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A Facile Total Synthesis of Imatinib Base and Its Analogues

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Abstract:

Imatinib and its analogues were successfully synthesized by an improved method in 19.5– 46.2% total yield of six main steps. Pyrimidinyl amine was prepared by the reaction of enaminone and guanidine nitrate without the use of a toxic cyanamide. *N*-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl) pyrimidin-2-amine as a key intermediate for the synthesis of imatinib was prepared by copper-catalyzed *N*-arylation of heteroarylamine in 82% yield. The copper salts were used instead of the expensive palladium compounds in this C−N bond-forming reaction. The intermediate nitro compound was reduced by a $N_2H_4 \cdot H_2O/FeCl_3/C$ system using water as a solvent in good yield.

Introduction

Imatinib mesylate (Gleevec, *N*-(4-methyl-3-(4-(pyridin-3-yl)-pyrimidin-2-ylamino)phenyl)-4-((4-methyl piperazin-1-yl)methyl)benzamide methanesulfonate, STI571, its base such as 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] Imatinib is a 2-phenylamino-pyrimidine derivative. It was developed by Novartis Pharma AG, Basel, Switzerland, and licensed for treatment of patients with chronic myeloid leukaemia by the U.S. Food and Drug Administration (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. Imatinib was

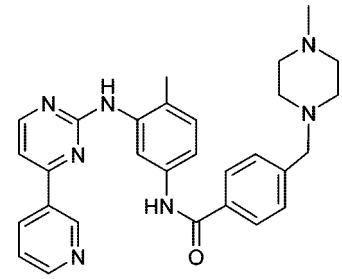

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Figure 1. **Chemical structure of imatinib base.**

first synthesized by Zimmermann in 1993 (Scheme 1).[2] This method dealt with virulent cyanamide which was used for the synthesis of phenylguanidine derivatives. In this protocol, the synthesis of enaminone was complicated by three steps involving metal sodium and low temperature. The yields of all steps were not shown in Zimmermann's paper and patent document.

Loiseleur et al.[3] described a process for the preparation of imatinib base (Scheme 2), in which compound **10** was prepared by the reductive amination of aldehydes using Pt/C-catalyzed hydrogenation. This scheme involved $Pd_2(dba)_3CHCl_3$-catalyzed C−N coupling reaction with the of use of organophosphorus reagent *rac*-BINAP as ligand. Subsequently, Kompella[4] and Szakacs[5] also respectively provided an improved process based on Loiseleur's method. However, the insufficiencies of these approaches are (i) the use of a toxic, hazardous reagent cyanamide and (ii) using high-cost palladium as catalyst for C−N coupling reaction. Therefore, these approaches cannot be used in large-scale industrial applications.

We aimed our research work towards developing an industrially feasible and cost-effective process for the preparation of imatinib and its analogues. An improved method for the preparation of imatinib is described in this paper (Scheme 3). In this protocol, the reaction of enaminone with guanidine nitrate gave pyrimidinyl amine (compound **13**),[6] and the coupling reaction of 2-bromo-1-methyl-4- nitrobenzene with compound **13** was processed in the presence of CuI and *N,N′*-dimethyl-ethylene-diamine (DMEDA) ligand to give the key intermediate

