



# An efficient one-pot synthesis of 6-alkoxy-8,9-dialkylpurines via reaction of 5-amino-4-chloro-6-alkylaminopyrimidines with *N,N*-dimethylalkaneamides and alkoxide ions

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**Abstract**—The synthesis of a number of new 6-alkoxy-8,9-(disubstituted)purines has been accomplished by the cyclization of the corresponding intermediate 5-amino-4-chloro-6-(alkylamino)pyrimidines promoted by alkoxides and various *N,N*-dimethyl amides, where the latter act as solvent–reagents. By this three-component condensation reaction we are able to introduce an alkyl group in the 8 position of the purine ring with the concomitant nucleophilic replacement of the 6-chloro group with an alkoxy moiety. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Purines are involved in a large number of biological processes, and the purine scaffold is a component of guanine and adenine, and therefore appears in nucleic acids and cofactors that play an essential role in the modulation of protein function and signal transduction.<sup>1</sup> Over the past years, purine derivatives substituted in position 9 with an alkoxy group constitute an important class of pharmacologically active compounds for which different targets can be postulated, such as platelet activating factor (PAF)<sup>2</sup> and cyclin-dependent kinase (CDK)<sup>3</sup> involved in asthma and cancer, respectively.

The synthetic strategy for the synthesis of 6-alkoxy-8,9-dialkyl purines involve a simple and straightforward three-step approach which consists in the treatment of 4-alkyl-amino-5-amino-6-chloropyrimidines with an alkyl orthoester in presence of acetic anhydride,<sup>4</sup> or catalytic amounts of ethanesulfonic acid,<sup>5</sup> to yield the corresponding 6-chloro-8,9-dialkyl purines. These derivatives were subsequently transformed in the 6-trimethylammonio, 6-[1-azabicyclo[2,2,2]octane] (quinuclidine) or 6-[1,4-diazabicyclo[2,2,2]octane] (DABCO) purines, which undergo facile displacement reactions with alkoxides in dimethyl sulfoxide to afford the corresponding 6-alkoxy purines.<sup>6</sup> This

methodology suffers from drawbacks such as low overall yield, long reaction times, cumbersome product-isolation procedures and the limited availability of the appropriate orthoester which allows the introduction of the substituent in the 8 position of the purine ring. The preparation of 6-benzoyloxypurine from 6-chloropurine by reaction with benzyl alcohol under phase-transfer conditions has been also reported.<sup>7,8</sup> The subsequent *N*-alkylation of this 6-alkoxy purine with alkyl and benzyl halides furnished an equimolar mixture of two *N*<sub>7</sub> and *N*<sub>9</sub> alkylated regioisomer products. Recently, Dang and co-workers reported that 6-chloro-8,9-dialkylsubstituted purine analogues were efficiently synthesized in good yields and under mild reaction conditions via cyclization of 4-alkylamino-5-amino-6-chloropyrimidines and various aldehydes promoted by FeCl<sub>3</sub>–SiO<sub>2</sub>.<sup>9</sup>

