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Bioorganic & Medicinal Chemistry 13 (2005) 6360–6373
Bioorganic & Medicinal Chemistry

Selective anti-tubercular purines: Synthesis and chemotherapeutic properties of 6-aryl- and 6-heteroaryl-9-benzylpurines

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Received 26 April 2005; revised 24 June 2005; accepted 24 June 2005
Available online 2 August 2005

Abstract—6-Aryl- and 6-heteroaryl-9-benzylpurines have been synthesized employing palladium-catalyzed coupling reactions in the step forming the C–C or C–N bond between the aryl- or heteroaryl and the purine. The compounds were screened for activity against *Mycobacterium tuberculosis* as well as representative Gram+ and Gram− bacteria, and for cytotoxic effects on mammalian cells. Several potent antimycobacterials were identified. These compounds probably act by a novel and selective mechanism; they exhibit low toxicity toward other bacteria as well as mammalian cells.

1. Introduction

Globally, tuberculosis (TB) takes a life every 15 s, and it is estimated that ca. one-third of the world's population is infected with *Mycobacterium tuberculosis*. In sub-Saharan Africa, two-thirds of all HIV infected are co-infected with TB, and TB is the actual cause of death for 30% of the AIDS patients worldwide. Today, the standard drug combinations used to treat tuberculosis must be taken for 6–9 months. There has been no major breakthrough in TB drug development for 30 years and at the same time multi-drug resistant TB (MDR-TB) is a growing problem.[1]

We have identified 6-(2-furyl)purines as potent inhibitors of *M. tuberculosis* in vitro.[2–4] These compounds generally exhibit low toxicity toward mammalian cells. The mechanism for the antimycobacterial activity is not yet known. We have shown earlier that a carbon-substituent was required in the purine 6-position and that 6-alkyl- or cycloalkylpurines generally exhibits low activity toward *M. tuberculosis*.[2] The alkenyl- and alkynylpurines are often cytotoxic to mammalian cells and hence less useful as antibacterials.[5] Herein, we report the synthesis of 6-aryl- or 6-heteroarylpurines and screening of their chemotherapeutic properties; activity against *M. tuberculosis* as well as other bacteria, and toxicity toward mammalian cells.

Keywords: Antimycobacterial; *N*-Arylation; Cross-coupling; Purines.
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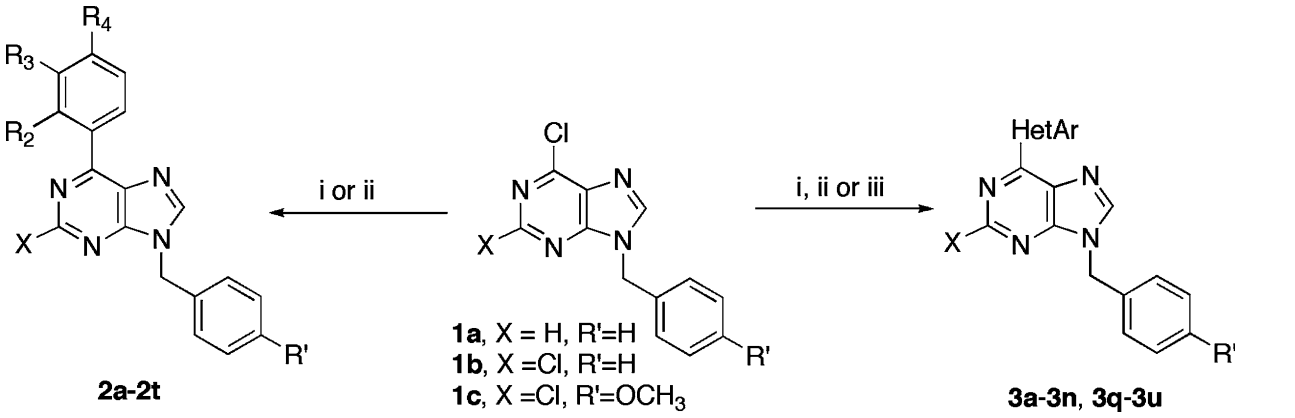
doi:10.1016/j.bmc.2005.06.054

2. Chemistry

Aryl- or heteroaryl groups can easily be introduced in the purine 6-position by palladium-catalyzed cross-coupling between 6-chloropurines **1** and organometallic reagents.[6] We prepared the 6-arylpurines **2** and 6-heteroarylpurines **3** by Stille, Negishi, or Suzuki couplings (Scheme 1). The choice of reaction was determined by the availability, stability, and reactivity of the organometallic coupling partner. Detailed reaction conditions and results are summarized in Tables 1 and 2. These versatile cross-couplings allowed us to prepare purines carrying aryl- or heteroaryl groups with various electronic properties and steric requirements, in the 6-position.

6-(*N*-Pyrrolyl)-9-alkylpurines are traditionally made in two steps; reaction between adenine and 2,5-dimethoxytetrahydrofuran,[7] followed by *N*-alkylation.[7,8] Moderate or even low yields are often reported in both steps. Pyrrole and indole have been *N*-arylated using Hartwig–Buchwald-type coupling reactions,[9] and we chose to employ this strategy for the first time in the synthesis of an *N*-pyrrolylpurine. When an excess of pyrrole was used the 6-(*N*-pyrrolyl)purine (**3o**) was isolated in high yield (Scheme 2).

The imidazolyl group in **3p** was introduced by direct displacement of the bromide in the halopurine **1d**. 6-Chloropurine is reported to react with imidazole when melted at 150 °C,[7b] whereas 6-bromopurines react more readily with weakly nucleophilic amines and imidazole (Scheme 2).[10]



Scheme 1. Reagents and conditions: (i) ArZnBr or HetArZnBr, $(Ph_3P)_4Pd$, THF, Δ; (ii) $ArB(OH)_2$ or $HetArB(OH)_2$, K_2CO_3, $(Ph_3P)_4Pd$, $PhCH_3$ or dioxane, 100 °C; (iii) $HetArSnBu_3$, Pd-catalyst, DMF; see also Tables 1 and 2.

Table 1. Synthesis of novel compounds **2**[a]

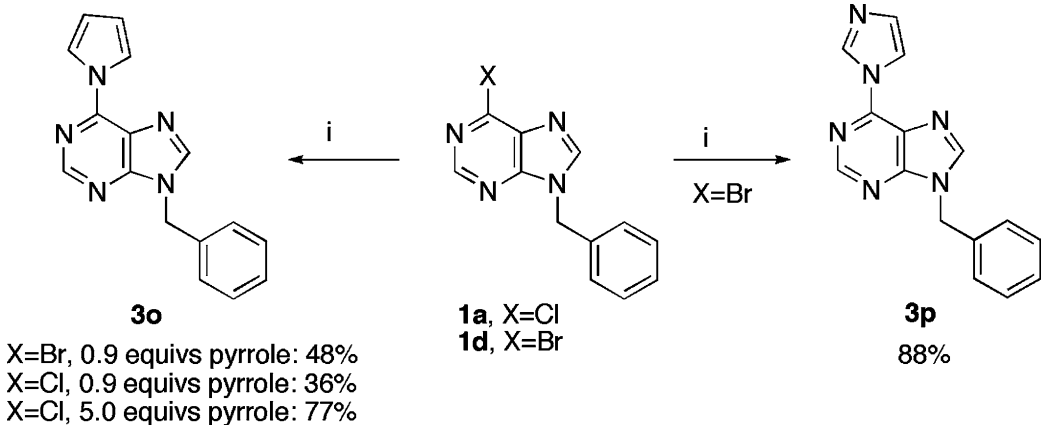
X	R^2	R^3	R^4	R′	Met	Solvent (base)	Temp (°C)	Time (h)	Yield (%) **2**
H	H	H	Cl	H	ZnBr	THF	50	4	71, **2c**
H	H	Cl	Cl	H	$B(OH)_2$	$PhCH_3(K_2CO_3)$	100	19	34, **2d**
Cl	H	H	OCH_3	OCH_3	ZnBr	THF	50	18	61, **2f**
H	CH_3	H	OCH_3	H	ZnBr	THF	50	2	67, **2g**
H	OCH_3	H	OCH_3	H	ZnBr	THF	50	23	74, **2h**
H	H	H	OPr^n	H	ZnBr	THF	50	21	81, **2i**
H	H	H	OPh	H	ZnBr	THF	50	21	63, **2j**
H	H	H	OH[b]	H	ZnBr	THF	50	20	34, **2k**
H	H	H	$N(CH_3)_2$	H	ZnBr	THF	Δ	21	70, **2l**
H	H	H	CH_3	H	$B(OH)_2$	$PhCH_3(K_2CO_3)$	100	20	70, **2m**
H	H	CH_3	CH_3	H	ZnBr	THF	50	14	58, **2n**
H	CH_3	H	CH_3	H	ZnBr	THF	50	16	66, **2o**
H	H	H	$C(CH_3)_3$	H	ZnBr	THF	Δ	3.5	80, **2p**
H	H	Cl	H	H	$B(OH)_2$	$PhCH_3(K_2CO_3)$	100	23	49, **2q**
H	H	NO_2	H	H	$B(OH)_2$	Dioxane (K_2CO_3)	100	6	60, **2r**
H	H	OCH_3	H	H	ZnBr	THF	50	14	55, **2s**
H	OCH_3	H	H	H	ZnBr	THF	50	23	70, **2t**

[a] General structure, see Scheme 1.
[b] Protected as TBDMS-ether under the coupling reaction.

