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Synthesis, structure, and antimycobacterial activity of 6-[1(3*H*)-isobenzofuranylidenemethyl]purines and analogs

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ABSTRACT

6-Benzofuryl-, styryl, benzyl, and furfurylpurines as well as 6-[1(3*H*)-isobenzofuranylidenemethyl]purines have been synthesized and their activities against *Mycobacterium tuberculosis* (*Mtb*) determined. Several compounds displayed profound antimycobacterial activity in combination with low toxicity towards mammalian cells. NMR and X-ray crystallography were employed to determine the detailed structures and the results were supported by quantum chemical calculations.

1. Introduction

Tuberculosis (TB) still claims ca. two-million deaths per year world-wide and resistance to existing drugs is a growing problem.[1] We have previously reported selective antibacterial activity against *Mycobacterium tuberculosis* (*Mtb*) for certain 9-benzylpurines.[2] Fig. 1 shows examples of purines with profound antimycobacterial activity as well as a summary of SAR knowledge. Previous results have led us to believe that an aryl group in the purine 6-position is a requirement for significant antimycobacterial effect,[2a] and among the 6-aryl- and 6-heteroarylpurines examined, especially high activities are found for 6-(2-furyl)purines,[2e] for instance compounds **1a**–**1d** (Fig. 1). The more bulky 6-(benzofur-2-yl)purine **2a** is less active than the corresponding furylpurine **1a**.[2d] However, we recently found MIC values for antimycobacterial activity of 6-[1(3*H*)-isobenzofuranylidenemethyl]purines **3a** and **4a** only one titer step higher than 6-furylpurine **1a**.[3] Since we have shown that compound **4a** easily isomerizes into the *Z*-isomer **3a**,[3] it may be that compound **4a** also isomerizes into compound **3a** in the antimycobacterial assay.

The profound, and somewhat unexpected, effect on *Mtb* growth found for the *Z*-6-[1(3*H*)-isobenzofuranylidenemethyl]purine **3a**, prompted us to synthesize and determine antimycobacterial activity for the related compound **3b** (Fig. 1) where the substitution pattern elsewhere in the molecule is optimized according to our current SAR knowledge, as well as the optimized 6-(benzofur-2-yl)purine **2b** (Fig. 1) and the styryl- **5**, benzyl- **6**, and furfurylpurine **7**. The structural relationship between compounds **5**–**7** and the (isobenzofuranylidenemethyl)purine **3b**, is illustrated in Figure 2. It was previously shown that compound **3a** exists only as a (isobenzofuranylidenemethyl)purine, and not as an aromatic, but quinoid, benzo[*c*]furylmethylpurine.[3] On the other hand, the simple furyl derivative **7**, may exist as tautomer **7b** rather than **7a**. Hence, we included a structural study of the synthesized compounds employing NMR, X-ray, and quantum chemical calculations in order to reveal their detailed structures and broaden our SAR knowledge.

2. Synthesis

Z-6-[1(3*H*)-Isobenzofuranylidenemethyl]purine **3b** was synthesized essentially as reported for the preparation of compound **3a** before.[3] When the dichloropurine **8** was reacted with the alkyne **9** under Sonogashira coupling conditions, cyclization took place to give mainly the *E*-isomer **4b**. The mixture of isomers was treated with TFA to give the pure *Z*-6-[1(3*H*)-isobenzofuranylidenemethyl]purine **3b** (Scheme 1).

The other target molecules, **2b** and **5**–**7**, were available by regioselective Stille- or Negishi-coupling on the dichloropurine **8** (Scheme 2, Table 1) a synthetic strategy employed by us in the synthesis of several 6-substituted purines.[1,4] Furfuryl halides are regarded as unstable and difficult to utilize for synthetic purposes.[5] However, we found that the desired furfurylzinc chloride could be generated from furfuryl chloride and Rieke zinc following the protocol previously used for generation of benzylzinc chloride.[6]

