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Novel and Efficient Access to Phenylamino-pyrimidine Type Protein Kinase C Inhibitors Utilizing a Negishi Cross-Coupling Strategy†

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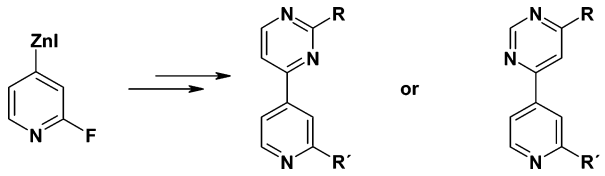


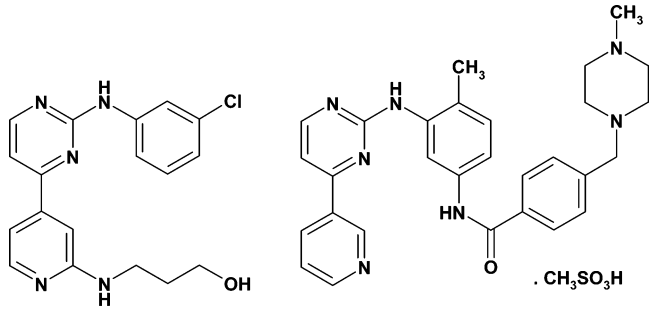
A novel, short, and efficient synthetic pathway to 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]-pyridin-2-ylamino}-propanol (CGP 60474) and a series of analogues was developed. The synthetic sequence consisted of a Negishi-type cross-coupling reaction in the key step followed by two subsequent nucleophilic substitution reactions. This strategy represents a versatile and robust protocol to access diverse analogues of the title compound for subsequent SAR studies as potential phenylamino-pyrimidine type protein kinase C inhibitors.

Introduction

The protein kinase C (PKC) enzyme family consists of cytosolic serine/threonine kinases, and several representatives play a crucial role in signal transductions, cellular proliferation, and differentiation.[1] The individual PKC subtypes show differences in the mode of activation and in the specificity with respect to the natural protein substrates.[2,3] From animal tumor models it is already known that various inhibitors of PKC show antitumor activity.[4,5] Therefore, the discovery and the development of specific protein kinase inhibitors will have the potential to define more clearly the respective functional roles of protein kinases in cells.

Phenylamino-pyrimidines such as 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]-pyridin-2-ylamino}-propanol (CGP 60474)[6] represent a promising class of inhibitors of PKC with a high degree of selectivity versus other serine/threonine and tyrosine kinases and show competitive kinetics relative to ATP. *Imatinib* (Glivec),[7] a tyrosine kinase inhibitor with high activity against chronic myeloid leukemia (CML), was introduced to the pharmaceutical market as the first commercial product of this type very recently by Novartis (Scheme 1).[8]

SCHEME 1. Proteine Kinase Inhibitors of the Phenylamino-pyrimidine Type



CGP 60474 *Imatinib*, Glivec™

In the literature the synthesis of CGP 60474 is reported via a classical cyclization pathway (Scheme 2).[6] Chlorine is introduced into the 2-position of 4-acetylpyridine via oxidation to the *N*-oxide and subsequent reaction with

† Dedicated to Prof. Fritz Sauter on the occasion of his 75th birthday.

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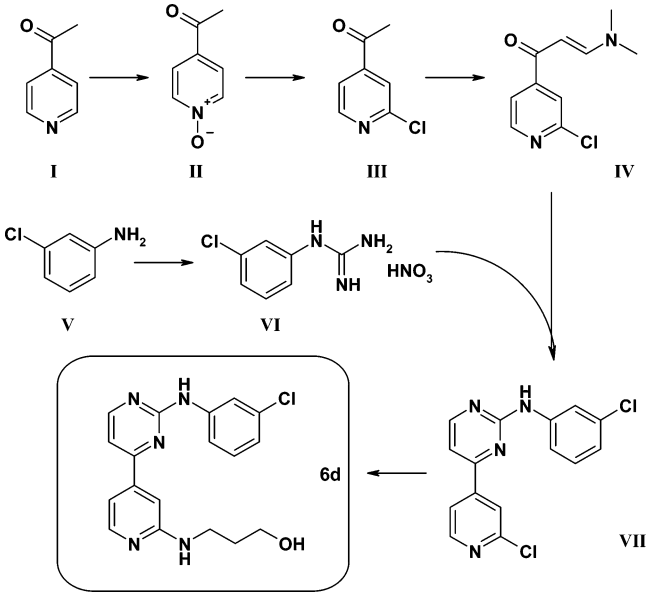
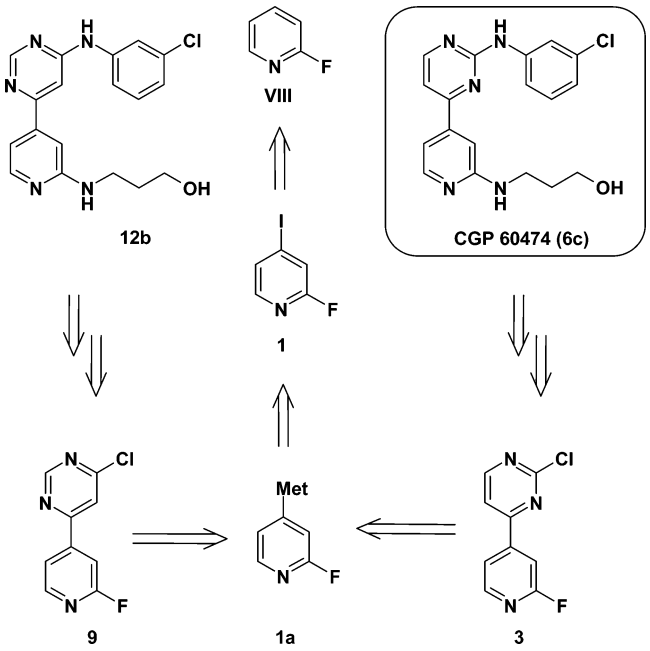
SCHEME 2. Classical Cyclization Route toward CGP 60474[a]



[a] For reaction conditions see ref 6.