Table 2. Synthesis of novel compounds **3**[a]

X	R′	Heteroaryl-Met or hetroarylH	Solvent (base)	Catalyst	Temp (°C)	Time (h)	Yield (%), **3**
Cl	OCH_3	(2-Thienyl)$SnBu_3$	DMF	$[(2\text{-Fur})_3P]_4P$	50	20	94, **3c**
H	H	(2-thiazolyl)$SnBu_3$	DMF	$(Ph_3P)_2PdCl_2$	90	16	70, **3d**
H	H	(3-Thienyl)$B(OH)_2$	$PhCH_3$ (K_2CO_3)	$(Ph_3P)_4Pd$	100	18	68, **3e**
H	H	2-[(5-Methyl)furyl]$SnBu_3$	DMF	$(Ph_3P)_2PdCl_2$	90	16	66, **3j**
H	H	2-[(5-Methoxy)furyl]$SnBu_{33}$	DMF	$(Ph_3P)_2PdCl_2$	90	16	78, **3k**
H	H	(2-Benzo[*b*]furyl)$SnBu_3$	DMF	$(Ph_3P)_2PdCl_2$	90	16	63, **3l**
H	H	(2-Oxazolyl)$ArSnBu_3$	DMF	$(Ph_3P)_2PdCl_2$	90	16	90, **3m**
H	H	(3-Furyl)ZnBr	THF	$(Ph_3P)_4Pd$	Δ	21	47, **3n**
H	H	Pyrrole	$PhCH_3$ (Cs_2CO_3)	$(Bu^t{}_3P)_2Pd$	100	18	77, **3o**
H	H	Imidazole	DMF	—	100	24	88, **3p**
H	H	[2-(1-Methylpyrrolyl)]ArZnBr	THF	$(Ph_3P)_4Pd$	Δ	4	77, **3q**
H	H	[2-(1-Methylimidazolyl)]ZnBr	THF	$(Ph_3P)_4Pd$	Δ	4	61, **3r**
H	H	(2-Pyridyl)$SnBu_3$	DMF	$(Ph_3P)_2PdCl_2$	90	16	20, **3s**
H	H	(3-Pyridyl)ZnBr	THF	$(Ph_3P)_4Pd$	Δ	18	88, **3t**
H	H	(4-Pyridyl)$SnBu_3$	DMF	$(Ph_3P)_2PdCl_2$	90	20	29, **3u**

[a] General structure, see Scheme 1.



Scheme 2. Reagents and conditions: (i) Pyrrole, *t*-Bu_3P, $Pd_2(dba)_3$, Cs_2CO_3, $PhCH_3$, 100 °C; (ii) Imidazole, DMF, 100 °C.

3. Biology

3.1. Antimycobacterial activity

The 6-arylpurines (**2**) and 6-heteroarylpurines (**3**) were screened for inhibitory activity against *M. tuberculosis* $H_{37}Rv$, and the results are presented in Tables 3 and 4. A few previously published results[2–4] are also included for comparison.

6-Phenyl-9-benzylpurine (**2a**) was moderately active against *M. tuberculosis* at 6.25 μg/mL concentration. Introduction of chlorine in the 2-position and a methoxy group in the benzylic *para*-position increased the activity, as reported earlier for other 6-substituted purines.[2–4] Generally, an electron-donating substituent, alkyl, alkoxy, aryloxy or hydroxy, in the *para*-position of the 6-phenyl group resulted in equal or increased activity, and the 6-(4-methyoxyphenyl)purine (**2f**) is the most potent compounds **2** examined in this study. 4-Dimethylaminophenylpurine (**2l**), on the other hand, was less active than the unsubstituted compound **2a.** In the heterocyclic series also (compounds **3**) the introduction of nitrogen always led to decreased antimycobacterial effect (Table 4).

Our results also indicate that electron-withdrawing substituents in the *para*-position of the 6-phenyl group (**2c**, **d**) and any kind of substituent in the *meta*-position (compounds **2d**, **2n**, and **2q**–**s**), should be avoided. The importance of an electron-rich aryl substituent in the purine 6-positions is also demonstrated in the heterocyclic series (compounds **3**, Table 4 below). It is more difficult to draw conclusions regarding substitution pattern in the aryl *ortho*-position, from the results described herein.

Mycobacteria are surrounded by a thick and waxy cell wall; hence, efficient drugs should have a reasonably lipophilicity in order to penetrate this barrier. We chose to study compounds **2** with Clog *P* values mostly in the range of 2–5 (data not shown). An antituberculosis drug should be taken orally, and, according to the 'Lipinski rule of five', a compound with good oral bioavailability generally has log $P < 5$.[11] Only in the case of the *tert*-butylphenylpurine **2p**, was the limit exceeded. Clog *P* for compound **2p** was found to be 5.18.

All 6-heteroarylpurines (**3**) examined had Clog $P < 5$. The Clog *P* values range from 1.07 (compound **3p**) to 4.12 (compound **3l**). Antimycobacterial activity for compounds **3** is reported in Table 4.

We have previously shown that exchange of the 6-phenyl substituent (compounds **2a**,**b**) with a 2-thienyl- (compounds **3a**–**c**) and even more so, a 2-furyl group (compounds **3f**–**i**) in the purine 6-position resulted in more active antimycobacterials (Table 4). We have now found that the exact position of the heteroatom is crucial. The isomeric 3-thienyl **3e** and 3-furylpurines **3n** were essentially inactive. Substituents on the furyl ring are, to some extent, tolerated (compounds **3j**–**l**).

Introducing nitrogen in the heterocyclic substituent in compounds **3** did not lead to higher activity against *M. tuberculosis*. On the contrary, the 2-thiazolylpurine **3d** and 2-oxazolylpurine **3m** were substantially less potent than the corresponding 2-thienylpurine **3a** or 2-furylpurine **3f**. Most pyrrole, imidazole, and pyridine derivatives were more or less inactive at the concentration examined. It may be argued that basic nitrogen in the 6-substituent is detrimental for antimycobacterial activity because the protonated structure may not be able to penetrate the bacterial cell wall, but there is no direct correlation between antimycobacterial activity of compounds **2l**, **3d**, **3m**, and **3o**–**u**, and the basicity of the substituent in the purine 6-position. For instance, the pyrrole and oxazole rings are associated with very low basicity, yet compounds **3m**, **3o**, and **3q** are more or less inactive. On the other hand, the moderately active compound **3p** carries relatively basic imidazole substituent. 2-Pyridylpurine (**3s**) was considerably more active than the isomers **3t** and **3u**.

As mentioned above, multi-drug resistant TB (MDR-TB) is a growing problem.[1] The activity of 6-(2-furyl)purine (**3h**) against several drug-resistant strains of *M. tuberculosis* were examined (Table 5). Except for the ethionamine-resistant organisms, minimum inhibitory concentration (MICs) found for the resistant mycobacteria were less than for the $H_{37}RV$ strain. In other words, compound **3h** exhibits no cross-resistance with most of the drugs used to treat tuberculosis today.

Table 3. Antimycobacterial activity against *Mycobacterium Tuberculosis*, *S. aureus* and *E. coli*, and cytotoxic activity against VERO cells for 6-arylpurines **2**

Comp. No.	X	R_2	R_3	R_4	R′	% Inhib. *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) at 6.25 μg/mL conc.	MIC *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) (μg/mL)[a]	MIC *S. aureus* (ATCC 25923) (μg/ml)[b]	MIC *E. coli* (ATCC 25922) (μg/ml)[c]	IC_{50} VERO cells (μg/mL)
2a	-H	-H	-H	-H	-H	56	n.d.	n.d.	n.d.	n.d.
2b	-Cl	-H	-H	-H	-H	90	12.5[d]	n.d.	n.d.	—[e]
2c	-H	-H	-H	-Cl	-H	27	n.d.	n.d.	n.d.	n.d
2d	-H	-H	-Cl	-Cl	-H	0	n.d.	n.d.	n.d.	n.d.
2e	-H	-H	-H	$-OCH_3$	-H	93	6.25	>32	>32	>10
2f	-Cl	-H	-H	$-OCH_3$	$-OCH_3$	98	1.56	>32	>32	>10
2g	-H	$-CH_3$	-H	$-OCH_3$	-H	45	n.d.	n.d.	n.d.	n.d.
2h	-H	$-OCH_3$	-H	$-OCH_3$	-H	9	n.d.	n.d.	n.d.	n.d.
2i	-H	-H	-H	$-OPr^n$	-H	31	n.d.	n.d.	n.d.	n.d.
2j	-H	-H	-H	-OPh	-H	61	n.d.	>32	>32	n.d.
2k	-H	-H	-H	-OH	-H	52	n.d.	>32	>32	n.d.
2l	-H	-H	-H	$-N(CH_3)_2$	-H	20	n.d.	>32	>32	n.d.
2m	-H	-H	-H	$-CH_3$	-H	69	n.d.	n.d.	n.d.	n.d.
2n	-H	-H	$-CH_3$	$-CH_3$	-H	33	n.d.	n.d.	n.d.	n.d.
2o	-H	$-CH_3$	-H	$-CH_3$	-H	37	n.d.	n.d.	n.d.	n.d.
2p	-H	-H	-H	$-C(CH_3)_3$	-H	90	>6.25	n.d.	n.d.	n.d.
2q	-H	-H	-Cl	-H	-H	3	n.d.	n.d.	n.d.	n.d.
2r	-H	-H	$-NO_2$	-H	-H	0	n.d.	n.d.	n.d.	n.d.
2s	-H	-H	$-OCH_3$	-H	-H	61	n.d.	>32	>32	n.d.
2t	-H	$-OCH_3$	-H	-H	-H	88	n.d.	>32	>32	n.d.

[a] MIC Rifampin 0.25 μg/mL.
[b] MIC Gentamycin 0.03 μg/mL.
[c] MIC Gentamycin 0.125 μg/mL.
[d] Taken from Ref. 2.
[e] Solubility to low to determine IC_{50}.

Table 4. Antibacterial activity against *Mycobacteriumt tuberculosis* $H_{37}Rv$, *S. aureus* and *E. coli*, and cytotoxic activity against VERO cells for 6-hetroarylpurines **3**

Comp. No.	X	HetAr-	R′	% Inhib. of *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) at 6.25 μg/mL conc.	MIC *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) (μg/mL)[a]	MIC *S. aureus* (ATCC 25923) (μg/ml)[b]	MIC *E. coli* (ATCC 25922) (μg/ml)[c]	IC_{50} VERO cells (μg/mL)
3a	-H	2-Thienyl-	-H	92[d]	6.26	>32	>32	>10
3b	-Cl	2-Thienyl-	-H	98[d]	1.56	n.d.	n.d.	>10
3c	-Cl	2-Thienyl-	$-OCH_3$	98	0.78	>32	>32	>10
3d	-H	2-Thiazolyl-	-H	47	n.d.	n.d.	n.d.	n.d.
3e	-H	3-Thienyl-	-H	25	n.d.	n.d.	n.d.	n.d.
3f	-H	2-Furyl-	-H	95[d]	3.13	>32	>32	8.6
3g	-Cl	2-Furyl-	-H	98[d]	0.78	n.d.	n.d.	8.1
3h	-H	2-Furyl-	$-OCH_3$	97[e]	1.56	n.d.	n.d.	>62.5
3i	-Cl	2-Furyl-	$-OCH_3$	98[e]	0.39	>32	>32	>10
3j	-H	5-Methylfur-2-yl-	-H	92	3.13	>32	>32	n.d.
3k	-H	5-Methoxyfur-2-yl-	-H	60	n.d.	>32	>32	n.d.
3l	-H	Benzo[*b*]fur-2-yl-	-H	71	n.d.	>32	>32	n.d.
3m	-H	2-Oxazolyl-	-H	0	n.d.	n.d.	n.d.	n.d.
3n	-H	3-Furyl-	-H	0	n.d.	n.d.	n.d.	n.d.
3o	-H	1-Pyrrolyl-	-H	9	n.d.	n.d.	n.d.	n.d.
3p	-H	1-Imidazolyl-	-H	65	n.d.	>32	>32	n.d.
3q	-H	1-Methylpyrrol-2-yl-	-H	0	n.d.	n.d.	n.d.	n.d.
3r	-H	1-Methylimidazole-2-yl-	-H	0	n.d.	n.d.	n.d.	n.d.
3s	-H	2-Pyridyl-	-H	84	n.d.	n.d.	n.d.	n.d.
3t	-H	3-Pyridyl-	-H	6	n.d.	n.d.	n.d.	n.d.
3u	-H	4-Pyridyl-	-H	0	n.d.	n.d.	n.d.	n.d.