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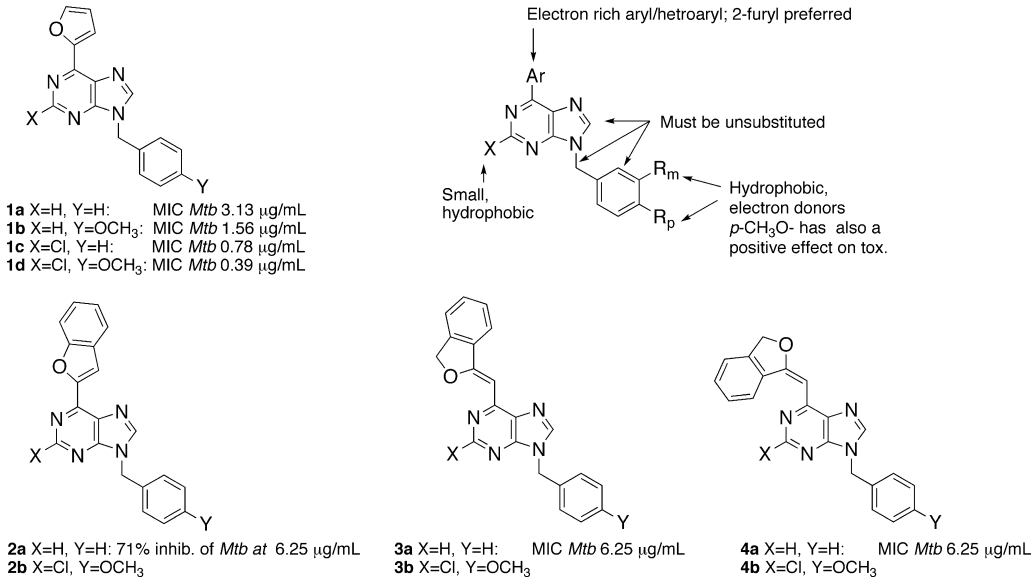


Figure 1. Structures of antimycobacterial purines and previously reported MIC values,[2a,d,e,3] summary of SAR for antimycobacterial 9-benzylpurines, and target molecules in the study.

This constitutes the first formation and synthetic application of a furfurylmetal reagent carrying no stabilizing groups on the furyl ring.

3. Structure

In line with our previous observations on compound **3a**,[3] no quinoid benzo[*c*]furylmethylpurine tautomer could be detected in the ^{1}H NMR spectrum of the *Z*-6-[1(3*H*)-isobenzofuranylidenemethyl]purine **3b** or the isomer **4b**. On the other hand, ^{1}H NMR revealed that compound **7** was present only as the furfurylpurine **7b**. Electronic structure calculations supported these findings (see Supplementary data). The furfurylpurine **7** also crystallized as the **7b** tautomer (Fig. 3). The benzyl group in crystalline compound **7b** is oriented quite different from what is previously found by X-ray crystallography for the benzylic substituent in the 6-furylpurine **1d**[7] and related structures,[8] for further discussions, see Supplementary data.

4. Antimycobacterial activity

The novel purine derivatives **2b**, **3b**, **5**, **6**, and **7b** were screened for antibacterial activity against *M. tuberculosis* $H_{37}Rv$ in vitro and the IC_{90} and IC_{50} values are presented in Table 2 together with comparable data for the compounds **1d** and **3a** synthesized earlier. Previously determined MIC values (*Mtb*) for compounds **1a**–**1d**, **2a**, **3a**, and **4a** are displayed in Figure 1.

Both the 6-furyl- **1d** and 6-benzofurylpurine **2b** were found to be highly potent inhibitors of *Mtb* (IC_{90} <0.20 μg/mL, <0.6 μM). As expected, both (isobenzofuranylidenemethyl)purines **3a** and **3b** also displayed considerable growth inhibition (IC_{90} 3–5 μg/mL, 8–12 μM). However, the furfurylpurine **7b** was essentially inactive (IC_{90} >100 μg/mL) whereas the benzyl- **6** and styrylpurine **5** were only slightly weaker inhibitors (IC_{90} 6–11 μg/mL, 16–30 μM) compared to the (isobenzofuranylidenemethyl)purines **3**. None of the novel compounds described herein could compete with 6-furyl- **1d** or 6-benzofurylpurine **2b** where the aryl substituent is connected

