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Synthetic Studies Directed towards Agelasine Analogs – Synthesis, Tautomerism, and Alkylation of 2-Substituted *N*-Methoxy-9-methyl-9*H*-purin-6-amines

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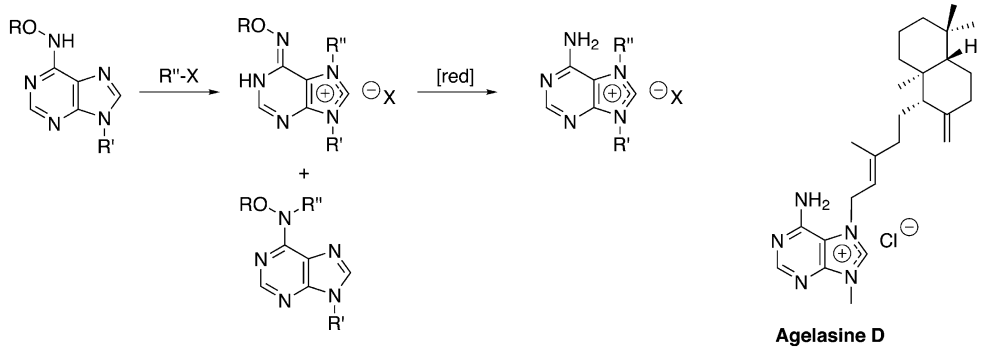
N-Methoxy-9-methyl-9*H*-purin-6-amines, carrying various substituents in the 2 positions, were synthesized by the *N*-methylation of known 6-chloropurines, followed by a displacement of the chlorine. Great variations in the amino/imino tautomer ratio among the compounds studied were observed. The tautomers were identified by NMR methods. Treatment of *N*-methoxy-9-methyl-9*H*-purin-6-amines carrying alkyl, alkoxy, or amino substituents in the 2 position with benzyl bromide resulted in a mixture of *N*-7- and N^6-benzylated compounds with the former as the major products. *N*-Methoxy-9-methyl-9*H*-purin-6-amines with strongly electronegative substituents at C-2 hardly reacted at all under the same set of reaction conditions.

Introduction

Agelasines[1] are 7,9-dialkylated adeninium salts associated with various bioactivities, including antimicrobial and cytotoxic effects, and are isolated from marine sponges (*Agelas* sp). We have synthesized agelasine D (Scheme 1)[2] and E[3] as well as a number of agelasine analogs[2–4] and studied their activities against various microorganisms and cancer cell lines. The synthesis of agelasines requires a regioselective alkylation of an adenine derivative to give a 7,9-dialkylated purinium salt. However, the alkylation of 9-substituted adenine gives mainly 1,9-dialkyl derivatives, and when 7-alkyladenines are reacted with alkyl halides, the second *N*-substituent attaches preferentially at N-3. Treatment of *N*-alkoxy-9-methyl-9*H*-purin-6-amine with alkylating agents gives, on the other hand, the desired alkylating pattern.[5] Thus, agelasines and their analogs have generally been synthesized as depicted in Scheme 1.[2–4,6]

In our project directed towards antimicrobial and neoplastic agelasine analogs we have examined structure-activity relationships (SAR) by varying the substituents at the purine N^6, N-7, and N-9 positions, and several potent antimicrobial and/or neoplastic compounds have been identified.[2–4] A logical continuation of this project would be to study agelasine analogs carrying substituents in the purine 2 or 8 position. However, we found that the *N*-7-alkylation of *N*-alkoxy-9-alkyl-9*H*-purin-6-amines carrying any substituent at C-2 has not been described before, and herein we report our synthesis of 2-substituted *N*-alkoxy-9-alkyl-9*H*-purin-6-amines, their tautomeric ratios, as well as their reactivity in alkylation reactions.



Scheme 1. General synthetic route to agelasines and analogs and the structure of agelasine D.

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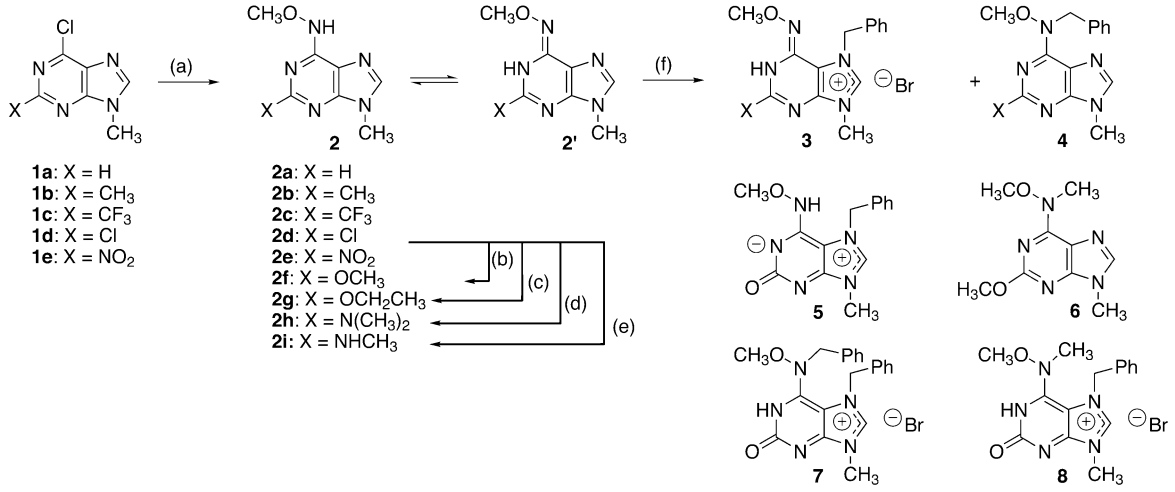
Results and Discussion

N-Methoxy-9-methyl-9*H*-purin-6-amines **2**, carrying various substituents in the purine 2 position, were synthesized by the *N*-methylation of known 6-chloropurines to give compounds **1**, followed by a displacement of the chlorine in the 6 position of purines **1a**–**e** with methoxyamine, essentially as described before.[2–4] The 2-alkoxy derivatives **2f** and **2g** and amines **2h** and **2i** were synthesized from 2-chloropurine **2d** (Scheme 2, Table 1). Also, the primary amine analog of compounds **2h** and **2i** was formed from ammonia and chloropurine **2d** by this route, but low chromatographic stability precluded isolation of the pure substance and further studies on the 2-amino compound. With the 6-methoxyamino group present, relatively harsh conditions were required for exchange of the 2-chloro substituent in compound **2d**. The alkoxypurines **2f** and **2g**, for instance, were formed in good yields after treatment with RONa/ROH at reflux for 12 and 5 d, respectively. The alternative strategy of introducing the desired C-2 substituent before the methoxyamino group in the 6 position was also considered, but the synthesis of the dimethylaminopurine **2h** from 6-chloro-2-dimethylamino-9-methylpurine[7] met with little success, because the dimethylamino group deactivated the system for nucleophilic attack. The nitro group in compound **1e** was introduced by the tetrabutylammonium nitrate/TFAA nitration[8] of 6-chloro-9-methylpurine **1a**.