[a] MIC Rifampin 0.25 μg/mL.
[b] MIC Gentamycin 0.03 μg/mL.
[c] MIC Gentamycin 0.125 μg/mL.
[d] Taken from Ref. 3.
[e] Taken from Ref. 4.

Table 5. Ratio between minimum inibitory concentration of compound **3h** against *M. tuberculosis* $H_{37}Rv$ and single-drug resistant strains of *M. tuberculosis*

Single-drug resistant strains of *M. tuberculosis*[a]	MIC *M. tuberculosis* $H_{37}Rv$: MIC *M. tuberculosis* drug resistant strain
INH	0.50
RMP	0.25
EMB	0.50
ETA	2.00
CIP	0.25
PAS	0.50
TAC	0.50

[a] *M. tuberculosis* strains resistant to INH (isoniazid), RMP (rifampin), EMB (ethambutol) ETA (Ethionamine), CIP (ciprofloxacin), PAS (*p*-aminosalicylic acid), and TAC (thiacetazone).

3.2. Activity against other bacteria

Selected 6-arylpurines **2** and 6-heteroarylpurines **3** were also screened against other bacteria. *Staphyloccocus aureus* (Gram+) and *Escherichia coli* (Gram−) were chosen. None of the compounds examined, were active against any of these microorganisms at a concentration of 32 μg/mL (Tables 3 and 4). These findings points toward a rather narrow spectrum for the purines as antibacterial compounds. For treatment of mycobacterial infections, organism-specific agents are recommended.[12]

3.3. Cytotoxicity

A certain therapeutic window is required if the antimycobacterials identified should have a drug potential. In order to gain insight into their potential toxicity toward mammalian cells, compounds **2** and **3**, exhibiting an MIC $\leqslant$6.25 μg/mL against *M. tuberculosis*, were screened for cytotoxicity against VERO cells. The results are presented in Tables 3 and 4. Most compounds examined exhibited relatively low cytotoxicity in this assay, but on several occasions accurate determination of IC_{50} values were precluded for solubility reasons.

4. Conclusions

Several 6-aryl- or heteroarylpurines are potent antimycobacterials. The aromatic substituent should preferably be electron rich and not contain any nitrogen. The 2-furyl group is the best substituent identified to date. Among the compounds studied there are potential drug candidates. Since low activity against other bacteria and mammalian cells are found and no cross-resistance with commonly used antituberculosis drugs is observed, the 6-arylpurines **2** and **3** probably act by a novel and selective mechanism toward *M. tuberculosis*.

5. Experimental section

The ^1H NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer, a Bruker Avance DPX 300 spectrometer, a Bruker Avance DPX 200, or a Varian Gemini 200 spectrometer at 500, 300, or 200 MHz, respectively. The ^1H decoupled ^{13}C NMR spectra were recorded at 125, 75, or 50 MHz using the above-mentioned spectrometers. Mass spectra under electron impact (EI) conditions were recorded at 70 eV ionizing voltage with a VG Prospec instrument, and are presented as *m/z* (% relativity intensity). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany or Laboratory of Organic Elemental Analysis CL, Prague, Czech Republic. Melting points were determined with a C. Reichert melting point apparatus and are uncorrected. DMF was distilled from BaO and stored over 4 Å molecular sieve. THF and dioxane were distilled from Na/benzophenone, and toluene and diethyl ether were dried over Na wire. The following compounds were available by literature methods: 1-Iodo-4-[(*tert*-butyldimethylsilyl)oxybenzene,[13] tributyl(5-methyl-2-furyl)stannane,[14] tributyl(5-methoxy-2-furyl)stannane,[15] tributyl(benzo[*b*]fur-2-yl)stannane,[16] 2-(butylstannyl)oxazole,[17] 6-chloro-9-(phenylmethyl)-9*H*-purine **1a**,[18] 2,6-dichloro-9-(phenylmethyl)-9*H*-purine **1b**,[19] 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **1c**[4] 6-phenyl-9-(phenylmethyl)-9*H*-purine **2a**,[18] 2-chloro-6-phenyl-9-(phenylmethyl)-9*H*-purine **2b**,[19] 6-(4-methoxyphenyl)-9-(phenylmethyl)-9*H*-purine **2e**,[18] 6-(2-thienyl)-9-(phenylmethyl)-9*H*-purine **3a**,[18] 2-chloro-6-(2-thienyl)-9-(phenylmethyl)-9*H*-purine **3b**,[19] 6-(2-furyl)-9-(phenylmethyl)-9*H*-purine **3f**,[2] 2-chloro-6-(2-furyl)-9-(phenylmethyl)-9*H*-purine **3g**,[19] 6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **3h**.[4] 2-Chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **3i**.[4] All other reagents were commercially available and used as received. Activity against *M. tuberculosis*,[2–4,] and other antibacterial activities[21] as well as cytotoxicity against VERO cells[2–4,] was determined as reported earlier. Clog *P* values were calculated using MaclogP 4.0 from Biobyte Corp., Claremont, USA.

5.1. 6-Bromo-9-(phenylmethyl)-9*H*-purine (1d) and 6-bromo-7-(phenylmethyl)-7*H*-purine (1e)

Potassium carbonate (1.69 g, 12.3 mmol) was added to a continuously stirring solution of 6-bromopurine (813 mg, 4.09 mmol) in dry DMF (40 mL) at ambient temperature under N_2. After 20 min, benzyl bromide (730 μL, 6.13 mmol) was added. The resulting mixture was stirred for 16 h, filtered, and evaporated in vacuo. The isomers were separated by flash chromatography on silica using EtOAc–hexane (2:1) followed by EtoAc–hexane (4:1) for elution.

5.1.1. 6-Bromo-9-(phenylmethyl)-9*H*-purine (1d). Yield 693 mg (59%), colorless crystals, mp 108–109 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.41 (s, 2H, CH_2), 7.26–7.35 (m, 5H, Ph), 8.09 (s, 1H, H-8), 8.69 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 47.8 (CH_2), 127.8, (CH in Ph), 128.8 (CH in Ph), 129.2 (CH in Ph), 134.0 (C-5), 134.4 (C in Ph), 143.1 (C-6), 144.8 (C-8), 150.5 (C-4), 152.0 (C-2); MS EI *m/z* (rel. %): 288/290 (48/46, M^+), 287/289 (40/46), 182 (19), 91 (100); HRMS: Found 288.0011. Anal. Calcd for $C_{12}H_9N_4Br$ 288.0011; Found: 50.23; H, 3.15; N, 19.30. $C_{12}H_9N_4Br$ requires C, 49.85; H, 3.14; N, 19.38%.

5.1.2. 6-Bromo-7-(phenylmethyl)-7*H*-purine (1e). Yield 201 mg (17%), colorless powdery crystals, mp

153–154 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.71 (s, 2H, CH_2), 7.11–7.15 (m, 2H, Ph), 7.30–7.36 (m, 3H, Ph), 8.23 (s, 1H, H-8), 8.78 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 50.2 (CH_2), 124.7 (C-5), 126.9 (CH in Ph), 128.8 (CH in Ph), 129.3 (CH in Ph), 133.4 (C-6), 134.6 (C in Ph), 149.8 (C-8), 152.4 (C-2), 160.9 (C-4); MS EI *m*/*z* (rel. %): 288/290 (28/27, M^+), 287/289 (7/11), 209 (5), 91 (100); HRMS: Found 287.9998. Anal. Calcd for $C_{12}H_9N_4Br$ 288.0011; Found: 50.13; H, 3.23; N, 19.81. $C_{12}H_9N_4Br$ requires C, 49.85; H, 3.14; N, 19.38%.

5.2. 6-(4-Chlorophenyl)-9-(phenylmethyl)-9*H*-purine (2c)

n-Butyllithium (0.69 mL, 1.1 mmol, 1.6 M hexane solution) was added dropwise to a stirred solution of 1-chloro-4-iodobenzene (262 mg, 1.10 mmol) in dry THF (4 mL) under N_2 at −78 °C. After 15 min, a 1 M solution of anhydrous zinc bromide in dry THF (1.2 mL, 1.2 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-(phenylmethyl)-9*H*-purine **1a** (245 mg, 1.00 mmol) in dry THF (4 mL) was added followed by a solution of tetrakis(triphenylphosphine)palladium(0) [generated in situ from tris(dibenzylideneacetone)dipalladium chloroform adduct (27 mg, 0.025 mmol) and triphenylphosphine (52 mg, 0.20 mmol)] in dry THF (2 mL). The resulting mixture was heated at 50 °C for 4 h and cooled to ambient temperature. Satd 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. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:3); yield 229 mg (71%), off-white small needles, mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.47 (s, 2H, CH_2), 7.33–7.34 (m, 5H, Ph), 7.51 (d, J = 8.8 Hz, 2H, Ar), 8.08 (s, 1H, H-8), 8.78 (d, J = 8.8 Hz, 2H, Ar), 9.02 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.1 (CH_2), 127.7 (CH in Ar), 128.5 (CH in Ar), 128.7 (CH in Ar), 129.0 (CH in Ar), 130.6 (C-5), 131.0 (CH in Ar), 134.0 (C in Ar), 135.0 (C in Ar), 137.0 (C in Ar), 144.1 (C-8), 152.4 (C-2), 152.5 (C-4 / C-6), 153.2 (C-4 / C-6); MS EI *m*/*z* (rel. %): 322/320 (25/69, M^+), 292 (5), 243 (6), 229 (9), 175 (6), 123 (6), 114 (6), 91 (100). Anal. Found: C, 67.32; H, 4.23; N, 17.37. $C_{18}H_{13}ClN_4$ requires C, 67.40; H, 4.08; N, 17.47%.

