High-Yielding Two-Step Synthesis of 6,8-Disubstituted N-9-Unprotected Purines

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We report herein a convenient method for the synthesis of libraries of 6,8-disubstituted-9-*H*-purines in two steps, including cyclization of 6-chloro-4,5-diaminopyrimidine with various arylcarboxylic acids or chlorides, followed by S_NAr with amines and alkoxides or Pd-catalyzed amidations at C-6. These reactions were highly efficient and allowed the synthesis of a 32-member library of 6,8-disubstituted purines.

Introduction

8-Substituted purines, particularly, 8-aryl or 8-alkylxanthines,[1] have demonstrated their interest as, for example, inhibitors of phosphodiesterases[2,3] or antagonists of adenosine receptors,[4−8] and many of them have been proposed as novel therapeutic agents for neurodegenerative diseases (PD, AD),[9] inflammation,[10] or type 2 diabetes.[11] The interest of 8-substituted-purines has increased recently with the discovery of several 8-substituted adenine derivatives as potent inhibitors of Hsp90 molecular chaperone.[12−14] The synthesis of 8-substituted purines can be achieved in two steps and high yield from 5,6-diaminouracils, in the case of xanthines, by condensation with an aryl carboxylic acid, followed by ring closure with sodium hydroxide.[7,15,16,10] Other methods have been developed for the preparation of 8-substituted purines from 8-halogenopurines, by Suzuki or Stille reactions[17−20] or by catalyzed direct arylation at C-8[21−23] with aryl iodides. An amidation/cyclization of a 4-iodo-5-aminopyrimidine precursor has also been described.[24] In this context, the synthesis of various nonxanthine 8-substituted purines bearing a halogen at position 6 for further nucleophilic substitution or palladium-catalyzed cross-coupling,[25] from a cheap readily available pyrimidine precursor remains very attractive for the synthesis of large purine libraries. Few examples of syntheses of 6-chloro-8-substituted purines **2** have been achieved from a 4,5-diaminopyrimidine precursor (**1**, R^1 = H). The yield of these syntheses may be moderate or low, depending on the substituent at position 9, and on the nature of the aryl group at C-8. In addition, the hydroxy derivative **3** may be formed by concomitant hydrolysis of the C-6 chlorine atom (Scheme 1).[26]

Thus, Chang and co-workers have described the synthesis of 6-chloropurines bearing a phenyl at position 2 and a phenyl or an aliphatic substituent at position 8.[27]

Dang and co-workers have also prepared various 6-chloro-8-substituted purines from a 6-chloro-4,5-diaminopyrimidine precursor (**1**, R = H, R^1 = alkyl).[28] The cyclization step was performed with various aryl- or alkyl-aldehydes in the presence of $FeCl_3-SiO_2$, in moderate to good yields (48−88%). However, these results contradict the results of Yang who claimed that when a pyrimidine such as **1** (R = Me, R^1 = n-Pr) is treated with 2-furaldehyde with $FeCl_3-SiO_2$ in DMSO at 100 °C, only the hydrolysis product (6-hydroxypurine) is obtained in 78% yield.[26] Liu and co-workers have used the reaction of 5-alkylamino-4-amino-6-arylthiopyrimidine with various alkylcarboxylic acids or aldehydes which led to 7,8-disubstituted purines on cyclization in refluxing toluene in the presence of PPA (polyphosphoric acid).[29] The use of PPA in this case was possible because of the presence of a 6-thiophenyl substituent rather than a labile chlorine atom The use of the phenylthio group was a key feature of this strategy because it was stable enough to all required reactions and was readily activated for replacement by nucleophiles.

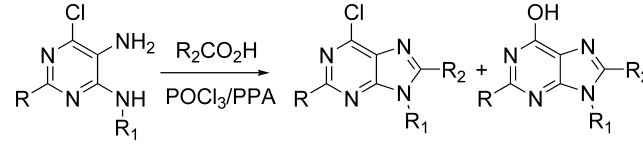
Results and Discussion

In this context, we report herein a straightforward method for the synthesis of N-9 unprotected 6-chloro-8-arylpurines **5** from 6-chloropyrimidine-4,5-diamine **4**, where the 6-chlorine atom was not hydrolyzed.

The chlorine atom at position 6 was preferred to the phenylthio group for further S_NAr and Pd catalyzed cross-coupling reactions.

Starting from diamino pyrimidine **4**,[29] we have employed several literature methods for the cyclization step. For example, using benzoic acid in PPA, 6-hydroxy-8-phenylpurine as well as an uncylized intermediate were obtained, as judged by LC-MS. Condensation with fluorobenzaldehyde in the presence of 3−4 equiv of acetic acid in methanol, gave after 72 h, a mixture of products and 70% of untransformed starting material. Two products were identified

Scheme 1. Synthesis of 6-Chloro-8-Substituted Purines (**2**)



1 R = H, Me, Ph **2** (40-78%) **3** (8-34%)

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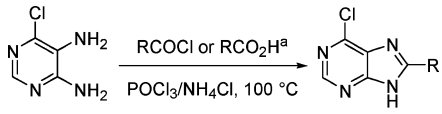
Scheme 2. Synthesis of 6-Chloro-8-Substituted Purines[a]



4 **5a-p**

product	R	Yield (%)
5a	Pyridin-3-yl	95
5b	3-bromophenyl	96
5c	3-chlorophenyl	83
5d	phenyl	80
5e	3-aminophenyl	56
5f	4-bromophenyl	80
5g	n-butyl	30[b]
5h	thiophen-3-yl	63
5i	m-tolyl	81
5j	3-benzonitrile	73
5k	naphthalen-2-yl	75
5l	(E)-styryl	84
5m	methyl	80
5n	isopropyl	45
5o	Cyclopent-3-enyl	65

[a] (a) $POCl_3$ in excess, NH_4Cl (6 equiv), 100°C, 24h; (b) 25% of starting material was recovered.

by LCMS and corresponded to the diimino- and monoimino-pyrimidine derivatives. Reaction of **4** with nicotinoyl chloride, using 6 equiv of $POCl_3$ in toluene or acetonitrile gave only traces of **5a** after 24 h, while using a large excess of $POCl_3$ gave **5a** in 30% yield. These methods thus lacked both generality, and efficacy, especially with more complex substituents at 8 such as pyridines or various halophenyls.

Interestingly, the mixture of NH_4Cl and $POCl_3$ greatly improved the rate, the yield and the purity of the resulting purines, since purine **5a** was obtained in 95% yield.

In the present method, the diaminopyrimidine **4** cyclized in refluxing $POCl_3$, in the presence of 6 equiv of NH_4Cl and 1 equiv of either carboxylic acids or carboxylic acid chlorides at 100 °C for 24 h.

We next examined the scope of this cyclization with various aryl (**5a**, **b**, **c**, **d**, **f**, **i**, **j**, **k**, **l**) and alkyl carboxylic acids or acid chlorides (**5m**) (Scheme 2).

6-Chloro-8-substituted purine derivatives were thus obtained in one step and in good yield (Scheme 2), while preserving the chlorine atom at position 6, as any hydrolyzed product is rechlorinated by the $POCl_3/NH_4Cl$ mixture.

However in some cases the 8-alkyl-purines were obtained in low yield (Scheme 2, **5g**, **5n**), along with significant amounts of uncyclized pyrimidine.

These 8-substituted purines **5** could be further functionalized at position 6 by nucleophilic substitution with various amines in ethanol, anilines in isopropanol/HCl, or in the presence of Na in pure alcohol (cyclopentanol, cyclohexylmethanol).

A diverse library of 6,8-disubstituted purines **6** was thus prepared in good yield by this methodology (Figure 1).

The chlorine atom at 6 can also undergo further palladium cross-coupling reactions to introduce other types of substituents such as amides, contrary to the phenylthio group often used to replace the labile chlorine atom at position 6 of the purine.[29] It should be noted that the palladium cross-coupling reactions of unprotected 6-chloropurine are not well explored. It is known for example that the Suzuki cross-coupling and S_NAr at position 6 may fail unless the N-9 nitrogen is suitably protected.[27,17,30]

Hocek's group showed,[17] however, that aqueous-phase Suzuki-Miyaura cross-coupling reactions of free halopurines was quite efficient in the presence of a water-soluble phosphine ligand. Gundersen's group also reported[31] Stille couplings of various aryl(tributyl)tin in DMF with N-9-unprotected 6-chloropurines. However palladium-catalyzed amidation reactions of unprotected purine have, to the best of our knowledge, never been described.

