Supporting Information: Self-complementary purines by quadruple hydrogen bonding

Alisha M. Martin, Roslyn S. Butler, Ion Ghiviriga, Rachel E. Giessert, Khalil A. Abboud, and Ronald K. Castellano*

Department of Chemistry, P.O. Box 117200, University of Florida, Gainesville, FL 32611, USA

Table of Contents

I. Experimental Protocol ............................................................................................................. S2
   A. General ............................................................................................................................... S2
   B. Synthetic Details for Compounds 1 and 3–5................................................................. S2

II. Structural Details by NMR, Computation, and X-ray Analysis ........................................ S8
   A. Analysis of Dimers 1a and 1b by NMR................................................................. S8
      1. gHMBC Results.......................................................................................................... S8
      2. NOESY Spectra ......................................................................................................... S9
      3. Variable Temperature $^1$H NMR Spectra ............................................................ S9
      4. Dilution Studies .......................................................................................................... S10
         a. Experimental Protocol......................................................................................... S10
         b. Representative Stacked Dilution Spectra for 1b ...... S11
         c. Representative Curve Fitting for 1a and 1b ..................... S11
   B. Computational Details ................................................................................................. S12
   C. X-ray Crystallographic Analysis of 5 ................................................................. S13

III. $^1$H NMR Spectra for Compounds 1 and 3–5 ................................................................. S13
I. Experimental Protocol

A. General. Reagents were purchased from Acros or Aldrich, and were used without further purification unless stated otherwise. Dry solvents were degassed and purified under an atmosphere of argon using the GlassContour solvent system (GlassContour, Inc.). Pyridine was distilled onto 3 Å activated molecular sieves. Column chromatography was carried out using Whatman 230–400 mesh silica gel. Thin layer chromatography (TLC) was performed on Duracil TLC aluminum sheets with visualization by UV light. Melting points (Mp) were determined on a MEL-TEMP melting apparatus and are uncorrected. $^1$H (300, 500 MHz) and $^{13}$C (75, 125 MHz) nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 300, Mercury 300BB, and Inova 500 spectrometer at room temperature unless otherwise specified. Chemical shifts ($\delta$) are given in parts per million (ppm) relative to TMS and referenced to residual protonated solvent (CHCl$_3$: $\delta_H$ 7.24 ppm, $\delta_C$ 77.0 ppm; DMSO: $\delta_H$ 2.49 ppm, $\delta_C$ 39.5 ppm). Abbreviations used are singlet (s), doublet (d), triplet (t), multiplet (m), and broad (b). High resolution mass spectrometry (HRMS) spectra were recorded on a Finnigan LCQ-Ion Trap Spectrometer.

B. Synthetic Details for Compounds 1 and 3–5.

![Chemical Structure](image)

2-Amino-6-chloro-N-9-(2,4,6-trimethylbenzyl)purine (3a).

6-Chloro-2-aminopurine$^1$ 2 (2.08 g, 11.1 mmol), 2-bromomethyl-1,3,5-trimethylbenzene$^2$ (3.52 g, 16.5 mmol), and K$_2$CO$_3$ (2.30 g, 16.6 mmol) were placed in an oven-dried round-bottomed flask and dried under argon. Dry DMF (180 mL) was added and the mixture was stirred overnight at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (5% MeOH/CH$_2$Cl$_2$) to yield a yellow/white powder (1.42 g, 40%). Mp 205–208 °C; $^1$H NMR (CDCl$_3$) $\delta$ 2.25 (s, 6H), 2.31 (s, 4H), 5.17 (s, 4H), 6.94 (s, 2H), 7.25 (s, 1H); $^1$H NMR
(DMSO-\textit{d}_6) \delta 2.23 (s, 3H), 2.25 (s, 6H), 5.16 (s, 2H), 6.92 (s, 2H), 6.95 (s, 2H), 7.55 (s, 1H); $^{13}$C NMR (DMSO-\textit{d}_6) \delta 19.4, 20.5, 123.1, 128.2, 128.3, 129.1, 129.2, 137.5, 141.7, 149.3, 153.9, 159.7; HRMS (ESI-FT-ICR) calculated for C_{15}H_{16}N_{5}Cl (M + H)$^+$ 302.1167, found 302.1166.

