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# Synthesis, biological activity, and SAR of antimycobacterial 2- and 8-substituted 6-(2-furyl)-9-(*p*-methoxybenzyl)purines

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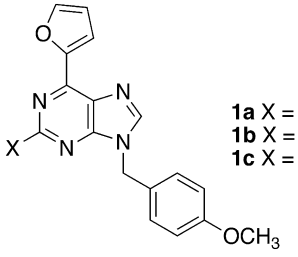
**Abstract**—A number of 6-(2-furyl)-9-(*p*-methoxybenzyl)purines carrying a variety of substituents in the 2- or 8-position have been synthesized and their ability to inhibit growth of *Mycobacterium tuberculosis* in vitro has been determined. It is demonstrated that sterical hindrance in the purine 8-position reduces activity and that C-8 should be unsubstituted. In the purine 2-position small, hydrophobic substituents are beneficial. The electronic properties of the 2-substituents appear to have only a minor influence on bioactivity. The compounds studied exhibit low toxicity toward mammalian cells (VERO cells) and are essentially inactive toward *Staphylococcus aureus* and *Escherichia coli*. The most active and selective antimycobacterial in the series detected to date is the novel 2-methyl-6-furyl-9-(*p*-methoxybenzyl)purine with MIC = 0.20 μg/mL against *M. tuberculosis* and $IC_{50}$ against VERO cells >62.5 μg/mL. Also the novel 2-fluoro analog and the previously known 2-chloro compound, both with MIC = 0.39 μg/mL, are highly interesting drug candidates.


## 1. Introduction

We have previously reported that certain 6,9-disubstituted purines are potent inhibitors of *Mycobacterium tuberculosis* (*Mtb*) in vitro.[1] Our antimycobacterial purines display several properties which make them highly interesting as potential drugs against tuberculosis; high selectivity toward *Mtb* compared to other microorganisms, activity against several drug-resistant strains of *Mtb*, generally low toxicity toward mammalian cells, and ability to affect *Mtb* inside macrophages. Even though the mode of action for this class of antimycobacterials has not yet been established, our findings point toward a novel target. For treatment of mycobacterial infections, organism-specific agents, preferably with a novel mechanism of action in order to avoid development of resistance as long as possible, are recommended.[2] WHO[3] and others[4] list antimycobacterial purines among compounds that should be pursued further (discovery research) as potential TB-drugs.[5]

In preceding papers, we have discussed SAR for the substituent in the purine 6-position[1e] and at *N*-9[1b,d] for our class of antimycobacterial purines.[6] The most active compounds contain an electron rich aryl group, preferably 2-furyl-, in the purine 6-position, and a benzyl group at *N*-9. The benzylic moiety should not be substituted in the *ortho*- or α-positions, but several substituents in the *meta*- and *para*-positions are well tolerated. A *p*-methoxy group seems to be very favorable. This substituent generally increases antimycobacterial activity and decreases toxicity toward mammalian cell. Some of the most active and selective antimycobacterial purines, **1a** and **1b**, are shown in Figure 1. As can be seen from Figure 1, the introduction of chlorine in the purine 2-position significantly enhances antimycobacterial activity in vitro, and the same trend is seen for several 6-aryl-9-benzylpurines.[1] We have now further explored synthesis, antibacterial activity, and SAR for 2-substituted




**1a** X = H; MIC *M. tuberculosis* 1.56 μg/mL
**1b** X = Cl; MIC *M. tuberculosis* 0.39 μg/mL
**1c** X = F

**Figure 1.** Structure of potent antimycobacterial purines.

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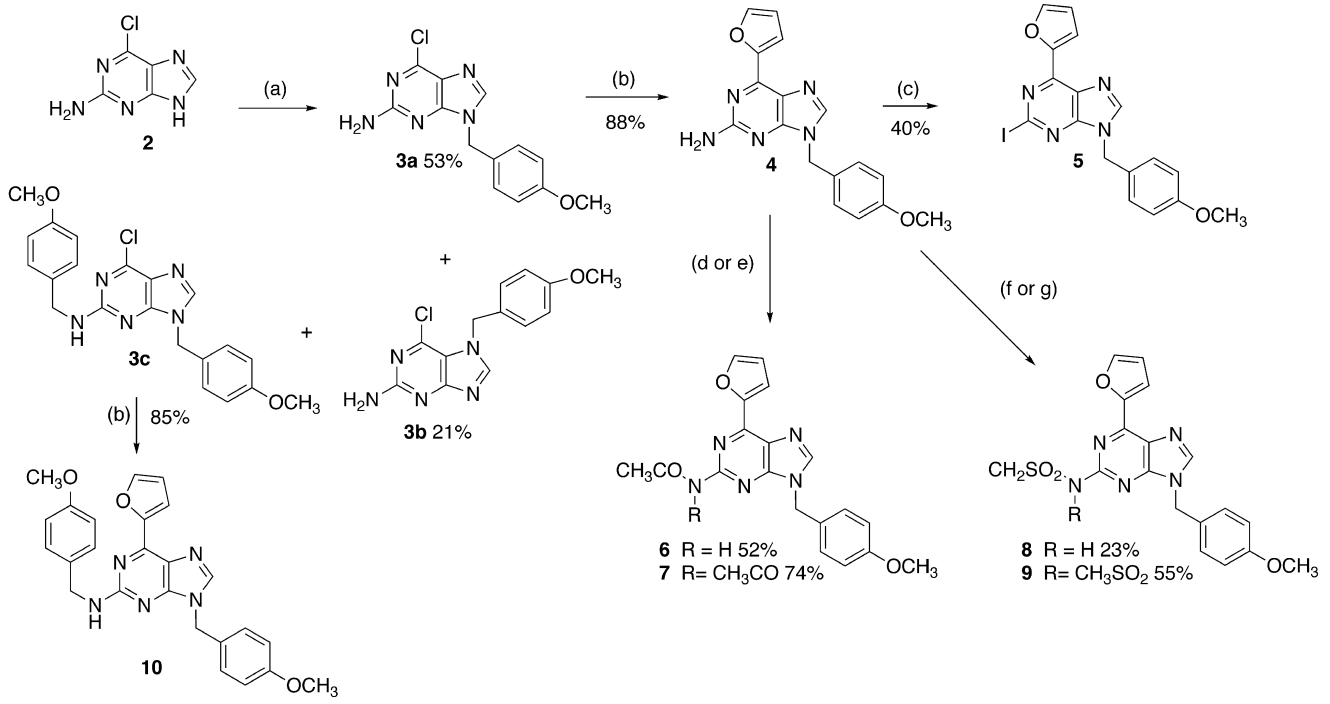
6-(2-furyl)-9-(*p*-methoxybenzyl)purines. Analogs substituted at C-8 have been synthesized and evaluated as antimycobacterials as well.

## 2. Chemistry

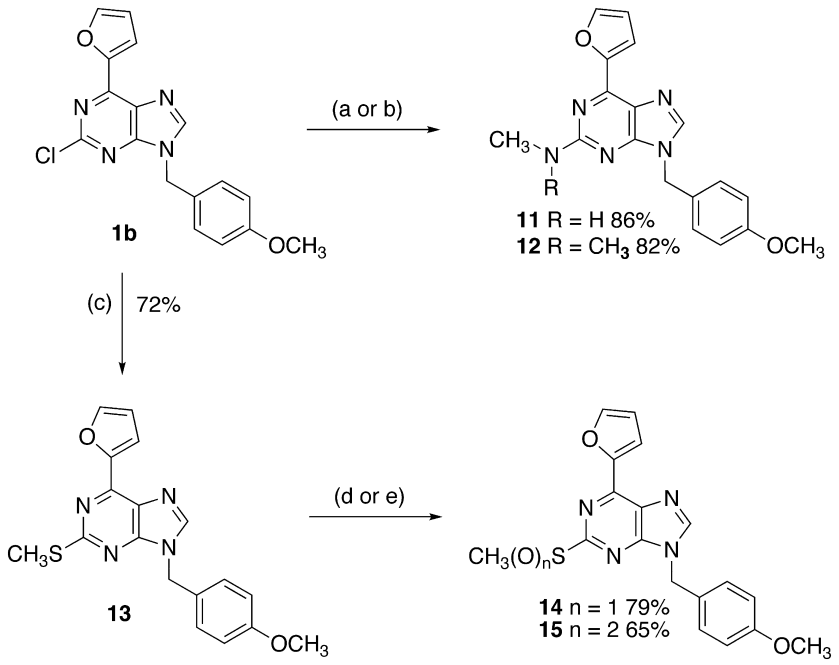
Because the introduction of chlorine in the 2-position of 6-aryl-9-benzylpurines generally enhances antimycobacterial activity (see above), we were interested in the antimycobacterial activity of other 2-halopurines. We have recently reported the synthesis of the 2-fluoropurine **1c**[7] (Fig. 1), and that of the 2-iodo analog **5** is shown in Scheme 1. N-Alkylation of 2-amino-6-chloropurine **2** with 4-methoxybenzyl chloride gave the desired compound **3a** together with the *N*-7 alkylated isomer **3b** (Scheme 1). Minor amounts of the dialkylated product **3c** could also be isolated. Compound **3a** was converted to the 2-amino-6-(2-furyl)purine **4**, a key compound in the syntheses of several 2-substituted 6-(2-furyl)purines (Scheme 1). The 2-iodopurine **5** was prepared from the aminopurine **4** by treatment with isoamylnitrite and diiodomethane. However, compound **5** was only isolated in 40% yield due to tedious separation from the 2-isoamyloxypurine formed as a by-product under these reaction conditions. Attempts to prepare the corresponding 2-bromopurine by the bromination method published by Nair,[8] or several modifications of the original procedure, failed because complete separation of the desired product from 2-alkoxypurine by-products was not achieved. Synthesis of the bromo analog, or the 2-iodo compound **5**, employing the same strategy as in the reported synthesis of 2-fluoropurine **1c**, was also not successful.[7] The aminopurine **4** could be mono- or diacylated or sulfonylated depending on the reaction conditions to give compounds **6**–**9**. Coupling of the $N^2$-benzylated purine **3c** with 2-furyl(tributyl)tin led to compound **10**.

Synthesis of 2-alkylamino-6-furylpurines by reductive acylation of compound **4**, as reported for the preparation of other 2-alkylaminopurines,[9] met with little success. Instead we prepared the methyl- and dimethylaminopurines **11** and **12** from the 2-chloropurine **1b** (Scheme 2). Compound **1b** was reacted with methylamine to give the *N*-methylaminopurine **11** and reaction with the HCl salt of glycine methylester gave compound **12**. A similar reaction on a 2-chloropurine is reported to take place at room temperature,[10] but in our case a reaction temperature of 85 °C was required. Reaction of compound **1b** with sodium methylthiolate gave the 2-methylthio derivative **13**, which could be oxidized with mCPBA selectively to the sulfoxide **14** or sulfone **15** depending on the reaction conditions.

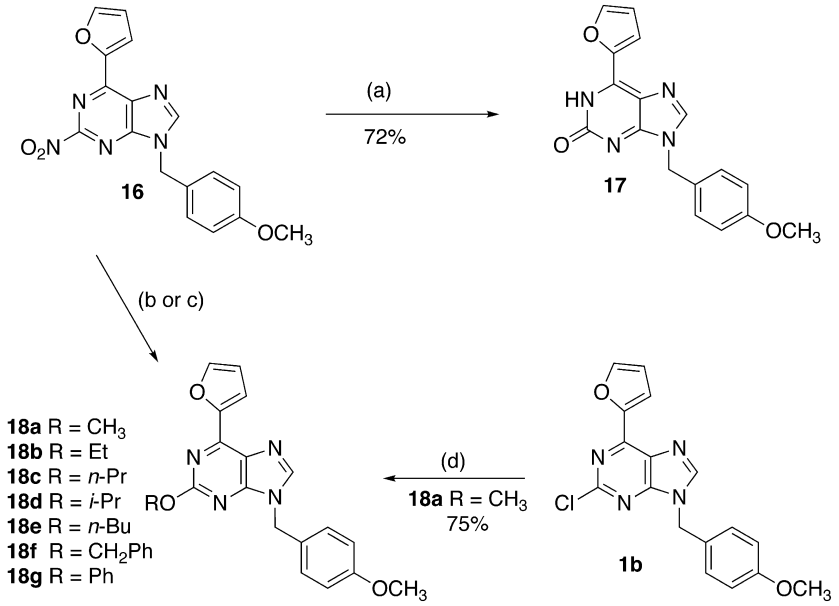
We have recently reported the synthesis of the 2-nitropurine **16** and its facile conversion to the 2-fluoropurine **1c**.[7] We report here that nitropurine **16** can also easily be converted to other 2-substituted purines (Scheme 3). Treatment of compound **16** with tetrabutylammonium hydroxide at room temperature gave the 2-oxopurine **17**. 2-Oxopurines are traditionally synthesized under more harsh conditions, that is, treatment of 2-chloropurines with hydrochloric acid, cleavage of certain alkoxypurines, treatment of methylthiopurines with hydrogen peroxide, or diazotation–hydrolysis of aminopurines.[11] Alternatively, 2-oxopurines are available in several steps from cytosine.[12]




**Scheme 1.** Reagents and conditions: (a) *p*-$CH_3O$–$C_6H_4$–$CH_2Cl$, $K_2CO_3$, DMF; (b) (2-furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (c) $CH_2I_2$, isoamylONO, 85 °C; (d) $Ac_2O$, $Et_3N$, toluene, Δ; (e) $Ac_2O$, toluene, Δ; (f) $CH_3SO_2Cl$, pyridine; (g) $CH_3SO_2Cl$, DMAP, $Et_3N$, $CH_2Cl_2$.




**Scheme 2.** Reagents and conditions: (a) $CH_3NH_2$, $H_2O$, THF, 85 °C; (b) $H_2NCH_2CO_2CH_3$·HCl, $Et_3N$, DMF, 85 °C; (c) $CH_3SNa$, DMF, 90 °C; (d) *m*-CPBA (1.0 equiv), $CH_2Cl_2$, −10 °C; (e) *m*-CPBA (2.3 equiv), $CH_2Cl_2$.




**Scheme 3.** Reagents and conditions: (a) $Bu_4NOH$, $H_2O$, THF; (b) ROH, KF; (c) ROH, KCN; (d) $CH_3ONa$, $CH_3OH$, Δ.

2-Chloropurine **1b** could be converted to the corresponding 2-methoxypurine **18a** by treatment with sodium methoxide in methanol at reflux temperature (Scheme 3). Since it is known that a 2-nitro group in certain purines have been displaced by nucleophiles, such as methanol,[13] we also explored the possibility of converting nitropurine **16** into a variety of 2-alkoxypurines **18**. The results are presented in Table 1. 2-Nitropurine **16** did not react with methanol at room temperature, but compound **16** was easily converted to the 2-methoxyderivative **18** when potassium fluoride or potassium cyanide was added. The reaction with methanol took place at ambient temperature; the other alcohols explored required heating. Both primary and secondary alkoxy groups, as well as the phenoxy group, could be introduced to the purine 2-position. Generally the conversion was faster in the presence of potassium cyanide compared to potassium fluoride, but both salts could be used to synthesize compounds **18** in generally high yields. Only very minor amounts of 2-fluoro- or 2-cyanopurines were formed in these reactions.

Purines **19**, carrying an alkyl-, alkenyl- or aryl-substituent in the 2-position, were easily available by Stille- or

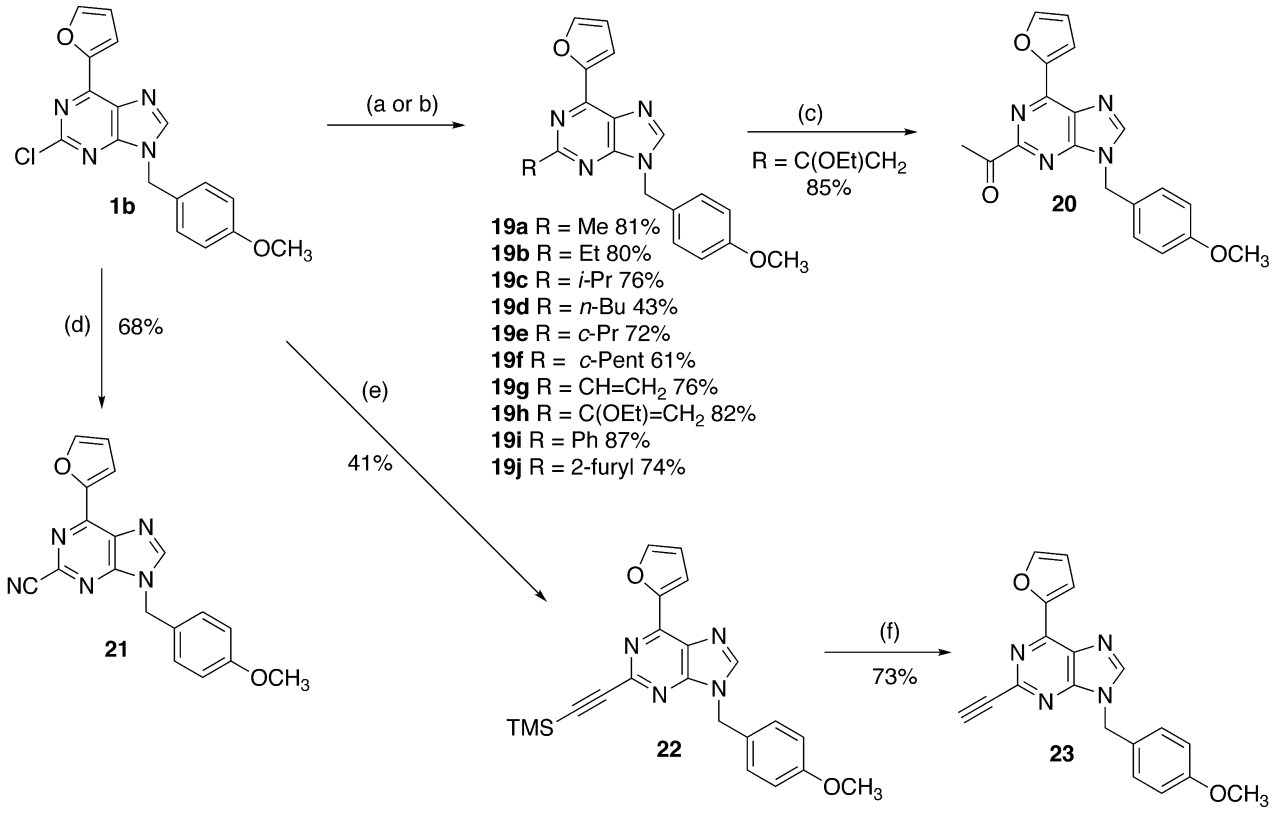
**Table 1.** Synthesis of 2-alkoxypurines **18** from 2-nitropurine **16**

| ROH | Additive | Temperature (°C) | Time (h) | Yield (%), **18**[a] |
|---|---|---|---|---|
| $CH_3OH$ | None | 50 | 24 | No react. |
| $CH_3OH$ | KF, satd soln, ca. 56 equiv | rt | 50 | 87, **18a** |
| $CH_3OH$ | KCN, satd soln, ca. 37 equiv | rt | 1.5 | 75, **18a** |
| $CH_3OH$ | KF, satd soln, ca. 56 equiv | 50 | 6 | 93, **18a** |
| $CH_3OH$ | KCN, satd soln, ca. 37 equiv | 50 | 1.5 | 98, **18a** |
| $CH_3OH$ | KF, 4 equiv | 50 | 50 | 16, **18a** |
| $CH_3OH$ | KCN, 4 equiv | 50 | 1.5 | 90, **18a** |
| EtOH | KF, satd soln, ca. 6 equiv | 70 | 48 | 82, **18b** |
| EtOH | KCN, satd soln, ca. 1.8 equiv | 50 | 4 | 94, **18b** |
| *n*-PrOH | KF, 4 equiv | 97 (Δ) | 6 | 74, **18c** |
| *n*-PrOH | KCN, 4 equiv | 97 (Δ) | 2 | 94, **18c** |
| *i*-PrOH | KF, 4 equiv | 82 (Δ) | 48 | —[b] |
| *i*-PrOH | KCN, 4 equiv | 82 (Δ) | 48 | 53, **18d** |
| *n*-BuOH | KF, 4 equiv | 100 | 7 | 81, **18e** |
| *n*-BuOH | KCN, 4 equiv | 100 | 24 | 95, **18e** |
| BnOH | KF, 4 equiv | 100 | 2.5 | 71, **18f** |
| BnOH | KCN, 4 equiv | 100 | 21 | 83, **18f** |
| PhOH | KF, 4 equiv | 100 | 21 | 65, **18g** |
| PhOH | KCN, 4 equiv | 100 | 1.5 | 68, **18g** |