SCHEME 3. Retrosynthetic Analysis of CGP 60474 (6c) and Its Isomer (12b)



$POCl_3$. The so obtained chloride **III** is then transformed to **IV** by reaction with *N*,*N*-dimethylformamide dimethylacetal. The second cyclization partner is prepared by reaction of aniline derivatives with cyanamide and equimolar amounts of HNO_3 to give the corresponding guanidine nitrates **VI**. Compounds **IV** and **VI** are then cyclized to give **VII**, which led to the target compound CGP 60474 (**6c**) via a nucleophilic exchange reaction. This sequence leads to **6c** in five steps with an overall yield of 34% based on 4-acetylpyridine.

A drawback of this pathway is that for each variation of the aniline part of the target molecule a corresponding guanidine derivative has to be prepared. Even more problems occur when variations of the heterocyclic ring system are envisioned, as a new synthetic strategy has to be developed in most cases.

In the present paper we report a new, short, and efficient synthesis of CGP 60474 based on a Pd-assisted cross-coupling reaction, which was also applied to the synthesis of a series of various new analogues and isomers of the title compound.[9] These synthetic targets represent useful models for SAR studies and antiproliferative activity, and the methodology can also be extended easily to the synthesis of various other structural analogues.

Results and Discussion

As a key step for the synthesis of the target compounds depicted in Scheme 3, a Pd-catalyzed cross-coupling reaction was envisioned followed by two subsequent nucleophilic substitution reactions.

The Suzuki−Miyaura and the Stille reaction are the most common cross-coupling methods because of certain advantages such as easy access and relatively high stability of the reagents (boronic acids/esters or tin organyls) and a high tolerance of both methodologies toward a wide range of functional groups.[10] However, there are also a number of limitations: tin organyls are highly toxic, and many heterocyclic boronic acids[11] could not be successfully prepared, so far. In particular, boronic acids of nitrogen heterocycles with two or more heteroatoms are only poorly covered in the literature.[12] Consequently, we favored a Negishi protocol[10] that allowed us to perform the preparation of the zinc organyl and the coupling reaction in a one-pot reaction.

An important key intermediate within our strategy was the pyridine zinc organyl **1a**. It was obtained from 2-fluoro-4-iodopyridine **1**[13] via lithium halogen exchange with *n*-BuLi in the 4-position and addition of thoroughly dried $ZnCl_2$. Subsequent regioselective coupling with 2,4-dichloropyrimidine **2** under $Pd(PPh_3)_4$ catalysis (0.005 equiv) in the 4-position[14] afforded the desired pyridinylpyrimidine **3** in 69% yield in a one-pot reaction (Scheme 4). In the initial experiment equimolar amounts of *n*-BuLi and iodide **1** were used and the product was accompanied by symmetrical bipyridinyl **4** (14%). This problem was

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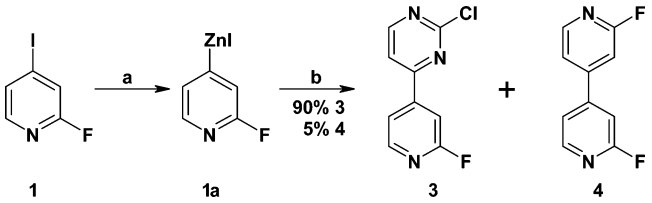
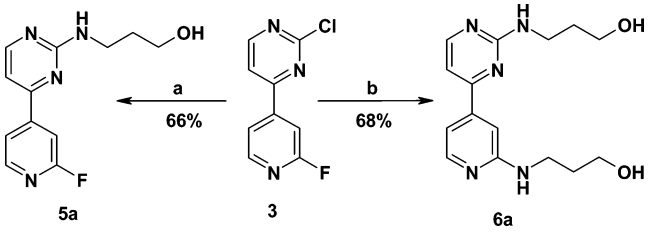
SCHEME 4. Negishi Cross-Coupling for the Formation of Intermediate 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, $ZnCl_2$, THF; (b) 2,4-dichloropyrimidine, $Pd(PPh_3)_4$, reflux, THF, 4 h.

SCHEME 5. Nucleophilic Exchange Reactions on 3[a]



[a] Reagents and conditions: (a) 3-aminopropanol (1.4 equiv), DMF, reflux, 1.5 h; (b) 3-aminopropanol (excess), 160 °C, 16 h.

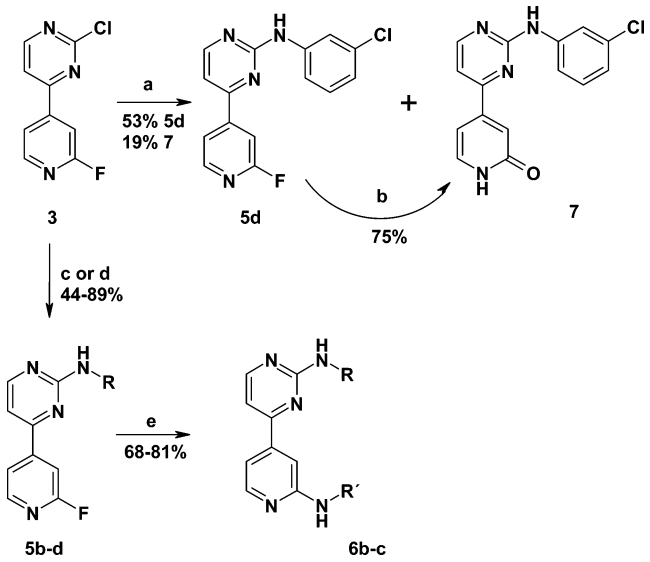
solved by using a slight excess of *n*-BuLi (1.05 equiv), and **3** was obtained in an excellent 90% yield with only traces of **4**.

Alternatively, the cross-coupling reaction can be carried out under microwave conditions facilitating the reaction within 5 min. In contrast to the thermal conditions the 2-chloro atom was also active enough for cross-coupling to form 2,4-bis-(2-fluoropyridin-4-yl)-pyrimidine.[15]

According to our strategy two consecutive nucleophilic substitution steps are required to yield the desired target compounds. A bibliographic investigation indicated that the relative reaction rate in a nucleophilic exchange reaction of 2-chloropyrimidine is about 8 orders of magnitude higher than that in 2-chloropyridine.[16] As no data for exchange rates of 2-chloro and 2-fluoropyridine are available, we compared those reported for various chloro- and fluoronitrobenzenes. Thus, exchange rates for the corresponding fluoro compound in each case were approximately 3 orders of magnitude higher.[17] Consequently, the Cl atom in **3** should be exchanged more easily than F, although the difference in reactivity is decreased. To confirm the above hypothesis, a control experiment using 3-aminopropanol was carried out and compound **5a** was obtained in 66% yield, as expected (Scheme 5). Under extended reaction time with an excess of 3-aminopropanol at 160 °C we could demonstrate successful substitution of the fluorine atom as well. After workup and purification we obtained the expected product **6a** in 68% yield.

