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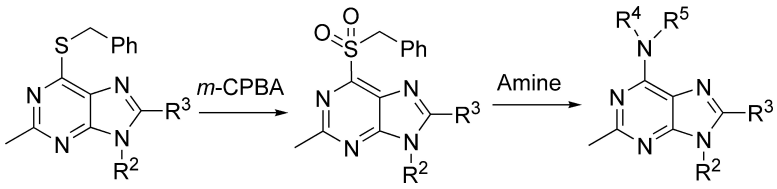

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Parallel Solution-Phase Synthesis of a 2,6,8,9-Tetrasubstituted Purine Library via a Sulfur Intermediate

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Purine analogues exhibiting a wide range of pharmacological activities have been considered a privileged structure in medicinal chemistry. In addition, the purine core consisting of four points of structural diversity is a well-sought scaffold in combinatorial chemistry. Although most of the efforts have been focused on 2,6,9-, 6,8,9-, or 2,8,9-trisubstituted purines, syntheses of 2,6,8,9-tetrasubstituted purines are rare. This paper presents a parallel solution phase approach for the synthesis of fully substituted purines via a 6-sulfur-substituted pyrimidine as the key intermediate. This strategy combining construction and modification of the purine ring thus increases the structural diversity of the final products. Sequential substitution of chlorines in 4,6-dichloro-2-methyl-5-nitropyrimidine with primary amine and benzylmercaptan afforded the 4-(substituted)amino-6-benzylthio-5-nitropyrimidine, which was readily converted to its diaminopyrimidine analogue by reduction of the nitro group. The diaminopyrimidine intermediate was cyclized to construct the purine ring with a C-8 substituent. Eventual oxidation of sulfur to sulfone and subsequent displacement by a primary or secondary amine provided the desired 2,6,8,9-tetrasubstituted purine analogues. This synthetic methodology was validated with the synthesis of a 216-member purine library.

Introduction

Purines are essential components of various life molecules and play vital roles in many biological processes. Their analogues, hence, have been the interest of drug discovery programs targeting various enzymes and receptors, such as CDK inhibitors,[1] Hsp 90 family inhibitors,[2] p38 kinase inhibitors[3], and selective sulfotransferase inhibitors[4] (Figure 1). Consequently, the purine ring has been considered a privileged structure in medicinal chemistry. In another aspect, the purine core consisting of four points of structural diversity is a well-sought scaffold in combinatorial chemistry. Several reports on the synthesis of purine libraries have been disclosed in the literature. In general, two strategies are applied in preparation of purine libraries. In the first, a preformed purine ring with displaceable functionalities is directly modified.[5] This method has the advantage of allowing straightforward synthesis of highly substituted purine derivatives with fixed substitution at the 8-position, but it may suffer from poor regiocontrol in N-9 functionalization. The second method, utilizing substituted pyrimidine as precursors, allows more flexibility with respect to the substitutions at the 6-, 8-, and 9-positions and better regiocontrol at N-9.[6]

Although most of the efforts in library preparation have been focused on 2,6,9-, 6,8,9-, or 2,8,9-trisubstituted purines, syntheses of 2,6,8,9-tetrasubstituted purines are rare.[7,8] We envisioned that a fully substituted purine library may be readily accessible by combining the two literature methods and incorporating an alkylthio group at the 6-position. This strategy can be accomplished either in solution phase or through sulfur-linked solid phase, as outlined in Scheme 1.

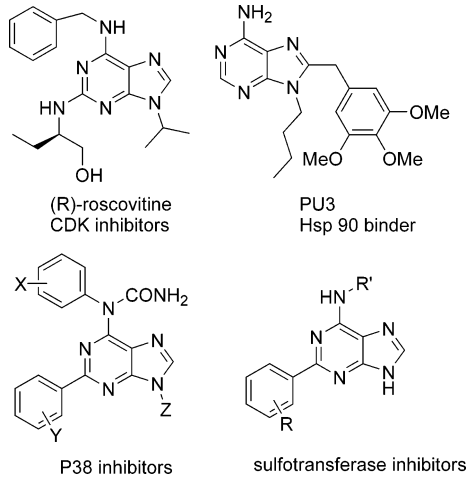

Figure 1.

The pathways illustrated in Scheme 1 take advantage of the fact that an alkylthio group RS at the 6-position of purine is relatively reactive toward oxidation to yield its corresponding sulfone, which could be easily displaced by various amines. To illustrate the feasibility of the above design, a fully substituted purine library was attempted starting with benzylthio-substituted pyrimidines, which could also serve as a prelude to a solid-phase synthesis. Herein, we report the construction of a parallel solution-phase 216-member library of fully substituted purines, which should allow systematic exploration of all four positions of the purine ring.

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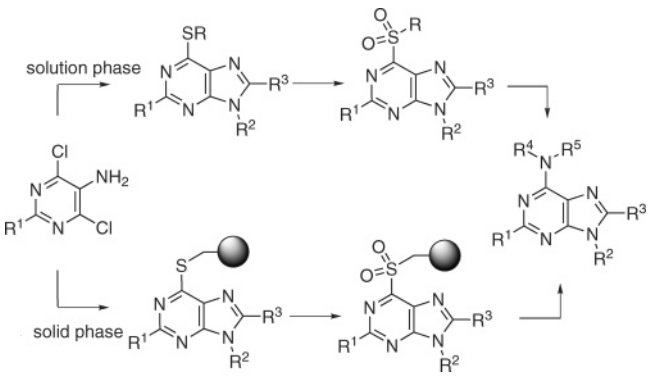
Scheme 1



Experimental Section

General Methods. Commercial reagents were used without purification. The melting points were determined on an XT5 apparatus and are uncorrected. ^{1}H NMR data were recorded on a 300-MHz Varian VXR-300S NMR spectrometer with $CDCl_3$ as solvent and TMS as the internal standard. The following abbreviations were used to designate the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Purity of compounds was assessed by LC/MS (Agilent 1100, API-ES), ELSD (Alltech 2000). Compound **1** was prepared from amidine as described in the literature.[9]

5-Amino-4,6-dichloro-2-methyl-pyrimidine (2). 4,6-Dichloro-2-methyl-5-nitropyrimidine **1** (20.2 g, 0.097 mol) was dissolved in a mixture of hydrochloric acid (10 mL) and ethanol (200 mL). Iron powder (16.4 g, 0.293 mol) was added to it in one portion. The mixture was then refluxed for 8 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was extracted with EtOAc, and the organic extract was washed with 1 N NaOH, water, and brine and dried over anhydrous $MgSO_4$. It was then filtered and concentrated in vacuo to a tan solid. Purification by recrystallized from water yielded the pure product as off-white solid **2**, (14.3 g, 83%). ES-MS: 178 ($M + H^+$). ^{1}H NMR: δ 2.56 (s, 3H), 4.37 (br, 2H).

***N*^{4}-Butyl-6-chloro-2-methylpyrimidine-4,5-diamine (3).** 5-Amino-4,6-dichloropyrimidine (**2**) (0.177 g, 1.0 mmol), the butylamine (0.146 g, 2.0 mmol), and triethylamine (0.22 mL, 2.0 mmol) were dissolved in butyl alcohol (2.5 mL), and the mixture was stirred for 6 h at 100 °C. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with EtOAc. The combined EtOAc layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to the crude product. Purification by flash chromatography (elution with hexane followed by 20% EtOAc in hexane) afforded the desired pure product **3**. (0.173 g, 81%). ES-MS: 215 ($M + H^+$). ^{1}H NMR: δ 4.85 (br, 1H), 3.50−3.53 (m, 2H), 3.33 (br, 2H), 2.45 (s, 3H), 1.58−1.68 (m, 2H), 1.36−1.49 (m, 2H), 0.96 (t, 3H, J = 7.5 Hz).

General Procedure for the Preparation of Compounds 4. To a solution of **4**, 6-dichloro-2-methyl-5-nitropyrimidine (**1**) (5.2 g, 25 mmol), and triethylamine (5.25 g, 50 mmol) in anhydrous tetrahydrofuran (48 mL) was added a solution of the appropriate amine in THF (48 mL) slowly. The reaction mixture was stirred at room temperature for 20 min. Benzyl mercaptan (4.65 g, 37.5 mmol) was added in one portion, and the mixture was stirred for 16 h at room temperature (TLC showed complete consumption of starting material). The reaction mixture was concentrated in vacuo, diluted with water, and extracted with EtOAc; the organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield a solid, which was recrystallized from petroleum ether to afford the desired pure product **4**.

6-(Benzylthio)-2-methyl-5-nitro-*N*-phenylpyrimidin-4-amine (4a, R^2 = Phenyl). Orange solid. Yield: 87%. mp ~106.1 to 108.3 °C. ES-MS: 353 ($M + H^+$). ^{1}H NMR: δ 10.77 (br, 1H), 7.2−7.66 (m, 10H), 4.41 (s, 2H), 2.57 (s, 3H).