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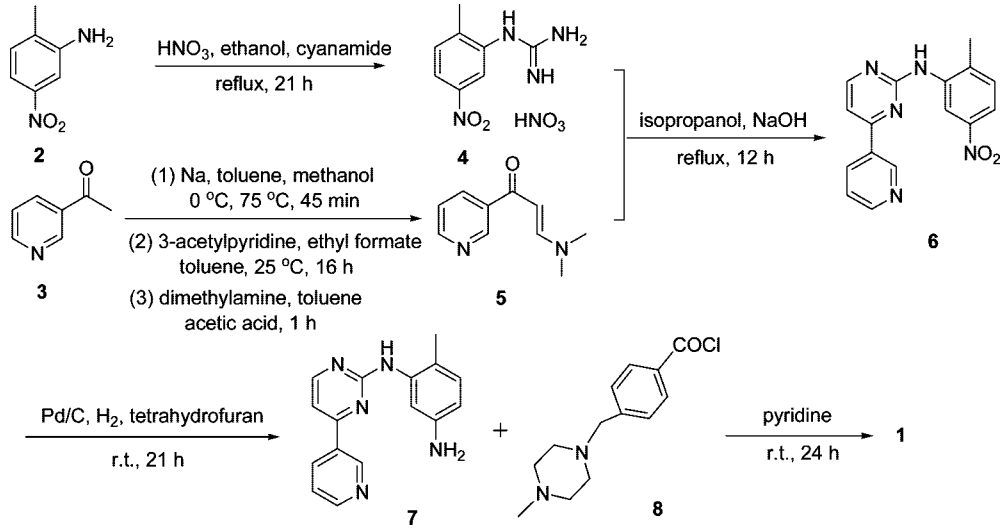
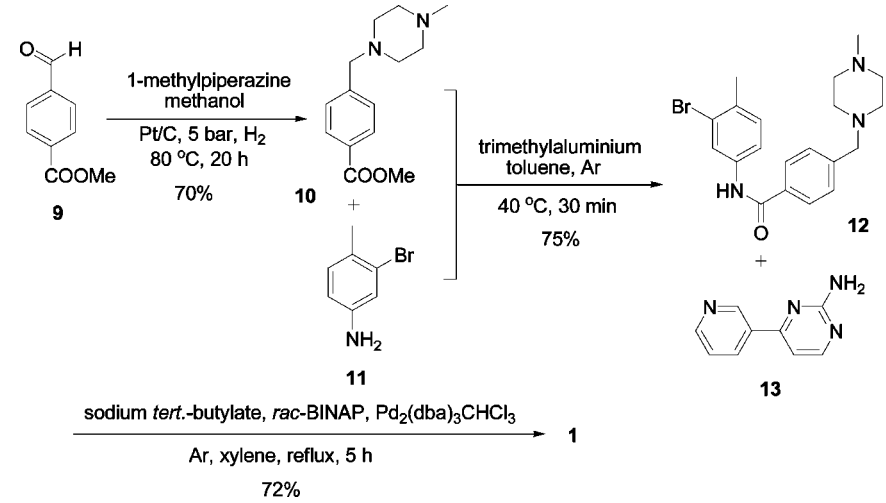
Scheme 1. **Zimmermann's route for the preparation of imatinib base**



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



6 in 82% yield. Intermediate **6** was reduced by $N_2H_4 \cdot H_2O$/$FeCl_3$/C system in water solvent. Sequentially, compound **7** was acylated with the corresponding acid chlorides to give the amide **18**. The aminating reaction of benzyl chloride on the amide **18** molecule with 1-methylpiperazine finally yielded imatinib base.

Results and Discussion

N,*N*-Dimethylformamide dimethyl acetal (DMF-DMA), as well as other *N*,*N*-dimethylformamide dialkyl acetals are very useful reagents in organic synthesis. As a formylating reagent, DMF-DMA is used in the synthesis of enaminones from active methylene compounds. Enaminones are found to be useful intermediates in the formation and modification of many heterocyclic compounds. In general, enaminone formation has been conducted in refluxing aromatic hydrocarbons. In this paper, The enamination of acetylpyridine with DMF-DMA in xylene provided enaminone **5** in 92.6% yield.[7] The refluxing reaction of enaminone **5** with guanidine nitrate was processed in *n*-butanol for 10 h, to give pyrimidinyl amine **13** in 85.5% yield. In contrast to Zimmermann's route, formation of pyrimidinyl cycle by the reaction of enaminone with guanidine nitrate (not to use *N*-arylguanidine prepared by a toxic cyanamide) is more valuable. Though the C−N coupling reaction was not used in Zimmermann's route, the synthesis of 4-((4-methylpiperazin-1-yl)methyl)benzoyl chloride (compound **8**) was complicated by expensive Pt/C-catalyzed hydrogenation. Compounds **15** and **17** were easily synthesized by conventional method, or purchased from a chemical company.

