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# 2-Chloro-6-(2-furyl)-9-(4-methoxybenzyl)-9*H*-purine

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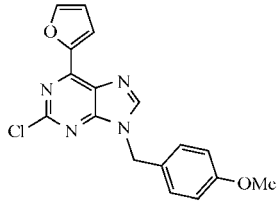
The title compound, $C_{17}H_{13}ClN_4O_2$, displays profound and selective activity against *Mycobacterium tuberculosis*. In the crystal structure, there are two independent molecules in the asymmetric unit. Intermolecular hydrogen bonding between a CH group of the purine ring and the O atom of the furan ring, and also $\pi$–$\pi$ stacking in another direction, builds the three-dimensional network.

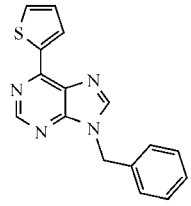
## Comment

Tuberculosis (TB) claims *ca* two million lives every year, and infection with multidrug-resistant strains is an increasing problem, but nevertheless, no new drugs have been launched to treat TB for approximately 40 years (Dye, 2006; Tripathi *et al.*, 2005). We have previously reported that certain 6,9-disubstituted purines are potent inhibitors of *Mycobacterium tuberculosis* (*Mtb*) *in vitro*. Our antimycobacterial purines display several properties which make them highly interesting as potential drugs against tuberculosis. These properties include high selectivity towards *Mtb* compared with other microorganisms, activity against several drug-resistant strains of *Mtb*, generally low toxicity towards mammalian cells, and an ability to affect *Mtb* inside macrophages (Bakkestuen *et al.*, 2000, 2005; Gundersen *et al.*, 2002; Braendvang & Gundersen, 2005). Our most active 6,9-disubstituted purine identified to date is 2-chloro-6-(2-furyl)-9-[(4-methoxyphenyl)methyl]-9*H*-purine, which displays an MIC against *Mtb* of 0.39 μg ml$^{-1}$ (Bakkestuen *et al.*, 2005). (MIC is defined as the minimum concentration of compound required to give 90% inhibition of bacterial growth. MIC for the currently used drug, rifampicin, is 0.25 μg ml$^{-1}$.) The present work reports the X-ray crystallographic study of the potent antimycobacterial title compound, (I).

Compound (I) crystallizes as two crystallographically independent molecules, *A* and *B*, and their molecular geometries are illustrated in Fig. 1. Selected bond lengths and angles are listed in Table 1. The conformations of molecules *A* and *B* are slightly different, as revealed by a molecular fit using the quaternion transformation method (Mackay, 1984). The overlay of all atoms in molecule *A* with those of molecule *B*, except the H atoms, gives r.m.s. bond and angle fits of 0.0034 Å and 0.32°, respectively. The differences are mainly in the orientations of the methoxy and benzyl groups (Table 1). The purine ring system (C1–N9) is almost perfectly planar; the displacements of the atoms from their mean planes do not exceed 0.007 (1) Å in molecule *A* and 0.006 (1) Å in molecule *B*.




(I)




(II)

The conformations of molecules *A* and *B* in (I) very much resemble that in the previously reported crystal structure of the related antimycobacterial 9-benzyl-6-(2-thienyl)-9*H*-purine, (II) (Mazumdar *et al.*, 2001). The bond lengths from the purine ring atoms to the substituents are compared in Table 1. The 6-aryl group in the title compound is nearly coplanar with the purine ring. The angles between the mean plane of the purine ring system and that of the furyl group are 2.31 (6)° in molecule *A* and 2.79 (5)° in molecule *B*, compared with 6.39 (4)° in compound (II). This coplanarity has also been reported for other 6-hetroarylpurines (Zhong *et al.*, 2006). The positions of the benzyl groups are slightly different in compounds (I) and (II), as seen from the torsion angles C4—N9—C10—C11 and N9—C10—C11—C12 (Table 1). The benzene ring plane is inclined at an angle of 73.64 (5)° to the purine ring plane in molecule *A* and at 77.80 (4)° in molecule *B*. In compound (II), the angle between the corresponding planes is 64.03 (5)°.