To establish the correct substitution pattern the first nucleophilic exchange reaction requires transformation

SCHEME 6. Sequential Nucleophilic Exchange Reactions on 3[a]



[a] Reagents and conditions: (a) HCl, acetone/water 4/1, reflux, 3 h; (b) 2 N aqueous HCl, reflux, 45 min; (c)−(e) see Table 1.

with an aryl-containing amine (benzylamine and anilines) followed by a subsequent conversion with 3-aminopropanol. In the case of benzylamine the nucleophilic exchange reaction led to the desired compound in good yield (72% **5b**). Because of the low nucleophilicity, reaction with aniline required prior deprotonation by *n*-BuLi to finally yield the desired compound **5c** in 44% yield, accompanied by a number of not identified decomposition products. We therefore looked for an alternative method to improve the yield.

Instead of increasing the reactivity of the N-nucleophile the reactivity of the aromatic center in **3** can be increased by protonation of the ring nitrogen. Although in the presence of catalytic amounts (0.1 equiv) of HCl under aqueous conditions only traces of the desired product were obtained, addition of HCl in equimolar quantities was crucial for good conversion, ultimately leading to 51% of **5c**. With 3-chloroaniline product **5d** was formed in 53% yield accompanied by 19% of a byproduct **7**. The identity of 2-pyridinone **7** was confirmed by acid-catalyzed hydrolysis of the fluorine atom in a control experiment: when **5d** was refluxed in aqueous HCl, **7** was obtained in 75% yield (Scheme 6). The method of choice to avoid this side reaction was finally found in using a catalytic amount of *p*-TSA in dry dioxane, which led to **5d** in 89% yield (Table 1).

The introduction of the basic side chain was finally accomplished by heating the corresponding intermediates (**5b**−**d**) in an excess of 3-aminopropanol and led to the desired products (**6b**−**c**).

In a final experiment we also successfully performed the nucleophilic exchange reactions sequentially as a one-pot reaction. Compound **3** was first refluxed with 3-chloroaniline (1.5 equiv) and *p*-TSA (0.85 equiv) in dry dioxane for 5 h, then the solvent was evaporated, 3-aminopropanol was added, and the reaction mixture was refluxed for another 4 h. After workup and purification the desired compound **6c** (CGP 60474) was obtained in 81% overall yield.

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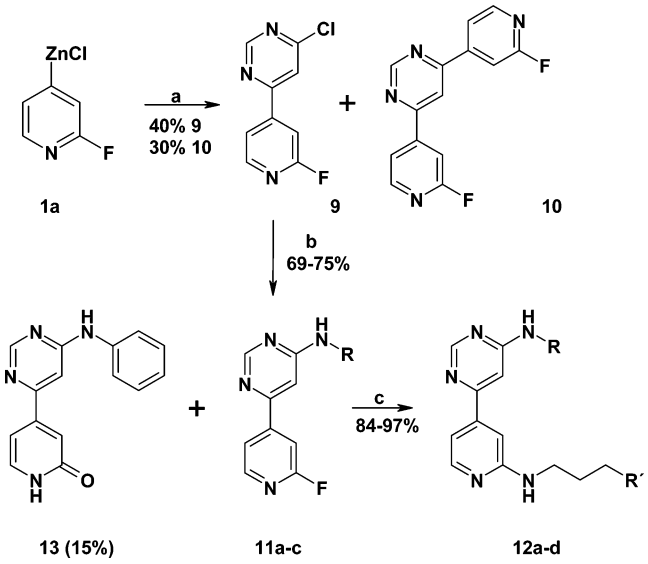
TABLE 1. Nucleophilic Exchange Reactions of 3

R	R'	compound	conditions	yield (%)
$(CH_2)_3OH$		**5a**	a	66
Bn		**5b**	a	72
Ph		**5c**	b	44
Ph		**5c**	c	51
3-Cl-Ph		**5d**	c	53
3-Cl-Ph		**5d**	d	89
$(CH_2)_3OH$	$(CH_2)_3OH$	**6a**	e	68
Bn	$(CH_2)_3OH$	**6b**	e	75
3-Cl-Ph	$(CH_2)_3OH$	**6c**	e	88

[a] DMF, amine, reflux. [b] *n*-BuLi, aniline, −30 °C to reflux. [c] Aniline derivative, HCl, acetone/water, reflux. [d] 3-Chloroaniline, *p*-TSA, dry dioxane, reflux. [e] 3-Aminopropanol, reflux.

SCHEME 7. Formation of Isomers of CGP 60474[a]



[a] Reagents and conditions: 4,6-dichloropyrimidine, $Pd(PPh_3)_4$, reflux, THF; (b) aniline derivative, HCl, acetone/water, reflux; (c) amine, reflux.

Synthesis of the Isomeric System 12. The cross-coupling reaction conditions optimized for the synthesis of **3** were applicable also for the formation of the isomeric biaryl intermediate **9**, which in turn led to isomeric target compounds **12a**−**d** (Scheme 7).

When 4,6-dichloropyrimidine **8** was coupled with the organyl **1a** the desired compound **9** (40%) was the major reaction product but accompanied by bis-coupled material **10** (30%).

Similar to conversion of compound **3** nucleophilic attack by aniline derivatives led to substitution of the pyrimidine-chlorine prior to the pyridine-fluorine. When aqueous HCl was used for this transformation the reaction was accompanied by formation of byproduct **13** (15% yield) similar to compound **7**. However in a mixture of acetone and water the nucleophilic substitution progressed smoothly to the expected products **11a**−**c** (Scheme 7). The subsequent substitution of the fluorine atom gave the desired isomeric analogues (**12a**−**d**) to CGP 60474 in good to excellent yields (Table 2).