6-(Benzylthio)-*N*-cyclohexyl-2-methyl-5-nitropyrimidin-4-amine (4b, R^2 = Cyclohexyl). Yellow solid. Yield: 68%. mp ~136.0 to 136.9 °C. ES-MS: 359 ($M + H^+$). ^{1}H NMR: δ 8.86−8.88 (br, 1H), 7.39−7.42 (m, 2H), 7.23−7.33 (m, 3H), 4.36 (s, 2H), 4.24−4.27 (m, 1H), 2.52 (s, 3H), 1.97−2.01 (br, 2H), 1.63−1.67 (br, 2H), 1.25−1.48 (m, 6H).

6-(Benzylthio)-*N*-butyl-2-methyl-5-nitropyrimidin-4-amine (4c, R^2 = *n*-Butyl). Pale yellow solid. Yield: 74%. mp ~103.8 to 106.6 °C. ES-MS: 333 ($M + H^+$). ^{1}H NMR: δ 8.90 (br, 1H), 7.39−7.42 (m, 2H), 7.21−7.33(m, 3H), 4.37 (s, 2H), 3.59−3.66 (m, 2H), 2.53 (s, 3H), 1.59−1.69 (m, 2H), 1.36−1.48 (m, 2H), 0.96 (t, 3H, J = 7.5 Hz).

6-(Benzylthio)-*N*-((furan-2-yl)methyl)-2-methyl-5-nitropyrimidin-4-amine [4d, R^2 = (Furan-2-yl)methyl]. Yellow solid. Yield: 78%. mp ~122.6 to 124.6 °C. ES-MS: 356.9 ($M + H^+$). ^{1}H NMR: δ 9.06 (br, 1H), 7.38−7.42 (m, 2H), 7.22−7.33 (m, 4H), 6.29−6.34 (m, 2H), 4.83 (d, 2H, J = 5.7 Hz), 4.38 (s, 2H), 2.56 (s, 3H).

6-(Benzylthio)-*N*-isobutyl-2-methyl-5-nitropyrimidin-4-amine (4e, R^2 = Isobutyl). Yellow solid. Yield: 72%. mp ~109.1 to 111.9 °C. ES-MS: 333 ($M + H^+$). ^{1}H NMR: δ 8.99 (br, 1H), 7.39−7.42 (m, 2H), 7.21−7.34 (m, 3H), 4.37 (s, 2H), 3.45−3.49 (m, 2H), 2.52 (s, 3H), 1.91−2.00 (m, 1H), 0.99 (d, 6H, J = 6.6 Hz).

***N*-Benzyl-6-(benzylthio)-2-methyl-5-nitropyrimidin-4-amine (4f, R^2 = Benzyl).** Pale yellow solid. Yield: 80%. mp ~98.4 to 100.1 °C. ES-MS: 367 ($M + H^+$). ^{1}H NMR: δ 9.17 (br, 1H), 7.24−7.46 (m, 10H), 4.84 (d, 2H, J = 5.7 Hz), 4.38 (s, 2H), 2.54 (s, 3H).

General Procedure for the Preparation of Compounds 5. Compound **4** was dissolved in a mixture of EtOH and water (v/v = 3.6/1). Iron powder and NH_4Cl were added to it, and the mixture was then stirred in reflux for 8 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was extracted with EtOAc, and the organic extract was washed with saturated $NaHCO_3$, water, and brine and dried over anhydrous $MgSO_4$. It was then filtered and concentrated in vacuo to a dark oil. Mixtures were purified by flash column chromatography (silica gel column; separation of the mixture was monitored by UV at 254 nm), which yielded the pure product **5**.

6-(Benzylthio)-2-methyl-*N*^{4}-phenylpyrimidine-4,5-diamine (5a, R^2 = Phenyl). Yellow solid. Yield: 67%. mp 79.3−80.6 °C. ES-MS: 323 ($M + H^+$). ^{1}H NMR: δ 7.59−

7.63 (m, 2H), 7.21−7.41 (m, 8H), 4.48 (s, 2H), 2.88 (br, 2H), 2.57 (s, 3H).

6-(Benzylthio)-*N*^{4}-cyclohexyl-2-methylpyrimidine-4,5-diamine (5b, R^2 = Cyclohexyl). Pale yellow solid. Yield: 72%. mp ∼93.0 to 94.9 °C. ES-MS: 329 (M + H$^+$). ^{1}H NMR: δ 7.19−7.36 (m, 5H), 4.76 (br, 1H), 4.42 (s, 2H), 3.90−4.01 (m, 1H), 2.74 (br, 2H), 2.49 (s, 3H), 1.99−2.04 (m, 2H), 1.70−1.77 (m, 2H), 0.98−1.50 (m, 6H).

6-(Benzylthio)-*N*^{4}-butyl-2-methylpyrimidine-4,5-diamine (5c, R^2 = Butyl). General Procedure. Pale yellow solid. Yield: 90%. **Method a.** *N*^{4}-Butyl-6-chloro-2-methylpyrimidine-4,5-diamine (**3**) (1.034 g, 4.82 mmol), benzyl mercaptan (1.195 g, 9.64 mmol), and triethylamine (1.30 mL, 9.64 mmol) were dissolved in butyl alcohol (10 mL) and stirred for 8 h at 100 °C. After the reaction mixture was cooled, the solvent was removed in vacuo, the residue was taken up into CH_2Cl_2, and the organic phase was washed with water, dried over anhydrous $MgSO_4$, and filtered. Solvent removal in the vacuum gave an oil that was purified by flash chromatography (silica gel) using EtOAc/hexane (1:9) to yield the desired product as a pale yellow solid (0.604 g, 32%). mp 162.9−164.8 °C. ES-MS: 303 (M + H$^+$). ^{1}H NMR: δ 7.21−7.36 (m, 5H), 4.84 (br, 1H), 4.43 (s, 2H), 3.41−3.47 (m, 2H), 2.76 (br, 2H), 2.50 (s, 3H), 1.54−1.63 (m, 2H), 1.34−1.44 (m, 2H), 0.95 (t, 3H, J = 7.5 Hz).

6-(Benzylthio)-*N*^{4}-furan-2-ylmethyl-2-methylpyrimidine-4,5-diamine (5d, R^2 = Furanmethyl). Yellow solid. Yield: 74%. mp ∼122.6 to 124.6 °C. ES-MS: 327 (M + H$^+$). ^{1}H NMR: δ 7.21−7.35 (m, 6H), 6.31−6.34 (m, 1H), 6.24−6.25 (m, 1H), 5.12−5.14 (br, 1H), 4.64 (d, 2H, J = 5.4 Hz), 4.43 (s, 2H), 2.79 (br, 2H), 2.51 (s, 3H).

6-(Benzylthio)-*N*^{4}-isobutyl-2-methylpyrimidine-4,5-diamine (5e, R^2 = Isobutyl). Yellow oil. Yield: 83%. ES-MS: 303 (M + H$^+$). ^{1}H NMR: δ 7.17−7.34 (m, 5H), 5.01 (br, 1H), 4.41 (s, 2H), 3.24−3.29 (m, 2H), 2.75 (br, 2H), 2.48 (s, 3H), ∼1.81 to 1.90 (m, 1H), 0.94 (d, 6H, J = 6.9 Hz).

***N*^{4}-Benzyl-6-(benzylthio)-2-methylpyrimidine-4,5-diamine (5f, R^2 = Benzyl).** Yellow solid. Yield: 83%. mp ∼62.3 to 64.8 °C. ES-MS: 337 (M + H$^+$). ^{1}H NMR: δ 7.20−7.36 (m, 10H), 5.13 (br, 1H), 4.62 (d, 2H, J = 4.8 Hz), 4.42 (s, 2H), 2.77 (br, 2H), 2.51 (s, 3H).

General Procedure for the Preparation of Compounds 6. A solution of **5** (4 mmol) and the appropriate aldehyde (8 mmol) in anhydrous dioxane (50 mL) was treated with 15% $FeCl_3/SiO_2$ (2 equiv) at 100 °C under nitrogen for ∼24 to 72 h. The cooled reaction mixture was filtered through a pad of Celite and washed with EtOAc(3 × 20 mL), and the filtrate was concentrated in vacuo. The residue was dissolved with EtOAc, and the organic extract was washed with saturated $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. It was then filtered and concentrated in vacuo to a dark oil. Purification by parallel flash chromatography (eluting with a gradient of EtOAc in hexane) yielded the product as **6**.

6-(Benzylthio)-9-butyl-2,8-dimethyl-9*H*-purine (6Aa, R^2 = Butyl, R^3 = Methyl). White solid. Yield: 45%. ES-MS: 327 (M + H$^+$). ^{1}H NMR: δ7.45−7.49 (m, 2H), 7.21−7.30 (m, 3H), 4.63 (s, 2H), 4.13 (t, 2H, J = 7.5 Hz), 2.75 (s, 3H), 2.59 (s, 3H), 1.71−1.78 (m, 2H), 1.32−1.39 (m, 2H), 0.95 (t, 3H, J = 7.2 Hz).

