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An efficient synthesis of 6,9-disubstituted purin-8-ones via copper-catalyzed coupling/cyclization

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ABSTRACT

An efficient and novel synthesis of 6,9-disubstituted purin-8-ones has been developed. Starting from dichloropyrimidin-5-ylcarbamate, CuCl/amino acid catalyzed coupling/cyclization reaction with amines was achieved to afford 9-substituted 6-chloropurin-8-ones. Then a microwave-assisted amination procedure was carried out for the synthesis of 6,9-disubstituted purin-8-ones in moderate to good yields.

1. Introduction

Purine derivatives constitute an enormous class of compounds, some of which are well-known as therapeutic agents. These fused planar heterocycles present key hydrogen bond donating/accepting functionalities, making them interesting scaffolds for targeting many biosynthetic, regulatory and signal transduction proteins including cellular kinases, G proteins, and polymerases.[1] Purinones are derivatives of purine, such as purin-8-one or 8-hydroxypurine derivatives reported to possess a wide range of biological activities. As described in Figure 1, 9-aryl-purin-8-one **1** has an excellent binding affinity to the corticotropin-releasing hormone (CRH) receptor, a key player in anxiety related disorders.[2] Others stimulate the humoral immune responses by binding selectively to B-cells.[3] 8-Hydroxypurine derivatives **2** and **3** were also reported as potent interferon-inducing agents for treatment of hepatitis C,[4] or as cyclin-dependent kinases (CDKs) inhibitors by binding to the ATP pockets of the proteins.[5] Especially the 6,9-diaryl purin-8-one **4** and its derivatives were reported to possess strong p38 MAP kinase inhibiting activities.[6] Accordingly, the development of more efficient, convenient and environmentally friendly methods for the synthesis of 6,9-disubstituted purin-8-ones is extremely necessary.

Three approaches were reported for the construction of purin-8-one skeleton. The first way is the modification of adenine or guanine derivatives.[7] The second route involves the construction of the fused heterocyclic skeleton via the useful intermediate

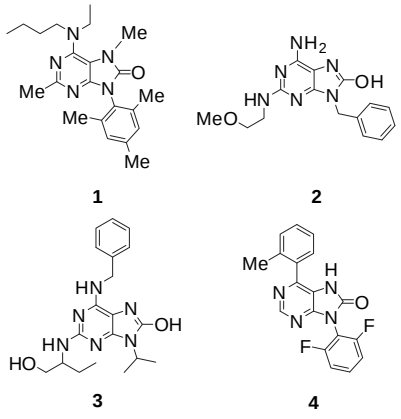

Figure 1. Examples of biologically active purinones.

1-substituted 5-amino-4-cyano-2-oxoimidazole.[8] Still there are several problems associated with these methodologies, including long synthetic routes,[7b] the long reaction times required,[9] and, more significantly, in some cases, the poor yields reported.[10] As a third alternative, purin-8-one derivatives can be synthesized through the classical method that involves nucleophilic displacement of *ortho*-nitro substituted pyrimidinyl halides with amines and subsequent reduction and cyclization with carbonyldiimidazole or triphosgene,[11] which is the limitation of the diversity of the products because of the commercial unavailability of the key reagent of *ortho*-nitro substituted pyrimidinyl halides. These drawbacks had prompted Kuethe and co-workers to develop

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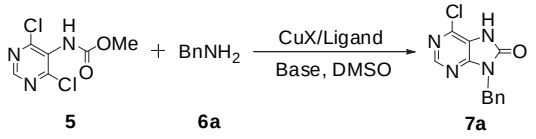
a Palladium-catalyzed aryl amination strategy leading to substituted imidazo[4,5-*b*]pyridin-2-ones but obtained low yields.[12]In recent years, copper-catalyzed C–N coupling reactions have been reported to be used extensively for the synthesis of heterocycles in good yields,[13] including benzimidazol-2-one relatives,[14] which is much similar to purin-8-ones, for example, several groups have reported the synthesis of 1,3-dihydrobenzimidazol-2-ones by using CuI-catalyzed intramolecular cyclization very recetenly,[14a–d] However, copper-catalyzed synthesis of purin-8-one skeletons has not been seen in literatures as yet. As a part of our continuing effort to assemble heterocycles by copper-catalyzed cross-coupling reactions,[15] we are interested in developing a novel protocol for the construction of purin-8-one skeleton. Here we disclose an efficient synthesis of 6,9-disubstituted purin-8-ones via copper-catalyzed coupling/cyclization process.

