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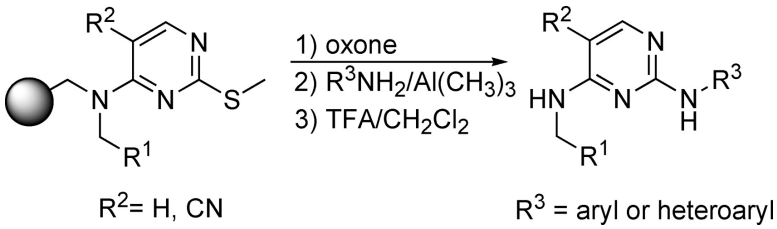

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Solid-Phase Synthesis of 2,4-Diaminopyrimidines via Lewis Acid-Mediated Aromatic Nucleophilic Substitution

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Primary amines were immobilized on (4-formyl-3,5-dimethoxyphenoxy)methylpolystyrene resin via reductive amination. Attachment of two different 4-chloro-2-methylthiopyrimidines, followed by sulfide oxidation, led to their corresponding sulfone intermediates. Aromatic nucleophilic substitution with various anilines or heteroaromatic amines in the presence of trimethyl aluminum afforded the desired 2,4-diaminopyrimidines after acidic cleavage from the resin. The synthetic methodology described herein was validated with the synthesis of a small 162-member library.

Introduction

Protein kinases have received great attention in recent years as they are intricately implicated in many different cellular signal transduction pathways.[1] Blocking or regulating the kinase phosphorylation process in a signaling cascade may be the key in treating conditions such as cancer or inflammatory processes. One feature of protein kinases is their ability to bind the ATP-purine moiety in a hydrophobic pocket. As a result, most ATP-competitive protein kinase inhibitors are planar aromatic heterocycles,[2] such as purines, quinazolines, indolinones, or phthalazines,[3] that possess both hydrogen bond-accepting and -donating abilities. 2-Amino or 2,4-diamino pyrimidines[4] belong to these privileged kinase scaffolds and substitution with an aromatic amine at the 2-position proves to be particularly important for activity (Figure 1).[5]

Synthetically, the 2,4-diaminosubstitution can be introduced by sequential aromatic nucleophilic substitutions (S_NAr) or palladium-catalyzed amination.[6] For 2,4-dichloropyrimidines, regioselectivity can be partially controlled due to the 4-position's being more reactive than the 2-position toward nucleophilic displacement. However, once the first group has been introduced (generally an electron donor, such as a primary or secondary amine), the reactivity of the resultant 4-aminopyrimidine toward a second S_NAr is greatly diminished, thus ruling out the use of poor nucleophiles, such as anilines, or requiring high temperatures[2c] and high concentration of these nucleophiles[7] to drive reactions to completion.[8] In any case, the reaction outcome is controlled greatly by the amine reactivity and yields are low to moderate.[9]

As part of our efforts to discover small-molecule kinase inhibitors, we were particularly interested in developing a robust synthetic strategy for the synthesis of 2,4-diaminopyrimidines that would not only allow the use of a wide range of primary amines and anilines but would also be amenable to either large or small focused library syntheses for screening and SAR studies. It occurred to us that 4-chloro-2-methylthiopyrimidines would be ideal scaffolds for an orthogonal synthetic pathway for several reasons. Regioselective attachment at the 4-position of the pyrimidine to the resin can be achieved by nucleophilic displacement of the chloride with supported secondary amines. Subsequent oxidation of the sulfide to the sulfone would then enhance the reactivity of the pyrimidine toward a second S_NAr at the 2-position with less nucleophilic amines. We are describing the use of trimethyl aluminum for the displacement of the methyl sulfone group with anilines and heteroaromatic amines of different electronic properties in the solid-phase synthesis of 2,4-diaminopyrimidines.

Results and Discussion

The 4-formyl-3,5-dimethoxyphenoxy linker **2** has found widespread application in solid-phase organic synthesis because it can be derivatized easily with primary amines via reductive amination. The resultant supported secondary amino group can then be utilized as a handle for the attachment or synthesis of a small-molecule scaffold via amide formation, aromatic nucleophilic substitution, alkylation, or acylation.

A sulfur-based linker was introduced in solid-phase synthesis by Suto et al., who demonstrated the use of the thio-PEG resin as a safety catch linker for the synthesis of 2-aminopyrimidines.[10] Oxidation of the thio group to the sulfone allowed concomitant nucleophilic displacement with primary or secondary amines and traceless cleavage from the resin. The advantages the sulfone group offers in facilitating and directing sequential aromatic nucleophilic substitutions have since been recognized and used in the solid-phase synthesis of 2,4,6-triaminopyrimidines,[7a] 1,3,5-triaminotriazines,[11] and 4-alkoxy-2-aminopyrimidines.[9] In these studies, the successful S_NAr nucleophiles were only secondary alkylamines. We chose to make use of two different 4-chloro-2-methylthiopyrimidines [**5a**−**b**] in order to explore the chemistry outlined in Scheme 1. All prelimi-