\begin{center}
\includegraphics{image.png}
\end{center}

\textbf{2-Amino-6-chloro-N-7-(2,4,6-trimethylbenzyl)purine (3a').}

Using conditions identical to those designed for 3a, the N(7) regioisomer was isolated as a yellow/white solid from 5.30 g (28.1 mmol) of starting material 2 to give 1.04 g (12%) of 3a'. Mp 223–225 °C; $^1$H NMR (CDCl$_3$) \delta 2.25 (s, 6H), 2.30 (s, 3H), 5.16 (s, 2H), 5.26 (bs, 2H), 6.94 (s, 2H), 7.25 (s, 1H); $^1$H NMR (DMSO-\textit{d}_6) \delta 2.22 (s, 3H), 2.24 (s, 6H), 5.14 (s, 2H), 6.90 (s, 2H), 6.95 (bs, 2H), 7.54 (s, 1H); $^{13}$C NMR (DMSO-\textit{d}_6; 100 °C) \delta 19.4, 20.5, 41.1, 123.2, 128.3, 129.2, 137.5, 137.6, 141.8, 149.4, 154.0, 159.8.

\begin{center}
\includegraphics{image.png}
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\textbf{2,6-Diamino-N-9-(2,4,6-trimethylbenzyl)purine (4a).}

Vacuum dried starting material 3a (1.05 g, 3.30 mmol) was placed in a 330 mL pressure tube. Methanolic ammonia (95 mL, 7 N) was added to the solid followed by heating under pressure to 90 °C for 16 h. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (5% MeOH/CH$_2$Cl$_2$) to yield 4a (0.640 g, 50%) as a white powder. Mp 275–278 °C; $^1$H NMR (CDCl$_3$) \delta 2.24 (s, 6H), 2.29 (s, 3H), 4.72 (bs, 2H), 5.11 (s, 2H), 5.30 (bs, 2H), 6.92 (s, 2H), 6.97 (s, 1H); $^1$H NMR (DMSO-\textit{d}_6) \delta 2.24 (s, 9H), 5.04 (s, 2H), 5.80 (bs, 2H), 6.65 (bs, 2H), 6.91 (s, 2H), 7.04 (s, 1H); $^{13}$C NMR (DMSO-\textit{d}_6; 100 °C) \delta 18.9, 20.1, 40.2, 112.9, 128.7, 128.7, 135.6, 136.9, 137.1,
151.7, 155.8, 159.9; HRMS (ESI-FT-ICR) calculated for C_{15}H_{18}N_{6} (M + H)^{+} 283.1666, found 283.1668.

2,6-Diamino-N-7-(2,4,6-trimethylbenzyl)purine (4a').

This compound was prepared by the same procedure as 4a from 1.00 g (3.11 mmol) of 3a to yield 4a' as a white solid (0.530 g, 42%). Mp 282–285 °C; 1H NMR (CDCl₃) δ 2.24 (s, 6H), 2.29 (s, 3H), 4.72 (bs, 2H), 5.11 (s, 2H), 5.29 (bs, 2H), 6.92 (s, 2H), 6.97 (s, 1H); 1H NMR (DMSO-d₆) δ 2.24 (s, 6H), 2.26 (s, 6H) 5.08 (s, 2H), 5.46 (bs, 2H), 6.27 (bs, 2H), 6.91 (s, 2H), 7.05 (s, 1H); 13C NMR (DMSO-d₆; 100 °C) δ 18.7, 19.9, 113.0, 128.5, 128.6, 135.5, 136.8, 136.9, 151.6, 155.7, 159.8.

6-Amino-N-9-(2,4,6-trimethylbenzyl)-2-N-(4-phenylamino)ureidopurine (1a).