2. Results and discussion

Initially we tried to get methyl (4,6-dichloropyrimidin-5-yl) carbamate[16] starting from 4,6-dichloropyrimidin-5-amine, [17] unfortunately, the very low yield of the carbamate product was provided. Then we synthesized dichloropyrimidin-5-ylcarbamate **5** according to an efficient procedure described by Gerhard and Felix in 3 steps,[18] which then underwent the copper-catalyzed coupling/cyclization reaction with amines in order to afford the target 9-substituted 6-chloropurin-8-ones **7** (Scheme 1).



5 6a 7a

Scheme 1.

As shown in Table 1, the model coupling/cyclization reaction of **5** with benzylamine **6a** was conducted under the action of 20 mol % of CuI, 40 mol % of L-proline and K_2CO_3 in THF at 70 °C. It was found that after 24 h most of **5** was consumed, and only the cross-coupling product was identified, indicating that the condensative cyclization reaction maybe required higher reaction temperatures. After some trials, we found that the desired cyclization product **7a** could be obtained in moderate yield under the high reaction temperature in DMSO for 3 h after the initial cross-coupling step (Table 1, entry 1). This result was consistent with that reported by Ma.[14a] Switching the base to Cs_2CO_3 or K_3PO_4 provided a fairly poor result (Table 1, entries 2 and 3), while the cross-coupling reaction was failed when K_3PO_4 was used as the base and dmeda (*N*,*N*′-dimethylethanediamine) as the ligand (Table 1, entry 4). *trans*-4-Hydroxy-L-proline was obviously efficient than L-proline as a ligand (Table 1, entry 5). We then carried out copper catalyst screen using *trans*-4-hydroxy-L-proline (40 mol %) as the ligand and K_2CO_3 (2 equiv) as the base in DMSO at 70–130 °C. Three commercially available cuprous salts were evaluated for the coupling reaction, and among them, the catalyst of CuCl gave the most promising result. Heating a mixture of dichloropyrimidin-5-ylcarbamate **5** and amine **6a** together with CuI catalyst in the presence of 40 mol % *trans*-4-hydroxy-L-proline in DMSO at 70–130 °C afforded the expected purin-8-one skeleton **7a** in 56% yield (Table 1, entry 5). When CuBr was used, the yield was increased to 65% (Table 1, entry 6), while the best yield was observed when CuCl was employed (81%, Table 1, entry 7). It was demonstrated that certain cuprous salts play important roles for rate accelerations in the cross-coupling reaction. The amino-acid ligands are thought to increase catalyst solubility and stability and to prevent aggregation of the metal.[19] It was clear that the optimized reaction condition was to use 20 mol % CuCl in combination of 40 mol % *trans*-4-hydroxy-L-proline as the ligand, K_2CO_3 as the base and DMSO as the solvent.

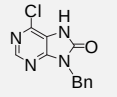
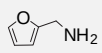
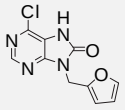
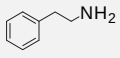
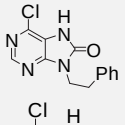
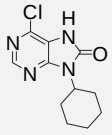
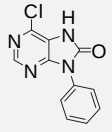
To explore the scope and limits of the coupling reaction of dichloropyrimidin-5-ylcarbamate **5** with amines, other amines **6b–e** were tested under the above optimized conditions, and the results are summarized in Table 2. We were pleased to find that aliphatic amines worked well for this reaction (Table 2, entries 1–4), but it was failed with aromatic amines (Table 2, entry 5), even under microwave irradiation. For the cyclization reaction, sterically hindered amines generally required longer reaction times (Table 2, entry 4).