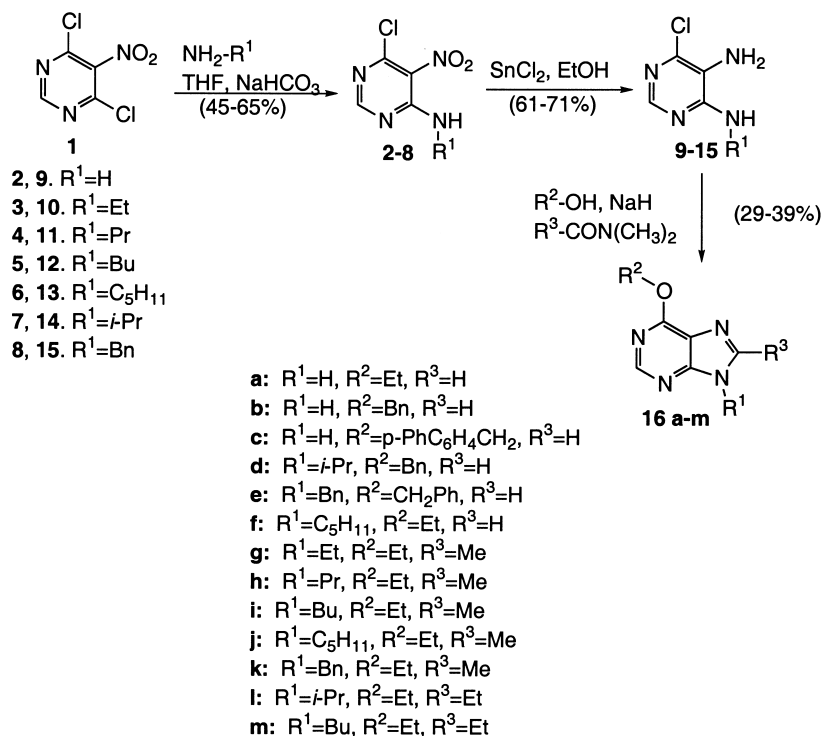
In this article, we report a new preparation of 6-alkoxy-8,9-alkyl purines which were obtained in moderate yields by the one-pot cyclocondensation reaction of 4-alkylamino-5-amino-6-chloropyrimidines promoted by different combinations of *N,N*-dimethylamides and alkoxides.

## 2. Results and discussion

The purines with general formula **16** were prepared from **1** following the procedure outlined in Scheme 1. Amination of commercially available 4,6-dichloro-5-nitropyrimidine **1** with ammonia or different alkyl amines in the presence of an equimolar amount of sodium bicarbonate and THF as

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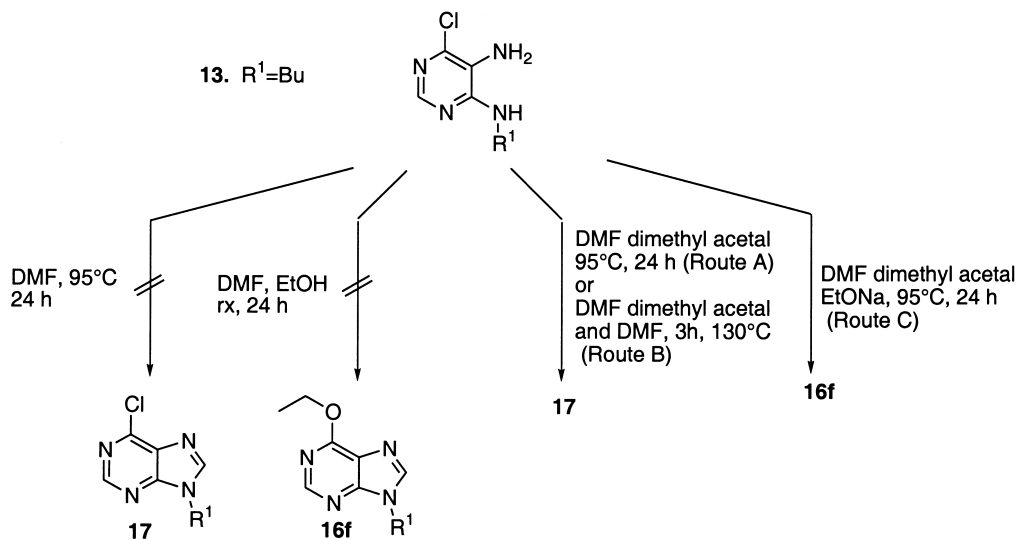


Scheme 1.

solvent afforded the corresponding 4-alkylamino-5-nitro-6-chloropyrimidines **2–8** in 45–65% yields, which were used without purification for the next reaction. The subsequent reduction of the nitro group using stannous chloride as reductant furnished the corresponding 4-alkylamino-5-amino-6-chloropyrimidines **9–15** which were cyclized by treatment for 24 h at 95°C with a mixture constituted from the appropriate alkoxide (generate in situ by the corresponding alcohol and sodium hydride) and a large excess of the suitable *N,N*-dimethyl amide, to give exclusively the corresponding 6-alkoxy-8,9-disubstituted alkyl purines **16a–m** in acceptable yields. By this strategy, it is possible to introduce simultaneously two different substituents in the

6 and 8 position of the purine ring. The structures of these products were established by nuclear magnetic resonance (NMR) spectra and mass spectra analysis.

