Synthesis, Biological Activity, and SAR of Antimycobacterial 9-Aryl-, 9-Arylsulfonyl-, and 9-Benzyl-6-(2-furyl)purines

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9-Aryl-, 9-arylsulfonyl- and 9-benzyl-6-(2-furyl)purines were synthesized by *N*-alkylation or *N*-arylation of the purine followed by Stille coupling to introduce the furyl substituent in the 6-position and the compounds screened for activity against *Mycobacterium tuberculosis*. The 9-aryl- and 9-sulfonylarylpurines exhibited weak activity toward the bacteria, but 9-benzylpurines were good inhibitors especially those carrying electron-donating substituents on the phenyl ring. A chlorine atom in the purine 2-position further enhanced activity. The high antimycobacterial activity (MIC 0.39 μg/mL against *M. tuberculosis*), low toxicity against mammalian cells and activity inside macrophages found for 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine makes this compound a highly interesting potential antituberculosis drug.

Introduction

Today, one-third of the world population is infected with *Mycobacterium tuberculosis* including those carrying dormant infections. It has been estimated that ca. 30 million people will die from tuberculosis in the next 10 year period. HIV infections have increased TB morbidity and mortality, and multidrug resistant tuberculosis (MDR-TB) is a growing problem among HIV-infected patients.[1] There is an urgent need for new antimycobacterial drugs especially for treatment of MDR-TB.

We have identified certain 6-aryl-9-alkylpurines as potent antimycobacterials.[2,3] Among the aryl- or heteroarylpurines examined, the most effective compounds were 6-(2-furyl)purines. Furthermore, it has been demonstrated that the identity of the 9-substituent is crucial for activity against *Mycobacterium tuberculosis* (Figure 1).[3] Compounds without the *N*-9 substituent or only small alkyl groups in the 9-position were essentially inactive, whereas *N*-benzylated purines were highly potent. When the length of the *N*-9 side chain was further increased (CH_2CH_2Ph), activity was substantially reduced. Our lead is 2-chloro-6-(2-furyl)-9-benzylpurine (Figure 1). This compound exhibits relatively low toxicity toward mammalian cells, and no acute toxicity in rats has been detected. The lead structure is also highly active against several singly drug resistant strains of *M. tuberculosis*.[3] Currently, the mechanism of action for antimycobacterial 6-aryl-9-benzylpurines is not known.

In addition to our work, we are only aware of a few other papers on antimycobacterial purine derivatives. Weak activity has been observed for some 6-alkylamino-9-benzylpurines.[4] The natural product agelasine F[5] and certain synthetic 9-sulfonyl-6-mercaptopurines or 6-alkylthiopurines are quite active against *M. tuberculosis*, the same is true for 2-methyladenosine (Figure 1).[6] Only in the latter case, a mechanism of action is suggested in the literature; 2-methyladenosine is phosphorylated by adenosine kinase to metabolites that affect DNA and protein synthesis.[6c] We have previously reported that 6-arylpurine nucleosides are completely inactive as inhibitors of *M. tuberculosis* growth,[3] and it is not very likely that our 6-aryl-9-benzylpurines exert their activity by the same mechanism as 2-methyladenine. Cytotoxicity toward cancer cell lines have been reported for certain 6-arylpurines,[7] but our antimycobacterial 6-arylpurines exhibited very little toxicity toward mammalian cells.[3] For 9-benzylpurines, anticonvulsant activity[8] and antirhinoviral activity[9] are also reported. However these compounds all carry an amino group in the purine 6-position and are structurally more related to the 6-alkylamino-9-benzylpurines[4] shown in Figure 1 than our antimycobacterials.

In the present paper we report the synthesis, antimycobacterial activity, and SAR of 6-furylpurines carrying a substituted benzyl or an aryl substituent in the purine 9-position. Substituents with various electronic, steric and lipophilic properties were introduced at *N*-9.

Synthesis. The most commonly employed synthetic routes to 6-aryl-9-alkylpurines are *N*-alkylation of a 6-halopurine, followed by Pd-catalyzed coupling with an organometallic reagents,[3] or reaction of a 5-amino-4,6-dihalopyridine with an alkylamine followed by a ring closing reaction employing for instance triethyl orthoformate,[8] and again a final Pd-catalyzed coupling reaction to introduce the 6-aryl substituent. In this study, most 6-furyl-9-benzylpurines **7** and **8** were synthesized according to the former strategy (Scheme 1.) 6-Chloropurine **1** or 2,6-dichloropurine **2** were reacted with the desired benzyl halide in the presence of base. Both the 9-benzylpurines **3** or **5** and minor amounts of the 7-alkylated isomers **4** and **6** were formed in most cases. The furyl substituents in the targets **7** and **8** were introduced by Stille coupling. When mild reaction conditions were applied, the dichloropurine **5** reacted with almost complete regioselectivity to give the desired coupling products **8** (Scheme 1). Further transformations in the *para*-position of the phenyl substituent of

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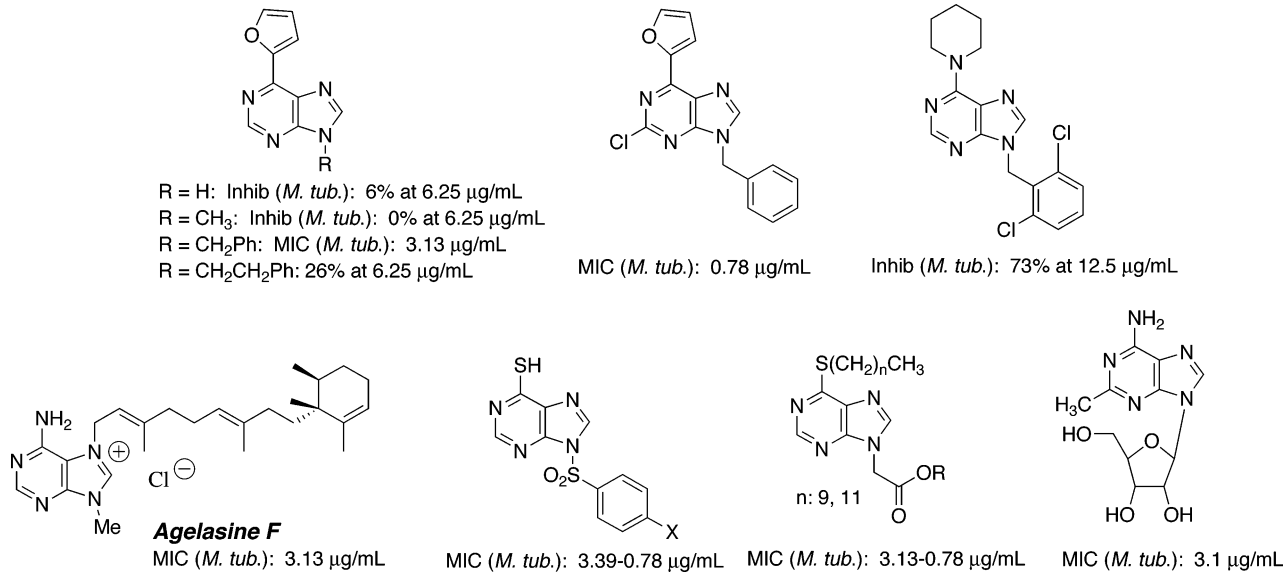
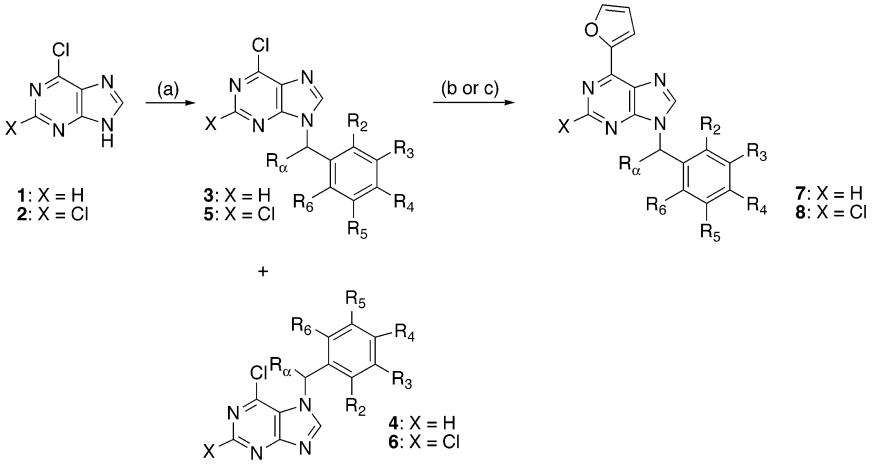


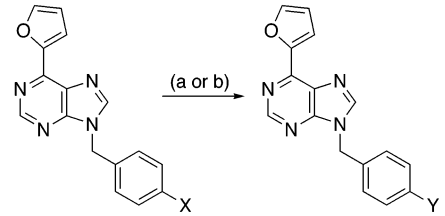
Figure 1. Structures of known antimycobacterial purines.

Scheme 1[a]



[a] (a) $ArCH(R_\alpha)X$, K_2CO_3, DMF; (b) 2-furylSnBu_3, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (c) 2-furylSnBu_3, $[(2\text{-furyl})_3P]_4Pd$, DMF, 50 °C.

Scheme 2[a]



[a] (a) Ac_2O, DMAP, CH_2Cl_2; (b) 48% HBr (aq), 90 °C.

7z and **7cc** to give compounds **7y** and **7dd** are shown in Scheme 2.

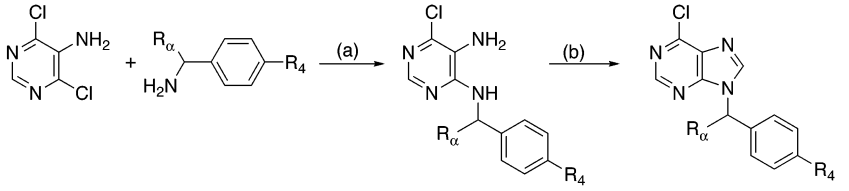
The 6-chloropurines **3bb**, **3ff** and **3gg** were not available by the route depicted in Scheme 1. *p*-Aminobenzyl halides required for the preparation **3bb** are extremely activated and difficult to handle,[10] and the enantiopure compounds **3ff** and **3gg** could not, of course, be formed by alkylation with a secondary benzyl halide. These three compounds were prepared as previously reported for **3ff** and **3gg**[8] (Scheme 3).

The high antimycobacterial activity found for certain 6-mercapto-9-sulfonylpurines[6a] (general structure; see Figure 1) inspired our synthesis of the 6-furyl-9-sulfonylpurine **13** (Scheme 4). 6-Chloropurine **1** was *N*-sulfonylated with complete regioselectivity applying the same set of reaction conditions as reported for the sulfonylation of 6-mercaptopurine,[6a] and the furyl substituent was introduced by Negishi coupling. Compound **13** was not stable under our standard workup procedure for Stille couplings.

NOESY NMR spectroscopy supported the structure of the sulfonylpurine **13** and hence the position of *N*-sulfonylation. Correlations between the phenyl *ortho* protons and both H-8 and H-2, but not any furyl protons, exclude *N*-7 sulfonylation.

As discussed in the Introduction, much higher antimycobacterial activity was found for the 9-benzyl-6-furylpurine **7a** than for the 9-phenylethyl homologue (Figure 1).[3] Hence, it was desirable to investigate if the distance between the phenyl- and purine ring could be shortened. We thus prepared the 9-aryl-6-(2-furyl)-purines **16** and **17** by regioselective *N*-arylation on

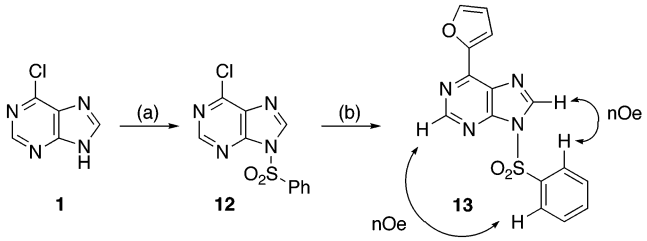
Scheme 3[a]



9 **10** **11a**: R_α=H, R_4=$N(CH_3)_2$; **11b**: R_α=CH_3 (*S*), R_4=H; **11c**: R_α=CH_3 (*R*), R_4=H; **3bb**: R_α=H, R_4=$N(CH_3)_2$; **3ff**: R_α=CH_3 (*S*), R_4=H; **3gg**: R_α=CH_3 (*R*), R_4=H

[a] (a) Et_3N, *n*-BuOH, 100 °C; (b) $EtSO_3H$, $CH(OEt)_3$.

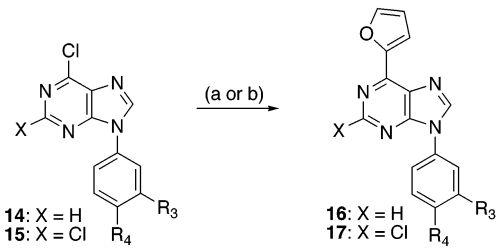
Scheme 4[a]



1 **12** **13**

[a] (a) KOH(aq), $PhSO_2Cl$, acetone, 0 °C; (b) 2-furylZnBr, $(Ph_3P)_4Pd$, THF, 50 °C.

Scheme 5[a]



14: X = H, **15**: X = Cl; **16**: X = H, **17**: X = Cl

[a] (a) 2-FurylSnBu_3, $(Ph_3P)_2PdCl_2$, DMF, 90 °C; (c) 2-furylSnBu_3, $[(2\text{-furyl})_3P]_4Pd$, DMF, 50 °C.

compounds **1** and **2**[11] followed by Stille coupling in the purine 6-position (Scheme 5).

Antibacterial Activity toward *Mycobacterium tuberculosis*. The 9-benzylpurines **7**, **8**, **13**, **16** and **17** were screened for antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ according to procedures previously published by the TAACF organization,[12] and the results are presented in Table 1.

We have previously shown that for the class of antimycobacterial purines discussed herein, a chlorine atom in the purine 2-position generally increases activity,[2,3] and when the potent benzylpurines **7** (MIC ≤ 3.31 μg/mL) were compared with the otherwise identical 2-chloropurines **8**, compounds **8** were generally two times more active against the bacteria. The most potent compound identified to date is the *para* methoxy benzylpurine **8g** exhibiting a MIC very close to what was found for the tuberculosis first-line drug rifampin.

The antimycobacterial activities found for the benzylpurines **7** and **8** indicate that the *ortho* positions in the phenyl ring should not be substituted. Restricted rotation may inhibit adoption of the, yet unknown, active conformation. Also substitution of the benzylic methylene moiety (see below) led to reduced activity.

