p*-chloromethyl benzonitrile with *N*-methyl piperazine followed by acid hydrolysis of the nitrile group with 96% HPLC purity in two steps. In this contribution we report a simple, scalable process for 4-(4-methylpiperazino)-methyl benzoic acid dihydrochloride (**14**) of 99.9% HPLC purity by changing mode of addition of *N*-methyl piperazine to *p*-bromomethyl benzonitrile and hydrolysis conditions to get maximum purity and yield.

In this protocol the preparation of key intermediate 4-(4-methylpiperazino)methyl benzoic acid dihydrochloride (**14**) comprises (a) α-bromination of *p*-tolunitrile to get 4-bromomethyl benzonitrile (**12**), (b) condensation of bromo compound (**12**) with *N*-methyl piperazine in chloroform to get 4-(4-methylpiperazinomethyl)benzonitrile (**13**), (c) in situ hydrolysis of 4-(4-methylpiperazinomethyl)benzonitrile with concentrated hydrochloric acid to give 4-[(4-methyl-1-

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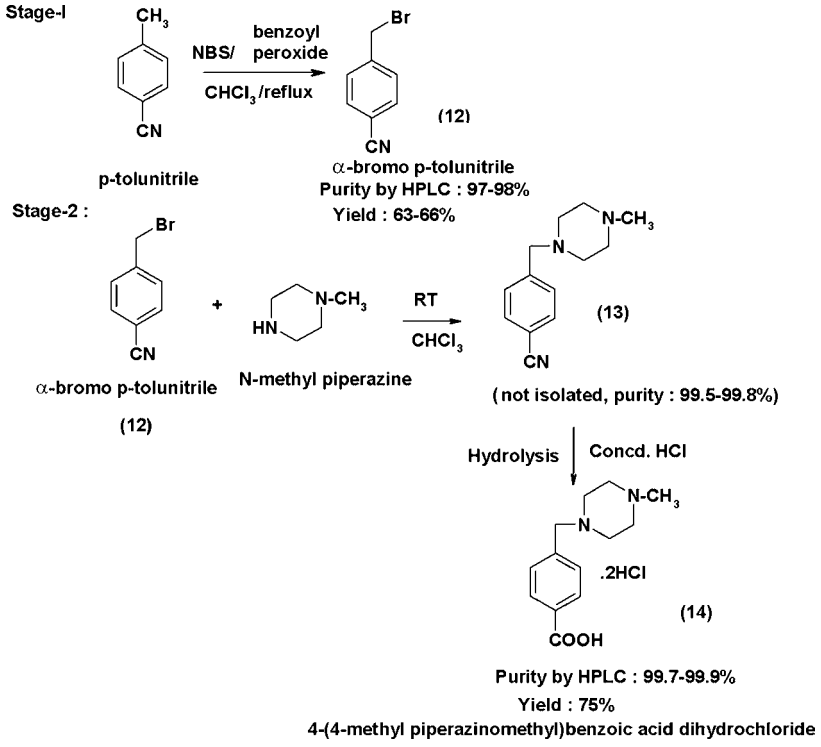
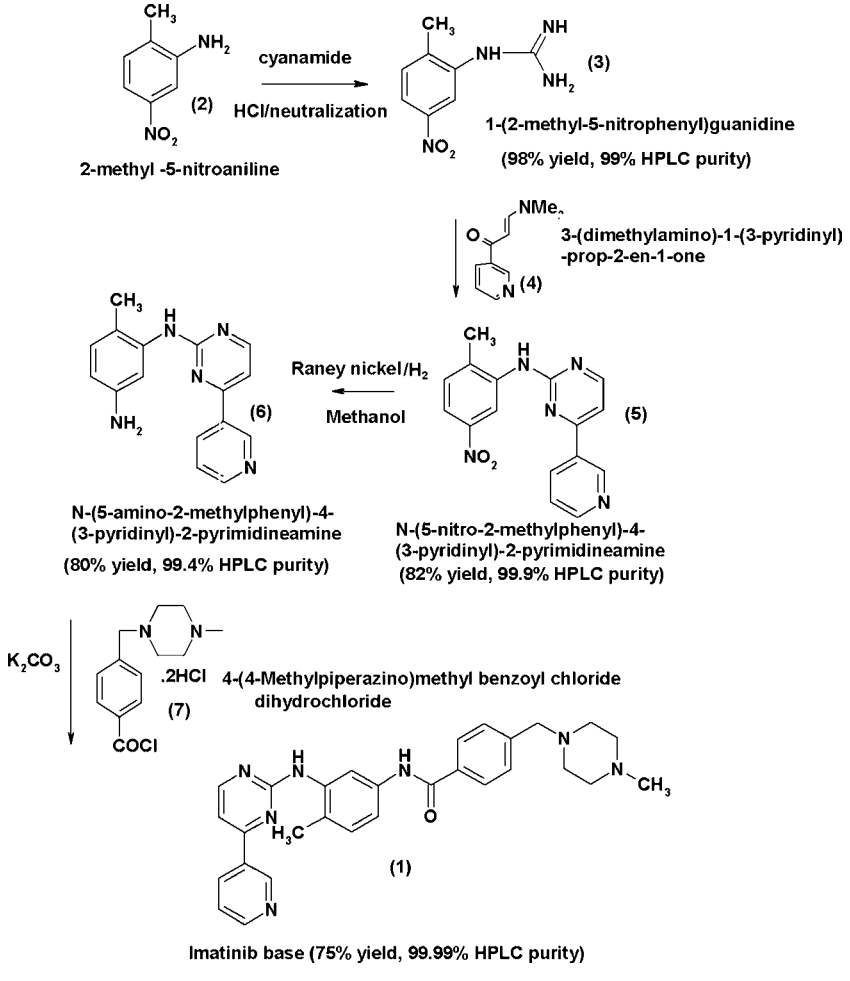
Scheme 6. Schematic synthetic procedure for 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride



Scheme 7. Schematic synthetic procedure for highly pure imatinib base



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piperazinyl)methyl]benzoic acid dihydrochloride (**14**) of 99.9% purity (Scheme 6).

