A General and Facile Route to New Trisubstituted Purin-8-ones

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Abstract: A facile general route was developed to synthesise new trisubstituted purin-8-one derivatives starting from cheap and readily available 5-bromouracil. These fused planar heterocycles present key hydrogen bond donating/accepting functionalities, making them interesting scaffolds for binding to biological targets.

Key words: purin-8-ones, fused-ring systems, nucleophilic aromatic substitution, ring-closure, microwave-assisted synthesis

Purine derivatives constitute an enormous class of compounds, which are well-known as therapeutic agents. These fused heterocycles show strong binding to various proteins due to their planar structure and their hydrogen bond donating/accepting ability.[1] Purin-8-one or 8-hydroxypurine derivatives for example are reported to possess a wide range of biological activities. Some of them have excellent binding affinity to the corticotropin-releasing hormone (CRH) receptor, a key player in anxiety related disorders.[2] Others stimulate the humoral immune response by binding selectively to B-cells.[3] 8-Hydroxypurine derivatives were also reported as potent interferon inducing agents in the treatment of hepatitis C virus,[4] or as cyclin-dependent kinases (CDKs) inhibitors by binding to the ATP pocket of the protein.[5]

We were interested in the synthesis of purin-8-ones with the general formula **1** (Figure 1). Only a few examples of this particular family of purine derivatives are known in the literature.[3a,4b,6] To our knowledge, no trisubstituted derivative (R^1, R^2 and R^3 are different from H) has been reported and only one derivative substituted in the position N-7 (R^1 = *n*-propyl, R^2 = *n*-butyl, R^3 = H) was described in a study of potential immunostimulatory purine derivatives.[3a] In contrast, the position N-9 (R^2) was found to be more diversely substituted by either alcohols and diols (identified as enzymic oxidation intermediates of antiherpetic 6-deoxyacyclovir[6c] and famciclovir[6a]), a benzyl functionality[4b] or ribosyl groups.[6b,d]

Two strategies are used in the literature to synthesise these purin-8-ones. In the first, the modification of guanine derivatives[4b,6b,d] involved long synthetic pathways and gave low yields. The second more general route involved the construction of the fused heterocyclic skeleton by modification of the pyrimidine derivatives 2-amino-4,6-dichloropyrimidine[3] and 2,4-diaminopyrimidine-5-carboxylic acid.[6e] However, these starting materials did not appear suitable for the construction of trisubstituted compounds like **1**, as they lead to purin-8-ones in which R^3 = H or R^1, R^2 and R^3 = H. Therefore, an improved synthetic route was needed in order to access a wide range of trisubstituted purin-8-ones **1**. Here, we report a facile and general five-step pathway to synthesise compounds of type **1** (Figure 1) starting from cheap and readily available 5-bromouracil.

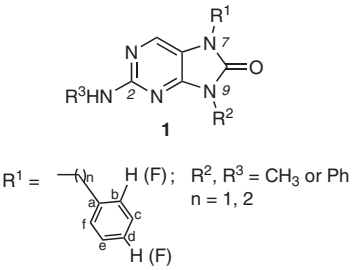

Figure 1

The synthetic pathway is outlined in Scheme 1. First, following the nucleophilic amination procedure reported by Phillips,[7] we synthesised a variety of 5-alkylaminouracils (**2a**,**d**–**g**, Table 1), starting from 5-bromouracil and the corresponding alkylamine, in 90–94% yields.

5-Alkylaminouracils **2** were then converted into the corresponding 2,4-dichloropyrimidines **3** using phosphorus oxychloride and Et_3N[8a] as a base (Scheme 1). The reactions, performed at 120 °C, proceeded in similar yields as reported in the literature,[8] ranging from 12% to 33% after chromatography (**3a**,**d**–**g**, Table 1). The presence of the secondary amine in position 5 of uracils **2** (Scheme 1) deactivates the ring toward nucleophilic chlorination and is responsible for the moderate yields.[9] Attempts to optimise further this dichlorination reaction were performed by first forming the monosodium salt of the uracil with NaH[10a] or NaOH[10b] followed by reaction with phenylphosphonyldichloride at 160 °C. This procedure, reported in the literature to activate the uracil derivative towards chlorination,[10] led in our case to similar yields as previously obtained. However, in the case of **2e**, we managed to improve the yield from 14% to 23% by using phenylphosphonyldichloride instead of phosphorus oxychloride and by conducting the reaction at 160 °C instead of 120 °C.

Although we were not able to improve the yields for the chlorination reaction, the cheap and readily available starting material combined with the straightforward puri-

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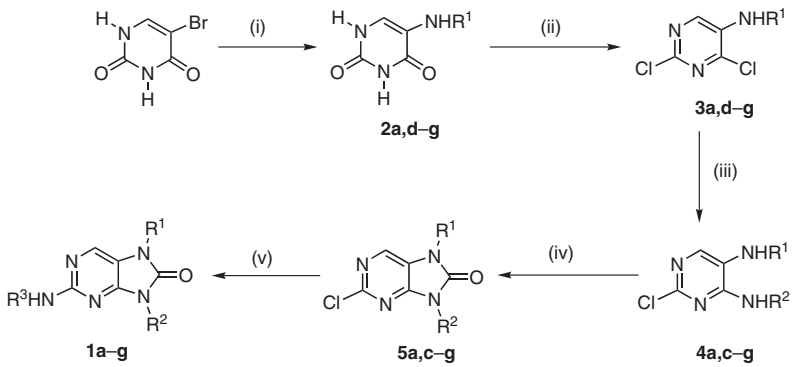

Scheme 1 *Reagents and conditions*: (i) R^1NH_2, 160 °C; (ii) $POCl_3/Et_3N$, 120 °C or $PhPOCl_2/Et_3N$, 160 °C; (iii) R^2NH_2, HCl, H_2O, EtOH, reflux; (iv) triphosgene, Et_3N, THF, 0 °C–reflux; (v) for **1a**,**c**–**g**: $MeNH_2$, EtOH, microwaves, 140 °C; for **1b**: $PhNH_2$, HCl, H_2O, EtOH, microwaves, 140 °C.