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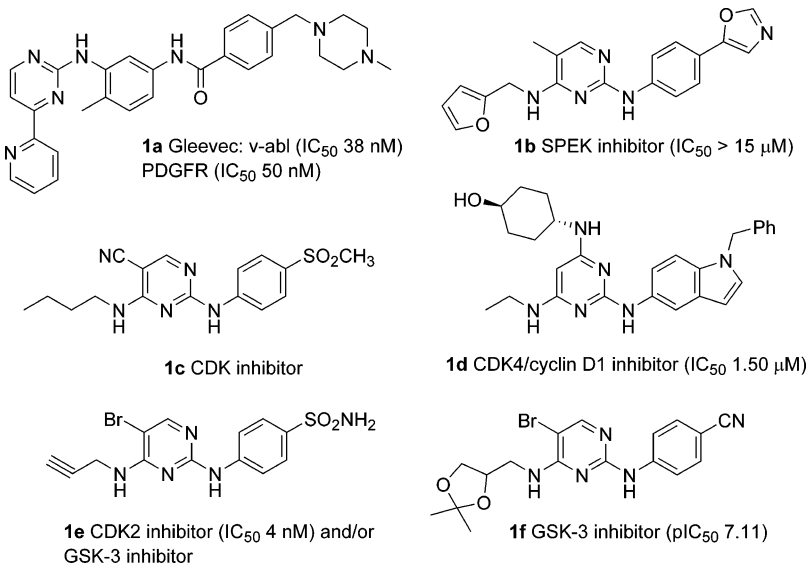
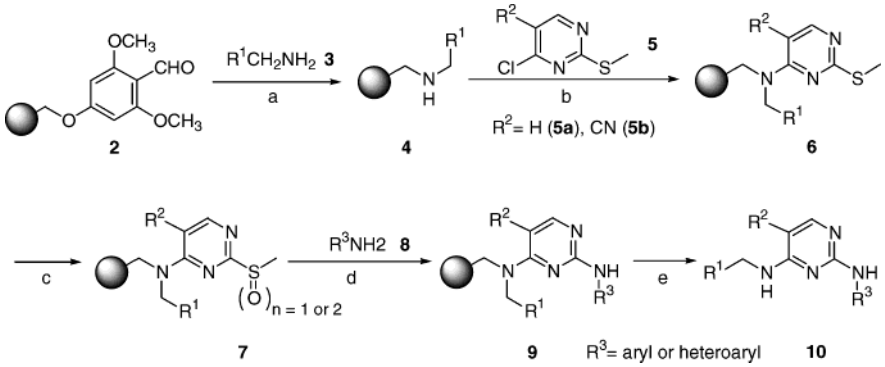


Figure 1. Kinase inhibitors (see ref 5).

Scheme 1. Solid-Phase Synthesis of 2,4-Diaminopyrimidines[a]



[a] Reactions and conditions: (a) $NaBH(OAc)_3$, 5% $AcOH/CH_2Cl_2$; (b) *i*-Pr_2EtN, DMF, 50 °; (c) oxone, THF/1 N NaOH; (d) $Al(CH_3)_3$, THF/toluene (1:3), 50 °C; (e) 10% TFA/CH_2Cl_2.

nary chemistry validation was carried out using MicroKans in order to directly optimize the reaction concentrations, times, and temperatures. Pyrimidine **5b** was synthesized in two steps from the condensation of thiomethyluronium salt with ethyl (ethoxymethylene)cyanoacetate and subsequent chlorination.[12]

Attachment of the two pyrimidines [**5a**−**b**] to a supported secondary amine **4** was achieved in the presence of *i*-Pr_2-EtN in DMF at 50 °C. Quantitative attachment was obtained for a minimum pyrimidine concentration of 0.2 M for 48 h. Reaction times were decreased when higher concentrations of pyrimidine were used (0.3, 0.4, and 0.5 M). Resin loadings were verified after acetylation of intermediates [**6a**−**b**] and subsequent cleavage.

Oxidation of the methyl sulfide group to the corresponding sulfone proved to be more challenging than expected. Bradley et al.[7a] reported that it was necessary to buffer the reaction medium with 1 M aqueous NaOH when using *m*-chloroperbenzoic acid (*m*CPBA) in CH_2Cl_2 in order to avoid premature cleavage of the pyrimidine substrate from the equally acid-sensitive Rink-amide resin linker. Under these conditions (*m*CPBA, dioxane, 1 M aqueous NaOH, 24 h), quantitative oxidation of sulfide **6a** was achieved, but only 80% of sulfide **6b** was converted, even after prolonged treatment (48 h or double treatment). Oxone proved to be a better oxidant when used as a suspension in THF/1 M aqueous NaOH. After 48 h, complete oxidation of both pyrimidines was achieved to afford a mixture of sulfoxide and sulfone. Complete oxidation to the sulfone was intended; however, in **6b**, concomitant oxidation of the cyano group to the amide was observed with longer reaction times. In any case, the subsequent S_NAr reaction on the sulfoxide/sulfone mixture proceeded in high purity, indicating that the sulfoxide is also an adequate leaving group.