The amino tautomer **2a** exists in equilibrium with imino tautomer **2a′** in [D$_6$]DMSO in a 2:8 ratio.[3] We observed great variations in the **2**:**2′** ratio in solution among compounds **2a**–**2i** (Table 2). The tautomers were identified mainly from their ^{13}C NMR and ^{15}N NMR shift values. In amino tautomers **2**, the resonance from C-4 appeared at ca. 152 ppm, and the resonance from C-6 appeared at ca. 155 ppm, values one would expect from a 6-aminopurine.[9] In imino tautomers **2′**, however, the C-4 resonance appeared at ca. 142 ppm, and the resonance from C-6 appeared at ca. 141 ppm. Also, C-2, C-8 and the methyl group in the 6 position substituent resonated at higher field in imines **2′** than they did in amines **2**. The chemical shift values for N^6 were ca. –210 ppm in amino tautomers **2** and ca. –95 ppm in imines **2′** (relative to $MeNO_2$ at 0 ppm), as reported for **2a′** previously.[3] All iminopurines **2′** are drawn with the NH at N-1 and in their most probable double bond configuration (*syn*, Scheme 2), in accordance with earlier



Scheme 2. (a) CH_3ONH_3Cl, Et_3N, *n*BuOH or CH_3OH, Δ; (b) CH_3ONa, CH_3OH, Δ; (c) Na, CH_3CH_2OH, Δ; (d) $(CH_3)_2NH$, H_2O, 85 °C; (e) CH_3NH_2, H_2O, 85 °C; (f) $PhCH_2Br$, DMA, 50 °C.

Table 1. Synthesis and alkylation of compounds **2**/**2′** at 50 °C for 25 h.

Entry	X in **2**–**4**	% Yield of **2**/**2′** from **1**	% Yield of **3**	% Yield of **4**	% Recovered **2**/**2′**
1	**a**: H	72	51	35	8
2	**b**: CH_3	56	57	29	5
3	**c**: CF_3	34	<2[b]	–	66
4	**d**: Cl	67	4[c]	–	86
5	**e**: NO_2	62	–	–	95
6	**f**: OCH_3	92[a]	–[d]	11	14
7	**g**: OCH_2CH_3	72[a]	52	20	22
8	**h**: $N(CH_3)_2$	90[a]	61	7	12
9	**i**: $NHCH_3$	65[a]	56	22	–

[a] Yield from **2d**. [b] From NMR. [c] Isolated as betaine. [d] Formed, but not isolated in pure form; compound **5** (19%) and **6** (1%) were also isolated.

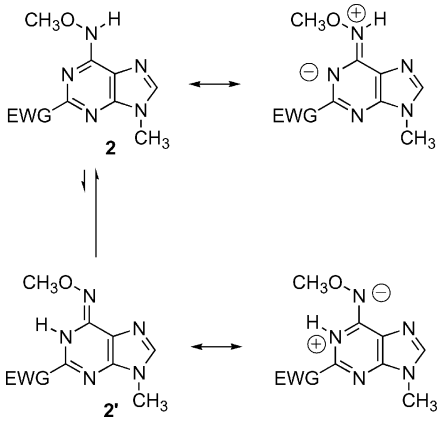
NMR[3,10,11] and UV[10] studies of imine **2a′** and other 6-(methoxyamino)purines. We have no indication that chromatographic separation of any of the tautomer pairs would be possible.

Table 2. % Amino tautomer **2** in [D_6]DMSO solution.

Entry		X	*F*[a]	% Tautomer **2**[b]		
				25 °C	40 °C	70 °C
1	**2a**	H	0.03	20	25	32
2	**2b**	CH_3	0.01	18	21	29
3	**2c**	CF_3	0.38	100	100	100
4	**2d**	Cl	0.42	100	100	100
5	**2e**	NO_2	0.65	100	100	100
6	**2f**	OCH_3	0.29	92	92	92
7	**2g**	OCH_2CH_3	0.26	94	93	94
8	**2h**	$N(CH_3)_2$	0.15	100	100	100
9	**2i**	$NHCH_3$	0.03	28	33	37

[a] Calculated *F* values taken from ref.[12] [b] Determined by ^{1}H NMR spectroscopy.

Approximately the same tautomeric ratios were observed for unsubstituted compound **2a**, 2-methyl derivative **2b**, and methylaminopurine **2i**. Tautomers **2a′** and **2b′** were the dominating species in both [D_6]DMSO and CD_3OD solutions (data not shown), and the equilibria were shifted slightly towards the amino forms at higher temperatures. In case of the trifluoromethyl, chloro, nitro, alkoxy, and dimethylamino compounds, the dominating tautomers were the amines **2c**–**2h**. The ratios were not significantly affected by temperature in the range studied (25–70 °C). Inductively electron-withdrawing substituents in the 2 position favor the amino form. All purines **2** that exist mainly as amines have substituents in the 2 position with a substantially more positive field/inductive parameter *F*[12] (Table 2) than that for the purines where the imine form is preferred. Also, a 2-amino-6-(methoxyamino)purine was reported to exist mainly as an imine in [D_6]DMSO [$F(NH_2)$ = 0.08].[11] Scheme 3 illustrates how an electron-withdrawing substituent in 2 position might stabilize a partial negative charge in the pyrimidine ring of amine tautomer **2** and destabilize a partial positive charge in imine **2′**.



Scheme 3. Possible electronic influence on the amino/imino ratio from an electron withdrawing group (EWG) at C-2.

Treatment of purines **2a**, **2b** and **2g**–**2i** with benzyl bromide in dimethylacetamide (DMA) at 50 °C resulted in the expected[2–4] mixture of *N*-7-benzylated purinium salts **3** and the N^6-benzylated isomers **4**, with the former compounds as the major products (Scheme 2 and Table 1). Only minor amounts of starting material **2** were unreacted after 25 h. The 2-(trifluoromethyl)purine **2c**, on the other hand, hardly reacted at all under the same set of reaction conditions. The same was true for the 2-chloro- and 2-nitropurines (compounds **2d** and **2e**, respectively). The reactivity in the benzylation appears not to be influenced by the same factors that govern tautomerism in the starting materials **2**, but compounds carrying 2-substituents associated with rather large positive σ-values (σ_m or σ_p),[12] **2c**–**2e**, were essentially unreactive towards benzyl bromide under the conditions applied.

