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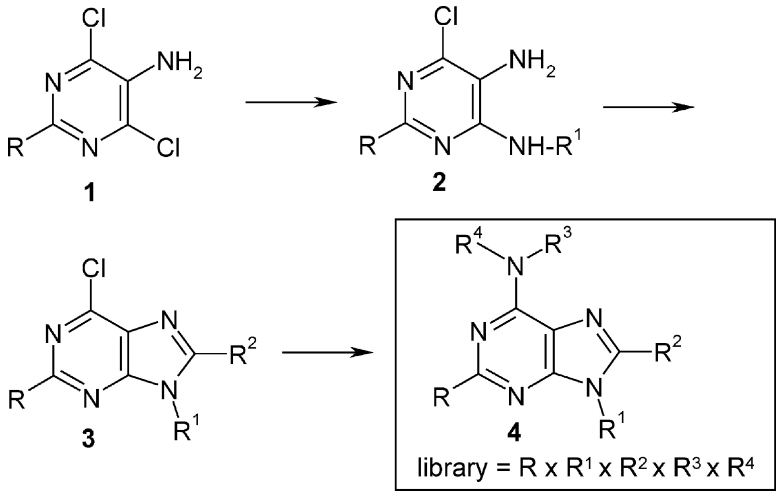

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Preparation of a Fully Substituted Purine Library

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A library of tetra-substituted purine analogues was readily prepared via parallel synthesis. This strategy relies on a key cyclization of a 4,5-diaminopyrimidine with either a carboxylic acid or its derivative to construct the 2,8,9-trisubstituted 6-chloropurine core. Further elaborations of this core allow the introduction of other diversity points. This methodology is demonstrated through the preparation of a 135-membered library of tetra-substituted purines in good yields and high purity.

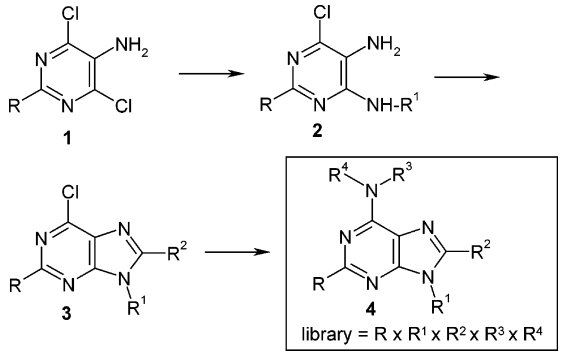
Introduction

Purine analogues are often shown to possess a wide range of interesting pharmacological activities.[1] For example, the purine nucleus is the key structural feature of many types of biologically active compounds, such as CDK inhibitors,[2] microtubule assembly inhibitors,[3] phosphodiesterase inhibitors[4] and Hsp 90 family inhibitors.[5] Consequently, purines have become a well-sought privileged class of compounds in drug discovery programs and a practical strategy for the construction of a library of purines that should aid both SAR studies and screenings for new leads. The unique structural feature of purines, which consists of four diversity points, has also attracted the attention of combinatorial chemistry, and two libraries have been reported.[6] Although many methodologies have been developed for the synthesis of various trisubstituted purines, few examples exist for the synthesis of fully substituted purine analogues. We envisioned an efficient strategy that should lead to a library of fully substituted purine analogues and with the five possible diversity points presented in the purine system. This strategy should lead to a large number of analogues, as shown in Scheme 1. Herein, we report the demonstration of this strategy via the preparation of a 135-membered library in good yields and high purity.

Experimental Section

General. Commercial reagents were used as received without additional purification. Melting point was uncorrected. Mass spectra and HPLC (ELSD) data were recorded on an 1100 LC/MS system (Agilent Technology Corporation) with Alltech ELSD 2000 using a YMC ODS-A, 5-μm, 120-Å, 4.6 × 50 mm (Waters, Inc.). HPLC (ELSD) run for the compounds from **4.30** to **4.35**, **4.37**, **4.38**, **4.48** and **4.90**−**4.135** were carried out using a linear gradient of 35−80% CH_3CN/H_2O (0.035% TFA) in 5−7 min, and others were 15−35% CH_3CN/H_2O (0.035% TFA) in 5 min. The retention time (t_R) for the expected (major) product was recorded. ^{1}H NMR data were obtained using a 300-MHz Varian VXR-300S NMR spectrometer with TMS as the internal standard and $CDCl_3$ as solvent. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; br, broad. Coupling constants (*J* values) where noted are quoted in Hertz. Compounds **1** were prepared according to the literature method.[7]

Scheme 1. The Synthetic Strategy to a Library of Fully Substituted Purine Analogs



General Procedure for the Preparation of 6-Chloro-2-substituted N^4-pyrimidine-4,5-diamines (2) (Method A). 5-Amino-4,6-dichloropyrimidine (**1**) (0.179 g, 1.0 mmol), the appropriate amine (2.0 mmol), and triethylamine (0.22 mL, 2.0 mmol) were dissolved in normal butyl alcohol (2.5 mL), and the mixture was stirred under reflux for 6 h. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to the crude product. Purification was by flash chromatography (elution with hexane followed by 20% ethyl acetate in hexane for the compounds **2.1**, **2.2**, **2.3**, **2.9**, and **2.10,** elution with hexane followed by 10% ethyl acetate in hexane for the compounds **2.5**, **2.6**, **2.7**, and **2.8).**

6-Chloro-2-methyl-N^4-propylpyrimidine-4,5-diamine (2.1). Pale yellow solid; yield, 97%. mp: 113.5−115.8 °C. ES-MS: 201 ($(M + 1)^+$). ^{1}H NMR δ 5.02 (br, 1H), 3.41−3.48 (m, 2H), 3.26 (br, 2H), 2.44 (s, 3H), 1.58−1.70 (m, 2H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

N^4-*sec*-Butyl-6-chloro-2-methylpyrimidine-4,5-diamine (2.2). Pale yellow solid; yield, 93%. mp: 117.7−118.2 °C. ES-MS: 215 ($(M + 1)^+$). ^{1}H NMR δ 4.67−4.69 (br, 1H), 4.12−4.21 (m, 1H), 3.13 (br, 1H), 2.45 (s, 3H), 1.52−1.61 (m, 2H), 1.20−1.22 (d, J = 6.0 Hz, 3H), 0.92−0.97 (t, J = 7.5 Hz, 3H).

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6-Chloro-N^4-(4-fluorophenyl)-2-methylpyrimidine-4,5-diamine (2.3). Pale yellow solid; yield, 27%. mp: 178.2−180.5 °C. ES-MS: 253 ((M + 1)$^+$). ^{1}H NMR δ 7.90 (br, 1H), 7.58−7.63 (m, 2H), 7.03−7.07 (d, J = 6.0 Hz, 1H), 2.52 (s, 3H).

Method B. 5-Amino-4,6-dichloropyrimidine (1.00 g, 5.6 mmol) and *p*-fluorophenylamine (0.54 mL, 5.6 mmol) were dissolved in a mixture of water and alcohol (25 mL, alcohol/water = 1:7), and the mixture was stirred under reflux for 5 h. Then the mixture was cooled, filtered, and recrystallized with methanol to yield the red solid. The solid was dissolved in 1 N NaOH aq until the pH was 10 and was extracted with ethyl acetate (3 × 25 mL). The combined ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield compound **2.3** (1.08 g, 77%. mp: 181.9−182.8 °C).

6-Chloro-2-methyl-N^4-pyridin-2-ylpyrimidine-4,5-diamine (2.4). Only starting material was recovered.

6-Chloro-2-phenyl-N^4-propylpyrimidine-4,5-diamine (2.5). Pale red solid; yield, 92%. mp: 134.9−134.3 °C. ES-MS: 263 ((M + 1)$^+$). ^{1}H NMR δ 8.30−8.32 (d, J = 6.0 Hz, 2H), 7.40−7.42 (d, J = 6.0 Hz, 3H), 5.00 (br, 1H), 3.58 (br, 2H), 1.69−1.76 (m, 2H), 1.00−1.05 (t, J = 7.5 Hz, 3H).

***N*^{4}-*sec*-Butyl-6-chloro-2-phenylpyrimidine-4,5-diamine (2.6).** White solid; yield, 88%. mp: 185.0−186.3 °C. ES-MS: 277 ((M + 1)$^+$). ^{1}HNMR δ 8.30 (br, 2H), 7.42 (br, 3H), 4.34 (br, 1H), 3.50 (br, 2H), 1.62−1.73 (m, 2H), 1.30−1.32 (d, J = 6.0 Hz, 3H), 0.97−1.02 (t, J = 7.5 Hz, 3H).

6-Chloro-2-(3-nitrophenyl)-N^4-propylpyrimidine-4,5-diamine (2.7). Yellow solid; yield, 85%. mp: 172.4−174.2 °C. ES-MS: 308 ((M + 1)$^+$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.70−8.72 (d, J = 10.0 Hz, 1H), 8.28−8.30 (d, J = 10.0 Hz, 1H), 7.63−7.66 (t, J = 7.5 Hz, 1H), 3.65−3.68 (t, J = 7.5 Hz, 1H), 1.77−1.81 (m, 2H), 1.03−1.06 (t, J = 7.5 Hz, 3H).

