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UNEXPECTED BEHAVIOUR OF 6-CYANOPURINES TOWARDS SECONDARY AMINES

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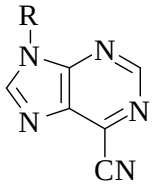
Abstract - Reaction of 6-cyanopurines with excess dimethylamine and excess piperidine at room temperature or by reflux-respectively-yielded a mixture of 6-purinecarboximidamides and *N*,*N*-dialkylpurines or piperidin-1-yl(purin-6-yl)methanimine and (piperidin-1-yl)-9*H*-purine, respectively. 6-Purinecarboximidamides were initially formed from the reaction, whereas *N*,*N*-dialkylpurines were detected in the mixture 30 min afterward. Both purines appeared to be generated from different mechanistic pathways.

Over the last few decades, a large number of 6-substituted purines, including *N*,*N*-dialkylpurine derivatives, have been produced for their various biological activities[1-23] with their activities depending mainly on the type and position of substituents available. Several *N*,*N*-dialkylpurine derivatives have been reported in the literature to act as anti-inflammatory, anti-allergic, and antirhinoviral agents whereas others have been reported to act as antibacterial agents for *Mycobacterium turberculosis* strain $H_{37}Rv$. Other derivatives have been used successfully for the treatment of Alzheimer's disease.[24,25]



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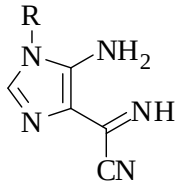

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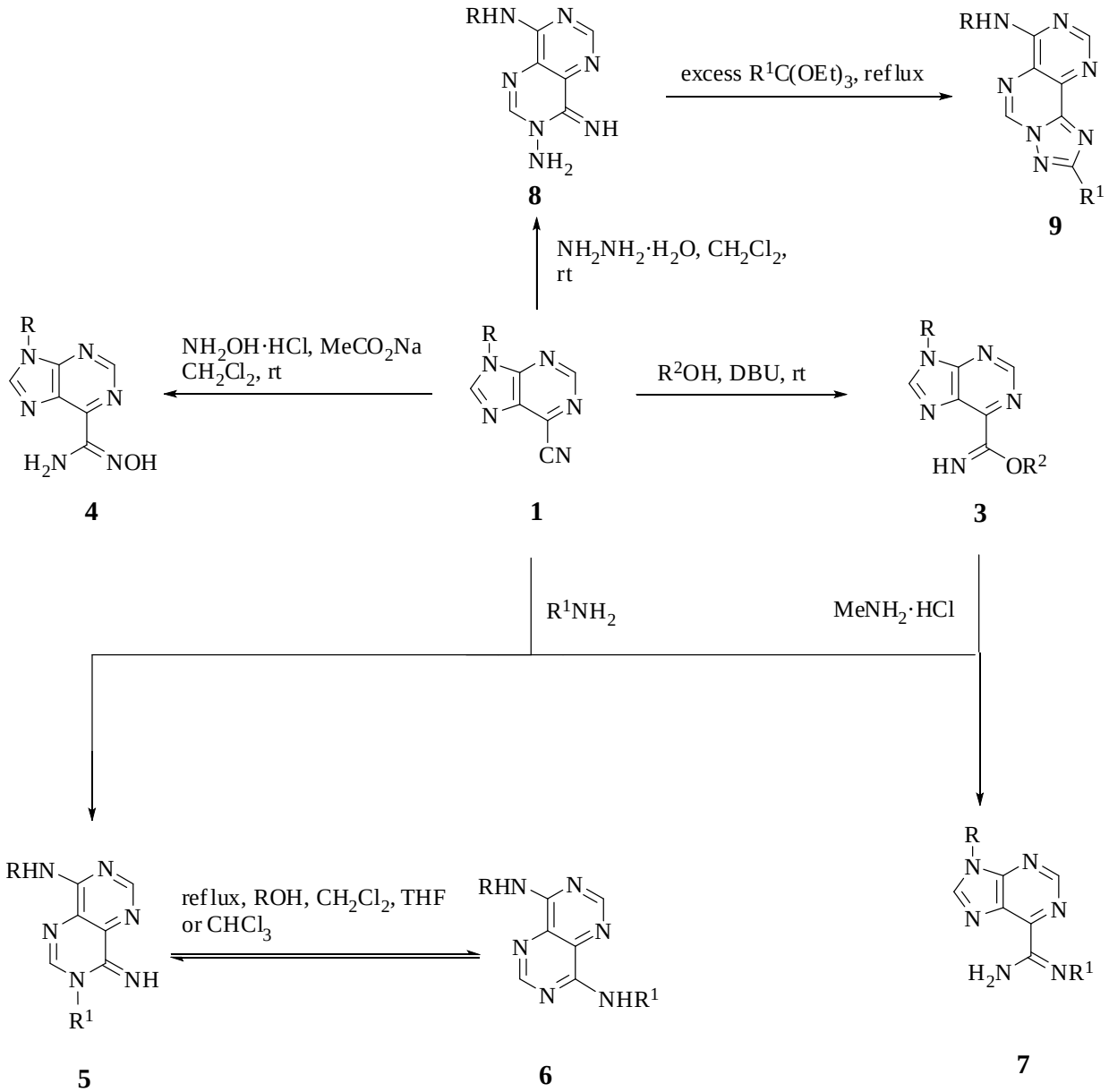
Proneça[23,24] described two different synthetic routes for *N*,*N*-dialkylpurinederivatives: (1) reaction of 5-amino-4-cyanoformimidoylimidazole **2** and *N*,*N*-dimethylformamide diethyl acetal followed by addition