Table 1
Synthesis of *N*-benzyl-6-chloropurin-8-one **7a**[a]

Entry	CuX	Ligand	Base	Yield[b] (%)
1	CuI	L-proline	K_2CO_3	41
2	CuI	L-proline	Cs_2CO_3	20
3	CuI	L-proline	K_3PO_4	22
4	CuI	Dmeda	K_3PO_4	0
5	CuI	*trans*-4-Hydroxy-L-proline	K_2CO_3	56
6	CuBr	*trans*-4-Hydroxy-L-proline	K_2CO_3	65
7	CuCl	*trans*-4-Hydroxy-L-proline	K_2CO_3	81
8	CuCl	*trans*-4-Hydroxy-L-proline	K_3PO_4	48
9	CuCl	L-proline	K_2CO_3	63

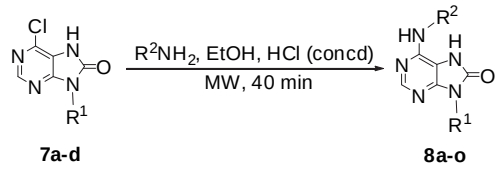
[a] Reaction conditions: chloride **5** (0.5 mmol), amine **6a** (0.55 mmol), CuX (0.1 mmol), ligand (0.2 mmol), base (1.0 mmol), DMSO (2.5 mL), 70 °C, 1 h, then 130 °C, 3 h.
[b] Isolated yield.

Table 2
Synthesis of 9-substituted 6-chloropurin-8-ones **7a–e**[a]

Entry	Amine		Product		Yield[b] (%)
1	$BnNH_2$	**6a**		**7a**	81
2		**6b**		**7b**	62
3		**6c**		**7c**	77
4		**6d**		**7d**	84[c]
5		**6e**		**7e**	0

[a] Reaction conditions: chloride **5** (0.5 mmol), amine **6** (0.55 mmol), CuCl (0.1 mmol), *trans*-4-hydroxy-L-proline (0.2 mmol), K_2CO_3 (1.0 mmol), DMSO (2.5 mL), 70 °C, 1 h, then 130 °C, 3 h.
[b] Isolated yield.
[c] Reaction was conducted at 70 °C for 1 h, and then 130 °C for 5 h.

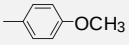
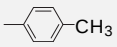
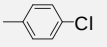
Finally, we examined the amination reaction of **7** in order to obtain a number of structurally diverse purin-8-ones **8** (Scheme 2). It was initially observed that the reaction of **7a** with 1.2 equiv aniline occurred slowly, and after refluxing for 12 h in the presence of concd HCl in *n*-BuOH, only 79% yield of **8a** was afforded. However, performing the reaction with aniline under microwave irradiation at 120 °C dramatically decreased the reaction time from 12 h to 40 min,[20] and the yield was increased to 90% (Table 3, entry 1). We also found that EtOH was better than *n*-BuOH as a solvent. Initially,



7a-d 8a-o

Scheme 2.

Table 3
Synthesis of 6,9-disubstituted purin-8-ones **8a**–**o**[a]

Entry	Product	R^1	R^2	Yield[b] (%)
1	**8a**	–Bn		90
2	**8b**	–Bn		81[c]
3	**8c**	–Bn		74
4	**8d**	–Bn		92
5	**8e**	–Bn		39
6	**8f**	–Bn		70
7	**8g**	–Bn		40
8	**8h**			44
9	**8i**			28
10	**8j**			38
11	**8k**			66
12	**8l**			80
13	**8m**			74
14	**8n**			56
15	**8o**			41

[a] Reaction conditions: **7** (0.5 mmol), R^2NH_2 (0.6 mmol), concd HCl (50 μL), EtOH (3 mL), microwaves, 120 °C, 40 min.
[b] Isolated yield.
[c] Reaction was conducted in *n*-BuOH at 120 °C for 40 min to afford **8b** in 58% yield.

we chose *n*-BuOH as the solvent, **8b** was afforded in 58% isolated yield under microwave irradiation at 120 °C for 40 min, while a better yield was observed when EtOH was employed (Table 3, entry 2).