***N*^{4}-*sec*-Butyl-6-chloro-2-(3-nitrophenyl)-pyrimidine-4,5-diamine (2.8).** Yellow solid; yield, 70%. mp: 183.1−186.2 °C. ES-MS: 322 ((M + 1)$^+$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.64−8.66 (d, J = 10.0 Hz, 1H), 8.23−8.25 (d, J = 10.0 Hz, 1H), 7.57−7.60 (t, J = 7.5 Hz, 1H), 4.69 (br, 1H), 4.31−4.34 (t, J = 7.5 Hz, 1H), 3.44 (br, 1H), 1.62−1.72 (m, 2H), 1.31−1.32 (d, J = 5.0 Hz, 3H), 1.00−1.03 (t, J = 7.5 Hz, 3H).

6-Chloro-2-(4-chloro-phenyl)-N^4-propyl-pyrimidine-4,5-diamine (2.9). gray solid; yield, 90%. mp: 156.8−159.4 °C. ES-MS: 297 ((M + 1)$^+$). ^{1}H NMR δ 8.25−8.27 (dd, J = 6.0 Hz, 2H), 7.37−7.40 (dd, J = 9.0 Hz, 2H), 5.68 (br, 1H), 3.75 (br, 2H), 3.56−3.61 (t, J = 7.5 Hz, 2H), 1.70−1.77 (m, 2H), 1.00−1.05 (t, J = 7.5 Hz, 3H).

***N*^{4}-*sec*-Butyl-6-chloro-2-(4-chlorophenyl)-pyrimidine-4,5-diamine (2.10).** pale red solid; yield, 82%. mp: 203.3−204.3 °C. ES-MS: 311 ((M + 1)$^+$). ^{1}H NMR δ 8.25−8.27 (d, J = 6.0 Hz, 2H), 7.37−7.40 (dd, J = 9.0 Hz, 2H), 4.30 (br, 1H), 1.63−1.71 (m, 2H), 1.29−1.31 (d, J = 6.0 Hz, 3H), 0.97−1.02 (t, J = 7.5 Hz, 3H).

8-(2-Furanyl)-2-methyl-9-propyl-6-hydroxypurine (3.0). A solution of 6-chloro-2-methyl-N^4-*n*-propylpyrimidinyl-4,5-diamine (**2.1**) (0.202 g, 1 mmol) and 2-furaldehyde (2 mmol) in anhydrous DMSO (10 mL) was treated with 15% $FeCl_3$−SiO_2 (2 equiv) at 100 °C under nitrogen for 4 h. The cooled reaction mixture was filtered (washed with EtOAc, 3 × 20 mL). The filtrates were evaporated and purified by flash chromatography (4% methanol in DCM) to give 8-(2-furanyl)-2-methyl-9-propyl-6-hydroxypurine (**3.0**) as a white solid (78%). mp: 225 °C (decomposed). ES-MS: 259 ((M + 1)$^+$). ^{1}H NMR δ 7.59−7.60 (d, J = 3.0 Hz, 1H), 7.33−7.34 (d, J = 3.0 Hz, 1H), 6.59−6.61 (m, 1H), 4.45−4.50 (t, J = 7.5 Hz, 2H), 2.65 (s, 3H), 1.83−1.90 (m, 2H), 0.94−0.99 (t, J = 7.5 Hz, 3H).

8-(4-Fluorophenyl)-2-methyl-9-propyl-6-hydroxypurine (3.30). A mixture of 6-chloro-2-methyl-N^4-*n*-propylpyrimidinyl-4,5-diamine (**2.1**) (0.166 g, 0.8 mmol), 4′-fluorobenzoic acid (0.166 g, 1.2 mmol), and PPA (1.087 g, 3.2 mmol) in xylene (2.0 mL), was stirred under reflux for 24 h. The resulted mixture was diluted with water (15 mL), and extracted with ethyl acetate (3 × 10 mL). The water layer was treated with saturated $NaHCO_3$ to pH 8 to cause precipitation, which was filtered to yield gray solids (0.091 g, 38%) as the desired product **3.30**. The combined ethyl acetate layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (10% methanol in DCM) to give white solids **3.30** (0.047 g, 20%). mp: 230 °C (decomposed). ES-MS: 287 ((M + 1)$^+$). ^{1}H NMR δ 13.17 (br, 1H), 7.69−7.76 (m, 2H), 7.15−7.23 (m, 2H), 4.19−4.24 (m, 2H), 2.65 (s, 3H), 1.72−1.82 (m, 2H), 0.83−0.88 (t, J = 7.5 Hz, 3H).

6-Chloro-8-(4-fluorophenyl)-2-methyl-9-propyl-9*H*-purine (3.1). Method A. A mixture of 6-chloro-2-methyl-N^4-*n*-propylpyrimidinyl-4,5-diamine (**2.1**) (0.210 g, 1.0 mmol), and 4′-fluorobenzoic acid (0.144 g, 1.0 mmol) in $POCl_3$ (4.0 mL) was stirred under reflux for 5 h. The reaction mixture was concentrated in vacuo, diluted with water (10 mL), and extracted with ethyl acetate (3 × 10 mL), The combined ethyl acetate layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (10% ethyl acetate in hexane) to yield **3.1** (0.042 g, 13%. mp: 107.7−110.3 °C).

Method B. A mixture of 6-chloro-2-methyl-N^4-*n*-propylpyrimidinyl-4,5-diamine (**2.1**) (0.215 g, 1.0 mmol), 4′-fluorobenzoic acid (0.172 g, 1.2 mmol), and PPA (0.977 g, 2.9 mmol) in $POCl_3$ (4.5 mL) was stirred under reflux for 5 h. The reaction mixture was concentrated in vacuo, diluted with water (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (20% ethyl acetate in hexane) to yield **3.1** (0.111 g, 34%. mp: 108.7−111.3 °C). ES-MS: 305 ((M + 1)$^+$). ^{1}H NMR δ 7.74−7.79 (m, 2H), 7.22−7.29 (m, 2H), 4.26−4.31 (t, J = 7.5 Hz, 3H), 2.82 (s, 3H), 1.75−1.87 (m, 2H), 0.83−0.88 (t, J = 7.5 Hz, 3H).

General Procedure for the Preparation of 2,8,9-Trisubstituted 6-Chloropurines (3). 6-Chloro-2-substituted N^4-pyrimidinyl-4,5-diamines (**2**) (1.0 mmol), the appropriate acid or its derivatives (∼1.2 to 1.5 mmol) and PPA (0.5 g, 1.5 mmol) were dissolved in $POCl_3$ (5.0 mL) and stirred under reflux for 6−12 h. The reaction mixture was concentrated in vacuo, diluted with water (15 mL), and extracted with

ethyl acetate (3 × 10 mL). The water layer was treated with 5 N NaOH to pH 10 and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (10−25% ethyl acetate in hexane). In certain cases, the crude product was used directly in the next nucleophilic substitution.

6-Chloro-2-methyl-8-phenyl-9-propyl-9*H*-purine (3.2). White solid; yield, 52%. mp: 106.1−109.3 °C. ES-MS: 287 ((M + 1)$^+$). ^{1}H NMR δ 7.74−7.77 (m, 2H), 7.54−7.57 (m, 3H), 4.28−4.33 (t, J = 7.5 Hz, 2H), 2.82 (s, 3H), 1.78−1.86 (m, 2H), 0.84−0.89 (t, J = 7.5 Hz, 3H).

6-Chloro-2,8-dimethyl-9-propyl-9*H*-purine (3.3). Yellow oil; yield, 52%. ES-MS: 225 ((M + 1)$^+$). ^{1}H NMR δ 4.14−4.19 (t, J = 7.5 Hz, 2H), 2.77 (s, 3H), 2.67 (s, 3H), 1.81−1.90 (m, 2H), 0.95−1.00 (t, J = 7.5 Hz, 3H).

6-Chloro-8-ethyl-2-methyl-9-propyl-9*H*-purine (3.4). Yellow wax solid; yield, 60%. ES-MS: 239 ((M + 1)$^+$). ^{1}H NMR δ 4.26−4.31 (t, J = 7.5 Hz, 3H), 3.23−3.25 (m, 2H), 2.84 (s, 3H), 1.91−1.97 (m, 2H), 1.54−1.59 (t, J = 7.5 Hz, 3H), 1.01−1.06 (t, J = 7.5 Hz, 3H).