of excess secondary alkylamine or (2) treatment of 5-amino-4-cyanoformimidoylimidazole **2** with a secondary alkylamine and then addition of either *N*,*N*-dimethylformamide diethyl acetal, salicyladehyde, or 4-hydroxybenzaldehyde.

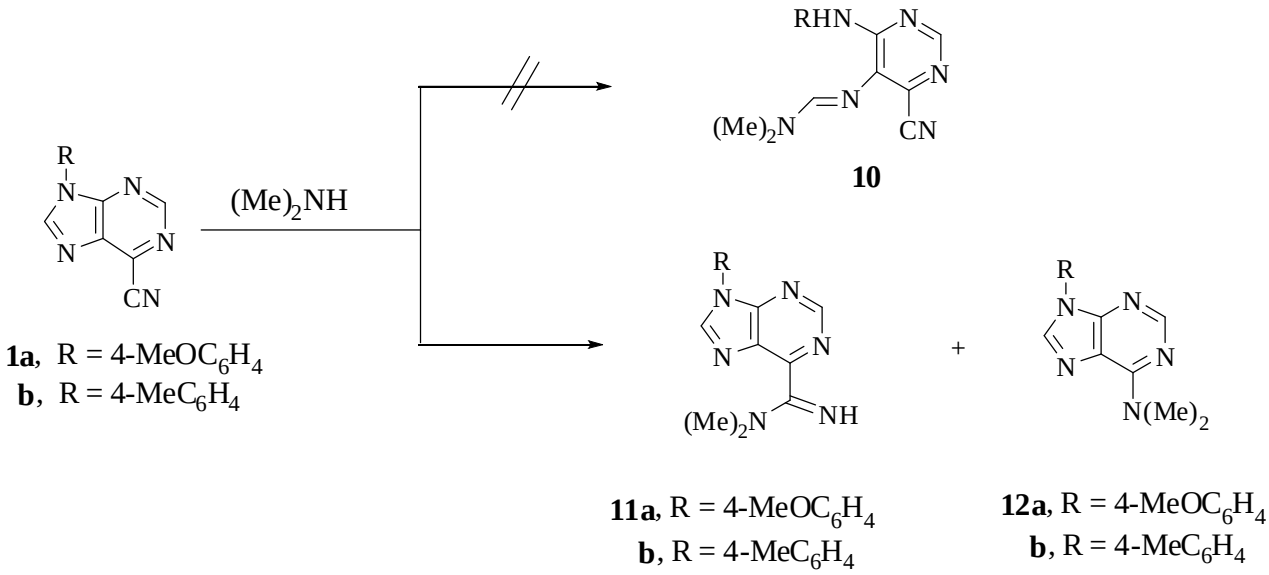
Over the last few years, our group has investigated the reactions of 6-cyanopurines with primary amines.[4,26] 6-Cyanopurine **1** has proven to be a fruitful precursor for new and novel transformations (**Scheme 1**).