For the coupling reaction of compounds **13** and **15**, we incipiently adopted the conventional Ullmann reaction.[8] Using copper powder as a catalyst, the reaction of 2-iodo-1-methyl-4-nitrobenzene with pyrimidinyl amine **13** at elevated temperatures (200 °C) yielded only 5% of the aimed for compound, and the main products were biaryl compound. In recent years, the "classic" Ullmann reaction has been transformed into "Ullmann-type" reactions including copper-catalyzed nucleophilic aromatic substitution between various nucleophiles with aryl halides. In "Ullmann-type" reactions, the use of copper salts of catalyst, base, and ligand allowed the coupling reaction

(7) (a) Schuda, P. F.; Ebner, C. B.; Morgan, T. M. *Tetrahedron Lett.* **1986**, *27*, 2567. (b) Lowe, W.; Braun, B.; Muller, B. *J. Heterocycl. Chem.* **1994**, *31*, 1577. (c) Selic, L.; Gradadolnik, S. G.; Stanovnik, B. *Helv. Chim. Acta* **1997**, *80*, 2418.

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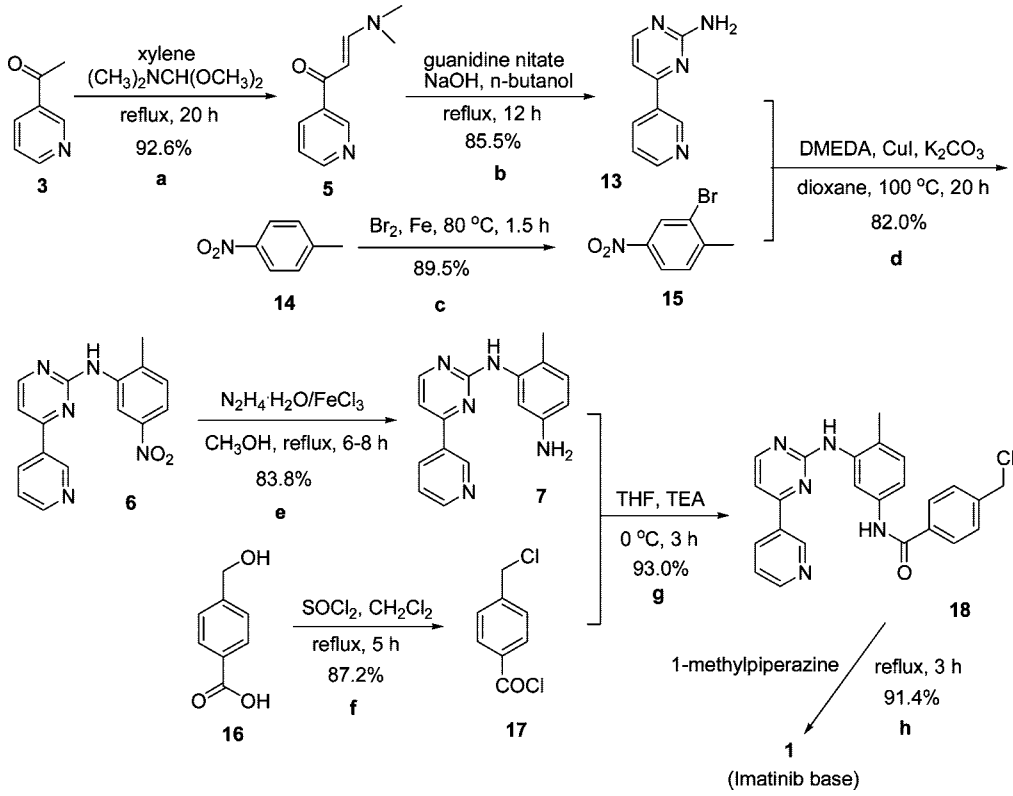
Scheme 3. **Schematic synthetic procedure of imatinib and its analogues**



to go smoothly in mild conditions.[9] However, copper-mediated *N*-arylation of heteroarylamines based on the "Ullmann-type" reaction was rarely reported, although there were a few examples of Pd-catalyzed *N*-arylation of heteroarylamines by the Buchwald−Hartwig cross-coupling reaction in the past literature.[3,10] However, the high cost of palladium and the use of toxic organophosphous reagents still remained for this method. We used copper salts instead of expensive palladium compounds in the coupling reaction of heteroarylamine and employed various copper sources, ligands, bases, and solvents to evaluate and set up the most effective conditions. The detailed contents about optimization of the reaction conditions for copper-mediated *N*-arylation of the heteroarylamines has been published.[11] The optimal reaction conditions were the use of CuI as catalyst, *N,N′*-dimethylethylenediamine as ligand, KI as accelerant, and K_2CO_3 as base, and the reaction was processed in dioxane at 100 °C for 20 h. A key intermediate **6** was first prepared by this copper-catalyzed C−N bond-forming reaction on the optimized condition in 82% yield.