Under this optimized conditions, a number of 6,9-disubstituted purin-8-ones were synthesized. As shown in Table 3, the anilines bearing chloro-, methyl-, and methoxyl-substitutions were well tolerated (Table 3, entries 2, 3, 6, 12, and 14), although those containing an electron-withdrawing group typically gave lower yields (Table 3, entries 5 and 10), *para*-fluoroaniline gave an exception (Table 3, entry 4). No significant electronic effects were observed for the *ortho*- and *para*-substituted anilines (Table 3, entries 2 and 6). Moreover, 9-(furan-2-ylmethyl) substituted derivatives were afforded in relatively poor yields than other alkyl substituted ones (Table 3, entries 8–10). Except for anilines, we also used aliphatic amine such as cyclohexylamine for the amination reaction under the same reaction conditions, but it provided a fairly poor yield (Table 3, entry 7).

3. Conclusion

In conclusion, we have developed here an efficient and novel synthesis of new 6,9-disubstituted purin-8-ones **8**. Starting from the readily available methyl (4,6-dichloropyrimidin-5-yl) carbamate **5**, CuCl/*trans*-4-hydroxy-L-proline catalyzed coupling and subsequent cyclization reaction was carried out for the construction of 9-substituted 6-chloropurin-8-ones. Introduction of diversity in the position C-6 could be achieved by the microwave-assisted amination reaction of **7** to afford 6,9-disubstituted purin-8-one derivatives. Our synthesis is of interest for the generation of purin-8-ones libraries with *anti*-tumor bioactivities. Work toward this goal is currently in progress in our laboratory.

4. Experimental section

4.1. General informations

^{1}H NMR were recorded on a Bruker AV-300 spectrometer. Chemical shifts are reported in parts per million related to the residual solvent from TMS as internal standard (scale). Multiplicity is designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m), or broad singlet (br s). Infrared (IR) spectra were taken on a Nicolet Impact 410 FT-IR spectro- photometer as KBr pellets. Mass spectra (MS) were measured on a Finnigan Shimadzu GC–MS mass spectrometer. Melting points were measured in a hot stage microscope. Elemental analyses are within ±0.5% of theoretical values and were done by China Pharmaceutical University. All reactions were monitored by HPTLC using UV light. Column chromatography was completed on silica gel (100–200 mesh) made in Qingdao Haiyang Chemical Co. Ltd.

4.2. Experimental details and spectroscopic data

*4.2.1. Methyl (4,6-dichloropyrimidin-5-yl) carbamate (**5**)*[18]. The product was afforded by the procedure described by Gerhard and Felix as a light yellow solid in 76% isolated yield. Mp 92–93 °C; IR (KBr): 3213, 1701, 1536, 1513, 1415, 1390 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.38 (s, 1H), 8.69 (s, 1H) ppm; MS (EI) *m*/*z* 221 (M^+).

General procedure A for the synthesis of 9-substituted 6-chloropurin-8-ones 7a–d from dichloropyrimidin-5-ylcarbamate 5: A two-neck bottle was charged with dichloropyrimidin-5-ylcarbamate **5** (110 mg, 0.5 mmol), CuCl (10 mg, 0.1 mmol), *trans*-4-hydroxy-L-proline (26 mg, 0.2 mmol), and K_2CO_3 (138 mg, 1.0 mmol), backfilled with N_2 atmosphere. Amine **6** (0.55 mmol) and DMSO (2.5 mL) were successively added. The reaction mixture was stirred at 70 °C until the coupling was completed detected by TLC. The solution was then heated at 130 °C until the coupling product was consumed monitored by TLC. The cold mixture was partitioned between EtOAc (20 mL) and saturated NH_4Cl (20 mL). The organic layer was washed with brine (1×20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether 1:3) to provide the desired product **7** (Table 2).