Table 1 Yields Obtained for the Synthesis of 6-Deoxypurin-8-ones **1**

Compound	R^1	R^2	R^3	**2**	**3**	**4**	**5**	Yield (%) of **1**
a	Benzyl	CH_3	CH_3	90	18[a]	92	100	74
b	Benzyl	CH_3	Ph	90	18[a]	92	100	81
c	Benzyl	Ph	CH_3	90	18[a]	50	100	87
d	2-Fluorobenzyl	CH_3	CH_3	94	23[a]	100	100	87
e	4-Fluorobenzyl	CH_3	CH_3	92	14,[a] 23[b]	90	90	95
f	2,4-Difluorobenzyl	CH_3	CH_3	91	12[a]	91	100	82
g	Phenylethyl	CH_3	CH_3	91	33[a]	90	100	96

[a] $POCl_3$, Et_3N, 120 °C.
[b] $PhPOCl_2$, Et_3N, 160 °C.

fication method allowed us to perform this step on a multigram scale, meaning that this step is suitable for scale-up procedures.

To prepare 4,5-dialkylaminopyrimidine derivatives **4** selectively, we took advantage of the difference in reactivity of the 2- and 4-chloro substituents of **3** towards nucleophilic substitution (Scheme 1). Indeed, reacting **3a** and **3d**–**g** with an excess of methylamine in an acidic mixture of EtOH and water[11] afforded the expected 2-chloro-4-methylamino derivatives **4a**,**d**–**g** as the sole products and in high yields (Table 1). Surprisingly, when the reaction was conducted under the same conditions with excess aniline, a weaker nucleophile compared to primary alkylamines, we observed the formation of a mixture of the expected 4-anilino-2-chloro derivative **4c** with the 2,4-dianilino derivative in a ratio of 7:3. Apparently, unlike the case of the 4-methylamino derivatives, the electron-donating ability of the 4-anilino substituent proves to be insufficient to completely deactivate the 2-chloro position towards nucleophilic substitution by a second molecule of aniline. However, using one equivalent of aniline instead of an excess and extending the reaction time from one hour to 15 hours afforded **4c** and the 2,4-dianilino product in a ratio of 10:1 with 64% conversion (according to ^1H NMR spectroscopy). We managed to isolate pure **4c** in 50% yield.

The next step of the synthesis consisted of forming the cyclic urea of the purin-8-one skeleton. This was conveniently achieved in quantitative yields by using triphosgene[12] in THF (Scheme 1, **5a**,**c**–**g**, Table 1). Whereas triphosgene reacted rapidly with the first amino functionality (presumably the more nucleophilic 5-amino substituent) at room temperature to form a non-cyclised intermediate,[13] heating to reflux was required for complete cyclisation into purin-8-ones **5**.

Finally, the chlorine atom in position 2, made more labile by the urea formation as compared to **4** (Scheme 1), was displaced by methylamine (**1a**, **1c**–**g**, Table 1) or aniline (**1b**, Table 1) to afford the desired products **1a**–**g**. It was initially observed that the substitution of this final chlorine occurred slowly when **5a** was refluxed with 10 equivalents of methylamine in EtOH. Under those conditions, 72 hours was required for full conversion as assessed by TLC. However, performing the reaction with methylamine under microwave irradiation[14] at 140 °C dramatically decreased the reaction time from 72 hours to 35 minutes. Following this procedure, purin-8-ones **1a** and **1c**–**g** were obtained in 74–96% isolated yields. Substitu-

tion of the final chlorine by aniline failed to give **1b** using the same conditions as for methylamine. Aniline is apparently not nucleophilic enough to displace the chlorine under those conditions. Addition of two equivalents of silver tetrafluoroborate to the reaction mixture (in order to facilitate the chlorine displacement by complexation) resulted in only 77% conversion after 40 minutes under microwave irradiation at 140 °C (according to ^{1}H NMR spectroscopy). Considering the disubstitution occurring when **3c** was reacted with excess aniline (vide supra), we decided to use the same acidic aqueous medium (0.1 M aq HCl–EtOH, 1:2) and a stoicheometric amount of aniline, under microwave irradiation at 140 °C. Total conversion was then achieved within 30 minutes and **4b** was isolated in 81% yield. This new method appears to be a good alternative (faster and less expensive) for the palladium-catalyzed cross-coupling reaction described by Ding et al.[15]

In conclusion, we describe here a facile and general route to access a variety of new trisubstituted purin-8-ones **1**, starting from the cheap commercially available 5-bromouracil. Although the dichlorination step gives rather disappointing yields, this reaction using cheap and readily available starting materials can be easily performed on a large scale. All other steps are reproducible and high yielding and can be easily extended to a wide range of amino functionalities. In addition, this route is suitable for the introduction of substituents other than amines at position C-2 (like aryl or aryloxy functionalities[14,15]) making this scaffold even more versatile. Thus, these new trisubstituted purin-8-ones possess key hydrogen donating/accepting functionalities for binding to biological targets. This makes them and their range of readily accessible derivatives potentially interesting compounds for medicinal chemistry purposes.

Anhydrous THF (packed under N_2) was purchased from Aldrich. $POCl_3$ was redistilled prior to use. Et_3N was dried over KOH and redistilled prior to use. Microwave-assisted synthesis was performed with the CEM Focused Microwave™ synthesis system, model Discover (parameters: power = 220 W, $P_{allowed}$ = 200 psi for T = 140 °C). The applied wattage is continuously adjusted to maintain the desired temperature. Reactions were conducted in their proprietary 5 mL sealed vials. Chromatography was performed with 40–60 μm Merck Si-60 silica gel under medium pressure (1 bar). TLC was performed on precoated sheets of Kieselgel 60 F_{254} (Merck). Low-resolution EI and FAB spectra were performed on a VG-2AB-SE double focusing magnetic sector mass spectrometer (Fisons Instruments), operating at a resolution of 1000. High-resolution accurate mass spectra were determined on the same system, but with a resolution set to 8000–10000. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC250 spectrometer in DMSO-d_6 using TMS as a reference. Chemical shifts (δ) are given in ppm. Elemental analyses were determined by Butterworth Laboratories Ltd. (Teddington, Middlesex, UK).