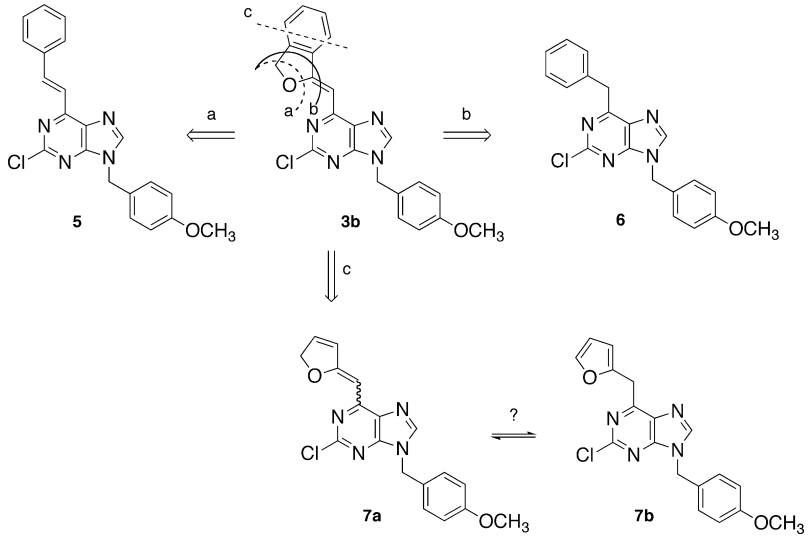
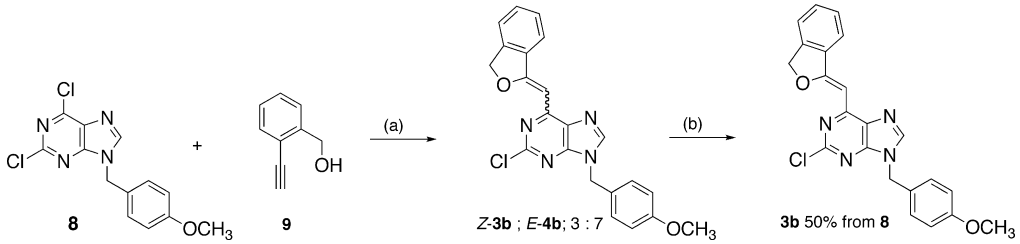
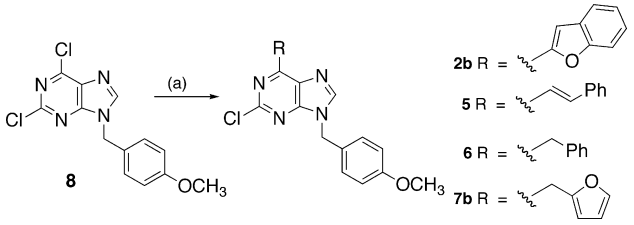


Figure 2. Target molecules **5–7** and their structural relationship with target molecule **3b**.



Scheme 1. Reagents and conditions: (a) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NH$, DMF, 60 °C; (b) TFA, CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) R-Met, Pd-cat, 50 °C, for more details, see Table 1.

Table 1
Reaction conditions applied in synthesis of compounds **5**–**7**

–Met	Pd-catalyst	Solvent	Time (h)	Yield (%)
$-SnBu_3$	$[(2\text{-Furyl})_3P]_4Pd$	DMF	8	78, **2b**
$-SnBu_3$	$[(2\text{-Furyl})_3P]_4Pd$	DMF	7	77, **5**
–ZnCl	$(Ph_3P)_4Pd$	THF	5	69, **6**
–ZnCl	$(Ph_3P)_4Pd$	THF	3	59, **7**

directly to C-6 in the purine, with respect to inhibition of *Mtb*. However, and in contrast to our previous believe (Fig. 1),[2] also other substituents (i.e., styryl- or isobenzofuranylidenemethyl-) in the 6-position may result in purines with a considerable antimycobacterial activity. The compounds displaying IC_{90} values against *Mtb* lower than 10 μg/mL were also screened for toxicity towards mammalian cells (VERO cells, Table 2). All compounds examined, except **3a**, showed IC_{50} against VERO cells >40 μg/mL. We have previously reported that compound **1c** (Fig. 1) showed virtually no cross resistance against a panel of drug-resistant *Mtb* strains.[2b] We assume that the closely related structures reported herein act by the same, currently unknown, mechanism of action as purine **1c**, so we have reasons to believe that cross resistance will not be an issue for the novel compounds described herein.