5.3. 6-(3,4-Dichlorophenyl)-9-(phenylmethyl)-9*H*-purine (2d)

A mixture of 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (245 mg, 1.00 mmol), potassium carbonate (200 mg, 1.50 mmol), 3,4-dichlorophenylboronic acid (286 mg, 1.50 mmol), and tetrakis(triphenylphosphine)palladium(0) [generated in situ from tris(dibenzylideneacetone)dipalladium chloroform adduct (27 mg, 0.025 mmol) and triphenylphosphine (52 mg, 0.20 mmol)] in dry toluene (10 mL) was stirred at 100 °C under N_2 for 19 h, cooled to ambient temperature, and evaporated in vacuo. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:3); yield 119 mg (34%), off-white small needles, mp 150–151 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.48 (s, 2H, CH_2), 7.34 (m, 5H, Ph), 7.61 (d, J = 8.4 Hz, 1H, Ar), 8.10 (s, 1H, H-8), 8.74 (dd, J = 8.4 and 2.0 Hz, 1H, Ar), 8.98 (d, J = 2.0 Hz, 1H, Ar), 9.03 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.4 (CH_2), 127.8 (CH in Ar), 128.7 (CH in Ar), 128.9 (CH in Ar), 129.2 (CH in Ar), 130.6 (CH in Ar), 130.9 (C-5), 131.4 (CH in Ar), 133.0 (C in Ar), 135.0 (C in Ar), 135.2 (C in Ar), 135.6 (C in Ar), 144.5 (C-8), 152.0 (C-4/C-6), 152.4 (C-2), 152.8 (C-4/C-6); MS EI *m*/*z* (rel. %): 358/356/354 (12/65/100, M^+), 326 (5), 279 (5), 277 (8), 265 (5), 263 (8), 209 (8), 159 (6), 91 (68). Anal. Found: C, 60.84; H, 3.37; N, 16.01. $C_{18}H_{12}Cl_2N_4$ requires C, 60.86; H, 3.40; N, 15.77%.

5.4. 2-Chloro-6-(4-methoxyphenyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (2f)

The title compound was prepared by Negishi coupling between 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **1c** (309 mg, 1.00 mmol) and 4-methoxyphenylzinc bromide (1.1 mmol) as described for compound **2c** and in Table 1. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:3); yield 231 mg (61%), colorless needles, mp 152–154 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.87 (d, J = 8.6 Hz, 2H, Ar), 7.02 (d, J = 9.0 Hz, 2H, Ar), 7.26 (d, J = 8.6 Hz, 2H, Ar), 7.94 (s, 1H, H-8), 8.79 (d, J = 9.0 Hz, 2H, Ar), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 46.8 (CH_2), 55.2 (CH_3), 55.3 (CH_3), 113.9 (CH in Ar), 114.3 (CH in Ar), 126.6 (C in Ar), 127.0 (C in Ar), 129.2 (C-5), 129.4 (CH in Ar), 131.7 (CH in Ar), 143.9 (C-8), 153.6 (C-2/C-4/C-6), 153.9 (C-2/C-4/C-6), 155.9 (C-2/C-4/C-6), 159.6 (C in Ar), 162.3 (C in Ar); MS EI *m*/*z* (rel. %): 382/380 (12/36, M^+), 122 (8), 121 (100), 91 (2); HRMS: Found 380.1055. Anal. Calcd for $C_{20}H_{17}ClN_4O_2$ 380.1045; Found: C, 62.75; H, 4.40; N, 14.54. $C_{20}H_{17}ClN_4O_2$ requires C, 63.08; H, 4.50; N, 14.71%.

5.5. 6-(4-Methoxy-2-methylphenyl)-9-(phenylmethyl)-9*H*-purine (2g)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 4-methoxy-2-methylphenylzinc bromide [generated in situ from 1-bromo-4-methoxy-2-methylbenzene (85 μL, 0.60 mmol)]. EtOAc–hexane (1:5) followed by EtOAc–hexane (1:1) was used for flash chromatography; yield 110 mg (67%), colorless crystals, mp 128–129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.49 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.45 (s, 2H, CH_2), 6.87–6.88 (m, 2H, Ar), 7.33–7.37 (m, 5H, Ph), 7.78–7.79 (m, 1H, Ar), 8.04 (s, 1H, H-8), 9.04 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (CH_3), 47.1 (CH_2), 55.1 (OCH_3), 111.1 (C-3 in Ar), 116.7 (C-5 in Ar), 127.4 (C-1 in Ar), 127.8 (CH in Ph), 128.4 (CH in Ph), 129.0 (CH in Ph), 131.8 (C-5), 132.6 (C-6 in Ar), 135.1 (C-1 in Ph), 139.3 (C-2 in Ar), 143.9 (C-8), 151.7 (C-4), 152.2 (C-2), 158.6 (C-6), 160.5 (C-4 in Ar); MS EI *m*/*z* (rel. %) 330 (29, M^+), 241 (1), 240 (16), 239

(100), 225 (1), 224 (8), 196 (5), 195 (4), 169 (3), 91 (17); HRMS: Found 330.1486. Anal. Calcd for $C_{20}H_{18}N_4O$ 330.1481; Found: C, 72.83; H, 5.27; N, 16.68. $C_{20}H_{18}N_4O$ requires C, 72.71; H, 5.49; N, 16.96%.

5.6. 6-(2,4-Dimethoxyphenyl)-9-(phenylmethyl)-9*H*-purine (2h)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine (123 mg, 0.50 mmol) and 2,4-dimethoxyphenylzinc bromide [generated from 1-bromo-2,4-dimethoxybenzene (89 μL, 0.60 mmol)] as described for compound (**2c**). EtOAc–hexane (1:2) followed by EtOAc–hexane (4:1) was used for flash chromatography; yield 129 mg (74%), colorless crystals, mp 149–151 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.44 (s, 2H, CH_2), 6.63–6.66 (m, 2H, Ar), 7.30–7.37 (m, 5H, Ph), 7.72 (d, J = 8.5 Hz, 1H, Ar), 8.03 (s, 1H, H-8), 9.06 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 47.1 (CH_2), 55.4 (OCH_3), 55.9 (OCH_3), 99.3 (CH in Ar), 104.9 (CH in Ar), 117.6 (C in Ar), 127.8 (CH in Ph), 128.4 (CH in Ph), 129.0 (CH in Ph), 132.3 (C-5), 133.0 (CH in Ar), 135.2 (C in Ph), 143.7 (C-8), 151.5 (C-4), 152.3 (C-2), 156.3 (C-6), 158.9 (C in Ar), 162.4 (C in Ar); MS EI *m*/*z* (rel. %): 346 (49, M^+), 345 (4), 317 (2), 316 (3), 315 (11), 256 (14), 255 (100), 240 (3), 225 (2), 91 (36); HRMS: Found 346.1433. Anal. Calcd for $C_{20}H_{18}N_4O_2$ 346.1430; Found: C, 69.97; H, 5.24; N, 17.01. $C_{20}H_{18}N_4O_2$ requires C, 69.72; H, 5.26; N, 15.86%.

5.7. 6-(4-*n*-Propoxyphenyl)-9-(phenylmethyl)-9*H*-purine (2i)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 4-*n*-propoxyphenylzinc bromide [generated from 4-*n*-propoxybromobenzene (95 μL, 0.60 mmol)]. EtOAc–hexane (1:5) followed by EtOAc–hexane (1:2) was used for flash chromatography; yield 140 mg (81%), colorless powdery crystals, mp 130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (t, J = 7.5 Hz, 3H, CH_3), 1.80–1.86 (m, 2H, CH_2), 4.00 (t, J = 6.6 Hz, 2H, OCH_2), 5.43 (s, 2H, NCH_2), 7.05 (d, J = 8.9 Hz, 2H, Ar), 7.26–7.35 (m, 5H, Ph), 8.03 (s, 1H, H-8), 8.81 (d, J = 8.9 Hz, 2 H, Ar), 8.98 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.4 (CH_3), 22.4 (CH_2), 47.1 (NCH_2), 69.5 (OCH_2), 114.5 (C-3 and C-5 in Ar), 127.7 (CH in Ph), 128.0 (C-1 in Ar), 128.4 (CH in Ph), 129.0 (CH in Ph), 130.2 (C-5), 131.4 (C-2 in Ar), 135.2 (C-1 in Ph), 143.8 (C-8), 152.2 (C-4), 152.5 (C-2), 154.5 (C-6), 161.6 (C-4 in Ar); MS EI *m*/*z* (rel. %) 344 (100, M^+), 343 (5), 302 (49), 301 (97), 274 (4), 225 (14), 211 (6), 209 (2), 92 (3), 91 (56); HRMS: Found 344.1631. Anal. Calcd for $C_{21}H_{20}N_4O$ 344.1637; Found: C, 73.51; H, 5.84; N, 16.11. $C_{21}H_{20}N_4O$ requires C, 73.23; H, 5.85; N, 16.27%.

5.8. 6-(4-Phenoxyphenyl)-9-(phenylmethyl)-9*H*-purine (2j)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 4-phenoxyphenylzinc bromide [generated in situ from 4-phenoxyphenyl bromide (105 μL, 0.60 mmol)]. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:5) followed by EtOAc–hexane (1:2); yield 120 mg (63%), colorless crystals, mp 108–109 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (s, 2H, CH_2), 7.10 (d, J = 7.8 Hz, 2H, Ar), 7.14–7.16 (m, 3H, Ar), 7.30–7.38 (m, 7H, Ar/Ph), 8.06 (s, 1H, H-8), 8.81 (d, J = 8.8 Hz, 2H, Ar), 9.01 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.2 (CH_2), 118.2 (CH in Ar), 119.6 (2 × CH in Ar), 123.9 (CH in Ar), 127.7 (CH in Ar), 128.5 (CH in Ar), 129.1 (CH in Ar), 129.8 (CH in Ar), 130.4 (C in Ar), 130.5 (C-5), 131.6 (CH in Ar), 135.2 (C-1 in Ar), 143.8 (C-8), 152.4 (C-4), 152.5 (C-2), 154.2 (C-6), 156.2 (C in Ar), 160.0 (C in Ar); MS EI *m*/*z* (rel. %) 378 (100, M^+), 377 (61), 350 (3), 301 (4), 287 (6), 92 (2), 91 (36); HRMS: Found 378.1476. Anal. Calcd for $C_{24}H_{18}N_4O$ 378.1481; Found: C, 76.04; H, 4.80; N, 14.91. $C_{24}H_{18}N_4O$ requires C, 76.17; H, 4.79; N, 14.81%.