6-Chloro-2-methyl-8,9-dipropyl-9*H*-purine (3.5). Yellow oil; yield, 59%. ES-MS: 253 ((M + 1)$^+$). ^{1}H NMR δ 4.13−4.18 (t, J = 7.5 Hz, 2H), 2.86−2.91 (t, J = 7.5 Hz, 2H), 2.77 (s, 3H), 1.83−1.98 (m, 4H), 1.06−1.11 (t, J = 7.5 Hz, 3H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

6-Chloro-8-furan-2-yl-2-methyl-9-propyl-9*H*-purine (3.6). White solid; yield, 33%. mp: 119.9−122.9 °C. ES-MS: 277 ((M + 1)$^+$). ^{1}H NMR δ 7.69 (s, 1H), 7.39−7.41 (d, J = 6.0 Hz, 1H), 6.66−6.68 (m, 1H), 4.53−4.58 (t, J = 7.5 Hz, 2H), 2.78 (s, 3H), 1.86−1.94 (m, 2H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-8-(4-fluorophenyl)-2-methyl-9*H*-purine (3.7). White solid; yield, 32%. mp: 183.6−185.0 °C. ES-MS: 319 ((M + 1)$^+$). ^{1}H NMR δ 7.63−7.67 (m, 2H), 7.22−7.25 (d, J = 9.0 Hz, 2H), 4.36−4.44 (m, 1H), 2.80 (s, 3H), 2.37−2.47 (m, 1H), 1.91−2.01 (m, 1H), 1.73−1.75 (d, J = 6.0 Hz, 3H), 0.65−0.70 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-2-methyl-8-phenyl-9*H*-purine (3.8). White solid; yield, 40%. mp: 170.8−173.4 °C. ES-MS: 301 ((M + 1)$^+$). ^{1}H NMR δ 7.63−7.66 (m, 2H), 7.55−7.56 (br, 3H), 4.41−4.48 (m, 1H), 2.80 (s, 3H), 2.31−2.47 (m, 1H), 1.90−2.02 (m, 1H), 1.73−1.75 (d, J = 6.0 Hz, 3H), 0.65−0.70 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-2,8-dimethyl-9*H*-purine (3.9). Yellow oil; yield, 47%. ES-MS: 239 ((M + 1)$^+$). ^{1}H NMR δ 4.44−4.52 (m, 1H), 2.77 (s, 6H), 2.29−2.39 (m, 1H), 1.96−2.06 (m, 1H), 1.69−1.71 (d, J = 6.0 Hz, 3H), 0.80−0.85 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-8-ethyl-2-methyl-9*H*-purine (3.10). Yellow solid; yield, 42%. mp: 62.8−64.4 °C. ES-MS: 253 ((M + 1)$^+$). ^{1}H NMR δ 4.36−4.43 (m, 1H), 2.89−3.00 (m, 2H), 2.72 (s, 3H), 2.31−2.43 (m, 1H), 1.96−2.08 (m, 1H), 1.68−1.70 (d, J = 6.0 Hz, 3H), 1.43−1.48 (t, J = 7.5 Hz, 3H), 0.79−0.84 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-2-methyl-8-propyl-9*H*-purine (3.11). White solid; yield, 58%. mp: 122.2−123.1 °C. ES-MS: 267 ((M + 1)$^+$). ^{1}H NMR δ 4.36−4.39 (m, 1H), 2.89−2.92 (t, J = 4.5 Hz, 2H), 2.75 (s, 3H), 2.31−2.40 (m, 1H), 1.97−2.06 (m, 1H), 1.88−1.93 (m, 2H), 1.67−1.69 (d, J = 6.0 Hz, 3H), 1.05−1.10 (t, J = 7.5 Hz, 3H), 0.78−0.83 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-8-furan-2-yl-2-methyl-9*H*-purine (3.12). Pale yellow solid; yield, 13%. mp: 104.1−107.4 °C. ES-MS: 291 ((M + 1)$^+$).^{1}H NMR δ 7.67 (s, 1H), 7.30−7.31 (d, J = 3.0 Hz, 1H), 6.64−6.65 (t, J = 3.0 Hz 1H), 5.02−5.09 (m, 1H), 2.78 (s, 3H), 2.40−2.50 (m, 1H), 1.98−2.15 (m, 1H), 1.74−1.76 (d, J = 6.0 Hz, 3H), 0.77−0.82 (t, J = 7.5 Hz, 3H).

6-Chloro-8,9-*bis*(4-fluorophenyl)-2-methyl-9*H*-purine (3.13). White solid; yield, 32%. mp: 201.2−203.2 °C. ES-MS: 257 ((M + 1)$^+$). ^{1}H NMR δ 7.56−7.61 (m, 2H), 7.20−7.34 (m, 4H), 7.03−7.09 (t, J = 9.0 Hz, 2H), 2.76 (s, 3H).

6-Chloro-9-(4-fluorophenyl)-2-methyl-8-phenyl-9*H*-purine (3.14). White solid; yield, 51%. mp: decomposed. ES-MS: 339 ((M + 1)$^+$). ^{1}H NMR δ 7.57−7.60 (d, J = 9.0 Hz, 2H), 7.22−7.36 (m, 7H), 2.76 (s, 3H).

6-Chloro-9-(4-fluorophenyl)-2,8-dimethyl-9*H*-purine (3.15). White solid; yield, 85%. mp: decomposed. ES-MS: 277 ((M + 1)$^+$). ^{1}H NMR δ 7.31−7.38 (m, 4H), 2.72 (s, 3H), 2.57 (s, 3H).

6-Chloro-8-ethyl-9-(4-fluorophenyl)-2-methyl-9*H*-purine (3.16). White solid; yield, 84%. mp: 159.7−161.3 °C. ES-MS: 291 ((M + 1)$^+$). ^{1}H NMR δ 7.30−7.37 (m, 4H), 2.80−2.90 (m, 2H), 2.71 (s, 3H), 1.32−1.37 (t, J = 7.5 Hz, 3H).

6-Chloro-9-(4-fluorophenyl)-2-methyl-8-propyl-9*H*-purine (3.17). White solid; yield, 78%. mp: 134.1−134.8 °C. ES-MS: 305 ((M + 1)$^+$). ^{1}H NMR δ 7.31−7.39 (m, 4H), 2.76−2.81 (t, J = 7.5 Hz, 2H), 2.71 (s, 3H), 1.76−1.83 (m, 2H), 1.92−0.97 (t, J = 7.5 Hz, 3H).

6-Chloro-9-(4-fluorophenyl)-8-furan-2-yl-2-methyl-9*H*-purine (3.18). White solid; yield, 8%. mp: 265−266 °C. ES-MS: 329 ((M + 1)$^+$). ^{1}H NMR δ 7.54 (s, 1H), 7.39−7.42 (m, 2H), 7.31−7.34 (t, J = 4.5 Hz, 2H), 6.43−6.44 (m, 1H), 6.40−6.41 (m, 1H), 2.72 (s, 3H).

6-Chloro-8-methyl-2-phenyl-9-propyl-9*H*-purine (3.19). Yellow solid; yield, 78%. mp: 95.4−98.0 °C. ES-MS: 287 ((M + 1)$^+$). ^{1}H NMR δ 8.49−8.52 (dd, J = 9.0 Hz, 2H), 7.48−7.50 (t, J = 3.0 Hz, 3H), 4.24−4.29 (t, J = 7.5 Hz, 2H), 2.72 (s, 3H), 1.89−1.98 (m, 2H), 0.99−1.04 (t, J = 7.5 Hz, 3H).

6-Chloro-8-(4-fluorophenyl)-2-phenyl-9-propyl-9*H*-purine (3.20). Yellow solid; yield, 39%. mp: 170.0−171.6 °C. ES-MS: 367 ((M + 1)$^+$). ^{1}H NMR δ 8.53−8.55 (dd, J = 6.0 Hz, 2H), 7.79−7.84 (m, 2H), 7.50−7.52 (t, J = 3.0 Hz, 3H), 7.25−7.30 (m, 2H), 4.37−4.42 (t, J = 7.5 Hz, 2H), 1.88−1.93 (m, 2H), 0.90−0.95 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-8-methyl-2-phenyl-9*H*-purine (3.21). White solid; yield, 78%. mp: 74.1−76.2 °C. ES-MS: 301 ((M + 1)$^+$). ^{1}H NMR δ 8.47−8.50 (dd, J = 9.0 Hz, 2H), 7.48−7.52 (m, 3H), 4.44−4.49 (m, 1H), 2.72 (s, 3H), 2.43−2.53 (m, 1H), 2.02−2.11 (m, 1H), 1.77−1.79 (d, J = 6.0 Hz, 3H), 0.83−0.88 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-8-(4-fluorophenyl)-2-phenyl-9*H*-purine (3.22). Yellow solid; yield, 37%. mp: 143.3−146 °C. ES-MS: 381 ((M + 1)$^+$). ^{1}H NMR δ 8.51−8.54 (dd, J = 9.0 Hz, 2H), 7.66−7.71 (m, 2H), 7.50−7.56 (m, 3H),

7.25−7.50 (m, 2H), 4.43−4.51 (m, 1H), 2.50−2.60 (m, 1H), 1.98−2.10 (m, 1H), 1.84−1.86 (d, J = 6.0 Hz, 3H), 0.69−0.74 (t, J = 7.5 Hz, 3H).