Scheme 1

However, to the best of our knowledge, the direct reaction of 6-cyanopurines with secondary amines has yet to be examined. This paper describes the reaction of 6-cyanopurine **1** with dimethylamine and piperidine.

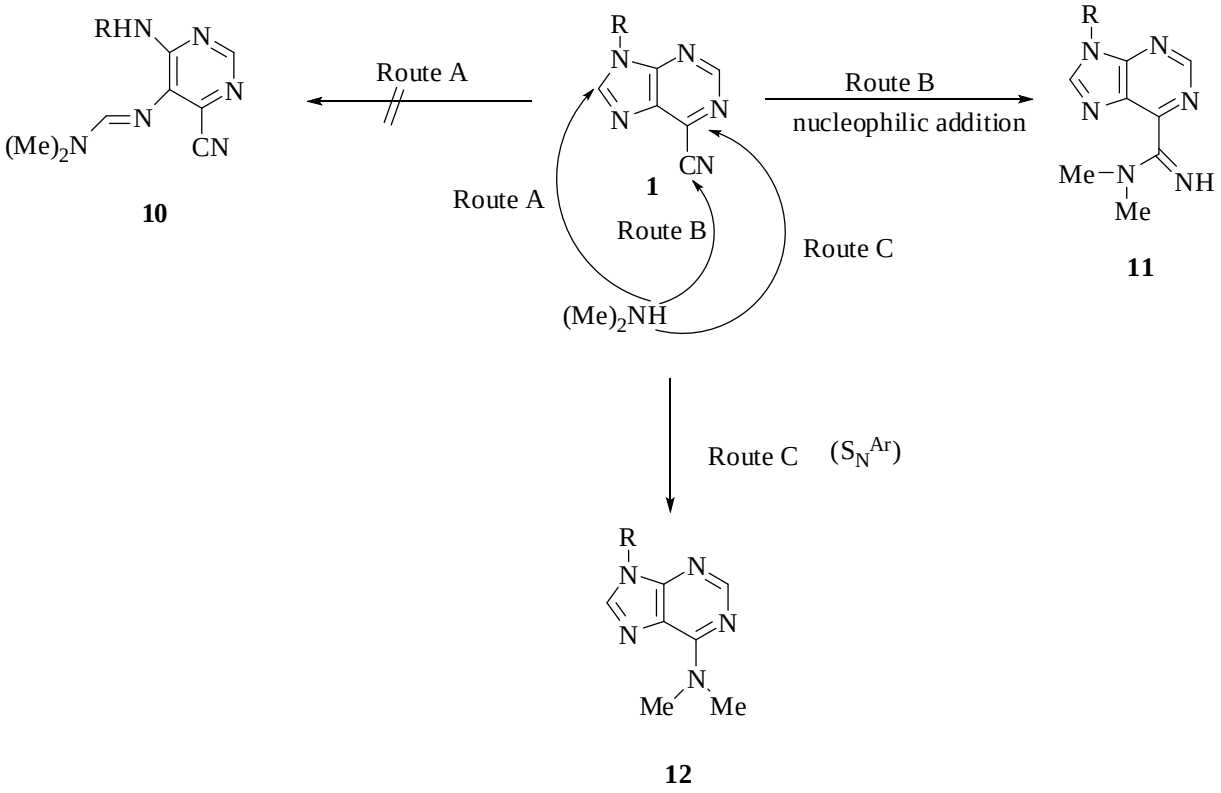
When a mixture of **1a** and excess dimethylamine was stirred at room temperature, formation of a product occurred within 1 min to 2 min, as shown by TLC. Stirring was continued to drive the reaction to completion. Approximately 30 min later, TLC again indicated the formation of another product. The starting material was fully consumed within 5 d, and the two products were separated by column chromatography. Reaction of 6-cyanopurine **1a** with dimethylamine was carried out in an attempt to isolate pyrimidine **10**, as shown in **Scheme 3**, **Route A**. Dimethylamine was assumed to behave in a manner similar to methylamine by opening the imidazole ring.[4,15] IR and ^{13}C NMR spectra of the isolated solids showed the disappearance of the cyano group. Both products were fully characterised by spectroscopic analyses and identified as *N6*,*N6*-dimethyl-9-(4-methoxyphenyl)-9*H*-6-purinecarboximidamide (R_f = 0.78) **11a**, and *N*-[9-(4-methoxyphenyl)-9*H*-6-purinyl]-*N*,*N*-dimethylamine **12a** (R_f = 0.53) in 2:1 (EtOAc:hexane). Another derivative, **1b**, was also made to react with excess dimethylamine, generating the purines **11b** and **12b**, as shown in **Scheme 2**, **Table 1**.