During our preliminary studies on the Lewis acid-mediated S_NAr, we found that a mixture of anhydrous toluene/THF (3:1) was the best for solubilizing various anilines. The aniline was premixed with trimethylaluminum (2 M solution in anhydrous toluene), and the resultant solution was shaken for 1.5 h before adding the encapsulated resin and heating at 50 °C while shaking for 24 h. We observed that the purity of the products was directly dependent upon the solubility of the aniline−trimethylaluminum complex and the workup procedure. It is essential to remove the reaction mixture by aspiration, rinse with THF, and then quench with methanol so as to avoid the formation of insoluble aluminum oxide salts throughout the MicroKan's polypropylene mesh. A small 9 × 2 × 9 library was synthesized in order to explore the scope and limitations of this step when using anilines/heteroaromatic amines with different stereoelectronic proper-

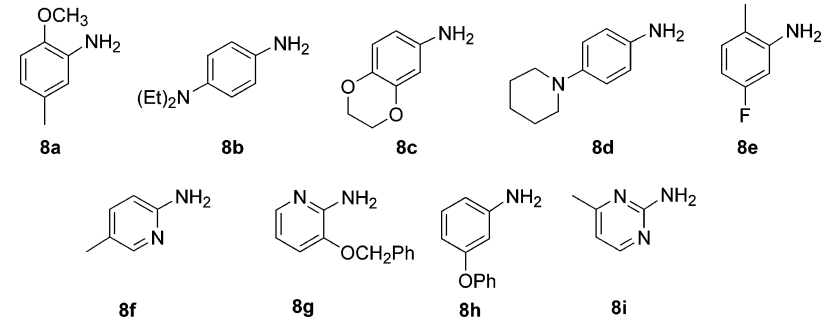


Figure 2. Set of anilines and heteroaromatic amines for the S_NAr step.

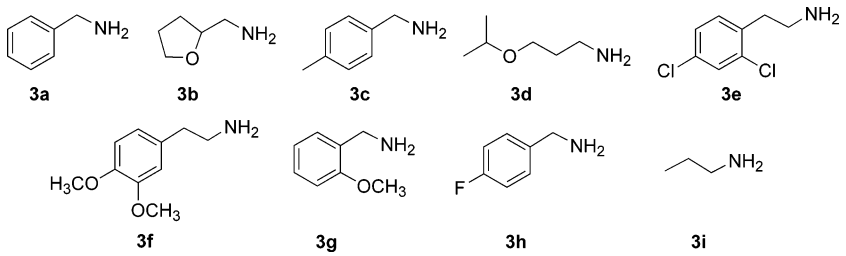


Figure 3. Set of primary amines for the reductive amination step.

Table 1. Average Percent Purity of 2,4-Diaminopyrimidines for Each Aniline/Heteroaromatic Amine Used Per Pyrimidine Core[a]

	8a	8b	8c	8d	8e	8f	8g	8h	8i
3a	80.4	100	98.4	100	94.6	99.3	86.41	95.04	76.24
3b	99	92	97	92	95	94	71	97	77

[a] % Purities are based upon ELS detection.

ties [**8a**−**i**] (Figure 2). A set of nine primary amines [**3a**−**i**] (Figure 3) was utilized for the derivatization of the FDMP linker by reductive amination. The only difficulty encountered during the library synthesis was the poor solubility in toluene of some anilines/heteroaromatic amines. Reagents **8g**, **8h**, and **8i** were taken up instead in an anhydrous mixture of THF/toluene (3:1) in order to achieve complete dissolution. The average purity for the 162-member library was 90.5%, and 86% of products **10** had purity above or equal to 80%. Table 1 summarizes the average purity obtained for products, whereas purities and overall yields for all 2,4-diaminopyrimidines synthesized are reported in the Supplemental Information.

Conclusion

A small library of 162 2,4-diaminopyrimidines of general structure **10** was synthesized in order to explore the trimethylaluminum-assisted aromatic nucleophilic substitution of supported 2-methylsulfonyl-4-aminopyrimidines [**7a**−**b**] with anilines or heteroaromatic amines [**8a**−**i**]. Of the 2,4-diaminopyrimidines, 139 had purity above 80%, thus demonstrating the robustness of this methodology that will be utilized for the synthesis of a larger library.

Experimental Procedures

(4-Formyl-3,5-dimethoxyphenoxy)methylpolystyrene (FDMP) resin (50−100 mesh, 1.5 mmol/g loading) was purchased from Polymer Laboratories. All solvents and reagents were purchased from either Sigma-Aldrich or Fisher Scientific and used without further purification.