The first amidation assays with 6-chloro-8-phenylpurine **5d** and valeramide, using Pd_2dba_3/Xantphos in dioxane at 100 °C[32,33] led to a low yield (27%) of **7m** and 73% recovery of starting material after 3 days at 100 °C. Under the same conditions, a 50% yield of amidation product was obtained when the N-9 nitrogen was protected by a tetrahydropyranyl group, but several degradation products were observed.

Reaction of **5l** with benzamide using the Buchwald protocol (Pd_2dba_3/2-diterbutylphosphino-3,4,5,6 tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl ligand/ K_3PO_4/*t*-BuOH at 130 °C) for the coupling of amides with aryl chlorides[34] led to 14% of the corresponding 6-hydroxy compound as observed by LC-MS. Replacing *t*-BuOH by DMF led to extensive degradation as judged by TLC. However, the use of dioxane at 130 °C instead of *t*-BuOH gave complete conversion of **5** (Scheme 4, Figure 2) with no hydrolysis of the chlorine atom.

No protection of the N-9-nitrogen was necessary, and several amide derivatives were thus obtained in good yields (**7a**−**o**, Scheme 4, Figure 2).

Conclusion

The method reported in this paper describes a rapid synthesis of 6,8-disubstituted purines from the readily available 6-chloro-4,5-diaminopyrimidine precursor. This method allowed the introduction of various aryl, heteroaryl, alkenyl, and alkyl substituents at position 8, followed by functionalization at position 6 with various amines, ethers, thioethers, and amides. It should be noted that palladium-catalyzed amidations of 6-chloro N-9-unprotected purines are reported for the first time in the present article. Together, these methods seem particularly suitable for the synthesis of large libraries of purines with high biological potential.[35]

Experimental Section

NMR spectra were recorded at 300 MHz (^{1}H NMR) or 75.3 MHz (^{13}C NMR) with DMSO-d_6, CD_3OD, or $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard on a Bruker AC300 spectrometer. Chemical shifts are expressed in ppm (δ) downfield from TMS. *J* values are expressed in Hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet, br, broad. MS spectra were recorded on a Waters ZQ2000 mass spectrometer with direct injection. Reagents: All reactions were carried out in a sealed tube (containing a stirbar) with a screw cap, Pd_2dba_3 and ligand (2-diterbutylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl) were purchased from Sigma-Aldrich and used without further purification. K_3PO_4 was purchased from

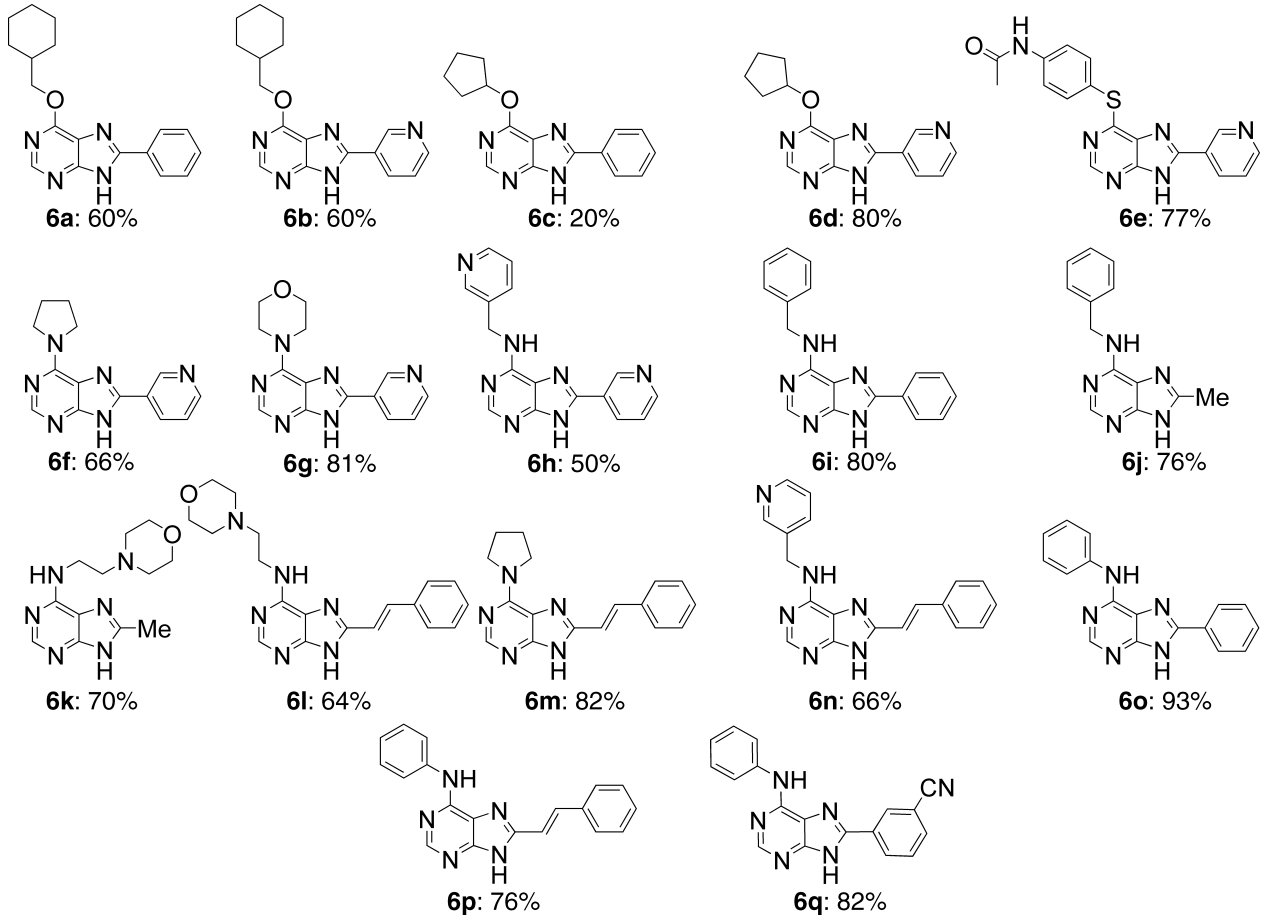
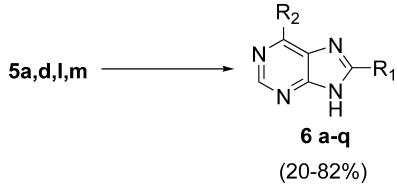


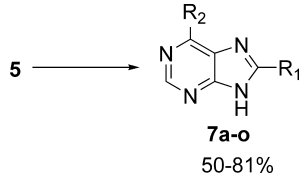
Figure 1. Library of 6,8-disubstituted purines bearing amine, ether, or thioether at position 6.

Scheme 3. Functionalization of 8-Substituted Purines at Position 6[a]



[a] See Figure 1 for R_1 and R_2: EtOH, Et_3N, or DIEA, amine, 1.1 equiv for $R_2 = -NHRa$, $-NRaRb$, or thiol, 1.1 equiv for $R_2 = -SAr$, for 24 h, 70 °C; cycloalkyl-ONa, 1−2 equiv in cycloalkyl−OH, 100 °C, 24 h for $R_2 = -O$ cycloalkyls.

Scheme 4. Direct Amidation of 8-Substituted Purines[a]



[a] See Figure 2 for R_1 and R_2: amide, 1.1 equiv, Pd_2dba_3, 3 mol %, ligand, 15 mol %, K_3PO_4, 3 equiv, 1,4-dioxane, 130 °C, 32−48 h.

Alfa Aesar and anhydrous 1,4-dioxane from SDS. Flash chromatography was performed with SDS silica gel 60 (35−70 μM) under low pressure (2−10 bar). Melting points were taken on a Kofler apparatus and are uncorrected.

General Procedure for the Synthesis of 8-Aryl/Alkyl-6-chloropurines. A mixture of 1 equiv of 6-chloro-4,5-diaminopyrimidine (**4**),[29] 1 equiv of ArCOCl/ArCOOH or alkylCOCl/alkylCOOH and 6 equiv of ammonium chloride in $POCl_3$ (4 mL/100 mg of **4**) was heated for 24 h at 100 °C. After it was cooled to room temperature, the mixture was poured into ice/water and neutralized with an ammonia solution (25%) (pH 7−8). It was extracted with EtOAc and the organic layers were combined and dried over $MgSO_4$. After evaporation under vacuum, the crude material was filtered on silica gel column in DCM/EtOH 0−5% (unless mentioned otherwise).