5.9. 6-(4-Hydroxyphenyl)-9-(phenylmethyl)-9*H*-purine (2k)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (245 mg, 1.0 mmol), and 4-[*tert*-butyldimethylsilyloxy]phenylzinc bromide (1.2 mmol) as described for compound **2c** above and in Table 1. The crude *O*-silylated product was stirred with anhydrous tetrabutylammonium fluoride (513 mg, 1.63 mmol) in THF (12 mL) over night. Satd aq NH_4Cl (10 mL) and water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (2:1) followed by EtOAc–hexane (3:1) yield 102 mg (34%), colorless oil which could be crystallized from CH_2Cl_2–hexane, mp 183–186 °C. ^{1}H NMR (acetone-d_6, 500 MHz) δ 5.58 (s, 2H, CH_2), 7.01 (br d, J = 8.2 Hz, 2H, Ar) 7.29–7.31 (m, 1H, Ph), 7.33–7.36 (m, 2H, Ph), 7.42–7.43 (m, 2H, Ph), 8.52 (s, 1H, H-8), 8.87 (s, 1H, H-2), 8.91 (dt, J = 8.8 and 1.7 Hz, 2H, Ar), 8.94 (s, 1H, OH); ^{13}C NMR (acetone-d_6, 125 MHz): δ 47.3 (CH_2), 115.9 (CH in Ar), 128.2 (C in Ar), 128.5 (CH in Ph), 128.6 (CH in Ph), 129.4 (CH in Ph), 130.7 (C-5), 132.4 (CH in Ar), 137.5 (C in Ph), 145.4 (C-8), 152.7 (C-2), 153.2 (C-4), 154.2 (C-6), 160.9 (C-4 in Ar); MS EI *m*/*z* (rel. %) 302 (100, M^+), 301 (91), 274 (5), 225 (5), 211 (6), 91 (56); HRMS: Found 302.1179. Anal. Calcd for $C_{18}H_{14}N_4O$ 302.1168; Found: C, 71.20; H, 4.74; N, 18.16. $C_{18}H_{14}N_4O$ requires C, 71.51; H, 4.67; N, 18.53%.

5.10. 6-(4-*N*,*N*-Dimethylaminophenyl)-9-(phenylmethyl)-9*H*-purine (2l)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 4-*N*,*N*-dimethylaminophenylzinc bromide (0.60 mmol) as described for compound **2c** and in Table 1. EtOAc–hexane (1:2) followed by EtOAc–hexane (1:1) were used for flash

chromatography; yield 115 mg (70%), yellow microcrystalline solid, mp 186–188 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.01 (s, 6H, CH_3), 5.44 (s, 2H, CH_2), 6.81 (d, J = 9.2 Hz, 2H, Ar), 7.31–7.32 (m, 5H, Ph), 7.99 (s, 1H, H-8), 8.77 (d, J = 9.2 Hz, 2H, Ar), 8.92 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.1 (CH_3), 47.1 (CH_2), 111.5 (CH in Ar), 123.1 (C in Ar), 127.7 (CH in Ar), 128.3 (CH in Ar), 129.0 (CH in Ar), 129.8 (C-5), 131.2 (CH in Ar), 135.4 (C in Ar), 142.8 (C-8), 151.9 (C-4/C-6/C in Ar), 152.2 (C-4/C-6/C in Ar), 152.4 (C-2), 155.0 (C-4/C-6/C in Ar); MS EI *m*/*z* (rel. %): 329 (100, M^+), 328 (45), 312 (3), 238 (6), 184 (5), 165 (3), 164 (3), 91 (16); HRMS: Found 329.1651. Anal. Calcd for $C_{20}H_{19}N_5$: 329.1640. Found: C, 75.05; H, 5.98; N, 21.13. $C_{20}H_{19}N_5$ requires C, 72.93; H, 5.81; N, 21.26.

5.11. 6-(4-Methylphenyl)-9-(phenylmethyl)-9*H*-purine (2m)

The title compound was prepared by Suzuki coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 4-methylphenylboronic acid (0.75 mmol) as described for compound **2d** and in Table 1. EtOAc–hexane (1:3) was used for flash chromatography; yield 105 mg (70%), colorless small needles, mp 128–130 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 7.34–7.37 (m, 7H, Ar), 8.07 (s, 1H, H-8), 8.68 (d, J = 8.2 Hz, 2H, Ar), 9.01 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.4 (CH_3), 46.0 (CH_2), 126.5 (CH in Ar), 127.2 (CH in Ar), 127.8 (CH in Ar), 128.1 (CH in Ar), 128.5 (CH in Ar), 129.5 (C-5), 131.7 (C in Ar), 134.0 (C in Ar), 140.1 (C in Ar), 142.6 (C-8), 151.1 (C-4/C-6), 151.2 (C-2), 153.6 (C-4/C-6); MS EI *m*/*z* (rel. %): 300 (100, M^+), 299 (100), 285 (3), 272 (6), 223 (6), 209 (17), 91 (46); HRMS: Found 300.1364. Anal. Calcd for $C_{19}H_{16}N_4$: 300.1375; Found: C, 76.12; H, 5.29; N, 18.62. $C_{19}H_{16}N_4$ requires C, 75.98; H, 5.37; N, 18.65%.

5.12. 6-(3,4-Dimethylphenyl)-9-(phenylmethyl)-9*H*-purine (2n)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine (196 mg, 0.80 mmol) and 3,4-dimethylphenylzinc bromide (1.2 mmol) as described for compound **2c** and in Table 1. EtOAc–hexane (1:2) was used for flash chromatography; yield 146 mg (58 %), colorless powdery crystals, mp 156–158 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 7.28–7.35 (m, 6H, Ph/Ar), 8.05 (s, 1H, H-8), 8.52 (s, 1H, Ar), 8.55 (d, J = 8.0 Hz, 1H, Ar), 9.00 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 ($2\times CH_3$), 47.2 (CH_2), 127.6 (CH in Ar), 127.7 (CH in Ar), 128.5 (CH in Ph), 129.1 (CH in Ph), 130.0 (CH in Ph), 130.4 (CH in Ar), 130.7 (C-5), 133.2 (C in Ar), 135.2 (C in Ar), 136.9 (C in Ph), 140.2 (C in Ar), 143.8 (C-8), 152.3 (C-4), 152.5 (C-2), 155.1 (C-6); MS EI *m*/*z* (rel. %): 314 (100, M^+), 313 (91), 299 (3), 223 (12), 91 (29); HRMS: Found 314.1525. Anal. Calcd for $C_{20}H_{18}N_4$: 314.1531; Found: C, 76.42; H, 5.70; N, 18.13. $C_{20}H_{18}N_4$requires C, 76.41; H, 5.77; N, 17.82%.

5.13. 6-(2,4-Dimethylphenyl)-9-(phenylmethyl)-9*H*-purine (2o)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 2,4-dimethylphenylzinc bromide [generated in situ from 4-bromo-1,3-dimethyl-benzene (84 μL, 0.60 mmol)] as described for compound **2c** and in Table 1. EtOAc–hexane (1:5) followed by EtOAc–hexane (1:1) was used for flash chromatography; yield 104 mg (66%), pale yellow crystalline compound, mp 102–103 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 7.14–7.16 (m, 2H, Ar), 7.33–7.38 (m, 5H, Ph), 7.65 (d, J = 7.8 Hz, 1H, Ar), 8.04 (s, 1H, H-8), 9.06 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.4 (CH_3), 21.2 (CH_3), 47.2 (CH_2), 126.4 (CH in Ph), 127.8 (CH in Ph), 128.5 (CH in Ph), 129.1 (CH in Ph), 130.8 (CH in Ar), 131.9 (CH in Ar), 131.9 (C-5/C in Ar), 132.0 (C-5/C in Ar), 135.1 (C in Ph), 136.9 (C in Ar), 144.0 (C-8), 151.7 (C-4), 152.3 (C-2), 159.0 (C-6); MS EI *m*/*z* (rel. %): 314 (29, M^+), 224 (17), 223 (100), 208 (4), 195 (1), 194 (1), 169 (2), 91 (15); HRMS: Found 314.1528. Anal. Calcd for $C_{20}H_{18}N_4$: 314.1531. Found: C, 76.45; H, 5.77; N, 17.70. $C_{20}H_{18}N_4$ requires C, 76.41; H, 5.77; N, 17.82%.

5.14. 6-(4-*tert*-Butylphenyl)-9-(phenylmethyl)-9*H*-purine (2p)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 4-*tert*-butylphenylzinc bromide (0.60 mmol) as described for compound **2c** and in Table 1. EtOAc–hexane (1:4) was used for flash chromatography; yield 136 mg (80%), colorless microcrystalline solid, mp 143–145 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (s, 9H, *t*-Bu), 5.46 (s, 2H, CH_2), 7.33 (m, 5H, Ph), 7.57 (d, J = 8.6 Hz, 2H, Ar), 8.06 (s, 1H, H-8), 8.67 (d, J = 8.6 Hz, 2H, Ar), 9.02 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.2 (CH_3 in *t*-Bu), 34.9 (C in *t*-Bu), 47.2 (CH_2), 125.6 (CH in Ar), 127.7 (CH in Ar), 128.4 (CH in Ar), 129.0 (CH in Ar), 129.5 (CH in Ar), 130.8 (C-5), 132.8 (C in Ar), 135.2 (C in Ar), 143.8 (C-8), 152.3 (C-4/C-6), 152.5 (C-2), 154.3 (C in Ar), 155.0 (C-4/C-6); MS EI *m*/*z* (rel. %): 342 (44, M^+), 328 (24), 237 (100), 299 (3), 163 (4), 91 (45); HRMS: Found 342.1837. Anal. Calcd for $C_{22}H_{22}N_4$: 342.1844. Found: C, 77.07; H, 6.60; N, 16.24. $C_{19}H_{16}N_4$ requires C, 77.16; H, 6.47; N, 16.36%.