Reduction of nitro compounds can be achieved by several reagents in solution-phase reactions. Reactions with metals (usually Fe, Sn, Zn, or Al) in the presence of small amounts of acids are the most vigorous reduction methods. We used respectively Fe/HCl, $SnCl_2$/HCl, hydrazine hydrate/Raney Ni, hydrazine hydrate/$FeCl_3$/C system as reducing agents. The observed results show that Fe/HCl and $SnCl_2$/HCl were inconvenient for the isolation of the product due to production of the emulsions of metallic hydroxides. $SnCl_2$ also was more expensive and toxic. In comparison to other reduction process, the reduction with hydrazine hydrate produces harmless byproducts such as nitrogen gas and water.[12] Nitro compound **6** was reduced efficiently by hydrazine hydrate in the presence of a catalytic amount of $FeCl_3$/C in 83.8% yield.

The acylating reaction of compound **7** was more easily processed in very good yield due to high activity of 4-(chloromethyl)benzoyl chloride. Finally, the mixture of intermediate **18** and 1-methylpiperazine was heated to reflux temperature and maintained for 2 h, and imatinib base was obtained in 91.4% yield (HPLC purity of 99.5%). Nine analogues of imatinib were also synthesized (Table 1).

According to our scheme for the preparation of imatinib, six main steps (a, b, d, e, g, h in Scheme 3) in the reaction may produce some byproducts such as in step a: methanol; step b: sodium nitrate, dimethylamine; step d: potassium bromide, a small amount of catalyst and ligand; step e: nitrogen gas, a small amount of catalyst; steps g, h: hydrogen chloride gas. Proper post treatment of these byproducts is harmless to the environment. Dimethylamine and hydrogen chloride gas can be absorbed by respectively the diluent solution of HCl and NaOH. Toxic cyanamide and organophosphorus reagent were not used for consideration of the safety of operator and environment.

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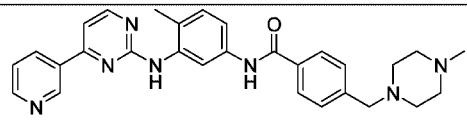
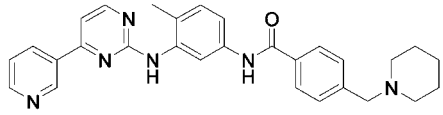
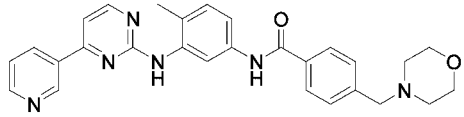
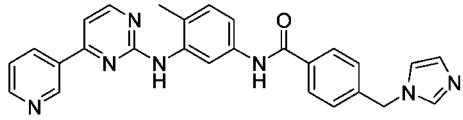
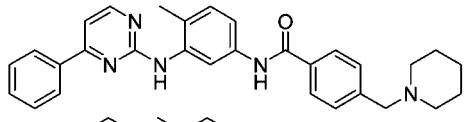
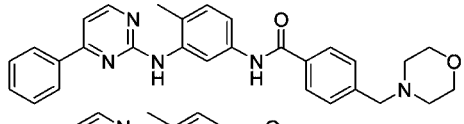
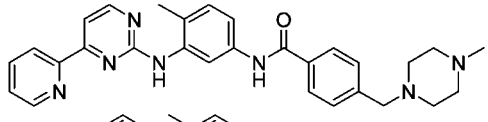
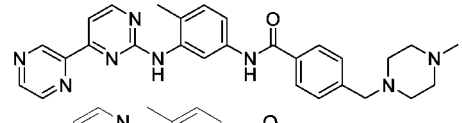
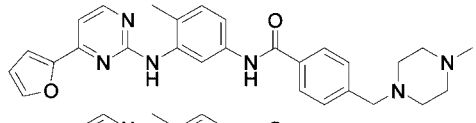
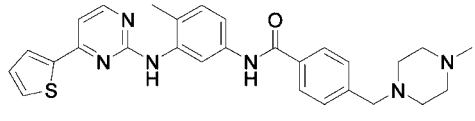
(12) Larsen, J. W.; Freund, M.; Kim, K. Y.; Sidovar, M.; Stuart, J. *Carbon* **2000**, *38*, 655.