6-(Benzylthio)-9-butyl-2-methyl-8-propyl-9*H*-purine (6Ab, R^2 = Butyl, R^3 = Propyl). Pale yellow solid. Yield: 51%. ES-MS: 355 (M + H$^+$). ^{1}H NMR: δ 7.46−7.49 (m, 2H), 7.24−7.31 (m, 3H), 4.65 (s, 2H), 4.14 (t, 2H, J = 7.5 Hz), 2.80−2.85 (m, 2H), 2.75 (s, 3H), 1.76−1.92 (m, 4H), 1.35−1.38 (m, 2H), 1.04 (t, 3H, J = 7.2 Hz), 0.96 (t, 3H, J = 7.2 Hz).

8-Benzyl-6-(benzylthio)-9-butyl-2-methyl-9*H*-purine (6Ac, R^2 = Butyl, R^3 = Benzyl). Brown oil. Yield: 66%. ES-MS: 403 (M + H$^+$). ^{1}H NMR: δ 7.19−7.49 (m, 10H), 4.65 (s, 2H), 4.26 (s, 2H), 3.93 (t, 2H, J = 7.5 Hz), 2.73 (s, 3H), 1.44−1.49 (m, 2H), 1.17−1.24 (m, 2H), 0.81 (t, 3H, J = 6.9 Hz).

6-(Benzylthio)-9-butyl-2-methyl-8-phenyl-9*H*-purine (6Ad, R^2 = Butyl, R^3 = Phenyl). Pale yellow solid. Yield: 51%. ES-MS: 389 (M + H$^+$). ^{1}H NMR: δ 7.70−7.73 (m, 2H), 7.48−7.53 (m, 5H), 4.68 (s, 2H), 4.30 (t, 2H, J = 7.5 Hz), 2.79 (s, 3H), 1.69−1.77 (m, 2H), 1.18−1.25 (m, 2H), 0.83 (t, 3H, J = 7.2 Hz).

6-(Benzylthio)-9-butyl-8-(4-methoxyphenyl)-2-methyl-9*H*-purine (6Ae, R^2 = Butyl, R^3 = 4-Methoxyphenyl). White solid. Yield: 57%. ES-MS: 419 (M + H$^+$). ^{1}H NMR: δ 7.67 (d, 2H, J = 8.7 Hz), 7.48−7.50 (m, 2H), 7.22−7.32 (m, 3H), 7.02 (d, 2H, J = 9.0 Hz), 4.67 (s, 2H), 4.28 (t, 2H, J = 7.5 Hz), 3.88 (s, 3H), 2.78 (s, 3H), 1.68−1.75 (m, 2H), 1.19−1.27 (m, 2H), 0.84 (t, 3H, J = 7.2 Hz).

6-(Benzylthio)-9-butyl-8-furan-2-yl-2-methyl-9*H*-purine (6Af, R^2 = *n*-Butyl, R^3 = Furanyl). Brown solid. Yield: 40%. ES-MS: 379 (M + H$^+$). ^{1}H NMR: δ 7.61−7.62 (m, 1H), 7.47−7.50 (m, 2H), 7.22−7.32 (m, 3H), 6.60−6.61 (m, 2H), 4.66 (s, 2H), 4.52 (t, 2H, J = 7.5 Hz), 2.77 (s, 3H), 1.76−1.79 (m, 2H), 1.35−1.38 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz).

6-(Benzylthio)-9-isobutyl-2,8-dimethyl-9*H*-purine (6Ba, R^2 = Isobutyl, R^3 = Methyl). White solid. Yield: 58%. ES-MS: 327 (M + H$^+$). ^{1}H NMR: δ 7.46−7.49 (m, 2H), 7.18−7.31 (m, 3H), 4.63 (s, 2H), 3.93 (d, 2H, J = 7.8 Hz), 2.74 (s, 3H), 2.58 (s, 3H), 2.21−2.30 (m, 1H), 0.92 (d, 6H, J = 6.6 Hz).

6-(Benzylthio)-9-isobutyl-2-methyl-8-propyl-9*H*-purine (6Bb, R^2 = Isobutyl, R^3 = Propyl). Yellow solid. Yield: 41%. ES-MS: 355 (M + H$^+$). ^{1}H NMR: δ 7.46−7.49 (m, 2H), 7.20−7.31 (m, 3H), 4.64 (s, 2H), 3.94 (d, 2H, J = 7.5 Hz), 2.80 (t, 2H, J = 7.5 Hz), 2.74 (s, 3H), 2.24−2.28 (m, 1H), 1.85−1.92 (m, 2H), 0.98−1.08 (m, 3H), 0.91 (d, 6H, J = 6.9 Hz).

8-Benzyl-6-(benzylthio)-9-isobutyl-2-methyl-9*H*-purine (6Bc, R^2 = Isobutyl, R^3 =Benzyl). Brown oil. Yield: 50%. ES-MS: 403 (M + H$^+$). ^{1}H NMR: δ 7.17−7.50 (m, 10H), 4.65 (s, 2H), 4.40 (s, 2H), 2.73 (s, 2H), 2.48 (s, 3H), 2.15−2.24 (m, 1H), 0.95 (d, 6H, J = 6.6 Hz).

6-(Benzylthio)-9-isobutyl-2-methyl-8-phenyl-9*H*-purine (6Bd, R^2 = Isobutyl, R^3 = Phenyl). White solid. Yield: 44%. ES-MS: 389 (M + H$^+$). ^{1}H NMR: δ 7.68−7.71 (m, 2H), 7.49−7.51 (m, 5H), 7.20−7.32 (m, 3H), 4.67 (s, 2H), 4.16 (d, 2H, J = 7.8 Hz), 2.78 (s, 3H), 2.04−2.11-(m, 1H), 0.71(d, 6H, J = 6.9 Hz).

6-(Benzylthio)-9-isobutyl-8-(4-methoxyphenyl)-2-methyl-9*H*-purine (6Be, R^2 = Isobutyl, R^3 = 4-Methoxyphenyl). Yellow solid. Yield: 71%. ES-MS: 419 ($M + H^+$). ^{1}H NMR: δ 7.65 (d, 2H, J = 8.4 Hz), 7.48−7.50 (m, 2H), 7.22−7.31 (m, 3H), 7.00 (d, 2H, J = 8.4 Hz), 4.67 (s, 2H), 4.15 (d, 2H, J = 7.8 Hz), 3.86 (s, 3H), 2.78 (s, 3H), 2.08−2.12 (m, 1H), 0.72 (d, 6H, J = 6.6 Hz).

6-(Benzylthio)-8-furan-2-yl-9-isobutyl-2-methyl-9*H*-purine (6Bf, R^2 = isobutyl, R^3 = furanyl). Yellow solid. Yield: 53%. ES-MS: 379 ($M + H^+$). ^{1}H NMR: δ 7.60−7.61 (m, 1H), 7.47−7.49 (m, 2H), 7.19−7.32 (m, 4H), 6.57−6.60 (m, 1H), 4.66 (s, 2H), 4.36 (d, 2H, J = 6.6 Hz), 2.76 (s, 3H), 2.15−2.24 (m, 1H), 0.89 (d, 6H, J = 6.9 Hz).

6-(Benzylthio)-9-cyclohexyl-2,8-dimethyl-9*H*-purine (6Ca, R^2 = Cyclohexyl, R^3 = Methyl). Pale yellow solid. Yield: 54%. ES-MS: 353 ($M + H^+$). ^{1}H NMR: δ 7.44−7.47 (m, 2H), 7.18−7.30 (m, 3H), 4.62 (s, 2H), 4.19−4.27 (m, 1H), 2.73 (s, 3H), 2.62 (s, 3H), 2.38−2.50 (br, 2H), 1.76−1.96 (br, 5H), 1.25−1.50 (br, 3H).

6-(Benzylthio)-9-cyclohexyl-2-methyl-8-propyl-9*H*-purine (6Cb, R^2 = Cyclohexyl, R^3 = Propyl). White solid. Yield: 56%. ES-MS: 381 ($M + H^+$). ^{1}H NMR: δ 7.46−7.49 (m, 2H), 7.21−7.30 (m, 3H), 4.64 (s, 2H), 4.10−4.16 (m, 1H), 2.88 (t, 2H, J = 7.8 Hz), 2.73 (s, 3H), 2.52−2.59 (br, 2H), 1.94−1.97 (br, 2H), 1.78−1.86 (br, 5H), 1.38−1.44 (br, 3H), 1.05 (t, 3H, J = 7.2 Hz).

8-Benzyl-6-(benzylthio)-9-cyclohexyl-2-methyl-9*H*-purine (6Cc, R^2 = Cyclohexyl, R^3 = Benzyl). Yellow oil. Yield: 31%. ES-MS: 429 ($M + H^+$). ^{1}H NMR: δ 7.18−7.51 (m, 10H), 4.64 (s, 2H), 4.30 (s, 2H), 3.94−4.03 (m, 1H), 2.71 (s, 3H), 2.35−2.45 (br, 2H), 1.05−1.75 (br, 8H).