Strongly electron withdrawing substituents in the *para* position were not tolerated (**7k**−**m**). Substituents with negative σ-values generally increased activity against *M. tuberculosis*, but electron donating substituents with largely negative π-values (**7z**: R_4 = OH, π = −0.61; **7cc**: R_4 = $NHCOCH_3$, π = −0.97; **7dd**: R_4 = NH_2 π = −1.23) should be avoided. *M. tuberculosis* contains a thick and waxy cell wall, which may preclude efficient penetration of the most polar compounds. It seems like the ideal substituent has a relatively small positive π-value. Compounds **7o** (R_4 = Bu^t, σ = −0.20, π = 1.98, MIC > 6.25 μg/mL) and **7x** (R_4 = OBn, σ = −0.42, π = 2.13, MIC = 1.56 μg/mL) carries more powerful electron donating substituents, but are only less or equally effective than compounds **7n** (R_4 = CH_3, σ = −0.17, π = 0.56, MIC = 3.13 μg/mL) and **7p** (R_4 = OCH_3, σ = −0.27, π = 0.56, MIC = 1.56 μg/mL), respectively. However, it is currently not clear whether the reduced activity is mainly a consequence of high lipophilicity or the sterical requirements for the Bu^t and OBn group.

Replacing the methylene in the benzylpurines with a sulfonyl group did not result in desirable activity even though several 9-arylsulfonyl-6-mercaptopurines (Figure 1) are highly potent antimycobacterials.[6a] The benzenesulfonylpurine **13** was only a very modest inhibitor of *M. tuberculosis* (Table 1), and the *N*-sulfonyl-6-chloropurine **12** was completely inactive (data not shown). Also introduction of a second phenyl substituent on the benzylic carbon, compound **7ee**, resulted in a substantial decrease in antimycobacterial activity, but an α-methyl group resulted in only moderately reduced inhibition of bacterial growth. The enantiomers **7ff** and **7gg** were equally active.

The 6-furyl-9-arylpurines **16** and **17** were substantially less potent than most 9-benzylpurines compounds **7** and **8** (Table 1). In this series of compounds, a chlorine atom in the purine 2-position had no profound effect on activity, and no clear correlation between compounds **16** and **17** and the benzylpurines **7** and **8** with the same substitution pattern in the phenyl ring could be found. However, also in the 9-arylpurine series, highest activity was observed for the *p*-methoxy group; compound **16e**.

Toxicity toward Mammalian Cells. Potent inhibitors of *M. tuberculosis* were tested for cytotoxicity (IC_{50}) in mammalian VERO cells and a selectivity index (SI), defined as IC_{50}:MIC, was calculated[12b] (Table 1). In addition to an increase in antimycobacterial activity, the *para* methoxy substituent on the benzyl group in compounds **7p** and **8g** resulted in a substantial reduction of toxicity against mammalian VERO cells (Table 1). Hence these compounds have a much larger selectivity index and are safer drug candidates than the previously reported compound **8a**. Also the *para* methyl group in compound **8f** afforded reduced toxicity toward

Table 1. Antimycobacterial Activity against *Mycobacterium tuberculosis* and Cytotoxic Activity against VERO Cells for 6-(2-Furyl)purines **7**, **8**, **13**, **16**, and **17**

no.	X	R_α	R_2	R_3	R_4	R_5	R_6	% inhibition of *M.* tuberculosis, 6.25 μg/mL concn	MIC M. tuber*culosis* $H_{37}Rv$ (μg/mL)[a]	IC_{50} VERO cells (μg/mL)	selectivity index (IC_{50}: MIC)
7a	H	H	H	H	H	H	H	95[b]	3.13	8.6	2.7
7b	H	H	H	H	Cl	H	H	94	6.25	>62.5[c]	>10
7c	H	H	H	Cl	Cl	H	H	95	6.25	>10[c]	>1.6
7d	H	H	H	Cl	H	H	H	94	3.13	>10[c]	>3.2
7e	H	H	Cl	H	Cl	H	H	90	6.25	*d*	n.d.
7f	H	H	Cl	H	H	H	H	71	n.d.	n.d.	n.d.
7g	H	H	Cl	H	H	H	Cl	17	n.d.	n.d.	n.d.
7h	H	H	H	H	F	H	H	91	6.25	>10[c]	>1.6
7i	H	H	F	H	H	H	H	93	6.25	>10[c]	>1.6
7j	H	H	F	H	H	H	F	52	n.d.	n.d.	n.d.
7k	H	H	H	H	CF_3	H	H	52	n.d.	n.d.	n.d.
7l	H	H	H	H	NO_2	H	H	12	n.d.	n.d.	n.d.
7m	H	H	H	H	SO_2CH_3	H	H	23	n.d.	n.d.	n.d.
7n	H	H	H	H	CH_3	H	H	95	3.13	*d*	n.d.
7o	H	H	H	H	$C(CH_3)_3$	H	H	98	12.5	n.d.	n.d.
7p	H	H	H	H	OCH_3	H	H	97	1.56	>62.5[c]	>40
7q	H	H	OCH_3	H	H	H	H	82	n.d.	n.d.	n.d.
7r	H	H	H	OCH_3	H	H	H	98	6.25	>62.5[c]	>10
7s	H	H	H	CH_3	OCH_3	H	H	99	0.78	n.d.	n.d.
7t	H	H	H	OCH_3	OCH_3	OCH_3	H	8	n.d.	n.d.	n.d.
7u	H	H	H	H	OCF_3	H	H	88	n.d.	n.d.	n.d.
7v	H	H	H	OCF_3	H	H	H	89	n.d.	n.d.	n.d.
7w	H	H	H	H	OCH_2CH_3	H	H	97	3.13	37.41	12
7x	H	H	H	H	OCH_2Ph	H	H	99	1.56	1.70	1
7y	H	H	H	H	$OCOCH_3$	H	H	32	n.d.	n.d.	n.d.
7z	H	H	H	H	OH	H	H	79	n.d.	n.d.	n.d.
7aa	H	H	H	H	SCH_3	H	H	98	6.25	6.90	1.10
7bb	H	H	H	H	$N(CH_3)_2$	H	H	91	12.5	n.d.	n.d.
7cc	H	H	H	H	$NHCOCH_3$	H	H	0	n.d.	n.d.	n.d.
7dd	H	H	H	H	NH_2	H	H	23	n.d.	n.d.	n.d.
7ee	H	Ph	H	H	H	H	H	30	n.d.	n.d.	n.d.
7ff	H	CH_3 (S)	H	H	H	H	H	100	12.5	n.d.	n.d.
7gg	H	CH_3 (R)	H	H	H	H	H	100	12.5	n.d.	n.d.
8a	Cl	H	H	H	H	H	H	98[b]	0.78	8.1	11
8b	Cl	H	H	H	Cl	H	H	98	1.56	*d*	n.d.
8c	Cl	H	H	Cl	Cl	H	H	98	6.25	>10[c]	>1.6
8d	Cl	H	H	Cl	H	H	H	99	3.13	>10[c]	>3.20
8e	Cl	H	H	H	F	H	H	96	3.13	11.53	n.d.
8f	Cl	H	H	H	CH_3	H	H	98	0.78	>10[c]	>13
8g	Cl	H	H	H	OCH_3	H	H	98	0.39	>10[c]	>26
8h	Cl	H	OCH_3	H	H	H	H	80	n.d.	n.d.	n.d.
8i	Cl	H	H	OCH_3	H	H	H	99	3.13	>10[c]	>3.20
8j	Cl	H	H	CH_3	OCH_3	H	H	99	0.78	>10[c]	>12.8
13	H	*N*9 subst: SO_2Ph						14	n.d.	n.d.	n.d.
16a	H	*N*9 subst: Ph						13	n.d.	n.d.	n.d.
16b	H	*N*9 subst: C_6H_4-*p*-Cl						17	n.d.	n.d.	n.d.
16c	H	*N*9 subst: C_6H_4-*m*-Cl						7	n.d.	n.d.	n.d.
16d	H	*N*9 subst: C_6H_4-*p*-CH_3						24	n.d.	n.d.	n.d.
16e	H	*N*9 subst: C_6H_4-*p*-OCH_3						81	n.d.	n.d.	n.d.
17a	Cl	*N*9 subst: Ph						2	n.d.	n.d.	n.d.
17b	Cl	*N*9 subst: C_6H_4-*p*-CH_3						14	n.d.	n.d.	n.d.

[a] MIC rifampicin 0.25 μg/mL. [b] At 12.5 μg/mL. [c] Low solubility precludes determination at higher concentrated. [d] Solubility in tissue culture to low to determine IC_{50}.

VERO cells, but certain other *para* substituents, OBn in **7x** and SMe in **7aa**, actually enhanced cytotoxicity compared to the unsubstituted compound **7a**. Unfortunately, many compounds exhibited low solubility in the tissue culture, and the IC_{50} could not be determined exactly. Hence, information of SAR regarding toxicity toward mammalian cells is currently limited.

Activity against *Mycobacterium avium* Complex. *Mycobacterium avium* complex (MAC) consists of several related species of mycobacterium that are ubiquitous in the environment. MAC rarely causes disease in individuals with an uncompromised immune system, and disseminated infections are usually associated with HIV infection. In patients with AIDS, MAC causes some of the most common serious opportunistic infections.[12b,13,14] Compounds **7p**, **8a** and **8g** were all highly active against *M. tuberculosis*, but they were only found to be weak inhibitors of the *M. avium* complex (Table 2).

Activity against *Mycobacterium tuberculosis* in Macrophages. The *M. tuberculosis* is a facultative intracellular parasite, usually of macrophages. In the early days of an infection the organism multiplies virtually unrestricted within macrophages until the cell burst. Later on activation of macrophages occur, but inside the tubercles, many macrophages are poorly

Table 2. Antimycobacterial Activity against *Mycobacterium avium* and Efficacy in vitro in a TB-Effected [*M. tuberculosis* Erdman (ATCC 35801)] Macrophage Model for Selected 6-(2-Furyl)purines **7** and **8**

no.	X	R_4	MIC *M. avium* complex (μg/mL)	EC_{90} (μg/mL) macrophage model[a]	EC_{99} (μg/mL) macrophage model[b]	EC_{90}/MIC[c]
7p	H	OCH_3	>32	>12.5	>12.5	>8.01
8a	Cl	H	25	0.04	8.46	0.05
8g	Cl	OCH_3	>32	0.02	0.67	0.05

[a] Concentrated effecting 90% reduction in residual mycobacterial growth after 7 days, compared with untreated controls. [b] Concentrated effecting 99% reduction in residual mycobacterial growth after 7 days, compared with untreated controls. [c] MIC from Table 1; Compounds with $EC_{90} > 16 \times$ MIC are considered inactive.

activated and the bacteria uses these cells to replicate.[15] Hence it is extremely important that a potential drug against tuberculosis is able to penetrate macrophages and destroy the bacteria inside. The efficacy of compounds **7p**, **8a** and **8g** in vitro in a TB-infected macrophage model were examined[12b] (Table 2), and both 2-chloropurines **8** and especially **8g**, were found to be highly active.

Conclusions

6-(2-Furyl)-9-benzylpurines are shown to be excellent inhibitors of *M. tuberculosis* growth, especially those benzylpurines carrying electron donating substituents on the phenyl ring. No modifications of the methylene moiety in the benzyl group appear to be allowed. A chlorine atom in the purine 2-position further enhanced activity. The high antimycobacterial activity (MIC 0.39 μg/mL against *M. tuberculosis*), low toxicity against mammalian cells and activity inside macrophages reported makes 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine a highly interesting potential antituberculosis drug.

Currently, the mechanism of action for the antimycobacterials **7** and **8** is not known, and the same is true for most other antimycobacterial purines shown in Figure 1. We previously observed little cross resistance,[3] which indicates a novel mode of action compared to known antimycobacterial drugs. Also the fact that no significant activity against *Lactobacillus casei*,[3] and only low activity against *M. Avium*, was found[3] supports this hypothesis. At this point, we can only speculate regarding the mechanism of action for purines **7** and **8** as antimycobacterials. However, certain 6-oxo-9-benzylpurines and 6-oxo-9-benzyl-9-deazapurines are known to inhibit human purine nucleoside phosphorylase (PNP).[16] PNP from *M. tuberculosis* resembles the mammalian structure.[17] We have found 6-oxo-9-benzylpurine to be essentially inactive toward *M. tuberculosis*,[2] but substitution of the oxo-function with a furyl group in the purine 6-position increases lipophilicity and may also improve ability to penetrate the thick and waxy mycobacterial cell wall. Hence, it would certainly be interesting to explore the ability of 6-(2-furyl)-9-benzylpurines to inhibit mycobacterial PNP.

Experimental Section

The ^{1}H NMR spectra were recorded 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 ^{1}H decoupled ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using instruments mentioned above. Unless otherwise stated, the spectra are recorded at ambient temperature. NOESY NMR was performed on the Bruker Avance DRX 500 instrument. 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.). Optical rotation was recorded at 20 °C on a Perkin-Elmer 341 polarimeter. 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 mol sieves, and dichloromethane was distilled from CaH_2, and THF from Na/benzophenone, prior to use. The following compounds were prepared as previously described: 6-chloro-9-(phenylmethyl)-9*H*-purine **3a**,[17] (*S*)-6-chloro-9-(1-phenylethyl)-9*H*-purine **3ff**,[8] (*R*)-6-chloro-9-(1-phenylethyl)-9*H*-purine **3gg**,[8] 6-chloro-7-(phenylmethyl)-7*H*-purine **4a**,[17] 2,6-dichloro-9-(phenylmethyl)-9*H*-purine **5a**,[18] 2,6-dichloro-7-(phenylmethyl)-7*H*-purine **6a**,[18] 6-(2-furyl)-9-(phenylmethyl)-9*H*-purine **7a**,[3] 2-chloro-6-(2-furyl)-9-(phenylmethyl)-9*H*-purine **8a**,[18] and 9-arylpurines **14** and **15**.[11] All other reagents were commercially available and used as received.

General Procedure for the Synthesis of *N*-Benzylpurines (3−6) by *N*-Alkylation of 6-Chloropurine or 2,6-Dichloropurine. A mixture of 6-chloropurine **1** or 2,6-dichloropurine **2** (5.0 mmol) and potassium carbonate (2.07 g, 15 mmol) in DMF (20 mL) was stirred at ambient temperature under N_2 atm. for 30 min, before the benzyl halide (10 mmol) was added. After stirring for 20 h, the reaction mixture was filtered and evaporated in vacuo. The products were isolated by flash chromatography on silica gel. The 9-alkylated isomers **3** or **5** eluted first.

6-Chloro-9-(4-chlorophenylmethyl)-9*H*-purine (3b). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 953 mg (68%), mp 130−133 °C, colorless small needles (lit.[8] 133−135 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.41 (s, 2H, CH_2), 7.24 (d, J = 8.0 Hz, 2H, Ar), 7.33 (d, J = 8.0 Hz, 2H, Ar), 7.99 (s, 1H, H-8), 8.76 (s, 1H, H-2).

6-Chloro-7-(4-chlorophenylmethyl)-7*H*-purine (4b). EtOAc was used as eluent for flash chromatography; yield 223 mg (16%), mp 167−169 °C, colorless microcrystalline solid (lit.[8] 168−170 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.65 (s, 2H, CH_2), 7.09 (d, J = 8.6 Hz, 2H, Ar), 7.35 (d, J = 8.6 Hz, 2H, Ar), 8.22 (s, 1H, H-8), 8.89 (s, 1H, H-2).