5-[(Aralkyl)amino]dihydropyrimidine-2,4(1*H*,3*H*)-diones (2); General Procedure

A mixture of 5-bromouracil (1 equiv, 10–26 mmol) and alkylamine (3–5 equiv) was heated at 160 °C for 2 h. After cooling to r.t., the mixture was poured into water (40 mL) and the pH was adjusted to 7 by addition of 1 N HCl. The precipitate was collected by filtration and washed successively with water and acetone, giving **2** in 90–94% yield.

5-(Benzylamino)dihydropyrimidine-2,4(1*H*,3*H*)-dione (2a)

From 5-bromouracil (3.53 g, 18 mmol) and benzylamine (10.1 mL, 92 mmol, 5 equiv) **2a** was obtained as a white solid (3.48 g, 90%).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.09 (d, J = 6.1 Hz, 2 H, CH_2), 4.96 (t, J = 6.1 Hz, 1 H, N*H*CH_2), 6.10 (d, J = 5.5 Hz, 1 H, H-6), 7.18–7.40 (m, 5 H, Ph), 10.02 (br s, 1 H, H-1), 11.14 (br s, 1 H, H-3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 46.8 (CH_2), 112.8 (C-6), 123.2 (C-5), 126.7 (*p*-Ph), 127.0 (*o*-Ph), 128.2 (*m*-Ph), 139.2 (*n*-Ph), 149.1 (C-2), 161.2 (C-4).

5-[(2-Fluorobenzyl)amino]dihydropyrimidine-2,4(1*H*,3*H*)-dione (2d)

From 5-bromouracil (5 g, 26 mmol) and 2-fluorobenzylamine (9 mL, 78 mmol, 3 equiv) **2d** was obtained as an off-white solid (5.75 g, 94%).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.14 (d, J = 6.4 Hz, 2 H, CH_2), 4.90 (t, J = 6.4 Hz, 1 H, N*H*CH_2), 6.21 (s, 1 H, H-6), 7.12–7.39 (m, 4 H, H-arom), 10.06 (br s, 1 H, H-1), 11.16 (br s, 1 H, H-3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 40.5 (CH_2), 113.1 (C-6), 114.9 (d, J_{C-F} = 21.4 Hz, C-c), 123.0 (C-5), 124.3 (d, J_{C-F} = 3.2 Hz, C-e), 125.7 (d, J_{C-F} = 14.5 Hz, C-a), 128.7 (d, J_{C-F} = 8.2 Hz, C-d or C-f), 129.2 (d, J_{C-F} = 4.6 Hz, C-d or C-f), 149.2 (C-2), 160.0 (d, J_{C-F} = 243.6 Hz, C-b), 161.2 (C-4).

5-[(4-Fluorobenzyl)amino]dihydropyrimidine-2,4(1*H*,3*H*)-dione (2e)

From 5-bromouracil (5 g, 26 mmol) and 4-fluorobenzylamine (11.9 mL, 104 mmol, 4 equiv) **2e** was obtained as a white solid (5.6 g, 92%).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.07 (d, J = 6.3 Hz, 2 H, CH_2), 5.01 (t, J = 6.3 Hz, 1 H, N*H*CH_2), 6.11 (s, 1 H, H-6), 7.13 (t, J = 8.8 Hz, 2 H, H-c, H-e), 7.34 (dd, J = 8.8, 5.6 Hz, 2 H, H-b, H-f), 10.06 (br s, 1 H, H-1), 11.11 (br s, 1 H, H-3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 46.0 (CH_2), 113.0 (C-6), 115.0 (d, J_{C-F} = 21.1 Hz, C-c, C-e), 123.1 (C-5), 128.9 (d, J_{C-F} = 8.0 Hz, C-b, C-f), 135.4 (d, J_{C-F} = 3.0 Hz, C-a), 149.2 (C-2), 161.0 (d, J_{C-F} = 242.0 Hz, C-d), 161.3 (C-4).

5-[(2,4-Difluorobenzyl)amino]dihydropyrimidine-2,4(1*H*,3*H*)-dione (2f)

From 5-bromouracil (1.9 g, 9.98 mmol) and 2,4-difluorobenzylamine (5 g, 34.9 mmol, 3.5 equiv) **2f** was obtained as an off-white solid (2.3 g, 91%).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.10 (d, J = 6.3 Hz, 2 H, CH_2), 4.95 (t, J = 6.3 Hz, 1 H, N*H*CH_2), 6.22 (d, J = 4.6 Hz, 1 H, H-6), 7.04 (td, J = 8.5, 2.5 Hz, 1 H, H-c), 7.20 (ddd, J = 10.6, 9.5, 2.5 Hz, 1 H, H-e), 7.38 (td, J = 8.5, 7.0 Hz, 1 H, H-f), 10.11 (br s, 1 H, H-1), 11.20 (br s, 1 H, H-3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 40.0 (CH_2), 103.6 (t, J_{C-F} = 25.9 Hz, C-c), 111.3 (dd, J_{C-F} = 21.1, 3.9 Hz, C-e), 113.2 (C-6), 122.1 (dd, J_{C-F} = 14.9, 3.7 Hz, C-a), 122.9 (C-5), 130.4 (dd, J_{C-F} = 9.6, 6.4 Hz, C-f), 149.3 (C-2), 160.0 (d, J_{C-F} = 246.4 Hz, C-b), 161.0 (d, J_{C-F} = 245.0 Hz, C-d), 161.2 (C-4).

5-[(2-Phenylethyl)amino]dihydropyrimidine-2,4(1*H*,3*H*)-dione (2g)

From 5-bromouracil (5 g, 26 mmol) and phenethylamine (16.3 mL, 130 mmol, 5 equiv) **2g** was obtained as an off-white solid (5.43 g, 91%).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.81 (t, J = 7.1 Hz, 2 H, CH_2Ph), 3.04 (q, J = 6.9 Hz, 2 H, CH_2NH), 4.16 (t, J = 6.1 Hz, 1 H,

N*H*CH_2), 6.37 (s, 1 H, H-6), 7.15–7.32 (m, 5 H, Ph), 10.20 (br s, 1 H, H-1), 11.06 (br s, 1 H, H-3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 34.2 (*C*H_2Ph), 44.8 (CH_2NH), 112.8 (C-6), 123.6 (C-5), 126.0 (*p*-Ph), 128.2 (*o*-Ph), 128.6 (*m*-Ph), 139.6 (*n*-Ph), 149.3 (C-2), 161.2 (C-4).

