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Synthesis of 6-cyano and 6-unsubstituted 2-aryl-8-oxopurine from a common 2-oxoimidazole precursor

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ABSTRACT

The benzyl urea of diaminomaleonitrile, prepared from commercially available starting materials, was reacted with aromatic aldehydes at room temperature. Intramolecular cyclization of the product, in basic solution, generated a substituted 2-oxoimidazole. This compound proved to be a common precursor for 2-aryl-6-cyano-8-oxopurines upon treatment with acid and for 2-aryl-6-unsubstituted-8-oxopurines, in the presence of base. A ^{1}H NMR study of these simple and versatile reactions supports the mechanistic proposal.

1. Introduction

The purine scaffold is a key component in an increasing number of biologically active compounds.[1] Derivatives incorporating the aryl substituent in the 2-position have recently attracted much attention due to their potential biological activity namely as interferon inducers,[2] c-AMP phosphodiesterase inhibitors,[3] sulfotransferase inhibitors,[4] A_1 adenosine receptor ligands[5,6] and adenosine deaminase ligands.[6a]

The synthesis of 2-arylpurine derivatives classically involves ring construction of the imidazole moiety from a 2-aryl-4,5-diaminopyrimidine. A recent approach by Itoh[7] used Suzuki–Miyaura cross-coupling of 2-halo pyrimidines with arylboronic acid. Reaction of the 4,5-diamino substituents with activated carboxylic acids ultimately generates the purine core. Direct arylation of purine derivatives was also performed,[8] in particular Pd- assisted reactions of 2-halo purines,[9–11] including Pd-catalyzed cross-coupling with arylboronic acids.[12,13] Recent work by Zhang et al.[14] describes the synthesis of 2-aryl-8-oxopurines from a 2-aryl pyrimidine with a substituted amine and a carboxylic acid in the 4- and 5-position, respectively. Reaction with diphenylphosphinic azide followed by Curtius rearrangement leads to the in situ formation of an isocyanate, with subsequent intramolecular cyclization through nucleophilic attack by the neighbouring secondary amine.

The synthesis of 8-oxopurines also requires a halogen atom at the 8-position of the purine nucleus and the nucleophilic substitution is usually performed in aqueous base. The experimental conditions depend on the nature and position of the ring substituents, in particular if selectivity is an important issue and other halogen atoms are present.[15]

As part of our interest to develop new and simple methods for the synthesis of purine derivatives,[16] we studied the reactivity of diaminomaleonitrile urea **1**, as a simple and easily accessible precursor of substituted 8-oxopurines.

Previous work on the reaction of compound **1** with aromatic aldehydes in the presence of base (triethyl amine) resulted in the formation of 2-aryl-6-carbamoyl purines 3 (Scheme 1).[17]

In these reactions, imine formation was assisted by intramolecular elimination of the water molecule through hydrolysis of the neighbouring cyano group. Compound **2** was never isolated, as the basic medium accelerates a cascade intramolecular cyclization process with formation of the imidazole and pyrimidine rings, ultimately leading to the 6-carbamoyl purine **3**.

2. Results and discussion

In the present work, urea **1** was combined with an aromatic aldehyde (1.2 M equiv) in acetonitrile, using sulfuric acid catalysis (Scheme 2). This procedure allowed the isolation of imine derivatives **4** in excellent yield (Table 1), after 5–10 min at room

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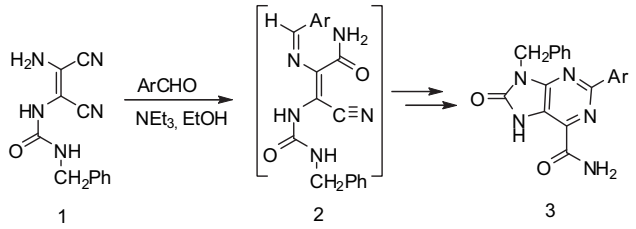
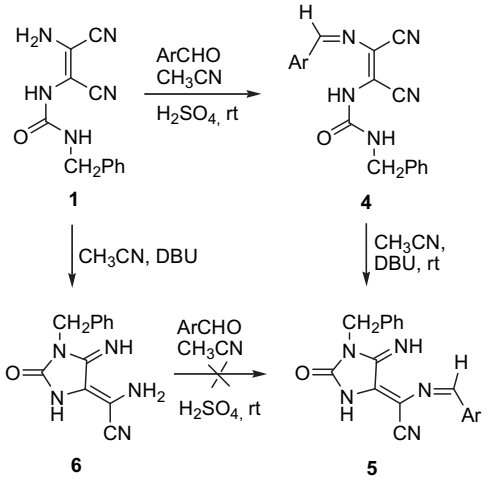


Scheme 1. Synthesis of 8-oxo-6-carbamoyl purines **3**.

temperature. Intramolecular cyclization between the urea nitrogen and the nitrile carbon to generate imidazole **5** occurred at room temperature upon addition of a catalytic amount of DBU to a suspension of compound **4** in acetonitrile (Table 1).



Scheme 2. Reaction of urea **1** with aldehydes followed by cyclization to oxoimidazole **5**.

Table 1
Isolated yield of products **4** and **5**

Ar	Product	Yield (%)	Product	Yield (%)
4-H_3C–C_6H_4	**4a**	91	**5a**	85
4-H_3CO–C_6H_4	**4b**	87	**5b**	92
4-NC–C_6H_4	**4c**	86	**5c**	86
4-O_2N–C_6H_4	**4d**	86	**5d**	80
4-HO–C_6H_4	**4e**	52	**5e**	84
4-Br–C_6H_4	**4f**	89	**5f**	91
4-F–C_6H_4	**4g**	96	**5g**	88

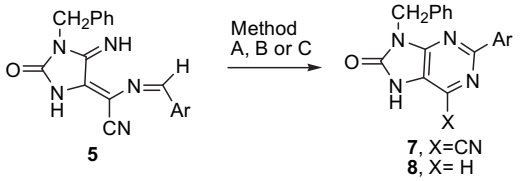
The structure of imidazole **5** was confirmed by ^{1}H NMR, where the imine C–H (δ 8.43–8.73 ppm), the imine N–H (δ 9.54–8.76 ppm) and the methylene substituent (δ 4.81–4.76 ppm) were always present as two sets of signals, assigned to distinct isomeric structures. When the ^{1}H NMR spectrum of a DMSO solution of compound **5b** (6.7 mg in 600 μl of solvent) was registered at 80 °C, a single set of bands was obtained for all the signals except for the imine N–H, where two broad singlets (δ 9.1–8.8 ppm) were present in a 1:1 ratio. This result supports the assumption that two conformational isomers are present in solution and the energy of the molecule overcomes the rotation barrier at a higher temperature.

A UV study of a DMSO solution of the same compound, showed the absence of isosbestic points when the concentration was varied from 6.96×10^{-4} M to 3.48×10^{-4} M and 1.70×10^{-4} M. This confirms the presence of a single species in solution, excluding the possibility of monomer–dimer or tautomeric equilibria, other equally plausible causes for band duplication. In the ^{13}C NMR, two sets of bands are also visible for most carbon atoms.