Scheme 2

Isolation of purines **11a** and **11b** suggested that the previously reported mechanism for the reaction of methylamine with 6-cyanopurines could be interpreted *via* a different approach.

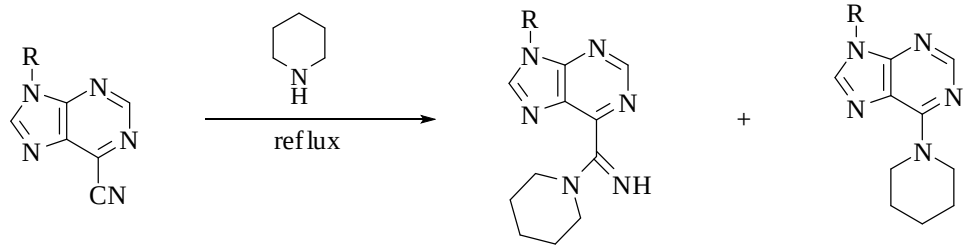
Previous papers[4,15] reported that imidazole ring opening by methylamine and attack on the electrophilic carbon of the cyano group are necessary to generate pyrimidopyrimidine. However, isolation of **11a** and **11b** indicated that the mechanism may actually start by nucleophilic attack of the amine on the cyano group (**Scheme 3**, **Route B**).



Scheme 3

Purines **11** and **12** were clearly produced by two reaction intermediates. Formation of purine **11** represents an example of a nucleophilic addition reaction, whereas formation of purine **12** shows an example of a typical S_N^{Ar} reaction. Purines **12a** and **12b** were previously believed to form when excess dimethylamine reacts with purines **11a** and **11b**, causing displacement of the carboximidine moiety. Purines **11a** and **11b** were stirred with excess dimethylamine at room temperature for 7 d, and their reaction was monitored by TLC. No change in the composition of the primary reaction mixture was observed.

To generalise this observation, another two reactions were carried out and it was found that both purines **1a**,**b** furnished the two expected products **13a**,**b** and **14a**,**b**, when refluxed with piperidine (**Scheme 4**, **Table 1**).



1a, R = 4-$MeOC_6H_4$
1b, R = 4-MeC_6H_4

13a, R = 4-$MeOC_6H_4$
13b, R = 4-MeC_6H_4

14a, R = 4-$MeOC_6H_4$
14b, R = 4-MeC_6H_4

Scheme 4

Table 1. Reaction conditions used to synthesize compounds (**11-14**).