N-Benzyl-2,4-dichloropyrimidin-5-amine (3a); Typical Procedure

$POCl_3$ (7.7 mL, 82 mmol) was slowly added to a mixture of **2a** (1.78 g, 8.2 mmol) and Et_3N (2.5 mL, 18 mmol) at 0 °C under a N_2 atmosphere. The mixture was stirred at 120 °C for 15 h and the excess of $POCl_3$ was removed in vacuo. The resulting brown residue was diluted with CH_2Cl_2 (40 mL) and poured into flaked ice (about 25 g) whilst stirring vigorously. The pH was adjusted to 7 by careful addition of a sat. aq solution of Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layer was washed with water (2 × 40 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a brown residue which was purified by chromatography on silica gel (petroleum ether–Et_2O, 9:1 → 7:3) to afford **3a** (362 mg, 18%) as a pale yellow solid; R_f 0.40 (petroleum ether–Et_2O, 1:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.48 (d, *J* = 6.2 Hz, 2 H, CH_2), 6.96 (t, *J* = 6.2 Hz, 1 H, N*H*CH_2), 7.20–7.40 (m, 5 H, Ph), 7.94 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 45.0 (CH_2), 126.8 (*p*-Ph), 127.0 (*o*-Ph), 128.4 (*m*-Ph), 137.8 (*n*-Ph or C-5), 138.0 (*n*-Ph or C-5), 140.8 (C-6), 143.2 (C-4), 144.9 (C-2).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}N_3Cl_2$: 254.0252; found: 254.0238.

2,4-Dichloro-*N*-(2-fluorobenzyl)pyrimidin-5-amine (3d)

From **2d** (3 g, 12.7 mmol), performing the reaction at 120 °C for 2.5 h, **3d** (770 mg, 23%) was obtained as yellow crystals after chromatography on silica gel (petroleum ether–Et_2O, 8:2 → 1:1); R_f 0.54 (petroleum ether–Et_2O, 1:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.54 (d, *J* = 5.7 Hz, 2 H, CH_2), 6.83 (t, *J* = 5.7 Hz, 1 H, N*H*CH_2), 7.12–7.37 (m, 4 H, H-arom), 7.99 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 39.3 (CH_2), 115.2 (d, J_{C-F} = 20.9 Hz, C-c), 124.4 (d, J_{C-F} = 3.5 Hz, C-e), 124.5 (d, J_{C-F} = 14.2 Hz, C-a), 128.7 (d, J_{C-F} = 4.4 Hz, C-d or C-f), 129.1 (d, J_{C-F} = 8.3 Hz, C-d or C-f), 138.0 (C-5), 140.7 (C-6), 143.5 (C-4), 145.0 (C-2), 160.0 (d, J_{C-F} = 244.3 Hz, C-b).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9N_3FCl_2$: 272.0158; found: 272.0185.

2,4-Dichloro-*N*-(4-fluorobenzyl)pyrimidin-5-amine (3e)

$PhPOCl_2$ (2.5 mL, 17.3 mmol) was added to a suspension of **2e** (1 g, 4.3 mmol) in Et_3N (1.3 mL, 9.5 mmol) and the mixture was heated at 160 °C for 2 h. After cooling, the solution was poured into a mixture of flaked ice (80 g) and EtOAc (80 mL) and stirring was continued for 30 min. The organic layer was then washed with aq sat. $NaHCO_3$ (2 × 40 mL), water (2 × 40 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether–Et_2O, 8:2 → 7:3) to afford **3e** (270 mg, 23%) as a pale yellow solid; R_f 0.27 (petroleum ether–Et_2O, 1:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.48 (d, *J* = 6.2 Hz, 2 H, CH_2), 6.96 (t, *J* = 6.2 Hz, 1 H, N*H*CH_2), 7.20–7.40 (m, 4 H, H-arom), 7.94 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 44.3 (CH_2), 115.2 (d, J_{C-F} = 21.3 Hz, C-c, C-e), 129.0 (d, J_{C-F} = 8.1 Hz, C-b, C-f), 134.0 (d, J_{C-F} = 3.0 Hz, C-a), 138.0 (C-5), 140.8 (C-6), 143.4 (C-4), 145.0 (C-2), 161.2 (d, J_{C-F} = 242.7 Hz, C-d).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9N_3FCl_2$: 272.0158; found: 272.0189.

2,4-Dichloro-*N*-(2,4-difluorobenzyl)pyrimidin-5-amine (3f)

From **2f** (3 g, 11.8 mmol), performing the reaction at 120 °C for 2.5 h, **3f** (360 mg, 12%) was obtained as a yellow solid after chromatography on silica gel (petroleum ether–Et_2O, 8:2 → 7:3); R_f 0.39 (petroleum ether–Et_2O, 1:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.49 (d, *J* = 5.3 Hz, 2 H, CH_2), 6.81 (t, *J* = 5.3 Hz, 1 H, N*H*CH_2), 7.04 (tdd, *J* = 8.5, 2.6, 1.0 Hz, 1 H, H-c), 7.25 (ddd, *J* = 10.6, 9.2, 2.6 Hz, 1 H, H-e), 7.37 (td, *J* = 8.7, 6.6 Hz, 1 H, H-f), 8.01 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 39.0 (CH_2), 103.8 (t, J_{C-F} = 26.0 Hz, C-c), 111.3 (dd, J_{C-F} = 20.8, 3.5 Hz, C-e), 120.9 (dd, J_{C-F} = 14.8, 3.5 Hz, C-a), 130.0 (dd, J_{C-F} = 9.9, 5.7 Hz, C-f), 137.9 (C-5), 140.7 (C-6), 143.6 (C-4), 145.0 (C-2), 160.2 (d, J_{C-F} = 247.4 Hz, C-b), 161.5 (d, J_{C-F} = 245.5 Hz, C-d).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8N_3F_2Cl_2$: 290.0063; found: 290.0066.