Table 1. **Results of synthesis of imatinib and its analogues**[a]

No.	products	yield [b] / %						
		a	b	d	e	g	h	total [c]
1		92.6	85.5	82.0	83.8	93.0	91.4	46.2
1a		92.6	85.5	82.0	83.8	93.0	87.6	44.3
1b		92.6	85.5	82.0	83.8	93.0	75.3	38.1
1c		92.6	85.5	82.0	83.8	93.0	76.2	38.6
1d		86.6	79.3	76.5	78.2	86.6	88.6	31.5
1e		86.6	79.3	76.5	78.2	86.6	98.4	35.0
1f		89.1	52.2	80.5	79.6	93.1	70.1	19.5
1g		90.2	78.5	84.2	78.3	91.2	78.4	33.4
1h		86.8	70.7	77.5	72.4	95.7	81.2	26.8
1i		90.5	72.5	71.4	70.0	96.6	88.9	28.2

[a] Experiments were performed on a 0.1 mol scale for steps a, b, c, f; 1 mmol scale for steps d, e, g, h. [b] Isolated yield. [c] The total is the total yields of six main steps (a, b, d, e, g, h) in Scheme 3.

Conclusions

In conclusion, we have developed a mild, convenient, and inexpensive approach for the preparation of imatinib and its analogues. Imatinib and nine analogues were obtained in good yield. In this protocol, the reaction of enaminone with guanidine was processed to give pyrimidinyl amine without the use of a toxic cyanamide. It is exciting that *N*-(2-methyl-5-nitrophenyl)-4-(pyridin-3-yl) pyrimidin-2-amine as a key intermediate for the synthesis of imatinib was prepared by a copper-catalyzed C−N bond-forming reaction of heteroarylamine. We also used the $N_2H_4 \cdot H_2O/FeCl_3/C$ system to reduce the intermediate nitro compound. As a result this improved method for the preparation of imatinib is less hazardous and more environmentally friendly, and has potential for industrial application.

Experimental Section

General. All reactions were processed under a nitrogen atmosphere in oven-dried Schlenk-type glassware. Elemental analyses were performed by Elementar Vario EL III. IR spectra were recorded on a Bruker Equinox-55. ^{1}H NMR(400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Inova 400 MHz instrument using DMSO-d_6 and $CDCl_3$ as the solvent with chemical shifts reported relative to tetramethylsilane (TMS). The purity of products was analyzed by Shimadzu LC-10AT high performance liquid chromatograph with a DAD detector and a Shim-pack VP-ODS C_{18} column (150 mm × 4.6 mm). All materials were weighed in the air. Flash column chromatography was performed with silica gel (100–200 mesh). All reagents were used as purchased from commercial suppliers without further purification.

Synthetic Procedure for Imatinib and Its Analogues. Here is detailed approach for the preparation of imatinib base. The same synthetic procedure used to make imatinib was used for all the imatinib analogues.

3-(Dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (5). Into a 250 mL, one neck, round-bottomed flask equipped with a mechanical stirrer and reflux condenser were charged acetylpyridine (11 mL, 0.1 mol), *N*,*N*-dimethylformamide dimethylacetal (27 mL, 0.2 mol), and xylene (35 mL). The reaction mass was heated to 140 °C and maintained for 20 h, and the methanol formed in the reaction was removed every 4 h by distillation. When TLC of reaction mass indicated the absence of starting compound, the reaction mixture was cooled down to room temperature. Hexane (20 mL) was added to the reaction mass and kept under stirring for 20 min without allowing the mass temperature to change more than 5 °C. The resultant reaction mass was collected by filtration and washed with hexane, and the crude product was recrystallized from xylene to give 16.3 g (92.6%) of the desired product as yellow crystals. Mp 81–82 °C (lit.:[13] 82–84 °C).