*4.2.2. 9-Benzyl-6-chloro-7H-purin-8(9H)-one (**7a**).* The general procedure A was followed for the synthesis and purification giving a light yellow solid in 81% isolated yield. Mp 250–251 °C; IR (KBr): 3407, 1712, 1634, 1587, 1495, 733, 696 cm^{-1}; ^{1}H NMR (300 MHz,

DMSO-d_6): δ 5.02 (s, 2H), 7.28–7.34 (m, 5H), 8.44 (s, 1H), 12.22 (br s, 1H) ppm; MS (EI) m/z 260 (M^+).

*4.2.3. 6-Chloro-9-(furan-2-ylmethyl)-7H-purin-8(9H)-one (**7b**).* The general procedure A was followed for the synthesis and purification giving a light yellow solid in 62% isolated yield. Mp 217–218 °C; IR (KBr): 3393, 1712, 1633, 1584, 1486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.15 (s, 2H), 6.33–6.48 (m, 2H), 7.36 (s, 1H), 8.56 (s, 1H), 9.02 (s, 1H) ppm; MS (EI) m/z 250 (M^+).

*4.2.4. 6-Chloro-9-phenethyl-7H-purin-8(9H)-one (**7c**).* The general procedure A was followed for the synthesis and purification giving a light yellow solid in 77% isolated yield. Mp 204–205 °C; IR (KBr): 3381, 1712, 1633, 1583, 1491, 733, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.04 (t, J=7.2 Hz, 2H), 4.06 (t, J=7.2 Hz, 2H), 7.16–7.28 (m, 5H), 8.42 (s, 1H), 12.04 (br s, 1H) ppm; MS (EI) m/z 274 (M^+).

*4.2.5. 6-Chloro-9-cyclohexyl-7H-purin-8(9H)-one (**7d**).* The general procedure A was followed for the synthesis and purification giving a light yellow solid in 84% isolated yield. Mp 252–254 °C; IR (KBr): 3415, 1708, 1631, 1574, 1478 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.16–1.38 (m, 3H), 1.64–1.84 (m, 5H), 2.16–2.24 (m, 2H), 4.17 (t, J=9.0 Hz, 1H), 8.43 (s, 1H), 12.05 (br s, 1H) ppm; MS (EI) m/z 252 (M^+).

General procedure B for the synthesis of 6,9-disubstituted purin-8-ones 8a–o: To a solution of **7** (0.5 mmol) in EtOH (3 mL) were added 12 M concd HCl (50 μL) and aniline or cyclohexylamine (0.60 mmol). The vial was sealed and heated by microwave at 120 °C for 40 min. After cooling to rt, the obtained crystals were collected by filtration and washed with cold EtOH to afford the pure product **8** (Table 3).

*4.2.6. 9-Benzyl-6-(phenylamino)-7H-purin-8(9H)-one (**8a**).* The general procedure B was followed for the synthesis and purification giving a light yellow solid in 90% isolated yield. Mp 297–299 °C; IR (KBr): 3415, 3363, 1699, 1646, 1622, 1594, 1500, 1467, 1437, 747, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.99 (s, 2H), 7.02 (t, J=7.2 Hz, 1H), 7.28–7.37 (m, 7H), 7.68 (d, J=7.8 Hz, 2H), 8.26 (s, 1H), 8.70 (s, 1H), 10.41 (s, 1H) ppm; MS (EI) m/z 317 (M^+). Anal. Calcd for $C_{18}H_{15}ON_5$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.26; H, 4.49; N, 21.70.

*4.2.7. 9-Benzyl-6-(4-methoxyphenylamino)-7H-purin-8(9H)-one (**8b**).* The general procedure B was followed for the synthesis and purification giving a white solid in 81% isolated yield. Mp 283–284 °C; IR (KBr): 3355, 1698, 1647, 1619, 1586, 1511, 1461, 1432, 1411, 1382, 822, 776, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 3H), 4.98 (s, 2H), 6.93 (d, J=9.0 Hz, 2H), 7.25–7.36 (m, 5H), 7.55 (d, J=9.0 Hz, 2H), 8.20 (s, 1H), 8.58 (s, 1H), 10.32 (br s, 1H) ppm; MS (EI) m/z 347 (M^+). Anal. Calcd for $C_{19}H_{17}O_2N_5$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.98; H, 4.74; N, 20.01.