6-(Benzylthio)-9-cyclohexyl-2-methyl-8-phenyl-9*H*-purine (6Cd, R^2 = Cyclohexyl, R^3 = Phenyl). White solid. Yield: 58%. ES-MS: 415 ($M + H^+$). ^{1}H NMR: δ 7.60−7.64 (m, 2H), 7.47−7.53 (m, 5H), 7.19−7.31 (m, 3H), 4.70 (s, 2H), 4.21−4.29 (m, 1H), 2.80 (s, 3H), 2.65−2.73 (br, 2H), 1.68−1.91 (br, 5H), 1.24−1.40 (br, 3H).

6-(Benzylthio)-9-cyclohexyl-8-(4-methoxyphenyl)-2-methyl-9*H*-purine (6Ce, R^2 = Cyclohexyl, R^3 = 4-Methoxyphenyl). White solid. Yield: 67%. ES-MS: 445 ($M + H^+$). ^{1}H NMR: δ 7.57 (d, 2H, J = 8.4 Hz), 7.47−7.49 (m, 2H), 7.19−7.31 (m, 3H), 7.03 (d, 2H, J = 8.7 Hz), 4.68 (s, 2H), 4.21−4.26 (m, 1H), 3.87 (s, 3H), 2.78 (s, 3H), 2.65−2.76 (br, 2H), 1.68−1.92 (br 5H), 1.25−1.40 (br, 3H).

6-(Benzylthio)-9-cyclohexyl-8-furan-2-yl-2-methyl-9*H*-purine (6Cf, R^2 = Cyclohexyl, R^3 = Furanyl). Pale yellow solid. Yield: 43%. ES-MS: 405 ($M + H^+$). ^{1}H NMR: δ 7.65−7.66 (m, 1H), 7.47−7.50 (m, 2H), 7.19−7.31 (m, 3H), 6.60−6.62 (m, 2H), 4.76−4.80 (m, 1H), 4.72 (s, 2H), 2.80 (s, 3H), 2.61−2.70 (br, 2H), 1.76−1.97 (br, 5H), 1.26−1.45 (br, 3H).

9-Benzyl-6-(benzylthio)-2, 8-dimethyl-9*H*-purine (6Da, R^2 = Benzyl, R^3 = Methyl). Pale yellow solid. Yield: 32%. ES-MS: 361 ($M + H^+$). ^{1}H NMR: δ 7.47−7.50 (m, 2H), 7.24−7.32 (m, 6H), 7.09−7.12 (m, 2H), 5.36 (s, 2H), 4.65 (s, 2H), 2.76 (s, 3H), 2.45 (s, 3H).

9-Benzyl-6-(benzylthio)-2-methyl-8-propyl-9*H*-purine (6Db, R^2 = Benzyl, R^3 = Propyl). Pale yellow solid. Yield: 47%. ES-MS: 389 ($M + H^+$). ^{1}H NMR: δ 7.48−7.51 (m, 2H), 7.22−7.32 (m, 6H), 7.07−7.10 (m, 2H), 5.38 (s, 2H), 4.66 (s, 2H), 2.76 (s, 3H), 2.68 (t, 2H, J = 7.8 Hz), 1.69−1.76 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz).

8,9-Dibenzyl-6-(benzylthio)-2-methyl-9*H*-purine (6Dc, R^2 = Benzyl, R^3 = Benzyl). Yellow oil. Yield: 52%. ES-MS: 437 ($M + H^+$).^{1}H NMR: δ 7.19−7.61 (m, 15H), 5.44 (s, 2H), 4.68 (s, 2H), 4.32 (s, 2H), 2.74 (s, 3H).

9-Benzyl-6-(benzylthio)-2-methyl-8-phenyl-9*H*-purine (6Dd, R^2 = Benzyl, R^3 = Phenyl). White solid. Yield: 55%. ES-MS: 423 ($M + H^+$). ^{1}H NMR: δ 7.58−7.61 (m, 2H), 7.24−7.52 (m, 11H), 7.01−7.04 (m, 2H), 5.48 (s, 2H), 4.69 (s, 2H), 2.78 (s, 3H).

9-Benzyl-6-(benzylthio)-8-(4-methoxyphenyl)-2-methyl-9*H*-purine (6De, R^2 = Benzyl, R^3 = 4-Methoxyphenyl). White solid. Yield: 55%. ES-MS: 453 ($M + H^+$). ^{1}H NMR: δ 7.49−7.57 (m, 4H), 7.23−7.33 (m, 6H), 7.03−7.06 (m, 2H), 6.89−7.03 (m, 2H), 5.47 (s, 2H), 4.69 (s, 2H), 3.83 (s, 3H), 2.77 (s, 3H).

9-Benzyl-6-(benzylthio)-8-furan-2-yl-2-methyl-9*H*-purine (6Df, R^2 = Benzyl, R^3 = Furanyl). Yellow solid. Yield: 41%. ES-MS: 413 ($M + H^+$). ^{1}H NMR: δ 7.48−7.56 (m, 3H), 7.10−7.32 (m, 9H), 6.50−6.52 (m, 1H), 5.74 (s, 2H), 4.67 (s, 2H), 2.77 (s, 3H).

6-(Benzylthio)-2, 8-dimethyl-9-phenyl-9*H*-purine (6Ea, R^2 = Phenyl, R^3 = Methyl). White solid. Yield: 23%. ES-MS: 347 ($M + H^+$). ^{1}H NMR: δ 7.50−7.59 (m, 4H), 7.23−7.37 (m, 6H), 4.69 (s, 2H), 2.72 (s, 3H), 2.52 (s, 3H).

6-(Benzylthio)-2-methyl-9-phenyl-8-propyl-9*H*-purine (6Eb, R^2 = Phenyl, R^3 = Propyl). White solid. Yield: 28%. ES-MS: 375 ($M + H^+$). ^{1}H NMR: δ 7.51−7.61 (m, 4H), 7.24−7.35 (m, 6H), 4.77 (s, 2H), 2.76−2.81 (m, 2H), 2.74 (s, 3H), 1.71−1.78 (m, 2H), 0.90 (t, 3H, J = 7.5 Hz).

8-Benzyl-6-(benzylthio)-2-methyl-9-phenyl-9*H*-purine (6Ec, R^2 = Phenyl, R^3 = Benzyl). Brown oil. Yield: 82%. ES-MS: 423 ($M + H^+$).^{1}H NMR: δ 7.18−7.52 (m, 15H), 4.65 (s, 2H), 4.35 (s, 2H), 2.72 (s, 3H).

6-(Benzylthio)-8, 9-diphenyl-2-methyl-9*H*-purine (6Ed, R^2 = R^3 = Phenyl). Yellow solid. Yield: 53%. ES-MS: 409 ($M + H^+$). ^{1}H NMR: δ 7.46−7.53 (m, 6H), 7.23−7.37 (m, 9H), 4.70 (s, 2H), 2.73 (s, 3H).

6-(Benzylthio)-8-(4-methoxyphenyl)-2-methyl-9-phenyl-9*H*-purine (6Ee, R^2 = Phenyl, R^3 = 4-Methoxyphenyl). Yellow solid. Yield: 37%. ES-MS: 439 ($M + H^+$). ^{1}H NMR: δ 7.43−7.52 (m, 6H), 7.23−7.34 (m, 6H), 6.79 (d, 2H, J = 8.7 Hz), 4.70 (s, 2H), 3.79 (s, 3H), 2.72 (s, 3H).

6-(Benzylthio)-8-furan-2-yl-2-methyl-9-phenyl-9*H*-purine (6Ef, R^2 = Phenyl, R^3 = Furanyl). Brown solid. Yield: 33%. ES-MS: 399 ($M + H^+$). ^{1}H NMR: δ 7.57−7.60 (m, 3H), 7.48−7.51 (m, 3H), 7.22−7.40 (m, 5H), 6.33−6.35 (m, 1H), 6.13−6.14 (m, 1H), 4.68 (s, 2H), 2.70 (s, 3H).

6-(Benzylthio)-9-furan-2-ylmethyl-2,8-dimethyl-9*H*-purine (6Fa, R^2 = Furan-2-ylmethyl, R^3 = Methyl). Brown solid. Yield: 40%. ES-MS: 351 ($M + H^+$). ^{1}H NMR: δ 7.45−7.48 (m, 2H), 7.20−7.33 (m, 4H), 6.29−6.30 (m, 2H), 5.31 (s, 2H), 4.63 (s, 2H), 2.76 (s, 3H), 2.62 (s, 3H).

6-(Benzylthio)-9-furan-2-ylmethyl-2-methyl-8-propyl-9*H*-purine (6Fb, R^2 = Furan-2-ylmethyl, R^3 = Propyl). White solid. Yield: 41%. ES-MS: 379 ($M + H^+$). ^{1}H NMR: δ 7.45−7.48 (m, 2H), 7.22−7.33 (m, 4H), 6.30−

6.33 (m, 2H), 5.38 (s, 2H), 4.69 (s, 2H), 2.90−2.95 (m, 2H), 2.80 (s, 3H), 1.80−1.86 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz).