The cyclization reaction that furnished 6,8,9-trisubstituted purines **16a–m** may proceed through the addition of the 6-chloro/alkoxy-4,5-diamino pyrimidine with the acetal of the corresponding amide used (generated in situ by reaction of the amide with the alkoxide). This hypothesis has been corroborated by reference to the reaction of the 4-*n*-pentylamino-5-amino-6-chloropyrimidine **13** with a strong excess (50 equiv.) of dimethylformamide (DMF) at 95°C for 24 h or with a mixture of DMF and ethanol (50 equiv. of



Scheme 2.

each reagent)) at reflux for 24 h which failed to yield the desired 6-chloropurine **17** and 6-ethoxypurine **16f**, respectively (Scheme 2). The failure of several amides to yield the purine ring system starting from the derivative **13** led us to try the commercially available *N,N*-dimethylformamide dimethyl acetal as a possible cyclizing agent, in view of the successful synthesis of 6-chloro-8,9-disubstituted adenines via condensation of the 4-alkylamino-5-amino-6-chloropyrimidines using alkylorthoesters. In fact, when the compound **13** was treated with *N,N*-dimethylformamide dimethyl acetal (10 equiv.) as solvent/reagent at 95°C for 24 h (Route A) or with a mixture of *N,N*-dimethylformamide dimethyl acetal (5 equiv.) and DMF (10 equiv.) at 130°C for 3 h (Route B), the 6-chloropurine **17** was formed with a 65 and 68% of yield, respectively. Finally, the reaction of compound **13** with a ten-fold excess both of *N,N*-dimethylformamide dimethyl acetal (as solvent/reagent) and sodium ethoxide (generated in situ by EtOH and NaH) at 95°C for 24 h (Route C) afforded **16f** in good yield (57%).

In conclusion, a one-step cyclization reaction with concomitant introduction of an alkoxy group in the 6-position of 6-chloro-4,5-diaminopyrimidines with various amides as solvent/reagent and by the presence of a ten-fold excess of alkoxides was developed. This reaction is suitable for synthesis of 6-alkoxy-8,9-disubstituted purines, and the strategy described herein can be also utilized to generate large combinatorial libraries containing the purine scaffold.

### 3. Experimental

#### 3.1. General

Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F<sub>254</sub> Merck plates) and visualized with aqueous KMnO<sub>4</sub>. Chromatography was performed with Merck 60–200 mesh silica gel. Melting points were determined on a Buchi-Tottoli apparatus and are uncorrected. <sup>1</sup>H NMR spectra were obtained in CD<sub>3</sub>OD, (CD<sub>3</sub>)<sub>2</sub>CO, CDCl<sub>3</sub> or *d*<sub>6</sub>-DMSO solutions on a Bruker AC 200 spectrometer. Infrared (IR) spectra were measured with a Jasco A-102 diffraction grating IR spectrometer. Chemical shifts ( $\delta$ ) are given in ppm upfield from tetramethylsilane. All products reported showed <sup>1</sup>H and <sup>13</sup>C NMR spectra in agreement with the assigned structures. Mass spectra were obtained by electron impact at 70 eV with a Fisons MD 800 instrument.

#### 3.2. General procedure for the preparation of compounds (2–8)

To a stirred solution of commercially available 4,6-dichloro-5-nitropyrimidine **1** (10 mmol) in anhyd. THF (15 mL) was added NaHCO<sub>3</sub> (11 mmol, 1.1 equiv.). The mixture was then heated to 55°C and at this temperature the appropriate amine (11 mmol, 1.1 equiv.) dissolved in THF (5 mL) was added dropwise. After 1 h, the mixture was cooled at room temperature, filtered and evaporated to give a crude product, which was directly used for the next step without purification.