Highly pure imatinib base of 99.99% purity is prepared by considering the Zimmermann[2] route as a basis and thoroughly studying and optimizing parameters, thereby making the process commercially viable as follows: (a) reacting 2-methyl-5-nitroaniline with cyanamide in the presence of hydrochloric acid followed by neutralization to obtain 1-(2-methyl-5-nitrophenyl)guanidine (**3**); (b) reacting 3-(dimethylamino)-1-(3-pyridinyl)-prop-2-en-1-one (**4**) with 1-(2-methyl-5-nitrophenyl)guanidine (**3**) to obtain *N*-(5-nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**5**); (c) reducing *N*-(5-nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**5**) in the presence of Raney nickel to obtain *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**); (d) condensing *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**) with 4-(4-methylpiperazino)methyl benzoyl chloride dihydrochloride (**7**) in the presence of an inorganic base (Scheme 7). In thus formed imatinib base all the genotoxic impurities are well controlled by incorporating extra purification steps.

2. RESULTS AND DISCUSSION

2.1. Optimization of the Process for the Preparation of 4-(4-Methylpiperazinomethyl)benzoic Acid Dihydrochloride (14).

2.1.1. New Process Conditions for the Condensation of 4-Bromomethyl Benzonitrile and N-Methyl Piperazine To Yield 4-(4-Methylpiperazinomethyl)-benzonitrile.

2.1.1.1. Selection of Solvent for Reaction Medium for α-Bromination. For the α-bromination of *p*-tolunitrile to prepare 4-bromomethyl benzonitrile (**12**) detailed literature search was done. As per literature methods to obtain benzylic bromides are either a direct bromination using bromine or a free redical bromination using *N*-bromosuccinimide (NBS). Photo irradiation is the disadvantage of direct bromination reaction as this technique is not viable on commercial scale. Carbon tetrachloride has been accepted as general solvent in *N*-bromosuccinimide side-chain brominations.[17] Water was described as an excellent medium for free radical reactions,[18] due to its remarkable nonreactivity towards radicals (OH bond resistancy to hemolytic breaking). Unfortunately, *p*-tolunitrile was insoluble in water; thus, experiment with water medium was not successful. The methyl formate solvent reported in the literature did not seem to offer any advantage.[19] Cyclohexane and acetic acid solvents were also tried, but the reactions resulted in low-yielding product. Other solvents comparable with carbon tetrachloride are chloroform, methylene chloride, and benzene. Table 1 shows results for the screening of solvents. For environmental and toxic reasons we optimized chloroform for the α-bromination step. After reaction completion, the chloroform layer was water washed and distilled, and **12** was isolated using a mixture of chloroform and hexane. In commercial scale, maximum recovery of chloroform was established, and recovered solvent was reused for the same step. The ratio of recovered mixture of chloroform and hexane was adjusted to 1:4 by the addition of required fresh solvent (Tables 2 and3).

2.1.1.2. Selection of Solvent for the Condensation of 4-Bromomethyl Benzonitrile and N-Methyl Piperazine to Yield 4-(4-Methylpiperazinomethyl)benzonitrile. Initial experiments were tried in different solvents such as xylene, acetone, isopropyl alcohol, DMF, and chloroform using potassium carbonate as the base in different experimental conditions. All of these experiments resulted in the formation of the following quaternary salt (**13A**, Figure 3) as the main product. To avoid the formation of the quaternary salt, usage of potassium carbonate was avoided. With water-miscible solvents the workup involved a number of operations: pouring the reaction mass into water, extraction with solvent, distillation, and isolation. Moreover, all of these solvents resulted in greater amounts of quaternary salt, and solvent recovery is not possible

Table 1. Solvent optimization for the preparation of 12

entry	solvent	temp (°C)	time (h)	purity (%)	yield (%)
1.0	methyl formate	32	12	96	51
2.0	water[a]	70	6		
3.0	acetic acid[b]	60	6		
		80	3		
4.0	dichloromethane[c]	38	8		
5.0	benzene	80	3	97.5	60
6.0	cyclohexane	80	3	97	48
6.0	chloroform	60	3	98.5	65

[a]10% reaction completed; therefore, solid is not isolated. [b]50% reaction completed; therefore, solid is not isolated. [c]Reaction not initiated; therefore, solid is not isolated.

Table 2. Experimental results of 12 on commercial scale using recovered chloroform

entry	**12** purity (%)	**12** yield (%)	solvent purity (%)	solvent recovery (%)
1.0	98.5	67	99.8	77
2.0	98.7	66	99.7	80
3.0	98.5	67	99.8	78

Table 3. Experimental results of 12 on commercial scale using a recovered mixture of chloroform and hexane (1:4)

entry	**12** purity (%)	**12** yield (%)[a]	solvent purity (%)	solvent recovery (%)
1.0	98.5	67	99.7	77
2.0	98.7	66	99.8	78
3.0	98.5	67	99.8	77

[a]Purity of recovered mixture of chloroform and hexane by GC.