Attempts to prepare imidazole **5** from the reaction of **6**[17] with 4-anisaldehyde in the presence of sulfuric acid led to the recovery of the starting material (**6**, 86%) after 3 days at room temperature.

Intramolecular cyclization of imidazole **5** to generate the 6-cyano-8-oxopurine **7** is a slow process (7–14 days at room temperature for the complete consumption of the starting material) but trifluoroacetic acid catalysis allows a clear evolution to the final product, which is isolated in excellent yield after 2–10 days (Table 2, method A). When the same reaction was carried out in the presence of a large excess of piperidine (5 M equiv) at room temperature, purine **8** was the major product, isolated after 2–5 days. (Table 2, method C). The structure assigned to this compound was mainly based on the NMR data, where correlation techniques (HMBC and HMQC) unequivocally placed the proton (δ 8.3–8.4 ppm) in the 6-position of purine ring. Purine **8** was also identified in the NMR spectrum of imidazoles **5**, when the solubilization of these compounds in DMSO-d_6 was assisted by heating. This observation inspired a new method for the preparation of these compounds (Table 2, method B), simply by heating a DMSO suspension of **5**, until the temperature reaches the boiling point of the solution and keeping this high temperature for 2–3 min.

Table 2
Synthesis of 6-substituted 2-oxopurines **7** and **8**



Product	Ar	X	Method[a]	Yield (%)
7a	4-$H_3CC_6H_4$	CN	A (7 days)	85
7b	4-$CH_3OC_6H_4$	CN	A (7 days)	92
7c	4-NCC_6H_4	CN	A (14 days)	92
7d	4-HOC_6H_4	CN	A (10 days)	52
7e	4-BrC_6H_4	CN	A (7 days)	85
7f	4-FC_6H_4	CN	A (7 days)	66
8a	4-$H_3CC_6H_4$	H	B	78
			C (48 h)	88
8b	4-$CH_3OC_6H_4$	H	B	62
			C (72 h)	75
8c	4-NCC_6H_4	H	B	71
			C (48 h)	98
8d	4-$O_2NC_6H_4$	H	B	57
			C (72 h)	95
8e	4-HOC_6H_4	H	B	54
			C (5 days)	63
8f	4-BrC_6H_4	H	C (5 days)	79
8g	4-FC_6H_4	H	C (5 days)	81

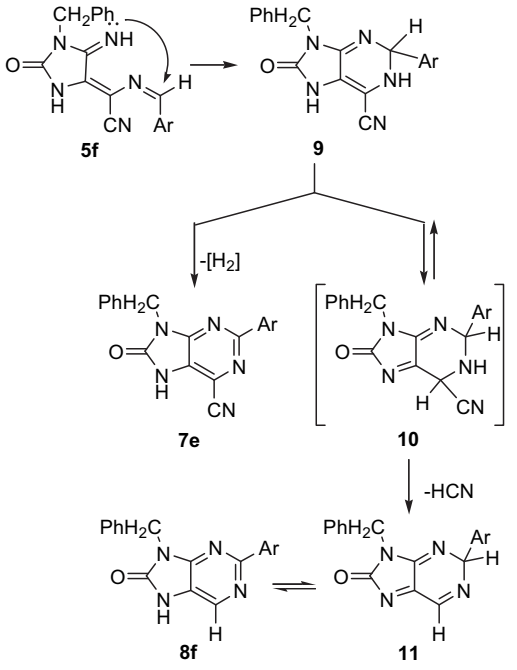
[a] Reaction conditions for method A: ethanol, TFA (cat.), rt; method B: DMSO, boiling for 2–3 min; method C: ethanol, piperidine (5 M equiv), rt.

The base-catalyzed cyclization of the substituted 2-oxoimidazole **5** to generate the 2-aryl-8-oxopurine **8** is a straightforward method to create this compound family. By comparing with the approach recently described by Zhang,[14] it has the advantage of milder and less hazardous reaction conditions and the possibility to incorporate a wide range of aromatic substituents with both electron-withdrawing and electron-donating groups in the 2-position of purine ring.

In an attempt to understand the pathway leading either to purine **7** or **8** from a common precursor **5**, the evolution of imidazole **5f** (17 mg) in DMSO-d_6 solution (600 μl) was studied by ^{1}H NMR. The spectrum was recorded at intervals over approximately 10 days and the two singlets at δ 8.45 and 8.51 ppm (in a 2:1 ratio) for the

C–H proton of the imine substituent in **5f** was used to quantify this compound.

Compound **5f**, the only component identified when the solution was prepared, slowly evolves to the 1,2-dihydropurine **9** (Scheme 3). The signals for C_2–H (δ 5.76 ppm, J=6.5 Hz) and N_1–H (δ 5.98 ppm, J=6.5 Hz) clearly support the cyclic structure of this compound. A correlation study (HMBC and HMQC) on the NMR solution confirms that the proton at δ 5.76 ppm is linked to a sp^3 carbon (δ 68.6 ppm). Two- and three-bond correlations are visible with C_iAr (δ 141.39 ppm), C_4 (δ 151.14 ppm), C_6 (δ 98.07 ppm) and C_oAr (δ 128.85 ppm). The N–H proton was localized on N_1 considering the three-bond correlations of this proton with C_5 (δ 119.93 ppm), C_iAr (δ 141.39 ppm) and the 6-CN group (δ 113.32 ppm).



Scheme 3. Proposed mechanism for the formation of purines **7e** and **8f** from 2-oxoimidazole **5f** in DMSO.

The methylene protons on N_9 are non-equivalent, leading to slightly different chemical shifts in the NMR spectrum (δ 4.63 and 4.70 ppm, J=15.2 Hz). This non-equivalence may result from the formation of a tetrahedral stereocenter in the molecule.

After 18 h, compound **9** corresponds to approximately 13% of the reaction mixture, where the starting material **5f** is present in a large excess (ca. 87%) and traces of purines **7e** and **8f** are already visible. The signal at δ 8.35 ppm, for the C_6-H proton of **8f** was used to quantify this compound and the amount of 6-cyanopurine **7e** was obtained from the signal at δ 5.10 ppm, corresponding to the methylene group of the benzyl substituent. A singlet at δ 6.3 ppm was assigned to the proton of HCN and the integration of this signal indicated that the amount of HCN evolved was exactly the same as the amount of C_6-H purine **8f** that was formed.

The evolution is summarized in Fig. 1, which indicates that after 41 h at room temperature, imidazole **5f** cyclized to the dihydropurine **9** in a large extent and this compound was the common precursor of both purines **7e** and **8f**. The formation of purine **7e** is the direct result of oxidation of **9** but the formation of purine **8f** is possible through tautomer **10**. Compound **10** was not identified in the reaction mixture, possibly due to the prompt elimination of HCN to generate **11**, a tautomer of purine **8f**.