6-Chloro-8-pyridin-3-yl-9*H*-purine (5a). 5a was obtained as yellow solid. Yield: 95%. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.45 (s br, 1H), 9.35 (s, 1H), 8.74 (dd, $J = 3$ Hz, $J' = 6$ Hz, 1H), 8.71 (s, 1H), 8.53 (td, $J = 3$ Hz, $J' = 9$ Hz, 1H), 7.60 (q, $J = 3$ Hz, $J' = 6$ Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 154.1, 153.6, 153.3, 149.8, 136.3, 126.2, 125.7. MS (Electrospray) *m*/*z* (%): 232.2 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{10}H_7ClN_5$ $[MH^+]$: 232.0390; found 232.0387.

8-(3-Bromo-phenyl)-6-chloro-9*H*-purine (5b). The product was obtained as a beige solid in 96% yield. mp: >260 °C.^{1}H NMR (DMSO-d_6): δ 8.75 (s, 1H), 8.45 (s, 1H), 8.27 (d, $J = 9$ Hz, 1H), 7.82 (dd, $J = 9$ Hz, 1H), 7.58 (t, $J = 6$ Hz, $J' = 9$ Hz). ^{13}C NMR (DMSO-d_6): δ 152.1, 134.6, 131.8, 131.0, 130.1, 126.7; 122.7 (1C). MS (Electrospray) *m*/*z* (%): 231.8 (100) $[M - Br]^+$; 309.0 (300) $[M + H]^+$. Anal. Calcd for $C_{11}H_6BrClN_4$: C, 42.68; H, 1.95; N, 18.10; found C, 42.71; H, 1.84; N, 17.76.

6-Chloro-8-(3-chloro-phenyl)-9*H*-purine (5c). The product was isolated as a white solid in 83% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.4 (s br, 1H), 8.74 (s, 1H),

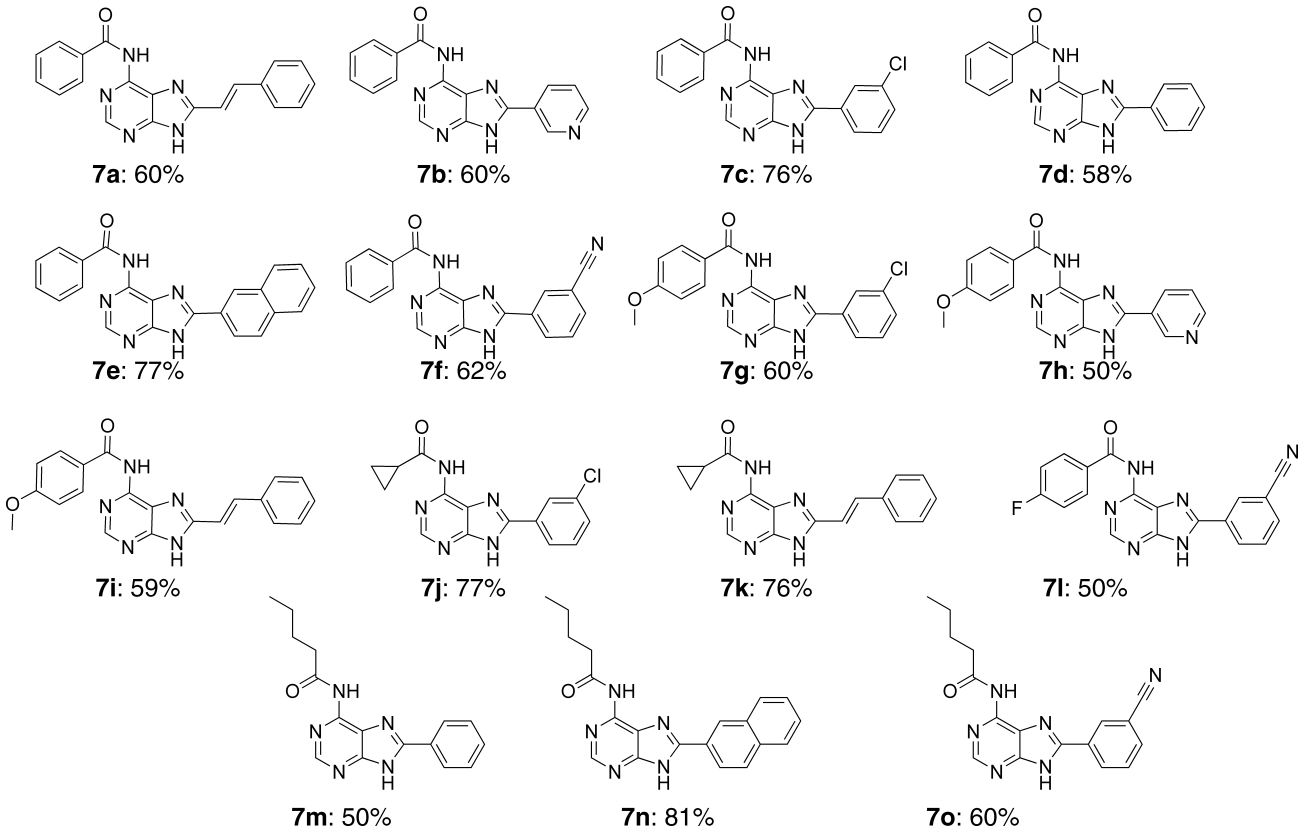


Figure 2. Library of 8-substituted-6-amidopurines.

8.29 (s, 1H), 8.22 (td, $J = 6$ Hz, 1H), 7.67 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 153.6, 135.8, 133.2, 133.0, 132.3, 128.8, 127.9. MS (Electrospray) *m/z* (%): 265.2 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{11}H_7N_4Cl_2$ [MH$^+$]: 265.0048; found 265.0057.

6-Chloro-8-phenyl-9*H*-purine (5d). A mixture of **4** (50 mg, 0.35 mmol), benzoic acid (39 mg, 0.32 mmol), and ammonium chloride (112 mg, 2.1 mmol) was stirred at 100 °C in $POCl_3$ for 24 h. Product **5d** (70 mg) was isolated as a white solid in 80% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 8.73 (s, 1H), 8.29 (m, 2H), 7.62 (t, $J = 3$ Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 151.8, 132.0, 129.6, 128.8, 127.8. MS (Electrospray) *m/z* (%): 231.2 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{11}H_8N_4Cl$ [MH$^+$]: 231.0437; found 231.0432.

3-(6-Chloro-9*H*-purin-8-yl)-phenylamine (5e). 5e was obtained as a yellow-white solid in 56% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 8.69 (s, 1H), 7.55 (s, 1H), 7.36 (d, $J = 9$ Hz, 1H), 7.22 (t, $J = 9$ H, $J' = 6$ Hz, 1H), 6.78 (d, $J = 6$ Hz, 1H), 5.45 (s br, 2H). ^{13}C NMR (DMSO-d_6) δ 154.9, 154.0, 150.8, 149.0, 147.0, 131.4, 129.3, 128.5, 116.8, 114.3, 111.9. MS (Electrospray) *m/z* (%): 246.2 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{11}H_9N_5Cl$ [MH$^+$]: 246.0546; found 246.0539.

8-(4-Bromo-phenyl)-6-chloro-9*H*-purine (5f). 5f was isolated as a beige solid in 80% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.40 (s, 1H), 8.74 (s, 1H), 8.21 (d, $J = 9$ Hz, 2 H), 7.82 (d, $J = 9$ Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 152.0, 132.6, 129.6, 128.0, 125.7. MS (Electrospray) *m/z* (%): 309.1 (100) [M + H]$^+$; HRMS (ESI) calcd for $C_{11}H_7N_4ClBr$ [MH$^+$]: 308.9543; found 308.9542.

8-Butyl-6-chloro-9*H*-purine (5g). 5g was obtained as a white solid in 30% yield. mp: 233−235 °C. ^{1}H NMR (DMSO-d_6): δ 13.67 (s br, 1H), 8.69 (s, 1H), 1.45 (s, 9 H). ^{13}C NMR (DMSO-d_6): δ 168.2, 156.5, 153.2, 149.4, 132.6, 36.2, 30.8. MS (Electrospray) *m/z* (%): 233.2 (100) [M + Na]$^+$, 274.2 (80) [M + Na + MeCN]$^+$, 211.2 (20%) [M + H]$^+$. HRMS (ESI) calcd for $C_9H_{12}N_4Cl$: 211.0750 [MH$^+$]; found 211.0753.