4-(Pyridin-3-yl)pyrimidin-2-amine (13). Into a 250 mL, one neck, round-bottomed flask equipped with a mechanical stirrer and reflux condenser were charged 3-(dimethylamino)-1-(pyridin-3-yl) prop-2-en-1-one (17.6 g, 0.1 mol), guanidine nitrate (12.2 g, 0.1 mol), sodium hydroxide (4 g, 0.1 mol), and *n*-butanol (125 mL). The reaction mass was heated to reflux temperature and maintained for 12 h. TLC of reaction mass indicated the absence of starting compound. The reaction mixture was cooled down to room temperature. The precipitate was collected by filtration and was washed with 500 mL of water. The wet cake was dried in the oven at 75–80 °C, and 14.7 g (85.5%) of the desired product was obtained as white crystals. Mp 189–191 °C (lit.:[14] 186–188 °C).

2-Bromo-1-methyl-4-nitrobenzene (15). See: *Organic Syntheses*; Wiley and Sons: New York, 1963; Collect. Vol. 4, p 114 and 1958; Vol. 38, p 11.

***N*-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (6).** 4-(Pyridin-3-yl)pyrimidin-2- amine (0.189 g, 1.1 mmol), CuI (47.6 mg, 0.25 mmol), and anhydrous K_2CO_3 (0.276 g, 2 mmol) were added to a Schlenk-type three-neck flask fitted with thermometer, magnetic stirbar, and septum. The flask was evacuated and back filled with N_2 three times. Dioxane (5 mL), 2-bromo-1-methyl-4- nitrobenzene (0.216 g, 1 mmol), and DMEDA (22.0 mg, 0.25 mmol) were added by syringe at room temperature. The reaction mixture was stirred at 100 °C for 20 h and cooled to room temperature. Concentrated ammonia (4 mL) and a saturated solution of NaCl (20 mL) were added, and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layers were concentrated in vacuo, and the residue was purified by column chromatography on silica gel to give 0.252 g (82.0%) of the title compound as yellowish powder. Mp 194–195 °C (lit.:[4] 194–199 °C).

6-Methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (7). Into a 100 mL, one neck, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and thermometer socket were charged *N*-(2-methyl-5-nitrophenyl)-4-(pyridin-3-yl) pyrimidin-2-amine (0.307 g, 1 mmol), hydrazine monohydrate (0.154 g of 65% solution in water, 2 mmol), $FeCl_3$ (2.1 mg, 0.013 mmol), active carbon (0.02 g), and water (40 mL). The reaction mass was heated to 80 °C and maintained for 6–8 h. TLC of reaction mass indicated the absence of starting compound. The reaction mixture was cooled down to room temperature. Insoluble materials were filtered off, and the filtrate was extracted with ethyl acetate (10 mL × 5). The organic layers were then washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo, and the resultant precipitate was purified by Kugelrohr distillation to give 0.232 g (83.8%) of the product as yellow crystals. Mp 140–141 °C (lit.:[4] 140–143 °C).

4-(Chloromethyl)benzoyl Chloride (17). Into a 250 mL, one neck, round-bottomed, flask equipped with a mechanical stirrer and reflux condenser were charged 4-(hydroxymethyl)-benzoic acid (15.2 g, 0.1 mol), dichloromethane (50 mL), and thionyl chloride (50 mL). The reaction mass was heated to reflux temperature and maintained for 5 h. The excess thionyl chloride and dichloromethane were removed off in vacuo. The residue was cooled to 0–5 °C, and maintained for 12 h to give 16.5 g (87.2%) of the title compound as white crystals. mp 30–32 °C.