Benzylation of 2-methoxypurine **2f** resulted in a complex mixture. The expected product **3f** was most probably present according to NMR, but isolation of the pure compound was not achieved. Minor amounts of isomer **4f** as well as unconverted starting material **2f** were isolated, in addition to 2-oxopurine **5** (19%) and N^6-methylated compound **6** (1%). According to NMR, compounds **7** and **8** were most probably also formed, but these compounds were not isolated in pure form, and their structures were not determined with absolute certainty. It appears that the O^2-methyl group in starting material **2f** and/or product **3f** is prone to nucleophilic attack resulting in demethylation. It is most likely that demethylation occurs after *N*-benzylation, because the starting material is completely stable in DMA at 50 °C. Compound **6** may, for instance, have been formed from an attack on the O^2-methyl group in **3f** by N^6 of starting material **2f**. We have also previously observed demethylation of certain other methoxypurines.[13] Ethoxypurine **2g**, on the other hand, gave the corresponding benzylated products (**3g** and **4g**) without any detectable cleavage of the alkoxy group. All compounds **3** existed solely as imino tautomers in [D_6]DMSO according to NMR, as previously reported for compound **3a**[2b] and related structures.[3]

With the exception of the unselective synthesis of 6-amino-7,9-dimethyl-2-(methylthio)-7*H*-purinium iodide from 2-methylthioadenine,[14] we have reported the very first syntheses of adenine derivatives substituted simultaneously in the 2, 7, and 9 positions, as well as studied the scope and limitation of the synthetic route employed. From the results described above, it is evident that the reactivity of *N*-methoxy-9-methyl-9*H*-purin-6-amines **2** towards alkylating agents is highly dependent on the identity of the substituent in the 2 position. Alkyl, ethoxy, or amino groups allow formation of compounds **3** in reasonably good isolated yields, and the synthesis of agelasine analogs carrying these groups as well as bioactivity studies will be reported in due course. Electron-withdrawing substituents like trifluoromethyl, chloro or nitro groups deactivate the 6-(alkoxyamino)purines **2c**–**e** as nucleophiles towards alkylation agents, and if the synthesis of agelasine analogs carrying such groups at C-2 is to be achieved, other synthetic strategies must be sought.

Experimental Section

General: The ^{1}H NMR spectra were recorded at 600 MHz with a Bruker AV600 or a AVII600 instrument equipped with TCI cryo probes, at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument, or at 200 MHz with a Bruker Avance DPX 200 instrument. The decoupled ^{13}C NMR spectra were recorded at 150 MHz or 75 MHz with the instruments mentioned above. ^{15}N NMR shifts, reported relative to liquid ammonia (δ = 0 ppm) according to literature guidelines,[15] were taken from gs-[^{1}H,^{15}N] HSQC and gs-[^{1}H,^{15}N] HMBC spectra recorded at 60 MHz with the Bruker AVII600 instrument or at 50 MHz with the Bruker Avance DRX 500 instrument with $Me^{15}NO_2$ as an external standard.[3] ^{19}F NMR spectra were recorded at 188 MHz with the Avance DPX 200 instrument with CCl_3F as a reference (δ = 0 ppm). Mass spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage and are presented as *m*/*z* (% relative intensity). Electrospray MS spectra were recorded with a Micromass Q-Tof-2 mass spectrometer. Elemental analyses were performed by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, Germany. Dimethylacetamide (DMA) was distilled from BaO and stored over molecular sieves (3 Å). Triethylamine, dimethylformamide (DMF), and CH_2Cl_2 were distilled from CaH_2 and stored over molecular sieves (3 Å). Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385), and flash chromatography was performed manually or with an Isco Inc. CombiFlash Companion instrument. Compounds available by literature methods: 6-Chloro-2-trifluoromethyl-9*H*-purine,[16] 6-chloro-9-methyl-9*H*-purine (**1a**),[17] 2,6-dichloro-9-dimethyl-9*H*-purine (**1d**),[18] and *N*-methoxy-9-methyl-9*H*-purin-6-amine (**2a**).[3] All other reagents were commercially available and used as received.

6-Chloro-2,9-dimethyl-9*H*-purine (1b): 5-Amino-4-imidazolecarboxamide hydrochloride (1.00 g, 6.15 mmol), followed by EtOAc (6.0 mL, 61 mmol), was added to a solution of sodium ethoxide in ethanol [prepared by adding metallic sodium (2.1 g, 0.9 mol) to ethanol (72 mL, 1.2 mol)], and the resulting mixture was heated at reflux for 24 h under Ar. The reaction mixture was cooled to room temperature and filtered. The solid was washed twice with a mixture of diethyl ether and iced water and once with diethyl ether and dried in vacuo to give 1.37 g of crude 2-methylhypoxathine; m.p. > 260 °C (ref.[19] > 350 °C). ^{1}H NMR (300 MHz, D_2O): δ = 7.85 (s, 1 H, H-8), 2.46 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 166.4 (C-6), 161.3 (C-4), 159.6 (C-2), 151.2 (C-8), 122.4 (C-5), 24.1 (CH_3) ppm. MS (EI): *m*/*z* (%) = 150 (46) $[M]^+$, 44 (100). HRMS (EI): calcd. for $C_6H_6N_4O$ 150.0542; found 150.0545. A mixture of crude 2-methylhypoxathine (1.114 g, 5.00 mmol), phosphorus oxychloride (14.75 mL, 161.1 mmol), and *N*,*N*-dimethylaniline (3.0 mL, 24 mmol) was heated at reflux for 1 h. The reaction mixture was evaporated in vacuo. CH_2Cl_2 (30 mL) and HCl in diethyl ether (10 mL, 1 M, 10 mmol) were added, and the solid was filtered and washed repeatedly with a mixture of CH_2Cl_2 and diethyl ether to yield 6-chloro-2-methyl-9*H*-purine hydrochloride (0.997 g, ca. 96% pure according to NMR) as a pale yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 9.27 (s, 1 H, H-8), 2.81 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 166.0 (C-2), 153.4 (C-4 or C-6), 148.4 (C-4 or C-6), 146.3 (C-8), 121.6 (C-5), 25.3 (CH_3) ppm. MS (EI): *m*/*z* (%) = 170/168 (32/100) $[M - HCl]^+$, 133 (100), 121 (37), 120 (50). HRMS (EI): calcd. for $C_6H_5ClN_4$ 168.0203; found 168.0200. Methyl iodide (1.2 mL, 19.3 mmol) was added to a stirring mixture of 6-chloro-2-methyl-9*H*-purine hydrochloride (2.50 g, 12.2 mmol) and K_2CO_3 (6.71 g, 48.6 mmol) in DMF (50 mL), and the resulting mixture was stirred for 25 h under Ar and filtered. The filtrate was evaporated in vacuo, and the product was purified by flash chromatography on silica gel, eluting with 15–30% acetone in EtOAc/hexanes (2:8) to yield 0.729 g (33%) of the title compound **1b** as a colorless solid; m.p. 168–171 °C (ref.[20] 167–169 °C). ^{1}H NMR (300 MHz, CD_3OD): δ = 8.39 (s, 1 H, H-8), 3.89 (s, 3 H, NCH_3), 2.73 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 163.6 (C-2), 154.2 (C-4), 150.5 (C-6), 148.4 (C-8), 129.9 (C-5), 30.5 (NCH_3), 25.3 (CH_3) ppm. MS (EI): *m*/*z* (%) = 184/182 (32/100) $[M]^+$, 147 (87). HRMS (EI): calcd. for $C_7H_7ClN_4$ 182.0359; found 182.0357. The N-7-alkylated isomer was also formed, but not isolated.

