Efficient Synthesis of 2-Ureaguanines via the in situ Reactions of 2-Isocyanatopurines with Amines

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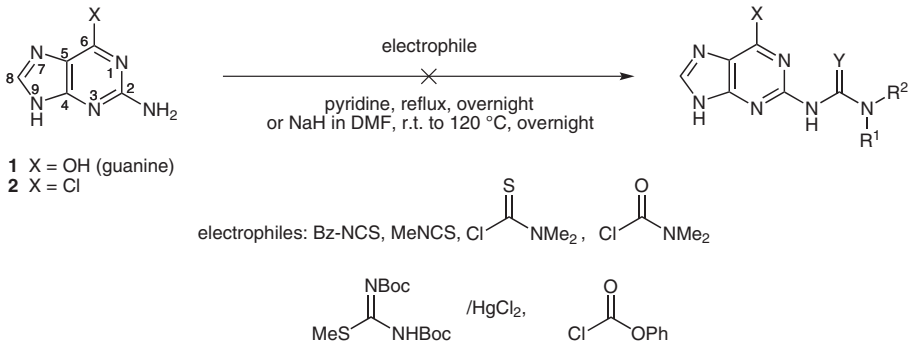
Abstract: The synthesis of 2-ureaguanines is reported. The preparation involves a suitably protected intermediate, formation of a 2-isocyanatopurine and in situ trapping with a diverse range of amines followed by double deprotection. This is the first application of 2-isocyanatopurines for the synthesis of 2-ureaguanines.

Key words: guanine, purines, heterocycles, isocyanates, ureas, triphosgene

Purines, and especially guanine derivatives, are of particular importance in the field of heterocyclic chemistry.[1] As constituents of oligonucleotides, purines have been widely studied in medicinal chemistry[2] and in supramolecular chemistry,[3] owing to their ability to form Watson–Crick[4] and Hoogsteen[5] base pairs. Although the synthesis of guanines modified at positions 2 and 6 has been studied extensively,[1] there are only a few examples of the preparation of 2-ureaguanines[6] and 2-ureapurines.[7,8] Isocyanates such as phenyl isocyanate[7] and *n*-butyl isocyanate[8] have been used, but the reaction appeared to be very dependent on the isocyanate, and sometimes forcing conditions were required. The use of phenyl chloroformate has also been described to introduce cyclohexylamine derivatives[9] or ammonia.[10] To the best of our knowledge, however, there is no general method for the preparation of this class of compounds.

In the course of our research to access 2-ureaguanines and related compounds, we investigated several methods to functionalize the 2-amino group of purines. Although the reaction with isocyanates and related compounds emerged as the most straightforward toward this end, the low reactivity of the amino group of 2-aminopurines imposed the use of stronger electrophiles.[3] This lack of reactivity was confirmed in the reactions of guanine (**1**) or 2-amino-6-chloropurine (**2**) with several electrophiles under a variety of conditions (Scheme 1).[11] This is not surprising since the 2-amino group donates its electron density to the purine system. Additionally, the imidazole nitrogen can also react under these conditions. In order to achieve insertion of diverse ureas at position 2 of purines, we turned our attention toward a more efficient method to generate 2-isocyanatopurines, which were expected to be more reactive and selective. Such compounds have already been used as intermediates for the insertion of carbamates at position 2,[12] and their preparation involved the use of triphosgene as the reagent, but they have not been used with amines. This appeared as a promising alternative to generate ureas from a diverse range of amines.

Initial results indicated that the imidazole moiety interfered with electrophiles such as triphosgene, thus this moiety was protected with a 2-tetrahydropyran (THP) group.[13] Although this group is not often used for purine protection, it can be easily cleaved under mild acidic conditions and suited our needs perfectly. It was inserted using standard Vorbrüggen conditions by employing 2-acetoxytetrahydropyran (**3**) as an electrophile (Scheme 2). This method gave superior results in terms of purity compared to the direct reaction of **1** or **2** with 2,3-dihydropy-



Scheme 1

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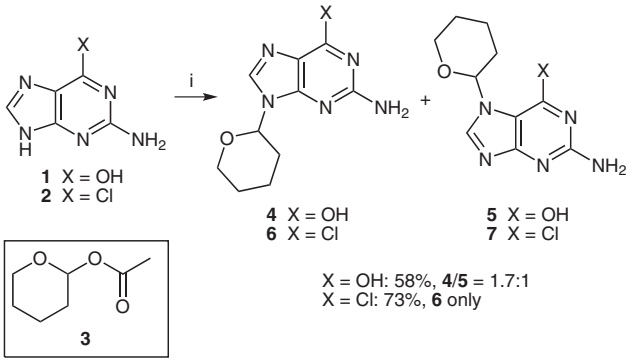
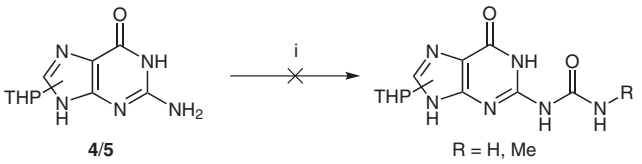
ran in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA). The silylation of **1** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in refluxing acetonitrile, followed by addition of **3** and trimethylsilyl trifluoromethanesulfonate (TMSOTf) allowed the isolation of a 1.7:1 mixture of N^9 (**4**) and N^7 (**5**) protected guanines, respectively, in a moderate 58% combined yield. Under the same conditions, protection of **2** occurred in 73% yield and regioisomer **6** was recovered as the major compound, the N^7 regioisomer **7** being only observed as traces (Scheme 2).[14] The mixture of isomers **4** and **5** was then reacted with triphosgene in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in tetrahydrofuran for one hour, followed by the addition of a methanolic solution of ammonia. After 16 hours at room temperature, only starting materials were recovered (Scheme 3). The same was observed with aqueous methylamine.