2,4-Dichloro-*N*-(2-phenylethyl)pyrimidin-5-amine (3g)

From **2g** (1.5 g, 6.5 mmol), **3g** (589 mg, 33%) was obtained as a yellow solid after chromatography on silica gel (petroleum ether–Et_2O, 9:1 → 8:2); R_f 0.34 (petroleum ether–Et_2O, 1:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.87 (t, *J* = 6.9 Hz, 2 H, C*H*$_2$Ph), 3.45 (t, *J* = 6.9 Hz, 2 H, C*H*$_2$NH), 6.16 (br s, 1 H, N*H*CH_2), 7.13–7.43 (m, 5 H, Ph), 8.18 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 34.2 (*C*H_2Ph), 43.5 (CH_2NH), 126.1 (*p*-Ph), 128.2 (*o*-Ph), 128.7 (*m*-Ph), 138.3, 139.0 (*n*-Ph, C-5), 140.8 (C-6), 142.9 (C-4), 144.5 (C-2).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_3Cl_2$: 268.0408; found: 268.0455.

N^5-Benzyl-2-chloro-N^4-methylpyrimidine-4,5-diamine (4a); Typical Procedure

To a solution of **3a** (200 mg, 0.79 mmol) in EtOH (3 mL) were added 0.1 M aq HCl (5 mL) and methylamine (33 weight% in EtOH, 1 mL, 7.9 mmol). The mixture was heated at reflux for 1 h and concentrated under reduced pressure until crystals appeared in the flask (2 mL). The crystals were collected by filtration and washed with water to afford **4a** (180 mg, 92%) as an off-white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.86 (d, *J* = 4.5 Hz, 3 H, CH_3), 4.27 (d, *J* = 5.4 Hz, 2 H, CH_2), 5.44 (t, *J* = 5.4 Hz, 1 H, N*H*CH_2), 7.18 (s, 1 H, H-6), 7.25–7.40 (m, 6 H, Ph, N*H*CH_3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.5 (CH_3), 46.4 (CH_2), 127.0 (C-5, *p*-Ph), 127.5 (*o*-Ph), 128.3 (*m*-Ph), 131.7 (C-6), 138.4 (*n*-Ph), 147.2 (C-2), 154.3 (C-4).

N^5-Benzyl-2-chloro-N^4-phenylpyrimidine-4,5-diamine (4c)

From **3c** (100 mg, 0.39 mmol) and aniline (39 μL, 0.433 mmol), heating the mixture at reflux for 15 h, **4c** (60 mg, 50%) was isolated as an off-white solid by washing the crude solid with H_2O and $CHCl_3$.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.38 (s, 2 H, CH_2), 7.08 (t, *J* = 7.3 Hz, 1 H, *p*-PhNH), 7.25–7.44 (m, 9 H, H-arom, H-6, N*H*CH_2), 7.69 (d, *J* = 7.7 Hz, 2 H, *o*-PhNH), 9.08 (s, 1 H, N*H*Ph).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 46.2 (CH_2), 121.0 (*o*-PhN), 123.3 (*p*-PhN), 127.0 (C-5), 127.5, 127.7 (*o*-Ph, *p*-Ph), 128.4, 128.6 (*m*-Ph, *m*-PhN), 133.1 (C-6), 138.2, 138.8 (*n*-PhN, *n*-Ph), 144.9 (C-2), 150.5 (C-4).

2-Chloro-N^5-(2-fluorobenzyl)-N^4-methylpyrimidine-4,5-diamine (4d)
From **3d** (200 mg, 0.73 mmol) **4d** (196 mg, 100%) was obtained as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.85 (d, J = 4.5 Hz, 3 H, CH_3NH), 4.30 (d, J = 5.4 Hz, 2 H, CH_2), 5.39 (t, J = 5.4 Hz, 1 H, NHCH_2), 7.15–7.45 (m, 6 H, H-arom, H-6, NHCH_3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.4 (CH_3), 40.2 (CH_2), 115.2 (d, J_{C-F} = 21.0 Hz, C-c), 124.3 (d, J_{C-F} = 3.5 Hz, C-e), 125.0 (d, J_{C-F} = 14.2 Hz, C-a), 126.9 (C-5), 129.2 (d, J_{C-F} = 4.5 Hz, C-d or C-f), 129.9 (d, J_{C-F} = 8.5 Hz, C-d or C-f), 131.6 (C-6), 147.4 (C-2), 154.3 (C-4), 160.4 (d, J_{C-F} = 244.3 Hz, C-b).

2-Chloro-N^5-(4-fluorobenzyl)-N^4-methylpyrimidine-4,5-diamine (4e)
From **3e** (170 mg, 0.62 mmol) **4e** (150 mg, 90%) was obtained as an off-white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.85 (d, J = 4.5 Hz, 3 H, CH_3NH), 4.25 (d, J = 5.4 Hz, 2 H, CH_2), 5.42 (t, J = 5.4 Hz, 1 H, NHCH_2), 7.18 (m, 4 H, H-c, H-e, H-6, NHCH_3), 7.39 (dd, J = 5.7, 8.4 Hz, 2 H, H-b, H-f).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.4 (CH_3), 45.6 (CH_2), 115.0 (d, J_{C-F} = 21.2 Hz, C-c, C-e), 126.9 (C-5), 129.4 (d, J_{C-F} = 8.1 Hz, C-b, C-f), 131.8 (C-6), 134.5 (d, J_{C-F} = 3.0 Hz, C-a), 147.0 (C-2), 154.4 (C-4), 161.0 (d, J_{C-F} = 243.0 Hz, C-d).