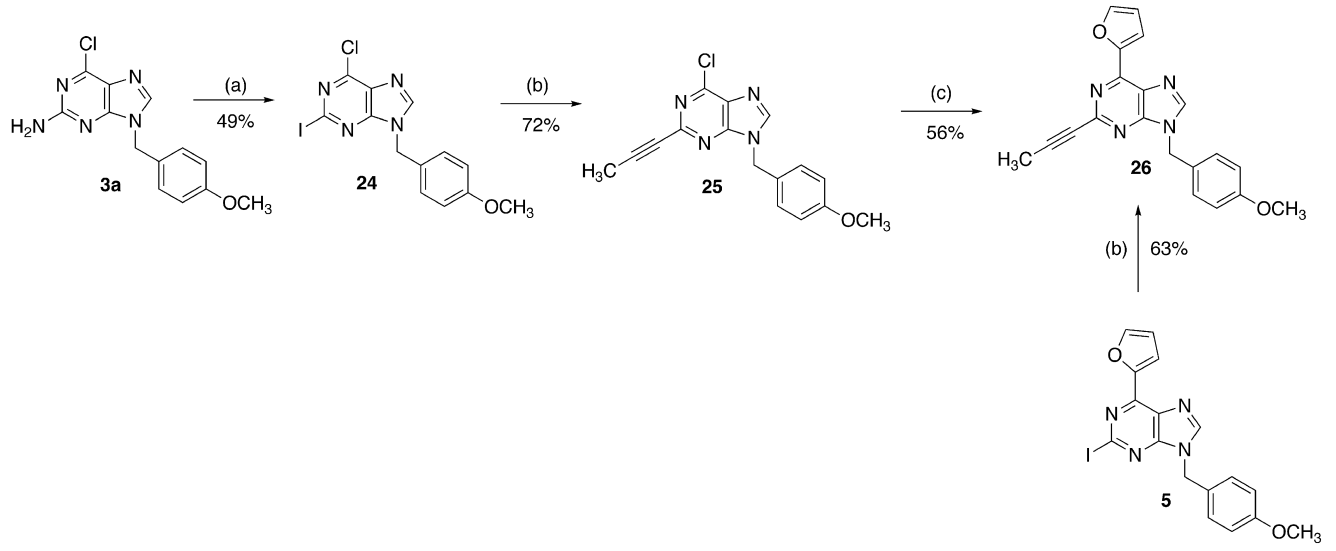
[a] Yield of isolated compound.
[b] Not obtained pure, contaminated with 2-fluoropurine **1c**.

Negishi coupling of 2-chloropurine **1b** with the desired organometallic reagent (Scheme 4).[14] The 2-acetylpurine **20** was formed by hydrolysis of the enol ether **19h**, and 2-cyanopurine **21** was available from compound **1b** by treatment of zinc cyanide in the presence of palladium(0).[15] Sonogashira coupling of compound **1b** with trimethylsilylacetylene, followed by cleavage of the TMS-group, afforded the ethynylpurine **23**.

Elevated temperature (120 °C) was required for the formation of the acetylene **22** (Scheme 4), and Sonogashira coupling of the chloropurine **1b** with propyne was not successful. On the other hand, 2-iodopurines **24** and **5** reacted with propyne in a sealed tube to give alkynes **25** and **26** (Scheme 5). The reaction on the dihalopurine **24** was performed at 0 °C to minimize formation of dipropynylpurine.




**Scheme 4.** Reagents and conditions: (a) RZnX, Pd-complex, THF; (b) $RSnR'_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (c) HCl(aq), acetone; (d) $Zn(CN)_2$, $(Ph_3P)_4Pd$, NMP, 120 °C; (e) TMSC≡CH, $(Ph_3P)_2PdCl_2$, CuI, $Et_3N$, DMF, 120 °C; (f) $K_2CO_3$, MeOH, $CH_2Cl_2$.




**Scheme 5.** Reagents and conditions: (a) $CH_2I_2$, isoamylONO, 85 °C; (b) $CH_3C{\equiv}CH$, $(Ph_3P)_2PdCl_2$, CuI, $Et_3N$, $CH_3CN$; (c) (2-furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C.

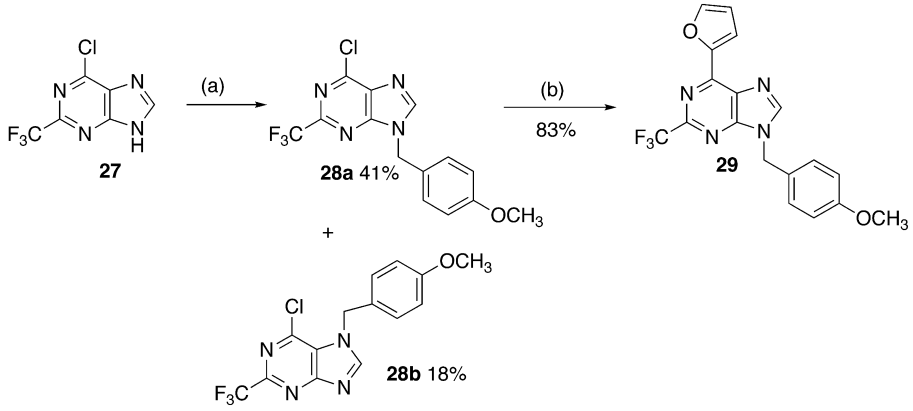
2-Trifluoromethylpurines have been synthesized from the corresponding 2-iodopurines by treatment with '$CF_3Cu$', generated in situ from Zn, $CF_3Br$, and CuI, but the reaction required the extremely toxic co-solvent HMPA.[16] Hence, we decided to prepare the target **29** (Scheme 6) from 6-chloro-2-trifluoromethylpurine **27**[17] by N-alkylation followed by Stille coupling.

After synthesizing 6-furyl-9-(*p*-methoxybenzyl)purines carrying a variety of substituents in the purine 2-position, we turned to synthesis of 8-substituted analogs (Scheme 7). 6-Chloropurine **30** was lithiated at C-8 and trapped with methyl iodide or hexachloroethane to give compound **31**, which was subjected to Stille coupling to give 6-furylpurines **32a** and **32b**. In the synthesis of compound **32b**, mild conditions were used in order to achieve selective coupling in the 8-position,[18] but a small amount of the difurylpurine **32d** was formed. Compound **32b** was converted to the methoxypurine **33**. A minor amount of the oxopurine **34** was also isolated. We believe that compound **34** is formed by cleavage of the methoxypurine **33** and not directly from chloropurine **32b**. We have previously observed low hydrolytic stability of certain other 8-methoxypurines.[19]

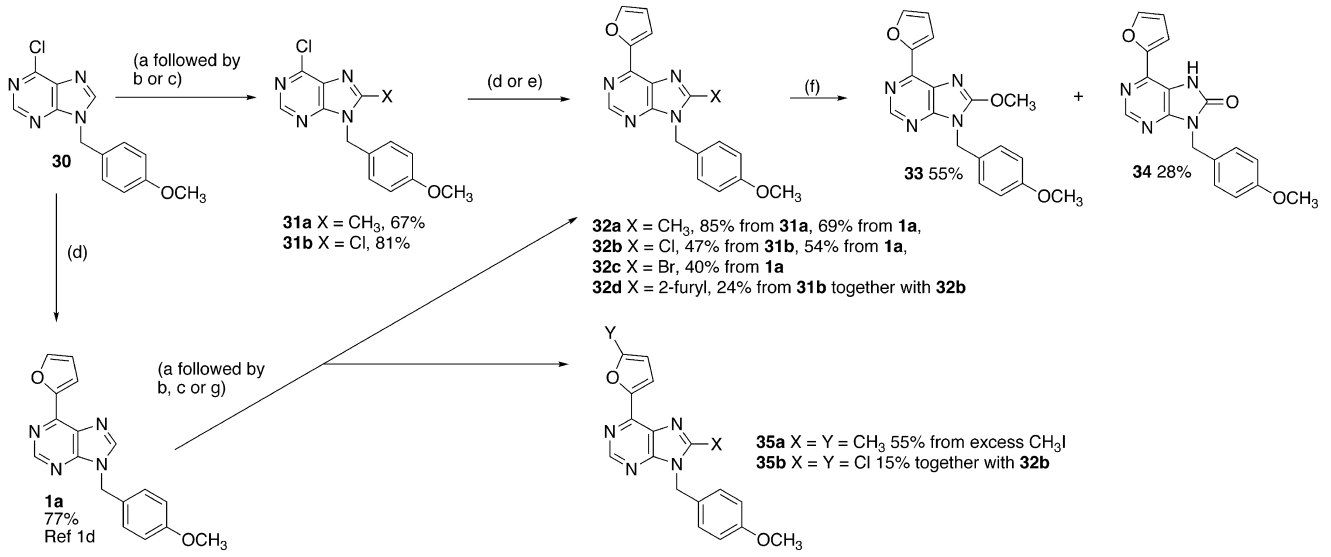
In order to avoid problems with regioselectivity in the cross-coupling of the dichloropurine **31b**, we also synthesized compound **32b** from the furylpurine **1a** by lithiation followed by trapping with hexachloroethane. However lithiation in the furyl ring was also observed and compound **35b** was isolated in minor amounts. Lithiation of compound **1a** followed by trapping with 1,2-dibromo-1,1,2,2-tetrachloroethane gave the 8-bromopurine **32c**. No reaction at the furyl ring could be observed. Also the 8-methylpurine **32a** could be formed selectively from **1a**, and the dimethylated compound was formed when an excess of methyl iodide was used. The total yields of compounds **32a** and **32b** from 6-chloropurine **30** are approximately the same from both synthetic sequences employed. The 8-bromopurine **32c** can only be prepared via the furylpurine **1a**, since couplings on 8-bromo-6-chloropurines take place preferably at C-8.[18]

## 2.1. Biological activity

The 2- and 8-substituted 6-furylpurines were screened for antibacterial activity against *M. tuberculosis* $H_{37}Rv$ and the results are presented in Tables 2 and 3. For




**Scheme 6.** Reagents and conditions: (a) *p*-$CH_3O$–$C_6H_4$–$CH_2Cl$, $K_2CO_3$, DMF; (b) (2-furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C.




**Scheme 7.** Reagents and conditions: (a) LDA, THF, −78 °C; (b) $CH_3I$, THF, −78 °C, rt; (c) $C_2Cl_6$, THF, −78 °C; (d) (2-furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (e) (2-furyl)$SnBu_3$, $[(2\text{-furyl})_3P]_4Pd$, DMF, 50 °C; (f) $CH_3ONa$, $CH_3OH$, Δ; (g) $CBrCl_2CBrCl_2$, THF, −78 °C, rt.

compounds displaying MIC against *Mtb* ⩽ 6.25 mg/mL, toxicity toward mammalian cells (VERO cells) was also determined (Tables 2 and 3). Selected compounds were screened against *Staphylococcus aureus* and *Escherichia coli* as well (Tables 2 and 3).

Several 2-substituted purines exhibited inhibitory activity against *Mtb* (Table 2). Compared to the previously examined 2-chloropurine **1b**, fluoropurine **1c** was equally active (MIC = 0.39 μg/mL) and the methylpurine **19a** slightly more active (MIC = 0.20 μg/mL). Also the introduction of a methoxy (**18a** MIC = 0.78 μg/mL) and a methylthio group (**13a** MIC = 0.78 μg/mL) in the 2-position increased antimycobacterial activity somewhat compared to the unsubstituted compound **1a** (MIC = 1.56 μg/mL). The 2-ethylpurine **19b** was found to be equally active as the parent compound **1a**. For all 2-substituted compounds examined, the MICs against other bacteria, *S. aureus* (Gram positive) and *E. coli* (Gram negative), were >32 μg/mL. This confirms our previous observation that the 6-aryl-9-benzylpurines are highly selective against *Mtb*.

In most cases examined, the active 2-substituted antimycobacterial purines exhibited low toxicity toward mammalian cells (VERO cells). For 2-methylpurine **19a**, a selectivity index ($IC_{50}$ VERO cells : MIC *Mtb*) greater than 313 was calculated. The 2-ethynylpurine **23** was, however, highly toxic to VERO cells ($IC_{50}$ = 0.14 μg/mL). Also the ethenylpurine **19g** and methylthiopurine **13a** displayed relatively high toxicity ($IC_{50}$ < 10 μg/mL). It is worth mentioning that we previously observed an increase in toxicity toward VERO cells when the methylthio substituent was introduced in the benzylic *para*-position of related structures.[1d]

Introduction of a substituent at C-8 in 6-furyl-9-(*p*-methoxybenzyl)purine **1a** turned out not to have a positive effect on antimycobacterial activity (Table 3). All compounds examined were less active than the parent compound **1a**. Again, low toxicity toward VERO cells and low activity against other bacteria were observed.

From the results presented in Table 2, it can be seen that the introduction of a polar substituent at C-2 resulted in reduced antimycobacterial activity. Compounds with π-values[20] < 0 generally exhibited MIC against *Mtb* > 6.25 mg/mL. Exceptions were the methoxy group (π = −0.02, MIC **18a** = 0.78 μg/mL) and the acetyl group (π = −0.55, MIC **20** = 6.25 μg/mL). We have previously found low tolerance for polar substituents (π < 0) on the benzyl group in 6-aryl-9-benzylpurines.[1d] *Mtb* contains a thick and waxy cell wall, which may preclude efficient penetration of the more polar compounds.

Purines carrying C-2 substituents with different electronic properties (F, Cl, OMe, SMe, and Me) exhibit high inhibitory activity against *Mtb*, indicating that the electronic properties of the substituents have only minor influence on the antimycobacterial activity.

Substituent size, on the other hand, appears to be much more important for biological activity. Both in the alkoxy/aryloxy-series (compounds **18**) and the alkyl/alkenyl/aryl series (compounds **19**), the activity generally decreases as the size of the 2-substituent increases. The iodopurine **5** is also much less active than chloro- **1b** or fluoro-analog **1c**. Introduction of unsaturations in a C-2 side chain appears not to be favorable. Activity against *Mtb* was found to be ethyl (**19b**, MIC = 1.56 μg/mL) > ethenyl (**19g**, MIC = 3.13 μg/mL) > ethynyl (**23**, MIC 6.25 = μg/mL). Our results indicate that the not yet identified target for the antimycobacterial purines contains a pocket that can accommodate relatively small and hydrophobic C-2 substituents.