*4.2.8. 9-Benzyl-6-(3-chlorophenylamino)-7H-purin-8(9H)-one (**8c**).* The general procedure B was followed for the synthesis and purification giving an off-white solid in 74% isolated yield. Mp 322–324 °C; IR (KBr): 3413, 3354, 1698, 1650, 1622, 1590, 1472, 1431, 1406, 768, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.99 (s, 2H), 7.06 (d, J=6.9 Hz, 1H), 7.32–7.45 (m, 7H), 8.00 (s, 1H), 8.32 (s, 1H), 8.92 (s, 1H), 10.42 (s, 1H) ppm; MS (EI) m/z 351 (M^+). Anal. Calcd for $C_{18}H_{14}ON_5Cl$: C, 61.46; H, 4.01; N, 19.91. Found: C, 61.62; H, 3.94; N, 19.66.

*4.2.9. 9-Benzyl-6-(4-fluorophenylamino)-7H-purin-8(9H)-one (**8d**).* The general procedure B was followed for the synthesis and purification giving an off-white solid in 92% isolated yield. Mp 306–308 °C; IR (KBr): 3360, 1697, 1647, 1621, 1597, 1510, 1465, 1432, 1412, 829, 781, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.98 (s, 2H), 7.19 (t, J=8.7 Hz, 2H), 7.25–7.32 (m, 5H), 7.65–7.66 (m, 2H), 8.25 (s, 1H), 8.74 (s, 1H), 10.37 (s, 1H) ppm; MS (EI) m/z 335 (M^+). Anal. Calcd for $C_{18}H_{14}ON_5F$: C, 64.47; H, 4.21; N, 20.88. Found: C, 64.49; H, 4.14; N, 20.76.

*4.2.10. 9-Benzyl-6-(3-chloro-4-fluorophenylamino)-7H-purin-8(9H)-one (**8e**).* The general procedure B was followed for the synthesis and purification giving a white solid in 39% isolated yield. Mp 318–320 °C; IR (KBr): 3401, 3352, 1698, 1645, 1618, 1598, 1587, 1493, 1462, 1408, 806, 778, 747, 718, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.99 (s, 2H), 7.25–7.48 (m, 7H), 8.06 (dd, J=2.7, 2.4 Hz, 1H), 8.30 (s, 1H), 8.91 (s, 1H), 10.38 (br s, 1H) ppm; MS (EI) m/z 369 (M^+). Anal. Calcd for $C_{18}H_{13}ON_5FCl$: C, 58.47; H, 3.54; N, 18.94. Found: C, 58.88; H, 3.83; N, 18.53.

*4.2.11. 9-Benzyl-6-(2-methoxyphenylamino)-7H-purin-8(9H)-one (**8f**).* The general procedure B was followed for the synthesis and purification giving an off-white solid in 70% isolated yield. Mp 274–276 °C; IR (KBr): 3333, 3148, 1712, 1663, 1626, 1587, 1488, 1453, 747, 699 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H), 4.98 (s, 2H), 6.94 (t, J=7.5 Hz, 1H), 7.04–7.06 (m, 2H), 7.30–7.34 (m, 5H), 8.08 (s, 1H), 8.14 (d, J=7.5 Hz, 1H), 8.22 (s, 1H), 11.08 (s, 1H) ppm; MS (EI) m/z 347 (M^+). Anal. Calcd for $C_{19}H_{17}O_2N_5$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.83; H, 4.89; N, 19.94.