Each Irori MicroKan was loaded with resin (25−30 mg) and a radio frequency tag using the Irori resin and tag dispensers (Discovery Partners). MicroKans were then sorted in the corresponding reaction vessel according to their tag code with the Irori Accutag instrument. Reactions were performed in Schott bottles equipped with an open-top screw cap and a Teflon seal (Chemglass). The washing procedure consisted of the following steps: the MicroKans were suspended in the appropriate solvent, the Schott bottles were placed on an New Brunswick Innova 2100 platform shaker (Fisher Scientific) for 15−20 min, and the solvent was removed by aspiration. Cleavage of the final compounds was performed in the Irori Accucleave-192 station. Products were collected in Matrix 2-mL 96-deep-well plates (Apogent). Solvent evaporation under high vacuum was achieved using a Genevac HT-12 evaporator. Yield determination was done by transferring products isolated in 2-mL 96-deep-well plates into tared 2D-barcode 96-tube racks (Matrix) and weighing the dried residues with the Bohdan Balance Automator (Mettler Toledo Autochem).

All compounds were analyzed by LC−MS with a Waters HPLC system equipped with a Sedere evaporative light scattering detector (Sedex 75) and four Phenomenex columns (60 Å, 5 μm, 3 × 50 mm) coupled to a Micromass ZQ electrospray mass spectrometer with 4-channel MUX capability (Micromass, Waters). Two mobile phases (A, 99.9% water, 0.1% TFA; B, 99.9% acetonitrile, 0.1% TFA) were employed as a linear gradient from 25 to 100% B in 1.8 min and 100% B for 0.45 min with a flow rate of 6.0 mL/min. Compounds {**3a**−**i,5a,8i**} were reanalyzed by LC−MS with a Shimadzu HPLC system (SCL-10A) equipped with a Sedere evaporative light scattering detector (Sedex 75) and a Princeton SPHER HTS column (60 Å, 5 μm, 3 × 50 mm) coupled to a Finnigan AQA electrospray mass spectrometer. Two mobile phases (A, 99.9% water, 0.1% TFA; B, 99.9% acetonitrile, 0.1% TFA) were employed as a linear gradient from 10 to 100% B in 2.2 min and 100% B for 0.2 min with a flow rate of 6.0 mL/min.

^{1}H NMR spectra were acquired on a Varian VXR-300S spectrometer. Residual solvent was used as an internal standard.

Derivatization of the Resin by Reductive Amination. The MicroKans (18 Microkans/150 mL bottle) were suspended in a solution of the appropriate amine (0.5 M, 11 mmol) in 5% acetic acid in CH_2Cl_2 (22 mL/bottle) and shaken for 2 h before adding $NaBH(OAc)_3$ (0.5 M, 11 mmol, 2.33 g). Degassing of the bottles was necessary in order to avoid pressure build up. The bottles were shaken for 18 h. The suspension was removed by aspiration, and the MicroKans were washed four times alternatively with MeOH/CH_2Cl_2 before being dried under high vacuum at 40 °C.

Attachment of the Pyrimidine Core. The MicroKans (81 Microkans/250 mL bottle) were suspended in a solution of the appropriate pyrimidine (0.2 M, 18 mmol) and *i*-Pr_2EtN (0.3 M, 27 mmol, 4.7 mL) in DMF (90 m L/bottle) and shaken for 48 h at 50 °C. The solution was removed by aspiration, and the MicroKans were washed twice with DMF and three times alternatively with EtOH/CH_2Cl_2 before being dried under high vacuum at 40 °C.

Sulfide Oxidation. The MicroKans (81 Microkans/250 mL bottle) were suspended in a suspension of Oxone (0.3 M with respect to THF, 27 mmol, 16.60 g) in THF/1 M aqueous NaOH (90 mL/54 mL, respectively) and shaken at room temperature for 48 h. The suspension was removed by aspiration, and the MicroKans were washed with H_2O, THF/H_2O (2:1), THF, MeOH, THF and then MeOH/CH_2Cl_2 twice alternatively before being dried under high vacuum at 40 °C.

Derivatization of the Resin by S_NAr. To a solution of the appropriate aniline (0.3 M, 6 mmol) in anhydrous THF/toluene (5 mL:15 mL, respectively, per bottle) was added dropwise a 2 M solution of $Al(CH_3)_3$ in toluene (0.3 M, 6 mmol) under argon. The solution was shaken at 50 °C for 2 h before adding the MicroKans (18 Microkans/150 mL bottle) and shaking for an additional 18 h (not kept under argon). The suspension was removed by aspiration, and the MicroKans were washed twice with the following solvent cycle: THF, MeOH, THF/H_2O (3:1) followed by MeOH/CH_2Cl_2 twice alternatively before being dried under high vacuum at 40 °C.

Cleavage of Diaminopyrimidines from Solid Support. Using the Accucleave-192 station, each MicroKan was suspended in a solution of 10% trifluoroacetic acid in CH_2Cl_2 (1.7 mL) for 30 min. The solutions were collected in a Matrix 2-mL deep-well 96-plate. Each MicroKan was suspended in CH_2Cl_2 (1.5 mL) for an additional 30 min. The solutions were collected in a second Matrix 2-mL deep-well 96-plate. After evaporation of the solvent using the Genevac HT-12 evaporator, the contents of both deep-well plates were combined.