6-Chloro-9-methyl-2-(trifluoromethyl)-9*H*-purine (1c): Methyl iodide (0.41 mL, 6.6 mmol) was added dropwise to a stirring mixture of 6-chloro-2-(trifluoromethyl)-9*H*-purine (1.228 g, 5.52 mmol) and K_2CO_3 (1.155 g, 8.36 mmol) in DMF (40 mL) at 0 °C, and the resulting mixture was stirred at ambient temperature for 23 h under Ar. CH_2Cl_2 (20 mL) was added, and the mixture was filtered and evaporated in vacuo. The product was purified by flash chromatography on silica gel, eluting with acetone/EtOAc/isohexane (9:8:33), followed by acetone/EtOAc/isohexane (10:3:12) to yield 0.733 g (56%) as a colorless solid; m.p. 69–70 °C (ref.[21] 73–74 °C). ^{1}H NMR (300 MHz, CD_3OD): δ = 8.66 (s, 1 H, H-8), 3.99 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 153.7 (C-4), 151.7 (C-6), 151.3 (C-8), 150.4 (q, J_{CF} = 37.8 Hz, C-2), 133.4 (C-5), 120.9 (q, J_{CF} = 274 Hz, CF_3), 31.0 (CH_3) ppm. ^{19}F NMR (188 MHz, CD_3OD): δ = –68.6 ppm. MS (EI): *m*/*z* (%) = 238/236 (39/100) $[M]^+$, 237 (18), 235 (21), 201 (19). HRMS (EI): calcd. for $C_7H_4ClF_3N_4$ 236.0077; found 236.0076. 6-Chloro-7-methyl-2-trifluoromethyl-7*H*-purine (0.355 g, 26%) was also isolated as a colorless solid; m.p. 157–159 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.73 (s, 1 H, H-8), 4.23 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 162.6 (C-4), 154.1 (C-8), 150.7 (q, J_{CF} = 37.5 Hz, C-2), 145.7 (C-6), 125.6 (C-5), 120.9 (q, J_{CF} = 274 Hz, CF_3), 35.0 (CH_3) ppm. ^{19}F NMR (188 MHz, CD_3OD): δ = –68.7 ppm. MS (EI): *m*/*z* (%) = 238/236 (35/100) $[M]^+$, 201 (60), 170 (6), 168 (17), 69 (29). HRMS (EI): calcd. for $C_7H_4ClF_3N_4$ 236.0077; found 236.0074. $C_7H_4ClF_3N_4$ (236.0): C 35.54, H 1.70, N 23.68; found C 35.57, H 1.82, N 23.74.

6-Chloro-9-methyl-2-nitro-9*H*-purine (1e): A nitrating mixture was prepared by adding 2,2,2-trifluoroacetic anhydride (TFAA, 4.95 mL, 35.6 mmol) to a solution of tetrabutylammonium nitrate (TBAN, 10.82 g, 35.5 mmol) in dry CH_2Cl_2 (72 mL) at 0 °C. 6-Chloro-9-methyl-9*H*-purine (**1a**) (2.39 g, 14.2 mmol) was added after 70 min, and the reaction mixture was stirred at ambient temperature under Ar for 24 h. More of the nitrating mixture [prepared as above from TBAN (5.0 g, 16.4 mmol) and TFAA (2.5 mL, 18 mmol) in CH_2Cl_2 (20 mL)] was added, and the reaction mixture was stirred overnight, evaporated in vacuo, and purified twice by dry flash chromatography, eluting with 0–5% acetone in CH_2Cl_2 and twice by column flash chromatography (CombiFlash, 0–5% MeOH in CH_2Cl_2) to yield 1.10 g (36%) as pale yellow crystals; m.p. 162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, H-8), 4.05 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4 (C-2, C-4 or C-6), 152.3 (C-2, C-4 or C-6), 152.2 (C-2, C-4 or C-6), 149.6 (C-8), 134.2 (C-5), 31.0 (CH_3) ppm. MS (EI): *m*/*z* (%) = 215/213 (6/18) $[M]^+$, 185 (4), 183 (11), 169 (32), 167 (100), 106 (21). HRMS (EI): calcd. for $C_6H_8ClN_5O$ 213.0054; found 213.0058.

2,9-Dimethyl-*N*-methoxy-9*H*-purin-6-amine (2b): Methoxyamine hydrochloride (0.792 g, 9.48 mmol) and triethylamine (1.46 mL, 10.6 mmol) were added to a solution of 6-chloro-2,9-dimethyl-9*H*-purine (**1b**) (0.385 g, 2.11 mmol) in MeOH (18 mL), and the resulting solution was heated at reflux for 65 h under Ar. The reac-

tion mixture was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with HCl (2 M, 2 × 30 mL). The aqueous phase was extracted with CH_2Cl_2 (30 mL), neutralized with $NaHCO_3$ (saturated aqueous), and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with water (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (80 mL column, 30 g silica gel, 0–10% MeOH in CH_2Cl_2) to yield 0.123 g (30%) of a pale pinkish solid; m.p. 174–175 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2b**): δ = 10.66 (br. s, 1 H, NH), 8.06 (s, 1 H, H-8), 3.73 (s, 3 H, OCH_3), 3.69 (s, 3 H, NCH_3), 2.44 (s, 3 H, CH_3) ppm. ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2b′**): δ = 10.66 (br., 1 H, NH), 7.68 (s, 1 H, H-8), 3.74 (s, 3 H, OCH_3), 3.58 (s, 3 H, NCH_3), 2.27 (s, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO, tautomer **2b′**): δ = 153.1 (C-2), 141.9 (C-4), 141.3 (C-6), 138.3 (C-8), 116.3 (C-5), 60.8 (OCH_3), 29.3 (NCH_3), 21.3 (CH_3) ppm. ^{15}N NMR (50 MHz, [D$_6$]DMSO, tautomer **2b′**): δ = –94.0 (N^6), –136.3 (N-7), –173.2 (N-3), –226.1 (N-9), –245.7 (N-1) ppm. MS (EI): *m*/*z* (%) = 193 (51) [M]$^+$, 163 (100), 148 (50), 123 (22), 107 (24). HRMS (EI): calcd. for $C_8H_{11}N_5O$ 193.0964; found 193.0963. $C_8H_{11}N_5O$ (193.2): C 49.73, H 5.74, N 36.25; found C 49.74, H 5.69, N 36.16.

9-Methyl-*N*-methoxy-2-(trifluoromethyl)-9*H*-purin-6-amine (2c): Methoxyamine hydrochloride (1.256 g, 15.0 mmol) and triethylamine (2.26 mL, 16.2 mmol) were added to a mixture of 6-chloro-9-methyl-2-trifluoromethyl-9*H*-purine (**1c**) (0.698 g, 2.95 mmol) in MeOH (21 mL), and the resulting mixture was heated at reflux for 55 h under Ar. The solution was cooled to –45 °C and filtered. The solid was washed with cold MeOH and dried in vacuo to yield 0.251 g (34%) of a colorless solid; m.p. 208–210 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2c**): δ = 11.50 (s, 1 H, NH), 8.37 (s, 1 H, H-8), 3.79 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO, tautomer **2c**): δ = 154.9 (C-6), 150.2 (C-4), 148.6 (q, J_{CF} = 35.2 Hz, C-2), 144.7 (C-8), 120.0 (q, J_{CF} = 275 Hz, CF_3), 117.8 (C-5), 63.7 (OCH_3), 29.8 (NCH_3) ppm. ^{15}N NMR (50 MHz, [D$_6$]-DMSO, tautomer **2c**): δ = –140 (N-7), –157 (N-3), –210 (N^6), –227 (N-9) ppm. N-1 was not observed. ^{19}F NMR (188 MHz, [D$_6$]-DMSO, tautomer **2c**): δ = –67.4 ppm. MS (EI): *m*/*z* (%) = 247 (37) [M]$^+$, 217 (100), 202 (34), 162 (21), 148 (60), 133 (27). HRMS (EI): calcd. for $C_8H_8F_3N_5O$ 247.0681; found 247.0681. $C_8H_8F_3N_5O$ (247.2): C 38.87, H 3.26, N 28.33; found C 38.73, H 3.26, N 28.17.