6-Chloro-8-thiophen-3-yl-9*H*-purine (5h). 5h was obtained as a yellow solid in 63% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.40 (s br, 1H), 8.69 (s, 1H), 8.05 (s, 1H), 7.93 (d, $J = 6$ Hz, 1H), 7.31 (dd, $J = 3$ Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 149.4; 129.7; 129.6; 127.9; 126.8. MS (Electrospray) *m/z* (%): 259.1 (100) [M + Na]$^+$; 237.1 (20) [M + H]$^+$. HRMS (ESI) calcd for $C_9H_{16}N_4SCl$ [MH$^+$]: 237.0002; found 236.9994.

6-Chloro-8-*m*-tolyl-9*H*-purine (5i). Compound **5i** was isolated as a white solid in 81% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.20 (s br, 1H), 8.67 (s, 1H), 8.07 (s, 1H), 8.00 (d, $J = 9$H, 1H), 7.42 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 155.2, 151.7, 138.9, 132.6, 129.4, 128.6, 128.2, 124.9, 21.3. MS (Electrospray) *m/z* (%): 243.2 (100) [M − H]$^-$. HRMS (ESI) calcd for $C_{12}H_{10}N_4Cl$ [MH$^+$]: 245.0594; found 245.0599.

3-(6-Chloro-9*H*-purin-8-yl)-benzonitrile (5j). 5j was obtained as a yellow solid in 73% yield. mp: 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 14.24 (s br, 1H), 8.56 (s, 1H), 8.40 (s, 1H), 8.34 (d, $J = 6$ Hz, 1H), 7.87 (d, $J = 3$ Hz, 1H), 7.62 (t, $J = 6$ Hz, $J' = 9$ Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 153.0, 152.2, 135.1, 132.1, 131.4, 131.0, 130.9, 129.9, 118.4, 112.7; MS (Electrospray) *m/z* (%): 256.2 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{12}H_7N_5Cl$ [MH$^+$]: 256.0390; found 256.0393.

6-Chloro-8-naphtalen-2-yl-9*H*-purine (5k). 5k was obtained as a white solid in 75% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.53 (s br, 1H), 8.99 (s, 1H), 8.84 (s, 1H), 8.45 (dd, J = 9 Hz, 1H), 8.42−8.18 (m, 2H), 8.13−8.10 (m, 1H), 7.74 (t, J = 3 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 151.8, 134.5, 132.9, 129.2, 128.4, 128.2, 128.1, 127.6, 126.1, 124.2; M (Electrospray) *m*/*z* (%): 303.0 (100) $[M + Na]^+$; 343.9 (80) $[M + Na + MeCN]^+$; 281.0 (50) $[M + H]^+$. Anal. Calcd for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; N, 19.96; found C, 64.17; H, 3.11; N, 19.66.

6-Chloro-8-styryl-9*H*-purine (5l). A mixture of **4** (100 mg, 0.7 mmol), *trans*-cinnamic acid (100 mg, 0.7 mmol), and ammonium chloride (224 mg, 4.2 mmol), was stirred at 100 °C for 24 h in $POCl_3$ (5 mL). The mixture was cooled, poured onto ice, and neutralized with ammonia (25% in water), and the product precipitated. It was filtered, washed with water, and dried in the desiccator under vacuum. **5l** was obtained as a beige solid in 84% yield. mp: 240−242 °C.^{1}H NMR (DMSO-d_6): δ 8.67 (s, 1H), 7.93 (d, J = 18 Hz, 1H), 7.72 (d, J = 6 Hz, 2H), 7.47 (m, 3H), 7.30 (d, J = 15 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 155.5, 155.3, 151.6, 146.6, 139.0, 135.4, 130.1, 129.4, 127.9, 116.8. MS (Electrospray) *m*/*z* (%): 357.2 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{13}H_{10}N_4Cl$ $[MH^+]$: 257.0594; found 257.0592.

6-Chloro-8-methyl-9*H*-purine (5m). 5m was isolated as a white solid in 80% yield. mp: 226−228 °C. ^{1}H NMR (DMSO-d_6): δ 13.63 (s br, 1H), 8.63 (s, 1H), 2.58 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 156.8, 151.2, 15.5. MS (Electrospray) *m*/*z* %: 169.1 (100) $[M + H]^+$, 191.1 (50) $[M + Na]^+$, 232.1 (40) $[M + Na + MeCN]^+$. Anal. Calcd for $C_6H_5ClN_4$: C, 42.75; H, 2.99; N, 33.23; found C, 42.85; H, 2.94; N, 33.15.

6-Chloro-8-isopropyl-9*H*-purine (5n). 5n was obtained as a white solid in 45% yield. mp = 172−174 °C. ^{1}H NMR (DMSO-d_6): δ 13.60 (s br, 1H), 8.65 (s, 1H), 3.20 (H, J = 6 Hz, 1H), 1.36 (d, J = 6 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 164.5, 154.4, 151.6, 147.9, 141.0, 131.5, 29.6, 21.5. MS (Electrospray) *m*/*z* (%): 219.1 (100) $[M + Na]^+$, 260.1 (70) $[M + Na + MeCN]^+$, 197.2 (20) $[M + H]^+$. Anal. Calcd for $C_8H_9ClN_4$: C, 48.86; H, 4.61; N, 28.49; found C, 48.79; H, 4.63; N, 28.37.

6-Chloro-8-cyclopent-3-enyl-9*H*-purine (5o). 5o was obtained as white crystals in 65% yield. mp: 200−202 °C. ^{1}H NMR (DMSO-d_6): δ 13.71 (s br, 1H), 8.67 (s, 1H), 5.80 (s, 2H), 3.78 (m, 1H); 2.82 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 162.8, 154.4, 151.2, 129.5, 38.9 38.1, 37.3. MS (Electrospray) *m*/*z*: 243.1 (100) $[M + Na]^+$, 284.1 (90) $[M + Na + MeCN]^+$, 221.2 (30) $[M + H]^+$. HRMS (ESI) calcd for $C_{10}H_{10}ClN_4$ $[MH^+]$: 221.0594; found 221.0592. Anal. Calcd for $C_{10}H_9ClN_4$: C, 54.43; H, 4.11; N, 25.39; found C, 54.44; H, 4.12; N, 25.18.

General Procedure for S_NAr Reactions with Alcohols. The required alkoxide was generated in situ, by dissolving sodium (1−2 equiv) in the appropriate alcohol before addition of the purine derivative **5** (3 equiv) and heating at 100 °C with stirring for the indicated time. The solvent was then evaporated under vacuum and the crude material was purified as indicated. The product crystallized from the indicated solvent.

6-Cyclohexylmethoxy-8-phenyl-9*H*-purine (6a). After 4 h of reaction and workup, **6a** crystallized from heptane/EtOAc as a white solid in 60% yield. mp: 236−238 °C. ^{1}H NMR (DMSO-d_6): δ 13.70 (s, 1H), 8.38 (s, 1H), 8.12 (m, 2H), 7.46 (m, 3H), 4.27 (d, J = 6.18 Hz, 2H), 1.78−1.56 (6H), 1.16−0.97 (5H).^{13}C NMR (DMSO-d_6): δ 151.7, 131.0, 129.6, 129.4, 127.2, 71.5, 37.2, 29.5, 26.3, 25.5. MS (electrospray) *m*/*z* (%): 309.3 (100) $[M + H]^+$, 331.3 (50) $[M + Na]^+$. Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17; found C, 69.77; H, 6.56; N,18.1.

6-Cyclohexylmethoxy-8-pyridin-3-yl-9*H*-purine (6b). The mixture was stirred overnight at 100 °C. The solvent was removed by evaporation and the product was triturated in water, filtered and dried in a desiccator in 60% yield as a white solid. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.01 (s br, 1H), 9.36 (s br, 1H), 8.71 (d, J = 3 Hz,1H), 8.55−8.50 (2H), 7.60 (dd, J = 3 Hz, J' = 6 Hz, 1H), 4.39 (d, J = 6 Hz, 2 H), 1.78 (m, 2 H), 1.17 (m, 3 H), 1.23−1.10 (m, 6H). ^{13}C NMR (DMSO-d_6): δ 151.8, 151.4, 148.1, 134.5, 126.0, 124.3, 71.6, 37.1, 29.6, 26.3, 25.5. MS (Electrospray) *m*/*z* (%): 214.2 $[M -$ cyclohexyl$]^+$; 310.3 (90) $[M + H]^+$. ES^-: 308.3 (100) $[M- H]^-$. HRMS (ESI) calcd for $C_{17}H_{19}N_5ONa$ $[MNa^+]$: 332.1487; found 332.1487.