6-Chloro-9-(3,4-dichlorophenylmethyl)-9*H*-purine (3c). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 1.039 g (66%), mp 150−153 °C, off-white powder (lit.[8] 151−153 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.39 (s, 2H, CH_2), 7.13 (dd, J = 8.0 and 2.0 Hz, 1H, Ar), 7.40 (br s, 1H, Ar), 7.42 (d, J = 8.0 Hz, 1H, Ar), 8.10 (s, 1H, H-8), 8.76 (s, 1H, H-2).

6-Chloro-7-(3,4-dichlorophenylmethyl)-7*H*-purine (4c). EtOAc was used as eluent for flash chromatography; yield 252 mg (16%), mp 172−174 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.64 (s, 2H, CH_2), 6.95 (dd, J = 8.2 and 1.8 Hz, 1H, Ar), 7.24 (br s, 1H, Ar), 7.43 (d, J = 8.2 Hz, 1H, Ar), 8.26 (s, 1H, H-8), 8.89 (s, 1H, H-2); HRMS: Found 311.9726, calcd for $C_{12}H_7Cl_3N_4$ 311.9736; Anal.($C_{12}H_7Cl_3N_4$) C, H, N.

6-Chloro-9-(3-chlorophenylmethyl)-9*H*-purine (3d). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 685 mg (49%), mp 94−96 °C, off-white powder (lit.[8] 90−92 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.41 (s, 2H, CH_2), 7.15−7.30 (m, 4H, Ar), 8.10 (s, 1H, H-8), 8.76 (s, 1H, H-2).

6-Chloro-7-(3-chlorophenylmethyl)-7*H*-purine (4d). EtOAc was used as eluent for flash chromatography; yield 99

mg (7%), mp 133−136 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.65 (s, 2H, CH_2), 7.00−7.02 (m, 1H, Ar), 7.15 (s, 1H, Ar), 7.30−7.33 (m, 2H, Ar), 8.24 (s, 1H, H-8), 8.89 (s, 1H, H-2); HRMS: Found 278.0130, calcd for $C_{12}H_8Cl_2N_4$ 278.0126; Anal. ($C_{12}H_8Cl_2N_4$) C, H, N.

6-Chloro-9-(2,4-dichlorophenylmethyl)-9*H*-purine (3e). EtOAc−hexane (1:2) was used as eluent for flash chromatography; yield 994 mg (63%), mp 131−132 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.50 (s, 2H, CH_2), 7.19−7.33 (m, 2H, Ar), 7.42 (d, J = 2.0 Hz, 1H, Ar), 8.16 (s, 1H, H-8), 8.73 (s, 1H, H-2); Anal. ($C_{12}H_7Cl_3N_4$) C, H, N.

6-Chloro-7-(2,4-dichlorophenylmethyl)-7*H*-purine (4e). EtOAc was used as eluent for flash chromatography; yield 241 mg (15%), mp 179−181 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.74 (s, 2H, CH_2), 6.73 (d, J = 8.4 Hz, 1H, Ar), 7.18−7.24 (m, 1H, Ar), 7.50 (d, J = 2.0 Hz, 2H, Ar), 8.20 (s, 1H, H-8), 8.89 (s, 1H, H-2); HRMS: Found 311.9727, calcd for $C_{12}H_7Cl_3N_4$ 311.9736; Anal. ($C_{12}H_7Cl_3N_4$) C, H, N.

6-Chloro-9-(2-chlorophenylmethyl)-9*H*-purine (3f). EtOAc−hexane (1:2) was used as eluent for flash chromatography; yield 784 mg (56%), mp 134−137 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.56 (s, 2H, CH_2), 7.21−7.46 (m, 4H, Ar), 8.17 (s, 1H, H-8), 8.76 (s, 1H, H-2); Anal. ($C_{12}H_8Cl_2N_4$) C, H, N.

6-Chloro-7-(2-chlorophenylmethyl)-7*H*-purine (4f). EtOAc was used as eluent for flash chromatography; yield 227 mg (16%), mp 186−187 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.78 (s, 2H, CH_2), 6.83 (br d, J = 7.4 Hz, 1H, Ar), 7.20−7.37 (m, 2H, Ar), 7.46−7.50 (m, 1H, Ar), 8.18 (s, 1H, H-8), 8.90 (s, 1H, H-2); HRMS: Found 278.0133, calcd for $C_{12}H_{18}Cl_2N_4$ 278.0126; Anal. ($C_{12}H_8Cl_2N_4$) C, H, N.

6-Chloro-9-(2,6-dichlorophenylmethyl)-9*H*-purine (3g). EtOAc−hexane (1:2) and then EtOAc−hexane (1:1) were used as eluents for flash chromatography; yield 1.026 g (66%), mp 190−192 °C, colorless needles (lit.[19] 186−188 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.72 (s, 2H, CH_2), 7.28−7.45 (m, 3H, Ar), 7.92 (s, 1H, H-8), 8.79 (s, 1H, H-2).

6-Chloro-9-(4-fluorophenylmethyl)-9*H*-purine (3h). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 672 mg (51%), mp 129−131 °C, colorless needles (lit.[8] 118−120 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.41 (s, 2H, CH_2), 7.00−7.08 (m, 2H, Ar), 7.27−7.34 (m, 2H, Ar), 8.07 (s, 1H, H-8), 8.77 (s, 1H, H-2).

6-Chloro-7-(4-fluorophenylmethyl)-7*H*-purine (4h). EtOAc was used as eluent for flash chromatography; yield 205 mg (16%), mp 161−164 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.64 (s, 2H, CH_2), 7.02−7.20 (m, 4H, Ar), 8.20 (s, 1H, H-8), 8.88 (s, 1H, H-2); HRMS: Found 262.0428, calcd for $C_{12}H_8FClN_4$ 262.0422; Anal. ($C_{12}H_8ClFN_4$) C, H, N.

6-Chloro-9-(2-fluorophenylmethyl)-9*H*-purine (3i). EtOAc−hexane (2:3) was used as eluent for flash chromatography; yield 800 mg (61%), mp 98−100 °C, colorless crystals (lit.[8] 97−99 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.48 (s, 2H, CH_2), 7.06−7.16 (m, 2H, Ar), 7.29−7.42 (m, 2H, Ar), 8.16 (s, 1H, H-8), 8.76 (s, 1H, H-2).

6-Chloro-7-(2-fluorophenylmethyl)-7*H*-purine (4i). EtOAc was used as eluent for flash chromatography; yield 249 mg (19%), mp 164−165 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.71 (s, 2H, CH_2), 7.09 (m, 3H, Ar), 7.31−7.34 (m, 1H, Ar), 8.27 (s, 1H, H-8), 8.80 (s, 1H, H-2); HRMS: Found 262.0431, calcd for $C_{12}H_8ClFN_4$ 262.0422; Anal. ($C_{12}H_8ClFN_4$) C, H, N.

6-Chloro-9-(2,6-difluorophenylmethyl)-9*H*-purine (3j). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 875 mg (62%), mp 147−149 °C, colorless powdery crystals (lit.[20] 147−148 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.58 (s, 2H, CH_2), 7.09 (t, J = 7.6 Hz, 2H, Ar), 7.40 (m, 1H, Ar), 8.20 (s, 1H, H-8), 8.82 (s, 1H, H-2).

6-Chloro-7-(2,6-difluorophenylmethyl)-7*H*-purine (4j). EtOAc was used as eluent for flash chromatography; yield 139 mg (10%), mp 141−144 °C (dec), off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.77 (s, 2H, CH_2), 7.01 (t, J = 5.8 Hz, 2H, Ar), 7.39 (m, 1H, Ar), 8.17 (s, 1H, H-8), 8.83 (s, 1H, H-2); Anal. ($C_{12}H_7F_2ClN_4$) C, H, N.

6-Chloro-9-(4-trifluoromethylphenylmethyl)-9*H*-purine (3k). EtOAc−hexane (3:4) was used as eluent for flash chromatography; yield 932 mg (60%), mp 130−132 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.51 (s, 2H, CH_2), 7.41 (d, J = 8.1 Hz, 2H, Ar), 7.63 (d, J = 8.1 Hz, 2H, Ar), 8.12 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 312.0379, calcd for $C_{13}H_8F_3ClN_4$ 312.0390; Anal. ($C_{13}H_8F_3ClN_4$) C, H, N.

6-Chloro-7-(4-trifluoromethylphenylmethyl)-7*H*-purine (4k). EtOAc was used as eluent for flash chromatography; yield 266 mg (17%), mp 135−136 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.75 (s, 2H, CH_2), 7.24 (d, J = 8.2 Hz, 2H, Ar), 7.63 (d, J = 8.2 Hz, 2H, Ar), 8.27 (s, 1H, H-8), 8.89 (s, 1H, H-2); HRMS: Found 312.0383, calcd for $C_{13}H_8F_3ClN_4$ 312.0390; Anal. ($C_{13}H_8F_3ClN_4$) C, H, N.

6-Chloro-9-(4-nitrophenylmethyl)-9*H*-purine (3l). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 538 mg (37%), mp 181−183 °C, yellow powdery crystals (lit.[21] 180 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.56 (s, 2H, CH_2), 7.46 (d, J = 8.7 Hz, 2H, Ar), 8.15 (s, 1H, H-8), 8.21 (d, J = 8.7 Hz, 2H, Ar), 8.76 (s, 1H, H-2).

6-Chloro-7-(4-nitrophenylmethyl)-7*H*-purine (4l). EtOAc was used as eluent for flash chromatography; yield 64 mg (4%), yellow wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.80 (s, 2H, CH_2), 7.28 (d, J = 8.8 Hz, 2H, Ar), 8.24 (d, J = 8.8 Hz, 2H, Ar), 8.32 (s, 1H, H-8), 8.92 (s, 1H, H-2); NMR data were in good agreement with those reported before.[21]

6-Chloro-9-(4-methylsulfonylphenylmethyl)-9*H*-purine (3m). EtOAc was used as eluent for flash chromatography; yield 937 mg (58%), mp 211−212 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.00 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 7.34 (d, J = 8.2 Hz, 2H, Ar), 7.97 (d, J = 8.2 Hz, 2H, Ar), 8.15 (s, 1H, H-8), 8.76 (s, 1H, H-2); HRMS: Found 322.0282, calcd for $C_{13}H_{11}ClN_4O_2S$ 322.0291; Anal. ($C_{13}H_{11}ClN_4O_2S$) C, H, N.

6-Chloro-7-(4-methylsulfonylphenylmethyl)-7*H*-purine (4m). EtOAc was used as eluent for flash chromatography; yield 249 mg (15%), mp 216−219 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.07 (s, 3H, CH_3), 5.82 (s, 2H, CH_2), 7.48 (d, J = 8.2 Hz, 2H, Ar), 7.91 (d, J = 8.2 Hz, 2H, Ar), 8.36 (s, 1H, H-8), 8.94 (s, 1H, H-2); HRMS: Found 322.0288, calcd for $C_{13}H_{11}ClN_4O_2S$ 322.0291; Anal. ($C_{13}H_{11}ClN_4O_2S$) C, H; N: calcd, 17.36; found, 16.88.

6-Chloro-9-(4-methylphenylmethyl)-9*H*-purine (3n). EtOAc−hexane (3:4) was used as eluent for flash chromatography; yield 648 mg (50%), mp 135−136 °C, colorless small needles (lit.[8] 132−134 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.32 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 7.17 (m, 4H, Ar), 8.05 (s, 1H, H-8), 8.76 (s, 1H, H-2).

6-Chloro-7-(4-methylphenylmethyl)-7*H*-purine (4n). EtOAc was used as eluent for flash chromatography; yield 235 mg (18%), mp 154−156 °C, colorless needles (lit.[8] 148−149 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 7.06 (d, J = 8.2 Hz, 2H, Ar), 7.18 (d, J = 8.2 Hz, 2H, Ar), 8.17 (s, 1H, H-8), 8.87 (s, 1H, H-2); MS EI *m/z* (rel. %): 260/258 (11/34, M^+), 257 (6), 223 (2), 106 (10), 105 (100), 104 (5), 103 (7), 79 (11), 78 (4), 77 (15).

9-(4-*tert*-Butylphenylmethyl)-6-chloro-9*H*-purine (3o). EtOAc−hexane (1:2) and then EtOAc−hexane (1:1) were used as eluents for flash chromatography; yield 636 mg (42%), off-white wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 9H, *t*-Bu), 5.40 (s, 2H, CH_2), 7.23 (d, J = 8.4 Hz, 2H, Ar), 7.37 (d, J = 8.4 Hz, 2H, Ar), 8.07 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 300.1137, calcd for $C_{16}H_{17}ClN_4$ 300.1142; Anal. ($C_{16}H_{17}ClN_4$) C, H, N.

7-(4-*tert*-Butylphenylmethyl)-6-chloro-7*H*-purine (4o). EtOAc was used as eluent for flash chromatography; yield 11 mg (0.7%), off-white wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (s, 9H, *t*-Bu), 5.63 (s, 2H, CH_2), 7.11 (d, J = 8.2 Hz, 2H, Ar), 7.37 (d, J = 8.2 Hz, 2H, Ar), 8.07 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 300.1124, calcd for $C_{16}H_{17}ClN_4$ 300.1142.

6-Chloro-9-(4-methoxyphenylmethyl)-9*H*-purine (3p). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 611 mg (44%), mp 127−128 °C, colorless crystals

(lit.[8] 122−124 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 6.87 (d, J = 8.6 Hz, 2H, Ar), 7.26 (d, J = 8.6 Hz, 2H, Ar), 8.04 (s, 1H, H-8), 8.77 (s, 1H, H-2).

6-Chloro-7-(4-methoxyphenylmethyl)-7*H*-purine (4p). EtOAc was used as eluent for flash chromatography; yield 109 mg (8%), mp 138−140 °C, colorless needles (lit.[8] 134−136 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 6.89 (d, J = 8.8 Hz, 2H, Ar), 7.21 (d, J = 8.8 Hz, 2H, Ar), 8.16 (s, 1H, H-8), 8.87 (s, 1H, H-2).

6-Chloro-9-(2-methoxyphenylmethyl)-9*H*-purine (3q). EtOAc−hexane (2:3) was used as eluent for flash chromatography; yield 667 mg (49%), mp 110−112 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.88 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 6.93−7.01 (m, 2H, Ar), 7.30−7.40 (m, 2H, Ar), 8.04 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 274.0620, calcd for $C_{13}H_{11}ClN_4O$ 274.0621. Anal. ($C_{13}H_{11}ClN_4O$) C, H, N.

6-Chloro-7-(2-methoxyphenylmethyl)-7*H*-purine (4q). EtOAc was used as eluent for flash chromatography; yield 244 mg (18%), mp 149−151 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.75 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 6.79−6.86 (m, 2H, Ar), 7.03−7.07 (m, 1H, Ar), 7.21−7.29 (m, 1H, Ar), 8.20 (s, 1H, H-8), 8.76 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 46.1 (CH_2), 55.2 (CH_3), 110.5 (CH in Ar), 120.6 (CH in Ar), 122.4 (C-5 and C in Ar), 129.2 (CH in Ar), 130.3 (CH in Ar), 142.7 (C-6), 149.5 (C-2/C-8), 151.6 (C-2/C-8), 156.8 (C in Ar), 161.6 (C-4); MS EI *m/z* (rel. %): 276/274 (29/76, M^+), 245 (7), 243 (24), 122 (11), 121 (100), 91 (74), 78 (10), 65 (11); HRMS: Found 274.0616, calcd for $C_{13}H_{11}ClN_4O$ 274.0621. Anal. ($C_{13}H_{11}ClN_4O$) C, H; N: calcd, 20.40; found, 19.83.