#### 3.3. General procedure for the preparation of compounds (9–15)

A solution of **2–8** (5 mmol) in EtOH (10 mL) containing SnCl<sub>2</sub>·2H<sub>2</sub>O (25 mmol, 5 equiv.) was refluxed for 1 h, monitoring the reaction by TLC. The mixture was then cooled at room temperature and NaHCO<sub>3</sub> was added until pH 8 was reached. After two extractions with EtOAc (10 mL for each one), the organic phase was washed with an aq. saturated solution of NaCl (2×5 mL) and dried on Na<sub>2</sub>SO<sub>4</sub>. Evaporation under vacuum gave a solid that was purified by column chromatography eluting with ethyl acetate/petroleum ether solutions.

**3.3.1. 4,5-Diamino-6-chloropyrimidine (9).** Light tan needles; yield 67%; mp 241–242°C (lit.<sup>10</sup> mp 236–238°C).

**3.3.2. 4-Ethylamino-5-amino-6-chloropyrimidine (10).** Yellow solid; yield 71%; mp 145–147°C (lit.<sup>11</sup> mp 148–149°C);  $\delta_{\text{H}}$  (200 MHz, CD<sub>3</sub>OD): 7.72 (1H, s, NCHN), 3.12 (2H, m, NCH<sub>2</sub>CH<sub>3</sub>), 0.96 (3H, t, *J*=7.1 Hz, NCH<sub>2</sub>CH<sub>3</sub>).

**3.3.3. 4-*n*-Propylamino-5-amino-6-chloropyrimidine (11).** Light yellow solid; yield 68%; mp 111–114°C (lit.<sup>12</sup> mp 113–114°C).

**3.3.4. 4-*n*-Butylamino-5-amino-6-chloropyrimidine (12).** Yellow solid; yield 61%; mp 75–77°C (lit.<sup>12</sup> mp 80–81°C);  $\nu_{\text{max}}$  (KBr): 3310 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz, CDCl<sub>3</sub>): 7.71 (1H, s, NCHN), 5.62 (1H, t, *J*=7.1 Hz, NHCH<sub>2</sub>), 3.68 (2H, s, NH<sub>2</sub>), 3.31 (2H, m, NHCH<sub>2</sub>), 1.63 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.86 (3H, t, *J*=7.4 Hz, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

**3.3.5. 4-*n*-Pentylamino-5-amino-6-chloropyrimidine (13).** Yellow solid; yield 66%; mp 81–83°C (lit.<sup>12</sup> mp 84–85°C);  $\nu_{\text{max}}$  (KBr): 3330 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz, CDCl<sub>3</sub>): 8.05 (1H, s, NCHN), 5.06 (1H, t, *J*=7.2 Hz, NHCH<sub>2</sub>), 3.41 (4H, m, NH<sub>2</sub> and NHCH<sub>2</sub>), 1.61 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 1.33 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.88 (3H, t, *J*=7.2 Hz, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

**3.3.6. 4-Isopropylamino-5-amino-6-chloropyrimidine (14).** Light yellow solid; yield 73%; mp 185–186°C (lit.<sup>13</sup> mp 188–189°C);  $\nu_{\text{max}}$  (KBr): 3310 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz, CD<sub>3</sub>OD): 7.76 (1H, s, NCHN), 4.28 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>), 1.26 (6H, d, *J*=6.5 Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

**3.3.7. 4-Benzylamino-5-amino-6-chloropyrimidine (15).** Yellow solid; yield 65%; mp 205–206°C (lit.<sup>14</sup> mp 207–209°C);  $\nu_{\text{max}}$  (KBr): 3330 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz, CD<sub>3</sub>OD): 7.71 (1H, s, NCHN), 7.30 (5H, m, Ph), 4.61 (2H, d, *J*=5.6 Hz, CH<sub>2</sub>Ph).