2-Chloro-N^5-(2,4-difluorobenzyl)-N^4-methylpyrimidine-4,5-diamine (4f)
From **3f** (250 mg, 0.86 mmol) **4f** (221 mg, 91%) was obtained as an off-white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.85 (d, J = 4.5 Hz, 3 H, CH_3NH), 4.27 (d, J = 5.3 Hz, 2 H, CH_2), 5.33 (t, J = 5.3 Hz, 1 H, NHCH_2), 7.04–7.34 (m, 4 H, H-c, H-e, H-6, NHCH_3), 7.46 (td, J = 8.6, 6.9 Hz, 1 H, H-f).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.4 (CH_3), 39.9 (CH_2), 103.7 (t, J_{C-F} = 25.7 Hz, C-c), 111.2 (dd, J_{C-F} = 21.1, 3.6 Hz, C-e), 121.4 (dd, J_{C-F} = 14.8, 3.5 Hz, C-a), 126.8 (C-5), 131.1 (dd, J_{C-F} = 9.8, 6.1 Hz, C-f), 131.7 (C-6), 147.5 (C-2), 154.3 (C-4), 160.0 (d, J_{C-F} = 247.4 Hz, C-b), 161.0 (d, J_{C-F} = 245.5 Hz, C-d).

2-Chloro-N^4-methyl-N^5-(2-phenylethyl)pyrimidine-4,5-diamine (4g)
From **3g** (200 mg, 0.74 mmol) **4g** (176 mg, 90%) was obtained as a pale yellow solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.85 (d, J = 4.4 Hz, 3 H, CH_3NH), 2.87 (t, J = 7.7 Hz, 2 H, CH_2Ph), 3.25 (td, J = 7.7, 5.2 Hz, 2 H, CH_2NH), 4.96 (t, J = 5.2 Hz, 1 H, NHCH_2), 7.06–7.41 (m, 7 H, Ph, H-6, NHCH_3).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.5 (CH_3), 34.3 (CH_2Ph), 44.4 (CH_2NH), 126.1 (*p*-Ph), 127.3 (C-5), 128.2 (*o*-Ph), 128.7 (*m*-Ph), 131.2 (C-6), 139.4 (*n*-Ph), 147.0 (C-2), 154.2 (C-4).

7-Benzyl-2-chloro-9-methyl-7,9-dihydro-8*H*-purin-8-one (5a); Typical Procedure
To a solution of **4a** (170 mg, 0.68 mmol) and Et_3N (0.2 mL, 1.43 mmol) in THF (5 mL), at 0 °C under a N_2 atmosphere, was added a solution of triphosgene (202 mg, 0.68 mmol) in THF (5 mL). The mixture was allowed to warm to r.t. and then heated at reflux overnight. The solution was cooled to r.t., filtrated over cotton to remove the ammonium salts and the solvent was evaporated under reduced pressure. The obtained crystals were washed with a small amount of cold EtOH to afford **5a** (186 mg, 100%) as a pale pink powder.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.34 (s, 3 H, CH_3), 5.08 (s, 2 H, CH_2), 7.28–7.40 (m, 5 H, Ph), 8.25 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 26.2 (CH_3), 44.2 (CH_2), 122.0 (C-5), 127.5 (*p*-Ph), 127.7 (*o*-Ph), 128.6 (*m*-Ph), 133.4 (C-6), 135.6 (*n*-Ph), 150.7, 151.2, 152.6 (C-2, C-4, C=O).

7-Benzyl-2-chloro-9-phenyl-7,9-dihydro-8*H*-purin-8-one (5c)
From **4c** (55 mg, 0.18 mmol) **5c** (59 mg, 100%) was obtained as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 5.16 (s, 2 H, CH_2), 7.30–7.67 (m, 10 H, H-arom), 8.39 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 44.5 (CH_2), 122.2 (C-5), 126.5 (*o*-PhN), 127.7 and 127.8 (*o*-Ph, *p*-Ph), 128.5 and 128.7 (*m*-Ph, *p*-PhN), 129.1 (*m*-PhN), 131.9 (C-6), 134.4 and 135.4 (*n*-PhN, (*n*-Ph), 150.7, 150.9 and 151.6 (C-2, C-4, C=O).

2-Chloro-7-(2-fluorobenzyl)-9-methyl-7,9-dihydro-8*H*-purin-8-one (5d)
From **4d** (180 mg, 0.67 mmol) **5d** (197 mg, 100%) was obtained as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.33 (s, 3 H, CH_3), 5.14 (s, 2 H, CH_2), 7.14–7.42 (m, 4 H, H-arom), 8.24 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 26.2 (CH_3), 38.9 (CH_2), 115.4 (d, J_{C-F} = 20.8 Hz, C-c), 122.1 (C-5), 122.3 (d, J_{C-F} = 14.8 Hz, C-a), 124.5 (d, J_{C-F} = 3.5 Hz, C-e), 129.9 (d, J_{C-F} = 4.0 Hz, C-d or C-f), 130.0 (d, J_{C-F} = 8.2 Hz, C-d or C-f), 133.5 (C-6), 150.7, 151.3, 152.4 (C-2, C-4, C=O), 160.0 (d, J_{C-F} = 246.0 Hz, C-b).

2-Chloro-7-(4-fluorobenzyl)-9-methyl-7,9-dihydro-8*H*-purin-8-one (5e)
From **4e** (116 mg, 0.43 mmol) **5e** (114 mg, 90%) was obtained as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.33 (s, 3 H, CH_3), 5.07 (s, 2 H, CH_2), 7.18 (t, J = 8.8 Hz, 2 H, H-c, H-e), 7.42 (dd, J = 5.5, 8.4 Hz, 2 H, H-b, H-f), 8.29 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 26.2 (CH_3), 43.5 (CH_2), 115.4 (d, J_{C-F} = 21.4 Hz, C-c, C-e), 121.9 (C-5), 129.8 (d, J_{C-F} = 8.4 Hz, C-b, C-f), 131.9 (d, J_{C-F} = 3.1 Hz, C-a), 133.4 (C-6), 150.7; 151.3, 152.6 (C-2, C-4, C=O), 161.0 (d, J_{C-F} = 243.0 Hz, C-d).