Entry	Reactant	Secondary amine	Reaction Conditions	Product/ yield(%)
1	**1a**	$(Me)_2NH$	excess $(Me)_2NH$, rt, 5 days	**11a (33)/ 12a (36)**
2	**1a**	piperidine	excess piperdine, reflux 1 h, CH_2Cl_2:hexane 1:4	**13a (29)/ 14a (38)**
3	**1b**	$(Me)_2NH$	excess $(Me)_2NH$, rt, 3 days	**11b (39)/ 12b (54)**
4	**1b**	piperidine	excess piperdine, reflux 3 h, CH_2Cl_2:hexane 1:4	**13b (12)/ 14b (69)**

Like the previous reactions in **Scheme 2**, the S_N^{Ar} products **14a**,**b** were the major for both **1a** and **1b**.

In conclusion, this paper describes a mild, efficient, and direct method for preparing two 6-substituted purines from easily made 6-cyanopurines. The products obtained showed the presence of two competing reaction mechanisms, affording two different purines with acceptable yields.

EXPERIMENTAL

General

6-Cyanopurines **1a** and **1b** were prepared according to literature procedures.[4] ^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz. $CDCl_3$ or DMSO-d_6 was used as the solvent, and tetramethylsilane was used as the internal standard. Chemical shifts are reported in δ units (ppm). ^{13}C NMR spectra were obtained using a Bruker DPX 400 spectrometer at 100 MHz. Mass spectra were recorded on a VG autospec Q spectrometer with digital data output. IR spectra were recorded on FTIR-JASCO-FT/IR-6300 instrument using KBr discs. The (ν_{max}) is recorded in cm^{-1}. Melting points were determined by a Gallenkamp melting point apparatus and are reported uncorrected. TLC was performed on 0.25 mm pre-coated silica gel plates (Merck).

Reaction of 6-cyanopurine 1a with dimethylamine

Excess dimethylamine (20 mmol) was added to 6-cyanopurine **1a** (0.28 g, 1.12 mmol), and the suspension was stirred at room temperature. After a few minutes, the mixture yielded a clear solution. TLC showed the presence of two products: one (R_f = 0.78) appearing 1 min to 2 min after stirring and the other (R_f = 0.53) (EtOAc:hexane, 2:1) appearing 30 min later. Stirring was continued until TLC indicated completion of the reaction 5 d. The resulting solids, which were composed of the two products, were filtered off, and products were separated by column chromatography starting with a mobile phase of 1:9 EtOAc:hexane, gradually increasing to 100% EtOAc.

N6,N6-Dimethyl-9-(4-methoxyphenyl)-9H-6-purinecarboximidamide **11a**: Yellow needles (0.11 g, 0.37 mmol, 33%), mp 160-163 °C [Found accurate mass: 296.1380; *m/z* (EI) (M^+) 296, 100%; $C_{15}H_{16}N_6O$ requires: 296.1380; M 296]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 3.32 (s, 6H, $N(CH_3)_2$), 3.75 (s, 3H, OCH_3), 6.93 (d, 2H, *J* 8.8 Hz, ArH), 7.85 (d, 2H, *J* 9.2 Hz, ArH), 8.50 (s, 1H, CH), 8.53 (s, 1H, CH), 9.82 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, TMS) 158.30, 156.69, 155.63, 153.51, 151.80, 134.12, 133.07, 131.65, 123.01, 113.70, 55.24, 40.82; ν_{max}: (KBr) 3318, 2925, 1605, 1541, 1411, 1240, 1180, 1008, 835 cm^{-1}.

N-[9-(4-Methoxyphenyl)-9H-6-purinyl]-N,N-dimethylamine **12a**: Cream powder (0.11 g, 0.40 mmol, 36%), mp 166-169 °C [Found accurate mass: 269.1271; *m/z* (EI) (M^+) 269, 100%; $C_{14}H_{15}N_5O$ requires: 269.1271; M 269]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 3.32 (s, 6H, $N(CH_3)_2$), 3.82 (s, 3H, OCH_3), 7.12 (d, 2H, *J* 9.2 Hz, ArH), 7.71 (d, 2H, *J* 9.2 Hz, ArH), 8.24 (s, 1H, CH), 8.46 (s, 1H, CH); δ_C 100 MHz (DMSO-*d*$_6$, TMS) 158.56, 154.48, 152.35, 150.08, 138.77, 127.88, 125.08, 119.56, 114.58, 55.54, 40.93; ν_{max}: (KBr) 3090, 2921, 1598, 1521, 1430, 1258, 1183, 1070, 970, 821 cm^{-1}.