Scheme 2 *Reagents and conditions*: (i) BSA, MeCN, reflux, 3 h, then **3**, TMSOTf, 0 °C to r.t., overnight.

In contrast, when compound **6** was reacted with triphosgene and *N*,*N*-diisopropylethylamine, followed by quenching with methanolic ammonia, urea **9** was isolated

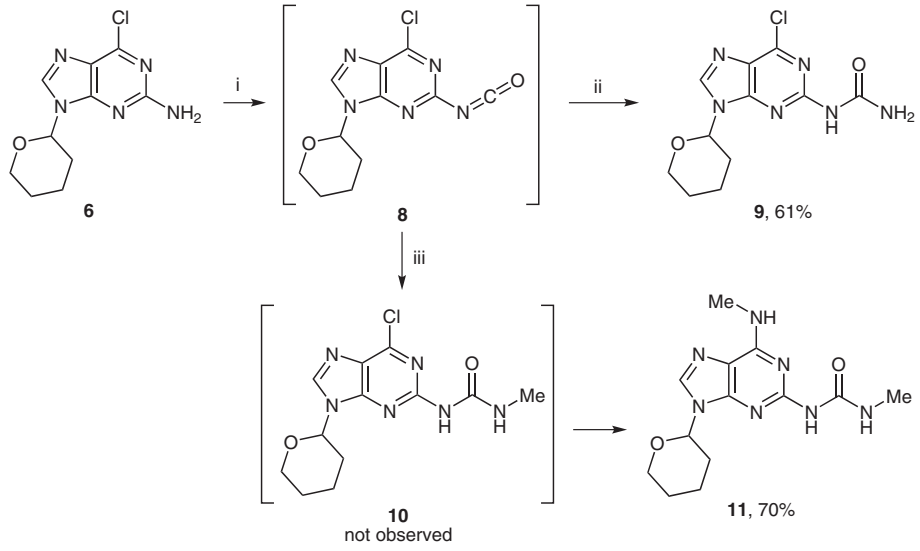


Scheme 3 *Reagents and conditions*: (i) triphosgene, DIPEA, THF, 0 °C to r.t., 1 h, then NH_3/MeOH or aq $MeNH_2$.

in 61% yield (Scheme 4), however, when the intermediate isocyanate **8** was quenched with ethanolic methylamine, compound **10** was not observed. Instead, urea **11** was isolated in a good yield (70%), but only after reaction for five minutes at 0 °C. The same reaction performed with one equivalent of morpholine delivered only the double addition product after five minutes of reaction at 0 °C, as was observed by LC–MS.

Accordingly, protection of position 6 appeared to be necessary. As 6-*O*-alkyl groups can be cleaved under the same conditions as the tetrahydropyran moiety, the ethoxy (**12**) and benzyloxy (**13**) groups were selected (Scheme 5). Compounds **12** and **13** were obtained in 81% and 93% yields, respectively, by reacting purine **6** with the corresponding alkoxide for four hours at room temperature. It is noteworthy that this reaction on an N^9-protected 2-amino-6-chloropurine proceeded under mild conditions, whereas the 6-chloro substitution of unprotected 2-amino-6-chloropurine usually requires forcing conditions.[15]

With 6,9-diprotected guanines **12** and **13** in hand, the previous procedure was repeated with a wide range of amines (Table 1). The use of ammonia, and primary and secondary amines gave moderate to good yields (53–81%) of products **14a**–**k**. Piperidine gave a very satisfactory 81% yield of isolated **14k**. Complete chemoselectivity was observed when 2-aminoethanol was used, to yield 53% of



Scheme 4 *Reagents and conditions*: (i) triphosgene, DIPEA, 0 °C to r.t., 1 h; (ii) NH_3/MeOH, 0 °C to r.t., 1 h; (iii) $MeNH_2$/EtOH, 0 °C to r.t., 1 h.

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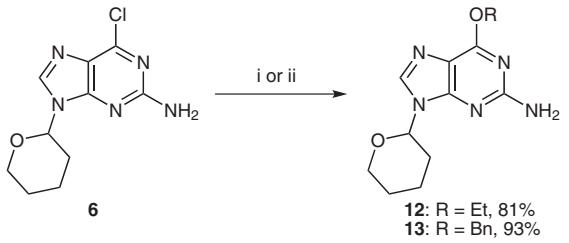
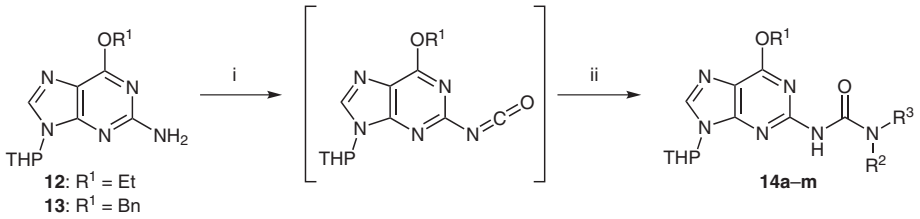


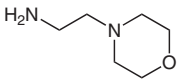
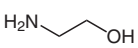
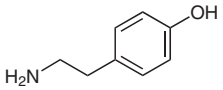
Scheme 5 *Reagents and conditions*: (i) Na, EtOH, r.t., 4 h; (ii) BnOH, NaH, THF, r.t., 4 h.

product **14i**. In this case, no trace of the corresponding carbamate was evident by LC–MS. The use of tyramine led to urea **14l** in 40% yield; whilst the use of hydrazine gave a complex mixture, and compound **14m** was not observed by LC–MS.