5. Experimental

The ^1H NMR spectra were recorded at 300 MHz with a Bruker Avance DPX 300 instrument, and the ^1H decoupled ^{13}C NMR spectra were recorded 75 MHz using the same 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.). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points were determined with a C. Reichert melting point apparatus or a Büchi Melting Point B-545 apparatus and are uncorrected. DMF was distilled from BaO and stored over 4 Å mol. sieve, dichloromethane was distilled from CaH_2, and THF from Na/benzophenone. Antimycobacterial activity was determined as previously reported.[2] The following compounds were prepared according to literature procedures: 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **1d**,[2d] (*Z*)-9-benzyl-6-[isobenzofuran-1(3*H*)-ylidenemethyl]-9*H*-purine **3a**,[2] 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **8**,[2d] (*E*)-tributyl(phenylethenyl)stannane,[9] tributyl(benzo[*b*]fur-2-yl)stannane,[10] and furfuryl chloride.[11] Benzylzinc chloride was generated from benzyl chloride and Rieke zinc[12] according to a published procedure[6] and the concentration of the solution was determined by hydrolysis and iodolysis.[13] Furfurylzinc chloride was generated from furfuryl chloride following the same protocol.

5.1. X-ray crystallographic analysis for compound 7b

Crystals of **7b** suitable for X-ray crystallography were obtained from benzene solution at +4 °C. X-ray data were collected on a Siemens SMART CCD diffractometer[14] using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Data collection method: ω-scan, step 0.3°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs. Absorption corrections were applied by the use of the SADABS program.[15] The structure was determined and refined using the SHELX program package.[16] The non-hydrogen atoms were refined with isotropic thermal parameters; H atoms were positioned geometrically and allowed to ride and rotate (for the CH_3 group) on their carrier atoms, with C–H bond lengths of 0.95 (aromatic C–H), 0.99 (CH_2) or 0.98 Å (CH_3) and with $U_{iso}(H) = 1.2U_{eq}(C)$ for CH_2 and aromatic C–H or $1.5U_{eq}(C)$ for CH_3. Crystal structure data for **7b** are available from the Cambridge Crystallographic Data Center, CCDC no. 643827.

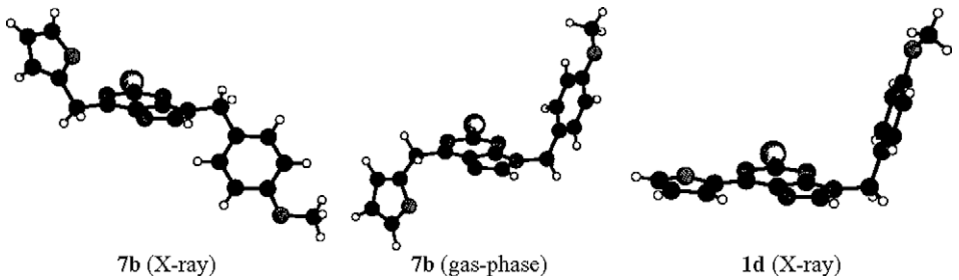


Figure 3. X-ray structure of compound **7b**, the gas-phase equilibrium structure of compound **7b**, and X-ray structure of compound **1d**.[7]

Table 2
Activity against *M. tuberculosis* for purines **1d, 2b**, **3a**, **3b**, **5**, **6**, and **7b** as well as cytotoxicity against VERO cells for selected compounds[a]

Compound	IC_{90} *M. tuberculosis* $H_{37}Rv$ (μg/mL), μM values in brackets[b]	IC_{50} *M. tuberculosis* $H_{37}Rv$ (μg/mL), μM values in brackets[b]	IC_{50} VERO cells (μg/mL)[c]
1d	<0.20 (<0.59)	<0.20 (<0.59)	>40
2b	<0.20 (<0.51)	<0.20 (<0.51)	>40
3a	2.7 (7.9)	1.5 (4.3)	17
3b	4.9 (12)	<0.20 (<0.48)	>40
5	6.1 (16)	3.0 (8.0)	>40
6	11 (30)	7.4 (20)	n.d.
7b	>100 (>280)	>100 (>280)	n.d.

[a] Structures of compounds are shown in Schemes 1 and 2.
[b] IC_{90} amicain 0.13 μg/mL (0.22 μM) and IC_{50} amicain 0.07 μg/mL (0.12 μM).
[c] EC_{50} hyamine 0.01 μg/mL.

5.2. Crystal data for $C_{18}H_{15}ClN_4O_2$ 7b

M = 354.79, monoclinic, $P2(1)/n$ a = 4.5528 (6) Å, b = 18.867(3) Å, c = 18.955(3) Å, β = 96.486(2)°, V = 1617.8(4) Å^3, Z = 4, Dx = 1.457 Mg m^{-3}, μ = 0.26 mm^{-1}, T = 105(2) K, measured 16,774 reflections in 2θ range 6.2–60.6°, R_{int} = 0.032. To 128 parameters refined against 4518 F^2, R = 0.0333 for 3293 $I_o > 2\sigma(I_o)$ and 0.0553 for all data.