4-(Chloromethyl)-*N*-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)benzamide (18). Into a 25 mL, one neck, round-bottomed, flask equipped with a mechanical stirrer and reflux condenser were charged 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (0.277 g, 1 mmol), THF (5 mL), and TEA (0.29 mL, 2 mmol). The reaction mass was cooled down to 0 °C and maintained for 10 min. A solution of 4-(chloromethyl)benzoyl chloride (0.217 g, 1.15 mmol) in THF (2 mL) was added dropwise within 10 min. TLC of reaction mass indicated the absence of starting compound. After stirring at 0 °C for 3 h, to the reaction mass was added water (15 mL) dropwise, and a light-yellow precipitate appeared. Then, the resultant precipitate was collected by filtration, washe with 100 mL of water, and dried at 75–80 °C to yield 0.399 g (93.0%) of the desired product as light-yellow crystals. Mp 266–268 °C.

***N*-(4-Methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (1).** Into a 25 mL, one neck, round-bottomed, flask equipped with a mechanical stirrer and reflux condenser were charged 4-(chloromethyl)-*N*-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino) phenyl)benzamide (0.429 g, 1 mmol), and 1-methylpiperazine (11.1 mL, 0.1 mol). The reaction mass was heated to reflux temperature and maintained for 3 h. TLC of reaction mass indicated the absence of compound (**18**). The reaction mixture was cooled down to room temperature, and water (10 mL) was added. At the same time, a white precipitate appeared. Then, the resultant precipitate was collected by filtration. Washing with 100 mL of water and drying at 75–80 °C yielded 0.45 g (91.4%, HPLC purity of 99.5%) of the desired product as white crystals. Mp 207–210 °C (lit.:[5] 206–209 °C); IR (KBr) 3412, 3291, 2969, 2966, 2935, 2804, 2720, 1630, 1590, 1534, 1509, 1480, 1452, 1418, 1384, 1350, 1009, 831, 763, 703, 669; ^{1}H NMR(DMSO-d_6) δ 10.19(s, 1H), 9.28(s, 1H), 9.02(s, 1H), 8.69(d, J = 4.0 Hz, 1H),8.52(d, J = 5.2 Hz, 1H), 8.48(d, J = 8.0 Hz, 1H),

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8.08(s, 1H), 7.90(d, J = 8.0 Hz, 2H), 7.55–7.43(m, 5H), 7.20(d, J = 8.8 Hz, 1H), 3.52(s, 2H), 2.34(bs, 8H), 2.22(s, 3H), 2.15(s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.8, 165.4, 162.7, 159.0, 151.5, 148.5, 142.5, 137.8, 136.5, 134.9, 133.8, 132.7, 130.8, 129.3, 126.9, 124.1, 123.8, 124.0, 115.2, 112.9, 108.4, 62.5, 55.1, 53.1, 46.0, 17.7; 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.

***N*-(4-Methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-(piperidin-1-ylmethyl)benzamide (1a):** mp 197–200 °C; ^{13}C NMR ($CDCl_3$) δ 173.8, 165.5, 160.5, 159.0, 148.5, 147.4, 142.6, 137.8, 136.6, 135.0, 133.8, 132.6, 130.8, 129.5, 127.0, 124.1, 123.8, 115.3, 112.9, 108.4, 63.2, 54.5, 25.8, 17.7; Anal. Calcd for $C_{29}H_{30}N_6O$: C, 72.77; H, 6.32; N, 17.57. Found: C, 72.46; H, 6.10; N, 17.35.

***N*-(4-Methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-(morpholinomethyl)benzamide (1b):** mp 210–212 °C; ^{13}C NMR ($CDCl_3$) δ 173.8, 165.4, 162.7, 160.5, 159.0, 151.5, 148.5, 137.7, 136.6, 134.9, 134.0, 132.6, 130.8, 129.3, 127.1, 124.2, 123.7, 115.3, 113.0, 108.3,66.9, 62.9, 53.6, 17.7; Anal. Calcd for $C_{28}H_{28}N_6O_2$: C, 69.97; H, 5.88; N, 17.50. Found: C, 69.71; H, 5.65; N, 17.25.

4-((1H-Imidazol-1-yl)methyl)-*N*-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)benzamide (1c): mp 200–203 °C; ^{13}C NMR ($CDCl_3$) δ 172.8, 163.1, 160.9, 155.7, 150.2, 148.6, 142.1, 138.9, 136.0, 134.7, 133.7, 133.1, 131.0, 130.5, 129.0, 128.4, 127.6, 125.3, 124.5, 120.5, 110.9, 102.8, 54.1, 17.2; Anal. Calcd for $C_{27}H_{23}N_7O$: C, 70.25; H, 5.03; N, 21.25. Found: C, 69.99; H, 5.15; N, 21.01.