2-Chloro-9-methyl-*N*-methoxy-9*H*-purin-6-amine (2d): Methoxyamine hydrochloride (2.025 g, 24.25 mmol) and triethylamine (3.7 mL, 27 mmol) were added to a mixture of 2,6-dichloro-9-methyl-9*H*-purine (**1d**) (0.960 g, 4.73 mmol) in MeOH (38 mL), and the resulting mixture was heated at reflux for 20 h under an argon atmosphere. The reaction mixture was evaporated in vacuo, and the residue was purified by flash chromatography [25–40% acetone in EtOAc/hexanes (2:8)] to yield 0.686 g (68%) of a colorless solid; m.p. 223–224 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2d**): δ = 11.37 (s, 1 H, NH), 8.16 (s, 1 H, H-8), 3.76 (s, 3 H, OCH_3), 3.70 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, tautomer **2d**): δ = 155.2 (C-6), 152.7 (C-4), 151.7 (C-2), 143.1 (C-8), 116.0 (C-5), 63.7 (OCH_3), 29.6 (NCH_3) ppm. ^{15}N NMR (50 MHz, [D$_6$]DMSO, tautomer **2d**): δ = –141 (N-7), –156 (N-3), –211 (N^6), –229 (N-9) ppm. N-1 was not observed. MS (EI): *m*/*z* (%) = 215/213 (14/43) [M]$^+$, 185 (26), 183 (81), 148 (100). HRMS (EI): calcd. for $C_7H_8ClN_5O$ 213.0417; found 213.0421. $C_7H_8ClN_5O$ (213.6): C 39.36, H 3.77, N 32.78; found C 39.35, H 3.77, N 32.66.

9-Methyl-*N*-methoxy-2-nitro-9*H*-purin-6-amine (2e): Methoxyamine hydrochloride (0.426 g, 5.10 mmol) and triethylamine (0.77 mL, 5.5 mmol) were added to a mixture of 6-chloro-9-methyl-2-nitro-9*H*-purine (**1e**) (0.214 g, 1.00 mmol) in MeOH (8 mL), and the resulting mixture was heated at reflux for 8 h under Ar. The solution was cooled to ambient temperature, stored at 2 °C overnight, and finally filtered. The solid was washed with MeOH and dried in vacuo to yield 0.140 g (62%) of a yellow crystals; m.p. ca. 174 °C (dec.). ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2e**): δ = 11.84 (s, 1 H, NH), 8.43 (s, 1 H, H-8), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, tautomer **2e**): δ = 155.2 (C-6), 154.5 (C-2), 150.1 (C-4), 145.9 (C-8), 118.8 (C-5), 63.9 (OCH_3), 30.0 (NCH_3) ppm. ^{15}N NMR (50 MHz, [D$_6$]-DMSO, tautomer **2e**): δ = –138 (N-7), –170 (N-3), –208 (N^6), –227 (N-9) ppm. N-1 and NO_2 were not observed. MS (EI): *m*/*z* (%) = 224 (25) [M]$^+$, 194 (27), 148 (89), 147 (100), 146 (26). HRMS (EI): calcd. for $C_7H_8N_6O_3$ 224.0658; found 224.0658.

***N*,2-Dimethoxy-9-methyl-9*H*-purin-6-amine (2f):** To a mixture of 2-chloro-*N*-methoxy-9-methyl-9*H*-purin-6-amine (**2d**) (0.84 g, 3.9 mmol) in MeOH (40 mL) was added sodium methoxide (5.6 g, 103 mmol), and the resulting mixture was heated at reflux under Ar for 12 d. The reaction mixture was evaporated in vacuo. The residue was dissolved in EtOAc (30 mL) and saturated aqueous ammonium chloride (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 × 30 mL). The organic phases were washed with water (30 mL), and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by dry flash chromatography [4 × 4 cm silica column, 0–60% acetone in EtOAc/hexane (2:8)] to yield 0.75 g (92%) of a colorless solid; m.p. 191–196 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO, tautomer **2f**): δ = 10.88 (br. s, 1 H, NH), 7.97 (s, 1 H, H-8), 3.85 (s, 3 H, OCH_3), 3.75 (s, 3 H, $NOCH_3$), 3.64 (s, 3 H, NCH_3) ppm. ^{1}H NMR (500 MHz, [D$_6$]DMSO, tautomer **2f′**): δ = 10.59 (br. s, 1 H, NH), 7.61 (s, 1 H, H-8), 3.85 (s, 3 H, OCH_3), 3.70 (s, 3 H, $NOCH_3$), 3.56 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, tautomer **2f**): δ = 161.5 (C-2), 155.9 (C-6), 152.3 (C-4), 141.2 (C-8), 113.5 (C-5), 63.5 ($NOCH_3$), 54.1 (OCH_3), 29.2 (NCH_3) ppm. ^{15}N NMR (50 MHz, [D$_6$]DMSO, tautomer **2f**): δ = –185 (N-1), –192 (N-3), –140 (N-7), –211 (N^6), –230 (N-9) ppm. MS (EI): *m*/*z* (%) = 209 (100) [M]$^+$, 179 (50), 164 (46), 149 (76). HRMS (EI): calcd. for $C_8H_{11}N_5O_2$ 209.0913; found 209.0907. $C_8H_{11}N_5O_2$ (209.2): C 45.93, H 5.30, N 33.48; found C 46.02, H 5.28, N 33.39.