6-Chloro-8-methyl-2-(3-nitrophenyl)-9-propyl-9*H*-purine (3.23). Yellow solid; yield, 60%. mp: 193.3−195.3 °C. ES-MS: 332 ((M + 1)$^+$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.84−8.86 (d, J = 10.0 Hz, 1H), 8.30−8.32 (d, J = 10.0 Hz, 1H), 7.65−7.68 (t, J = 7.5 Hz, 1H), 4.29−4.31 (t, J = 7.5 Hz, 2H), 2.74 (s, 3H), 1.94−1.98 (m, 2H), 1.02−1.05 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-8-methyl-2-(3-nitrophenyl)-9*H*-purine (3.24). Yellow solid; yield, 64%. mp: 233.0−234.1 °C. ES-MS: 346 ((M + 1)$^+$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.83−8.84 (d, J = 5.0 Hz, 1H), 8.31−8.33 (d, J = 10.0 Hz, 1H), 7.65−7.68 (t, J = 7.5 Hz, 1H), 4.50−4.53 (m, 1H), 2.73 (s, 3H), 2.43−2.45 (m, 1H), 2.07−2.10 (m, 1H), 1.78−1.80 (d, J = 10.0 Hz, 3H), 0.85−0.88 (t, J = 7.5 Hz, 3H).

6-Chloro-2-(4-chlorophenyl)-8-methyl-9-propyl-9*H*-purine (3.25). Yellow solid; yield, 70%. mp: 184.2−185.1 °C. ES-MS: 321 ((M + 1)$^+$). ^{1}H NMR δ 8.43−8.46 (dd, J = 9.0 Hz, 2H), 7.43−7.46 (dd, J = 9.0 Hz, 2H), 4.23−4.27 (t, J = 6.0 Hz, 2H), 2.70 (s, 3H), 1.90−1.97 (m, 2H), 0.99−1.04 (t, J = 7.5 Hz, 3H).

6-Chloro-2-(4-chlorophenyl)-8-(4-fluorophenyl)-9-propyl-9*H*-purine (3.26). Yellow solid; yield, 30%. mp: 188.7−189.3 °C. ES-MS: 401 ((M + 1)$^+$). ^{1}H NMR δ 8.45−8.48 (dd, J = 9.0 Hz, 2H), 7.78−7.83 (m, 2H), 7.44−7.47 (dd, J = 9.0 Hz, 2H), 7.25−7.30 (m, 2H), 4.35−4.40 (t, J = 7.5 Hz, 2H), 1.87−1.94 (m, 2H), 0.89−0.94 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-2-(4-chlorophenyl)-8-methyl-9*H*-purine (3.27). White solid; yield, 74%. mp: 118.6−119.1 °C. ES-MS: 335 ((M + 1)$^+$). ^{1}H NMR δ 8.41−8.44 (d, J = 9.0 Hz, 2H), 7.43−7.46 (d, J = 9.0 Hz, 2H), 4.40−4.58 (m, 1H), 2.71 (s, 3H), 2.38−2.58 (m, 1H), 2.00−2.18 (m, 1H), 1.75−1.77 (d, J = 6.0 Hz, 3H), 0.82−0.87 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-6-chloro-2-(4-chlorophenyl)-8-(4-fluorophenyl)-9*H*-purine (3.28). Yellow solid; yield, 26%. mp: 179.6−181.9 °C. ES-MS: 415 ((M + 1)$^+$). ^{1}H NMR δ 8.45−8.48 (d, J = 9.0 Hz, 2H), 7.68−7.71 (m, 2H), 7.46−7.49 (d, J = 9.0 Hz, 2H), 7.25−7.30 (m, 2H), 4.46−4.49 (m, 1H), 2.40−2.60 (m, 1H), 2.00−2.20 (m, 1H), 1.83−1.85 (d, J = 6.0 Hz, 3H), 0.69−0.74 (t, J = 7.5 Hz, 3H).

General Procedure for the Preparation of 2,6,8,9-Tetrasubstituted Purines (4). 6-Chloropurine (**3**) (0.05−0.2 mmol) was dissolved in DCM (3.0 mL), divided into six equilibrations in glass tubes, and concentrated in vacuo. Ten times of the appropriate amine in butyl alcohol (2.0 mL) was added. The tubes were sealed and heated under 110 °C for 7−17 h. The reaction mixture was concentrated in vacuo and purified by HPLC/MS.

Butyl-[8-(4-fluorophenyl)-2-methyl-9-propyl-9*H*-purin-6-yl]-amine (4.2). White solid; yield, 87%. ES-MS: 342 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.57 min). ^{1}H NMR δ 7.64−7.68 (m, 2H), 7.19−7.25 (m, 2H), 4.17−4.22 (t, J = 7.5 Hz, 2H), 3.71 (br, 2H), 2.62 (s, 3H), 1.62−1.82 (m, 4H), 1.40−1.50 (m, 2H), 0.94−0.99 (t, J = 7.5 Hz, 3H), 0.79−0.84 (t, J = 7.5 Hz, 3H).

8-(4-Fluorophenyl)-2-methyl-6-morpholin-4-yl-9-propyl-9*H*-purine (4.4). Yellow oil; yield, 81%. ES-MS: 356 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.31 min). ^{1}H NMR δ 7.63−7.67 (m, 2H), 7.22−7.28 (m, 2H), 4.46 (br, 4H), 4.29−4.34 (t, J = 7.5 Hz, 2H), 3.86−3.89 (m, 4H), 2.74 (s, 3H), 1.68−1.82 (m, 2H), 0.82−0.87 (t, J = 7.5 Hz, 3H).

8-(4-Fluorophenyl)-2-methyl-9-propyl-6-pyrrolidin-1-yl-9*H*-purine (4.5). Yellow wax solid; yield, 96%. ES-MS: 340 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.07 min). ^{1}H NMR δ 7.66−7.71 (m, 2H), 7.23−7.29 (m, 2H), 4.37 (br, 2H), 4.25−4.30 (t, J = 7.50 Hz, 2H), 4.00 (br, 2H), 2.78 (s, 3H), 2.10−2.14 (br, 4H), 1.70−1.85 (m, 2H), 0.83−0.88 (t, J = 7.5 Hz, 3H).

Butyl-(2-methyl-8-phenyl-9-propyl-9*H*-purin-6-yl)-amine (4.7). Pale yellow solid; yield, 85%. ES-MS: 324 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.43 min). ^{1}H NMR δ 7.64−7.68 (m, 2H), 7.49−7.54 (m, 3H), 5.72 (br, 1H), 4.19−4.24 (t, J = 7.5 Hz, 2H), 3.68−3.71 (br, 2H), 2.62 (s, 3H), 1.62−1.83 (m, 4H), 1.43−1.53 (m, 2H), 0.94−0.99 (t, J = 7.5 Hz, 3H), 0.79−0.84 (t, J = 7.5 Hz, 3H).

Benzyl-(8-ethyl-2-methyl-9-propyl-9*H*-purin-6-yl)-amine (4.16). White solid; yield, 78%. ES-MS: 310 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.83 min). ^{1}H NMR δ 11.40 (br, 1H), 7.50−7.52 (d, J = 6.0 Hz, 2H), 7.27−7.35 (m, 3H), 7.31−7.34 (m, 2H), 5.30−5.32 (d, J = 6.0 Hz, 2H), 4.03−4.08 (t, J = 7.5 Hz, 2H), 2.80−2.87 (m, 2H), 2.64 (s, 3H), 1.74−1.84 (m, 2H), 1.44−1.49 (t, J = 7.5 Hz, 3H), 0.94−0.99 (t, J = 7.5 Hz, 3H).

Butyl-(8-ethyl-2-methyl-9-propyl-9*H*-purin-6-yl)-amine (4.17). White solid; yield, 84%. ES-MS: 276 ((M + 1)$^+$). HPLC (ELSD): 95% (t_R = 2.51 min). ^{1}H NMR δ 4.04−4.10 (m, 4H), 2.80−2.85 (m, 2H), 2.65 (s, 3H), 1.74−1.84 (m, 4H), 1.41−1.49 (m, 5H), 0.94−1.00 (m, 6H).

Cyclohexyl-(8-ethyl-2-methyl-9-propyl-9*H*-purin-6-yl)-amine (4.18). White solid; yield, 71%. ES-MS: 302 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.87 min). ^{1}H NMR δ 10.49−10.51 (br, 1H), 4.71−4.74 (br, 1H), 4.04−4.09 (t, J = 7.5 Hz, 2H), 2.79−2.86 (m, 2H), 2.63 (s, 3H), 1.27−2.10 (m, 12H), 1.42−1.47 (t, J = 7.5 Hz, 3H), 0.94−0.99 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-8-(4-fluorophenyl)-2-methyl-6-morpholin-4-yl-9*H*-purine (4.33). White solid; yield, 75%. ES-MS: 370 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.85 min). ^{1}H NMR δ 7.52−7.59 (m, 2H), 7.20−7.29 (m, 2H), 4.32−4.40 (br, 5H), 3.85−3.88 (t, J = 4.5 Hz, 4H), 2.69 (s, 3H), 2.30−2.40 (m, 1H), 1.85−1.94 (m, 1H), 1.68−1.70 (d, J = 6.0 Hz, 3H), 0.65−0.70 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-8-(4-fluorophenyl)-2-methyl-6-pyrrolidin-1-yl-9*H*-purine (4.35). White solid; yield, 92%. ES-MS: 354 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.77 min). ^{1}H NMR δ 7.53−7.59 (m, 2H), 7.21−7.30 (m, 2H), 4.29−4.38 (m, 3H), 4.03 (br, 2H), 2.76 (s, 3H), 2.28−2.39 (m, 1H), 2.06−2.10 (m, 4H), 1.83−1.97 (m, 1H), 1.68−1.70 (d, J = 6.0 Hz, 3H), 0.65−0.70 (t, J = 7.5 Hz, 3H).