Compound 4a (0.050 g, 0.21 mmol) was placed in an oven-dried two-necked round-bottomed flask and dried under vacuum. Under argon atmosphere CH₂Cl₂ (29 mL) was added to the solid and the mixture was heated to 50–55 °C to dissolve 4a. When the starting material was completely dissolved, the temperature was lowered to 40 °C. Pyridine (0.034 mL, 0.43 mmol) and phenyl isocyanate (0.051 mL, 0.47 mmol) were added. The mixture was stirred at 40 °C for 20.5 h followed by evaporation. Purification by column chromatography on silica gel (1% MeOH/CH₂Cl₂) afforded 1a (0.058 g, 70%). Mp 263–265 °C; 1H NMR (CDCl₃) δ 2.29 (s, 6H) 2.32 (s, 3H), 5.26 (s, 2H), 6.96 (s, 2H), 7.09 (t, J = 7.1 Hz, 3H), 7.16 (bs, 1H), 7.34 (t, J = 7.3 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 9.34 (bs, 1H), 12.04 (s, 1H); 1H NMR (DMSO-d₆) δ 2.24 (s, 3H), 2.26 (s, 6H),
5.20 (s, 2H), 6.92 (s, 2H), 7.02 (t, J = 7.0 Hz, 1H), 7.30 (t, J = 7.3 Hz, 2H), 7.37 (s, 1H),
7.61 (s, 2H), 7.73 (d, J = 7.7 Hz, 2H), 9.31 (s, 1H), 11.82 (s, 1H); 13C NMR (DMSO-d$_6$; 100 °C) δ 18.8, 19.9, 40.7, 114.6, 119.3, 122.2, 128.1, 128.7, 137.0, 137.1, 137.9, 138.6, 149.8, 151.4, 153.1, 155.2; HRMS (ESI-FT-ICR) calculated for C$_{19}$H$_{17}$N$_7$O (M + H)$^+$ 402.2037, found 402.2027; calculated for 2(C$_{19}$H$_{17}$N$_7$O) (2M + H)$^+$ 803.4001, found 803.4088.

![Chemical structure](image)

**6-Amino-N-7-(2,4,6-trimethylbenzyl)-2-N-(4-phenylamino)ureidopurine (1a').**

Starting material 4a' (0.052g, 0.22 mmol) was dried under vacuum in a 50 mL two-necked round-bottomed flask fitted with a reflux condenser. CH$_2$Cl$_2$ (45 mL) was added and the mixture was heated to reflux until 4a' was dissolved. The temperature was reduced to 40 °C. Without equilibration of the temperature, pyridine (0.035 mL, 0.44 mmol) was added followed by phenyl isocyanate (0.024 mL, 0.22 mmol). The mixture was stirred 24 h. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (2% MeOH/CH$_2$Cl$_2$) to yield 1a' (0.064 g, 72%).

Mp 243–246 °C; $^1$H NMR (CDCl$_3$) δ 2.27 (s, 3H), 2.32 (s, 3H), 4.94 (s, 2H), 5.17 (s, 2H), 6.95 (s, 2H), 7.13 (t, J = 7.1 Hz, 1H), 7.35 (m, 2H), 7.36 (s, 1H), 7.59 (d, J = 7.5, 2H), 7.81 (s, 1H), 11.52 (s, 1H); $^1$H NMR (DMSO-d$_6$) δ 2.23 (s, 3H), 2.26 (s, 6H), 5.13 (s, 2H), 6.83 (s, 2H), 6.92 (s, 1H), 7.05 (t, J = 7.0 Hz, 1H), 7.32 (t, J = 7.3 Hz, 2H), 7.38 (s, 1H), 7.75 (d, J = 7.7 Hz, 2H), 9.35 (s, 1H), 11.81 (s, 1H); $^{13}$C NMR (DMSO-d$_6$) δ 19.4, 20.6, 113.1, 119.9, 123.0, 128.6, 128.7, 129.1, 137.4, 137.5, 138.5, 138.9, 150.0, 151.2, 153.1, 158.6.
2-Amino-6-chloro-N-9-(3,5-bis-heptyloxybenzyl)purine (3b).