8-Benzyl-6-(benzylthio)-9-furan-2-ylmethyl-2-methyl-9*H*-purine (6Fc, R^2 = Furan-2-ylmethyl, R^3 = Benzyl). Brown oil. Yield: 54%. ES-MS: 427 (M + H$^+$). ^{1}H NMR: δ 7.46−7.49 (m, 2H), 7.18−7.39 (m, 9H), 6.20−6.30 (m, 2H), 5.10 (s, 2H), 4.33 (s, 2H), 2.75 (s, 2H), 2.51 (s, 3H).

6-(Benzylthio)-9-furan-2-ylmethyl-2-methyl-8-phenyl-9*H*-purine (6Fd, R^2 = Furan-2-ylmethyl, R^3 = Phenyl). White solid. Yield: 54%. ES-MS: 413 (M + H$^+$). ^{1}H NMR: δ 7.74−7.77 (m, 2H), 7.47−7.53 (m, 4H), 7.22−7.32 (m, 5H), 6.26−6.28 (m, 1H), 6.15−6.16 (m, 1H), 5.42 (s, 2H), 4.67 (s, 2H), 2.80 (s, 3H).

6-(Benzylthio)-9-furan-2-ylmethyl-8-(4-methoxyphenyl)-2-methyl-9*H*-purine (6Fe, R^2 = Furan-2-ylmethyl, R^3 = 4-Methoxyphenyl). Yellow solid. Yield: 14%. ES-MS: 443 (M + H$^+$). ^{1}H NMR: δ 7.73−7.75 (m, 2H), 7.48−7.50 (m, 2H), 7.22−7.33 (m, 4H), 7.00−7.02 (m, 2H), 6.28−6.30 (m, 1H), 6.19−6.20 (m, 1H), 5.42 (s, 2H), 4.69 (s, 2H), 3.87 (s, 3H), 2.80 (s, 3H).

6-(Benzylthio)-8-furan-2-yl-9-furan-2-ylmethyl-2-methyl-9*H*-purine (6Ff, R^2 = Furan-2-ylmethyl, R^3 = Furanyl). Brown solid. Yield: 47%. ES-MS: 403 (M + H$^+$). ^{1}H NMR: δ 7.63−7.64 (m, 1H), 7.46−7.49 (m, 2H), 7.22−7.31 (m, 5H), 6.58−6.59 (m, 1H), 6.18−6.24 (m, 2H), 5.72 (s, 2H), 4.66 (s, 2H), 2.80 (s, 3H).

General Procedure for the Preparation of Compounds 8. A solution of *m*-chloroperbenzoic acid (5 equiv) in CH_2Cl_2 (15 mL) was added to 6-(benzylthio) 8,9-disubstituted 2-methylpurine **6** (1 equiv), and the resulting mixture was stirred for 4 h in an ice-water bath. The mixture was stirred until disappearance of the starting material **6** as judged by TLC on silica gel in EtOAc/hexane = 3/10 (4 h). Water was added, and after workup (CH_2Cl_2 extraction, water washing, saturated $NaHSO_3$ and $MgSO_4$ drying of the organic phase), the residue was evaporated under reduced pressure, and the residue was divided into six portions. Each portion was transferred to a reaction tube, 2 mL of ethanol and the appropriate amine were then added to it, and the tube was sealed by fusing, then kept in 110 °C for 24 h and subsequently cooled to room temperature. The mixture was evaporated under reduced pressure, and the residue was purified by preparative LC.

2-Methyl-9-phenyl-*N*,8-dipropyl-9*H*-purin-6-amine (8a). White solid. Yield: 48%. ES-MS: 310 (M + H$^+$). ^{1}H NMR: δ 10.33 (br, 1H), 7.57−7.65 (m, 2H), 7.27−7.42 (m, 3H), 4.06−4.12 (m, 2H), 2.68 (t, 2H, J = 7.8 Hz), 2.59 (s, 3H), 1.70−1.86 (m, 4H), 1.08 (t, 3H, J = 7.5 Hz), 0.93 (t, 3H, J = 7.2 Hz).

9-((Furan-2-yl)methyl)-*N*-isobutyl-2-methyl-8-phenyl-9*H*-purin-6-amine (8b). Pale yellow solid. Yield: 28%. ES-MS: 362 (M + H$^+$). ^{1}H NMR: δ 10.85 (br, 1H), 7.76−7.80 (m, 2H), 7.54−7.61 (m, 3H), 7.35−7.44 (m, 1H), 6.24−6.33 (m, 2H), 5.42 (s, 2H), 3.95−3.99 (m, 2H), 2.70 (s, 3H), 2.05−2.13 (m, 1H), 1.04 (d, 6H, J = 6.6 Hz).

8-Benzyl-9-cyclohexyl-*N*-isobutyl-2-methyl-9*H*-purin-6-amine (8c). White solid. Yield: 28%. ES-MS: 378 (M + H$^+$). ^{1}H NMR: δ 10.51 (br, 1H), 7.18−7.35 (m, 5H), 5.29−5.30 (m, 1H), 4.25 (s, 2H), 3.91−3.95 (m, 2H), 2.62 (s, 3H), 2.26−2.33 (br, 2H), 2.01−2.08 (m, 1H), 1.09−1.82 (br, 8H), 1.02 (m, 6H).

9-((Furan-2-yl)methyl)-*N*-isobutyl-8-(4-methoxyphenyl)-2-methyl-9*H*-purin-6-amine (8d). Yellow solid. Yield: 46%. ES-MS: 392 (M + H$^+$). ^{1}H NMR: δ 10.91 (br, 1H), 7.72−7.76 (m, 2H), 7.37−7.39 (m, 1H), 7.04−7.08 (m, 2H), 6.27−6.35 (m, 2H), 5.40 (s, 2H), 3.94−3.99 (m, 2H), 3.90 (s, 3H), 2.69 (s, 3H), 2.07−2.11 (m, 1H), 1.03 (d, 6H, J = 6.3 Hz).

9-((Furan-2-yl)methyl)-8-(4-methoxyphenyl)-2-methyl-6-morpholino-9*H*-purine (8e). White solid. Yield: 53%. ES-MS: 406 (M + H$^+$). ^{1}H NMR: δ 7.64−7.68 (m, 2H), 7.31−7.32 (m, 1H), 6.98−7.03 (m, 2H), 6.20−6.28 (m, 2H), 5.42 (s, 2H), 4.36 (br, 4H), 3.87 (s, 3H), 3.82−3.86 (m, 4H), 2.62 (s, 3H).

8-Benzyl-2-methyl-6-morpholino-9-phenyl-9*H*-purine (8f). Pale yellow solid. Yield: 14%. ES-MS: 386 (M + H$^+$). ^{1}H NMR: δ 6.91−7.53 (m, 10H), 4.45 (br, 4H), 4.06 (s, 2H), 3.89−3.92 (m, 4H), 2.56 (s, 3H).

9-Benzyl-2-methyl-6-(piperidin-1-yl)-8-propyl-9*H*-purine (8g). White solid. Yield: 36%. ES-MS: 350 (M + H$^+$). ^{1}H NMR: δ 7.27−7.39 (m, 3H), 7.08−7.11 (m, 2H), 5.43 (s, 2H), 4.33 (br, 4H), 2.70 (s, 3H), 2.62−2.68 (m, 2H), 1.68−1.76 (m, 6H), 1.51 (br, 2H), 0.96 (t, 3H, J = 7.5 Hz).

9-Butyl-*N*-cyclohexyl-8-(furan-2-yl)-2-methyl-9*H*-purin-6-amine (8h). Pale yellow solid. Yield: 22%. ES-MS: 354 (M + H$^+$). ^{1}H NMR: δ 10.71 (br, 1H), 7.62−7.65 (m, 1H), 7.18−7.19 (m, 1H), 6.62−6.65 (m, 1H), 4.74−4.76 (m, 1H), 4.52 (t, 2H, J = 7.2 Hz), 2.59 (s, 3H), 1.60−1.88 (m, 6H), 1.29−1.56 (m, 8H), 0.96 (t, 3H, J = 7.2 Hz).

9-Benzyl-2-methyl-*N*,8-dipropyl-9*H*-purin-6-amine (8i). White solid. Yield: 66%. ES-MS: 324 (M + H$^+$). ^{1}H NMR: δ 10.82 (br, 1H), 7.25−7.37 (m, 3H), 7.11−7.13 (m, 2H), 5.30 (s, 2H), 3.89−4.04 (m, 2H), 2.66 (s, 3H), 2.64 (br, 2H), 1.73−1.82 (m, 4H), 0.88−0.92 (m, 6H).

9-Cyclohexyl-2,8-dimethyl-*N*-propyl-9*H*-purin-6-amine (8j). White solid. Yield: 53%. ES-MS: 288 (M + H$^+$). ^{1}H NMR: δ 10.68 (br, 1H), 4.23−4.26 (m, 1H), 3.97−4.04 (m, 2H), 2.63 (s, 3H), 2.60 (s, 3H), 2.36−2.39 (m, 2H), 1.74−1.95 (m, 6H), 1.38−1.50 (m, 4H), 1.01 (t, 3H, J = 7.2 Hz).