2-Ethoxy-*N*-methoxy-9-methyl-9*H*-purin-6-amine (2g): 2-Chloro-*N*-methoxy-9-methyl-9*H*-purin-6-amine (**2d**) (0.21 g, 1.0 mmol) was added to a mixture of sodium ethoxide in ethanol [prepared in situ from sodium (0.47 g, 20 mmol) and ethanol (7.5 mL, 0.13 mol)], and the reaction mixture was heated at reflux under Ar. for 4.5 d and evaporated in vacuo. The residue was dissolved in EtOAc (25 mL) and saturated aqueous ammonium chloride (25 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with saturated aqueous ammonium chloride (25 mL), and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography [1 × 18 cm silica column, 33–40% acetone in EtOAc/hexane (2:8)] to yield 0.16 g (72%) of a colorless solid; m.p. 173–174 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2g**): δ = 10.82 (s, 1 H, NH), 7.95 (s, 1 H, H-8), 4.29 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.74 (s, 3 H, OCH_3), 3.63 (s, 3 H, NCH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2) ppm. ^{1}H NMR (300 MHz, [D$_6$]DMSO, tautomer **2g′**): δ = 10.41 (s, 1 H, NH), 7.60 (s, 1 H, H-8), 4.29 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.68 (s, 3 H, CH_3), 3.55 (s, 3 H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, tautomer **2g**): δ

= 161.0 (C-2), 155.9 (C-6), 152.3 (C-4), 141.1 (C-8), 113.5 (C-5), 63.5 (OCH_3), 62.1 (CH_2), 29.1 (NCH_3), 14.5 (CH_2CH_3) ppm. ^{15}N NMR (50 MHz, [D$_6$]DMSO, tautomer **2g**): δ = –140 (N-7), –191 (N-3), –212 (N^6), –231 (N-9) ppm. N-1 was not observed. MS (EI): *m*/*z* (%) = 223 (100) $[M]^+$, 193 (28), 178 (31), 165 (33), 150 (25), 149 (84), 148 (31), 122 (38). HRMS (EI): calcd. for $C_9H_{13}N_5O_2$ 223.1069; found 223.1062. $C_9H_{13}N_5O_2$ (223.2): C 48.42, H 5.87, N 31.37; found C 48.42, H 5.89, N 31.21.

2-(Dimethylamino)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (2h): 2-Chloro-*N*-methoxy-9-methyl-9*H*-purin-6-amine (**2d**) (0.278 g, 1.30 mmol) was dissolved in dimethylamine (40% aqueous solution, 8.0 mL, 63 mmol), and the resulting solution was stirred at 85 °C in a 10 mL sealed container for 17 h and evaporated in vacuo. The residue was purified by flash chromatography (Combiflash, 0–3% MeOH in CH_2Cl_2) to yield 0.259 g (90%) of a pale grey solid; m.p. 184–185 °C. ^1H NMR (300 MHz, [D$_6$]DMSO, tautomer **2h**): δ = 10.33 (s, 1 H, NH), 7.75 (s, 1 H, H-8), 3.75 (s, 3 H, OCH_3), 3.58 (s, 3 H, NCH_3), 3.10 [s, 6 H, $N(CH_3)_2$] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, tautomer **2h**): δ = 159.0 (C-2), 155.4 (C-6), 152.9 (C-4), 139.3 (C-8), 111.0 (C-5), 63.2 (OCH_3), 37.0 [$N(CH_3)_2$], 28.8 (NCH_3) ppm. ^{15}N NMR (60 MHz, [D$_6$]DMSO, tautomer **2h**): δ = –140 (N-7), –182 (N-3), –186 (N-1), –212 (N^6), –234 (N-9), –315 (N-2) ppm. MS (EI): *m*/*z* (%) = 222 (100) $[M]^+$, 191 (37), 148 (52). HRMS (EI): calcd. for $C_9H_{14}N_6O$ 222.1229; found 222.1226.

***N*-Methoxy-2-(methylamino)-9-methyl-9*H*-purin-6-amine (2i):** 2-Chloro-*N*-methoxy-9-methyl-9*H*-purin-6-amine (**2d**) (0.279 g, 1.31 mmol) was dissolved in methylamine (40% aqueous solution, 5.5 mL, 65 mmol), and the resulting solution was stirred at 85 °C in a 10 mL sealed container for 24 h and evaporated in vacuo. The residue was purified by flash chromatography (Combiflash, 5–10% MeOH in CH_2Cl_2) to yield 0.176 g (65%) of a colorless solid; m.p. 225–226 °C. ^1H NMR (300 MHz, [D$_6$]DMSO, tautomer **2i**): δ = 10.28 (s, 1 H, NH), 7.69 (s, 1 H, H-8), 6.58 (br. s, 1 H, N*H*CH_3), 3.71 (s, 3 H, OCH_3), 3.51 (s, 3 H, NCH_3), 2.78 (d, *J* = 4.7 Hz, 3 H, NHC*H*$_3$) ppm. ^1H NMR (300 MHz, [D$_6$]DMSO, tautomer **2i′**): δ = 9.67 (s, 1 H, NH), 7.44 (s, 1 H, H-8), 6.58 (br. s, 1 H, N*H*CH_3), 3.71 (s, 3 H, OCH_3), 3.51 (s, 3 H, NCH_3), 2.78 (d, *J* = 4.7 Hz, 3 H, NHC*H*$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO, tautomer **2i′**): δ = 151.2 (C-2), 144.3 (C-4), 141.7 (C-6), 135.8 (C-8), 111.1 (C-5), 60.7 (OCH_3), 28.9 (NCH_3), 27.3 ($NHCH_3$) ppm. ^{15}N NMR (60 MHz, [D$_6$]DMSO, tautomer **2i′**): δ = –95 (N^6), –140 (N-7), –234 (N-9), –315 (N-2) ppm. N-1 and N-3 were not observed. MS (EI): *m*/*z* (%) = 208 (100) $[M]^+$, 178 (22), 177 (22), 163 (25), 150 (31), 148 (31). HRMS (EI): calcd. for $C_8H_{12}N_6O$: 208.1073; found 208.1066.

7-Benzyl-6-(methoxyamino)-9-methyl-7*H*-purinium Bromide (3a) and *N*-Benzyl-*N*-methoxy-9-methyl-9*H*-purin-6-amine (4a): Benzyl bromide (0.105 mL, 0.883 mmol) was added to a solution of *N*-methoxy-9-methyl-9*H*-purin-6-amine (**2a**) (0.13 g, 0.73 mmol) in DMA (6.2 mL), and the reaction mixture was stirred under an argon atmosphere at 50 °C for 25 h and evaporated in vacuo. The products were separated by flash chromatography (2 × 20 cm silica column, 3–10% MeOH in CH_2Cl_2, followed by 10% saturated NH_3 in MeOH in CH_2Cl_2, followed by 5% saturated NH_3 in MeOH in MeOH) to yield 0.130 g (51%) of **3a** and 0.061 g (31%) of **4a**. The spectroscopic data for **3a** and **4a** were in accordance with those reported before.[2b]