6-Chloro-2-aminopurine\textsuperscript{1} 2 (0.175 g, 0.931 mmol), 2-bromomethyl-3,5-bis-heptyloxybenzene\textsuperscript{3} (0.464 g, 1.16 mmol), and K\textsubscript{2}CO\textsubscript{3} (0.322 g, 2.33 mmol) were placed in an oven-dried round-bottomed flask and dried under argon. Dry DMF (50 mL) was added to the solid mixture and the mixture was stirred overnight at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (5% MeOH/CH\textsubscript{2}Cl\textsubscript{2}) to yield a yellow/white powder (0.386 g, 85%). Mp 110–111 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 0.86 (t, \( J = 6.6 \) Hz, 6H), 1.35 (m, 16H), 1.72 (m, 4H), 3.87 (t, \( J = 3.9 \) Hz, 4H), 5.14 (s, 2H), 5.20 (s, 2H), 6.34 (m, 3H), 7.74 (s, 1H); \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}) \( \delta \) 0.85 (t, \( J = 6.6 \) Hz, 6H), 1.32 (m, 16H), 1.64 (m, 4H), 3.88 (t, \( J = 3.9 \) Hz, 4H), 5.17 (s, 2H), 6.38 (s, 3H), 6.96 (s, 2H), 8.21 (s, 1H); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}) \( \delta \) 13.9, 22.0, 25.4, 28.4, 28.6, 31.2, 38.7, 46.1, 67.4, 99.8, 105.7, 123.2, 138.7, 143.15, 149.43, 154.0, 159.9, 160.0; HRMS (ESI-FI-ICR) calculated for C\textsubscript{26}H\textsubscript{40}N\textsubscript{6}O\textsubscript{2} (M + H\textsuperscript{+}) 488.2787, found 488.2790.

2,6-Diamino-N-9-(3,5-bis-heptyloxybenzyl)purine (4b).

Vacuum dried starting material 3b (0.323 g, 0.717 mmol) was placed in a 100 mL pressure tube. Methanolic ammonia (60 mL, 7 N) was added to the solid followed by heating under pressure to 90 °C for 19 h. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (5% MeOH/CH\textsubscript{2}Cl\textsubscript{2}) to yield 4b (0.231 g, 69%) as a white powder. Mp 151–152 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 0.85 (t,
$J = 6.6 \text{ Hz, } 6H)$, 1.34 (m, 16H), 1.70 (m, 4H), 3.84 (t, $J = 3.9 \text{ Hz, } 4H$), 4.88 (bs, 2H), 5.067 (s, 2H), 5.68 (bs, 2H), 6.33 (m, 3H), 7.44 (s, 1H); $^1H$ NMR (DMSO-$d_6$) $\delta$ 0.85 (t, $J = 6.6 \text{ Hz, } 6H$), 1.30 (m, 16H), 1.64 (m, 4H), 3.87 (t, $J = 3.9 \text{ Hz, } 4H$), 5.06 (s, 2H), 6.34 (s, 2H), 6.66 (s, 2H), 7.75 (s, 1H); $^{13}C$ NMR (CDCl$_3$) $\delta$ 14.3, 22.8, 26.2, 29.2, 29.4, 32.0, 46.9, 68.3, 100.8, 106.3, 114.4, 138.2, 152.4, 156.1, 160.2, 160.9; HRMS (ESI-FT-ICR) calculated for $C_{26}H_{40}N_6O_2$ (M + H)$^+$ 469.3286, found 469.3285.

![Diagram](image)

6-Amino-N-9-(3,5-bis-heptyloxybenzyl)-2-N-(4-phenylamino)ureidopurine (1b).