#### 3.4. General procedure for the preparation of compounds (16a–m)

A suspension of NaH (50%) in mineral oil (10 mmol, 10 equiv.) was dissolved in a mixture cooled at 0°C constituted both from the appropriate alcohol (10 mmol, 10 equiv.) and amide (50 mmol, 10 equiv.). The solution was stirred at room temperature for 30 min and then at 90°C for the same time. At 90°C, compounds **9–15** (1 mmol) dissolved in the appropriate amide (50 mmol, 50 equiv.)

were added dropwise and the mixture heated for 24 h. The reaction mixture, quenched to pH 7 with an aq saturated  $\text{NH}_4\text{Cl}$  solution, was then extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  mL), the combined organic extracts dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent evaporated. The residue was chromatographed on silica gel using ethyl acetate/petroleum ether (3/1; v/v).

**3.4.1. 6-Ethoxy-9H-purine (16a).** Colorless crystals; yield 34%; mp 228–230°C (lit.<sup>15</sup> mp 223–224°C).

**3.4.2. 6-Benzyloxy-9H-purine (16b).** Light brown solid; yield 39%; mp 170–171°C (lit.<sup>7</sup> mp 170–172°C);  $\delta_{\text{H}}$  (200 MHz,  $d_6$ -DMSO): 13.5 (1H, s, NH), 8.52 (1H, s, NCHN), 8.36 (1H, s, NHCHN), 7.42 (5H, m, Ph), 5.62 (2H, s,  $\text{CH}_2\text{Ph}$ ).  $\delta_{\text{C}}$  (75 MHz,  $d_6$ -DMSO): 160.7, 154.6, 153.1, 142.4, 137.3, 130.2, 130.08, 129.5, 128.5, 128.3, 120.9, 64.5. MS (70 eV)  $m/z$  (%): 227.09 ( $\text{M}^+$ ), 135.05.  $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$  requires C, 63.71; H, 4.46; N, 24.77. Found: C, 63.46; H 4.28; N, 24.77.

**3.4.3. 6-(Biphenyl-4-ylmethoxy)-9H-purine (16c).** White solid; yield 32%; mp 215–216°C;  $\delta_{\text{H}}$  (200 MHz,  $d_6$ -DMSO): 13.5 (1H, s, NH), 8.53 (1H, s, NCHN), 8.40 (1H, s, NHCHN), 7.66 (4H, m,  $\text{CH}_2\text{C}_6\text{H}_4\text{Ph}$ ), 7.44 (5H, m, Ph), 5.67 (2H, s,  $\text{CH}_2\text{C}_6\text{H}_4$ ).  $\delta_{\text{C}}$  (75 MHz,  $d_6$ -DMSO): 160.7, 154.5, 153.0, 142.4, 138.1, 137.8, 136.7, 131.3, 131.0, 130.2, 130.0, 129.5, 129.4, 129.1, 128.9, 128.8, 120.9, 64.4. MS (70 eV)  $m/z$  (%): 303.12 ( $\text{M}^+$ ), 135.05.  $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}$  requires C, 71.51; H, 4.67; N, 18.53. Found: C, 71.25; H 4.59; N, 18.34.

**3.4.4. 6-Benzyloxy-9-(isopropyl)-9H-purine (16d).** White solid; yield 38%; mp 167–169°C;  $\delta_{\text{H}}$  (200 MHz,  $\text{CDCl}_3$ ): 8.55 (1H, s, NCHN), 7.99 (1H, s, NHCHN); 7.54 (1H, m, 1H of Ph), 7.34 (4H, m, 4H of Ph), 5.68 (2H, s,  $\text{CH}_2\text{C}_6\text{H}_5$ ), 4.90 (1H, d,  $J=6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 1.63 (6H, d,  $J=6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ): 160.7, 154.6, 153.1, 142.4, 137.2, 130.2, 130.1, 129.5, 128.5, 128.3, 120.9, 64.4, 13.6, 11.2, 10.9. MS (70 eV)  $m/z$  (%): 268.13 ( $\text{M}^+$ ), 225.1, 177.08.  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}$  requires C, 67.15; H, 6.01; N, 20.88. Found: C, 67.02; H, 5.89; N, 20.67.