Reaction of 6-cyanopurine 1b with dimethylamine

A methanolic solution of dimethylamine (10 mL, 20 mmol) was added to 6-cyanopurine **1b** (0.47 g, 2.0 mmol), and the suspension was stirred at room temperature. After 10 min to 15 min, the reaction mixture yielded a light brown clear solution. Stirring was continued until the reaction reached completion, approximately 2 d to 3 d. The reaction mixture revealed the presence of two solids. Addition of MeOH dissolved one of the solids, leaving the other product undissolved for collection by filtration. The second product was obtained by concentration of the MeOH layer followed by crystallisation from acetone.

N6,N6-Dimethyl-9-(4-methylphenyl)-9H-6-purinecarboximidamide **11b**: Light brown crystals, (0.22 g, 0.78 mmol, 39%), mp 161-165 °C [Found accurate mass: 280.1430; *m/z* (EI) (M^+) 280, 100%; $C_{15}H_{16}N_6$ requires: 280.1430; M 280]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 2.29 (s, 3H, CH_3), 3.35 (s, 6H, $N(CH_3)_2$), 7.16 (d, 2H, *J* 8.4 Hz, ArH), 7.85 (d, 2H, *J* 8.4 Hz, ArH), 8.52 (s, 1H, CH), 8.53 (s, 1H, CH), 9.78 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, TMS) 158.26, 156.67, 153.56, 151.67, 136.11, 134.10, 133.11, 132.60, 128.97, 121.18, 40.86, 20.55; ν_{max}: (KBr) 3329, 1598, 1576, 1525, 1447, 1409, 1359, 1234, 1003, 822, 626 cm^{-1}.

N,N-Dimethyl-N-[9-(4-methylphenyl)-9H-6-purinyl]amine **12b**: Off-white powder (0.27 g, 1.06 mmol, 54%), mp 136-139 °C [Found accurate mass: 253.1321; *m/z* (EI) (M^+) 253, 100%; $C_{14}H_{15}N_5$ requires: 253.1321; M 253]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 2.38 (s, 3H, CH_3), 3.35 (s, 6H, $N(CH_3)_2$), 7.37 (d, 2H,

J 8.4 Hz, ArH), 7.71 (d, 2H, *J* 8.4 Hz, ArH), 8.25 (s, 1H, CH), 8.51 (s, 1H, CH); δ_C 100 MHz (DMSO-*d*$_6$, TMS) 154.48, 152.39, 149.99, 138.58, 137.10, 132.54, 129.86, 123.23, 121.21, 119.72, 37.96, 20.64; ν_{max}: (KBr) 3100, 2923, 1598, 1517, 1421, 1296, 974, 810, 641 cm^{-1}.

Reaction of 6-cyanopurine 1a and 1b with piperidine

Excess of piperidine was added to 6-cyanopurine **1a** (0.6 g, 2.39 mmol), or **1b** (0.52 g, 2.21 mmol). The mixture was refluxed for 1 h (**1a)** and 3 h (**1b**). Two new spots were detected using TLC and the reaction reached completion. The mixture was concentrated and the residue was dissolved with a minimum amount of DCM, then excess of hexane and left to precipitate (24 h). The solids formed were filtered off, and separated by column chromatography starting with a mobile phase of hexane, and gradually increasing to 100% EtOAc.