*4.2.12. 9-Benzyl-6-(cyclohexylamino)-7H-purin-8(9H)-one (**8g**).* The general procedure B was followed for the synthesis and purification giving a white solid in 40% isolated yield. Mp 244–246 °C; IR (KBr): 3414, 3340, 1692, 1646, 1620, 1598, 1456, 699 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.21–1.37 (m, 5H), 1.60–1.96 (m, 5H), 3.93 (s, 1H), 4.92 (s, 2H), 6.32 (d, J=7.5 Hz, 1H), 7.29 (s, 5H), 8.08 (s, 1H), 10.20 (s, 1H) ppm; MS (EI) m/z 323 (M^+). Anal. Calcd for $C_{18}H_{21}ON_5$: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.42; H, 6.97; N, 21.54.

*4.2.13. 6-(4-Chlorophenylamino)-9-(furan-2-yl-methyl)-7H-purin-8(9H)-one (**8h**).* The general procedure B was followed for the synthesis and purification giving a pink solid in 44% isolated yield. Mp 314–316 °C; IR (KBr): 3417, 3339, 1698, 1649, 1622, 1591, 1493, 1460, 1413 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.98 (s, 2H), 6.36–6.40 (m, 2H), 7.38 (d, J=9.0 Hz, 2H), 7.57 (s, 1H), 7.74 (d, J=9.0 Hz, 2H), 8.29 (s, 1H), 9.05 (s, 1H), 10.56 (s, 1H) ppm; MS (EI) m/z 341 (M^+). Anal. Calcd for $C_{16}H_{12}O_2N_5Cl$: C, 56.23; H, 3.54; N, 20.49. Found: C, 56.20; H, 3.66; N, 20.16.

*4.2.14. 6-(p-Toluidino)-9-(furan-2-ylmethyl)-7H-purin-8(9H)-one (**8i**).* The general procedure B was followed for the synthesis and purification giving a white solid in 28% isolated yield. Mp 291–293 °C; IR (KBr): 3415, 3352, 1703, 1649, 1624, 1605, 1585, 1513, 1461, 1416, 1384 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H), 4.97 (s, 2H), 6.36–6.40 (m, 2H), 7.15 (d, J=8.4 Hz, 2H), 7.56 (d, J=8.4 Hz, 2H), 7.57 (s, 1H), 8.25 (s, 1H), 8.61 (s, 1H), 10.35 (s, 1H) ppm; MS (EI) m/z 321 (M^+). Anal. Calcd for $C_{17}H_{15}O_2N_5$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.46; H, 4.67; N, 21.50.

*4.2.15. 6-(3-Chloro-4-fluorophenylamino)-9-(fu-ran-2-ylmethyl)-7H-purin-8(9H)-one (**8j**).* The general procedure B was followed for the synthesis and purification giving a red solid in 38% isolated yield. Mp 330–332 °C; IR (KBr): 3414, 3353, 1702, 1647, 1625, 1598, 1495, 1466, 1424, 807, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.98 (s, 2H), 6.36–6.41 (m, 2H), 7.39–7.44 (m, 2H), 7.58 (s, 1H), 8.07 (dd, J=2.4, 2.1 Hz, 1H), 8.31 (s, 1H), 8.91 (s, 1H), 10.36 (s, 1H) ppm; MS (EI) m/z 359 (M^+). Anal. Calcd for $C_{16}H_{11}O_2N_5FCl$: C, 53.42; H, 3.08; N, 19.47. Found: C, 53.54; H, 3.53; N, 19.11.

*4.2.16. 9-Phenethyl-6-(phenylamino)-7H-purin-8(9H)-one (**8k**).* The general procedure B was followed for the synthesis and purification giving a white solid in 66% isolated yield. Mp 269–271 °C; IR (KBr):

3358, 3222, 1705, 1645, 1626, 1590, 1498, 1471, 1435, 1402, 751, 703, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.05 (t, J=7.5 Hz, 2H), 4.03 (t, J=7.5 Hz, 2H), 7.02 (t, J=7.2 Hz, 1H), 7.19–7.36 (m, 7H), 7.71 (d, J=8.1 Hz, 2H), 8.26 (s, 1H), 8.81 (s, 1H), 10.22 (br s, 1H) ppm; MS (EI) m/z 331 (M^+). Anal. Calcd for $C_{19}H_{17}ON_5$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.63; H, 5.03; N, 20.93.