Fig. 2 shows the crystal packing of molecules *A* and *B* in the unit cell. The molecular packing appears to be stabilized by

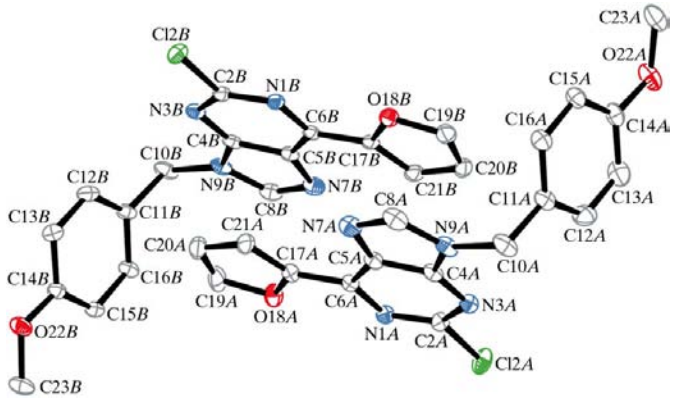



**Figure 1**
The two molecules, *A* and *B*, in the asymmetric unit of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

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segregation of alternate hydrophobic and hydrophilic zones. In the hydrophobic region, the conformation adopted by the benzene rings allows for C—H···$\pi$ interactions, *viz*. C19*A*—H19*A*···*Cg*1*B* and C19*B*—H19*B*···*Cg*1*A* within the asymmetric unit (Fig. 3 and Table 2) (*Cg*1*B* and *Cg*1*A* are the centroids of the C11–C16 benzene rings in molecules *B* and *A*, respectively).

In the hydrophilic region, the conformation allows for $\pi$–$\pi$ interactions between the heterocycles in the asymmetric unit and these occur between the furyl and pyrimidine rings (Fig. 3). The average interplanar distance between furyl ring C17*A*/O18*A*/C19*A*–C21*A* (molecule *A*) and pyrimidine ring N1*B*/C2*B*/N3*B*/C4*B*–C6*B* (molecule *B*) is 3.379 Å, and the centroids of the two rings are slipped by 17.2° relative to their ring normals. The corresponding interaction between furyl ring C17*B*/C18*B*/C19*B*–C21*B* and pyrimidine ring N1*A*/C2*A*/N3*A*/C4*A*–C6*A* results in a distance of 3.332 Å, with the two ring centroids slipped by 18.6° relative to their ring normals. The *Cg*2*A*···*Cg*3*B* and *Cg*2*B*···*Cg*3*A* distances are 3.5357 (7) and 3.5160 (7) Å, respectively (*Cg*2 and *Cg*3 are the centroids of the furyl and pyrimidine rings, respectively), while the mean angle between the purine ring planes is 2.04 (3)°.

The crystal packing (Fig. 2) gives further $\pi$–$\pi$ interactions along the *c* axis between the imidazole ring (C4*A*/C5*A*/N7*A*/C8*A*/N9*A*) in molecule *A* and the pyrimidine ring (N1*B*/C2*B*/N3*B*/C4*B*–C6*B*) in molecule $B^{iv}$ [symmetry code: (iv) $\frac{3}{2} - x, y, -\frac{1}{2} + z$]. Moving down the *c* axis, the ring centroid-to-centroid distance *Cg*4*A*···*Cg*3$B^{iv}$ is 3.4516 (6) Å (*Cg*4*A* is the centroid of the imidazole ring C4*A*/C5*A*/N7*A*/C8*A*/N9*A*). In this interaction, the average interplanar distance is 3.28 Å and the centroids of the two rings are slipped by 18.1° relative to their ring normals, while the mean angle between the purine ring planes is 0.58 (3)°.

Finally, moving along the *a* axis, the two molecules *A* and *B* separately build up their own infinite chains *via* C8*A*—H8*A*···O18$A^{i}$ and C8*B*—H8*B*···O18$B^{ii}$ hydrogen bonds [Table 2 and Fig. 3; symmetry codes: (i) $x + 1, y, z$; (ii) $x - 1, y, z$]. These values are in agreement with C—H···O hydrogen bonding reported for the C-8 H atom in other purine ring systems (Trávníček & Popa, 2007).