This experiment indicates that in the absence of external acid or base, both pathways operate generating mixtures of purines **7** and **8**. Addition of acid (TFA) prevents the elimination of HCN from **10** and the equilibrium with its tautomer **9** results in the efficient consumption of this intermediate through the oxidation process that leads to the 6-cyanopurine **7**. Heating the DMSO solution forces HCN (gas) to escape and drives the equilibrium to the preferential formation of purine **8**.

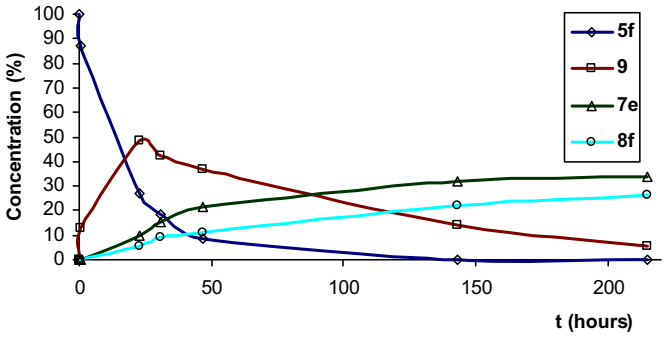
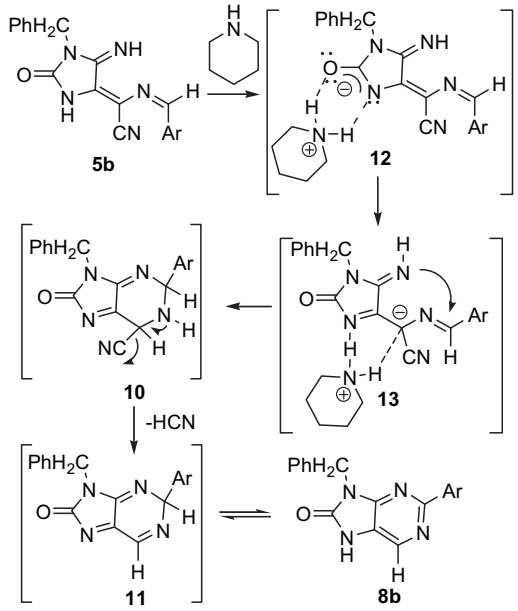


Fig. 1. ^{1}H NMR study of the evolution of 2-oxoimidazole **5f** in DMSO-d_6.

The evolution of imidazole **5** in piperidine was also followed by ^{1}H NMR. In this experiment, imidazole **5b** (20 mg) was combined with 4.5 M equiv of piperidine, in 600 μl of DMSO-d_6. The first spectrum was registered within the next 5 min and the acidic proton of the imidazole (a broad singlet at δ 11.7 ppm) was already absent. Two different compounds were formed, each of them with a single set of bands, where the acidic N–H is absent. A plausible structure for these compounds corresponds to the anion **12**, initially formed and stabilized by intermolecular H-bonding with the piperidinium cation, that progressively evolves to the anion **13** (Scheme 4). Structure **12** was assigned on the basis of ^{1}H NMR data, that shows the imine N–H as a broad singlet at δ 8.3 ppm, considerably shielded compared with the starting material **5b** (NH at δ 9.31 and δ 8.74 ppm). The C–H proton of the imine is not affected by the formation of the anion (**5b**, δ_{CH} 8.40 and δ 8.46 ppm, **12** δ_{CH} 8.43 ppm), supporting the assumption that the negative charge is localized in the imidazole ring. After 1 h at room temperature, compound **12** completely evolves to **13**, the major product in solution (94%) where the presence of a small amount of purine **8b** (6%) is already detected.



Scheme 4. Proposed mechanism for the formation of purine **8b** from 2-oxoimidazole **5b** in DMSO, in the presence of piperidine.

In a separate experiment, intermediate **13** was generated and studied by ^{13}C NMR and correlation techniques (HMQC and HMBC), unequivocally confirming the structure assigned to the imidazole moiety by comparison with the data previously registered for compound **14**[18] (Fig. 3, C_2 δ 166.6 ppm, C_4 δ 151.9 ppm, C_5 δ 159.8 ppm). The chemical shift of the carbon atoms in the imidazole ring of **13** (C_2 δ 166.37 ppm, C_4 δ 153.74 ppm, C_5 δ 160.50 ppm) increase by 10–15 ppm compared with the values registered for **5b** (C_2 δ 153.35 ppm, C_4 δ 138.78 ppm, C_5 δ 150.29 ppm). In contrast, the chemical shift of the carbon atoms of the linear substituent in the 4-position shifts to lower values. In particular, the chemical shift of the imine carbon in compound **13** (δ 148.04 ppm) decreases by approximately 10 ppm units compared with the same carbon atom in **5b** (δ 157.71 ppm). This was considered to be due to the transfer of the negative charge to this substituent.

Intramolecular cyclization is a comparatively slow process and leads to a transient intermediate **10** (not visible in the NMR spectrum) that rapidly evolves to the final product **8b** through tautomer **11**. Elimination of HCN is now assisted by the presence of base through the formation of piperidinum cyanide, evidenced ^1H NMR spectrum.

The mechanistic proposal presented in Scheme 4 is associated with the kinetic evolution summarized in Fig. 2. Purine **8b** was the only product in solution after 3 days at room temperature.

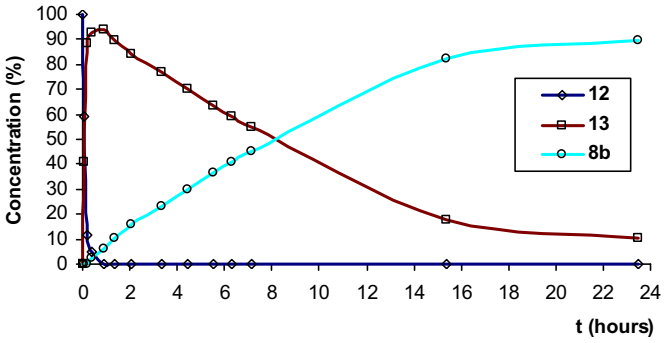
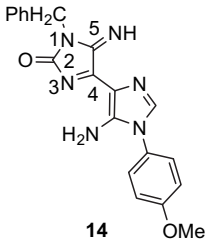


Fig. 2. ^1H NMR study of the evolution of 2-oxoimidazole **5b** in DMSO-d_6 in the presence of 5 M equiv of piperidine.



14

Fig. 3. Structure of compound **14**, reported in previous work.

3. Conclusion

A simple and efficient method was developed for the synthesis of 2-aryl-6-cyano and 6-unsubstituted 8-oxopurines. The reaction occurs from a common 2-oxoimidazole precursor that evolves to the 6-cyanopurine in the presence of acid (TFA) or to the 6-unsubstituted analogue in the presence of base (piperidine) or upon heating in DMSO. These products were isolated in a high purity form by simple filtration. Both compounds are difficult to prepare by the synthetic methods currently available. Mechanistic studies performed by ^1H NMR on the evolution of 2-oxoimidazole **5** confirm that the cyclization reaction is selective, leading exclusively to 8-oxopurines **7** or **8**.