**Table 2.** Antibacterial activity against *M. tuberculosis*, *S. aureus*, and *E. coli*, and cytotoxic activity against VERO cells for 2-substituted purines[a]

| Compound | X | % Inhibition of *M. tuberculosis* (ATCC 27294) at 6.25 μg/mL concd. | MIC *M. tuberculosis* $H_{37}Rv$ (μg/mL)[b] | MIC *S. aureus* (ATCC 25923) (μg/mL)[c] | MIC *E. coli* (ATCC 25922) (μg/mL)[d] | $IC_{50}$ VERO cells (μg/mL) | Selectivity index (SI = $IC_{50}$: MIC *M. tuberculosis*) |
|---|---|---|---|---|---|---|---|
| **1a** | –H | 97[e] | 1.56[e] | n.d. | n.d. | >62.5[e,f] | >40 |
| **1b** | –Cl | 98[e] | 0.39[e] | >32 | >32 | >10[e,f] | >26 |
| **1c** | –F | 97 | 0.39 | >32 | >32 | >10 | >26 |
| **5** | –I | 43 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **4** | $–NH_2$ | 60 | n.d. | >32 | >32 | n.d. | n.d. |
| **6** | $–NHCOCH_3$ | 0 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **7** | $–N(COCH_3)_2$ | 7 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **8** | $–NHSO_2CH_3$ | 30 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **9** | $–N(SO_2CH_3)_2$ | 0 | n.d. | >32 | >32 | n.d. | n.d. |
| **10** | $–NHCH_2–p\text{-}C_6H_4–OCH_3$ | 5 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **11** | $–NHCH_3$ | 77 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **12** | $–N(CH_3)_2$ | 34 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **13** | $–SCH_3$ | 98 | 0.78 | n.d. | n.d. | 3.05 | 3.9 |
| **14** | $–SOCH_3$ | 60 | n.d. | >32 | >32 | n.d. | n.d. |
| **15** | $–SO_2CH_3$ | 0 | n.d. | >32 | >32 | n.d. | n.d. |
| **16** | $–NO_2$ | 56 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **17** | –OH | 42 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **18a** | $–OCH_3$ | 97 | 0.78 | >32 | >32 | >62.5[f] | >80 |
| **18b** | $–OCH_2CH_3$ | 89 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **18c** | $–O(CH_2)_2CH_3$ | 73 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **18d** | $–OCH(CH_3)_2$ | 53 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **18e** | $–O(CH_2)_3CH_3$ | 76 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **18f** | $–OCH_2Ph$ | 59 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **18g** | –OPh | 72 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **19a** | $–CH_3$ | 99 | 0.20 | >32 | >32 | >62.5[f] | >313 |
| **19b** | $–CH_2CH_3$ | 99 | 1.56 | n.d. | n.d. | n.d.[g] | n.d. |
| **19c** | $–CH(CH_3)_2$ | 60 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **19d** | $–(CH_2)_3CH_3$ | 97 | >6.25 | n.d. | n.d. | n.d. | n.d. |
| **19e** | –*c*-Propyl | 62 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **19f** | –*c*-Pentyl | 96 | 6.25 | n.d. | n.d. | >10[f] | >1.6 |
| **19g** | $–CH{=}CH_2$ | 99 | 3.13 | n.d. | n.d. | 8.85 | 2.82 |
| **19h** | $–C(OEt){=}CH_2$ | 91 | >6.25 | n.d. | n.d. | n.d. | n.d. |
| **19i** | –Ph | 99 | 6.25 | n.d. | n.d. | >10[f] | >1.6 |
| **19j** | –(2-Furyl) | 37 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **20** | $–COCH_3$ | 97 | 6.25 | >32 | >32 | >10[f] | >1.6 |
| **21** | –CN | 69 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **23** | $–C{\equiv}CH$ | 97 | 6.25 | n.d. | n.d. | 0.14 | 0.02 |
| **26** | $–C{\equiv}CCH_3$ | 42 | n.d. | n.d. | n.d. | n.d. | n.d. |
| **29** | $–CF_3$ | 82 | n.d. | >32 | >32 | n.d. | n.d. |

[a] For a general structure, see Figure 2.
[b] MIC Rifampin 0.25 μg/mL.
[c] MIC Gentamycin 0.03 μg/mL.
[d] MIC Gentamycin 0.125 μg/mL.
[e] Taken from Ref. 1d.
[f] Low solubility precludes determination at higher concentration.
[g] Solubility in tissue culture to low to determine $IC_{50}$.

The results presented in Table 3 demonstrate that C-8, in the class of purines studied, should be unsubstituted. Again, it seems like sterical factors are the most important. The compounds containing the larger substituents (Br **32c**, 2-furyl **32d**) are the least active antimycobacterials. C-8 substituents may influence the spatial orientation of the *N*-9 benzyl group. 8-Substituted purine nucleosides often prefer the *syn* conformation whereas the unsubstituted analogs prefer the *anti* conformation.[21] Previously we observed that introduction of substituents to the benzylic *ortho*- or α-positions of the benzyl group also resulted in reduced activity.[1d] It appears that the benzylimidazole part of the molecules is extremely sensitive to sterical hindrance and substituents that may interfere with the conformation of the benzyl group required for binding to target must be avoided. Figure 3 summarizes our current knowledge on SAR regarding antimycobacterial 6-aryl-9-benzylpurines.

## 3. Conclusions

We have synthesized a number of 6-(2-furyl)-9-(*p*-methoxybenzyl)purines carrying a variety of substituents in the purine 2- or 8-position and determined their ability to inhibit growth of *M. tuberculosis* in vitro. The results

**Table 3.** Antibacterial activity against *M. tuberculosis*, *S. aureus*, and *E. coli*, and cytotoxic activity against VERO Cells for 8-substituted purines[a]

| Compound | X | Y | % Inhibition of *M. tuberculosis* (ATCC 27294) at 6.25 μg/mL concd | MIC *M. tuberculosis* $H_{37}Rv$ (μg/mL)[b] | MIC *S. aureus* (ATCC 25923) (μg/mL)[c] | MIC *E. coli* (ATCC 25922) (μg/mL)[d] | $IC_{50}$ VERO cells (μg/mL) |
|---|---|---|---|---|---|---|---|
| **32a** | $-CH_3$ | –H | 93 | 6.25 | n.d. | n.d. | >62.5[e] |
| **32b** | –Cl | –H | 90 | >6.25 | >32 | >32 | n.d. |
| **32c** | –Br | –H | 40 | n.d. | n.d. | n.d. | n.d. |
| **32d** | –(2-Furyl) | –H | 0 | n.d. | n.d. | n.d. | n.d. |
| **33** | $-OCH_3$ | –H | 95 | 3.13 | >32 | >32 | >10[e] |
| **34** | –OH | –H | 64 | n.d. | >32 | >32 | n.d. |
| **35a** | $-CH_3$ | $-CH_3$ | 72 | n.d. | n.d. | n.d. | n.d. |
| **35b** | –Cl | –Cl | 10 | n.d. | n.d. | n.d. | n.d. |

[a] For a general structure, see Figure 2.
[b] MIC Rifampin 0.25 μg/mL.
[c] MIC Gentamycin 0.03 μg/mL.
[d] MIC Gentamycin 0.125 μg/mL.
[e] Low solubility precludes determination at higher concentration.

show that sterical hindrance at C-8 reduces activity, and the 8-position should be unsubstituted. In the purine 2-position small, hydrophobic substituents are beneficial. The electronic properties of the 2-substituents appear to have little influence on bioactivity. Generally the compounds studied exhibited low toxicity toward mammalian cells and were essentially inactive toward *S. aureus* and *E. coli*. The most active and selective antimycobacterial in the series detected to date is 2-methyl-6-furyl-9-(*p*-methoxybenzyl)purine **19a** with MIC = 0.20 μg/mL against *Mtb* and $IC_{50}$ against VERO cells > 62.5 μg/mL. Also the 2-fluoro **1c** and the previously known 2-chloro analog **1b**, both with MIC = 0.39 μg/mL, are highly interesting drug candidates.

## 4. Experimental

The $^1H$ NMR spectra were recorded at 600 MHz with a Bruker AV 600 instrument, at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument, or at 200 MHz with a Bruker Avance DPX 200 instrument or a Varian Gemini 200 instrument. The $^1H$ decoupled $^{13}C$ NMR spectra were recorded at 150, 125, 75 or 50 MHz using instruments mentioned above. $^{19}F$ NMR spectra were recorded at 188 MHz with the Avance DPX 200 instrument using $CCl_3F$ in $CDCl_3$ as reference ($\delta$ 0 ppm). Mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing voltage with a VG Prospec instrument and are presented as *m/z* (% rel int.). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points were determined with a C. Reichert melting point apparatus and are uncorrected. DMF was distilled from BaO and stored over 4 Å molsieve. Triethylamine, diisopropylamine, pyridine, dichloromethane, and acetonitrile were distilled from $CaH_2$, and THF from Na/benzophenone. Toluene was dried over Na-wire. *N*-Methylpyrrolidine (NMP) was purchased on SureSeal bottles from Aldrich and used as received. The Grignard reagents used were titrated using salicylaldehyde phenylhydrazone.[22] The following compounds were prepared as previously described: 6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1a**.[1d] 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b**,[1d]2-fluoro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1c**,[7] 2-nitro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **16**,[7] 6-chloro-2-trifluoromethyl-1*H*-purine **27**,[17] and 6-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine **30**.[1d] All other reagents were commercially available and used as received. Activities against *M. tuberculosis*,[1] *S. aureus*,[23] *E. coli*,[23] and VERO cells[1] were determined as reported before.

### 4.1. 2-Amino-6-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine (3a) and 2-amino-6-chloro-7-(4-methoxyphenylmethyl)-7*H*-purine (3b)

Potassium carbonate (2.49 mg, 18.0 mmol) and 2-amino-6-chloro-9*H*-purine **2** (1.02 g, 6.00 mmol) were stirred in dry DMF (25 mL) at ambient temperature under $N_2$. After 20 min, 4-methoxyphenylmethyl chloride (1.63 mL, 12.0 mmol) was added. The resulting mixture was stirred for 16 h, filtered, and evaporated in vacuo. The isomers **3a** and **3b** were separated by flash chromatography on silica gel eluting with $CH_2Cl_2$/MeOH (19:1). Various amounts of compound **3c** could also be isolated depending on the amount of heat employed in the evaporation of the reaction mixture.

**4.1.1. 2-Amino-6-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine (3a).[24]** Yield: 917 mg (53%), colorless powdery

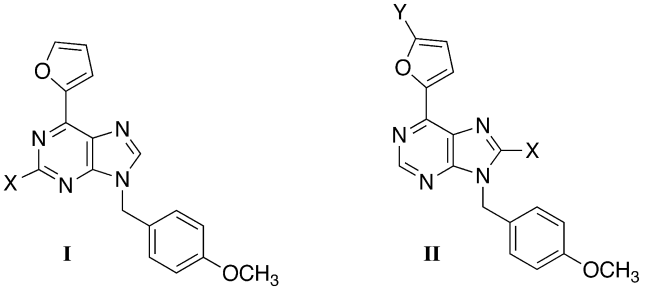



**Figure 2.** General structures of purines discussed in Table 2 (compounds **I**) and in Table 3 (compounds **II**).

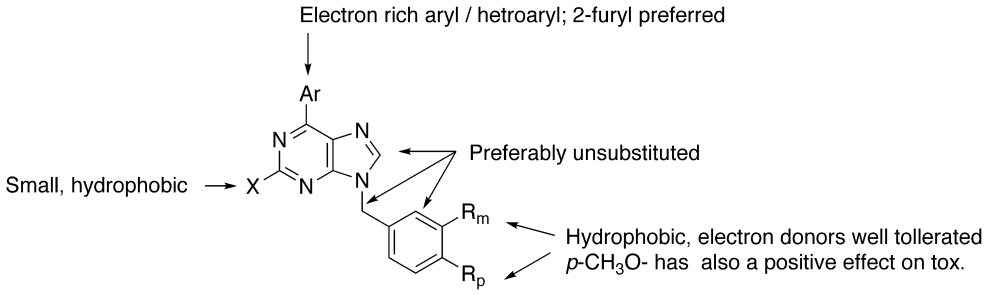



**Figure 3.** Summary of SAR knowledge for 6-aryl-9-benzylpurines.

crystals, mp 178 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.78 (s, 3H, $CH_3$), 5.15 (br s, 4H, $CH_2$ and $NH_2$), 6.86 (d, $J$ = 8.6 Hz, 2H, Ar), 7.20 (d, $J$ = 8.6 Hz, 2H, Ar), 7.68 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 46.7 ($CH_2$), 55.3 ($CH_3$), 114.4 (CH in Ar), 125.1 (C-5), 126.9 (C-1 in Ar), 129.2 (CH in Ar), 142.0 (C-8), 151.1 (C-4/C-6), 153.7 (C-4/C-6), 159.1 (C-4 in Ar), 159.6 (C-2); MS-EI $m/z$ (rel %) 291/289 (6/18 $M^+$), 121 (100), 91 (2), 78 (4), 77 (3); HRMS: Found 289.0730, Calcd for $C_{13}H_{12}ClN_5O$ 289.0732.

**4.1.2. 2-Amino-6-chloro-7-(4-methoxyphenylmethyl)-7*H*-purine (3b).**[24] Yield: 361 mg (21%), colorless crystals, mp 225–227 °C. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 3.67 (s, 3H, $CH_3$), 5.43 (s, 2H, $CH_2$), 6.63 (br s, 2H, $NH_2$), 6.86 (m, 2H, Ar), 7.09 (m, 2H, Ar), 8.50 (s, 1H, H-8); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 48.7 ($CH_2$), 55.1 ($CH_3$), 114.1 (CH in Ar), 114.7 (C-5), 128.1 (CH in Ar), 128.8 (C-1 in Ar), 142.3 (C-6/C-2), 149.8 (C-8), 158.8 (C-4 in Ar), 160.0 (C-2/C-6), 164.4 (C-4); MS-EI $m/z$ (rel %) 291/289 (3/13, $M^+$), 121 (100), 91 (2), 78 (6), 77 (5); HRMS: Found 289.0730, Calcd for $C_{13}H_{12}ClN_5O$ 289.0730.

**4.1.3. 6-Chloro-9-(4-methoxyphenylmethyl)-2-(4-methoxyphenylmethylamino)-9*H*-purine (3c).** Colorless needles, mp 161–164 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.815 (s, 3H, $CH_3$), 3.824 (s, 3H, $CH_3$), 4.65 (br s, 2H, C$H_2$NH), 5.18 (s, 2H, $CH_2$), 5.75 (br s, 1H, NH), 6.84–6.90 (m, 4H, Ar), 7.21–7.34 (m, 4H, Ar), 7.71 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 45.4 ($CH_2$), 46.8 ($CH_2$), 55.3 (2× $CH_3$), 113.9 (CH in Ar), 114.3 (CH in Ar), 124.5 (C-5), 127.2 (C in Ar), 128.7 (CH in Ar), 129.4 (CH in Ar), 130.9 (C in Ar), 141.3 (C-8), 151.0 (C-4/C-6), 153.6 (C-4/C-6), 158.69 (C in Ar), 158.74 (C in Ar), 159.6 (C-2); MS-EI $m/z$ (rel %) 411/409 (14/39, $M^+$), 290 (7), 288 (22), 136 (2), 121 (100); Anal. Found: C, 61.41; H, 4.83; N, 17.00. $C_{21}H_{20}ClN_5O_2$ requires C, 61.54; H, 4.92; N, 17.09%.

### 4.2. 2-Amino-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (4)[25]

2-(Tributylstannyl)furan (0.26 mL, 0.80 mmol) was added to a solution of 2-amino-6-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine **3a** (195 mg, 0.67 mmol) and bis(triphenylphosphine)palladium(II) chloride (24 mg, 0.034 mmol) in DMF (5 mL). The resulting mixture was stirred at 90 °C under $N_2$ for 16 h, cooled, and evaporated in vacuo. A saturated solution of potassium fluoride in methanol (10 mL) was added and the mixture was stirred at ambient temperature for at least 4 h and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) followed by EtOAc/hexane (2:1) and finally pure EtOAc; yield 189 mg (88%), colorless crystals, mp 235–237 °C (dec). $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.77 (s, 3H, $CH_3$), 5.10 (br s, 2H, $NH_2$), 5.19 (s, 2H, $CH_2$), 6.61 (dd, $J$ = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.6 Hz, 2H, Ar), 7.22 (d, $J$ = 8.6 Hz, 2H, Ar), 7.70 (m, 2H, H-5 in furyl and H-8), 7.77 (br d, $J$ = 3.6 Hz, 1H, H-3 in furyl); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 45.1 ($CH_2$), 55.0 ($CH_3$), 112.3 (C-4 in furyl), 113.9 (CH in Ar), 116.2 (C-3 in furyl), 121.6 (C-5), 128.6 (CH in Ar), 128.8 (C-4 in Ar), 142.2 (C-8), 145.2 (C-5 in furyl), 145.4 (C-6), 149.3 (C-2 in furyl), 153.6 (C-4), 158.6 (C-2), 160.2 (C in Ar); MS-EI $m/z$ (rel %) 321 (55, $M^+$), 121 (100), 91 (3), 78 (5), 77 (5); HRMS: Found 321.1234, Calcd for $C_{17}H_{15}N_5O_2$ 321.1226.

### 4.3. 6-(2-Furyl)-9-iodo-9-(4-methoxyphenylmethyl)-9*H*-purine (5)

A mixture of 2-amino-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **4** (80 mg, 0.25 mmol), diiodomethane (2.5 mL), and isoamyl nitrite (670 μL, 5.00 mmol) was heated at 85 °C for 75 min. After cooling, the solution was evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 43 mg (40%), colorless oil. Crystallization from $CH_2Cl_2$–acetone afforded an analytical sample, colorless crystalline compound, mp 145–148 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.80 (s, 3H, $OCH_3$), 5.33 (s, 2H, $CH_2$), 6.65 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.89 (d, $J$ = 8.7 Hz, 2H, Ar), 7.27 (d, $J$ = 8.7 Hz, 2H, Ar), 7.77 (d, $J$ = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 7.82 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.91 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.9 ($CH_2$), 55.2 ($OCH_3$), 112.7 (C-4 in furyl), 114.4 (CH in Ar), 118.4 (C-3 in furyl), 119.6 (C-2), 126.5 (C-1 in Ar), 128.0 (C-5), 129.5 (CH in Ar), 144.1 (C-8), 146.5 (C-5 in furyl), 146.6 (C-6), 148.7 (C-2 in furyl), 152.8 (C-4), 159.8 (C-4 in Ar); MS-EI $m/z$ (rel %) 432 (56, $M^+$), 305 (2), 184 (2), 121 (100), 106 (2); Anal. Found: C, 47.29; H, 3.15; N, 12.89. $C_{17}H_{13}IN_4O_2$ requires C, 47.24; H, 3.03; N, 12.96%.

### 4.4. *N*-[6-(2-Furyl)-9-(4-methoxybenzyl)-9*H*-purine-2-yl]-acetamide (6)

A stirred suspension of 2-amino-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **4** (80 mg, 0.25 mmol) and triethylamine (174 μL, 1.25 mmol) in toluene (2 mL) was heated at reflux. Acetic anhydride (236 μL, 2.50 mmol) was added and the reaction mixture was heated at reflux for 22 h, cooled, and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (9:1) followed by $CH_2Cl_2$/acetone (7:3); yield 47 mg (52%), off-white crystalline compound, mp 167–168 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.55 (s, 3H, $CH_3CO$), 3.75 (s, 3H, $OCH_3$), 5.26 (s, 2H, $NCH_2$), 6.61 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.71 (dd, $J$ = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 7.75 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.91 (s, 1H, H-8), 8.27 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 25.1 ($CH_3CO$), 46.9 ($NCH_2$), 55.3 ($OCH_3$), 112.6 (C-4 in furyl), 114.4 (CH in Ar), 117.6 (C-3 in furyl), 125.1 (C-5), 127.0 (C-1 in Ar), 129.5 (CH in Ar), 143.7 (C-8), 146.0 (C-5 in furyl), 146.5 (C-6), 149.5 (C-2 in furyl), 152.7 (C-2), 153.0 (C-4), 159.7 (C-4 in Ar), 171.0 (C=O); MS-EI *m*/*z* (rel %) 363 (100, $M^+$), 348 (6), 322 (4), 321 (21), 320 (3), 121 (99); Anal. Found: C, 62.65; H, 4.74; N, 19.13. $C_{19}H_{17}N_5O_3$ requires C, 62.80; H, 4.72; N, 19.27%. 2-(*N*,*N*-Diacetylamino)-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **7** was also isolated; yield 39 mg (38%), data see below.