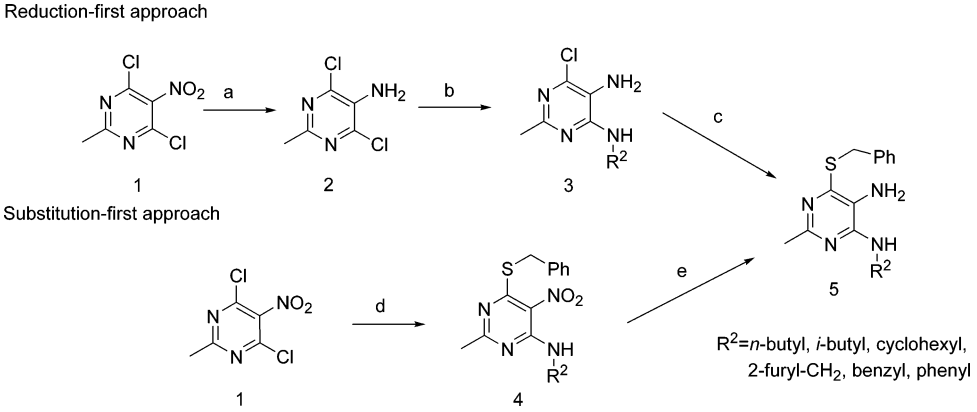
9-Isobutyl-2-methyl-8-phenyl-6-(piperidin-1-yl)-9*H*-purine (8k). White solid. Yield: 69%. ES-MS: 350 (M + H$^+$). ^{1}H NMR: δ 7.64−7.67 (m, 2H), 7.52−7.54 (m, 3H), 4.35 (br, 4H), 4.22 (d, 2H, J = 7.5 Hz), 2.70 (s, 3H), 2.02−2.06 (m, 1H), 1.75 (br, 6H), 0.71 (d, 6H, J = 6.6 Hz).

9-Cyclohexyl-2,8-dimethyl-6-(pyrrolidin-1-yl)-9*H*-purine (8l). Yellow solid. Yield: 63%. ES-MS: 300 (M + H$^+$). ^{1}H NMR: δ 4.26 (br, 4H), 4.00 (br,1H), 2.75 (s, 3H), 2.59 (s, 3H), 1.77−2.11 (m, 8H), 1.31−1.46 (m, 6H).

Results and Discussions

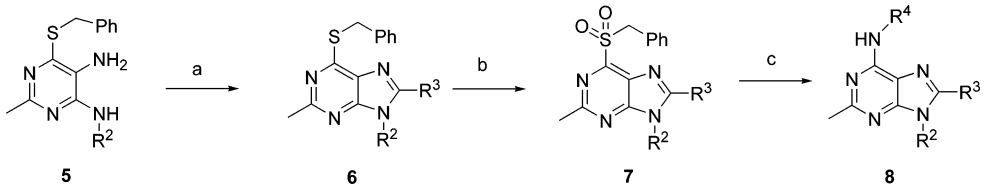
The starting material, 4,6-dichloro-2-methyl-5-nitropyrimidine (**1**) was prepared according to the literature.[9] The substituent R^1 at C-2 (first point of diversity) can be readily introduced from nitriles, such as alkyl, aryl, or heterocyclic nitriles, although only the methyl group (R^1 = Me) was used for illustration purpose.

Scheme 2



(a) Fe/HCl; (b) *n*-$BuNH_2$, Et_3N, *n*-BuOH, 100 °C; (c) $PhCH_2SH$, Et_3N, *n*-BuOH, 100 °C; (d) R^2NH_2, then $PhCH_2SH$, rt; (e) Fe/NH_4Cl.

Scheme 3



(a) R^3-CHO, $FeCl_3/SiO_2$; (b) *m*CPBA, CH_2Cl_2; (c) R^4-NH_2 (excess).

Table 1. Reduction of Nitropyrimidine **4** (R^2 = *n*-Bu)

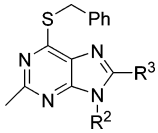
entry	reduction conditions	yield of **5** (%)
1	2 M $SnCl_2 \cdot 2H_2O$/HCl/rt	10
2	$SnCl_2 \cdot 2H_2O$/EtOAc/70 °C	3
3	Fe/HOAc/EtOH/rt	39
4	$Na_2S_2O_4/NH_4OH$/rt	50
5	Fe/HCl/EtOH/reflux	85
6	Fe/NH_4Cl/EtOH/reflux	90

Preparation of diaminopyrimidine **5** is depicted in Scheme 2. Compound **5** can in principle be synthesized by either reduction of the nitro to amino group, followed by substitution of a chlorine atom by an amine (reduction first), or substitution of chlorine atoms, followed by reduction (substitution first). In the reduction-first approach, nitro compound **1** was reduced by Fe/HCl to yield 5-amino-4,6-dichloro-2-methylpyrmidine **2**. Treatment of compound **2** with *n*-butylamine and benzylmercaptan in sequence afforded the desired compound **5**. This procedure only resulted in 19−22% overall yields. Moreover, the conditions are not suitable for the preparation of compounds using a parallel synthesis due to complicated workup in solution.

In the substitution-first approach, compound **1** was treated with an amine, followed by benzylmercaptan, to give compound **4**, which was in turn reduced to the desired diaminopyrimidine **5**. To avoid double substitution of the second chlorine in **1**, slow addition of a dilute solution of 1 equiv of the primary amine at room temperature was crucial. The workup of this reaction is quite simple, since **4** was readily crystallized in petroleum ether with 64−70% yields.

Reduction of the nitro group in **4** was more complicated, since catalytic reduction could not be employed due to sulfur poisoning and reduction by $LiAH_4$ might lead to diazo compounds.[10] A few reactions were explored, and iron powder in NH_4Cl solution was found to be the best reduction condition, with up to 90% yield, as shown in Table 1. The overall yield of this approach was higher than that of the

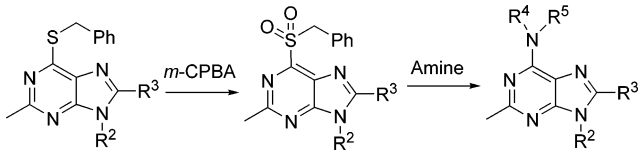
Table 2. Yields and Purity of Purine **6**[a]



	R^3					
R^2	Me (a)	*n*-Pr (b)	benzyl (c)	Ph (d)	4-MeO−Ph (e)	2-furyl (f)
			Yields (%)			
n-Bu (A)	45 (100)	51 (90)	66 (95)	51 (100)	57 (100)	40 (100)
i-Bu (B)	58 (100)	41 (85)	50 (68)	44 (100)	71 (87)	53 (100)
cyclohexyl (C)	54 (97)	56 (80)	31 (93)	58 (100)	67 (77)	43 (100)
benzyl (D)	32 (94)	47 (100)	52 (65)	55 (100)	55 (100)	41 (97)
Ph (E)	23 (96)	28 (86)	82 (67)	53 (97)	37 (97)	33 (96)
2-furyl-CH_2 (F)	40 (96)	41 (100)	54 (73)	54 (100)	14 (99)	47 (100)

[a] LC-ELSD purity is indicated in parentheses.