With the protected 2-ureaguanines **14** in hand, we next turned our attention to the simultaneous deprotection of the 2-tetrahydropyranyl and 6-*O*-alkyl groups. Compounds **14a–l** were dissolved in 1,4-dioxane, then a 10% aqueous solution of hydrochloric acid was added (Table 2). After one hour at room temperature, LC–MS analyses showed that in all cases the tetrahydropyran moiety had been cleaved. With compounds **14a–d** (R = Et), only intermediates **15a–d** were observed, and continuous stirring did not lead to complete cleavage of the ethoxy group. Heating to reflux temperature appeared necessary to effect complete conversion of intermediates **15a–d**, but was

Table 1 Formation of Ureas **14**[a]



Product	R^1	R^2R^3NH	Yield[b]
14a	Et	NH_3[c]	56%
14b	Et	$MeNH_2$[d]	58%
14c	Et	*n*-$BuNH_2$	65%
14d	Et		72%
14e	Bn	NH_3[b]	71%
14f	Bn	$MeNH_2$[c]	78%
14g	Bn		54%
14h	Bn		54%
14i	Bn		53%
14j	Bn		66%
14k	Bn		81%
14l	Bn		40%
14m	Bn	N_2H_4	0%

[a] Reaction conditions: (i) triphosgene, DIPEA, THF, 0 °C to r.t., 1 h; (ii) R^1R^2NH, 0 °C to r.t., 1 h.
[b] Yield of isolated product.
[c] Used as a 7 M solution in MeOH, 20 equivalents.
[d] Used as a 33% solution in EtOH, 20 equivalents.

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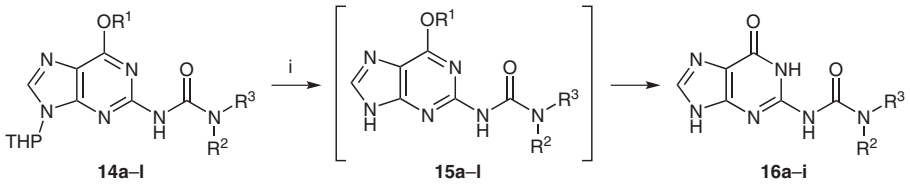
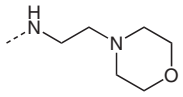
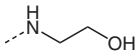
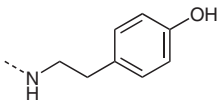
Table 2 Double Deprotection by Acidolysis[a]



Product	R^1	R^2R^3N-	Yield
16a	Et	-NH_2	45%
16b	Et	-NHMe	31%
16c	Et	-NH*n*-Bu	44%
16d	Et		0%
16a	Bn	-NH_2	56%
16b	Bn	-NHMe	53%
16d	Bn		37%
16e	Bn		76%
16f	Bn		56%
16g	Bn		40%
16h	Bn		71%
16i	Bn		82%

[a] Reaction conditions: (i) HCl (10%), 1,4-dioxane, r.t., overnight.

accompanied by some degradation of the final compound. Compounds **16a**–**c** were recovered in moderate yields whereas compound **16d** was completely degraded. With substrates **14e–l** (R = Bn), LC–MS after one hour at room temperature indicated complete cleavage of the tetrahydropyran group as well as partial cleavage of the benzyl ether. Further stirring overnight at room temperature led to complete conversion into ureas **16e–i** without any trace of degradation. The products were isolated by trituration in water, and in some cases, subsequent purification of the filtrate by preparative HPLC increased the yield above 70% (**16e**, **16h** and **16i**).

In summary, we have reported a general methodology to prepare 2-ureaguanines. The simultaneous use of the 9-tetrahydropyranyl and 6-benzyloxy protective groups appeared to be the most suitable combination. Subsequent acidolysis of both protecting groups allowed straightforward recovery of the 2-ureaguanines by simple trituration. This procedure was also applicable to the preparation of 6-*O*-alkyl-2-ureaguanines.

All reactions were carried out under an Ar atmosphere. THF was distilled over Na with benzophenone. Thin-layer chromatography (TLC) was conducted with Merck KGA silica gel 60 F254 pre-coated plates and samples were made visual by exposure to UV light (254 nm). Flash chromatography was performed using normal phase silica (230–400 mesh, Merck KGA). Melting points were recorded on a Buchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 300 MHz and are reported relative to the deuterated solvent signals. ^{1}H NMR spectroscopic data are reported as follows: chemical shift (δ ppm), multiplicity (s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, quin: quintet, sext: sextet), integration and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Bruker spectrometer at 75 MHz. ^{13}C NMR spectroscopic data are reported in terms of chemical shift (δ ppm). LC–MS spectra were recorded on a Waters Alliance 2695 HPLC apparatus using H_2O + 0.1% TFA and MeCN + 0.1% TFA

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as eluents, with detection at 254 nm; MS were recorded on a Waters Micromass ZQ2000 (electrospray) instrument. The purities of the final compounds were determined using a Dionex HPLC with a HILIC column (Inertsil Amide, purchased from GL Sciences), with a gradient made with MeCN and 10 mM ammonium formate buffer. Preparative HPLC was performed using Waters equipment (Autosampler 2707, Quaternary gradient module 2535, UV detector 2489, fraction collector WFCIII) using H_2O + 0.1% TFA and MeCN as eluents. Exact mass measurements (HRMS) were recorded on an electrospray quadrupole time-of-flight Maxis 3G from Bruker using positive mode.