***N*-(4-Methyl-3-(4-phenylpyrimidin-2-ylamino)phenyl)-4-(piperidin-1-ylmethyl)benzamide (1d):** mp 202–207 °C; ^{13}C NMR ($CDCl_3$) δ 173.7, 165.4, 160.4, 158.5, 138.0, 137.0, 136.5, 133.7, 130.8, 129.4, 129.0, 128.8, 127.2, 126.9, 123.8, 116.9, 115.0, 112.6, 108.6., 63.3, 54.5, 25.9, 17.7; Anal. Calcd for $C_{30}H_{31}N_5O$: C, 75.43; H, 6.55; N, 14.67. Found: C, 75.20; H, 6.38; N, 14.49.

***N*-(4-Methyl-3-(4-phenylpyrimidin-2-ylamino)phenyl)-4-(morpholinomethyl)benzamide (1e):** mp 200–206 °C; ^{13}C NMR ($CDCl_3$) δ 174.1, 163.7, 161.0, 158.9, 142.1, 139.0, 133.5, 133.0, 132.4, 130.2, 129.7, 129.1, 127.9, 127.6, 127.1, 124.3, 111.8, 107.4, 104.8, 67.2, 59.9, 54.4, 17.6; Anal. Calcd for $C_{29}H_{29}N_5O_2$: C, 72.62; H, 6.09; N, 14.61. Found: C, 72.46; H, 5.89; N, 14.29.

***N*-(4-Methyl-3-(4-(pyridin-2-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl) benzamide (1f):** mp 159–161 °C; ^{13}C NMR ($CDCl_3$) δ 173.5, 163.4, 162.9, 161.0, 155.1, 149.3, 142.5, 138.7, 137.0, 134.2, 132.6, 130.5, 129.3, 126.8, 124.7, 124.1, 120.4, 110.8, 107.4, 61.5, 55.6, 53.1, 44.5, 17.7; Anal. Calcd for $C_{29}H_{31}N_7O$: C, 70.55; H, 6.33; N, 19.87. Found: C, 70.23; H, 6.42; N, 19.08.

***N*-(4-Methyl-3-(4-(pyrazin-2-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide(1g).** mp 195–197 °C; ^{13}C NMR ($CDCl_3$) δ 172.7, 164.2, 163.4, 159.1, 145.9, 144.2, 143.8, 142.0, 141.5, 138.7, 133.6, 132.3, 130.0, 128.7, 126.9, 124.3, 112.1, 61.8, 55.0, 52.9, 45.7, 17.8; Anal. Calcd for $C_{28}H_{30}N_8O$: C, 67.98; H, 6.12; N, 22.66. Found: C, 67.57; H, 6.19; N, 22.13.

***N*-(3-(4-(Furan-2-yl)pyrimidin-2-ylamino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl) benzamide (1h):** mp 170–172 °C; ^{13}C NMR ($CDCl_3$) δ 168.1, 158.4, 156.3, 151.8, 144.8, 142.3, 137.9, 136.5, 133.9, 130.7, 129.2, 127.0, 123.9, 112.8, 112.5, 106.6, 54.9, 52.9, 45.9, 17.7; Anal. Calcd for $C_{28}H_{30}N_6O_2$: C, 69.67; H, 6.27; N, 17.42. Found: C, 69.85; H, 6.04; N, 17.11.

***N*-(4-Methyl-3-(4-(thiophen-2-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (1i):** mp 186–188 °C; ^{13}C NMR ($CDCl_3$) δ 172.3, 163.6, 159.9, 157.0, 141.8, 140.0, 138.7, 133.2, 132.0, 130.1, 129.3, 127.5, 127.3, 127.0, 124.9, 123.8, 111.5, 108.2, 104.7, 62.3, 54.4, 52.7, 42.9, 17.6; Anal. Calcd for $C_{28}H_{30}N_6OS$: C, 52.32; H, 4.71; N, 13.08. Found: C, 52.48; H, 4.51; N, 13.16.

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