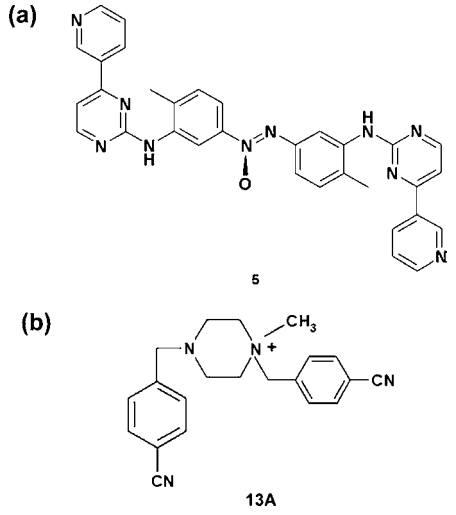

Figure 3. (A) Diazoxy impurity of compound **5** formed in Raney nickel/hydrazine reduction. (B) Structure of impurity **13A**.

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with water-miscible solvents. Compared to the case of chloroform, lower yields were observed in all other solvents. To minimize workup, the water-immiscible solvent, chloroform, was chosen as the medium. After reaction completion water was added, and chloroform was removed. Thus, chloroform is an appropriate solvent for the preparation of compound **13**. In commercial scale the maximum recovery (80%) of chloroform was established, and recovered solvent was reused for the same step (Table 4).

Table 4. Experimental results of 13 on commercial scale using recovered chloroform

entry	**13** purity (%)	**13** yield (%)	solvent purity (%)	solvent recovery (%)
1.0	99.8	99.7	99.7	76
2.0	99.8	99.5	99.7	78
3.0	99.7	99.5	99.8	80

2.1.1.3. Mole Ratios Study. Molar equivalents of 1, 1.2, 1.5, and 2.8 *N*-methyl piperazine (NMP) were studied with respect to 4-bromomethyl benzonitrile (**12**) and, finally 2.8 molar equivalents were optimized to prevent the formation of quaternary salt. The experimental results indicated the optimum yield and purity were obtained with 2.8 molar equivalents of *N*-methyl piperazine (Table 5).

Table 5. Optimization of *N*-methyl piperazine mole ratio for condensation of 4-bromomethyl benzonitrile (12)

entry	*N*-methyl piperazine mole ratio	yield (%)	purity (%)	remarks
1.0	1.2	51.0	96	yield is low because of quaternary salt formation
2.0	1.5	49.0	96.9	yield is low because of quaternary salt formation
3.0	2.8	94.5	97.4	yield is high because of minimization of quaternary salt

2.1.1.4. Mode of Addition of Reagent. In some experiments NMP was dissolved in chloroform and added to 4-bromomethyl benzonitrile solution. It was found that *N*-methyl piperazine dissolution in chloroform resulted in an exothermic reaction (45−50 °C); further during workup, quaternary salt (Figure 3) formation is noticed affecting the yield of the product. Thus, in the later reactions reverse addition of 4-bromomethyl benzonitrile (**12**) solution to NMP was adopted and optimized to avoid quaternary salt formation (Table 6).

*2.1.2. Study Conducted for Hydrolysis of 4-(4-Methylpiperazinomethyl)benzonitrile (**13**).* For initial experiments hydrolysis of 4-(4-methylpiperazinomethyl)benzonitrile was studied with base hydrolysis by heating with 10% sodium hydroxide solution; after reaction completion, acidification with concentrated hydrochloric acid liberated the desired acid. It has resulted in 99% purity containing about 1% inorganic impurities. (Table 7)

Table 6. Optimization of mode of addition of *N*-methyl piperazine (NMP)

entry	NMP mode of addition	yield (%)	purity (%)
1.0	NMP to **12**	82.0	98.5
2.0	NMP to **12**	79.0	98.5
3.0	**12** to NMP	97.0	99.8
4.0	**12** to NMP	97.0	99.7

Table 7. Hydrolysis of compound (9) with 10% sodium hydroxide solution

entry	yield (%)	purity (%)/single impurity (%)	residue on ignition (%)
1.0	80.0	99.0/0.18	0.7
2.0	79.0	99.2/0.17	0.7
3.0	80.0	99.3/0.18	0.6

For later experiments acid hydrolysis was studied by taking concentrated hydrochloric acid (10−15 vol) as the medium. For initial experiments after reaction completion the workup comprised concentrated hydrochloric acid complete distillation, and the desired product 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride (**10**) was isolated with different solvents such as methanol and isopropyl alcohol. HPLC purity for these experiments was about 99%. Later on antisolvents such as isopropyl alcohol were added to the reaction mass to avoid distillation. HPLC purity for these experiments was about 99% with about 80% yield.

Concentrated hydrochloric acid volume was minimized from 10 vol with respect to starting material to 8 vol, and the product was isolated from the reaction medium by cooling and filtration. Isopropyl alcohol is used for washing purposes as the solubility of this intermediate in water is very high. The filtration temperature was fixed at 40−45 °C to obtain 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride (**14**) of purity greater than 99.5% (Table 8).

Table 8. Acid hydrolysis of compound (9) with concentrated hydrochloric acid

entry	filtration temp (°C)	yield (%)	purity (%)	residue on ignition (%)
1.0	25−35	81.0	99.12	0.02
2.0	40−45	79.0	99.99	0.01

2.2. Optimization of the Process of 4-(4-Methyl-piperazin-1-ylmethyl)-*N*-{4-methyl-3-[(4-pyridin-3-yl)-pyrimidin-2-ylamino]phenyl}benzamide (I, Imatinib Base (1)). *2.2.1. Preparation of (2-Methyl-5-nitrophenyl)-guanidine (**3**).* Preparation of (2-methyl-5-nitrophenyl)-guanidine was studied in the laboratory by the condensation of 2-methyl-5-nitroaniline with different molar equivalents of cyanamide in *n*-butanol solvent with concentrated hydrochloric acid addition. Formed product 1-(2-methyl-5-nitrophenyl)-guanidine hydrochloride salt was neutralized using 10% aqueous sodium hydroxide to get (2-methyl-5-nitrophenyl)-guanidine (**3**). The following parameters were studied thoroughly for optimization of reaction conditions.