Conclusion

An efficient and versatile synthesis for CGP 60474 (**6c**) was developed. Starting from 2-fluoropyridine the target compound was obtained in five steps with an overall yield of 64% (2-fluoro-3-iodopyridine was prepared according to the literature[13a] but in an improved 90% yield, 2-fluoro-4-iodopyridine[13b] in an improved 98% yield) compared to 34% overall yield by the established method (also five steps). The major advantage compared to the previous strategy is the flexibility of the presented protocol giving access to a large variety of derivatives and isomers.

TABLE 2. Nucleophilic Exchange Reactions of 9

R	R′	compound	yield (%)
Ph		**11a**	75
3-Cl-Ph		**11b**	85[a]
3-CF_3-Ph		**11c**	69[a]
Ph	OH	**12a**	87
3-Cl-Ph	OH	**12b**	97
3-CF_3-Ph	OH	**12c**	92
3-Cl-Ph	$N(CH_3)_2$	**12d**	84

[a] Isolated as hydrochloride.

Experimental Section

General Procedure 1. Negishi Cross-Coupling Reaction (Representative Procedure for the Preparation of 3). 4-Iodo-2-fluoropyridine **1** (15.52 g, 69.60 mmol, 1 equiv) was dissolved in dry THF (150 mL) and cooled to −70 °C. Then *n*-BuLi (73.08 mmol, 1.05 equiv) was added and the reaction mixture was stirred at −70 °C for 20 min. Subsequently, dry $ZnCl_2$ (10.44 g, 76.61 mmol, 1.1 equiv) was added as a solution in dry THF (60 mL) keeping the temperature below −60 °C. The reaction mixture was then warmed to room temperature, $Pd(PPh_3)_4$ (0.40 g, 0.35 mmol, 0.005 equiv) and **2** (7.26 g, 48.73 mmol, 0.75 equiv in 100 mL dry THF) were added, and the reaction mixture was refluxed until complete conversion.

Workup 1. The reaction mixture was poured onto a 10% aqueous EDTA solution, basified with saturated aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The crude material was recrystallized or purified by flash column chromatography (FCC).

Workup 2. Most of the solvent was evaporated and the residue was poured onto water. The resulting precipitate was filtered and the crude material was again recrystallized or purified by flash column chromatography (FCC).

2-Chloro-4-(2-fluoropyridin-4-yl)pyrimidine, 3.[18] Prepared by general procedure 1. Mp 157−159 °C; 90% (9.17 g, 43.75 mmol, beige crystals); workup 1; FCC PE/EtOAc 10:1. Anal. Calcd for $C_9H_5ClFN_3$: C, 51.57; H, 2.40; N, 20.05. Found: C, 51.78; H, 2.33; N, 20.01.

2,2′-Difluoro-[4,4′-bipyridine], 4.[18] Prepared via general procedure 1. Mp 155−200 °C (decomp); 5% (0.33 g, 1.72 mmol, colorless crystals); workup 1; FCC PE/EtOAc 10:1. Anal. Calcd for $C_{10}H_6F_2N_2$: C, 62.50; H, 3.15; N, 14.58. Found: C, 62.21; H, 3.29; N, 14.33.

3-[[4-(2-Fluoropyridin-4-yl)-2-pyrimidin-4-yl]amino]-propanol, 5a. Substrate **3** (0.32 g, 1.53 mmol, 1 equiv) was refluxed with 1.4 equiv (0.16 g, 2.13 mmol) of 3-aminopropanol for 1.5 h in dry DMF (20 mL). The reaction mixture was then poured onto water and extracted with EtOAc. The crude material was purified by FCC PE/EtOAc 10:1 to yield 66% (0.25 g, 1.01 mmol, yellow crystals) **5a**. Mp 123−124 °C; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.72 (quin, ^3J = 7 Hz, 2H), 3.39−3.57 (m, 4H), 4.49 (t, ^3J = 7 Hz, 1H), 7.28 (d, ^3J = 5 Hz, 1H), 7.38 (t, ^3J = 7 Hz, 1H), 7.79 (s, 1H), 8.00 (d, ^3J = 5 Hz, 1H), 8.39 (d, ^3J = 5 Hz, 1H), 8.47 (d, ^3J = 5 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.1 (t), 38.1 (t), 58.7 (t), 106.1 (d), 106.5 (d, $^2J_{CF}$ = 46 Hz), 119.2 (d, $^4J_{CF}$ = 4 Hz), 148.4 (d, $^3J_{CF}$ = 15

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Hz), 150.6 (d, $^3J_{CF}$ = 8 Hz), 159.9 (d), 162.6 (s), 164.0 (d, $^1J_{CF}$ = 233 Hz). Anal. Calcd for $C_{12}H_{13}N_4O$: C, 58.06; H, 5.28; N, 22.57. Found: C, 57.71; H, 5.33; N, 22.62.

***N*-(Phenylmethyl)-4-(2-fluoropyridin-4-yl)-2-pyrimidinamine, 5b.** Substrate **3** (1.51 g, 7.20 mmol, 1 equiv) and benzylamine (1.00 g, 9.33 mmol, 1.3 equiv) were heated in dry DMF (30 mL) to 150 °C for 1 h. The reaction mixture was poured onto water and the resulting precipitate filtered and dried in vacuo at 50 °C to give 72% (1.45 g, 5.17 mmol, yellow crystals) of **5b**. Mp 167−169 °C; recrystallized from EtOAc; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 4.61 (d, ^3J = 7 Hz, 2H), 7.22 (t, ^3J = 8 Hz, 1H), 7.30 (d, ^3J = 5 Hz, 1H), 7.31 (t, ^3J = 8 Hz, 2H), 7.32−7.42 (m, 2H), 7.75 (s, 1H), 7.92−8.05 (m, 2H), 8.38 (d, ^3J = 5 Hz, 1H,), 8.48 (d, ^3J = 5 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 44.1 (d), 106.5 (d), 106.6 (d, $^2J_{CF}$ = 39 Hz), 119.2 (d, $^4J_{CF}$ = 4 Hz), 126.5 (d), 127.1 (d), 128.2 (d), 140.3 (s), 148.4 (d, $^3J_{CF}$ = 15 Hz), 150.4 (d, $^3J_{CF}$ = 8 Hz), 160.1 (d), 162.5 (s), 164.0 (d, $^1J_{CF}$ = 233 Hz). Anal. Calcd for $C_{16}H_{13}FN_4$: C, 68.56; H, 4.67; N, 19.99. Found: C, 68.31; H, 4.87; N, 19.75.