### 4.5. 2-(*N*,*N*-Diacetylamino)-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (7)

A stirred suspension of 2-amino-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **4** (160 mg, 0.50 mmol) in toluene (4 mL) was heated at reflux for 24 h. Acetic anhydride (472 μL, 5.00 mmol) was added. After additional 24 h reflux, the solution was cooled and evaporated in vacuo. The product was isolated by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (9:1); yield 151 mg (74%), colorless crystalline compound, mp 187–189 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.28 (s, 6H, 2× $CH_3CO$), 3.71 (s, 3H, $OCH_3$), 5.27 (s, 2H, $NCH_2$), 6.60 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.80 (d, $J$ = 8.7 Hz, 2H, Ar), 7.21 (d, $J$ = 8.7 Hz, 2H, Ar), 7.70 (dd, $J$ = 1.7 and 0.7 Hz, 1H, H-5 in furyl), 7.85 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 8.06 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 26.3 (2× $CH_3CO$), 47.0 ($NCH_2$), 55.1 ($OCH_3$), 112.7 (C-4 in furyl), 114.3 (CH in Ar), 118.7 (C-3 in furyl), 126.5 (C-1 in Ar), 127.4 (C-5), 129.4 (CH in Ar), 145.6 (C-8), 146.3 (C-5 in furyl), 147.2 (C-6), 148.7 (C-2 in furyl), 153.2 (C-2/C-4), 153.4 (C-4/C-2), 159.7 (C-4 in Ar), 172.1 (2× C=O); MS-EI *m*/*z* (rel %) 405 (34, $M^+$), 363 (70), 349 (17), 348 (80), 321 (12), 121 (100); Anal. Found: C, 62.35; H, 4.82; N, 17.17. $C_{21}H_{19}N_5O_4$ requires C, 62.22; H, 4.72; N, 17.27%.

### 4.6. 6-(2-Furyl)-2-methylsulfonylamino-9-(4-methoxyphenylmethyl)-9*H*-purine (8)

A solution of methanesulfonyl chloride (259 μL, 3.33 mmol) was added dropwise to a suspension of 2-amino-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **4** (106 mg, 0.33 mmol) in pyridine (3 mL). The suspension was stirred at ambient temperature for 24 h, poured into ice water (40 mL), and extracted with $CH_2Cl_2$ (2× 30 mL). The combined organic extracts were washed with satd aq $NH_4Cl$ (40 mL), water (40 mL), satd aq $NH_4Cl$ (40 mL), and brine (40 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$ gradually increasing the amount of acetone to $CH_2Cl_2$/acetone (9:1); yield 30 mg (23%), colorless crystals, mp 127–128 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.47 (s, 3H, $SO_2CH_3$), 3.76 (s, 3H, $OCH_3$), 5.27 (s, 2H, $NCH_2$), 6.62 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.71 (dd, $J$ = 1.7 and 0.6 Hz, 1H, H-5 in furyl), 7.78 (dd, $J$ = 3.5 and 0.6 Hz, 1H, H-3 in furyl), 7.93 (s, 1H, H-8), 8.02 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 41.7 ($SO_2CH_3$), 47.1 ($CH_2$), 55.3 ($OCH_3$), 112.7 (C-4 in furyl), 114.5 (CH in Ar), 118.1 (C-3 in furyl), 125.3 (C-5), 126.9 (C-1 in Ar), 129.5 (CH in Ar), 143.6 (C-8), 146.3 (C-5 in furyl), 146.8 (C-6/C-2), 149.3 (C-2 in furyl), 152.4 (C-2/C-6), 153.1 (C-4), 159.8 (C-4 in Ar); MS-EI *m*/*z* (rel %) 399 (19, $M^+$), 321 (3), 320 (4), 200 (3), 121 (100); Anal. Found: C, 53.95; H, 4.55; N, 17.44. $C_{18}H_{17}N_5O_4S$ requires C, 54.13; H, 4.29; N, 17.53%.

### 4.7. 6-(2-Furyl)-2-(*N*,*N*-Dimethylsulfonylamino)-9-(4-methoxyphenylmethyl)-9*H*-purine (9)

Triethylamine (464 μL, 3.33 mmol) was added to a suspension of 2-amino-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **4** (106 mg, 0.33 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (4.0 mg, 0.033 mmol) in $CH_2Cl_2$ (5 mL). A solution of methanesulfonyl chloride (259 μL, 3.33 mmol) was added dropwise. The resulting solution was stirred at ambient temperature for 4 h, poured into ice water (40 mL), and extracted with $CH_2Cl_2$ (2× 25 mL). The combined organic extracts were washed with water (25 mL) and brine (2× 25 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (29:1) followed by $CH_2Cl_2$/acetone (19:1); yield 87 mg (55%), colorless powdery crystals, mp 234–236 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.72 (s, 6H, 2× $SO_2CH_3$), 3.78 (s, 3H, $OCH_3$), 5.33 (s, 2H, $NCH_2$), 6.64 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.88 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.70 (br s, 1H, H-5 in furyl), 7.79 (d, $J$ = 3.5 Hz, 1H, H-3 in furyl), 8.04 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 44.5 (2× $SO_2CH_3$), 47.3 ($CH_2$), 55.3 ($OCH_3$), 112.8 (C-4 in furyl), 114.6 (CH in Ar), 118.4 (C-3 in furyl), 126.3 (C-1 in Ar), 127.9 (C-5), 129.5 (CH in Ar), 145.8 (C-8), 146.6 (C-5 in furyl), 147.0 (C-6/C-2), 149.2 (C-2 in furyl), 149.7 (C-2/C-6), 153.3 (C-4), 159.9 (C-4 in Ar); MS-EI *m*/*z* (rel %) 477 (6, $M^+$), 399 (8), 398 (6), 122 (3), 121

(100); Anal. Found: C, 47.69; H, 4.14; N, 14.71. $C_{19}H_{19}N_5O_6S_2$ requires C, 47.79; H, 4.01; N, 14.67%.

### 4.8. 6-(2-Furyl)-2-(4-methoxyphenylmethylamino)-9-(4-methoxyphenylmethyl)-9*H*-purine (10)

The title compound was prepared by Stille coupling on 6-chloro-9-(4-methoxyphenylmethyl)-2-(4-methoxyphenylmethylamino)-9*H*-purine **3c** (0.70 mmol) as described for compound **4** above. EtOAc/hexane (1:1) followed by EtOAc/hexane (2:1) were used for flash chromatography; yield 262 mg (85%), colorless crystals, mp 153–154 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.75 (s, 3H, $CH_3$), 3.76 (s, 3H, $CH_3$), 4.63 (br d, $J$ = 5.8 Hz, 2H, $CH_2$NH), 5.16 (s, 2H, $CH_2$) 6.09 (br s, 1H, NH), 6.59 (dd, $J$ = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 6.78–6.84 (m, 4H, Ar), 7.16–7.31 (m, 4H, Ar), 7.70 (m, 1H, H-5 in furyl), 7.71 (s, 1H, H-8), 7.79 (br d, $J$ = 3.4 Hz, 1H, H-3 in furyl); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 45.3 ($CH_2$), 46.4 ($CH_2$), 55.2 (2× $CH_3$), 112.5 (C-4 in furyl), 113.8 (CH in Ar), 114.2 (CH in Ar), 117.7 (C-3 in furyl), 122.1 (C-5), 127.5 (C-1 in Ar), 128.7 (CH in Ar), 129.4 (CH in Ar), 131.2 (C-1 in Ar), 141.9 (C-8), 145.8 (C-6), 145.9 (C-5 in furyl), 148.6 (C-2 in furyl), 154.3 (C-4), 158.1 (C-2/C-4 in Ar), 158.6 (C-2/C-4 in Ar), 159.4 (C-2/C-4 in Ar); MS-EI *m*/*z* (rel %) 441 (100, $M^+$), 426 (4), 320 (67), 136 (6), 121 (64); HRMS: Found 441.1780, Calcd for $C_{25}H_{23}N_5O_3$ 441.1801. Anal. Found: C, 68.02; H, 5.28; N, 15.09. $C_{17}H_{15}N_5O_2$ requires C, 68.04; H, 5.25; N, 15.86%.

### 4.9. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-(*N*-methylamino)-9*H*-purine (11)

A solution of 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (112 mg, 0.33 mmol) in THF (3 mL) and 40% methylamine in water (3 mL) was stirred under $N_2$ in a sealed tube at 85 °C for 15 h. After cooling the solution was evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1) followed by $CH_2Cl_2$/acetone (9:1); yield 95 mg (86%), off-white crystalline compound, mp 144–145 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.06 (d, $J$ = 5.1 Hz, 3H, $NCH_3$), 3.76 (s, 3H, $OCH_3$), 5.20 (s, 2H, $NCH_2$), 5.32 (br s, 1H, NH), 6.58 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.84 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.67 (br s, H-5 in furyl and H-8), 7.73 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 28.8 ($NCH_3$), 46.2 ($NCH_2$), 55.3 ($OCH_3$), 112.2 (C-4 in furyl), 114.2 (CH in Ar), 116.4 (C-3 in furyl), 122.4 (C-5), 127.9 (C-1 in Ar), 129.4 (CH in Ar), 140.9 (C-8), 145.1 (C-5 in furyl), 146.5 (C-6), 150.0 (C-2 in furyl), 154.1 (C-4), 159.5 (C-4 in Ar), 160.2 (C-2); MS-EI *m*/*z* (rel %) 335 (100, $M^+$), 320 (1), 214 (3), 121 (81), 106 (1); Anal. Found: C, 64.48; H, 4.97; N, 21.27. $C_{18}H_{17}N_5O_2$ requires C, 64.47; H, 5.11; N, 20.88%.

### 4.10. 2-(*N*,*N*-Dimethylamino)-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (12)

Triethylamine (1.05 mL, 7.50 mmol) was added to a mixture of glycine methyl ester hydrochloride (471 mg, 3.75 mmol) and 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (112 mg, 0.33 mmol) in DMF (3 mL) and the reaction mixture was heated in a sealed tube under $N_2$ at 85 °C for 15 h. After cooling the precipitate was filtered off and the solution evaporated in vacuo, and the residue was dissolved in $CH_2Cl_2$ (15 mL). Again, the precipitate was filtered off, and the solution was evaporated in vacuo. The residue was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1); yield 95 mg (82%), colorless crystalline compound, mp 163–164 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.27 (s, 6H, $N(CH_3)_2$), 3.75 (s, 3H, $OCH_3$), 5.18 (s, 2H, $NCH_2$), 6.57 (dd, $J$ = 3.4 and 1.7 Hz, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.62 (br d, $J$ = 3.4 Hz, H-3 in furyl), 7.67 (s, 1H, H-8), 7.70 (br s, 1H, H-5 in furyl); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 37.4 [$N(CH_3)_2$], 46.1 ($NCH_2$), 55.2 ($OCH_3$), 111.9 (C-4 in furyl), 114.2 (CH in Ar), 115.2 (C-3 in furyl), 121.3 (C-5), 128.1 (C-1 in Ar), 129.4 (CH in Ar), 140.9 (C-8), 145.1 (C-5 in furyl), 146.1 (C-6), 151.2 (C-2 in furyl), 154.3 (C-4), 159.4 (C-4 in Ar), 159.7 (C-2); MS-EI *m*/*z* (rel %) 349 (100, $M^+$), 334 (7), 321 (3), 320 (14), 121 (52); Anal. Found: C, 65.28; H, 5.41; N, 20.05. $C_{21}H_{19}N_5O_4$ requires C, 65.32; H, 5.48; N, 20.04%.

### 4.11. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-methylthio-9*H*-purine (13)

A solution of 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (341 mg, 1.00 mmol) and sodium methythiolate (1.05 g, 15.0 mmol) in dry DMF (8 mL) was heated at 90 °C under $N_2$ for 1.5 h and cooled. The reaction mixture was diluted with water (5 mL) and EtOAc (10 mL), the phases were separated, and the aqueous phase extracted with EtOAc (4× 25 mL). The combined organic extracts were washed with brine (2× 50 mL) and dried ($MgSO_4$). The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1); yield 255 mg (72%), pale yellow crystals, mp 147–148 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.62 (s, 3H, $SCH_3$), 3.71 (s, 3H, $OCH_3$), 5.24 (s, 2H, $CH_2$), 6.57 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.80 (d, $J$ = 8.7 Hz, 2H, Ar), 7.21 (d, $J$ = 8.7 Hz, 2H, Ar), 7.70 (m, 1H, H-5 in furyl), 7.71 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.84 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.6 ($SCH_3$), 46.5 ($CH_2$), 55.1 ($OCH_3$), 112.3 (C-4 in furyl), 114.2 (CH in Ar), 117.0 (C-3 in furyl), 125.4 (C-5), 127.1 (C-1 in Ar), 129.4 (CH in Ar), 142.9 (C-8), 145.6 (C-6), 145.8 (C-5 in furyl), 149.7 (C-2 in furyl), 152.8 (C-4), 159.5 (C-4 in Ar), 165.8 (C-2); MS-EI *m*/*z* (rel %) 352 (56, $M^+$), 231 (8), 121 (100), 78 (4), 77 (5); Anal. Found: C, 61.30; H, 4.56; N, 15.86. $C_{18}H_{16}N_4O_2S$ requires C, 61.35; H, 4.58; N, 15.90%.

### 4.12. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-methylsulfinyl-9*H*-purine (14)

A solution of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-2-methylthio-9*H*-purine **13a** (88 mg, 0.25 mmol) in $CH_2Cl_2$ (2 mL) was cooled to −10 °C, before a cold solution of *m*-CPBA (21.6 mg, 0.125 mmol) in $CH_2Cl_2$

(1 mL) was added dropwise, and the mixture was stirred for 30 min. Additional *m*-CPBA (21.6 mg, 0.125 mmol) in $CH_2Cl_2$ (1 mL) was added and the mixture stirred for 30 min. The solution was washed with 5% aq $Na_2S_2O_4$ (10 mL), satd aq $NaHCO_3$ (10 mL), and brine (10 mL). The dried ($MgSO_4$) solution was evaporated and the product was purified by flash chromatography on silica gel eluting with EOAc/hexane (4:1) followed by $CH_2Cl_2$/MeOH (19:1); yield 73 mg (79%), colorless oil which was crystallized from EtOAc–hexane, mp 186–187 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.01 (s, 3H, $SOCH_3$), 3.77 (s, 3H, $OCH_3$), 5.45 (s, 2H, $CH_2$), 6.65 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.87 (d, $J$ = 8.7 Hz, 2H, Ar), 7.29 (d, $J$ = 8.7 Hz, 2H, Ar), 7.77 (dd, $J$ = 1.7 and 0.6 Hz, 1H, H-5 in furyl), 7.86 (dd, $J$ = 3.5 and 0.6 Hz, 1H, H-3 in furyl), 8.08 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 40.7 ($SOCH_3$), 47.2 ($CH_2$), 55.3 ($OCH_3$), 112.8 (C-4 in furyl), 114.5 (CH in Ar), 118.7 (C-3 in furyl), 126.4 (C-1 in Ar), 128.3 (C-5), 129.8 (CH in Ar), 145.6 (C-8), 146.2 (C-6), 146.7 (C-5 in furyl), 149.1 (C-2 in furyl), 153.0 (C-4), 159.9 (C-4 in Ar), 166.8 (C-2); MS-EI *m*/*z* (rel %) 368 (6, $M^+$), 352 (9), 322 (3), 249 (13), 121 (100); Anal. Found: C, 58.64 H, 4.57; N, 15.05. $C_{18}H_{16}N_4O_3S$ requires C, 58.68; H, 4.38; N, 15.21%.

### 4.13. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-methylsulfonyl-9*H*-purine (15)

A solution of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-2-methylthio-9*H*-purine **13a** (70 mg, 0.20 mmol) in $CH_2Cl_2$ (3 mL) was cooled to 0 °C, before a cold solution of *m*-CPBA (77.7 mg, 0.45 mmol) in $CH_2Cl_2$ (3 mL) was added dropwise. The mixture was stirred at ambient temperature for 21 h before cold 10% aq $Na_2S_2O_4$ (6 mL) was added. After 15 min, the mixture was diluted with $CH_2Cl_2$ (10 mL), the phases were separated, and the organic layer was washed with satd aq $NaHCO_3$ (2× 10 mL) and brine (20 mL). The dried ($MgSO_4$) solution was evaporated and the product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (4:1); yield 50 mg (65%), colorless crystalline compound, mp 184–185 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.45 (s, 3H, $SO_2CH_3$), 3.76 (s, 3H, $OCH_3$), 5.41 (s, 2H, $CH_2$), 6.65 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.27 (d, $J$ = 8.7 Hz, 2H, Ar), 7.78 (m, H-5 in furyl), 7.84 (br d, $J$ = 3.5 Hz, 1H, H-3 in furyl), 8.17 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 39.7 ($SO_2CH_3$), 47.5 ($CH_2$), 55.3 ($OCH_3$), 112.9 (C-4 in furyl), 114.6 (CH in Ar), 119.1 (C-3 in furyl), 126.1 (C-1 in Ar), 129.2 (C-5), 129.8 (CH in Ar), 146.2 (C-6), 146.8 (C-8), 147.2 (C-5 in furyl), 149.0 (C-2 in furyl), 152.2 (C-4), 159.5 (C-2), 159.9 (C-4 in Ar); MS-EI *m*/*z* (rel %) 384 (45, $M^+$), 369 (3), 305 (2), 121 (100), 91 (2); Anal. Found: C, 56.32; H, 4.26; N, 14.33. $C_{18}H_{16}N_4O_4S$ requires C, 56.24; H, 4.20; N, 14.57%.