2.2.1.1. Study of Cyanamide Moles. The quantities of 2.0, 2.5, and 3.0 molar equivalents of cyanamide were studied. It was observed that, with 2.0 and 2.5 molar equivalents of cyanamide, reaction was incomplete with 5−10% unconverted starting material; thus, the obtained product needed further purification for the removal of starting material. Three moles of cyanamide yielded product with good quality and high yield. On the basis of this study 3 molar equivalents of cyanamide were chosen for process development (Table 9).

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Table 9. Study of cyanamide moles for the condensation of 2-methyl-5-nitroaniline

entry	cyanamide (mol)	yield (%)	purity (%)
1.0	2.0	80.0	90.0
2.0	2.5	90.0	95.0
3.0	3.0	98.0	98.0

2.2.1.2. Selection of Hydrochloric Acid and Its Mode of Addition. In the original process concentrated nitric acid was added in one lot to 2-methyl-5-nitroaniline to facilitate salt formation. With this condition it was observed that the reaction was incomplete with many impurities formed, and the final realized yield was only 35%. A study was undertaken to replace concentrated nitric acid, and it has been found that concentrated hydrochloric acid improves yield considerably (up to 85%). Further availability of concentrated hydrochloric acid to the reaction mass has been increased by its lot-wise addition. This dramatically improved the yield (98%) and gave product with 99% HPLC purity (Table 10).

Table 10. Study of mineral acid selection and the mode of addition

entry	mineral acid	mode of addition	yield (%)	purity (%)
1.0	concd nitric acid	one lot	35.0	90.0
2.0	concd hydrochloric acid	one lot	87.0	98.6
3.0	concd hydrochloric acid	lot-wise	98.0	98.8

*2.2.2. Condensation of (2-Methyl-5-nitrophenyl)guanidine (**3**) and (Dimethylamino)-1-(3-pyridinyl)-prop-2-en-1-one (**4**). 2.2.2.1. Study of Solvents.* Solvents such as methanol, ethanol, isopropyl alcoho, and *n*-butanol were tried for the condensation step. It was observed that in methanol, ethanol, and isopropyl alcohol solvents the reaction was incomplete even after prolonged hours. It was found that *n*-butanol was the suitable solvent with high reflux temperature. Consequently, condensation of (2-methyl-5-nitrophenyl)guanidine (**3**) with 1.1 molar equivalent of (dimethylamine)-1-(3-pyridinyl)-prop-2-en-1-one (**4**) was studied at *n*-butanol reflux temperature, and the reaction was found to be complete after 9 h. After reaction completion the reaction mass was diluted with purified water, filtered, and dried to yield *N*-(5-nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**5**) with 65−70%, yield and 99.2−99.5% purity by HPLC.

*2.2.3. Reduction of N-(5-Nitro-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidineamine (**5**).* Reduction of nitro compounds can be achieved by several reagents in solution-phase reactions. Reactions with metals (usually Fe, Sn, and Zn) in the presence of small amounts of acids are the most vigorous reduction methods. We tried respectively iron powder/acetic acid, iron powder/6 N HCl, iron powder/30% HCl, 10% Pd−C/ethyl acetate, 10% Pd−C/dimethyl formamide, stannous chloride/HCl, Raney nickel/hydrazine and Raney nickel/methanol. The observed results showed that, in experiments with iron powder and hydrochloric acid, product was obtained as oil due to the formation of a large number of impurities. With 10% Pd−C/ethyl acetate or 10% Pd−C/dimethyl formamide reaction was incomplete after prolonged hydrogenation, and formed product was impure with a broad melting range. With Pd−C of Johnson Mattew grade also same results were obtained. With Raney nickel/hydrazine we identified a new impurity at about 40%. On the basis of the LC−MS data, this impurity was identified as diazoxy impurity of nitropyrimidine **5** (Figure 3A). A process has been developed with stannous chloride/HCl as a reducing agent, and this technology was successfully commercialized in 100-kg scale. (Table 11). For batches involving stannous chloride/HCl as the reducing agent, a heavy metal test with a limit of 10 ppm was incorporated at the imatinib base stage to ensure that no tin traces were carried over to the API.

Later on, this reduction step was reworked with an aim of minimization of effluents. Thus, Raney nickel was chosen as reducing agent to meet these objectives and consequently to meet cost economics.