Compound 4b (0.055 g, 0.12 mmol) was placed in an oven-dried round-bottomed flask and dried under vacuum. Methylene chloride (6 mL), pyridine (0.012 mL, 0.015 mmol), and phenyl isocyanate (0.017 mL, 0.015 mmol) were added sequentially. The mixture was stirred at room temperature for 19 h. Solvent was removed under vacuum. Purification of the residue was performed by column chromatography on silica gel (1% MeOH/CH$_2$Cl$_2$) to afford 1b (0.050 g, 73%). Mp 217–220 °C; $^1H$ NMR (CDCl$_3$) 0.86 (t, $J = 6.6 \text{ Hz, } 6H$), 1.26 (m, 16H), 1.69 (m, 4H), 3.80 (t, $J = 3.9 \text{ Hz, } 4H$), 5.23 (s, 2H), 6.33 (m, 1H), 6.37 (m, 2H), 7.05 (t, $J = 7.0 \text{ Hz, } 1H$), 7.27 (t, $J = 7.3 \text{ Hz, } 3H$), 7.37 (d, $J = 7.4 \text{ Hz } 3H$), 7.65 (s, 1H), 9.41 (s, 1H), 11.84 (s, 1H); $^1H$ NMR (DMSO-$d_6$) $\delta$ 0.83 (t, $J = 6.6 \text{ Hz, } 6H$), 1.22 (m, 16H), 1.59 (m, 4H), 3.82 (t, $J = 3.8 \text{ Hz, } 4H$), 5.25 (s, 2H), 6.35 (s, 1H), 6.41 (s, 2H), 7.00 (t, $J = 7.0 \text{ Hz, } 1H$), 7.26 (t, $J = 7.2 \text{ Hz, } 2H$), 7.58 (d, $J = 7.6 \text{ Hz, } 2H$), 7.61 (s, 1H), 8.11 (s, 1H), 9.30 (s, 1H), 11.75 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$; 100 °C) $\delta$ 13.3, 21.5, 25.0, 27.9, 28.2, 28.5, 30.7, 46.0, 67.4, 100.4, 105.7, 114.8, 119.2, 122.2, 128.2, 138.7, 139.7, 149.5, 151.4, 153.4, 155.5, 159.9; HRMS (ESI-FT-ICR) calculated for $C_{33}H_{45}N_7O_3$ (M + H)$^+$ 588.3657, found 588.3678; calculated for 2($C_{33}H_{45}N_7O_3$) (2M + H)$^+$ 1175.7241, found 1175.7484.
N-9-benzyl-6-dimethylamino-2-N-(4-phenylamino)ureidopurine (5).
Phenyl isocyanate (0.65 mL, 6.0 mmol) was added dropwise to 2-amino-6-dimethylamino-9-benzyl purine\(^4\) (0.10 g, 0.37 mmol) dissolved in dry pyridine (7.5 mL). After stirring at room temperature for 1 h the crude reaction mixture was concentrated under reduced pressure and the crude solid was recrystallized with ethanol to give a white solid (0.137 g, 94%). Mp 234–236 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.56 (bs, 6H), 5.31 (s, 2H), 7.16 (s, 1H), 7.33 (m, 10H), 7.61 (s, 1H) 11.39 (s, 1H); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 3.62 (bs, 6H), 5.40 (s, 2H), 7.28 (m, 10H), 8.13 (s, 1H), 9.41 (1.37, 1H), 11.45 (s, 1H); \(^1\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 46.1, 60.0, 115.46, 119.17, 122.7, 126.8, 126.9, 127.6, 128.7, 128.8, 136.8, 138.7, 138.9, 151.8, 153.0, 154.1. HRMS (ESI-FT-ICR) calculated for C\(_{21}\)H\(_{22}\)N\(_7\)O (M + H\(^+\)) \(^\text{+}\) 388.1886, found 388.1921.

II. Structural Details by NMR, Computation, and X-ray Analysis.
A. Analysis of Dimers 1a and 1b by NMR. NMR spectra were recorded at 25 °C on a Varian Inova spectrometer equipped with a 5 mm indirect detection probe, operating at 500 MHz for \(^1\)H and at 125 MHz for \(^1\)C. Chemical shifts are reported in ppm relative to TMS.

1. gHMBC Results. The gHMBC spectrum was recorded with the standard pulse sequence in vnmr, in 512 increments, each acquired in 16 transients. The number of points in the FIDs was 4k, and the same number was used for the spectrum in f2. The number of points for the spectrum in f1 was 2k. The preacquisition delay was 0.5 s. The 8 Hz. Spectrum was taken in CDCl\(_3\) at an approximate concentration of 2 mM. All shifts are reported in ppm downfield of TMS, and \(^1\)C shifts are listed in bold.
2. NOESY Spectrum. The NOESY spectrum was recorded at 25 °C with the standard pulse sequence in vnmr, in 2k increments, each acquired in 32 transients. The number of points in the FIDs was 4k, and the same number was used for the spectrum, in both f1 and f2. The preacquisition delay was 1 s and the mixing time 0.5 s. Spectrum was obtained in CDCl₃ at an approximate concentration of 2 mM.