5.3. Antimycobacterial data

The purines were screened for antimycobacterial activities essentially as described before.[2,17] Compounds were tested in 10 twofold dilutions, from 100 to 0.19 μg/mL, against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA). The IC_{90} and IC_{50} values are determined from the dose–response curve as the IC_{90} using the curve fitting program XLFIT, formula 205.

5.4. Activity against VERO cells

The compounds were screened for mammalian cell cytotoxicity to VERO cells essentially as described before;[2] after 72 h exposure, viability is assessed using the CellTiter 96® Non-Radioactive Cell Proliferation Assay (MTT) reagent from Promega. Cytotoxicity is determined from the dose–response curve as the EC_{50} using the curve fitting program XLFIT, formula 205.

5.5. 6-(Benzofuran-2-yl)-2-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine (2b)

A mixture of tris(dibenzylideneacetone)dipalladium, Pd_2dba_3 (28 mg, 0.030 mmol), and tri(2-furyl)phosphine (51 mg, 0.22 mmol) in dry DMF (4 mL) was stirred at ambient temperature for 5 min, before a solution of 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **8** (309 mg, 1.0 mmol) in DMF (4 mL) was added. After an additional 5 min, tributyl(benzo[*b*]fur-2-yl)stannane (575 mg, ca. 1.20 mmol, ca. 85% pure) was introduced, the resulting mixture stirred at 50 °C for 8 h and evaporated in vacuo. A satd solution of potassium fluoride in methanol (40 mL) was added to the residue, the mixture was stirred over night and evaporated in vacuo together with a small amount of silica gel. The residue was added on top of a silica gel column, and the product purified by flash chromatography eluting with CH_2Cl_2–acetone (29:1), followed by CH_2Cl_2–acetone (19:1); yield 303 mg (78%), mp 189 °C, colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.75 (s, 3H, OCH_3), 5.32 (s, 2H, NCH_2), 6.87 (d, J = 8.7 Hz, 2H, Ar), 7.24–7.30 (m, 3H, Ar and benzofuryl), 7.38–7.43 (m, 1H, benzofuryl), 7.67–7.70 (m, 2H, benzofuryl), 8.02 (s, 1H, 8-H) and 8.28 (s, 1H, 3-H in benzofuryl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 47.1 (NCH_2), 55.3 (OCH_3), 112.4 (CH in benzofuryl), 114.6 (CH in Ar), 115.2 (CH in benzofuryl), 122.4 (CH in benzofuryl), 123.6 (CH in benzofuryl), 126.4 (C-1 in Ar), 127.2 (CH in benzofuryl), 128.1 (C in benzofuryl), 128.4 (C-5), 129.6 (CH in Ar), 145.1 (C-8), 147.6 (C-6/C-2), 149.7 (C-2 in benzofuryl), 153.7 (C-4), 154.5 (C-2/C-6), 156.0 (C in benzofuryl) and 159.9 (C-4 in Ar) ppm. MS (EI): *m/z* (%): 392/390 (15/42) [M]$^+$, 234 (1), 195 (1), 181 (2), 122 (9), 121 (100). HRMS (EI): calcd for $C_{21}H_{15}ClN_4O_2$ 390.0884, found 390.0886. $C_{21}H_{15}ClN_4O_2$ (390.8): C, 64.54; H, 3.87; N, 14.34. Found: C, 64.50; H, 3.93; N, 14.20.

5.6. 2-Chloro-6-[(*Z*)-1(3*H*)-isobenzofuranylidenemethyl]-9-(methoxyphenylmethyl)-9*H*-purine (3b)