Analytical Data for Selected Examples 10. 2-(4-Diethylaminophenylamino)-4-(3-isopropoxypropylamino)pyrimidine-5-carbonitrile {**3d,5b,8b**}**.** Yield, 4.1 mg (17.9%); ^{1}H NMR (300 MHz, CD_3CN): δ 1.08 (t, J = 7.5 Hz, 6H), 1.13 (d, J = 6.5 Hz, 6H), 1.87 (septet, J = 6.5 Hz, 1H), 3.50−3.58 (m, 8H), 3.63 (quartet, J = 6.5 Hz, 2H), 7.35 (broad singlet, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 9.0 Hz, 2H), 8.27 (s, 1H). m/z $[M + 1]^+$ 383.32; HPLC, 100.00% pure (R_t = 0.72 min).

2-(4-Diethylaminophenylamino)-4-[2-(3,4-dimethoxyphenyl)ethylamino]pyrimidine-5-carbonitrile {**3f, 5b,8b**}**.** Yield, 4.58 mg (18.0%);^{1}H NMR (300 MHz, CD_3CN): δ 1.08 (t, J = 7.0 Hz, 6H), 2.87 (t, J = 7.0 Hz, 2H), 3.54 (quartet, J = 7.0 Hz, 4H), 3.73 (s, 3H), 3.74 (s, 3H), 3.75 (quartet, J = 7.0 Hz, 2H), 6.73 (dd, J = 2.0, 8.0 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.0 Hz, 2H), 7.84 (d, J = 7.0 Hz, 2H), 8.27 (s, 1H). m/z $[M + 1]^+$ 447.31; HPLC, 98.61% pure (R_t = 0.72 min).

4-(4-Fluorobenzylamino)-2-(5-methylpyridin-2-ylamino)pyrimidine-5-carbonitrile {**3h,5b,8f**}**.** Yield, 5.53 mg (26.2%);^{1}H NMR (300 MHz, CD_3CN): δ 2.37 (s, 3H), 4.66 (d, J = 6.0 Hz, 2H), 7.09 (td, J = 4.5, 9.0 Hz, 2H), 7.35 (broad singlet, 1H), 7.44−7.48 (m, 3H), 8.03−8.06 (m, 2H), 8.46 (s, 1H). m/z $[M + 1]^+$ 335.24; HPLC, 100.00% pure (R_t = 0.90 min).

4-(3-Isopropoxypropylamino)-2-(2-methoxy-5-methylphenylamino)pyrimidine-5-carbonitrile {**3d,5b,8a**}**.** Yield, 7.0 mg (40.0%);^{1}H NMR (300 MHz, CD_3CN): δ 1.10 (s, 3H), 1.12 (s, 3H), 1.83 (quintet, J = 6.5 Hz, 2H), 2.29 (s, 3H), 3.47−3.59 (m, 5H), 3.82 (s, 3H), 6.94 (d, J = 8.0 Hz, 1H), 7.02 (dd, J = 2.5, 8.0 Hz, 1H), 7.26 (broad singlet, 1H), 7.71 (d, J = 2.5 Hz, 1H), 8.20 (s, 1H). m/z $[M + 1]^+$ 409.02; HPLC, 98.63% pure (R_t = 1.19 min).

4-(3-Isopropoxypropylamino)-2-(5-methylpyridin-2-ylamino)pyrimidine-5-carbonitrile {**3d,5b,8f**}**.** Yield, 9.88 mg (47.5%); ^{1}H NMR (300 MHz, CD_3CN): δ 1.14 (s, 3H), 1.16 (s, 3H), 1.85 (quintet, J = 6.0 Hz, 2H), 2.37 (s, 3H), 3.54−3.63 (m, 5H), 7.18 (broad singlet, 1H), 7.40 (d, J = 9.0 Hz, 1H), 8.03 (dd, J = 2.0, 9.0 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.42 (s, 1H). m/z $[M + 1]^+$ 327.26; HPLC, 100% pure (R_t = 0.81 min).

2-(3-Benzyloxyphenylamino)-4-(3-isopropoxypropylamino)pyrimidine-5-carbonitrile {**3d,5b,8h**}**.** Yield, 7.46 mg (37.4%); ^{1}H NMR (300 MHz, CD_3CN): δ 1.09 (s, 3H), 1.11 (s, 3H), 1.85 (quintet, J = 6.5 Hz, 2H), 3.46−3.55 (m, 3H), 3.63 (quartet, J = 5.0 Hz, 2H), 5.10 (s, 2H), 6.81 (ddd, J = 1.0, 2.5, 8.0 Hz, 1H), 7.21 (ddd, J = 1.0, 2.0, 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.33−7.47 (m, 7H), 8.22 (s, 1H). MS (ESI): m/z $[M + 1]^+$ 418.28; HPLC, 100% pure (R_t = 1.46 min).