5.15. 6-(3-Chlorophenyl)-9-(phenylmethyl)-9*H*-purine (2q)

The title compound was prepared by Suzuki coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (245 mg, 1.00 mmol) and 3-chlorophenylboronic acid (1.50 mmol) as described for compound **2d** and in Table 1. EtOAc–hexane (1:3) was used for flash chromatography; yield 158 mg (49%), colorless small needles, mp 152–154 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.47 (s, 2H, CH_2), 7.33–7.34 (m, 5H, Ar), 7.45–7.49 (m, 2H, Ar), 8.09 (s, 1H, H-8), 8.70–8.76 (m, 1H, Ar), 8.80 (br s, 1H, Ar), 9.04 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.3 (CH_2),

127.7 (CH in Ar), 127.9 (CH in Ar), 128.5 (CH in Ar), 129.1 (CH in Ar), 129.4 (CH in Ar), 129.8 (CH in Ar), 130.8 (CH in Ar), 134.6 (C in Ar), 134.9 (C in Ar), 137.3 (C in Ar), 144.3 (C-8), 152.4 (C-2), 152.5 (C-4/C-6), 153.0 (C-4/C-6), C-5 was hidden; MS EI *m/z* (rel. %): 322/320 (32/98, M^+), 321/319 (49/100), 292 (5), 285 (3), 243 (7), 229 (10), 209 (5), 91 (81); HRMS: Found 320.0824. Anal. Calcd for $C_{18}H_{13}ClN_4$: 320.0829. Found: C, 67.41; H, 4.17; N, 17.28. $C_{18}H_{13}ClN_4$ requires C, 67.40; H, 4.08; N, 17.47%.

5.16. 6-(3-Nitrophenyl)-9-(phenylmethyl)-9*H*-purine (2r)[22]

The title compound was prepared by Suzuki coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (121 mg, 0.50 mmol) and 3-nitrophenylboronic acid (1.00 mmol) using dioxane as solvent. Other conditions were as described for compound **2d** and in Table 1. EtOAc–hexane (1:4) was used for flash chromatography; yield 99 mg (60%), colorless solid, mp 189–191 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.50 (s, 2H, CH_2), 7.28–7.42 (m, 5H, Ar), 7.67–7.75 (m, 1H, Ar), 8.15 (s, 1H, H-8), 8.32–8.37 (m, 1H, Ar), 9.08 (s, 1H, H-2), 9.19 (d, J = 7.8 Hz, 1H, Ar), 9.73 (br s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.5 (CH_2), 124.7 (CH in Ar), 125.3 (CH in Ar), 127.9 (CH in Ar), 128.7 (CH in Ar), 129.2 (CH in Ar), 129.6 (CH in Ar), 131.1 (C-5), 134.9 (C in Ar), 135.4 (CH in Ar), 137.4 (C in Ar), 144.9 (C-8), 148.6 (C in Ar), 151.8 (C-4/C-6), 152.6 (C-2), 152.9 (C-4/C-6); MS EI *m/z* (rel. %): 331 (97, M^+), 330 (79), 301 (27), 300 (8), 285 (9), 284 (10), 254 (4), 209 (4), 91 (100); HRMS Calcd for $C_{18}H_{13}N_5O_2$, 331.1069; found, 331.1060.

5.17. 6-(3-Methoxyphenyl)-9-(phenylmethyl)-9*H*-purine (2s)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 3-methoxyphenylzinc bromide as described for compound **2c** and in Table 1. EtOAc–hexane (1:1) was used for flash chromatography; yield 173 mg (55%), pale yellow crystals, mp 116 °C (lit.[23] 114–116 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.91 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 7.05–7.07 (m, 1H, Ar) 7.30–7.37 (m, 5H, Ph), 7.45 (t, J = 8.0 Hz, 1H, Ar), 8.07 (s, 1H, H-8), 8.34 (m, 1H, Ar), 8.42–8.44 (m, 1H, Ar), 9.03 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.3 (CH_2), 55.4 (OCH_3), 113.9 (CH in Ar), 117.6 (CH in Ar), 122.6 (CH in Ar), 127.8 (CH in Ph), 128.6 (CH in Ph), 129.1 (CH in Ph), 129.6 (CH in Ar), 131.0 (C-5), 135.2 (C-1 in Ph), 136.9 (C-1 in Ar), 144.1 (C-8), 152.5 (C-2), 152.6 (C-4), 154.7 (C-6), 159.8 (C-3 in Ar); MS EI *m/z* (rel. %): 316 (100, M^+), 315 (83), 287 (6), 286 (16), 225 (7), 91 (53); HRMS: Found 316.1316, calcd for $C_{19}H_{16}N_4O$ 316.1324.

5.18. 6-(2-Methoxyphenyl)-9-(phenylmethyl)-9*H*-purine (2t)

The title compound was prepared by Negishi coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 2-methoxyphenylzinc bromide as described for compound **2c** and in Table 1. EtOAc–hexane (2:1) was used for flash chromatography; yield 111 mg (70%), colorless crystalline solid, mp 183 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 1H, OCH_3), 5.43 (s, 2H, CH_2), 7.04–7.08 (m, 2H, Ar), 7.30–7.34 (m, 5H, Ph), 7.42–7.45 (m, 1H, Ar), 7.62–7.65 (m, 1H, Ar), 8.01 (s, 1H, H-8), 9.06 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.1 (CH_2), 55.9 (OCH_3), 111.8 (CH in Ar), 120.7 (CH in Ar), 124.7 (C-1 in Ar), 127.9 (CH in Ph), 128.5 (CH in Ph), 129.0 (CH in Ph), 131.3 (CH in Ar), 131.6 (CH in Ar), 132.3 (C-5), 135.1 (C in Ph), 144.0 (C-8), 151.6 (C-4), 152.4 (C-2), 156.6 (C-6), 157.4 (C-2 in Ar); MS EI *m/z* (rel. %): 316 (34, M^+), 315 (9), 285 (7), 226 (10), 225 (100), 91 (43); HRMS: Found 316.1320. Anal. Calcd for $C_{19}H_{16}N_4O$: 316.1324. Found: C, 71.92; H, 5.28; N, 18.09. $C_{19}H_{16}N_4O$ requires C, 72.13; H, 5.10; N, 17.71%.

5.19. 2-Chloro-9-(4-methoxyphenylmethyl)-6-(2-thienyl)-9*H*-purine (3c)

A mixture of tris(dibenzylideneacetone)dipalladium chloroform adduct (31 mg, 0.030 mmol) and tri(2-furyl)phosphine (51 mg, 0.22 mmol) in DMF (8 mL) was stirred at ambient temperature under N_2 atm for 15 min, before 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **1c** (309 mg, 1.00 mmol) and 2-thienyl(tributyl)tin (0.38 mL, 1.20 mmol) were added. The resulting mixture was stirred for 20 h at 50 °C and evaporated in vacuo. A satd 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 gel by eluting with EtOAc–hexane (2:5); yield 335 mg (94%), colorless crystals, mp 183–185 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.88 (d, J = 8.4 Hz, 2H, Ar), 7.20–7.28 (m, 3H, 2H in Ar and 1H in thienyl), 7.64 (br d, J = 5.0 Hz, 1H, thienyl), 7.95 (s, 1H, H-8), 8.62 (br d, J = 3.8 Hz, 1H, thienyl); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.0 (CH_2), 55.3 (CH_3), 114.4 (CH in Ar), 126.5 (C in Ar), 127.8 (C-5), 128.6 (CH in thienyl), 129.5 (CH in Ar), 131.9 (CH in thienyl), 133.4 (CH in thienyl), 138.5 (C in thienyl), 144.4 (C-8), 151.6 (C-2/C-4/C-6), 153.5 (C-2/C-4/C-6), 154.9 (C-2/C-4/C-6), 159.8 (C in Ar); MS EI *m/z* (rel. %): 358/356 (9/27, M^+), 122 (7), 121 (100), 91 (1); HRMS: Found 356.0499. Anal. Calcd for $C_{17}H_{13}ClN_4OS$: 356.0489. Found: C, 57.55; H, 3.82; N, 15.42. $C_{17}H_{13}ClN_4OS$ requires C, 57.22; H, 3.67; N, 15.70%.

5.20. 9-(Phenylmethyl)-6-(2-thiasolyl)-9*H*-purine (3d)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol), and 2-tributylstannanylthiazole [295 mg, 0.75 mmol (purity 95%)] as described for compound **3c** above and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (4:1) followed by EtOAc, and finally CH_2Cl_2–acetone (7:3); yield 103 mg (70%), off-white crystals, mp

224–225 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (s, 2H, CH_2), 7.25–7.30 (m, 5H, Ph), 7.57 (s, 1H, thiazolyl), 8.18 (s, 2H, H-8 and thiazolyl), 8.97 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.3 (CH_2), 123.0 (CH in thiazolyl), 127.6 (CH in Ph), 128.5 (CH in Ph), 128.9 (C-5), 129.0 (CH in Ph), 134.8 (C-1 in Ph), 145.9 (CH in thiazolyl), 146.2 (C-8), 147.7 (C-6), 152.3 (C-2), 153.2 (C-4), 164.9 (C-1 in thiazolyl); MS EI *m*/*z* (rel. %): 293 (100, M^+), 292 (76), 266 (3), 266 (3), 265 (3), 248 (2), 216 (7), 209 (3), 182 (2), 161 (2), 146 (2), 92 (5), 91 (75); HRMS: Found 293.0725. Anal. Calcd for $C_{15}H_{11}N_5S$: 293.0735. Found: C, 61.30; H, 3.89. $C_{15}H_{11}N_5S$ requires C, 61.42; H, 3.78%.

5.21. 9-(Phenylmethyl)-6-(3-thienyl)-9*H*-purine (3e)

The title compound was prepared by Suzuki coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (123 mg, 0.50 mmol) and 3-thienylboronic acid (0.75 mmol) as described for compound **2d** above. EtOAc–hexane (1:2) was used for flash chromatography; yield 100 mg (68%), colorless crystals, mp 152–154 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.46 (s, 2H, CH_2), 7.27–7.36 (m, 5H, Ph), 7.43 (dd, J = 5.0 and 3.0 Hz, 1H, thienyl), 8.04 (s, 1H, H-8), 8.27 (dd, J = 5.0 and 1.2 Hz, 1H, thienyl), 8.90 (dd, J = 3.0 and 1.2 Hz, 1H, thienyl), 8.97 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.1 (CH_2), 125.7 (CH in Ar), 127.7 (2 × CH in Ar), 128.4 (CH in Ar), 129.0 (CH in Ar), 129.8 (C-5), 130.5 (CH in Ar), 135.1 (C in Ar), 138.1 (C-3 in thienyl), 143.8 (C-8), 150.6 (C-4/C-6), 152.1 (C-4/C-6), 152.6 (C-2); MS EI *m*/*z* (rel. %): 292 (93, M^+), 291 (100), 264 (4), 202 (1), 92 (3), 91 (81); HRMS: Found 292.0782. Anal. Calcd for $C_{16}H_{12}N_4S$: 292.0783. Found: C, 65.83; H, 4.02; N, 19.47. $C_{16}H_{12}N_4S$ requires C, 65.73; H, 4.14; N, 19.16%.