### 4.14. 6-(2-Furyl)-2-hydroxy-9-(4-methoxyphenylmethyl)-9*H*-purine (17)

A mixture of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-2-nitro-9*H*-purine **16** (176 mg, 0.50 mmol) in THF (8 mL) was heated at 50 °C until the purine dissolved and cooled to ambient temperature. Tetrabutylammonium hydroxide (670 μL, 1.0 mmol, 1.5 M in water) was added drop wise over 20 min. The resulting mixture was stirred at ambient temperature for 48 h. Satd aq $NH_4Cl$ (20 mL) and water (20 mL) were added and the mixture extracted with $CH_2Cl_2$ (4× 40 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/EtOH (19:1) followed by $CH_2Cl_2$/EtOH (9:1); yield 116 mg (72%), pale yellow crystalline compound, mp 239–240 °C. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 3.72 (s, 3H, $OCH_3$), 5.24 (s, 2H, $NCH_2$), 6.80 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.90 (d, $J$ = 8.7 Hz, 2H, Ar), 7.29 (d, $J$ = 8.7 Hz, 2H, Ar), 7.79 (dd, $J$ = 3.5 and 0.7 Hz, H-3 in furyl), 7.90 (dd, $J$ = 1.7 and 0.7 Hz, H-5 in furyl), 8.37 (s, 1H, H-8), 11.8 (br s, 1H, NH/OH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.1 ($NCH_2$), 55.2 ($OCH_3$), 113.4 (C-4 in furyl), 114.4 (C-3 in Ar), 118.8 (C-5), 120.1 (C-3 in furyl), 127.0 (C-1 in Ar), 129.5 (C-2 in Ar), 137.4 (C-6/C-2), 143.7 (C-2 in furyl), 145.8 (C-8), 147.8 (C-5 in furyl), 158.2 (C-2/C-6), 159.5 (C-4), 159.7 (C-4 in Ar); MS-EI *m*/*z* (rel %) 322 (39, $M^+$), 121 (100), 91 (3), 78 (6), 77 (6); HRMS: Found 322.1069 Calcd for $C_{17}H_{14}N_4O_3$ 322.1066.

### 4.15. 6-(2-Furyl)-2-methoxy-9-(4-methoxyphenylmethyl)-9*H*-purine (18a)

A mixture of 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (299 mg, 0.88 mmol) in a 0.7 M solution of sodium methoxide in methanol (15 mL) was stirred at reflux under $N_2$-atm for 4 h, cooled, and poured into cold satd aq $NH_4Cl$. Most of the methanol was removed by evaporation in vacuo and the aqueous mixture was extracted with EtOAc (5× 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 223 mg (75%), colorless crystals, mp 167–169 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.74 (s, 3H, $CH_3$), 4.08 (s, 3H, $CH_3$), 5.25 (s, 2H, $CH_2$), 6.60 (m, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.6 Hz, 2H, Ar), 7.24 (d, $J$ = 8.6 Hz, 2H, Ar), 7.71 (br s, 1H, furyl), 7.72 (s, 1H, furyl/H-8), 7.84 (s, 1H, furyl/H-8); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 46.6 ($CH_2$), 55.1 ($CH_3$), 55.3 ($CH_3$), 112.3 (C-4 in furyl), 114.3 (CH in Ar), 116.7 (C-3 in furyl), 124.6 (C-5), 127.2 (C-1 in Ar), 129.3 (CH in Ar), 143.0 (C-8), 145.9 (C-5 in furyl), 147.0 (C-2 in furyl/C-6), 150.2 (C-2 in furyl/C-6), 154.2 (C-4), 159.6 (C-4 in Ar), 162.0 (C-2); MS-EI *m*/*z* (rel %) 336 (56, $M^+$), 321 (2), 121 (100), 78 (4), 77 (4); Anal. Found: C, 64.06; H, 4.73; N, 16.27. $C_{18}H_{16}N_4O_3$ requires C, 64.28; H, 4.80; N, 16.66%.

### 4.16. General procedure for the synthesis of 2-alkoxypurines 18 from 2-nitropurine (16)

A mixture of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-2-nitro-9*H*-purine **16** (88 mg, 0.25 mmol) and KF or KCN (amount see Table 1) in the desired alcohol

(10 mL) was stirred at the temperature and for the time given in Table 1. The reaction mixture was evaporated, and the product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1). Yields, see Table 1.

**4.16.1. 2-Ethoxy-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (18b).** Colorless crystalline compound, mp 137–138 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.47 (t, $J$ = 7.1 Hz, 3H, $CH_3$), 3.77 (s, 3H, $OCH_3$), 4.53 (q, $J$ = 7.1 Hz, 2H, $OCH_2$), 5.27 (s, 2H, $NCH_2$), 6.61 (dd, $J$ = 3.3 and 1.9 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.72–7.73 (m, 2H, H-3 and H-5 in furyl), 7.85 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.5 ($CH_3$), 46.5 ($NCH_2$), 55.2 ($OCH_3$), 63.6 ($OCH_2$), 112.3 (C-4 in furyl), 114.3 (CH in Ar), 116.6 (C-3 in furyl), 124.5 (C-5), 127.3 (C-1 in Ar), 129.4 (CH in Ar), 142.9 (C-8), 145.9 (C-5 in furyl), 147.1 (C-6), 150.2 (C-2 in furyl), 154.3 (C-4), 159.6 (C-4 in Ar), 161.7 (C-2); MS-EI $m/z$ (rel %) 350 (41, $M^+$), 335 (12), 322 (3), 321 (3), 121 (100); Anal. Found: C, 64.83; H, 5.31; N, 15.77. $C_{19}H_{18}N_4O_3$ requires C, 65.13; H, 5.18; N, 15.99%.

**4.16.2. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-propoxy-9*H*-purine (18c).** Colorless oil. Evaporation from acetone–hexane gave colorless crystals, mp 119 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.06 (t, $J$ = 7.4 Hz, 3H, $CH_3$), 1.81–1.93 (m, 2H, $CH_2$), 3.75 (s, 3H, $OCH_3$), 4.41 (t, $J$ = 6.8 Hz, 2H, $OCH_2$), 5.26 (s, 2H, $NCH_2$), 6.59 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.84 (d, $J$ = 8.8 Hz, 2H, Ar), 7.23 (d, $J$ = 8.8 Hz, 2H, Ar), 7.71–7.73 (m, 2H, H-3 and H-5 in furyl), 7.83 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 10.6 ($CH_3$), 22.2 ($CH_2$), 46.5 ($NCH_2$), 55.3 ($OCH_3$), 69.5 ($OCH_2$), 112.3 (C-4 in furyl), 114.3 (CH in Ar), 116.7 (C-3 in furyl), 124.5 (C-5), 127.3 (C-1 in Ar), 129.4 (CH in Ar), 142.9 (C-8), 145.8 (C-5 in furyl), 147.1 (C-6), 150.2 (C-2 in furyl), 154.3 (C-4), 159.6 (C-4 in Ar), 161.9 (C-2); MS-EI $m/z$ (rel %) 364 (27, $M^+$), 335 (9), 334 (3), 322 (14), 121 (100); Anal. Found: C, 66.15; H, 5.53; N, 15.29. $C_{20}H_{20}N_4O_3$ requires C, 65.92; H, 5.53; N, 15.38%.

**4.16.3. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-isopropoxy-9*H*-purine (18d).** Off-white crystalline compound, mp 145–146 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.42 (d, $J$ = 6.2 Hz, 6H, 2× $CH_3$), 3.75 (s, 3H, $OCH_3$), 5.24 (s, 2H, $NCH_2$), 5.40 [sept, $J$ = 6.2 Hz, 1H, C$H$($CH_3$)$_2$], 6.61 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.7 Hz, 2H, Ar), 7.23 (d, $J$ = 8.7 Hz, 2H, Ar), 7.70–7.71 (m, 2H, H-3 and H-5 in furyl), 7.82 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 21.9 (2× $CH_3$), 46.5 ($NCH_2$), 55.2 ($OCH_3$), 70.4 [$C$H($CH_3$)$_2$], 112.2 (C-4 in furyl), 114.3 (CH in Ar), 116.5 (C-3 in furyl), 124.3 (C-5), 127.3 (C-1 in Ar), 129.4 (CH in Ar), 142.8 (C-8), 145.8 (C-5 in furyl), 147.2 (C-6), 150.3 (C-2 in furyl), 154.3 (C-4), 159.6 (C-4 in Ar), 161.3 (C-2); MS-EI $m/z$ (rel %) 364 (26, $M^+$), 349 (14), 322 (12), 306 (9), 121 (100); Anal. Found: C, 65.80; H, 5.41; N, 15.54. $C_{20}H_{20}N_4O_3$ requires C, 65.92; H, 5.53; N, 15.38%.

**4.16.4. 2-Butoxy-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (18e).** Colorless crystals, mp 113 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.94 (t, $J$ = 7.4 Hz, 3H, $CH_3$), 1.43–1.56 (m, 2H, $CH_2$), 1.76–1.85 (m, 2H, $CH_2$), 3.72 (s, 3H, $OCH_3$), 4.43 (t, $J$ = 6.7 Hz, 2H, $OCH_2$), 5.22 (s, 2H, $NCH_2$), 6.56 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.80 (d, $J$ = 8.7 Hz, 2H, Ar), 7.20 (d, $J$ = 8.7 Hz, 2H, Ar), 7.68–7.71 (m, 2H, H-3 and H-5 in furyl), 7.81 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 13.8 ($CH_3$), 19.1 ($CH_2$), 30.9 ($CH_2$), 46.4 ($NCH_2$), 55.1 ($OCH_3$), 67.6 ($OCH_2$), 112.2 (C-4 in furyl), 114.2 (CH in Ar), 116.6 (C-3 in furyl), 124.4 (C-5), 127.3 (C-1 in Ar), 129.3 (CH in Ar), 142.9 (C-8), 145.7 (C-5 in furyl), 147.0 (C-6), 150.1 (C-2 in furyl), 154.2 (C-4), 159.5 (C-4 in Ar), 161.8 (C-2); MS-EI $m/z$ (rel %) 378 (21, $M^+$), 349 (6), 335 (6), 322 (16), 121 (100); Anal. Found: C, 66.37; H, 5.85; N, 14.79. $C_{21}H_{22}N_4O_3$ requires C, 66.65; H, 5.86; N, 14.81%.

**4.16.5. 2-Benzyloxy-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (18f).** Colorless crystalline compound, mp 122 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.74 (s, 3H, $OCH_3$), 5.24 (s, 2H, $NCH_2$), 5.54 (s, 2H, $OCH_2$), 6.60 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.81 (d, $J$ = 8.7 Hz, 2H, Ar), 7.19 (d, $J$ = 8.7 Hz, 2H, Ar), 7.27–7.36 (m, 3H, H-3 and H-4 in Ph), 7.50–7.55 (m, 2H, H-2 in Ph), 7.71–7.75 (m, 2H, H-3 and H-5 in furyl), 7.84 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.5 ($NCH_2$), 55.2 ($OCH_3$), 69.4 ($OCH_2$), 112.3 (C-4 in furyl), 114.3 (CH in Ar), 116.8 (C-3 in furyl), 124.7 (C-5), 127.3 (C-1 in Ar), 127.8 (CH in Ph), 128.3 (CH in Ph), 129.3 (CH in Ar), 136.9 (C-1 in Ph), 143.1 (C-8), 145.9 (C-5 in furyl), 147.1 (C-6), 150.1 (C-2 in furyl), 154.2 (C-4), 159.6 (C-4 in Ar), 161.4 (C-2); MS-EI $m/z$ (rel %) 412 (68, $M^+$), 335 (9), 306 (22), 291 (47), 121 (100); Anal. Found: C, 69.97; H, 4.78; N, 14.01. $C_{23}H_{18}N_4O_3$ requires C, 69.89; H, 4.89; N, 13.58%.

**4.16.6. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-phenoxy-9*H*-purine (18g).** After completing reaction, the mixture was cooled to ambient temperature and $CH_2Cl_2$ (50 mL) was added to the residue. The solution was washed with satd aq $Na_2CO_3$ (4× 25 mL), water (25 mL), brine (2× 25 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in $CH_2Cl_2$ (50 mL), washed with aq NaOH (4× 25 mL, pH 10), water (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$ followed by $CH_2Cl_2$/acetone (19:1) and $CH_2Cl_2$/acetone (9:1). Colorless crystalline compound, mp 133–135 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.73 (s, 3H, $OCH_3$), 5.11 (s, 2H, $NCH_2$), 6.56 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.78 (d, $J$ = 8.8 Hz, 2H, Ar), 7.14 (d, $J$ = 8.8 Hz, 2H, Ar), 7.19–7.28 (m, 3H, Ph), 7.36–7.43 (m, 2H, Ph), 7.65 (dd, $J$ = 3.5 and 0.8 Hz, 1H, H-3 in furyl), 7.69 (dd, $J$ = 1.7 and 0.8 Hz, 1H, H-5 in furyl), 7.89 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.8 ($NCH_2$), 55.2 ($OCH_3$), 112.4 (C-4 in furyl), 114.2 (CH in Ar), 117.1 (C-3 in furyl), 121.5 (CH in Ph), 124.7 (CH in Ph), 125.2 (C-5), 126.9 (C-1 in Ar), 129.1 (CH in Ph), 129.7 (CH in Ar), 143.5 (C-8), 146.1 (C-5 in furyl), 147.3 (C-6), 149.9 (C-2 in furyl), 153.5 (C-1 in Ph), 154.0 (C-4),

159.6 (C-4 in Ar), 161.1 (C-2); MS-EI *m*/*z* (rel %) 398 (52, $M^+$), 381 (1), 278 (2), 277 (7), 121 (100); Anal. Found: C, 69.49; H, 4.67; N, 13.84. $C_{23}H_{18}N_4O_3$ requires C, 69.34; H, 4.55; N, 14.06%.

### 4.17. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-methyl-9*H*-purine (19a)

Zinc bromide (1.40 mL, 1.44 mmol, 1.03 M in THF) was added dropwise to a stirred solution of methyllithium (1.0 mL, 1.4 mmol, 1.4 M in diethyl ether) and THF (2 mL) at −78 °C under $N_2$. After stirring for 1 h, the cooling bath was removed and the mixture was stirred at ambient temperature for 20 min. A solution of 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (248 mg, 0.73 mmol), in dry THF (8 mL) was added followed by a solution of tetrakis(triphenylphosphine)palladium(0) [generated in situ from tris-(diphenylmethylideneacetone)dipalladium chloroform adduct (16 mg, 0.016 mmol) and triphenylphosphine (31 mg, 0.12 mmol)] in dry THF (4 mL). The resulting mixture was heated at reflux for 21 h and cooled to ambient temperature. Satd aq $NH_4Cl$ (10 mL) was added and the aq phase was extracted with EtOAc (2× 25 mL). The combined organic extracts were washed with brine (2× 20 mL), dried ($MgSO_4$), and evaporated. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 189 mg (81%), colorless crystals, mp 127–130 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.85 (s, 3H, $CH_3$), 3.76 (s, 3H, $OCH_3$), 5.32 (s, 2H, $CH_2$), 6.61 (dd, $J$ = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.8 Hz, 2H, Ar), 7.23 (d, $J$ = 8.8 Hz, 2H, Ar), 7.72 (br d, $J$ = 3.6 Hz, 1H, H-3 in furyl), 7.81 (s, 1H, H-5 in furyl/H-8), 7.90 (s, 1H, H-5 in furyl/H-8); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 26.3 ($CH_3$), 46.5 ($CH_2$), 55.3 ($OCH_3$), 112.4 (C-4 in furyl), 114.4 (CH in Ar), 117.1 (C-3 in furyl), 126.3 (C-5), 127.2 (C-1 in Ar), 129.3 (CH in Ar), 143.6 (C-8), 145.48 (C-5 in furyl), 145.54 (C-6), 149.7 (C-2 in furyl), 152.6 (C-4), 159.6 (C-4 in Ar), 162.4 (C-2); MS-EI *m*/*z* (rel %) 320 (47, $M^+$), 305 (3), 122 (8); Anal. Found: C, 67.29; H, 4.83; N 16.92. $C_{18}H_{16}N_4O_3$ requires C, 67.49; H, 5.03; N, 17.49%.

### 4.18. 2-Ethyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19b)

$ZnBr_2$ (1.0 mL, 1.0 mmol, 1.0 M in THF) was added to [1,1-bis(diphenylphosphino) ferrocene]dichloro-palladium(II) complex with $CH_2Cl_2$ (1:1) (20 mg, 0.025 mmol). After cooling to −78 °C, ethylmagnesium bromide (610 μL, 0.50 mmol, 0.82 M in THF) was added dropwise over 15 min, and the resulting mixture was stirred for an additional 15 min at −78 °C before a solution of 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (170 mg, 0.50 mmol) in THF (5 mL) was added. After 1 h, the mixture was allowed to reach ambient temperature and stirred for 15 h. Satd aq $NH_4Cl$ (20 mL) was added and the resulting mixture was extracted with EtOAc (3× 30 mL). The organic phase was washed with water (30 mL) and brine (30 mL). The dried ($MgSO_4$) solution was evaporated together with a small amount of silica and added at the top of a silica gel column. The product was purified by flash chromatography eluting with $CH_2Cl_2$/acetone (19:1); yield 133 mg (80%), colorless oil, crystallized from $CH_2Cl_2$-hexane, mp 119–120 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.43 (t, $J$ = 7.6 Hz, 3H, $CH_3$), 3.13 (q, $J$ = 7.6 Hz, 2H, $CH_2$) 3.74 (s, 3H, $OCH_3$), 5.32 (s, 2H, $NCH_2$), 6.60 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.70–7.72 (m, 1H, H-5 in furyl), 7.82 (br d, $J$ = 3.5 Hz, 1H, H-3 in furyl), 7.93 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 13.2 ($CH_3$), 32.6 ($CH_2$), 46.5 ($NCH_2$), 55.2 ($OCH_3$), 112.3 (C-4 in furyl), 114.3 (CH in Ar), 117.0 (C-3 in furyl), 126.3 (C-5), 127.3 (C-1 in Ar), 129.5 (CH in Ar), 143.6 (C-8), 145.4 (C-6), 145.5 (C-5 in furyl), 149.8 (C-2 in furyl), 152.6 (C-4), 159.6 (C-4 in Ar), 166.6 (C-2); MS-EI *m*/*z* (rel %) 334 (63, $M^+$), 319 (4), 121 (100), 78 (5), 77 (5); Anal. Found: C, 68.08; H, 5.39; N, 16.55. $C_{19}H_{18}N_4O_2$ requires C, 68.25; H, 5.43; N, 16.76%.