*4.2.17. 6-(2-Methoxyphenylamino)-9-phenethyl-7H-purin-8(9H)-one (**8l**).* The general procedure B was followed for the synthesis and purification giving a white solid in 80% isolated yield. Mp 270–272 °C; IR (KBr): 3319, 3156, 1715, 1626, 1587, 1537, 1488, 1450, 1401, 752, 701 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.04 (t, J=7.2 Hz, 2H), 3.87 (s, 3H), 4.01 (t, J=7.2 Hz, 2H), 6.93–7.05 (m, 3H), 7.18–7.26 (m, 5H), 8.04 (s, 1H), 8.14 (d, J=7.5 Hz, 1H), 8.21 (s, 1H), 10.96 (br s, 1H) ppm; MS (EI) m/z 361 (M^+). Anal. Calcd for $C_{20}H_{19}O_2N_5 \cdot 0.2H_2O$: C, 65.81; H, 5.36; N, 19.19. Found: C, 65.76; H, 5.00; N, 19.52.

*4.2.18. 9-Cyclohexyl-6-(phenylamino)-7H-purin-8(9H)-one (**8m**).* The general procedure B was followed for the synthesis and purification giving a white solid in 74% isolated yield. Mp 236–238 °C; IR (KBr): 3400, 3333, 1697, 1645, 1596, 1497, 1467, 743, 686 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.18–1.42 (m, 3H), 1.66–1.85 (m, 5H), 2.22–2.36 (m, 2H), 4.17 (t, J=12.0 Hz, 1H), 7.02 (t, J=7.2 Hz, 1H), 7.34 (t, J=7.8 Hz, 2H), 7.69 (d, J=8.1 Hz, 2H), 8.26 (s, 1H), 8.68 (s, 1H), 10.36 (s, 1H) ppm; MS (EI) m/z 309 (M^+). Anal. Calcd for $C_{17}H_{19}ON_5$: C, 66.00; H, 6.19; N, 22.64. Found: C, 65.68; H, 6.47; N, 22.50.

*4.2.19. 6-(4-Chlorophenylamino)-9-cyclohexyl-7H-purin-8(9H)-one (**8n**).* The general procedure B was followed for the synthesis and purification giving a white solid in 56% isolated yield. Mp 282–284 °C; IR (KBr): 3397, 1702, 1663, 1641, 1592, 1537, 1493, 1454, 823 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.18–1.42 (m, 3H), 1.70–1.86 (m, 5H), 2.22–2.34 (m, 2H), 4.17 (t, J=12.0 Hz, 1H), 7.38 (d, J=9.0 Hz, 2H), 7.70 (d, J=9.0 Hz, 2H), 8.27 (s, 1H), 8.78 (s, 1H), 10.30 (s, 1H) ppm; MS (EI) m/z 343 (M^+). Anal. Calcd for $C_{17}H_{18}ON_5Cl$: C, 59.39; H, 5.28; N, 20.37. Found: C, 59.18; H, 5.64; N, 20.66.

*4.2.20. 9-Cyclohexyl-6-(2-methoxyphenylamino)-7H-purin-8(9H)-one (**8o**).* The general procedure B was followed for the synthesis and purification giving a white solid in 41% isolated yield. Mp 244–246 °C; IR (KBr): 3314, 3142, 1702, 1626, 1584, 1486, 1462, 746 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.18–1.42 (m, 3H), 1.69–1.86 (m, 5H), 2.23–2.34 (m, 2H), 3.88 (s, 3H), 4.17 (t, J=11.4 Hz, 1H), 6.92–7.08 (m, 3H), 8.01 (s, 1H), 8.14 (d, J=7.8 Hz, 1H), 8.21 (s, 1H), 10.98 (s, 1H) ppm; MS (EI) m/z 339 (M^+). Anal. Calcd for $C_{18}H_{21}O_2N_5$: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.68; H, 6.68; N, 20.42.

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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.2010.04.106.

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