6-Cyclopentyloxy-8-phenyl-9*H*-purine (6c). The mixture was stirred for 24 h at 100 °C. The product was purified by chromatography on Al_2O_3 column using cyclohexane/EtOAc 10% as eluent in 20% yield. A white solid was obtained. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.78 (s, 1H), 8.47 (s, 1H), 8.20 (m, 2H), 7.54 (m, 3H), 5.69 (s,1H), 2.03−1.64 (8H). ^{13}C NMR (DMSO-d_6): δ 151.7, 130.9, 129.6, 129.4, 127.1, 79.1, 32.8, 23.9. MS (Electrospray) *m*/*z* (%): 281.2 (100) $[M + H]^+$; 213.2 (40) $[M -$ cyclopentane $+ H]^+$. HRMS (ESI) calcd for $C_{16}H_{16}N_4ONa$ $[MNa^+]$: 303.1222; found 303.1219.

6-Cyclopentyloxy-8-pyridin-3-yl-9*H*-purine (6d). After 12 h of reaction, the solvent was removed under vacuum, and the crude material was then extracted with EtOAc in the presence of water. **6d** was obtained as a white solid in 80% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.89 (1H, NH9), 9.35 (s, 1H), 8.70 (d, J = 3 Hz, 1H), 8.52 (d + s, 2H), 7.59 (dd, $J = J'$ = 6 Hz, 1H), 5.69 (m, 1H), 2.04−1.68 (m, 8H). ^{13}C NMR (DMSO-d_6): δ 151.0, 150.5, 147.0, 133.5, 124.7, 123.3, 78.2, 31.8, 22.9. MS (Electrospray) *m*/*z* (%): ES^+: 214.2 (100) $[M -$ cyclopentyl$]^+$; 304.2(50) $[M + Na]^+$; 282.3 (40) $[M + H]^+$. ES^-: 280.3 (100) $[M - H]^-$. HRMS (ESI) calcd for $C_{15}H_{15}N_5ONa$ $[MNa^+]$: 304.1174; found 304.1171.

***N*-[4-[8-Pyridin-3-yl-9*H*-purin-6-ylsulfanyl)-phenyl]-acetamide (6e).** A mixture of **5a** (150 mg, 0.65 mmol), 1-(4-mercaptophenyl)ethanone (114 mg, 0.75 mmol), and of DIEA (100.6 mg, 0.78 mmol) was heated at 70 °C for 2 h. After the mixture was cooled, the product precipitated in the reaction mixture. It was filtered and dried in a desiccator. **6e** was obtained as a yellow powder in 77% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.2 (s br, 1H), 10.20 (s, 1H), 9.37 (s, 1H), 8.75 (dd, J = 1.2 Hz, J' = 6 Hz, 1H), 8.54 (m, 2H, H2 and HPyr), 7.72 (d, J = 9 Hz, 2H), 7.66 (dd, 1H, J = 6 Hz, J' = 3 Hz, 1H), 7.60 (d, J = 9 Hz, 2H), 2.09 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ 168.1, 151.4, 151.0,

147.4, 140.1, 135.9, 133.9, 124.5, 123.6, 119.2, 119.1, 23.6. MS (Electrospray) *m/z* (%): 361.2 (100) $[M - H]^-$. HRMS calcd for $C_{18}H_{14}N_6ONaS$ $[MNa^+]$: 385.0848; found 385.0849.

General Procedure for S_NAr Reactions with Amines. A mixture of the purine derivative **5** (1 equiv), the appropriate amine (1−2 equiv), and Et_3N or DIEA (1−2 equiv) in ethanol was heated at 70 °C for the indicated time. Upon cooling the product precipitated (unless otherwise mentioned). It was filtered, washed with water and heptane, and dried in a desiccator at 50 °C.

8-Pyridin-3-yl-6-pyrrolidin-1-yl-9*H*-purine (6f). A mixture of **5a** (80 mg, 0.346 mmol), pyrrolidine (30 mg, 0.42 mmol), and Et_3N (43 mg, 0.42 mmol) in EtOH (4 mL) was heated at 70 °C for two hours. The reaction mixture was cooled to room temperature, and the product precipitated in the reaction mixture. It was then filtered and washed with ether to give **6f** as a white solid. Yield: 66%. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.57 (s br, 1H), 9.30 (d, $J = 3$ Hz, 1H), 8.66 (d, $J = 3$ Hz, 1H), 8.44 (d, $J = 9$ Hz, 1 H,), 8.21 (s, 1H), 7.54 (q, $J = 6$ Hz, $J' = 3$ Hz, 1H), 4.16 (s, 2H), 3.70 (s, 2H), 1.99 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 152.9, 152.6, 152.5, 147.4, 145.3, 133.6, 126.2, 124.3, 120.8, (the carbons of pyrrolidine are hidden under the pic of DMSO-d_6). MS (Electrospray) *m/z* (%): 267.2 (100) $[M + H]^+$; 289.2 (70) $[M + Na]^+$; 330 (30) $[M + Na + MeCN]^+$. Anal. Calcd for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.56; found C, 63.18; H, 5.34; N, 31.96.

6-Morpholin-4-yl-8-pyridin-3-yl-9*H*-purine (6g). Synthesized from **5a** according to the general procedure, **6g** was obtained as a white solid in 81% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.76 (s br, 1H), 9.31 (d, $J = 1.8$ Hz, 1H), 8.67 (dd, $J = 3$ Hz, $J' = 6$ Hz, 1H), 8.46 (td, $J = 3$ Hz, $J' = 9$ Hz, 1H), 8.27 (s, 1H), 7.57 (q, $J = 3$ Hz, 1H), 4.27 (s, 4H), 3.76 (t, $J = 6$ Hz, 4H). ^{13}C NMR (DMSO-d_6): δ 151.9, 151.8, 151.0, 149.5, 146.2, 143.9, 132.4, 124.4, 122.9, 118.9, 65.1, 44.2. MS (Electrospray) *m/z* (%): 283.2 (100) $[M + H]^+$; 305.2 (40) $[M + Na]^+$. Anal. Calcd for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77; found C, 59.32; H, 5.11; N, 29.81.

Pyridin-3-ylmethyl-(8-pyridin-3-yl-9*H*-purin-6-yl)-amine (6h). According to the general procedure from **5a**, **6h** was obtained as a white solid in 50% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.79 (s br,1H), 9.44 (s, 1H), 8.80 (d, $J = 3$ Hz,1H), 8.74 (s, 1H, H Pyr 6), 8.57 (m, 2H, H Pyr 8 and 6), 8.36 (s, 1H, H2), 7.90 (d, $J = 9$ Hz, 1H, H pyr 6), 7.71 (dd, $J = J' = 6$ Hz, 1H, H pyr8), 7.45 (dd, $J = 3$ Hz, $J' = 6$ Hz, 1H, H Pyr 6), 4.87 (s, 2H), 3.47 (s br, 1H). ^{13}C NMR (DMSO-d_6): δ 154.3, 153.2, 150.9, 149.4, 148.4, 147.7, 146.4, 136.0, 135.6, 133.8, 126.3, 124.5, 123.9, 106.9, 39.0. MS (Electrospray) *m/z* (%): ES^+ 304.2 (100) $[M + H]^+$; 326.2 (70) $[M + Na]^+$. ES^-: 302.3 (100) $[M - H]^-$. HRMS (ESI) calcd for $C_{16}H_{13}N_7$ $[MH^+]$: 304.1311; found 304.1310.

Benzyl-(8-phenyl-9*H*-purin-6-yl)-amine (6i). From **5d**, according to the general procedure, **6i** was obtained as a white solid in 80% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.74 (s br, 1H), 8.67 (s, 1H), 8.25 (m, 3H), 7.64 (m, 7H), 4.87 (m, 3H). ^{13}C NMR (DMSO-d_6): δ 153.2, 151.4, 139.9, 130.6, 129.7, 129.4, 128.6, 127.7, 127.2, 126.6, 43.5. MS (Electrospray) *m/z* (%): 302.1 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{16}N_5$ $[MH^+]$: 302.1406; found: 302.1417.

Benzyl-(8-methyl-9*H*-purin-6-yl)-amine (6j). From **5n**, according to the general procedure, **6j** was obtained as a pink solid in 76% yield; mp >260 °C; ^{1}H NMR (DMSO-d_6): δ 8.12 (s, H), 8.07 (s br, 1H), 7.30 (m, 5H), 4.71 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 151.9, 140.8, 128.7, 128.5, 128.3, 127.5, 126.9, 43.3, 15.0. MS (Electrospray) *m/z* (%): 240.2 (100) $[M + H]^+$. HRMS (ESI) calcd. for $C_{13}H_{14}N_5$ $[MH^+]$: 240.1249; found 240.1247.