2-Chloro-7-(2,4-difluorobenzyl)-9-methyl-7,9-dihydro-8*H*-purin-8-one (5f)
From **4f** (200 mg, 0.70 mmol) **5f** (218 mg, 100%) was obtained as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.31 (s, 3 H, CH_3), 5.11 (s, 2 H, CH_2), 7.06 (tdd, J = 8.5, 2.6, 1.0 Hz, 1 H, H-c), 7.28 (ddd, J = 10.6, 9.3, 2.5 Hz, 1 H, H-e), 7.46 (td, J = 8.7, 6.6 Hz, 1 H, H-f), 8.26 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 26.2 (CH_3), 39.5 (CH_2), 104.0 (t, J_{C-F} = 25.8 Hz, C-c), 111.4 (dd, J_{C-F} = 21.3, 3.6 Hz, C-e), 118.8 (dd, J_{C-F} = 15.1, 3.6 Hz, C-a), 122.0 (C-5), 131.3 (dd, J_{C-F} = 10.0, 5.5 Hz, C-f), 133.4 (C-6), 150.7, 151.3, 152.4 (C-2, C-4, C=O), 160.1 (dd, J_{C-F} = 248.5, 12.5 Hz, C-b), 161.0 (d, J_{C-F} = 246.6, 12.0 Hz, C-d).

2-Chloro-9-methyl-7-(2-phenyletyl)-7,9-dihydro-8*H*-purin-8-one (5g)
From **4g** (150 mg, 0.57 mmol) **5g** (164 mg, 100%) was obtained as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.97 (t, J = 7.2 Hz, 2 H, CH_2Ph), 3.29 (s, 3 H, CH_3), 4.09 (t, J = 7.2 Hz, 2 H, CH_2N), 7.18–7.29 (m, 5 H, Ph), 8.10 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 26.1 (CH_3), 33.6 (CH_2Ph), 42.5 (CH_2N), 122.1 (C-5), 126.5 (*p*-Ph), 128.3 (*o*-Ph), 128.8 (*m*-

Ph), 133.6 (C-6), 137.9 (*n*-Ph), 150.3, 150.8, 152.4 (C-2, C-4, C=O).

7-Benzyl-9-methyl-2-(methylamino)-7,9-dihydro-8*H*-purin-8-one (1a); Typical Procedure

To a solution of **5a** (50 mg, 0.18 mmol) in EtOH (1 mL) was added methylamine (33 weight% solution in EtOH, 0.45 mL, 3.6 mmol). The vial was sealed and heated by microwave at 140 °C for 35 min. After cooling to r.t., the solvent was evaporated in vacuo and the residue was purified by silica gel chromatography (EtOAc–cyclohexane, 3:2) to afford **1a** (36 mg, 74%) as a white solid; R_f 0.18 (EtOAc–cyclohexane, 3:2).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.74 (d, *J* = 4.8 Hz, 3 H, CH_3NH), 3.25 (s, 3 H, CH_3N), 4.96 (s, 2 H, CH_2), 6.73 (q, *J* = 4.8 Hz, 1 H, N*H*CH_3), 7.23–7.40 (m, 5 H, Ph), 7.81 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 25.5 (CH_3N), 28.1 (CH_3NH), 43.8 (CH_2), 114.1 (C-5), 127.4 (*p*-Ph, *o*-Ph), 128.5 (*m*-Ph), 133.7 (C-6), 136.4 (*n*-Ph), 150.5, 152.6 (C-4, C=O), 158.9 (C-2).

Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.04; H, 5.61; N, 25.75.

2-Anilino-7-benzyl-9-methyl-7,9-dihydro-8*H*-purin-8-one (1b)

To a solution of **5a** (55 mg, 0.20 mmol) in EtOH (0.75 mL) were added 0.1 M aq HCl (1.5 mL) and aniline (23 μL, 0.24 mmol). The vial was sealed and heated by microwave at 140 °C for 1 h. After cooling to r.t., the obtained crystals were collected by filtration and washed with water and cold EtOH to afford **1b** (53 mg, 81%) as a white solid.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.33 (s, 3 H, CH_3), 5.02 (s, 2 H, CH_2), 6.88 (t, *J* = 7.2 Hz, 1 H, *p*-PhNH), 7.23 (t, *J* = 7.8 Hz, 1 H, *p*-Ph), 7.29–7.40 (m, 6 H, H-arom), 7.75 (d, *J* = 8.3 Hz, 2 H, H-arom), 8.00 (s, 1 H, H-6), 9.41 (s, 1 H, NH).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 25.8 (CH_3), 43.9 (CH_2), 115.8 (C-5), 117.9 (*o*-PhNH), 120.4 (*p*-PhNH), 127.5 (*p*-Ph, *o*-Ph), 128.2, 128.5 (*m*-Ph, *m*-PhNH), 133.0 (C-6), 136.2 (*n*-Ph), 140.9 (*n*-PhNH), 150.2, 152.6 (C-4, C=O), 155.0 (C-2).

Anal. Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.49; H, 5.14; N, 21.18.

7-Benzyl-2-(methylamino)-9-phenyl-7,9-dihydro-8*H*-purin-8-one (1c)

From **5c** (59 mg, 0.17 mmol) **1c** (51 mg, 87%) was obtained as a white solid after silica gel chromatography (EtOAc–cyclohexane, 2:3 → 1:1); R_f 0.37 (EtOAc–cyclohexane, 3:2).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.70 (d, *J* = 4.8 Hz, 3 H, CH_3NH), 5.05 (s, 2 H, CH_2), 6.75 (q, *J* = 4.8 Hz, 1 H, N*H*CH_3), 7.28–7.75 (m, 10 H, H-arom), 7.95 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 28.0 (CH_3), 44.0 (CH_2), 113.9 (C-5), 126.2 (*o*-PhN, *p*-PhN), 127.5 (*o*-Ph, *p*-Ph), 128.5, 128.7 (*m*-Ph, *m*-PhN), 132.8 (C-6), 134.7 (*n*-PhN), 136.2 (*n*-Ph), 150.0, 151.4 (C-4, C=O), 159.0 (C-2).

Anal. Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.36; H, 5.01; N, 21.12.