N-(5-Nitro-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidineamine (**5**) was reduced by the catalytic hydrogenation with Raney nickel to yield *N*-(5-amino-2-methylphenyl)-4-(3-pyr-

Table 11. Study of reducing agent for compound 5 reduction

entry	reducing agent	experimental conditions	yield (%)	purity/remarks (%)
1.0	Fe powder/acetic acid	reflux for 4 h	solid is not obtained	50% purity with unconverted starting material with other impurities
2.0	Fe powder/6 N HCl	90−95 °C/30 min	77.7	90% purity with 5% unconverted starting material with other impurities
3.0	Fe powder/30% HCl	90−95 °C/2.5 h	77.5	80% purity with 20% unconverted starting material and impurities
4.0	10% Pd−C/ethyl acetate	solution was not clear; 30 h hydrogenation	46.7	reaction was incomplete with 20% starting material and other impurities.
5.0	10% Pd−C/ ethyl acetate + DMF	for clear solution mixture of solvents taken; 20 h hydrogenation		reaction was incomplete with 10% starting material and other impurities. obtained melting range:106−115 °C reported melting range: 140−142 °C
6.0	10% Pd−C/DMF	for clear solution excess DMF taken and distilled after Pd−C filtration; 20 h hydrogenation	55	reaction incomplete with 10% starting material and other impurities. obtained melting range:106−115 °C reported melting range: 140−142 °C
7.0	$SnCl_2$/concd HCl	addition at 10 °C and 1 h maintenance at RT	60.0	purity: 99.0 obtained melting range:140−142 °C reported melting range: 140−142 °C)
8.0	Raney nickel/hydrazine	RT hours	product not isolated	about 50% purity with 10% starting material and 40% diazoxy impurity
9.0	Raney nickel/methanol	hydrogenation for 45 h	60%	99.5% purity

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idinyl)-2-pyrimidineamine (**6**) in methanol solvent. The reaction parameters were studied thoroughly to get product with good quality and yield.

2.2.3.1. Washing of Raney Nickel. It was found that washing Raney nickel thoroughly with purified water until the pH is ≤8.0 is essential for the initiation of the reaction. Without water washing the reaction was not at all initialized.

2.2.3.2. Raney Nickel Quantity. About 30% (w/w) Raney nickel was found to be essential for the completion of reaction. This is based on the observation that with lesser quantities of Raney nickel (10−20 wt/wt) the starting material remained unreacted along with nitroso impurity (Figure 4) formation. Reducing *N*-(5-nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine using 30% Raney nickel (w/w) was carried out in methanol.

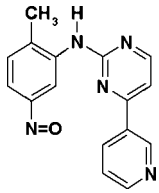

Figure 4. Nitroso impurity formed in catalytic hydrogenation.

2.2.3.3. Reaction Time. About 45 h reaction time was found to be essential for the completion of reaction. Further, it was also found that with fewer reaction hours (10−40), the starting material remained unreacted along with nitroso impurity (Figure 4) formation. Reducing *N*-(5-nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine using 30% Raney nickel (w/w) was carried out in methanol for 45 h. The yield of the reaction is 80% and HPLC purity is 99.4%.

*2.2.4. Study Conducted for the Condensation of N-(5-Amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**) with 4-(4-Methylpiperazino methyl)benzoyl Chloride (**7**).*

2.2.4.1. Study of Mole Ratios. Condensing *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (VI) with 4-(4-methylpiperazinomethyl)benzoyl chloride(**7**) in the presence of an inorganic base to obtain imatinib base (**1**) is carried out using between about 1 and 2 molar equivalents of 4-(4-methylpiperazino)methyl benzoyl chloride dihydrochloride with respect to *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine and optimized as 1.5 molar equivalents. The condensation was studied in the presence of excess of inorganic base using between about 2 and 6 molar equivalents and optimized as 4 molar equivalents. This optimization is based on completion of reaction, yield, and quality of the obtained imatinib base.

2.2.4.2. Base Selection. Inorganic bases such as sodium hydroxide, sodium carbonate, and sodium bicarbonate were tried. Sodium carbonate was found to be suitable, because the condensation yielding product was good quality and yield.

2.2.4.3. Solvent(s) Selection. Condensation was studied in solvents chloroform and isopropyl alcohol (IPA). It was observed that the reaction was going to completion in chloroform solvent after 8 h. In IPA solvent reaction was completed after 2 h. In chloroform solvent medium purified water was added after reaction was complete to move excess potassium carbonate. In IPA medium the product along with potassium carbonate was filtered and slurry washed with purified water to remove excess potassium carbonate. Imatinib base obtained from both the solvents was purified by in situ by salt formation with methane sulfonic acid in aqueous medium, washing with organic solvent to remove acidic impurities, followed by basification, extraction, distillation triturating with ethyl acetate, and filtration. Finally, isopropyl alcohol solvent was selected for commercialization, thereby avoiding the chlorohydrocarbon solvent chloroform.

Thus, condensation of *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**) with 1.5 molar equivalents of 4-(4-methylpiperazinomethyl)benzoyl chloride (**7**) in the presence of 4 molar equivalents of potassium carbonate carried out in isopropyl alcohol solvents yielded imatinib base of about 99% purity (impurity profile: 0.4% 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride, unknown impurity: 0.3%, impurity-**D6**: 400−500 ppm, *o*-toluidine: 5−6 ppm and impurity-**D9**: 0.3−0.5 ppm). This on further purification with in situ salt formation with methane sulfonic acid and basification with aqueous sodium hydroxide yielded imatinib base. In the thus-formed imatinib base, all the genotoxic impurities were controlled in ppm levels. Separate HPLC methods were developed for the estimation of genotoxic impurities and are given under the Experimental Section. The yield of the reaction is 75%, and HPLC purity is 99.99%. By this process the cost of imatinib base is about $300 (US).

3. SUMMARY

A cost-effective, high-yielding, production-friendly process for the production of highly pure imatinib base is described. The present work also describes the processes for the preparation of key intermediates, *N*-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**) and 4-(4-methylpiperazinomethyl)-benzoyl chloride (**7**).