### 4.19. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-(1-methylethyl)-9*H*-purine (19c)

The title compound was prepared by Negishi coupling between 1-methylethylzinc bromide (generated from 1-methylethylmagnesium bromide 327 μL, 0.50 mmol, 1.53 M in THF) and 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (85 mg, 0.25 mmol) as described for compound **19b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 66 mg (76%), off-white crystalline solid, mp 123 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.47 (d, $J$ = 6.9 Hz, 6H, 2× $CH_3$), 3.39 [sept, $J$ = 6.9 Hz, 1H, C*H*($CH_3$)$_2$], 3.75 (s, 3H, $OCH_3$), 5.33 (s, 2H, $NCH_2$), 6.60 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.84 (d, $J$ = 8.7 Hz, 2H, Ar), 7.29 (d, $J$ = 8.7 Hz, 2H, Ar), 7.72 (dd, $J$ = 1.6 and 0.7 Hz, 1H, H-5 in furyl), 7.77 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.94 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 22.2 ($CH_3$), 37.6 (CH), 46.6 ($NCH_2$), 55.2 ($OCH_3$), 112.2 (C-4 in furyl), 114.3 (CH in Ar), 116.4 (C-3 in furyl), 126.5 (C-5), 127.5 (C-1 in Ar), 129.5 (CH in Ar), 143.6 (C-8), 145.5 (C-6), 145.6 (C-5 in furyl), 150.4 (C-2 in furyl), 152.7 (C-4), 159.6 (C-4 in Ar), 170.0 (C-2); MS-EI *m*/*z* (rel %) 348 (51, $M^+$), 333 (31), 320 (7), 149 (3), 121 (100); Anal. Found: C, 68.82; H, 5.77; N, 16.14 $C_{20}H_{20}N_4O_2$ requires C, 68.95; H, 5.79; N, 16.08%.

### 4.20. 2-*n*-Butyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19d)

The title compound was prepared by Negishi coupling between *n*-butylzinc bromide (generated from *n*-BuLi, 280 μL, 0.50 mmol, 1.80 M in hexane) and 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (85 mg, 0.25 mmol) as described for compound **19b** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 39 mg (43%), colorless crystalline solid, mp 103 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.96 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 1.42–1.49 (m, 2H, $CH_2$) 1.85–1.93 (m, 2H, $CH_2$), 3.09–3.14 (m, 2H, $CH_2$), 3.76 (s, 3H, $OCH_3$),

5.33 (s, 2H, $NCH_2$), 6.61 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.26 (d, $J$ = 8.7 Hz, 2H, Ar), 7.73 (m, 1H, H-5 in furyl), 7.84 (br d, $J$ = 3.5 Hz, 1H, H-3 in furyl), 7.93 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0 ($CH_3$), 22.5 ($CH_2$), 31.2 ($CH_2$), 39.2 ($CH_2$), 46.6 ($NCH_2$), 55.2 ($OCH_3$), 112.4 (C-4 in furyl), 114.3 (CH in Ar), 117.0 (C-3 in furyl), 126.3 (C-5), 127.3 (C-1 in Ar), 129.5 (CH in Ar), 143.7 (C-8), 145.5 (C-6), 145.6 (C-5 in furyl), 149.8 (C-2 in furyl), 152.6 (C-4), 159.6 (C-4 in Ar), 165.9 (C-2); MS-EI $m/z$ (rel %) 362 (7,$M^+$), 347 (4), 333 (9), 320 (83), 121 (100); Anal. Found: C, 70.01; H, 6.25; N, 15.52. $C_{21}H_{22}N_4O_2$ requires C, 69.59; H, 6.12; N, 15.46%.

### 4.21. 2-Cyclopropyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19e)

The title compound was prepared by Negishi coupling between cyclopropylzinc bromide (generated from cyclopropylmagnesium bromide 1.14 mL, 0.44 M, 0.50 mmol) and 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (85 mg, 0.25 mmol) as described for compound **19b** above. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1); yield 62 mg (72%), colorless oil. Evaporation from acetone–hexane gave colorless crystalline compound, mp 115–116 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.02–1.09 (m, 2H, $CH_2$), 1.18–1.25 (m, 2H, $CH_2$), 2.42 (tt, $J$ = 8.1 and 4.8 Hz, 1H, CH), 3.76 (s, 3H, $OCH_3$), 5.27 (s, 2H, $NCH_2$), 6.60 (dd, $J$ = 3.4 and 1.7 Hz, 1H, H-4 in furyl), 6.84 (d, $J$ = 8.7 Hz, 2H, Ar), 7.24 (d, $J$ = 8.7 Hz, 2H, Ar), 7.71–7.74 (m, 2H, H-5 and H-3 in furyl), 7.89 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 10.7 (2× $CH_2$), 18.3 (CH), 46.5 ($NCH_2$), 55.2 ($OCH_3$), 112.3 (C-4 in furyl), 114.3 (CH in Ar), 116.4 (C-3 in furyl), 126.4 (C-5), 127.4 (C-1 in Ar), 129.5 (CH in Ar), 143.3 (C-8), 145.4 (C-6), 145.5 (C-5 in furyl), 150.3 (C-2 in furyl), 152.9 (C-4), 159.6 (C-4 in Ar), 166.5 (C-2); MS-EI $m/z$ (rel %) 346 (78, $M^+$), 331 (4), 239 (2), 225 (6), 121 (100); Anal. Found: C, 69.37; H, 5.18; N, 16.12. $C_{20}H_{18}N_4O_2$ requires C, 69.35; H, 5.24; N, 16.17%.

### 4.22. 2-Cyclopentenyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19f)

A round-bottomed flask with condenser was charged with magnesium turnings (243 mg, 10.0 mmol) and a few crystals of $I_2$. A solution of cyclopentyl bromide [2 mL of a solution of cyclopentyl bromide (1.49 g, 10.0 mmol) in dry THF (10 mL)] was added. The stirred mixture was heated gently to start the reaction. The rest of the cyclopentyl bromide solution was added at a rate to keep gentle reflux. The mixture was stirred for additional 2 h, cooled, and filtered under $N_2$, and the resulting cyclopentylmagnesium bromide was titrated. Cyclopentylmagnesium bromide (1.00 mL, 0.50 M, 0.50 mmol) was cooled to 0 °C and $ZnBr_2$ (500 μL, 1.00 M, 0.50 mmol) was added. The mixture was stirred 1 h at room temperature before a solution of 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (85 mg, 0.25 mmol) in dry THF (1.5 mL) and tetrakis(triphenylphosphine)palladium(0) [generated in situ from tris(dibenzylideneacetone)dipalladium (5.7 mg, 6.25 μmol) and triphenylphosphine (13.1 mg, 0.050 mmol)] in THF (1 mL) was added. The resulting mixture was then refluxed for 21 h, cooled, and worked up as described for compound **19b** above. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1); yield 57 mg (61%), colorless oil. Evaporation from acetone–hexane gave colorless crystalline compound, mp 114–115 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.63–1.79 (m, 2H, $CH_2$), 1.79–1.95 (m, 2H, $CH_2$), 1.95–2.08 (m, 2H, $CH_2$), 2.08–2.21 (m, 2H, $CH_2$), 3.77 (s, 3H, $OCH_3$), 5.33 (s, 2H, $NCH_2$), 6.61 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.28 (d, $J$ = 8.7 Hz, 2H, Ar), 7.73 (dd, $J$ = 1.8 and 0.7 Hz, H-5 in furyl), 7.76 (br d, $J$ = 3.5 Hz, H-3 in furyl), 7.94 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 26.0 (2× $CH_2$), 33.5 (2× $CH_2$), 46.6 ($NCH_2$), 48.9 (CH), 55.3 ($OCH_3$), 112.3 (C-4 in furyl), 114.4 (CH in Ar), 116.5 (C-3 in furyl), 126.5 (C-5), 127.6 (C-1 in Ar), 129.6 (CH in Ar), 143.6 (C-8), 145.5 (C-5 in furyl), 150.4 (C-2 in furyl), 152.8 (C-4), 159.7 (C-4 in Ar), 169.1 (C-2), C-6 was hidden; MS-EI $m/z$ (rel %) 374 (44, $M^+$), 346 (27), 333 (75), 253 (5), 225 (4), 121 (100); Anal. Found: C, 70.53; H, 5.98; N, 15.01. $C_{22}H_{22}N_4O_2$ requires C, 70.57; H, 5.92; N, 14.96%.

### 4.23. 2-Ethenyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19g)

The title compound was prepared by Stille coupling between 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (341 mg, 1.00 mmol) and ethenyl(tributyl)stannane (350 μL, 1.20 mmol) as described for compound **4** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 254 mg (76%), colorless crystals, mp 94–95 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.79 (s, 3H, $OCH_3$), 5.38 (s, 2H, $NCH_2$), 5.74 (dd, $J$ = 10.5 and 1.9 Hz, 1H, =$CH_2$), 6.65 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.73 (dd, $J$ = 17.3 and 1.9 Hz, 1H, =$CH_2$), 6.88 (d, $J$ = 8.7 Hz, 2H, Ar), 7.07 (dd, $J$ = 17.3 and 10.5 Hz, 1H, =CH), 7.30 (d, $J$ = 8.7 Hz, 2H, Ar), 7.77 (dd, $J$ = 1.8 and 0.7 Hz, 1H, H-5 in furyl), 7.83 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.99 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.6 ($NCH_2$), 55.2 ($OCH_3$), 112.4 (C-4 in furyl), 114.4 (CH in Ar), 116.8 (C-3 in furyl), 122.4 (=$CH_2$), 127.1 (C-5), 127.3 (C-1 Ar), 129.5 (CH in Ar), 136.9 (=CH), 144.4 (C-8), 145.6 (C-5 in furyl), 145.6 (C-6), 150.1 (C-2 in furyl), 152.7 (C-4), 158.9 (C-2), 159.7 (C-4 in Ar); MS-EI $m/z$ (rel %) 332 (60, $M^+$), 317 (3), 121 (100), 78 (6), 77 (6); Anal. Found: C, 69.01; H, 4.84; N, 16.67. $C_{19}H_{16}N_4O_2$ requires C, 68.66; H, 4.85; N, 16.86%.

### 4.24. 2-(1-Ethoxyvinyl)-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19h)

The title compound was prepared by Stille coupling between 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (170 mg, 0.50 mmol) and 1-(ethoxyvinyl)tributylstannane (203 μL, 0.60 mmol) as described

for compound **4** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1); yield 155 mg (82%), colorless powdery crystals, mp 144–145 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.53 (t, $J$ = 7.0 Hz, 3H, $CH_3$), 3.77 (s, 3H, $OCH_3$), 4.06 (q, $J$ = 7.0 Hz, 2H, $OCH_2$), 4.63 (d, $J$ = 1.9 Hz, 1H, =$CH_2$), 5.38 (s, 2H, $NCH_2$), 5.77 (d, $J$ = 1.9 Hz, 1H, =$CH_2$), 6.61 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 furyl), 6.86 (d, $J$ = 8.7 Hz, 2H, Ar), 7.29 (d, $J$ = 8.7 Hz, 2H, Ar), 7.73 (m, 1H, H-5 in furyl), 7.78 (dd, $J$ = 3.5 and 0.7 Hz, 1H, H-3 in furyl), 7.96 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 14.4 ($CH_3$), 46.8 ($NCH_2$), 55.2 ($OCH_3$), 64.1 ($OCH_2$), 89.4 (=$CH_2$), 112.3 (C-4 in furyl), 114.4 (CH in Ar), 116.8 (C-3 in furyl), 127.0 (C-1 in Ar), 127.4 (C-5), 129.7 (CH in Ar), 144.6 (C-8), 145.6 (C-6), 145.7 (C-5 in furyl), 150.1 (C-2 in furyl), 152.6 (C-4), 156.2 (C-2), 157.9 (=CO), 159.7 (C-4 in Ar); MS-EI $m/z$ (rel %) 376 (4, $M^+$), 362 (16), 361 (69), 332 (15), 331 (15), 121 (100); Anal. Found: C, 67.16; H, 5.50; N, 14.78. $C_{21}H_{20}N_4O_3$ requires C, 67.01; H, 5.36; N, 14.88%.

### 4.25. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-phenyl-9*H*-purine (19i)

The title compound was prepared by Stille coupling between 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (125 mg, 0.367 mmol) and trimethyl-(phenyl)stannane (100 μL, 0.55 mmol) as described for compound **4** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:3), followed by EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 122 mg (87%), colorless crystalline compound, mp 140–142 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.72 (s, 3H, $OCH_3$), 5.35 (s, 2H, $NCH_2$), 6.64 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.7 Hz, 2H, Ar), 7.28 (d, $J$ = 8.7 Hz, 2H, Ar), 7.42–7.53 (m, 3H, Ph), 7.78 (dd, $J$ = 1.8 and 0.8 Hz, H-5 in furyl), 7.82 (dd, $J$ = 3.5 and 0.8 Hz, H-5 in furyl), 7.97 (s, 1H, H-8), 8.61–8.64 (m, 2H, Ph); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.7 ($NCH_2$), 55.2 ($OCH_3$), 112.3 (C-4 in furyl), 114.4 (CH in Ar), 116.4 (C-3 in furyl), 127.0 (C-5), 127.5 (C-1 in Ar), 128.3 (CH in Ph), 128.4 (CH in Ph), 129.5 (CH in Ar), 130.1 (CH in Ph), 138.1 (C-1 in Ph), 144.4 (C-8), 145.8 (C-5 in furyl), 145.8 (C-6), 150.8 (C-2 in furyl), 153.1 (C-4), 158.9 (C-2), 159.7 (C-4 in Ar); MS-EI $m/z$ (rel %) 382 (70, $M^+$), 367 (4), 121 (100), 78 (5), 77 (7); Anal. Found: C, 72.27; H, 4.82; N, 14.73. $C_{23}H_{18}N_4O_2$ requires C, 72.24; H, 4.74; N, 14.65%.

### 4.26. 2,6-(Di-2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (19j)

The title compound was prepared by Stille coupling between 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine (77 mg, 0.25 mmol) and 2-(tributylstannyl)furan (236 μL, 0.75 mmol) as described for compound **4** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1); yield 69 mg (74%), off-white powdery crystals, mp 155–156 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.75 (s, 3H, $OCH_3$), 5.38 (s, 2H, $CH_2$), 6.56 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in 2-furyl), 6.63 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in 6-furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.27 (d, $J$ = 8.7 Hz, 2H, Ar), 7.39 (dd, $J$ = 3.4 and 0.7 Hz, 1H, H-3 in 2-furyl), 7.63–7.64 (m, H-5 in 2-furyl), 7.75–7.76 (m, H-5 in 6-furyl), 7.83 (dd, $J$ = 3.5 and 0.6 Hz, 1H, H-3 in 6-furyl), 7.94 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.7 ($CH_2$), 55.2 ($OCH_3$), 112.0 (C-4 in 2-furyl), 112.4 (C-4 in 6-furyl), 112.7 (C-3 in 2-furyl), 114.4 (CH in Ar), 117.2 (C-3 in 6-furyl), 126.7 (C-5), 127.0 (C-1 in Ar), 129.6 (CH in Ar), 144.3 (C-8), 144.6 (C-5 in 2-furyl), 145.9 (C-5 in 6-furyl), 146.1 (C-2/C-4/C-6), 149.9 (C-2 in 6-furyl), 152.3 (C-2 in 2-furyl), 152.6 (C-2/C-4/C-6), 152.7 (C-4/C-2/C-6), 159.7 (C-4 in Ar); MS-EI $m/z$ (rel %) 372 (55, $M^+$), 357 (2), 121 (100), 78 (6), 77 (6); Anal. Found: C, 67.89; H, 4.50; N, 14.89. $C_{21}H_{16}N_4O_3$ requires C, 67.73; H, 4.33; N, 15.05%.

### 4.27. 2-Acetyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (20)

A mixture of 2-(1-ethoxyvinyl)-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **19h** (87 mg, 0.23 mmol), acetone (1.6 mL), and 1 M HCl (0.4 mL) was stirred for 20 h at ambient temperature, before water (5 mL) was added and the mixture was extracted with EtOAc (4× 15 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 68 mg (85%), colorless powdery crystals, mp. 166–167 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.87 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 5.42 (s, 2H, $CH_2$), 6.63 (dd, $J$ = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.84 (d, $J$ = 8.6 Hz, 2H, Ar), 7.26 (d, $J$ = 8.6 Hz, 2H, Ar), 7.76 (dd, $J$ = 1.6 and 0.7 Hz, 1H, H-5 in furyl), 7.81 (dd, $J$ = 3.5 and 0.6 Hz, 1H, H-3 in furyl), 8.13 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 27.2 ($CH_3$), 47.1 ($CH_2$), 55.2 ($OCH_3$), 112.6 (C-4 in furyl), 114.4 (CH in Ar), 117.6 (C-3 in furyl), 126.6 (C-1 in Ar), 128.9 (C-5), 129.7 (CH in Ar), 145.7 (C-6), 146.3 (C-5 in furyl), 146.6 (C-8), 149.7 (C-2 in furyl), 152.5 (C-4), 154.5 (C-2), 159.8 (C-4 in Ar), 197.7 (C=O); MS-EI $m/z$ (rel %) 348 (55, $M^+$), 333 (7), 305 (2), 121 (100), 91 (3); Anal. Found: C, 65.38; H, 4.66; N, 15.86. $C_{19}H_{16}N_4O_3$ requires C, 65.51; H, 4.63; N, 16.08%.