General Procedure 2. Nucleophilic Substitution under Acidic Conditions (5c, 11a−c). The corresponding substrate was mixed with the aniline derivative (1.05 equiv) and concentrated HCl (1.1 equiv) in a mixture of acetone/water (4/1) and refluxed for 3 h. The reaction mixture was cooled and the formed precipitate was filtered and washed with water. The product (as hydrochloride) was dried in vacuo at 50 °C. Alternatively, the product can also be isolated as free amine; therefore the reaction mixture is basified with aqueous $NaHCO_3$ solution and again the resulting precipitate filtered, washed with water, and dried in vacuo at 50 °C. If necessary the crude material was purified by flash column chromatography.

4-(2-Fluoropyridin-4-yl)-*N*-phenyl-2-pyrimidinamine, 5c. Prepared via general procedure 2. Mp 180−183 °C; 51% (0.13 g, 0.49 mmol, yellow crystals); FCC PE/EtOAc 5:1. Alternative procedure under basic conditions: aniline (0.14 g, 1.5 mmol, 1.1 equiv) in dry THF (20 mL) was deprotonated with *n*-BuLi (0.63 mL, 1.50 mmol, 1.1 equiv) at −30 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min before **3** (0.28 g, 1.34 mmol, 1 equiv in 5 mL dry THF) was added at that temperature. The reaction mixture was warmed to room temperature and refluxed for 18 h. The solvent was subsequently evaporated and the crude material purified by FCC (PE/EtOAc 5:1) to give 44% (0.16 g, 0.60 mmol). ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.00 (t, ^3J = 8 Hz, 1H), 7.32 (t, ^3J = 8 Hz, 2H), 7.56 (d, ^3J = 5 Hz, 1H), 7.80 (d, ^3J = 8 Hz, 2H), 7.82 (s, 1H), 8.03 (d, ^3J = 5 Hz, 1H), 8.42 (d, ^3J = 5 Hz, 1H), 8.68 (d, ^3J = 5 Hz, 1H), 9.82 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 106.8 (d, $^2J_{CF}$ = 39 Hz), 108.8 (d), 119.2 (d), 119.3 (d, $^4J_{CF}$ = 4 Hz), 121.8 (d), 128.5 (d), 140.1 (s), 148.6 (d, $^3J_{CF}$ = 15 Hz), 150.2 (d, $^3J_{CF}$ = 8 Hz), 159.9 (d), 160.1 (s), 160.2 (s), 164.0 (d, $^1J_{CF}$ = 234 Hz).

***N*-(3-Chlorophenyl)-4-(2-fluoropyridin-4-yl)-2-pyrimidinamine, 5d.** Substrate **3** (0.34 g, 1.62 mmol, 1 equiv) was refluxed in dioxane with 3-chloroaniline (0.26 g, 2.04 mmol, 1.26 equiv) and *p*-TSA (0.26 g, 1.37 mmol, 0.85 equiv) for 5 h. The reaction mixture was concentrated in vacuo, poured onto water, and basified with saturated aqueous $NaHCO_3$ solution. The resulting precipitate was filtered and dried in vacuo at 50 °C to give 89% (0.43 g, 1.43 mmol, yellow crystals) **5d** without further purification. Mp 188−190 °C. Alternatively **5d** was prepared via general procedure 2 to yield 53% (0.83 g, 2.76 mmol). ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.05 (d, ^3J = 8 Hz, 1H), 7.35 (t, ^3J = 8 Hz, 1H), 7.62 (d, ^3J = 5 Hz, 1H), 7.70 (d, ^3J = 8 Hz, 1H), 7.83 (s, 1H), 8.00−8.10 (m, 2H), 8.45 (d, ^3J = 5 Hz, 1H), 8.72 (d, ^3J = 5 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 106.8 (d, $^2J_{CF}$ = 39 Hz), 109.3 (d), 117.2 (d), 118.2 (d), 119.2 (d, $^4J_{CF}$ = 4 Hz), 121.1 (d), 130.0 (d), 132.9 (s), 141.7 (s), 148.5 (d, $^3J_{CF}$ = 15 Hz), 149.9 (d, $^3J_{CF}$ = 8 Hz), 159.9 (s), 160.0 (d), 164.0 (d, $^1J_{CF}$ = 234 Hz). Anal. Calcd for $C_{15}H_{10}ClFN_4$: C, 59.91; H, 3.35; N, 18.63. Found: C, 59.76; H, 3.43; N, 18.52.

3-[[4-[2-(3-Hydroxypropylamino)-pyridin-4-yl]-2-pyrimidin-4-yl]amino]-propanol, 6a. Substrate **3** (0.29 g, 1.40 mmol, 1 equiv) was heated in 3-aminopropanol (5 mL) to 160 °C for 16 h. The reaction mixture was poured onto water and extracted with EtOAc. Recrystallization from EtOAc gave 68% (0.29 g, 0.96 mmol, yellow crystals) of **6a**. Mp 169−172 °C; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.65−1.80 (m, 4H), 3.28−3.39 (m, 4H), 3.43−3.57 (m, 4H), 4.50 (bs, 2H), 6.58−6.70 (m, 2H), 7.03 (d, ^3J = 5 Hz, 1H), 7.10 (s, 1H), 7.19 (t, ^3J = 7 Hz, 1H), 8.07 (d, ^3J = 5 Hz, 1H), 8.39 (d, ^3J = 5 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.2 (d), 32.4 (d), 38.1 (d), 58.7 (d), 58.8 (d), 105.2 (d), 105.7 (d), 108.6 (d), 145.0 (s), 148.3 (d), 159.2 (d), 159.7 (s), 162.6 (s). Anal. Calcd for $C_{15}H_{21}N_5O_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.67; H, 7.09; N, 22.79.

General Procedure 3. Introduction of the Aminopropanol Side Chain (6b, 6c, 12a−c). The corresponding substrate was heated in 3-aminopropanol (10 mL for 0.5 g) to 150−160 °C until completion. The reaction mixture was cooled to 0 °C and the product was precipitated by addition of water. The residue was filtered, and the product was washed with cold water and dried in vacuo at 50 °C. In some cases the precipitate could not be filtered and the product was isolated by extraction with EtOAc and subsequent purification by column chromatography.