3.1. Experimental Section. Melting points were determined on a Mettler melting point apparatus, in open capillary tubes, and are uncorrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded on a Bruker Avance-III 400 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane as an internal standard and are given in δ units. The solvent used for NMR spectra is deuterodimethyl sulfoxide (DMSO) unless otherwise stated. Infrared spectra were taken on a Bruker spectrometer in potassium bromide pellets unless otherwise stated. High-resolution mass spectra were obtained with a Waters mass spectrometer. All reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60F254 (Merck) plates using UV light (254 and 366 nm). The gas chromatography on Agilent Technologies 6890B with head space was used for analyzing the residual solvents. Common reagent grade commercially available chemicals were used without further purification.

*3.1.1. Preparation 1: 4-(4-Methylpiperazinomethyl)-benzoyl Chloride (**7**). 3.1.1.1. Step A: Preparation of 4-Bromomethyl Benzonitrile (**12**).* *p*-Tolunitrile (150.0 kg, 1282.0 mol), *N*-bromosuccinimide (228.0 kg, 1281.0 mol), dibenzoyl peroxide (2.985 kg, 12.32 mol), and chloroform (900L) were placed into the reactor. The reaction mixture was heated to 60−65 °C for 3.5 h. The reaction mass was brought to room temperature and washed with water (2 × 1180 L). Chloroform was distilled under vacuum, and to the residue was charged a mixture chloroform (151 L) and hexane (590 L). The slurry was stirred, filtered, and washed with hexane. (168.4 kg, yield 66.8%, purity by HPLC: 98.5%).

*3.1.1.2. Step B: 4-(4-Methylpiperazinomethyl)benzoic Acid Dihydrochloride (**14**).* N-methyl piperazine (184.48 kg,

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1844.83 mol) was placed into reactor. 4-Bromomethyl benzonitrile (168.4 kg, 859.18 mol) was dissolved in chloroform (946 L) and added slowly to the reaction mass during one hour at 20−25 °C. The reaction mass was maintained at room temperature for 3 h. After completion of the reaction, water (1655 L) was charged to the reaction mass, and the chloroform layer was separated. The chloroform layer was water washed and distilled under vacuum to yield 4-(4-methylpiperazinomethyl)benzonitrile (**13**, 184.5 kg, 99.7% percentage yield) as residual oil.

To the above oil was charged concentrated hydrochloric acid (35%, 1290 L), and the resulting mixture was heated to 90−95 °C for 5 h. After reaction completion the reaction mass was brought to 40−45 °C and filtered at the same temperature. The filter cake was washed with isopropyl alcohol and dried to yield 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride (198.7 kg, 75% percentage yield, 99.9% HPLC purity). Melting point: 310−312 °C. IR (KBr) (cm^{-1}): 3460, 2927, 2416.5, 1713.9. ^1H NMR (AV 400 MHz, DMSO-d_6) δ 8.04 (d, 2H), 7.61 (d, 2H), 4.55 (s, 2H), 3.73 (m, 8H), 3.03 (s, 3H).

*3.1.1.3. Step C: Preparation of 4-(4-Methylpiperazinomethyl)benzoyl Chloride Dihydrochloride (**14**).* A mixture of 4-(4-methylpiperazinomethyl)benzoic acid dihydrochloride (198.7 kg, 642.23 mol) and thionyl chloride (1816.7 kg, 591.53 mol) was placed into the reactor and heated to 80 °C for 24 h. The reaction mass was filtered and washed with chloroform to yield 4-(4-methylpiperazinomethyl)benzoyl chloride dihydrochloride (198.7 kg yield).

*3.1.2. Preparation 2: 4-(3-Pyridinyl)-N-(5-amino-2-methylphenyl)-2-pyrimidine Amine (**6**). 3.1.2.1. Step A: 1-(2-Methyl-5-nitrophenyl)guanidine (**3**).* 2-Methyl-5-nitroaniline (150.0 kg, 986.84 mol) and *n*-butanol (600 L) were charged into a reactor. Concentrated hydrochloric acid (35%, 57 L) was added to the reaction mass during 15 min. The reaction mass was stirred for 15 min, and 50% aqueous cyanamide solution (247 L, 2940 mol) was added during 15 min. The reaction mixture was heated to 90−95 °C and stirred at the same temperature for 4 h; then concentrated hydrochloric acid (57 L) was added during 15 min. The reaction mixture was further stirred for 4 h while the temperature was maintained at 90−95 °C. Concentrated hydrochloric acid (87 L) was added dropwise, and the reaction mixture was kept at 90 °C for 4 h. The reaction mass was maintained at the same temperature for a total of 20 h. After the completion of reaction, the reaction mass was cooled down to 10 °C and basified with 10% aqueous sodium hydroxide solution (1200 L). The solid product was filtered, washed with water, and dried to afford 1-(2-methyl-5-nitrophenyl)guanidine (189.0 kg; yield 98.7%. Purity by HPLC: 99%). Melting point: 136−140 °C.

*3.1.2.2. Step B: N-(5-Nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidine Amine (**5**).* 1-(2-Methyl-5-nitrophenyl)guanidine (189.0 kg, 974.22 mol), 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (187.5 kg, 1065.34 mol), and *n*-butanol (1680 L) were placed in the reactor. The reaction mixture was heated to 120 °C for 9 h and was then brought to room temperature. Water (1350 L) was added, and the mixture was stirred at room temperature for 3−4 h. The precipitated solid was isolated by filtration and dried to afford 2-(2-methyl-5-nitroanilino)-4-(3-pyridinyl)pyrimidine (221.0 kg, yield 81.9%, purity by HPLC: 99.9%). Melting point: 195.6−195.9 °C.