(9-*sec*-Butyl-2-methyl-8-phenyl-9*H*-purin-6-yl)-cyclohexylamine (4.38). White solid; yield, 94%. ES-MS: 364 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.60 min). ^{1}H NMR δ 7.56−7.59 (m, 5H), 4.72−4.92 (br, 1H), 4.40−4.50 (m,

1H), 2.66 (s, 3H), 1.22−2.38 (m, 12H), 1.70−1.72, (d, J = 6.0 Hz, 3H), 0.66−0.71 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-2-methyl-8-phenyl-6-pyrrolidin-1-yl-9*H*-purine (4.41). White solid; yield, 92%. ES-MS: 336 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.61 min). ^{1}H NMR δ 7.56 (s, 5H), 4.36−4.40 (m, 3H), 4.06 (br, 2H), 2.79 (s, 3H), 2.28−2.42 (m, 1H), 2.09 (br, 4H), 1.82−1.98 (m, 1H), 1.68−1.70 (d, J = 6.0 Hz, 3H), 0.65−0.70 (t, J = 7.5 Hz, 3H).

Benzyl-(9-*sec*-butyl-8-furan-2-yl-2-methyl-9*H*-purin-6-yl)-amine (4.55). White solid; yield, 76%. ES-MS: 362 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.84 min). ^{1}H NMR δ 7.65 (s, 1H), 7.50−7.53 (d, J = 9.0 Hz, 2H), 7.29−7.37 (m, 3H), 7.13−7.14 (d, J = 3.0 Hz, 1H), 6.63−6.65 (m, 1H), 5.30−5.35 (br, 2H), 5.01−5.03 (m, 1H), 2.66 (s, 3H), 2.30−2.35 (m, 1H), 1.93−2.03 (m, 1H), 1.68−1.70 (d, J = 6.0 Hz, 3H), 0.78−0.83 (t, J = 7.5 Hz, 3H).

9-(4-Fluorophenyl)-2-methyl-6-morpholin-4-yl-8-phenyl-9*H*-purine (4.69). White solid; yield, 76%. ES-MS: 390 ((M + 1)$^+$). HPLC (ELSD): 100%(t_R = 2.98 min). ^{1}H NMR δ 7.14−7.47 (m, 9H), 4.46 (br, 4H), 3.88−3.91 (t, J = 4.5 Hz, 4H), 2.61 (s, 3H).

Butyl-[8-ethyl-9-(4-fluorophenyl)-2-methyl-9*H*-purin-6-yl]-amine (4.79). White solid; yield, 90%. ES-MS: 328 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.69 min). ^{1}H NMR δ 7.29−7.34 (m, 4H), 4.11−4.13 (br, 2H), 2.68−2.76 (m, 2H), 2.58 (s, 3H), 1.76−1.81 (m, 2H), 1.45−1.52 (m, 2H), 1.29−1.34 (t, J = 7.5 Hz, 3H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

8-Ethyl-9-(4-fluorophenyl)-2-methyl-6-morpholin-4-yl-9*H*-purine (4.81). Sorrel wax solid; yield, 94%. ES-MS: 342 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 1.96 min). ^{1}H NMR δ 7.23−7.35 (m, 4H), 4.41 (br, 4H), 3.86−3.89 (t, J = 4.5 Hz, 4H), 2.65−2.72 (m, 2H), 2.57 (s, 3H), 1.23−1.38 (t, J = 7.5 Hz, 3H).

8-Methyl-6-morpholin-4-yl-2-phenyl-9-propyl-9*H*-purine (4.93). White solid; yield, 92%. ES-MS: 338 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 4.31 min). ^{1}H NMR δ 8.42−8.45 (dd, J = 9.0 Hz, 2H), 7.42−7.45 (m, 3H), 4.31−4.34 (t, J = 4.5 Hz, 4H), 4.16−4.21 (t, J = 7.5 Hz, 2H), 3.86−3.89 (t, J = 4.5 Hz, 4H), 2.61 (s, 3H), 1.82−1.98 (m, 2H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

8-Methyl-2-phenyl-9-propyl-6-pyrrolidin-1-yl-9*H*-purine (4.95). White solid; yield, 78%. ES-MS: 322 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 1.56 min). ^{1}H NMR δ 8.41−8.44 (dd, J = 9.0 Hz, 2H), 7.46−7.48 (t, J = 3.0 Hz, 3H), 4.24−4.29 (t, J = 7.5 Hz, 2H), 3.95 (br, 4H), 2.82 (s, 3H), 2.07 (br, 4H), 1.87−1.99 (m, 2H), 0.99−1.04 (t, J = 7.5 Hz, 3H).

Benzyl-[8-(4-fluorophenyl)-2-phenyl-9-propyl-9*H*-purin-6-yl]-amine (4.96). Yellow oil; yield, 97%. ES-MS: 438 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.71 min). ^{1}H NMR δ 8.35−8.47 (br, 2H), 7.73−7.77 (m, 2H), 7.51 (br, 3H), 7.30−7.36 (m, 2H), 5.41 (br, 1H), 5.30 (br, 1H), 4.32−4.37 (t, J = 7.5 Hz, 2H), 1.89 (br, 2H), 0.90−0.95 (t, J = 7.5 Hz, 3H).

Butyl-[8-(4-fluorophenyl)-2-phenyl-9-propyl-9*H*-purin-6-yl]-amine (4.97). Yellow oil; yield, 77%. ES-MS: 404 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.30 min). ^{1}H NMR δ 8.47 (br, 2H), 7.69−7.74 (m, 2H), 7.47 (br, 3H), 7.22−7.28 (m, 2H), 4.28−4.33 (t, J = 7.5 Hz, 2H), 3.79 (br, 2H), 1.70−1.91 (m, 4H), 1.44−1.56 (m, 2H), 0.96−1.01 (t, J = 7.5 Hz, 3H), 0.87−0.92 (t, J = 7.5 Hz, 3H).

Benzyl-(9-*sec*-butyl-8-methyl-2-phenyl-9*H*-purin-6-yl)-amine (4.102). White solid; yield, 93%. ES-MS: 372 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 2.75 min). ^{1}H NMR δ 9.09 (br, 1H), 8.43 (br, 2H), 7.47−7.52 (m, 5H), 7.21−7.34 (m, 3H), 4.96 (br, 2H), 4.44−4.51 (m, 1H), 2.80 (s, 3H), 2.48 (br, 1H), 2.02−2.11 (m, 1H), 1.78−1.80 (d, J = 6.0 Hz, 3H), 0.83−0.88 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-8-methyl-6-morpholin-4-yl-2-phenyl-9*H*-purine (4.105). White solid; yield, 92%. ES-MS: 338 ((M + 1)$^+$). HPLC (ELSD): 99% (t_R = 2.84 min). ^{1}H NMR δ 8.39−8.45 (m, 2H), 7.44−7.50 (m, 3H), 4.48−4.55 (m, 1H), 4.20−4.23 (t, J = 4.5 Hz, 4H), 3.87−3.90 (t, J = 4.5 Hz, 4H), 2.74 (s, 3H), 2.43−2.53 (m, 1H), 2.00−2.08 (m, 1H), 1.75−1.77 (d, J = 6.0 Hz, 3H), 0.82−0.87 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-8-methyl-2-phenyl-6-pyrrolidin-1-yl-9*H*-purine (4.107). White solid; yield, 93%. ES-MS: 336 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 1.96 min). ^{1}H NMR δ 8.41−8.44 (m, 2H), 7.46−7.48 (m, 3H), 4.53−4.56 (m, 1H), 3.98 (br, 4H), 2.86 (s, 3H), 2.45−2.53 (m, 1H), 2.03−2.12 (m, 5H), 1.79−1.81 (d, J = 6.0 Hz, 3H), 0.83−0.88 (t, J = 7.5 Hz, 3H).

9-*sec*-Butyl-8-(4-fluorophenyl)-6-morpholin-4-yl-2-phenyl-9*H*-purine (4.111). White solid; yield, 88%. ES-MS: 432 ((M + 1)$^+$). HPLC (ELSD): 99% (t_R = 4.77 min). ^{1}H NMR δ 8.45−8.48 (dd, J = 9.0 Hz, 2H), 7.59−7.64 (m, 2H), 7.45−7.50 (t, J = 7.5 Hz, 3H), 7.20−7.23 (d, J = 9.0 Hz, 2H), 4.33−4.39 (m, 5H), 3.87−3.90 (t, J = 4.5 Hz, 4H), 2.56−2.61 (m, 1H), 1.92−2.01 (m, 1H), 1.80−1.82 (d, J = 6.0 Hz, 3H), 0.66−0.71 (t, J = 7.5 Hz, 3H).