**3.4.5. 6-Benzyloxy-9-(benzyl)-9H-purine (16e).** White solid; yield 28%; mp 125–127°C (lit.<sup>8</sup> mp 127–128°C);  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.55 (1H, s, NCHN), 8.34 (1H, s, NHCHN), 7.53 (2H, m, 2H of Ph), 7.35 (8H, m, 3H of Ph and 5H of the other Ph), 5.67 (2H, s,  $\text{OCH}_2\text{C}_6\text{H}_4$ ), 5.52 (2H, s,  $\text{NCH}_2\text{C}_6\text{H}_4$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 161.7, 155.4, 153.3, 144.8, 137.6, 137.4, 130.0, 129.8, 129.5, 129.5, 129.4, 129.4, 129.2, 129.1, 128.9, 128.8, 121.9, 69.7, 48.4. MS (70 eV)  $m/z$  (%): 317.36 ( $\text{M}^+$ ), 339.15.  $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}$  requires C, 72.13; H, 5.10; N, 17.71. Found: C, 71.89; H, 4.86; N, 17.52.

**3.4.6. 6-Ethoxy-9-(n-pentyl)-9H-purine (16f).** Light yellow viscous oil; yield 32%; oil;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.42 (1H, s, NCHN), 7.77 (1H, s, NCHN), 4.63 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2$ ), 4.22 (2H, t,  $J=7.2$  Hz,  $\text{NCH}_2$ ), 1.80 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 1.49 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.34 (4H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.91 (3H, t,  $J=7.2$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 160.6, 154.3, 153.5, 152.3, 120.6, 64.2, 44.16, 30.2, 29.8, 23.2, 14.8, 14.3. MS (70 eV)  $m/z$  (%): 235.15 ( $\text{M}^+$ ), 206.1.  $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}$

requires C, 61.52; H, 7.74; N, 23.91. Found: C, 61.36; H, 7.58; N, 23.77.

**3.4.7. 6-Ethoxy-8-methyl-9-(ethyl)-9H-purine (16g).** Light brown solid; yield 39%; mp 145–147°C;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.41 (1H, s, NCHN); 4.64 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2$ ), 4.31 (2H, q,  $J=7.2$  Hz,  $\text{NCH}_2\text{CH}_3$ ), 2.64 (3H, s,  $\text{CCH}_3$ ), 1.48 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (3H, t,  $J=7.2$  Hz,  $\text{NCH}_2\text{CH}_3$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 160.8, 154.2, 153.5, 142.3, 120.7, 64.1, 39.0, 15.1, 14.8, 13.6. MS (70 eV)  $m/z$  (%): 206 ( $\text{M}^+$ ); 191; 162; 123; 107.  $\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}$  requires C, 58.24; H, 6.84; N, 27.17. Found: C, 58.01; H, 6.67; N, 27.03.

**3.4.8. 6-Ethoxy-8-methyl-9-(n-propyl)-9H-purine (16h).** Light brown solid; yield 29%; mp 163–165°C;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.41 (1H, s, NCHN), 4.62 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2$ ), 4.21 (2H, t,  $J=7.4$  Hz,  $\text{NCH}_2\text{CH}_2$ ), 2.62 (3H, s,  $\text{CCH}_3$ ), 1.85 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 1.47 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 0.95 (3H, t,  $J=7.4$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 160.8, 154.3, 153.7, 152.3, 120.7, 64.1, 45.5, 23.9, 14.8, 13.8, 11.3. MS (70 eV)  $m/z$  (%): 221.3 ( $\text{M}^+$ ), 243.2.  $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}$  requires C, 59.98; H, 7.32; N, 25.44. Found: C, 59.78; H, 7.04; N, 25.12.

**3.4.9. 6-Ethoxy-8-methyl-9-(n-butyl)-9H-purine (16i).** Light yellow solid; yield 33%; mp 265–267°C;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.41 (1H, s, NCHN), 4.61 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2$ ), 4.23 (2H, t,  $J=7.4$  Hz,  $\text{NCH}_2\text{CH}_2$ ), 2.60 (3H, s,  $\text{CCH}_3$ ), 1.78 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 1.46 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.36 (2H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.95 (3H, t,  $J=7.4$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 160.8, 154.3, 153.7, 152.3, 120.8, 64.1, 43.9, 32.7, 20.9, 14.8, 14.0, 13.9. MS (70 eV)  $m/z$  (%): 235.2 ( $\text{M}^+$ ), 257.1, 229.1.  $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}$  requires C, 61.52; H, 7.74; N, 23.91. Found: C, 61.28; H, 7.55; N, 23.78.