### 4.28. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine-2-carbonitrile (21)

A mixture of zinc cyanide (70 mg, 0.60 mmol), 2-chloro-6-(2-furyl)-9-(4-methoxy-phenylmethyl)-9*H*-purine **1b** (170 mg, 0.50 mmol) and tetrakis(triphenylphosphine)-palladium(0) [generated in situ from tris(diphenylmethylideneacetone)dipalladium (32 mg, 0.035 mmol) and triphenylphosphine (73 mg, 0.28 mmol)] in dry NMP (4 mL) was stirred at 120 °C under $N_2$ for 24 h and cooled, before 2 M aq ammonia (5 mL) was added. The mixture was extracted with EtOAc (3× 20 mL), and the combined organic extracts were washed with 2 M aq ammonia (15 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was isolated by flash chromatography on silica gel eluting

with $CH_2Cl_2$/acetone (19:1); yield 112 mg (68%), colorless crystals, mp 205–207 °C. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 3.78 (s, 3H, $OCH_3$), 5.37 (s, 2H, $CH_2$), 6.67 (dd, $J$ = 3.4 and 1.5 Hz, 1H, H-4 in furyl), 6.88 (d, $J$ = 8.6 Hz, 2H, Ar), 7.29 (d, $J$ = 8.6 Hz, 2H, Ar), 7.79 (br s, H-5 in furyl), 7.87 (br d, $J$ = 3.5 Hz, 1H, H-3 in furyl), 8.17 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 47.5 ($CH_2$), 55.3 ($OCH_3$), 113.0 (C-4 in furyl), 114.6 (CH in Ar), 116.4 (CN), 119.2 (C-3 in furyl), 126.1 (C-1 in Ar), 129.2 (C-5), 129.8 (CH in Ar), 137.6 (C-6/C-2), 146.6 (C-2/C-6), 146.6 (C-8), 147.1 (C-5 in furyl), 148.6 (C-2 in furyl), 151.7 (C-4), 160.0 (C-4 in Ar); MS-EI $m/z$ (rel %) 331 (26, $M^+$), 121 (100), 91 (4), 78 (6), 77 (5); HRMS: Found 331.1056 Calcd for $C_{18}H_{13}N_5O_2$ 331.1069; Anal. Found: C, 65.08; H, 3.94; N, 20.76. $C_{18}H_{13}N_5O_2$ requires C, 65.25; H, 3.95; N, 21.14%.

### 4.29. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-trimethylsilylethynyl-9*H*-purine (22)

A mixture of CuI (9.5 mg, 0.050 mmol), bis(triphenylphosphine)palladium(II) chloride (17.5 mg, 0.025 mmol), 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1b** (170 mg, 0.50 mmol), triethylamine (250 μL, 1.79 mmol), and ethynyltrimethylsilane (139 μL, 1.00 mmol) in dry DMF (1.5 mL) was heated at 120 °C for 5 h in a sealed tube. After cooling, the solution was evaporated in vacuo, dissolved in $CH_2Cl_2$ (20 mL), and filtered through a plug of silica gel (5 g) eluting with $CH_2Cl_2$/acetone (7:3) (100 mL). The solution was evaporated in vacuo and the product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (39:1); yield 82 mg (41%), off-white crystalline compound, mp 155–157 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.26 (s, 9H, TMS), 3.71 (s, 3H, $OCH_3$), 5.31 (s, 2H, $NCH_2$), 6.58 (dd, $J$ = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.80 (d, $J$ = 8.7 Hz, 2H, Ar), 7.17 (d, $J$ = 8.7 Hz, 2H, Ar), 7.70 (m, 1H, H-5 in furyl), 7.79 (br d, $J$ = 3.5 Hz, H-3 in furyl), 7.96 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ −0.4 (TMS), 46.6 ($NCH_2$), 55.2 ($OCH_3$), 92.1 (C≡), 103.2 (C≡), 112.5 (C-4 in furyl), 114.4 (CH in Ar), 117.8 (C-3 in furyl), 126.7 (C-1 in Ar), 127.4 (C-5), 129.4 (CH in Ar), 145.1 (C-8), 145.8 (C-6/C-2), 146.0 (C-5 in furyl), 149.1 (C-2 in furyl), 152.0 (C-4), 159.7 (C-4 in Ar), C-2 or C-6 was hidden; MS-EI $m/z$ (rel %) 402 (56, $M^+$), 387 (9), 251 (3), 121 (100), 108 (2); Anal. Found: C, 65.66; H, 5.53; N, 13.88. $C_{22}H_{22}N_4O_2Si$ requires C, 65.65; H, 5.51; N, 13.92%.

### 4.30. 2-Ethynyl-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (23)

A mixture of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-2-trimethylsilylethynyl-9*H*-purine **22** (120 mg, 0.298 mmol) and $K_2CO_3$ (413 mg, 3.13 mmol) in $CH_2Cl_2$ (2.5 mL) and MeOH (2.5 mL) was stirred for 1.5 h at ambient temperature, diluted with $CH_2Cl_2$ (20 mL), washed with brine (3× 15 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (9:1); yield 72 mg (73%), off-white powdery crystals, mp 155 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.09 (s, 1H, ≡CH), 3.75 (s, 3H, $OCH_3$), 5.31 (s, 2H, $NCH_2$), 6.62 (dd, $J$ = 3.5 Hz, $J$ = 1.7 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.24 (d, $J$ = 8.7 Hz, 2H, Ar), 7.74 (m, 1H, H-5 in furyl), 7.82 (br d, $J$ = 3.5 Hz, H-3 in furyl), 8.03 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 46.8 ($NCH_2$), 55.3 ($OCH_3$ in Ar), 74.4 (≡CH), 82.6 (*C*≡CH), 112.6 (C-4 in furyl), 114.5 (CH in Ar), 117.9 (C-3 in furyl), 126.8 (C-1 in Ar), 127.7 (C-5), 129.6 (CH in Ar), 145.2 (C-2), 145.3 (C-8), 146.2 (C-6), 146.3 (C-5 in furyl), 149.2 (C-2 in furyl), 152.1 (C-4), 159.8 (C-4 in Ar); MS-EI $m/z$ (rel %) 330 (54, $M^+$), 315 (3), 121 (100), 78 (6), 77 (6); Anal. Found: C, 69.26; H, 4.37; N, 16.71. $C_{19}H_{14}N_4O_2$ requires C, 69.08; H, 4.27; N, 16.96%.

### 4.31. 6-Chloro-2-iodo-9-(4-methoxyphenylmethyl)-9*H*-purine (24)

2-Amino-6-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine **3a** (290 mg, 1.00 mmol), diiodomethane (10 mL), and isoamyl nitrite (2.7 mL, 20 mmol) were heated at 85 °C for 75 min. After cooling, the solution was evaporated in vacuo, dissolved in EtOAc (30 mL), washed with brine (2× 15 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 197 mg (49%), colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.79 (s, 3H, $OCH_3$), 5.31 (s, 2H, $CH_2$), 6.89 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 7.90 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 47.5 ($CH_2$), 55.2 ($OCH_3$), 114.4 (CH in Ar), 116.5 (C-2), 125.8 (C-1 in Ar), 129.6 (CH in Ar), 131.2 (C-5), 144.9 (C-8), 150.0 (C-6), 152.4 (C-4), 159.8 (C-4 in Ar); MS-EI $m/z$ (rel %) 402/400 (16/46, $M^+$), 136 (2), 121 (100), 78 (8), 77 (6); Anal. Found: C, 39.07; H, 2.60; N, 13.91. $C_{13}H_{10}ClN_4O$ requires C, 38.98; H, 2.52; N, 13.99%.

### 4.32. 6-Chloro-9-(4-methoxyphenylmethyl)-2-propynyl-9*H*-purine (25)

Propyne (41 mg, 1.02 mmol) was condensed at −78 °C in a sealed tube. CuI (3.9 mg, 0.021 mmol), bis(triphenylphosphine)palladium(II) chloride (5.4 mg, 0.008 mmol), triethylamine (0.50 mL), and a solution of 6-chloro-2-iodo-9-(4-methoxyphenyl)-9*H*-purine **24** (82 mg, 0.205 mmol) in dry $CH_3CN$ (1.5 mL) were added. The tube was sealed and the mixture was stirred at 0 °C for 2 h. The reaction mixture was cooled to −78 °C, the flask was opened, and the reaction mixture was allowed to reach room temperature under $N_2$. The mixture was diluted with $CH_2Cl_2$ (5 mL) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) followed by EtOAc/hexane (2:1) and EtOAc/hexane (4:1); yield 46 mg (72%), colorless crystalline compound, mp 148–150 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.14 (s, 3H, $CH_3$), 3.79, (s, 3H, $OCH_3$), 5.35 (s, 2H, $CH_2$), 6.88 (d, $J$ = 8.7 Hz, 2H, Ar), 7.25 (d, $J$ = 8.7 Hz, 2H, Ar), 8.00 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 4.4 ($CH_3$), 47.3 ($CH_2$), 55.3 ($OCH_3$), 78.7 (C≡), 86.5 (C≡), 114.6 (CH in Ar), 126.2 (C-1 in Ar), 129.5 (CH

in Ar), 130.5 (C-5), 145.4 (C-8), 145.9 (C-6/C-2), 150.8 (C-2/C-6), 151.8 (C-4), 160.0 (C-4 in Ar); MS-EI *m/z* (rel %) 314/312 (18/47, $M^+$), 297 (3), 121 (100), 78 (8), 77 (7); Anal. Found: C, 61.45; H, 3.93; N, 17.80. $C_{16}H_{13}ClN_4O$ requires C, 61.44; H, 4.19; N, 17.91%.

### 4.33. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-(1-propynyl)-9*H*-purine (26)

*Method A.* The title compound was prepared by Stille coupling between 6-chloro-9-(4-methoxyphenylmethyl)-2-(1-propynyl)-9*H*-purine **25** (29 mg, 0.093 mmol) and 2-(tributylstannyl)furan (35 μL, 0.11 mmol) as described for compound **4** above. The product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1); yield 18 mg (56%), off-white crystalline compound, mp 158–160 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.12 (s, 3H, $CH_3$), 3.76 (s, 3H, $OCH_3$), 5.35 (s, 2H, $NCH_2$), 6.61 (dd, $J$ = 3.5 Hz, $J$ = 1.7 Hz, 1H, H-4 in furyl), 6.85 (d, $J$ = 8.7 Hz, 2H, Ar), 7.23 (d, $J$ = 8.7 Hz, 2H, Ar), 7.73 (m, 1H, H-5 in furyl), 7.82 (dd, $J$ = 3.5 and 0.6 Hz, H-3 in furyl), 7.96 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 4.5 ($CH_3$), 46.6 ($NCH_2$), 55.2 ($OCH_3$), 79.7 (C≡), 84.6 (C≡), 112.5 (C-4 in furyl), 114.4 (CH in Ar), 117.6 (C-3 in furyl), 126.8 (C-1 in Ar), 127.1 (C-5), 129.5 (CH in Ar), 144.7 (C-8), 146.0 (C-5 in furyl), 146.1 (C-6/C-2), 146.6 (C-2/C-6), 149.2 (C-2 in furyl), 152.1 (C-4), 159.7 (C-4 in Ar); MS-EI *m/z* (rel %) 344 (100, $M^+$), 330 (2), 329 (10), 315 (2), 121 (78); Anal. Found: C, 69.71; H, 4.78; N, 16.20. $C_{20}H_{16}N_4O_2$ requires C, 69.76; H, 4.68; N, 16.27%.

*Method B.* Propyne (476 mg, 11.9 mmol) was condensed at −78 °C in a sealed tube. CuI (2.2 mg, 0.0116 mmol), bis(triphenylphosphine)palladium(II) chloride (4.9 mg, 0.007 mmol), a solution of 6-(2-furyl)-2-iodo-9-(4-methoxyphenylmethyl)-9*H*-purine **5** (50 mg, 0.12 mmol) in dry $CH_3CN$ (1 mL), and triethylamine (0.50 mL, 3.6 mmol) were added. The tube was sealed and the mixture was stirred at ambient temperature for 24 h. The reaction mixture was cooled to −78 °C, the flask was opened, and the reaction mixture was allowed to reach ambient temperature under $N_2$. The mixture was evaporated in vacuo and the product was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/acetone (19:1); yield 25 mg (63%).

### 4.34. 6-Chloro-9-(4-methoxyphenylmethyl)-2-trifluoromethyl-9*H*-purine (28a) and 6-chloro-7-(4-methoxyphenylmethyl)-2-trifluoromethyl-7*H*-purine (28b)

Potassium carbonate (610 mg, 4.41 mmol) and 6-chloro-2-trifluoromethyl-9*H*-purine **27** (328 mg, 1.47 mmol) in dry DMF (10 mL) were stirred at ambient temperature under $N_2$ for 20 min, before 4-methoxyphenylmethyl chloride (400 μL, 2.95 mmol) was added. The resulting mixture was stirred for 16 h, filtered, and evaporated in vacuo. The isomers were separated by flash chromatography on silica gel eluting with EtOAc/hexane (1:1).

**4.34.1. 6-Chloro-9-(4-methoxyphenylmethyl)-2-trifluoromethyl-9*H*-purine (28a).** Yield: 206 mg (41%) colorless crystalline compound, mp 104–106 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.78 (s, 3H, $OCH_3$), 5.41 (s, 2H, $CH_2$), 6.88 (d, $J$ = 8.7 Hz, 2H, Ar), 7.30 (d, $J$ = 8.7 Hz, 2H, Ar), 8.18 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 48.0 ($CH_2$), 55.3 ($OCH_3$), 114.7 (CH in Ar), 119.3 (q, $J_{CF}$ = 275 Hz, $CF_3$), 125.7 (C-1 in Ar), 129.9 (CH in Ar), 132.6 (C-5), 146.9 (C-8), 149.8 (q, $J_{CF}$ = 38 Hz, C-2), 151.6 (C-4/C-6), 151.7 (C-6/C-4), 160.1 (C-4 in Ar); $^{19}$F NMR ($CDCl_3$, 188 MHz) −69.20 ($CF_3$); MS-EI *m/z* (rel %) 344/342 (12/36, $M^+$), 121 (100), 91 (3), 78 (7), 77 (6); Anal. Found: C, 49.55; H, 3.23; N, 16.35 $C_{14}H_{10}ClF_3N_4O$ requires C, 49.07; H, 2.94; N, 16.35%.

**4.34.2. 6-Chloro-7-(4-methoxyphenylmethyl)-2-trifluoromethyl-7*H*-purine (28b).** Yield: 93 mg (18%), colorless powdery crystals, mp 173–175 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.78 (s, 3H, $OCH_3$), 5.65 (s, 2H, $CH_2$), 6.89 (d, $J$ = 8.7 Hz, 2H, Ar), 7.15 (d, $J$ = 8.7 Hz, 2H, Ar), 8.31 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 50.7 ($CH_2$), 55.3 ($OCH_3$), 114.8 (CH in Ar), 119.3 (q, $J_{CF}$ = 275 Hz, $CF_3$), 123.5 (C-1 in Ar), 125.5 (C-5), 129.0 (CH in Ar), 144.0 (C-6), 150.2 (q, $J_{CF}$ = 38 Hz, C-2), 150.8 (C-8), 160.1 (C-4 in Ar), 162.0 (C-4); MS-EI *m/z* (rel %) 344/342 (7/23, $M^+$), 121 (100), 91 (2), 78 (5), 77 (4); Anal. Found: C, 49.31; H, 3.34; N, 16.44. $C_{14}H_{10}ClF_3N_4O$ requires C, 49.07; H, 2.94; N, 16.35%.

### 4.35. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-2-trifluoromethyl-9*H*-purine (29)

The title compound was prepared by Stille coupling between 6-chloro-9-(4-methoxyphenylmethyl)-2-trifluoromethyl-9*H*-purine **28a** (130 mg, 0.38 mmol) and 2-(tributylstannyl)furan (143 μL, 0.46 mmol) as described for compound **4** above. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) followed by EtOAc/hexane (2:1); yield 118 mg (83%), colorless crystals, mp 149–150 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.78 (s, 3H, $OCH_3$), 5.41 (s, 2H, $CH_2$), 6.66 (dd, $J$ = 3.6 and 1.7 Hz, 1H, H-4 in furyl), 6.88 (d, $J$ = 8.6 Hz, 2H, Ar), 7.30 (d, $J$ = 8.6 Hz, 2H, Ar), 7.79 (m, 1H, H-5 in furyl), 7.89 (br d, $J$ = 3.5 Hz, 1H, H-3 in furyl), 8.13 (s, 1H, H-8); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 47.2 ($CH_2$), 55.3 ($OCH_3$), 112.8 (C-4 in furyl), 114.5 (CH in Ar), 118.7 (C-3 in furyl), 120.0 (q, $J_{CF}$ = 275 Hz, $CF_3$), 126.4 (C-1 in Ar), 128.8 (C-5), 129.7 (CH in Ar), 146.1 (C-8), 146.2 (C-6), 146.8 (C-5 in furyl), 149.1 (C-2 furyl), 150.4 (q, $J_{CF}$ = 36.5 Hz, C-2), 152.1 (C-4), 159.9 (C-4 in Ar); $^{19}$F NMR ($CDCl_3$, 188 MHz) −69.3 ($CF_3$); MS-EI *m/z* (rel %) 374 (40, $M^+$), 187 (2), 121 (100), 91 (2), 78 (4); Anal. Found: C, 57.97; H, 3.82; N, 15.15. $C_{18}H_{13}F_3N_4O_2$ requires C, 57.76; H, 3.50; N, 14.97%.

### 4.36. 6-Chloro-9-(4-methoxyphenylmethyl)-8-methyl-9*H*-purine (31a)

6-Chloro-9-(4-methoxyphenylmethyl)-9*H*-purine **30** (137 mg, 0.50 mmol) in THF (2 mL) was added dropwise to a stirred solution of LDA [generated in situ from diisopropylamine (0.11 mL, 0.77 mmol) and *n*-BuLi (0.44 mL, 0.7 mmol, 1.6 M in hexane)] in THF (2 mL)

at −78 °C under $N_2$. After stirring for 1 h at −78 °C, iodomethane (0.31 mL, 5.0 mmol) was added dropwise and the resulting mixture was stirred at −78 °C for 3.5 h, gradually warmed to ambient temperature over 2 h, and stirred at ambient temperature for 15 h. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (2× 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 96 mg (67%), colorless crystals, mp 121–123 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.59 (s, 3H, $CH_3$), 3.76 (s, 3H, $OCH_3$), 5.36 (s, 2H, $CH_2$), 6.83 (d, $J$ = 8.6 Hz, 2H, Ar), 7.12 (d, $J$ = 8.6 Hz, 2H, Ar), 8.70 (s, 1H, H-2); MS-EI *m/z* (rel %) 290/288 (10/30, $M^+$), 275 (1), 273 (4), 246 (1), 121 (100); HRMS: Found 288.0776, Calcd for $C_{14}H_{13}ClN_4O$ 288.0778; Anal. Found: C, 58.36; H, 4.44. $C_{14}H_{13}ClN_4O$ requires C, 58.82; H, 4.54%.