6-Chloro-9-(3-methoxyphenylmethyl)-9*H*-purine (3r). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 793 mg (58%), mp 104−105 °C, colorless crystals (lit.[8] 103−104 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.76 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.83−6−87 (m, 3H, Ar), 7.23−7.31 (m, 1H, Ar), 8.07 (s, 1H, H-8), 8.76 (s, 1H, H-2).

6-Chloro-7-(3-methoxyphenylmethyl)-7*H*-purine (4r). EtOAc was used as eluent for flash chromatography; yield 299 mg (22%), mp 160−162 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.76 (s, 3H, CH_3), 5.63 (s, 2H, CH_2), 6.69−6−74 (m, 2H, Ar), 6.85−6.89 (m, 1H, Ar), 7.24−7.32 (m, 1H, Ar), 8.20 (s, 1H, H-8), 8.88 (s, 1H, H-2); HRMS: Found 274.0616, calcd for $C_{13}H_{11}ClN_4O$ 274.0621. Anal. ($C_{13}H_{11}ClN_4O$) C, H; N: calcd, 20.40; found, 19.92.

6-Chloro-9-(4-methoxy-3-methylphenylmethyl)-9*H*-purine (3s). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 505 mg (35%), colorless wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.33 (s, 2H, CH_2), 6.77 (d, J = 8.0 Hz, 1H, Ar), 7.08−7.14 (m, 2H, Ar), 8.04 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 288.0769, calcd for $C_{14}H_{13}ClN_4O$ 288.0778. Anal. ($C_{14}H_{13}ClN_4O$) C, H; N: calcd, 19.41; found, 18.94.

6-Chloro-7-(4-methoxy-3-methylphenylmethyl)-7*H*-purine (4s). EtOAc was used as eluent for flash chromatography; yield 14 mg (1%), colorless wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.56 (s, 2H, CH_2), 6.78 (d, J = 8.0 Hz, 1H, Ar), 6.98−7.02 (m, 2H, Ar), 8.16 (s, 1H, H-8), 8.85 (s, 1H, H-2).

6-Chloro-9-(3,4,5-trimethoxyphenylmethyl)-9*H*-purine (3t). EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 850 mg (51%), mp 115−116 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 9H, 3 × OCH_3), 5.31 (s, 2H, CH_2), 6.49 (s, 2H, Ar), 8.07 (s, 1H, H-8), 8.72 (s, 1H, H-2); HRMS: Found 334.0835, calcd for $C_{15}H_{15}N_4O_3Cl$ 334.0832; Anal. ($C_{15}H_{15}N_4O_3Cl$) C, H, N.

6-Chloro-7-(3,4,5-trimethoxyphenylmethyl)-7*H*-purine (4t). EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 332 mg (20%), mp 121−122 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.73 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 5.55 (s, 2H, CH_2), 6.38 (s, 2H, Ar), 8.09 (s, 1H, H-8), 8.71 (s, 1H, H-2); HRMS: Found 334.0836, calcd for $C_{15}H_{15}N_4O_3Cl$ 334.0832; Anal. ($C_{15}H_{15}N_4O_3Cl$) C, H, N.

6-Chloro-9-(4-trifluoromethoxyphenylmethyl)-9*H*-purine (3u). The reaction was performed in 2.0 mmol scale, and EtOAc−hexane (2:3) was used as eluent for flash chromatography; yield 338 mg (51%), mp 115−116 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) 5.45 (s, 2H, CH_2), 7.18−7.27 (m, 2H, Ar), 7.33−7.37 (m, 2H, Ar), 8.10 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 328.0330, calcd for $C_{13}H_{18}ClF_3N_4O$ 328.0339; Anal. ($C_{13}H_{18}ClF_3N_4O$) C, H, N.

6-Chloro-7-(4-trifluoromethoxyphenylmethyl)-7*H*-purine (4u). The reaction was performed in 2.0 mmol scale, and EtOAc was used as eluent for flash chromatography; yield 139 mg (21%), mp 111−114 °C, colorless waxy solid. ^{1}H NMR ($CDCl_3$, 200 MHz) 5.68 (s, 2H, CH_2), 7.21 (m, 4H, Ar), 8.24 (s, 1H, H-8), 8.89 (s, 1H, H-2); HRMS: Found 328.0335, calcd for $C_{13}H_{18}ClF_3N_4O$ 328.0339; Anal. ($C_{13}H_{18}ClF_3N_4O$) C, H, N.

6-Chloro-9-(3-trifluoromethoxyphenylmethyl)-9*H*-purine (3v). The reaction was performed in 2.2 mmol scale, and acetone−hexane (2:5) was used as eluent for flash chromatography; yield 343 mg (47%), colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) 5.46 (s, 2H, CH_2), 7.18−7.25 (m, 3H, Ar), 7.35−7.43 (m, 1H, Ar), 8.11 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 328.0335, calcd for $C_{13}H_{18}ClF_3N_4O$ 328.0339.

6-Chloro-9-(4-ethoxyphenylmethyl)-9*H*-purine (3w). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 606 mg (42%), mp 110−112 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (t, J = 7.2 Hz, 3H, CH_3), 3.99 (q, J = 7.2 Hz, 2H, OCH_2), 5.35 (s, 2H, CH_2), 6.85 (d, J = 8.8 Hz, 2H, Ar), 7.25 (d, J = 8.8 Hz, 2H, Ar), 8.04 (s, 1H, H-8), 8.76 (s, 1H, H-2); HRMS: Found 288.0777, calcd for $C_{14}H_{13}ClN_4O$ 288.0778; Anal. ($C_{14}H_{13}ClN_4O$) C, H; N: calcd, 19.41; found, 18.95.

6-Chloro-7-(4-ethoxyphenylmethyl)-7*H*-purine (4w). EtOAc was used as eluent for flash chromatography; yield 64 mg (4%), mp 169−171 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (t, J = 7.0 Hz, 3H, CH_3), 4.01 (q, J = 7.0 Hz, 2H, OCH_2), 5.59 (s, 2H, CH_2), 6.88 (d, J = 8.8 Hz, 2H, Ar), 7.13 (d, J = 8.8 Hz, 2H, Ar), 8.15 (s, 1H, H-8), 8.87 (s, 1H, H-2); HRMS: Found 288.0769, calcd for $C_{14}H_{13}ClN_4O$ 288.0778; Anal. ($C_{14}H_{13}ClN_4O$) C, H, N.

9-(4-Benzyloxyphenylmethyl)-6-chloro-9*H*-purine (3x). EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 1.140 g (65%), mp 127−128 °C, colorless crystals (lit.[8] 121−125 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.90 (s, 2H, CH_2), 5.22 (s, 2H, CH_2), 6.79−7.51 (m, 9H, Ar), 7.91 (s, 1H, H-8), 8.63 (s, 1H, H-2).

7-(4-Benzyloxyphenylmethyl)-6-chloro-7*H*-purine (4x). EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 360 mg (20%), mp 142−143 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.04 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 6.95−7.58 (m, 9H, Ar), 8.03 (s, 1H, H-8), 8.86 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 50.3 (CH_2), 70.0 (OCH_2), 115.6 (CH in Ar), 126.4 (C in Ar), 127.4 (CH in Ar), 128.1 (CH in Ar), 128.6 (CH in Ar), 128.8 (CH in Ar), 132.4 (C-5), 136.3 (C in Ar), 143.7 (C-8), 148.1 (C-6), 148.8 (C-4), 152.5 (C-2), 159.1 (C in Ar); MS EI *m/z* (rel. %): 352/350 (9/28, M^+), 243 (5), 91 (100), 65 (6); HRMS: Found 350.0936, calcd for $C_{19}H_{15}N_4OCl$ 350.0934; Anal. ($C_{19}H_{15}N_4OCl$) C, H, N.

9-(4-Acetoxyphenylmethyl)-6-chloro-9*H*-purine (3y). The reaction was performed in 2.5 mmol scale, and EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 387 mg (51%), mp 120−122 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.27 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 7.08 (d, J = 8.6 Hz, 2H, Ar), 7.23 (d, J = 8.6 Hz, 2H, Ar), 8.09 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 302.0575, calcd for $C_{14}H_{11}ClN_4O_2$ 302.0571; Anal. ($C_{14}H_{11}ClN_4O_2$) C, H, N.

7-(4-Acetoxyphenylmethyl)-6-chloro-7*H*-purine (4y). The reaction was performed in 2.5 mmol scale, and EtOAc was used as eluent for flash chromatography; yield 222 mg (29%), mp 155−157 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.28 (s, 3H, CH_3), 5.66 (s, 2H, CH_2), 7.10 (d, J = 8.6 Hz, 2H, Ar), 7.22 (d, J = 8.6 Hz, 2H, Ar), 8.22 (s, 1H, H-8), 8.88 (s, 1H, H-2); HRMS: Found 302.0580, calcd for $C_{14}H_{11}ClN_4O_2$ 302.0571; Anal. ($C_{14}H_{11}ClN_4O_2$) C, H, N.

6-Chloro-9-(4-methylthiophenylmethyl)-9*H*-purine (3aa). The reaction was performed in 2.5 mmol scale, and EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 346 mg (49%), mp 95−97 °C, colorless needles.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.45 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 7.22 (s, 4H, Ar), 8.07 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 290.0400, calcd for $C_{13}H_{11}ClN_4S$ 290.0393; Anal. ($C_{13}H_{11}ClN_4S$) C, H, N.

6-Chloro-7-(4-methylthiophenylmethyl)-7*H*-purine (4aa). The reaction was performed in 2.5 mmol scale, and EtOAc was used as eluent for flash chromatography; yield 96 mg (13%), mp 150−152 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.44 (s, 3H, CH_3), 5.61 (s, 2H, CH_2), 7.08 (d, J = 6.8 Hz, 2H, Ar), 7.22 (d, J = 6.8 Hz, 2H, Ar), 8.20 (s, 1H, H-8), 8.86 (s, 1H, H-2); HRMS: Found 290.0390, calcd for $C_{13}H_{11}ClN_4S$ 290.0393; Anal. ($C_{13}H_{11}ClN_4S$) C, H, N.

9-(4-Acetamidophenylmethyl)-6-chloro-9*H*-purine (3cc). The reaction was performed in 2.3 mmol scale, and acetone−hexane (2:3) was used as eluent for flash chromatography; yield 431 mg (62%), mp 240−242 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 7.19 (br s, 1H, NH), 7.28 (d, J = 8.0 Hz, 2H, Ar), 7.50 (d, J = 8.0 Hz, 2H, Ar), 8.06 (s, 1H, H-8), 8.76 (s, 1H, H-2); HRMS: Found 301.0724, calcd for $C_{14}H_{12}ClN_5O$ 301.0730; Anal. ($C_{14}H_{12}ClN_5O$) C, H.

6-Chloro-9-(diphenylmethyl)-9*H*-purine (3ee). EtOAc−hexane (1:2) was used as eluent for flash chromatography; yield 337 mg (21%), mp 173−175 °C, colorless crystals (lit.[22] 161−162 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.11−7.17 (s, 5H, Ar/CH), 7.33−7.40 (m, 6H, Ar/CH), 7.92 (s, 1H, H-8), 8.71 (s, 1H, H-2).

6-Chloro-7-(diphenylmethyl)-7*H*-purine (4ee). EtOAc was used as eluent for flash chromatography; yield 132 mg (8%), pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.07−7.08 (s, 4H, Ar/CH), 7.36−7.39 (m, 7H, Ar/CH), 7.92 (s, 1H, H-8), 8.84 (s, 1H, H-2); HRMS: Found 320.0838, calcd for $C_{18}H_{13}ClN_4$ 320.0829.

9-(4-Chlorophenylmethyl)-2,6-dichloro-9*H*-purine (5b). EtOAc−hexane (2:3) was used as eluent for flash chromatography; yield 856 mg (55%), mp 162−164 °C, colorless small needles (lit.[9] 158−160 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.36 (s, 2H, CH_2), 7.21−7.26 (m, 2H, Ar), 7.33−7.37 (m, 2H, Ar), 8.04 (s, 1H, H-8).

7-(4-Chlorophenylmethyl)-2,6-dichloro-7*H*-purine (6b). EtOAc was used as eluent for flash chromatography; yield 295 mg (19%), mp 180−182 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.61 (s, 2H, CH_2), 7.08 (d, J = 8.2 Hz, 2H, Ar), 7.35 (d, J = 8.2 Hz, 2H, Ar), 8.22 (s, 1H, H-8); HRMS: Found 311.9746, calcd for $C_{12}H_7Cl_3N_4$ 311.9736; Anal.($C_{12}H_7Cl_3N_4$): C, H, N.

2,6-Dichloro-9-(3,4-dichlorophenylmethyl)-9*H*-purine (5c). EtOAc−hexane (1:2) and then EtOAc−hexane (1:1) were used as eluents for flash chromatography; yield 962 mg (56%), mp 175−177 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.35 (s, 2H, CH_2), 7.14 (dd, J = 8.2 and 2.2 Hz, 1H, Ar), 7.39 (d, J = 2.2 Hz, 1H, Ar), 7.44 (d, J = 8.2 Hz, 1H, Ar), 8.06 (s, 1H, H-8); HRMS: Found 345.9351, calcd for $C_{12}H_6Cl_4N_4$ 345.9347; Anal. ($C_{12}H_6Cl_4N_4$) C, N; H: calcd, 1.16; found, 1.81.

2,6-Dichloro-7-(3,4-dichlorophenylmethyl)-7*H*-purine (6c). EtOAc was used as eluent for flash chromatography; yield 295 g (17%), mp 178−179 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.73 (s, 2H, CH_2), 7.18 (br d, J = 8.4 Hz, 1H, Ar), 7.51−7.61 (m, 2H, Ar), 9.01 (s, 1H, H-8); HRMS: Found 345.9352, calcd for $C_{12}H_6Cl_4N_4$ 345.9347; Anal. ($C_{12}H_6Cl_4N_4$) C, H, N.

9-(3-Chlorophenylmethyl)-2,6-dichloro-9*H*-purine (5d). EtOAc−hexane (1:3) was used as eluent for flash chromatography; yield 871 mg (56%), mp 122−125 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.36 (s, 2H, CH_2), 7.18−7.32 (m, 4H, Ar), 8.05 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.3 (CH_2), 126.0 (CH in Ar), 128.0 (CH in Ar), 129.2 (CH in Ar), 130.2 (C-5), 130.6 (CH in Ar), 135.2 (C in Ar), 135.9 (C in Ar), 145.2 (C-8), 151.9 (C-2/C-4/C-6), 153.0 (C-2/C-4/C-6), 153.2 (C-2/C-4/C-6); MS EI *m/z* (rel. %): 316/314/312 (12/39/41, M^+), 279 (11), 277 (18), 201 (6), 127 (31), 125 (100), 99 (7), 89 (21); HRMS: Found 311.9737, calcd for $C_{12}H_7Cl_3N_4$ 311.9736; Anal. ($C_{12}H_7Cl_3N_4$) C, H, N.