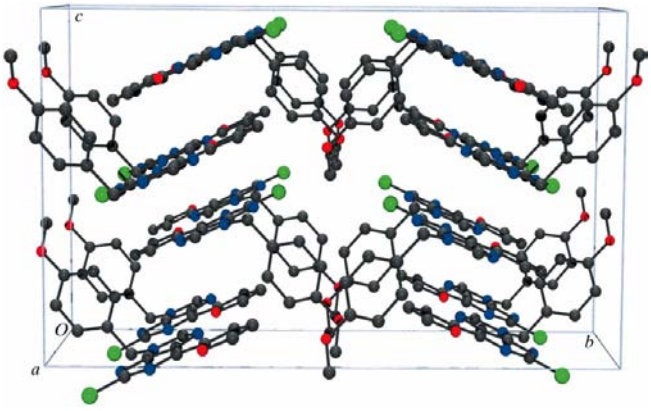


**Figure 2**
The packing of *A* and *B* molecules of (I) (with the unit cell), showing the stacking of alternate *A* and *B* molecules, viewed down the *a* axis.

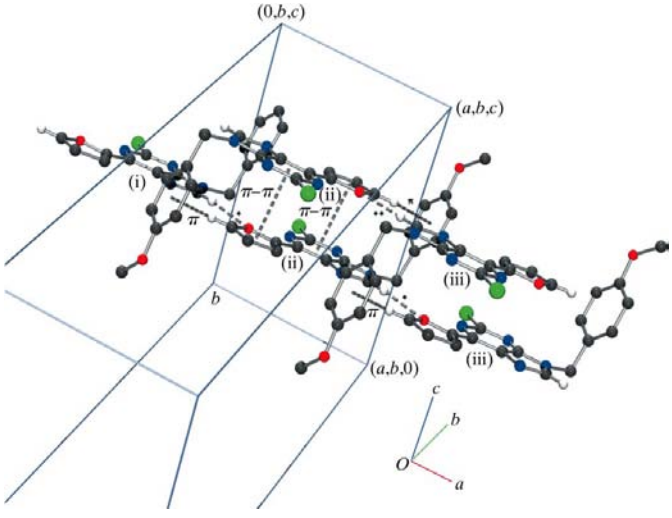


**Figure 3**
A partial packing view, showing the different intermolecular interactions (dashed lines) between molecules *A* and *B* in (I). Dashed lines labelled $\pi$–$\pi$ are the intermolecular $\pi$–$\pi$ interactions between the furan and pyrimidine rings in molecules *A* and *B* in the asymmetric unit. Dashed lines labelled $\pi$ are the C—H···$\pi$ interactions between the C19—H19 group of one molecule and the benzene ring (C11–C16) of the other molecule in the asymmetric unit. Dashed lines labelled with an asterisk (*) or a double asterisk (**) are the C8*A*—H8*A*···O18$A^{i}$ and C8*B*—H8*B*···O18$B^{ii}$ interactions, respectively. H atoms not involved in hydrogen-bonding interactions have been omitted for clarity. [Symmetry codes: (i) $x + 1, y, z$; (ii) $x - 1, y, z$; (iii) $x, y, z$.]

## Experimental

The title compound was synthesized as described by Bakkestuen *et al.* (2005). Crystals of (I) suitable for X-ray diffraction studies were obtained by dissolving the compound (50 mg) in deuterated dichloromethane (0.6 ml) with heating, followed by slow evaporation of the solvent in a refrigerator.

*Crystal data*

$C_{17}H_{13}ClN_4O_2$
$M_r$ = 340.76
Orthorhombic, $Pca2_1$
$a$ = 8.6963 (4) Å
$b$ = 24.5966 (11) Å
$c$ = 14.3247 (7) Å
$V$ = 3064.0 (2) Å$^3$
$Z$ = 8
Mo $K\alpha$ radiation
$\mu$ = 0.27 mm$^{-1}$
$T$ = 105 (2) K
0.4 × 0.3 × 0.02 mm

*Data collection*

Siemens SMART CCD area-detector diffractometer
Absorption correction: empirical (using intensity measurements) (*SADABS*; Sheldrick, 1996)
$T_{min}$ = 0.83, $T_{max}$ = 0.995
49273 measured reflections
17784 independent reflections
12073 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.039

*Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.088
$S$ = 0.89
17784 reflections
435 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.46 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.30 e Å$^{-3}$
Absolute structure: Flack (1983), with 8178 Friedel pairs
Flack parameter: −0.01 (3)