Table 3. MS, LC-ELSD Purities and Yields of Library Compounds **8**



entry	R^2	R^3	amine	MW	mass found	purity (%)	yield (%)
1	Ph	Me	pyrrolidine	293	294	100	84
2	Ph	Me	piperidine	307	308	100	66
3	Ph	Me	cyclohexanamine	321	322	100	58
4	Ph	Me	morpholine	309	310	100	49
5	Ph	Me	*n*-$PrNH_2$	281	282	100	71
6	Ph	Me	*i*-$BuNH_2$	295	296	100	60
7	Ph	Pr	pyrrolidine	321	322	88.2	87
8	Ph	Pr	piperidine	335	336	93.1	98
9	Ph	Pr	cyclohexanamine	349	350	100	56
10	Ph	Pr	morpholine	337	338	100	33
11	Ph	Pr	*n*-$PrNH_2$	309	310	100	48
12	Ph	Pr	*i*-$BuNH_2$	323	324	100	61
13	Ph	Ph	pyrrolidine	335	336	100	44
14	Ph	Ph	piperidine	369	370	88.8	13
15	Ph	Ph	cyclohexanamine	383	384	100	29
16	Ph	Ph	morpholine				
17	Ph	Ph	*n*-$PrNH_2$	343	344	100	28
18	Ph	Ph	*i*-$BuNH_2$	357	358	100	19
19	Ph	Bn	pyrrolidine	369	370	83.2	23
20	Ph	Bn	piperidine	383	384	94.5	10
21	Ph	Bn	cyclohexanamine	397	398	90.8	9
22	Ph	Bn	morpholine	385	386	95.0	14
23	Ph	Bn	*n*-$PrNH_2$	357	358	73.1	30
24	Ph	Bn	*i*-$BuNH_2$	371	372	94.5	20
25	Ph	*p*-MeO−Ph	pyrrolidine	385	386	95.6	50
26	Ph	*p*-MeO−Ph	piperidine	399	400	100	12
27	Ph	*p*-MeO−Ph	cyclohexanamine	413	414	100	36
28	Ph	*p*-MeO−Ph	morpholine	401	402	100	35
29	Ph	*p*-MeO−Ph	*n*-$PrNH_2$	373	374	87.4	42
30	Ph	*p*-MeO−Ph	*i*-$BuNH_2$	387	388	100	31
31	Ph	furan-2-yl	pyrrolidine	345	346	100	61
32	Ph	furan-2-yl	piperidine	359	360	93.1	37
33	Ph	furan-2-yl	cyclohexanamine	373	374	100	35
34	Ph	furan-2-yl	morpholine	361	362	100	35
35	Ph	furan-2-yl	*n*-$PrNH_2$	333	334	96.0	51
36	Ph	furan-2-yl	*i*-$BuNH_2$	347	348	100	41
37	Bn	Me	pyrrolidine	307	308	100	56
38	Bn	Me	piperidine	321	322	100	36
39	Bn	Me	cyclohexanamine	335	336	100	31
40	Bn	Me	morpholine	323	324	100	38
41	Bn	Me	*n*-$PrNH_2$	295	296	100	44
42	Bn	Me	*i*-$BuNH_2$	309	310	100	51
43	Bn	Pr	pyrrolidine	335	336	100	69
44	Bn	Pr	piperidine	349	350	100	36
45	Bn	Pr	cyclohexanamine	363	364	100	67
46	Bn	Pr	morpholine	350	351	100	23
47	Bn	Pr	*n*-$PrNH_2$	323	324	34.1	66
48	Bn	Pr	*i*-$BuNH_2$	337	338	100	63
49	Bn	Ph	pyrrolidine	369	370	93.1	57
50	Bn	Ph	piperidine	383	384	100	53
51	Bn	Ph	cyclohexanamine	397	398	100	68
52	Bn	Ph	morpholine	385	386	100	52
53	Bn	Ph	*n*-$PrNH_2$	357	358	94.3	78
54	Bn	Ph	*i*-$BuNH_2$	371	372	96.1	68
55	Bn	Bn	pyrrolidine	383	384	91.4	28
56	Bn	Bn	piperidine	397	398	100	20
57	Bn	Bn	cyclohexanamine	411	412	100	19
58	Bn	Bn	morpholine	399	400	100	20
59	Bn	Bn	*n*-$PrNH_2$	371	372	85.7	27
60	Bn	Bn	*i*-$BuNH_2$	385	386	100	24
61	Bn	*p*-MeO−Ph	pyrrolidine	399	400	88.3	67
62	Bn	*p*-MeO−Ph	piperidine	413	414	100	50
63	Bn	*p*-MeO−Ph	cyclohexanamine	427	428	100	50
64	Bn	*p*-MeO−Ph	morpholine	415	416	100	49
65	Bn	*p*-MeO−Ph	*n*-$PrNH_2$	387	388	84.0	60
66	Bn	*p*-MeO−Ph	*i*-$BuNH_2$	401	402	100	40
67	Bn	furan-2-yl	pyrrolidine	359	360	96.3	30
68	Bn	furan-2-yl	piperidine	373	374	96.6	16

Table 3. (Continued)

entry	R^2	R^3	amine	MW	mass found	purity (%)	yield (%)
69	Bn	furan-2-yl	cyclohexanamine	387	388	77.0	28
70	Bn	furan-2-yl	morpholine	375	376	100	13
71	Bn	furan-2-yl	*n*-$PrNH_2$	347	348	98.3	36
72	Bn	furan-2-yl	*i*-$BuNH_2$	361	362	97.4	40
73	*n*-Bu	Me	pyrrolidine	273	274	100	54
74	*n*-Bu	Me	piperidine	287	288	100	44
75	*n*-Bu	Me	cyclohexanamine	301	302	100	75
76	*n*-Bu	Me	morpholine	289	290	100	32
77	*n*-Bu	Me	*n*-$PrNH_2$	261	262	100	59
78	*n*-Bu	Me	*i*-$BuNH_2$	275	276	100	52
79	*n*-Bu	Pr	pyrrolidine	301	302	95.8	74
80	*n*-Bu	Pr	piperidine	315	316	100	58
81	*n*-Bu	Pr	cyclohexanamine	329	330	100	63
82	*n*-Bu	Pr	morpholine	317	318	98.2	46
83	*n*-Bu	Pr	*n*-$PrNH_2$	289	290	100	53
84	*n*-Bu	Pr	*i*-$BuNH_2$	303	304	100	64
85	*n*-Bu	Ph	pyrrolidine	335	336	85.3	75
86	*n*-Bu	Ph	piperidine	349	350	100	65
87	*n*-Bu	Ph	cyclohexanamine	363	364	100	61
88	*n*-Bu	Ph	morpholine	351	352	100	45
89	*n*-Bu	Ph	*n*-$PrNH_2$	323	324	91.6	58
90	*n*-Bu	Ph	*i*-$BuNH_2$	337	338	96.9	63
91	*n*-Bu	Bn	pyrrolidine	349	350	98.4	16
92	*n*-Bu	Bn	piperidine	363	364	100	16
93	*n*-Bu	Bn	cyclohexanamine	377	378	100	12
94	*n*-Bu	Bn	morpholine	365	366	100	14
95	*n*-Bu	Bn	*n*-$PrNH_2$	337	338	87.0	14
96	*n*-Bu	Bn	*i*-$BuNH_2$	351	352	95.7	27
97	*n*-Bu	*p*-MeO−Ph	pyrrolidine	365	366	90.4	69
98	*n*-Bu	*p*-MeO−Ph	piperidine	379	380	100	37
99	*n*-Bu	*p*-MeO−Ph	cyclohexanamine	393	394	100	55
100	*n*-Bu	*p*-MeO−Ph	morpholine	381	382	100	35
101	*n*-Bu	*p*-MeO−Ph	*n*-$PrNH_2$	353	354	100	53
102	*n*-Bu	*p*-MeO−Ph	*i*-$BuNH_2$	367	368	100	57
103	*n*-Bu	furan-2-yl	pyrrolidine	325	326	100	33
104	*n*-Bu	furan-2-yl	piperidine	339	340	97.7	31
105	*n*-Bu	furan-2-yl	cyclohexanamine	353	354	98.5	22
106	*n*-Bu	furan-2-yl	morpholine	–	–	–	–
107	*n*-Bu	furan-2-yl	*n*-$PrNH_2$	313	314	100	31
108	*n*-Bu	furan-2-yl	*i*-$BuNH_2$	327	328	100	23
109	*i*-Bu	Me	pyrrolidine	273	274	100	55
110	*i*-Bu	Me	piperidine	287	288	100	38
111	*i*-Bu	Me	cyclohexanamine	301	302	100	62
112	*i*-Bu	Me	morpholine	289	290	100	52
113	*i*-Bu	Me	*n*-$PrNH_2$	261	262	100	42
114	*i*-Bu	Me	*i*-$BuNH_2$	275	276	100	45
115	*i*-Bu	Pr	pyrrolidine	301	302	93.6	56
116	*i*-Bu	Pr	piperidine	315	316	100	36
117	*i*-Bu	Pr	cyclohexanamine	329	330	100	39
118	*i*-Bu	Pr	morpholine	317	318	100	43
119	*i*-Bu	Pr	*n*-$PrNH_2$	289	290	100	57
120	*i*-Bu	Pr	*i*-$BuNH_2$	303	304	100	41
121	*i*-Bu	Ph	pyrrolidine	335	336	93.7	56
122	*i*-Bu	Ph	piperidine	349	350	100	69
123	*i*-Bu	Ph	cyclohexanamine	363	364	83.2	56
124	*i*-Bu	Ph	morpholine	-	-	-	-
125	*i*-Bu	Ph	*n*-$PrNH_2$	323	324	95.8	64
126	*i*-Bu	Ph	*i*-$BuNH_2$	337	338	100	44
127	*i*-Bu	Bn	pyrrolidine	349	350	88.9	44
128	*i*-Bu	Bn	piperidine	363	364	100	29
129	*i*-Bu	Bn	cyclohexanamine	377	378	100	32
130	*i*-Bu	Bn	morpholine	365	366	98.5	27
131	*i*-Bu	Bn	*n*-$PrNH_2$	337	338	94.7	18
132	*i*-Bu	Bn	*i*-$BuNH_2$	351	352	100	32
133	*i*-Bu	*p*-MeO−Ph	pyrrolidine	365	366	81.5	71
134	*i*-Bu	*p*-MeO−Ph	piperidine	379	380	100	39
135	*i*-Bu	*p*-MeO−Ph	cyclohexanamine	393	394	94.8	36
136	*i*-Bu	*p*-MeO−Ph	morpholine	381	382	100	49
137	*i*-Bu	*p*-MeO−Ph	*n*-$PrNH_2$	353	354	97.2	22
138	*i*-Bu	p-MeO−Ph	*i*-$BuNH_2$	367	368	100	38
139	*i*-Bu	furan-2-yl	pyrrolidine	325	326	96.9	49
140	*i*-Bu	furan-2-yl	piperidine				
141	*i*-Bu	furan-2-yl	cyclohexanamine	353	354	98.1	44
142	*i*-Bu	furan-2-yl	morpholine				
143	*i*-Bu	furan-2-yl	*n*-$PrNH_2$	313	314	100	57