2,6-Dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **8** (155 mg, 0.50 mmol) was added to a stirring solution of CuI (9.5 mg, 0.050 mmol), bis(triphenylphosphine)palladium(II) chloride (18 mg, 0.025 mmol), and dry diisopropylamine (420 μL, 3.00 mmol) in dry DMF (2.5 mL) under N_2. The solution was heated to 60 °C before 2-ethynylbenzenemethanol **9** (79 mg, 0.60 mmol) dissolved in DMF (1 mL) was added dropwise over 1 h. After stirring for additional 4 h at 60 °C, the reaction mixture evaporated in vacuo with a small amount of silica. The residue was added on top of a silica gel column, and the product, as a ca. 7:3 *E*/*Z* mixture was isolated by flash chromatography eluting with CH_2Cl_2–acetone (19:1) followed by CH_2Cl_2–acetone (9:1). The isomeric mixture was dissolved in CH_2Cl_2 (30 mL) and trifluoroacetic acid (74 μL, 0.96 mmol) was added. After stirring for 1 h at ambient temperature the reaction mixture was washed with satd aq $NaHCO_3$ (2 × 20 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2–acetone (9:1); yield 101 mg (50%), pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.76 (s, 3H, OCH_3), 5.28 (s, 2H, NCH_2), 5.71 (s, 2H, OCH_2), 6.72 (s, 1H, =CH), 6.87 (d, J = 8.7 Hz, 2 H, Ar), 7.25 (d, J = 8.7 Hz, 2H, Ar), 7.40–7.48 (m, 3H, Ar′), 7.79–7.82 (m, 1H, Ar′) and 7.84 (s, 1H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 46.8 (NCH_2), 55.3 (OCH_3), 77.2 (OCH_2), 88.6 (=CH), 114.5 (CH in Ar), 121.3 (CH in Ar′), 121.8 (CH in Ar′), 126.9 (C-1 in Ar), 128.5 (CH in Ar′), 129.0 (C-5), 129.6 (CH in Ar), 131.1 (CH in Ar′), 133.9 (C in Ar′), 141.5 (C in Ar′), 142.7 (C-8), 152.1 (C-4), 154.6 (C-2/C-6), 156.2 (C-6/C-2), 159.8 (C-4 in Ar) and 165.7 (=C) ppm. MS (EI): *m/z* (%): 406/404 (9/25) [M]$^+$, 285 (3), 284 (2), 283 (8), 140 (2), 121 (100). HRMS (EI): calcd for $C_{22}H_{17}ClN_4O_2$ 404.1040, found 404.1030. $C_{22}H_{17}ClN_4O_2$ (404.9): C, 65.27; H, 4.23; N, 13.84. Found: C, 64.94; H, 4.16; N, 13.81.

5.7. (*E*)-2-Chloro-9-(4-methoxybenzyl)-6-(2-phenylethenyl)-9*H*-purine (5)

The product was formed by Stille coupling between 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **8** (309 mg, 1.0 mmol) and (*E*)-tributyl(phenylethenyl)stannane (1.12 g, 1.20 mmol, ca. 42% purity) as described for compound **3b** above. The reaction time was 7 h, and the product purified by flash chromatography on silica gel eluting with CH_2Cl_2–acetone (29:1), followed by CH_2Cl_2–acetone (19:1) and finally CH_2Cl_2–acetone (9:1); yield 292 mg (77%), colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.75 (s, 3H, OCH_3), 5.30 (s, 2H, NCH_2), 6.88 (d, J = 8.8 Hz, 2H, Ar), 7.26 (d, J = 8.8 Hz, 2H, Ar), 7.32–7.42 (m, 3H, Ph), 7.59 (d, J = 16.1 Hz, 1H, CH=), 7.66–7.69 (m, 2H, Ph), 7.94 (s, 1H, 8-H) and 8.42 (d, J = 16.1 Hz, 1H, CH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 47.0 (NCH_2), 55.3 (OCH_3), 114.5 (CH in Ar), 121.4 (CH=), 126.6 (C-1 in Ar), 128.1 (CH in Ph), 128.8 (CH in Ph), 129.6 (CH in Ar), 129.8 (CH in Ph), 130.0 (C-5), 135.7 (C-1 in Ph), 141.7 (CH=), 144.3 (C-8), 153.4 (C-4), 154.3 (C-2), 155.8 (C-6) and 159.9 (C-4 in Ar) ppm. MS (EI): *m/z* (%): 378/376 (13/36) [M]$^+$, 257 (1), 255 (4), 122 (9), 121 (100). HRMS (EI): calcd for $C_{21}H_{17}ClN_4O$ 376.1091, found 376.1093. $C_{21}H_{17}ClN_4O$ (376.8): C, 66.93; H, 4.55; N, 14.87. Found: C, 66.76; H, 4.46; N, 14.71.