**3.4.10. 6-Ethoxy-8-methyl-9-(n-pentyl)-9H-purine (16j).** Light brown solid; yield 29%; mp 153–155°C;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.42 (1H, s, NCHN), 4.63 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2$ ), 4.24 (2H, t,  $J=7.4$  Hz,  $\text{NCH}_2\text{CH}_2$ ), 2.62 (3H, s,  $\text{CCH}_3$ ), 1.82 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 1.48 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.35 (4H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.91 (3H, t,  $J=6.9$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 160.7, 154.2, 153.6, 152.3, 120.7, 64.1, 44.1, 30.3, 29.9, 23.3, 14.9, 14.2, 13.8. MS (70 eV)  $m/z$  (%): 248 ( $\text{M}^+$ ); 233; 219; 205; 191; 177; 163; 149; 134; 123.  $\text{C}_{13}\text{H}_{20}\text{N}_4\text{O}$  requires C, 62.88; H, 8.12; N, 22.56. Found: C, 62.67; H, 8.00; N, 22.44.

**3.4.11. 6-Ethoxy-8-methyl-9-(benzyl)-9H-purine (16k).** Light brown solid; yield 34%; mp 294–295°C;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{OD}$ ): 8.49 (1H, s, NCHN), 7.34 (5H, m, Ph); 5.52 (2H, s,  $\text{NCH}_2\text{Ph}$ ), 4.68 (2H, q,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.52 (3H, s,  $\text{CCH}_3$ ), 1.51 (3H, t,  $J=7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ).  $\delta_{\text{C}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 160.9, 154.6, 153.9, 152.7, 137.2, 130.1, 130.0, 129.1, 128.1, 127.9, 120.8, 64.3, 46.9, 14.8, 14.0. MS (70 eV)  $m/z$  (%): 268 ( $\text{M}^+$ ); 253; 149; 131; 103; 91.  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}$  requires C, 67.15; H, 6.01; N, 20.88. Found: C, 66.97; H, 5.89; N, 20.77.

**3.4.12. 6-Ethoxy-8-ethyl-9-(isopropyl)-9H-purine (16l).** Yellow viscous oil; yield 29%; viscous oil;  $\delta_{\text{H}}$  (200 MHz,

CD<sub>3</sub>OD): 8.35 (1H, s, NCHN), 4.80 (1H, d,  $J=6.8$  Hz, NCH(CH<sub>3</sub>)<sub>2</sub>), 4.58 (2H, q,  $J=7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.94 (2H, q,  $J=7.5$  Hz, CCH<sub>2</sub>CH<sub>3</sub>), 1.67 (6H, d,  $J=6.8$  Hz, NCH(CH<sub>3</sub>)<sub>2</sub>), 1.42 (3H, t,  $J=7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.36 (3H, t,  $J=7.5$  Hz, CCH<sub>2</sub>CH<sub>3</sub>).  $\delta_C$  (75 MHz, CD<sub>3</sub>OD): 160.5, 155.8, 154.6, 150.8, 121.8, 62.8, 48.9, 22.0, 21.2, 21.0, 14.8, 11.8. MS (70 eV)  $m/z$  (%): 235.1 (M<sup>+</sup>), 257.1. C<sub>12</sub>H<sub>18</sub>N<sub>4</sub>O requires C, 61.52; H, 7.74; N, 23.91. Found: C, 61.44; H, 7.62; N, 23.77.