Compound **4a** was included in a chemical collection of molecules submitted to virtual screening of their biological activity on a number of protein targets. This structure was identified as a novel antagonist of all four adenosine receptor subtypes.[19] Synthetic efforts are currently focussed on the preparation of a number of derivatives for in vitro testing of their activity on the adenosine receptor family.

4. Experimental section

4.1. General

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C or at 400 MHz for ^1H and 100 MHz for ^{13}C, including the ^1H–^{13}C correlation spectra (HMQC and HMBC). Deuterated DMSO was used as solvent. The chemical shifts are expressed in δ (ppm) and the coupling constants (J) in Hertz (Hz). IR spectra were recorded on an FT-IR using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel. The melting points were determined on a melting point apparatus and are uncorrected. Samples UV/vis absorption spectra were obtained using a quartz cell with 1 cm path in UV/vis spectrometer (Shimadzu, UV-2501) controlled by Shimadzu UV Probe 2.00 software.

4.2. General procedure for the synthesis of *N*-benzyl-*N*′-(1,2-dicyano-2-[aryl-methylene]amino vinyl)urea 4

A catalytic amount of sulfuric acid was added to a suspension of *N*-[2-amino-1,2-dicyanovinyl]-*N*′-benzylurea[17] (**1**, 700 mg, 2.90 mmol) and the appropriate aldehyde (1.2 M equiv) in acetonitrile (5 mL) and the reaction mixture was stirred at room temperature. The suspension was partially solubilized and 5 min later a yellow solid was formed. Stirring was continued for another 5 min, when the solid was collected and washed with acetonitrile and ethanol leading to the title compounds **4** in pure form.

*4.2.1. N-Benzyl-N′-(1,2-dicyano-2-{[(4-methylphenyl) methylene] amino}vinyl)urea (**4a**).* Yellow solid (0.91 g, 91%). Mp 230–231 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 9.32 (br s, 1H), 8.47 (s, 1H), 7.98 (d, J=8.4 Hz, 2H), 7.90 (t, J=5.4 Hz, 1H), 7.28–7.39 (m, 7H), 4.35 (d, J=5.6 Hz, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.8, 151.2, 143.6, 138.7, 132.0, 130.0, 129.6, 128.5, 127.6, 127.2, 118.3, 113.8, 113.2, 112.2, 43.2, 21.4 ppm; IR (Nujol mull): ν 2221, 2212, 1724, 1633, 1578 cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_5O$: C, 69.96; H, 4.99; N, 20.40, found: C, 69.61; H, 5.08; N, 20.29.

*4.2.2. N-Benzyl-N′-(1,2-dicyano-2-{[(4-methoxyphenyl) methylene] amino}vinyl)urea (**4b**).* Yellow solid (0.91 g, 87%). Mp 218–219 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 9.32 (s, 1H), 8.45 (s, 1H), 8.06 (d, J=8.7 Hz, 2H), 7.85 (t, J=5.7 Hz, 1H), 7.25–7.40 (m, 5H), 7.08 (d, J=8.7 Hz, 2H), 4.35 (d, J=5.7 Hz, 2H), 3.85 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 163.3, 160.4, 151.3, 138.7, 132.1, 128.5, 127.6, 127.4, 127.2, 117.4, 114.6, 114.2, 113.3, 112.3, 55.6, 43.2 ppm; IR (Nujol mull): ν 2221, 2212, 1711, 1660, 1606 cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49, found: C, 66.82; H, 4.91; N, 19.41.

*4.2.3. N-Benzyl-N′-(1,2-dicyano-2-{[(4-cyanophenyl) methylene] amino}vinyl)urea (**4c**).* Yellow solid (0.89 g, 86%). Mp 215–216 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 8.60 (s, 1H), 8.25 (d, J=8.4 Hz, 2H), 8.00 (d, J=8.4 Hz, 2H), 7.87 (t, J=5.6 Hz, 1H), 7.27–7.39 (m, 5H), 4.36 (d, J=4.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 151.0, 138.6, 138.4, 132.8, 130.1, 128.5, 127.6,

127.3, 120.2, 118.4, 114.3, 112.9, 112.88, 112.0, 43.2; IR (Nujol mull): ν 2228, 2213, 1706, 1663, 1604 cm^{-1}. Anal. Calcd for $C_{20}H_{14}N_6O\cdot 0.2H_2O$: C, 67.10; H, 4.06; N, 23.48, found: C, 66.89; H, 4.02; N, 23.41.

*4.2.4. N-Benzyl-N′-(1,2-dicyano-2-{[(4-nitrophenyl) methylene]amino} vinyl)urea (**4d**).* Orange solid (0.93 g, 86**%**). Mp 207–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.66 (s, 1H), 8.65 (s, 1H), 8.33 (s, 5H), 7.89 (t, J=5.7 Hz, 1H), 7.27–7.40 (m, 5H), 4.37 (d, J=5.7 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 151.0, 149.4, 140.1, 138.6, 130.7, 128.5, 127.6, 127.3, 124.0, 120.5, 112.90, 112.89, 112.0, 43.2; IR (Nujol mull): ν 2224, 2214, 1708, 1660, 1604 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_6O_3$: C, 60.96; H, 3.77; N, 22.45, found: C, 60.60; H, 3.91; N, 22.34.

*4.2.5. N-Benzyl-N′-(1,2-dicyano-2-{[(4-hydroxyphenyl) methylene] amino}vinyl)urea (**4e**).* Red solid (0.53 g, 52%). Mp 187–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.78 (br s, 2H), 8.38 (s, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.85 (t, J=5.6 Hz, 1H), 7.26–7.38 (m, 5H), 6.89 (d, J=8.8 Hz, 2H), 4.34 (d, J=5.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.5, 160.5, 151.4, 138.8, 132.5, 128.5, 127.5, 127.2, 125.9, 116.9, 116.0, 114.5, 113.4, 112.3, 43.1 ppm; IR (Nujol mull): ν 2228, 1709, 1661, 1604 cm^{-1}. Anal. Calcd for $C_{19}H_{15}N_5O_2\cdot H_2O$: C, 62.80; H, 4.72; N, 19.27, found: C, 62.85; H, 4.58; N, 19.05.

*4.2.6. N-Benzyl-N′-(1,2-dicyano-2-{[(4-bromophenyl)methyl-ene] amino}vinyl)urea (**4f**).* Red solid (1.05 g, 89%). Mp 228–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.48 (s, 1H), 8.51 (s, 1H), 8.03 (d, J=8.4 Hz, 2H), 7.87 (t, J=5.6 Hz, 1H), 7.75 (d, J=8.4 Hz, 2H), 7.27–7.39 (m, 5H), 4.37 (d, J=4.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.8, 151.1, 138.6, 133.8, 132.0, 131.5, 128.5, 127.6, 127.2, 126.8, 119.1, 113.3, 113.0, 112.1, 43.2 ppm; IR (Nujol mull): ν 2225, 2215, 1659, 1606 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_5BrO$: ν C, 55.90; H, 3.46; N, 17.15, found: C, 56.28; H, 3.75; N, 17.48.