[2-(4-Chlorophenyl)-8-methyl-9-propyl-9*H*-purin-6-yl]-cyclohexylamine (4.116). Gray solid; yield, 88%. ES-MS: 384 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 6.54 min). ^{1}H NMR δ 8.39−8.42 (dd, J = 9.0 Hz, 2H), 7.39−7.42 (dd, J = 9.0 Hz, 2H), 4.30 (br, 1H), 4.12−4.17 (t, J = 7.5 Hz, 2H), 2.58 (s, 3H), 2.14−2.18 (br, 2H), 1.79−1.90 (m, 4H), 1.67−1.70 (br, 1H), 1.24−1.53 (m, 5H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

2-(4-Chlorophenyl)-8-methyl-6-morpholin-4-yl-9-propyl-9*H*-purine (4.117). Pale yellow solid; yield, 90%. ES-MS: 372 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 6.01 min). ^{1}H NMR δ 8.37−8.40 (dd, J = 9.0 Hz, 2H), 7.38−7.42 (dd, J = 12.0 Hz, 2H), 4.33−4.36 (t, J = 4.5 Hz, 4H), 4.15−4.20 (t, J = 7.5 Hz, 3H), 3.86−3.90 (t, J = 4.5 Hz, 4H), 2.59 (s, 3H), 1.85−1.93 (m, 2H), 0.96−1.01 (t, J = 7.5 Hz, 3H).

2-(4-Chlorophenyl)-8-methyl-9-propyl-6-pyrrolidin-1-yl-9*H*-purine (4.118). Pale yellow solid; yield, 88%. ES-MS: 356 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 5.08 min). ^{1}H NMR δ 8.41−8.45 (dd, J = 12.0 Hz, 2H), 7.37−7.42 (dd, J = 15.0 Hz, 2H), 4.14−4.18 (t, J = 6.0 Hz, 2H), 4.03 (br, 4H), 2.60 (s, 3H), 2.04 (br, 4H), 1.82−1.94 (m, 2H), 0.95−1.00 (t, J = 7.5 Hz, 3H).

***sec*-Butyl-[9-*sec*-butyl-2-(4-chlorophenyl)-8-methyl-9*H*-purin-6-yl]-amine (4.128).** Pale yellow solid; yield, 96%. ES-MS: 372 ((M + 1)$^+$). HPLC (ELSD): 100% (t_R = 3.52 min). ^{1}H NMR δ 8.40−8.43 (d, J = 9.0 Hz, 2H), 7.39−

Table 1. Results of Amino Substitution 4,6-Dichloropyrimidines **1** Based on Equation 1

entry	R	R^1	solvent	product	MW	M + 1	yield
1	methyl	*n*-propyl	*n*-BuOH	**2.1**	200	201	97
2	methyl	*sec*-butyl	*n*-BuOH	**2.2**	214	215	93
3	methyl	*p*-fluorophenyl	*n*-BuOH	**2.3**	252	253	27
4	methyl	*p*-fluorophenyl	EtOH/HCl	**2.3**	252	253	77
5	methyl	pyridin-2-yl	*n*-BuOH	**2.4**	235		0
6	phenyl	*n*-propyl	*n*-BuOH	**2.5**	262	263	92
7	phenyl	*sec*-butyl	*n*-BuOH	**2.6**	276	277	88
8	*m*-nitrophenyl	*n*-propyl	*n*-BuOH	**2.7**	307	308	85
9	*m*-nitrophenyl	*sec*-butyl	*n*-BuOH	**2.8**	321	322	70
10	*p*-chlorophenyl	*n*-propyl	*n*-BuOH	**2.9**	296	297	90
11	*p*-chlorophenyl	*sec*-butyl	*n*-BuOH	**2.10**	310	311	82

Table 2. Exploration Results of Purine Ring Formation Based on Equation 2

entry	R^2	X	condition	time, h	product	R^6	yield, %
1	2-furanyl	H	$FeCl_3-SiO_2$	4	**3.0**	OH	78
2	4′-fluorophenyl	OH	$POCl_3$	5	**3.1**	Cl	13
3	4′-fluorophenyl	OH	PPA/xylene	24	**3.30**	OH	58
4	4′-fluorophenyl	OH	$POCl_3$/PPA	5	**3.1**	Cl	34

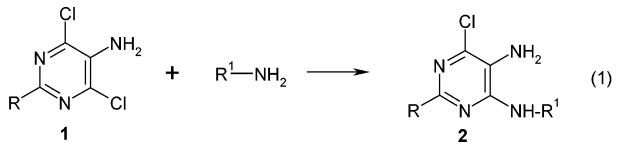
Table 3. Preparation of 6-Chloropurines **3** Based on Equation 3

entry	R	R^1	R^2	X	product	MW	M + 1	yield[a], %
1	methyl	*n*-propyl	*p*-fluorophenyl	OH	**3.1**	304	305	34
2	methyl	*n*-propyl	phenyl	Cl	**3.2**	286	287	52
3	methyl	*n*-propyl	methyl	OAc	**3.3**	224	225	52
4	methyl	*n*-propyl	ethyl	OCOEt	**3.4**	238	239	60
5	methyl	*n*-propyl	*n*-propyl	Cl	**3.5**	252	253	59
6	methyl	*n*-propyl	furan-2-yl	OH	**3.6**	276	277	33
7	methyl	*sec*-butyl	*p*-fluorophenyl	OH	**3.7**	318	319	32
8	methyl	*sec*-butyl	phenyl	Cl	**3.8**	300	301	40
9	methyl	*sec*-butyl	methyl	OAc	**3.9**	238	239	47
10	methyl	*sec*-butyl	ethyl	OCOEt	**3.10**	252	253	42
11	methyl	*sec*-butyl	*n*-propyl	Cl	**3.11**	266	267	58
12	methyl	*sec*-butyl	furan-2-yl	OH	**3.12**	290	291	13
13	methyl	*p*-fluorophenyl	*p*-fluorophenyl	OH	**3.13**	356	257	32
14	methyl	*p*-fluorophenyl	phenyl	Cl	**3.14**	338	339	51
15	methyl	*p*-fluorophenyl	methyl	OAc	**3.15**	276	277	85
16	methyl	*p*-fluorophenyl	ethyl	OCOEt	**3.16**	290	291	84
17	methyl	*p*-fluorophenyl	*n*-propyl	Cl	**3.17**	304	305	78
18	methyl	*p*-fluorophenyl	furan-2-yl	OH	**3.18**	328	329	8
19	phenyl	*n*-propyl	methyl	OAc	**3.19**	286	287	78
20	phenyl	*n*-propyl	*p*-fluorophenyl	OH	**3.20**	366	367	39
21	phenyl	*sec*-butyl	methyl	OAc	**3.21**	300	301	78
22	phenyl	*sec*-butyl	*p*-fluorophenyl	OH	**3.22**	380	381	37
23	*m*-nitrophenyl	*n*-propyl	methyl	OAc	**3.23**	331	332	60
24	*m*-nitrophenyl	*sec*-butyl	methyl	OAc	**3.24**	345	346	64
25	*p*-chlorophenyl	*n*-propyl	methyl	OAc	**3.25**	320	321	70
26	*p*-chlorophenyl	*n*-propyl	*p*-fluorophenyl	OH	**3.26**	400	401	30
27	*p*-chlorophenyl	*sec*-butyl	methyl	OAc	**3.27**	334	335	74
28	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	OH	**3.28**	414	415	26

7.42 (d, $J = 9.0$ Hz, 2H), 4.30−4.58 (m, 2H), 2.58 (s, 3H), 2.38−2.52 (m, 1H), 1.88−2.02 (m, 1H), 1.71−1.73 (m, 5H), 1.30−1.32 (d, $J = 6.0$ Hz, 3H), 0.99−1.04 (t, $J = 7.5$ Hz, 3H), 0.80−0.85 (t, $J = 7.5$ Hz, 3H).

Results and Discussions

The starting material 4,6-dichloro-5-aminopyrimidines (**1**) were synthesized according to literature procedures,[7] which introduced the first diversity point, R. The second diversity point R^1 was introduced by the substitution of pyrimidines **1** with an amine to give pyrimidines **2**, as shown in eq 1.[8]



The substitution reactions were carried out with both aliphatic and aromatic amines, and results are summarized in Table 1. The reactions of pyrimidines **1** with an aliphatic amine generally gave the desired pyrimidines **2** in high yields, entries 1−2 and 6−11 in Table 1; however, 2-aminopyridine failed to yield the desired product, whereas *p*-fluorophenylaniline gave a low yield under standard reaction conditions (entries 3 and 5, Table 1). It is postulated that protonation of compound **1** could activate the chloro group toward nucleophilic substitution reactions, which has been reported in the literature.[9] Therefore, when the reaction with *p*-fluoroaniline was conducted in dilute HCl/EtOH solution, the desired product **2.3** was isolated in a higher yield of 77%.