7-(3-Chlorophenylmethyl)-2,6-dichloro-7*H*-purine (6d). EtOAc was used as eluent for flash chromatography; yield 221 mg (14%), mp 129−131 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.61 (s, 2H, CH_2), 6.99 (br s, 1H, Ar), 7.12 (br s, 1H, Ar), 7.22−7.32 (m, 2H, Ar), 8.24 (s, 1H, H-8); HRMS: Found 311.9754, calcd for $C_{12}H_7Cl_3N_4$ 311.9736; Anal. ($C_{12}H_7Cl_3N_4$) C, H, N.

2,6-Dichloro-9-(4-fluorophenylmethyl)-9*H*-purine (5e). EtOAc−hexane (1:3) was used as eluent for flash chromatography; yield 817 mg (55%), mp 120−122 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.36 (s, 2H, CH_2), 7.01−7.10 (m, 2H, Ar), 7.27−7.34 (m, 2H, Ar), 8.02 (s, 1H, H-8); HRMS: Found 296.0019, calcd for $C_{12}H_7Cl_2FN_4$ 296.0032; Anal. ($C_{12}H_7Cl_2FN_4$) C, H, N.

2,6-Dichloro-7-(4-fluorophenylmethyl)-7*H*-purine (6e). EtOAc was used as eluent for flash chromatography; yield 319 mg (21%), mp 164−166 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.61 (s, 2H, CH_2), 7.08−7.24 (m, 4H, Ar), 8.20 (s, 1H, H-8); HRMS: Found 296.0034, calcd for $C_{12}H_7Cl_2FN_4$ 296.0032; Anal. ($C_{12}H_7Cl_2FN_4$) C, H, N.

2,6-Dichloro-9-(4-methylphenylmethyl)-9*H*-purine (5f). EtOAc−hexane (1:2) was used as eluent for flash chromatography; yield 772 mg (53%), mp 138−141 °C colorless microcrystalline solid (lit.[9] 147−148 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 7.18 (m, 4H, Ar), 8.00 (s, 1H, H-8).

2,6-Dichloro-7-(4-methylphenylmethyl)-7*H*-purine (6f). EtOAc was used as eluent for flash chromatography; yield 329 mg (23%), mp 175−176 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.34 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.05 (d, J = 7.8 Hz, 2H, Ar), 7.22 (d, J = 7.8 Hz, 2H, Ar), 8.17 (s, 1H, H-8); HRMS: Found 292.0273, calcd for $C_{13}H_{10}Cl_2N_4$ 292.0283; Anal. ($C_{13}H_{10}Cl_2N_4$) C, H, N.

2,6-Dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine (5g). EtOAc−hexane (2:3) was used as eluent for flash chromatography; yield 837 mg (54%), mp 128−130 °C, colorless crystals (lit.[9] 132−134 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.88 (d, J = 8.2 Hz, 2H, Ar), 7.26 (d, J = 8.2 Hz, 2H, Ar), 7.99 (s, 1H, H-8).

2,6-Dichloro-7-(4-methoxyphenylmethyl)-7*H*-purine (6g). EtOAc was used as eluent for flash chromatography; yield 330 mg (21%), mp 146−148 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 5.56 (s, 2H, CH_2), 6.89 (d, J = 8.6 Hz, 2H, Ar), 7.13 (d, J = 8.8 Hz, 2H, Ar), 8.16 (s, 1H, H-8); HRMS: Found 308.0246, calcd for $C_{13}H_{10}Cl_2N_4O$ 308.0232; Anal. ($C_{13}H_{10}Cl_2N_4$) C, H, N.

2,6-Dichloro-9-(2-methoxyphenylmethyl)-9*H*-purine (5h). EtOAc−hexane (2:3) was used as eluent for flash chromatography; yield 763 mg (49%), mp 156−157 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.84 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 6.87−6.98 (m, 2H, Ar), 7.29−7.38 (m, 2H, Ar), 8.12 (s, 1H, H-8); HRMS: Found 308.0246, calcd for $C_{13}H_{10}Cl_2N_4O$ 308.0232; Anal. ($C_{13}H_{10}Cl_2N_4O$) C, H, N.

2,6-Dichloro-7-(2-methoxyphenylmethyl)-7*H*-purine (6h). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 326 mg (21%), mp 145−147 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.83 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 6.90−6.99 (m, 2H, Ar), 7.17 (br d, J = 7.4 Hz, 1H, Ar), 7.36 (td, J = 8.4 and 1.8 Hz, 1H, Ar), 8.21 (s, 1H, H-8); HRMS: Found 308.0245, calcd for $C_{13}H_{10}Cl_2N_4O$ 308.0232; Anal. ($C_{13}H_{10}Cl_2N_4O$) C, H, N.

2,6-Dichloro-9-(3-methoxyphenylmethyl)-9*H*-purine (5i). EtOAc−hexane (1:2) was used as eluent for flash chromatography; yield 835 mg (54%), mp 119−121 °C, colorless small needles.^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.83−6.89 (m, 3H, Ar), 7.28 (t, J = 8.2 Hz, 1H, Ar), 8.02 (H-8); HRMS: Found 308.0238, calcd for $C_{13}H_{10}Cl_2N_4O$ 308.0232; Anal. ($C_{13}H_{10}Cl_2N_4O$) C, H, N.

2,6-Dichloro-7-(3-methoxyphenylmethyl)-7*H*-purine (6i). EtOAc was used as eluent for flash chromatography; yield 377 mg (24%), mp 106−108 °C, off-white small needles.^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.72 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 6.64−6.69 (m, 2H, Ar), 6.81−6.87 (m, 1H, Ar), 7.20−7.28 (m, 1H,

Ar), 8.24 (s, 1H, H-8); HRMS: Found 308.0243, calcd for $C_{13}H_{10}Cl_2N_4O$ 308.0232; Anal. ($C_{13}H_{10}Cl_2N_4O$) C, H, N.

2,6-Dichloro-9-(4-methoxy-3-methylphenylmethyl)-9*H*-purine (5j). EtOAc−hexane (1:2) was used as eluent for flash chromatography; yield 625 mg (39%), mp 134−135 °C, colorless powdery crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.28 (s, 2H, CH_2), 6.79 (d, J = 8.2 Hz, 1H, Ar), 7.08−7.16 (m, 2H, Ar), 7.99 (s, 1H, H-8); HRMS: Found 322.0382, calcd for $C_{14}H_{12}Cl_2N_4O$ 322.0388; Anal. ($C_{14}H_{12}Cl_2N_4O$) C, H, N.

2,6-Dichloro-7-(4-methoxy-3-methylphenylmethyl)-7*H*-purine (6j). EtOAc was used as eluent for flash chromatography; yield 227 mg (14%), mp 153−155 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.53 (s, 2H, CH_2), 6.79 (d, J = 8.0 Hz, 1H, Ar), 6.97−7.02 (m, 2H, Ar), 8.14 (s, 1H, H-8); HRMS: Found 322.0386, calcd for $C_{14}H_{12}Cl_2N_4O$ 322.0388; Anal. ($C_{14}H_{12}Cl_2N_4O$) C, H, N.

6-Chloro-9-(4-dimethylaminophenylmethyl)-9*H*-purine (3bb). Ethanesulfonic acid (0.010 mL, 0.12 mmol) was added to a stirred suspension of 5-amino-4-chloro-6-(4-dimethylaminyphenyl)pyrimidine **13** (316 mg, 1.14 mmol) in triethyl orthoformate (15 mL). The resulting mixture was stirred for 3 days and evaporated in vacuo. The residue was dissolved in dichloromethane (50 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (2 × 10 mL), dried ($MgSO_4$) end evaporated in vacuo. The crude product was purified by flash chromatography on silica gel eluting with acetone−hexane (2:5); yield 215 mg (66%), mp 125−127 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.94 (s, 6H, CH_3), 5.32 (s, 2H, CH_2), 6.68 (d, J = 8.6 Hz, 2H, Ar), 7.22 (d, J = 8.6 Hz, 2H, Ar), 8.04 (s, 1H, H-8), 8.77 (s, 1H, H-2); HRMS: Found 287.0932, calcd for $C_{14}H_{14}ClN_5$ 287.0938.

Stille coupling between 9-benzyl-6-chloropurines 3 and 2-furyl(tributyl)tin. A mixture of 9-substituted 6-chloropurine **3** (1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and 2-furyl(tributyl)tin (0.47 mL, 1.4 mmol) in DMF (5 mL) was stirred at 90 °C under N_2 atm. for 18 h and evaporated in vacuo. A sat. solution of potassium fluoride in methanol was added to the residue and the mixture was stirred overnight and evaporated in vacuo together with a small amount of silica gel. The residue was added on top of a chromatography column, and the product was isolated by flash chromatography on silica.

9-(4-Chlorophenylmethyl)-6-(2-furyl)-9*H*-purine (7b). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 239 mg (77%), mp 156−159 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.42 (s, 2H, CH_2), 6.65 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.23 (d, J = 8.6 Hz, 2H, Ar), 7.32 (d, J = 8.6 Hz, 2H, Ar), 7.75 (br d, J = 1.8 Hz, 1H, H-5 in furyl), 7.83 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.05 (s, 1H, H-8), 9.06 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 46.5 (CH_2), 112.6 (C-4 in furyl), 117.4 (C-3 in furyl), 129.1 (CH in Ar), 129.3 (CH in Ar), 129.6 (C-5), 133.6 (C in Ar), 134.6 (C in Ar), 144.0 (C-8), 145.9 (C-5 in furyl), 146.0 (C-6), 149.6 (C-2 in furyl), 152.0 (C-4), 152.8 (C-2); MS EI *m/z* (rel. %): 312/310 (37/100, M^+), 281 (11), 199 (10), 138 (7), 127 (26), 126 (6), 125 (71), 199 (4), 90 (5), 89 (16); HRMS: Found 310.0625, calcd for $C_{16}H_{11}ClN_4O$ 310.0621; Anal. ($C_{16}H_{10}Cl_2N_4O$) C, H, N.

9-(3,4-Dichlorophenylmethyl)-6-(2-furyl)-9*H*-purine (7c). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 282 mg (82%), mp 183−185 °C, colorless microcrystalline solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.40 (s, 2H, CH_2), 6.66 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 7.13 (dd, J = 8.4 and 1.8 Hz, 1H, Ar), 7.39 (br s, 1H, Ar), 7.42 (d, J = 8.4 Hz, 1H, Ar), 7.76 (dd, J = 1.8 and 0.8 Hz, 1H, H-5 in furyl), 7.84 (dd, J = 3.4 and 1.8 Hz, 1H, H-3 in furyl), 8.07 (s, 1H, H-8), 8.96 (s, 1H, H-2); Anal. ($C_{16}H_{10}Cl_2N_4O$) C, H, N.

9-(3-Chlorophenylmethyl)-6-(2-furyl)-9*H*-purine (7d). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 256 mg (83%), mp 175−177 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.43 (s, 2H, CH_2), 6.66 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.19 (m, 1H, Ar), 7.28−7.30 (m, 3H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.83 (br d, J = 3.4, 1H, H-3 in furyl), 8.07 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found 310.0616, calcd for $C_{16}H_{11}ClN_4O$ 310.06.21; Anal. ($C_{16}H_{10}Cl_2N_4O$) C, H, N.

9-(2,4-Dichlorophenylmethyl)-6-(2-furyl)-9*H*-purine (7e). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 262 mg (76%), mp 178−180 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.52 (s, 2H, CH_2), 6.65 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.22−7.28 (m, 2H, Ar), 7.44 (d, J = 1.6 Hz, 1H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.82 (br d, J = 3.4, 1H, H-3 in furyl), 8.15 (s, 1H, H-8), 8.94 (s, 1H, H-2); HRMS: Found 344.0217, calcd for $C_{16}H_{10}Cl_2N_4O$ 344.0232; Anal. ($C_{16}H_{11}Cl_2N_4O$) C, H, N.

9-(2-Chlorophenylmethyl)-6-(2-furyl)-9*H*-purine (7f). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 44.8 (CH_2), 112.5 (C-4 in furyl), 117.2 (C-3 in furyl), 127.3 (CH in Ar), 127.9 (C-5), 129.8 (CH in Ar), 129.9 (CH in Ar), 130.1 (CH in Ar), 132.5 (C in Ar), 133.3 (C in Ar), 144.3 (C-8), 145.7 (C-5 in furyl), 145.8 (C-6), 149.5 (C-2 in furyl), 151.9 (C-4), 152.6 (C-2); MS EI *m/z* (rel. %): 312/310 (5/14, M^+), 276 (35), 275 (100), 246 (2), 220 (2), 138 (8), 127 (10), 125 (30), 99 (3), 89 (9).

9-(2,6-Dichlorophenylmethyl)-6-(2-furyl)-9*H*-purine (7g). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 185 mg (54%), mp 203−205 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.73 (s, 2H, CH_2), 6.64 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.24−7.45 (m, 3H, Ar), 7.74 (m, 1H, H-5 in furyl), 7.81 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 7.88 (s, 1H, H-8), 8.99 (s, 1H, H-2); HRMS: Found 344.0227, calcd for $C_{16}H_{10}Cl_2N_4O$ 344.0232; Anal. ($C_{16}H_{10}Cl_2N_4O$) C, H, N.

9-(4-Fluorophenylmethyl)-6-(2-furyl)-9*H*-purine (7h). EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 269 mg (91%), mp 162−164 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.42 (s, 2H, CH_2), 6.64 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 7.03−7.12 (m, 2H, Ar), 7.32−7.38 (m, 2H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.82 (dd, J = 3.4 and 0.6 Hz, 1H, H-3 in furyl), 8.13 (s, 1H, H-8), 8.98 (s, 1 H, H-2); HRMS: Found 294.0889, calcd for $C_{16}H_{11}FN_4O$ 294.0917; Anal. ($C_{16}H_{11}FN_4O$) C, H, N.

9-(2-Fluorophenylmethyl)-6-(2-furyl)-9*H*-purine-9*H*-purine (7i). EtOAc−hexane (3:2) was used as eluent for flash chromatography; yield 260 mg (88%), mp 177−179 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.55 (s, 2H, CH_2), 6.69 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.11−7.16 (m, 2H, Ar), 7.32−7.45 (m, 2H, Ar), 7.79 (m, 1H, H-5 in furyl), 7.87 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.19 (s, 1H, H-8), 9.01 (s, 1 H, H-2); HRMS: Found 294.0916, calcd for $C_{16}H_{11}FN_4O$ 294.0917; Anal. ($C_{16}H_{11}FN_4O$) C, H, N.

9-(2,6-Difluorophenylmethyl)-6-(2-furyl)-9*H*-purine (7j). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 131 mg (84%), mp 209−211 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.54 (s, 2H, CH_2), 6.64 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 6.92 (t, J = 7.6 Hz, 2H, Ar), 7.34 (m, 1H, Ar), 7.74 (m, 1H, H-5 in furyl), 7.81 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.13 (s, 1H, H-8), 8.98 (s, 1 H, H-2); HRMS: Found 312.0819, calcd for $C_{16}H_{10}F_2N_4O$ 312.0823; Anal. ($C_{16}H_{10}F_2N_4O$) C, H, N.