4-[2-(2,4-Dichlorophenyl)ethylamino]-2-(2-methoxy-5-methylphenylamino)pyrimidine-5-carbonitrile {**3e,5b,8a**}**.** Yield, 7.29 (35.8%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.25 (s, 3H), 2.95 (t, J = 7.0 Hz, 2H), 3.63 (quartet, J = 7.0 Hz, 2H), 3.81 (s, 3H), 6.97 (d, J = 8.5 Hz, 1H), 7.08 (dd, J = 8.0 Hz, 1H), 7.18 (dd, J = 2.0, 8.0 Hz, 1H), 7.24−7.26 (m, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.50 (s, 1H), 8.20 (s, 1H). MS (ESI): m/z $[M + 1]^+$ 428.15; HPLC, 100% pure (R_t = 1.46 min).

4-[2-(3,4-Dimethoxyphenyl)ethylamino]-2-(2-methoxy-5-methylphenylamino)pyrimidine-5-carbonitrile {**3f,5b,8a**}**.** Yield, 10.21 mg (51.0%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.23 (s, 3H), 2.78 (t, J = 7.0 Hz, 2H), 3.61 (quartet, J = 7.0 Hz, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 6.59 (broad d, 1H), 6.69 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.28 (broad s, 1H),

7.56 (broad s, 1H), 8.20 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 420.27; HPLC, 99.02% pure ($R_t = 1.16$ min).

2-(2,3-Dihydrobenzo[1,4]dioxin-6-ylamino)-4-[2-(3,4-dimethoxyphenyl)ethylamino]-pyrimidine-5-carbonitrile {**3f,5b,8c**}**.** Yield, 7.92 mg (38.6%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.92 (t, $J = 7.5$ Hz, 2H), 3.67 (quartet, $J = 7.5$ Hz, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 4.23 (s, 4H), 6.70 (dd, $J = 2.0$, 8.0 Hz, 1H), 6.75 (d, $J = 2.0$ Hz, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.85 (d, $J = 8.5$ Hz, 1H), 7.02 (dd, $J = 2.0$, 8.5 Hz, 1H), 7.21 (d, $J = 2.0$ Hz, 1H), 8.19 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 434.27; HPLC, 98.92% pure ($R_t = 1.00$ min).

4-[2-(3,4-Dimethoxyphenyl)ethylamino]-2-(4-piperidin-1-yl-phenylamino)pyrimidine-5-carbonitrile {**3f,5b,8d**}**.** Yield, 6.89 mg (26.8%); ^{1}H NMR (300 MHz, CD_3CN): δ 1.71−1.74 (m, 2H), 1.92−1.99 (covered by CH_3CN signal, 2H), 2.00 (quintet, $J = 6.0$ Hz, 2H), 2.86 (t, $J = 7.0$ Hz, 2H), 3.49 (dd, $J = 5.5$, 5.5 Hz, 4H), 3.71 (s, 3H), 3.75 (s, 3H), 3.76 (quartet, $J = 7.0$ Hz, 2H), 6.75 (d, $J = 2.0$ Hz, 1H), 6.71 (dd, $J = 2.0$, 8.0 Hz), 6.83 (d, $J = 8.0$ Hz, 1H), 7.20 (broad singlet, 1H), 7.57 (d, $J = 9.0$ Hz, 2H), 7.79 (d, $J = 9.0$ Hz, 2H), 8.26 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 459.33; HPLC, 99.06% pure ($R_t = 0.76$ min).

4-[2-(3,4-Dimethoxyphenyl)ethylamino]-2-(5-fluoro-2-methylphenylamino)pyrimidine-5-carbonitrile {**3f,5b,8e**}**.** Yield, 11.77 mg (60.2%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.26 (s, 3H), 2.70 (t, $J = 7.5$ Hz, 2H), 3.51 (t, $J = 7.5$ Hz, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.51 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.65 (d, $J = 1.5$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 7.04 (td, $J = 3.0$, 8.5 Hz, 1H), 7.24 (broad singlet, 1H), 7.28−7.34 (m, 2H), 8.24 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 408.28; HPLC, 99.32% pure ($R_t = 1.17$ min).

2-(3-Benzyloxyphenylamino)-4-[2-(3,4-dimethoxyphenyl)ethylamino]pyrimidine-5-carbonitrile {**3f,5b,8h**}**.** Yield, 12.17 mg (54.5%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.83 (t, $J = 7.0$ Hz, 2H), 3.69 (s, 3H), 3.72 (s, 3H), 3.69−3.77 (m, 2H), 5.04 (s, 2H), 6.66 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.71 (d, $J = 1.5$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.84−6.88 (m, 1H), 7.18−7.22 (m, 1H), 7.21−7.39 (m, 7H), 8.22 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 482.28; HPLC, 99.41% pure ($R_t = 1.32$ min).