**Table 1**
A comparison of selected geometric parameters (Å, °) of molecules *A* and *B* in (I) and of compound (II).

| | Molecule *A* in (I)† | Molecule *B* in (I)† | Compound (II)‡ |
|---|---|---|---|
| C6—C17 | 1.4479 (15) | 1.4497 (15) | 1.449 (2) |
| C10—N9 | 1.4755 (15) | 1.4740 (15) | 1.469 (2) |
| C10—C11 | 1.5128 (16) | 1.5127 (16) | 1.504 (2) |
| C14—O22—C23 | 118.12 (10) | 116.93 (9) | § |
| C15—C14—O22—C23 | 11.24 (17) | −2.45 (17) | § |
| C4—N9—C10—C11 | 78.72 (15) | −70.99 (15) | 88.3 (2) |
| N9—C10—C11—C12 | −94.59 (14) | 91.21 (13) | −91.0 (2) |

† This work. ‡ Mazumdar *et al.* (2001). § Compound (II) does not contain a methoxy group.

**Table 2**
Hydrogen-bond geometry (Å, °).

*Cg*1*B* and *Cg*1*A* are the centroids of the C11–C16 benzene rings in molecules *B* and *A*, respectively.

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| C8*A*—H8*A*···O18*A*$^{i}$ | 0.95 | 2.46 | 3.4037 (13) | 176 |
| C8*B*—H8*B*···O18*B*$^{ii}$ | 0.95 | 2.44 | 3.3924 (14) | 179 |
| C19*A*—H19*A*···*Cg*1*B* | 0.95 | 2.78 | 3.5261 (14) | 136 |
| C19*B*—H19*B*···*Cg*1*A* | 0.95 | 2.85 | 3.6163 (13) | 139 |

Symmetry codes: (i) $x+1, y, z$; (ii) $x-1, y, z$.

Friedel pairs were not merged and the absolute structure has been determined reliably. H atoms were positioned geometrically and allowed to ride and rotate (for the $CH_3$ group) on their carrier atoms, with C—H = 0.95 (aromatic), 0.99 ($CH_2$) or 0.98 Å ($CH_3$), and with $U_{iso}(H) = 1.2U_{eq}(C)$ for $CH_2$ and aromatic CH groups or $1.5U_{eq}(C)$ for $CH_3$ groups.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Version 1.08; Farrugia, 1997) and *POV-RAY for Windows* (Cason, 2004); software used to prepare material for publication: *SHELXL97* and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN3042). Services for accessing these data are described at the back of the journal.

## References

Bakkestuen, A. K., Gundersen, L.-L., Langli, G., Liu, F. & Nolsøe, J. M. J. (2000). *Bioorg. Med. Chem. Lett.* **10**, 1207–1210.
Bakkestuen, A. K., Gundersen, L.-L. & Utenova, B. T. (2005). *J. Med. Chem.* **48**, 2710–2723.
Braendvang, M. & Gundersen, L.-L. (2005). *Bioorg. Med. Chem.* **13**, 6360–6373.
Bruker (1998). *SMART* (Version 5.625) and *SAINT* (Version 6.02). Bruker AXS Inc., Madison, Wisconsin, USA.
Cason, C. J. (2004). *POV-RAY*. Version 3.6. Persistence of Vision Raytracer Pty. Ltd, Victoria, Australia. URL: http://www.povray.org/download/.
Dye, C. (2006). *Lancet*, **367**, 938–940.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Gundersen, L.-L., Nissen-Meyer, J. & Spilsberg, B. (2002). *J. Med. Chem.* **45**, 1383–1386.
Mackay, A. L. (1984). *Acta Cryst.* A**40**, 165–166.
Mazumdar, P. A., Das, A. K., Bakkestuen, A. K., Gundersen, L.-L. & Bertolasi, V. (2001). *Acta Cryst.* E**57**, o1052–o1054.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Trávníček, Z. & Popa, I. (2007). *Acta Cryst.* E**63**, o728–o730.
Tripathi, R. P., Tewari, N., Dwivedi, N. & Tiwari, V. K. (2005). *Med. Res. Rev.* **25**, 93–131.
Zhong, M., Nowak, I., Cannon, J. F. & Robins, M. J. (2006). *J. Org. Chem.* **71**, 4216–4221.