(8-Methyl-9*H*-purin-6-yl)-(2-morpholin-4-yl-ethyl)-amine (6k). From **5n**, according to the general procedure, **6k** was obtained as a yellow solid after trituration in water in 70% yield. mp: 251−253 °C. ^{1}H NMR (DMSO-d_6): δ 12.67 (s, br, 1H), 8.15 (s, 1H), 7.28 (s br, 1H), 3.60 (s, 7H), 2.48 (s, 8H). ^{13}C NMR (DMSO-d_6): δ 153.7; 151.9; 148.1; 119.1; 66.5; 57.8; 53.7; 15.0. MS (electrospray) *m/z* (%): 263.2 (100) $[M + H]^+$. Anal. Calcd for $C_{12}H_{18}N_6O.1/3\ H_2O$: C, 53.72; H, 7.01; N, 31.32; found C, 54.03; H, 6.99; N, 31.01.

(2-Morpholin-4-yl-ethyl)-(8-styryl-9*H*-purin-6-yl)-amine (6l). From **5m**, according to the general procedure, **6l** was obtained in 64% yield (white solid). mp: 232−234 °C. ^{1}H NMR (DMSO-d_6): 13.02 (s br, 1H), 8.06 (s, 1H), 7.50 (m, 3H), 7.27 (m, 3H), 7.00 (d, $J = 18$ Hz, 1H), 3.46 (m, 5H), 2.44 (t, $J = 6$ Hz, $J' = 9$ Hz, 2 H), 2.32 (s br, 4H); 1.97 (s, 2 H). ^{13}C NMR (DMSO-d_6): 153.9, 152.6, 147.7, 139.0, 135.6, 134.0, 129.0, 128.9, 126.9, 117.4, 66.2, 53.3, 30.7. MS (Electrospray) *m/z* (%): 351.1 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{22}N_6O$: C, 65.12; H, 6.33; N, 23.98; found C, 65.01; H, 6.23; N, 23.96.

6-Pyrrolidin-1-yl-8-styryl-9*H*-purine (6m). From **5m**, according to the general procedure, **6m** was obtained in 82% yield (white solid). mp: >260 °C. ^{1}H NMR (DMSO-d_6): 13.01 (s, 1H), 8.04 (s, 1H), 7.50 (m, 3H), 7.27 (m, 3H), 7.03 (d, $J = 18$ Hz, 1H), 3.96 (s br, 2H), 3.52 (s br, 2H), 1.83 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 152.7, 152.3, 152.1, 147.6, 136.1, 134.0, 129.3, 129.0, 129.3, 120.8, 118.1. MS (Electrospray) *m/z* (%): 292.1 (100) $[M + H]^+$. Anal. Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04; found C, 70.08; H, 5.76; N, 24.12.

Pyridin-3-ylmethyl-(8-styryl-9*H*-purin-6yl)-amine (6n). From **5m**, according to the general procedure, **6n** was obtained in 66% yield (beige solid). mp: 236−238 °C. ^{1}H NMR (DMSO-d_6): δ 13.19 (s, 1H), 8.59 (s, 1H), 8.42 (d, $J = 3$ Hz), 8.35 (s br, 1H), 8.17 (s, 1H), 7.75 (d, $J = 3$ Hz, 1H), 7.61 (m, 3 H), 7.38 (m, 4 H), 7.12 (d, $J = 18$ Hz, 1H), 4.73 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 153.9, 152.9, 149.3, 148.4, 148.3, 136.0, 135.9, 135.4, 134.6, 129.4, 129.3, 127.3, 123.8, 117.7, 40.0. Anal. Calcd for $C_{19}H_{16}N_6$: C, 69.5; H, 4.91; N, 25.59; found C, 68.91; H, 4.87; N, 25.47.

General Procedure for SNAr Reactions with Anilines. A mixture of the purine derivative **5** (1 equiv), aniline (1.36 equiv), and concentrated HCl (1 drop) in isopropanol (1−2 mL) was stirred for 2−3 h under reflux. Upon cooling, the solid precipitated, and the suspension was then diluted with a bicarbonate solution. The precipitate was then filtered, dried in a desiccator at 50 °C, and then crystallized from EtOAc.

***N*,8-Diphenyl-9*H*-purin-6-amine (6o).** From **5d**, according to the general procedure, **6o** was obtained as a yellow solid in 93% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.67 (s br, 1H), 9.80 (s, 1H), 8.40 (s, 1H), 8.23 (d, $J = 6$ Hz, 2H), 8.00 (d, $J = 9$ Hz, 2H), 7.56 (m, 3H), 7.35 (t, $J = 6$ Hz, $J' = 9$ Hz, 3H), 7.05 (t, $J = 6$ Hz, $J' = 9$ Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 151.9, 149.6, 139.4, 130.4, 129.7, 129.2, 128.6, 126.7, 122.6, 120.8. MS (electrospray) *m*/*z* (%): 310.0 (100) $[M + H]^+$; 288.1 (50) $[M + Na]^+$; 351.0 (40) $[M + MeCN + Na]^+$. Anal. Calcd for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; 24.37; found C, 69.93; H, 4.31; N, 24.9.

(*E*)-*N*-Phenyl-8-styryl-9*H*-purin-6-ylamine (6p). From **5m**, according to the general procedure, **6p** was obtained in 76% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.01 (s br, 1H), 9.81 (s, 1H), 8.37 (s, 1H), 7.98 (d, $J = 6$ Hz), 7.65 (m, 3H), 7.46 (m, 1H), 7.17 (d, $J = 18$ Hz), 7.03 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ 152.3, 149.3, 140.3, 135.8, 135.5, 129.5, 129.4, 128.7, 127.4, 122.6, 120.8, 117.4. MS (Electrospray) *m*/*z* (%): 314.1 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{15}N_5$: C, 72.83; H, 4.82; N, 22.35; found C, 72.39; H, 4.77; N, 22.31.

3-(6-(Phenylamino)-9*H*-purin-8-yl)benzonitrile (6q). From **5k**, according to the general procedure, **6q** was obtained in 82% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.81 (s br, 1H), 9.82 (s, 1H), 8.60−8.40 (m,3H) 7.98 (d, $J = 6$ Hz, 3H), 7.80 (t, $J = 6$ Hz, 1H), 7.35 (s, 2H), 7.05 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 153.8, 148.7, 141.1, 134.8, 132.3, 132.2, 131.9, 131.4, 129.9, 124.0, 122.2, 119.8, 113.7. MS (Electrospray) *m*/*z* (%): 313.1 (100) $[M + H]^+$. Anal. Calcd for $C_{18}H_{12}N_6$: C, 69.22; H, 3.87; N, 26.91; found: C, 68.68; H, 3.76; N, 26.91.

General Procedure for Amidation Reactions. An oven-dried Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd_2dba_3 (3 mol %), ligand (15 mol %), amide (1.1 equiv), purine **5** (1 equiv), and K_3PO_4 (3 equiv). The Schlenk tube was capped with a rubber septum, evacuated, and backfilled with argon, and then 2 mL of anhydrous degassed dioxane was added. The septum was replaced with a screw cap, and the mixture was heated at 130 °C, with stirring for 24 h. The reaction was not complete and the Schlenk tube was cooled to rt, opened, and charged again with Pd_2dba_3 (0−3 mol %) and ligand (0−15 mol %). It was evacuated and backfilled again with argon, and the mixture was heated at 130 °C with stirring for 8−24 additional hours. The reaction was allowed to cool at room temperature, diluted with ethanol and ethyl acetate, and directly adsorbed onto silica gel, for purification by column chromatography on silica gel (eluting with DCM/EtOH 100/0−95/5%).

(*E*)-*N*-(8-Styryl-9*H*-purin-6-yl)benzamide (7a). Intermediate **5l** (50 mg, 0.19 mmol) was treated with benzamide (26 mg, 0.21 mmol), using the general procedure as above for 32 h. After general workup, **7a** crystallized as a yellow solid in 60% yield. mp: 140−142 °C. ^{1}H NMR (CD_3OD): δ 8.66 (s, 1H), 8.13 (d, $J = 6$ Hz, 1H), 7.94 (d, $J = 15$ Hz, 1H), 5.61 (m, 5H), 7.36 (m, 4H). ^{13}C NMR (CD_3OD): δ 169.3, 153.6, 142.0, 137.3, 134.7, 131.6, 130.7, 130.4, 130.0, 129.4, 116.6. MS (electrospray) *m*/*z* (%): 364.0 (100) $[M + Na]^+$; 342.2 (20) $[M + H]^+$. HRMS (ESI) calcd for $C_{20}H_{15}N_5ONa$ $[MNa^+]$: 364.1174; found 364.1183.