Tetrahydro-2*H*-pyran-2-yl Acetate (3)

To a mixture of AcOH (5.6 mL, 97 mmol, 0.9 equiv) and PPTS (1 g) in CH_2Cl_2 (100 mL) at 0 °C was added dropwise 2,3-dihydrofuran (10 mL, 110 mmol, 1 equiv), and the mixture was stirred overnight from 0 °C to r.t. The mixture was then washed with sat. aq $NaHCO_3$ soln (3 × 50 mL) and brine (3 × 50 mL), dried over Na_2SO_4 and concentrated in vacuo to yield 13.3 g of **3** (92 mmol, 95%) as a yellowish colored liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94 (m, 1 H), 3.94–3.86 (m, 1 H), 3.71–3.64 (m, 1 H), 2.09 (s, 3 H), 1.87–1.75 (m, 2 H), 1.68–1.60 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 87.9, 58.6, 24.4, 20.1, 16.4, 13.9.

2-Amino-9-(tetrahydro-2*H*-pyran-2-yl)-1,9-dihydro-6*H*-purin-6-one (4) and 2-Amino-7-(tetrahydro-2*H*-pyran-2-yl)-1,7-dihydro-6*H*-purin-6-one (5)

To a suspension of guanine (2 g, 13.2 mmol, 1 equiv) in MeCN (200 mL) was added BSA (16.2 mL, 66 mmol, 5 equiv) and the mixture was heated at reflux temperature for 4 h under Ar. After cooling to r.t. and then to 0 °C, compound **3** (2.5 g, 17.2 mmol, 1.5 equiv) was added, followed by the dropwise addition of TMSOTf (3.6 mL, 19.8 mmol, 1.2 equiv), and the mixture was stirred overnight from 0 °C to r.t. The mixture was quenched by the addition of aq Na_2CO_3 soln (1 M) and then extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Concentration of the aqueous phase followed by recrystallization of the solid residue from H_2O allowed recovery of another fraction of a mixture of **4** and **5**. The combined fractions yielded 1.8 g (7.6 mmol, 58%) of a 1.7:1 mixture of **4** and **5** as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ (major isomer) = 8.16 (s, 1 H), 6.18 (br s, 2 H), 5.75 (dd, *J* = 10.4 Hz, *J* = 2.5 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.63–3.55 (m, 1 H), 2.12–1.87 (m, 3 H), 1.69–1.50 (m, 3 H).

^{1}H NMR (300 MHz, DMSO-d_6): δ (minor isomer) = 7.87 (s, 1 H), 6.52 (br s, 2 H), 5.35 (dd, *J* = 11.3 Hz, *J* = 2.5 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.63–3.55 (m, 1 H), 2.12–1.87 (m, 3 H), 1.69–1.50 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major isomer) = 159.8, 154.3, 152.9, 140.8, 107.3, 83.1, 67.7, 30.6, 24.5, 22.5.

MS (ES): *m*/*z* = 235.8 $[M + H]^+$.

6-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-amine (6)

To a suspension of 2-amino-6-chloropurine (5 g, 29.5 mmol, 1 equiv) in MeCN (500 mL) was added BSA (21 mL, 85.9 mmol, 2.9 equiv) and the mixture was heated at reflux temperature for 4 h. After cooling to r.t. and then to 0 °C, compound **3** (6.3 g, 44.2 mmol, 1.3 equiv) was added, followed by the dropwise addition of TMSOTf (8 mL, 44.2 mmol, 1.5 equiv), and the mixture was stirred overnight from 0 °C to r.t. The mixture was quenched by the addition of aq Na_2CO_3 soln (1 M) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by silica gel chromatography (CH_2Cl_2–MeOH, 100:0 to 95:5) to yield 5.5 g of **6** as a beige solid (21.7 mmol, 73%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.33 (s, 1 H), 6.99 (br s, 2 H), 5.48 (dd, *J* = 11.0 Hz, *J* = 2.2 Hz, 1 H), 4.02–3.98 (m, 1 H), 3.66–3.57 (m, 1 H), 2.29–2.15 (m, 1 H), 1.97–1.89 (m, 2 H), 1.73–1.52 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.9, 153.5, 149.6, 140.9, 123.2, 80.8, 67.7, 29.7, 24.5, 22.5.

MS (ES): *m*/*z* = 253.7 (100%) $[^{35}Cl, M + H]^+$, 255.7 (37%) $[^{37}Cl, M + H]^+$.

6-Ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-amine (12)

Na (291 mg, 12.7 mmol, 2.2 equiv) was dissolved in abs EtOH (100 mL), and **6** (1.46 g, 5.8 mmol, 1 equiv) was added in portions. The mixture was stirred at r.t. until completion of the reaction. The mixture was quenched by the addition of sat. aq NH_4Cl soln and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo, and the crude residue was purified by silica gel chromatography (CH_2Cl_2–MeOH, 100:0 to 95:5) to yield 1.23 g of **12** as a beige solid (4.7 mmol, 81%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.04 (s, 1 H), 6.44 (br s, 2 H), 5.45 (dd, *J* = 11.0 Hz, *J* = 2.2 Hz, 1 H), 4.45 (q, *J* = 7.1 Hz, 2 H), 4.01–3.97 (m, 1 H), 3.64–3.56 (m, 1 H), 2.24–2.11 (m, 1 H), 1.99–1.85 (m, 2 H), 1.75–1.52 (m, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.3, 159.9, 153.6, 137.3, 113.6, 80.4, 67.7, 61.5, 30.0, 24.5, 22.6, 14.5.