7-Benzyl-2,9-dimethyl-6-(methoxyamino)-7*H*-purinium Bromide (3b) and *N*-Benzyl-2,9-dimethyl-*N*-methoxy-9*H*-purin-6-amine (4b): The products were prepared from purine **2b** (0.14 g, 0.73 mmol) as described for compounds **3a** and **4a** above, and the products were separated by flash chromatography (2 × 20 cm silica column, 3–10% MeOH in CH_2Cl_2, followed by 5% saturated NH_3 in MeOH in CH_2Cl_2, followed by 10% saturated NH_3 in MeOH in MeOH). **3b**: Yield 0.11 g (57%), colorless solid, m.p. 214–216 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.71 (s, 1 H, NH), 9.39 (s, 1 H, H-8), 7.47–7.36 (m, 5 H, Ph), 5.59 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.77 (s, 3 H, NCH_3), 2.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 158.9 (C-2), 141.5 (C-4), 137.7 (C-8), 136.8 (C-6), 134.5 (C-1 in Ph), 128.8 (CH in Ph), 128.7 (CH in Ph), 128.4 (CH in Ph), 108.3 (C-5), 61.9 (OCH_3), 52.0 (CH_2), 31.7 (NCH_3), 21.5 (CH_3) ppm. MS (ESI): *m*/*z* (%) = 284 (100). [M – HBr]$^+$, HRMS (EI): calcd. for $C_{15}H_{18}N_5O$ 284.1511, found 284.1508. **4b**: Yield 0.060 g (29%), yellow oil. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 8.14 (s, 1 H, H-8), 7.35–7.20 (m, 5 H, Ph), 5.27 (s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.71 (s, 3 H, NCH_3), 2.50 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 160.3 (C-2), 154.6 (C-6), 152.3 (C-4), 142.1 (C-8), 137.2 (C-1 in Ph), 128.4 (CH in Ph), 128.2 (CH in Ph), 127.2 (CH in Ph), 116.3 (C-5), 61.6 (OCH_3), 52.3 (CH_2), 29.4 (NCH_3), 25.7 (CH_3) ppm. MS (EI): *m*/*z* (%) = 283 (10) $[M]^+$, 253 (24), 252 (100), 147 (14), 106 (9), 91 (22). HRMS (EI): calcd. for $C_{15}H_{17}N_5O$ 283.1434; found 283.1433.

7-Benzyl-2-chloro-6-(methoxyamino)-9-methyl-7*H*-purinium (3d): The product was prepared from purine **2d** (0.16 g, 0.73 mmol) as described for compounds **3a** and **4a** above and purified by flash chromatography (2 × 20 cm silica column, 3–10% MeOH in CH_2Cl_2, followed by 5% saturated NH_3 in MeOH in CH_2Cl_2) to yield 0.010 g (4%) of a yellow solid; m.p. 225–228 °C (dec.). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 9.01 (s, 1 H, H-8), 7.48–7.33 (m, 5 H, Ph), 5.57 (s, 2 H, CH_2), 3.63 (s, 3 H, NCH_3), 3.60 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 157.5 (C-2 or C-6), 146.5 (C-2 or C-6), 145.6 (C-4), 135.6 (C-1 in Ph), 134.0 (C-8), 128.7 (CH in Ph), 128.4 (CH in Ph), 128.3 (CH in Ph), 107.5 (C-5), 60.4 (OCH_3), 51.3 (CH_2), 31.0 (NCH_3) ppm. MS (EI): *m*/*z* (%) = 305/303 (7/25) $[M]^+$, 276 (11), 274 (36), 187 (7), 185 (28), 148 (18), 91 (100). HRMS (EI): calcd. for $C_{14}H_{14}ClN_5O$ 303.0887; found 303.0887.

***N*-Benzyl-2-methoxy-*N*-methoxy-9-methyl-9*H*-purin-6-amine (4f), 7-Benzyl-6-(methoxyamino)-9-methyl-2-oxo-7*H*-purinium Bromide (5) and *N*,2-Dimethoxy-*N*,9-dimethyl-9*H*-purin-6-amine (6):** The products were prepared from purine **2f** (0.36 g, 1.71 mmol) as described for compounds **3a** and **4b** above. The products were separated by flash chromatography (Combiflash, 0–15% MeOH in CH_2Cl_2). Compounds **4f**, **5**, and **6** were isolated in pure form. **4f**: Yield 0.058 g (11%), colorless oil. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 8.03 (s, 1 H, H-8), 7.35–7.24 (m, 5 H, Ph), 5.27 (s, 2 H, CH_2), 3.85 (s, 3 H, $COCH_3$), 3.77 (s, 3 H, $NOCH_3$), 3.66 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 161.0 (C-2), 155.3 (C-6), 153.4 (C-4), 141.3 (C-8), 137.1 (C-1 in Ph), 128.2 (CH in Ph), 128.2 (CH in Ph), 127.2 (CH in Ph), 114.2 (C-5), 61.6 ($NOCH_3$), 54.2 ($COCH_3$), 52.2 (CH_2), 29.3 (NCH_3) ppm. MS (EI): *m*/*z* (%) = 299 (17) $[M]^+$, 269 (25), 268 (100), 149 (19), 91 (31). HRMS (EI): calcd. for $C_{15}H_{17}N_5O_2$: 299.1382, found 299.1373. **5**: Yield 0.094 g (19%), yellow wax. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 8.90 (s, 1 H, H-8), 8.40 (br. s, 1 H, NH), 7.46–7.34 (m, 5 H, Ph), 5.44 (s, 2 H, CH_2), 3.69 (s, 3 H, NCH_3), 3.55 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 155.6 (C-2), 148.5 (C-4), 141.0 (C-6), 135.2 (C in Ph), 133.0 (C-8), 128.8 (CH in Ph), 128.5 (CH in Ph), 128.4 (CH in Ph), 98.9 (C-5), 61.1 (OCH_3), 51.4 (CH_2), 30.5 (NCH_3) ppm. MS (EI): *m*/*z* (%) = 285 (62) $[M]^+$, 254 (28), 91 (100). HRMS (EI): calcd. for $C_{14}H_{15}N_5O$ 285.1226, found 285.1226. **6**: Yield 0.004 g (1%), pinkish oil. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 8.01 (s, 1 H, H-8), 3.86 (s, 3 H, $COCH_3$), 3.82 (s, 3 H, $NOCH_3$), 3.66 [s, 3 H, N-9-CH_3], 3.47 (s, 3 H, N^6-CH_3) ppm. ^{13}C NMR

(150 MHz, [D$_6$]DMSO): δ = 160.9 (C-2), 156.3 (C-6), 153.3 (C-4), 141.3 (C-8), 114.7 (C-5), 61.1 (CO*C*H$_3$), 54.1 (NO*C*H$_3$), 36.5 [N-9-*C*H$_3$], 29.3 (N^6-*C*H$_3$) ppm. ^{15}N NMR (60 MHz, [D$_6$]DMSO): δ = –137 (N-7), –214 (N^6), –230 (N-9) ppm. N-1 and N-3 were not observed. MS (EI): *m*/*z* (%) = 223 (63) [M]$^+$, 193 (45), 192 (100), 164 (27), 163 (27), 149 (71), 148 (39). HRMS (EI): calcd. for $C_9H_{13}N_5O_2$ 223.1069; found 223.1071.