*3.1.2.3. Step C: N-(5-Amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidine Amine (**6**).* Into a hydrogenation reactor were added *N*-(5-nitro-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (50 kg, 162.86 mol) and methanol (1000 L). Wet Raney's nickel (20 kg) was washed thoroughly with water and charged into the hydrogenation kettle. Hydrogenation was conducted at 60 psi for 45 h. The reaction mixture was filtered and washed with methanol (500 L). The combined filtrates were concentrated in vacuum and treated with a mixture of water (250 L) and chloroform (500 L). The organic layer was washed with water (3 × 125 L) and was distilled under vacuum. Residual solid was brought to room temperature, and ethyl acetate (375 L) was charged. The solution was heated to reflux temperature and with stirring was cooled down to 0−5 °C. The crystalline solid was filtered off and washed with chilled ethyl acetate (25 L) and dried to afford the title compound (37.5 kg, yield: 82.7%; purity by HPLC: 99.40%). Melting point: 143−147 °C.

*3.1.3. Preparation 3: 4-(4-Methyl-piperazin-1-ylmethyl)-N-{4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl}-benzamide (I, Imatinib Base (**1**)).* *N*-(5-Amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (**6**, 37.5 kg; 135.377 mol), potassium carbonate (112.5 kg, 814.0376 mol), and isopropyl alcohol (675 L) were charged into the reactor and stirred at room temperature for 15 min. 4-(4-Methylpiperazinomethyl)benzoyl chloride dihydrochloride (**7**, 65 kg, 200 mol) was charged to the reaction mass, stirred for 15 min at room temperature, and refluxed for 1.5 h. Reaction mass was brought to room temperature, filtered, and washed with isopropyl alcohol (37.5 L). Wet-filtered compound was slurry washed with water (750 L) and dried at 55 °C to yield 57.5 kg (yield 86%, HPLC purity 98.7%. Impurity **D6**: 469 ppm, impurity **D9**: 0.4 ppm, *o*-toluidine: 5.6 ppm) of the crude product as cream-colored crystalline solid.

Into a GLR were charged under stirring crude imatinib base (57.5 kg, 116.467 mol) (obtained above) and water (1150 L). Methane sulfonic acid (16.75 kg, 174.55 mol) was added slowly and stirred at room temperature for 30 min. Reaction mass was washed with chloroform (3 × 288 L), and the separated aqueous layer was basified with 20% sodium hydroxide solution (432 L). The aqueous layer was extracted with chloroform (1 × 720 L, 2 × 270 L). The separated organic layer was washed with water (3 × 820 L) and charcoalized. The organic layer was distilled under vacuum, and a mixture of chloroform (190 L) and ethyl acetate (314 L) was charged to the residual mass. Reaction mass was heated to 60 °C, maintained for 30 min, and then brought to 50 °C. The solid was filtered, washed with hot ethyl acetate (58 L), and dried at 55 °C. Yield of the desired product as a cream-colored crystalline solid was 55 kg (yield 82.3%, HPLC^{20} purity 99.99%; impurity **D6**: 4 ppm; impurity **D9**: not detected; *o*-toluidine: not detected). Melting point: 207−209 °C. IR (KBr, cm^{-1}): 3424.22, 3280.01, 2966, 2928.44, 2795.98, 2695.71, 1647.76, 1575.16, 1451.83, 1416.67, 1374.17, 1351.92, 1290.92, 857.77, 797.12, 702.93, 646.54. ^1H NMR (AV 400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.28 (s, 1H), 8.97 (s, 1H), 8.69 (d, 1H), 8.51 (d, 1H), 8.48 (d, 1H), 8.08 (s, 1H), 7.91 (d, 2H), 7.53−7.42 (m, 5H), 7.21 (d, 1H), 3.52 (s, 2H), 2.37 (bs, 8H), 2.22 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (AV 400 MHz, DMSO-d_6) δ 165.43, 161.75, 161.21 159.63, 151.49, 148.25, 142.20,137.80, 137.17, 134.64, 133.80, 132.36, 130.22, 128.86, 127.68, 123.98, 117.18, 116.85, 107.73, 61.73, 54.74, 52.62, 45.79, 17.73 (24 signals). Anal. Calcd for $C_{29}H_{31}N_7O$: C, 70.55, H, 6.33; N, 19.87. Found: C, 70.13; H, 6.20; N, 19.32.

*3.1.4. Preparation of Quaternary Salt (Impurity **13A**).* Dimethyl formamide (30 mL), 4-bromomethyl benzonitrile (10.0 g, 0.050 mol), and potassium carbonate (7.0 g, 0.05 mol)

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were charged sequentially into a reaction flask. *N*-Methyl piperazine (5.0 g, 0.05 mol) was dissolved in dimethyl formamide (30 mL) and added slowly to the reaction mass during 30 min at 25−30 °C. The reaction mass was maintained at room temperature for 2 h and filtered. The filtrate was distilled under vacuum, and the residual dimethyl formamide traces were removed by charging ethyl acetate and then distilling to yield impurity **13A** (12 g). Melting point: 120−123 °C. ^{1}H NMR (AV 400 MHz, DMSO-d_6): δ 8.04 (d, 2H), 7.80 (d, 2H), 7.52 (d, 2H), 4.81 (s, 2H), 3.54 (t, 2H), 3.56 (t, 2H), 3.74 (s, 2H), 3.01 (s, 3H), 2.86 (t, 2H), 2.73 (t, 2H); ^{13}C NMR (AV 400 MHz, DMSO-d_6): δ 143.64, 134.29, 132.83, 132.64, 132.46, 132.27, 129.78, 119.016, 118.41, 113.22, 110.14, 66.37, 61.42, 59.84, 59.42, 54.63, 52.44, 45.59, 45.13; IR (KBr, cm^{-1}): 3408, 3093, 2935, 2851, 2223, 1630, 1606, 1506, 1472, 1413, 1351, 1323, 1303, 1265, 1214; MS(m/z): 331(M^+ + H)