The third diversity point was introduced via the construction of the purine ring system from diaminopyrimidines **2**,

Table 4. Results of Fully Substituted Purine Analogs **4** Based on Equation 4[a]

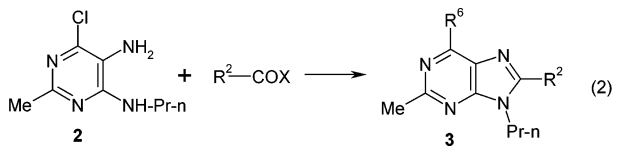
entry	R	R^1	R^2	R^3	product	MW	M + 1	yield
1	methyl	*n*-propyl	*p*-fluorophenyl	Bn	**4.1**	375	376	97
2	methyl	*n*-propyl	*p*-fluorophenyl	*n*-butyl	**4.2**	341	342	87
3	methyl	*n*-propyl	*p*-fluorophenyl	cyclohexyl	**4.3**	367	368	74
4	methyl	*n*-propyl	*p*-fluorophenyl	morpholinyl	**4.4**	355	356	81
5	methyl	*n*-propyl	*p*-fluorophenyl	pyrrolidinyl	**4.5**	339	340	96
6	methyl	*n*-propyl	phenyl	Bn	**4.6**	357	358	92
7	methyl	*n*-propyl	phenyl	*n*-butyl	**4.7**	323	324	85
8	methyl	*n*-propyl	phenyl	morpholinyl	**4.8**	337	338	97
9	methyl	*n*-propyl	phenyl	pyrrolidinyl	**4.9**	321	322	96
10	methyl	*n*-propyl	methyl	Bn	**4.10**	295	296	76
11	methyl	*n*-propyl	methyl	*n*-butyl	**4.11**	261	262	95
12	methyl	*n*-propyl	methyl	cyclohexyl	**4.12**	287	288	93
13	methyl	*n*-propyl	methyl	morpholinyl	**4.13**	275	276	83
14	methyl	*n*-propyl	methyl	*sec*-butyl	**4.14**	261	262	87
15	methyl	*n*-propyl	methyl	pyrrolidinyl	**4.15**	259	260	82
16	methyl	*n*-propyl	ethyl	Bn	**4.16**	309	310	78
17	methyl	*n*-propyl	ethyl	*n*-butyl	**4.17**	275	276	84
18	methyl	*n*-propyl	ethyl	cyclohexyl	**4.18**	301	302	71
19	methyl	*n*-propyl	ethyl	pyrrolidinyl	**4.19**	273	274	83
20	methyl	*n*-propyl	*n*-propyl	Bn	**4.20**	323	324	93
21	methyl	*n*-propyl	*n*-propyl	*n*-butyl	**4.21**	289	290	93
22	methyl	*n*-propyl	*n*-propyl	cyclohexyl	**4.22**	315	316	84
23	methyl	*n*-propyl	*n*-propyl	morpholinyl	**4.23**	303	304	92
24	methyl	*n*-propyl	*n*-propyl	*sec*-butyl	**4.24**	289	290	92
25	methyl	*n*-propyl	*n*-propyl	pyrrolidinyl	**4.25**	287	288	86
26	methyl	*n*-propyl	furan-2-yl	Bn	**4.26**	347	348	91
27	methyl	*n*-propyl	furan-2-yl	*n*-butyl	**4.27**	313	314	91
28	methyl	*n*-propyl	furan-2-yl	cyclohexyl	**4.28**	339	340	88
29	methyl	*n*-propyl	furan-2-yl	morpholinyl	**4.29**	327	328	84
30	methyl	*sec*-butyl	*p*-fluorophenyl	Bn	**4.30**	389	390	87
31	methyl	*sec*-butyl	*p*-fluorophenyl	*n*-butyl	**4.31**	355	356	94
32	methyl	*sec*-butyl	*p*-fluorophenyl	cyclohexyl	**4.32**	381	382	89
33	methyl	*sec*-butyl	*p*-fluorophenyl	morpholinyl	**4.33**	369	370	75
34	methyl	*sec*-butyl	*p*-fluorophenyl	*sec*-butyl	**4.34**	355	356	94
35	methyl	*sec*-butyl	*p*-fluorophenyl	pyrrolidinyl	**4.35**	353	354	92
36	methyl	*sec*-butyl	phenyl	Bn	**4.36**	371	372	80
37	methyl	*sec*-butyl	phenyl	*n*-butyl	**4.37**	337	338	94
38	methyl	*sec*-butyl	phenyl	cyclohexyl	**4.38**	363	364	94
39	methyl	*sec*-butyl	phenyl	morpholinyl	**4.39**	351	352	86
40	methyl	*sec*-butyl	phenyl	*sec*-butyl	**4.40**	337	338	97
41	methyl	*sec*-butyl	phenyl	pyrrolidinyl	**4.41**	335	336	92
42	methyl	*sec*-butyl	methyl	Bn	**4.42**	309	310	96
43	methyl	*sec*-butyl	methyl	*n*-butyl	**4.43**	275	276	93
44	methyl	*sec*-butyl	methyl	cyclohexyl	**4.44**	301	302	90
45	methyl	*sec*-butyl	methyl	*sec*-butyl	**4.45**	275	276	89
46	methyl	*sec*-butyl	ethyl	Bn	**4.46**	323	324	92
47	methyl	*sec*-butyl	ethyl	*n*-butyl	**4.47**	289	290	97
48	methyl	*sec*-butyl	ethyl	cyclohexyl	**4.48**	315	316	93
49	methyl	*sec*-butyl	ethyl	*sec*-butyl	**4.49**	289	290	90
50	methyl	*sec*-butyl	*n*-propyl	Bn	**4.50**	337	338	90
51	methyl	*sec*-butyl	*n*-propyl	*n*-butyl	**4.51**	303	304	97
52	methyl	*sec*-butyl	*n*-propyl	cyclohexyl	**4.52**	329	330	77
53	methyl	*sec*-butyl	*n*-propyl	*sec*-butyl	**4.53**	303	304	95
54	methyl	*sec*-butyl	*n*-propyl	pyrrolidinyl	**4.54**	301	302	92
55	methyl	*sec*-butyl	furan-2-yl	Bn	**4.55**	361	362	76
56	methyl	*sec*-butyl	furan-2-yl	*n*-butyl	**4.56**	327	328	87
57	methyl	*sec*-butyl	furan-2-yl	cyclohexyl	**4.57**	353	354	81
58	methyl	*sec*-butyl	furan-2-yl	*sec*-butyl	**4.58**	327	328	73
59	methyl	*sec*-butyl	furan-2-yl	pyrrolidinyl	**4.59**	325	326	75
60	methyl	*p*-fluorophenyl	*p*-fluorophenyl	Bn	**4.60**	427	428	86
61	methyl	*p*-fluorophenyl	*p*-fluorophenyl	*n*-butyl	**4.61**	393	394	84
62	methyl	*p*-fluorophenyl	*p*-fluorophenyl	cyclohexyl	**4.62**	419	420	95
63	methyl	*p*-fluorophenyl	*p*-fluorophenyl	morpholinyl	**4.63**	407	408	75
64	methyl	*p*-fluorophenyl	*p*-fluorophenyl	*sec*-butyl	**4.64**	393	394	87
65	methyl	*p*-fluorophenyl	*p*-fluorophenyl	pyrrolidinyl	**4.65**	391	392	79
66	methyl	*p*-fluorophenyl	phenyl	Bn	**4.66**	409	410	73
67	methyl	*p*-fluorophenyl	phenyl	*n*-butyl	**4.67**	375	376	93
68	methyl	*p*-fluorophenyl	phenyl	cyclohexyl	**4.68**	401	402	99
69	methyl	*p*-fluorophenyl	phenyl	morpholinyl	**4.69**	389	390	76
70	methyl	*p*-fluorophenyl	phenyl	*sec*-butyl	**4.70**	375	376	87
71	methyl	*p*-fluorophenyl	phenyl	pyrrolidinyl	**4.71**	373	374	93
72	methyl	*p*-fluorophenyl	methyl	Bn	**4.72**	347	348	85
73	methyl	*p*-fluorophenyl	methyl	*n*-butyl	**4.73**	313	314	95
74	methyl	*p*-fluorophenyl	methyl	cyclohexyl	**4.74**	339	340	77
75	methyl	*p*-fluorophenyl	methyl	morpholinyl	**4.75**	327	328	95