3-[[4-[2-[(Phenylmethyl)amino]pyrimidin-4-yl]-pyridin-2-yl]amino]-propanol, 6b. Prepared via general procedure 3. Mp 152−154 °C; 75% (1.24 g, 3.70 mmol, yellow crystals); precipitated from water; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.70 (quin, ^3J = 7 Hz, 2H), 3.33 (q, 2H, J = 2 Hz), 3.50 (q, ^3J = 7 Hz, 2H), 4.50−4.64 (m, 3H), 6.68 (t, ^3J = 7 Hz, 1H,), 7.02 (d, ^3J = 5 Hz, 1H), 7.06 (d, ^3J = 5 Hz, 1H), 7.12 (s, 1H), 7.20−7.41 (m, 5H), 7.84 (t, ^3J = 7 Hz, 1H,), 8.07 (d, ^3J = 5 Hz, 1H), 8.38 (d, ^3J = 5 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.3 (t), 38.1 (t), 44.1 (t), 58.7 (t), 105.0 (d), 106.1 (d), 108.6 (d), 126.5 (d), 127.2 (d), 128.2 (d), 140.5 (s), 144.9 (s), 148.3 (d), 159.4 (d), 159.7 (s), 162.5 (s). Anal. Calcd for $C_{19}H_{21}N_5O$: C, 68.04; H, 6.31; N, 20.88. Found: C, 67.74; H, 6.43; N, 20.72.

3-[[4-[2-[(3-Chlorophenyl)amino]pyrimidin-4-yl]pyridin-2-yl]amino]-propanol, 6c. Prepared via general procedure 3. Mp 144−147 °C, 88% (0.32 g, 0.90 mmol, yellow crystals); precipitated from water; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.72 (quin, ^3J = 7 Hz, 2H), 3.33 (q, ^3J = 7 Hz, 2H), 3.52 (q, ^3J = 7 Hz, 2H), 4.51 (t, ^3J = 7 Hz, 1H), 6.72 (t, ^3J = 7 Hz, 1H,), 7.02 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H), 7.12 (d, ^3J = 5 Hz, 1H), 7.13 (s, 1H), 7.34 (t, ^3J = 8 Hz, 1H), 7.38 (d, ^3J = 5 Hz, 1H), 7.78 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H), 8.03 (t, ^4J = 2 Hz, 1H), 8.12 (d, ^3J = 5 Hz, 1H), 8.65 (d, ^3J = 5 Hz, 1H), 9.95 (s, 1H,); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.2 (t), 38.2 (t), 58.7 (t), 104.9 (d), 108.6 (d), 108.9 (d), 117.1 (d), 118.0 (d), 120.9 (d), 130.1 (d), 133.0 (s), 142.0 (s), 144.5 (s), 148.6 (d), 159.4 (d), 159.7 (s), 159.9 (s), 162.7 (s). Anal. Calcd for $C_{18}H_{18}ClN_5O$: C, 60.76; H, 5.10, N, 19.68. Found: C, 60.51; H, 5.09; N; 19.61.

Formation of 6c via One-pot Reaction. Substrate **3** (0.98 g, 4.68 mmol), 3-chloroaniline (0.89 g, 6.98 mmol) and *p*-TSA (0.76 g, 4.00 mmol) were refluxed for 5 h in dry dioxane. The solvent was then evaporated, and an excess of 3-aminopropanol was added and heated for 4 h to 170 °C. The reaction mixture was then cooled to room temperature, water was added, and the mixture was basified with saturated aqueous $NaHCO_3$ solution. The resulting precipitate was filtered and dried and the crude material was recrystallized from EtOAc. Yield: 81% (1.35 g, 3.79 mmol) yellow crystals.

4-[2-[Amino-(3-chlorophenyl)]pyrimidin-4-yl]pyridin-2(1*H*)-one, 7. Mp 286−288 °C; **5e** (0.04 g, 0.13 mmol, 1 equiv) was refluxed for 45 min in 2 N aqueous HCl (15 mL). The reaction mixture was cooled and basified with saturated aqueous $NaHCO_3$ solution. The formed precipitate was filtered and the product was dried in vacuo at 50 °C to give 75% (0.03 g, 0.10 mmol, yellow crystals) of **7** (also formed in 22% yield as byproduct during the formation of **5e** under aqueous conditions). ^{1}H NMR (d_6-DMSO, 200 MHz) δ 6.85 (dd, ^3J = 5

Hz, ^4J = 1 Hz, 1H), 7.02 (d, ^3J = 8 Hz, 1H), 7.10 (d, ^4J = 1 Hz, 1H), 7.35 (t, ^3J = 8 Hz, 1H), 7.46 (d, ^3J = 5 Hz, 1H), 7.58 (d, ^3J = 5 Hz, 1H), 7.70 (d, ^3J = 8 Hz, 1H), 8.02 (t, ^4J = 1 Hz, 1H), 8.66 (d, ^3J = 5 Hz, 1H), 9.99 (s, 1H.); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 102.5 (d), 109.4 (d), 117.2 (d), 117.9 (d), 118.1 (d), 121.0 (d), 130.1 (d), 133.0 (s), 136.2 (d), 141.9 (s), 148.2 (s), 159.8 (s), 161.4 (s), 162.6 (s). Anal. Calcd for $C_{15}H_{11}ClN_4O$: C, 60.31; H, 3.71; N, 18.75. Found: C, 60.02; H, 3.84; N, 18.54.

4-Chloro-6-(2-fluoropyridin-4-yl)pyrimidine, 9. Prepared via general procedure 1. Mp 120−121 °C; 40% (1.56 g, 7.44 mmol, beige crystals); workup 2; FCC PE/EtOAc 20:1; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.88 (s, 1H), 8.08 (d, ^3J = 5 Hz, 1H), 8.41 (d, ^3J = 5 Hz, 1H), 8.47 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 107.4 (d, $^2J_{CF}$ = 40 Hz), 119.0 (d), 119.6 (d, $^4J_{CF}$ = 4 Hz), 148.0 (d, $^3J_{CF}$ = 8 Hz), 148.9 (d, $^3J_{CF}$ = 15 Hz), 159.2 (d), 161.3 (d, $^4J_{CF}$ = 4 Hz), 162.0 (s), 164.0 (d, $^1J_{CF}$ = 234 Hz). Anal. Calcd for $C_9H_5ClFN_3$: C, 51.57; H, 2.40; N, 20.05. Found: C, 51.67; H, 2.67; N, 19.82.