*3.1.5. Preparation of Quaternary Salt (Impurity **14A**).* *n*-Butanol (30 mL) and 4-(bromomethyl)benzoic acid (Aldrich, 5.0 g, 0.023 mol) were charged into a reaction flask. *N*-methyl piperazine (3.5g, 0.0348 mol) was dissolved in *n*-butanol (12 mL) and added slowly to the reaction mass during 10 min at 25−40 °C. The reaction mass was maintained at room temperature for 12 h, filtered, and washed with *n*-butanol (10 mL). Filtered salt was dissolved in 2 M sodium hydroxide solution, acidified with concentrated hydrochloric acid (5 mL), and maintained at room temperature for 2 h. The separated solid was filtered and washed with *n*-butanol (10 mL) which afforded impurity **14A** after drying. Yield: 2.4 g. Melting point: 250 °C dec. ^{1}H NMR (AV 400 MHz, DMSO-d_6): δ 13.30 (s, 2H), 8.06 (d, 2H), 8.01 (d, 2H), 7.72 (d, 2H), 4.87 (s, 2H), 4.38 (s, 2H), 3.76 (d,s, 7H), 3.16 s, 4H); ^{13}C NMR (AV 400 MHz, DMSO-d_6): δ 166.85, 166.75, 134.7, 133.72, 132.59, 131.71, 131.47, 129.75, 57.57, 55.81, 44.38; IR(KBr, cm^{-1}): 3407, 3024, 2635, 1707, 1616, 1475, 1422; MS(m/z): 369 (M^+ + H)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS:

Chronic Myelogenous Leukemia (CML); Gastrointestinal Stromal Tumors (GISTs); U.S. Food and Drug Administration (FDA); Glass Lined Reactor (GLR)

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(20) **HPLC Method I** (for estimation of *o*-toluidine and impurity **D6** in parts per million concentration): Column: Develosil ODS-HG-5, 150 mm × 4.6 mm, 5 μm; flow: 1 mL/min. Mobile phase A: buffer solution A and methanol (1:1 v/v); mobile phase B: buffer solution A and methanol (4:96 v/v). Diluents: water and methanol (1:1 v/v). Buffer solution A preparation: dissolve 4.56 g of octane-1-sulfonic acid sodium salt in 1000 mL of water and adjust pH to 8.0 with diluted sodium hydroxide solution. Reference solution 1: dissolve 10 mg each of *o*-toluidine and impurity **D6** in a 100 mL volumetric flask with diluents. Transfer 0.5 mL of this solution into a 50 mL volumetric flask and dilute to volume with diluents. Again transfer 2.0 mL of this solution into a 10 mL volumetric flask and dilute to volume with diluents. Reference solution 2: transfer 0.75 mL of reference solution 1 into a 10 mL volumetric flask and dilute to volume with diluents. Test solution: dissolve 100 mg of test sample in 5 mL of methanol, sonicate, and make up to volume with diluents in a 10 mL volumetric flask. Gradient: 0 min: 100% A, 0% B; 15 min: 80% A, 20% B; 40 min: 35% A, 65% B; 42 min: 100% A, 0% B; 50 min: 100% A, 0% B; UV detection: 240 nm. **HPLC Method II** (for estimation of impurity **D9** in parts per million concentration): Column: Develosil ODS-HG-3, 150 mm × 4.6 mm, 3 μm; flow: 1 mL/min. Mobile phase: buffer, methanol, and acetonitrile in 50:30:20 v/v/v. Diluents: water and methanol (1:1 v/v). Buffer solution preparation: Dissolve 3.0 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water and

adjust pH to 2.5 with diluted phosphoric acid. Reference solution 1: Dissolve 10 mg impurity **D9** in a 50 mL volumetric flask with methanol and acetonitrile mixture (3:2 v/v). Transfer 1 mL of this solution into a 20 mL volumetric flask and dilute to volume with diluents. Again transfer 0.5 mL of this solution into a 50 mL volumetric flask and dilute to volume with diluents. Reference solution 2: Transfer 3.0 mL of reference solution 1 into a 10 mL volumetric flask and dilute to volume with diluents. Test solution: Dissolve 100 mg of test sample in 5 mL of methanol, sonicate, and make up to volume with diluents in a 10 mL volumetric flask. UV detection: 240 nm. **Method III** (for estimation of related substances): Column: Develosil ODS-HG-5, 150 mm × 4.6 mm, 5 μm; flow: 1 mL/min. Solvent mixture: Mix 300 mL of methanol and 200 mL of acetonitrile. Mobile phase preparation: Dissolve 1.65 g of sodium dihydrogen phosphate dihydrate in 550 mL of water and adjust pH to 8.0 with triethyl amine and add 450 mL of solvent mixture. Test solution: dissolve 50 mg of test sample in a 50 mL volumetric flask with mobile phase. Reference solution 1: Transfer 1 mL of test solution into 50 mL volumetric flask and dilute to volume with mobile phase. Transfer 1 mL of this solution into a 20 mL volumetric flask and dilute to volume with mobile phase. Reference solution 2: Dissolve 50 mg of imatinib impurity premix in mobile phase in a 50 mL volumetric flask (1000 μg/mL of the imatinib and each 1 μg/mL of impurities). UV detection: 230 nm.

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