7-(2-Fluorobenzyl)-9-methyl-2-(methylamino)-7,9-dihydro-8*H*-purin-8-one (1d)

From **5d** (100 mg, 0.34 mmol) **1d** (85 mg, 87%) was isolated as a white solid by filtration and washing with cold EtOH of the crystals obtained while cooling the reaction mixture to r.t.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.74 (d, *J* = 4.8 Hz, 3 H, CH_3NH), 3.24 (s, 3 H, CH_3N), 5.02 (s, 2 H, CH_2), 6.75 (q, *J* = 4.8 Hz, 1 H, N*H*CH_3), 7.13–7.41 (m, 4 H, H-arom), 7.78 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 25.6 (CH_3N), 28.2 (CH_3NH), 38.3 (CH_2), 114.1 (C-5), 115.4 (d, J_{C-F} = 21.0 Hz, C-c), 123.0 (d, J_{C-F} = 14.9 Hz, C-a), 124.5 (d, J_{C-F} = 3.4 Hz, C-e), 129.8 (d, J_{C-F} = 6.7 Hz, C-d or C-f), 129.9 (d, J_{C-F} = 5.4 Hz, C-d or C-f), 133.6 (C-6), 150.6, 152.4 (C-4, C=O), 158.9 (C-2), 159.9 (d, J_{C-F} = 245.5 Hz, C-b).

Anal. Calcd for $C_{14}H_{14}FN_5O$: C, 58.53; H, 4.91; F, 6.61; N, 24.38. Found C, 58.35; H, 4.86; F, 6.55; N, 24.43.

7-(4-Fluorobenzyl)-9-methyl-2-(methylamino)-7,9-dihydro-8*H*-purin-8-one (1e)

From **5e** (109 mg, 0.37 mmol) **1e** (100 mg, 95%) was obtained as a white solid after silica gel chromatography (EtOAc–cyclohexane, 7:3); R_f 0.36 (EtOAc).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.74 (d, *J* = 4.7 Hz, 3 H, CH_3NH), 3.24 (s, 3 H, CH_3N), 4.95 (s, 2 H, CH_2), 6.74 (q, *J* = 4.7 Hz, 1 H, N*H*CH_3), 7.16 (t, *J* = 8.9 Hz, 2 H, H-c, H-e), 7.37 (dd, *J* = 5.6 Hz, 8.5 Hz, 2 H, H-b, H-f), 7.85 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 5.5 (CH_3N), 28.1 (CH_3NH), 43.1 (CH_2), 114.0 (C-5), 115.3 (d, J_{C-F} = 21.5 Hz, C-c, C-e), 129.6 (d, J_{C-F} = 8.3 Hz, C-b, C-f), 132.7 (d, J_{C-F} = 3.1 Hz, C-a), 133.7 (C-6), 150.5, 152.5 (C-4, C=O), 159.0 (C-2), 161.4 (d, J_{C-F} = 243.6 Hz, C-d).

Anal. Calcd for $C_{14}H_{14}FN_5O$: C, 58.53; H, 4.91; F, 6.61; N, 24.38. Found: C, 58.32; H, 4.88; F, 6.90; N, 24.50.

7-(2,4-Difluorobenzyl)-9-methyl-2-(methylamino)-7,9-dihydro-8*H*-purin-8-one (1f)

From **5f** (100 mg, 0.32 mmol) **1f** (81 mg, 82%) was isolated as a white solid by filtration and washing with cold EtOH of the crystals obtained while cooling the reaction mixture to r.t.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.75 (d, *J* = 4.7 Hz, 3 H, CH_3NH), 3.23 (s, 3 H, CH_3N), 4.99 (s, 2 H, CH_2), 6.75 (q, *J* = 4.7 Hz, 1 H, N*H*CH_3), 7.06 (td, *J* = 8.5, 2.4 Hz, 1 H, H-c), 7.26 (ddd, *J* = 10.5, 9.5, 2.5 Hz, 1 H, H-e), 7.39 (td, *J* = 8.6, 6.7 Hz, 1 H, H-f), 7.80 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 25.5 (CH_3N), 28.2 (CH_3NH), 37.9 (d, J_{C-F} = 3.3 Hz, CH_2), 104.0 (t, J_{C-F} = 25.7 Hz, C-c), 111.5 (dd, J_{C-F} = 21.3, 3.7 Hz, C-e), 114.0 (C-5), 119.5 (dd, J_{C-F} = 15.2, 3.7 Hz, C-a), 131.2 (dd, J_{C-F} = 9.9, 5.7 Hz, C-f), 133.7 (C-6), 150.6, 152.4 (C-4, C=O), 158.9 (C-2), 160.0 (dd, J_{C-F} = 248.5, 12.6 Hz, C-b), 161.9 (d, J_{C-F} = 246.3, 12.0 Hz, C-d).

Anal. Calcd for $C_{14}H_{13}F_2N_5O$: C, 55.08; H, 4.29; F, 12.45; N, 22.94. Found: C, 54.87; H, 4.29; F, 12.29; N, 23.06.

9-Methyl-2-(methylamino)-7-(2-phenylethyl)-7,9-dihydro-8*H*-purin-8-one (1g)

From **5g** (144 mg, 0.50 mmol) **1g** (137 mg, 96%) was obtained as a white solid after silica gel chromatography (EtOAc–cyclohexane, 7:3); R_f 0.15 (EtOAc–cyclohexane, 7:3).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.75 (d, *J* = 4.8 Hz, 3 H, CH_3NH), 2.93 (t, *J* = 7.2 Hz, 2 H, CH_2Ph), 3.18 (s, 3 H, CH_3N), 3.98 (t, *J* = 7.2 Hz, 2 H, CH_2N), 6.68 (q, *J* = 4.8 Hz, 1 H, N*H*CH_3), 7.16–7.29 (m, 5 H, Ph), 7.78 (s, 1 H, H-6).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 25.4 (CH_3N), 28.2 (CH_3NH), 33.8 (*C*H_2Ph), 42.0 (CH_2N), 114.3 (C-5), 126.3 (*p*-Ph), 128.2 (*o*-Ph), 128.7 (*m*-Ph), 133.7 (C-6), 138.2 (*n*-Ph), 150.2, 152.4 (C-4, C=O), 158.7 (C-2).

Anal. Calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.24; H, 6.02; N, 24.62.

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