4,6-bis-(2-Fluoropyridin-4-yl)pyrimidine, 10.[18] Prepared via general procedure 1. Mp 166−168 °C; 30% as byproduct (1.50 g, 5.55 mmol, yellow crystals); FCC PE/EtOAc 20:1. Anal. Calcd for $C_{14}H_8F_2N_4$: C, 62.22; H, 2.98; N, 20.73. Found: C, 61.92; H, 3.27; N, 20.85.

6-(2-Fluoropyridin-4-yl)-*N*-phenyl-4-pyrimidinamine, 11a. Prepared via general procedure 2. Mp 151−153 °C; 75% (0.45 g, 1.69 mmol, colorless crystals); FCC PE:EtOAc 5:1; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.00 (d, ^3J = 8 Hz, 1H), 7.34 (s, 1H), 7.36 (t, ^3J = 8 Hz, 2H), 7.69 (bs, 1H), 7.71 (d, ^3J = 8 Hz, 2H), 7.89 (d, ^3J = 5 Hz, 1H), 8.40 (d, ^3J = 5 Hz, 1H), 8.75 (s, 1H), 9.88 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 103.7 (d), 106.4 (d, $^2J_{CF}$ = 39 Hz), 119.0 (d, $^4J_{CF}$ = 4 Hz), 120.1 (d), 122.9 (d), 128.8 (d), 139.3 (s), 148.5 (d, $^3J_{CF}$ = 15 Hz), 150.3 (d, $^3J_{CF}$ = 8 Hz), 157.5 (d, $^4J_{CF}$ = 4 Hz), 158.6 (d), 161.1 (s), 163.9 (d, $^1J_{CF}$ = 234 Hz). Anal. Calcd for $C_{15}H_{11}FN_4$: C, 67.66; H, 4.16; N, 21.04. Found: C, 67.44; H, 3.94; N, 20.77.

***N*-(3-Chlorophenyl)-6-(2-fluoropyridin-4-yl)-4-pyrimidinamine hydrochloride, 11b.** Prepared via general procedure 2. Mp 203−205 °C; 85% (1.10 g, 3.26 mmol, yellow crystals); ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.16 (d, ^3J = 8 Hz, 1H), 7.40 (t, ^3J = 8 Hz, 1H), 7.36 (s, 1H), 7.70 (s, 1H), 7.80−7.98 (m, 2H), 8.05 (t, ^4J = 1 Hz, 1H), 8.48 (d, ^3J = 5 Hz, 1H), 8.91 (s, 1H), offset (1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 105.0 (d), 107.0 (d, $^2J_{CF}$ = 39 Hz), 118.8 (d), 119.3 (d, $^4J_{CF}$ = 4 Hz), 119.8 (d), 123.1 (d), 130.4 (d), 133.1 (d), 140.3 (s), 147.9 (d, $^3J_{CF}$ = 8 Hz), 148.8 (d, $^3J_{CF}$ = 15 Hz), 154.8 (s), 156.9 (d), 161.1 (s), 163.8 (d, $^1J_{CF}$ = 234 Hz). Anal. Calcd for $C_{15}H_{11}Cl_2FN_4$: C, 53.43; H, 3.29; N, 16.62. Found: C, 53.26; H, 3.35; N, 16.39.

***N*-(3-Trifluoromethylphenyl)-6-(2-fluoropyridin-4-yl)-4-pyrimidinamine hydrochloride, 11c.** Prepared via general procedure 2. Mp 187−190 °C; 69% (0.66 g, 1.78 mmol, yellow crystals); ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.43 (d, ^3J = 8 Hz, 1H), 7.59 (t, ^3J = 8 Hz, 1H), 7.60 (s, 1H), 7.70 (s, 1H), 7.88 (d, ^3J = 5 Hz, 1H), 8.01 (d, ^3J = 8 Hz, 1H), 8.28 (bs, 1H), 8.48 (d, ^3J = 5 Hz, 1H), 8.91 (s, 1H), offset (1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 105.0 (d), 106.9 (d, $^2J_{CF}$ = 40 Hz), 116.3 (d, $^3J_{CF}$ = 4 Hz), 119.2 (d, $^4J_{CF}$ = 4 Hz), 119.6 (d, $^4J_{CF}$ = 4 Hz), 123.8 (d), 124.1 (q, $^1J_{CF}$ = 270 Hz), 129.4 (d, $^2J_{CF}$ = 31 Hz), 130.0 (d), 139.7 (s), 148.1 (d, $^3J_{CF}$ = 8 Hz), 148.8 (d, $^3J_{CF}$ = 15 Hz), 155.2 (d, $^4J_{CF}$ = 4 Hz), 157.1 (d), 161.2 (s), 163.8 (d, $^1J_{CF}$ = 234 Hz)

3-[[4-[6-(Phenylamino)pyrimidin-4-yl]pyridin-2-yl]amino]-propanol, 12a. Prepared via general procedure 3. Mp 200−202 °C; 87% (0.47 g, 1.46 mmol, pale yellow crystals); FCC EtOAc; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.71 (quin, ^3J = 7 Hz, 2H), 3.32 (q, ^3J = 7 Hz, 2H), 3.50 (q, ^3J = 7 Hz, 2H), 4.55 (t, ^3J = 7 Hz, 1H), 6.74 (t, 1H, ^3J = 7 Hz), 6.97 (dd, ^3J = 5 Hz, ^4J = 1 Hz, 1H), 7.05 (t, ^3J = 8 Hz, 1H), 7.12 (s, 1H), 7.20 (s, 1H), 7.35 (t, ^3J = 8 Hz, 2H), 7.71 (d, ^3J = 8 Hz, 2H), 8.09 (d, ^3J = 5 Hz, 1H), 8.71 (s, 1H), 9.77 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.4 (t), 38.1 (t), 58.7 (t), 102.7 (d), 105.1 (d), 108.2 (d), 120.0 (d), 122.7 (d), 128.9 (d), 139.7 (s), 144.8 (s), 148.5 (d), 158.4 (d), 159.8 (s), 159.9 (s), 161.1 (s). Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.56; H, 5.86; N, 21.66.