2-(2,3-Dihydrobenzo[1,4]dioxin-6-ylamino)-4-(2-methoxybenzylamino)pyrimidine-5-carbonitrile {**3 g,5b,8c**}**.** Yield, 9.8 mg (52.0%); ^{1}H NMR (300 MHz, CD_3CN): δ 3.86 (s, 3H), 4.24 (s, 4H), 4.65 (d, $J = 6.0$ Hz, 2H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.86−6.90 (m, 2H), 7.00 (dd, $J = 1.0$, 7.0 Hz, 1H), 7.07 (s, 1H), 7.14 (d, $J = 7.0$ Hz, 1H), 7.29 (td, $J = 1.5$, 8.0 Hz, 1H), 7.61 (broad singlet, 1H), 8.27 (s, 1H), 11.67 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 390.24; HPLC, 99.20% pure ($R_t = 1.09$ min).

4-(2-Methoxybenzylamino)-2-(4-piperidin-1-yl-phenylamino)pyrimidine-5-carbonitrile {**3 g,5b,8d**}**.** Yield, 8.29 mg (34.4%); ^{1}H NMR (300 MHz, CD_3CN): δ 1.71−1.74 (m, 2H), 1.92−1.99 (covered by CH_3CN signal, 2H), 2.00 (quintet, $J = 5.5$ Hz, 2H), 3.49 (dd, $J = 5.5$, 5.5 Hz, 4H), 3.87 (s, 3H), 4.68 (d, $J = 6.0$ Hz, 2H), 6.89 (td, $J = 1.0$, 7.5 Hz, 1H), 7.04 (dd, $J = 1.0$, 7.5 Hz, 1H), 7.17 (dd, $J = 1.0$, 7.5 Hz, 1H), 7.30 (td, $J = 1.0$, 7.5 Hz, 1H), 7.49 (d, $J = 9.5$ Hz, 2H), 7.62 (d, $J = 9.5$ Hz, 2H), 8.30 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 415.27; HPLC, 99.55% pure ($R_t = 0.89$ min).

2-(3-Benzyloxyphenylamino)-4-(2-methoxybenzylamino)pyrimidine-5-carbonitrile {**3 g,5b,8h**}**.** Yield, 6.39 mg (31.0%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.74 (d, $J = 5.9$ Hz, 2H), 5.1 (s, 2H), 6.79 (dt, $J = 1.0$, 7.6 Hz, 1H), 6.87−6.94 (m, 2H), 7.10 (broad t, 1H), 7.18 (dt, $J = 1.0$, 9 Hz, 1H), 7.29−7.45 (m, 9H), 8.13 (s, 1H), 11.95 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 438.26; HPLC, 99.12% pure ($R_t = 1.48$ min).

4-(4-Fluorobenzylamino)-2-(5-fluoro-2-methylphenylamino)pyrimidine-5-carbonitrile {**3h,5b,8e**}**.** Yield, 8.95 (51.3%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.17 (s, 3H), 4.41 (d, $J = 6.0$ Hz, 2H), 6.80−7.40 (m, 7H), 7.64 (broad singlet, 1H), 8.26 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 352.21; HPLC, 99.50% pure ($R_t = 1.27$ min).

2-(2-Methoxy-5-methylphenylamino)-4-propylaminopyrimidine-5-carbonitrile {**3i,5b,8a**}**.** Yield, 7.07 mg (45.8%); ^{1}H NMR (300 MHz, CD_3CN): δ 0.89 (t, $J = 7.0$ Hz, 3H), 1.61 (sextet, $J = 7.0$ Hz, 2H), 2.29 (s, 3H), 3.35−3.42 (quartet, 2H), 3.81 (s, 3H), 6.93 (d, $J = 8.0$ Hz, 1H), 7.01 (dd, $J = 2.5$, 8.0 Hz, 1H), 7.75 (d, $J = 2.5$ Hz, 1H), 8.20 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 298.20; HPLC, 99.18% pure ($R_t = 1.08$ min).

2-(2,3-Dihydrobenzo[1,4]dioxin-6-ylamino)-4-propylaminopyrimidine-5-carbonitrile {**3i,5b,8c**}**.** Yield, 4.51 mg (28.%); ^{1}H NMR (300 MHz, CD_3CN): δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.63 (sextet, $J = 7.5$ Hz, 2H), 3.39−3.46 (quartet, 2H), 4.24 (s, 4H), 6.85 (d, $J = 9.0$ Hz, 1H), 7.02 (dd, $J = 2.5$, 9.0 Hz, 1H), 7.25 (d, $J = 2.5$ Hz, 1H), 8.19 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 312.21; HPLC, 100% pure ($R_t = 0.97$ min).