5.22. 6-(5-Methyl-2-furyl)-9-(phenylmethyl)-9*H*-purine (3j)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and tributyl(5-methyl-2-furyl)stannane (278 mg, 0.75 mmol) as described for compound **3c** above and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:1); yield 96 mg (66%), off-white crystalline solid, mp 189–190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 1H, CH_3), 5.37 (s, 2H, CH_2), 6.21 (d, J = 3.3 Hz, 1H, furyl), 7.20–7.30 (m, 5H, Ph), 7.76 (d, J = 3.3 Hz, 1H, furyl), 7.96 (s, 1H, H-8), 8.89 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 47.1 (CH_2), 109.4 (C-4 in furyl), 119.7 (C-3 in furyl), 127.7 (C-2 in Ph and C-5), 127.8 (CH in Ph), 128.5 (CH in Ph), 135.1 (C-1 in Ph), 143.8 (C-8), 145.9 (C-6), 147.7 (C-2 in furyl), 151.6 (C-4), 152.8 (C-2), 156.6 (C-5 in furyl); MS EI *m*/*z* (rel. %): 290 (100, M^+), 289 (70), 247 (14), 213 (4), 199 (4), 91 (59); HRMS: Found 290.1173. Anal. Calcd for $C_{17}H_{14}N_4O$ 290.1168; Found: C, 70.23; H, 5.03; N, 19.37. $C_{17}H_{14}N_4O$ requires C, 70.33; H, 4.86; N, 19.30%.

5.23. 6-(5-Methoxy-2-furyl)-9-(phenylmethyl)-9*H*-purine (3k)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and tributyl(5-methoxy-2-furyl)stannane (290 mg, 0.75 mmol) as described for compound **3c** above and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (2:1); yield 120 mg (78%), colorless crystalline solid, mp 163–164 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.99 (s, 3H, OCH_3), 5.43 (s, 2H, CH_2), 5.50 (d, J = 3.5 Hz, 1H, furyl), 7.28–7.37 (m, 5H, Ph), 7.85 (d, J = 3.5 Hz, 1H, furyl), 8.00 (s, 1H, H-8), 8.90 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.1 (CH_2), 57.9 (OCH_3), 84.3 (CH in furyl), 121.4 (CH in furyl), 127.2 (C-5), 127.7 (CH in Ph), 128.4 (CH in Ph), 129.0 (CH in Ph), 135.2 (C-1 in Ph), 139.8 (C-2 in furyl), 143.4 (C-8), 145.7 (C-6), 151.3 (C-4), 152.8 (C-2), 164.4 (C-5 in furyl); MS EI *m*/*z* (rel. %): 306 (68, M^+), 291 (8), 92 (7), 91 (100); HRMS: Found 306.1128. Anal. Calcd for $C_{17}H_{14}N_4O_2$ 306.1117; Found: C, 66.56; H, 4.71; N, 18.50. $C_{17}H_{14}N_4O_2$ requires C, 66.66; H, 4.61; N, 18.29%.

5.24. 6-(2-Benzo[*b*]furyl)-9-(phenylmethyl)-9*H*-purine (3l)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and tributyl(benzo[*b*]fur-2-yl)stannane (305 mg, 0.75 mmol) as described for compound **3c** and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:1); yield 103 mg (63%), off-white crystalline solid, mp 202–203 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.48 (s, 2H, CH_2), 7.28–7.45 (m, 7H, Ph and benzofuryl), 7.71–7.74 (m, 2H, benzofuryl), 8.13 (s, 1H, H-8), 8.31 (s, 1H, CH in benzofuryl), 9.09 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.3 (CH_2), 112.2 (CH in benzofuryl), 114.1 (C-3 in benzofuryl), 122.3 (CH in benzofuryl), 123.5 (CH in benzofuryl), 126.8 (benzofuryl), 127.8 (CH in Ph), 128.4 (C in benzofuryl), 128.7 (CH in Ph), 129.2 (CH in Ph), 129.4 (C-5), 134.9 (C-1 in Ph), 144.7 (C-8), 146.1 (C-6), 150.5 (C in benzofuryl), 152.0 (C-4), 152.9 (C-2), 155.7 (C in benzofuryl); MS EI *m*/*z* (rel. %): 326 (100, M^+), 325 (55), 298 (4), 297 (3), 249 (4), 163 (2), 156 (2), 91 (52); HRMS: Found 326.1156. Anal. Calcd for $C_{20}H_{14}N_4O$ 326.1168; Found: C, 73.44; H, 4.68; N, 16.94. $C_{20}H_{14}N_4O$ requires C, 73.61; H, 4.32; N, 17.17%.

5.25. 6-(2-Oxazolyl)-9-(phenylmethyl)- 9*H*-purine (3m)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and 2-(tributylstannyl)oxazole (336 mg, ca. 0.60 mmol, purity 64%) as described for compound **3c** and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (2:1) followed by EtOAc, and finally CH_2Cl_2–MeOH (19:1); yield 125 mg (90%), colorless crystalline solid, mp 227–228 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.47 (s, 2H, CH_2), 7.26–7.33 (m, 5H, Ph), 7.50 (s, 1H, oxazolyl), 7.93 (s, 1H, oxazolyl), 8.22 (s, 1H), 9.09 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 47.4 (CH_2), 127.7 (CH in Ph), 128.6 (CH in Ph), 129.1 (CH in Ph), 130.1 (CH in oxazolyl and C-5), 134.6 (C in Ph), 140.8 (CH in oxazolyl), 142.4 (C-6), 146.4 (C-8), 152.6 (C-2),

153.3 (C-4), 157.9 (C-2 in oxazolyl); MS EI *m/z* (rel. %): 277 (100, M^+), 276 (73), 249 (3), 248 (11), 222 (2), 221 (3), 209 (2), 200 (5), 92 (5), 91 (85); HRMS: Found 277.0974, calcd for $C_{15}H_{11}N_5O$ 277.0964.

5.26. 6-(3-Furyl)-9-(phenylmethyl)-9*H*-purine (3n)

The title compound (122 mg, 0.05 mmol) was prepared from 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** and 3-furylzinc bromide [generated from 3-bromfurane (66 μL, 0.75 mmol) by treatment with *n*-butyllithium (0.47 mL, 0.75 mmol, 1.6 M hexane solution) in dry THF (1 mL) and dry diethyl ether (3 mL) under N_2 at −78 °C for 1 h followed by 1 M solution of anhydrous zinc bromide in dry THF (0.75 mL, 0.75 mmol) for 1 h at −78 °C] as described for **2c** and in Table 2. The product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (1:2); yield 65 mg (47%), colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.44 (s, 2H, CH_2), 7.31–7.37 (m, 6H, Ph and furyl), 7.56 (m, 1H, furyl), 8.01 (s, 1H, H-8), 8.75 (br s, 1H, furyl), 8.94 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.1 (CH_2), 109.1 (C-4 in furyl), 123.1 (C-3 in furyl), 127.7 (CH in Ph), 128.4 (CH in Ph), 129.0 (CH in Ph), 129.9 (C-5), 135.1 (C-1 in Ph), 143.6 (CH in furyl and C-8), 146.7 (CH in furyl), 150.1 (C-4/C-6), 151.5 (C-4/C-6), 152.7 (C-2); MS EI *m/z* (rel. %): 276 (100, M^+), 275 (89), 248 (14), 247 (18), 209 (4), 199 (7), 91 (78), 65. HRMS: Found 276.1005. Anal. Calcd for $C_{16}H_{12}N_4O$ 276.1011; Found: C, 69.21; H, 4.43; N, 19.99. $C_{16}H_{12}N_4O$ requires C, 69.55; H, 4.38; N, 20.28%.

5.27. 9-(Phenylmethyl)-6-(1-pyrrolyl)-9*H*-purine (3o)

To a stirred mixture of tris(dibenzylidenacetone)dipalladium (12.7 mg, 0.0138 mmol), 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (135 mg, 0.55 mmol) and cesium carbonate (277 mg, 0.85 mmol) in dry toluene (1.5 mL) under N_2, tri-*tert*-butylphosphine (650 μL, 0.0275 mmol, 0.422 M in toluene) and pyrrole (191 μL, 2.75 mmol) were added. The resulting mixture was heated for 18 h at 100 °C and cooled to ambient temperature. The reaction mixture was added on top of a silica gel column and the product was purified by flash chromatography by eluting with EtOAc–hexane (1:4) followed by EtOAc–hexane (1:2); yield 104 mg (77%), colorless powdery crystals, mp 164–165 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.42 (s, 2H, CH_2), 6.41 (t, J = 2.0 Hz, 1H, pyrrolyl), 7.28–7.36 (m, 5H, Ph), 7.96 (s, 1H, H-8), 8.31 (br t, J = 2.0 Hz, 1H, pyrrolyl), 8.80 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.4 (CH_2), 112.5 (CH in pyrrolyl), 120.6 (CH in pyrrolyl), 122.0 (C-5), 127.8 (CH in Ph), 128.6 (CH in Ph), 129.1 (CH in Ph), 135.0 (C in Ph), 143.1 (C-8), 147.8 (C-6), 152.3 (C-2), 153.3 (C-4); MS EI *m/z* (rel. %): 275 (100, M^+), 274 (60), 198 (5), 182 (5), 91 (67); HRMS: Found 275.1173. Anal. Calcd for $C_{16}H_{13}N_5$ 275.1171. Found: C, 69.72; H, 4.74; N, 25.57. $C_{16}H_{13}N_5$ requires C, 69.80; H, 4.76; N, 25.44%.