*4.2.7. N-Benzyl-N′-(1,2-dicyano-2-{[(4-fluorophenyl) methylene] amino}vinyl)urea (**4g**).* Red solid (0.96 g, 96%). Mp 222–223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.44 (s, 1H), 8.52 (s, 1H), 8.17 (dd, J=8.7 , 5.4 Hz, 2H), 7.85 (t, J=5.4 Hz, 1H), 7.28–7.42 (m, 7H), 4.36 (d, J=5.7 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.9 (J=250.88 Hz), 159.7, 151.2, 138.7, 132.5 (d, J=9.15 Hz), 131.4 (d, J=2.85 Hz), 128.5, 127.6, 127.3, 118.8, 116.2 (J=21.98 Hz), 113.5, 113.1, 112.2, 43.2 ppm; IR (Nujol mull): ν 2223, 1709, 1658, 1611, 1604 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_5FO$: C, 65.70; H, 4.06; N, 20.16, found: C, 65.36; H, 4.27; N, 20.56.

4.3. General procedure for the synthesis of (1-benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(1)arylmethylene]-amino} acetonitrile 5

A catalytic amount of DBU was added to a suspension of *N*-benzyl-*N′*-(1,2-dicyano-2-[aryl-methylene]amino}vinyl)urea (**4**, 2.00 mmol) in acetonitrile (5 mL) and the mixture was stirred at room temperature for 10 min–1 h. The yellow solid was filtered and washed with acetonitrile and diethyl ether. This procedure was used to prepare compounds **5**.

*4.3.1. 2-(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-methylphenyl)methylene]amino} acetonitrile (**5a**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 30 min. Yellow solid (0.59 g, 85%). Mp 228–229 °C; imidazole **5a** was present in the NMR spectra as two isomeric forms **A**, **B** in a 1.8:1 ratio. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.72 (br s, 1H, **A**+**B**), 9.36 (s, 1H, **A**), 8.80 (s, 1H, **B**), 8.48 (s, 1H, **B**), 8.43 (s, 1H, **A**), 8.04 (d, J=8.1 Hz, 2H, **A**+**B**), 7.20–7.40 (m, 7H, **A**+**B**), 4.80 (s, 2H, **A**), 4.76 (s, 2H, **B**), 2.37 (s, 3H, **A**+**B**) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.3 (**B**), 158.2 (**A**), 154.0 (**B**); 153.4 (**A**), 150.3 (**A**), 142.7 (**B**), 142.3 (**A**), 139.4 (**A**), 136.6 (**B**), 136.3 (**A**), 132.9 (**A**), 132.7 (**B**), 129.7 (**B**), 129.6 (**A**+**B**), 129.4 (**A**), 128.6 (**A**), 128.5 (**B**), 127.5 (**B**), 127.4 (**A**), 127.1 (**A**+**B**), 113.3 (**B**), 112.1 (**A**), 98.84 (**A**+**B**), 41.8 (**B**), 40.9 (**A**), 21.3 (**A**+**B**) ppm; IR (Nujol mull): ν 2205, 1742, 1632, 1591 cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_5O\cdot 0.1H_2O$: C, 69.59; H, 5.02; N, 20.29, found: C, 69.47; H, 5.13; N, 20.33.

*4.3.2. 2(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-methoxyphenyl)methylene]amino} acetonitrile (**5b**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 15 min. Yellow solid (0.66 g, 92%). Mp 231–232 °C; imidazole **5b** was present in the NMR spectra as two isomeric forms **A**, **B** in a 1.6:1 ratio. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (br s, 1H, **A**+**B**), 9.30 (s, 1H, **A**), 8.75 (s, 1H, **B**), 8.46 (s, 1H, **B**), 8.41 (s, 1H, **A**), 8.10 (d, J=8.8 Hz, 2H, **A**+**B**), 7.25–7.37 (m, 5H, **A**+**B**), 7.04 (d, J=8.8 Hz, 2H, **A**+**B**), 4.80 (s, 2H, **A**), 4.75 (s, 2H, **B**), 3.84 (s, 3H, **A**+**B**) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6 (**B**); 162.5 (**A**), 158.5 (**B**), 157.7 (**A**), 154.2 (**B**), 153.4 (**A**), 150.2 (**A**), 138.8 (**A**+**B**), 136.7 (**B**), 136.3 (**A**), 131.6 (**B**), 131.5 (**A**), 128.6 (**A**), 128.4 (**B**), 128.3 (**A**), 128.2 (**B**), 127.4 (**B**), 127.3 (**B**), 127.2 (**B**), 127.1 (**A**), 114.3 (**B**), 114.26 (**A**), 113.6 (**B**), 112.2 (**A**), 99.4 (**B**), 99.0 (**A**), 55.5 (**A**+**B**), 41.7 (**B**), 40.8 (**A**) ppm; IR (Nujol mull): ν 2201, 1736, 1631 cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_5O_2\cdot 0.1H_2O$: C, 66.50; H, 4.80; N, 19.39, found: C, 66.32; H, 4.85; N, 19.33.

*4.3.3. 2(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-cyanophenyl)methylene]amino}acetonitrile (**5c**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 1 h. Yellow solid (0.61 g, 85%). Mp 304–305 °C; imidazole **5c** was present in the NMR spectra as two isomeric forms **A**, **B** in a 2.3:1 ratio. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (br s, 1H, **A**+**B**), 9.54 (s, 1H, **A**), 8.90 (s, 1H, **B**), 8.59 (s, 1H, **B**), 8.53 (s, 1H, **A**), 8.35 (d, J=8.4 Hz, 2H, **A**+**B**), 7.96 (d, J=8.4 Hz, 2H, **A**+**B**), 7.26–7.37 (m, 5H, **A**+**B**), 4.81 (s, 2H, **A**), 4.76 (s, 2H, **B**) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.4 (**B**), 156.3 (**A**), 153.9 (**B**), 153.3 (**A**), 150.1 (**A**), 141.4 (**A**+**B**), 139.3 (**A**), 139.2 (**B**), 136.5 (**B**), 136.2 (**A**), 132.6 (**A**+**B**), 129.9 (**A**+**B**), 128.6 (**A**), 128.4 (**B**), 127.44 (**A**), 127.40 (**B**), 127.1 (**A**), 118.6 (**A**+**B**), 113.5(**B**) 113.4 (**A**), 113.3 (**B**) 111.9 (**A**), 98.1 (**A**+**B**), 41.8 (**B**), 41.0 (**A**) ppm; IR (Nujol mull): ν 2229, 2217, 1735, 1635 cm^{-1}. Anal. Calcd for $C_{20}H_{14}N_6O$: C, 67.79; H, 3.98; N, 23.72, found: C, 67.67; H, 4.08; N, 23.94.