Table 3. (Continued)

entry	R^2	R^3	amine	MW	mass found	purity (%)	yield (%)
144	*i*-Bu	furan-2-yl	*i*-$BuNH_2$	327	328	100	44
145	cyclohexyl	Me	pyrrolidine	299	300	100	63
146	cyclohexyl	Me	piperidine	313	314	100	49
147	cyclohexyl	Me	cyclohexanamine	327	328	100	53
148	cyclohexyl	Me	morpholine	315	316	100	39
149	cyclohexyl	Me	*n*-$PrNH_2$	287	288	100	53
150	cyclohexyl	Me	*i*-$BuNH_2$	301	302	100	51
151	cyclohexyl	Pr	pyrrolidine	327	328	88.0	99
152	cyclohexyl	Pr	piperidine	341	342	100	42
153	cyclohexyl	Pr	cyclohexanamine	355	356	94.2	54
154	cyclohexyl	Pr	morpholine	343	344	100	42
155	cyclohexyl	Pr	*n*-$PrNH_2$	315	316	100	62
156	cyclohexyl	Pr	*i*-$BuNH_2$	329	330	100	50
157	cyclohexyl	Ph	pyrrolidine	361	362	95.7	32
158	cyclohexyl	Ph	piperidine	375	376	100	17
159	cyclohexyl	Ph	cyclohexanamine	389	390	91.6	19
160	cyclohexyl	Ph	morpholine	377	378	100	24
161	cyclohexyl	Ph	*n*-$PrNH_2$	349	350	56.6	26
162	cyclohexyl	Ph	*i*-$BuNH_2$	363	364	94.5	20
163	cyclohexyl	Bn	pyrrolidine	375	376	87.0	73
164	cyclohexyl	Bn	piperidine	389	390	100	36
165	cyclohexyl	Bn	cyclohexanamine	403	404	97.0	43
166	cyclohexyl	Bn	morpholine	391	392	100	32
167	cyclohexyl	Bn	*n*-$PrNH_2$	363	364	85.7	47
168	cyclohexyl	Bn	*i*-$BuNH_2$	377	378	100	28
169	cyclohexyl	*p*-MeO−Ph	pyrrolidine	391	392	95.6	47
170	cyclohexyl	*p*-MeO−Ph	piperidine	405	406	100	17
171	cyclohexyl	*p*-MeO−Ph	cyclohexanamine	419	420	100	17
172	cyclohexyl	*p*-MeO−Ph	morpholine	407	408	97.9	20
173	cyclohexyl	*p*-MeO−Ph	*n*-$PrNH_2$	379	380	81.1	11
174	cyclohexyl	*p*-MeO−Ph	*i*-$BuNH_2$	393	394	96.6	13
175	cyclohexyl	furan-2-yl	pyrrolidine	351	352	55.6	32
176	cyclohexyl	furan-2-yl	piperidine	365	366	100	5
177	cyclohexyl	furan-2-yl	cyclohexanamine	379	380	100	13
178	cyclohexyl	furan-2-yl	morpholine				
179	cyclohexyl	furan-2-yl	*n*-$PrNH_2$	339	340	46.4	33
180	cyclohexyl	furan-2-yl	*i*-$BuNH_2$	353	354	95.4	18
181	(furan-2-yl)-CH_2	Me	pyrrolidine	297	298	100	52
182	(furan-2-yl)-CH_2	Me	piperidine	311	312	100	56
183	(furan-2-yl)-CH_2	Me	cyclohexanamine	325	326	100	56
184	(furan-2-yl)-CH_2	Me	morpholine	313	314	97.8	43
185	(furan-2-yl)-CH_2	Me	*n*-$PrNH_2$	285	286	100	52
186	(furan-2-yl)-CH_2	Me	*i*-$BuNH_2$	299	300	100	40
187	(furan-2-yl)-CH_2	Pr	pyrrolidine	325	326	100	56
188	(furan-2-yl)-CH_2	Pr	piperidine	339	340	100	63
189	(furan-2-yl)-CH_2	Pr	cyclohexanamine	353	354	100	49
190	(furan-2-yl)-CH_2	Pr	morpholine	341	342	96.0	29
191	(furan-2-yl)-CH_2	Pr	*n*-$PrNH_2$	313	314	100	43
192	(furan-2-yl)-CH_2	Pr	*i*-$BuNH_2$	327	328	100	52
193	(furan-2-yl)-CH_2	Ph	pyrrolidine	359	360	100	43
194	(furan-2-yl)-CH_2	Ph	piperidine	373	374	100	25
195	(furan-2-yl)-CH_2	Ph	cyclohexanamine	387	388	100	26
196	(furan-2-yl)-CH_2	Ph	morpholine	375	376	100	27
197	(furan-2-yl)-CH_2	Ph	*n*-$PrNH_2$	347	348	100	33
198	(furan-2-yl)-CH_2	Ph	*i*-$BuNH_2$	361	362	100	28
199	(furan-2-yl)-CH_2	Bn	pyrrolidine	373	374	89.6	19
200	(furan-2-yl)-CH_2	Bn	piperidine	387	388	100	18
201	(furan-2-yl)-CH_2	Bn	cyclohexanamine	401	402	100	19
202	(furan-2-yl)-CH_2	Bn	morpholine	389	390	96.9	16
203	(furan-2-yl)-CH_2	Bn	*n*-$PrNH_2$	361	362	95.1	23
204	(furan-2-yl)-CH_2	Bn	*i*-$BuNH_2$	375	376	100	14
205	(furan-2-yl)-CH_2	*p*-MeO−Ph	pyrrolidine	389	390	95.2	51
206	(furan-2-yl)-CH_2	*p*-MeO−Ph	piperidine	403	404	100	26
207	(furan-2-yl)-CH_2	*p*-MeO−Ph	cyclohexanamine	417	418	100	60
208	(furan-2-yl)-CH_2	*p*-MeO−Ph	morpholine	405	406	100	53
209	(furan-2-yl)-CH_2	*p*-MeO−Ph	*n*-$PrNH_2$	377	378	96.0	57
210	(furan-2-yl)-CH_2	*p*-MeO−Ph	*i*-$BuNH_2$	391	392	100	46
211	(furan-2-yl)-CH_2	furan-2-yl	pyrrolidine	349	350	94.7	29
212	(furan-2-yl)-CH_2	furan-2-yl	piperidine	363	364	100	37
213	(furan-2-yl)-CH_2	furan-2-yl	cyclohexanamine	377	378	95.2	38
214	(furan-2-yl)-CH_2	furan-2-yl	morpholine	365	366	97.0	14
215	(furan-2-yl)-CH_2	furan-2-yl	*n*-$PrNH_2$	337	338	100	36
216	(furan-2-yl)-CH_2	furan-2-yl	*i*-$BuNH_2$	351	352	100	41

reduction-first approach, and the conditions are mild. At this stage, the second point of diversity (R^2) at N-9 was introduced.

The sequence of reactions leading to a purine library with four substituents is depicted in Scheme 3. Reaction of diamine **5** with an aldehyde in the presence of $FeCl_3$ and SiO_2 led to the desired purine structure **6** with a newly introduced C-8 substituent[11] (R^3, the third diversity point). Compound **6** was easily purified by flash chromatographic separation in good yields and high purities in most cases, as shown in Table 2. *m*CPBA oxidation of compound **6** led to sulfone **7** in excellent crude yield, which without further purification was used to react with an excess amount of primary or secondary amine in ethanol at 100 °C in sealed tubes to give the final target compounds **8**. Herein, a set of test compounds containing 216 tetrasubstituted purines (1 × 6 × 6 × 6 in diversity) were prepared. All the final compounds were purified and characterized by LC/MS-ELSD (Table 3).

Conclusion

A synthetic strategy for the construction of a 2,6,8,9-tetrasubstituted purine library using parallel solution phase synthesis has been demonstrated. The strategically pre-arranged sulfide substituent in the key intermediate pyrimidine can sustain reaction conditions for ring closure to form the purine core and is easily converted to the corresponding sulfone for the introduction of the fourth diversity point by nucleophilic displacement. This methodology provides a practical and efficient means for the preparation of a large number of diverse tetrasubstituted purines that are useful in the process of lead screening and optimization. The introduction of the sulfide group at the pyrimidine stage of purine synthesis provides a model study in feasibility of using sulfur-linked Merrifield resin as a traceless linker in solid-phase synthesis for combinatorial libraries of purines.

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