#### 3.4.13. 6-Ethoxy-8-ethyl-9-(*n*-butyl)-9*H*-purine (16m).

Yellow viscous oil; yield 31%; viscous oil;  $\delta_H$  (200 MHz, CD<sub>3</sub>OD): 8.42 (1H, s, NCHN), 4.59 (2H, q,  $J=7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.23 (t,  $J=7.4$  Hz, 2H), 2.93 (2H, q,  $J=7.5$  Hz, CCH<sub>2</sub>CH<sub>3</sub>), 1.79 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 1.43 (3H, t,  $J=7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.39 (3H, t,  $J=7.5$  Hz, CCH<sub>2</sub>CH<sub>3</sub>), 1.38 (2H, m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 0.93 (3H, t,  $J=7.4$  Hz, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).  $\delta_C$  (75 MHz, CD<sub>3</sub>OD): 160.3, 156.3, 154.7, 151.4, 121.1, 62.9, 42.9, 32.5, 21.3, 20.5, 14.8, 13.9, 11.4. MS (70 eV)  $m/z$  (%): 249.2 (M<sup>+</sup>); 271.1; 221.1. C<sub>13</sub>H<sub>20</sub>N<sub>4</sub>O requires C, 62.88; H, 8.12; N, 22.56. Found: C, 62.76; H, 8.01; N, 22.48.

#### 3.4.14. Synthesis of 6-chloro-9-(*n*-pentyl)-9*H*-purine (17). Route A.

A mixture of 4-*n*-pentylamino-5-amino-6-chloro-pyrimidine **13** (214 mg, 1 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.34 mL, 1.19 g, 10 mmol, 10 equiv.) was heated at 95°C for 24 h. The solution was evaporated and the residue purified by flash chromatography (eluent EtOAc/petroleum ether, 4/1, v/v) furnished the compound **17** as yellow viscous oil (146 mg, 65% yield);  $\delta_H$  (CDCl<sub>3</sub>): 8.31 (1H, s, NCHN), 7.68 (1H, s, NCHNCH<sub>2</sub>), 4.12 (2H, t,  $J=7.4$  Hz, NCH<sub>2</sub>), 1.84 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 1.29 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.84 (3H, t, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

**Route B.** A mixture of the compound **13** (214 mg, 1 mmol), *N,N*-dimethylformamide dimethyl acetal (0.67 mL, 600 mg, 5 mmol, 5 equiv.) and DMF (0.77 mL, 730 mg, 10 mmol, 10 equiv.) was heated at 130°C for 3 h. After this time, the work-up of the reaction and the purification of the crude product was performed following the same procedure as reported in Route A. The compound **17** was isolated as viscous oil (153 mg, 68% yield).

#### 3.4.15. Synthesis of 6-ethoxy-9-(*n*-pentylamino)-9*H*-purine (compound 16f) using DMF-dimethylacetal and sodium ethoxide. Route C.

A suspension of NaH (50%) in mineral oil (480 mg of suspension, 10 mmol, 10 equiv.) was dissolved in a mixture cooled at 0°C constituted from ethanol (0.58 mL, 10 mmol, 10 equiv.) and *N,N*-dimethylformamide dimethyl acetal (1.34 mL, 1.19 g, 10 mmol, 10 equiv.). The reaction was stirred at room temperature for 30 min and at the same temperature, compound **13** (215 mg, 1 mmol) dissolved in DMF-dimethylacetal (1 mL) was added dropwise and the mixture heated for 24 h at 95°C. The reaction quenched to pH 7 with an aqueous saturated NH<sub>4</sub>Cl solution was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL), the combined organic extracts dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated. The residue chromatographed on silica gel using ethyl acetate/petroleum ether (3/1; v/v) as solvent furnished **16f** as a viscous oil (133 mg, 57% yield).

amide dimethyl acetal (1.34 mL, 1.19 g, 10 mmol, 10 equiv.). The reaction was stirred at room temperature for 30 min and at the same temperature, compound **13** (215 mg, 1 mmol) dissolved in DMF-dimethylacetal (1 mL) was added dropwise and the mixture heated for 24 h at 95°C. The reaction quenched to pH 7 with an aqueous saturated NH<sub>4</sub>Cl solution was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL), the combined organic extracts dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated. The residue chromatographed on silica gel using ethyl acetate/petroleum ether (3/1; v/v) as solvent furnished **16f** as a viscous oil (133 mg, 57% yield).

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