*4.3.4. 2(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-nitrophenyl)methylene]amino}acetonitrile (**5d**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 10 min. Yellow solid (0.60 g, 80%). Mp 289–300 °C; imidazole **5d** was present in the NMR spectra as two isomeric forms **A**, **B** in a 1.7:1 ratio. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.50 (s, 1H, A), 8.73 (s, 1H, **B**), 8.66 (s, 1H, **B**), 8.57 (s, 1H, **A**), 8.40 (d, J=8.7 Hz, 2H, **A**), 8.29 (d, J=9.3 Hz, 2H, **A**+**B** and 2H, **B**), 7.25–7.35 (m, 5H, **A**+**B**), 4.80 (d, 2H, **A**), 4.72 (d, 2H, **B**) ppm; evolution in the NMR tube, with formation of both 6-unsubstituted purine and 6-cyanopurine prevents the identification of the ^{13}C NMR signals for the 2-oxoimidazole; IR (Nujol mull): ν 2214, 1737, 1634 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_6O_3\cdot 0.1H_2O$: C, 60.67; H, 3.81; N, 22.34, found: C, 60.59; H, 3.96; N, 21.99.

*4.3.5. 2(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-hydroxyphenyl)methylene]amino} acetonitrile (**5e**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 20 min. Yellow solid (0.58 g, 82%). Mp 229–230 °C; imidazole **5e** was present in the NMR spectra as two isomeric forms **A**, **B** a 1.5:1 ratio. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (br s, 1H, **A**+**B**), 9.24 (s, 1H,

A), 8.69 (s, 1H, **B**), 8.39 (s, 1H, **B**), 8.35 (s, 1H, **A**), 7.98 (d, *J*=8.4 Hz, 2H, **A**+**B**), 7.25–7.37 (m, 5H, **A**+**B**), 6.85 (d, *J*=8.4 Hz, 2H, **A**+**B**), 4.79 (s, 2H, **A**), 4.74 (s, 2H, **B**) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.6 (**B**), 161.4 (**A**) 158.3 (**B**), 157.9 (**A**), 154.7 (**B**), 153.4 (**A**), 150.4 (**A**), 136.9 (**B**), 136.3 (**A**), 131.8 (**A**+**B**), 128.6 (**A**), 128.4 (**B**), 127.4 (**B**), 127.3 (**A**), 127.2 (**B**), 127.1 (**A**), 126.9 (**B**), 115.7 (**A**+**B**), 114.0 (**B**), 112.3 (**A**), 99.2 (**A**+**B**), 41.7 (**B**), 40.8 (**A**) ppm; IR (Nujol mull): ν 2215, 1736, 1637 cm^{-1}. Anal. Calcd for $C_{19}H_{15}N_5O_2 \cdot 0.5H_2O$: C, 64.40; H, 4.55, found: C, 64.07; H, 4.72.

*4.3.6. 2(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-bromophenyl)methylene]amino} acetonitrile (**5f**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 20 min. Yellow solid (0.74 g, 91%). Mp 265–266 °C; imidazole **5f** was present in the NMR spectra as two isomeric forms **A**, **B** in a 2:1 ratio. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (br s, 1H, **A**+**B**), 9.44 (s, 1H, **A**), 8.85 (s, 1H, **B**), 8.51 (s, 1H, **B**), 8.45 (s, 1H, **A**), 8.11 (d, *J*=8.4 Hz, 2H, **A**+**B**), 7.70 (d, *J*=8.4 Hz, 2H, **A**+**B**), 7.26–7.37 (m, 5H, **A**+**B**), 4.80 (s, 2H, **A**), 4.76 (s, 2H, **B**) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.1 (**B**), 157.0 (**A**), 153.8 (**B**), 153.3 (**A**), 150.2 (**A**), 140.0 (**A**+**B**), 136.6 (**B**), 136.2 (**A**), 134.6 (**A**), 134.5 (**B**), 131.79 (**B**), 131.75 (**A**), 131.31 (**B**), 131.26 (**A**), 128.6 (**A**), 128.4 (**B**), 127.43 (**B**), 127.35 (**B**), 127.3 (**A**), 127.1 (**A**), 126.0 (**B**), 125.6 (**A**), 113.2 (**B**), 112.0 (**A**), 99.0 (**B**), 98.4 (**A**), 41.8 (**B**), 40.9 (**A**) ppm; IR (Nujol mull): ν 2215, 1735, 1634 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_5$ Br O: C, 55.90; H, 3.46; N, 17.15, found: C, 55.93; H, 3.60; N, 17.22.

*4.3.7. 2(1-Benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(4-fluorophenyl)methylene]amino}acetonitrile (**5g**).* The title compound was prepared following the general procedure, and was isolated after stirring the reaction mixture at room temperature for 10 min. Yellow solid (0.61 g, 88%). Mp 239–240 °C; imidazole **5g** was present in the NMR spectra as two isomeric forms **A**, **B** in a 1.9:1 ratio. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.79 (br s, 1H, **A**+**B**), 9.41 (s, 1H, **A**), 8.83 (s, 1H, **B**), 8.57 (s, 1H, **B**), 8.47 (s, 1H, **A**), 8.26 (s, 1H, **A**), 8.23 (dd, *J*=8.5 , 5.8 Hz, 2H, **A**+**B**), 7.24–7.40 (m, 7H, **A**+**B**), 4.80 (s, 2H, **A**), 4.76 (s, 2H, **B**) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.5 (*J*=250.27 Hz, **B**), 164.4 (*J*=249.07 Hz, **A**), 158.1 (**B**), 157.0 (**A**), 153.9 (**B**), 153.7 (**B**), 153.4 (**A**), 150.2 (**A**), 139.9 (**A**), 136.6 (**B**), 136.3 (**A**), 132.1(*J*=10.87 Hz, **B**), 132.0 (*J*=8.55 Hz, **A**), 128.6 (**A**), 128.5 (**B**), 127.5 (**A**), 127.4 (**B**), 127.3 (**B**), 127.1 (**A**), 115.9 (*J*=21.75 Hz, **A**+**B**), 113.2 (**B**), 112.1 (**A**), 99.2 (**B**), 98.5 (**A**), 41.8 (**B**), 40.9 (**A**) ppm; IR (Nujol mull): ν 2213, 1735, 1635 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_5FO$: C, 65.70; H, 4.06; N, 20.16, found: C, 65.60; H, 4.10; N, 20.40.

4.4. General procedure for the synthesis of 2-aryl-6-cyano-8-oxopurines 7 and 2-aryl-8-oxopurines 8

Method A: A suspension of (1-benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(1)arylmethylene]-amino}acetonitrile (**5**, 0.30 mmol) in ethanol (100 mL) with a catalytic amount of trifluoroacetic acid was stirred at room temperature for 7–14 days. The solvent was removed under reduced pressure and addition of diethyl ether led to a solid precipitate that was filtered and washed with diethyl ether. This procedure was used to prepare compounds **7**.