6-(2-Furyl)-9-(4-trifluoromethylphenylmethyl)-9*H*-purine (7k). EtOAc−hexane (2:1) and then pure EtOAc were used as eluents for flash chromatography; yield 328 mg (95%), mp 159−161 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.52 (s, 2H, CH_2), 6.66 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.40 (d, J = 8.2 Hz, 2H, Ar), 7.60 (d, J = 8.2 Hz, 2H, Ar), 7.76 (m, 1H, H-5 in furyl), 7.84 (br d, J = 3.4, 1H, H-3 in furyl), 8.07 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 344.0871, calcd for $C_{17}H_{11}F_3N_4O$ 344.0885. Anal. ($C_{17}H_{11}F_3N_4O$) C, H, N.

6-(2-Furyl)-9-(4-nitrophenylmethyl)-9*H*-purine (7l). EtOAc−hexane (2:1) and then EtOAc−hexane (5:2) and EtOAc were used as eluents for flash chromatography; yield 215 mg (71%), mp 229−232 °C, yellow small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.57 (s, 2H, CH_2), 6.67 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.44 (d, J = 8.6 Hz, 2H, Ar), 7.76 (m, 1H,

H-5 in furyl), 7.85 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.11 (s, 1H, H-8), 8.20 (d, J = 8.6 Hz, 2H, Ar), 8.95 (s, 1H, H-2); HRMS: Found 321.0858, calcd for $C_{16}H_{10}N_5O_3$ 321.0862; Anal. ($C_{16}H_{10}N_5O_3$) C, H, N.

6-(2-Furyl)-9-(4-methylsulfonylphenylmethyl)-9*H*-purine (7m). EtOAc and then EtOAc-EtOH (20:1) were used as eluents for flash chromatography; yield 288 mg (81%), mp 187−188 °C, colorless small needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.00 (s, 3H, CH_3), 5.55 (s, 2H, CH_2), 6.66 (m, 1H, H-4 in furyl), 7.47 (d, J = 8.0 Hz, 2H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.84 (br d, J = 3.2 Hz, 1H, H-3 in furyl), 7.91 (d, J = 8.0 Hz, 2H, Ar), 8.12 (s, 1H, H-8), 8.95 (s, 1H, H-2); HRMS: Found 354.0725, calcd for $C_{17}H_{14}N_4O_3S$ 354.0787; Anal. ($C_{17}H_{14}N_4O_3S$) C, H, N.

6-(2-Furyl)-9-(4-methylphenylmethyl)-9*H*-purine (7n). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 245 mg (84%), mp 166−167 °C, off-white powdery crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.64 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 7.14 (d, J = 8.4 Hz, 2H, Ar), 7.20 (d, J = 8.4 Hz, 2H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.82 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.04 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 290.1167, calcd for $C_{17}H_{14}N_4O$ 290.1168; Anal. ($C_{17}H_{14}N_4O$) C, H, N.

9-(4-*tert*-Butylphenylmethyl)-6-(2-furyl)-9*H*-purine (7o). EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 263 mg (79%), mp 185−187 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 9H, *t*-Bu), 5.42 (s, 2H, CH_2), 6.65 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.23 (d, J = 8.4 Hz, 2H, Ar), 7.37 (d, J = 8.4 Hz, 2H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.83 (br d, J = 3.4, 1H, H-3 in furyl), 8.06 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found 322.1631, calcd for $C_{20}H_{20}N_4O$ 322.1637; Anal. ($C_{20}H_{20}N_4O$) C, H, N.

6-(2-Furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (7p). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 237 mg (77%), mp 175−176 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 6.64 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 6.86 (d, J = 8.0 Hz, 2H, Ar), 7.26 (d, J = 8.4 Hz, 2H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.81 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.02 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 306.1130, calcd for $C_{17}H_{14}N_4O_2$ 306.1117; Anal. ($C_{17}H_{14}N_4O_2$) C, H, N.

6-(2-Furyl)-9-(2-methoxyphenylmethyl)-9*H*-purine (7q). The reaction was performed in 2 mmol scale and EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 538 mg (88%), mp 156−158 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 6.63 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 6.86−6.96 (m, 2H, Ar), 7.26−7.36 (m, 2H, Ar), 7.73 (m, 1H, H-5 in furyl), 7.79 (dd, J = 3.6 and 0.6 Hz, 1H, H-3 in furyl), 8.16 (s, 1H, H-8), 8.95 (s, 1H, H-2); HRMS: Found 306.1115, calcd for $C_{17}H_{14}N_4O_2$ 306.1117; Anal. ($C_{17}H_{14}N_4O_2$) C, H, N.

6-(2-Furyl)-9-(3-methoxyphenylmethyl)-9*H*-purine (7r). The reaction was performed in 2 mmol scale and EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 575 mg (94%), mp 138−139 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.75 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 6.65 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.83−6.87 (m, 3H, Ar), 7.21−7.30 (m, 1H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.83 (dd, J = 3.4 and 0.6 Hz, 1H, H-3 in furyl), 8.06 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found 306.1112, calcd for $C_{17}H_{14}N_4O_2$ 306.1117; Anal. ($C_{17}H_{14}N_4O_2$) C, H, N.

6-(2-Furyl)-9-(4-methoxy-3-methylphenylmethyl)-9*H*-purine (7s). EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 285 mg (89%), mp 169−170 °C, colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.34 (s, 2H, CH_2), 6.64 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 6.77 (d, J = 8.4 Hz, 1H, Ar), 7.08−7.15 (m, 2H, Ar), 7.75 (m, 1H, furyl), 7.82 (m, 1H, furyl), 8.02 (s, 1H, H-8), 8.87 (s, 1H, H-2); HRMS: Found 320.1288, calcd for $C_{18}H_{16}N_4O_2$ 320.1273; Anal. ($C_{18}H_{16}N_4O_2$) C, H, N.

6-(2-Furyl)-9-(3,4,5-trimethoxyphenylmethyl)-9*H*-purine (7t). EtOAc−hexane (3:1) was used for flash chromatography; yield 246 mg (67%), mp 195−196 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 6H, 2 × CH_3), 3.79 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.52 (s, 2H, Ar), 6.65 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 7.74 (m, 1H, furyl), 7.82 (m, 1H, furyl), 8.06 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 366.1323, calcd for $C_{19}H_{18}N_4O_4$ 366.1328; Anal. ($C_{19}H_{18}N_4O_4$) C, H, N.

6-(2-Furyl)-9-(4-trifluoromethoxyphenylmethyl)-9*H*-purine (7u). The reaction was performed in 0.5 mmol scale, and EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 158 mg (88%), mp 146−147 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.46 (s, 2H, CH_2), 6.66 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 7.19 (d, J 8.6 Hz, 2H, Ar), 7.34 (d, J = 8.6 Hz, 2H, Ar), 7.76 (m, 1H, H-5 in furyl), 7.84 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.08 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found 360.0839, calcd for $C_{17}H_{11}F_3N_4O_2$ 360.0834; Anal. ($C_{17}H_{11}F_3N_4O_2$) C, H, N.

6-(2-Furyl)-9-(3-trifluoromethoxyphenylmethyl)-9*H*-purine (7v). The reaction was performed in 0.28 mmol scale, and acetone−hexane (2:5) was used as eluent for flash chromatography; yield 72 mg (71%), mp 133−135 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.48 (s, 2H, CH_2), 6.66 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 7.18−7.24 (m, 3H, Ar), 7.34−7.38 (m, 1H, Ar), 7.77 (m, 1H, H-5 in furyl) 7.87 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.09 (s, 1H, H-8), 8.98 (s, 1H, H-2); HRMS: Found 360.0840, calcd for $C_{17}H_{11}F_3N_4O_2$ 360.0834; Anal. ($C_{17}H_{11}F_3N_4O_2$) C, H, N.

9-(4-Ethoxyphenylmethyl)-6-(2-furyl)-9*H*-purine (7w). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 277 mg (87%), mp 165−166 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (t, J = 7.0 Hz, 3H, CH_3), 4.00 (q, J = 7.0 Hz, 2H, OCH_2), 5.37 (s, 2H, CH_2), 6.65 (dd, J 3.6 and 1.6 Hz, 1H, H-4 in furyl), 6.86 (d, J = 8.8 Hz, 2H, Ar), 7.22 (d, J = 8.8 Hz, 2H, Ar), 7.74 (m, 1H, H-5 in furyl), 7.82 (br d, J 3.6 Hz, 1H, H-3 in furyl), 8.03 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 320.1277, calcd for $C_{18}H_{16}N_4O_2$ 320.1273; Anal. ($C_{18}H_{16}N_4O_2$) C, H, N.

9-(4-Benzyloxyphenylmethyl)-6-(2-furyl)-9*H*-purine (7x). EtOAc−hexane (3:1) was used for flash chromatography; yield 110 mg (71%), mp 145−146 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.03 (s, 2H, OCH_2), 5.37 (s, 2H, NCH_2), 6.65 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 6.92−6.95 (m, 2H, Ar), 7.26−7.39 (m, 7H, Ar), 7.75 (br s, 1H, H-5 in furyl), 7.81 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.03 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 382.1424, calcd for $C_{23}H_{18}N_4O_2$ 382.1429; Anal. ($C_{23}H_{18}N_4O_2$) C, H, N.

6-(2-Furyl)-9-(4-hydroxyphenylmethyl)-9*H*-purine (7z). EtOAc−hexane (2:1) and then EtOAc was used as eluent for flash chromatography; yield 181 mg (56%), mp 231−233 °C, colorless crystals. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.37 (s, 2H, CH_2), 6.70 (br d, J = 8.4 Hz, 2H, Ar), 6.79 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.21 (br d, J 8.4 Hz, 2H, Ar), 7.81 (m, 1H, furyl), 8.04 (m, 1H, furyl), 8.70 (s, 1H, H-8), 8.88 (s, 1H, H-2), 9.46 (s, 1H, OH); HRMS: Found 292.0972, calcd for $C_{16}H_{12}N_4O_2$ 292.0960; Anal. ($C_{16}H_{12}N_4O_2$) C, H, N.

6-(2-Furyl)-9-(4-methylthiophenylmethyl)-9*H*-purine (7aa). Acetone−hexane (2:3) was used as eluent for flash chromatography; yield 309 mg (96%), mp 157−159 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.50 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.65 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 7.22−7.24 (m, 4H, Ar), 7.75 (m, 1H, furyl), 7.82 (m, 1H, furyl), 8.05 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 322.0898, calcd for $C_{17}H_{14}N_4OS$ 322.0888; Anal. ($C_{17}H_{14}N_4OS$) C, H, N.

9-(4-Dimethylaminophenylmethyl)-6-(2-furyl)-9*H*-purine (7bb). The reaction was performed in 0.5 mmol scale, and acetone−hexane (2:5) was used as eluent for flash chromatography; yield 140 mg (88%), mp 158−160 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.93 (s, 6H, CH_3), 5.33 (s, 2H, CH_2), 6.64 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 6.69 (d, J = 8.6 Hz, 2H, Ar), 7.22 (d, J = 8.6 Hz, 2H, Ar), 7.74 (dd, J = 1.6 and 0.6 Hz, 1H, H-5 in furyl), 7.81 (dd, J = 3.6

and 0.6 Hz, 1H, H-3 in furyl), 8.02 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found 319.1430, calcd for $C_{18}H_{17}N_5O$ 319.1433; Anal. ($C_{18}H_{17}N_5O$) C, H; N: calcd, 21.93; found, 21.25.

9-(4-Acetamidophenylmethyl)-6-(2-furyl)-9*H*-purine (7cc). The reaction was performed in 1.1 mmol scale and MeOH−$CHCl_3$ (1:15) was used as eluent for flash chromatography; yield 335 mg (88%), mp 278−280 °C, colorless powdery crystals. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.00 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 6.80 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.30 (d, J = 8.4 Hz, 2H, Ar), 7.52 (d, J = 8.4 Hz, 2H, Ar), 7.83 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.05 (m, 1H, H-5 in furyl), 8.72 (s, 1H, H-8), 8.88 (s, 1H, H-2), 9.94 (br s, 1H, NH); HRMS: Found 333.1229, calcd for $C_{18}H_{15}N_5O_2$ 333.1226; Anal. ($C_{18}H_{15}N_5O_2$) C, H, N.

9-(Diphenylmethyl)-6-(2-furyl)-9*H*-purine (7ee). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 61.5 (CH), 112.5 (C-4 in furyl) 117.3 (C-3 in furyl), 127.9 (CH in Ar), 128.3 (C-5), 128.5 (CH in Ar), 129.0 (CH in Ar), 137.9 (C in Ar), 143.8 (C-8), 145.7 (C-5 in furyl), 146.0 (C-6), 149.6 (C-2 in furyl), 151.9 (C-4), 152.7 (C-2); MS EI *m/z* (rel. %): 352 (45, M^+), 168 (12), 167 (100), 166 (8), 165 (24), 152 (12), 137 (1).

(*S*)-6-(2-Furyl)-9-(1-phenylethyl)-9*H*-purine (7ff). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) were used as eluents for flash chromatography; yield 248 mg (86%), mp 138−140 °C, pale yellow crystals; $[\alpha]_D$: +44.8° (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.99 (d, J = 7.0 Hz, 3H, CH_3), 5.99 (q, J = 7.0 Hz, 1H, C*H*CH_3), 6.62 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.31 (br s, 5H, Ar), 7.72 (m, 1H, H-5 in furyl), 7.80 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.06 (s, 1H, H-8), 8.92 (s, 1H, H-2); HRMS: Found 290.1164, calcd for $C_{17}H_{14}N_4O$ 290.1168; Anal. ($C_{17}H_{14}N_4O$) C, H, N.

(*R*)-6-(2-Furyl)-9-(1-phenylethyl)-9*H*-purine (7gg). EtOAc−hexane (1:1) and then EtOAc−hexane (2:1) was used as eluent for flash chromatography; yield 274 mg (94%), mp 136−139 °C, pale yellow powdery crystals. Spectral data, see **7ff**. $[\alpha]_D$: −47.2° (c 1.2, $CHCl_3$); Anal. ($C_{17}H_{14}N_4O$) C, H, N.

9-(4-Acetoxyphenylmethyl)-6-(2-furyl)-9*H*-purine (7y). Acetic anhydride (0.05 mL, 0.53 mmol) was added dropwise to a stirred suspension of 6-(2-furyl)-9-(4-hydroxyphenylmethyl)-9*H*-purine **3z** (77 mg, 0.26 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (65 mg, 0.53 mmol) in dry dichloromethane (5 mL) at ambient temperature under N_2-atm. The resulting reaction mixture was stirred for 45 min, diluted with dichloromethane (50 mL), washed with saturated aqueous $CuSO_4$ (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography in silica gel eluting with EtOAc−hexane (2:1); yield 81 mg (93%), mp 170−172 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.27 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 6.66 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 7.07 (d, J = 8.2 Hz, 2H, Ar), 7.32 (d, J = 8.2 Hz, 2H, Ar), 7.75 (m, 1H, H-5 in furyl), 7.84 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.07 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 334.1070, calcd for $C_{18}H_{14}N_4O_3$ 334.1066; Anal. ($C_{18}H_{14}N_4O_3$) C, H, N.