(9-(4-Methoxyphenyl)-9H-purin-6-yl)(piperidin-1-yl)methanimine **13a**: Cream powder (0.23 g, 0.68 mmol, 29%), mp 173-176 °C [Found accurate mass: 336.1694; *m/z* (EI) (M^+) 336, 42%; $C_{18}H_{20}N_6O$ requires: 336.1693; M 336]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 1.65 (s, 6H, $3CH_2$), 3.76 (s, 3H, OCH_3), 4.35 (s, 4H, $2CH_2$), 6.94 (d, 2H, *J* 8.8 Hz, ArH), 7.85 (d, 2H, *J* 9.2 Hz, ArH), 8.50 (s, 1H, CH), 8.53 (s, 1H, CH), 9.85 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, TMS) 157.50, 156.91, 155.65, 153.54, 151.78, 134.40, 132.94, 131.59, 123.05, 113.68, 55.23, 48.04, 26.01, 24.19; ν_{max}: (KBr) 3447, 3344, 3102, 3043, 3019, 2940, 2917, 2853, 1601, 1578, 1543, 1517, 1505 cm^{-1}.

9-(4-Methoxyphenyl)-6-(piperidin-1-yl)-9H-purine **14a**: light red crystals (0.28 g, 0.9 mmol, 38%), mp 151-155 °C [Found accurate mass: 309.1583; *m/z* (EI) (M^+) 309, 100%; $C_{17}H_{19}N_5O$ requires: 309.1584; M 309]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 1.56 (m, 4H, $2CH_2$), 1.65 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.23 (s, 4H, $2CH_2$), 7.11 (d, 2H, *J* 8.8 Hz, ArH), 7.70 (d, 2H, *J* 8.8 Hz, ArH), 8.24 (s, 1H, CH), 8.45 (s, 1H, CH), δ_C 100 MHz (DMSO-*d*$_6$, TMS) 158.56, 153.30, 152.40, 150.32, 138.65, 127.82, 125.12, 119.22, 114.54, 55.51, 45.72, 25.72, 24.29; ν_{max}: (KBr) 3445, 3103, 3073, 3023, 2978, 2927, 2915, 2847, 1921, 1888, 1698, 1650, 1576, 1558, 1521 cm^{-1}.

Piperidin-1-yl(9-p-tolyl-9H-purin-6-yl)methanimine **13b**: off-white powder (0.082 g, 0.25 mmol, 12%), mp 169-172 °C [Found accurate mass: 320.1743; *m/z* (EI) (M^+) 320, 100%; $C_{18}H_{20}N_6$ requires: 320.1743; M 320]; δ_H 400 MHz (DMSO-*d*$_6$, TMS) 1.64 (m, 6H, $3CH_2$), 2.29 (s, 3H, CH_3), 4.33 (s, 4H, $2CH_2$), 7.16 (d, 2H, *J* 8.4 Hz, ArH), 7.85 (d, 2H, *J* 8.4 Hz, ArH), 8.52 (s, 1H, CH), 8.53 (s, 1H, CH), 9.81 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, TMS) 157.48, 156.90, 153.59, 151.66, 136.03, 134.38, 132.99, 132.64, 128.92,

121.24, 48.03, 26.00, 24.15, 20.51; ν_{max}: (KBr) 3349, 3038, 2963, 2919, 2855, 1902, 1598, 1536, 1443 cm^{-1}.

6-(Piperidin-1-yl)-9-p-tolyl-9H-purine **14b**: light yellow powder (0.44 g, 1.5 mmol, 69%), mp 141-145 °C [Found accurate mass: 293.1634; *m/z* (EI) (M^+) 293, 100%; $C_{17}H_{19}N_5$ requires: 293.1634; M 293]; δ_H 400 MHz (DMSO-d_6, TMS) 1.60 (m, 4H, $2CH_2$), 1.69 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 4.23 (s, 4H, $2CH_2$), 7.37 (d, 2H, *J* 8 Hz, ArH), 7.71 (d, 2H, *J* 8.4 Hz, ArH), 8.26 (s, 1H, CH), 8.51 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, TMS) 153.31, 152.45, 150.24, 138.49, 137.12, 132.47, 129.82, 123.31, 119.36, 45.66, 25.72, 24.28, 20.62; ν_{max}: (KBr) 3447, 3106, 3081, 3044, 3021, 2924, 2862, 2848, 1590, 1578, 1554, 1524 cm^{-1}.

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