Method B: A suspension of (1-benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(1)arylmethylene]-amino}acetonitrile (**5**, 0.30 mmol) in dimethylsulfoxide (3 mL) was heated under reflux for 2–3 min. The solution was cooled and poured onto water (25 mL). The off-white solid precipitate was filtered and washed with water. This method was used to prepare compounds **8**.

Method C: A suspension of (1-benzyl-5-imino-2-oxoimidazolidin-4-ylidene){[(1)arylmethylene]-amino}acetonitrile (**5**, 0.30 mmol) and piperidine (5 M equiv) in ethanol (100 mL) was stirred at room temperature for 2–5 days. The solvent was removed under reduced pressure and addition of diethyl ether led to a solid precipitate that was filtered and washed with diethyl ether. This method was used to prepare compounds **8**.

*4.4.1. 9-Benzyl-2-(4-methylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbonitrile (**7a**).* The title compound was prepared following method A and the reaction mixture was stirred at room temperature for 7 days. Off-white solid (0.09 g, 85%). Mp 265–266 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (br s, 1H), 8.14 (d, *J*=8.1 Hz, 2H), 7.43 (d, *J*=7.2 Hz, 2H), 7.25–7.36 (m, 5H), 5.08 (s, 2H), 2.35 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.1, 152.9, 152.2, 140.2, 135.7, 133.4, 129.0, 128.4, 127.7, 127.5, 127.0, 124.3, 114.3, 113.6, 42.9, 20.7 ppm; IR (Nujol mull): ν 2239, 1725, 1631, 1601 cm^{-1}. Anal. Calcd for $C_{20}H_{15}N_5O \cdot 0.75H_2O$: C, 67.69; H, 4.69, found: C, 68.03; H, 4.89.

*4.4.2. 9-Benzyl-2-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbonitrile (**7b**).* The title compound was prepared following method A, and the reaction mixture was stirred at room temperature for 7 days. Off-white solid (0.10 g, 92%). Mp 277–278 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.62 (br s, 1H), 8.19 (d, *J*=8.7 Hz, 2H), 7.42 (d, *J*=6.6 Hz, 2H), 7.25–7.37 (m, 3H), 7.03 (d, *J*=8.7 Hz, 2H), 5.06 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 156.1, 153.2, 152.3, 135.9, 128.9, 128.7, 128.6, 127.9, 127.8, 124.1, 114.6, 114.0, 113.7, 55.3, 43.0 ppm; IR (Nujol mull): ν 1725, 1631, 1600 cm^{-1}. Anal. Calcd for $C_{20}H_{15}N_5O_2 \cdot 0.3H_2O$: C, 66.22; H, 4.33, found: C, 66.55; H, 4.71.

*4.4.3. 9-Benzyl-2-(4-cyanophenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbonitrile (**7c**).* The title compound (**7c**) was prepared following method A, and the reaction mixture was stirred at room temperature for 14 days. The yellow suspension evolved to a white suspension and the solid was filtered and washed by diethyl ether and ethanol. Off-white solid (0.10 g, 93%). Mp >350 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.88 (br s, 1H), 8.40 (d, *J*=8.4 Hz, 2H), 7.93 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=6.6 Hz, 2H), 7.27–7.37 (m, 3H), 5.10 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.0, 153.2, 152.5, 140.2, 135.7, 132.8, 128.6, 127.9, 127.8, 125.7, 118.6, 114.3, 113.6, 112.7, 43.1 ppm; IR (Nujol mull): ν 2229, 2227, 1726, 1632, 1604 cm^{-1}. Anal. Calcd for $C_{20}H_{12}N_6O \cdot 0.5H_2O$: C, 66.48; H, 3.63; N, 23.26, found: C, 66.86; H, 3.71; N, 22.87.

*4.4.4. 9-Benzyl-2-(4-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbonitrile (**7d**).* The title compound was prepared following method A, and the reaction mixture was stirred at room temperature for 10 days. Off-white solid (0.06 g, 52%). Mp 325–326 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.60 (br s, 1H), 9.96 (s, 1H), 8.13 (d, *J*=8.4 Hz, 2H), 7.20–7.45 (m, 5H), 6.85 (d, *J*=8.4 Hz, 2H), 5.06 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.9, 156.5, 153.2, 152.3, 136.0, 129.1, 128.6, 127.8, 127.7, 127.2, 123.9, 115.5, 114.6, 113.7, 42.9 ppm; IR (Nujol mull): ν 2254, 2222, 1719, 1633 cm^{-1}. Anal. Calcd for $C_{19}H_{13}N_5O_2 \cdot 1.1H_2O$: C, 62.84; H, 4.22; N, 19.28, found: C, 63.15; H, 4.09; N, 18.90.

*4.4.5. 9-Benzyl-2-(4-bromophenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbonitrile (**7e**).* The title compound was prepared following method A, and the reaction mixture was stirred at room temperature for 7 days. Off-white solid (0.10 g, 85%). Mp 321–322 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.67 (br s, 1H), 8.21 (d, *J*=8.4 Hz, 2H), 7.69 (d, *J*=8.4 Hz, 2H), 7.42 (d, *J*=6.9 Hz, 2H), 7.25–7.37 (m, 3H), 5.1 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.0, 153.0, 152.3, 135.5, 135.3, 131.5, 129.0, 128.3, 127.6, 127.5, 124.9, 124.0, 114.1, 113.5, 42.9 ppm; IR (Nujol mull): ν 2238, 1725, 1629, 1600 cm^{-1}. Anal. Calcd for $C_{19}H_{12}N_5BrO$: C, 56.18; H, 2.97; N, 17.23, found: C, 56.12; H, 3.14; N, 17.33.

*4.4.6. 9-Benzyl-2-(4-fluorophenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbonitrile (**7f**).* The title compound was prepared following method A, and the reaction mixture was stirred at room

temperature for 7 days. Off-white solid (0.07 g, 66%). Mp 334–335 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.73 (br s, 1H), 8.29 (dd, J=9.0 , 5.4 Hz, 2H), 7.43 (d, J=6.9 Hz, 2H), 7.25–7.37 (m, 5H), 5.08 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.7 (J=246.83 Hz), 155.1, 153.1, 152.4, 135.8, 132.6 (J=2.85 Hz), 129.5 (J=8.85 Hz), 128.6, 127.9, 127.8, 124.7, 115.6 (J=21.68 Hz), 114.4, 113.6, 43.1 ppm; IR (Nujol mull): ν 2236, 1725, 1634, 1602 cm^{-1}. Anal. Calcd for $C_{19}H_{12}N_5FO$: C, 66.08; H, 3.50; N, 20.28, found: C, 66.15; H, 3.42; N, 20.56.