***N*-(8-Pyridin-3-yl)-9*H*-purin-6-yl)benzamide (7b).** 6-Chloro-8-(pyridin-3-yl)-9*H*-purine **5a** (50 mg, 0.215 mmol) was treated with benzamide (26.6 mg, 0.22 mmol) for 36 h according to the general procedure. After workup, **7b** was isolated as off white solid and could be crystallized from EtOAc in 60% yield. mp >260 °C. ^{1}H NMR (DMSO-d_6): δ 12.79 (NH9/NH7), 11.45 (s br, 1H), 9.41 (s, 1H), 8.77 (s, 2H), 8.58 (d, $J = 3$ Hz, 1H), 8.12 (d, $J = 9$ Hz, 2H), 7.62 (m, 4H). MS (Electrospray) *m*/*z* (%): 339.0 (100) $[M + Na]^+$; 380.0 (60) $[M + Na + MeCN]^+$. HRMS (ESI) calcd for $C_{17}H_{12}N_6ONa$ $[MNa^+]$: 339.0970; found 339.0972.

***N*-(8-(3-Chlorophenyl)-9*H*-purin-6-yl)benzamide (7c).** 6-Chloro-8-(3-chlorophenyl)-9*H*-purine **5c** (50 mg, 0.19 mmol) was treated with benzamide (25 mg, 0.21 mmol) for 36 h according to the general procedure. After workup, **7c** was isolated as a white solid and crystallized from EtOAc in 76% yield. mp: 209−211 °C. ^{1}H NMR (DMSO-d_6): δ 14.02−12.62 (NH9/NH7 isomers = 3/7), 11.53 (NH conformers = 7/3), 8.77 (s, 1H), 8.24 (m, 4H), 7.62 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 150.8, 140.5, 132.8, 131.7, 130.1, 127.7, 127.5, 126.0. MS (Electrospray) *m*/*z* (%): 371.9 (100) $[M + Na]^+$; 412.9 (60) $[M + MeCN + Na]^+$. Anal. Calcd for $C_{18}H_{12}ClN_5O.1/3\ H_2O$: C, 60.77; H, 3.59; N, 19.68; found C, 60.87; H, 3.57; N, 19.67.

***N*-(8-Phenyl-9*H*-purin-6-yl)benzamide (7d).** 6-Chloro-8-phenyl-9*H*-purine **5d** (50 mg, 0.217 mmol) was treated with benzamide (29 mg, 0.24 mmol) for 42 h according to the general procedure. Compound **7d** crystallized from EtOAc in 58% yield. mp: 239−241 °C. ^{1}H NMR (DMSO-d_6): δ 13.90−12.50 (NH9/NH7 isomers = 1/6), 11.48−11.10 (NH conformers 7/3), 8.77 (1H), 8.17 (m, 4H), 7.62 (m, 6H). ^{13}C NMR (DMSO-d_6): δ 166.0, 162.6, 155.2, 151.9, 144.5, 133.3, 133.0, 131.8, 131.3, 129.4, 129.0, 128.8, 128.0, 127.4, 118.0. MS (Electrospray) *m*/*z* (%): 316.0 (100) $[M + H]^+$; 338.0 (30) $[M + Na]^+$; Anal. Calcd for $C_{18}H_{13}N_5O$: C, 68.56; H, 4.16; N, 22.21; found C, 68.07; H, 4.12; N, 22.04.

***N*-(8-(Naphthalen-2-yl)-9*H*-purin-6-yl)benzamide (7e).** 6-Chloro-8-(naphtalen-2-yl)-9*H*-purine **5k** (60 mg, 0.213 mmol) was treated with benzamide (28 mg, 0.23 mmol) for 48 h according to the general procedure. It crystallized from EtOAc (white solid) in 77% yield. mp: 231−233 °C. ^{1}H NMR (DMSO-d_6): δ 12.60 (s, 1H, NH), 11.50−11.10 (NH conformers), 8.92 (s, 1H), 8.79 (s, 1H), 8.37 (3, 1H), 8.13 (m, 5H), 7.62 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 166.6, 162.7, 155.3, 152.0, 144.5, 134.5, 133.4, 132.9, 129.0, 128.8, 128.2, 127.5, 126.4, 124.6, 118.2. MS (Electrospray) *m*/*z* (%): 366.0 (100) $[M + H]^+$, 388.0 (70) $[M + Na]^+$, 429.0 (40) $[M + MeCN + Na]^+$. HRMS (ESI) calcd for $C_{22}H_{16}N_5O$ $[MH^+]$: 366.1355; found 366.1366.

***N*-(8-(3-Cyanophenyl)-9*H*-purin-6-yl)benzamide (7f).** 3-(6-Chloro-9H-purin-8-yl)benzonitrile **5j** (50 mg, 0.2) was treated with benzamide (30 mg, 0.24 mmol) for 36 h, according to the general procedure. **7f** crystallized from EtOAc (white solid) in 62% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 14.11−12.67 (NH9/NH7 isomers= 3/7), 11.59−11.20 (NH conformers= 7/3), 8.70 (m, 3H), 8.07−7.60 (7 H). ^{13}C NMR (DMSO-d_6): δ 166.3, 152.9, 151.9, 134.6, 132.8, 132.4,

130.5, 129.9, 128.7, 128.5, 118.2, 112.2. MS (Electrospray) *m/z* (%): 404.0 (100) [M + Na + MeCN]$^+$; 362.9 (70) [M + Na]$^+$. HRMS (ESI) calcd for $C_{19}H_{11}N_6O$ [M$^-$]: 339.0994; found 339.0999.

***N*-(8-(3-Chlorophenyl)-9*H*-purin-6-yl)-4-methoxybenzamide (7g).** 6-Chloro-8-(3-chlorophenyl)-9*H*-purine **5c** (50 mg, 0.19 mmol) was treated with 4-methoxybenzamide (31 mg, 0.2 mmol) for 36 h according to the general procedure. Compound **7g** crystallized from EtOAc (white solid) in 60% yield. mp: 213−215 °C. ^{1}H NMR (DMSO-d_6): δ 13.98−12.55 (NH9/NH7 isomers = 3/7), 11.35−10.97 (NH conformers= 7/3), 8.73 (s, 1H), 8.23 (m, 4H), 7.63 (m, 2H), 7.10 (d, J = 9 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 163.1, 157.4, 152.2, 134.2, 131.4, 131.1, 114.1, 109.5, 108.1, 55.9. MS (Electrospray) *m/z* (%): 401.9 (100) [M + Na]$^+$; 417.9 (60) [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{13}N_5O_2Cl$ [MH$^+$]: 380.0914; found 380.0927.

4-Methoxy-*N*-(8-(pyridin-3-yl)-9*H*-purin-6-yl)benzamide (7h). 6-Chloro-8-(Pyridin-3-yl)-9*H*-purine **5a** (50 mg, 0.215 mmol) was treated with 4-methoxybenzamide (33 mg, 0.22 mmol) for 36 h, according to the general procedure. Compound **7h** crystallized from EtOAc in 50% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 12.79 (s, br, NH9/NH7), 11.29 (s, 1H), 9.41 (s, 1H), 8.76 (s, 1H), 8.60 (d, J = 6 Hz, 1H), 8.13 (d, J = 9 Hz, 2 H), 7.63 (t, J = 9 Hz, J = 3 Hz, 1H), 7.12 (d, J = 9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 163.0, 152.0, 148.9, 135.4, 131.1, 125.4, 124.4, 114.1, 55.9. MS (Electrospray) *m/z* (%): 368.9 (100) [M + Na]$^+$; 410.0 (60) [M + MeCN + Na]$^+$; HRMS (ESI) calcd for $C_{18}H_{14}N_6O_2Na$ [MNa$^+$]: 369.1076; found 369.1089.