9-(4-Aminophenylmethyl)-6-(2-furyl)-9*H*-purine (7dd). A mixture of 9-(4-acetamidophenylmethyl)-6-(2-furyl)-9*H*-purine **7cc** (140 mg, 0.42 mL) in 48% aqueous HBr (2 mL) was stirred at 90 °C for 17 h and cooled to ambient temperature, before 10% aqueous K_2CO_3 (10 mL) was added carefully and the pH was adjusted to ca. 11 by addition of solid K_2CO_3. The mixture was extracted with EtOAc (4 × 25 mL) and the combined organic layers were dried ($MgSO_2$) and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel eluting with EtOAc; yield 82 mg (70%), mp 195−197 °C, yellow powdery crystals.^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.10 (br s, 2H, NH_2), 5.28 (s, 2H, CH_2), 6.49 (d, J = 8.4 Hz, 2H, Ar), 6.79 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 7.08 (d, J = 8.4 Hz, 2H, Ar), 7.81 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.04 (br s, 1H, H-5 in furyl), 8.66 (s, 1H, H-8), 8.88 (s, 1H, H-2); HRMS: Found 291.1125, calcd for $C_{16}H_{13}N_5O$ 291.1120; Anal. ($C_{16}H_{13}N_5O$) C, H.

Stille Coupling between 9-Benzyl-2,6-dichloropurines 5 and 2-Furyl(tributyl)tin. A mixture of tris(dibenzylideneacetone)dipalladium chloroform adduct (16 mg, 0.015 mmol) and tri(2-furyl)phosphine (26 mg, 0.11 mmol) in DMF (4 mL) was stirred at ambient temperature under N_2 atm. for 15 min., before the 9-substituted 2,6-dichloropurine **5** (0.5 mmol) and 2-furyl(tributyl)tin (0.20 mL, 0.6 mmol) were added. The resulting mixture was stirred for 8 h at 50 °C and evaporated in vacuo, and the products were purified as described for compounds **7**.

2-Chloro-9-(4-chlorophenylmethyl)-6-(2-furyl)-9*H*-purine (8b). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 46.7 (CH_2), 112.8 (C-4 in furyl), 118.8 (C-3 in furyl), 128.0 (C-5), 129.2 (CH in Ar), 129.3 (CH in Ar), 133.1 (C in Ar), 134.7 (C in Ar), 144.5 (C-8), 146.7 (C-5 in furyl), 147.3 (C-6), 148.7 (C-2 in furyl), 153.5 (C-4), 156.0 (C-2); MS EI *m/z* (rel. %): 348/346/344 (6/53/84, M^+), 343 (25), 315 (2), 309 (5), 233 (1), 127 (29), 126 (4), 125 (100), 99 (2), 90 (3).

2-Chloro-9-(3,4-dichlorophenylmethyl)-6-(2-furyl)-9*H*-purine (8c). EtOAc−hexane (1:2) and then EtOAc−hexane (1:1) were used as eluents for flash chromatography; yield 142 mg (75%), mp 191−193 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.36 (s, 2H, CH_2), 6.66 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 7.13 (dd, J = 8.4 and 1.8 Hz, 1H, Ar), 7.38−7.46 (m, 2H, Ar), 7.78 (m, 1H, H-5 in furyl), 7.87 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.02 (s, 1H, H-8); HRMS: Found 377.9838, calcd for $C_{16}H_{19}Cl_3N_4O$ 377.9842; Anal. ($C_{16}H_{19}Cl_3N_4O$) C, H; N: calcd, 14.76; found, 14.16.

2-Chloro-9-(3-chlorophenylmethyl)-6-(2-furyl)-9*H*-purine (8d). EtOAc−hexane (2:3) were used as eluents for flash chromatography; yield 164 mg (95%), mp 196−198 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.38 (s, 2H, CH_2), 6.66 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.16−7.18 (m, 1H, Ar), 7.27−7.31 (m, 3H, Ar), 7.78 (m, 1H, H-5 in furyl), 7.86 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.01 (s, 1H, H-8); HRMS: Found 344.0246, calcd for $C_{16}H_{10}Cl_2N_4O$ 344.0232; Anal. ($C_{16}H_{10}Cl_2N_4O$) C, H, N.

2-Chloro-9-(4-fluorophenylmethyl)-6-(2-furyl)-9*H*-purine (8e). EtOAc−hexane (2:3) was used as an eluent for flash chromatography; yield 127 mg (77%), mp 152−155 °C, pale yellow crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.38 (s, 2H, CH_2), 6.65 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.01−7.09 (m, 2H, Ar), 7.24−7.34 (m, 2H, Ar), 7.77 (m, 1H, H-5 in furyl), 7.86 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 7.99 (s, 1H, H-8); HRMS: Found 328.0517, calcd for $C_{16}H_{10}ClFN_4O$ 328.0527. Anal. ($C_{16}H_{10}ClFN_4O$) H, N; C: calcd, 58.46; found, 59.18.

2-Chloro-6-(2-furyl)-9-(4-methylphenylmethyl)-9*H*-purine (8f).[23] EtOAc−hexane (1:2) was used as an eluent for flash chromatography; yield 120 mg (74%), mp 171−173 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.65 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 7.18 (m, 4H, Ar), 7.76 (m, 1H, H-5 in furyl), 7.84 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 7.97 (s, 1H, H-8); HRMS: Found 324.0775, calcd for $C_{17}H_{13}ClN_4O$ 3240778.

2-Chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (8g). EtOAc−hexane (1:1) was used as an eluent for flash chromatography; yield 104 mg (61%), mp 184−186 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 6.65 (dd, J = 3.6 and 1.6 Hz, 1H, H-4 in furyl), 6.88 (d, J = 8.8 Hz, 2H, Ar), 7.26 (d, J = 8.8 Hz, 2H, Ar), 7.76 (m, 1H, H-5 in furyl), 7.84 (dd, J = 3.6 and 0.6 Hz, 1H, H-3 in furyl), 7.96 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 46.7 (CH_2), 55.2 (CH_3), 112.7 (C-4 in furyl), 114.4 (CH in Ar), 118.6 (C-3 in furyl), 126.4 (C-1 in Ar), 127.1 (C-5), 129.4 (CH in Ar), 144.6 (C-8), 146.5 (C-5 in furyl), 147.1 (C-6), 148.7 (C-2 in furyl), 153.5 (C-4), 154.3 (C-2), 159.7 (C-4 in Ar); MS EI *m/z* (rel. %): 342/340 (12/38, M^+), 222 (3) 220 (10), 192 (2), 122 (9), 121 (100) 106 (3), 91 (4), 78 (9), 77 (8); HRMS: Found 340.0735, calcd for $C_{17}H_{13}ClN_4O_2$ 340.0727; Anal. ($C_{17}H_{13}ClN_4O_2$) C, H, N.

2-Chloro-6-(2-furyl)-9-(2-methoxyphenylmethyl)-9*H*-purine (8h). EtOAc−hexane (1:1) was used as an eluent for flash chromatography; yield 305 mg (90%), mp 168−170 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 6.63 (dd, J = 3.4 and 1.6 Hz, 1H, H-4 in furyl), 6.87−6.97 (m, 2H, Ar), 7.27−7.37 (m, 2H, Ar), 7.74

(m, 1H, H-5 in furyl), 7.81 (br d, J = 3.4, 1H, H-3 in furyl), 8.09 (s, 1H, H-8); HRMS: Found 340.0715, calcd for $C_{17}H_{13}ClN_4O_2$ 340.0727; Anal. ($C_{17}H_{13}ClN_4O_2$) C, H, N.

2-Chloro-6-(2-furyl)-9-(3-methoxyphenylmethyl)-9*H*-purine (8i). EtOAc−hexane (2:3) was used as an eluent for flash chromatography; yield 161 mg (94%), mp 160−161 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 6.65 (dd, J = 3.6 and 1.8 Hz, 1H, H-4 in furyl), 6.84−6.88 (m, 3H, Ar), 7.26−7.31 (m, 1H, Ar), 7.77 (m, 1H, H-5 in furyl), 7.85 (br d, J = 3.6 Hz, 1H, H-3 in furyl), 8.00 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.3 (CH_2), 55.3 (CH_3), 112.8 (C-4 in furyl), 113.7 (CH in Ar), 114.0 (CH in Ar), 118.7 (C-3 in furyl), 120.0 (CH in Ar), 127.1 (C-5), 130.3 (CH in Ar), 136.0 (C in Ar), 144.8 (C-8), 146.6 (C-5 in furyl), 147.3 (C-6), 148.7 (C-2 in furyl), 153.6 (C-4), 154.4 (C-2), 160.1 (C-3 in Ar); MS EI *m/z* (rel. %): 342/340 (33/100, M^+), 311 (7), 305 (14), 233 (7), 121 (100), 91 (27), 78 (14), 77 (10); HRMS: Found 340.0743, calcd for $C_{17}H_{13}ClN_4O_2$ 340.0727; Anal. ($C_{17}H_{13}ClN_4O_2$) C, H, N.

2-Chloro-6-(2-furyl)-9-(4-methoxy-3-methylphenylmethyl)-9*H*-purine (8j). EtOAc−hexane (2:3) was used as an eluent for flash chromatography; yield 117 mg (66%), mp 177−179 °C, off-white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2), 6.64 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.78 (d, J = 8.0 Hz, 1H, Ar), 7.07−7.14 (m, 2H, Ar), 7.75 (br s, 1H, H-5 in furyl), 7.83 (br d, J 3.4 Hz, 1H, H-3 in furyl), 7.96 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.2 (CH_3), 47.1 (CH_2), 55.4 (OCH_3), 110.2 (CH in Ar), 112.7 (C-4 in furyl), 118.6 (C-3 in furyl), 125.9 (C in Ar), 126.9 (CH in Ar), 127.2 (C-5), 127.6 (C in Ar), 130.5 (CH in Ar), 144.8 (C-8), 146.5 (C-5 in furyl), 147.2 (C-6), 148.8 (C-2 in furyl), 153.6 (C-4), 154.3 (C-2), 158.0 (C-4 in Ar); MS EI *m/z* (rel. %): 356/354 (9/28, M^+), 177 (2), 136 (9), 135 (100), 120 (2), 103 (1), 91 (6); HRMS: Found 354.0872, calcd for $C_{18}H_{15}ClN_4O_2$ 354.0884; Anal. ($C_{18}H_{15}ClN_4O_2$) C, H, N.

5-Amino-4-chloro-6-(4-dimethylaminyphenyl)pyrimidine (11a). Triethylamine (1.12 mL, 8 mmol) was added to a stirred suspension of 4-dimethyaminobenzylamine dihydrochloride (447 mg, 2 mmol) in *n*-butanol (10 mL). After stirring for 5 min, 5-amino-4,6-dichloropyrimidine (328 mg, 2 mmol) was added and the reaction mixture was stirred at 100 °C for 22h. Upon cooling to ambient temperature needles of triethylammonium chloride was formed. The reaction mixture was filtered, and the solid washed with *n*-hexane. The combined filtrates were evaporated in vacuo and the residue subjected to flash chromatography on silica gel eluting with acetone−hexane (2:5); yield 316 mg (57%), mp 153−156 °C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.83 (s, 6H, CH_3), 4.46 (d, J = 5.2 Hz, 2H, CH_2), 5.03 (br s, 2H, NH_2), 6.66 (d, J = 8.4 Hz, 2H, Ar), 7.11−7.15 (m, 3H, Ar and NH), 7.71 (s, 1H, H-2); MS EI *m/z* (rel. %): 279/277 (2/9, M^+), 134 (100), 118 (7), 91 (2); HRMS: Found 277.1093, calcd for $C_{13}H_{16}ClN_5$ 277.1094; Anal. ($C_{13}H_{16}ClN_5$) C, H.

6-Chloro-9-phenylsulfonyl-9*H*-purine (12). A solution of potassium hydroxide (360 mg, 6.0 mmol) in water (15 mL) and then phenylsulfonyl chloride (0.38 mL, 3.0 mmol) were added dropwise to a stirred mixture of 6-chloropurine (464 mg, 3.0 mmol) in acetone (30 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h, the pH was adjusted to ca. 7 and acetone was removed in vacuo. The solid was filtered off, washed with water and diethyl ether and recrystallized from EtOH; yield 566 mg (64%), mp 175−176 °C (dec), colorless needles. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.59−7.75 (m, 3H, Ph), 8.28 (d, J = 7.4 Hz, 2H, Ph), 8.56 (s, 1H, H-8), 8.84 (s, 1H, H-2); HRMS: Found 293.9964, calcd for $C_{11}H_7ClN_4O_2S$ 293.9987.

6-(2-Furyl)-9-phenylsulfonyl-9*H*-purine (13). *n*-Butyllithium (0.38 mL, 0.60 mmol, 1.6 M hexane solution) was added dropwise to a stirred solution of furan (0.055 mL, 0.76 mmol) in dry THF (4 mL) under N_2 at 0 °C. The resulting mixture was stirred for 2 h at 0 °C and 1 h at ambient temperature, before it was cooled to −78 °C. A 1 M solution of anhydrous zinc bromide in dry THF (0.67 mL, 0.6 mmol) was added dropwise, and the resulting mixture was stirred for 1 h at −78 °C before the cooling bath was removed and the reaction mixture was allowed to reach ambient temperature. A solution of 6-chloro-9-phenylsulfonyl-9*H*-purine (147 mg, 0.50 mmol) in dry THF (8 mL) was added followed by a solution of tetrakis(triphenylphosphine)palladium(0) [generated in situ from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 0.013 mmol) and triphenylphosphine (26 mg, 0.10 mmol)] in dry THF (2 mL). The mixture was heated at 50 °C for 19 h and cooled to ambient temperature. Sat. aq. ammonium chloride (10 mL) was added, and the aq. phase extracted with EtOAc (2 × 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 (2:3); yield (75 mg) 46%, colorless crystals, mp 218−220 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.65 (dd, J = 3.6 and 1.6 Hz, 1 H, H-4 in furyl), 7.54−7.83 (m, 5H, Ph and furyl), 8.30 (br d, J = 6.0 Hz, 2 H, Ph), 8.53 (s, 1 H, H-8), 9.01 (s, 1 H, H-2); HRMS: Found 326.0487, calcd for $C_{15}H_{10}N_4O_3S$ 326.0474; Anal. ($C_{15}H_{10}N_4O_3S$) C, H; N: calcd, 17.17; found, 16.52.

Synthesis of 9-Aryl-6-(2-furyl)purines 16. The compounds **16** were prepared by palladium catalyzed coupling between 9-aryl-6-chloropurines **14** and 2-furyl(tributyl)tin following the same general procedure as given for the synthesis of the 9-benzylpurines **7** above.

6-(2-Furyl)-9-phenyl-9*H*-purine (16a). The reaction was performed in 0.22 mmol scale, and MeOH−CH_2Cl_2 (3:100) was used as eluent for flash chromatography; yield 35 mg (61%), mp 190−192 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.67 (m, 1H, H-4 in furyl), 7.47 (m, 1H, Ph), 7.58 (m, 2H, Ph), 7.71 (d, J = 7.8 Hz, 2H, Ph), 7.77 (br s, 1H, H-5 in furyl), 7.88 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.35 (s, 1H, H-8), 8.99 (s, 1H, H-2); HRMS: Found 262.0865, calcd for $C_{15}H_{10}ClN_4O$ 262.0855; Anal. ($C_{15}H_{10}ClN_4O$) C, H, N.