3. Variable Temperature ¹H NMR Spectra. The variable temperature spectrum was recorded on a sample in CDCl₃ (~ 4 mM), on automation, arraying the temperature from -55 °C to 55 °C in steps of 10 °C. For each change in temperature, a delay of 300 s allowed
for the temperature equilibration, followed by shimming z1-z2 on the lock level, then acquisition in 128 transients with an acquisition time of 5 s.

\[
\begin{array}{c}
\text{H}^1' - \text{N} - \text{H}^1' \\
\text{H}^2 \\
\text{N} \text{N} \text{N} \\
\text{N} \text{N} \\
\text{H}^2 \\
\text{N} - \text{C} \text{H}_3 \\
\text{H}_2 \\
\text{H}^1 \\
\end{array}
\]

4. Dilution Studies

a. Experimental Protocol. Stock solutions were made by transferring the purified urea compound, dissolved in methylene chloride, to 10 mL screw-capped volumetric flasks. The solvent was removed under vacuum. The residue was dried overnight, and placed in a dessicator until addition of CDCl₃. Deuterated chloroform was placed over activated
molecular sieves to sit overnight. Before use it was then decanted onto fresh activated molecular sieves and stored under argon. Dilutions of the stock solution were made at 1 mL volumes sequentially. The dilutions were monitored by $^1$H NMR (Inova 500).

b. Representative Stacked Dilution Spectra for 1b.

c. Representative Curve Fitting for 1a and 1b. Plots of the chemical shift of N(H$^2$) versus concentration were fit to a non-linear binding equation using Associate 1.6. Two representative curve fits, one from 1a and the other from 1b, are shown below. The fit for 1a corresponds to the following calculated parameters: $K_{\text{dim}} = 1180 \pm 170$ M$^{-1}$; $\delta_{\text{dimer}} = 10.1 \pm 0.05$ ppm; $\delta_{\text{monomer}} = 7.2 \pm 0.1$ ppm. The fit for 1b corresponds to the following calculated parameters: $K_{\text{dim}} = 1520 \pm 270$ M$^{-1}$; $\delta_{\text{dimer}} = 10.1 \pm 0.05$ ppm; $\delta_{\text{monomer}} = 7.2 \pm 0.1$ ppm. All data points for all runs fall within the 20–80% saturation range.
B. Computational Details.

Monte Carlo conformational searching was done on a Dell PC (2.4 GHz) running the Fedora Core using MacroModel v. 9.0 (Schrodinger, LLC)\(^6\) and the MCMM method (relevant parameters include: steps = 100, iterations = 2000, solvent (GB/SA) = CHCl\(_3\), force field = Amber*). The two low-energy anti conformers (1\(^{N3}\) and 1\(^{N1}\)) were identified as well as the two lowest energy syn conformers (with respect to the urea) for the N(9) methyl derivative shown above. The energies of the conformers are given at various levels of theory. Only 1\(^{N3}\) and 1\(^{N1}\) were further refined using ab initio methods (using Gaussian 03 (revision D.01)\(^7\)) as implemented through the National Center for
Supercomputing Applications, SGI Altix cluster “Cobalt” (http://www.ncsa.uiuc.edu/UserInfo/Resources/Hardware/SGIAltix/).

C. X-ray Crystallographic Analysis of 5.
Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK\(_\alpha\) radiation (\(\lambda = 0.71073\) Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the \(\omega\)-scan method (0.3° frame width). The first 50 frames were re-measured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in SHELXTL6, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 272 parameters were refined in the final cycle of refinement using 3194 reflections with I > 2\(\sigma(I)\) to yield R\(_1\) and wR\(_2\) of 3.74% and 9.66%, respectively. Refinement was done using F\(^2\). The structure has been deposited with the Cambridge Crystallographic Data Centre as CCDC 615504.

III. \(^1\)H NMR Spectra for 1 and 3–5.
All proton spectra for precursors to the ureidopurines are shown in DMSO unless otherwise specified. For the urea compounds, CDCl\(_3\) spectra are also included.
4 Synthetic details will be published elsewhere.