(*E*)-4-Methoxy-*N*-(8-styryl-9*H*-purin-6yl)benzamide (7i). (*E*)-6-chloro-8-styryl-9*H*-purine **5l** (50 mg, 0.19 mmol) was treated with 4-methoxybenzamide (32 mg, 0.21 mmol) for 36 h according to the general procedure. Compound **7i** crystallized from EtOAc in 59% yield (white solid). mp: 204−207 °C. ^{1}H NMR (DMSO-d_6): δ 13.61−12.18 (NH7/NH9 isomers = 7/1), 11.34−10.90 (NH conformers 7/1), 8.69 (s, 1H), 8.16 (d, J = 9 Hz, 2 H), 7.95 (d, J = 15 Hz, 1H), 7.71 (d, J = 6 Hz, 2H), 7.50 (m, 4 H), 7.12 (d, J = 9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 163.7, 160.9, 152.5, 149.6, 136.4, 133.5, 128.8, 127.6, 127.2, 125.6, 122.9, 114.4, 111.9, 53.7. MS (Electrospray) *m/z* (%): 372.0 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{21}H_{18}N_5O_2$ [MH$^+$]: 372.1461; found 372.1466.

***N*-(8-(3-Chlorophenyl)-9*H*-purin-6-yl)cyclopropanecarboxamide (7j).** 6-Chloro-8-(3-Chlorophenyl)-9*H*-purine **5c** (50 mg, 0.19 mmol) was treated with cyclopropanecarboxamide (18 mg, 0.21 mmol) for 36 h according to the general procedure. Compound **7j** crystallized from EtOAc in 77% yield (white solid). mp >260 °C. ^{1}H NMR (DMSO-d_6): δ 13.97−12.22 (NH9/NH7 isomers), 11.49−10.96 (NH conformers), 8.66 (s, 1H), 8.28 (s, 1H), 8.18 (d, J = 6 Hz, 1H), 7.63 (m, 2H), 2.21 (s, 1H), 0.97 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 158.2, 152.2, 134.2, 131.5, 127.3, 126.5, 14.5, 8.9. MS (Electrospray) *m/z* (%): 336.0 (100) [M + Na]$^+$; 377.0 (90) [M + MeCN + Na]$^+$; 314.0 (10) [M + H]$^+$. Anal. Calcd for $C_{15}H_{12}ClN_5O$: C, 57.42; H, 3.86; N, 22.32; found C, 56.98; H, 3.59; N, 22.07.

(*E*)-*N*-(8-Styryl-9*H*-purin-6-yl)cyclopropanecarboxamide (7k). (*E*)-6-Chloro-8-styryl-9*H*-purine **5l** (50 mg, 0.19 mmol) was treated with cyclopropane carboxamide (18 mg, 0.21 mmol) for 32 h, according to the general procedure. Compound **7k** was isolated as a white solid after crystallization from EtOAc. Yield: 76%. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 11.80 (s br, 1H), 11.40 (s br, 1H), 8.48 (s, 1H), 7.78 (d, J = 18 Hz, 1H), 7.56 (m, 3 H), 7.32 (m, 3H), 2.07 (s, 1H), 0.87 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 152.0, 138.6, 135.8, 129.9, 129.4, 127.8, 116.8, 14.4, 8.6. MS (electrospray) *m/z* (%): 328.0 (100) [M + Na]$^+$. Anal. Calcd for $C_{17}H_{15}N_7O$: C, 66.87; H, 4.95; N, 22.94; found C, 66.22; H, 4.88; N, 22.62.

***N*-(8-(3-Cyanophenyl)-9*H*-purin-6-yl)-4-fluorobenzamide (7l).** 3-(6-Chloro-9H-purin-8-yl)benzonitrile **5j** (50 mg, 0.2) was treated with 4-fluorobenzamide (36 mg, 0.25 mmol) for 3 days according to the general procedure. Compound **7l** crystallized from EtOAc in 50% yield. mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 12.82 (NH9/NH7), 11.71 (s, 1H), 8.96 (s, 1H), 8.87 (s, 1H), 8.76 (d, J = 9 Hz, 1H), 8.39 (m, 2H), 8.24 (d, J = 9 Hz), 8.00 (t, J = 9 Hz, J' = 6 Hz, 1 H), 7.61 (t, J = 9 Hz, J' = 6 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 165.0 (d, J = 249 Hz), 165.5, 152.2, 134.8, 132.4, 131.9 (d, J = 8.6 Hz), 131.1, 130.8, 130.3, 129.9, 118.5, 115.9 (d, J = 21.7 Hz), 112.6, 109.5. MS (Electrospray) *m/z* (%): 421.9 (100) [M + MeCN + Na]$^+$, 380.9 (90) [M + Na]$^+$. HRMS (ESI) calcd for $C_{19}H_{11}N_6ONaF$ [MNa$^+$]: 381.0876; found 381.0877.

***N*-(8-(Phenyl)-9*H*-purin-6-yl)pentamide (7m).** 6-Chloro-8-phenyl-9*H*-purine **5d** (50 mg, 0.217 mmol) was treated with valeramide (24 mg, 0.23 mmol) for 48 h, according to the general procedure. Compound **7m** crystallized from EtOAc in 50% yield (white crystals). mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 10.97 (s, 1H), 8.65 (s, 1H), 8.22 (2H), 7.60 (m, 3H), 2.60 (t, J = 6 Hz, J' = 9 Hz, 2H), 1.31 (m, 2H), 0.92 (m, 2H), 0.92 (t, J = 9 Hz, J' = 6 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 151.9, 131.6, 129.5, 129.0, 127.7, 35.9, 27.1, 22.1, 14.1. MS (Electrospray) *m/z* (%): 318.1 (100) [M + Na]$^+$; 359.0 (60) [M + Na + MeCN]$^+$. HRMS (ESI) calcd for $C_{16}H_{17}N_5ONa$ [MNa$^+$]: 318.1331; found 318.1335.

***N*-(8-(Naphtalen-2-yl)-9*H*-purin-6-yl)pentamide (7n).** 6-Chloro-8-(naphtalen-2-yl)-9*H*-purine **5k** (60 mg, 0.213 mmol) was treated with valeramide (24 mg, 0.23 mmol), for 48 h, according to the general procedure. Compound **7n** crystallized from EtOAc in 81% yield (white solid). mp: >260 °C. ^{1}H NMR (DMSO-d_6): δ 12.66 (s br, 1H), 11.10 (s, br, 1H), 8.98 (s, 1H), 8.79 (s, 1H), 8.47 (d, J = 9 Hz, 1H), 8.26 (d, J = 9 Hz, 2H), 8.15 (m, 1H), 7.77 (t, J = 3 Hz, 1H), 2.75 (t, J = 9 Hz, J' = 6 Hz, 2H), 1.81 (m, 2H), 1.54 (m, 2H), 1.07 (t, J = 6 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 173.2, 153.8, 152.0, 134.4, 132.9, 129.1, 129.0, 128.2, 128.1, 127.7, 127.5, 126.6, 124.4, 35.9, 27.2, 22.2, 14.2. MS (Electrospray) *m/z* (%): 409.1 (100) [M + MeCN + Na]$^+$, 368.0 (50) [M + Na]$^+$. Anal. Calcd for $C_{20}H_{19}N_{50}$: C, 69.55; H, 5.54; N, 20.28; found C, 69.16; H, 5.51; N, 20.17.

***N*-(8-(3-Cyanophenyl)-9*H*-purin-6-yl)pentamide (7o).** 3-(6-Chloro-9*H*-purin-8-yl)benzonitrile **5j** (50 mg, 0.2 mmol) was treated with valeramide (25.5 mg, 0.25 mmol) for 36 h, according to the general procedure. Compound **7o** crystal-

lized from EtOAc in 60% yield (white solid). mp >260 °C. ^{1}H NMR (DMSO-d_6): δ 12.32 (s br, NH), 11.15−10.59 (NH conformers= 7/3), 8.67 (s, 2 H), 8.54 (d, J = 6 Hz, 1H), 8.05 (d, J = 6 Hz, 1H), 7.82 (t, J = 9 Hz, J' = 6 Hz, 1H), 2.58 (t, J = 6 Hz, 2H), 1.66 (m, 2H), 1.39 (m, 2H), 0.93 (t, J = 6 Hz, J' = 9 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 152.3, 134.7, 132.6, 130.8, 118.5, 112.5, 27.1, 22.1, 14.1. MS (Electrospray) *m*/*z* (%): 343.1 (100) $[M + Na]^+$, 384.0 (90) $[M + MeCN + Na]^+$. HRMS (ESI) calcd for $C_{17}H_{16}N_6ONa$ $[MNa^+]$: 343.1283; found 343.1290.

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Supporting Information Available. ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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