5.28. 6-(1-Imidazolyl)-9-(phenylmethyl)-9*H*-purine (3p)

A solution of imidazole (204 mg, 3.00 mmol) in dry DMF (3 mL) was added to a solution of 6-bromo-9-(phenylmethyl)-9*H*-purine **1d** (145 mg, 0.50 mmol) in dry DMF (8 mL) and heated to 100 °C for 24 h under N_2. After cooling to ambient temperature, EtOAc (50 mL) was added and the mixture was washed with water (30 mL) and satd aq NaCl (30 mL), dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified by flash chromatography on silica by eluting with EtOAc–EtOH; yield 121 mg (88 %), colorless powdery crystals, mp 195 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.45 (s, 2H, CH_2), 7.22 (s, 1H, imidazolyl), 7.29–7.37 (m, 5H, Ph), 8.05 (s, 1H, H-8), 8.37 (s, 1H, imidazolyl), 8.79 (s, 1H, H-2), 9.15 (s, 1H, imidazolyl); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.6 (CH_2), 117.3 (CH in imidazolyl), 122.3 (C-5), 127.9 (CH in Ph), 128.8 (CH in Ph), 129.2 (CH in Ph), 130.6 (CH in imidazolyl), 134.7 (C-1 in Ph), 137.6 (CH in imidazolyl), 144.2 (C-8), 145.7 (C-6), 152.4 (C-2), 153.7 (C-4); MS EI *m/z* (rel. %): 276 (100, M^+), 275 (56), 250 (4), 248 (2), 199 (3), 182 (5), 92 (6), 91 (84); HRMS: Found 276.1121. Anal. Calcd for $C_{15}H_{12}N_6$ 276.1123. Found: C, 64.85; H, 4.29; N, 30.77. $C_{15}H_{12}N_6$ requires C, 65.21; H, 4.38; N, 30.42%.

5.29. 6-(1-Metylpyrrol-2-yl)-9-(phenylmethyl)-9*H*-purine (3q)

The title compound was prepared from 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and 1-metylpyrr-2-ylzinc bromide [generated from 1-methylpyrrole (89 μL, 1.0 mmol) by treatment with *tert*-butyllithium (625 μL, 1.0 mmol, 1.6 M pentane solution) at −78 °C for 30 min at ambient temperature, followed by 1 M anhydrous zinc bromide in dry THF (1.1 mL, 1.1 mmol) for 1 h at ambient temperature]. Other condition were as described for **2c** above and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (1:3) followed by EtOAc–hexane (1:2); yield 111 mg (77%), colorless powdery crystals, mp 136–137 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.19 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 6.29 (dd, J = 4.1 and 2.6 Hz, 1H, CH in pyrrolyl), 6.85–6.86 (m, 1H, CH in pyrrolyl), 7.27–7.35 (m, 5H, Ph), 7.83 (dd, J = 4.1 and 1.7 Hz, 1H, CH in pyrrolyl), 7.96 (s, 1H, H-8), 8.84 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.3 (CH_3), 47.0 (CH_2), 109.0 (pyrrolyl), 119.5 (pyrrolyl), 127.1 (pyrrolyl), 127.7 (CH in Ph), 128.4 (CH in Ph), 128.9 (C-5), 129.0 (CH in Ph), 129.4 (pyrrolyl), 135.4 (C-1 in Ph), 142.8 (C-8), 149.8 (C-6), 151.2 (C-4), 151.9 (C-2); MS EI *m/z* (rel. %): 289 (100, M^+), 288 (71), 199 (6), 198 (53), 171 (4), 144 (4), 92 (6), 91 (63); HRMS: Found 289.1326. Anal. Calcd for $C_{17}H_{15}N_5$ 289.1327; Found: C, 70.20; H, 5.09; N, 24.50. $C_{17}H_{15}N_5$ requires C, 70.57; H, 5.23; N, 24.21%.

5.30. 6-(1-Methylimidazol-2-yl)-9-(phenylmethyl)-9*H*-purine (3r)

The title compound was prepared from 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and 1-metylimidazol-2-ylzinc bromide [generated from 1-methylimidazole (80 μL, 1.0 mmol)] as described for **2c** above and in Table 2. The product was purified by flash chromatography on silica gel by eluting with EtOAc–hexane (2:1) followed by EtOAc–hexane (4:1), and

finally pure EtOAc; yield 88 mg (61%), colorless crystals, mp 168–169 °C. ^{1}H NMR (CD_3CN, 500 MHz) δ 4.37 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.36–7.45 (m, 6H, Ph and imidazolyl), 7.51 (s, 1H, imidazolyl), 8.90 (s, 1H, H-8), 9.14 (s, 1H, H-2); ^{13}C NMR (CD_3CN, 125 MHz) δ 39.0 (CH_3), 49.1 (CH_2), 127.0 (C-5), 129.2 (CH in imidazolyl), 129.4 (CH in Ph), 129.6 (CH in imidazolyl), 129.7 (CH in Ph), 130.0 (CH in Ph), 135.6 (C-1 in Ph), 140.2 (C-2 in imidazolyl), 144.0 (C-6), 148.2 (C-8), 152.3 (C-4), 154.2 (C-2); MS EI *m*/*z* (rel. %): 290 (26, M^+), 289 (100), 288 (83), 199 (9), 198 (67), 171 (5), 144 (7), 92 (10), 91 (87); HRMS: Found 290.1270. Anal. Calcd for $C_{16}H_{14}N_6$ 290.1280; Found: C, 66.03; H, 4.91. $C_{16}H_{14}N_6$ requires C, 66.19; H, 4.86%.

5.31. 9-(Phenylmethyl)-6-(2-pyridinyl)-9*H*-purine (3s)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and 2-(tributylstannyl)pyridine (276 mg, 0.75 mmol) as described for compound **3c** and in Table 2. The product was purified by flash chromatography on silica gel by eluting with CH_2Cl_2/acetone (1:1); yield 29 mg (20%), pale brown crystalline solid, mp 132–135 °C (lit.[23] 134–137 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.51 (s, 2H, CH_2), 7.28–7.35 (m, 5H, Ph), 7.38–7.43 (m, 1H, pyridyl), 7.87–7.93 (m, 1H, pyridyl), 8.17 (s, 1H, H-8), 8.80 (br d, *J* 8.0 Hz, 1H, pyridyl), 8.95 (br d, *J* 4.8 Hz, 1H, pyridyl), 9.15 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.3 (CH_2), 124.8 (CH in pyridyl), 125.5 (CH in pyridyl), 127.7 (CH in Ph), 128.5 (CH in Ph), 129.1 (CH in Ph), 131.2 (C-5), 135.0 (C in Ph), 136.7 (CH in pyridyl), 145.3 (C-8), 150.3 (CH in pyridyl), 152.7 (C-2), 153.2 (C-4/C-6), 153.8 (C-4/C-6).

5.32. 9-(Phenylmethyl)-6-(3-pyridinyl)-9*H*-purine (3t)

3-Bromopyridine (96 μL, 1.0 mmol) was added dropwise to a stirred solution of *n*-butyllithium (688 μL, 1.1 mmol, 1.6 M hexane solution) in dry diethyl ether (2 mL). After 30 min, a 1 M solution of anhydrous zinc bromide in dry THF (1.1 mL, 1.1 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-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) in dry THF (2 mL) was added and the title compound was prepared by Negishi coupling as described for **2c** above and in Table 2. The product was purified by flash chromatography on silica gel by eluting with acetone–CH_2Cl_2 (3:7); yield 127 mg (88%), pale yellow powdery crystals, mp 141–142 °C (lit.[23] 145–147 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (s, 2H, CH_2), 7.29–7.35 (m, 5H, Ph), 7.45 (dd *J* = 7.5 and 4.7 Hz, 1H, Ar), 8.09 (s, 1H, H-8), 8.72 (br s, 1H, pyridyl), 9.04 (s, 1H, H-2), 9.05 (d, *J* = 8.8 Hz, 1H, pyridyl), 9.96 (br s, 1H, pyridyl); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.3 (CH_2), 123.4 (CH in pyridyl), 127.8 (CH in Ph), 128.7 (CH in Ph), 129.1 (CH in Ph), 131.0 (C-5), 131.5 (C-3 in pyridyl), 135.0 (C-1 in Ph), 136.9 (CH in pyridyl), 144.6 (C-8), 150.9 (CH in pyridyl), 151.4 (CH in pyridyl), 152.4 (C-6), 152.5 (C-4), 152.6 (C-2); MS EI *m*/*z* (rel. %): 287 (100, M^+), 286 (65), 260 (2), 259 (4), 210 (6), 209 (2), 197 (5), 196 (42), 169 (3), 144 (3), 142 (2), 92 (5), 91 (66); HRMS: Found 287.1168, calcd for $C_{17}H_{13}N_5$ 287.1171.

5.33. 9-(Phenylmethyl)-6-(4-pyridinyl)-9*H*-purine (3u)

The title compound was prepared by Stille coupling between 6-chloro-9-(phenylmethyl)-9*H*-purine **1a** (122 mg, 0.50 mmol) and 4-tributylstannanylpyridine (276 mg, 0.75 mmol) as described for compound **3c** and in Table 2. The product was purified by flash chromatography on silica gel by eluting with CH_2Cl_2–acetone (7:3); yield 42 mg (29%), pale yellow crystals, mp 243–246 °C (lit.[23] 138–144 °C) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.47 (s, 2H, CH_2), 7.28–7.37 (m, 5H, Ph), 8.12 (s, 1H, H-8), 8.62 (dd, *J* = 4.6 and 1.6 Hz, 2H, pyridyl), 8.80 (dd, *J* = 4.6 and 1.6 Hz, 2H, pyridyl), 9.07 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.4 (CH_2), 123.3 (CH in pyridyl), 127.9 (CH in Ph), 128.7 (CH in Ph), 129.2 (CH in Ph), 131.6 (C-5), 134.9 (C-1 in Ph), 142.7 (C-4 in pyridyl), 145.0 (C-8), 150.5 (CH in pyridyl), 152.0 (C-6), 152.6 (C-2), 153.0 (C-4); MS EI *m*/*z* (rel. %): 287 (100, M^+), 286 (89), 259 (4), 210 (6), 209 (4), 196 (7), 144 (2), 92 (4), 91 (64); HRMS: Found 287.1162, calcd for $C_{17}H_{13}N_5$ 287.1171.

Acknowledgments

Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the US National Institute of Allergy and Infectious Diseases. We are grateful for all help provided by Dr. Cecil Kwong and co-workers. Other antibacterial data were provided by University Hospital North Norway, Department of Microbiology, Tromsø, Norway. The Norwegian Research Council is gratefully acknowledged for partial financing of the Bruker Avance NMR instruments used in this study.

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