MS (ES): *m*/*z* = 263.8 $[M + H]^+$.

6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-amine (13)

NaH (60% in oil, 790 mg, 19.7 mmol, 2.5 equiv) was added to a soln of benzyl alcohol (1.71 mL, 16.5 mmol, 2.1 equiv) in THF (50 mL), and the mixture was stirred at r.t. for 1 h. Compound **6** (2 g, 7.9 mmol, 1 equiv) was then added, and the mixture stirred at r.t. until completion of the reaction. The mixture was quenched with sat. aq NH_4Cl soln and extracted with EtOAc (3 × 25 mL). The combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by silica gel chromatography (CH_2Cl_2–MeOH, 100:0 to 95:5) to yield 2.40 g of **13** as a beige solid (7.4 mmol, 93%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.06 (s, 1 H), 7.51–7.48 (m, 2 H), 7.43–7.34 (m, 3 H), 6.54 (br s, 2 H), 5.49 (s, 2 H), 5.45 (dd, *J* = 11.0 Hz, *J* = 1.9 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.65–3.60 (m, 1 H), 2.25–2.12 (m, 1 H), 1.98–1.85 (m, 2 H), 1.76–1.52 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.1, 159.8, 153.9, 137.6, 136.6, 128.5, 128.4, 128.1, 113.5, 80.5, 67.7, 66.9, 30.0, 24.5, 22.6.

MS (ES): *m*/*z* = 325.8 $[M + H]^+$.

2-Ureapurines; General Procedure

To a soln of the 2-aminopurine (1 equiv) in THF (0.5 M) at 0 °C was added triphosgene (0.36 equiv) and DIPEA (3.5 equiv). The mixture was stirred for 30 min at 0 °C, then the ice bath was removed and the mixture was stirred for another 30 min, before again cooling to 0 °C. The amine (2 equiv) was then added, and the mixture was stirred for 1 h at 0 °C and at r.t. until completion of the reaction. EtOAc was added and the mixture was washed with brine (three times), dried Na_2SO_4 and concentrated in vacuo. The crude residue was purified by silica gel chromatography (CH_2Cl_2–MeOH, 100:0 to 95:5).

1-[6-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]urea (9)

Prepared according to the general procedure starting from 200 mg of **6**, yielding 143 mg of **9** as a white solid (61%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.89 (br s, 1 H), 8.63 (s, 1 H), 8.06 (br s, 1 H), 7.27–7.12 (m, 1 H), 5.72 (dd, *J* = 10.7 Hz, *J* = 2.2 Hz, 1 H), 4.03–3.99 (m, 1 H), 3.71–3.63 (m, 1 H), 2.26–2.16 (m, 1 H), 2.01–1.96 (m, 2 H), 1.80–1.57 (m, 3 H).

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^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.1, 153.4, 151.7, 149.7, 143.7, 126.0, 81.4, 67.6, 29.6, 24.5, 22.2.

MS (ES): m/z = 296.8 (100%) [^{35}Cl, M + H]$^+$, 298.8 (37%) [^{37}Cl, M + H]$^+$.

1-Methyl-3-[6-(methylamino)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]urea (11)
Prepared according to the general procedure starting from 200 mg of **6**, yielding 170 mg of **11** as a white solid (70%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.26 (q, J = 4.7 Hz, 1 H), 8.93 (br s, 1 H), 8.13 (s, 1 H), 7.92–7.91 (m, 1 H), 5.50 (d, J = 9.6 Hz, 1 H), 4.02–3.98 (m, 1 H), 3.67–3.59 (m, 1 H), 2.92 (d, J = 4.1 Hz, 3 H), 2.79 (d, J = 4.7 Hz, 3 H), 2.26–2.14 (m, 1 H), 1.98–1.90 (m, 2 H), 1.77–1.56 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.1, 154.7, 154.1, 137.2, 80.8, 67.6, 29.9, 27.0, 26.1, 24.6, 22.5.

MS (ES): m/z = 305.8 [M + H]$^+$.

1-[6-Ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]urea (14a)
Prepared according to the general procedure starting from 200 mg of **12**, yielding 130 mg of **14a** as a white solid (56%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.34 (br s, 1 H), 8.34 (s, 1 H), 8.29 (br s, 1 H), 7.04 (br s, 1 H), 5.61 (dd, J = 10.7 Hz, J = 1.9 Hz, 1 H), 4.54 (q, J = 7.1 Hz, 2 H), 4.02–3.98 (m, 1 H), 3.69–3.60 (m, 1 H), 2.28–2.16 (m, 1 H), 1.97–1.93 (m, 2 H), 1.78–1.56 (m, 3 H), 1.39 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.2, 154.7, 153.5, 151.8, 140.1, 116.0, 81.1, 67.6, 62.8, 29.8, 24.5, 22.4, 14.4.

1-[6-Ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]-3-methylurea (14b)
Prepared according to the general procedure starting from 142 mg of **12**, yielding 100 mg of **14b** as a white solid (58%).