*4.4.7. 9-Benzyl-2-(4-methylphenyl)-7,9-dihydro-8H-purin-8-one (**8a**).* The title compound was prepared following method B (0.075 g, 78%) and following method C (0.08 g, 88%), by stirring the reaction mixture at room temperature for 48 h. Off-white solid, mp 303–304 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.48 (br s, 1H), 8.31 (s, 1H), 8.20 (d, J=8.4 Hz, 2H), 7.40 (d, J=7.2 Hz, 2H), 7.32 (t, J=7.5 Hz, 3H), 7.25 (d, J=8.4 Hz, 2H), 5.1 (s, 2H), 2.33 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2, 153.4, 150.3, 139.5, 136.7, 135.0, 133.3, 128.7, 127.91, 127.9, 127.7, 127.1, 120.5, 42.6, 21.0 ppm; IR (Nujol mull): ν 1721, 1623, 1603 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_4O\cdot 0.2H_2O$: C, 71.32; H, 5.17; N, 17.51, found: C, 71.20; H, 5.38; N, 17.57.

*4.4.8. 9-Benzyl-2-(4-methoxyphenyl)-7,9-dihydro-8H-purin-8-one (**8b**).* The title compound was prepared following method B (0.06 mg, 62%) and using method C (0.075 g, 75%), by stirring the reaction mixture at room temperature for 72 h. Off-white solid, mp 263–264 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.42 (br s, 1H), 8.28 (s, 1H), 8.26 (d, J=8.7 Hz, 2H), 7.39(d, J=6.9 Hz, 2H), 7.32 (t, J=6.9 Hz, 2H), 7.28 (t, J=6.9 Hz 1H), 7.00 (d, J=8.7 Hz, 2H), 5.06 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.7, 156.1, 153.3, 150.3, 136.6, 133.2, 130.2, 128.63, 128.61,127.8, 127.6, 120.0, 113.9, 55.2, 42.5 ppm; IR (Nujol mull): ν 1716, 1623, 1601 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_4O_2\cdot 0.2H_2O$: C, 67.93; H, 4.92; N, 16.68, found: C, 67.66; H, 4.79; N, 16.97.

*4.4.9. 9-Benzyl-2-(4-cyanophenyl)-7,9-dihydro-8H-purin-8-one (**8c**).* The title compound was prepared following method B (0.07 g, 71%) and using method C (0.10 g, 98%), by stirring the reaction mixture at room temperature for 48 h. Off-white solid, mp 273–274 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.57 (br s, 1H), 8.45 (d, J=8.4 Hz, 2H), 8.38 (s, 1H), 7.91 (d, J=8.7 Hz, 2H), 7.40 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.28 (t, J=7.5 Hz 1H), 5.08 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.0, 153.3, 150.3, 141.7, 136.4, 133.2, 132.6, 128.6, 127.8, 127.7, 127.6, 121.4, 118.8, 112.0, 42.6 ppm; IR (Nujol mull): ν 2228, 1725, 1619, 1607 cm^{-1}. Anal. Calcd for $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.39, found: C, 69.45; H, 4.18; N, 21.52.

*4.4.10. 9-Benzyl-2-(4-nitrophenyl)-7,9-dihydro-8H-purin-8-one (**8d**).* The title compound was prepared following method B (0.06 g, 57%) and using method C (0.10 mg, 95%), by stirring the reaction mixture at room temperature for 72 h. Off-white solid, mp 346–347 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.59 (br s, 1H), 8.52 (d, J=9.0 Hz, 2H), 8.40 (s, 1H), 8.29 (d, J=9.0 Hz, 2H), 7.42 (d, J=7.5 Hz, 2H), 7.34 (t, J=7.5 Hz, 2H), 7.27 (t, J=7.5 Hz, 1H) 5.09 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 153.7, 153.3, 150.4, 148.1, 143.4, 136.4, 133.2, 128.6, 128.0, 127.8, 127.7, 123.8, 121.6, 42.7; IR (Nujol mull): ν 1716, 1620, 1608 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_5O_3\cdot 0.2H_2O$: C, 61.61; H, 3.85; N, 19.96, found: C, 61.56; H, 3.71; N, 19.90.

*4.4.11. 9-Benzyl-2-(4-hydroxyphenyl)-7,9-dihydro-8H-purin-8-one (**8e**).* The title compound was prepared following method B (0.06 g, 54%) and using method C (0.07 mg, 63%), by stirring the reaction mixture at room temperature for 5 days. Off-white solid, mp 307–308 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.38 (br s, 1H), 9.84 (br s, 1H), 8.26 (s,1H), 8.17 (d, J=8.7 Hz, 2H), 7.39 (d, J=6.9 Hz, 2H), 7.33 (t, J=6.9 Hz, 2H), 7.25 (t, J=6.9 Hz, 1H), 6.84 (d, J=8.7 Hz, 2H), 5.05 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.3, 156.5, 153.3, 150.3, 136.7, 133.3, 128.8, 128.73, 128.68, 127.8, 127.6, 119.8, 115.3, 42.5 ppm; IR (Nujol mull): ν 1717, 1627, 1603 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_4O_2\cdot 1.4H_2O$. 0.2 DMSO: C, 61.53; H, 4.88; N, 15.60, found: C, 61.50; H, 4.60; N, 15.39.

*4.4.12. 9-Benzyl-2-(4-bromophenyl)-7,9-dihydro-8H-purin-8-one (**8f**).* The title compound was prepared following method C (0.09 g, 79%), by stirring the reaction mixture at room temperature for 5 days. Off-white solid, mp 331–332 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.56 (br s, 1H), 8.34 (s, 1H), 8.25 (d, J=8.7 Hz, 2H), 7.66 (d, J=8.7 Hz, 2H), 7.40 (d, J=7.2 Hz, 3H), 7.33 (t, J=7.2 Hz, 2H), 7.28 (t, J=7.2 Hz, 1H), 5.07 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.0, 153.2, 150.3, 136.8, 136.5, 133.2, 131.6, 129.0, 128.6, 127.8, 127.6, 123.5, 120.9, 42.5 ppm; IR (Nujol mull): ν 1719, 1622, 1600 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_4BrO$: C, 56.71; H, 3.44; N, 14.70, found: C, 56.64; H, 3.54; N, 14.79.

*4.4.13. 9-Benzyl-2-(4-fluorophenyl)-7,9-dihydro-8H-purin-8-one (**8g**).* The title compound was prepared following method C (0.08 g, 83%), by stirring the reaction mixture at room temperature for 5 days. Off-white solid, mp 292–293 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.35 (dd, J=9.0 , 5.7 Hz, 2H), 8.33 (s, 1H), 7.25–7.45 (m, 7H), 5.07(s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3 (J=245.48 Hz), 155.4, 153.4, 150.4, 136.6, 134.1 (J=2.93 Hz), 133.2, 129.3 (J=8.55 Hz), 128.6, 127.8, 127.6, 120.9, 115.4 (J=21.45 Hz), 42.5 ppm; IR (Nujol mull): ν 1722, 1623, 1610 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_4FO\cdot 0.6H_2O$: C, 65.29; H, 4.32; N, 16.92, found: C, 65.65; H, 4.28; N, 17.01.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.11.064. These data include MOL files and InChIKeys of the most important compounds described in this article.

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