7-Benzyl-2-ethoxy-6-(methoxyamino)-9-methyl-7*H*-purinium Bromide (3g) and *N*-Benzyl-2-ethoxy-*N*-methoxy-9-methyl-9*H*-purin-6-amine (4g): The products were prepared from purine **2g** (0.163 g, 0.73 mmol) as described for compounds **3a** and **4a** above. The products were separated by flash chromatography (2 × 20 cm silica column, 3–10% MeOH in CH_2Cl_2, followed by 5–10% saturated NH_3 in MeOH in CH_2Cl_2). **3g**: Yield 0.150 g (52%), off-white solid, m.p. 170–171 °C. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 11.75 (br., 1 H, NH), 9.42 (s, 1 H, H-8), 7.46–7.36 (m, 5 H, Ph), 5.58 (s, 2 H, CH_2), 4.40 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.76 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 156.8 (C-2), 142.3 (C-4), 137.0 (C-8), 136.8 (C-6), 134.5 (C in Ph), 128.7 (CH in Ph), 128.6 (CH in Ph), 128.3 (CH in Ph), 106.0 (C-5), 64.7 (OCH_2), 61.7 (OCH_3), 51.8 (NCH_2), 31.5 (NCH_3), 13.9 (CH_2CH_3) ppm. MS (ESI): *m*/*z* (%) = 314.1 (100) [M – HBr]$^+$. HRMS (EI): calcd. for $C_{16}H_{20}N_5O_2$ 314.1617, found 314.1617. $C_{16}BrH_{21}N_5O_2$ (385.3): C 48.62, H 5.35, N 17.72; found C 48.60, H 5.13, N 17.69. **4g**: Yield 0.046 g (20%), purple solid, m.p. 122–124 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.02 (s, 1 H, H-8), 7.34–7.24 (m, 5 H, Ph), 5.26 (s, 2 H, CH_2), 4.29 (q, *J* = 7.0 Hz, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.65 (s, 3 H, NCH_3), 1.28 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 160.4 (C-2), 155.4 (C-6), 153.4 (C-4), 141.3 (C-8), 137.1 (C in Ph), 128.2 (CH in Ph), 128.1 (CH in Ph), 127.2 (CH in Ph), 114.1 (C-5), 62.3 (OCH_2), 61.7 (OCH_3), 52.2 (NCH_2), 29.2 (NCH_3), 14.4 (CH_2CH_3) ppm. MS (EI): *m*/*z* (%) = 313 (41) [M]$^+$, 283 (100), 282 (64), 255 (30), 254 (9), 149 (42), 106 (40), 91 (52). HRMS (EI): calcd. for $C_{16}H_{19}N_5O_2$ 313.1539; found 313.1532.

7-Benzyl-2-(dimethylamino)-6-(methoxyamino)-9-methyl-7*H*-purinium Bromide (3h) and *N*-Benzyl-2-(dimethylamino)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (4h): The products were prepared from purine **2h** (0.163 g, 0.73 mmol) as described for compounds **3a** and **4a** above. The crude product was purified twice by flash chromatography (Combiflash, 0–10% MeOH in CH_2Cl_2). **3h**: Yield 0.178 g (61%), pale yellow solid, m.p. 79–82 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 10.52 (s, 1 H, H-8), 8.32 (s, 1 H, NH), 7.68–7.65 (m, 2 H, Ph), 7.39–7.32 (m, 3 H, Ph), 5.66 (s, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 3.83 (s, 3 H, NCH_3), 3.14 [s, 6 H, N(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 152.0 (C-2), 144.9 (C-4), 137.6 (C-6), 136.2 (C-8), 134.7 (C-1 in Ph), 129.4 (CH in Ph), 129.2 (CH in Ph), 129.1 (CH in Ph), 102.5 (C-5), 62.6 (OCH_3), 52.6 (CH_2), 37.6 [N(CH_3)$_2$], 31.6 (NCH_3) ppm. MS (ESI): *m*/*z* (%) = 313 (100), [M]$^+$. HRMS (ESI): calcd. for $C_{16}H_{21}N_6O$ 313.1776, found 313.1786. **4h**: Yield 0.016 g (7%), yellow wax. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.81 (s, 1 H, H-8), 7.35–7.34 (m, 2 H, Ph), 7.30–7.27 (m, 2 H, Ph), 7.24–7.23 (m, 1 H, Ph), 5.20 (s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.59 (s, 3 H, NCH_3), 3.09 [s, 6 H, N(CH_3)$_2$] ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 158.5 (C-2), 154.9 (C-6), 153.9 (C-4), 139.4 (C-8), 137.6 (C-1 in Ph), 128.3 (CH in Ph), 128.1 (CH in Ph), 127.1 (CH in Ph), 111.7 (C-5), 61.6 (OCH_3), 52.6 (CH_2), 36.9 [N(CH_3)$_2$], 28.9 (NCH_3) ppm. MS (EI): *m*/*z* (%) = 312 (47) [M]$^+$, 282 (49), 284 (100), 91 (22). HRMS (EI): calcd. for $C_{16}H_{20}N_6O$ 312.1699; found 312.1705.

7-Benzyl-6-(methoxyamino)-2-(methylamino)-9-methyl-7*H*-purinium Bromide (3i) and *N*-Benzyl-2-(methylamino)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (4i): The products were prepared from purine **2i** (0.147 g, 0.73 mmol) as described for compounds **3a** and **4a** above. The crude product was purified twice by flash chromatography (Combiflash, 0–10% MeOH in CH_2Cl_2). **3i**: Yield 0.149 g (56%), pale yellow solid, m.p. 252 °C (dec.). ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.44 (s, 1 H, NH), 9.26 (s, 1 H, H-8), 7.46–7.45 (s, 2 H, Ph), 7.41–7.38 (s, 2 H, Ph), 7.37–7.34 (s, 1 H, Ph), 7.16 (q, *J* = 4.7 Hz, 1 H, N*H*CH_3), 5.51 (s, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.69 (s, 3 H, NCH_3), 2.82 (d, *J* = 4.7 Hz, 3 H, NHC*H*$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 153.3 (C-2), 144.2 (C-4), 137.1 (C-6), 135.4 (C-8), 134.6 (C-1 in Ph), 128.7 (CH in Ph), 128.5 (CH in Ph), 128.3 (CH in Ph), 102.4 (C-5), 61.6 (OCH_3), 51.7 (CH_2), 31.1 (NCH_3), 27.4 ($NHCH_3$) ppm. MS (ESI): *m*/*z* (%) = 299 (100), [M]$^+$. HRMS (ESI): calcd. for $C_{15}H_{19}N_6O$ 299.1620, found 299.1630. **4i**: Yield 0.046 g (22%), yellow sticky solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.78 (s, 1 H, H-8), 7.35–7.22 (m, 5 H, Ph), 6.57 (q, *J* = 4.7 Hz, 1 H, N*H*CH_3), 5.22 (s, 2 H, CH_2), 3.73 (s, 3 H, OCH_3), 3.58 (s, 3 H, NCH_3), 2.79 (d, *J* = 4.7 Hz, 3 H, NHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 159.3 (C-2), 155.4 (C-6), 153.8 (C-4), 139.0 (C-8), 137.6 (C-1 in Ph), 128.4 (CH in Ph), 128.1 (CH in Ph), 127.0 (CH in Ph), 112.2 (C-5), 61.6 (OCH_3), 52.5 (CH_2), 29.0 (NCH_3), 28.2 ($NHCH_3$) ppm. MS (EI): *m*/*z* (%) = 298 (39) [M]$^+$, 268 (92), 267 (100), 163 (30), 162 (22), 91 (28). HRMS (EI): calcd. for $C_{15}H_{18}N_6O$ 298.1542; found 298.1547.

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