^{1}H NMR (300 MHz, CD_3OD): δ = 9.07 (q, J = 4.4 Hz, 1 H), 8.19 (s, 1 H), 5.64 (dd, J = 10.4 Hz, J = 2.2 Hz, 1 H), 4.54 (q, J = 7.1 Hz, 3 H), 4.12–4.08 (m, 1 H), 3.81–3.73 (m, 1 H), 2.95 (d, J = 4.4 Hz, 3 H), 2.08–1.66 (m, 6 H), 1.46 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 161.9, 157.5, 154.9, 152.6, 141.0, 117.4, 83.6, 69.5, 64.6, 31.7, 26.7, 26.1, 23.7, 14.7.

MS (ES): m/z = 320.8 [M + H]$^+$.

1-Butyl-3-[6-ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl)urea (14c)
Prepared according to the general procedure starting from 200 mg of **12**, yielding 180 mg of **14c** as a white solid (65%).

^{1}H NMR (300 MHz, CD_3OD): δ = 9.11 (t, J = 5.2 Hz, 1 H), 8.19 (s, 1 H), 5.59 (dd, J = 10.2 Hz, J = 2.5 Hz, 1 H), 4.53 (q, J = 7.1 Hz, 2 H), 4.12–4.08 (m, 1 H), 3.79–3.70 (m, 1 H), 3.37 (q, J = 6.6 Hz, 2 H), 2.18–2.04 (m, 4 H), 1.80–1.56 (m, 6 H), 1.46 (t, J = 7.1 Hz, 3 H), 0.98 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.2, 153.8, 153.5, 151.6, 140.0, 116.0, 81.4, 67.7, 62.8, 31.6, 24.5, 22.4, 19.7, 14.3, 13.7.

MS (ES): m/z = 362.9 [M + H]$^+$.

***N*-[6-Ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl)morpholine-4-carboxamide (14d)**
Prepared according to the general procedure starting from 200 mg of **12**, yielding 207 mg of **14d** as a white solid (72%).

^{1}H NMR (300 MHz, CD_3OD): δ = 8.24 (s, 1 H), 5.77 (dd, J = 10.7 Hz, J = 2.2 Hz, 1 H), 4.59 (q, J = 6.9 Hz, 3 H), 4.11–4.07 (m, 1 H), 3.81–3.76 (m, 1 H), 3.73 (t, J = 4.9 Hz, 4 H), 3.57 (t, J = 4.9 Hz, 4 H), 2.15–2.02 (m, 3 H), 1.85–1.59 (m, 3 H), 1.45 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.0, 154.4, 154.1, 152.6, 139.9, 116.3, 80.8, 67.8, 66.1, 62.4, 46.8, 44.6, 29.9, 24.5, 22.5, 14.4.

MS (ES): m/z = 376.9 [M + H]$^+$.

1-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]urea (14e)
Prepared according to the general procedure starting from 250 mg of **13**, yielding 200 mg of **14e** as a white solid (71%).

^{1}H NMR (300 MHz, CD_3OD): δ = 8.19 (s, 1 H), 7.49–7.19 (m, 5 H), 5.61 (dd, J = 10.7 Hz, J = 2.5 Hz, 1 H), 5.51 (s, 2 H), 4.08–4.03 (m, 1 H), 3.75–3.68 (m, 1 H), 2.13–1.97 (m, 3 H), 1.76–1.55 (m, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 161.7, 158.0, 154.8, 152.9, 141.2, 137.2, 129.5, 129.3, 117.5, 83.5, 70.0, 69.5, 31.7, 26.0, 23.7.

1-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]-3-methylurea (14f)
Prepared according to the general procedure starting from 250 mg of **13**, yielding 230 mg of **14f** as a white solid (78%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.65 (br s, 1 H), 8.70 (q, J = 4.7 Hz, 1 H), 8.34 (s, 1 H), 7.57–7.54 (m, 2 H), 7.43–7.35 (m, 3 H), 5.64 (dd, J = 10.7 Hz, J = 1.9 Hz, 1 H), 5.58 (s, 2 H), 4.03–3.99 (m, 1 H), 3.72–3.64 (m, 1 H), 2.81 (d, J = 4.7 Hz, 3 H), 2.28–2.16 (m, 1 H), 1.98–1.94 (m, 2 H), 1.80–1.58 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.9, 154.5, 153.3, 151.8, 140.2, 136.1, 128.8, 128.5, 128.3, 116.0, 81.2, 67.9, 67.6, 29.7, 26.3, 24.6, 22.3.

MS (ES): m/z = 382.7 [M + H]$^+$.

***N*-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]morpholine-4-carboxamide (14g)**
Prepared according to the general procedure starting from 240 mg of **13**, yielding 176 mg of **14g** as a white solid (54%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.41 (br s, 1 H), 8.36 (s, 1 H), 7.56–7.53 (m, 2 H), 7.43–7.31 (m, 3 H), 5.61–5.54 (m, 3 H), 4.03–3.99 (m, 1 H), 3.67–3.59 (m + t, J = 4.9 Hz, 5 H), 3.44 (t, J = 4.9 Hz, 4 H), 2.31–2.19 (m, 1 H), 1.99–1.90 (m, 2 H), 1.78–1.57 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.8, 154.3, 154.0, 152.9, 140.1, 136.3, 128.8, 128.5, 128.2, 116.2, 80.9, 67.8, 67.6, 66.1, 44.7, 29.9, 24.5, 22.5.

MS (ES): m/z = 438.8 [M + H]$^+$.