Table 4 (Continued)

entry	R	R^1	R^2	R^3	product	MW	M + 1	yield
76	methyl	*p*-fluorophenyl	methyl	*sec*-butyl	**4.76**	313	314	89
77	methyl	*p*-fluorophenyl	methyl	pyrrolidinyl	**4.77**	311	312	85
78	methyl	*p*-fluorophenyl	ethyl	Bn	**4.78**	361	362	90
79	methyl	*p*-fluorophenyl	ethyl	*n*-butyl	**4.79**	327	328	90
80	methyl	*p*-fluorophenyl	ethyl	cyclohexyl	**4.80**	353	354	97
81	methyl	*p*-fluorophenyl	ethyl	morpholinyl	**4.81**	341	342	94
82	methyl	*p*-fluorophenyl	ethyl	*sec*-butyl	**4.82**	327	328	90
83	methyl	*p*-fluorophenyl	ethyl	pyrrolidinyl	**4.83**	325	326	93
84	methyl	*p*-fluorophenyl	*n*-propyl	Bn	**4.84**	375	376	78
85	methyl	*p*-fluorophenyl	*n*-propyl	*n*-butyl	**4.85**	341	342	84
86	methyl	*p*-fluorophenyl	*n*-propyl	cyclohexyl	**4.86**	367	368	80
87	methyl	*p*-fluorophenyl	*n*-propyl	morpholinyl	**4.87**	355	356	94
88	methyl	*p*-fluorophenyl	*n*-propyl	*sec*-butyl	**4.88**	341	342	98
89	methyl	*p*-fluorophenyl	*n*-propyl	pyrrolidinyl	**4.89**	339	340	91
90	phenyl	*n*-propyl	methyl	Bn	**4.90**	357	358	96
91	phenyl	*n*-propyl	methyl	*n*-butyl	**4.91**	323	324	96
92	phenyl	*n*-propyl	methyl	cyclohexyl	**4.92**	349	350	82
93	phenyl	*n*-propyl	methyl	morpholinyl	**4.93**	337	338	92
94	phenyl	*n*-propyl	methyl	*sec*-butyl	**4.94**	323	324	71
95	phenyl	*n*-propyl	methyl	pyrrolidinyl	**4.95**	321	322	78
96	phenyl	*n*-propyl	*p*-fluorophenyl	Bn	**4.96**	437	438	97
97	phenyl	*n*-propyl	*p*-fluorophenyl	*n*-butyl	**4.97**	403	404	77
98	phenyl	*n*-propyl	*p*-fluorophenyl	cyclohexyl	**4.98**	429	430	89
99	phenyl	*n*-propyl	*p*-fluorophenyl	morpholinyl	**4.99**	403	404	83
100	phenyl	*n*-propyl	*p*-fluorophenyl	*sec*-butyl	**4.100**	417	418	95
101	phenyl	*n*-propyl	*p*-fluorophenyl	pyrrolidinyl	**4.101**	401	402	86
102	phenyl	*sec*-butyl	methyl	Bn	**4.102**	371	372	93
103	phenyl	*sec*-butyl	methyl	*n*-butyl	**4.103**	337	338	93
104	phenyl	*sec*-butyl	methyl	cyclohexyl	**4.104**	363	364	89
105	phenyl	*sec*-butyl	methyl	morpholinyl	**4.105**	337	338	92
106	phenyl	*sec*-butyl	methyl	*sec*-butyl	**4.106**	351	352	86
107	phenyl	*sec*-butyl	methyl	pyrrolidinyl	**4.107**	335	336	93
108	phenyl	*sec*-butyl	*p*-fluorophenyl	Bn	**4.108**	451	451	90
109	phenyl	*sec*-butyl	*p*-fluorophenyl	*n*-butyl	**4.109**	417	418	85
110	phenyl	*sec*-butyl	*p*-fluorophenyl	cyclohexyl	**4.110**	443	443	91
111	phenyl	*sec*-butyl	*p*-fluorophenyl	morpholinyl	**4.111**	431	432	88
112	phenyl	*sec*-butyl	*p*-fluorophenyl	*sec*-butyl	**4.112**	417	418	91
113	phenyl	*sec*-butyl	*p*-fluorophenyl	pyrrolidinyl	**4.113**	415	416	91
114	*p*-chlorophenyl	*n*-propyl	methyl	Bn	**4.114**	391	392	86
115	*p*-chlorophenyl	*n*-propyl	methyl	*n*-butyl	**4.115**	357	358	85
116	*p*-chlorophenyl	*n*-propyl	methyl	cyclohexyl	**4.116**	383	384	88
117	*p*-chlorophenyl	*n*-propyl	methyl	morpholinyl	**4.117**	371	372	90
118	*p*-chlorophenyl	*n*-propyl	methyl	pyrrolidinyl	**4.118**	355	356	88
119	*p*-chlorophenyl	*n*-propyl	*p*-fluorophenyl	*n*-butyl	**4.119**	437	438	91
120	*p*-chlorophenyl	*n*-propyl	*p*-fluorophenyl	cyclohexyl	**4.120**	463	464	90
121	*p*-chlorophenyl	*n*-propyl	*p*-fluorophenyl	morpholinyl	**4.121**	451	452	97
122	*p*-chlorophenyl	*n*-propyl	*p*-fluorophenyl	*sec*-butyl	**4.122**	437	438	91
123	*p*-chlorophenyl	*n*-propyl	*p*-fluorophenyl	pyrrolidinyl	**4.123**	435	436	83
124	*p*-chlorophenyl	*sec*-butyl	methyl	Bn	**4.124**	405	406	94
125	*p*-chlorophenyl	*sec*-butyl	methyl	*n*-butyl	**4.125**	371	372	90
126	*p*-chlorophenyl	*sec*-butyl	methyl	cyclohexyl	**4.126**	397	398	95
127	*p*-chlorophenyl	*sec*-butyl	methyl	morpholinyl	**4.127**	385	386	90
128	*p*-chlorophenyl	*sec*-butyl	methyl	*sec*-butyl	**4.128**	371	372	96
129	*p*-chlorophenyl	*sec*-butyl	methyl	pyrrolidinyl	**4.129**	369	370	90
130	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	Bn	**4.130**	485	486	80
131	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	*n*-butyl	**4.131**	451	452	97
132	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	cyclohexyl	**4.132**	477	478	82
133	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	morpholinyl	**4.133**	465	466	84
134	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	*sec*-butyl	**4.134**	451	452	97
135	*p*-chlorophenyl	*sec*-butyl	*p*-fluorophenyl	pyrrolidinyl	**4.135**	449	450	97

[a] All products were isolated by preparative LC/MS and purities of final products were all >95% based on ELSD.

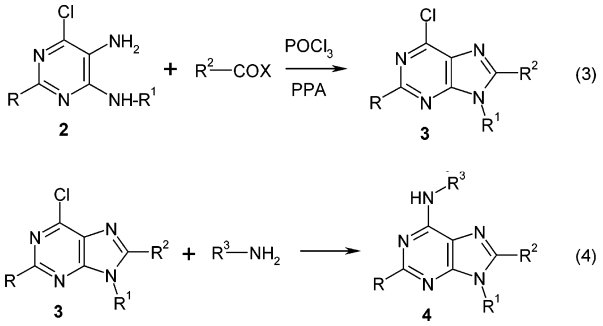
which has been extensively reported in the literature.[10] For our library preparation, three methods were screened for their simplicity to obtain 6-chloropurines **3**, as depicted in eq 2, and the results are summarized in Table 2.



First, the silica gel-supported $FeCl_3$ promoted cyclization of aldehydes with pyrimidines **2.1** was investigated.[8] Treatment of pyrimidine **2.1** and 2-furaldehyde with $FeCl_3-SiO_2$ in DMSO at 100 °C for 4 h gave only the 6-hydroxypurine **3.0** in 78% yield, which is apparently a hydrolysis product of the corresponding 6-chloropurine due to moisture present in the reaction. The result suggests that this method may not be easily applied to the current library, since moisture will have to be excluded carefully. The next method

investigated was the phosphoryl chloride reaction in which pyrimidine **2.1** and 4-fluorobenzoic acid were treated with $POCl_3$ for 6 h to give 6-chloro-9-(4′-fluorophenyl)-2-methyl-8-propylpurine (**3.1**) in 13% yield. However, when the same reaction was conducted using PPA instead of $POCl_3$ for 24 h, the hydroxy analogue **3.30** was isolated in 58%. Although purine **3.30** can be converted to **3.1** by treatment with $POCl_3$, the same transformation can be achieved using $POCl_3$/PPA to give **3.1** in 34% yield. To the best of our knowledge, this is the first report that the combination of $POCl_3$ and PPA is developed to form 6-chloropurine in one pot. Thus, the $POCl_3$/PPA condition was chosen for the construction of the purine ring system, and the results are summarized in Table 3. In general, most cyclization reactions proceed with moderate to good yields, although two of them (**3.12**, **3.18**) gave low yields when 2-furoic acid was used.

The final diversity point was introduced via the substitution of 6-chloropurines **3** with an amine (eq 4), which was



exemplified by six selected amines, and results are summarized in Table 4. As evident from Table 4, all six amines proceed well in the substitution reaction to give the desired purines **4** as a 135-member library in high yields and high purity.

In conclusion, a 135-member library of tetra-substituted purines was generated in solution phase from readily available amidines, amines, carboxylic acids, or its derivatives in good to high yields and high purity. This new strategy provides an efficient way to access a large number of fully substituted purines, which is of great interest for medicinal chemistry.

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