### 4.37. 6,8-Dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine (31b)

6-Chloro-9-(4-methoxyphenylmethyl)-9*H*-purine **30** (275 mg, 1.00 mmol) in THF (4 mL) was added dropwise to a stirred solution of LDA [generated in situ from diisopropylamine (0.21 mL, 1.50 mmol) and *n*-BuLi (0.88 mL, 1.40 mmol, 1.6 M in hexane)] in THF (4 mL) at −78 °C under $N_2$. After stirring for 1 h at −78 °C, a solution of hexachloroethane (473 mg, 2.00 mmol) in THF (4 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 2 h, and 10 min without cooling. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (2× 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) followed by EtOAc/hexane (1:3); yield 251 mg (81%), colorless crystals, mp 110–112 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.73 (s, 3H, $OCH_3$), 5.38 (s, 2H, $CH_2$), 6.81 (d, $J$ = 8.5 Hz, 2H, Ar), 7.30 (d, $J$ = 8.5 Hz, 2H, Ar), 8.72 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 47.1 ($CH_2$), 55.3 ($OCH_3$), 114.3 (CH in Ar), 126.0 (C-1 in Ar), 129.6 (CH in Ar), 130.5 (C-5), 144.1 (C-8), 149.4 (C-6), 152.0 (C-2), 152.4 (C-4), 159.7 (C-4 in Ar); MS-EI *m/z* (rel %) 312/310/308 (1/10/16, $M^+$), 273 (2), 121 (100), 78 (5), 77 (5); Anal. Found: C, 50.24; H, 3.11; N 17.83. $C_{13}H_{10}Cl_2N_4O$ requires C, 50.50; H, 3.26; N, 18.12%.

### 4.38. 6-(2-Furyl)-9-(4-methoxyphenylmethyl)-8-methyl-9*H*-purine (32a)

*Method A:* The title compound was prepared by Stille coupling on 6-chloro-9-(4-methoxyphenylmethyl)-8-methyl-9*H*-purine **31a** (0.65 mmol) as described for compound **4** above and the product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 176 mg (85%), colorless wax. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.56 (s, 3H, $CH_3$), 3.72 (s, 3H, $OCH_3$), 5.34 (s, 2H, $CH_2$), 6.61 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.79 (d, $J$ = 8.6 Hz, 2H, Ar), 7.09 (d, $J$ = 8.6 Hz, 2H, Ar), 7.72 (br s, 1H, H-5 in furyl), 7.76 (br d, $J$ = 3.4 Hz, 1H, H-3 in furyl), 8.88 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 14.9 ($CH_3$), 45.4 ($CH_2$), 55.2 ($OCH_3$), 112.4 (C-4 in furyl), 114.3 (CH in Ar), 116.5 (C-3 in furyl), 127.3 (C-1 in Ar), 127.6 (C-5), 128.4 (CH in Ar), 145.4 (C-5 in furyl), 145.7 (C-6), 149.9 (C-2 in furyl), 151.8 (C-2), 153.5 (C-4/C-8), 154.3 (C-4/C-8), 159.3 (C-4 in Ar); MS-EI *m/z* (rel %) 320 (77, $M^+$), 305 (8), 213 (1), 160 (3), 121 (100); HRMS: Found 320.1276, Calcd for $C_{18}H_{16}N_4O_2$ 320.1273; Anal. Found: C, 67.30; H, 5.02; N 17.26. $C_{18}H_{16}N_4O_2$ requires C, 67.75; H, 5.22; N, 17.49%.

*Method B:* LDA [generated from diisopropylamine (0.085 mL, 0.60 mmol) and *n*-BuLi (0.34 mL, 0.55 mmol, 1.6 M in hexane)] in THF (2 mL) was added dropwise to a stirred solution of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1a** (153 mg, 0.50 mmol) in THF (10 mL) at −78 °C under $N_2$. After stirring for 50 min at −78 °C, iodomethane (0.62 mL, 1.0 mmol) was added dropwise and the resulting mixture was stirred at −78 °C for 5 h, gradually warmed to ambient temperature over ca. 2 h and stirred at ambient temperature for ca. 15 h. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (3× 25 mL). The combined organic extracts were washed with brine (2× 20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 110 mg (69%).

### 4.39. 8-Chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (32b)

*Method A:* A mixture of tris(diphenylmethylideneacetone)-dipalladium chloroform adduct (23 mg, 0.022 mmol) and tri(2-furyl)phosphine (37 mg, 0.16 mmol) in DMF (8 mL) was stirred at ambient temperature under $N_2$-atm for 15 min., before 6,8-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **31b** (228 mg, 0.74 mmol) and 2-furyl(tributyl)tin (0.28 mL, 0.88 mmol) were added. The resulting mixture was stirred for 18 h at 50 °C and evaporated in vacuo. The residue was dissolved in acetonitrile (30 mL) and washed with hexane (15× 10 mL). The acetonitrile layer was evaporated and the product was isolated by flash chromatography on silica eluting with EtOAc/hexane (1:5) followed by EtOAc/hexane (1:2); yield 118 mg (47%), colorless small needles, mp 156–157 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.76 (s, 3H, $OCH_3$), 5.41 (s, 2H, $CH_2$), 6.64 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.84 (d, $J$ = 8.4 Hz, 2H, Ar), 7.33 (d, $J$ = 8.4 Hz, 2H, Ar), 7.74 (br s, 1H, H-5 in furyl), 7.80 (br d, $J$ = 3.4 Hz, 1H, H-3 in furyl), 8.94 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 46.4 ($CH_2$), 55.3 ($OCH_3$), 112.6 (C-4 in furyl), 114.2 (CH in Ar), 117.6 (C-3 in furyl), 126.6 (C-1 in Ar), 127.2 (C-5), 129.5 (CH in Ar), 143.2 (C-6/C-8), 144.5 (C-6/C-8), 145.9 (C-5 in furyl), 149.0 (C-2 in furyl), 152.7 (C-2), 153.1 (C-4), 159.6 (C-4 in Ar); MS-EI *m/z* (rel %) 342/340 (10/30, $M^+$), 170 (1), 121 (100), 78 (4), 77 (5); Anal. Found: C, 59.54; H, 3.84; N 16.57. $C_{17}H_{13}ClN_4O_2$ requires C, 59.92; H, 3.84; N, 16.44%. Fractions containing 6,8-di-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **32d** (see below) were also isolated.

*Method B:* LDA [generated from diisopropylamine (0.13 mL, 0.89 mmol) and *n*-BuLi (0.51 mL, 0.81 mmol, 1.6 M in hexane)] in THF (4 mL) was added dropwise to a stirred solution of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1a** (227 mg, 0.74 mmol) in THF (10 mL) at −78 °C under $N_2$. After stirring for 55 min at −78 °C, hexachloroethane (350 mg, 1.48 mmol) in THF (4 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 3 h and without cooling for 15 min. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (3× 25 mL). The combined organic extracts were washed with brine (2× 20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:5) followed by EtOAc/hexane (1:2); yield 137 mg (54%). 8-Chloro-6-(5-chloro-2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **35b** (41 mg, 15%) was also isolated (data see below).

### 4.40. 8-Bromo-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (32c)

LDA [generated from diisopropylamine (0.17 mL, 1.2 mmol) and *n*-BuLi (0.69 mL, 1.1 mmol, 1.6 M in hexane)] in THF (4 mL) was added dropwise to a stirred solution of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1a** (306 mg, 1.00 mmol) in THF (20 mL) at −78 °C under $N_2$. After stirring for 50 min at −78 °C, a solution of 1,2-dibromo-1,1,2,2,-tetrachloroethane (651 mg, 2.00 mmol) in THF (2 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 5 h, gradually warmed to ambient temperature over ca. 4 h, and stirred at ambient temperature for ca. 14 h. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (3× 25 mL). The combined organic extracts were washed with brine (2× 20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:5) followed by EtOAc/hexane (1:1); yield 153 mg (45%), colorless crystals, mp 150–151 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.74 (s, 3H, $OCH_3$), 5.39 (s, 2H, $CH_2$), 6.62 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.81 (d, $J$ = 8.6 Hz, 2H, Ar), 7.30 (d, $J$ = 8.6 Hz, 2H, Ar), 7.68 (br s, 1H, H-5 in furyl), 7.72 (br d, $J$ = 3.4 Hz, 1H, H-3 in furyl), 8.81 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 47.2 ($CH_2$), 55.3 ($OCH_3$), 112.6 (C-4 in furyl), 114.2 (CH in Ar), 117.8 (C-3 in furyl), 126.8 (C-1 in Ar), 128.5 (C-5), 129.4 (CH in Ar), 133.0 (C-8), 144.4 (C-6), 145.9 (C-5 in furyl), 149.0 (C-2 in furyl), 152.7 (C-2), 153.0 (C-4), 159.5 (C-4 in Ar); MS-EI *m*/*z* (rel %) 386/384 (15/15, $M^+$), 305 (6), 121 (100), 78 (5), 77 (5); HRMS: Found 384.0220, Calcd for $C_{17}H_{13}BrN_4O_2$ 3840222; Anal. Found: C, 53.25; H, 3.47; N 14.04. $C_{17}H_{13}BrN_4O_2$ requires C, 53.01; H, 3.40; N, 14.54%.

### 4.41. 6,8-Di(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (32d)

Fractions containing a mixture of the title compound and 8-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **32b** (from the synthesis of **32b** by method A, see above) were subjected to flash chromatography on silica gel eluting with acetone/hexane (1:4); yield 65 mg (24%), off-white crystalline solid, mp 134–136 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.72 (s, 3H, $OCH_3$), 5.76 (s, 2H, $CH_2$), 6.60 (dd, $J$ = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 6.65 (dd, $J$ = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 6.77 (d, $J$ = 8.6 Hz, 2H, Ar), 7.16 (d, $J$ = 8.6 Hz, 2H, Ar), 7.27 (br d, $J$ = 3.6 Hz, 1H, H-3 in furyl), 7.66 (m, 1H, H-5 in furyl), 7.74 (m, 1H, H-5 in furyl), 7.94 (br d, $J$ = 3.4 Hz, 1H, H-3 in furyl), 8.94 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 46.5 ($CH_2$), 55.2 ($OCH_3$), 112.4 (C-4 in furyl), 112.6 (C-4 in furyl), 114.1 (CH in Ar), 114.9 (C-3 in furyl), 117.6 (C-3 in furyl), 128.1 (C-1 in Ar and C-5), 128.4 (CH in Ar), 144.7 (C-8), 144.8 (C-5 in furyl), 145.5 (C-6 and C-5 in furyl), 149.4 (2× C-2 in furyl), 152.4 (C-2), 153.5 (C-4), 159.1 (C-4 in Ar); MS-EI *m*/*z* (rel %) 372 (43, $M^+$), 265 (1), 121 (100), 78 (5), 77 (6); Anal. Found: C, 67.92; H, 4.44; N 15.30. $C_{21}H_{16}N_4O_3$ requires C, 67.73; H, 4.33; N, 15.05%.

### 4.42. 6-(2-Furyl)-8-methoxy-9-(4-methoxyphenylmethyl)-9*H*-purine (33)

A mixture of 8-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **32b** (205 mg, 0.60 mmol) in a 0.7 M solution of sodium methoxide in methanol (10 mL) was stirred at reflux under $N_2$-atm for 4 h, cooled, and poured into cold satd aq $NH_4Cl$ (10 mL). Most of the methanol was removed by evaporated in vacuo and the aqueous mixture was extracted with EtOAc (4× 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporation in vacuo. The product was purified by flash chromatography on silica gel eluting with acetone/hexane (2:7); 111 mg (55%), colorless crystals, mp 143–144 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.75 (s, 3H, $OCH_3$), 4.28 (s, 3H, $OCH_3$), 5.18 (s, 2H, $CH_2$), 6.61 (dd, $J$ = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.82 (d, $J$ = 8.6 Hz, 2H, Ar), 7.31 (d, $J$ = 8.6 Hz, 2H, Ar), 7.72 (br s, 1H, H-5 in furyl), 7.81 (br d, $J$ = 3.4 Hz, 1H, H-3 in furyl), 8.81 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 44.2 ($CH_2$), 55.2 ($OCH_3$), 57.5 ($OCH_3$), 112.2 (C-4 in furyl), 114.0 (CH in Ar), 115.9 (C-3 in furyl), 126.1 (C-5), 127.7 (C-1 in Ar), 129.3 (CH in Ar), 141.3 (C-6), 145.6 (C-5 in furyl), 149.4 (C-2 in furyl), 150.7 (C-2), 152.3 (C-4), 158.3 (C-8), 159.2 (C-4 in Ar); MS-EI *m*/*z* (rel %) 336 (34, $M^+$), 168 (1), 121 (100), 78 (4), 77 (5); Anal. Found: C, 64.28; H, 4.69; N, 16.38. $C_{18}H_{16}N_4O_3$ requires C, 64.28; H, 4.80; N, 16.66%. 6-(2-Furyl)-8-hydroxy-9-(4-methoxyphenylmethyl)-9*H*-purine **34** 54 mg (28%) was also isolated (data see below).

### 4.43. 6-(2-Furyl)-8-hydroxy-9-(4-methoxyphenylmethyl)-9*H*-purine (34)

Colorless crystals, mp 249–251 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.75 (s, 3H, $OCH_3$), 5.07 (s, 2H, $CH_2$), 6.61 (dd, $J$ = 3.2 and 1.8 Hz, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.8 Hz, 2H, Ar), 7.28 (br d, $J$ = 3.2 Hz, 1H, H-3 in furyl), 7.45 (d, $J$ = 8.8 Hz, 2H, Ar), 7.64 (br s, 1H, H-5 in furyl), 8.65 (s, 1H, H-2), 8.97 (br s, 1H, NH); $^1$H NMR (DMSO-$d_6$, 600 MHz) $\delta$ 3.70 (s, 3H, $OCH_3$), 4.96 (s, 2H, $CH_2$), 6.73 (m, 1H, H-4 in furyl), 6.88 (d,

$J$ = 8.4 Hz, 2H, Ar), 7.29–7.31 (m 3H, H-3 in furyl and Ar), 7.91 (s, 1H, H-5 in furyl), 8.55 (s, 1H, H-2), 11.66 (br s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150 MHz) $\delta$ 42.1 ($CH_2$), 55.0 ($OCH_3$), 111.9 (C-3 in furyl), 112.4 (C-4 in furyl), 113.9 (CH in Ar), 115.3 (C-5), 128.4 (C-1 in Ar), 129.0 (CH in Ar), 132.3 (C-6), 145.5 (C-5 in furyl), 149.6 (C-2 in furyl), 150.4 (C-2), 150.5 (C-4), 153.4 (C-8), 158.7 (C-4 in Ar); MS-EI *m/z* (rel %) 322 (35, $M^+$), 122 (4), 121 (100), 78 (1), 77 (2); Anal. Found: C, 63.28; H, 4.52; N, 17.15. $C_{17}H_{14}N_4O_3$ requires C, 63.35; H, 4.38; N, 17.38%.

### 4.44. 9-(4-Methoxyphenylmethyl)-8-methyl-(5-methyl-2-furyl)-9*H*-purine (35a)

To a stirred solution of LDA [generated from diisopropylamine (0.25 mL, 1.74 mmol) and *n*-BuLi (0.91 mL, 1.45 mmol, 1.6 M in hexane)] in THF (4 mL) at −78 °C under $N_2$ was added dropwise a solution of 6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1a** (177 mg, 0.58 mmol) in THF (12 mL). After stirring for 1 h at −78 °C, iodomethane (0.36 mL, 5.8 mmol) was added dropwise and the resulting mixture was stirred at −78 °C for 6 h, gradually warmed to ambient temperature over ca. 2 h, and stirred at ambient temperature for ca. 15 h. Satd aq $NH_4Cl$ (15 mL) was added and the mixture was extracted with EtOAc (3× 25 mL). The combined organic extracts were washed with brine (2× 20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1); yield 106 mg (55%), off-white wax. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.44 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 3.68 (s, 3H, $OCH_3$), 5.28 (s, 2H, $CH_2$), 6.20 (d, $J$ = 3.4 Hz, 1H, H-4 in furyl), 6.75 (d, $J$ = 8.6 Hz, 2H, Ar), 7.06 (d, $J$ = 8.6 Hz, 2H, Ar), 7.73 (d, $J$ = 3.4 Hz, 1H, H-3 in furyl), 8.84 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 14.0 ($CH_3$), 14.7 ($CH_3$), 45.2 ($CH_2$), 55.1 ($OCH_3$), 109.2 (C-4 in furyl), 114.2 (CH in Ar), 118.9 (C-3 in furyl), 127.1 (C-5), 127.3 (C-1 in Ar), 128.4 (CH in Ar), 144.0 (C-6), 147.9 (C-2 in furyl), 151.8 (C-2), 153.0 (C-4), 153.8 (C-8), 156.0 (C-5 in furyl), 159.3 (C-4 in Ar); MS-EI *m/z* (rel %) 334 (53, $M^+$), 319 (5), 291 (1), 277 (2), 121 (100); HRMS: Found 334.1434, Calcd for $C_{19}H_{18}N_4O_2$ 334.1430.

### 4.45. 8-Chloro-6-(5-chloro-2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (35b)

Isolated in 15% yield in the synthesis of **32b** (Method B). Colorless microcrystalline solid, mp 166–168 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.76 (s, 3H, $OCH_3$), 5.40 (s, 2H, $CH_2$), 6.43 (d, $J$ = 3.6 Hz, 1H, H-4 in furyl), 6.83 (d, $J$ = 8.6 Hz, 2H, Ar), 7.33 (d, $J$ = 8.6 Hz, 2H, Ar), 7.82 (d, $J$ = 3.6 Hz, 1H, H-3 in furyl), 8.94 (s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 46.5 ($CH_2$), 55.3 ($OCH_3$), 109.7 (C-4 in furyl), 114.2 (CH in Ar), 120.0 (C-3 in furyl), 126.6 (C-1 in Ar), 127.0 (C-5), 129.5 (CH in Ar), 141.0 (C-6/C-8/C-5 in furyl), 143.28 (C-6/C-8/C-5 in furyl), 143.32 (C-6/C-8/C-5 in furyl), 148.1 (C-2 in furyl), 152.6 (C-4), 152.7 (C-2), 159.6 (C-4 in Ar); MS-EI *m/z* (rel %) 378/376/374 (1/10/15, $M^+$), 121 (100), 91 (3), 78 (5), 77 (5); Anal. Found: C, 54.87; H, 3.45; N 15.18. $C_{17}H_{12}Cl_2N_4O_2$ requires C, 54.43; H, 3.22; N, 14.93%.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