9-(4-Chlorophenyl)-6-(2-furyl)-9*H*-purine (16b). The reaction was performed in 0.12 mmol scale, and MeOH−$CHCl_3$ (1:100) was used as eluent for flash chromatography; yield 34 mg (94%), mp 240−242 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.76 (m, 1H, H-4 in furyl), 7.54 (d, J = 8.5 Hz, 2H, Ar), 7.68 (d, J = 8.5 Hz, 2H, Ar), 7.76 (br s, 1H, H-5 in furyl), 7.87 (br d, J = 3.1 Hz, 1H, H-3 in furyl), 8.32 (s, 1H, H-8), 8.96 (s, 1H, H-2); HRMS: Found 296.0456, calcd for $C_{15}H_9ClN_4O$ 296.0465; Anal. ($C_{15}H_9ClN_4O$) C, H; N: calcd, 18.88; found, 18.42.

9-(3-Chlorophenyl)-6-(2-furyl)-9*H*-purine (16c). The reaction was performed in 0.19 mmol scale, and EtOAc−hexane (1:1) was used as eluent for flash chromatography; yield 44 mg (80%), mp 181−183 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.66 (m, 1H, H-4 in furyl), 7.42 (d, J = 8.0 Hz, 1H, Ar), 7.49 (m, 1H, Ar), 7.64 (d, J = 8.2 Hz, 2H, Ar), 7.76 (br s, 1H, H-5 in furyl), 7.78 (br s, 1H, Ar), 7.86 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.33 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found 296.0452, calcd for $C_{15}H_9ClN_4O$ 296.0465.

6-(2-Furyl)-9-(4-methylphenyl)-9*H*-purine (16d). The reaction was performed in 0.39 mmol scale, and EtOAc−hexane (1:1) and then EtOAc−hexane (3:1) were used as eluents for flash chromatography; yield 90 mg (83%), mp 184−186 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.34 (s, 3H, CH_3), 6.60 (m, 1H, H-4 in furyl), 7.28 (d, J = 8.2 Hz, 2H, Ar), 7.49 (d, J = 8.2 Hz, 2H, Ar), 7.70 (br s, 1H, H-5 in furyl), 7.81 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.25 (s, 1H, H-8), 8.91 (s, 1H, H-2); HRMS: Found 276.1011, calcd for $C_{16}H_{12}ClN_4O$ 276.1010; Anal. ($C_{16}H_{12}ClN_4O$) H; C: calcd, 69.55; found, 69.09; N: calcd, 20.28; found, 19.82.

6-(2-Furyl)-9-(4-methoxyphenyl)-9*H*-purine (16e). The reaction was performed in 0.17 mmol scale, and $CHCl_3$ and then MeOH−$CHCl_3$ (1:100) were used as eluents for flash chromatography; yield 37 mg (77%), mp 222−224 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.87 (s, 3H, CH_3), 6.68 (m, 1H, H-4 in furyl), 7.08 (d, J = 8.9 Hz, 2H, Ar), 7.58 (d, J = 8.8 Hz, 2H, Ar), 7.78 (br s, 1H, H-5 in furyl), 7.89 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.29 (s, 1H, H-8), 8.97 (s, 1H, H-2); HRMS: Found: 292.0960, calcd for $C_{16}H_{12}ClN_4O_2$ 292.0960; Anal. ($C_{16}H_{12}ClN_4O_2$) C, H, N.

Synthesis of 9-Aryl-2-chloro-6-(2-furyl)purines 17. The compounds **17** were prepared by palladium-catalyzed coupling between 9-aryl-2,6-dichloropurines **15** and 2-furyl(tributyl)-tin following the same general procedure as given for the synthesis of the 9-benzyl-2-chloropurines **8** above.

2-Chloro-6-(2-furyl)-9-phenyl-9*H*-purine (17a). The reaction was performed in 0.25 mmol scale at 40 °C, and MeOH−CH_2Cl_2 (1:100) was used as eluent for flash chromatography; yield 51 mg (69%), mp 222−223 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.68 (m, 1H, H-4 in furyl), 7.48 (m, 1H, Ph), 7.58 (m, 2H, Ph), 7.68 (d, J = 8.1 Hz, 2H, Ph), 7.80 (br s, 1H, H-5 in furyl), 7.91 (br d, J = 3.4 Hz, 1H, H-3 in furyl), 8.32 (s, 1H, H-8); HRMS: Found 296.0470, calcd for $C_{15}H_9ClN_4O$ 296.0465.

2-Chloro-6-(2-furyl)-9-(4-methylphenyl)-9*H*-purine (17b). The reaction was performed in 0.20 mmol scale, and MeOH−CH_2Cl_2 (1:100) was used as eluent for flash chromatography; yield 35 mg (56%), mp 265−267 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 3H, CH_3), 6.68 (m, 1H, H-4 in furyl), 7.37 (d, J = 8.2 Hz, 2H, Ar), 7.54 (d, J = 8.2 Hz, 2H, Ar), 7.79 (br s, 1H, H-5 in furyl), 7.91 (br d, J = 3.5 Hz, 1H, H-3 in furyl), 8.28 (s, 1H, H-8); HRMS: Found 310.0621, calcd for $C_{16}H_{11}ClN_4O$ 310.0621; Anal. ($C_{16}H_{11}ClN_4O$) C, H, N.

Activity against *Mycobacterium tuberculosis*. The primary screening against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) was conducted at 6.25 μg/mL in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA).[12] Compounds exhibiting fluorescence were tested in the BACTEC 460-radiometric system,[12] and compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentrations against *M. tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in the MABA. MIC for rifampin was 0.25 μg/mL.

Activity against *Mycobacterium avium* Complex. Primary screening against *Mycobacterium avium* complex (ATCC 25291) was conducted at a range of 0.25 μg/mL to 32 μg/mL against clinical isolates of *Mycobacterium avium* in Middlebrook 7H9 broth using the Microplate Alamar Blue Assay and in the BACTEC 460-radiometric system.[12b]

Cytotoxicity against VERO Cell Lines. Compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations less than or equal to 62.5 μg/mL. After 72 h exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega CellTiter 96 Non-radioactive Cell Proliferation Assay. [12b]

Determination of 90% and 99% Effective Concentration in *M. tuberculosis* Infected Macrophages. Compounds were tested for the ability to kill *M. tuberculosis* Erdman (ATCC 35801) in monolayers of mouse bone marrow macrophages[12b,24] at 4-fold concentrations equivalent to 0.25, 1, 4 and 16 times the MIC. The results are presented in Table 2 as EC_{90} and EC_{99}: lowest concentration effecting a 90% and 99% reduction, respectively, in colony forming units at 7 days compared to drug-free controls.

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Supporting Information Available: Elemental analysis results, ^{13}C NMR of novel compounds and MS data for compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Duncan, K. Towards the Next Generation of Drugs and Vaccines for Tuberculosis. *Chem. Ind.* **1997**, 861−865.
(2) Bakkestuen, A. K.; Gundersen, L.-L.; Langli, G.; Liu, F.; Nolsøe, J. M. J. 9-Benzylpurines with Inhibitory Activity against *Mycobacterium tuberculosis*. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1207−1210.
(3) Gundersen, L.-L.; Nissen-Meyer, J.; Spilsberg, B. Synthesis and Antimycobacterial Activity of 6-Arylpurines; the Requirements for the *N*-9 Substituent in Active Antimycobacterial Purines. *J. Med. Chem*. **2002**, *45*, 1383−1386.
(4) Alksnis, E.; Korneeva, D.; Lukevics, E. Adenine and Uracil Derivatives with Antitubercular Activity. *Chem. Heterocycl. Compd*. **2001**, *37*, 743−746.
(5) Mangalindan, G. C.; Talaue, M. T.; Cruz, L. J.; Franzblau, S. G.; Adams, L. B.; Richardson, A. D.; Ireland, C. M.; Conception, G. P. Agelasine F from a Philippine *Agelas* sp Sponge Exhibits *in vitro* Antituberculosis Activity. *Planta Med*. **2000**, *66*, 364−365.
(6) (a) Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. Antimycobacterial Activity of 9-Sulfonylated/Sulfenylated-6-mercaptopurine Derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1675−1678. (b) Pathak, A. K.; Pathak, V.; Seitz, L. E.; Suling, W. J.; Reynolds, R. C. Antimycobacterial Agents. 1. Thio Analogues of Purine. *J. Med. Chem*. **2004**, *47*, 273−276. (c) Barrow, E. W.; Westbrook, L.; Bansal, N.; Suling, W. J.; Maddry, J. A.; Parker, W. B.; Barrow, W. W. Antimycobacterial activity of 2-methyladenosine. *J. Antimicrob. Chemother*. **2003**, *52*, 801−808.
(7) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. Synthesis and cytostatic activity of substituted 6-phenylpurine bases and nucleosides: Application of the Suzuki-Miyaura cross-coupling reactions of 6-chloropurine derivatived with phenylboronic acids. *J. Med. Chem*. **2000**, *43*, 1817−1825.
(8) Kelley, J. L.; Krochmal, M. P.; Linn, J. A.; McLean, E. W.; Soroko, F. E. 6-(Alkylamino)-9-benzyl-9*H*-purines. A New Class of Anticonvulsant Agents. *J. Med. Chem.* **1988**, *31*, 606−612.
(9) Kelley, J. L.; Linn, J. A.; Krochmal, M. P.; Selway, J. W. T. 9-Benzyl-6-(dimethylamino-9*H*-purines with Antirhinovirus Activity. *J. Med. Chem*. **1988**, *31*, 2001−2004.
(10) Dome, M.; Wakselman, M.; Alkylation by Amino- and Amidobenzylic Halides in Aqueous Media II. Reaction with Nucleophiles. *Bull. Soc. Chim. Fr*. **1975**, 576−582.
(11) Bakkestuen, A. K.; Gundersen, L.-L. Regioselective *N*-9 Arylation of Purines Employing Arylboronic Acids in the Presence of Cu(II). *Tetrahedron Lett*. **2003**, *44*, 3359−3362.
(12) (a) Collins, L.; Franzblau. S. G. Microplate Alamar Blue Assay versus BACTEC 460 System for High-Throughput Screening of Compounds against *Mycobacterium tuberculosis* and *Mycobacterium avium*. *Antimicrob. Agents Chemother*. **1997**, *41*, 1004−1009. (b) http://www.taacf.org/; (c) Orme, I.; Secrist, J.; Anathan, S.; Kwong, C.; Maddry, J.; Reynolds, R.; Poffenberger, A.; Michael, M.; Miller, L.; Krahenbuh, J.; Adams, L.; Biswas, A.; Franzblau, S.; Rouse, D.; Winfield, D.; Brooks, J. Search for New Drugs for Treatment of Tuberculosis. *Antimicrob. Agents Chemother*. **2001**, *45*, 1943−1946.
(13) Chaisson, R. E.; Moore, R. D.; Richman, D. D.; Keruly, J.; Creagh, T. Incidence and natural history of *Mycobacterium avium*-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *Am. Rev. Respir. Dis*. **1992**, *146*, 285−289.
(14) Nightinggale, S. D.; Byrd, L. T.; Souther, P. M.; Hockusch, J. D.; Cal, S. X.; Wynne, B. A. Incidence of *Mycobacterium avium-intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. *J. Infect. Dis*. **1992**, *165*, 1082−1085.
(15) McKinney, J. D.; Bentrup, K. H. Z.; Munos-Elias, E. J.; MicZak, A.; Chen, B.; Chan, W.-T.; Swenson, D.; Sacchettini, J. C.; Jacobs, W. R.; Russel, D. G. Persistence of Mycobacterium tuberculosis in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. *Nature* **2000**, *406*, 735−738, and references therein.
(16) (a) Montgomery, J. A.; Niwas, S.; Rose, J. D.; Secrist, J. A., III.; Babu, Y. S.; Bugg, C. E.; Erion, M. D.; Guida, W. C.; Ealick, S. E. Structure-based design of inhibitors of purine nucleoside phosphorylase. 1. 9-(Arylmethyl) derivatives of 9-deazaguanine. *J. Med. Chem*. **1993**, *36*, 55−69. (b) Parker, W. B.; Allan, P. W.; Niwas, S.; Montgomery, J. A.; Bennett, L., Jr. Effect of 9-benzyl-9-deazaguanine, a potent inhibitor of purine nucleoside phosphorylase, on the cytotoxicity and metabolism of 6-thio-2′-deoxyguanosine. *Cancer Res*. **1994**, *54*, 1742−1745. (c) Babu, Y. S.; Ealick, S. E.; Bugg, C. E.; Erion, M. D.; Guida, W. C.; Montgomery, J. A.; Secrist, J. A., III. Structure-based design of inhibitors of purine nucleoside phosphorylase. *Acta Crystallogr*. **1995**, *D51*, 529−535.
(17) Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; ØverÅs, H.; Rise, F. 6-Halopurines in Palladium-Catalyzed Coupling with Organotin and Organozinc Reagents. *Tetrahedron* **1994**, *50*, 9743−9756.

(18) Langli, G.; Gundersen, L.-L.; Rise, F. Regiochemistry in Stille Couplings of 2,6-Dihalopurines. *Tetrahedron*, **1996**, *52*, 5625−5638.
(19) Ramzaeva, N. P.; Goldberg, Y. S.; Alksnis, E. R.; Lidak, M. Y.; Shimanskaya, M. V. Synthesis of N,N, 9-Trisubstituted Adenines under Conditions of Phase-Transfer Catalysis. *J. Org. Chem. USSR* **1990**, 1611−1615.
(20) Maruyama, T.; Kozai, S.; Uchida, M. Synthesis of N-aryl Uracils and Hypoxantine and Their Biological Properties. *Nucleosides, Nucleotides* **1999**, *18*, 661−671.
(21) Gharbaoui, T.; Benhida, R.; Chastanet, J.; Lechvallier, A.; Maillos, P.; Beugelmans, R. Dérivés N-alkylés en série purine. Synthése par chimie radicalaire $S_{RN}1$ at améngagements fonctionnels. *Bull. Chem. Soc. Fr.* **1994**, *313*, 561−574.
(22) Pappo, D.; Kashman, Y. Synthesis of 9-substituted tetrahydrodiazepinopurines − asmarine A analouges. *Tetrahedron* **2003**, *59*, 6493−6501.
(23) Gillespie, R. J.; Lerpiniere, J.; Dawson, C. E.; Gaur, S.; Pratt, R. M.; Stratton, G. C.; Weiss, S. M. Preparation of purine derivatives as purinergic receptor antagonists. PCT Int. Appl., 2002, 111 pp.
(24) Skinner, P. S., S. K.; Furney, M. R.; Jacobs, G.; Klopman, J. J.; Ellner, Orme, I. M. A bone marrow-derived murine macrophage model for evaluating efficacy of antimycobacterial drugs under relevant physiological conditions. *Antimicrob. Agents Chemother.* **1994**, *38*, 2557−2563.

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