1-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]-3-(2-morpholinoethyl)urea (14h)
Prepared according to the general procedure starting from 250 mg of **13**, yielding 200 mg of **14h** as a white solid (54%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.66 (br s, 1 H), 8.81 (t, J = 5.2 Hz, 1 H), 8.36 (s, 1 H), 7.58–7.55 (m, 2 H), 7.43–7.36 (m, 3 H), 5.62–5.57 (m, 3 H), 4.04–4.00 (m, 1 H), 3.69–3.61 (m, 1 H), 3.51 (t, J = 4.4 Hz, 4 H), 3.37 (q, J = 6.3 Hz, 2 H), 2.47 (t, J = 6.3 Hz, 2 H), 2.38 (t, J = 4.4 Hz, 4 H), 2.29–2.17 (m, 1 H), 1.98–1.95 (m, 2 H), 1.74–1.58 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.9, 153.9, 153.3, 151.9, 140.3, 135.9, 128.9, 128.5, 128.4, 116.0, 81.2, 68.1, 67.7, 66.1, 57.9, 53.4, 36.5, 29.7, 24.5, 22.4.

1-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]-3-(2-hydroxyethyl)urea (14i)
Prepared according to the general procedure starting from 250 mg of **13**, yielding 167 mg of **14i** as a white solid (53%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.67 (br s, 1 H), 9.27 (t, J = 5.2 Hz, 1 H), 8.36 (s, 1 H), 7.58–7.55 (m, 2 H), 7.44–7.36 (m, 3 H), 5.66 (dd, J = 10.7 Hz, J = 1.9 Hz, 1 H), 5.58 (s, 2 H), 4.97 (t, J = 4.9 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.75–3.66 (m, 1 H), 3.57 (q, J = 5.2 Hz, 2 H), 3.36–3.31 (m, 2 H), 2.33–2.11 (m, 1 H), 1.97–1.91 (m, 2 H), 1.79–1.56 (m, 3 H).

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^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.1, 154.0, 153.4, 151.6, 140.0, 136.0, 129.0, 128.5, 128.3, 115.8, 80.9, 68.0, 67.7, 60.1, 42.1, 30.0, 24.5, 22.4.

***N*-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]pyrrolidine-1-carboxamide (14j)**
Prepared according to the general procedure starting from 250 mg of **13**, yielding 170 mg of **14j** as a white solid (66%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.04 (br s, 1 H), 8.35 (s, 1 H), 7.57–7.54 (m, 2 H), 7.43–7.35 (m, 3 H), 5.60–5.54 (m, 3 H), 4.02–3.99 (m, 1 H), 3.67–3.58 (m, 1 H), 3.43–3.39 (m, 4 H), 2.31–2.16 (m, 1 H), 1.95–1.90 (m, 2 H), 1.86–1.81 (m, 4 H), 1.75–1.57 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.7, 154.0, 152.9, 152.7, 140.1, 136.4, 128.8, 128.5, 128.2, 116.1, 80.8, 67.8, 67.5, 46.0, 30.0, 25.1, 25.0, 24.5, 22.5.

***N*-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]piperidine-1-carboxamide (14k)**
Prepared according to the general procedure starting from 250 mg of **13**, yielding 273 mg of **14k** as a white solid (81%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.25 (br s, 1 H), 8.33 (s, 1 H), 7.56–7.53 (m, 2 H), 7.42–7.35 (m, 3 H), 5.57–5.53 (m, 3 H), 4.03–3.99 (m, 1 H), 3.67–3.58 (m, 1 H), 3.42–3.39 (m, 4 H), 2.32–2.16 (m, 1 H), 1.98–1.90 (m, 2 H), 1.76–1.43 (m, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.7, 154.7, 153.8, 152.9, 139.9, 136.4, 128.8, 128.5, 128.2, 116.0, 80.8, 67.8, 67.5, 45.2, 29.9, 25.5, 24.5, 24.1, 22.5.

1-[6-(Benzyloxy)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-2-yl]-3-(4-hydroxyphenethyl)urea (14l)
Prepared according to the general procedure (using 5.4 equiv of DIPEA) starting from 250 mg of **13**, yielding 152 mg of **14l** as a white solid (40%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.67 (br s, 1 H), 9.18 (br s, 1 H), 8.90 (t, *J* = 5.8 Hz, 1 H), 8.33 (s, 1 H), 7.55–7.48 (m, 2 H), 7.43–7.36 (m, 3 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 6.64 (d, *J* = 8.5 Hz, 2 H), 5.47 (s, 2 H), 5.43 (dd, *J* = 11.0 Hz, *J* = 1.9 Hz, 1 H), 3.99–3.95 (m, 1 H), 3.60–3.37 (m, 3 H), 2.72–2.67 (m, 2 H), 2.27–2.11 (m, 1 H), 1.93–1.90 (m, 2 H), 1.73–1.48 (m, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.9, 155.7, 153.9, 153.3, 151.7, 140.2, 136.0, 129.6, 129.5, 128.9, 128.5, 128.4, 116.0, 115.2, 81.4, 67.9, 67.6, 41.4, 34.9, 29.6, 24.5, 22.3.

MS (ES): *m*/*z* = 488.8 $[M + H]^+$.

Double Deprotection; General Procedure
To a soln of the protected urea **14a–l** (1 equiv) in 1,4-dioxane (1 M) was added an aq soln of HCl (10%, 1 M), and the mixture was stirred at r.t. (R = Bn) or at reflux temperature (R = Et) until LC–MS showed that the double deprotection was complete. The mixture was concentrated in vacuo, and the solid residue triturated with H_2O. When required, purification by preparative HPLC on a C-18 column was performed.