3-[[4-[6-[(3-Chlorophenyl)amino]pyrimidin-4-yl]pyridin-2-yl]amino]-propanol, 12b. Prepared via general procedure 3. Mp 180−183 °C; 97% (0.43 g, 1.21 mmol, colorless crystals); FCC PE/EtOAc 10:1; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.72 (quin, ^3J = 7 Hz, 2H), 3.35 (q, ^3J = 7 Hz, 2H), 3.50 (t, ^3J = 7 Hz, 2H), 4.55 (bs, 1H), 6.77 (t, ^3J = 7 Hz, 1H), 6.98 (d, ^3J = 5 Hz, 1H), 7.08 (d, ^3J = 8 Hz, 1H), 7.14 (s, 1H), 7.22 (s, 1H), 7.36 (t, ^3J = 8 Hz, 1H), 7.56 (d, ^3J = 8 Hz, 1H), 8.04 (bs, 1H), 8.10 (d, ^3J = 5 Hz, 1H), 8.79 (s, 1H), 9.94 (bs, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.4 (t), 38.1 (t), 58.7 (t), 103.4 (d), 105.1 (d), 108.2 (d), 117.9 (d), 119.0 (d), 121.9 (d), 130.3 (d), 133.2 (s), 141.3 (s), 144.6 (s), 148.5 (d), 158.3 (d), 159.8 (s), 160.1 (s), 160.8 (s). Anal. Calcd for $C_{18}H_{18}ClN_5O$: C, 60.76; H, 5.10; N, 19.68. Found: C, 60.47; H, 4.94; N, 19.44.

3-[[4-[6-[(3-Trifluoromethylphenyl)amino]pyrimidin-4-yl]pyridin-2-yl]amino]-propanol, 12c. Prepared via general procedure 3. Mp 212−214 °C; 92% (0.36 g, 0.92 mmol, yellow crystals); FCC PE/EtOAc 10:1; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.72 (quin, ^3J = 7 Hz, 2H), 3.33 (q, ^3J = 7 Hz, 2H), 3.49 (t, ^3J = 7 Hz, 2H), 4.58 (bs, 1H), 6.75 (t, ^3J = 7 Hz, 1H), 6.98 (d, ^3J = 5 Hz, 1H), 7.14 (s, 1H), 7.24 (s, 1H), 7.35 (d, ^3J = 8 Hz, 1H), 7.59 (t, ^3J = 8 Hz, 1H), 7.92 (d, ^3J = 8 Hz, 1H), 8.10 (d, ^3J = 5 Hz, 1H), 8.26 (bs, 1H), 8.80 (s, 1H), 10.12 (bs, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 32.4 (t), 38.2 (t), 58.8 (t), 103.5 (d), 105.2 (d), 108.2 (d), 115.5 (d), 118.5 (d), 123.1 (d), 124.3 (q, $^1J_{CF}$ = 271 Hz), 129.7 (d, $^2J_{CF}$ = 31 Hz), 130.0 (d), 140.7 (s), 144.6 (s), 148.6 (d), 158.3 (d), 159.9 (s), 160.3 (s), 160.9 (s). Anal. Calcd for $C_{19}H_{18}F_3N_5O$: C, 58.61; H, 4.66; N, 17.99. Found: C, 58.40; H, 4.57; N, 17.82.

***N*⁴-[4-[6-(3-Chlorophenylamino)pyrimidin-4-yl]pyridin-2-yl]-*N*,*N*-dimethylpropan-1,3-diamine, 12d.** Compound **11b** (0.43 g, 1.28 mmol) was refluxed for 4 h in 10 mL of *N*,*N*-dimethyl-1,3-propandiamine. The reaction mixture was cooled to room temperature and water was added. The product was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Recrystallization from DIPE gave **12d**. Yield 84% (0.41 g, 1.07 mmol, yellow crystals); mp 185−187 °C; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 1.69 (quin, ^3J = 7 Hz, 2H), 2.12 (s, 6H), 2.30 (t, ^3J = 7 Hz, 2H), 3.30 (q, ^3J = 7 Hz, 2H), 6.79 (t, ^3J = 7 Hz, 1H), 6.98 (d, ^3J = 5 Hz, 1H), 7.08 (d, ^3J = 8 Hz, 1H), 7.12 (s, 1H), 7.20 (s, 1H), 7.37 (t, ^3J = 8 Hz, 1H), 7.56 (d, ^3J = 8 Hz, 1H), 8.04 (bs, 1H), 8.11 (d, ^3J = 5 Hz, 1H), 8.80 (s, 1H), 9.95 (bs, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 27.0 (t), 39.2 (t), 45.2 (q), 57.0 (t), 103.3 (d), 105.0 (d), 108.0 (d), 117.9 (d), 118.9 (d), 121.9 (d), 130.3 (d), 133.1 (s), 141.3 (s), 144.4 (s), 148.6 (d), 158.2 (d), 159.7 (s), 160.1 (s), 160.8 (s). Anal. Calcd for $C_{20}H_{23}ClN_6$: C, 62.74; H, 6.05; N, 21.95. Found: C, 62.55; H, 5.95; N, 21.70.

4-[6-(Phenylamino)pyrimidin-4-yl]pyridin-2(1*H*)-one, 13. Mp 284−286 °C; 15% (0.11 g, 0.42 mmol, pale yellow crystals) as byproduct during the formation of **11a**; FCC PE/EtOAc 5:1; ^{1}H NMR (d_6-DMSO, 200 MHz) δ 6.71 (dd, ^3J = 5 Hz, ^4J = 1 Hz, 1H), 6.92 (d, ^4J = 1 Hz, 1H), 7.04 (t, ^3J = 8 Hz, 1H), 7.21 (s, 1H), 7.35 (t, ^3J = 8 Hz, 2H), 7.52 (d, ^3J = 5 Hz, 1H), 7.70 (d, ^3J = 8 Hz, 2H), 8.70 (s, 1H), 9.79 (s, 1H), offset (1H); ^{13}C NMR (d_6-DMSO, 50 MHz) δ 102.6 (d), 103.6 (d), 117.0 (d), 120.0 (d), 122.8 (d), 128.8 (d), 136.1 (d), 139.5 (s), 148.7 (s), 158.4 (d), 158.7 (s), 161.0 (s), 162.7 (s). Anal. Calcd for $C_{15}H_{12}N_4O$: C, 65.49; H, 4.84; N, 20.37. Found: C, 65.69; H, 4.76; N, 20.38.

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Supporting Information Available: Crystallographic data for compound **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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