5.8. 6-Benzyl-2-chloro-9-(4-methoxyphenylmethyl)-9*H*-purine (6)

2,6-Dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **8** (309 mg, 1.0 mmol) was added to a solution of tetrakis(triphenylphosphine)palladium(0) [generated in situ from tris(diphenylmethylideneacetone)dipalladium chloroform adduct (23 mg, 0.025 mmol) and triphenylphosphine (53 mg, 0.20 mmol)] in dry THF (4 mL) at ambient temperature under N_2. After 10 min, a solution of benzylzinc chloride (1.83 mL, 1.52 mmol, 0.83 M) in THF was added and the mixture stirred at 50 °C for 5 h. Satd aq NH_4Cl (10 mL) was added and the resulting mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo with a small amount on silica. The residue was added on top of a silica gel column, and the product purified by flash chromatography eluting with CH_2Cl_2–acetone (29:1), followed by CH_2Cl_2–acetone (19:1) and finally CH_2Cl_2–acetone (9:1); yield 250 mg (69%), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.74 (s, 3H, OCH_3), 4.43 (CH_2), 5.25 (s, 2H, NCH_2), 6.85 (d, J = 8.7 Hz, 2H, Ar), 7.11–7.27 (m, 2H, Ar and 3H, Ph), 7.45–7.48 (m, 2H, Ph) and 7.92 (s, 1H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.5 (CH_2), 47.0 (NCH_2), 55.3 (OCH_3), 114.5 (CH in Ar), 126.4 (C-1 in Ar), 126.7 (CH in Ph), 128.5 (CH in Ph), 129.3 (CH in Ph), 129.6 (CH in Ar), 131.7 (C-5), 137.0 (C-1 in Ph), 144.4 (C-8), 152.8 (C-4), 154.1 (C-2), 159.9 (C-4 in Ar) and 162.8 (C-6) ppm. MS (EI): *m/z* (%): 366/364 (24/60) $[M]^+$, 245 (9), 243 (27), 207 (2), 180 (3), 153 (2), 121 (100). HRMS (EI): calcd for $C_{20}H_{17}ClN_4O$ 364.1091, found 364.1090. $C_{20}H_{17}ClN_4O$ (363.8): C, 65.84; H, 4.70; N, 15.36. Found: C, 65.83; H, 4.84; N, 15.26.

5.9. 2-Chloro-6-(furan-2-ylmethyl)-9-(4-methoxyphenylmethyl)-9*H*-purine (7b)

The product was formed by Negishi coupling between 2,6-dichloro-9-(4-methoxyphenylmethyl)-9*H*-purine **8** (309 mg, 1.0 mmol) and furfurylzinc chloride (3.9 mL, 1.60 mmol, 0.41 M) as described for compound **6** above. The reaction time was 3 h, and the product purified by flash chromatography on silica gel eluting with CH_2Cl_2–acetone (29:1), followed by CH_2Cl_2–acetone (19:1) and finally CH_2Cl_2–acetone (9:1); yield 208 mg (59%), mp 135 °C, colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.74 (s, 3H, OCH_3), 4.46 (s, 2H, CH_2), 5.27 (s, 2H, NCH_2), 6.22 (dd, J = 3.2 and 0.7 Hz, 1H, 3-H in furyl), 6.25 (dd, J = 3.2 and 1.9 Hz, 1H, 4-H in furyl), 6.85 (d, J = 8.7 Hz, 2H, Ar), 7.25 (d, J = 8.7 Hz, 2H, Ar), 7.28 (dd, J = 1.8 and 0.8 Hz, 1H, 5-H in furyl) and 7.94 (s, 1H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 32.2 (CH_2), 47.0 (NCH_2), 55.3 (OCH_3), 107.6 (C-3 in furyl), 110.5 (C-4 in furyl), 114.5 (CH in Ar), 126.4 (C-1 in Ar), 129.6 (CH in Ar), 131.7 (C-5), 141.9 (C-5 in furyl), 144.7 (C-8), 149.9 (C-2 in furyl), 152.9 (C-4), 154.1 (C-2), 159.8 (C-6) and 159.9 (C-4 in Ar) ppm. MS (EI): *m/z* (%): 356/354 (15/43) $[M]^+$, 121 (100), 91 (3), 78 (5), 77 (5). HRMS (EI): calcd for $C_{18}H_{15}ClN_4O_2$ 354.0884, found 354.0873. $C_{18}H_{15}ClN_4O_2$ (354.8): C, 60.94; H, 4.26; N, 15.79. Found: C, 60.92; H, 4.28; N, 15.71.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.08.012.

References and notes

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