1-(6-Oxo-6,9-dihydro-1*H*-purin-2-yl)urea (16a)
Prepared according to the general procedure starting from 130 mg of **14a** or 200 mg of **14e**, yielding 37 mg (R = Et, 45%) or 59 mg (R = Bn, 56%) of **16a** as a white solid (100% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.47 (br s, 1 H), 10.43 (br s, 1 H), 8.86 (s, 1 H), 7.34 (br s, 1 H), 6.92 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.3, 152.6, 150.3, 149.9, 138.1, 111.7.

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_6H_6N_6O_2Na$: 217.0444; found: 217.0444.

1-Methyl-3-(6-oxo-6,9-dihydro-1*H*-purin-2-yl)urea (16b)
Prepared according to the general procedure starting from 100 mg of **14b** or 230 mg of **14f**, yielding 20 mg (R = Et, 31%) or 66 mg (R = Bn, 53%) of **16b** as a white solid (97% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.39 (br s, 1 H), 10.55 (br s, 1 H), 8.87 (s, 1 H), 7.36 (q, *J* = 4.7 Hz, 1 H), 2.72 (d, *J* = 4.7 Hz, 3 H).

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_7H_8N_6O_2Na$: 231.0601; found: 231.0601

1-Butyl-3-(6-oxo-6,9-dihydro-1*H*-purin-2-yl)urea (16c)
Prepared according to the general procedure starting from 180 mg of **14c**, yielding 55 mg (44%) of **16c** as a brown solid.

Mp >250 °C.

^{1}H NMR (300 MHz, 10% NaOD–D_2O): δ = 7.27 (s, 1 H), 2.81 (t, *J* = 6.9 Hz, 2 H), 1.10 (quin, *J* = 6.9 Hz, 2 H), 0.91 (sext, *J* = 7.1 Hz, 2 H), 0.44 (t, *J* = 7.1 Hz, 3 H).

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{14}N_6O_2Na$: 273.1070; found: 273.1075.

***N*-(6-Oxo-6,9-dihydro-1*H*-purin-2-yl)morpholine-4-carboxamide (16d)**
Prepared according to the general procedure starting from 176 mg of **14g**, yielding 39 mg (37%) of **16d** as a white solid (98% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.62 (br s, 1 H), 10.59 (br s, 1 H), 8.93 (s, 1 H), 3.62–3.59 (m, 4 H), 3.53–3.50 (m, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.8, 152.7, 150.5, 150.1, 138.5, 112.1, 65.8, 44.4.

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{12}N_6O_3Na$: 287.0863; found: 287.0871.

1-(2-Morpholinoethyl)-3-(6-oxo-6,9-dihydro-1*H*-purin-2-yl)urea (16e)
Prepared according to the general procedure starting from 200 mg of **14h**, yielding 96 mg (76%) of **16e** as a white solid (97% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.81 (br s, 1 H), 10.48 (br s, 1 H), 10.22 (br s, 1 H), 7.98 (s, 1 H), 7.77 (br s, 1 H), 3.95 (br s, 2 H), 3.76 (br s, 2 H), 3.59–3.49 (m, 4 H), 3.25–3.11 (m, 4 H).

HRMS (ES): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}N_7O_3Na$: 308.1466; found: 308.1466.

1-(2-Hydroxyethyl)-3-(6-oxo-6,9-dihydro-1*H*-purin-2-yl)urea (16f)
Prepared according to the general procedure starting from 167 mg of **14i**, yielding 53 mg (56%) of **16f** as a white solid (99% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.84 (br s, 1 H), 9.72 (br s, 1 H), 7.97 (s, 1 H), 7.26 (br s, 1 H), 4.86 (br s, 1 H), 3.47 (t, *J* = 5.5 Hz, 2 H), 3.22 (q, *J* = 5.5 Hz, 2 H).

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{10}N_6O_3Na$: 261.0707; found: 261.0706.

***N*-(6-Oxo-6,9-dihydro-1*H*-purin-2-yl)pyrrolidine-1-carboxamide (16g)**
Prepared according to the general procedure starting from 172 mg of **14j**, yielding 40 mg (40%) of **16g** as a white solid (99% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.97 (br s, 1 H), 10.36 (br s, 1 H), 8.97 (s, 1 H), 3.46–3.38 (m, 4 H), 1.85 (br s, 4 H).

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HRMS (ES): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{12}N_6O_2Na$: 271.0914; found: 271.0917.

_N_-(6-Oxo-6,9-dihydro-1_H_-purin-2-yl)piperidine-1-carboxamide (16h)

Prepared according to the general procedure starting from 273 mg of **14k**, yielding 115 mg (71%) of **16h** as a white solid.

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.78 (br s, 1 H), 10.51 (br s, 1 H), 8.93 (s, 1 H), 3.50–3.47 (m, 4 H), 1.59–1.50 (m, 6 H).

HRMS (ES): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}N_6O_2Na$: 285.1070; found: 285.1077.

1-(4-Hydroxyphenethyl)-3-(6-oxo-6,9-dihydro-1_H_-purin-2-yl)urea (16i)

Prepared according to the general procedure starting from 152 mg of **14l**, yielding 80 mg (82%) of **16i** as a white solid (95% purity).

Mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.09 (br s, 1 H), 10.08 (br s, 1 H), 9.22 (br s, 1 H), 8.41 (s, 1 H), 7.26 (t, *J* = 5.5 Hz, 1 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 6.70 (d, *J* = 8.5 Hz, 2 H), 3.34 (q, *J* = 6.9 Hz, 2 H), 2.66 (t, *J* = 6.9 Hz, 2 H).

HRMS (ES): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}N_6O_3Na$: 337.1020; found: 337.1022.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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