2-(5-Methylpyridin-2-ylamino)-4-propylaminopyrimidine-5-carbonitrile {**3i,5b,8f**}**.** Yield, 6.34 mg (34.1%); ^{1}H NMR (300 MHz, CD_3CN): δ 0.95 (t, $J = 7.0$ Hz, 3H), 1.66 (sextet, $J = 7.0$ Hz, 2H), 2.37 (s, 3H), 2.53 (broad singlet, 1H), 3.43−3.49 (quartet, 2H), 6.88 (broad singlet, 1H), 7.46 (d, $J = 9.0$ Hz, 1H), 8.02 (dd, $J = 1.5$, 9.0 Hz, 1H), 8.07 (s, 1H), 8.41 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 269.16; HPLC, 100% pure ($R_t = 0.73$ min).

2-(3-Benzyloxyphenylamino)-4-propylaminopyrimidine-5-carbonitrile {**3i,5b,8h**}**.** Yield, 5.53 mg (31.0%); ^{1}H NMR (300 MHz, CD_3CN): δ 0.90 (t, $J = 7.0$ Hz, 3H), 1.65 (sextet, $J = 7.0$ Hz, 2H), 3.44−3.51 (quartet, 2H), 5.1 (s, 2H), 6.82 (ddd, $J = 1.0$, 2.5, 8.0 Hz, 1H), 7.18−7.22 (m, 1H), 7.28−7.47 (m, 7H), 8.22 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 360.27; HPLC, 100% pure ($R_t = 1.34$ min).

2-(3-Benzyloxyphenylamino)-4-benzylaminopyrimidine {**3a,5a,8h**}**.** Yield, 11.53 mg (62.0%); ^{1}H NMR (300 MHz, CD_3CN): δ 4.68 (d, $J = 6.0$ Hz, 2H), 5.00 (s, 2H), 6.18 (d, $J = 7.5$ Hz, 1H), 6.77 (ddd, $J = 1.0$, 2.5, 8.0 Hz, 1H), 7.09 (ddd, $J = 1.0$, 2.5, 8.0 Hz, 1H), 7.21−7.42 (m, 13 H), 7.60 (d, $J = 7.5$ Hz, 1H), 11.12 (s, 1H). MS (ESI): *m/z* $[M + 1]^+$ 383.39; HPLC, 94.49% pure ($R_t = 1.37$ min).

2-(6-Benzyloxypyridin-2-ylamino)-4-(3-isopropoxypropylamino)pyrimidine {**3d,5a,8g**}**.** Yield, 15.5 mg (66.4%); ^{1}H NMR (300 MHz, CD_3CN): δ 1.08 (s, 3H), 1.10 (s, 3H), 1.80 (quintet, $J = 6.0$ Hz, 2H), 3.47 (t, $J = 6.0$ Hz, 2H), 3.49−3.58 (m, 3H), 5.29 (s, 2H), 6.32 (d, $J = 7.0$ Hz, 1H),

7.14 (dd, $J = 5.0$, 8.0 Hz, 1H), 7.34−7.52 (m, 7H), 7.71 (d, $J = 7.0$ Hz, 1H), 7.92 (dd, $J = 1.5$, 5.0 Hz, 1H). MS (ESI): m/z $[M + 1]^+$ 394.44; HPLC, 90.05% pure ($R_t = 1.07$ min).

2-(6-Benzyloxypyridin-2-ylamino)-4-(4-methylbenzylamino)pyrimidine {**3c,5a,8g**}**.** Yield, 17.4 mg (74%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.31 (s, 3H), 4.65 (d, $J = 6.5$ Hz, 2H), 5.28 (s, 2H), 6.38 (d, $J = 7.0$ Hz, 1H), 7.12−7.51 (m, 11 H), 7.66 (broad singlet, 1H), 7.75 (d, $J = 7.0$ Hz, 1H), 7.92 (dd, $J = 1.5$, 5.0 Hz, 1H). MS (ESI): m/z $[M + 1]^+$ 398.42; HPLC, 86.89% pure ($R_t = 1.20$ min).

2-(4-methylpyrimidin-2-ylamino)-4-(2-methoxybenzylamino)pyrimidine {**3 g,5a,8i**}**.** Yield, 15.5 mg (94.8%); ^{1}H NMR (300 MHz, CD_3CN): δ 2.54 (s, 3H), 3.87 (s, 3H), 4.67 (d, $J = 6.0$ Hz, 2H), 6.41 (d, $J = 7.0$ Hz, 1H), (td, $J = 1.0$, 6.5 Hz, 1H), 7.00 (broad d, $J = 8.0$ Hz, 1H), 7.10 (dd, $J = 1.0$, 5.0 Hz, 1H), 7.26−7.36 (m, 1H), 7.39 (d, $J = 7.0$ Hz, 1H), 7.72 (broad singlet, 1H), 7.77 (d $J = 7.0$ Hz, 1H), 8.49 (d $J = 5.0$ Hz, 1H). MS (ESI): m/z $[M + 1]^+$ 323.14; HPLC, 83.05% pure ($R_t = 1.37$ min).

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Supporting Information Available. Table listing purity and yield information for all compounds in this library; experimental data for libraries and compounds formulated. This material is available free of charge via the Internet at http://pubs.acs.org.

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